



JOHANNES GUTENBERG
UNIVERSITÄT MAINZ

Electrosynthesis of Carboxylic Acid Derivatives, Sulfonic Acid Derivatives, and Electrochemical Allylic Oxidation Reaction

Dissertation

for attaining the academic degree of
“doctor rerum naturalium“ (Dr. rer. nat.) in chemistry

submitted to the Department of Chemistry, Faculty of Chemistry,
Pharmaceutical Sciences, Geography, and Geosciences
at the Johannes Gutenberg University Mainz

submitted by
Johannes Schneider geb. Zielke
born in Dahn

Mainz, 2025

Dean: Prof. Dr. Eva Rentschler

Date of PhD Defense: November 14th, 2025

D77 (Johannes Gutenberg–Universität Mainz)

License: CC-BY-4.0

for my family

„[...] aber was prinzipiell Neues? Das werden Sie nicht finden!“ ^[1]

Max Planck quoting his mentor, Prof. Philipp von Jolly, who advised Planck in 1878 to avoid studying theoretical physics, because von Jolly believed nothing fundamentally new remained to be discovered. Planck ignored the advice, continued to study, later invented quantum theory, and was awarded the Nobel Prize in 1918.

Table of Contents

1	Introduction.....	11
1.1	Advantages of Electrosynthesis	12
1.2	Experimental Aspects of Electrosynthesis	15
1.2.1	Electrolysis Cells	16
1.2.2	Electrode Materials	19
1.2.3	Operational Modes.....	20
1.2.4	Amount of Applied Charge and Current Density	22
1.2.5	Solvents	23
1.2.6	Supporting Electrolytes	25
1.2.7	Terminal Cell Voltage and Electrode Potentials.....	26
1.2.8	Electrode-Electrolyte Interface and Mass Transfer.....	27
1.2.9	Scale-up and Downstream Processing	29
1.2.10	Flow Chemistry	30
1.2.11	Reaction Optimization in Electrosynthesis.....	32
1.2.12	Design of Experiments (DoE).....	34
2	Objectives.....	35
3	Overview of Publications	36
4	Results and Discussion	37
4.1	Electrochemical Dehydration Reactions.....	37
4.2	Electrochemical Multicomponent Reactions using SO ₂	85
4.3	Automated Electrosynthesis in Flow.....	99
4.4	Electrochemical Allylic Oxidation	126
5	Conclusions.....	141
6	Outlook.....	142
6.1	Automated Electrosynthesis using Flow Chemistry.....	142
6.2	Electrochemical Dehydration Reactions.....	143
6.3	Electrochemical Multicomponent Reactions of SO ₂	144
6.3.1	Sulfonyl Fluorides.....	144
6.3.2	Sulfonyl Azides.....	145
6.3.3	Primary Sulfonamides	146
6.3.4	Asymmetric Sulfamides.....	146
6.3.5	Sulfonamides and Sulfonates of Electron-Deficient Arenes	146
6.3.6	Liquid SO ₂ as a Medium for Electrosynthesis	147
6.3.7	Cathodic Reduction of SO ₂ for Mediated Reductions.....	147
6.3.8	Sulfones	148
6.3.9	Sulfonylureas	148

6.3.10	Electrosynthesis involving Cheletropic Reactions of SO ₂	148
6.4	Electrosynthesis of Selenium Compounds	148
6.5	Electrochemical Allylic Oxidation	149
6.6	Electrosynthesis of Aminocrotonitriles	149
6.7	Closing Remarks	150
7	References	151
8	Appendix	160
8.1	Utilized Software and Tools	160
8.2	List of Abbreviations	161
8.3	Attended Conferences, Posters, and Presentations.....	163
8.4	Supervised Students and Courses	164
8.5	Curriculum Vitae.....	164
8.6	Supporting Information of Publications.....	165

Declaration

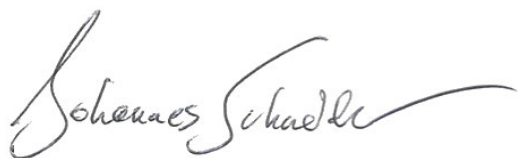
I hereby declare that I, Johannes Schneider geb. Zielke, born on Aug 10th, 1994, in Dahn, wrote this PhD thesis titled “*Electrosynthesis of Carboxylic Acid Derivatives, Sulfonic Acid Derivatives, and Electrochemical Allylic Oxidation Reaction*” purely by myself and without any external help other than the software and tools I mentioned in the appendix of this thesis. For writing of this PhD thesis and all the publications associated with it, I did not utilize any artificial intelligence tools.

All of my contributions related to experimental work and scientific publishing were carried out to the best of my knowledge, and by submission of this PhD thesis, I take full responsibility for all content. All texts, figures, and other material of any kind which originates from work that is not my own is appropriately labeled as such by citation. I checked the sources of these citations for scientific and ethical correctness to the best of my knowledge and included them based on my agreement.

This PhD thesis was written purely for obtaining a PhD degree from Mainz University, and not for any other course assessments or certificates.

The experimental work that I contributed was carried out in the group of Prof. Dr. Siegfried R. Waldvogel at Mainz University between February 2022 and July 2025.

I am aware that any violation of the above-mentioned rules may lead to legal consequences, particularly the revocation of my PhD thesis or the grading of the PhD examination as “failed”. The enrollment can be revoked for up to two years if students cheat on examinations twice or more (§ 69 Abs. 4 und 5 HochSchG).

A handwritten signature in black ink, reading 'Johannes Schneider', with a long, sweeping horizontal stroke extending to the right.

Johannes Schneider

Mainz, Aug 28th, 2025

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Abstract

This dissertation explored the electrochemical synthesis of carboxylic acid derivatives, sulfonic acid derivatives, and electrochemical allylic oxidation reaction. To achieve this, research in various areas of electrosynthesis was carried out, such as electrochemical dehydration reactions and electrochemical multicomponent reactions using sulfur dioxide. The cooperation of electrosynthesis with other evolving technologies such as flow chemistry and laboratory automation was investigated and further developed. Carboxylic anhydrides were synthesized by electrochemical dehydration of their corresponding carboxylic acids. Sulfonamides and sulfonates were synthesized via electrochemical multicomponent reactions of arenes with amines or alcohols and SO₂, and also by electrochemical dehydration of sulfonic acids to their sulfonic anhydrides via subsequent treatment of the sulfonic anhydrides with an excess of amines or alcohols. The recent progress in electrochemical dehydration reactions was summarized in a review article. To establish an open-source platform for automated electrosynthesis, the LABS system (Laboratory Automation and Batch Scheduling) was developed, which was benchmarked by using a flow electrolysis cell with electrochemical phenol cross coupling and electrochemical multicomponent synthesis of sulfonates as test reactions. Furthermore, a simplified approach for electrochemical allylic oxidation was developed, which is an important topic for late-stage functionalization of natural compounds to highly value-added products.

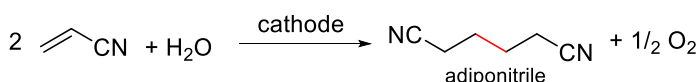
Kurzzusammenfassung

Im Rahmen dieser Dissertation wurde die elektrochemische Synthese von Carbonsäurederivaten, Sulfonsäurederivaten, sowie die elektrochemische allylische Oxidation erforscht. Hierfür wurden Forschungsarbeiten in vielfältigen Bereichen der Elektrosynthese durchgeführt, z. B. elektrochemische Dehydratisierungsreaktionen und elektrochemische Multikomponentenreaktionen mit Schwefeldioxid. Das Zusammenspiel von Elektrosynthese mit anderen aufstrebenden Technologien wie Flow Chemie und Laborautomatisierung wurde untersucht und weiterentwickelt. Carbonsäureanhydride wurden synthetisiert durch elektrochemische Dehydratisierung der entsprechenden Carbonsäuren. Sulfonsäureamide und Sulfonate wurden durch elektrochemische Multikomponentenreaktion von Arenen mit Aminen bzw. Alkoholen und SO_2 synthetisiert, sowie auch durch elektrochemische Dehydratisierung von Sulfonsäuren zu den entsprechenden Sulfonsäureanhydriden, welche nachfolgend mit Alkoholen oder Aminen umgesetzt wurden. Der Fortschritt im Gebiet der elektrochemischen Dehydratisierungsreaktionen wurde in einem Review-Artikel zusammenfassend erörtert. Um eine open-source Plattform für automatisierte Elektrosynthese zu entwerfen wurde das LABS-System (Laboratory Automation and Batch Scheduling) hervorgebracht, welches unter Verwendung einer Durchflusszelle mithilfe einer elektrochemischen Phenol-Kreuzkupplungsreaktion sowie der elektrochemischen Synthese von Sulfonaten als Modellreaktionen entwickelt wurde. Abschließend wurde ein vereinfachter Ansatz zur elektrochemischen allylischen Oxidation entwickelt, was eine wichtige Methode zur Funktionalisierung von Naturstoffen zu Hochwertprodukten darstellt.

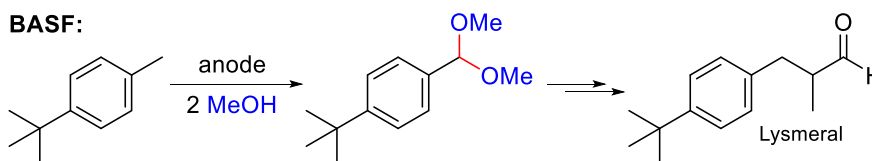
1 Introduction

Electrosynthesis is the utilization of electricity to carry out interesting and valuable chemical reactions via anodic oxidation and cathodic reduction.^[2] For several reasons, the field of electrosynthesis is currently experiencing a remarkable renaissance.^[3] Although electro-organic chemistry has a rich history dating back to the first half of the 19th century, it is only after the year 2000 that the field started to attract significant attention again due to the numerous advantages which electrosynthesis has to offer. It was Hermann Kolbe's publications from 1848 and 1849 on the electrolysis of carboxylic acids (Kolbe electrolysis) which laid the groundwork for organic electrochemistry and electrosynthesis.^[4] Characterization of reaction products is one of the core principles of synthetic organic chemistry, and while Michael Faraday laid the groundwork for electrolysis,^[5] it was Kolbe who was the first to characterize the reaction products. Nowadays, there are many large-scale electrochemical processes, such as the cathodic electrohydrodimerization of acrylonitrile to adiponitrile, known as the Baizer process, which is operated on a scale of 300 000 tons per year. Further examples are the electrosynthesis of Lysmeral by BASF or the Otsuka process (Figure 1).^[6]

Baizer process:



BASF:



Otsuka:

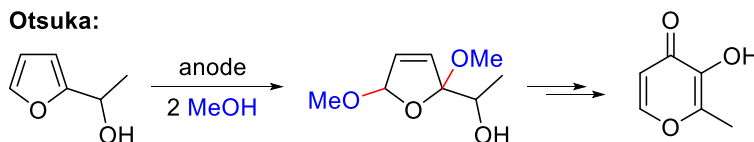


Figure 1. Examples for electrosynthetic transformations on technical scale.^[6]

1.1 Advantages of Electrosynthesis

Electrochemical reactions offer a broad palette of advantages.^[3,7–9] Electrolysis is usually characterized by comparably mild reaction conditions, while at the same time offering enormous thermodynamic driving force for chemical transformations.^[6] Most electrochemical reactions are carried out at room temperature and under ambient pressure, which means no excessive heating or cooling of the reaction setup is required. This way, thermal runaway reactions are prevented.^[10] Electrosynthesis is also cost and energy efficient compared with other oxidation or reduction methods because electricity is used as comparably inexpensive, universal, and traceless redox agent.^[11] Renewable energy sources such as wind and solar energy can be utilized, and fluctuations in power supply can be circumvented by electrosynthesis of highly value-added products.^[9] Electrosynthesis directly utilizes anodic oxidation and cathodic reduction reactions, which prevents the use of hazardous oxidizing or reducing agents, and avoids the generation of the hazardous reagent waste which would originate from those reagents. These aspects and the fact that electrolysis can be turned off to stop the reaction (e.g. by switching a button or by an automatic control system) adds immensely to the process safety of electro-organic transformations.^[12] Because electrosynthesis is characterized by single electron transfer (SET) reactions, electrochemical methods offers unique reactivity and selectivity,^[13] and this innovative nature of electro-organic reactions can help to minimize the number of required synthetic steps.^[14] Electrosynthesis also allows for the electro (re)regeneration of reagents, in which case only catalytic amounts of a reagent are required instead of stoichiometric quantities.^[15] Electro-organic reactions are typically known to be scalable,^[16] and the robust demonstration of scalability of an electrolysis is important since it opens the way for an application on technical scale.^[17] Furthermore, the use of electricity for synthesis offers new intellectual property (IP) space, which means many new developments in electrosynthesis have the potential to be submitted as a patent. Electrosynthesis is a very flexible technique, because it comes with additional experimental parameters,^[18] cell designs, and operational modes. It can be used in conjunction with many other technologies such as flow chemistry and laboratory automation.^[19]

It's very interesting to evaluate electrosynthesis in context of the principles of Atom Economy and Green Chemistry (Table 1). Atom Economy is a concept that was introduced in 1991 by Barry M. Trost,^[20] and it started a vivid global discussion about the overall efficiency of synthetic methods. Subsequently, the concept of Green Chemistry was formulated by John C. Warner and Paul T. Anastas,^[21] and it embodies 12 principles for a green and sustainable chemical reactions.^[22] It should be mentioned that many similar concepts have been developed subsequently, for example the Principles of Green Engineering,^[23] or the RESILIENCE Principle.^[24] While every (electro)chemical process must always be evaluated in its entirety in order to assess how "green" it is,^[25] remarkably many aspects of electrosynthesis inherently align with the principles of Green Chemistry.^[26] In several further cases, electrosynthesis can positively contribute to a principle of Green Chemistry, and the extent of the contribution depends on the details of the envisioned process. Most notably, there is not a single characteristic of electrosynthesis which inherently disagrees with any of those principles, meaning that the decision to carry out a chemical transformation via electrolysis does not inevitably render it "not green".

Table 1. Advantages of electrosynthesis in the context of Green Chemistry (personal opinion).^[26]

✓ denotes that an advantage of electrosynthesis inherently agrees with a principle of Green Chemistry. * denotes that an advantage of electrosynthesis can contribute to a principle of Green Chemistry, and the details of the contribution depend on the envisioned chemical transformation.	1. Waste Prevention	2. Atom Economy	3. Less Hazardous Synthesis	4. Design Safer Chemicals	5. Safer Solvents and Auxiliaries	6. Design for Energy Efficiency	7. Use Renewable Feedstocks	8. Minimize Use of Derivatives	9. Use Catalysis	10. Design for Degradation	11. Real-Time Process Analysis	12. Accident Prevention
Anodic oxidation and cathodic reduction prevents reagent waste	✓	✓	✓	*	*	✓		✓	✓	*		✓
Electrons as universal, comparably inexpensive, and traceless reagent	✓	✓	✓	*	✓	✓		✓	✓	*		*
Novel, unique, and innovative reactivity and selectivity	*	*	*	*	*	✓	✓	✓	✓	*	*	*
Mild reaction conditions (room temperature, ambient pressure)			✓	*	*	✓				*	*	✓
Prevention of thermal runaway reactions	*		✓	*	*	✓						✓
Direct use of renewable energy sources	✓					✓	✓				*	*
Simple to scale-up, ideally with increased yield and productivity	*					*					*	*
Number of synthesis steps can be decreased	✓	✓	✓		*	✓			✓			
Reagents can be (re)generated by electrolysis	✓	✓	✓		*	✓	*	*	✓			✓
Flexible conjunction with other technologies	*	*	*		*	*	*				*	
Many types of electrolysis available (paired, mediated..)	*	*	*		*	*						
The reaction can be stopped by interrupting electrolysis			✓									✓

The field of electrosynthesis is growing more than ever, as can be seen in the number of articles which are published every year that contain the word “electrosynthesis” in the title (Figure 2). Summarizing this analysis, it becomes evident that electrosynthesis is indeed a 21st century technique, and this evolving research field is striving towards greater utilization in academia and industry.^[6]

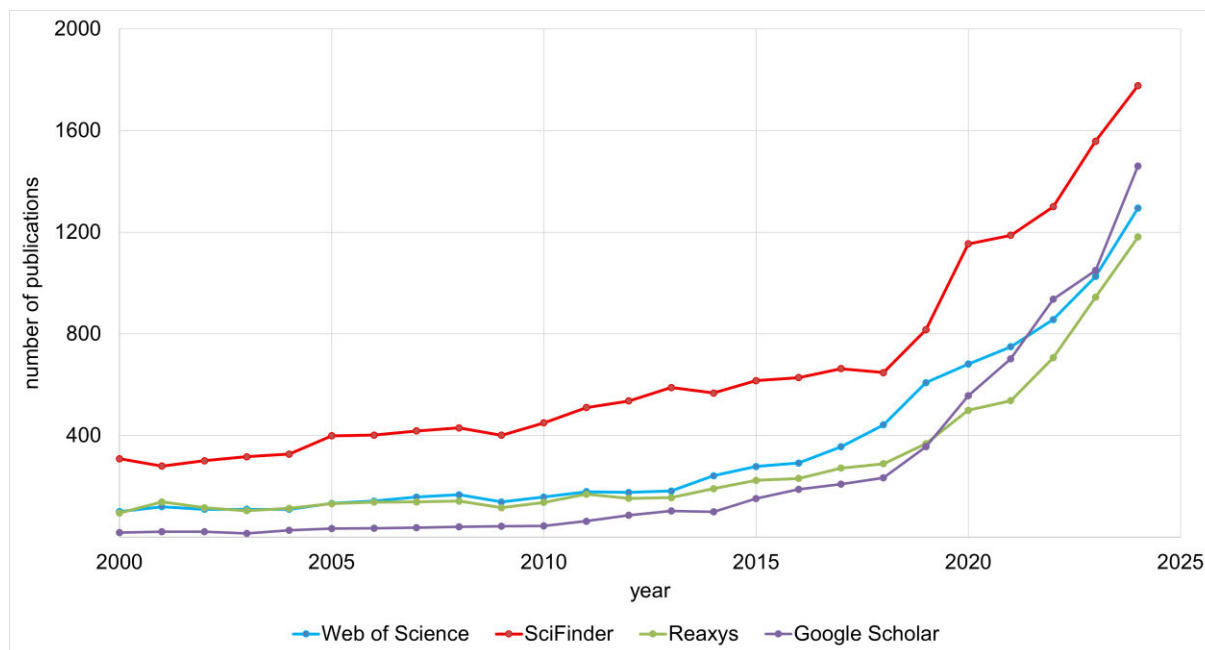


Figure 2. Number of articles that are published per year which contain the keyword "electrosynthesis" in their title, according to common databases.^[27]

Electrosynthesis is especially interesting in the shadow of the urgent need to solve the man-made climate crisis and increasing resource scarcity, which is likely the most important problem that mankind has to face.^[28] One of the biggest challenges of climate change is the fact that it's self-perpetuating after certain tipping points have been reached.^[29] The consequences of climate change are already affecting daily life and will continue to do so unless effective action is taken.^[30] However, the climate crisis should also be viewed as a great opportunity to make meaningful scientific impact. Electrosynthesis is a promising technology especially for replacing the fossil fuel based processes in chemical industry with renewable methods that strive towards a circular economy of resources.^[31] The direct utilization of renewable energy sources for electrosynthesis helps to decentralize the production of highly value-added products and it offers great cooperation with other renewable techniques.^[6]

1.2 Experimental Aspects of Electrosynthesis

Electrolysis always requires at least two electrodes: an anode and a cathode.^[32] The oxidation takes place at the anode, and reduction occurs at the cathode.^[33] For any electrolysis to function, both anodic oxidation and cathodic reduction reactions are required to operate simultaneously.^[32] The electrode at which the reaction of synthetic interest is taking place is termed working electrode (WE) and it can be either the anode or the cathode. The electrode opposite to the working electrode is termed counter electrode (CE). The electron transfer between electrode and substrate is heterogeneous,^[33] and if it occurs between electrode and the substrate directly, it is called direct electrolysis. In mediated electrolysis, the heterogeneous electron transfer occurs between electrode and a mediator, and the mediator undergoes subsequent homogeneous electron transfer with the substrate (Figure 3).^[34]

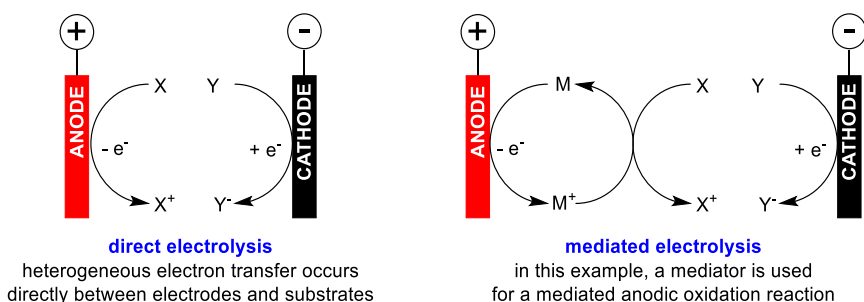


Figure 3. Direct electrolysis and mediated electrolysis.

Most transformations in electrosynthesis are based on either anodic oxidation or cathodic reduction, in which case the counter reaction is not of synthetic interest.^[3] However, there are also transformations which utilize both reactions, which is termed paired electrolysis.^[35] There are many different types of paired electrolysis (Figure 4). In a convergent paired electrolysis, two different substrates undergo anodic oxidation and cathodic reduction separately, and the two resulting intermediates react with each other to form one product. In a divergent paired electrolysis, one substrate reacts in parts at both the anode and the cathode to two different products which don't react with each other. In a parallel paired electrolysis, two substrates undergo anodic oxidation and cathodic reduction separately to two different products. In a domino paired electrolysis, a substrate undergoes anodic oxidation and cathodic reduction sequentially (in any order) to form a product, which fulfills the criteria for a domino reaction.^[36] In a linear paired electrolysis, a substrate can be transformed into a product by utilizing both anodic oxidation and cathodic reduction with the help of mediators.^[37]

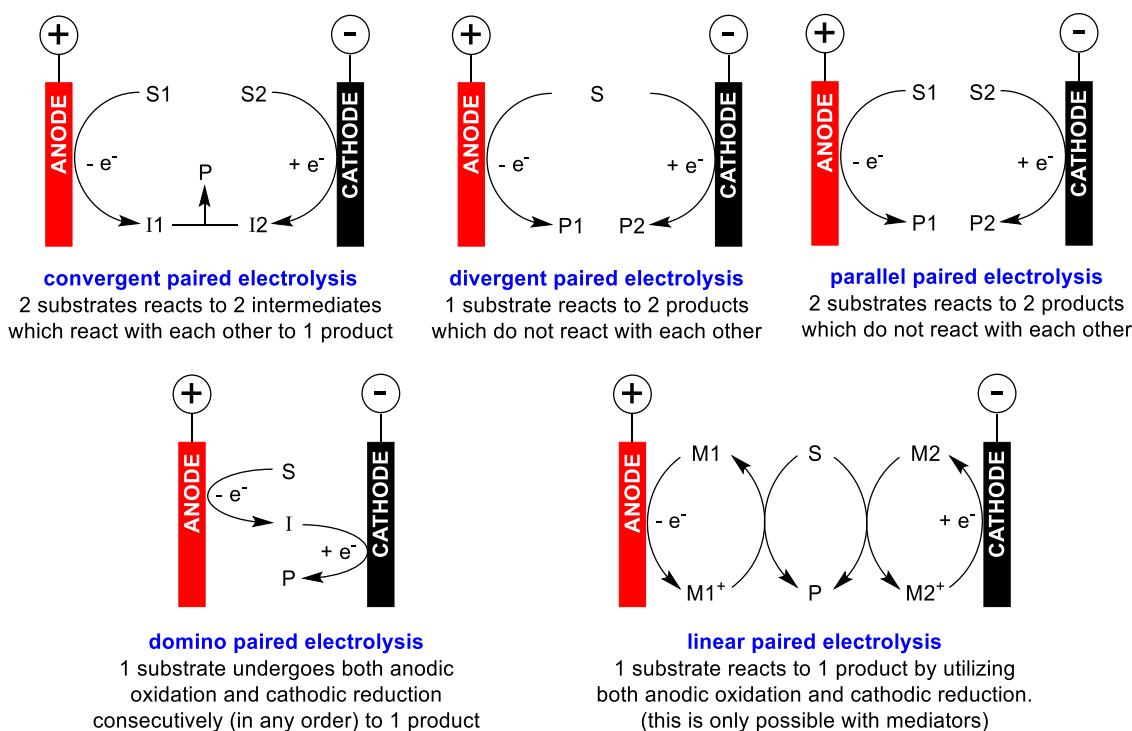


Figure 4. Overview of the different types of paired electrolysis.^[6,38,39]

1.2.1 Electrolysis Cells

Various types of electrolysis cells are available, which adds another aspect of flexibility to the field of electrosynthesis. In general, electrolysis can be carried out in a batch-type cell or in a flow cell (flow microreactor). In any case, electrolysis cells are inert reaction containers in which the anode and the cathode are placed. In between the electrodes there is an electrolyte, which consists of solvent(s), substrate(s), reagent(s), intermediate(s), and supporting electrolyte(s). In a flow cell, the electrodes are embedded in a frame with a typically small inter-electrode gap, and the flow electrolysis cell is part of a flow setup with pumps and other devices. Both batch-type and flow cells can be either divided or undivided electrolysis cells (Figure 5). A divided cell uses a separator to divide the electrolysis cell into an anodic compartment and a cathodic compartment. In this case, the portions of the electrolyte in the anodic and cathodic compartment of the cell are termed anolyte and catholyte, respectively. Such a separator prevents the anolyte from getting into contact with the cathode, and the anode from getting into contact with the catholyte, which helps to avoid unwanted electrochemical reactions.^[38] A separator prevents substrates and intermediates from passing through, but allows some species to pass to ensure the charge balance required for electrical current to flow. Various materials can be chosen as separator, for example a frit made of glass or Teflon, or a Nafion membrane.^[40]

Another special type of batch electrolysis cell is the quasi-divided cell, which is an undivided cell in which one of the electrodes has a very small surface compared with the other electrode, which can be achieved by using a small wire for example.^[38,41] Just like in a divided cell, a quasi-divided cell can help to minimize side reactions at a specific electrode.

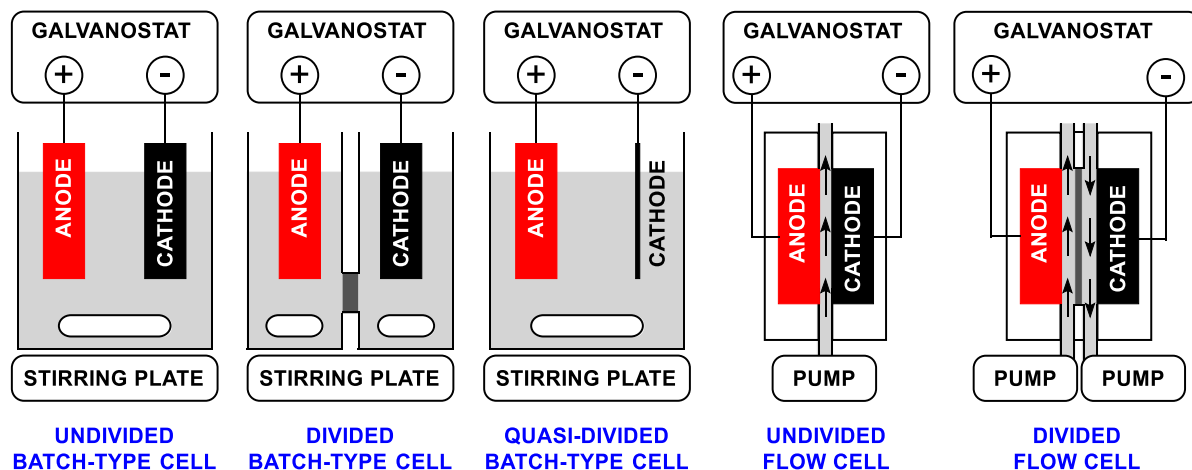


Figure 5. Illustration of an undivided batch-type cell, a divided batch-type cell, a quasi-divided batch-type cell, an undivided flow cell, and a divided flow cell. In divided cells, a separator divides the anodic compartment from the cathodic compartment. In the quasi-divided cell, the cathode was chosen to have a smaller surface area in this example, but it could be the anode as well instead.

Flow cells offer a continuous process compared with batch-type electrolysis, along with other advantages which will be discussed later in detail. However, optimization of reaction conditions can be faster in small batch-type screening cells because multiple reactions can be carried out simultaneously. Flow chemistry is especially useful when utilized in conjunction with laboratory automation.^[42]

In general, a simple cell design should always be preferred over a more complex setup because of the cost of cell manufacturing, reproducibility, and scalability. If possible, an undivided cell should be employed, because this results in lower terminal cell voltage due to the absence of a separator, which decreases cost of operation by minimizing power consumption.^[38] The simplest electrolysis cell is an undivided batch-type cell. Details of such a setup are depicted in Figure 6 and an assembled screening block containing 8 of these Teflon cells is depicted in Figure 7.

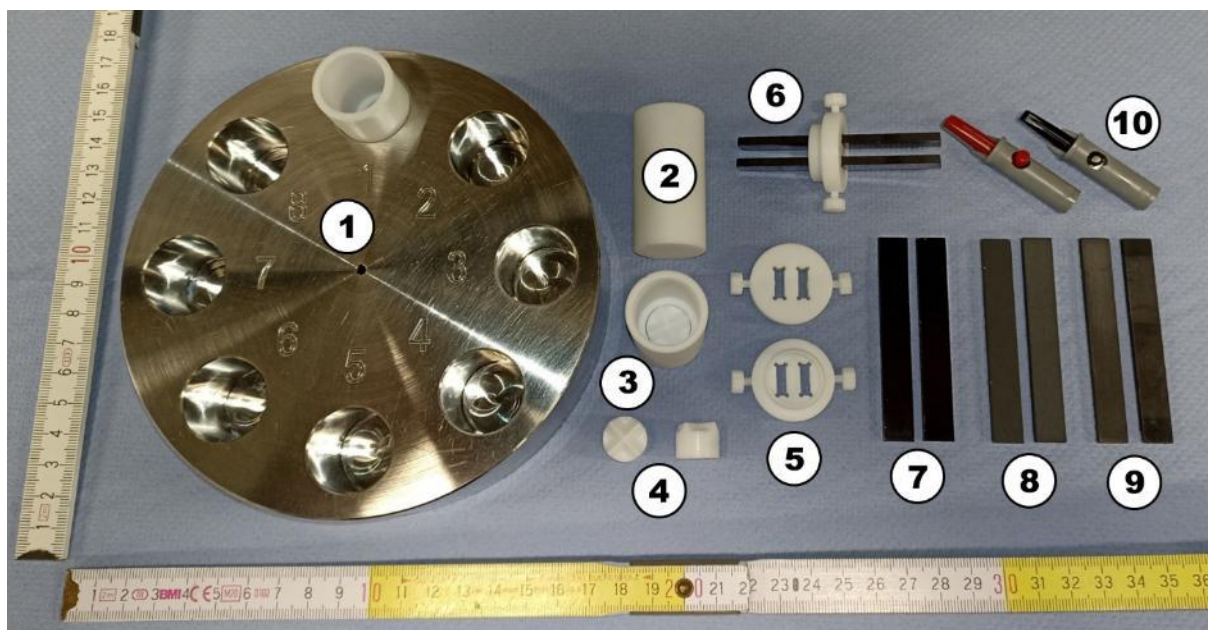


Figure 6. Example for an undivided electrolysis cell setup: stainless steel block with a Teflon cell placed in it (1), side view of a Teflon cell (2), top view of a Teflon cell with a stirring bar in it (3), top and side view of stirring bars (4), top and bottom view of a Teflon electrode holder (5), two glassy carbon electrodes in a Teflon electrode holder (6), glassy carbon electrodes (7), boron-doped diamond (BDD) electrodes (8), graphite electrodes (9), crocodile clips for contacting of the electrodes (10).^[43]

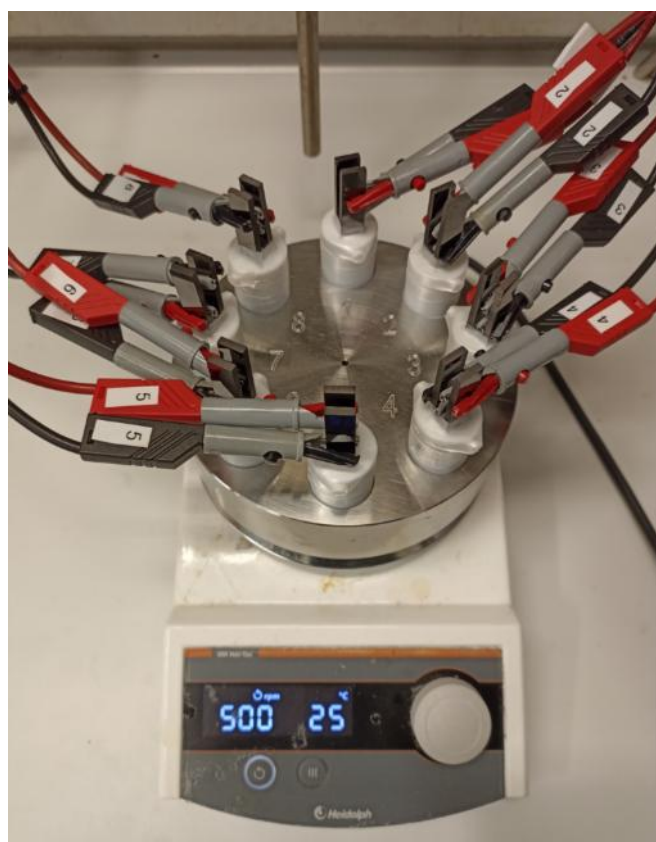


Figure 7. An assembled screening cell set on a stirring plate during electrolysis.^[43]

1.2.2 Electrode Materials

Electrolysis is inherently linked to heterogeneous electron transfer.^[33] Therefore, the electrode material used for anode and cathode is of utmost importance for electrosynthesis. There are several materials to choose from.^[44] Important characteristics of an electrode material is its (electro)chemical and mechanical stability, the electrochemical window of stability (usable voltage range) it offers, its shape and microstructure, its cost, its commercially available sizes, and its toxicity. The usable potential range depends on the reaction conditions and it's often limited by electrochemical decomposition of solvents and supporting electrolytes under strongly oxidizing or reducing potentials.^[33] Several materials must be tested to find the right electrode material for the envisioned electrosynthetic transformation and it is not trivial to find the right electrode material purely based on theoretical considerations.^[45] Especially, cathodic corrosion must be prevented when using metal-based electrodes.^[46] Metal-based electrode materials such as stainless steel, nickel, or lead are commonly employed.^[44] Carbon-based electrode materials are graphite, glassy carbon, and reticulated vitreous carbon (RVC).^[45] Toxic electrode materials based on lead, tin, or mercury should be avoided if possible. It should be noted that sacrificial anodes such as magnesium or zinc are not green,^[44] because the production of those metal electrodes is too expensive and associated with a high ecological footprint.^[47] Expensive electrode materials such as gold or platinum are also disadvantageous.^[48] Besides metals or other conducting materials, semiconductor materials can also be employed as electrodes.^[49] Boron-doped diamond (BDD) is a commonly utilized non-toxic semiconductor electrode material.^[50] It's commercially available in various sizes (Figure 8).



Figure 8. BDD electrodes (top: 2 cm x 6 cm x 0.3 cm, bottom: 1 cm x 7 cm x 0.3 cm).

BDD electrodes offer a wide electrochemical window of stability in acetonitrile or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and it has a beneficially high overpotential for hydrogen evolution reaction (HER) and oxygen evolution reaction (OER).^[51] BDD is carbon-based, because it's produced by chemical vapor deposition (CVD) using methane and diborane on silicon as carrier material.^[52] While diamond itself is an insulator, doping it with boron results in a p-doped semiconductor with a narrow band gap of 5.5 eV.^[52,53] BDD is remarkably stable against corrosion under highly acidic or oxidative reaction conditions.^[54] Another advantage of BDD is that it can be fully electrochemically cleaned by electrolysis of dilute sulfuric acid.^[50] This is important for its application in electrosynthesis, because it lowers the effort that is required to maintain a clean electrode surface.^[55] BDD allows for the generation and stabilization of highly reactive intermediates such as oxyl radicals, or the generation of ozone in water for wastewater treatment.^[56] The fact that electrolysis can be carried out using metal-free electrode materials such as boron-doped diamond (BDD) opens the possibility for an overall metal-free electrochemical synthesis. This is very important in medicinal chemistry, which is often very reluctant to traces of metals which could originate from the production process.^[57,58] While BDD is very (electro)chemically stable, its disadvantages are the comparably high cost and the fragility of the carrier material, which is often silicon.^[52]

1.2.3 Operational Modes

Electrolysis can be carried out in two fundamentally different modes of operation: galvanostatic electrolysis or potentiostatic electrolysis.^[39] In a galvanostatic electrolysis, the electrical current is kept constant over time by using a galvanostat, and no electrode potential is measured or in control. This is also called constant current electrolysis (CCE).^[33] In contrast, in a potentiostatic electrolysis the potential of the working electrode (WE) is controlled with the help of an additional reference electrode (RE) by adjusting the electrical current over time with a potentiostat. This is termed constant potential electrolysis (CPE).^[33] Electrosynthesis should almost always be carried out as galvanostatic electrolysis and not as potentiostatic electrolysis for reasons of scalability, reproducibility, productivity, and overall simplicity.^[38] Direct current (DC) should be used instead of alternating current (AC) in almost all cases, because alternating current can lead to fast electrode degradation.^[59]

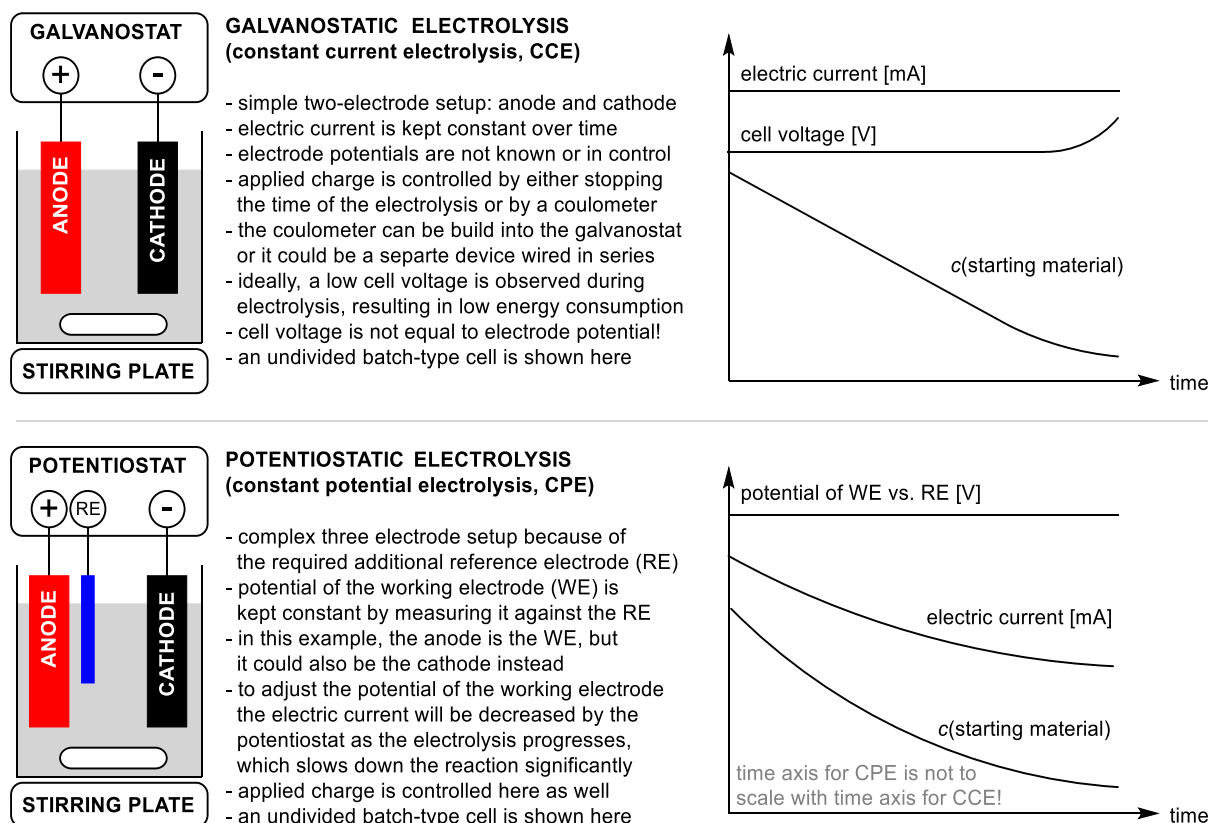


Figure 9. Comparison of galvanostatic electrolysis (top) with potentiostatic electrolysis (bottom).^[39]

A galvanostatic electrolysis requires only two electrodes. In contrast, a potentiostatic electrolysis always requires three electrodes, because a reference electrode is necessary in this mode of operation.^[32] The reproducibility of a potentiostatic electrolysis depends critically on the arrangement of electrodes and the overall cell design, which also makes the scale-up of potentiostatic electrolysis difficult.^[38] It is often mentioned that potentiostatic electrolysis can offer better selectivity over galvanostatic electrolysis. However, this is often a question of reaction optimization, and good yield and selectivity can be achieved with galvanostatic electrolysis as well in many cases. Besides yield and selectivity, the time required for electrolysis is also important, because this affects the productivity (amount of product per electrolysis time). Here originates another major disadvantage of potentiostatic electrolysis, because the electrical current will be decreased by the potentiostat over time to adjust the WE potential (Figure 9), decreasing the reaction rate.^[39] In general, one should aim for a galvanostatic electrolysis which employs high current densities, because this is associated with a high electrical current, which results in a fast electrolysis. The amount of applied charge should be minimized as well, as this also decreases the electrolysis time, minimizes the cost of required electrical energy, and increases the productivity.

1.2.4 Amount of Applied Charge and Current Density

The amount of applied charge can be calculated using Faraday's law.^[39] The electrical charge in units of coulomb Q_C is the integral of the electrical current I over time t . In a galvanostatic electrolysis, the electrical current is constant over time, which means $Q_C = I \cdot t$. While the electrical current is set at the power supply in units of ampere, it is advantageous to specify a current density j which divides the electrical current I by the anode or cathode area A , so that $j = I / A$. The active electrode surface can be approximated by the size of the electrode that is facing the counter electrode. The higher the active electrode surface is, the more electrical current can be applied at the same current density, which allows for a faster electrolysis.^[60] The amount of applied charge is expressed as multiples of the Faraday constant $F = 96485 \text{ C / mol}$. For example, if in an electrosynthesis $Q_F = 2.5 F$ are applied, this means that $2.5 \cdot 96485 \text{ C / mol}$ are utilized. The advantage of this is that this is independent of the amount of starting material that is employed, meaning that this expression of the amount of applied charge is independent of the scale of the electrolysis. To calculate the amount of applied charge in coulomb, the value must be multiplied with the amount of starting material. For example, $2.5 F$ and 0.5 mmol give $Q_C = 0.5 \cdot 10^{-3} \text{ mol} \cdot 2.5 \cdot 96485 \text{ C / mol} = 120.6 \text{ C}$. This amount of applied charge is then set in the coulometer of the galvanostat. In a galvanostatic electrolysis, the electrolysis time can be calculated easily by Faraday's law: $t = Q_C / I$. Considering the current density and the amount of applied charge in multiples of Faraday's constant, this gives $t = (n_{\text{substrate}} \cdot Q_F \cdot F) / (j \cdot A_{\text{electrode}})$.



Figure 10. A commonly used power supply for galvanostatic electrolysis.

If the upper terminal voltage limit of the power supply is reached during the electrolysis, it can no longer be considered galvanostatic, because the current density has then fallen under the desired value or even diminished completely.^[38] A galvanostatic electrolysis should be planned so that only the amount of charge that is really required for the electrochemical transformation is applied.^[39]

1.2.5 Solvents

Solvents can be classified according to their acidity, nucleophilicity, and polarity.^[61] Important physical properties of a solvent are its boiling point, relative permittivity (dielectric constant), viscosity, and vapor pressure, among others. In addition, the electrochemical window of stability (usable potential range) of a solvent is relevant for its use in electrosynthesis. It depends on the reaction conditions and the utilized electrode materials.^[33] An ideal solvent should fully dissolve all starting materials, supporting electrolytes, and reagents. It should stabilize intermediates and not participate in electrochemical reactions, and it should be easy to separate from the crude reaction mixture by distillation to make downstream processing inexpensive. Commonly, mixtures of solvents are utilized to adjust the properties of the reaction medium. The lower the dielectric constant of a solvent is, the more supporting electrolyte is required to ensure sufficient electric conductivity.^[62] However, the set of available supporting electrolytes is often limited by their solubility in the employed solvent. Commonly utilized solvents for electrosynthesis are listed in Table 2.

Table 2. Physical properties of solvents that are commonly employed in electrosynthesis.^[61–63]

Solvent	Dielectric Constant	Boiling Point / °C
acetonitrile (MeCN)	37	82
dichloromethane (DCM)	9	40
dimethyl carbonate (DMC)	3	90
<i>N,N</i> -dimethylformamide (DMF)	37	153
dimethyl sulfoxide (DMSO)	47	189
ethanol (EtOH)	25	78
1,1,1,3,3,3-hexafluoroisopropanol (HFIP)	17	58
methanol (MeOH)	33	65
nitromethane	37	101
propylene carbonate (PC)	69	241
pyridine	12	115
tetrahydrofuran (THF)	7	66
water	78	100

Water is a readily available solvent, but a major disadvantage is the comparably low solubility of many apolar organic compounds in it. Furthermore, hydrogen evolution reaction (HER) at the cathode and oxygen evolution reaction (OER) at the anode limit the available electrochemical window of stability when using water as solvent for electrosynthesis.^[61] Alcohols like methanol (MeOH) and ethanol (EtOH) can be utilized, as long as their nucleophilicity does not cause side reactions.

A commonly utilized solvent for electrosynthesis is acetonitrile (MeCN). This polar aprotic solvent dissolves many organic and inorganic compounds and it offers advantageous electrochemical stability.^[61] 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) is a polar protic solvent that is also commonly used in electrosynthesis due to its (electro)chemical stability,^[64] its strong hydrogen bond donor properties,^[65] and its unique formation of domains.^[66] MeCN and HFIP are simple to recover by distillation.

Dimethyl sulfoxide (DMSO) is a readily available solvent because it's a byproduct of the kraft process.^[67] While DMSO is an excellent solvent for many organic and inorganic substances, it's usually not the first solvent of choice because it is easily cathodically reduced to dimethyl sulfide, which has an unpleasant smell. It is also utilized in medicinal chemistry to enhance transport of substances into the bloodstream, meaning that reagents which are dissolved in DMSO can resemble a serious hazard.^[62] While dichloromethane (DCM) offers good solubility for many organic compounds, its low dielectric constant is a major disadvantage, and only few supporting electrolytes can be dissolved in it.^[62] The same also applies to ethers such as tetrahydrofuran (THF), which in addition can also form explosive peroxides. Nitromethane is one of the few solvents which is very suitable for anodic oxidation reactions.^[61] *N,N*-Dimethylformamide (DMF) is a polar aprotic solvent which has a usable potential range comparable to MeCN for cathodic reductions, but it is inferior for oxidations.^[62] Pyridine is a basic solvent which is very resistant towards anodic oxidation, and it shows good solubility for many organic and inorganic compounds. In recent years, propylene carbonate (PC) and dimethyl carbonate (DMC) have been increasingly discussed as green solvents for electrosynthesis.^[63] However, one disadvantage of PC is its high boiling point. This can be an advantage though in case the product can be distilled off from the crude reaction solution.

Lastly, the toxicity and carcinogenic potential of a solvent is another important aspect to consider. For example, hexamethylphosphoramide (HMPA) should not be used in electrosynthesis or conventional synthesis due to its extreme carcinogenicity.^[68] It should be noted that DMF also shows considerable carcinogenicity. Carbon tetrachloride should not be utilized due to its very strong hepatotoxicity.^[69] While MeCN has comparably low toxicity, other nitriles like isobutyronitrile and propionitrile can release hydrogen cyanide (HCN) upon heating or when being metabolized.^[62]

1.2.6 Supporting Electrolytes

Supporting electrolytes fulfill several roles in electrosynthesis. They increase the electric conductivity of the electrolyte, influence the structure and behavior of the electric double-layer on the electrode surface, minimize the contribution of migration current to mass transfer, and they interact with the electrochemically generated intermediates and products.^[33,61] A supporting electrolyte must be chosen based on its compatibility with the electrochemical reaction that is carried out and its solubility in the solvent that is utilized.^[33] Although supporting electrolytes are usually chosen to be electrochemically inert, they can fulfill a dual-role as enabler of conductivity and reagent or mediator.^[70] Anodic oxidation or cathodic reduction reactions of supporting electrolytes often also determine the potential range that is available for electrosynthesis.^[62] When selecting an appropriate supporting electrolyte, several combinations of cations and anions can be chosen from. Common cations are tetraalkylammonium ions and alkali metal ions. Common anions are tetrafluoroborate, hexafluorophosphate, trifluoromethanesulfonate, nitrate, and halides.^[62]

For some electro-organic reactions, the electric conductivity of the electrolyte solution is already sufficient enough so that no supporting electrolyte needs to be employed at all.^[71] This simplifies downstream processing, and if the components of the electrolyte are all volatile, they can even be recovered by distillation. In the interest of process safety, electrosynthesis should aim to avoid potentially explosive supporting electrolytes such as perchlorates.^[61] Ideally, only small amounts of an inexpensive and inert supporting electrolyte should be employed,^[43] because this lowers cost, improves process safety, and simplifies downstream processing. Perchlorate supporting electrolytes can in some cases be replaced with tetrafluoroborates, hexafluorophosphates, or trifluoromethanesulfonates.^[43,61]

Certain other types of supporting electrolytes should be avoided as well if possible.^[61] For example, tetramethylammonium compounds should not be utilized because of their high toxicity.^[72] Ionic liquids should be employed judiciously because of their comparably high cost. In addition, these exhibit relatively high viscosities, which is inferior for mass transfer. While tetraalkylammonium salts are versatile supporting electrolytes with good solubility in a variety of solvents, they also show phase-transfer catalyst behavior, which can complicate downstream processing. Cesium supporting electrolytes should be avoided due to their potential cardiotoxicity.^[73]

1.2.7 Terminal Cell Voltage and Electrode Potentials

The meaning of cell voltage in electrosynthesis is often completely misunderstood.^[38] Controlling the terminal cell voltage in a galvanostatic electrolysis does not mean that the electrode potential is known, or even in control.^[62] The terminal cell voltage which is measured at the galvanostat is composed of several contributions which are not known in parts, and the composition changes during electrolysis (Figure 11).^[38] Especially the individual components of overpotential are not trivial to determine.^[33]

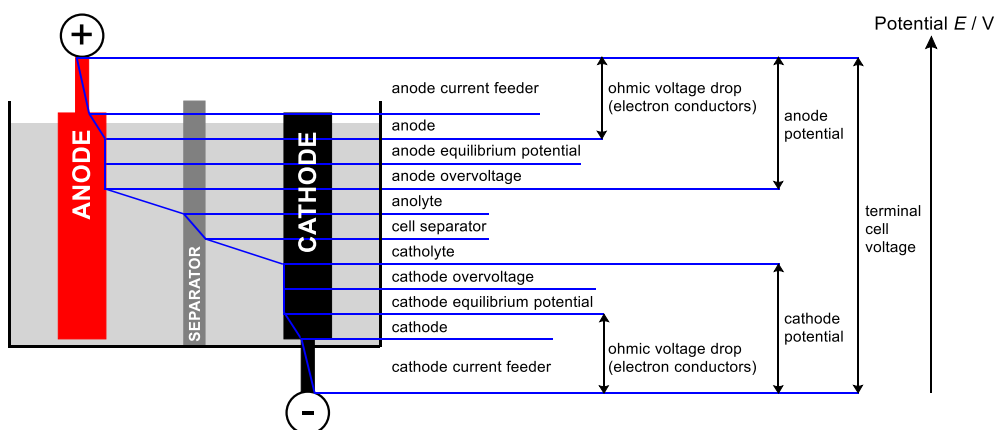


Figure 11. Composition of the voltage in a divided electrolysis cell along the current path.^[39,62]

If control of the working electrode's potential is desired, a potentiostatic electrolysis with a three-electrode setup using a reference electrode is inevitably required.^[62] Also, carrying out electrolysis at constant cell voltage is strongly discouraged because this does not allow for control of either electrode potentials or electrical current, which also complicates measuring the amount of applied charge.^[38] Cell voltage should mainly be viewed as a measure of power consumption of the electrolysis. If the cell voltage reaches the upper terminal voltage limit of the power supply, the electrolysis is no longer galvanostatic, and the power consumption is too high. If the cell voltage is too low, a short circuit is likely present. One of the many advantages of flow chemistry is that it usually employs a very small inter-electrode gap (for example 0.25 mm),^[71] which results in lower cell voltages, minimizing the power consumption required for operation. Furthermore, the cell voltage as a function of electrolysis time can be recorded with modern power supplies, which can be used to investigate the long-time operability of the process. It should be noted that carrying out electrolysis just by attaching a battery to the electrolysis setup is also strongly discouraged, because in such a case, neither the electrical current nor the applied charge is in control. Such an electrolysis is also not potentiostatic at all.^[38]

1.2.8 Electrode-Electrolyte Interface and Mass Transfer

There are two different classes of processes which occur at electrodes when a potential is applied: faradaic and non-faradaic processes.^[33] Faradaic processes are based on the heterogeneous electron transfer which occurs at the electrode-electrolyte interface,^[74] which is described by Faraday's law. This electron transfer results in electrosynthetic transformation. However, it can also be that no electron transfer occurs at electrodes in a certain potential range that is applied, because electron transfer is thermodynamically or kinetically unfavorable.^[33] Non-faradaic processes do not involve electron transfer through the electrode-electrolyte interface, but they can still lead to a transient electrical current because the electrode surface or electrolyte composition changes.^[33] One important phenomena is the build-up of the electric double-layer on the electrode surface, which is a process that involves rearrangement of charged species to compensate for the charge imbalance (Figure 12). This process resembles a capacitor and the associated electrical current is called capacitive current.^[33] The electric double-layer, whose thickness is typically between 1–10 nm,^[32] is of utmost importance for electrosynthesis, because this is the region where the heterogeneous electron transfer occurs. The portion of the electrolyte in between the electrodes is called the bulk solution and it's homogeneous compared with the double-layer.^[62] In the electric double-layer, very steep potential gradients are observed, which can be in orders of 10^6 V / cm or higher,^[32] while the potential gradient in the bulk solution is comparably small.^[39] The electric double-layer is best described by the Stern model, which combines the model of a rigid double-layer (Helmholtz model) with an adjacent diffuse regime (Gouy-Chapman model).^[33,39,74,75]

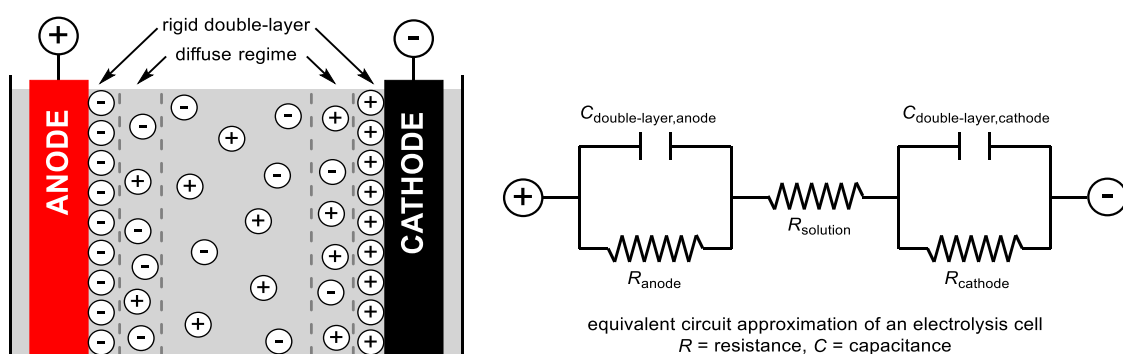


Figure 12. Electric double-layer on anode and cathode and the simplified equivalent circuit.^[33,39,74,75]

Two edge cases of electrode behavior result from this.^[33] The ideally polarizable electrode shows exclusively non-faradaic behavior, meaning that applying a potential does not result in any electron transfer through the electrode-electrolyte interface. The ideally non-polarizable electrode shows faradaic behavior, meaning that applying a potential immediately results in an electrical current flowing.^[74] Real electrodes always shows both behaviors partially and applying a potential leads to the build-up of an electric double-layer and an electrical current flowing through the electrolysis cell.^[74] The transport of species through the electrolyte solution is termed mass transfer,^[33] and it is especially important for the transport of species from the bulk solution to the electrode surface and back (Figure 13). There are three phenomena which contribute to mass transfer: diffusion, convection, and migration.^[39] Diffusion is the ever-present movement of species due to the thermal energy.^[76] Convection is movement of segments of the electrolyte through the electrolysis cell due to stirring of the solution. Migration is the movement of charged species in the electric field between the electrodes.^[39]

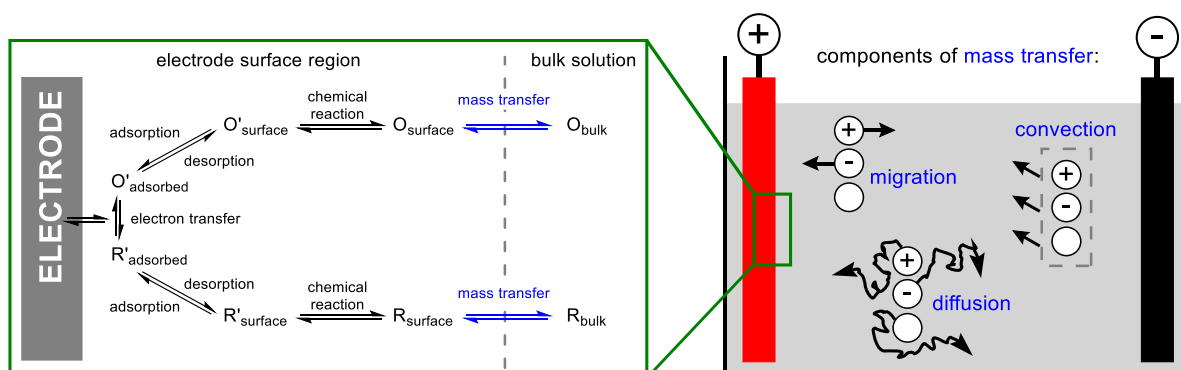


Figure 13. Pathway of an electrode reaction (left),^[33] and the components of mass transfer (right).^[39]

Electrical current is a direct measure of the reaction rate at the working electrode.^[33] The energy of the electrons in the working electrode can be approximated by the Fermi level.^[49] Electron transfer occurs depending on the Fermi level of the electrode surface with respect to the HOMO and LUMO energies of the substrate (Figure 14).^[32] In general, electron transfer is characterized by an activation energy barrier that must be overcome.^[32] If the Fermi level of the electrode is higher than the LUMO level of the molecule, no electron transfer from molecule to electrode occurs. With increasingly positive potential at the working electrode, the Fermi level changes so that electron transfer from substrate to the electrode is feasible.^[32] The required overpotential is the result for the activation barrier.^[39]

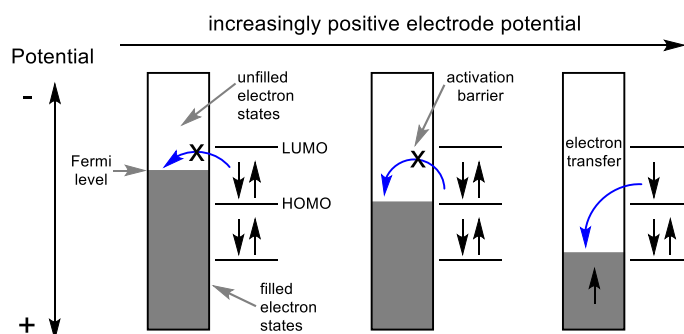


Figure 14. Fermi level of a working electrode upon increasingly positive potential compared with the LUMO and HOMO energy of a substrate.^[32]

1.2.9 Scale-up and Downstream Processing

Demonstrating the robust scalability of an electrosynthetic transformation is important because this opens the way for an application on technical scale, and therefore should be part of every publication in the field of electrosynthesis.^[17] When doing so, it is very important to utilize inexpensive purification methods, for example recrystallization or distillation.^[77] On technical scale, column chromatography is almost never employed because of the high cost. In addition, technical processes will always aim for recycling of starting materials, solvents, and reagents.^[78] If any component is being disposed of instead of being recycled, both the disposal of the old material and the purchase of the new material will add to the cost of production. This means that recovery of those components, for example by distillation, is a very important aspect of scale-up reactions in any synthetic scientific publication, no matter if it's an electrosynthetic method or not. Demonstrating that chromatography can be avoided in scale-up is a very important selling point of any new (electro)synthetic transformation.^[43]



Figure 15. Recrystallization and distillation are simple and inexpensive purification techniques. Left: recrystallization of lanosterol from MeCN. Right: MeCN / HFIP / SO₂ in a cooling trap.^[71]

1.2.10 Flow Chemistry

Flow chemistry utilizes tubes, channels, and microreactors to carry out chemical reactions in a continuous process instead of a batch setup.^[42,79] Flow chemistry offers numerous advantages over conventional batch-type reactions,^[80] because it allows for unique ways of controlling both conventional and electrochemical reaction parameters.^[81] A flow electrolysis cell (Figure 16) is characterized by a large ratio of electrode surface to cell volume, which allows for improved mixing and heat-transfer.^[82] This is beneficial for mass transfer when carrying out electrosynthesis in flow. Flow chemistry allows for precise control of stoichiometry and reaction rate by controlling the concentration of reagents, flow rate, and residence time in the flow cell.^[83] The narrow inter-electrode-gap in flow cells allows for small terminal cell voltages during operation, which lowers the cost by minimizing the required electrical power.^[84] Flow setups can help to improve the selectivity and reproducibility of electrosynthetic transformations.^[85] In some cases, the advantages of electrosynthesis in flow can outweigh the performance of a batch-type electrolysis to an extent where the reaction can only be carried out in flow.^[86] Passing the electrolyte through a flow electrolysis cell once is termed single-pass flow, passing it multiple times is called cyclic flow.^[87,88]

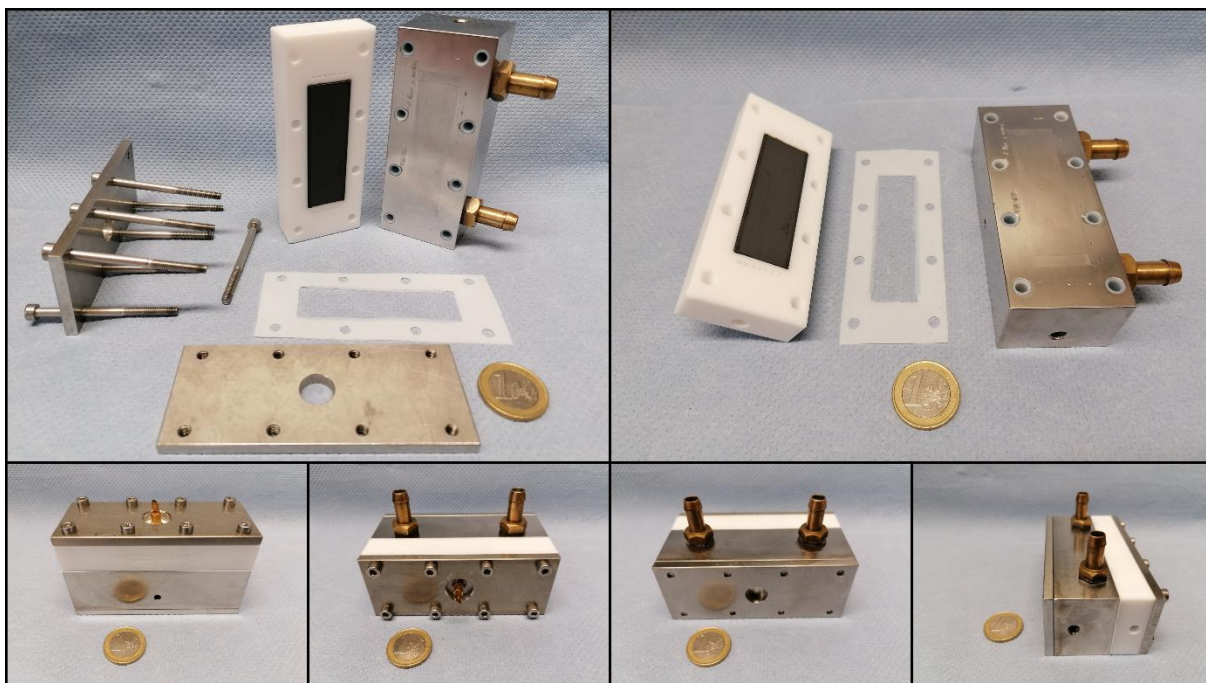


Figure 16. Undivided electrolysis flow cell with a BDD anode in a Teflon frame and a stainless steel cathode block with attachments for a temperature control unit.^[71] The depicted Teflon spacer has a thickness of 0.25 mm, resulting in a narrow inter-electrode gap.

In single-pass flow, the amount of applied charge, current density, and flow speed is inherently linked. In general, the flow speed is the volume of the reaction solution V_{solution} divided by the electrolysis time $t_{\text{electrolysis}}$. The electrolysis time can be calculated by Faraday's law:

$$v_{\text{flow}} = \frac{V_{\text{solution}}}{t_{\text{electrolysis}}} = \frac{V_{\text{solution}}}{\left(\frac{Q_{\text{applied}}}{I}\right)}$$

The flow speed decreases with higher amounts of applied charge, because the residence time in the flow cell is then required to be longer, and the flow speed also decreases with lower current densities. One of the challenges when attempting electrosynthesis using single-pass flow can be low conversion, in which case cyclic flow is required.^[89] In cyclic flow, it is common to utilize the flow speed which would be required for single pass flow multiplied with a constant, termed flow multiplier.^[87,88] The flow multiplier does not affect the applied charge or the current density, but it affects the residence time in the flow cell. This can prevent the formation of layers on the electrodes or improve the selectivity of the reaction. Flow chemistry is becoming increasingly important in various fields of chemistry,^[90] including electrosynthesis.^[91]

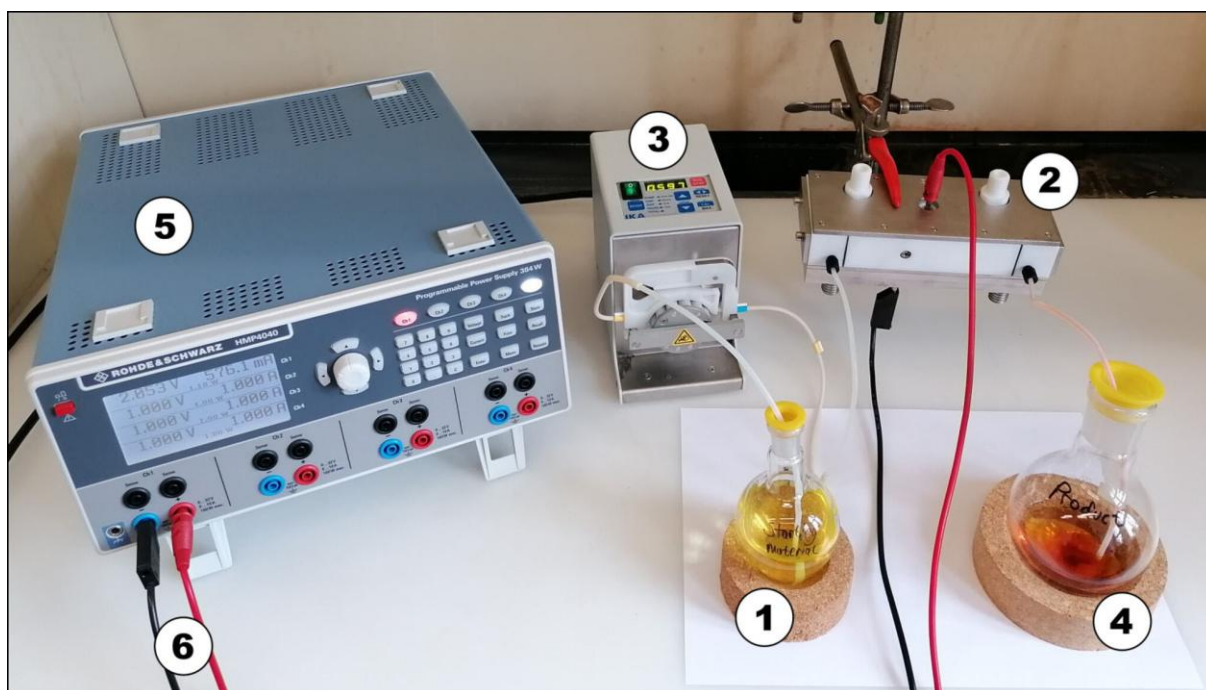


Figure 17. An experimental setup for electrosynthesis in single-pass flow.^[71] The reaction solution of the starting material (1) is pumped through the flow electrolysis cell (2) with the help of a peristaltic pump (3) into a round bottom flask (4). The power supply (5) is connected to the cell with wires (6).

1.2.11 Reaction Optimization in Electrosynthesis

The simplest setup for electrosynthesis is an undivided batch-type cell using a galvanostatic electrolysis with direct current.^[38] An overview of the (electro)chemical reaction parameters for such a type of electrolysis are depicted in Figure 18. In this section, the optimization of electrosynthetic reactions will be discussed. These aspects of optimization are generalized and independent of the utilized optimization technique.

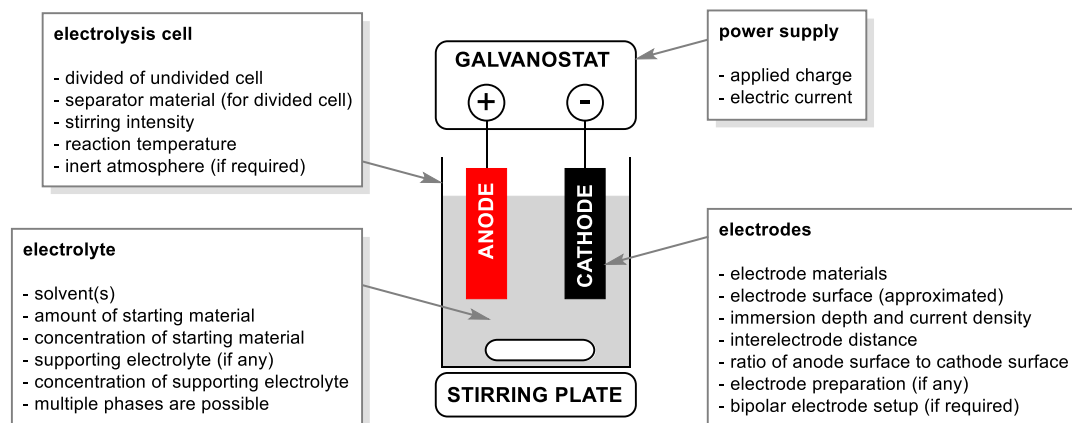


Figure 18. Parameters of a galvanostatic electrolysis in an undivided batch-type cell.

Electrolysis Cell Setup: In general, the experimental setup should be as simple as possible and only as complex as needed. If the electrochemical transformation allows for it, an undivided cell (no separator) should be preferred over a divided cell. This helps to lower the cell voltage, which decreases the required electric power to operate. The electrolysis should be carried out at room temperature, if possible, because this avoids the need for extensive heating or cooling of the setup. An inert gas atmosphere should be avoided, if possible, as this keeps the setup simple. A proper stirring setup is required to ensure sufficient mass transfer.^[92] The amount of starting material should be chosen appropriately to allow for fast initial small-scale screening experiments.

Power Supply: In general, the amount of applied charge should be kept as minimal as possible, and it should be chosen to approximately match the increase of cell voltage towards the end of the electrolysis. The less amount of charge is applied, the faster the electrolysis is completed, which improves productivity. A larger electrode surface area (which also depends on immersion depth) permits a higher electric current for a given current density to be used, which allows for a faster electrolysis. Ideally, a galvanostat is used as power supply which has a built-in coulometer that stops the electrolysis after the required amount of charge has been fully applied.

Electrolyte: The electrolyte is the medium between the electrodes, and it is composed of starting material(s), reagent(s), supporting electrolyte(s) and solvent(s).^[70] Ideally, a nontoxic, inexpensive solvent that is easy to separate from the crude reaction mixture by distillation is employed, which should fully dissolve all components. A setup with multiple phases is also possible. The electrolyte must have an appropriate electrochemical window of stability under the reaction conditions.^[61] The concentration of starting material should be as high as possible to achieve a high productivity with respect to the amount of solvent that is used. The concentration of supporting electrolyte should be kept as small as possible, because this decreases the cost and can also simplify the downstream processing. However, if the cell voltage is too high, the choice of supporting electrolyte and its concentration must be revised to lower the resistance of the solution. In some cases, the electric conductivity is sufficiently high enough to leave away the supporting electrolyte entirely.^[70] Very long electrolysis times caused by low electrical currents in combination with large amounts of required charge should be avoided because of low productivity, and this can also lead to solvent evaporation from the electrolysis cell, which affects the concentration of starting materials, supporting electrolytes, and reagents.^[33] Solvent evaporation also decreases coverage of the electrodes, which alters current densities. Of course, the equivalents of reagents with respect to the starting material should be minimized as well to decrease cost.

Electrodes: Electrodes should be immersed as deep into the electrolyte as possible because this allows for a larger active electrode surface, allowing for a higher electrical current to be applied for a given current density.^[44] Narrow inter-electrode gaps help to decrease the cell voltage, which results in lower consumption of electric power. Electrodes must be as parallel to each other as possible to achieve a uniform electric field between them since unparallel electrodes result in a gradient.^[93] Electrochemically stable and reusable electrode materials such as boron-doped diamond (BDD), stainless steel, graphite, or glassy carbon should be utilized.^[44] Sacrificial electrode materials such as magnesium or zinc are not green, because the production of these metals is very energy and resource intensive. Toxic metals like lead, nickel, tin, or mercury should be avoided as electrode materials. Metal-free electrode materials like BDD are beneficial especially for medicinal chemistry, because it is often very reluctant to the use of metals in the synthesis of active pharmaceutical ingredients (APIs).^[57]

1.2.12 Design of Experiments (DoE)

Design of Experiments (DoE) is the analysis and optimization of processes based on statistics using an experiment plan.^[94] DoE is utilized in various fields of engineering,^[95] and it can also be used to systematically analyze and optimize electrochemical reactions.^[96] A contrary approach for optimization is called one variable at a time (OVAT, also called OFAT for one factor at a time), which does not involve an experiment plan, and it does not allow to analyze interactions between parameters.^[97] Design of Experiments can only be discussed briefly here. A good DoE plan requires good preliminary experiments and thorough planning. For a fully comprehensive discussion, various books have been published.^[94,98,99] These books contain extensive general guidelines on how to approach DoE.

DoE allows for an optimal utilization of the experimental effort by aiming to utilize the least number of experiments to acquire meaningful experimental results.^[100] DoE is an iterative process (Figure 19),^[94] which means that the result of a DoE plan can be used in the next iteration. It is therefore the operator's choice to decide when to stop with further experimentation, which depends on whether the experimental results are satisfactory.^[101] Two categories of parameters which can be included in a DoE plan exist: continuous parameters and categorical parameters.^[99] Continuous parameters can be interpolated, while categorical parameters cannot. Organic synthesis already has a large parameters space, which is extended by electrochemical parameters in electrosynthesis. Categorical electrochemical parameters are for example solvent, supporting electrolyte, and electrode material. Continuous electrochemical parameters are current density, concentration of starting material or supporting electrolyte, and the amount of applied charge. In a DoE plan, meaningful parameters are included in a statistical model which is used for regression based on the experimental results. For optimal statistical treatment, the experiments are carried out in randomized order.^[99]

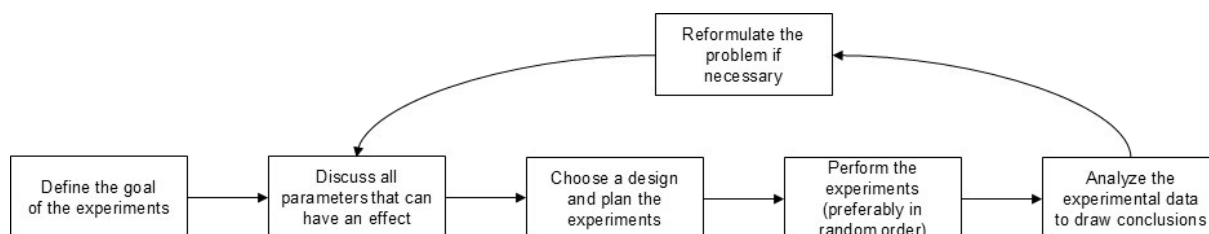


Figure 19. Design of Experiments is an iterative process.^[102]

2 Objectives

The electrochemical dehydration reaction should be developed further because it's an underexplored field of research, which offers an innovative access to carboxylic acid derivatives. Electrochemical dehydration of sulfonic acids should also be explored, since sulfonic acid derivatives are also highly important for all areas of chemistry. Electrochemical multicomponent reactions using SO_2 should be investigated in cooperation with other uprising technologies such as flow chemistry and laboratory automation, especially the electrochemical multicomponent synthesis of sulfonamides and sulfonates using SO_2 stock solutions in flow. For the transfer of an electrosynthesis from a divided batch-type protocol into a flow setup, the use of undivided flow cells and single-pass flow should be attempted. Since automated electrosynthesis is an underexplored aspect of laboratory automation, an open-source platform is required to be developed which allows for a flexible experimental setup to be controlled via automation. Because electrochemical allylic oxidation is an important topic for late-stage functionalization of natural compounds to highly interesting building blocks, a simplified approach to electrochemical allylic oxidation should be developed, which utilizes safer supporting electrolytes and an overall simplified electrolysis setup. All these objectives resemble progress in various fields of electrosynthesis (Figure 20).

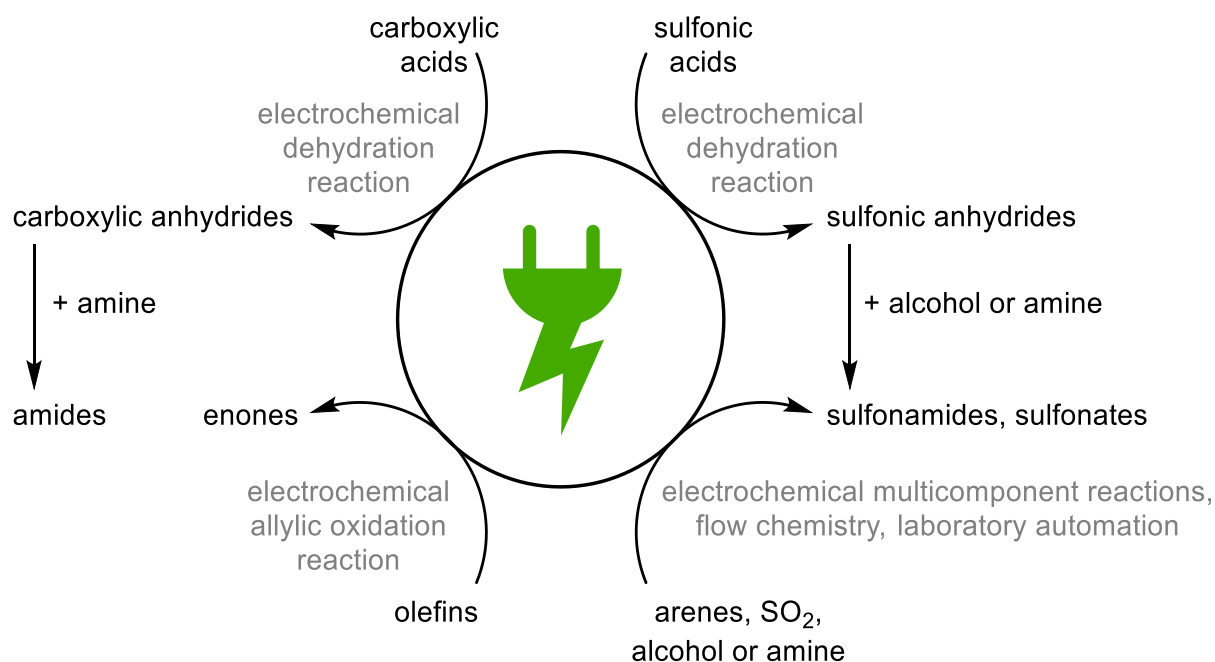


Figure 20. Overview of the relations between the various topics of this PhD thesis.

3 Overview of Publications

‡ These authors contributed equally to the work.

- 1) A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, **J. Schneider**, S. R. Waldvogel, *Beyond Kolbe and Hofer-Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids*, *ChemistryOpen* **2022**, 11, e2022000. DOI: [10.1002/open.202200059](https://doi.org/10.1002/open.202200059), CC BY-NC-ND 4.0.
- 2) M. M. Hielscher,‡ M. Dörr,‡ **J. Schneider**, S. R. Waldvogel, *LABS: Laboratory Automation and Batch Scheduling – A Modular Open Source Python Program for the Control of Automated Electrochemical Synthesis with a Web Interface*, *Chem. Asian J.* **2023**, 18, e2023003. DOI: [10.1002/asia.202300380](https://doi.org/10.1002/asia.202300380), CC BY 4.0.
- 3) **J. Schneider**, S. P. Blum, S. R. Waldvogel, *Electrochemical Synthesis of Sulfonamides in Single-Pass Flow*, *ChemElectroChem* **2023**, 10, e202300456. DOI: [10.1002/celc.202300456](https://doi.org/10.1002/celc.202300456), CC BY 4.0.
- 4) M. M. Hielscher,‡ **J. Schneider**,‡ A. H. J. Lohmann, S. R. Waldvogel, *Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell*. *ChemElectroChem* **2024**, e202400360. DOI: [10.1002/celc.202400360](https://doi.org/10.1002/celc.202400360), CC BY 4.0.
- 5) **J. Schneider**, A. P. Häring, S. R. Waldvogel, *Electrochemical Dehydration of Dicarboxylic Acids to Their Cyclic Anhydrides*, *Chem. Eur. J.* **2024**, 202400403. DOI: [10.1002/chem.202400403](https://doi.org/10.1002/chem.202400403), CC BY 4.0.
- 6) K. Hofman,‡ **J. Schneider**,‡ R. Goy, J. Schütz, W. Bonrath, S. R. Waldvogel, *A Simplified Approach for Electrochemical Allylic Oxidation of Olefins*, *Helv. Chim. Acta* **2025**, e202500068, DOI: [10.1002/hlca.202500068](https://doi.org/10.1002/hlca.202500068), CC BY 4.0.
- 7) E. Lunghi, A. M. van Koten, **J. Schneider**, S. R. Waldvogel, *Electrochemical Dehydration of Sulfonic Acids to their Anhydrides*, *J. Org. Chem* **2025**, [accepted], DOI: [10.1021/acs.joc.5c01155](https://doi.org/10.1021/acs.joc.5c01155), CC BY 4.0. A preprint version of this manuscript was uploaded to **ChemRxiv** on July 17th, 2025, DOI: [10.26434/chemrxiv-2025-wm3z6](https://doi.org/10.26434/chemrxiv-2025-wm3z6), CC BY-NC-ND 4.0.
- 8) **J. Schneider**,‡ E. Lunghi,‡ S. R. Waldvogel, *Electrochemical Dehydration Reaction*, *ChemSusChem* **2025**, (Review Article), [accepted], CC BY 4.0.

4 Results and Discussion

The publications are discussed grouped by topic, not in chronological order. First, the results of my work related to electrochemical dehydration reactions are discussed, followed by electrochemical multicomponent reactions of SO₂, then automated electrosynthesis in flow, and then the electrochemical allylic oxidation reaction. For simplicity, the labelling numbers of products in each chapter of this thesis are kept consistent with the numbers in each corresponding publication.

4.1 Electrochemical Dehydration Reactions

The following results have been published in a peer-reviewed publication.^[103]

J. Schneider[‡], E. Lunghi[‡], S. R. Waldvogel *

Electrochemical Dehydration Reaction

ChemSusChem, **2025**

[accepted]

License: CC BY 4.0.

[‡] These authors contributed equally

* Corresponding author

Explanation of my contribution:

J. Schneider and E. Lunghi wrote the manuscript for this review, searched for appropriate references to include, and created the required schemes. E. Lunghi created the cover picture for this review article. **J. Schneider** proposed the mechanistic classification and finalized the revision. S. R. Waldvogel supervised the project and assisted in writing of the manuscript.

Electrochemical Dehydration Reaction

Johannes Schneider⁺,^[a] Enrico Lunghi⁺,^[b] and Siegfried R. Waldvogel⁺,^[b,c]



REVIEW

Johannes Schneider received both his B.Sc. and M.Sc. degrees in Chemistry from Johannes Gutenberg-University Mainz. In his bachelor's thesis in the group of Prof. Dr. R. Zentel, he carried out research on RAFT polymerization of ethylsulfonyl protected methacrylates. He pursued his master's studies under Prof.



Dr. S. R. Waldvogel, working on electrochemical multicomponent synthesis of sulfonamides using flow chemistry. His main research interest is sustainable organic chemistry. He is currently completing his PhD thesis in the Waldvogel group, where his work includes a variety of topics such as electrochemical dehydration reactions, electrochemical multicomponent reactions, electrosynthesis using flow microreactors, electrochemical allylic oxidation reactions, as well as design of experiments, laboratory automation, and machine learning.

Enrico Lunghi received his PhD in Organic Chemistry from the University of Pavia, under the supervision of Prof. Zanoni. His research focused on electrochemical decarboxylation and Friedel-Crafts type cycloalkylation cascades. He then worked as a postdoctoral scientist at University of Pavia in collaboration with SpiroChem AG, developing custom synthesis and generating building block libraries. Currently, he is a postdoctoral researcher at the Max-Planck-Institute for Chemical Energy Conversion in Mülheim an der Ruhr (DE), working in the group of Prof. Dr. S. R. Waldvogel. His research interests include flow chemistry, electrochemistry, and synthesis. He has a strong background in process development, flow chemistry, and organic electrochemistry. His work aims to develop new technologies for accessing industrially relevant organic molecules.



Siegfried R. Waldvogel studied chemistry in Konstanz and in 1996 he received his PhD from the University of Bochum/Max Planck Institute of Coal Research (Prof. Dr. M. T. Reetz). After post-doctoral research in La Jolla, CA (Prof. Dr. J. Rebek Jr.), he started his own research at the University of Münster, and later Bonn, and Mainz. His research focusses on electro-organic transformations including bio-based feedstocks. In 2023, he became director at the Max-Planck-Institute for Chemical Energy Conversion. He initiated large research projects such as BMBF future cluster Electrifying Technical Organic Syntheses (ETOS), and he coordinates them. In 2018, he cofounded ESy-Labs GmbH, which provides custom electrosynthesis and contract R&D.



[a] J. Schneider*

Department of Chemistry

Johannes Gutenberg University (JGU)

Duesbergweg 10–14, 55128 Mainz (Germany)

[b] Dr. E. Lunghi*, Prof. Dr. S. R. Waldvogel

Max-Planck-Institute for Chemical Energy Conversion

Department of Electrosynthesis

Stiftstraße 34–36, 45470 Mülheim an der Ruhr (Germany)

E-mail: siegfried.waldvogel@cec.mpg.de

URL: www.cec.mpg.de/de/forschung/elektrosynthese

[c] Prof. Dr. S. R. Waldvogel

Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS–FMS)

Karlsruhe Institute of Technology (KIT)

Kaiserstraße 12, 76131 Karlsruhe (Germany)

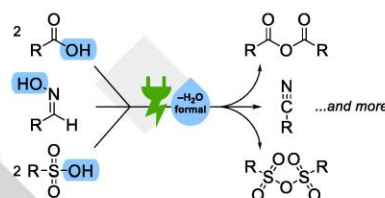
+ These authors contributed equally.

Abstract: The electrochemical dehydration reaction is a fascinating and underexplored field of research, which has started to attract significant attention in recent years. Dehydration reactions are characterized by the formal removal of water in the course of the transformation, and they are among the most fundamental types of reactions found throughout chemistry. Examples are esterification reactions, amidation reactions, and the synthesis of carbon-heteroatom multiple bonds. In general, dehydration reactions are not considered to be redox reactions, because no oxidation states change in the substrate from which water is eliminated, or in the dehydration reagent that is utilized. At first glance, there doesn't seem to be a link between dehydration reactions and redox chemistry. In recent years, however, it has been demonstrated that dehydration reactions can be carried out by electrolysis. Given the enormous importance of dehydration reactions from academic to technical scale, electrochemical dehydration reactions offer a more sustainable approach to such transformations. In this review, we survey the recent progress and highlight the opportunities of this new and evolving field. Electrochemical dehydration reactions are an interesting new discipline in the emerging domain of electro-organic chemistry, which is currently experiencing a remarkable renaissance to establish itself as a 21st century technique.

1. Introduction

Dehydration reactions are conventionally performed by using an excess of a dehydration reagent, which results in harsh reaction conditions and in the generation of hazardous reagent waste.^[1] This also complicates the downstream processing.^[2] Electrosynthesis is a first-class technique for replacing such dangerous and waste intense transformations with safer electrochemical alternatives which are characterized by milder reaction conditions.^[3,4] One of many advantages of electrosynthesis is the direct use of electricity as a comparably inexpensive and universal redox agent, which avoids the generation of reagent waste by utilizing anodic oxidation and cathodic reduction reactions instead of oxidizing or reducing agents.^[5] Since the chemical bonds consists of electrons, the addition of an electron to a bond (reduction) or the removal of an electron from a bond (oxidation) activates the substrates for chemical conversion. This can proceed either via Brønsted acid/base or by radical type reactivity.^[6] The avoidance of metal catalysts^[7] and the decreased number of synthesis steps makes electrosynthesis an innovative production technology which goes way beyond other sustainable improvements.^[8] Furthermore, the transformation usually occurs at the electrodes or close by them. Switching off the electricity stops anodic oxidation and cathodic reduction and helps to prevent runaway reactions, which adds an inherent safety aspect to electrosynthetic transformations.^[9] In addition, galvanostatic electro-organic transformations are typically simple to scale-up.^[10] In the field of electrosynthesis, dehydrative transformations have not been in the focus of research until recently. Most likely, such reactions are more common than currently known and they might be facilitated by the strong electrical field close to the electrodes. In this regime the nature of the electrolyte plays an utmost important role.^[11] Especially in the context of Green Chemistry, dehydration reactions have often been discussed as chemical processes for which significantly more innovation is required.^[12] One of the major advantages of dehydration reactions is that water is one of the most uncritical and simple leaving groups, because disposal of water is much easier than the disposal of reagent waste originating from other leaving groups such as mesylates, triflates, or tosylates.^[13] In addition, water is not toxic, corrosive, or environmentally harmful. As in any dehydration reaction, the activation of the OH group in the substrate to form a good leaving group is the key. While many conventional dehydration reactions employ an excess of dehydration agent, it would be advantageous to generate the dehydration reagent in-situ by electrolysis. In other electrochemical dehydration reactions, the electrolysis acts as an activation step for the substrate to trigger a subsequent dehydration reaction, in which case no electrochemically generated

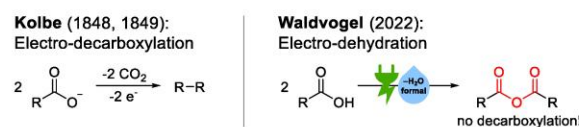
dehydration reagent is involved. The electro-generation of reagents is already a well-established concept in other areas of electrosynthesis,^[14] for example for the generation of carbocations^[15] or bases.^[16] The overall simplicity of electrochemical dehydration reactions can also contribute to their atom economy.^[17] The basic underlying concept of electrochemical dehydration reactions offers fascinating opportunities for other new applications: Electrolysis is used as the key technique to apply the thermodynamic driving force to carry out transformations which are typically not associated with redox reactions. Electrochemical dehydration reactions should therefore be viewed as a source of inspiration for other types of reactions that are not redox reactions but still might be carried out via electrolysis. This will lead to applications of electrosynthesis in areas where electrolysis was not considered as the key technology before.^[18] In this review, we discuss notable examples of electrochemical dehydration reactions and we propose how to classify them mechanistically.



Scheme 1. Some examples of electrochemical dehydration reactions.

2. Electrochemical Dehydration of Carboxylic Acids to their Anhydrides

In 2022, our group reported a conceptually new and non-decarboxylative electrochemical synthesis of carboxylic anhydrides from carboxylic acids (Scheme 2).^[19] This result was rather surprising, because the electrolysis of carboxylic acids, known as the Kolbe electrolysis, has been known and studied for more than 170 years at the time of our discovery. The Kolbe electrolysis is one of the very few named reactions from the field of organic electrosynthesis that is known to even those organic chemists which are not working with electrolysis.^[20] Even more so, Hermann Kolbe's pioneering publications from 1848 and 1849 mark a cornerstone of organic electrochemistry,^[21] and the electrolysis of carboxylic acids has since then been a major research topic.^[22,23] Nonetheless, a dehydrative reaction pathway when electrolyzing carboxylic acids that is not accompanied by decarboxylation step has not been reported before 2022.^[19]

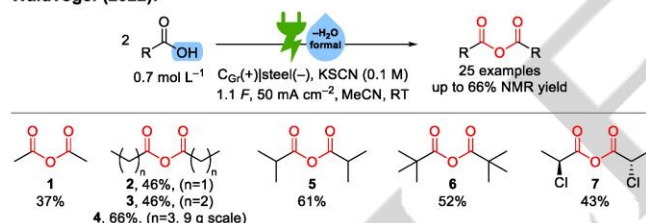


Scheme 2. Comparison of Kolbe electrolysis (left) with electrochemical dehydration of carboxylic acids to their carboxylic anhydrides (right).^[19,24]

REVIEW

Importantly, the Kolbe reaction is always characterized by a decarboxylation step, which means that one carbon atom of the carboxylic acid function in the starting material is eliminated as CO_2 in the course of the reaction.^[25] In contrast, the electrochemical synthesis of carboxylic anhydrides from their carboxylic acids that was found by our group is a non-decarboxylative dehydration reaction, and all carbon atoms of the starting material are preserved in the product anhydride (Scheme 3). Noteworthy, for the Kolbe electrolysis at least a partial neutralization of the acid is necessary.^[25] However, in our approach, the electrolysis is carried out without base, and only a supporting electrolyte is added. No conventional dehydration reagent is utilized, and hydrogen evolution reaction at the cathode could be detected. The electrochemical valorization of carboxylic acids is interesting because they are naturally abundant, non-toxic, readily available, and inexpensive starting materials.^[22] In general, the carboxylic anhydrides which are obtained by electrolysis are highly valuable reagents for organic synthesis, and they are commonly utilized for example in acylation reactions of amines for the synthesis of amides. Such amidation reactions are of utmost importance from academic to technical scale,^[26] especially in the context of medicinal chemistry.^[27]

Waldvogel (2022):

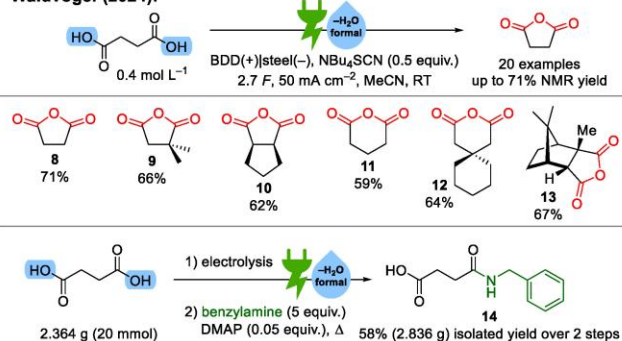


Scheme 3. Examples from the electrochemical dehydration of carboxylic acids to their anhydrides. RT = room temperature.^[19]

In the initial publication, 25 carboxylic anhydrides were reported with NMR yields up to 66%.^[19] Notably, the selectivity of this electrochemical synthesis of carboxylic anhydrides from carboxylic acids can be very high, in some cases over 95%. A graphite (C_{Gr}) anode and a stainless steel cathode are used as inexpensive and environmentally friendly electrode materials.^[28] The electrolysis is carried out under mild reaction conditions, because neither heating nor cooling increases the yield of anhydride, and no other additive than a thiocyanate supporting electrolyte is required. The reaction conditions tolerate double bonds and halo substituents in the substrate. Notably, the electrolysis requires only a small amount of applied charge (1.1 F) in combination with a high current density of 50 mA cm^{-2} . Such conditions allow for a fast electrolysis. The mechanistic concurse at that time was not identified yet, and in particular the fate of the oxygen in the carboxylic acid starting material was unknown. No intermediates or side

products which would give any hint about the reaction mechanism besides hydrogen could be detected.^[24] In particular, typical products of a Kolbe electrolysis or a Hofer-Moest pathway were absent. Since this reaction is a dehydration reaction, the key to understanding the mechanism is to analyze where the water remains that is eliminated during the electrolysis of the carboxylic acid to form the carboxylic anhydride. This is an interesting question because the reaction is carried out only with addition of a supporting electrolyte, and no conventional dehydration reagent or other reagents are added. Acetonitrile is used as solvent, but it does not act as a dehydration reagent, because the reaction works as well in other solvents such as acetone. By control experiments, it could be ruled out that oxygen is evolving from the solution during electrolysis. At the cathode, hydrogen evolution reaction (HER) is observed, which is quite common.^[29] Thiocyanate supporting electrolytes give the highest yields of anhydrides, although other supporting electrolytes also result in anhydride formation, albeit with lower yields. Several electrode materials can be chosen, and the reaction is not limited to a specific combination of materials.^[28] Cyclic voltammetry (CV) measurements revealed the irreversible oxidation of the thiocyanate supporting electrolyte. When performing the reaction in the anodic compartment of a divided cell instead of an undivided cell setup, only traces of anhydride are found. In general, the reaction conditions are mild and simple, because the electrolysis is carried out at room temperature (RT) under air. It could be demonstrated in control experiments that the carboxylic anhydride product decomposes again to the carboxylic acid upon electrolysis. Interestingly, a yield higher than 50% could be achieved when using less than 0.5 equivalents of thiocyanate supporting electrolyte, which indicates that if thiocyanate was responsible for the electrochemical dehydration, one equivalent of thiocyanate can react with more than one equivalent of carboxylic acid in the course of the electrolysis to form the carboxylic anhydride. Most importantly, the reaction does not work at all without electricity.

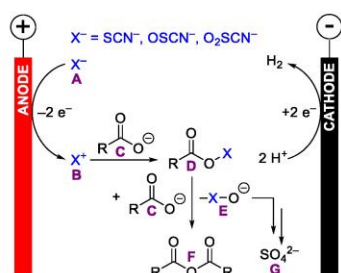
Waldvogel (2024):



Scheme 4. Examples from the electrochemical dehydration of dicarboxylic acids to their cyclic anhydrides.^[24] BDD = boron-doped diamond. DMAP = 4-(dimethylamino)pyridine.^[30]

REVIEW

Subsequently, this research was extended to dicarboxylic acids, which are electrochemically dehydrated to the corresponding cyclic anhydrides (Scheme 4).^[24] In addition, we carried out mechanistic investigations which allowed us to propose a mechanism (Scheme 5). In total, 20 examples were demonstrated with NMR yields up to 71%. The cyclic carboxylic anhydrides which were generated in-situ by electrolysis were employed in amidation reactions by addition of amines. The products of such acylation reactions are amides with a ω -carboxylic acid side chain, which allows for further functionalization. Such addition reactions of amines to cyclic anhydrides offer a favorable atom economy, because no reagent waste from the cyclic carboxylic anhydride is generated.^[17]



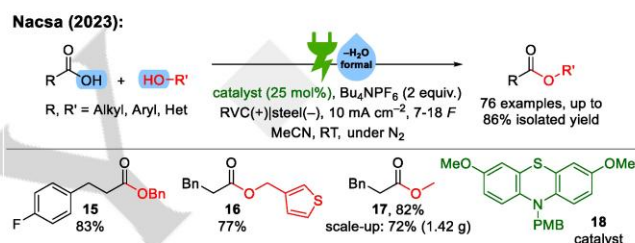
Scheme 5. Proposed mechanism for the electrochemical dehydration of carboxylic acids to their anhydrides.^[24] By ^{18}O isotope labelling of the carboxylic acid starting material, ^{18}O labelled sulfate was detected in the reaction solution after electrolysis.

In these mechanistic investigations, we found that the electrochemical dehydration proceeds via anodic oxidation of the thiocyanate supporting electrolyte **A** to **B**, which acts as an electro-generated dehydration reagent (Scheme 5).^[24] **B** then reacts with one equivalent of carboxylate **C** to an active ester **D**. Another equivalent of **C** reacts with **D** to form the carboxylic anhydride **F**, while **E** is eliminated as a good leaving group. Most importantly, one equivalent of thiocyanate can take up several equivalents of water in the course of the electrochemical dehydration reaction, which is accompanied by the formation of increasingly oxygenated sulfur species **E**. In the last step, sulfate **G** is formed. The sulfate is unequivocally detected by high-resolution mass spectrometry (HRMS) with ^{18}O isotope labelled dicarboxylic acid as starting material, since ^{18}O labelled sulfate was found.^[24] This proposed mechanism represents a simplified picture, because many of the oxygenated sulfur species **E** are known to undergo a variety of other reactions.^[31]

3. Electrochemical Catalytic Dehydration of Carboxylic Acids to their Anhydrides

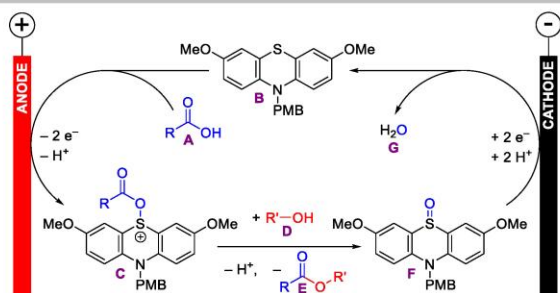
The group of Nacsa reported an electrochemical design for catalytic dehydration of carboxylic acids with alcohols to obtain esters in 2023 (Scheme 6).^[32,33] This interesting report came after our findings of the

electrochemical dehydration of carboxylic acids in 2022,^[19] and it uses a different approach. Instead of thiocyanates in a dual role as supporting electrolyte and electrochemically generated dehydration reagent,^[11] the group of Nacsa utilized an electron-rich phenothiazine derivative **18** as catalyst for electrochemically driven catalytic dehydration of carboxylic acids with alcohols to the corresponding esters. Notably, both our approach and the approach by Nacsa are realized based on sulfur compounds. Nacsa attempted to utilize catalysts based on phosphorous, but these attempts were unsuccessful because of the difficult reduction of the $\text{P}=\text{O}$ bond.^[34] No acid or base is required as additive, and the electrolysis is carried out at room temperature using a catalyst loading of 25 mol%. Reticulated vitreous carbon (RVC) is used as anode material and stainless steel as cathode material. The highest yields are obtained when nitrogen is utilized as inert gas. In total, 76 examples are demonstrated with isolated yields up to 86%.



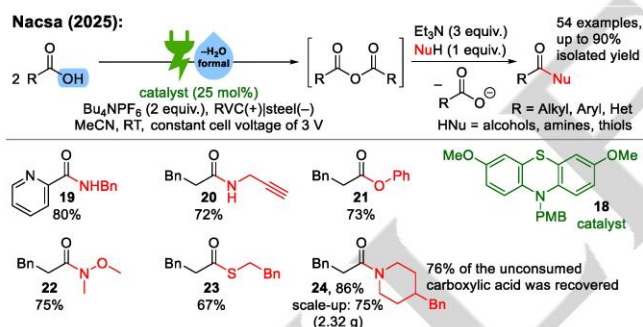
Scheme 6. Examples from the electrochemical esterification of carboxylic acids with alcohols to esters.^[32,33] PMB = *p*-methoxy benzene. The scale-up was carried out via electrolysis under constant cell voltage.

Nacsa noted a comparably high amount of applied charge that is required (7 to 18 F), which is attributed to electron transfer between the electrodes by the phenothiazine catalyst **18**, which does not contribute to the conversion of substrates. Such a large amount of required charge prolongs electrolysis. The scalability of the transformation was demonstrated, and an analysis of stereochemical outcome demonstrated the retention of configuration. As depicted in Scheme 7, Nacsa proposed that the phenothiazine-based catalyst **B** undergoes anodic oxidation to react with the carboxylic acid **A** to a sulfonium species **C**, which activates the OH group of the carboxylic acid so that nucleophilic acyl substitution with an alcohol **D** can take place. The product of this step is an ester **E**, and the corresponding sulfoxide (phenothiazine-S-oxide) **F**. Cathodic reduction of sulfoxide **F** regenerates the catalyst **B** by elimination of water **G**, which is the driving force for catalytic turnover. It should be mentioned that further oxidation of the sulfoxide **F** to the corresponding sulfone is possible in theory as well. Such a separate catalytic cycle based on the sulfoxide **F** and sulfone could also contribute to conversion of the substrate.



Scheme 7. Proposed mechanism of the phenothiazine-mediated electrochemical catalytic esterification of carboxylic acids with alcohols to esters.^[32,33,35] PMB = *p*-methoxy benzene.

Nacsa modified this approach in 2025 into a carboxylic acid substitution platform for the synthesis of amides, esters, and thioesters by utilizing carboxylic anhydrides as key intermediates (Scheme 8).^[35] In this follow-up work, the carboxylic anhydride is generated in-situ by electrochemical dehydration of the carboxylic acid, and then the nucleophile is added after the electrolysis has completed in a subsequent step to access the corresponding carboxylic acid derivative in a one-pot reaction. Because nucleophiles like thiols or amines are susceptible to anodic oxidation,^[36] these nucleophiles were added to the reaction solution subsequently after electrolysis. In total, 54 examples are demonstrated with isolated yields up to 90%.



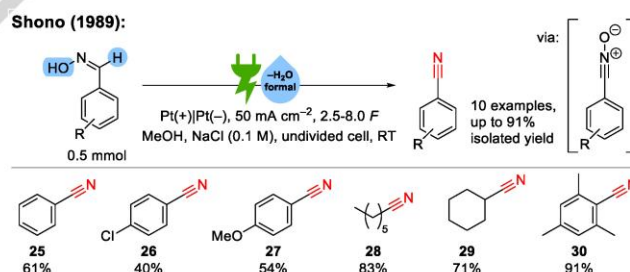
Scheme 8. Examples from the electrochemical dehydration of carboxylic acids to carboxylic anhydrides for the synthesis of amides, esters, and thioesters.^[35]

The reaction mechanism is similar to Nacsa's previous publication (Scheme 7). A key difference in the follow-up publication is the subsequent addition of the nucleophile after the electrolysis has been completed. This avoids side reactions of the nucleophile which could occur if the nucleophile was present already during electrolysis. Only the electrochemical part is depicted in Scheme 7. It should be noted that Nacsa carried out this work by using an electrolysis under constant cell voltage without mentioning the amount of applied charge.^[35] This approach was also utilized for the scale-up reaction in the previous work (product **17** in Scheme 6). While Nacsa's work is highly interesting, such an electrolysis type is not recommended because it is not galvanostatic, and the electric current will decrease in the course of electrolysis due to the increase in internal resistance.^[37] This means by

specifying the cell voltage and the electrolysis time, the applied charge cannot be calculated. Such an approach is also not potentiostatic either because the terminal cell voltage is not equal to the electrode potential.^[38] Electrosynthesis should preferably be carried out as galvanostatic electrolysis by specifying the employed electric current in mA (or the current density in units of mA/cm² if the electrode surface can be approximated). The amount of applied charge should be expressed as multiples of the Faraday constant (e.g. $3 F = 3 \cdot 96485 \text{ C/mol}$).^[38] The advantage of expressing the amount of applied charge like this is that it's independent of the amount of mol of substrate that is used, meaning that such a definition (e.g. $3 F$) is completely independent of the scale of the electrolysis. Note also that it's F , not F/mol , because the Faraday constant F has units of C/mol, so F/mol would result in units of C/mol².^[18]

4. Electrochemical Dehydration of Aldoximes to Nitriles

In 1989, the group of Shono published an electrosynthesis of nitriles from aldoximes using halogen ions as mediators (Scheme 9).^[39] In this report, Shono already noted the interesting link between this dehydration reaction and electrolysis: "... passing electricity is necessary ... although it is formally a simple dehydration process which is unrelated to oxidation and reduction".^[39] In total, 10 examples are demonstrated with isolated yields up to 91%. All reactions were carried out on a 0.5 mmol scale.^[39]

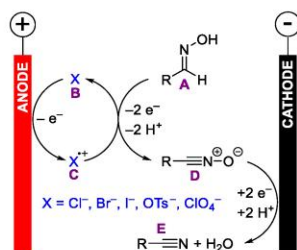


Scheme 9. Examples from the electrochemical dehydration of aldoximes to nitriles.^[39]

The initial reaction step is a mediated (**B**, **C**) anodic oxidation of the aldoxime **A** to a nitrile oxide **D** as intermediate, which consecutively undergoes cathodic reduction to the nitrile product **E** (Scheme 10). In summary, water is eliminated from the aldoxime in the course of the electrolysis. Such a transformation is a form of consecutive paired electrolysis, and it fulfills the criteria for a domino reaction.^[40] Interestingly, only a limited number of such consecutive paired electrolysis are known.^[41] It should be noted that the term "domino reaction" was not established yet in 1989, as it was later introduced by Tietze in 1993.^[40] The nitrile oxide intermediates **D** are themselves valuable substrates for

REVIEW

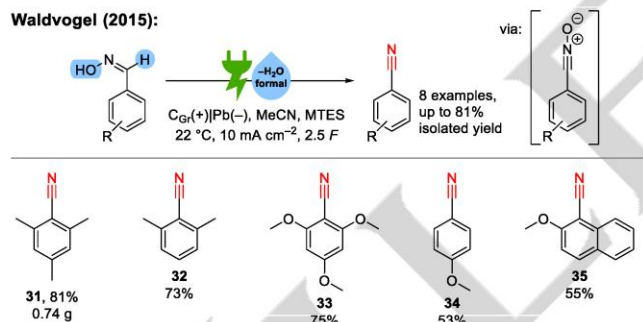
organic synthesis, especially for 1,3-dipolar cycloadditions.^[42] Shono was unable to isolate the nitrile oxide intermediates **D**, but by utilizing a divided cell, they could be quenched by addition of styrene to form the corresponding isoxazolines in a 1,3-dipolar cycloaddition (not shown in Scheme 10). Noteworthy, the recommended platinum electrodes corrode strongly when chloride is used as mediator.^[43]



Scheme 10. Proposed mechanism for the mediated electrochemical dehydration of aldoximes to nitriles via nitrile oxide intermediates.^[39]

Inspired by the work of Shono, in 2015 our group published an electrochemical synthesis of nitriles via a halogen-free domino oxidation-reduction sequence.^[44,45] In this work, the aldoxime is directly anodically oxidized without any mediator to the corresponding nitrile oxide intermediate, which is then cathodically reduced to the nitrile. In total, we reported 8 substrates with isolated yields up to 81% (Scheme 11).

Waldvogel (2015):



Scheme 11. Examples from the halogen-free electrochemical dehydration of aldoximes to nitriles. C_{Gr} = graphite. MTES = methyl triethylammonium methylsulfate.^[44,45]

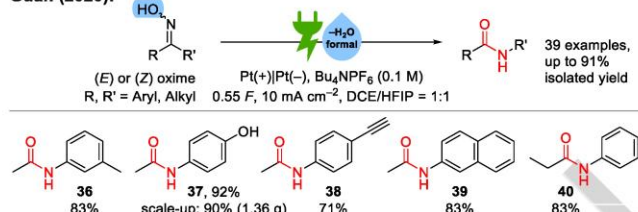
In analogy to the work of Shono, this reaction proceeds via a domino oxidation-reduction sequence (Scheme 10), which is a form of paired electrolysis.^[3] In contrast to Shono's work though, no mediator is required. When using this reaction in flow electrolyzers, the use of leaded bronzes as substitute for the soft and mechanically labile lead is recommended.^[46]

5. Electrochemical Beckmann Rearrangement

In 2020, an electrochemical variant of the Beckmann rearrangement was reported by the Guan group (Scheme 12).^[47] Interestingly, in this approach the Beckmann rearrangement proceeds through a radical pathway which does not follow the *trans*-migration rule, which states that the substituent that is *trans* to the

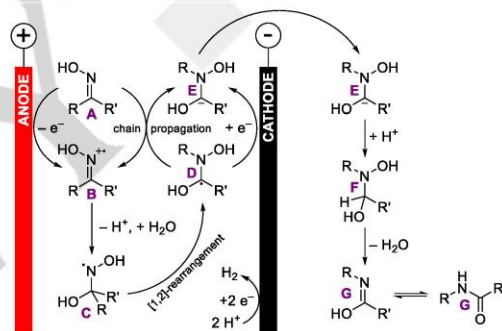
oxime function in the substrate will migrate, as is the case in the classical Beckmann rearrangement. In total, 39 examples are reported with isolated yields up to 91%.

Guan (2020):



Scheme 12. Examples from the electrochemical Beckmann rearrangement. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, DCE = dichloroethane.^[47]

The proposed reaction mechanism is depicted in Scheme 13. An initial oxidation of the oxime **A** (either by anodic oxidation or by chain propagation) to **B** is followed by deprotonation and addition of water to **C**. After a radical [1,2]-rearrangement to **D**, cathodic reduction to **E**, and protonation to **F**, water is eliminated again to form the product **G**. This is also an example for a paired electrolysis. In this electrolysis, no dehydration reagent is generated.



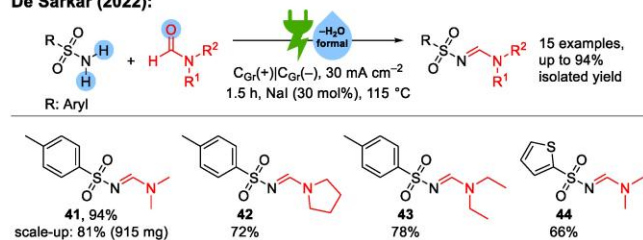
Scheme 13. Proposed reaction mechanism of the electrochemical Beckmann rearrangement.^[47]

6. Synthesis of *N*-Sulfonyl Amidines by Electrochemical Dehydrative Coupling

In 2022, the group of De Sarkar developed an electrochemical method for the functionalization of dimethyl formamide (DMF) (Scheme 14).^[48] In this work, electrochemically activated derivatives of DMF can react either in a dehydrative coupling reaction with a primary sulfonamide to an *N*-sulfonyl amidine, or it can react in an oxidative cyclization reaction with hydrazides to form 1,3,4-oxadiazoles. In this review we the focus only on the dehydrative coupling reaction to *N*-sulfonyl amidines.

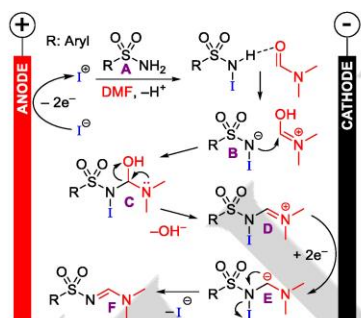
REVIEW

De Sarkar (2022):



Scheme 14. Examples from the synthesis of *N*-sulfonyl amidines by electrochemical dehydrative coupling of primary sulfonamides with derivatives of DMF. C₆₀ = graphite.^[48]

The electrochemical functionalization of DMF is an interesting strategy because DMF is readily available. The concept of a dehydrative coupling is also interesting because in principle, water is one of the simplest and least hazardous leaving groups. The disposal of water is much simpler than the disposal of reagent waste which originates from other leaving groups such as triflates, mesylates or tosylates.^[13] The authors propose an iodine-mediated paired electrolysis as reaction mechanism (Scheme 15). Anodic oxidation of iodide leads to the formation of an iodine cation, which activates the sulfonamide **A**. By formation of an iminium ion pair **B**, water is eliminated from **C**, and the resulting iminium ion **D** is reduced again to **E**, followed by elimination of the iodide from **E**, which forms the product *N*-sulfonyl amidine **F**.

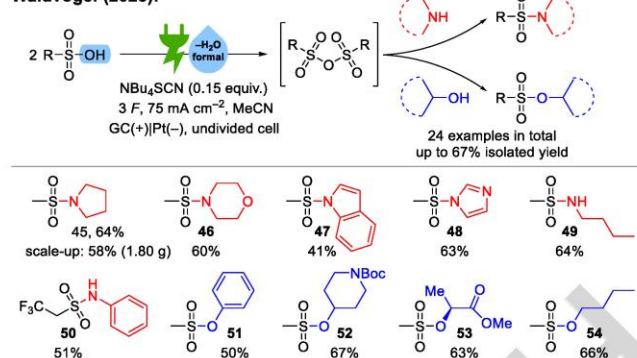


Scheme 15. The proposed reaction mechanism of the electrochemical dehydrative coupling of primary sulfonamides with derivatives of dimethyl formamide to *N*-sulfonyl amidines.^[48]

7. Electrochemical Dehydration of Sulfonic Acids to Their Anhydrides

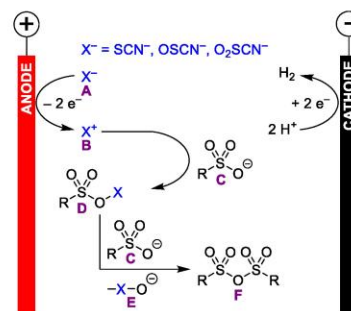
Very recently, our group extended our work on electrochemical dehydration reactions to sulfonic acids (Scheme 16).^[49,50] In this work, sulfonic acids are electrochemically dehydrated to their corresponding sulfonic anhydrides. These in-situ generated sulfonic anhydrides are then utilized in sulfonylation reactions: by addition of alcohols or amines, the corresponding sulfonates and sulfonamides were isolated, respectively. In total, we reported 24 substrates with isolated yields up to 67%. The scalability was also demonstrated.

Waldvogel (2025):



Scheme 16. Examples from the electrochemical dehydration of sulfonic acids to their sulfonic anhydrides and their subsequent reactions with alcohols or amines to sulfonates or sulfonamides, respectively.^[50]

This is the first work which applies the concept of electrochemical dehydration to sulfonic acids, as most of the previous work by us and other groups has focused on carboxylic acids. The mechanism of the electrochemical dehydration of sulfonic acids to their sulfonic anhydrides (Scheme 17) is similar to our proposed mechanism for the electrosynthesis of carboxylic anhydrides from carboxylic acids. The thiocyanate supporting electrolyte **A** is anodically oxidized to **B** and reacts with a sulfonic acid anion **C** to an active ester **D**. Another equivalent of sulfonic acid anion **C** reacts with **D** to the corresponding sulfonic anhydride **F** under elimination of **E**. Upon addition of alcohols or amines after electrolysis (not shown in Scheme 17), the sulfonic anhydrides react in sulfonylation reactions to the corresponding sulfonates or sulfonamides, respectively.

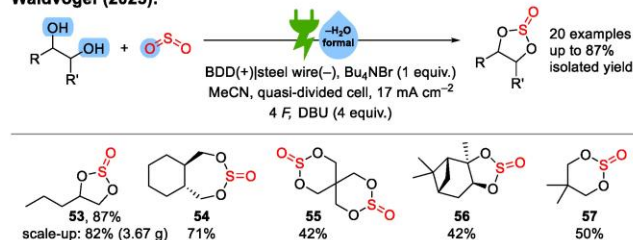


Scheme 17. Proposed mechanism of the electrochemical dehydration of sulfonic acids to their anhydrides.^[50]

8. Electrochemical Synthesis of Cyclic Sulfites from Diols using Sulfur Dioxide Upcycling

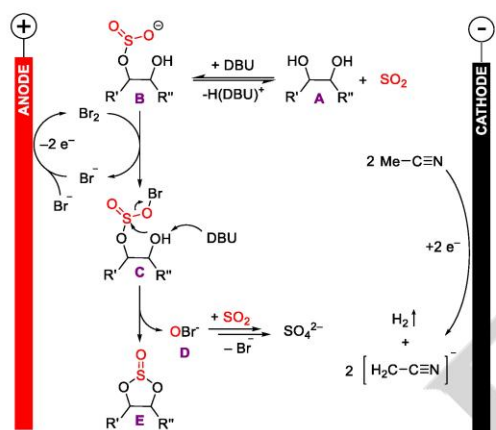
Also recently, our group reported an electrochemical synthesis of cyclic sulfites from diols and sulfur dioxide (Scheme 18).^[51] This work is part of the very recent progress in both the field of electrochemical dehydration reactions and the field of electrochemical multicomponent reactions using sulfur dioxide stock solutions,^[52] as it merges both topics in one reaction.

Waldvogel (2025):



Scheme 18. Electrochemical synthesis of cyclic sulfites from diols and SO_2 . DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.^[51]

The work of our group on electrochemical multicomponent reactions using SO_2 incorporation for the synthesis of highly value-added products started with the electrosynthesis of sulfonates,^[53] and has since then been extended to sulfamides,^[54] sulfonamides,^[55] alkenesulfonates,^[56] enaminy sulfonates,^[57] and most recently, cyclic sulfites.^[51]

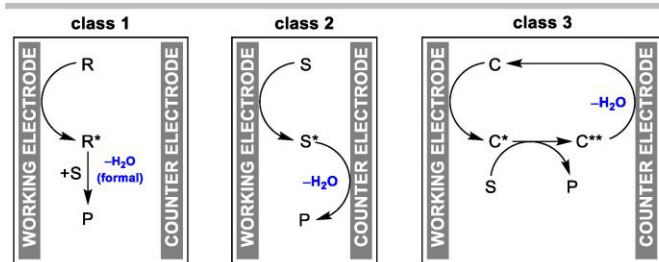


Scheme 19. Proposed reaction mechanism of the electrochemical synthesis of cyclic sulfites from diols and SO_2 .^[51] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

The proposed reaction mechanism is depicted in Scheme 19. The reaction is carried out in a quasi-divided cell with a steel wire as cathode. Sulfur dioxide reacts with an alcohol function of the diol **A** to a Lewis acid-base adduct (not shown here) which is deprotonated by DBU to an acyclic sulfite intermediate **B**. Anodic oxidation of the bromide, which plays a dual role as supporting electrolyte and mediator,^[11] leads to the formation of intermediate **C** from which hypobromite **D** is eliminated as a good leaving group while the other alcohol function of the diol attacks the sulfur atom in the acyclic sulfite intermediate to form the cyclic sulfite **E** as product. The hypobromite **D** is reduced again to bromide by sulfur dioxide. In summary, the OH group of the sulfite is converted into a good leaving group by derivatization to a hypobromite. This reaction represents both an electrochemical multicomponent reaction with sulfur dioxide and an electrochemical dehydration reaction by electrochemical (re)generation of the dehydration reagent. At the cathode, hydrogen evolution reaction is observed.^[29] In total, we reported 20 examples with isolated yields up to 87%.^[51]

9. Classification of Mechanisms

Electrochemical dehydration reactions can be grouped into three different classes (Scheme 20). Note that the terms working electrode and counter electrode are used, since the reaction steps of the overall dehydration could in principle proceed at the anode or the cathode. In **class 1** (Scheme 20, left), a dehydration reagent R^* is generated by electrolysis from a reagent **R**, which then reacts with the substrate **S** in a subsequent non-electrochemical dehydration step to product **P**. In the course of the reaction, one equivalent of water remains chemically bound to the dehydration reagent that was electrochemically generated. Examples developed by our group are the electrochemical dehydration of carboxylic acids or sulfonic acids to the corresponding anhydrides,^[19,24,50] and the electrosynthesis of cyclic sulfites.^[51] The work of De Sarkar on the dehydration of primary sulfonamides with DMF derivatives to *N*-sulfonyl amidines could also be assigned to this class.^[48] In **class 2** (Scheme 20, center), a domino sequence of anodic oxidation and cathodic reduction takes place (in any order), which is characterized by an overall dehydration. Here, the substrate **S** reacts at one electrode to intermediate S^* , and this intermediate consecutively reacts at the opposite electrode to the product **P**. In the course of such a reaction, one equivalent of water is eliminated. This is a form of paired electrolysis.^[3] This sequence can be mediated, and the halogen-mediated electrochemical dehydration of aldoximes to nitriles by Shono is a good example for such a reaction.^[39] An example for an unmediated case is the subsequent work of our group on this topic.^[44,45] The electrochemical Beckmann rearrangement developed by Guan also falls under this category.^[47] In **class 3** (Scheme 20, right), catalytic dehydration occurs via electrochemical generation of a dehydration catalyst C^* from a precatalyst **C**, which reacts with the substrate **S** to the reaction product **P** and an oxygenated species C^{**} . The catalyst **C** is electrochemically regenerated from C^{**} to achieve catalytic turnover. In the course of one turnover of the catalytic cycle, one equivalent of water is eliminated. An example of this type is the work by Nacsá.^[32,33,35] Lastly, a clear distinction between the terms deoxygenation and dehydration must be made. The term deoxygenation is broad and it can for example represent a reduction reaction.^[58] Electrochemical deoxygenation reactions have been reviewed already.^[59] A dehydration on the other hand is redox-neutral with respect to the substrate which undergoes the dehydration reaction.



Scheme 20. Mechanistic classification of electrochemical dehydration reactions.

Summary and Outlook

In recent years, significant progress has been made to further develop electrochemical dehydration reactions, which are a fascinating and uprising research field within the domain of electrosynthesis. Electrochemical dehydration can either proceed via electro (re)generation of a dehydration reagent or the electrolysis results in intermediates from which water is easily eliminated without any mediator. Electrochemical dehydration reactions are especially interesting if they resemble a dehydrative coupling reaction, in which a new chemical bond is formed between two components by the removal of water, which is likely the least hazardous leaving group. Given the fundamental importance of dehydration reactions for all disciplines of chemistry, electrochemical dehydration reactions offer a more sustainable and milder alternative to hazardous dehydration reagents. Dehydration reactions are not redox reactions, because no change in oxidation state occurs in the substrate from which water is eliminated, or in the dehydration reagent that is used. This could have contributed to the fact that dehydration was not viewed earlier in the context of electrolysis. The underlying idea behind this new field is to use electrolysis as a thermodynamic driving force to carry out reactions which are typically not associated with redox reactions, and this idea should serve as inspiration for other types of non-redox reactions which might be performed via electrolysis. This will lead to applications of electrosynthesis in fields where it was not considered to be the key technology before. In theory, every dehydration reaction that is currently carried out with conventional dehydration reagents could be achieved using electrochemical dehydration, which renders this new field as a promising and fascinating opportunity for many new and sustainable developments.

Acknowledgements

Financial support from the BMFTR Clusters4Future ETOS in the frame of E-Sonata and E-Scope (FKZ 03ZU1205LB and FKZ 03ZU1205IA) is highly appreciated. The authors thank the Max-Planck-Gesellschaft (MPG) for the open access opportunity within the frame of Projekt DEAL, and the RESOLV

cluster (Ruhr Explores Solvation, EXC-2033–390677874).

Keywords: electrolysis • sustainable chemistry • dehydrative reaction • carboxylic acids • sulfonic acids

References

- [1] a) Z. J. Kamiński, B. Kolesińska, M. Małgorzata, *Synth. Commun.* **2004**, 34, 3349–3358; b) R. Kocz, J. Roestamadj, S. Mobashery, *J. Org. Chem.* **1994**, 59, 2913–2914; c) R. C. Larock, *Comprehensive Organic Transformations*, Wiley, **2018**.
- [2] J.-F. P. Hamel, J. B. Hunter, S. K. Sikdar, *Downstream Processing and Bioseparation*, American Chemical Society, Washington, DC, **1990**.
- [3] D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, 11, 12386–12400.
- [4] a) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, 57, 5594–5619; *Angew. Chem.* **2018**, 130, 5694–5721; b) C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, 53, 72–83; c) M. C. Leech, K. Lam, *Nat. Rev. Chem.* **2022**, 6, 275–286; d) C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen, C. E. Willans, *Green Chem.* **2020**, 22, 3358–3375; e) N. E. S. Tay, D. Lehnher, T. Rovis, *Chem. Rev.* **2022**, 122, 2487–2649; f) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu, L. Ackermann, *ACS Cent. Sci.* **2021**, 7, 415–431; g) J. Rein, S. B. Zacate, K. Mao, S. Lin, *Chem. Soc. Rev.* **2023**, 52, 8106–8125; h) M. Brachi, W. El Housseini, K. Beaver, R. Jadhav, A. Dantanarayana, D. G. Boucher, S. D. Minter, *ACS Org. Inorg. Au* **2024**, 4, 141–187.
- [5] a) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, 117, 13230–13319; b) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, 57, 6018–6041; *Angew. Chem.* **2018**, 130, 6124–6149; c) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, 2, 302–308.
- [6] a) P. Di Matteo, M. Bortolami, M. Feroci, V. Scarano, R. Petrucci, *ChemElectroChem* **2021**, 8, 2754–2763; b) M. Feroci, I. Chiarotto, M. Orsini, F. Pandolfi, D. Zane, A. Inesi, *ChemElectroChem* **2018**, 5, 651–658.
- [7] D. R. Abernethy, A. J. Destefano, T. L. Cecil, K. Zaidi, R. L. Williams, *Pharm. Res.* **2010**, 27, 750–755.
- [8] J. Seidler, J. Strugatchi, T. Gärtner, S. R. Waldvogel, *MRS Energy Sustain.* **2020**, 7, E42.
- [9] M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs, K. Lam, *React. Chem. Eng.* **2020**, 5, 977–990.

REVIEW

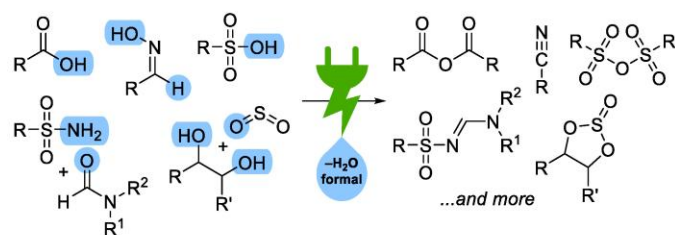
- [10] D. Lehnher, L. Chen, *Org. Process Res. Dev.* **2024**, 28, 338–366.
- [11] L. G. Gombos, J. Nikl, S. R. Waldvogel, *ChemElectroChem* **2024**, 11, e202300730.
- [12] a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells et al., *Green Chem.* **2007**, 9, 411–420; b) M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine et al., *Green Chem.* **2018**, 20, 5082–5103.
- [13] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, 39, 301–312.
- [14] O. Hammerich, B. Speiser (Hrsg.) *Organic Electrochemistry. Chapter 43: Electrogenated Bases and Nucleophiles*. J. H. P. Utley, M. F. Nielsen, P. B. Wyatt, CRC Press, Boca Raton, London, **2015**.
- [15] a) T. Caruso, M. Feroci, A. Inesi, M. Orsini, A. Scettri, L. Palombi, *Adv. Synth. Catal.* **2006**, 348, 1942–1947; b) L. Palombi, M. Feroci, M. Orsini, A. Inesi, *Chem. Commun.* **2004**, 1846–1847; c) M. Feroci, M. Orsini, L. Palombi, A. Inesi, *Green Chem.* **2007**, 9, 323–325; d) J. H. P. Utley, *Electrochemistry I* **1987**, 142, 131–165.
- [16] a) C. M. Stork, E. Glöckler, V. Derdau, P. Schnieders, S. R. Waldvogel, *Org. Biomol. Chem.* **2025**, 23, 6526–6532; b) B. C. Hawkins, J. M. Chalker, M. L. Coote, A. C. Bissember, *Angew. Chem. Int. Ed.* **2024**, 63, e202407207.
- [17] B. M. Trost, *Science* **1991**, 254, 1471–1477.
- [18] S. B. Beil, D. Pollok, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, 60, 14750–14759; *Angew. Chem.* **2021**, 133, 14874–14883.
- [19] A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, J. Schneider, S. R. Waldvogel, *ChemistryOpen* **2022**, 11, e202200059.
- [20] L. Kürti, B. Czako, *Strategic applications of named reactions in organic synthesis. Background and detailed mechanisms ; 250 named reactions*, Elsevier Acad. Press, Amsterdam, Heidelberg, **2009**.
- [21] a) H. Kolbe, *Justus Liebigs Ann. Chem.* **1848**, 64, 339–341; b) H. Kolbe, *Justus Liebigs Ann. Chem.* **1849**, 69, 257–294.
- [22] M. C. Leech, K. Lam, *Acc. Chem. Res.* **2020**, 53, 121–134.
- [23] a) H.-J. Schäfer in *Top. Curr. Chem.* (Hrsg.: M. J. S. Dewar, J. D. Dunitz, K. Hafner, E. Heilbronner, Š. Itô, J.-M. Lehn, K. Niedenzu, K. N. Raymond, C. W. Rees, F. Vögtle et al.), Springer Berlin Heidelberg, Berlin, Heidelberg, **1987**, S. 101–129; b) N. Kurig, R. Palkovits, *Green Chem.* **2023**, 25, 7508–7517; c) D. Klüh, W. Waldmüller, M. Gaderer, *Clean Technol.* **2021**, 3, 1–18.
- [24] J. Schneider, A. P. Häring, S. R. Waldvogel, *Chem. Eur. J.* **2024**, 30, e202400403.
- [25] S. Liu, N. Govindarajan, H. Prats, K. Chan, *Chem Catal.* **2022**, 2, 1100–1113.
- [26] a) P. Acosta - Guzmán, A. Ojeda - Porras, D. Gamba - Sánchez, *Adv. Synth. Catal.* **2023**, 365, 4359–4391; b) J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, 20, 140–177; c) J. Magano, *Org. Process Res. Dev.* **2022**, 26, 1562–1689; d) P. W. Seavill, J. D. Wilden, *Green Chem.* **2020**, 22, 7737–7759; e) A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, 111, 6557–6602.
- [27] a) P. Ertl, E. Altmann, J. M. McKenna, *J. Med. Chem.* **2020**, 63, 8408–8418; b) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, 59, 4443–4458.
- [28] D. M. Heard, A. J. J. Lennox, *Angew. Chem.* **2020**, 59, 18866–18884.
- [29] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, 61, e202204140; *Angew. Chem.* **2022**, 134, e202204140.
- [30] S. Lips, S. R. Waldvogel, *ChemElectroChem* **2019**, 6, 1649–1660.
- [31] a) J. Kalmár, K. L. Woldegiorgis, B. Biri, M. T. Ashby, *J. Am. Chem. Soc.* **2011**, 133, 19911–19921; b) T. J. Barrett, C. L. Hawkins, *Chem. Res. Toxicol.* **2012**, 25, 263–273.
- [32] J. Han, C. A. Haines, J. J. Pian, L. L. Filien, E. D. Nacsa, *J. Am. Chem. Soc.* **2023**, 145, 15680–15687.
- [33] C. A. Haines, J. Han, E. D. Nacsa, *Synlett* **2024**, 35, 1733–1738.
- [34] a) J. S. Elias, C. Costentin, D. G. Nocera, *J. Am. Chem. Soc.* **2018**, 140, 13711–13718; b) S. Manabe, C. M. Wong, C. S. Sevov, *J. Am. Chem. Soc.* **2020**, 142, 3024–3031.
- [35] J. Han, J. J. Pian, H. Gizenski, E. Elacqua, E. D. Nacsa, *Org. Lett.* **2025**, 27, 1923–1928.
- [36] H. Roth, N. Romero, D. Nicewicz, *Synlett* **2016**, 27, 714–723.
- [37] G. Hilt, *ChemElectroChem* **2020**, 7, 395–405.
- [38] A. J. Bard, L. R. Faulkner, H. S. White, *Electrochemical Methods. Fundamentals and Applications*, Wiley, Hoboken, NJ, USA, Chichester, West Sussex, UK, **2022**.
- [39] T. Shono, Y. Matsumura, K. Tsubata, T. Kamada, K. Kishi, *J. Org. Chem.* **1989**, 54, 2249–2251.
- [40] L. F. Tietze, *Chem. Rev.* **1996**, 96, 115–136.
- [41] a) X. Dong, J. L. Roeckl, S. R. Waldvogel, B. Morandi, *Science* **2021**, 371, 507–514; b) X. Dong, M. Klein, S. R. Waldvogel, B. Morandi, *Angew. Chem. Int. Ed.* **2023**, 62, e202217110; c) G. Hilt, *Curr. Opin. Electrochem.* **2024**, 43, 101425.
- [42] M. Breugst, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2020**, 59, 12293–12307; *Angew. Chem.* **2020**, 132, 12389–12404.

REVIEW

- [43] T. Wirtanen, T. Prenzel, J.-P. Tessonier, S. R. Waldvogel, *Chem. Rev.* **2021**, *121*, 10241–10270.
- [44] M. F. Hartmer, S. R. Waldvogel, *Chem. Commun.* **2015**, *51*, 16346–16348.
- [45] C. Gütz, V. Grimaudo, M. Holtkamp, M. Hartmer, J. Werra, L. Frensemeier, A. Kehl, U. Karst, P. Broekmann, S. R. Waldvogel, *ChemElectroChem* **2018**, *5*, 247–252.
- [46] a) C. Gütz, M. Bänziger, C. Bucher, T. R. Galvão, S. R. Waldvogel, *Org. Process Res. Dev.* **2015**, *19*, 1428–1433; b) V. Grimaudo, P. Moreno-García, A. Riedo, S. Meyer, M. Tulej, M. B. Neuland, M. Mohos, C. Gütz, S. R. Waldvogel, P. Wurz et al., *Analyt. Chem.* **2017**, *89*, 1632–1641; c) C. Gütz, M. Selt, M. Bänziger, C. Bucher, C. Römel, N. Hecken, F. Gallou, T. R. Galvão, S. R. Waldvogel, *Chem. Eur. J.* **2015**, *21*, 13878–13882; d) P. Moreno-García, M. J. de Gálvez-Vázquez, T. Prenzel, J. Winter, L. Gálvez-Vázquez, P. Broekmann, S. R. Waldvogel, *Adv. Mater.* **2024**, *36*, e2307461.
- [47] L. Tang, Z.-L. Wang, Y.-H. He, Z. Guan, *ChemSusChem* **2020**, *13*, 4929–4936.
- [48] K. Mahanty, A. Halder, S. de Sarkar, *Adv. Synth. Catal.* **2023**, *365*, 96–103.
- [49] E. Lunghi, A. M. van Koten, J. Schneider, S. R. Waldvogel, *J. Org. Chem.* **2025**; DOI: 10.1021/acs.joc.5c01155.
- [50] E. Lunghi, A. M. van Koten, J. Schneider, S. R. Waldvogel, *Electrochemical Dehydration of Sulfonic Acids to their Anhydrides*. ChemRxiv [preprint] 10.26434/chemrxiv-2025-wm3z6, **2025**.
- [51] C. Krumbiegel, F. A. Breitschaft, S. R. Waldvogel, *Chem. Commun.* **2025**, *61*, 11267–11270.
- [52] S. P. Blum, K. Hofman, G. Manolikakes, S. R. Waldvogel, *Chem. Commun.* **2021**, *57*, 8236–8249.
- [53] a) S. P. Blum, D. Schollmeyer, M. Turks, S. R. Waldvogel, *Chem. Eur. J.* **2020**, *26*, 8358–8362; b) M. M. Hielscher, J. Schneider, A. H. J. Lohmann, S. R. Waldvogel, *ChemElectroChem* **2024**, e202400360.
- [54] S. P. Blum, L. Schäffer, D. Schollmeyer, S. R. Waldvogel, *Chem. Commun.* **2021**, *57*, 4775–4778.
- [55] S. P. Blum, T. Karakaya, D. Schollmeyer, A. Klapars, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 5056–5062; *Angew. Chem.* **2021**, *133*, 5114.
- [56] a) A. de A Bartolomeu, F. A. Breitschaft, D. Schollmeyer, R. A. Pilli, S. R. Waldvogel, *Chem. Eur. J.* **2024**, *30*, e202400557; b) P.-C. Chien, F. A. Breitschaft, H. Kelm, S. R. Waldvogel, G. Manolikakes, *ChemSusChem* **2025**, e2500186.
- [57] F. A. Breitschaft, A. L. Saak, C. Krumbiegel, A. d. A. Bartolomeu, T. Weyhermüller, S. R. Waldvogel, *Org. Lett.* **2025**, *27*, 1210–1215.
- [58] a) H. Ohmori, H. Maeda, M. Kikuoka, T. Maki, M. Masui, *Tetrahedron* **1991**, *47*, 767–776; b) H. Maeda, T. Maki, H. Ohmori, *Tetrahedron Lett.* **1992**, *33*, 1347–1350; c) H. Maeda, T. Maki, H. Ohmori, *Chem. Lett.* **1995**, *24*, 249–250; d) H. Maeda, T. KOIDE, T. Maki, H. Ohmori, *Chem. Pharm. Bull.* **1995**, *43*, 1076–1080; e) Z. Xu, Y. Zheng, Z. Wang, X. Shao, L. Tian, Y. Wang, *Chem. Commun.* **2019**, *55*, 15089–15092; f) L. M. Großmann, V. Beier, L. Duttchenhofer, L. Lennartz, T. Opatz, *Chem. Eur. J.* **2022**, *28*, e202201768; g) Q. Guo, Y. Jiang, R. Zhu, W. Yang, P. Hu, *Angew. Chem. Int. Ed.* **2024**, *63*, e202402878.
- [59] a) X. Shao, Y. Zheng, V. Ramadoss, L. Tian, Y. Wang, *Org. Biomol. Chem.* **2020**, *18*, 5994–6005; b) Y. Wang, J. Xu, Y. Pan, Y. Wang, *Org. Biomol. Chem.* **2023**, *21*, 1121–1133.

REVIEW

Entry for the Table of Contents



Electrochemical dehydration reactions are a fascinating and underexplored field of research in the domain of electrosynthesis. They offer a sustainable alternative to hazardous and harsh dehydration reagents. In this review, we survey the recent progress that has been made in this emerging research topic.

The following results have been published in a peer-reviewed publication.^[104]

A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, **J. Schneider**, S. R. Waldvogel *

Beyond Kolbe and Hofer-Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids

ChemistryOpen **2022**, 11, e2022000

DOI: [10.1002/open.202200059](https://doi.org/10.1002/open.202200059)

License: CC BY-NC-ND 4.0

* Corresponding author

Explanation of my contribution:

The reactivity described in this publication was discovered by A. P. Häring in 2020. A. P. Häring, V. Kilian, **J. Schneider**, and B. R. Strücker carried out reaction optimization. All contributions by **J. Schneider** to this publication are based on his research module report “*Studies towards the synthesis of carboxylic anhydrides from carboxylic acids*” which he wrote for a research internship in the group of Prof. Dr. S. R. Waldvogel from Oct 17th – Nov 11th, 2020, as a part of his master studies in Chemistry. In the research module report, **J. Schneider** prepared part of the reaction scope, analyzed reaction products, and carried out initial experiments for the synthesis of cyclic anhydrides from dicarboxylic acids. A. P. Häring wrote the Supporting Information and was responsible for data analysis and curation. A. P. Häring was responsible for finishing the experimental results (reaction optimization, reaction scope, control experiments, compound characterization), and writing of the initial version of the manuscript, but it was rewritten and finished by D. Pollok and S. R. Waldvogel after A. P. Häring left Mainz University. S. R. Waldvogel supervised the project and assisted in writing of the manuscript and the Supporting Information.

Introduction: In 2020, the Waldvogel group observed the electrochemical dehydration of pivalic acid to pivalic anhydride.^[104] This observation was very surprising, because the electrolysis of carboxylic acids (Kolbe-electrolysis) had been known and studied for more than 170 years at that time.^[105] The Kolbe-reaction (and the Hofer-Moest reaction) are always characterized by a decarboxylation step.^[106] No decarboxylation was observed in this reaction. Instead, a non-decarboxylative dehydration reaction was discovered. This is interesting because dehydration reactions are some of the most important and fundamental reactions in all of chemistry, and they are usually not

considered to be redox reactions, since no oxidation states change in the substrate from which the water is eliminated. This reaction therefore hinted at an interesting link between dehydration reactions and electrolysis. The electrochemical valorization of carboxylic acids is important because they are naturally abundant, safe, inexpensive, and readily available starting materials.^[105] To optimize the reaction conditions, isobutyric acid **1h** was selected as test substrate. Because anhydrides are susceptible to hydrolysis, no isolated yields are reported for the reaction optimization. Instead, the yield was determined by using NMR spectroscopy and gas chromatography (GC) by using internal standards. The yield was optimized following the one-variable at a time approach. Based on the optimized reaction conditions, the scope was carried out along with mechanistic control experiments.

Optimization: As test reaction for the optimization of reaction conditions, the electrochemical synthesis of isobutyric anhydride **2h** from isobutyric acid **1h** was utilized (Figure 21). The standard reaction conditions are listed in Table 3. The reaction is carried out in acetonitrile and no other additive than a thiocyanate supporting electrolyte is required. Notably, high current densities can be employed (Table 3, entries 3–5). This allows for a fast electrolysis. However, the optimal yield was obtained for 50 mA cm⁻² (entry 1). Inert conditions did not result in an improved yield (entry 6). Employing supporting electrolytes such as TEABF₄ or LiClO₄ instead of KSCN resulted in yields of 15% and 18%, respectively (entries 7–8). Decreasing the concentration of the thiocyanate supporting electrolyte from resulted in a lower yield (entry 9). Increasing the applied charge to 1.5 *F* decreased the yield as well (entry 10). Platinum can be employed as anode instead of graphite (entry 11) which results in a yield of 52%. The reaction is carried out under mild reaction conditions, because heating did not increase the yield (entry 12). Changing the concentration of the starting material from 0.7 mol/L to 1.0 mol/L and 0.4 mol/L resulted in lower yields (entries 13–14). When employing *i*-PrCN instead of MeCN and EMIMSCN instead of KSCN, a yield of 33% was obtained (entry 15). In summary, the electrochemical dehydration of carboxylic acids is best carried out utilizing a starting material concentration of 0.7 mol/L, a concentration of thiocyanate supporting electrolyte of 0.1 mol/L, a current density of 50 mA cm⁻², and an applied charge of 1.1 *F* (entry 1). Graphite is used as anode material and stainless steel as cathode material. The reaction is carried out in acetonitrile at room temperature in an undivided cell.

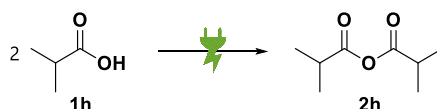


Figure 21. Isobutyric acid is employed as the test reaction for optimization of the electrochemical dehydration of carboxylic acids to their carboxylic anhydrides, which gives isobutyric anhydride.^[104]

Table 3. Optimization of the test reaction.^[104]

#	Deviation from standard conditions ^[a]	Yield 2h [%] ^[b]
1	None	58
2	No current	0
3	$j = 10 \text{ mA/cm}^2$	25
4 ^[c]	$j = 100 \text{ mA/cm}^2$	39
5 ^[c]	$j = 200 \text{ mA/cm}^2$	36
6 ^[d]	Inert conditions	40
7 ^[e]	TEABF ₄ instead of KSCN	15
8 ^[e]	LiClO ₄ instead of KSCN	18
9	$c(\text{KSCN}) = 0.05 \text{ M}$	37
10	$Q = 1.5 F$	44
11	Pt stainless steel	52
12	$T = 313 \text{ K}$	42
13 ^[f]	$c(\text{isobutyric acid}) = 1.0 \text{ M}$	45
14	$c(\text{isobutyric acid}) = 0.4 \text{ M}$	29
15 ^[g]	<i>i</i> -PrCN instead of MeCN and EMIMSCN instead of KSCN	33

[a] Reaction conditions: undivided cell, under air, 298 K, 0.7 M isobutyric acid (**1h**) in 5.0 mL MeCN, 0.10 M KSCN, 1.1 *F*, 50 mA/cm², graphite anode, stainless steel cathode; [b] Quantification by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard; [c] Cell temperature not controlled; [d] 7.0 mmol scale; [e] BDD anode; [f] Quantification by GC-FID with dibutyl fumarate as internal standard; [g] Conductivity with KSCN was too low to perform the experiment.^[104]

Scope: Acetic anhydride **2a** was obtained in 37% yield (Figure 22). Carboxylic anhydrides with longer chains or higher branching gave significantly higher yields and better selectivity (**2b–2k**). Notably, the reaction conditions tolerate double bonds (**2l**, **2m**), bromo substituents (**2n**, **2o**), and chloro substituents (**2p**). Sterically hindered carboxylic acids gave low yields (**2q**, **2r**). Carboxylic acids with a ketone function (**2s**), a TBS protected alcohol (**2t**), aromatic rests (**2u**, **2v**) and higher unsaturated fatty acids (**2w**, **2x**) were observed to give low yields. The in-situ generated trifluoromethanesulfonic anhydride (**2y**) was quenched with an excess of benzylamine to isolated product **3y** in 34% yield over 2 steps.

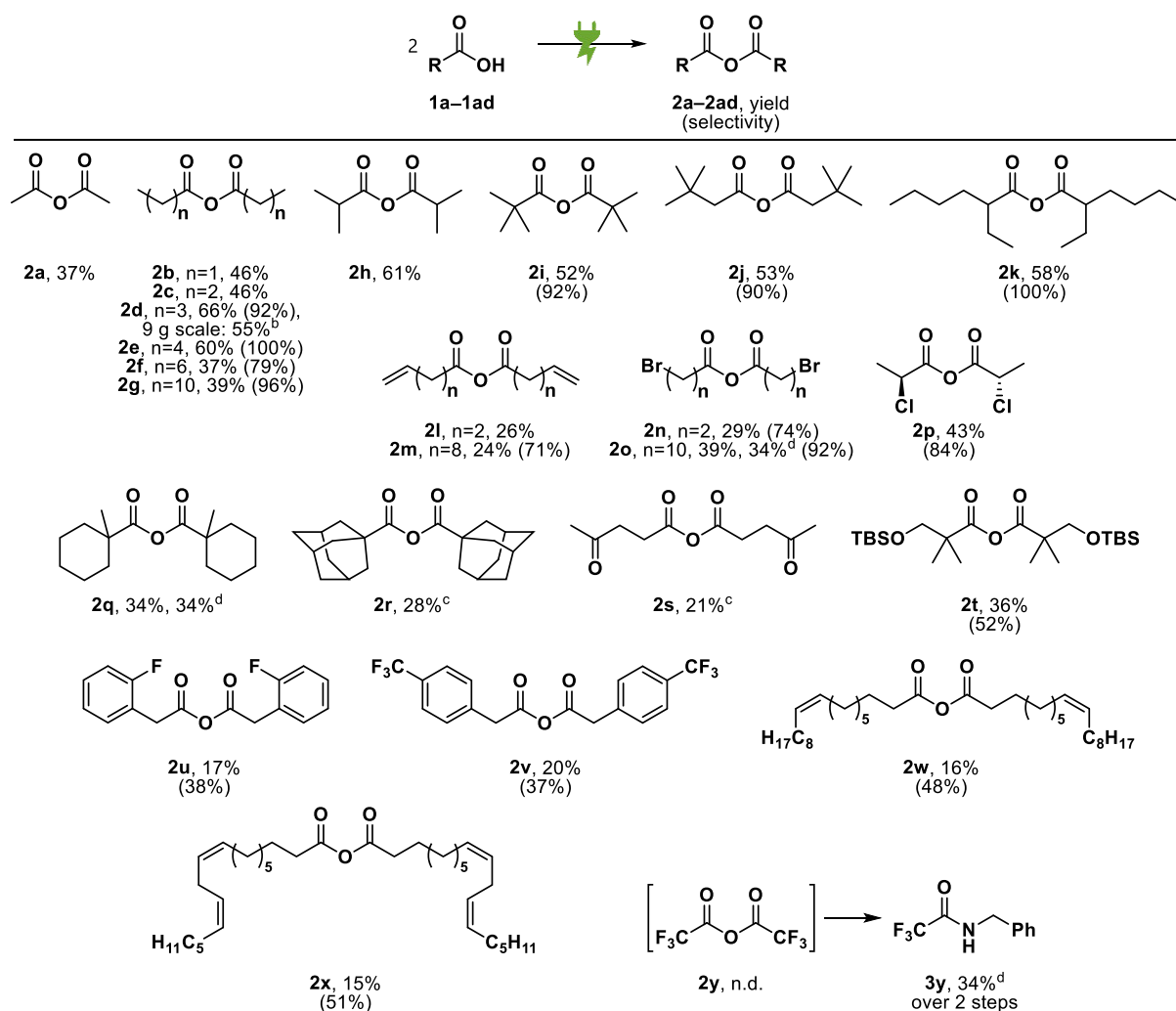


Figure 22. Scope of carboxylic anhydrides. [a] Reaction conditions: undivided cell, under air, 298 K, 0.7 mol/L carboxylic acid 1 in 5.0 mL MeCN, 0.10 mol/L KSCN, 1.1 F, 50 mA/cm², graphite anode, stainless steel cathode; Quantification by ¹H NMR with 1,3,5-trimethoxybenzene as internal standard. Selectivity = yield/conversion. For individual deviations from standard conditions see Supporting Information. [b] Quantification by GC-FID with dibutyl fumarate or dibromomethane as internal standard. [c] Quantification by inverse-gated ¹³C NMR with 1,3,5-trimethoxybenzene as internal standard. [d] Isolated yield.^[104]

Mechanistic Experiments: At the time of this publication,^[104] a mechanistic picture was not yet established, which was resolved in the follow-up work on the electrochemical dehydration of dicarboxylic acids to their cyclic anhydrides.^[107] Interestingly, the reaction is redox neutral with respect to the carboxylic acid and carboxylic anhydride, which was rather surprising considering that electrolysis is inherently linked to redox reactions. The electrolysis is carried out in an undivided cell. Only 1.1 F of charge is required. In combination with a current density of 50 mA cm⁻², this allows for a fast electrolysis. At the cathode, hydrogen evolution reaction (HER) was observed. No intermediates or side products could be observed which would give any hints on the mechanistic pathways. Especially the products of a Kolbe- or Hofer-

Moest reaction were absent. Because this reaction is an electrochemical dehydration reaction, the key to understanding the mechanism is to analyze where the water remains that is eliminated from the carboxylic acid starting material in the course of the reaction. Acetonitrile was utilized as solvent, but it does not act as the dehydration reagent, because the reaction can also be carried out in other solvents such as acetone.

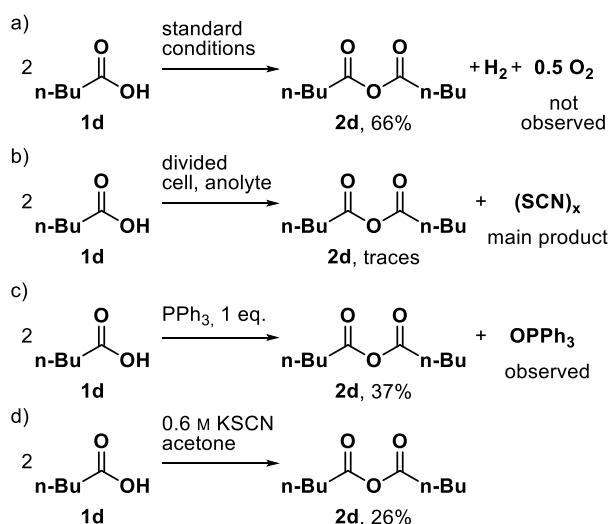


Figure 23. Control experiments on the electrochemical synthesis of carboxylic anhydrides from carboxylic acids.^[104]

By control experiments (Figure 23), it could be ruled out that oxygen is evolving from the reaction solution during electrolysis. Cyclic voltammetry (CV) studies revealed an irreversible oxidation of the thiocyanate supporting electrolyte. If the reaction is carried out in the anodic compartment of a divided cell setup, only traces of anhydride are observed. It was demonstrated that the carboxylic anhydride decomposes again in the course of the electrolysis. Interestingly, a yield higher than 50% could be achieved when using less than 0.5 equiv. of thiocyanate supporting electrolyte.

Conclusion: A conceptually new electrochemical dehydration reaction of carboxylic acids to their anhydrides was discovered. No conventional dehydration reagent is required. Interestingly, the reaction is formally redox neutral with respect to the carboxylic acid starting material. This observation was rather surprising, because while the electrolysis of carboxylic acids had been known and studied for more than 170 years, a non-decarboxylative dehydration reaction has never been reported before. Graphite and stainless steel are employed as inexpensive electrode materials. The reaction is carried out in an undivided cell using MeCN as solvent. In total, 25 carboxylic anhydrides were reported with yields up to 66%. The reaction conditions tolerate halogen substituents and olefins. Notably, the selectivity of this electro-dehydration reaction can be very high, in some cases over 95%.

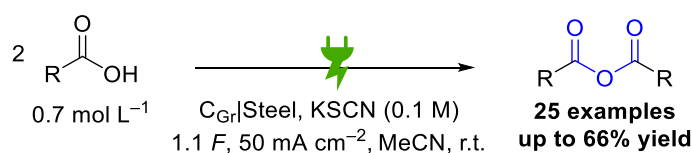


Figure 24. Electrochemical dehydration of carboxylic acids to carboxylic anhydrides.^[104]

Beyond Kolbe and Hofer–Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids

Andreas P. Häring, Dennis Pollok, Benjamin R. Strücker, Vincent Kilian, Johannes Schneider, and Siegfried R. Waldvogel^{*,[a]}

Herein we report a conceptually new non-decarboxylative electrolysis of carboxylic acids to obtain their corresponding anhydrides as highly valuable reagents in organic synthesis. All carbon atoms of the starting material are preserved in the product in an overall redox-neutral reaction. In a broad substrate scope of carboxylic acids the anhydrides are gen-

erated with high selectivity, which demonstrates the versatility of the developed method. Beneficially, no dehydrating reagents are required in comparison to conventional methods and the synthesis is based on uncritical starting materials using graphite and stainless steel as very inexpensive and eco-friendly electrode materials.

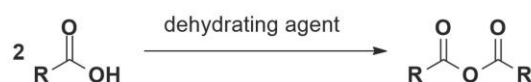
Introduction

Carboxylic acid anhydrides have been known for decades as versatile reagents and valuable reactive intermediates in organic synthesis.^[1] They demonstrate various advantages over their analogues, the carboxylic acid halogenides. The use of acid anhydrides does not free hydrogen halides as by-products which might interfere in the synthesis of complex structures, and the reaction is often rather mild in comparison with the corresponding acyl halogenide which facilitates more selective transformations. Carboxylic anhydrides are mainly used for the introduction of protective groups in natural product and active pharmaceutical ingredient (API) synthesis towards high-value esters and amides.^[2] Moreover, the anhydrides can also be employed as reagents to access a broad variety of different valuable structural motifs.^[3,4]

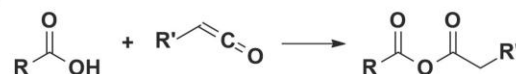
Their conventional synthesis is mostly performed starting from the corresponding carboxylic acids by addition of a dehydration agent; among others, highly toxic phosgene,^[5] thionyl chloride,^[6] phosphorus pentoxide,^[1] 1,2,3-triazines,^[7] or carbodiimides (Scheme 1) are routinely employed.^[8] Moreover, carboxylic acid anhydrides can be accessed using pre-functionalized substrates. The addition of carboxylic acids to ketenes and the oxidative cross-dehydrogenative coupling of aldehydes or alcohols are two of the possible routes.^[9] However, for these methods, non-commercial starting materials and toxic reagents

Synthesis of carboxylic acid anhydrides

a) Dehydration of carboxylic acids



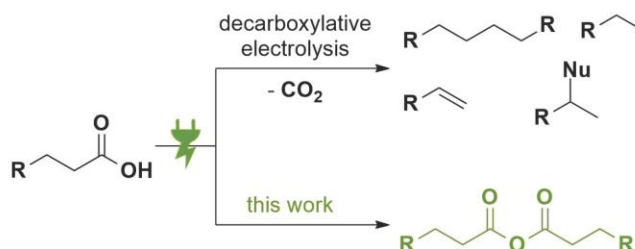
b) Addition to ketenes



c) Cross-dehydrogenative coupling



Electrolysis of carboxylic acids



Scheme 1. Conventional synthesis approaches of carboxylic acid anhydrides and electrolysis of carboxylic acids in organic media towards Kolbe, non-Kolbe, and Hofer–Moest products in comparison to this work.

are used, excessive thermal treatment is required, and low functional group tolerance is observed.^[9,10]

There is a recent, very acute and continuous urge for more sustainable synthetic methods which has led to a new dawn of organic electrosynthesis.^[11–15] In comparison to conventional synthesis, this method is highlighted by the means of economic and ecological benefits. The limitation of reagent waste by using electricity as a traceless activator obtained from renewable resources enables a sustainable synthesis protocol. With the use of carbon-based materials as electrodes, the synthesis can be performed metal-free which is of major interest in

[a] Dr. A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, J. Schneider, Prof. Dr. S. R. Waldvogel
Department of Chemistry
Johannes Gutenberg University Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: waldvogel@uni-mainz.de

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/open.202200059>

© 2022 The Authors. Published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

complex synthesis protocols of APIs.^[16] Moreover, the inherently safe character of an electrolysis should be also highlighted as no reaction can outrun when no current is applied. Additionally, using electricity has shown tremendous effects on the conversion of renewable resources toward the formation of valuable fine chemicals.^[17] In this case, carboxylic acids are important degradation components in the valorization of biomass to serve as sustainable reagent source.^[18–20]

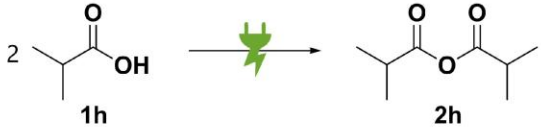
With respect to using carboxylic acids in electro-organic synthesis, seminal experiments have been performed by Kolbe in the 19th century, demonstrating the successful decarboxylation of such acids by application of electricity.^[21,22] Besides the well-known character of such recombined radical products, commonly denoted as Kolbe products, the non-Kolbe pathway includes a further subsequent anodic oxidation with an elimination leading to unsaturated products (Scheme 1). The intermediates in the latter pathway were trapped with the addition of nucleophiles like hydroxides as shown by Hofer and Moest.^[23] This results in a possible functionalization of the decarboxylated products with *O*-nucleophiles to enable access to a variety of compounds.^[24–27]

In this work we demonstrate a conceptually different outcome in the electrolysis of carboxylic acids towards the generation of their corresponding anhydrides without the observation of decarboxylated (non-)Kolbe products and without the requirement for additional dehydration agents.

Results and Discussion

The mechanism of the Kolbe reaction was studied extensively for more than a century.^[28] Surprisingly, even though carboxylic anhydrides were discussed as potential intermediates already at the end of the 19th century,^[29] neither any experimental evidence, nor the anhydrides themselves have ever been observed in the electrolysis of carboxylic acids. Our current study shows that Kolbe and non-Kolbe pathways can be completely suppressed, and carboxylic anhydrides are obtained instead. The formation of carboxylic anhydrides became evident for the first time when pivalic acid (**1i**) was electrolyzed at 100 mA cm^{−2} in acetonitrile using an undivided cell, graphite electrodes, and tetraethylammonium tetrafluoroborate (TEABF₄) as the supporting electrolyte. Intrigued by this result, we investigated several reaction parameters (for details, see the Supporting Information). Notably, throughout our studies, no decarboxylated products were found with the exception of *N*-tert-butylacetamide, which was formed as a side-product in the electrolysis of pivalic acid (**1i**). Isobutyric acid (**1h**) was then chosen as an appropriate model substrate for the investigation of the parameter set for electrolysis. Testing of electrode materials revealed graphite and stainless steel as the best anode and cathode materials, respectively. The influence of the anode material on the anhydride yield is low. Besides graphite, glassy carbon, boron-doped diamond (BDD),^[30] iridium-titanium mixed metal oxide (DSA[®]), and platinum, which is the material of choice for Kolbe electrolysis,^[31,32] gave similar yields (Table 1 entry 11, see Supporting Information). Graphite, as the most

Table 1. Optimization and control experiments.

		
#	Deviation from standard conditions ^[a]	Yield 2h [%] ^[b]
1	None	58
2	No current	0
3	$j = 10 \text{ mA cm}^{-2}$	25
4 ^[c]	$j = 100 \text{ mA cm}^{-2}$	39
5 ^[c]	$j = 200 \text{ mA cm}^{-2}$	36
6 ^[d]	Inert conditions	40
7 ^[e]	TEABF ₄ instead of KSCN	15
8 ^[e]	LiClO ₄ instead of KSCN	18
9	$c(\text{KSCN}) = 0.05 \text{ M}$	37
10	$Q = 1.5 \text{ F}$	44
11	Pt stainless steel	52
12	$T = 313 \text{ K}$	42
13 ^[f]	$c(\text{isobutyric acid}) = 1.0 \text{ M}$	45
14	$c(\text{isobutyric acid}) = 0.4 \text{ M}$	29
15 ^[g]	<i>i</i> -PrCN instead of MeCN and EMIMSCN instead of KSCN	33

[a] Reaction conditions: undivided cell, under air, 298 K, 0.7 M isobutyric acid (**1h**) in 5.0 mL MeCN, 0.10 M KSCN, 1.1 F, 50 mA cm^{−2}, graphite anode, stainless steel cathode; [b] quantification by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; [c] cell temperature not controlled; [d] 7.0 mmol scale; [e] BDD anode; [f] quantification by GC-FID with dibutyl fumarate as internal standard; [g] conductivity with KSCN was too low to perform the experiment.

economic choice, gives the highest yields but gets severely degraded when supporting electrolytes other than thiocyanates are used in acetonitrile. However, in the presence of thiocyanate, fouling can be suppressed. On the cathodic side, stainless steel, platinum, niobium, and nickel provide the highest yields, while copper, graphite, and glassy carbon show significantly lower yields. At 50 mA cm^{−2} in the presence of KSCN, platinum cathodes in acetonitrile show obvious corrosion^[31–33] in contrast to inexpensive stainless steel.

The supporting electrolyte has significant impact on the anhydride yield. Thiocyanate, a rather unusual anion for a supporting electrolyte, stands out from the others (Table 1, entries 7 and 8, see Supporting Information). Importantly, the formation of anhydrides is not limited to SCN[−] but occurs with most conventional supporting electrolytes, albeit in lower yields. In some experiments with SCN[−] as supporting electrolyte, the formation of an orange solid was observed (see Supporting Information), insoluble in common organic solvents and water. The infrared spectrum indicates the presence of parathiocyanogen (SCN)_x, an inorganic polymer,^[34] is formed from oxidation of SCN[−] and subsequent polymerization.^[35] Lowering the amount of potassium thiocyanate for optimized atom and cost efficiency does however not increase the yield of the desired product (Table 1, entry 9).

A variation of the applied current density revealed a maximum yield of the carboxylic anhydride **2h** at 50 mA cm^{−2} (Table 1, entry 3–5). Neither increasing the temperature of the reaction (Table 1, entry 12) nor a variation of the concentration

of the carboxylic acid (Table 1, entries 13 and 14) result in an increased yield of the desired product. However, with respect to the applied charge, a maximum was observed at 1.1 F with decreasing yields for higher amounts of charge (Table 1, entry 10; for detailed studies, see the Supporting Information). However, in these experiments we observed that the acid was not completely consumed at the end of the electrolysis. Corresponding control experiments with both the carboxylic acid and the corresponding anhydride present in the reaction mixture show that only up to 70% yield of additional anhydride is formed in the cell. Therefore, we postulate a depletion of the anhydrides at low concentrations of the carboxylic acids to take place.

The promising results in the reaction with isobutyric acid (**1h**) were then used to explore the scope of the reaction. The variety of investigated aliphatic carboxylic acids gave the

corresponding anhydrides with high selectivity (Figure 1). Notably, the NMR spectra and gas chromatograms of the crude reaction mixtures do not show any by-products (see Supporting Information).

Several functional groups, including double bonds (**2l**, **2m**, **2w**, **2x**) and halogen atoms (**2n**, **2o**, **2p**, **2u**, **2v**, **2y**) are tolerated. This valuable functional group tolerance is of high interest for subsequent functionalization in complex synthesis protocols. The low solubility of some longer-chain carboxylic acids in acetonitrile at room temperature was overcome by increasing the temperature to 313 K or by addition of EtOAc. With KSCN as the supporting electrolyte, caprylic acid (**1f**) and longer linear carboxylic acids quickly form a thick layer of potassium carboxylate on the cathode impeding electrical conductivity. With 1-ethyl-3-methylimidazolium thiocyanate (EMIMSCN) as the supporting electrolyte, no corrosion was visible at the

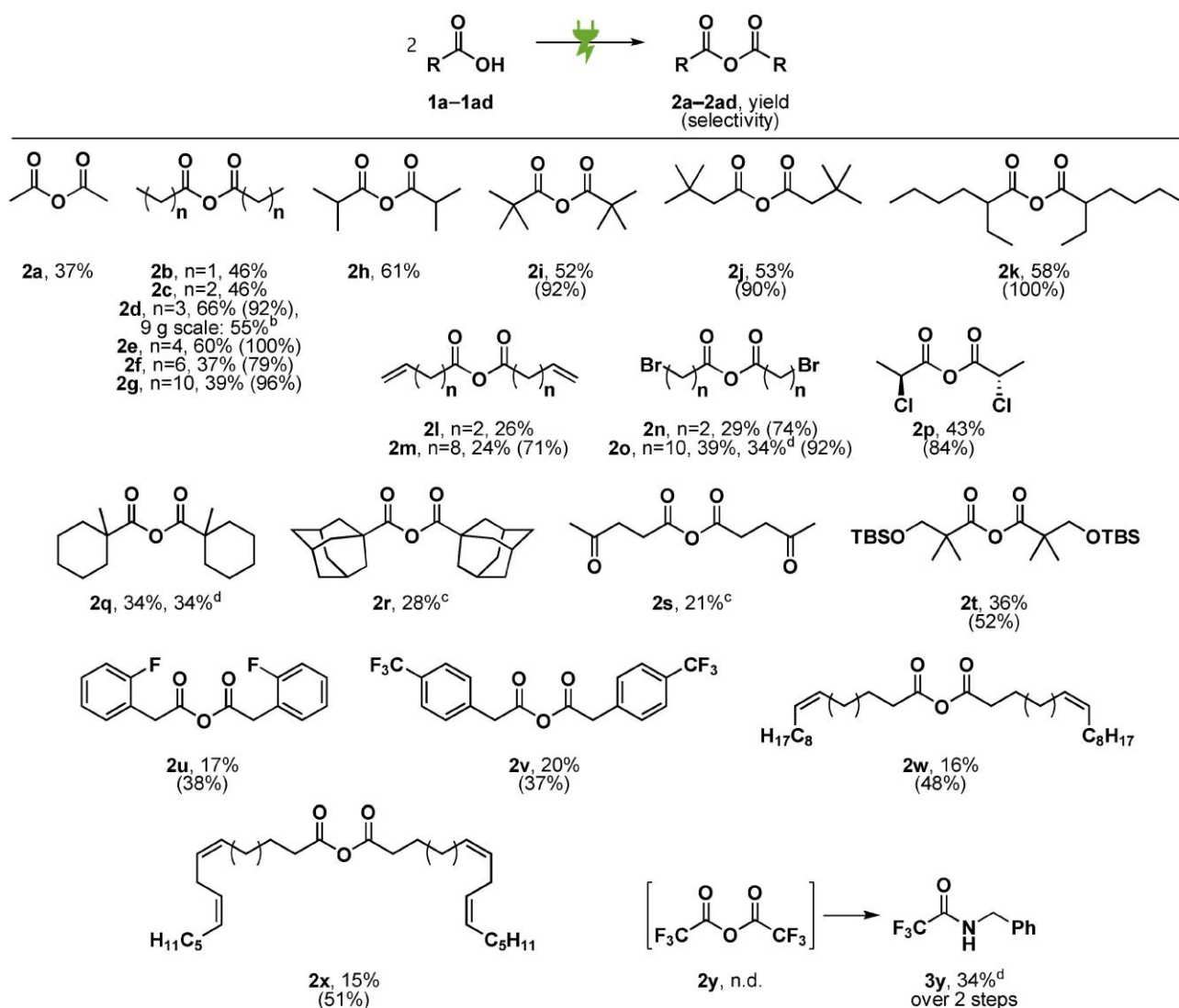
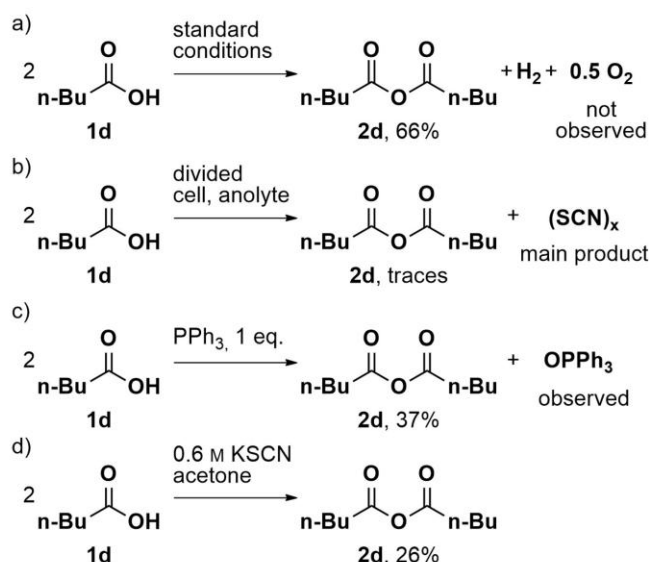


Figure 1. Electrochemically generated carboxylic anhydrides; [a] reaction conditions: undivided cell, under air, 298 K, 0.7 M carboxylic acid **1** in 5.0 mL MeCN, 0.10 M KSCN, 1.1 F, 50 mA cm⁻², graphite anode, stainless steel cathode; quantification by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; selectivity = yield/conversion; for individual deviations from standard conditions see Supporting Information; [b] quantification by GC-FID with dibutyl fumarate or dibromomethane as internal standard; [c] quantification by inverse-gated ¹³C NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; [d] isolated yield.

platinum surface. Changing to EMIMSCN as the supporting electrolyte restores conductivity and, furthermore, enables the conversion of long-chain fatty acids and carboxylic acids with dominating alkyl moieties (**2f**, **2g**, **2m**, **2o**, **2q**, **2r**, **2w**, **2x**). Due to its low boiling point, trifluoroacetic anhydride (**2y**) was not isolated but directly converted to *N*-benzyltrifluoroacetamide (**3y**). This demonstrates the in situ applicability of the generated carboxylic acid anhydrides in subsequent transformations. The electrolysis of valeric acid (**1d**) was successfully scaled up to 9 g (88 mmol), resulting in 55 % yield of **2d**.

In our hands, the carboxylic anhydrides could not be purified by chromatography on silica without the sacrifice of losing most or all the material. However, aqueous work-up with saturated NaHCO_3 and subsequent distillation, or filtration over silica and K_2CO_3 , gave analytically pure samples. The isolated yields match the yields determined by NMR quantification (**2o**, **2q**).

Peculiarly, no by-products were found in the crude reaction mixtures, as mentioned before. Acetamide, the obvious by-product from solvent oxidation, was not found in any experiment. The heterogeneous electron transfer from the electrode to the electrolyte, and vice versa, as well as the absence of any literature precedent render coming up with precise mechanistic model for the electrochemical formation of carboxylic anhydrides difficult at this point. Control experiments and experimental observations rule out some potential reaction pathways (Scheme 2). During electrolysis, gas evolution is observed at the cathode but not at the anode. Quick verification tests indicate hydrogen evolution but no oxygen evolution. These rule out water as stoichiometric by-product. However, at this time, the oxygenated species yet remains unidentified. We are confident that no O_2 is formed in the electrolysis (see mechanistic studies in the Supporting Information).



Scheme 2. Control experiments with deviations from standard conditions; Yields determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard; standard conditions: undivided cell, under air, 298 K, 0.70 M carboxylic acid in 5.0 mL MeCN, 0.10 M KSCN, 1.1 F, 50 mA cm^{-2} , graphite anode, stainless steel cathode.

Cyclic voltammetry (see Supporting Information) confirms the irreversible oxidation of SCN^- to $(\text{SCN})_x$ formed in trace amounts only, but does not provide any other insights.^[36] However, when the electrolysis is performed in the anode chamber of a divided cell, $(\text{SCN})_x$ is the main product, and the anhydride is only found in traces (Scheme 2b). In the presence of 1 equiv. PPh_3 , the yield of the anhydride is lowered to 37 % but formation of triphenylphosphine oxide is observed (Scheme 2c).^[37] Since there is no other source of oxygen present, it has to derive from the acid. We note that another mechanism might be active in this case and has to be investigated in further studies. With high probability, acetonitrile and KSCN can be ruled out as oxygen acceptors as compounds pointing in this direction could not be observed (Scheme 2d). Albeit in lower yields, anhydride **2d** is also formed in acetone, even in the absence of KSCN. Again, another mechanism might be at work here, but that notwithstanding, the reaction is unprecedented. Despite careful experimental analysis, we did not find an oxygenated by-product. The control experiments suggest that neither the solvent nor the supporting electrolyte are crucial for the anhydride formation, although thiocyanate has major influence on the yields of the products. Studies on the mechanism of the demonstrated transformation are ongoing in our laboratories, aiming to deepen our insight into this conceptually novel transformation.

Conclusion

In summary, we have discovered a conceptually new reaction pathway in the electrolysis of carboxylic acids, which enables the synthesis of carboxylic anhydrides without the need for a dehydrating agent. The use of thiocyanates as unusual supporting electrolytes is crucial to obtain the carboxylic anhydrides in reasonable yields. Products of Kolbe and non-Kolbe pathways have not been observed in the transformation of 25 different carboxylic acids under our conditions, potentially due to the absence of base. The direct electrochemical synthesis of carboxylic anhydrides from carboxylic acids can be expected to open broad applications in the valorization of carboxylic acids derived from renewable resources.

Experimental Section

Detailed information on reaction optimization, general procedures, and detailed product characterization can be found in the Supporting Information, including NMR spectra and GC chromatograms.

Acknowledgements

We are highly grateful to all members of the Waldvogel group for helpful discussions and support. A. P. H. thanks the state Rhineland-Palatinate for support in the frame of SusInnoScience. Financial support from the Verband der Chemischen Industrie (Kekulé Fellowship to D. P.) is highly acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carboxylic acids · carboxylic anhydrides · electrochemistry · electrosynthesis · sustainable chemistry

- [1] H. Held, A. Rengstl, D. Mayer, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2000, p. 3.
- [2] A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, 111, 6557–6602.
- [3] A. Alizadeh, M. M. Khodaei, E. Nazari, *Bull. Korean Chem. Soc.* **2007**, 28, 1854–1856.
- [4] Q. Chen, X.-H. Fan, L.-P. Zhang, L.-M. Yang, *RSC Adv.* **2014**, 4, 53885–53890.
- [5] R. Kocz, J. Roestamadj, S. Mobashery, *J. Org. Chem.* **1994**, 59, 2913–2914.
- [6] W. K. Fife, Z.-d. Zhang, *Tetrahedron Lett.* **1986**, 27, 4937–4940.
- [7] Z. J. Kamiński, B. Kolesińska, M. Małgorzata, *Synth. Commun.* **2004**, 34, 3349–3358.
- [8] A. Stadler, C. O. Kappe, *Tetrahedron* **2001**, 57, 3915–3920.
- [9] P. A. Keller, in *Category 3, Compounds with Four and Three Carbon Heteroatom Bonds* (Ed.: J. S. Panek), Georg Thieme Verlag, Stuttgart, 2006.
- [10] Z. Yang, S. Chen, F. Yang, C. Zhang, Y. Dou, Q. Zhou, Y. Yan, L. Tang, *Eur. J. Org. Chem.* **2019**, 5998–6002.
- [11] D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, 11, 12386–12400.
- [12] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, 117, 13230–13319.
- [13] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, 57, 5594–5619; *Angew. Chem.* **2018**, 130, 5694–5721.
- [14] E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, 2, 302–308.
- [15] S. B. Beil, D. Pollok, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, 60, 14750–14759; *Angew. Chem.* **2021**, 133, 14874–14883.
- [16] D. R. Abernethy, A. J. Destefano, T. L. Cecil, K. Zaidi, R. L. Williams, *Pharm. Res.* **2010**, 27, 750–755.
- [17] S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, 57, 6018–6041; *Angew. Chem.* **2018**, 130, 6124–6149.
- [18] D. Klüh, W. Waldmüller, M. Gaderer, *Clean Technol.* **2021**, 3, 1–18.
- [19] S. Palkovits, R. Palkovits, *Chem. Ing. Tech.* **2019**, 91, 699–706.
- [20] Q. Wu, X. Bao, W. Guo, B. Wang, Y. Li, H. Luo, H. Wang, N. Ren, *Biotechnol. Adv.* **2019**, 37, 599–615.
- [21] H. Kolbe, *Ann. Chem. Pharm.* **1848**, 64, 339–341.
- [22] H. Kolbe, *Ann. Chem. Pharm.* **1849**, 69, 257–294.
- [23] H. Hofer, M. Moest, *Justus Liebigs Ann. Chem.* **1902**, 323, 284–323.
- [24] J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. H. Reisberg, M. Chen, P. Mykhailiuk, G. Beutner, M. R. Collins, A. Davies, M. Del Bel, G. M. Gallego, J. E. Spangler, J. Starr, S. Yang, D. G. Blackmond, P. S. Baran, *Nature* **2019**, 573, 398–402.
- [25] M. Berger, J. D. Herszhan, Y. Kurimoto, G. H. M. de Kruijff, A. Schüll, S. Ruf, S. R. Waldvogel, *Chem. Sci.* **2020**, 11, 6053–6057.
- [26] G. H. M. de Kruijff, S. R. Waldvogel, *ChemElectroChem* **2019**, 6, 4180–4183.
- [27] X. Ma, D. F. Dewez, Le Du, X. Luo, I. E. Markó, K. Lam, *J. Org. Chem.* **2018**, 83, 12044–12055.
- [28] H.-J. Schäfer, in *Topics in Current Chemistry* (Ed.: E. Steckhan), Springer-Verlag, Berlin/Heidelberg, 1990, pp. 91–151.
- [29] C. Schall, *Z. Elektrochem.* **1896**, 3, 83.
- [30] S. Lips, S. R. Waldvogel, *ChemElectroChem* **2019**, 6, 1649–1660.
- [31] A. I. Yanson, P. Rodriguez, N. Garcia-Araez, R. V. Mom, F. D. Tichelaar, M. T. M. Koper, *Angew. Chem. Int. Ed.* **2011**, 50, 6346–6350; *Angew. Chem.* **2011**, 123, 6470–6474.
- [32] T. J. P. Hersbach, A. I. Yanson, M. T. M. Koper, *Nat. Commun.* **2016**, 7, 12653.
- [33] T. Wirtanen, T. Prenzel, J.-P. Tessonnier, S. R. Waldvogel, *Chem. Rev.* **2021**, 121, 10241–10270.
- [34] H. A. Früchtl, T. van Mourik, C. J. Pickard, J. D. Woollins, *Chem. Eur. J.* **2009**, 15, 2687–2692.
- [35] P. Krishnan, *J. Solid State Electrochem.* **2007**, 11, 1327–1334.
- [36] A. Gitkis, J. Y. Becker, *Electrochim. Acta* **2010**, 55, 5854–5859.
- [37] H. Maeda, T. Maki, H. Ohmori, *Chem. Lett.* **1995**, 24, 249–250.

Manuscript received: March 21, 2022

Revised manuscript received: April 17, 2022

The following results have been published in a peer-reviewed publication.^[107]

J. Schneider, A. P. Häring, S. R. Waldvogel *

Electrochemical Dehydration of Dicarboxylic Acids to Their Cyclic Anhydrides

Chem. Eur. J. **2024**, 202400403

DOI: [10.1002/chem.202400403](https://doi.org/10.1002/chem.202400403)

License: CC BY 4.0

* Corresponding author

Explanation of my contribution:

Based on the initial results from A. P. Häring, S. R. Waldvogel instructed **J. Schneider** to complete the study on the electrochemical dehydration of dicarboxylic acids to their cyclic anhydrides so these results can be published. **J. Schneider** was responsible for obtaining all experimental results which are in the publication. **J. Schneider** carried out reaction optimization, reactions of the scope, ¹⁸O isotope labelling experiments, gas chromatography experiments for the determination of hydrogen evolution reaction (HER), cyclic voltammetry (CV) studies, and the derivatization (amidation) reactions. The proposed reaction mechanism was conceptualized by **J. Schneider** and S. R. Waldvogel based on the experimental results. **J. Schneider** wrote the manuscript and the Supporting Information, and A. P. Häring assisted in writing of the manuscript. An entirely new reaction optimization was carried out by **J. Schneider** based on the groundwork of A. P. Häring. The dicarboxylic acids which were employed by A. P. Häring in his initial experiments were re-evaluated by **J. Schneider** using the new optimized reaction conditions. All analytical data for the publication and the Supporting Information were obtained by **J. Schneider**. S. R. Waldvogel supervised the project and assisted in writing of the manuscript and the Supporting Information.

Introduction: Based on the initial publication from the Waldvogel group,^[104] it was decided to extend the electrochemical dehydration of carboxylic acids to dicarboxylic acids as starting materials in a follow-up publication, which give the corresponding cyclic anhydrides as products. The reaction conditions were optimized further. The in-situ generated anhydrides were employed in amidation reactions (Figure 25). In addition, mechanistic studies were carried out to formulate a proposed mechanism.^[107]

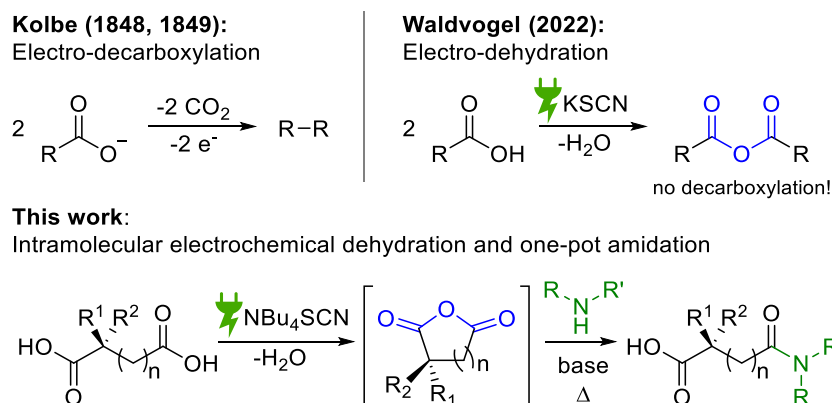


Figure 25. Comparison of the Kolbe-electrolysis with electrochemical dehydration of carboxylic acids to their anhydrides.^[107]

Optimization: The reaction optimization was carried out using succinic acid, which gave succinic anhydride **1**. The standard reaction conditions are depicted in Figure 26, which gave an NMR yield of 70% (Table 4, entry 1). Testing various amounts of applied charge of 2.4 *F*, 3.0 *F*, and 3.3 *F* resulted in NMR yields of 45%, 69%, and 66%, respectively (entries 2–4). The standard conditions (entry 1) employ 2.7 *F*, which hence is the optimum amount of applied charge. Changing the current density from 50 mA cm⁻² (standard reaction conditions, entry 1) to 30 mA cm⁻² or 70 mA cm⁻² resulted in yields of 58% and 59% (entries 5–6). Using a current density of 70 mA cm⁻² with 3.0 *F* did also not increase the yield (64%, entry 7) compared with standard reaction conditions (entry 1). As anode material, glassy carbon or graphite can be employed as alternative to BDD, albeit with lower yields of 50% yield in both cases (entries 8–9). However, for graphite, electrode decomposition was observed. Using BDD as electrode material for both anode and cathode resulted in only 16% yield (entry 10). Neither cooling (entry 11) nor heating (entry 12) of the reaction solution gave an increase in yield compared with the standard reaction conditions. Changing the concentration of the starting material (entries 13–14) did also not improve the yield. While employing less thiocyanate supporting electrolyte than the standard reaction conditions resulted in lower yield (entry 15), increasing it to 1.0 equiv. or 1.5 equiv. did not increase the yield significantly (entries 16–17). When replacing NBu₄SCN with EMIMSCN, BMIMSCN or NH₄SCN, yields of 36%, 19%, and 3% were obtained, respectively (entries 18–19). In the case of NH₄SCN, the upper terminal voltage limit of the power supply was reached, and the electrolysis had to be stopped after 2.1 *F* (entry 20). Without NBu₄SCN or without electricity, no anhydride product was found (entries 21–22). In summary, the standard reaction conditions in Figure 26 (Table 4, entry 1) are the optimal reaction conditions.

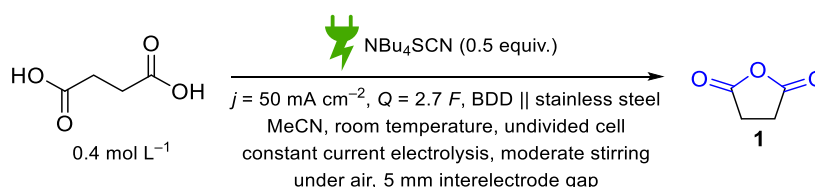


Figure 26. Electrochemical dehydration of succinic acid to succinic anhydride.^[107]

Table 4. Optimization of the electrochemical dehydration of succinic acid to succinic anhydride.^[107]

#	Deviation from standard conditions (Figure 26)	NMR yield ^[a]
1	none	70
2	2.4 <i>F</i>	45
3	3.0 <i>F</i>	69
4	3.3 <i>F</i>	66
5	30 mA cm ⁻²	58
6	60 mA cm ⁻²	59
7	70 mA cm ⁻² , 3.0 <i>F</i>	64
8	glassy carbon stainless steel	50
9	graphite stainless steel	50 ^[b]
10	BDD BDD	16
11	0 °C	58
12	60 °C	55
13	1.5 mmol SM, <i>c</i> (SM) = 0.3 mol L ⁻¹	44
14	2.5 mmol SM, <i>c</i> (SM) = 0.5 mol L ⁻¹	59
15	0.3 equiv. NBu ₄ SCN	31
16	1.0 equiv. NBu ₄ SCN	71
17	1.5 equiv. NBu ₄ SCN	70
18	no NBu ₄ SCN, 0.5 equiv. EMIMSCN	36
19	no NBu ₄ SCN, 0.5 equiv. BMIMSCN	19
20	no NBu ₄ SCN, 1.0 equiv. NH ₄ SCN	3 ^[c]
21	no NBu ₄ SCN	0 ^[d]
22	no electricity	0

SM: starting material (dicarboxylic acid). BDD: boron-doped diamond. EMIMSCN: 1-ethyl-3-methylimidazolium thiocyanate. BMIMSCN: 1-butyl-3-methylimidazolium thiocyanate. [a] The yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] The upper terminal voltage limit of the power supply was reached during electrolysis, nonetheless 2.7 *F* was fully applied. [c] The reaction had to be stopped after 2.1 *F* because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes. [d] The electrolysis can't be carried out without NBu₄SCN, because the upper terminal voltage limit of the power supply is reached, demonstrating that the thiocyanate supporting electrolyte is indispensable for the reaction.

Scope: Succinic anhydride **1**, 2-methyl succinic anhydride **2**, and 2,2-dimethylsuccinic anhydride **3** were obtained in NMR yields of 71%, 56%, and 66%, respectively (Figure 27). The yield for 2-phenylsuccinic anhydride **4** was only 16%, likely because of the steric bulk of the phenyl substituent. Maleic anhydride **5** was found in traces, which could be due to side reactions of the double bond. *cis*-Cyclopentane-1,2-dicarboxylic anhydride **6** was obtained in 62% yield, and *cis*-cyclohexane-1,2-dicarboxylic anhydride **7** in 57% yield. *cis*-4-Cyclohexene-1,2-dicarboxylic anhydride **8** was observed in only 17% yield. The terpene derived carboxylic anhydrides **9** and **10** were found in high yields of 67% and 60%, respectively. Glutaric anhydride **11**, 2,2-dimethyl glutaric anhydride **12**, and 3,3-dimethylglutaric anhydride **13** were obtained in 59%, 52%, and 46%, respectively. 1,1-Cyclopentanediacetic anhydride **14** was found in 57% yield, and 1,1-cyclohexanediacetic anhydride **15** in 64%. Anhydrides of dicarboxylic acids with longer chains (products **16–20**) were observed in yields of 19%–36%.

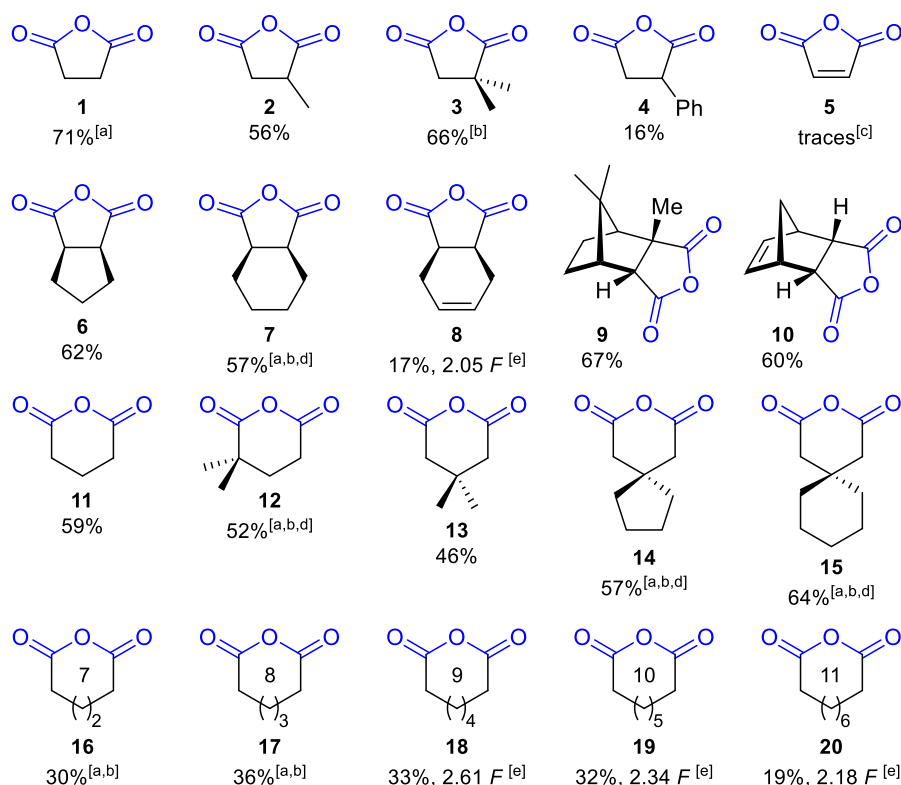


Figure 27. Anhydride scope. The electrolysis conditions of Figure 26 were applied as standard reaction conditions. The yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [a] 1.0 equiv. NBu_4SCN . [b] 3.0 F. [c] The upper terminal voltage limit of the power supply was reached during electrolysis, but 2.7 F of charge were fully applied. [d] MeCN / isobutyronitrile 2:1 (vol%). [e] The electrolysis had to be stopped after the mentioned amount of applied charge because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes.^[107]

Amide Synthesis and Scale-up: The cyclic anhydrides which are generated in-situ by electrolysis can be employed in amidation reactions (Figure 28 and Table 5). Benzylamine gave higher yields than morpholine when employed with succinic anhydride. Entry 3 in Table 5 was carried out in a 10-fold scale-up, which gave 58% isolated yield over 2 steps (NMR yield: 61%).

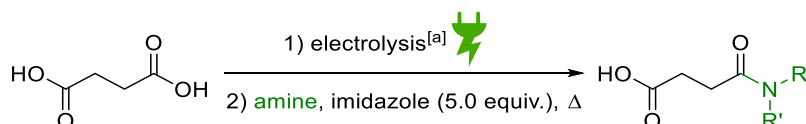


Figure 28. Amidation test reaction. [a] electrolysis reaction conditions: MeCN, succinic acid (0.4 mol L⁻¹), NBu₄SCN (1.0 equiv.) constant current electrolysis, current density $j = 50 \text{ mA cm}^{-2}$, amount of applied charge $Q = 3.0 F$, BDD || stainless steel, 5 mm interelectrode gap, under air, moderate stirring.^[107]

Table 5. Optimization of the amidation test reaction.^[107]

#	Deviation from standard conditions (Figure 28)	NMR yield ^[a]
1	benzylamine (5.0 equiv.), no imidazole	68
2	benzylamine (5.0 equiv.)	71
3	benzylamine (5.0 equiv.), no imidazole, DMAP (0.05 equiv.)	73
4	benzylamine (5.0 equiv.), DMAP (0.05 equiv.)	72
5	morpholine (5.0 equiv.), no imidazole	36
6	morpholine (5.0 equiv.)	31
7	morpholine (5.0 equiv.), no imidazole, DMAP (0.05 equiv.)	38
8	morpholine (5.0 equiv.), DMAP (0.05 equiv.)	32

DMAP: 4-(dimethylamino)pyridine. [a] The amide yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.^[107]

CV Measurements: Cyclic voltammetry (CV) studies were carried out (Figure 29). As a supporting electrolyte for CV measurements, a solution of NEt₄BF₄ (0.1 mol/L in MeCN) was utilized. No anodic current peak was observed for succinic acid (starting material) or succinic anhydride (product). The solution of NBu₄SCN did show an anodic current peak at +2.31 V. Interestingly, there is a shift of this peak towards +1.68 V when NBu₄SCN is mixed with succinic acid. This peak shifts to +1.31 V when NBu₄SCN is in solution with succinic anhydride. This result indicates that the formation of an intermediate which facilitates electron transfer could occur. Succinic anhydride did not show any peak in the cathodic current. NBu₄SCN does also not show any cathodic current peak. Succinic acid however does show a cathodic current peak at -3.01 V, and the cathodic current peak shifts towards -1.57 V when mixed with NBu₄SCN.

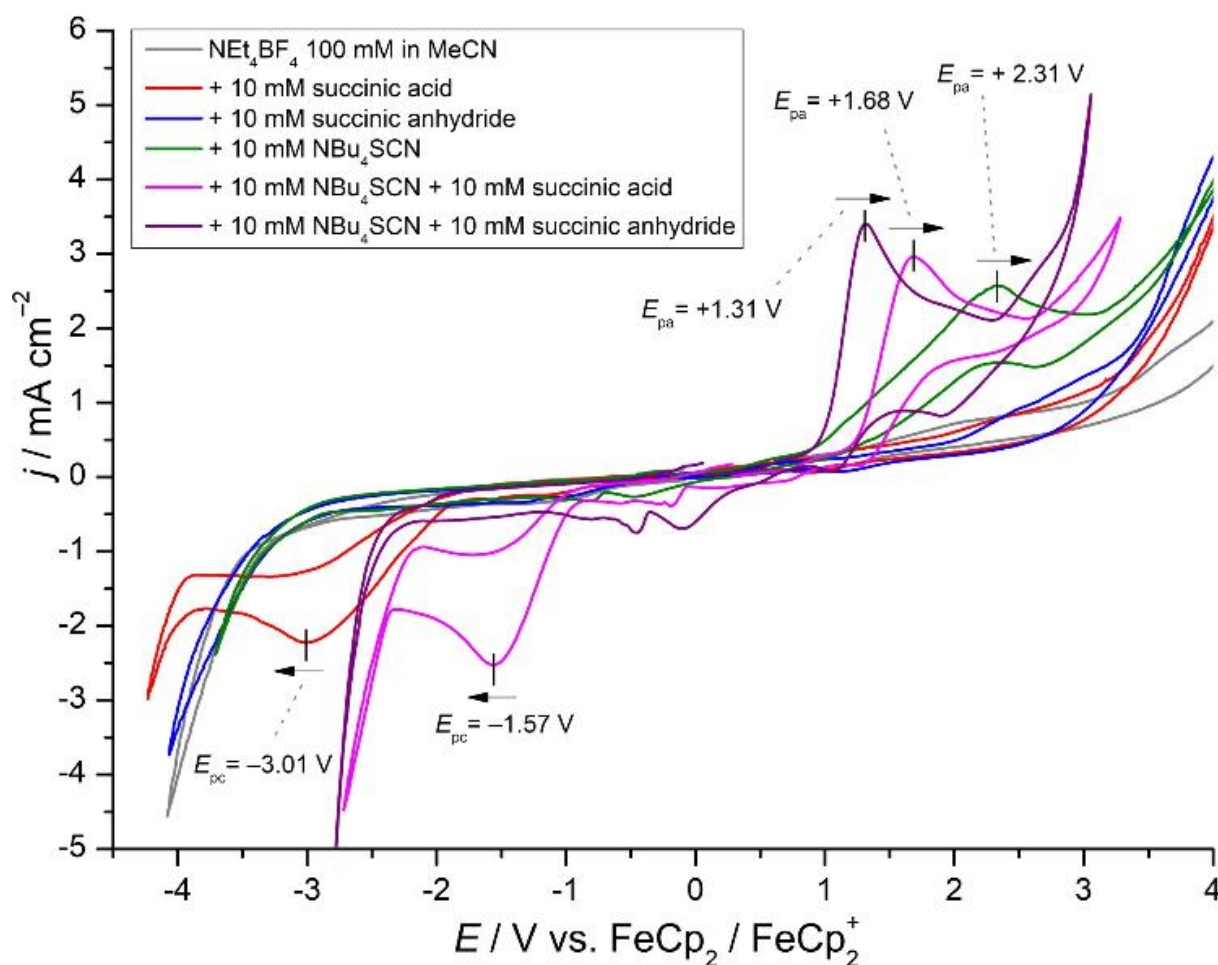


Figure 29. Cyclic voltammetry (CV) measurements. Working electrode: boron-doped diamond (BDD, circular electrode with diameter 2 mm), counter electrode: Pt wire, reference electrode: Ag/AgCl in EtOH/saturated LiCl; Sweep rate: 0.1 V/s. One cycle was measured for each sample starting from 0 V to towards anodic current, then cathodic current, and back to 0 V. All CV measurements were carried out under argon atmosphere. Each CV measurement was referenced against ferrocene.^[107]

Mechanism: The proposed reaction mechanism is depicted in Figure 30. The thiocyanate supporting electrolyte undergoes initial anodic oxidation, which forms an active ester with the carboxylic acid to activate the OH group. Substitution leads to elimination of hypothiocyanite and the formation of the carboxylic anhydride product. The hypothiocyanite can undergo further oxidation, which results in the formation of sulfate in the final step. By ¹⁸O isotope labelling of the carboxylic acid starting material, the formation of sulfate was detected via high resolution mass spectrometry (HRMS) measurements. Hydrogen evolution reaction (HER) at the cathode was proven via gas chromatography (GC). The proposed mechanism represents a simplified picture, because thiocyanates can undergo various other reactions.^[108]

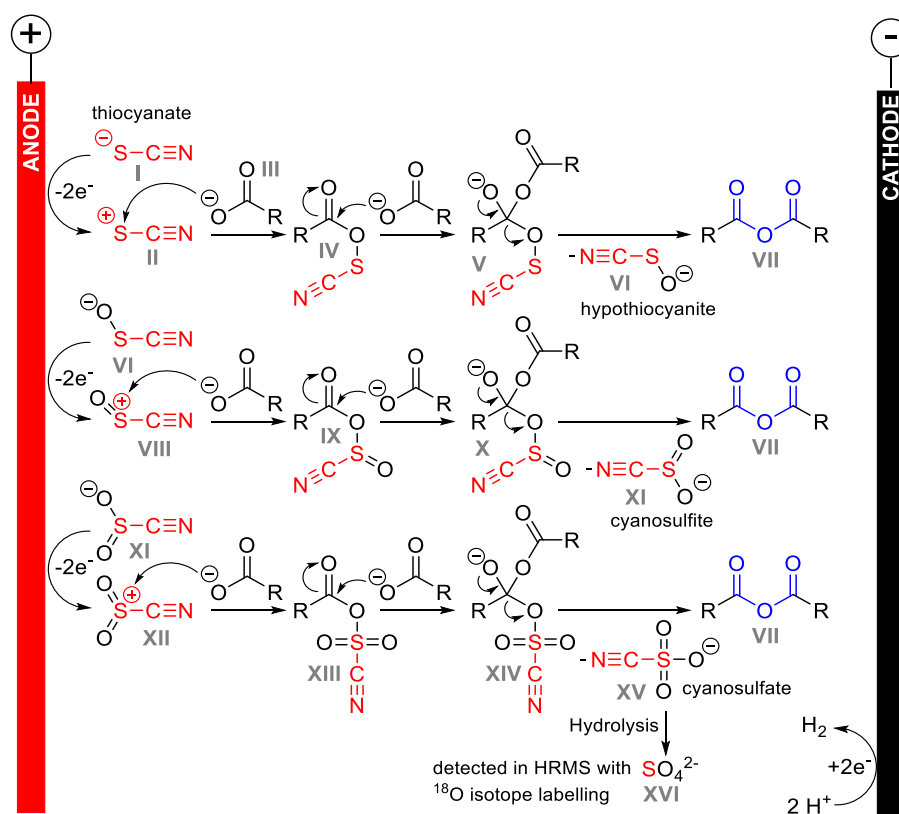


Figure 30. The proposed reaction mechanism of the electrochemical dehydration of carboxylic acids to their carboxylic anhydrides.^[107]

Conclusion: The electrochemical dehydration of carboxylic acids to the corresponding carboxylic anhydrides was successfully extended to dicarboxylic acids, which allowed for the electrochemical synthesis of cyclic anhydrides. No conventional dehydration reagent is required. In total, 20 examples were demonstrated with NMR yields up to 71%. Mechanistic studies revealed the hydrolysis of the thiocyanate supporting electrolyte as electro-generated dehydration reagent. No conventional dehydration reagent is employed. The mechanism was investigated using ^{18}O labelling, cyclic voltammetry (CV) studies. The cyclic carboxylic anhydrides which were generated in-situ by electrolysis can be employed in amidation reaction to obtain amides with a ω -carboxylic acid side chain, which allows for further functionalization.

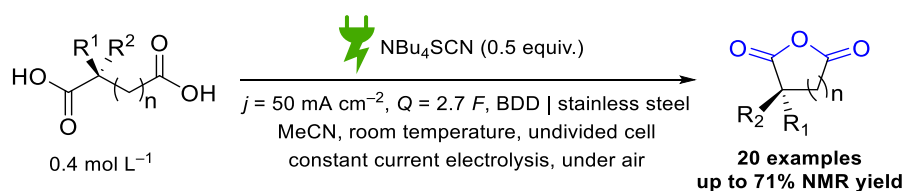


Figure 31. Electrochemical dehydration of dicarboxylic acids to their anhydrides.^[107]

Electrochemical Dehydration of Dicarboxylic Acids to Their Cyclic Anhydrides

Johannes Schneider,^[a] Andreas P. Häring,^[a] and Siegfried R. Waldvogel^{*,[a, b, c]}

An intramolecular electrochemical dehydration reaction of dicarboxylic acids to their cyclic anhydrides is presented. This electrolysis allows dicarboxylic acids as naturally abundant, inexpensive, safe, and readily available starting materials to be transformed into carboxylic anhydrides under mild reaction conditions. No conventional dehydration reagent is required. The obtained cyclic anhydrides are highly valuable reagents in organic synthesis, and in this report, we use them in-situ for acylation reactions of amines to synthesize amides. This work is part of the recent progress in electrochemical dehydration,

which – in contrast to electrochemical dehydrogenative reactions for example – is an underexplored field of research. The reaction mechanism was investigated by ¹⁸O isotope labeling, revealing the formation of sulfate by electrochemical oxidation and hydrolysis of the thiocyanate-supporting electrolyte. This transformation is not a classical Kolbe electrolysis, because it is non-decarboxylative, and all carbon atoms of the carboxylic acid starting material are contained in the carboxylic anhydride. In total, 20 examples are shown with NMR yields up to 71 %.

Introduction

Carboxylic anhydrides are highly valuable reagents in organic synthesis, commonly used in acylation reactions of amines for the synthesis of amides.^[1] Amidation reactions like these are of utmost importance in organic synthesis from laboratory to industrial scale,^[2] since amides are among the most common functional groups in medicinal chemistry.^[3] The valorization of carboxylic acids is important because they are naturally abundant, inexpensive, safe, and readily available starting materials.^[4] Due to the reluctant use of fossil feedstock, such valorization must proceed in a renewable manner.^[5] Conventional synthetic approaches to anhydrides require the use of hazardous dehydration reagents, which commonly result in harsh reaction conditions, accompanied by the generation of reagent waste.^[6] Organic electrosynthesis, which is currently experiencing a remarkable renaissance,^[7] offers several advantages that are required for such renewable processes.^[8] Electro-organic reactions are typically carried out under mild reaction

conditions. The use of electricity as inexpensive and universal redox reagent, which should preferably originate from renewable energy sources, prevents the formation of reagent waste.^[9] In 2022, our group reported the first electrochemical synthesis of carboxylic anhydrides directly from carboxylic acids.^[10] In this conceptually new, non-decarboxylative reaction, carboxylic acids are electrochemically dehydrated to their corresponding anhydrides under mild conditions. This finding was rather surprising, since the electrolysis of carboxylic acids, known as the Kolbe electrolysis, had been known and studied already for more than 170 years (Figure 1).^[11] Even more so, it is Herrmann Kolbe's publications from 1848 and 1849 that mark a cornerstone of organic electrosynthesis.^[12] Despite this, an electrochemical dehydration of carboxylic acids had not been reported before. Although electrochemical amide bond formation is a hot topic,^[13] the electrochemical dehydrative electrolysis represents an underexplored field of research, which has only recently received attention.^[14] This is in strong contrast to electrochemical dehydrogenative coupling reactions for example, which have been studied to great extent already.^[15]

[a] J. Schneider, Dr. A. P. Häring, Prof. Dr. S. R. Waldvogel

Department of Chemistry
Johannes Gutenberg University
Duesbergweg 10–14, 55128 Mainz (Germany)

[b] Prof. Dr. S. R. Waldvogel
Karlsruhe Institut für Technologie
Kaiserstraße 12,
76131 Karlsruhe (Germany)

[c] Prof. Dr. S. R. Waldvogel
Max-Planck-Institute for Chemical Energy Conversion (MPI CEC)
Stiftstraße 34–36, 45470 Mülheim an der Ruhr (Germany)
E-mail: siegfried.waldvogel@cec.mpg.de

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/chem.202400403>

© 2024 The Authors. Chemistry – A European Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

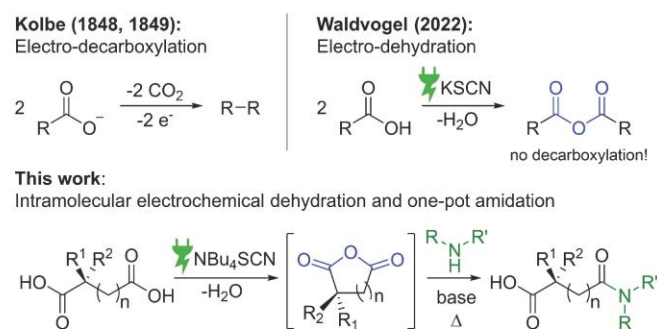


Figure 1. The Kolbe reaction is an electro-decarboxylation, whereas this reaction we reported is a non-decarboxylative dehydrative electrolysis, in which all carbon atoms of the carboxylic acid are preserved in the carboxylic anhydride.

Considering the enormous importance of dehydration reactions in organic synthesis,^[1] electrochemical dehydrations could offer many new interesting reactivities to explore, which will help to eliminate commonly accepted limits and myths about synthetic electrochemistry.^[16]

In this report, we further developed the electrochemical dehydration of dicarboxylic acids for the synthesis of cyclic carboxylic anhydrides. The obtained anhydrides were used in-situ for acylation reactions of amines to synthesize amides that contain an ω -carboxylic acid side chain, which allows for further functionalization.

Results and Discussion

To optimize the reaction, the conditions shown in Table 1 were applied to the test reaction depicted in Figure 2, in which succinic acid is electrochemically dehydrated to succinic anhydride. The yields were determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. It is known from our initial publication that the highest yields are obtained with thiocyanates as supporting electrolytes,^[10] hence NBu₄SCN was chosen as supporting electrolyte in this work, which offers higher solubility with dicarboxylic acids compared with KSCN. The standard reaction conditions (Table 1, entry 1) gave succinic anhydride in 70% yield. Using only 2.4 F resulted in a decreased yield of 45% (entry 2). Increasing the amount of applied charge to 3.0 F or 3.3 F led to 69% (entry 3) and 66% (entry 4), respectively. A current density of 30 mA cm⁻² or 60 mA cm⁻² gave 58% (entry 5) and 59% (entry 6) yield, respectively. An even higher current density of 70 mA cm⁻² combined with a higher amount of applied charge of 3.0 F resulted in 64% yield (entry 7). Next, other electrode materials were tested. For glassy carbon as anode material (entry 8), 50% yield was found and for graphite as anode material (entry 9), 50% yield was observed as well. Using BDD (boron-doped diamond)^[17] as metal-free electrode material for both anode and cathode resulted in only 16% yield (entry 10). This underlines the importance of the counter reaction in electro-organic synthesis and optimization.^[18] Based on these results, all further reactions were carried out using BDD as anode material and stainless steel as cathode material. The reaction should be carried out at room temperature because cooling it to 0 °C gave 58% yield (entry 11) and heating it to 60 °C gave 55% yield (entry 12). Diluting the electrolyte to 0.3 mol L⁻¹ succinic acid gave 44% yield (entry 13), while carrying out the reaction at 0.5 mol L⁻¹ resulted in 59% yield (entry 14). Using 0.3 equiv. NBu₄SCN instead of 0.5 equiv. resulted in a lower yield of 31% (entry 15). This could be because thiocyanates can undergo other electrochemical oxidation reactions which do not contribute to electrochemical dehydration.^[19] Increasing it to 1.0 equiv. or 1.5 equiv. gave 71% (entry 16) and 70% (entry 17), respectively. Using the ionic liquids 1-ethyl-3-methylimidazolium thiocyanate (EMIMSCN) or 1-butyl-3-methylimidazolium thiocyanate (BMIMSCN) instead of NBu₄SCN as supporting electrolyte resulted in 36% and 19% yield, respectively (entries 18 and 19). Replacing NBu₄SCN with NH₄SCN (1.0 equiv.) gave only 3% yield (entry 20), and the electrolysis had to be stopped after 2.1 F because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes.

Table 1. Optimization of the test reaction.

#	Deviation from standard conditions depicted in Figure 2	NMR yield ^[a]
1	none	70
2	2.4 F	45
3	3.0 F	69
4	3.3 F	66
5	30 mA cm ⁻²	58
6	60 mA cm ⁻²	59
7	70 mA cm ⁻² , 3.0 F	64
8	glassy carbon stainless steel	50
9	graphite stainless steel	50 ^[b]
10	BDD BDD	16
11	0 °C	58
12	60 °C	55
13	1.5 mmol SM, c(SM) = 0.3 mol L ⁻¹	44
14	2.5 mmol SM, c(SM) = 0.5 mol L ⁻¹	59
15	0.3 equiv. NBu ₄ SCN	31
16	1.0 equiv. NBu ₄ SCN	71
17	1.5 equiv. NBu ₄ SCN	70
18	no NBu ₄ SCN, 0.5 equiv. EMIMSCN	36
19	no NBu ₄ SCN, 0.5 equiv. BMIMSCN	19
20	no NBu ₄ SCN, 1.0 equiv. NH ₄ SCN	3 ^[c]
21	no NBu ₄ SCN	0 ^[d]
22	no electricity	0

SM: starting material (dicarboxylic acid). BDD: boron-doped diamond. EMIMSCN: 1-ethyl-3-methylimidazolium thiocyanate. BMIMSCN: 1-butyl-3-methylimidazolium thiocyanate. [a] The yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] The upper terminal voltage limit of the power supply was reached during electrolysis, nonetheless 2.7 F were fully applied. [c] The reaction had to be stopped after 2.1 F because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes. [d] The electrolysis can't be carried out without NBu₄SCN, because the upper terminal voltage limit of the power supply is reached, demonstrating that the thiocyanate supporting electrolyte is indispensable for the reaction.

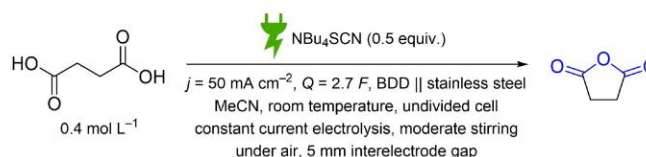


Figure 2. The standard reaction conditions of the test reaction: electrochemical dehydrative reaction of succinic acid to succinic anhydride. More details about the experimental setup can be found in the Supporting Information.

yield (entry 20), and the electrolysis had to be stopped after 2.1 F because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes.

Without any supporting electrolyte (entry 21), the electrolysis cannot be carried out, because the high ohmic resistivity of the electrolyte causes the upper terminal voltage of the power supply to be reached. This demonstrates that the thiocyanate supporting electrolyte is essential for the reaction. Without the application of any electric current, no traces of anhydride product were found (entry 22).

Scope

The anhydrides shown in Figure 3 were obtained from the corresponding commercially available dicarboxylic acids by electrochemical dehydration according to the reaction conditions shown in Figure 2. The yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Succinic anhydride **1** was found in 71% yield, 2-methylsuccinic anhydride **2** in 56% yield, and 2,2-dimethylsuccinic anhydride **3** in 66% yield. Phenylsuccinic anhydride **4** was obtained in 16% yield, and maleic anhydride **5** was found only in traces. *cis*-Cyclopentane-1,2-dicarboxylic anhydride **6** was obtained in 62% yield, and *cis*-cyclohexane-1,2-dicarboxylic anhydride **7** in 57% yield. *cis*-4-Cyclohexene-1,2-dicarboxylic anhydride **8** was observed in 17% yield. The low yields for substrates **5** and **8** could be the result of side reactions of the double bond. (+)-Camphoric anhydride **9** was found in 67% yield, and *cis*-norbornene-*endo*-2,3-carboxylic anhydride **10** was found in 60%. For glutaric anhydride **11**, a yield of 59% was achieved, and 2,2-dimethylglutaric anhydride **12** was observed

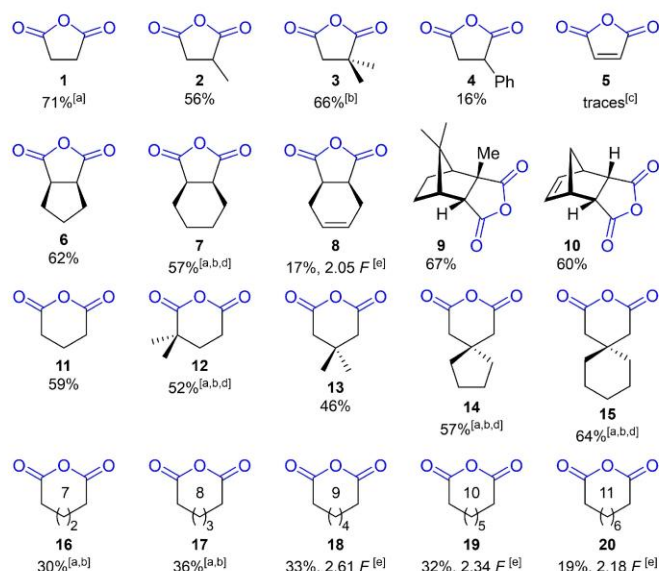


Figure 3. Anhydride scope. The electrolysis conditions of Figure 2 were applied as standard reaction conditions. The yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [a] 1.0 equiv. NBu_4SCN . [b] 3.0 F. [c] The upper terminal voltage limit of the power supply was reached during electrolysis, but 2.7 F of charge were fully applied. [d] $\text{MeCN/isobutyronitrile}$ 2:1 (vol%). [e] The electrolysis had to be stopped after the mentioned amount of applied charge because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes.



Figure 4. Amidation test reaction. [a] electrolysis reaction conditions: MeCN , succinic acid (0.4 mol L^{-1}), NBu_4SCN (1.0 equiv.) constant current electrolysis, current density $j = 50 \text{ mA cm}^{-2}$, amount of applied charge $Q = 3.0 \text{ F}$, BDD || stainless steel, 5 mm interelectrode gap, under air, moderate stirring. More details can be found in the Supporting Information.

in 52% yield, while 3,3-dimethylglutaric anhydride **13** was found in 46%. 1,1-Cyclopentanediacetic anhydride **14** was found in 57% yield, and 1,1-cyclohexanediacetic anhydride **15** in 64%. For adipic anhydride **16**, pimelic anhydride **17**, suberic anhydride **18**, azelaic anhydride **19**, and sebacic anhydride **20**, yields of 30%, 36%, 33%, 32%, and 19% were obtained, respectively. The yield for substrates **17** to **20** likely decrease because of increasing ring size of the anhydride product. For some substrates in Figure 3, the formation of a precipitate is observed, which could be caused by side reactions of the thiocyanate supporting electrolyte.^[19]

Amide Synthesis

The cyclic carboxylic anhydrides which are obtained by electrolysis were used in-situ for amidation reactions, as depicted in Figure 4. The atom economy of acylation reactions with cyclic anhydrides is beneficial because the reaction product contains a ω -carboxylic acid side chain, which allows for further functionalization, and no reagent waste from the cyclic anhydride is generated during the acylation reaction. To optimize the reaction conditions, benzylamine and morpholine were tested as amines, as shown in Table 2. The yields for benzylamine were higher than the yields for morpholine in all

Table 2. Optimization of the amidation test reaction.

#	Deviation from standard conditions depicted in Figure 4	NMR yield ^[a]
1	benzylamine (5.0 equiv.), no imidazole	68
2	benzylamine (5.0 equiv.)	71
3	benzylamine (5.0 equiv.), no imidazole, DMAP (0.05 equiv.)	73
4	benzylamine (5.0 equiv.), DMAP (0.05 equiv.)	72
5	morpholine (5.0 equiv.), no imidazole	36
6	morpholine (5.0 equiv.)	31
7	morpholine (5.0 equiv.), no imidazole, DMAP (0.05 equiv.)	38
8	morpholine (5.0 equiv.), DMAP (0.05 equiv.)	32

DMAP: 4-(dimethylamino)pyridine. [a] The amide yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. More details can be found in the Supporting Information.

experiments. With 5.0 equiv. of benzylamine and without any additional base, an NMR yield of 68% was found (Table 2, entry 1). When using 5.0 equiv. benzylamine with 5.0 equiv. of imidazole, a slightly higher yield of 71% was found (entry 2). Using no additional base, 5.0 equiv. benzylamine, and 0.05 equiv. of DMAP gave 73% yield (entry 3). The reaction which used 5.0 equiv. benzylamine with 5.0 equiv. imidazole and 0.05 equiv. DMAP resulted in a yield of 72% (entry 4). These four experiments were repeated with morpholine instead of benzylamine, which gave 36%, 31%, 38%, and 32% NMR yield, respectively (entries 5–8). To investigate the scalability of this reaction, a 10-fold scale-up of entry 3 in Table 2 was carried out (see Supporting Information for details), and an NMR yield of 61% was obtained (isolated yield: 58% from succinic acid over two steps).

Reaction Mechanism

The postulated reaction mechanism is depicted in Figure 5. The thiocyanate anion I is likely anodically oxidized to intermediate II, which acts as an electrophile for carboxylate III. The resulting species IV is an active ester and reacts subsequently with another carboxylate. The tetrahedral intermediate V is formed, from which hypothiocyanite VI is eliminated, resulting in the formation of carboxylic anhydride VII. Hypothiocyanite VI can be oxidized further in analogous steps from VIII to cyanosulfite XI, resulting in one more equivalent of anhydride being generated. Cyanosulfite XI can be oxidized further as well in steps from XII to cyanosulfate XV. The mechanism presented here represents a simplified picture, as hypothiocyanite species VI is known to undergo various hydrolysis, comproportionation, and disproportionation reactions.^[20] By ¹⁸O isotope labeling of the dicarboxylic acid, sulfate was unequivocally detected within the mixture upon electrolysis, providing strong evidence for the

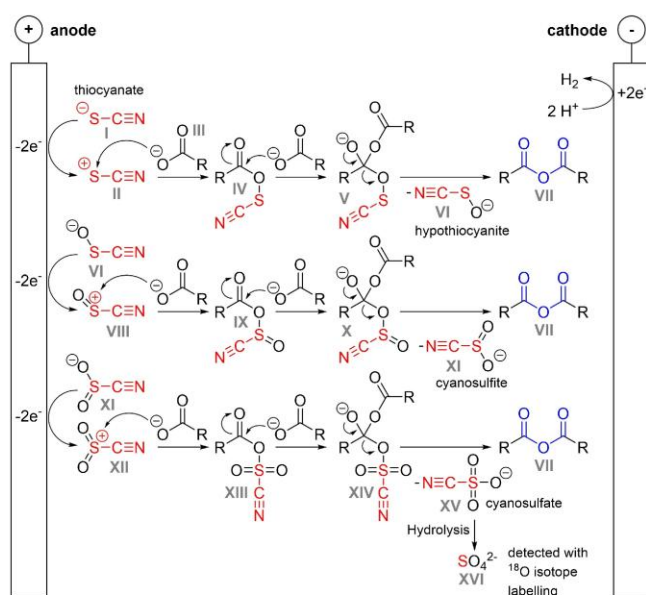


Figure 5. Proposed reaction mechanism.

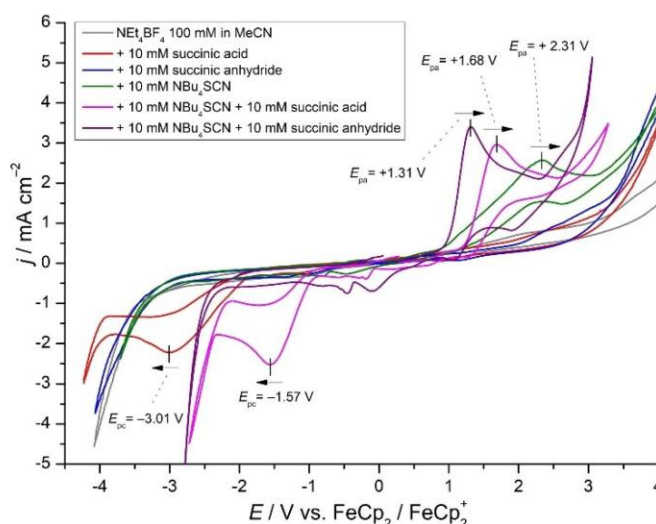


Figure 6. Cyclic voltammetry (CV) measurements. Working electrode: boron-doped diamond (BDD, circular electrode with diameter 2 mm), counter electrode: Pt wire, reference electrode: Ag/AgCl in EtOH/saturated LiCl; Sweep rate: 0.1 V/s. One cycle was measured for each sample starting from 0 V to towards anodic current, then towards cathodic current, and back to 0 V. All CV measurements were carried out under argon atmosphere. Each CV measurement was referenced against ferrocene.

mechanism proposed here. Most likely sulfate XVI is formed from XV by hydrolysis. At the cathode, hydrogen evolution reaction occurs and H₂ was detected by gas chromatography (see Supporting Information). This reaction is not a Kolbe electrolysis, but instead it is a non-decarboxylative electrochemical dehydration reaction. This is another example of the dual role of a supporting electrolyte as reagent and enabler of conductivity.^[21]

CV Measurements

Cyclic voltammetry (CV) measurements are depicted in Figure 6. For succinic acid and succinic anhydride, no anodic current peak is observed. The solution of NBu₄SCN shows an anodic current peak at +2.31 V. Notably, this peak shifts towards +1.68 V for NBu₄SCN mixed with succinic acid, and to +1.31 V in solution of NBu₄SCN with succinic anhydride. This observation indicates that there could be formation of a species which facilitates electron transfer. Succinic anhydride does not show a cathodic current peak and neither does NBu₄SCN. Succinic acid shows a cathodic current peak at −3.01 V, and the cathodic current peak for succinic acid mixed with NBu₄SCN shifts towards −1.57 V.

Conclusions

A method for the electrochemical dehydration of dicarboxylic acids to their cyclic carboxylic anhydrides was established. In this reaction, two carboxylic acid moieties are electrochemically dehydrated to their cyclic anhydride. This method allows

conversion of naturally abundant, inexpensive, safe, and readily available dicarboxylic acids as starting into anhydrides as highly valuable compounds. The cyclic anhydrides obtained by electrolysis were employed in-situ for amide synthesis. The mechanism of the reaction was investigated by mass spectrometry, cyclic voltammetry, and isotope labeling, revealing the anodic oxidation and hydrolysis of the thiocyanate supporting electrolyte as driving force for the dehydration. This reaction is not a classical Kolbe electrolysis, because it is a non-decarboxylative, and all carbon atoms of the dicarboxylic acid starting material are conserved in the cyclic anhydride. This work is part of the recent progress in the underexplored field of electrochemical dehydration reactions. Considering the importance of dehydration reactions in organic synthesis, electrochemical dehydrations could offer many new avenues to explore. This will open-up fields wherein electrosynthesis was not previously considered as future technology.

Supporting Information

Detailed information on general procedures, reaction optimization, and mechanistic studies can be found in the Supporting Information. The authors have cited additional references within the Supporting Information.^[22]

Acknowledgements

We would like to thank Dr. Simon Clausen for help with gas chromatography and Dr. Christopher Kampf for high-resolution mass spectrometry measurements. Nicole C. Roesner and Bernhard Hauk are appreciated for reaction optimization experiments. Financial support by SusInnoScience in frame of Forschungsinitiative Rheinland-Pfalz is highly appreciated. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: electrolysis · anhydrides · carboxylic acids · dehydrative reaction · green chemistry

- [2] a) J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, *20*, 140–177; b) P. Acosta-Guzmán, A. Ojeda-Porras, D. Gamba-Sánchez, *Adv. Synth. Catal.* **2023**, *365*, 4359–4391.
- [3] P. Ertl, E. Altmann, J. M. McKenna, *J. Med. Chem.* **2020**, *63*, 8408–8418.
- [4] M. C. Leech, K. Lam, *Acc. Chem. Res.* **2020**, *53*, 121–134.
- [5] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312.
- [6] J. Magano, *Org. Process Res. Dev.* **2022**, *26*, 1562–1689.
- [7] a) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319; b) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619; *Angew. Chem.* **2018**, *130*, 5694–5721; c) S. R. Waldvogel, B. Janza, *Angew. Chem.* **2014**, *126*, 7248–7249; *Angew. Chem. Int. Ed.* **2014**, *53*, 7122–7123.
- [8] a) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041; *Angew. Chem.* **2018**, *130*, 6124–6149; b) J. Seidler, J. Strugatchi, T. Gärtner, S. R. Waldvogel, *MRS Energy Sustainability* **2020**, *7*, E42.
- [9] a) D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386–12400; b) B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099; c) E. Steckhan, T. Arns, W. R. Heineman, G. Hilt, D. Hoormann, J. Jörissen, L. Kröner, B. Lewall, H. Pütter, *Chemosphere* **2001**, *43*, 63–73.
- [10] A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, J. Schneider, S. R. Waldvogel, *ChemistryOpen* **2022**, *11*, e202200059.
- [11] a) F. J. Holzhäuser, J. B. Mensah, R. Palkovits, *Green Chem.* **2020**, *22*, 286–301; b) D. Klüh, W. Waldmüller, M. Gaderer, *Clean Technol.* **2021**, *3*, 1–18; c) H. J. Schäfer, *C. R. Chim.* **2011**, *14*, 745–765.
- [12] a) H. Kolbe, *Ann. Chem. Pharm.* **1848**, *64*, 339–341; b) H. Kolbe, *Ann. Chem. Pharm.* **1849**, *69*, 257–294.
- [13] a) S. Nagahara, Y. Okada, Y. Kitano, K. Chiba, *Chem. Sci.* **2021**, *12*, 12911–12917; b) L. M. Großmann, V. Beier, L. Düttenhofer, L. Lennartz, T. Opatz, *Chem. Eur. J.* **2022**, *28*, e202202725.
- [14] a) J. Han, C. A. Haines, J. J. Piane, L. L. Filien, E. D. Nacs, *J. Am. Chem. Soc.* **2023**, *145*, 15680–15687; b) K. Mahanty, A. Halder, S. de Sarkar, *Adv. Synth. Catal.* **2023**, *365*, 96–103; c) Y. Wang, J. Xu, Y. Pan, Y. Wang, *Org. Biomol. Chem.* **2023**, *21*, 1121; d) X. Shao, Y. Zheng, V. Ramadoss, L. Tian, Y. Wang, *Org. Biomol. Chem.* **2020**, *18*, 5994–6005.
- [15] a) J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, *53*, 45–61; b) J. L. Röckl, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Angew. Chem.* **2020**, *132*, 323–327; *Angew. Chem. Int. Ed.* **2020**, *59*, 315–319; c) Y. Imada, J. L. Röckl, A. Wiebe, T. Gieshoff, D. Schollmeyer, K. Chiba, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 12136–12140; *Angew. Chem.* **2018**, *130*, 12312–12317; d) V. M. Breising, T. Gieshoff, A. Kehl, V. Kilian, D. Schollmeyer, S. R. Waldvogel, *Org. Lett.* **2018**, *20*, 6785–6788; e) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765; f) T. Gieshoff, D. Schollmeyer, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2016**, *55*, 9437–9440; *Angew. Chem.* **2016**, *128*, 9587–9590.
- [16] S. B. Beil, D. Pollok, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14750–14759; *Angew. Chem.* **2021**, *133*, 14874–14883.
- [17] a) S. Lips, S. R. Waldvogel, *ChemElectroChem* **2019**, *6*, 1649–1660; b) S. R. Waldvogel, S. Mentizi, A. Kirste, *Top. Curr. Chem.* **2012**, *320*, 1–31; c) Y. Einaga, *Acc. Chem. Res.* **2022**, *55*, 3605–3615; d) N. Yang, S. Yu, J. V. Macpherson, Y. Einaga, H. Zhao, G. Zhao, G. M. Swain, X. Jiang, *Chem. Soc. Rev.* **2019**, *48*, 157–204.
- [18] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204140; *Angew. Chem.* **2022**, *134*, e202204140.
- [19] S. A. Kahani, M. Sabeti, *J. Inorg. Organomet. Polym.* **2011**, *21*, 458–464.
- [20] J. Kalmár, K. L. Woldegiorgis, B. Biri, M. T. Ashby, *J. Am. Chem. Soc.* **2011**, *133*, 19911–19921.
- [21] L. G. Gombos, J. Nikl, S. R. Waldvogel, *ChemElectroChem* **2024**, e202300730.
- [22] a) A. F. Lopes, T. S. M. Fernandes, R. F. do Nascimento, *Crit. Rev. Anal. Chem.* **2023**, *53*, 614–633; b) W. L. F. Armarego, *Purification of laboratory chemicals*. 8. ed., Elsevier, **2017**; c) M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204140; *Angew. Chem.* **2022**, *134*, e202204140.

Manuscript received: January 30, 2024

Accepted manuscript online: March 25, 2024

Version of record online: April 17, 2024

[1] R. C. Larock, *Comprehensive Organic Transformations*, Wiley, **2018**.

The following results have been published in a peer-reviewed publication.^[109]

E. Lunghi, A. M. van Koten, **J. Schneider**, S. R. Waldvogel *

Electrochemical Dehydration of Sulfonic Acids to their Anhydrides

J. Org. Chem. **2025**

[accepted]

License: CC BY 4.0

* Corresponding author

Explanation of my contribution:

J. Schneider carried out initial investigations into the electrochemical dehydration of sulfonic acids to their anhydrides. E. Lunghi and A. M. van Koten performed reaction optimization, reactions for the scope of sulfonates and sulfonamides, scale-up reactions, control experiments, and cyclic voltammetry studies. **J. Schneider** and E. Lunghi wrote the manuscript and the Supporting Information. **J. Schneider** formulated a proposed mechanism. S. R. Waldvogel supervised the project and assisted in writing of the manuscript and the Supporting Information.

Introduction: Based on the previous work on the electrochemical dehydration of carboxylic acids to their anhydrides,^[104,107] this reactivity was extended to sulfonic acids. Like carboxylic anhydrides, the sulfonic anhydrides which are generated in-situ via electrolysis are too sensitive to be isolated. Instead, they are directly employed in sulfonylation reactions by subsequent addition of an excess of alcohol or amine after electrolysis, which yields the corresponding sulfonates or sulfonamides, respectively.

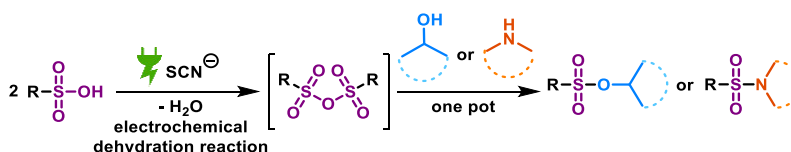


Figure 32. Electrochemical dehydration of sulfonic acids to sulfonic anhydrides, which are subsequently treated with an excess of alcohol or amine to isolate the corresponding sulfonate or sulfonamide.^[109]

Optimization: The reaction optimization is carried out using methanesulfonic acid **1** as starting material, which is electrochemically dehydrated to methanesulfonic anhydride **2**. The standard reactions are depicted in Figure 33. The standard reaction conditions gave an NMR yield of 74% (Table 6, entry 1). Using only 2 F resulted in a slightly lower yield of 62% (entry 2). A current density of 50 mA cm^{-2} gave only 34% NMR yield (entry 3). An inter-electrode gap of 3 mm resulted in a yield of 32% (entry 4).

Graphite as cathode material gave 49% yield, and 37% when employed as anode material (entries 5–6). Using KSCN instead of NBu₄SCN resulted in 51% yield (entry 7). Lowering the concentration from 0.7 mol/L to 0.5 mol/L decreased the yield to 44% (entry 8). Increasing the equivalents of NBu₄SCN gave a yield of 42% (entry 9), which is lower than the 0.15 equiv. of the standard reaction conditions. Employing DMF instead of MeCN gave no product at all (entry 10). Heating the reaction solution to 50 °C did not increase the yield (45%, entry 11). Without NBu₄SCN or without electricity, no product was observed at all (entries 12–13).

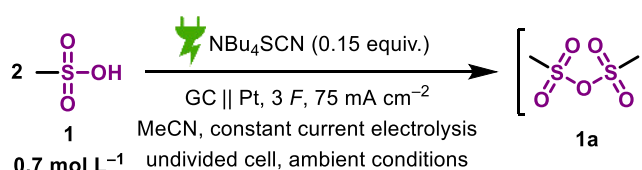


Figure 33. Optimization of the test reaction.^[109]

Table 6. Optimization of the test reaction: electrochemical dehydration of sulfonic acids.^[109]

Entry	Deviation from optimal conditions	NMR yield ^[a]
1	none	74%
2	2 F	62%
3	50 mA cm ⁻²	34%
4	Inter-electrode gap 3 mm	32%
5	graphite as cathode material	49% ^[c]
6	graphite as anode material	37%
7	KSCN instead of NBu ₄ SCN	51% ^[c]
8	c(1) = 0.5 mol L ⁻¹	44%
9	c(NBu ₄ SCN) = 0.3 mol L ⁻¹ (0.45 equiv.)	42%
10	DMF instead of MeCN	0%
11	50 °C	45%
12	no NBu ₄ SCN ^[d]	0%
13	no electricity	0%

[a] The yields were determined using ¹H NMR spectroscopy using 1,3,5-trichlorobenzene as internal standard. Further details about the experimental set-up can be found in the Supporting Information.

[b] Cathodic corrosion was observed. [c] The upper terminal voltage limit of the power supply was reached, but the mentioned amount of applied charge were fully applied. [d] For better conductivity,

NBu₄PF₆ (0.1 mol L⁻¹) was used in this case.^[109]

Scope: Based on the reaction optimization, various alcohols and amines were employed with methanesulfonic anhydride, which was generated in-situ by electrolysis to obtain the corresponding sulfonates and sulfonamides, respectively (Figure 34). Of all employed amines, pyrrolidine and *n*-butylamine gave the highest sulfonamides (both **2a** and **2f** in 64%). Imidazole gave product **2d** in 63% isolated yield. Morpholine gave sulfonamide **2c** in 60% yield. For aniline and ethyl methyl amine, sulfonamides **2b** and **2g** were both isolated in 56%. Employing indole as amine gave product **2e** in only 41% isolated yield. Next, various alcohols were tested. The highest isolated yield was obtained for product **3e** (67%), followed by *n*-butanol, which gave **2b** in 66%. Sulfonates **3d** and **3f** were obtained in 65% and 63% yield. Cyclohexanol yielded compound **3c** in 58% yield, and phenol gave **3a** in 50%. Next, various sulfonic acids were tested and quenched with pyrrolidine or aniline (**4a–4k**). Notably, the yields are higher for aliphatic sulfonic acids than for aromatic sulfonic acids. Especially para-substituted electron-poor arenes demonstrated low yield (**4a–4e**, **4i**, **4k**). In these cases, evidence for ipso-substitution was observed, which could explain the low yields. In contrast, products **4f–4j** were isolated in yields over 50%.

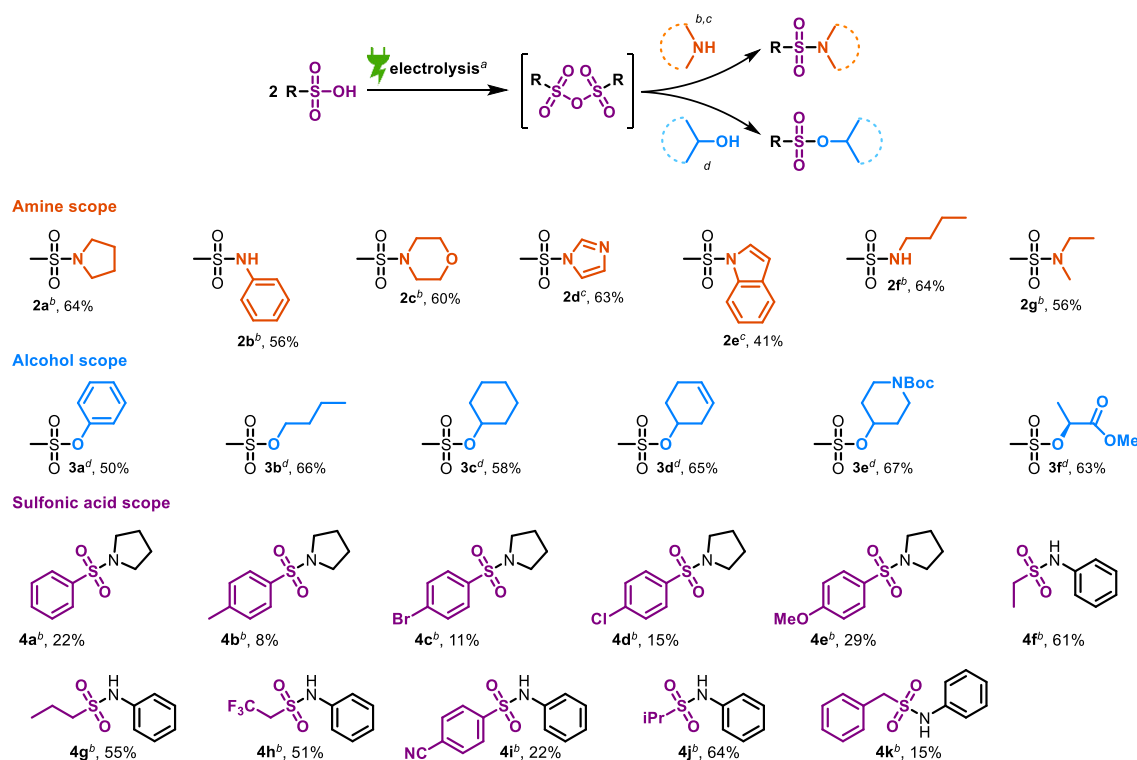


Figure 34. Scope of amines, alcohols, and sulfonic acids. [a] Unless stated otherwise, the optimized reaction conditions of Figure 33 were used. [b] Amine (5 equiv.) [c] Triethylamine (2 equiv.) and amine (2 equiv.); [d] Triethylamine (2 equiv.) and alcohol (2 equiv.).^[109]

Conclusion: The electrochemical dehydration reaction was successfully extended from carboxylic acids to sulfonic acids. No conventional dehydration reagent is required. This method is another interesting contribution to the underexplored field of electrochemical dehydration reactions. In total, 24 examples are demonstrated with NMR yields up to 67%. The robust scalability of the method was demonstrated. The reaction is carried out in an undivided cell under mild reaction conditions. As in previous work on the electrochemical dehydration of carboxylic acids, the thiocyanate supporting electrolyte plays a dual role as enabler of conductivity and as reagent.

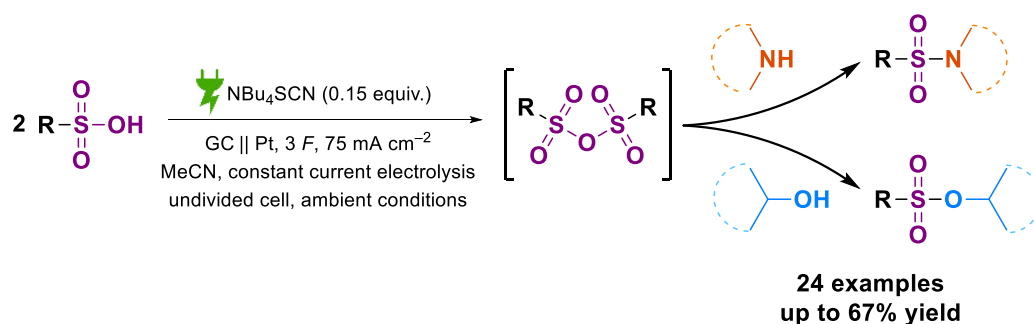


Figure 37. Electrochemical dehydration of sulfonic acids to their anhydrides.^[109]

Electrochemical Dehydration of Sulfonic Acids to Their Anhydrides

Enrico Lunghi, Annemijn M. van Koten, Johannes Schneider, and Siegfried R. Waldvogel*

Cite This: <https://doi.org/10.1021/acs.joc.5c01155>

Read Online

ACCESS |



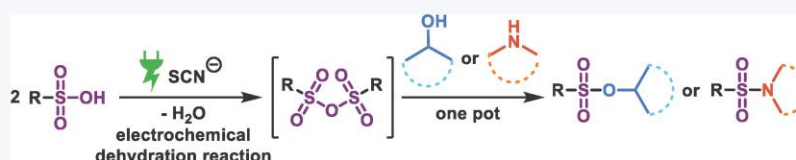
Metrics & More



Article Recommendations



Supporting Information



ABSTRACT: We developed an electrochemical method for sulfonic anhydride synthesis and one-pot derivatization into sulfonamides and mesylates under mild conditions. Aliphatic sulfonic anhydrides were electrogenerated in up to a 74% yield. Since isolating these moisture-sensitive intermediates is challenging, the in situ-generated sulfonic anhydrides were directly converted into sulfonamides or alkyl sulfonates using amines or alcohols, respectively. This scalable process enables the synthesis of various nitrogen- and oxygen-based products in the multigram range.

INTRODUCTION

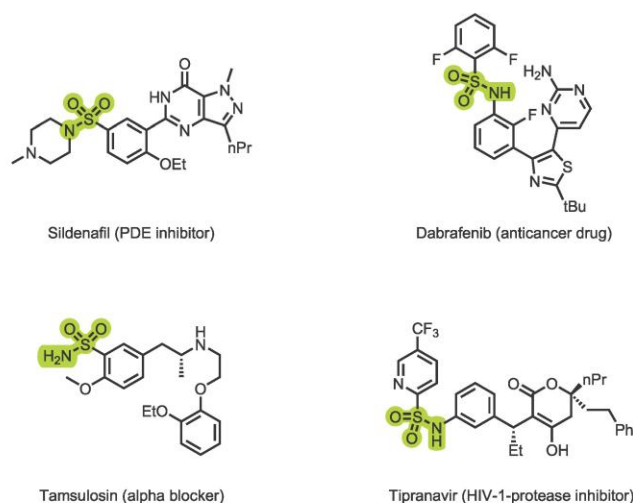
The sulfonic anhydride functionality represents a very versatile structural motif in organic synthesis, as it serves as a key intermediate in the preparation of highly value-added compounds.¹ The simplest representative is methanesulfonic anhydride, which is a widely used reagent from academic to industrial scale.² Sulfonic anhydrides enable the direct preparation of sulfonamides, sulfonates, and other sulfonyl-containing compounds, which are prevalent in pharmaceuticals (Scheme 1), agrochemicals, and materials science.³ Because of their electrophilic nature, sulfonic anhydrides facilitate efficient and selective transformations of various nucleophiles under mild reaction conditions, making them indispensable reagents

in contemporary synthetic chemistry. Despite their broad usefulness, conventional methods for the synthesis of sulfonic anhydrides often rely on harsh dehydrating agents such as phosphorus pentoxide or thionyl chloride,⁴ leading to toxic waste and operational hazards.⁵ Sulfur-based functionalization strategies typically rely on prefunctionalized sulfonyl halides, which are often expensive, difficult to store due to their moisture sensitivity, and not widely commercially available.⁶ In contrast, sulfonic acids are inexpensive, widely available, and environmentally benign starting materials, making their direct electrochemical valorization highly desirable. The electrochemical dehydration of sulfonic acids to sulfonic anhydrides therefore represents an interesting alternative to conventional dehydration reactions.

The field of electrosynthesis is currently experiencing a remarkable and ongoing renaissance,⁷ because electrochemical reactions offer a variety of advantages over conventional transformations.⁸ Electrochemical reactions are characterized by mild reaction conditions.⁹ Electricity, preferably originating from renewable energy sources, is utilized as a comparably inexpensive and universal redox agent, which helps to minimize reagent waste.¹⁰ These and further advantages are the reason electrosynthesis is establishing itself as a 21st-century technique.¹¹

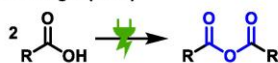
Specifically, there has been notable progress in the underexplored field of electrochemical dehydration in recent years (Scheme 2). In 2022, our group discovered the

Scheme 1. Examples of Active Pharmaceutical Ingredients (APIs) that Contain a Sulfonamide Structural Motif

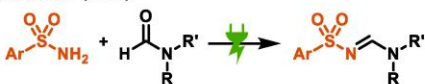


Scheme 2. Recent Progress in Electrochemical Dehydration

Waldvogel (2022):



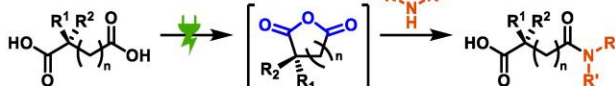
De Sarkar (2022):



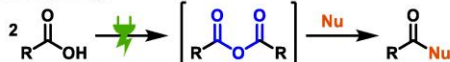
Nacsa (2023):



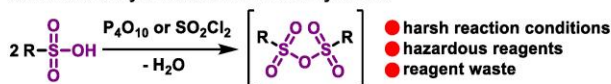
Waldvogel (2024):



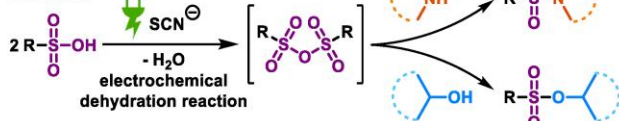
Nacsa (2025):



Conventional synthesis of sulfonic anhydrides:



This work:



- operationally simple
- mild reaction conditions
- comparably safe reaction conditions
- thiocyanates in a dual role as reagent and supporting electrolyte

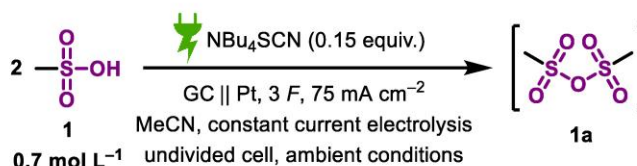
electrochemical dehydration of carboxylic acids to their carboxylic anhydrides,¹² and the group of De Sarkar developed an electrochemical dehydrative coupling of sulfonamides with derivatives of dimethylformamide to *N*-sulfonyl amidines.¹³ In 2023, the group of Nacsa developed an electrochemical design for catalytic dehydration of carboxylic acids for the synthesis of esters,¹⁴ and in 2024, our group reported on the electrochemical dehydration of dicarboxylic acids to their cyclic anhydrides.¹⁵ Recently, the Nacsa group developed an electrochemical design for catalytic carboxylic acid substitution via carboxylic anhydrides for the synthesis of amides, esters, and thioesters.¹⁶ These rapid developments emphasize the increasing interest in electrochemical dehydration reactions. Until now, the main focus in the field of electrochemical dehydration reactions has been the electrosynthesis of carboxylic anhydrides from carboxylic acids. In this work, we report an electrochemical dehydration of sulfonic acids to their sulfonic anhydrides under mild reaction conditions. The sulfonic anhydrides are electrochemically generated, and by the addition of amines or alcohols, they are directly employed in a one-pot reaction for the synthesis of highly value-added sulfonamides and sulfonates, respectively. This approach circumvents the need for conventional dehydrating agents while offering a scalable, milder, and operationally simple route to a class of compounds with broad synthetic applicability.

RESULTS AND DISCUSSION

The reaction optimization started with the knowledge from our previous publications, which used thiocyanate-supporting

electrolytes for the electrochemical dehydration of carboxylic acids to their carboxylic anhydrides.^{12,15} The optimized reaction conditions for methanesulfonic anhydride are depicted in Scheme 3. The yields were determined using ¹H

Scheme 3. Optimized Reaction Conditions



NMR spectroscopy with 1,3,5-trichlorobenzene as internal standard.¹⁷ With the optimized conditions (Table 1, entry 1),

Table 1. Optimization of the Test Reaction

entry	deviation from optimal conditions	NMR yield ^a
1	none	74%
2	2 F	62%
3	50 mA cm ⁻²	34%
4	interelectrode gap 3 mm	32%
5	graphite as a cathode material	49% ^b
6	graphite as an anode material	37%
7	KSCN instead of NBu ₄ SCN	51% ^c
8	<i>c</i> (1) = 0.5 mol L ⁻¹	44%
9	<i>c</i> (NBu ₄ SCN) = 0.3 mol L ⁻¹ (0.45 equiv)	42%
10	DMF instead of MeCN	0%
11	50 °C	45%
12	no NBu ₄ SCN ^d	0%
13	no electricity	0%

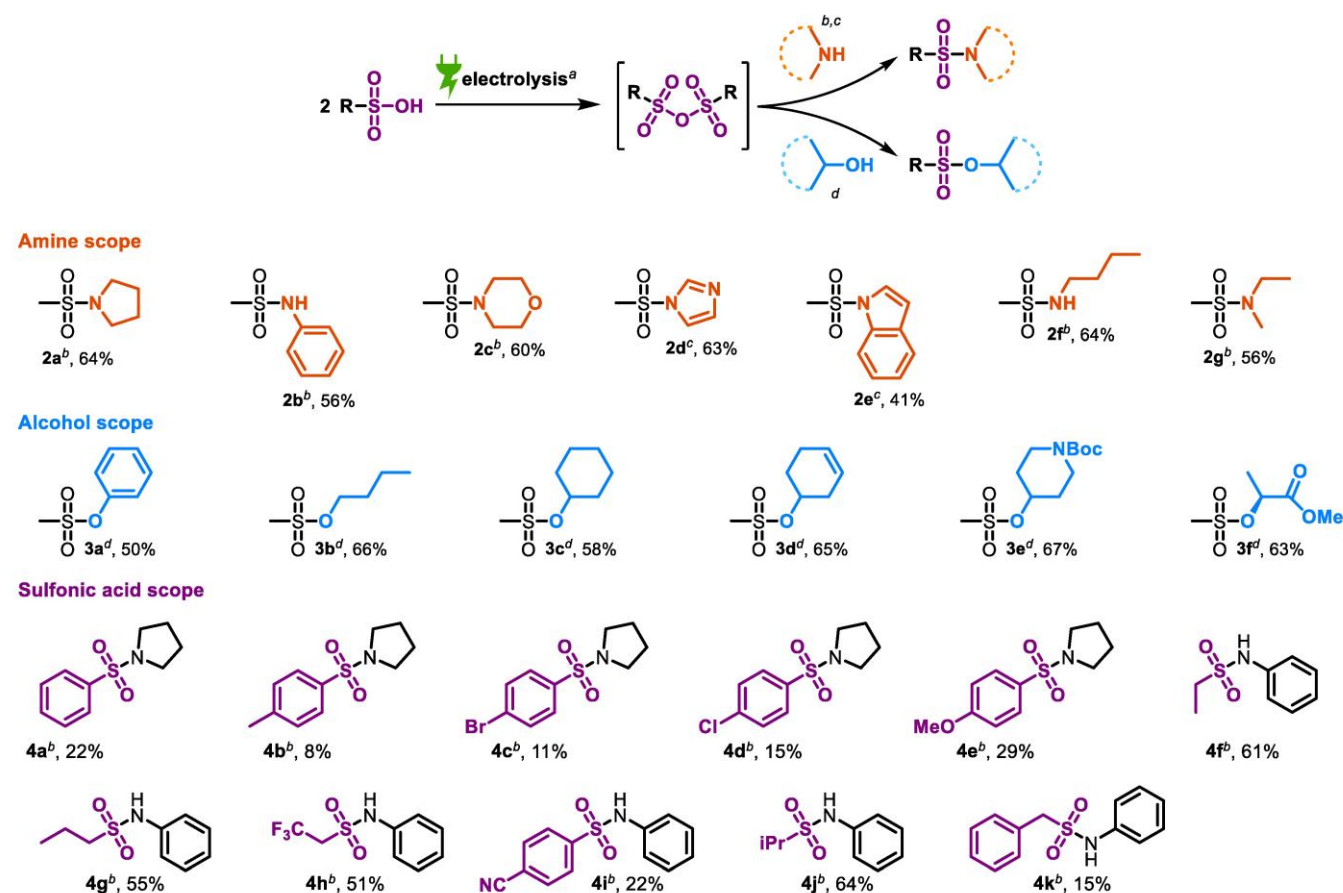
^aThe yields were determined using ¹H NMR spectroscopy using 1,3,5-trichlorobenzene as an internal standard. Further details about the experimental setup can be found in the Supporting Information.

^bCathodic corrosion was observed. ^cThe upper terminal voltage limit of the power supply was reached, but the mentioned amount of applied charge was fully applied. ^dFor better conductivity, NBu₄PF₆ (0.1 mol L⁻¹) was used in this case.

an NMR yield of 74% was achieved. To analyze the reaction, we varied the current density and the amount of applied charge (Table 1, entries 2 and 3). Decreasing the amount of applied charge to only 2 F, a yield of only 62% was obtained (entry 2), and for 50 mA cm⁻², a lower yield was also observed (entry 3). When using an interelectrode gap of only 3 mm, a yield of 32% was found (entry 4). Next, different electrode materials were evaluated. Notably, the use of graphite as a cathode material resulted in a 49% NMR yield (entry 5), although cathodic corrosion was observed.¹⁸ When graphite was tested as the anode material, the yield decreased to 37% (entry 6).

The use of KSCN instead of NBu₄SCN provided moderate yields (entry 7), and the upper terminal voltage limit of the power supply was reached. Additionally, we explored varying concentrations of both the starting material and thiocyanate-supporting electrolyte (entries 8 and 9), as well as different solvents (entry 10), with acetonitrile affording the highest yields. The reaction works best in acetonitrile, which is likely because of its optimal balance of polarity, low nucleophilicity, and high oxidative stability. Increasing the temperature did not lead to an improvement in the yield (entry 11). Without NBu₄SCN, no traces of product were found. When no

Scheme 4. Scope of Amines, Alcohols, and Sulfonic Acids



^aUnless stated otherwise, the optimized reaction conditions of Scheme 3 were used. ^bAmine (5 equiv) ^cTriethylamine (2 equiv) and amine (2 equiv); ^dTriethylamine (2 equiv) and alcohol (2 equiv)

electricity was applied, no traces of the product were found (entry 13).

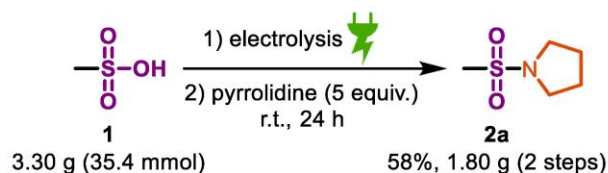
Scope. With the optimized conditions in hand, we investigated the scope of this reaction by employing various sulfonic acids as starting materials to generate the corresponding sulfonic anhydrides by electrolysis (Scheme 4). Additionally, by adding various amines or alcohols to the reaction solution after electrolysis, we directly employ the in situ-generated sulfonic anhydrides in one-pot sulfonation reactions to yield the corresponding sulfonamides and sulfonates, respectively. Noteworthy, the sulfonamides and related compounds can also be made electrochemically by multicomponent reactions.¹⁹ Aliphatic cyclic and acyclic amines were evaluated as nucleophiles in reactions using methanesulfonic acid as starting material, affording the corresponding sulfonamides in up to 64% overall yield (Scheme 4, substrates 2a to 2g). Pyrrolidine gave sulfonamide 2a in 64% isolated yield. Aromatic amines were also examined, yielding compounds 2b for aniline and 2d for imidazole in 56 and 63% yields, respectively. Morpholine, an aliphatic heterocyclic amine, provided the sulfonamide product 2c in 60% isolated yield. Furthermore, indole was tested as a nucleophile, affording the corresponding sulfonamide 2e in 41% overall isolated yield, likely due to its decreased nucleophilicity.²⁰ Products 2f and 2g were isolated in 64 and 56% yield, respectively. Next, several alcohols were tested to quench the methanesulfonic anhydride that was generated in situ by electrolysis. Phenol underwent mesylation to furnish 3a

in a 50% yield. Aliphatic primary and secondary alcohols provided mesylates 3b and 3c in 66 and 58% isolated yield, respectively. Similarly, 3d and 3e were obtained in relatively high yields. The α -hydroxy ester (–) methyl L-lactate was also employed, affording mesylate 3f in 63% yield. To further explore the scope of this transformation, various sulfonic acids were evaluated as starting materials for the electrochemical generation of the corresponding sulfonic anhydrides, which were subsequently intercepted with pyrrolidine or aniline in a one-pot procedure. The study encompassed both aromatic and aliphatic sulfonic acids to assess their reactivity and influence on the product yield. Aromatic sulfonic acids generally resulted in lower yields, with electron-poor para-substituted derivatives exhibiting particularly poor efficiency (4a, 4b, 4c, 4d, 4e, and 4i). We observed evidence of ipso-substitution side reactions, which likely contribute to the lower yields obtained with aromatic substrates (see the Supporting Information). 4k was also isolated in poor yields, probably due to the fact that the benzylic position is easily electrochemically oxidizable.²¹ In contrast, aliphatic sulfonic acids demonstrated significantly higher yields, suggesting a more favorable formation of the anhydride intermediate under the electrochemical conditions. The superior reactivity of aliphatic sulfonic acids may stem from their electronic and steric properties, which facilitate a more efficient anhydride formation and subsequent nucleophilic attack (4f, 4g, 4h, and 4j). Moreover, the reaction proceeded smoothly with a variety of aliphatic substrates, reinforcing the robustness and general applicability of this

method. These findings highlight the crucial role of electronic effects in determining the efficiency of the sulfonic acid activation and provide valuable insights into substrate selection for optimal reaction performance.

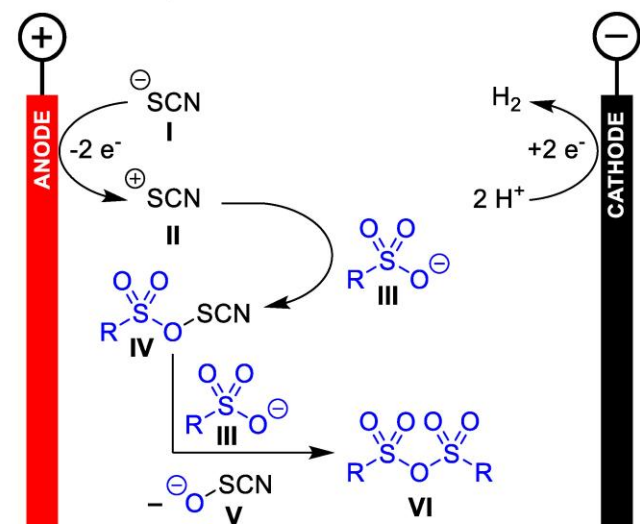
Scale-up. It is important to demonstrate the scalability of an electrochemical protocol because this opens the way for an application on an industrial scale.²² To demonstrate the robustness and scalability of our electrochemical dehydration, methanesulfonic acid **1** was electrolyzed to generate methanesulfonic anhydride in situ in a 10-fold scale-up, which is quenched after electrolysis by adding an excess of pyrrolidine as an amine. Upon workup, product **2a** was obtained in 58% yield over two steps (Scheme 5). Further details about this scale-up reaction can be found in the Supporting Information.

Scheme 5. Scale-up Reaction



Proposed Mechanism. The proposed mechanism for this electrochemical dehydration of sulfonic acids to their sulfonic anhydrides is depicted in Scheme 6. The thiocyanate anion **I** is

Scheme 6. Proposed Reaction Mechanism



anodically oxidized to intermediate **II**, which reacts with sulfonate **III** to activated intermediate **IV**. This can react with another equivalent of **III** to form the sulfonic anhydride **VI**, while **V** is eliminated as a good leaving group. The mechanism proposed here represents a simplified picture, as species **V** is known to undergo a variety of hydrolysis, comproportionation, and disproportionation reactions.²³ It should be noted that during the addition of alcohol or amine after electrolysis, species **IV** is likely to still be present because it has not yet completely reacted with sulfonic acid **III** to the sulfonic anhydride **VI**. If this is the case, then species **IV** itself will react as the electrophile instead of the sulfonic anhydride.

In this electrolysis, the thiocyanate-supporting electrolyte acts in a dual role as an enabler of conductivity and as a reagent.²⁴ Cyclic voltammetry (CV) studies reveal a non-

reversible oxidation of SCN^- at +1.45 V, which persisted over multiple scans (Supporting Information, page S11). Upon addition of methanesulfonic acid, this peak decreased and disappeared on the second scan, indicating the rapid trapping of the oxidized species by MsOH . This suggests that oxidized SCN^- participates in MsOH anhydride formation. In radical trapping experiments using TEMPO (2,2,6,6-tetramethylpiperidinyloxy), no radical intermediate could be observed (see the Supporting Information). At the cathode, hydrogen evolution reactions occur as counter reactions.²⁵

CONCLUSIONS

In summary, we have transferred our electrochemical dehydration protocol from carboxylic acids to sulfonic acids and established the electrochemical synthesis of sulfonic anhydrides and their subsequent one-pot reaction with amines or alcohols to sulfonamides and sulfonates, respectively. The reaction proceeds under a galvanostatic setup in a simple undivided cell and is carried out at ambient conditions. In total, 24 substrates are demonstrated with up to 67% isolated yield, and the scalability of the protocol is also demonstrated. The thiocyanate-supporting electrolyte serves a dual role as a reagent and enabler of conductivity. This research is part of the very recent advances in the field of electrochemical dehydration,^{26,27} which is an underexplored field of research. Given the enormous importance of dehydration reactions for organic chemistry, electrochemical dehydration reactions promise a milder, safer, and more sustainable approach to such transformations.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.5c01155>.

General aspects, experimental procedures, details of reaction optimization, control experiments, cyclic voltammetry (CV) studies, and NMR spectra of isolated compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Siegfried R. Waldvogel – Max-Planck-Institute for Chemical Energy Conversion (MPI CEC), Mülheim an der Ruhr 45470, Germany; Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS FMS), Karlsruhe Institute of Technology (KIT), Karlsruhe 76131, Germany; orcid.org/0000-0002-7949-9638; Email: siegfried.waldvogel@cec.mpg.de

Authors

Enrico Lunghi – Max-Planck-Institute for Chemical Energy Conversion (MPI CEC), Mülheim an der Ruhr 45470, Germany

Annemijn M. van Koten – Max-Planck-Institute for Chemical Energy Conversion (MPI CEC), Mülheim an der Ruhr 45470, Germany

Johannes Schneider – Department of Chemistry, Johannes Gutenberg University (JGU), Mainz 55128, Germany

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.joc.5c01155>

Funding

Open access funded by Max Planck Society.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful for funding by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy—EXC-2033-390677874-RE-SOLV. Andreas P. Häring is acknowledged for helpful discussions.

REFERENCES

- (1) (a) Field, L.; Settlage, P. H. Alkanesulfonic Acid Anhydrides 1. *J. Am. Chem. Soc.* **1954**, *76* (5), 1222–1225. (b) Larock, R. C. *Comprehensive Organic Transformations*; Wiley, 2018 DOI: .
- (2) (a) Kim, S.; Lee, S. Electrochemical synthesis of sulfinic and sulfonic esters from sulfonyl hydrazides. *Org. Biomol. Chem.* **2024**, *22* (22), 4436–4444. (b) *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001;.
- (3) (a) Talebi, M. R.; Nematollahi, D. Electrochemical Synthesis of Sulfonamide Derivatives: Electrosynthesis Conditions and Reaction Pathways. *ChemElectroChem.* **2024**, *11* (10), No. e202300728. (b) Chinthakindi, P. K.; Naicker, T.; Thota, N.; Govender, T.; Kruger, H. G.; Arvidsson, P. I. Sulfonimidamides in Medicinal and Agricultural Chemistry. *Angew. Chem., Int. Ed.* **2017**, *56* (15), 4100–4109.
- (4) Bögemann, M.; Böhme, H.; Eckoldt, H.; Goerdeler, J.; Muth, F.; Petersen, S.; Quaadvlieg, M.; Rheinboldt, H.; Schöberl, A.; Schönborg, A.; Schultz, O.-E.; Söll, H.; Wagner, A. *Schwefel-, Selen-, Tellur-Verbindungen*; Georg Thieme Verlag, 1955. DOI: .
- (5) (a) Bretherick's handbook of reactive chemical hazards: An indexed guide to published data, 7th ed.; Academic, 2007 (b) *Hazardous chemicals handbook* 2nd ed.; Butterworth-Heinemann, 2006
- (6) Vaillancourt, V.; Cudahy, M. M. Methanesulfonic Anhydride. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001. DOI: .
- (7) (a) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117* (21), 13230–13319. (b) Gomollón-Bel, F. IUPAC's 2023 Top Ten Emerging Technologies in Chemistry. *Chem. Int.* **2023**, *45* (4), 14–22. (c) Xu, H.-C.; Moeller, K. D. Electrochemistry in Synthetic Organic Chemistry. *J. Org. Chem.* **2021**, *86* (22), 15845–15846. (d) Shatskiy, A.; Lundberg, H.; Kärkäs, M. D. Organic Electrosynthesis: Applications in Complex Molecule Synthesis. *ChemElectroChem.* **2019**, *6* (16), 4067–4092.
- (8) Waldvogel, S. R.; Janza, B. Renaissance elektrochemischer Methoden zum Aufbau komplexer Moleküle. *Angew. Chem.* **2014**, *126* (28), 7248–7249.
- (9) Zhu, C.; Ang, N. W. J.; Meyer, T. H.; Qiu, Y.; Ackermann, L. Organic Electrochemistry: Molecular Syntheses with Potential. *ACS Cent. Sci.* **2021**, *7* (3), 415–431.
- (10) Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem., Int. Ed.* **2018**, *57* (21), 6018–6041.
- (11) (a) Pollok, D.; Waldvogel, S. R. Electro-organic synthesis - a 21st century technique. *Chem. Sci.* **2020**, *11* (46), 12386–12400. (b) Beil, S. B.; Pollok, D.; Waldvogel, S. R. Reproducibility in Electroorganic Synthesis-Myths and Misunderstandings. *Angew. Chem., Int. Ed.* **2021**, *60* (27), 14750–14759. (c) Leech, M. C.; Lam, K. A practical guide to electrosynthesis. *Nat. Rev. Chem.* **2022**, *6* (4), 275–286. (d) Little, R. D. A Perspective on Organic Electrochemistry. *J. Org. Chem.* **2020**, *85* (21), 13375–13390.
- (12) Häring, A. P.; Pollok, D.; Strücker, B. R.; Kilian, V.; Schneider, J.; Waldvogel, S. R. Beyond Kolbe and Hofer-Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids. *ChemistryOpen* **2022**, *11* (5), No. e202200059.
- (13) Mahanty, K.; Halder, A.; de Sarkar, S. Synthesis of N -Sulfonyl Amidines and 1,3,4-Oxadiazoles through Electrochemical Activation of DMF. *Adv. Synth. Catal.* **2023**, *365* (1), 96–103.
- (14) Han, J.; Haines, C. A.; Pian, J. J.; Filien, L. L.; Nacs, E. D. An Electrochemical Design for Catalytic Dehydration: Direct, Room-Temperature Esterification without Acid or Base Additives. *J. Am. Chem. Soc.* **2023**, *145* (29), 15680–15687.
- (15) Schneider, J.; Häring, A. P.; Waldvogel, S. R. Electrochemical Dehydration of Dicarboxylic Acids to Their Cyclic Anhydrides. *Chem.—Eur. J.* **2024**, *30* (30), No. e202400403.
- (16) Han, J.; Pian, J. J.; Gizinski, H.; Elacqua, E.; Nacs, E. D. An Electrochemical Design for a General Catalytic Carboxylic Acid Substitution Platform via Anhydrides at Room Temperature: Amidation, Esterification, and Thioesterification. *Org. Lett.* **2025**, *27* (8), 1923–1928.
- (17) Rundlöf, T.; Mathiasson, M.; Bekiroglu, S.; Hakkarainen, B.; Bowden, T.; Arvidsson, T. Survey and qualification of internal standards for quantification by ¹H NMR spectroscopy. *J. Pharm. Biomed. Anal.* **2010**, *52* (5), 645–651.
- (18) Wirtanen, T.; Prenzel, T.; Tessonnier, J.-P.; Waldvogel, S. R. Cathodic Corrosion of Metal Electrodes-How to Prevent It in Electroorganic Synthesis. *Chem. Rev.* **2021**, *121* (17), 10241–10270.
- (19) (a) Blum, S. P.; Hofman, K.; Manolikakes, G.; Waldvogel, S. R. Advances in photochemical and electrochemical incorporation of sulfur dioxide for the synthesis of value-added compounds. *Chem. Commun.* **2021**, *57* (67), 8236–8249. (b) Blum, S. P.; Schäffer, L.; Schollmeyer, D.; Waldvogel, S. R. Electrochemical synthesis of sulfamides. *Chem. Commun.* **2021**, *57* (39), 4775–4778. (c) Blum, S. P.; Karakaya, T.; Schollmeyer, D.; Klapars, A.; Waldvogel, S. R. Metal-Free Electrochemical Synthesis of Sulfonamides Directly from (Hetero)arenes, SO₂, and Amines. *Angew. Chem., Int. Ed.* **2021**, *60* (10), 5056–5062. (d) Blum, S. P.; Schollmeyer, D.; Turks, M.; Waldvogel, S. R. Metal- and Reagent-Free Electrochemical Synthesis of Alkyl Arylsulfonates in a Multi-Component Reaction. *Chem.—Eur. J.* **2020**, *26* (38), 8358–8362. (e) Schneider, J.; Blum, S. P.; Waldvogel, S. R. Electrochemical Synthesis of Sulfonamides in Single-Pass Flow. *ChemElectroChem.* **2023**, *10* (23), No. e202300456. (f) Breitschaft, F. A.; Saak, A. L.; Krumbiegel, C.; Bartolomeu, A. d. A.; Weyhermüller, T.; Waldvogel, S. R. Multicomponent Electrosynthesis of Enaminy Sulfonates Starting from Alkylamines, SO₂, and Alcohols. *Org. Lett.* **2025**, *27* (5), 1210–1215. (g) Bartolomeu, A. D. A.; Breitschaft, F. A.; Schollmeyer, D.; Pilli, R. A.; Waldvogel, S. R. Electrochemical Multicomponent Synthesis of Alkyl Alkenesulfonates using Styrenes, SO₂ and Alcohols. *Chem.—Eur. J.* **2024**, *30* (21), No. e202400557.
- (20) Eicher, T. *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*; John Wiley & Sons Incorporated, 2012.
- (21) (a) Peng, F.; Xiang, J.; Qin, H.; Chen, B.; Duan, R.; Zhao, W.; Liu, S.; Wu, T.; Yuan, W.; Li, Q.; Li, J.; Kang, X.; Han, B. Selective Electrochemical Oxidation of Benzylic C-H to Benzylic Alcohols with the Aid of Imidazolium Radical Mediators. *J. Am. Chem. Soc.* **2023**, *145* (44), 23905–23909. (b) Marko, J. A.; Durgam, A.; Bretz, S. L.; Liu, W. Electrochemical benzylic oxidation of C-H bonds. *Chem. Commun.* **2019**, *55* (7), 937–940.
- (22) Lehnher, D.; Chen, L. Overview of Recent Scale-Ups in Organic Electrosynthesis (2000–2023). *Org. Process Res. Dev.* **2024**, *28* (2), 338–366.
- (23) Kalmár, J.; Woldegiorgis, K. L.; Biri, B.; Ashby, M. T. Mechanism of decomposition of the human defense factor hypothiocyanite near physiological pH. *J. Am. Chem. Soc.* **2011**, *133* (49), 19911–19921.
- (24) Gombos, L. G.; Nikl, J.; Waldvogel, S. R. Dual Roles of Supporting Electrolytes in Organic Electrosynthesis. *ChemElectroChem.* **2024**, *11* (8), No. e202300730.

- (25) Klein, M.; Waldvogel, S. R. Counter Electrode Reactions-Important Stumbling Blocks on the Way to a Working Electro-organic Synthesis. *Angew. Chem., Int. Ed.* **2022**, *61* (47), No. e202204140.
- (26) Krumbiegel, C.; Breitschaft, A. F.; Waldvogel, S. R. Electrochemical synthesis of cyclic sulfites using diols and sulfur dioxide. *Chem. Commun.* **2025**, *61*, 11267.
- (27) Lunghi, E.; van Koten, A. M.; Schneider, J.; Waldvogel, S. R. Electrochemical Dehydration of Sulfonic Acids to Their Anhydrides. *ChemRxiv* **2025**.

4.2 Electrochemical Multicomponent Reactions using SO₂

The following results have been published in a peer-reviewed publication.^[71]

J. Schneider, S. P. Blum, S. R. Waldvogel *

Electrochemical Synthesis of Sulfonamides in Single-Pass Flow

ChemElectroChem **2023**, 10, e202300456

DOI: [10.1002/celec.202300456](https://doi.org/10.1002/celec.202300456)

License: CC BY 4.0

* Corresponding author

Explanation of my contribution:

In this publication, the electrochemical multicomponent synthesis of sulfonamides which was initially discovered by Stephan P. Blum in the Waldvogel group in 2021 was transferred by **J. Schneider** from a divided batch-type cell to an undivided flow cell setup using single-pass flow. The results of this publication are partially based on the master thesis of **J. Schneider** “*electrochemical synthesis of sulfonamides in flow*” under S. P. Blum in the Waldvogel group from June 21st – December 31st, 2022. **J. Schneider** carried out reaction optimization, preparation of SO₂ stock solutions, preparation and isolation of reaction scope, scale-up experiments, recycling of reaction medium, and design of the new flow cell for scale-up with the help of A. Stenglein from the Werkstatt Chemie at Mainz University. **J. Schneider**, S. P. Blum and S. R. Waldvogel are responsible for writing of the manuscript and of the Supporting Information. All experimental results for this publication were obtained by **J. Schneider**. Data analysis was carried out by **J. Schneider** and S. P. Blum. S. R. Waldvogel supervised the project and assisted in writing of the manuscript and the Supporting Information.

Introduction: The electrochemical multicomponent synthesis of sulfonamides was transferred from a divided batch-type setup into an undivided flow electrolysis cell employing single-pass flow. Interestingly, this reaction is not feasible in an undivided batch-type cell, but it can be achieved in an undivided flow electrolysis cell. This demonstrates again how flow chemistry can offer entirely different reaction conditions,^[80] which makes its application in conjunction with electrosynthesis so interesting. The use of single-pass flow is advantageous, because the electrolyte is passed through the flow cell only once.^[83]

Sulfonamides are an important substance class in medicinal chemistry, agricultural chemistry, and life science.^[110] Conventionally, sulfonamides are synthesized by reaction of an arene with chlorosulfuric acid to a sulfonyl chloride intermediate, which is then quenched with an excess of amine (Figure 38).

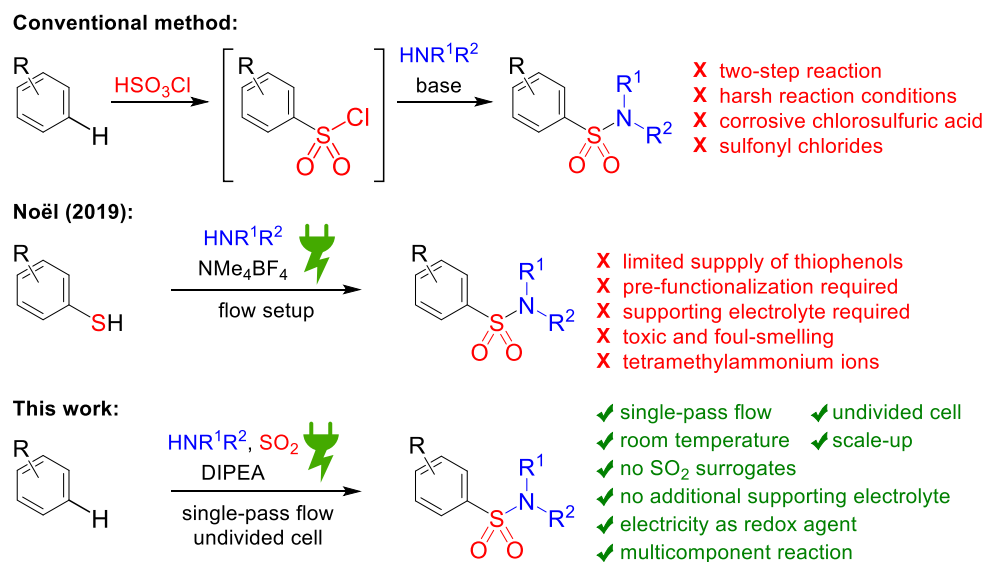


Figure 38. Overview of approaches to sulfonamides.^[71]

This two-step reaction utilizes harsh reaction conditions and the obtained sulfonyl chlorides are highly moisture sensitive, which complicates their storage. In 2019, The Noël group reported an electrochemical oxidative coupling of thiols with amines to sulfonamides.^[111] While this method is interesting, it employs toxic and foul smelling thiophenols, which are not readily commercially available. This method requires the arene to be pre-functionalized. In 2020, the Waldvogel group reported an electrochemical multicomponent reaction of sulfonates using SO₂ stock solutions. This method directly employs sulfur dioxide and avoids the use of SO₂ surrogates (Figure 39). This work has since then been extended to sulfamides,^[112] sulfonamides,^[113] alkenesulfonates,^[114] enaminy sulfonates,^[115] and cyclic sulfites.^[116]

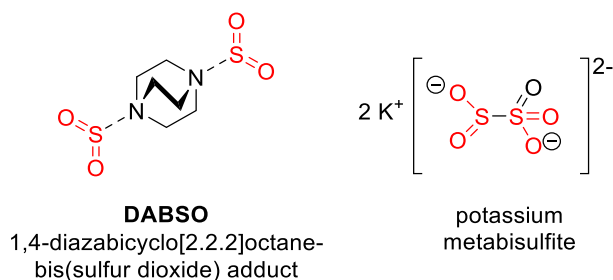


Figure 39. Common SO₂ surrogates.^[117]

Optimization: The standard reaction conditions are depicted in Figure 40. The standard reaction conditions gave sulfonamide **1** in 72% NMR yield (Table 7, entry 1). Replacing BDD with glassy carbon as anode material resulted in a similar yield of 71% (entry 2). This is beneficial, because glassy carbon is a less expensive alternative to BDD. When using graphite as anode material (entry 3), only 35% yield was found. When using BDD as electrode material for both the anode and the cathode, no product formation was observed (entry 4), and the reaction solution decomposed upon electrolysis. Using glassy carbon as both anode and cathode gave 45% yield (entry 5). Changing the reaction temperature from room temperature to 10 °C, 35 °C, or 50 °C gave 55%, 34%, and 14% (entries 6–8). This is also beneficial, since no excessive heating or cooling is required to carry out this reaction. Using only 3.0 *F* resulted in 53% yield (entry 9), while increasing the applied charge to 6.0 *F* resulted in 55% yield (entry 10). Increasing the current densities to 18.0 mA cm⁻², 24.0 mA cm⁻², and 30.0 mA cm⁻² resulted in a slight increase in yield of 59%, 61%, 64%, respectively (entries 11–13). Combining an increased current density of 24.0 mA cm⁻² with 6.0 *F* (entry 14) or 8.0 *F* (entry 15) gave only 25% and 48% yield, respectively. Using more equivalents of morpholine (entry 16) or DIPEA (entry 17) did not increase the yield much. It was the combination of using more equivalents of DIPEA with a higher vol% of HFIP that led to an increase in yield to 88% (entry 18, isolated yield: 84%). If glassy carbon electrodes are utilized, 88% NMR yield and 86% isolated yield are observed (entry 19). However, based on these observations, increasing the equivalents of DIPEA (entry 20) resulted in a lower yield again, even more so when combined with a further increase of the equivalents of SO₂ in solution (entry 21). Replacing DIPEA with pyridine as base resulted in a drastic decrease of yield to only 46% (entry 22). Using only HFIP without MeCN together with 6.0 equiv. of DIPEA resulted in only 10% yield (entry 23). Without electricity, no product formation was observed at all (entry 24).

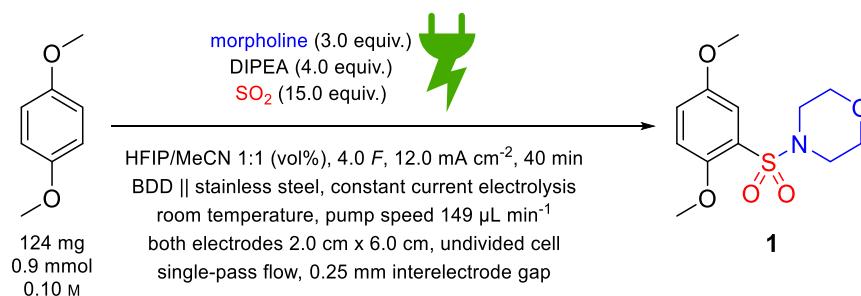


Figure 40. The test reaction employed for optimization.^[71]

Table 7. Optimization of the test reaction: electrochemical multicomponent synthesis of sulfonamides in single-pass flow using arenes, amines, and SO₂ stock solutions.^[71]

#	Deviation from standard reaction conditions ^[a]	Yield [%] ^[b]
1	none	72
2	glassy carbon stainless steel	71
3	graphite stainless steel	35
4	BDD BDD	0
5	glassy carbon glassy carbon	45
6	10 °C	55
7	35 °C	34
8	50 °C	14
9	3.0 <i>F</i> , 200 µL min ⁻¹	53
10	6.0 <i>F</i> , 100 µL min ⁻¹	55
11	18.0 mA cm ⁻² , 224 µL min ⁻¹	59
12	24.0 mA cm ⁻² , 298 µL min ⁻¹	61
13	30.0 mA cm ⁻² , 373 µL min ⁻¹	64
14	24.0 mA cm ⁻² , 6.0 <i>F</i> , 200 µL min ⁻¹	25
15	24.0 mA cm ⁻² , 8.0 <i>F</i> , 149 µL min ⁻¹	48
16	6.0 equiv. morpholine	72
17	6.0 equiv. DIPEA	75
18	HFIP/MeCN 2:1, 6.0 equiv. DIPEA, 1.8 mmol scale	88 (84% isolated)
19	HFIP/MeCN 2:1, 6.0 equiv. DIPEA, 1.8 mmol scale, glassy carbon stainless steel	88 (86% isolated)
20	HFIP/MeCN 2:1, 8.0 equiv. DIPEA	70
21	HFIP/MeCN 2:1, 8.0 equiv. DIPEA, 20.0 equiv. SO ₂	60
22	HFIP/MeCN 2:1, 6.0 equiv. pyridine, no DIPEA	46
23	HFIP (no MeCN), 6.0 equiv. DIPEA, 224 µL min ⁻¹ , <i>c</i> (1,4-dimethoxybenzene) = 0.10 mol L ⁻¹	10
24	No electricity	0

[a] The standard reaction conditions are the conditions shown in Figure 40. More details can be found in the Supporting Information. BDD: boron-doped diamond. DIPEA: *N,N*-diisopropylethylamine, HFIP: 1,1,1,3,3,3-hexafluoropropan-2-ol. [b] Unless stated otherwise, the yields were determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

Scope: For 1,4-dimethoxybenzene, sulfonamide **1** was obtained in 84% isolated yield, and in 86% isolated yield in scale-up (Figure 41). 1,2-Dimethoxybenzene gave the two possible isomeric products **2a** and **2b** in 41% and 14% isolated yield under conditions [c], and in 12% and 9% isolated yield respectively under conditions [a]. 2-Bromo-1,4-dimethoxybenzene gave product isomers **3a** and **3b** in 53% and 19% isolated yield. For 1,4-dimethoxy-2,3-dimethylbenzene, product **4** was found in 26% under conditions [a] and in similar yield under conditions [d]. In analogy to products **3a** and **3b**, products **5a** and **5b** were isolated in 50% and 11% yield, respectively. This is similar to products **6a** and **6b**, which were isolated in 56% and 11% under conditions [c] and only in low yields under conditions [a]. Sulfonamides **7a** and **7b** were isolated in 41% and 14% under conditions [c] and in lower yields under conditions [a]. Next, some other amines were tested with 1,4-dimethoxybenzene as arene. Employing azepane, dibutylamine, or diisobutylamine as amines gave yields of 43%, 31%, and 66% for **8**, **9**, and **10**.

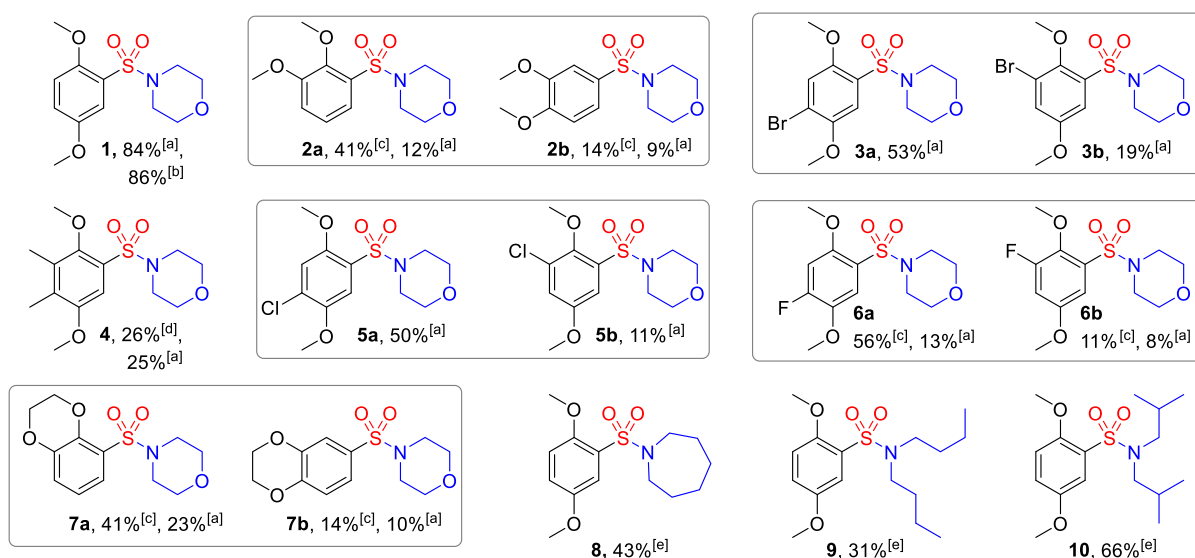


Figure 41. Scope of arenes and amines. [a] Reaction conditions: starting material (1.8 mmol, 0.15 mol L⁻¹), morpholine (3.0 equiv.), DIPEA (6.0 equiv.), SO₂ (15.0 equiv., 2.25 mol L⁻¹), HFIP (1.10 mL), MeCN (1.12 mL), HFIP/MeCN 2:1 (vol%), amount of applied charge Q=4.0 F, current density j=12.0 mA cm⁻², room temperature, BDD anode (2.0 cm×6.0 cm), stainless steel cathode (2.0 cm×6.0 cm), undivided cell, pumping rate: 149 μL min⁻¹, constant current electrolysis, single-pass flow, interelectrode gap: 0.25 mm. [b] Deviations from conditions [a]: glassy carbon instead of BDD. [c] Deviations from conditions [a]: starting material (2.4 mmol, 0.10 mol L⁻¹), DIPEA (4.0 equiv.), HFIP/MeCN 1:1 (vol%), amount of applied charge Q=3.5 F. [d] Deviations from conditions [a]: starting material (1.5 mmol, 0.13 mol L⁻¹). [e] Reaction conditions: starting material (1.8 mmol, 0.15 mol L⁻¹), amine (3.0 equiv.), DIPEA (6.0 equiv.), SO₂ (15.0 equiv., 2.25 mol L⁻¹), HFIP (1.10 mL), MeCN (1.12 mL), HFIP/MeCN 2:1 (vol%), amount of applied charge Q=4.0 F, current density j=12.0 mA cm⁻², room temperature, BDD anode (2.0 cm×6.0 cm), stainless steel cathode (2.0 cm×6.0 cm), undivided cell, pumping rate: 149 μL min⁻¹, constant current electrolysis, single-pass flow, interelectrode gap: 0.25 mm.^[71]

Scale-up: An 8-fold scale-up of the reaction in Figure 40 was carried out (1.8 mmol to 14.4 mmol). The scale-up was carried two times in two different cells, a small flow electrolysis cell (both electrodes each 12 cm²) and a larger flow electrolysis cell (both electrodes each 48 cm²). In the experiment with the small flow electrolysis cell, glassy carbon was employed as electrode material. In both experiments, an isolated yield was determined, and the starting material (SM) was recovered. Since the larger flow cell allowed for a higher electrical current to be applied while keeping the same current density, it allowed for a faster electrolysis, which resulted in a higher productivity. Both the isolated yield (92%, entry 2 in Table 8) and the productivity is higher in scale-up. Also, the unconsumed starting material could be recovered. The experimental setup of the scale-up experiment which utilized the large flow cell is depicted in Figure 42.

Table 8. Scale-up of the electrochemical multicomponent synthesis of sulfonamides in single-pass flow using arenes, amines, and SO₂ stock solutions.^[71]

Entry	Deviation from the standard reaction conditions (Table 7, entry 19)	Isolated Yield [%]	Recovered SM [%]	Productivity [g/h]
1	14.4 mmol scale, glassy carbon stainless steel	86	14	0.33
2	14.4 mmol scale, Large flow electrolysis cell (Figure 42)	92	8	1.43

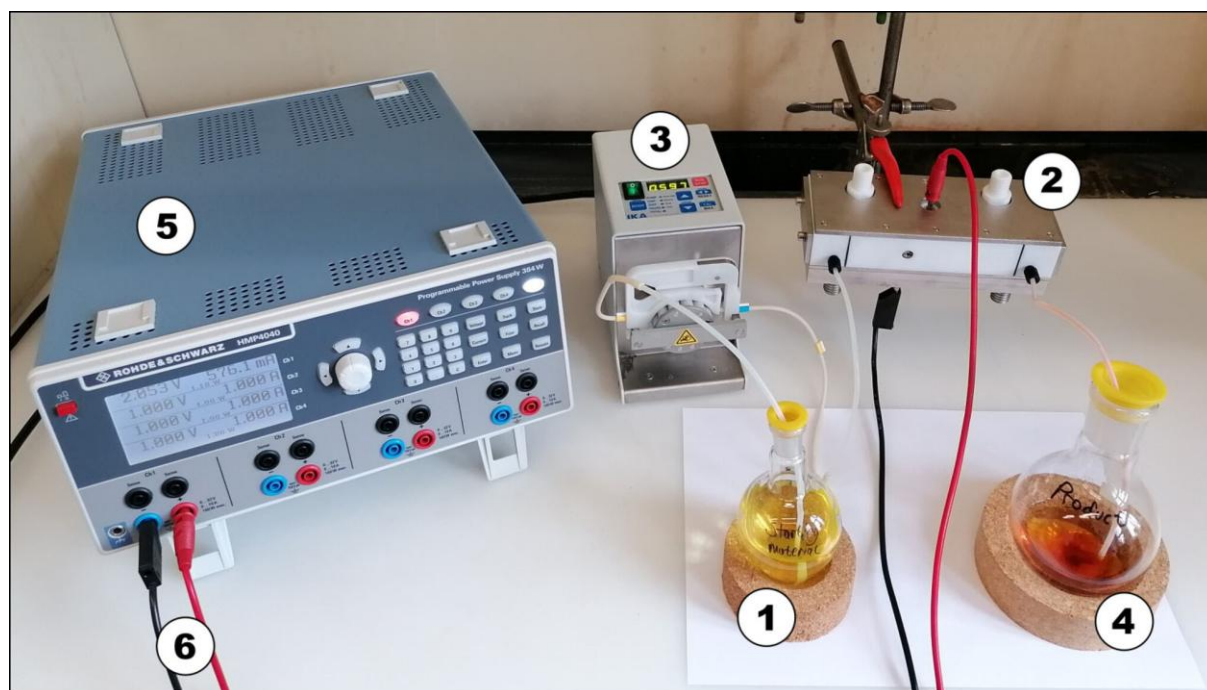


Figure 42. The scale-up reaction.^[71] The reaction solution of the starting material (1) is pumped through the flow electrolysis cell (2) with the help of a peristaltic pump (3) into a round bottom flask (4). The power supply (5) is connected to the cell with wires (6).

The electrolyte can be recovered by distillation, since HFIP, MeCN, and SO₂ are volatile. The recovered medium can be saturated with SO₂ again to be re-used without loss of yield. This is important for application on technical scale.

Mechanism: The proposed mechanism is depicted in Figure 43. This dehydrogenative reaction proceeds via electrochemical C–H activation. The amine **I** reacts with SO₂ to a Lewis acid-base adduct **II**. Deprotonation of **II** leads to the formation of an amidosulfinate intermediate **III**. The formation of the amidosulfinate is supported by hydrogen bonding of HFIP. Because of this strong hydrogen bonding of HFIP, the amidosulfinate intermediate exclusively reacts as sulfur nucleophile, and not as oxygen nucleophile.^[118] The amidosulfinate acts as both reagent and as supporting electrolyte. Mixtures of HFIP with amines show a high electric conductivity.^[78] Initial anodic oxidation of the arene **IV** leads to formation of cationic radical intermediate **V**, which reacts with the amidosulfinate to the sulfonamide product **VI**. At the cathode, sulfur dioxide is reduced.^[119] Noteworthy, all components of the electrolyte are volatile and can be recovered by distillation, which simplifies downstream processing.^[71]

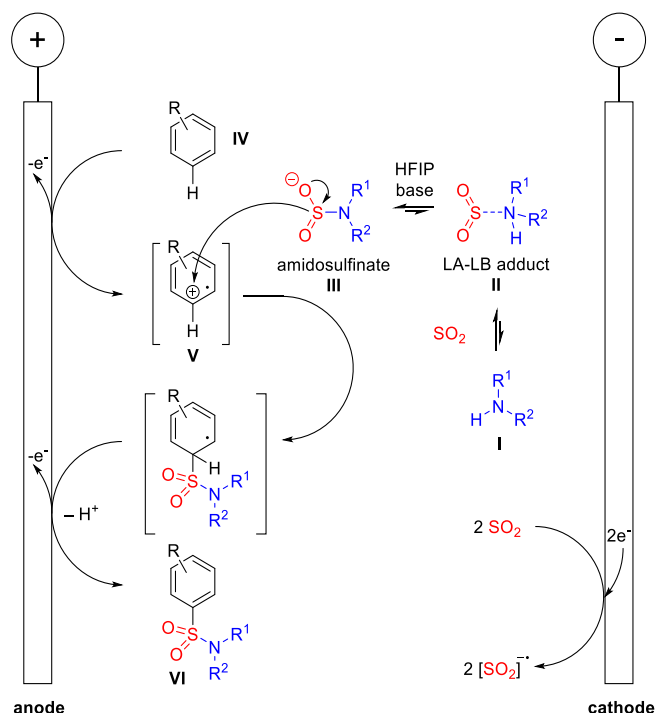


Figure 43. The proposed reaction mechanism of the electrochemical multicomponent synthesis of sulfonamides in single-pass flow using arenes, amines, and SO₂ stock solutions.^[71]

Conclusion: The electrochemical multicomponent synthesis of sulfonamides was successfully transferred from a divided batch protocol into an undivided flow cell using single-pass flow. Simple and inexpensive SO₂ stock solutions are employed to avoid the use of SO₂ surrogates. In total, 10 examples were demonstrated with up to 92% isolated yield in scale-up. It has been shown that the reaction medium can be recovered simply by distillation, because all components are volatile. The reaction does not require an additional supporting electrolyte. The robust scalability was demonstrated in an 8-fold scale-up. Both isolated yield and productivity could be improved in the scale-up reaction by employing a larger flow cell. The reaction is best carried out at room temperature, and glassy carbon or boron-doped diamond can be chosen as anode material. As cathode material, stainless steel is employed.

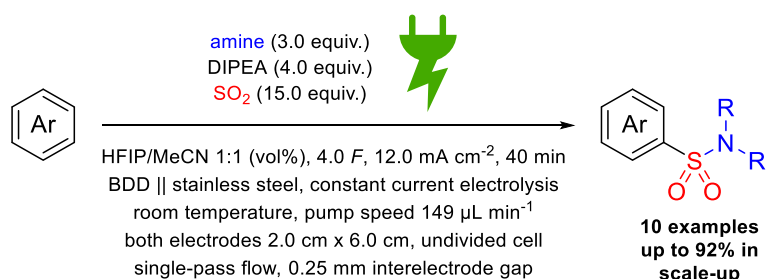


Figure 44. Electrochemical multicomponent synthesis of sulfonamides in single-pass flow using arenes, amines, and SO₂ stock solutions.^[71]

Electrochemical Synthesis of Sulfonamides in Single-Pass Flow

Johannes Schneider,^[a] Stephan P. Blum,^[a] and Siegfried R. Waldvogel^{*,[a, b]}

An electrochemical multicomponent synthesis of sulfonamides at room temperature in single-pass flow is presented. In contrast to batch-type electrolysis, an undivided flow cell setup with a stainless-steel cathode and either a boron-doped diamond (BDD) anode or a glassy carbon anode can be employed. Simply by using SO₂ stock solutions, less atom-economic sulfur dioxide surrogates can be avoided. Moreover, no additional supporting electrolytes are required due to the

in-situ generation of amidosulfonates, which also serve as intermediate for this transformation. This protocol allows sulfonamides to be synthesized directly from non-prefunctionalized electron-rich arenes with amines and SO₂. In total, 10 examples are demonstrated with isolated yields up to 92%. The robust scalability of this electrosynthesis with an easy downstream processing was also proven.

Introduction

Sulfonamides are an important class of compounds in medicinal chemistry,^[1] agrochemistry,^[2] and other life science applications.^[3] Remarkably, 25% of all sulfur-containing drugs approved by the U.S. Food and Drug Administration (FDA) in 2018 involve sulfonamide functionalities.^[4] Several of them can be found in the List of Essential Medicines of the World Health Organization (WHO).^[5] Gerhard Domagk received the Nobel Prize in 1939 for his discovery of the antibacterial effect of the sulfonamide Prontosil.^[6] Additionally, sulfonamide functionalities can be found in polymers,^[7] dyes,^[8] solvents,^[9] fungicides,^[10] insecticides,^[11] plasticizers,^[12] and electrolytes for batteries.^[13] This broad variety of application makes it evident that efficient methods for the synthesis of sulfonamides are required. Especially, the direct introduction of a sulfonamide functionality into non-pre-functionalized (hetero)arenes is of current research interest.^[14] Sulfonamides are traditionally synthesized in two steps by reaction of an aromatic compound with chlorosulfuric acid to a sulfonyl chloride intermediate, which then reacts with an amine to the sulfonamide product,^[15] as shown in Figure 1. Noteworthy, these sulfonyl chlorides are usually obtained as regioisomeric mixture. Moreover, this synthesis suffers from

further drawbacks, such as the low overall atom economy and necessity of harsh reaction conditions.^[16] In 2019, the Noël group reported the synthesis of sulfonamides in single-pass flow by electrochemical oxidative coupling of amines and thiols.^[17] Despite the usefulness of this method, toxic thiophenols, which are of limited availability, are required as starting materials. In 2021, our group reported the first direct synthesis of sulfonamides from non-prefunctionalized (hetero)-arenes, amines and SO₂.^[18] Inexpensive stock solutions of sulfur dioxide omit the need for non-atom economic and expensive SO₂ surrogates. This synthetic approach demonstrates several advantages organic electrosynthesis can offer:^[19] (i) The reaction is carried out with comparably mild reaction conditions; (ii) electricity, preferably from renewable sources, is used as an inexpensive redox agent, preventing the generation of toxic reagent waste; (iii) metal-free reaction conditions. This protocol is a representative example of the recent progress in the area of electrochemical incorporation of SO₂ into organic molecules. It illustrates that organic electrosynthesis can offer new chemical reactivity and enable novel reaction pathways.^[20] Just as with organic electrosynthesis, increasing attention is paid to the field of flow chemistry, which offers several benefits over reactions in batch.^[21] Flow chemistry provides unique ways of precisely

[a] J. Schneider, Dr. S. P. Blum, Prof. Dr. S. R. Waldvogel
Department of Chemistry
Johannes Gutenberg University Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: waldvogel@uni-mainz.de

[b] Prof. Dr. S. R. Waldvogel
Institute of Biological and Chemical Systems – Functional Molecular
Systems (IBCS-FMS)
Kaiserstrasse 12,
76131 Karlsruhe (Germany)

Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/celec.202300456>

© 2023 The Authors. ChemElectroChem published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

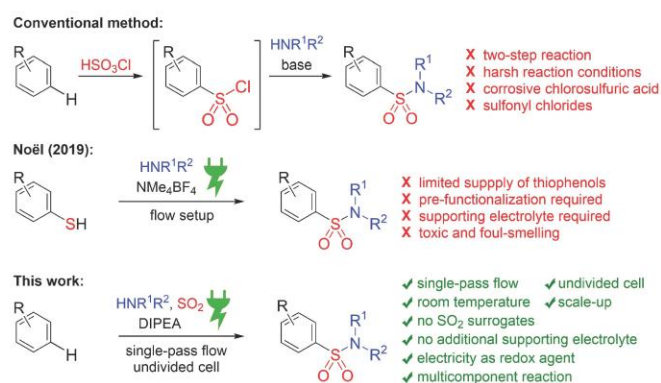


Figure 1. Synthetic approaches to sulfonamides.

controlling both conventional and electrochemical reaction parameters,^[22] it allows for greater control of stoichiometry as well as reaction time,^[23] and it can also increase selectivity and reproducibility of reactions.^[24] Based on previous studies, we further developed the batch protocol into flow by employing an undivided flow cell setup in single-pass mode. To our delight, no separator between the electrodes is required, which is not feasible in batch-type electrolysis. Additionally, the electrochemical flow reaction is not disturbed by a disruptive hydrogen evolution reaction, as SO₂ is reduced cathodically as counter reaction.^[25]

Results and Discussion

To investigate the reaction in single-pass flow, the conditions for the test reaction displayed in Figure 2 were optimized.

Unless stated otherwise, the yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. The standard conditions gave a yield of 72% (Table 1, entry 1). To our delight, a similar yield of 71% (entry 2) was obtained when using glassy carbon instead of boron-doped diamond (BDD) as anode material. This is beneficial, as glassy carbon is a significantly less expensive alternative to BDD.^[26] Employing graphite as anode material resulted in a much lower yield of only 35% (entry 3). When using BDD as material for both the anode and the cathode, no trace of product formation was detected (entry 4). In this case, the reaction mixture decomposed during electrolysis and no other product could be found. Using glassy carbon as anode and cathode material resulted in a yield of 45% (entry 5). Such a setup allows the reaction to be carried out with a metal-free electrode material for both anode and cathode. However, all further optimization experiments were carried out using stainless steel as cathode material because of the higher yield (entry 1 and 2). Next, the influence of the reaction temperature was investigated. Cooling the flow cell to 10 °C decreased the yield to 55% (entry 6). Increasing the temperature to 35 °C or 50 °C resulted in 34% (entry 7) and 14% (entry 8) yield, respectively. These results indicate that the reaction is best carried out at room temperature, which is beneficial because no external heating or cooling of the undivided flow cell is required. Thereafter, the amount of applied charge and the current density were optimized. In those experiments the flow rate had to be adjusted to control the required applied charge for the specified current density. The application of only 3.0 *F* instead

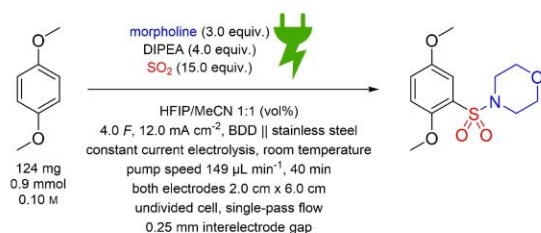


Figure 2. The test reaction used for optimization.

Table 1. Optimization of the test reaction.

#	Deviation from standard reaction conditions ^[a]	Yield [%] ^[b]
1	none	72
2	glassy carbon stainless steel	71
3	graphite stainless steel	35
4	BDD BDD	0
5	glassy carbon glassy carbon	45
6	10 °C	55
7	35 °C	34
8	50 °C	14
9	3.0 <i>F</i> , 200 μL min ⁻¹	53
10	6.0 <i>F</i> , 100 μL min ⁻¹	55
11	18.0 mA cm ⁻² , 224 μL min ⁻¹	59
12	24.0 mA cm ⁻² , 298 μL min ⁻¹	61
13	30.0 mA cm ⁻² , 373 μL min ⁻¹	64
14	24.0 mA cm ⁻² , 6.0 <i>F</i> , 200 μL min ⁻¹	25
15	24.0 mA cm ⁻² , 8.0 <i>F</i> , 149 μL min ⁻¹	48
16	6.0 equiv. morpholine	72
17	6.0 equiv. DIPEA	75
18	HFIP/MeCN 2:1, 6.0 equiv. DIPEA, 1.8 mmol scale	88 (84% isolated)
19	HFIP/MeCN 2:1, 6.0 equiv. DIPEA, 1.8 mmol scale, glassy carbon stainless steel	88 (86% isolated)
20	HFIP/MeCN 2:1, 8.0 equiv. DIPEA	70
21	HFIP/MeCN 2:1, 8.0 equiv. DIPEA, 20.0 equiv. SO ₂	60
22	HFIP/MeCN 2:1, 6.0 equiv. pyridine, no DIPEA	46
23	HFIP (no MeCN), 6.0 equiv. DIPEA, 224 μL min ⁻¹ , c(1,4-dimethoxybenzene) = 0.10 mol L ⁻¹	10
24	No electricity	0

[a] The standard reaction conditions are the conditions shown in Figure 2. More details can be found in the Supporting Information. BDD: boron-doped diamond. DIPEA: *N,N*-diisopropylethylamine, HFIP: 1,1,1,3,3,3-hexafluoropropan-2-ol. [b] Unless stated otherwise, the yields were determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

of 4.0 *F* resulted in 53% yield (entry 9). Increasing the amount of applied charge from 4.0 *F* to 6.0 *F* resulted in 55% yield (entry 10). Changing the current density from 12.0 mA cm⁻² to 18.0 mA cm⁻² (entry 11), 24.0 mA cm⁻² (entry 12) or 30.0 mA cm⁻² (entry 13) resulted in yields of 59%, 61%, and 64%, respectively, which are all inferior to the standard reaction conditions. Using 24.0 mA cm⁻² in combination with an increase of applied charge to 6.0 *F* (entry 14) or 8.0 *F* (entry 15) gave 25% and 48% yield, respectively. Based on these results, all subsequent optimization was carried out using 4.0 *F* and 12.0 mA cm⁻². When increasing the amount of morpholine to 6.0 equivalents (entry 16), no change in yield was observed. Using 6.0 equivalents of DIPEA, a slightly higher yield of 75% was found (entry 17). A further increase of yield was observed when a higher amount of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was used in combination with an additional amount of base: For a ratio of HFIP/MeCN 2:1 (vol%) and 6.0 equivalents

of DIPEA, an isolated yield of 84% was obtained (entry 18, 88% NMR yield). These conditions were tested again with glassy carbon as anode material instead of BDD, which gave an even slightly higher isolated yield of 86% (entry 19, 88% NMR yield). Those two reactions (entry 18 and 19) were carried out in 1.8 mmol scale. Increasing the amount of DIPEA further up to 8.0 equivalents resulted in a decrease of yield to 70% (entry 20). When adjusting the amount of sulfur dioxide to 20.0 equiv., with 8.0 equiv. DIPEA, a yield of 60% was obtained (entry 21). The use of pyridine instead of DIPEA resulted a yield of only 46% (entry 22). The use of HFIP as solvent without any MeCN, in combination with 6.0 equiv. of DIPEA was tested. For this experiment, the concentration of the starting material had to be lowered to 0.10 mol L^{-1} because of the lower solubility of SO_2 in HFIP compared with its splendid solubility in MeCN. This resulted in a yield of only 10% (entry 23). In general, the concentration of the starting material should be kept as high as possible because of the increased space-time yield in flow electrolysis. No product formation was found when no electricity was applied (entry 24).

Reaction scope

In all reactions, only sulfonamides were found as products, as shown in Figure 3, and no side products could be isolated. The highest isolated yield was obtained for 1,4-dimethoxybenzene, which gave sulfonamide **1** in 84% isolated yield when BDD was employed as anode material and 86% for a glassy carbon anode. 1,2-Dimethoxybenzene gave the two possible sulfonamide isomers **2a** and **2b** in isolated yields of 41% and 14% (combined yield: 55%), respectively with reaction conditions [c] and only 12% for **2a** and 9% for **2b** (combined yield: 21%) by conditions [a]. For all halogen-containing substrates, the major product was the isomer wherein the sulfonamide moiety is located in position para to the halo substituent: For 1-bromo-2,5-dimethoxybenzene, product **3a** was obtained in 53% isolated yield and isomer **3b** in 19% (combined yield: 72%). With 1,4-dimethoxy-2,3-dimethyl-benzene as starting material, product **4** was found in 26% isolated yield with reaction conditions [d] and 25% isolated yield with conditions [a]. Sulfonamide **5a** was found as major product in 50% isolated yield and isomer **5b** as minor product with 11% for 1-chloro-2,5-dimethoxybenzene as substrate (combined yield: 61%). With reaction conditions [c], for 1-fluoro-2,5-dimethoxybenzene, **6a** was found in 56% isolated yield and **6b** in 11% (combined yield: 67%). With conditions [a], **6a** and **6b** were obtained in only 13% and 8%, respectively (combined yield: 21%). For 1,4-benzodioxane, the two possible sulfonamides **7a** and **7b** were isolated in yields of 41% and 14% (combined yield: 55%), respectively for reaction conditions [c]. With conditions [a], only 23% of **7a** and 10% of **7b** (combined yield: 33%) was isolated.

As shown in Figure 4, other amines have been successfully employed in the synthesis of sulfonamides. The use of azepane gave sulfonamide **8** in 43% isolated yield. Using dibutylamine

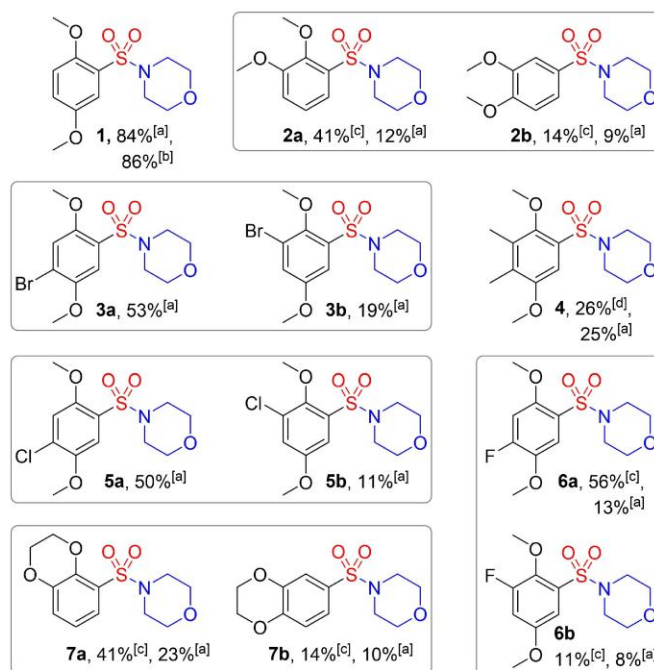


Figure 3. The scope. [a] Reaction conditions: starting material (1.8 mmol, 0.15 mol L^{-1}), morpholine (3.0 equiv.), DIPEA (6.0 equiv.), SO_2 (15.0 equiv., 2.25 mol L^{-1}), HFIP (1.10 mL), MeCN (1.12 mL), HFIP/MeCN 2:1 (vol%), amount of applied charge $Q=4.0 \text{ F}$, current density $j=12.0 \text{ mA cm}^{-2}$, room temperature, BDD anode ($2.0 \text{ cm} \times 6.0 \text{ cm}$), stainless steel cathode ($2.0 \text{ cm} \times 6.0 \text{ cm}$), undivided cell, pumping rate: $149 \mu\text{L min}^{-1}$, constant current electrolysis, single-pass flow, interelectrode gap: 0.25 mm. [b] Deviations from conditions [a]: glassy carbon instead of BDD. [c] Deviations from conditions [a]: starting material (2.4 mmol, 0.10 mol L^{-1}), DIPEA (4.0 equiv.), HFIP/MeCN 1:1 (vol%), amount of applied charge $Q=3.5 \text{ F}$. [d] Deviations from conditions [a]: starting material (1.5 mmol, 0.13 mol L^{-1}). More details can be found in the Supporting Information.



Figure 4. Other amines which have been tested. [a] Reaction conditions: starting material (1.8 mmol, 0.15 mol L^{-1}), morpholine (3.0 equiv.), DIPEA (6.0 equiv.), SO_2 (15.0 equiv., 2.25 mol L^{-1}), HFIP (1.10 mL), MeCN (1.12 mL), HFIP/MeCN 2:1 (vol%), amount of applied charge $Q=4.0 \text{ F}$, current density $j=12.0 \text{ mA cm}^{-2}$, room temperature, BDD anode ($2.0 \text{ cm} \times 6.0 \text{ cm}$), stainless steel cathode ($2.0 \text{ cm} \times 6.0 \text{ cm}$), undivided cell, pumping rate: $149 \mu\text{L min}^{-1}$, constant current electrolysis, single-pass flow, interelectrode gap: 0.25 mm. More details can be found in the Supporting Information.

or diisobutylamine resulted in isolated yields of 31% for product **9** and 66% for **10**, respectively.

Scale-up

To demonstrate the scalability of this method, the reaction was carried out in an 8-fold scale up from 1.8 mmol to 14.4 mmol starting material. In the first scale-up experiment, an isolated yield of 86% of the sulfonamide product **1** could be achieved

(Table 2, entry 1), which is the same yield that was obtained when the reaction was carried out in 1.8 mmol scale. In addition, 14% of the unconsumed starting material (SM) could be recovered during purification via flash column chromatography. Dividing the mass of isolated product by electrolysis time results in a productivity of 0.33 g/h. To improve the space-time yield of the scale-up reaction, another 8-fold scale-up experiment was carried out in a larger flow cell (Table 2, entry 2). The modular cell employed in the scale-up reaction was previously described,^[27] and more information about the flow cells can be found in the Supporting Information. This cell has an electrode surface that is 4 times the size of the small flow cell: both electrodes have a surface of 48 cm². In order to obtain the same current density and amount of applied charge, a higher electric current is applied in combination with a higher pumping rate, which decreases the reaction time (see Supporting Information for more details). In this experiment, BDD was used as anode material. To our delight, sulfonamide **1** was obtained in 92% isolated yield (Table 2, entry 2), and 8% starting material was recovered during purification using flash column chromatography. For this reaction, 1.43 g/h of product can be obtained, which means that both isolated yield and space-time yield are improved. In Figure 5, the experimental setup of entry 2 in Table 2 is displayed.

Table 2. Scale-up reactions.

#	Deviation from the standard reaction conditions ^[a]	Isolated Yield [%]	Recovered SM [%]	Productivity [g/h]
1	14.4 mmol scale, glassy carbon stainless steel	86	14	0.33
2	14.4 mmol scale, both electrodes each 48 cm ²	92	8	1.43

[a] The standard reaction conditions are the conditions shown in Figure 2.

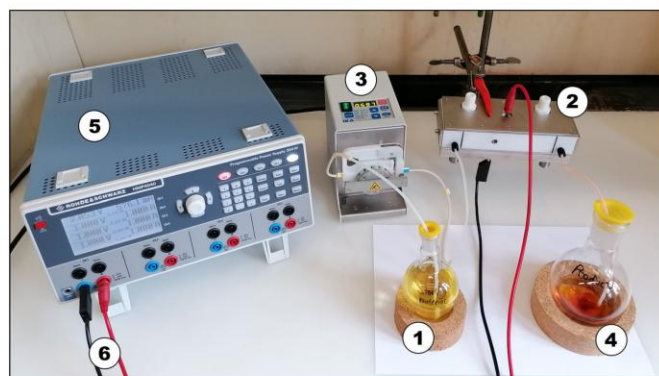


Figure 5. A simple experimental setup: The reaction solution is prepared in a round bottom flask (1) and then directly pumped out of there through the undivided electrolysis cell (2) once by using a peristaltic pump (3). The solution coming from the outlet of the electrolysis cell is collected again in a round bottom flask (4). The anode and cathode of the electrolysis cell are connected to a galvanostat (5) with wires (6). More details can be found in the Supporting Information.

Recycling of the electrolyte (reaction medium)

The HFIP/MeCN solvent mixture used in the reaction can be recycled simply by using vacuum distillation into a cooling trap, as shown in Figure 6. For the scale-up experiment of entry 2 in Table 2, 84 vol% of the HFIP/MeCN 2:1 solvent mixture was recovered, which contained 0.8 mol L⁻¹ sulfur dioxide. This recovered solvent mixture was purged again with SO₂ to obtain a new stock solution, which was then used in a reaction of the same conditions as entry 19 in Table 1 (see Supporting Information for more details). To our delight, an isolated yield of 86% for sulfonamide **1** was obtained when using the recycled solvent mixture. This clearly demonstrates that the reaction medium can be recycled and re-used easily.

Mechanism

As displayed in Figure 7, it is postulated that this dehydrogenative reaction proceeds via electrochemical C–H activation. The amine **11** reacts as a Lewis base with SO₂, forming the Lewis acid-base adduct **12**. Deprotonation of **12** with a base forms amidosulfinate species **13**. This amidosulfinate acts as both the nucleophile and as supporting electrolyte. The formation of **13** is promoted by the hydrogen bonding power of HFIP. In addition, the hydrogen bonding triggers an exclusive reactivity of the sulfur center as solvent effect.^[28] HFIP and amine mixtures show an unusually high electrical conductivity.^[29] Consequently, there is no need for an additional supporting electrolyte in the solution, which simplifies the reaction and the workup. After the initial anodic oxidation of the arene **14** to cationic radical intermediate **15**,^[30] the amidosulfinate acts as a nucleophile on it. The subsequent oxidation of **15** results in loss of a proton and rearomatization to form the sulfonamide product **16**. At the cathode, sulfur dioxide is reduced as counter reaction.^[25] Noteworthy, all components except the target compound sulfonamide are volatile, facilitating work up and translation into application.^[31]



Figure 6. Left: Easy recovery of the HFIP/MeCN solvent mixture from the crude reaction medium using vacuum distillation/condensation into a cooling trap. Right: Isolated sulfonamide product of the reaction which used a SO₂ stock solution that was made from recovered HFIP/MeCN (see Supporting Information for more details).

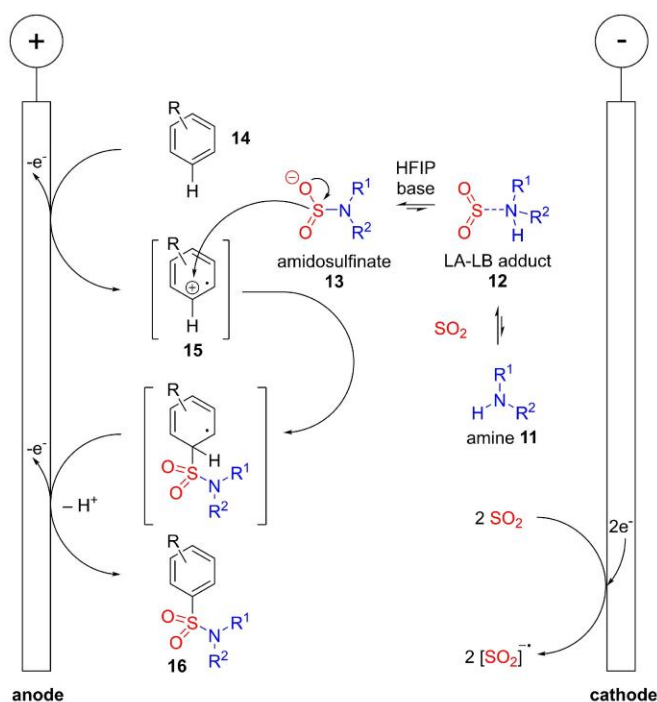


Figure 7. Proposed reaction mechanism.

Conclusions

A method for the electrochemical synthesis of sulfonamides at room temperature in single-pass flow with an undivided cell was developed. Sulfur dioxide stock solutions as atom-economic source of SO_2 are utilized and the use of electricity omits the application of expensive redox agents. The amount of HFIP and base in the reaction solution could be identified as major parameters to optimize the yield. Either BDD or glassy carbon can be chosen as anode material. In total, 10 examples were demonstrated with isolated yields up to 92%. Beneficially, the reagents and electrolyte components are volatile. Consequently, the down-stream processing is strongly facilitated. It has been demonstrated that the HFIP/MeCN solvent mixture can be recovered and re-used for further electrolysis runs. The scalability of the electrolysis was demonstrated in an 8-fold upscaled electrolysis. The space-time yield of the scale-up reaction could be improved by using a larger flow cell. This method allows sulfonamides to be synthesized electrochemically in a continuous process.

Experimental Section

Standard reaction conditions: 1,4-dimethoxybenzene (124 mg, 0.9 mmol, 0.15 mol L^{-1}) was dissolved in MeCN (1.12 mL) and HFIP (1.10 mL). Then, morpholine (3.0 equiv., 2.7 mmol, 0.24 mL) and DIPEA (4.0 equiv., 3.6 mmol, 0.61 mL) was added. To this, a stock solution of SO_2 in HFIP/MeCN 1:1 (15.0 equiv. SO_2 , 13.5 mmol, 2.25 mol L^{-1} SO_2 in solution) was added. During addition the reaction solution was cooled, as some heat-up is expected. The peristaltic pump was calibrated with acetonitrile before every

experiment. BDD was used as anode material and stainless steel as cathode material. A Teflon spacer of thickness 0.25 mm was used. The reaction solution is pumped through the electrolysis cell and the electrolysis was started (4.0 F , $149 \mu\text{L min}^{-1}$, 12.0 mA cm^{-2}). For isolation of the product, a saturated aqueous solution of NaHCO_3 (50 mL) was added and the aqueous layer was extracted with ethyl acetate ($3 \times 50 \text{ mL}$). The combined organic fractions were dried over MgSO_4 and the solvent was removed using a rotary evaporator. The crude extract was adsorbed on silica and the product(s) were isolated using flash column chromatography.

Supporting Information

Detailed information on experimental setup, general procedures, reaction optimization, scale-up, and product characterization can be found in the Supporting Information, including NMR spectra. The authors have cited additional references within the Supporting Information.^[32–36]

Acknowledgements

Financial support the Deutsche Forschungsgemeinschaft (WA 1276/17-2) and BMBF (FKZ 03ZU1205IA) is highly appreciated. Maurice Dörr is acknowledged for the helpful discussions about flow chemistry. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: electrolysis • microreactors • multicomponent reactions • radical reactions • sulfonamides

- [1] a) C. Zhao, K. P. Rakesh, L. Ravidar, W.-Y. Fang, H.-L. Qin, *Eur. J. Med. Chem.* **2019**, 162, 679–734; b) P. Ertl, E. Altmann, J. M. McKenna, *J. Med. Chem.* **2020**, 63, 8408–8418.
- [2] C. Lamberth, *J. Sulfur Chem.* **2004**, 25, 39–62.
- [3] X. Jiang (Editor) *Sulfur Chemistry (Topics in Current Chemistry Collections)*, Springer International Publishing; Springer International Publishing AG, Cham, **2019**.
- [4] K. A. Scott, J. T. Njardarson, *Top. Curr. Chem.* **2018**, 376, 5.
- [5] World Health Organization, *World Health Organization model list of essential medicines: 22nd list (2021)*. Technical documents, World Health Organization, **2021**.
- [6] H. Otten, *J. Antimicrob. Chemother.* **1986**, 17, 689–696.
- [7] a) H. Chen, H. Li, S. Pei, X. Wen, Y. Zhang, *Polymer* **2009**, 50, 4317–4324; b) P. Zhang, D. Chen, N. Chen, K. Huang, D. Tao, M. Li, S. Dai, *ChemSusChem* **2018**, 11, 1751–1755.
- [8] D. K. Sharma, S. T. Adams, K. L. Liebmann, A. Choi, S. C. Miller, *Org. Lett.* **2019**, 21, 1641–1644.
- [9] H. G. Richey, J. Farkas, *J. Org. Chem.* **1987**, 52, 479–483.

- [10] C. Liu, X. Yan, M. Wang, P. Qin, Z. Qi, M. Ji, X. Liu, P. V. Babu, X. Li, Z.-N. Cui, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 271–276.
- [11] T. Chen, W.-Q. Li, Z. Liu, W. Jiang, T. Liu, Q. Yang, X.-L. Zhu, G.-F. Yang, *J. Agric. Food Chem.* **2021**, *69*, 12039–12047.
- [12] P. de Groote, P. G. Rouxhet, J. Devaux, P. Godard, *Appl. Spectrosc.* **2001**, *55*, 877–887.
- [13] S. Feng, M. Huang, J. R. Lamb, W. Zhang, R. Tataru, Y. Zhang, Y. G. Zhu, C. F. Perkinson, J. A. Johnson, Y. Shao-Horn, *Chem* **2019**, *5*, 2630–2641.
- [14] a) S. Tummampalli, S. Bodige, K. C. Gulipalli, S. Endoori, S. Medaboina, K. Mallidi, *Tetrahedron Lett.* **2022**, *97*, 153781; b) S. P. Blum, K. Hofman, G. Manolikakes, S. R. Waldvogel, *Chem. Commun.* **2021**, 8236–8249; c) T. S.-B. Lou, Y. Kawamata, T. Ewing, G. A. Correa-Otero, M. R. Collins, P. S. Baran, *Angew. Chem. Int. Ed.* **2022**, *61*, e202208080; d) S. P. Blum, L. Schäffer, D. Schollmeyer, S. R. Waldvogel, *Chem. Commun.* **2021**, *57*, 4775–4778; e) S. P. Blum, D. Schollmeyer, M. Turks, S. R. Waldvogel, *Chem. Eur. J.* **2020**, *26*, 8358–8362; f) O. M. Mulina, A. I. Ilovaisky, A. O. Terent'ev, *Eur. J. Org. Chem.* **2018**, 4648–4672; g) S. Mondal, S. Malakar, *Tetrahedron Lett.* **2020**, *76*, 131662; h) Z. Ye, X. Zhang, W. Maa, F. Zhang, *Green Chem.* **2023**, *25*, 2524–2540.
- [15] M. Bögemann, H. Böhme, H. Eckoldt, J. Goerdeler, F. Muth, S. Petersen, M. Quaedvlieg, H. Rheinboldt, A. Schöberl, A. Schönberg et al. (Editors) *Schwefel-, Selen-, Tellur-Verbindungen*, Georg Thieme Verlag, Stuttgart, **1955**.
- [16] R. C. Larock (Editor) *Comprehensive organic transformations. A guide to functional group preparations*, Wiley, New York, NY, **2018**.
- [17] G. Laudadio, E. Bampoutsis, C. Schotten, L. Struik, S. Govaerts, D. L. Browne, T. Noël, *J. Am. Chem. Soc.* **2019**, *141*, 5664–5668.
- [18] S. P. Blum, T. Karakaya, D. Schollmeyer, A. Klapars, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 5056–5062; *Angew. Chem.* **2021**, *133*, 5114–5120.
- [19] D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386–12400.
- [20] a) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319; b) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041; *Angew. Chem.* **2018**, *130*, 6124–6149; c) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619; *Angew. Chem.* **2018**, *130*, 5694–5721.
- [21] a) T. Noël, Y. Cao, G. Laudadio, *Acc. Chem. Res.* **2019**, *52*, 2858–2869; b) M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
- [22] a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893; b) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* **2020**, *24*, 1802–1813; c) S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456–1472; d) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, 47, 4583–4592.
- [23] F. Darvas, G. Dormán, V. Hessel, S. V. Ley (Editor) *Flow Chemistry*, De Gruyter, Berlin, Boston, **2021**.
- [24] a) D. Pletcher, R. A. Green, R. C. D. Brown, *Chem. Rev.* **2018**, *118*, 4573–4591; b) N. Kockmann, M. Gottsponer, B. Zimmermann, D. M. Roberge, *Chem. Eur. J.* **2008**, *14*, 7470–7477.
- [25] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204140; *Angew. Chem.* **2022**, *134*, e2022041.
- [26] a) D. M. Heard, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, *59*, 18866–18884; b) S. Lips, S. R. Waldvogel, *ChemElectroChem* **2019**, *6*, 1649–1660; c) S. R. Waldvogel, S. Mentizi, A. Kirste, *Top. Curr. Chem.* **2012**, *320*, 1–31; d) Y. Einaga, *Acc. Chem. Res.* **2022**, *55*, 3605–3615.
- [27] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- [28] L. Schulz, S. Waldvogel, *Synlett* **2019**, *30*, 275–286.
- [29] a) J. L. Röckl, M. Dörr, S. R. Waldvogel, *ChemElectroChem* **2020**, *7*, 3686–3694; b) J. L. Röckl, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2020**, *59*, 315–319; *Angew. Chem.* **2020**, *132*, 323–327.
- [30] a) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765; b) J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, *53*, 45–61.
- [31] J. Seidler, J. Strugatchi, T. Gärtner, S. R. Waldvogel, *MRS Energy Sustainability* **2020**, *7*, E42.
- [32] W. Armarego, *Purification of Laboratory Chemicals*, 8th Edition, 8. Ed., Butterworth-Heinemann, **2017**.
- [33] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.
- [34] M. Zirbes, T. Graßl, R. Neuber, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2023**, *62*, e202219217; *Angew. Chem.* **2023**, *135*, e202219217.
- [35] B. Gleede, M. Selt, C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2020**, *24*, 1916–1926.
- [36] G. Jander, K. F. Jahr, G. Schulze, J. Simon, R. Martens-Menzel, *Maßanalyse. Titrationen mit chemischen und physikalischen Indikationen*, 19. ed., De Gruyter, Berlin, Boston, **2017**.

Manuscript received: September 8, 2023
Revised manuscript received: October 13, 2023
Version of record online: October 31, 2023

4.3 Automated Electrosynthesis in Flow

The following results have been published in a peer-reviewed publication.^[120]

M. M. Hielscher,[‡] M. Dörr,[‡] **J. Schneider**, S. R. Waldvogel *

LABS: Laboratory Automation and Batch Scheduling – A Modular Open Source Python Program for the Control of Automated Electrochemical Synthesis with a Web Interface

Chem. Asian J. **2023**, 18, e2023003

DOI: [10.1002/asia.202300380](https://doi.org/10.1002/asia.202300380)

License: CC BY 4.0

[‡] These authors contributed equally

* Corresponding author

Explanation of my contribution:

M. M. Hielscher, M. Dörr, and S. R. Waldvogel were responsible for conceptualization of the project. M. M. Hielscher was responsible for programming of the front end of the LABS software and M. Dörr for the back end of LABS. M. M. Hielscher and M. Dörr were responsible for data analysis and curation, conceptualization and evaluation of the Design of Experiment (DoE) plan. M. M. Hielscher and **J. Schneider** were responsible for setup and maintenance of the automated experimental electrolysis flow setup. **J. Schneider** was responsible for carrying out the electrolysis experiments, supervision of the experimental setup for the automated electrolysis, and for preparation of gas chromatography samples for yield determination. M. M. Hielscher and M. Dörr wrote the manuscript and the Supporting Information. **J. Schneider** assisted in writing of the Supporting Information. The name LABS (Laboratory Automation and Batch Scheduling) was proposed by S. R. Waldvogel. S. R. Waldvogel supervised the project and assisted in writing of the manuscript and the Supporting Information.

Introduction: Chemists are already quite familiar with laboratory automation in their daily work life. Most analytical devices such as NMR spectrometers have autosamplers, which automatically measure a magazine of samples over a weekend.^[121] In synthetic organic chemistry, automation has also been well established already, for example the Merryfield apparatus for automated peptide synthesis.^[122]

While laboratory automation has extended its influence in many fields of chemistry like photochemistry or even inorganic chemistry using automated Schlenk setups, the use of laboratory automation in electrosynthesis is an underexplored field.^[123,124] A major issue with laboratory automation for electrosynthesis is the lack of standardized commercially available setups. There are several factors which contribute to this. Laboratory automation deals with a wide range of different devices and experimental setups (thermostats, various types of pumps...), and especially in the context of flow chemistry, many setups are highly customized for the reaction that is under investigation. While this demonstrates the flexibility of flow chemistry when used in conjunction with electrosynthesis,^[80] it also adds a level of complexity if one attempts to develop a more generalized solution. This complexity poses major challenges to the development of a software which attempts to coordinate an automated experimental setup because a good model of abstraction is required to achieve this. This implies that a robust software architecture is required.^[125] To solve this problem, the Waldvogel group developed LABS: Laboratory Automation and Batch Scheduling (Figure 45).

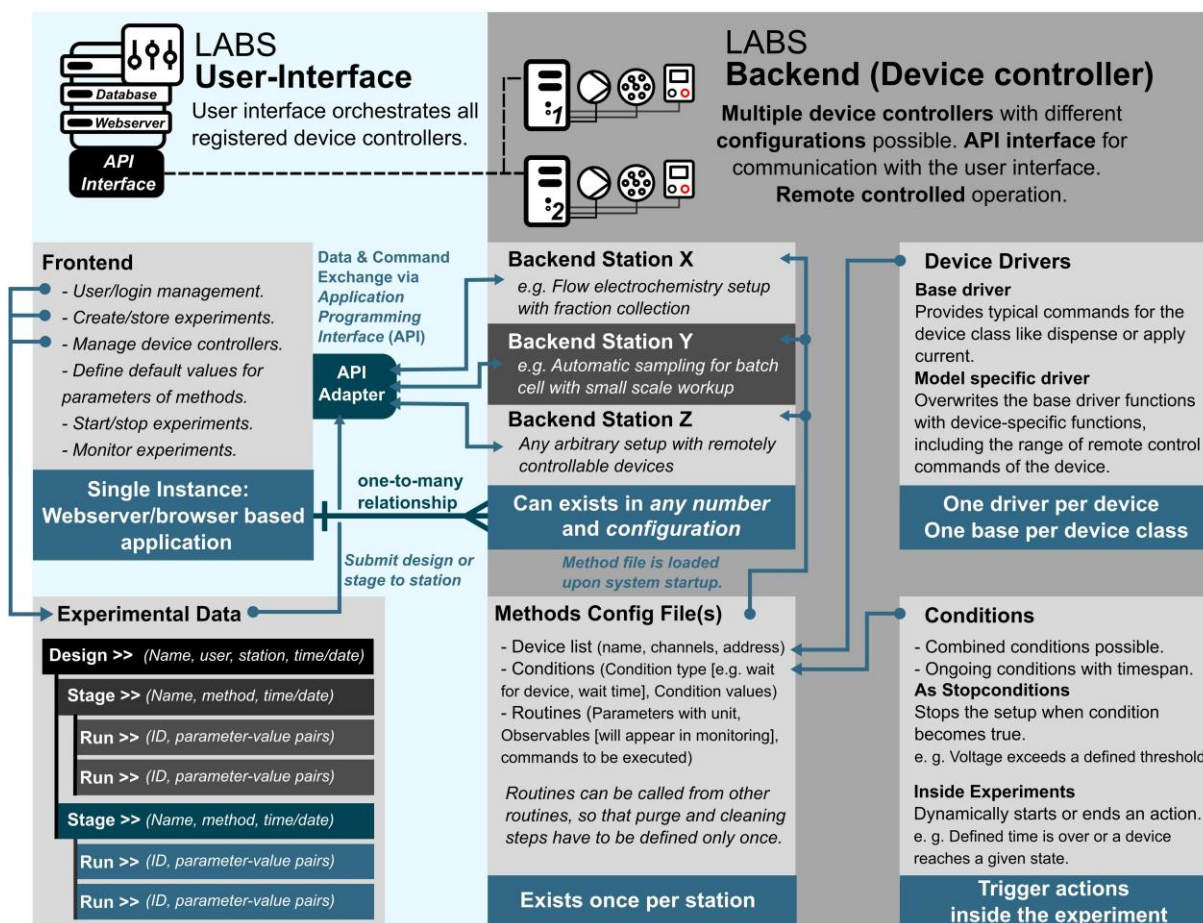


Figure 45. Overview of the LABS software architecture.^[120]

LABS is a software solution written in Python and it's responsible for controlling the automated experimental setup by allowing the users to customize it and to submit experiment plans. LABS is split in frontend and a backend (Figure 45). The frontend can be accessed simply in a web browser, and it allows users to upload Excel files to submit experiments to be carried out. This user interface also displays information on the experiments which are currently running. This is designed to be operated without any programming knowledge. The general idea behind the LABS backend is to abstract the automated experimental setup by writing so called device drivers for the individual types of devices which are employed in the automated experimental setup, which is just a piece of Python code which abstract controlling the device in generalized commands. Once a driver file is written for a specific device type, for example a pump, an arbitrary number of devices of this type can be employed in the automated experimental setup. This implies that programming knowledge is needed only for writing device drivers. Even then, the required amount of programming knowledge is comparably moderate. In LABS, the experimental setup and the sequence of commands that is used for a certain method is specified in a very flexible way by using configuration files. This means to add new methods or a new device of a known type to the automated experimental setup, no programming knowledge is required at all. The frontend and backend communicate with each other and record experimental data.

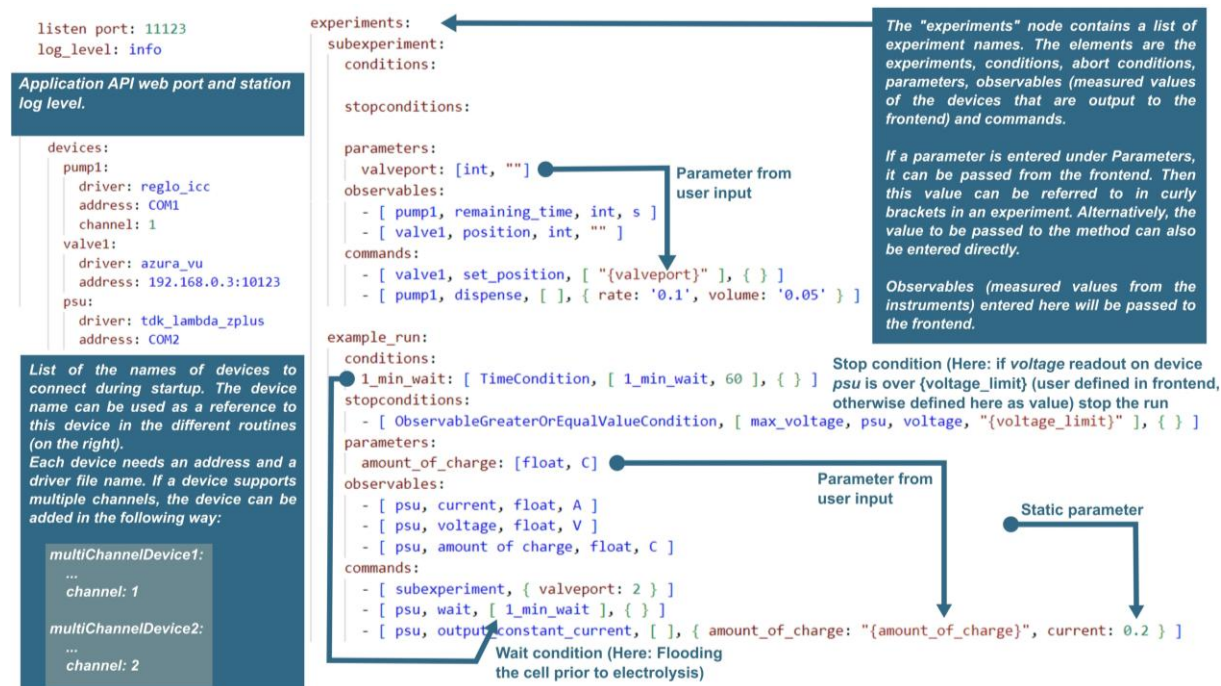


Figure 46. Example of a LABS configuration file.^[120]

Test Reaction: As a starting point for the development of the LABS software, a test reaction was required. Ideally, the test reaction is an electrochemical synthesis which is already studied to great extent so it can be used as a known benchmarking system. Therefore, the electrochemical cross-coupling of phenols was selected (Figure 47), which has been pioneered and extensively investigated by the Waldvogel group.^[126]

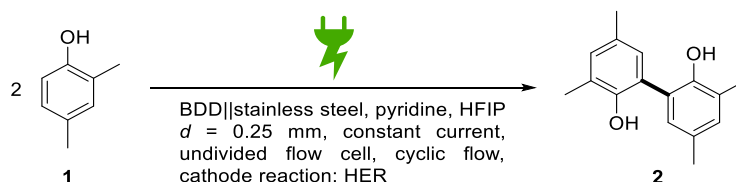


Figure 47. The test reaction utilized for benchmarking the automated experimental setup.^[120]

Experimental Setup: An experimental setup as depicted in Figure 48 was chosen. The starting materials are employed as stock solutions. The most important components are the reservoir, in which the reaction solution is prepared, and the flow electrolysis cell. One peristaltic pump was employed in this setup for dosing of reagents and for pumping the electrolyte solution through the cell. From the flow electrolysis cell, the electrolyte solution can be transferred back into the reservoir, or into a fraction collector, or into the waste. All devices are connected to a computer, and the LABS software is responsible for controlling the automated electrosynthesis setup. Ideally, the user submits a catalog of reactions to be carried out, and the automated system performs them without further input from the user. The system is also programmed to add rinsing and cleaning steps in between electrolysis. It's important to note that because of the flexibility of LABS, any other experimental setup would have been possible as well. LABS is even capable of controlling multiple of such automated electrosynthesis stations simultaneously. This offers great scalability for an automated laboratory on large-scale.^[124]

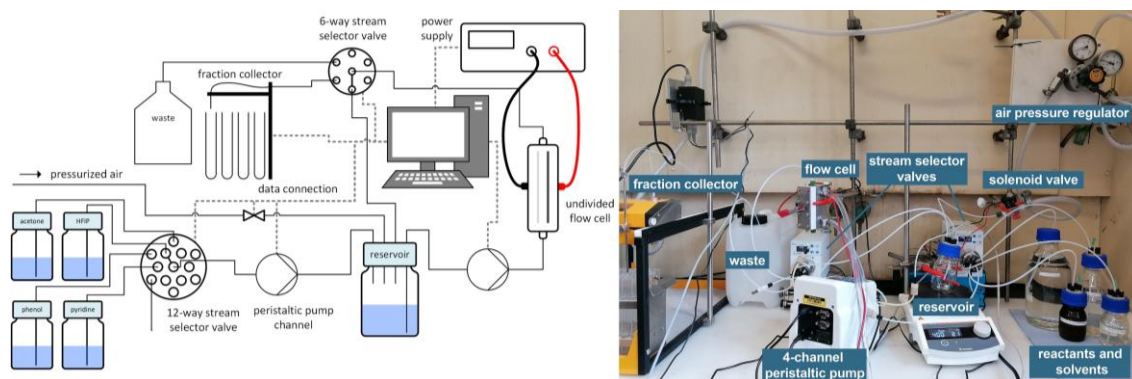


Figure 48. The automated experimental setup (left: flow scheme, right: photograph).^[120]

Design of Experiments: The DoE plan in Table 9 was chosen for the test reaction (Figure 47). The current density, applied charge, flowrate multiplier, concentration of the starting material, concentration of pyridine (equivalents), and the reaction temperature was investigated in a 2^{6-2} fractional factorial design. Each experiment was repeated once, resulting in 32 experiments which were carried out by the automated experimental setup using LABS.

Table 9. Parameters and levels for the Design of Experiments (DoE) plan.^[120]

Parameter	Unit	Low level	High level
Current density j	mA / cm ⁻²	20	40
Applied charge Q	F	0.70	0.90
Flow multiplier	–	5	15
$c(2,4\text{-dimethylphenol})$	mol / L	0.75	1.25
$c(\text{pyridine})$	vol. %	5	10
Temperature	°C	10	25

The 32 experiments of the design were grouped into 4 blocks which each contained 8 experiments. A new tube was inserted into the peristaltic pump at the start of each block. In the analysis of the results, it can be seen that there is a significant drop in yield with increasing experiment number (Figure 49). This is due to the deterioration of the employed tubing material. In the regression model of the DoE, no parameter could be excluded by ANOVA ($R^2 = 74\%$) with $\alpha=10\%$. The current density, applied charge, and the flowrate multiplier are below the significance threshold, but they are involved in two-parameter interactions.

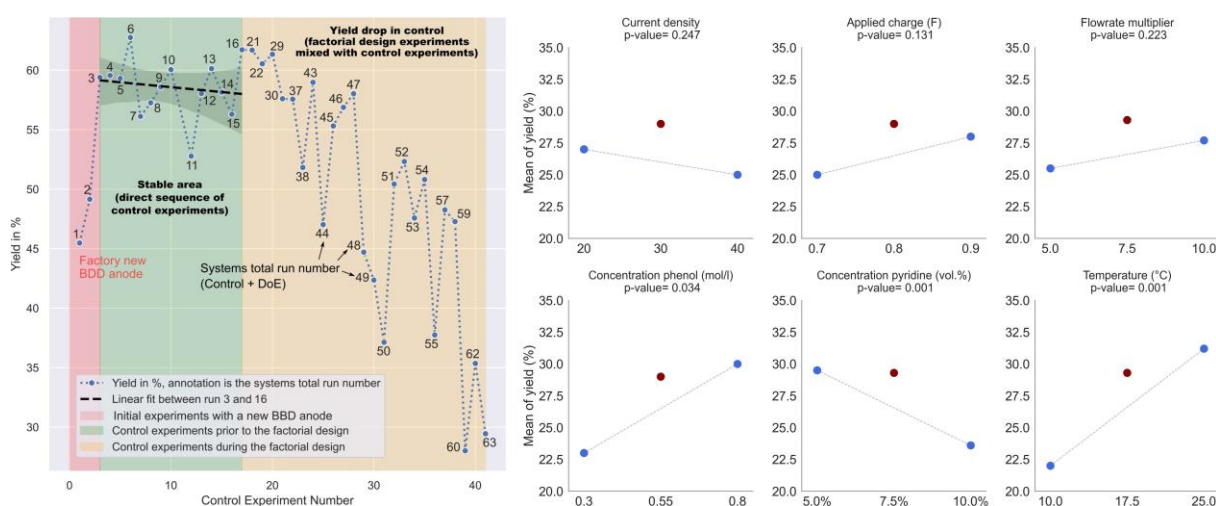


Figure 49. The analysis of the yield as a function of experiment number shows a systematic decrease which is caused by the deterioration of the tubing in the peristaltic pumps, which implies that improved pump systems are required for further development of automated electrosynthesis.^[120]

Conclusion: With LABS, the Waldvogel group developed a highly flexible software solution for automated electrosynthesis. LABS is split in a frontend and a backend, and no programming knowledge is required to operate it. The flexible software architecture allows for easy modification of the experimental setup. If a known device type is added to the system, no programming knowledge is required at all. If a completely new device type is added, a device driver must be written in Python for it. While the development of LABS was a success, it became evident that further work is required to solve the problems associated with the employed pumps. It has been demonstrated that the tubing in peristaltic pumps deteriorates over long-time operation, which renders these types of pumps unsuitable for operations which require high precision for preparation of the electrolyte solution or for pumping the electrolyte through the flow electrolysis cell. The use of peristaltic pumps is further discouraged by the comparably high cost of the tubing material. Furthermore, because the calibration is lost rapidly when employing peristaltic pumps, frequent manual calibration of the pump is required, which is not in agreement with the basic idea of automation. These challenges were subsequently overcome by utilizing piston pumps in our follow-up work on the automated optimization of alkyl arenesulfonates in flow.^[89]

LABS: Laboratory Automation and Batch Scheduling – A Modular Open Source Python Program for the Control of Automated Electrochemical Synthesis with a Web Interface

Maximilian M. Hielscher^{+, [a]} Maurice Dörr^{+, [a]} Johannes Schneider^{+, [a]} and Siegfried R. Waldvogel^{*, [a, b]}

Dedicated to Prof. Dr. Dennis Curran on the occasion of his 70th birthday.

Abstract: With LABS, an open source Python-based lab software is established that enables users to orchestrate automated synthesis setups. The software consists of a user-friendly interface for data input and system monitoring. A flexible backend architecture enables the integration of multiple lab devices. The software allows users to easily modify experimental parameters or routines and switch between different lab devices. Compared to previously

published projects, we aim to provide a more widely applicable and easily customizable automation software for any experimental setup. The usefulness of this tool was demonstrated in the oxidative coupling of 2,4-dimethylphenol to the corresponding 2,2'-biphenol. In this context, the suitable electrolysis parameters for flow electrolysis were optimized by way of design of experiments.

Introduction

In recent years, electro-organic chemistry has developed into a cost-friendly synthesis alternative compatible with green chemistry principles^[1] for the preparation of small molecules, the liberation of value-added products from waste streams, and the sustainable production of platform oxidizers.^[2] The use of electrons as a reagent often facilitates the generation of radical intermediates, which can offer shortcuts from multi-step reaction sequences to a single direct step.^[3,4] The direct (or mediated) electron transfer to or from the electrode often allows a metal-free catalytic reaction to be carried out.^[4,5] Typical setups for electrochemical reactions are either batch-type mode,^[6] or electrochemical flow cells through which the electrolyte is pumped, either in a single pass, or pumped multiple times through the flow cell using a reservoir.^[7] Electrochemical reactions in flow setups often exhibit better scalability

and higher space-time yields, and the (typically) shorter interelectrode distances allow more sustainable syntheses using significantly smaller amounts of supporting electrolyte.^[8,9] However, electrochemical reactions in flow require more peripheral equipment such as pumps, valves, and fraction collectors, and are therefore often operated with only a single electrolyzer, whereas for screening in batch a variety of systems exist that allow parallel operation of several reactions. A review article for high-throughput screening in electro-organic synthesis was compiled by J. C. Vantourout and co-workers.^[10] With regards to electrochemical flow cells, methods like 3D printing allow prototyping and miniaturization to speed up development.^[11] Additional reaction parameters for electrolysis in flow, such as flow rate, can complicate the optimization. This challenge can be overcome systematically by methodological approaches such as design of experiments or Bayesian optimization.^[12]

Automation of the setup for electrolysis in flow can help to increase the efficiency of screening runs, while at the same time observables such as the cell voltage can be continuously monitored. Analysis of this data can provide information on reproducibility and status of the electrodes, e.g., fouling or corrosion events.^[17] Due to the growing importance of electronic laboratory notebooks, flexible control loops capable of automated processing of measurement data are required.

Automated systems are increasingly being established not only for commercial applications, but also as free and open source software.^[18] In particular, if the functional scope of the control software is to be changed, open source projects offer great advantages over closed source. One such advantage is that changes can be implemented, tested, and made generally available to the community by the user. Since 2016 several groups have reported projects dealing with laboratory automation (Figure 1). These are commonly built using LabView or

[a] M. M. Hielscher, M. Dörr, J. Schneider, Prof. Dr. S. R. Waldvogel
Department of Chemistry
Johannes Gutenberg University
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: waldvogel@uni-mainz.de

[b] Prof. Dr. S. R. Waldvogel
Institute of Biological and Chemical Systems – Functional Molecular
Systems (IBCS-FMS)
Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen (Germany)

[†] These authors contributed equally to this work.

Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/asia.202300380>

This manuscript is part of an Indo-German Workshop (IGW) special collection.

© 2023 The Authors. Chemistry - An Asian Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

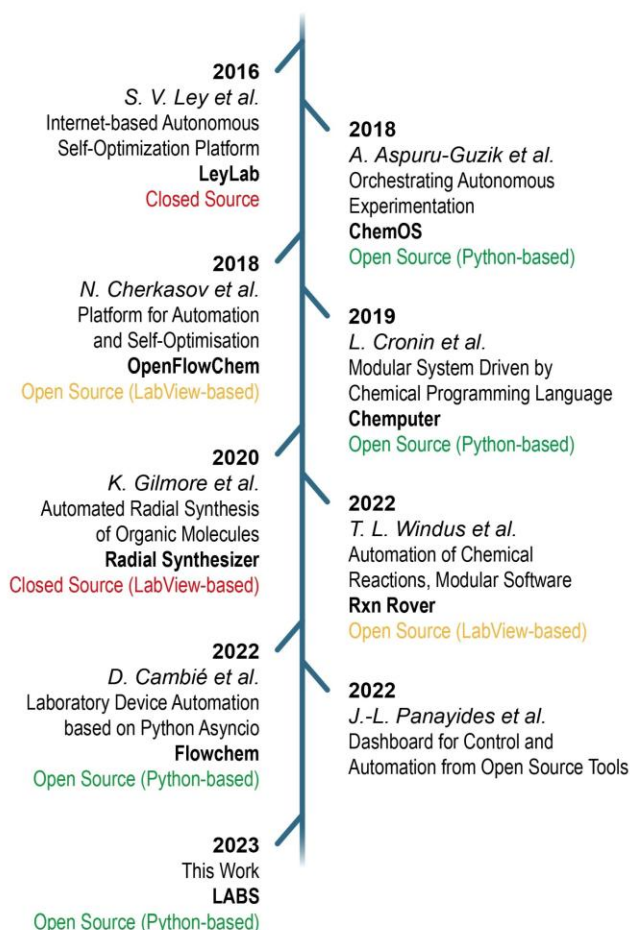


Figure 1. Recent projects towards automated synthesis platforms.^[13,14–16]

Python and the majority were published in an open source fashion. While these projects are all very inspiring and impressive contributions, they unfortunately did not lead to the sought after communalization and widespread availability of automated reaction setups. Our initial contributions to this field were published in 2021; a semi-automated setup for electrolysis using a reservoir with variable electrolysis parameters in flow cells with an automated fraction collector.^[19] However, no purging step was possible with this setup and the control was implemented in LabView as a closed source file. In contrast to single setup automation, Aspuru Guzik *et al.* emphasized the orchestration of multiple setups and the use of AI informed experimental planning. However, they did not report the actual code that controlled the experimental setup itself.^[14,16] Cronin *et al.* elegantly showed the applicability of a formal and general description of chemical experiments in a machine-readable format.^[20] As with the previously mentioned work, the focus was not on the communication to the physical devices.^[15] More recently, Cambié *et al.* published their project Flowchem on GitHub; it is the only open source code among those discussed that is actively maintained in 2023.^[21,22] Its aim was to expose an interface that makes the devices' functionality available to other software (a RESTful API) for every given device in a setup, wherein the flow of commands in the experiment has to be

implemented by the user in a programming language of their choice.^[22] This is undeniably valuable to users with programming skills, however, for the uninitiated it can be a roadblock to implementing these systems. While the *Chempur* abstracts the setup on an even higher level and *Flowchem* on a similar level than LABS, many of the above-mentioned projects lack generalizability or abstraction layers in regard to the devices used in the setups. Their accordingly high degree of specialization is a disadvantage for broader application, and adaptation and subsequent application of the experimental setup is often difficult, especially if software components need to be refactored on a major scale. Furthermore, the use of LabView as basis for the software adds upfront cost and the need to familiarize oneself with LabView in order to run and adapt the programs. In our project, we aim to close this gap by providing a free and open source software base for sequence-based control of arbitrary experimental setups. At the same time, we want to provide the user with a modern, centralized user interface where experimental conditions can be planned and running experiments can be monitored. Furthermore, an administrative view allows for the adjustment of general parameters (e.g., a flush step between two different runs or within one run).

Although automated chemistry is of interest to the wider chemical community, it is outside of many traditional chemists' skillset to operate and adapt custom solutions to these software packages. Therefore, we aim to provide a package that enables the facile building of automated systems from the supported devices with negligible prior knowledge needed. Since only the configuration for the experimental setup has to be defined, little to no programming knowledge is required.

Results and Discussion

Our approach to implement the system is based on two components (Figure 2): the web-based user interface provides an interface for the user while the backend deals with the logic for controlling the setups. The backend communicates with the connected devices based on the asynchronous network framework *Twisted*, and communicates with the user interface in a many-to-one relationship.^[23] The use of *Twisted* for device communication has been pioneered by Ley *et al.* with their project octopus.^[24] This framework is especially well suited, since it is designed to allow a simple implementation of networking protocols independent of the physical connection like RS232 and Ethernet. A setup class organizes the execution of the scheduled experiments and can stop the sequence if necessary. The experiment sequence is provided by the experiment class, which reads the commands to be executed from a configuration file in YAML format. This can be changed by the user, and individual sequences can be combined into larger sequences, so that any intermediate steps, such as purging routines, can be actualized in addition to the actual experiment to be carried out. A device driver class provides generic adapters for communication with the devices, such as pumps or power supply units, which provide device-specific functions.

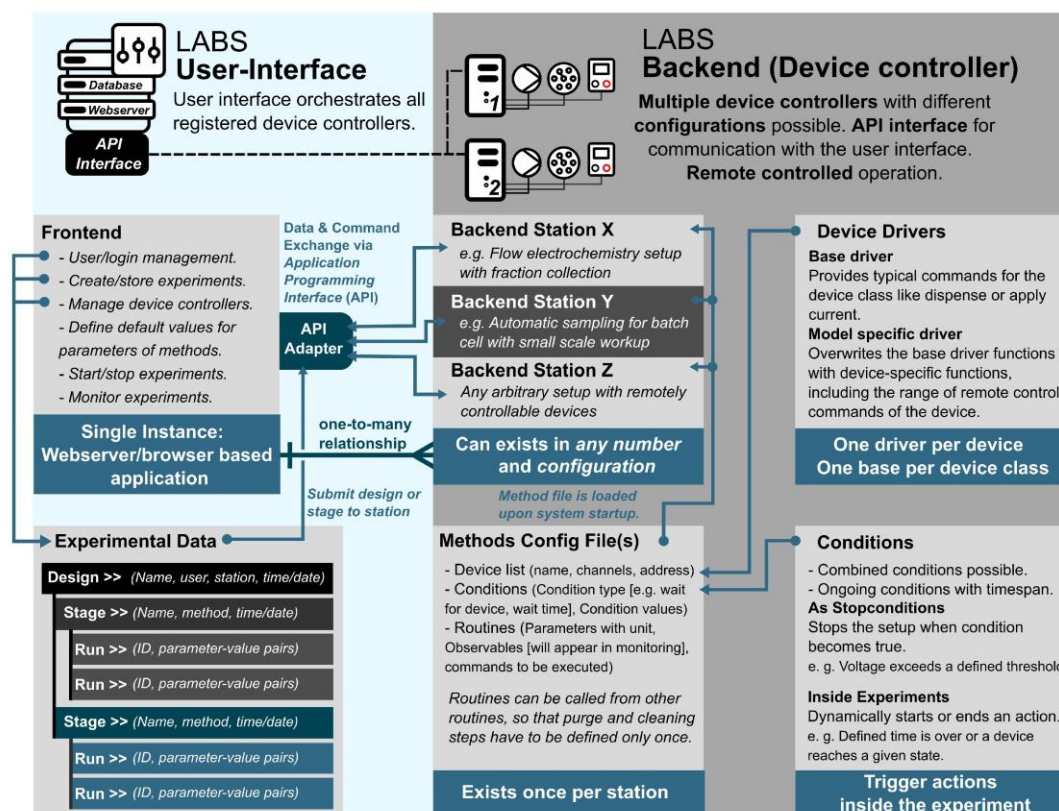


Figure 2. Representation of the link between the user frontend and the backends at the experimental stations.

The adapter then accesses a driver file that contains the model-specific control commands and overwrites the generic functions of the adapter so that any device can be used, provided they can map the required basic functions. The user interface is a *Flask*-based^[25] Python application that provides a web management platform for users and experimental parameters, as well as monitoring of the various backends. *Flask* is a popular choice for web development because of its simplicity and flexibility, allowing developers to quickly create scalable and efficient web applications. The rich ecosystem of *Flask* already provides additional functionalities such as database integration, authentication, API development. It provides a web server so that the user interface can be accessed with common web browsers.

The user interface is designed in a modular fashion, the functionality modules are organized as so-called blueprints, so far there is the module "Users", which provides the functionality to create different users in a database, to authenticate and authorize them to use the user interface. The module "Monitoring" offers an overview page of all integrated backends with their current state, as well as a detailed view, which displays the queued experiments of a selected station in table form. Also displayed there are the observables (which are defined in the configuration file of the station) as line plots (voltage, current, temperature), progress bars (remaining dosing time of the pump, applied charge), or as data tables (positions of the switching valves over time). The module "Experiments" allows the hierarchical management of the experimental data. First, an experimental design is created, which is assigned to a user and

a backend. In this design, individual stages can be created, each of which is linked to a method (the experimental sequence to be carried out) provided by the corresponding backend. For example, additional cleaning steps can be added between experiments. Individual runs can then be created within a stage. The stage overview page offers a down- and upload function (Excel) to add, update, or delete the runs of a stage. Any number of backends can be added on an administrative level. The currently loaded configuration can be downloaded from the stations to the user interface's database. For each method known at the particular device, parameters can be set as static and do not have to be defined for each run (e.g., the volume of purging solvent). This should enhance reproducibility in multi-user scenarios.

The configuration syntax (Figure 3) was designed to implement the following features: multichannel devices can be used as one device with the channel as a parameter in each command or each channel as a separate device. Experiments can contain other experiments to allow high reuse of common processes, like purging a compartment or tube. A full description of the configuration file can be found in the supporting information.

To test the sequence of the methods in a dry run, we created virtual "dummies" of the devices used. These behave like the devices in terms of device communication. The readouts can be counting down times or randomized values, the cell voltage of a current source, etc. As of now, the core functions for the devices we use are programmed into the

Methods Config File Example

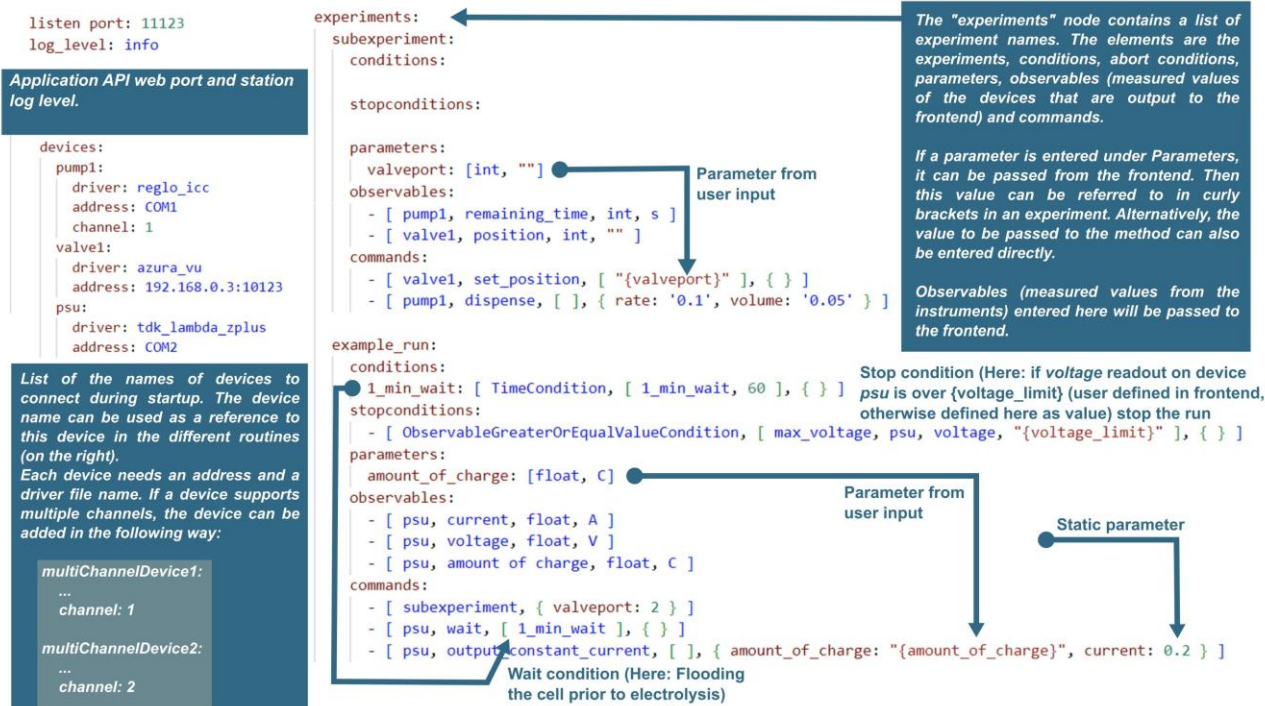


Figure 3. Configuration file example. Left: General settings and device configuration; demonstrated features: channel of a multichannel device is treated as a single device, COM- and TCP/IP ports can be used. Top right: First experiment named *subexperiment* (demonstrated features: experiment has a variable parameter named *valveport*). Bottom right: Second experiment named *example_run* (demonstrated features: condition *1_min_wait* used in wait command, stop-condition utilized to cancel experiment if voltage is above configurable threshold, parameter valve port handed to *subexperiment*).

dummies. The function for generating random numbers can be coupled with a user-defined function that simulates, for example, a time-dependent increase in voltage. In this way, more complex stop conditions for the automated run observation can be tested efficiently prior to the actual experiment. For the devices used in this project we provide virtual devices in a simple framework. We employed this to test changes in the configuration before running it in the laboratory. This "virtual experimental setup" can also be integrated into the user interface to control it. This facilitates the further development of the user interface, as no real devices are needed to test new features.

Due to our experience with studying dehydrogenative C–C coupling of and with phenols, we chose the anodic oxidative homocoupling reaction of 2,4-dimethylphenol as an example for the first test runs.^[19,26,27,28] This electrochemical transformation to the corresponding 2,2'-biphenol is particularly challenging as it is very prone to side reactions, such as the formation of polycyclic by-products.^[28,29] Therefore, our first experimental setup (Figure 4) consisted of a dead-end selector switching valve (*Knauer*) to which 2,4-dimethylphenol, pyridine, hexafluoro-isopropanol (HFIP), and isopropanol reservoirs were connected. The common outlet connects to one channel of a four-channel Reglo ICC peristaltic pump with independent channel control (*Ismatec*) into a mixing chamber, in our case a 50 mL *Schott* glass screw-cap bottle with a lid with a plug-in insert for four 1/8" OD tubes. An additional hole was drilled in

the center of the lid to allow flushing with compressed air. The compressed air was set to 1.5 bar using a pressure regulator and fed in via a switchable normally closed solenoid valve. An Arduino Uno microcontroller (*Arduino*) opens and closes the valve via a relay. The reservoir was clamped at a slight angle to enable full drainage via the second channel of the pump. This channel leads to a flow electrolysis cell with a 2×6 cm² anode made of boron-doped diamond on silica and a stainless-steel cathode block with temperature control. A spacer made of PTFE adjusted the electrode gap to 0.25 mm.^[9] The outlet of the flow cell was connected to the common port of another switching valve, from where the flow can be directed back to the reservoir, to a waste canister, or to a fraction collector. The fraction collector used was a low-cost Lambda Omnicoll fraction collector (*Lambda Instruments*), which can be operated with different sized collection vessels.

In previous studies on electrochemical conversions in flow with active electrode areas of 2×6 cm² peristaltic pumps were typically used. These offer the possibility to work in divided cells with separate channels for anolyte and catholyte solutions, or to operate several cells in parallel with one pump. In the past, we used PharMed® BPT tubing as peristaltic pump tubing, which has a high mechanical stability but only moderate chemical stability. We therefore also tested peristaltic tubing made of fluororubber (FPM, Viton® *Optubus*). However, these were not mechanically stable in the original cassettes that came with the pumps and ruptured within the first few minutes.

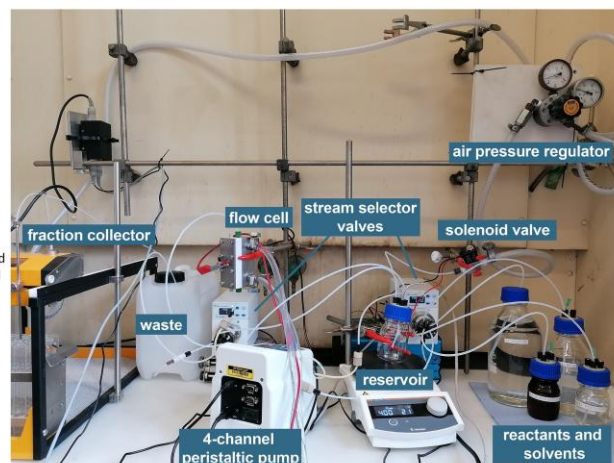
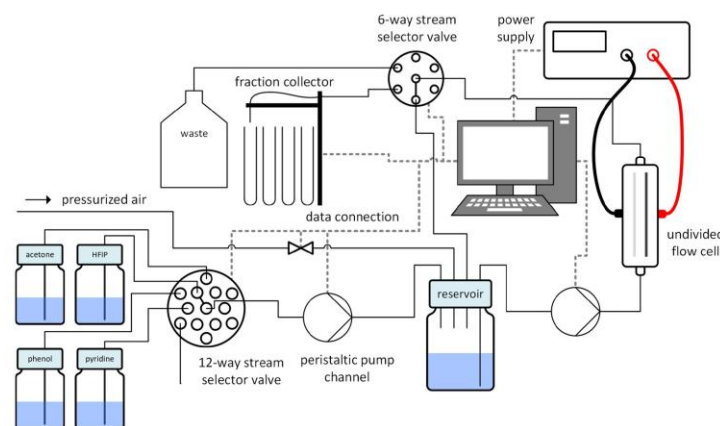


Figure 4. Left: Scheme of the automated flow setup enabling continuous and cyclic electrolysis. Right: Picture of the setup in use, the components are labelled. Electrolyte flow goes from right to left. Picture on the right by J. Schneider.

Consequently, we equipped the pump with PharMed® BPT tubing for the initial experiments (Scheme 1).

We started with a test series of the same electrolysis conditions to investigate the overall behavior of the system in terms of yield (Conditions: $j = 10 \text{ mA/cm}^2$, $Q = 0.9 F$, $v = 1.99 \text{ mL/min}$ ($15 \times \text{Single pass rate}$), $C(1) = 1.25 \text{ mol/L}$, $\text{vol.}(\text{Pyridine}) = 5\%$, $T = 25^\circ\text{C}$). This included a purge phase in which the system was purged with acetone then primed with HFIP. The electrolyte was then prepared in the reservoir, electrolyzed in cyclic flow, and collected by the fraction collector.

By starting with a new, pristine BDD anode, we observed a sharp increase in yield in the first three experiments (red area, Figure 5). We attribute this to the known change in surface termination from H-type to OH-termination.^[30] Runs 7, 11, and 15 were each the first run after the cell was idle overnight during the initial test phase where the interface was open to the air. From previous studies, deposit formation (fouling) is known to occur while electrolysis, and its modification by oxidation may contribute to the observed effect.^[31] The system subsequently behaved in a largely stable manner over 15 electrolysis reactions with respect to the yield of coupling product (green area). We equipped the pump with new peristaltic tubing and began submission of all runs necessary for the factorial design Table 1) in sections mixed with the control experiments (orange area). The system initially continued to behave stable in terms of yield, but a steady downward trend was observed after control experiment 30. The anode did not show any deposit formation or fouling during a

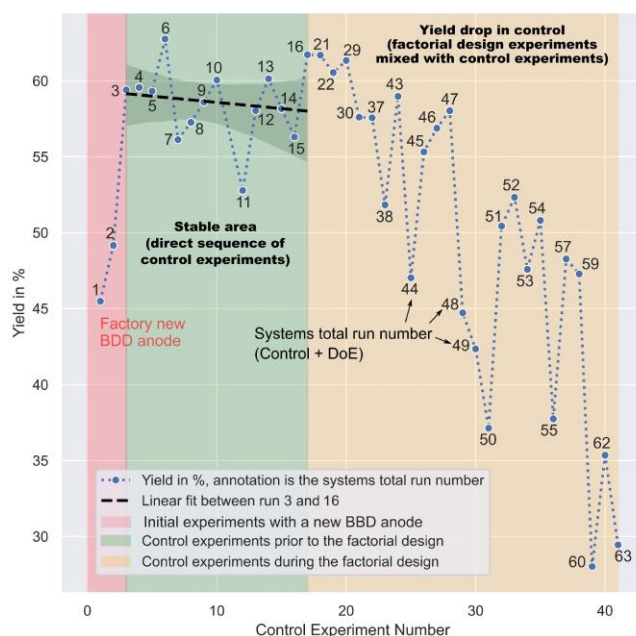
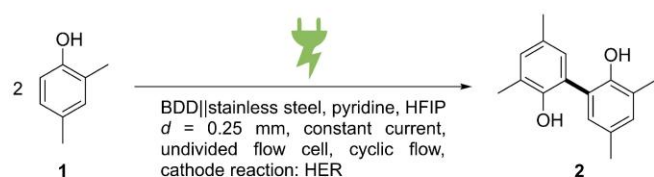


Figure 5. Yield of the control experiment with increasing number of experiments of the automation system. The annotations at the markers indicate the actual run number of the data point. In the green highlighted area, the yields of the consecutive control experiments are plotted. In the brown highlighted area, the yields of the control experiments that were performed between the experiments for the DoE design are plotted. The number next to the markers indicates the total consecutive experiment number associated with the data point.



Scheme 1. Anodic dehydrogenative C–C homocoupling reaction of 2,4-dimethylphenol (1) to 3,3',5,5'-Tetramethyl-2,2'-biphenol (2).

visual inspection, and it was concluded that the drift could be explained by the deterioration of the peristaltic tubing.

Since our default peristaltic tubing choice was not suitable for continuous operation, we equipped the peristaltic pump with a new cassette that provided control over the contact pressure of the tubing. This allowed us to use the fluorocarbon rubber (FPM) for a longer operating time. We repeated the experimental design but halved the concentration range from 0.75–1.25 mol/L to 0.38–0.63 mol/L. This forced us to reduce the flow multiplier in the high setting from 15 to 10 times, as the

Table 1. Fractional factorial 2^{6-2} design for the investigation of the homocoupling of 2,4-dimethylphenol. Each experiment was performed in duplicate, with a total of two central points.

Parameter	Unit	Low level	High level
Current density	mA/cm ²	20	40
Applied charge	F	0.70	0.90
Flowrate multiplier ^[a]	–	5	15
Concentration of 2,4-dimethylphenol	mol/L	0.75	1.25
Concentration of pyridine	vol.%	5	10
Temperature	°C	10	25

[a] We calculated the flowrate needed for a single pass electrolysis and multiplied it by this parameter value.

flow rates were otherwise greater than the pumps could handle. The 32 experiments of the design were divided into 4 blocks of eight experiments each. Three central point experiments were performed before each block. For this, a new tube was inserted into each pump channel. The dosing tube was calibrated to 1 mL/min, and the tube at the flow cell was calibrated to 6 mL/min. After each block of 11 experiments, the flow rate was determined, the tubing was changed and recalibrated. Since flow rate deviations to lower but also higher flow rates were determined, we determined a correction factor for all experiments. This was determined from a linear fit between the actual flow rate before and after each block of experiments (See SI for more information). The concentrations of **1** and the yields of **2** were corrected using this factor. In addition, the deviation of the dosing tube was included as a covariate in the regression and analysis of variance.

No parameter could be excluded by ANOVA from the obtained regression model ($R^2 = 74\%$) with $\alpha = 10\%$, however, current density, charge quantity, and the flow rate multiplier are below the significance threshold. However, these are involved in two-parameter interactions. The model obtained, subject to the corrections discussed, shows values in agreement with our previous studies with respect to the main effects and the curvature analysis (Figure 6).^[27]

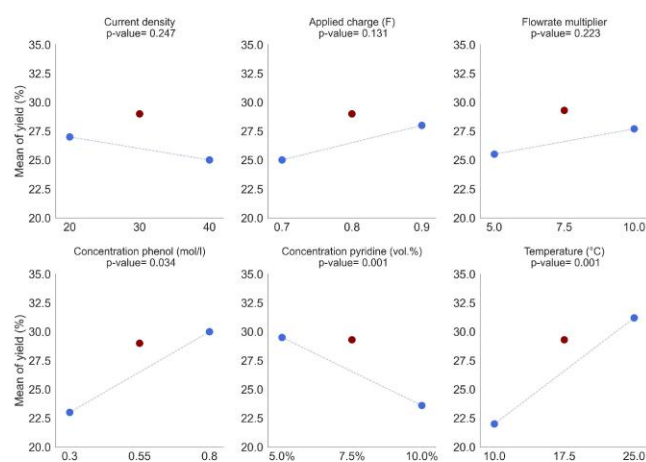


Figure 6. Main effects plot for the yield of **2**. The yield was determined using GC-FID with *n*-octylbenzene as internal reference material.

The optimum of the applied charge is equal to the central point of the model at 0.8 F. Higher concentrations of **1** favor the dehydrodimerization reaction, in agreement with the previously performed reactions at 1.25 mol/l of phenol **1**. The positive effect of the higher temperature could be an artifact since there was not sufficient condensation of the solvent in the reservoir. Turbulence in the tube with the cathodically generated hydrogen facilitates the evaporation of the solvent.

We have refrained from expanding the model to a CCD due to the poor suitability of the pump. Nonetheless, automation with LABS has worked successfully. In our next project, we want to implement a driver for piston pumps to replace the peristaltic pumps.

Conclusion

We have developed and successfully applied LABS, a Python-based software for automating laboratory setups. It can simultaneously control any number of devices, to run any combination of supported devices, in this work an electrochemical flow setup capable of single-pass and cyclic electrolysis. The focus of this project goes beyond the previously published frameworks. With only the configuration of the setup and experiments left to the user, we enable scientists with less programming experience to get in touch with automated synthesis. A centralized user front-end allows the submission of experiments and the monitoring of any number of experimental stations. The ability to implement stop conditions allows for safe, unattended operation. The open programming allows the user to customize LABS to use additional sensors or measurement devices for their specific use case to enable more complex feedback loops. The program code for front and backend has been published as open source on GitHub.^[31–33] The continuous operation has enabled us to increase our sample throughput for electrosynthetic screening in flow cells enormously.

This project lays the foundation for future implementation of advanced autonomous systems, including methods like Bayesian optimization. As such we will base upcoming projects on LABS and gradually support more devices not limited to but showcased in electrochemical setups. The use of an API interface for communication between the two modules also allows the control of third stations, provided that they offer corresponding API interfaces. Our main goal is to make LABS easier accessible and widely applicable in many areas of chemistry. Enabling future releases of LABS to be compatible with *Cronins* χ DL^[20,34] for example, would vastly improve the accessibility of LABS and the reusability of procedures run by LABS driven setups.

Data and materials availability

Full details of the experimental methods and equipment used are given in the electronic supporting information. The program code for the controller was published in three separate

repositories: LABS-Backend,^[32] LABS-Frontend,^[31] and LABS-DeviceDummies.^[33]

Acknowledgements

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under FOR 2982/1–UNODE (WA1276/24-1). Support by Forschungsinitiative Rheinland-Pfalz within the frame of SusInnoScience was very helpful. We would like to express our sincere thanks to R. M. Hamill for the effort she put into improving the language of this manuscript. We would like to thank F. Weyer for fruitful discussions regarding programming. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in LABS-Backend: Beta-Publication_submission at <https://doi.org/10.5281/zenodo.7879589>, reference number 7879589, Labs-Frontend: Beta-Publication submission at <https://doi.org/10.5281/zenodo.7879586>, reference number: 7879586, LABS-DeviceDummies at <https://doi.org/10.5281/zenodo.7879590>, reference number 7879590.

Keywords: electrochemistry · automation · anodic oxidation · cheminformatics · phenol coupling reaction

- [1] a) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312; b) B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099.
- [2] a) A.-K. Seitz, P. J. Kohlpaintner, T. van Lingen, M. Dyga, F. Sprang, M. Zirbes, S. R. Waldvogel, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2022**, *61*, e202117563; *Angew. Chem.* **2022**, *134*, e202117563; b) N. Kurig, J. Meyers, F. J. Holzhäuser, S. Palkovits, R. Palkovits, *ACS Sustainable Chem. Eng.* **2021**, *9*, 1229–1234; c) S. Arndt, D. Weis, K. Donsbach, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2020**, *59*, 8036–8041; *Angew. Chem.* **2020**, *132*, 8112–8118; d) D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386–12400; e) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041; *Angew. Chem. Int. Ed.* **2014**, *53*, 7122–7123; *Angew. Chem.* **2014**, *126*, 7248–7249.
- [3] a) J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, *53*, 45–61; b) J. L. Röckl, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2020**, *59*, 315–319; *Angew. Chem.* **2020**, *132*, 323–327; c) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765; d) A. Wiebe, S. Lips, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2017**, *56*, 14727–14731; *Angew. Chem.* **2017**, *129*, 14920–14925; e) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302–308.
- [4] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
- [5] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619; *Angew. Chem.* **2018**, *130*, 5694–5721.
- [6] D. Pollok, B. Gleede, A. Stenglein, S. R. Waldvogel, *Aldrichimica Acta* **2021**, *54*, 3–15.
- [7] a) N. Amri, T. Wirth, *J. Org. Chem.* **2021**, *86*, 15961–15972; b) N. Amri, T. Wirth, *Synlett* **2020**, *31*, 1894–1898.
- [8] a) E. Sato, M. Fujii, H. Tanaka, K. Mitsudo, M. Kondo, S. Takizawa, H. Sasai, T. Washio, K. Ishikawa, S. Suga, *J. Org. Chem.* **2021**, *86*, 16035–16044; b) M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
- [9] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- [10] A. G. Wills, S. Charvet, C. Battilocchio, C. C. Scarborough, K. M. P. Wheelhouse, D. L. Poole, N. Carson, J. C. Vantourout, *Org. Process Res. Dev.* **2021**, *25*, 2587–2600.
- [11] N. Kurig, J. Meyers, E. Richter, S. Palkovits, R. Palkovits, *Chem. Ing. Tech.* **2022**, *94*, 786–790.
- [12] a) E. Sato, G. Tachiwaki, M. Fujii, K. Mitsudo, T. Washio, S. Takizawa, S. Suga, *Org. Process Res. Dev.* **2023**; b) M. Dörr, M. M. Hielscher, J. Proppe, S. R. Waldvogel, *ChemElectroChem* **2021**, *8*, 2621–2629; c) M. M. Hielscher, B. Gleede, S. R. Waldvogel, *Electrochim. Acta* **2021**, *368*, 137420; d) M. Dörr, J. L. Röckl, J. Rein, D. Schollmeyer, S. R. Waldvogel, *Chem. Eur. J.* **2020**, *26*, 10195–10198; e) M. Santi, J. Seitz, R. Cicala, T. Hardwick, N. Ahmed, T. Wirth, *Chem. Eur. J.* **2019**, *25*, 16230–16235; f) R. Möckel, J. Hille, E. Winterling, S. Weidemüller, T. M. Faber, G. Hilt, *Angew. Chem. Int. Ed.* **2018**, *57*, 442–445; *Angew. Chem.* **2018**, *130*, 450–454.
- [13] a) Z. Crandall, K. Basemann, L. Qi, T. L. Windus, *React. Chem. Eng.* **2022**, *7*, 416–428; b) C. J. van der Westhuizen, J. Du Toit, N. Neyt, D. Riley, J.-L. Panayides, *Digital Discovery* **2022**, *1*, 596–604; c) S. Chatterjee, M. Guidi, P. H. Seeberger, K. Gilmore, *Nature* **2020**, *579*, 379–384; d) N. Cherkasov, Y. Bai, A. J. Expósito, E. V. Rebrov, *React. Chem. Eng.* **2018**, *3*, 769–780; e) D. E. Fitzpatrick, C. Battilocchio, S. V. Ley, *Org. Process Res. Dev.* **2016**, *20*, 386–394.
- [14] L. M. Roch, F. Häse, C. Kreisbeck, T. Tamayo-Mendoza, L. P. E. Yunker, J. E. Hein, A. Aspuru-Guzik, *Sci. Robot.* **2018**, *3*.
- [15] S. Steiner, J. Wolf, S. Glatzel, A. Andreou, J. M. Granda, G. Keenan, T. Hinkley, G. Aragon-Camarasa, P. J. Kitson, D. Angelone et al., *Science* **2019**, 363.
- [16] L. M. Roch, F. Häse, C. Kreisbeck, T. Tamayo-Mendoza, L. P. E. Yunker, J. E. Hein, A. Aspuru-Guzik, *PLoS One* **2020**, *15*, e0229862.
- [17] T. Wirtanen, T. Prenzel, J.-P. Tessonnier, S. R. Waldvogel, *Chem. Rev.* **2021**, *121*, 10241–10270.
- [18] M. Seifrid, R. Pollice, A. Aguilar-Granda, Z. Morgan Chan, K. Hotta, C. T. Ser, J. Vestfrid, T. C. Wu, A. Aspuru-Guzik, *Acc. Chem. Res.* **2022**, *55*, 2454–2466.
- [19] M. M. Hielscher, B. Gleede, S. R. Waldvogel, *Electrochim. Acta* **2021**, *368*, 137420.
- [20] A. J. S. Hammer, A. I. Leonov, N. L. Bell, L. Cronin, *JACS Au* **2021**, *1*, 1572–1587.
- [21] a) GitHub, “ChemputerSoftware/client at master · croningp/Chemputer-Software”, can be found under <https://github.com/croningp/ChemputerSoftware>, **2023**; b) GitHub, “GitHub - aspuru-guzik-group/ChemOS”, can be found under <https://github.com/aspuru-guzik-group/ChemOS>, **2023**; c) GitHub, “GitHub - RxnRover/RxnRover”, can be found under <https://github.com/RxnRover/RxnRover>, **2023**; d) SourceForge, “OpenFlowChem”, can be found under <https://sourceforge.net/projects/open-flowchem/>, **2023**.
- [22] GitHub, “GitHub – cambiegroup/flowchem: Flowchem is an application to simplify the control of instruments and devices commonly found in chemistry labs”, can be found under <https://github.com/cambiegroup/flowchem>, **2023**.
- [23] “Twisted”, can be found under <https://twisted.org/>, **2023**.
- [24] a) GitHub, “richardingham/octopus: Real-time laboratory automation and monitoring in Python”, can be found under <https://github.com/richardingham/octopus>, **2023**; b) R. J. Ingham, C. Battilocchio, J. M. Hawkins, S. V. Ley, *Beilstein J. Org. Chem.* **2014**, *10*, 641–652.
- [25] “Welcome to Flask – Flask Documentation (2.2.x)”, can be found under <https://flask.palletsprojects.com/en/2.2.x/>, **2023**.
- [26] a) M. Selt, S. Mentzi, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Synlett* **2019**, *30*, 2062–2067; b) B. Riehl, K. Dyballa, R. Franke, S. Waldvogel, *Synthesis* **2016**, *49*, 252–259.
- [27] M. Selt, R. Franke, S. R. Waldvogel, *Org. Process Res. Dev.* **2020**, *24*, 2347–2355.
- [28] I. M. Malkowsky, U. Griesbach, H. Pütter, S. R. Waldvogel, *Eur. J. Org. Chem.* **2006**, *2006*, 4569–4572.
- [29] a) J. Barjau, G. Schnakenburg, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1415–1419; *Angew. Chem.* **2011**, *123*, 1451–1455; b) I. M. Malkowsky, C. E. Rommel, K. Wedeking, R. Fröhlich, K. Bergander, M. Nieger, C. Quaiser, U. Griesbach, H. Pütter, S. R. Waldvogel, *Eur. J. Org. Chem.* **2006**, *2006*, 241–245.

- [30] a) S. Palmas, A. M. Polcaro, A. Vacca, M. Mascia, F. Ferrara, *J. Appl. Electrochem.* **2006**, *37*, 63–70; b) I. Duo, C. Levy-Clement, A. Fujishima, C. Comninellis, *J. Appl. Electrochem.* **2004**, *34*, 935–943.
- [31] J. Fangmeyer, A. Behrens, B. Gleede, S. R. Waldvogel, U. Karst, *Angew. Chem. Int. Ed.* **2020**, *59*, 20428–20433; *Angew. Chem.* **2020**, *46*, 20608–20613.
- [32] M. M. Hielscher, M. Dörr, *LABS-Frontend* **2023**, DOI 10.5281/ZENODO.7879586.
- [33] M. Dörr, M. M. Hielscher, *LABS-Backend* **2023**, DOI 10.5281/ZENODO.7879588.
- [34] M. Dörr, M. M. Hielscher, *LABS-DeviceDummys* **2023**, DOI 10.5281/ZENODO.7879590.
- [35] "Cronin Group/Chemputer/XDL GitLab", can be found under <https://gitlab.com/croningroup/chemputer/xdl>, **2023**.

Manuscript received: April 30, 2023
Revised manuscript received: May 27, 2023
Accepted manuscript online: June 3, 2023
Version of record online: June 12, 2023

The following results have been published in a peer-reviewed publication.^[89]

M. M. Hielscher,[‡] **J. Schneider**,[‡] A. H. J. Lohmann, S. R. Waldvogel *

Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell

ChemElectroChem **2024**, e202400360

DOI: [10.1002/celec.202400360](https://doi.org/10.1002/celec.202400360)

License: CC BY 4.0

[‡] These authors contributed equally

* Corresponding author

Explanation of my contribution:

M. M. Hielscher and **J. Schneider** were responsible for conceptualization of the project. M. M. Hielscher and **J. Schneider** were responsible for writing of the manuscript and writing of the Supporting Information. M. M. Hielscher, A. H. J. Lohmann and **J. Schneider** carried out data analysis and evaluation. A. H. J. Lohmann and **J. Schneider** were responsible for carrying out the experiments with the automated flow setup for electrosynthesis. A. H. J. Lohmann and **J. Schneider** were responsible for maintenance of the experimental setup. A. H. J. Lohmann and **J. Schneider** carried out reactions for the scope and were responsible for data analysis of isolated compounds. **J. Schneider** performed the scale-up reaction. S. R. Waldvogel supervised the project and assisted in writing of the manuscript and the Supporting Information.

Introduction: In the development of the LABS system (Laboratory Automation and Batch Scheduling) for the initial publication on automated electrosynthesis in flow,^[120] it became evident that an important limiting factor of the automated experimental setup is the durability of the employed tubing materials in the utilized pumps. All tested materials have worn out over the course of long-time operation, which resulted in loss of calibration and frequent cracking of the tubing. In these cases, extensive maintenance and repair of the automated laboratory setup was required before automated experiments could be continued. Even highly resistant and expensive tubing materials such as FFKM (perfluoroelastomer) did break after a short time. To further develop LABS and the automated electrosynthesis setup, the electrochemical multicomponent synthesis of aryl alkenesulfonates in flow was selected as a test

reaction, which was previously developed by the Waldvogel group in a divided batch-type cell setup, and was transferred to an undivided flow electrolysis cell setup^[127] This project is hence a combination of laboratory automation with electrochemical multicomponent reaction using SO_2 .^[117] It was decided to replace peristaltic pumps with piston pumps for operations which required high precision and durability, such as the preparation of the reaction solution and the pumping of the electrolyte through the electrolysis cell. Piston pumps are commonly employed in HPLC systems,^[121] and they are considerably more expensive than peristaltic pumps. However, they offer high precision and require less maintenance. To add the piston pumps to the experimental setup (Figure 50), a device driver was written in Python for the LABS system. In theory, a syringe pump could be utilized in the LABS system as well, but the available pumps did not offer any temperature control for the solutions in the syringe. Because it is essential to keep the temperature of the SO_2 stock solution at +4 °C,^[117] syringe pumps were not an option for this project.

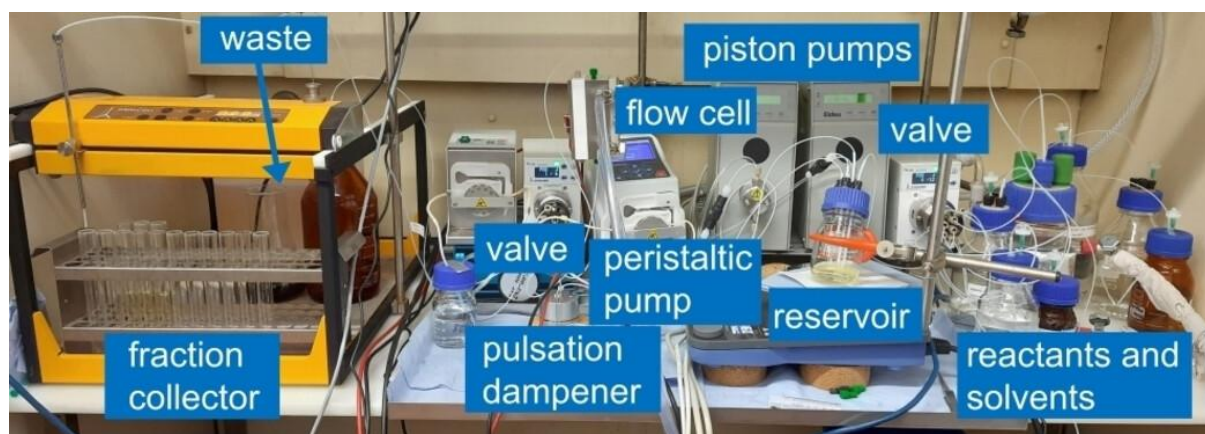


Figure 50. Improved experimental setup for the automated electrosynthesis of alkyl arenesulfonates in flow via electrochemical multicomponent reaction using SO_2 stock solutions.^[89]

A summary of this project is depicted in Figure 51. As test reaction, the electrochemical multicomponent synthesis of alkyl arenesulfonates from arenes, SO_2 , and alcohols was employed. Specifically, 1,4-dimethoxybenzene was utilized as arene with ethanol as alcohol component. Pyridine was employed as base. An undivided flow electrolysis cell with a BDD anode and a stainless-steel cathode was chosen. Initial experiments revealed that the conversion was too low for single-pass flow, so cyclic flow was chosen instead. The reaction optimization was done with an automated experimental setup that was controlled by the LABS software. The reaction is carried out at room temperature using mixtures of HFIP and MeCN as solvents.

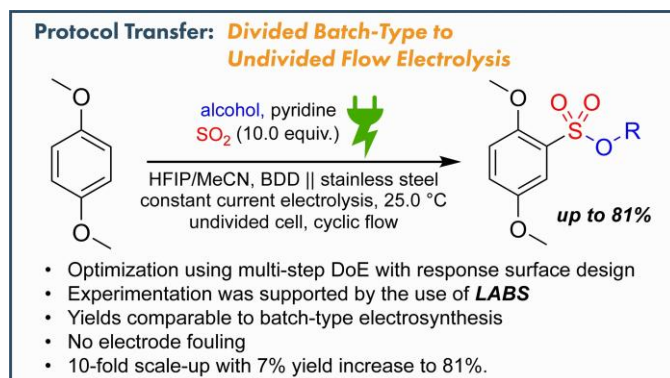


Figure 51. Overview of the automated electrochemical synthesis of alkyl arenesulfonates in flow.^[89]

Experimental Setup: The experimental setup was significantly improved compared with the previous setup. Peristaltic pumps were replaced with piston pumps for operations which require high precision and durability. The SO_2 stock solution was cooled by a separate cryostat. Before every piston pump, either a filter is employed, or the stock solutions were filtered before use to avoid any clogging of the pumps. After each piston pump, a back pressure regulator (BPR) is installed. For emptying the reservoir, a peristaltic pump is utilized because this step does not require high precision. The reservoir is rinsed with solvent after each electrolysis. Because piston pumps tend to pulse more compared with peristaltic pumps, a pulsation dampener was installed before the flow electrolysis cell.

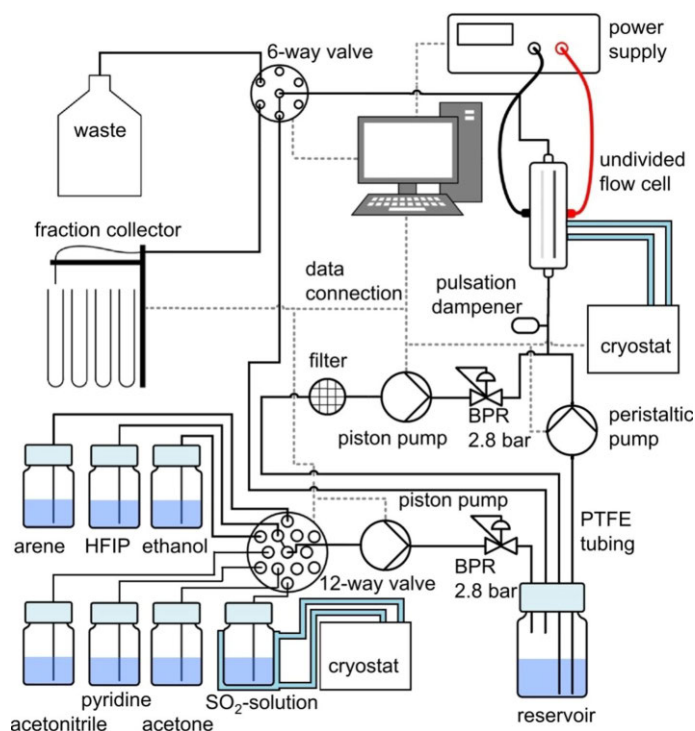


Figure 52. Diagram of the improved experimental setup using piston pumps for operations which require high precision and durability.^[89] The SO_2 stock solution is cooled by a separate cryostat.

Flow Multiplier and Durability Test: For the test reaction depicted in Figure 53 (left), various flowrate multipliers were tested (right). It was decided to employ the highest flowrate multiplier 5 for the cyclic flow to prevent formation of layers on the electrodes. The test reaction was carried out 10 times in sequence using the automated laboratory setup with flowrate multiplier 5 (Figure 53, right), and the yield, and did not decrease over these 10 reactions. In between each electrolysis, the automated setup performed a cleaning and rinsing step.

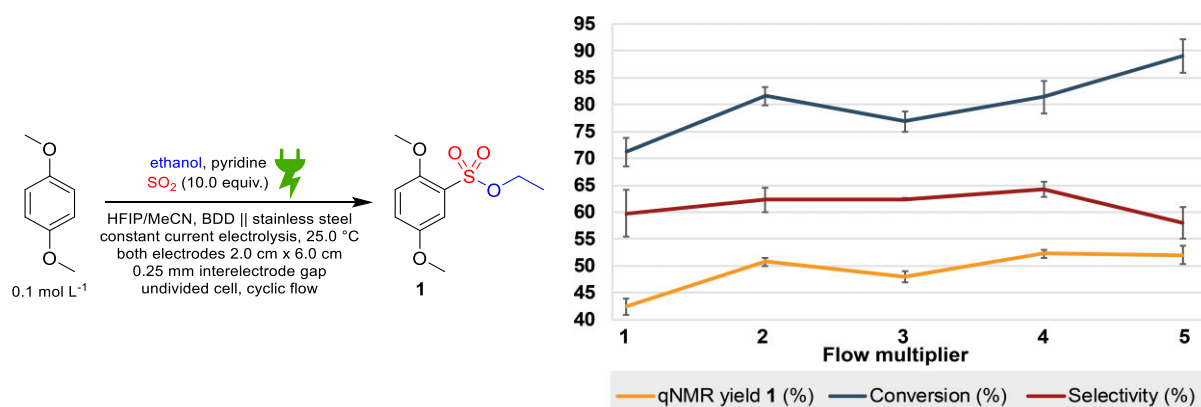


Figure 53. Reaction conditions for the stability test and the analysis of the influence of the flow multiplier on NMR yield, conversion, and selectivity.^[89]

Optimization: After adopting a flowrate multiplier 5 and demonstrating the robustness of this electrosynthesis over 10 reactions in sequence, the reaction optimization was carried out using Design of Experiments (Figure 54). This work represents a good example for the iterative nature of a DoE plan. The experimental results of a DoE are usually the foundation for the next DoE, and it is the operator's decision when to stop with further optimization depending on whether the results are satisfactory. In this optimization, an initial 2^{5-1} design was chosen with parameters current density, applied charge, equiv. of ethanol, and equiv. of pyridine (Figure 54, left).

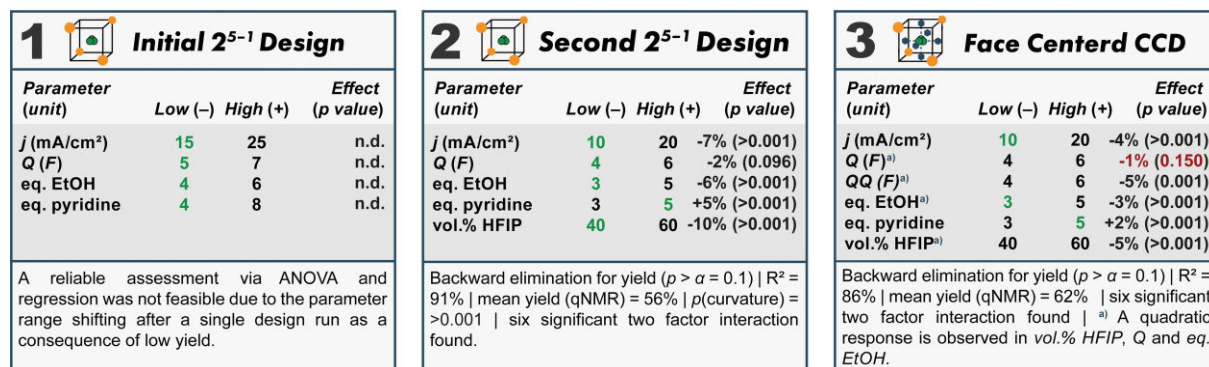


Figure 54. Iterative Design of Experiments (DoE) for the optimization of electrolysis conditions.^[89]

Based on these initial results, a second 2^{5-1} design was chosen, which also included the vol% of HFIP as fifth reaction parameter (Figure 54, center). After backward elimination of yield ($p > \alpha = 0.1$), an $R^2 = 91\%$ was observed for this model. Interestingly, a curvature in the employed model was found to be significant, which led to improvement of this design by applying star points in a face-centered central composite design (CCD) (Figure 54, right). After backward elimination of yield for this CCD model ($p > \alpha = 0.1$), an $R^2 = 0.86$ was found. The final results are summarized in Figure 55. Interestingly, a quadratic response was found for vol%(HFIP), applied charge Q , and the equiv. of ethanol. A current density of 10 mA cm^{-2} results in higher yield than 20 mA cm^{-2} .

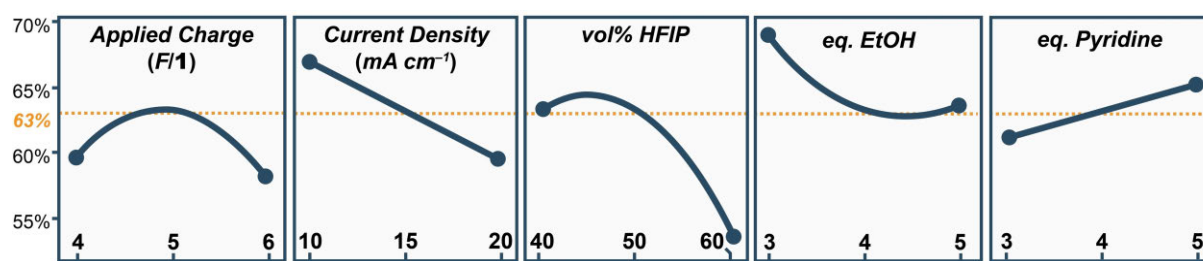


Figure 55. Main effect plots for the yield of the test reaction.^[89]

Scope: Various alcohols were employed in this electrochemical multicomponent synthesis of alkyl arenesulfonates in cyclic flow, as summarized in Figure 56. The highest yield was obtained for *n*-pentanol, which gave sulfonate **6** in 74% (even 81% in the scale-up reaction). Ethanol and methanol gave products **1** and **2** in yields of 67% and 42%, respectively. Isopropanol gave sulfonate **3** in only 21% yield, which is the lowest yield of all employed alcohols. Sulfonate **4** was synthesized in 72% using 2-methyl propanol. Using 2,2-dimethyl propyl alcohol resulted in product **5** in 62% yield.

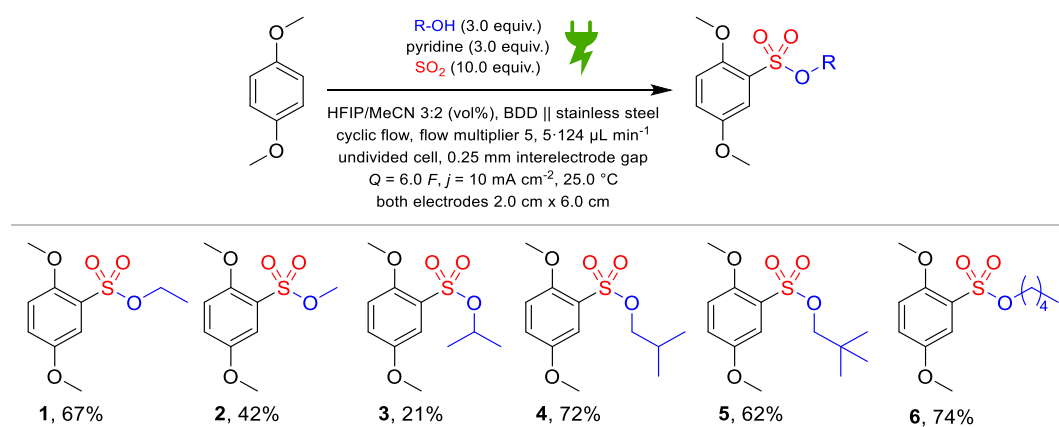


Figure 56. Scope of alcohols.^[89]

Scale-up: The scalability of this method was demonstrated in a 10-fold scale-up using *n*-pentanol and 1,4-dimethoxybenzene. This reaction was carried out in a larger flow electrolysis cell, which was already employed for the scale-up reaction of the electrochemical multicomponent synthesis of sulfonamides in single-pass flow.^[71] In the smaller flow electrolysis cell (Figure 57, top), the reaction was carried out in 74% isolated yield with a productivity of 0.159 g/h. In the larger flow cell (Figure 57, bottom), the yield increased to 81%, and the production also increased to 0.663 g/h (Table 10).

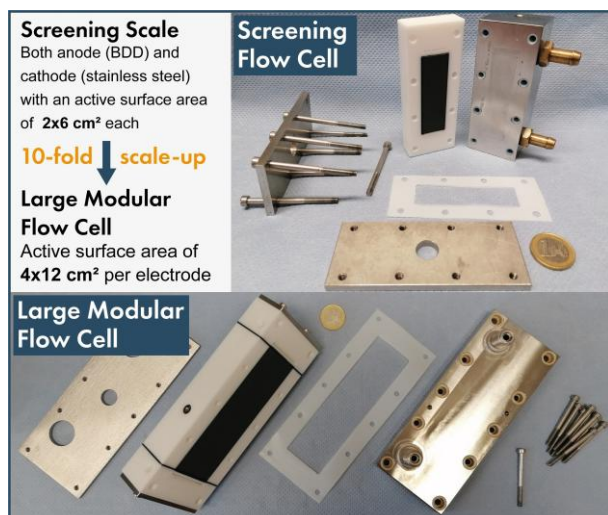


Figure 57. The flow cells.^[89]

Table 10. Scale-up reaction of the electrochemical synthesis of alkyl arenesulfonates in cyclic flow.^[89]

Electrolyzer	Isolated Yield [%]	Productivity [g/h]
Small flow cell	74	0.159
Larger flow cell	81	0.663

Conclusion: LABS was successfully employed in the automated optimization of the synthesis of alkyl arene sulfonates in cyclic flow. This project combined the topic of electrochemical multicomponent reactions using SO₂ stock solutions with automated electrosynthesis. In total, 6 substrates are demonstrated with isolated yields of 81% in scale-up. The robust scalability of this method was demonstrated in a 10-fold scale-up, which resulted in an increase in yield and an increase in productivity.

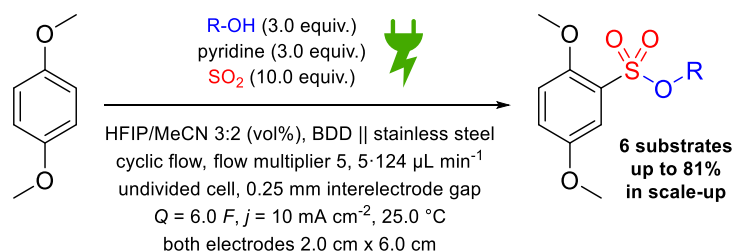


Figure 58. Overview of the automated optimization of the electrochemical multicomponent synthesis of alkyl arenesulfonates in cyclic flow.^[89]

Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell

Maximilian M. Hielscher^{+, [a]}, Johannes Schneider^{+, [a]}, Alexander H. J. Lohmann^[c] and Siegfried R. Waldvogel^{*, [a, b, c]}

The necessary separation of anodic and cathodic compartments in the electrochemical multicomponent synthesis of alkyl arenesulfonates in batch was overcome by the transfer of this reaction in an undivided electrochemical flow cell. The yield was increased from an initial 23% to 67% by optimization using Design of Experiments (DoE). The experiments were carried out using an automated experimental flow electrolysis setup controlled by the automation software LABS (*Laboratory*

Automation and Batch Scheduling), an open-source software that allows to plan and conduct experiments with an arbitrary, freely selectable experimental setup. The automated experimental setup turned out to be stable and provides reproducible results. In total, 6 examples are demonstrated with isolated yields up to 81%. In addition, the robust scalability of the electrochemical reaction was demonstrated in a 10-fold scale-up.

Introduction

Organic Electrosynthesis has begun to experience a remarkable and ongoing renaissance, because it offers a variety of advantages over conventional synthetic methods.^[1] Electro-organic reactions are typically carried out under mild reaction conditions. Electricity, which can originate from sources of renewable energy, is used as inexpensive and universal redox agent.^[2] This allows for innovative electrochemical reaction pathways, which avoid the use of hazardous reagents,^[3] and minimize the generation of reagent waste.^[4]

In 2020, our group reported the first electrochemical multicomponent synthesis of alkyl arenesulfonates in batch.^[5] In this transformation, stock solutions of sulfur dioxide are employed as atom-economic, inexpensive, and simple source of SO₂, entirely avoiding expensive sulfur dioxide surrogates. This work is part of the recent progress in the field of electrochemical incorporation of sulfur dioxide into organic molecules (Fig-

ure 1).^[6] The electrosynthesis of sulfonates was the basis for following work on the electrosynthesis of sulfonamides,^[7] sulfamides,^[8] and alkenesulfonates.^[9] In addition to the use of SO₂ stock solutions, the synthesis of sulfonamides in flow was demonstrated by the Noël group by an electrochemical coupling between thiols and amines.^[10] Previous work by our group used SO₂ multicomponent reactions for the synthesis of sulfonamides in flow by carrying out experiments manually.^[11] In recent years however, significant progress was made in automatizing chemical synthesis,^[12] often by employing flow chemistry.^[13]

Many solutions for laboratory automation require the use of commercial third-party software, or the software which is developed internally is not openly published. In 2022, our group developed LABS: *Laboratory Automation and Batch Scheduling*,^[14] a modular, open-source Python based solution. The graphical user interface of the LABS frontend enables the addition of experiments in individual segments, which can then be transferred to the experimental setup. The modular design

[a] M. M. Hielscher,⁺ J. Schneider,⁺ Prof. Dr. S. R. Waldvogel
Department of Chemistry
Johannes Gutenberg University Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)

[b] Prof. Dr. S. R. Waldvogel
Institute of Biological and Chemical Systems – Functional Molecular
Systems (IBCS-FMS)
Karlsruhe Institute of Technology (KIT)
Kaiserstraße 12, 76131 Karlsruhe (Germany)

[c] A. H. J. Lohmann, Prof. Dr. S. R. Waldvogel
Max-Planck-Institute for Chemical Energy Conversion
Stiftstraße 34–36, 45470 Mülheim an der Ruhr (Germany)
E-mail: siegfried.waldvogel@cec.mpg.de

[*] These authors contributed equally.

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/celec.202400360>

© 2024 The Authors. ChemElectroChem published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

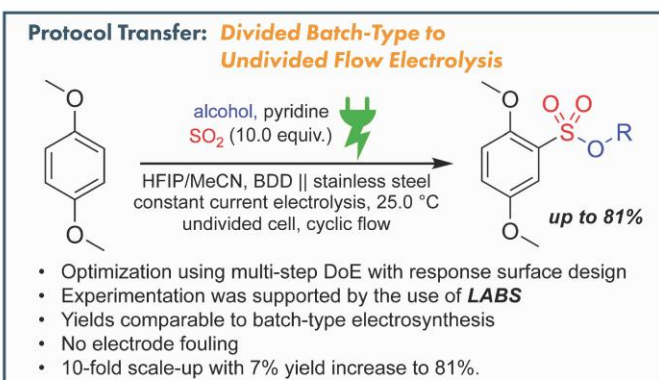


Figure 1. The combination of LABS (Laboratory Automation and Batch Scheduling) and a multi-step DoE-based optimization allowed the transfer of reaction conditions from divided batch to undivided flow without loss of yield.

allows for the automation of any combination of devices by adapting the configuration file. If the device drivers are already available in the LABS repository, no programming knowledge is required on the part of the user to realize these implementations. The flexible architecture allows for the rapid modification of this automated setup, thereby facilitating the user's ability to readily accommodate specific requirements to the test setup.

Here, the study demonstrates the adaptation and utilization of LABS for the automated electrochemical synthesis of sulfonates in flow. To this end, the handling of stock solutions of SO₂ was incorporated into the automation configuration. The electrolysis flow cells utilized as part of the experimental framework presented in this work were devised within our research group and are commercially available.^[15] Previously, we employed peristaltic pumps, which revealed that the stability of the tubing rapidly deteriorates due to the high load during electrolysis and rinsing sequences. This results in inconsistent flow rates. We therefore equipped our experimental setup with two piston pumps from *Eldex*. These were integrated into LABS with a corresponding driver file. Design of Experiments (DoE) was used as key technique for the systematic analysis and optimization of the reaction conditions.^[16]

Results and Discussion

To transfer the original protocol, which described the conversion in a divided batch cell to flow, several reactions with different settings of the continuous parameters were first carried out without automation (Table S3 in the Supporting Information). The initial maximum yield in a single-pass undivided flow cell was 22%, whereas alterations in the reaction conditions resulted in a 13% decrease in yield.

This prompted us to transfer the whole system to a LABS-controlled setup. To this end, the modified setup was first calibrated regarding the stability of the dosed volumes and the stability of the electrolysis in the operating range of the applied flow rates. Further preliminary experiments have shown that cyclic electrolysis with a reservoir gives better yields than single-pass electrolysis. In this study, the flow rate is always

expressed as a multiple of the flow rate required for a single pass (flow multiplier).

An initial 2⁵⁻¹ design showed strong main effects after the first run with higher yields at the respective low (–) parameter settings (Figure 2). A reproduction for a significance-based evaluation of the effects was dispensed with and the parameter range of the optimization was shifted to lower parameter levels. The analysis of the yield in the second design showed a curvature of the response space. Due to physical limitations, the model was extended to a response surface model using a face-centered central composite design (CCD) instead of an orthogonal CCD. The determination of the yield by qNMR permitted the simultaneous measurement of the conversion and selectivity based on the yield of 1. The corresponding models were analyzed according to the same protocol to verify the plausibility of the data for the yield.

Automated Flow Setup

The principal advancement in comparison to our previous work using LABS is the utilization of piston pumps in combination with peristaltic pumps for procedures requiring high precision and durability. One piston pump is employed to prepare the electrolyte at the beginning of each experiment, while a second piston pump is utilized to pump the electrolyte through the flow-through electrolysis cell (Figure 3).

As the piston pumps are unable to self-prime, an additional peristaltic pump was employed to flush the reservoir residue-free in the cleaning procedure. The vessel for the SO₂ stock solution was cooled to 0 °C separately to ensure concentration stability over the duration of the experiment (Figure 4). The LABS method for cyclic flow electrolysis entails the dosing of reagents in the reservoir, the filling of the electrolysis flow cell with electrolyte solution, and the initiation of cyclic flow electrolysis. Upon completion of the electrolysis process, the reaction solution is pumped to the fraction collector, including additional rinsing with acetonitrile. As a cleaning step, the entire system is flushed first with acetone and then with

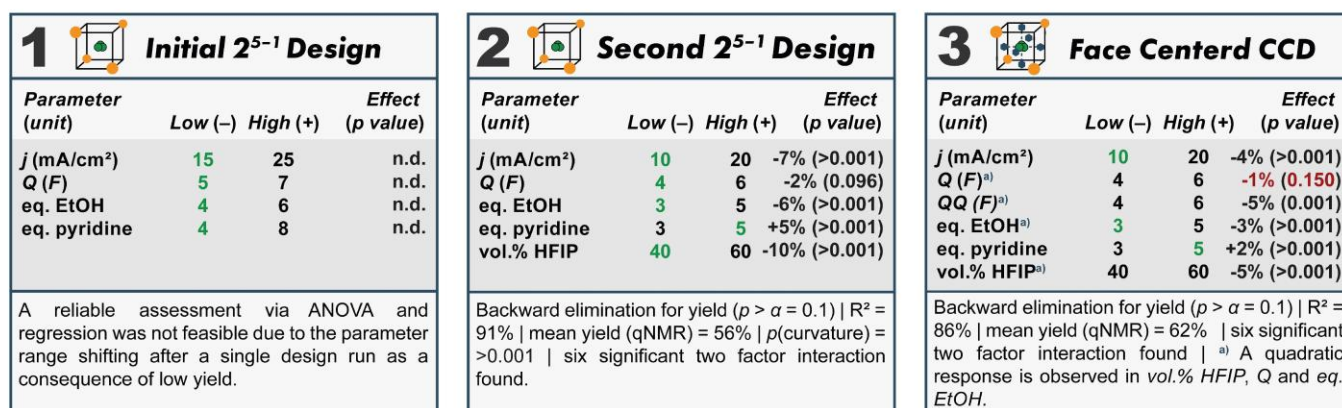


Figure 2. Optimization strategy for the yield. The same modeling via regression and analysis of variance (ANOVA) was also done for the system responses conversion and selectivity. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. CCD = Central Composite Design.

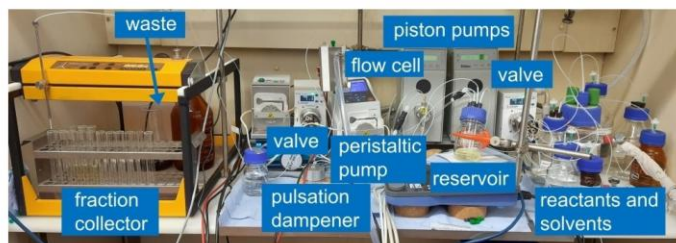


Figure 3. Photograph of the automated electrolysis setup. The reactants are held in screw-cap glass bottles (right). The electrolyte is prepared in the reservoir with stirring (center). The valve downstream of the electrolysis cell allows the electrolyte to be returned to the reservoir, to the fraction collector, or the waste. Picture by A. H. J. Lohmann.

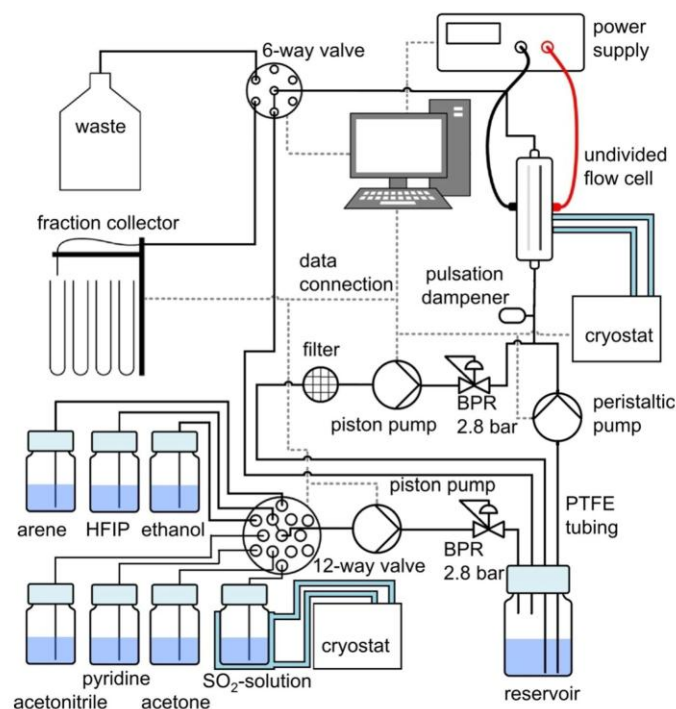


Figure 4. Flow diagram of the electrolysis setup. BPR: back pressure regulator.

acetonitrile. Further details on the experimental setup can be found in the Supporting Information.

Investigation of Flow Multiplier and System Stability

First, the influence of the flow multiplier for the cyclic flow mode was analyzed in relation to the flow rate required for single-pass electrolysis. The resulting higher flow rates can have a positive effect on mass transport to and from the interface. However, to apply the necessary charge, the solution must either be pumped through the cell several times from one reservoir or a cascade mode with a second reservoir must be chosen.^[17] Due to the simpler implementation, we have decided in favor of the first case (Scheme 1).^[18] To investigate which flow multiplier to use, the reaction was carried out in duplicates with



Scheme 1. Electrochemical multi-component synthesis of ethyl 2,5-dimethoxy-benzenesulfonate (**1**) directly from 1,4-dimethoxybenzene, SO_2 , and ethanol in an undivided flow electrolysis cell.

flow multipliers ranging from 1 to 5 in steps of 1 (Table S4 in the SI).

For all subsequent experiments, we have chosen a flow multiplier of 5 to ensure a sufficient passing rate of the total electrolyte. Moreover, the single-pass experiments at the beginning of the study yielded 22–23% at high current densities of 25 mA cm^{-2} , whereas experiments with lower current densities and thus lower flow rates yielded poorer yields. This could be indicative of a positive influence of improved mass transport.^[19] To demonstrate the reproducibility of the electrolysis sequence conducted by the automated experimental setup, the reaction depicted in Scheme 2 was carried out 10 times consecutively with flow multiplier 5.

The NMR yield of **1** was determined to be $53(\pm 3)\%$. The conversion was found to be $90(\pm 4)\%$, and the selectivity was determined to be $59(\pm 3)\%$ (Table S5 in the SI). In Figure 5, the results of the flow multiplier screening and the system stability analysis are combined in one graph (the data for this plot can be found in Table S4 and Table S5 in the SI). Following the completion of the final electrolysis and clean-up program, the flow cell was disassembled, and no evidence of electrode fouling was observed, which can appear with electron-rich arenes in anodic processes.^[20]

Initial Fractional Factorial Design

Based on our initial investigations we included the following five continuous parameters for the DoE-based investigation: the amount of applied charge Q , the current density j , the equivalents of ethanol and of pyridine, and the amount of HFIP



Scheme 2. Reaction conditions for the stability test. The yield, conversion, and selectivity (= yield / conversion) for each of the 10 runs was analyzed using quantitative ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

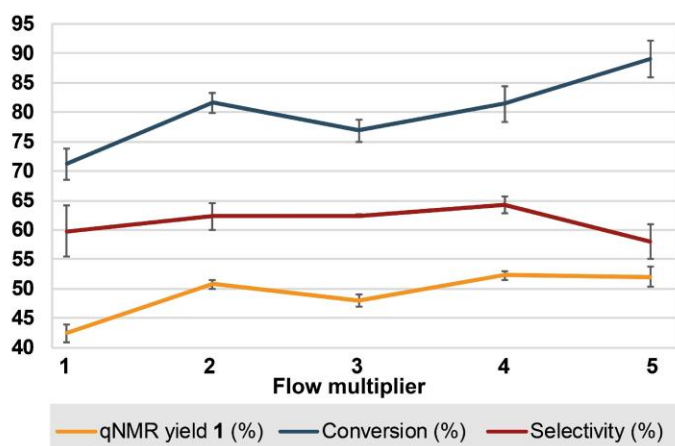


Figure 5. Flow multiplier screening and analysis of system stability. Plot of qNMR yield of 1, conversion, and selectivity (= yield / conversion) with 1,3,5-trimethoxybenzene as internal standard. For flow multipliers 1 to 4, two runs are shown. 11 runs are shown for flow multiplier 5 (see Table S4 and S5 in the Supporting Information).

in the reaction solution. HFIP plays a key role in this reaction as hydrogen bond donor (see mechanism section in the SI).^[21] The following parameters were kept constant: electrode materials (BDD | stainless-steel), interelectrode gap (0.25 mm), temperature of the cathode (25.0 °C), concentration of the starting material in the reaction solution (0.1 mol L⁻¹), equivalents of SO₂ (10.0 equiv.), cyclic flow mode (flow multiplier 5). BDD was chosen as metal-free, electrochemically stable anode material.^[22] Using this range of values for the parameters, a 2⁵⁻¹ fractional factorial design without replication was chosen for initial experiments. The yield, conversion, and selectivity (= yield / conversion) were determined using quantitative ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. This was maintained for all subsequent optimization experiments to ensure comparability of the measured values. Each experiment required for the initial experimental design was first performed once and the experimental design was analyzed without replication (Figure 2 left). The analysis showed that the selected parameter range was far from the optimum for the reaction (see Table S6 in the SI). We therefore dispensed with further replication and adjusted the parameter limits for a follow-up design. Experiments with upper limit of current density of 25 mA cm⁻² or amount of applied charge of 7.0 F showed poorer yields. We therefore adjusted the parameter range accordingly.

Second Fractional Factorial Design

The results of the first experimental design (Table S6 in the SI) indicated that a shift in the parameter limits of the design was necessary to further enhance the yield (Figure 2 middle). Consequently, the adapted 2⁵⁻¹ design with resolution V was run in duplicate at the corner points for a total of 32 experiments. The central point was systematically run after every fifth experiment to monitor system stability over the

course of the campaign. The corner points were executed in randomized order. The results are listed in Table S7 in the Supporting Information. After execution of the experiments and analytics, non-significant terms were excluded from the model using backward elimination ($p < \alpha = 0.1$). The analysis of variance (ANOVA) for the system response yield resulted in a significant p value for curvature in the model ($p < 0.001$).^[23] To check for nonlinear behaviour within the parameter range of the model, we added star points to achieve a central composite design (CCD). Given that an optimal α -distance for the star points would have resulted in runs that were not feasible due to physical limitations, a non-orthogonal, face-centered CCD was selected as the optimal solution. An orthogonal CCD would have necessitated a range for the HFIP volume percentage that is not attainable without either diluting the starting material in the reaction solution or decreasing the SO₂ equivalents. Furthermore, it is challenging to pump SO₂ stock solutions with concentrations greater than 2.0 mol L⁻¹ without loss of SO₂ due to degassing.

Extension to a Central Composite Design

The analysis of the CCD (second FFD including the surface-centered star points, Table S8 in the SI) is carried out analogously using backward elimination ($p < \alpha = 0.1$; Figure 2 right). As previously indicated in the ANOVA of the FFD, the main effect analysis of the CCD reveals the presence of several quadratic terms that contribute significantly to the model of the yield. These terms are primarily associated with the amount of applied charge and the volume fraction of HFIP in the electrolyte (Figure 6). The yield model shows a robust R² of 87%. However, the evaluation using cross-validation reveals a R²_{predicted} of 75% indicating a slight overfitting of the model, which may be due to a more complex response surface of the reactions true functional. This evidence holds true for the models based on conversion and selectivity as well.

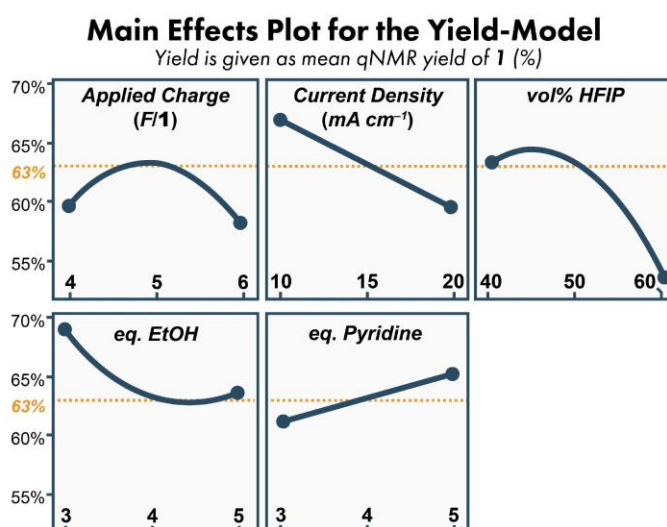


Figure 6. Main effect plot of the CCD model for the system response yield of 1. The models overall average yield was 63% indicated as dotted line.

A corresponding test of the smallest quadratic main effect (equivalents of ethanol) showed a linear response, contrary to the predicted quadratic behavior of the main effect. We therefore probed the model using a response optimizer algorithm (Minitab 21) to predict the reaction conditions for the maximum yield within the investigated range. Here, previously untested experimental settings were proposed for the respective effect maxima of the applied charge and the volume fraction HFIP (see Figure 6). The experimental validation revealed an offset of 17% (predicted: 77%, qNMR yield found: 60%). As the predictive power of the model inside the investigated area appeared low, the optimal experimental point was identified from the CCD, and **1** was successfully isolated in a yield of 67% (Figure 7). Further details are available in the SI.

Scope

Using the optimized reaction conditions obtained by Design of Experiments (DoE), several alcohols were tested (Figure 7).

For ethanol, product **1** was obtained in 67% isolated yield. Methanol gave **2** in 42% isolated yield. The use of isopropanol resulted in 21% isolated yield for **3**. Sulfonate **4** was synthesized in 72% isolated yield using 2-methylpropanol. 2,2-dimethylpropyl alcohol gave **5** in 62% isolated yield. Using pentanol, product **6** was isolated in a yield of 74%, which is the highest yield of all substrates.

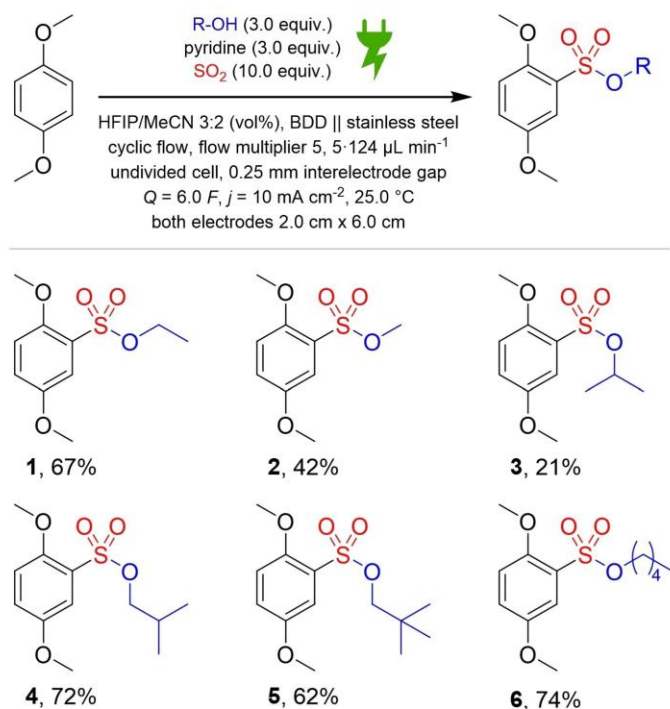


Figure 7. Scope of this electrochemical transformation with isolated yields.

Scale-Up

It's of great importance to demonstrate the robust scalability of electrochemical reactions, because this leads the way to application on industrial scale.^[24] Therefore we carried out a 10-fold scale-up of the reaction depicted in in Figure 7 using pentanol as nucleophile (Table 1), since pentanol gave the highest yields of all tested alcohols (Figure 7). In this case, the isolated yield on the larger scale was 81%, which corresponds to a cell productivity of 0.6 g/h of product **6**. The space-time yield of the two cells remains nearly the same, due to the scaling factor and unchanged current density. The flow cells employed are described in Figure 8, and further details about them can be found in the Supporting Information.

Conclusions

An automated experimental setup for the electrochemical synthesis of sulfonates in a multicomponent reaction in an undivided flow cell was developed. LABS: *Laboratory Automation and Batch Scheduling*, a modular, open-source Python software developed in our group, was used to plan, and to carry out the reactions. We did show that a simple and inexpensive stock solutions of sulfur dioxide can be employed in an automated flow electrolysis setup in a concentration of up to 2.0 mol L⁻¹. Design of Experiments (DoE) was used to systemati-

Electrolyzer	Isolated Yield [%]	Productivity [g/h]
small flow cell	74	0.159
large modular flow cell	81	0.663

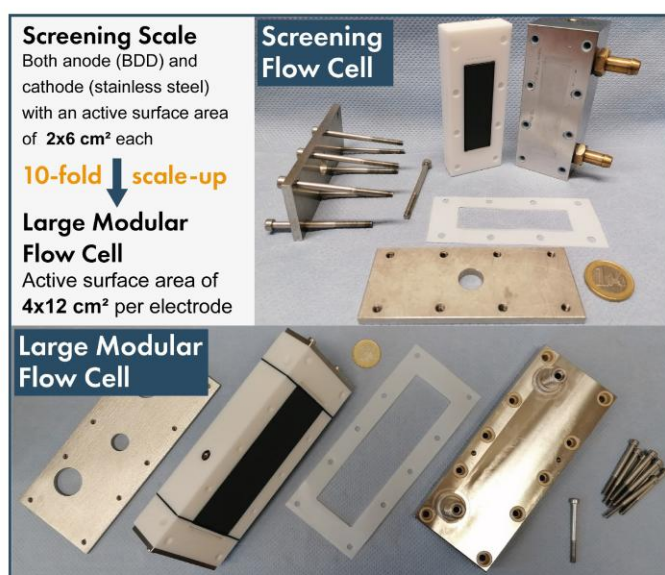


Figure 8. The two flow cells used.^[25] Details can be found in the Supporting Information. Pictures by J. Schneider. The screening-scale flow cell is commercially available as "ElectraSyn flow" from IKA-Werke GmbH & CO. KG, Staufen.

cally analyze the parameters affecting the reaction, and to optimize the yield. In total, 6 examples were demonstrated with isolated yields up to 81 %. The robust scalability of the electrochemical reaction was demonstrated in a 10-fold scale-up in a larger flow cell, which resulted in an increase of yield and an improved productivity. No hydrogen evolution reaction is observed during electrolysis, which could disrupt the flow setup.^[26] The reaction components (HFIP, MeCN, alcohol, SO₂, and pyridine) are volatile, which simplifies reaction workup. The reaction does not require any additional supporting electrolyte, because the reaction mixture itself ensures enough conductivity. This is another example of the dual role of a supporting electrolyte as enabler of conductivity and reagent.^[27]

Supporting Information

Detailed information on experimental setup, general procedures, reaction optimization, product characterization, and proposed mechanism can be found in the Supporting Information. The source code of LABS: Laboratory Automation and Batch Scheduling is available on GitHub under MIT license.^[28] The authors have cited additional references within the Supporting Information (Ref. [29]).

Acknowledgements

We would like to thank Maurice Dörr for helpful discussions about the setup and the development of the Eldex pump driver and Stephan Blum for helpful discussions about electrochemical multicomponent reactions involving sulfur dioxide. Financial support by the Federal Ministry of Education and Research via the project ETOS (E-SCOPE 2.0 with number 03ZU1205LB) is acknowledged. M. M. Hielscher thanks the German Science Foundation (DFG) for the opportunity to participate in the research training group GRK2516. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: electrolysis · automation · design of experiments · multicomponent reactions · sulfonates

- [1] a) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041; *Angew. Chem.* **2018**, *130*, 6124–6149; b) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619; *Angew. Chem.*

- 2018**, *130*, 5694–5721; c) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319; d) N. E. S. Tay, D. Lehnher, T. Rovis, *Chem. Rev.* **2022**, *122*, 2487–2649; e) S. R. Waldvogel, B. Janza, *Angew. Chem. Int. Ed.* **2014**, *53*, 7122–7123; *Angew. Chem.* **2014**, *126*, 7248–7249; f) K. D. Moeller, *Chem. Rev.* **2018**, *118*, 4817–4833.
- [2] a) J. Seidler, J. Strugatchi, T. Gärtner, S. R. Waldvogel, *MRS Energy Sustainability* **2020**, *7*, E42; b) S. O. Ganiyu, C. A. Martínez-Huitle, *Curr. Opin. Electrochem.* **2020**, *22*, 211–220.
- [3] N. Sbei, T. Hardwick, N. Ahmed, *ACS Sustainable Chem. Eng.* **2021**, *9*, 6148–6169.
- [4] a) D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386–12400; b) G. Kreysa, K. Ota, R. F. Savinell, *Encyclopedia of Applied Electrochemistry*. Springer New York, New York, NY, **2014**, 964–971.
- [5] S. P. Blum, D. Schollmeyer, M. Turks, S. R. Waldvogel, *Chem. Eur. J.* **2020**, *26*, 8358–8362.
- [6] a) S. P. Blum, K. Hofman, G. Manolikakes, S. R. Waldvogel, *Chem. Commun.* **2021**, *57*, 8236–8249; b) N. Amri, T. Wirth, *Chem. Rec.* **2021**, *21*, 2526–2537.
- [7] S. P. Blum, T. Karakaya, D. Schollmeyer, A. Klapars, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 5056–5062; *Angew. Chem.* **2021**, *133*, 5114–5120.
- [8] S. P. Blum, L. Schäffer, D. Schollmeyer, S. R. Waldvogel, *Chem. Commun.* **2021**, *57*, 4775–4778.
- [9] A. de A. Bartolomeu, F. A. Breitschaft, D. Schollmeyer, R. A. Pilli, S. R. Waldvogel, *Chem. Eur. J.* **2024**, *30*, e202400557.
- [10] G. Laudadio, E. Barmoutsis, C. Schotten, L. Struik, S. Govaerts, D. L. Browne, T. Noël, *J. Am. Chem. Soc.* **2019**, *141*, 5664–5668.
- [11] J. Schneider, S. P. Blum, S. R. Waldvogel, *ChemElectroChem* **2023**, *10*, e202300456.
- [12] a) A. Slattery, Z. Wen, P. Tenblad, J. Sanjosé-Orduna, D. Pintossi, T. den Hartog, T. Noël, *Science* **2024**, *383*, ead1817; b) J.-M. Lu, J.-Z. Pan, Y.-M. Mo, Q. Fang, *Artificial Intelligence Chemistry* **2024**, *2*, 100057; c) N. L. Bell, F. Boser, A. Bubliauskas, D. R. Willcox, V. S. Luna, L. Cronin, *Nat. Chem. Eng.* **2024**, *1*, 180–189; d) J. Ke, C. Gao, A. A. Folgueiras-Amador, K. E. Jolley, O. de Frutos, C. Mateos, J. A. Rincón, R. C. D. Brown, M. Poliakoff, M. W. George, *Appl. Spectrosc.* **2022**, *76*, 38–50.
- [13] a) L. Capaldo, Z. Wen, T. Noël, *Chem. Sci.* **2023**, *14*, 4230–4247; b) T. Noël, Y. Cao, G. Laudadio, *Acc. Chem. Res.* **2019**, *52*, 2858–2869; c) D. Pletcher, R. A. Green, R. C. D. Brown, *Chem. Rev.* **2018**, *118*, 4573–4591.
- [14] M. M. Hielscher, M. Dörr, J. Schneider, S. R. Waldvogel, *Chem. Asian J.* **2023**, *18*, e202300380.
- [15] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- [16] a) M. Dörr, M. M. Hielscher, J. Proppe, S. R. Waldvogel, *ChemElectroChem* **2021**, *8*, 2621–2629; b) M. Zirbes, T. Graßl, R. Neuber, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2023**, *62*, e202219217; *Angew. Chem.* **2023**, *135*; c) S. Arndt, D. Weis, K. Donsbach, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2020**, *59*, 8036–8041; *Angew. Chem.* **2020**, *132*, 8112–8118; d) R. Möckel, E. Babaoglu, G. Hilt, *Chem. Eur. J.* **2018**, *24*, 15781–15785; e) M. Santi, J. Seitz, R. Cicala, T. Hardwick, N. Ahmed, T. Wirth, *Chem. Eur. J.* **2019**, *25*, 16230–16235.
- [17] M. Selt, R. Franke, S. R. Waldvogel, *Org. Process Res. Dev.* **2020**, *24*, 2347–2355.
- [18] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.
- [19] M. M. Hielscher, B. Gleede, S. R. Waldvogel, *Electrochim. Acta* **2021**, *368*, 137420.
- [20] J. Fangmeyer, A. Behrens, B. Gleede, S. R. Waldvogel, U. Karst, *Angew. Chem. Int. Ed.* **2020**, *59*, 20428–20433; *Angew. Chem.* **2020**, *132*, 20608–20613.
- [21] a) L. Schulz, S. Waldvogel, *Synlett* **2019**, *30*, 275–286; b) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Chem. Rev.* **2017**, *1*, 0088; c) J. L. Röckl, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2020**, *59*, 315–319; *Angew. Chem.* **2020**, *132*, 323–327.
- [22] a) D. M. Heard, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, *59*, 18866–18884; b) S. Lips, S. R. Waldvogel, *ChemElectroChem* **2019**, *6*, 1649–1660; c) Y. Einaga, *Acc. Chem. Res.* **2022**, *55*, 3605–3615; d) J. V. Macpherson, *Phys. Chem. Chem. Phys.* **2015**, *17*, 2935–2949; e) S. R. Waldvogel, B. Elsler, *Electrochim. Acta* **2012**, *82*, 434–443.
- [23] D. C. Montgomery, *Design and analysis of experiments*, John Wiley & Sons, Hoboken, **2020**, p. 187–200.
- [24] D. Lehnher, L. Chen, *Org. Process Res. Dev.* **2024**, *28*, 338–366.
- [25] B. Gleede, M. Selt, C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2020**, *24*, 1916–1926.

- [26] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204140; *Angew. Chem.* **2022**, *134*, e202204140.
- [27] L. G. Gombos, J. Nikl, S. R. Waldvogel, *ChemElectroChem* **2024**, *11*, e202300730.
- [28] a) Maurice Dörr, Maximilian M. Hielscher, Waldvogel-Group/LABS-DeviceDummys: Beta-Publication_submission. Reference number: 7879590, Zenodo, **2023**; b) Maurice Dörr, Maximilian M. Hielscher, Waldvogel-Group/LABS-Backend: Beta-Publication_submission. Reference number: 7879589, Zenodo, **2023**; c) Maximilian M. Hielscher, Maurice Dörr, Waldvogel-Group/LABS-Frontend: Beta-Publication_submission. Reference number: 7879586, Zenodo, **2023**.
- [29] a) W. L. F. Armarego, *Purification of laboratory chemicals*, Butterworth-Heinemann is an imprint of Elsevier, Amsterdam, **2017**; b) G. Jander, K. F. Jahr, R. Martens-Menzel, L. Harwardt, H.-J. Krauss, *Massanalyse. Titrationen mit chemischen und physikalischen Indikationen*, 20. Aufl., De Gruyter, Berlin, Boston, **2022**; c) T. Rundlöf, M. Mathiasson, S. Bekiroglu, B. Hakkarainen, T. Bowden, T. Arvidsson, *J. Pharm. Biomed. Anal.* **2010**, *52*, 645–651; d) R. B. Dean, W. J. Dixon, *Anal. Chem.* **1951**, *23*, 636–638; e) J. L. Röckl, M. Dörr, S. R. Waldvogel, *ChemElectroChem* **2020**, *7*, 3686–3694.

Manuscript received: May 9, 2024

Revised manuscript received: June 19, 2024

Version of record online: August 19, 2024

4.4 Electrochemical Allylic Oxidation

The following results have been published in a peer-reviewed publication.^[43]

K. Hofman,[‡] **J. Schneider**,[‡] R. Goy, J. Schütz, W. Bonrath, S. R. Waldvogel *

A Simplified Approach for Electrochemical Allylic Oxidation of Olefins

Helv. Chim. Acta **2025**, e202500068

DOI: [10.1002/hlca.202500068](https://doi.org/10.1002/hlca.202500068)

License: CC BY 4.0

[‡] These authors contributed equally

* Corresponding author

Explanation of my contribution:

K. Hofman, R. Goy, J. Schütz, W. Bonrath, and S. R. Waldvogel conceptualized the project. **J. Schneider** performed reaction optimization, preparation and isolation of the compounds of the reaction scope, data analysis and evaluation. All experimental data which is found in the publication and in the Supporting Information was obtained by **J. Schneider** based on the groundwork of K. Hofman. **J. Schneider** carried out cyclic voltammetry (CV) measurements and the scale-up experiment. R. Goy, J. Schütz, W. Bonrath, and S. R. Waldvogel assisted in writing of the manuscript and the Supporting Information. S. R. Waldvogel supervised the project.

Introduction: Electrochemical allylic oxidation is an important method for the transformation of natural compounds to highly value-added products, especially when being applied as a method for late-stage functionalization.^[128] Several approaches to electrochemical allylic oxidation have been developed (Figure 59). Ozaki in 1985 published an approach using glassy carbon electrodes in a potentiostatic setup with a perchlorate supporting electrolyte using air.^[129] As mentioned in the introduction, perchlorates must be avoided if possible, because they can form explosive precipitates, especially in organic solutions. This is particularly important for carrying out electrosynthesis as a large-scale industrial process. The potentiostatic setup complicates scale-up of this reaction as well.^[38] Utley in 1987 reported on the electrochemical allylic oxidation of β -ionone using platinum electrodes, a perchlorate supporting electrolyte, and a galvanostatic electrolysis.^[130] In addition to the previously mentioned disadvantages which apply to this work as well, and the fact that only one

substrate is reported, expensive platinum electrodes were employed, and the yield was rather low. An important contribution was made by Baran in 2016 by reporting an electrochemical allylic oxidation using *t*-BuOOH, RVC electrodes, and a perchlorate supporting electrolyte.^[131] A machine learning approach was developed by Jensen in 2024, which utilized electrolysis conditions which are reported in the literature.^[132] Lui in 2025 reported an approach which extended the report of Ozaki by using graphite felt as electrode material.^[133] Although this approach is interesting as well, it employs large amounts of supporting electrolyte. These developments demonstrate the need for a simplified approach for electrochemical allylic oxidation of olefins, which was developed by the Waldvogel group in 2025.^[43]

Ozaki, 1985: glassy carbon electrodes potentiostatic electrolysis 0.85 V vs SCE NaClO₄ (0.1 mol L⁻¹), NHPI (25 mol%) pyridine (25 mol%), MeCN, air divided cell or undivided cell 10 examples up to 60% ✗ perchlorates as supporting electrolyte ✗ NHPI required as mediator	Jensen, 2024: RVC Ni various reaction conditions 8 examples up to 89% ✓ machine learning ✗ requires additional mediator ✗ complex setup ✗ RVC anode and nickel cathode
Utley, 1987: Pt carbon potentiostatic electrolysis HOAc, NaOAc (0.6 mol L⁻¹) LiClO₄ (0.09 mol L⁻¹) undivided cell 1 example up to 15% ✗ perchlorates as supporting electrolyte	Liu, 2025: graphite felt electrodes, air, 10 mA cm⁻² Et₄NBF₄ (2 equiv.), NHPI (20 mol%) undivided cell, DCM/MeCN (1/1) HOAc (10 equiv.) or 2,4,6-collidine (0.4 equiv.) 37 examples up to 89% ✓ galvanostatic electrolysis ✗ NHPI required as mediator ✗ graphite felt electrodes ✗ requires high amounts of supporting electrolyte
Baran, 2016: <i>t</i>-BuOOH (1.5 equiv.) RVC RVC, 10 mA mmol⁻¹ LiClO₄ (0.1 mol L⁻¹), pyridine (2–4 equiv.) Cl₄NHPI (20–40 mol%), undivided cell 40 examples up to 93% ✗ perchlorates as supporting electrolyte ✗ RVC electrodes ✗ Cl₄NHPI required as mediator	Waldvogel, 2025: pyridine (2–10 equiv.) <i>t</i>-BuOOH (3.5–10 equiv.) 1–10 mA cm⁻², 4–6 F, carbon-based electrodes butanone or acetonitrile, NaBF₄ (0.02 mol L⁻¹) 25 examples up to 80% ✓ galvanostatic electrolysis ✓ metal-free electrode materials ✓ <i>t</i>-BuOOH in a dual role as both oxygen source and mediator ✓ only small amounts of NaBF₄ as a safe and inexpensive supporting electrolyte

Figure 59. Overview of electrochemical allylic oxidation reactions.^[43,129–133]

To simplify electrochemical allylic oxidation, NaBF₄ was selected as an inexpensive and safe supporting electrolyte to avoid the use of perchlorates. Acetonitrile or butanone can be employed as solvent. Both solvents are miscible with water and an aqueous *t*-BuOOH solution was used as source of oxygen. Butanone is a better solvent for very unpolar compounds like steroids, which only partially dissolve in acetonitrile, especially when acetonitrile contains traces of water. Glassy carbon was utilized as carbon-based, inexpensive, nontoxic, and stable electrode material. The reaction is carried out as galvanostatic electrolysis. As test reaction, the electrochemical allylic oxidation of β -isophorone **1a** to 4-oxoisophorone **2a** was utilized (Figure 60). Extensive reaction optimization was carried out to find a balance between the equivalents of *t*-BuOOH and the current density. Interestingly, only very small concentrations of NaBF₄ are required as supporting electrolyte.

Optimization: To summarize the reaction optimization (Table 11), a current density of 10 mA cm^{-2} only results in acceptable yields if 10 equiv. of *t*-BuOOH are employed. Alternatively, only 3.5 equiv. of *t*-BuOOH can be employed with a current density of only 1 mA cm^{-2} . This implies that although a higher amount of reagent is required, the productivity of the reaction can be higher, because higher current density results in a faster electrolysis. As will be discussed in the mechanism section, *t*-BuOOH serves a dual role as reagent and mediator.^[70] The reaction optimization also demonstrated that graphite or BDD can be employed as electrode materials, albeit with lower yields.

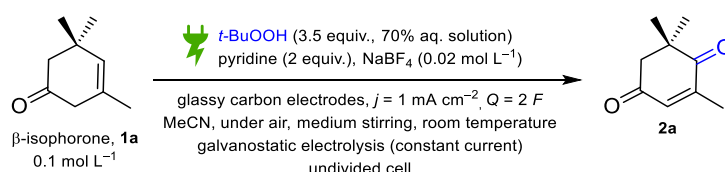


Figure 60. The test reaction utilized for the optimization of electrochemical allylic oxidation.^[43]

Table 11. Optimization of the test reaction of electrochemical allylic oxidation.^[43]

#	Deviation from standard reaction conditions ^[a]	yield% (selectivity%) ^[b]
1	none	35 (55)
2	NEt_4BF_4 instead of NaBF_4	39 (60)
3	NBu_4PF_6 instead of NaBF_4	33 (50)
4	NBu_4HSO_4 instead of NaBF_4	29 (62)
5	ethyl acetate instead of MeCN ^[c]	44 (58)
6	ethanol instead of MeCN	20 (30)
7	acetone instead of MeCN ($1.8 F$) ^[d]	37 (50)
8	butanone instead of MeCN	39 (59)
9	5 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$	36 (51)
10	5 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.2 \text{ mol L}^{-1}$	51 (70)
11	10 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.2 \text{ mol L}^{-1}$	62 (84)
12	10 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.2 \text{ mol L}^{-1}$, BDD electrodes	45 (62)
13	10 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.2 \text{ mol L}^{-1}$, butanone instead of MeCN	62 (90)
14	10 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.3 \text{ mol L}^{-1}$, butanone instead of MeCN	56 (81)
15	10 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.2 \text{ mol L}^{-1}$, butanone instead of MeCN, BDD electrodes	44 (58)
16	10 equiv. pyridine, 10 equiv. <i>t</i> -BuOOH, 10 mA cm^{-2} , $4 F$, $c(1a) = 0.2 \text{ mol L}^{-1}$, butanone instead of MeCN, graphite electrodes	49 (71)
17	no electricity	0 (–)

[a] The standard reaction conditions are depicted in Figure 60. [b] The yield and selectivity (= yield / conversion) were determined using ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. [c] The upper terminal voltage limit of the power supply was reached during electrolysis, but the desired amount of charge could be fully applied. [d] The upper terminal voltage limit of the power supply was reached during electrolysis, and only the specified amount of charge could be applied.

Scope: Various terpenes, steroids, and derivatives thereof were employed as substrates in the electrochemical allylic oxidation of olefins to enones (Figure 61 and Figure 62).^[43] Because of the reaction mechanism (Figure 65), 4-ketoisophorone **2a** was obtained as product when employing α -isophorone, β -isophorone, and 2,6,6-trimethyl-2-cyclohexen-1-one. The highest isolated yield of all terpene-derived substrates was obtained for α -cetone, which gave 3-oxo- α -cetone **2k** in 52% isolated yield. From pinene and (+)- α -limonene, allylic oxidation products **2b** and **2c** were obtained in 15% and 19%, respectively. The electrochemical allylic oxidation of α -ionone, vinyl- α -ionol, and ethynyl- α -ionol resulted in products **2d**, **2e**, and **2f** in yields of 47%, 38%, and 43%, respectively. In comparison, β -ionone, vinyl- β -ionol, and ethynyl- β -ionol gave allylic oxidation products **2g**, **2h**, and **2i** in lower isolated yields of 18%, 16%, and 16%, respectively. (+)-Valencene could be oxidized to **2l** in 22% yield. (1*R*)-myrtenyl acetate gave allylic oxidation product **2m** in 21% isolated yield. From α -cedrene, product **2n** was isolated with 20%.

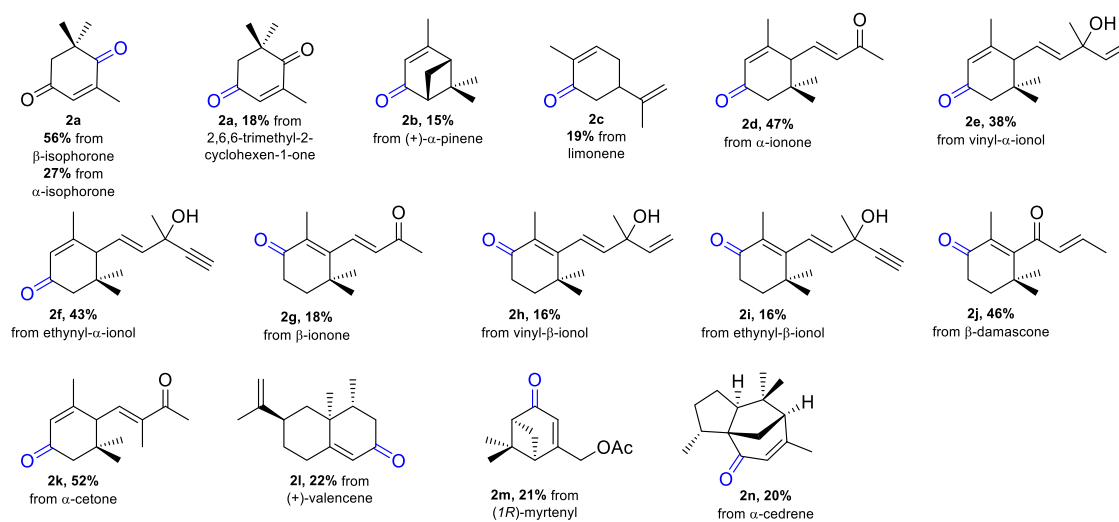


Figure 61. Electrochemical allylic oxidation of terpenes and terpene derivatives.^[43]

Stigmasterol acetate was the steroid which gave the highest isolated yield for the allylic oxidation 7-ketostigmasterol acetate **4f**, which was obtained in 80% yield. 7-Ketocholesterol **4a**, 7-ketocholesteryl acetate **4b**, and 7-ketocholesteryl benzoate **4c** were obtained in yields of 63%, 67%, and 26%, respectively. 7-ketodiosgenin acetate **4d** and 7-keto- β -sitosterol **4e** could be obtained in 45% isolated yield both. Both 7-ketopregnenolone acetate **4g** and 7-dehydroepiandrosterone acetate **4h** could be isolated in 67% yield. Lower yields were observed for 7-ketomethandriol **4i** and 3-ketolynestrenol **4j**, which were obtained in 32% and 17%, respectively.

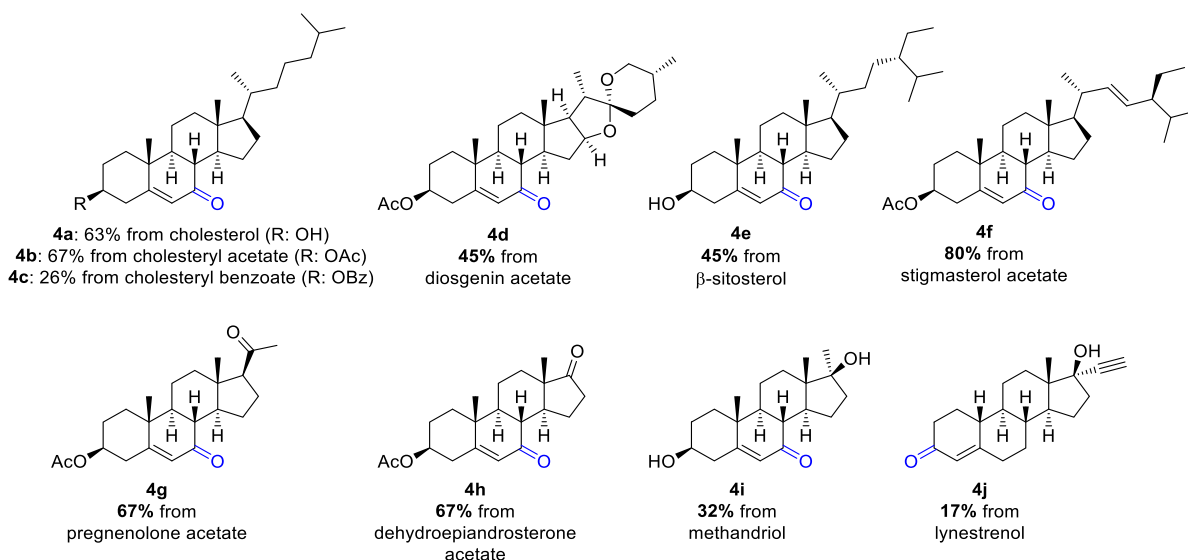


Figure 62. Electrochemical allylic oxidation of steroids and steroid derivatives.^[43]

Unsuccessful Substrates: The electrochemical allylic oxidation of some substrates was unsuccessful (Figure 63). While (1*R*)-myrtenyl acetate gave the allylic oxidation product **2m** in 21%, the unprotected starting material (1*R*)-myrtenol **u1** gave no product. For γ -terpinene **u2**, no conversion was observed, and the starting material was partially recovered after electrolysis. Carvone **u3**, which is the product of the allylic oxidation of limonene, could not be oxidized further. For piperitone **u4** no conversion was found.

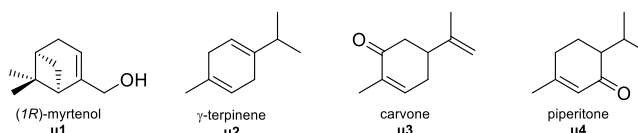


Figure 63. Electrochemical allylic oxidation of terpenes and terpene derivatives.^[43]

Scale-up: To demonstrate the scalability of this method, a 20-fold scale-up of cholesteryl acetate **3b** was carried out, which gave the product 7-ketocholesteryl acetate **4b** in 54% isolated yield (Figure 64). Notably, the product could be purified by recrystallization, and no column chromatography was required in scale-up. The product **4b** is an important precursor for the synthesis of vitamin D₃.^[134]

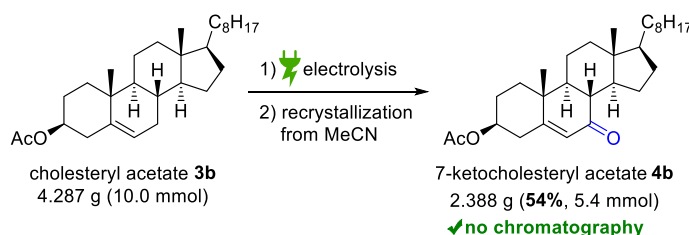


Figure 64. Electrochemical allylic oxidation of steroids.^[43]

Mechanism: The proposed reaction mechanism is depicted in Figure 65. *t*-BuOOH serves a dual role as mediator and as reagent (source of oxygen). Initially, *t*-BuOOH is deprotonated by pyridine (abbreviated as Py). The anodic oxidation of *t*-BuOO[−] **I** results in radical **II**, which undergoes hydrogen atom abstraction with the starting material **III** to a radical **IV**. Intermediate **IV** combines with another radical **II**, which results in intermediate **V**, from which *t*-BuOH is eliminated to form the allylic oxidation product **VI**. Hydrogen evolution reaction occurs at the cathode, regenerating pyridine.^[119]

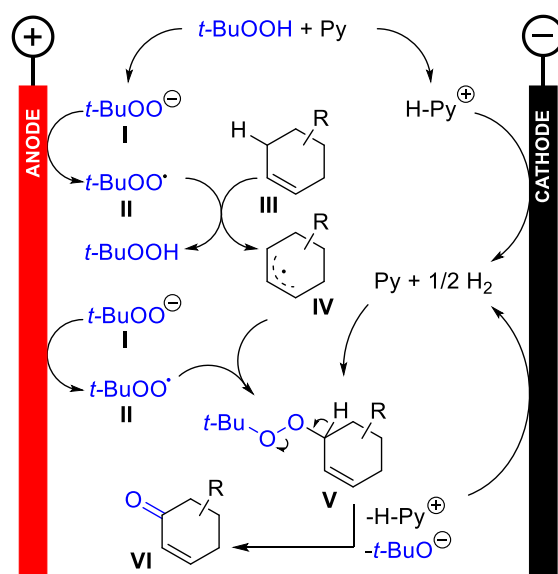


Figure 65. Proposed reaction mechanism of the electrochemical allylic oxidation of olefins to enones.^[43]

Conclusion: A simplified approach for the electrochemical allylic oxidation of olefins to enones was successfully developed. *t*-BuOOH serves a dual role as mediator and as reagent (source of oxygen). Acetonitrile or butanone can be employed as solvent. Only very low concentrations of NaBF₄ are required as a comparably inexpensive and safe supporting electrolyte, which simplifies scale-up and downstream processing. This method does not require perchlorate supporting electrolytes and it avoids the use of additional mediators. In total, 25 examples were reported in isolated yields up to 80%. Glassy carbon, boron-doped diamond (BDD) or graphite can be employed as electrode material. These metal-free reaction conditions are predestined for application in medicinal chemistry. The robust scalability of the method was demonstrated in a 20-fold scale-up of ketocholesteryl acetate, and chromatography could be avoided in scale-up. Delicate terpenes and biologically active steroidal derivatives are functionalized to highly value-added synthetic intermediates.

A Simplified Approach for Electrochemical Allylic Oxidation of Olefins

Kamil Hofman,^a Johannes Schneider,^a Roman Goy,^b Jan Schütz,^b Werner Bonrath,^b and Siegfried R. Waldvogel^{*c, d}

^a Department of Chemistry, Johannes Gutenberg University (JGU), Duesbergweg 10-14, Mainz 55128, Germany

^b dsm-firmenich AG, Wurmisweg 576, Kaiseraugst CH-4303, Switzerland

^c Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS–FMS), Karlsruhe Institute of Technology (KIT), Kaiserstraße 12, Karlsruhe 76131, Germany, e-mail: siegfried.waldvogel@cec.mpg.de

^d Max-Planck-Institute for Chemical Energy Conversion (MPI CEC), Stiftstraße 34-36, Mülheim an der Ruhr 45470, Germany

© 2025 The Author(s). Helvetica Chimica Acta published by Wiley-VHCA AG. This is an open access article under the terms of the [Creative Commons Attribution](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

A simple method for the electrochemical allylic oxidation of olefins to enones based on peroxide-mediated C–H activation is presented. *t*-Butyl hydroperoxide serves a dual role as mediator and oxygen source, avoiding the utilization of expensive transition metal catalysts, potentially explosive supporting electrolytes such as perchlorates, or additional environmentally harmful mediators. This elegant methodology allows for an operationally simple and sustainable late-stage transformation of delicate natural compounds such as terpenes or steroids into highly value-added building blocks. Such an approach provides a greener alternative to conventional oxidation methods used for industrial applications. In total, 25 examples are demonstrated with isolated yields up to 80%. The robust scalability of the method was also demonstrated, and chromatography could be avoided in scale-up simply by using recrystallization, which decreases the cost of downstream processing.

Keywords: allylic oxidation, electrolysis, enones, natural products, sustainability

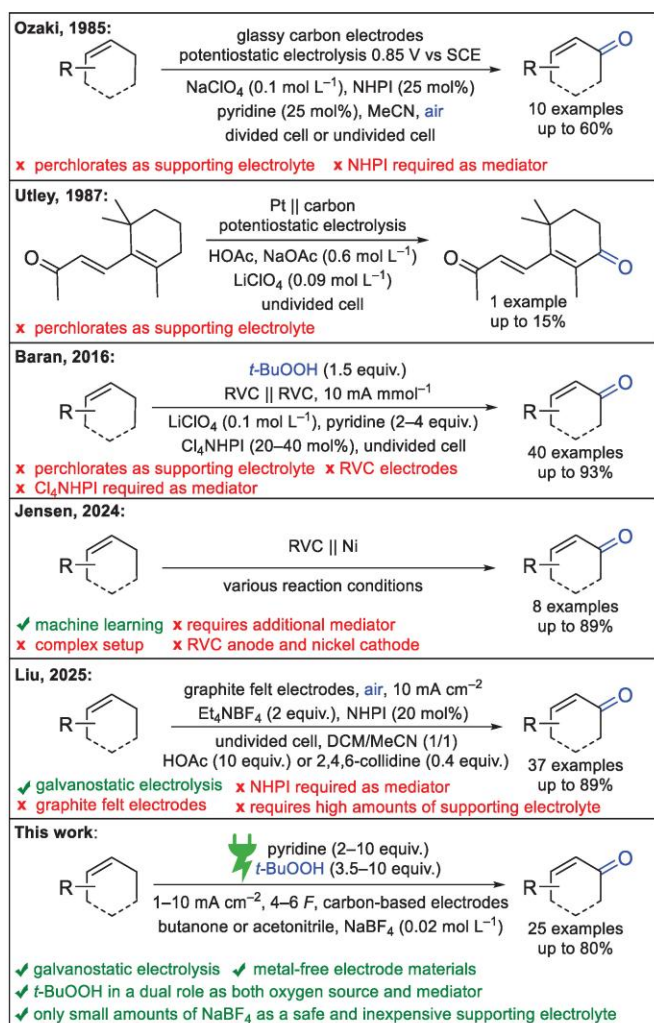
1. Introduction

The direct allylic oxidation of olefins by C–H activation is a principal method to access value-added α,β -unsaturated ketone motifs in fine chemicals,^[1] highly interesting building blocks (e.g., 7-ketocholesterol),^[2] flavor compounds and fragrances,^[3] as well as pharmaceuticals.^[4–5] The conventional methods^[6–7] feature the use of toxic or expensive transition metals,^[8–16] excess oxidizers,^[17–18] (photo-)catalysts,^[19–21] or enzymes.^[22–25] However, these approaches are often less attractive for industrial applications because of complicated reaction setups, unfavorable atom economy, and overall low efficiency. Organic

electrosynthesis provides a more sustainable methodology to achieve these transformations.^[26] One of the many advantages of electrochemistry is the direct use of electricity as a comparably inexpensive and universal redox agent – which can originate from renewable energy sources – avoiding additional oxidizers, and minimizing costs, CO₂ footprint, and reagent waste.^[27–28]

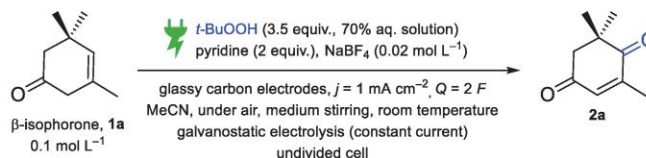
Despite the fact that electro-organic synthesis is currently experiencing an ongoing renaissance,^[34–41] electrochemical approaches for allylic oxidations to provide α,β -unsaturated ketones have been rarely described in the literature until recently (Scheme 1). The first method was reported in 1985 by Ozaki et al. using *N*-hydroxyphthalimide (NHPI) as mediator in the presence of molecular oxygen and NaClO₄ as supporting electrolyte in a potentiostatic electrolysis setup.^[29] In this

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/hlca.202500068>



Scheme 1. Overview of electrochemical allylic oxidation reactions.^[29–33]

work, only a limited number of 10 substrates were tested with isolated yields up to 60%. Another method was subsequently established by Utley et al. for the allylic oxidation of β -ionone.^[30] By using platinum anodes and water as a nucleophile, the corresponding 4-oxo- β -ionone was obtained in 15% yield. In addition to their limited scope and rather sophisticated setups, these methods utilize various perchlorates as potentially explosive supporting electrolytes, and brittle or expensive electrode materials, making them unsuitable for larger technical applications. Based on this groundwork, Baran et al. reported an improved method in 2016.^[31] Despite the usefulness of their work, it requires brittle reticulated vitreous carbon (RVC) electrodes,^[42] tetrachloro-*N*-hydroxylphthalimide (Cl₄NHPI) as a rather unusual and environmentally critical mediator,^[43–44] and NaClO₄ as a potentially explosive supporting electrolyte as well.^[45]



Scheme 2. The standard reaction conditions of the test reaction used for optimization. Note that no care must be taken to exclude moisture because *t*-BuOOH is added as an aqueous solution anyways. More information about the experimental setup can be found in the [Supporting Information](#).

Also recently, an interesting approach was published in 2024 by Jensen et al., which uses machine learning to optimize the reaction conditions already published in the literature.^[32] Another method was recently developed in 2025 by Liu et al.,^[33] which further develops the approach by the group of Ozaki, utilizing air as an inexpensive oxidizer. While this protocol is interesting, and it does not rely on perchlorates, it requires many equivalents of supporting electrolyte and NHPI as a mediator as well.

Here, we present a simplified method for electrochemical allylic oxidation using *t*-BuOOH in a dual role as mediator and oxygen source.^[46] Acetonitrile or butanone can be chosen as the solvent, and pyridine is used as an (electro)chemically stable base. Glassy carbon, boron-doped diamond (BDD), or graphite can be employed as metal-free electrode materials. NaBF₄ is used as a safe, inexpensive, and inert supporting electrolyte, which is required in only very small concentrations. This approach simplifies downstream processing and provides a more attractive and greener protocol compared with the previously mentioned ones. Moreover, the method established here also features the valorization of biogenic substrates such as terpenes and biologically active steroid derivatives to the desired enones, which makes this approach particularly attractive for industrial and interdisciplinary applications.

2. Results and Discussion

For reaction optimization, β -isophorone **1a** was chosen as test substrate due to its established role in the synthesis of 4-oxoisophorone **2a**, which serves as a building block in the production of tocopherols and carotenoids like astaxanthin.^[47–48] The reactions were performed in small Teflon cells,^[49–52] which have proven to be very successful in our group (see [Supporting Information](#)).^[53–56] The standard reaction conditions are depicted in Scheme 2. The yield and selec-

Table 1. Optimization of the test reaction.

#	Deviation from Standard Reaction Conditions ^[a]	Yield% (Selectivity%) ^[b]
1	None	35 (55)
2	NEt ₄ BF ₄ instead of NaBF ₄	39 (60)
3	NBu ₄ PF ₆ instead of NaBF ₄	33 (50)
4	NBu ₄ HSO ₄ instead of NaBF ₄	29 (62)
5	ethyl acetate instead of MeCN ^[c]	44 (58)
6	ethanol instead of MeCN	20 (30)
7	acetone instead of MeCN (1.8 F) ^[d]	37 (50)
8	butanone instead of MeCN	39 (59)
9	5 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F	36 (51)
10	5 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.2 mol L ⁻¹	51 (70)
11	10 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.2 mol L ⁻¹	62 (84)
12	10 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.2 mol L ⁻¹ , BDD electrodes	45 (62)
13	10 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.2 mol L ⁻¹ , butanone instead of MeCN	62 (90)
14	10 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.3 mol L ⁻¹ , butanone instead of MeCN	56 (81)
15	10 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.2 mol L ⁻¹ , butanone instead of MeCN, BDD electrodes	44 (58)
16	10 equiv pyridine, 10 equiv <i>t</i> -BuOOH, 10 mA cm ⁻² , 4 F, <i>c</i> (1a) = 0.2 mol L ⁻¹ , butanone instead of MeCN, graphite electrodes	49 (71)
17	no electricity	0 (–)

^{a)} The standard reaction conditions are depicted in Scheme 2.

^{b)} The yield and selectivity (= yield / conversion) were determined using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

^{c)} The upper terminal voltage limit of the power supply was reached during electrolysis, but the desired amount of charge could be fully applied.

^{d)} The upper terminal voltage limit of the power supply was reached during electrolysis, and only the specified amount of charge could be applied.

tivity (= yield / conversion) was determined using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard.^[57] The standard reaction conditions (Scheme 2 and Table 1, entry 1) gave **2a** in 35% yield and 55% selectivity. To our delight, all subsequent optimization reactions could be carried out with such a small concentration of supporting electrolyte (only 0.02 mol L⁻¹), which simplifies downstream processing.

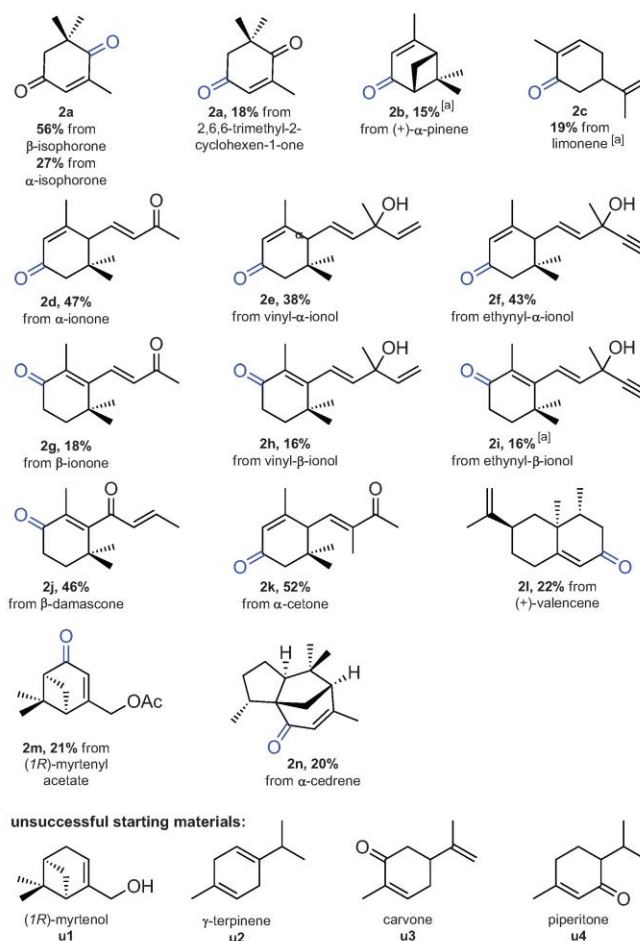
Testing other supporting electrolytes such as NEt₄BF₄, NBu₄PF₆, or NBu₄HSO₄ (Table 1, entries 2–4) gave no noteworthy increase in yield or selectivity. To simplify downstream processing, and to decrease cost, subsequent optimization reactions were continued using NaBF₄. Next, different solvents were tested. For ethyl acetate, ethanol, and acetone, yields of 44%, 20%, and 37% were obtained, respectively (entries 5–7). For ethyl acetate and acetone however, the upper terminal voltage limit was reached during electrolysis. In the case of ethyl acetate, the full 2 F could be applied, while the electrolysis came to an end after 1.8 F when acetone was used as the solvent. In general, high cell voltages cause high power consumption, meaning ethyl acetate and acetone were not further tested in optimization reactions. Since the yield was low as well when using ethanol as solvent, it was not tested further either. Butanone was also tested and gave 39% yield (entry 8). The objective of the optimization was not only to improve the yield and to investigate the selectivity, but also to increase the productivity by increasing the current density, which shortens the electrolysis time. Therefore, a current density of 10 mA cm⁻² was tested in combination with an increase of equivalents of pyridine and *t*-BuOOH and an increase of applied charge to 4 F, which did not result in a significant increase in yield or selectivity (entry 9). Using the same reaction conditions as entry 9 but increasing the concentration of the starting material to 0.2 mol L⁻¹ gave an increase in yield to 51% with a selectivity of 70% (entry 10). Repeating the experiment from entry 10 with more pyridine (entry 11) gave 62% yield with a selectivity of 84%. While these reaction conditions require more equivalents of pyridine and *t*-BuOOH and more applied charge, they allow for an increased productivity by using a higher current density and a higher concentration of starting material. The reaction conditions of entry 11 were used again with boron-doped diamond electrodes instead of glassy carbon,^[58] which gave 45% yield (entry 12). Next, optimization was refined using butanone as solvent, because the scope of our work also includes steroids, for which butanone is a better solvent than MeCN. The use of butanone instead of acetonitrile does not complicate downstream processing, because both solvents can easily be removed by distillation after electrolysis. Using 10 equivalents of pyridine and *t*-BuOOH, 4 F, and 10 mA cm⁻², the product was obtained in 62% yield with 90% selectivity (entry 13). Using these reaction conditions from entry 13 but increasing the current density to 10 mA cm⁻² and increasing the concentration of the starting material to 0.3 mol L⁻¹ resulted in a yield of 56% with 81% selectivity (entry 14).

Based on these results, two optimization experiments using BDD electrodes (entry 15) and graphite electrodes (entry 16) were carried out, which gave 44% and 49% yield, respectively. This demonstrates that boron-doped diamond or graphite can be employed as an alternative to glassy carbon electrodes. Since all electrode materials which were tested are metal-free, this method is interesting for applications in medicinal chemistry, which is very reluctant about traces of transition metals.^[59] Without electricity, no product could be found (entry 17).

2.1. Scope

Several substrates have been tested, as depicted in the following Scheme 3. The allylic oxidation product 4-oxoisophorone **2a** can be obtained from different starting materials, as will be later explained in the mechanism section. The numbering of starting materials and products is explained in the [Supporting Information](#). In all schemes, the newly installed oxo functions are indicated in blue. Using β -isophorone or α -isophorone, product **2a** is obtained in 56% and 27%, respectively. With 2,6,6-trimethyl-2-cyclohexen-1-one as starting material, **2a** is isolated in 18% yield. Using (+)- α -pinene as starting material, product **2b** could be isolated in 15% yield, and for limonene, **2c** was obtained in 19% yield. One reason for the low yield of **2c** could be oxidation reactions at the exocyclic double bond. The Starting materials α -ionone, vinyl- α -ionol, and ethynyl- α -ionol gave products **2d**, **2e**, and **2f** in 47%, 38%, and 43% isolated yield, respectively. For β -ionone **2g**, vinyl- β -ionol **2h**, and ethynyl- β -ionol **2i**, overall lower yields of only 18%, 16%, and 16% were obtained. Higher yields than those were obtained for β -damascone and α -cetone, which gave the corresponding allylic oxidation products **2j** and **2k** in 46% and 52%. Using (+)-valencene, a yield of 22% was found for nootkatone **2l**. Myrtenyl acetate gave **2m** in 21% yield. From α -cedrene, **2n** was obtained in 20% yield. The low yield of product **2b**, **2m**, and **2n** could be due to the steric hindrance of the bridging CH_2 group, or its influence on the stability of the allylic radical intermediate.

The allylic oxidation of some substrates was unsuccessful. For example, while myrtenyl acetate could undergo allylic oxidation to product **2m** successfully, the corresponding unprotected starting material myrtenol **u1** could not be oxidized, as no reaction product could be found. When using gamma-terpinene **u2**, no conversion was observed, and the starting material was partially recovered upon workup.

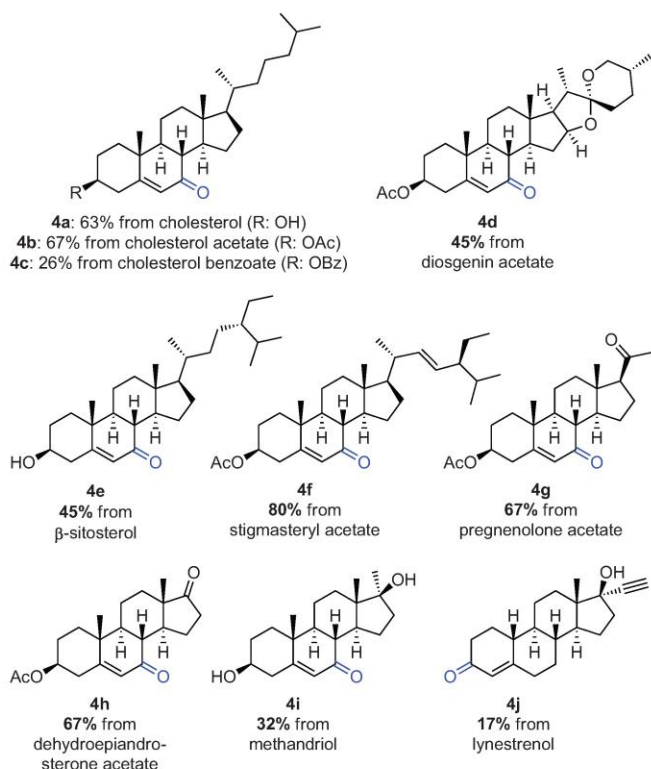


Scheme 3. Scope of transformation. Reaction conditions: starting material (0.5 mmol, 0.1 mol L⁻¹), butanone (5.0 mL), NaBF₄ (0.02 mol L⁻¹), amount of applied charge $Q = 4 F (= 193 \text{ C for } 0.5 \text{ mmol starting material})$, current density $j = 1 \text{ mA cm}^{-2}$, *t*-BuOOH (3.5 equiv, 70% in aqueous solution), pyridine (5 equiv), glassy carbon electrodes, room temperature, undivided cell, under air, galvanostatic electrolysis (constant current). Note that no care must be taken to exclude moisture because *t*-BuOOH is an aqueous solution anyways. More details about the experimental setup can be found in the [Supporting Information](#). [a] Using the aforementioned reaction conditions gave no product but using the following deviations from the reaction conditions was successful: MeCN instead of butanone, 2 equiv pyridine.

Using carvone **u3**, which is the product of the allylic oxidation of limonene, no further allylic oxidation could be observed either. Similarly, for piperitone **u4**, which is also already an enone, no conversion was found.

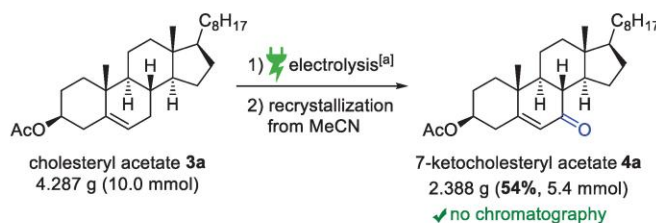
2.2. Steroids

Several steroids were also employed as substrates, as depicted in Scheme 4. From cholesterol,



Scheme 4. Scope of steroids. Reaction conditions: starting material (0.5 mmol, 0.1 mol L⁻¹), butanone (5.0 mL), NaBF₄ (0.02 mol L⁻¹), amount of applied charge $Q = 6 F (= 289 \text{ C for } 0.5 \text{ mmol starting material})$, current density $j = 10 \text{ mA cm}^{-2}$, *t*-BuOOH (10 equiv, 70% in aqueous solution), pyridine (10 equiv), glassy carbon electrodes, room temperature, undivided cell, under air, medium stirring, galvanostatic electrolysis (constant current). Note that no care must be taken to exclude moisture because *t*-BuOOH is an aqueous solution anyways. More details about the experimental setup can be found in the [Supporting Information](#).

cholesteryl acetate, and cholesteryl benzoate, allylic oxidation products **4a**, **4b**, and **4c** were obtained in 63%, 67%, and 26%, respectively. For diosgenin acetate and β -sitosterol, the corresponding enones **4d** and **4e** were both obtained in 45% yield. Stigmasteryl acetate gave the highest yield of all substrates, as **4f** was obtained in 80% isolated yield. To compare this with methods reported in the literature: **4f** can be prepared by oxidation of stigmasteryl acetate with an excess of highly carcinogenic pyridinium chlorochromate (PCC) in 71% isolated yield.^[60] From pregnenolone acetate, product **4g** was obtained in 67% yield, and from dehydroepiandrosterone acetate (DHEA acetate), **4h** was obtained in 67% as well. Methandriol (methylandrostenediol) and lynestrenol gave products **4i** and **4j** in lower yields of only 32% and 17%, respectively.



Scheme 5. Scale-up reaction of cholesteryl acetate (20-fold scale-up from 0.5 mmol to 10.0 mmol). [a] Electrolysis reaction conditions: $c(\text{starting material}) = 0.1 \text{ mol L}^{-1}$, *t*-BuOOH (10 equiv), pyridine (10 equiv), NaBF₄ (0.02 mol L⁻¹), $j = 10 \text{ mA cm}^{-2}$, $Q = 6 F$, glassy carbon electrodes, butanone (100 mL), room temperature, undivided cell, galvanostatic electrolysis. More details about the experimental setup can be found in the [Supporting Information](#).

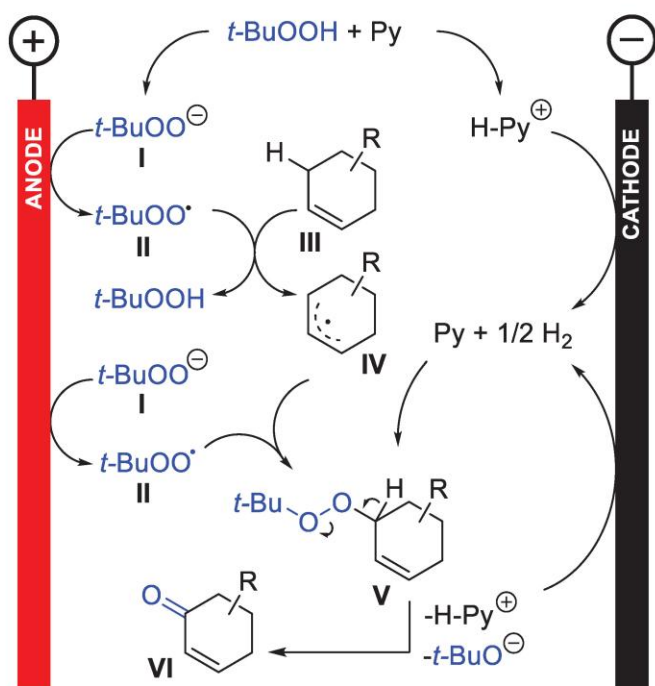
2.3. Scale-up

Demonstrating the robust scalability of an electrosynthetic method is important, because this paves the way for an application on technical scale.^[61–62] Furthermore, scale-up reactions must avoid expensive and sophisticated purification techniques such as chromatography in order to be operationally simple and economically feasible. This is important because cost-efficient work-up is usually the key for the translation of electrosynthetic conversions.^[63–64] Therefore, a gram-scale electrolysis of cholesteryl acetate was carried out as depicted in Scheme 5. The product 7-ketocholesteryl acetate **4a** was obtained in 54% yield. According to the ¹H NMR spectrum, it is 92% pure and contains 8% of the starting material cholesteryl acetate. After recrystallization, the rest of the remaining starting material stays dissolved in acetonitrile.

2.4. Reaction Mechanism

The proposed reaction mechanism is depicted in Scheme 6. Deprotonation of *t*-BuOOH by pyridine gives intermediate **I**, and its subsequent anodic oxidation results in the formation of radical **II**. This radical species undergoes hydrogen atom abstraction with olefin **III**, which results in the formation of a stabilized allylic radical **IV**. Another radical of type **II** recombines with **IV** to form intermediate **V**. Deprotonation of **V** by pyridine induces the elimination of *t*-BuO⁻, forming the allylic oxidation product **VI**. At the cathode, hydrogen evolution is the counter reaction.^[65] Pyridine proved to be essential for the success of this reaction.

In the presence of pyridine, the reduction potential of the starting material increases dramatically, and the reduction potential of *t*-BuOOH decreases, making **I** more susceptible to oxidation and decreasing the chance



Scheme 6. The proposed reaction mechanism. Py is pyridine.

of a possible direct oxidation of olefin **III** (see CV measurements in Supporting Information). In addition to that, the direct oxidation of either β -isophorone or α -isophorone via a carbocation species would lead to different isomers, proving that *t*-BuOOH serves both as a mediator and the oxygen source in the reaction. The formation of 4-oxoisophorone **2a** starting from either β -isophorone, α -isophorone, or 2,6,6-trimethyl-2-cyclohexen-1-one indicates an allylic intermediate **IV**.

3. Conclusion

A simplified method for the mediated electrochemical allylic oxidation of olefins to their corresponding enones was established. *t*-BuOOH serves a dual role as mediator and source of oxygen, which avoids the use of additional mediators such as NHPI or transition metals. Acetonitrile or butanone can be chosen as the solvent with pyridine as a base. Only very low concentrations of NaBF_4 are required as a safe and inexpensive supporting electrolyte, which strongly simplifies downstream processing. Glassy carbon, boron-doped diamond or graphite can be used as mechanically robust and metal-free electrode materials, making this approach predestined for applications in medicinal chemistry. The scalability of the electrolysis was demonstrated in a scale-up reaction of cholesteryl acetate, which utilized a simple recrystallization to avoid chromatography, and gave 7-

ketocholesteryl acetate in 54% yield. In total, 25 examples are demonstrated with up to 80% isolated yield. This method valorizes delicate terpenes and biologically active steroidal derivatives to obtain highly value-added synthetic intermediates.

4. Experimental Section

The starting material (0.5 mmol, 0.1 mol L⁻¹) and the supporting electrolyte NaBF_4 (109.79 g mol⁻¹, 11 mg, 0.01 mmol, 0.02 mol L⁻¹) are dissolved in acetonitrile or butanone (5.0 mL) at room temperature in a small Teflon cell under medium stirring (500 rpm). The electrodes (1.0 cm x 7.0 cm x 0.3 cm) are assembled and put into the cell so that both electrodes have an immersion depth of 2.0 cm into the reaction solution. To prevent solvent evaporation, the assembled electrolysis cell is sealed with some stretch film (Parafilm). Pyridine (2.0 equiv, 1.0 mmol, 0.08 mL, 79.10 g mol⁻¹) and *t*-BuOOH (70% aqueous solution, 3.5 equiv, 1.75 mmol, 0.24 mL, 90.12 g mol⁻¹) are added through the top of the electrode holder using a syringe. Under continued medium stirring at room temperature, the electrolysis is started (current density $j = 1.0 \text{ mA cm}^{-2}$, amount of applied charge $Q = 4 F$). To determine NMR yield, 1,3,5-trimethoxybenzene (168.19 g mol⁻¹, 1.0 mL of a stock solution of 2.1001 g in 250.0 mL MeCN, 8.4 mg, 0.05 mmol) is added after electrolysis. The reaction solution is transferred into a round bottom flask, and the solvents are removed by distillation at reduced pressure using a rotary evaporator (40 °C water bath, 50 mbar, 10 min). The residue is dissolved in CDCl_3 (0.5 mL), and a ¹H NMR spectrum is measured. To isolate the product, the reaction solution is transferred into a round bottom flask, and the solvents are removed using a rotary evaporator under reduced pressure (40 °C water bath, 50 mbar, 10 min). The residue is transferred into a separatory funnel using a saturated aqueous solution of NaHCO_3 (30 mL). The round bottom flask is rinsed once with ethyl acetate (30 mL), which is also added to the separatory funnel. After mixing and separation of the ethyl acetate layer, the aqueous layer is extracted with ethyl acetate twice more ($2 \times 30 \text{ mL}$). The combined ethyl acetate fractions are dried over MgSO_4 (10 g), and the solution is filtered. The solvent was removed from the filtrate by distillation using a rotary evaporator at reduced pressure (40 °C water bath, 50 mbar, 10 min). The crude residue is dissolved in ethyl acetate again (5 mL) and adsorbed on Celite 545 (10 g). Depending on the substrate, either cyclohexane with ethyl acetate (normal phase) or water and acetonitrile (reversed phase) (linear

gradient: 100:0 → 95:5 in 10 column volumes) is used for flash column chromatography.

Supporting Information

The authors have cited additional references within the Supporting Information.^[66–81]

Acknowledgements

The authors gratefully acknowledge the financial support by dsm-firmenich AG. Benjamin R. Strücker is acknowledged for reaction optimization. Kamil Hofman would like to thank J. Nikl and L. G. Gombos for helpful discussions. The authors thank the MPG for the open access opportunity within the frame of DEAL agreement.

Open access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Author Contributions

K.H. and J. Schneider contributed equally to this work. S. R. Waldvogel, R. Goy, J. Schütz, and W. Bonrath devised and supervised the project. K. Hofman and J. Schneider carried out optimization reactions, scope reactions, cyclic voltammetry studies, and data analysis. J. Schneider performed the scale-up reaction. All authors contributed to the discussion of results, writing of the manuscript, and writing of the Supporting Information.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

- [1] R. A. Sheldon, H. van Bekkum, *Fine Chemicals through Heterogeneous Catalysis*, Wiley-VCH, Weinheim, New York **2001**, p. 519.
- [2] Z. Yao, X. Hu, J. Mao, H. Li, 'An Environmentally Benign Catalytic Oxidation of Cholesteryl Acetate With Molecular Oxygen by Using N-hydroxyphthalimide', *Green Chem.* **2009**, *11*, 2013–2017.
- [3] S. Schulz, M. Girhard, S. K. Gaßmeyer, V. D. Jäger, D. Schwarze, A. Vogel, V. B. Urlacher, 'Selective Enzymatic Synthesis of the Grapefruit Flavor (+)-Nootkatone', *ChemCatChem* **2015**, *7*, 601–604.
- [4] G. J. Schroepfer Jr., 'Oxysterols: Modulators of Cholesterol Metabolism and Other Processes', *Physiol. Rev.* **2000**, *80*, 361–554.
- [5] Y. Sato, Y. Sonoda, M. Morisaki, N. Ikekawa, 'Oxygenated Sterols as Inhibitors of Enzymatic Conversion of Dihydrolanosterol into Cholesterol', *Chem. Pharm. Bull.* **1984**, *32*, 3305–3308.
- [6] A. Nakamura, M. Nakada, 'Allylic Oxidations in Natural Product Synthesis', *Synthesis* **2013**, *45*, 1421–1451.
- [7] V. Weidmann, W. Maison, 'Allylic Oxidations of Olefins to Enones', *Synthesis* **2013**, *45*, 2201–2221.
- [8] H. Choi, M. P. Doyle, 'Optimal TBHP Allylic Oxidation of Δ^5 -Steroids Catalyzed by Dirhodium Caprolactamate', *Org. Lett.* **2007**, *9*, 5349–5352.
- [9] T. Akihisa, T. Matsumoto, H. Sakamaki, M. Take, Y. Ichinohe, 'Platinum-Catalyzed Oxidation of Cholesterol', *Bull. Chem. Soc. Jpn.* **1986**, *59*, 680–682.
- [10] D. Kishore, A. E. Rodrigues, 'Liquid Phase Catalytic Oxidation of Isophorone With tert-butylhydroperoxide Over Cu/Co/Fe–MgAl Ternary Hydrotalcites', *Appl. Catal., A* **2008**, *345*, 104–111.
- [11] T. Hirao, S. Mikami, M. Mori, Y. Ohshiro, 'Novel Allylic Oxidation of Conjugate Ketones With VO(OR)Cl₂', *Tetrahedron Lett.* **1991**, *32*, 1741–1744.
- [12] J. Liu, R. Huang, H. Zhu, 'An Improved and Efficient Synthesis for IPL576,092 and its Analogues', *Monatsh. Chem.* **2013**, *144*, 1081–1085.
- [13] J. A. R. Salvador, J. H. Clark, 'The Allylic Oxidation of Unsaturated Steroids by Tert-butyl Hydroperoxide Using Surface Functionalised Silica Supported Metal Catalysts', *Green Chem.* **2002**, *4*, 352–356.
- [14] C. N. de Melo, A. Moreira Meireles, V. S. Da Silva, P. Robles-Azocar, G. DeFreitas-Silva, 'Manganese Complex Catalyst for Valencene Oxidation: The First Use of Metalloporphyrins for the Selective Production of Nootkatone', *Inorg. Chim. Acta* **2021**, *515*, 120031.
- [15] C. Nunes de Melo, Y. B. Rodrigues, P. A. Robles-Azocar, 'Pd-Catalyzed Aerobic Oxidation of the Sesquiterpene Isolongifolene: A Green and Heterogeneous Process', *Inorg. Chim. Acta* **2021**, *517*, 120192.
- [16] J. Liu, S. Ma, 'Iron-Catalyzed Aerobic Oxidation of Allylic Alcohols: The Issue of C=C Bond Isomerization', *Org. Lett.* **2013**, *15*, 5150–5153.
- [17] P. Marwah, A. Marwah, H. A. Lardy, 'An Economical and Green Approach for the Oxidation of Olefins to Enones', *Green Chem.* **2004**, *6*, 570–577.
- [18] S. M. Silvestre, J. A. Salvador, 'Allylic and Benzylic Oxidation Reactions with Sodium Chlorite', *Tetrahedron* **2007**, *63*, 2439–2445.
- [19] P. Zhang, Y. Wang, J. Yao, C. Wang, C. Yan, M. Antonietti, H. Li, 'Visible-Light-Induced Metal-Free Allylic Oxidation Utilizing a Coupled Photocatalytic System of g-C₃N₄ and N-Hydroxy Compounds', *Adv. Synth. Catal.* **2011**, *353*, 1447–1451.
- [20] P. Zhang, H. Li, Y. Wang, 'Post-Functionalization Of Graphitic Carbon Nitrides by Grafting Organic Molecules: Toward C–H Bond Oxidation Using Atmospheric Oxygen', *Chem. Commun.* **2014**, *50*, 6312–6315.
- [21] C. Liu, H. Liu, X. Zheng, S. Chen, Q. Lai, C. Zheng, M. Huang, K. Cai, Z. Cai, S. Cai, 'Visible-Light-Enabled Allylic C–H Oxidation: Metal-free Photocatalytic Generation of Enones', *ACS Catal.* **2022**, *12*, 1375–1381.

- [22] V. Weidmann, M. Schaffrath, H. Zorn, J. Rehbein, W. Maison, 'Elucidation of the Regio- And Chemoselectivity of Enzymatic Allylic Oxidations With *Pleurotus Sapidus* – Conversion of Selected Spirocyclic Terpenoids and Computational Analysis', *Beilstein J. Org. Chem.* **2013**, *9*, 2233–2241.
- [23] C. Aranda, M. Muncioy, V. Guallar, J. Kiebish, K. Scheibner, R. Ullrich, J. C. del Río, M. Hofrichter, A. T. Martínez, A. Gutiérrez, 'Selective Synthesis Of 4-Hydroxyisophorone and 4-Ketoisophorone by Fungal Peroxygenases', *Catal. Sci. Technol.* **2019**, *9*, 1398–1405.
- [24] P. C. Peart, K. P. McCook, F. A. Russell, W. F. Reynolds, P. B. Reese, 'Hydroxylation of Steroids by *Fusarium Oxysporum*, *Exophiala Jeanselmei* and *Ceratocystis Paradoxa*', *Steroids* **2011**, *76*, 1317–1330.
- [25] J. Solé, J. Brummund, G. Caminal, M. Schürman, G. Álvaro, M. Guillén, 'Ketoisophorone Synthesis With An Immobilized Alcohol Dehydrogenase', *ChemCatChem* **2019**, *11*, 4862–4870.
- [26] S. R. Waldvogel, M. Selt, 'Electrochemical Allylic Oxidation of Olefins: Sustainable and Safe', *Angew. Chem., Int. Ed.* **2016**, *55*, 12578–12580.
- [27] D. Pollok, S. R. Waldvogel, 'Electro-Organic Synthesis – a 21st Century Technique', *Chem. Sci.* **2020**, *11*, 12386–12400.
- [28] M. C. Leech, K. Lam, 'A Practical Guide to Electrosynthesis', *Nat. Rev. Chem.* **2022**, *6*, 275–286.
- [29] M. Masui, K. Hosomi, K. Tsuchida, S. Ozaki, 'Electrochemical Oxidation of Olefins Using N-Hydroxyphthalimide as a Mediator', *Chem. Pharm. Bull.* **1985**, *33*, 4798–4802.
- [30] A. Guirado, G. P. Moss, J. H. P. Utley, 'Selective Allylic Electro-Oxidation of α - and β -ionones', *J. Chem. Soc., Chem. Commun.* **1987**, 1987, 41–42.
- [31] E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, 'Scalable and Sustainable Electrochemical Allylic C–H Oxidation', *Nature* **2016**, *533*, 77–81.
- [32] Z. Zheng, F. Florit, B. Jin, H. Wu, S.-C. Li, K. Y. Nandiwale, C. A. Salazar, J. G. Mustakis, W. H. Green, K. F. Jensen, 'Integrating Machine Learning and Large Language Models to Advance Exploration of Electrochemical Reactions', *Angew. Chem., Int. Ed.* **2024**, *64*, e202418074.
- [33] T. Shen, J. Zhao, X. Ren, Z.-Q. Liu, S. Liu, 'Metal-Free Electrochemical Allylic C–H Aerobic Oxidation', *J. Org. Chem.* **2025**, *90*, 1148–1158.
- [34] M. Yan, Y. Kawamata, P. S. Baran, 'Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance', *Chem. Rev.* **2017**, *117*, 13230–13319.
- [35] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, 'Electrifying Organic Synthesis', *Angew. Chem., Int. Ed.* **2018**, *57*, 5594–5619.
- [36] S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, 'Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products', *Angew. Chem., Int. Ed.* **2018**, *57*, 6018–6041.
- [37] S. R. Waldvogel, B. Janza, 'Renaissance of Electrosynthetic Methods for the Construction of Complex Molecules', *Angew. Chem., Int. Ed.* **2014**, *53*, 7122–7123.
- [38] N. E. S. Tay, D. Lehnher, T. Rovis, 'Photons or Electrons? A Critical Comparison of Electrochemistry and Photoredox Catalysis for Organic Synthesis', *Chem. Rev.* **2022**, *122*, 2487–2649.
- [39] C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu, L. Ackermann, 'Organic Electrochemistry: Molecular Syntheses with Potential', *ACS Cent. Sci.* **2021**, *7*, 415–431.
- [40] H.-C. Xu, K. D. Moeller, 'Electrochemistry in Synthetic Organic Chemistry', *J. Org. Chem.* **2021**, *86*, 15845–15846.
- [41] R. D. Little, 'A Perspective on Organic Electrochemistry', *J. Org. Chem.* **2020**, *85*, 13375–13390.
- [42] D. M. Heard, A. J. J. Lennox, 'Electrode Materials in Modern Organic Electrochemistry', *Angew. Chem., Int. Ed.* **2020**, *59*, 18866–18884.
- [43] R. Francke, R. D. Little, 'Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments', *Chem. Soc. Rev.* **2014**, *43*, 2492–2521.
- [44] R. Francke, M. Májek, *Sustainable and Functional Redox Chemistry, Chapter 6: Mediated Electron Transfer in Electrosynthesis: Concepts, Applications, and Recent Influences from Photoredox Catalysis*, The Royal Society of Chemistry, London **2022**, pp. 119–153.
- [45] J. R. Long, 'Perchlorate safety: Reconciling inorganic and organic guidelines', *Chem. Health Saf.* **2002**, *9*, 12–18.
- [46] L. G. Gombos, J. Nikl, S. R. Waldvogel, 'Dual Roles of Supporting Electrolytes in Organic Electrosynthesis', *ChemElectroChem* **2024**, *11*, e202300730.
- [47] M.-A. Müller, C. Schäfer, G. Litta, A.-M. Klünter, M. G. Traber, A. Wyss, T. Ralla, M. Eggersdorfer, W. Bonrath, '100 Years of Vitamin E: From Discovery to Commercialization', *Eur. J. Org. Chem.* **2022**, 2022, e202201190.
- [48] E. Widmer, 'Synthetic Advances in the Carotenoid Field', *Pure Appl. Chem.* **1985**, *57*, 741–752.
- [49] C. Gütz, B. Klöckner, S. R. Waldvogel, 'Electrochemical Screening for Electroorganic Synthesis', *Org. Process Res. Dev.* **2016**, *20*, 26–32.
- [50] M. M. Hielscher, B. Gleede, S. R. Waldvogel, 'Get Into Flow: Design of Experiments as a Key Technique in the Optimization of Anodic Dehydrogenative C,C Cross-Coupling Reaction of Phenols in Flow Electrolyzers', *Electrochim. Acta* **2021**, *368*, 137420.
- [51] M. Dörr, M. M. Hielscher, J. Proppe, S. R. Waldvogel, 'Electrosynthetic Screening and Modern Optimization Strategies for Electrosynthesis of Highly Value-Added Products', *ChemElectroChem* **2021**, *8*, 2621–2629.
- [52] S. B. Beil, D. Pollok, S. R. Waldvogel, 'Reproducibility in Electroorganic Synthesis—Myths and Misunderstandings', *Angew. Chem., Int. Ed.* **2021**, *60*, 14750–14759.
- [53] J. Nikl, K. Hofman, S. Mossazghi, I. C. Möller, D. Mondeshki, F. Weinelt, F.-E. Baumann, S. R. Waldvogel, 'Electrochemical Oxo-Functionalization of Cyclic Alkanes and Alkenes Using Nitrate and Oxygen', *Nat. Commun.* **2023**, *14*, 4565.
- [54] F. Sprang, J. D. Herszhan, S. R. Waldvogel, 'Electrochemical Oxidation of Phenols in Flow: A Versatile and Scalable Access to Para-Benzoquinones', *Green Chem.* **2022**, *24*, 5116–5124.
- [55] A.-K. Seitz, P. J. Kohlpaintner, T. van Lingen, M. Dyga, F. Sprang, M. Zirbes, S. R. Waldvogel, L. J. Gooßen, 'Peroxodisulfate as a Green Oxidizer for the Selective Degradation of Kraft Lignin Into Vanillin', *Angew. Chem., Int. Ed.* **2022**, *61*, e202219217.
- [56] S. Möhle, S. Herold, N. D. Hillerson, S. R. Waldvogel, 'Anodic Formation of Aryl Mesylates Through Dehydrogenative Coupling Reaction', *ChemElectroChem* **2019**, *6*, 121–125.

- [57] T. Rundlöf, M. Mathiasson, S. Bekiroglu, B. Hakkarainen, T. Bowden, T. Arvidsson, 'Survey and Qualification of Internal Standards for Quantification by ¹H NMR Spectroscopy', *J. Pharm. Biomed. Anal.* **2010**, 52, 645–651.
- [58] S. Lips, S. R. Waldvogel, 'Use of Boron-Doped Diamond Electrodes in Electro-Organic Synthesis', *ChemElectroChem* **2019**, 6, 1649–1660.
- [59] J. D. Lasso, D. J. Castillo-Pazos, C.-J. Li, 'Green Chemistry Meets Medicinal Chemistry: A Perspective on Modern Metal-Free Late-Stage Functionalization Reactions', *Chem. Soc. Rev.* **2021**, 50, 10955–10982.
- [60] J.-G. Cui, L. Fan, L.-L. Huang, H.-L. Liu, A.-M. Zhou, 'Synthesis and Evaluation of Some Steroidal Oximes as Cytotoxic Agents: Structure/Activity Studies (I)', *Steroids* **2009**, 74, 62–72.
- [61] D. Lehnher, L. Chen, 'Overview of Recent Scale-Ups in Organic Electrosynthesis (2000–2023)', *Org. Process Res. Dev.* **2024**, 28, 338–366.
- [62] M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs, K. Lam, 'Organic Electrosynthesis: From Academia to Industry', *React. Chem. Eng.* **2020**, 5, 977–990.
- [63] L. Lennartz, P. Stenner, S. B. Beil, S. R. Waldvogel, 'Electrochemical Processes for the Chemical Industry', *Chem. Eng.* **2022**, 22, 22–26.
- [64] F. Weinelt, F. E. Baumann, S. R. Waldvogel, S. Hofmann, J. Nikl, *Electrochemical oxidation of cycloalkenes to form α , ω -dicarboxylic acids and ketocarboxylic acids*, WO2023186658A1, **2023**.
- [65] M. Klein, S. R. Waldvogel, 'Counter Electrode Reactions—Important Stumbling Blocks on the Way to a Working Electro-organic Synthesis', *Angew. Chem., Int. Ed.* **2022**, 61, e202204140.
- [66] W. L. F. Armarego, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford **2017**.
- [67] A. Saib, R. Goy, J. Medlock, B. Wüstenberg, G. Kociok-Köhn, C. L. Lyall, J. P. Lowe, U. Hintermair, 'Catalyst Speciation and Deactivation in the Ruthenium-Mediated Transformation of Ethynyl- β -ionol to α , β -unsaturated Esters for Vitamin A Synthesis', *Catal. Sci. Technol.* **2025**, 15, 355–375.
- [68] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, 'NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist', *Organometallics* **2010**, 29, 2176–2179.
- [69] K. Izutsu, *Electrochemistry in Nonaqueous Solutions*, Wiley, Weinheim **2002**.
- [70] N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenhart, J. L. Dempsey, 'A Practical Beginner's Guide to Cyclic Voltammetry', *J. Chem. Educ.* **2018**, 95, 197–206.
- [71] R. G. Compton, C. E. Banks, *Understanding Voltammetry*, World Scientific, New Jersey **2025**.
- [72] M. Tavanti, F. Parmeggiani, J. R. G. Castellanos, A. Mattevi, N. J. Turner, 'One-Pot Biocatalytic Double Oxidation of α -Isophorone for the Synthesis of Ketoisophorone', *ChemCatChem* **2017**, 9, 3338–3348.
- [73] V. B. Kharitonov, E. Podyacheva, D. Chusov, Y. V. Nelyubina, D. V. Muratov, D. A. Loginov, 'Planar Chiral Rhodium Complex Based on the Tetrahydrofluorenyl Core for Enantioselective Catalysis', *Org. Lett.* **2023**, 25, 8906–8911.
- [74] T. J. Kuczmara, P. Puylaert, B. J. Nachtsheim, 'Oxidation of Benzylic Alcohols to Carbonyls Using N-heterocyclic Stabilized λ 3-iodanes', *Beilstein J. Org. Chem.* **2024**, 20, 1677–1683.
- [75] S. Serra, 'MnO₂/TBHP: A Versatile and User-Friendly Combination of Reagents for the Oxidation of Allylic and Benzylic Methylene Functional Groups', *Eur. J. Org. Chem.* **2015**, 2015, 6472–6478.
- [76] D. Clemente-Tejeda, A. López-Moreno, F. A. Bermejo, 'Non-heme Iron Catalysis in C=C, C-H, and CH₂ Oxidation Reactions. Oxidative Transformations on Terpenoids Catalyzed by Fe(bpmen)(OTf)₂', *Tetrahedron* **2013**, 69, 2977–2986.
- [77] C. Zanato, A. Pelagalli, K. F. M. Marwick, M. Piras, S. Dall'Angelo, A. Spinaci, R. G. Pertwee, D. J. A. Wyllie, G. E. Hardingham, M. Zanda, 'Synthesis, Radio-Synthesis and In Vitro Evaluation of Terminally Fluorinated Derivatives of HU-210 and HU-211 as Novel Candidate PET Tracers', *Org. Biomol. Chem.* **2017**, 15, 2086–2096.
- [78] W. S. Grainger, E. J. Parish, 'Allylic Oxidation of Steroidal Olefins by Vanadyl Acetylacetonate and tert-butyl Hydroperoxide', *Steroids* **2015**, 101, 103–109.
- [79] V. Amountzias, D. Abatis, N. Aliannis, 'Chemical Constituents from the Fruits of Paliurus spina-christi', *Chem. Nat. Compd.* **2024**, 60, 714–716.
- [80] Y. Zhao, Y.-Y. Yeung, 'An Unprecedented Method for the Generation of tert-Butylperoxy Radical Using DIB/TBHP Protocol: Solvent Effect and Application on Allylic Oxidation', *Org. Lett.* **2010**, 12, 2128–2131.
- [81] S. Nurfazilah Wan Yusop, S. Imran, M. Ilham Adenan, K. Ashraf, S. Sultan, 'Biocatalytic Modifications of Ethynodiol Diacetate by Fungi, Anti-Proliferative Activity, and Acetylcholinesterase Inhibitory of its Transformed Products', *Steroids* **2021**, 171, 108832.

Received April 8, 2025

Revised April 30, 2025

5 Conclusions

In this PhD thesis, progress in various fields of electrosynthesis was achieved. Electrochemical dehydration reactions for the synthesis of carboxylic anhydrides and sulfonic anhydrides from the corresponding carboxylic acids and sulfonic acids was established. By addition of amines and alcohols, these in-situ electrogenerated anhydrides were subsequently transformed into amides, sulfonamides, and sulfonates. Such electrochemical dehydration reactions are an underexplored topic of electrosynthesis, and these contributions will help to attract more attention to this interesting field of research. The recent progress in electrochemical dehydration reactions was summarized in a review article.

An electrochemical multicomponent synthesis of sulfonamides using sulfur dioxide was transferred from a divided batch-type cell setup into an undivided flow cell setup using single-pass flow. This development simplifies the electrosynthesis of such compounds, which are important for medicinal chemistry as well as agriculture, and allows for a continuous production process in a flow microreactor.

To establish a platform for automated electrosynthesis, the LABS system (Laboratory Automation and Batch Scheduling) was developed. The associated practical challenges were initially analyzed and evaluated by using a phenol cross coupling reaction in flow. In another subsequent publication, the electrochemical multicomponent synthesis of alkyl arenesulfonates using SO₂ in flow was utilized as test reaction for benchmarking of the automated setup. In of both projects, the experimental aspects, challenges, and requirements were studied, which helped to further develop the utilization of laboratory automation for electrosynthesis.

Lastly, a simplified approach for electrochemical allylic oxidation of olefins to enones was established, which represents an important method for late-stage functionalization of natural compounds such as terpenes or steroids to highly value-added products, such as for example the electrochemical allylic oxidation of cholesterol to 7-ketocholesterol.

6 Outlook

Electrosynthesis is establishing itself as a 21st century technique, and it's expected to reach a similar level of prevalence in academic and industrial research such as other modern trends, for example photoredox catalysis or flow chemistry.^[42] Reflecting on my work for this PhD thesis, I would like to summarize some remaining ideas for future research, which can be used as inspiration for future generations of PhD students.

6.1 Automated Electrosynthesis using Flow Chemistry

The field of laboratory automation is growing rapidly,^[135] especially in the context of latest developments in artificial intelligence and machine learning.^[136] However, automated electrosynthesis still requires further development.^[124] It is of utmost importance to continue this development with open-source software, which will allow newcomers in the field to adapt to the new technology. Scale-up in electrosynthesis should also be carried out via automation. Since scale-up in flow cells is usually carried out by using a larger flow cell with a higher electrode surface, automated electrosynthesis could investigate the effects of switching to the large flow electrolysis cell in scale-up. Downstream processing could also be included in the automated setup. Although the focus has been set so far on laboratory automation in flow cells, automated electrosynthesis could also be applied to batch-type cells. Further research is required to make automated electrosynthesis setup more maintainable. This will require more safety mechanisms to be installed such as automated leak detection. It has been demonstrated that durable pumps are essential to operate automated electrosynthesis with precision and piston pumps or double piston pumps will be the most suitable choice. Syringe pumps can be used as well, but it is not trivial to apply temperature control to solutions in a syringe pump. The development of automated electrosynthesis in flow is inherently linked to the further development of flow cells.^[137] For example, it is not trivial to design a flow cell which does not leak over a wide temperature range because of the thermal expansion. Online analytics such as NMR, IR, or Raman spectroscopy could be used for determination of yield and conversion in-situ in flow. Such approaches would be much simpler than attempting to use gas chromatography (GC) in an automated setup, as it requires a more complex sample preparation.^[121] Also, electrochemical impedance spectroscopy (EIS) could be utilized to analyze changes on the electrode surface.^[138]

6.2 Electrochemical Dehydration Reactions

Electrochemical dehydration reactions are a fascinating and underexplored field of research within the domain of electrosynthesis, and such transformations have rarely been described in literature until now.^[103] In principle, every dehydration reaction which is currently carried out using conventional dehydration agents such as e.g. P_4O_{10} could be achieved by electrochemical dehydration. This means that great inspiration can be directly taken from conventional organic chemistry to find new projects in electrochemical dehydration. For example, the electrochemical dehydration reaction of carboxamides to nitriles could be investigated, or the dehydration of formamides to isonitriles (Figure 66).



Figure 66. Ideas for further electrochemical dehydration reactions.

The future of this field critically depends on the species which acts as the electrogenerated dehydration reagent. Ideally, electrochemical dehydration reactions could be carried out in a catalytic fashion, where water is eliminated from the oxygenated species to electrochemically recover the dehydration reagent again. Reagents based on phosphorous are probably not going to work because the $P=O$ bond is very difficult to reduce again. Derivatives of thianthrenes could be investigated as catalysts for electrochemical dehydration. If a new reagent is found for electrochemical dehydration, it would be highly interesting to attempt to introduce steric hindrance near the center of reactivity which is used to activate the OH group. This way, maybe chemo- and regioselective dehydration reactions could be carried out via electrolysis.

Interestingly, the electrochemical synthesis of cyclic diols using multicomponent reactions involving SO_2 which was established by the Waldvogel group is also formally a dehydration reaction.^[116] These reaction conditions have not been applied to other electrochemical dehydration reactions. For example, the use of SO_2 and bromide for the electrochemical dehydration of carboxylic acids to their anhydrides should be investigated. Because SO_2 and bromide supporting electrolytes are inexpensive and simple reagents, this could be another valuable generalized approach to electrochemical dehydration reactions.

6.3 Electrochemical Multicomponent Reactions of SO₂

The use of SO₂ stock solutions for electrochemical multicomponent reactions using SO₂ incorporation remains an important and fruitful topic for future research.^[117] Considering the enormous variety of SO₂ containing functional groups, the surrogate-free electrosynthesis of certain structural motifs could be highly interesting.^[139]

6.3.1 Sulfonyl Fluorides

Of all functional groups which could be synthesized in an electrochemical multicomponent reaction with SO₂, sulfonyl fluorides (R-SO₂-F) are likely those with the highest research interest at the moment, because sulfonyl fluorides have established themselves as a promising functional group for click chemistry, commonly referred to as SuFEx (Sulfur Fluoride Exchange) in the literature.^[140] Given the enormous importance of click chemistry, electrochemical multicomponent reactions of SO₂ for the synthesis of sulfonyl fluorides would be a very interesting research project. However, the electrosynthesis of sulfonyl fluorides is accompanied by operational hazards and challenges. The main problem of fluorine chemistry is that there are really only two oxidation states of fluorine which could be utilized: fluorine gas F₂ (oxidation state 0), and fluorine anion F⁻ (oxidation state -1). Fluorine gas F₂ is way too reactive to be handled safely, and most reactions involving fluorine gas will involve unwanted oxidative breaking of C-C bonds.^[141] The problem with fluoride is that it is in general very challenging to employ it as a good nucleophile, because its ability to form very stable hydrogen bonds lowers its nucleophilicity drastically. One way to approach electrochemical multicomponent synthesis of sulfonyl fluorides would be the utilization of Olah's reagent (pyridine with HF) in MeCN with SO₂ and pyridine as a base.^[142] In theory, anodic oxidation should not affect pyridine, fluoride, or SO₂.

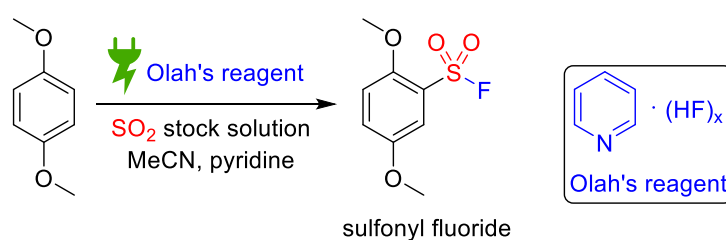


Figure 67. Proposal for the electrosynthesis of sulfonyl fluorides in an electrochemical multicomponent reaction using SO₂ stock solutions, pyridine, and Olah's reagent.

This way, the arene could be anodically oxidized to become an electrophile, which is attacked by a fluorosulfinate intermediate to form a sulfonyl fluoride.^[143] Another possible source of fluoride ions would be some triethylamine adduct with HF, but it should be noted that Olah's reagent is likely less sensitive to anodic oxidation compared with those triethylamine adducts. Once a suitable combination of reagents is found, it could be applied to several substrates to form the corresponding sulfonyl fluorides. It should be noted that all HF reagents are highly toxic.^[144]

6.3.2 Sulfonyl Azides

Another interesting functional group containing SO_2 are sulfonyl azides ($\text{R-SO}_2\text{-N}_3$). The most prevalent representative of this class of compounds is tosyl azide, which is a commonly used reagent for the transfer of a diazo group onto CH-acidic compounds (Regitz diazo transfer).^[145] The obtained diazo carbonyl compounds can then for example be irradiated to obtain a carbene, which then undergoes a $\sim[1,2]$ migration, commonly known as Wolff-rearrangement.^[146] This is used for homologation reactions of carboxylic acids, which itself is known as the Arndt-Eistert-reaction.^[147] Conventionally, sulfonyl azides are generated by substitution of a sulfonyl halide with azide anion. Since azides and sulfonyl azides can be explosive, it would be interesting to generate sulfonyl azides in-situ by using an electrochemical multicomponent reaction with SO_2 and tetrabutylammonium azide, and to employ the in-situ generated sulfonyl azides directly in some subsequent reaction, for example, in click chemistry for the synthesis of *N*-sulfonyl-1,2,3-triazoles.^[148] No electrochemical multicomponent reaction involving azides and SO_2 have been reported yet. Maybe this can be developed as a four-component reaction in one step.

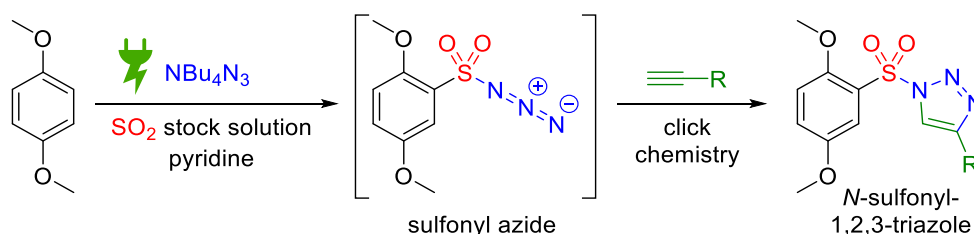


Figure 68. Proposal for the electrosynthesis of *N*-sulfonyl-1,2,3-triazoles by in-situ generation of sulfonyl azides, followed by quenching via click chemistry. Another isomer is possible as product.

6.3.3 Primary Sulfonamides

So far, attempts to use the electrochemical multicomponent reaction with SO_2 for the synthesis of primary sulfonamides ($\text{R-SO}_2\text{-NH}_2$) have been unsuccessful. This is mainly because ammonia cannot be utilized with SO_2 stock solutions easily, as it leads to various side reactions.^[149] It could be possible to synthesize sulfonyl azides in an electrochemical multicomponent reaction using SO_2 , and then to cleave the azide group by eliminating N_2 , so that a primary sulfonamide remains. The product of a Regitz diazo group transfer reaction is a primary sulfonamide. Maybe the electrosynthesis of sulfonyl azides could be accompanied by an in-situ diazo transfer reaction, which produces for example a diazo carbonyl compound and a primary sulfonamide, thereby making two value-added products in one step.

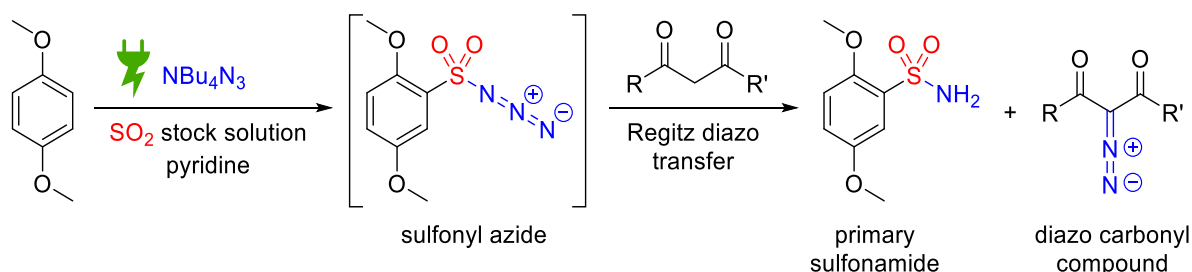


Figure 69. Proposal for the electrosynthesis of sulfonyl azides and subsequent in-situ Regitz diazo transfer reaction onto CH-acidic compounds. Such a reaction would allow for the synthesis of diazo carbonyl compound, which will undergo further reactions, and it would also give access to primary sulfonamides, which have not yet been reported by electrochemical multicomponent synthesis of SO_2 .

6.3.4 Asymmetric Sulfamides

So far, only symmetrical sulfamides with identical substituents ($\text{R-NH-SO}_2\text{-NH-R}$) have been synthesized by electrochemical multicomponent reaction using sulfur dioxide.^[112] Asymmetric sulfamides ($\text{R}^1\text{-NH-SO}_2\text{-NH-R}^2$) have not yet been attempted. An electrochemical multicomponent reaction involving SO_2 and two amines could lead to a product mixture of three different sulfamides, and it would be interesting how different concentrations of amines and other reaction conditions affect the product distribution.

6.3.5 Sulfonamides and Sulfonates of Electron-Deficient Arenes

The electrochemical multicomponent synthesis of sulfonamides and sulfonates developed by the Waldvogel group is currently limited to very electron-rich arenes and further work is required to overcome this limitation.

6.3.6 Liquid SO₂ as a Medium for Electrosynthesis

Liquid SO₂ has been well established as a medium for analytical chemistry.^[150] However it has not yet been utilized for synthetic organic electrochemistry.^[151] It should also be emphasized that while SO₂ is very stable towards anodic oxidation,^[152] it is easily reduced cathodically.^[153] Liquid SO₂ can be utilized as medium for cyclic voltammetry (CV) studies because of its very large window of electrochemical stability for anodic oxidation.^[154] Liquid SO₂ is known to have stabilization effects on radical and cationic intermediates.^[153] Furthermore, it offers a high solubility for a wide range of compounds, even inorganic salts which could be utilized as supporting electrolytes.^[155] Because SO₂ is easy to liquify at –10 °C under ambient pressure, one could imagine an electrosynthetic reaction in which SO₂ can be recovered from the electrolyte solution after the electrolysis has finished. However, the development of a containment system would be necessary to handle liquid SO₂ safely.

6.3.7 Cathodic Reduction of SO₂ for Mediated Reductions

The exact composition of the products of the cathodic reduction of SO₂ are not well studied. While the initial cathodic reduction leads to the formation of a SO₂ radical anion, likely followed by its dimerization to dithionite, further reactions are certainly possible. In addition to this, the product of this cathodic reduction has rarely been utilized so far. Usually, cathodic reduction of SO₂ is favored because it is a method to suppress hydrogen evolution reaction (HER) at the cathode.^[150,153] The dithionite which is accumulating because of the cathodic reduction of SO₂ during electrosynthetic transformation could maybe be utilized as an electrogenerated reducing agent. It should also be noted that for reactions which involve SO₂ incorporation, the cathodic reduction of SO₂ can be considered an unwanted side reaction because it lowers the SO₂ concentration in the electrolyte reaction solution. This is the reason why all electrochemical SO₂ multicomponent reactions usually employ an excess of SO₂ in solution.^[117] So far, the electrochemical synthesis of cyclic diols is the only electrochemical multicomponent reaction using SO₂ which utilizes the dithionite that is produced by cathodic reduction of SO₂, as it serves in the non-electrochemical reduction of the hypobromite.^[116] As mentioned earlier, this is not only an example of the utilization of the product of cathodic reduction of SO₂, but it also could be a versatile system for electrochemical dehydration reactions in general.

6.3.8 Sulfones

Attempts to carry out an electrosynthesis of sulfones ($R^1-SO_2-R^2$) via electrochemical multicomponent synthesis using SO_2 have been unsuccessful so far. Further work is required here as well. Sulfones are also interesting functional groups in medicinal chemistry.^[156]

6.3.9 Sulfonylureas

Sulfonylureas ($R^1-SO_2-NH-(C=O)-NH-R^2$) represent an important class of compounds in medicinal chemistry.^[157] Formally, they are sulfonamides of urea derivatives. The electrochemical multicomponent synthesis of sulfonyl ureas has so far been unsuccessful, likely because urea is not a suitable nucleophile for the formation of amidosulfinate intermediates.^[113]

6.3.10 Electrosynthesis involving Cheletropic Reactions of SO_2

It should be noted that SO_2 is a molecule which can undergo a special case of pericyclic reaction which are called cheletropic reactions.^[158] Cheletropic reactions can either be cycloadditions or cycloreversions, and they are characterized by pericyclic movement of electrons which starts and ends at the same atom.^[159] Cheletropic reactions of SO_2 are usually reversible. While such a cheletropic reaction is not directly linked to electrosynthesis, one could envision a reaction where a cheletropic reaction is part of a key step. For example, the reaction of SO_2 with a conjugated diene system could lead to a sulfone, which could undergo further electrochemical functionalization.

6.4 Electrosynthesis of Selenium Compounds

Similar to organosulfur chemistry,^[160] the chemistry of organoselenium compounds has attracted significant attention in recent years.^[161] It is known that selenium can in principle show similar structural motifs as sulfur. For example, just like sulfoxides, selenoxides exist. In contrast to sulfur, selenium has the major advantage of being an element which is easy to measure NMR spectroscopy with.^[162] Since SeO_2 is a much stronger oxidant than SO_2 ,^[163] electrochemical multicomponent reactions using SeO_2 seem unlikely to be achievable under these conditions. It should be noted that the Waldvogel group investigated SeO_2 as reagent for oxidative coupling reactions.^[164]

6.5 Electrochemical Allylic Oxidation

Allylic oxidation remains an important transformation in synthetic organic chemistry, which is still attracting much research interest from various fields of organic synthesis.^[43] While the results published by the Waldvogel group justify the use of *t*-BuOOH as oxidant,^[43] it would be beneficial to utilize air for allylic oxidation, as it is the most inexpensive oxidizing agent. However, attempts to carry out such a reaction have been unsuccessful so far. Challenges are the comparably low solubility of oxygen in MeCN, and the evaporation of solvent when passing a gas through the electrolysis cell. The electrochemical allylic oxidation developed by the Waldvogel group should be attempted in flow to systematically optimize the reaction, which still shows only limited yield for some substrates.^[43]

6.6 Electrosynthesis of Aminocrotonitriles

In the research module internship of Simón Töller, an interesting electrosynthesis of aminocrotonitriles was observed when attempting the electrochemical dehydration of sulfonic acids (Figure 70). Such aminocrotonitriles (β -enaminonitriles) are highly interesting building blocks for the synthesis of heterocycles.^[165] The reaction product has been fully characterized, including crystal structure analysis. Determination of yield is not trivial, because it is not certain what the limiting component of this reaction is. It is likely that acetonitrile undergoes electrochemical dimerization to diacetonitrile. Further research is required to investigate this interesting reaction.^[166] It should be noted that the reaction conditions are different from the electrochemical dehydration of sulfonic acids to their anhydrides which was published later.^[109]

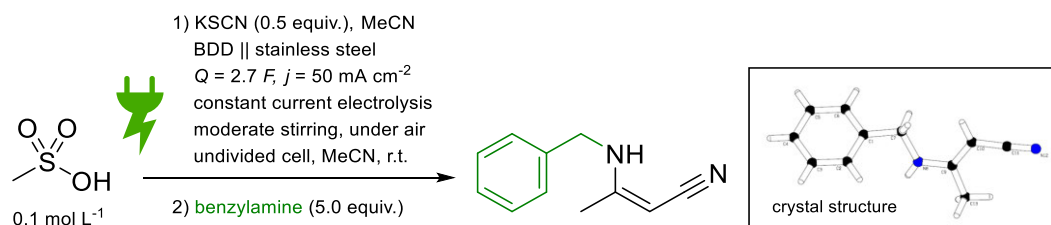


Figure 70. Electrochemical synthesis of aminocrotonitriles. The crystal structure was determined by Dr. Dieter Schollmeyer, Mainz University.

6.7 Closing Remarks

One of the most fascinating advantages of electrosynthesis is the fact that some electrosynthetic transformations do not have an analogy in conventional organic synthesis. One reason for the interesting and unique reactivity that electrosynthesis has to offer is its link to single electron transfer and the domain of radical chemistry.^[3] This means that electrosynthesis is not just an alternative to already established methods, but it should be viewed as a first-class approach for all kind of chemical transformations. This also implies that there is a plethora of fascinating and useful electro-organic transformations that are yet to be discovered, simply because they have not been attempted so far.^[7–9]

Furthermore, it is astonishing that electrosynthesis has a proven record of being the key breakthrough technology for chemical reactions which are very difficult – if not impossible – to achieve by other techniques.^[167] To this day, there are still countless open problems and unsolved challenges in synthesis and other areas of chemistry, and interestingly, there are only very few systematic and comprehensive lists of these open problems.^[168] It is possible the fact that some problems in chemistry are still unsolved and the fact that electrosynthesis has not been considered as a solution to those problems is actually not a coincidence. It could be that those problems are still open is being merely caused by the circumstance that they have not been approached by electrochemical methods so far, and electrochemistry will be the appropriate tool to solve them. Such a reversed way of thinking could lead to countless new discoveries in electrosynthesis, which implies that it will continue to establish itself as a 21st century technique.^[6]

7 References

- [1] Max Planck, *Geheimrat Max Planck*. Archiv der Berlin-Brandenburgischen Akademie der Wissenschaften, **1942**, Berlin.
- [2] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem.* **2018**, *130*, 5694–5721; *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619.
- [3] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
- [4] a) H. Kolbe, *Justus Liebigs Ann. Chem.* **1848**, *64*, 339–341; b) H. Kolbe, *Justus Liebigs Ann. Chem.* **1849**, *69*, 257–294.
- [5] M. Faraday, *Proc. R. Soc. Lond.* **1837**, *3*, 91–93.
- [6] D. Pollok, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*, 12386–12400.
- [7] S. R. Waldvogel, B. Janza, *Angew. Chem.* **2014**, *126*, 7248–7249; *Angew. Chem. Int. Ed.* **2014**, *53*, 7122–7123.
- [8] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619; *Angew. Chem.* **2018**, *130*, 5694–5721.
- [9] S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041; *Angew. Chem.* **2018**, *130*, 6124–6149.
- [10] F. Stoessel, *Thermal Safety of Chemical Processes*, Wiley, **2020**.
- [11] a) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu, L. Ackermann, *ACS Cent. Sci.* **2021**, *7*, 415–431; b) M. A. Matthews, *Pure Appl. Chem.* **2001**, *73*, 1305–1308.
- [12] M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs, K. Lam, *React. Chem. Eng.* **2020**, *5*, 977–990.
- [13] E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302–308.
- [14] M. Yan, Y. Kawamata, P. S. Baran, *Angew. Chem. Int. Ed.* **2018**, *57*, 4149–4155.
- [15] J. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265–2299.
- [16] a) G. G. Botte, *Electrochem. Soc. Interface* **2014**, *23*, 49–55; b) J. H. Wagenknecht, *J. Chem. Educ.* **1983**, *60*, 271.
- [17] D. Lehnherr, L. Chen, *Org. Process Res. Dev.* **2024**, *28*, 338–366.
- [18] a) K. D. Moeller, *Chem. Rev.* **2018**, *118*, 4817–4833; b) K. D. Moeller, *Tetrahedron* **2000**, *56*, 9527–9554.
- [19] N. E. S. Tay, D. Lehnherr, T. Rovis, *Chem. Rev.* **2022**, *122*, 2487–2649.
- [20] B. M. Trost, *Science* **1991**, *254*, 1471–1477.

- [21] P. T. Anastas, J. C. Warner, *Green chemistry. Theory and practice*, 1. Aufl., Oxford University Press, Oxford, **2000**.
- [22] a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, 35, 686–694; b) M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science* **2002**, 297, 807–810.
- [23] P. T. Anastas, J. B. Zimmerman, *Environ. Sci. Technol.* **2003**, 37, 94A–101A.
- [24] C. S. P. Vieira, D. Malafaia, D. R. Cunha, J. F. Leal, J. P. M. António, P. M. P. Gois, J. Garcia-Martinez, T. Noël, M. Poliakoff, *Green Chem.* **2025**, 27, 7742–7747.
- [25] P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, 39, 301–312.
- [26] B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, 12, 2099–2119.
- [27] <https://www.reaxys.com/>, <https://www.webofscience.com/>, <https://scifinder-n.cas.org/>, <https://scholar.google.com/>. July 7, 2025.
- [28] J. Dupont, P. Lozano, *Angew. Chem. Int. Ed.* **2025**, 137, e202416459.
- [29] D. I. Armstrong McKay, A. Staal, J. F. Abrams, R. Winkelmann, B. Sakschewski, S. Loriani, I. Fetzer, S. E. Cornell, J. Rockström, T. M. Lenton, *Science* **2022**, 377, eabn7950.
- [30] D. Vollmer, R. J.-R. Bednarz, S. Seiffert, B. Bednarz, *Nat. Phys.* **2022**, 18, 1383–1384.
- [31] P. de Luna, C. Hahn, D. Higgins, S. A. Jaffer, T. F. Jaramillo, E. H. Sargent, *Science* **2019**, 364.
- [32] T. Fuchigami, S. Inagi, M. Atobe, *Fundamentals and Applications of Organic Electrochemistry. Synthesis, Materials, Devices*, Wiley, Chichester, **2014**.
- [33] A. J. Bard, L. R. Faulkner, H. S. White, *Electrochemical Methods. Fundamentals and Applications*, Wiley, Hoboken, NJ, USA, Chichester, West Sussex, UK, **2022**.
- [34] R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, 43, 2492–2521.
- [35] a) G. Hilt, *Curr. Opin. Electrochem.* **2024**, 43, 101425; b) F. Marken, A. J. Cresswell, S. D. Bull, *Chem. Rec.* **2021**, 21, 2585–2600; c) Z. Zhang, J. Li, S. Yang, T. E. C. Peng, *Green Chem.* **2025**, 27, 6967–6988.
- [36] L. F. Tietze, *Chem. Rev.* **1996**, 96, 115–136.
- [37] S. Torabi, M. Jamshidi, G. Hilt, *J. Org. Chem.* **2024**, 89, 13953–13958.
- [38] G. Hilt, *ChemElectroChem* **2020**, 7, 395–405.
- [39] G. Wittstock, *Lehrbuch der Elektrochemie. Grundlagen, Methoden, Materialien, Anwendungen*, Wiley, Weinheim, **2023**.

- [40] D. E. Blanco, P. A. Prasad, K. Dunningan, M. A. Modestino, *React. Chem. Eng.* **2020**, *5*, 136–144.
- [41] B. K. Malviya, E. C. Hansen, C. J. Kong, J. Imbrogno, J. Verghese, S. M. Guinness, C. A. Salazar, J.-N. Desrosiers, C. O. Kappe, D. Cantillo, *Org. Process Res. Dev.* **2024**, *28*, 790–797.
- [42] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.
- [43] K. Hofman, J. Schneider, R. Goy, J. Schütz, W. Bonrath, S. R. Waldvogel, *Helv. Chim. Acta* **2025**, *108*, e202500068.
- [44] D. M. Heard, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, *59*, 18866–18884.
- [45] A. M. Couper, D. Pletcher, F. C. Walsh, *Chem. Rev.* **1990**, *90*, 837–865.
- [46] T. Wirtanen, T. Prenzel, J.-P. Tessonier, S. R. Waldvogel, *Chem. Rev.* **2021**, *121*, 10241–10270.
- [47] Y. Xia, X. Yang, *Acc. Chem. Res.* **2017**, *50*, 450–454.
- [48] B. J. Watson, R. G. Eggert, *J. Ind. Ecol.* **2021**, *25*, 890–899.
- [49] N. W. Ashcroft, N. D. Mermin, *Festkörperphysik*, Oldenbourg, München, Wien, **2001**.
- [50] S. R. Waldvogel, B. Elsler, *Electrochim. Acta* **2012**, *82*, 434–443.
- [51] S. Lips, S. R. Waldvogel, *ChemElectroChem* **2019**, *6*, 1649–1660.
- [52] N. Yang (Hrsg.) *Topics in Applied Physics Ser, v.121*, Springer, Cham, **2019**.
- [53] a) R. Hoffmann, A. Kriele, H. Obloh, J. Hees, M. Wolfer, W. Smirnov, N. Yang, C. E. Nebel, *Appl. Phys. Lett.* **2010**, *97*; b) V. V. S. S. Srikanth, P. Sampath Kumar, V. B. Kumar, *Int. J. Electrochem.* **2012**, *2012*, 1–7.
- [54] J. V. Macpherson, *Phys. Chem. Chem. Phys.* **2015**, *17*, 2935–2949.
- [55] E. Brillas, C. A. Martinez-Huitle, *Synthetic Diamond Films. Preparation, Electrochemistry, Characterization, and Applications*, John Wiley & Sons, **2011**.
- [56] Y. Honda, T. A. Ivandini, T. Watanabe, K. Murata, Y. Einaga, *Diamond Relat. Mater.* **2013**, *40*, 7–11.
- [57] D. R. Abernethy, A. J. Destefano, T. L. Cecil, K. Zaidi, R. L. Williams, *Pharm. Res.* **2010**, *27*, 750–755.
- [58] H. R. Stephen, J. L. Röckl, *ACS Org. Inorg. Au* **2024**, *4*, 571–578.
- [59] Y. Kawamata, K. Hayashi, E. Carlson, S. Shaji, D. Waldmann, B. J. Simmons, J. T. Edwards, C. W. Zapf, M. Saito, P. S. Baran, *J. Am. Chem. Soc.* **2021**, *143*, 16580–16588.

- [60] M. C. Leech, K. Lam, *Nat. Rev. Chem.* **2022**, *6*, 275–286.
- [61] K. Izutsu, *Electrochemistry in Nonaqueous Solutions*, Wiley, Weinheim, **2002**.
- [62] O. Hammerich, B. Speiser (Hrsg.) *Organic Electrochemistry*, CRC Press, Boca Raton, London, **2015**.
- [63] A. Prudlik, A. Matei, A. Scherkus, J. I. Bardagi, S. B. Beil, R. Francke, *Green Chem.* **2025**, *27*, 4280–4288.
- [64] S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765.
- [65] a) X. Marset, S. Montilla-Verdú, E. Rico, N. Guijarro, *ACS Electrochem.* **2025**, *1*, 3–19; b) L. Eberson, M. P. Hartshorn, O. Persson, *J. Chem. Soc.* **1995**, 1735–1744; c) T. Bhattacharya, A. Ghosh, D. Maiti, *Chem. Sci.* **2021**, *12*, 3857–3870.
- [66] a) O. Hollóczki, A. Berkessel, J. Mars, M. Mezger, A. Wiebe, S. R. Waldvogel, B. Kirchner, *ACS Catal.* **2017**, *7*, 1846–1852; b) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat Rev Chem* **2017**, *1*.
- [67] *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2000**.
- [68] J. A. Zapp, *Science* **1975**, *190*, 422.
- [69] W. F. Seifert, A. Bosma, A. Brouwer, H. F. J. Hendriks, P. J. M. Roholl, R. E. W. van Leeuwen, C. G. van Thiel-De Ruiter, I. Seifert-Bock, D. L. Knook, *Hepatology* **1994**, *19*, 193–201.
- [70] L. G. Gombos, J. Nikl, S. R. Waldvogel, *ChemElectroChem* **2024**, *11*, e202300730.
- [71] J. Schneider, S. P. Blum, S. R. Waldvogel, *ChemElectroChem* **2023**, *10*, e202300456.
- [72] C.-C. Lin, C.-C. Yang, J. Ger, J.-F. Deng, D.-Z. Hung, *Clin. Toxicol.* **2010**, *48*, 213–217.
- [73] *Toxicological profile for cesium*, Chamblee (Georgia), **2004**.
- [74] N. Eliaz, E. Gileadi, *Physical Electrochemistry. Fundamentals, Techniques and Applications*, Wiley-VCH, Weinheim, **2019**.
- [75] Hamann, Carl H., Vielstich W., *Elektrochemie*, 4. Aufl., Wiley-VCH, Weinheim, **2005**.
- [76] G. Wedler, H.-J. Freund, *Lehr- und Arbeitsbuch Physikalische Chemie*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2018**.

- [77] W. L. F. Armarego, *Purification of laboratory chemicals*, Butterworth-Heinemann, Amsterdam, **2017**.
- [78] J. L. Röckl, M. Dörr, S. R. Waldvogel, *ChemElectroChem* **2020**, *7*, 3686–3694.
- [79] L. Capaldo, Z. Wen, T. Noël, *Chem. Sci.* **2023**, *14*, 4230–4247.
- [80] T. Noël, Y. Cao, G. Laudadio, *Acc. Chem. Res.* **2019**, *52*, 2858–2869.
- [81] a) M. Baumann, T. S. Moody, M. Smyth, S. Wharry, *Org. Process Res. Dev.* **2020**, *24*, 1802–1813; b) S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456–1472.
- [82] A. R. Bogdan, A. W. Dombrowski, *J. Med. Chem.* **2019**, *62*, 6422–6468.
- [83] M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296.
- [84] a) M. Regnier, C. Vega, D. I. Ioannou, T. Noël, *Chem. Soc. Rev.* **2024**, *53*, 10741–10760; b) I. Rossetti, M. Compagnoni, *Chem. Eng. J.* **2016**, *296*, 56–70.
- [85] V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746–789.
- [86] J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896–9904.
- [87] F. Darvas, G. Dormán, V. Hessel, S. V. Ley, *Flow Chemistry – Fundamentals*, De Gruyter, **2021**.
- [88] F. Darvas, G. Dormán, V. Hessel, S. V. Ley, *Flow Chemistry – Applications*, De Gruyter, **2021**.
- [89] M. M. Hielscher, J. Schneider, A. H. J. Lohmann, S. R. Waldvogel, *ChemElectroChem* **2024**, e202400360.
- [90] a) L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noël, *Chem. Rev.* **2022**, *122*, 2752–2906; b) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583–4592; c) S. V. Ley, *Chem. Rec.* **2012**, *12*, 378–390.
- [91] D. Pletcher, R. A. Green, R. C. D. Brown, *Chem. Rev.* **2018**, *118*, 4573–4591.
- [92] V. A. Cherepanova, E. G. Gordeev, V. P. Ananikov, *JACS Au* **2025**, *5*, 3789–3798.
- [93] C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, *53*, 72–83.
- [94] D. C. Montgomery, *Design and analysis of experiments*, Wiley, Hoboken, NJ, **2020**.
- [95] S. A. Weissman, N. G. Anderson, *Org. Process Res. Dev.* **2015**, *19*, 1605–1633.
- [96] M. M. Hielscher, B. Gleede, S. R. Waldvogel, *Electrochim. Acta* **2021**, *368*, 137420.

- [97] M. Dörr, M. M. Hielscher, J. Proppe, S. R. Waldvogel, *ChemElectroChem* **2021**, *8*, 2621–2629.
- [98] A. Dean, D. Voss, D. Draguljić, *Design and Analysis of Experiments*, Springer International Publishing, Cham, **2017**.
- [99] K. Siebertz, D. van Bebber, T. Hochkirchen, *Statistische Versuchsplanung. Design of Experiments (DoE)*, 2. Aufl., Springer Berlin Heidelberg, Berlin, Heidelberg, **2017**.
- [100] R. Lee, *Chem. Ing. Tech.* **2019**, *91*, 191–200.
- [101] P. M. Murray, F. Bellany, L. Benhamou, D.-K. Bučar, A. B. Tabor, T. D. Sheppard, *Org. Biomol. Chem.* **2016**, *14*, 2373–2384.
- [102] R. Leardi, *Anal. Chim. Acta* **2009**, *652*, 161–172.
- [103] J. Schneider, E. Lunghi, S. R. Waldvogel, *ChemSusChem* **2025**; [accepted].
- [104] A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, J. Schneider, S. R. Waldvogel, *ChemistryOpen* **2022**, *11*, e202200059.
- [105] M. C. Leech, K. Lam, *Acc. Chem. Res.* **2020**, *53*, 121–134.
- [106] S. Liu, N. Govindarajan, H. Prats, K. Chan, *Chem Catal.* **2022**, *2*, 1100–1113.
- [107] J. Schneider, A. P. Häring, S. R. Waldvogel, *Chem. Eur. J.* **2024**, *30*, e202400403.
- [108] a) T. J. Barrett, C. L. Hawkins, *Chem. Res. Toxicol.* **2012**, *25*, 263–273; b) J. Kalmár, K. L. Woldegiorgis, B. Biri, M. T. Ashby, *J. Am. Chem. Soc.* **2011**, *133*, 19911–19921.
- [109] E. Lunghi, A. M. van Koten, J. Schneider, S. R. Waldvogel, *J. Org. Chem.* **2025**; [accepted], DOI: 10.1021/acs.joc.5c01155.
- [110] M. R. Talebi, D. Nematollahi, *ChemElectroChem* **2024**, *11*.
- [111] G. Laudadio, E. Barmopoulos, C. Schotten, L. Struik, S. Govaerts, D. L. Browne, T. Noël, *J. Am. Chem. Soc.* **2019**, *141*, 5664–5668.
- [112] S. P. Blum, L. Schäffer, D. Schollmeyer, S. R. Waldvogel, *Chem. Commun.* **2021**, *57*, 4775–4778.
- [113] S. P. Blum, T. Karakaya, D. Schollmeyer, A. Klapars, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 5056–5062; *Angew. Chem.* **2021**, *133*, 5114–5120.
- [114] a) A. de A Bartolomeu, F. A. Breitschaft, D. Schollmeyer, R. A. Pilli, S. R. Waldvogel, *Chem. Eur. J.* **2024**, *30*, e202400557; b) P.-C. Chien, F. A. Breitschaft, H. Kelm, S. R. Waldvogel, G. Manolikakes, *ChemSusChem* **2025**, e2500186.
- [115] F. A. Breitschaft, A. L. Saak, C. Krumbiegel, A. d. A. Bartolomeu, T. Weyhermüller, S. R. Waldvogel, *Org. Lett.* **2025**, *27*, 1210–1215.

- [116] C. Krumbiegel, F. A. Breitschaft, S. R. Waldvogel, *Chem. Commun.* **2025**, 61, 11267–11270.
- [117] S. P. Blum, K. Hofman, G. Manolikakes, S. R. Waldvogel, *Chem. Commun.* **2021**, 57, 8236–8249.
- [118] L. Schulz, S. Waldvogel, *Synlett* **2019**, 30, 275–286.
- [119] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, 61, e202204140; *Angew. Chem.* **2022**, 134, e202204140.
- [120] M. M. Hielscher, M. Dörr, J. Schneider, S. R. Waldvogel, *Chem. Asian J.* **2023**, 18, e202300380.
- [121] D. A. Skoog, F. J. Holler, S. R. Crouch, *Instrumentelle Analytik. Grundlagen - Geräte - Anwendungen*, 6. Aufl., Springer Spektrum, Berlin, Heidelberg, **2013**.
- [122] A. R. Mitchell, *Biopolymers* **2008**, 90, 175–184.
- [123] a) E. Rial-Rodríguez, J. D. Williams, D. Cantillo, T. Fuchß, A. Sommer, H.-M. Eggenweiler, C. O. Kappe, G. Laudadio, *Angew. Chem. Int. Ed.* **2024**, 63, e202412045; b) S. X. Leong, S. Pablo-García, Z. Zhang, A. Aspuru-Guzik, *Chem. Sci.* **2024**, 15, 17881–17891.
- [124] M. A. Pence, G. Hazen, J. Rodríguez-López, *Curr. Opin. Electrochem.* **2025**, 51, 101679.
- [125] R. C. Martin, K. Henney, *Clean Architecture. A craftsman's guide to software structure and design*, Prentice Hall, New York, **2018**.
- [126] J. L. Röckl, D. Pollok, R. Franke, S. R. Waldvogel, *Acc. Chem. Res.* **2020**, 53, 45–61.
- [127] S. P. Blum, D. Schollmeyer, M. Turks, S. R. Waldvogel, *Chem. Eur. J.* **2020**, 26, 8358–8362.
- [128] S. R. Waldvogel, M. Selt, *Angew. Chem. Int. Ed.* **2016**, 55, 12578–12580.
- [129] M. Masui, K. Hosomi, K. Tsuchida, Ozaki S., *Chem. Pharm. Bull.* **1985**, 33, 4798–4802.
- [130] A. Guirado, G. P. Moss, J. H. P. Utley, *J. Chem. Soc., Chem. Commun.* **1987**, 41–42.
- [131] E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, 533, 77–81.
- [132] Z. Zheng, F. Florit, B. Jin, H. Wu, S.-C. Li, K. Y. Nandiwale, C. A. Salazar, J. G. Mustakis, W. H. Green, K. F. Jensen, *Angew. Chem. Int. Ed.* **2024**, e202418074.
- [133] T. Shen, J. Zhao, X. Ren, Z.-Q. Liu, S. Liu, *J. Org. Chem.* **2025**, 90, 1148–1158.

- [134] J. Schütz, J. Witte, M. Marty, R. Goy, *Org. Process Res. Dev.* **2024**, *28*, 4046–4058.
- [135] N. L. Bell, F. Boser, A. Bubliauskas, D. R. Willcox, V. S. Luna, L. Cronin, *Nat. Chem. Eng.* **2024**, *1*, 180–189.
- [136] Z. Zheng, F. Florit, B. Jin, H. Wu, S.-C. Li, K. Y. Nandiwale, C. A. Salazar, J. G. Mustakis, W. H. Green, K. F. Jensen, *Angew. Chem. Int. Ed.* **2025**, *64*, e202418074.
- [137] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- [138] A. C. Lazanas, M. I. Prodromidis, *ACS Meas. Sci. Au* **2023**, *3*, 162–193.
- [139] G. Chen, Z. Lian, *Eur. J. Org. Chem.* **2023**, *26*, e202300217.
- [140] a) J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448; *Angew. Chem.* **2014**, *126*, 9584–9603; b) T. Guo, G. Meng, X. Zhan, Q. Yang, T. Ma, L. Xu, K. B. Sharpless, J. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 2605–2610; c) J. A. Homer, R. A. Koelln, A. S. Barrow, T. L. Gialelis, Z. Boiarska, N. S. Steinohrt, E. F. Lee, W.-H. Yang, R. M. Johnson, T. Chung et al., *Chem. Sci.* **2024**, *15*, 3879–3892; d) D. Serbetci, L. Marraffa, P. Natho, M. Andresini, R. Luisi, *Synthesis* **2025**, *57*, 1569–1582; e) C. J. Smedley, J. A. Homer, T. L. Gialelis, A. S. Barrow, R. A. Koelln, J. E. Moses, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112375; f) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong, J. E. Moses, *Chem. Soc. Rev.* **2019**, *48*, 4731–4758.
- [141] A. Haupt, *Organic and Inorganic Fluorine Chemistry. Methods and Applications*, 1. Aufl., Walter de Gruyter GmbH, Berlin/Boston, **2021**.
- [142] G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, J. A. Olah, *J. Org. Chem.* **1979**, *44*, 3872–3881.
- [143] a) B. J. Thomson, S. R. Khasnavis, E. C. Grigorian, R. Krishnan, T. D. Yassa, K. Lee, G. M. Sammis, N. D. Ball, *Chem. Commun.* **2023**, *59*, 555–558; b) T. Xiong, Q.-L. Chen, Z.-D. Chen, J.-T. Yi, S.-C. Wang, G. Lu, A. S. Chan, J. Weng, *Chem. Catalysis* **2023**, *3*, 100821.
- [144] D. L. Schwerin, J. D. Hatcher, *StatPearls. Hydrofluoric Acid Burns*, Treasure Island (FL), **2025**.
- [145] M. Regitz, *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 733–749.
- [146] W. Kirmse, *Eur. J. Org. Chem.* **2002**, *2002*, 2193–2256.

- [147] W. E. Bachmann, W. S. Struve in *Organic Reactions* (Hrsg.: S. E. Denmark), Wiley, **2004**, S. 38–62.
- [148] Y.-J. Kwon, S.-G. Lee, W.-S. Kim, *J. Org. Chem.* **2023**, *88*, 1200–1214.
- [149] Y. Guo, Z. Liu, Z. Huang, Q. Liu, S. Guo, *Ind. Eng. Chem. Res.* **2005**, *44*, 9989–9995.
- [150] H. P. Cady, R. Taft, *J. Phys. Chem.* **1925**, *29*, 1075–1084.
- [151] N. Tokura, *Synthesis* **1971**, *1971*, 639–645.
- [152] L. B. Hitchcock, A. K. Scribner, *Ind. Eng. Chem.* **1931**, *23*, 743–749.
- [153] L. A. Tinker, A. J. Bard, *J. Am. Chem. Soc.* **1979**, *101*, 2316–2319.
- [154] J. Ross, J. H. Percy, R. L. Brandt, A. I. Gebhart, J. E. Mitchell, S. Yolles, *Ind. Eng. Chem.* **1942**, *34*, 924–926.
- [155] P. J. Elving, J. M. Markowitz, *J. Chem. Educ.* **1960**, *37*, 75.
- [156] N.-W. Liu, S. Liang, G. Manolikakes, *Synthesis* **2016**, *48*, 1939–1973.
- [157] T. de Ventura, V. Zanirato, *Eur. J. Org. Chem.* **2021**, *2021*, 1201–1214.
- [158] S. Sankararaman, *Pericyclic Reactions - A textbook. Reactions, Applications and Theory*, Wiley-VCH; John Wiley, Weinheim, Chichester, **2005**.
- [159] I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, Hoboken, **2009**.
- [160] X. Jiang, *Sulfur Chemistry*, Springer International Publishing, Cham, **2019**.
- [161] J. M. Sonogo, S. I. de Diego, S. H. Szajnman, C. Gallo-Rodriguez, J. B. Rodriguez, *Chem. Eur. J.* **2023**, *29*, e202300030.
- [162] S. Bienz, L. Bigler, T. Fox, H. Meier, *Spectroscopic Methods in Organic Chemistry*, 3. Aufl., Thieme, Stuttgart, **2021**.
- [163] G. R. Waitkins, C. W. Clark, *Chem. Rev.* **1945**, *36*, 235–289.
- [164] a) T. Quell, N. Beiser, K. M. Dybala, R. Franke, S. R. Waldvogel, *Eur. J. Org. Chem.* **2016**, *2016*, 4307–4310; b) T. Quell, M. Mirion, D. Schollmeyer, K. M. Dybala, R. Franke, S. R. Waldvogel, *ChemistryOpen* **2016**, *5*, 115–119.
- [165] A. W. Erian, *Chem. Rev.* **1993**, *93*, 1991–2005.
- [166] T.-J. He, Z. Ye, Z. Ke, J.-M. Huang, *Nat. Commun.* **2019**, *10*, 833.
- [167] X. Dong, J. L. Roeckl, S. R. Waldvogel, B. Morandi, *Science* **2021**, *371*, 507–514.
- [168] T. Hudlický, J. W. Reed, *The way of synthesis. Evolution of design and methods for natural products*, Wiley-VCH, Weinheim, **2007**.

8 Appendix

8.1 Utilized Software and Tools

For writing of the publications and this dissertation, the following tools were utilized:

- Microsoft Word for writing of the dissertation as well as for the writing of the manuscripts and the associated Supporting Information (SI) files.
- Microsoft Excel for data analysis and curation.
- Microsoft PowerPoint for creation of presentations.
- Microsoft Teams for discussion of results with colleagues.
- MestreNova 14.3.2 for the analysis of NMR spectra.
- Citavi 7 for management of literature references.
- ChemDraw 20.0.0.41 for creating structural formulas and schemes.
- Minitab 21 for Design of Experiments (DoE).
- OPSIN parser for checking the systematic names of chemical structures.
- Paint.NET 5.1.8 for image editing.
- Adobe Reader 2025 for reading and annotating PDF files.
- Origin 7.5 for data analysis and visualization.
- Inkscape 1.4.2 for editing of vector graphics (SVG).
- Python 3 for programming of laboratory automation.
- Visual Studio Code 1.101.1 as a general-purpose text editor.
- www.dict.cc was used as a dictionary.

8.2 List of Abbreviations

APIs	Active Pharmaceutical Ingredients
AC	Alternating Current
ANOVA	Analysis of Variance
BDD	Boron-Doped Diamond
BMIMSCN	1-Butyl-3-methylimidazolium thiocyanate
BPR	Back Pressure Regulator
C	Coulomb
CCD	Central Composite Design
CCE	Constant Current Electrolysis
CE	Counter Electrode
CPE	Constant Potential Electrolysis
CV	Cyclic Voltammetry
CVD	Chemical Vapor Deposition
DC	Direct Current
DCM	Dichloromethane
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMC	Dimethyl Carbonate
DMSO	Dimethyl Sulfoxide
DoE	Design of Experiments
EMIMSCN	1-Ethyl-3-methylimidazolium thiocyanate
equiv.	Equivalents
<i>F</i>	Faraday Constant, 96485 C / mol
FDA	United States Food and Drug Administration
FFD	Fractional Factorial Design
FFKM	Perfluoroelastomer
GC	Gas Chromatography
HER	Hydrogen Evolution Reaction

HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
IP	Intellectual Property
IR	Infrared
j	Current Density [mA cm^{-2}]
LABS	Laboratory Automation and Batch Scheduling ^[120]
LC-MS	Liquid Chromatography Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
MeCN	Acetonitrile
NMR	Nuclear Magnetic Resonance
OVAT	One Variable at a Time
PC	Propylene Carbonate
RE	Reference Electrode
RVC	Reticulated Vitreous Carbon
SET	Single Electron Transfer
SI	Supporting Information
SM	Starting Material
SVG	Scalable Vector Graphics
TBS	<i>tert</i> -Butyldimethylsilyl ethers (protective group)
THF	Tetrahydrofuran
WE	Working Electrode

8.3 Attended Conferences, Posters, and Presentations

German Japanese Symposium of Electrochemistry (GJSE) 2022

October 1st – 2nd, 2022, Mainz University

Poster: *“Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids”*

Authors: J. Schneider, A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, S. R. Waldvogel.

International Shellac Symposium in Mainz (ISSM) 2023

October 17th – 18th, 2023, Max-Planck-Institute for Polymer Research

(No poster or presentation contributed)

Electrifying Technical Organic Syntheses (ETOS) PhD School 2024

September 23rd – 25th, 2024, Haus Saron, Wildberg

Presentation: *“Automated electrosynthesis of sulfonates in flow”* (E-SCOPE 2.0)

Authors: J. Schneider, A. H. J. Lohmann, F. A. Breitschaft, D. F. Nater.

Date of presentation: September 24th, 2024.

Electrifying Technical Organic Syntheses (ETOS) Symposium 2024

October 1st – 2nd, 2024, Max Planck Institute for Chemical Energy Conversion

Poster: *„Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell“*

Authors: A. H. J. Lohmann, J. Schneider, S. R. Waldvogel.

Winter School of Synthetic Organic (Electro)-Chemistry 2023

Jan 22nd – 27th, 2023, Kleinwalsertal (KWT), Hirschegg (Austria)

Presentation: *„Electrochemical Synthesis of Cyclic Anhydrides“*

Author: J. Schneider, date of presentation: Jan 23rd, 2023.

Winter School of Synthetic Organic (Electro)-Chemistry 2024

Jan 21st – 27th, 2024, Kleinwalsertal (KWT), Hirschegg (Austria)

Presentation: *„Progress in electrochemical dehydration reactions and sulfur dioxide multicomponent reactions in flow“*

Author: J. Schneider, date of presentation: Jan 23rd, 2024.

Winter School of Synthetic Organic (Electro)-Chemistry 2025

Jan 12th – 18th, 2024, Kleinwalsertal (KWT), Hirschegg (Austria)

Presentation: *„A simplified approach for electrochemical allylic oxidation of olefins“*

Author: J. Schneider, date of presentation: Jan 14th, 2025.

8.4 Supervised Students and Courses

Summer Semester 2022 at Mainz University

Praktikum Elektrochemie (Prof. Dr. Siegfried R. Waldvogel)

Praktikum Allgemeine Chemie (Dirk Beyelstein, Dr. Rudolf Robelek, Dr. Luca Carella)

Summer Semester 2023 at Mainz University

Praktikum Elektrochemie (Prof. Dr. Siegfried R. Waldvogel)

Winter Semester 2023/24 at Mainz University

Praktikum Organische Chemie für Fortgeschrittene (Prof. Dr. Heiner Detert)

Forschungsmodul of Simón Pablo Guerrero Töller

May 6th – June 16th, 2024, Mainz University

“Studies towards New Electrochemical Dehydration Reactions”

Date of report submission to Prof. Dr. S. R. Waldvogel: September 27th, 2024.

Forschungsmodul of Mtanios Ateyeh

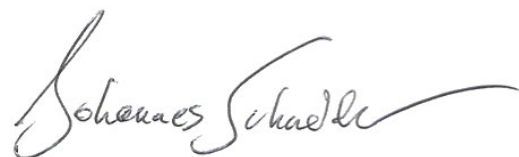
October 16th – November 29th, 2024, Mainz University

“Studies Towards New Electrochemical Dehydration Reactions And Experiments On The Synthesis Of Aminocrotonitriles”

Date of report submission to Prof. Dr. S. R. Waldvogel: March 11th, 2025.

8.5 Curriculum Vitae

Aug 10 th , 1994	born in Dahn
2001–2005	Grundschule Sauertal, Fischbach bei Dahn
2005–2014	Otfried-von-Weißenburg-Gymnasium Dahn
March 29 th , 2014	Abitur
2014–2020	Bachelor studies in Chemistry at Mainz University
2018	Tutor for Physical Chemistry under Prof. Dr. A. Kühnle
2019–2021	Tutor for Physical Chemistry under Prof. Dr. Sebastian Seiffert
2020	Tutor for Organic Chemistry 1 under Prof. Dr. H. Frey
2019–2022	Master studies in Chemistry at Mainz University
Oct 2020–Nov 2020	Internship in the Waldvogel Group
Feb 2022–Aug 2025	PhD studies (Waldvogel Group, Mainz University)



Johannes Schneider

Mainz, Aug 28th, 2025

8.6 Supporting Information of Publications

Pages	Publication
166–225	A. P. Häring, D. Pollok, B. R. Strücker, V. Kilian, J. Schneider , S. R. Waldvogel, <i>Beyond Kolbe and Hofer-Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids</i> , <i>ChemistryOpen</i> 2022 , 11, e2022000. DOI: 10.1002/open.202200059 , CC BY-NC-ND 4.0.
226–257	M. M. Hielscher, [‡] M. Dörr, [‡] J. Schneider , S. R. Waldvogel, <i>LABS: Laboratory Automation and Batch Scheduling – A Modular Open Source Python Program for the Control of Automated Electrochemical Synthesis with a Web Interface</i> , <i>Chem. Asian J.</i> 2023 , 18, e2023003. DOI: 10.1002/asia.202300380 , CC BY 4.0.
258–287	J. Schneider , S. P. Blum, S. R. Waldvogel, <i>Electrochemical Synthesis of Sulfonamides in Single-Pass Flow</i> , <i>ChemElectroChem</i> 2023 , 10, e202300456. DOI: 10.1002/celec.202300456 , CC BY 4.0.
288–323	M. M. Hielscher, [‡] J. Schneider , [‡] A. H. J. Lohmann, S. R. Waldvogel, <i>Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell</i> , <i>ChemElectroChem</i> 2024 , e202400360. DOI: 10.1002/celec.202400360 , CC BY 4.0.
324–334	J. Schneider , A. P. Häring, S. R. Waldvogel, <i>Electrochemical Dehydration of Dicarboxylic Acids to Their Cyclic Anhydrides</i> , <i>Chem. Eur. J.</i> 2024 , 202400403. DOI: 10.1002/chem.202400403 , CC BY 4.0.
335–484	K. Hofman, [‡] J. Schneider , [‡] R. Goy, J. Schütz, W. Bonrath, S. R. Waldvogel, <i>A Simplified Approach for Electrochemical Allylic Oxidation of Olefins</i> , <i>Helv. Chim. Acta</i> 2025 , e202500068, DOI: 10.1002/hlca.202500068 , CC BY 4.0.
485–532	E. Lunghi, A. M. van Koten, J. Schneider , S. R. Waldvogel, <i>Electrochemical Dehydration of Sulfonic Acids to their Anhydrides</i> , <i>J. Org. Chem</i> 2025 , [accepted], DOI: 10.1021/acs.joc.5c01155 , CC BY 4.0. A preprint version of this manuscript was uploaded to ChemRxiv on July 17 th , 2025, DOI: 10.26434/chemrxiv-2025-wm3z6 , CC BY-NC-ND 4.0.
none	J. Schneider , [‡] E. Lunghi, [‡] S. R. Waldvogel, <i>Electrochemical Dehydration Reaction</i> , <i>ChemSusChem</i> 2025 , (Review Article), [accepted], CC BY 4.0.

ChemistryOpen

Supporting Information

Beyond Kolbe and Hofer–Moest: Electrochemical Synthesis of Carboxylic Anhydrides from Carboxylic Acids

Andreas P. Häring, Dennis Pollok, Benjamin R. Strücker, Vincent Kilian, Johannes Schneider, and Siegfried R. Waldvogel*

Table of Contents

Materials and Methods.....	3
Chemicals.....	3
Gas Chromatography (GC-FID/GC-MS).....	3
High Resolution Mass Spectrometry (ESI-MS/APCI-MS).....	3
NMR Spectroscopy	3
IR Spectroscopy.....	3
Electrolysis Setup.....	3
Optimization	4
Anode Material.....	4
Cathode Material	4
Supporting Electrolyte.....	5
Carboxylic Acid Concentration.....	5
Supporting Electrolyte Concentration.....	6
Amount of Applied Charge Q [A]	6
Current Density j [mA/cm^2]	7
Mechanistic Studies	8
Analysis of Gaseous By-products	8
Electrolysis with Addition of Water	8
In situ-NMR Study.....	9
Cyclic Voltammetry	11
Electrolysis in a Divided Cell.....	11
Experimental Procedures	14
General Procedure A	14
General Procedure B.....	14
General Procedure C	14
Acetic Anhydride (2a).....	15
Propionic Anhydride (2b)	16
Butyric Anhydride (2c)	18
Valeric Anhydride (2d)	19
Caproic Anhydride (2e)	22
Caprylic Anhydride (2f).....	23
Lauric Anhydride (2g).....	25
Isobutyric Anhydride (2h).....	27
Pivalic Anhydride (2i).....	28
3,3-Dimethylbutanoic Anhydride (2j)	30
2-Ethylhexanoic Anhydride (2k).....	31

4-Pentenoic Anhydride (2l).....	33
10-Undecenoic Anhydride (2m)	34
3-Bromopropanoic Anhydride (2n)	35
11-Bromoundecanoic Anhydride (2o).....	37
(<i>S</i>)-2-Chloropropanoic Anhydride (2p).....	39
1-Methylcyclohexanecarboxylic Anhydride (2q).....	40
Adamantane-1-carboxylic Anhydride (2r)	43
Levulinic Anhydride (2s).....	44
3-((<i>tert</i> -Butyldimethylsilyl)oxy)-2,2-dimethylpropanoic Anhydride (2t).....	46
2-(2-Fluorophenyl)acetic Anhydride (2u).....	47
2-(4-(Trifluoromethyl)phenyl)acetic Anhydride (2v)	50
Oleic Anhydride (2w).....	52
Linoleic Anhydride (2x).....	55
<i>N</i> -Benzyltrifluoroacetamide (3y)	57
References.....	59
Author Contributions.....	59

Materials and Methods

Chemicals

All carboxylic acids, supporting electrolytes, solvents, and additives were used as received from commercial suppliers. For all experiments under ambient conditions, HPLC grade acetonitrile was used. For electrolysis under inert conditions, anhydrous acetonitrile was prepared by refluxing 500 mL acetonitrile with 1 g phosphorous pentoxide for 30 min, distilling it off under a nitrogen atmosphere, and storing it over activated 3 Å molecular sieves in the dark.

Gas Chromatography (GC-FID/GC-MS)

A GC-2010 (Shimadzu, Japan) equipped with a flame ionization detector (detector temperature: 583 K) was used for quantitative analysis. A GC-2010 in combination with a GCMS-QP2010 mass spectrometer (both Shimadzu, Japan) was used for qualitative analysis. Both gas chromatographs were equipped with a quartz capillary column ZB-5 (Phenomenex, USA, length: 30 cm, inner diameter: 0.25 mm, layer thickness of stationary phase: 0.25 µm, carrier gas: hydrogen, stationary phase: (5%-phenyl)methylpolysiloxane). For both, the following temperature program was used: 1 min@323 K, 15 K/min to 563 K, 8 min@563 K.

High Resolution Mass Spectrometry (ESI-MS/APCI-MS)

High resolution m/z were measured on a G6545A Q-ToF mass spectrometer (Agilent, Germany) with electrospray ionization (ESI) or chemical ionization at atmospheric pressure (APCI). The sample was introduced via a 1260 Infinity II HPLC system (Agilent, Germany) equipped with a G7111B 1260 Quaternary Pump, a G7129A 1260 Vialsampler, and a G7116A 1260 Multicolumn Thermostat. The mass calibration was performed on the day of the measurement using an external standard. The mass accuracy of the measurement is better than 5 ppm.

NMR Spectroscopy

NMR spectra were recorded on Avance III HD 300, Avance II 400, or Avance III 600 (Bruker, Germany) spectrometers. Chemical shifts are given as δ -values in ppm and are referenced to the residual proton signal of the deuterated solvent (CDCl_3 : ^1H , s, 7.26 ppm; ^{13}C , t, 77.1 ppm; $\text{DMSO}-d_6$: ^1H , p, 2.50 ppm; ^{13}C , hept, 39.5 ppm. Coupling constants J are given in Hz. Multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), hept (heptet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublets of doublets). Data analysis was done with MestReNova (Ver. 14.2, Mestrelab Research S.L., Spain).

IR Spectroscopy

IR spectra were recorded on an Alpha spectrometer (Bruker, Germany) using ATR.

Electrolysis Setup

Experiments up to 5 mL electrolyte volume were carried out under ambient atmosphere in undivided beaker-type cells made from Teflon® developed by the Waldvogel lab.^[1] Dimensions of the electrodes are 7 cm × 1 cm × 0.3 cm. The electrodes were cleaned with water and acetone after each use and sanded in case of strongly adhesive residues. The immersion depth into 5 mL electrolyte is 1.7 cm and 0.9 cm into 3 mL electrolyte volume. The current density is given in mA/cm². The current set at the galvanostat is calculated as $I [\text{mA}] = j [\text{mA}/\text{cm}^2] \times A [\text{cm}^2]$. The system including a magnetic stirrer, the electrolysis cells, and the galvanostat is commercially available from IKA®-Werke GmbH & CO. KG, Germany. For larger volume experiments, undivided beaker-type glass cells developed by the Waldvogel lab were used.

Optimization

Optimization of carboxylic anhydride yield was performed with isobutyric acid (**1h**, 99.0%). The yield was determined via ^1H NMR (general procedure A, see experimental data) using 1,3,5-trimethoxybenzene (98.0%) as absolute internal standard, or via GC (general procedure B) using dibutyl fumarate (4% in DMF) as relative internal standard. Both methods have the same error of measurement.

Anode Material

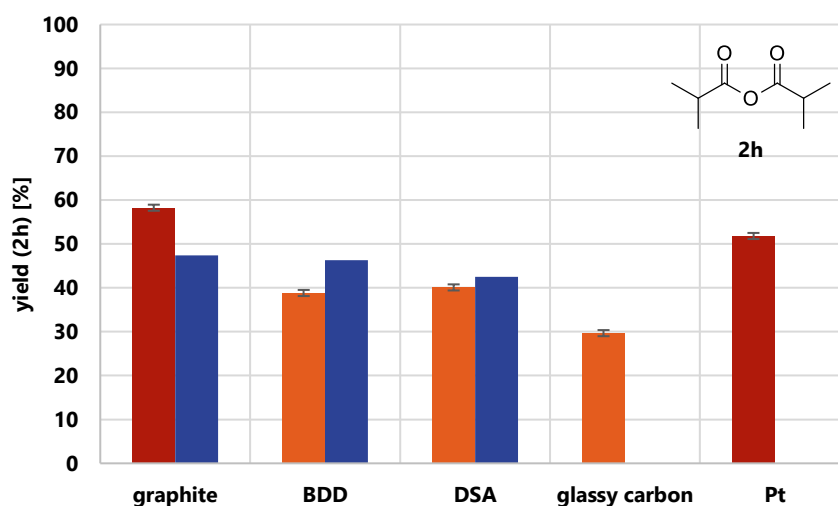


Figure S1: Reaction conditions: X||stainless steel, 0.7 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.1 F, 50 mA/cm², GC yields; X||Pt, 1.0 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.2 F, 50 mA/cm², NMR yields; X||stainless steel, 1.0 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.2 F, 50 mA/cm², GC yields.

Cathode Material

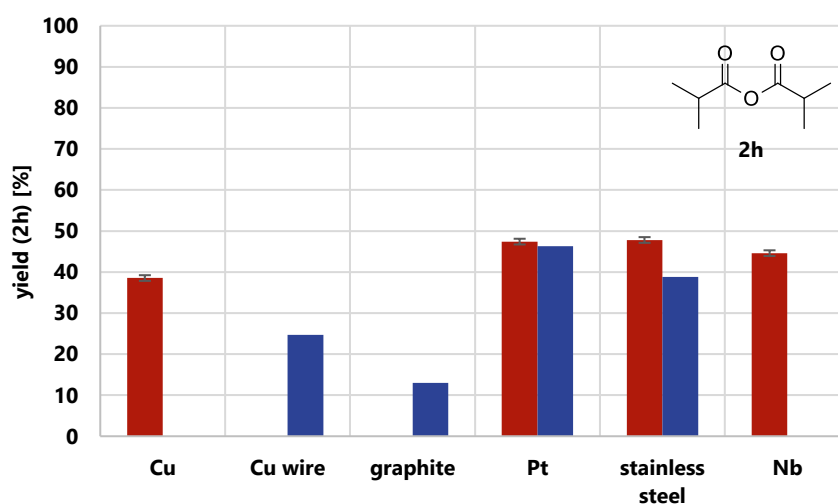


Figure S2: Reaction conditions: graphite||X, 1.0 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.2 F, 50 mA/cm², GC yields; BDD||X, 1.0 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.2 F, 50 mA/cm², GC yields.

Supporting Electrolyte

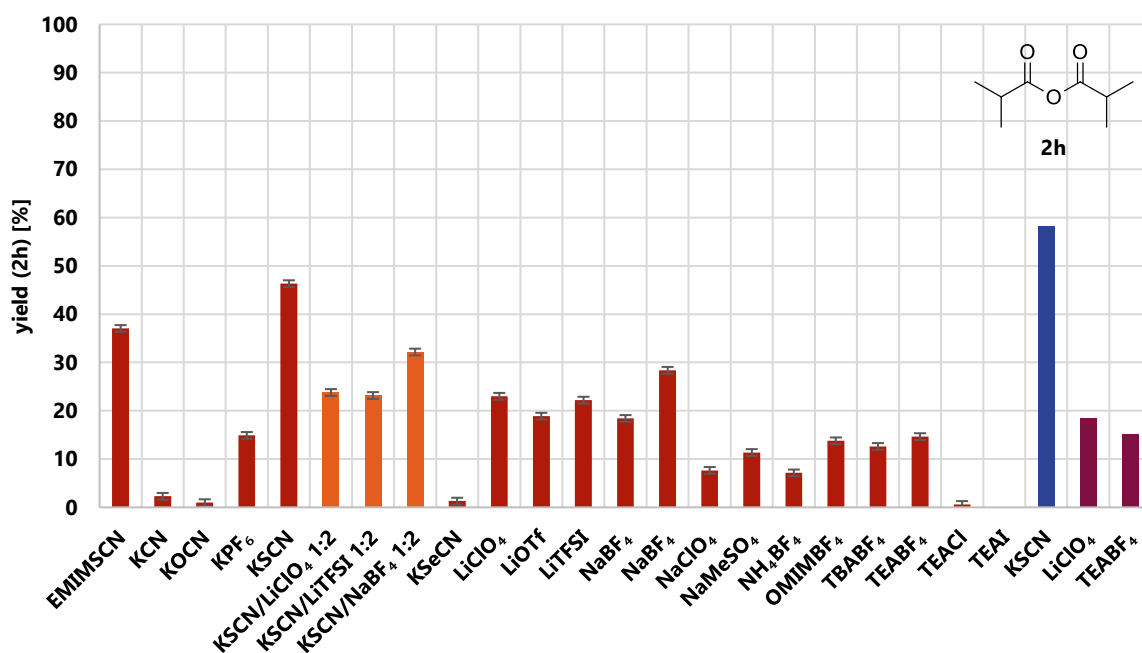


Figure S3: Reaction conditions: BDD||Pt, 1.0 M isobutyric acid (**1h**), 0.1 M supporting electrolyte, 5.0 mL MeCN, 1.2 F, 50 mA/cm², GC yields; BDD||Pt, 1.0 M isobutyric acid (**1h**), 0.05 M KSCN + 0.1 M X, 5.0 mL MeCN, 1.2 F, 50 mA/cm², GC yields; graphite||stainless steel, 0.7 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.1 F, 50 mA/cm², NMR yield; BDD||stainless steel, 0.7 M isobutyric acid (**1h**), 0.1 M supporting electrolyte, 5.0 mL MeCN, 1.1 F, 50 mA/cm², NMR yields.

Carboxylic Acid Concentration

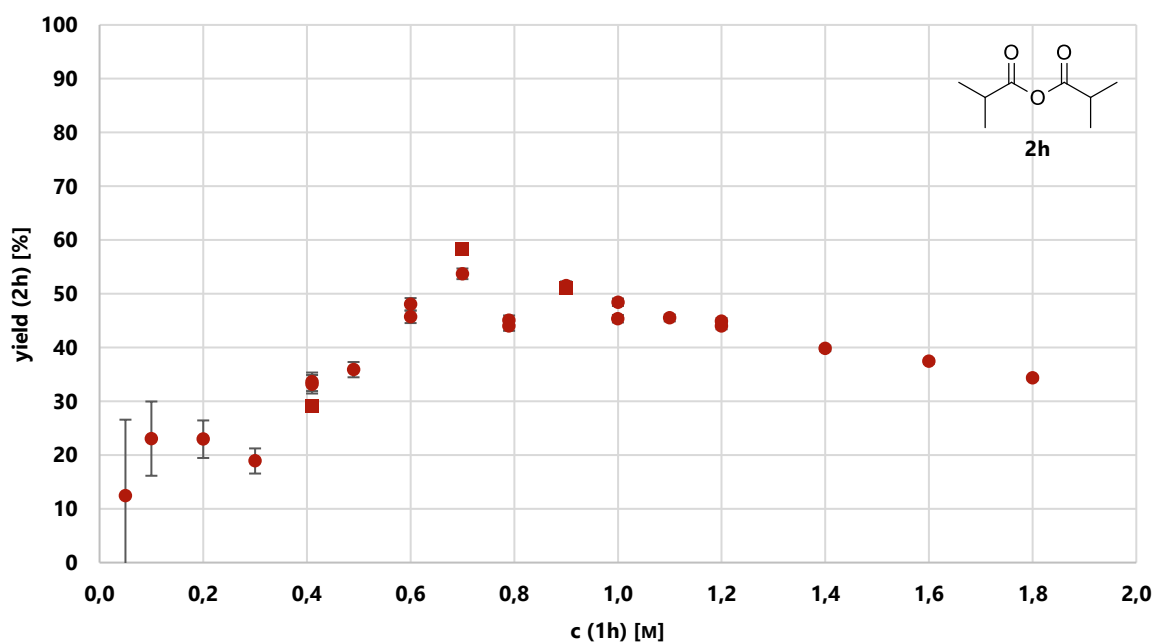


Figure S4: Reaction conditions: graphite||stainless steel, 0.1 M KSCN, 5.0 mL MeCN, 1.1 F, 50 mA/cm², circles: GC yields, squares: NMR yields.

Supporting Electrolyte Concentration

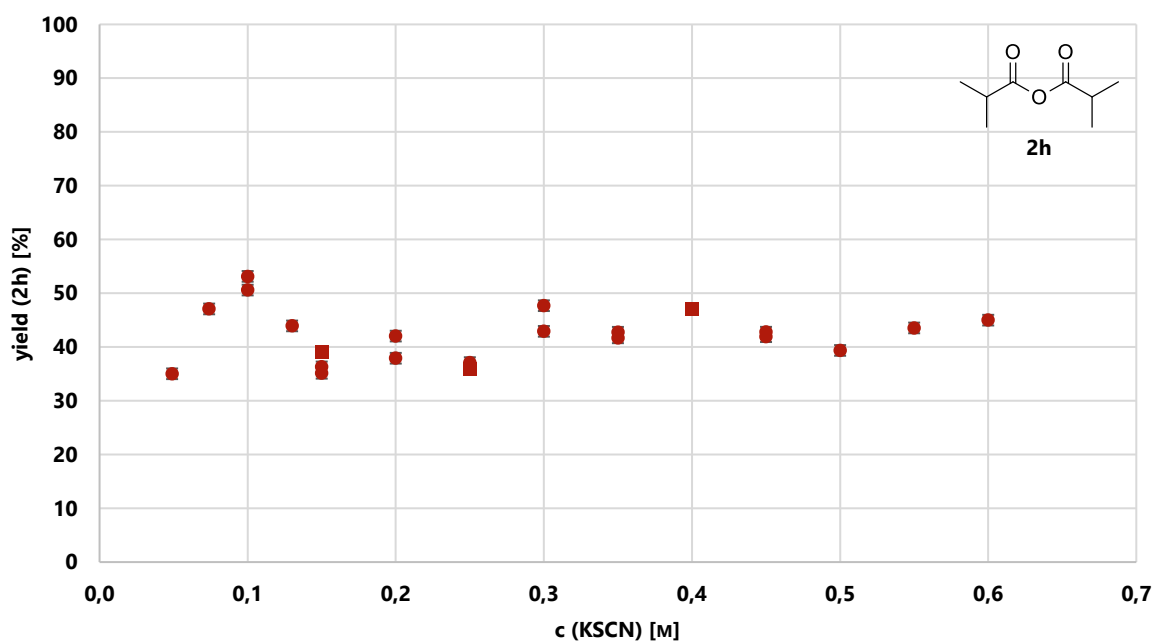


Figure S5: Reaction conditions: graphite||stainless steel, 0.7 M isobutyric acid (**1h**), 5.0 mL MeCN, 1.0 F, 50 mA/cm², GC yields.

Amount of Applied Charge Q [F]

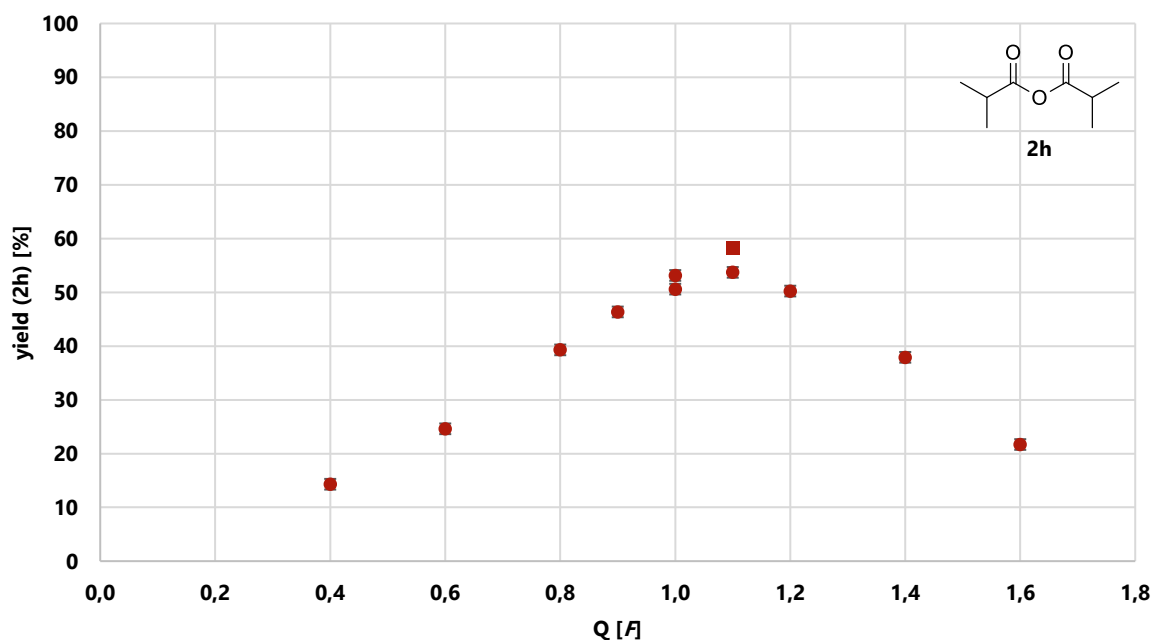


Figure S6: Reaction conditions: graphite||stainless steel, 0.7 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 50 mA/cm², circles: GC yields, squares: NMR yields.

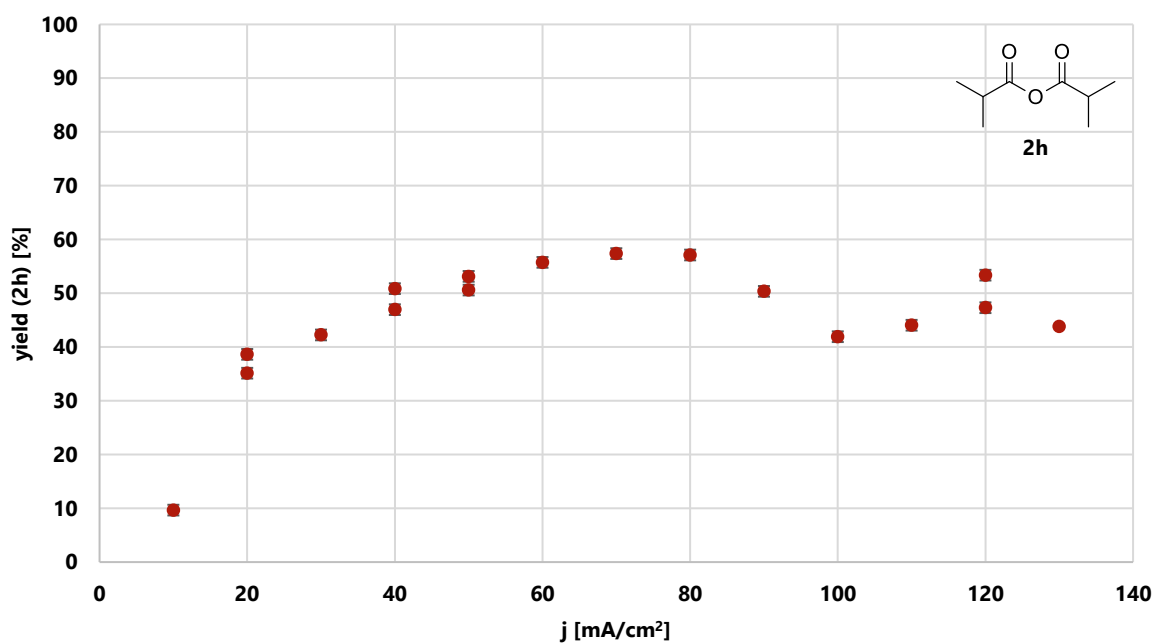
Current Density j [mA/cm²]

Figure S7: Reaction conditions: graphite||stainless steel, 0.7 M isobutyric acid (**1h**), 0.1 M KSCN, 5.0 mL MeCN, 1.0 *F*, GC yields.

Mechanistic Studies

Analysis of Gaseous By-products

Valeric acid (**1d**, 98.0%, 9.9 mL, 89 mmol, 0.89 M) and KSCN (0.972 g, 0.10 M) were dissolved in MeCN (100 mL) in an undivided glass cell equipped with a graphite anode and stainless steel cathode (active electrode area: 18 cm²). The electrolyte was degassed for 10 min by purging it with a stream of dry N₂. The headspace of the electrolysis chamber was purged with a slow stream of dry N₂ throughout the experiment. The mixture was electrolyzed at 80 mA/cm² and 288 K. The exhaust gas from the electrolysis cell was carried through two bubble counters in series (Figure S8), which were empty at the beginning of the electrolysis. After start of the electrolysis, the bubble counters were purged with the exhaust gas for 10 min. Each bubble counter was then filled under countercurrent from the electrolysis cell with 10 mL of a solution of pyrogallol (2.5 mg/mL) in aqueous 1 M NaOH, which was prepared under inert conditions. Until the end of the electrolysis after 1.1 F, no staining was visible in the bubble counters. Shortly after the end of the electrolysis, the N₂-stream was stopped. The solution in the right bubble counter (Figure S8) immediately started turning brown due to diffusion of air into the solution. 8 min after stopping the N₂-stream, the tubing from the electrolysis cell to the left bubble counter was removed. The solution in the left bubble counter immediately started turning brown (Figure S8, bottom right). We conclude that no O₂ is formed in the electrolysis cell.

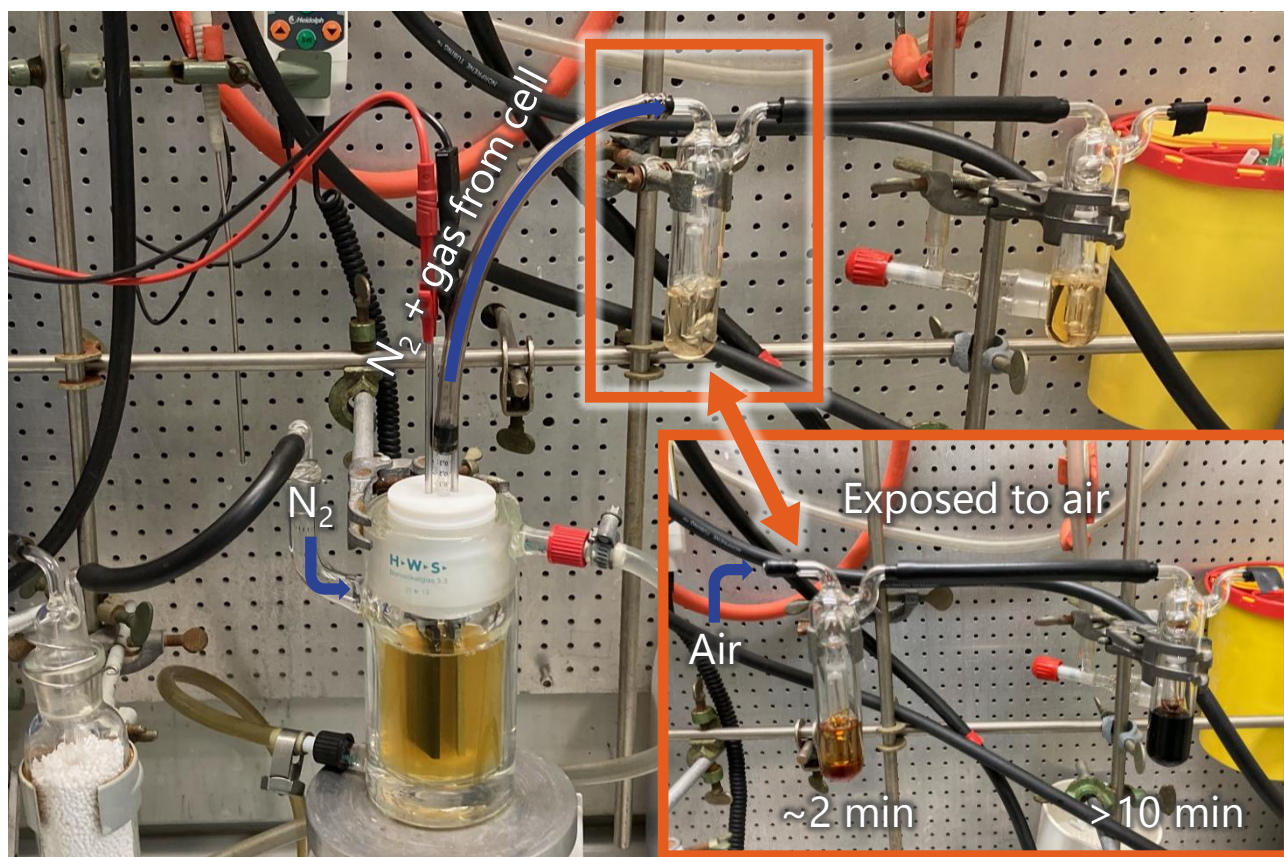


Figure S8: Analysis of gaseous by-products formed during electrolysis of valeric acid (**1d**).

Electrolysis with Addition of Water

The electrolysis of valeric acid (**1d**) was performed with addition of water to gain insight on the reaction mechanism (Table S1). Analogous to general procedure C, valeric acid (**1d**, 0.9 M) and KSCN (0.35 M) were dissolved in MeCN, and a defined amount of water was added. The mixture was electrolyzed, and the yield of valeric anhydride (**2d**) was determined via GC. As expected, the yield of **2d** is lower in the presence of water. Importantly, water does not

suppress the anhydride formation but only slows it down. If the amount of charge is increased, the anhydride yield increases too. The reaction can be considered self-drying since any water present at the beginning will react with the anhydride and form the acid again. We conclude that anhydrous conditions are not necessary, but the reaction can be run under ambient conditions.

Table S1: Electrolysis of valeric acid (**1d**) with addition of water; Reaction conditions: graphite||stainless steel, 0.35 M KSCN, 5.0 mL MeCN, 80 mA/cm², GC yields.

#	H ₂ O [equiv.]	Q [F]	Yield 2d [%]
1	0.25	1.1	28
2	0.25	1.6	46
3	0.50	1.1	9
4	0.50	1.35	18

In situ-NMR Study

Isobutyric acid (**1h**, 99.0%, 0.47 mL, 5.0 mmol, 1.0 M) and KSCN (49 mg, 0.10 M) were dissolved in D₃CCN (5.0 mL) in an undivided Teflon cell equipped with a BDD anode and Pt cathode (active electrode area: 1.7 cm²). The mixture was electrolyzed at 50 mA/cm². Four aliquots of 0.2 mL each were taken consecutively from the electrolyte after 0.33 F, 0.75 F, 1.1 F, and 1.2 F. To each aliquot, one drop of dibromomethane (99%) and 0.35 mL D₃CCN were added. ¹H NMR spectra were recorded within 1 h after the aliquot was taken from the electrolyte. ¹³C NMR spectra were recorded within 12 h after end of the electrolysis. No stoichiometric by-product is visible in any of the recorded spectra (Figure S9, Figure S10).

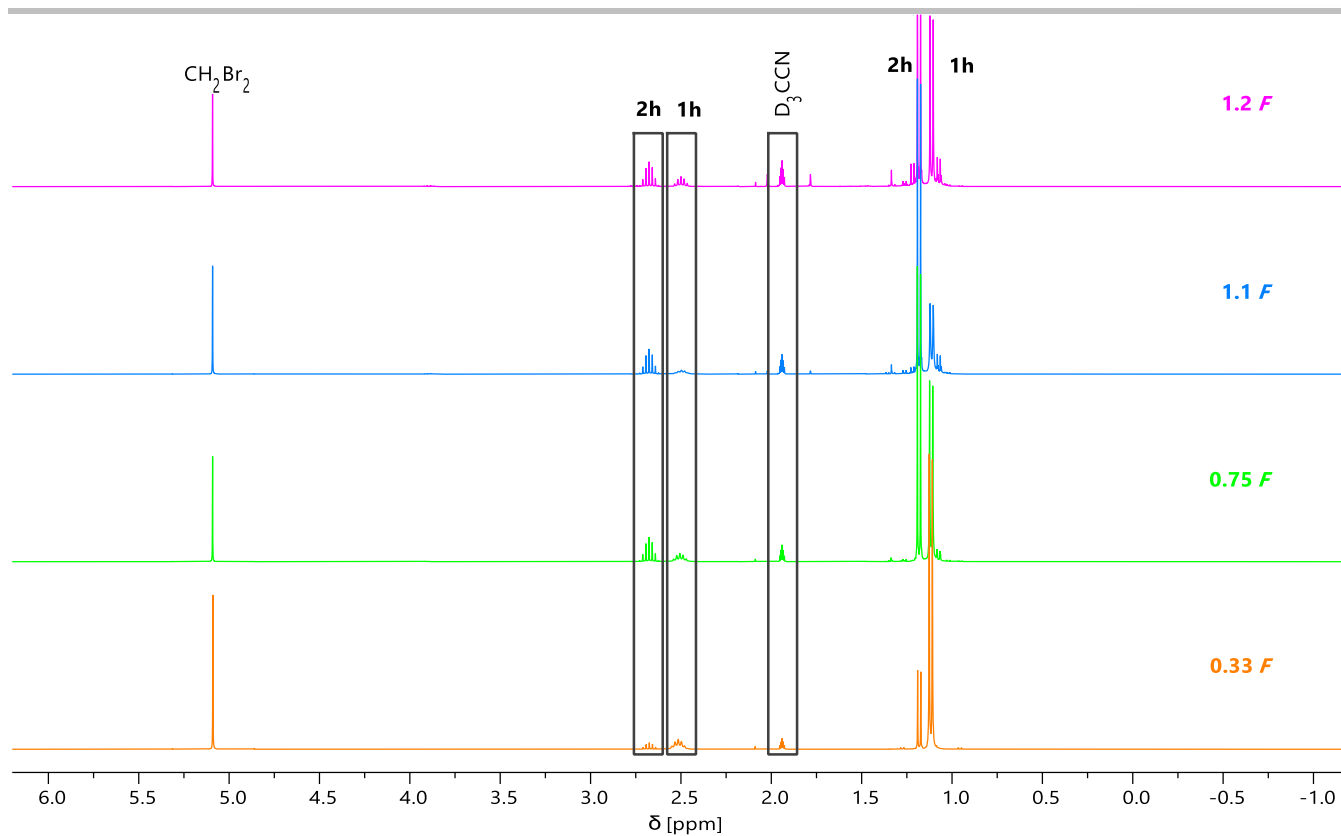


Figure S9: In situ- ^1H NMR of the electrolysis of isobutyric acid (**1h**).

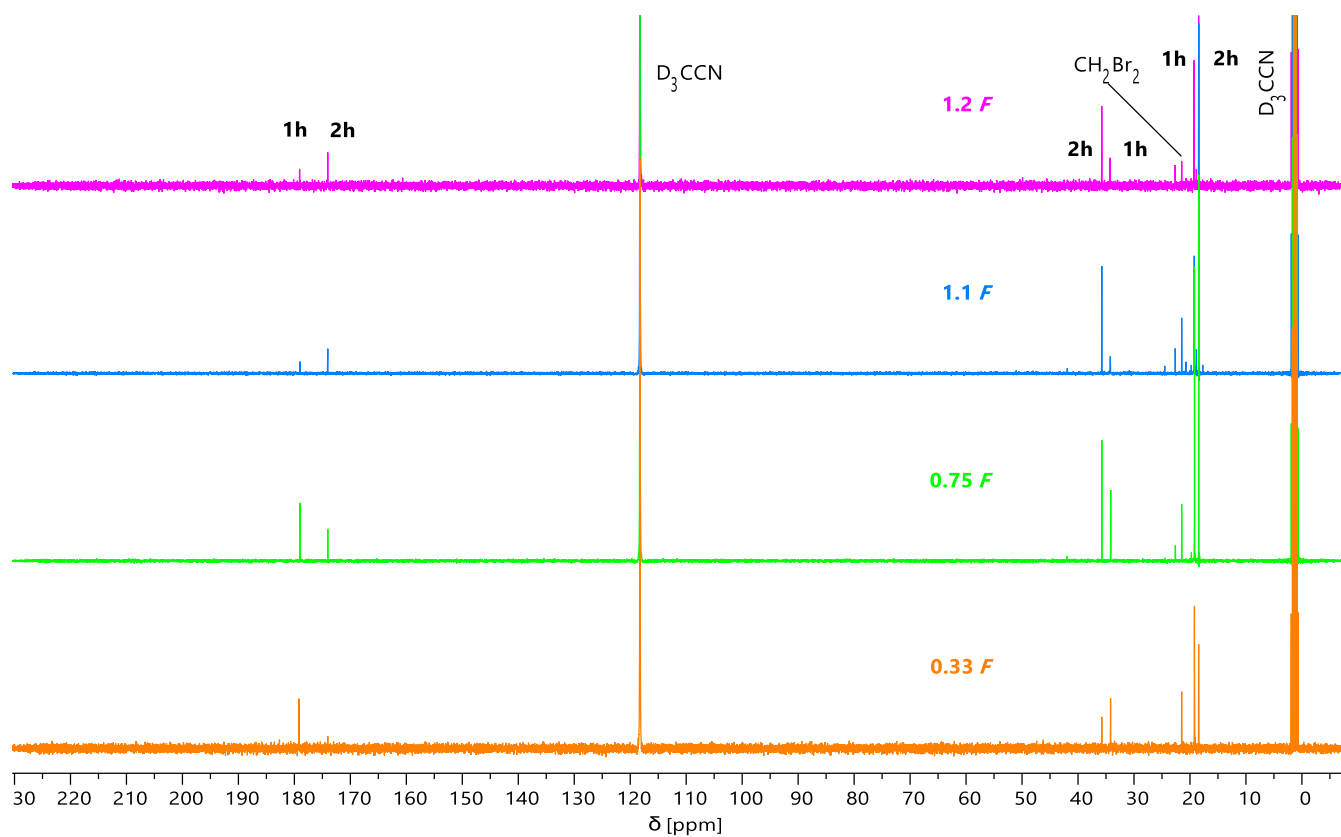


Figure S10: In situ- ^{13}C NMR of the electrolysis of isobutyric acid (**1h**).

Cyclic Voltammetry

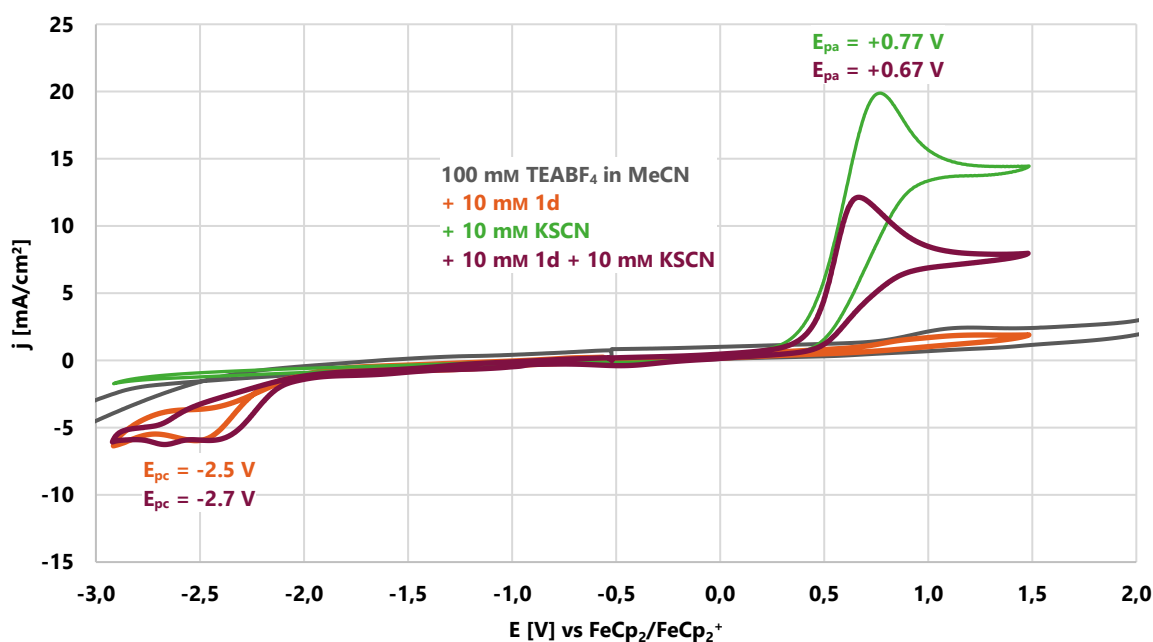


Figure S11: Cyclic voltammetry of 10 mM KSCN and 10 mM valeric acid (**1d**) in MeCN; Working electrode: BDD, 1 mm²; Counter electrode: Pt coil; Reference electrode: Ag/AgCl in EtOH/sat. LiCl; Sweep rate: 0.2 V/s.

Electrolysis in a Divided Cell

Divided cells made from Teflon[®] with a ceramic frit as separator^[1] were used to study the anodic reaction separately from the cathodic one. Each compartment was charged with KSCN (136 mg, 0.35 M), valeric acid (**1d**, 98.0%, 0.31 mL, 2.8 mmol, 0.70 M), and MeCN (4.0 mL). A graphite anode and stainless steel cathode were immersed into the cell, and the mixture was electrolyzed at 50 mA/cm² until 0.92 *F* had passed. During electrolysis, the cell voltage rose quickly to 32 V, the maximum output voltage of the used galvanostat, and consequently the current density dropped (Figure S14). In the anodic compartment, an orange solid was formed (Figure S15), which covered the anode completely. The anolyte was analyzed analogously general procedure A (Figure S12). No valeric anhydride (**2d**) was detected (ISTD: 27.9 mg ethylene carbonate (99%)). The conversion of **1d** was 1%.

Following the same procedure but changing **1d** in the anodic compartment to tetramethylammonium valerate (491 mg, 2.8 mmol, 0.70 M) gave a similar result (Figure S13). **2d** was obtained in 7% yield (ISTD: 28.4 mg ethylene carbonate (99%)). The conversion of **1d** was 23%.

The orange solid was filtered off and washed with H₂O and MeOH. The IR absorptions of the dried sample match those of (SCN)_x (Figure S15).^[2]

The experimental data suggest that the formation of the anhydride is a convergent paired electrolysis. No or only little anhydride is formed in a divided cell. Instead, the oxidation of SCN⁻ to (SCN)_x becomes the main reaction in the anodic compartment. The small amount of anhydride formed with tetramethylammonium valerate can be explained by imperfect separation of the two half cells. The experiment did not reveal the electroactive species on the anode.

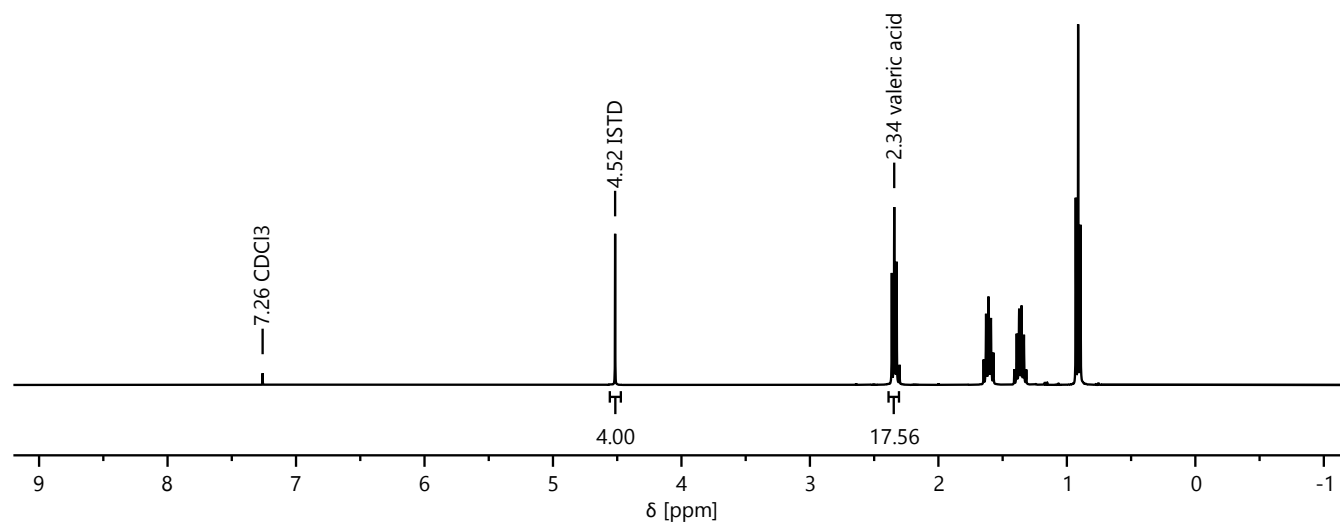


Figure S12: ^1H NMR of the crude anolyte from electrolysis of valeric acid (**1d**) in a divided cell; 400 MHz, 296 K.

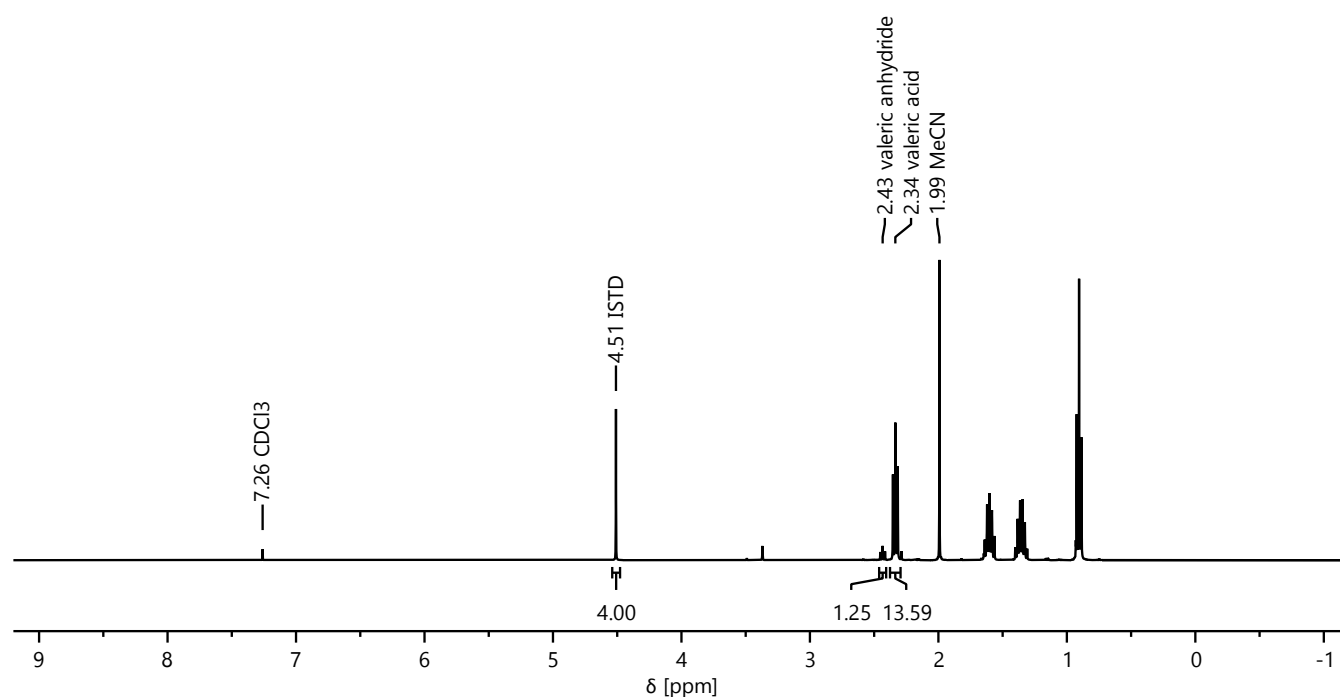


Figure S13: ^1H NMR of the crude anolyte from electrolysis of tetramethylammonium valerate in a divided cell; 400 MHz, 296 K.

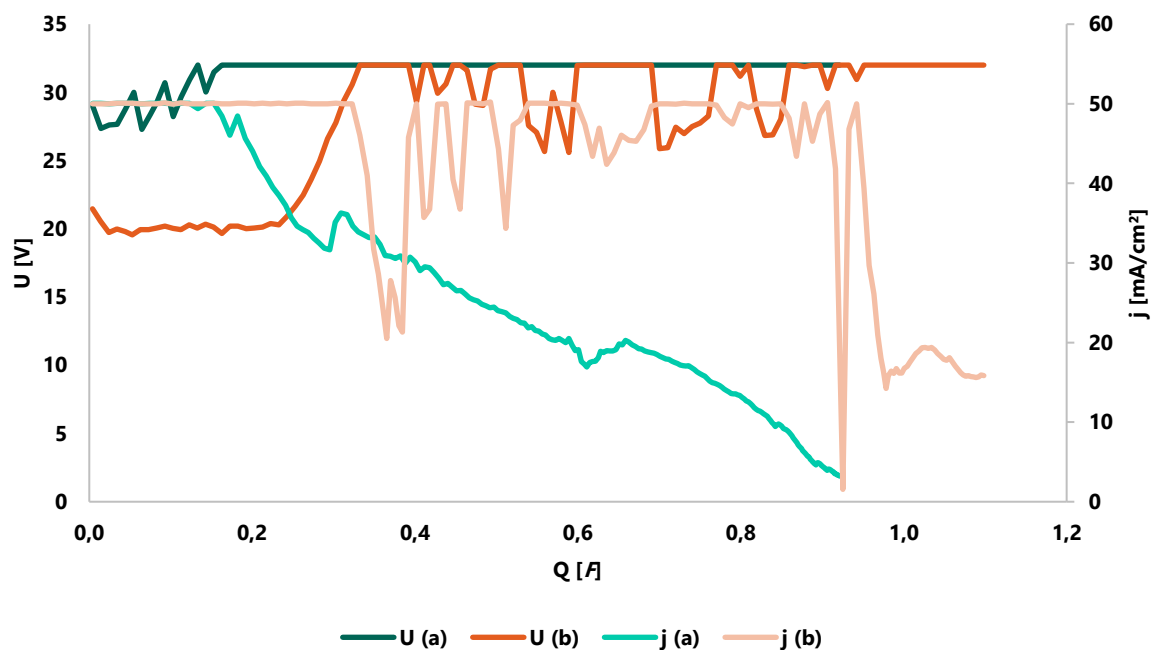


Figure S14: Cell voltage and current density during the electrolysis of **1d** (a), and tetramethylammonium valerate (b) in a divided cell.

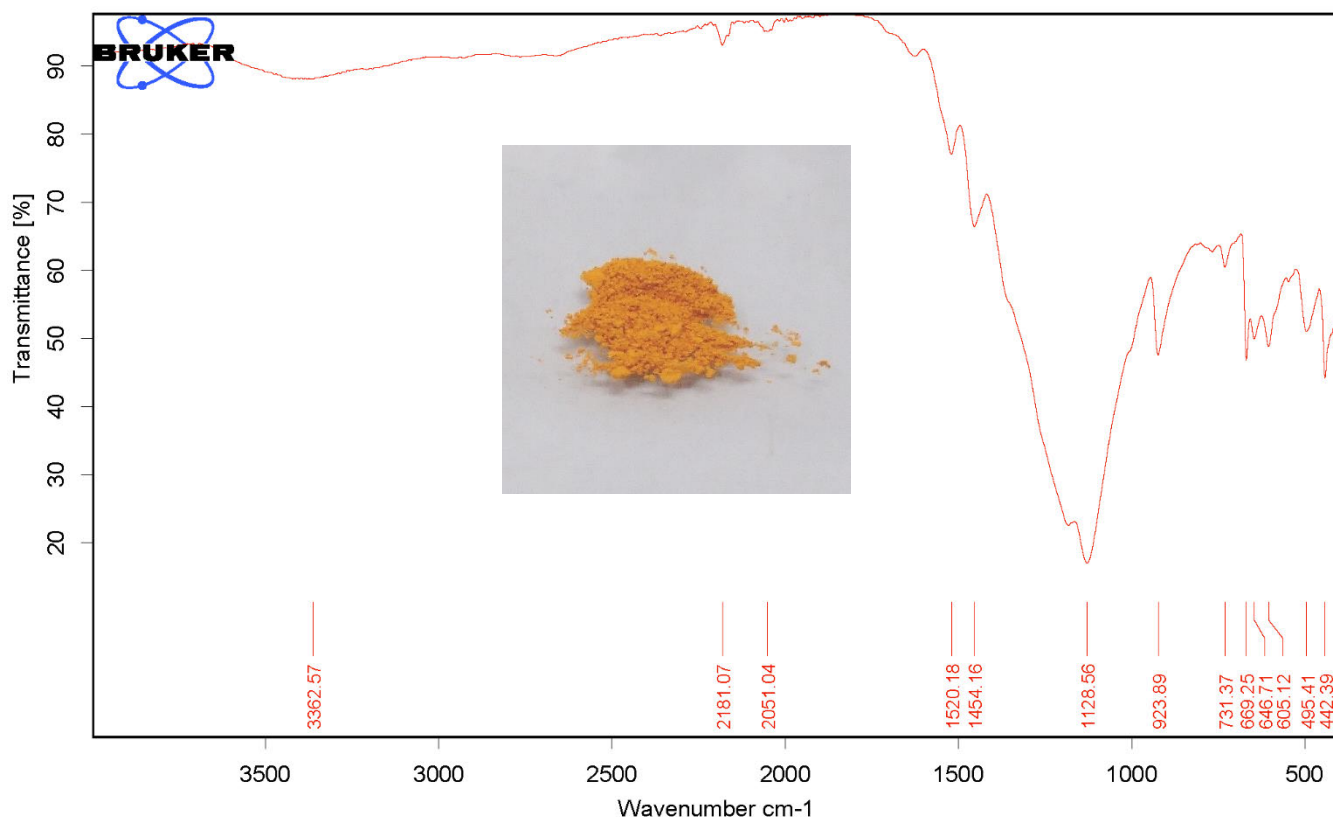


Figure S15: IR spectrum of $(\text{SCN})_x$ formed during electrolysis of **1d** or tetramethylammonium valerate in the anode compartment of a divided cell.

Experimental Procedures

General Procedure A

The supporting electrolyte and the starting material **1** were dissolved in MeCN in an undivided Teflon cell with a magnetic stirrer. A graphite anode and stainless steel cathode were immersed into the solution, and the mixture was electrolyzed without temperature control. An internal standard (ISTD) was added and the mixture was stirred for 5 min. An aliquot of 0.5–0.6 mL of the mixture was evaporated, and the residue was suspended in 0.5–0.6 mL CDCl₃. The suspension was filtered through a cotton plug into an NMR tube. The yield was determined via ¹H NMR with the following formula:

$$y_{\text{anhydride}} [\%] = \frac{200 \times 0.980 \times I_{\text{anhydride}} \times m_{\text{ISTD}} [\text{g}] \times z_{\text{ISTD}}}{z_{\text{anhydride}} \times I_{\text{ISTD}} \times n_{\text{acid}} [\text{mol}] \times 168.19 \frac{\text{g}}{\text{mol}}}$$

0.980 purity of 1,3,5-trimethoxybenzene
 168.19 g/mol molecular weight of 1,3,5-trimethoxybenzene
 I_x surface integral_{NMR} (x)
 z_x number of protons (x); in case of inverse-gated ¹³C NMR: number of carbon atoms (x)

General Procedure B

The supporting electrolyte and the starting material **1** were dissolved in MeCN in an undivided Teflon cell with a magnetic stirrer. A graphite anode and stainless steel cathode were immersed into the solution, and the mixture was electrolyzed without temperature control. The reaction mixture was transferred to a round-bottom flask and evaporated. Dibromomethane (99%) was added as internal standard (ISTD) and the mixture was shaken for 30 s. Ca. 30 mg of the mixture were dissolved in 0.5–0.6 mL CDCl₃. The yield was determined via ¹H NMR with the following formula:

$$y_{\text{anhydride}} [\%] = \frac{200 \times 0.99 \times I_{\text{anhydride}} \times m_{\text{ISTD}} [\text{g}] \times z_{\text{ISTD}}}{z_{\text{anhydride}} \times I_{\text{ISTD}} \times n_{\text{acid}} [\text{mol}] \times 173.83 \frac{\text{g}}{\text{mol}}}$$

0.99 purity of dibromomethane
 173.83 g/mol molecular weight of dibromomethane
 I_x surface integral_{NMR} (x)
 z_x number of protons (x); in case of inverse-gated ¹³C NMR: number of carbon atoms (x)

General Procedure C

The supporting electrolyte and isobutyric acid (**1h**, 99%) were dissolved in 5.0 mL MeCN in an undivided Teflon cell with a magnetic stirrer. The electrodes were immersed into the solution, and the mixture was electrolyzed without temperature control. 0.50 mL Dibutyl fumarate (4% in DMF) were added as internal standard (ISTD), and the mixture was stirred for 5 min. The mixture was added to 10 mL saturated aqueous NaHCO₃, and the mixture was shaken for 10 s. 0.8–1.0 mL of the organic phase were filtered through a plug of silica. 0.2 mL of the filtrate were diluted with 1 mL MeCN, and the yield was determined via GC-FID with the following formula:

$$y_{2h} [\%] = \sqrt[1.0561]{\frac{I_{2h}}{0.0386 \times I_{\text{ISTD}}}} \times \frac{1 \text{ g} \times 88.11 \frac{\text{g}}{\text{mol}}}{5 \times V_{1h} [\text{mL}] \times 0.990 \times 0.95 \frac{\text{g}}{\text{mL}} \times 158.19 \frac{\text{g}}{\text{mol}}}$$

88.11 g/mol molecular weight of isobutyric acid
 158.19 g/mol molecular weight of isobutyric anhydride (**2h**)

0.95 g/mL	density of isobutyric acid (1h)
0.990	purity of isobutyric acid (1h)
I_x	surface integral _{gc} (x)

The calibration curve was created as a power function $I_{\text{anhydride}}/I_{\text{ISTD}} = a \times m_{\text{anhydride}}^b$ from five calibration points. The error of measurement was calculated as the mean deviation of six control points. For the calibration and control points, a defined amount of isobutyric anhydride (**2h**, 97%) was dissolved in 5.0 mL MeCN. 0.50 mL Dibutyl fumarate (4% in DMF) were added as internal standard, and the mixture was stirred for 5 min. 0.2 mL of the solution were diluted with 1 mL MeCN and measured three times (calibration points) or once (control points).

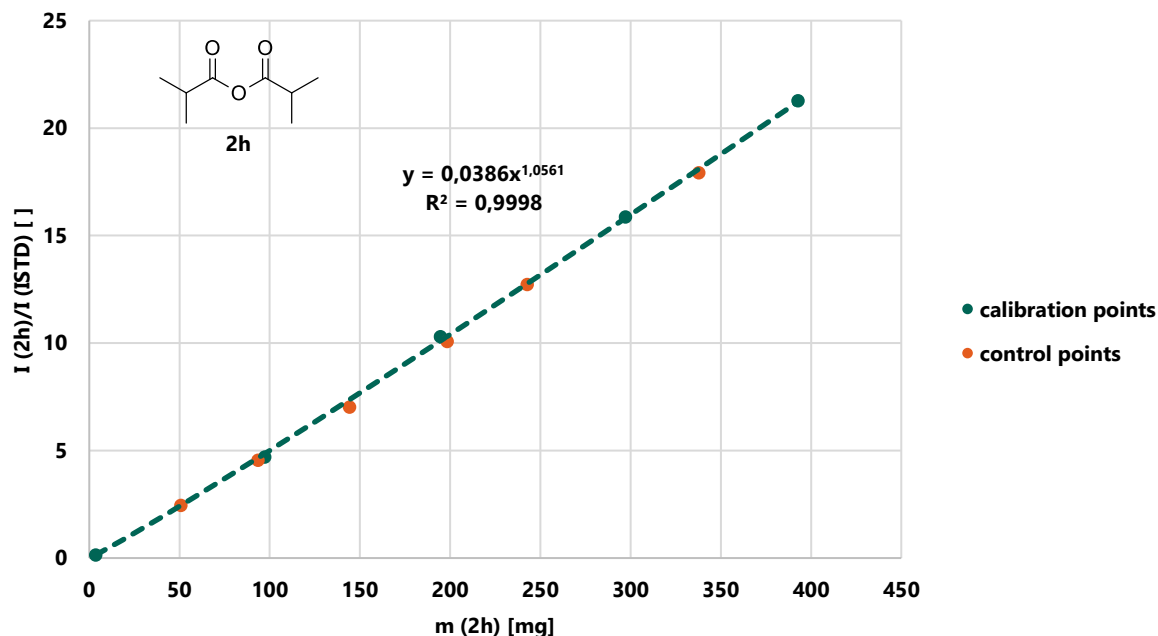


Figure S16: Calibration curve for isobutyric anhydride (**2h**).

Acetic Anhydride (**2a**)

Following general procedure A, electrolysis of acetic acid (**1a**, 100%, 0.35 mL, 6.1 mmol, 1.2 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave acetic anhydride (**2a**) in 37% yield after 1.1 *F* (ISTD: 43.6 mg 1,3,5-trimethoxybenzene (98.0%)).

GC t_R = 1.947 min; t_R (acetic anhydride (**2a**), authentic sample) = 1.949 min.

¹H NMR (400 MHz, CDCl₃) δ 2.13 (s, 6H) ppm.

The analytic data is in agreement with previously reported data.^[3]

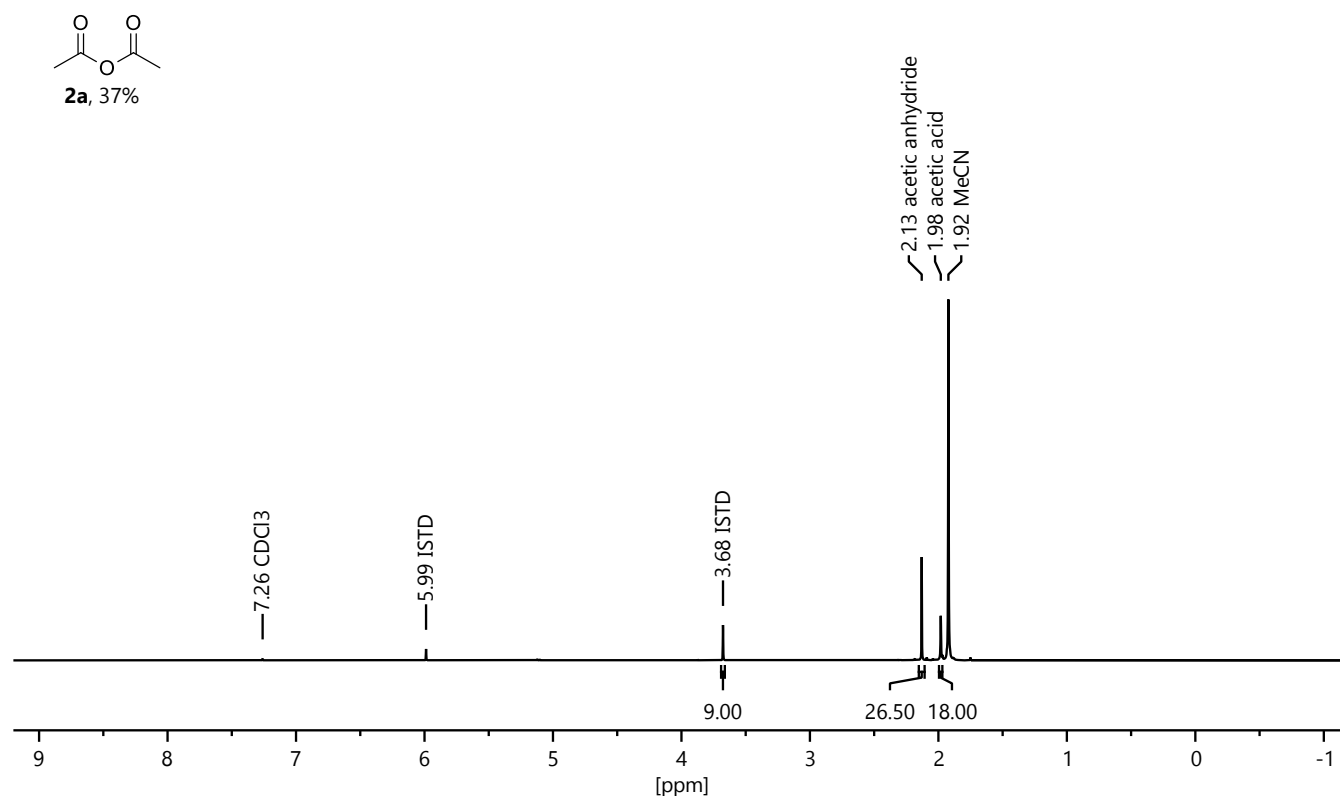


Figure S17: ^1H NMR of the crude mixture from electrolysis of acetic acid (**1a**); 400 MHz, 296 K.

Propionic Anhydride (**2b**)

Following general procedure B, electrolysis of propionic acid (**1b**, 99%, 0.38 mL, 5.0 mmol, 1.0 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave propionic anhydride (**2b**) in 46% yield after 1.1 F (ISTD: 92.0 mg dibromomethane (99%)).

^1H NMR The signals overlap partially with propionic acid (**1b**).

^{13}C NMR (101 MHz, CDCl₃) δ 170.4, 28.8, 8.5 ppm.

The analytic data is in agreement with previously reported data.^[3]

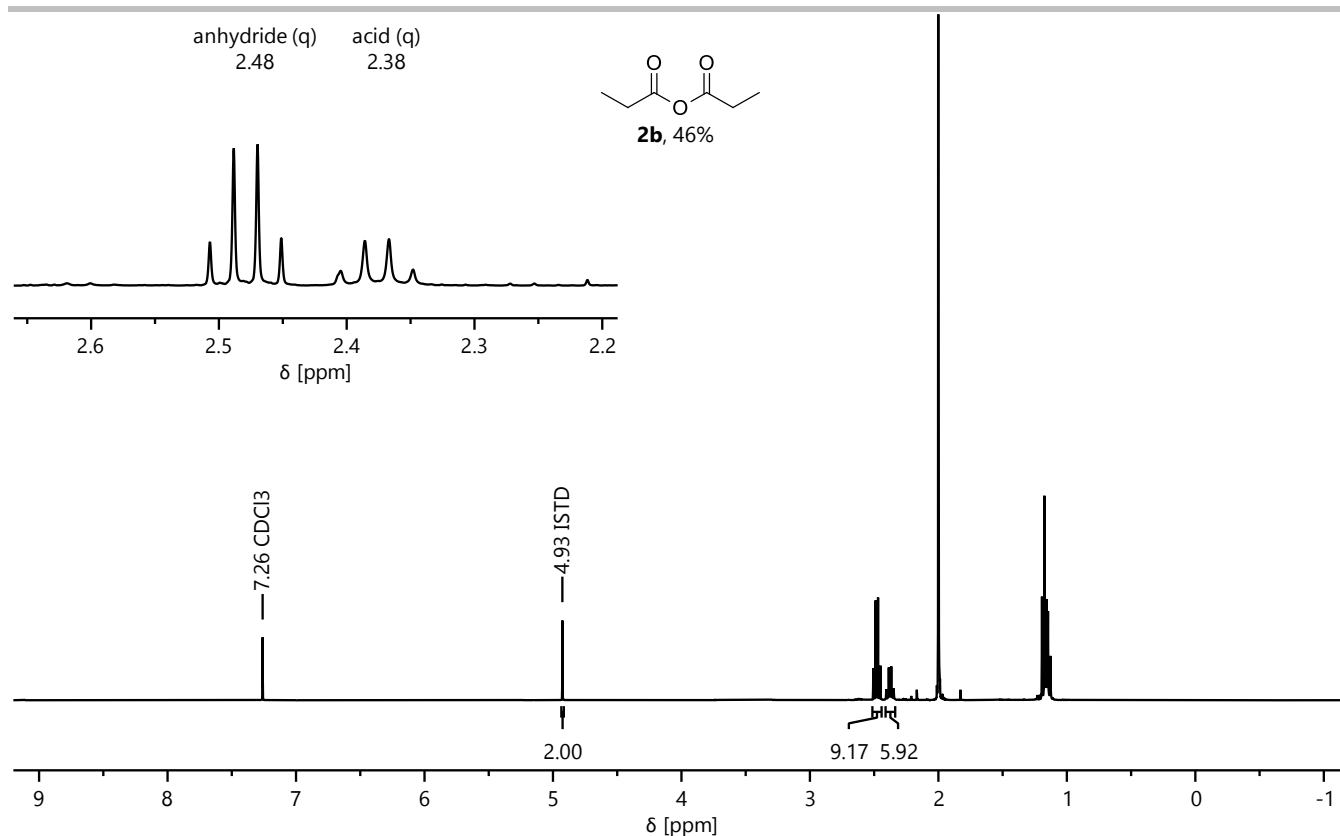


Figure S18: ¹H NMR of the crude mixture from electrolysis of propionic acid (**1b**); 400 MHz, 296 K.

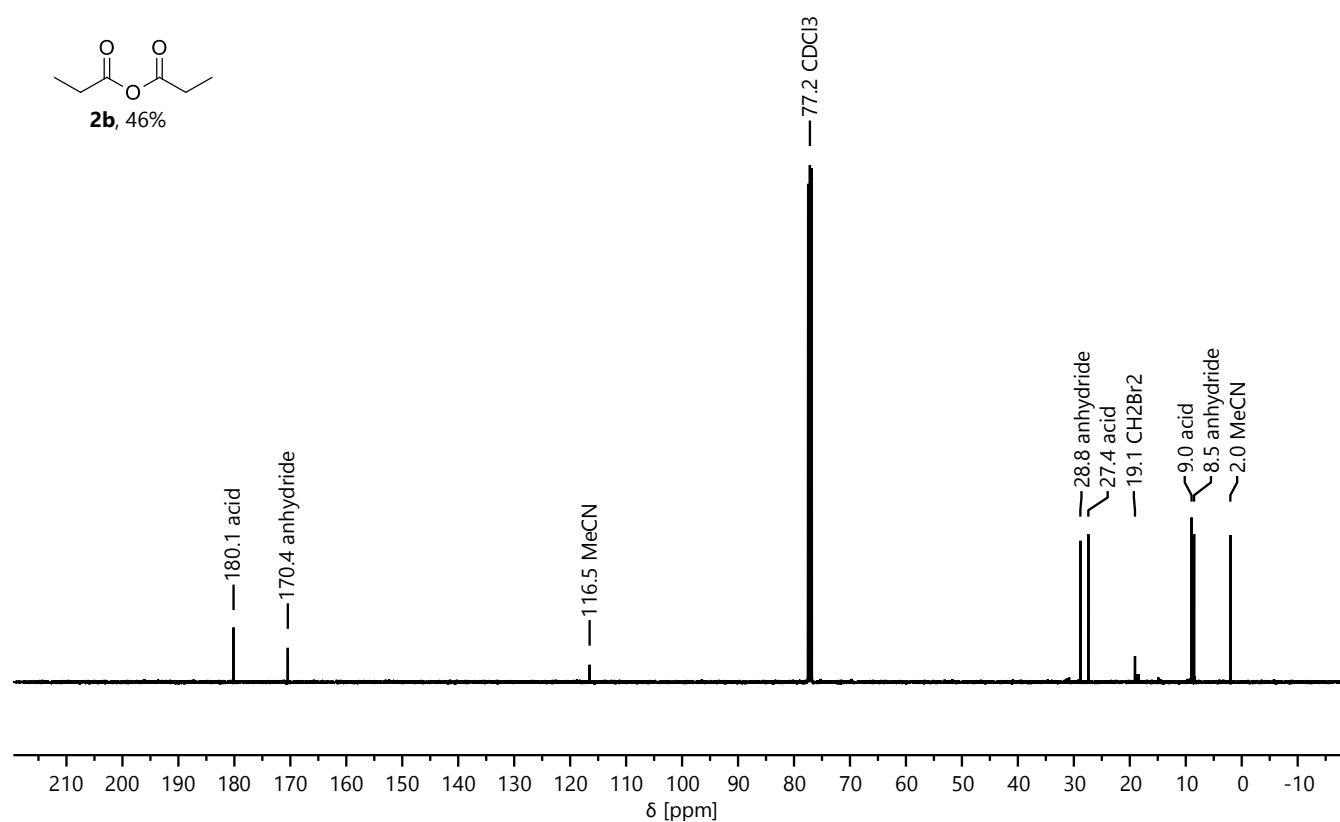


Figure S19: ¹³C NMR of the crude mixture from electrolysis of propionic acid (**1b**); 101 MHz, 296 K; STD: CH₂Br₂.

Butyric Anhydride (2c)

Following general procedure A, electrolysis of butyric acid (**1c**, 99%, 0.33 mL, 3.5 mmol, 0.71 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave butyric anhydride (**2c**) in 46% yield after 1.0 F (ISTD: 63.7 mg 1,3,5-trimethoxybenzene (98.0%)).

¹H NMR The signals overlap partially with butyric acid (**1c**).

¹³C NMR (101 MHz, CDCl₃) δ 169.6, 37.2, 17.9, 13.5 ppm.

The analytic data is in agreement with previously reported data.^[4]

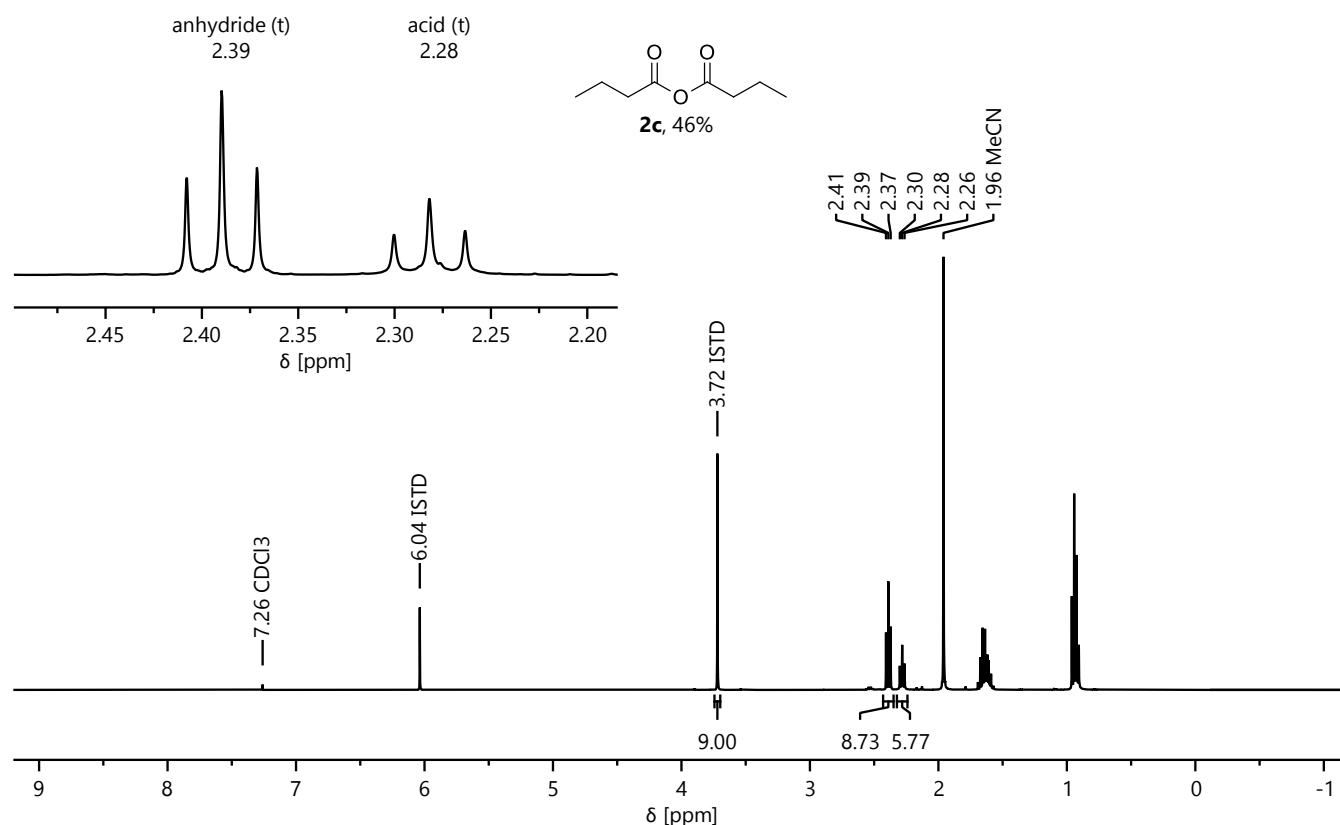


Figure S20: ¹H NMR of the crude mixture from electrolysis of butyric acid (**1c**); 400 MHz, 296 K.

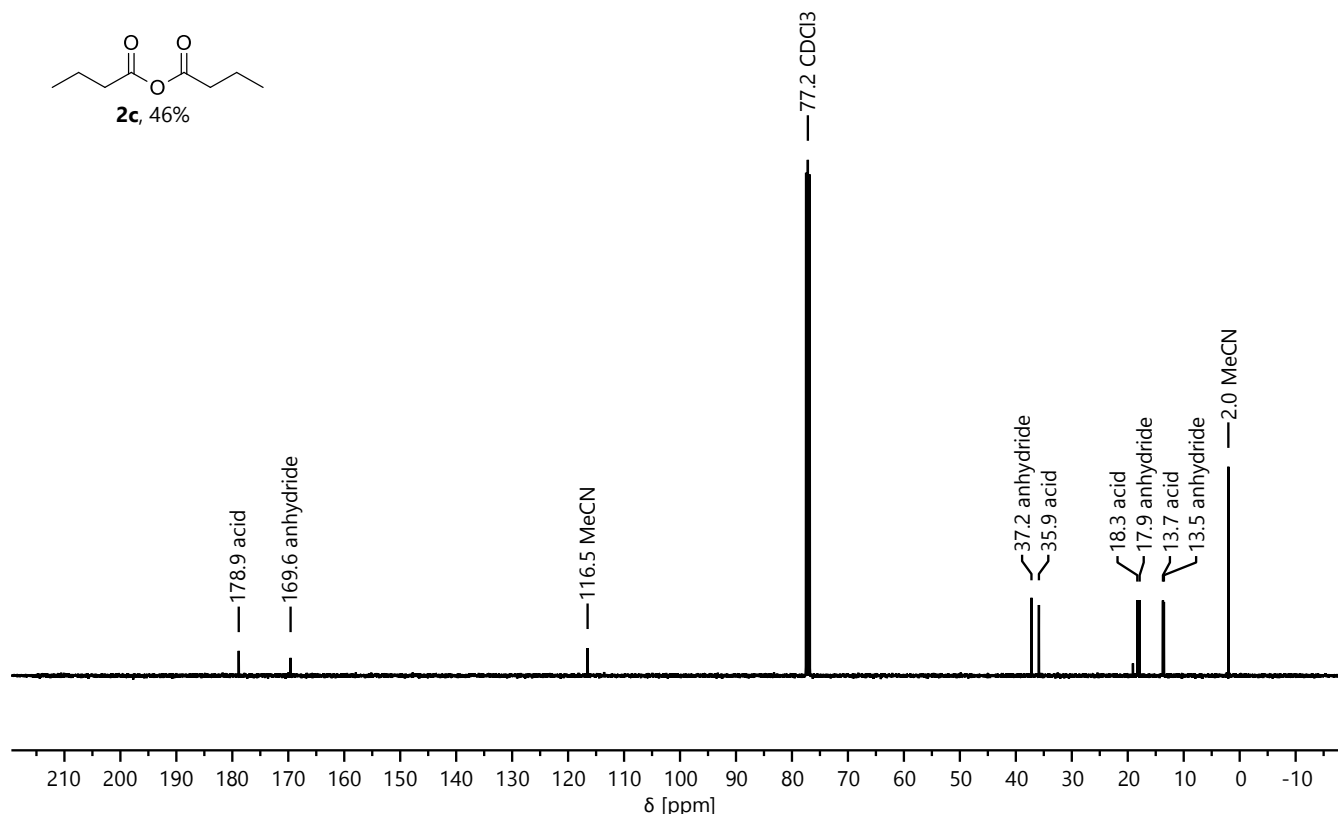


Figure S21: ^{13}C NMR of the crude mixture from electrolysis of butyric acid (**1c**); 101 MHz, 296 K; ISTD: CH_2Br_2 .

Valeric Anhydride (**2d**)

Following general procedure B, electrolysis of valeric acid (**1d**, 98.0%, 0.5 mL, 4.5 mmol, 0.90 M) at 80 mA/cm^2 with KSCN (170 mg, 0.35 M) as supporting electrolyte in MeCN (5.0 mL) gave valeric anhydride (**2d**) in 66% yield and 92% selectivity (72% conversion) after 1.1 F (ISTD: 90 mg dibromomethane (99%)).

The electrolysis of valeric acid was upscaled: Valeric acid (**1d**, 98.0%, 9.9 mL, 89 mmol, 0.89 M) and KSCN (3.401 g, 0.35 M) were dissolved in MeCN (100 mL) in an undivided glass cell equipped with a graphite anode and stainless steel cathode (active electrode area: 18 cm^2). The mixture was electrolyzed at 80 mA/cm^2 and 288 K until 1.1 F had been transferred. An aliquot was taken from the electrolyte and the yield of valeric anhydride (**2d**) was determined 55% by GC analogously general procedure C. The remaining electrolyte was diluted with EtOAc and washed with saturated aqueous NaHCO_3 . The aqueous phase was extracted with EtOAc and the combined organic phases were dried with MgSO_4 . The residue was distilled in high vacuum to afford 2.817 g (34%) valeric anhydride (**2d**) as colorless liquid.

^1H NMR (400 MHz, CDCl_3) δ 2.45 (t, J = 7.5 Hz, 4H), 1.71 – 1.59 (m, 4H), 1.45 – 1.32 (m, 4H), 0.93 (t, J = 7.3 Hz, 6H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ 169.8, 35.1, 26.4, 22.1, 13.8 ppm.

The analytic data is in agreement with previously reported data.^[5]

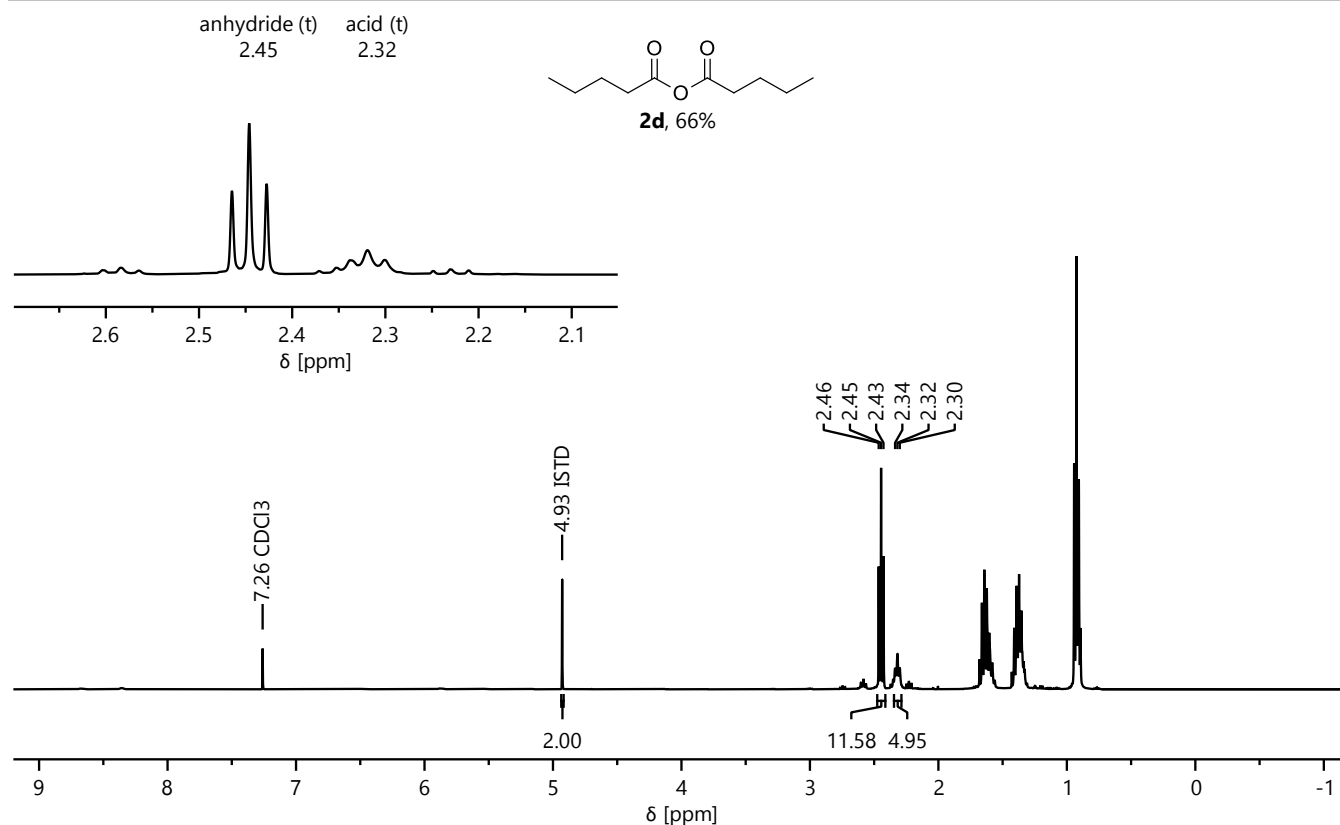


Figure S22: ^1H NMR of the crude mixture from electrolysis of valeric acid (**1d**); 400 MHz, 296 K.

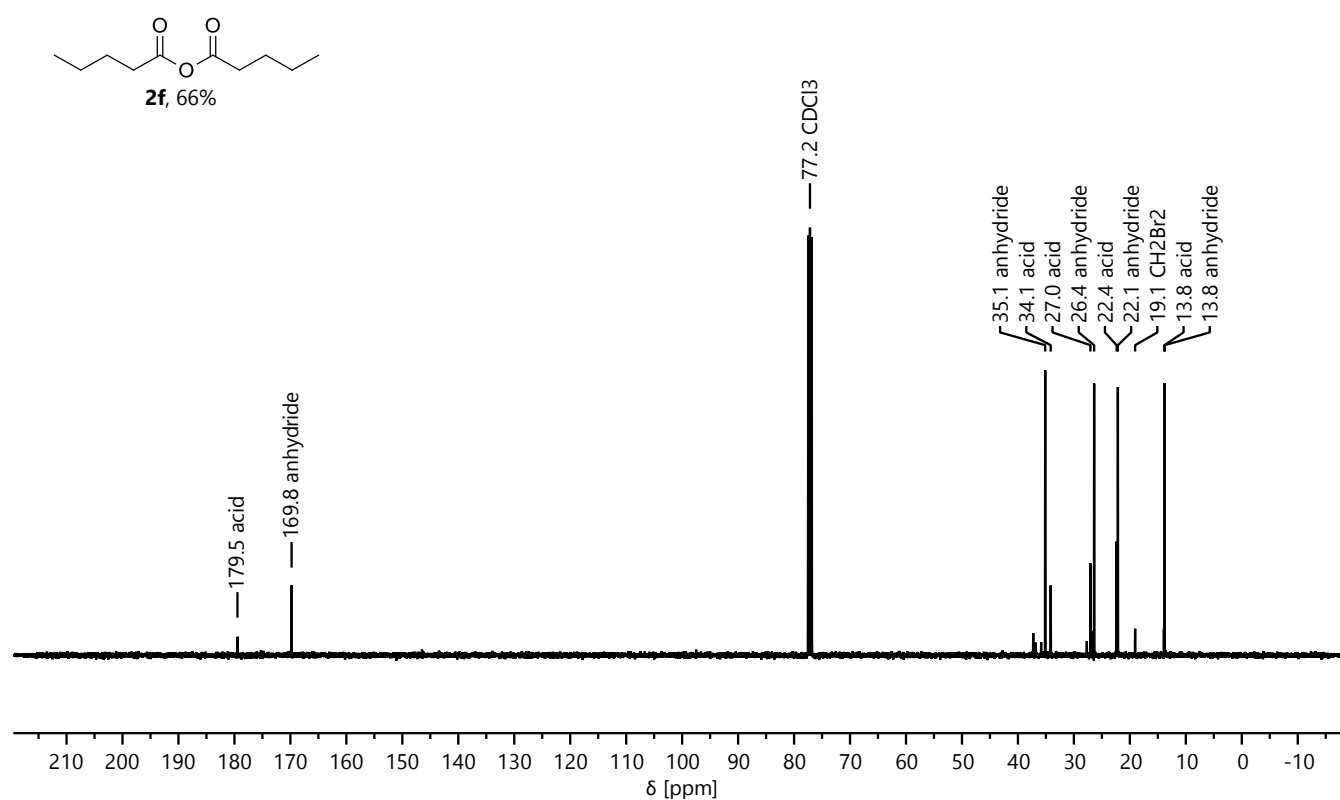


Figure S23: ^{13}C NMR of the crude mixture from electrolysis of valeric acid (**1d**); 101 MHz, 296 K.

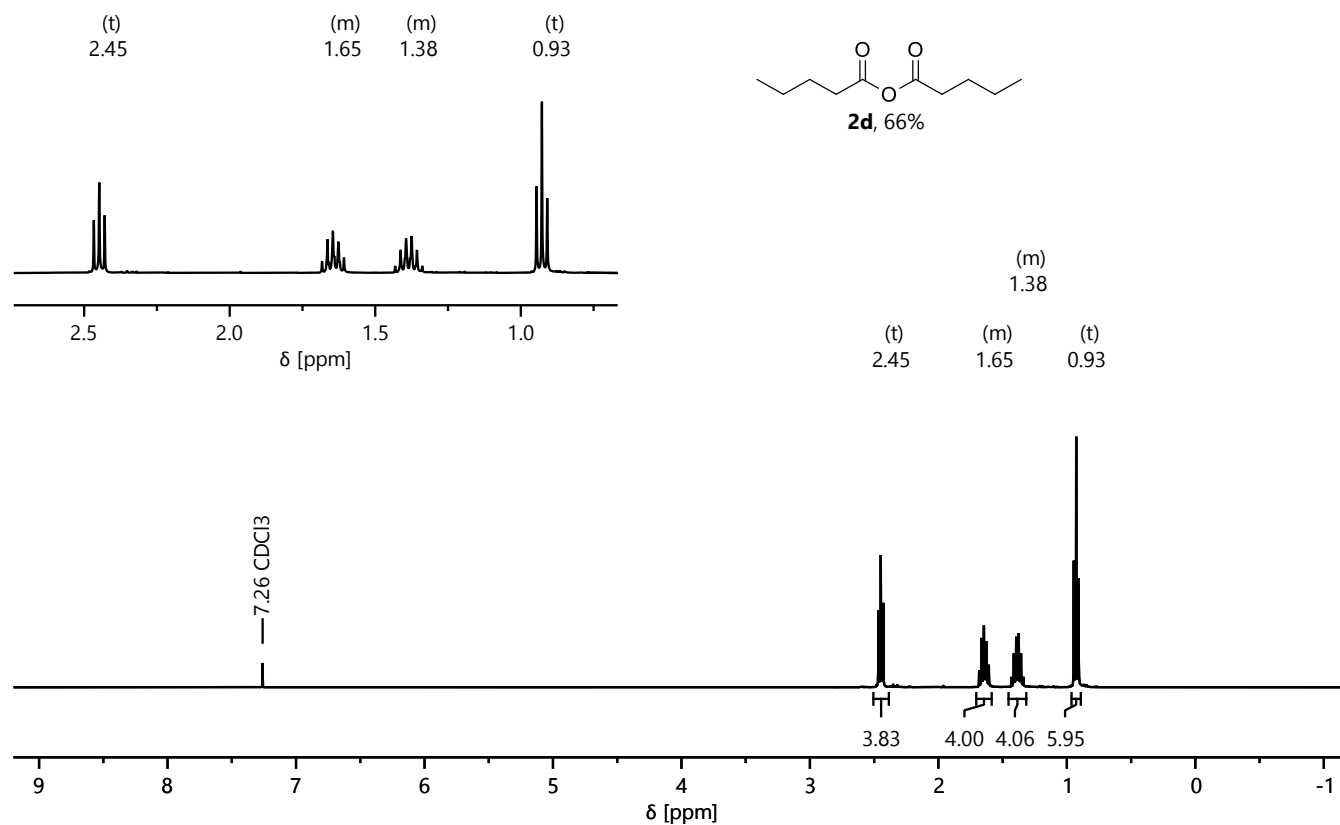


Figure S24: ¹H NMR of valeric anhydride (**2d**) after distillation; 400 MHz, 296 K.

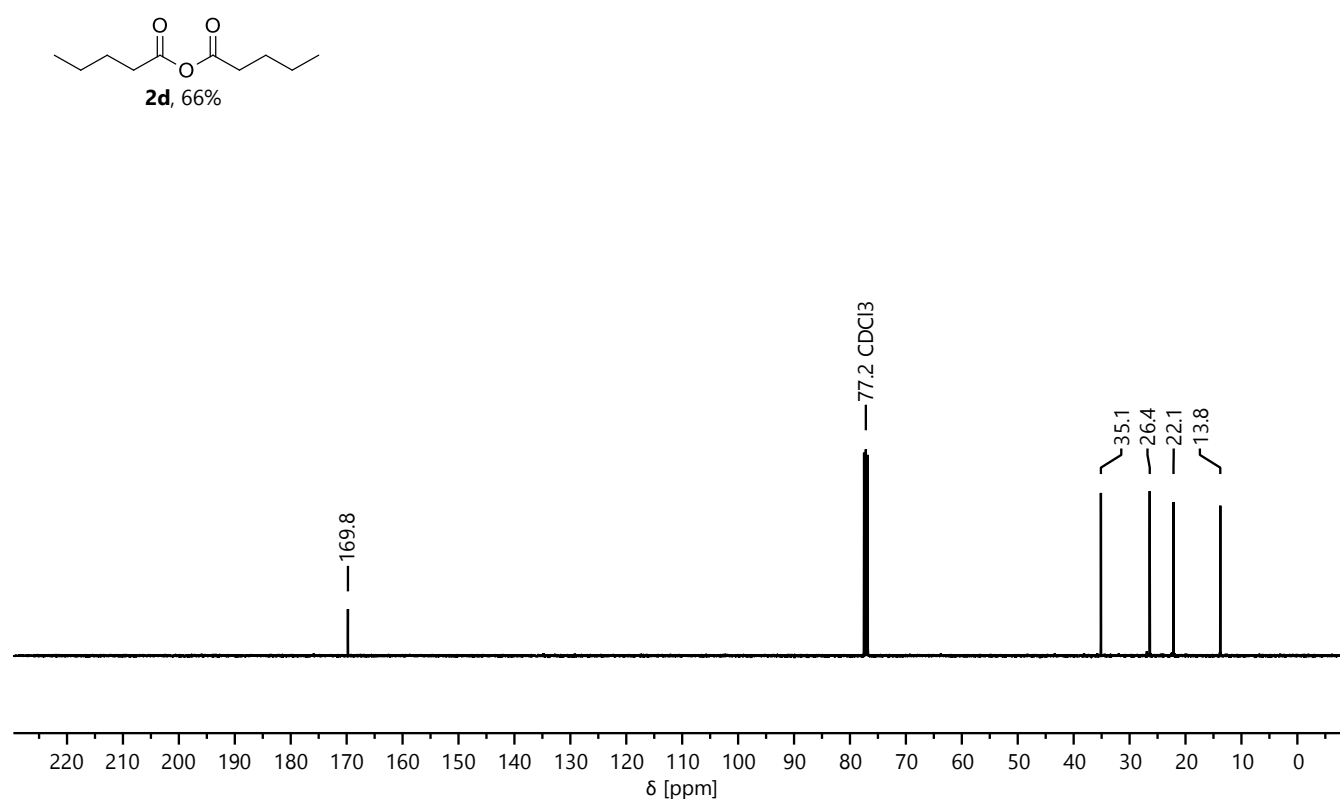


Figure S25: ¹³C NMR of valeric anhydride (**2d**) after distillation; 101 MHz, 296 K.

Caproic Anhydride (2e)

Following general procedure B, electrolysis of caproic acid (**1e**, 98%, 600 mg, 5.1 mmol, 1.0 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave caproic anhydride (**2e**) in 60% yield and >100% selectivity (57% conversion) after 1.1 *F* (ISTD: 62.0 mg dibromomethane (99%)).

¹H NMR The signals overlap partially with caproic acid (**1e**).

¹³C NMR (101 MHz, CDCl₃) δ 169.8, 35.4, 31.3, 24.0, 22.4, 14.0 ppm.

The analytic data is in agreement with previously reported data.^[6]

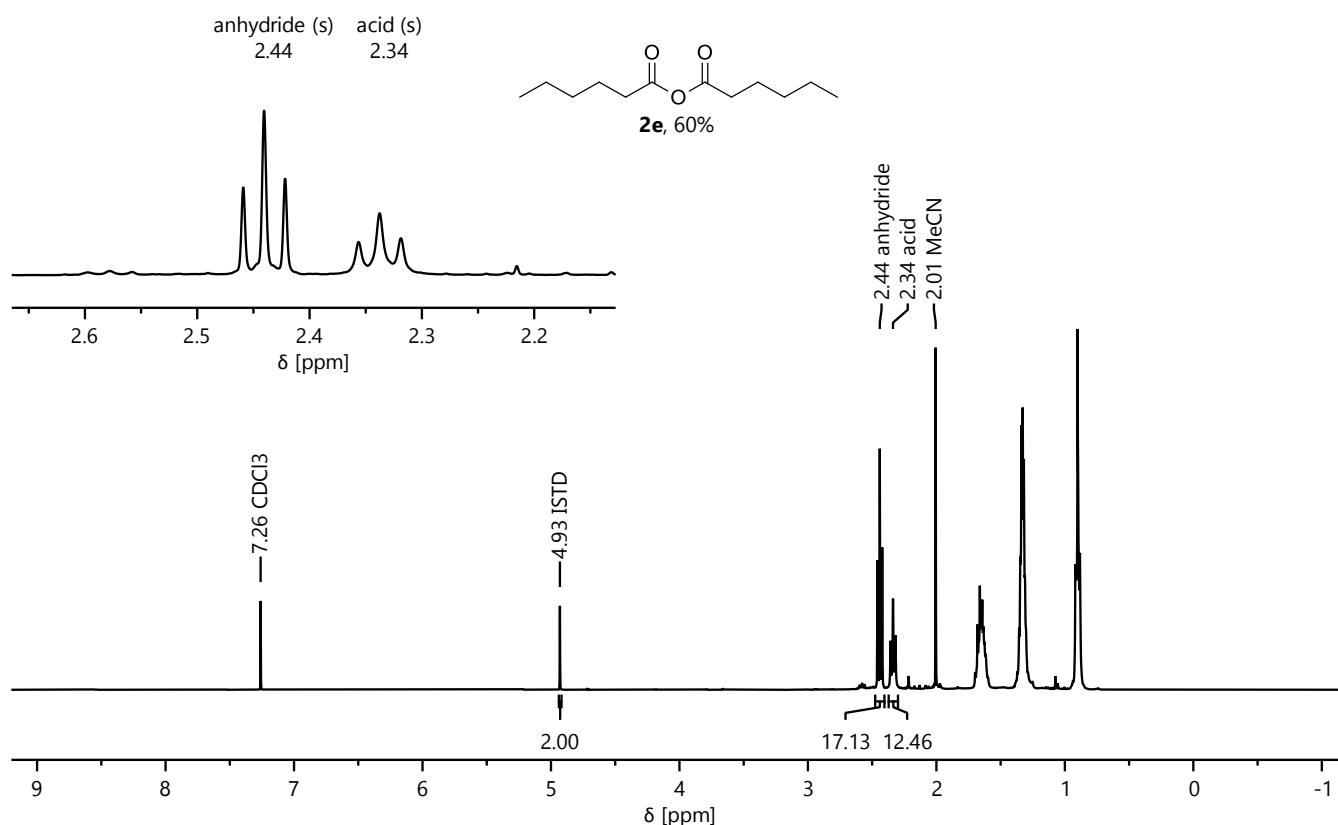


Figure S26: ¹H NMR of the crude mixture from electrolysis of caproic acid (**1e**); 400 MHz, 296 K.

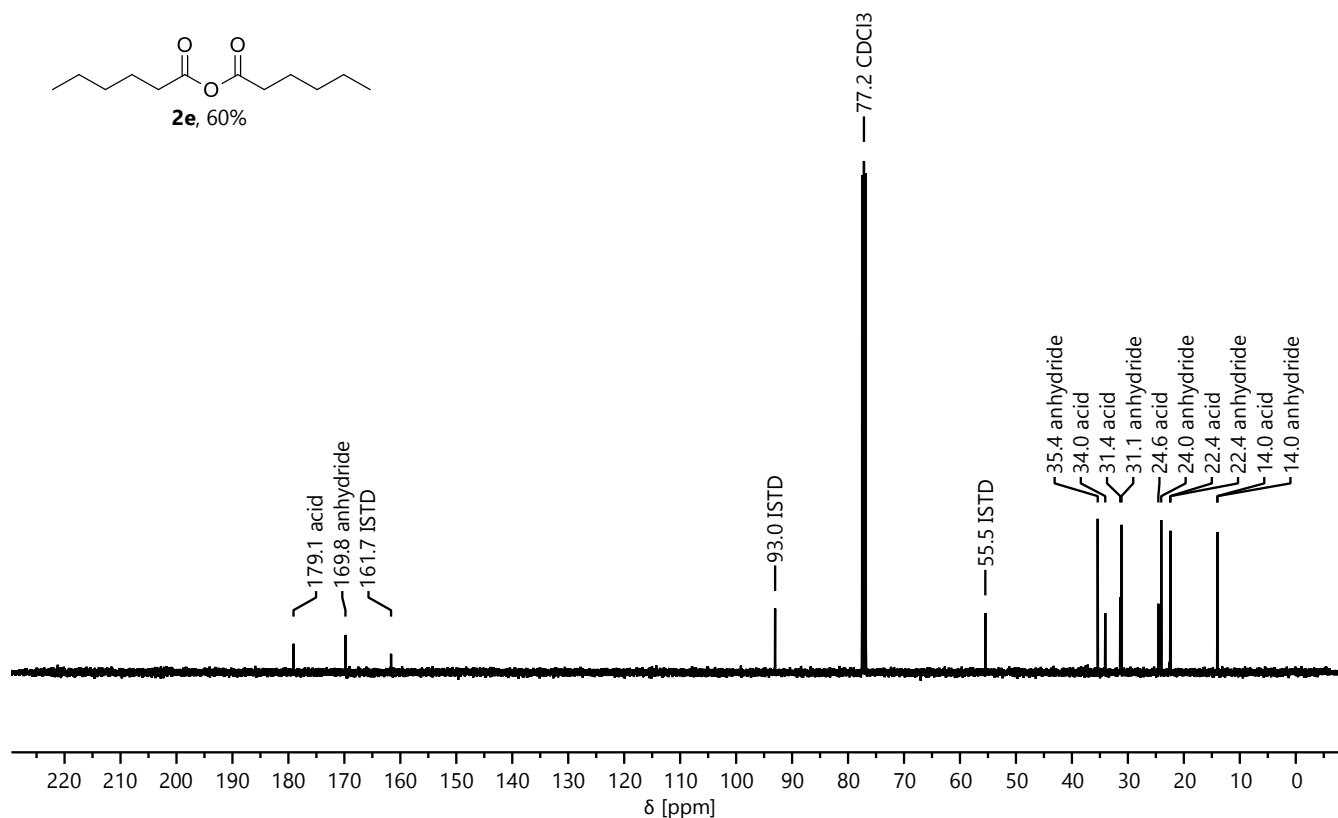


Figure S27: ^{13}C NMR of the crude mixture from electrolysis of caproic acid (**1e**); 101 MHz, 296 K.

Caprylic Anhydride (**2f**)

Following general procedure A, electrolysis of caprylic acid (**1f**, 99.5%, 507 mg, 3.5 mmol, 0.70 M) at 50 mA/cm² with EMIMSCN (85 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave caprylic anhydride (**2f**) in 37% yield and 79% selectivity (46% conversion) after 1.1 *F* (ISTD: 45.8 mg 1,3,5-trimethoxybenzene (98.0%)).

GCMS (EI) t_R = 12.970 min, $[m/z]$ 127 (100%), 98 (7%), 57 (75%), 43 (25%), 42 (11%), 41 (26%).

^1H NMR The signals overlap partially with caprylic acid (**1f**).

^{13}C NMR (101 MHz, CDCl_3) δ 169.8 ppm; The signals of the remaining carbon atoms cannot be assigned unambiguously.

The analytic data is in agreement with previously reported data.^[7]

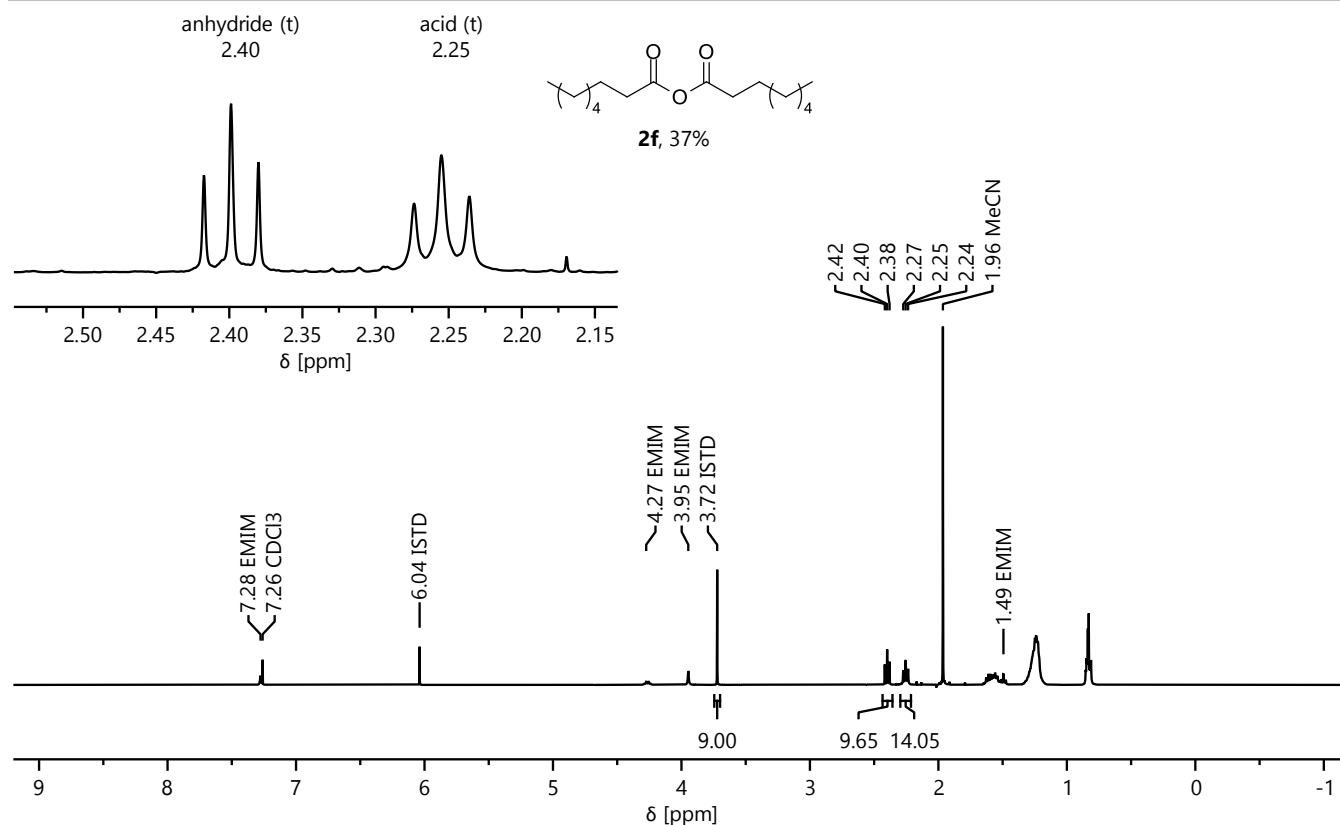


Figure S28: ¹H NMR of the crude mixture from electrolysis of caprylic acid (**1f**); 400 MHz, 296 K.

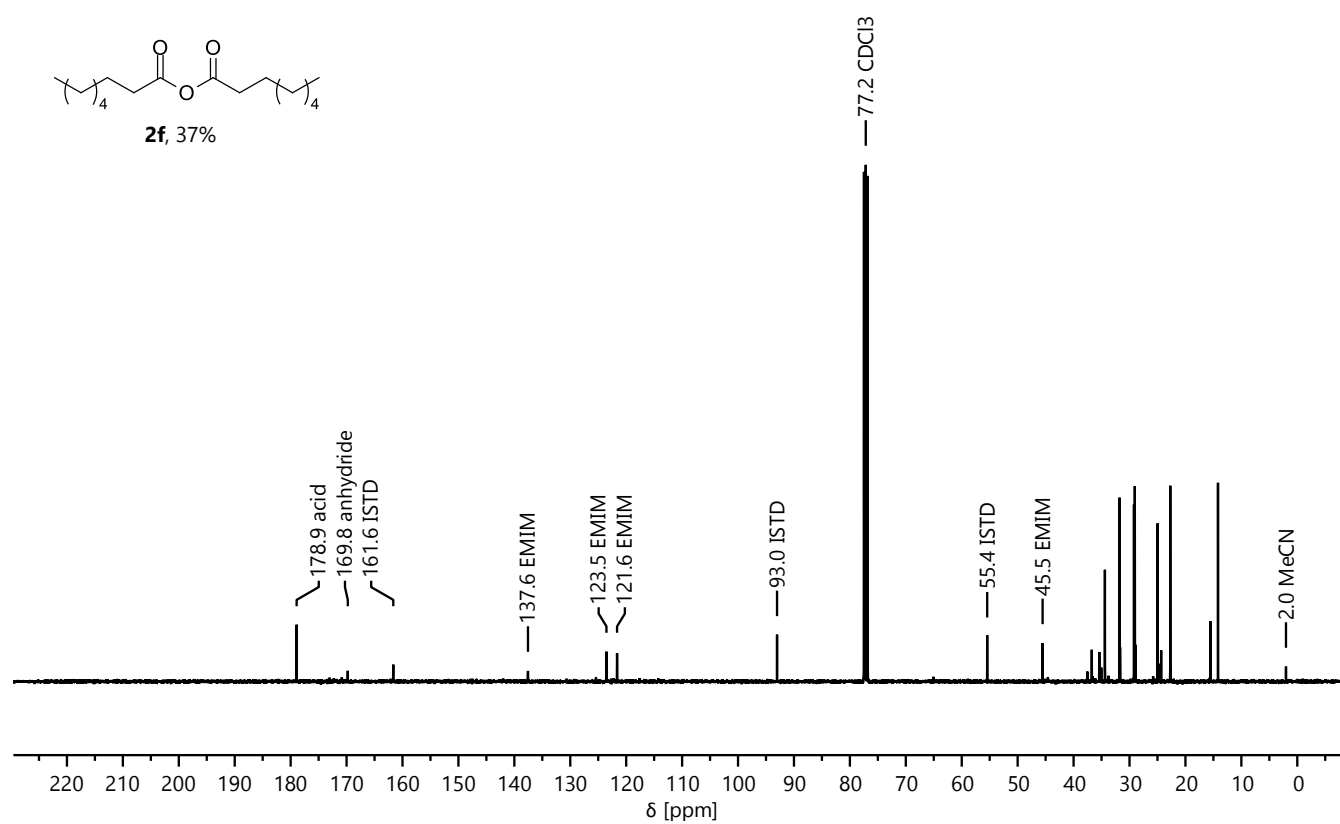


Figure S29: ¹³C NMR of the crude mixture from electrolysis of caprylic acid (**1f**); 101 MHz, 296 K.

TIC+

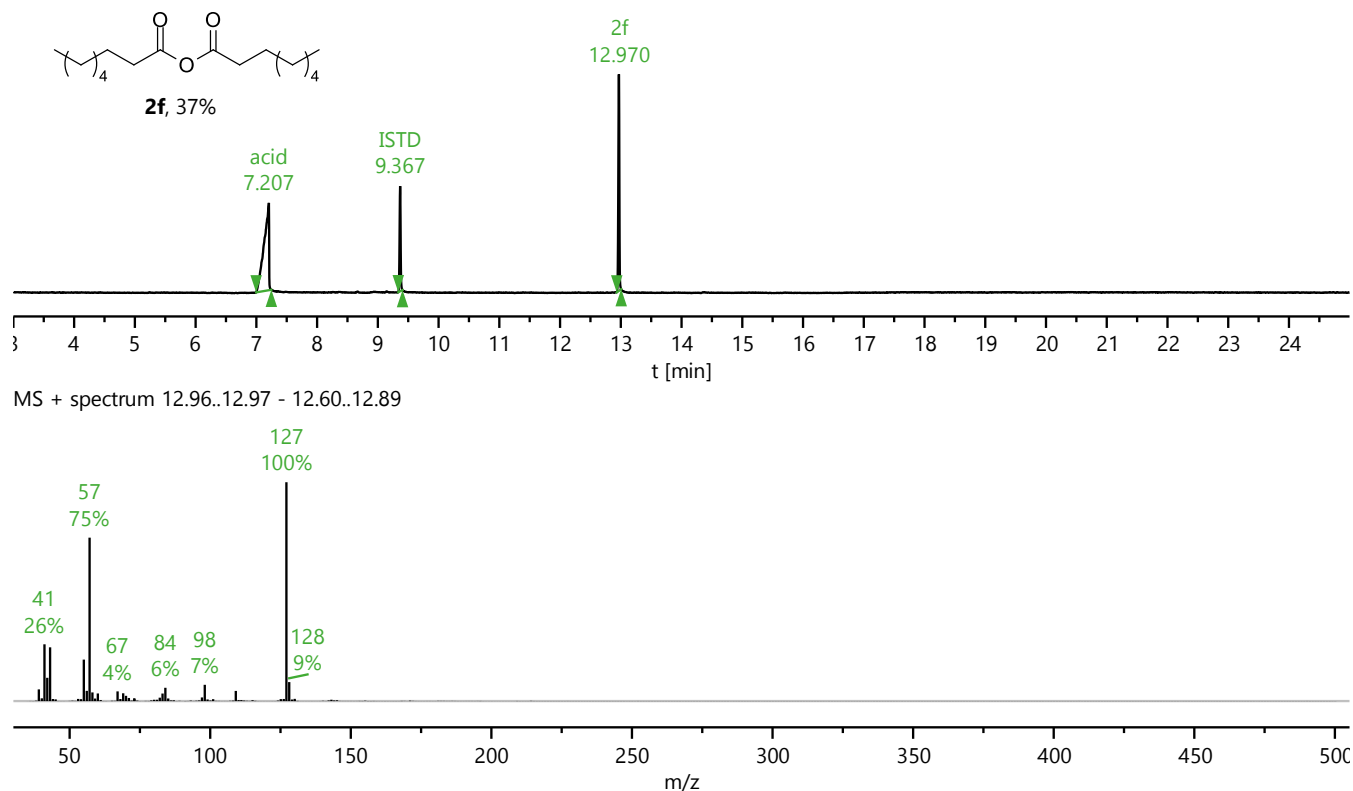


Figure S30: GCMS of the crude mixture from electrolysis of caprylic acid (**1f**) after filtration through silica.

Lauric Anhydride (**2g**)

Following general procedure A, electrolysis of lauric acid (**1g**, 98%, 715 mg, 3.5 mmol, 0.70 M) at 50 mA/cm² and 313 K with EMIMSCN (85 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave lauric anhydride (**2g**) in 39% yield and 96% selectivity (41% conversion) after 1.1 *F* (ISTD: 42.9 mg 1,3,5-trimethoxybenzene (98.0%)).

¹H NMR The signals overlap partially with lauric acid (**1g**).

¹³C NMR (101 MHz, CDCl₃) δ 169.7, 35.3 ppm; The remaining signals overlap with lauric acid (**1g**) or cannot be assigned unambiguously.

The analytic data is in agreement with previously reported data.^[8]

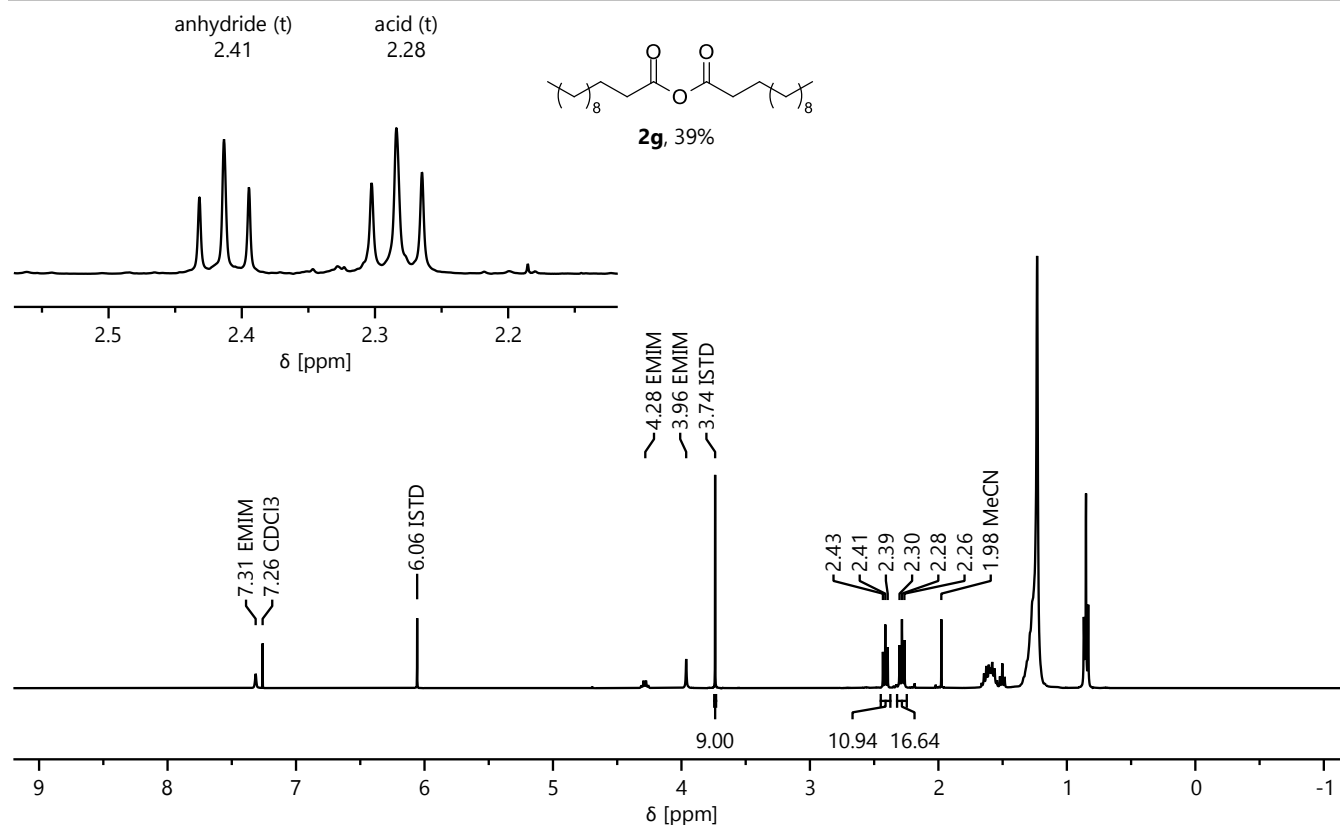


Figure S31: ^1H NMR of the crude mixture from electrolysis of lauric acid (**1g**); 400 MHz, 296 K.

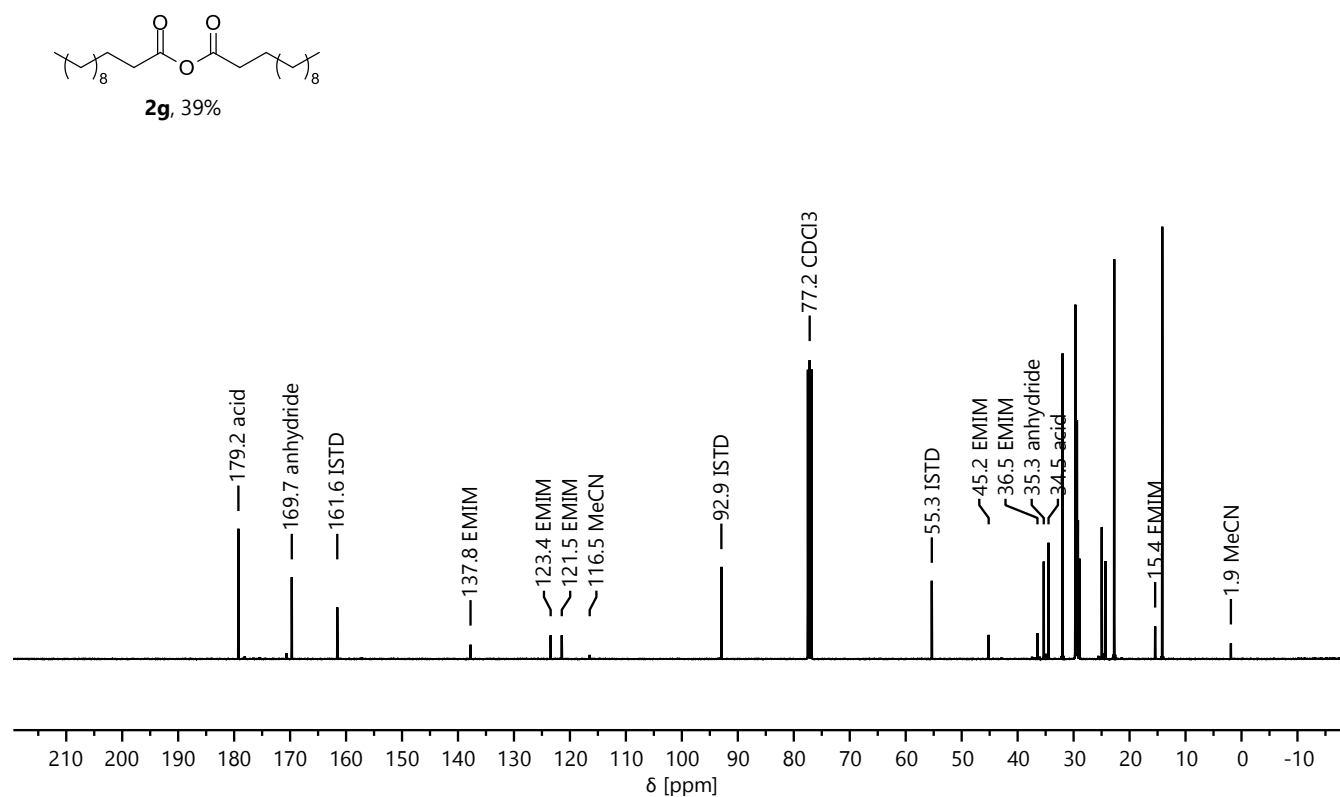


Figure S32: ^{13}C NMR of the crude mixture from electrolysis of lauric acid (**1g**); 101 MHz, 296 K.

Isobutyric Anhydride (2h)

Following general procedure A, electrolysis of isobutyric acid (**1h**, 99.0%, 0.33 mL, 3.5 mmol, 0.70 M) at 50 mA/cm² with KSCN (170 mg, 0.35 M) as supporting electrolyte in MeCN (5.0 mL) gave isobutyric anhydride (**2h**) in 61% yield after 1.1 F (ISTD: 37.4 mg 1,3,5-trimethoxybenzene (98.0%)).

GC t_R = 4.199 min; t_R (isobutyric anhydride (**2h**), authentic sample) = 4.193 min.

¹H NMR The signals overlap partially with isobutyric acid (**1h**).

¹³C NMR (101 MHz, CDCl₃) δ 173.0, 35.2, 18.4 ppm.

The analytic data is in agreement with previously reported data.^[3]

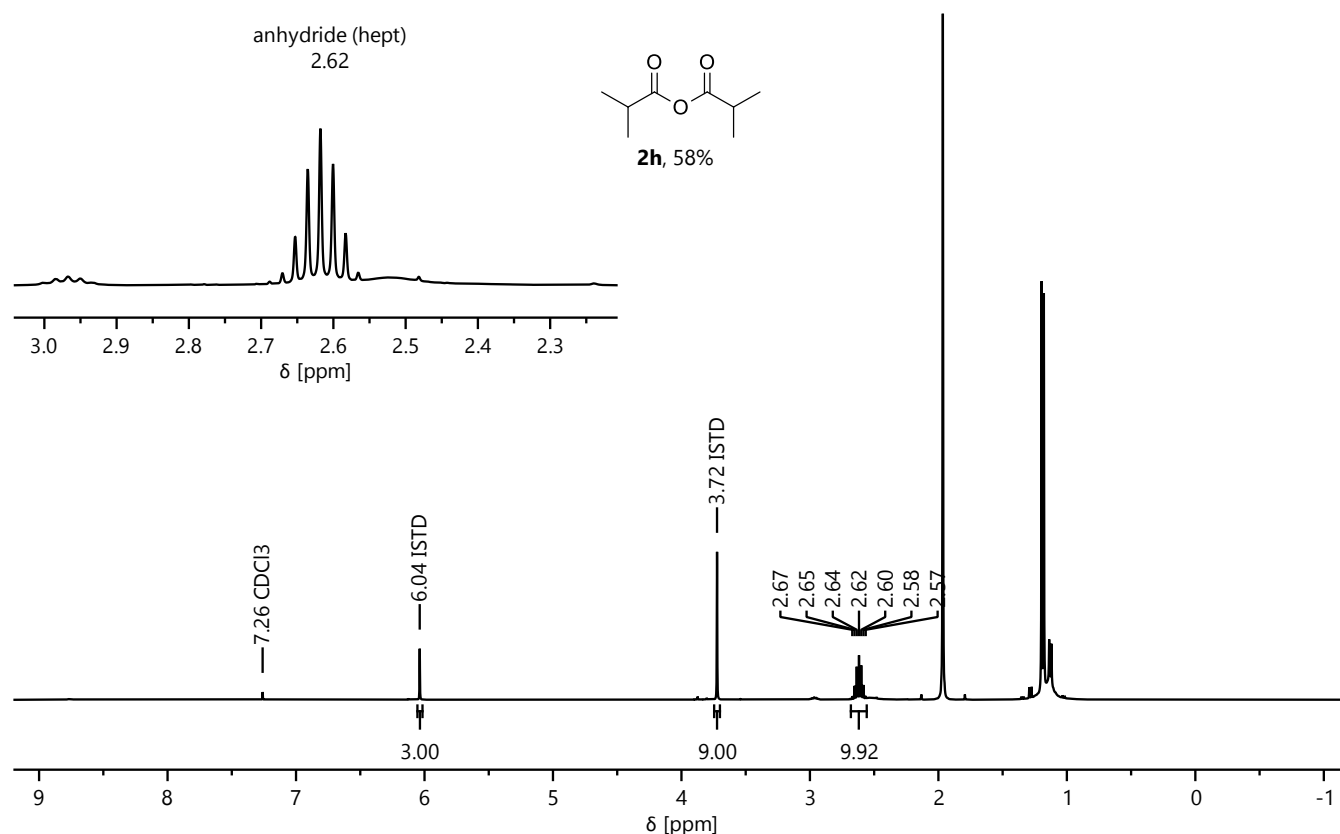
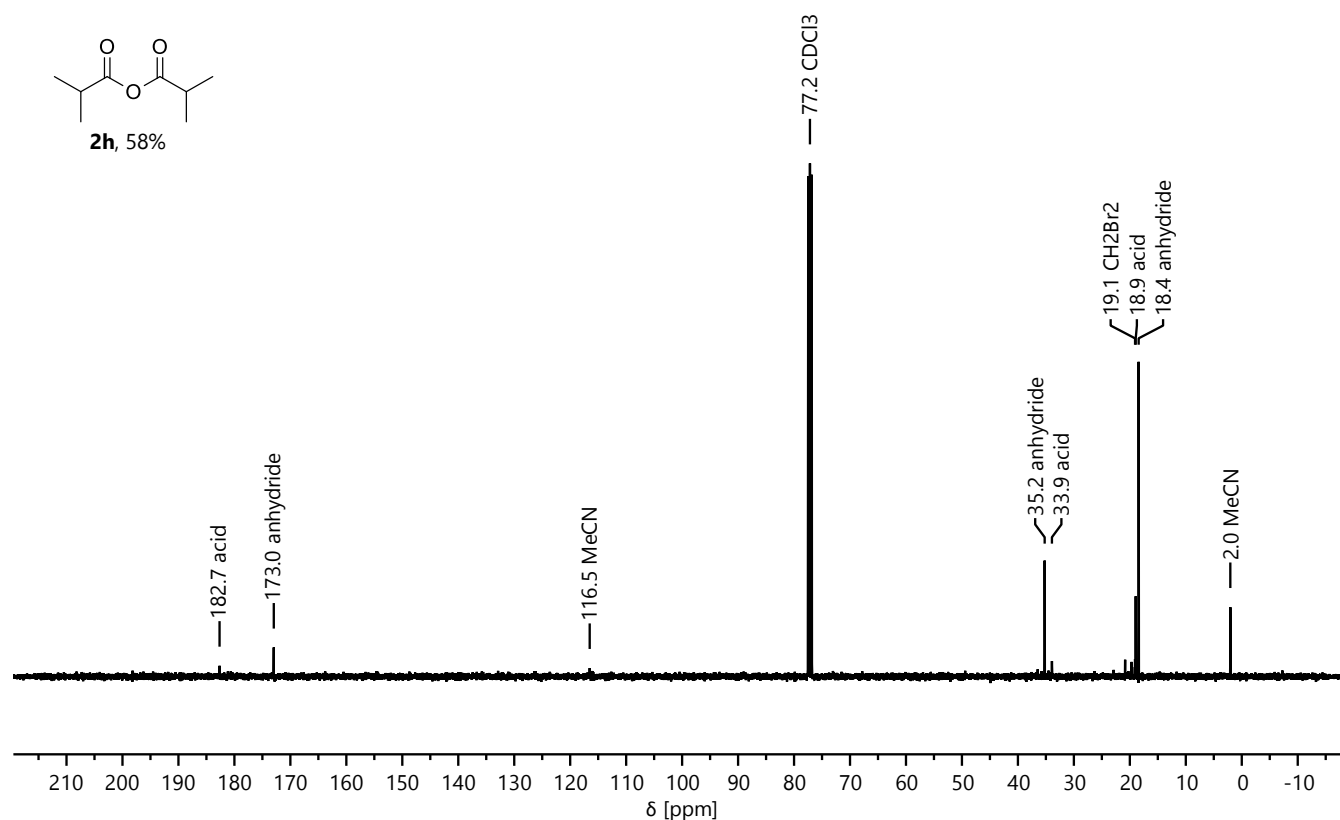


Figure S33: ¹H NMR of the crude mixture from electrolysis of isobutyric acid (**1h**); 400 MHz, 296 K.



Pivalic Anhydride (**2i**)

Following general procedure B, electrolysis of pivalic acid (**1i**, 99%, 516 mg, 5.0 mmol, 1.0 M) at 50 mA/cm² with KSCN 50 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave pivalic anhydride (**2i**) in 52% yield and 92% selectivity (57% conversion) after 1.1 *F* (ISTD: 66.1 mg dibromomethane (99%)). *N-tert*-Butyl acetamide was observed as side-product.

GCMS (EI) t_R = 5.960 min, [m/z] 85 (38%), 57 (100%), 41 (25%); t_R (pivalic anhydride (**2i**), authentic sample) = 5.970 min, [m/z] 85 (41%), 57 (100%), 41 (24%).

^1H NMR (400 MHz, CDCl_3) δ 1.26 (s, 18H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ 174.2, 40.3, 26.6 ppm.

The analytic data is in agreement with previously reported data.^[9,10]

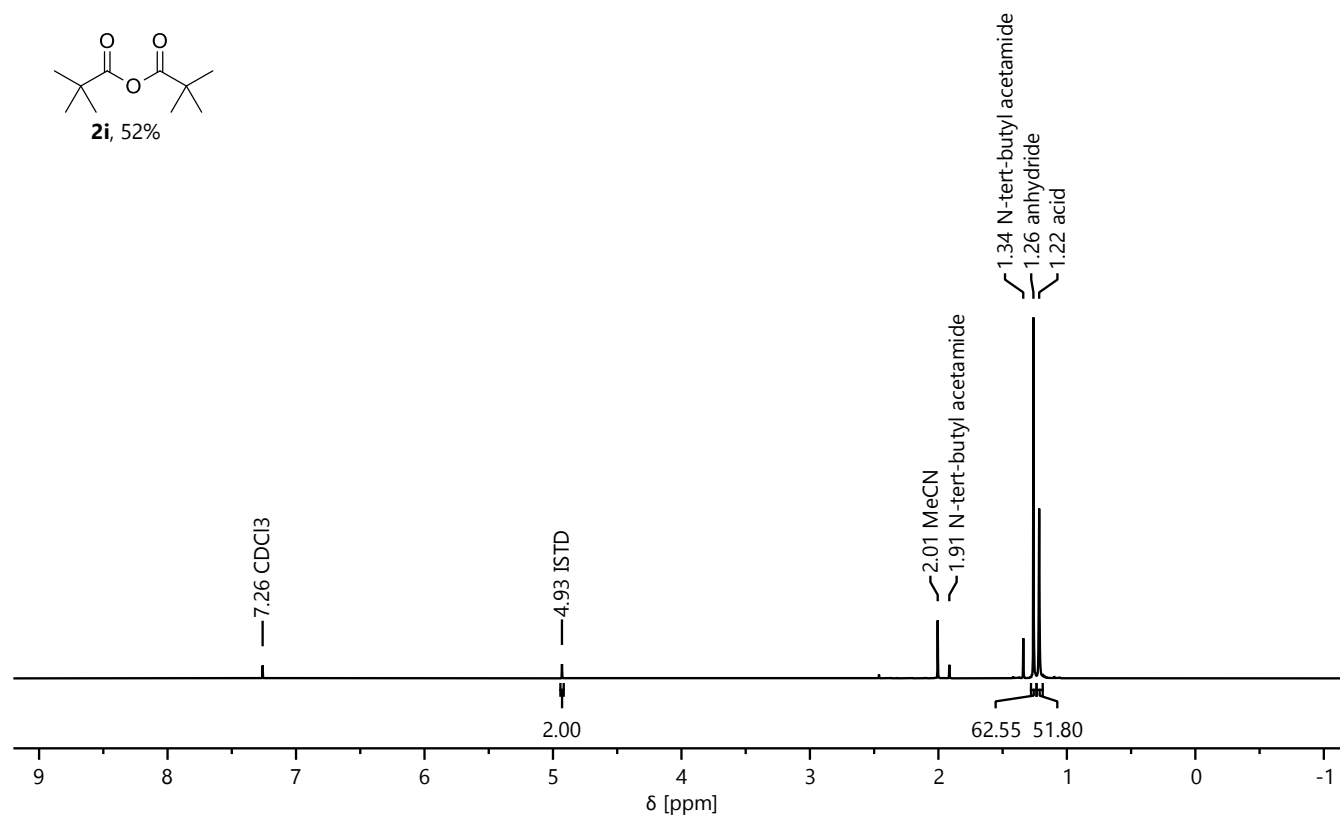


Figure S35: ¹H NMR of the crude mixture from electrolysis of pivalic acid (**1i**); 400 MHz, 296 K.

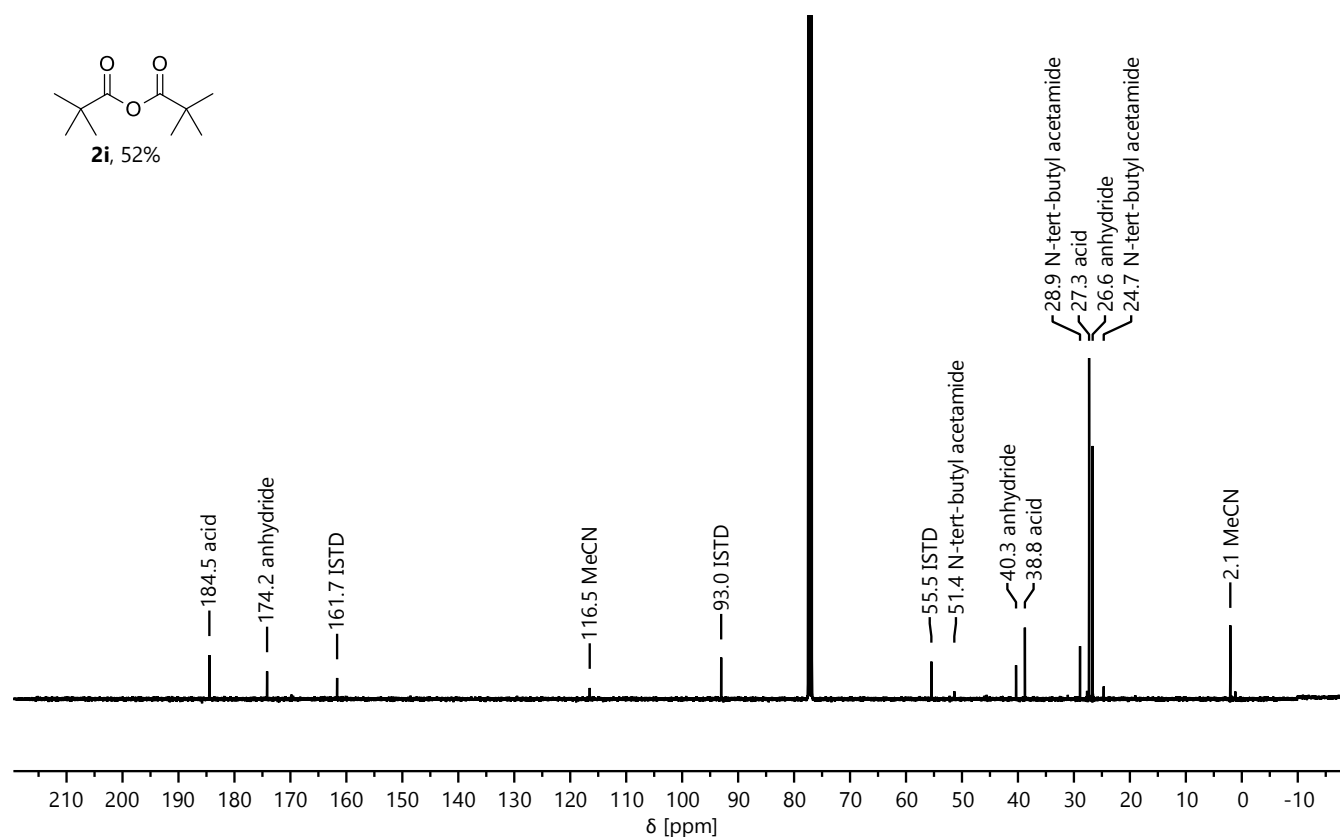


Figure S36: ¹³C NMR of the crude mixture from electrolysis of pivalic acid (**1i**); 101 MHz, 296 K; ISTD: 1,3,5-trimethoxybenzene.

3,3-Dimethylbutanoic Anhydride (2j)

Following general procedure B, electrolysis of 3,3-dimethylbutanoic acid (**1j**, 98%, 600 mg, 5.1 mmol, 1.0 M) at 50 mA/cm² with KSCN (50 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 3,3-dimethylbutanoic anhydride (**2j**) in 53% yield and 90% selectivity (59% conversion) after 1.1 *F* (ISTD: 113.8 mg dibromomethane (99%)).

¹H NMR (400 MHz, CDCl₃) δ 2.30 (s, 4H), 1.07 (s, 18H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ 168.1, 48.7, 29.8, 29.6 ppm.

The analytic data is in agreement with previously reported data.^[11]

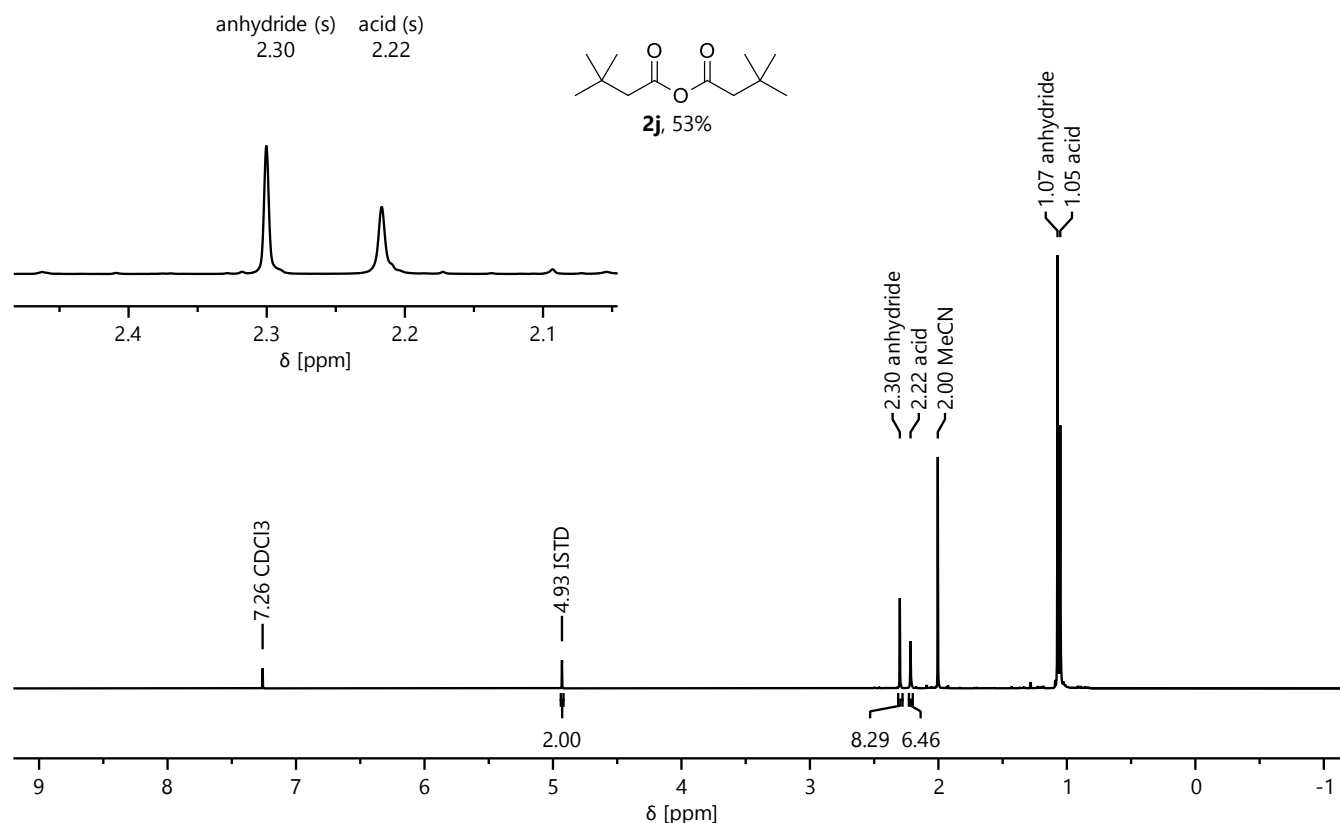


Figure S37: ¹H NMR of the crude mixture from electrolysis of 3,3-dimethylbutanoic acid (**1j**); 400 MHz, 296 K.

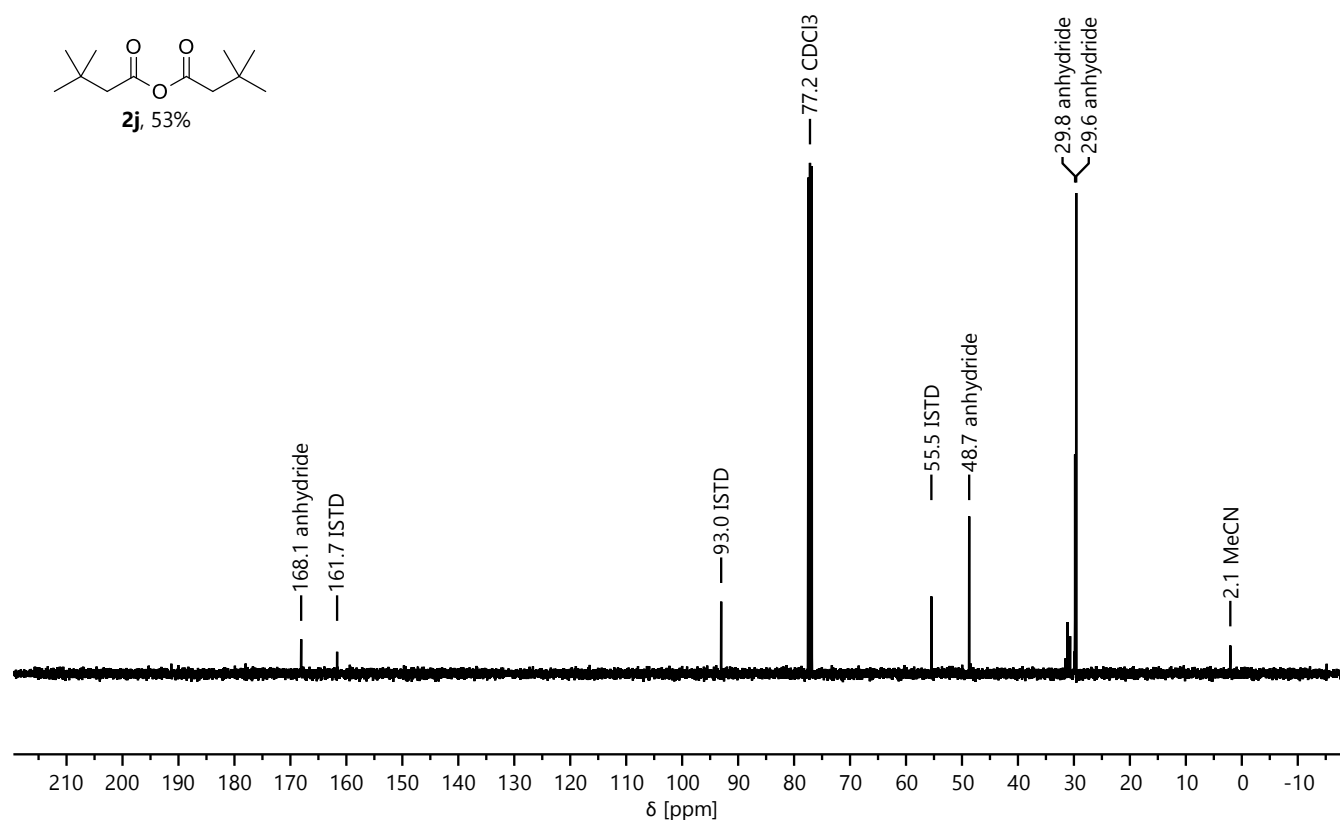


Figure S38: ¹³C NMR of the crude mixture from electrolysis of 3,3-dimethylbutanoic acid (**1j**); 101 MHz, 296 K; ISTD: 1,3,5-trimethoxybenzene.

2-Ethylhexanoic Anhydride (**2k**)

Following general procedure B, electrolysis of 2-ethylhexanoic acid (**1k**, 100%, 724 mg, 5.0 mmol, 1.0 M) at 50 mA/cm² with KSCN (50 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 2-ethylhexanoic anhydride (**2k**) in 58% yield and >100% selectivity (51% conversion) after 1.1 *F* (ISTD: 95.0 mg dibromomethane (99%)).

GCMS (EI) *t_R* = 11.453 min, [*m/z*] 127 (75%), 99 (38%), 57 (100%), 43 (22%), 41 (25%).

¹H NMR The signals overlap partially with 2-ethylhexanoic acid (**1k**).

¹³C NMR (101 MHz, CDCl₃) δ 171.9, 48.2, 31.0, 29.3, 24.8, 22.6, 13.9, 11.8 ppm.

The analytic data is in agreement with previously reported data.^[12]

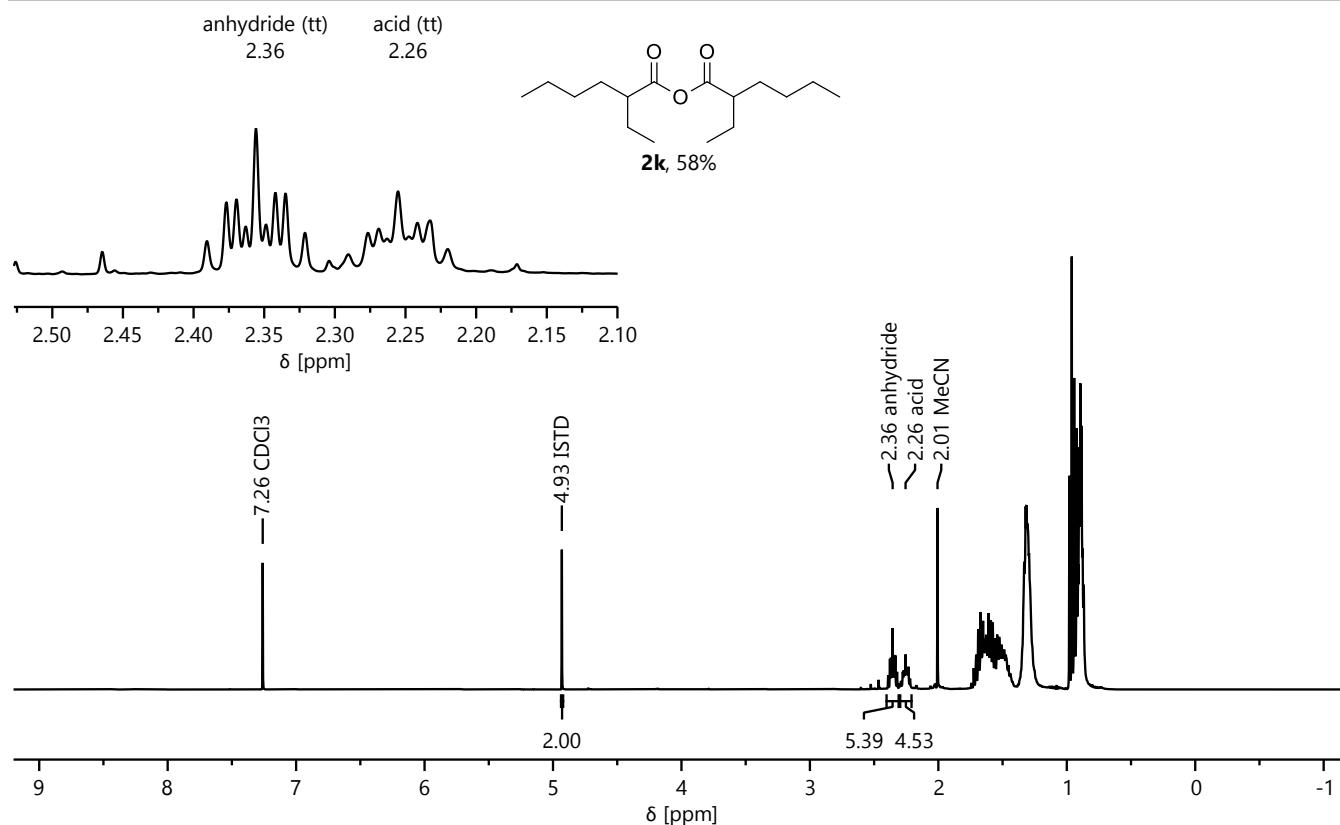


Figure S39: ¹H NMR of the crude mixture from electrolysis of 2-ethylhexanoic acid (**1k**); 400 MHz, 296 K.

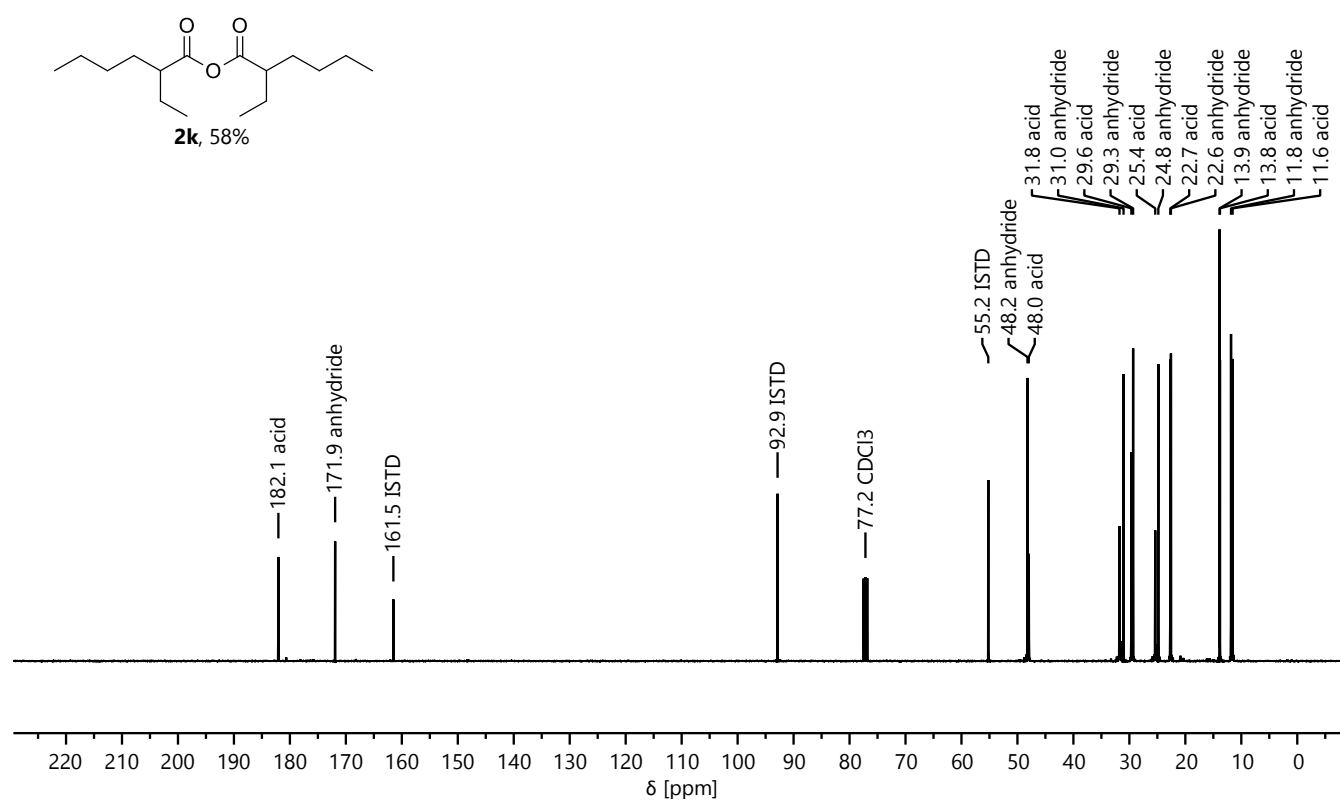


Figure S40: ¹³C NMR of the crude mixture from electrolysis of 2-ethylhexanoic acid (**1k**); 101 MHz, 296 K.

4-Pentenoic Anhydride (2I)

Following general procedure A, electrolysis of 4-pentenoic acid (**1I**, 100%, 0.36 mL, 3.5 mmol, 0.70 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 4-pentenoic anhydride (**2I**) in 26% yield after 1.0 *F* (ISTD: 60.3 mg 1,3,5-trimethoxybenzene (98.0%)).

¹H NMR The signals overlap partially with 4-pentenoic acid (**1I**).

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 135.8, 116.3, 34.7, 28.2 ppm.

The analytic data is in agreement with previously reported data.^[13]

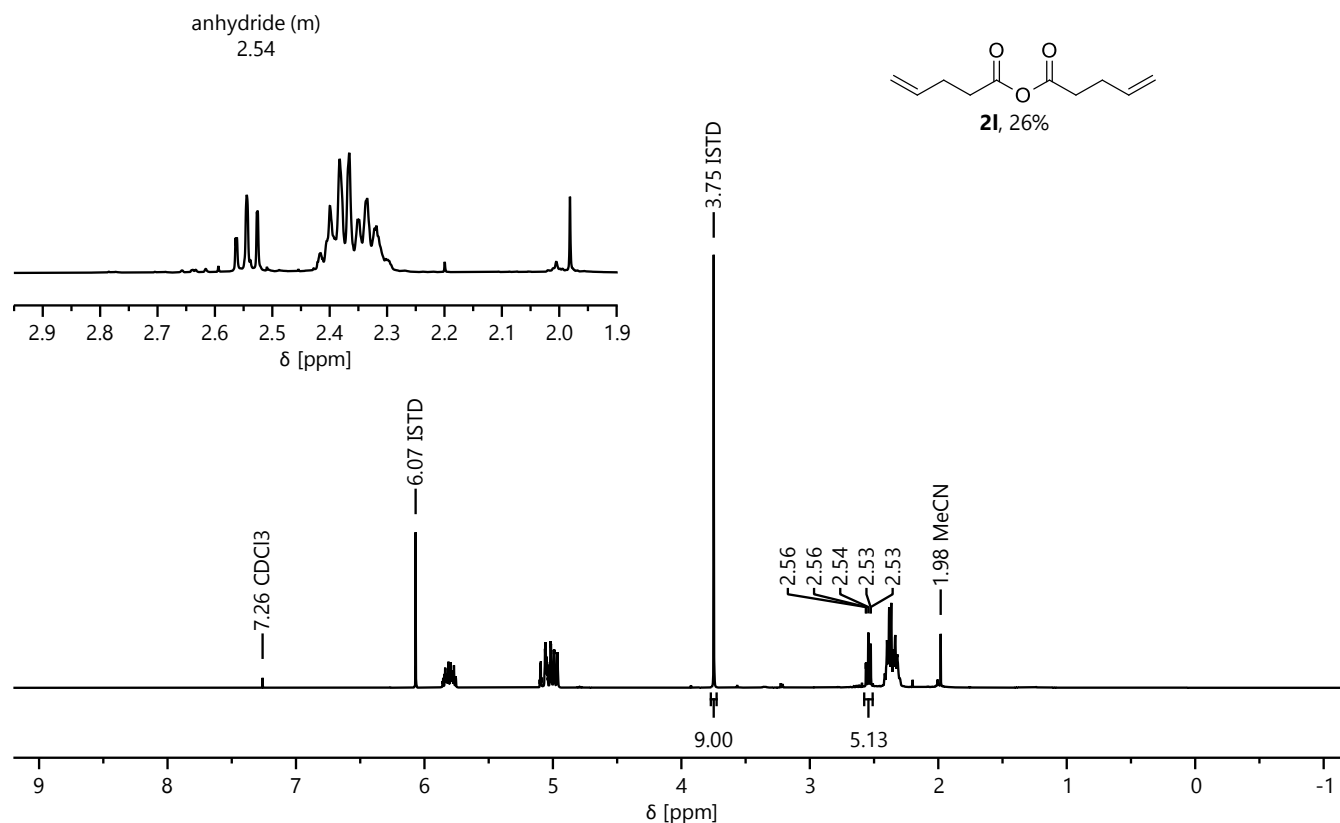


Figure S41: ¹H NMR of the crude mixture from electrolysis of 4-pentenoic acid (**1I**); 400 MHz, 296 K.

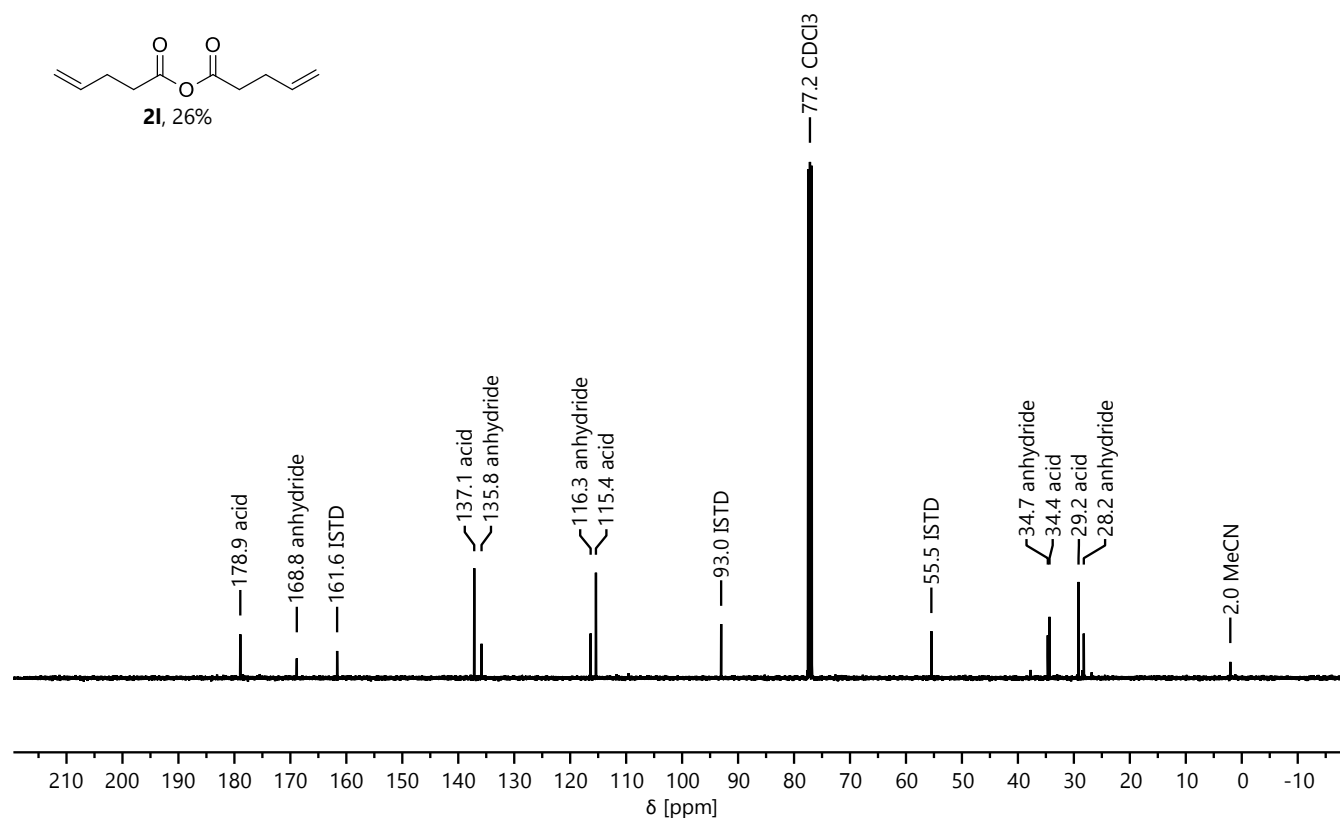


Figure S42: ^{13}C NMR of the crude mixture from electrolysis of 4-pentenoic acid (**1I**); 101 MHz, 296 K.

10-Undecenoic Anhydride (**2m**)

Following general procedure A, electrolysis of 10-undecenoic acid (**1m**, 99%, 465 mg, 2.5 mmol, 0.50 M) at 30 mA/cm² and 313 K with EMIMSCN (178 mg, 0.20 M) as supporting electrolyte in MeCN (5.0 mL) gave 10-undecenoic anhydride (**2m**) in 24% yield and 71% selectivity (34% conversion) after 1.1 *F* (ISTD: 37.6 mg 1,3,5-trimethoxybenzene (98.0%)).

HRMS (ESI) [*m/z*] calc'd for C₂₂H₃₈NaO₃⁺ [*M* + Na]⁺, 373.2713; found, 373.2716; deviation: +0.8 ppm.

^1H NMR (400 MHz, CDCl₃) δ 2.39 (t, *J* = 7.5 Hz, 4H) ppm; The remaining signals overlap with 10-undecenoic acid (**1m**).

The analytic data is in agreement with previously reported data.^[14]

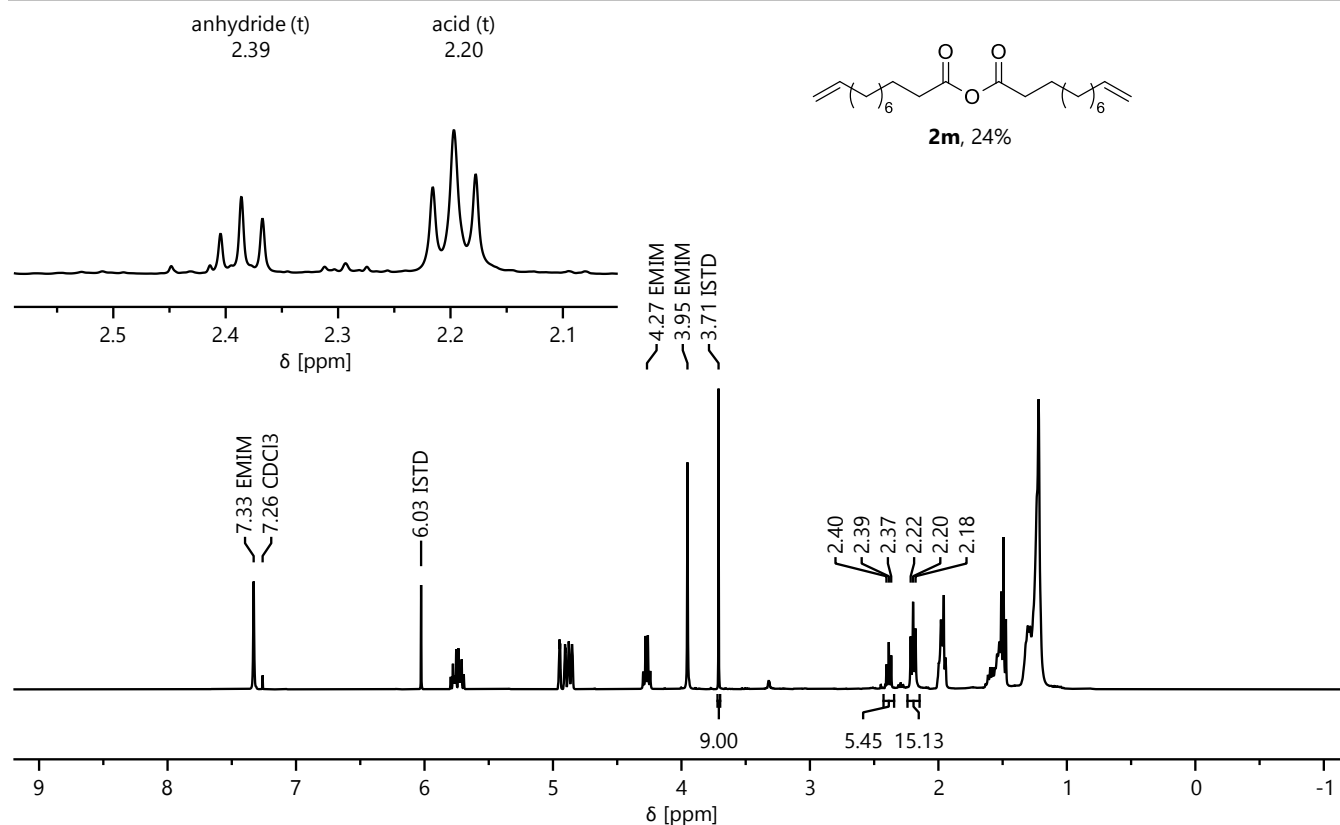


Figure S43: ^1H NMR of the crude mixture from electrolysis of 10-undecenoic acid (**1m**); 400 MHz, 296 K.

3-Bromopropanoic Anhydride (**2n**)

Following general procedure A, electrolysis of 3-bromopropanoic acid (**1n**, 97%, 552 mg, 3.5 mmol, 0.70 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 3-bromopropanoic anhydride (**2n**) in 29% yield and 74% selectivity (39% conversion) after 1.1 *F* (ISTD: 41.0 mg 1,3,5-trimethoxybenzene (98.0%)).

^1H NMR The signals overlap partially with 3-bromopropanoic acid (**1n**).

^{13}C NMR (101 MHz, CDCl_3) δ 166.0, 38.6, 24.2 ppm.

The analytic data is in agreement with previously reported data.^[15]

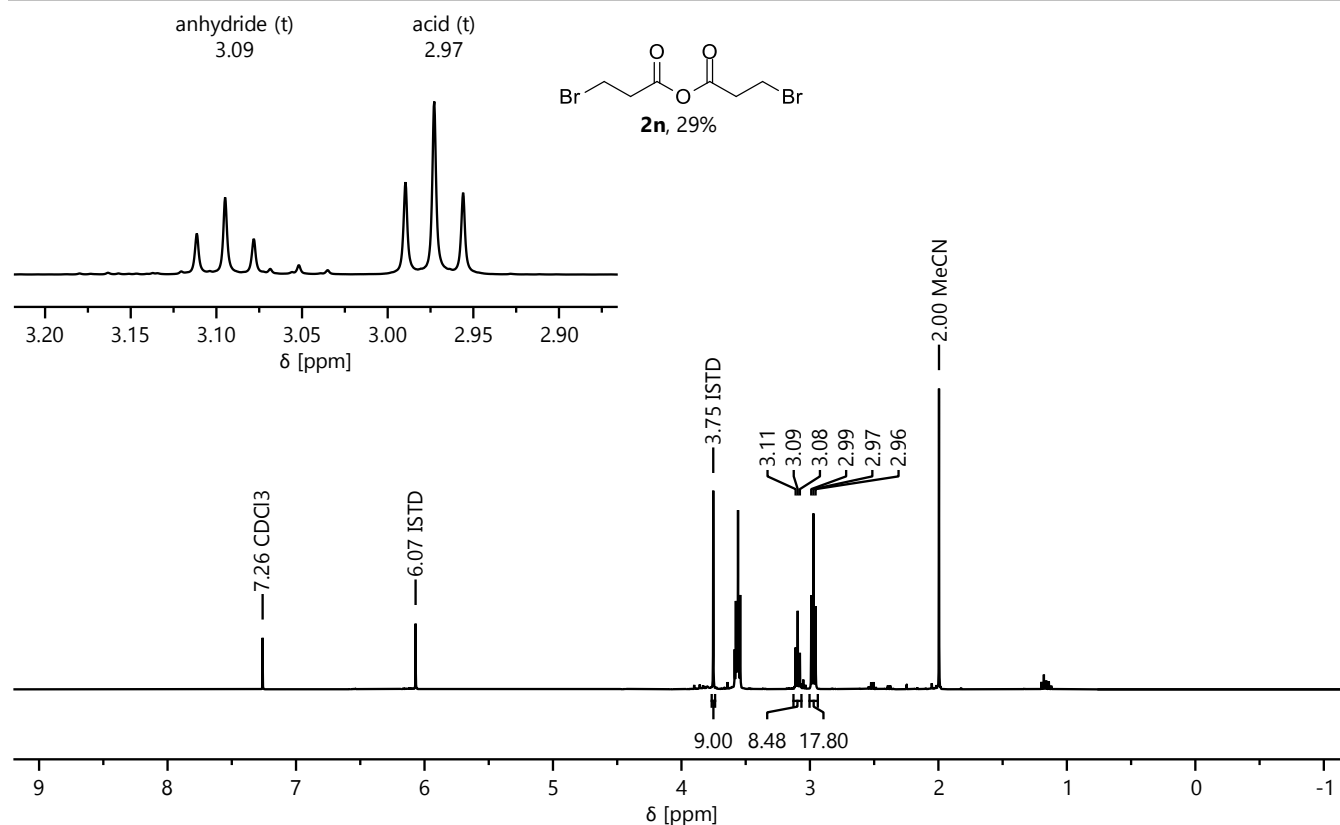


Figure S44: ^1H NMR of the crude mixture from electrolysis of 3-bromopropanoic acid (**1n**); 400 MHz, 296 K.

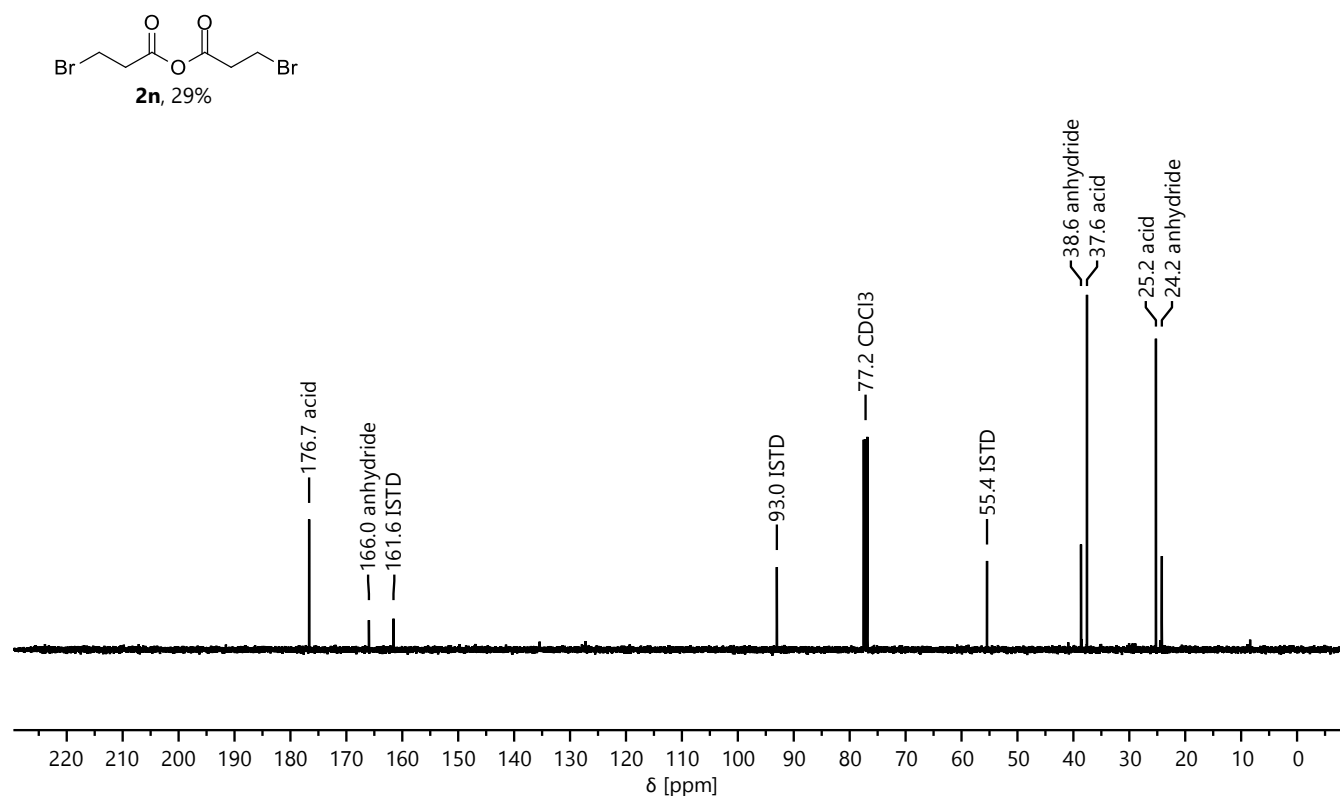


Figure S45: ^{13}C NMR of the crude mixture from electrolysis of 3-bromopropanoic acid (**1n**); 101 MHz, 296 K.

11-Bromoundecanoic Anhydride (2o)

Following general procedure A, electrolysis of 11-bromoundecanoic acid (**1o**, 93%, 1426 mg, 5.0 mmol, 1.0 M) at 50 mA/cm² and 313 K with EMIMSCN (89 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 11-bromoundecanoic anhydride (**2o**) in 39% yield and 92% selectivity (43% conversion) after 1.1 *F* (ISTD: 31.9 mg 1,3,5-trimethoxybenzene (98.0%)). For analytic purposes, the residual electrolyte was filtered through a mixture of silica (ca. 4 g) and K₂CO₃ (ca. 1 g) on a p4 frit. The silica layer was rinsed with 60 mL cyclohexane, and the filtrate was washed with cold aqueous K₂CO₃ (0.1 M, 20 mL). The organic phase was dried with MgSO₄ and the solvent was evaporated to give 465 mg of a mixture of 11-bromoundecanoic anhydride (**2o**, 95%) and 1,3,5-trimethoxybenzene (5%). The isolated amount of 11-bromoundecanoic anhydride (**2o**) corresponds to 34% yield.

HRMS (ESI) [*m/z*] calc'd for C₂₂H₄₀Br₂⁷⁹NaO₃⁺ [M + Na]⁺, 533.1236; found, 533.1239; deviation: +0.6 ppm.

¹H NMR (400 MHz, CDCl₃) δ 3.39 (t, *J* = 6.9 Hz, 4H), 2.43 (t, *J* = 7.4 Hz, 4H), 1.84 (dt, *J* = 14.5, 6.9 Hz, 4H), 1.64 (dt, *J* = 14.5, 7.4 Hz, 4H), 1.44 – 1.25 (m, 24H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ 169.7, 35.4, 34.1, 32.9, 29.4, 29.3, 29.2, 28.9, 28.8, 28.2, 24.3 ppm.

No spectroscopic data for this compound has been reported before.

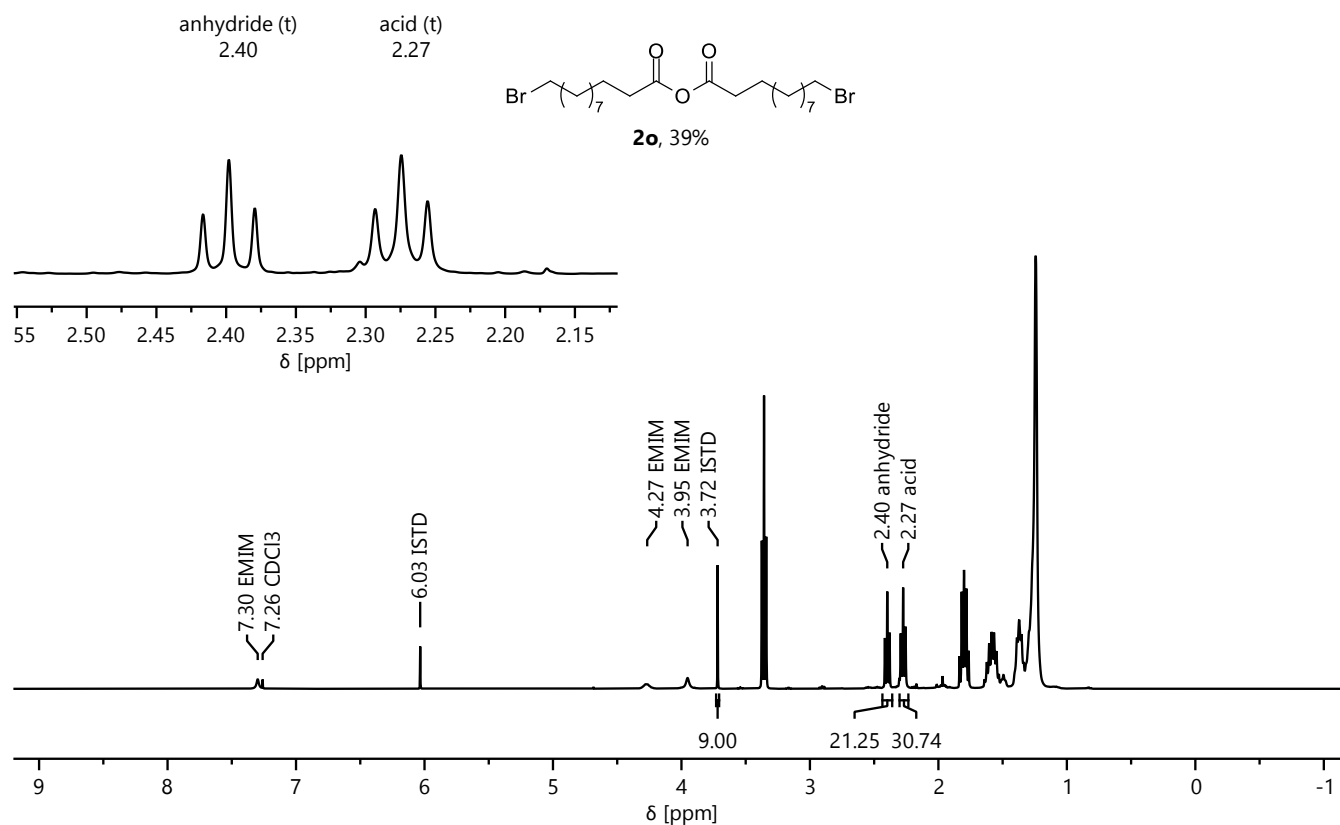
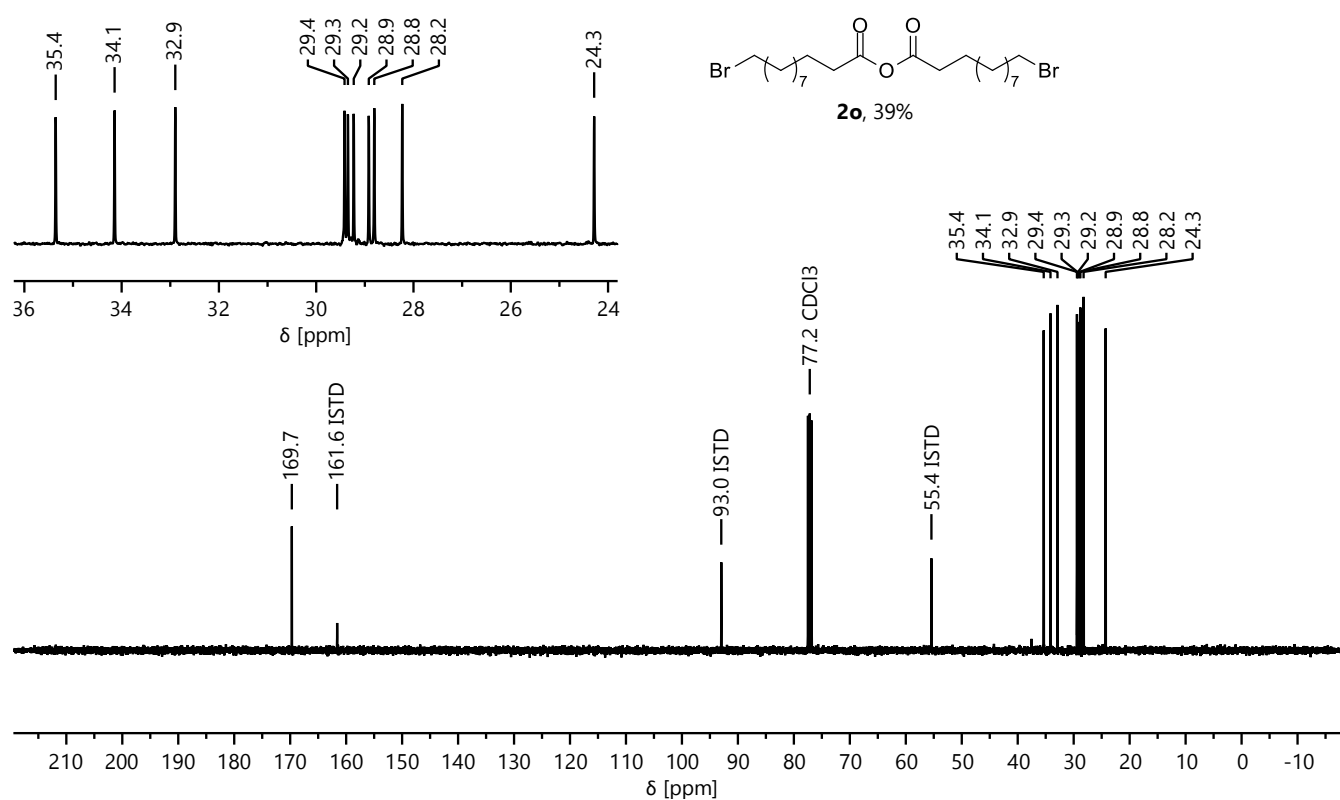
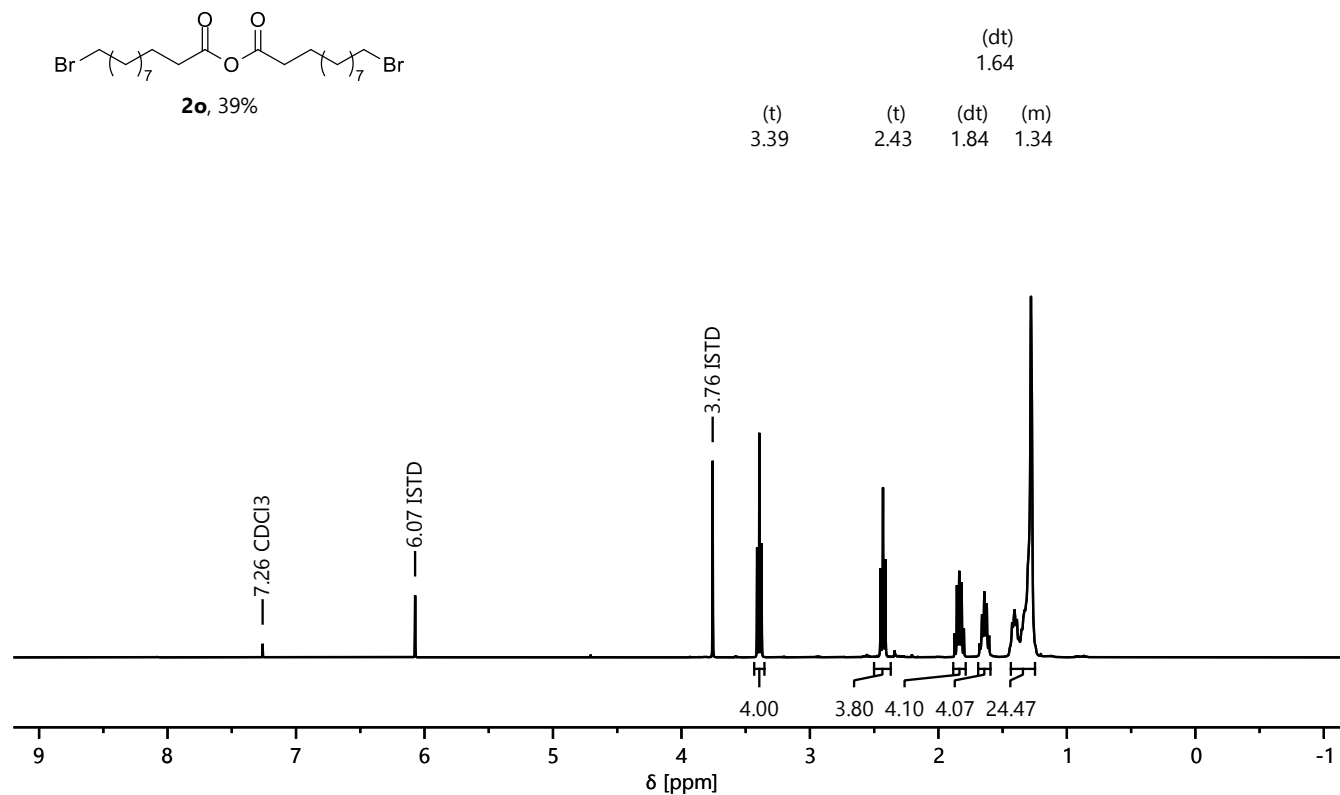


Figure S46: ¹H NMR of the crude mixture from electrolysis of 11-bromoundecanoic acid (**1o**); 400 MHz, 296 K.



(*S*)-2-Chloropropanoic Anhydride (2p)

Following general procedure A, electrolysis of (*S*)-2-chloropropanoic acid (**1p**, 100%, 380 mg, 3.50 mmol, 0.70 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave (*S*)-2-chloropropanoic anhydride (**2p**) in 43% yield and 84% selectivity (51% conversion) after 1.1 *F* (ISTD: 39.0 mg 1,3,5-trimethoxybenzene (98.0%)).

¹H NMR The signals overlap partially with (*S*)-2-chloropropanoic acid (**1p**).

¹³C NMR (151 MHz, CDCl₃) δ 164.5, 52.3, 20.8 ppm.

The analytic data is in agreement with previously reported data.^[16]

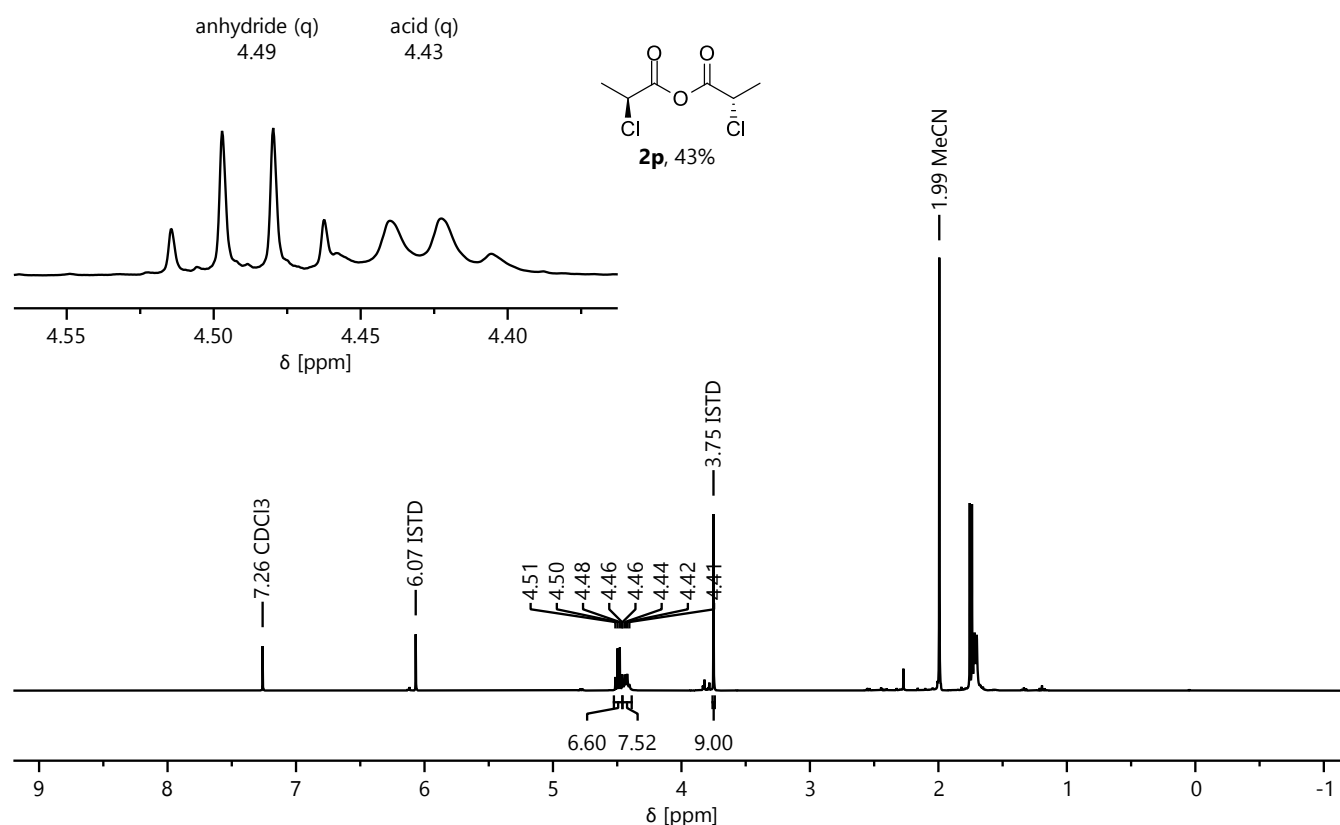


Figure S49: ¹H NMR of the crude mixture from electrolysis of (*S*)-2-chloropropanoic acid (**1p**); 400 MHz, 296 K.

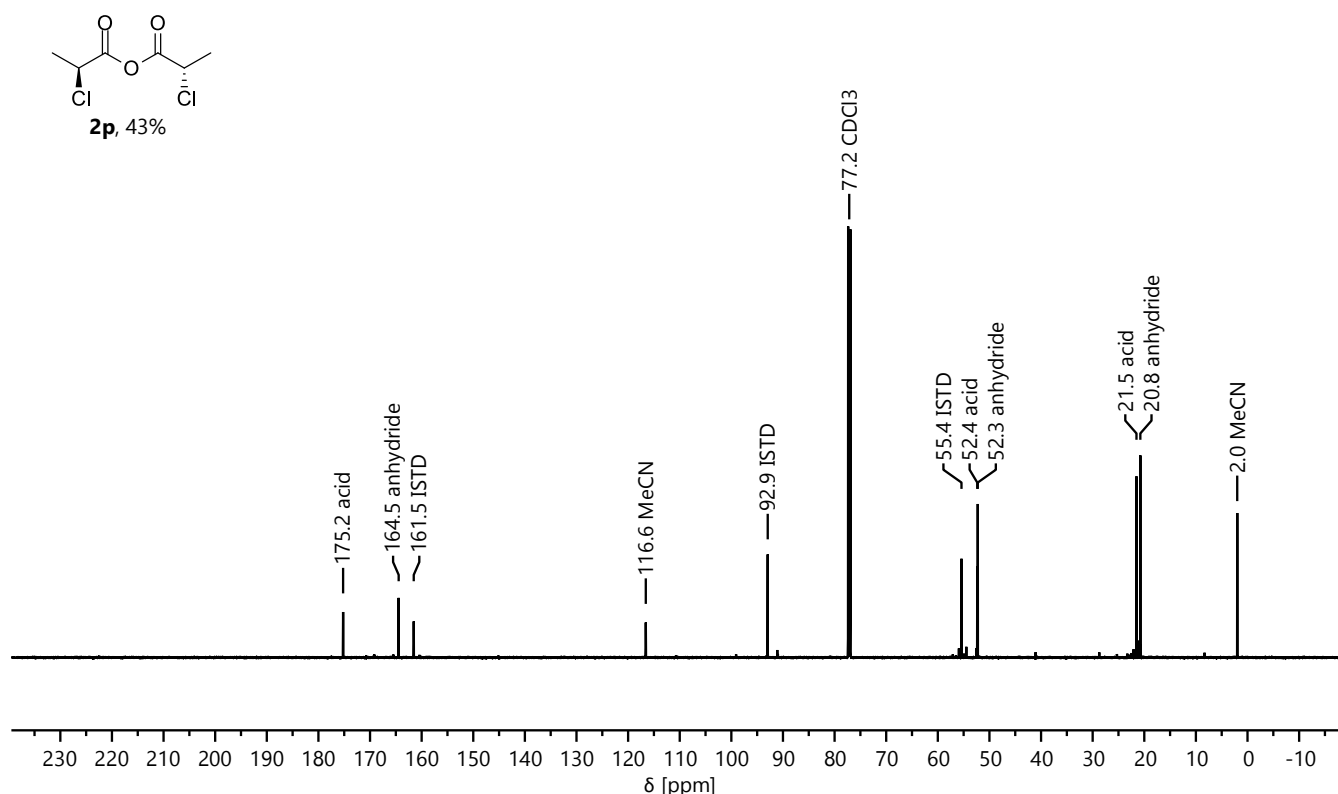


Figure S50: ¹³C NMR of the crude mixture from electrolysis of (S)-2-chloropropanoic acid (**1p**); 151 MHz, 294 K.

1-Methylcyclohexanecarboxylic Anhydride (**2q**)

Following general procedure A, electrolysis of 1-methylcyclohexanecarboxylic acid (**1q**, 99%, 718 mg, 5.00 mmol, 1.0 M) at 50 mA/cm² with EMIMSCN (89 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 1-methylcyclohexanecarboxylic anhydride (**2q**) in 34% yield after 1.1 *F* (ISTD: 40.5 mg 1,3,5-trimethoxybenzene (98.0%)). The yield was determined via inverse-gated ¹³C NMR because no isolated signal in the ¹H NMR spectrum was available. For analytic purposes, the residual electrolyte was filtered through a mixture of silica (ca. 4 g) and K₂CO₃ (ca. 1 g) on a p4 frit. The silica layer was rinsed with 60 mL cyclohexane, and the filtrate was washed with cold aqueous K₂CO₃ (0.1 M, 20 mL). The organic phase was dried with MgSO₄ and the solvent was evaporated to give 262 mg of a mixture of 1-methylcyclohexanecarboxylic anhydride (**2q**, 87%) and 1,3,5-trimethoxybenzene (13%). The isolated amount of 1-methylcyclohexanecarboxylic anhydride (**2q**) corresponds to 34% yield.

GCMS (EI) *t*_R = 12.720 min, [m/z] 125 (22%), 97 (100%), 55 (34%), 41 (11%).

HRMS (ESI) [m/z] calc'd for C₁₆H₂₆NaO₃⁺ [M + Na]⁺, 289.1774; found, 289.1766; deviation: -2.8 ppm.

¹H NMR (400 MHz, CDCl₃) δ 2.08 – 1.97 (m, 4H), 1.62 – 1.41 (m, 10H), 1.33 – 1.25 (m, 6H), 1.23 (s, 6H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ 173.5, 44.8, 35.3, 25.7, 25.6, 23.1 ppm.

No spectroscopic data for this compound has been reported before.

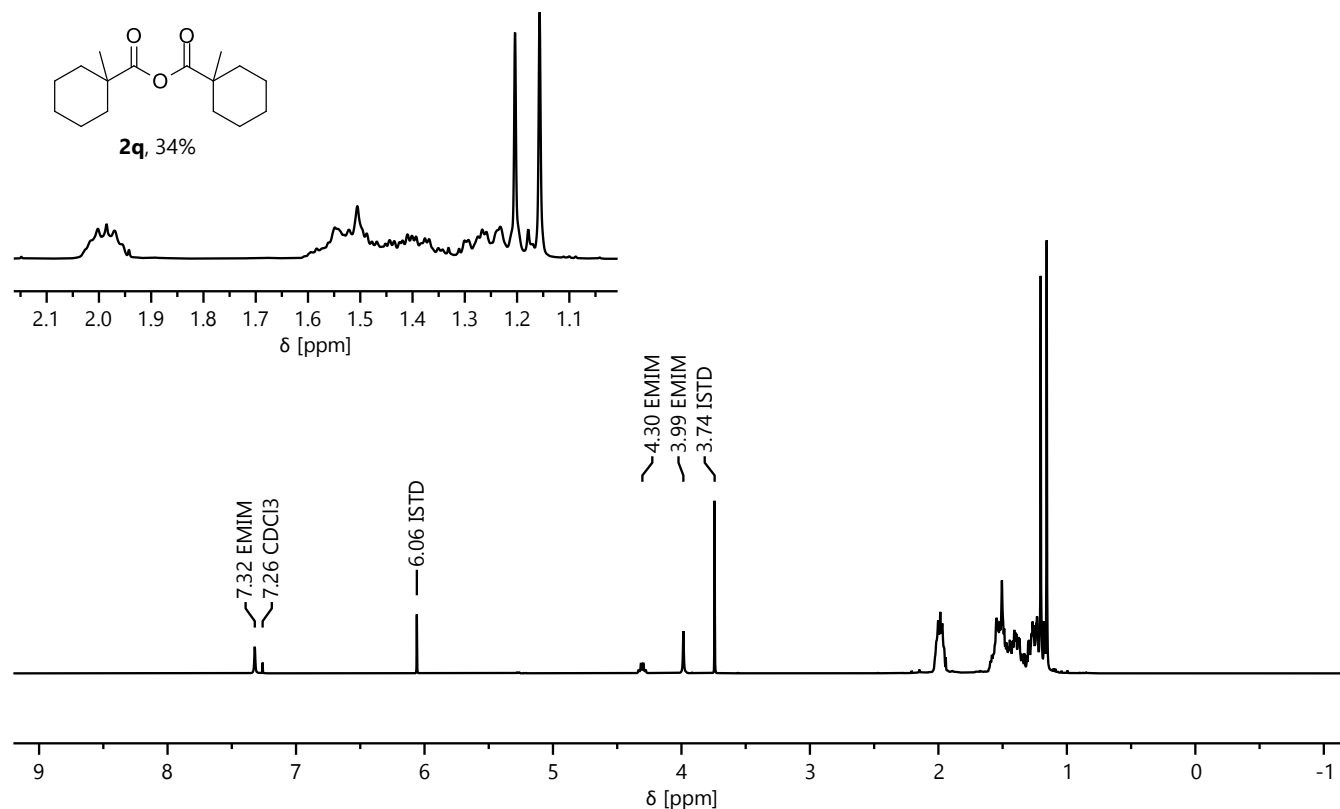


Figure S51: ¹H NMR of the crude mixture from electrolysis of 1-methylcyclohexanecarboxylic acid (**1q**); 400 MHz, 297 K.

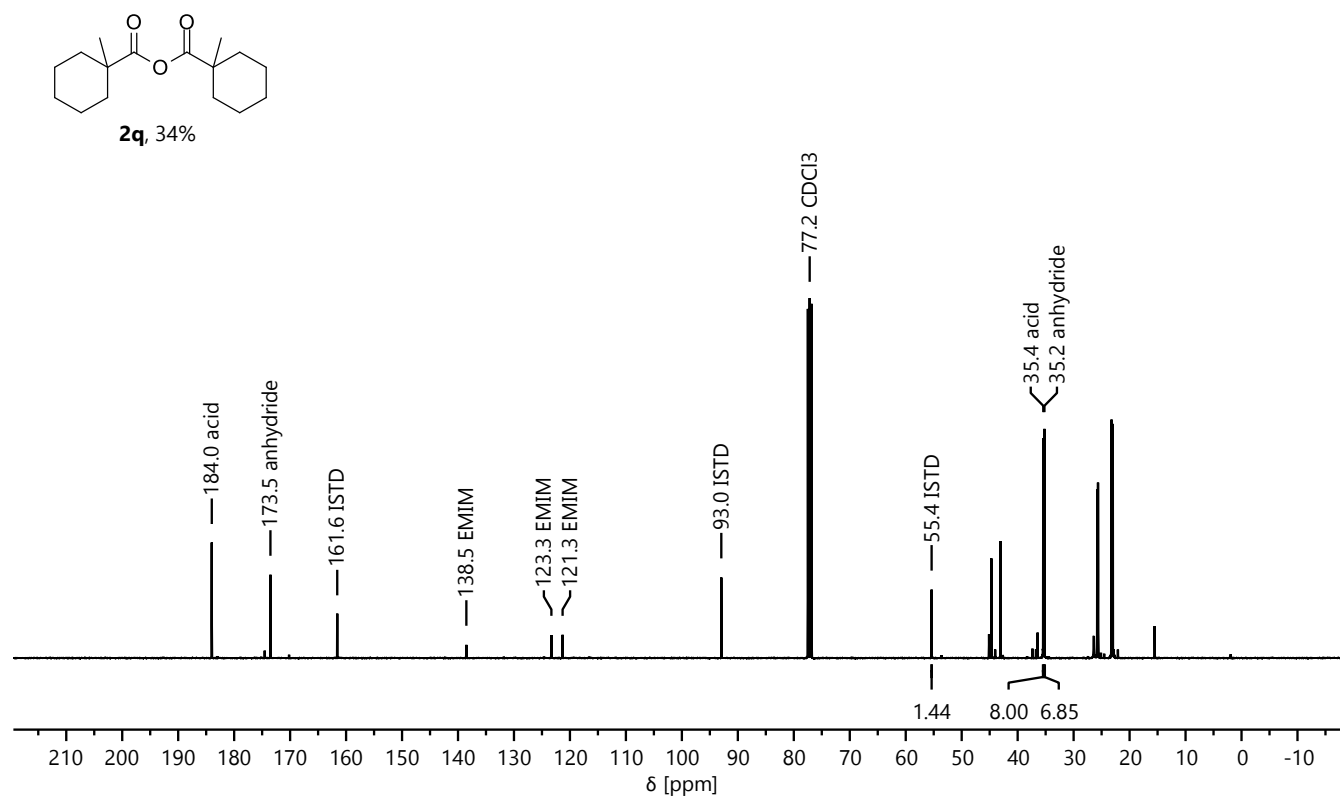


Figure S52: Inverse-gated ¹³C NMR of the crude mixture from electrolysis of 1-methylcyclohexanecarboxylic acid (**1q**); 101 MHz, 296 K.

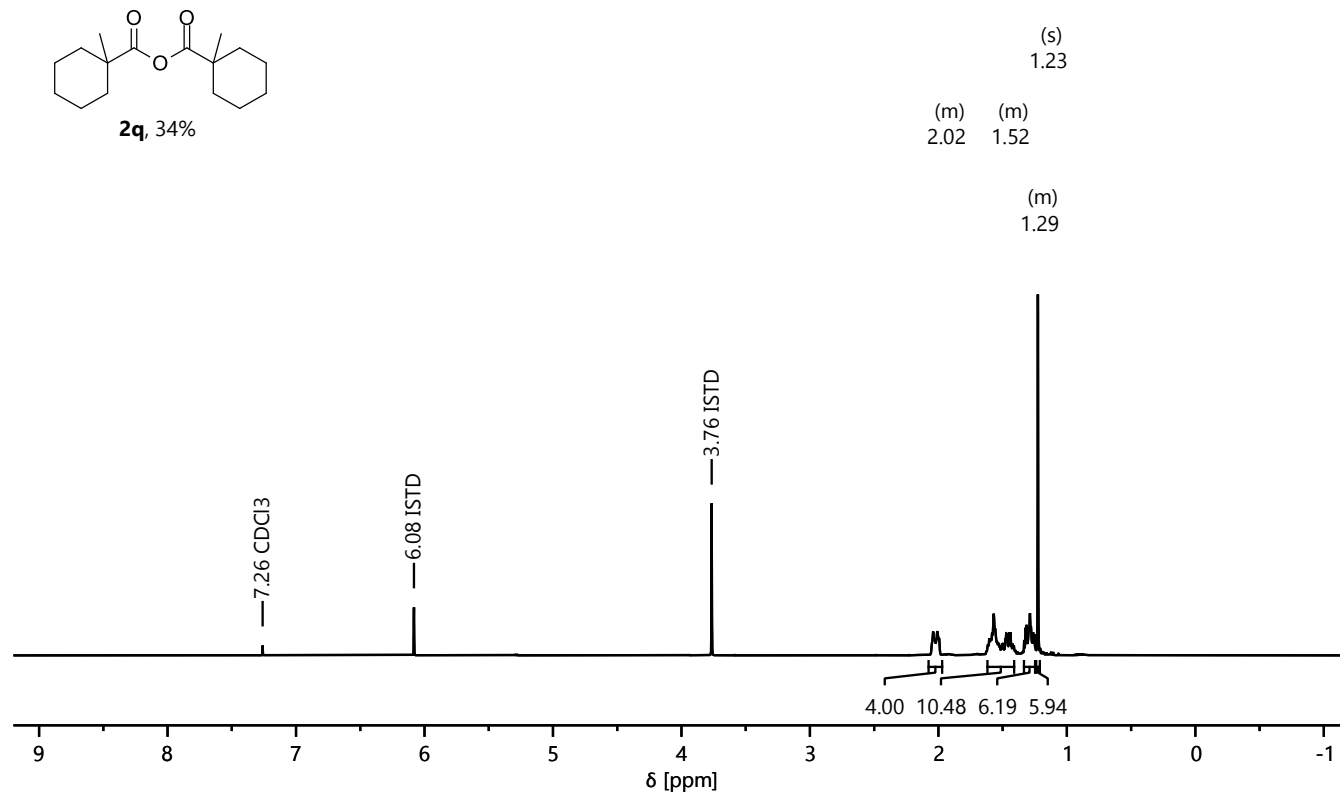


Figure S53: ¹H NMR of 1-methylcyclohexanecarboxylic anhydride (**2q**) after filtration; 400 MHz, 298 K.

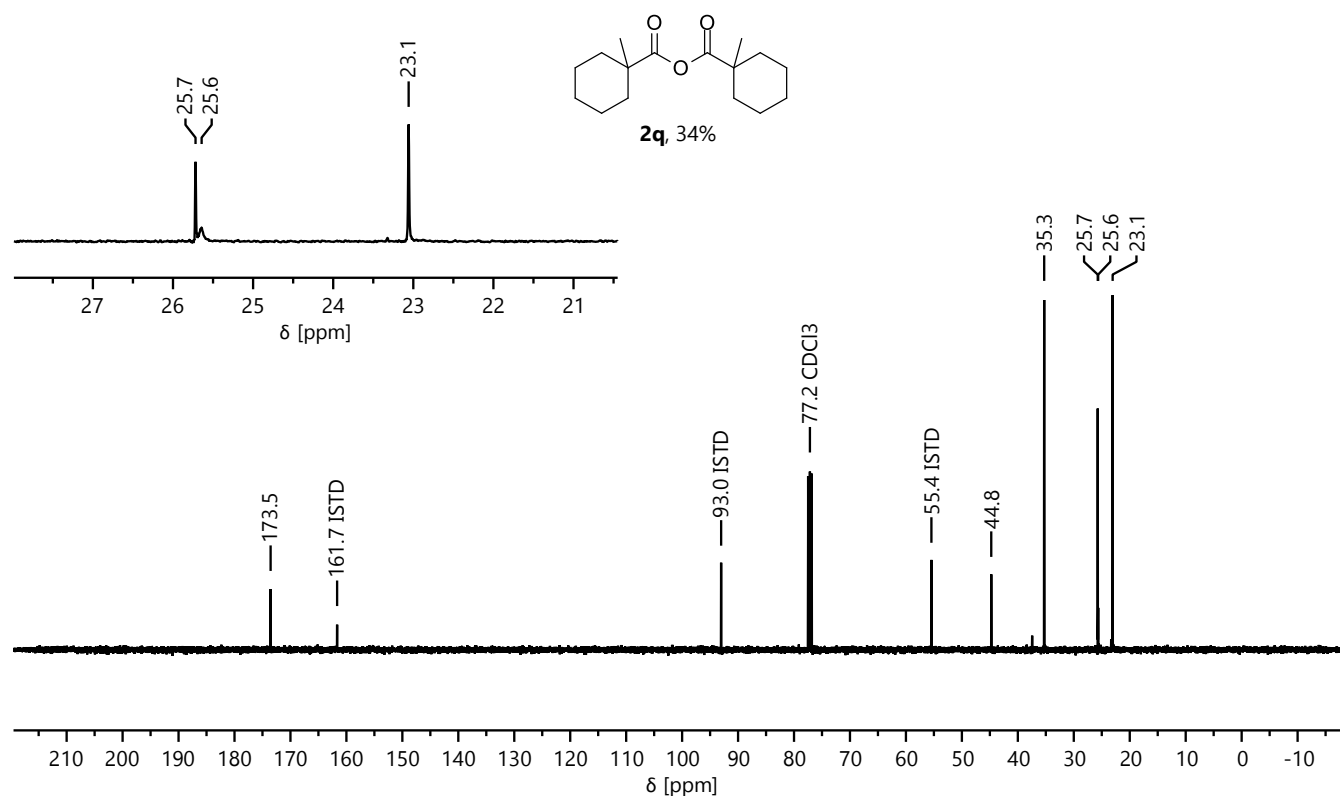


Figure S54: ¹³C NMR of 1-methylcyclohexanecarboxylic anhydride (**2q**) after filtration; 101 MHz, 298 K.

Adamantane-1-carboxylic Anhydride (2r)

Following general procedure A, electrolysis of adamantane-1-carboxylic acid (**1r**, 98.0%, 460 mg, 2.5 mmol, 0.50 M) at 30 mA/cm² and 313 K with EMINSCN (178 mg, 0.20 M) as supporting electrolyte in MeCN (5.0 mL) gave adamantane-1-carboxylic anhydride (**2r**) in 28% yield after 1.1 *F* (ISTD: 35.6 mg 1,3,5-trimethoxybenzene (98.0%)). The yield was determined via inverse-gated ¹³C NMR because no isolated signal in the ¹H NMR spectrum was available.

¹H NMR The signals overlap with adamantane-1-carboxylic acid (**1r**).

¹³C NMR (101 MHz, CDCl₃) δ 173.4, 42.2, 38.2, 36.5, 27.6 ppm.

The analytic data is in agreement with previously reported data.^[9]

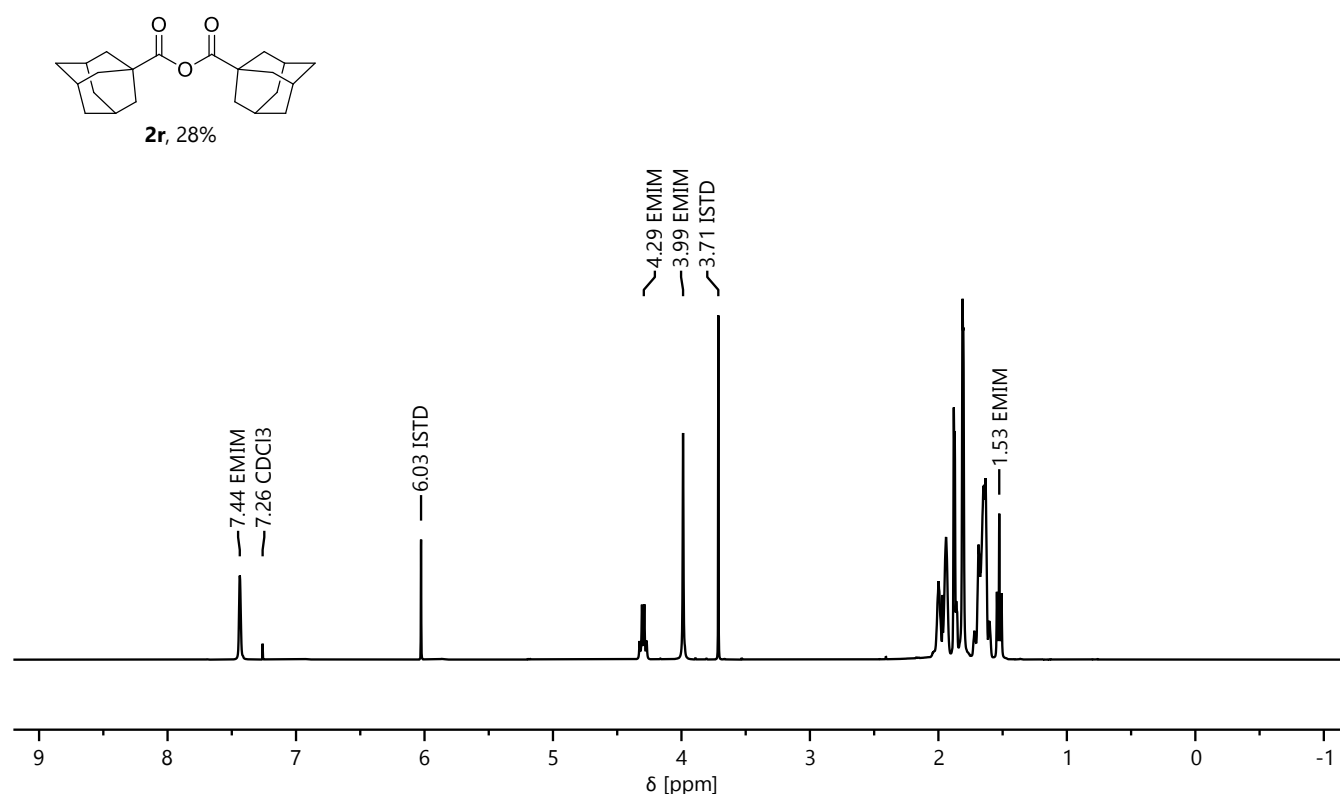


Figure S55: ¹H NMR of the crude mixture from electrolysis of adamantane-1-carboxylic acid (**1r**); 400 MHz, 296 K.

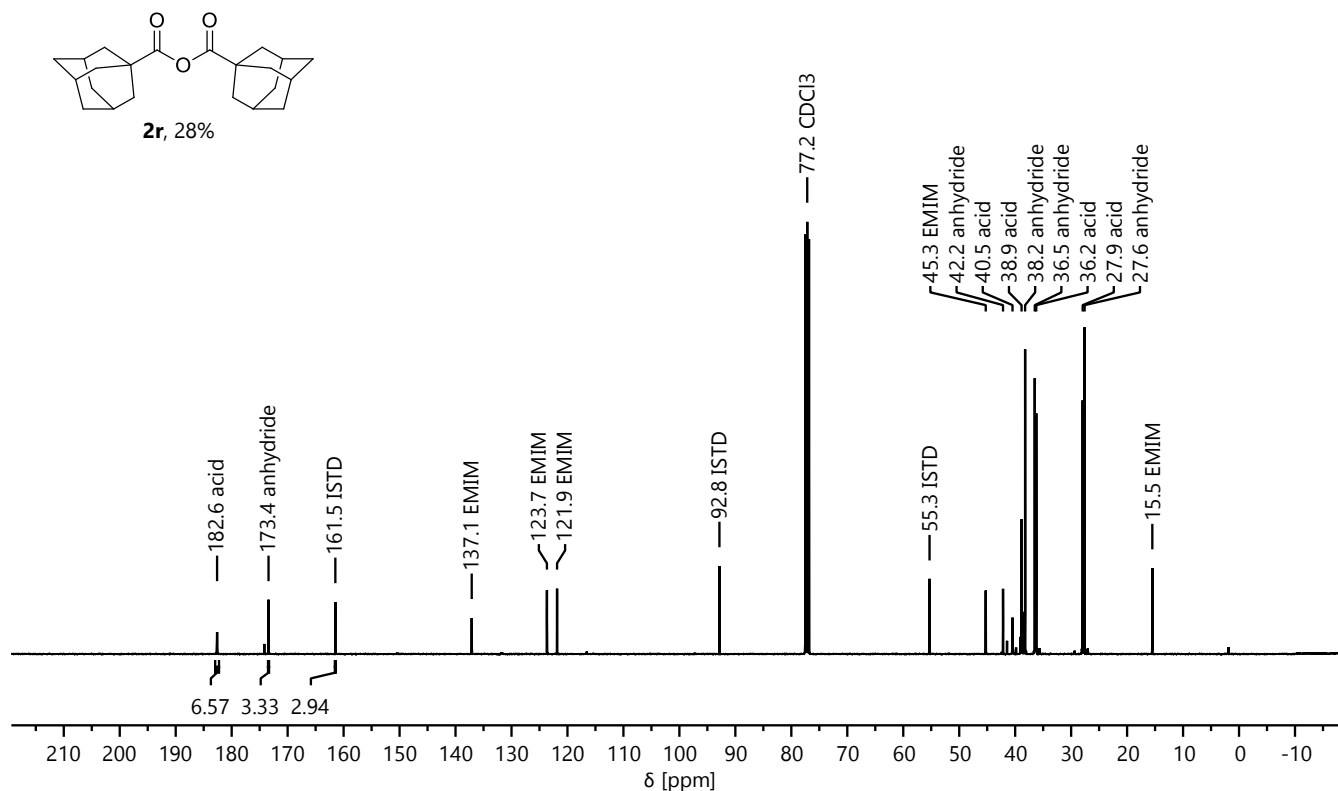


Figure S56: Inverse-gated ^{13}C NMR of the crude mixture from electrolysis of adamantane-1-carboxylic acid (**1r**); 101 MHz, 296 K.

Levulinic Anhydride (**2s**)

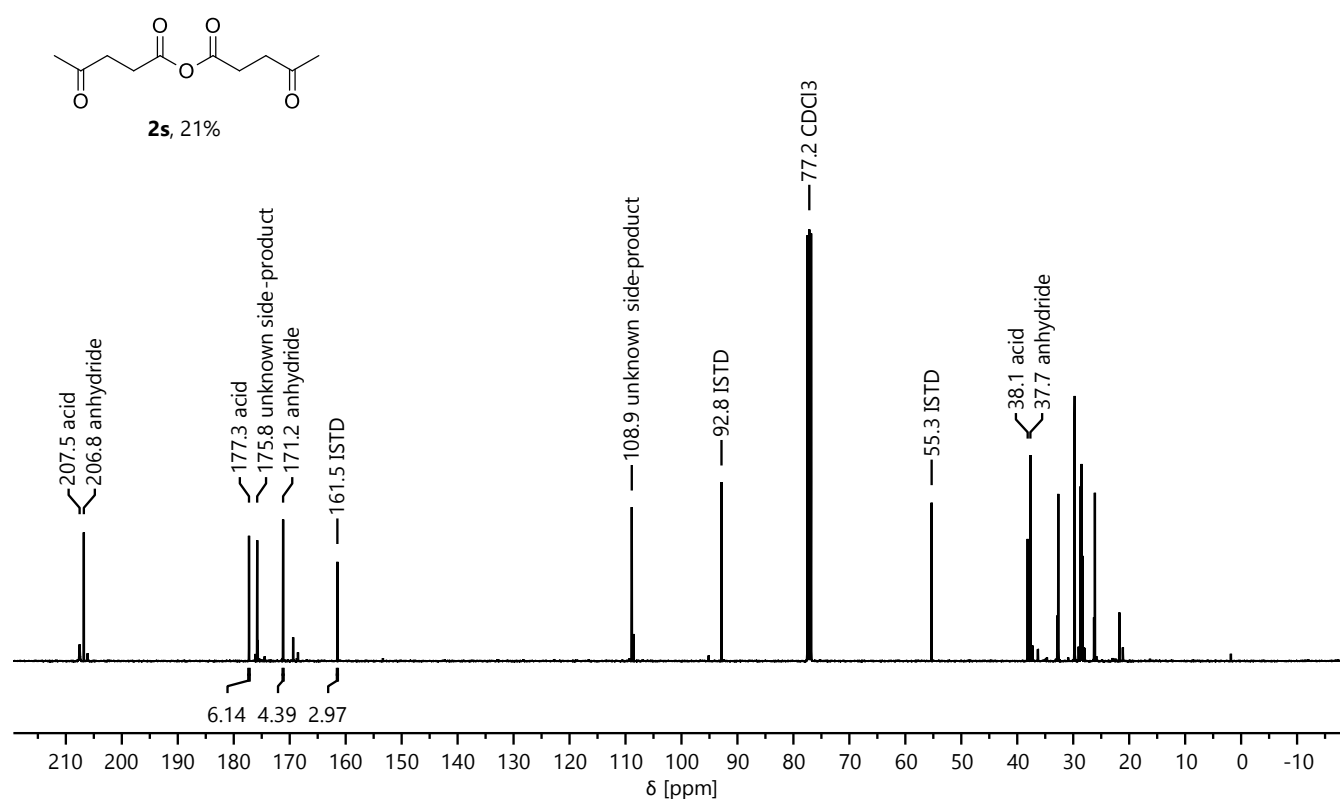
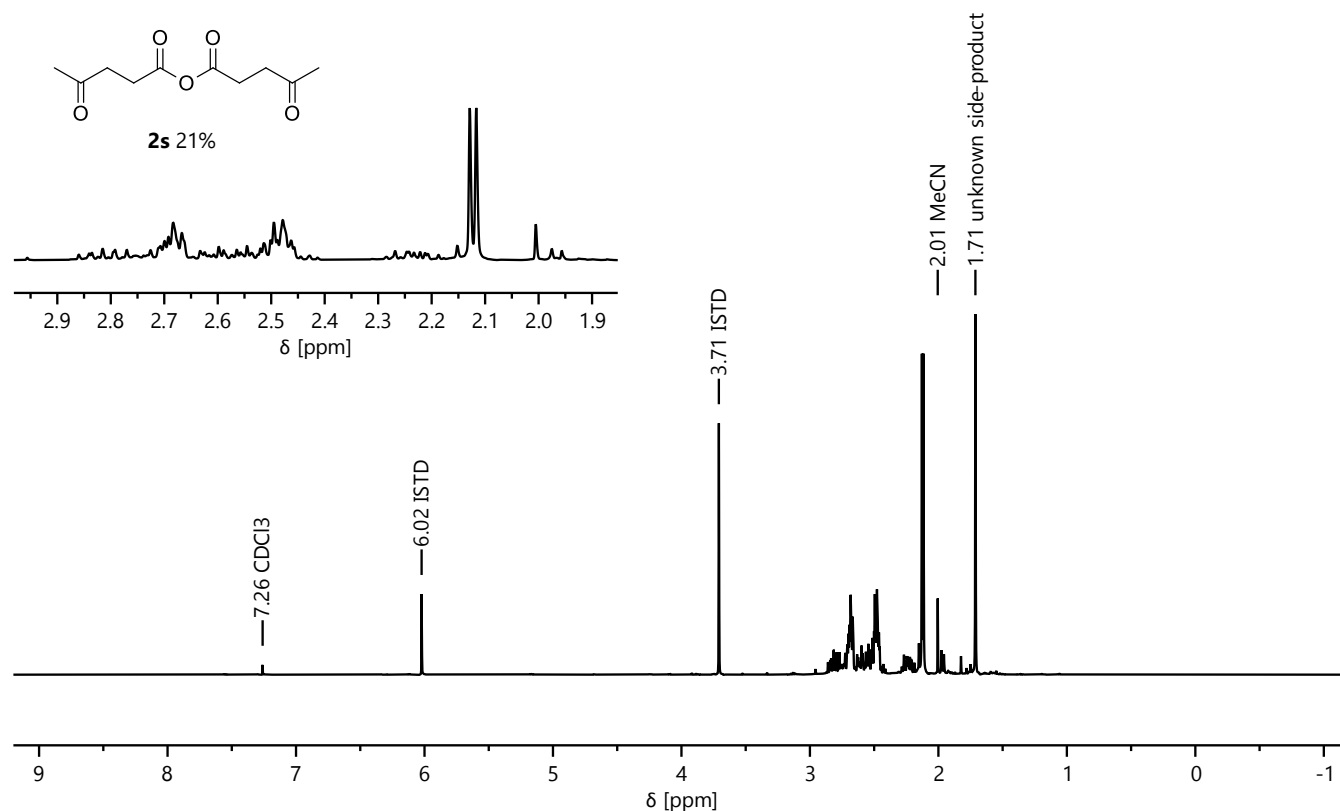
Following general procedure A, electrolysis of levulinic acid (**1s**, 98%, 0.37 mL, 3.5 mmol, 0.71 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave levulinic anhydride (**2s**) in 21% yield after 1.3 F (ISTD: 28.8 mg 1,3,5-trimethoxybenzene (98.0%)). The yield was determined via inverse-gated ^{13}C NMR because no isolated signal in the ^1H NMR spectrum was available. An unidentified side-product is visible in NMR.

GCMS (EI) t_{R} = 11.067 min, $[m/z]$ 99 (100%), 71 (14%), 43 (57%).

^1H NMR The signals overlap with levulinic acid (**1s**) and an unidentified side-product.

^{13}C NMR (101 MHz, CDCl_3) δ 206.8, 171.2, 37.7 ppm; The signals of the remaining methylene and methyl groups cannot be assigned unambiguously.

The analytic data is in agreement with previously reported data.^[17]



3-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylpropanoic Anhydride (2t**)**

Following general procedure A, electrolysis of 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanoic acid (**1t**, 100%, 818 mg, 3.5 mmol, 0.70 M) at 50 mA/cm² with KSCN (121 mg, 0.25 M) as supporting electrolyte in MeCN (5.0 mL) gave 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanoic anhydride (**2t**) in 36% yield and 52% selectivity (70% conversion) after 1.1 *F* (ISTD: 62.3 mg 1,3,5-trimethoxybenzene (98.0%)). An unidentified substance is visible in the NMR spectra.

¹H NMR The signals overlap partially with 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanoic acid (**1t**) and an unidentified substance.

¹³C NMR (101 MHz, CDCl₃) δ 172.1, 70.4, 45.9, -4.8 ppm; The signals of the remaining carbon atoms cannot be assigned unambiguously.

HRMS (ESI) [*m/z*] calc'd for C₂₂H₄₆NaO₅Si₂⁺ [*M* + Na]⁺, 469.2776; found, 469.2799; deviation: +4.9 ppm.

No spectroscopic data for this compound has been reported before.

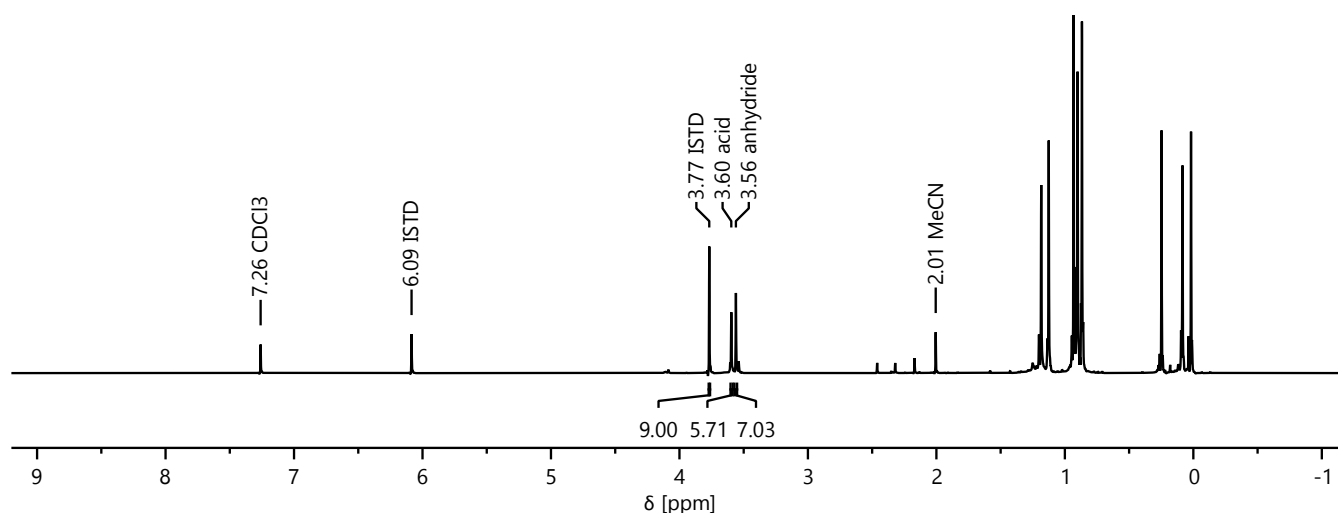
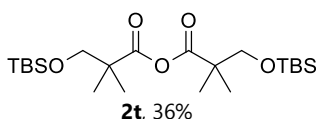
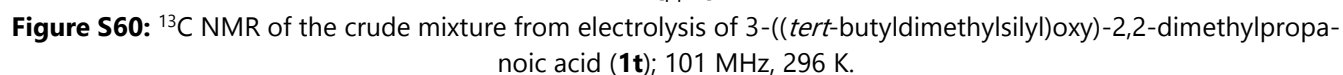


Figure S59: ¹H NMR of the crude mixture from electrolysis of 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanoic acid (**1t**); 400 MHz, 296 K.



Following general procedure A, electrolysis of 2-(2-fluorophenyl)acetic acid (**1u**, 98%, 330 mg, 2.1 mmol, 0.70 M) at 50 mA/cm² with KSCN (29 mg, 0.10 M) as supporting electrolyte in MeCN (3.0 mL) gave 2-(2-fluorophenyl)acetic anhydride (**2u**) in 17% yield and 38% selectivity (45% conversion) after 1.1 *F* (ISTD: 27.8 mg 1,3,5-trimethoxybenzene (98.0%)).

¹³C NMR (101 MHz, CDCl₃) δ 166.1, 161.1 (d, *J* = 247.2 Hz), 131.6 (d, *J* = 3.7 Hz), 129.8 (d, *J* = 8.2 Hz), 124.4 (d, *J* = 3.8 Hz), 119.5 (d, *J* = 15.8 Hz), 115.6 (d, *J* = 21.6 Hz), 35.4 (d, *J* = 3.1 Hz) ppm.

^{19}F { ^1H } NMR (377 MHz, CDCl_3) δ -118.0 ppm.

No spectroscopic data for this compound has been reported before.

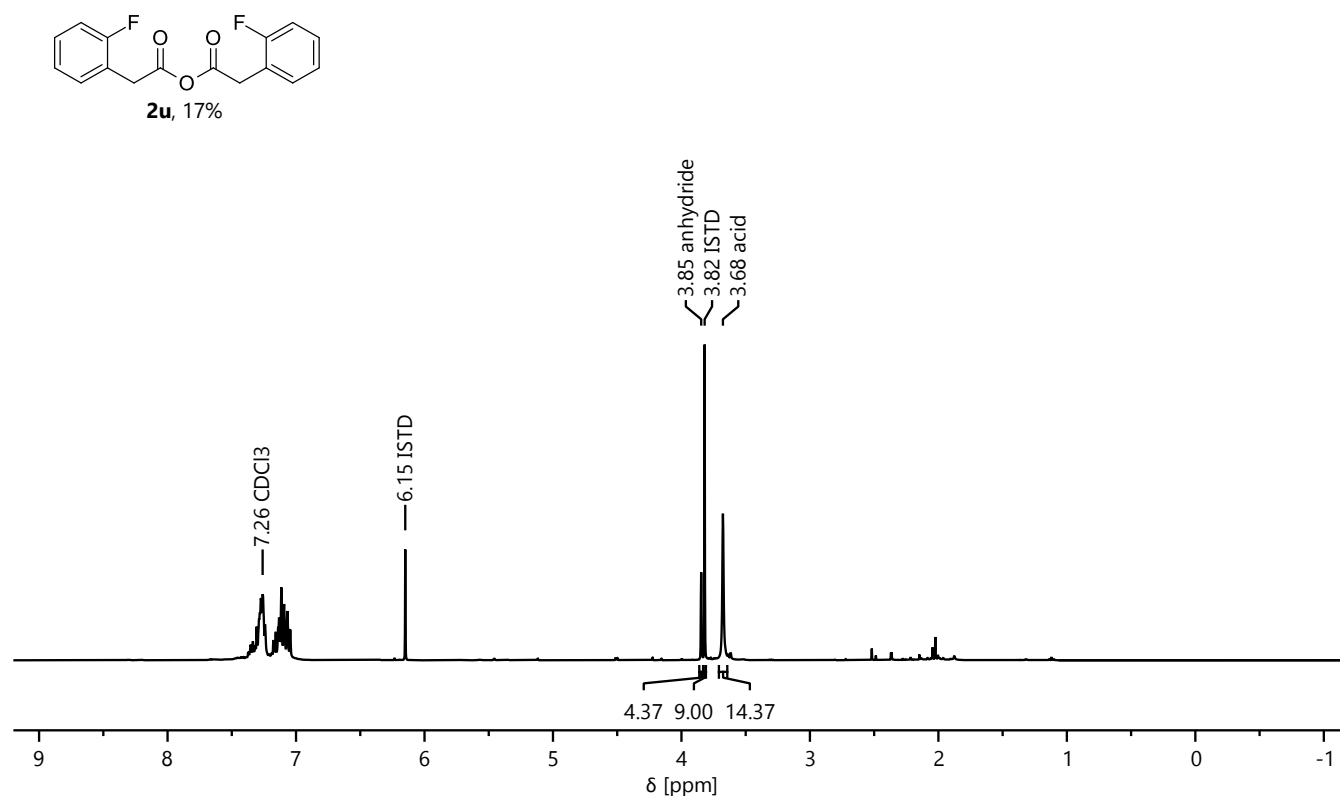


Figure S61: ^1H NMR of the crude mixture from electrolysis of 2-(2-fluorophenyl)acetic acid (**1u**); 400 MHz, 296 K.

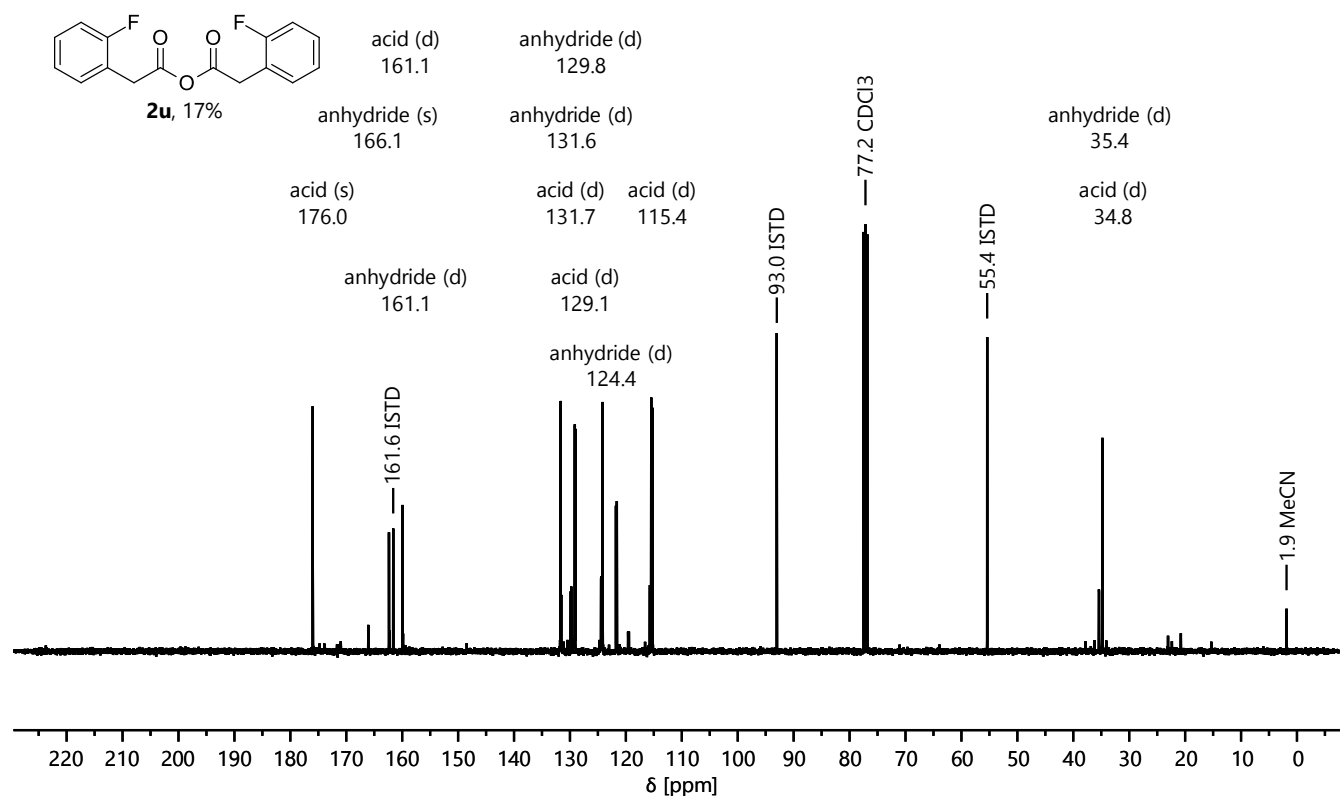


Figure S62: ^{13}C NMR of the crude mixture from electrolysis of 2-(2-fluorophenyl)acetic acid (**1u**); 101 MHz, 296 K.

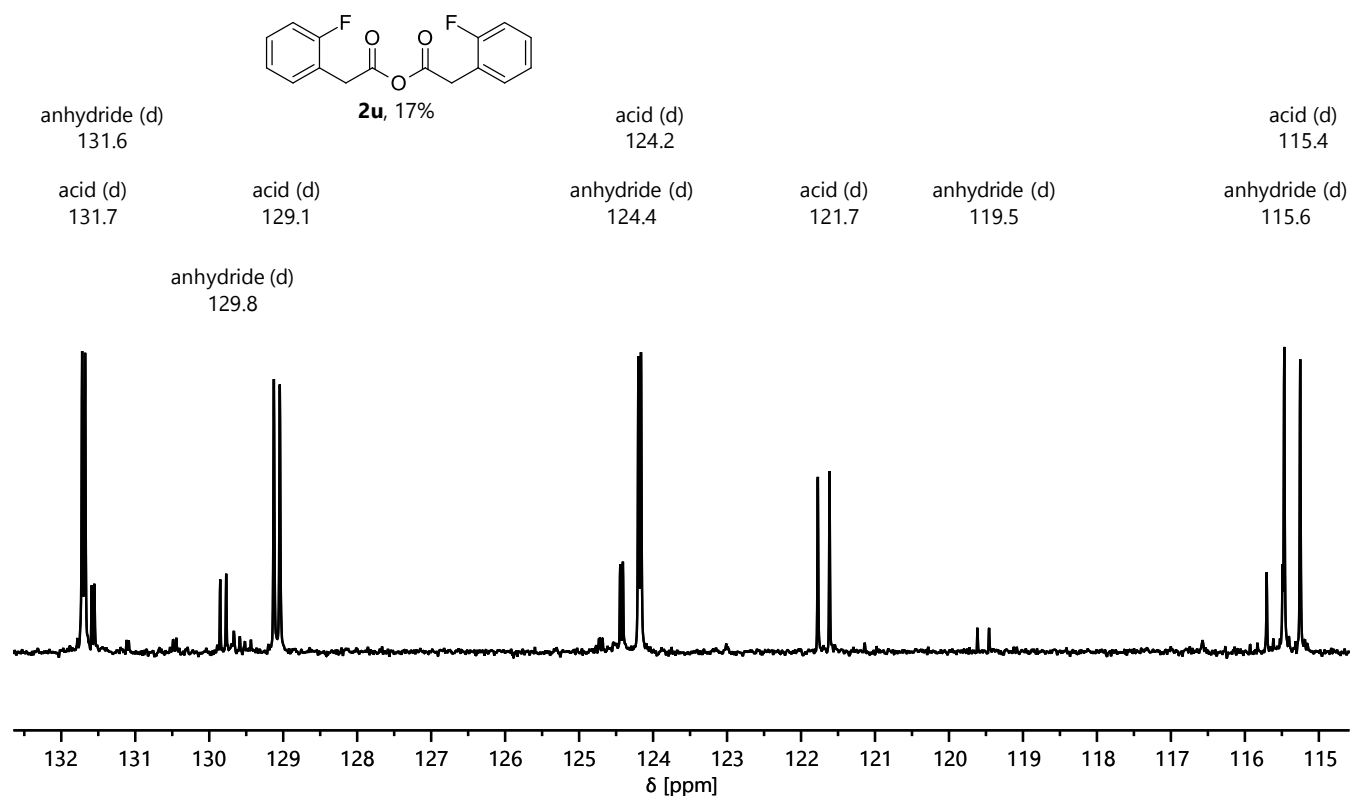


Figure S63: Enlarged aromatic region of the ^{13}C NMR of the crude mixture from electrolysis of 2-(2-fluorophenyl)acetic acid (**1u**); 101 MHz, 296 K.

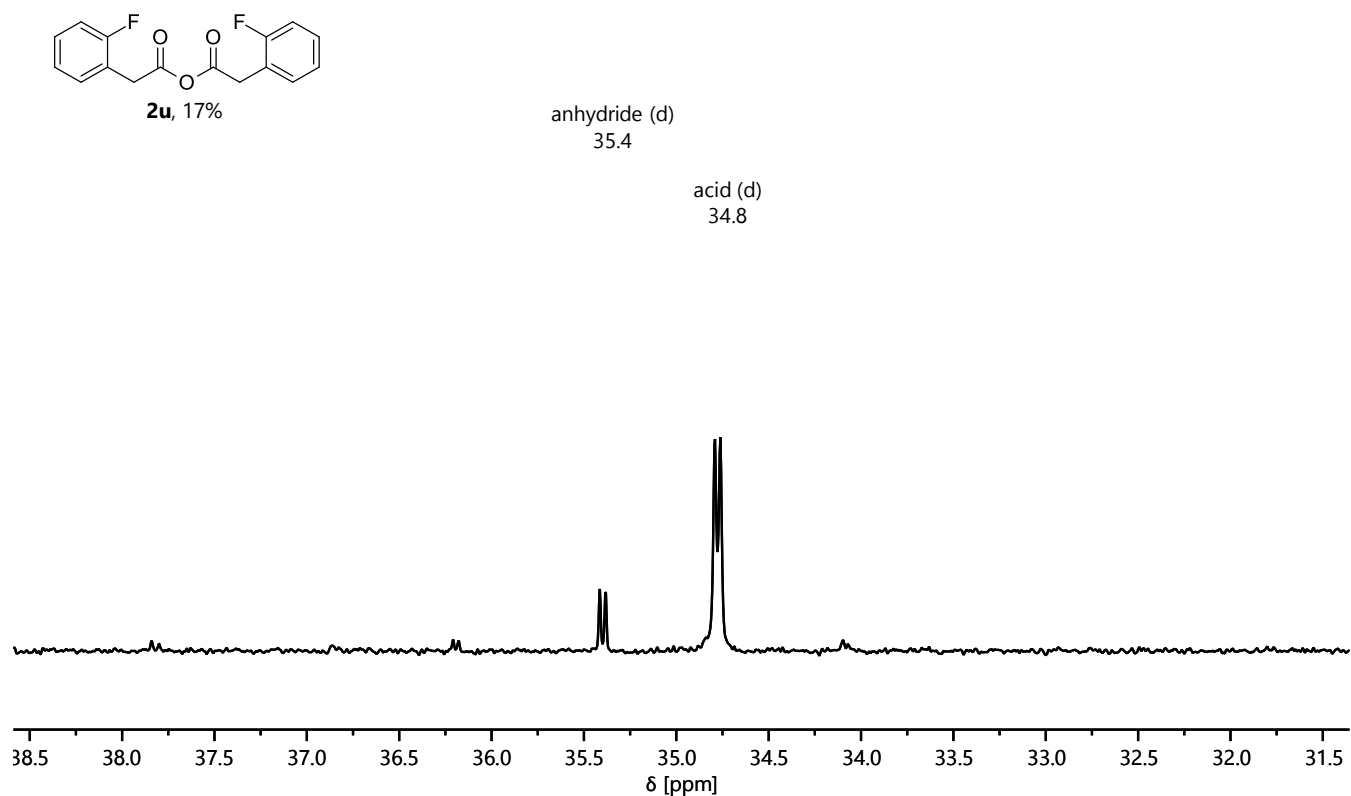


Figure S64: Enlarged aliphatic region of the ^{13}C NMR of the crude mixture from electrolysis of 2-(2-fluorophenyl)acetic acid (**1u**); 101 MHz, 296 K.

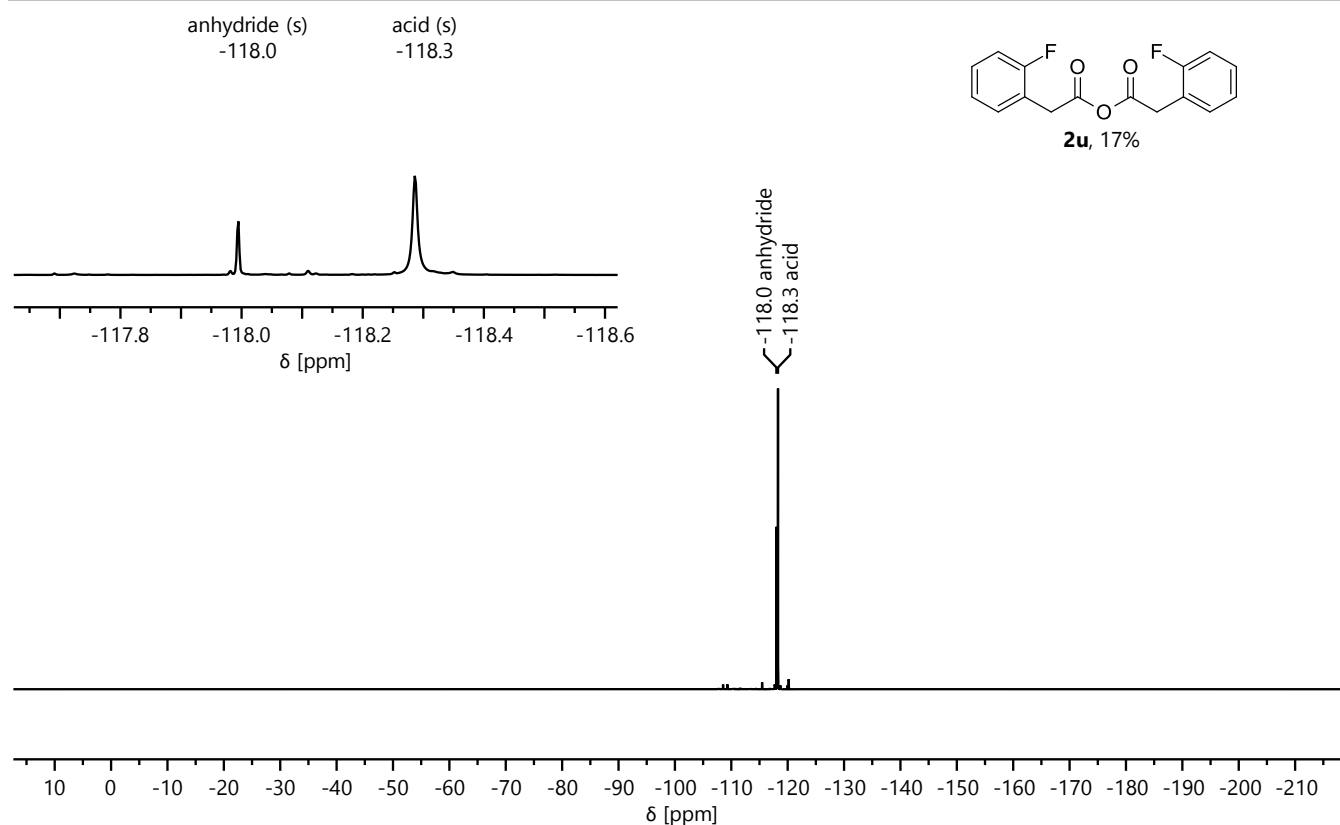


Figure S65: ^{19}F $\{^1\text{H}\}$ NMR of the crude mixture from electrolysis of 2-(2-fluorophenyl)acetic acid (**1u**); 377 MHz, 296 K.

2-(4-(Trifluoromethyl)phenyl)acetic Anhydride (**2v**)

Following general procedure A, electrolysis of 2-(4-(trifluoromethyl)phenyl)acetic acid (**1v**, 98%, 729 mg, 3.5 mmol, 0.70 M) at 80 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in MeCN (5.0 mL) gave 2-(4-(trifluoromethyl)phenyl)acetic anhydride (**2v**) in 20% yield and 37% selectivity (54% conversion) after 1.1 *F* (ISTD: 42.0 mg 1,3,5-trimethoxybenzene (98.0%)).

^1H NMR The signals overlap partially with 2-(4-(trifluoromethyl)phenyl)acetic acid (**1v**).

^{13}C NMR (101 MHz, CDCl_3) δ 166.1, 135.9, 129.9, 125.8 (q, $J = 3.9$ Hz), 41.7 ppm; The signals of the remaining carbon atoms overlap with 2-(4-(trifluoromethyl)phenyl)acetic acid (**1v**).

^{19}F $\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ -63.9 ppm.

The analytic data is in agreement with previously reported data.^[18]

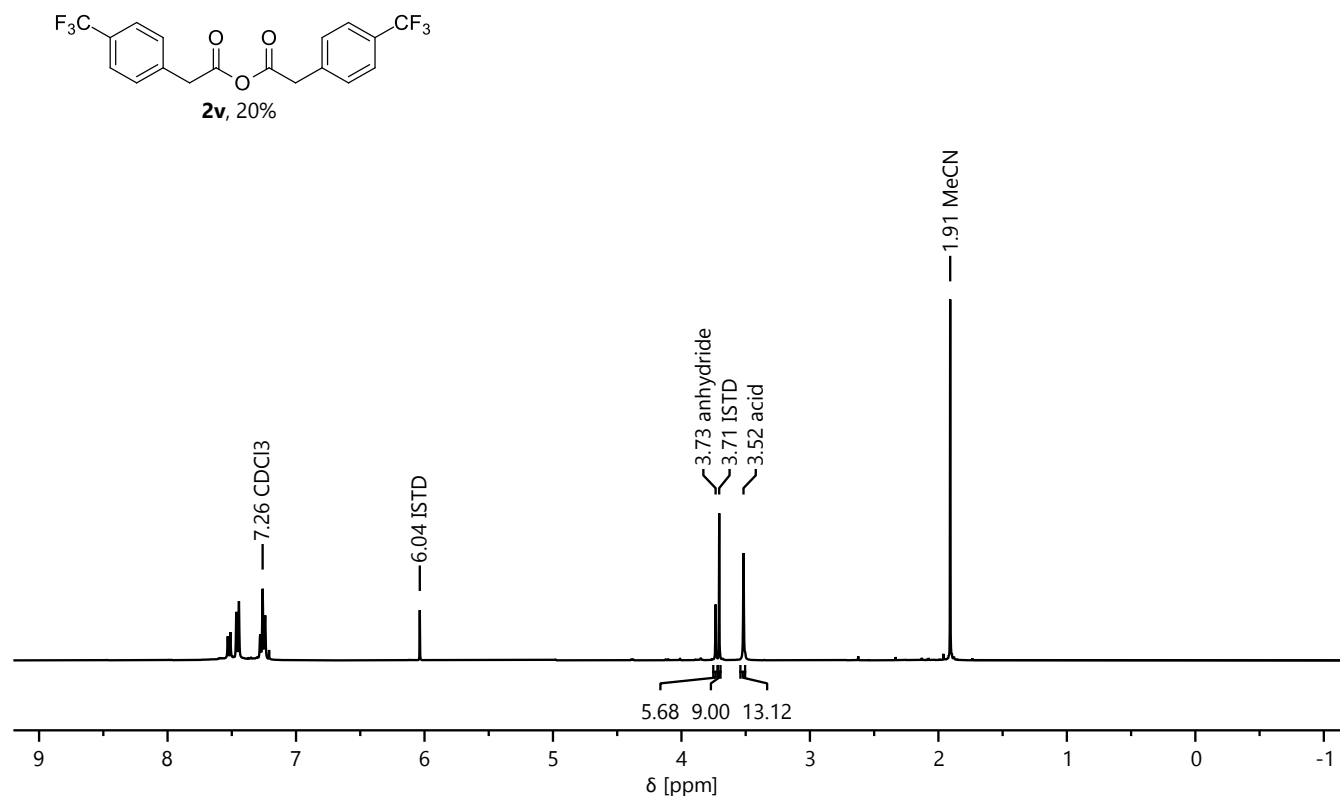


Figure S66: ^1H NMR of the crude mixture from electrolysis of 2-(4-(trifluoromethyl)phenyl)acetic acid (**1v**); 400 MHz, 296 K.

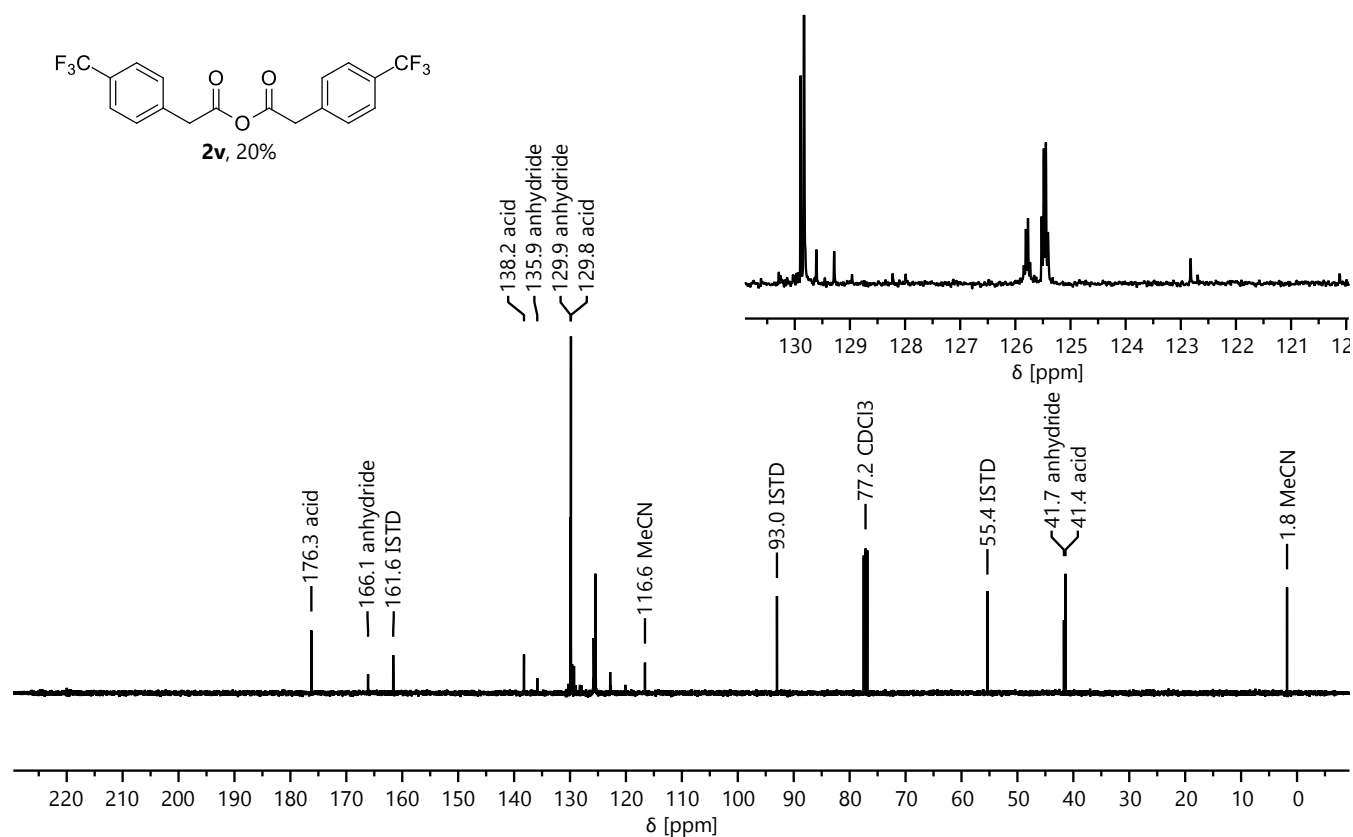


Figure S67: ^{13}C NMR of the crude mixture from electrolysis of 2-(4-(trifluoromethyl)phenyl)acetic acid (**1v**); 101 MHz, 296 K.

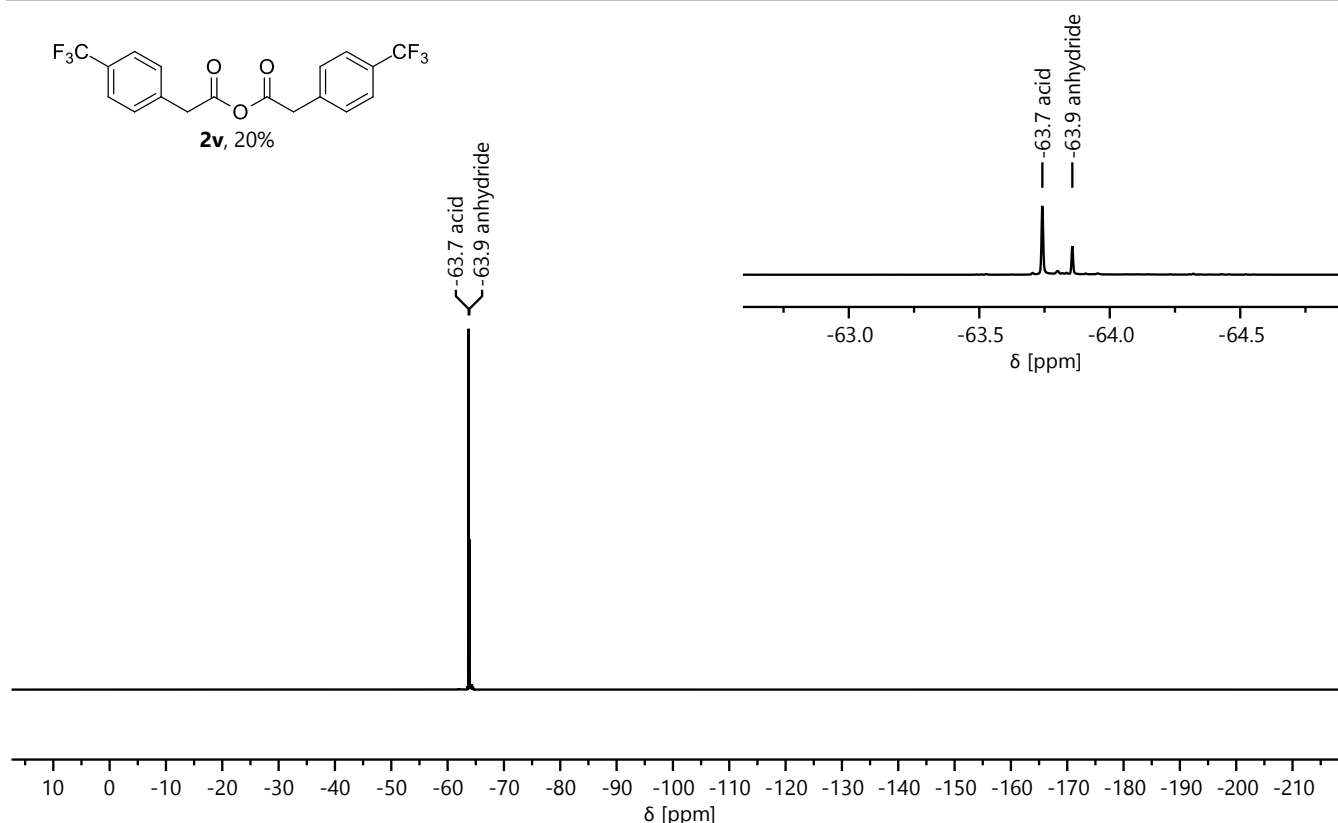


Figure S68: ^{19}F $\{^1\text{H}\}$ NMR of the crude mixture from electrolysis of 2-(4-(trifluoromethyl)phenyl)acetic acid (**1v**); 376 MHz, 296 K.

Oleic Anhydride (**2w**)

Following general procedure A, electrolysis of oleic acid (**1w**, 99.0%, 0.48 mL, 1.5 mmol, 0.50 M) at 30 mA/cm² and 313 K with EMIMSCN (187 mg, 0.35 M) as supporting electrolyte in MeCN/EtOAc 2:1 (v/v, 3.0 mL) gave oleic anhydride (**2w**) in 16% yield and 48% selectivity (34% conversion) after 1.1 *F* (ISTD: 23.9 mg 1,3,5-trimethoxybenzene (98.0%)). For analytic purposes, the residual electrolyte of two different experiments was combined and filtered through a mixture of silica (ca. 4 g) and K₂CO₃ (ca. 1 g) on a p4 frit. The silica layer was rinsed with 60 mL cyclohexane, and the filtrate was washed with cold aqueous K₂CO₃ (0.1 M, 20 mL). The organic phase was dried with MgSO₄ and the solvent was evaporated to give a mixture of oleic anhydride (**2w**), traces of oleic acid (**1w**), and 1,3,5-trimethoxybenzene.

^1H NMR (400 MHz, CDCl₃) δ 2.44 (t, *J* = 7.4 Hz, 4H) ppm; The signals of the remaining protons overlap with oleic acid (**1x**).

^{13}C NMR (101 MHz, CDCl₃) δ 169.7, 130.2, 129.8, 35.4, 32.1, 29.9, 29.8, 29.7, 29.5, 29.5, 29.2, 29.2, 29.0, 27.4, 27.3, 24.4, 22.8, 14.3 ppm.

No spectroscopic data for this compound has been reported before.

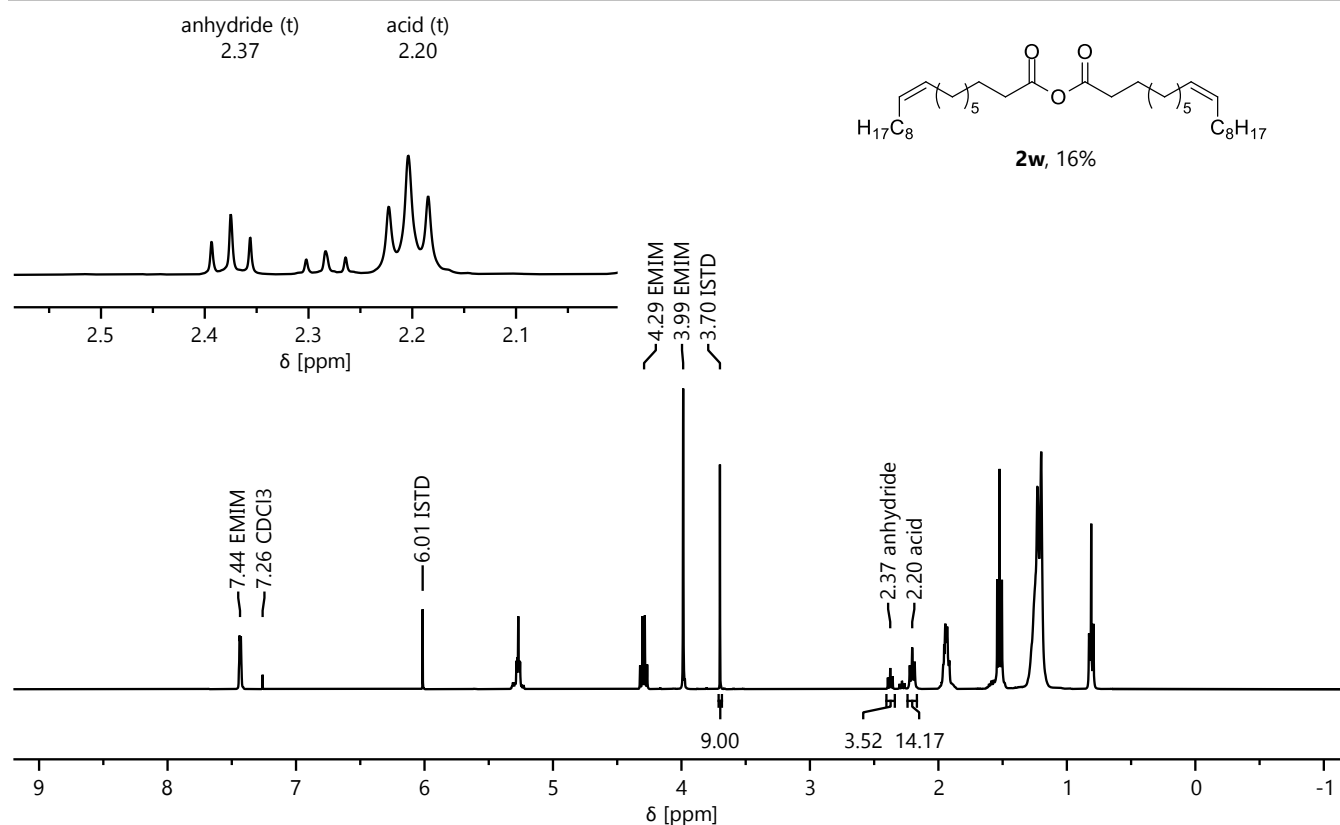


Figure S69: ¹H NMR of the crude mixture from electrolysis of oleic acid (**1w**); 400 MHz, 298 K.

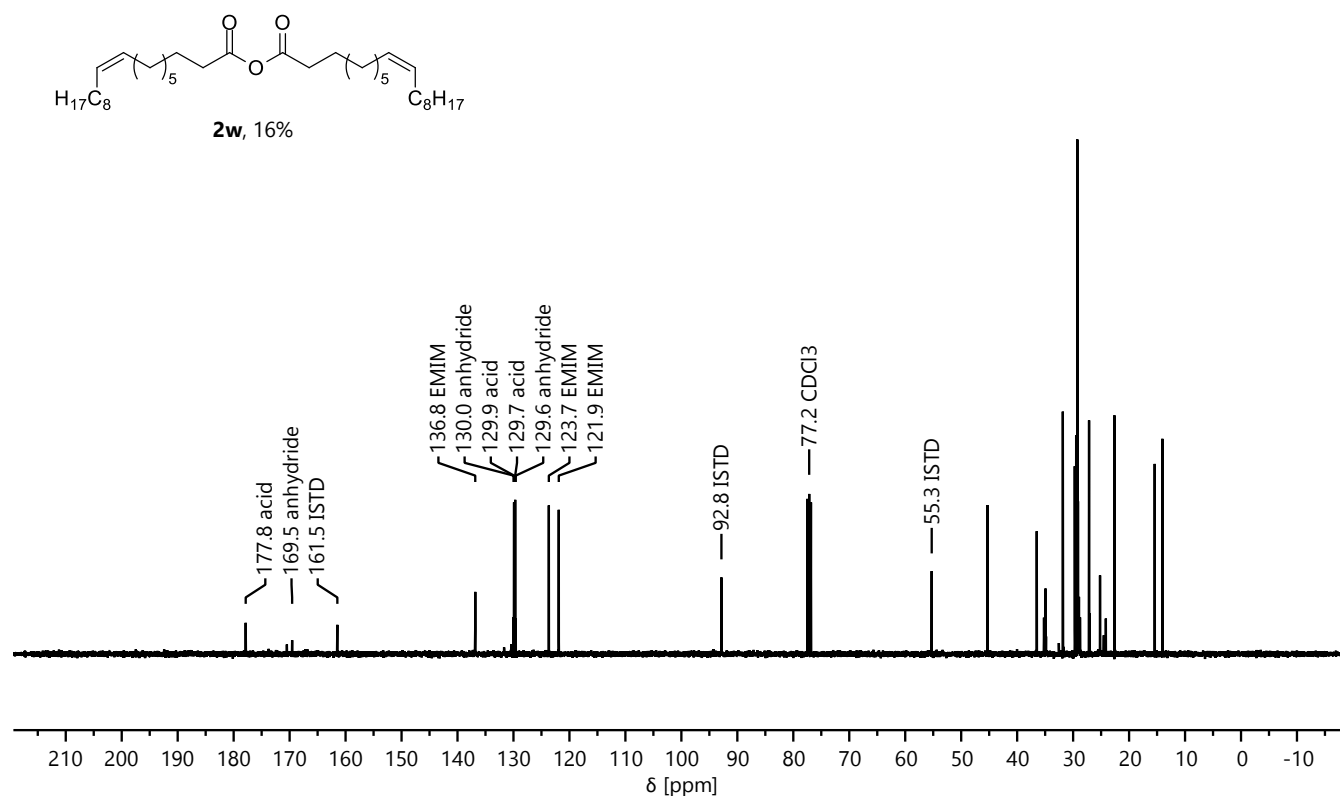
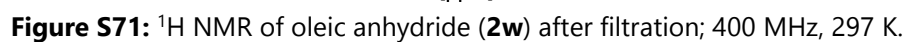


Figure S70: ¹³C NMR of the crude mixture from electrolysis of oleic acid (**1w**); 101 MHz, 298 K.



Linoleic Anhydride (2x)

Following general procedure A, electrolysis of linoleic acid (**1x**, 99%, 555 mg, 2.0 mmol, 0.39 M) at 50 mA/cm² with EMIMSCN (178 mg, 0.20 M) as supporting electrolyte in MeCN/EtOAc 2:1 (v/v, 5.0 mL) gave linoleic anhydride (**2x**) in 15% yield and 51% selectivity (30% conversion) after 1.3 *F* (ISTD: 26.2 mg 1,3,5-trimethoxybenzene (98.0%)). For analytic purposes, the residual electrolyte of two different experiments was combined and filtered through a mixture of silica (ca. 4 g) and K₂CO₃ (ca. 1 g) on a p4 frit. The silica layer was rinsed with 60 mL cyclohexane, and the filtrate was washed with cold aqueous K₂CO₃ (0.1 M, 20 mL). The organic phase was dried with MgSO₄ and the solvent was evaporated to give a mixture of linoleic anhydride (**2x**), traces of linoleic acid (**1x**), and 1,3,5-trimethoxybenzene.

HRMS (APCI) [*m/z*] calc'd for C₃₆H₆₃O₅⁺ [*M* + O₂ + H]⁺, 575.4670; found, 575.4650; deviation: -3.5 ppm; [*m/z*] calc'd for C₁₈H₃₁O₃⁺ [(*M* - linoleate) + O₂ + H]⁺, 295.2268; found, 295.2262; deviation: -2.0 ppm; The formation of the postulated hydroperoxide is assumed to happen during the ionization process because the ¹³C NMR spectra of the crude reaction mixture did not show a hydroperoxide signal.

¹H NMR (400 MHz, CDCl₃) δ 5.44 – 5.27 (m, 8H), 2.77 (t, *J* = 6.2 Hz, 4H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.05 (q, *J* = 6.8 Hz, 8H), 1.72 – 1.59 (m, 4H), 1.38 – 1.26 (m, 30H), 0.89 (t, *J* = 6.8 Hz, 6H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ 169.7, 130.4, 130.1, 128.2, 128.0, 35.4, 31.7, 29.7, 29.5, 29.2, 29.2, 29.0, 27.3, 27.3, 25.8, 24.3, 22.7, 14.2 ppm.

The analytic data is in agreement with previously reported data.^[19]

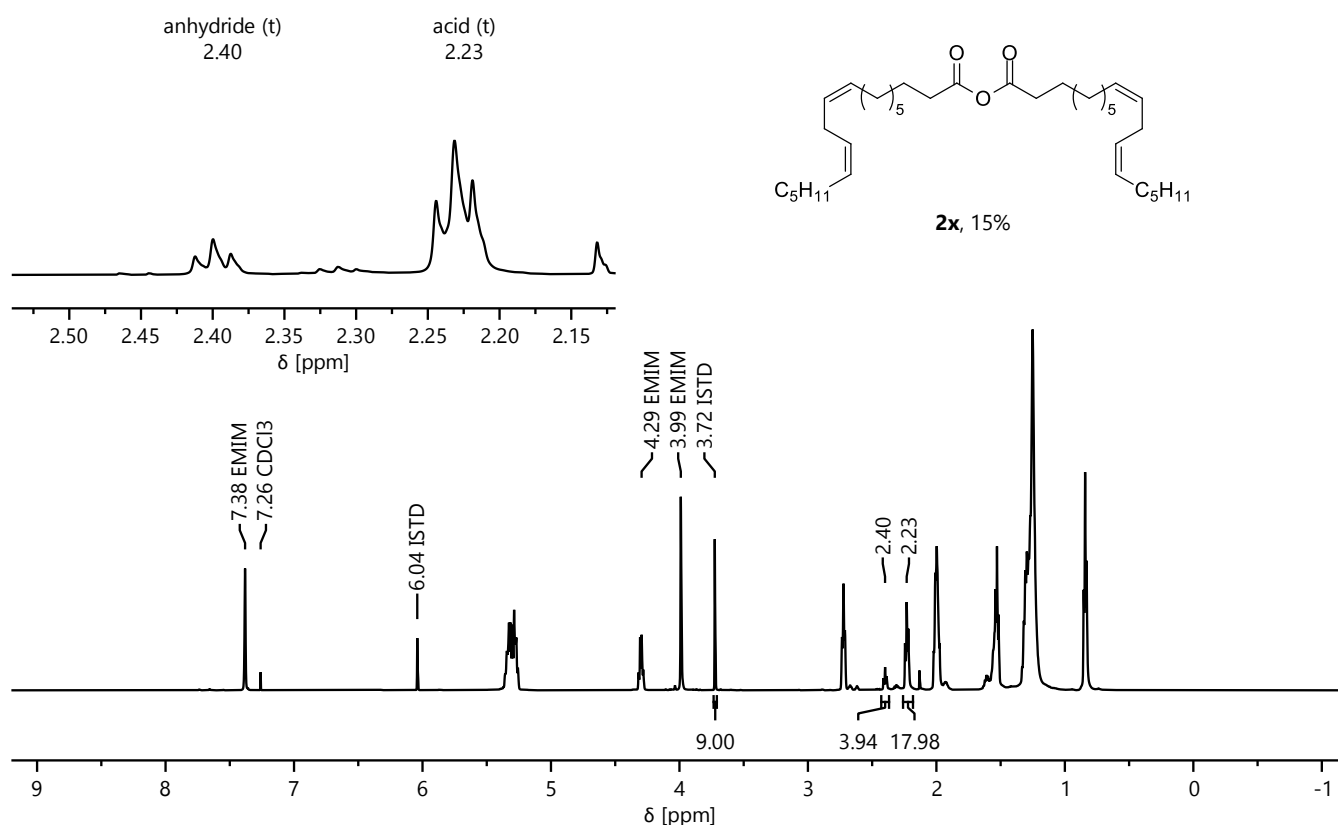


Figure S73: ¹H NMR of the crude mixture from electrolysis of linoleic acid (**1x**); 600 MHz, 294 K.

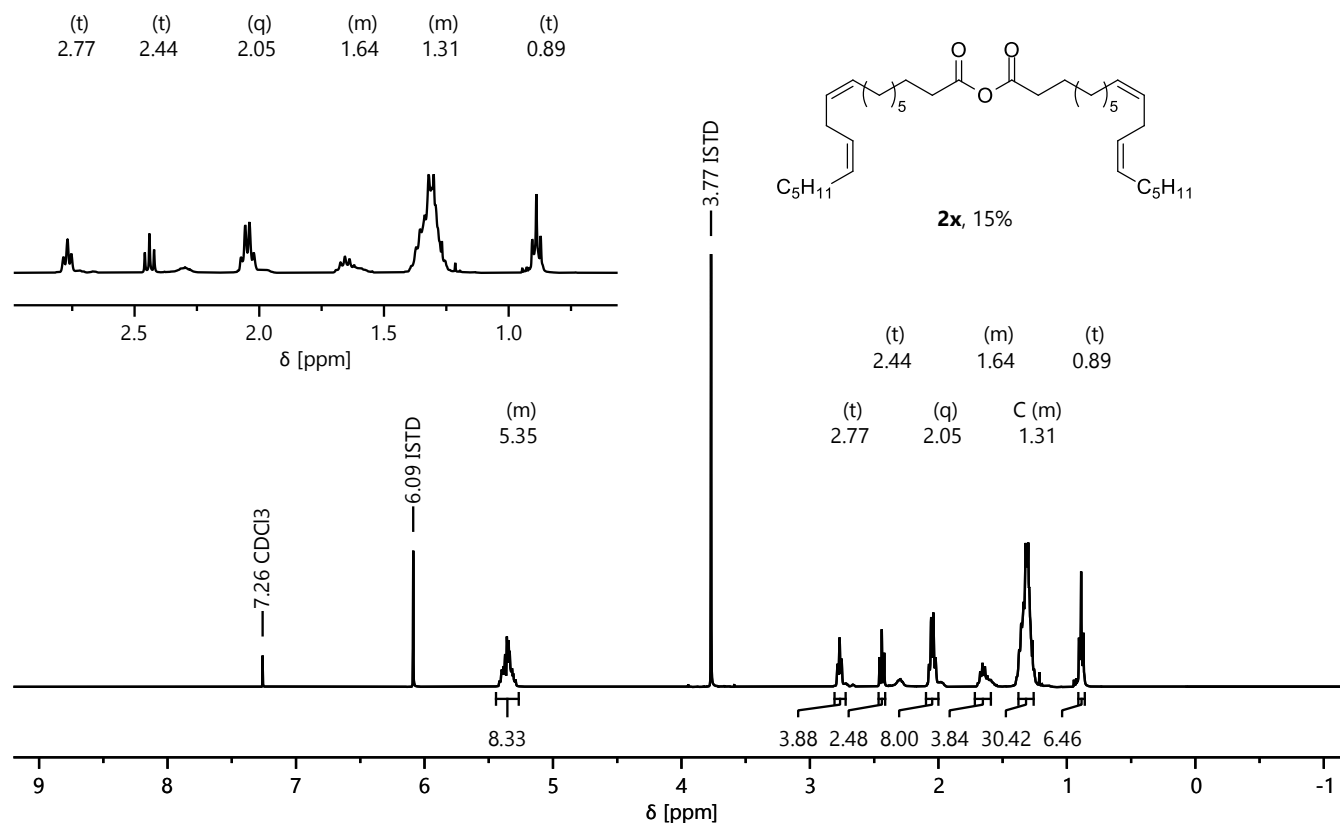


Figure S74: ^1H NMR of linoleic anhydride (**2x**) after filtration; 400 MHz, 297 K.

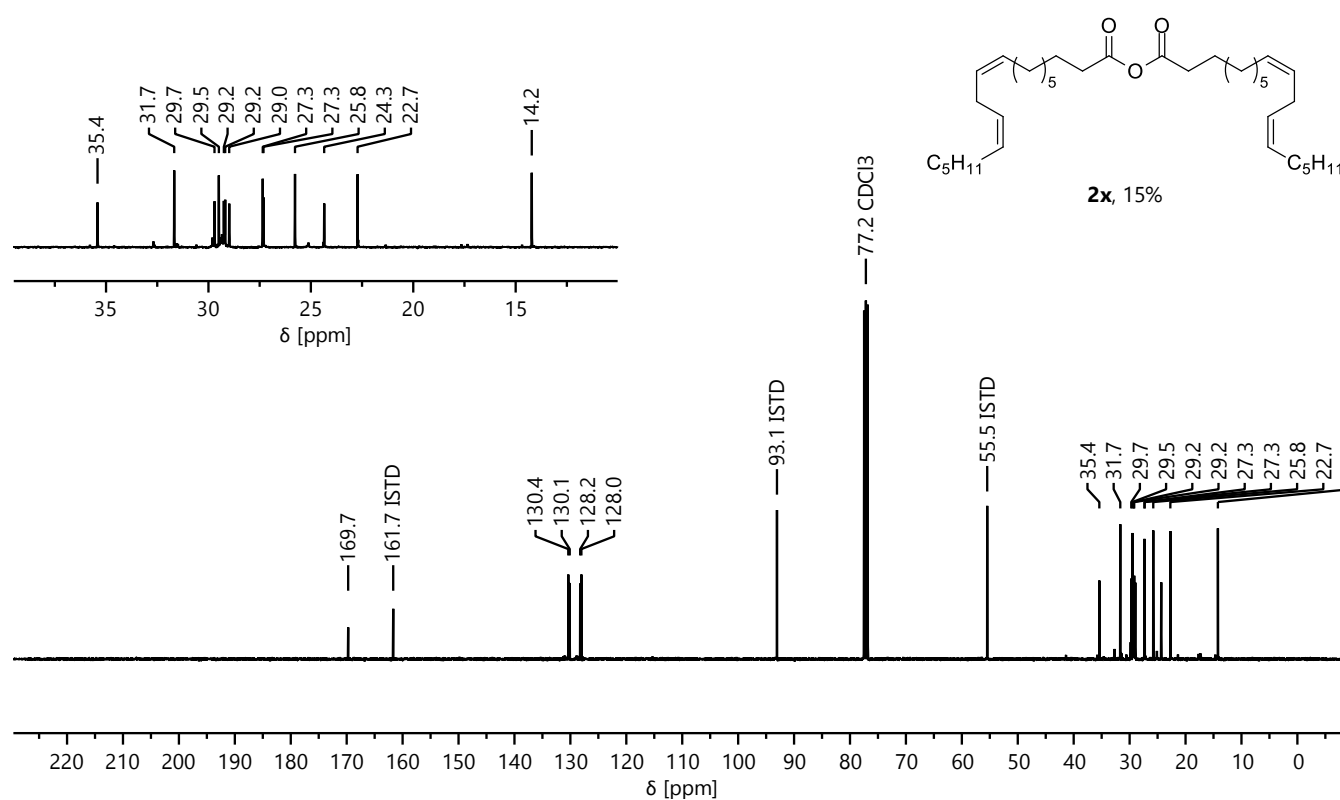


Figure S75: ^{13}C NMR of linoleic anhydride (**2x**) after filtration; 101 MHz, 297 K.

***N*-Benzyltrifluoroacetamide (3y)**

Following general procedure A, electrolysis of trifluoroacetic acid (**1y**, 100%, 0.27 mL, 3.5 mmol, 0.70 M) at 50 mA/cm² with KSCN (49 mg, 0.10 M) as supporting electrolyte in anhydrous MeCN (5.0 mL) gave trifluoroacetic anhydride (**2y**) after 1.1 *F*. Because of its fast hydrolysis, the anhydride **2y** was directly converted to an amide in the electrolysis vessel. Benzylamine (100%, 0.38 mL, 3.5 mmol, 0.99 eqs.) was added and the mixture was stirred for 18 h. 2 N Hydrochloric acid was added, and the mixture was extracted with EtOAc. The organic phase was washed with saturated aqueous NaHCO₃ and dried with MgSO₄. The residue was chromatographed on silica to give 120.9 mg (34%) *N*-benzyltrifluoroacetamide (**3y**) as white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.28 (m, 3H), 7.28 – 7.20 (m, 2H), 6.72 (s, 1H), 4.48 (d, *J* = 5.8 Hz, 2H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ 157.3 (q, *J* = 37.0 Hz), 136.0, 129.2, 128.4, 128.1, 116.0 (q, *J* = 287.8 Hz), 44.0 ppm.

¹⁹F NMR (377 MHz, CDCl₃) δ -77.0 ppm.

The analytic data is in agreement with previously reported data.^[20]

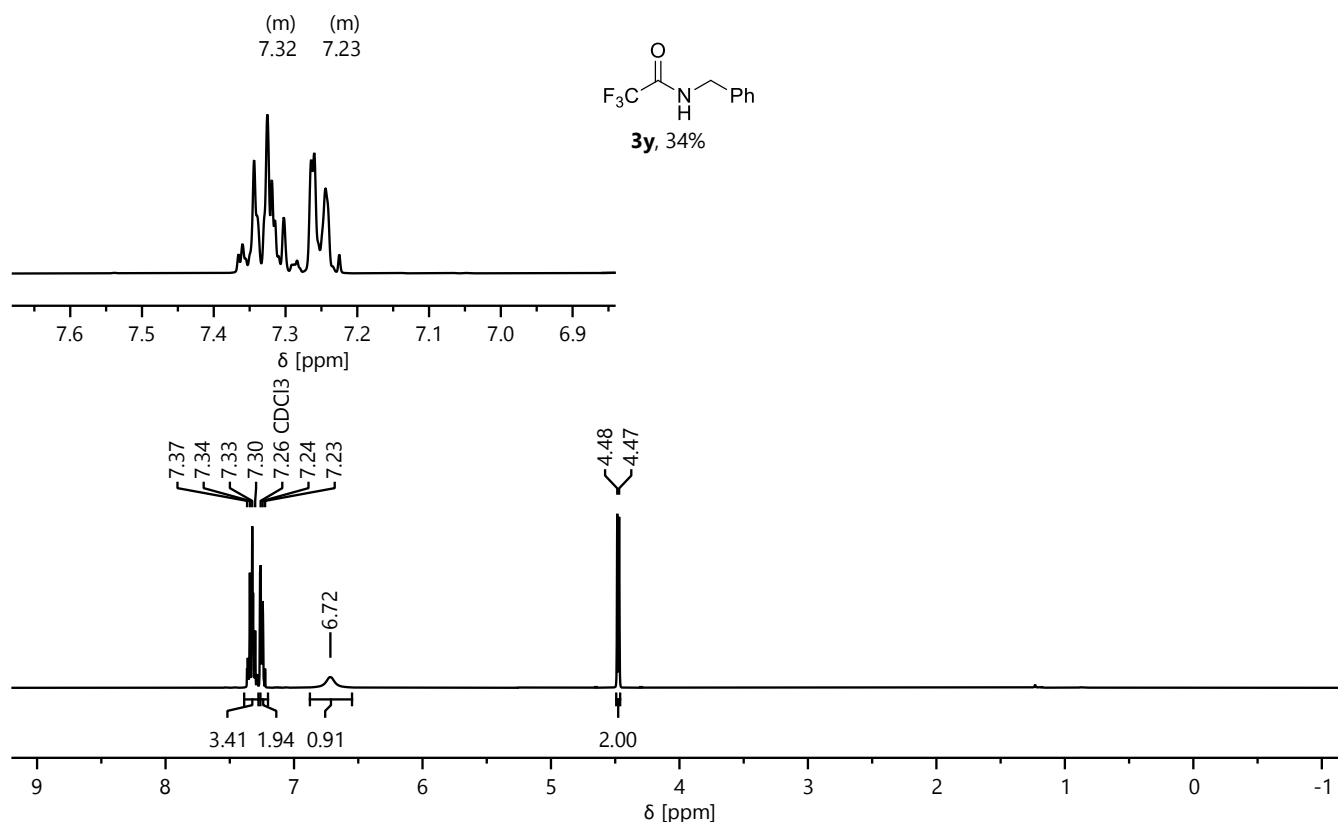


Figure S76: ¹H NMR of *N*-benzyltrifluoroacetamide (**3y**); 400 MHz, 296 K.

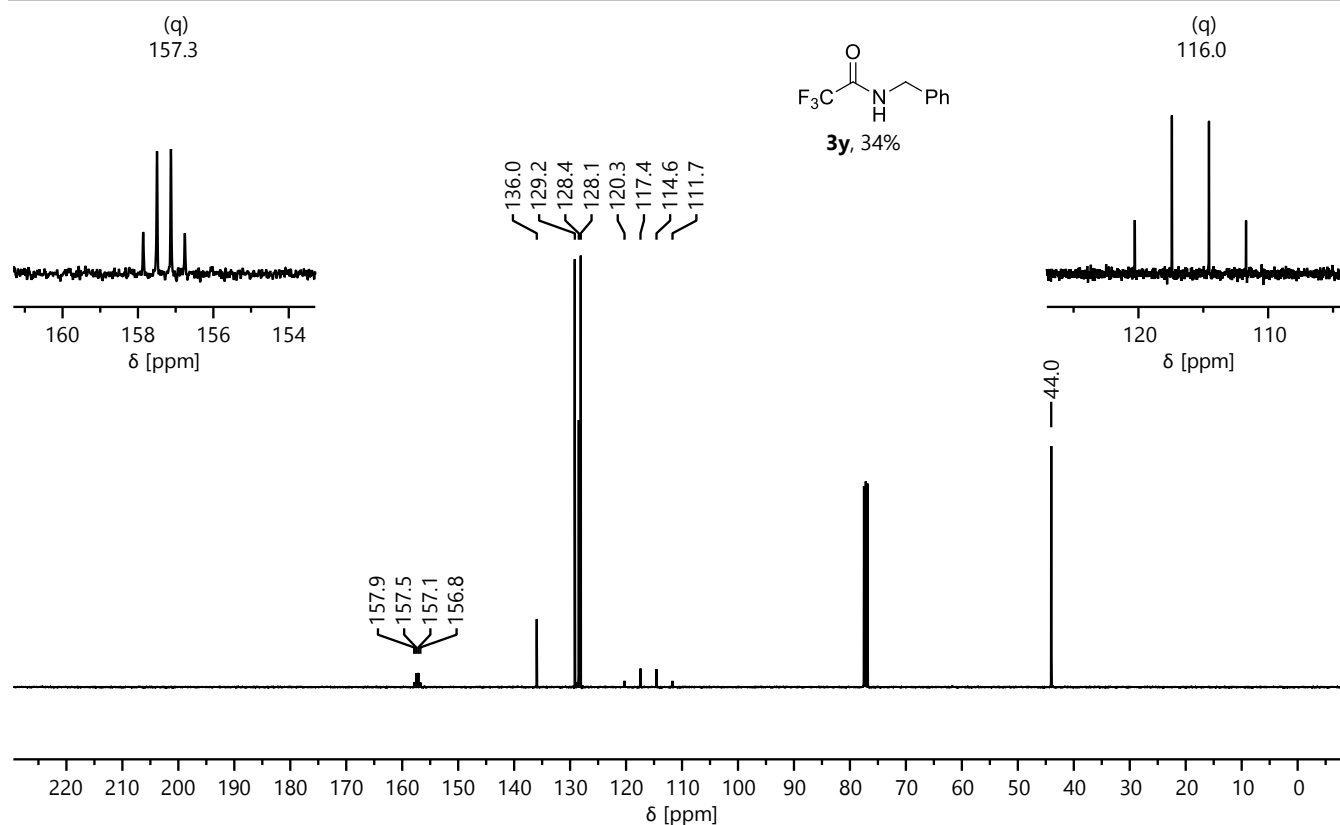


Figure S77: ^{13}C NMR of *N*-benzyltrifluoroacetamide (**3y**); 101 MHz, 296 K.

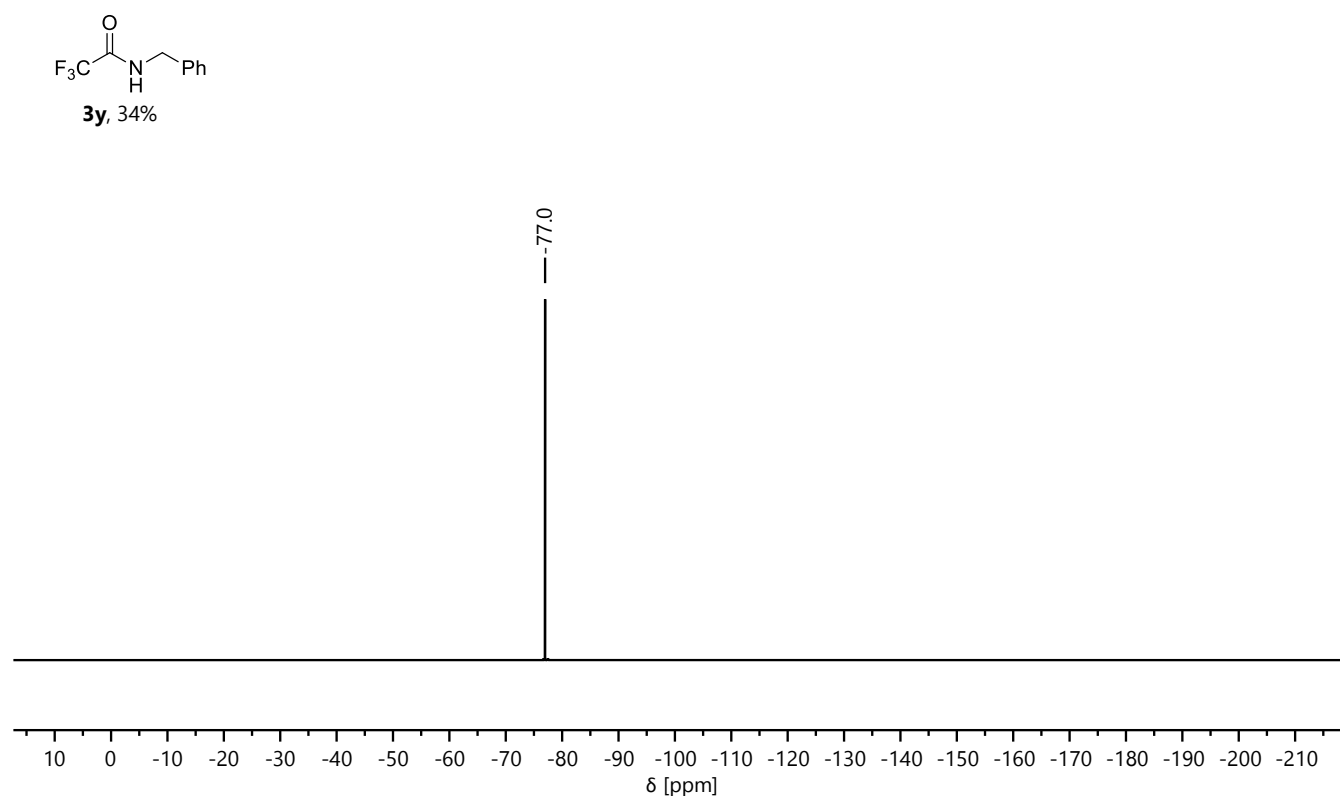


Figure S78: ^{19}F NMR of *N*-benzyltrifluoroacetamide (**3y**); 377 MHz, 296 K.

References

- [1] C. Gütz, B. Klöckner, S. R. Waldvogel, *Org. Process Res. Dev.* **2016**, *20*, 26–32.
- [2] S. A. Kahani, M. Sabeti, *J. Inorg. Organomet. Polym. Mater.* **2011**, *21*, 458–464.
- [3] S. Gaspa, I. Amura, A. Porcheddu, L. de Luca, *New J. Chem.* **2017**, *41*, 931–939.
- [4] K. L. Williamson, M. U. Hasan, D. R. Clutter, *J. Magn. Reson. (1969-1992)* **1978**, *30*, 367–383.
- [5] Y. Miyake, T. Kinsho, R. Komatsu, US20200199053A1.
- [6] Y.-D. Park, J.-J. Kim, H.-K. Kim, S.-D. Cho, Y.-J. Kang, K. H. Park, S.-G. Lee, Y.-J. Yoon, *Synth. Commun.* **2005**, *35*, 371–378.
- [7] H. K. Moon, G. H. Sung, B. R. Kim, J. K. Park, Y.-J. Yoon, H. J. Yoon, *Adv. Synth. Catal.* **2016**, *358*, 1725–1730.
- [8] L. C. Baldwin, M. C. Davis, A. M. Hughes, D. V. Lupton, *J. Am. Oil Chem. Soc.* **2019**, *96*, 571–583.
- [9] Z. Yang, S. Chen, F. Yang, C. Zhang, Y. Dou, Q. Zhou, Y. Yan, L. Tang, *Eur. J. Org. Chem.* **2019**, 5998–6002.
- [10] a) G. A. Urove, D. G. Peters, *J. Org. Chem.* **1993**, *58*, 1620–1622; b) Z.-P. Bao, R.-G. Miao, X. Qi, X.-F. Wu, *Chem. Commun.* **2021**, *57*, 1955–1958.
- [11] H. Seliger, H.-H. Görtz, *Ber. Dtsch. Chem. Ges.* **1978**, *111*, 3732–3739.
- [12] N. Moszner, J. Angermann, U. Fischer, A. Gianasmidis, M. Tabatabai, H. Ritter, A. Utterodt, *Macromol. Mater. Eng.* **2011**, *296*, 937–943.
- [13] U. Ellervik, G. Magnusson, *Acta Chem. Scand.* **1993**, *47*, 826–828.
- [14] O. Türlüç, M. A. R. Meier, *Green Chem.* **2011**, *13*, 314.
- [15] R. A. Zarkesh, M. D. Hopkins, R. F. Jordan, *Eur. J. Inorg. Chem.* **2014**, *2014*, 5491–5494.
- [16] M. Cocivera, A. Effio, *J. Org. Chem.* **1980**, *45*, 415–420.
- [17] S. Becherini, A. Mezzetta, C. Chiappe, L. Guazzelli, *New J. Chem.* **2019**, *43*, 4554–4561.
- [18] S. R. Smith, C. Fallan, J. E. Taylor, R. McLennan, D. S. B. Daniels, L. C. Morrill, A. M. Z. Slawin, A. D. Smith, *Chem. – Eur. J.* **2015**, *21*, 10530–10536.
- [19] L. Loghina, M. Grinco, A. Iakovleva, S. Slang, K. Palka, M. Vlcek, *New J. Chem.* **2018**, *42*, 14779–14788.
- [20] R. J. Bergeron, J. S. McManis, *J. Org. Chem.* **1988**, *53*, 3108–3111.

Author Contributions

A. P. H. discovered the reaction, performed the experiments, and supervised the project. B. R. S. performed experiments for the optimization and the scope. V. K. and J. S. helped with initial experimental work. A. P. H. and S. R. W. analyzed the data, and A. P. H., D. P. and S. R. W. wrote the manuscript.

CHEMISTRY

AN **ASIAN** JOURNAL

Supporting Information

LABS: Laboratory Automation and Batch Scheduling – A Modular Open Source Python Program for the Control of Automated Electrochemical Synthesis with a Web Interface

Maximilian M. Hielscher⁺, Maurice Dörr⁺, Johannes Schneider, and Siegfried R. Waldvogel* This manuscript is part of an Indo-German Workshop (IGW) special collection. © 2023 The Authors. Chemistry - An Asian Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

1	General Information.....	S2
2	Computer Hardware	S3
4	Data and Materials Availability.....	S4
5	Backend	S4
5.1	Architecture	S4
5.2	Configuration.....	S7
5.3	Implementing new drivers	S15
6	Frontend.....	S18
7	General protocol for dehydrating coupling reactions.....	S21
	Optimization Data.....	S23
7.1	Control Experiments with BPT Pharmed Tubing.....	S23
7.2	Fractional Factorial Design (Tubing: Pharmed®)	S25
7.3	Repetition of the experimental design.....	S27
8	References	S31

1 General Information

All reagents were used in analytical grades. Solvents were purified by standard methods.^[1]

2,4-Dimethoxyphenol: purchased from Tokyo Chemical Industry Co., Ltd., (>98.0%), LOT D0774.

1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP): purchased from Carbolution, St. Ingbert, Germany (99.0%), LOT CC03056.

Pyridine: purchased from VWR International S.A.S, Fontenay-sous-Bois, France (analytical grade $\geq 99.7\%$), LOT 21|034008.

Propan-2-ol: purchased from Fischer Chemical (Fisher Scientific GmbH, Schwerte, Germany), analytical reagent grade ($\geq 99.8\%$), LOT 2227290.

***n*-Octylbenzene:** purchased from ThermoFischer (Kandel) GmbH, Germany, (99%), LOT 10211400.

Ethyl acetate and **cyclohexane** were purchased in technical grade and purified by distillation prior to use.

Gas chromatography was performed on a Shimadzu GC-2025 (Shimadzu, Japan) using a HP-5ms capillary column (Agilent Technologies, Inc., Santa Clara, United States; length: 30 m, inner diameter: 0.25 mm, film: 0.25 μm , carrier gas: hydrogen). Hydrogen gas (99.9%) was purchased from Nippon Gases Deutschland GmbH, Germany. GC glass vials (1.5 mL, N9, LOT 202145521) and screw caps (PTFE, N9, LOT 1107021100) were purchased from MN (Macherey-Nagel, Düren, Germany). Yield was determined by internal referencing with *n*-octylbenzene relative to the FID integrals (Figure 1).

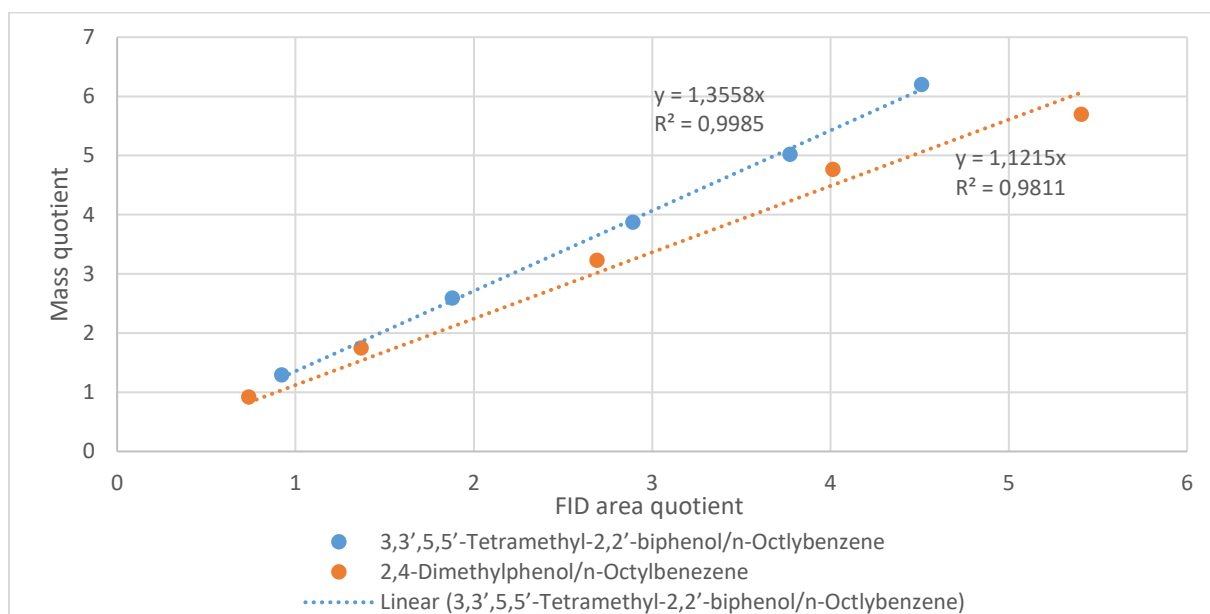


Figure 1: Calibration for substrate and coupling product using a GC-FID with *n*-octylbenzene as internal standard.

Temperature control: For external temperature control, a Julabo F33-MA refrigerated circulator (working temperature: $-30\text{ }^{\circ}\text{C}$ – $200\text{ }^{\circ}\text{C}$, heating power: 2 kW, cooling power (ethanol): 0.5 kW ($20\text{ }^{\circ}\text{C}$), 0.32 kW ($0\text{ }^{\circ}\text{C}$), 0.12 kW ($-20\text{ }^{\circ}\text{C}$), 0.03 kW ($-30\text{ }^{\circ}\text{C}$), flow rate: 11 – 16 L/min; Julabo GmbH, Seelbach, Germany).

Electrolysis cell: For electrochemical reactions boron-doped diamond (BDD) anodes were applied. BDD electrodes (DIACHEM™) were obtained from CONDIAS GmbH, Itzehoe, Germany. BDD (15 μm diamond layer) on support of silicon was used.

The Teflon flow electrolysis cell is also commercially available as ElectraSyn flow (IKA Werke GmbH & Co KG, Staufen, Germany) (IKA Werke, <https://www.ikaprocess.com/en/Products/ElectroOrganic-Synthesis-Systems-cph-45/ElectraSyn-flow-csb-ES/>, 2023-04-29).

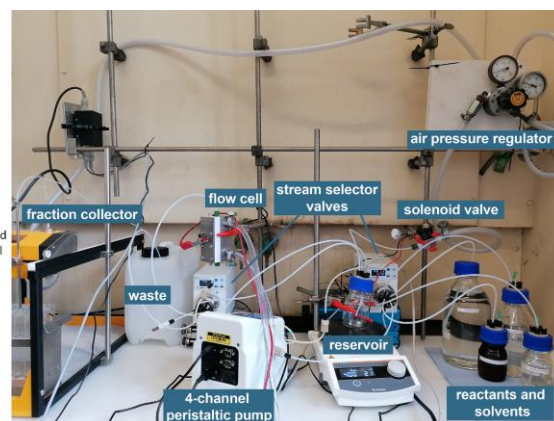
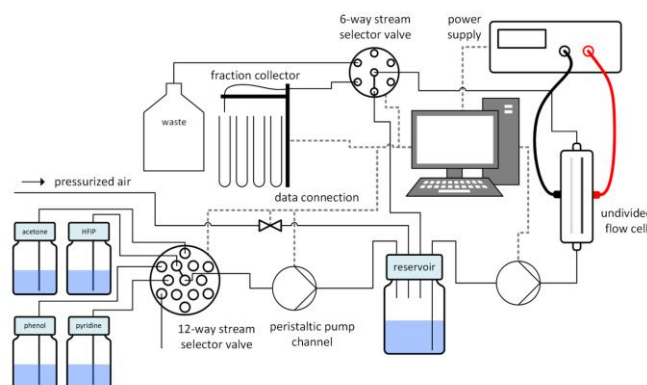
The dimensions of the electrodes used are 6.0 cm $\times$ 2.0 cm $\times$ 0.3 cm, which results in a total active electrode area of 24 cm². Temperature controlled stainless steel half-cell^[2] is designed and manufactured by the mechanical workshop of the Johannes Gutenberg University of Mainz, according to the Waldvogel Lab. A detailed description of the flow electrolysis cell has already been published.^[3]

Power supply: A Z60-3.5-L2 (TDK Lambda, Aachen, Germany, DC output 0-60 V ($\pm$ 0.01 V) and 0-3.5 A ($\pm$ 1 mA), 210 W) was used.

Peristaltic pump: An ISM 4408 Ismatec Reglo ICC peristaltic pump was used (VWR International, Darmstadt, Germany). For the peristaltic Pharmed® BPT Tubing (Saint-Gobain, France) and FKM (Optubus, Salem, Germany) was used.

Dead-end selector switching valve: Multiposition valves: 12 port and 6 port (stainless steel, diamond-like carbon coated), in combination with a valve drive VU 4.1 were used (Knauer, Berlin, Germany).

Fraction collector: OMNICOLL Fraction Collector and Sampler (LAMBDA Laboratory Instruments, Baar, Switzerland).



2 Computer Hardware

A PC with Microsoft Windows 11 Education (10.0.22000), MSI X570-A PRO (MS-7C37), AMD Ryzen 5 3600, Intel SSDPEKNW010T8 (1.0 TB), 16 GB RAM, NVidia GeForce GTX 1650, 2x Realtek PCIe GbE Family Controller was used to run the backend and the frontend.

4 Data and Materials Availability

The Software published in the context of this manuscript is available in three repositories on GitHub and as releases on Zenodo:

LABS-Backend:

GitHub: <https://github.com/Waldvogel-Group/LABS-Backend>

Zenodo: <https://doi.org/10.5281/zenodo.7879588>

LABS-Frontend:

GitHub: <https://github.com/Waldvogel-Group/LABS-User-Interface>

Zenodo: <https://doi.org/10.5281/zenodo.7879586>

LABS-DeviceDummies:

GitHub: <https://github.com/Waldvogel-Group/LABS-DeviceDummies>

Zenodo: <https://doi.org/10.5281/zenodo.7879590>

5 Backend

5.1 Architecture

The backend uses object-oriented programming and abstracts laboratory devices on multiple levels to generalize most aspects of their communication and their logic. The core (base) classes are presented in the simplified UML diagram (Figure 2). The central piece of the backend is given by the setup class. It holds devices, channels and experiments, queues of experiments and handles the device startup as well as configuration import. Not shown here, are the several base classes, that define common functionality of a certain type of laboratory equipment (e. g. thermostat_base or pump_base). These allow a generalization of the respective type of equipment that, if applied carefully, allows a relatively simple exchange of equipment within the same type, i. e. no major changes in the configuration are necessary. Besides the shown core components, the backend implements many structures handling the flow of command objects through the different layers (Experiment, Device, Protocol). The explanation of every single class and their interactions goes

far beyond the scope of this supporting information. We refer you to the published source code and included comments for deeper insight.

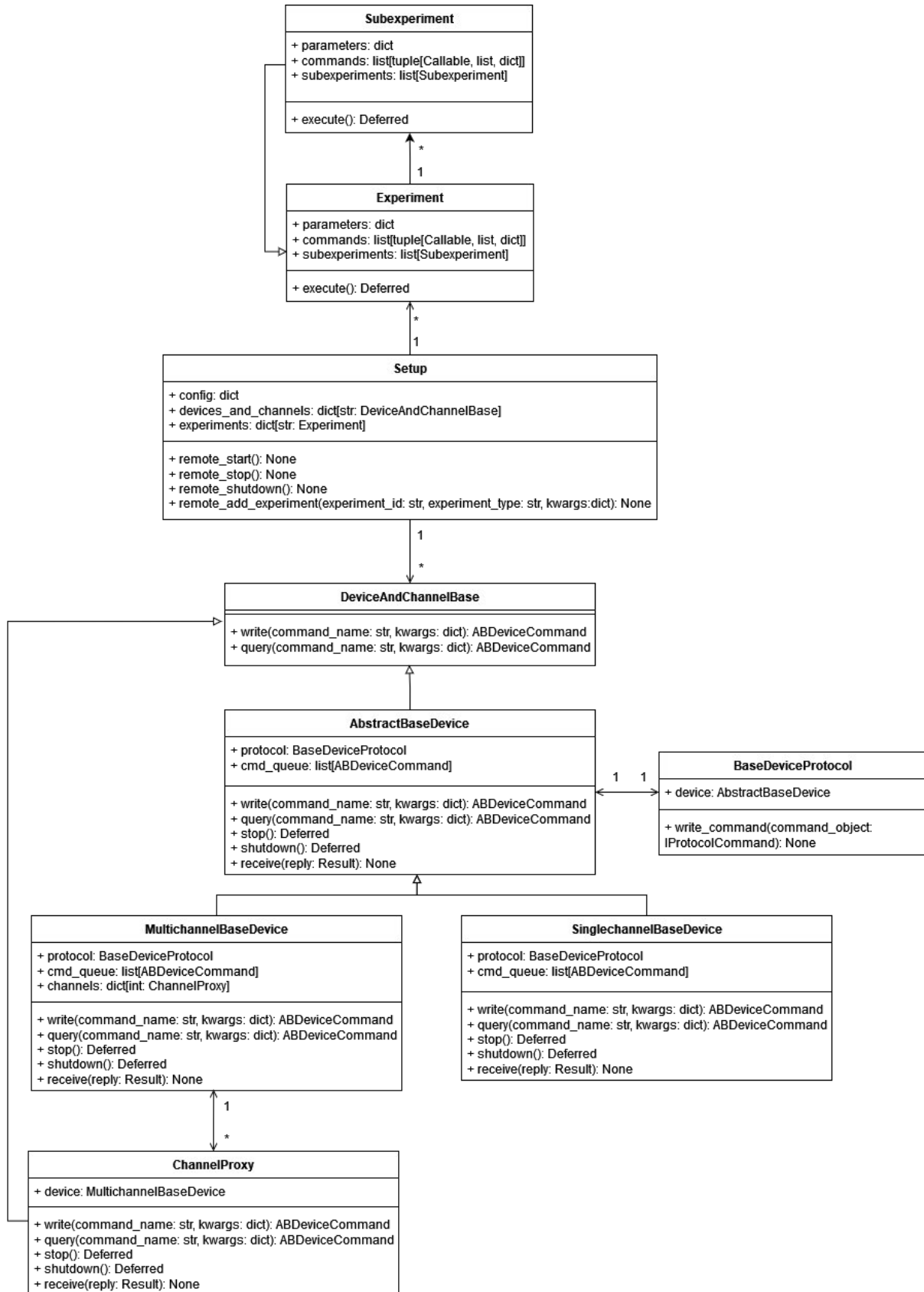


Figure 2: Simplified UML diagram to explain core components of the backend. Deferred is a class commonly used in *Twisted* based projects to realize asynchronous operations.^[4]

5.2 Configuration

The following is an example of a configuration file, as used in our experiments. It makes use of all functions implemented in our configuration logic. Examples of the implemented mechanisms are discussed here. First of all, the multichannel pump *reglo_icc* is imported as four devices (pump1 – 4). The experiment *empty_dosing_tube* is used in several other experiments. In *purge_and_temper*, the temperature is set as a user definable variable, in other words, it must be given a value from the frontend during experiment initialization. In drying, a condition of the type *TimeCondition* is used to define the duration the drying step. In *main_continuous_electrolysis*, a *stopcondition* of type *ObservableGreaterOrEqualValueCondition* is used, to end the run if the voltage passes the given threshold. Note that the voltage limit is handled as a user definable variable again, demonstrating how this is possible inside of condition arguments as well. In *cyclic_flow_electrolysis*, all the previously defined experiments are used, highlighting the great potential of code reuse and flexibility due to the possibility to hand parameter settings to encapsulated experiments.

```
listen port: 11123
log_level: info

devices:
  pump1:
    driver: reglo_icc
    address: COM5
    channel: 1
  pump2:
    driver: reglo_icc
    address: COM5
    channel: 2
  pump3:
    driver: reglo_icc
    address: COM5
    channel: 3
  pump4:
    driver: reglo_icc
    address: COM5
    channel: 4
  valve1:
    driver: azura_vu
    address: 169.254.220.3:10123
  valve2:
    driver: azura_vu
    address: 169.254.220.2:10123
  fractioncollector:
```

```

    driver: omnicoll
    address: COM3
psu:
    driver: tdk_lambda_zplus
    address: COM4
thermostat:
    driver: julabo_presto_a40
    address: COM7
airvalve:
    driver: airvalve
    address: COM12

experiments:
    # Experimentname:
    #   conditions:
    #     name as used in commands: [ type of the condition, [ args ], { kwargs } ]
    #   stopconditions:
    #     - [ type of the condition, [ args ], { kwargs } ]
    #   parameters:
    #     name as used in commands: [ accepted datatype (see below), unit (use '' if no unit) ]
    #     ...
    #   observables:
    #     - [ device, observable name, datatype (e. g. str or float), unit ]
    #     - ...
    #   commands:
    #     - [ device, function, [ args ], { kwargs } ]
    #     - [ other_experiment_inside_this_one, { keywordarguments for subexperiment } ]
    #     - ...

empty_dosing_tube:
    conditions:

    stopconditions:

    parameters:

    observables:
        - [ pump1, remaining_time, int, s ]
        - [ valve1, position, int, "" ]
    commands:
        - [ valve1, set_position, [ 6 ], { } ]
        - [ pump1, dispense, [ ], { rate: '0.1', volume: '0.05' } ]

purge_and_temper:
    conditions:

    stopconditions:

```



```

parameters:
  rate: [float, mL/min]
  volume: [float, mL]
  temperature: [float, °C]
observables:
  - [ pump2, remaining_time, int, s ]
  - [ thermostat, current_temperature, float, °C ]
commands:
  - [ thermostat, set_temperature, [ '{temperature}', 1.5, 30 ], { } ]
  - [ pump2, dispense, [ ], { rate: '{rate}', volume: '{volume}' } ]

drying:
conditions:
  drying: [TimeCondition, [drying_interval, 60], {}]
stopconditions:

parameters:

observables:

commands:
  - [ airvalve, open, [ ], { } ]
  - [ airvalve, wait, [ drying ], { } ]
  - [ airvalve, close, [ ], { } ]

add_component:
conditions:

stopconditions:

parameters:
  rate: [float, mL/min]
  volume: [float, mL]
  valve_position: [int, ""]
observables:
  - [ pump1, remaining_time, int, s ]
  - [ valve1, position, int, "" ]
commands:
  - [ valve1, set_position, [ '{valve_position}' ], { } ]
  - [ pump1, dispense, [ ], { rate: '{rate}', volume: '{volume}' } ]
  - [ empty_dosing_tube, { } ]

add_so2:
conditions:

stopconditions:

parameters:

```

```

    rate: [float, mL/min]
    volume: [float, mL]
observables:
  - [ pump3, remaining_time, int, s ]
commands:
  - [ pump3, dispense, [ ], { rate: '{rate}', volume: '{volume}' } ]

purge:
  conditions:

  stopconditions:

parameters:
  rate: [float, mL/min]
  volume: [float, mL]
observables:
  - [ pump2, remaining_time, int, s ]
commands:
  - [ pump2, dispense, [ ], { rate: '{rate}', volume: '{volume}' } ]

prerun:
  conditions:
    dispense_finished_condition: [DevicesWaitingCondition, [wait_for_pump, [pump2]], {}]

  stopconditions:

parameters:
  volume: [float, mL]
  rate: [float, mL/min]
  current: [float, A]
observables:
  - [ psu, current, float, A ]
  - [ psu, voltage, float, V ]
  - [ psu, amount of charge, float, C ]
  - [ pump2, remaining_time, int, s ]
commands:
  - [ psu, output_constant_current, [ '{current}' ], { } ]
  - [ pump2, dispense, [ ], { rate: '{rate}', volume: '{volume}' } ]
  - [ psu, busy, [ dispense_finished_condition ], { } ]
  - [ pump2, wait, [ dispense_finished_condition ], { } ]

main_continuous_electrolysis:
  conditions:

  stopconditions:
    - [ObservableGreaterOrEqualValueCondition, [max_voltage, psu, voltage, "{voltage_limit}"], {}]
parameters:
  current: [float, A]

```

```

    amount_of_charge: [float, C]
    rate: [float, mL/min]
    voltage_limit: [float, V]
observables:
  - [ psu, current, float, A ]
  - [ psu, voltage, float, V ]
  - [ psu, amount of charge, float, C ]
commands:
  - [ fractioncollector, next_fraction, [ ], { } ]
  - [ pump2, continuous_flow, [ ], { rate: '{rate}' } ]
  - [ psu, output_constant_current, [ ], { amount_of_charge: '{amount_of_charge}', current: '{current}' } ]

stop:
  conditions:

  stopconditions:

  parameters:

  observables:

  commands:
    - [ pump2, stop_pumping, [ ], { } ]
    - [ thermostat, stop_tempering, [ ], { } ]
    - [ fractioncollector, next_fraction, [ ], { } ]

continuous_flow_electrolysis:
  conditions:

  stopconditions:

  parameters:
    temperature: [float, °C]
    acetone_purge_rate: [float, mL/min]
    acetone_purge_volume: [float, mL]
    so2_purge_rate: [float, mL/min]
    so2_purge_volume: [float, mL]
    hfip_purge_rate: [float, mL/min]
    hfip_purge_volume: [float, mL]
    aryl_rate: [float, mL/min]
    aryl_volume: [float, mL]
    ethanol_rate: [float, mL/min]
    ethanol_volume: [float, mL]
    base_rate: [float, mL/min]
    base_volume: [float, mL]
    so2_rate: [float, mL/min]
    so2_volume: [float, mL]
    hfip_rate: [float, mL/min]

```

```

hfip_volume: [float, mL]
acetonitrile_rate: [float, mL/min]
acetonitrile_volume: [float, mL]
purgerate: [float, mL/min]
purgevolum: [float, mL]
fill_rate: [float, mL/min]
fill_volume: [float, mL]
prerunvolume: [float, mL]
current: [float, mA]
flowrate: [float, mL/min]
amount_of_charge: [float, C]
voltage_limit: [float, V]

observables:
- [ valve2, position, int, "" ]

commands:
- [ valve2, set_position, [ 3 ], { } ]
- [ purge_and_temper, { rate: '{purgerate}', volume: '{purgevolum}', temperature: '{temperature}' } ]
- [ add_component, { rate: '{acetone_purge_rate}', volume: '{acetone_purge_volume}', valve_position: 1 } ]
- [ purge, { rate: '{purgerate}', volume: '{purgevolum}' } ]
- [ drying, { } ]
- [ add_so2, { rate: '{so2_purge_rate}', volume: '{so2_purge_volume}' } ]
- [ purge, { rate: '{purgerate}', volume: '{purgevolum}' } ]
- [ add_component, { rate: '{hfip_purge_rate}', volume: '{hfip_purge_volume}', valve_position: 6 } ]
- [ purge, { rate: '{purgerate}', volume: '{purgevolum}' } ]
- [ drying, { } ]
- [ add_component, { rate: '{aryl_rate}', volume: '{aryl_volume}', valve_position: 2 } ]
- [ add_component, { rate: '{ethanol_rate}', volume: '{ethanol_volume}', valve_position: 9 } ]
- [ add_component, { rate: '{base_rate}', volume: '{base_volume}', valve_position: 4 } ]
- [ add_so2, { rate: '{so2_rate}', volume: '{so2_volume}' } ]
- [ add_component, { rate: '{hfip_rate}', volume: '{hfip_volume}', valve_position: 6 } ]
- [ add_component, { rate: '{acetonitrile_rate}', volume: '{acetonitrile_volume}', valve_position: 7 } ]
- [ valve2, set_position, [ 2 ], { } ]
- [ purge, { rate: '{fill_rate}', volume: '{fill_volume}' } ]
- [ prerun, { volume: '{prerunvolume}', rate: '{flowrate}', current: '{current}' } ]
- [ main_continuous_electrolysis, { current: '{current}', amount_of_charge: '{amount_of_charge}', rate:
'{flowrate}', voltage_limit: '{voltage_limit}' } ]
- [ stop, { } ]

collect_solution:

conditions:

stopconditions:

parameters:
rate: [float, mL/min]
volume: [float, mL]

observables:
- [ pump2, remaining_time, int, s ]

```

```

commands:
  - [ pump2, dispense, [ ], { rate: '{rate}', volume: '{volume}' } ]

main_cyclic_electrolysis:
  conditions:

  stopconditions:
    - [ObservableGreaterOrEqualValueCondition, [max_voltage, psu, voltage, "{voltage_limit}"], {}]

  parameters:
    current: [float, A]
    amount_of_charge: [float, C]
    rate: [float, mL/min]
    voltage_limit: [float, V]

  observables:
    - [ psu, current, float, A ]
    - [ psu, voltage, float, V ]
    - [ psu, amount of charge, float, C ]

  commands:
    - [ pump2, continuous_flow, [ ], { rate: '{rate}' } ]
    - [ psu, output_constant_current, [ ], { amount_of_charge: '{amount_of_charge}', current: '{current}' } ]

cyclic_flow_electrolysis:
  conditions:

  stopconditions:

  parameters:
    acetone_purge_rate: [float, mL/min]
    acetone_purge_volume: [float, mL]
    purgerate: [float, mL/min]
    purgevolume: [float, mL]
    reversepurgerate: [float, mL/min]
    reversepurgevolume: [float, mL]
    so2_purge_rate: [float, mL/min]
    so2_purge_volume: [float, mL]
    aryl_rate: [float, mL/min]
    aryl_volume: [float, mL]
    ethanol_rate: [float, mL/min]
    ethanol_volume: [float, mL]
    base_rate: [float, mL/min]
    base_volume: [float, mL]
    so2_rate: [float, mL/min]
    so2_volume: [float, mL]
    hfip_rate: [float, mL/min]
    hfip_volume: [float, mL]
    acetonitrile_rate: [float, mL/min]
    acetonitrile_volume: [float, mL]
    fill_loop_rate: [float, mL/min]

```



```

fill_loop_volume: [float, mL]
current: [float, A]
amount_of_charge: [float, C]
flowrate: [float, mL/min]
voltage_limit: [float, V]
collection_rate: [float, mL/min]
collection_volume: [float, mL]
observables:
  - [ valve2, position, int, "" ]
commands:
  - [ valve2, set_position, [ 3 ], { } ]
  - [ purge_and_temper, { } ]
  - [ add_component, { rate: '{acetone_purge_rate}', volume: '{acetone_purge_volume}', valve_position: 1 } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ add_component, { rate: '{acetone_purge_rate}', volume: '{acetone_purge_volume}', valve_position: 1 } ]
  - [ valve2, set_position, [ 1 ], { } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ purge, { rate: '-{purgerate}', volume: '{purgevolume}' } ]
  - [ valve2, set_position, [ 3 ], { } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ drying, { } ]
  - [ add_so2, { rate: '{so2_purge_rate}', volume: '{so2_purge_volume}' } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ add_component, { rate: '{hftpurge_rate}', volume: '{hftpurge_volume}', valve_position: 6 } ]
  - [ valve2, set_position, [ 1 ], { } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ purge, { rate: '-{purgerate}', volume: '{purgevolume}' } ]
  - [ valve2, set_position, [ 3 ], { } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ drying, { } ]
  - [ add_component, { rate: '{aryl_rate}', volume: '{aryl_volume}', valve_position: 2 } ]
  - [ add_component, { rate: '{ethanol_rate}', volume: '{ethanol_volume}', valve_position: 9 } ]
  - [ add_component, { rate: '{base_rate}', volume: '{base_volume}', valve_position: 4 } ]
  - [ add_so2, { rate: '{so2_rate}', volume: '{so2_volume}' } ]
  - [ add_component, { rate: '{hftpurge_rate}', volume: '{hftpurge_volume}', valve_position: 6 } ]
  - [ add_component, { rate: '{acetonitrile_rate}', volume: '{acetonitrile_volume}', valve_position: 7 } ]
  - [ valve2, set_position, [ 1 ], { } ]
  - [ purge, { rate: '{fill_loop_rate}', volume: '{fill_loop_volume}' } ]
  - [ main_cyclic_electrolysis, { current: '{current}', amount_of_charge: '{amount_of_charge}', flowrate:
'"{flowrate}"', voltage_limit: '{voltage_limit}' } ]
  - [ stop, { } ]
  - [ purge, { rate: '-{purgerate}', volume: '{purgevolume}' } ]
  - [ valve2, set_position, [ 2 ], { } ]
  - [ collect_solution, { rate: '{collection_rate}', volume: '{collection_volume}' } ]
  - [ add_component, { rate: '{hftpurge_rate}', volume: '{hftpurge_volume}', valve_position: 6 } ]
  - [ valve2, set_position, [ 1 ], { } ]
  - [ purge, { rate: '{purgerate}', volume: '{purgevolume}' } ]
  - [ purge, { rate: '-{purgerate}', volume: '{purgevolume}' } ]

```

```
- [ valve2, set_position, [ 2 ], { } ]
- [ purge, { rate: '{purgerate}', volume: '{purgevolum}' } ]
```

5.3 Implementing new drivers

The following is an example of a device driver (for the valve drive Knauer Azura Valve Unifier VU4.1). Implementing new devices, unfortunately requires a deeper understanding of *python*, *Twisted*^[4], *regular expressions* and the presented software. Therefore, we are not able to provide a full tutorial explaining the process of implementation. Nonetheless, this may give the reader a brief overview and good idea of what is needed to provide new device drivers.

In the first lines, the *baseclasses* are imported for the respective type of laboratory equipment (in this case *multipos_valve_base*). Every driver must implement a *Device* class that inherits from the imported *BaseDevice* and *SinglechannelBaseDevice* or *MultichannelBaseDevice*.

Inside the class scope, some class variables defined in the base class may be overridden to suit the characteristics and communication protocol of the device. Expected is a set of replies that lead directly to a given commandstate (e. g. *commandstate.Success*). Furthermore, complex errormessages may be defined as *regular expressions* to be caught and trigger the according commandstate. Also necessary is a *log_name*. Using the *CommandParameterFactory* class, the user may change a set of available command parameters, that influence how commands act and how long they take to be executed by the device. The commands dictionary contains the actual commands provided by the manufacturer of the device. The structure is described on the following example:

```
"GET_POS": ["POSITION", r"POSITION:(?P<position>.*)"]
```

"Name used in the driver": ["Command as expected by the device", expected reply as regular expression with observable parameters as named groups]

The following functions need to be implemented for all devices:

- *cmd_string*: returns the command string expected by the device, consisting of the command itself (as defined in the command dictionary above), a value and possibly a query sign.
- *initial_commands*: this is executed on software startup to get the device in a defined condition.
- *final_commands*: this is executed on errors, stop or shutdown the setup to turn off the devices or end possible actions.

- `handle_event`: *this handles incoming messages if the device supports it (for an example see the driver of the ismatec reglo ICC).*

The other functions included in the Device class, are either expected by the *BaseDevice* for *multipos_valve_base* (*next_position*, *previous_position*) or implement special or internal functionality for the given device.

```
from .multipos_valve_base import BaseDevice, SinglechannelBaseDevice, commandstate, CommandParameterFactory
import re

class Device(SinglechannelBaseDevice, BaseDevice):
    reply_to_state = {"OK": commandstate.Success}
    error_patterns = [r"ERROR:(?P<code>.*),(?P<message>.*)" ]
    replies_commands = True
    log_name = "Knauer AzuraVU"

    command_parameter_factory = CommandParameterFactory(inter_command_time=1)

    commands = {
        ### COMMON COMMANDS ###
        "GET_IDN": ["IDENTIFY",
                    r"IDENTIFY:(?P<device_type>.*),(?P<manufacturer>.*),(?P<model_name>.*),(?P<serial_number>.*),(?P<
firmware_version>.*),(?P<position_count>.*),(?P<ports_number>.*)" ],
        "SET_POS": ["POSITION"],
        "GET_POS": ["POSITION", r"POSITION:(?P<position>.*)" ],
        "GET_STATUS": ["STATUS",
                       r"STATUS:(?P<system_tick_count>.*),(?P<instrument_state>.*),(?P<current_error_code>.*),(?P<last_warning_code>.*),(?P<
current_position>.*),(?P<run_time_ms>.*),(?P<home_in_state>.*),(?P<backward_in_state>.*),(?P<forward_in_state>.*),(?P<
start_in_state>.*),(?P<event_out_state>.*),(?P<encoder_position>.*),(?P<encoder_angle>.*),(?P<valve_shaft_position>
.*),(?P<last_reposition_diagnostic>.*),(?P<interface_state>.*),(?P<CPU_temperature>.*)" ],
        "GET_VALVE": ["VALVE", r"VALVE:(?P<serial_number>[0-9A-Za-z]*),(?P<valve_type>-?[0-
9]*),(?P<position_count>[0-9]*),(?P<port_count>[0-9]*),(?P<home_angle>[0-9]*),(?P<maximum_pressure>[0-
9]*),(?P<velocity_factor>[0-9]*),(?P<maximum_seal_cycles>[0-9]*),(?P<switch_cycle_amount>[0-
9]*),(?P<global_scaler_override>[0-9]*),(?P<torque_range>[0-9]*),(?P<reserved_4>[0-
9]*),(?P<part_number>[^,]*),(?P<position_info>.*)" ],
    }

    def cmd_string(self, command_parameters: CommandParameterFactory) -> str:
        if command_parameters.query:
            query = "?"
        else:
            query = ""
        try:
            value = command_parameters.command_values["value"]
        except KeyError:
            sep = ""
```

```

        value = ""
    else:
        sep = ":"
    value = str(value)
    command = command_parameters.commandstring
    return f"{command}{sep}{value}{query}"

def set_position(self, position, **kwargs):
    with self.commandseries as series:
        result = self.write("SET_POS", command_values={"value": int(float(position))}, **kwargs)
        self.query("GET_POS")
    return result

def initial_commands(self):
    self.query("GET_IDN", inter_command_time=0)
    self.set_position(1)
    super().initial_commands()

def final_commands(self):
    self.set_position(1)

def handle_event(self, match: re.Match) -> None:
    pass

def _get_valve_positions(self):
    return self.query("GET_VALVE", inter_command_time=0)

def _move_position(self, result, step):
    pos = int(result.parameters["position"]) + step
    if pos > self.positions:
        pos -= self.positions
    elif pos < 1:
        pos += self.positions
    self.set_position(pos, urgent=True)

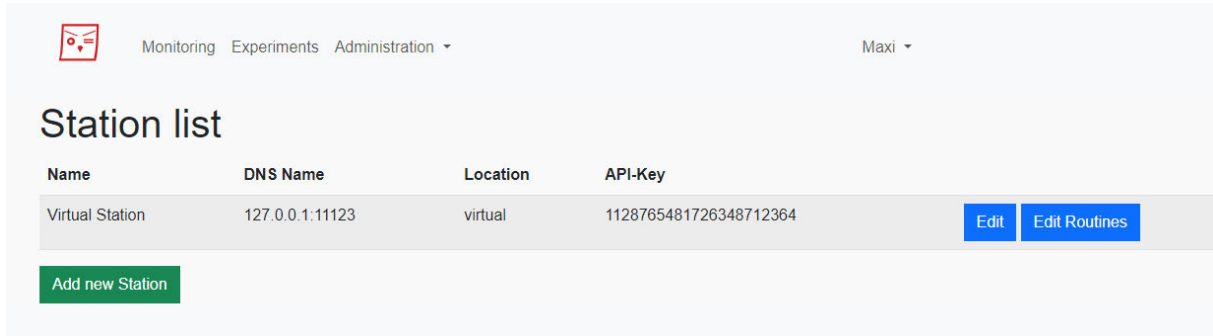
def next_position(self):
    return self.query("GET_POS").deferred_result.addCallback(self._move_position, +1)

def previous_position(self):
    return self.query("GET_POS").deferred_result.addCallback(self._move_position, -1)

```

6 Frontend

The station overview offers the possibility to add new stations or to change or remove existing stations.

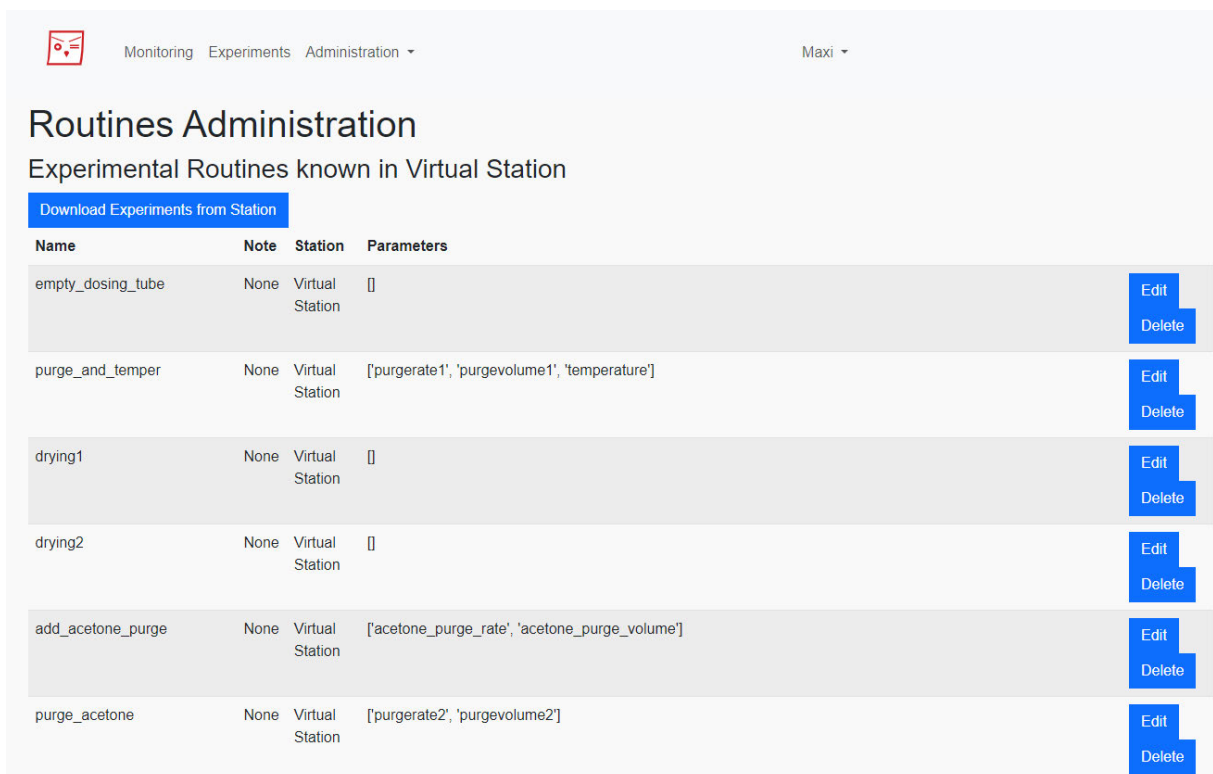


The screenshot shows the 'Station list' interface. At the top, there is a navigation bar with a logo, 'Monitoring', 'Experiments', and 'Administration' (with a dropdown arrow), and a user profile 'Maxi' (with a dropdown arrow). Below the navigation bar, the title 'Station list' is displayed. A table lists the stations with columns: Name, DNS Name, Location, and API-Key. The table contains one entry: 'Virtual Station' with DNS Name '127.0.0.1:11123', Location 'virtual', and API-Key '1128765481726348712364'. To the right of the table are two buttons: 'Edit' and 'Edit Routines'. Below the table is a green button labeled 'Add new Station'.

Name	DNS Name	Location	API-Key
Virtual Station	127.0.0.1:11123	virtual	1128765481726348712364

Buttons: Edit, Edit Routines, Add new Station

In the routine administration, adjustments can be made in the parameters of the individual routines. If a parameter is set as a static parameter in a routine, it does not have to be explicitly specified by the user. In this case it overwrites the user input.



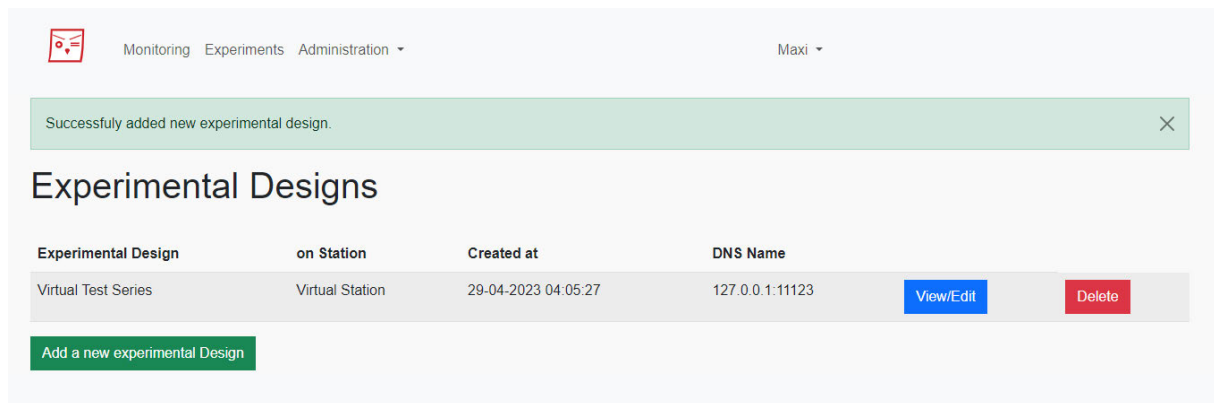
The screenshot shows the 'Routines Administration' interface. At the top, there is a navigation bar with a logo, 'Monitoring', 'Experiments', and 'Administration' (with a dropdown arrow), and a user profile 'Maxi' (with a dropdown arrow). Below the navigation bar, the title 'Routines Administration' is displayed, followed by the subtitle 'Experimental Routines known in Virtual Station'. A blue button labeled 'Download Experiments from Station' is located below the subtitle. A table lists the routines with columns: Name, Note, Station, and Parameters. The table contains six entries: 'empty_dosing_tube', 'purge_and_temper', 'drying1', 'drying2', 'add_acetone_purge', and 'purge_acetone'. Each entry has a corresponding 'Edit' and 'Delete' button to its right.

Name	Note	Station	Parameters
empty_dosing_tube	None	Virtual Station	[]
purge_and_temper	None	Virtual Station	['purgerate1', 'purgevolume1', 'temperature']
drying1	None	Virtual Station	[]
drying2	None	Virtual Station	[]
add_acetone_purge	None	Virtual Station	['acetone_purge_rate', 'acetone_purge_volume']
purge_acetone	None	Virtual Station	['purgerate2', 'purgevolume2']

Buttons: Edit, Delete (for each routine)

In the experimental designs overview, new experimental designs can be added and assigned to an experimental station. this results in the selection of experiment types that can be added to the

design.



Monitoring Experiments Administration ▾ Maxi ▾

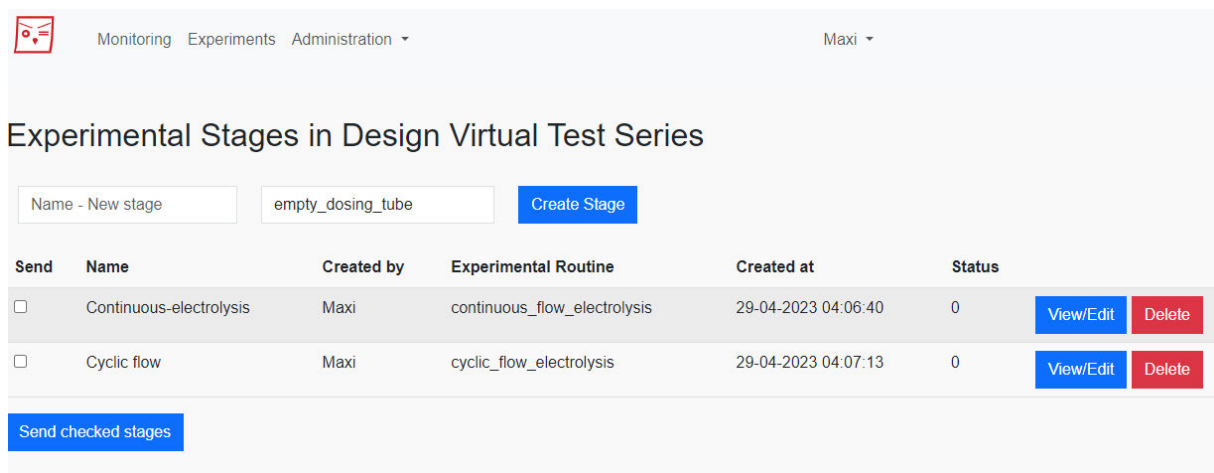
Successfully added new experimental design. ✕

Experimental Designs

Experimental Design	on Station	Created at	DNS Name		
Virtual Test Series	Virtual Station	29-04-2023 04:05:27	127.0.0.1:11123	View/Edit	Delete

[Add a new experimental Design](#)

Within an experimental design, multiple stages can be added. To add a stage, its name and a method case must be specified.



Monitoring Experiments Administration ▾ Maxi ▾

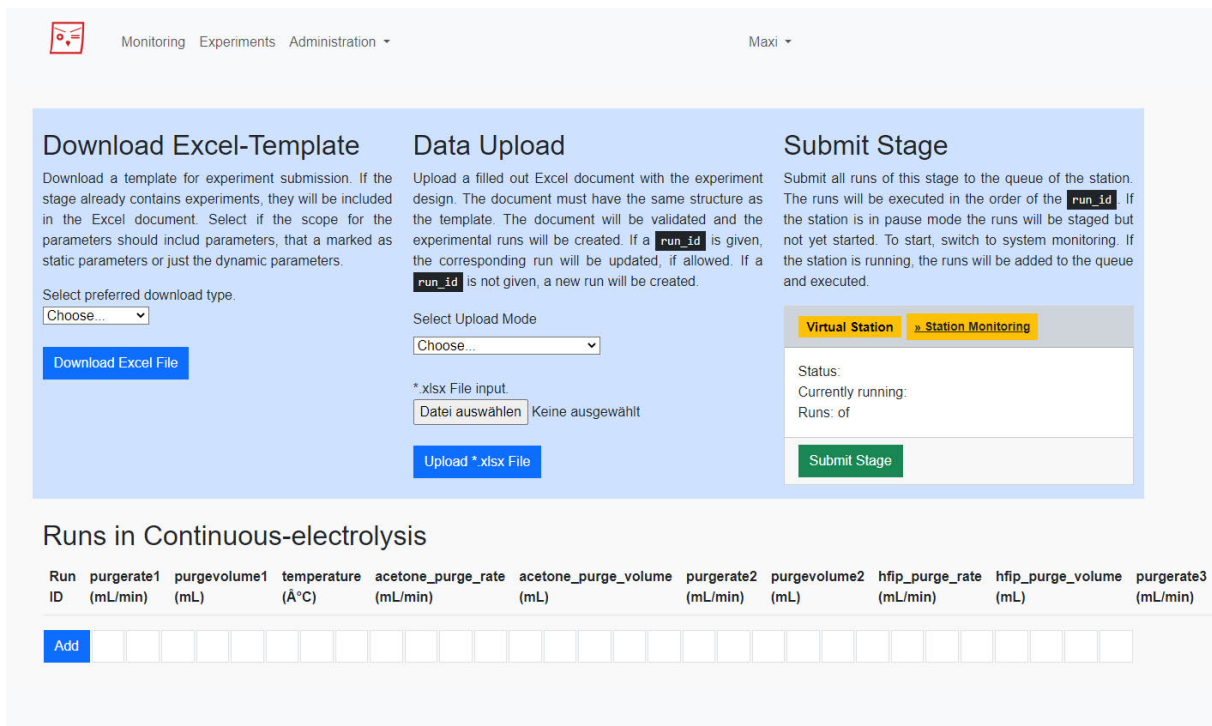
Experimental Stages in Design Virtual Test Series

[Create Stage](#)

Send	Name	Created by	Experimental Routine	Created at	Status		
☐	Continuous-electrolysis	Maxi	continuous_flow_electrolysis	29-04-2023 04:06:40	0	View/Edit	Delete
☐	Cyclic flow	Maxi	cyclic_flow_electrolysis	29-04-2023 04:07:13	0	View/Edit	Delete

[Send checked stages](#)

Within a stage, different runs can be added, deleted, and selected. The user can download the run-table as an excel-file. He can choose if he wants to export all parameters in this table (including the static parameters or only the active parameters without static parameters). The user can also upload an excel-sheet which contains the values for the experimental runs. These are then stored in the database of the frontend, or already existing runs (assigned via an ID column) are updated. The user can submit the runs of a stage to the experimental station from here.



The screenshot shows the 'Data Upload' and 'Submit Stage' sections of the software interface. The 'Data Upload' section includes a 'Download Excel-Template' button, a 'Select preferred download type' dropdown, and a 'Download Excel File' button. The 'Data Upload' section also includes a 'Select Upload Mode' dropdown, a '* .xlsx File input' field, and an 'Upload * .xlsx File' button. The 'Submit Stage' section includes a 'Submit Stage' button and a 'Status' section showing 'Currently running: Runs: of'.

Download Excel-Template

Download a template for experiment submission. If the stage already contains experiments, they will be included in the Excel document. Select if the scope for the parameters should include parameters, that a marked as static parameters or just the dynamic parameters.

Select preferred download type.
Choose...

[Download Excel File](#)

Data Upload

Upload a filled out Excel document with the experiment design. The document must have the same structure as the template. The document will be validated and the experimental runs will be created. If a `run_id` is given, the corresponding run will be updated, if allowed. If a `run_id` is not given, a new run will be created.

Select Upload Mode
Choose...

* .xlsx File input.
[Datei auswählen](#) Keine ausgewählt

[Upload * .xlsx File](#)

Submit Stage

Submit all runs of this stage to the queue of the station. The runs will be executed in the order of the `run_id`. If the station is in pause mode the runs will be staged but not yet started. To start, switch to system monitoring. If the station is running, the runs will be added to the queue and executed.

[Virtual Station](#) [Station Monitoring](#)

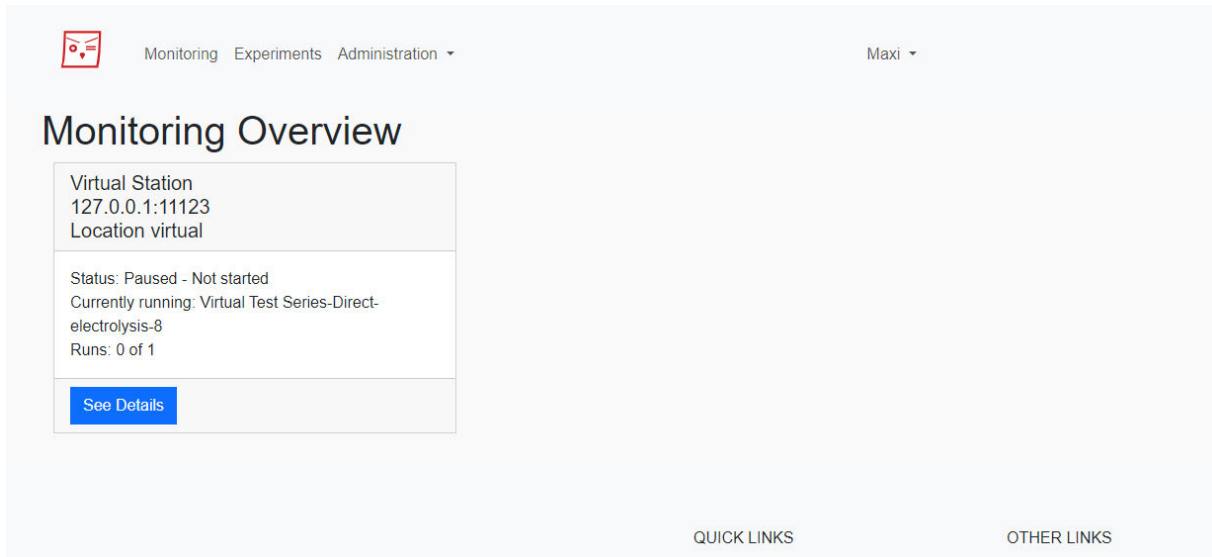
Status:
Currently running:
Runs: of

[Submit Stage](#)

Runs in Continuous-electrolysis

Run ID	purgerate1 (mL/min)	purgevolume1 (mL)	temperature (Å°C)	acetone_purge_rate (mL/min)	acetone_purge_volume (mL)	purgerate2 (mL/min)	purgevolume2 (mL)	hflip_purge_rate (mL/min)	hflip_purge_volume (mL)	purgerate3 (mL/min)
Add										

The monitoring overview provides an overview of all experimental stations registered in the frontend. The current state and the length of the queue of the respective station is displayed. A detailed view can be called up by clicking on a button.



The screenshot shows the 'Monitoring Overview' section of the software interface. It displays a table with columns for 'Virtual Station', 'Status', and 'Runs'. The 'Virtual Station' column shows '127.0.0.1:11123' and 'Location virtual'. The 'Status' column shows 'Paused - Not started', 'Currently running: Virtual Test Series-Direct-electrolysis-8', and 'Runs: 0 of 1'. The 'Runs' column shows '0 of 1'. A 'See Details' button is located below the table. At the bottom, there are 'QUICK LINKS' and 'OTHER LINKS' sections.

Monitoring Overview

Virtual Station	Status	Runs
127.0.0.1:11123 Location virtual	Paused - Not started Currently running: Virtual Test Series-Direct-electrolysis-8	0 of 1

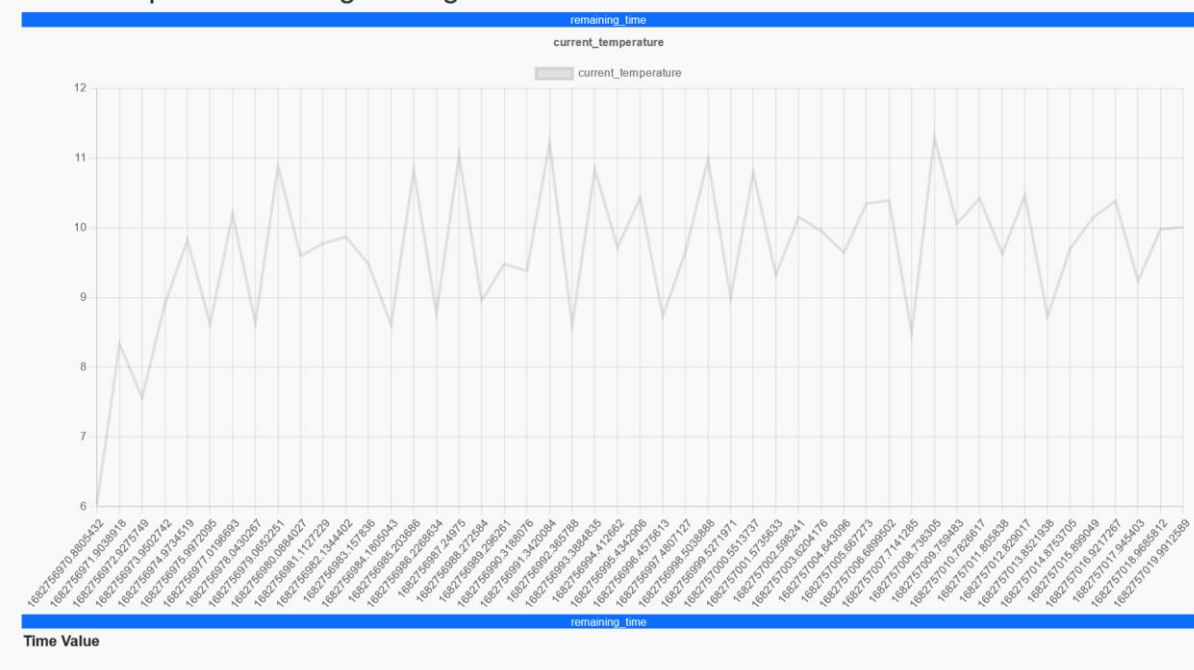
[See Details](#)

QUICK LINKS OTHER LINKS

The detailed view shows live data of all parameters defined as observables in the backends configuration file.

Detailed Run Information

Current experiment: Design1-Stage1-1



Used Software Packages for the framework:

Bootstrap is released under the MIT license and is copyright 2018 Twitter.
<https://getbootstrap.com/docs/5.0/getting-started/introduction/>

Flask: The BSD-3-Clause license applies to all files in the Flask repository and source distribution. This includes Flask's source code, the examples, and tests, as well as the documentation.
<https://flask.palletsprojects.com/en/2.3.x/>

Plotly JS is free and open-source software, licensed under the MIT license.
<https://plotly.com/graphing-libraries/>

Grid JS is released under the MIT license. <https://gridjs.io/docs>

The code for the frontend was published at the GitLab server of JGU Mainz:
<https://gitlab.rlp.net/hielscher/labs-frontend>

7 General protocol for dehydrating coupling reactions

Automated experiments: The experiments were performed according to the configuration file. Acetone or isopropanol was used as the rinsing solvent. The rinsing volume was set to 3 mL higher than the preparation volume. Before each electrolysis, the cell was primed with 2 mL HFIP. The

HFIP-pyridine system was used as the supporting electrolyte. Before starting electrolysis, the cell was flooded and, in the case of single-pass experiments, a first fraction of 2 mL electrolyzed mixture was discarded to allow the system to reach an equilibrium state. After each experiment, the electrolyte was collected with the fraction collector and the reservoir was purged with 3 mL of HFIP.

Yield determination: As internal standard, *n*-octylbenzene (145.2 mg, 0.762 mmol) was added into a 20 mL glass vial. The reaction solution was transferred from the fraction collector's test tube into the vial and rinsed with HFIP (2x5 mL). The vial was closed, and its contents homogenized by shaking. Using a pipette, 10 drops of this solution were filtered through a plug of silica into a GC vial using ethyl acetate. The sample was measured with a Shimadzu GC-2025. The yield was determined by a calibration of the product.

Pump calibration: Isopropanol or Acetone was used for calibrations. Each channel of the pump was calibrated separately by measuring the mass of isopropanol which was pumped into a glass vial in a defined time. To calculate the volume of isopropanol, a density of 0.786 g/mL was assumed. The dosing channel was calibrated using 5 mL/5 min and the channel for cyclic flow (through the flow cell and back into the reservoir) was calibrated using 6 mL/1 min. Each channel was calibrated threefold.

Optimization Data

7.1 Control Experiments with BPT Pharmed Tubing

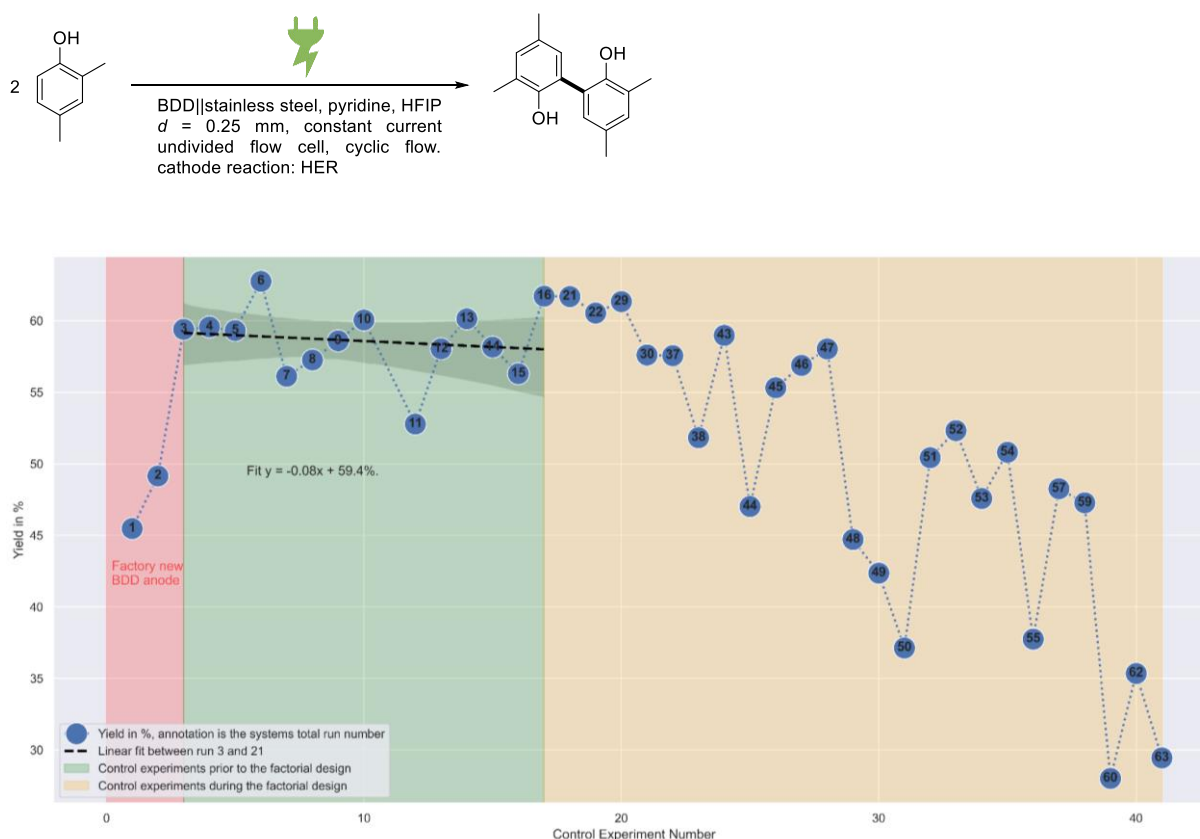


Figure 3: Dehydrodimerization yield (%) versus run number of the control experiment. The annotated number is the station wide run number for this control experiment. The area further investigated by a 2^{6-2} design is highlighted brown, here only the control experiments in between the DoE series are plotted.

The voltage curves for the control tests show a general increase in cell voltage with increasing run number. Nevertheless, the general features of a short increase at the beginning of the electrolysis with a decrease of the voltage during the electrolysis remain. Only the last two control experiments reach a plateau at the end of electrolysis. We attribute the initial higher cell voltage to insufficient substrate dosing and thus lower concentrations in the electrolyte mixing step. An additional contribution to the higher cell voltage results from a lower flow rate due to the abrasion of the tubing. This increases the residence time of the electrolyte in the cell, since the current density, the flow rate and the applied charge are coupled in flow electrolysis.

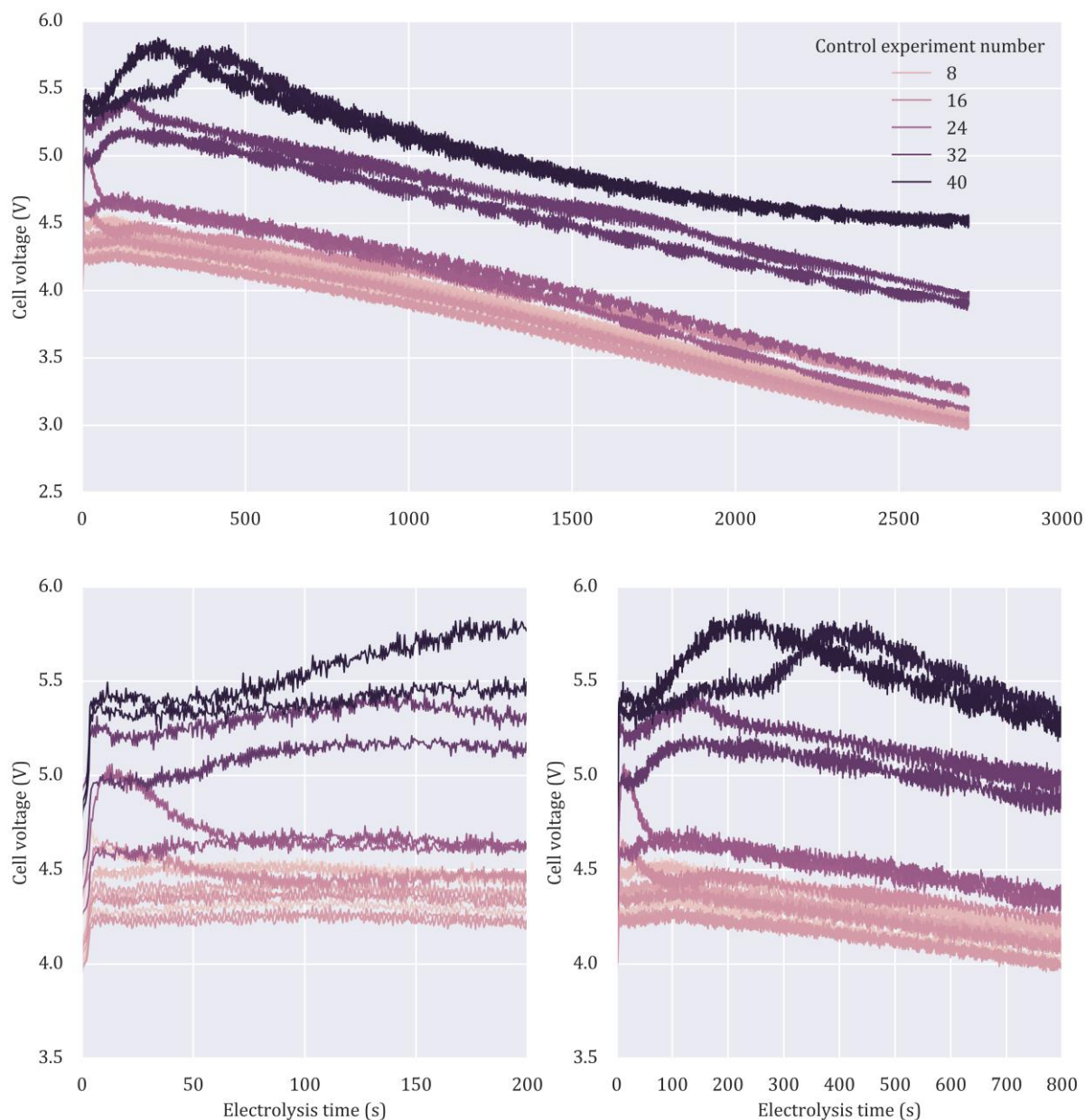


Figure 4: Cell voltage plots for the control experiments series. Total electrolysis time at top, first 200 seconds at bottom left, and first 800 seconds at bottom right.

Table 1: Experimental conditions of the Control Experiments: $j = 10\text{mA/cm}^2$, $Q = 0.9 F$, $v = 1.99\text{ mL/min}$ ($15 \times$ single pass rate), $c(1) = 1.25\text{ mol/L}$, $\text{vol.}(\text{pyridine}) = 5\%$, $T = 25^\circ\text{C}$.

Run	2-4-Dimethyl phenol (mmol)	<i>n</i> -Octylbenzene	FID Area (2-4-Dimethylphenol)	FID area (<i>n</i> -octylbenzene)	FID area (3.3'5.5'-tetramethyl-1.1'-biphenol)	Yield of 3.3'5.5'-tetramethyl-1.1'-biphenol (%)
1	7.5	146.00	147168	187015	390459	45.5%
2	7.5	145.40	145531	206180	467186	49.2%
3	7.5	144.70	231312	218128	600185	59.4%

4	7.5	146.50	310415	299791	816950	59.6%
5	7.5	144.70	178773	161525	443793	59.3%
6	7.5	144.80	254240	226452	657804	62.8%
7	7.5	144.10	280968	282959	738621	56.1%
8	7.5	144.10	235373	247686	659710	57.3%
9	7.5	148.20	244835	243023	644037	58.6%
10	7.5	145.70	292471	271556	750247	60.1%
12	7.5	145.40	104546	77420	188361	52.8%
13	7.5	145.50	127588	97543	260786	58.0%
14	7.5	143.90	160721	121292	339742	60.1%
15	7.5	144.90	101024	88577	238299	58.2%
16	7.5	147.10	388127	202979	520727	56.3%
17	7.5	145.10	268165	140449	400414	61.7%
18	7.5	146.10	295612	155564	440280	61.7%
19	7.5	148.10	308682	183919	503939	60.5%
20	7.5	144.30	412544	227767	648950	61.3%
21	7.5	144.40	42926	28869	77192	57.6%
22	7.5	144.00	44308	33625	90094	57.6%
23	7.5	150.30	49163	42043	97171	51.8%
24	7.5	145.60	61573	42852	116343	59.0%
25	7.5	146.30	112874	77214	166337	47.0%
26	7.5	146.50	111617	76572	193789	55.3%
27	7.5	145.00	143412	123166	323834	56.9%
28	7.5	145.60	134733	114531	305945	58.0%
29	7.5	145.70	41562	50117	103079	44.7%
30	7.5	148.50	32963	47373	90572	42.4%
31	7.5	145.20	164896	87956	150766	37.1%
32	7.5	147.30	114774	90585	207864	50.4%
33	7.5	145.00	118363	86438	209068	52.3%
34	7.5	146.20	59347	61350	133825	47.6%
35	7.5	147.00	107240	102281	236937	50.8%
36	7.5	144.70	252335	116341	203438	37.8%
37	7.5	145.10	126129	110135	245524	48.3%
38	7.5	146.70	171873	112969	244018	47.3%
39	7.5	144.80	113587	107042	138809	28.0%
40	7.5	144.70	100464	79298	129853	35.4%
41	7.5	145.70	73485	81196	109989	29.5%

7.2 Fractional Factorial Design (Tubing: Pharmed®)

We have included the data from the first Design of Experiments with the Pharmed® tubes here.

The reliability of the data is hardly given due to the continuous change of the flow rates during

dosing. Nevertheless, it can be concluded that higher phenol concentrations lead to significantly higher yields.

Model Summary

S	R ²	R ² (adj.)	R ² (pred.)
0,0885599	57,1%	41,2%	13,3%

Graphical visualisation of the model

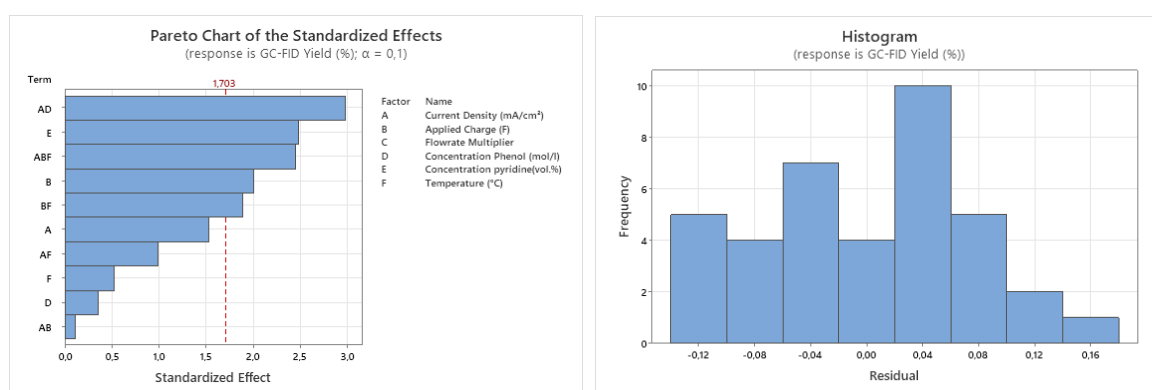


Figure 5: Pareto chart for the effects of the yield model (right) and histogram of residuals (left).

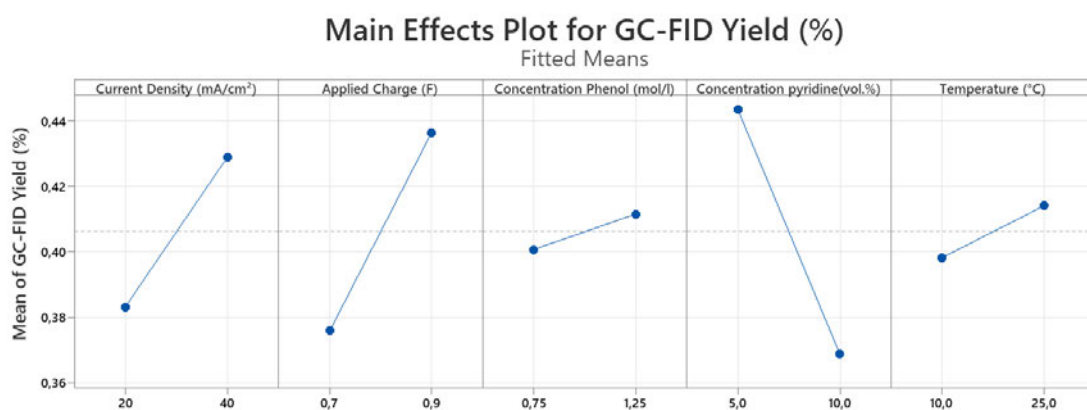


Figure 6: Main effect plots regarding the yield model of 2.

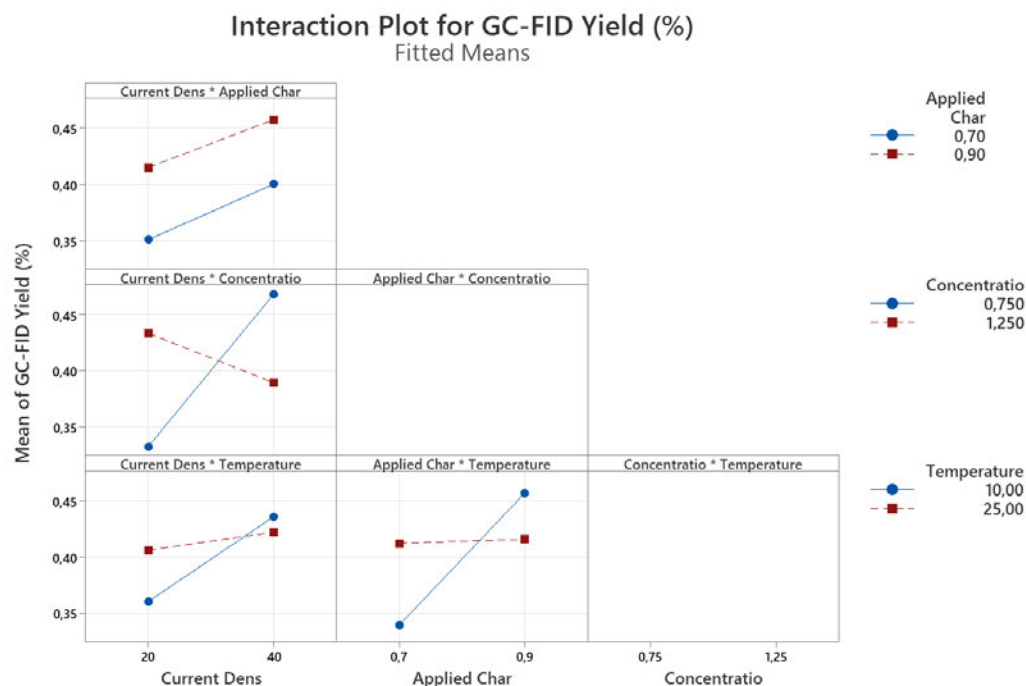


Figure 7: Interaction plots regarding the yield model of 2.

7.3 Repetition of the experimental design

For the fit of the estimated flow rate, a linear fit was applied between the calibration and test points.

Table 2: Experimental conditions of the Control Experiments: $j = 10\text{mA/cm}^2$, $Q = 0.9\text{ F}$, $v = 1.99\text{ mL/min}$ ($15 \times$ Single pass rate), $C(1) = 1.25\text{ mol/L}$, $\text{vol.}\%(\text{Pyridine}) = 5\%$, $T = 25^\circ\text{C}$.

ID	Current density	Applied charge (F)	Flowrate Multiplier	Concentration phenol (mol/l)	Concentration pyridine (vol.%)	Temperature ($^\circ\text{C}$)	Flowrate fit	Estimated total volume (mL)	Yield (%)
1	30	0,8	7,5	0,50	0,075	17,5	1,028	7,2	26%
2	30	0,8	7,5	0,50	0,075	17,5	1,026	7,2	25%
3	30	0,8	7,5	0,50	0,075	17,5	1,024	7,2	24%
4	20	0,9	5,0	0,63	0,100	10,0	1,021	7,2	20%
5	20	0,9	5,0	0,38	0,100	25,0	1,019	7,1	25%
6	40	0,7	10,0	0,63	0,050	10,0	1,017	7,1	25%
7	40	0,9	5,0	0,38	0,050	25,0	1,015	7,1	31%
8	40	0,9	5,0	0,38	0,050	25,0	1,012	7,1	32%
9	40	0,7	5,0	0,38	0,100	10,0	1,010	7,1	18%
10	40	0,7	5,0	0,38	0,100	10,0	1,008	7,1	19%
11	20	0,7	5,0	0,63	0,050	25,0	1,006	7,0	43%

12	30	0,8	7,5	0,50	0,075	17,5	1,003	7,0	26%
13	30	0,8	7,5	0,50	0,075	17,5	1,001	7,0	43%
14	30	0,8	7,5	0,50	0,075	17,5	0,999	7,0	37%
15	40	0,9	10,0	0,63	0,100	25,0	0,960	6,7	35%
16	20	0,9	5,0	0,38	0,100	25,0	0,922	6,5	31%
17	40	0,7	5,0	0,63	0,100	25,0	0,883	6,2	28%
18	40	0,9	5,0	0,63	0,050	10,0	0,845	5,9	33%
19	20	0,7	10,0	0,38	0,100	25,0	0,806	5,6	42%
20	20	0,9	10,0	0,63	0,050	25,0	0,768	5,4	48%
21	40	0,9	5,0	0,63	0,050	10,0	0,729	5,1	43%
22	20	0,7	10,0	0,38	0,100	25,0	1,011	7,1	30%
23	30	0,8	7,5	0,50	0,075	17,5	0,991	6,9	31%
24	30	0,8	7,5	0,50	0,075	17,5	1,021	7,1	33%
25	30	0,8	7,5	0,50	0,075	17,5	1,050	7,4	33%
26	20	0,9	5,0	0,63	0,100	10,0	1,080	7,6	16%
27	40	0,7	10,0	0,38	0,050	25,0	1,110	7,8	27%
28	40	0,7	5,0	0,63	0,100	25,0	1,140	8,0	12%
29	40	0,9	10,0	0,38	0,100	10,0	1,169	8,2	13%
30	20	0,7	5,0	0,63	0,050	25,0	1,199	8,4	33%
31	40	0,9	10,0	0,63	0,100	25,0	1,229	8,6	25%
32	20	0,7	10,0	0,63	0,100	10,0	1,258	8,8	18%
33	20	0,9	10,0	0,63	0,050	25,0	1,288	9,0	30%
34	30	0,8	7,5	0,50	0,075	17,5	1,027	7,2	22%
35	30	0,8	7,5	0,50	0,075	17,5	1,022	7,2	22%
36	30	0,8	7,5	0,50	0,075	17,5	1,017	7,1	22%
37	20	0,7	10,0	0,63	0,100	10,0	1,012	7,1	16%
38	20	0,9	10,0	0,38	0,050	10,0	1,007	7,1	21%
39	20	0,7	5,0	0,38	0,050	10,0	1,002	7,0	20%
40	20	0,7	5,0	0,38	0,050	10,0	1,022	7,2	17%
41	40	0,7	10,0	0,63	0,050	10,0	1,042	7,3	22%
42	40	0,7	10,0	0,38	0,050	25,0	1,062	7,4	24%
43	20	0,9	10,0	0,38	0,050	10,0	1,083	7,6	25%
44	40	0,9	10,0	0,38	0,100	10,0	1,103	7,7	19%
45	30	0,8	7,5	0,50	0,075	17,5	1,123	7,9	33%
46	30	0,8	7,5	0,50	0,075	17,5	1,143	8,0	26%
47	30	0,8	7,5	0,50	0,075	17,5	1,163	8,1	25%

We carried out ANOVA with backward elimination ($\alpha = 0.1$) for the calculated regression model that derives the following reduced model:

Coded Coefficients

Term	Effect	Coef	SE Coef	T-Value	P-Value	VIF
Constant		0,6967	0,0822	8,48	0,000	
Calibration		-0,4173	0,0783	-5,33	0,000	1,53
Current density	-	-	0,00843	-1,18	0,247	1,00
	0,01982	0,00991				
Applied charge (F)	0,02608	0,01304	0,00844	1,54	0,131	1,01
Flowrate multiplier	0,02154	0,01077	0,00868	1,24	0,223	1,07
Concentration phenol (mol/l)	0,0725	0,0362	0,0165	2,20	0,034	1,39
Concentration pyridine (vol.%)	-	-	0,00846	-3,47	0,001	1,01
	0,05871	0,02936				
Temperature (°C)	0,09184	0,04592	0,00842	5,46	0,000	1,00
Current density*Applied charge (F)	0,03588	0,01794	0,00841	2,13	0,040	1,00
Current density*Temperature (°C)	-	-	0,00865	-2,80	0,008	1,06
	0,04842	0,02421				
Ct Pt		0,0271	0,0149	1,81	0,078	1,01

Model Summary

S	R ²	R ² (adj.)	R ² (pred.)
0,0885599	74.2%	66.9%	61.9%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	10	0,233503	0,023350	10,31	0,000
Covariates	1	0,064271	0,064271	28,38	0,000
Calibration	1	0,064271	0,064271	28,38	0,000
Linear	6	0,119119	0,019853	8,77	0,000
Current density	1	0,003133	0,003133	1,38	0,247
Applied charge (F)	1	0,005398	0,005398	2,38	0,131
Flowrate multiplier	1	0,003486	0,003486	1,54	0,223
Concentration phenol (mol/l)	1	0,010964	0,010964	4,84	0,034
Concentration pyridine (vol.%)	1	0,027254	0,027254	12,03	0,001
Temperature (°C)	1	0,067425	0,067425	29,77	0,000
2-Way Interactions	2	0,027891	0,013945	6,16	0,005
Current density*Applied charge (F)	1	0,010293	0,010293	4,54	0,040
Current density*Temperature (°C)	1	0,017729	0,017729	7,83	0,008
Curvature	1	0,007441	0,007441	3,29	0,078
Error	36	0,081527	0,002265		
Total	46	0,315031			

Graphical visualisation of the model

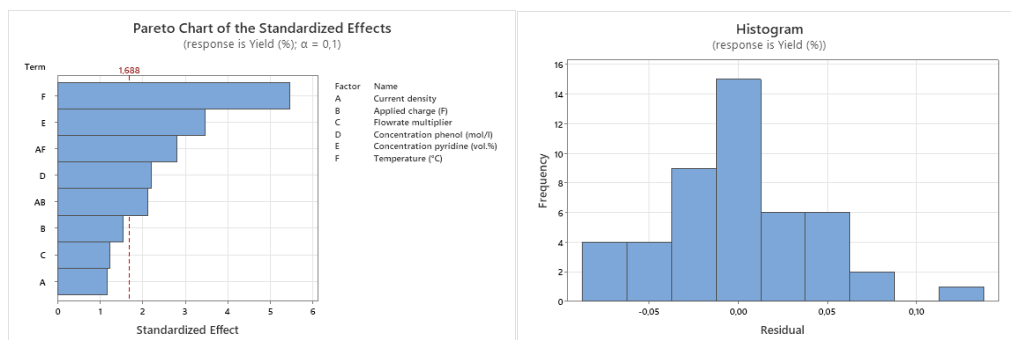


Figure 8: Pareto chart for the effects of the yield model (right) and histogram of residuals (left).

It should be mentioned that the parameters current density, applied charge and flowrate multiplier are not significant in the actual model with an $\alpha = 0.1$ but they occur in significant two factor interactions and therefore cannot be excluded from the model.

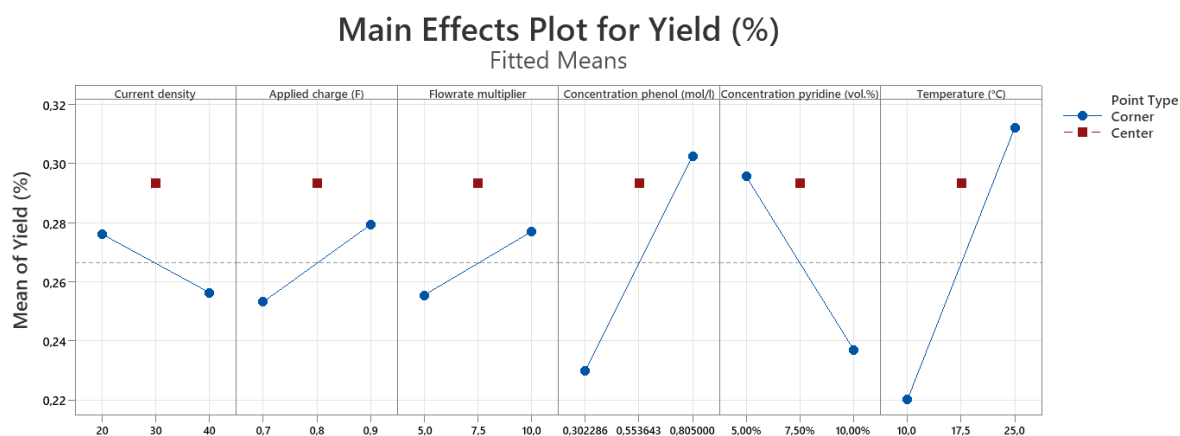


Figure 9: Main effect plots regarding the yield model.

8 References

- [1] W. L. F. Armarego, C. L. L. Chai, *Purification of laboratory chemicals*, 7. Aufl., Elsevier, Amsterdam, **2013**.
- [2] M. Zirbes, T. Graßl, R. Neuber, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2023**, 62, e202219217; *Angew. Chem.* **2023**, 135.
- [3] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, 21, 771–778.
- [4] “Twisted”, can be found under <https://twisted.org/>, **2023**.

ChemElectroChem

Supporting Information

Electrochemical Synthesis of Sulfonamides in Single-Pass Flow

Johannes Schneider, Stephan P. Blum, and Siegfried R. Waldvogel*

1. GENERAL INFORMATION	3
2. EXPERIMENTAL SETUP	4
3. EXPERIMENTAL PROCEDURES	6
4. OPTIMIZATION OF REACTION CONDITIONS	8
5. ANALYTICAL DATA	9
1. 4-((2,5-DIMETHOXYPHENYL)SULFONYL)MORPHOLINE (1)	9
2. 4-((2,3-DIMETHOXYPHENYL)SULFONYL)MORPHOLINE (2A) & 4-((3,4-DIMETHOXYPHENYL)SULFONYL)-MORPHOLINE (2B) 10	
3. 4-((4-BROMO-2,5-DIMETHOXYPHENYL)SULFONYL)MORPHOLINE (3A), 4-((3-BROMO-2,5-DIMETHOXY-PHENYL)SULFONYL)MORPHOLINE (3B)	10
4. 4-((2,5-DIMETHOXY-3,4-DIMETHYLPHENYL)SULFONYL)MORPHOLINE (4)	11
5. 4-((4-CHLORO-2,5-DIMETHOXYPHENYL)SULFONYL)MORPHOLINE (5A) & 4-((3-CHLORO-2,5-DIMETHOXY-PHENYL)SULFONYL)MORPHOLINE (5B)	11
6. 4-((4-FLUORO-2,5-DIMETHOXYPHENYL)SULFONYL)MORPHOLINE (6A) & 4-((3-FLUORO-2,5-DIMETHOXY-PHENYL)SULFONYL)MORPHOLINE (6B)	11
7. 4-((2,3-DIHYDRO-BENZO[B][1,4]DIOXIN-5-YL) SULFONYL)MORPHOLINE (7A) & 4-((2,3-DIHYDROBENZO[B][1,4]DIOXIN-6-YL) SULFONYL)MORPHOLINE (7B).....	12
8. 1-((2,5-DIMETHOXYPHENYL)SULFONYL)AZEPANE (8)	13
9. <i>N,N</i> -DIBUTYL-2,5-DIMETHOXYBENZENESULFONAMIDE (9).....	13
10. <i>N,N</i> -DIISOBUTYL-2,5-DIMETHOXYBENZENESULFONAMIDE (10).....	13
6. NMR SPECTRA.....	14
7. REFERENCES.....	30

1. General Information

All solvents and reagents used were obtained from commercial suppliers. If required, they were purified according to standard methods.^[1] Glassy carbon electrodes (SIGRADUR™ G) were purchased from HTW Hochtemperatur-Werkstoffe GmbH (Tierhaupten, Germany). Boron-doped diamond electrodes (DIACHEM™, 15 µm BDD on 3 mm silicon wafer as supporting material) were bought from CONDIAS GmbH (Itzehoe, Germany). For electrolysis, a Rohde & Schwarz HMP4040 programmable power supply 384W was used (Rohde & Schwarz GmbH & Co. KG, Munich, Germany). Flow chemistry was carried out using an Ismatec REGLO Digital ISM597D peristaltic pump (IKA-Werke GmbH & CO. KG, Staufen, Germany). A modular flow cell system, which was developed in our group, has been used.^[2] Gasket material for the large flow cell (FFKM/FFPM CKD900) was obtained from CKD Dichtungstechnik GmbH (Dreieich, Germany). Sulfur dioxide (purity 99.98%) was purchased from Linde in a 10 L steel bottle (Linde Gas GmbH, Stadl-Paura, Austria).

Column Chromatography was carried out using a preparative column chromatography system: Büchi Control Unit C-620, 2x Büchi Pump Modules C-605, Büchi Fraction Collector C-660, and Büchi UV Photometer C-635 ($\lambda = 254$ nm). Büchi SeparateControl 1.4.30000.18063 Standard Edition was used (Büchi Labortechnik AG, Flawil, Switzerland). As stationary phase, silica (60 M, 0.04 – 0.063 mm) was utilized (Mancherey-Nagel GmbH & Co. KG, Düren, Germany). As eluent, mixtures of cyclohexane and ethyl acetate in a gradient 95:5 → 50:50 were utilized.

Thin-layer chromatography was carried out using Supelco silica gel 60 F₂₅₄ aluminium TLC plates (Merck KGaA, Darmstadt, Germany) with 5 µL micropipettes (Blaubrand intraMARK, BRAND GmbH + CO KG, Wertheim, Germany).

Gas Chromatography was performed using a Shimadzu GC-2025 (Shimadzu, Japan) with a HP-5MS column (Agilent Technologies Deutschland GmbH, Waldbronn, 30 m length, 0.25 mm diameter, 0.25 µm film).

High-resolution mass spectra (HRMS) were recorded using a G6545A Q-ToF (Agilent GmbH, Waldbronn) with Electron Spray Ionization (ESI). For sample injection, a 1260 Infinity II HPLC-System (Agilent GmbH, Waldbronn) with a G7111B 1260 Quaternary Pump, G7129A 1260 vial sampler and G7116A 1260 Multicolumn thermostat was used.

NMR spectra of ¹H (400 MHz), ¹³C{¹H} (101 MHz), and ¹⁹F (376 MHz) were recorded at 23 °C using a Bruker Avance II 400 spectrometer (400 MHz, 5 mm BBFO-SmartProbe with z gradient and ATM, SampleXPress 60 sample changer, Analytische Messtechnik, Karlsruhe, Germany). Chemical shifts are reported in parts per million (ppm) relative to CDCl₃ (7.26 ppm in ¹H NMR spectra, 77.16 ppm in ¹³C NMR spectra).^[3]

Melting Points were determined using a Melting Point apparatus B-656 (Büchi, Flawil, Switzerland) and are uncorrected. Heating rate: 1°C/min.

2. Experimental setup

Small flow cell (anode surface: 2 cm x 6 cm)

A modular flow cell setup which was developed in our group has been used in all reactions.^[2] The flow cell depicted in Figure 1 was used for optimization of reaction conditions, scope, and the first of the two scale-up experiments. The Teflon frame can hold electrodes of the size 2 cm x 6 cm x 0.3 cm. As anode material, either a BDD electrode (shown here) or a glassy carbon electrode can be utilized. The Teflon holder acts as the in- and outlet of the reaction solution in the flow cell, and the anode cable can be contacted to the back of it. As cathode material, a stainless-steel (VA 1.4571) cathode block was used in all experiments.^[4] This has one side which is flat (shown here) and one side with holes for in- and outlet of a reaction solution. Note that the flat side was used, so in- and outlet of the reaction solution is exclusively carried out through the Teflon frame. The cathode also has attachments for a temperature control unit, which were used in the experiments where the influence of temperature was investigated. As separator material, a Teflon spacer of thickness 0.25 mm was used. To assemble the flow cell, stainless steel front and back plates and stainless-steel screws (DIN 921 A2 M4X55) were used. The back plates have matching gears for the screws.

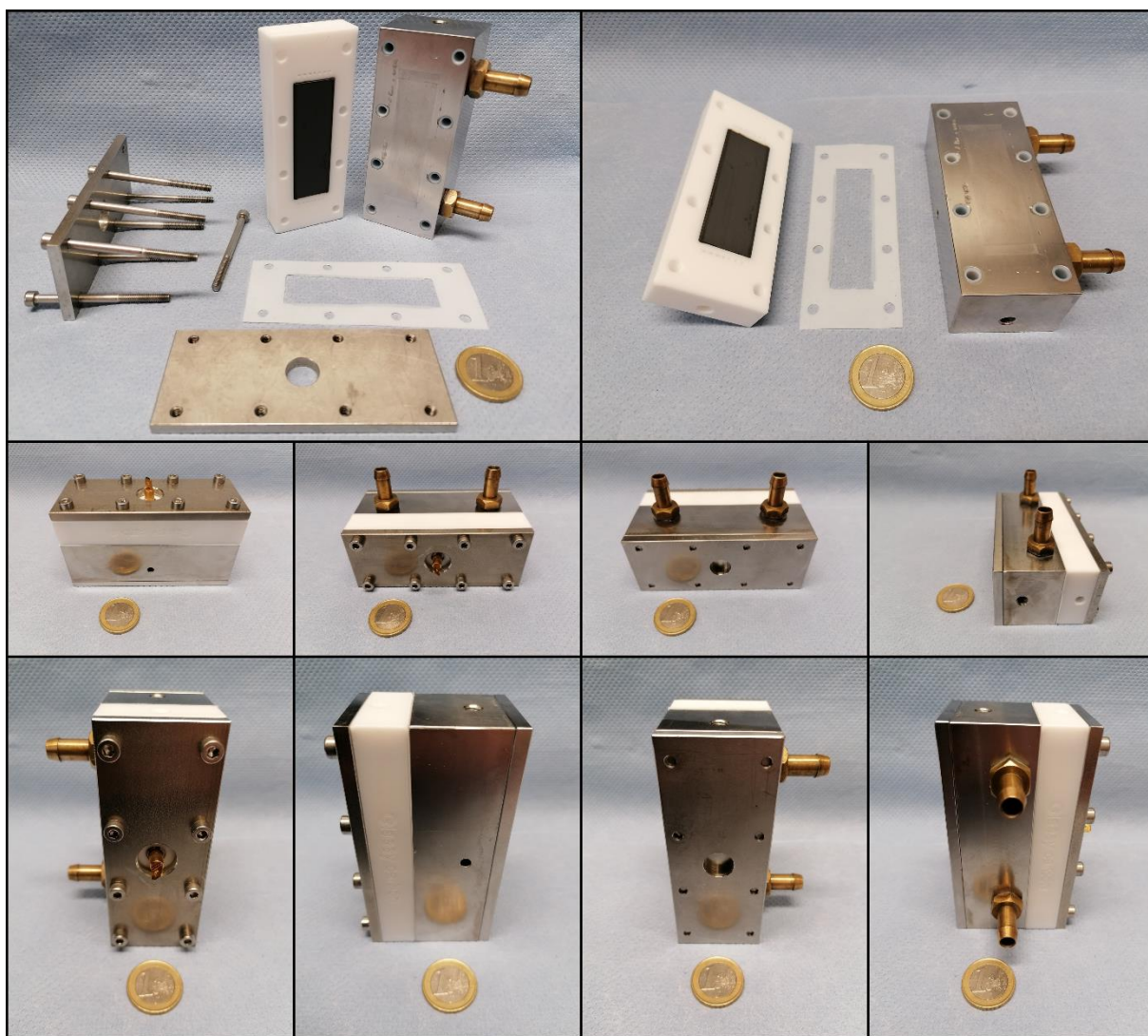


Figure 1. Modular flow cell used for optimization of reaction conditions, scope, and scale-up experiment 1. A one Euro coin is placed next to the electrolysis cell for size comparison.

Larger flow cell (anode surface: 4 cm x 12 cm)

For the second scale-up experiment, a larger flow cell as shown in Figure 2 was used.^[2,5] For this flow cell size, the design of the Teflon holder for the anode is different: because of the high thermal expansion in large pieces of Teflon, two gaskets (FFKM/FFPM CKD900) are installed to prevent reaction solution to leak underneath the BDD electrode. This also prevents damage of the BDD anode due to thermal expansion and contraction of the Teflon frame. Just as the small flow cell, the cathode is a flat stainless-steel block, so the in- and outlet of the reaction solution through the cell is carried out through the anode Teflon frame exclusively. A Teflon spacer of thickness 0.25 mm is used here as well. To assemble the cell, the stainless-steel screws are put from the cathode through the Teflon spacer, anode, and into a stainless-steel backing plate with threads.

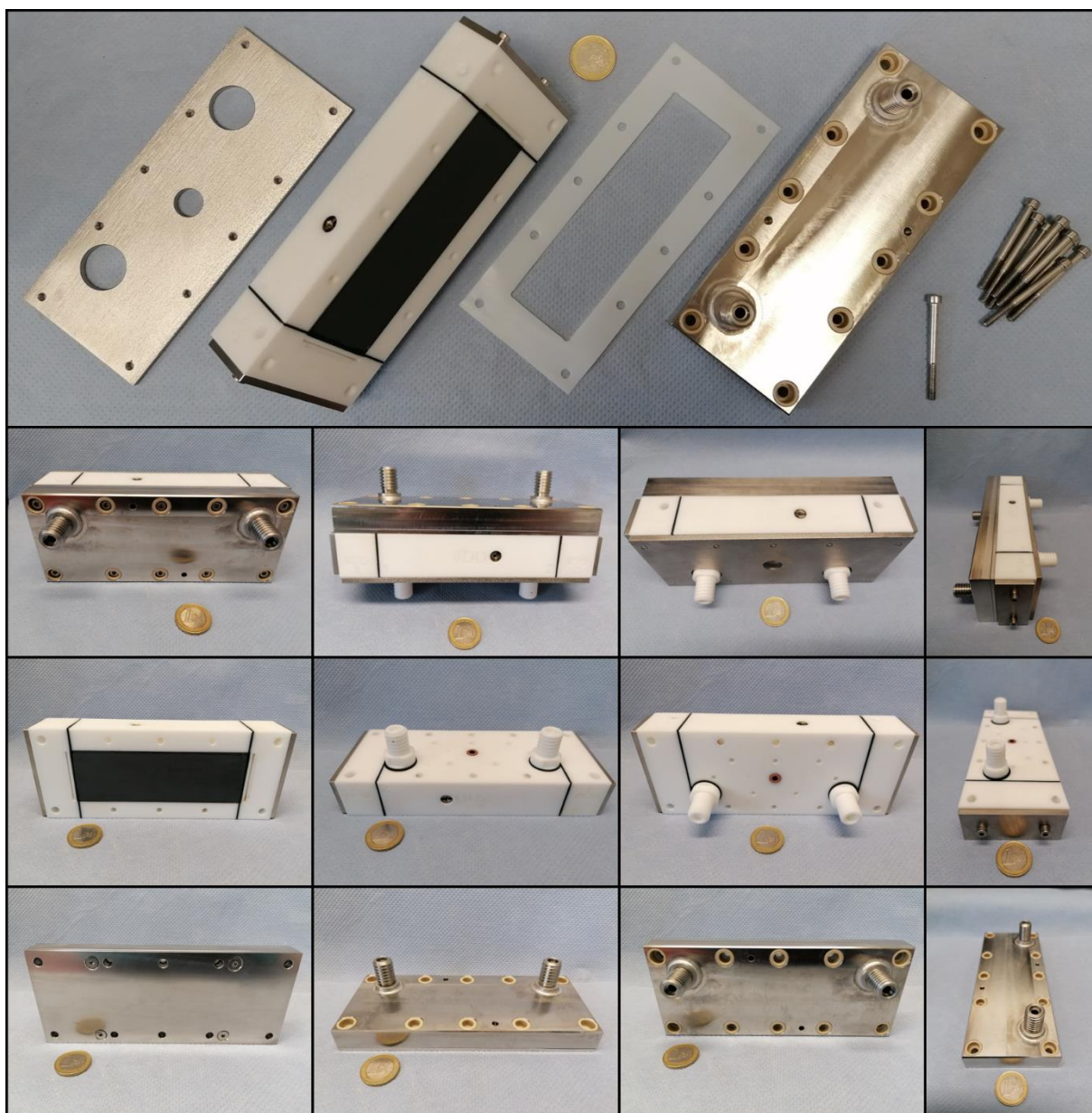


Figure 2. Large modular flow cell used for scale-up experiment 2. A one Euro coin is placed next to the electrolysis cell for size comparison.

3. Experimental procedures

General Procedure for the preparation of SO₂ stock solutions

For the preparation of the SO₂ stock solutions, the following apparatus was used:

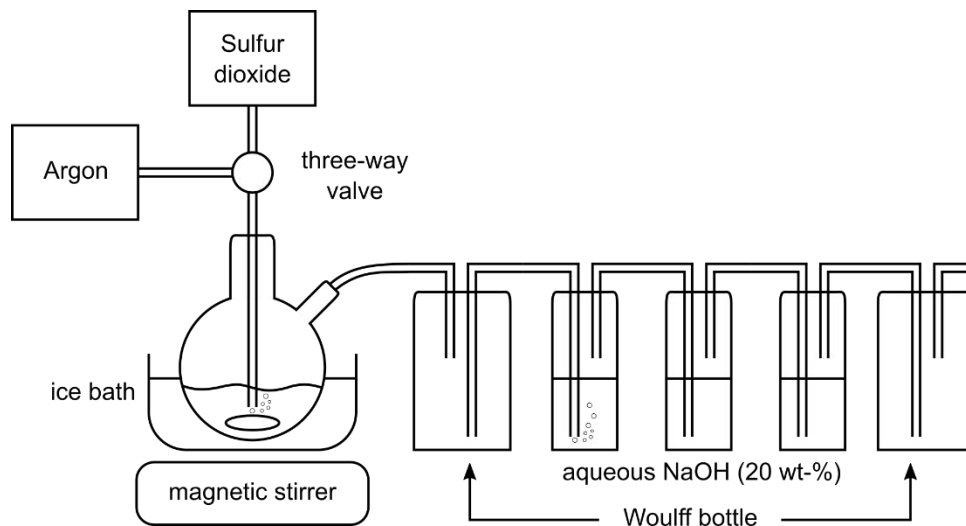


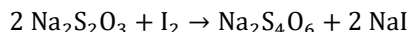
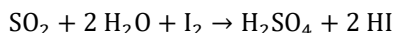
Figure 3. Experimental setup for the preparation of SO₂ stock solutions.

The entire apparatus as shown in Figure 3 was kept in a fume hood. The solvent (HFIP, MeCN, or a mixture of HFIP and MeCN) was transferred into a 500 mL two-neck round bottom flask. The round bottom flask was cooled to 0 °C with an ice bath on a magnetic stirrer. While being stirred slowly, the solvent was flushed with sulfur dioxide at 0 °C for 20 min. Excess SO₂ gas is neutralized with aqueous NaOH (20 wt%). At the end, the gas inlet apparatus is flushed with argon. The SO₂ concentration of the stock solution is determined using iodometry. The SO₂ stock solution was stored at +4 °C.

General procedure for the determination of SO₂ concentration in sulfur dioxide stock solutions

The concentration of SO₂ stock solutions can be determined by iodometry.^[6] To prepare the titrant solution, sodium thiosulfate pentahydrate (Na₂S₂O₃ · 5 H₂O, 4.964 g, 0.02 mol) is dissolved in distilled water (100.0 mL) in a volumetric flask at 25 °C. In a 250 mL Erlenmeyer flask, iodine (I₂, 1.269 g, 5.00 mmol) was dissolved together with potassium iodide (KI, 2.209 g, 13.3 mmol) in distilled water (100 mL). To promote the dissolution of iodine, it's recommended to pre-grind it in a mortar before weighing it out. A stirring bar is added to the solution of I₂ and KI. The solution is stirred at 25 °C until the iodine is completely dissolved. An aliquot of the SO₂ stock solution (1.0 mL at 4 °C) is injected slowly into the solution of iodine and potassium iodide. The aliquot of SO₂ stock solution must be injected under the liquid surface to prevent the evaporation of SO₂. While being stirred, the solution is back titrated using the freshly prepared Na₂S₂O₃ solution as titrant. A few drops of freshly prepared starch solution can be added to better identify the end point of titration.^[6]

Iodine is being reduced according to the following equations:



The concentration of the SO₂ stock solution $c(\text{SO}_2)$ can be calculated as follows:

$$c(\text{SO}_2) = \frac{n_0(\text{I}_2) - \frac{1}{2}(V(\text{Na}_2\text{S}_2\text{O}_3) \cdot c(\text{Na}_2\text{S}_2\text{O}_3))}{V(\text{SO}_2 \text{ aliquot})}$$

General procedure 1 for the optimization of reaction conditions

Standard reaction conditions: 1,4-dimethoxybenzene (124 mg, 0.9 mmol, 0.15 mol L⁻¹) was dissolved in MeCN (1.12 mL) and HFIP (1.10 mL). Then, morpholine (3.0 equiv., 2.7 mmol, 0.24 mL) and DIPEA (4.0 equiv., 3.6 mmol, 0.61 mL) was added. To this, a stock solution of SO₂ in HFIP/MeCN 1:1 (15.0 equiv. SO₂, 13.5 mmol, 2.25 mol L⁻¹ SO₂ in solution) was added. During addition the reaction solution was cooled, as some heat-up is expected. The peristaltic pump was calibrated with acetonitrile before every experiment. BDD was used as anode material and stainless steel as cathode material. A Teflon spacer of thickness 0.25 mm was used. The reaction solution is pumped through the electrolysis cell and the electrolysis was started (4.0 F, 149 μL min⁻¹, 12.0 mA cm⁻²). The pump speed in single-pass flow is calculated as follows:

$$v_{\text{pump}} = \frac{V_{\text{reaction solution}}}{t_{\text{reaction}}} = \frac{V_{\text{reaction solution}}}{\left(\frac{Q_{\text{reaction}}}{I}\right)}$$

After the electrolysis at room temperature, the flow cell was rinsed by pumping acetonitrile (5 mL) through it. 1,3,5-trimethoxybenzene (101 mg, 0.60 mmol) was added to the reaction solution as internal standard. The solvents were removed by distillation using a rotary evaporator and the yield was determined by measuring a ¹H NMR spectrum. For isolation of the product, a saturated NaHCO₃ (50 mL) was added and the aqueous layer was extracted with ethyl acetate (5x50 mL). The combined organic fractions were dried over MgSO₄ and the solvent was removed using a rotary evaporator. The crude extract was adsorbed on silica and the product(s) were isolated using flash column chromatography.

General procedure 2 for reaction scope:

Deviations from general procedure 1: DIPEA (6.0 equiv.), HFIP/MeCN 2:1 (vol%).

General procedure 3 for reaction scope:

Deviations from general procedure 1: starting material concentration: 0.10 mol L⁻¹, amount of applied charge $Q = 3.5 F$.

4. Optimization of reaction conditions

In Table 1, the data for the optimization of the test reaction is shown, which refers to the optimization table in the publication. The experiments were carried out according to general procedure 1 and the yields were determined by using ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. The yield is calculated as follows, where I is the integral in the ^1H NMR spectrum and N is the number of protons associated to that integral:

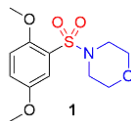
$$\% \text{NMR yield} = \frac{n_{\text{product}} \cdot 100}{n_{\text{starting material}}} = \frac{n_{\text{internal standard}} \cdot \frac{\left(\frac{I_{\text{product}}}{N_{\text{product}}}\right)}{\left(\frac{I_{\text{internal standard}}}{N_{\text{internal standard}}}\right)} \cdot 100}{n_{\text{starting material}}}$$

Table 1. Data of the optimization of the test reaction.

#	NMR-Yield%	$I(\text{STD})$	$m(\text{STD})/\text{mg}$	$n(\text{STD})/\text{mmol}$	$I(\text{product})$	$n(\text{product})/\text{mmol}$	$m(\text{SM})/\text{mg}$	$n(\text{SM})/\text{mmol}$
1	72	1	100.0	0.595	0.37	0.660	127.3	0.921
2	71	1	102.6	0.610	0.35	0.641	124.6	0.902
3	35	1	103.5	0.615	0.17	0.314	125.0	0.905
4	0	1	198.6	1.181	0.00	0.000	128.9	0.933
5	45	1	151.4	0.900	0.15	0.405	125.3	0.907
6	55	1	105.4	0.627	0.27	0.508	126.9	0.918
7	34	1	117.6	0.699	0.15	0.315	127.1	0.920
8	14	1	123.8	0.736	0.06	0.132	126.3	0.914
9	53	1	104.3	0.620	0.26	0.484	127.1	0.920
10	55	1	105.0	0.624	0.27	0.506	126.1	0.913
11	59	1	107.0	0.636	0.29	0.553	129.6	0.938
12	61	1	129.1	0.768	0.24	0.553	126.1	0.913
13	64	1	96.8	0.576	0.34	0.587	127.7	0.924
14	25	1	106.8	0.635	0.12	0.229	126.0	0.912
15	48	1	105.1	0.625	0.24	0.450	128.4	0.929
16	72	1	99.1	0.589	0.37	0.654	125.0	0.905
17	75	1	102.7	0.611	0.37	0.678	125.0	0.905
18	88 (84% isolated)	1	106.5	0.663	0.86	1.634	255.6	1.850
19	88 (86% isolated)	1	101.1	0.601	0.89	1.605	250.7	1.814
20	70	1	102.8	0.611	0.36	0.66	131.2	0.950
21	60	1	133.7	0.795	0.23	0.549	126.1	0.913
22	46	1	117.9	0.701	0.20	0.421	125.8	0.910
23	10	1	99.3	0.590	0.05	0.089	126.3	0.914
24	0	1	102.4	0.609	0.00	0.000	127.5	0.910

5. Analytical data

1. 4-((2,5-Dimethoxyphenyl)sulfonyl)morpholine (**1**)



According to the general procedure 2, 1,4-dimethoxybenzene (258 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamide **1** (464 mg, 1.6 mmol, **86%**) was obtained as a yellow oil.

Scale-up experiment 1 in small flow cell: According to the general procedure 2, 1,4-dimethoxybenzene (1.999 g, 14.4 mmol) was employed as substrate. All other solvents and reagents used in the reaction were scaled up by a factor of 8 as well. The electrolysis was started (4.0 F, 149 $\mu\text{L}/\text{min}$, 12.0 mA cm^{-2} , 10 h 43 min). After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamide **1** (3.557 g, 12.4 mmol, **86%**) was obtained as a yellow oil. The unconsumed starting material 1,4-dimethoxybenzene (290 mg, 2.0 mmol, 14%) could be recovered. Dividing the mass of product by the electrolysis time yields a productivity of:

$$productivity_1 = \frac{3.557 \text{ g}}{10 \text{ h } 43 \text{ min}} \approx 0.33 \frac{\text{g}}{\text{h}}$$

Scale-up experiment 2 in large flow cell: According to the general procedure 2, 1,4-dimethoxybenzene (2.008 g, 14.5 mmol) was employed as substrate using the large flow cell depicted in Figure 2. All other solvents and reagents used in the reaction were scaled up by a factor of 8 as well. The electrolysis was started (4.0 F, 597 $\mu\text{L}/\text{min}$, 12.0 mA cm^{-2} , 2 h 41 min). After the reaction, a mixture of HFIP (40 mL) and MeCN (20 mL) was pumped through the flow cell to clean it. Using vacuum distillation and a cold trap, 84 vol% of the HFIP/MeCN 2:1 solvent mixture used in the reaction could be recovered:

$$vol\%_{\text{recovered}} = \frac{100 \cdot V_{\text{recovered}}}{V_{\text{used}}} = \frac{100 \cdot 115.0 \text{ mL}}{\left(\underbrace{28.8 + 3.5 + 45.3}_{\text{used in reaction}} + \underbrace{40.0 + 20.0}_{\text{rinsing of cell}} \right) \text{ mL}} = 84 \text{ vol\%}$$

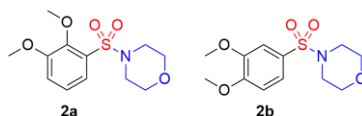
After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamide **1** (3.838 g, 13.4 mmol, **92%**) was obtained as a yellow oil. The unconsumed starting material 1,4-dimethoxybenzene (159 mg, 1.1 mmol, 8%) could be recovered. Dividing the mass of product by the electrolysis time yields a productivity of:

$$productivity_2 = \frac{3.838 \text{ g}}{2 \text{ h } 41 \text{ min}} \approx 1.43 \frac{\text{g}}{\text{h}}$$

Reusing the recovered HFIP/MeCN solvent from Scale-up experiment 2: The HFIP/MeCN 2:1 (vol%) solvent mixture which was recovered in the cold trap did contain 0.8 M sulfur dioxide. It was purged again with SO_2 according to the general procedure, and a 4.77 M SO_2 stock solution was obtained. This stock solution based on the recovered HFIP/MeCN solvent mixture was then used again in the following reaction: According to the general procedure, 1,4-dimethoxybenzene (252.7 mg, 1.8 mmol) was dissolved in MeCN (0.60 mL) and HFIP (1.10 mL). Morpholine (3.0 equiv., 5.4 mmol, 0.47 mL) and DIPEA (6.0 equiv., 10.8 mmol, 1.84 mL) were added. The SO_2 stock solution which was created using the recovered solvent mixture was then added (15 equiv. SO_2 , 13.5 mmol SO_2 , 8.00 mL of the 4.77 M SO_2 stock solution in HFIP/MeCN 2:1 vol%). In total, this gives 12.0 mL of reaction solution which has HFIP/MeCN 2:1 vol%. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamide **1** (450 mg, 1.6 mmol, **86%**) was obtained as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.32 (d, J = 3.2 Hz, 1H), 6.99 (m, 1H), 6.91 (d, J = 9.0 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.66–3.58 (m, 4H), 3.19–3.10 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 153.1, 151.1, 126.4, 120.5, 116.3, 114.1, 66.8, 56.7, 56.1, 46.1; m_p : 98 °C; HRMS for $\text{C}_{12}\text{H}_{18}\text{NO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 288.0900, found: 288.0897; R_f (cyclohexane:ethyl acetate = 95:5) = 0.11.

2. 4-((2,3-Dimethoxyphenyl)sulfonyl)morpholine (2a) & 4-((3,4-Dimethoxyphenyl)sulfonyl)morpholine (2b)



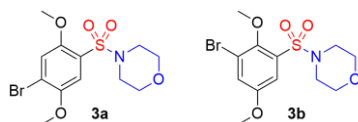
According to the general procedure 3, 1,2-dimethoxybenzene (332 mg, 2.4 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 $\rightarrow$ 50:50), sulfonamides **2a** (293 mg, 1.02 mmol, **41%**) and **2b** (102 mg, 0.35 mmol, **14%**) were obtained as colorless solids.

According to the general procedure 1, 1,2-dimethoxybenzene (250 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 $\rightarrow$ 50:50), sulfonamides **2a** (56 mg, 0.20 mmol, **12%**) and **2b** (43 mg, 0.15 mmol, **9%**) were obtained as colorless solids.

2a: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.42 (dd, J = 6.5, 3.0 Hz, 1H), 7.15 (s, 2H), 3.93 (d, J = 2.9 Hz, 6H), 3.74–3.68 (m, 4H), 3.23–3.18 (m, 4H); ^{13}C NMR (101 MHz, CD_3CN) δ [ppm] = 154.1, 147.3, 131.6, 124.4, 122.1, 117.0, 66.7, 61.5, 56.3, 46.2; m_R : 162–164 °C; HRMS for $\text{C}_{12}\text{H}_{17}\text{NO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 288.0900, found: 288.0900. R_f (cyclohexane:ethyl acetate = 1:1) = 0.36.

2b: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.35 (dd, J = 8.4, 2.1 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.93 (d, J = 8.4 Hz, 6H), 3.76–3.68 (m, 4H), 3.02–2.93 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.9, 149.1, 126.7, 121.8, 110.7, 110.2, 66.1, 56.3, 56.2, 46.0; m_R : 96–97 °C; HRMS for $\text{C}_{12}\text{H}_{17}\text{NO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 288.0900, found: 288.0902; R_f (cyclohexane:ethyl acetate = 1:1) = 0.20.

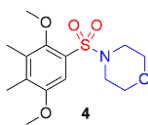
3. 4-((4-Bromo-2,5-dimethoxyphenyl)sulfonyl)morpholine (3a), 4-((3-Bromo-2,5-dimethoxyphenyl)sulfonyl)morpholine (3b)



According to the general procedure 2, 1-bromo-2,5-dimethoxybenzene (398 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 $\rightarrow$ 50:50), sulfonamides **3a** (357 mg, 0.98 mmol, **53%**) and **3b** (129 mg, 0.35 mmol, **19%**) were obtained as colorless solids.

3a: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.39 (s, 1H), 7.23 (s, 1H), 3.85 (s, 6H), 3.72–3.66 (m, 4H), 3.22–3.13 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 150.9, 149.8, 125.6, 118.3, 117.9, 114.3, 66.7, 57.1, 56.9, 46.0; m_R : 89–90 °C; HRMS for $\text{C}_{12}\text{H}_{17}^{79}\text{BrNO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 366.0005, found: 366.0000. R_f (cyclohexane:ethyl acetate = 95:5) = 0.20.

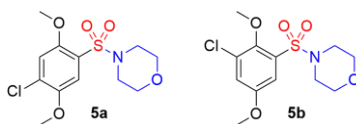
3b: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.30 (dd, J = 8 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.73–3.65 (m, 4H), 3.25–3.17 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 155.6, 148.5, 132.9, 123.8, 119.8, 115.5, 66.5, 62.3, 56.2, 46.1; m_R : 82–83 °C; HRMS for $\text{C}_{12}\text{H}_{17}^{79}\text{BrNO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 366.0005, found: 366.0001. R_f (cyclohexane:ethyl acetate = 95:5) = 0.31.

4. 4-((2,5-Dimethoxy-3,4-dimethylphenyl)sulfonyl)morpholine (**4**)

According to the general procedure 2, 1,4-dimethoxy-2,3-dimethylbenzene (258 mg, 1.5 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamide **4** (125 mg, 0.39 mmol, **26%**) was obtained as colorless oil.

According to the general procedure 1, 1,4-dimethoxy-2,3-dimethylbenzene (302 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamide **4** (126 mg, mmol, **25%**) was obtained as colorless oil.

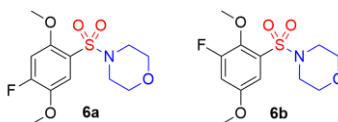
^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.12 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.69–3.67 (m, 4H), 3.15–3.13 (m, 4H), 2.22 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 153.3, 150.0, 133.4, 133.2, 127.2, 109.5, 66.5, 62.0, 56.0, 46.2, 12.9, 12.7; HRMS for $\text{C}_{14}\text{H}_{22}\text{NO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 316.1213, found: 316.1214; R_f (cyclohexane:ethyl acetate = 95:5) = 0.26.

5. 4-((4-Chloro-2,5-dimethoxyphenyl)sulfonyl)morpholine (**5a**) & 4-((3-Chloro-2,5-dimethoxy-phenyl)sulfonyl)morpholine (**5b**)

According to the general procedure 2, 1-chloro-2,5-dimethoxybenzene (312 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamides **5a** (289 mg, 0.90 mmol, **51%**) and **5b** (63 mg, 0.19 mmol, **11%**) were obtained as colorless solids.

5a: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.37 (s, 1H), 7.03 (s, 1H), 3.82 (s, 6H), 3.68–3.56 (m, 4H), 3.21–3.09 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 150.8, 148.7, 128.4, 124.8, 115.2, 115.7, 66.6, 56.9, 56.8, 46.0; mp: 151 °C; HRMS for $\text{C}_{12}\text{H}_{17}^{35}\text{ClNO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 322.0510, found: 322.0507; R_f (cyclohexane:ethyl acetate = 95:5) = 0.14.

5b: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.27 (d, J = 3.1 Hz, 1H), 7.13 (d, J = 3.1 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.73–3.67 (m, 4H), 3.25–3.15 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 155.3, 147.5, 133.0, 130.7, 120.9, 114.6, 66.5, 62.1, 56.1, 46.1; HRMS for $\text{C}_{12}\text{H}_{17}^{35}\text{ClNO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 322.0510, found: 322.0508; R_f (cyclohexane:ethyl acetate = 95:5) = 0.27.

6. 4-((4-Fluoro-2,5-dimethoxyphenyl)sulfonyl)morpholine (**6a**) & 4-((3-Fluoro-2,5-dimethoxy-phenyl)sulfonyl)morpholine (**6b**)

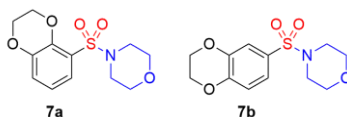
According to general procedure 3, 1-fluoro-2,5-dimethoxybenzene (375 mg, 2.4 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamides **6a** (426 mg, 1.39 mmol, **56%**) and **6b** (85 mg, 0.28 mmol, **11%**) were obtained as colorless solids.

According to general procedure 1, 1-fluoro-2,5-dimethoxybenzene (281 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamides **6a** (73 mg, 0.23 mmol, **13%**) and **6b** (18 mg, 0.06 mmol, **8%**) were obtained as colorless solids.

6a: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.52 (d, J = 9.2 Hz, 1H), 6.82 (d, J = 12.2 Hz, 1H), 3.87 (s, 6H), 3.75–3.69 (m, 4H), 3.25–3.19 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 155.8 (d, J = 254.1 Hz), 151.8 (d, J = 9.0 Hz), 141.2 (d, J = 11.3 Hz), 121.3 (d, J = 3.8 Hz), 117.1 (d, J = 4.3 Hz), 102.5 (d, J = 30.3 Hz), 66.8, 57.2, 56.9, 46.1; ^{19}F NMR (376 MHz, CDCl_3) δ [ppm] = -123.85 (dd, J = 11.3, 7.5 Hz); HRMS for $\text{C}_{12}\text{H}_{17}\text{FNO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 306.0806, found: 306.0803; R_f (cyclohexane:ethyl acetate = 95:5) = 0.13.

6b: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.12 (m, 1H), 6.86 (d, J = 12.2 Hz, 1H), 3.91 (s 3H), 3.79 (s, 3H), 3.75–3.69 (m, 4H), 3.25–3.19 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 156.8 (d, J = 252.1 Hz), 155.2 (d, J = 10.2 Hz), 139.5 (d, J = 13.9 Hz), 132.6 (d, J = 2.0 Hz), 110.5 (d, J = 2.9 Hz), 108.3 (d, J = 22.5 Hz), 66.5, 62.3 (d, J = 5.0 Hz), 56.1, 46.1; ^{19}F NMR (376 MHz, CDCl_3) δ [ppm] = -126.23 (d, J = 11.9 Hz); HRMS for $\text{C}_{12}\text{H}_{17}\text{FNO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 306.0806, found: 306.0806; R_f (cyclohexane:ethyl acetate = 95:5) = 0.20.

7. 4-((2,3-Dihydro-benzo[b][1,4]dioxin-5-yl) sulfonyl)morpholine (7a) & 4-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl) sulfonyl)morpholine (7b)



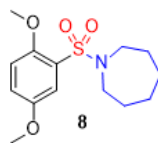
According to general procedure 3, 1,4-benzodioxane (327 mg, 2.4 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamides **7a** (88 mg, 0.31 mmol, **13%**) and **7b** (461 mg, 1.61 mmol, **65%**) were obtained as colorless solids.

According to general procedure 1, 1,4-benzodioxane (254 mg, 1.8 mmol) was employed as substrate. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 → 50:50), sulfonamides **7a** (43 mg, 0.15 mmol, **9%**) and **7b** (56 mg, 0.20 mmol, **12%**) were obtained as colorless solids.

7a: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.40 (dd, J = 7.9, 1.6 Hz, 1H), 7.08 (dd, J = 8.1, 1.6 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 4.34 (d, J = 8.5 Hz, 4H), 3.82–3.65 (m, 4H), 3.26–3.16 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 144.5, 141.8, 125.5, 123.6, 122.5, 120.8, 66.7, 64.6, 63.9, 46.1; m_R : 162–163 °C; HRMS for $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 286.0744, found: 286.0742; R_f (cyclohexane:ethyl acetate = 1:1) = 0.20.

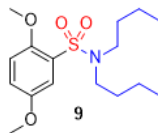
7b: ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.22 (dd, J = 8.4, 2.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 4.31 (s, 4H), 3.77–3.68 (m, 4H), 3.01–2.92 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 147.8, 143.6, 127.4, 121.6, 117.8, 117.4, 66.1, 64.6, 64.2, 46.0; HRMS for $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{H}]^+$: calc: 286.0744, found: 286.0745; R_f (cyclohexane:ethyl acetate = 1:1) = 0.30.

8. 1-((2,5-Dimethoxyphenyl)sulfonyl)azepane (8)



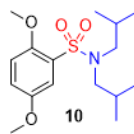
According to general procedure 3, 1,4-dimethoxybenzene (254 mg, 1.8 mmol) was employed as substrate with azepane (536 mg, 5.4 mmol, 3.0 equiv.) as amine component. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 $\rightarrow$ 50:50), sulfonamide **8** (236 mg, 0.79 mmol, **43%**) was obtained as yellow oil.

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.45 (d, J = 4.0 Hz, 1H), 7.00 (dd, J = 4.0, 8.0 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 4.00 (t, J = 4.0 Hz, 4H), 1.70 (m, 4H), 1.60 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.9, 150.8, 128.6, 119.8, 116.1, 113.6, 56.5, 56.1, 48.5, 29.6, 27.1; HRMS for $\text{C}_{14}\text{H}_{15}\text{NNaO}_5\text{S}^+$ (ESI^+) $[\text{M}+\text{Na}]^+$: calc: 322.1083, found: 322.1084; R_f (cyclohexane:ethyl acetate = 1:1) = 0.58.

9. *N,N*-Dibutyl-2,5-dimethoxybenzenesulfonamide (9)

According to general procedure 3, 1,4-dimethoxybenzene (257 mg, 1.8 mmol) was employed as substrate with dibutylamine (697 mg, 5.4 mmol, 3.0 equiv.) as amine component. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 $\rightarrow$ 50:50), sulfonamide **9** (189 mg, 0.57 mmol, **31%**) was obtained as yellow oil.

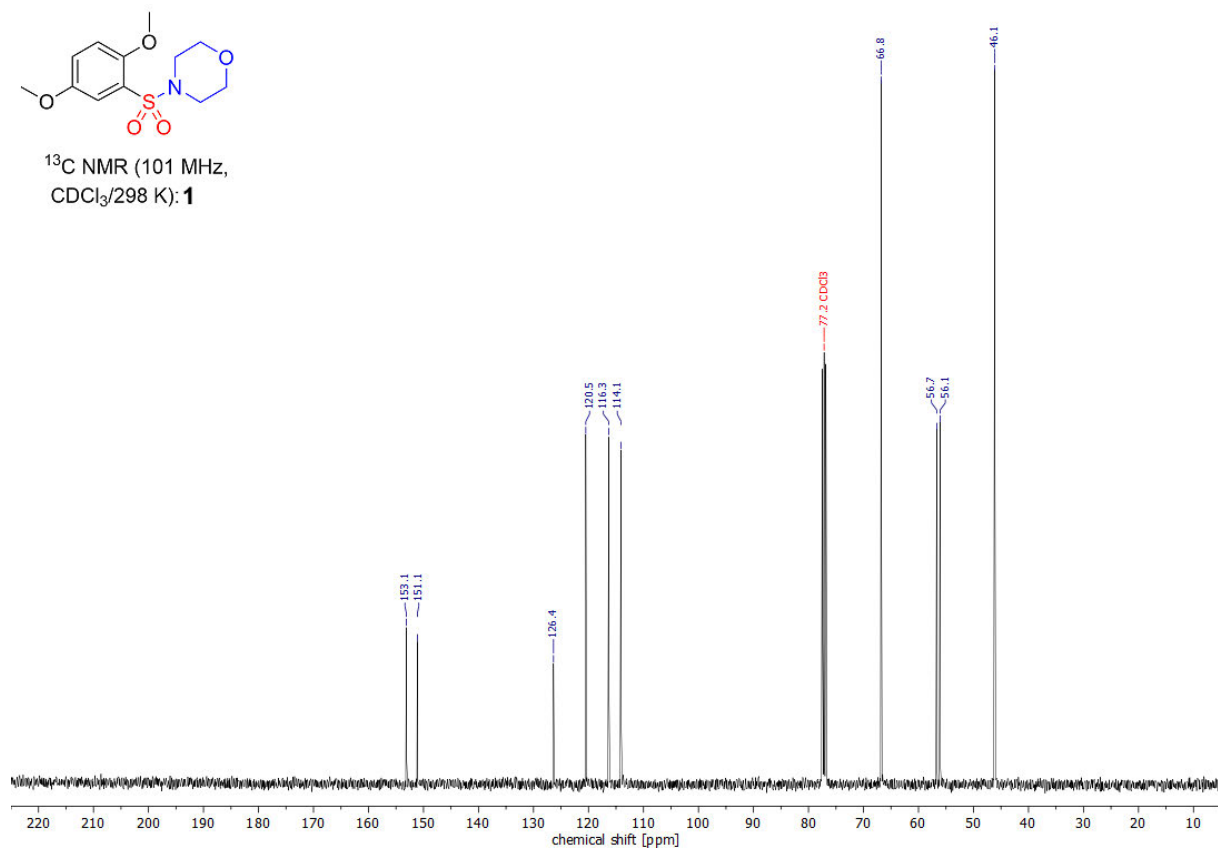
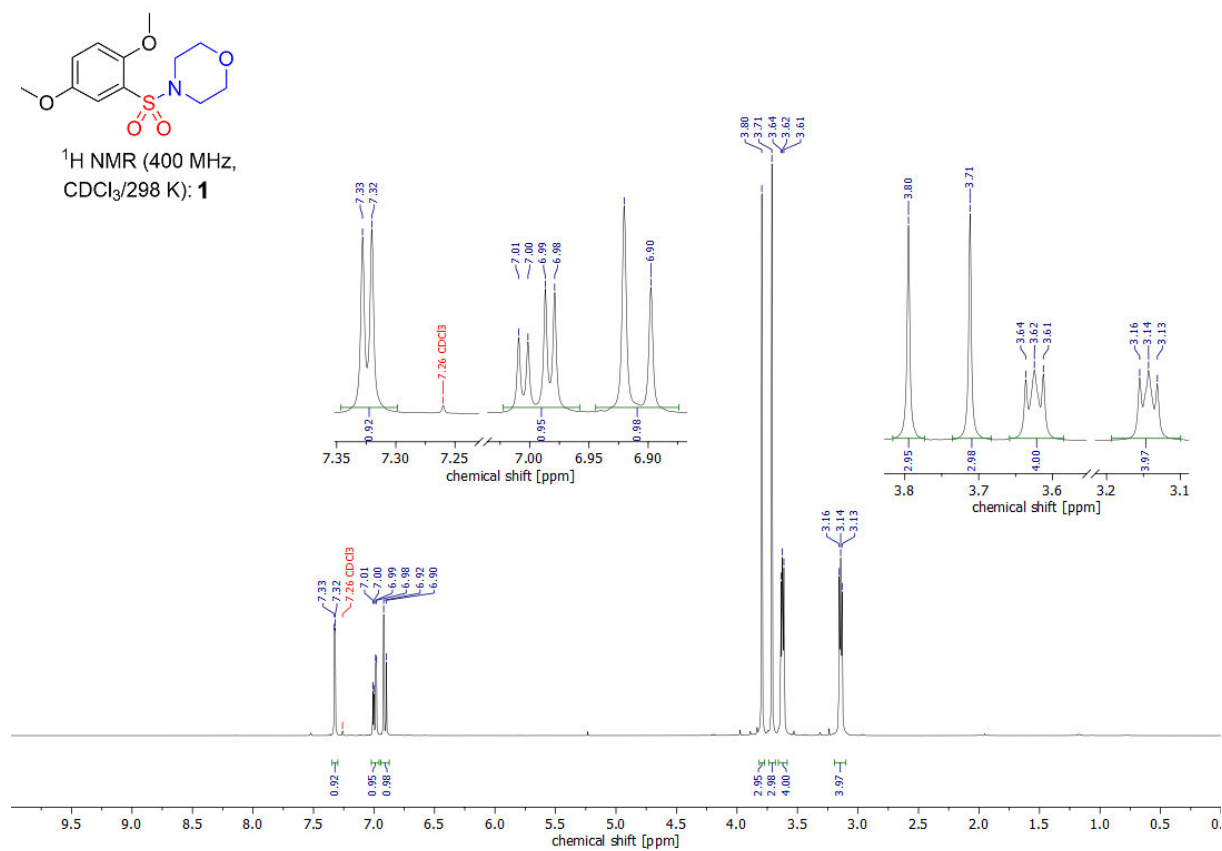
^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.48 (d, J = 4.0 Hz), 7.02 (dd, J = 4.0, 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz), 3.86 (s, 3H), 3.80 (s, 3H), 3.22 (t, J = 8.0 Hz, 4H), 1.48 (m, 4H), 1.27 (m, 4H), 0.87 (t, J = 8.0 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 153.0, 150.9, 129.6, 119.9, 116.0, 113.7, 56.6, 56.2, 47.7, 30.9, 20.1, 13.9; HRMS for $\text{C}_{16}\text{H}_{27}\text{NNaO}_4\text{S}^+$ (ESI^+) $[\text{M}+\text{Na}]^+$: calc: 352.1553, found: 352.1542; R_f (cyclohexane:ethyl acetate = 1:1) = 0.67.

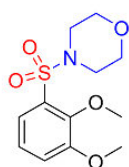
10. *N,N*-Diisobutyl-2,5-dimethoxybenzenesulfonamide (10)

According to general procedure 3, 1,4-dimethoxybenzene (250 mg, 1.8 mmol) was employed as substrate with diisobutylamine (697 mg, 5.4 mmol, 3.0 equiv.) as amine component. After purification of the product via column chromatography (cyclohexane:ethyl acetate 95:5 $\rightarrow$ 50:50), sulfonamide **9** (396 mg, 1.20 mmol, **66%**) was obtained as yellow oil.

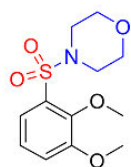
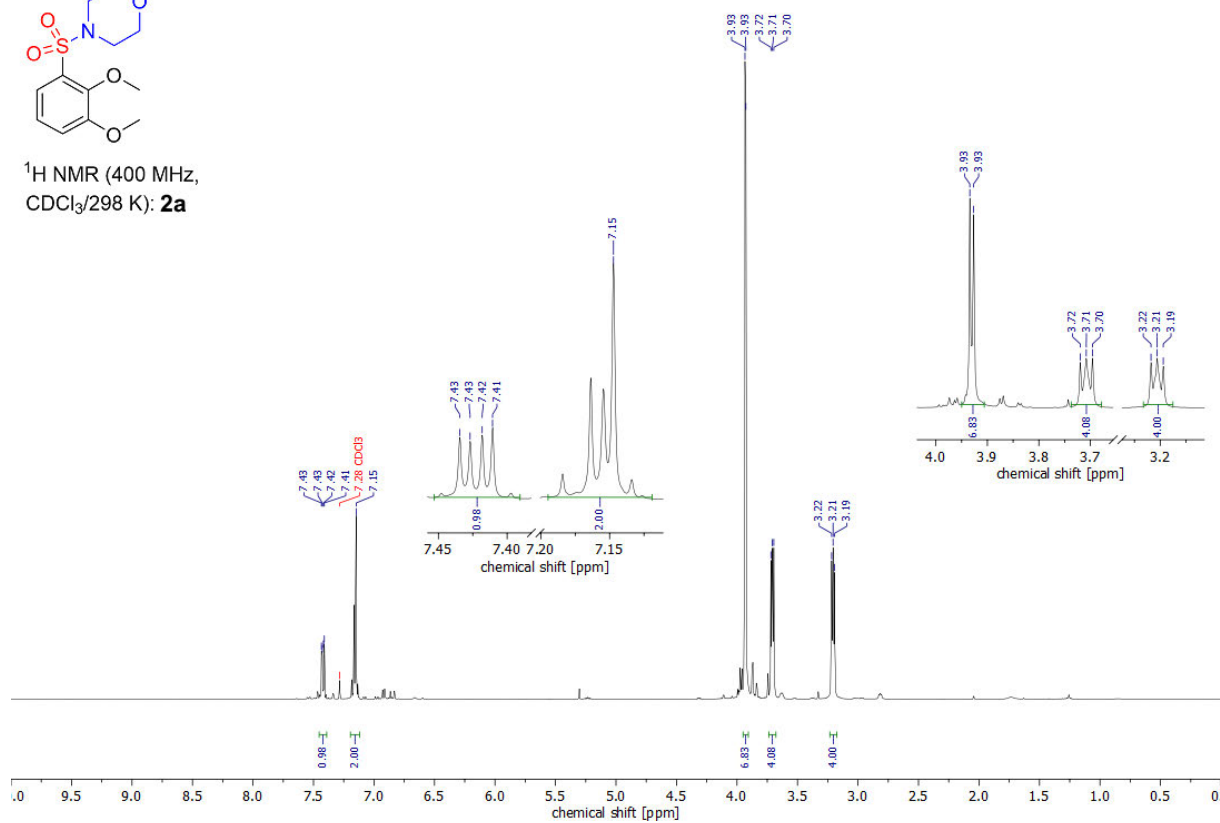
^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.43 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 4.0, 8.0 Hz, 1H), 6.86 (d, J = 4.0 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 1H), 2.99 (d, J = 8.0 Hz, 2H), 1.80 (sept, J = 4.0 Hz, 2H), 0.79 (d, J = 8.0 Hz, 12H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.8, 150.6, 129.2, 119.5, 116.1, 113.3, 56.3, 56.0, 55.8, 26.8, 20.0; HRMS for $\text{C}_{16}\text{H}_{27}\text{NNaO}_4\text{S}^+$ (ESI^+) $[\text{M}+\text{Na}]^+$: calc: 352.1553, found: 352.1551; R_f (cyclohexane:ethyl acetate = 1:1) = 0.83.

6. NMR spectra

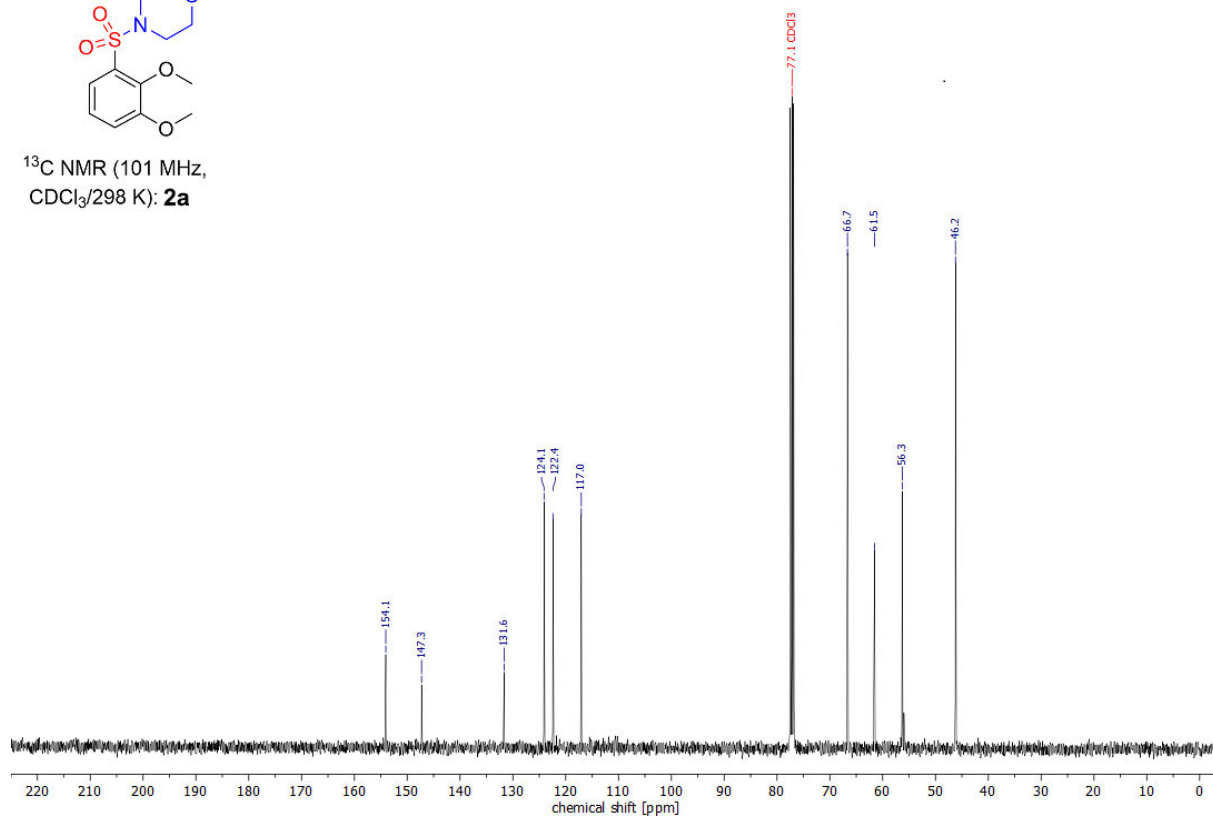


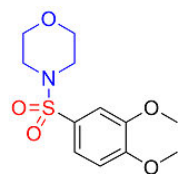


^1H NMR (400 MHz, CDCl_3 /298 K): **2a**

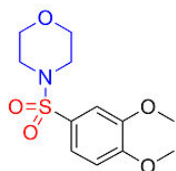
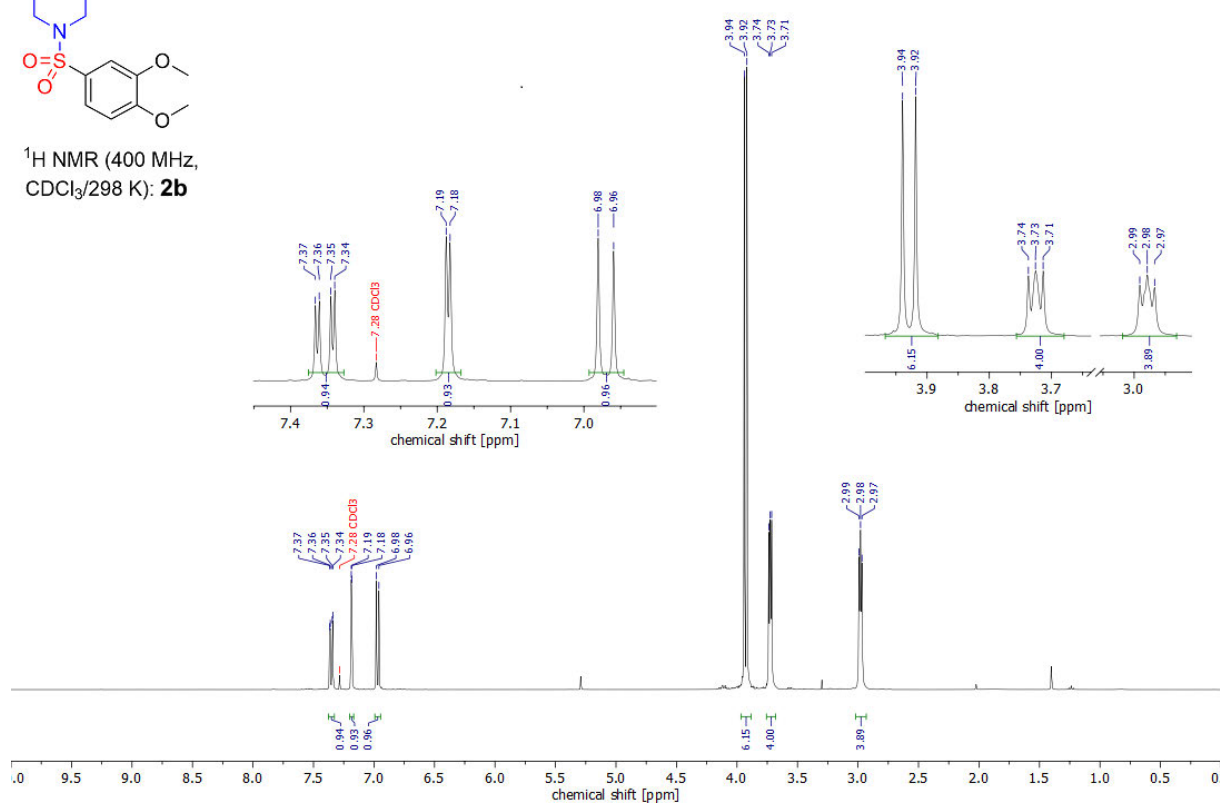


^{13}C NMR (101 MHz, CDCl_3 /298 K): **2a**

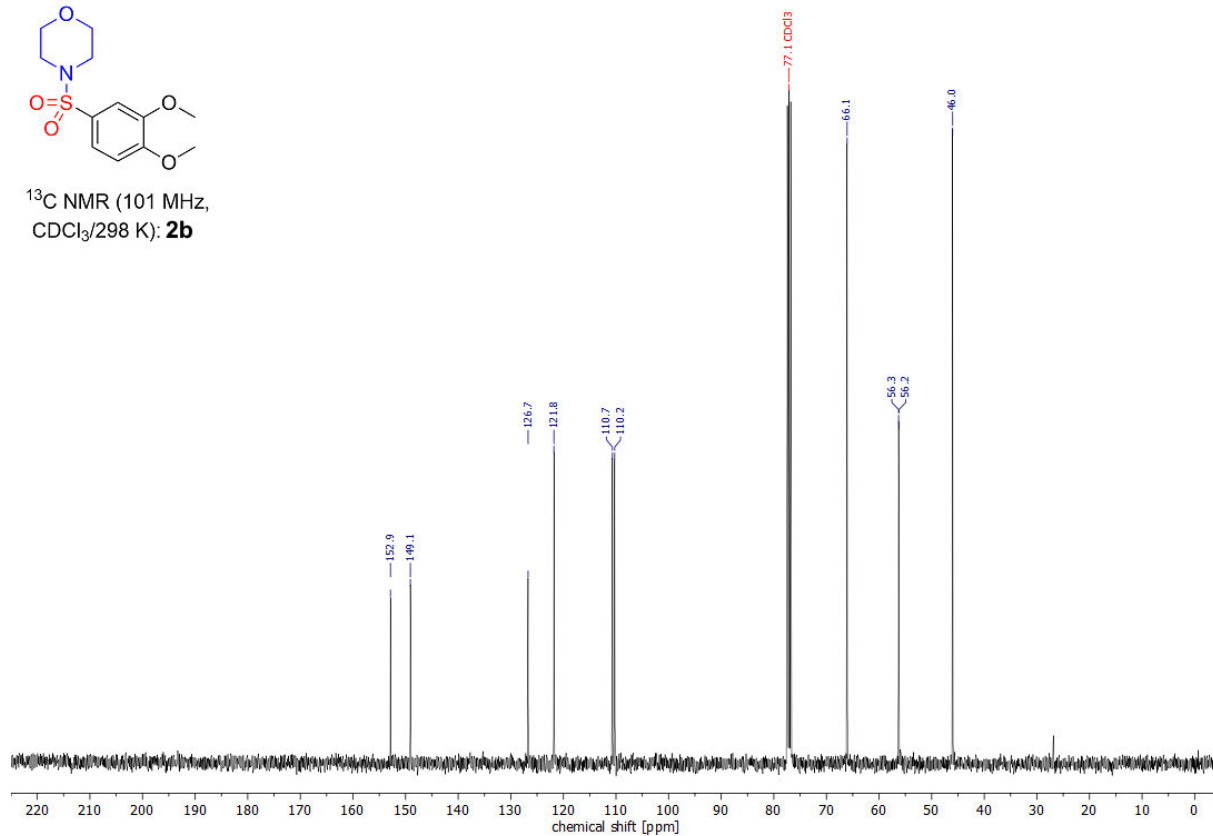


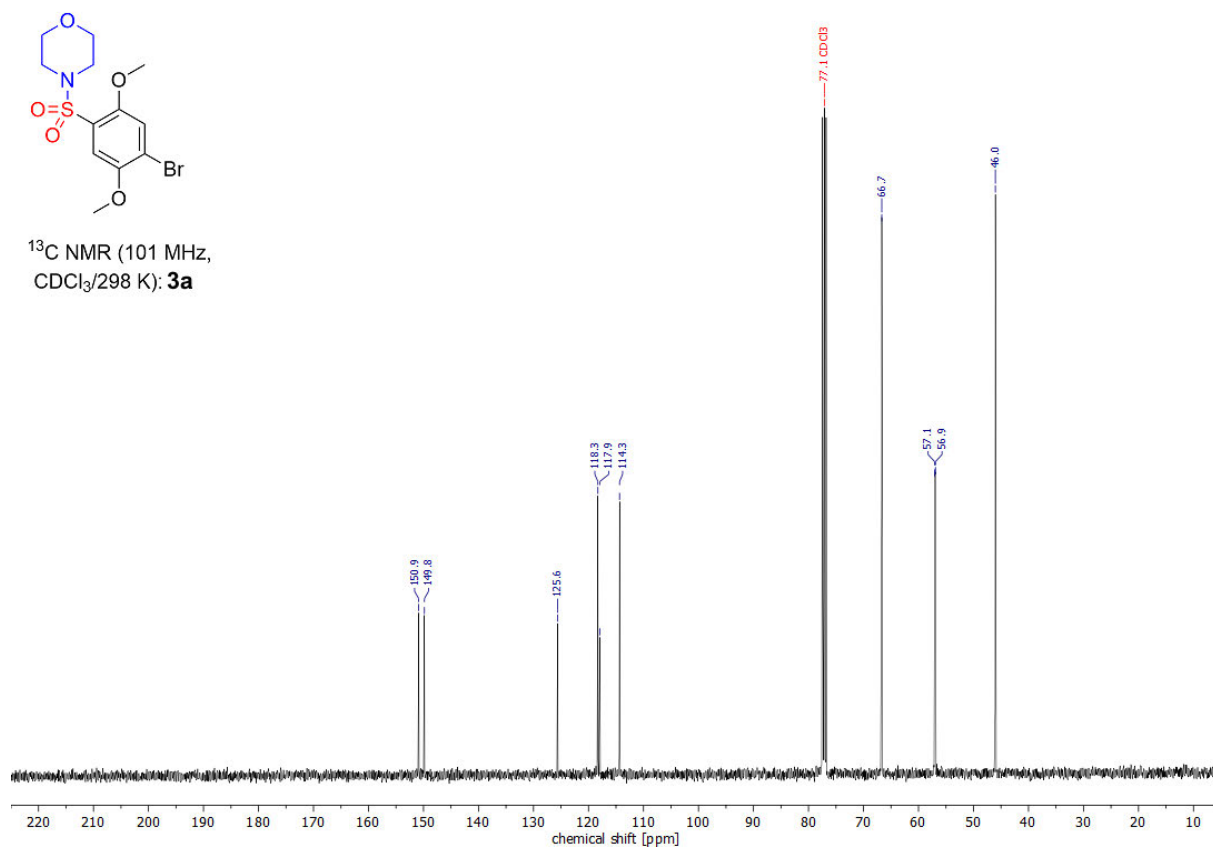
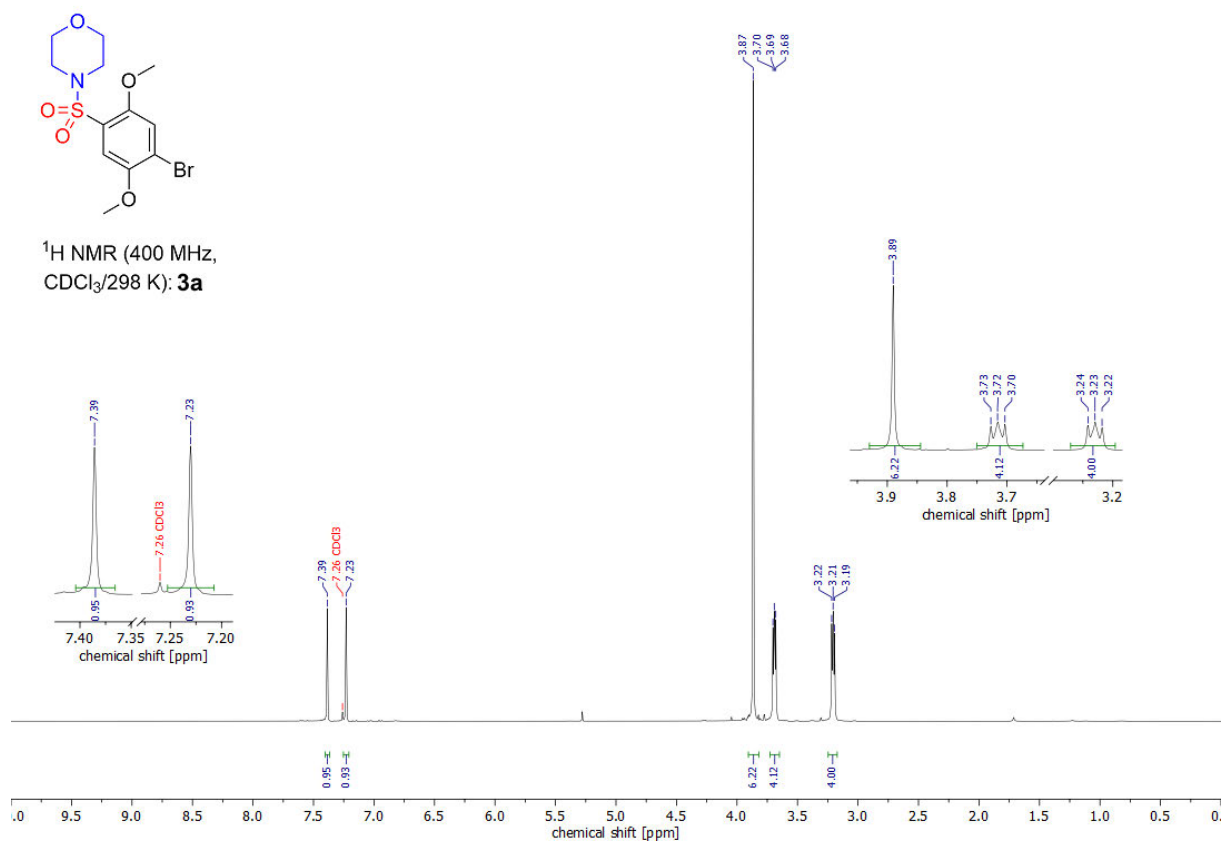


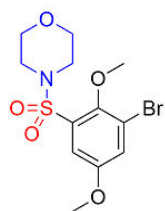
^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **2b**



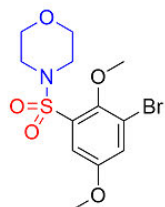
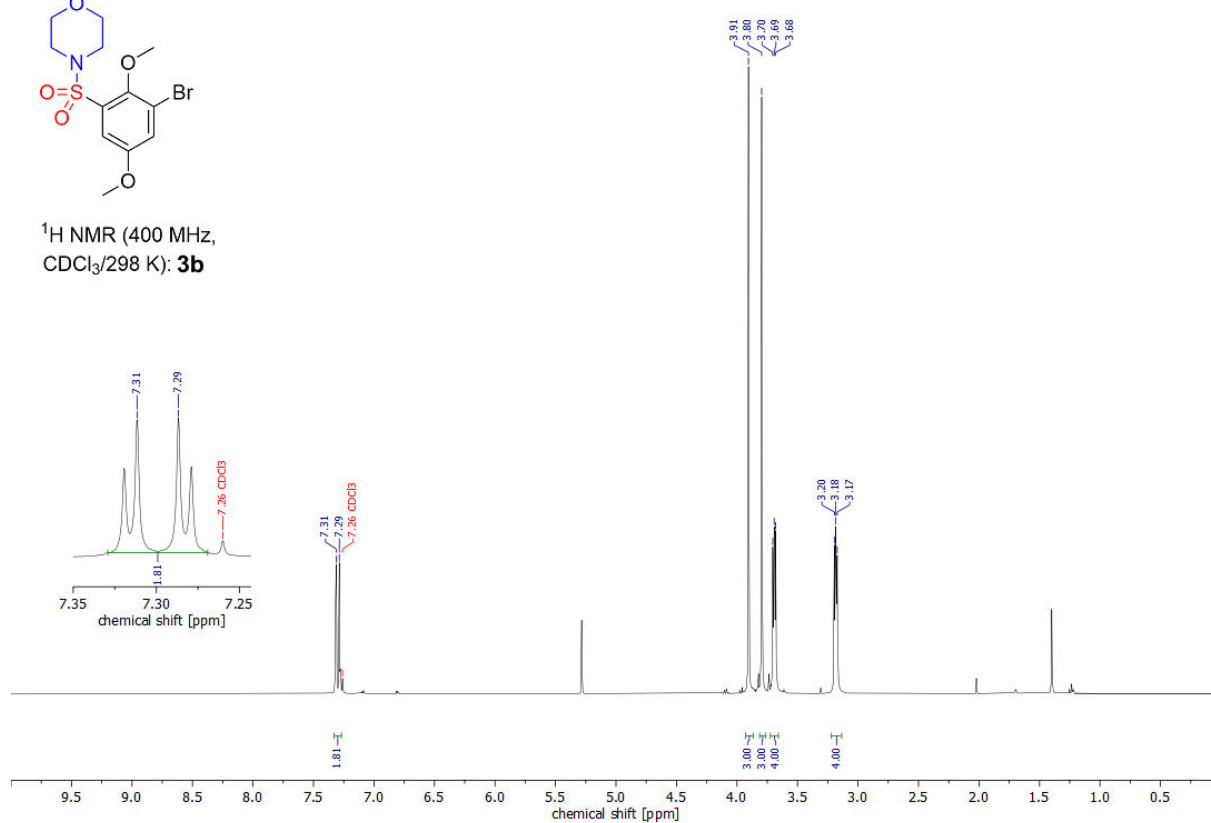
^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **2b**



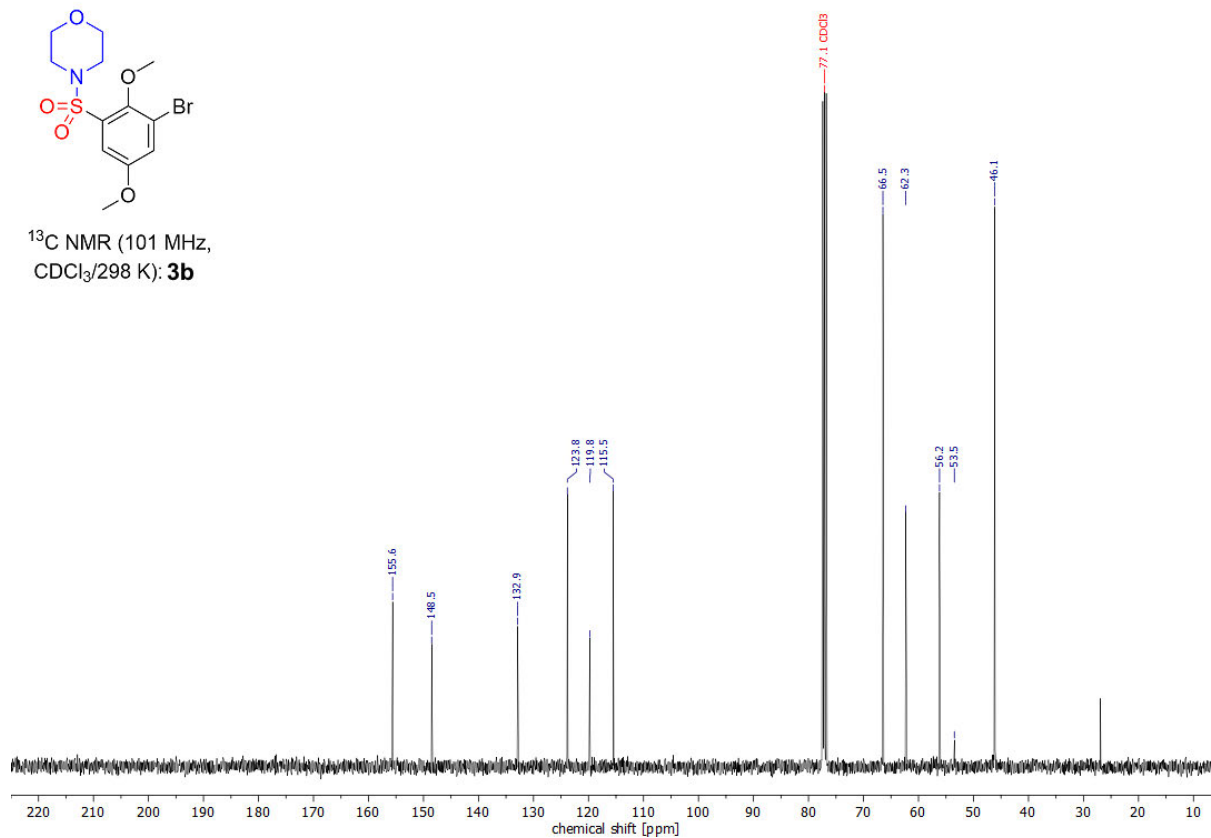


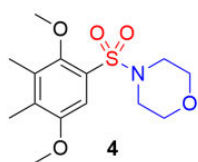


^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **3b**

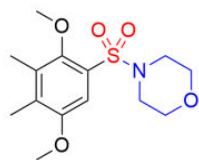
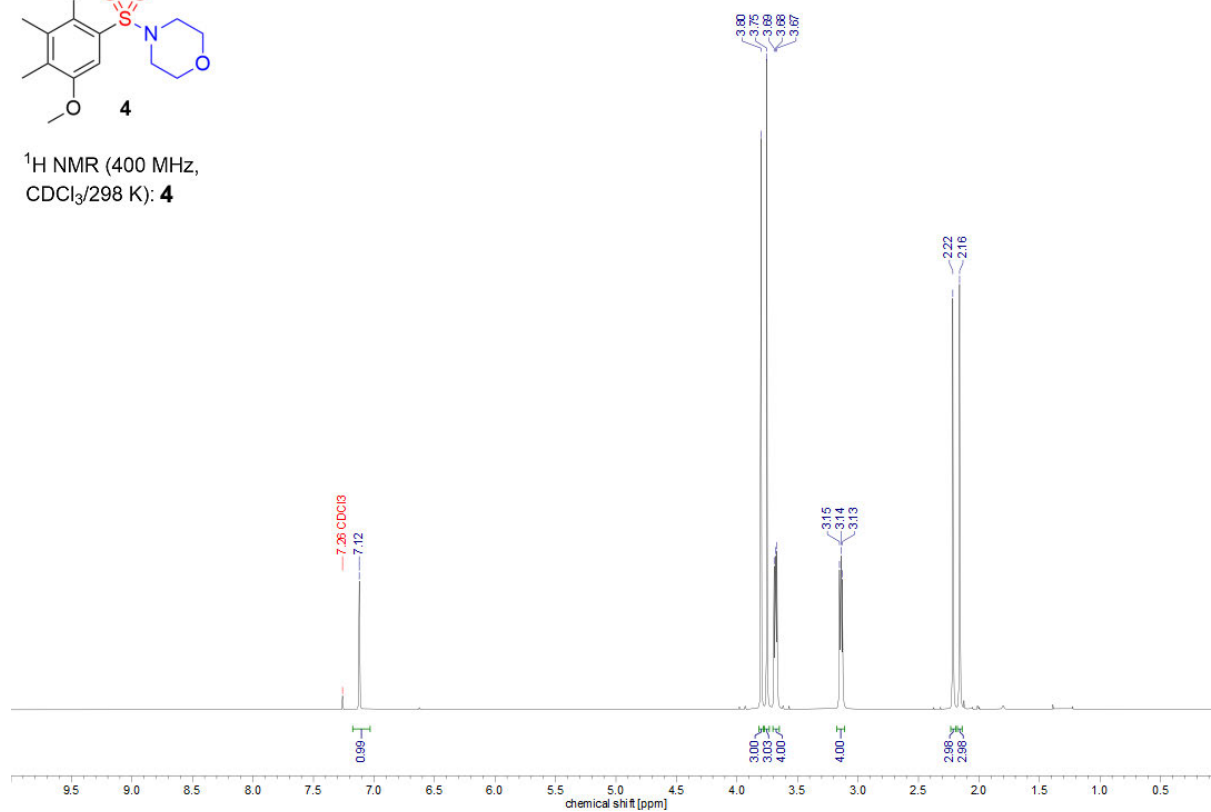


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **3b**

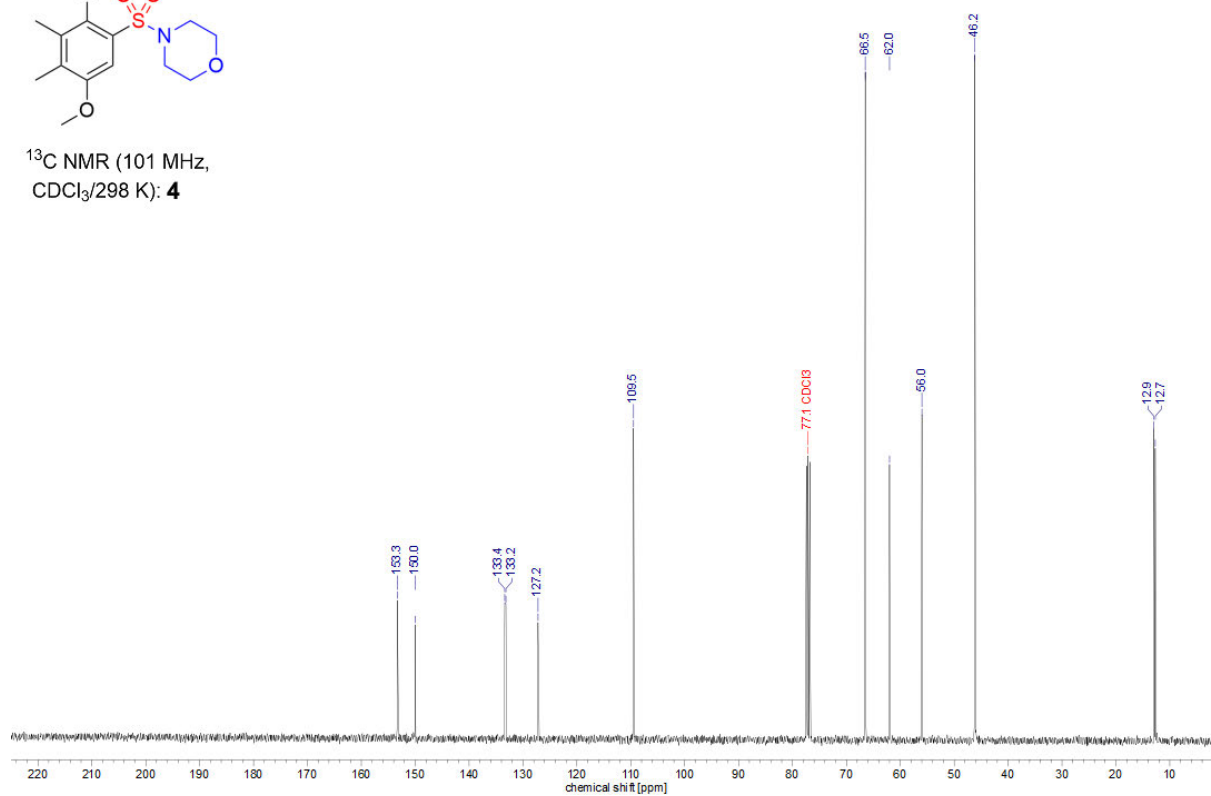




^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **4**

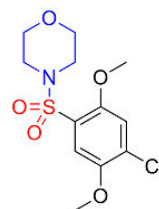
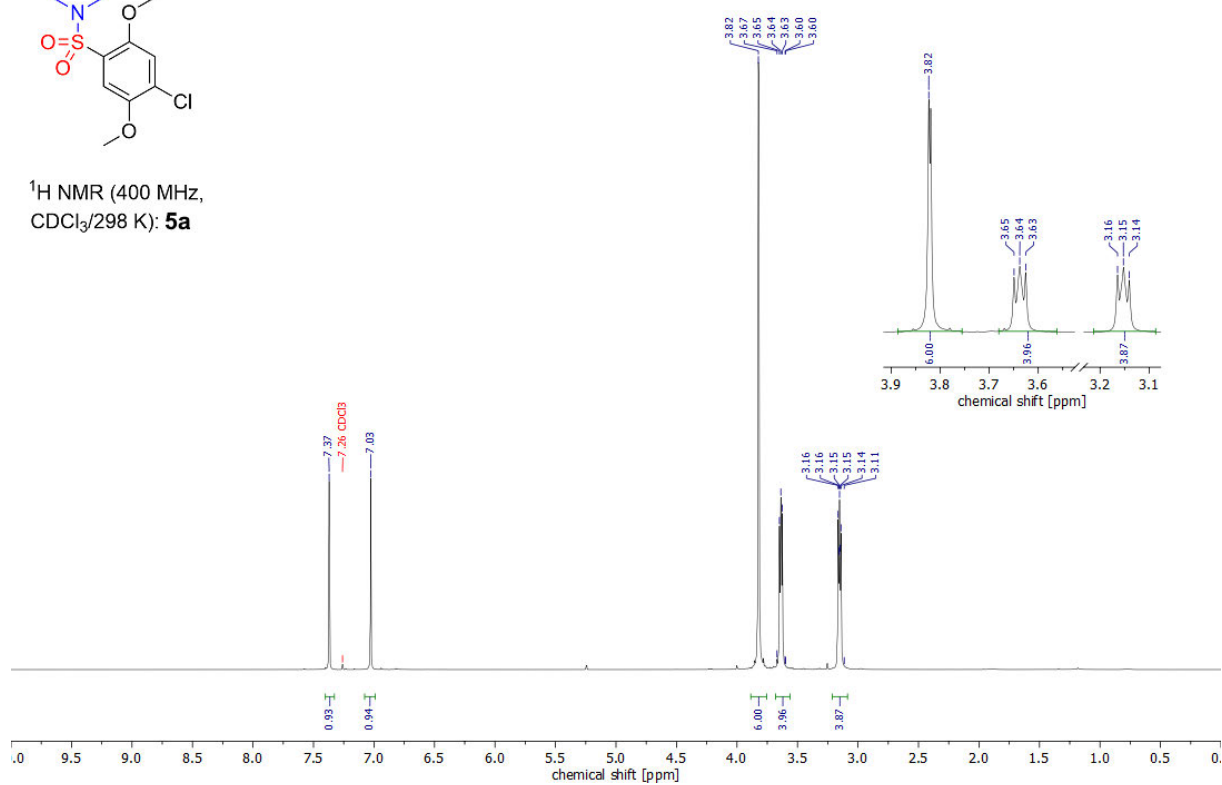


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **4**

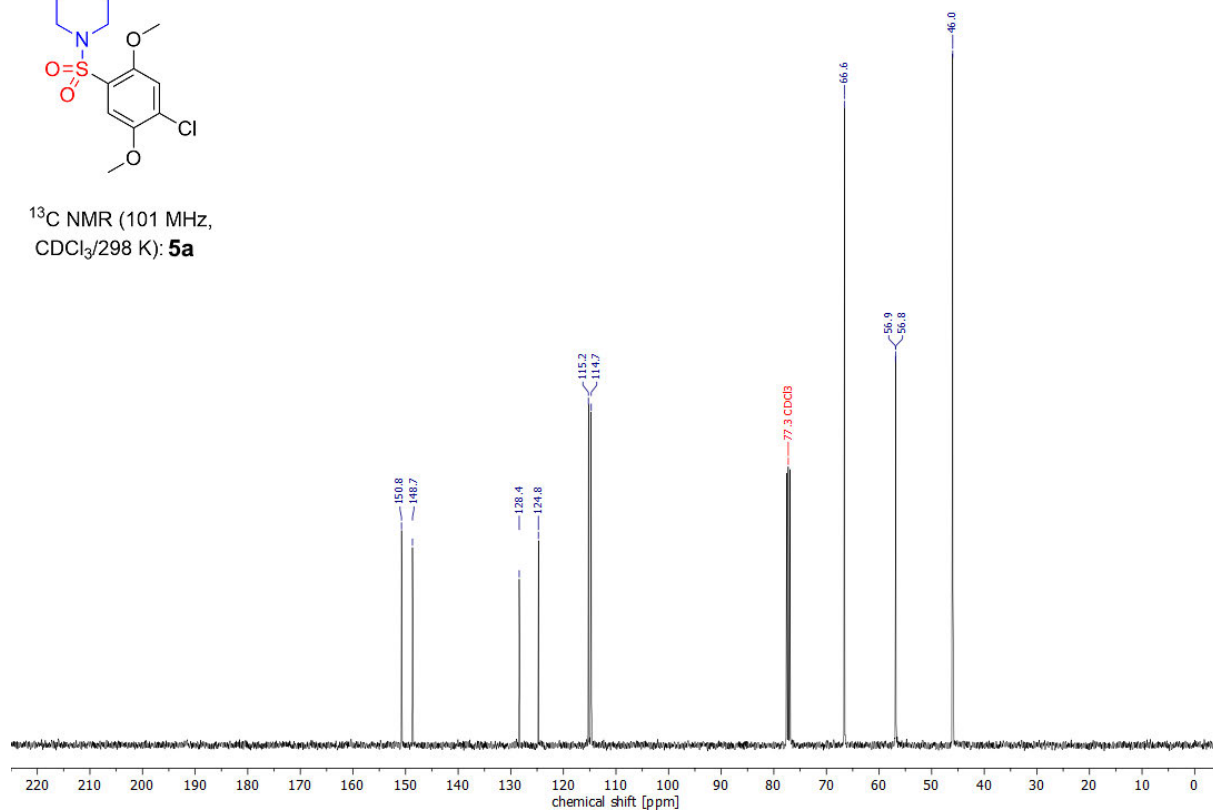


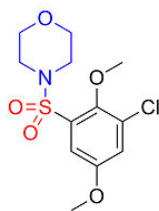


^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **5a**

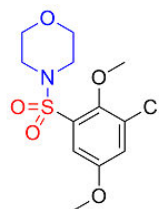
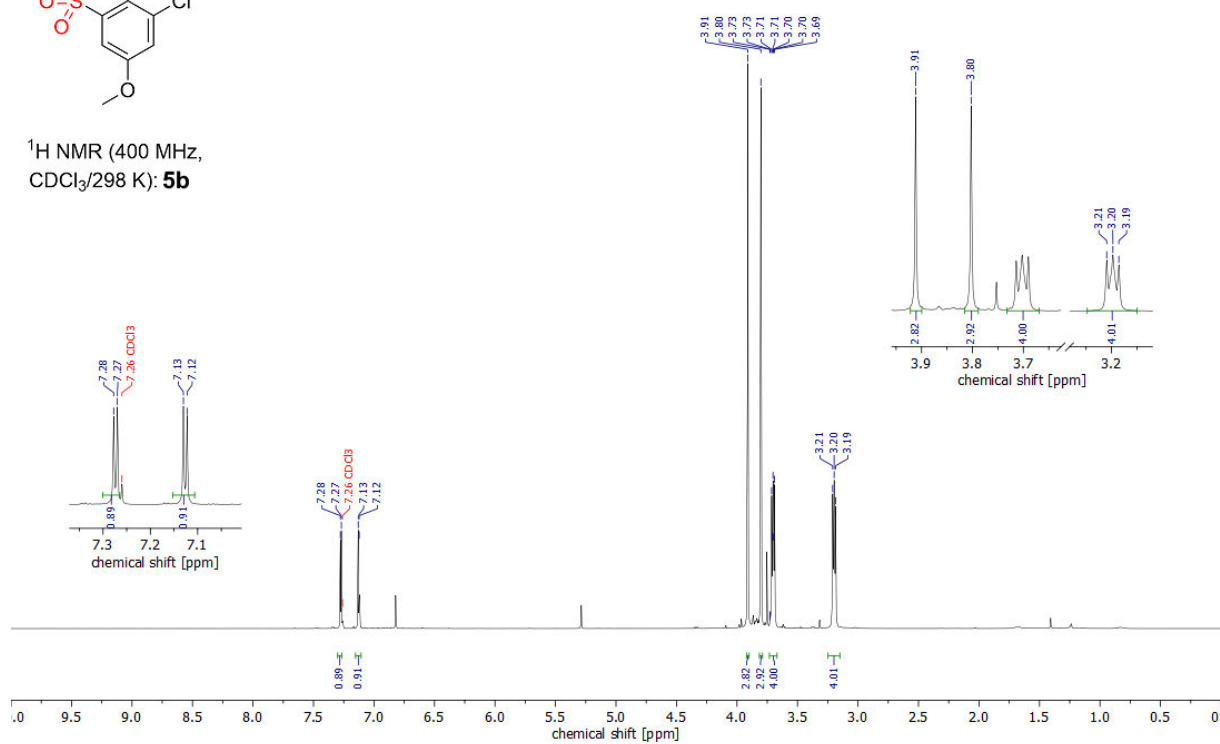


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **5a**

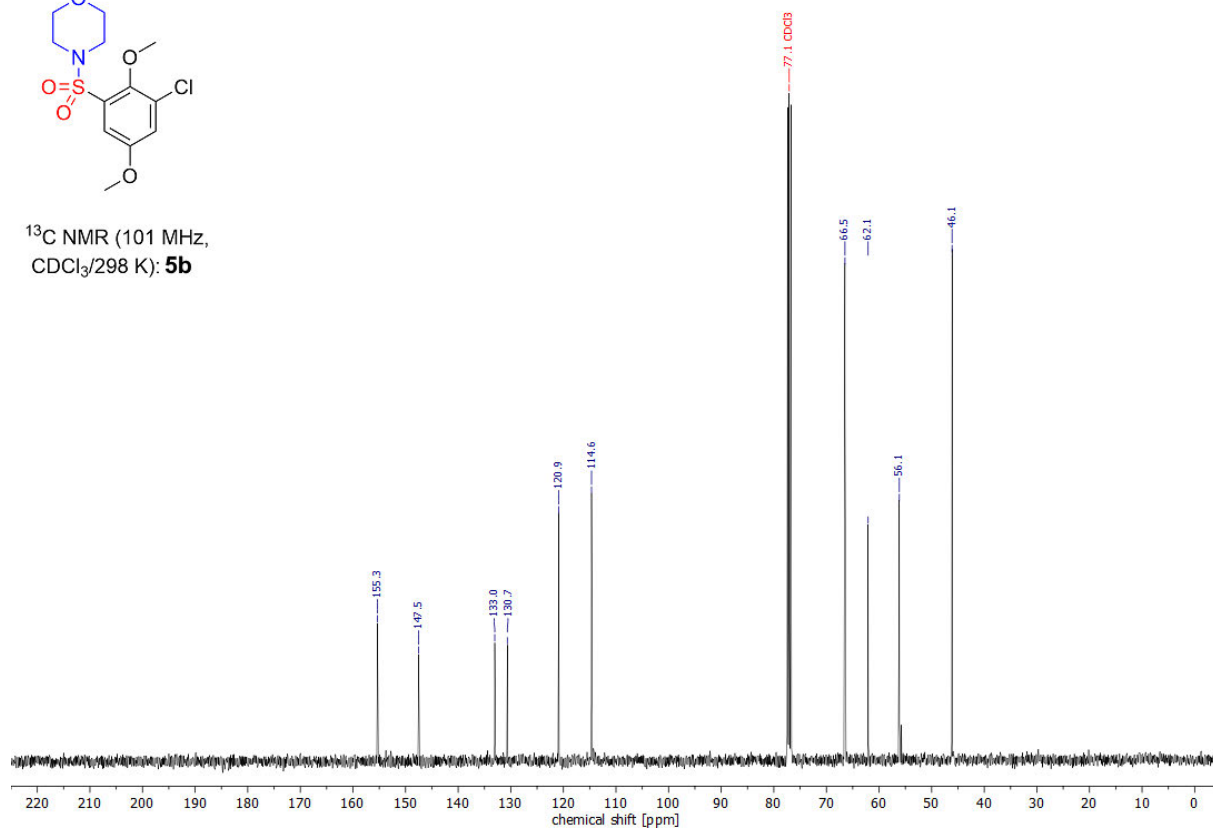


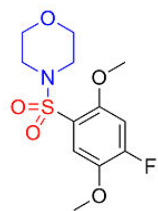


^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **5b**

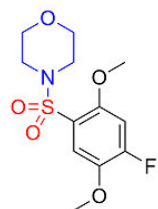
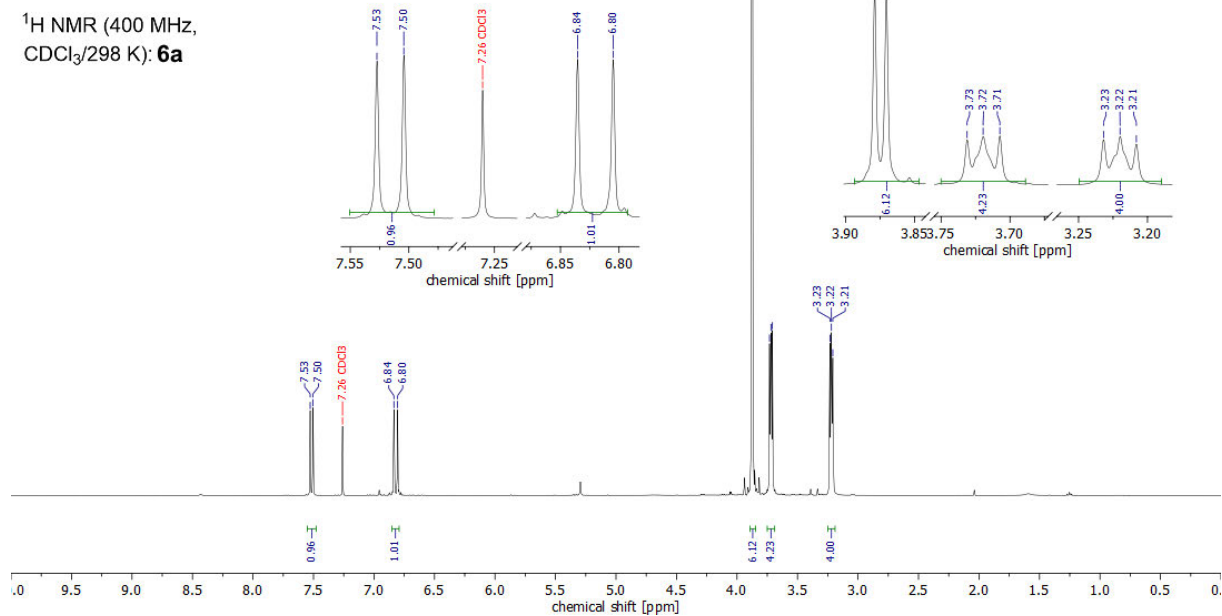


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **5b**

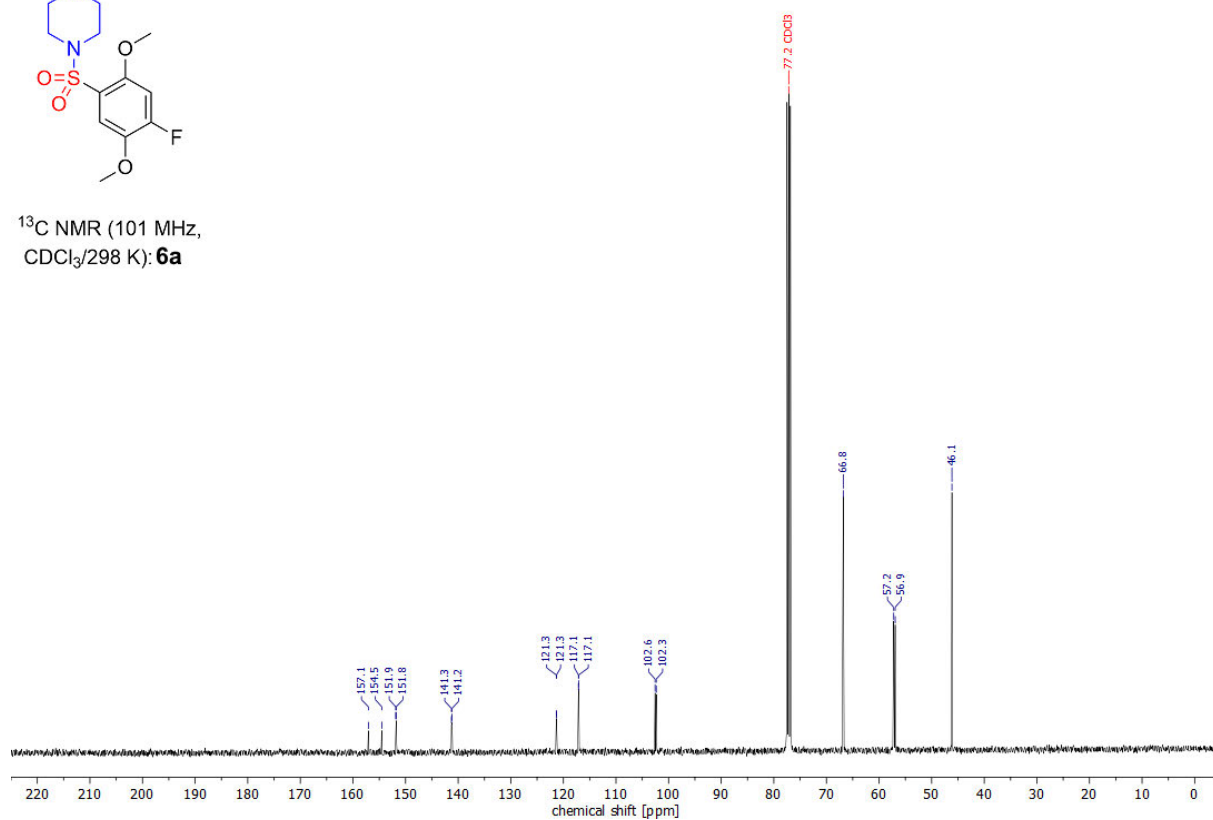


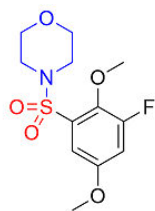


^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **6a**

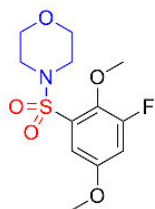
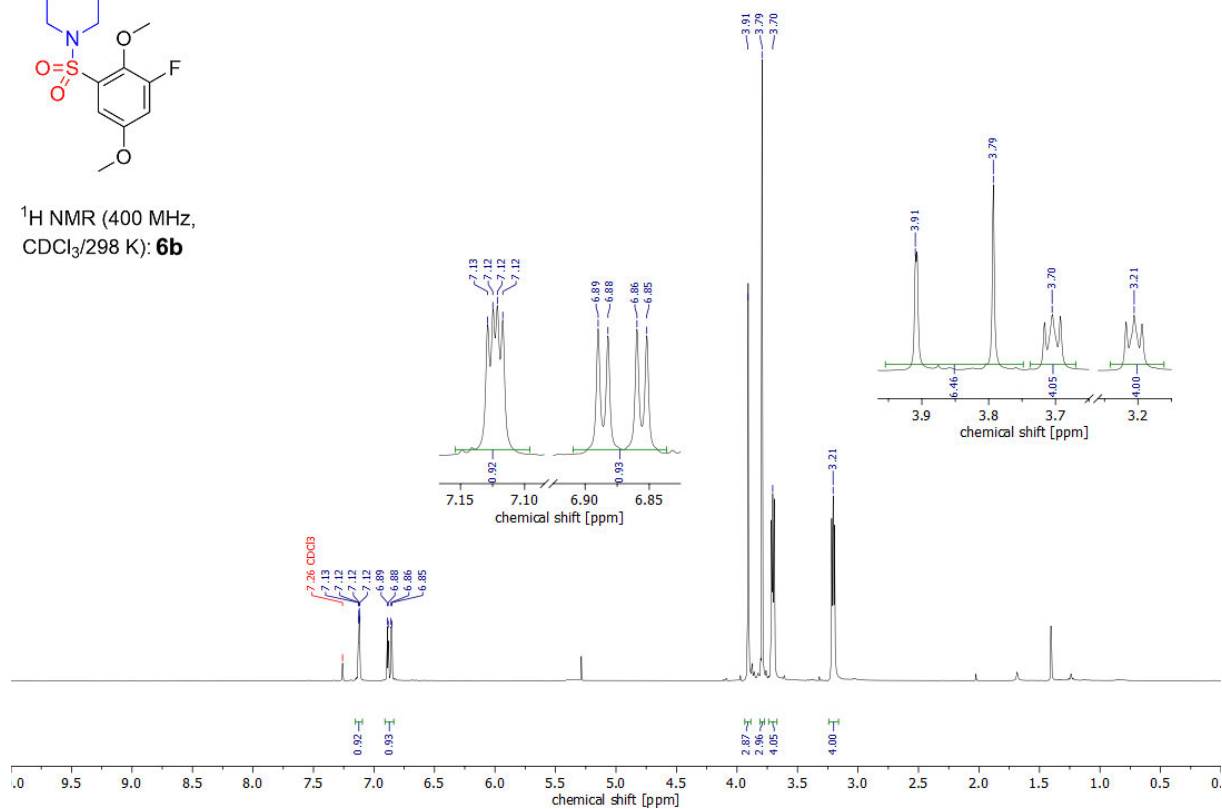


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **6a**

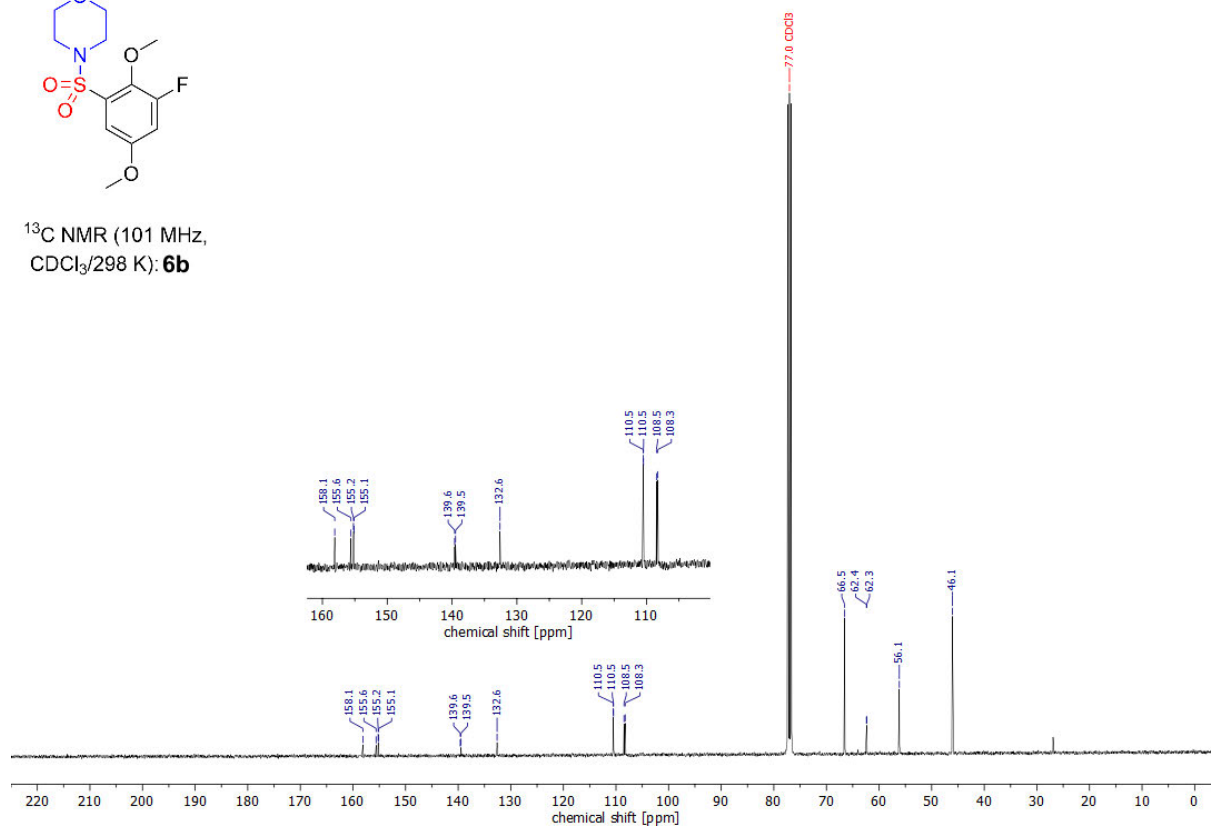


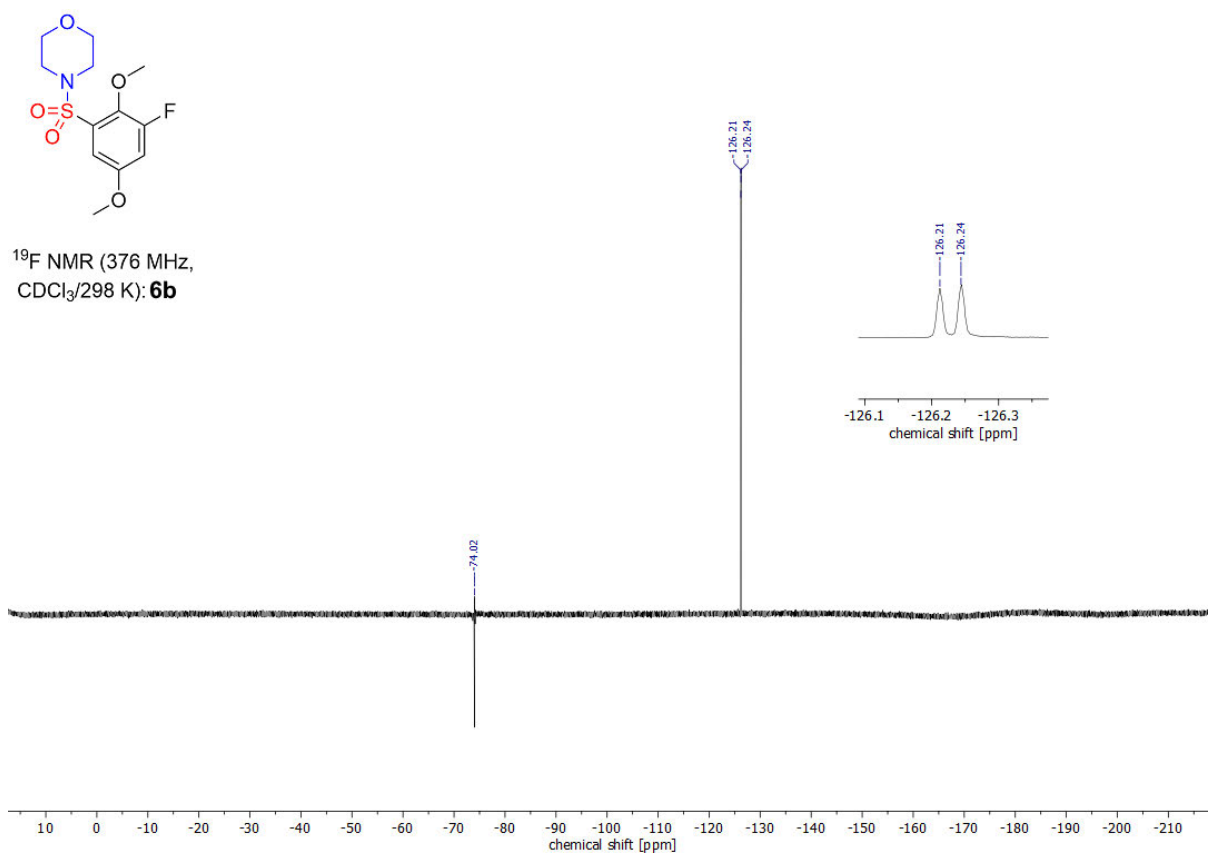
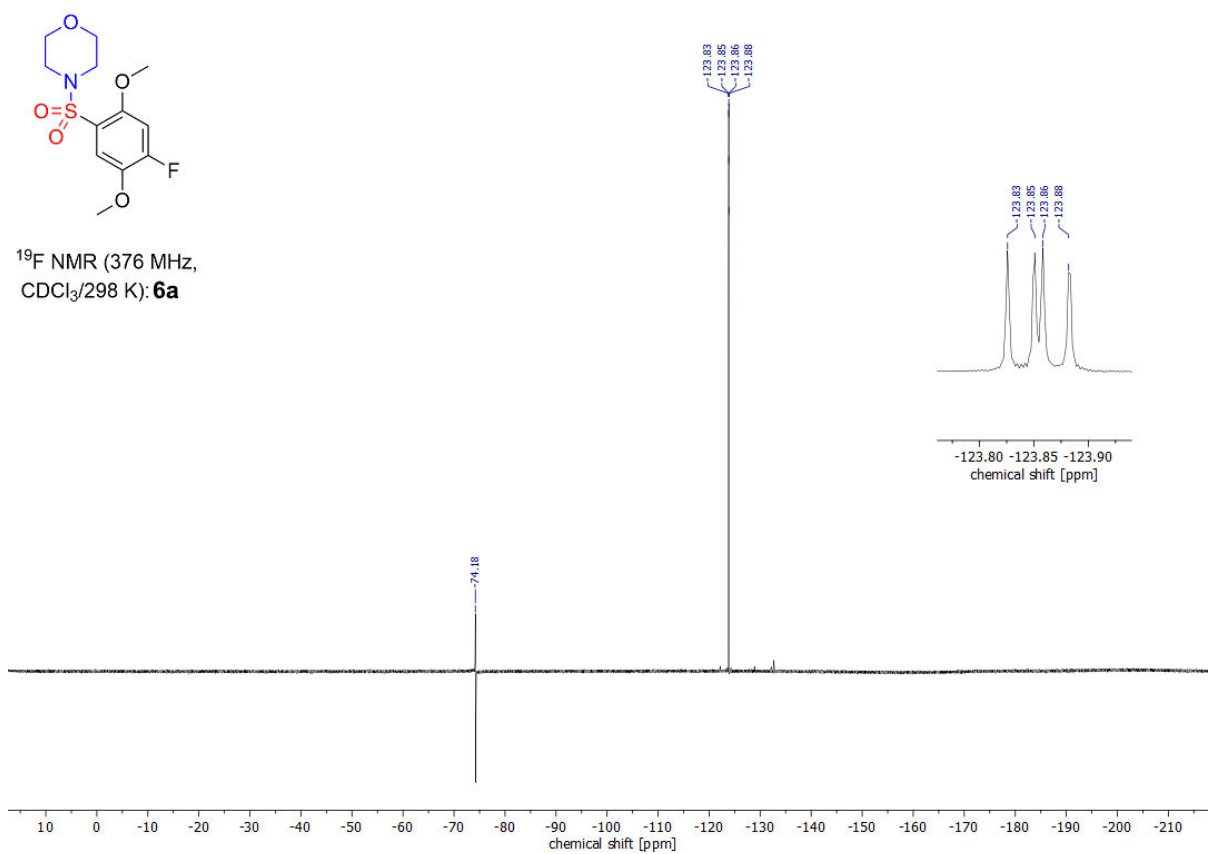


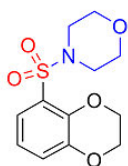
^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **6b**



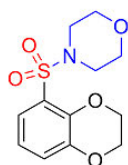
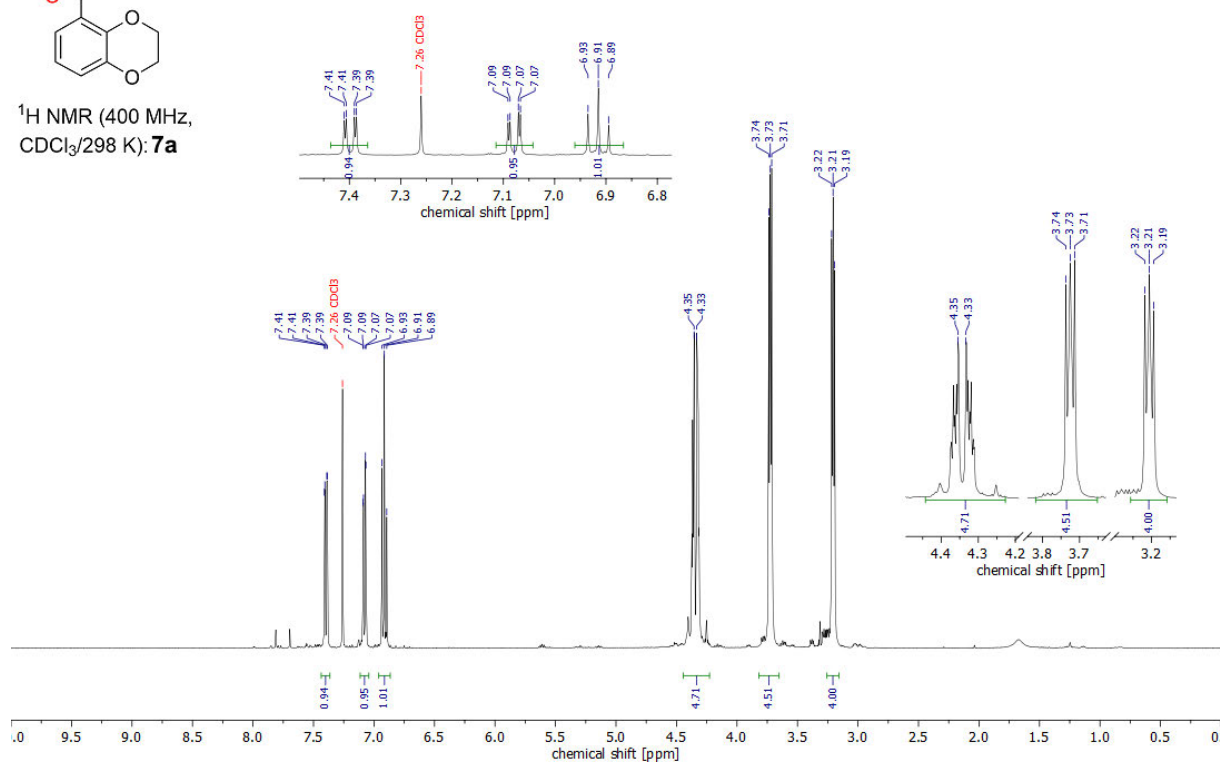
^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **6b**



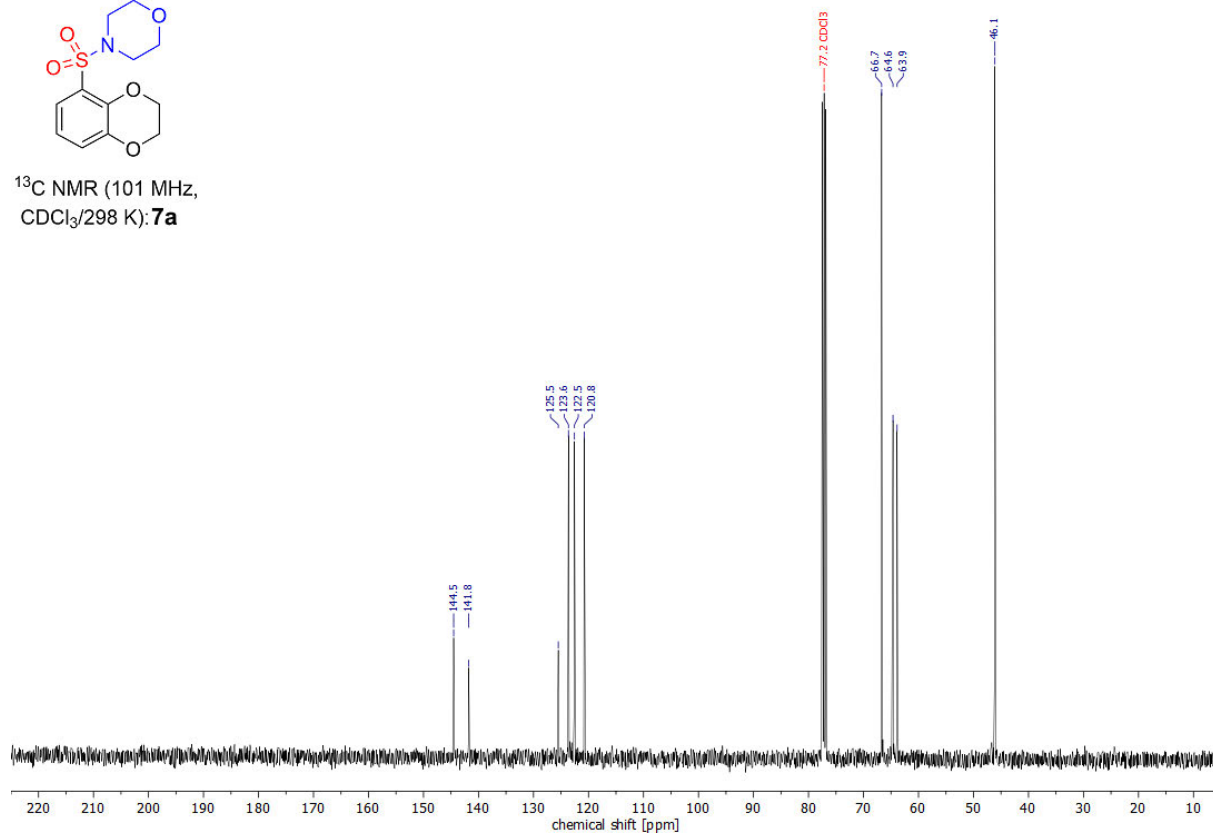


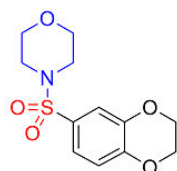


^1H NMR (400 MHz, CDCl_3 /298 K): **7a**

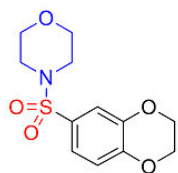
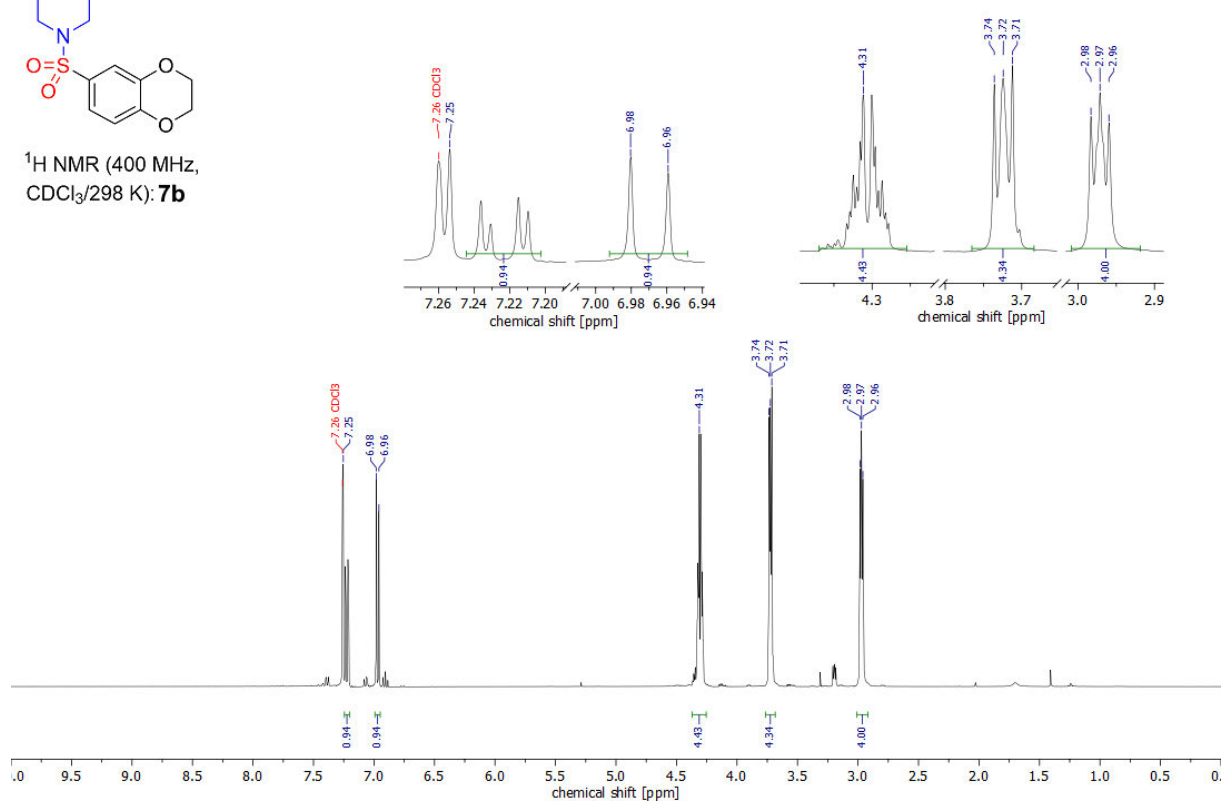


^{13}C NMR (101 MHz, CDCl_3 /298 K): **7a**

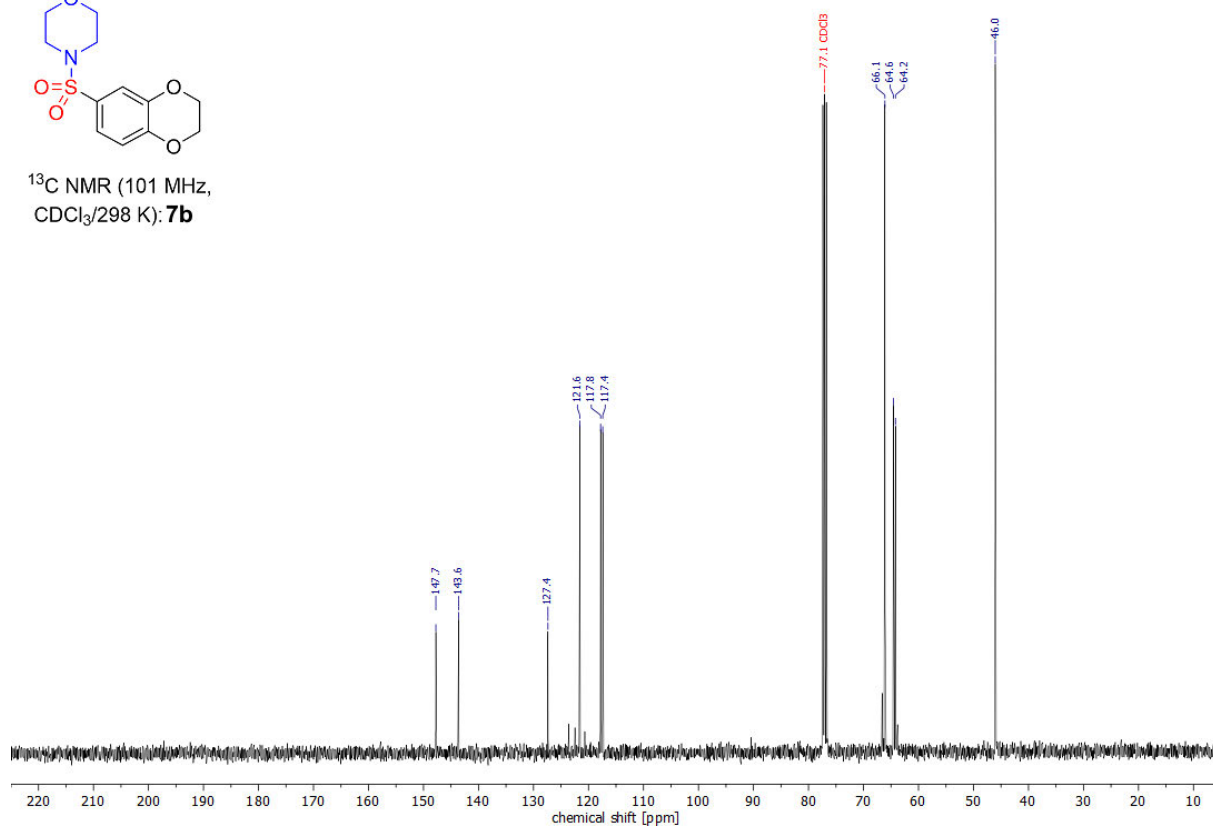


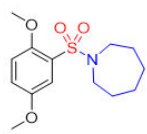


^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **7b**

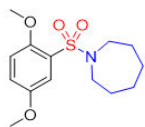
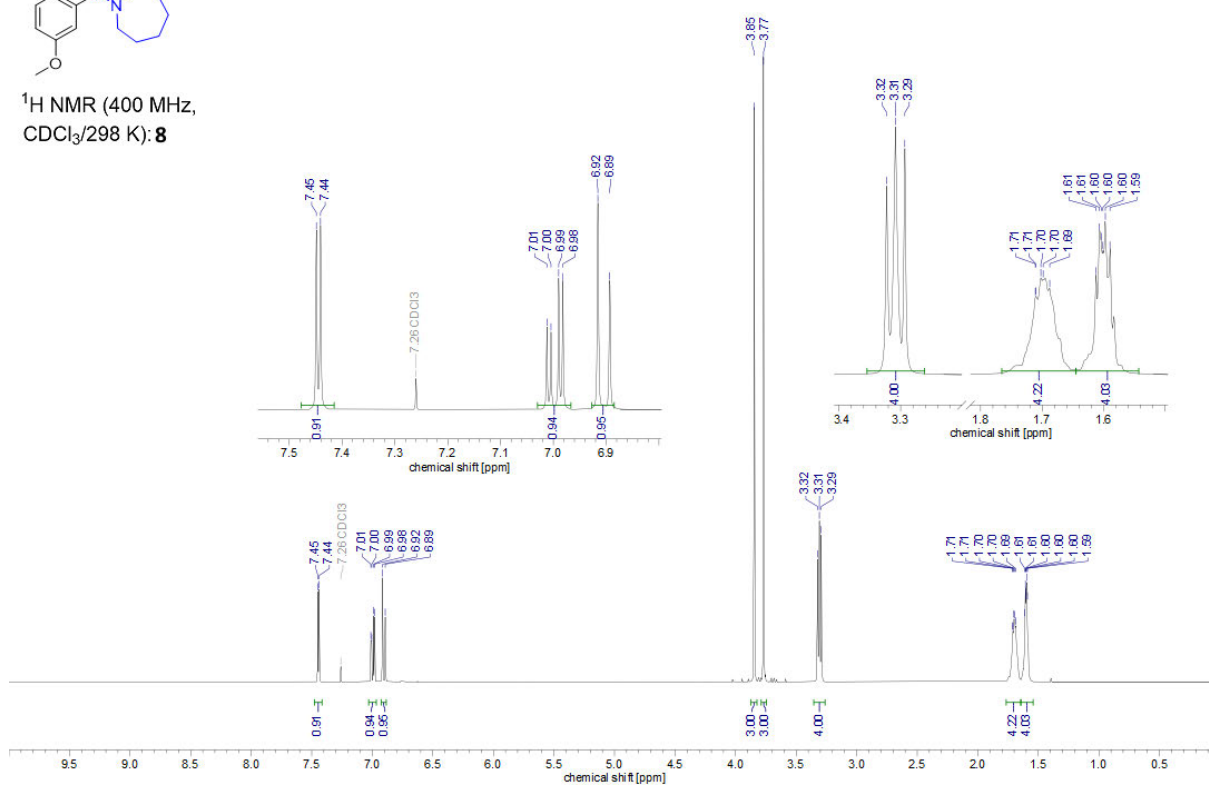


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **7b**

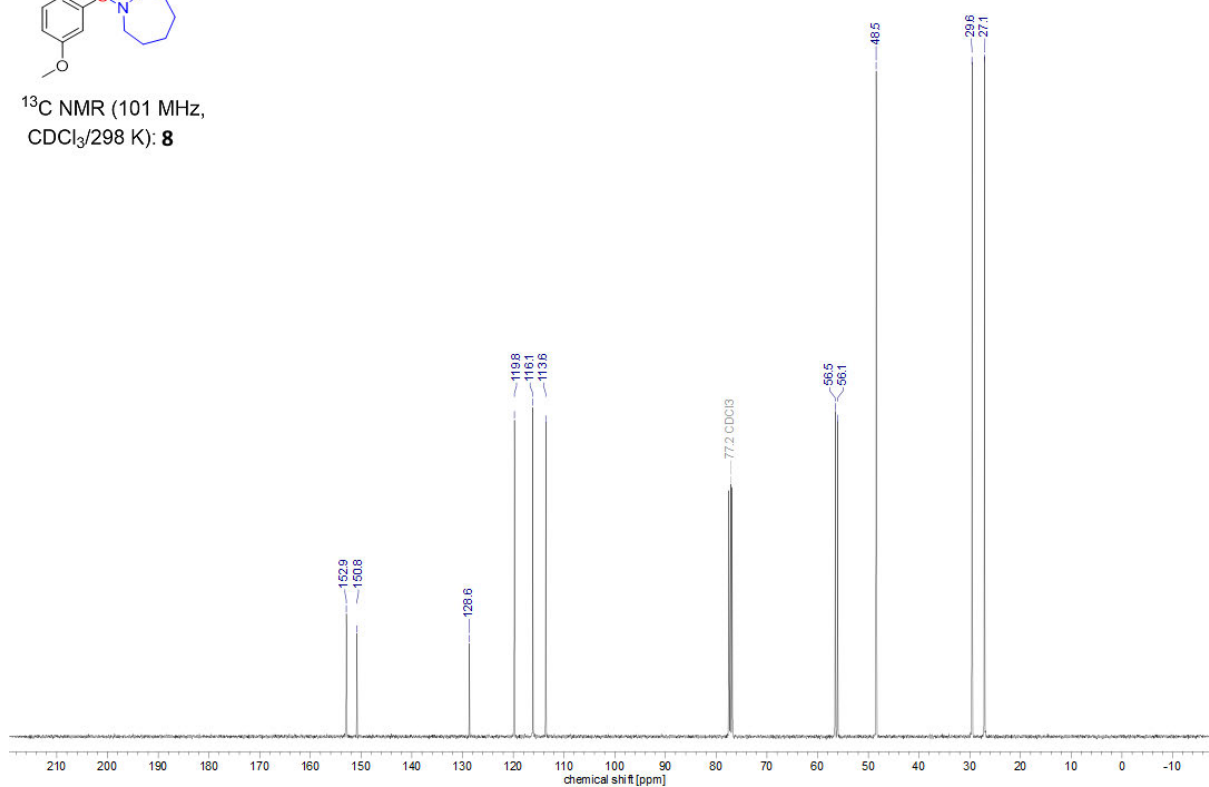




^1H NMR (400 MHz, CDCl_3 /298 K): **8**

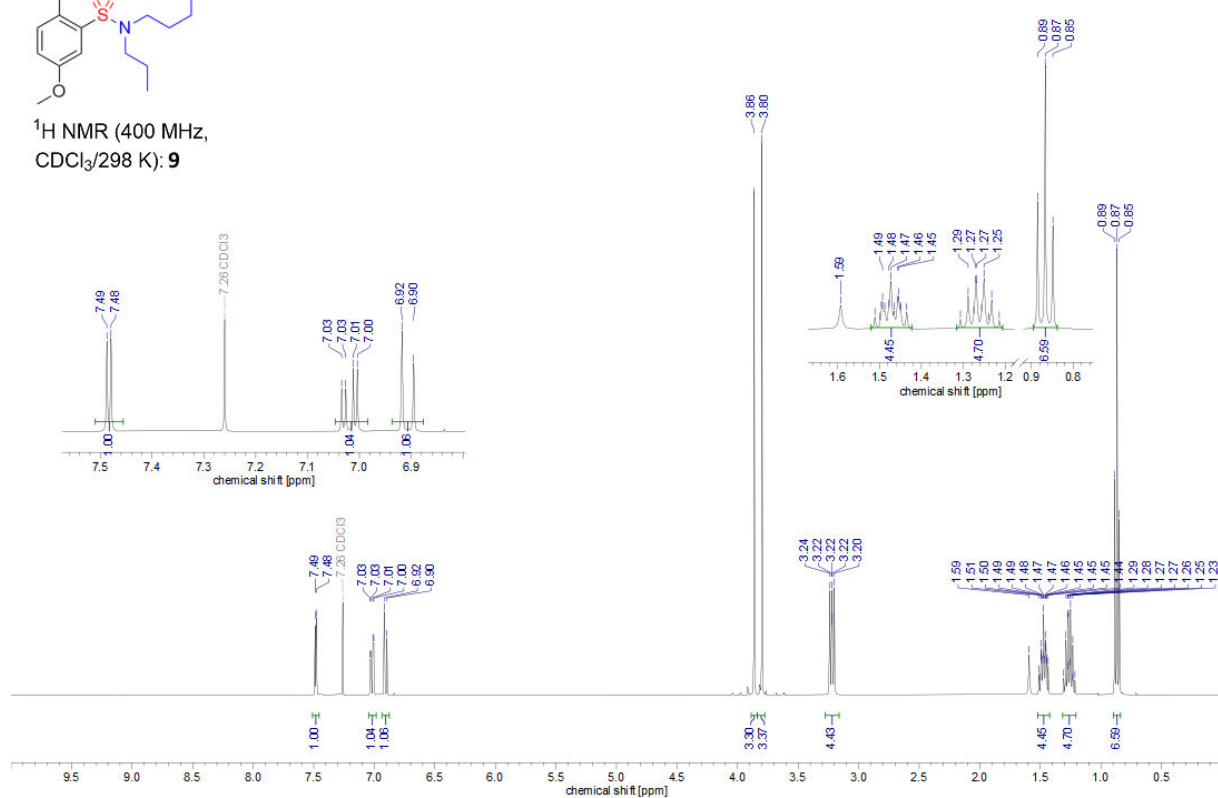


^{13}C NMR (101 MHz, CDCl_3 /298 K): **8**

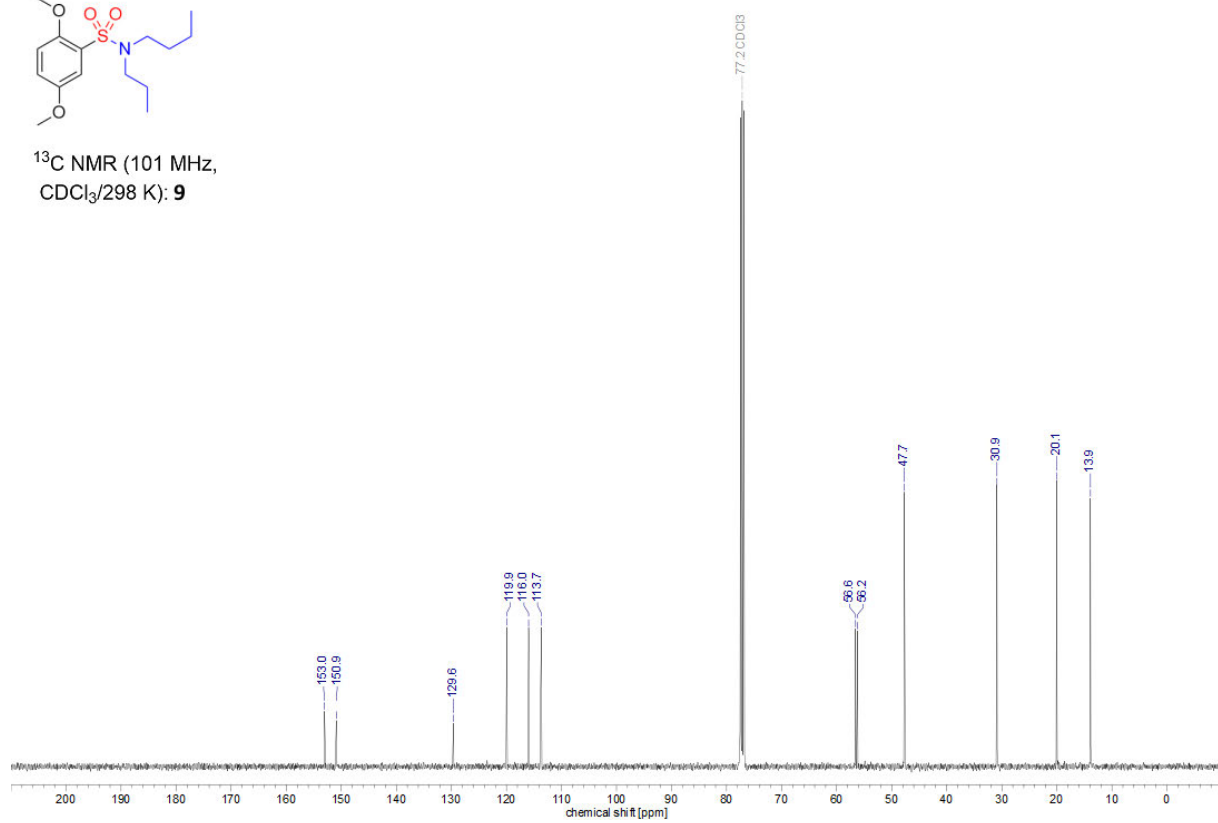


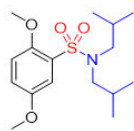


^1H NMR (400 MHz, $\text{CDCl}_3/298\text{ K}$): **9**

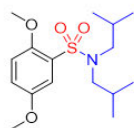
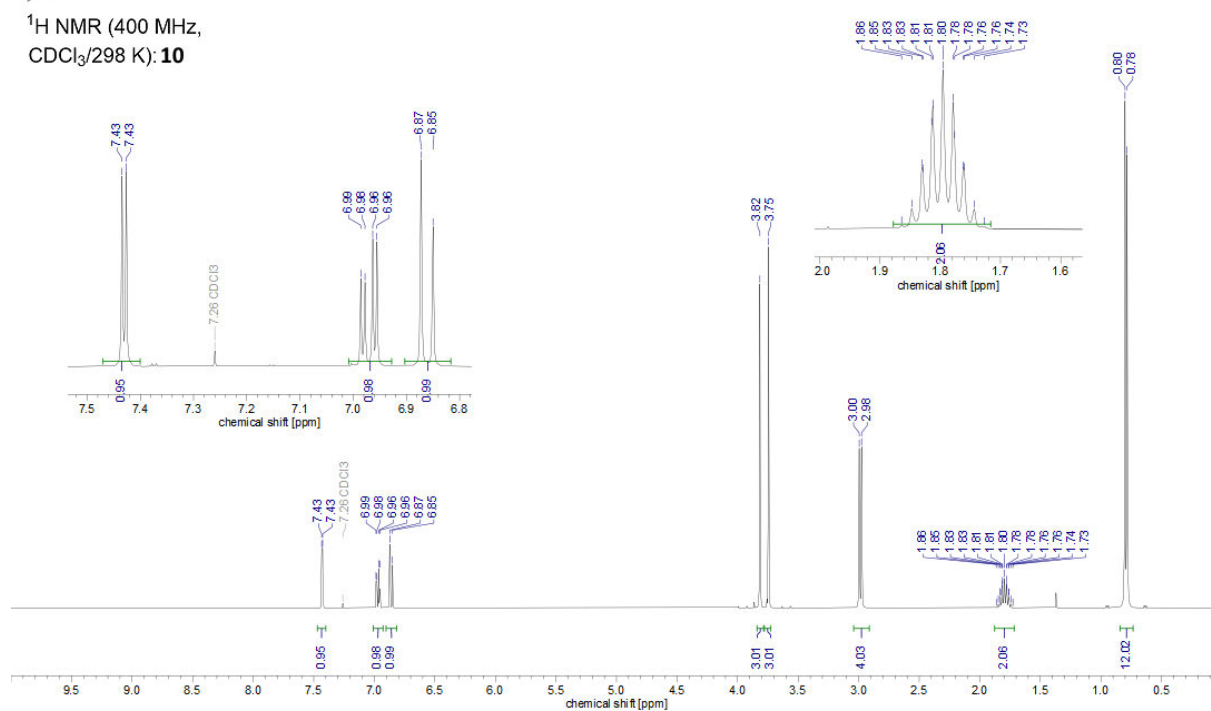


^{13}C NMR (101 MHz, $\text{CDCl}_3/298\text{ K}$): **9**

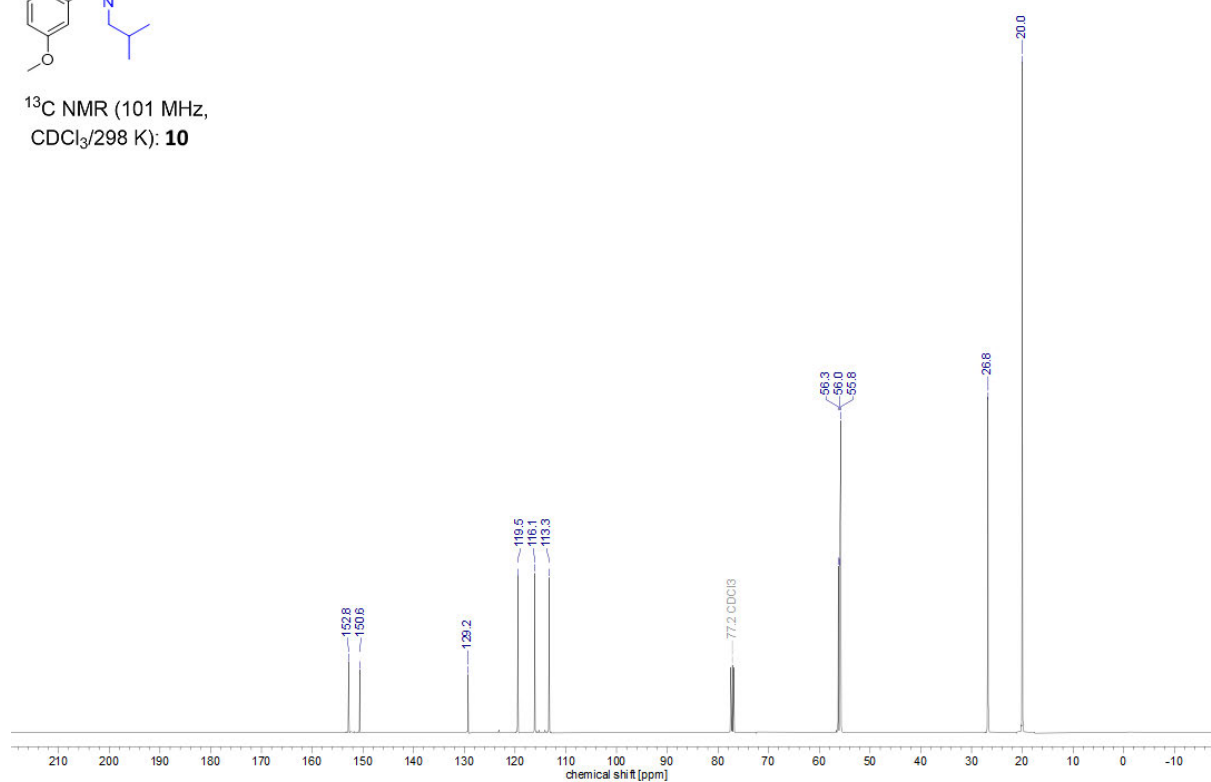




^1H NMR (400 MHz, CDCl_3 /298 K): **10**



^{13}C NMR (101 MHz, CDCl_3 /298 K): **10**



7. References

- [1] W. Armarego, *Purification of Laboratory Chemicals, 8th Edition*, 8. ed., Butterworth-Heinemann, **2017**.
- [2] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- [3] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.
- [4] M. Zirbes, T. Graßl, R. Neuber, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2023**, *62*, e202219217; *Angew. Chem.* **2023**, *135*, e202219217.
- [5] B. Gleede, M. Selt, C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2020**, *24*, 1916–1926.
- [6] G. Jander, K. F. Jahr, G. Schulze, J. Simon, R. Martens-Menzel, *Maßanalyse. Titrations mit chemischen und physikalischen Indikationen*, 19. ed., De Gruyter, Berlin, Boston, **2017**.

ChemElectroChem

Supporting Information

Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell

Maximilian M. Hielscher, Johannes Schneider, Alexander H. J. Lohmann, and
Siegfried R. Waldvogel*

Automated Optimization of the Synthesis of Alkyl Arenesulfonates in an Undivided Electrochemical Flow Cell

Maximilian M. Hielscher, Johannes Schneider, Alexander H. J. Lohmann, and Siegfried R. Waldvogel

Supporting Information

1. GENERAL INFORMATION	3
2. EXPERIMENTAL SETUP	3
2.1. COMPUTER HARDWARE AND LABS SOFTWARE	3
2.2. FLOW ELECTROLYSIS CELLS	4
3. GENERAL PROTOCOLS	6
3.1. GENERAL PROTOCOL FOR THE PREPARATION OF SULFUR DIOXIDE STOCK SOLUTIONS	6
3.2. GENERAL PROTOCOL FOR IODOMETRIC TITRATION OF SO ₂ STOCK SOLUTIONS	6
3.3. GENERAL PROTOCOL FOR ELECTROCHEMICAL SYNTHESIS OF ALKYL ARENESULFONATES IN FLOW	7
4. NMR YIELD, CONVERSION, AND SELECTIVITY	8
4.1. INITIAL EXPERIMENTS WITH SINGLE-PASS FLOW ELECTROLYSIS	8
4.2. INVESTIGATION OF THE FLOW MULTIPLIER	9
4.3. SYSTEM STABILITY ANALYSIS	9
4.4. INITIAL FRACTIONAL FACTORIAL DESIGN IN CYCLIC FLOW	10
4.5. SECOND FRACTIONAL FACTORIAL DESIGN	11
<i>Factorial Regression: NMR yield (%) ($p > \alpha = 0.1$)</i>	12
<i>Factorial Regression: Conversion (%) ($p > \alpha = 0.1$)</i>	14
<i>Factorial Regression: Selectivity (%) ($p > \alpha = 0.1$)</i>	16
4.6. EXTENSION TO A CENTRAL COMPOSITE DESIGN	18
<i>Response Surface Regression: NMR yield (%) ($p > \alpha = 0.1$)</i>	19
<i>Response Surface Regression: Conversion (%) ($p > \alpha = 0.1$)</i>	21
<i>Response Surface Regression: Selectivity (%) ($p > \alpha = 0.1$)</i>	23
4.7. RESPONSE OPTIMIZATION OF NMR YIELD	25
5. ANALYTICAL DATA OF PRODUCTS	26
6. PROPOSED MECHANISM	28
7. NMR SPECTRA OF PRODUCTS	29
8. REFERENCES	35

1. General Information

All solvents and reagents were obtained from commercial suppliers, and if necessary, purification was carried out according to standard methods.^[1] Cyclohexane and ethyl acetate used in flash column chromatography were distilled prior to use. Boron-doped diamond (BDD) electrodes (DIACHEM™, 20 mm x 60 mm x 3 mm with 15 µm BDD on silicon as supporting material) were purchased from CONDIAS GmbH (Itzehoe, Germany). A modular flow cell system, which was developed in our group, was used for flow electrolysis.^[2,3] It is commercially available as ElectraSyn Flow (<https://www.ikaprocess.com/en/Products/Electro-Organic-Synthesis-Systems-cph-45/>, 2024.06.05) from IKA-Werke GmbH & CO. KG (Staufen, Germany). Gasket polymer foil (FFKM/FFPM CKD900) for the construction of SO₂ resistant flow cells was purchased from CDK Dichtungstechnik GmbH (Dreieich, Germany). Sulfur dioxide (purity 99.98%) was purchased in a 10 L steel bottle from Linde Gas GmbH (Stadl-Paura, Austria).

Thin-layer chromatography (TLC) was carried out using Supelco silica gel 60 F₂₅₄ aluminium TLC plates (Merck KGaA, Darmstadt, Germany) with 5 µL micro pipettes (Blaubrand intraMARK, BRAND GmbH + CO KG, Wertheim, Germany) for sample location.

Preparative column chromatography was performed using an Interchim puriFlash™ XS520Plus flash column chromatography system using pre-packed 30 µm puriFlash™ PF-30SIHP-F0025 silica columns (Interchim, Montlucon Cedex, France).

Nuclear magnetic resonance (NMR) spectra of ¹H (400 MHz), and ¹³C{¹H} (101 MHz) were measured at 23 °C using a Bruker Avance II 400, 400 MHz field strength, 5 mm BBFO probe with z gradient and ATM, SampleXpress 60 sample changer (Bruker BioSpin, Ettlingen, Germany).

High-resolution mass spectra (HRMS) were recorded using a G6545A Q-ToF (Agilent GmbH, Waldbronn, Germany) with Electron Spray Ionization (ESI). For sample injection, a 1260 Infinity II HPLC-System with a G7111B 1260 quaternary pump, G7129A 1260 vial sampler and G7116A 1260 multicolumn thermostat was used (Agilent GmbH, Waldbronn, Germany).

2. Experimental Setup

Table S1: The devices used in the experimental setup.

Device	Model	Manufacturer	Note
Power supply	Z60-3.5-L2	TDK-Lambda GmbH, Achem, Germany	210 W, 0 – 60 V DC (±0.01 V), 0 – 3.5 V (±1 mA)
Fraction collector	OMNICOLL Fraction Collector and Sampler	LAMBDA Laboratory Instruments, Baar, Switzerland	–
Temperature control	F33-MA refrigerated circulator	Julabo GmbH, Seelbach, Germany	Working temperature: –30 °C to 200 °C, heating power: 2 kW, cooling power (ethanol): 0.50 kW (0 °C), 0.12 kW (–20 °C), 0.03 kW (–30 °C), flow rate: 11 – 16 L/min
Peristaltic pump	ISM 4408 Ismatec Reglo ICC	VWR International, Darmstadt, Germany	Tubing: Pharmed BPT™ (Saint-Grobain, France)

2.1. Computer Hardware and LABS Software

To run frontend and backend, a PC with Microsoft Windows 11 Education (10.0.22000) was used, which was built using the following components: MSI X570-A PRO (MS-7C37), AMD Ryzen 5 3600, Intel SSDPEKNW010T8 (1.0 TB), 16 GB RAM, NVidia GeForce GTX 1650, 2x Realtek PCIe GbE Family Controller. The software used in this work is listed in the following Table S2. Details about the architecture of LABS can be found in the initial LABS publication.^[4]

Table S2. The open-source software used in this work.

Software	GitHub	DOI (Zenodo)
LABS-Frontend	https://github.com/Waldvogel-Group/LABS-Backend	https://doi.org/10.5281/zenodo.7879588
LABS-Backend	https://github.com/Waldvogel-Group/LABS-User-Interface	https://doi.org/10.5281/zenodo.7879586

2.2. Flow Electrolysis Cells

Small flow cell (both anode and cathode: 2.0 cm x 6.0 cm)

A modular flow cell which was developed in our group was utilized in this work.^[3] The flow cell depicted in Figure S1 was used for all reactions except the scale-up reaction. Boron-doped diamond (BDD, 6.0 cm x 2.0 cm x 0.3 cm) was used as anode material, which is put into the Teflon frame, and a stainless-steel block (VA 1.4571; AISI 316Ti, temperature control attachment) with cooling circuit as cathode. As separator material within the cell, Teflon spacers of thickness 0.25 mm were used. To assemble the flow cell, stainless-steel front and back plates and stainless-steel screws (DIN 921 A2 M4X55) were used. The back plates have matching threads for the screws.

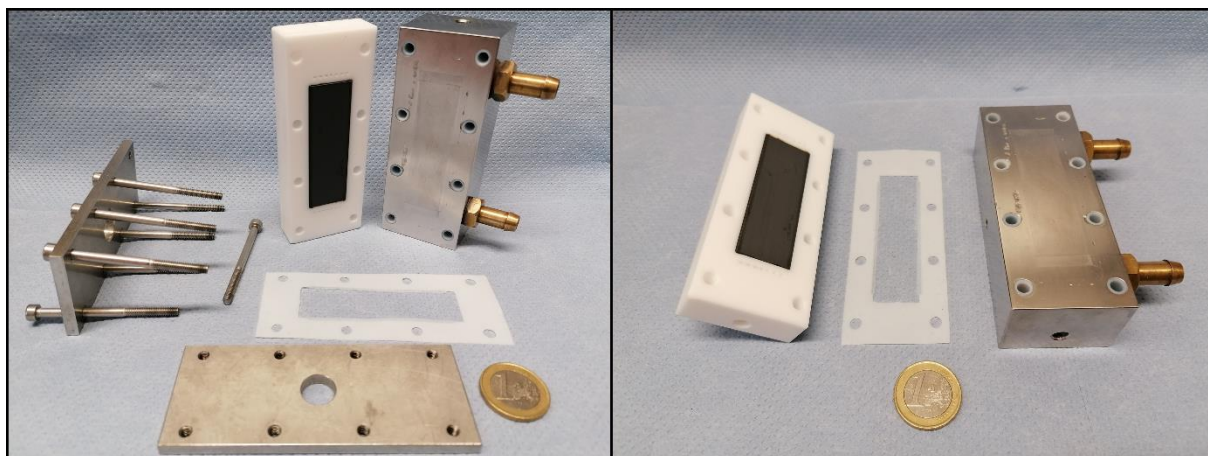


Figure S1. The small flow electrolysis cell, both anode and cathode surface: 2.0 cm x 6.0 cm. The pictures taken from Supporting Information of reference [5] (CC BY 4.0). A one Euro coin is placed next to the electrolysis cell for size comparison.

Large flow cell (both anode and cathode: 4.0 cm x 12.0 cm)

For scale-up experiments, a larger flow cell (4.0 cm x 12.0 cm BDD electrode) was used, as depicted in Figure S2. The cell design is different from the small flow cell. Due to the thermally induced expansion and contraction of Teflon, the shrinking of the Teflon holder for the large flow cell could potentially result in damage to the BDD electrode. To mitigate this, the flow cell comprises two gaskets (FFKM/FFPM CKD900), which act as a buffer between Teflon and the BDD electrode along the long axis. Additionally, the gaskets serve to prevent the reaction solution from percolating under the electrode. FFKM/FFPM is highly (electro)chemically resistant. As cathode, a solid block of stainless-steel is used, which does not require any gaskets. A Teflon spacer of thickness 0.25 mm is used. The assembly of the cell is conducted using stainless-steel screws and back plates with matching threads. The stainless-steel screws are put through the cathode, Teflon spacer, Teflon holder of the anode, and into the back plate. Note that there is no short circuit resulting from the screws, because the cathode cable is directly connected to the stainless-steel block, while anode cable is attached to the back of the Teflon holder, which has a copper plug that is attached to the bottom of the BDD electrode. Also, in each hole in the cathode, there is a piece of plastic which places the screw in the center of the hole, so the screws do not even have contact to the cathode itself.

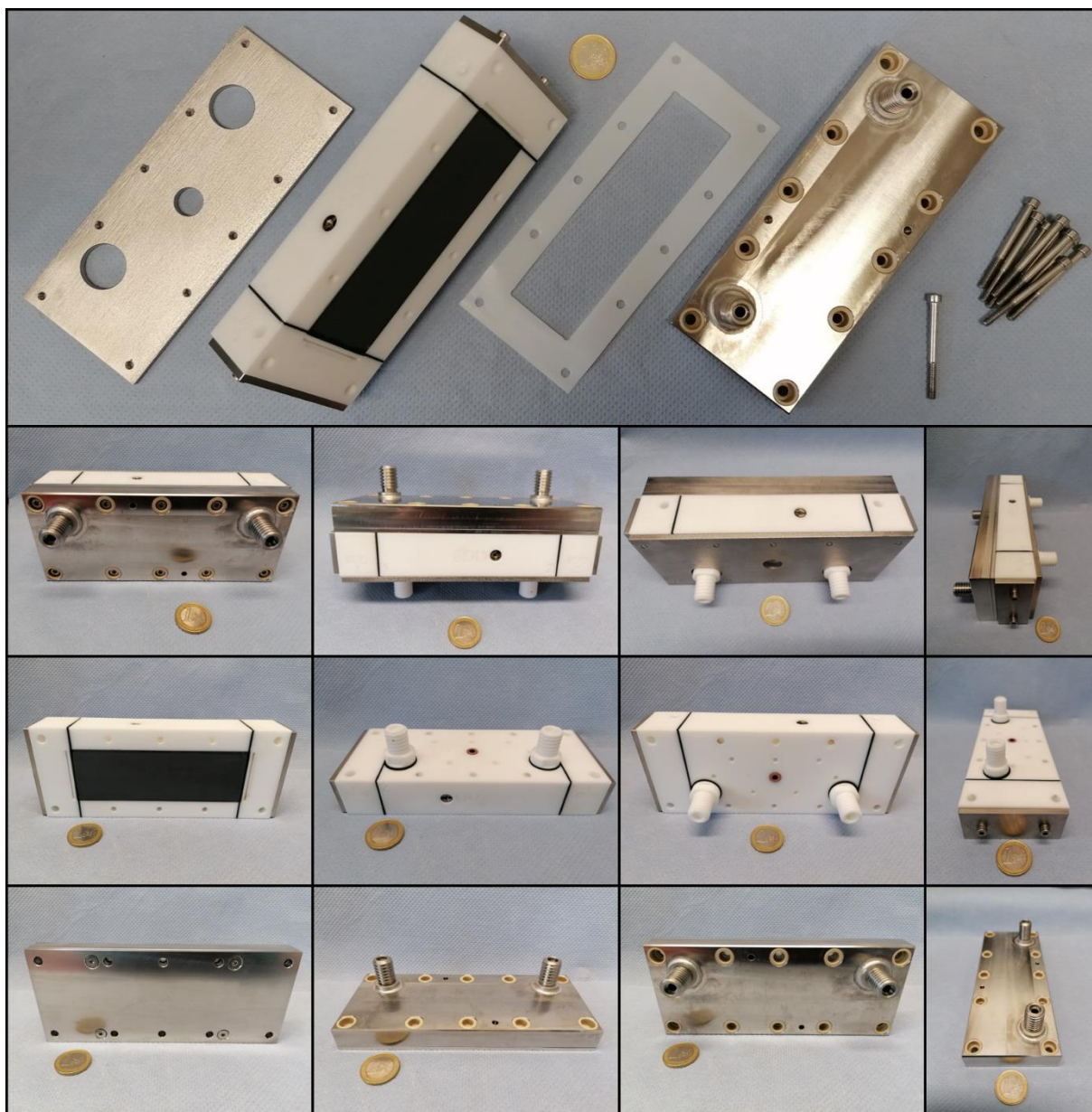


Figure S2. The large flow electrolysis cell, both anode and cathode surface: 4.0 cm x 12.0 cm. The pictures taken from Supporting Information of reference [5] (CC BY 4.0). A one Euro coin is placed next to the electrolysis cell for size comparison.

3. General Protocols

3.1. General protocol for the preparation of sulfur dioxide stock solutions

To prepare stock solutions of sulfur dioxide, the apparatus depicted in Figure S3 was used:

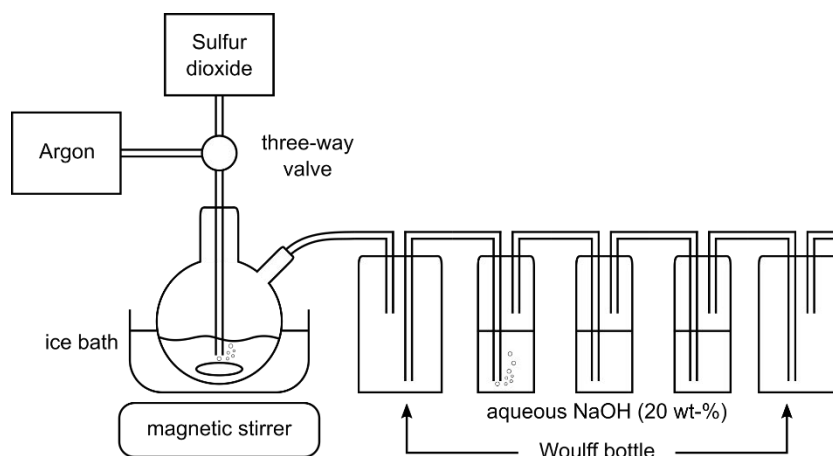


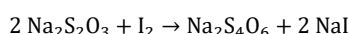
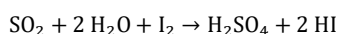
Figure S3. Schematic illustration of the apparatus used to prepare sulfur dioxide stock solutions.

This apparatus was assembled in a well-ventilated fume hood. The solvent (MeCN, HFIP, or a mixture of those) was transferred into a two neck round bottom flask that is cooled with an ice bath on a magnetic stirrer. Under slight stirring and under continuous cooling, the solvent was flushed with sulfur dioxide at 0 °C for 20 min. Excess SO₂ is neutralized with aqueous NaOH (20 wt%) in the downstream gas washing bottles. Upon completion, the apparatus was flushed with argon. The SO₂ concentration of the stock solution is determined using iodometry, and the stock solution is stored at +4 °C.

3.2. General protocol for iodometric titration of SO₂ stock solutions

The SO₂ concentration in the stock solution is determined by iodometric titration.^[6] The titrant solution was prepared by dissolving sodium thiosulfate pentahydrate (Na₂S₂O₃·5H₂O, 4.964 g, 0.02 mol) in distilled water (100.0 mL) in a volumetric flask at 25 °C. In an Erlenmeyer flask, iodine (I₂, 1.269 g, 5.00 mmol) was dissolved together with potassium iodide (KI, 2.209 g, 13.3 mmol) in distilled water (100 mL) at 25 °C. To facilitate the dissolution of I₂, it is recommended to pre-grind it in a mortar prior to weighing. A stirring bar is added to the solution of I₂ and KI, and the solution is stirred at 25 °C until the iodine is completely dissolved. An aliquot of the SO₂ stock solution (1.0 mL at +4 °C) is injected slowly into the solution of I₂ and KI. This aliquot of SO₂ stock solution must be injected under the liquid surface to prevent the evaporation of SO₂. While being stirred, the solution is titrated using the freshly prepared Na₂S₂O₃ solution as titrant. Do not store the Na₂S₂O₃ titrant solution because it decomposes.^[6] The addition of a small quantity of a freshly prepared starch solution can enhance the ability to identify the endpoint of the titration.^[6]

Iodine is reduced according to the following equations:



The concentration of the SO₂ stock solution $c(\text{SO}_2)$ is calculated as follows:

$$c(\text{SO}_2) = \frac{n_0(\text{I}_2) - \frac{1}{2}(V(\text{Na}_2\text{S}_2\text{O}_3) \cdot c(\text{Na}_2\text{S}_2\text{O}_3))}{V(\text{SO}_2 \text{ aliquot})}$$

3.3. General protocol for electrochemical synthesis of alkyl arenesulfonates in flow

The pump is calibrated with acetonitrile before the experiment. In a 50 mL round bottom flask with a stirring bar, 1,4-dimethoxybenzene ($138.17 \text{ g mol}^{-1}$, 1.2 mmol, 166 mg) is dissolved in acetonitrile (MeCN, 4.15 mL) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, 4.15 mL). Pyridine (8.0 equiv., 79.10 g mol^{-1} , 9.6 mmol, 759 mg, 0.98 g mL^{-1} , 0.77 mL) and ethanol (8.0 equiv., 46.07 g mol^{-1} , 9.6 mmol, 422 mg, 0.79 g mL^{-1} , 0.56 mL), and SO_2 stock solution (SO_2 in HFIP/MeCN 7:3 (vol%), $c(\text{stock solution}) = 2.0 \text{ mol L}^{-1}$, 10. equiv. SO_2 , 6.15 mL) is added. The flow electrolysis cell is filled with electrolyte, and the electrolysis is started in recirculating (cyclic) mode. The pump speed v is calculated by multiplying a flow multiplier constant f_{flow} with the pump rate which is theoretically required v_{theory}

$$v = f_{\text{flow}} \cdot v_{\text{theory}} = f_{\text{flow}} \cdot \frac{V_{\text{solution}}}{t_{\text{electrolysis}}}$$

The electrolysis time $t_{\text{electrolysis}}$ is calculated by dividing the required amount of applied charge Q by the electric current I

$$t_{\text{electrolysis}} = \frac{Q_{\text{applied}}}{I}$$

Electric current I is the product of current density j with the anode surface A_{anode}

$$j = \frac{I}{A_{\text{anode}}} \Rightarrow I = j \cdot A_{\text{anode}}$$

The amount of applied charge, for example with $Q_{\text{Faraday}} = 6.0 F$ with $n_{\text{starting material}} = 1.2 \text{ mmol}$ is calculated as follows:

$$Q_{\text{applied}} = 6.0 \cdot 96486 \frac{\text{C}}{\text{mol}} \cdot 1.2 \cdot 10^{-3} \text{ mol} \approx 695 \text{ C.}$$

Note that the unit of Q_{Faraday} is F , not F/mol , as this would result in an incorrect unit: $(F/\text{mol})/\text{mol}$. The electric current I and the amount of applied charge in the unit of Coulomb Q_{applied} are set in the coulometer of the DC power source. After the electrolysis is finished, the flow electrolysis cell is flushed with acetonitrile. To quantify the reactions outcome using qNMR spectroscopy, 1,3,5-trimethoxybenzene (0.60 mmol) is added as internal standard. The solvent is removed using a rotary evaporator (40°C water bath, 280 mbar to 50 mbar in 30 min) and an NMR sample in CDCl_3 is prepared from the crude solid. To isolate the reaction product, no internal standard is added, and the solvent is removed using a rotary evaporator. The crude residue is adsorbed in silica and purified using flash column chromatography (cyclohexane : ethyl acetate = 10:0 $\rightarrow$ 1:1 vol%).

General considerations for experiments which use SO_2 stock solutions

- 1) Stock solutions of SO_2 with concentrations higher than 2.0 mol L^{-1} tend to degas when being pumped using a piston pump or peristaltic pump, which can lead to unprecise dosing. Therefore, concentrations higher than this are not desirable in an automated flow setup where the stock solution is being dosed by a pump.
- 2) The volume ratio of HFIP/MeCN in the reaction solution must be considered once all components have been added, including the amount of HFIP and MeCN which was added by the SO_2 stock solution. This means the amount of HFIP and MeCN in the final reaction solution depends on the volume of SO_2 stock solution that was added (which itself depends on the concentration of the SO_2 stock solution) and the HFIP/MeCN ratio in the stock solution. When adding HFIP or MeCN to the reaction solution to adjust this ratio, the starting material must not be diluted (0.10 mol L^{-1}). This means you can't add as much HFIP or MeCN as you want afterwards to reach the desired HFIP/MeCN volume ratio.
- 3) These principles for HFIP/MeCN ratio in the final reaction solution also apply for other stock solutions of reagents and additives in HFIP, MeCN, or mixtures of them. For example, if a high amount of HFIP is desired in the reaction solution, but a reagent is added using a very dilute stock solution in pure MeCN, the desired equivalents of the reagent can only be achieved by diluting the reaction through addition of more HFIP to counter the MeCN addition of by the reagent stock solution. Therefore, the HFIP/MeCN volume ratio must be considered for reagents as well.
- 4) When handling SO_2 stock solutions manually using a syringe, degassing can also occur at SO_2 concentrations higher than 2 mol L^{-1} .
- 5) The solubility of SO_2 is higher in pure MeCN than in pure HFIP. Stock solutions with HFIP/MeCN 1:1 typically reach a saturation of 2.0 mol L^{-1} at $+4^\circ\text{C}$. For pure MeCN, concentrations up to $>3 \text{ mol L}^{-1}$ at $+4^\circ\text{C}$ can be reached, but these concentrations complicate handling of the stock solution because of degassing.

4. NMR yield, conversion, and selectivity

NMR yield is calculated using the following equation, where I is the integral of the signal in the ^1H NMR spectrum, and N is the number of protons corresponding to that signal.^[7] Because 1,3,5-trimethoxybenzene was used as internal standard and its three aromatic protons around 6.0 ppm are used for integration, $N_{\text{internal standard}} = 3$.

$$\% \text{yield}_{\text{NMR}} = \frac{n_{\text{product}} \cdot 100}{n_{\text{starting material}}} = \frac{n_{\text{internal standard}} \cdot \frac{\left(\frac{I_{\text{product}}}{N_{\text{product}}}\right)}{\left(\frac{I_{\text{internal standard}}}{N_{\text{internal standard}}}\right)} \cdot 100}{n_{\text{starting material}}}$$

Conversion is calculated as follows:

$$\% \text{conversion}_{\text{NMR}} = 100 - \left(\frac{n_{\text{remaining starting material}} \cdot 100}{n_{\text{starting material}}} \right) = 100 - \frac{\left(\frac{I_{\text{remaining starting material}}}{N_{\text{remaining starting material}}}\right) \cdot 100}{\left(\frac{I_{\text{internal standard}}}{N_{\text{internal standard}}}\right) \cdot 100}$$

Selectivity is determined by:

$$\% \text{selectivity}_{\text{NMR}} = \frac{\% \text{yield}_{\text{NMR}}}{\% \text{conversion}_{\text{NMR}}}$$

The following abbreviations will be used in indices: SM for starting material, STD for internal standard.

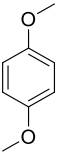
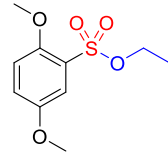
4.1. Initial Experiments with Single-Pass Flow Electrolysis

At the beginning, the single-pass flow experiments listed in Table S3 were carried out according to general protocol 3. Note that of the total reaction volume of 12.00 mL, a pre-run of 4.00 mL was discarded, and a fraction of 6.00 mL after the pre-run was collected and analyzed. The volume was collected by measuring the time it takes for this volume to be pumped at the set pump speed. The NMR yield, conversion, and selectivity was calculated accordingly:

$$n_{\text{product}} = \frac{12.00 \text{ mL}}{6.00 \text{ mL}} \cdot n_{\text{product, fraction}} = 2 \cdot n_{\text{product, fraction}}$$

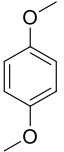
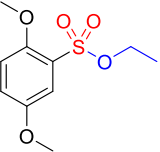
$$n_{\text{SM, remaining}} = 2 \cdot n_{\text{SM, remaining, fraction}}$$

Table S3. Data for single-pass experiments. $n_{\text{STD}} = 0.61 \text{ mmol}$, $I_{\text{STD, NMR}} = 3.00$, $N_{\text{STD}} = 3$, $N_{\text{product}} = 1$, $N_{\text{SM}} = 4$.

 0.10 mol L⁻¹ ethanol, pyridine SO₂ (10.0 equiv.) HFIP/MeCN 1:1 (vol%), BDD stainless-steel 25.0 °C, single-pass flow, undivided cell pre-run: 4.00 mL, collected: 6.00 mL total reaction volume: 12.00 mL 0.25 mm interelectrode gap 											
Entry	Q / F	j / mA cm ⁻²	equiv. ethanol	equiv. pyridine	I _{product, NMR}	N _{product} / mmol	I _{SM, remaining, NMR}	n _{SM, remaining} / mmol	NMR yield%	conversion%	selectivity%
1	7.0	25.0	8.0	8.0	4.44	0.26	5.74	0.17	22	86	25
2	6.0	25.0	6.0	6.0	4.15	0.25	8.31	0.25	20	80	25
3	6.0	20.0	6.0	6.0	4.70	0.28	10.50	0.31	23	74	31
4	6.0	20.0	4.0	4.0	3.14	0.19	12.27	0.36	15	70	22
5	6.0	15.0	6.0	6.0	2.68	0.16	13.68	0.41	13	66	20
6	4.0	15.0	6.0	6.0	2.04	0.12	15.33	0.46	10	62	16
7	6.0	10.0	4.0	4.0	2.37	0.14	16.73	0.50	12	59	20

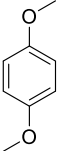
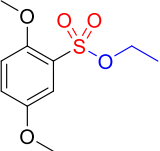
4.2. Investigation of the Flow Multiplier

Table S4. Data for flow multiplier experiments. $n_{\text{STD}} = 0.61$ mmol, $I_{\text{STD,NMR}} = 1.00$, $N_{\text{STD}} = 3$, $N_{\text{product}} = 1$, $N_{\text{SM}} = 4$.

 0.10 mol L⁻¹ ethanol (5.0 equiv.) pyridine (6.0 equiv.) SO₂ (10.0 equiv.) Q = 6.0 F, j = 20.0 mA cm⁻² HFIP/MeCN 58:42 (vol%) BDD stainless-steel, 25.0 °C 0.25 mm interelectrode gap cyclic flow, undivided cell 								
Entry	Multiplier	$I_{\text{product,NMR}}$	$n_{\text{product}} /$	$I_{\text{SM,remaining,NM}}$	$n_{\text{SM,remaining}} /$	NMR yield%	Conversion	Selectivity%
1	1.0	0.27	0.49	0.69	0.31	41	74	55
2	1.0	0.29	0.53	0.83	0.38	44	69	64
3	2.0	0.34	0.62	0.53	0.24	52	80	65
4	2.0	0.33	0.60	0.44	0.20	50	83	60
5	3.0	0.32	0.58	0.56	0.25	49	79	62
6	3.0	0.31	0.56	0.65	0.30	47	75	62
7	4.0	0.35	0.64	0.41	0.19	53	84	63
8	4.0	0.34	0.62	0.57	0.26	52	78	66
9	5.0	0.32	0.58	0.29	0.13	49	89	55
10	5.0	0.36	0.65	0.28	0.13	55	89	61

4.3. System Stability Analysis

Table S5. System stability analysis. $n_{\text{STD}} = 0.61$ mmol, $I_{\text{STD,NMR}} = 1.00$, $N_{\text{STD}} = 3$, $N_{\text{product}} = 1$, $N_{\text{SM}} = 4$. The highlighted entry is an outlier.

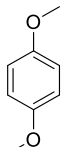
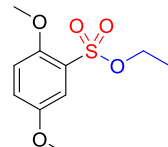
 0.10 mol L⁻¹ ethanol (5.0 equiv.) pyridine (6.0 equiv.) SO₂ (10.0 equiv.) Q = 6.0 F, j = 20.0 mA cm⁻² HFIP/MeCN 58:42 (vol%) BDD stainless-steel, 25.0 °C 0.25 mm interelectrode gap cyclic flow, undivided cell flow multiplier 5, 5-249 $\mu\text{L min}^{-1}$ 							
Entry	$I_{\text{product,NMR}}$	$n_{\text{product}} /$ mmol	$I_{\text{SM,remaining,NMR}}$	$n_{\text{SM,remaining}} /$	NMR yield%	Conversion%	Selectivity%
1	0.35	0.64	0.13	0.06	53	95	56
2	0.32	0.58	0.24	0.11	49	91	53
3 ^[a]	0.40	0.73	0.10	0.05	61	96	63
4	0.35	0.64	0.20	0.09	53	92	57
5	0.33	0.60	0.29	0.13	50	89	56
6	0.33	0.60	0.33	0.15	50	87	57
7	0.35	0.64	0.36	0.16	53	86	61
8	0.36	0.65	0.36	0.16	55	86	63
9	0.35	0.64	0.30	0.14	53	89	60
10	0.34	0.62	0.42	0.19	52	84	61

[a] To test if entry 3 (61% NMR yield) is an outlier, a q -test was performed.^[8] For an α of 0.05, entry 3 is a significant outlier with $p < 0.05$, and was therefore excluded from the calculation of the average NMR yield.

4.4. Initial Fractional Factorial Design in Cyclic Flow

Table S6. Data for the initial factorial design. The entries highlighted in blue are central points.

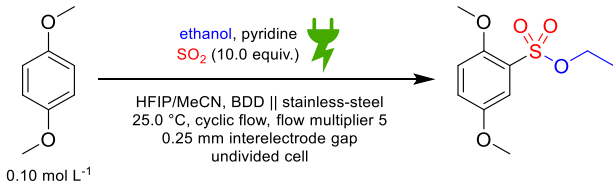
$$n_{\text{STD}} = 0.61 \text{ mmol}, I_{\text{STD,NMR}} = 1.00, N_{\text{STD}} = 3, N_{\text{product}} = 1, N_{\text{SM}} = 4$$

 0.10 mol L⁻¹ ethanol, pyridine SO₂ (10.0 equiv.) HFIP/MeCN 1:1 (vol%), BDD stainless-steel 25.0 °C, cyclic flow, flow multiplier 5 0.25 mm interelectrode gap undivided cell 											
Entry	Q / F	j / mA cm ⁻²	equiv. Ethanol	equiv. Pyridine	I _{product,NMR}	n _{product} / mmol	I _{SM,remaining,NMR}	n _{SM,remaining} / mmol	NMR yield%	Conversion%	Selectivity%
1	6.0	20.0	5.0	6.0	0.25	0.45	0.74	0.34	38	72	53
2	7.0	15.0	4.0	8.0	0.27	0.49	0.65	0.30	41	75	54
3	7.0	25.0	4.0	4.0	0.09	0.16	0.89	0.40	14	66	21
4	5.0	25.0	4.0	8.0	0.14	0.25	1.26	0.57	21	52	41
5	7.0	15.0	6.0	4.0	0.25	0.45	0.76	0.35	38	71	53
6	6.0	20.0	5.0	6.0	0.27	0.49	0.83	0.38	41	69	60
7	5.0	25.0	4.0	4.0	0.28	0.51	1.03	0.47	42	61	70
8	5.0	15.0	6.0	8.0	0.27	0.49	0.97	0.44	41	63	65
9	5.0	15.0	4.0	8.0	0.26	0.47	1.00	0.45	39	62	63
10	7.0	15.0	6.0	8.0	0.31	0.56	0.59	0.27	47	78	61
11	6.0	20.0	5.0	6.0	0.25	0.45	0.92	0.42	38	65	58
12	7.0	25.0	6.0	8.0	0.25	0.45	0.28	0.13	38	89	42
13	5.0	15.0	4.0	4.0	0.38	0.69	0.25	0.11	58	91	64
14	7.0	25.0	6.0	4.0	0.22	0.40	0.16	0.07	33	94	36
15	7.0	25.0	4.0	8.0	0.31	0.56	0.25	0.11	47	91	52
16	6.0	20.0	5.0	6.0	0.35	0.64	0.27	0.12	53	90	59
17	5.0	15.0	6.0	4.0	0.36	0.65	0.53	0.24	55	80	68
18	5.0	25.0	6.0	4.0	0.20	0.36	0.52	0.24	30	80	38
19	7.0	15.0	4.0	4.0	0.42	0.76	0.20	0.09	64	92	69
20	5.0	25.0	6.0	8.0	0.31	0.56	0.67	0.30	47	75	63
21	6.0	20.0	5.0	6.0	0.38	0.69	0.34	0.15	58	87	66

4.5. Second Fractional Factorial Design

Table S7. Data for the fractional factorial design. The entries highlighted in blue are central points.

$$n_{\text{STD}} = 0.61 \text{ mmol}, I_{\text{STD,NMR}} = 1.00, N_{\text{STD}} = 3, N_{\text{product}} = 1, N_{\text{SM}} = 4$$

 0.10 mol L⁻¹												
Entry	Q / F	j / mA cm ⁻²	equiv. Ethanol	equiv. Pyridine	vol% HFIP	I _{product} NMR	η _{product} / mmol	I _{SM,remaining} NMR	η _{SM,remaining} / mmol	NMR yield%	Conversion%	Selectivity%
1	5.0	15.0	4.0	4.0	50	0.42	0.76	0.27	0.12	64	90	71
2	6.0	10.0	5.0	5.0	40	0.42	0.76	0.36	0.16	64	86	74
3	6.0	10.0	3.0	3.0	40	0.46	0.84	0.43	0.20	70	84	83
4	4.0	20.0	3.0	3.0	40	0.37	0.67	0.47	0.21	56	82	68
5	4.0	10.0	5.0	5.0	60	0.34	0.62	0.73	0.33	52	72	71
6	5.0	15.0	4.0	4.0	50	0.44	0.80	0.32	0.15	67	88	76
7	6.0	10.0	5.0	3.0	60	0.25	0.45	0.98	0.45	38	63	60
8	4.0	10.0	3.0	3.0	60	0.35	0.64	0.52	0.24	53	80	66
9	4.0	10.0	5.0	3.0	40	0.43	0.78	0.35	0.16	65	87	75
10	4.0	10.0	3.0	5.0	40	0.44	0.80	0.20	0.09	67	92	72
11	5.0	15.0	4.0	4.0	50	0.42	0.76	0.41	0.19	64	84	75
12	4.0	20.0	5.0	3.0	60	0.33	0.60	0.57	0.26	50	78	64
13	6.0	10.0	3.0	5.0	60	0.44	0.80	0.23	0.10	67	91	73
14	4.0	20.0	5.0	5.0	40	0.37	0.67	0.84	0.38	56	68	82
15	4.0	20.0	3.0	5.0	60	0.41	0.75	0.68	0.31	62	74	84
16	5.0	15.0	4.0	4.0	50	0.47	0.86	0.55	0.25	71	79	90
17	6.0	20.0	5.0	5.0	60	0.33	0.60	0.35	0.16	50	87	58
18	6.0	20.0	3.0	5.0	40	0.42	0.76	0.46	0.21	64	83	77
19	6.0	20.0	3.0	3.0	60	0.23	0.42	0.32	0.15	35	88	40
20	6.0	20.0	5.0	3.0	40	0.35	0.64	0.34	0.15	53	87	61
21	5.0	15.0	4.0	4.0	50	0.42	0.76	0.45	0.20	64	83	77
22	5.0	15.0	4.0	4.0	50	0.42	0.76	0.26	0.12	64	90	71
23	6.0	10.0	5.0	5.0	40	0.38	0.69	0.47	0.21	58	82	70
24	6.0	10.0	3.0	3.0	40	0.46	0.84	0.34	0.15	70	87	80
25	4.0	20.0	3.0	3.0	40	0.39	0.71	0.30	0.14	59	89	67
26	4.0	10.0	5.0	5.0	60	0.37	0.67	0.65	0.30	56	75	74
27	5.0	15.0	4.0	4.0	50	0.43	0.78	0.23	0.10	65	91	71
28	6.0	10.0	5.0	3.0	60	0.27	0.49	0.83	0.38	41	69	60
29	4.0	10.0	3.0	3.0	60	0.38	0.69	0.37	0.17	58	86	67
30	4.0	10.0	5.0	3.0	40	0.47	0.86	0.26	0.12	71	90	79
31	4.0	10.0	3.0	5.0	40	0.38	0.69	0.15	0.07	58	94	61
32	5.0	15.0	4.0	4.0	50	0.40	0.73	0.26	0.12	61	90	67
33	4.0	20.0	5.0	3.0	60	0.30	0.55	0.34	0.15	45	87	52
34	6.0	10.0	3.0	5.0	60	0.44	0.80	0.13	0.06	67	95	70
35	4.0	20.0	5.0	5.0	40	0.31	0.56	0.74	0.34	47	72	65
36	4.0	20.0	3.0	5.0	60	0.38	0.69	0.57	0.26	58	78	73
37	5.0	15.0	4.0	4.0	50	0.40	0.73	0.36	0.16	61	86	70
38	6.0	20.0	5.0	5.0	60	0.30	0.55	0.32	0.15	45	88	52
39	6.0	20.0	3.0	5.0	40	0.44	0.80	0.35	0.16	67	87	77
40	6.0	20.0	3.0	3.0	60	0.26	0.47	0.31	0.14	39	88	45
41	6.0	20.0	5.0	3.0	40	0.35	0.64	0.28	0.13	53	89	59
42	5.0	15.0	4.0	4.0	50	0.41	0.75	0.37	0.17	62	86	72

Factorial Regression: NMR yield (%) ($p > \alpha = 0.1$)

Coded Coefficients

Term	Effect	Coef	SE Coef	T Value	P Value	VIF
Constant		56.003	0.605	92.54	0.000	
Q	-2.085	-1.042	0.605	-1.72	0.096	1.00
j	-7.012	-3.506	0.605	-5.79	0.000	1.00
vol% HFIP	-10.044	-5.022	0.605	-8.30	0.000	1.00
eq. EtOH	-6.444	-3.222	0.605	-5.32	0.000	1.00
eq. pyridine	4.927	2.464	0.605	4.07	0.000	1.00
Q*vol% HFIP	-4.359	-2.179	0.605	-3.60	0.001	1.00
Q*eq. EtOH	-3.032	-1.516	0.605	-2.51	0.018	1.00
Q*eq. pyridine	5.306	2.653	0.605	4.38	0.000	1.00
j*eq. pyridine	2.274	1.137	0.605	1.88	0.070	1.00
vol% HFIP*eq. pyridine	7.202	3.601	0.605	5.95	0.000	1.00
eq. EtOH*eq. pyridine	-3.601	-1.800	0.605	-2.98	0.006	1.00
Ct Pt		8.13	1.24	6.56	0.000	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.42	90.6%	86.7%	79.2%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F Value	PValue
Model	12	3276.14	273.01	23.30	0.000
Linear	5	1761.66	352.33	30.06	0.000
Q	1	34.77	34.77	2.97	0.096
j	1	393.36	393.36	33.57	0.000
vol% HFIP	1	807.13	807.13	68.87	0.000
eq. EtOH	1	332.16	332.16	28.34	0.000
eq. pyridine	1	194.24	194.24	16.57	0.000
2-Way Interactions	6	1010.85	168.47	14.38	0.000
Q*vol% HFIP	1	152.00	152.00	12.97	0.001
Q*eq. EtOH	1	73.56	73.56	6.28	0.018
Q*eq. pyridine	1	225.27	225.27	19.22	0.000
j*eq. pyridine	1	41.38	41.38	3.53	0.070
vol% HFIP*eq. pyridine	1	414.91	414.91	35.40	0.000
eq. EtOH*eq. pyridine	1	103.73	103.73	8.85	0.006
Curvature	1	503.63	503.63	42.97	0.000
Error	29	339.86	11.72		
Lack-of-Fit	4	56.89	14.22	1.26	0.313
Pure Error	25	282.97	11.32		
Total	41	3616.00			

Regression Equation in Uncoded Units

$$\begin{aligned}
 \text{NMR yield\%} = & 125.0 + 5.31 \text{ Q} - 1.611 \text{ j} - 0.853 \text{ vol\% HFIP} + 11.56 \text{ eq. EtOH} \\
 & - 25.02 \text{ eq. pyridine} \\
 & - 0.2179 \text{ Q*vol\% HFIP} - 1.516 \text{ Q*eq. EtOH} + 2.653 \text{ Q*eq. pyridine} \\
 & + 0.227 \text{ j*eq. pyridine} + 0.3601 \text{ vol\% HFIP*eq. pyridine} \\
 & - 1.800 \text{ eq. EtOH*eq. pyridine} + 8.13 \text{ Ct Pt}
 \end{aligned}$$

Fits and Diagnostics for Unusual Observations

Obs	NMR yield%	Fit	Resid	Std	Resid
14	56.10	50.22	5.88	2.17	
16	71.26	64.13	7.13	2.19	

Alias Structure

Factor	Name
A	Q
B	j
C	vol% HFIP
D	eq. EtOH
E	eq. pyridine

Aliases

I + ABCDE

A + BCDE

B + ACDE

C + ABDE

D + ABCE

E + ABCD

AC + BDE

AD + BCE

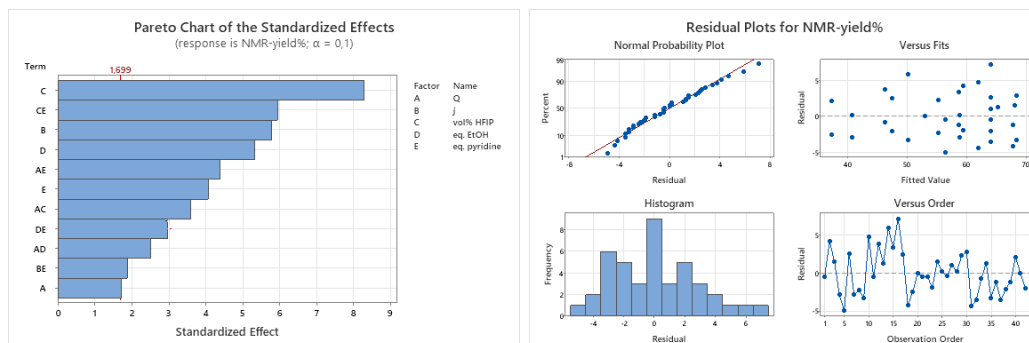
AE + BCD

BE + ACD

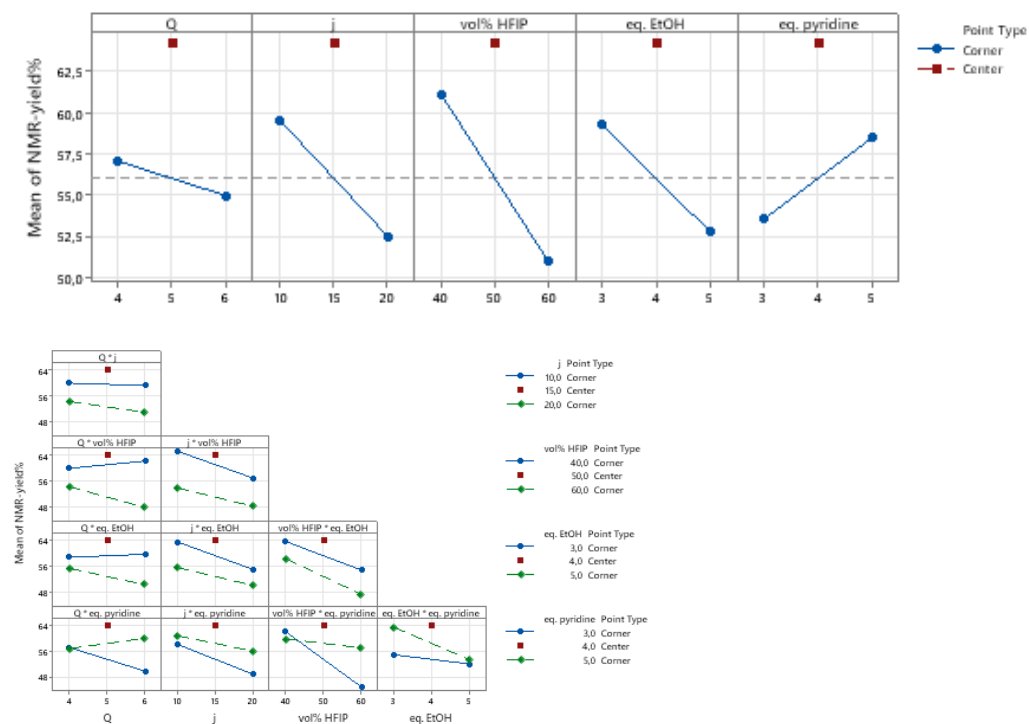
CE + ABD

DE + ABC

Pareto Chart and Residual Plots



Effect and Interaction Plots



Factorial Regression: Conversion (%) ($p > \alpha = 0.1$)**Backward Elimination of Terms** α to remove = 0.1**Coded Coefficients**

Term	Effect	Coef	SE Coef	T Value	P Value	VIF
Constant		83.133	0.621	133.97	0.000	
Q	2.938	1.469	0.621	2.37	0.025	1.00
j	-0.569	-0.284	0.621	-0.46	0.650	1.00
vol% HFIP	-3.696	-1.848	0.621	-2.98	0.006	1.00
eq. EtOH	-6.112	-3.056	0.621	-4.92	0.000	1.00
eq. pyridine	-0.521	-0.261	0.621	-0.42	0.678	1.00
Q*j	5.496	2.748	0.621	4.43	0.000	1.00
Q*eq. pyridine	6.017	3.009	0.621	4.85	0.000	1.00
j*vol% HFIP	5.212	2.606	0.621	4.20	0.000	1.00
j*eq. EtOH	4.596	2.298	0.621	3.70	0.001	1.00
j*eq. pyridine	-6.017	-3.009	0.621	-4.85	0.000	1.00
vol% HFIP*eq. pyridine	3.269	1.635	0.621	2.63	0.013	1.00
Ct Pt		3.68	1.27	2.89	0.007	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.51034	84.01%	77.39%	66.90%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F Value	P Value
Model	12	1877.62	156.468	12.70	0.000
Linear	5	481.90	96.380	7.82	0.000
Q	1	69.03	69.032	5.60	0.025
j	1	2.59	2.586	0.21	0.650
vol% HFIP	1	109.26	109.260	8.87	0.006
eq. EtOH	1	298.85	298.847	24.25	0.000
eq. pyridine	1	2.17	2.173	0.18	0.678
2-Way Interactions	6	1292.72	215.454	17.48	0.000
Q*j	1	241.65	241.650	19.61	0.000
Q*eq. pyridine	1	289.65	289.653	23.51	0.000
j*vol% HFIP	1	217.30	217.298	17.63	0.000
j*eq. EtOH	1	168.97	168.972	13.71	0.001
j*eq. pyridine	1	289.65	289.653	23.51	0.000
vol% HFIP*eq. pyridine	1	85.50	85.500	6.94	0.013
Curvature	1	102.99	102.992	8.36	0.007
Error	29	357.35	12.323		
Lack-of-Fit	4	72.37	18.093	1.59	0.209
Pure Error	25	284.98	11.399		
Total	41	2234.97			

Regression Equation in Uncoded Units

Conversion/% = 263.8 - 18.81 Q - 4.84 j - 1.620 vol% HFIP - 9.95 eq. EtOH
 - 14.45 eq. pyridine
 + 0.550 Q*j + 3.009 Q*eq. pyridine + 0.0521 j*vol% HFIP + 0.460 j*eq. EtOH
 - 0.602 j*eq. pyridine + 0.1635 vol% HFIP*eq. pyridine + 3.68 Ct Pt

Fits and Diagnostics for Unusual Observations

Obs	conversion%	Fit	Resid	Std Resid
16	79.15	86.81	-7.66	-2.30

Alias Structure

Factor	Name
A	Q
B	j
C	vol% HFIP
D	eq. EtOH
E	eq. pyridine

Aliases

I + ABCDE

A + BCDE

B + ACDE

C + ABDE

D + ABCE

E + ABCD

AB + CDE

AE + BCD

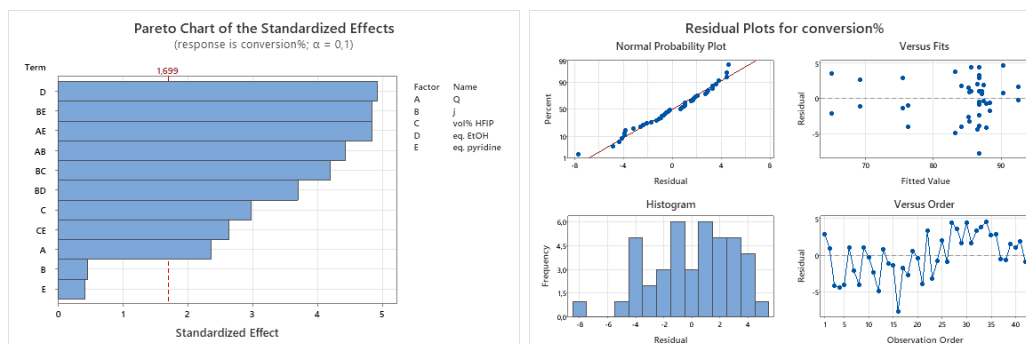
BC + ADE

BD + ACE

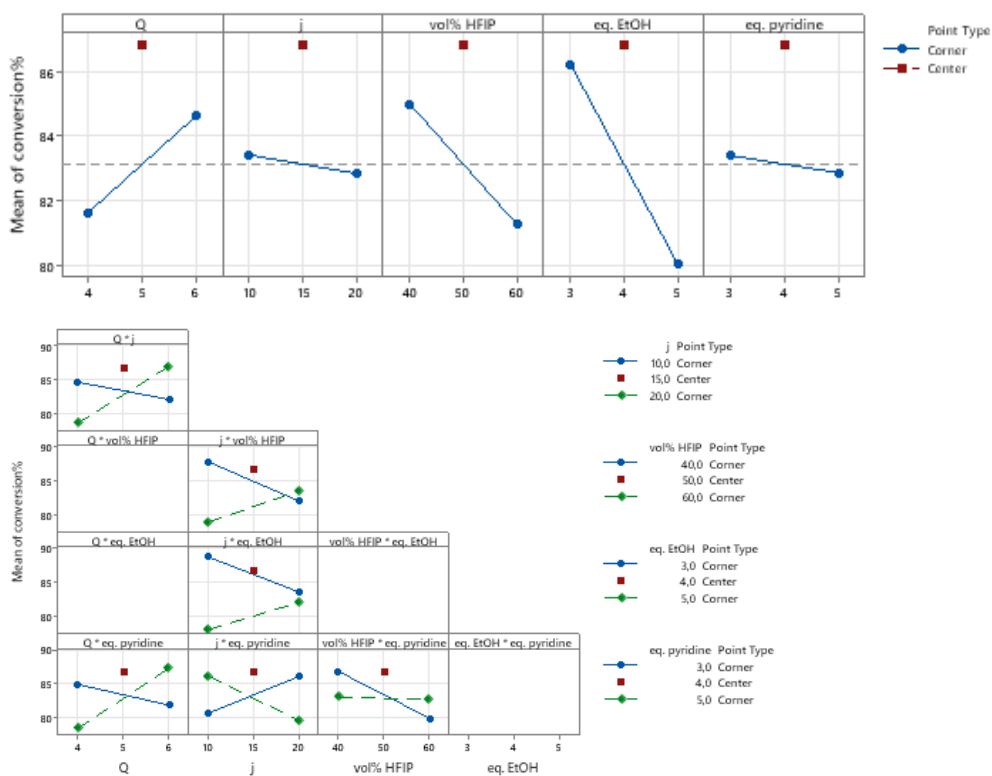
BE + ACD

CE + ABD

Pareto Chart and Residual Plots



Effect and Interaction Plots



Factorial Regression: Selectivity (%) ($p > \alpha = 0.1$)**Backward Elimination of Terms** α to remove = 0.1**Coded Coefficients**

Term	Effect	Coef	SE Coef	T Value	P Value	VIF
Constant		67.525	0.950	71.10	0.000	
Q	-5.221	-2.611	0.950	-2.75	0.010	1.00
j	-7.050	-3.525	0.950	-3.71	0.001	1.00
vol% HFIP	-8.904	-4.452	0.950	-4.69	0.000	1.00
eq. EtOH	-2.902	-1.451	0.950	-1.53	0.137	1.00
eq. pyridine	6.753	3.376	0.950	3.56	0.001	1.00
Q*j	-5.748	-2.874	0.950	-3.03	0.005	1.00
Q*vol% HFIP	-6.654	-3.327	0.950	-3.50	0.001	1.00
Q*eq. EtOH	-3.526	-1.763	0.950	-1.86	0.073	1.00
j*eq. pyridine	7.336	3.668	0.950	3.86	0.001	1.00
vol% HFIP*eq. pyridine	6.012	3.006	0.950	3.17	0.004	1.00
Ct Pt		6.57	1.95	3.37	0.002	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
5.37220	79.93%	72.57%	62.47%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F Value	P Value
Model	11	3448.40	313.49	10.86	0.000
Linear	5	1682.14	336.43	11.66	0.000
Q	1	218.07	218.07	7.56	0.010
j	1	397.65	397.65	13.78	0.001
vol% HFIP	1	634.26	634.26	21.98	0.000
eq. EtOH	1	67.37	67.37	2.33	0.137
eq. pyridine	1	364.79	364.79	12.64	0.001
2-Way Interactions	5	1437.68	287.54	9.96	0.000
Q*j	1	264.27	264.27	9.16	0.005
Q*vol% HFIP	1	354.22	354.22	12.27	0.001
Q*eq. EtOH	1	99.47	99.47	3.45	0.073
j*eq. pyridine	1	430.51	430.51	14.92	0.001
vol% HFIP*eq. pyridine	1	289.20	289.20	10.02	0.004
Curvature	1	328.58	328.58	11.39	0.002
Error	30	865.82	28.86		
Lack-of-Fit	5	118.72	23.74	0.79	0.564
Pure Error	25	747.09	29.88		
Total	41	4314.22			

Regression Equation in Uncoded Units

Selectivity/% = 48.3 + 29.70 Q - 0.77 j + 0.016 vol% HFIP + 7.36 eq. EtOH
 - 22.66 eq. pyridine
 - 0.575 Q*j - 0.3327 Q*vol% HFIP - 1.763 Q*eq. EtOH
 + 0.734 j*eq. pyridine
 + 0.3006 vol% HFIP*eq. pyridine + 6.57 Ct Pt

Fits and Diagnostics for Unusual Observations

Obs	Selectivity/%	Fit	Resid	Std Resid
16	90.03	74.09	15.93	3.13
35	65.32	74.96	-9.64	-2.21

Alias Structure

Factor Name

A	Q
B	j
C	vol% HFIP
D	eq. EtOH
E	eq. pyridine

Aliases

I + ABCDE

A + BCDE

B + ACDE

C + ABDE

D + ABCE

E + ABCD

AB + CDE

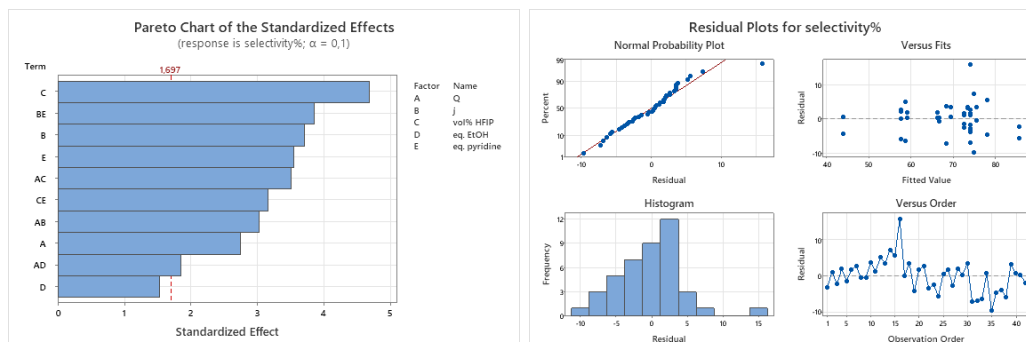
AC + BDE

AD + BCE

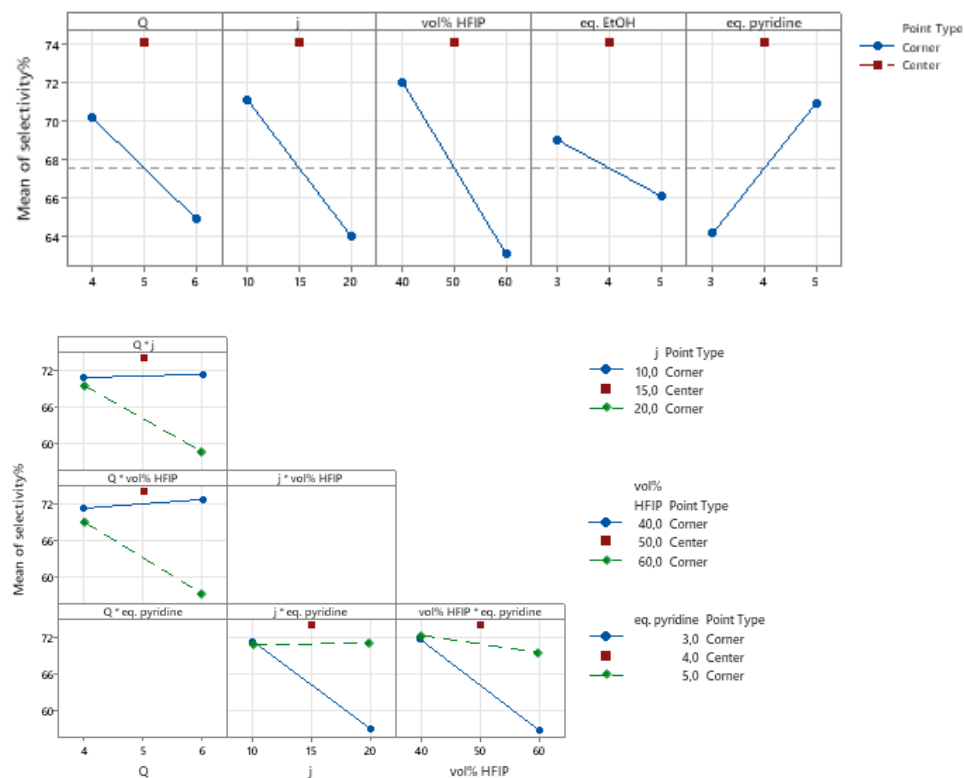
BE + ACD

CE + ABD

Pareto Chart and Residual Plots



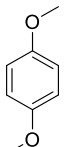
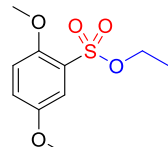
Effect and Interaction Plots



4.6. Extension to a Central Composite Design

Table S8. Extension of the 2^{5-1} fractional factorial design to a central composite design. The entries highlighted in blue are central points.

$$n_{\text{STD}} = 0.61 \text{ mmol}, I_{\text{STD,NMR}} = 1.00, N_{\text{STD}} = 3, N_{\text{product}} = 1, N_{\text{SM}} = 4$$

 0.10 mol L⁻¹ ethanol, pyridine SO₂ (10.0 equiv.) ⚡  HFIP/MeCN, BDD stainless-steel 25.0 °C, cyclic flow, flow multiplier 5 0.25 mm interelectrode gap undivided cell												
Entry	Q / F	j / mA cm ⁻²	equiv. Ethanol	equiv. Pyridine	vol% HFIP	$I_{\text{product,NMR}}$	η_{product} / mmol	$I_{\text{SM,remaining,NMR}}$	$\eta_{\text{SM,remaining}}$ / mmol	NMR yield%	Conversion%	Selectivity%
1	5.0	15.0	4.0	4.0	50	0.40	0.73	0.46	0.21	61	83	73
2	5.0	15.0	4.0	4.0	50	0.40	0.73	0.46	0.21	61	83	73
3	4.0	15.0	4.0	4.0	50	0.39	0.71	0.66	0.30	59	75	79
4	6.0	15.0	4.0	4.0	50	0.38	0.69	0.32	0.15	58	88	66
5	5.0	10.0	4.0	4.0	50	0.47	0.86	0.59	0.27	71	78	92
6	5.0	20.0	4.0	4.0	50	0.35	0.64	0.49	0.22	53	81	65
7	5.0	15.0	4.0	4.0	50	0.42	0.76	0.48	0.22	64	82	78
8	5.0	15.0	4.0	4.0	40	0.41	0.75	0.60	0.27	62	77	80
9	5.0	15.0	4.0	4.0	60	0.36	0.65	0.51	0.23	55	81	68
10	5.0	15.0	3.0	4.0	50	0.44	0.80	0.61	0.28	67	77	87
11	5.0	15.0	5.0	4.0	50	0.43	0.78	0.48	0.22	65	82	80
12	5.0	15.0	4.0	4.0	50	0.41	0.75	0.52	0.24	62	80	77
13	5.0	15.0	4.0	3.0	50	0.40	0.73	0.48	0.22	61	82	74
14	5.0	15.0	4.0	5.0	50	0.39	0.71	0.49	0.22	59	81	73
15	4.0	15.0	4.0	4.0	50	0.37	0.67	0.69	0.31	56	74	76
16	6.0	15.0	4.0	4.0	50	0.40	0.73	0.42	0.19	61	84	72
17	5.0	15.0	4.0	4.0	50	0.43	0.78	0.55	0.25	65	79	82
18	5.0	10.0	4.0	4.0	50	0.43	0.78	0.66	0.30	65	75	87
19	5.0	20.0	4.0	4.0	50	0.34	0.62	0.55	0.25	52	79	65
20	5.0	15.0	4.0	4.0	40	0.42	0.76	0.66	0.30	64	75	85
21	5.0	15.0	4.0	4.0	60	0.34	0.62	0.51	0.23	52	81	64
22	5.0	15.0	4.0	4.0	50	0.44	0.80	0.65	0.30	67	75	89
23	5.0	15.0	3.0	4.0	50	0.43	0.78	0.60	0.27	65	77	84
24	5.0	15.0	5.0	4.0	50	0.46	0.84	0.57	0.26	70	78	89
25	5.0	15.0	4.0	3.0	50	0.40	0.73	0.51	0.23	61	81	75
26	5.0	15.0	4.0	5.0	50	0.41	0.75	0.57	0.26	62	78	79
27	5.0	15.0	4.0	4.0	50	0.42	0.76	0.56	0.25	64	79	81

Response Surface Regression: NMR yield (%) ($p > \alpha = 0.1$)**Backward Elimination of Terms** α to remove = 0.1**Coded Coefficients**

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	62.848	0.631	99.62	0.000	
Q	-0.842	0.577	-1.46	0.150	1.00
j	-4.001	0.577	-6.93	0.000	1.00
vol% HFIP	-5.012	0.577	-8.68	0.000	1.00
eq. EtOH	-2.780	0.577	-4.82	0.000	1.00
eq. pyridine	2.190	0.577	3.80	0.000	1.00
Q*Q	-4.92	1.45	-3.40	0.001	3.00
vol% HFIP*vol% HFIP	-5.30	1.45	-3.66	0.001	3.00
eq. EtOH*eq. EtOH	3.42	1.45	2.37	0.022	3.00
Q*vol% HFIP	-2.179	0.612	-3.56	0.001	1.00
Q*eq. EtOH	-1.516	0.612	-2.48	0.016	1.00
Q*eq. pyridine	2.653	0.612	4.33	0.000	1.00
j*eq. pyridine	1.137	0.612	1.86	0.069	1.00
vol% HFIP*eq. pyridine	3.601	0.612	5.88	0.000	1.00
eq. EtOH*eq. pyridine	-1.800	0.612	-2.94	0.005	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.46241	85.55%	81.80%	75.14%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	14	3832.94	273.781	22.84	0.000
Linear	5	1956.82	391.364	32.65	0.000
Q	1	25.54	25.541	2.13	0.150
j	1	576.27	576.268	48.07	0.000
vol% HFIP	1	904.21	904.214	75.42	0.000
eq. EtOH	1	278.14	278.141	23.20	0.000
eq. pyridine	1	172.66	172.657	14.40	0.000
Square	3	865.27	288.424	24.06	0.000
Q*Q	1	138.70	138.700	11.57	0.001
vol% HFIP*vol% HFIP	1	160.91	160.909	13.42	0.001
eq. EtOH*eq. EtOH	1	67.18	67.178	5.60	0.022
2-Way Interaction	6	1010.85	168.475	14.05	0.000
Q*vol% HFIP	1	152.00	152.001	12.68	0.001
Q*eq. EtOH	1	73.56	73.558	6.14	0.016
Q*eq. pyridine	1	225.27	225.271	18.79	0.000
j*eq. pyridine	1	41.38	41.376	3.45	0.069
vol% HFIP*eq. pyridine	1	414.91	414.913	34.61	0.000
eq. EtOH*eq. pyridine	1	103.73	103.728	8.65	0.005
Error	54	647.37	11.988		
Lack-of-Fit	13	282.96	21.766	2.45	0.015
Pure Error	41	364.41	8.888		
Total	68	4480.31			

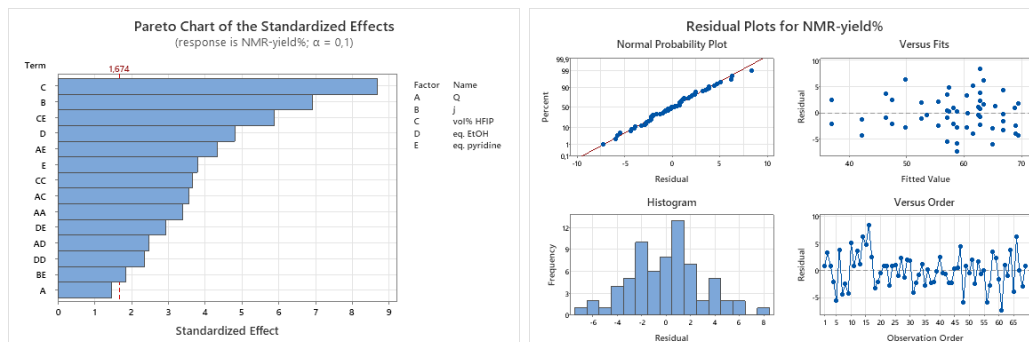
Regression Equation in Uncoded Units

$$\begin{aligned}
 \text{NMR yield\%} = & -69.0 + 54.7 Q - 1.710 j + 4.44 \text{ vol\% HFIP} - 15.4 \text{ eq. EtOH} \\
 & - 25.29 \text{ eq. pyridine} \\
 & - 4.92 Q^2 - 0.0530 \text{ vol\% HFIP}^2 + 3.42 \text{ eq. EtOH}^2 \\
 & - 0.2179 Q \text{ vol\% HFIP} - 1.516 Q \text{ eq. EtOH} + 2.653 Q \text{ eq. pyridine} \\
 & + 0.227 j \text{ eq. pyridine} + 0.3601 \text{ vol\% HFIP} \text{ eq. pyridine} \\
 & - 1.800 \text{ eq. EtOH} \text{ eq. Pyridine}
 \end{aligned}$$

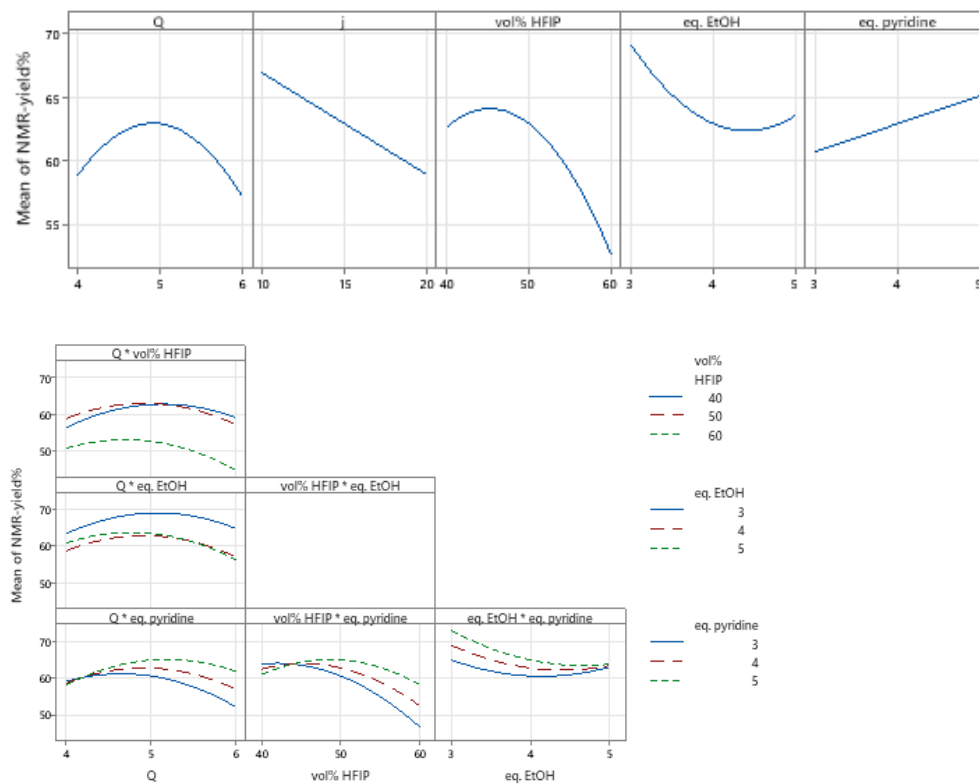
Fits and Diagnostics for Unusual Observations

Obs	NMR yield%	Fit	Resid	Std Resid
14	56.10	49.74	6.36	2.29
16	71.26	62.85	8.41	2.47
61	51.55	58.85	-7.30	-2.18
66	69.74	63.49	6.25	2.03

Pareto Chart and Residual Plots



Effect and Interaction Plots



Response Surface Regression: Conversion (%) ($p > \alpha = 0.1$)**Backward Elimination of Terms** α to remove = 0.1**Coded Coefficients**

Term	Coef	SE Coef	T Value	P Value	VIF
Constant	83.064	0.646	128.64	0.000	
Blocks					
1	3.193	0.540	5.92	0.000	1.56
Q	1.948	0.584	3.34	0.002	1.00
j	-0.032	0.584	-0.05	0.957	1.00
vol% HFIP	-1.390	0.584	-2.38	0.021	1.00
eq. EtOH	-2.548	0.584	-4.37	0.000	1.00
eq. pyridine	-0.305	0.584	-0.52	0.603	1.00
j*j	-2.95	1.05	-2.80	0.007	1.56
Q*j	2.748	0.619	4.44	0.000	1.00
Q*eq. pyridine	3.009	0.619	4.86	0.000	1.00
j*vol% HFIP	2.606	0.619	4.21	0.000	1.00
j*eq. EtOH	2.298	0.619	3.71	0.000	1.00
j*eq. pyridine	-3.009	0.619	-4.86	0.000	1.00
vol% HFIP*eq. pyridine	1.635	0.619	2.64	0.011	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
3.50233	76.33%	70.74%	61.56%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F Value	P Value
Model	13	2175.94	167.380	13.65	0.000
Blocks	1	429.25	429.248	34.99	0.000
Linear	5	443.23	88.646	7.23	0.000
Q	1	136.58	136.584	11.13	0.002
j	1	0.04	0.036	0.00	0.957
vol% HFIP	1	69.54	69.535	5.67	0.021
eq. EtOH	1	233.72	233.716	19.05	0.000
eq. pyridine	1	3.36	3.356	0.27	0.603
Square	1	96.07	96.069	7.83	0.007
j*j	1	96.07	96.069	7.83	0.007
2-Way Interaction	6	1292.72	215.454	17.56	0.000
Q*j	1	241.65	241.650	19.70	0.000
Q*eq. pyridine	1	289.65	289.653	23.61	0.000
j*vol% HFIP	1	217.30	217.298	17.71	0.000
j*eq. EtOH	1	168.97	168.972	13.78	0.000
j*eq. pyridine	1	289.65	289.653	23.61	0.000
vol% HFIP*eq. pyridine	1	85.50	85.500	6.97	0.011
Error	55	674.65	12.266		
Lack-of-Fit	14	321.83	22.988	2.67	0.007
Pure Error	41	352.82	8.605		
Total	68	2850.59			

Regression Equation in Uncoded Units

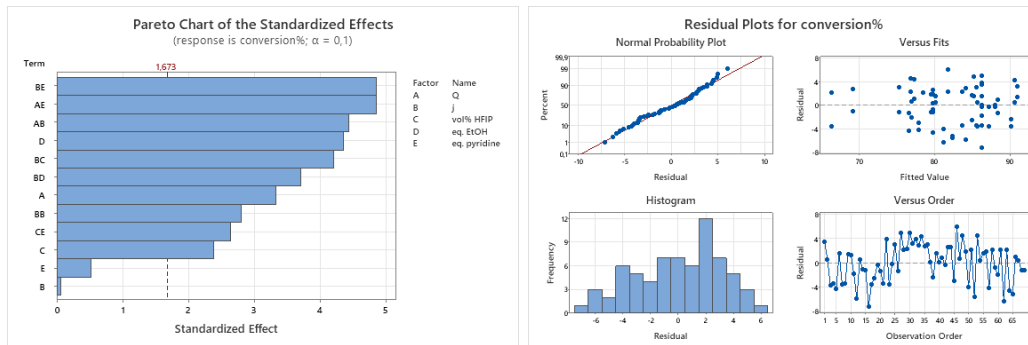
Conversion/% = 229.9 - 18.33 Q - 1.25 j - 1.575 vol% HFIP - 9.44 eq. EtOH
 - 14.50 eq. pyridine
 - 0.1181 j*j + 0.550 Q*j + 3.009 Q*eq. pyridine + 0.0521 j*vol% HFIP
 + 0.460 j*eq. EtOH - 0.602 j*eq. pyridine
 + 0.1635 vol% HFIP*eq. pyridine

Equation averaged over blocks.

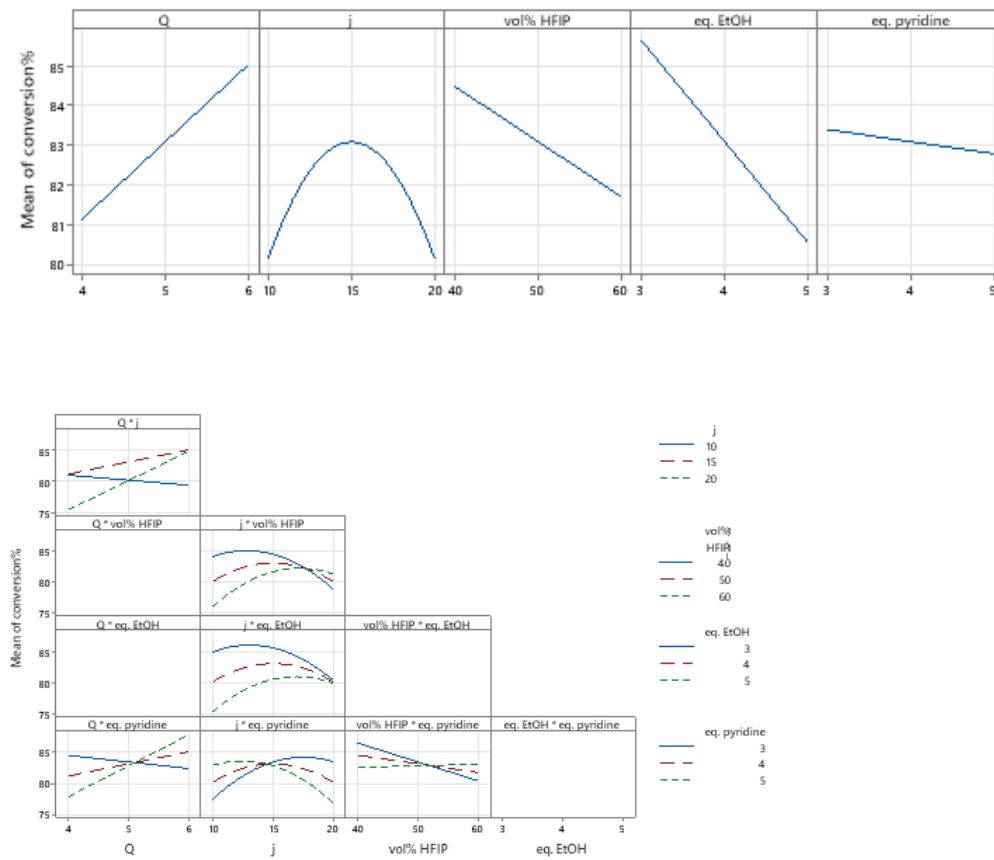
Fits and Diagnostics for Unusual Observations

Obs	Conversion/%	Fit	Resid	Std Resid
12	78.39	84.23	-5.84	-2.08
16	79.15	86.26	-7.10	-2.11

Pareto Chart and Residual Plots



Effect and Interaction Plots



Response Surface Regression: Selectivity (%) ($p > \alpha = 0.1$)**Backward Elimination of Terms** α to remove = 0.1**Coded Coefficients**

Term	Coef	SE Coef	T Value	P Value	VIF
Constant	76.05	1.08	70.32	0.000	
Blocks					
1	-2.372	0.880	-2.70	0.009	1.74
Q	-2.796	0.901	-3.10	0.003	1.00
j	-4.479	0.901	-4.97	0.000	1.00
vol% HFIP	-4.897	0.901	-5.43	0.000	1.00
eq. EtOH	-1.359	0.901	-1.51	0.137	1.00
eq. pyridine	3.073	0.901	3.41	0.001	1.00
Q*Q	-6.32	2.29	-2.75	0.008	3.10
vol% HFIP*vol% HFIP	-5.21	2.29	-2.27	0.027	3.10
eq. EtOH*eq. EtOH	5.50	2.29	2.40	0.020	3.10
Q*j	-2.874	0.956	-3.01	0.004	1.00
Q*vol% HFIP	-3.327	0.956	-3.48	0.001	1.00
Q*eq. EtOH	-1.763	0.956	-1.84	0.071	1.00
j*eq. pyridine	3.668	0.956	3.84	0.000	1.00
vol% HFIP*eq. pyridine	3.006	0.956	3.14	0.003	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
5.40895	77.77%	72.01%	64.91%

Analysis of Variance

Source	DF	Adj SS	Adj MS	F Value	P Value
Model	14	5528.54	394.90	13.50	0.000
Blocks	1	212.54	212.54	7.26	0.009
Linear	5	2273.43	454.69	15.54	0.000
Q	1	281.48	281.48	9.62	0.003
j	1	722.17	722.17	24.68	0.000
vol% HFIP	1	863.24	863.24	29.51	0.000
eq. EtOH	1	66.51	66.51	2.27	0.137
eq. pyridine	1	340.04	340.04	11.62	0.001
Square	3	645.21	215.07	7.35	0.000
Q*Q	1	222.01	222.01	7.59	0.008
vol% HFIP*vol% HFIP	1	151.04	151.04	5.16	0.027
eq. EtOH*eq. EtOH	1	168.34	168.34	5.75	0.020
2-Way Interaction	5	1437.68	287.54	9.83	0.000
Q*j	1	264.27	264.27	9.03	0.004
Q*vol% HFIP	1	354.22	354.22	12.11	0.001
Q*eq. EtOH	1	99.47	99.47	3.40	0.071
j*eq. pyridine	1	430.51	430.51	14.72	0.000
vol% HFIP*eq. pyridine	1	289.20	289.20	9.88	0.003
Error	54	1579.87	29.26		
Lack-of-Fit	13	539.10	41.47	1.63	0.115
Pure Error	41	1040.77	25.38		
Total	68	7108.40			

Regression Equation in Uncoded Units

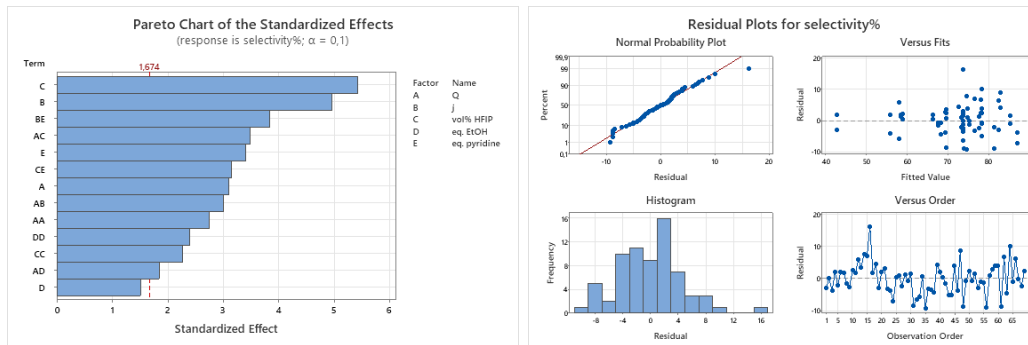
Selectivity/% = -136.6 + 92.7 Q - 0.96 j + 5.18 vol% HFIP - 36.6 eq. EtOH - 22.96 eq. pyridine
 - 6.32 Q*Q - 0.0521 vol% HFIP*vol% HFIP + 5.50 eq. EtOH*eq. EtOH
 - 0.575 Q*j
 - 0.3327 Q*vol% HFIP - 1.763 Q*eq. EtOH + 0.734 j*eq. pyridine
 + 0.3006 vol% HFIP*eq. pyridine

Equation averaged over blocks.

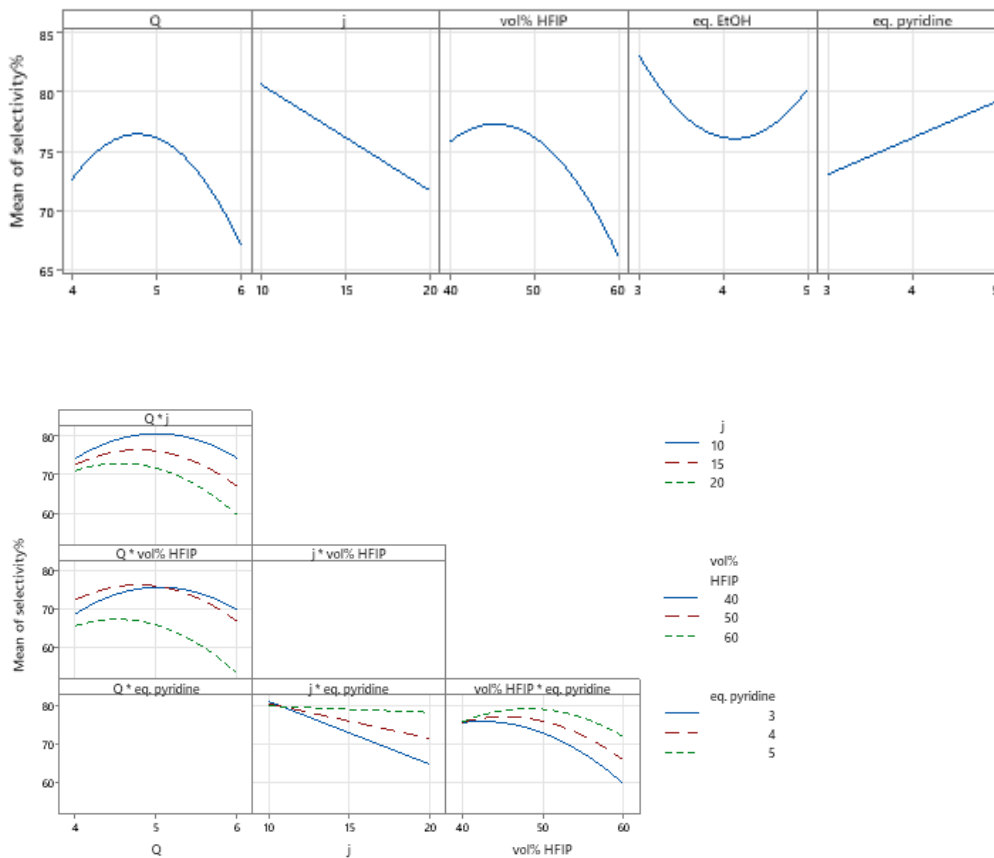
Fits and Diagnostics for Unusual Observations

Obs	Selectivity/%	Fit	Resid	Std Resid
16	90.03	73.68	16.34	3.17
35	65.32	74.55	-9.23	-2.08

Pareto Chart and Residual Plots



Effect and Interaction Plots



4.7. Response Optimization of NMR yield

Parameters

Response	Goal	Lower	Target	Upper	Weight	Importance
NMR yield%	Maximum	34.8713	71.2587		1	1

Solution

Solution	Q	j	vol% HFIP	eq. EtOH	eq. pyridine	NMR yield% Fit	Composite Desirability
1	5.39394	10	47.8788	3	5	76.6949	1

Multiple Response Prediction

Variable	Setting			
Q	5.39394			
j	10			
vol% HFIP	47.8788			
eq. EtOH	3			
eq. pyridine	5			
Response	Fit	SE Fit	95% CI	95% PI
NMR-yield%	76.69	1.94	(72.80; 80.59)	(68.74; 84.65)

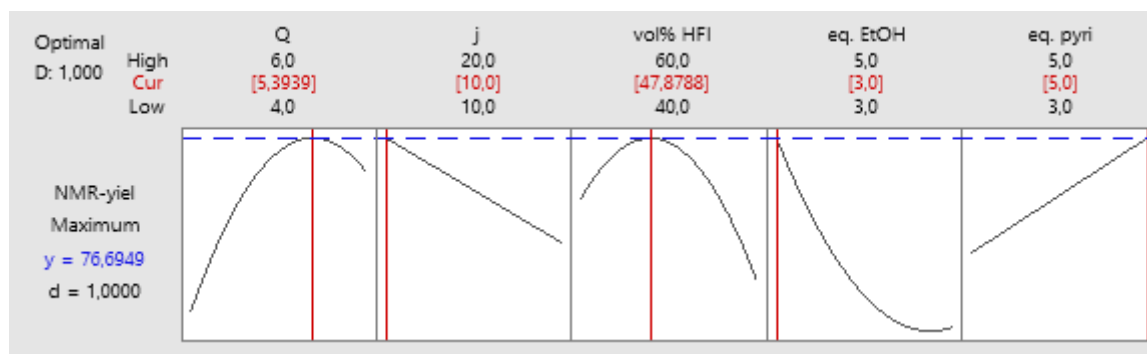
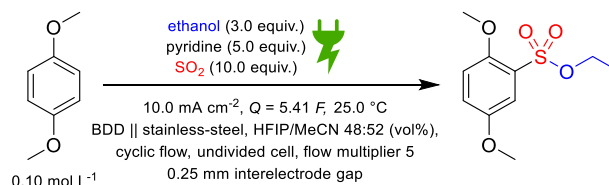


Table S9. Response optimization of NMR yield.

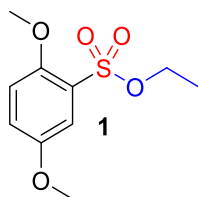
$$n_{\text{STD}} = 0.61 \text{ mmol}, I_{\text{STD,NMR}} = 1.00, N_{\text{STD}} = 3, N_{\text{product}} = 1, N_{\text{SM}} = 4$$



Entry	$I_{\text{product,NMR}}$	$n_{\text{product}} / \text{mmol}$	$I_{\text{SM,remaining,NMR}}$	$n_{\text{SM,remaining}} / \text{mmol}$	NMR yield%	Conversion%	Selectivity%
1	0.39	0.71	0.72	0.33	59	73	81
2	0.39	0.71	0.69	0.31	59	74	80
3	0.40	0.74	0.61	0.28	61	77	80
4	0.40	0.72	0.74	0.33	60	72	83

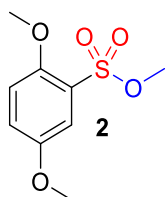
5. Analytical Data of Products

Ethyl 2,5-dimethoxybenzenesulfonate, **1**



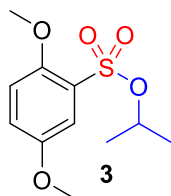
According to general protocol 3, 1,4-dimethoxybenzene (166 mg, 1.2 mmol) and ethanol were employed. After purification using flash column chromatography, ethyl 2,5-dimethoxybenzenesulfonate **1** (198 mg, 0.80 mmol, 67%) was obtained. ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.37 (d, J = 4.0 Hz, 1H), 7.08 (dd, J = 12.0, 4.0 Hz, 1H), 6.96 (d, J = 12.0 Hz, 1H), 4.15 (q, J = 8.0 Hz, 2H), 3.86 (s, 1H), 3.75 (s, 1H), 1.28 (t, J = 2.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.6, 151.2, 124.2, 120.9, 115.5, 114.0, 67.4, 56.5, 55.7, 14.6; HRMS for $\text{C}_{10}\text{H}_{18}\text{O}_5\text{NS}^+$ (ESI+) $[\text{M}+\text{NH}_4]^+$: calc.: 264.0900, found: 264.0894; R_f (cyclohexane/EtOAc 9:1 vol%) = 0.50.

Methyl 2,5-dimethoxybenzenesulfonate, **2**

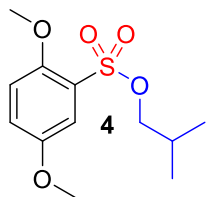


According to general protocol 3, 1,4-dimethoxybenzene (166 mg, 1.2 mmol) and methanol were employed. After purification using flash column chromatography, methyl 2,5-dimethoxybenzenesulfonate **2** (117 mg, 0.50 mmol, 42%) was obtained. ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.41 (d, J = 4.0 Hz, 1H), 7.11 (dd, J = 12.0, 4.0 Hz, 1H), 6.98 (d, J = 4.0 Hz, 1H), 3.89 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.9, 151.6, 123.6, 121.7, 115.8, 114.2, 56.9, 56.9, 56.1; HRMS for $\text{C}_9\text{H}_{12}\text{NaO}_5\text{S}^+$ (ESI+) $[\text{M}+\text{Na}]^+$: calc.: 255.0298, found: 255.0296; R_f (cyclohexane/EtOAc 9:1 vol%) = 0.45.

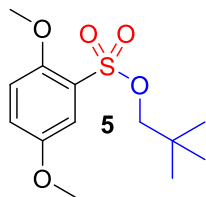
Isopropyl 2,5-dimethoxybenzenesulfonate, **3**



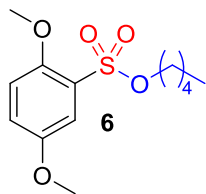
According to general protocol 3, 1,4-dimethoxybenzene (166 mg, 1.2 mmol) and isopropanol were employed. After purification using flash column chromatography, isopropyl 2,5-dimethoxybenzenesulfonate **3** (77 mg, 0.30 mmol, 25%) was obtained. ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.45 (d, J = 4.0 Hz, 1H), 7.11 (dd, J = 8.0 Hz, J = 4.0 Hz, 1H), 6.97 (d, J = 4.0 Hz, 1H), 4.82 (sept, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 1.31 (d, J = 4.0 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.9, 151.6, 125.7, 121.5, 115.5, 114.0, 77.9, 56.8, 56.2, 29.8, 22.9; HRMS for $\text{C}_{11}\text{H}_{16}\text{NaO}_5\text{S}^+$ (ESI+) $[\text{M}+\text{Na}]^+$: calc.: 283.0611, found: 283.0604; R_f (cyclohexane/EtOAc 9:1) = 0.52.

(2-Methyl-1-propyl) 2,5-dimethoxybenzenesulfonate, 4

According to general protocol 3, 1,4-dimethoxybenzene (166 mg, 1.20 mmol) and 2-methylpropan-1-ol were employed. After purification using flash column chromatography, (2-methyl-1-propyl) 2,5-dimethoxybenzenesulfonate **4** (238 mg, 0.87 mmol, 72%) was obtained. ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.43 (d, J = 4.0 Hz, 1H), 7.13 (dd, J = 12.0 Hz, J = 4.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.85 (d, J = 8.0 Hz, 2H), 3.79 (s, 3H), 1.96 (sept, J = 8.0 Hz, 1H), 0.90 (d, J = 4.0 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 153.0, 151.7, 124.4, 121.7, 115.8, 114.0, 77.2, 56.8, 56.2, 28.2, 18.8; HRMS for $\text{C}_{12}\text{H}_{22}\text{O}_5\text{S}^+$ (ESI+) $[\text{M}+\text{NH}_4]^+$: calc.: 292.1213, found: 292.1204; R_f (cyclohexane/EtOAc 9:1 vol%) = 0.80.

2,2-Dimethylpropyl 2,5-dimethoxybenzenesulfonate, 5

According to general protocol 3, 1,4-dimethoxybenzene (166 mg, 1.20 mmol) and 2,2-dimethylpropan-1-ol were employed. After purification using flash column chromatography, 2,2-dimethylpropyl-2,5-dimethoxybenzenesulfonate **5** (215 mg, 0.75 mmol, 62%) was obtained. ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.38 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.67 (s, 2H), 0.88 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.7, 151.4, 123.9, 121.3, 115.8, 113.8, 80.2, 56.5, 56.0, 31.6, 26.0; HRMS for $\text{C}_{13}\text{H}_{20}\text{NaO}_5\text{S}^+$ (ESI+) $[\text{M}+\text{Na}]^+$: calc.: 311.0924, found: 311.0919; R_f (cyclohexane/EtOAc 9:1 vol%) = 0.90.

Pentyl 2,5-dimethoxybenzenesulfonate, 6

According to general protocol 3, 1,4-dimethoxybenzene (166 mg, 1.20 mmol) and pentanol were employed. After purification using flash column chromatography, pentyl 2,5-dimethoxybenzenesulfonate **6** (255 mg, 0.89 mmol, 74%) was obtained. Dividing the product mass by electrolysis time results in a productivity of 0.255 g / (1 h 36 min) $\approx$ 0.159 g h^{-1} .

Scale-up: According to general protocol 3, 1,4-dimethoxybenzene (1.659 g, 12.00 mmol) and pentanol were employed. After purification using flash column chromatography, pentyl 2,5-dimethoxybenzenesulfonate **6** (2.652 g, 9.74 mmol, 81%) was obtained. Dividing the product mass by electrolysis time gives a productivity of 2.652 g / 4 h $\approx$ 0.663 g h^{-1} .

^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.34 (d, J = 4.0 Hz, 1H), 7.05 (dd, J = 8.0 Hz, 4.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 4.02 (t, J = 4.0 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 3H), 1.58 (quint, J = 8.0 Hz, 2H), 1.22 (m, 4H), 0.77 (t, J = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ [ppm] = 152.7, 151.3, 124.1, 121.1, 115.6, 113.9, 71.3, 56.5, 55.8, 28.5, 27.3, 21.8, 13.7; HRMS for $\text{C}_{13}\text{H}_{20}\text{O}_5\text{S}^+$ (ESI+) $[\text{M}+\text{Na}]^+$: calc.: 311.0924, found: 311.0918; R_f (cyclohexane/EtOAc 9:1 vol%) = 0.40.

6. Proposed Mechanism

A postulated reaction mechanism is shown in

Figure S4. Details on this can be found in an initial publication.^[9] The alcohol **I** reacts with SO_2 and pyridine as base to monoalkyl sulfite **II**. This formation of **II** is promoted by the hydrogen bonding power of HFIP.^[10] The anodic oxidation of arene **III** forms electrophilic cationic species **IV**, followed by nucleophilic attack of **II**. Because of the solvation shell by hydrogen bonding of HFIP, **II** reacts as a sulfur-centered nucleophile. The subsequent anodic oxidation results in the formation of the sulfonate **V** as terminal product. At the cathode, sulfur dioxide is reduced serving as counter reaction.^[11] Note that HFIP is very (electro)chemically stable, and it is not oxidized by SO_2 . If no other alcohol is present in the reaction solution during the electrolysis in our reaction, HFIP can react as nucleophile to a sulfonate, but this reaction proceeds in traces only.

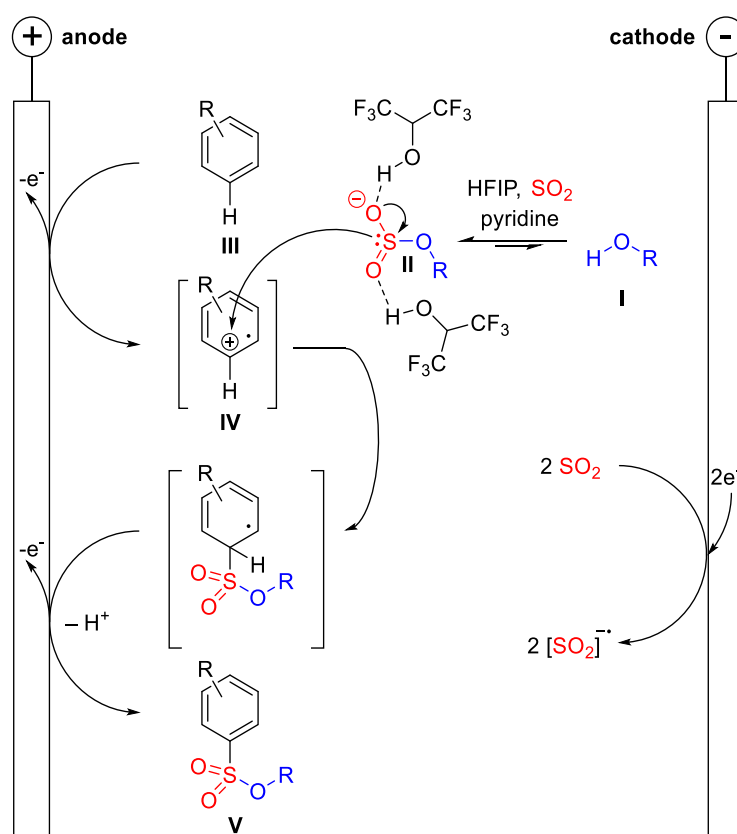
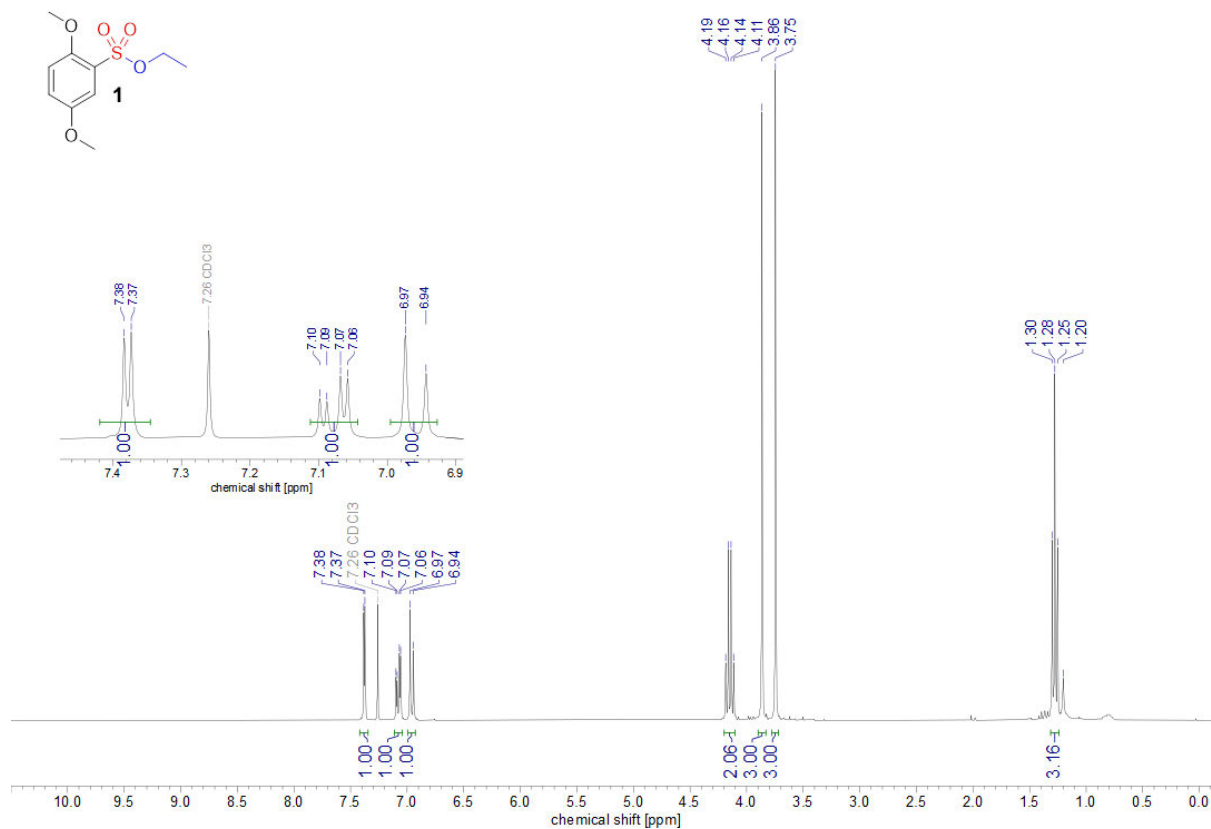
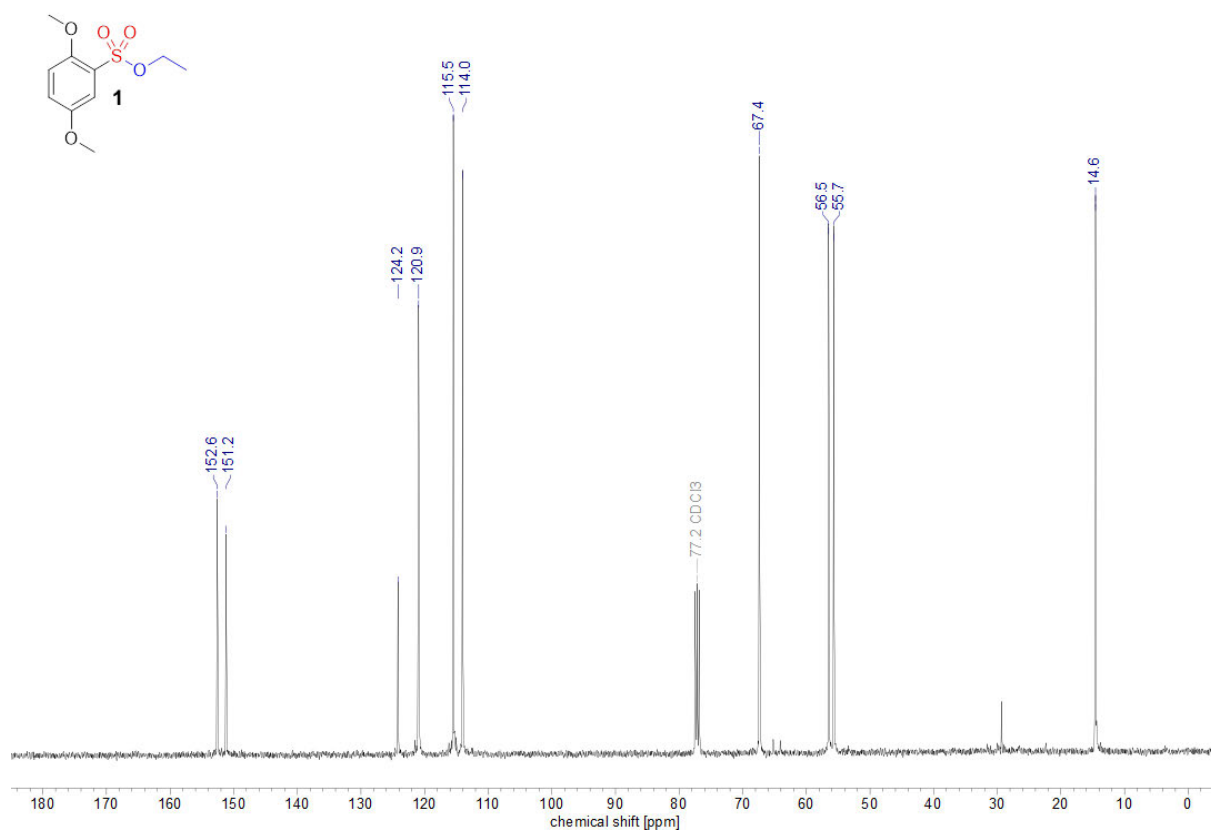


Figure S4. Proposed reaction mechanism.

7. NMR Spectra of Products

Figure S5. ¹H NMR spectrum of ethyl 2,5-dimethoxybenzenesulfonate **1**.Figure S6. ¹³C NMR spectrum of ethyl 2,5-dimethoxybenzenesulfonate **1**.

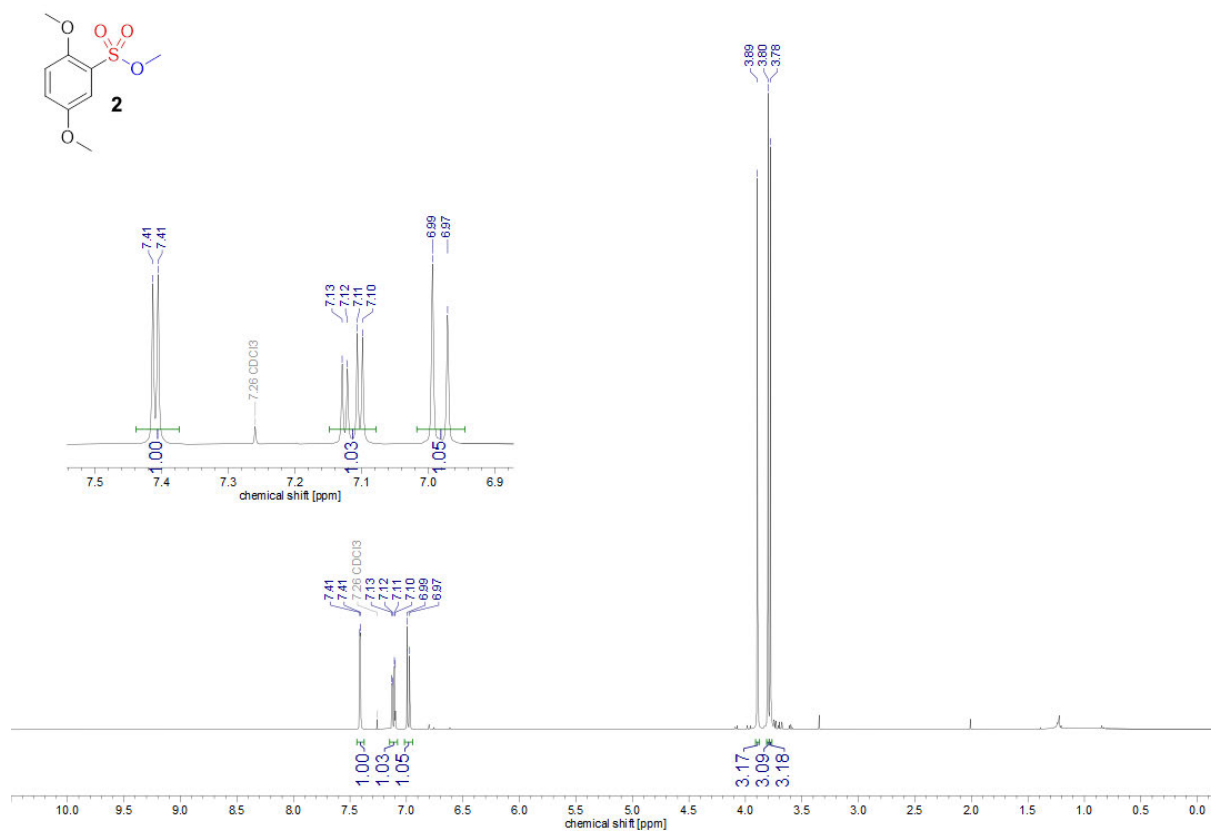


Figure S7. ¹H NMR spectrum of methyl 2,5-dimethoxybenzenesulfonate **2**.

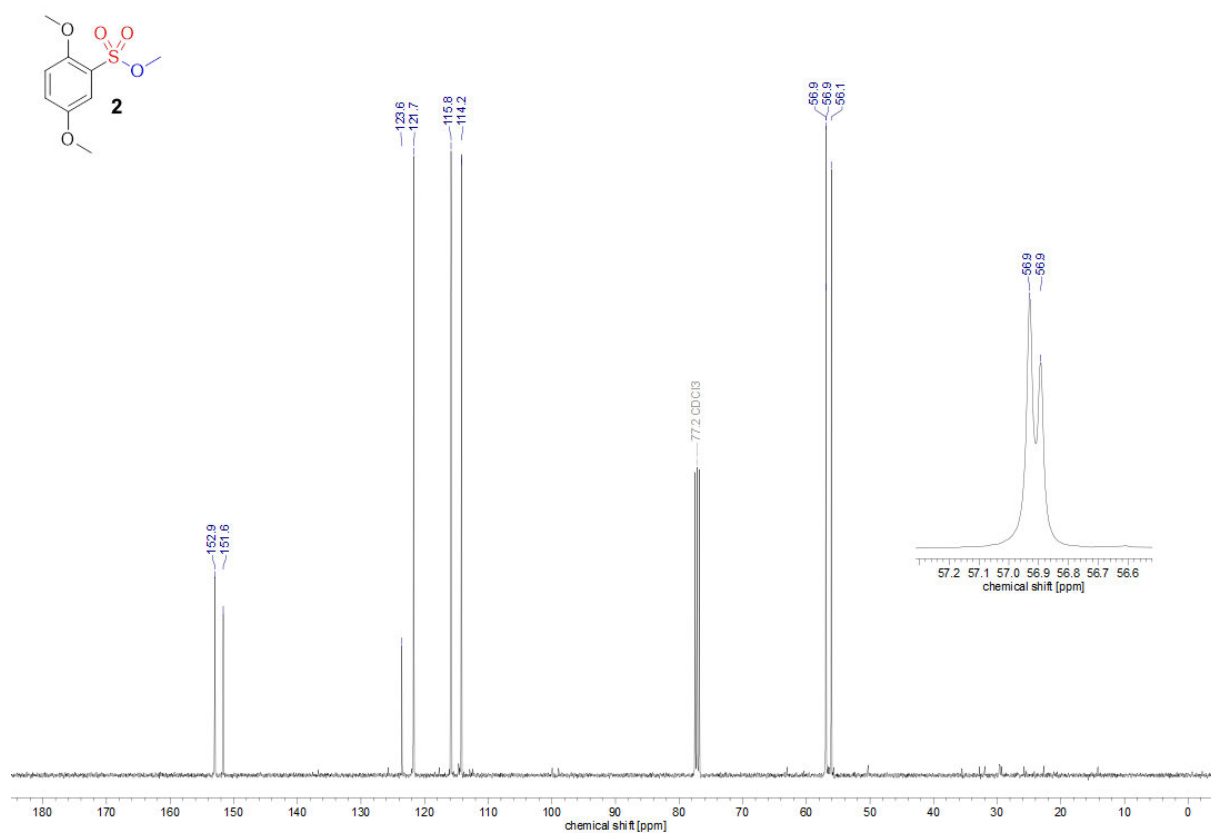
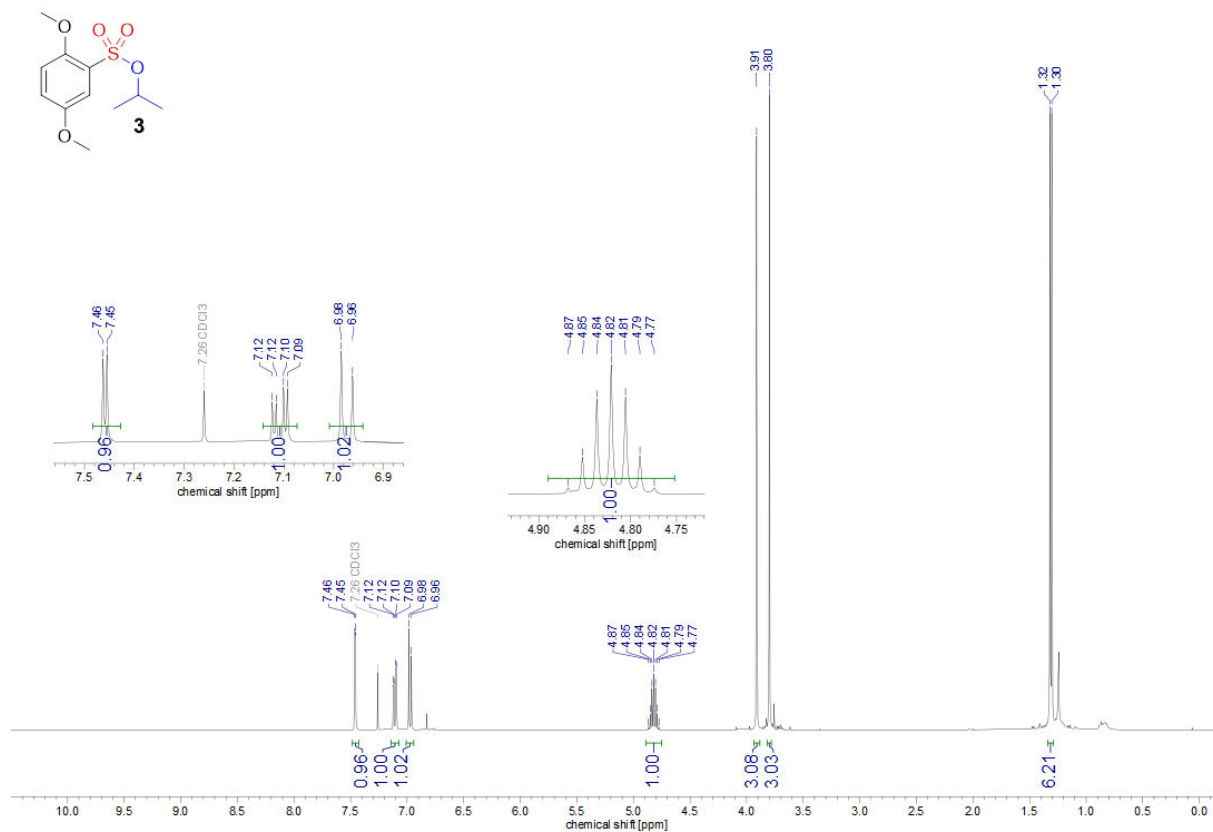
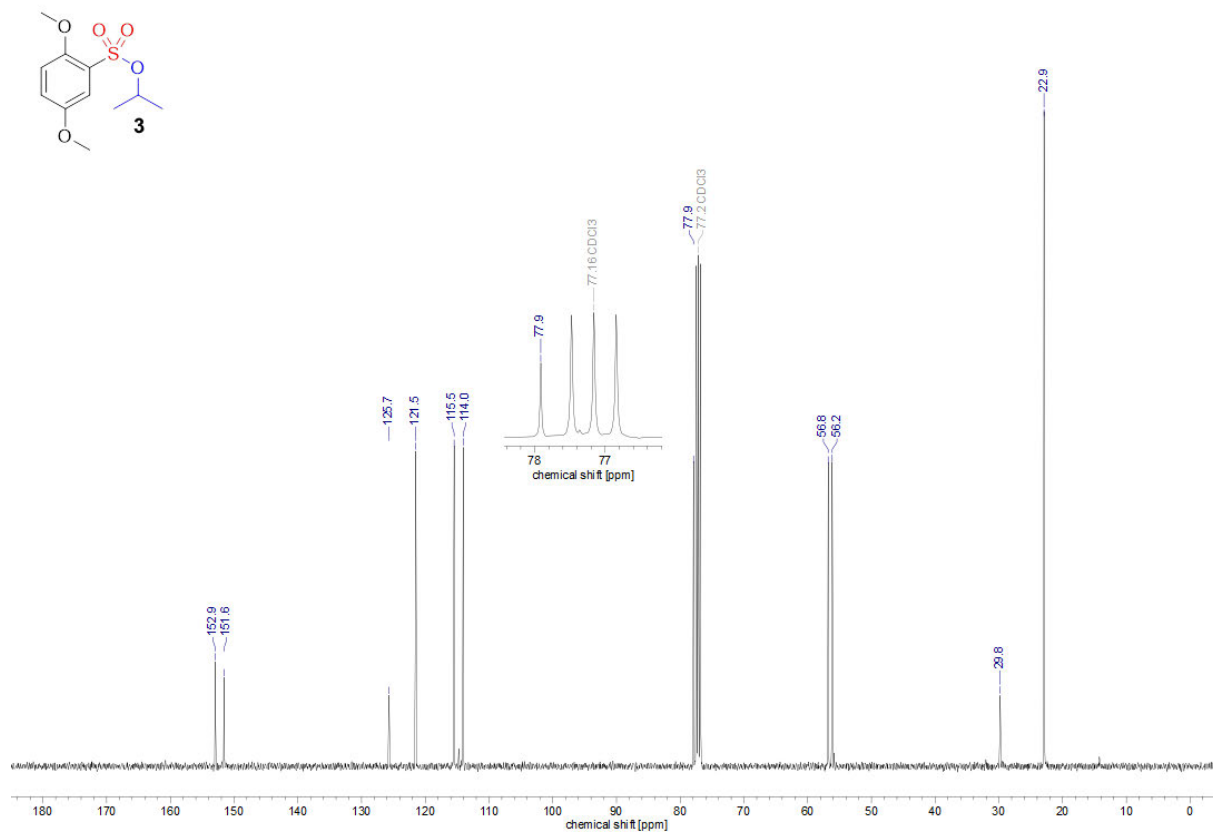


Figure S8. ¹³C NMR spectrum of methyl 2,5-dimethoxybenzenesulfonate **2**.

Figure S9. ¹H NMR spectrum of isopropyl 2,5-dimethoxybenzenesulfonate **3**.Figure S10. ¹³C NMR spectrum of isopropyl 2,5-dimethoxybenzenesulfonate **3**.

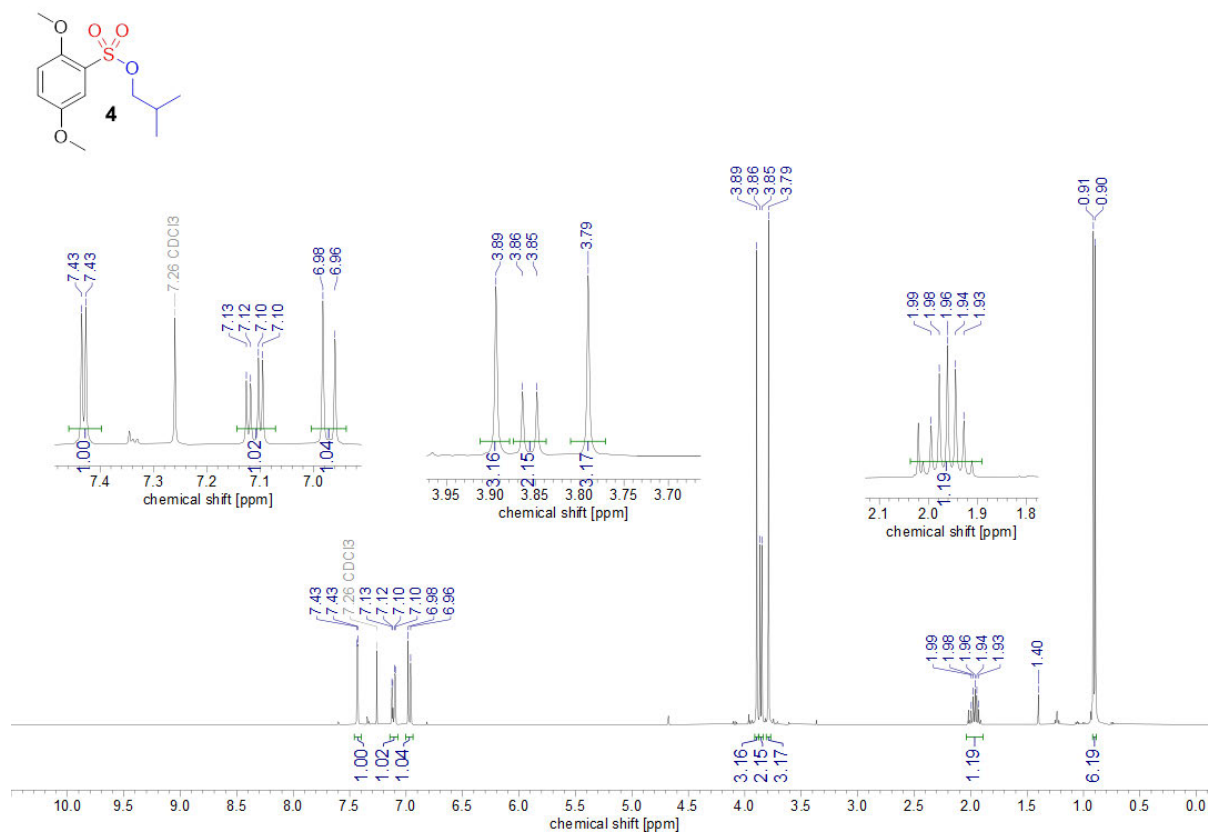


Figure S11. ¹H NMR spectrum of (2-methylprop-1-yl) 2,5-dimethoxybenzenesulfonate **4**.

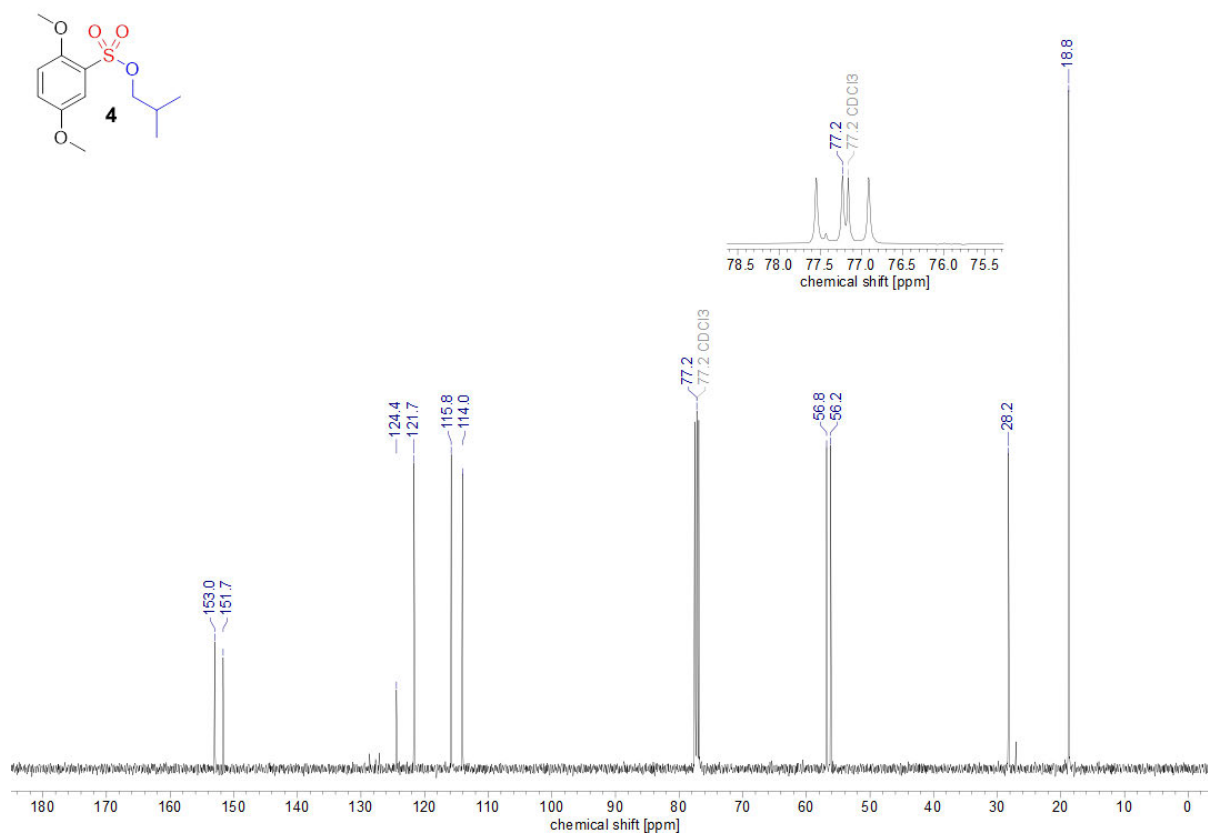


Figure S12. ¹³C NMR spectrum of (2-methylprop-1-yl) 2,5-dimethoxybenzenesulfonate **4**.

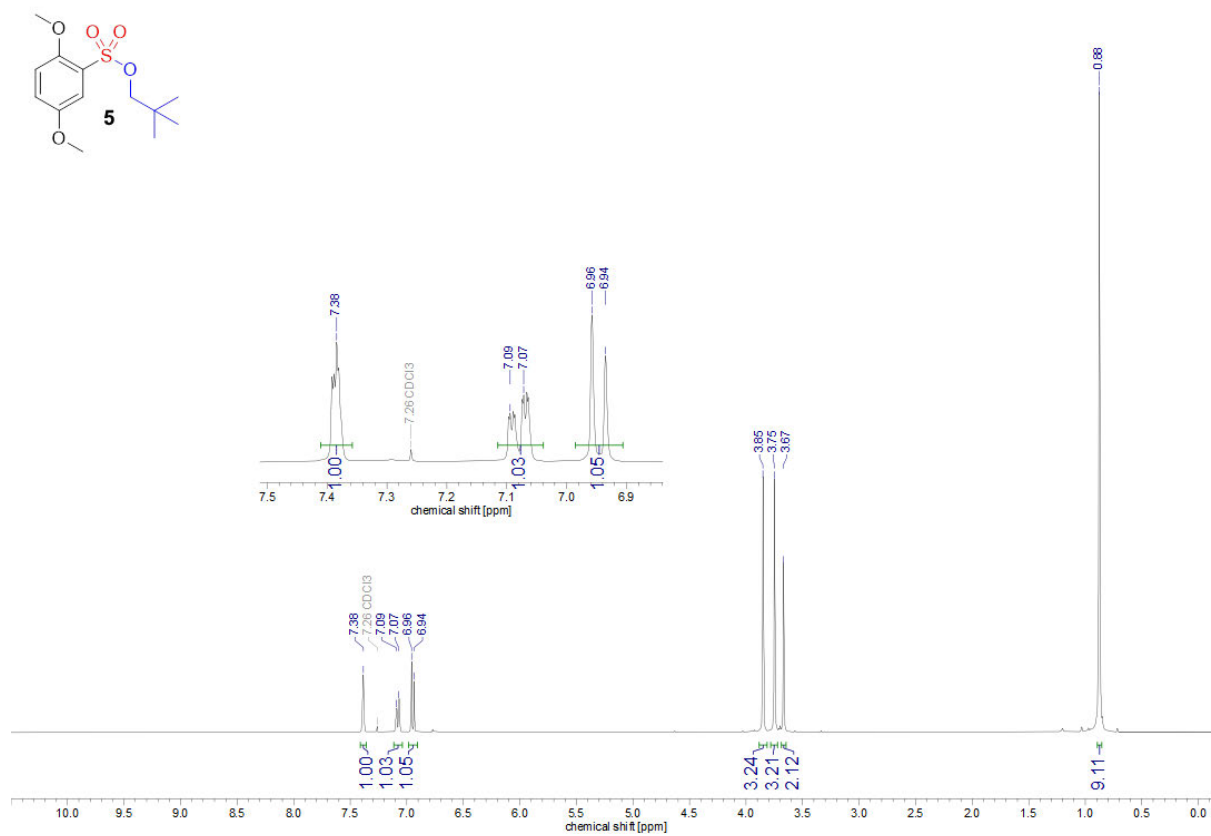


Figure S13. ¹H NMR spectrum of neopentyl 2,5-dimethoxybenzenesulfonate **5**.

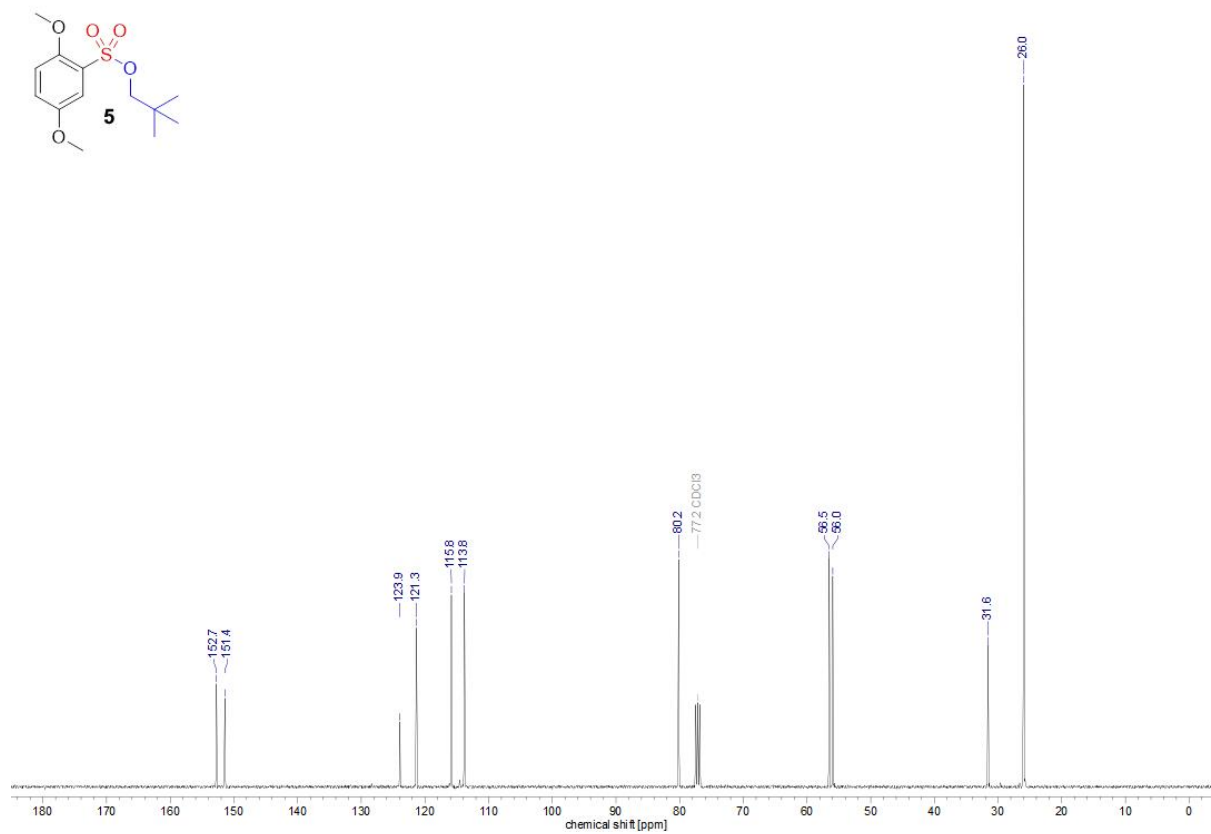


Figure S14. ¹³C NMR spectrum of neopentyl 2,5-dimethoxybenzenesulfonate **5**.

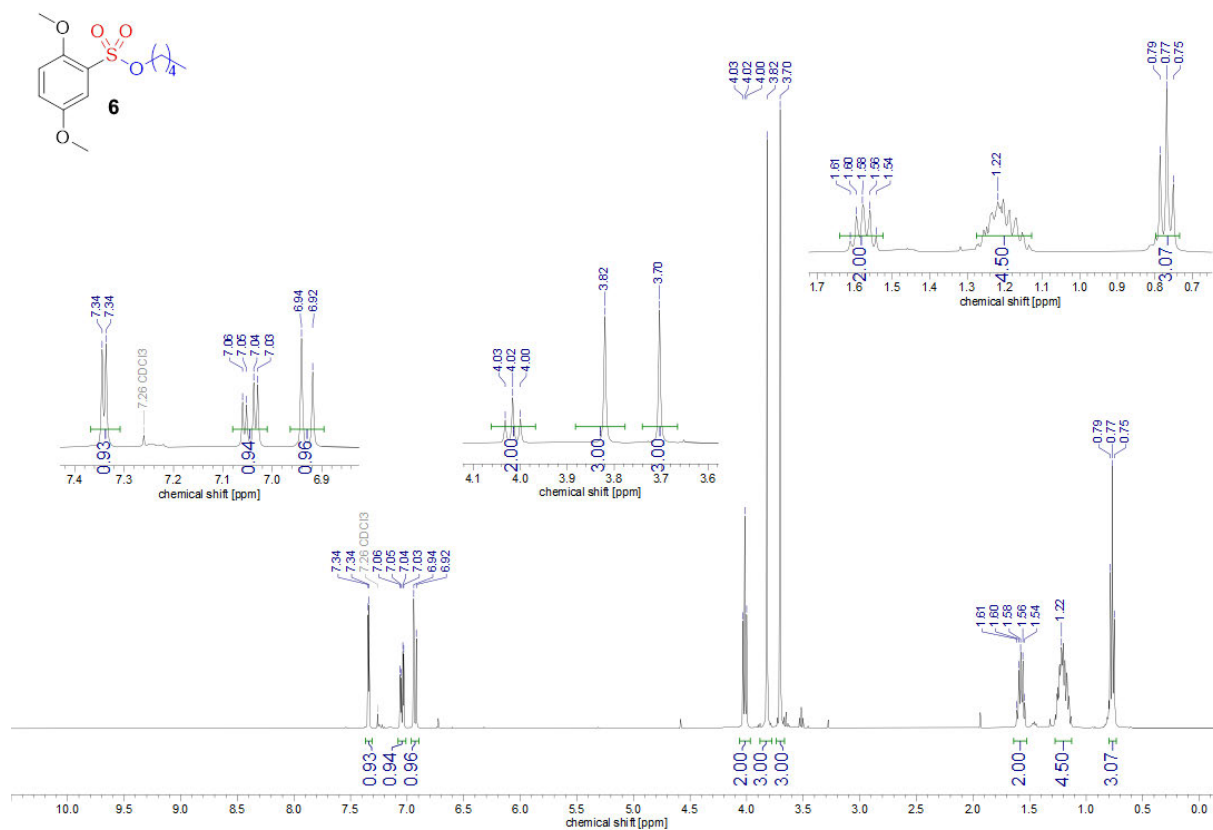


Figure S15. ¹H NMR spectrum of pentyl 2,5-dimethoxybenzenesulfonate **6**.

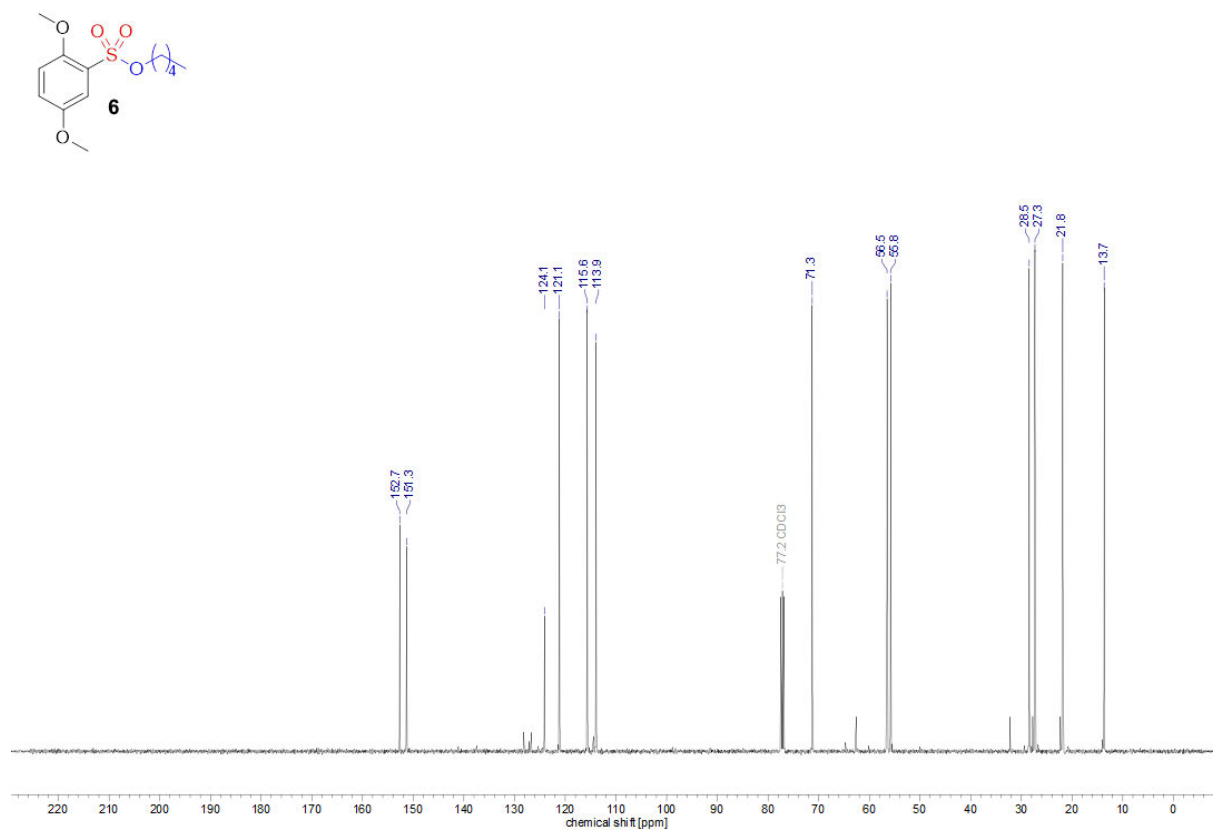


Figure S16. ¹³C NMR spectrum of pentyl 2,5-dimethoxybenzenesulfonate **6**.

8. References

- [1] W. L. F. Armarego, *Purification of laboratory chemicals*, Butterworth-Heinemann is an imprint of Elsevier, Amsterdam, **2017**.
- [2] D. Pletcher, R. A. Green, R. C. D. Brown, *Chem. Rev.* **2018**, *118*, 4573–4591.
- [3] C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.
- [4] M. M. Hielscher, M. Dörr, J. Schneider, S. R. Waldvogel, *Chem. Asian. J.* **2023**, *18*, e202300380.
- [5] J. Schneider, S. P. Blum, S. R. Waldvogel, *ChemElectroChem* **2023**, *10*, e202300456.
- [6] G. Jander, K. F. Jahr, R. Martens-Menzel, L. Harwardt, H.-J. Krauss, *Massanalyse. Titrationen mit chemischen und physikalischen Indikationen*, 20. Aufl., De Gruyter, Berlin, Boston, **2022**.
- [7] T. Rundlöf, M. Mathiasson, S. Bekiroglu, B. Hakkarainen, T. Bowden, T. Arvidsson, *J. Pharm. Biomed. Anal.* **2010**, *52*, 645–651.
- [8] R. B. Dean, W. J. Dixon, *Anal. Chem.* **1951**, *23*, 636–638.
- [9] S. P. Blum, D. Schollmeyer, M. Turks, S. R. Waldvogel, *Chem. Eur. J.* **2020**, *26*, 8358–8362.
- [10] J. L. Röckl, M. Dörr, S. R. Waldvogel, *ChemElectroChem* **2020**, *7*, 3686–3694.
- [11] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. ed.* **2022**, *61*, e202204140; *Angew. Chem.* **2022**, *134*, e202204140.

Chemistry—A European Journal

Supporting Information

Electrochemical Dehydration of Dicarboxylic Acids to Their Cyclic Anhydrides

Johannes Schneider, Andreas P. Häring, and Siegfried R. Waldvogel*

1.	GENERAL INFORMATION	2
2.	EXPERIMENTAL SETUP	2
3.	GENERAL PROCEDURES	3
3.1.	GENERAL PROCEDURE FOR ELECTROLYSIS OF DICARBOXYLIC ACIDS TO THEIR CYCLIC ANHYDRIDES	3
3.2.	GENERAL PROCEDURE FOR AMIDATION REACTION	3
3.3.	GENERAL PROCEDURE FOR SCALED-UP AMIDATION REACTION	3
4.	NMR YIELDS	3
4.1.	REACTION OPTIMIZATION	4
4.2.	ANHYDRIDE SCOPE	5
4.3.	AMIDATION REACTIONS	6
5.	MECHANISTIC STUDIES	7
5.1.	DETECTION OF ^{18}O -LABELED SULFATE BY ESI-HRMS	7
5.2.	DETECTION OF H_2 BY GAS CHROMATOGRAPHY	8
6.	REFERENCES	10

1. General Information

All solvents, reagents, and starting materials were purchased from commercial suppliers. If necessary, they were purified according to standard methods.^[1] Boron-doped diamond (BDD) electrodes (DIACHEM™, 15 µm BDD on 3 mm silicon wafer as supporting material) were purchased from CONDIAS GmbH (Itzehoe, Germany). For electrolysis, a Rohde & Schwarz HMP4040 programmable power supply 384 W was used (4 channels, max. output current per channel: 10 A, max. output power per channel: 160 W, total output power: 384 W, output voltage per channel: 0 V to 32 V, Rohde & Schwarz GmbH & Co. KG, Munich, Germany). Undivided Teflon electrolysis cells (IKA Screening System Package with 8 cells) were purchased from IKA (IKA-Werke GmbH & Co. KG, Staufen, Germany).

Gas Chromatography was carried out using a Shimadzu Nexus GC-2025 (Shimadzu Europa GmbH, Duisburg, Germany) with a barrier ionization discharge (BID) detector using helium as carrier gas. For sample collection, a 100 µL Hamilton™ Gastight™ SampleLock™ twist-valve syringe was used (Hamilton Bonaduz AG, Bonaduz, Switzerland).

Cyclic Voltammetry was measured with a Metrohm PGSTAT101 (Deutsche METROHM GmbH & Co. KG, Filderstadt, Germany). A Metrohm Ag/AgCl 6.0726.100 reference electrode was utilized. All cyclic voltammograms are referenced against ferrocene.

Flash column chromatography for isolation of amides was carried out using a Büchi Control Unit C-620, 2x Büchi Pump Modules C-605, Büchi Fraction Collector C-660, and Büchi UV-Photometer C-635 ($\lambda = 254$ nm). As eluent, mixtures of dichloromethane and ethyl acetate in a gradient 95:5 → 50:50 were utilized. Glacial acetic acid was used as eluent additive.

NMR spectra of ^1H were recorded at 23 °C using a Bruker Avance II 400 spectrometer (400 MHz, 5 mm BBFO-SmartProbe with z gradient and ATM, SampleXPress 60 sample changer (Analytische Messtechnik, Karlsruhe, Germany)).

High-resolution mass spectra (HRMS) were recorded using a G6545A Q-ToF (Agilent GmbH, Waldbronn, Germany) with Electron Spray Ionization (ESI). For sample injection, a 1260 Infinity II HPLC-System (Agilent GmbH, Waldbronn, Germany) with a G7111B 1260 quaternary pump, G7129A 1260 vial sampler and G7116A 1260 multicolumn thermostat was used.

2. Experimental Setup

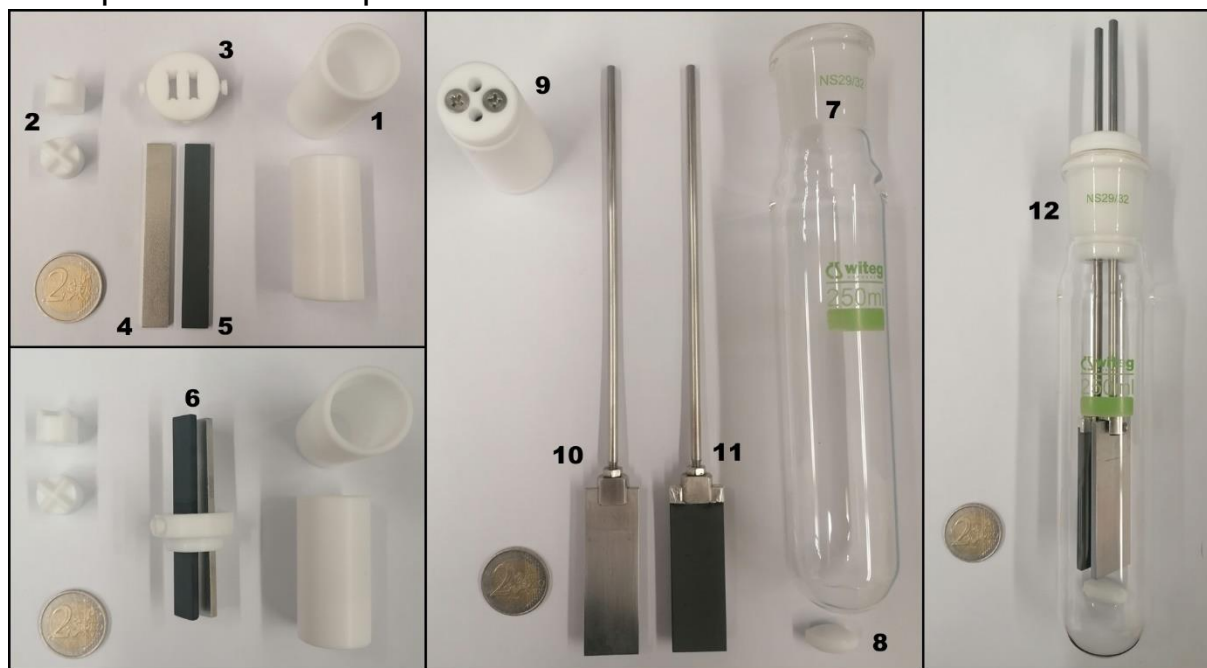


Figure S1: The electrolysis setup: A Teflon cell (1) with a stirring bar inside (2) was used for small-scale reactions (5 mL reaction solution). A Teflon holder with Teflon screws (3) was used to hold the stainless-steel cathode (4) and the BDD anode (5). The size of both (4) and (5) is 1 cm x 7 cm x 3 mm. Under (6), the assembled electrode setup is depicted inside of the holder. For large-scale reaction (50 mL, 10x scale-up), (7) was used with a stirring bar (8). A Teflon holder (9) was used to hold the electrodes (10, 11). In (12), the assembled setup is shown.

3. General Procedures

3.1. General procedure for electrolysis of dicarboxylic acids to their cyclic anhydrides

Into an undivided Teflon electrolysis cell with a stirring bar, acetonitrile (5.0 mL) was added. Tetrabutylammonium thiocyanate (NBu_4SCN , $\text{C}_{17}\text{H}_{36}\text{N}_2\text{S}$, $300.55 \text{ g mol}^{-1}$, 0.5 equiv., 1.0 mmol, 301 mg, 0.2 mol L^{-1}) was added. After it dissolved by stirring, succinic acid ($\text{C}_4\text{H}_6\text{O}_4$, $118.09 \text{ g mol}^{-1}$, 240 mg, 2.0 mmol, 0.4 mol L^{-1}) was added. Upon dissolution, the electrodes were put into the electrolyte and the galvanostatic electrolysis was started (2.7 F , 50 mA cm^{-2} , room temperature, under air, BDD (anode), stainless steel (cathode), both electrodes $1.0 \text{ cm} \times 7.0 \text{ cm}$, 5 mm interelectrode gap, 2.0 cm immersion depth, medium stirring). After the electrolysis completed, 1,3,5-trimethoxybenzene (100 mg, 0.60 mmol) was added as internal standard. The reaction solution was transferred into a 50 mL round-bottom flask, the solvent was removed using a rotary evaporator, dry CDCl_3 (0.5 mL) was added, and the sample was analyzed using ^1H NMR spectroscopy.

3.2. General procedure for amidation reaction

Into an undivided Teflon electrolysis cell with a stirring bar (depicted in the right of Figure S1), acetonitrile (5.0 mL) and tetrabutylammonium thiocyanate (NBu_4SCN , $\text{C}_{17}\text{H}_{36}\text{N}_2\text{S}$, $300.55 \text{ g mol}^{-1}$, 1.0 equiv., 1.0 mmol, 602 mg, 0.4 mol L^{-1}) were added. After it dissolved by stirring, succinic acid ($\text{C}_4\text{H}_6\text{O}_4$, $118.09 \text{ g mol}^{-1}$, 240 mg, 2.0 mmol, 0.4 mol L^{-1}) was added. After everything dissolved, the electrodes were put into the reaction solution and the galvanostatic electrolysis was started (2.7 F , 50 mA cm^{-2} , room temperature, under air, BDD || stainless steel, both electrodes $1.0 \text{ cm} \times 7.0 \text{ cm}$, 5 mm interelectrode gap, 2.0 cm immersion depth, medium stirring). After the electrolysis completed, benzylamine ($\text{C}_7\text{H}_9\text{N}$, $107.15 \text{ g mol}^{-1}$, 5.0 equiv., 1.09 mL) and DMAP (4-(dimethylamino)pyridine, $\text{C}_7\text{H}_{10}\text{N}_2$, $122.17 \text{ g mol}^{-1}$, 12 mg, 0.1 mmol, 0.05 equiv.) was added, and the reaction was heated to 80°C for 2 h. 1,3,5-trimethoxybenzene (100 mg, 0.60 mmol) was added as internal standard. The reaction solution was transferred into a 50 mL round-bottom flask, the solvent was removed using a rotary evaporator, dry CDCl_3 (0.5 mL) was added, and the sample was analyzed using ^1H NMR spectroscopy.

3.3. General procedure for scaled-up amidation reaction

Into the reaction container with a stirring bar (depicted in the right of Figure S1), acetonitrile (50.0 mL) and tetrabutylammonium thiocyanate (NBu_4SCN , $\text{C}_{17}\text{H}_{36}\text{N}_2\text{S}$, $300.55 \text{ g mol}^{-1}$, 1.0 equiv., 20.0 mmol, 6.011 g, 0.4 mol L^{-1}) were added. After it dissolved by stirring, succinic acid ($\text{C}_4\text{H}_6\text{O}_4$, $118.09 \text{ g mol}^{-1}$, 2.363 g, 20.0 mmol, 0.4 mol L^{-1}) was added. After everything dissolved, the electrodes were put into the reaction solution and the galvanostatic electrolysis was started (2.7 F , 50 mA cm^{-2} , room temperature, under air, BDD || stainless steel, both electrodes $2.0 \text{ cm} \times 7.0 \text{ cm}$, 5 mm interelectrode gap, 4.5 cm immersion depth, medium stirring). After the electrolysis completed, benzylamine ($\text{C}_7\text{H}_9\text{N}$, $107.15 \text{ g mol}^{-1}$, 5.0 equiv., 10.92 mL) and DMAP (4-(dimethylamino)pyridine, $\text{C}_7\text{H}_{10}\text{N}_2$, $122.17 \text{ g mol}^{-1}$, 122 mg, 1.0 mmol, 0.05 equiv.) was added, and the reaction was heated to 80°C for 2 h. 1,3,5-Trimethoxybenzene (486 mg, 2.89 mmol) was added as internal standard. An aliquot of 10 mL was taken, the solvent was removed using a rotary evaporator, CDCl_3 (0.5 mL) was added, and the sample was analyzed using ^1H NMR spectroscopy. For workup, crude product was adsorbed on silica and the amide was isolated using flash column chromatography. Eluent component A: DCM (1000 mL) + glacial acetic acid (50 mL). Eluent component B: ethyl acetate (1000 mL) + glacial acetic acid (50 mL). Gradient: A:B 95:5 $\rightarrow$ 50:50. 4-Oxo-4-((phenylmethyl)amino)butanoic acid (2.836 g, 13.68 mmol, 58% over 2 steps) was obtained. R_f (DCM/EtOAc/HOAc 1:1:0.1) = 0.19. ^1H NMR (400 MHz, CDCl_3) δ [ppm] = 7.3-7.2 (m, 5H, Ar), 4.42 (d, J = 4.0 Hz, 2H, CH_2NH), 2.74 (m, 2H, CH_2), 2.54 (m, 2H, CH_2).

4. NMR yields

The NMR yield is calculated as follows, where I denotes the integral of the ^1H NMR signal, and N is the number of protons corresponding to that signal (because 1,3,5-trimethoxybenzene was used as internal standard, $N_{\text{std}} = 3$, as the 3 aromatic protons around 6.0 ppm are used for integration):

$$\% \text{yield}_{\text{NMR}} = \frac{n_{\text{product}} \cdot 100}{n_{\text{starting material}}} = \frac{n_{\text{std}} \cdot \frac{\left(\frac{I_{\text{product}}}{N_{\text{product}}}\right)}{\left(\frac{I_{\text{std}}}{N_{\text{std}}}\right)} \cdot 100}{n_{\text{starting material}}}$$

4.1. Reaction optimization

In the following Table S1, the data of the reaction optimization experiments shown in Figure S2 are shown. This is the data shown in the main manuscript's Table 1. For succinic anhydride, $N_{\text{product}} = 4$.

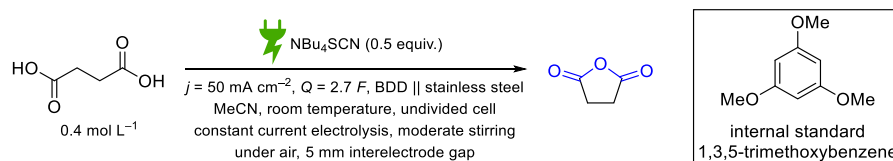


Figure S2: The standard reaction conditions of the test reaction: electrochemical dehydrative reaction of succinic acid to succinic anhydride.

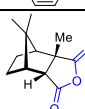
Table S1: Data for the calculation of NMR yields of the reaction optimization experiments. The standard reaction conditions are depicted in Figure S2. This is the data for Table 1 in the main manuscript.

#	Deviation from standard conditions ^[a]	NMR yield% ^[b]	<i>I</i> (STD)	<i>m</i> (STD) [mg]	<i>n</i> (STD) [mmol]	<i>I</i> (product)	<i>n</i> (product) [mmol]	<i>m</i> (SM) [mg]	<i>n</i> (SM) [mmol]
1	none	70	3.00	109	0.65	8.84	1.43	239.7	2.03
2	2.4 F	45	3.00	109	0.65	5.59	0.90	237.8	2.01
3	3.0 F	69	3.00	109	0.65	8.68	1.40	241.7	2.05
4	3.3 F	66	3.00	109	0.65	8.01	1.30	236.1	2.00
5	30 mA cm ⁻²	58	3.00	109	0.65	7.28	1.18	238.3	2.02
6	60 mA cm ⁻²	59	3.00	109	0.65	7.46	1.21	240.9	2.04
7	70 mA cm ⁻² , 3.0 F	64	3.00	109	0.65	8.07	1.31	241.6	2.05
8	glassy carbon stainless steel	50	3.00	109	0.65	6.29	1.02	238.9	2.02
9	graphite stainless steel	50 ^[b]	3.00	109	0.65	6.42	1.04	244.6	2.07
10	BDD BDD	16	3.00	109	0.65	2.03	0.33	244.6	2.07
11	0 °C	58	3.00	109	0.65	7.24	1.17	239.1	2.02
12	60 °C	55	3.00	109	0.65	6.95	1.12	241.5	2.05
13	1.5 mmol SM, <i>c</i> (SM) = 0.3 mol L ⁻¹	44	3.00	109	0.65	4.13	0.67	179.0	1.52
14	2.5 mmol SM, <i>c</i> (SM) = 0.5 mol L ⁻¹	59	3.00	109	0.65	9.25	1.50	298.3	2.53
15	0.3 equiv. NBu ₄ SCN	31	3.00	109	0.65	3.80	0.61	236.2	2.00
16	1.0 equiv. NBu ₄ SCN	71	3.00	109	0.65	8.94	1.45	239.4	2.03
17	1.5 equiv. NBu ₄ SCN	70	3.00	109	0.65	8.96	1.45	246.0	2.08
18	no NBu ₄ SCN, 0.5 equiv. EMIMSCN	36	3.00	109	0.65	4.48	0.72	239.1	2.02
19	no NBu ₄ SCN, 0.5 equiv. BMIMSCN	19	3.00	109	0.65	2.44	0.39	239.6	2.03
20	no NBu ₄ SCN, 1.0 equiv. NH ₄ SCN	3 ^[c]	3.00	109	0.65	0.36	0.06	239.7	2.03
21	no NBu ₄ SCN	0 ^[d]	3.00	109	0.65	0.00	0.00	238.2	2.02
22	no electricity	0	3.00	109	0.65	0.00	0.00	238.6	2.02

SM: starting material (dicarboxylic acid). BDD: boron-doped diamond. EMIMSCN: 1-ethyl-3-methylimidazolium thiocyanate. BMIMSCN: 1-butyl-3-methylimidazolium thiocyanate. [a] The yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] The upper terminal voltage limit of the power supply was reached during electrolysis, nonetheless 2.7 F was fully applied. [c] The reaction had to be stopped after 2.1 F because of the formation of a precipitate inside of the electrolysis cell, which resulted in blocking of the electrodes. [d] The electrolysis can't be carried out without NBu₄SCN, because the upper terminal voltage limit of the power supply is reached, demonstrating that the thiocyanate supporting electrolyte is indispensable for the reaction.

4.2. Anhydride Scope

Table S2: Data for calculation of the NMR yields for the anhydride scope.

#	Anhydride	Name	NMR yield%	l (STD)	m (STD) [mg]	n (STD) [mmol]	l (product)	product signal [ppm]	n (prod) [mmol]	m (SM) [mg]	n (SM) [mmol]
1		succinic anhydride	71	3.00	109	0.65	8.94	2.90 (s, 4H)	1.45	239.4	2.03
2		methylsuccinic anhydride	56	3.00	109	0.65	1.75	2.60 (m, 1H)	1.13	266.5	2.02
3		2,2-dimethylsuccinic anhydride	66	3.00	109	0.65	4.12	2.61 (s, 2H)	1.33	294.9	2.02
4		phenylsuccinic anhydride	16	3.00	109	0.65	0.51	2.61 (m, 1H)	0.33	390.4	2.01
5		maleic anhydride	2	3.00	109	0.65	0.12	7.40 (s, 2H)	0.04	233.7	2.01
6		<i>cis</i> -cyclopentane-1,2-dicarboxylic anhydride	62	3.00	109	0.65	4.23	3.40 (s, 2H)	1.37	346.4	2.19
7		<i>cis</i> -1,2-cyclohexane-dicarboxylic anhydride	57	3.00	109	0.65	3.56	3.08 (s, 2H)	1.15	346.1	2.01
8		<i>cis</i> -4-cyclohexene-1,2-dicarboxylic anhydride	17	3.00	109	0.65	1.06	5.88 (s, 2H)	0.34	344.7	2.03
9		(+)-camphoric anhydride	67	3.00	109	0.65	2.11	2.72 (d, 1H)	1.37	409.8	2.05
10		<i>cis</i> -5-norbornene- <i>endo</i> -2,3-dicarboxylic anhydride	60	3.00	109	0.65	3.77	3.36 (s, 2H)	1.22	369.6	2.03
11		glutaric anhydride	59	3.00	109	0.65	7.28	2.30 (t, 4H)	1.18	264.0	2.00
12		2,2-dimethylglutaric anhydride	52	3.00	109	0.65	3.38	2.16 (t, 2H)	1.09	339.9	2.12
13		3,3-dimethylglutaric anhydride	46	3.00	109	0.65	6.26	2.28 (t, 4H)	1.01	350.0	2.19
14		1,1-cyclopentanediacetic anhydride	57	3.00	109	0.65	7.06	2.53 (s, 4H)	1.14	376.1	2.02
15		1,1-cyclohexanediacetic anhydride	64	3.00	109	0.65	8.02	2.56 (s, 4H)	1.30	403.0	2.01
16		adipic anhydride	30	3.00	109	0.65	3.86	2.32 (t, 4H)	0.62	304.5	2.08
17		pimelic anhydride	36	3.00	109	0.65	4.53	2.31 (t, 4H)	0.73	325.6	2.03
18		suberic anhydride	33	3.00	109	0.65	4.03	2.22 (t, 4H)	0.65	348.0	2.00
19		azelaic anhydride	32	3.00	109	0.65	3.96	2.19 (t, 4H)	0.64	380.8	2.02
20		sebacic anhydride	19	3.00	109	0.65	2.41	2.22 (t, 4H)	0.39	423.5	2.09

4.3. Amidation reactions

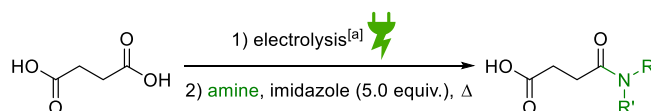


Figure S3: Amidation test reaction. [a] electrolysis reaction conditions: acetonitrile, succinic acid (0.4 mol L⁻¹), NBu₄SCN (1.0 equiv.) constant current electrolysis, current density $j = 50 \text{ mA cm}^{-2}$, amount of applied charge $Q = 3.0 F$, BDD || stainless steel, 5 mm interelectrode gap, under air, moderate stirring.

Table S3: Data for calculation of the NMR yields for the amidation reactions.

#	Deviation from standard conditions ^[a]	NMR yield ^[b]	<i>I</i> (STD)	<i>m</i> (STD) [mg]	<i>n</i> (STD) [mmol]	<i>I</i> (product)	<i>N</i> (product)	<i>n</i> (product) [mmol]	<i>m</i> (SM) [mg]	<i>n</i> (SM) [mmol]
1	benzylamine (5.0 equiv.), no imidazole	68	3.00	109	0.65	4.26	2	1.38	240.1	2.03
2	benzylamine (5.0 equiv.)	71	3.00	109	0.65	4.42	2	1.43	238.0	2.02
3	benzylamine (5.0 equiv.), no imidazole, DMAP (0.05 equiv.)	73	3.00	109	0.65	4.54	2	1.47	238.9	2.02
4	benzylamine (5.0 equiv.), DMAP (0.05 equiv.)	72	3.00	109	0.65	4.56	2	1.48	241.2	2.04
5	morpholine (5.0 equiv.), no imidazole	36	3.00	109	0.65	4.53	4	0.73	237.1	2.01
6	morpholine (5.0 equiv.)	31	3.00	109	0.65	3.85	4	0.62	236.5	2.00
7	morpholine (5.0 equiv.), no imidazole, DMAP (0.05 equiv.)	38	3.00	109	0.65	4.70	4	0.76	238.1	2.02
8	morpholine (5.0 equiv.), DMAP (0.05 equiv.)	32	3.00	109	0.65	4.04	4	0.65	237.5	2.01
9	10-fold scale-up of entry 3	61	3.00	486	2.89	8.51	2	12.28	2364.3	20.02

[a] The standard reaction conditions are shown in Figure S2. DMAP: 4-(dimethylamino)pyridine. [b] The amide yields were determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Reference synthesis: succinic anhydride (212 mg, 2.07 mmol) was dissolved in acetonitrile (50 mL) and benzylamine (5.0 equiv., 10.0 mmol, 1.07 g, 1.09 mL) was added. The reaction was heated under reflux and after purification using flash column chromatography (general procedure 3.2), 4-Oxo-4-((phenylmethyl)amino)butanoic acid was obtained (436 mg, 2.10 mmol, 99%).

5. Mechanistic Studies

5.1. Detection of ^{18}O -labeled sulfate by ESI-HRMS

The key mechanistic question of the electrochemical dehydration of dicarboxylic acids to cyclic carboxylic anhydrides is the remains of one equivalent of water, which is formally removed during the electrochemical dehydration reaction. To investigate this, ^{18}O -labeled succinic acid was synthesized by reaction of succinic anhydride with H_2^{18}O :

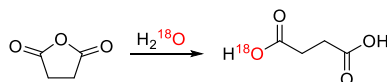


Figure S4: Isotope labeling of succinic acid by hydrolysis of succinic anhydride in H_2^{18}O .

Spectrum Peaks

m/z	m/z (Calc)	Diff (ppm)	Ion Species	Z	Formula	Abund	Abund %
61.9883	61.9895	-20.29				191958	89.80
68.9955						7292	3.41
73.0294	73.0295	-1.10		1		21084	9.86
75.0337	75.0337	-1.23				2498	1.17
89.0235	89.0244	-10.44				2445	1.14
99.0086	99.0088	-2.13		1		3893	1.82
112.9855						52098	24.37
117.0194				1		213761	100.00
118.0232				1		25222	11.80
119.0235	119.0236	-0.53	(M-H)-	1	C4 H6 O3 [18O]	76077	35.59
119.9469						3117	1.46
120.0267	120.0270	-2.19	(M-H)-	1	C4 H6 O3 [18O]	3726	1.74
121.0292	121.0295	-2.74		1		3931	1.84
132.8677						16521	7.73
134.8653						19748	9.24

Figure S5: Mass spectrum signals of ^{18}O labeled succinic acid.

The ^{18}O -labeled succinic acid was then used for electrochemical dehydration reaction under standard conditions to obtain succinic anhydride as reaction product again.

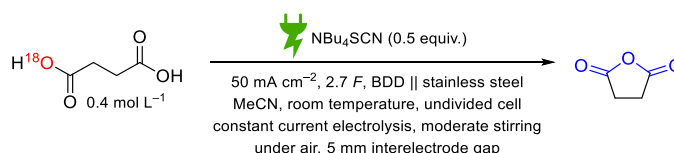


Figure S6: Electrolysis of ^{18}O -labeled succinic acid.

A sample was taken from the reaction solution before and after electrolysis, and then analyzed using ESI-HRMS. It was found that each reaction solution did not contain any sulfate before electrolysis, while in the reaction solution from after electrolysis ^{18}O -labeled sulfate was detected, as shown in Figure S7. This finding gives strong evidence that the electrochemical dehydration is driven by electrochemical oxidation and hydrolysis of the thiocyanate supporting electrolyte.

Spectrum Peaks

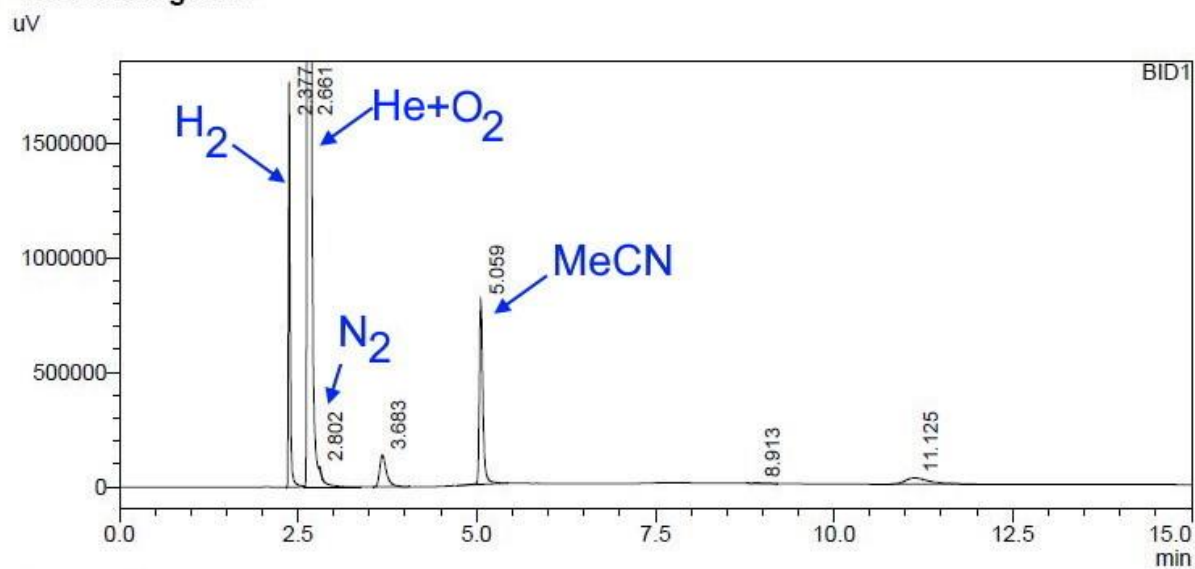
m/z	m/z (Calc)	Diff (ppm)	Ion Species	Z	Formula	Abund	Abund %
89.0486						588	1.42
89.9467						430	1.04
96.9603	96.9601	2.05	(M-H)-		H2 O4 S	722	1.74
97.9683	97.9689	-6.06				797	1.92
98.9645	98.9643	1.78	(M-H)-		H2 O3 [18O] S	254	0.61
103.0018						150	0.36
105.9602						5222	12.57

Figure S7: Detection of sulfate by ^{18}O -isotope labeling using ESI-HRMS. This isotope labeling gives strong evidence that the electrochemical dehydration is driven by electrochemical the oxidation and hydrolysis of the thiocyanate supporting electrolyte.

5.2. Detection of H₂ by gas chromatography

To answer the question if hydrogen evolution reaction occurs as counter reaction during electrolysis, a sample of the gas that is evolving from the reaction solution was analyzed using a gas chromatograph which uses helium as carried gas and a barrier ionization discharge (BID) detector.^[2] Such an experimental setup allows for hydrogen detection by comparing the retention times of the signals with those of reference gases. A gas chromatogram of the gas evolving from the reaction can be seen in Figure S8. In this chromatogram, a peak from H₂ can be found, meaning that hydrogen evolution reaction (HER) occurs as a counter reaction during electrolysis.^[3] Also, acetonitrile can be found at 5.059. The signals of N₂ and O₂ overlap with the helium carrier gas in the signal at 2.661. The signal at 3.683 could not be assigned.

<Chromatogram>



<Peak Table>

BID1

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	2.377	2977532	1760643	0.000	ppm		H2
2	2.661	17631991	4159725	0.000	ppm	SV	O2
3	2.802	31932	16202	0.000	ppm	T	N2
4	3.683	919008	138465	0.000			
5	5.059	2797076	804158	0.000			
6	8.913	30544	2788	0.000			
7	11.125	626046	26887	0.000			
Total		25014129	6908867				

Figure S8: Chromatogram of the gas evolving from the reaction solution. Because of the H₂ peak at 2.377, it can be clearly seen that hydrogen evolution reaction occurs during electrolysis, which is a common counter reaction.



Figure S9: A Shimadzu Nexis GC-2030 with helium as carrier gas and a BID (barrier ionization discharge) detector used for analysis, kindly provided by Dr. Simon Clausing from the group of Prof. Dr. Carsten Streb, Mainz University.



Figure S10: A 100 µL Hamilton™ Gastight™ SampleLock™ twist-valve syringe used to take samples for gas chromatography.

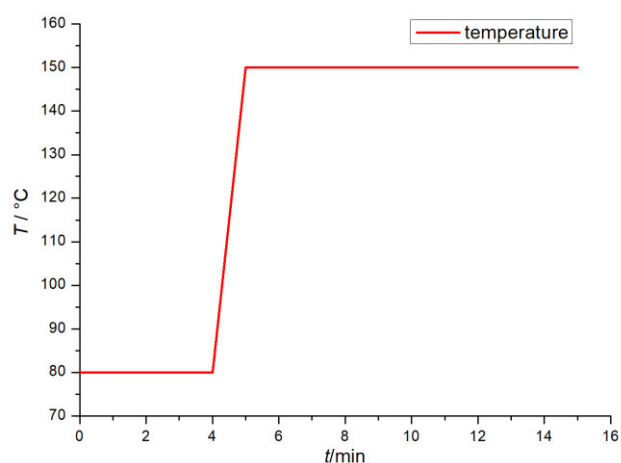


Figure S11: The temperature profile over time of the gas chromatograph used to analyze the samples.

6. References

- [1] W. L. F. Armarego, *Purification of laboratory chemicals*. 8. ed., Elsevier, **2017**.
- [2] A. F. Lopes, T. S. M. Fernandes, R. F. do Nascimento, *Crit. Rev. Anal. Chem.* **2023**, 53, 614–633.
- [3] M. Klein, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2022**, 61, e202204140; *Angew. Chem.* **2022**, 134, e202204140.

1. General Information	S3
2. General Protocols	S6
3. Reaction Optimization	S7
4. Synthesis of Non-commercially Available Starting Materials	S9
5. Analytical Data of Allylic Oxidation Products	S9
5.1. Terpenoid Substrates	S9
5.2. Steroidal Substrates	S12
6. Analytical Data of Starting Materials	S15
6.1. Terpenoid Substrates	S15
6.2. Steroidal Substrates	S17
7. NMR Spectra of Allylic Oxidation Products.....	S19
7.1. 4-Oxo-isophorone	S19
7.2. Verbenone.....	S21
7.3. Carvone	S24
7.4. 3-Oxo- α -ionone	S26
7.5. 3-Oxo-vinyl- α -ionol	S29
7.6. 3-Oxo-ethynyl- β -ionol.....	S31
7.7. 4-Oxo- β -ionone	S34
7.8. 4-Oxo-vinyl- β -ionol.....	S36
7.9. 4-Oxo-ethynyl- β -ionol.....	S39
7.10. 4-Oxo- β -damascone	S41
7.11. 3-Oxo- α -cetone	S44
7.12. Nootkatone.....	S46
7.13. Oxomyrtenyl acetate	S49
7.14. Cedrenone	S51
7.15. 7-Ketocholesterol	S54
7.16. 7-Ketocholesteryl acetate.....	S56
7.17. 7-Ketocholesteryl benzoate.....	S59
7.18. 7-Ketodiosgenin acetate	S61
7.19. 7-Ketositosterol	S64
7.20. 7-Ketostigmasteryl acetate.....	S66
7.21. 7-Ketopregnenolone acetate.....	S69
7.22. 7-Ketodehydroepiandrosterone acetate.....	S71
7.23. 7-Ketomethandriol.....	S74
7.24. 3-Ketolynestrenol	S76
8. NMR Spectra of Scale-up Reaction	S79
9. NMR Spectra of Commercially Obtained 4-Oxoisophorone.....	S81
10. NMR Spectra of Starting Materials.....	S84
10.1. β -Isophorone	S84
10.2. α -Isophorone.....	S86
10.3. 2,6,6-Trimethyl-2-cyclohex-1-one.....	S89
10.4. (+)- α -Pinene.....	S91
10.5. (+)-Limonene.....	S94
10.6. α -Ionone.....	S96
10.7. Vinyl- α -ionol	S99
10.8. Ethynyl- α -ionol	S101
10.9. β -Ionone.....	S104
10.10. Vinyl- β -ionol	S106
10.11. Ethynyl- β -ionol	S109
10.12. β -Damascone.....	S111
10.13. α -Cetone	S114
10.14. (+)-Valencene.....	S116
10.15. Myrtenyl acetate.....	S119
10.16. (–)- α -Cedrene	S121
10.17. Cholesterol.....	S124
10.18. Cholesteryl acetate	S126
10.19. Cholesteryl benzoate	S129

10.20.	Diosgenin acetate	S131
10.21.	β -Sitosterol.....	S134
10.22.	Stigmasteryl acetate.....	S136
10.23.	Pregnenolone acetate	S139
10.24.	Dehydroepiandrosterone (DHEA) acetate.....	S141
10.25.	Methylandrostenediol	S144
10.26.	Lynestrenol.....	S146
11.	Cyclic Voltammetry (CV)	S149
12.	References	S150

1. General Information

The numbering of substances in the main manuscript and in the Supporting Information is as follows: Terpenoid starting materials are designated by the number **1**, followed by a letter, for example **1a**. The corresponding allylic oxidation product of **1a** has number **2** with this letter, in this example **2a**. For steroidal substrates, the starting material starts with number **3** and a letter, and their corresponding allylic oxidation product has **4** with that letter. For example, **4a** is the product of the allylic oxidation of substrate **3a**. In the case of 4-oxoisophorone **2a**, three different starting materials result in the same reaction product (as will be discussed in the reaction mechanism). To account for this, and to keep the numbering simple, the starting materials corresponding to 4-oxoisophorone **2a** are labelled as: β -isophorone **1a**, α -isophorone **1a'**, and 2,6,6-trimethyl-2-cyclohexen-1-one **1a''**. Substrates for which allylic oxidation was not successful are labelled as **u1** to **u4**.

Starting materials, solvents, and reagents were purchased from commercial suppliers, and if necessary, they were purified according to standard methods.^[1] The following starting materials were kindly provided by dsm-firmenich AG (Kaiseraugst, Switzerland): ethynyl- α -ionol **1f**, ethynyl- β -ionol **1i**, vinyl- α -ionol **1e**, vinyl- β -ionol **1h**.^[2]

Electrolysis was carried out using a Rohde & Schwarz HMP4040 programmable power supply (4 channels per device; max. electric current per channel: 10 A; max. power per channel: 160 W; total output power per device: 384 W; upper terminal voltage limit per channel: 32 V; Rohde & Schwarz GmbH & Co. KG, Munich, Germany). The electrolysis setup was purchased from IKA (IKA-Werke GmbH & Co. KG, Staufen, Germany).

Preparative column chromatography was performed using an Interchim puriFlash™ XS520Plus flash column chromatography system using pre-packed 30 μ m puriFlash™ PF-30SIHP-JP-F0080 silica columns (Interchim, Montlucon Cedex, France) using cyclohexane (CH) and ethyl acetate (EtOAc) as eluents. Some substrates were isolated using reversed-phase chromatography, for which an Interchim puriFlash™ PF-30C18HP-F0080 column was used using mixtures of water and acetonitrile (MeCN). Soda ash flux-calcinated (Celite 545, CAS: 68855-54-9) was purchased from Carl Roth GmbH + Co. KG (Karlsruhe, Germany). For filtration during work-up, folded filter papers (type 303, 5-13 μ m, medium filtration rate, cat. no. 516-0298, VWR International, Leuven, Belgium) were used.

Thin-layer chromatography (TLC) was performed using aluminium TLC plates (Supelco silica gel 60 F₂₅₄, Merck KGaA, Darmstadt, Germany) and 5 μ L micro pipettes (Blaubrand intraMARK, BRAND GmbH + CO KG, Wertheim, Germany). For staining of TLC plates, an aqueous solution of phosphomolybdic acid with cerium(IV) sulfate in sulfuric acid is recommended as a general-purpose staining solution (see general protocol GP3 for its preparation). Spots of allylic oxidation products on TLC plates were made visible using a 254 nm UV lamp (Herolab UV-4 S/L, 254 nm (4 W) + 365 nm (4 W), Herolab GmbH Laborgeräte, Wiesloch, Germany).

Nuclear magnetic resonance (NMR) spectra (¹H, ¹³C{¹H}, COSY, HSQC, HMBC) were recorded at room temperature using a Bruker Avance II 400, 400 MHz, 5 mm BBFO probe with z gradient and ATM, SampleXPress 60 sample changer (Bruker BioSpin, Ettlingen, Germany). Chemical shifts are reported in parts per million (ppm) relative to CDCl₃ (7.26 ppm in ¹H NMR spectra, 77.2 ppm in ¹³C{¹H} NMR spectra).^[3] CDCl₃ is used in all NMR measurements.

Cyclic voltammetry (CV) measurements were recorded using an Autolab PGSTAT302N (Metrohm Deutschland GmbH & Co. KG, Filderstadt, Germany). Glassy carbon was used as electrode material. The working electrode is a glassy carbon slice in a Teflon holder with a diameter of 2 mm. The counter electrode is a glassy carbon rod. Every cyclic voltammogram was referenced against ferrocene,^[4-6] and the measurement before addition of ferrocene is depicted.

High-resolution mass spectra (HRMS) were measured using a G6545A Q-ToF (Agilent GmbH, Waldbronn, Germany) with electron spray ionization (ESI). Sample injection is carried out using a 1260 Infinity II HPLC-System (Agilent GmbH, Waldbronn, Germany) with a G7111B 1260 quaternary pump, G7129A 1260 vial sampler and G7116A 1260 multicolumn thermostat.

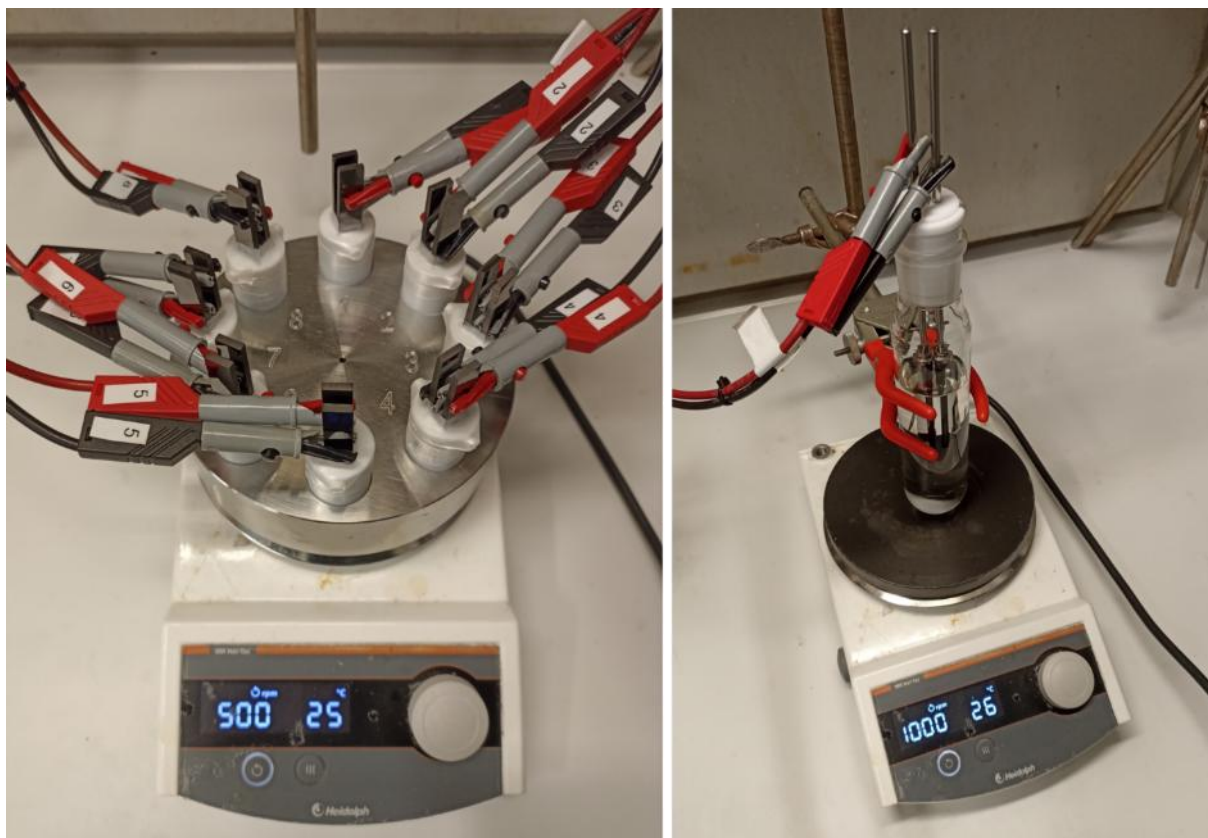


Figure S1. Electrolysis setup. **Left:** stainless steel screening block set-up with 8 small undivided Teflon cells for 5 mL reaction volume. Each Teflon cell is sealed with stretch film (Parafilm). **Right:** Scale-up reaction using two 2x6 cm glassy carbon electrodes, a Teflon electrode holder, and a 100 mL glass cell.

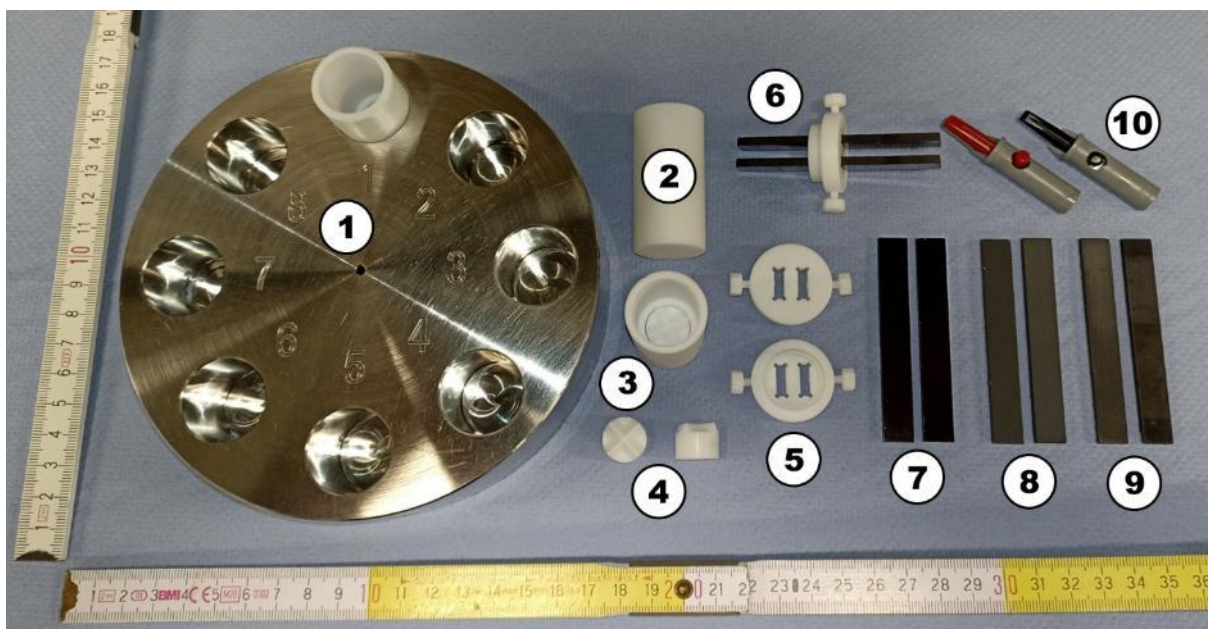


Figure S2. Electrolysis setup for screening and reaction optimization: stainless steel block with a Teflon cell placed in it (1), side view of a Teflon cell (2), top view of a Teflon cell with a stirring bar in it (3), top and side view of stirring bars (4), top and bottom view of a Teflon electrode holder (5), two glassy carbon electrodes in a Teflon electrode holder (6), glassy carbon electrodes (7), boron-doped diamond (BDD) electrodes (8), graphite electrodes (9), crocodile clips for contacting of the electrodes (10).

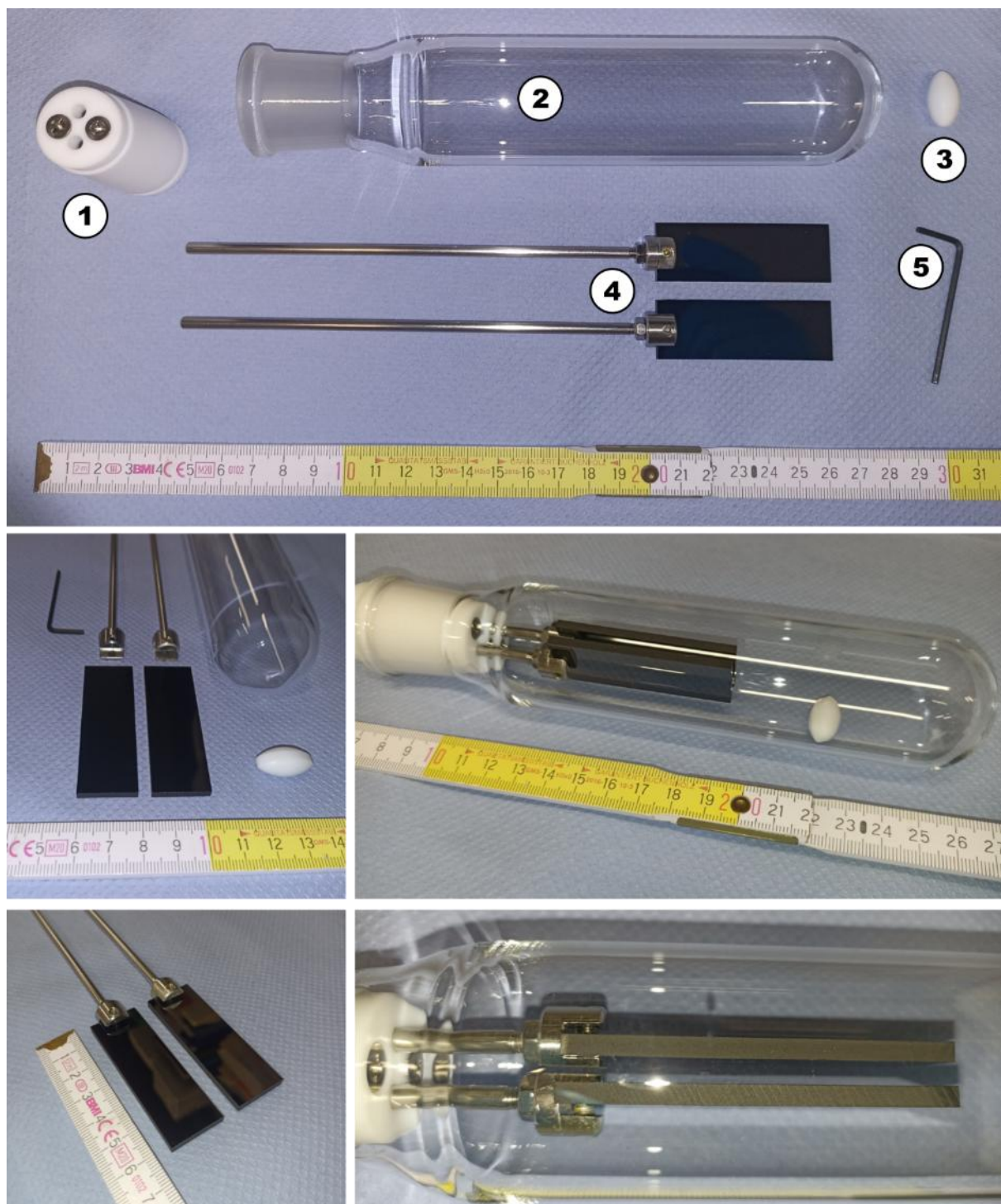


Figure S3. Electrolysis setup used for scale-up. Teflon electrode holder (1), 100 mL glass cell (2), stirring bar (3), stainless steel electrode holders with 2x6 cm glassy carbon electrodes (4), hex key for electrode holders (5). **Middle left:** electrode holders. **Middle right:** assembled cell. **Bottom left:** assembled electrodes. **Bottom right:** electrodes in the assembled cell.

2. General Protocols

GP1: General Protocol for Electrochemical Allylic Oxidation of Olefins

The starting material (0.5 mmol, 0.1 mol L⁻¹) and the supporting electrolyte NaBF₄ (109.79 g mol⁻¹, 11 mg, 0.01 mmol, 0.02 mol L⁻¹) are dissolved in acetonitrile or butanone (5.0 mL) at room temperature in a small Teflon cell under medium stirring (500 rpm). The electrodes (1.0 cm x 7.0 cm x 0.3 cm) are assembled and put into the cell so that both electrodes have an immersion depth of 2.0 cm into the reaction solution. To prevent solvent evaporation, the assembled electrolysis cell is sealed with some stretch film (Parafilm). Pyridine (2.0 equiv., 1.0 mmol, 0.08 mL, 79.10 g mol⁻¹) and *t*-BuOOH (70% aqueous solution, 3.5 equiv., 1.75 mmol, 0.24 mL, 90.12 g mol⁻¹) are added through the top of the electrode holder using a syringe. Under continued medium stirring at room temperature, the electrolysis is started (current density $j = 1.0 \text{ mA cm}^{-2}$, amount of applied charge $Q = 4 F$).

The amount of applied charge Q in Coulomb for 0.5 mmol substrate and 4 F is calculated as follows:

$$Q = 4 \cdot 96485 \cdot \frac{\text{C}}{\text{mol}} \cdot 0.5 \cdot 10^{-3} \text{ mol} = 193 \text{ C}$$

The electric current I which is to be used in electrolysis is calculated like this:

$$j = \frac{I}{A_{\text{anode}}} \Rightarrow I = j \cdot A_{\text{anode}}$$

For electrodes with a width of 1.0 cm and an immersion depth of 2.0 cm into the reaction solution this gives:

$$I = 1.0 \cdot \frac{\text{mA}}{\text{cm}^2} \cdot 1.0 \text{ cm} \cdot 2.0 \text{ cm} = 2.0 \text{ mA}$$

The electrolysis time $t_{\text{electrolysis}}$ is calculated as follows:

$$t_{\text{electrolysis}} = \frac{Q}{I} = \frac{193 \text{ C}}{2.0 \cdot 10^{-3} \text{ A}} = 96500 \text{ s} = 26 \text{ h } 48 \text{ min } 20 \text{ s}$$

To determine NMR yield, 1,3,5-trimethoxybenzene (168.19 g mol⁻¹, 1.0 mL of a stock solution of 2.1001 g in 250.0 mL MeCN, 8.4 mg, 0.05 mmol) is added after electrolysis. The reaction solution is transferred into a round bottom flask, and the solvents are removed by distillation at reduced pressure using a rotary evaporator (40°C water bath, 50 mbar, 10 min). The residue is dissolved in CDCl₃ (0.5 mL), and a ¹H NMR spectrum is measured.

To isolate the product, the reaction solution is transferred into a round bottom flask, and the solvents are removed using a rotary evaporator under reduced pressure (40°C water bath, 50 mbar, 10 min). The residue is transferred into a separatory funnel using a saturated aqueous solution of NaHCO₃ (30 mL). The round bottom flask is rinsed once with ethyl acetate (30 mL), which is also added to the separatory funnel. After mixing and separation of the ethyl acetate layer, the aqueous layer is extracted with ethyl acetate twice more (2x30 mL). The combined ethyl acetate fractions are dried over MgSO₄ (10 g), and the solution is filtered. The solvent was removed from the filtrate by distillation using a rotary evaporator at reduced pressure (40°C water bath, 50 mbar, 10 min). The crude residue is dissolved in ethyl acetate again (5 mL) and adsorbed on Celite 545 (10 g). Depending on the substrate, either cyclohexane with ethyl acetate (normal phase, linear gradient: 100:0 → 95:5 in 10 column volumes) or water and acetonitrile (reversed phase) is used for flash column chromatography.

GP2: General Protocol for Scale-up

The electrolysis is carried out in the setup depicted in Figure S3. At room temperature, cholesteryl acetate (428.70 g mol⁻¹, 4.287 g, 10.0 mmol) is dissolved in butanone (100 mL), and the supporting electrolyte NaBF₄ (109.79 g mol⁻¹, 220 mg, 2.0 mmol, 0.02 mol L⁻¹) is added. Pyridine (10 equiv.) and *t*-BuOOH (10 equiv.) are added. The glassy carbon electrodes (2.0 cm x 6.0 cm x 0.3 cm) are added with an immersion depth into the reaction solution of 4.5 cm. The electrolysis is started ($Q = 6 F$, 5789 C, $j = 10.0 \text{ mA cm}^{-2}$, $A_{\text{anode}} = 9.0 \text{ cm}^2$, $I = 90 \text{ mA}$, $t_{\text{electrolysis}} = 17 \text{ h } 52 \text{ min}$). After electrolysis, the reaction solution is transferred into a round bottom flask, and the solvents are removed at reduced pressure using a rotary evaporator (40°C water bath, 350 → 20 mbar in 45 min). To the crude residue, acetonitrile (30 mL) is added, and the solution is heated up until everything dissolved, and filtered. The filtrate is cooled to room temperature, and overnight, crystals of 7-ketocholesteryl acetate are allowed to form. The crystals are filtered off, and the purity of the reaction product is determined by ¹H NMR spectroscopy. Most of the cholesteryl acetate starting material stays dissolved in MeCN.

GP3: General Protocol for Preparation of TLC Staining Solution

Phosphomolybdic acid hydrate (2.2 g of $\text{H}_3[\text{P}(\text{Mo}_3\text{O}_{10})] \cdot x\text{H}_2\text{O}$) and cerium(VI) sulfate (2.2 g of $\text{Ce}(\text{SO}_4)_2$) are dissolved in water (200 mL). Into this, concentrated sulfuric acid (98%, 13.3 g) is added slowly under stirring. The solution is stored at room temperature in glass bottle.

GP4: General Protocol for Synthesis of Acetyl Protected Starting Materials

The starting material (10 mmol) is dissolved in pyridine (50 mL), and acetic anhydride (5 equiv.) is added. The reaction is stirred at room temperature for 24 h. After this, The solvent is removed using a rotary evaporator at reduced pressure (40°C water bath, 50 mbar, 10 min). To the residue, saturated aqueous NaHCO_3 solution (10 mL) is added, and the solution is extracted with ethyl acetate (3x50 mL). The combined ethyl acetate fractions are dried over MgSO_4 (10 g) and filtered. The crude residue is adsorbed on Celite 545 (10 g). Cyclohexane and ethyl acetate (gradient: 100:0 $\rightarrow$ 1:1 in 10 column volumes) is used for flash column chromatography.

3. Reaction Optimization

NMR yield used for reaction optimization is calculated using the following equation, where I is the integral of a peak in the ^1H NMR spectrum, and N is the number of protons corresponding to that peak. 1,3,5-Trimethoxybenzene was used as internal standard,^[7] and its three aromatic protons around 6.0 ppm are used for integration, so $N_{\text{internal standard}} = 3$.

$$\% \text{yield}_{\text{NMR}} = \frac{n_{\text{product}} \cdot 100}{n_{\text{starting material}}} = \frac{n_{\text{internal standard}} \cdot \frac{\left(\frac{I_{\text{product}}}{N_{\text{product}}}\right)}{\left(\frac{I_{\text{internal standard}}}{N_{\text{internal standard}}}\right)} \cdot 100}{\left(\frac{m_{\text{starting material}}}{M_{\text{starting material}}}\right)}$$

Conversion is calculated as follows:

$$\% \text{conversion}_{\text{NMR}} = 100 - \left(\frac{n_{\text{remaining starting material}} \cdot 100}{n_{\text{starting material}}} \right) = 100 - \frac{\frac{\left(\frac{I_{\text{remaining starting material}}}{N_{\text{remaining starting material}}}\right)}{\left(\frac{I_{\text{internal standard}}}{N_{\text{internal standard}}}\right)} \cdot 100}{\left(\frac{m_{\text{starting material}}}{M_{\text{starting material}}}\right)}$$

Selectivity is defined as yield divided by conversion:

$$\% \text{selectivity}_{\text{NMR}} = \frac{\% \text{yield}_{\text{NMR}}}{\% \text{conversion}_{\text{NMR}}}$$

The standard reaction conditions are depicted in the following Figure S4.

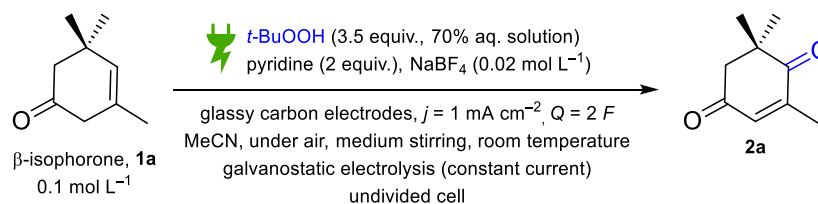


Figure S4. The standard reaction conditions.

Table S1. Data of the reaction optimization. In every reaction, 1,3,5-trimethoxybenzene (0.05 mmol) was added as internal standard. In each NMR spectrum, the signal of the internal standard is set to 3.00 (the three aromatic protons around 6.0 ppm, which means $N_{\text{internal standard}} = 3$), and all other signals are integrated relative to this. In each NMR spectrum, the product peak around 2.68 ppm ($N_{\text{product}} = 2$) was integrated. For the starting material, the peak around 5.75 ppm ($N_{\text{SM,remaining}} = 1$) was integrated. Using the data from this table, the yield, conversion, and selectivity can be calculated using the previously mentioned equations.

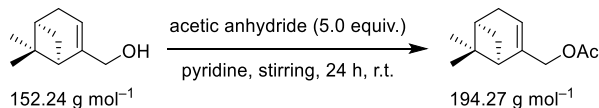
#	Deviation from standard reaction conditions ^[a]	I_{PROD}	m_{SM} [mg]	$I_{\text{SM,remaining}}$	yield% (selectivity%) ^[b]
1	none	7.54	75.4	4.00	35 (55)
2	NEt ₄ BF ₄ instead of NaBF ₄	9.12	79.9	4.01	39 (60)
3	NBu ₄ PF ₆ instead of NaBF ₄	7.30	77.0	3.78	33 (50)
4	NBu ₄ HSO ₄ instead of NaBF ₄	6.91	81.6	6.20	29 (62)
5	ethyl acetate instead of MeCN ^[c]	9.88	78.1	2.82	44 (58)
6	ethanol instead of MeCN	4.55	79.3	3.85	20 (30)
7	acetone instead of MeCN (1.8 F) ^[d]	7.97	73.7	2.66	37 (50)
8	butanone instead of MeCN	8.61	76.5	3.73	39 (59)
9	5 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F	8.01	77.1	3.35	36 (51)
10	5 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, $c(1a) = 0.2 \text{ mol L}^{-1}$	21.16	142.4	5.46	51 (70)
11	10 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, $c(1a) = 0.2 \text{ mol L}^{-1}$	25.89	145.0	5.66	62 (84)
12	10 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, $c(1a) = 0.2 \text{ mol L}^{-1}$, BDD electrodes	18.28	140.5	5.65	45 (62)
13	10 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, butanone instead of MeCN	12.81	72.0	3.29	62 (90)
14	10 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, $c(1a) = 0.3 \text{ mol L}^{-1}$, butanone instead of MeCN	33.76	208.9	9.31	56 (81)
15	10 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, $c(1a) = 0.2 \text{ mol L}^{-1}$, butanone instead of MeCN, BDD electrodes	18.13	143.7	5.10	44 (58)
16	10 equiv. pyridine, 10 equiv. t -BuOOH, 10 mA cm ⁻² , 4 F, $c(1a) = 0.2 \text{ mol L}^{-1}$, butanone instead of MeCN, graphite electrodes	20.53	143.2	6.25	49 (71)
17	no electricity	0	77.8	–	0 (–)

[a] The standard reaction conditions are depicted in Figure S4. [b] The yield and selectivity (= yield / conversion) were determined using ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. [c] The upper terminal voltage limit of the power supply was reached during electrolysis, but the desired amount of charge could be fully applied. [d] The upper terminal voltage limit of the power supply was reached during electrolysis, and only the specified amount of charge could be applied.

4. Synthesis of Non-commercially Available Starting Materials

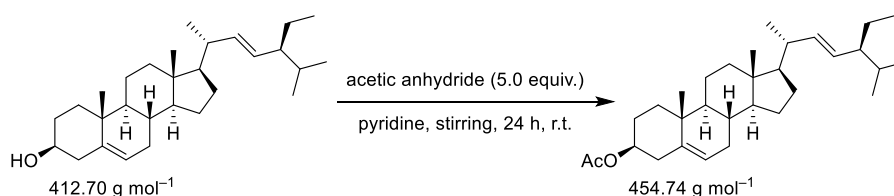
Synthesis of myrtenyl acetate

According to general protocol **GP4**, (1*R*)-myrtenol (1.539 g, 10 mmol) was employed as substrate. After workup and purification, myrtenyl acetate (1.369 g, 7.1 mmol, 71%) was obtained as colorless oil.



Synthesis of stigmasteryl acetate

According to general protocol **GP4**, stigmasterol (1.930 g, 4.7 mmol) was employed as substrate. After workup and purification, stigmasteryl acetate (2.030 g, 4.5 mmol, 95%) was obtained as colorless crystals.

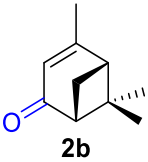
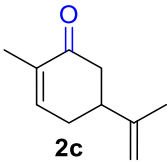
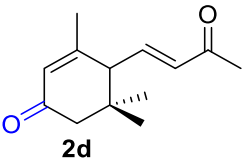
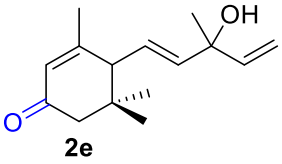
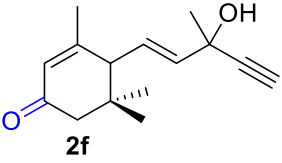


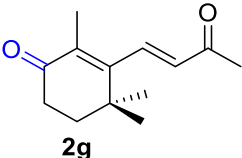
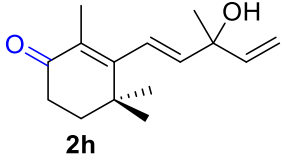
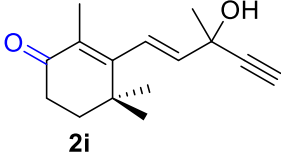
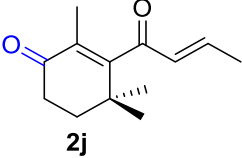
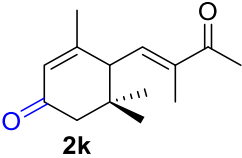
5. Analytical Data of Allylic Oxidation Products

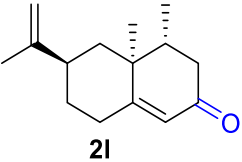
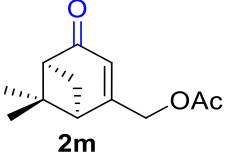
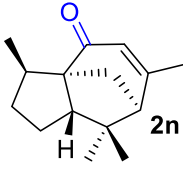
5.1. Terpenoid Substrates

The newly installed oxo functions are indicated in blue.

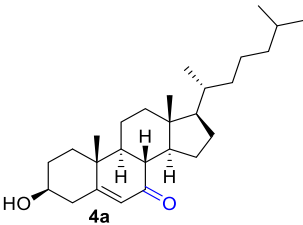
	4-Oxisophorone, 2a, C₉H₁₂O₂, CAS: 1125-21-9, <i>M</i> = 152.19 g mol⁻¹. According to general protocol GP1, β-isophorone 1a (69 mg, 0.50 mmol), was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 4 F, 1 mA cm⁻²), work up, and purification using flash column chromatography, 4-oxoisophorone 2a (43 mg, 0.28 mmol, 56%) was obtained as yellow oil. According to general protocol GP1, α-isophorone 1a' (77 mg, 0.55 mmol) was employed as substrate (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 4 F, 1 mA cm⁻²). After electrolysis, work up, and purification using flash column chromatography, 4-oxoisophorone 2a (23 mg, 0.15 mmol, 27%) was obtained as yellow oil. According to general protocol GP1, 2,6,6-trimethyl-2-cyclohexen-1-one 1a'' (82 mg, 0.59 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 4 F, 1 mA cm⁻²), work up, and purification using flash column chromatography, 4-oxoisophorone 2a (16 mg, 0.11 mmol, 18%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.55 (s, 1H), 2.71 (s, 2H), 2.00 (s, 3H), 1.24 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 203.6, 197.9, 149.1, 137.2, 52.0, 45.3, 26.2, 16.9. HRMS for C₉H₁₂O₂⁺ (ESI⁺, TOF) [M+H]⁺ : <i>m/z</i> calc. 153.0910, found 153.0912. This NMR data agrees with the data previously reported in the literature.^[8] R_f (V_{CH} / V_{EIOAc} = 4 / 1): 0.34. For reference: commercially obtained 4-oxoisophorone: ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.48 (s, 1H), 2.64 (s, 2H), 1.93 (s, 3H), 1.16 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 203.4, 197.6, 148.9, 137.0, 51.8, 45.1, 26.1, 16.8.
--	--

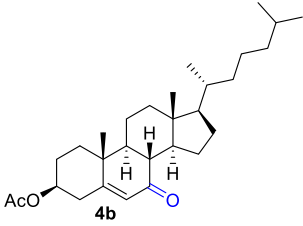
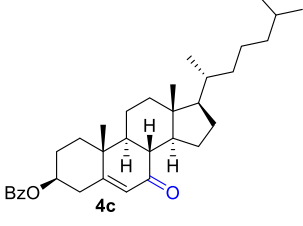
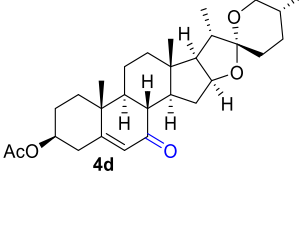
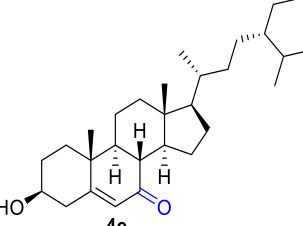
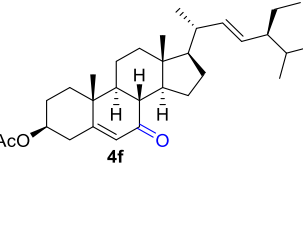
 2b	Verbenone, 2b, C₁₀H₁₄O, CAS: 18309-32-5, <i>M</i> = 150.22 g mol⁻¹. According to general protocol GP1, (+)-α-pinene 1b (74 mg, 0.54 mmol) was employed as substrate. After electrolysis (solvent: MeCN, 2 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, verbenone 2b (12 mg, 0.08 mmol, 15%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.72 (s, 1H), 2.79 (dt, <i>J</i> = 9.1, 5.5 Hz, 1H), 2.64 (td, <i>J</i> = 5.9, 1.8 Hz, 1H), 2.40 (t, <i>J</i> = 6.6 Hz, 1H), 2.07 (d, <i>J</i> = 9.2 Hz, 1H), 2.00 (d, <i>J</i> = 1.6 Hz, 3H), 1.49 (s, 3H), 1.00 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 204.2, 170.3, 121.3, 57.7, 54.2, 49.8, 41.0, 26.7, 23.7, 22.2. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 9 / 1): 0.30. This NMR data is in agreement with the data reported in literature.^[9] HRMS for C₁₀H₁₄O⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 151.1117, found 151.1110.
 2c	Carvone, 2c, C₁₀H₁₄O, CAS: 99-49-0, <i>M</i> = 150.22 g mol⁻¹. According to general protocol GP1, (+)-limonene 1c (76 mg, 0.58 mmol) was employed as substrate. After electrolysis (solvent: MeCN, 2 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, carvone 2c (10 mg, 0.11 mmol, 19%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.75 (ddd, <i>J</i> = 5.9, 2.7, 1.4 Hz, 1H), 4.78 (d, <i>J</i> = 20.8 Hz, 2H), 2.68 (ddt, <i>J</i> = 14.4, 10.4, 4.1 Hz, 1H), 2.58 (s, 1H), 2.41 (s, 1H), 2.36 – 2.30 (m, 1H), 1.78 (dt, <i>J</i> = 2.6, 1.4 Hz, 3H), 1.75 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 200.0, 146.9, 144.8, 135.6, 110.6, 43.3, 42.6, 31.4, 20.7, 15.9. This NMR data is in agreement with the data reported in literature.^[10] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 1 / 9): 0.25. HRMS for C₁₀H₁₄O⁺ (ESI⁺, TOF) [<i>M</i>]⁺: <i>m/z</i> calc. 150.1039, found 150.1032.
 2d	3-Oxo-α-ionone, 2d, C₁₃H₁₈O₂, CAS: 79734-43-3, <i>M</i> = 206.29 g mol⁻¹. According to general protocol GP1, α-ionone 1d (99 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 3-oxo-α-ionone 2d (50 mg, 0.24 mmol, 47%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.63 (dd, <i>J</i> = 15.8, 9.6 Hz, 1H), 6.14 (d, <i>J</i> = 15.8 Hz, 1H), 5.93 (s, 1H), 2.68 (d, <i>J</i> = 9.5 Hz, 1H), 2.32 (d, <i>J</i> = 16.9 Hz, 1H), 2.24 (s, 3H), 2.10 (d, <i>J</i> = 16.8 Hz, 1H), 1.85 (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 198.3, 197.6, 159.2, 143.6, 133.8, 126.9, 55.4, 47.4, 36.7, 27.9, 27.6, 27.4, 23.5. This NMR data is in agreement with the data reported in literature.^[11] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.08. HRMS for C₁₃H₁₈O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 207.1380, found 207.1380.
 2e	3-Oxo-vinyl-α-ionol, 2e, C₁₅H₂₀O₂, CAS: no CAS number found,^[2] <i>M</i> = 234.34 g mol⁻¹. According to general protocol GP1, vinyl-α-ionol 1e (115 mg, 0.52 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 3-oxo-vinyl-α-ionol 2e (46 mg, 0.20 mmol, 38%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.99 – 5.83 (m, 2H), 5.69 (d, <i>J</i> = 15.5 Hz, 1H), 5.56 (dd, <i>J</i> = 15.5, 9.2 Hz, 1H), 5.21 (d, <i>J</i> = 17.4 Hz, 1H), 5.05 (d, <i>J</i> = 10.6 Hz, 1H), 2.51 (d, <i>J</i> = 9.2 Hz, 1H), 2.31 (d, <i>J</i> = 16.8 Hz, 1H), 2.05 (d, <i>J</i> = 16.7 Hz, 2H), 1.86 (s, 3H), 1.37 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.4, 162.2, 143.9, 140.0, 125.9, 125.2, 112.5, 73.2, 55.6, 47.6, 36.3, 28.2, 28.0, 27.3, 23.6. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.06. HRMS for C₁₅H₂₂O₂⁺ (ESI⁺, TOF) [<i>M</i>+Na]⁺: <i>m/z</i> calc. 257.1512, found 257.1497.
 2f	3-Oxo-ethynyl-α-ionol, 2f, C₁₅H₂₀O₂, no CAS number found,^[2] <i>M</i> = 232.32 g mol⁻¹. According to general protocol GP1, ethynyl-α-ionol 1f (119 mg, 0.55 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 3-oxo-ethynyl-α-ionol 2f (54 mg, 0.23 mmol, 43%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.92 – 5.79 (m, 2H), 5.70 (d, <i>J</i> = 15.3 Hz, 1H), 2.53 (d, <i>J</i> = 6.9 Hz, 2H), 2.31 (d, <i>J</i> = 16.8 Hz, 1H), 2.06 (d, <i>J</i> = 16.8 Hz, 1H), 1.87 (s, 3H), 1.55 (s, 3H), 1.00 (s, 3H), 0.94 (d, <i>J</i> = 3.7 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.5, 162.0, 138.0, 126.7, 126.0, 86.1, 72.9, 67.5, 55.0, 47.5, 36.4, 30.7, 28.0, 27.2, 23.6. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.08. HRMS for C₁₅H₂₀O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 233.1536, found 233.1530.

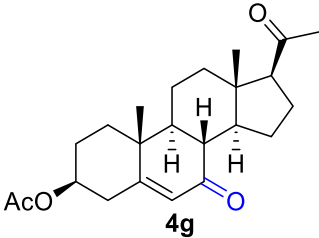
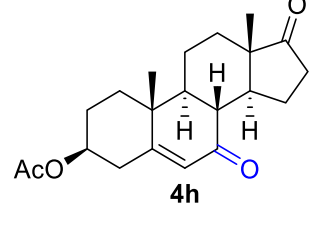
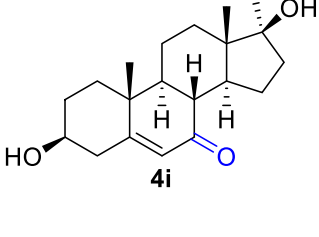
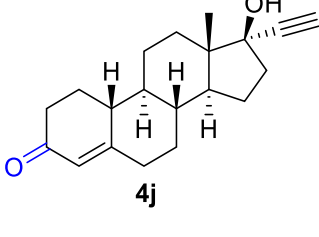
 2g	4-Oxo-β-ionone, 2g, C₁₃H₁₈O₂, CAS: 29790-29-2, <i>M</i> = 206.29 g mol⁻¹. According to general protocol GP1, β-ionone 1g (97 mg, 0.51 mmol) was employed as a substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 4-oxo-β-ionone 2g (19 mg, 0.09 mmol, 18%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 7.01 (d, <i>J</i> = 15.7 Hz, 1H), 6.28 (d, <i>J</i> = 15.6 Hz, 1H), 2.27 (s, 3H), 1.14 (s, 6H), 0.92 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 197.7, 142.8, 132.6, 70.7, 66.0, 35.6, 33.7, 29.9, 28.4, 26.0, 26.0, 21.0, 17.0. This NMR data is in agreement with the data reported in literature.^[12] R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.08. HRMS for C₁₃H₁₈O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 207.1380, found 207.1375.
 2h	4-Oxo-vinyl-β-ionol, 2h, C₁₅H₂₂O₂, no CAS number found,^[2] <i>M</i> = 234.34 g mol⁻¹. According to general protocol GP1, vinyl-β-ionol 1h (112 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 4-oxo-vinyl-β-ionol 2h (19 mg, 0.08 mmol, 16%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.26 (d, <i>J</i> = 16.3 Hz, 1H), 6.00 (dd, <i>J</i> = 17.3, 10.7 Hz, 1H), 5.71 (d, <i>J</i> = 16.3 Hz, 1H), 5.28 (d, <i>J</i> = 17.3 Hz, 1H), 5.12 (d, <i>J</i> = 10.7 Hz, 1H), 2.49 (s, 2H), 1.83 (s, 2H), 1.78 (s, 3H), 1.45 (s, 3H), 1.14 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.5, 161.1, 143.5, 141.6, 130.0, 124.2, 113.1, 73.7, 37.4, 35.7, 34.4, 28.2, 27.5, 13.5. R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.17. HRMS for C₁₅H₂₂O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 235.1693, found 235.1688.
 2i	4-Oxo-ethynyl-β-ionol, 2i, C₁₅H₂₀O₂, no CAS number found,^[2] <i>M</i> = 232.32 g mol⁻¹. According to general protocol GP1, ethynyl-β-ionol 1i (114 mg, 0.52 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 4-oxo-ethynyl-β-ionol 2i (20 mg, 0.09 mmol, 16%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.51 (dd, <i>J</i> = 16.1, 1.1 Hz, 1H), 5.72 (d, <i>J</i> = 16.1 Hz, 1H), 2.62 (s, 1H), 2.51 – 2.47 (m, 2H), 1.84 (dd, <i>J</i> = 7.4, 6.3 Hz, 2H), 1.78 (d, <i>J</i> = 1.1 Hz, 3H), 1.63 (s, 3H), 1.14 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.5, 160.2, 139.3, 130.3, 125.7, 85.6, 73.5, 67.9, 37.3, 35.7, 34.4, 30.5, 27.4, 13.4. R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.15. HRMS for C₁₅H₂₀O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 233.1536, found 233.1533.
 2j	4-Oxo-β-damascone, 2j, C₁₃H₁₈O₂, CAS: 119207-19-1, <i>M</i> = 206.29 g mol⁻¹. According to general protocol GP1, β-damascone 1j (104 mg, 0.50 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 4-oxo-β-damascone 2j (51 mg, 0.25 mmol, 46%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.72 (dq, <i>J</i> = 15.9, 6.9 Hz, 1H), 6.16 (dq, <i>J</i> = 15.9, 1.6 Hz, 1H), 2.54 (dd, <i>J</i> = 7.3, 6.3 Hz, 2H), 1.95 (dd, <i>J</i> = 6.9, 1.7 Hz, 3H), 1.90 (t, <i>J</i> = 6.8 Hz, 2H), 1.59 (s, 3H), 1.16 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.0, 198.0, 160.9, 148.2, 132.9, 129.5, 38.1, 34.8, 34.3, 27.4, 18.8, 13.2. This NMR data is in agreement with the data reported in literature.^[13] R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.43. HRMS for C₁₃H₁₈O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 207.1380, found 207.1374.
 2k	3-Oxo-α-cetone, 2k, C₁₄H₂₀O₂, CAS: 606495-56-1, <i>M</i> = 220.31 g mol⁻¹. According to general protocol GP1, α-cetone 1k (104 mg, 0.50 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5.0 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, 3-oxo-α-cetone 2k (58 mg, 0.25 mmol, 52%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.39 (dd, <i>J</i> = 11.0, 1.5 Hz, 1H), 5.93 (s, 1H), 3.05 (d, <i>J</i> = 10.9 Hz, 1H), 2.40 (d, <i>J</i> = 16.9 Hz, 1H), 2.31 (s, 3H), 2.17 (d, <i>J</i> = 16.9 Hz, 1H), 1.87 (d, <i>J</i> = 24.1 Hz, 7H), 1.07 (s, 4H), 0.94 (s, 4H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.4, 198.5, 160.6, 140.8, 139.4, 126.5, 51.9, 47.9, 37.0, 28.2, 26.7, 25.9, 23.6, 12.2. R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.10. HRMS for C₁₄H₂₀O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 221.1536, found 221.1528.

 2l	Nootkatone, 2l, C₁₅H₂₂O, CAS: 4674-50-4, <i>M</i> = 218.34 g mol⁻¹. According to general protocol GP1, (+)-valencene 1l (105 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, nootkatone 2l (23 mg, 0.11 mmol, 21%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.75 (s, 1H), 4.71 (d, <i>J</i> = 8.2 Hz, 2H), 2.50 (dddd, <i>J</i> = 15.6, 13.8, 5.1, 2.0 Hz, 1H), 2.41 – 2.16 (m, 5H), 2.05 – 1.84 (m, 4H), 1.72 (s, 4H), 1.33 (dtd, <i>J</i> = 13.9, 12.5, 4.2 Hz, 2H), 1.10 (s, 4H), 0.95 (d, <i>J</i> = 6.8 Hz, 4H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.8, 170.7, 149.2, 124.8, 109.4, 44.0, 42.2, 40.5, 40.4, 39.4, 33.1, 31.7, 20.9, 16.9, 15.0. This NMR data is in agreement with the data reported in literature.^[11] R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.36. HRMS for C₁₅H₂₂O⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 219.1743, found 219.1739.
 2m	Oxomyrtenyl acetate, 2m, C₁₂H₁₆O₃, CAS: 59555-40-7, <i>M</i> = 208.26 g mol⁻¹. According to general protocol GP1, myrtenyl acetate 1m (106 mg, 0.54 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, oxomyrtenyl acetate 2m (24 mg, 0.12 mmol, 21%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.85 (s, 1H), 4.70 (qd, <i>J</i> = 16.6, 1.9 Hz, 2H), 2.85 (dt, <i>J</i> = 9.3, 5.5 Hz, 1H), 2.67 (td, <i>J</i> = 5.8, 1.8 Hz, 1H), 2.42 (td, <i>J</i> = 5.8, 1.5 Hz, 1H), 2.11 (s, 3H), 1.50 (s, 3H), 0.99 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 203.1, 170.3, 165.8, 119.6, 64.2, 58.3, 54.4, 45.5, 40.9, 26.6, 22.2, 20.7. This NMR data is in agreement with the data reported in literature.^[14] R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.17. HRMS for C₁₂H₁₆O₃⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 209.1172, found 209.1168.
 2n	Cedrenone, 2n, C₁₅H₂₂O, CAS: 30960-39-5, <i>M</i> = 218.34 g mol⁻¹. According to general protocol GP1, (-)-α-cedrene 1n (104.8 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 5 equiv. pyridine, 3.5 equiv. <i>t</i>-BuOOH, 1 mA cm⁻², 4 <i>F</i>), workup, and purification using flash column chromatography, cedrenone 2p (22 mg, 0.10 mmol, 20%) was obtained as yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.63 (s, 1H), 2.32 (d, <i>J</i> = 3.9 Hz, 1H), 2.01 – 1.88 (m, 6H), 1.75 (d, <i>J</i> = 4.1 Hz, 5H), 1.54 – 1.42 (m, 1H), 1.30 (d, <i>J</i> = 6.9 Hz, 3H), 1.13 (s, 3H), 1.00 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 204.0, 165.6, 125.8, 65.8, 59.3, 58.4, 45.0, 44.2, 42.7, 39.6, 28.1, 27.3, 26.8, 25.4, 15.4. This NMR data is in agreement with the data reported in literature.^[11] R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.40. HRMS for C₁₅H₂₂O⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 219.1743, found 219.1742.

5.2. Steroidal Substrates

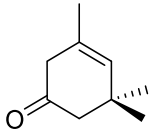
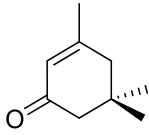
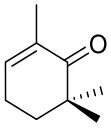
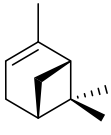
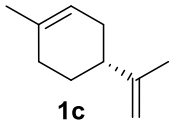
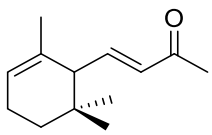
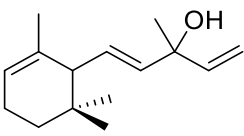
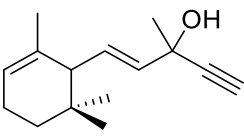
 4a	7-Ketocholesterol, 4a, C₂₇H₄₄O₂, CAS: 566-28-9, <i>M</i> = 400.65 g mol⁻¹. According to general protocol GP1, cholesterol 3a (195 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using reversed-phase flash column chromatography, 7-ketocholesterol 4a (126 mg, 0.32 mmol, 63%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.65 – 5.54 (m, 1H), 3.57 (s, 2H), 2.49 – 2.09 (m, 7H), 2.04 – 1.67 (m, 10H), 1.64 – 0.71 (m, 68H), 0.61 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.6, 166.1, 125.8, 77.4, 70.1, 54.8, 50.0, 49.9, 45.3, 43.1, 41.8, 39.4, 38.7, 38.3, 36.4, 36.2, 35.7, 31.0, 28.5, 27.9, 26.3, 23.8, 22.8, 22.6, 21.2, 18.9, 17.3, 11.9. This NMR data is in agreement with the data reported in literature.^[15] R_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 1 / 1): 0.50. HRMS for C₂₇H₄₄O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺: <i>m/z</i> calc. 401.3414, found 401.3401.
--	--

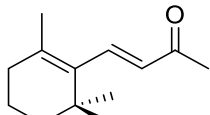
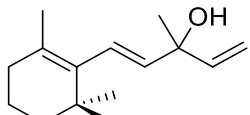
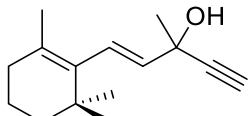
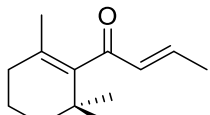
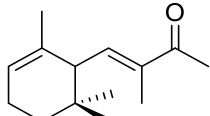
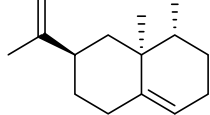
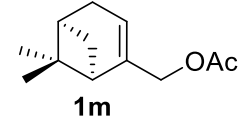
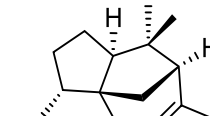
 4b	7-Ketocholesteryl acetate, 4b, C₂₉H₄₆O₃, CAS: 809-51-8, <i>M</i> = 442.68 g mol⁻¹. According to general protocol GP1, cholesteryl acetate 3b (214 mg, 0.50 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketocholesteryl acetate 4b (148 mg, 0.33 mmol, 67%) was obtained as yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.70 (d, <i>J</i> = 1.8 Hz, 1H), 4.71 (s, 1H), 2.59 – 2.34 (m, 3H), 2.28 – 2.18 (m, 1H), 2.05 (s, 3H), 2.03 – 1.84 (m, 5H), 1.76 – 1.22 (m, 16H), 1.20 (s, 3H), 1.18 – 0.95 (m, 9H), 0.91 (d, <i>J</i> = 6.5 Hz, 3H), 0.86 (dd, <i>J</i> = 6.6, 2.0 Hz, 8H), 0.68 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.1, 170.4, 164.0, 126.8, 72.4, 54.9, 50.1, 49.9, 45.5, 43.2, 39.6, 38.8, 38.4, 37.9, 36.3, 36.1, 35.9, 28.7, 28.1, 27.5, 26.4, 24.0, 22.9, 22.7, 21.4, 21.3, 19.0, 17.4, 12.1. This NMR data is in agreement with the data reported in literature.^[11] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 4 / 1): 0.47. HRMS for C₂₇H₄₂O⁺ (ESI⁺, TOF) [<i>M</i>+<i>H</i>]⁺: <i>m/z</i> calc. 383.3308, found 383.3304.
 4c	7-Ketocholesteryl benzoate, 4c, C₃₄H₄₈O₃, CAS: 6997-41-7, <i>M</i> = 504.76 g mol⁻¹. According to general protocol GP1, cholesteryl benzoate 3c (251 mg, 0.53 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketocholesteryl benzoate 4c (68 mg, 0.14 mmol, 26%) was obtained as yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 8.04 (d, <i>J</i> = 7.0 Hz, 2H), 7.57 (t, <i>J</i> = 7.4 Hz, 1H), 7.44 (t, <i>J</i> = 7.7 Hz, 2H), 5.75 (d, <i>J</i> = 1.7 Hz, 1H), 4.97 (tt, <i>J</i> = 11.3, 4.9 Hz, 1H), 1.25 (d, <i>J</i> = 3.0 Hz, 36H), 0.86 (dd, <i>J</i> = 6.6, 1.9 Hz, 9H), 0.69 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.2, 165.9, 164.0, 133.2, 130.4, 129.7, 128.5, 127.0, 72.9, 54.9, 50.1, 50.0, 45.6, 43.3, 39.6, 38.8, 38.5, 38.0, 36.3, 36.2, 35.9, 29.8, 28.7, 28.1, 27.6, 27.1, 26.5, 24.0, 23.0, 22.7, 21.3, 19.0, 17.5, 12.1. This NMR data is in agreement with the data reported in literature.^[11] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 4 / 1): 0.68. HRMS for C₂₅H₄₄O⁺ (ESI⁺, TOF) [<i>M</i>+<i>Na</i>]⁺: <i>m/z</i> calc. 383.3308, found 383.3301.
 4d	7-Ketodiosgenin acetate, 4d, C₂₉H₄₂O₅, CAS: 30155-20-5, <i>M</i> = 470.64 g mol⁻¹. According to general protocol GP1, diosgenin acetate 3d (230 mg, 0.54 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketodiosgenin acetate 4d (113 mg, 0.24 mmol, 45%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.69 (d, <i>J</i> = 1.8 Hz, 1H), 4.80 – 4.27 (m, 4H), 3.51 – 3.22 (m, 5H), 2.93 – 2.77 (m, 2H), 2.65 – 2.19 (m, 8H), 2.03 (s, 13H), 1.21 (s, 7H), 0.77 (d, <i>J</i> = 2.1 Hz, 13H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 201.5, 170.4, 164.2, 126.6, 109.3, 81.0, 72.3, 66.9, 61.2, 49.8, 49.6, 45.0, 41.7, 41.1, 38.8, 38.6, 37.9, 36.1, 33.8, 31.6, 30.4, 28.9, 27.4, 21.4, 21.0, 17.4, 17.2, 16.5, 14.8. This NMR data is in agreement with the data reported in literature.^[11] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.90. HRMS for C₂₉H₄₂O₅⁺ (ESI⁺, TOF) [<i>M</i>+<i>H</i>]⁺: <i>m/z</i> calc. 471.3105, found 471.3098.
 4e	7-Keto-β-sitosterol, 4e, C₂₉H₄₈O₂, CAS: 2034-74-4, <i>M</i> = 428.70 g mol⁻¹. According to general protocol GP1, β-sitosterol 3e (217 mg, 0.52 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-keto-β-sitosterol 4e (101 mg, 0.24 mmol, 45%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.68 (d, <i>J</i> = 1.8 Hz, 1H), 3.66 (td, <i>J</i> = 11.2, 5.6 Hz, 1H), 2.57 – 1.75 (m, 15H), 1.71 – 1.43 (m, 9H), 1.19 (s, 28H), 0.92 (d, <i>J</i> = 6.4 Hz, 7H), 0.87 – 0.72 (m, 15H), 0.67 (s, 4H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.6, 165.4, 126.2, 70.6, 54.8, 50.1, 50.0, 45.9, 45.5, 43.2, 41.9, 38.8, 38.4, 36.5, 36.2, 34.1, 31.3, 29.2, 28.7, 26.5, 26.2, 23.2, 21.3, 19.9, 19.2, 19.1, 17.4, 12.1. This NMR data is in agreement with the data reported in literature.^[16] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.45. HRMS for C₂₉H₄₈O₂⁺ (ESI⁺, TOF) [<i>M</i>+<i>H</i>]⁺: <i>m/z</i> calc. 429.3727, found 429.3722.
 4f	7-Ketostigmasteryl acetate, 4f, C₃₁H₄₈O₃, CAS: 33028-07-8, <i>M</i> = 468.71 g mol⁻¹. According to general protocol GP1, stigmasteryl acetate 3f (231 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketostigmasteryl acetate 4f (190 mg, 0.41 mmol, 80%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.69 (d, <i>J</i> = 1.8 Hz, 1H), 5.17 (dd, <i>J</i> = 15.2, 8.6 Hz, 1H), 5.01 (dd, <i>J</i> = 15.2, 8.7 Hz, 1H), 4.77 – 4.64 (m, 1H), 2.60 – 2.32 (m, 4H), 2.23 (t, <i>J</i> = 11.1 Hz, 1H), 2.05 (s, 9H), 1.82 – 0.73 (m, 45H), 0.69 (s, 5H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.0, 170.4, 164.0, 138.2, 129.6, 126.8, 72.3, 54.8, 51.3, 50.1, 49.9, 45.5, 43.1, 40.4, 38.7, 38.5, 37.9, 36.1, 32.0, 29.2, 27.5, 26.5, 25.5, 21.6, 21.4, 21.3, 21.2, 19.1, 17.4, 12.4, 12.3. This NMR data is in agreement with the data reported in literature.^[17] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.95. HRMS for C₃₁H₄₈O₃⁺ (ESI⁺, TOF) [<i>M</i>+<i>H</i>]⁺: <i>m/z</i> calc. 469.3676, found 469.3653.

	7-Ketopregnenolone acetate, 4g, C₂₃H₃₂O₄, CAS: 6748-09-0, <i>M</i> = 372.51 g mol⁻¹. According to general protocol GP1, pregnenolone acetate 3g (186 mg, 0.52 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketopregnenolone acetate 4g (117 mg, 0.31 mmol, 61%) was obtained as colorless solid ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.68 (s, 1H), 4.68 (s, 1H), 2.45 (s, 4H), 2.27 – 2.19 (m, 1H), 2.06 (d, <i>J</i> = 31.1 Hz, 12H), 1.82 – 1.20 (m, 11H), 1.18 (s, 3H), 0.62 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 209.7, 201.2, 170.3, 164.2, 126.5, 72.1, 62.3, 50.0, 49.7, 45.3, 44.4, 38.4, 37.8, 37.7, 36.1, 31.7, 27.4, 26.5, 23.6, 21.3, 21.1, 17.3, 13.3. This NMR data is in agreement with the data reported in literature.^[11] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.75. HRMS for C₂₃H₃₂O₄⁺ (ESI⁺, TOF) [<i>M</i>+NH₄]⁺ : <i>m/z</i> calc. 390.2639, found 390.2643.
	7-Ketodehydroepiandrosterone acetate, 4h, C₂₁H₂₈O₄, CAS: 1449-61-2, <i>M</i> = 344.45 g mol⁻¹. According to general protocol GP1, dehydroepiandrosterone acetate (DHEA acetate) 3h (165 mg, 0.50 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketodehydroepiandrosterone acetate 4h (115 mg, 0.33 mmol, 67%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.69 (s, 1H), 4.66 (td, <i>J</i> = 11.6, 5.6 Hz, 1H), 2.80 – 2.70 (m, 1H), 2.58 – 2.30 (m, 4H), 1.99 (s, 7H), 1.83 – 1.45 (m, 8H), 1.18 (s, 5H), 0.83 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 220.1, 200.7, 170.2, 164.8, 126.5, 71.9, 49.9, 47.8, 45.7, 44.3, 38.4, 37.8, 35.9, 35.6, 30.7, 27.3, 24.1, 21.2, 20.5, 17.4, 13.7. This NMR data is in agreement with the data reported in literature.^[11] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.70. HRMS for C₂₁H₂₈O₄⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 345.2060, found 345.2045.
	7-Ketomethandriol, 4i, C₂₀H₃₀O₃, CAS: 115248-77-6, <i>M</i> = 318.46 g mol⁻¹. According to general protocol GP1, methandriol (methylandrostenediol) 3i (156 mg, 0.51 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, 7-ketomethandriol 4i (52 mg, 0.16 mmol, 32%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.65 (s, 1H), 3.70 – 3.52 (m, 1H), 2.54 – 2.21 (m, 5H), 2.10 – 1.30 (m, 16H), 1.18 (d, <i>J</i> = 3.8 Hz, 11H), 1.01 (d, <i>J</i> = 27.3 Hz, 1H), 0.83 (s, 4H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.4, 166.1, 125.8, 81.0, 77.4, 70.3, 49.9, 46.2, 45.9, 44.4, 42.0, 39.0, 38.5, 36.5, 31.1, 30.8, 25.7, 20.9, 17.4, 14.1. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.18. HRMS for C₂₀H₃₀O₃⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 319.2268, found 319.2265.
	Norethisterone (3-ketolynestrenol), 4j, C₂₀H₂₆O₂, CAS: 68-22-4, <i>M</i> = 298.40 g mol⁻¹. According to general protocol GP1, lynestrenol 3j (151 mg, 0.53 mmol) was employed as substrate. After electrolysis (solvent: butanone, 10 equiv. pyridine, 10 equiv. <i>t</i>-BuOOH, 10 mA cm⁻², 6 <i>F</i>), workup, and purification using flash column chromatography, norethisterone 4j (26 mg, 0.09 mmol, 17%) was obtained as colorless solid. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.82 (s, 1H), 2.56 (s, 1H), 2.51 – 1.45 (m, 21H), 1.42 – 1.18 (m, 5H), 1.07 (tdd, <i>J</i> = 13.3, 11.6, 4.0 Hz, 1H), 0.89 (s, 5H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 200.1, 166.8, 124.7, 87.4, 79.7, 74.2, 49.2, 49.2, 47.0, 42.6, 41.1, 38.9, 36.6, 35.6, 32.5, 30.8, 26.7, 26.3, 23.0, 12.8. This NMR data is in agreement with the data reported in literature.^[18] <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.75. HRMS for C₂₀H₂₆O₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 299.2006, found 299.2001.

6. Analytical Data of Starting Materials

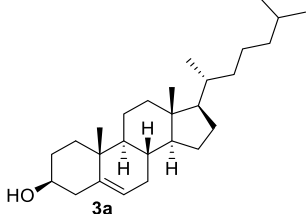
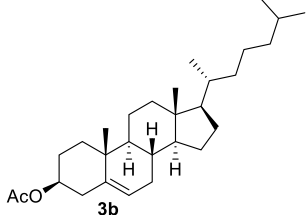
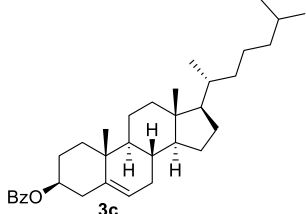
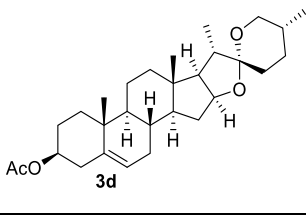
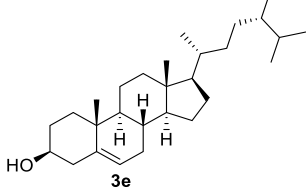
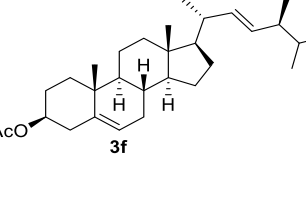
6.1. Terpenoid Substrates

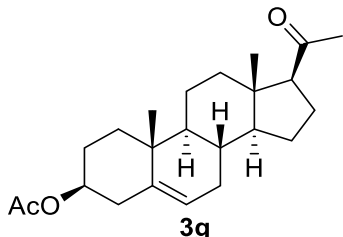
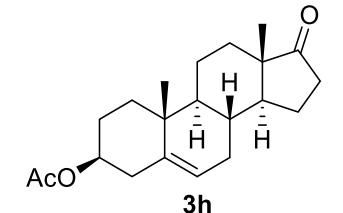
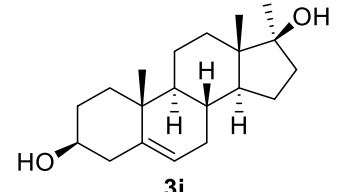
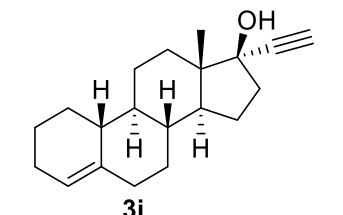
 1a	β-Isophorone, 1a, C₉H₁₄O, CAS: 471-01-2, <i>M</i> = 138.21 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.72 (s, 1H), 2.04 (s, 4H), 1.80 (s, 3H), 0.89 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.7, 160.3, 125.2, 50.6, 45.0, 33.4, 28.1, 24.4. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.14.
 1a'	α-Isophorone, 1a', C₉H₁₄O, CAS: 78-59-1, <i>M</i> = 138.21 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.74 (s, 1H), 2.06 (s, 4H), 1.81 (s, 3H), 0.91 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.7, 160.3, 125.3, 50.6, 45.1, 33.4, 28.2, 24.4. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 9 / 1): 0.25.
 1a''	2,6,6-Trimethyl-2-cyclohexen-1-one, 1a'', C₉H₁₄O, CAS: 20013-73-4, <i>M</i> = 138.21 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.37 (s, 1H), 2.06 (dtq, <i>J</i> = 8.2, 4.0, 2.0 Hz, 2H), 1.54 (t, <i>J</i> = 6.1 Hz, 2H), 1.47 (q, <i>J</i> = 1.8 Hz, 3H), 0.81 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 203.9, 143.1, 133.2, 40.7, 36.3, 23.9, 22.6, 16.0. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 9 / 1): 0.20.
 1b	(+)-α-Pinene, 1b, C₁₀H₁₆, CAS: 7785-70-8, <i>M</i> = 136.23 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.22 (dt, <i>J</i> = 3.1, 1.5 Hz, 1H), 2.37 (dt, <i>J</i> = 8.5, 5.6 Hz, 1H), 2.32 – 2.15 (m, 2H), 2.10 (tt, <i>J</i> = 5.9, 2.9, 1.3 Hz, 1H), 1.97 (td, <i>J</i> = 5.8, 1.5 Hz, 1H), 1.69 (q, <i>J</i> = 2.1 Hz, 3H), 1.30 (s, 3H), 1.20 (d, <i>J</i> = 8.5 Hz, 1H), 0.88 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 144.6, 116.3, 47.3, 41.0, 38.2, 31.7, 31.5, 26.6, 23.2, 21.0. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 9 / 1): 0.58.
 1c	(+)-Limonene, 1c, C₁₀H₁₆, CAS: 5989-27-5, <i>M</i> = 136.23 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.41 (s, 1H), 4.72 (s, 2H), 2.17 – 1.85 (m, 5H), 1.81 (ddq, <i>J</i> = 12.7, 4.9, 2.3 Hz, 1H), 1.74 (s, 3H), 1.66 (s, 3H), 1.56 – 1.42 (m, 1H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 150.3, 133.8, 120.8, 108.5, 41.2, 31.0, 30.7, 28.1, 23.6, 20.9. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 9 / 1): 0.60.
 1d	α-Ionone, 1d, C₁₃H₂₀O, CAS: 127-41-3, <i>M</i> = 192.30 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.55 (dd, <i>J</i> = 15.8, 9.7 Hz, 1H), 5.98 (d, <i>J</i> = 16.6 Hz, 1H), 5.43 (s, 1H), 2.26 – 2.20 (m, 1H), 2.19 (s, 3H), 1.98 (dq, <i>J</i> = 11.3, 4.0, 2.1 Hz, 2H), 1.50 (q, <i>J</i> = 1.9 Hz, 3H), 1.39 (dt, <i>J</i> = 13.4, 8.0 Hz, 1H), 1.16 (dt, <i>J</i> = 13.5, 4.4 Hz, 1H), 0.86 (s, 3H), 0.79 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 198.4, 149.0, 132.3, 131.9, 122.6, 54.2, 32.5, 31.2, 27.8, 26.9, 26.8, 23.0, 22.8. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.62.
 1e	Vinyl-α-ionol, 1e, C₁₅H₂₄O, CAS: 352199-94-1, <i>M</i> = 220.35 g mol⁻¹, provided by dsm-firmenich. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.93 (ddd, <i>J</i> = 17.4, 10.6, 2.0 Hz, 1H), 5.51 (s, 1H), 5.46 – 5.32 (m, 2H), 5.19 (dd, <i>J</i> = 17.3, 1.3 Hz, 1H), 5.00 (dd, <i>J</i> = 10.6, 1.3 Hz, 1H), 2.07 (d, <i>J</i> = 9.3 Hz, 1H), 1.96 (s, 3H), 1.54 (s, 3H), 1.39 (dt, <i>J</i> = 13.3, 8.1 Hz, 1H), 1.34 (s, 3H), 1.17 – 1.09 (m, 1H), 0.85 (s, 3H), 0.78 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 144.5, 137.3, 134.1, 129.5, 121.0, 111.9, 73.3, 54.0, 32.1, 31.6, 28.1, 27.7, 27.0, 23.1, 23.0. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.42. HRMS for C₁₅H₂₂O⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 221.1900, found 221.1889.
 1f	Ethynyl-α-ionol, 1f, C₁₅H₂₂O, no CAS number found, <i>M</i> = 218.34 g mol⁻¹, provided by dsm-firmenich. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.75 (ddd, <i>J</i> = 15.3, 9.5, 1.8 Hz, 1H), 5.59 – 5.51 (m, 1H), 5.39 (s, 1H), 2.52 (s, 1H), 2.10 (d, <i>J</i> = 9.5 Hz, 1H), 1.97 (ddq, <i>J</i> = 7.4, 3.7, 1.8 Hz, 2H), 1.54 (dd, <i>J</i> = 6.1, 2.3 Hz, 7H), 1.41 (dt, <i>J</i> = 13.2, 8.0 Hz, 1H), 1.15 (dt, <i>J</i> = 13.3, 5.0 Hz, 1H), 0.87 (s, 3H), 0.80 (d, <i>J</i> = 5.2 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 135.3, 133.7, 131.2, 121.3, 86.6, 72.5, 67.9, 53.5, 32.2, 31.6, 30.6, 27.6, 27.5, 27.0, 23.1. <i>R_f</i> (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.40. HRMS for C₁₅H₂₂O⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 201.1638, found 201.1626.

 1g	β-Ionone, 1g, C₁₃H₂₀O, CAS: 79-77-6, <i>M</i> = 192.30 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 7.11 (d, <i>J</i> = 16.4 Hz, 1H), 5.95 (d, <i>J</i> = 16.4 Hz, 1H), 2.12 (s, 3H), 1.90 (t, <i>J</i> = 6.3 Hz, 2H), 1.60 (s, 3H), 1.50 – 1.42 (m, 2H), 1.35 – 1.29 (m, 2H), 0.91 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 198.1, 142.7, 135.7, 131.3, 39.5, 33.8, 33.3, 28.5, 26.9, 21.5, 18.7. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.47.
 1h	Vinyl-β-ionol, 1h, C₁₅H₂₄O, CAS: 5208-93-5, <i>M</i> = 220.35 g mol⁻¹, provided by dsm-firmenich. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.05 (dd, <i>J</i> = 16.2, 1.1 Hz, 1H), 5.98 (dd, <i>J</i> = 17.4, 10.6 Hz, 1H), 5.51 (d, <i>J</i> = 16.2 Hz, 1H), 5.24 (dd, <i>J</i> = 17.3, 1.2 Hz, 1H), 5.04 (dd, <i>J</i> = 10.6, 1.2 Hz, 1H), 1.94 (t, <i>J</i> = 6.4 Hz, 3H), 1.63 (d, <i>J</i> = 1.0 Hz, 3H), 1.61 – 1.54 (m, 2H), 1.45 – 1.40 (m, 2H), 1.39 (s, 3H), 0.96 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 144.3, 139.0, 136.9, 128.4, 125.8, 112.1, 73.7, 39.4, 34.1, 32.7, 28.8, 28.1, 21.4, 19.3. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.45. HRMS for C₁₅H₂₂⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 203.1794, found 203.1786.
 1i	Ethynyl-β-ionol, 1i, C₁₅H₂₂O, no CAS number found, 218.34 g mol⁻¹, provided by dsm-firmenich. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.41 (dd, <i>J</i> = 15.9, 1.1 Hz, 1H), 5.55 (d, <i>J</i> = 15.9 Hz, 1H), 2.58 (s, 1H), 2.00 – 1.93 (m, 2H), 1.66 (d, <i>J</i> = 1.1 Hz, 3H), 1.60 (s, 6H), 1.48 – 1.41 (m, 2H), 0.99 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 136.7, 136.3, 129.3, 127.7, 86.4, 72.9, 68.3, 39.5, 34.2, 32.8, 30.5, 28.8, 28.8, 21.4, 19.3. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.45. HRMS for C₁₅H₂₂O⁺ (ESI⁺, TOF) [<i>M</i>+H]⁺ : <i>m/z</i> calc. 219.1743, found 219.1738.
 1j	β-Damascone, 1j, C₁₃H₂₀O, CAS: 35044-68-9, 192.30 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.69 (dq, <i>J</i> = 15.7, 6.9 Hz, 1H), 6.11 (dd, <i>J</i> = 15.7, 1.7 Hz, 1H), 1.95 (t, <i>J</i> = 6.9 Hz, 2H), 1.88 (dd, <i>J</i> = 6.9, 1.7 Hz, 3H), 1.66 (s, 2H), 1.48 (s, 3H), 1.46 – 1.40 (m, 2H), 0.99 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 202.3, 145.9, 140.3, 134.7, 130.5, 38.9, 33.5, 31.2, 28.9, 21.4, 19.0, 18.4. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.73.
 1k	α-Cetone, 1k, C₁₄H₂₂O, CAS: 127-51-5, <i>M</i> = 206.32 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 6.34 (dd, <i>J</i> = 11.1, 1.4 Hz, 1H), 5.39 (s, 1H), 2.59 (d, <i>J</i> = 11.1 Hz, 1H), 2.24 (s, 3H), 2.00 (s, 2H), 1.78 (d, <i>J</i> = 1.5 Hz, 3H), 1.47 (d, <i>J</i> = 2.0 Hz, 4H), 1.24 – 1.15 (m, 1H), 0.87 (s, 3H), 0.76 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 199.9, 145.0, 137.9, 133.2, 122.0, 50.2, 32.8, 31.8, 27.2, 27.0, 25.6, 23.0, 22.8, 11.7. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.73.
 1l	(+)-Valencene, 1l, C₁₅H₂₄, CAS: 4630-07-3, <i>M</i> = 204.35 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.33 (m, 1H), 4.69 (s, 2H), 2.45 – 2.15 (m, 3H), 2.15 – 1.80 (m, 6H), 1.80 – 1.65 (m, 6H), 1.65 – 1.50 (m, 1H), 1.50 – 1.30 (m, 4H), 1.30 – 1.05 (m, 2H), 1.05 – 0.80 (m, 8H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 150.8, 143.2, 120.3, 108.4, 45.1, 41.2, 41.1, 38.0, 33.3, 32.8, 27.3, 26.1, 21.0, 18.6, 15.8. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.89.
 1m	(1<i>R</i>)-Myrtenyl acetate, 1m, C₁₂H₁₈O₂, CAS: 35670-93-0, <i>M</i> = 194.27 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.51 (m, 1H), 4.40 (q, <i>J</i> = 12.6 Hz, 2H), 2.35 (dt, <i>J</i> = 8.7, 5.6 Hz, 1H), 2.31 – 2.14 (m, 2H), 2.06 (dd, <i>J</i> = 5.6, 1.6 Hz, 2H), 2.00 (s, 3H), 1.24 (s, 3H), 1.13 (d, <i>J</i> = 8.7 Hz, 1H), 0.77 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 171.1, 143.0, 121.4, 67.1, 43.6, 40.7, 38.0, 31.5, 31.3, 26.1, 21.0, 21.0. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.71.
 1n	(-)-α-Cedrene, 1n, C₁₅H₂₄, CAS: 469-61-4, <i>M</i> = 204.35 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.23 (s, 1H), 2.21 – 2.14 (m, 1H), 1.9 – 1.5 (m, 10H), 1.44 – 1.32 (m, 3H), 1.03 (s, 3H), 0.96 (s, 3H), 0.85 (d, <i>J</i> = 7.2 Hz, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 140.7, 119.4, 59.1, 55.0, 54.0, 48.3, 41.6, 40.8, 39.0, 36.2, 27.8, 25.7, 25.0, 24.9, 15.6. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EIOAc} = 4 / 1): 0.93.

6.2. Steroidal Substrates

The steroid-derived starting materials are numbered **3a** to **3j**, and the corresponding allylic oxidation products **4a** to **4j**.

 3a	Cholesterol, 3a, C₂₇H₄₈O, CAS: 57-88-5, <i>M</i> = 386.70 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.32 (d, <i>J</i> = 5.5 Hz, 1H), 3.57 – 3.41 (m, 1H), 2.33 – 2.16 (m, 2H), 2.14 (s, 1H), 1.97 (m, 2H), 1.81 (m, 3H), 1.61 – 1.02 (m, 19H), 0.99 (s, 5H), 0.90 (d, <i>J</i> = 6.5 Hz, 4H), 0.85 (dd, <i>J</i> = 6.6, 1.8 Hz, 6H), 0.66 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 140.9, 121.7, 71.8, 56.9, 56.3, 50.2, 42.4, 39.9, 39.6, 37.4, 36.6, 36.3, 35.9, 32.0, 31.7, 28.3, 28.1, 24.4, 24.0, 22.9, 22.7, 21.2, 19.5, 18.8, 12.0. <i>R_f</i> (V_{CH} / V_{EtOAc} = 4 / 1): 0.34.
 3b	Cholesteryl acetate, 3b, C₂₉H₄₈O₂, CAS: 604-35-3, <i>M</i> = 428.70 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.33 (s, 1H), 4.57 (s, 1H), 2.29 (s, 2H), 1.98 (s, 4H), 1.86 – 1.74 (m, 3H), 0.98 (s, 25H), 0.88 (d, <i>J</i> = 6.5 Hz, 3H), 0.83 (dd, <i>J</i> = 6.6, 1.8 Hz, 6H), 0.64 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 170.3, 139.6, 122.6, 73.9, 56.7, 56.2, 50.1, 42.3, 39.8, 39.6, 38.2, 37.1, 36.6, 36.3, 35.9, 31.9, 31.9, 28.3, 28.0, 27.8, 24.3, 23.9, 22.9, 22.6, 21.4, 21.1, 19.3, 18.8, 11.9. <i>R_f</i> (V_{CH} / V_{EtOAc} = 98 / 2): 0.19.
 3c	Cholesteryl benzoate, 3c, C₃₄H₅₀O₂, CAS: 604-32-0, <i>M</i> = 490.80 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 8.05 (d, <i>J</i> = 7.0 Hz, 2H), 7.54 (t, <i>J</i> = 7.4 Hz, 1H), 7.43 (t, <i>J</i> = 7.6 Hz, 2H), 5.43 (d, <i>J</i> = 2.8 Hz, 1H), 4.87 (ddt, <i>J</i> = 16.3, 8.2, 4.5 Hz, 1H), 2.47 (d, <i>J</i> = 7.0 Hz, 2H), 2.08 – 1.08 (m, 24H), 1.07 (s, 3H), 1.06 – 0.95 (m, 4H), 0.93 (d, <i>J</i> = 6.5 Hz, 3H), 0.88 (dd, <i>J</i> = 6.6, 1.8 Hz, 6H), 0.70 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 166.1, 139.8, 132.8, 131.0, 129.7, 128.4, 122.9, 74.7, 56.8, 56.3, 50.2, 42.5, 39.9, 39.7, 38.4, 37.2, 36.8, 36.3, 35.9, 32.1, 32.0, 28.4, 28.2, 28.0, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0. <i>R_f</i> (V_{CH} / V_{EtOAc} = 98 / 2): 0.38.
 3d	Diosgenin acetate, 3d, C₂₉H₄₄O₄, CAS: 1061-54-7, <i>M</i> = 456.70 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.36 (d, <i>J</i> = 5.2 Hz, 1H), 4.66 – 4.51 (m, 1H), 4.39 (q, <i>J</i> = 7.6 Hz, 1H), 3.46 (m, 1H), 3.36 (t, <i>J</i> = 10.9 Hz, 1H), 2.36 – 2.24 (m, 2H), 2.02 (s, 3H), 1.02 (s, 3H), 0.96 (d, <i>J</i> = 6.9 Hz, 4H), 0.77 (t, <i>J</i> = 3.2 Hz, 6H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 170.6, 139.8, 122.5, 109.4, 80.9z, 74.0, 66.9, 62.2, 56.5, 50.0, 41.7, 40.4, 39.8, 38.2, 37.1, 36.8, 32.2, 32.0, 31.5, 30.4, 28.9, 27.9, 21.5, 20.9, 19.4, 17.3, 16.4, 14.6. <i>R_f</i> (V_{CH} / V_{EtOAc} = 4 / 1): 0.74.
 3e	β-Sitosterol, 3e, C₂₉H₅₀O, CAS: 83-46-5, <i>M</i> = 414.70 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.34 (d, <i>J</i> = 5.4 Hz, 1H), 3.51 (td, <i>J</i> = 11.1, 5.2, 4.0 Hz, 1H), 2.33 – 2.16 (m, 2H), 2.05 – 1.74 (m, 8H), 1.74 – 1.39 (m, 9H), 1.39 – 1.01 (m, 15H), 1.00 (s, 4H), 0.98 – 0.94 (m, 2H), 0.91 (d, <i>J</i> = 6.7 Hz, 5H), 0.87 – 0.72 (m, 11H), 0.67 (s, 3H), 0.64 (s, 1H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 140.9, 121.8, 71.9, 56.9, 56.2, 50.2, 45.9, 42.4, 42.4, 39.9, 37.4, 36.6, 36.3, 34.0, 32.0, 32.0, 31.7, 29.3, 28.4, 26.2, 24.4, 23.2, 21.2, 20.0, 19.5, 19.2, 18.9, 12.1, 12.0. <i>R_f</i> (V_{CH} / V_{EtOAc} = 4 / 1): 0.30.
 3f	Stigmasteryl acetate, 3f, C₃₁H₅₀O₂, CAS: 4651-48-3, <i>M</i> = 454.70 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.36 (d, <i>J</i> = 3.3 Hz, 1H), 5.15 (dd, <i>J</i> = 15.1, 8.6 Hz, 1H), 5.01 (dd, <i>J</i> = 15.1, 8.6 Hz, 1H), 4.60 (m, 1H), 2.31 (d, <i>J</i> = 7.1 Hz, 2H), 2.02 (s, 6H), 1.90 – 1.80 (m, 2H), 1.77 – 1.64 (m, 1H), 1.64 – 1.34 (m, 10H), 1.34 – 1.07 (m, 6H), 1.01 (t, <i>J</i> = 3.3 Hz, 9H), 0.88 – 0.74 (m, 10H), 0.69 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 170.6, 139.8, 138.5, 129.4, 122.8, 74.1, 56.9, 56.1, 51.4, 50.2, 42.3, 40.7, 39.8, 38.3, 37.1, 36.7, 32.0, 32.0, 29.1, 27.9, 25.6, 24.5, 21.6, 21.4, 21.2, 21.1, 19.4, 19.1, 12.4, 12.2. <i>R_f</i> (V_{CH} / V_{EtOAc} = 98 / 2): 0.22.

 3g	Pregnenolone acetate, 3g, C₂₃H₃₄O₃, CAS: 1778-02-5, <i>M</i> = 358.5 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.34 (d, <i>J</i> = 5.2 Hz, 1H), 4.63 – 4.50 (m, 1H), 2.50 (t, <i>J</i> = 8.9 Hz, 1H), 2.33 – 2.21 (m, 2H), 2.18 – 2.11 (m, 1H), 2.09 (s, 3H), 1.99 (s, 3H), 1.94 (m, 1H), 1.88 – 1.78 (m, 2H), 1.72 – 1.36 (m, 8H), 1.26 – 1.05 (m, 3H), 0.98 (s, 4H), 0.59 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 209.5, 170.5, 139.7, 122.4, 73.9, 63.7, 56.9, 49.9, 44.0, 38.8, 38.1, 37.0, 36.6, 31.9, 31.8, 31.6, 27.8, 24.5, 22.9, 21.5, 21.1, 19.4, 13.3. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 98 / 2): 0.22.
 3h	Dehydroepiandrosterone acetate, 3h, C₂₁H₃₀O₃, CAS: 853-23-6, <i>M</i> = 330.50 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.38 (d, <i>J</i> = 5.4 Hz, 1H), 4.58 (m, 1H), 2.43 (m, 1H), 2.38 – 2.23 (m, 2H), 2.14 – 2.03 (m, 2H), 2.01 (s, 3H), 1.97 – 1.78 (m, 4H), 1.70 – 1.39 (m, 6H), 1.32 – 1.20 (m, 2H), 1.07 – 1.18 (m, 1H), 1.02 (s, 3H), 0.86 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 221.1, 170.6, 140.0, 1z21.9, z73.8, 51.8, 50.2, 47.6, 38.1, 37.0, 36.8, 35.9, 31.5, 31.5, 30.8, 27.8, 22.z0, 21.5, 20.4, 19.4, 13.6. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 4 / 1): 0.25.
 3i	Methylandrostenediol, 3i, C₂₀H₃₂O₂, CAS: 521-10-8, <i>M</i> = 304.50 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.35 (d, <i>J</i> = 4.9 Hz, 1H), 3.51 (m, 1H), 2.35 – 2.17 (m, 2H), 1.99 (m, 1H), 1.91 – 1.68 (m, 4H), 1.66 – 1.38 (m, 9H), 1.38 – 1.23 (m, 3H), 1.21 (s, 4H), 1.18 – 1.06 (m, 1H), 1.03 (s, 3H), 0.93 (m, 1H), 0.87 (s, 3H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 141.0, 121.5, 81.9, 71.9, 51.2, 50.3, 45.4, 42.4, 39.1, 37.4, 36.7, 31.8, 31.8, 31.7, 25.9, 23.5, 20.9, 19.6, 14.0. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.20.
 3j	Lynestrenol, 3j, C₂₀H₂₈O, CAS: 52-76-6, <i>M</i> = 284.40 g mol⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ [ppm] = 5.38 (s, 1H), 2.55 (s, 1H), 2.32 – 2.15 (m, 2H), 2.05 – 1.83 (m, 7H), 1.80 – 1.62 (m, 5H), 1.61 – 1.44 (m, 2H), 1.42 – 1.02 (m, 5H), 0.87 (s, 4H), 0.69 (dtd, <i>J</i> = 11.9, 10.4, 4.1 Hz, 1H). ¹³C{¹H} NMR (CDCl₃, 101 MHz) δ [ppm] = 140.4, 120.1, 87.7, 80.1, 74.0, 50.0, 49.6, 47.1, 42.1, 41.7, 39.0, 35.6, 32.8, 31.8, 28.9, 26.1, 25.6, 23.1, 22.2, 12.9. <i>R</i>_f (<i>V</i>_{CH} / <i>V</i>_{EtOAc} = 1 / 1): 0.66.

7. NMR Spectra of Allylic Oxidation Products

7.1. 4-Oxo-isophorone

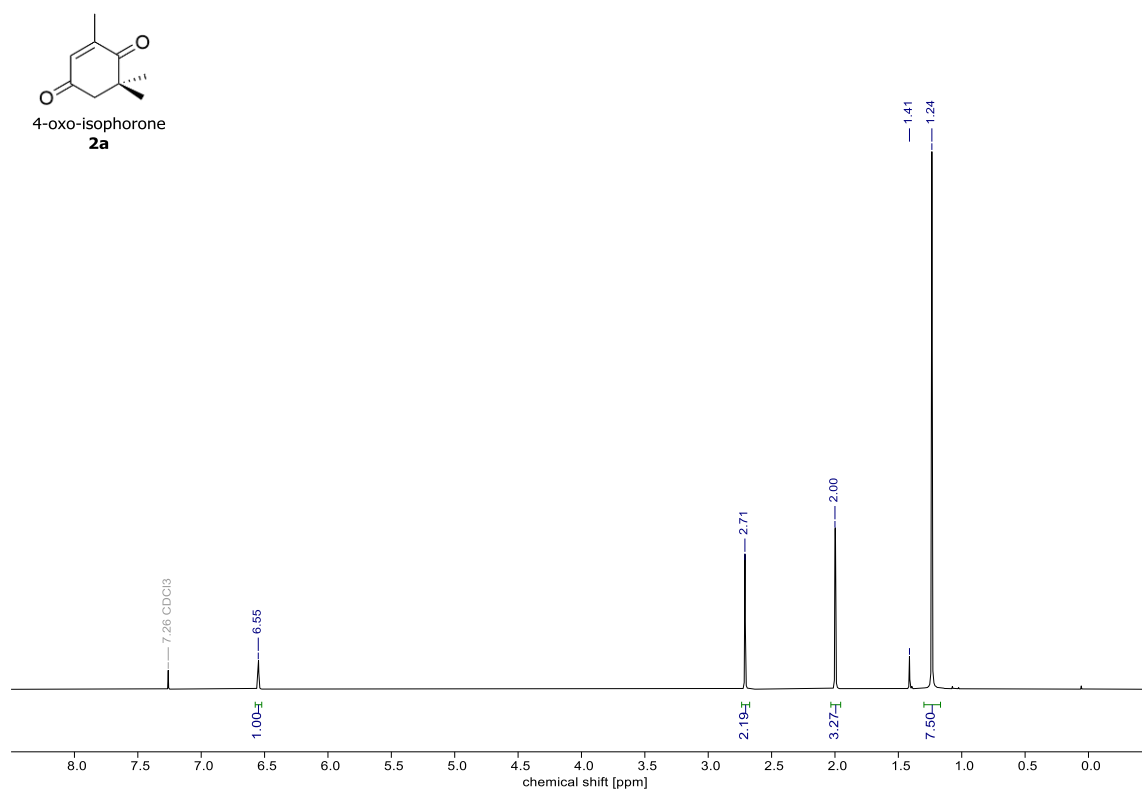


Figure S5. ¹H NMR spectrum (400 MHz) of product **2a**: 4-oxo-isophorone.

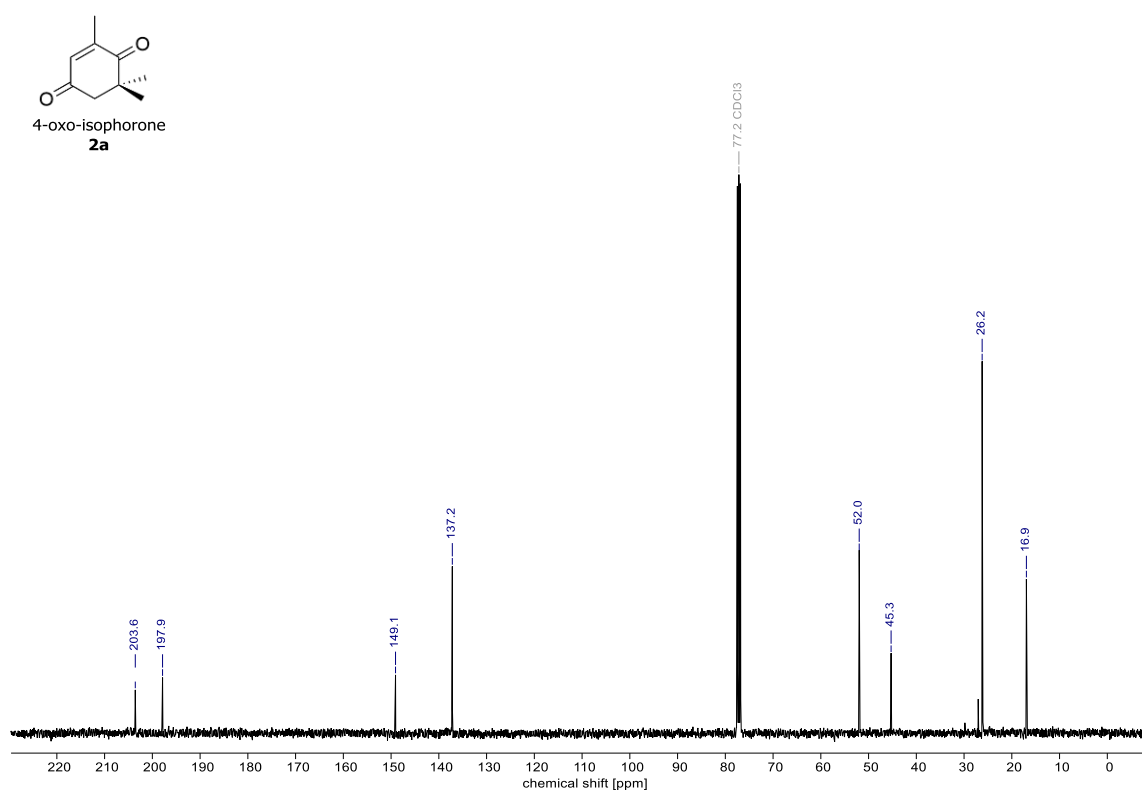


Figure S6. ¹³C NMR spectrum (101 MHz) of product **2a**: 4-oxo-isophorone.

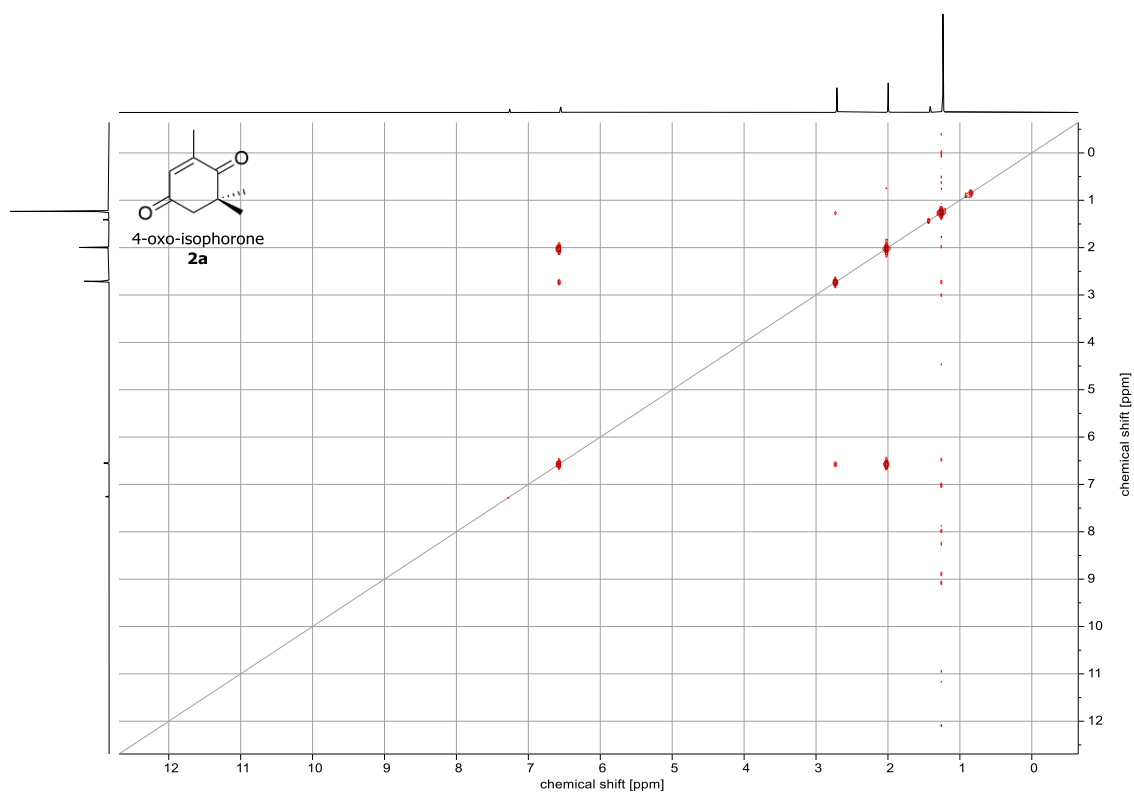


Figure S7. COSY spectrum of product **2a**: 4-oxo-isophorone.

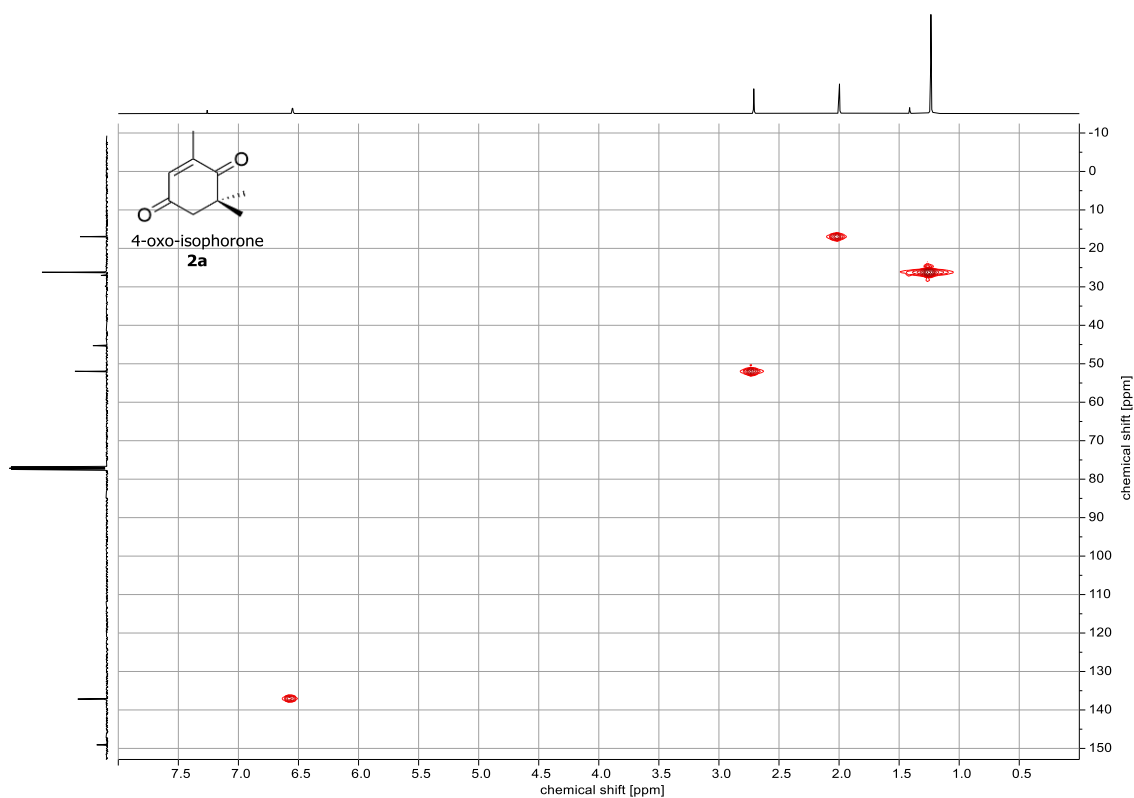


Figure S8. HSQC spectrum of product **2a**: 4-oxo-isophorone.

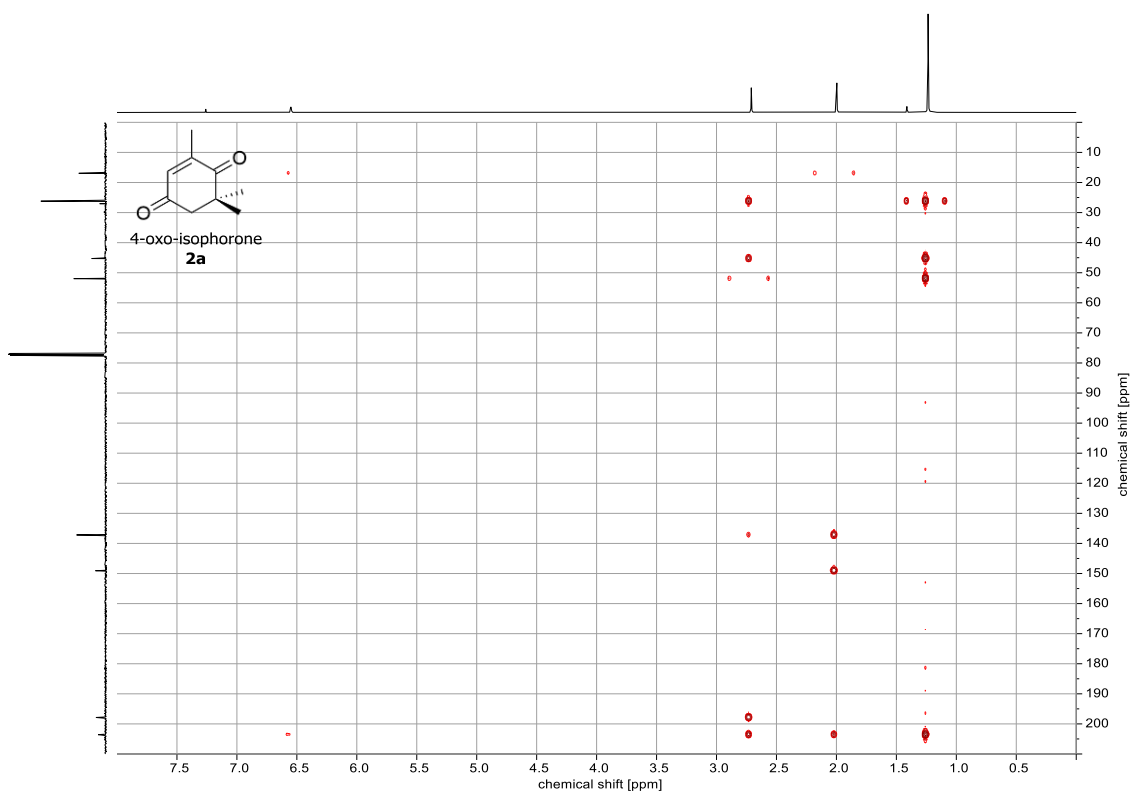


Figure S9. HMBC spectrum of product **2a**: 4-oxo-isophorone.

7.2. Verbenone

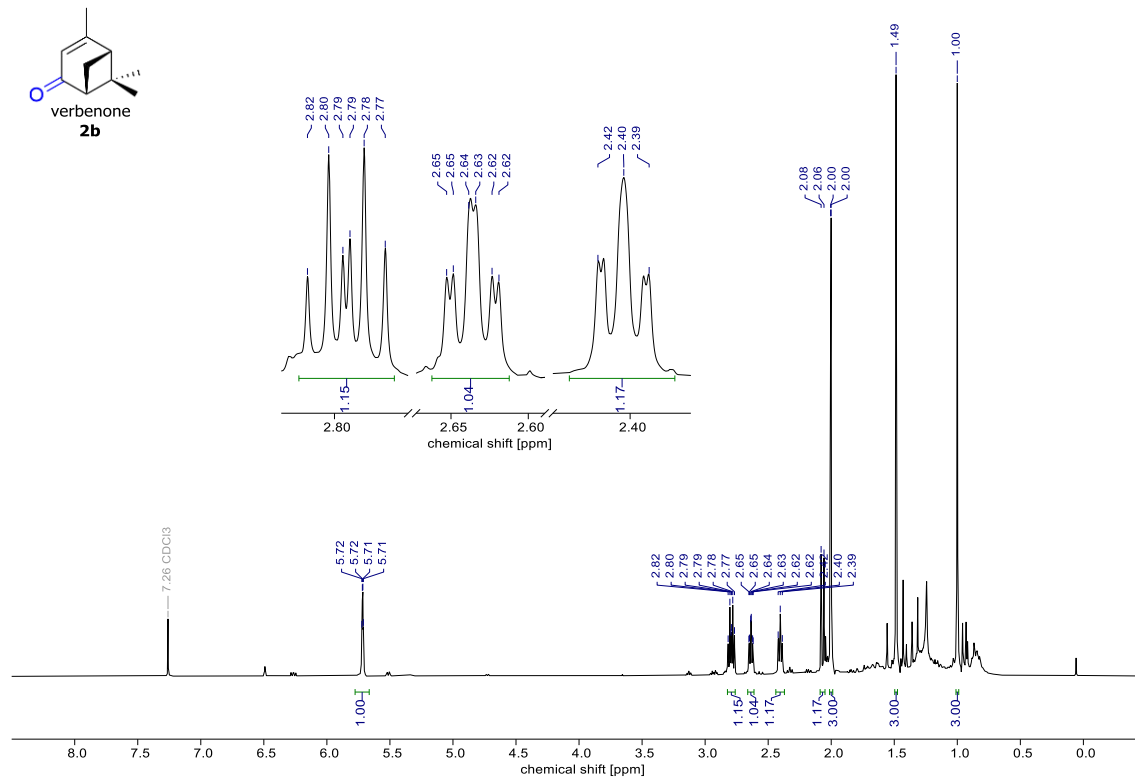


Figure S10. ¹H NMR spectrum (400 MHz) of product **2b**: verbenone.

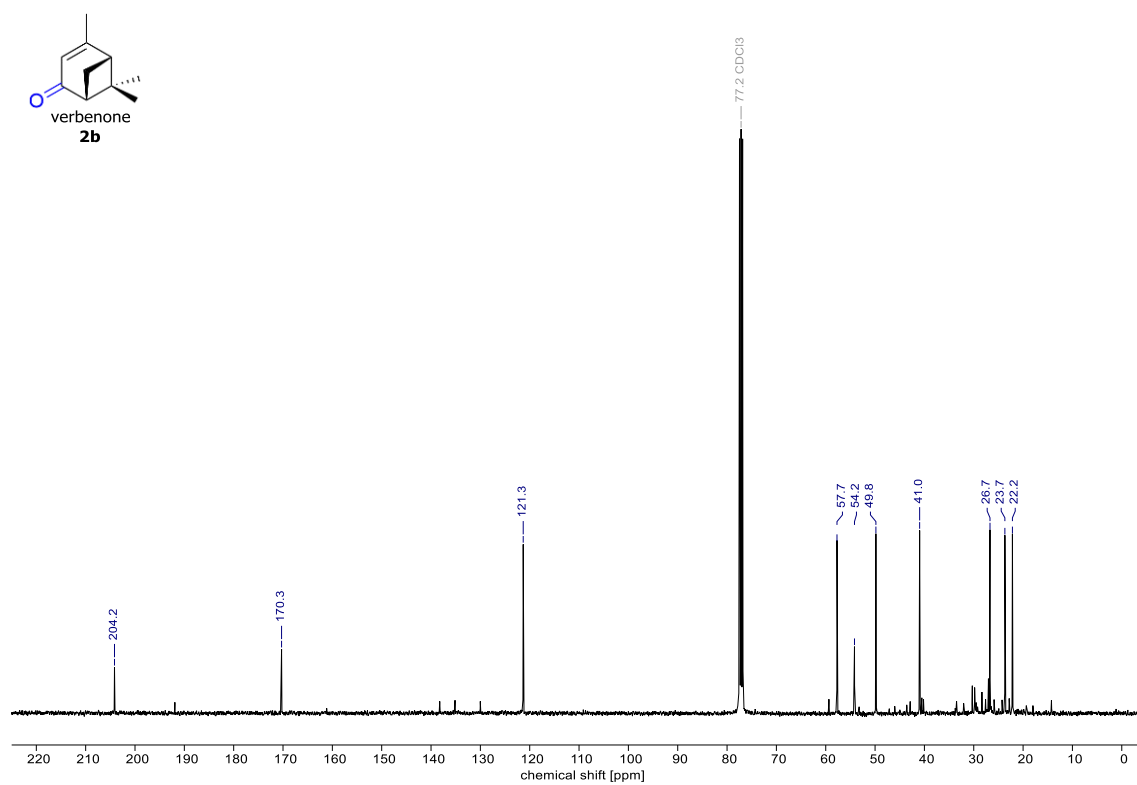


Figure S11. ¹³C NMR spectrum (101 MHz) of product **2b**: verbenone.

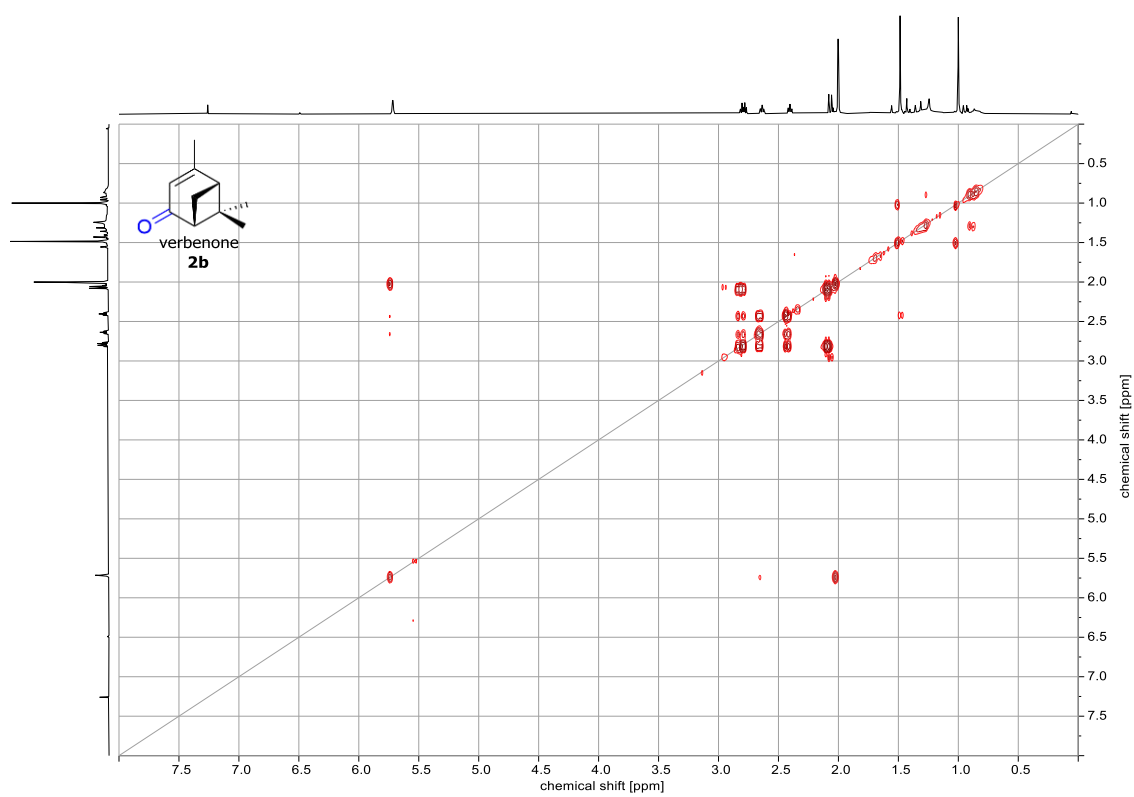


Figure S12. COSY spectrum of product **2b**: verbenone.

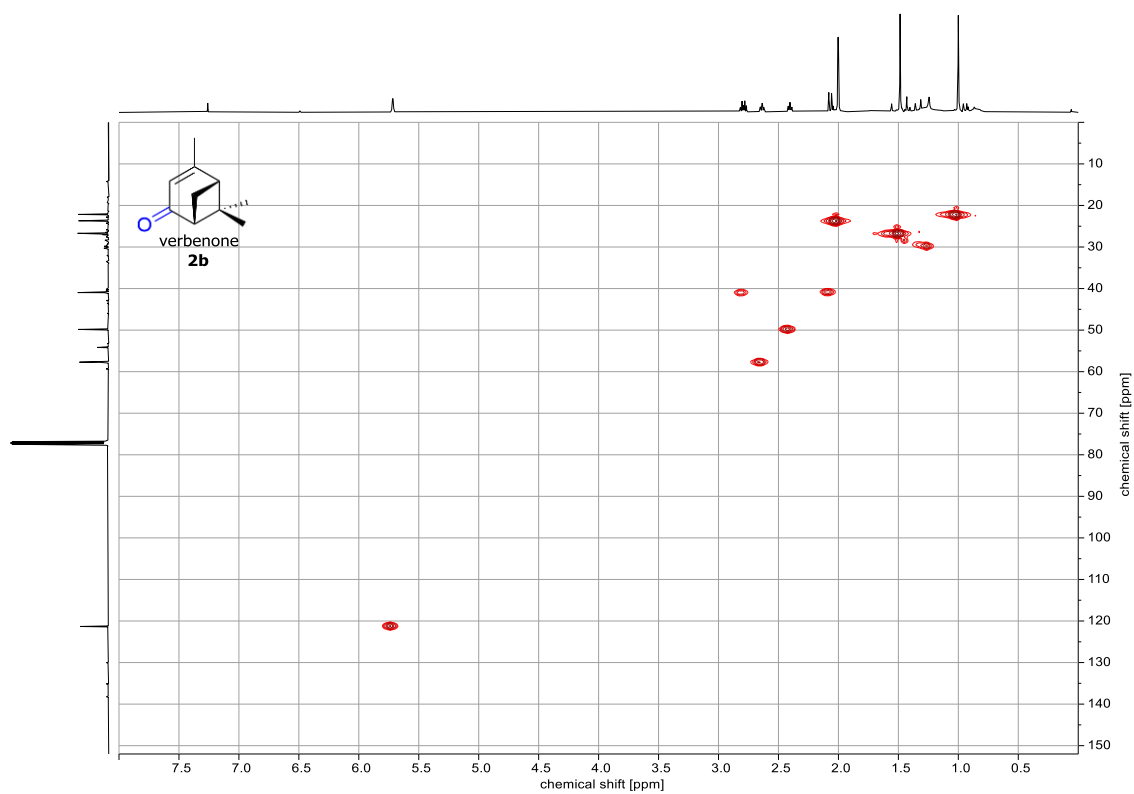


Figure S13. HSQC spectrum of product **2b**: verbenone.

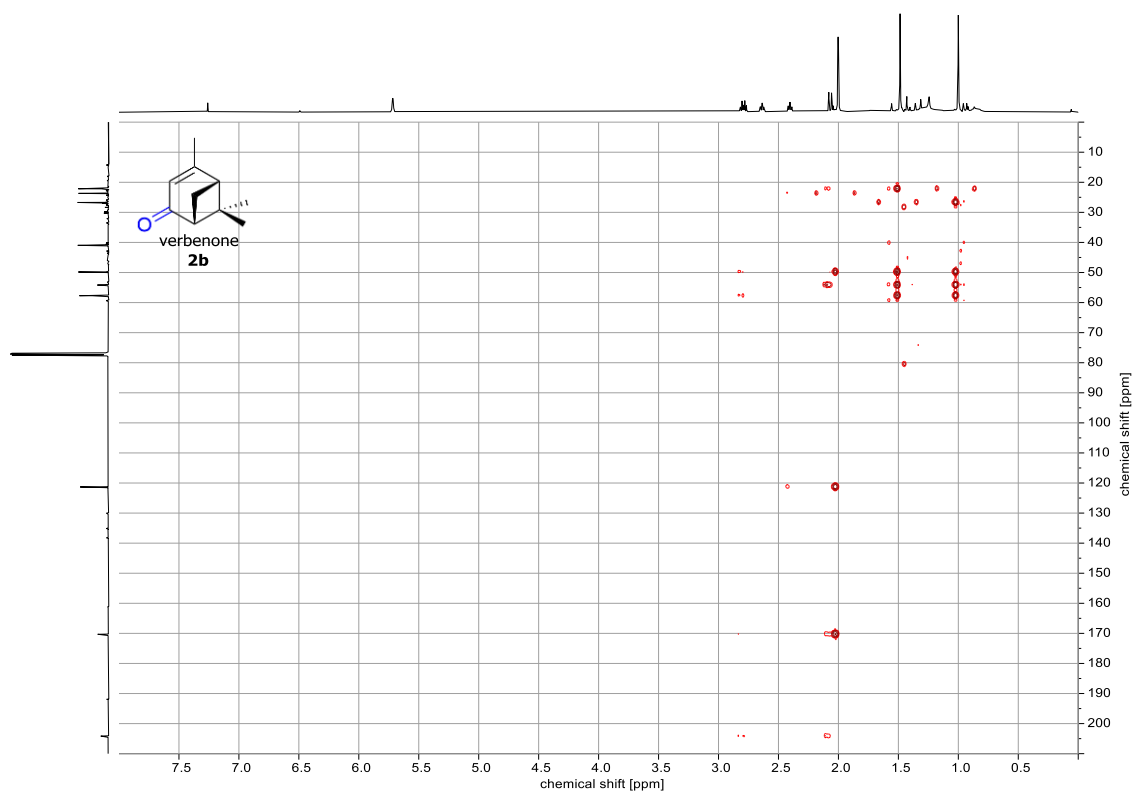
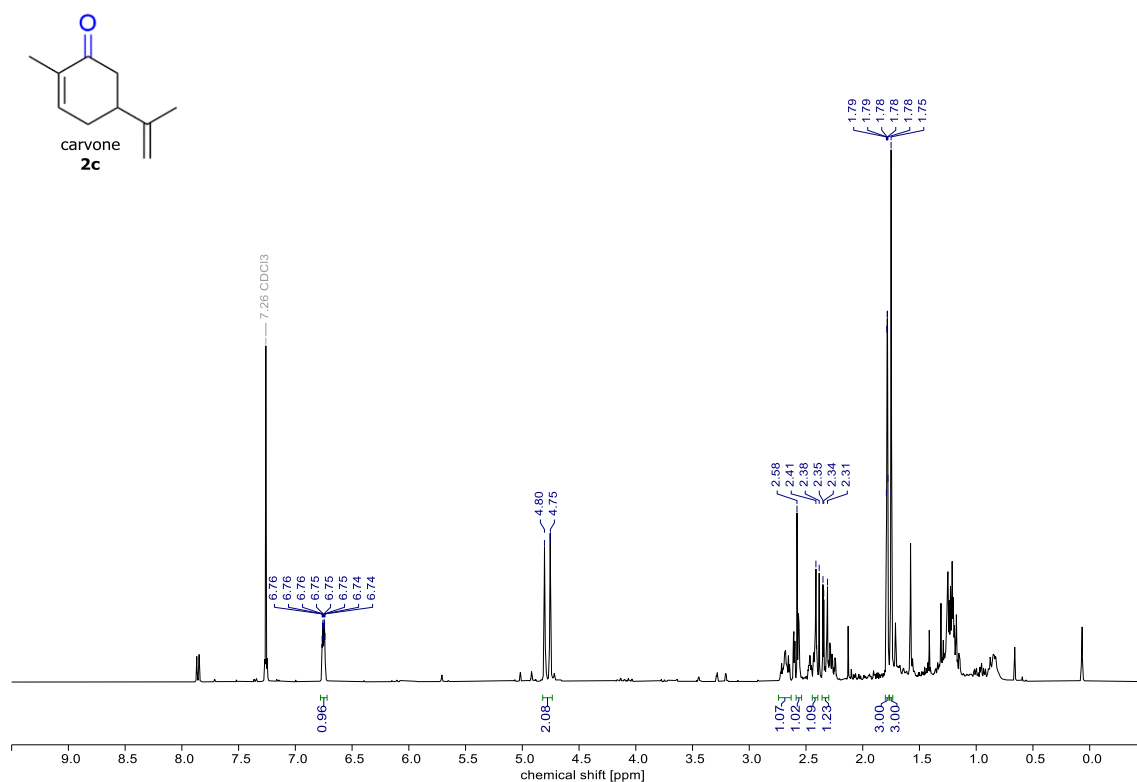
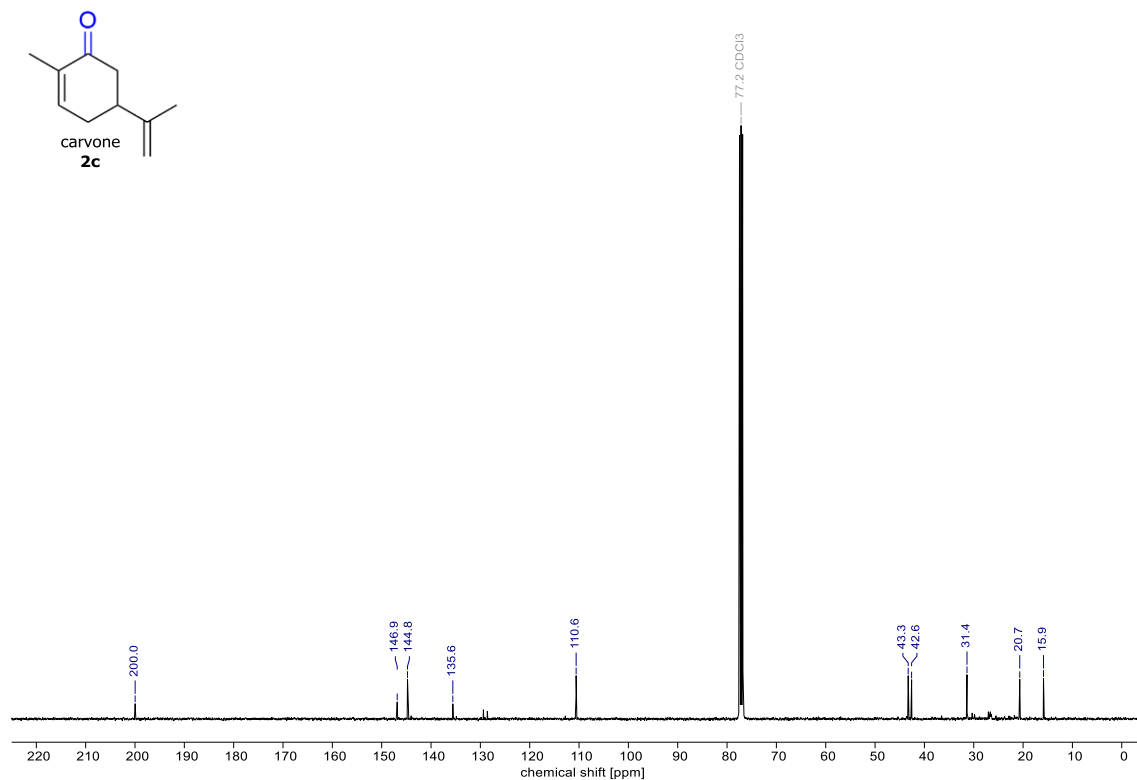


Figure S14. HMBC spectrum of product **2b**: verbenone.

7.3. Carvone

Figure S15. ¹H NMR spectrum (400 MHz) of product **2c**: carvone.Figure S16. ¹³C NMR spectrum (101 MHz) of product **2c**: carvone.

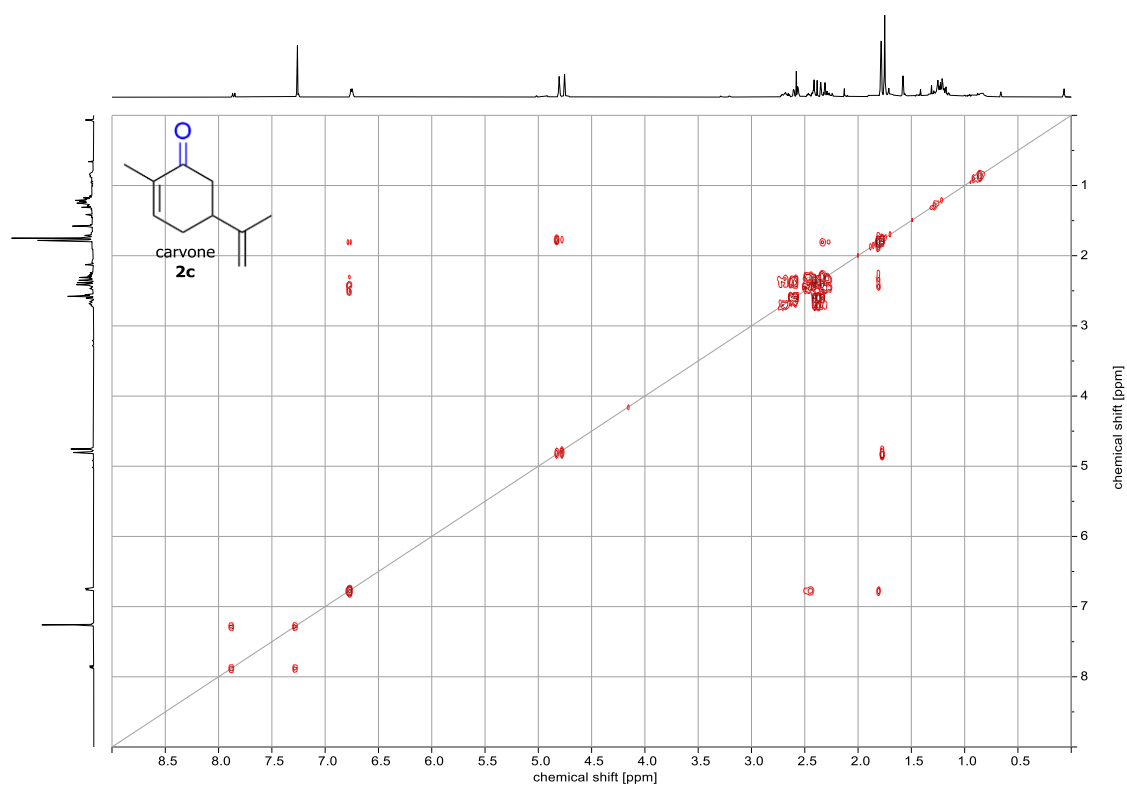


Figure S17. COSY spectrum of product 2c: carvone.

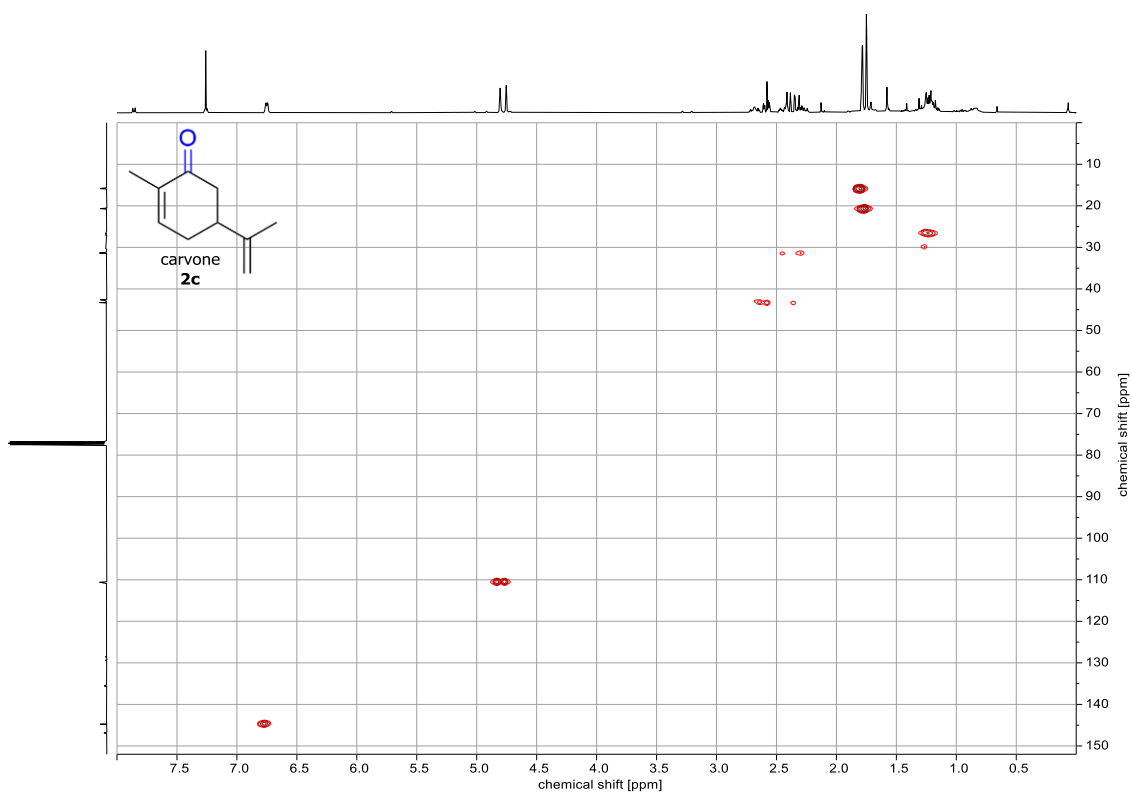


Figure S18. HSQC spectrum of product 2c: carvone.

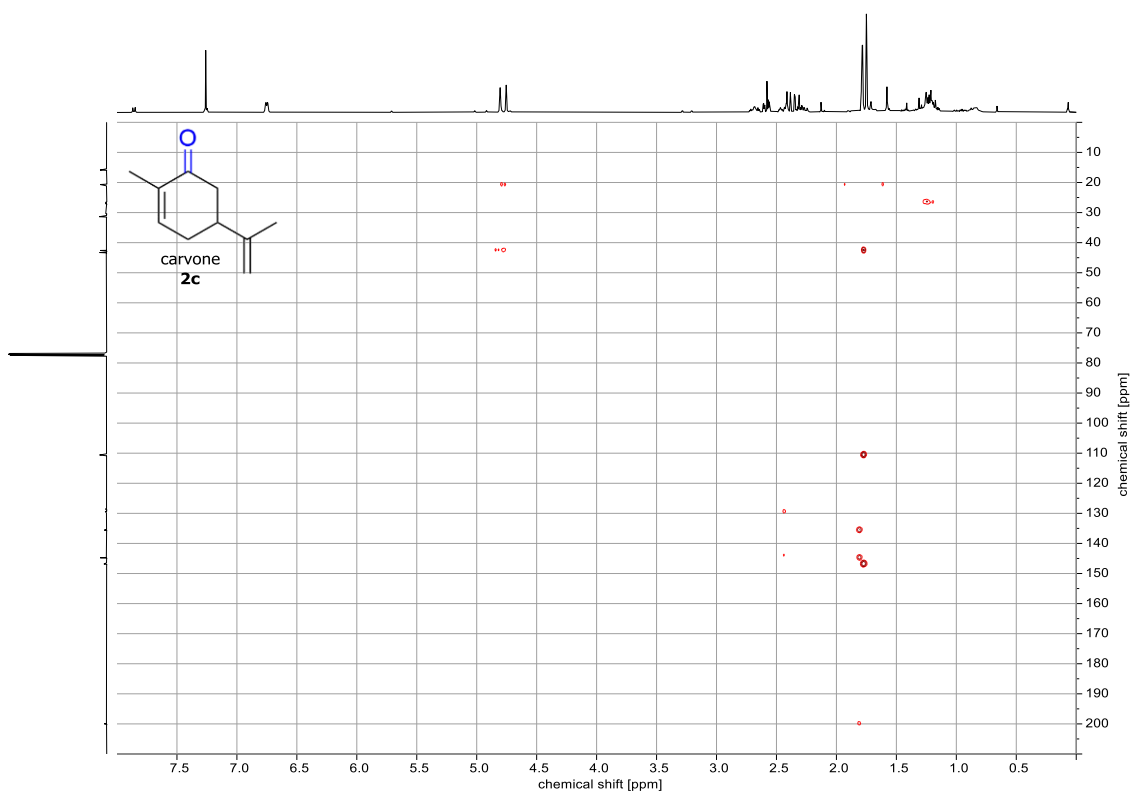
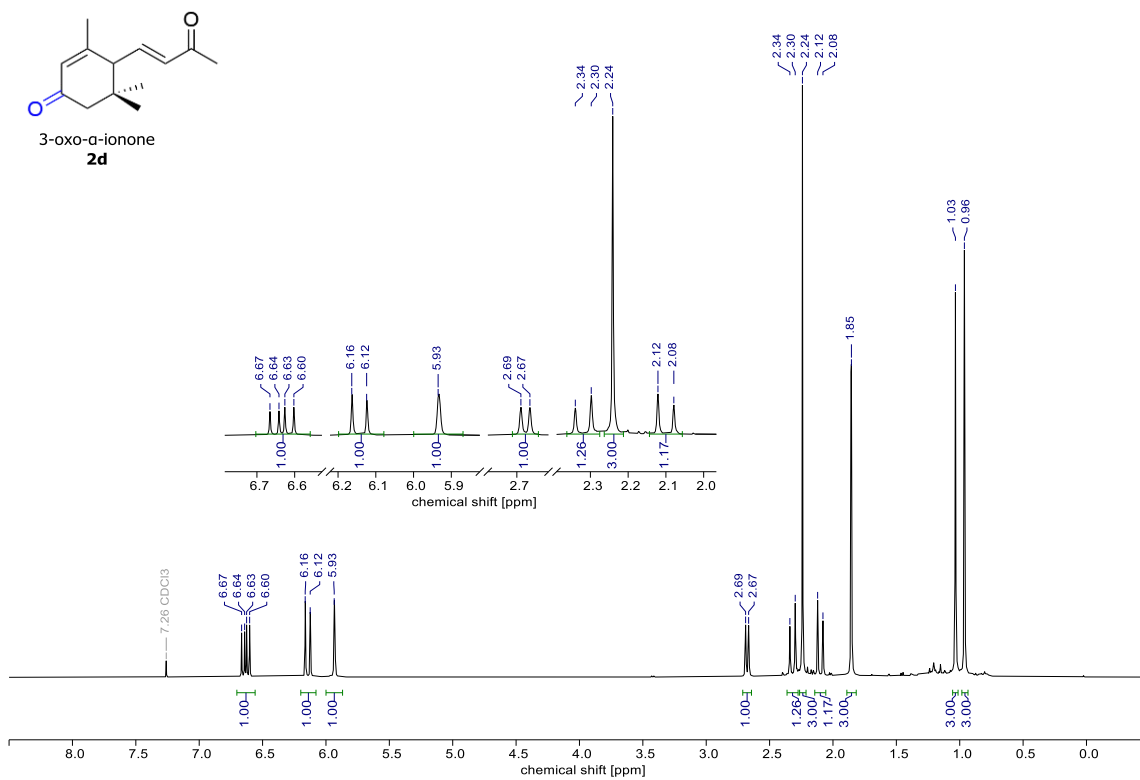


Figure S19. HMBC spectrum of product 2c: carvone.

7.4. 3-Oxo- α -iononeFigure S20. ¹H NMR spectrum (400 MHz) of product 2d: 3-oxo- α -ionone.

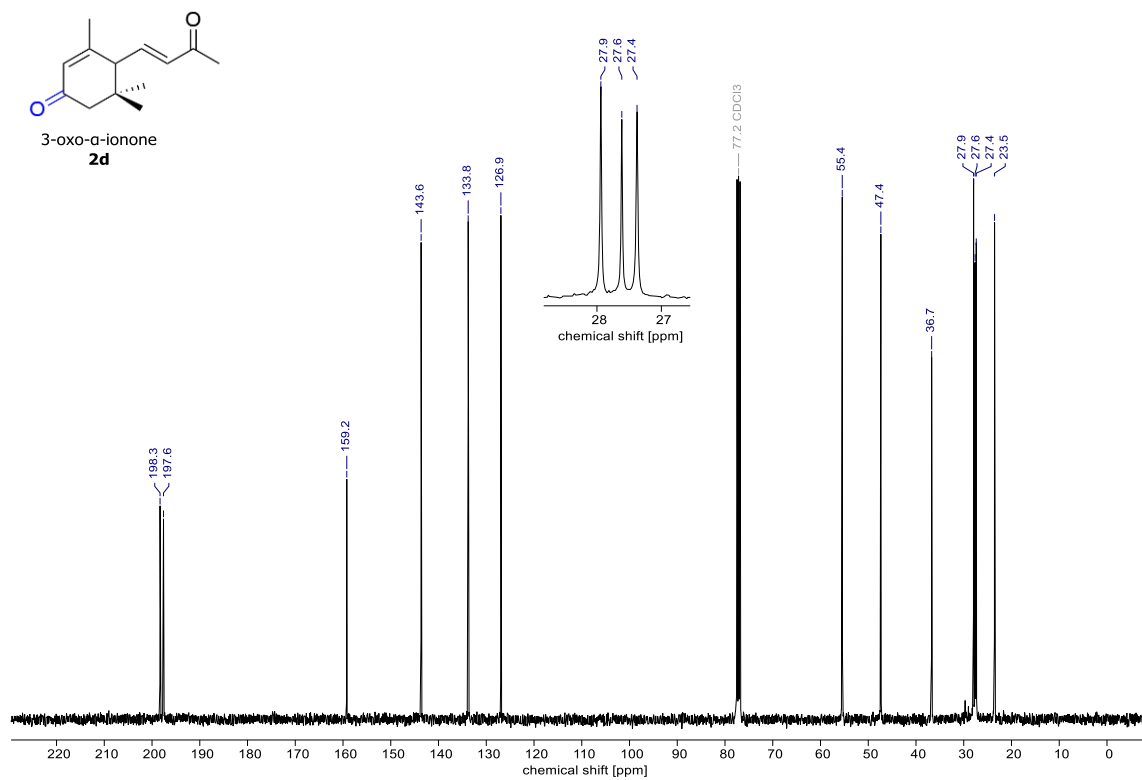


Figure S21. ¹³C NMR spectrum (101 MHz) of product **2d**: 3-oxo- α -ionone.

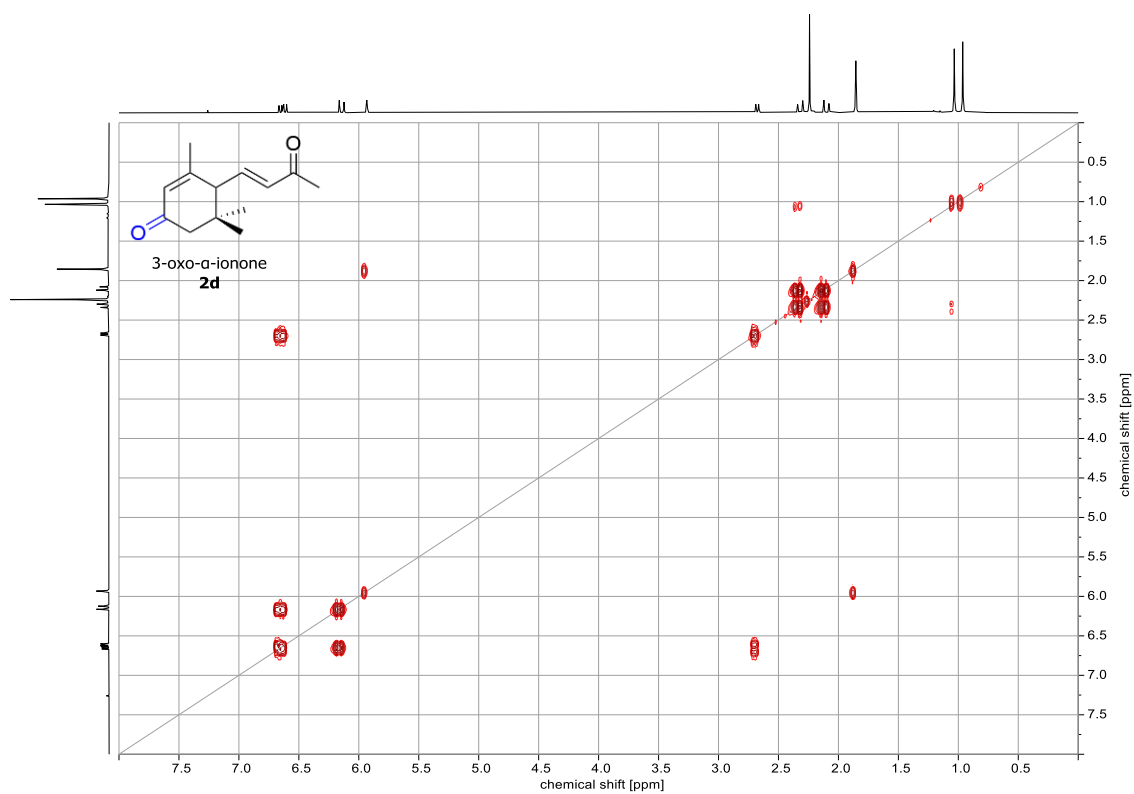


Figure S22. COSY spectrum of product **2d**: 3-oxo- α -ionone.

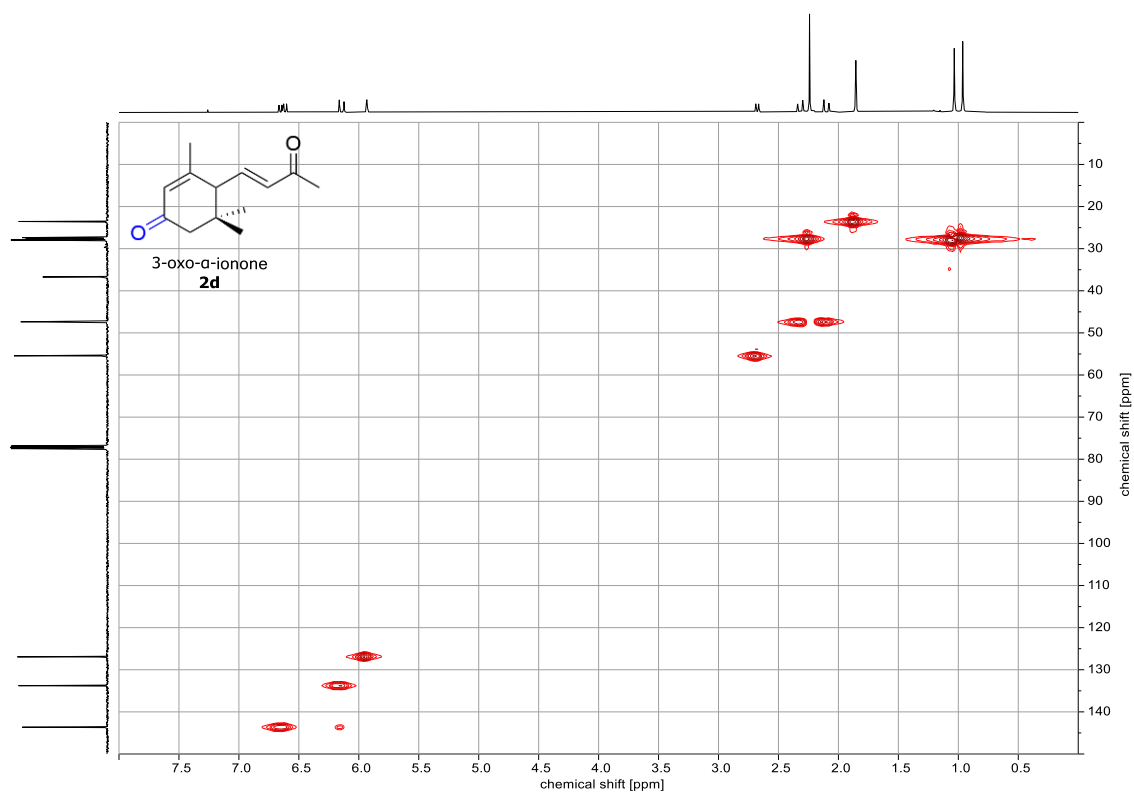


Figure S23. HSQC spectrum of product **2d**: 3-oxo- α -ionone.

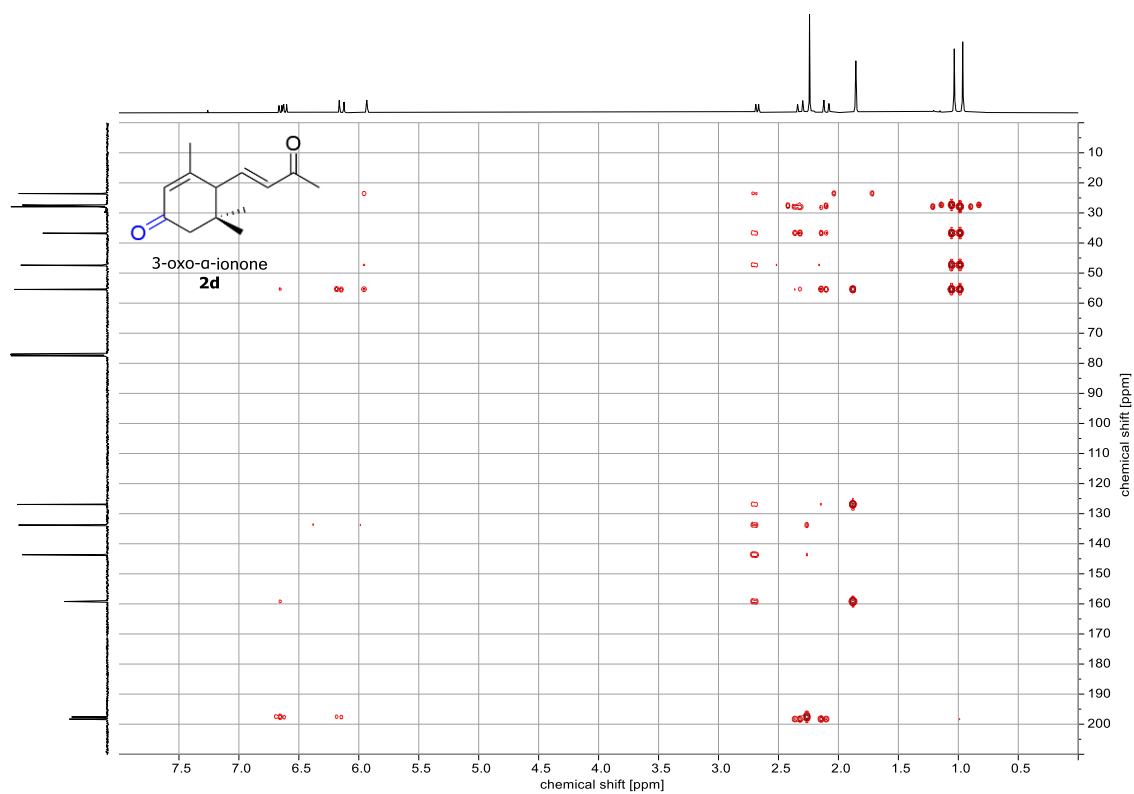
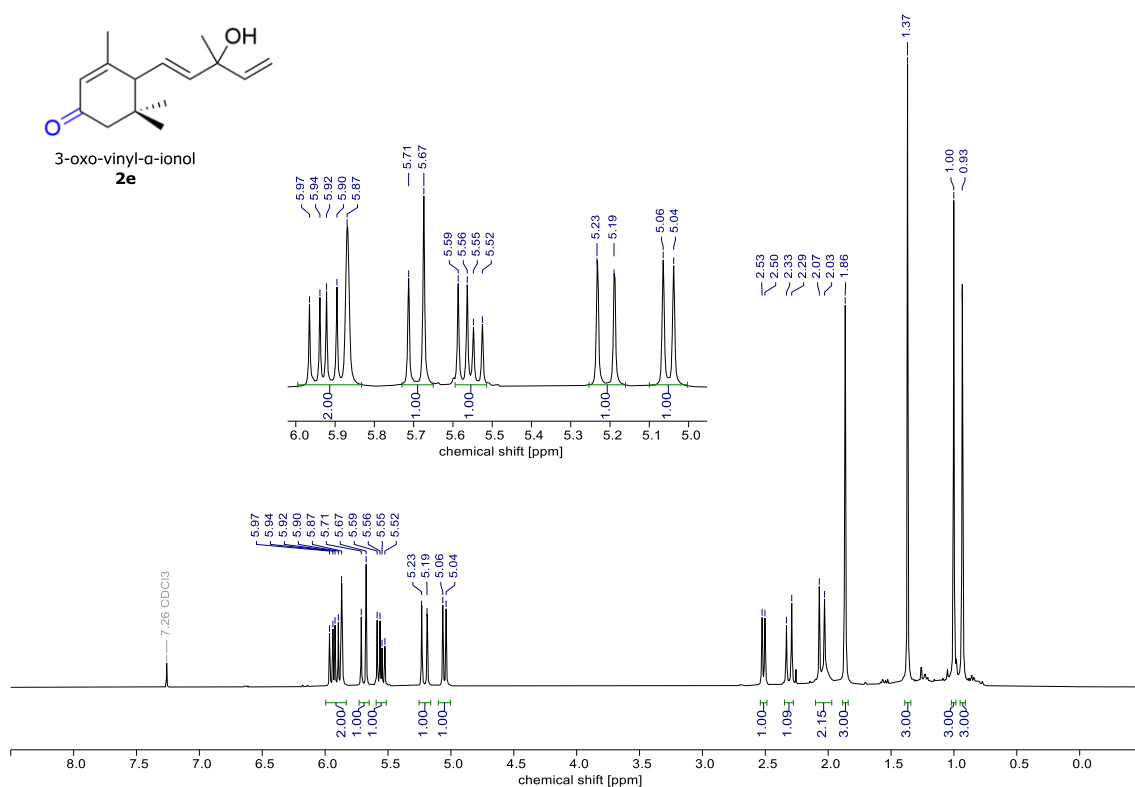
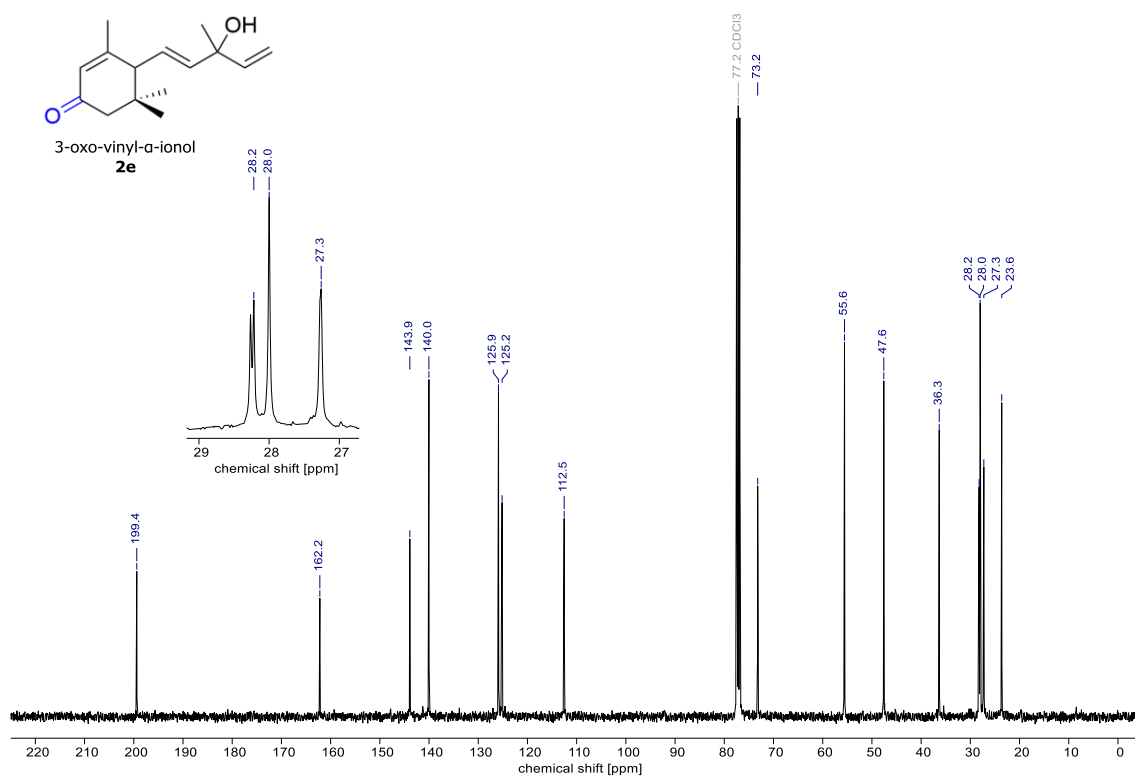


Figure S24. HMBC spectrum of product **2d**: 3-oxo- α -ionone.

7.5. 3-Oxo-vinyl- α -ionolFigure S25. ¹H NMR spectrum (400 MHz) of product **2e**: 3-oxo-vinyl- α -ionol.Figure S26. ¹³C NMR spectrum (101 MHz) of product **2e**: 3-oxo-vinyl- α -ionol.

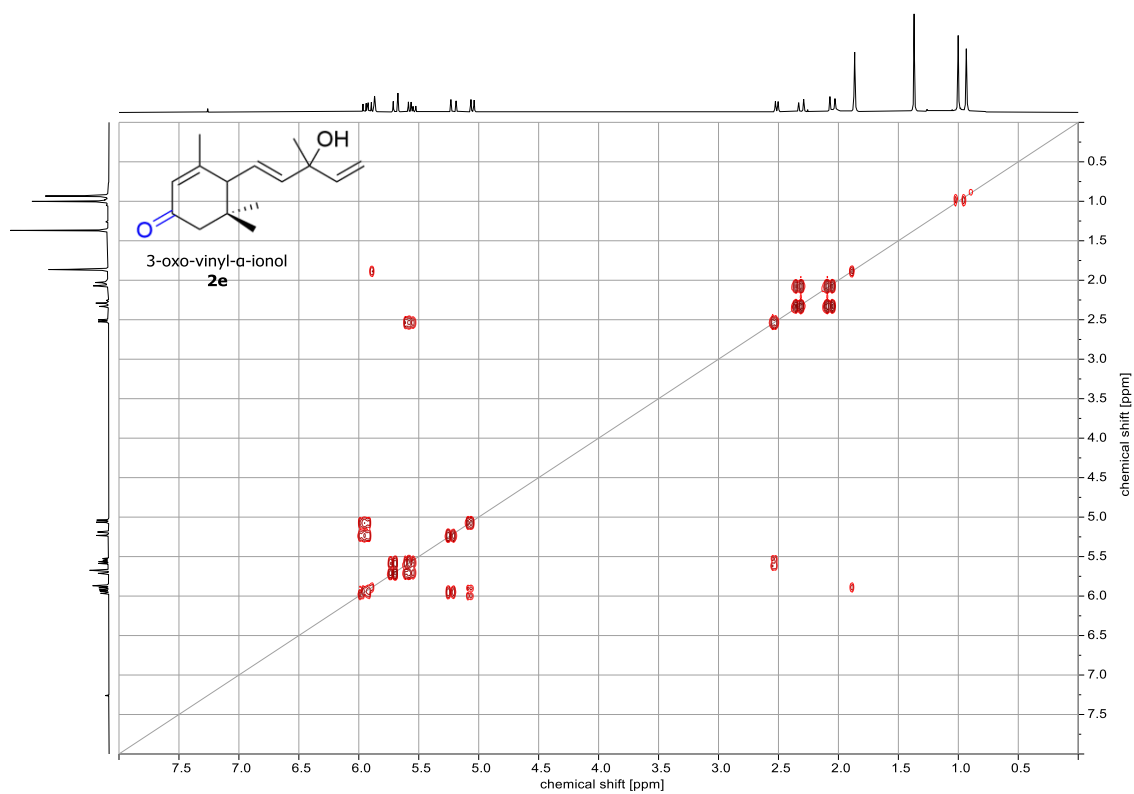


Figure S27. COSY spectrum of product **2e**: 3-oxo-vinyl- α -ionol.

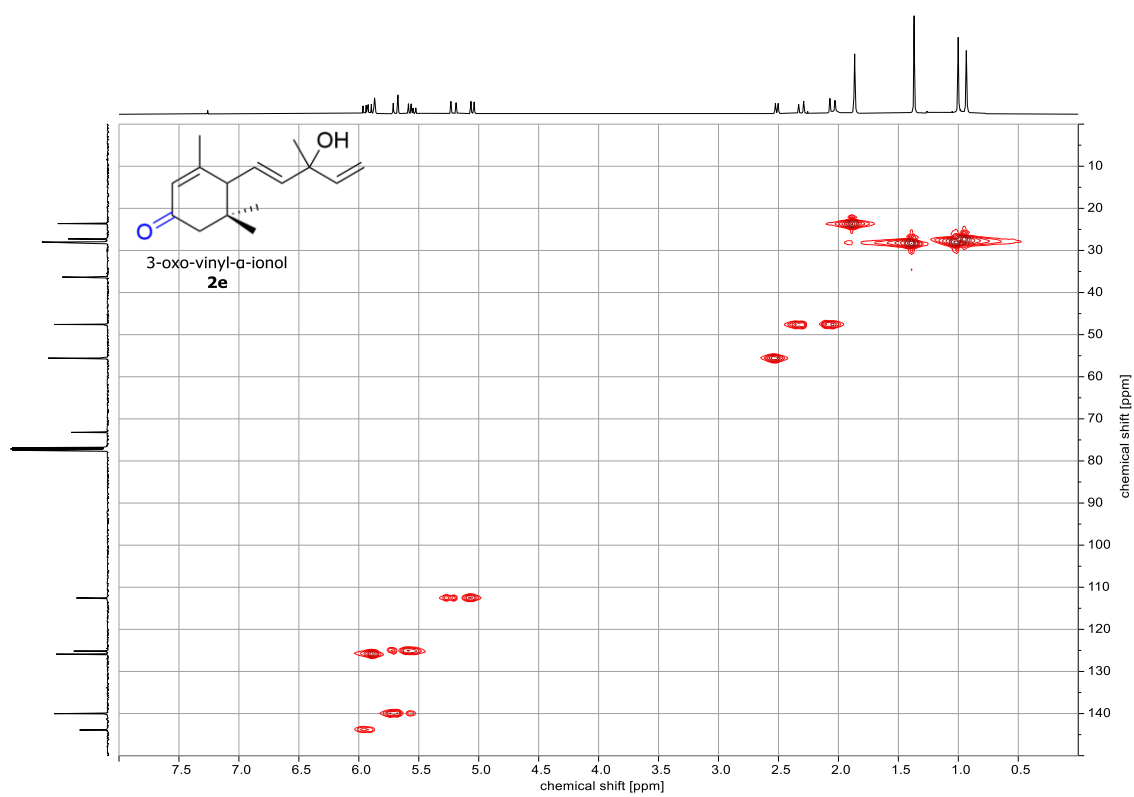
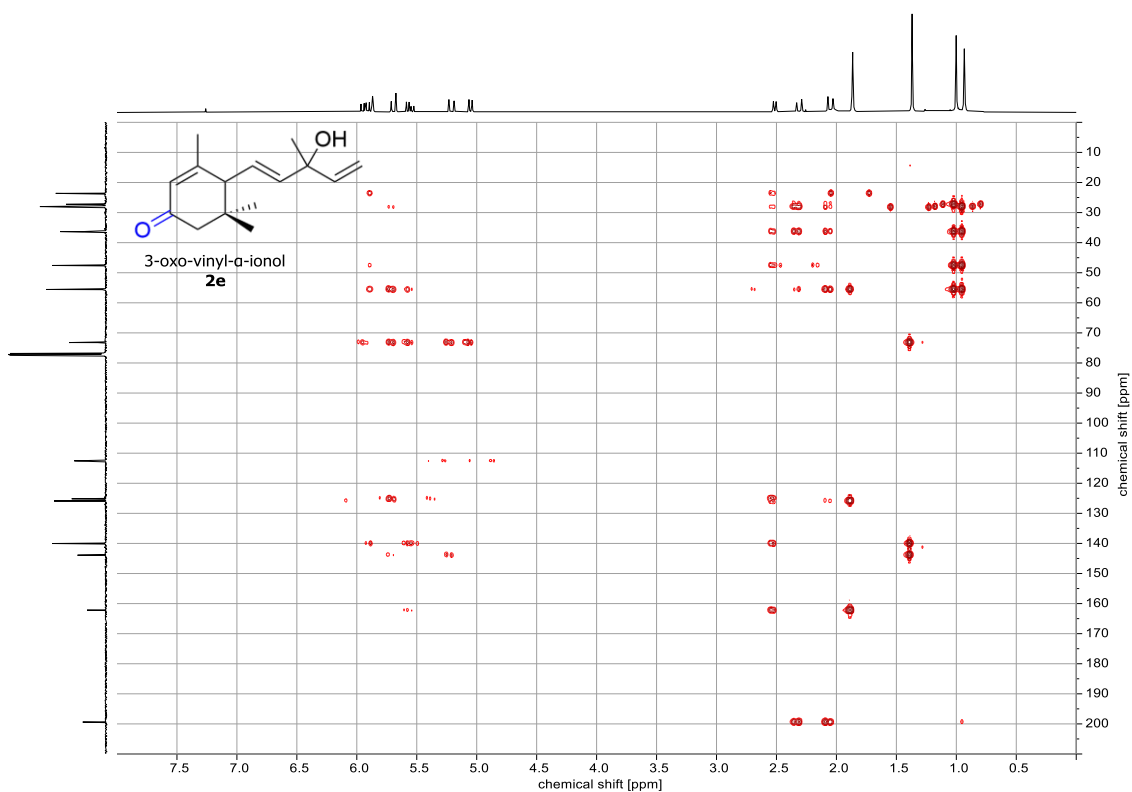
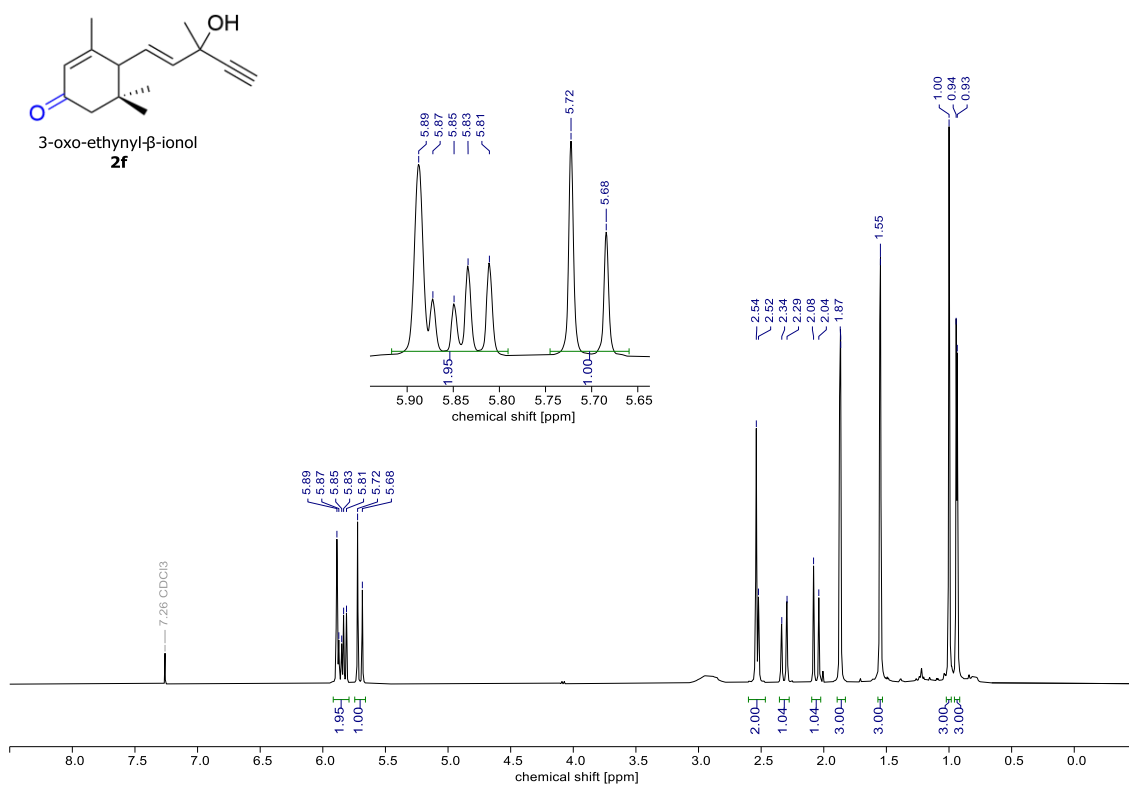


Figure S28. HSQC spectrum of product **2e**: 3-oxo-vinyl- α -ionol.

Figure S29. HMBC spectrum of product **2e**: 3-oxo-vinyl- α -ionol.7.6. 3-Oxo-ethynyl- β -ionolFigure S30. ¹H NMR spectrum (400 MHz) of product **2f**: 3-oxo-ethynyl- β -ionol.

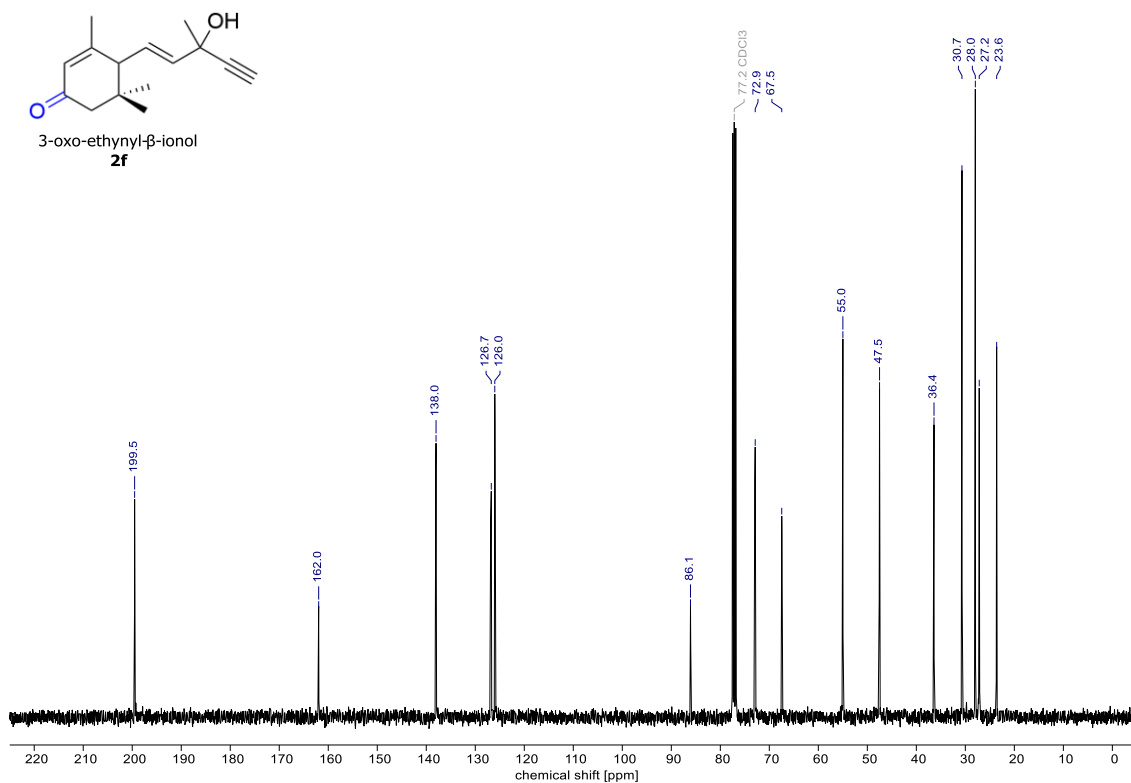


Figure S31. ¹³C NMR spectrum (101 MHz) of product **2f**: 3-oxo-ethynyl-β-ionol.

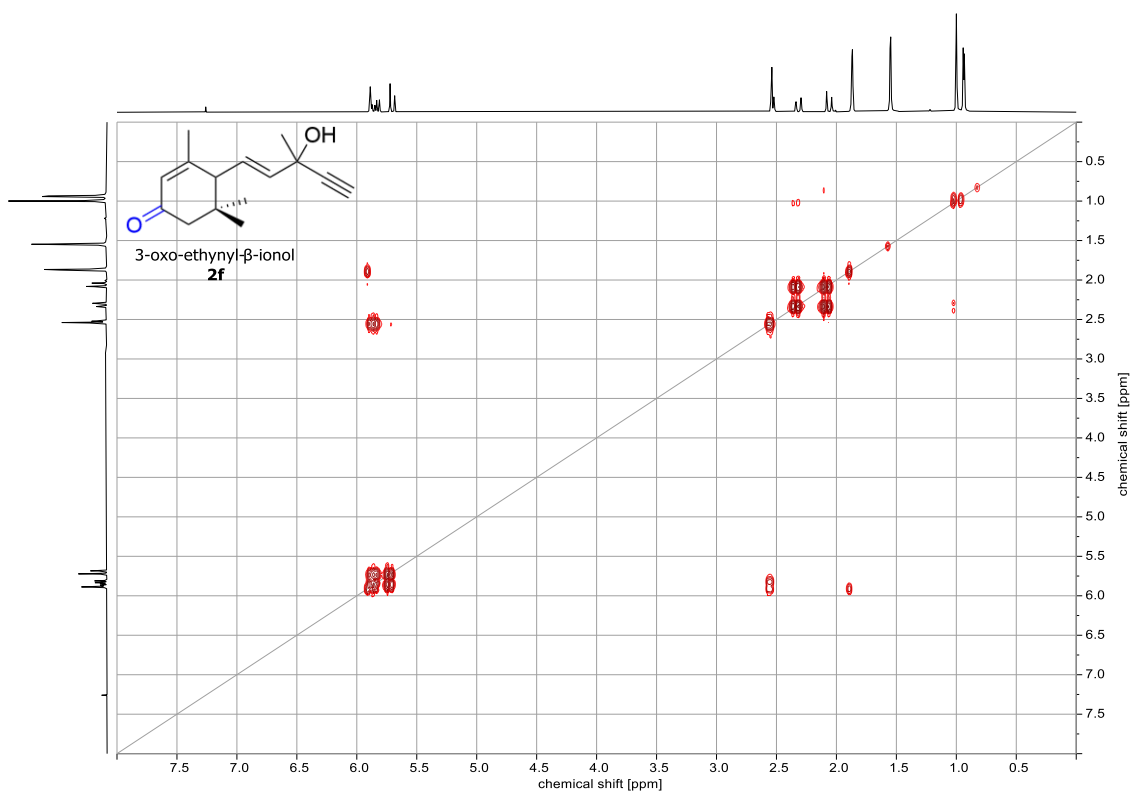


Figure S32. COSY spectrum of product **2f**: 3-oxo-ethynyl-β-ionol.

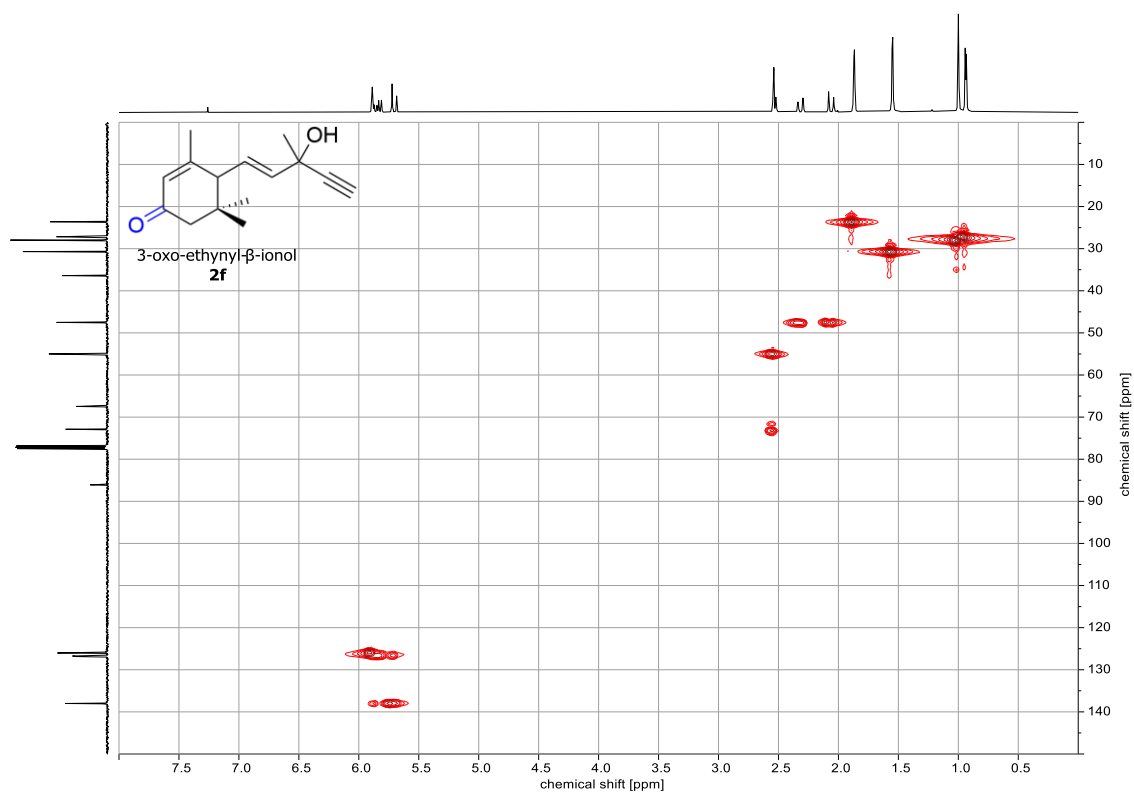


Figure S33. HSQC spectrum of product **2f**: 3-oxo-ethynyl- β -ionol.

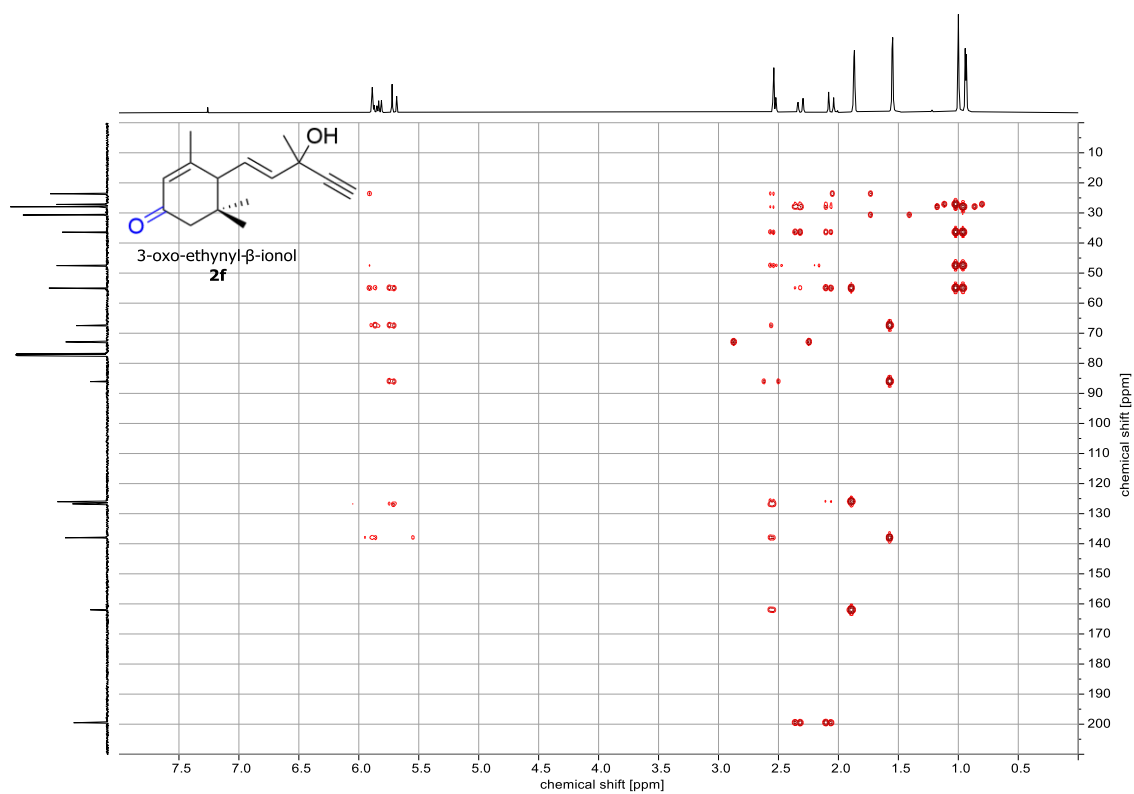
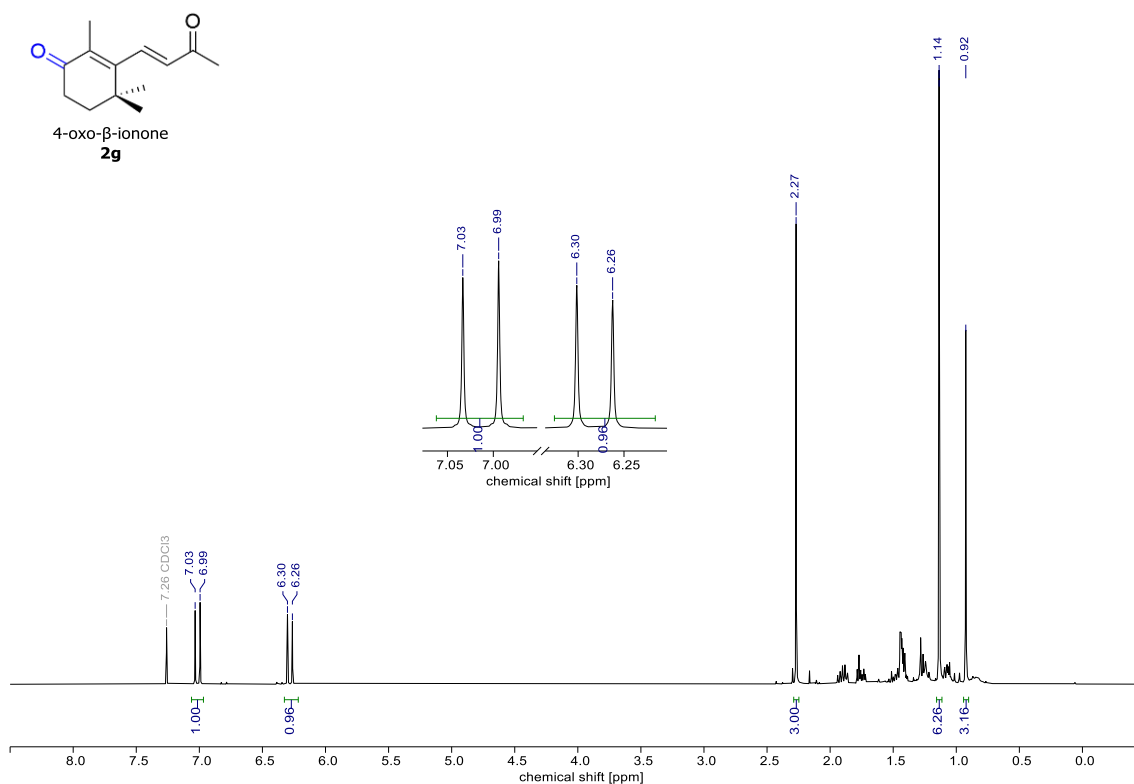
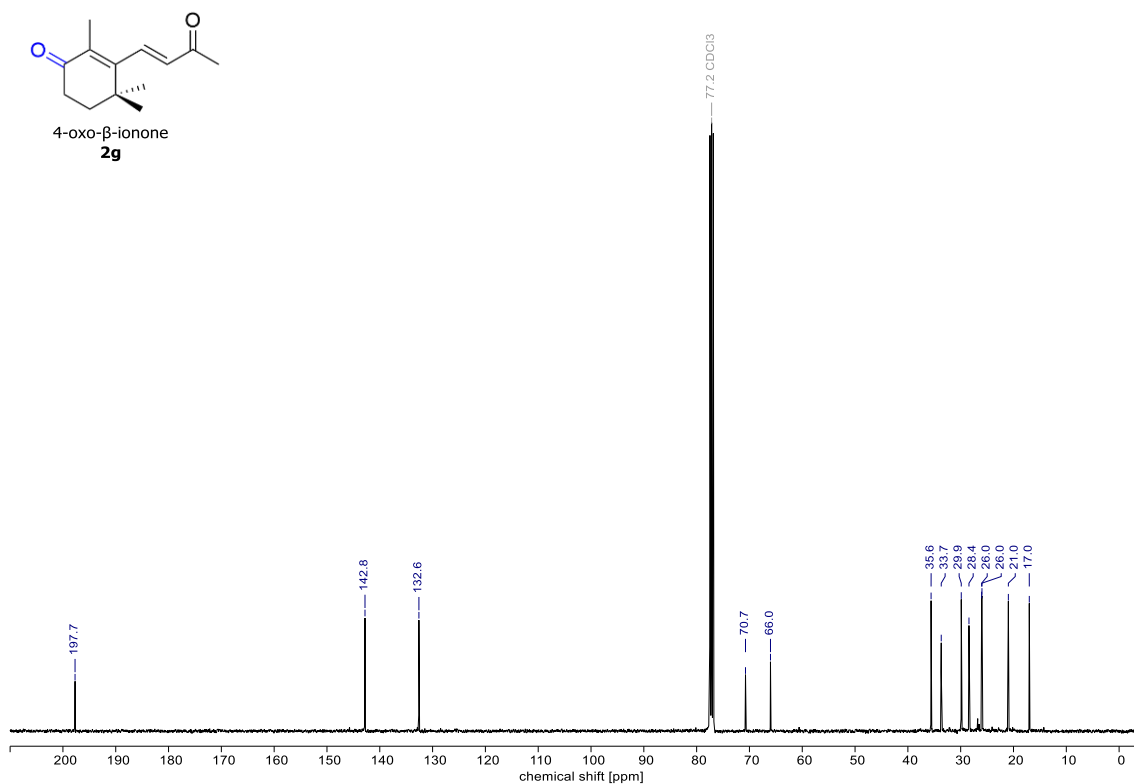


Figure S34. HMBC spectrum of product **2f**: 3-oxo-ethynyl- β -ionol.

7.7. 4-Oxo- β -iononeFigure S35. ¹H NMR spectrum (400 MHz) of product **2g**: 4-oxo- β -ionone.Figure S36. ¹³C NMR spectrum (101 MHz) of product **2g**: 4-oxo- β -ionone.

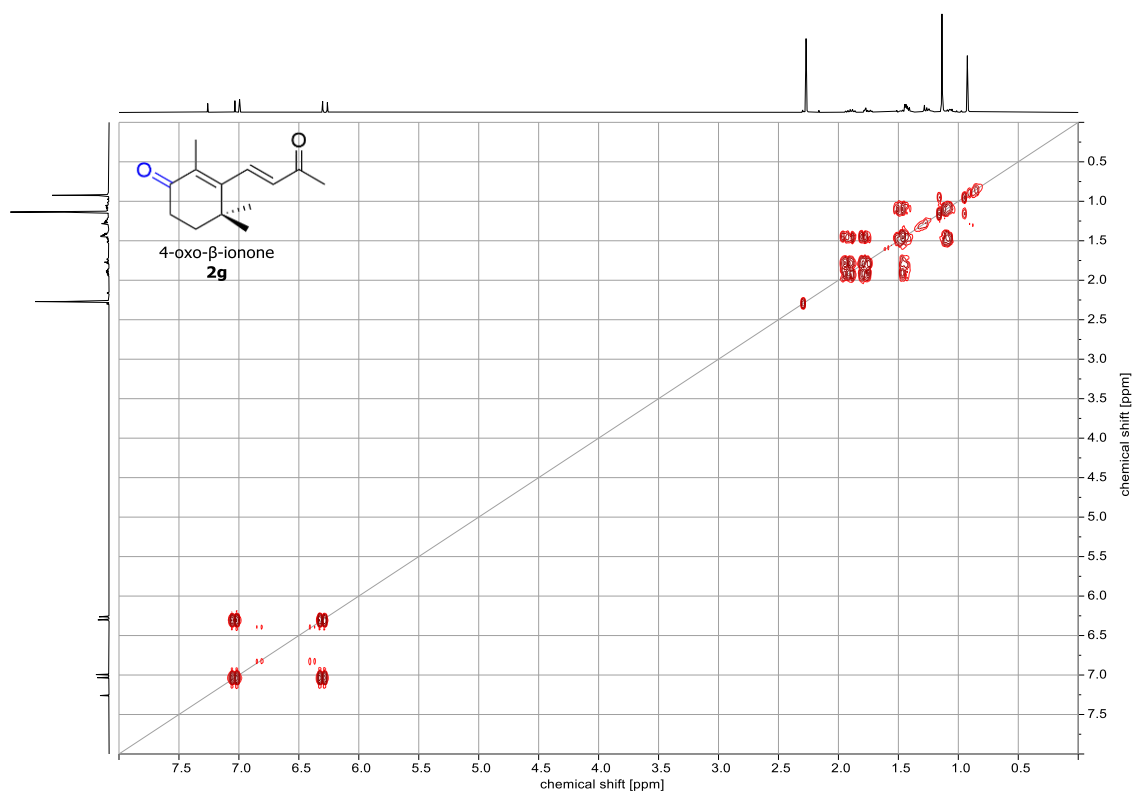


Figure S37. COSY spectrum of product **2g**: 4-oxo-β-ionone.

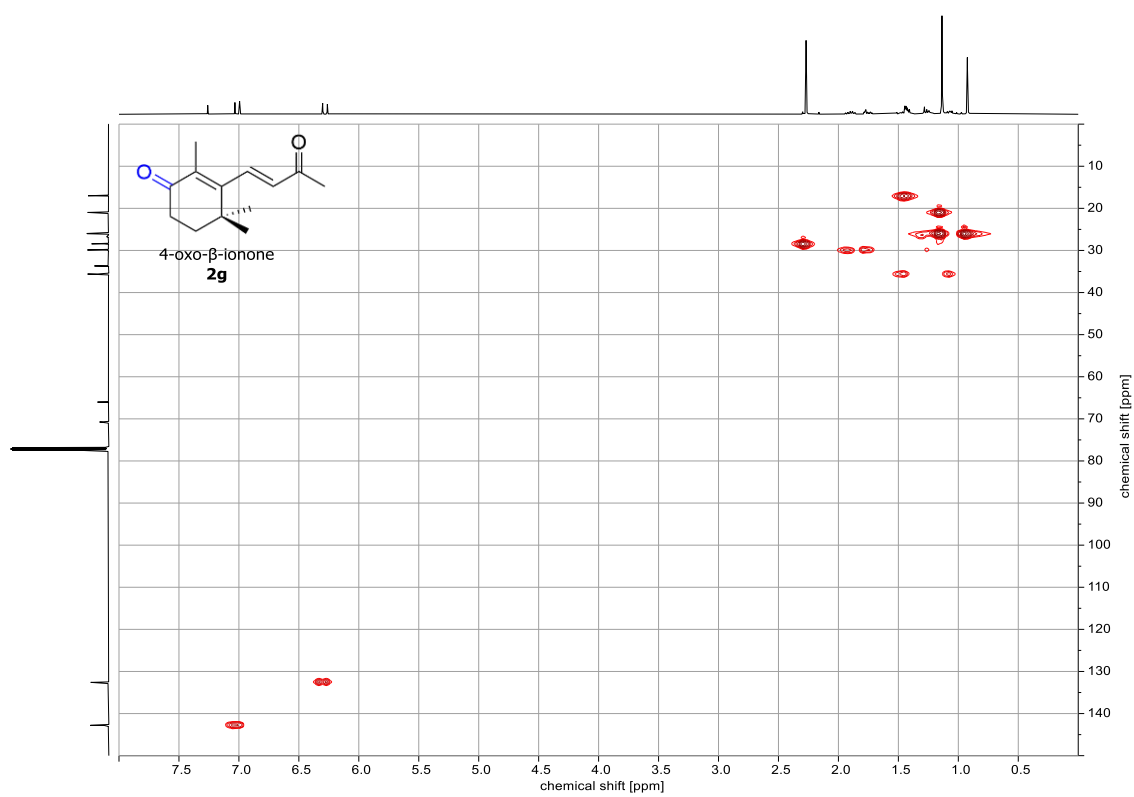


Figure S38. HSQC spectrum of product **2g**: 4-oxo-β-ionone.

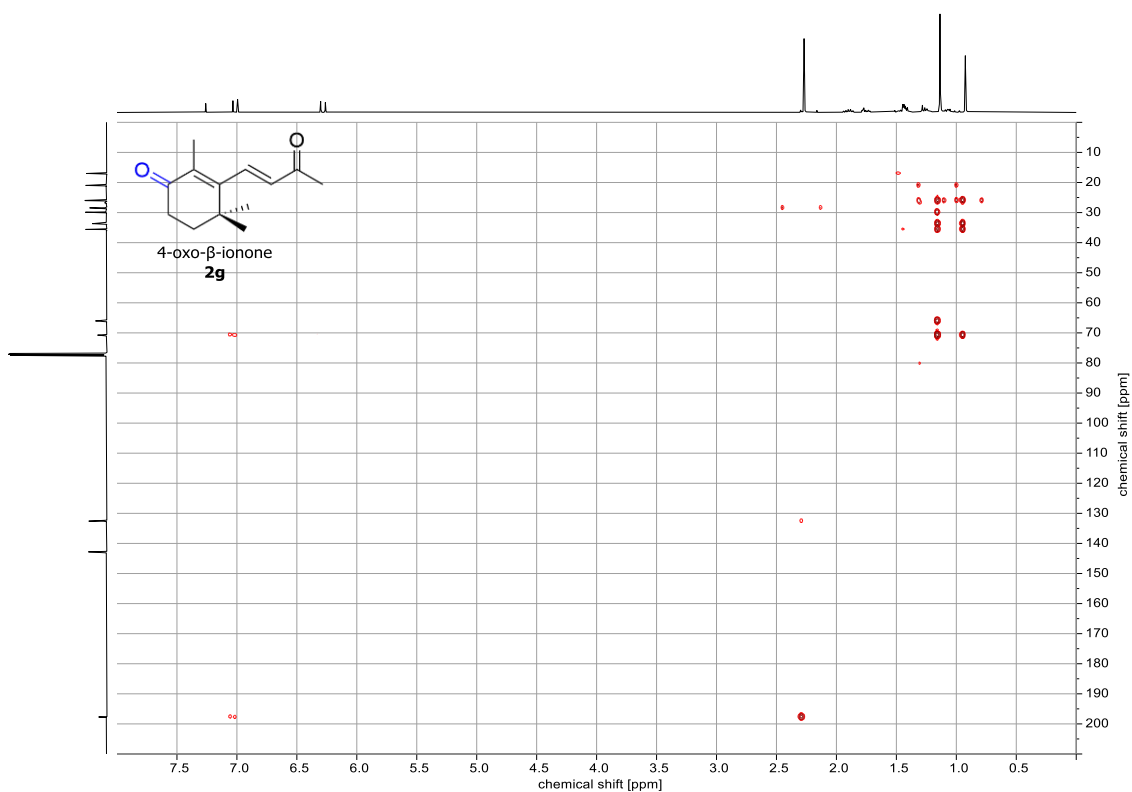


Figure S39. HMBC spectrum of product 2g: 4-oxo-β-ionone.

7.8. 4-Oxo-vinyl-β-ionol

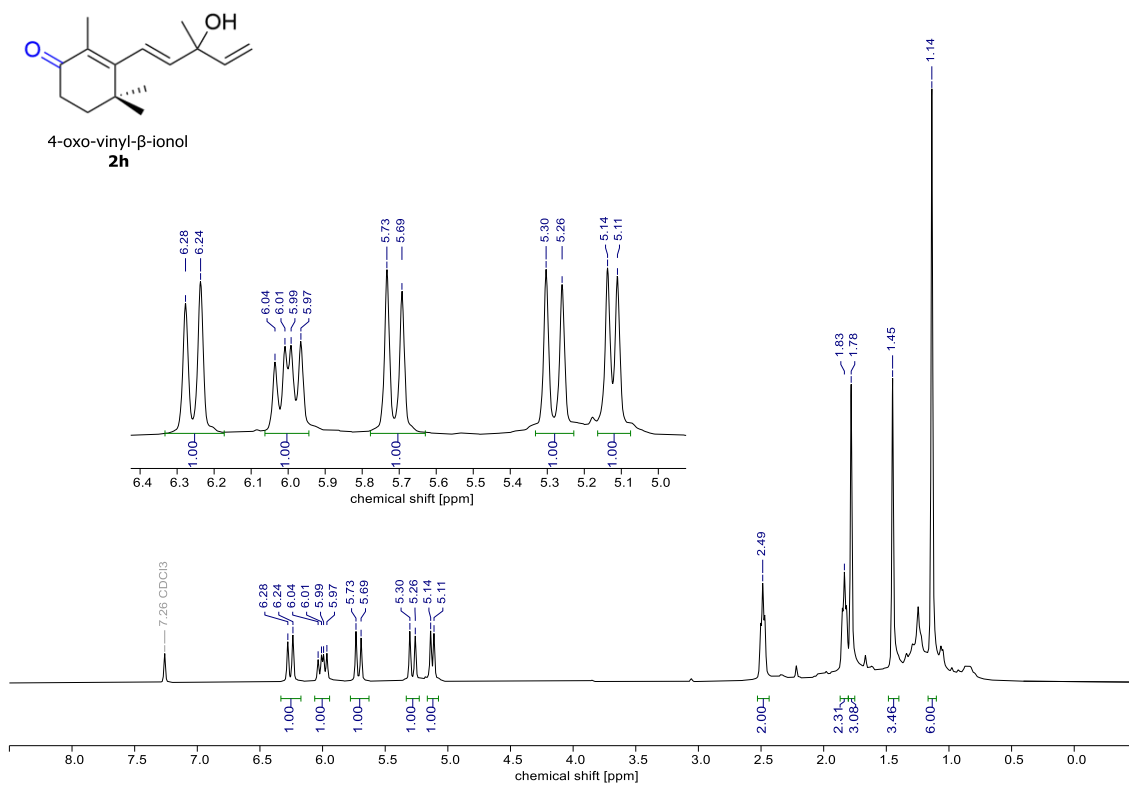


Figure S40. ^1H NMR spectrum (400 MHz) of product 2h: 4-oxo-vinyl-β-ionol.

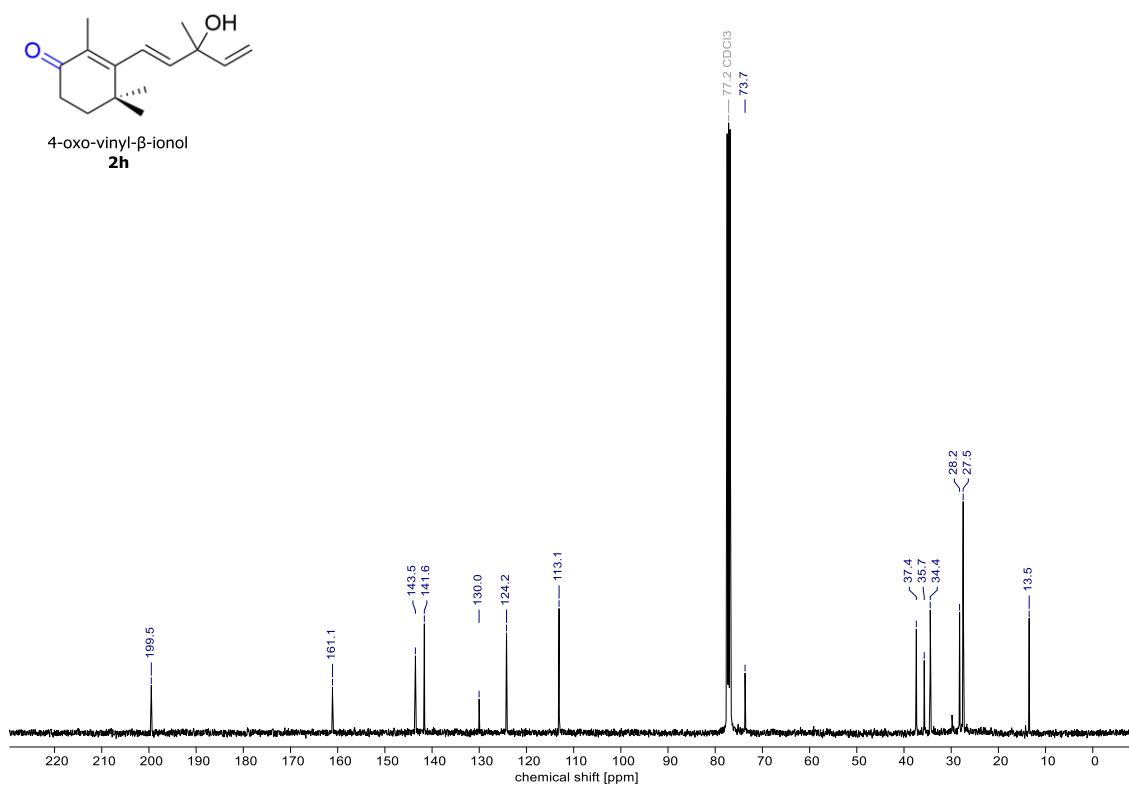


Figure S41. ¹³C NMR spectrum (101 MHz) of product **2h**: 4-oxo-vinyl- β -ionol.

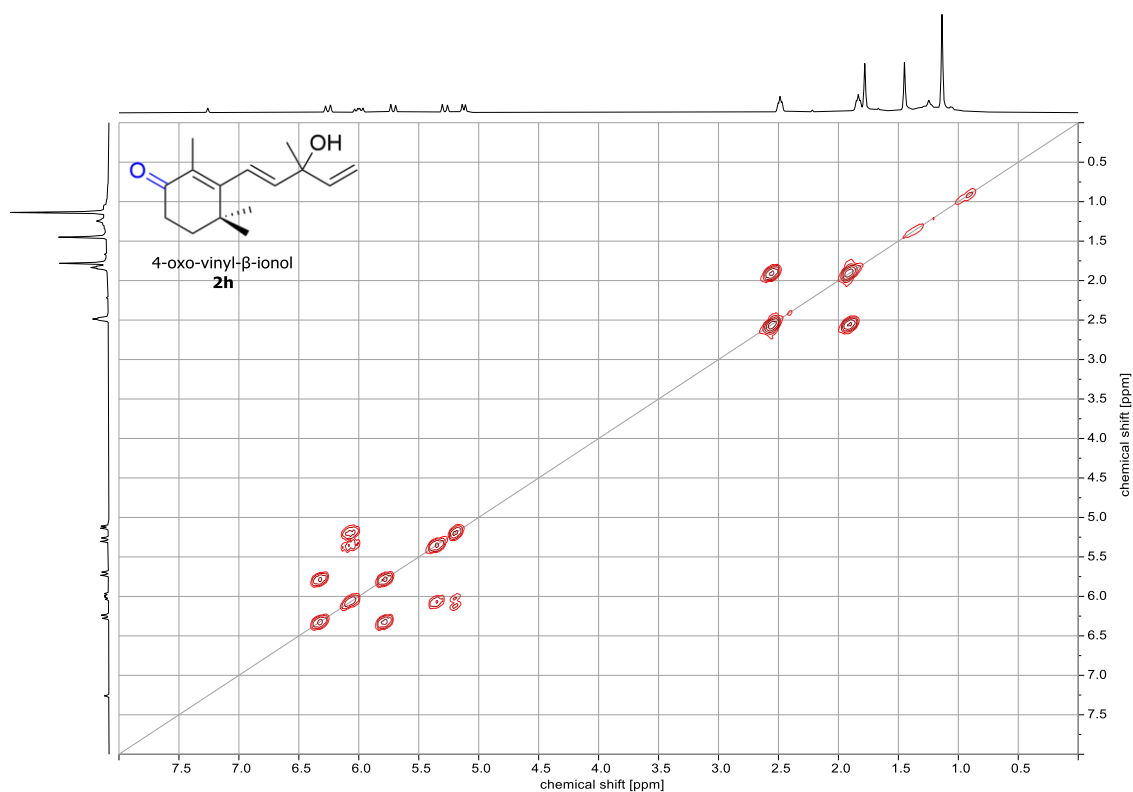


Figure S42. COSY spectrum of product **2h**: 4-oxo-vinyl- β -ionol.

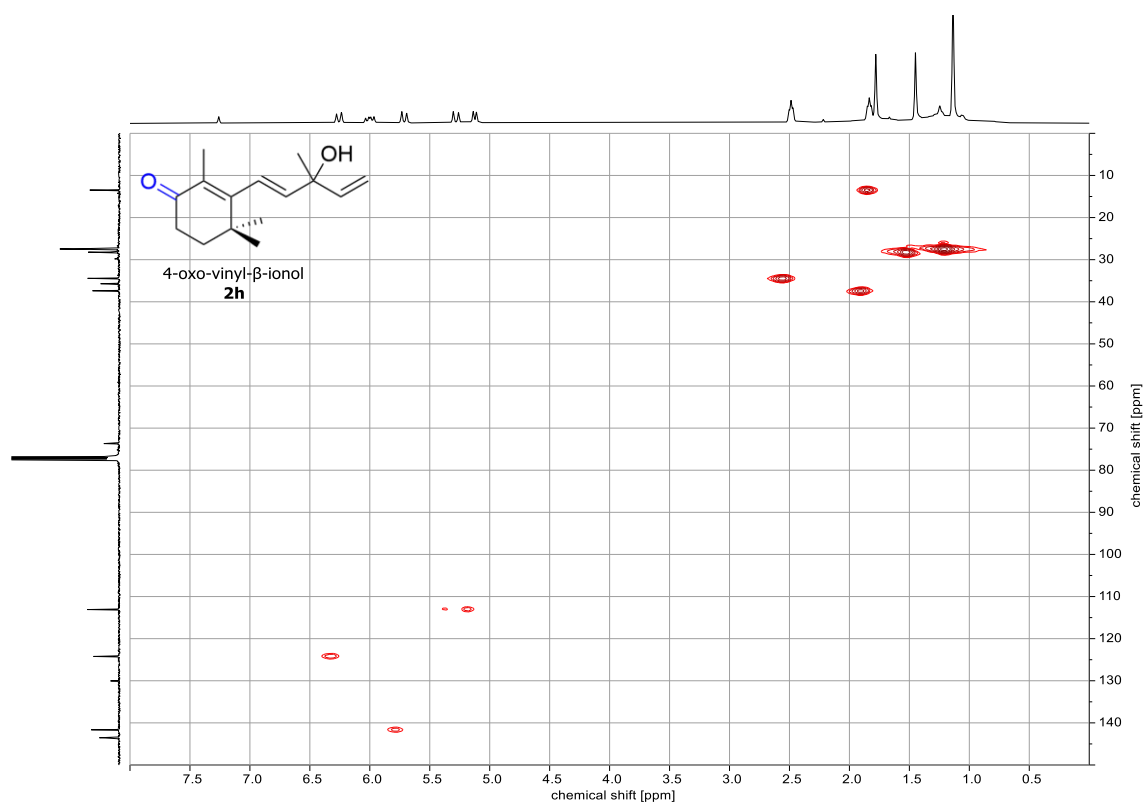


Figure S43. HSQC spectrum of product **2h**: 4-oxo-vinyl- β -ionol.

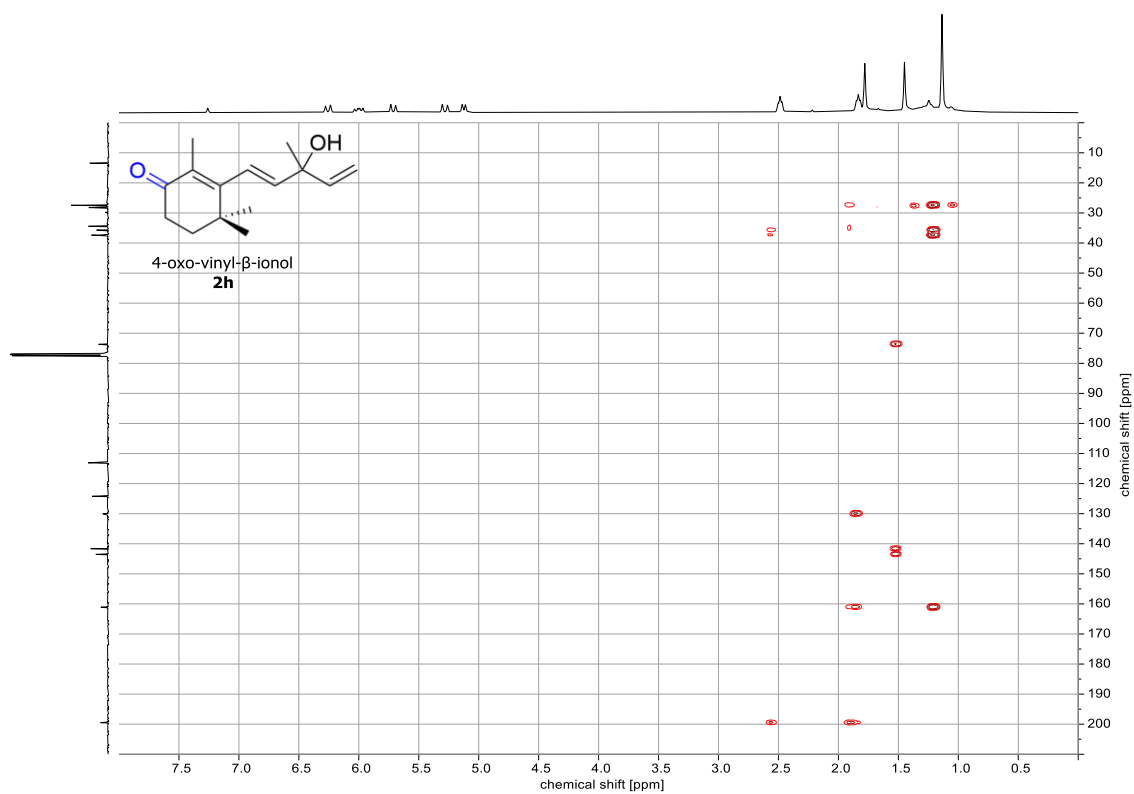
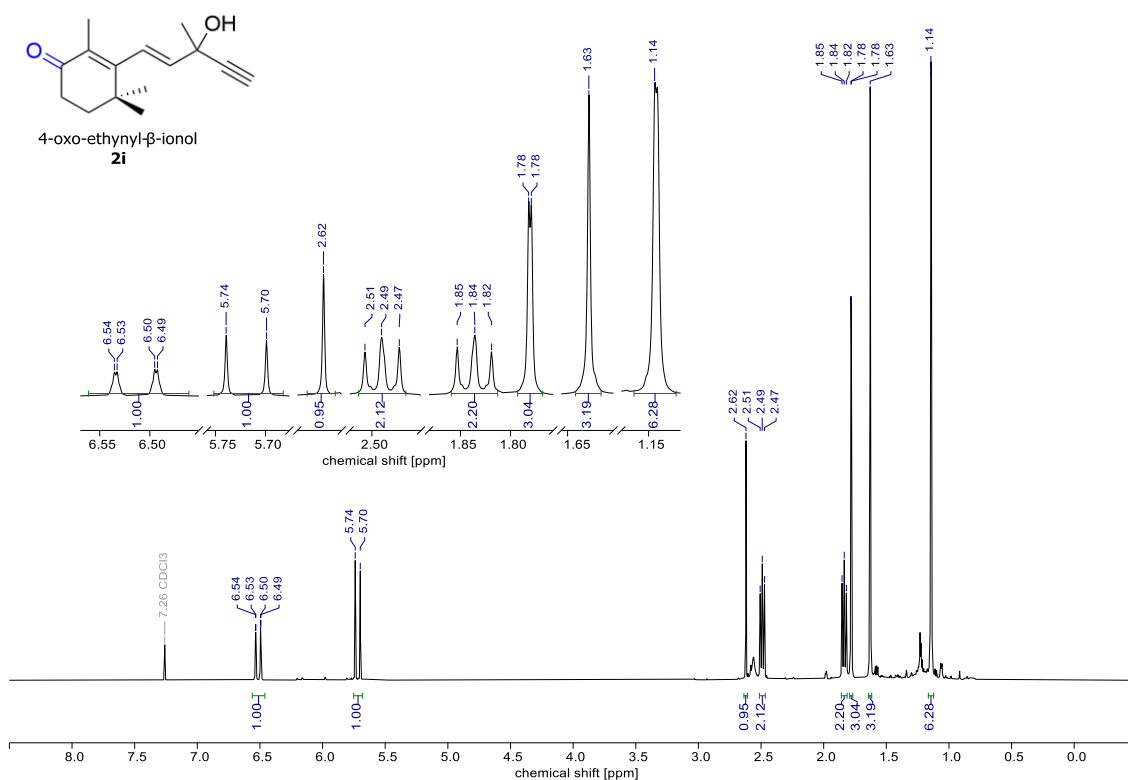
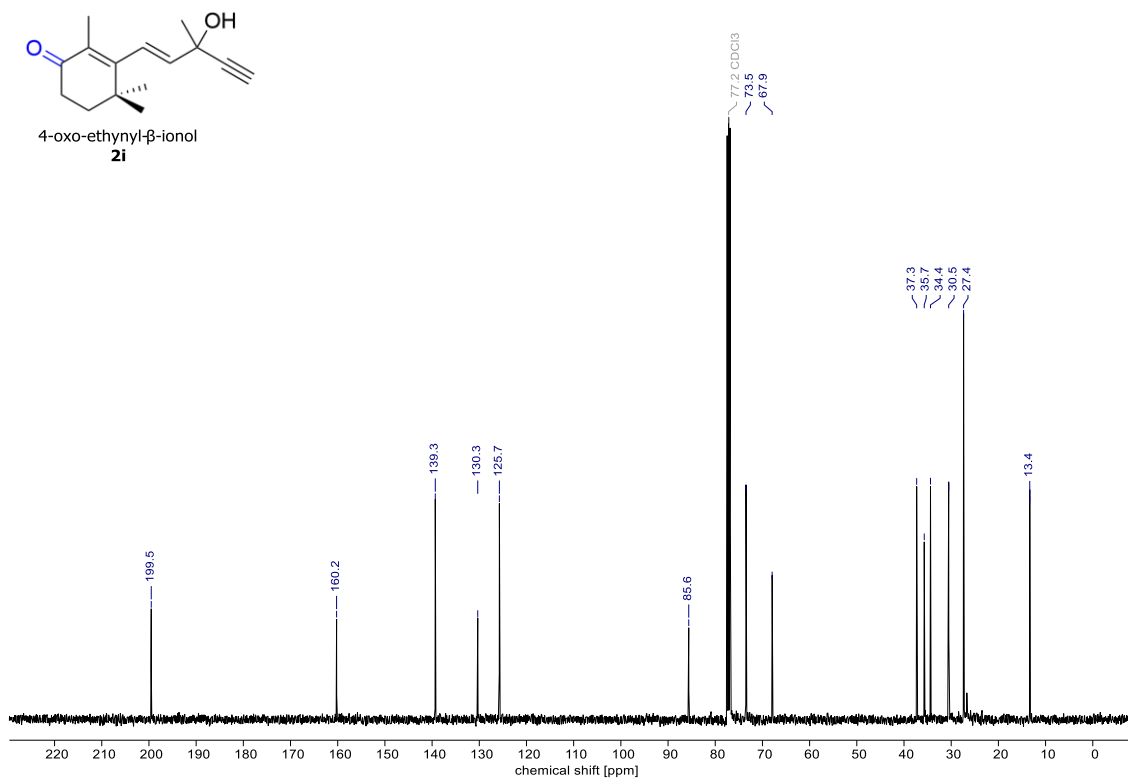


Figure S44. HMBC spectrum of product **2h**: 4-oxo-vinyl- β -ionol.

7.9. 4-Oxo-ethynyl- β -ionolFigure S45. ¹H NMR spectrum (400 MHz) of product **2i**: 4-oxo-ethynyl- β -ionol.Figure S46. ¹³C NMR spectrum (101 MHz) of product **2i**: 4-oxo-ethynyl- β -ionol.

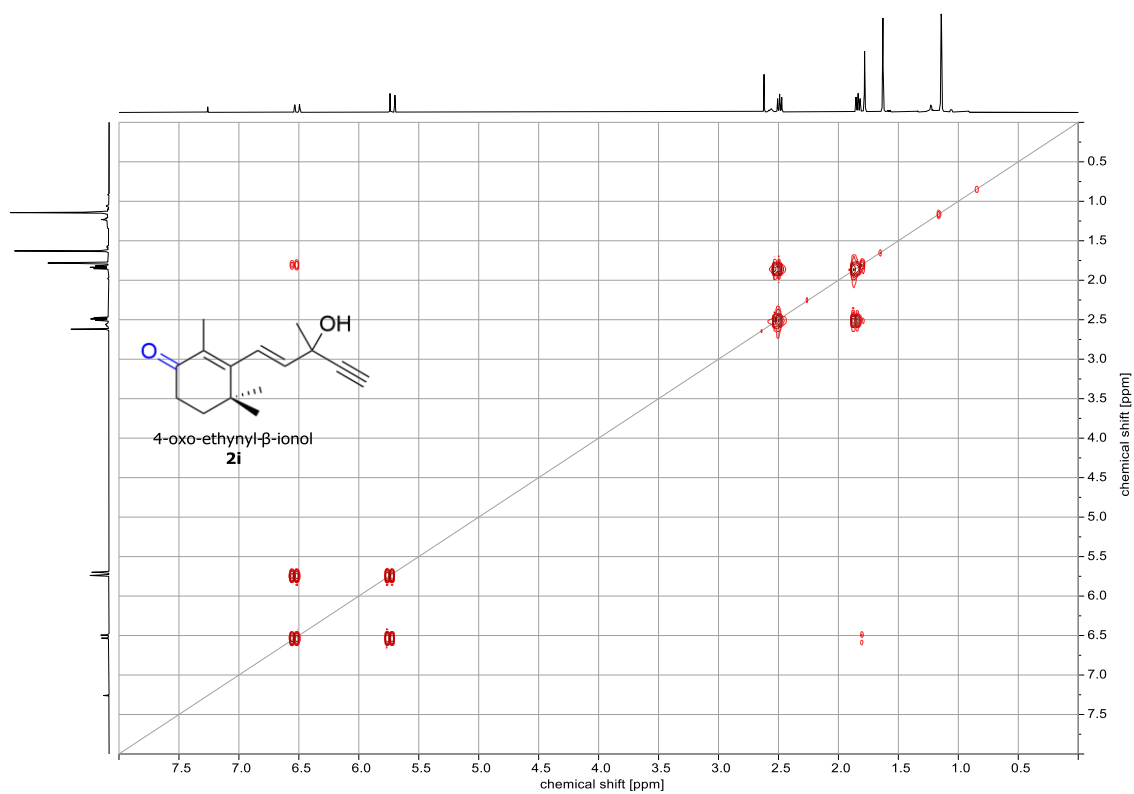


Figure S47. COSY spectrum of product **2i**: 4-oxo-ethynyl- β -ionol.

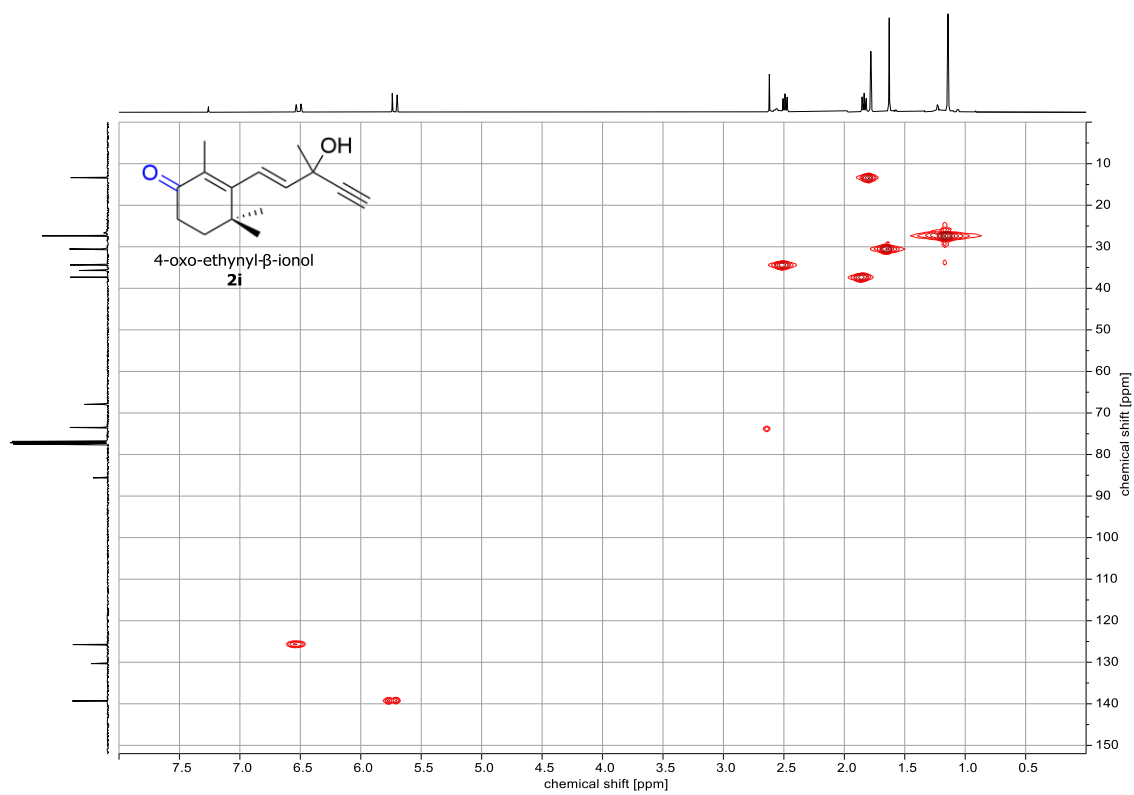
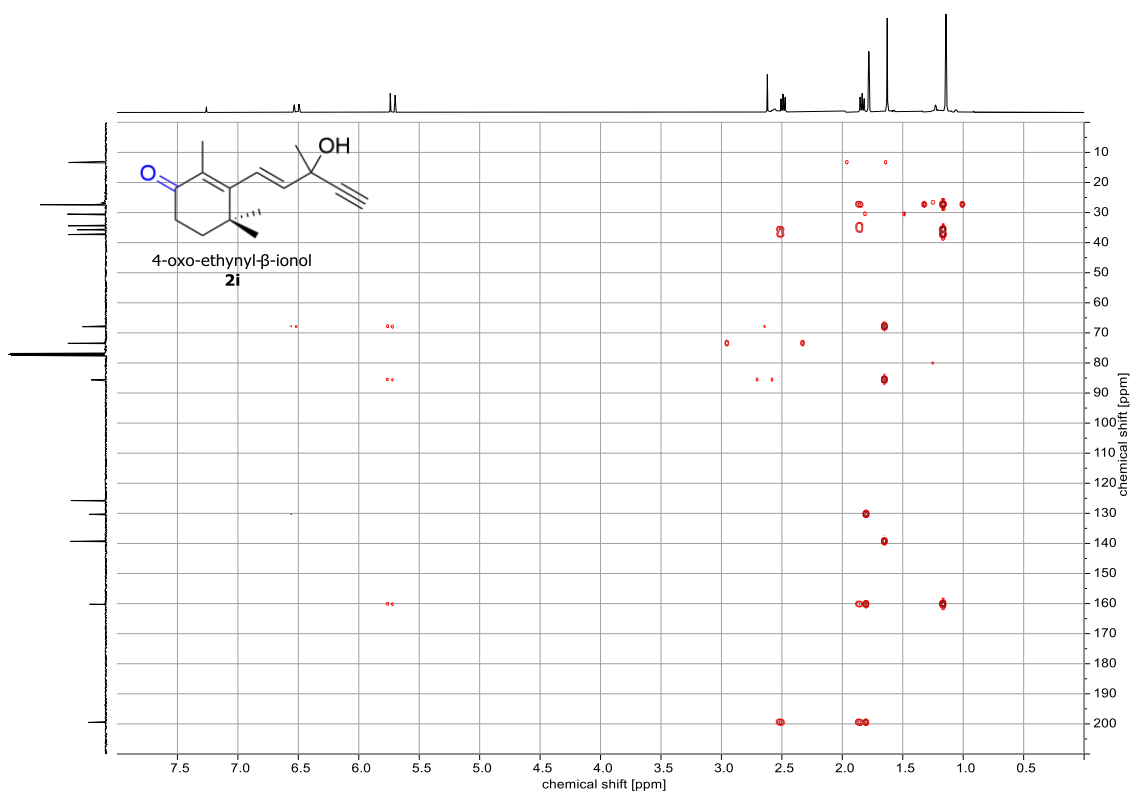
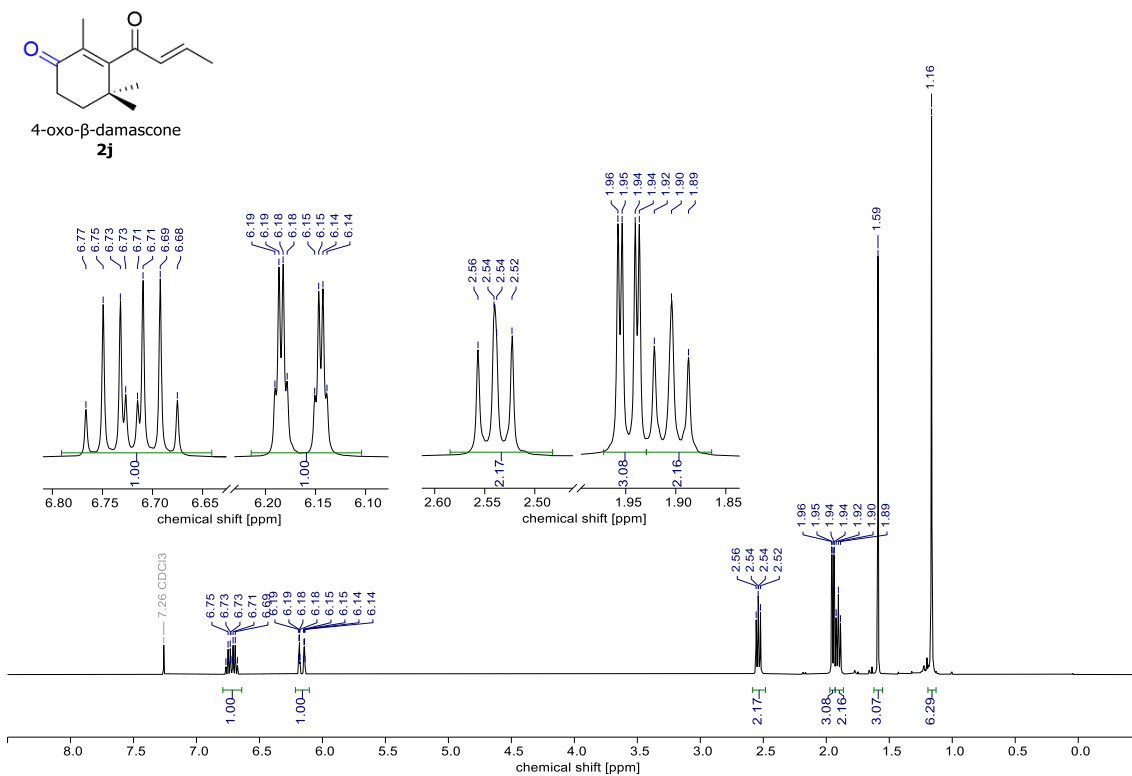


Figure S48. HSQC spectrum of product **2i**: 4-oxo-ethynyl- β -ionol.



7.10. 4-Oxo-β-damascone



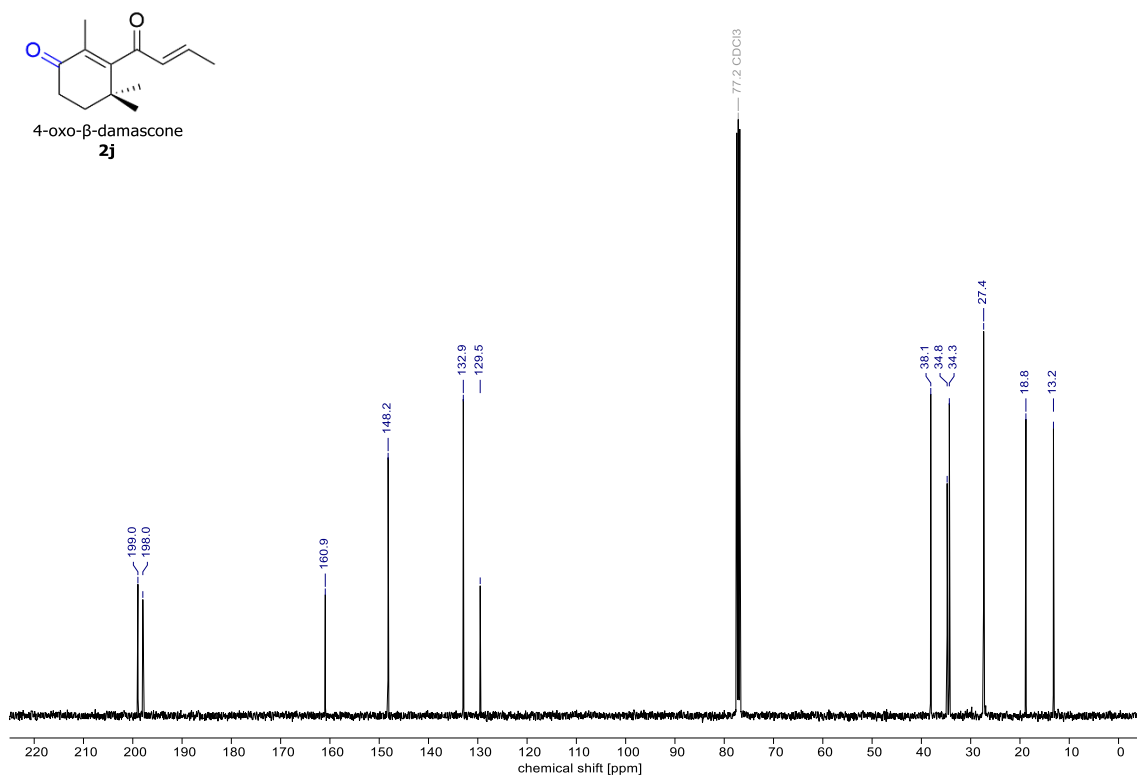


Figure S51. ¹³C NMR spectrum (101 MHz) of product **2j**: 4-oxo- β -damascone.

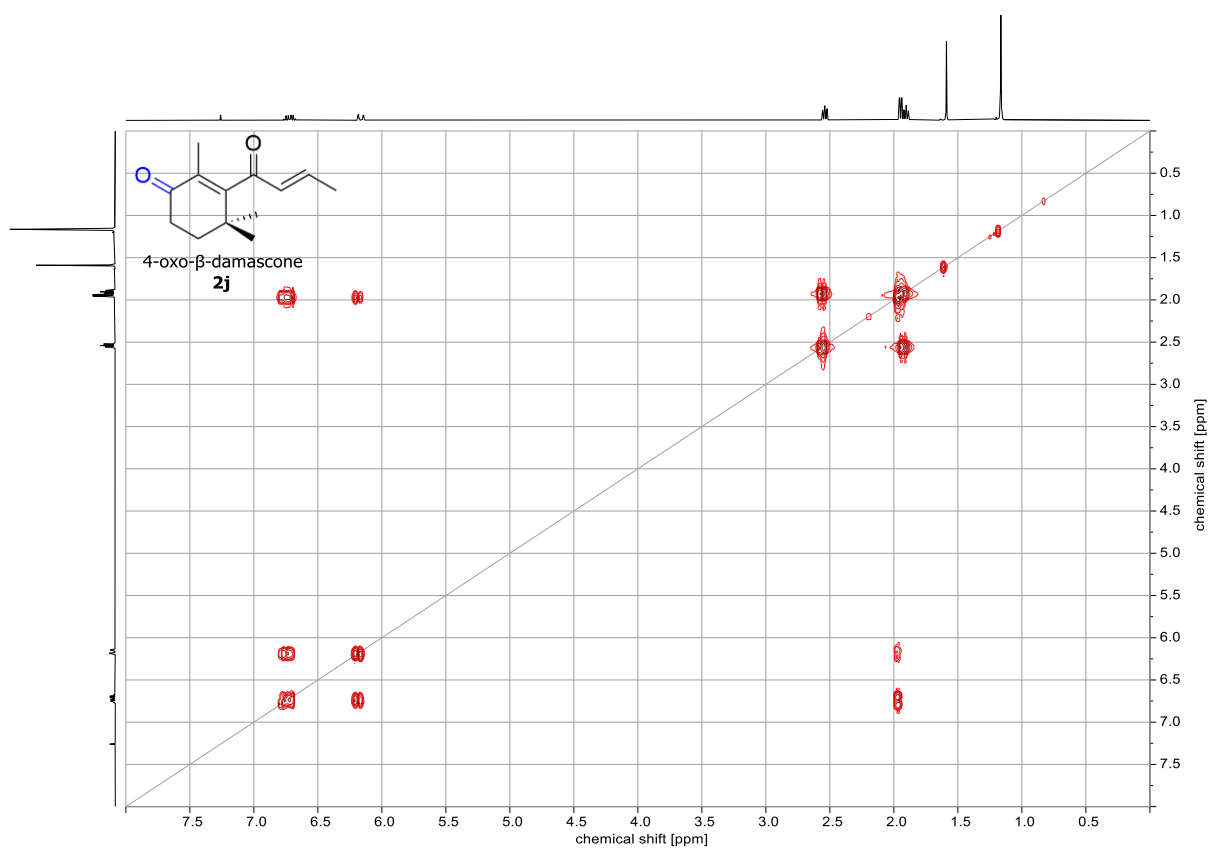


Figure S52. COSY spectrum of product **2j**: 4-oxo- β -damascone.

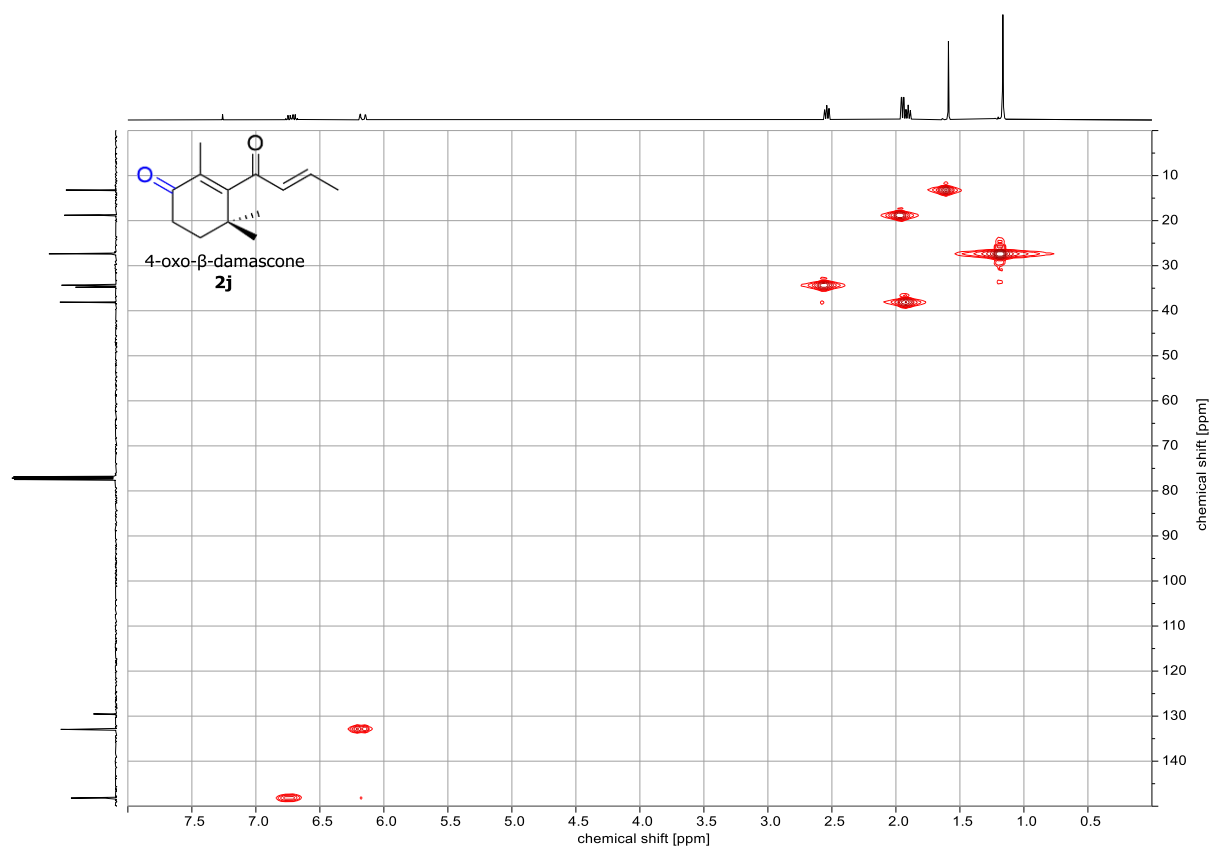


Figure S53. HSQC spectrum of product **2j**: 4-oxo-β-damascone.

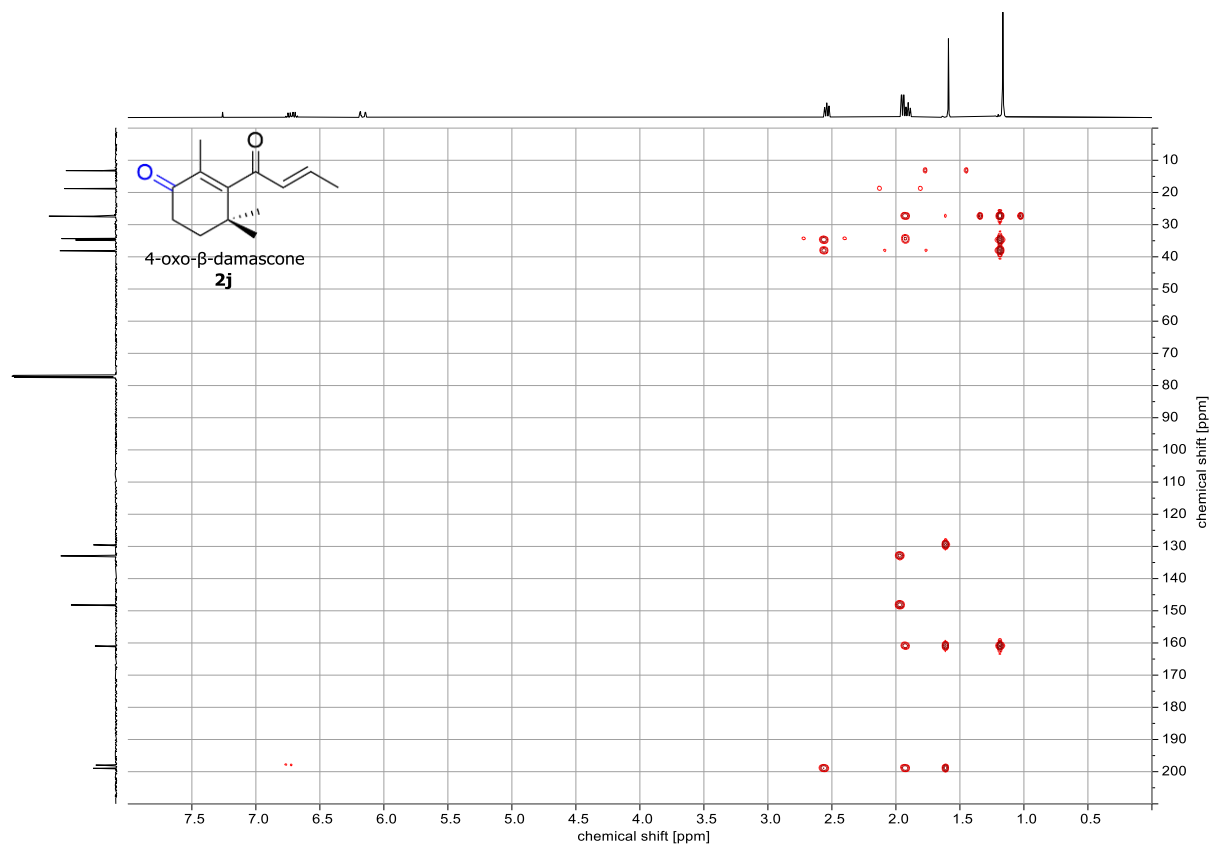
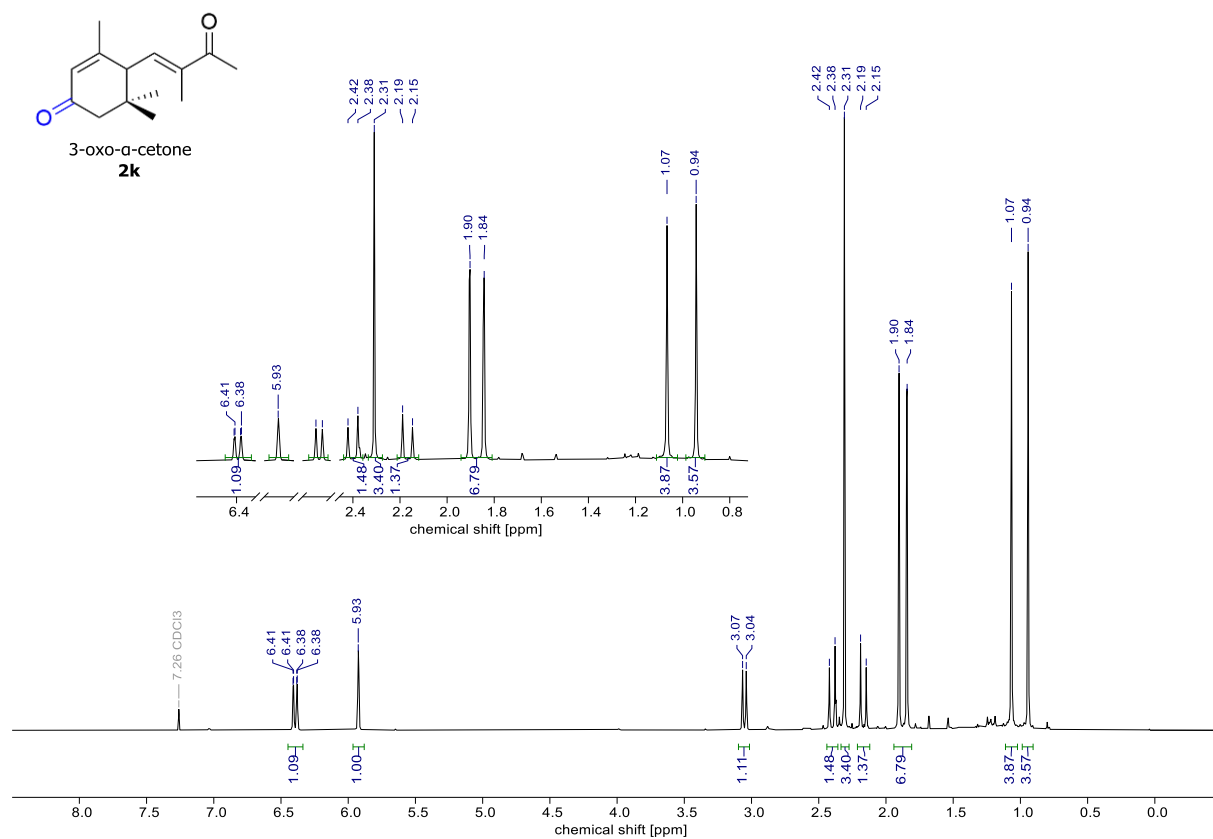
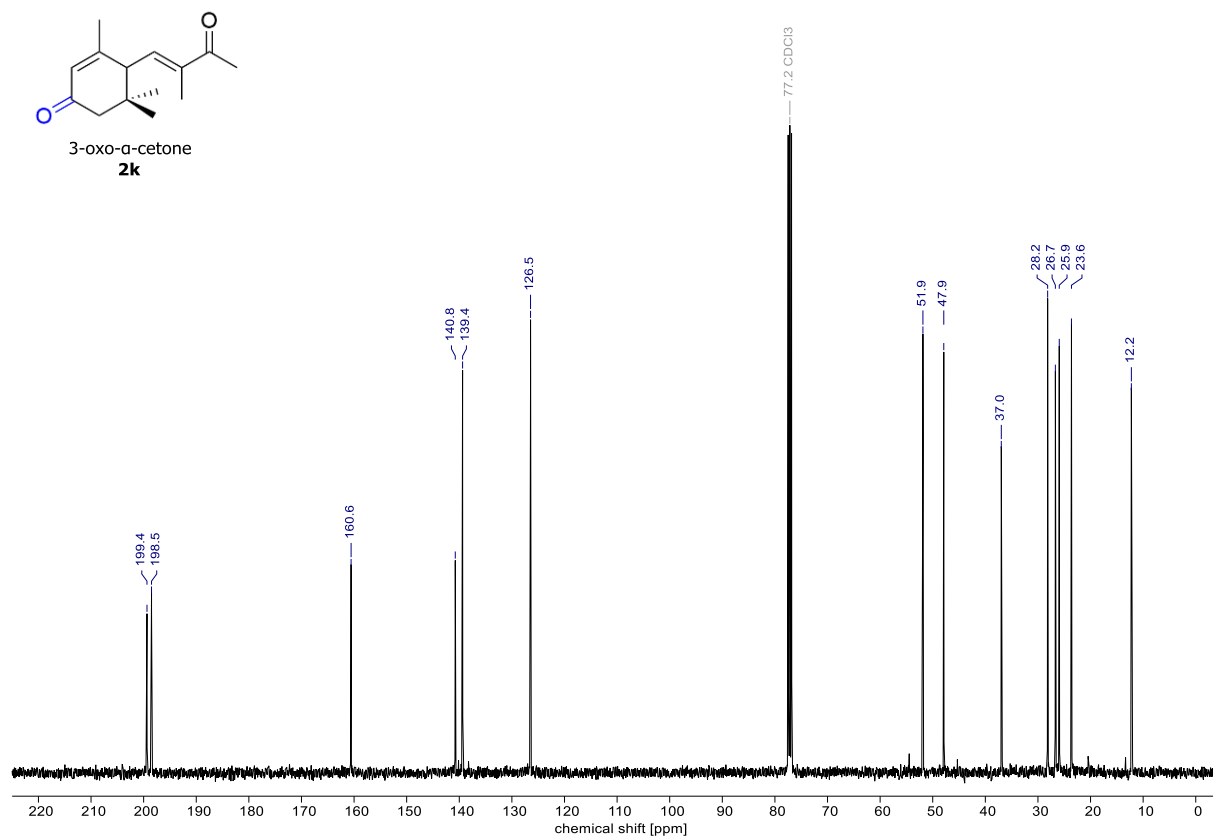


Figure S54. HMBC spectrum of product **2j**: 4-oxo-β-damascone.

7.11. 3-Oxo- α -ketoneFigure S55. ¹H NMR spectrum (400 MHz) of product **2k**: 3-oxo- α -ketone.Figure S56. ¹³C NMR spectrum (101 MHz) of product **2k**: 3-oxo- α -ketone.

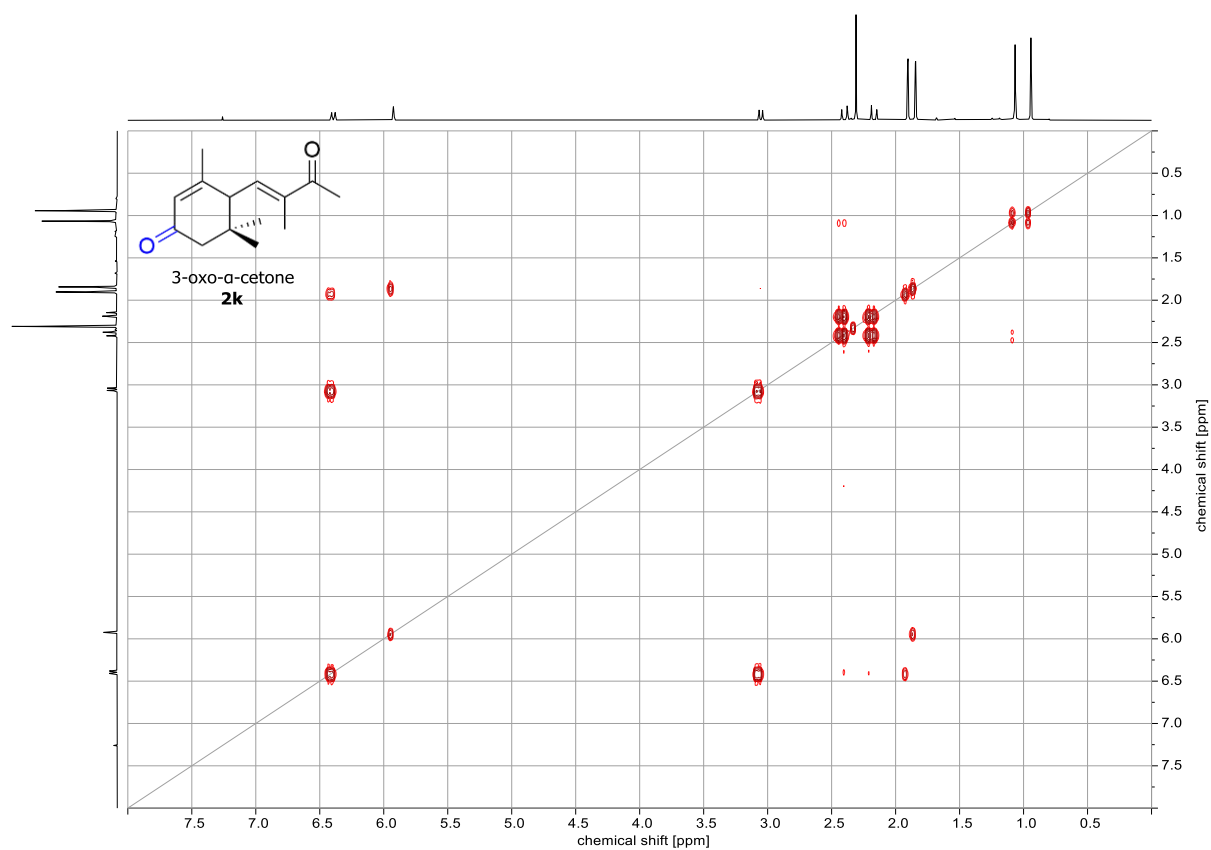


Figure S57. COSY spectrum of product **2k**: 3-oxo- α -cetone.

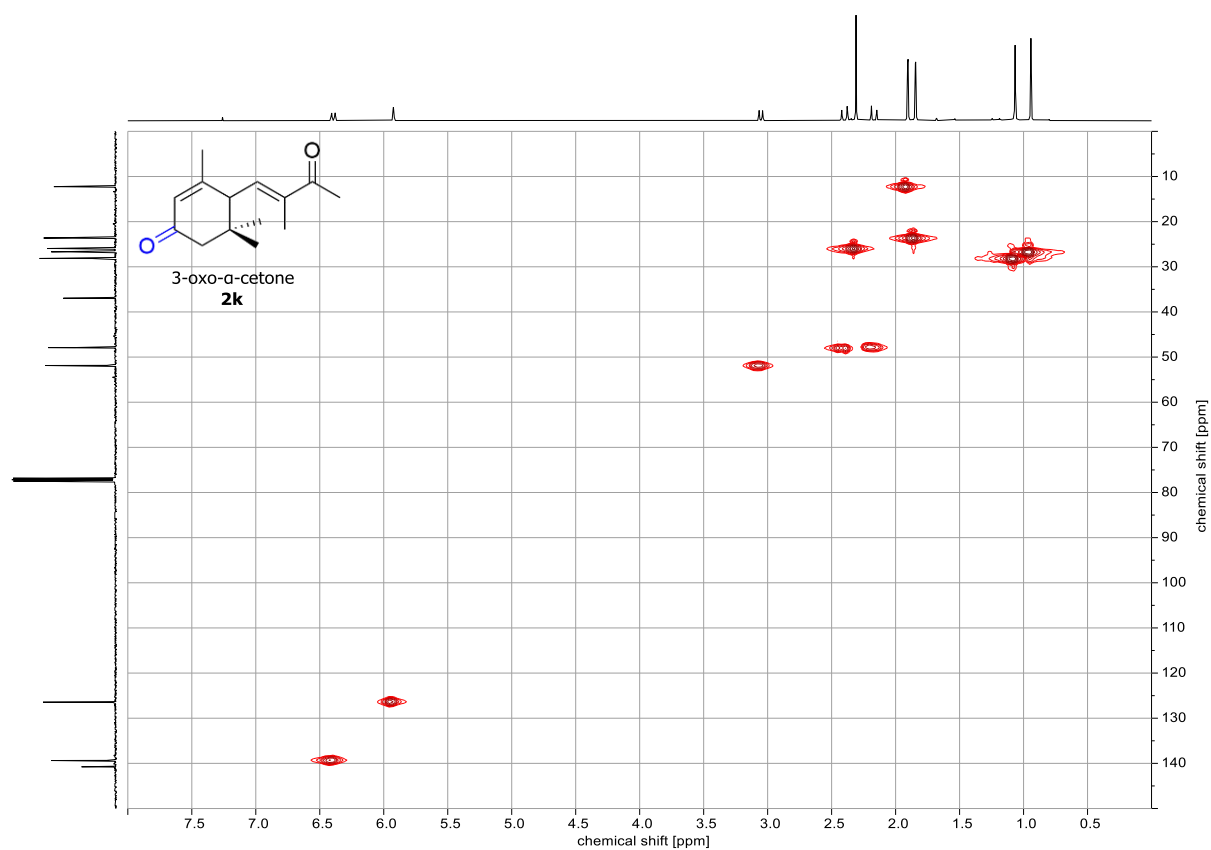
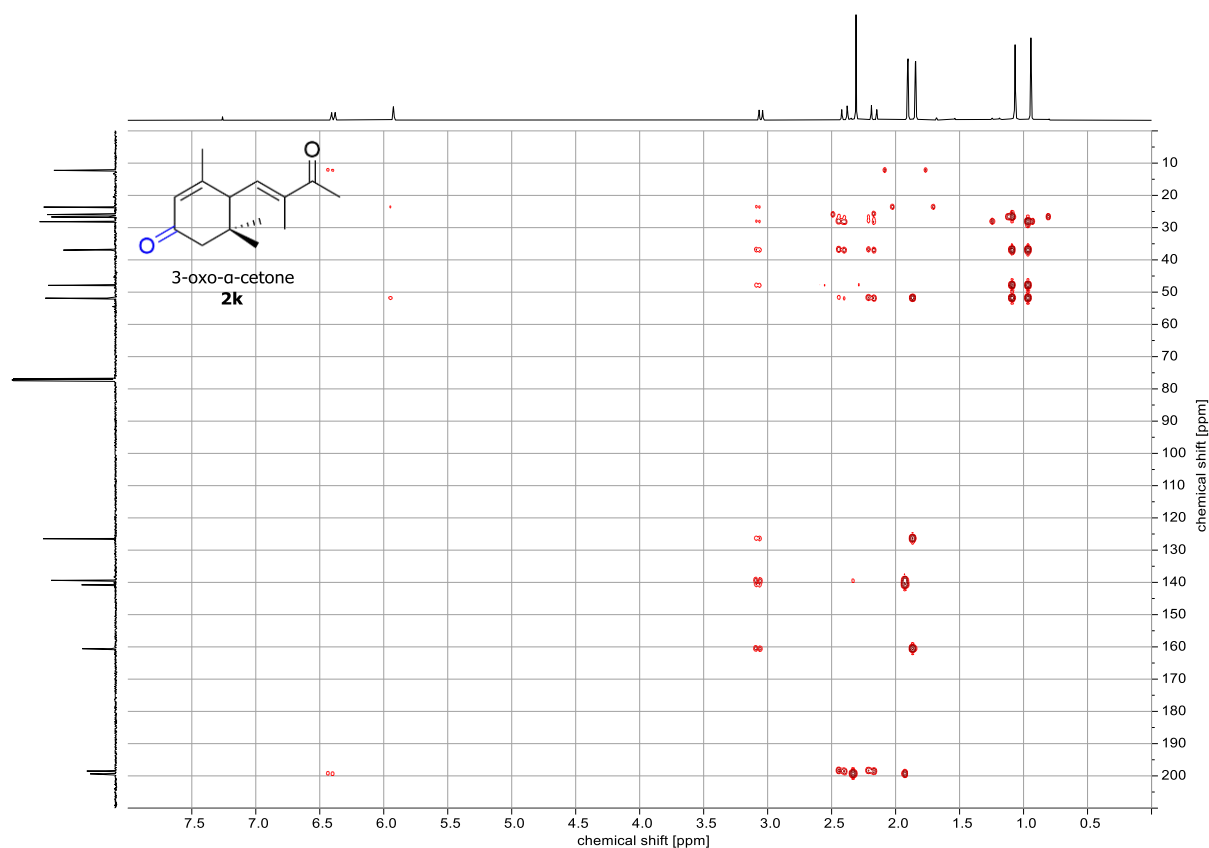
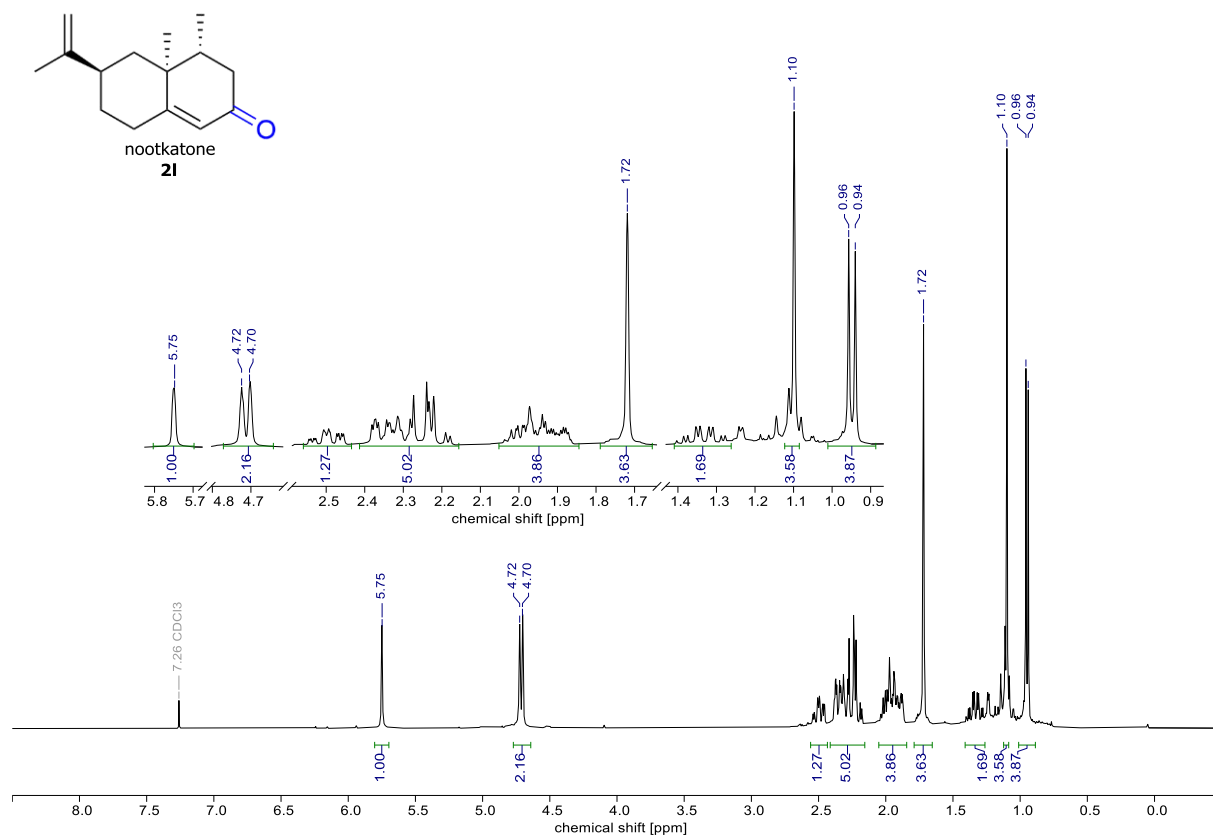


Figure S58. HSQC spectrum of product **2k**: 3-oxo- α -cetone.

Figure S59. HMBC spectrum of product **2k**: 3-oxo- α -cetone.

7.12. Nootkatone

Figure S60. ¹H NMR spectrum (400 MHz) of product **2l**: nootkatone.

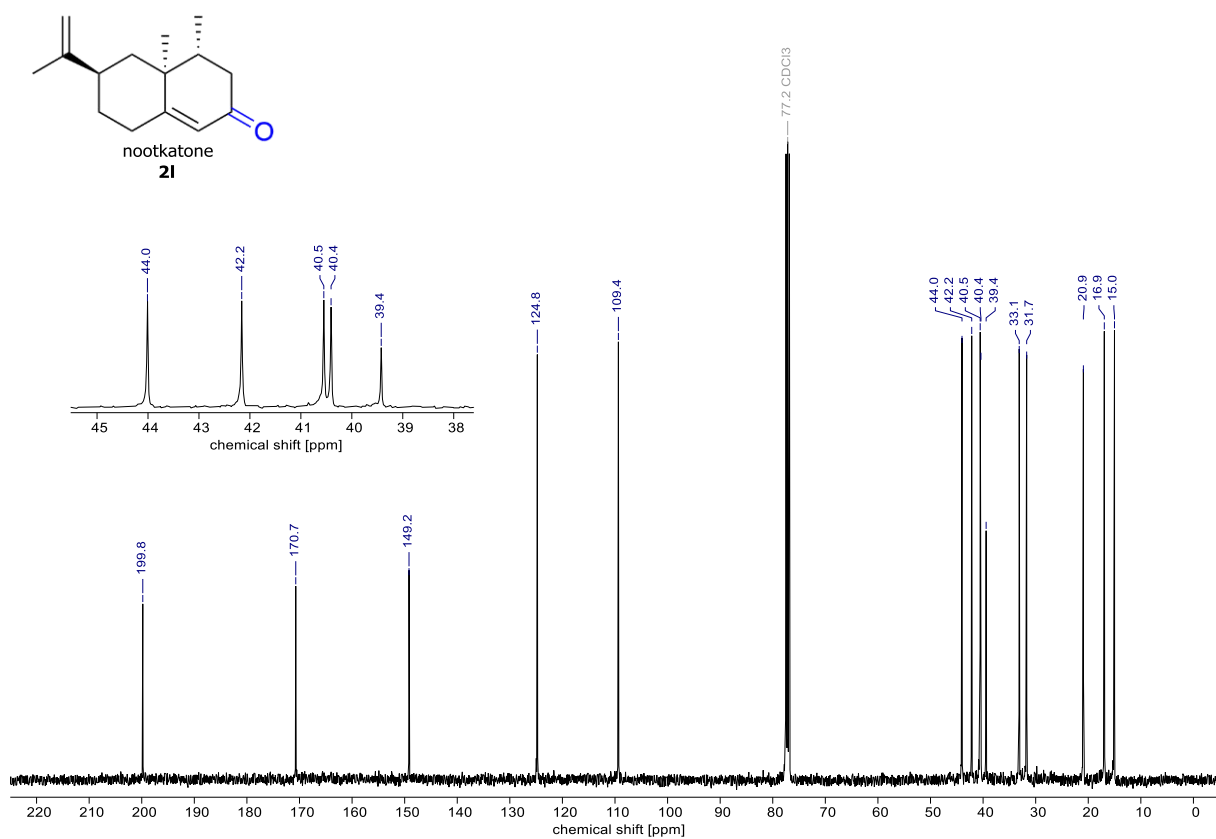


Figure S61. ^{13}C NMR spectrum (101 MHz) of product **2I**: nootkatone.

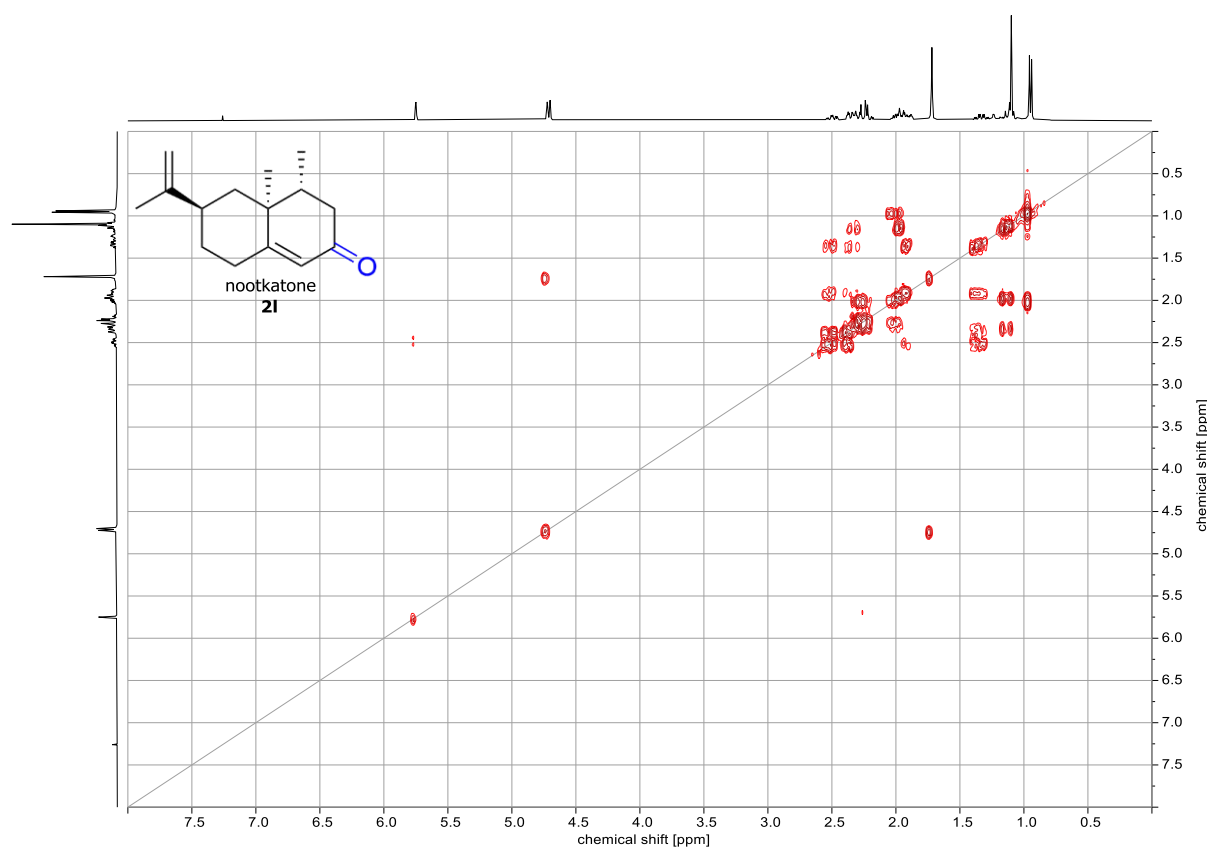


Figure S62. COSY spectrum of product **2I**: nootkatone.

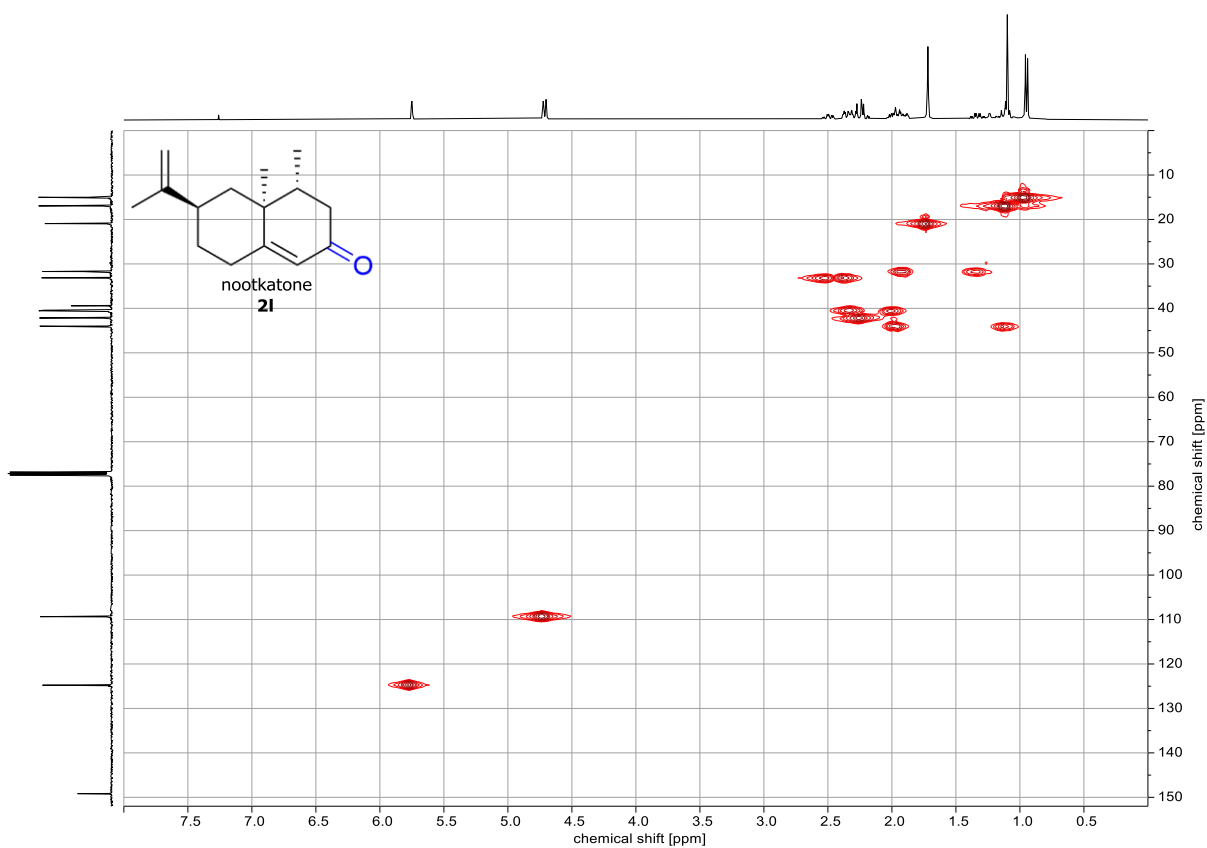


Figure S63. HSQC spectrum of product **2l**: nootkatone.

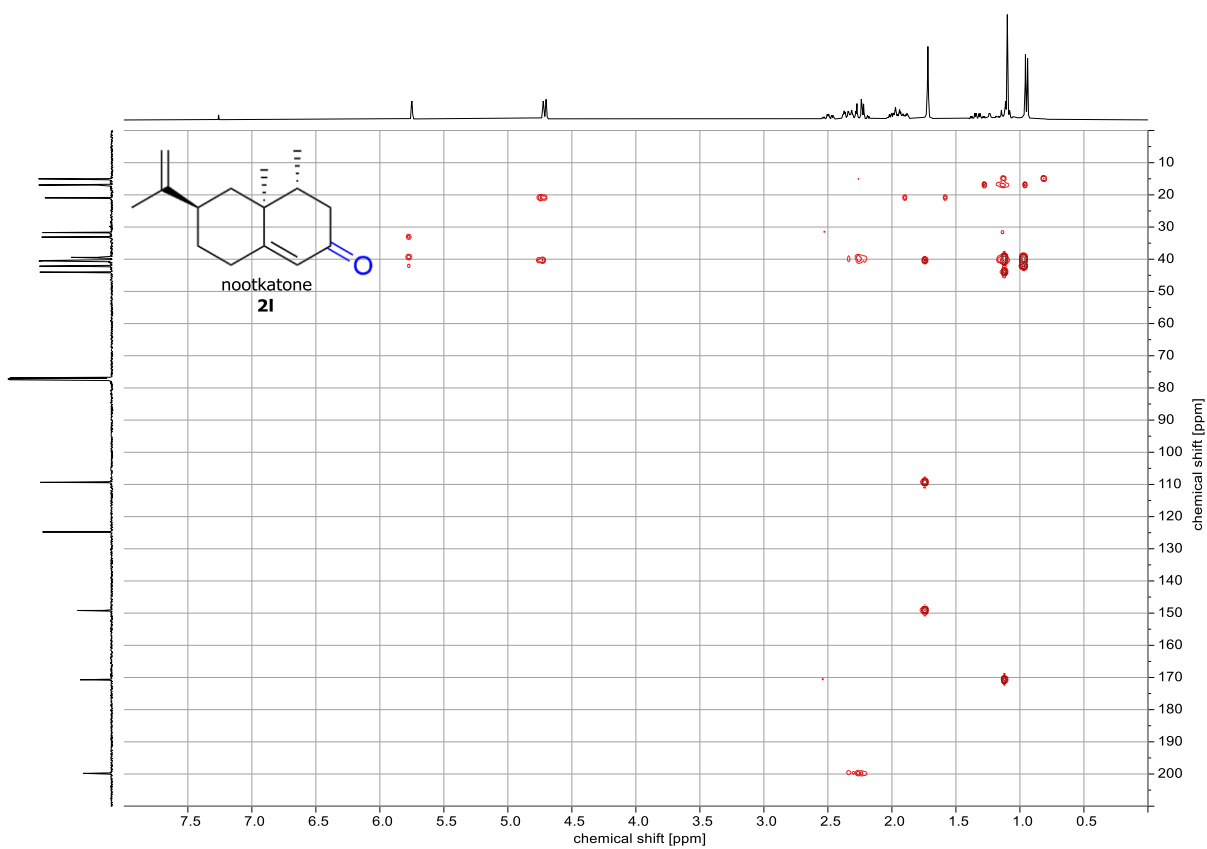
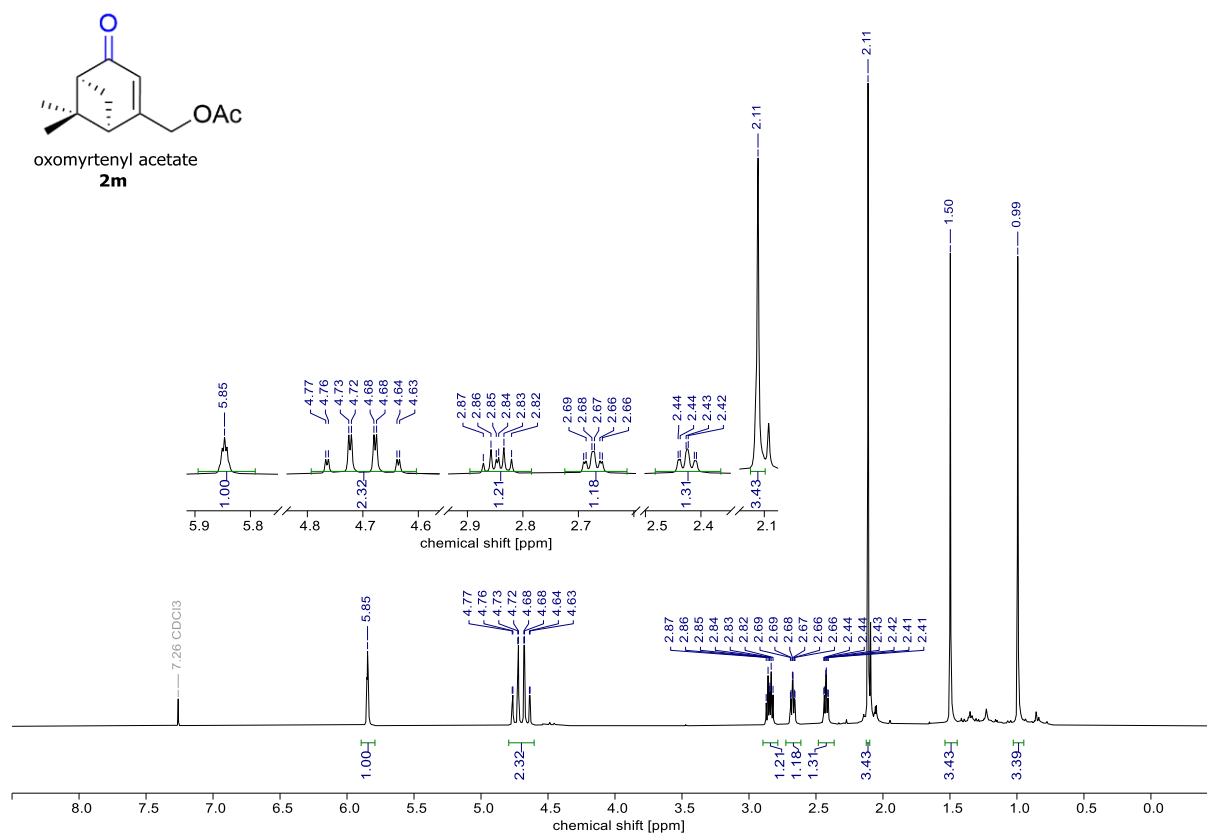
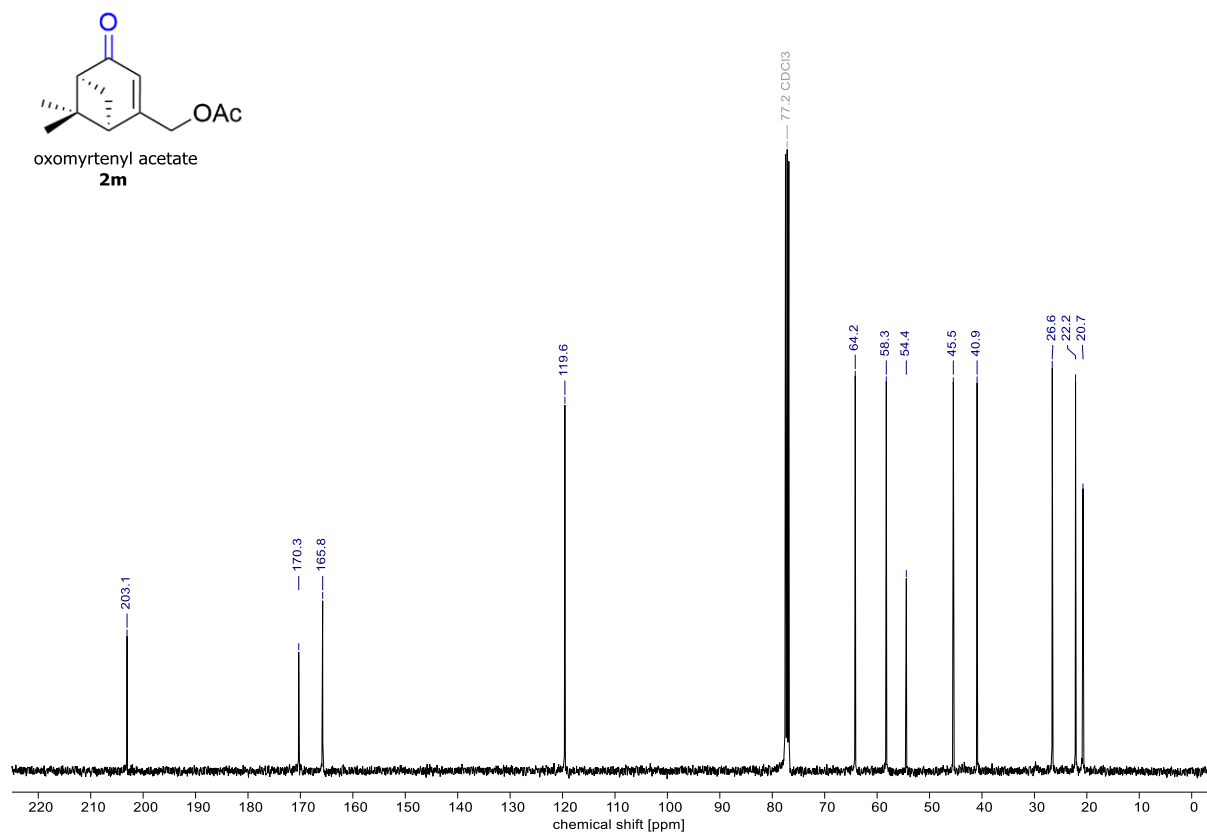
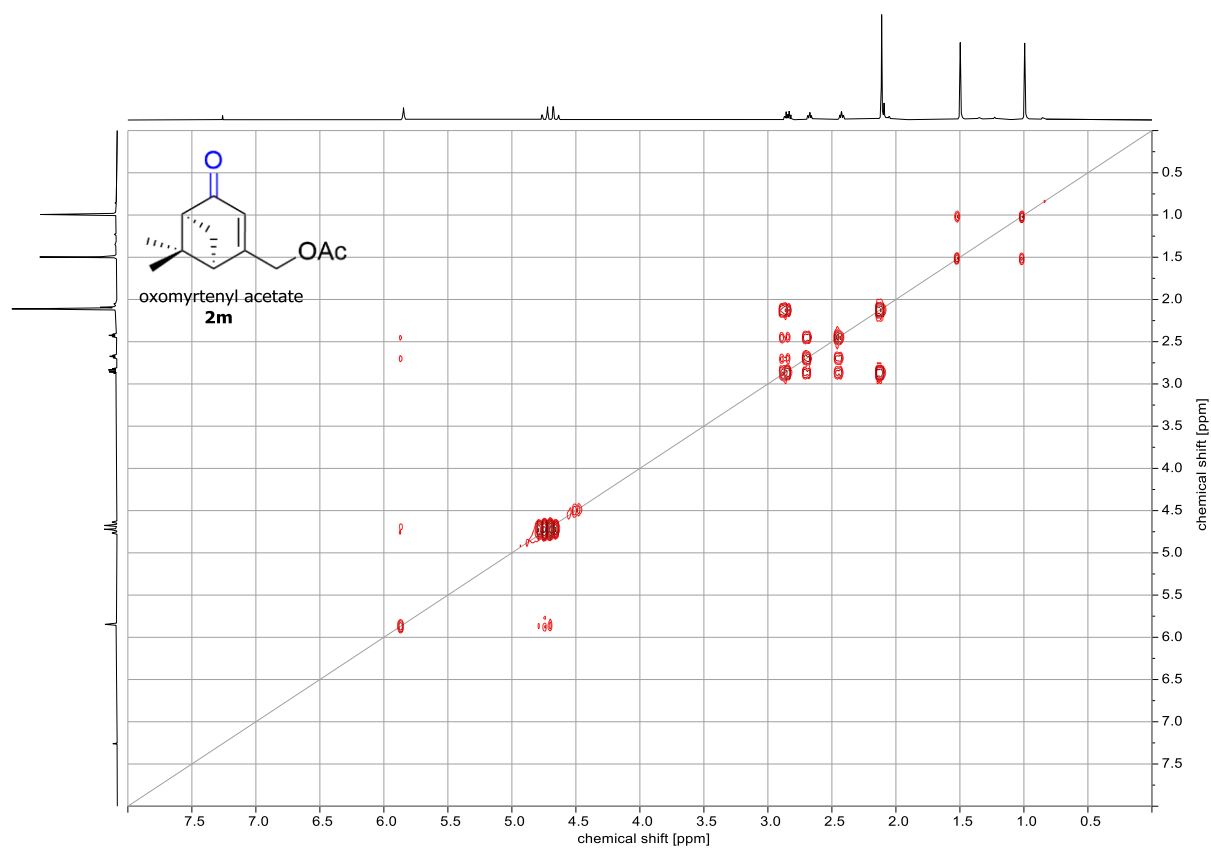
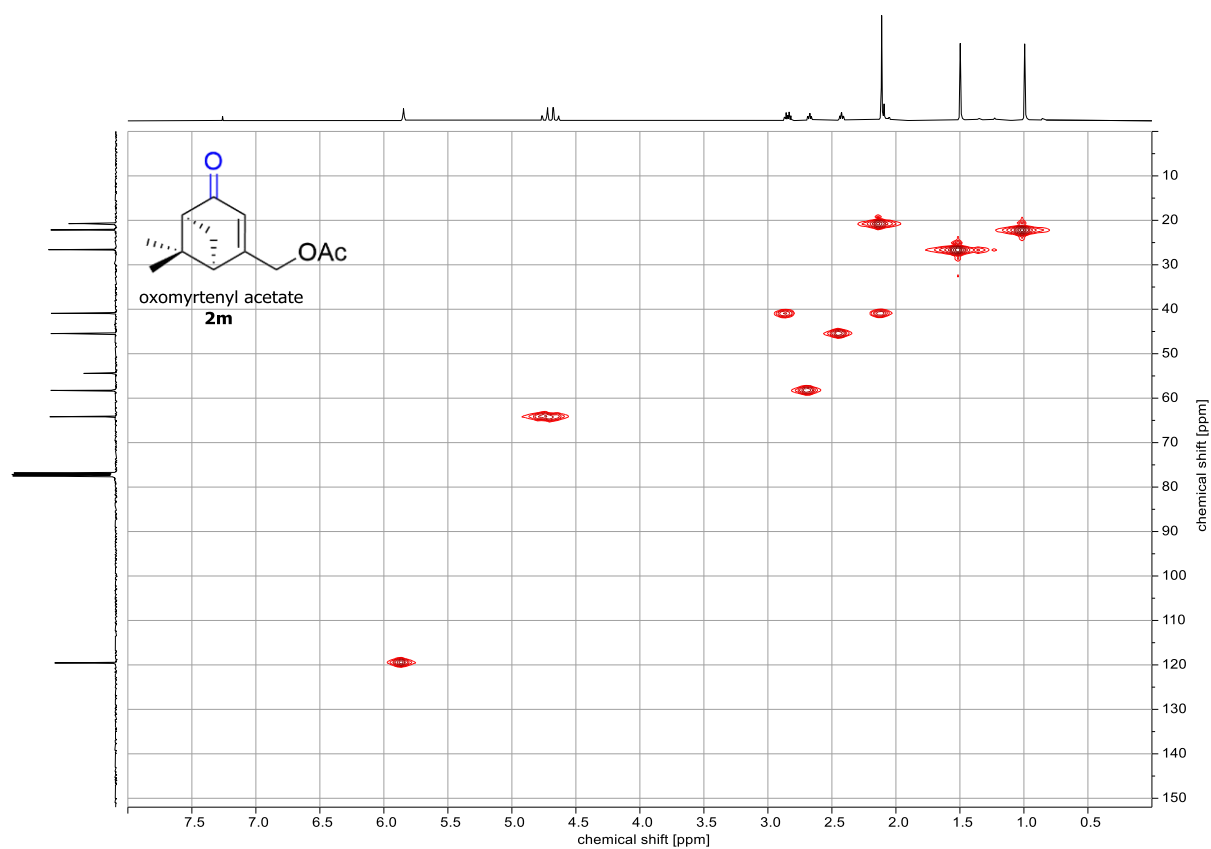


Figure S64. HMBC spectrum of product **2l**: nootkatone.

7.13. Oxomyrtenyl acetate

Figure S65. ¹H NMR spectrum (400 MHz) of product **2m**: oxomyrtenyl acetate.Figure S66. ¹³C NMR spectrum (101 MHz) of product **2m**: oxomyrtenyl acetate.

Figure S67. COSY spectrum of product **2m**: oxomyrtenyl acetate.Figure S68. HSQC spectrum of product **2m**: oxomyrtenyl acetate.

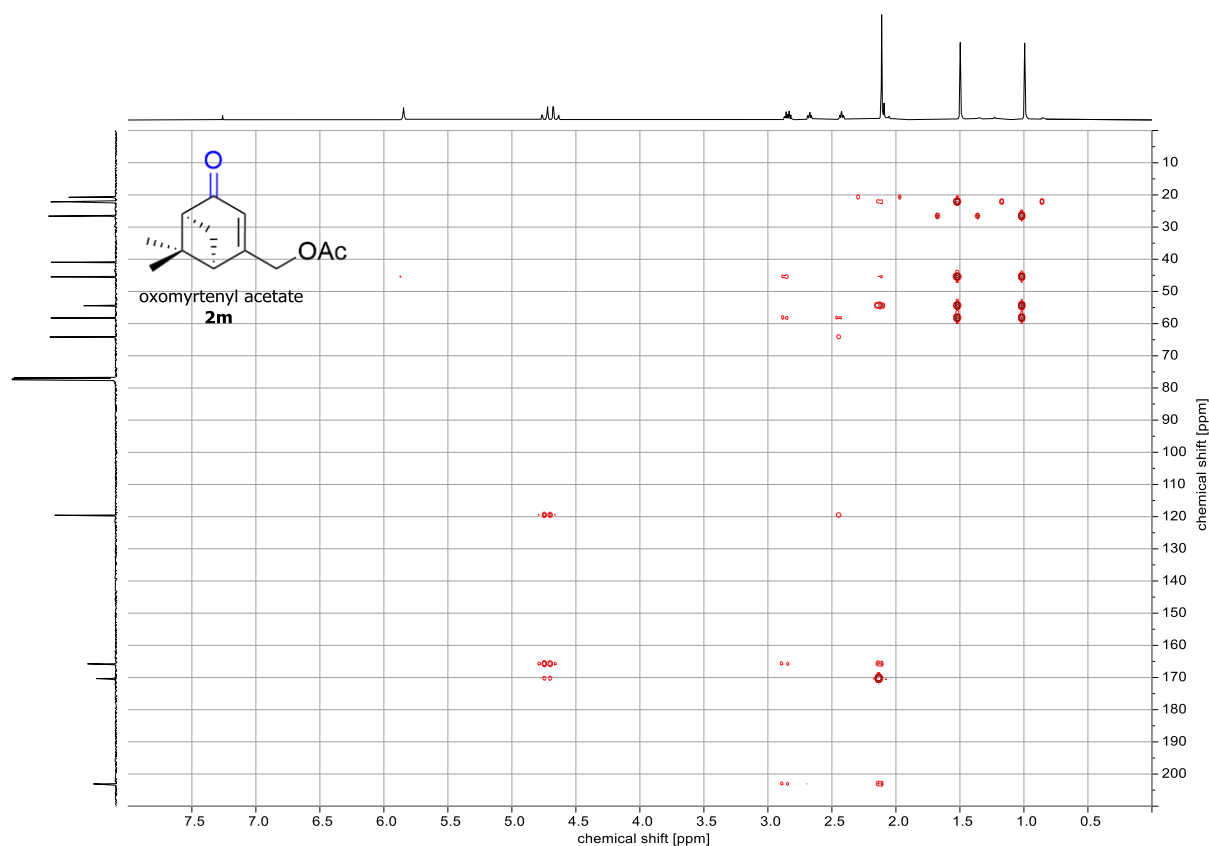


Figure S69. HMBC spectrum of product **2m**: oxomyrtenyl acetate.

7.14. Cedrenone

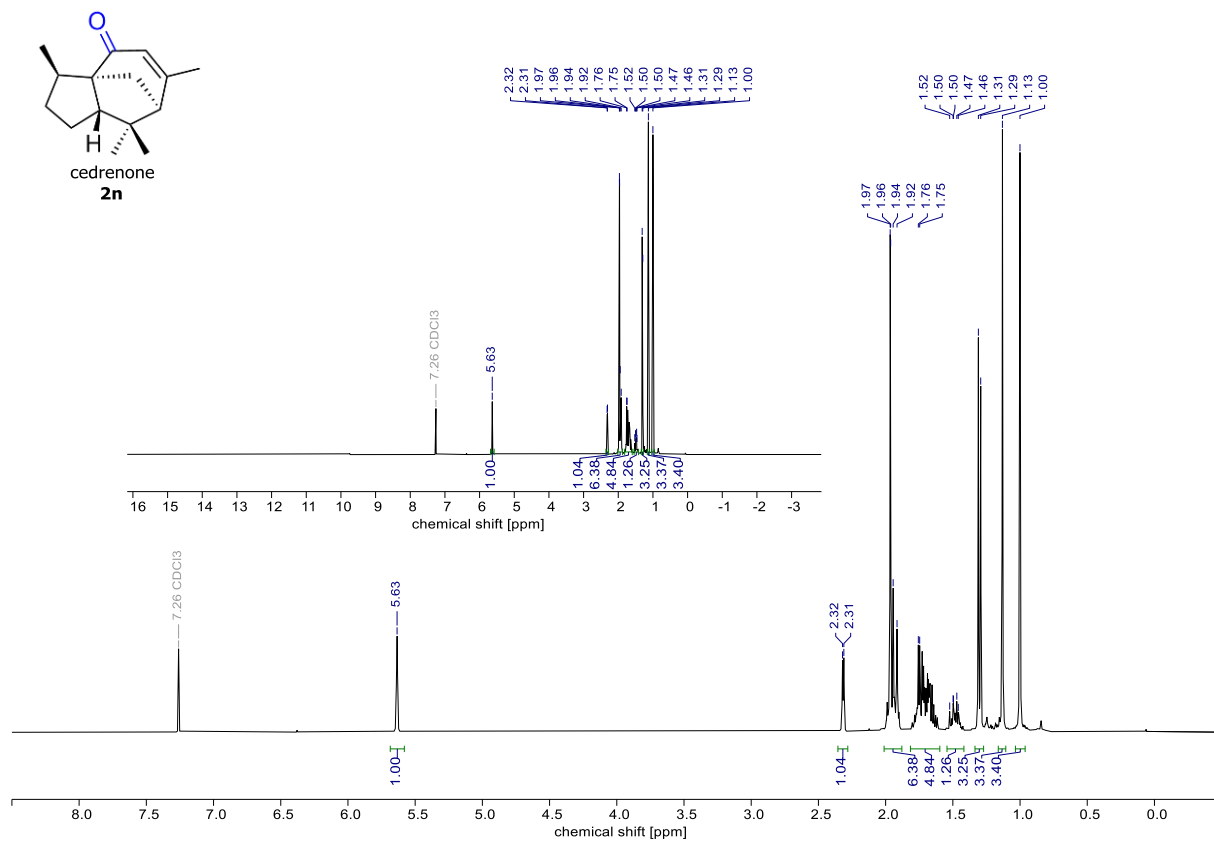


Figure S70. ^1H NMR spectrum (400 MHz) of product **2n**: cedrenone.

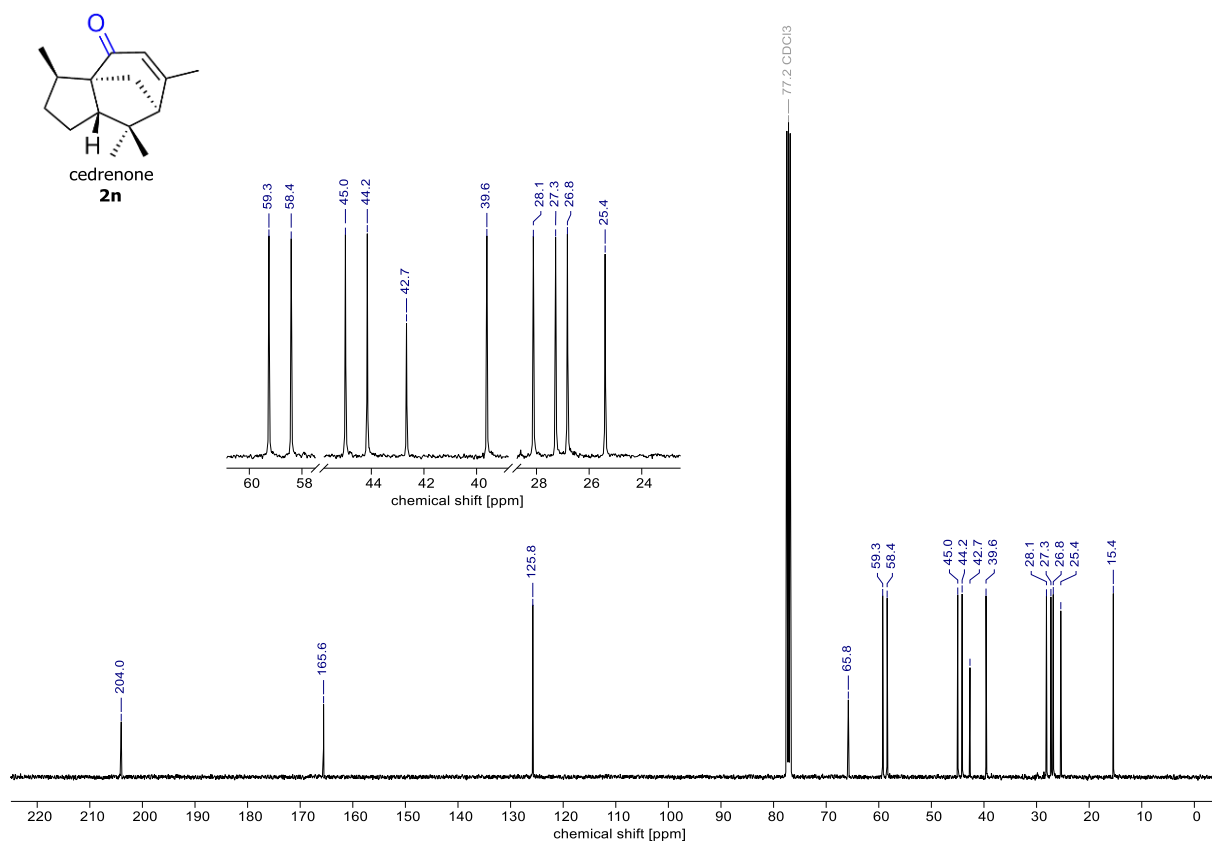


Figure S71. ^{13}C NMR spectrum (101 MHz) of product **2n**: cedrenone.

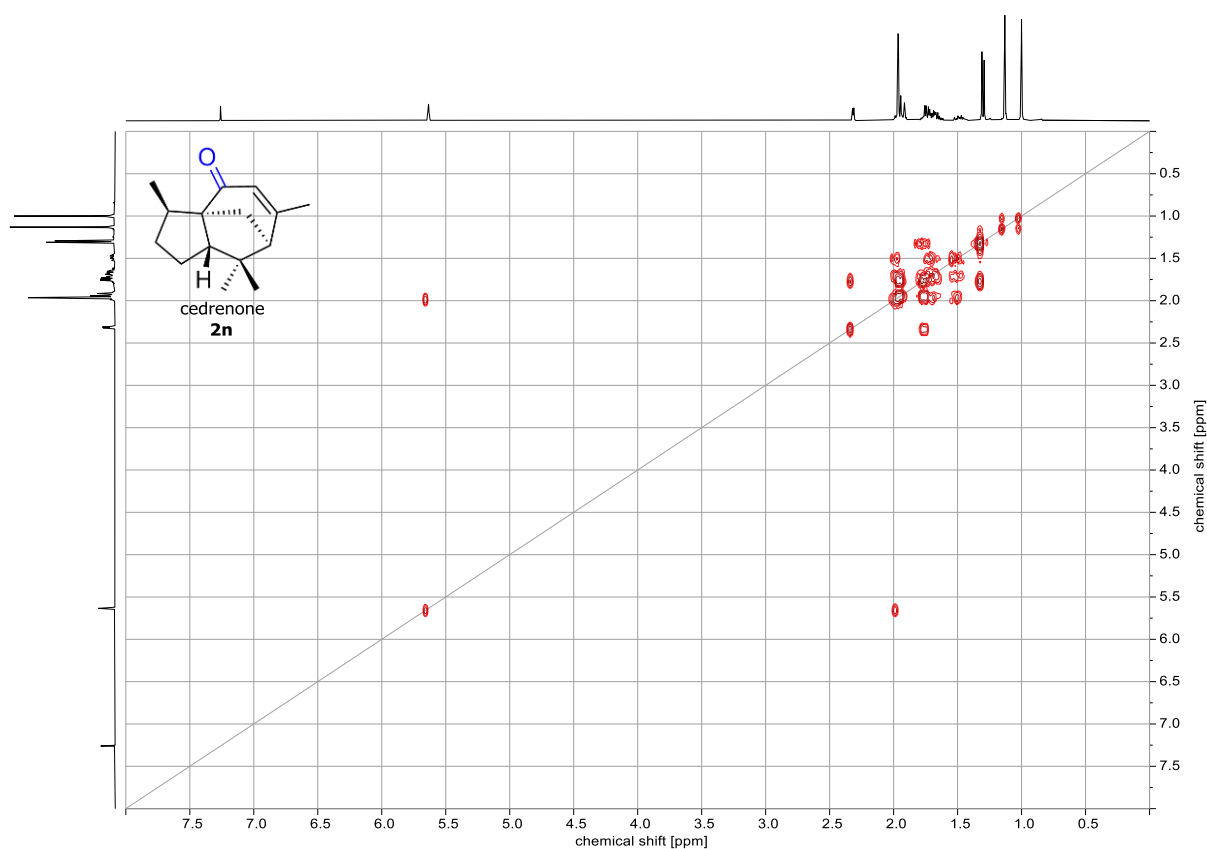
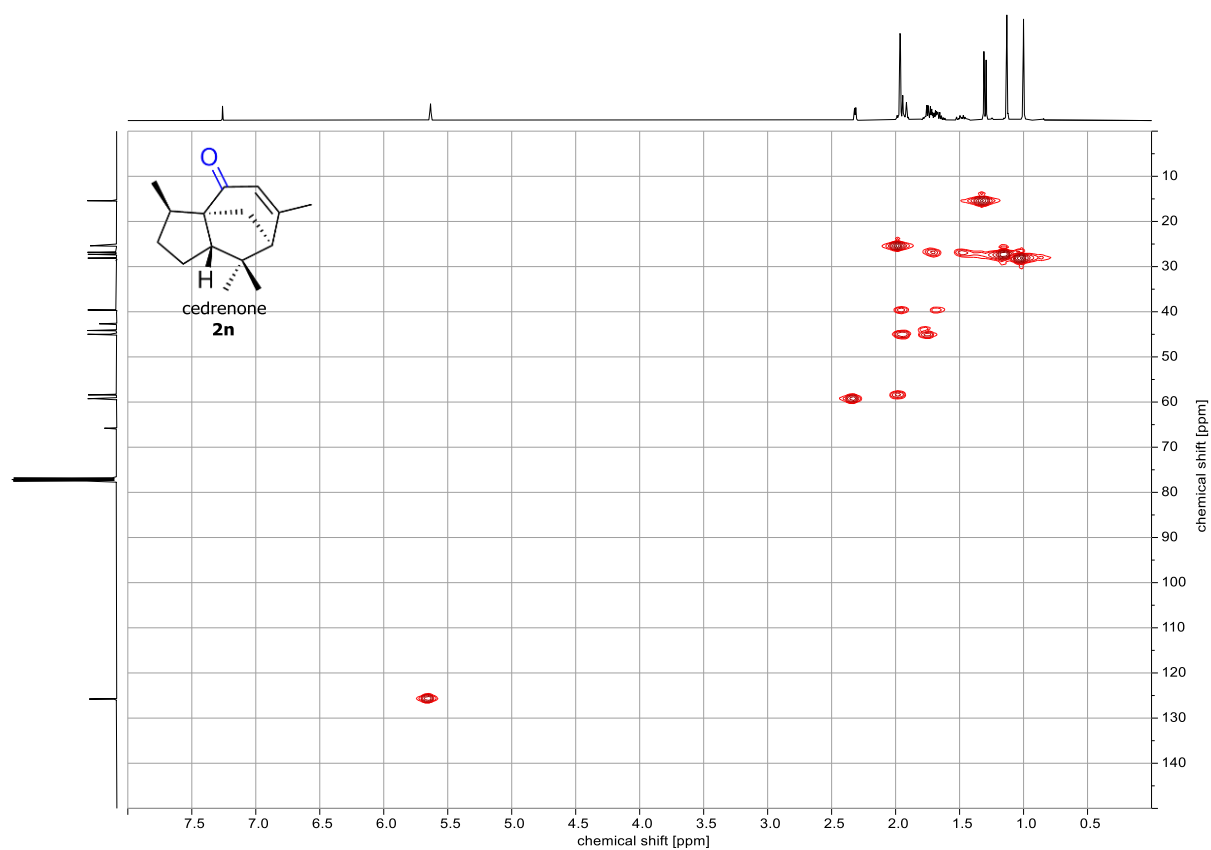
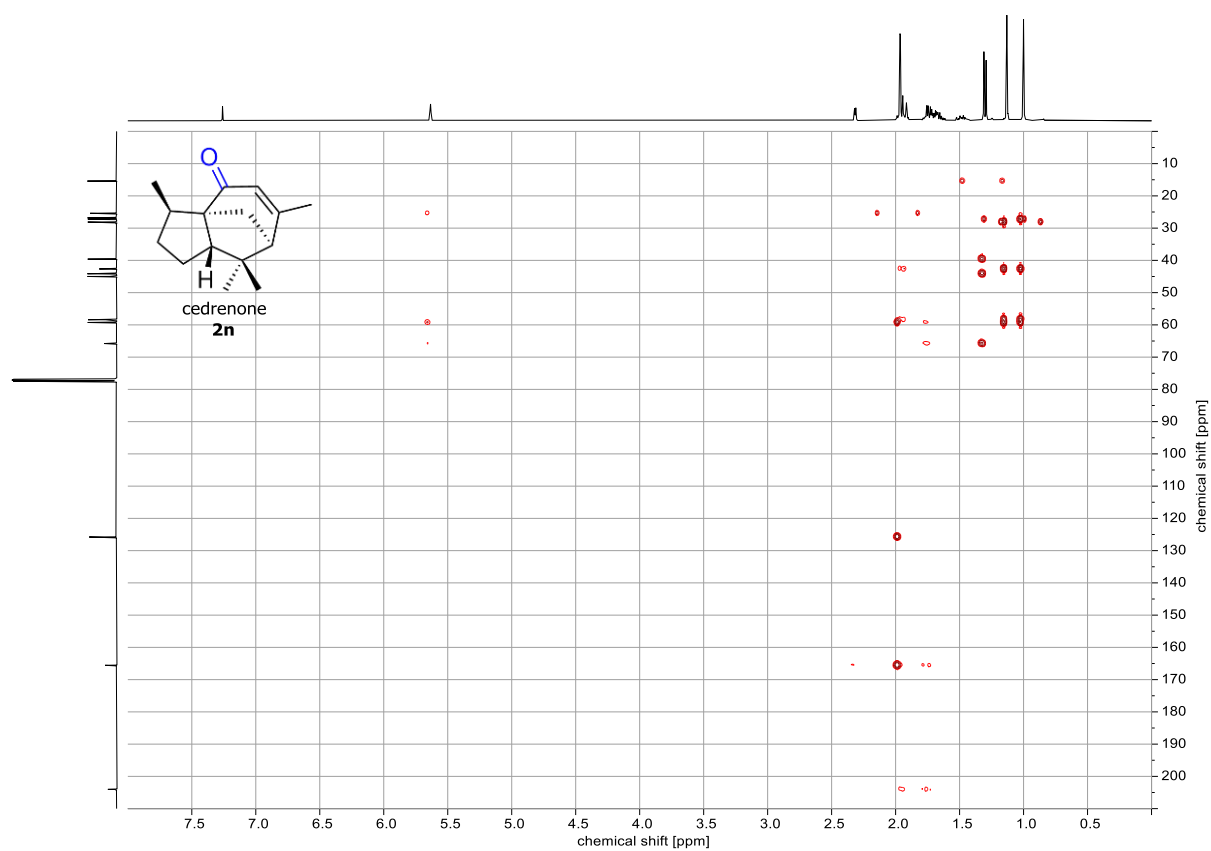
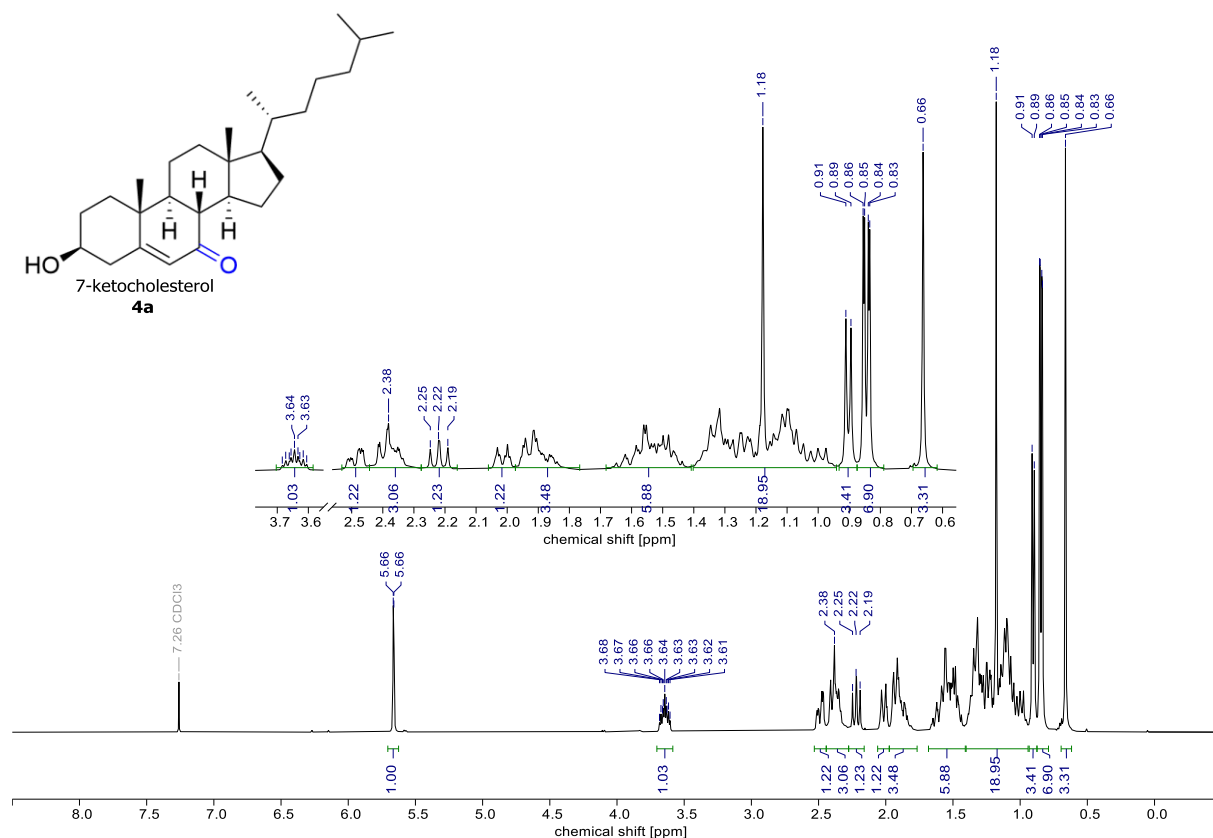
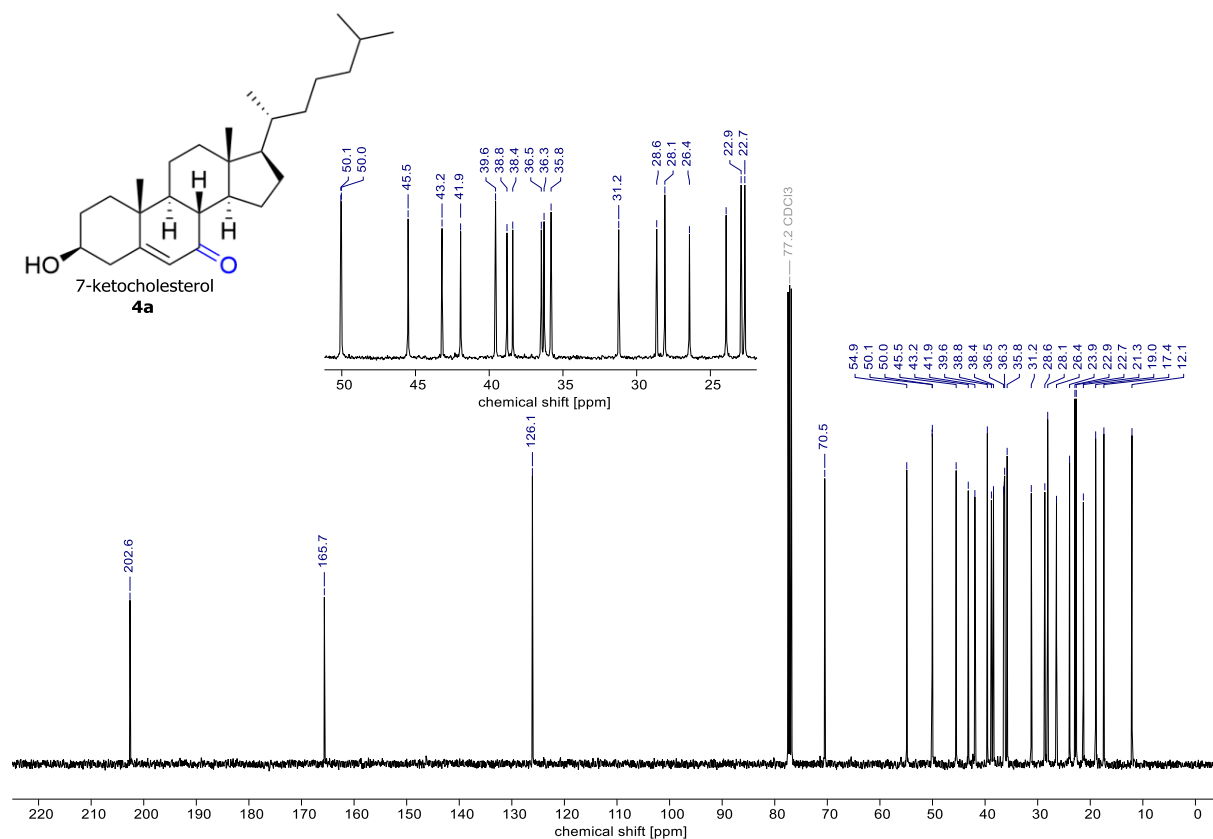


Figure S72. COSY spectrum of product **2n**: cedrenone.

Figure S73. HSQC spectrum of product **2n**: cedrenone.Figure S74. HMBC spectrum of product **2n**: cedrenone.

7.15. 7-Ketocholesterol

Figure S75. ^1H NMR spectrum (400 MHz) of product **4a**: 7-ketocholesterol.Figure S76. ^{13}C NMR spectrum (101 MHz) of product **4a**: 7-ketocholesterol.

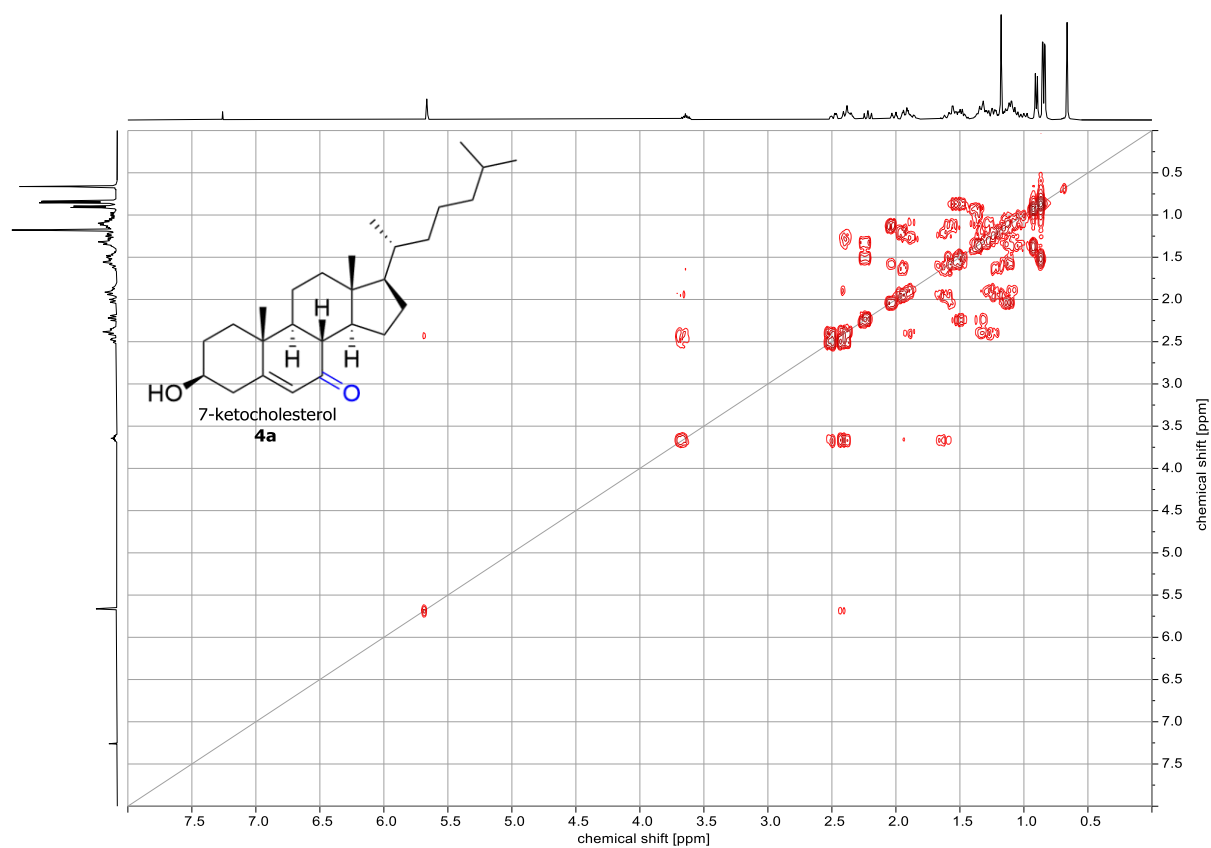


Figure S77. COSY spectrum of product **4a**: 7-ketocholesterol.

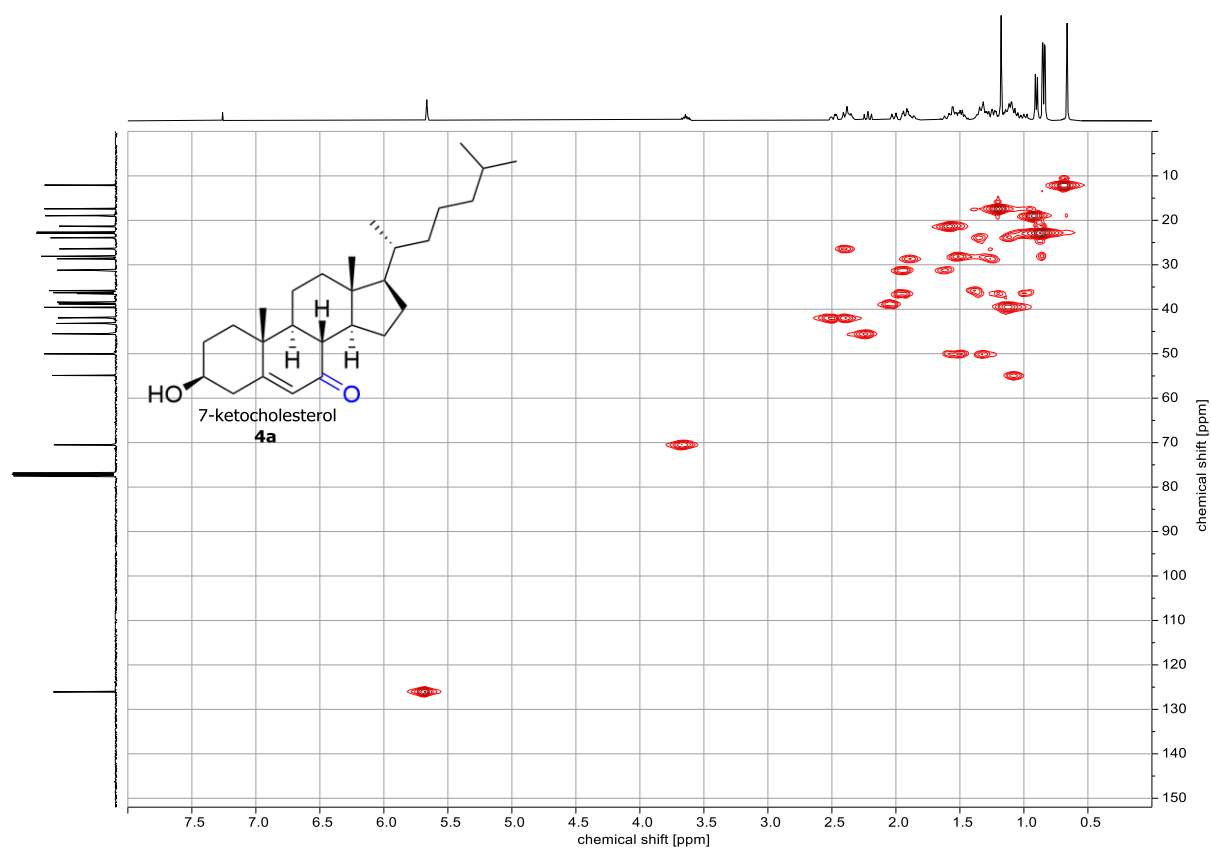
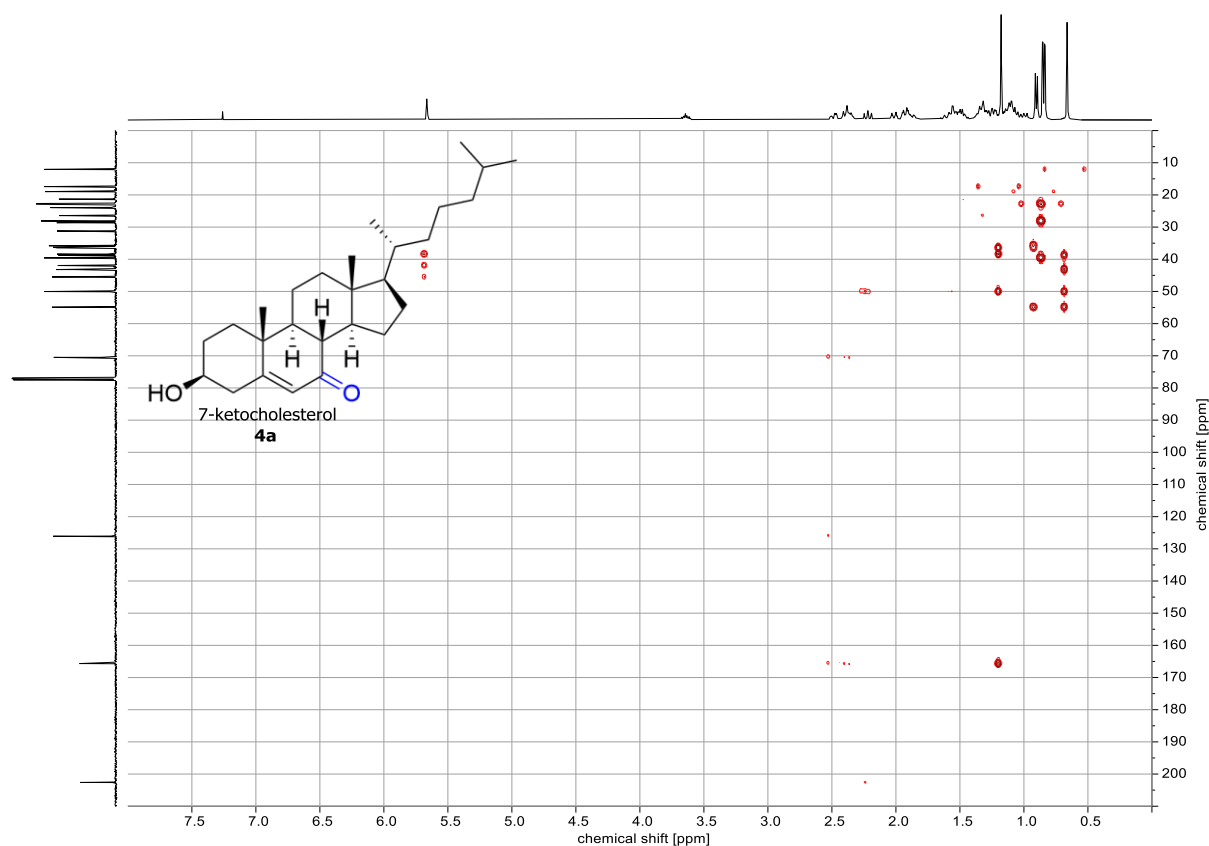
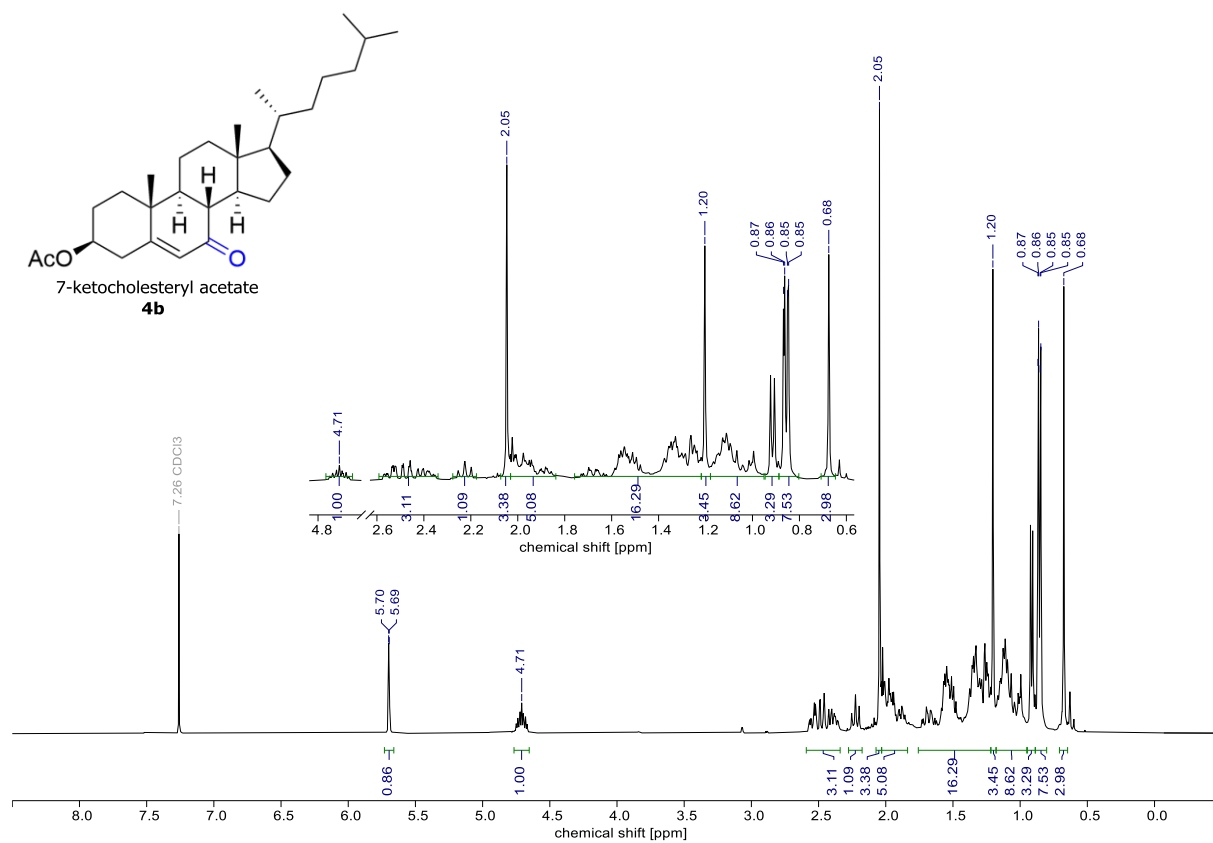


Figure S78. HSQC spectrum of product **4a**: 7-ketocholesterol.

Figure S79. HMBC spectrum of product **4a**: 7-ketocholesterol.

7.16. 7-Ketocholesteryl acetate

Figure S80. ^1H NMR spectrum (400 MHz) of product **4b**: 7-ketocholesteryl acetate.

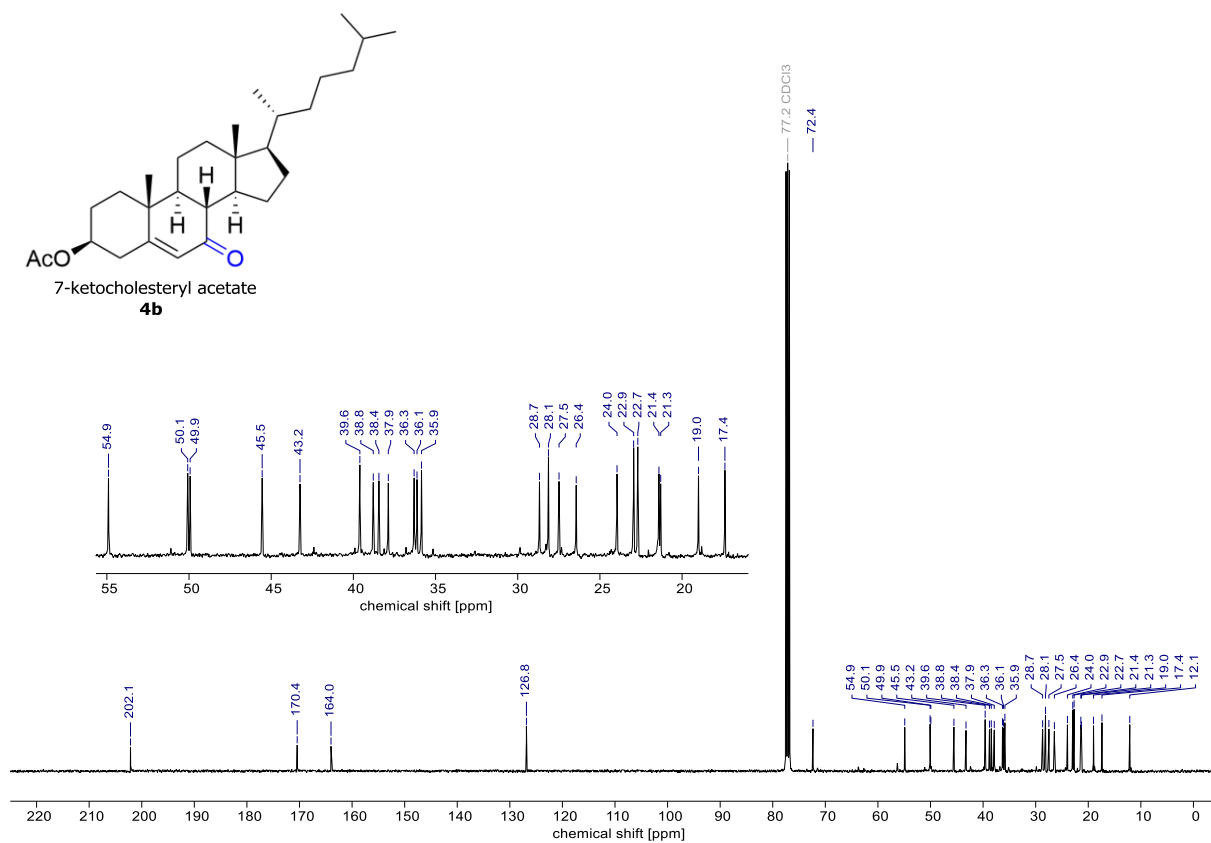


Figure S81. ^{13}C NMR spectrum (101 MHz) of product **4b**: 7-ketocholesteryl acetate.

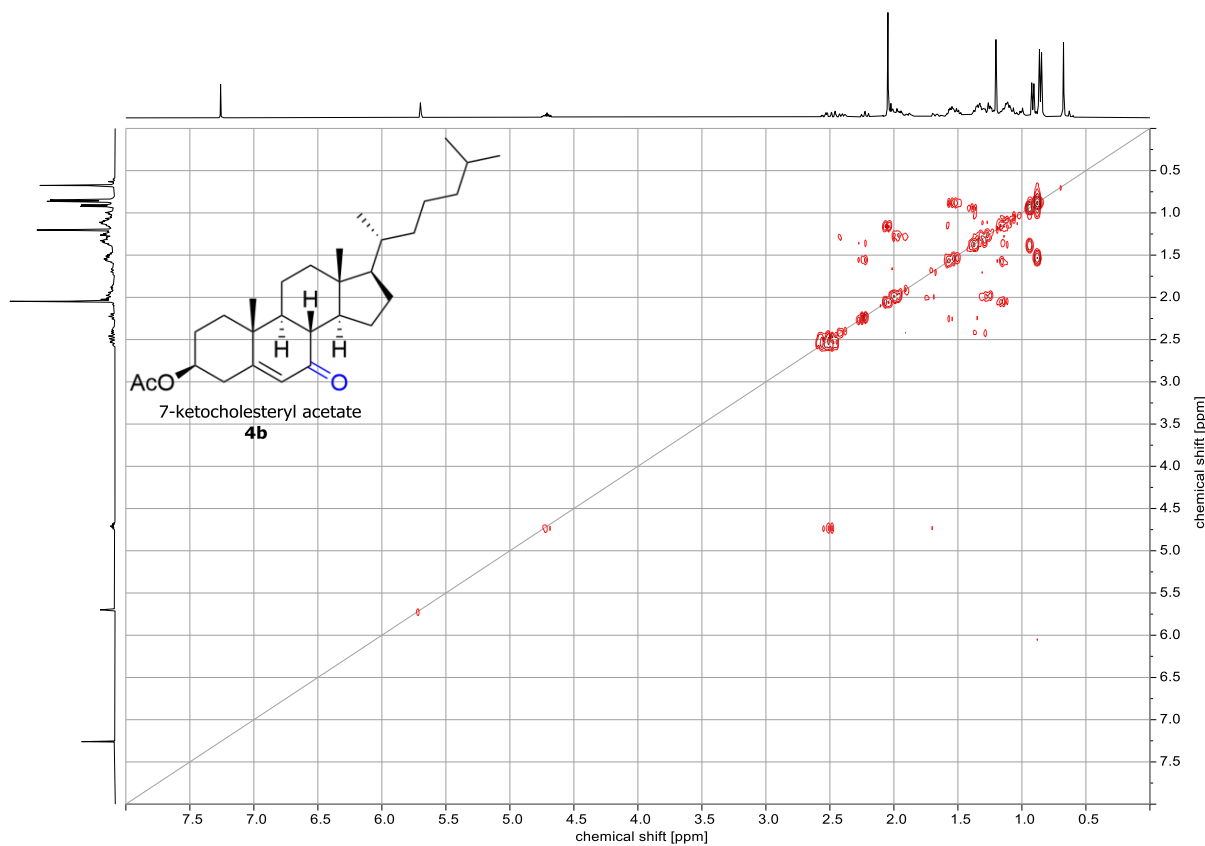


Figure S82. COSY spectrum of product **4b**: 7-ketocholesteryl acetate.

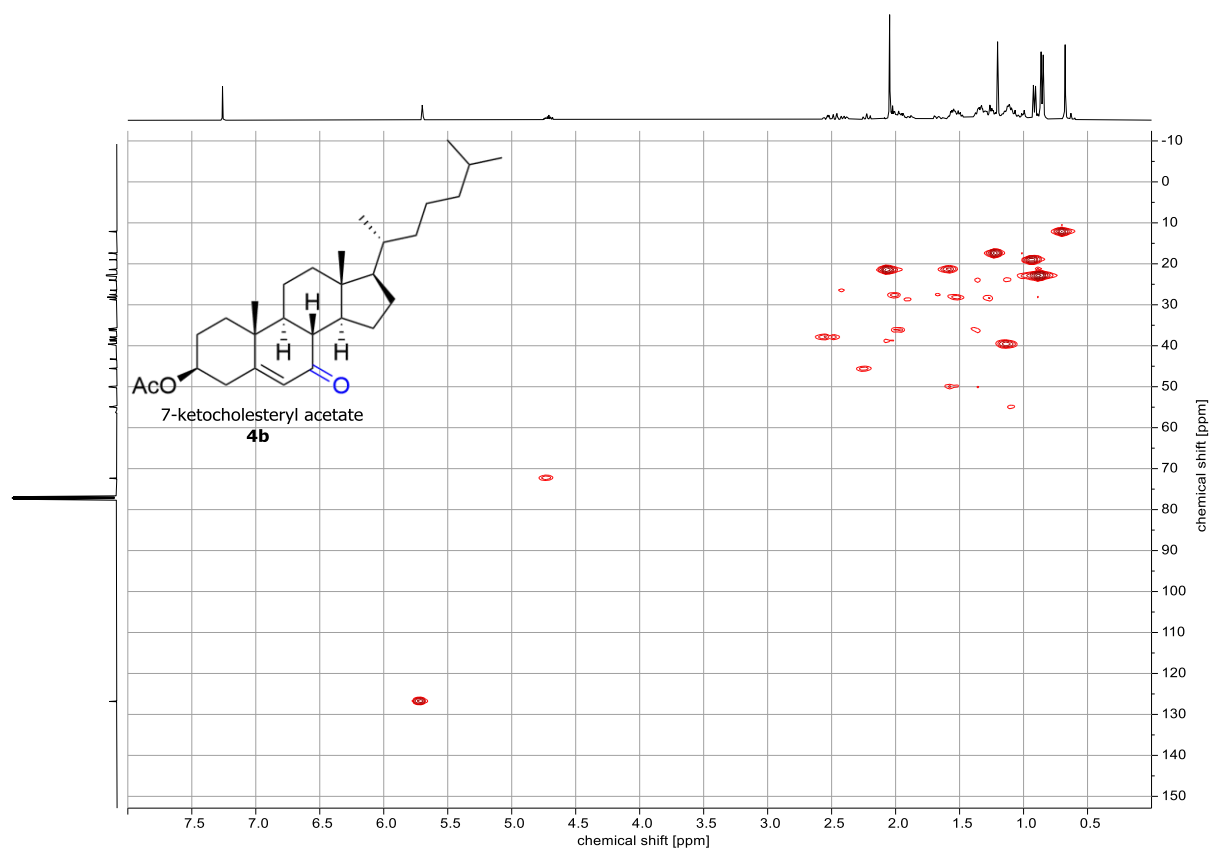


Figure S83. HSQC spectrum of product **4b**: 7-ketocholesteryl acetate.

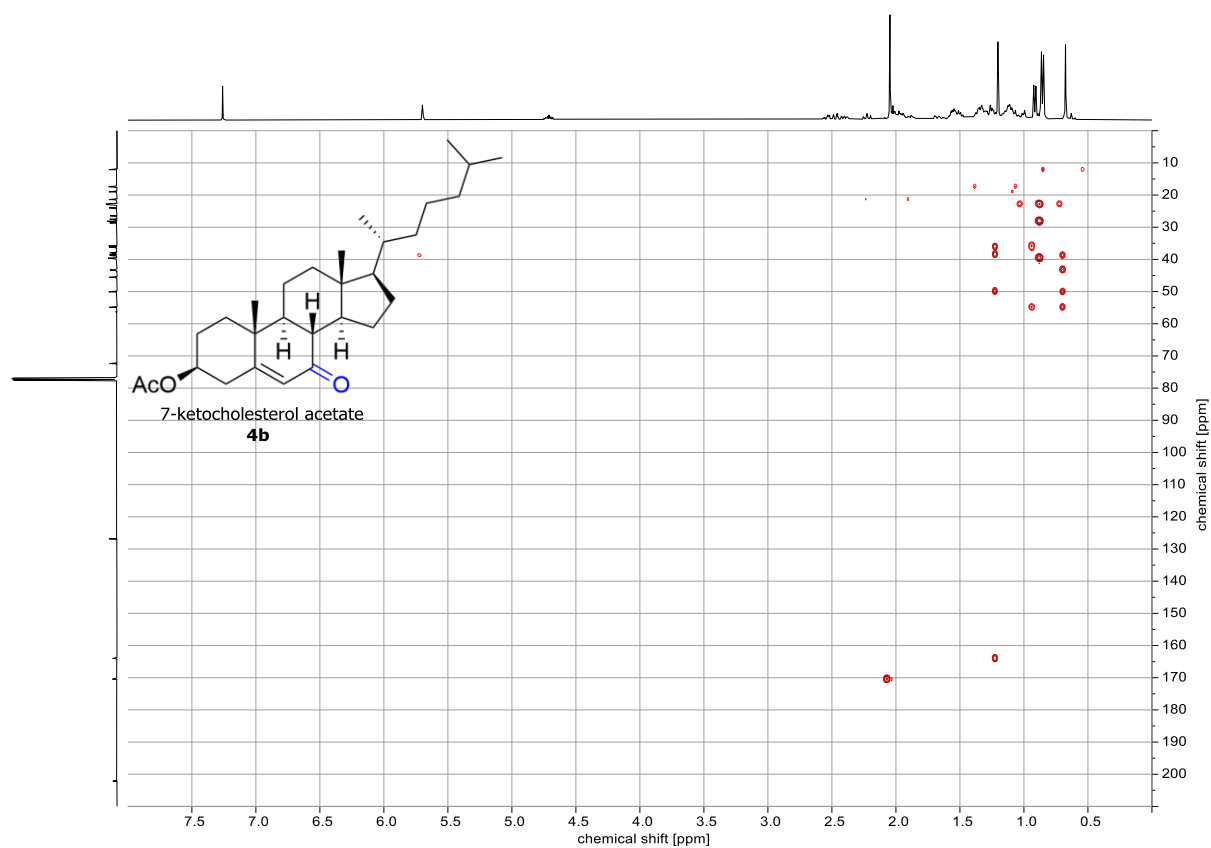
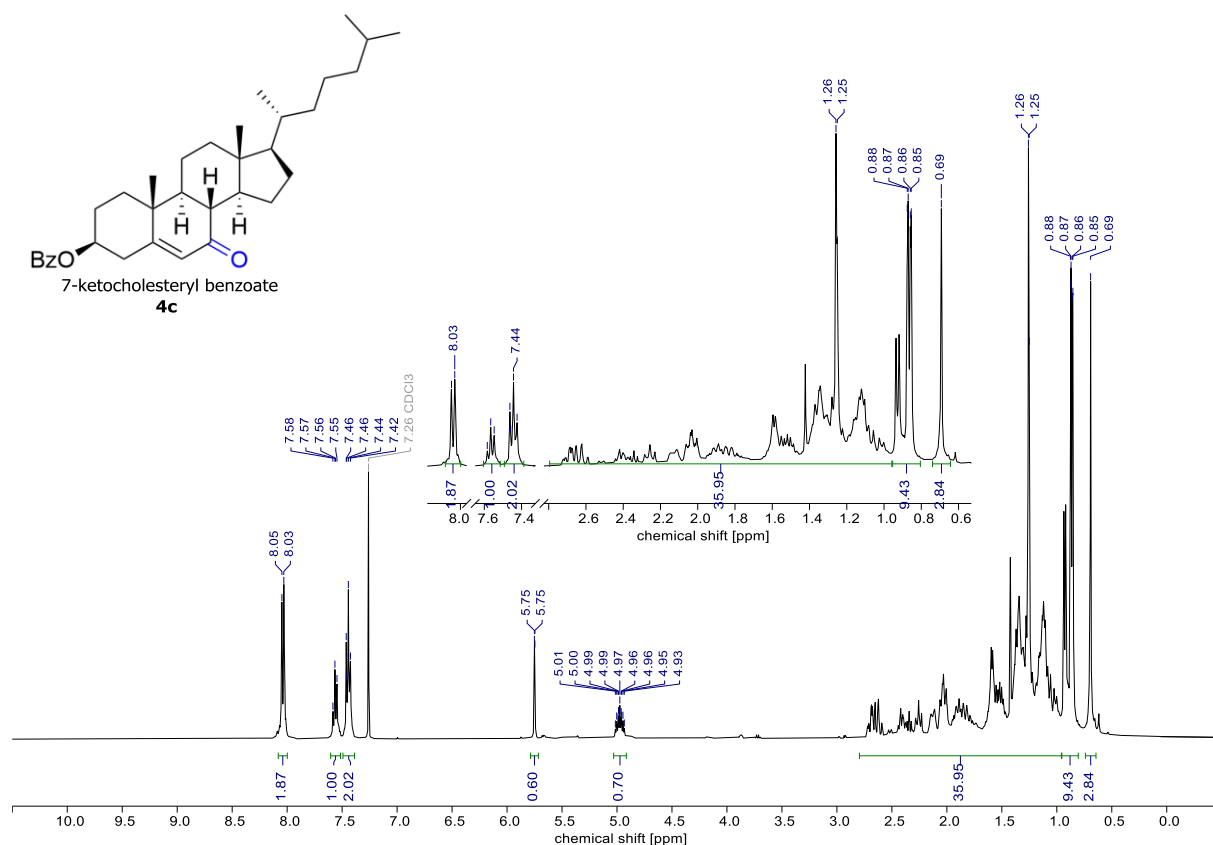
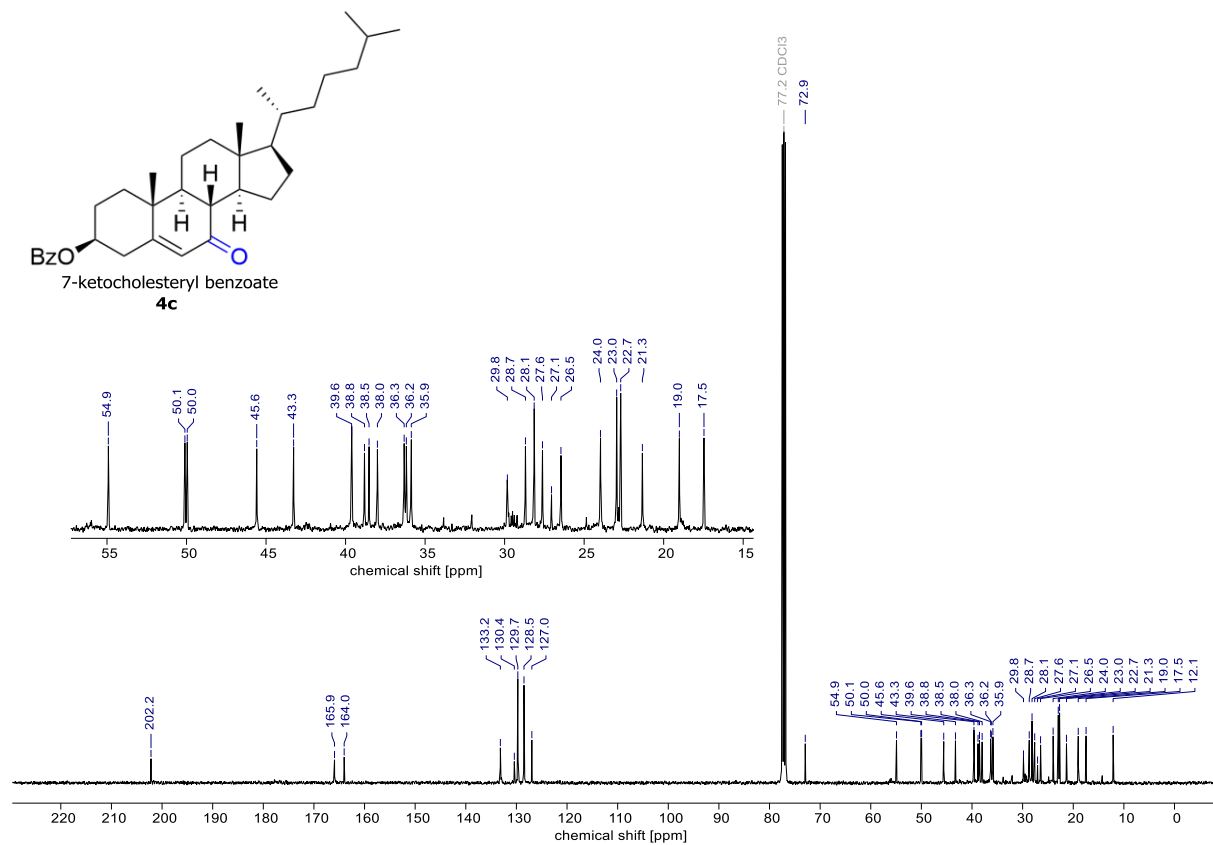


Figure S84. HMBC spectrum of product **4b**: 7-ketocholesteryl acetate.

7.17. 7-Ketocholesteryl benzoate

Figure S85. ^1H NMR spectrum (400 MHz) of product **4c**: 7-ketocholesteryl benzoate.Figure S86. ^{13}C NMR spectrum (101 MHz) of product **4c**: 7-ketocholesteryl benzoate.

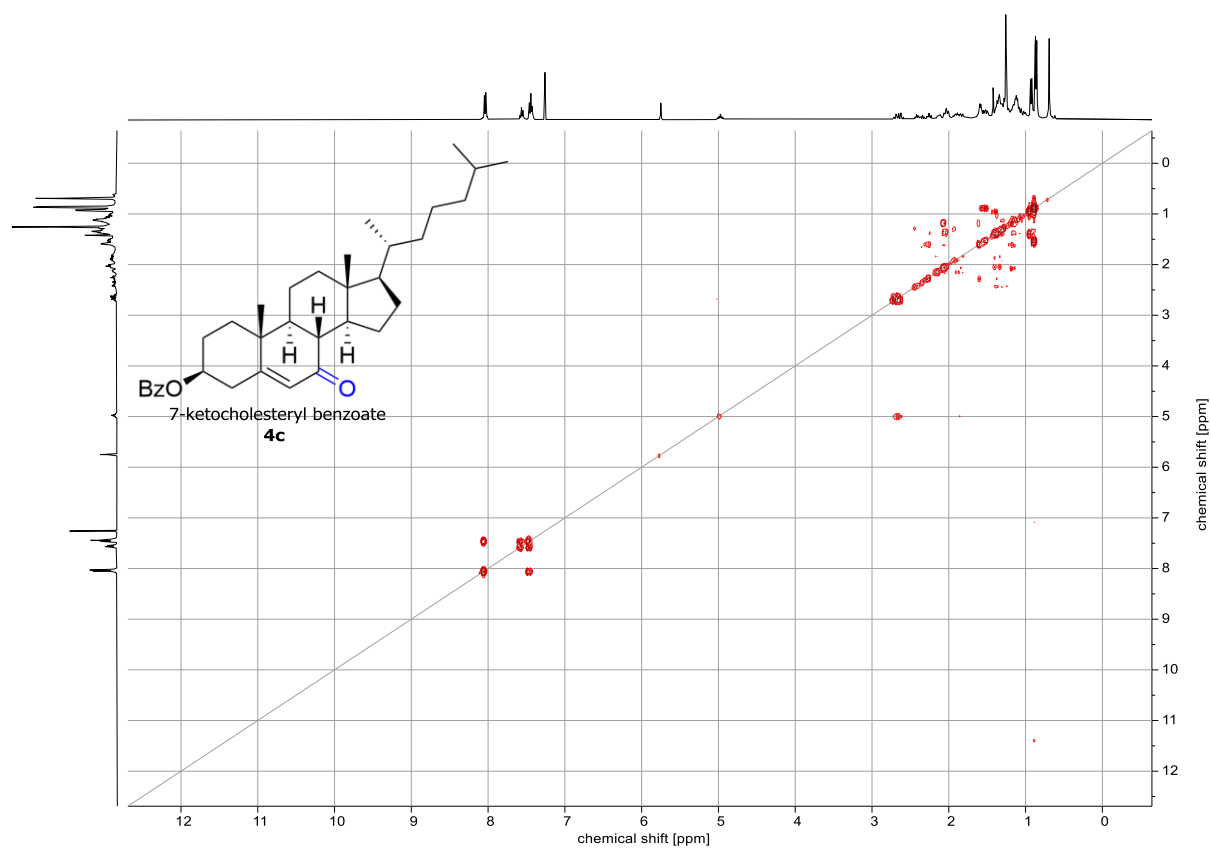


Figure S87. COSY spectrum of product **4c**: 7-ketocholesteryl benzoate.

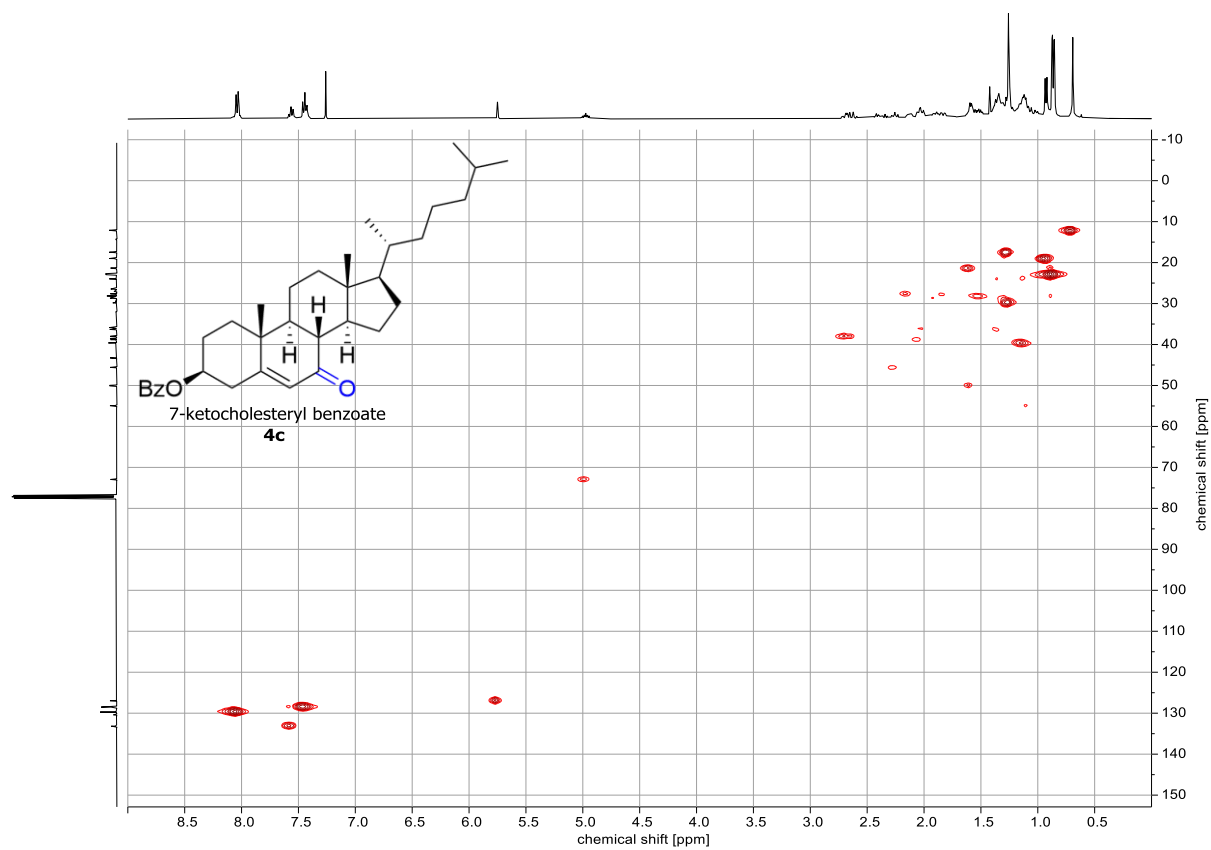


Figure S88. HSQC spectrum of product **4c**: 7-ketocholesteryl benzoate.

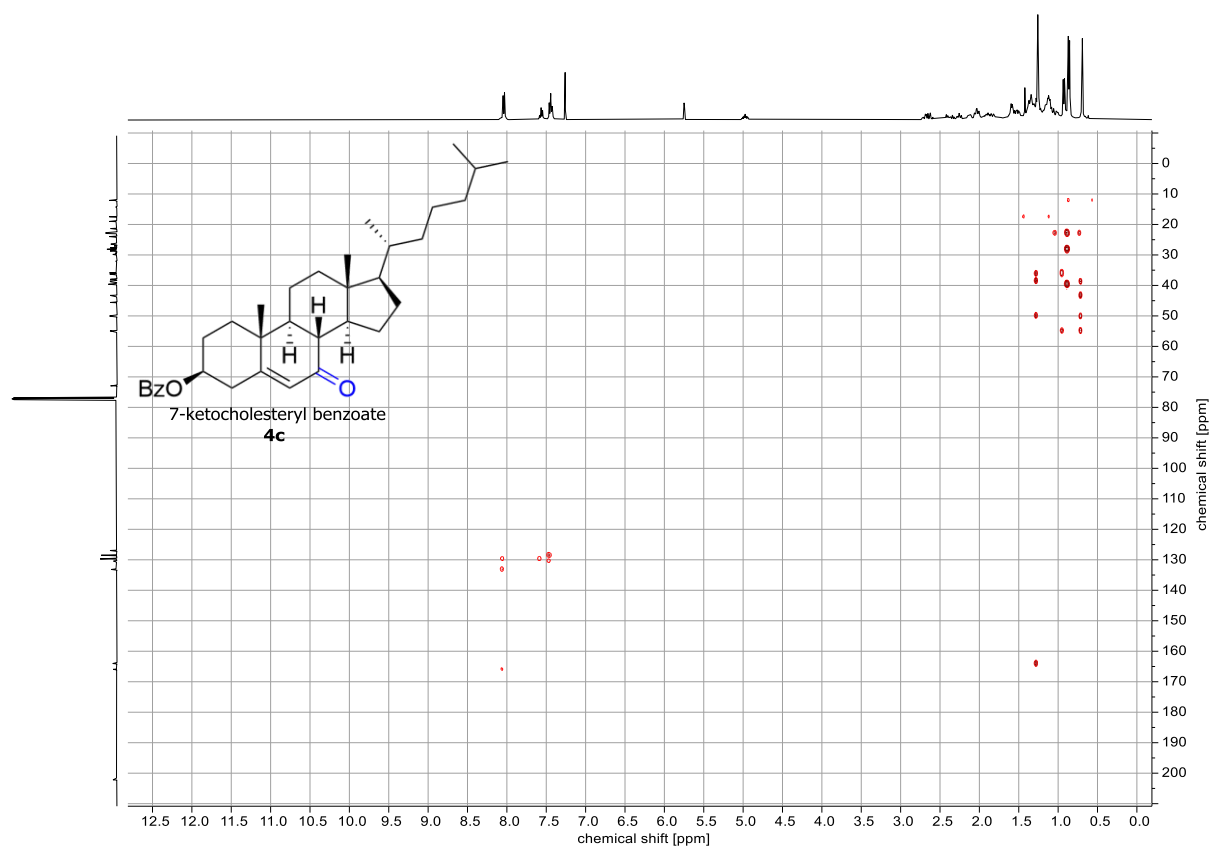


Figure S89. HMBC spectrum of product **4c**: 7-ketocholesteryl benzoate.

7.18. 7-Ketodiosgenin acetate

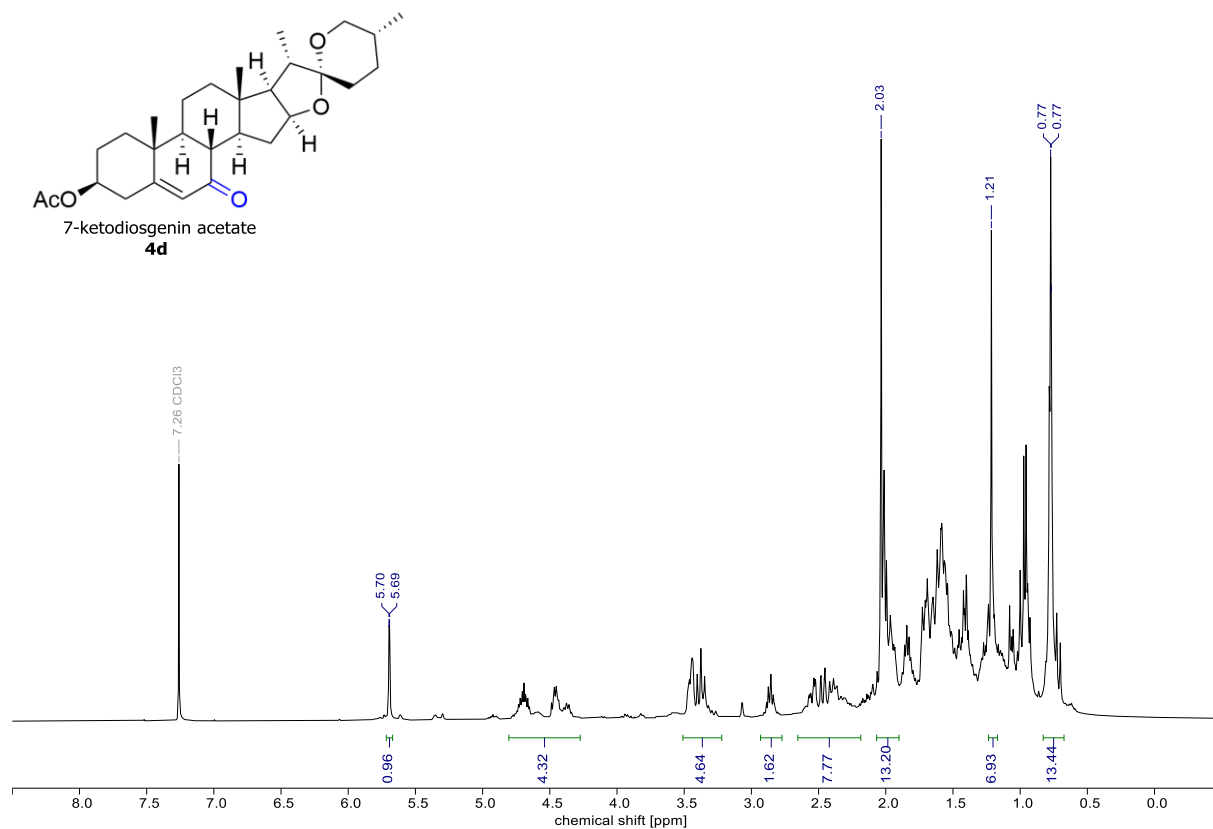


Figure S90. ^1H NMR spectrum (400 MHz) of product **4d**: 7-ketodiosgenin acetate.

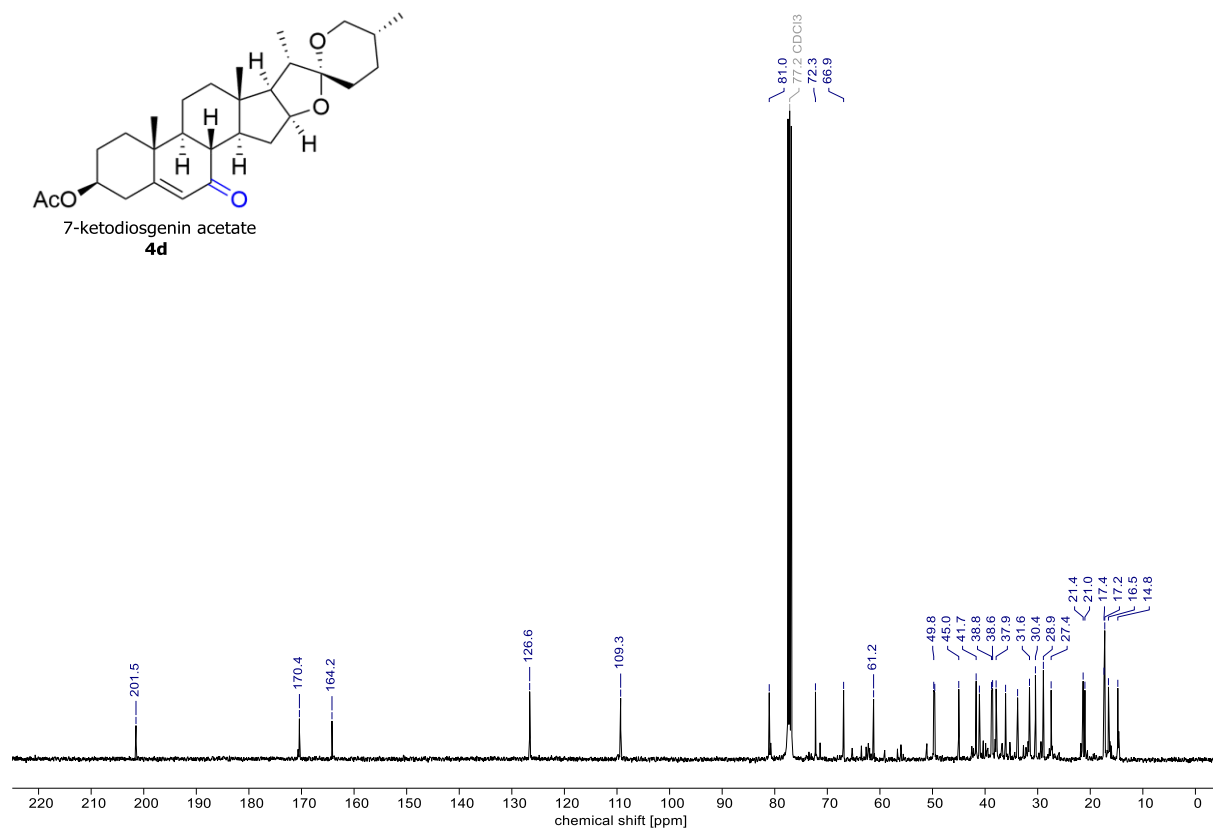


Figure S91. ^{13}C NMR spectrum (101 MHz) of product **4d**: 7-ketodiosgenin acetate.

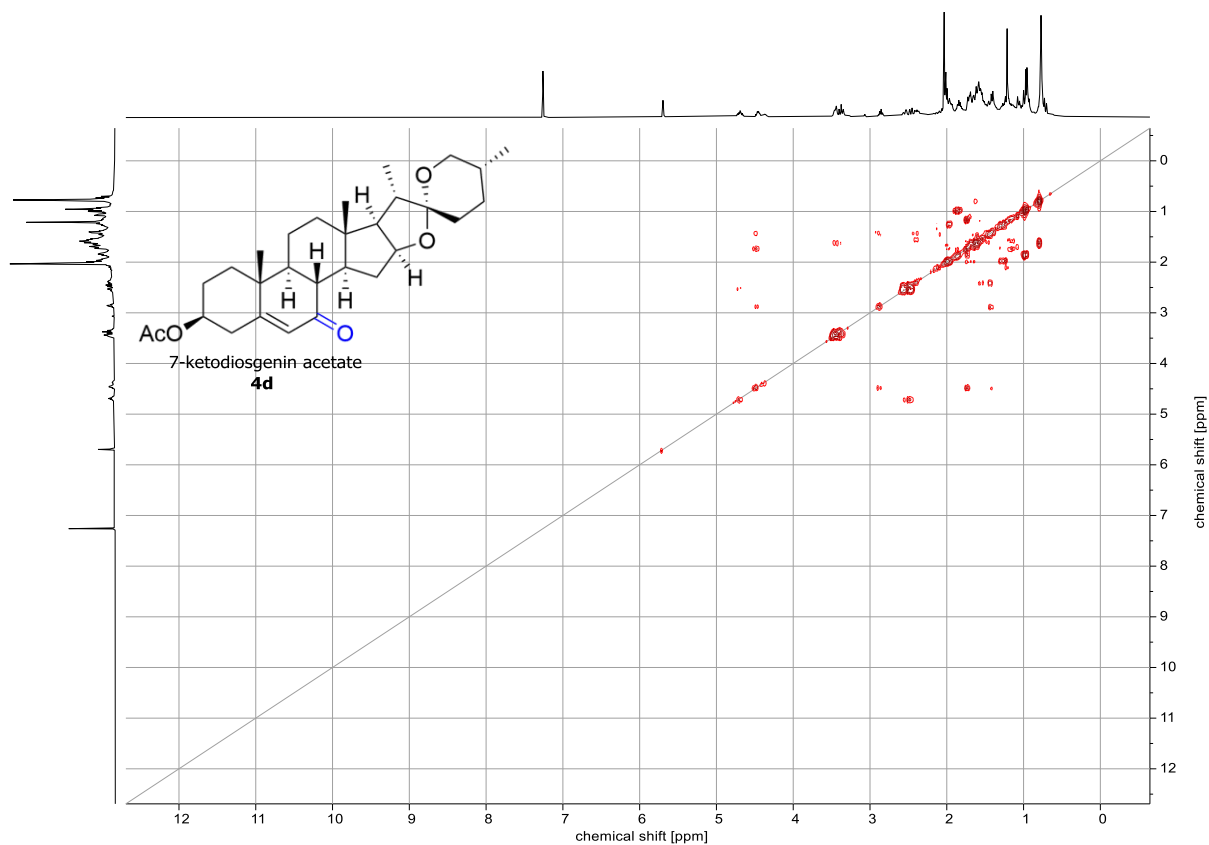


Figure S92. COSY spectrum of product **4d**: 7-ketodiosgenin acetate.

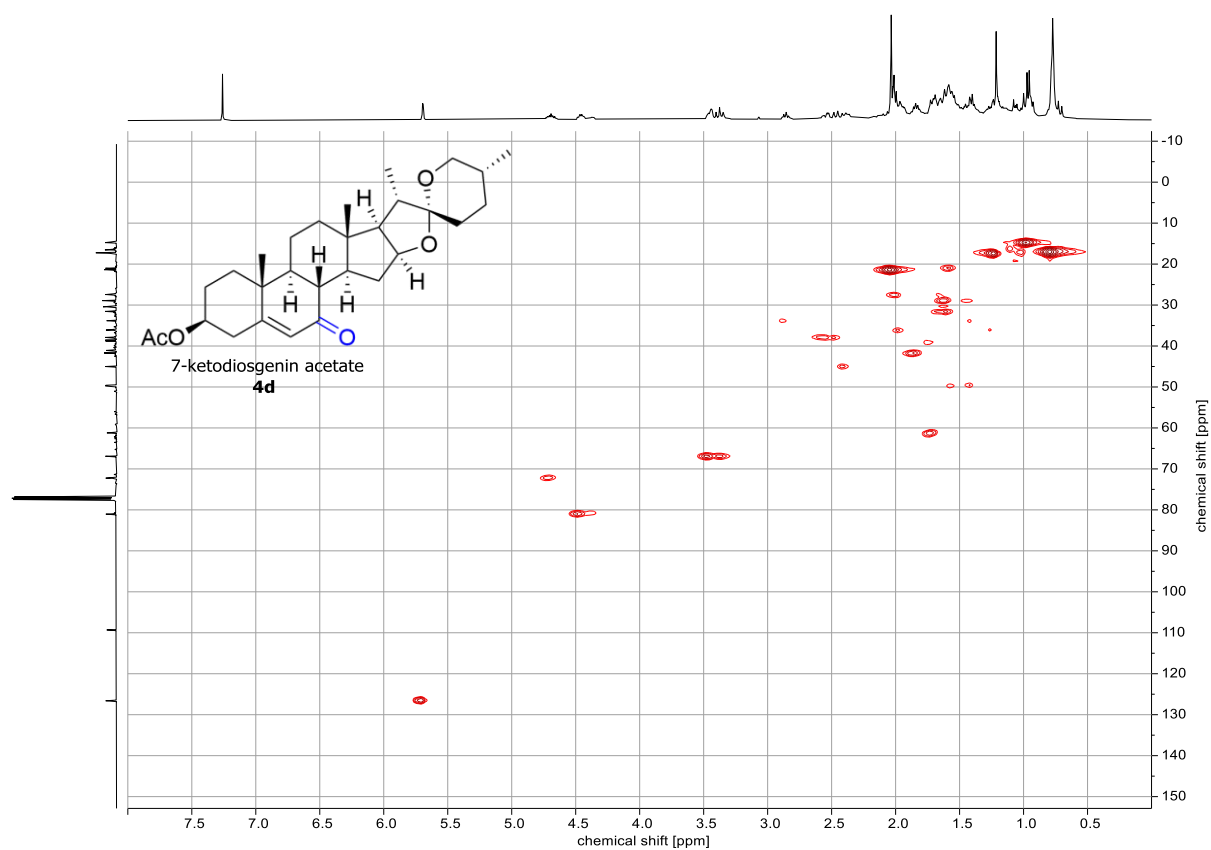


Figure S93. HSQC spectrum of product **4d**: 7-ketodiosgenin acetate.

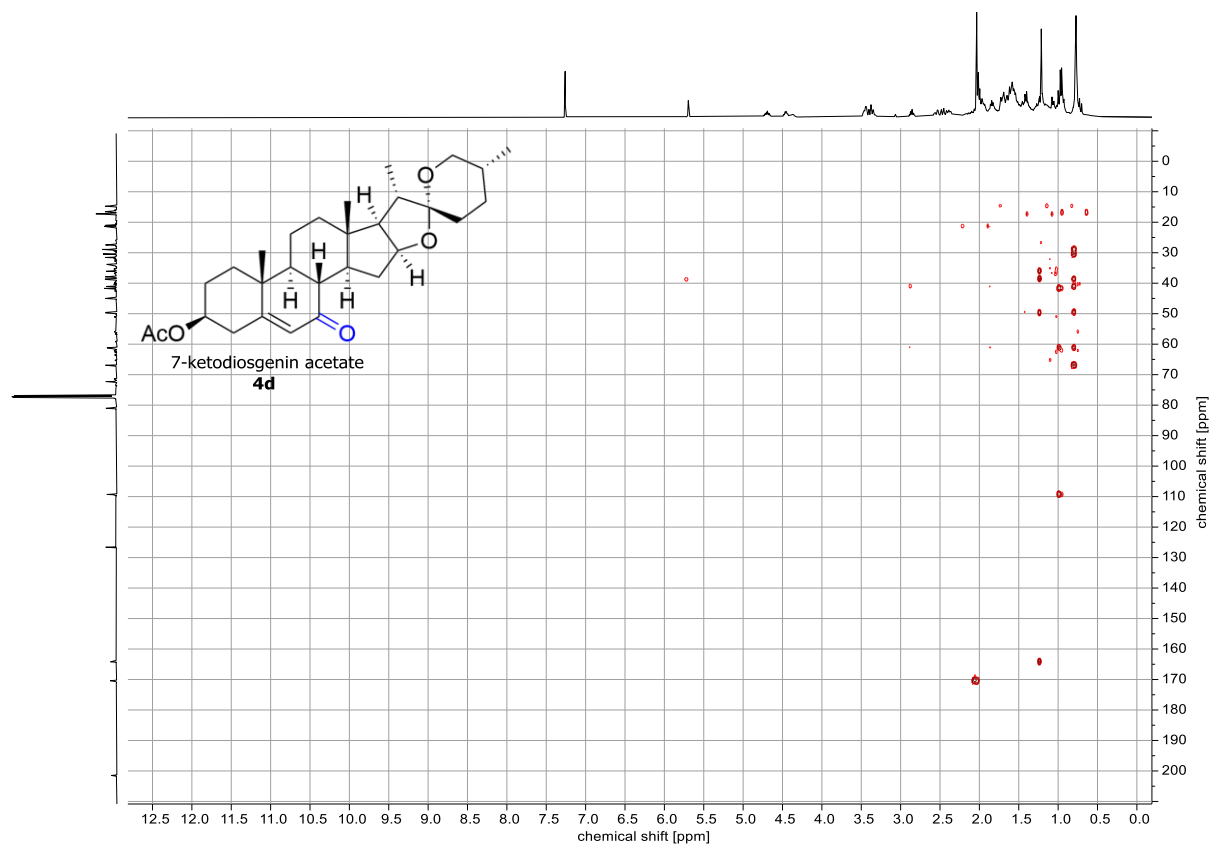
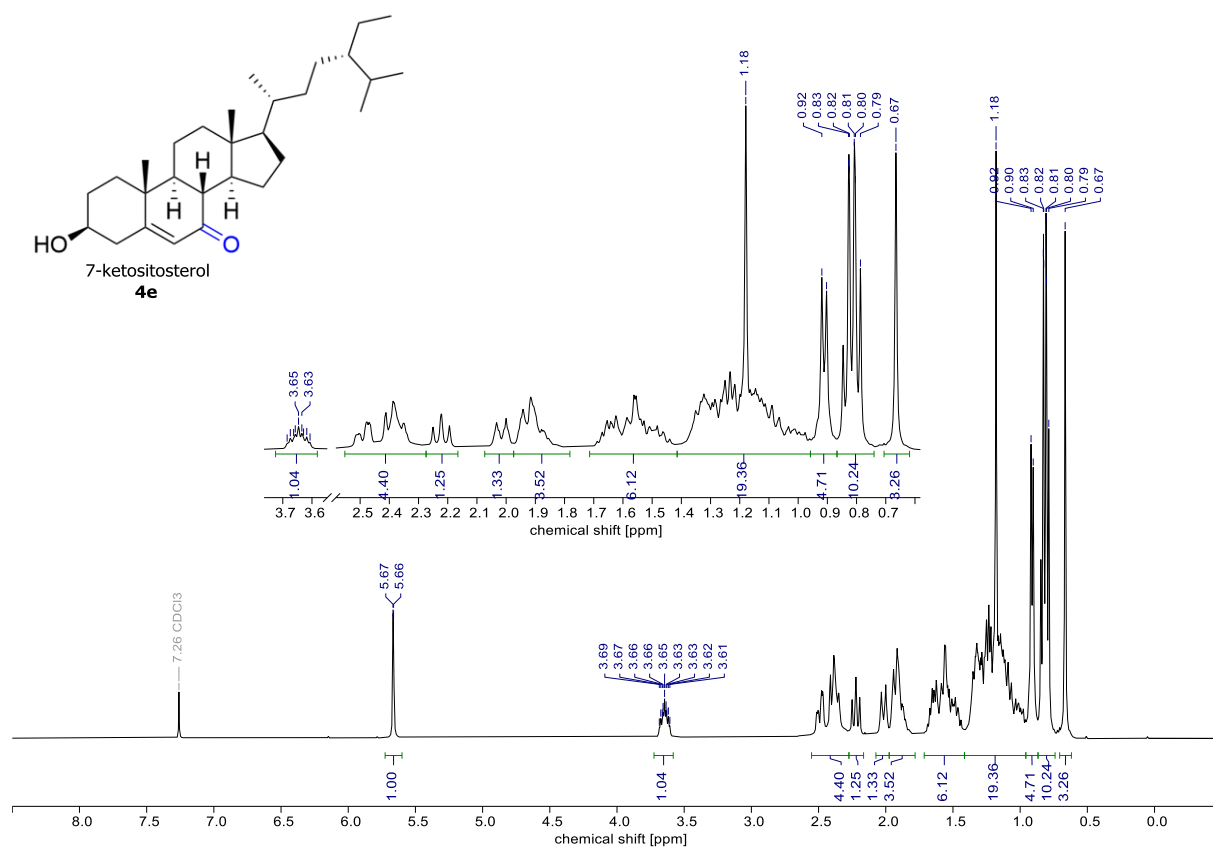
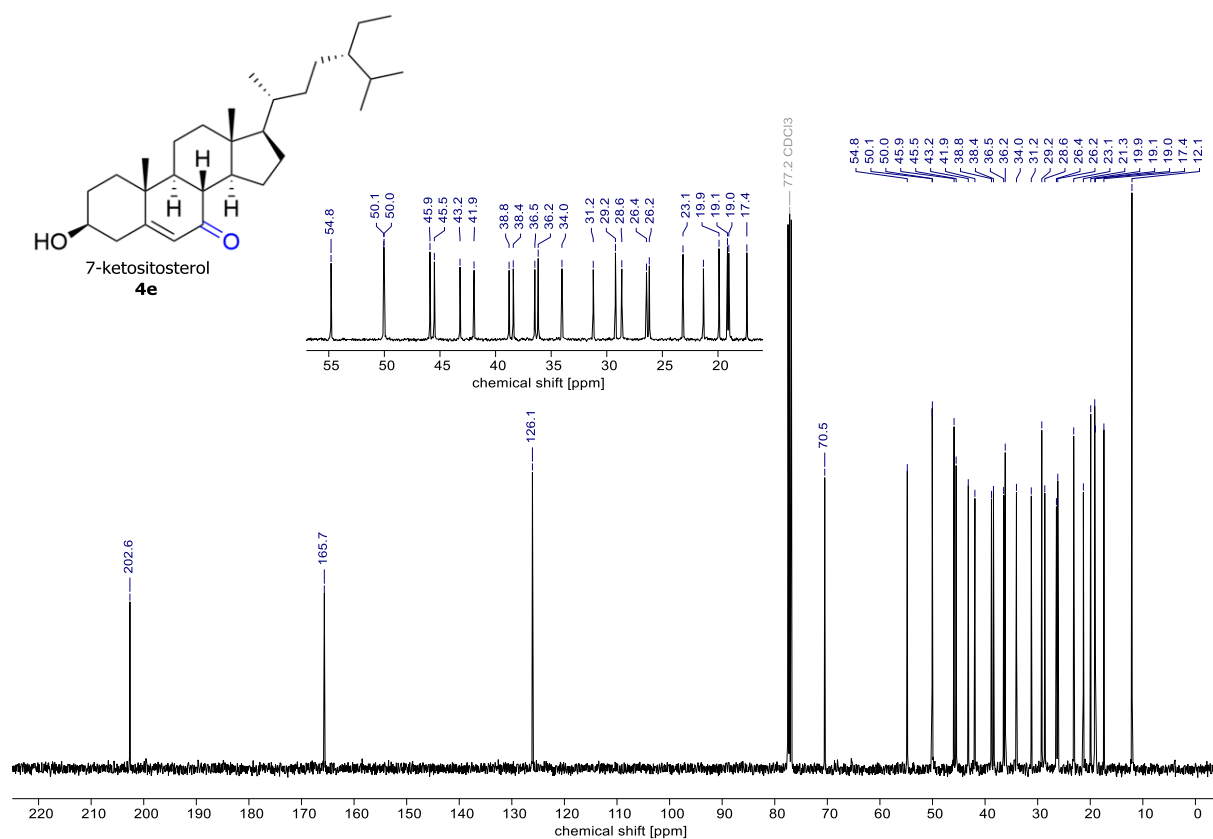


Figure S94. HMBC spectrum of product **4d**: 7-ketodiosgenin acetate.

7.19. 7-Ketositosterol

Figure S95. ¹H NMR spectrum (400 MHz) of product **4e**: 7-ketositosterol.Figure S96. ¹³C NMR spectrum (101 MHz) of product **4e**: 7-ketositosterol.

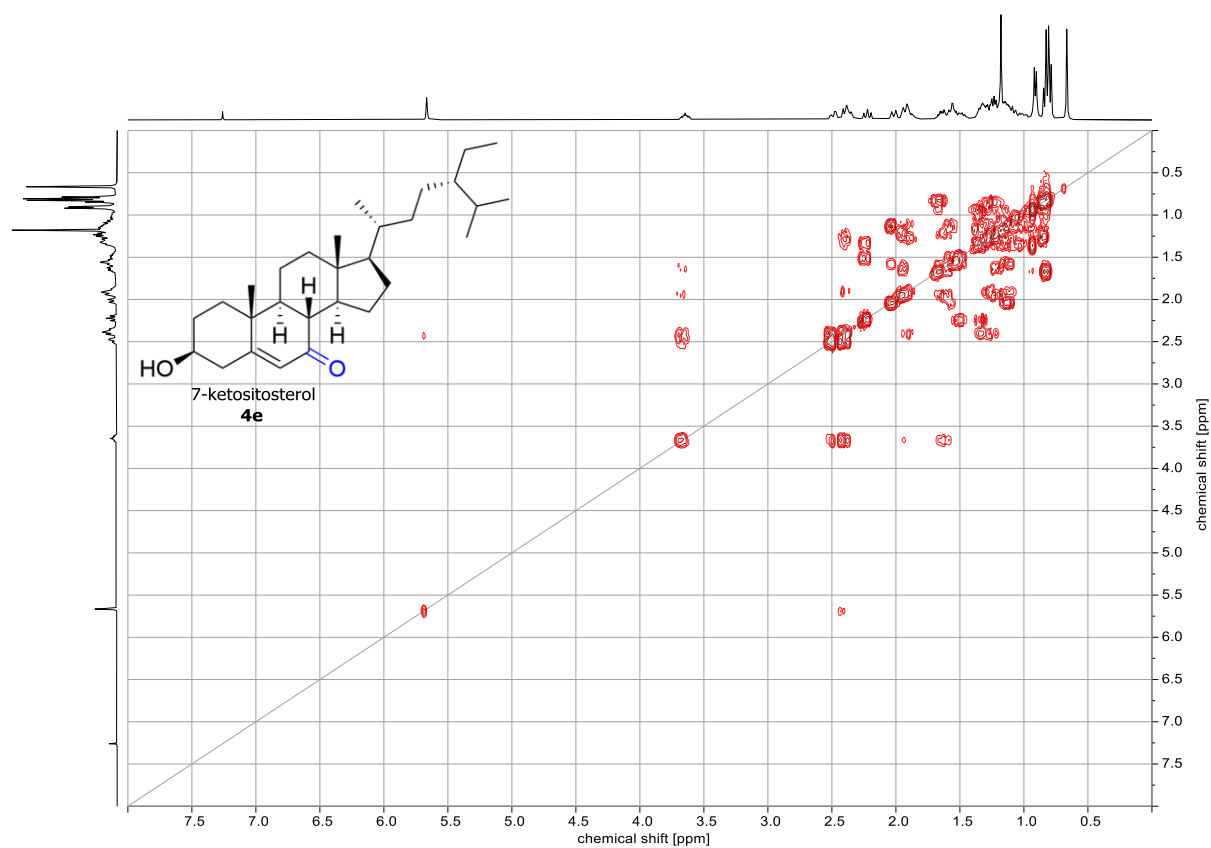


Figure S97. COSY spectrum of product 4e: 7-ketositolsterol.

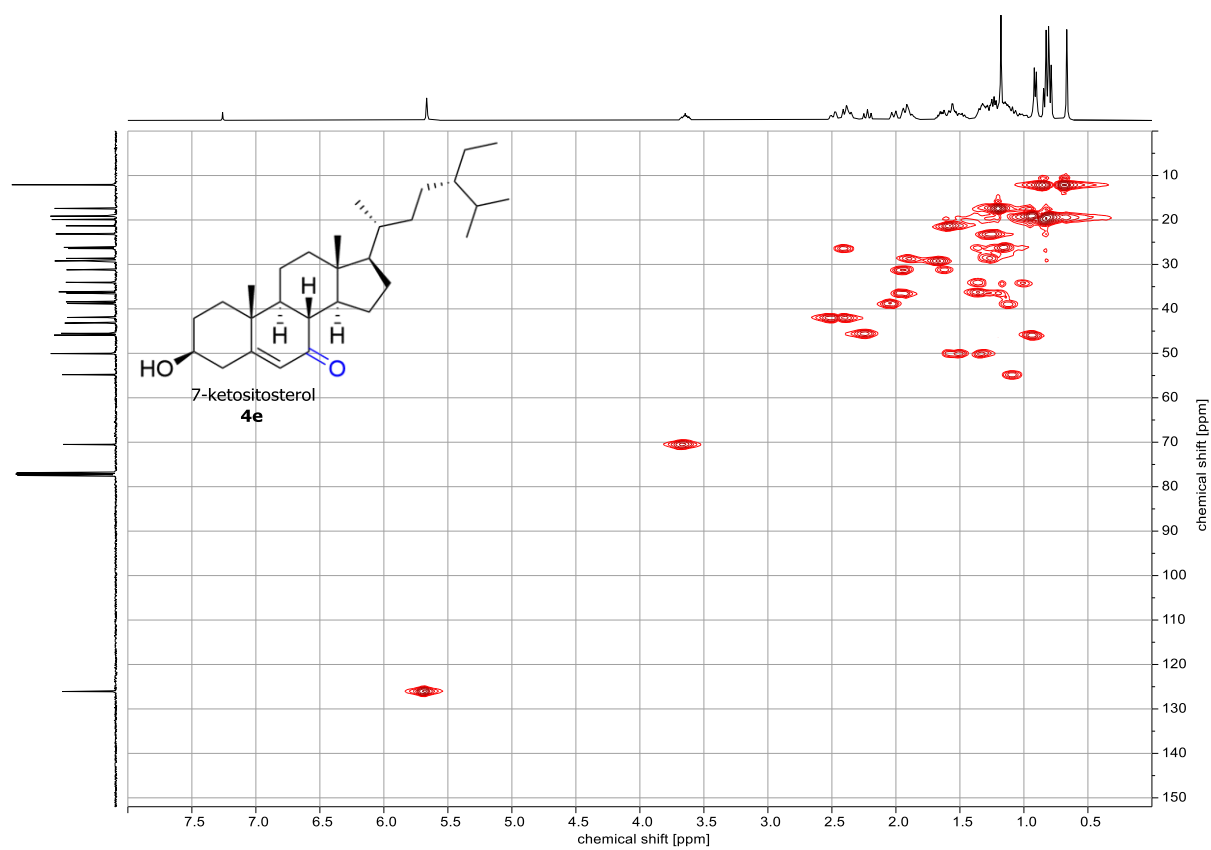
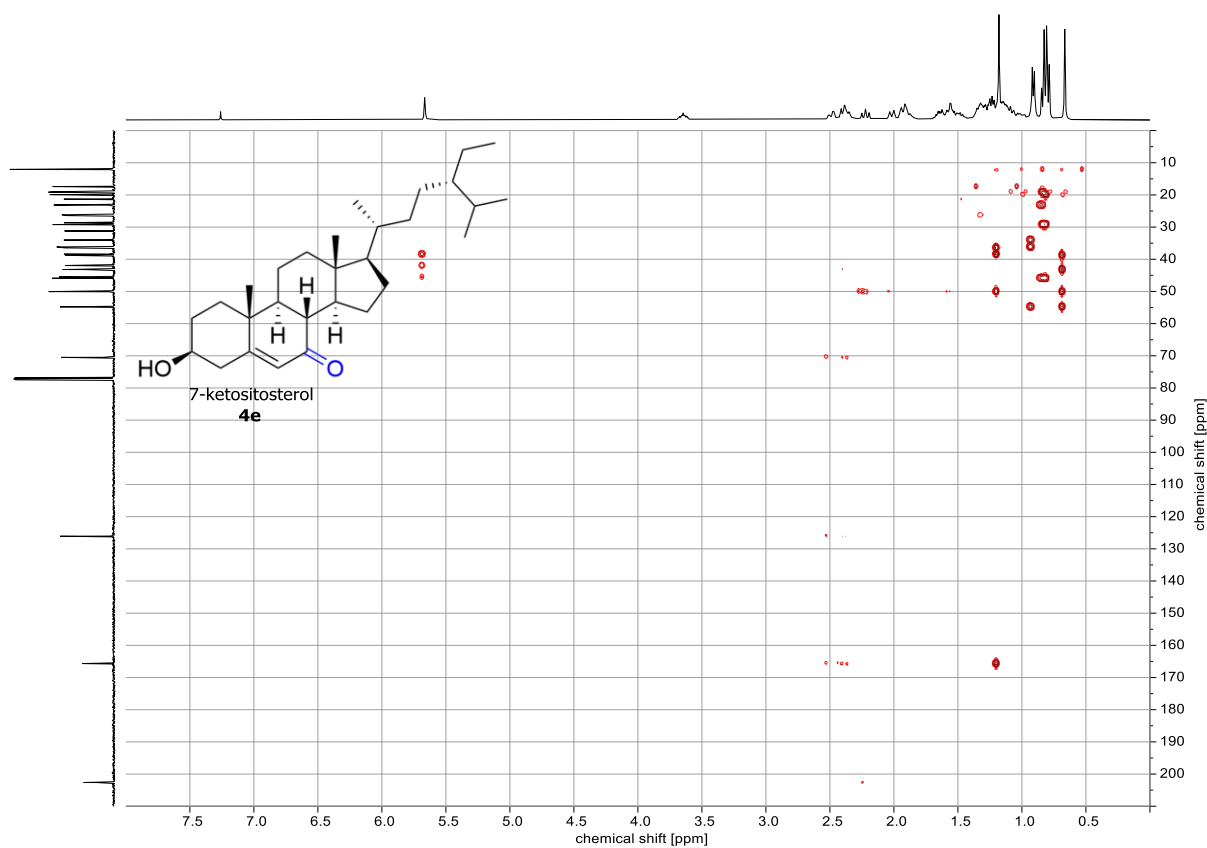
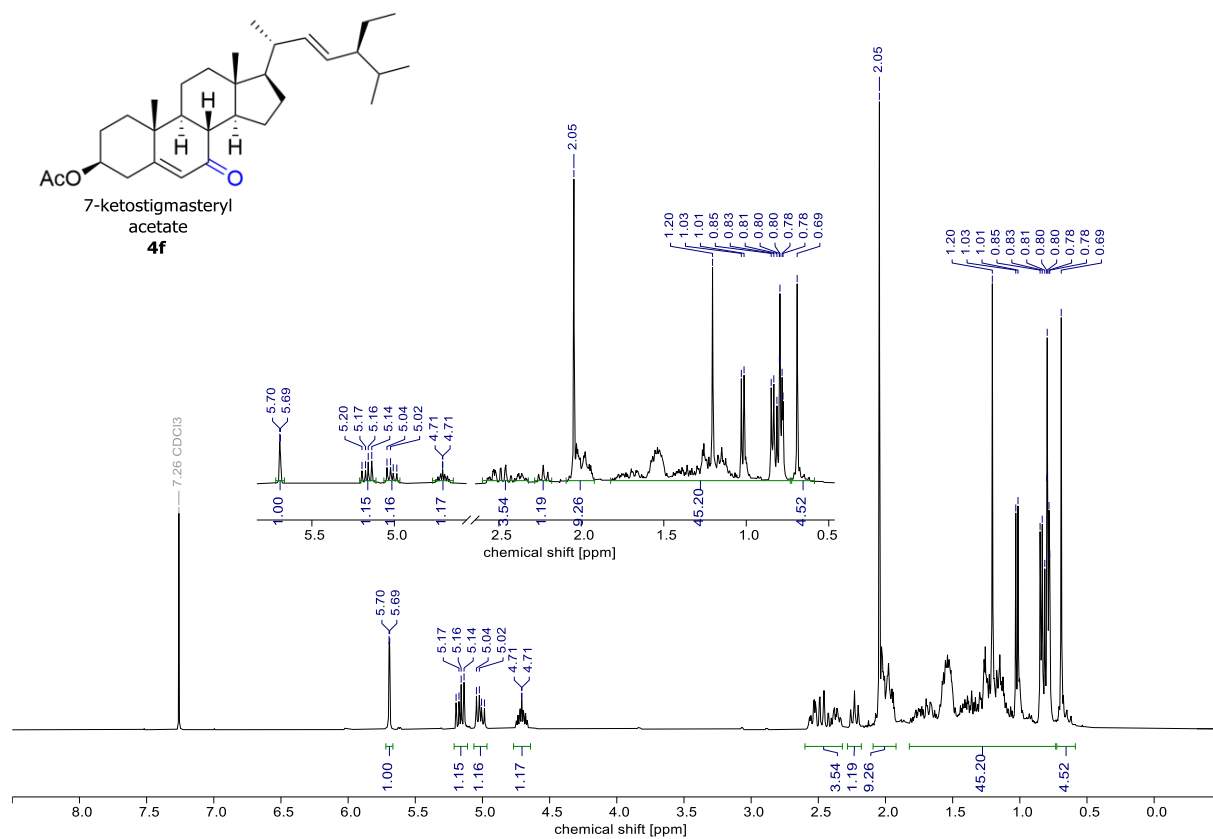


Figure S98. HSQC spectrum of product 4e: 7-ketositolsterol.

Figure S99. HMBC spectrum of product **4e**: 7-ketositosterol.

7.20. 7-Ketostigmasteryl acetate

Figure S100. ^1H NMR spectrum (400 MHz) of product **4f**: 7-ketostigmasteryl acetate.

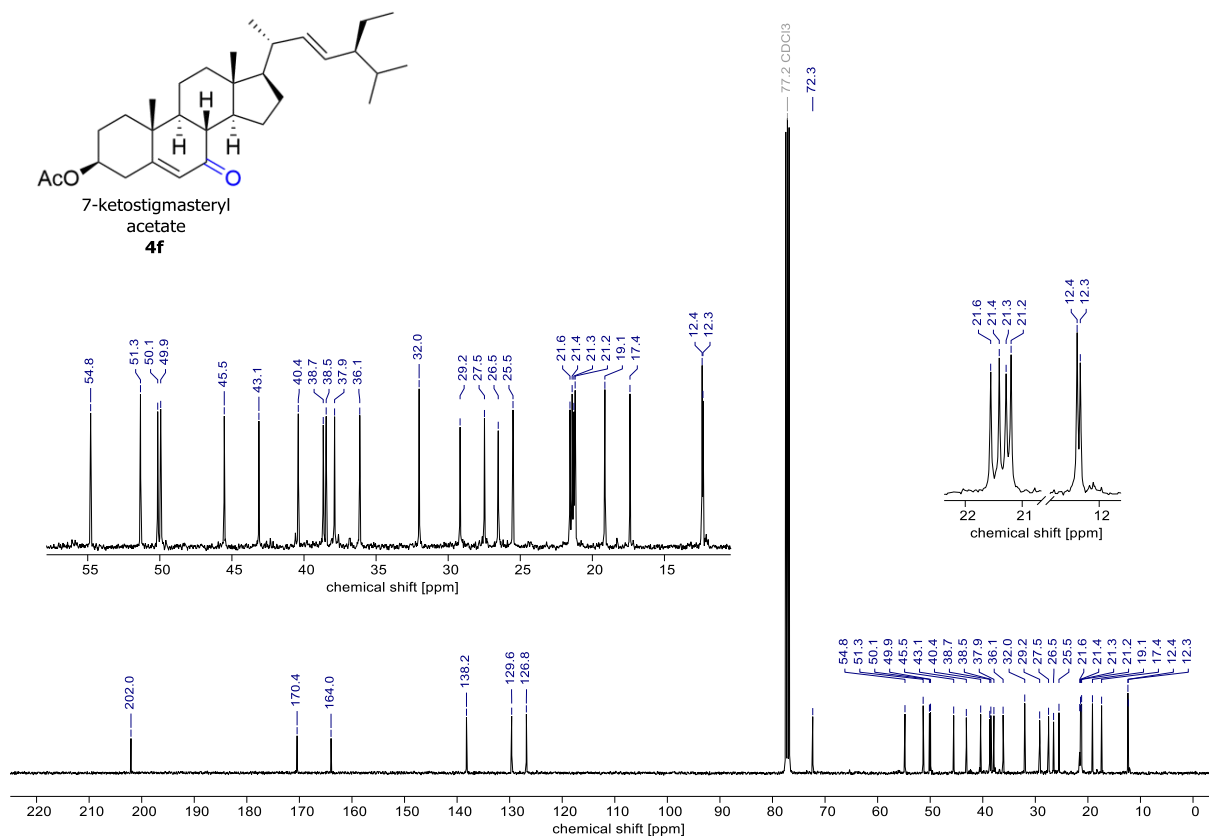


Figure S101. ¹³C NMR spectrum (101 MHz) of product **4f**: 7-ketostigmasteryl acetate.

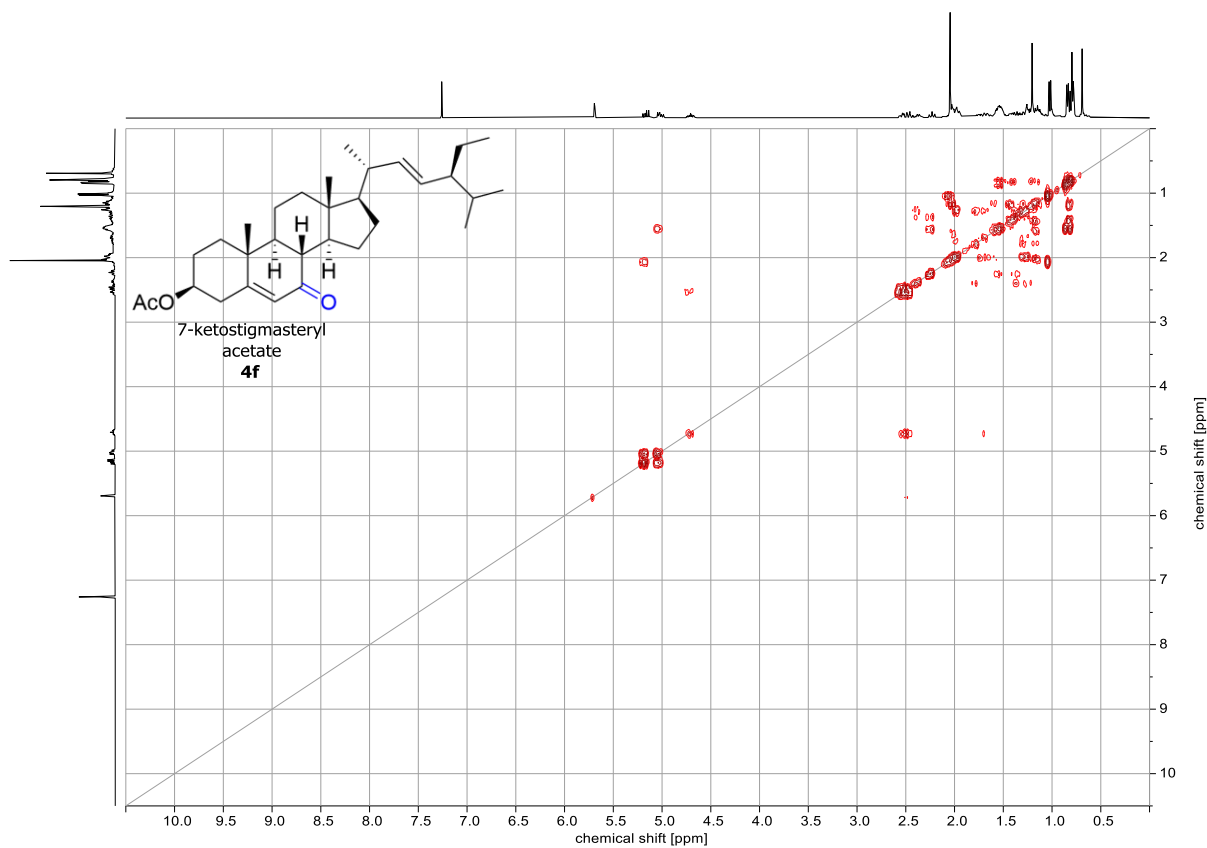


Figure S102. COSY spectrum of product **4f**: 7-ketostigmasteryl acetate.

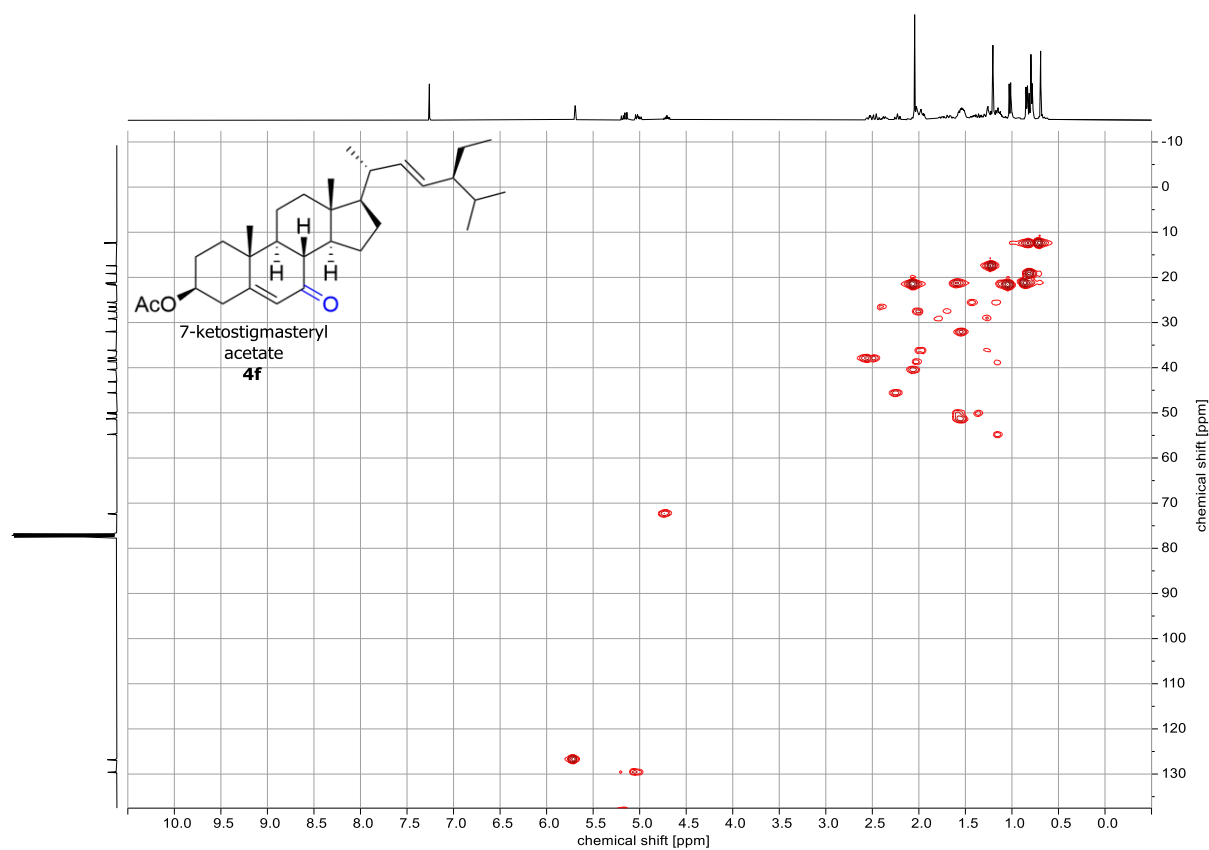


Figure S103. HSQC spectrum of product **4f**: 7-ketostigmasteryl acetate.

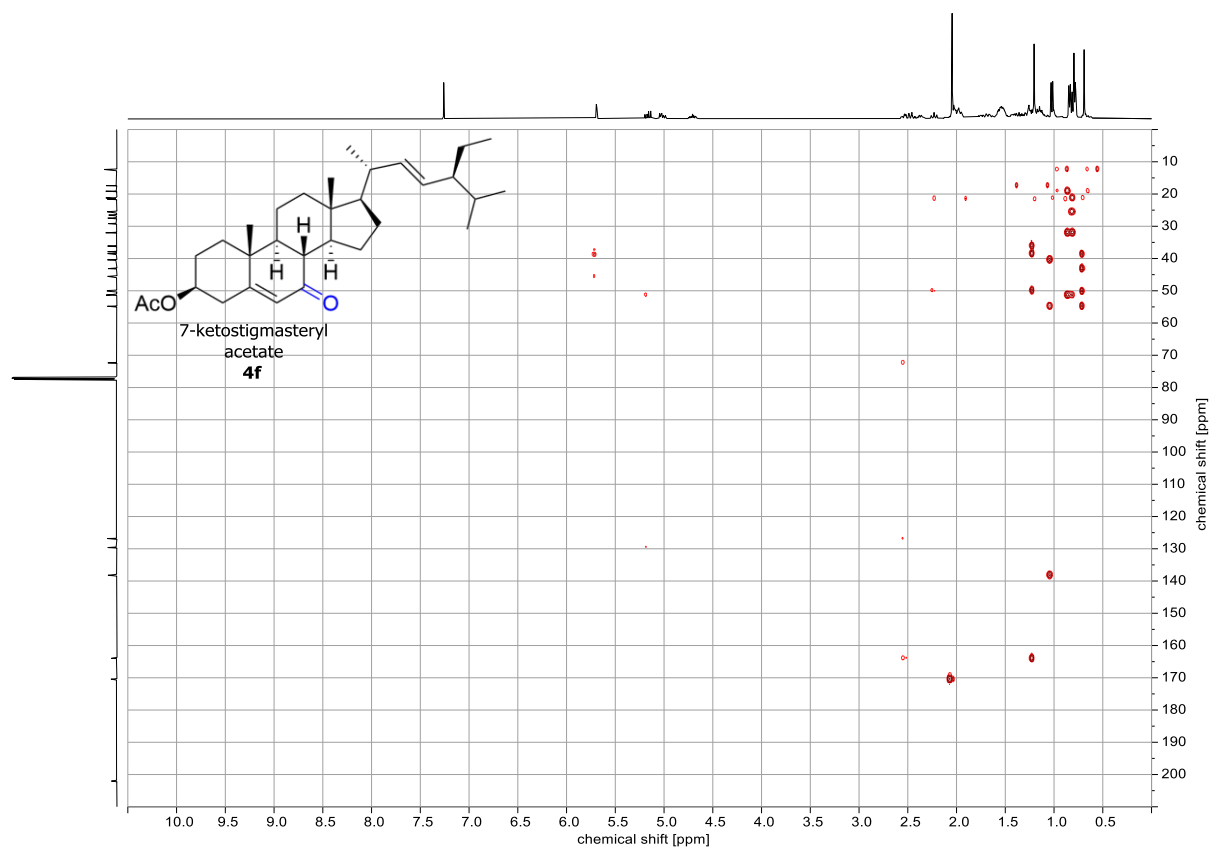
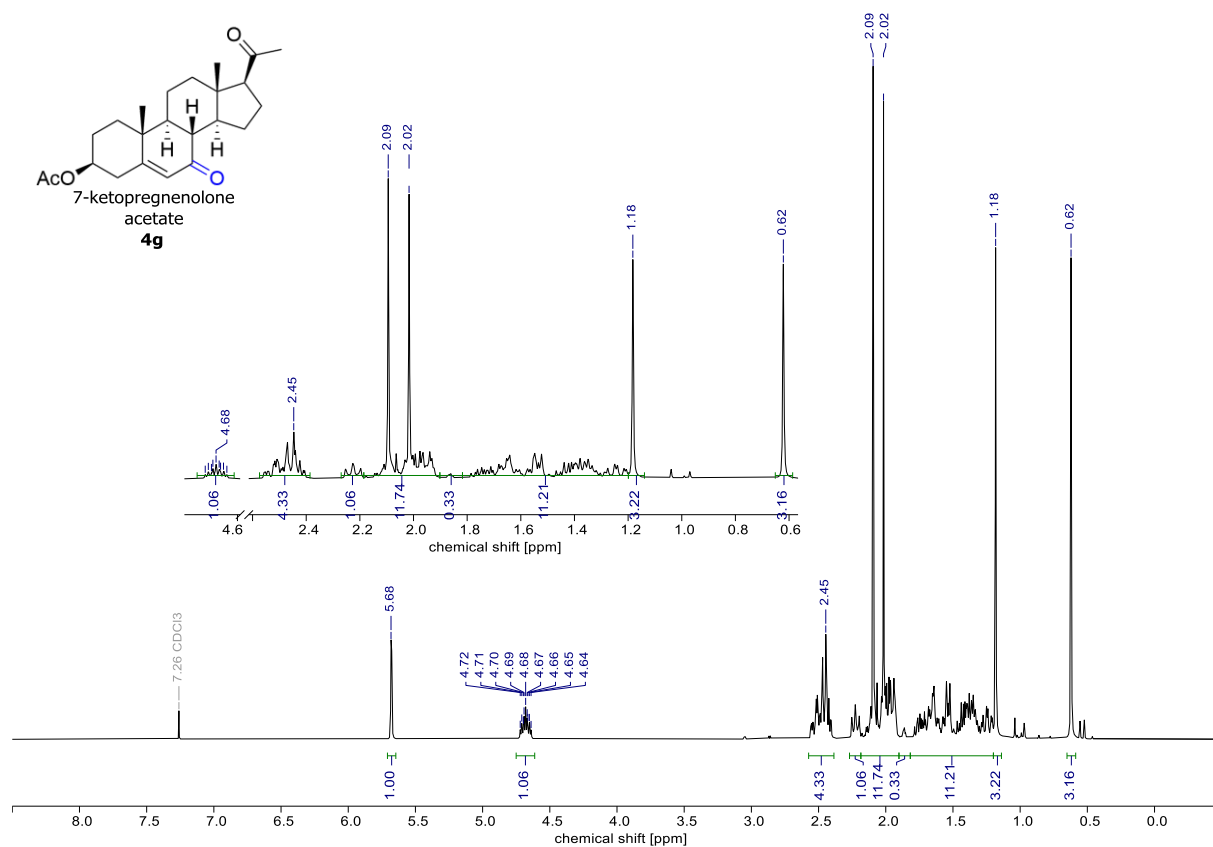
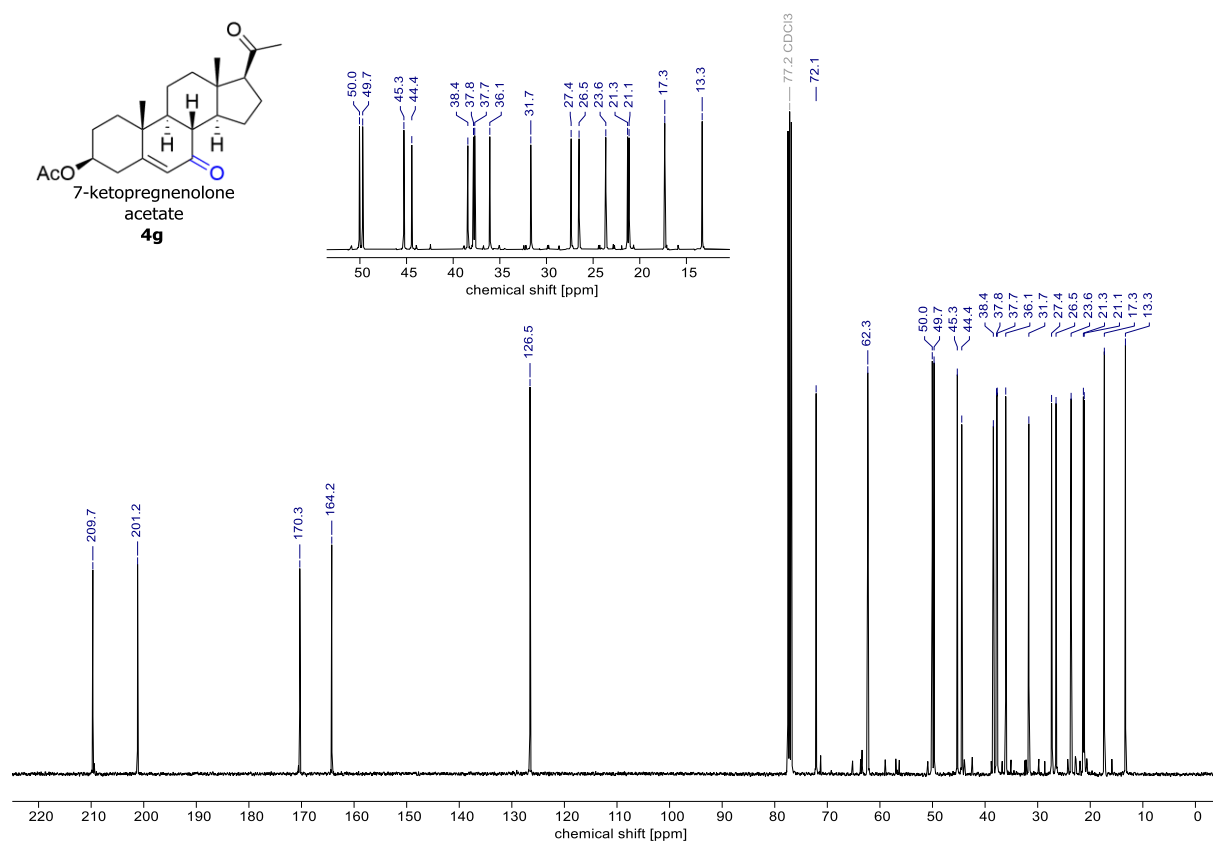


Figure S104. HMBC spectrum of product **4f**: 7-ketostigmasteryl acetate.

7.21. 7-Ketopregnenolone acetate

Figure S105. ¹H NMR spectrum (400 MHz) of product **4g**: 7-ketopregnenolone acetate.Figure S106. ¹³C NMR spectrum (101 MHz) of product **4g**: 7-ketopregnenolone acetate.

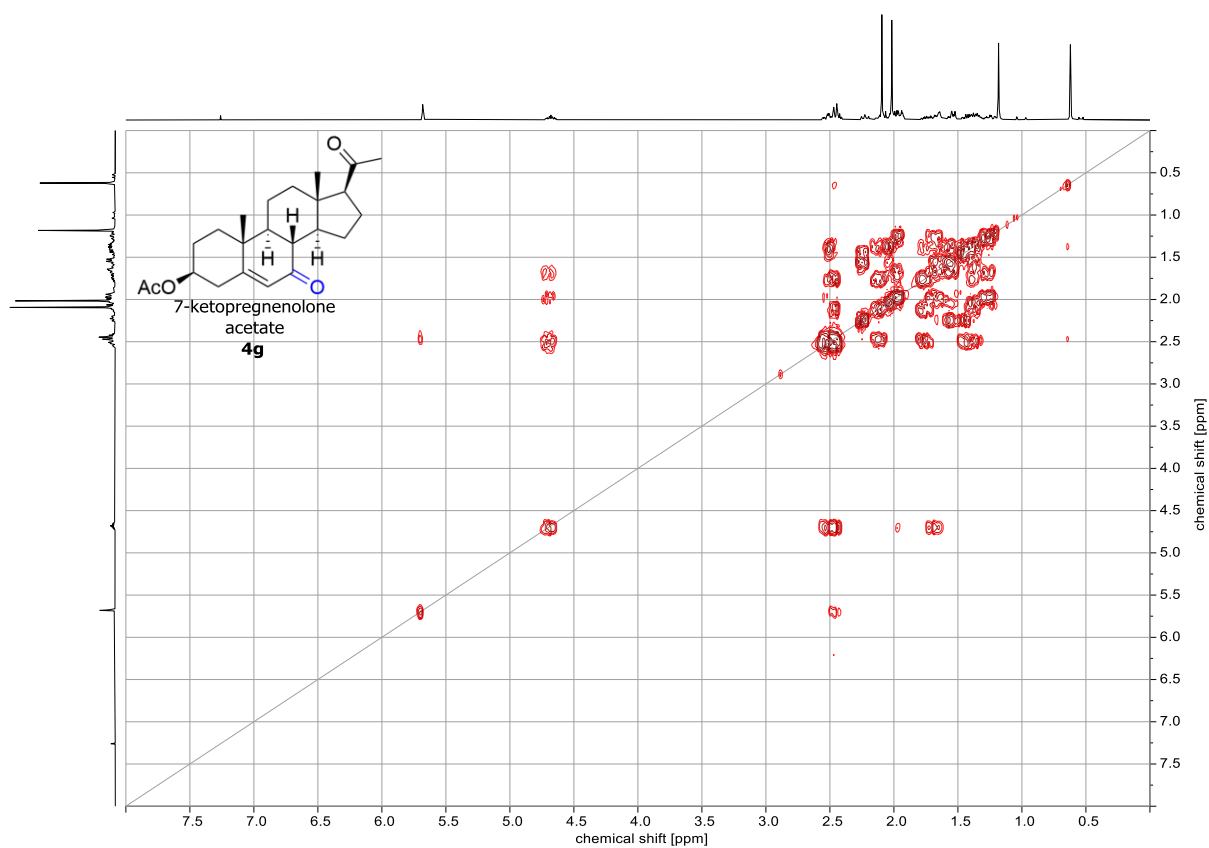


Figure S107. COSY spectrum of product **4g**: 7-ketopregnenolone acetate.

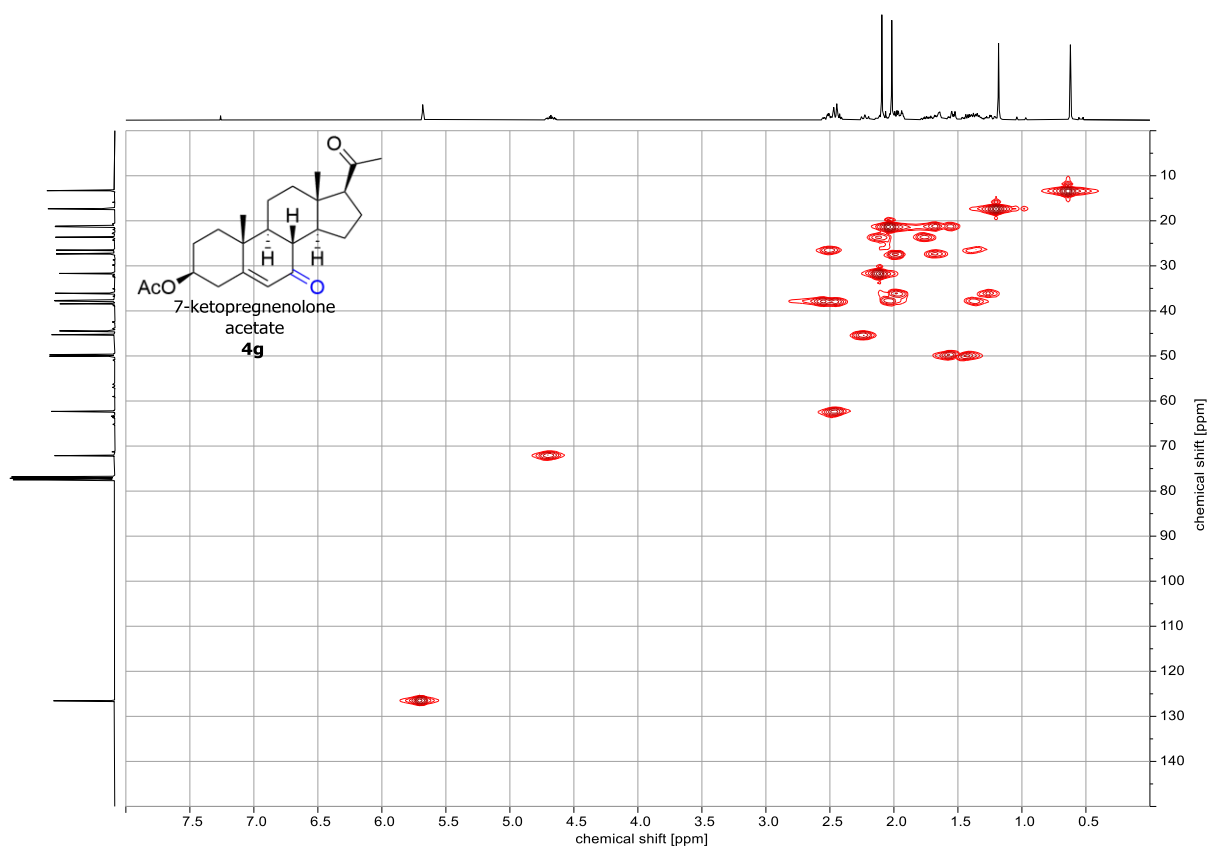


Figure S108. HSQC spectrum of product **4g**: 7-ketopregnenolone acetate.

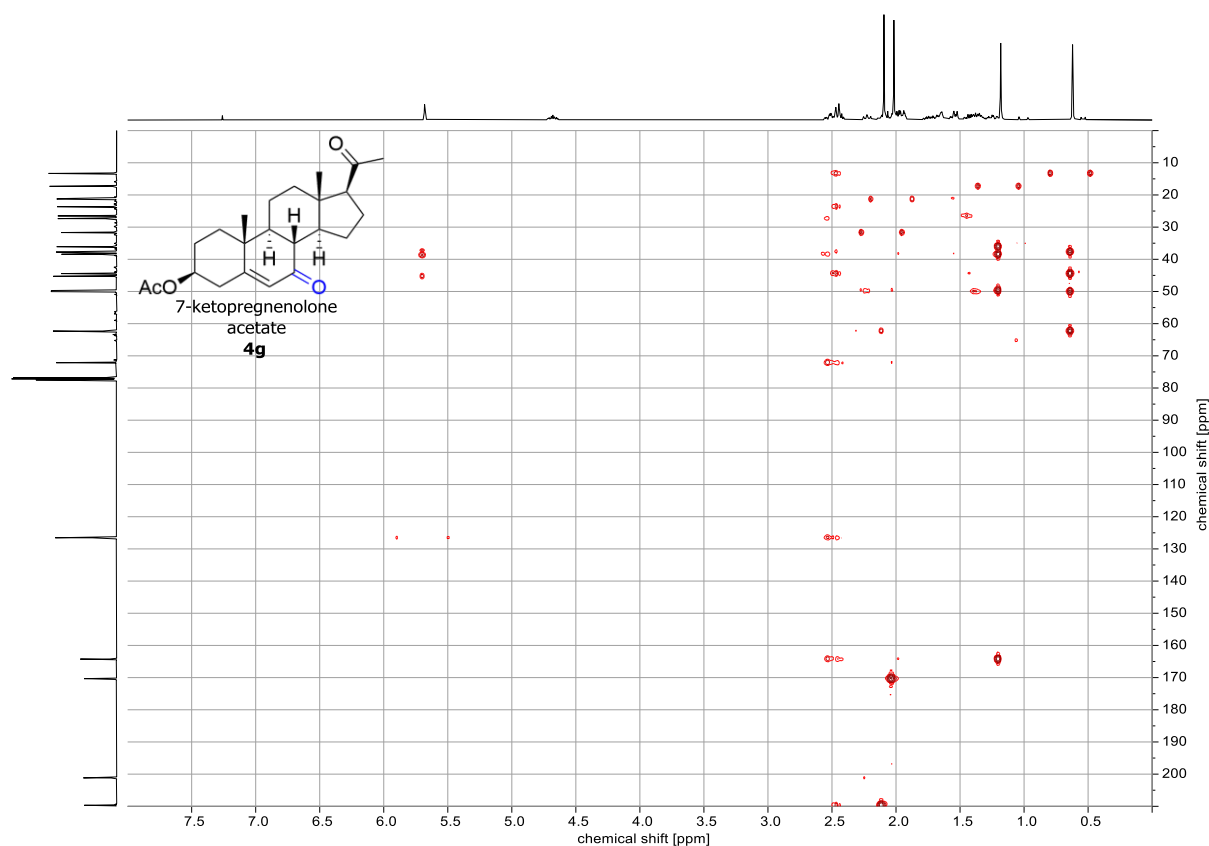


Figure S109. HMBC spectrum of product **4g**: 7-ketopregnenolone acetate.

7.22. 7-Ketodehydroepiandrosterone acetate

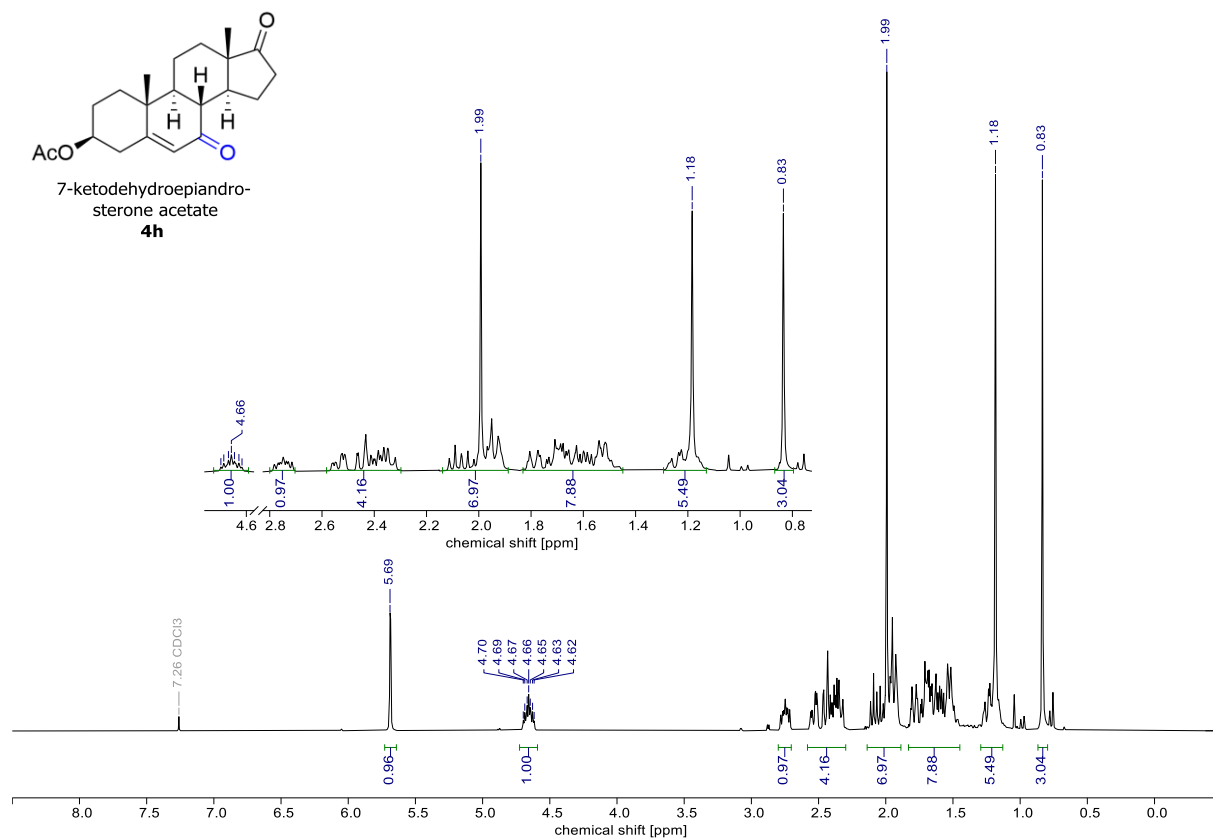


Figure S110. ¹H NMR spectrum (400 MHz) of product **4h**: 7-ketodehydroepiandrosterone acetate.

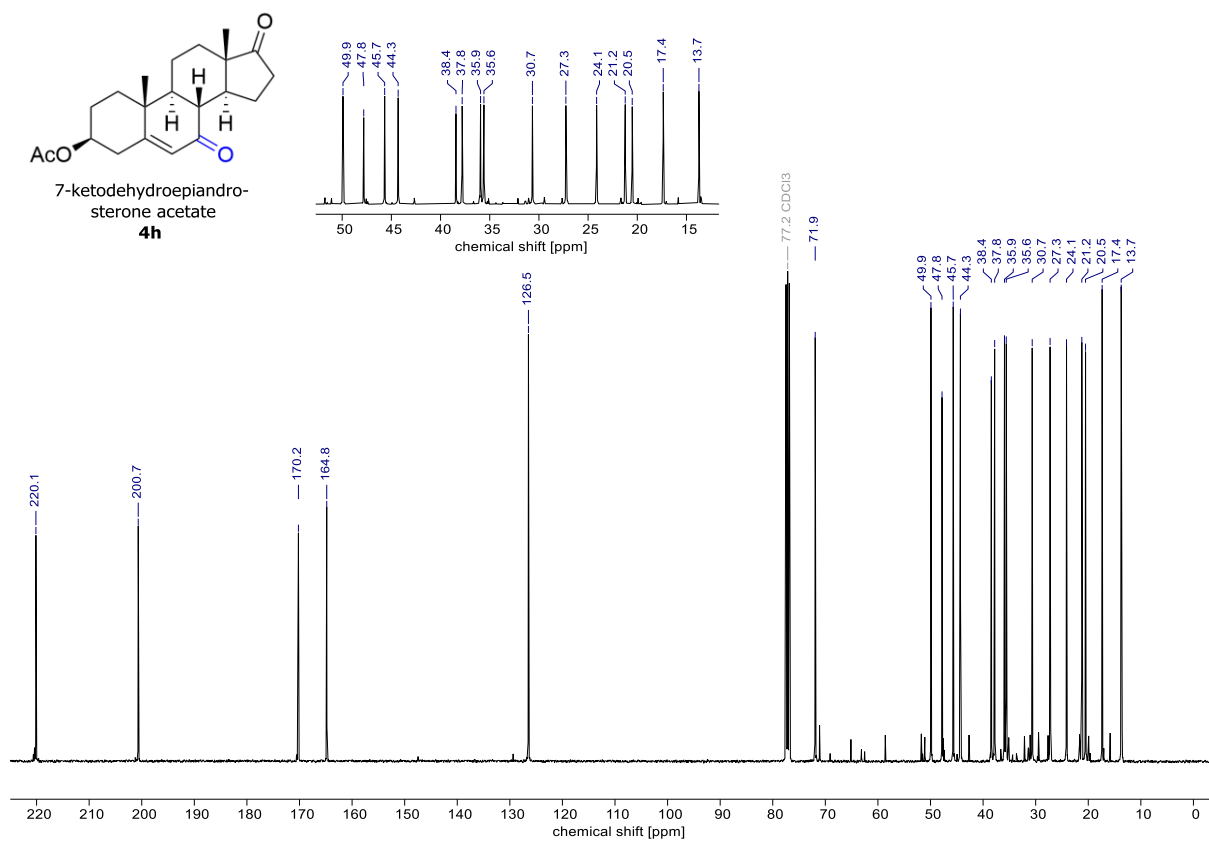


Figure S111. ¹³C NMR spectrum (101 MHz) of product **4h**: 7-ketodehydroepiandrosterone acetate.

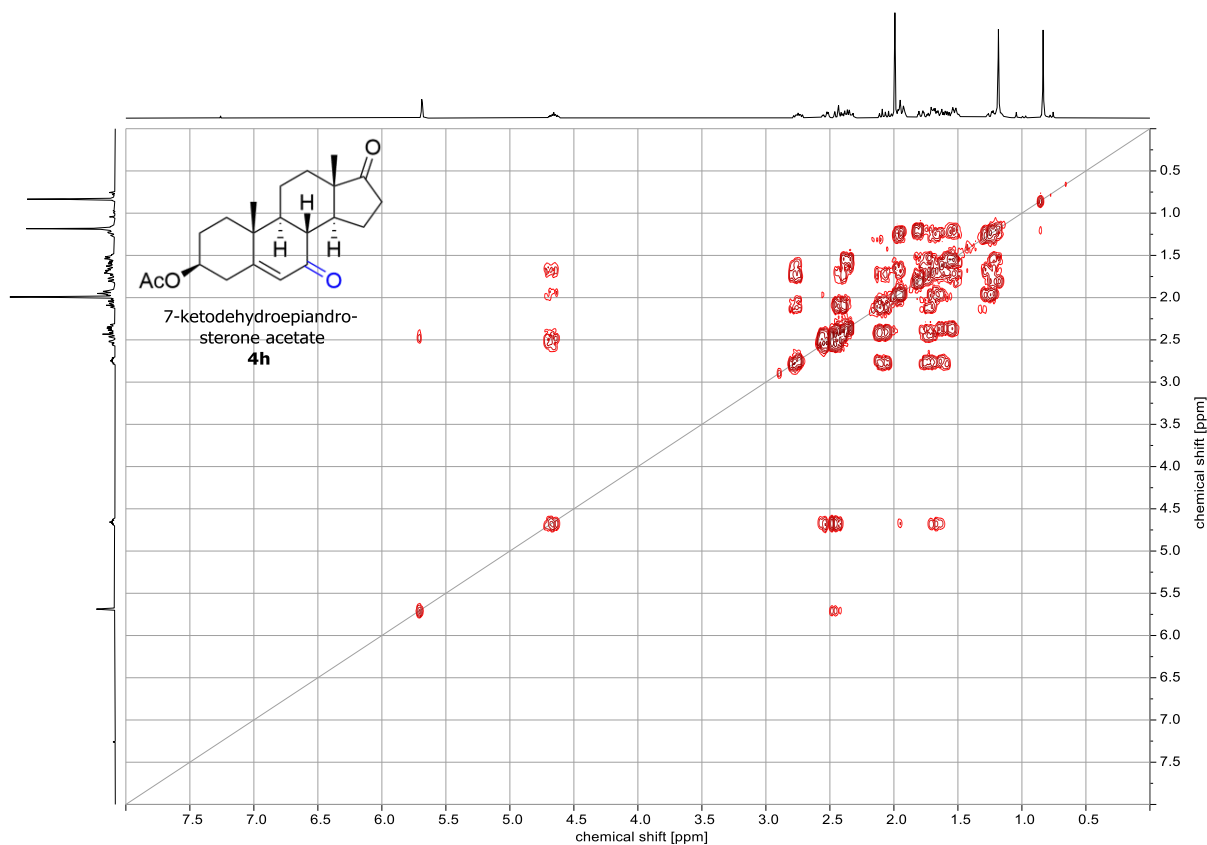


Figure S112. COSY spectrum of product **4h**: 7-ketodehydroepiandrosterone acetate.

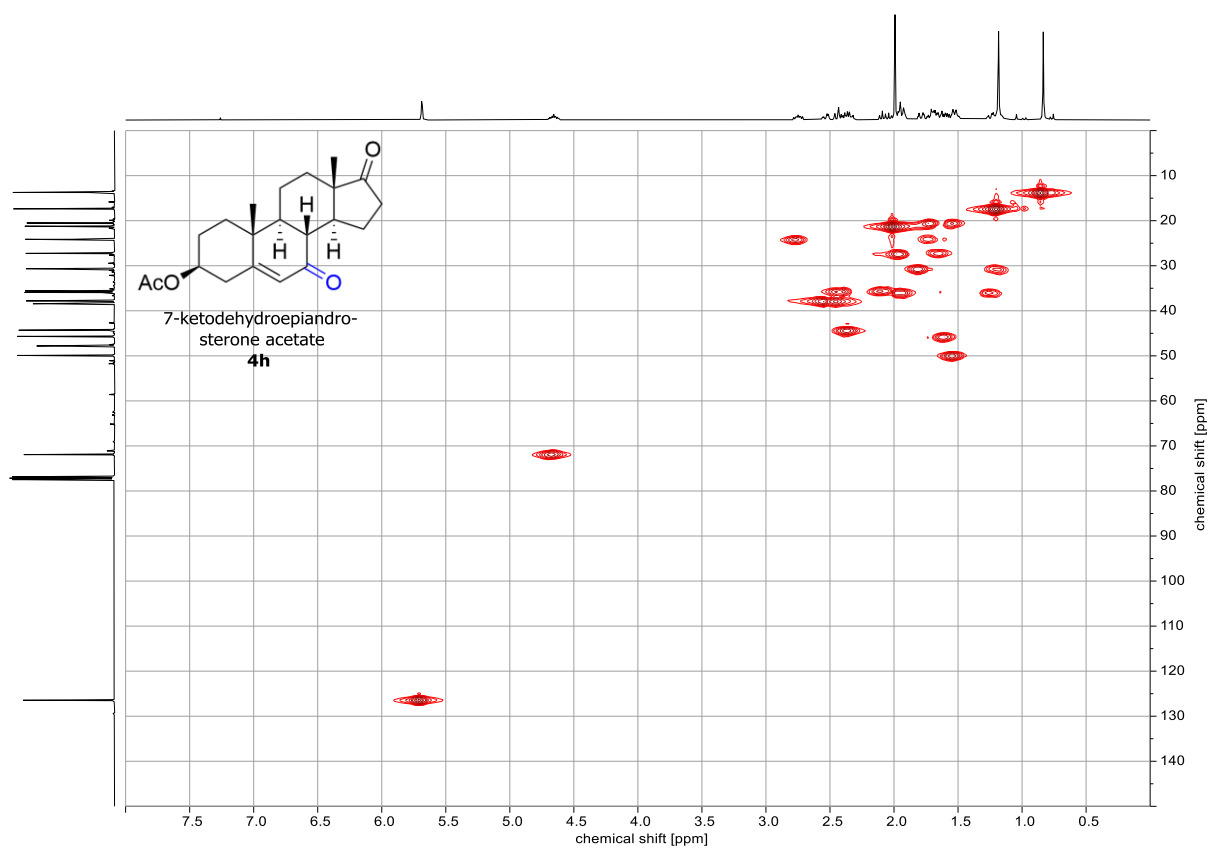


Figure S113. HSQC spectrum of product **4h**: 7-ketodehydroepiandrosterone acetate.

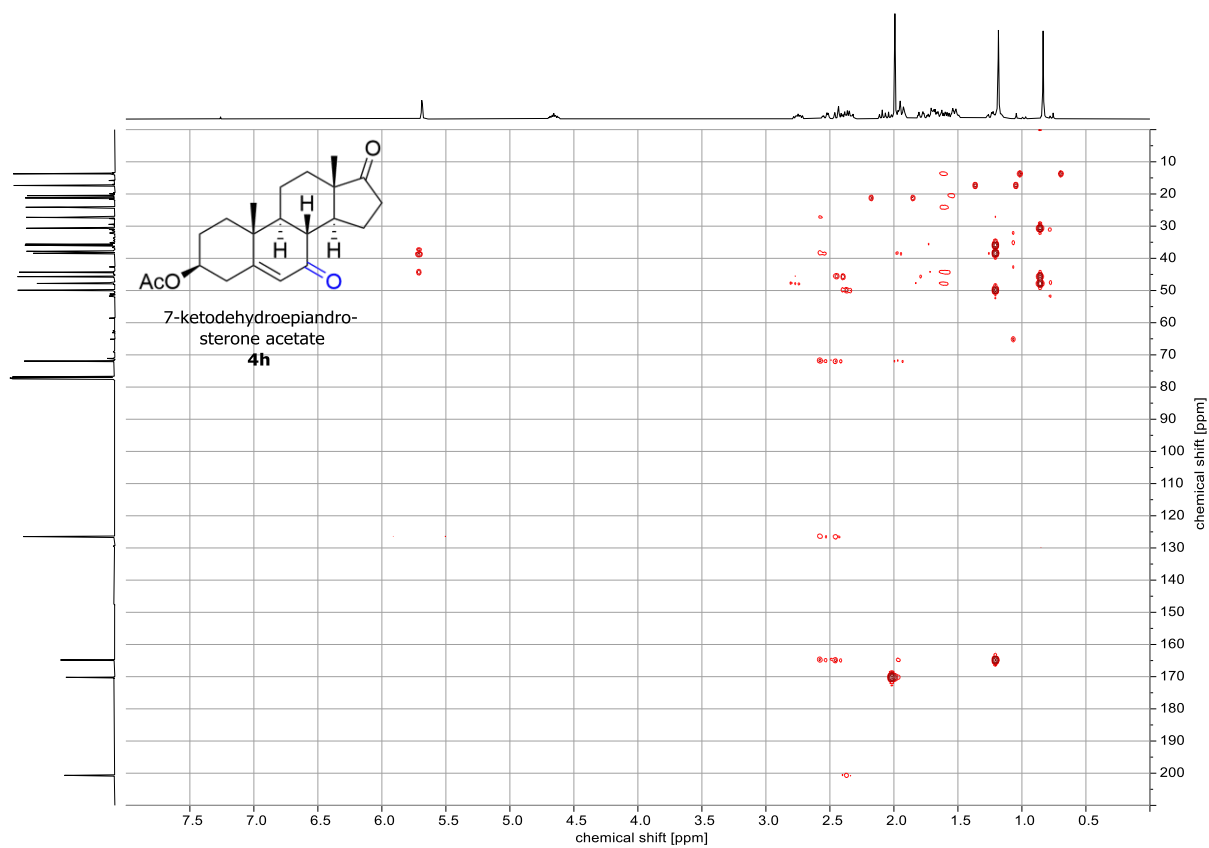


Figure S114. HMBC spectrum of product **4h**: 7-ketodehydroepiandrosterone acetate.

7.23. 7-Ketomethandriol

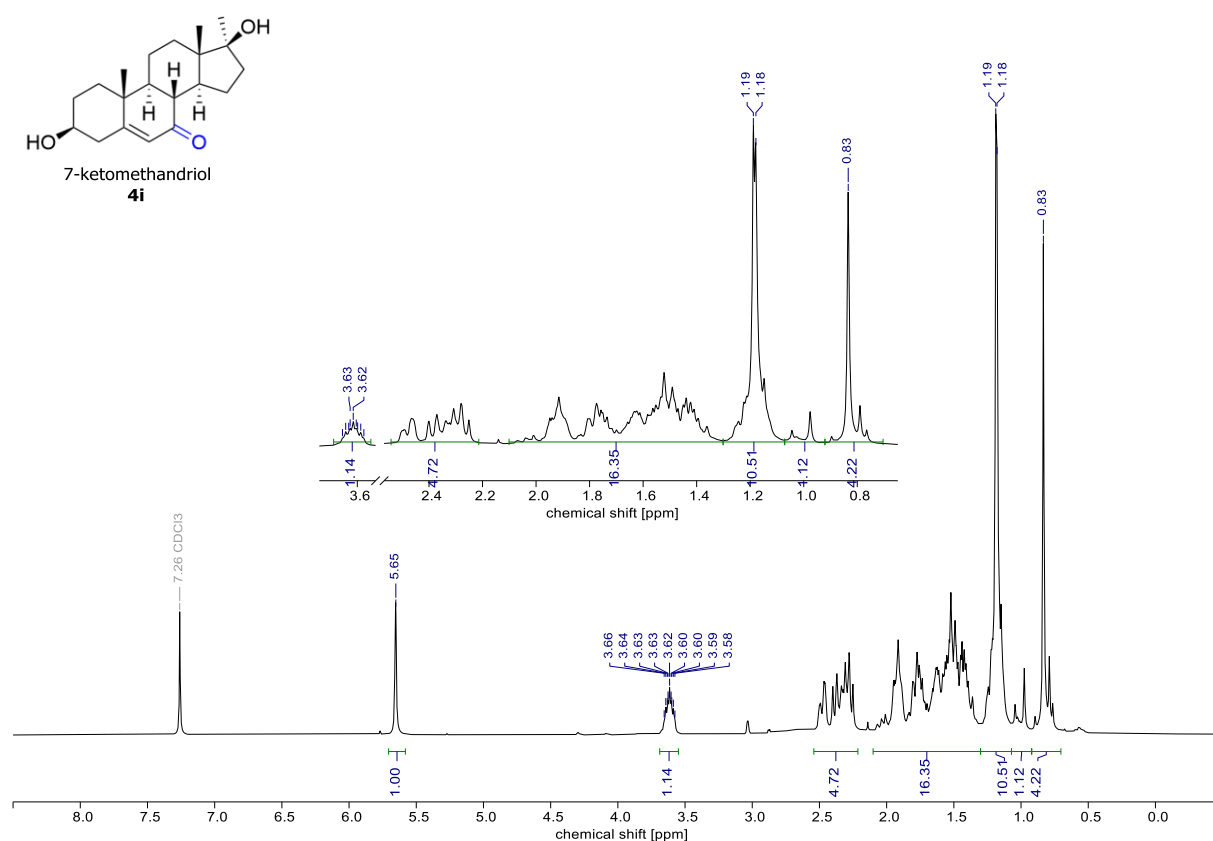


Figure S115. ^1H NMR spectrum (400 MHz) of product **4i**: 7-ketomethandriol.

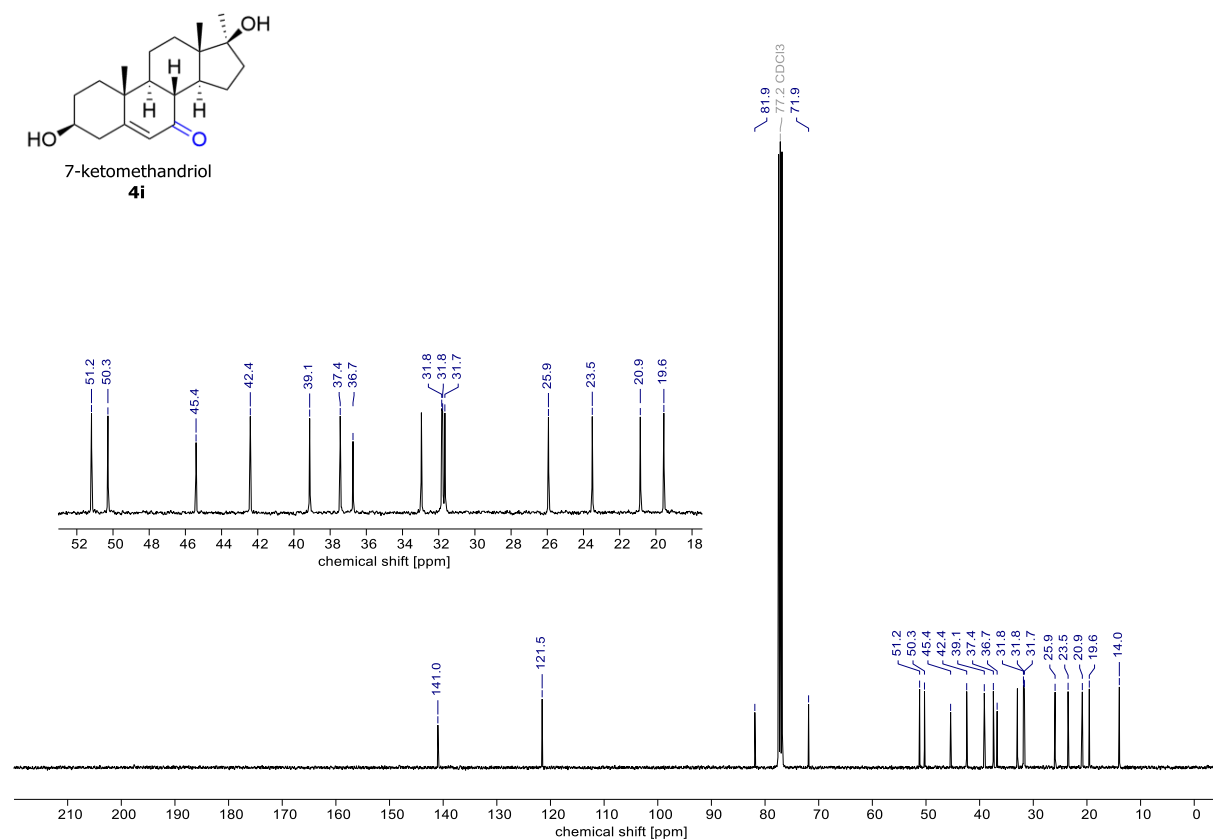
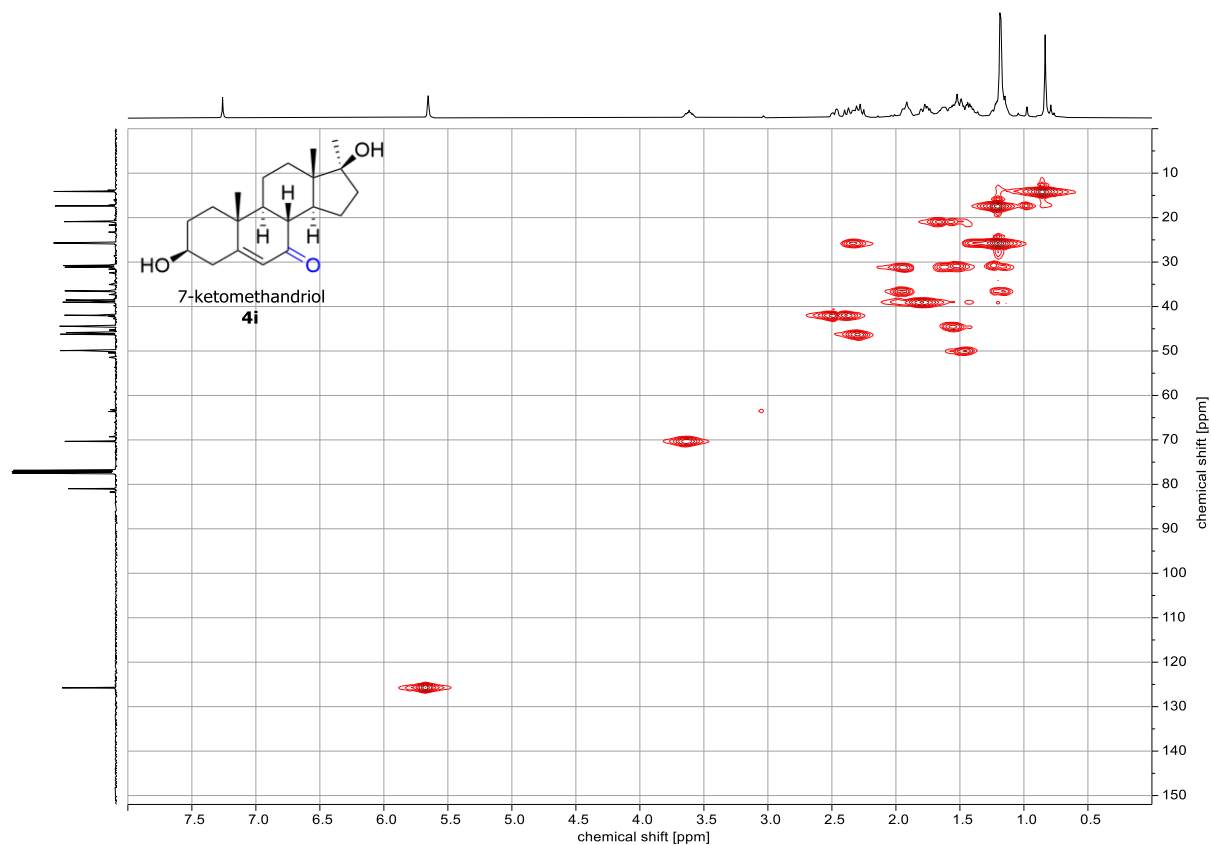
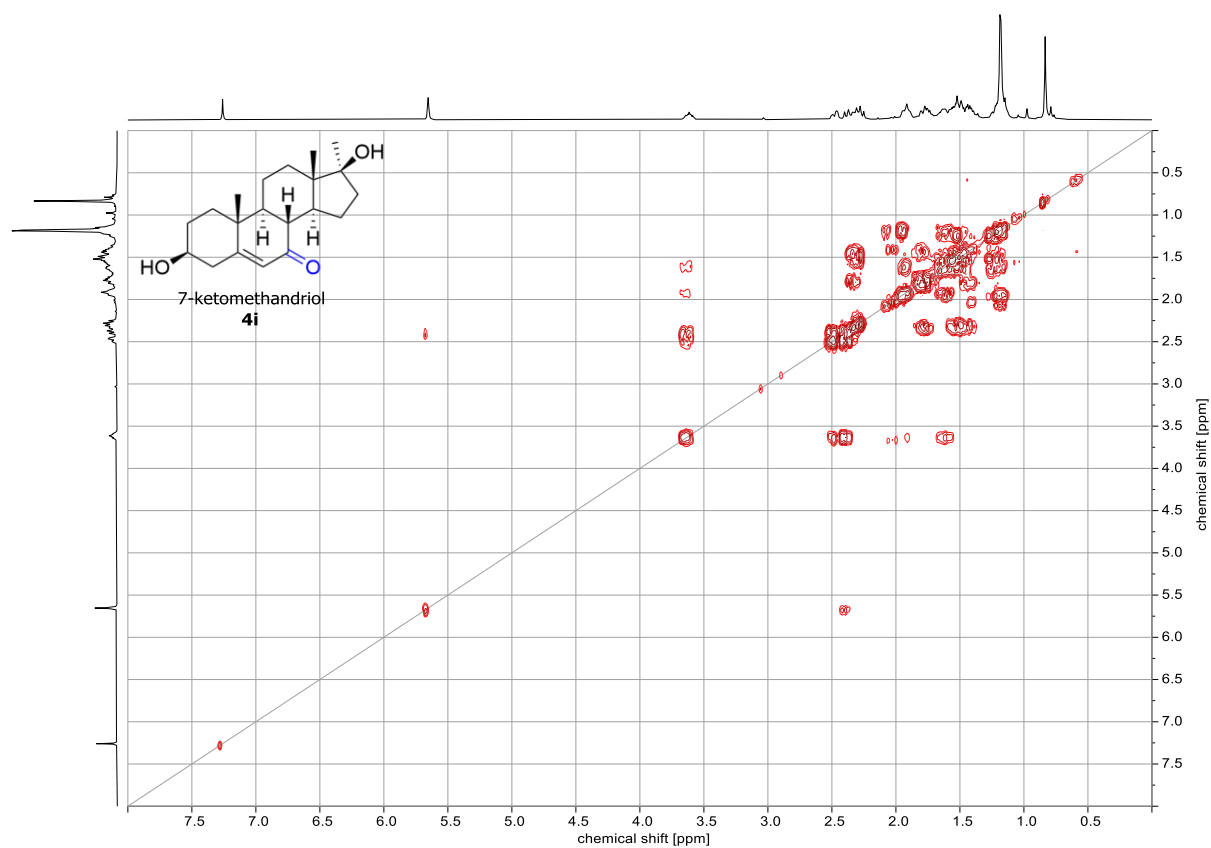
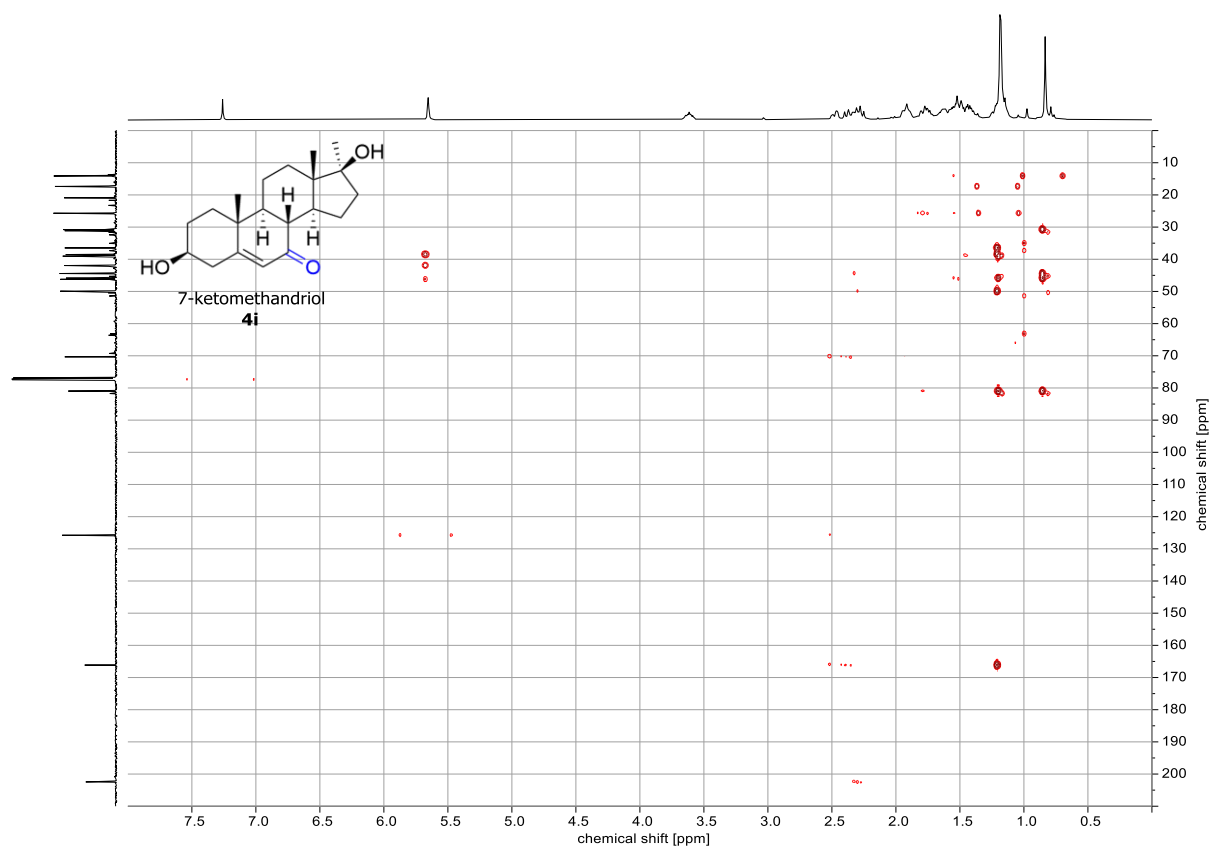
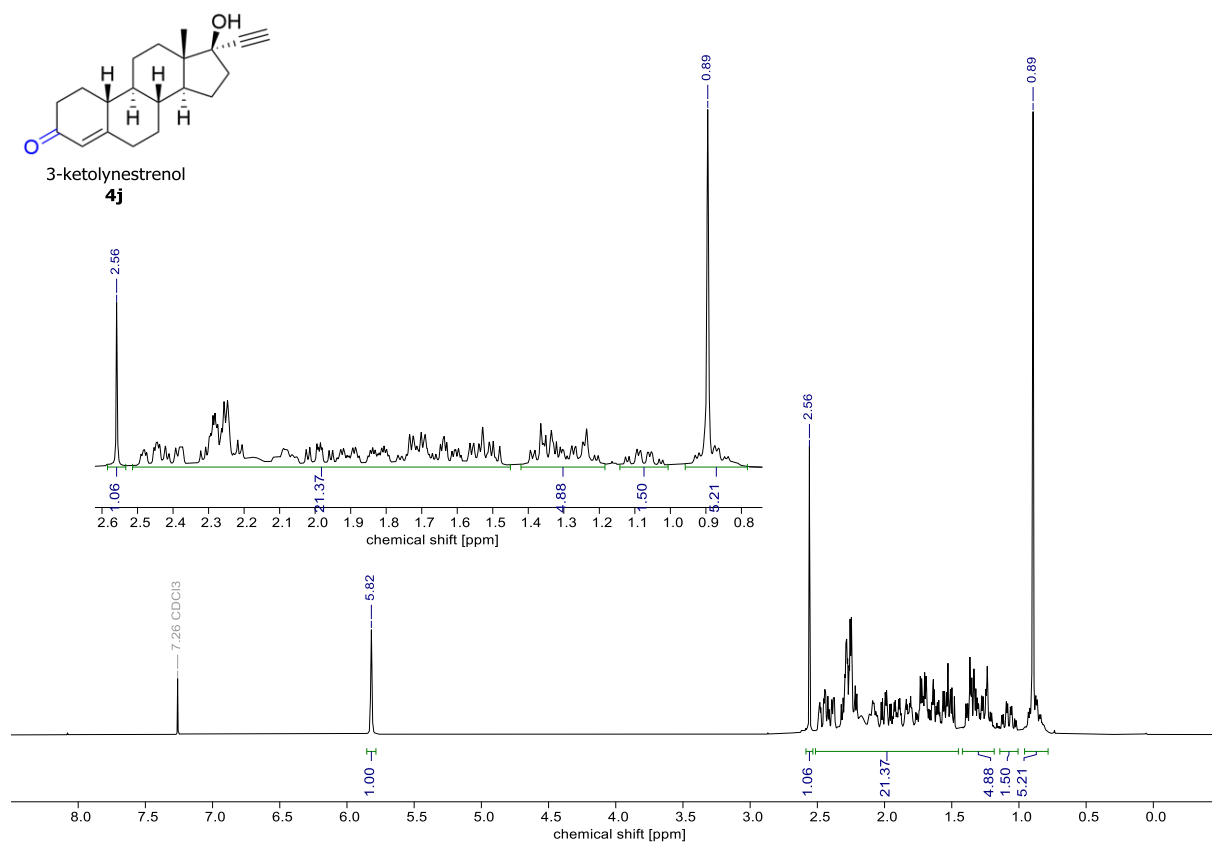


Figure S116. ^{13}C NMR spectrum (101 MHz) of product **4i**: 7-ketomethandriol.



Figure S119. HMBC spectrum of product **4i**: 7-ketomethandriol.

7.24. 3-Ketolynestrenol

Figure S120. ^1H NMR spectrum (400 MHz) of product **4j**: 3-ketolynestrenol.

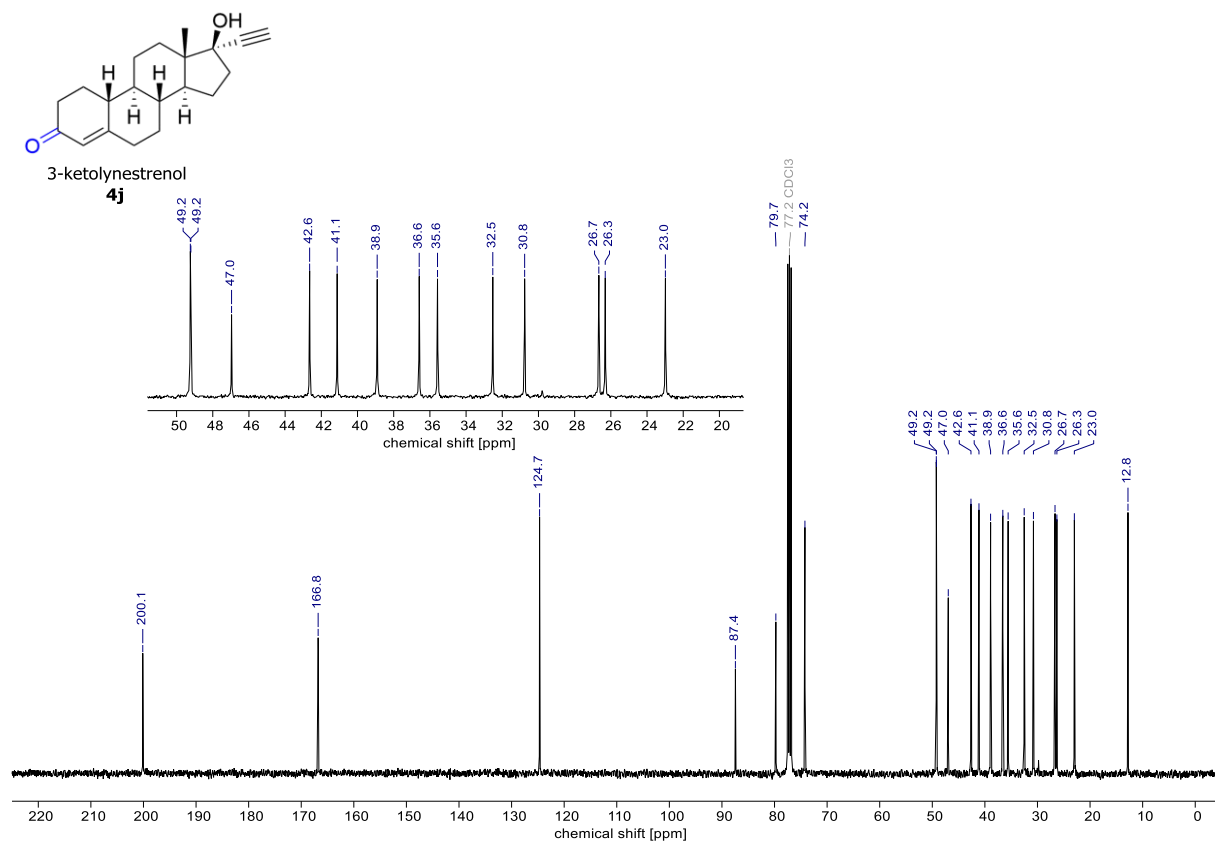


Figure S121. ¹³C NMR spectrum (101 MHz) of product **4j**: 3-ketolynestrenol.

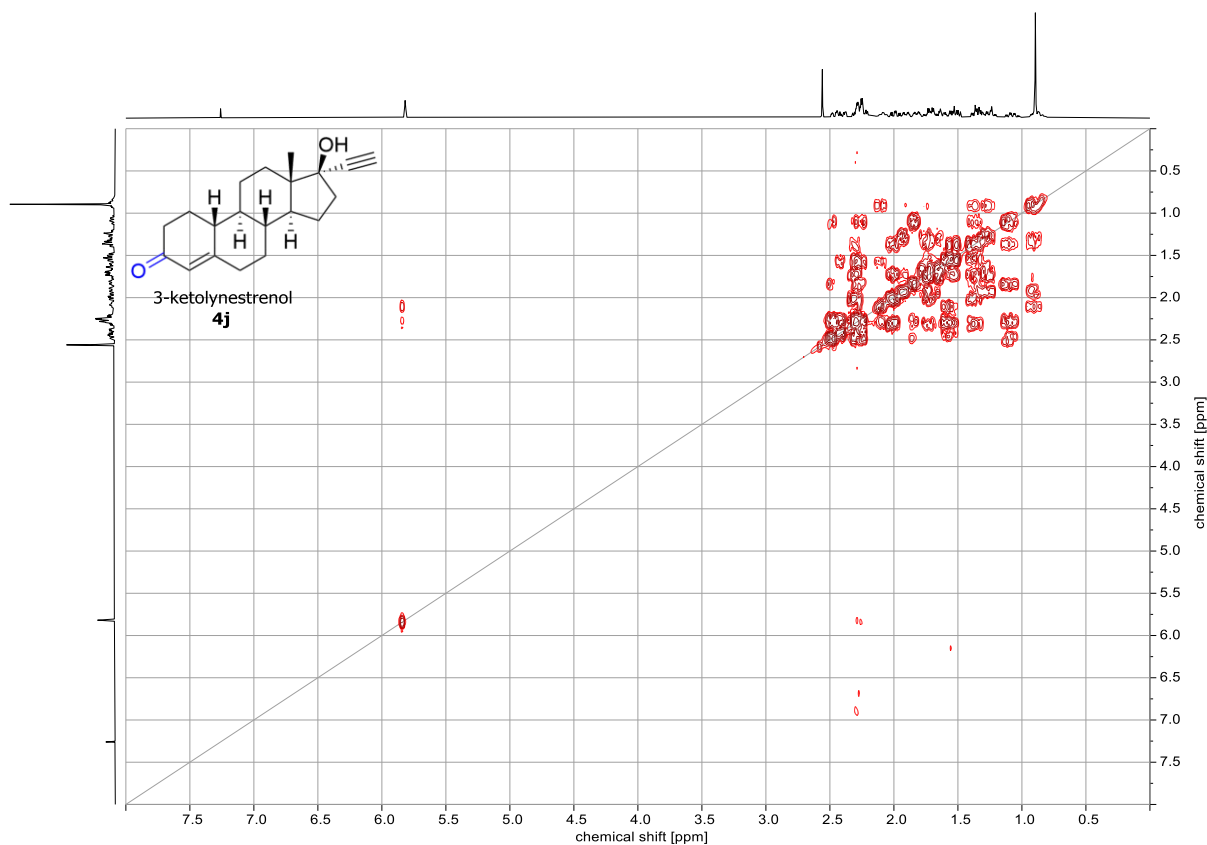


Figure S122. COSY spectrum of product **4j**: 3-ketolynestrenol.

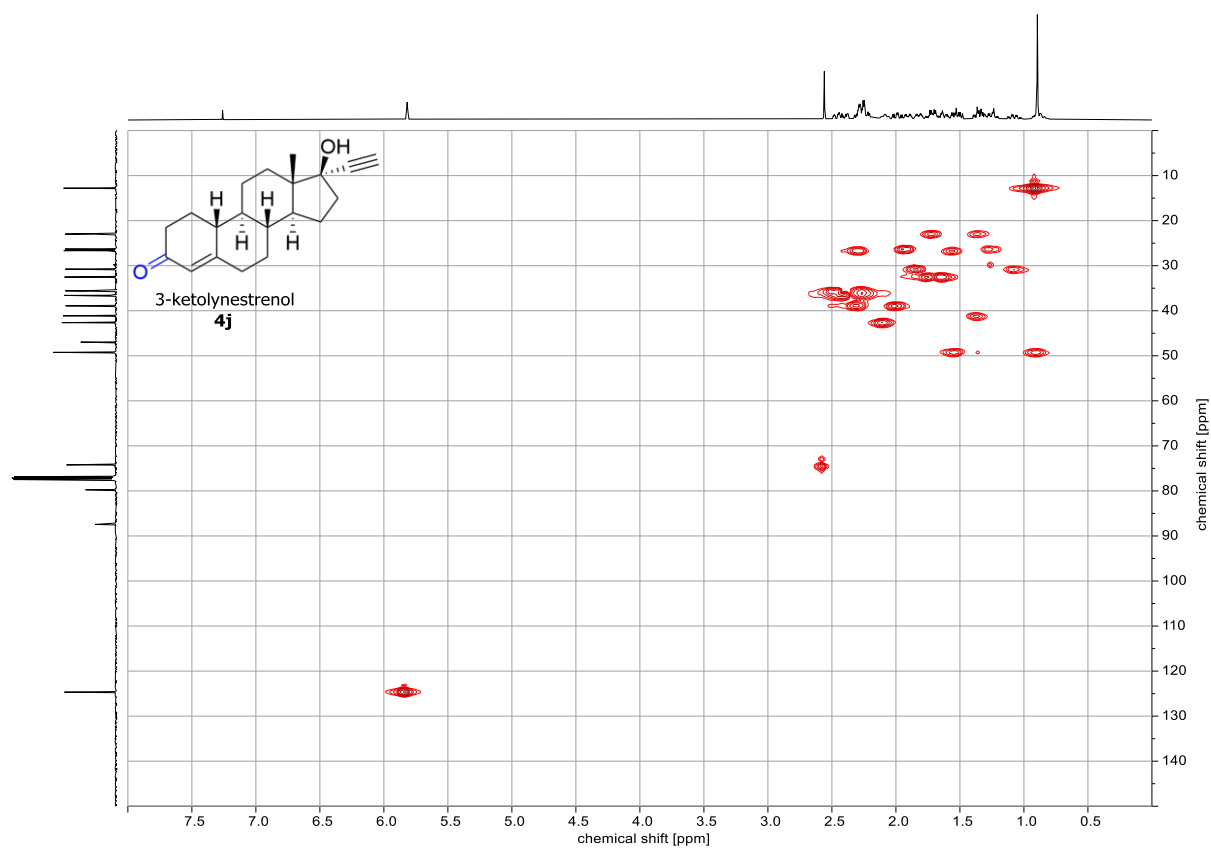


Figure S123. HSQC spectrum of product **4j**: 3-ketolynestrenol.

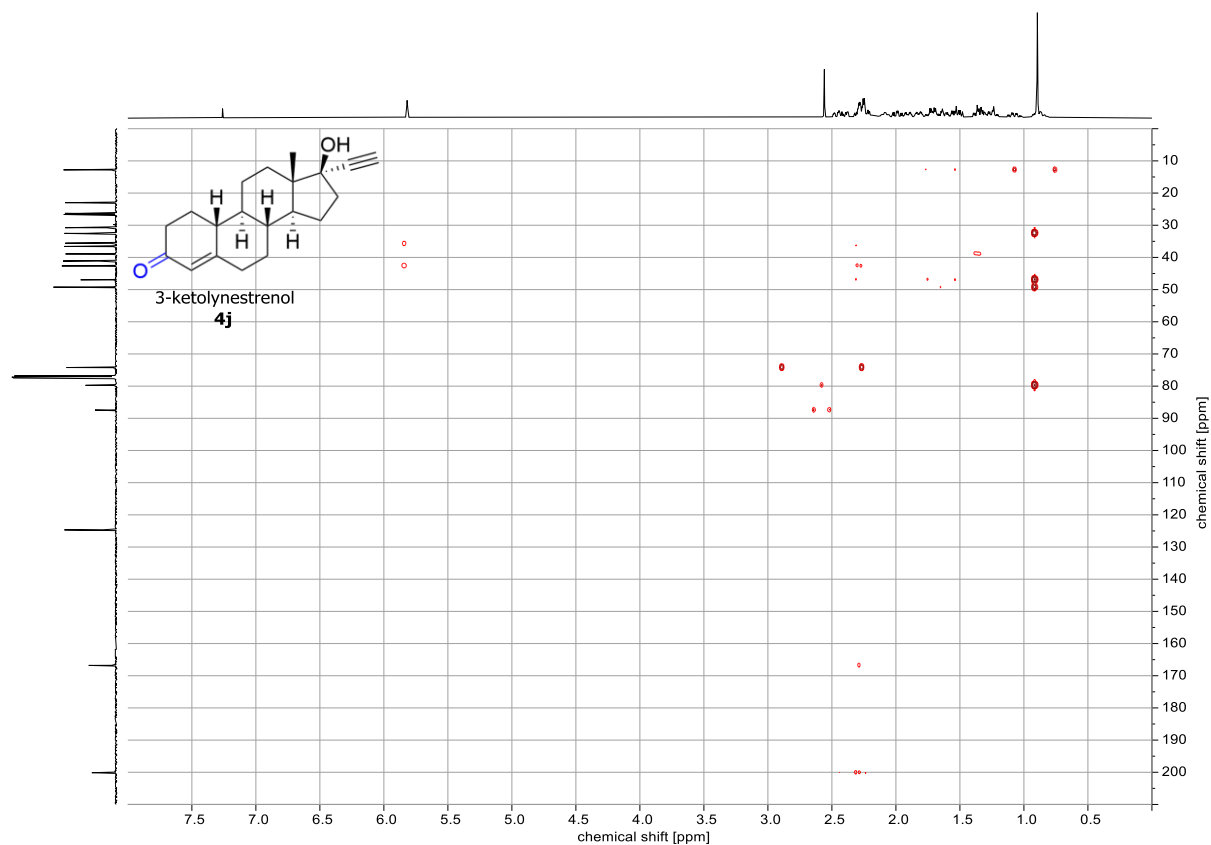


Figure S124. HMBC spectrum of product **4j**: 3-ketolynestrenol.

8. NMR Spectra of Scale-up Reaction

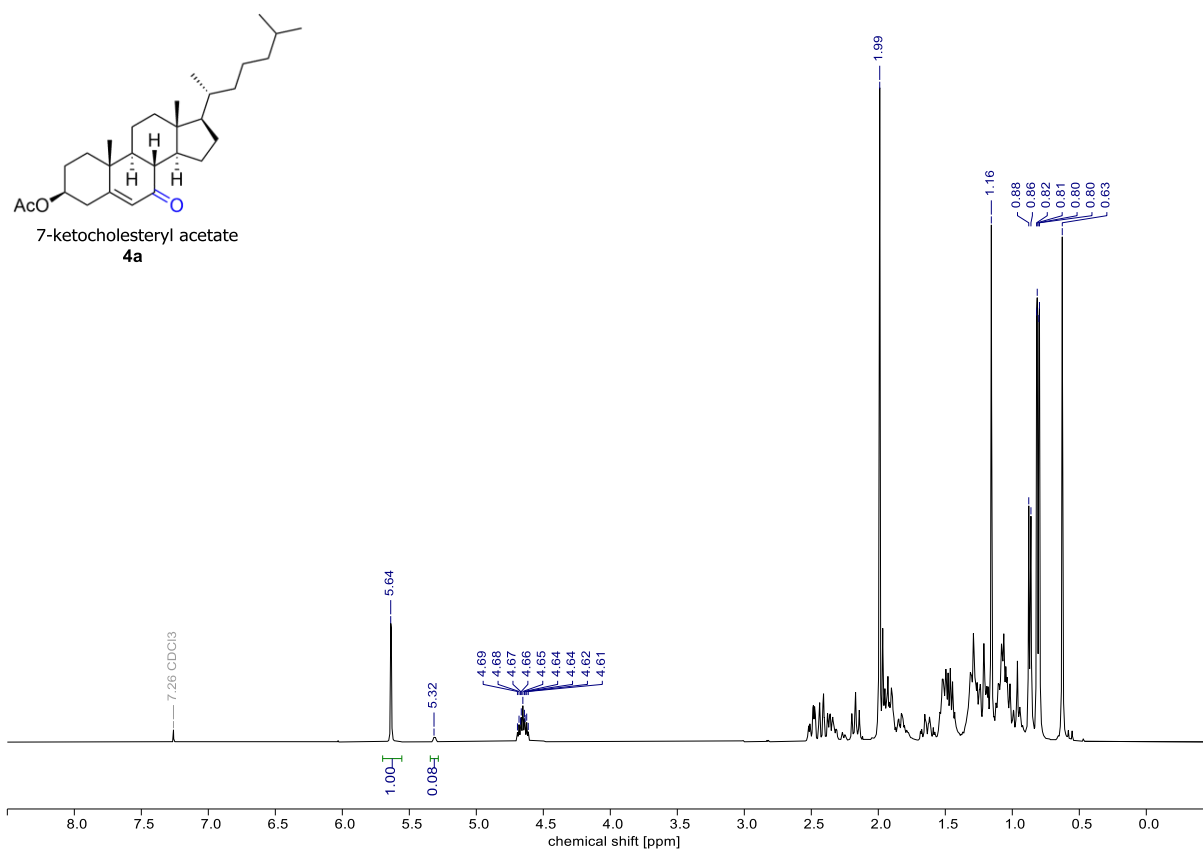


Figure S125. ¹H NMR spectrum (400 MHz) of the scale-up reaction using cholesteryl acetate. The allylic oxidation product 7-ketocholesteryl acetate **4a** is 92% pure after one recrystallization from acetonitrile and contains 8% cholesteryl acetate.

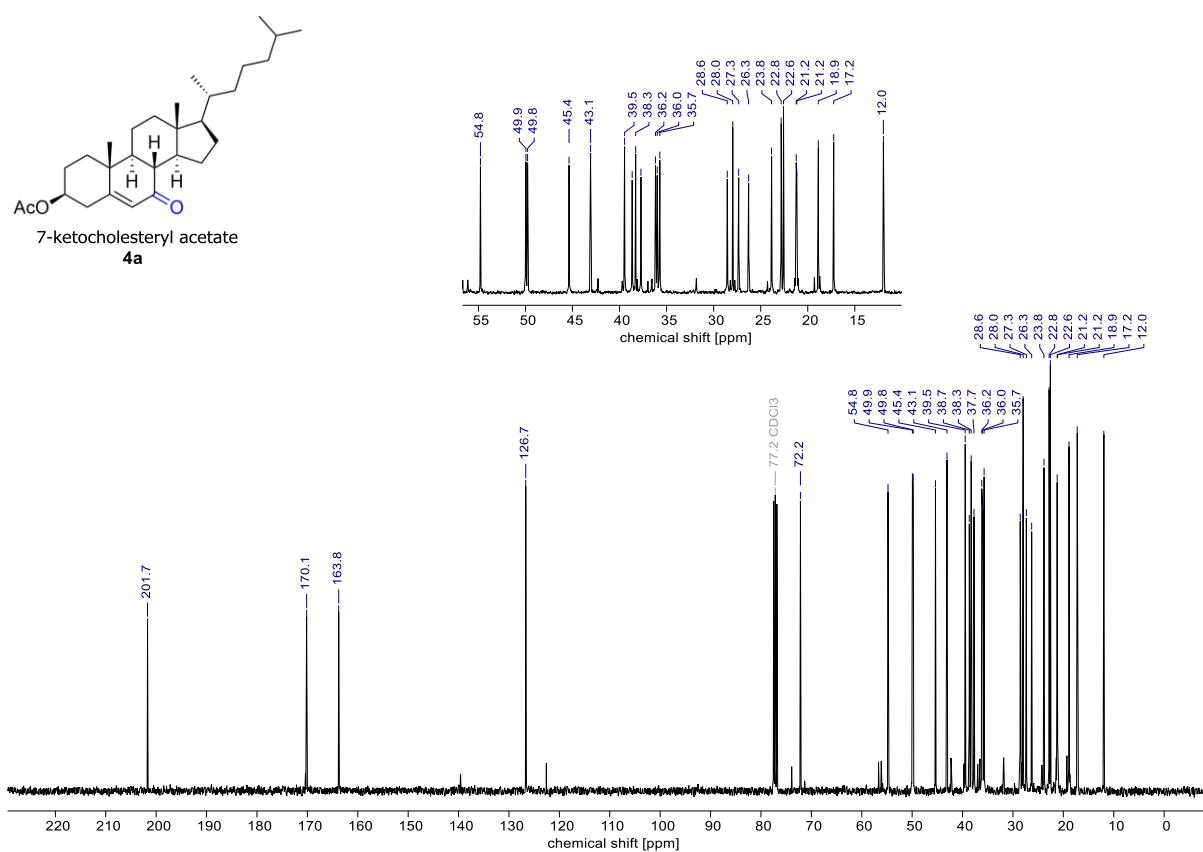


Figure S126. ¹³C NMR spectrum (101 MHz) of the scale-up reaction.

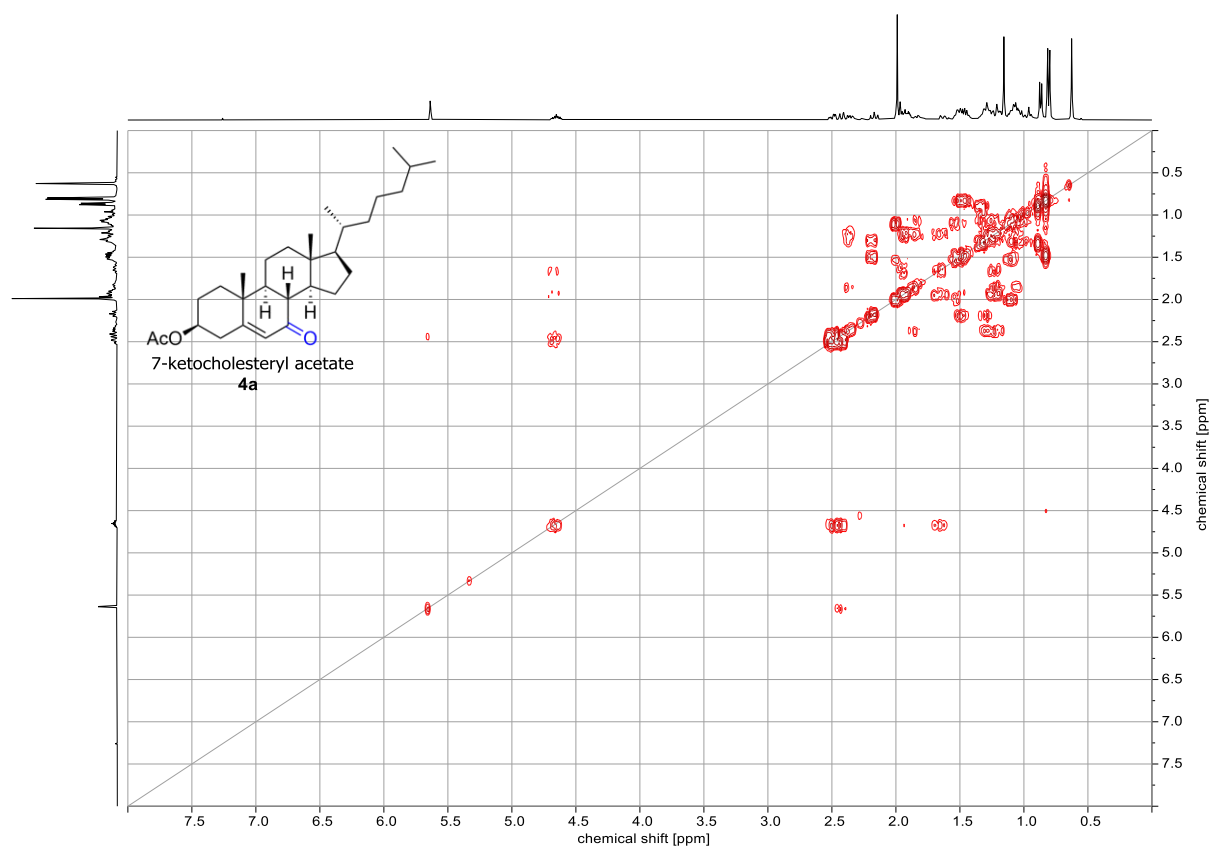


Figure S127. COSY spectrum of the scale-up reaction.

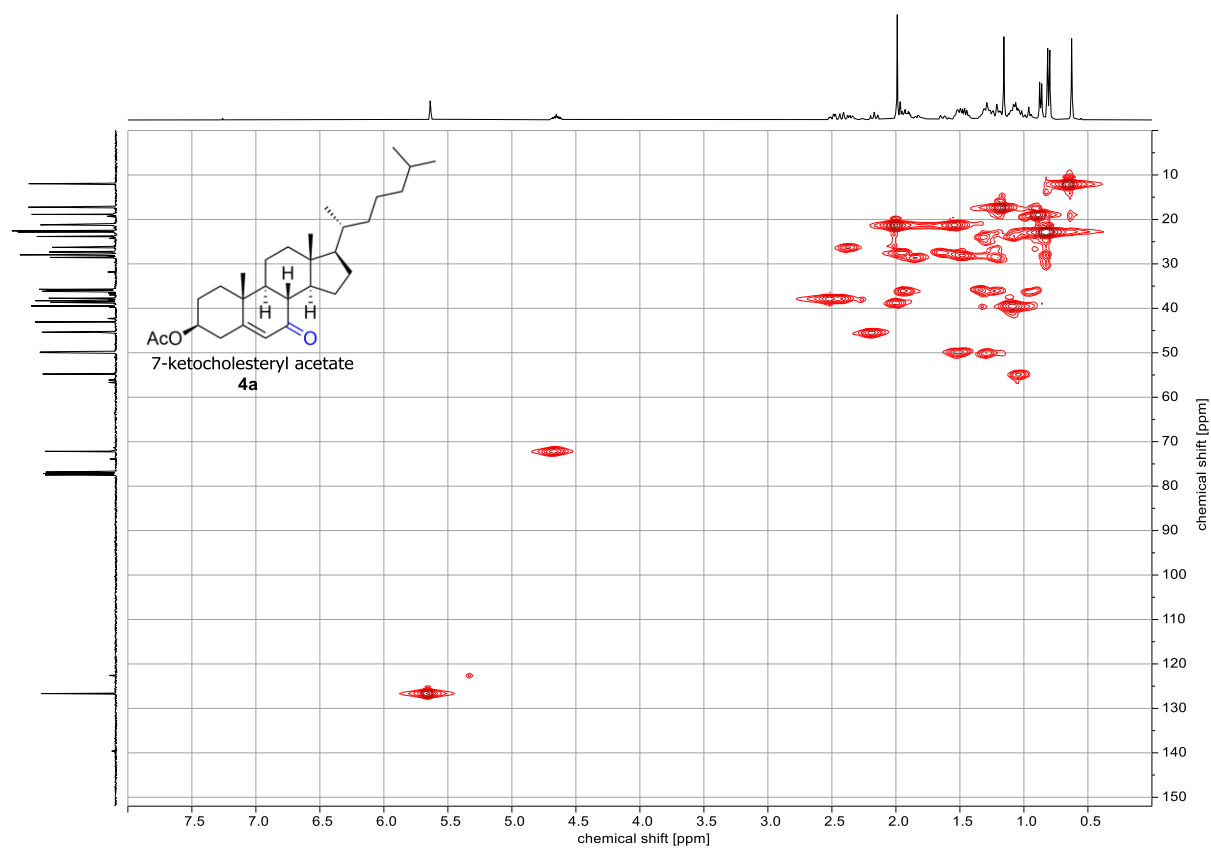


Figure S128. HSQC spectrum of the scale-up reaction.

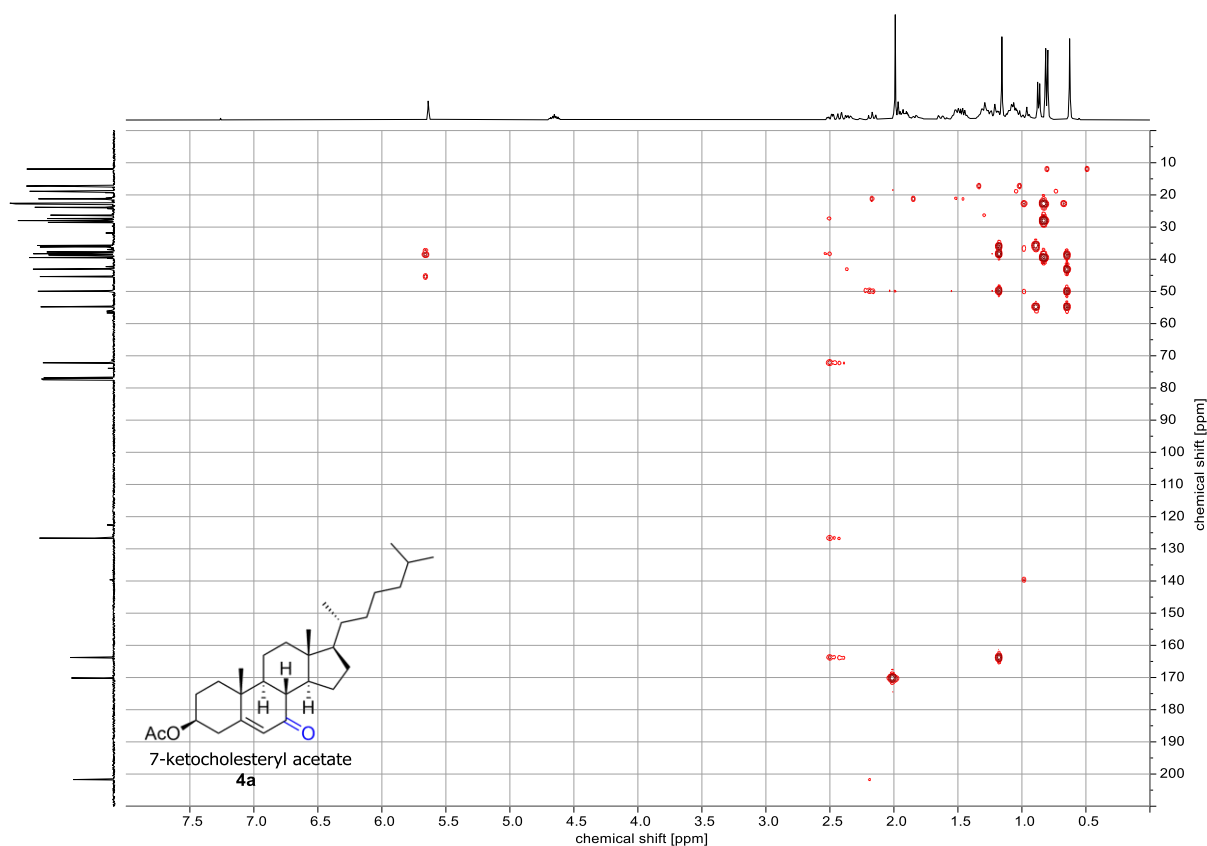
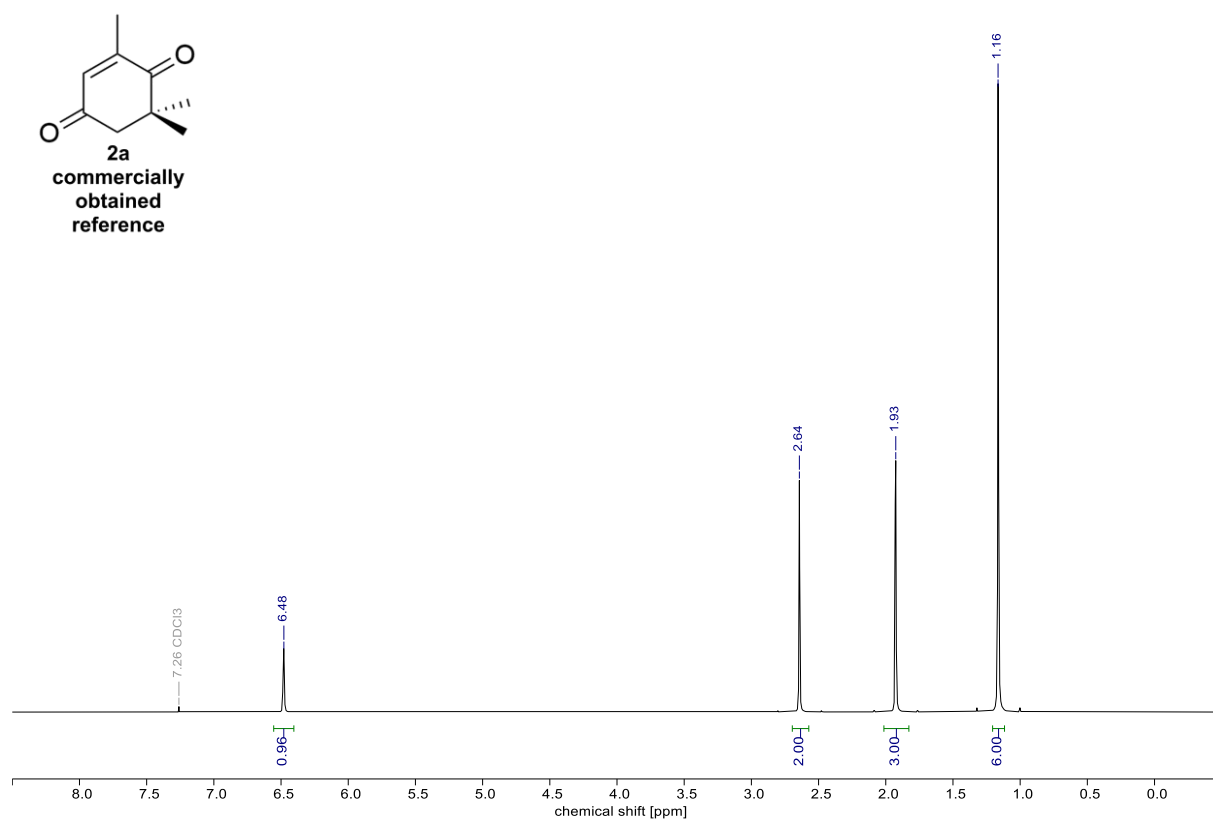


Figure S129. HMBC spectrum of the scale-up reaction.

9. NMR Spectra of Commercially Obtained 4-Oxoisophorone

Figure S130: ¹H NMR spectrum (400 MHz) of commercially obtained 4-oxoisophorone **2a**.

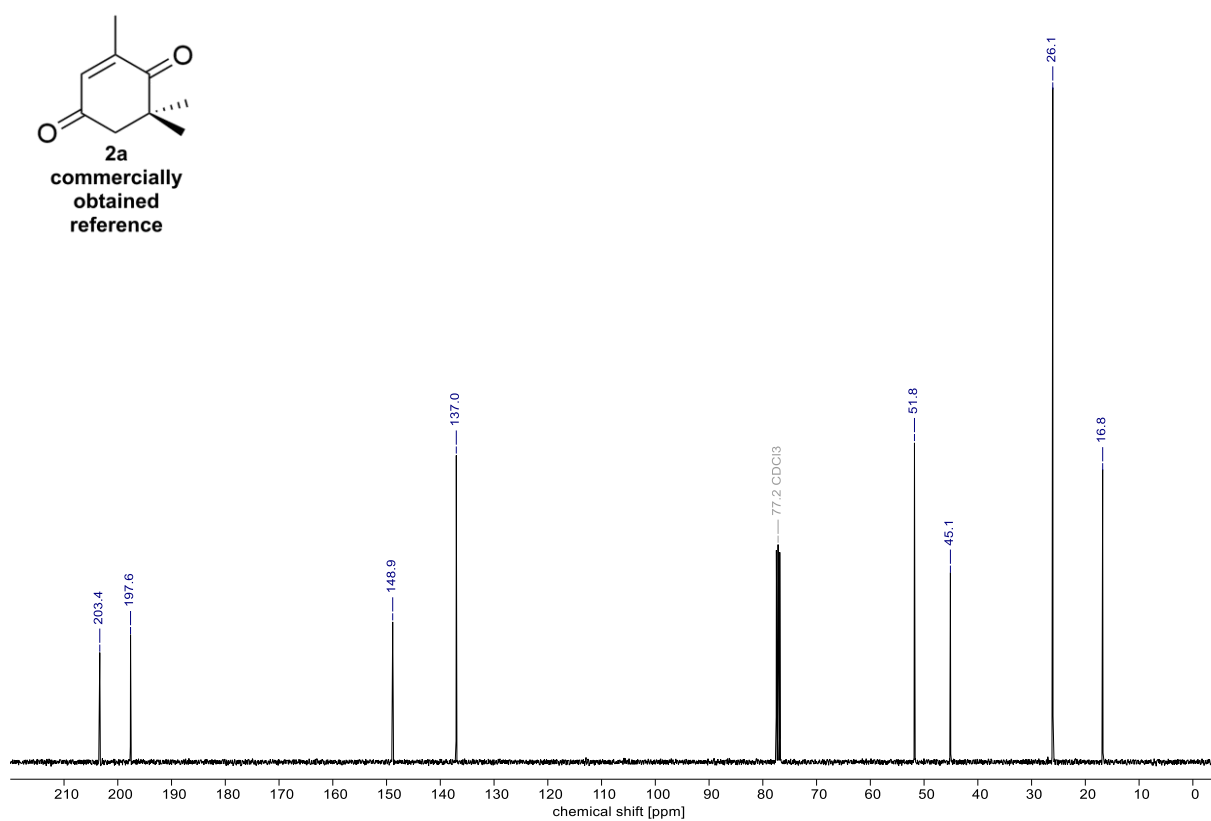


Figure S131: ^{13}C NMR spectrum (101 MHz) of commercially obtained 4-oxoisophorone **2a**.

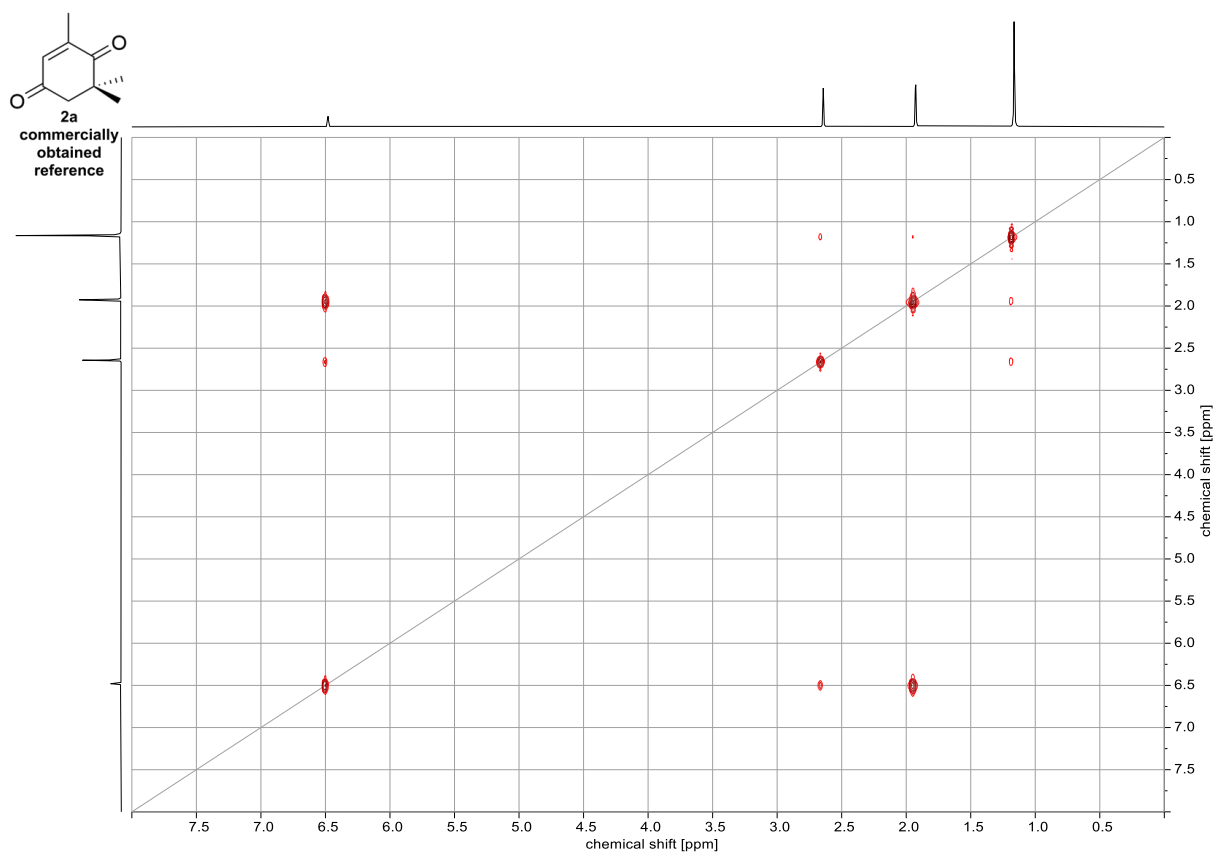


Figure S132: COSY spectrum of commercially obtained 4-oxoisophorone **2a**.

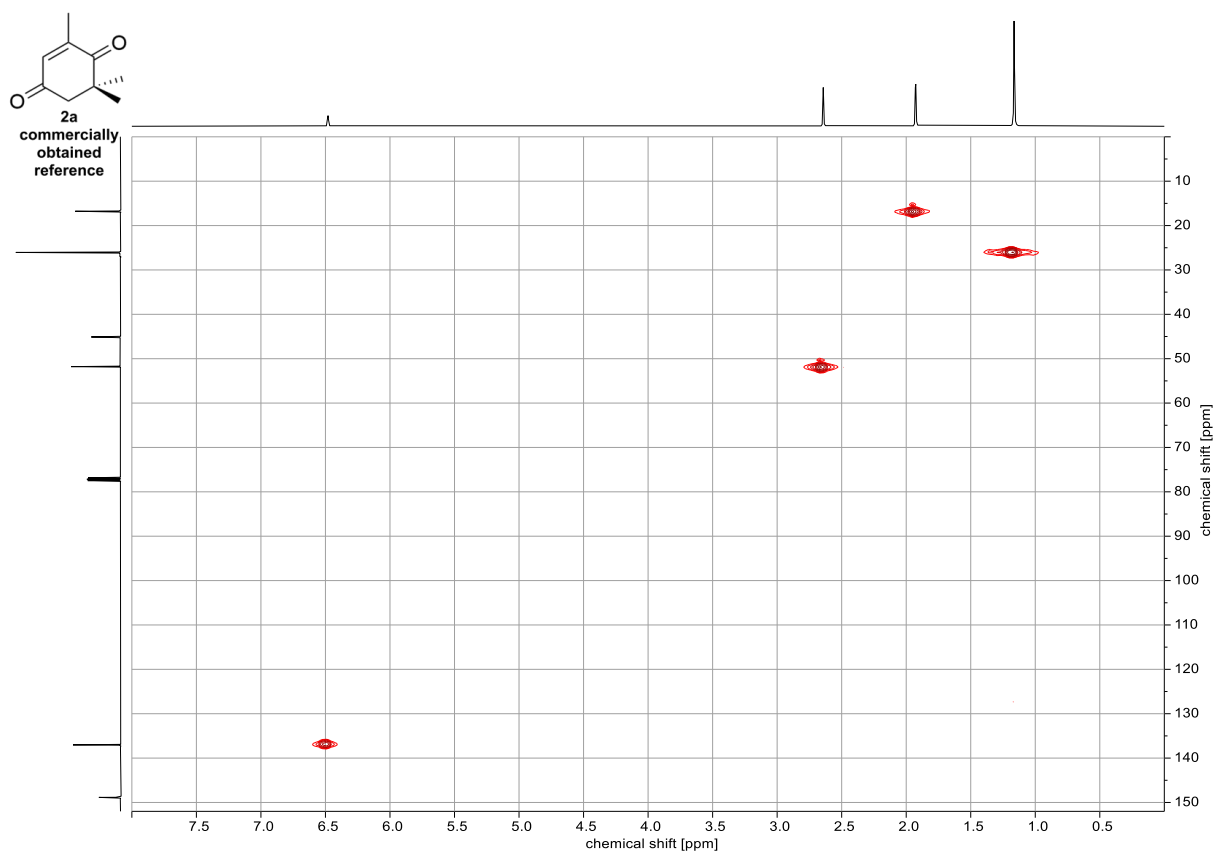


Figure S133: HSQC spectrum of commercially obtained 4-oxoisophorone 2a.

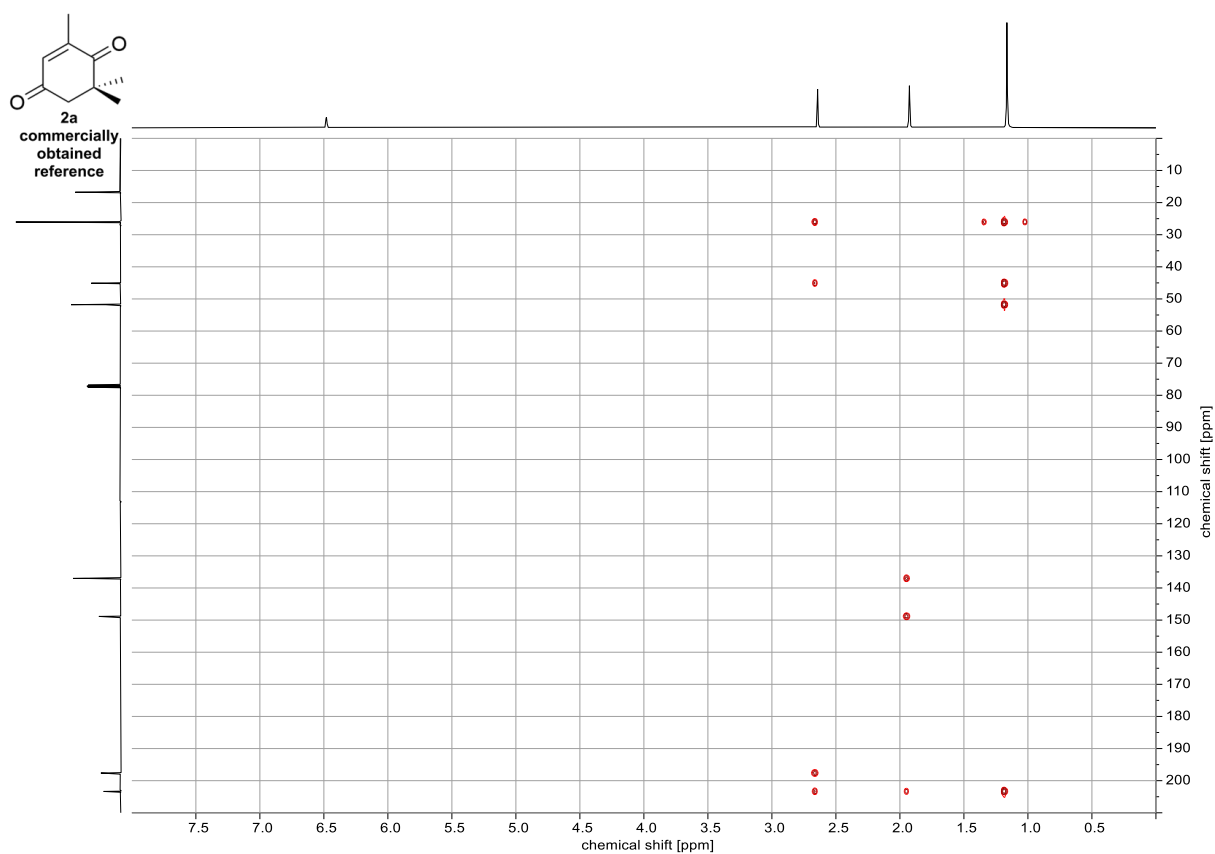


Figure S134: HMBC spectrum of commercially obtained 4-oxoisophorone 2a.

10. NMR Spectra of Starting Materials

10.1. β -Isophorone

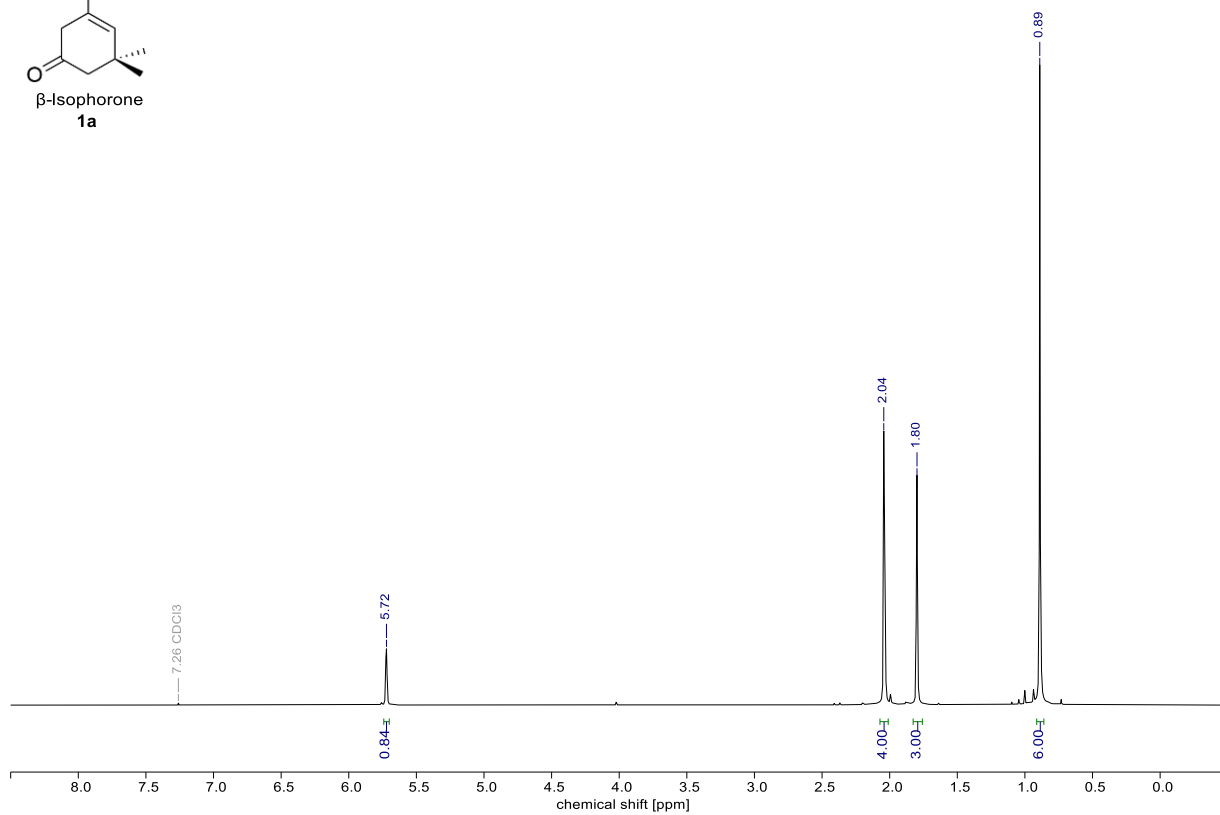
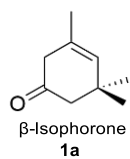


Figure S135. ¹H NMR spectrum (400 MHz) of starting material **1a**: β -isophorone.

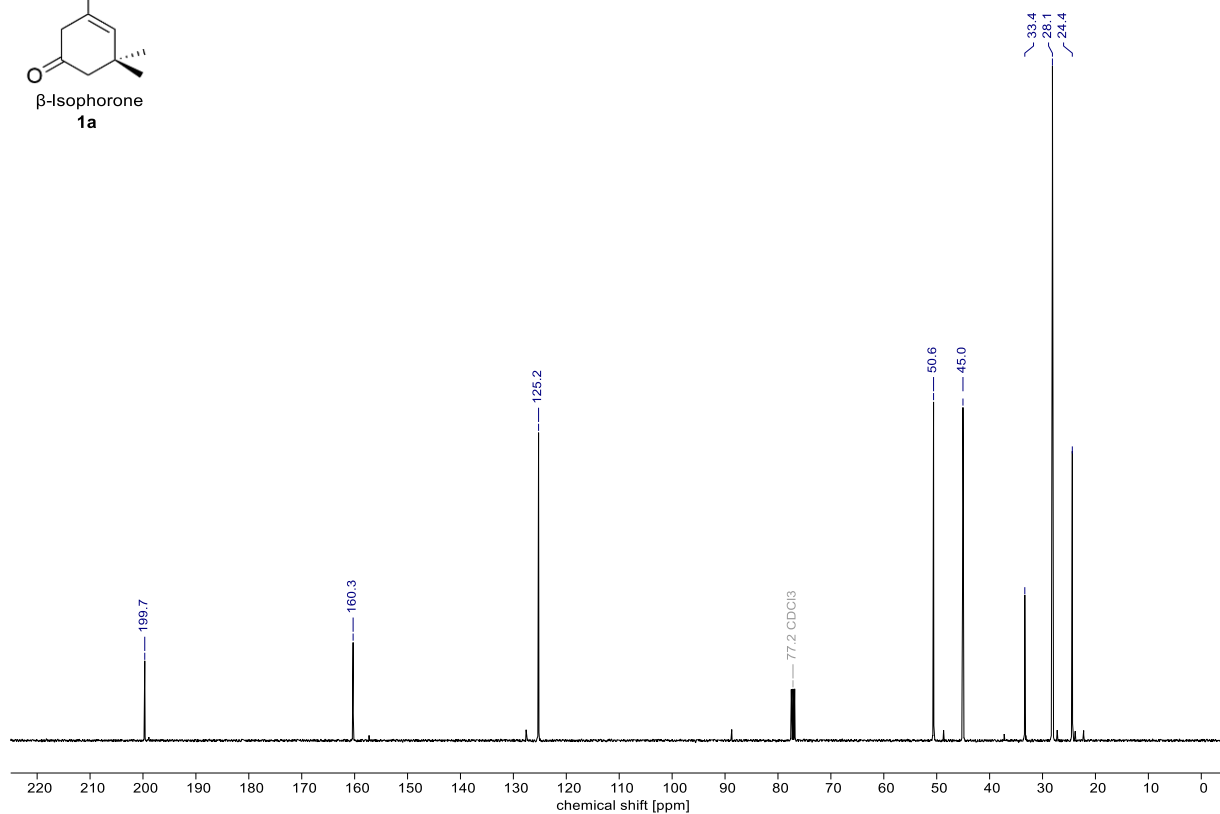
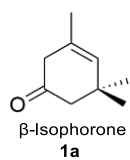


Figure S136. ¹³C NMR spectrum (101 MHz) of starting material **1a**: β -isophorone.

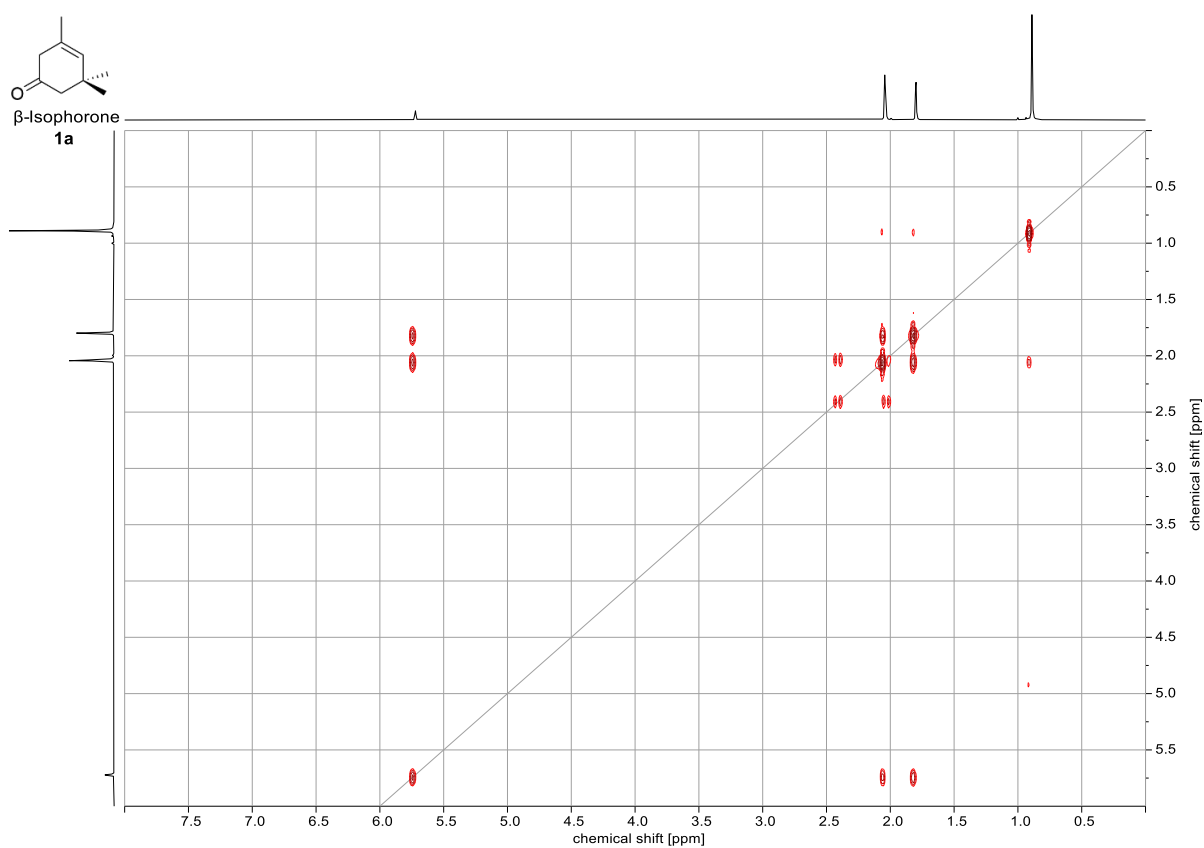


Figure S137. COSY spectrum of starting material 1a: β -isophorone.

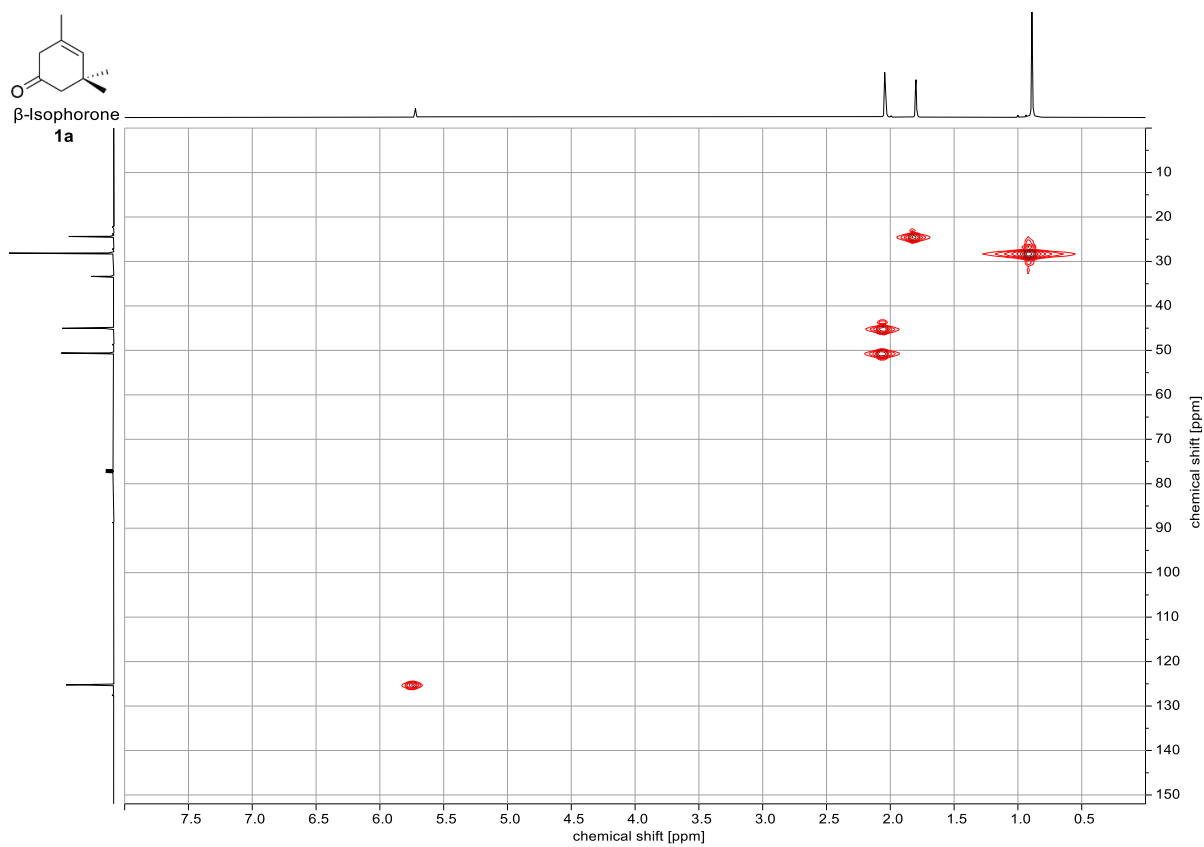


Figure S138. HSQC spectrum of starting material 1a: β -isophorone.

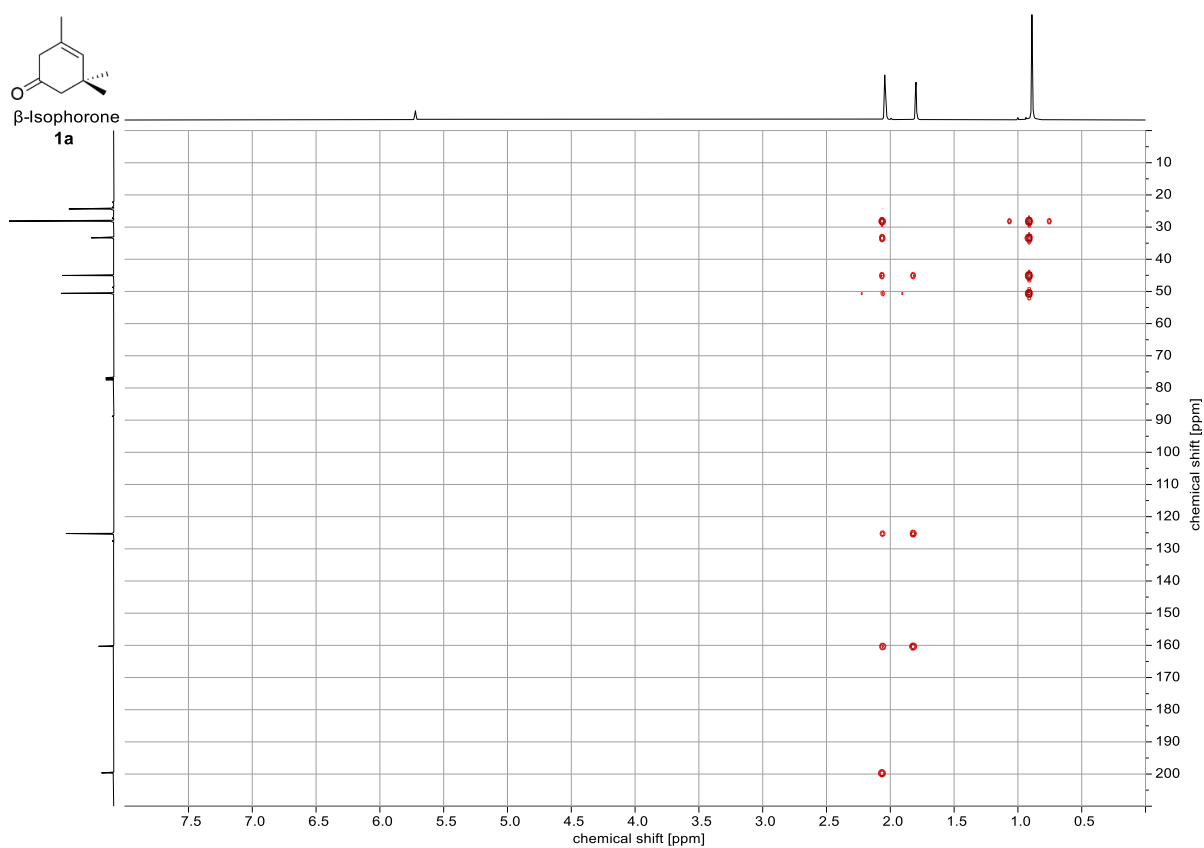


Figure S139. HMBC spectrum of starting material **1a**: β-isophorone.

10.2. α-Isophorone

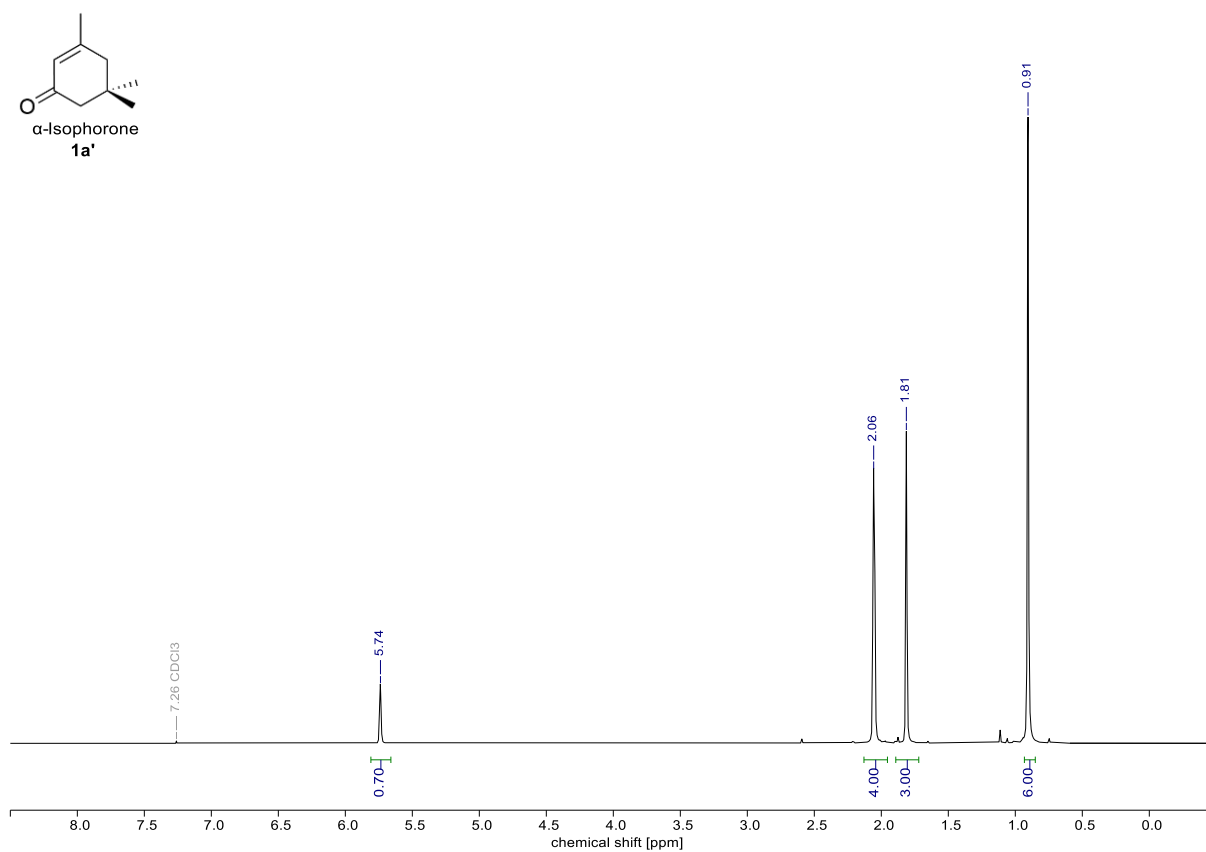


Figure S140. ¹H NMR spectrum (400 MHz) of starting material **1a'**: α-isophorone.

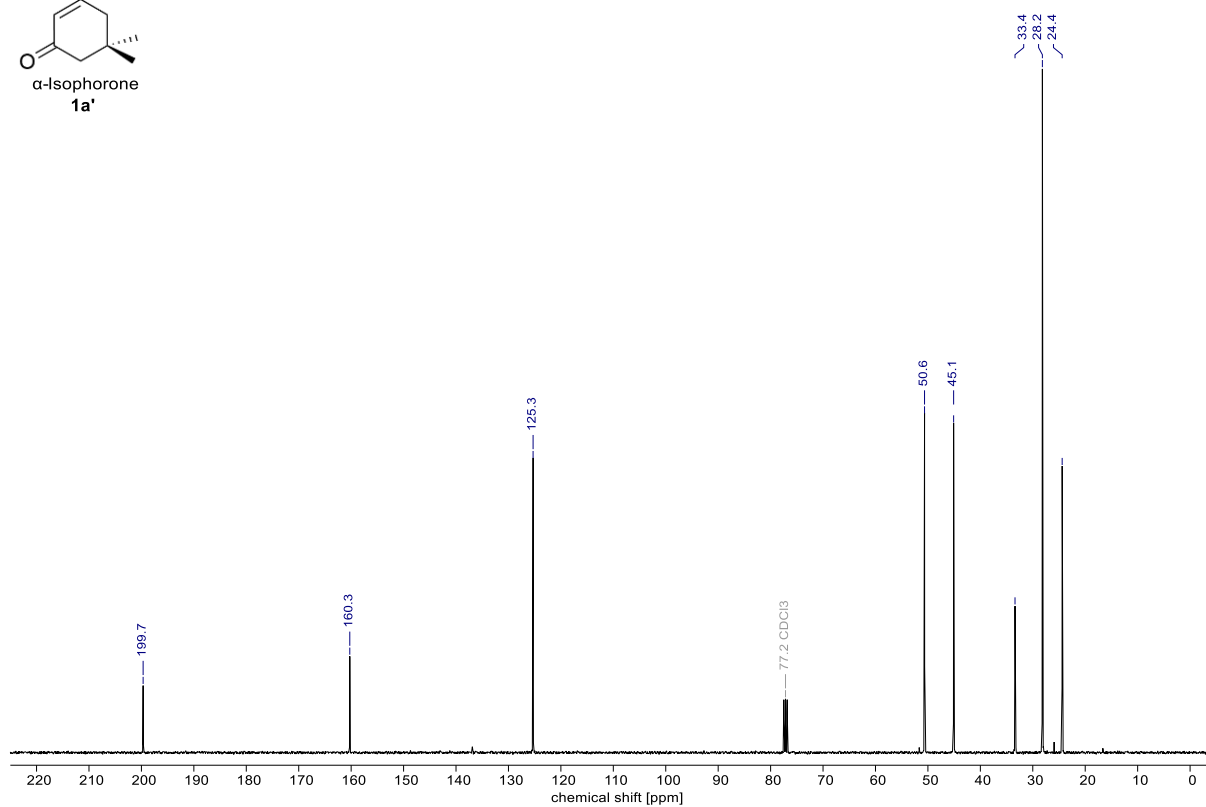
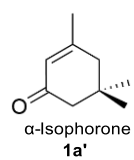


Figure S141. ¹³C NMR spectrum (101 MHz) of starting material 1a': α-isophorone.

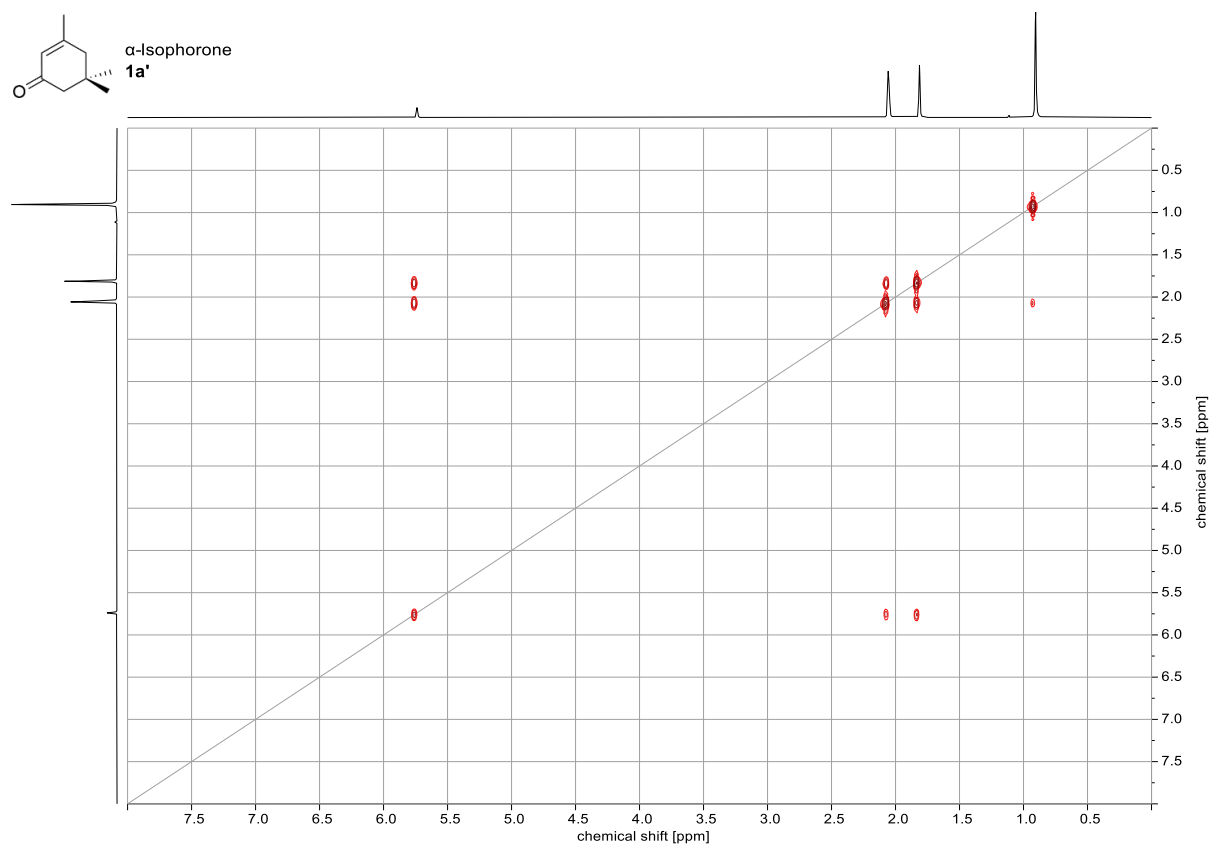


Figure S142. COSY spectrum of starting material 1a': α-isophorone.

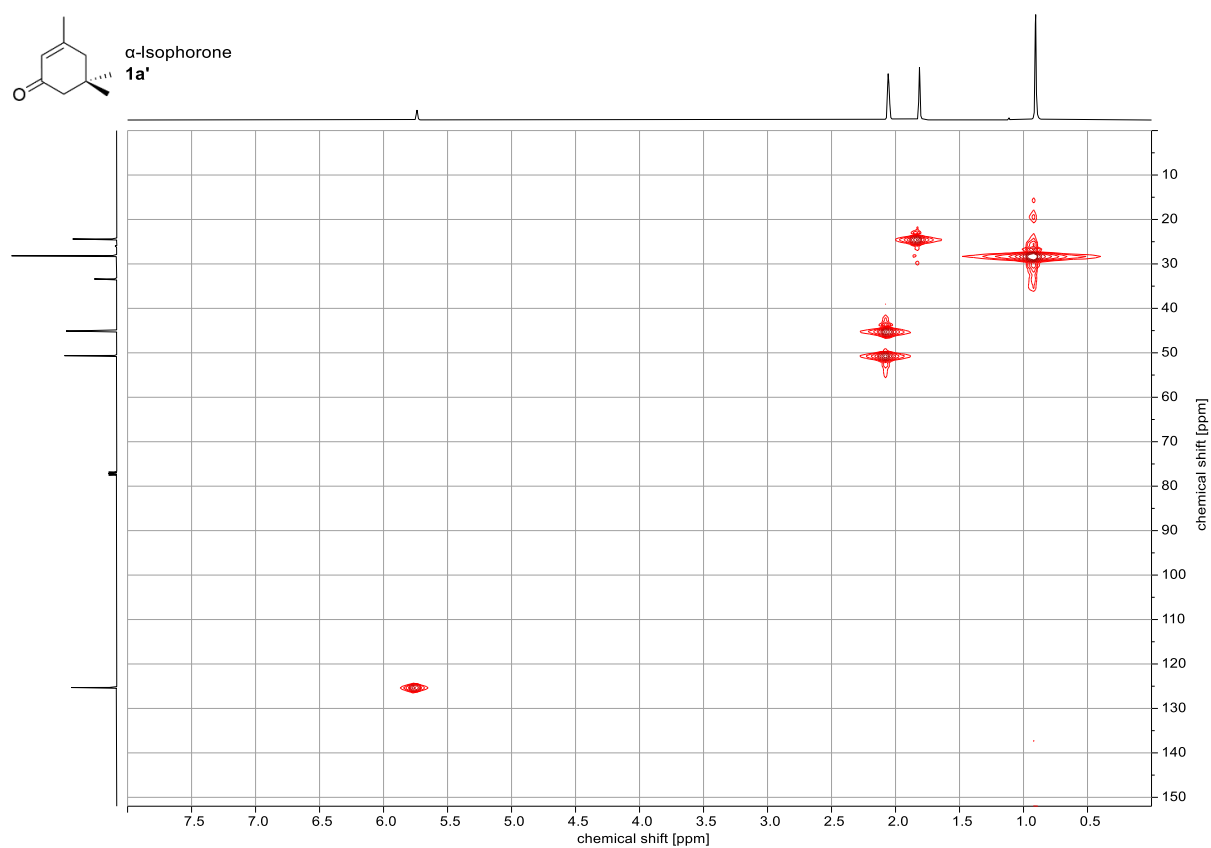


Figure S143. HSQC spectrum of starting material **1a'**: α -isophorone.

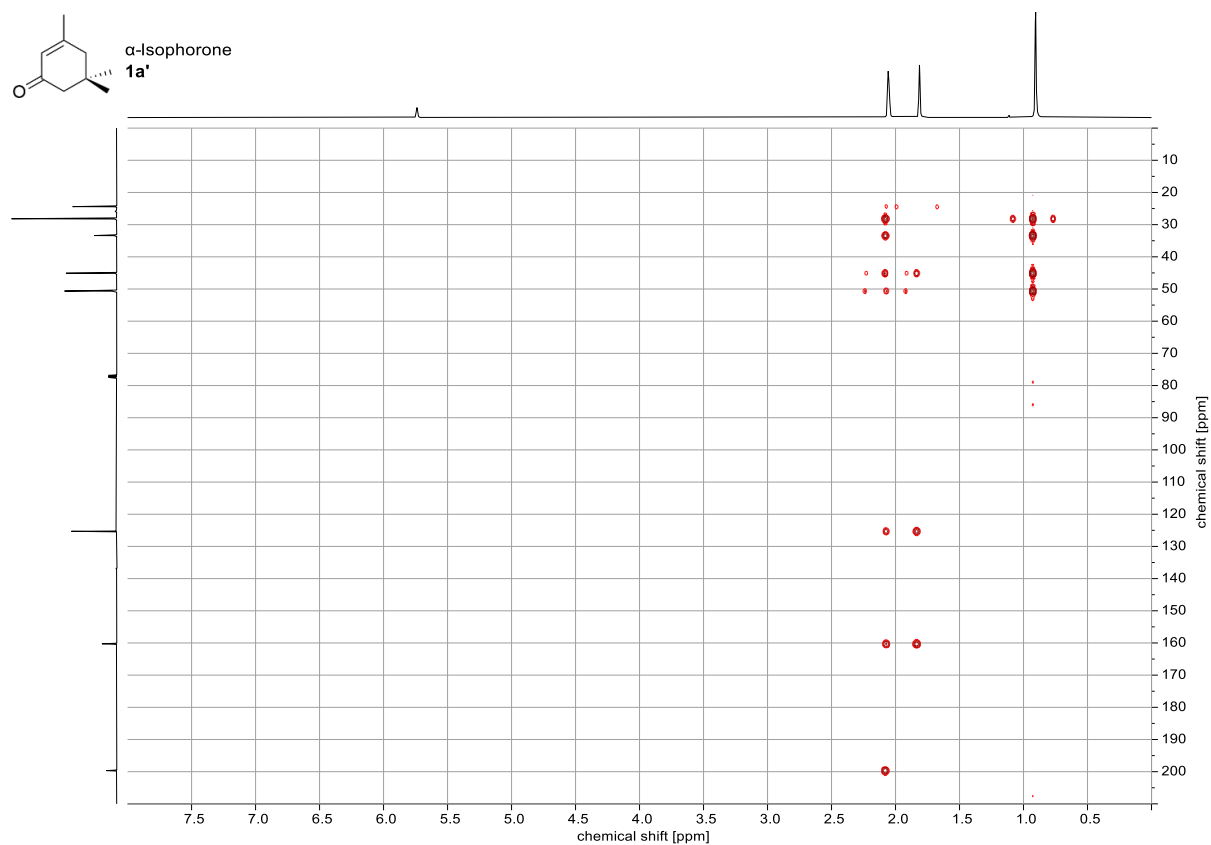
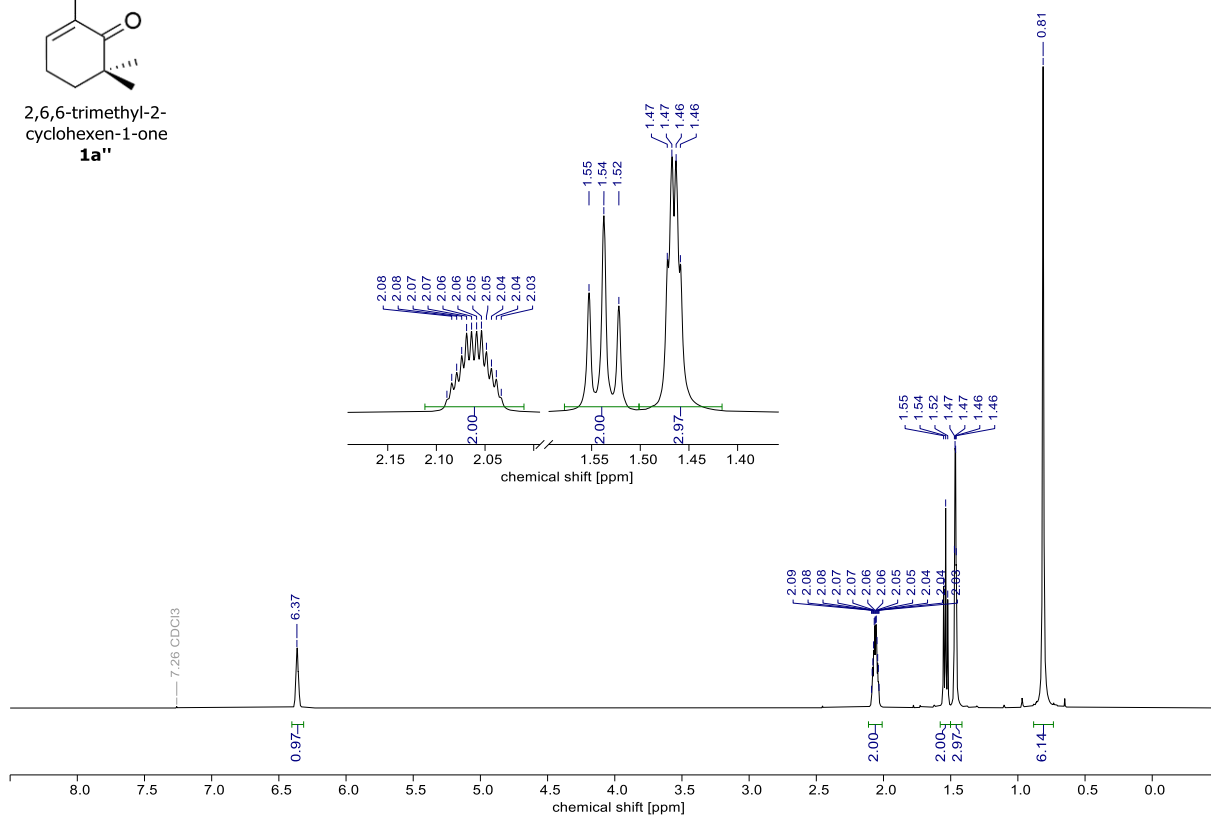
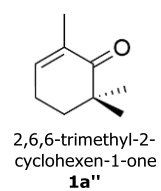
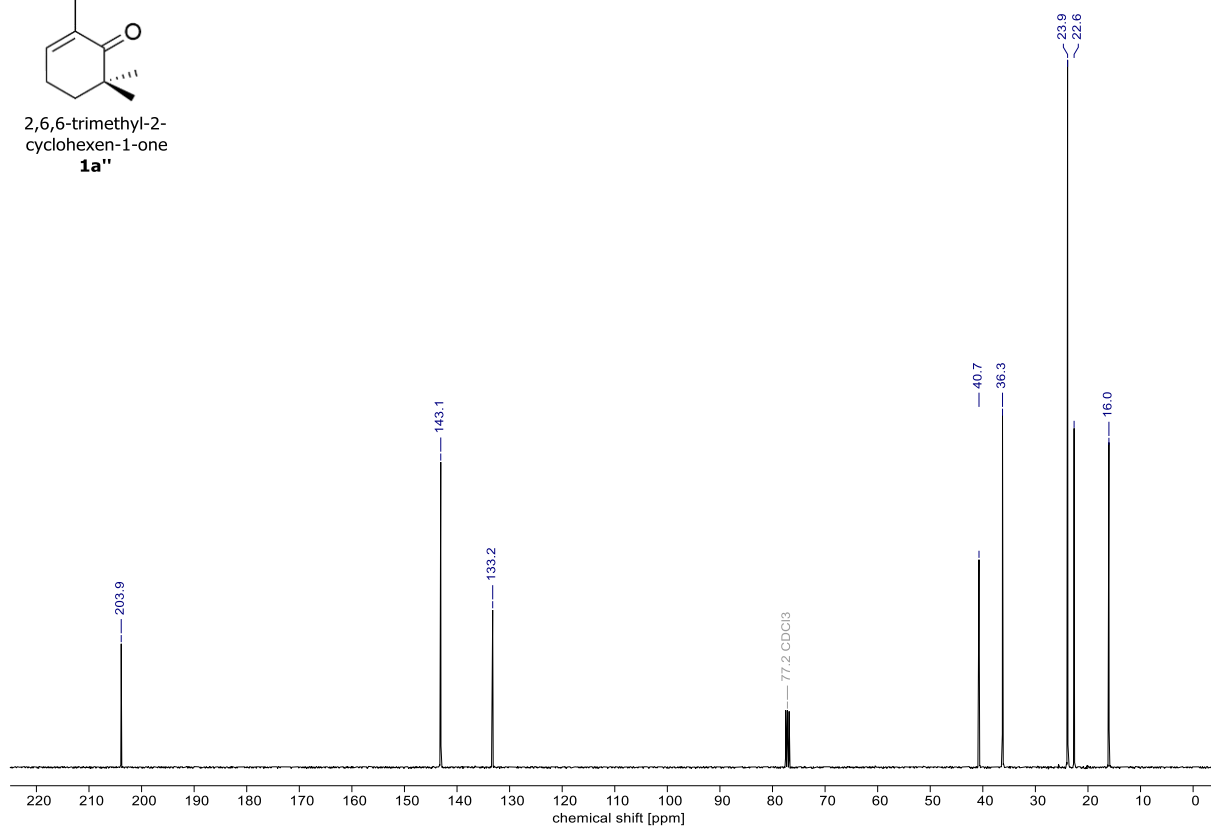
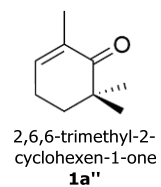


Figure S144. HMBC spectrum of starting material **1a'**: α -isophorone.

10.3. 2,6,6-Trimethyl-2-cyclohex-1-one

Figure S145. ¹H NMR spectrum (400 MHz) of starting material **1a''**: 2,6,6-trimethyl-2-cyclohex-1-one.Figure S146. ¹³C NMR spectrum (101 MHz) of starting material **1a''**: 2,6,6-trimethyl-2-cyclohex-1-one.

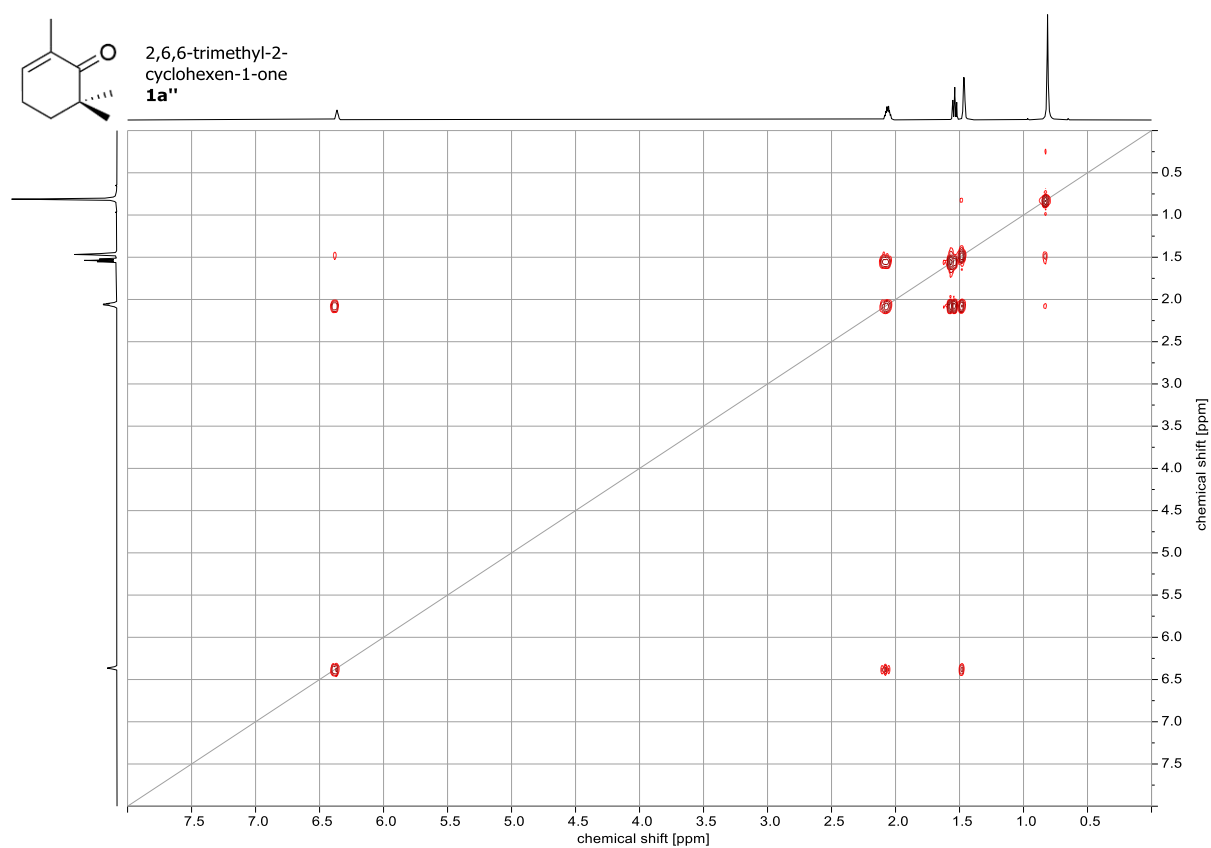


Figure S147. COSY spectrum of starting material **1a''**: 2,6,6-trimethyl-2-cyclohex-1-one.

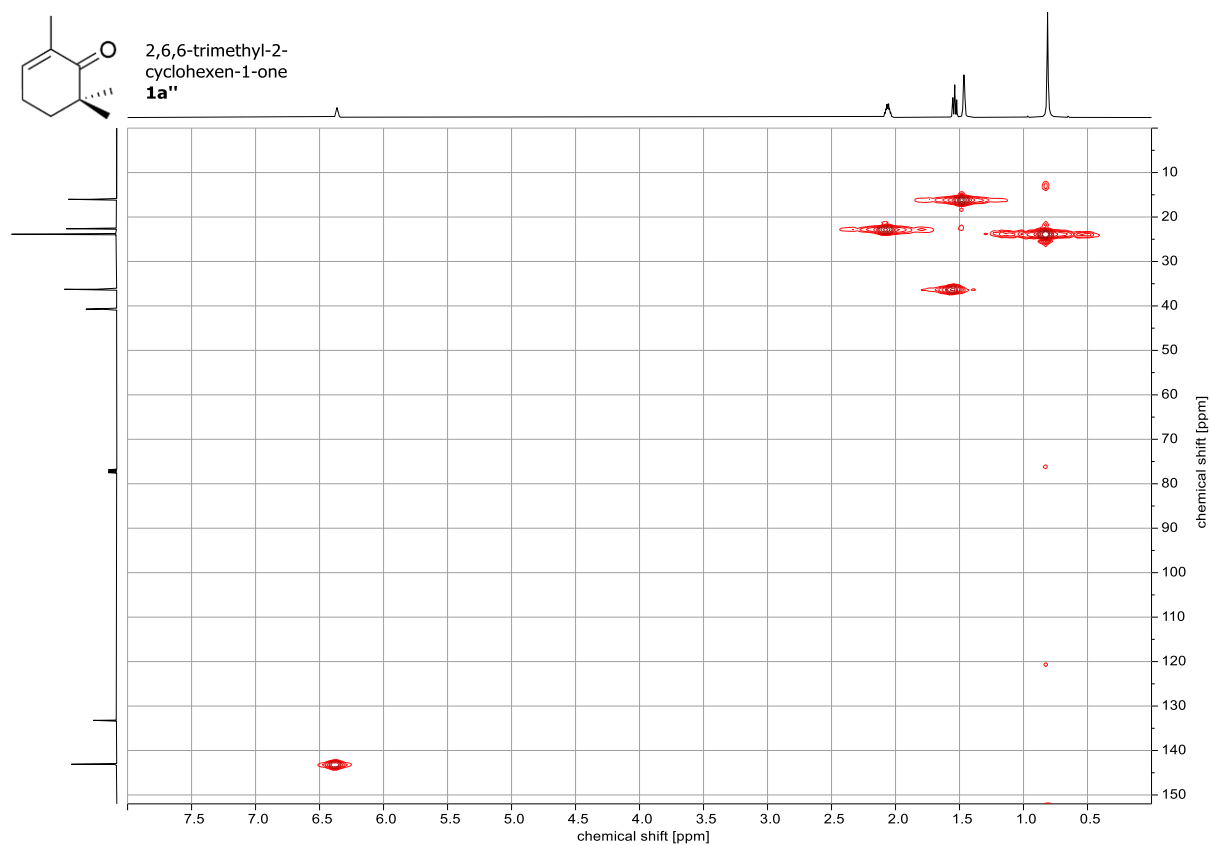


Figure S148. HSQC spectrum of starting material **1a''**: 2,6,6-trimethyl-2-cyclohex-1-one.

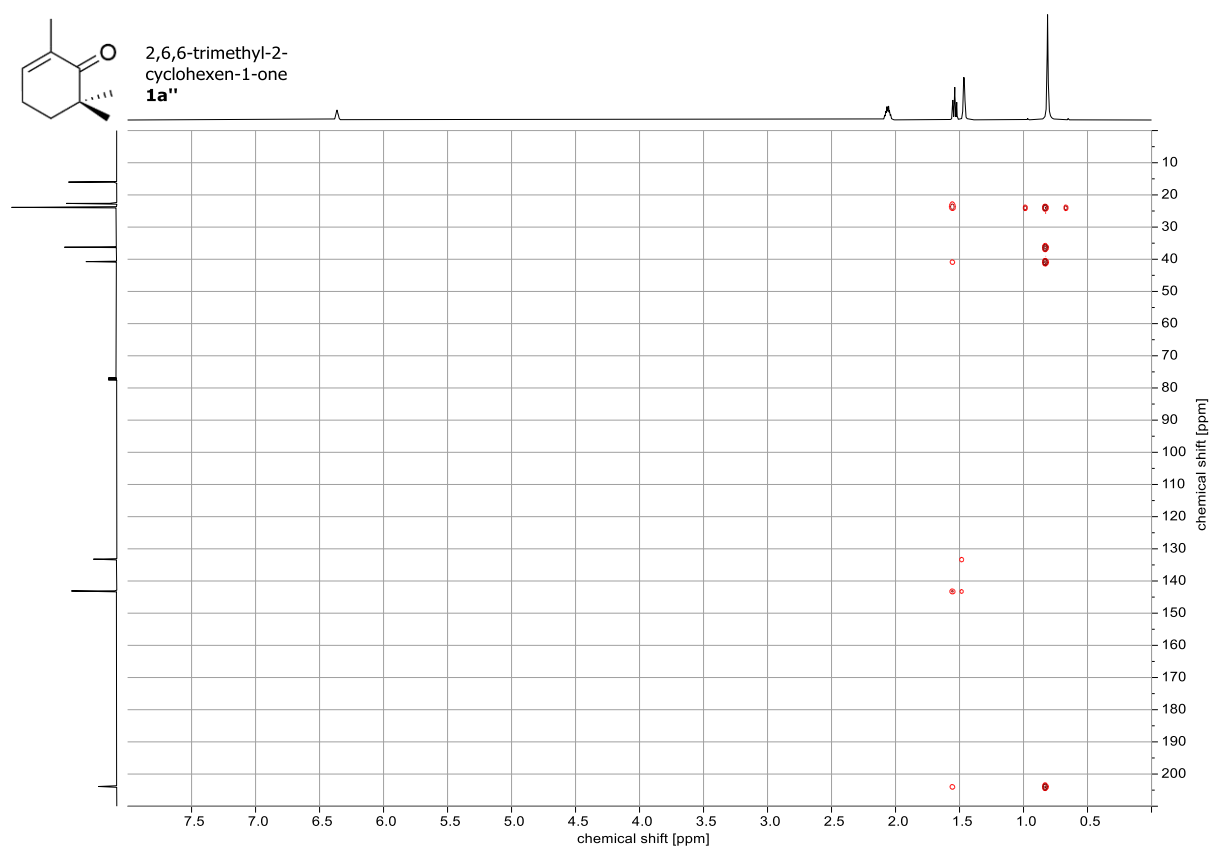


Figure S149. HMBC spectrum of starting material **1a''**: 2,6,6-trimethyl-2-cyclohex-1-one.

10.4. (+)- α -Pinene

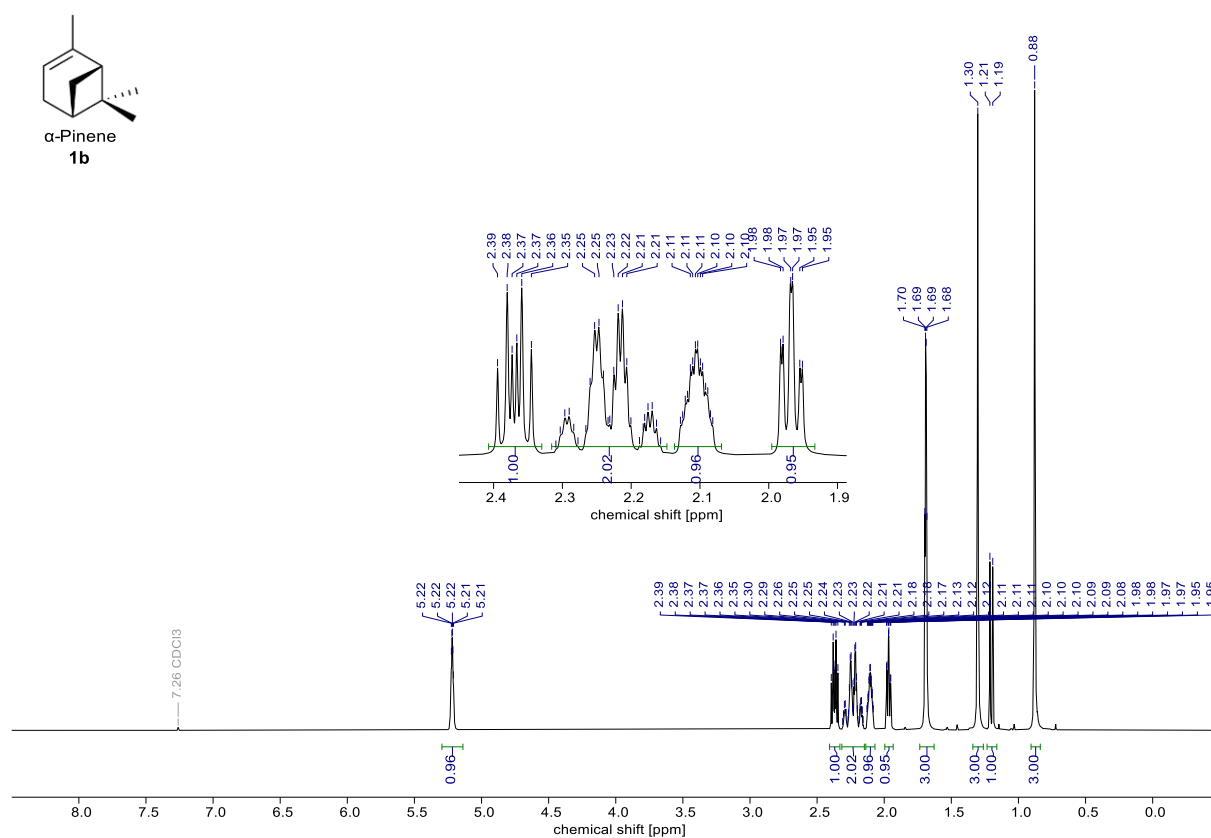


Figure S150. ¹H NMR spectrum (400 MHz) of starting material **1b**: (+)- α -pinene.

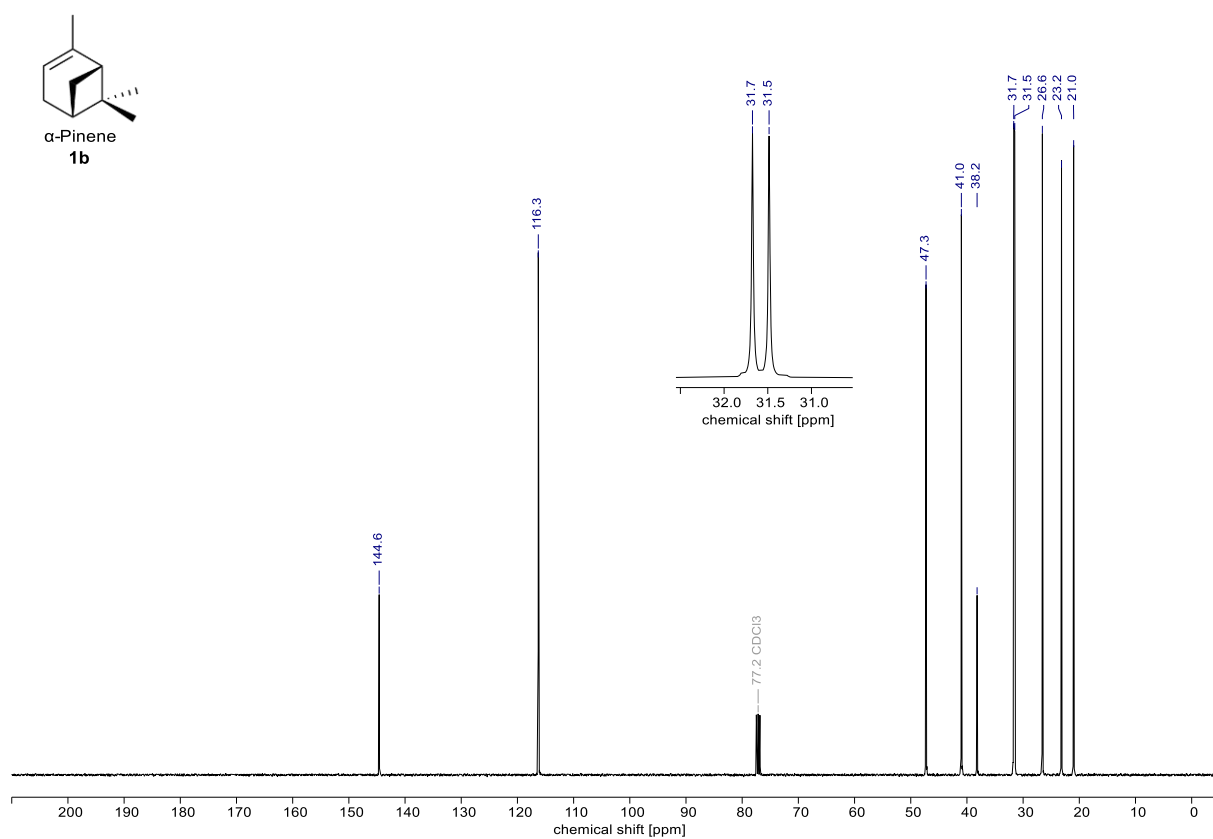


Figure S151. ^{13}C NMR spectrum (101 MHz) of starting material **1b**: (+)- α -pinene.

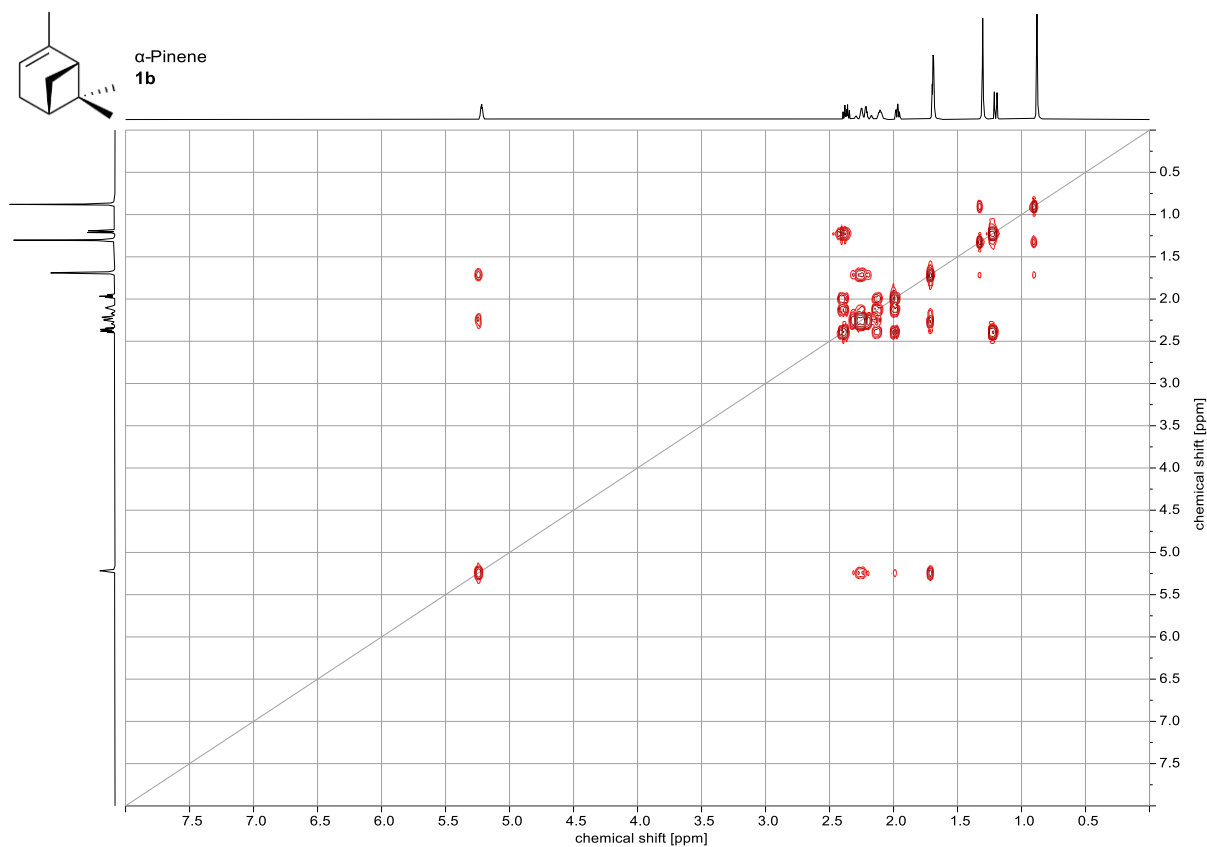


Figure S152. COSY spectrum of starting material **1b**: (+)- α -pinene.

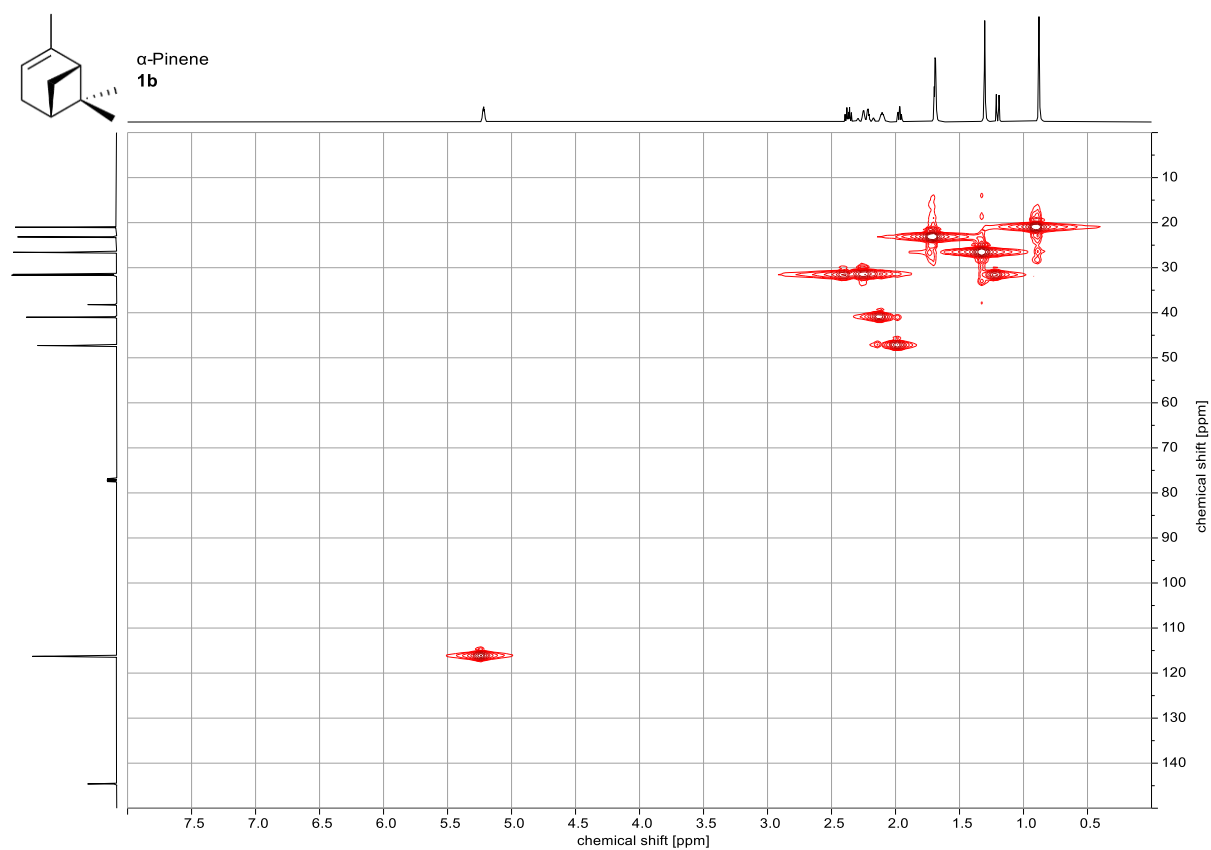


Figure S153. HSQC spectrum of starting material **1b**: (+)- α -pinene.

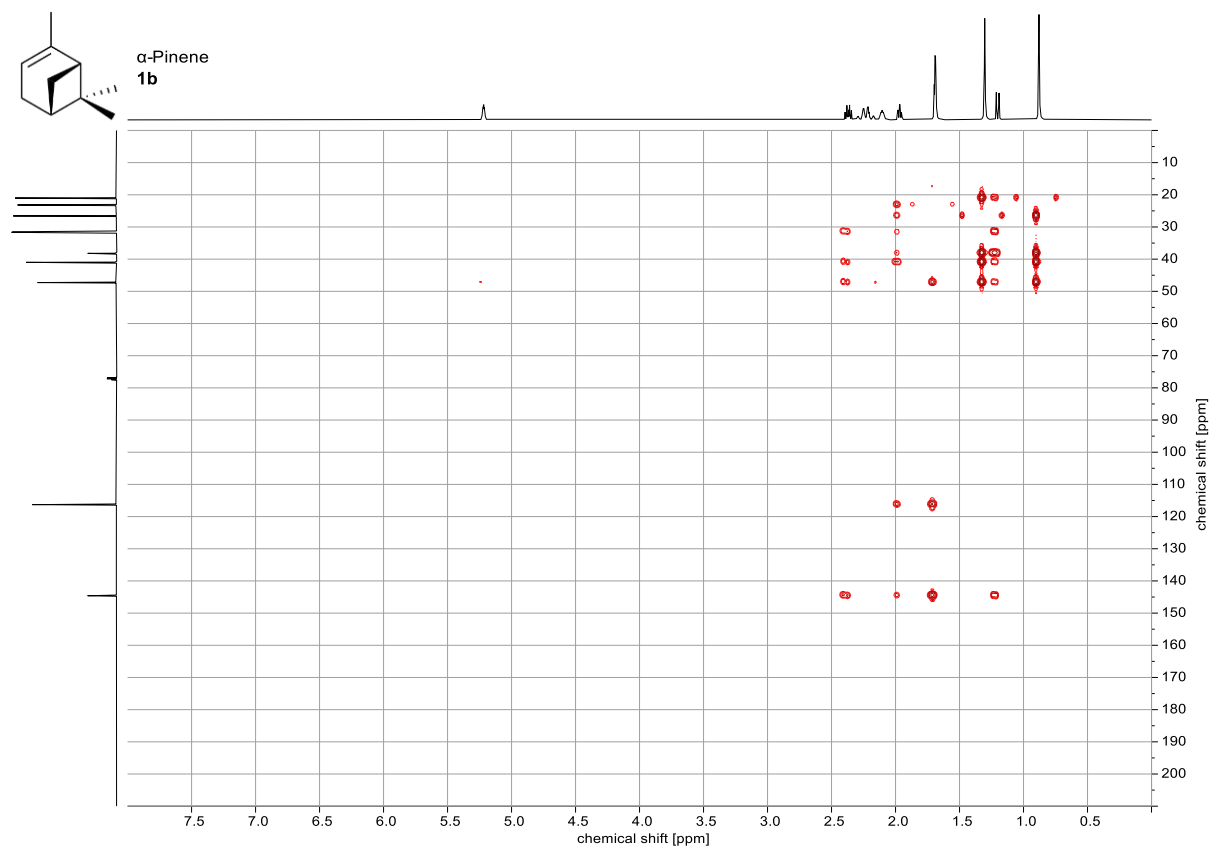
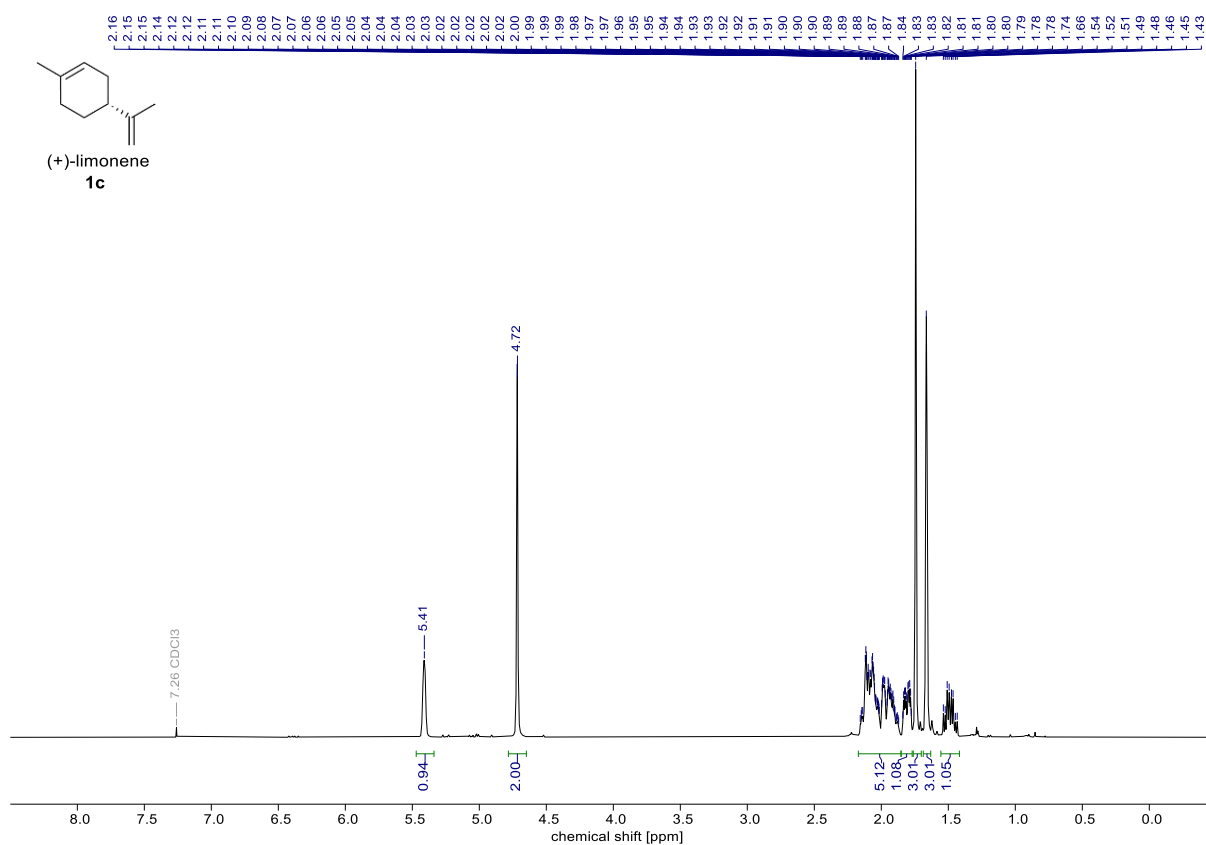
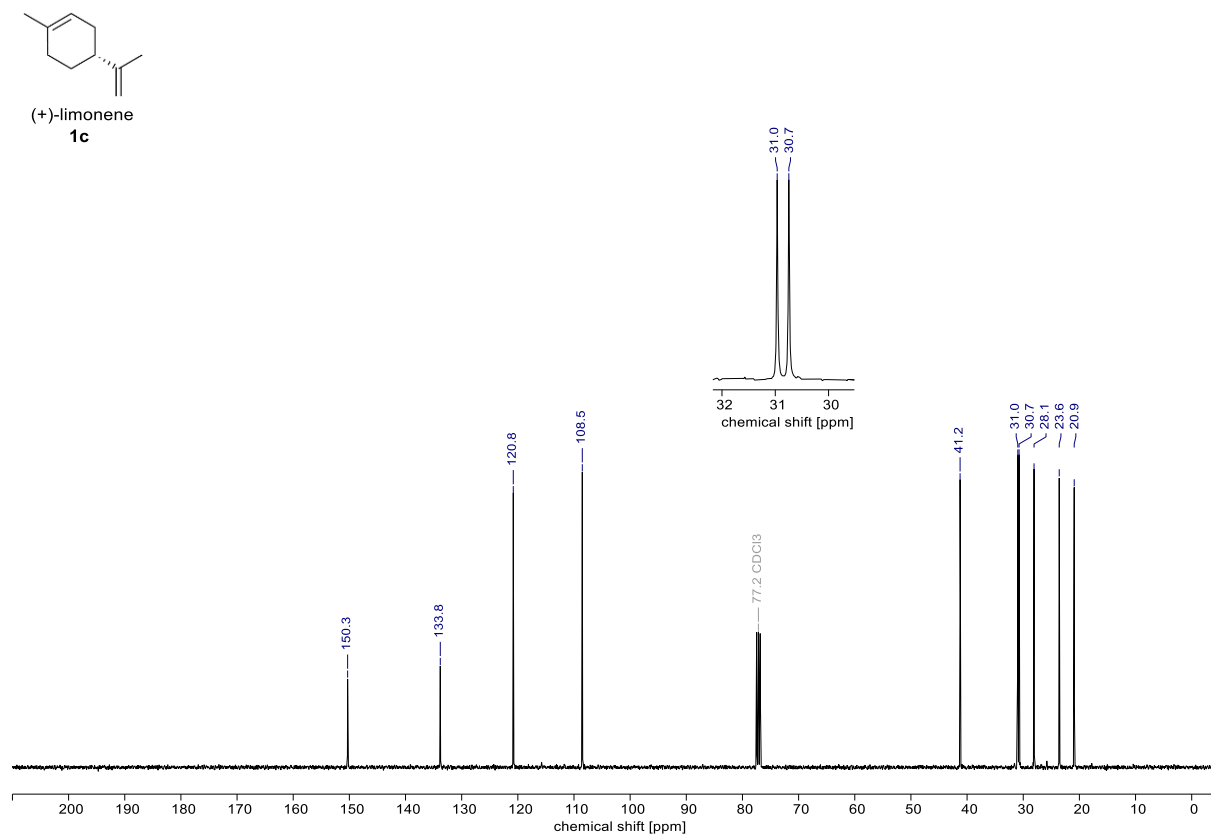


Figure S154. HMBC spectrum of starting material **1b**: (+)- α -pinene.

10.5. (+)-Limonene

Figure S155. ¹H NMR spectrum (400 MHz) of starting material **1c**: (+)-limonene.Figure S156. ¹³C NMR spectrum (101 MHz) of starting material **1c**: (+)-limonene.

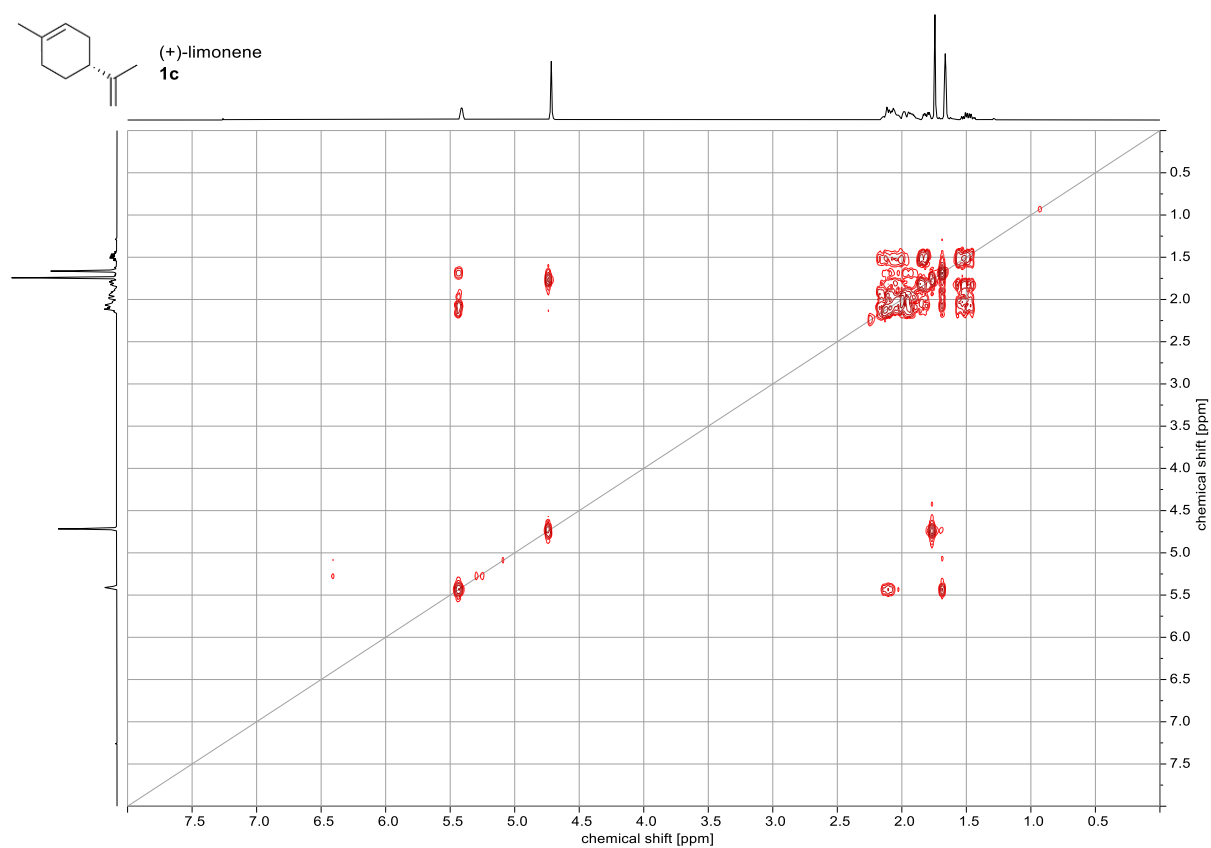


Figure S157. COSY spectrum of starting material 1c: (+)-limonene.

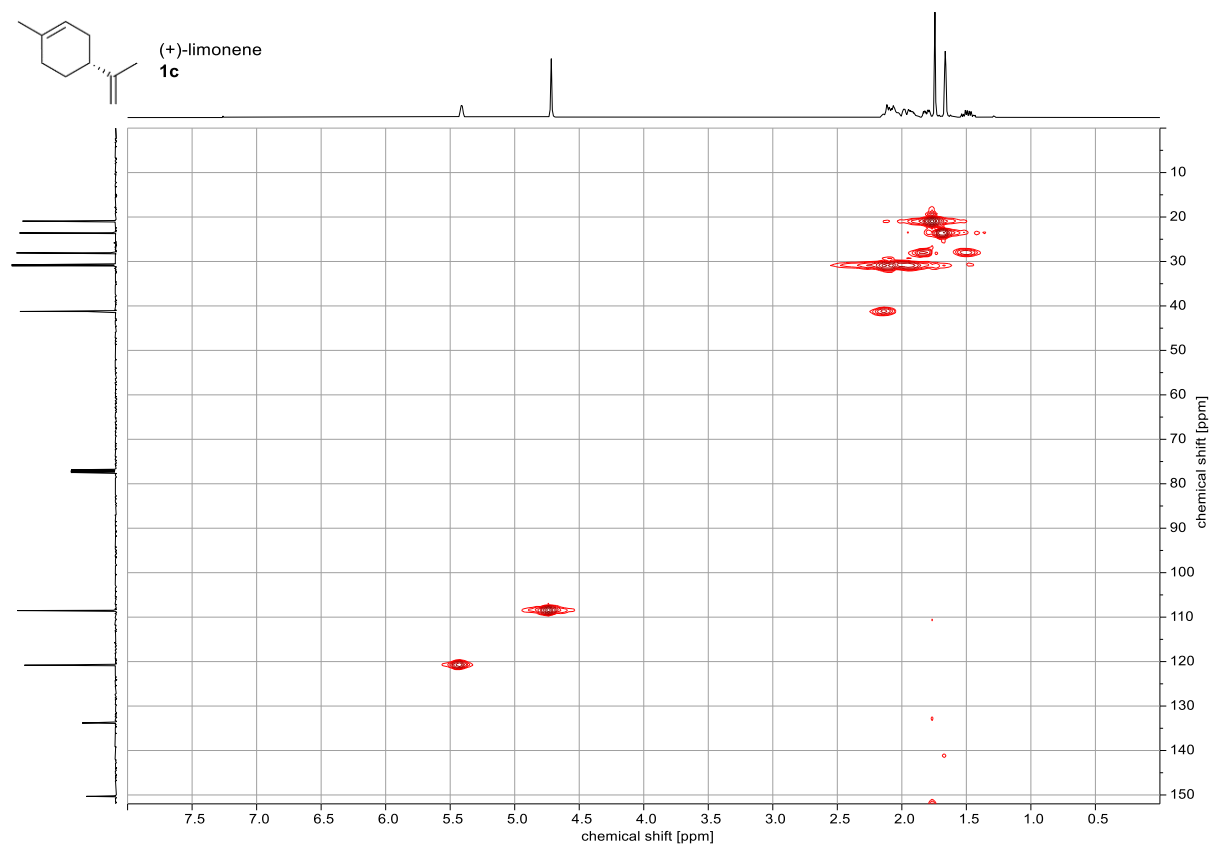
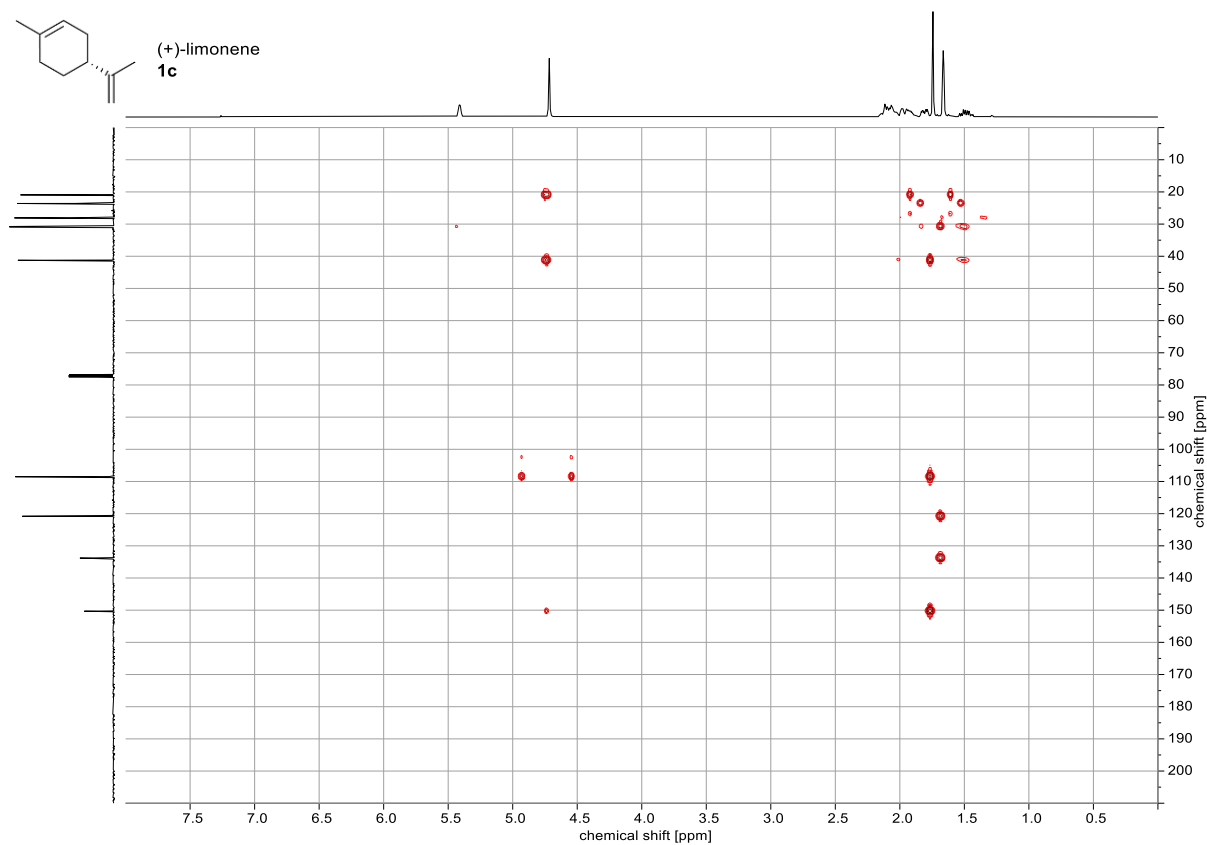
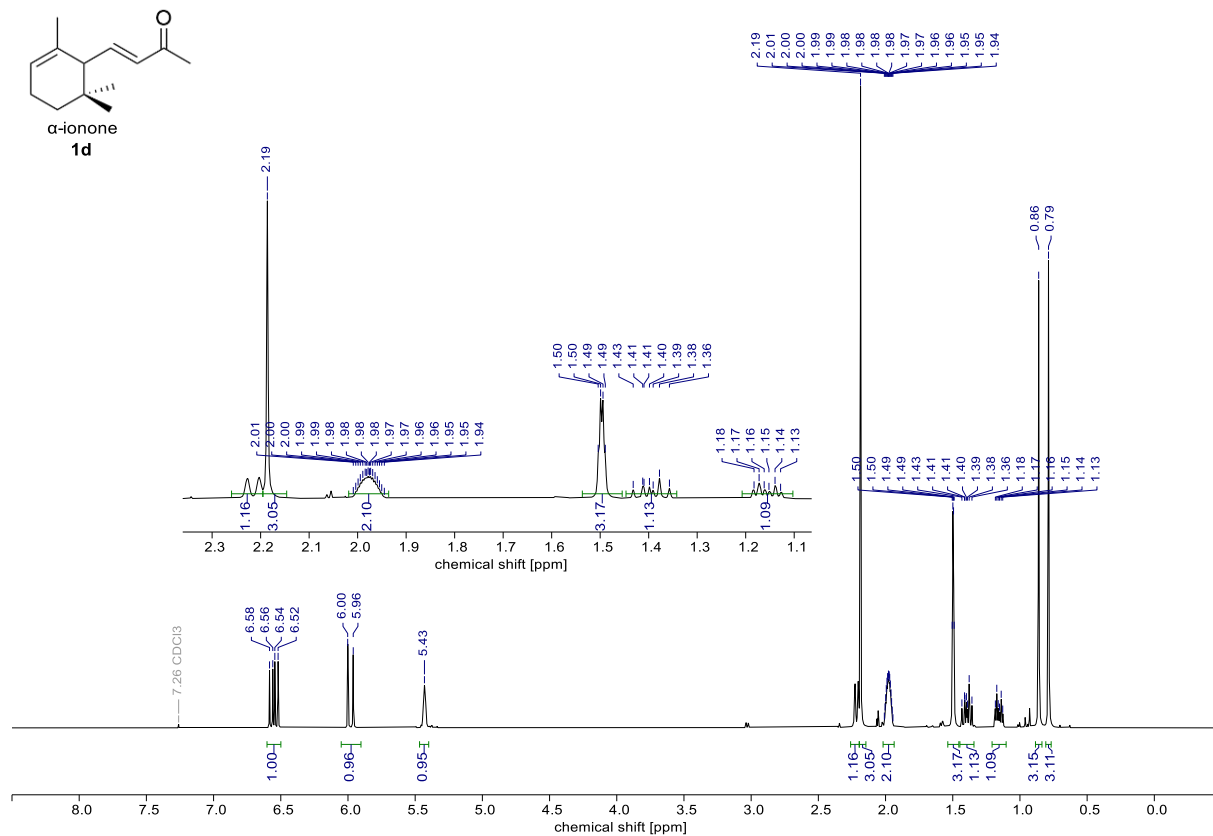


Figure S158. HSQC spectrum of starting material 1c: (+)-limonene.



10.6. α -Ionone



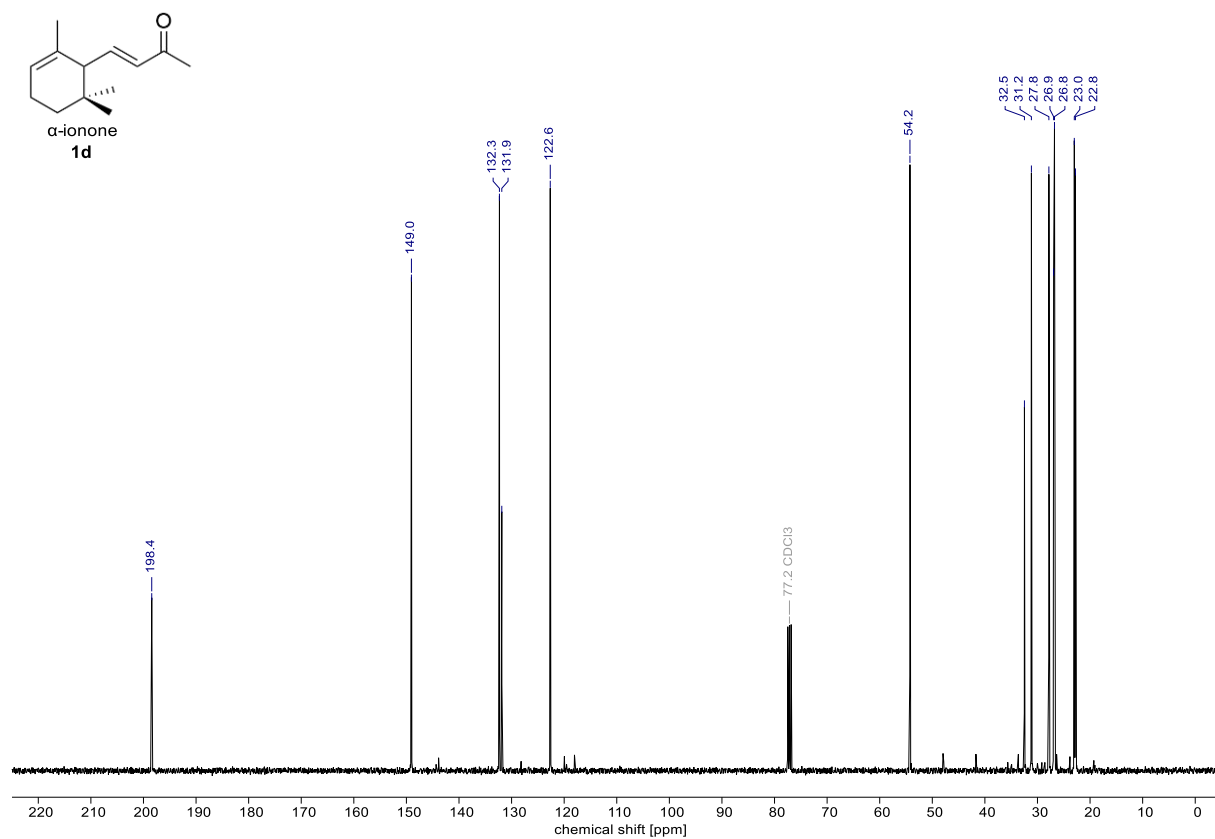


Figure S161. ^{13}C NMR spectrum (101 MHz) of starting material **1d**: α -ionone.

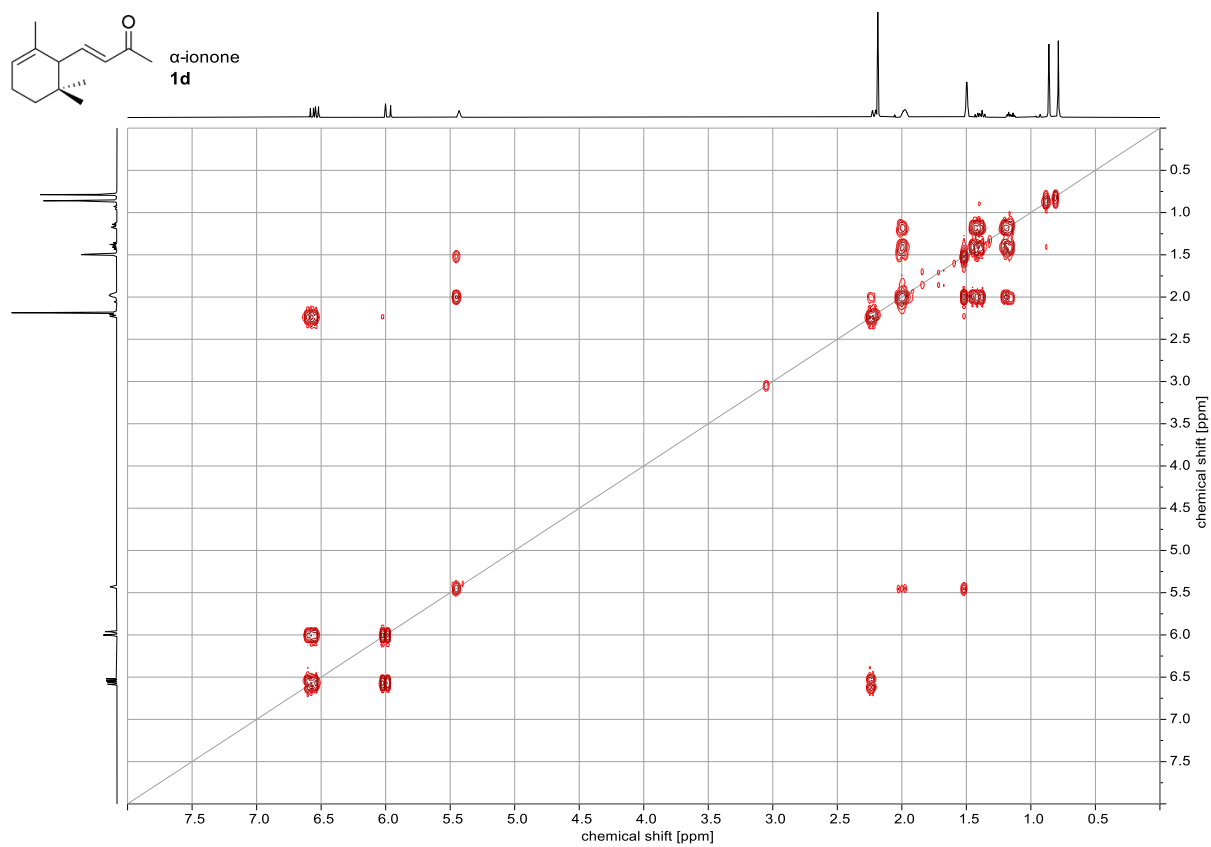
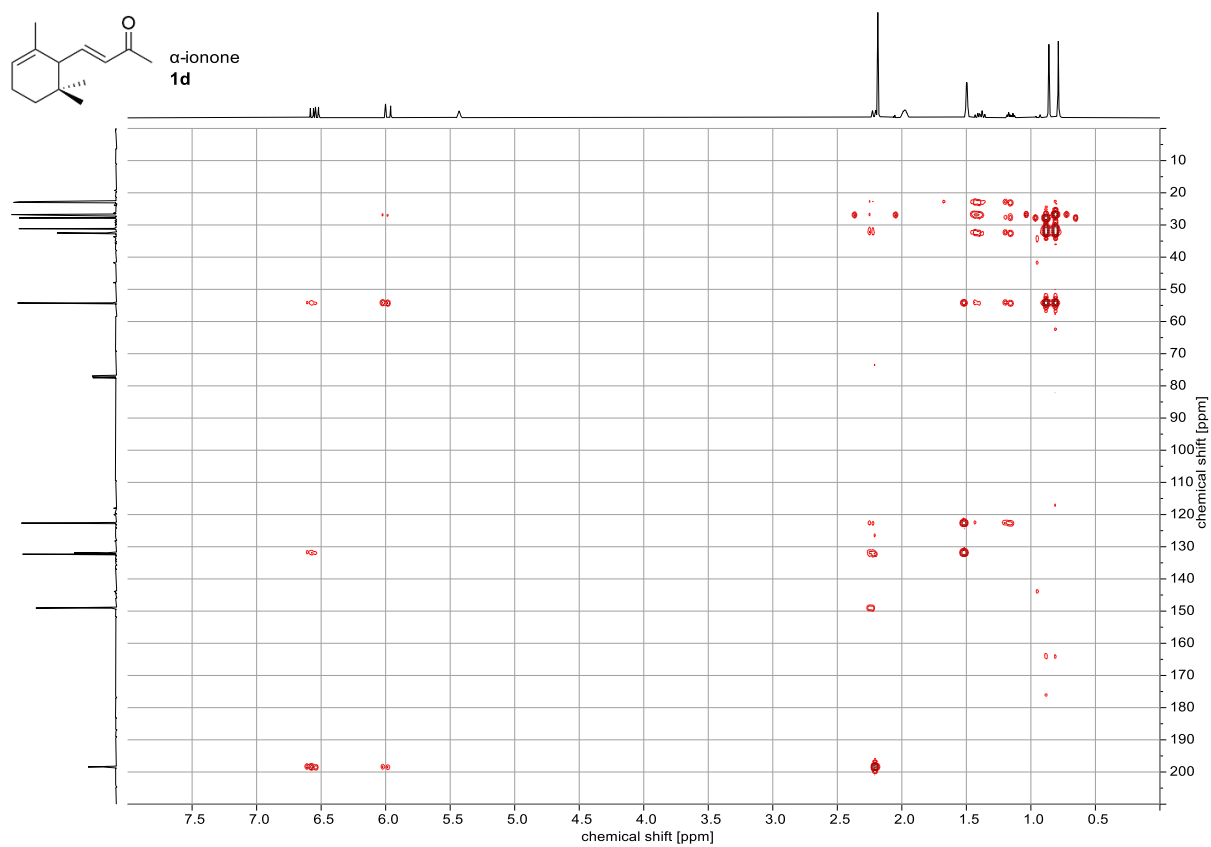
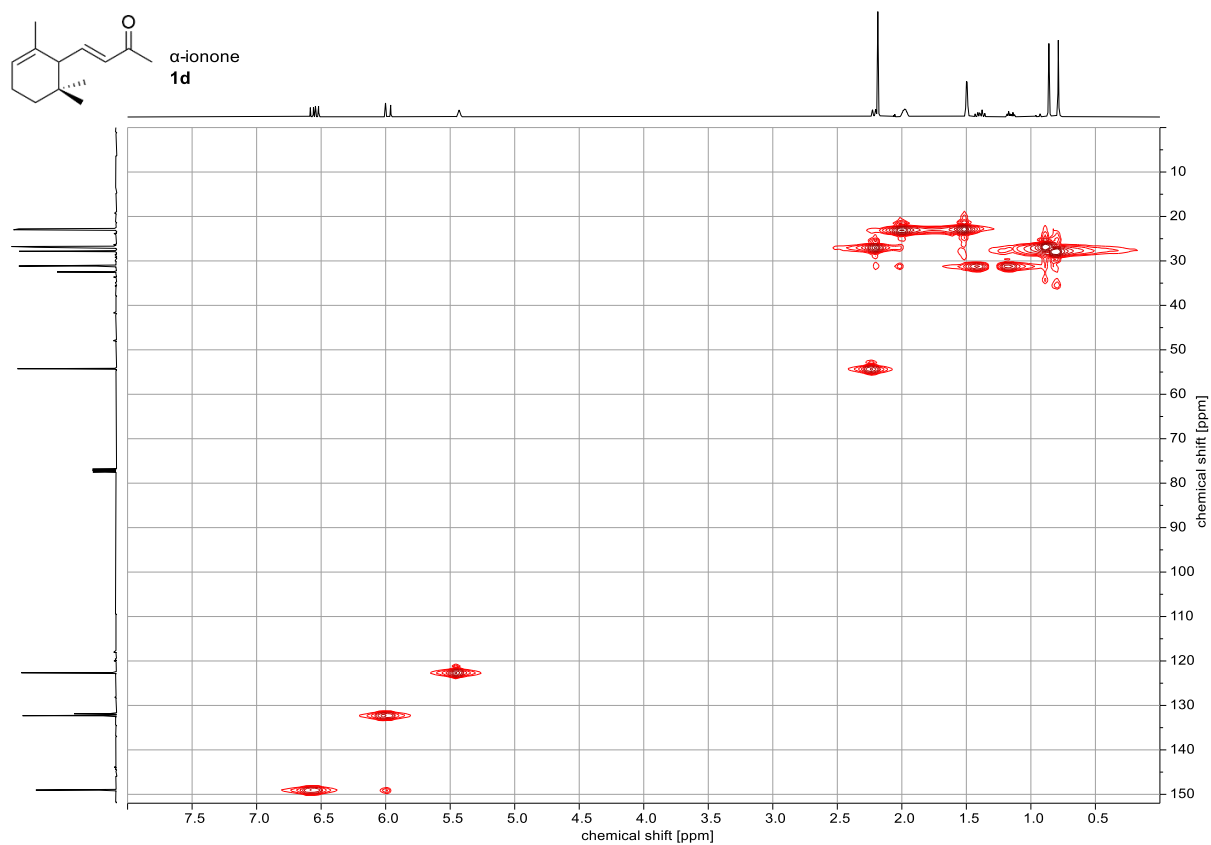
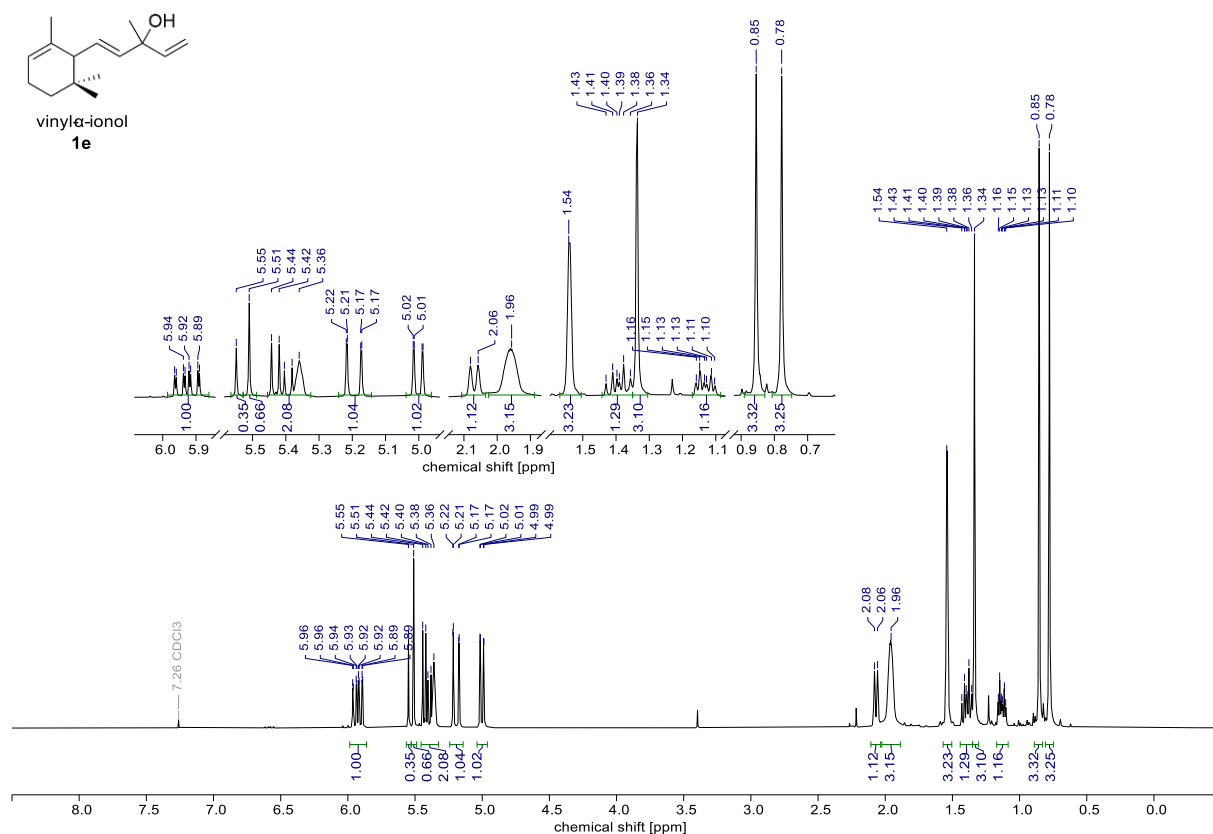
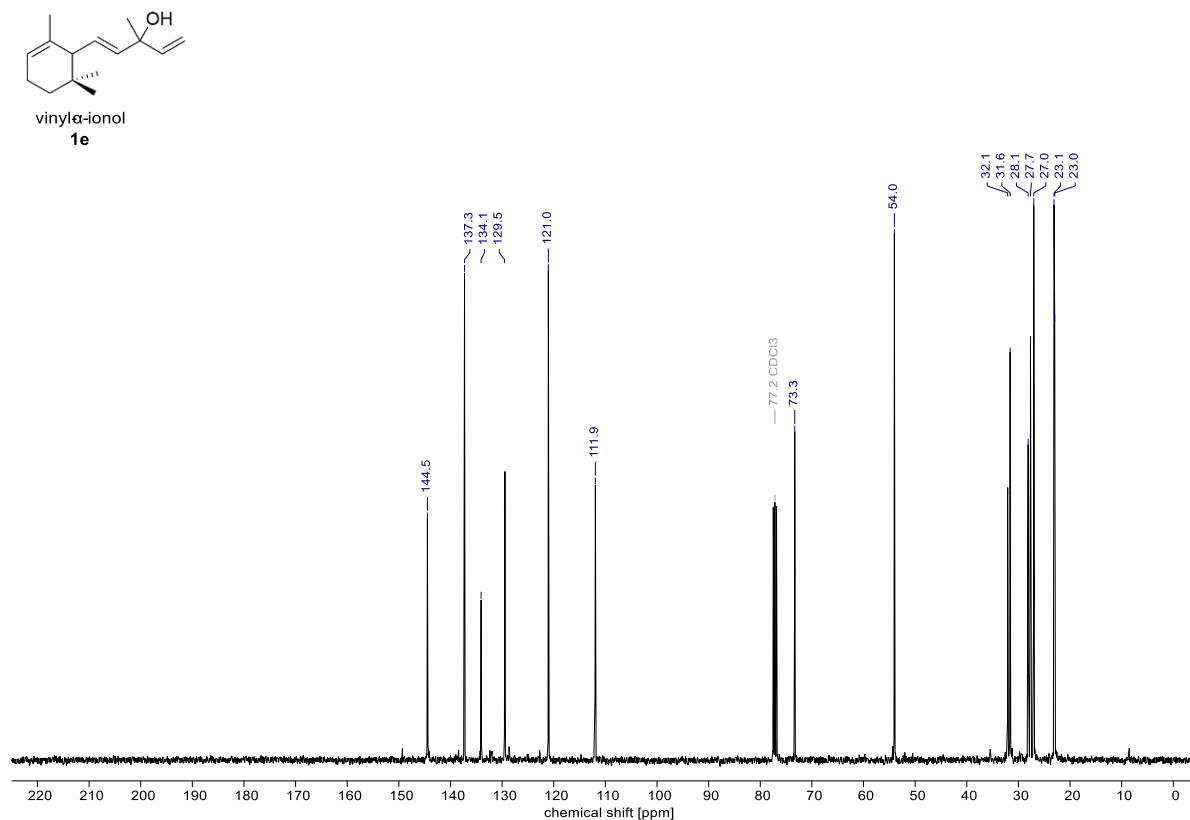
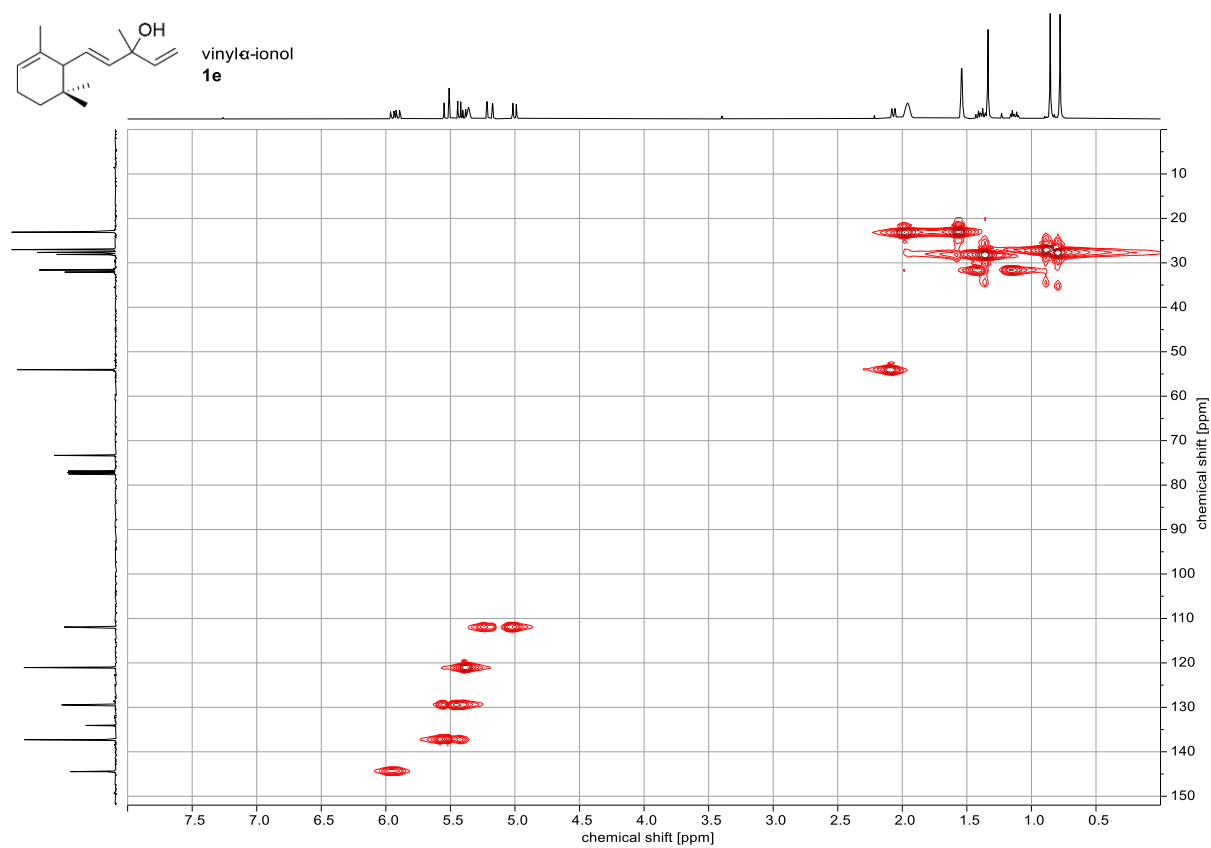
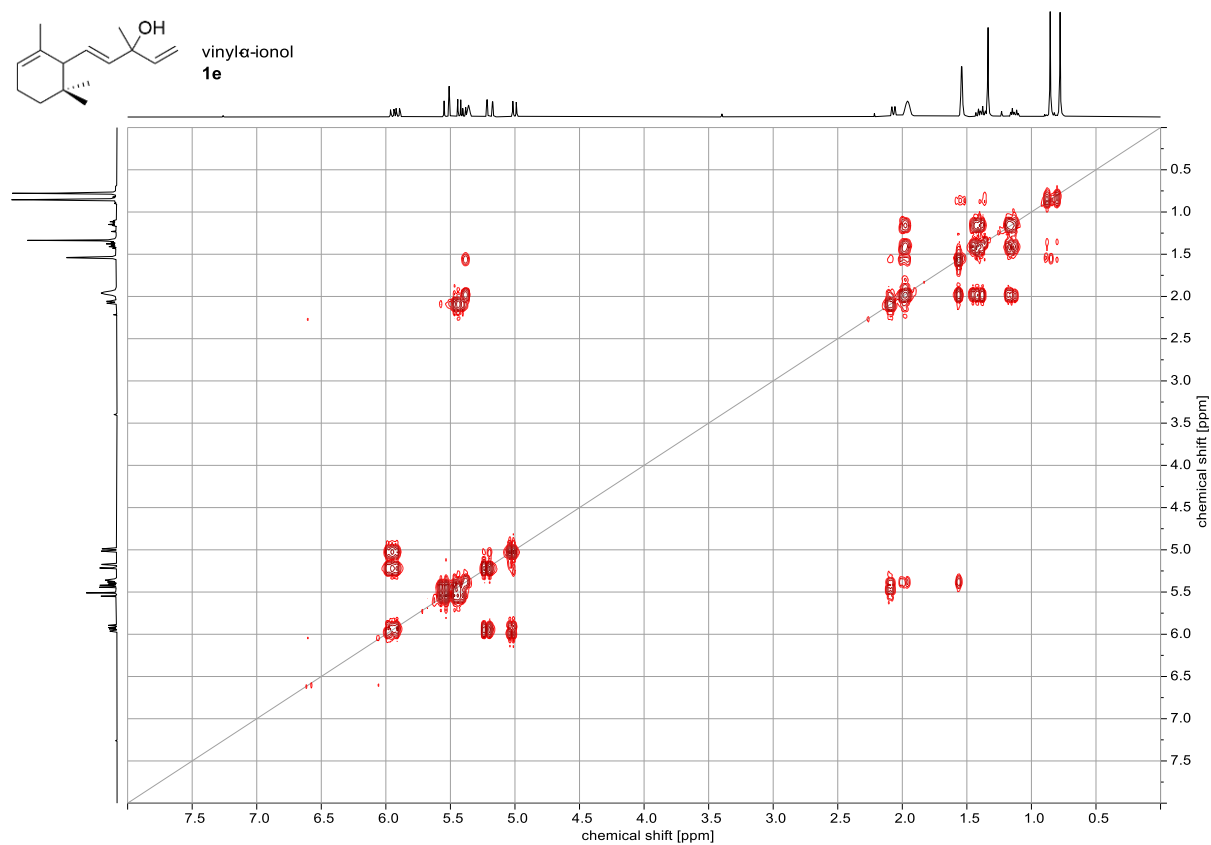
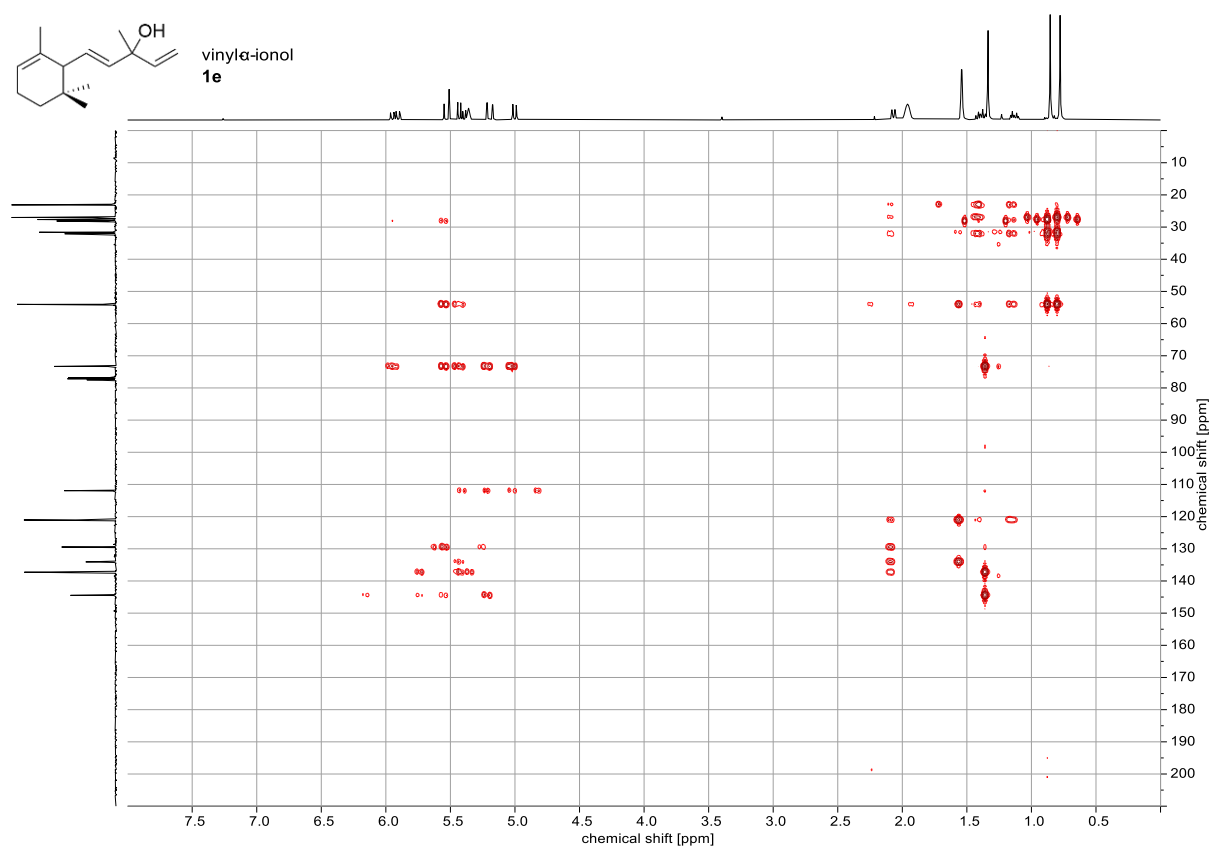
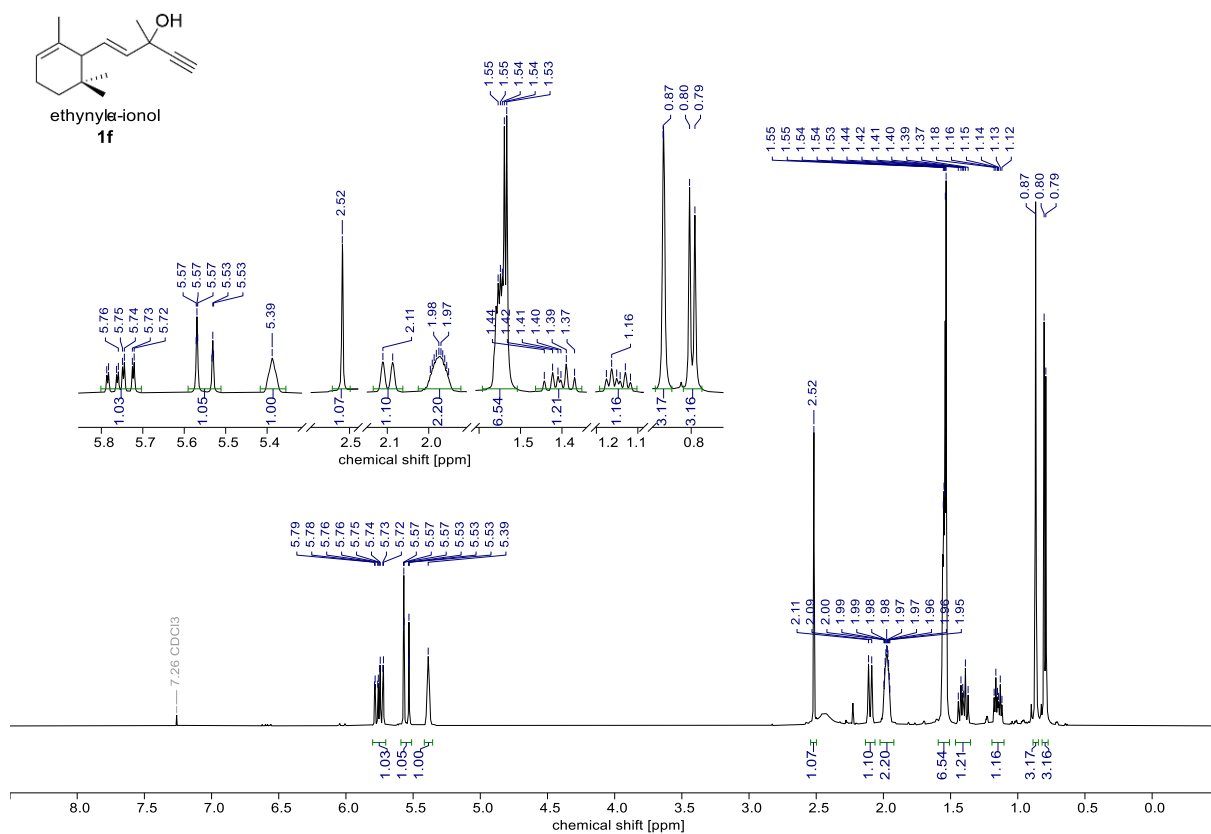


Figure S162. COSY spectrum of starting material **1d**: α -ionone.



10.7. Vinyl- α -ionolFigure S165. ¹H NMR spectrum (400 MHz) of starting material **1e**: vinyl- α -ionol.Figure S166. ¹³C NMR spectrum (101 MHz) of starting material **1e**: vinyl- α -ionol.



Figure S169. HMBC spectrum of starting material **1e**: vinyl- α -ionol.10.8. Ethynyl- α -ionolFigure S170. ^1H NMR spectrum (400 MHz) of starting material **1f**: ethynyl- α -ionol.

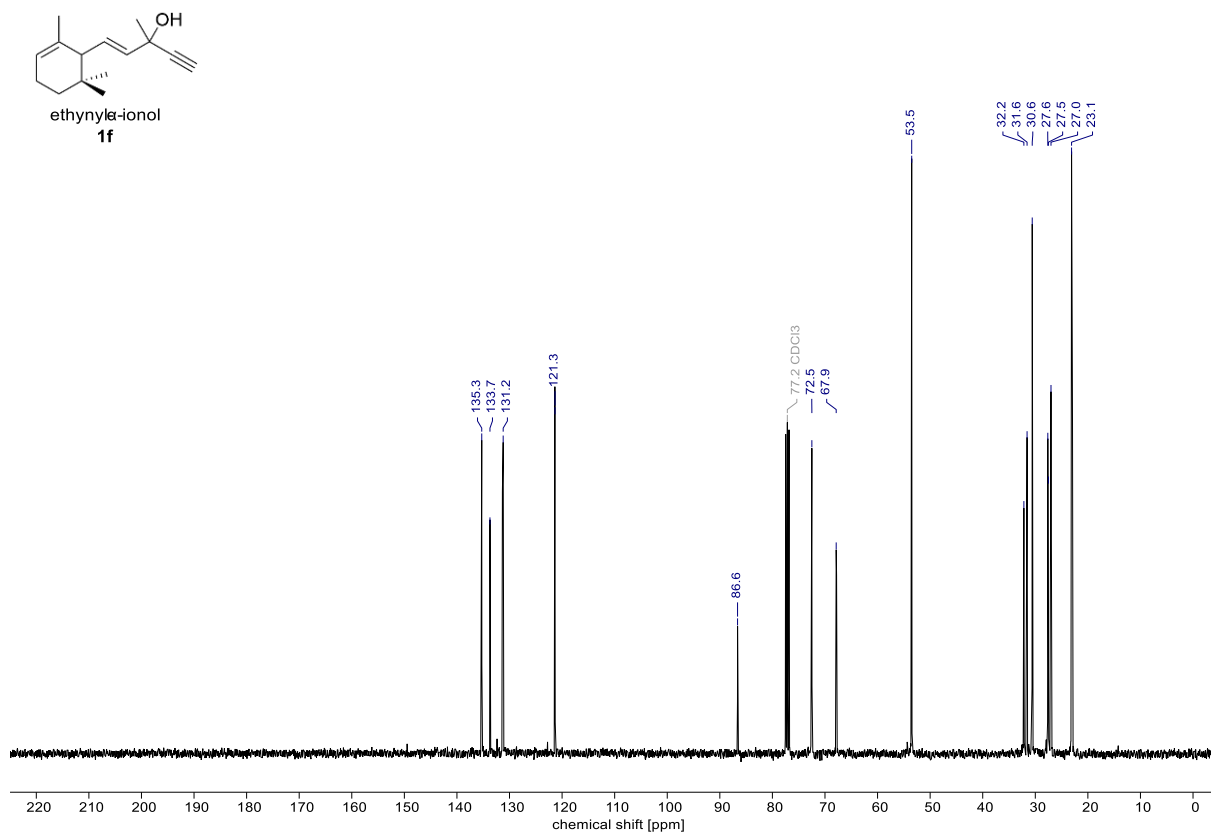


Figure S171. ¹³C NMR spectrum (101 MHz) of starting material **1f**: ethynyl- α -ionol.

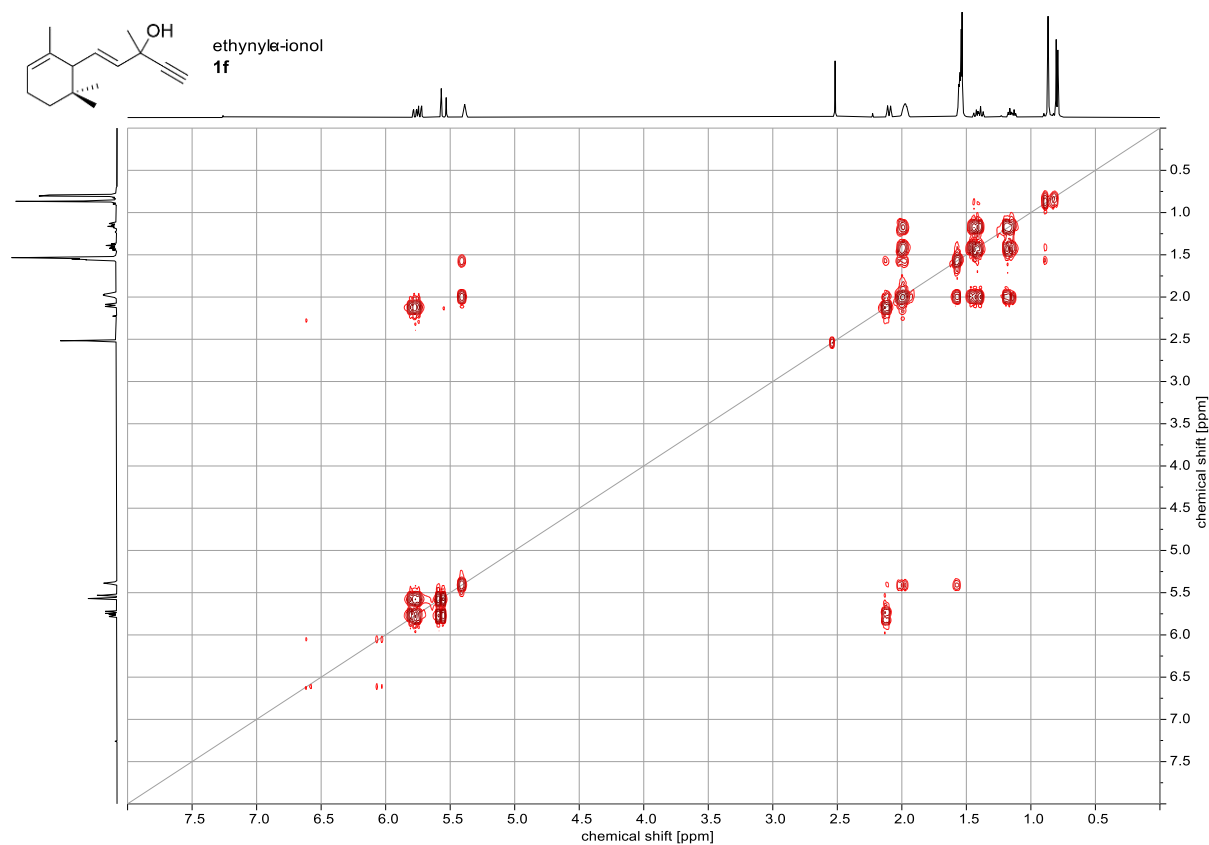


Figure S172. COSY spectrum of starting material **1f**: ethynyl- α -ionol.

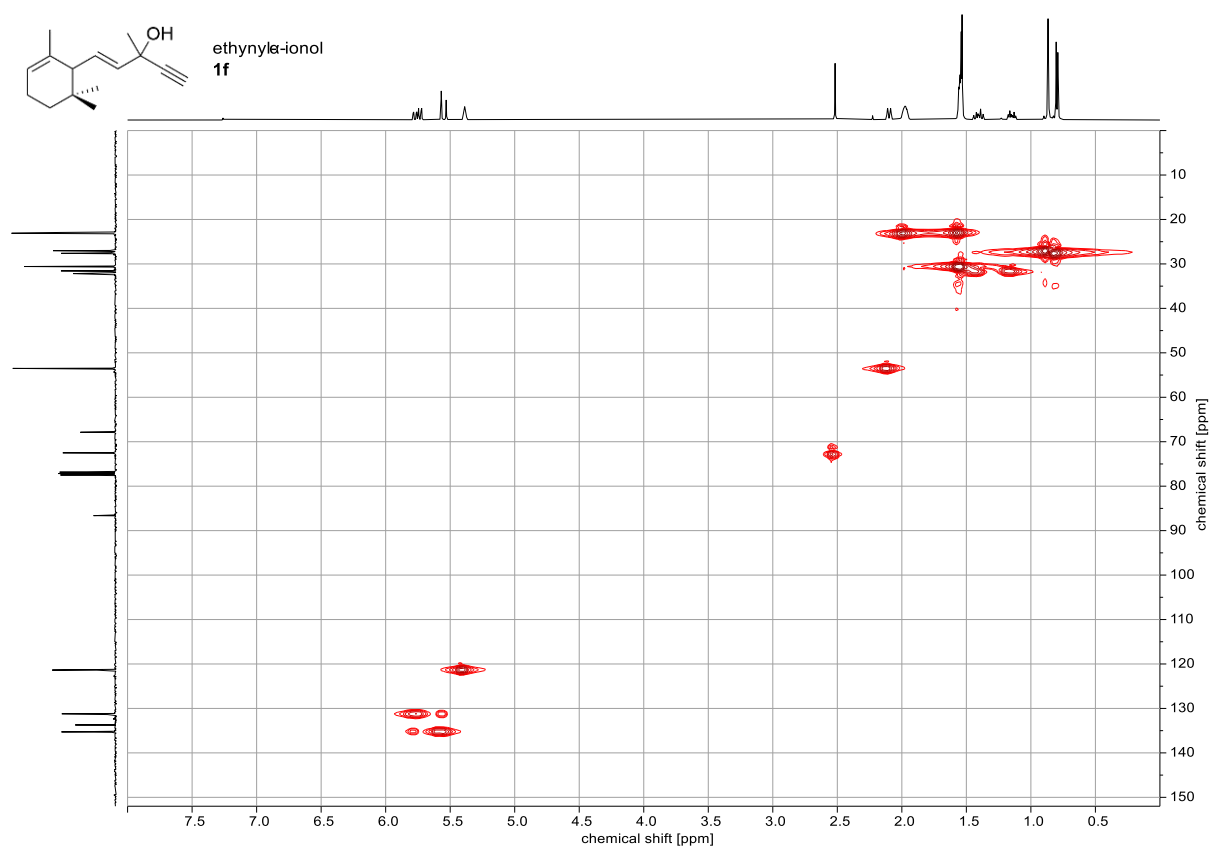


Figure S173. HSQC spectrum of starting material **1f**: ethynyl- α -ionol.

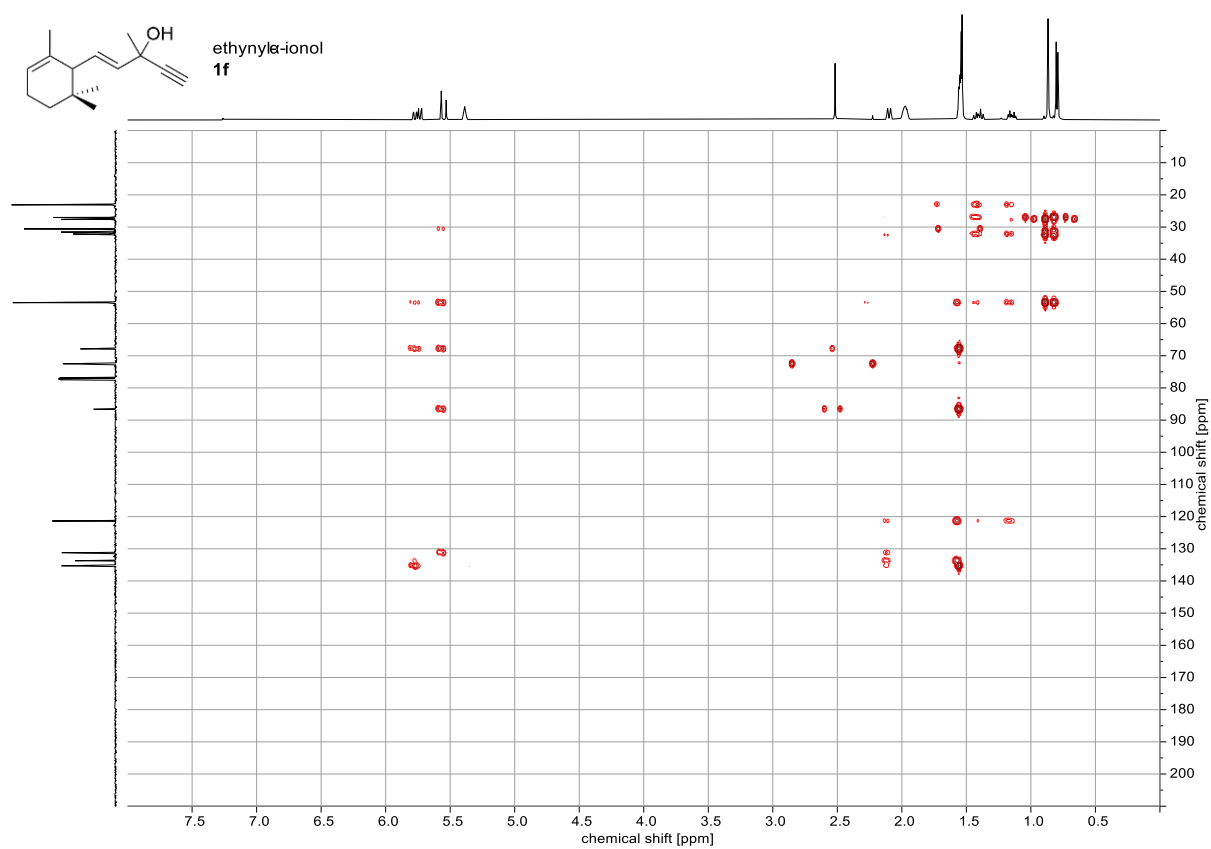
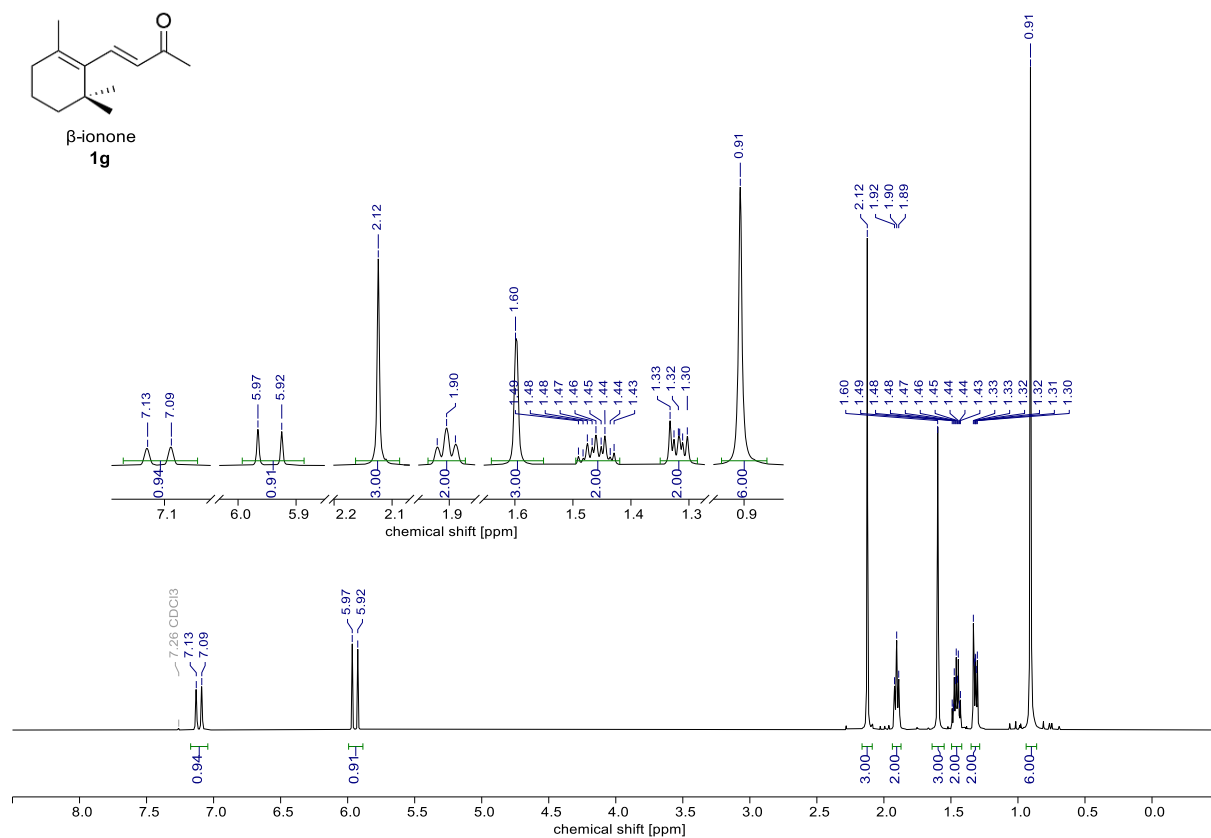
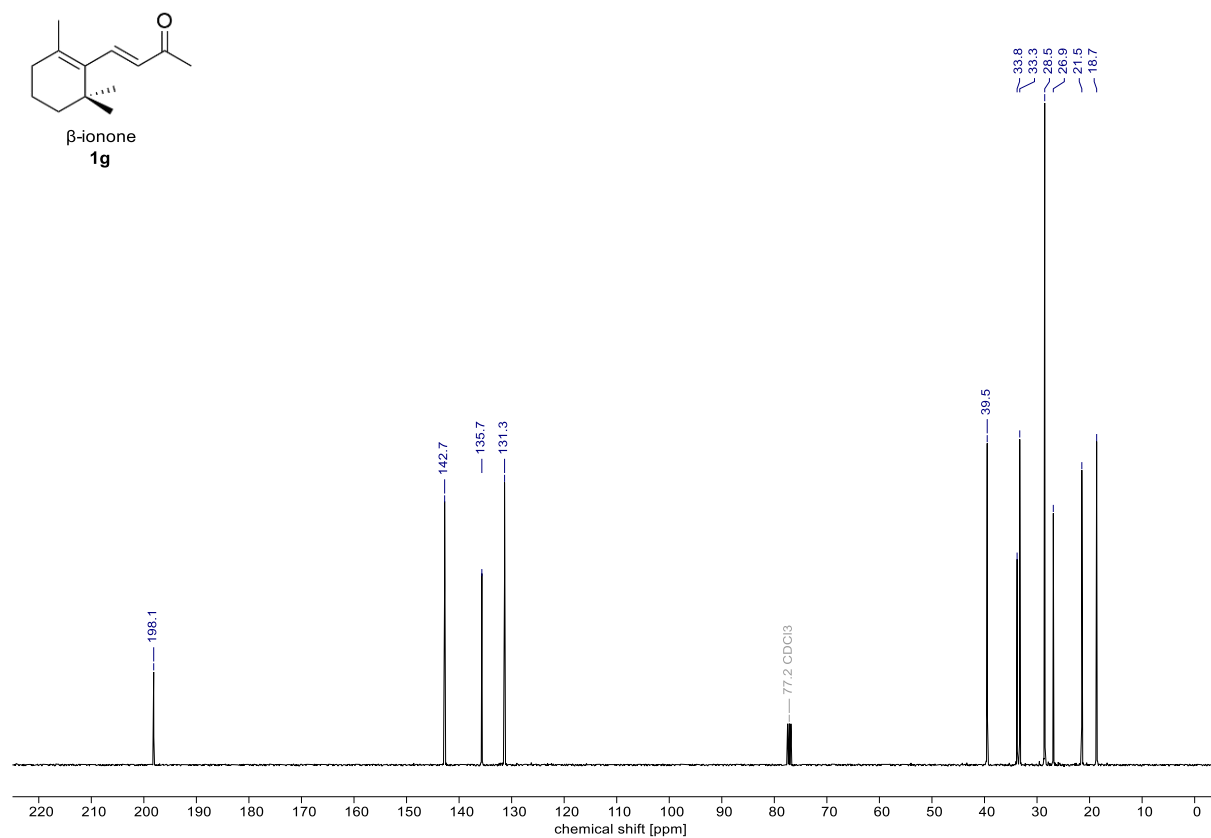


Figure S174. HMBC spectrum of starting material **1f**: ethynyl- α -ionol.

10.9. β -IononeFigure S175. ¹H NMR spectrum (400 MHz) of starting material **1g**: β -ionone.Figure S176. ¹³C NMR spectrum (101 MHz) of starting material **1g**: β -ionone.

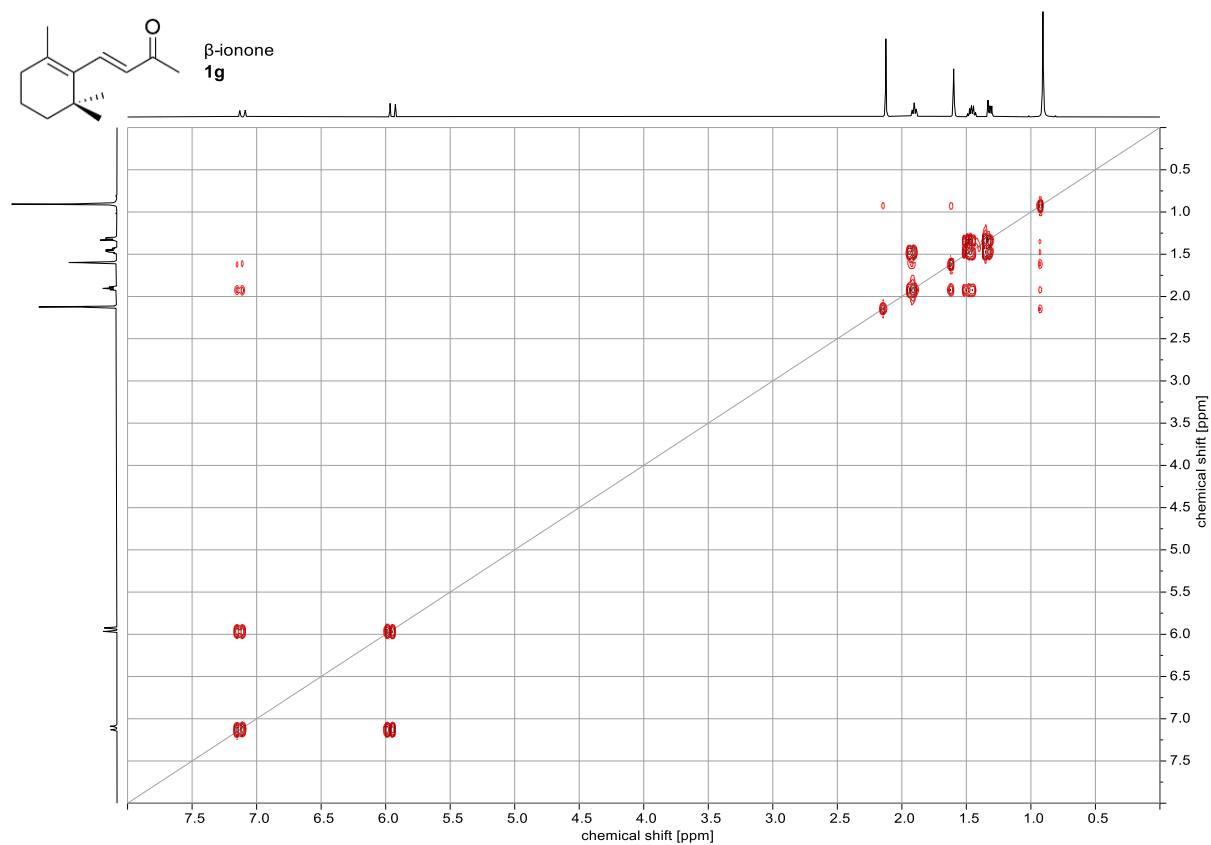


Figure S177. COSY spectrum of starting material **1g**: β -ionone.

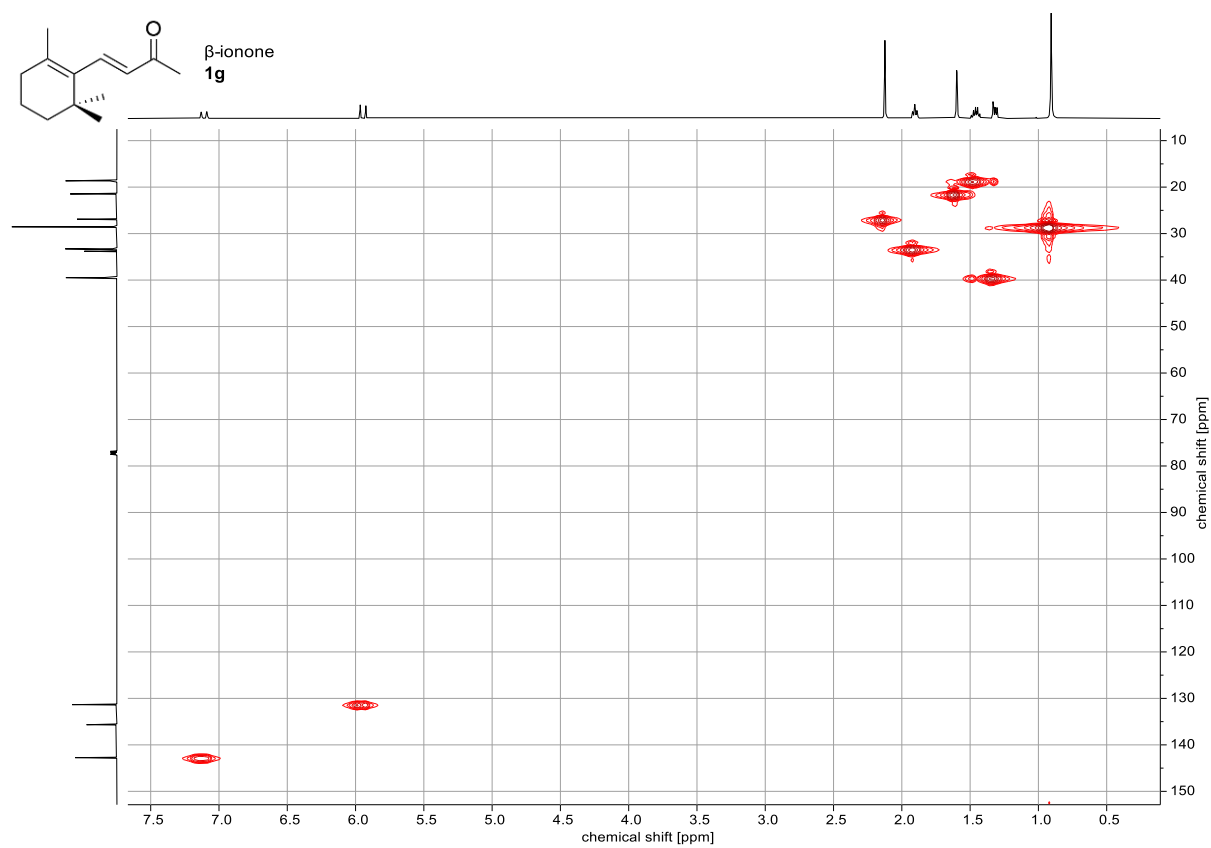


Figure S178. HSQC spectrum of starting material **1g**: β -ionone.

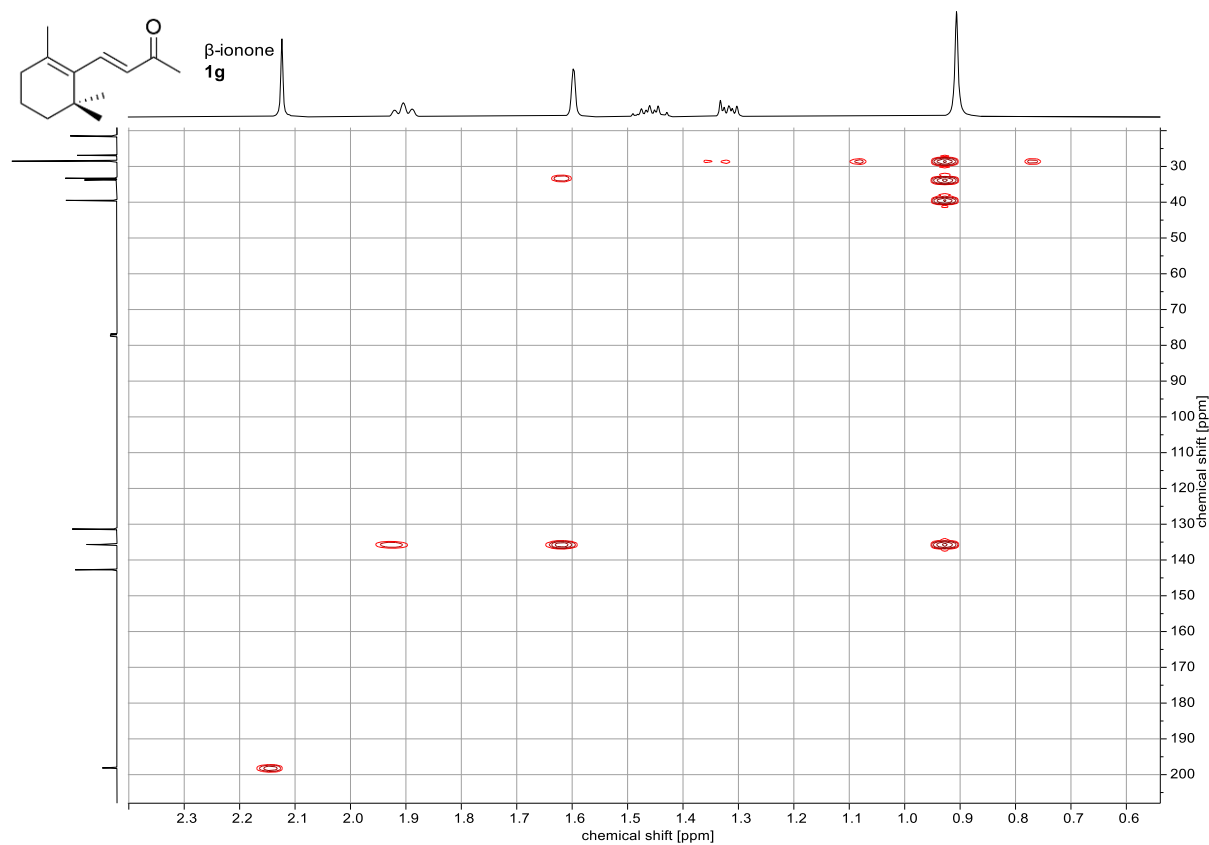
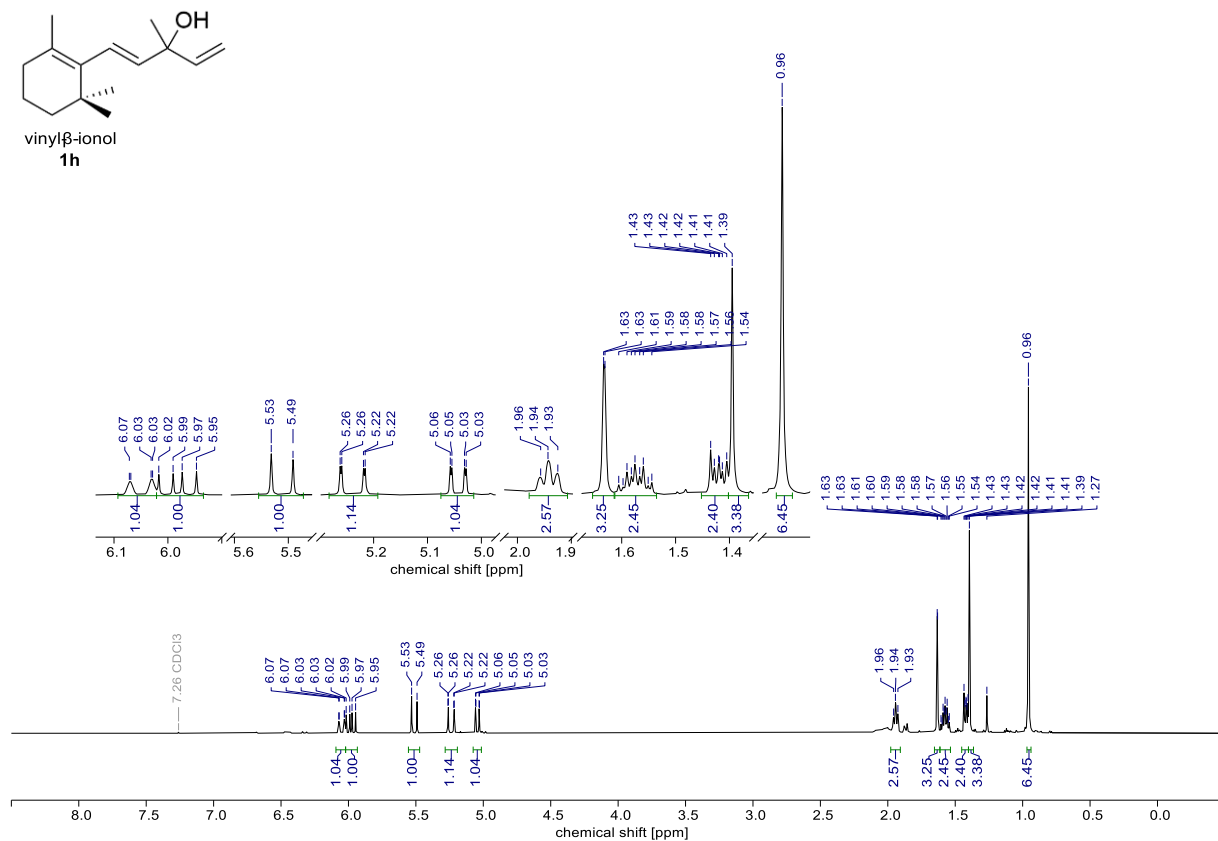


Figure S179. HMBC spectrum of starting material 1g: β-ionone.

10.10. Vinyl-β-ionol

Figure S180. ¹H NMR spectrum (400 MHz) of starting material 1h: vinyl-β-ionol.

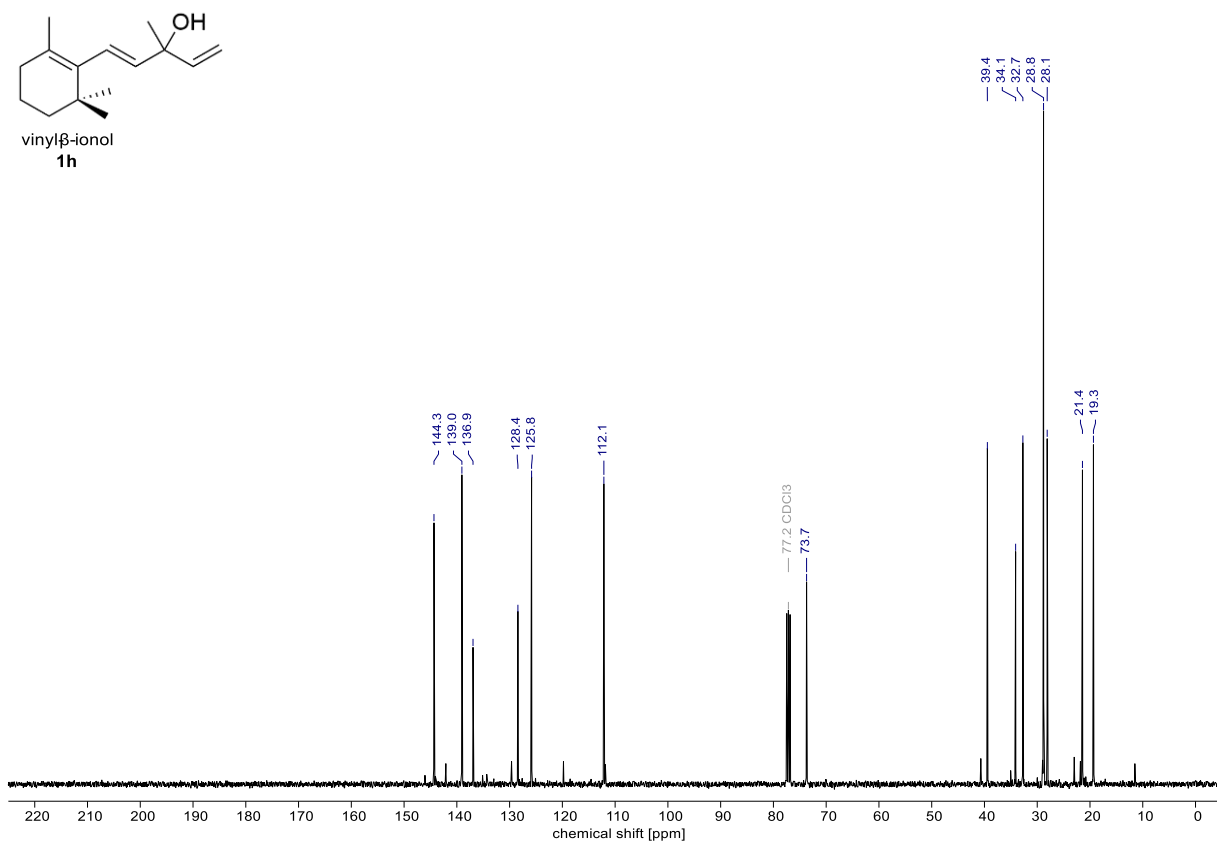


Figure S181. ^{13}C NMR spectrum (101 MHz) of starting material **1h**: vinyl- β -ionol.

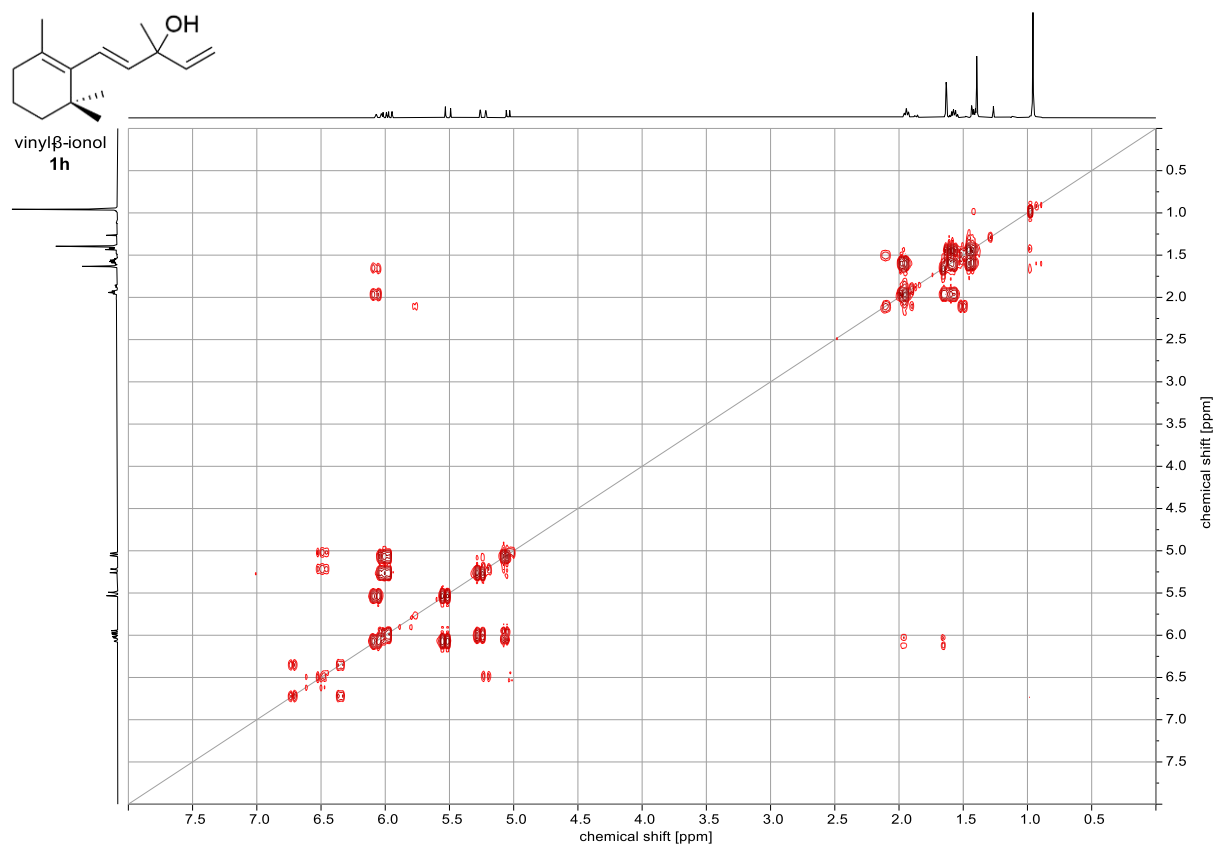


Figure S182. COSY spectrum of starting material **1h**: vinyl- β -ionol.

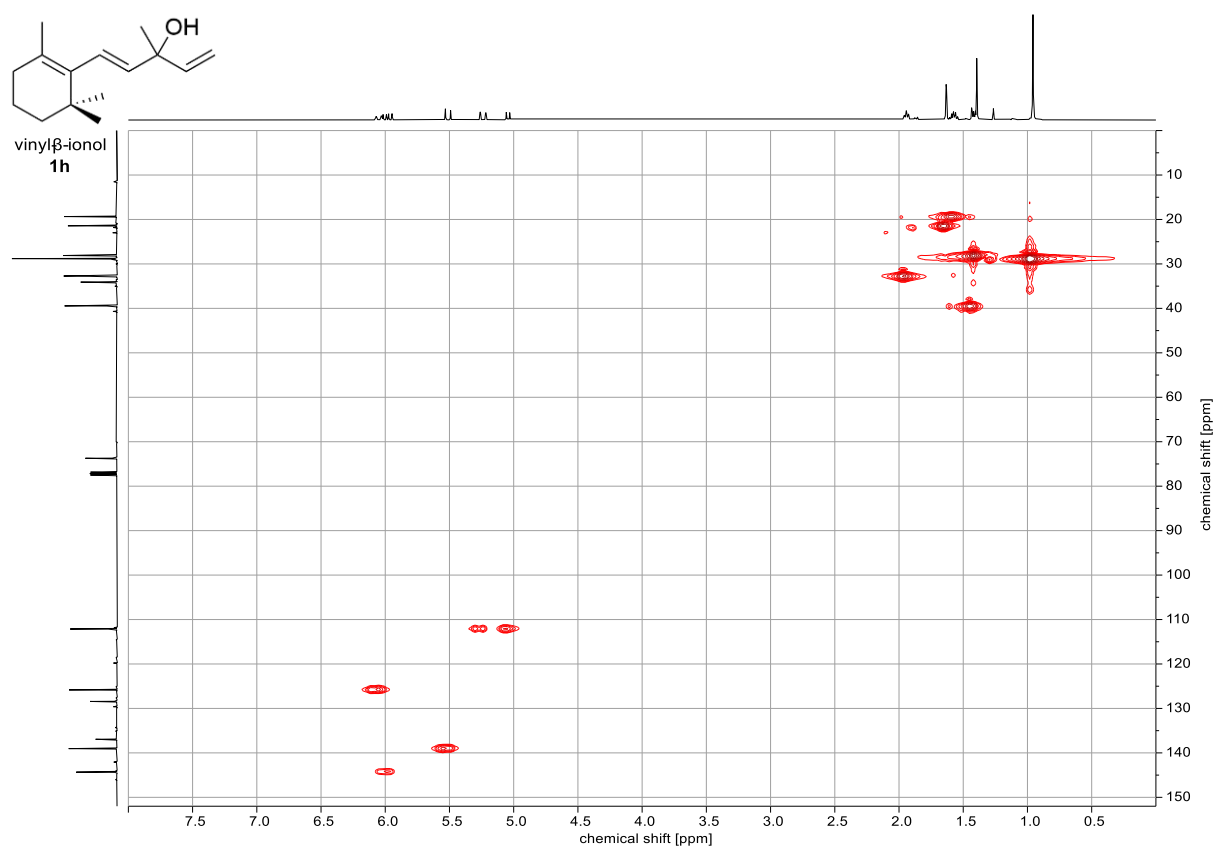


Figure S183. HSQC spectrum of starting material **1h**: vinyl- β -ionol.

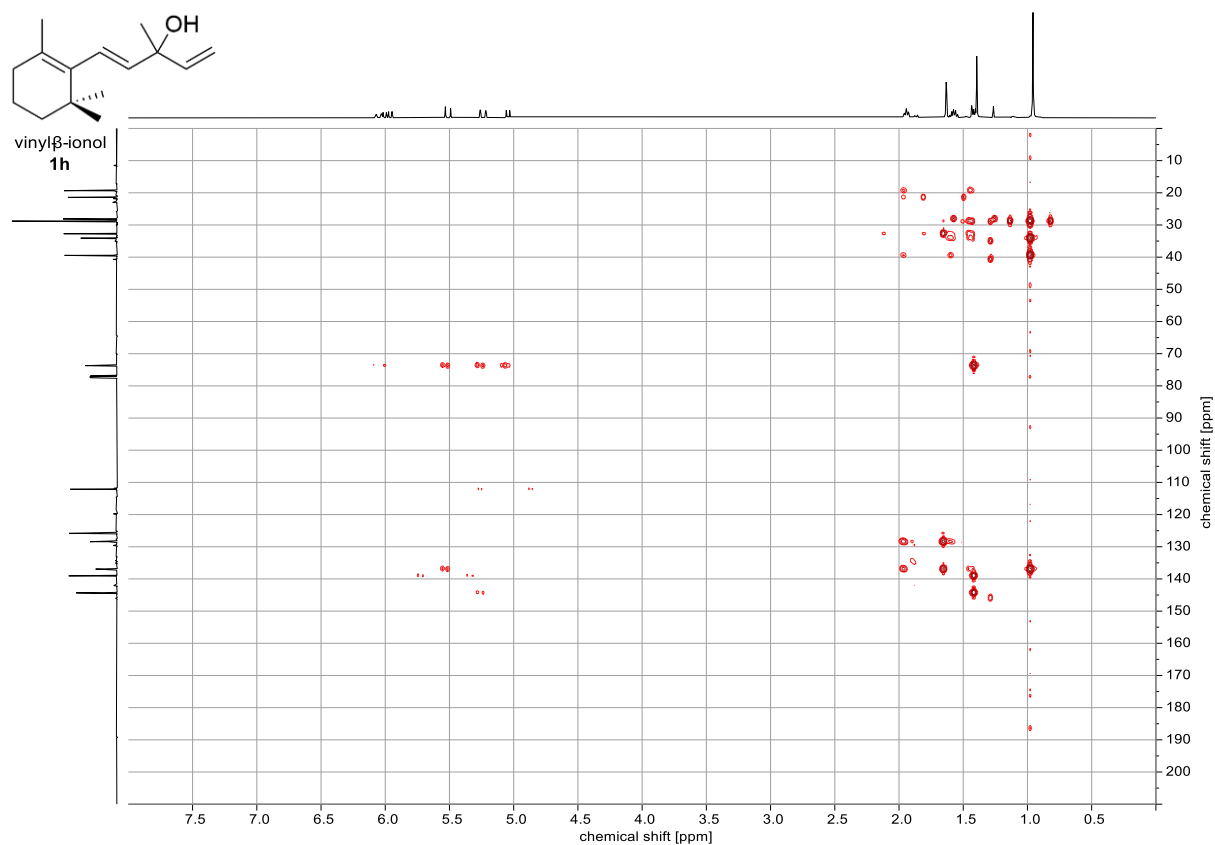
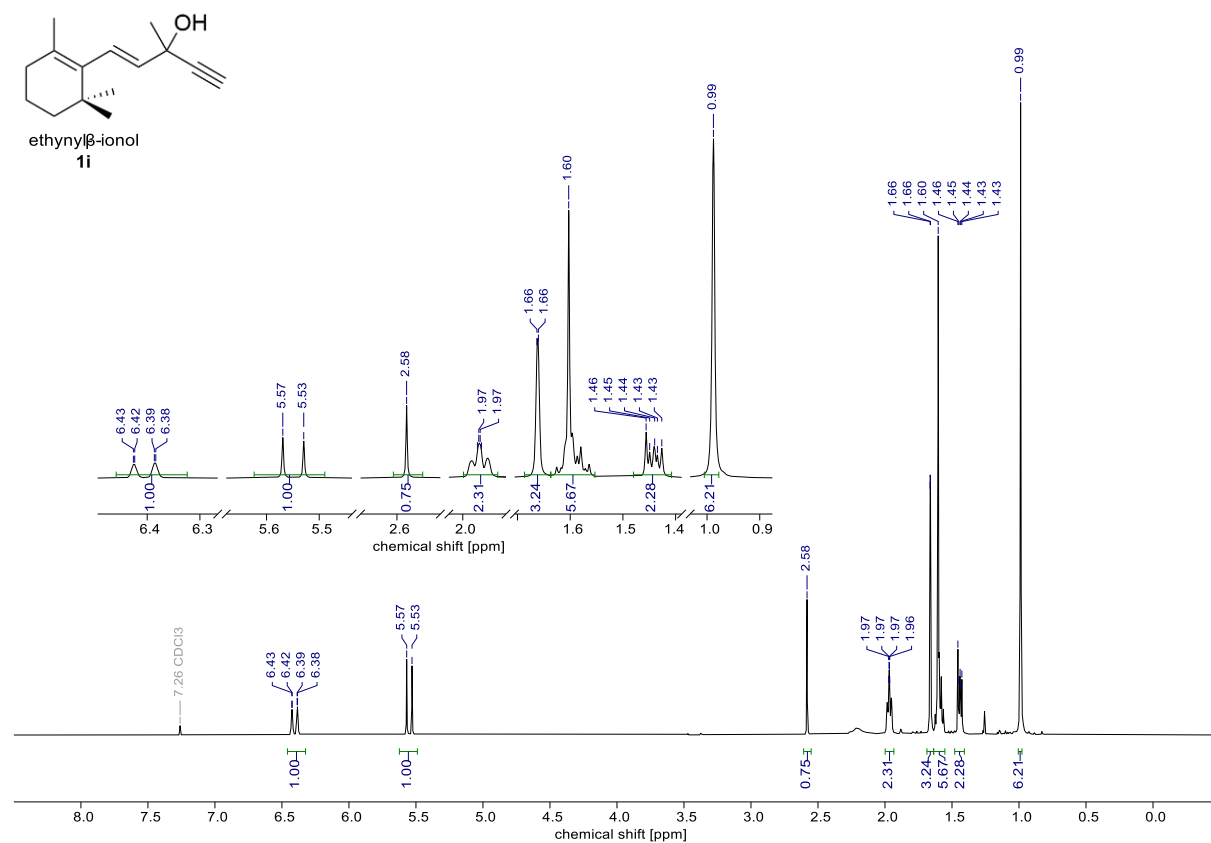
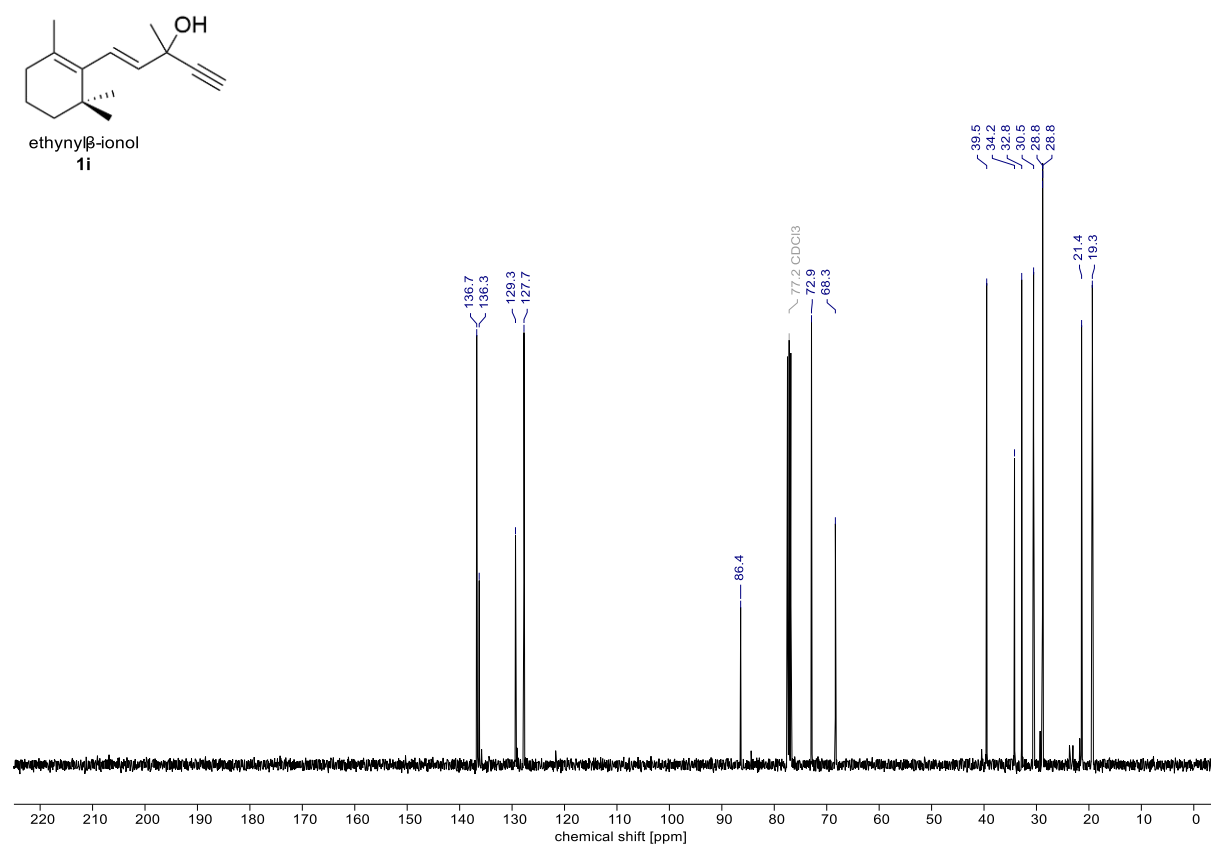


Figure S184. HMBC spectrum of starting material **1h**: vinyl- β -ionol.

10.11. Ethynyl- β -ionolFigure S185. ¹H NMR spectrum (400 MHz) of starting material **1i**: ethynyl- β -ionol.Figure S186. ¹³C NMR spectrum (101 MHz) of starting material **1i**: ethynyl- β -ionol.

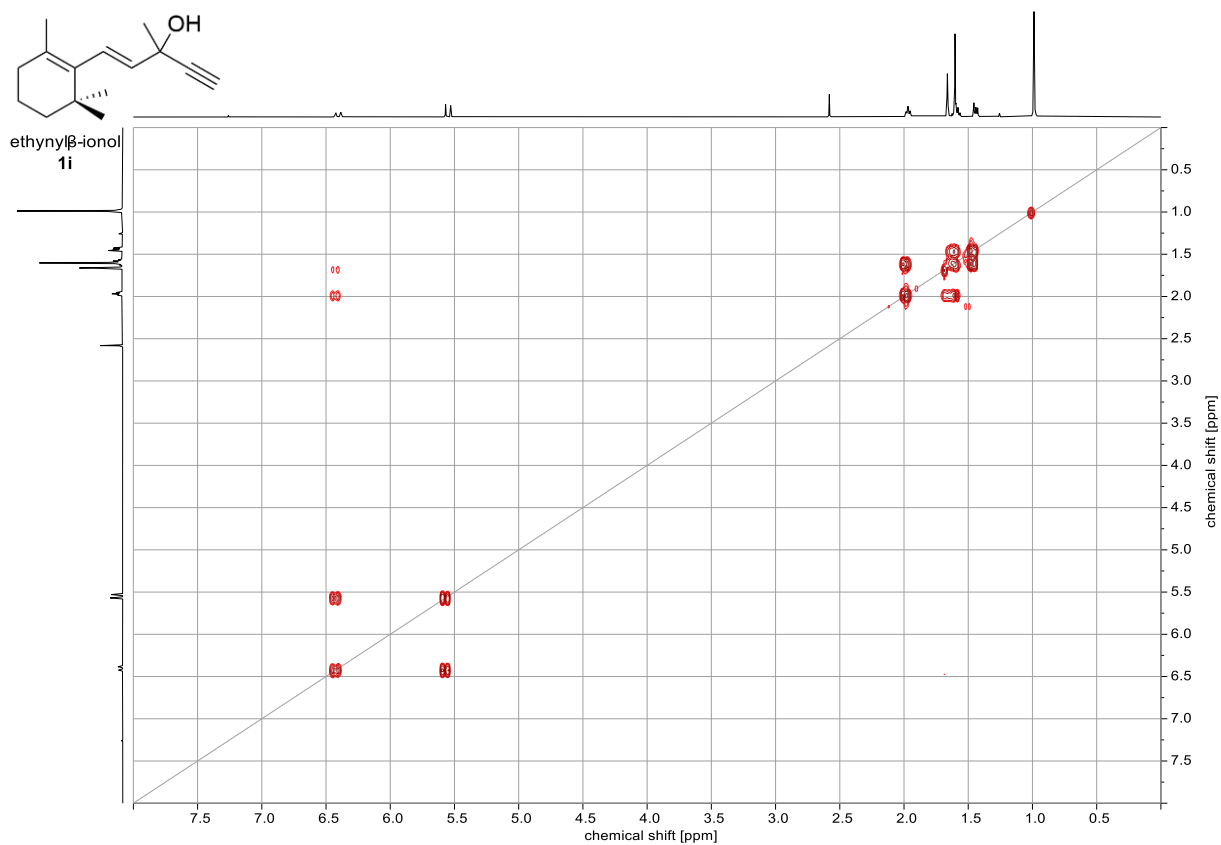


Figure S187. COSY spectrum of starting material 1i: ethynyl- β -ionol.

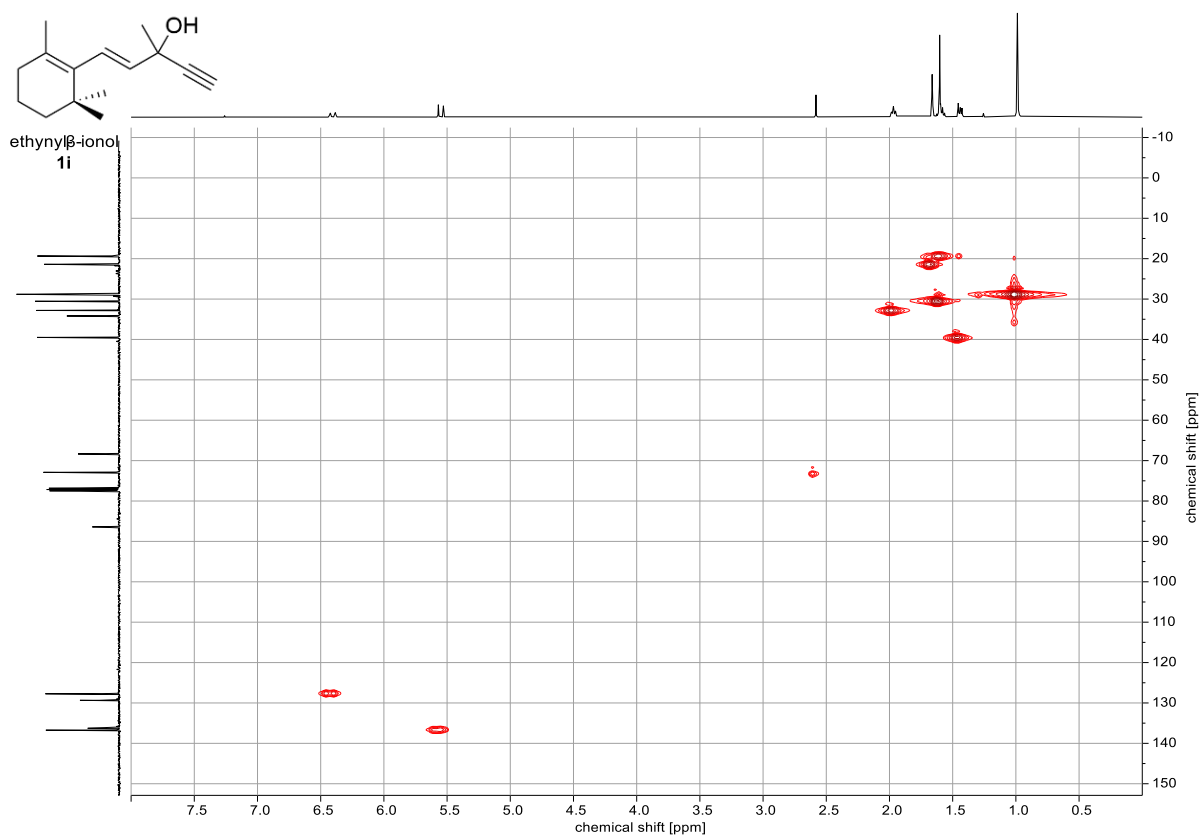


Figure S188. HSQC spectrum of starting material 1i: ethynyl- β -ionol.

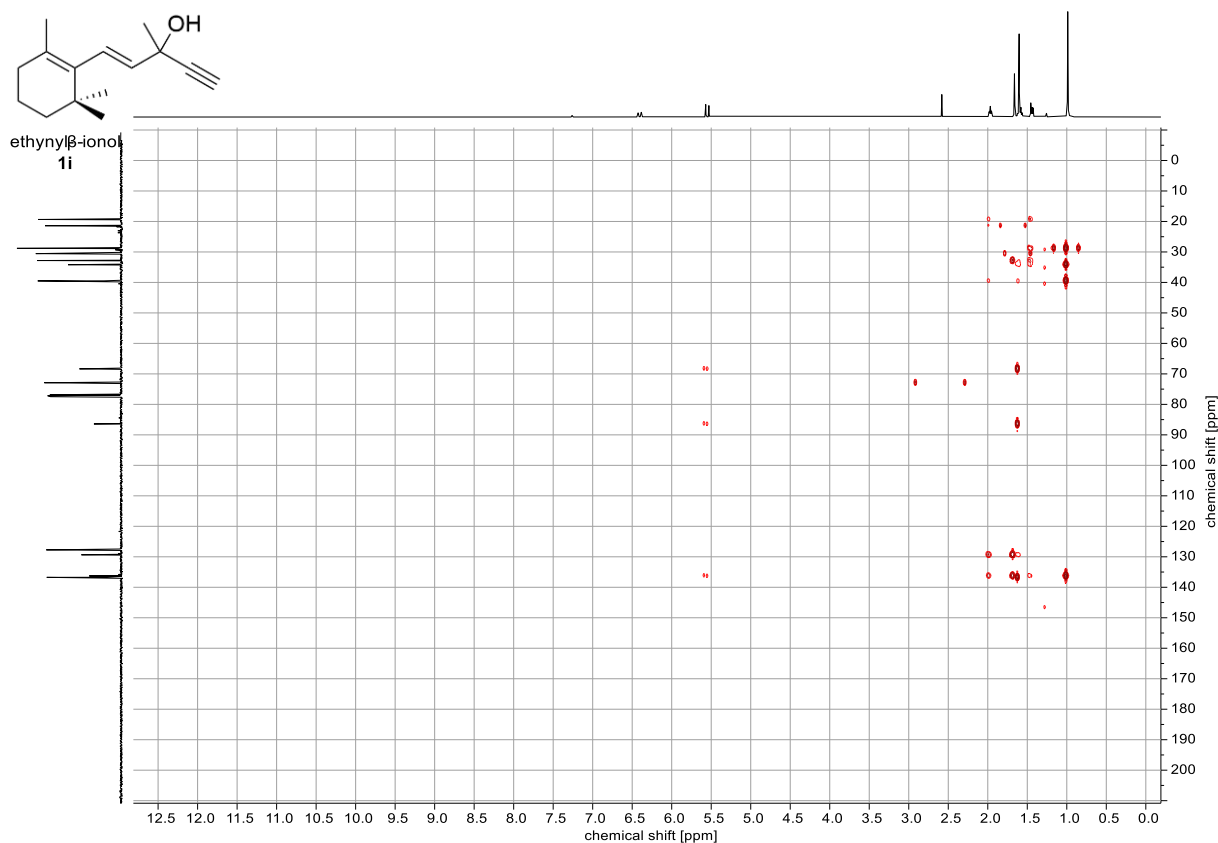


Figure S189. HMBC spectrum of starting material **1i**: ethynyl- β -ionol.

10.12. β -Damascone

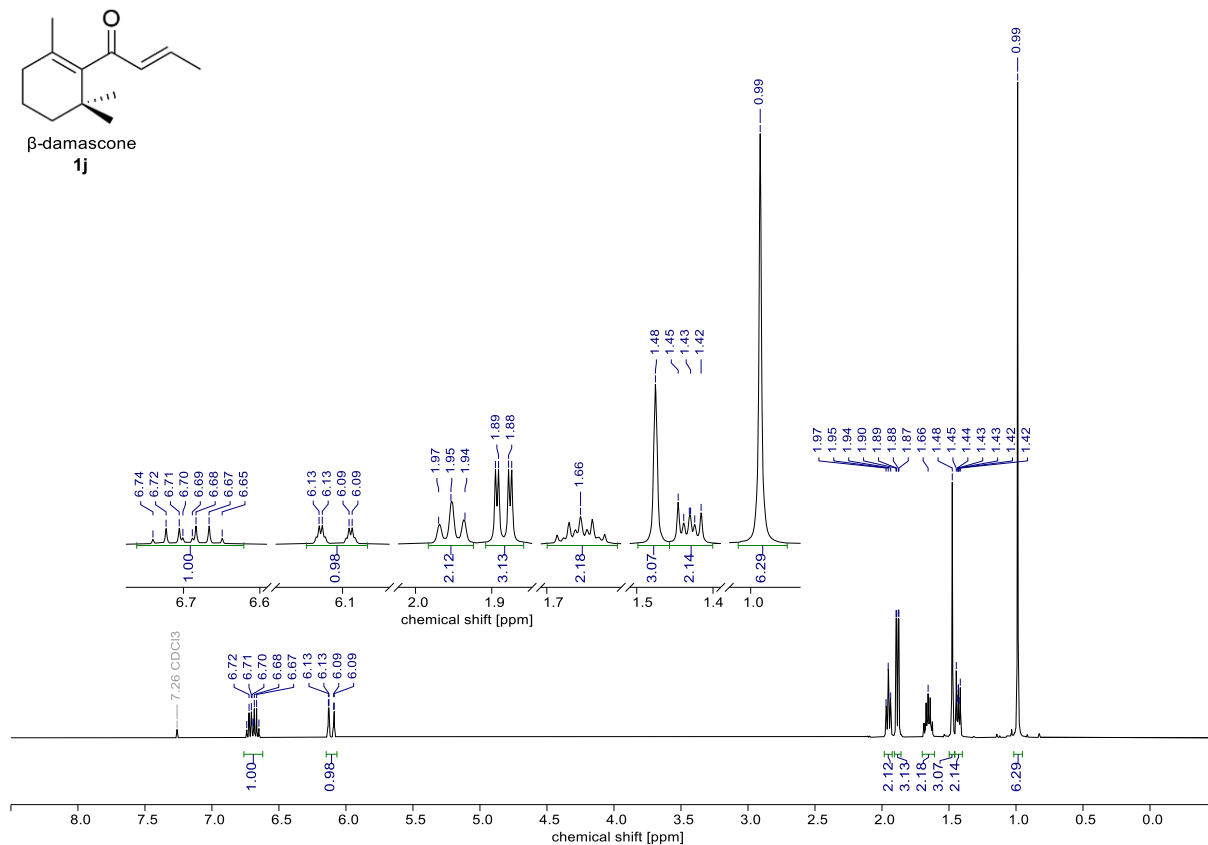


Figure S190. ^1H NMR spectrum (400 MHz) of starting material **1j**: β -damascone.

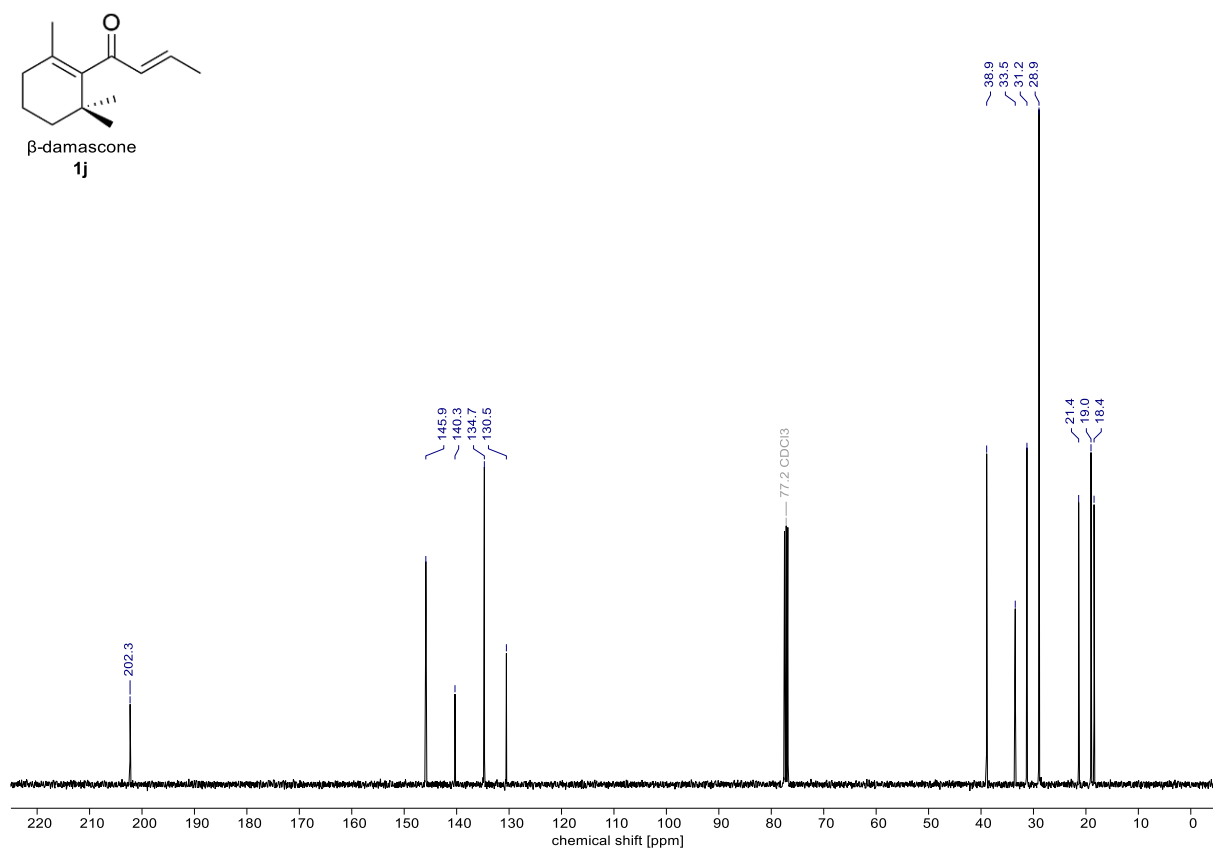


Figure S191. ^{13}C NMR spectrum (101 MHz) of starting material **1j**: β -damascone.

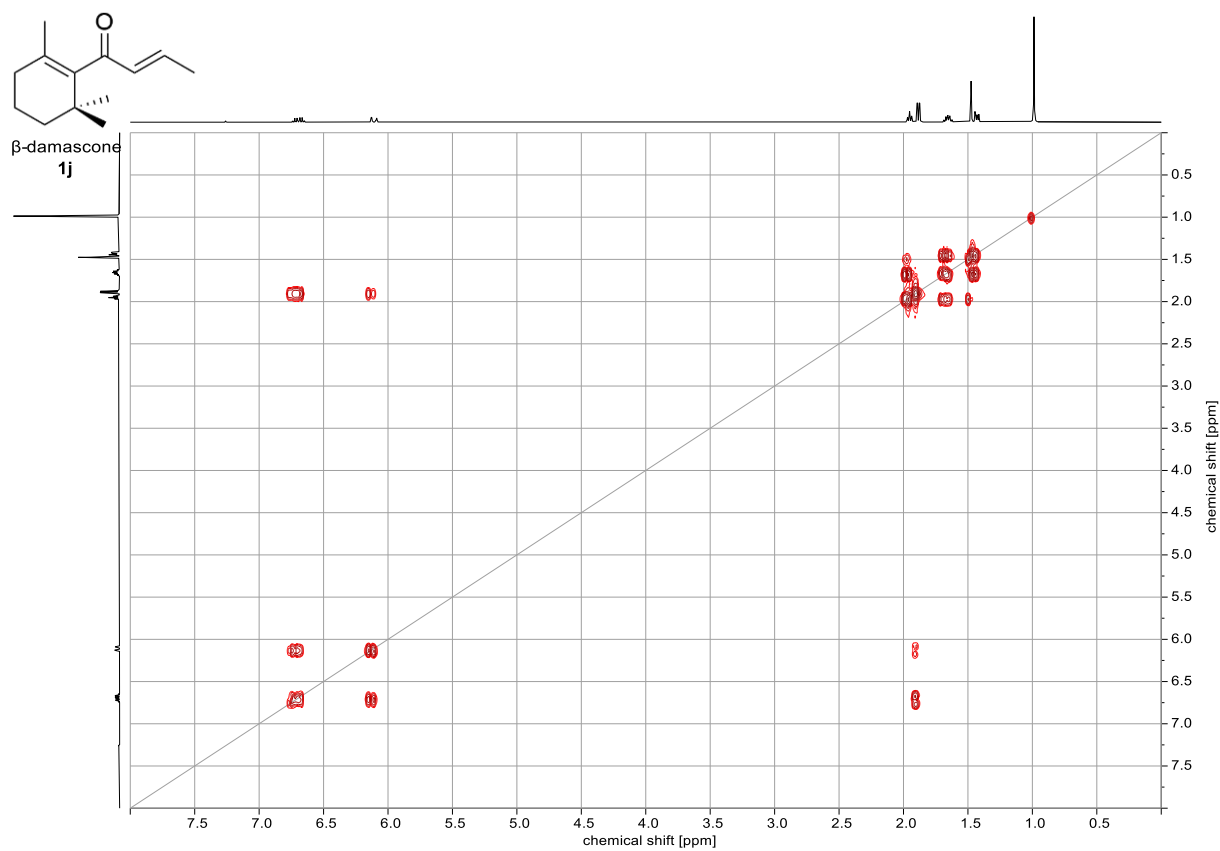


Figure S192. COSY spectrum of starting material **1j**: β -damascone.

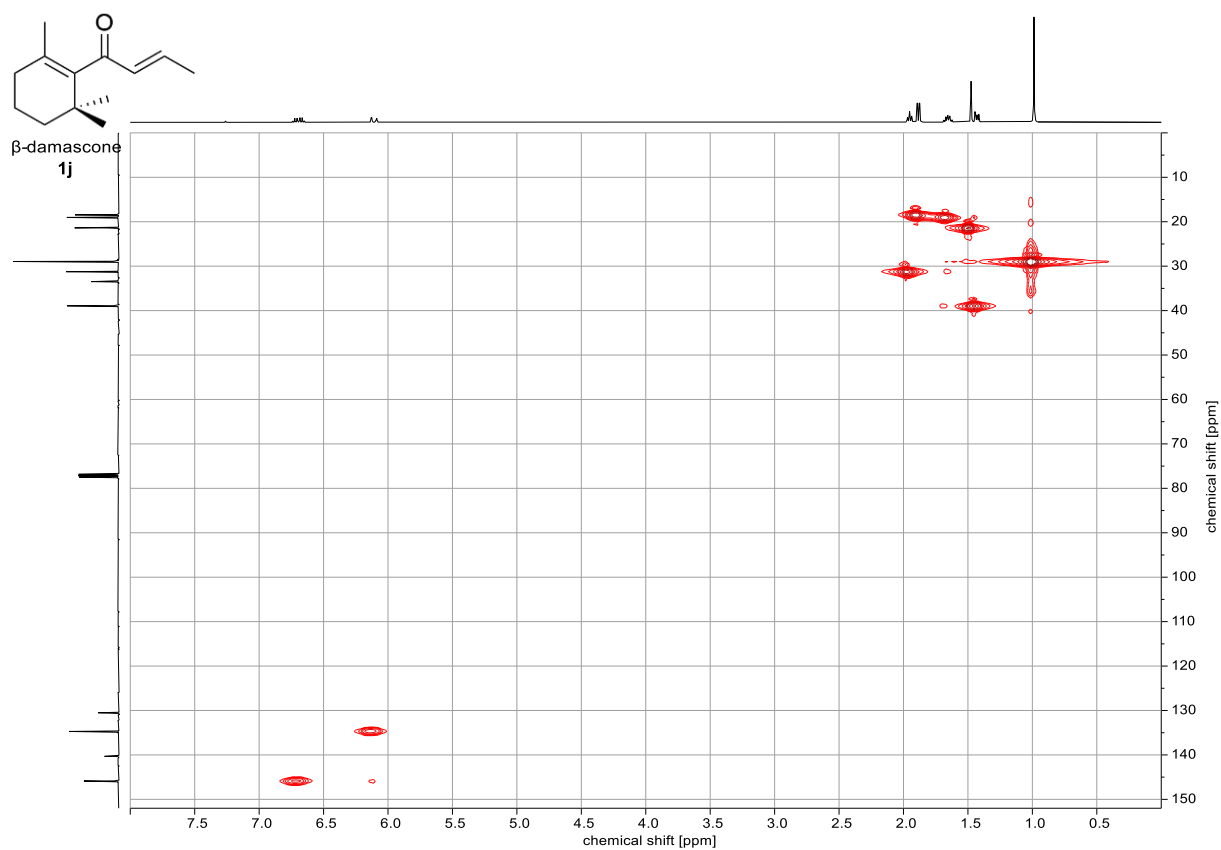


Figure S193. HSQC spectrum of starting material **1j**: β -damascone.

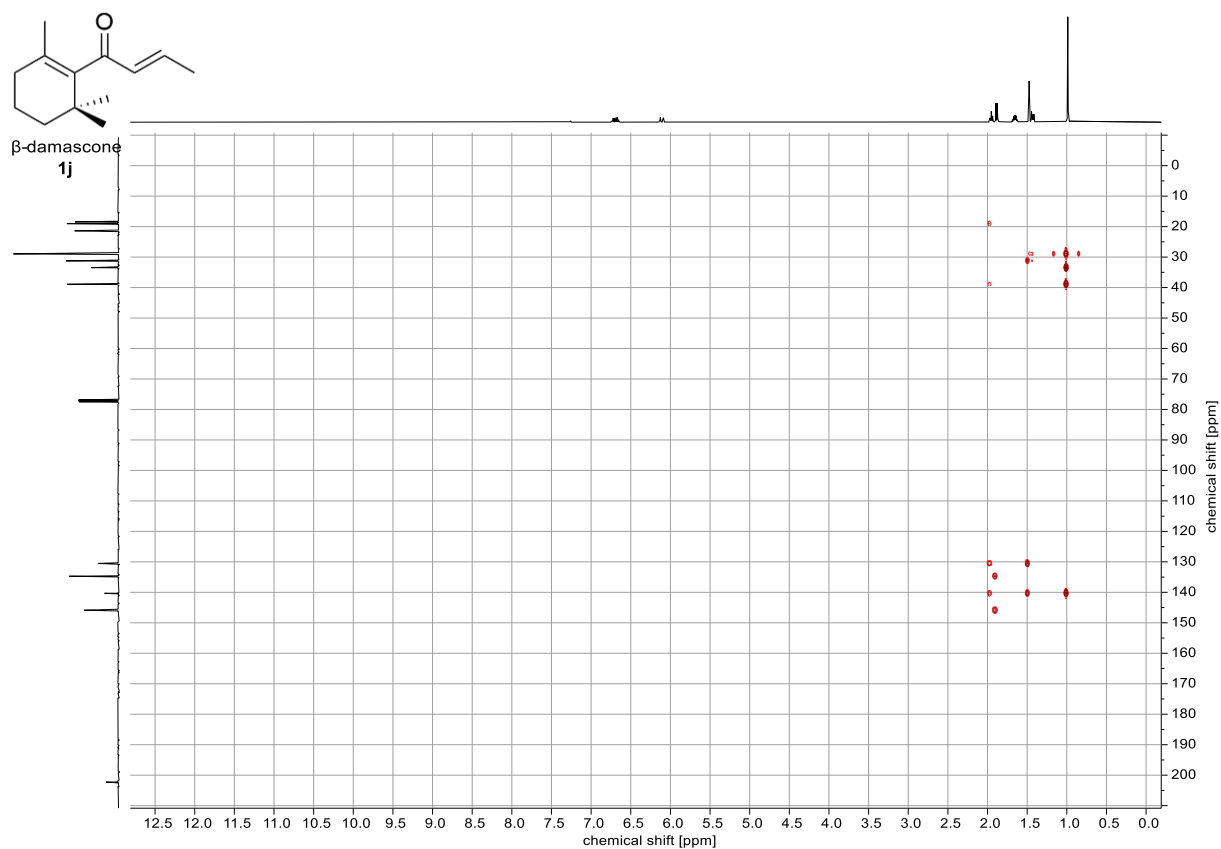
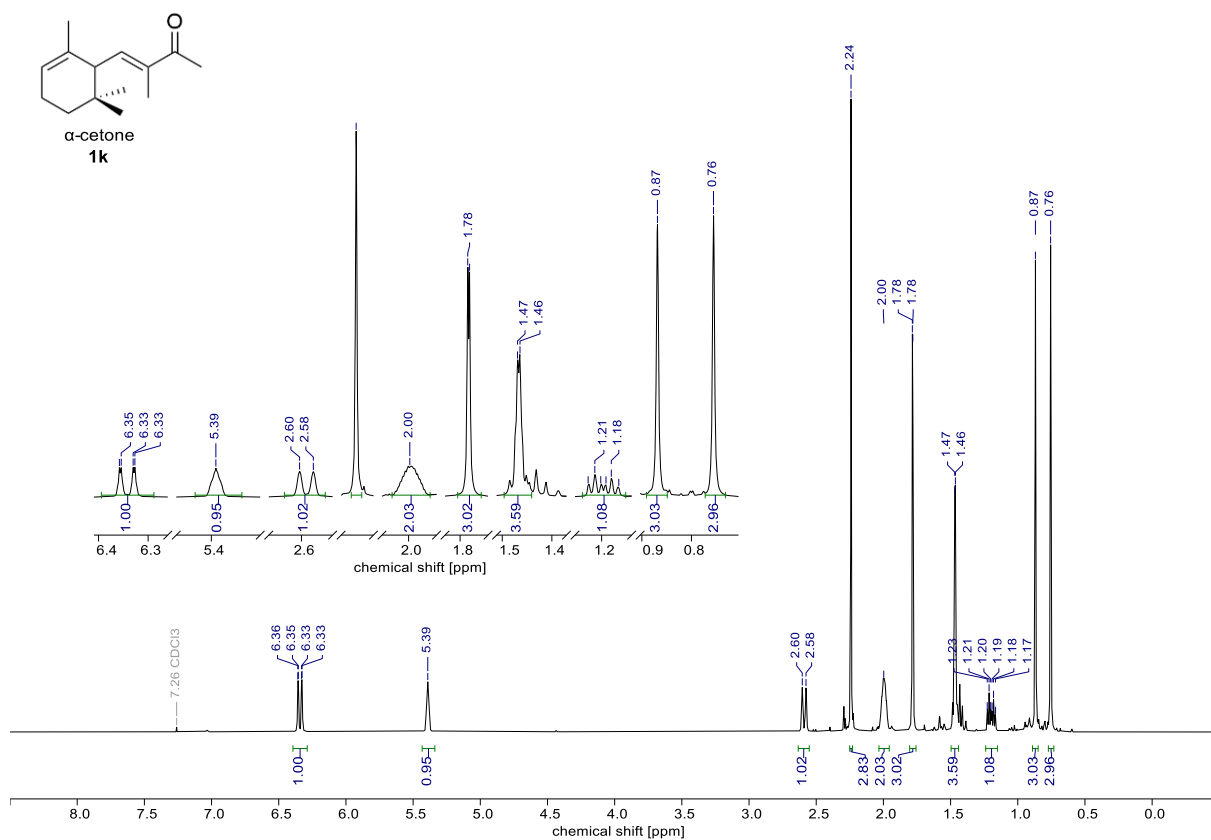
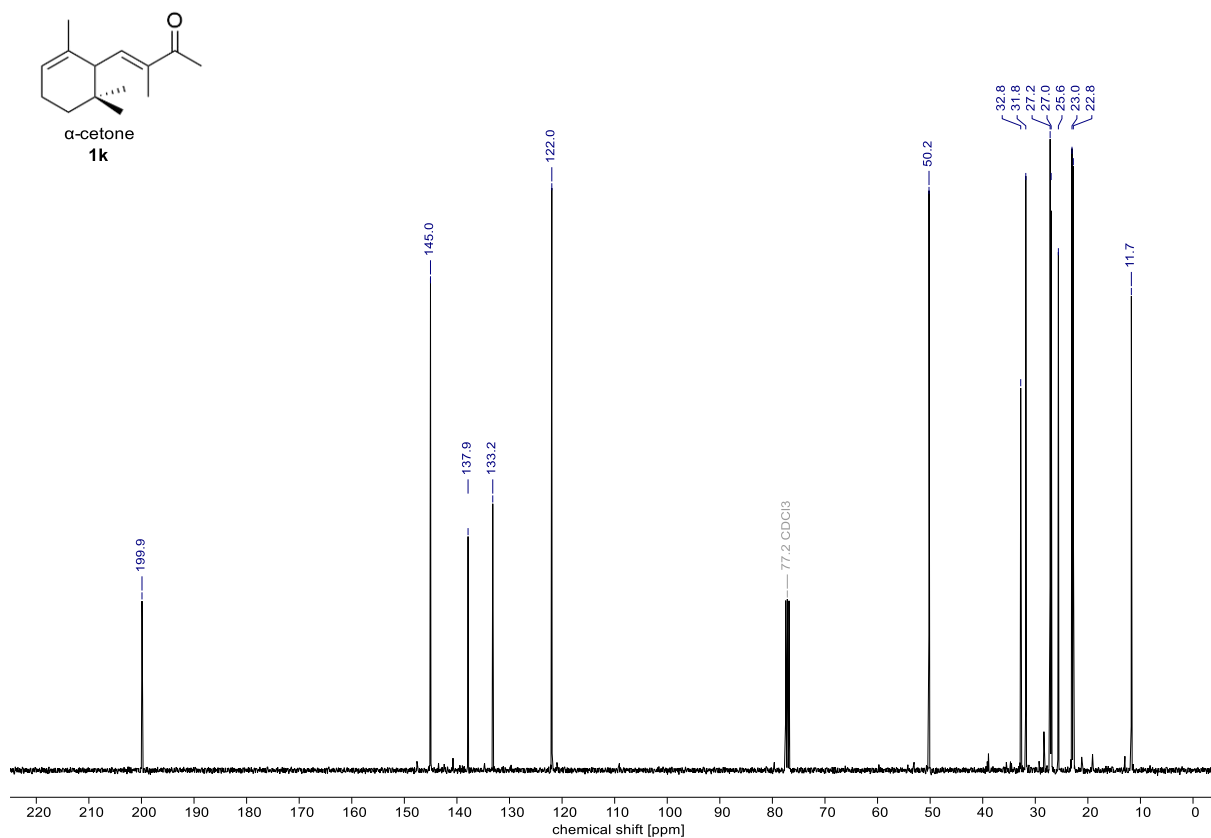
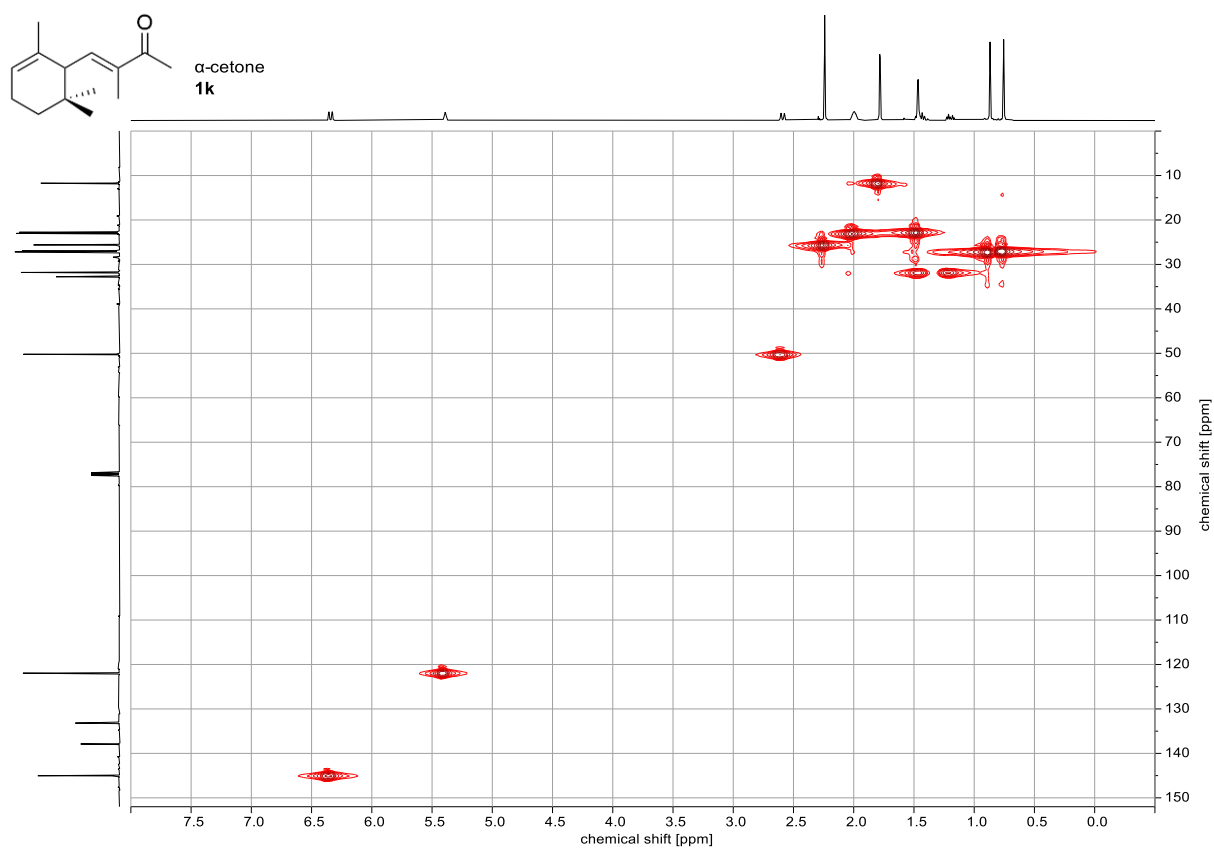
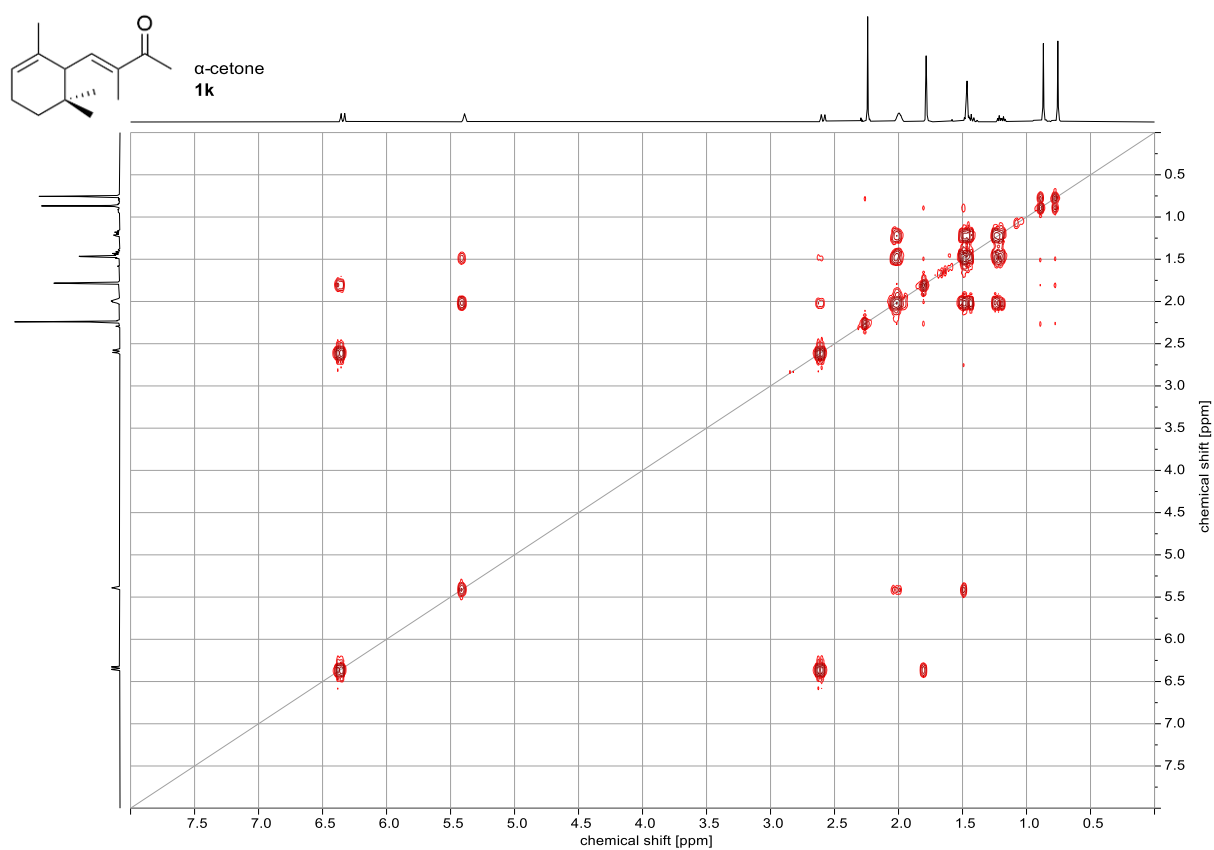


Figure S194. HMBC spectrum of starting material **1j**: β -damascone.

10.13. α -CetoneFigure S195. ^1H NMR spectrum (400 MHz) of starting material **1k**: α -cetone.Figure S196. ^{13}C NMR spectrum (101 MHz) of starting material **1k**: α -cetone.



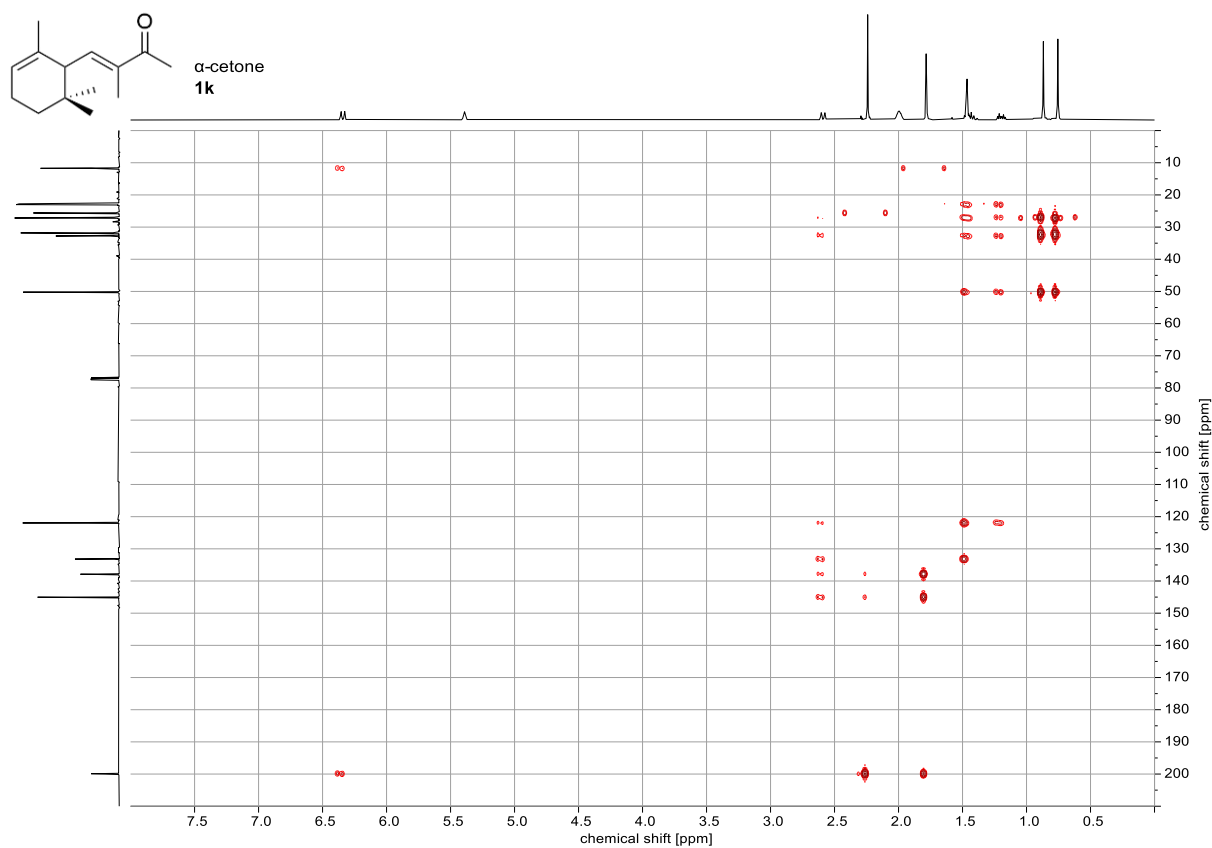
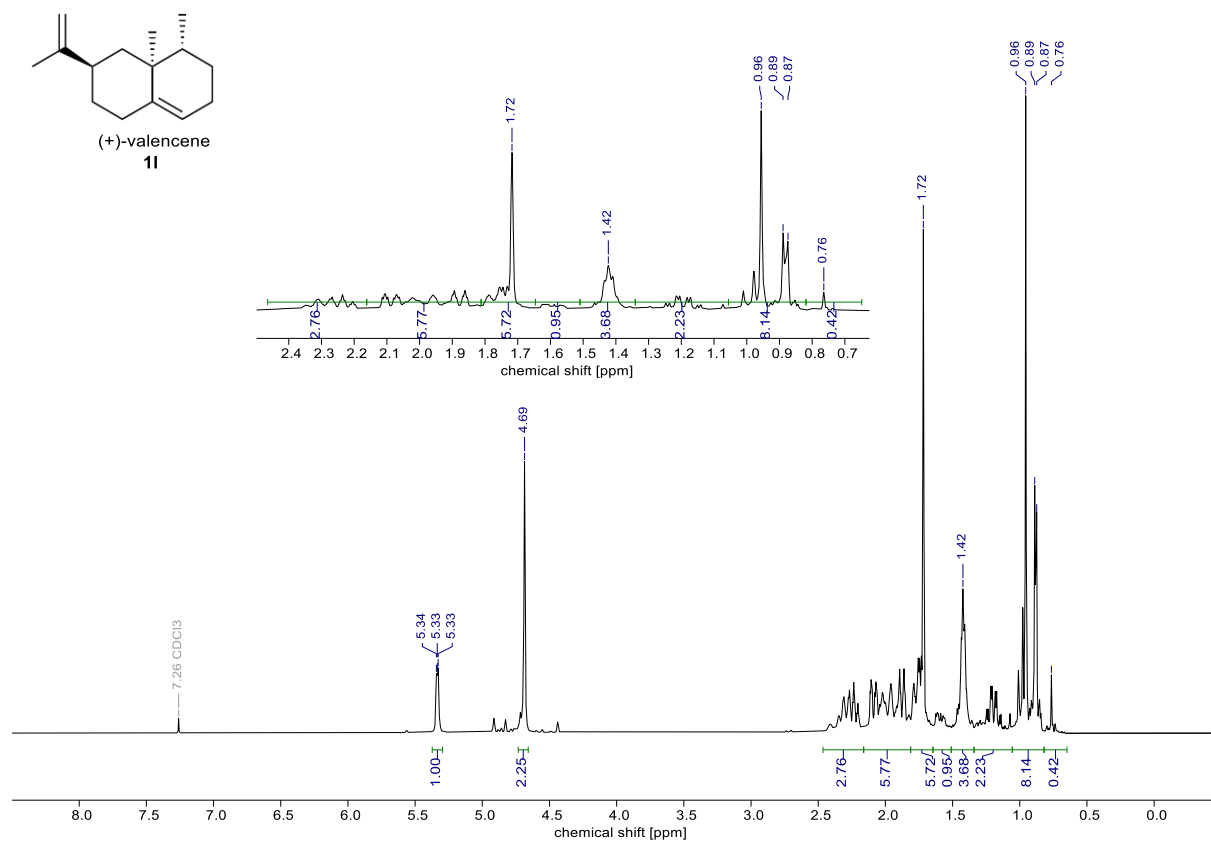


Figure S199. HMBC spectrum starting material 1k: α-cetone.

10.14. (+)-Valencene

Figure S200. ^1H NMR spectrum (400 MHz) of starting material 1l: (+)-valencene.

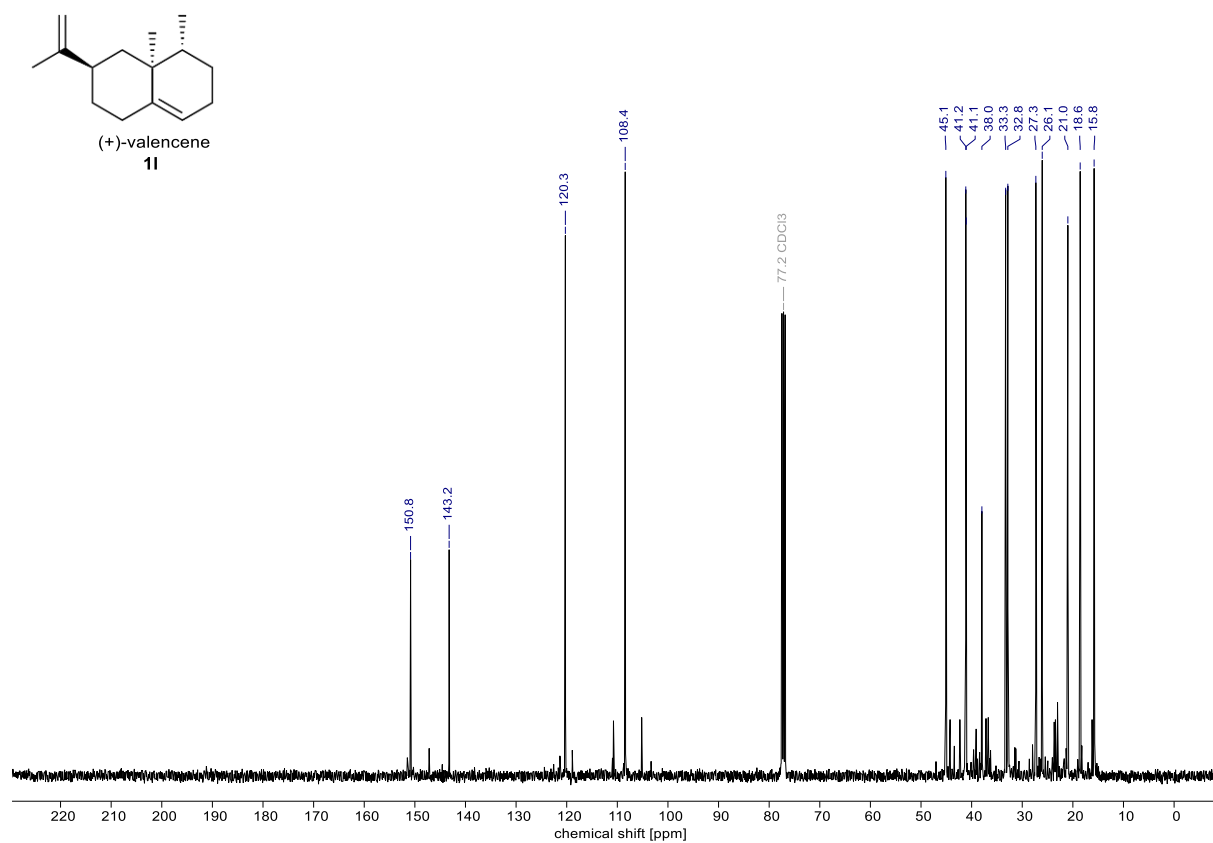


Figure S201. ¹³C NMR spectrum (101 MHz) of starting material 1I: (+)-valencene.

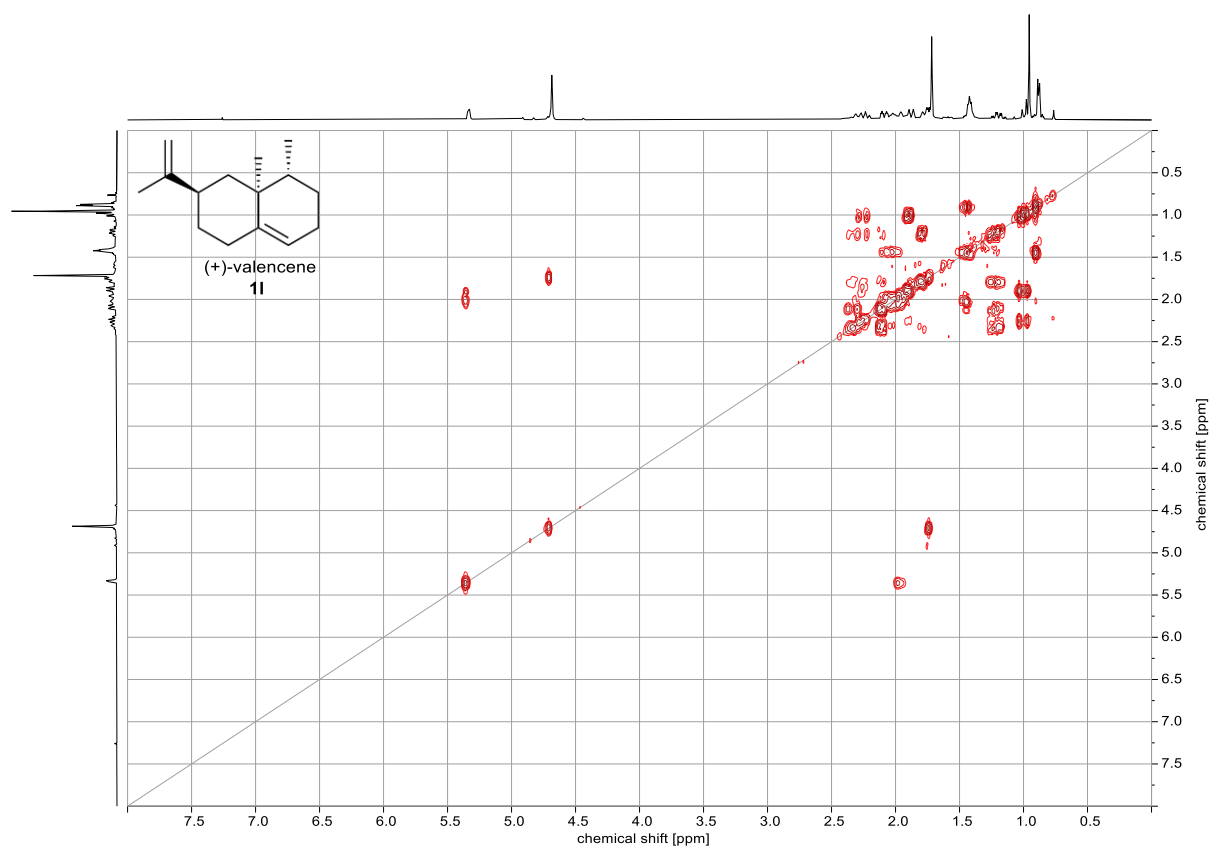


Figure S202. COSY spectrum of starting material 1I: (+)-valencene.

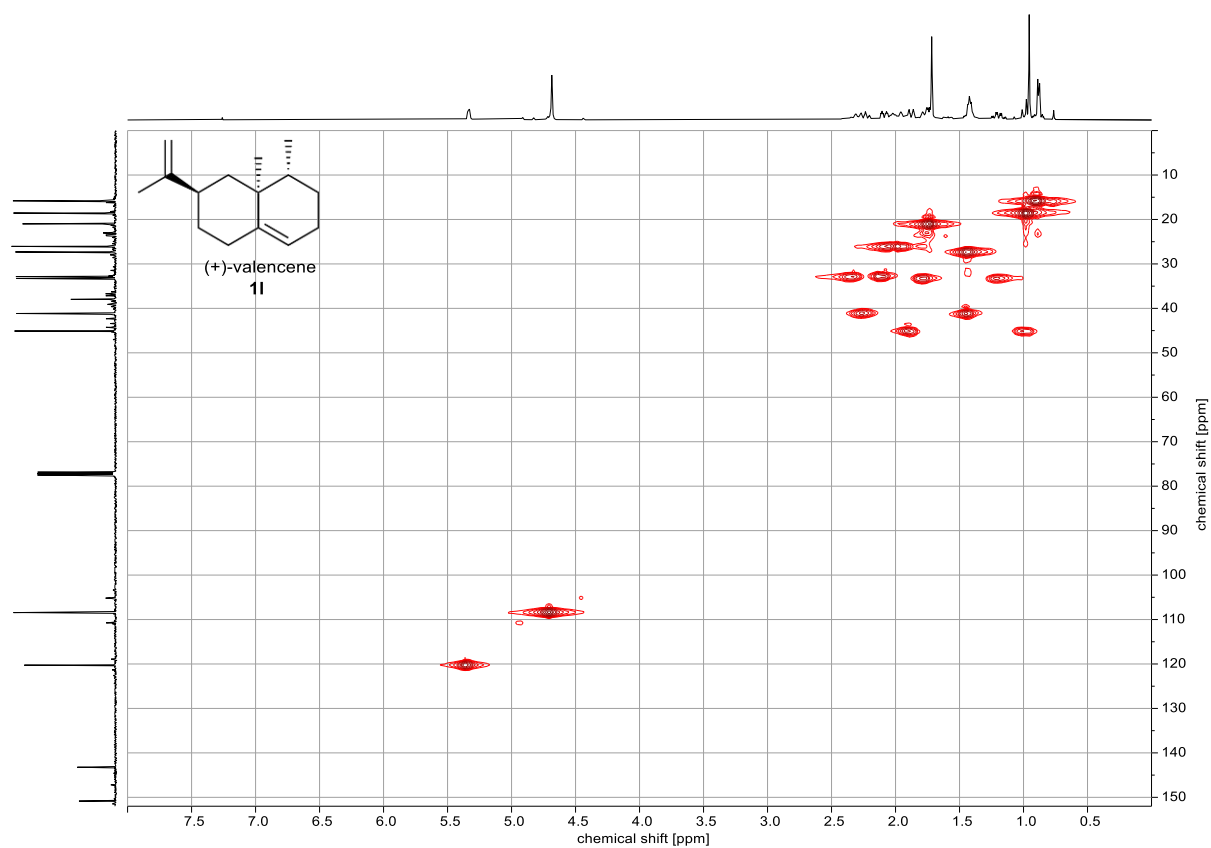


Figure S203. HSQC spectrum of starting material 1I: (+)-valencene.

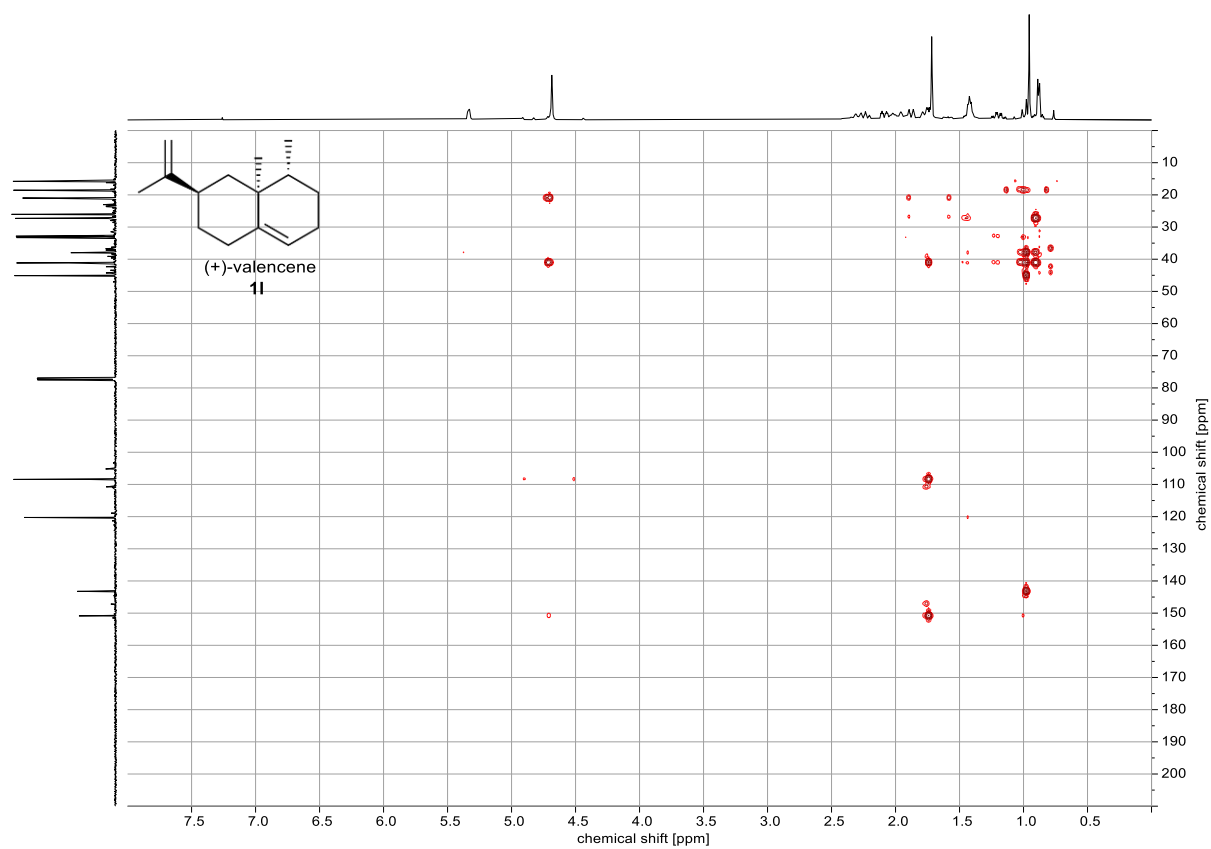
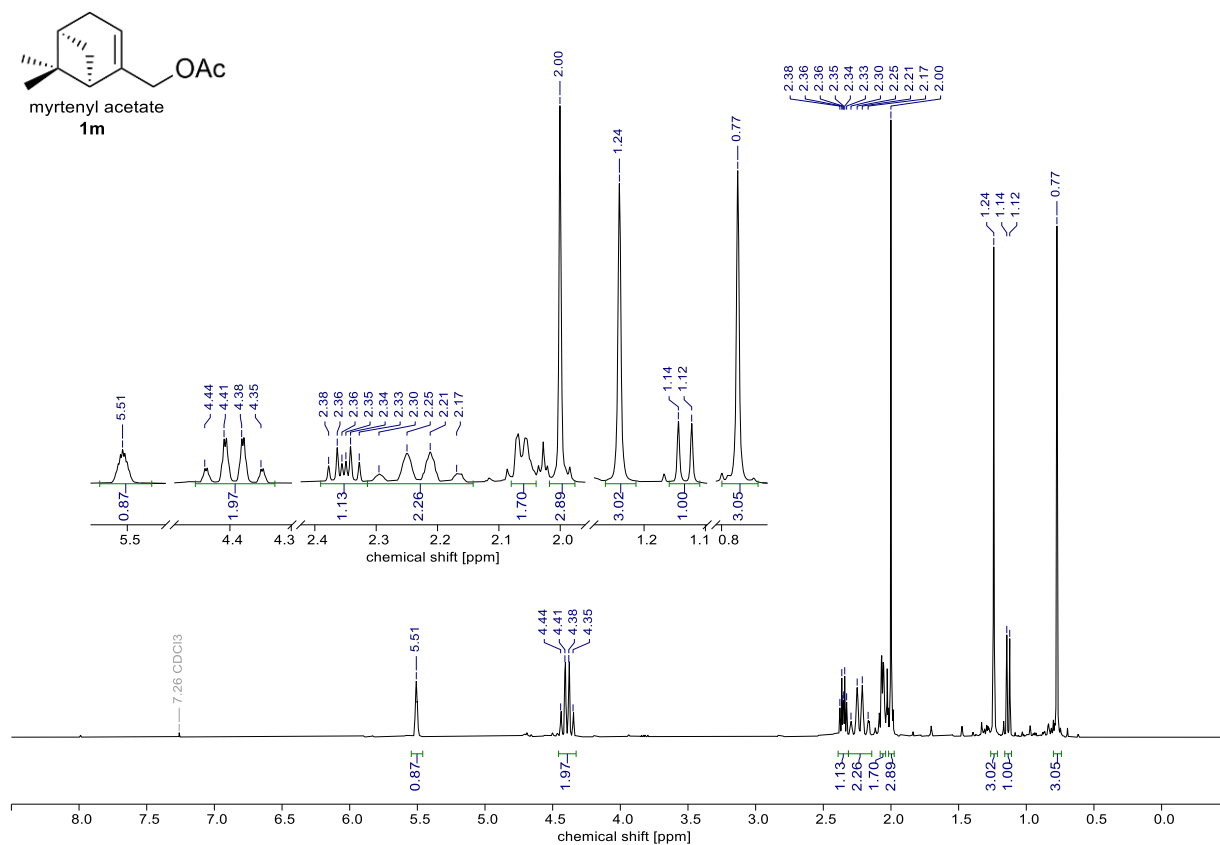
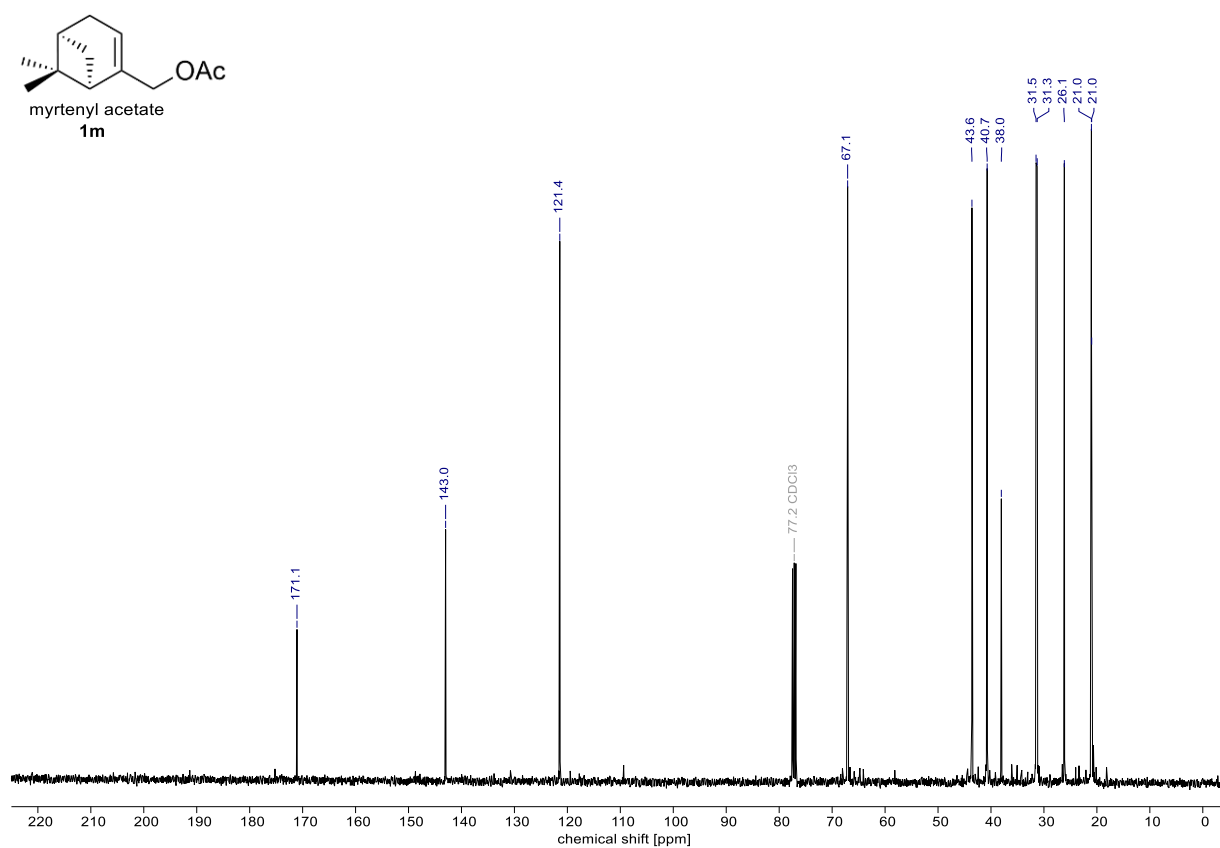


Figure S204. HMBC spectrum of starting material 1I: (+)-valencene.

10.15. Myrtenyl acetate

Figure S205. ¹H NMR spectrum (400 MHz) of starting material **1m**: myrtenyl acetate.Figure S206. ¹³C NMR spectrum (101 MHz) of starting material **1m**: myrtenyl acetate.

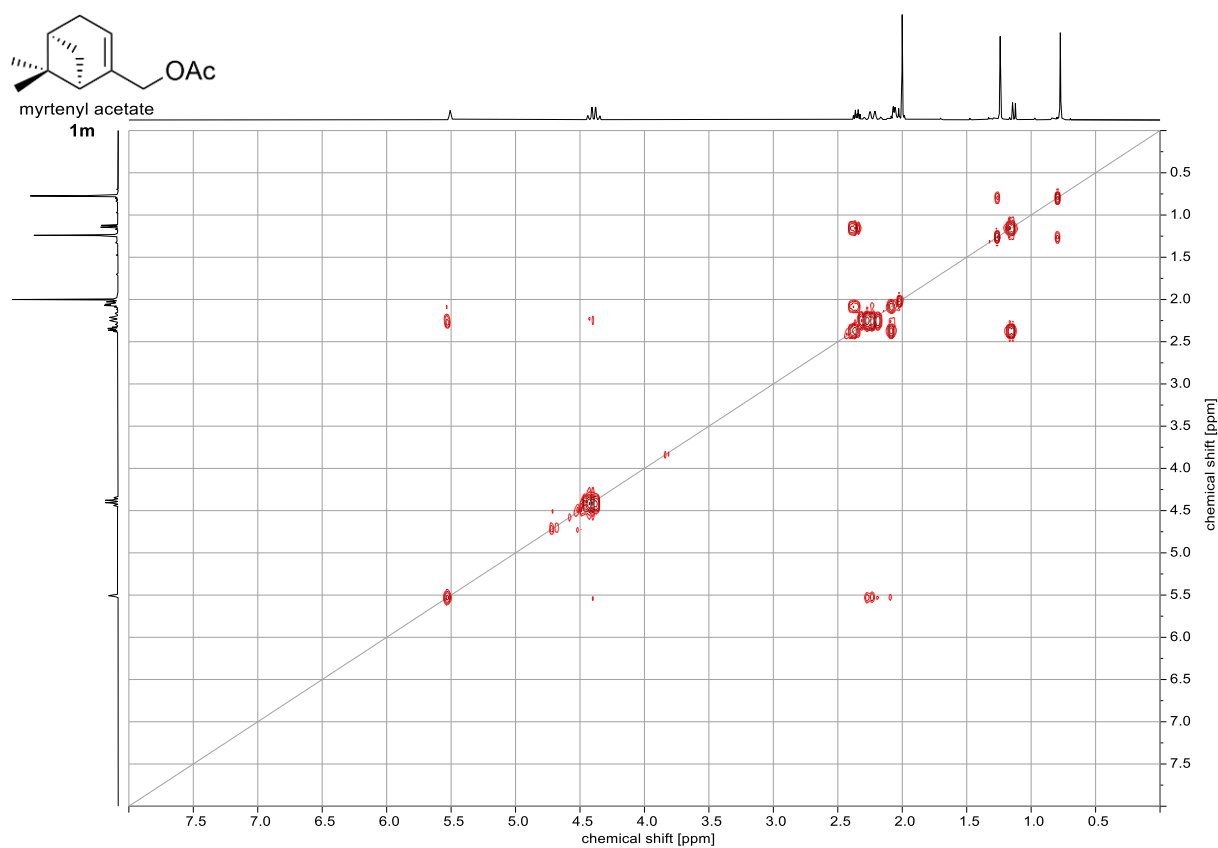


Figure S207. COSY spectrum of starting material **1m**: myrtenyl acetate.

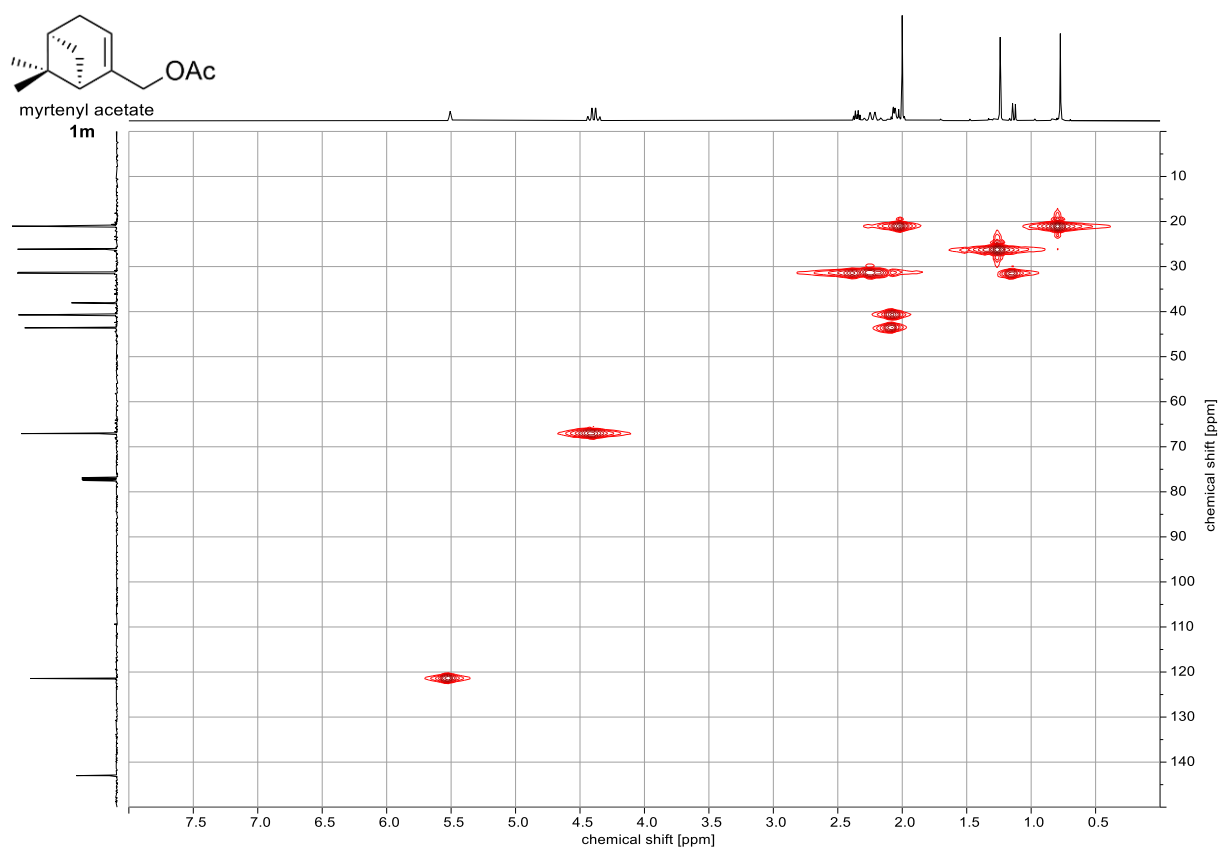


Figure S208. HSQC spectrum of starting material **1m**: myrtenyl acetate.

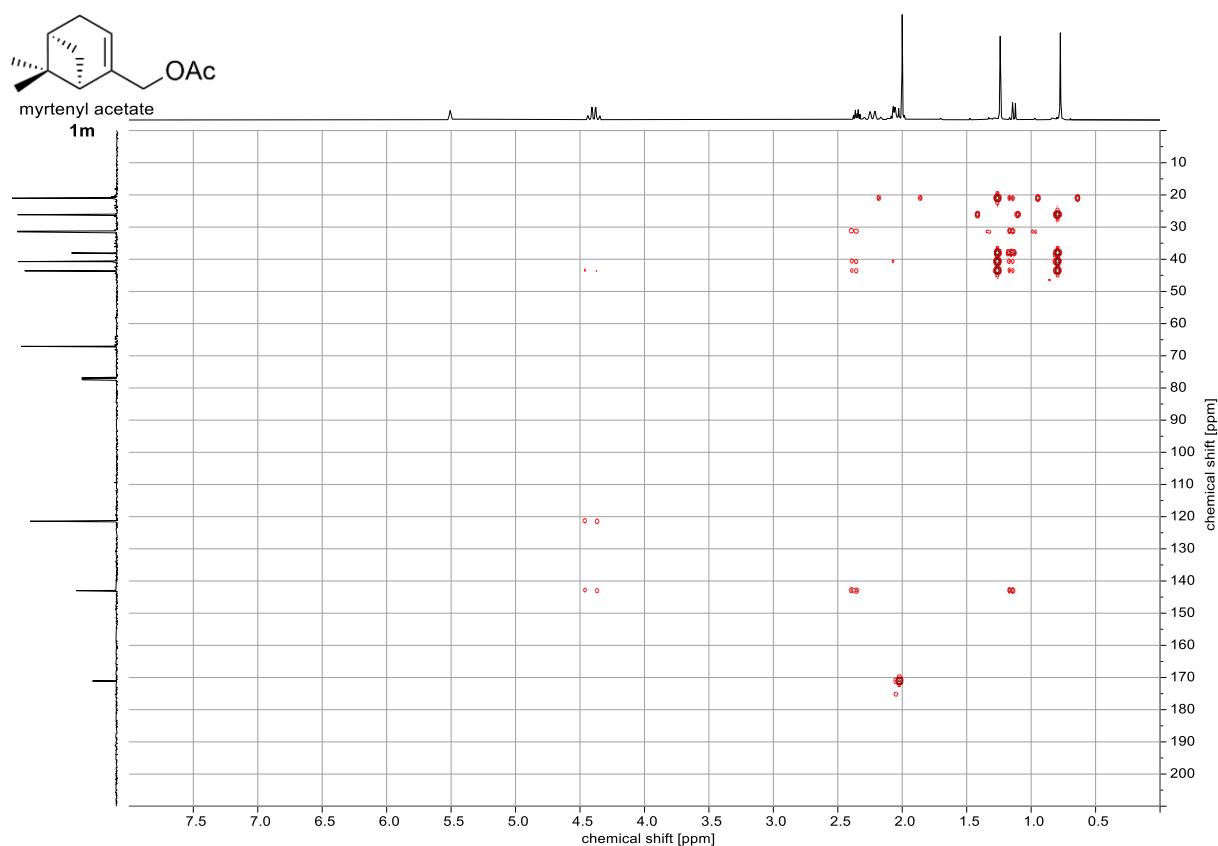
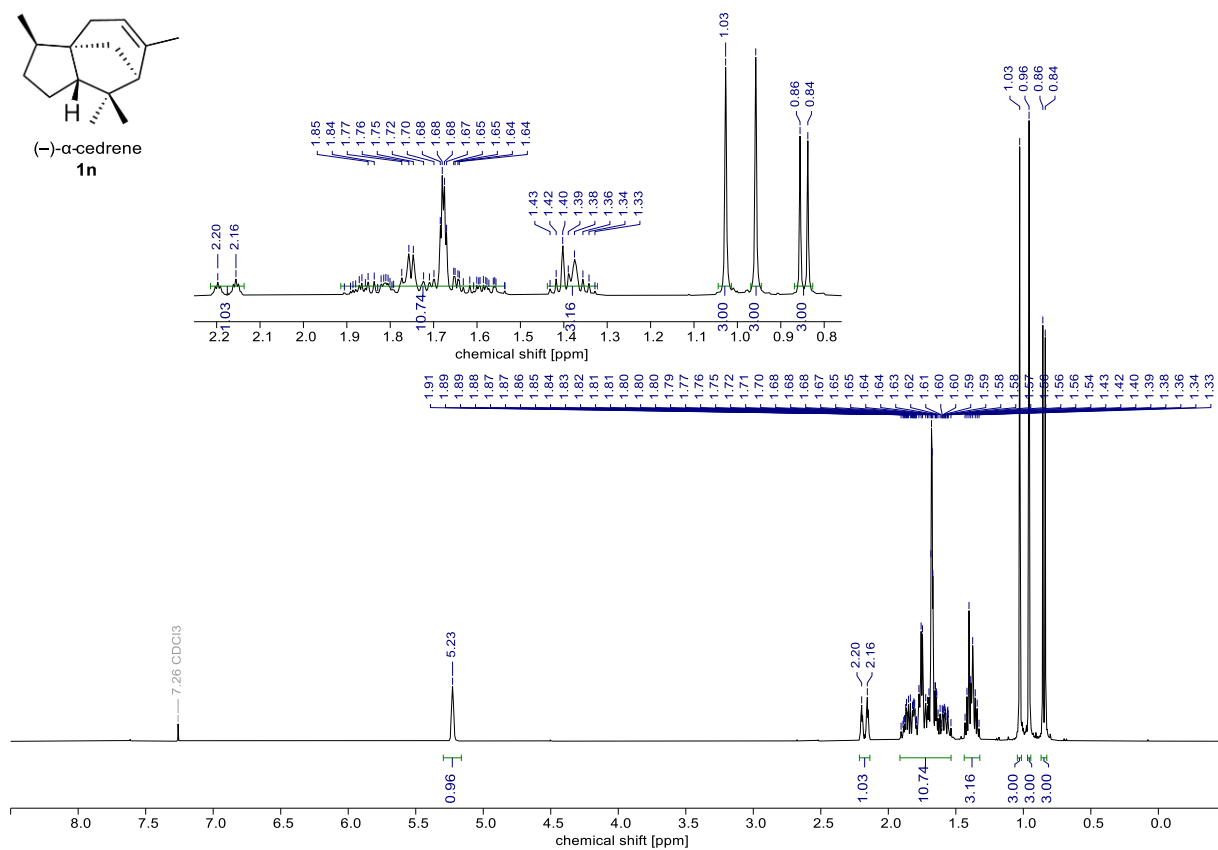


Figure S209. HMBC spectrum of starting material 1m: myrtenyl acetate.

10.16. (–)- α -CedreneFigure S210. ¹H NMR spectrum (400 MHz) of starting material 1n: (–)- α -cedrene.

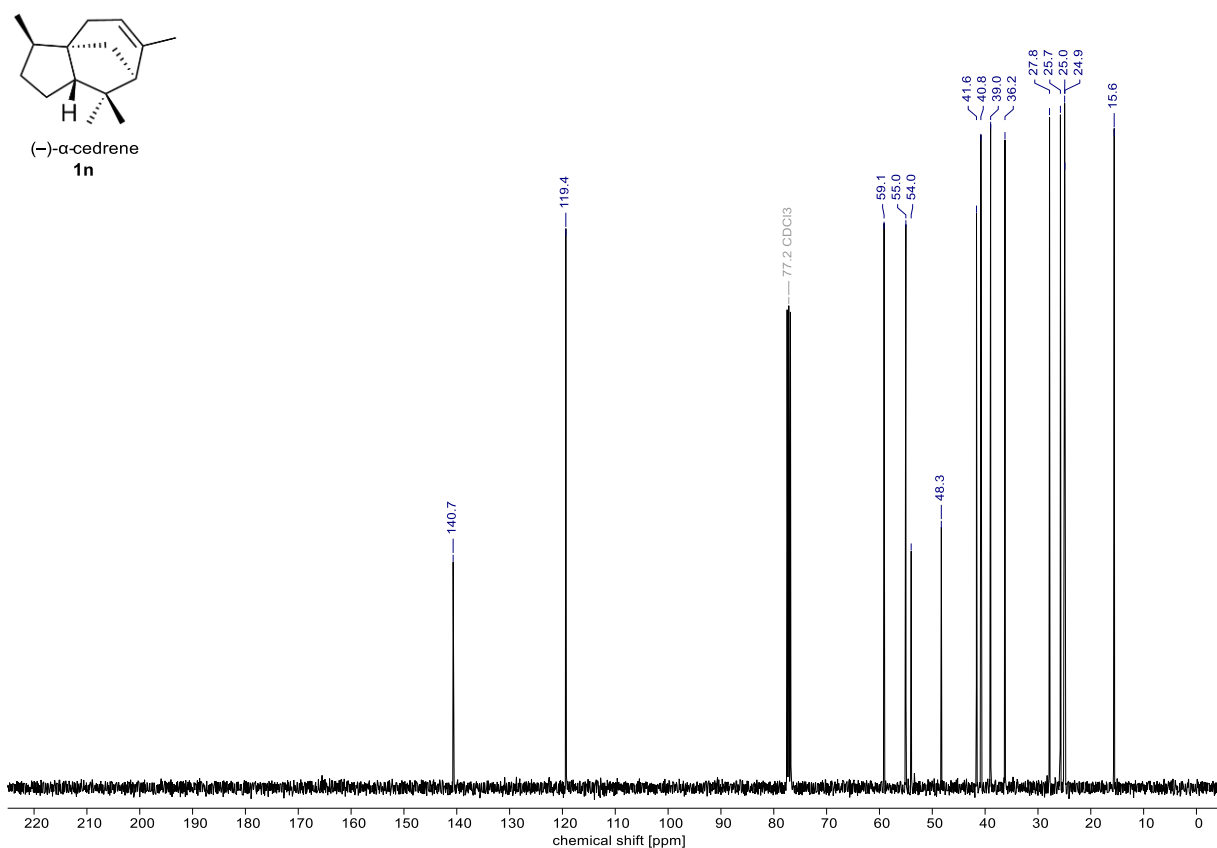


Figure S211. ^{13}C NMR spectrum (101 MHz) of starting material 1n: (-)-α-cedrene.

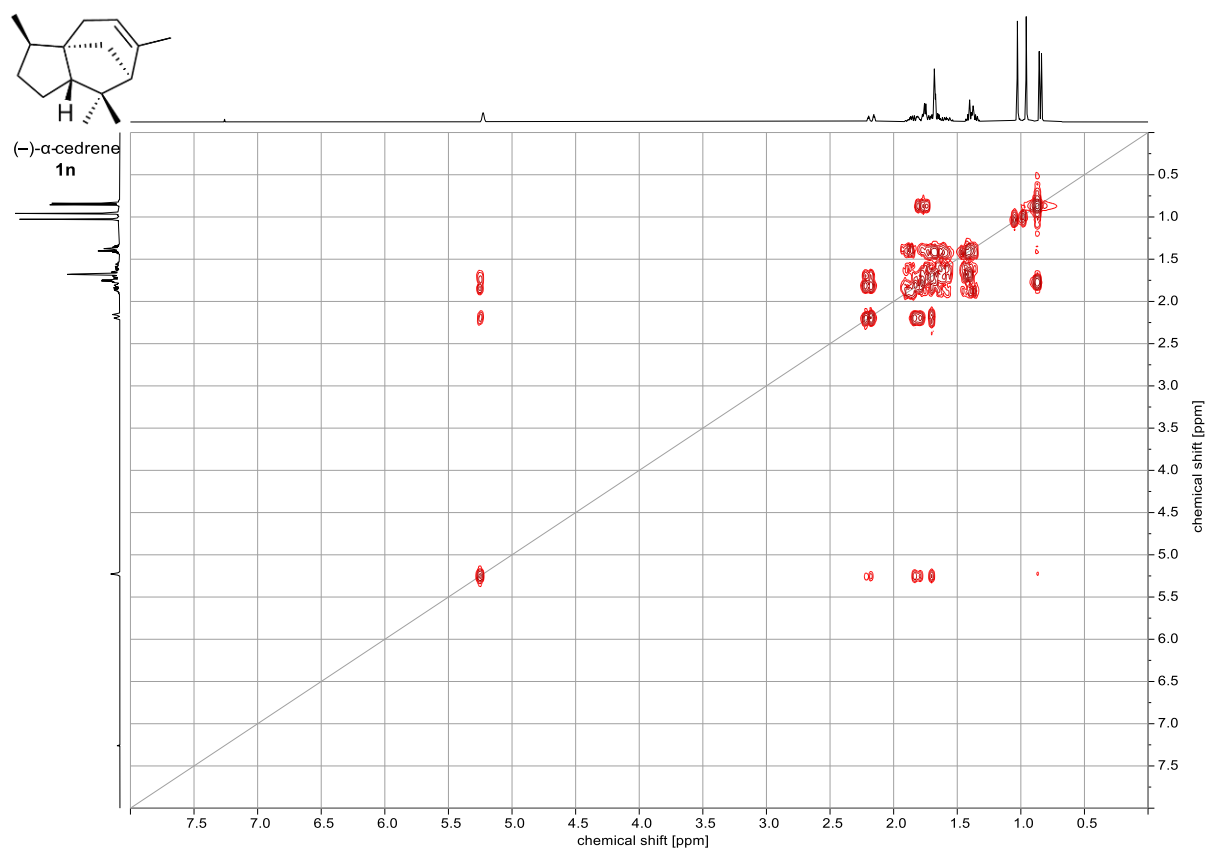


Figure S212. COSY spectrum of starting material 1n: (-)-α-cedrene.

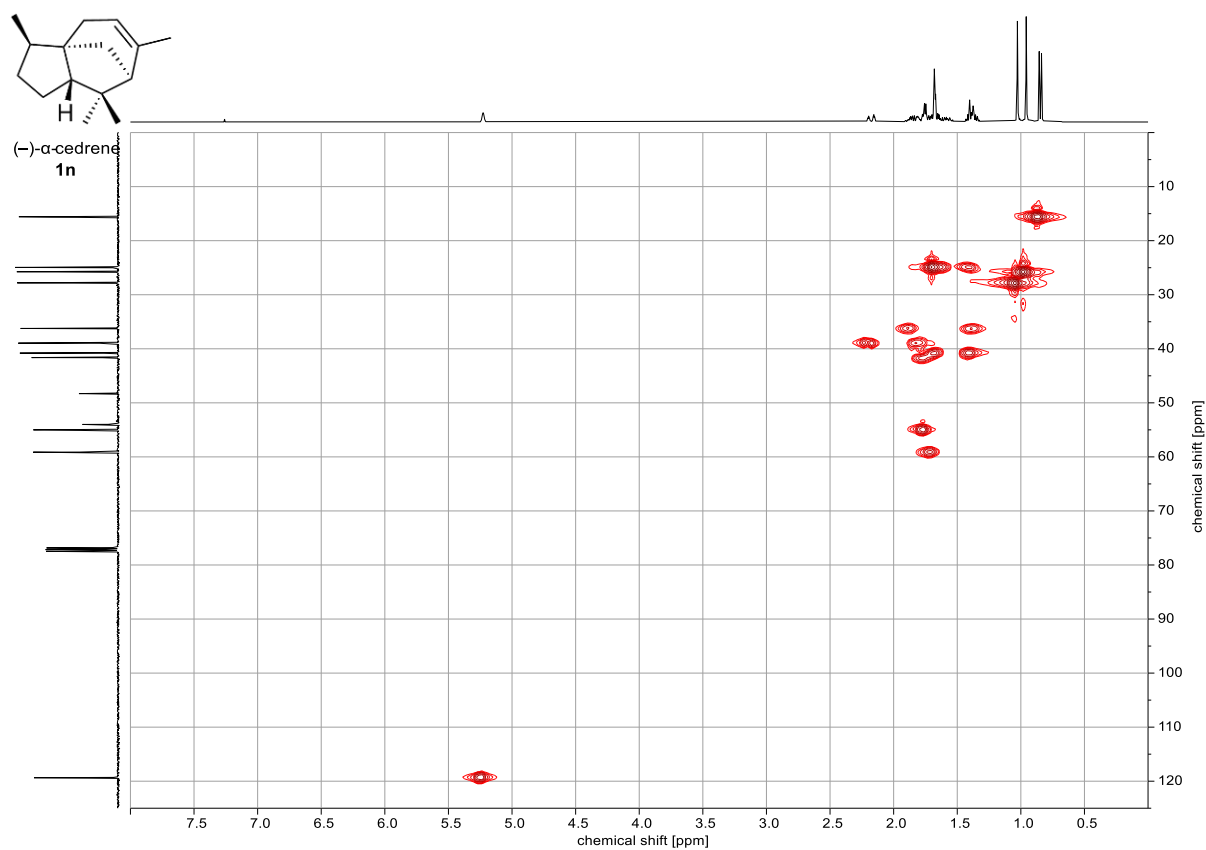


Figure S213. HSQC spectrum of starting material **1n**: (-)-α-cedrene.

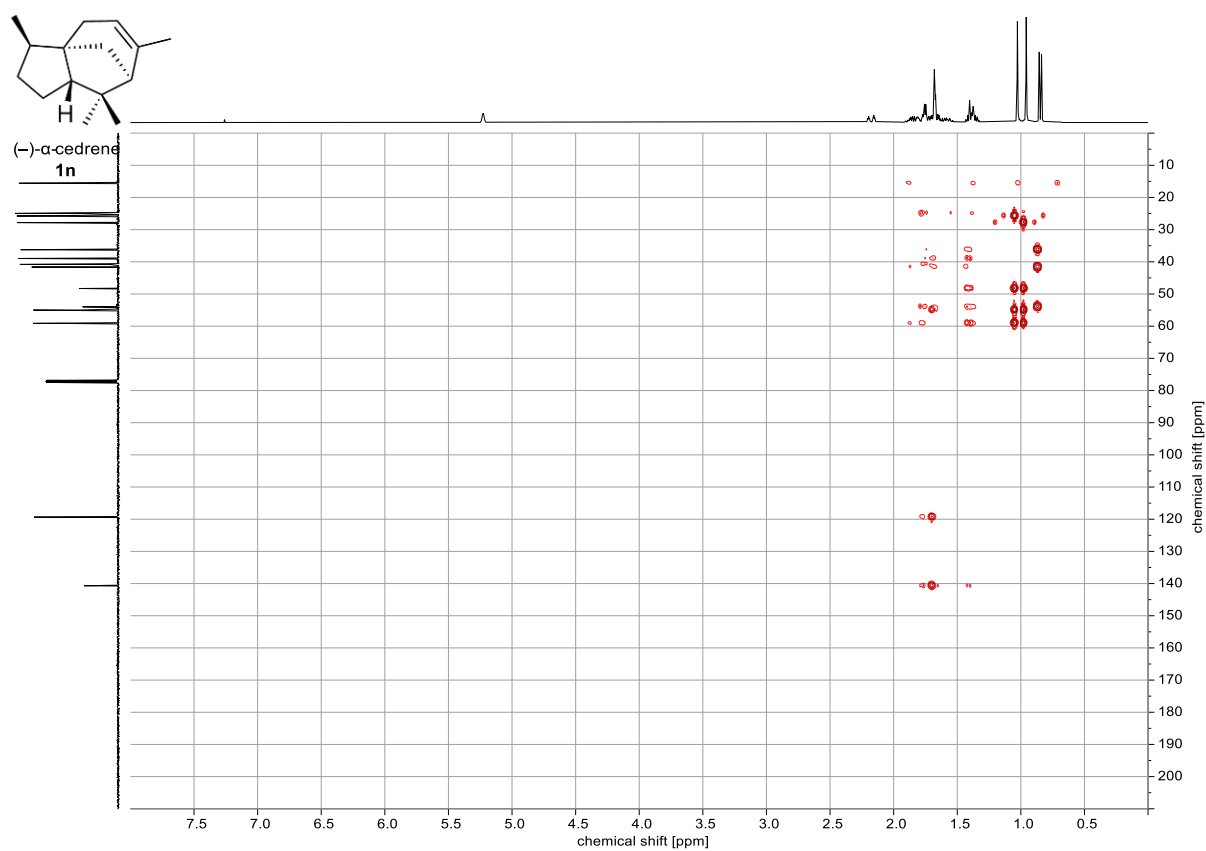
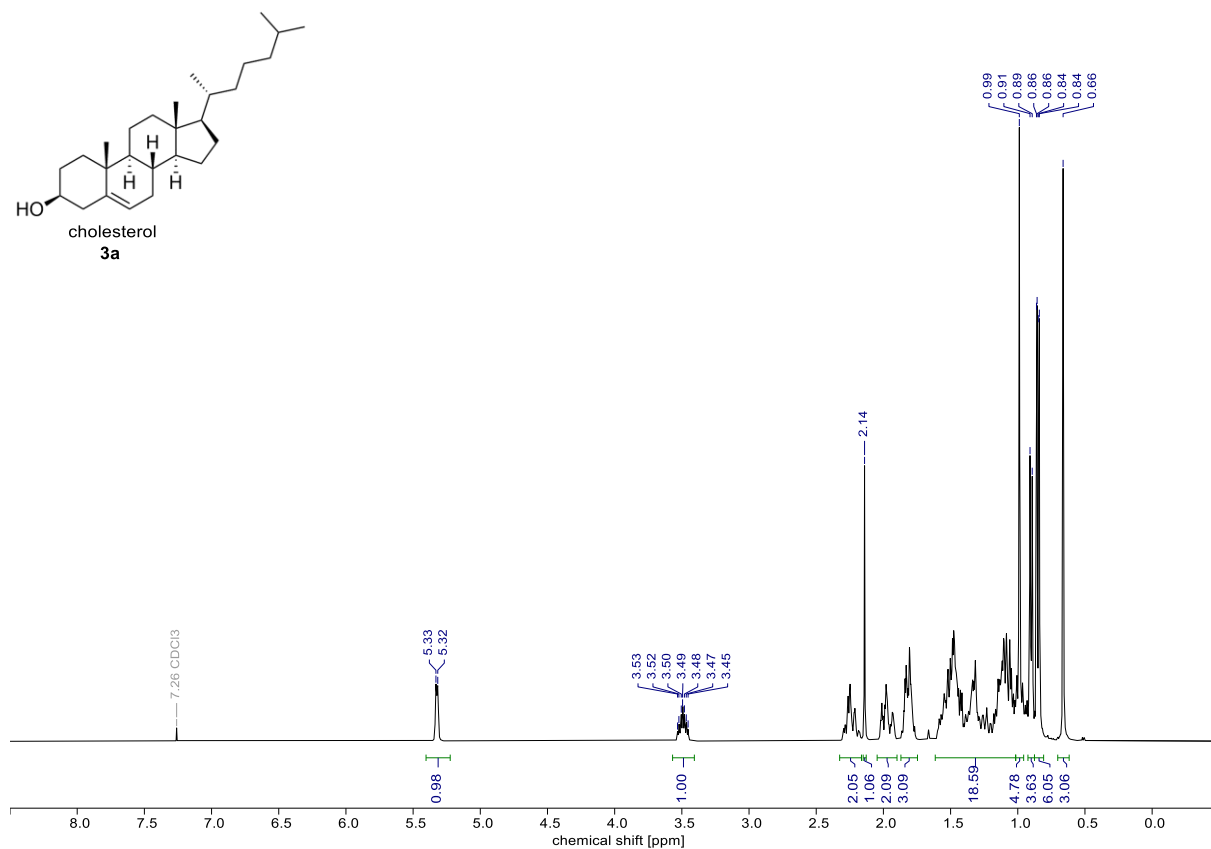
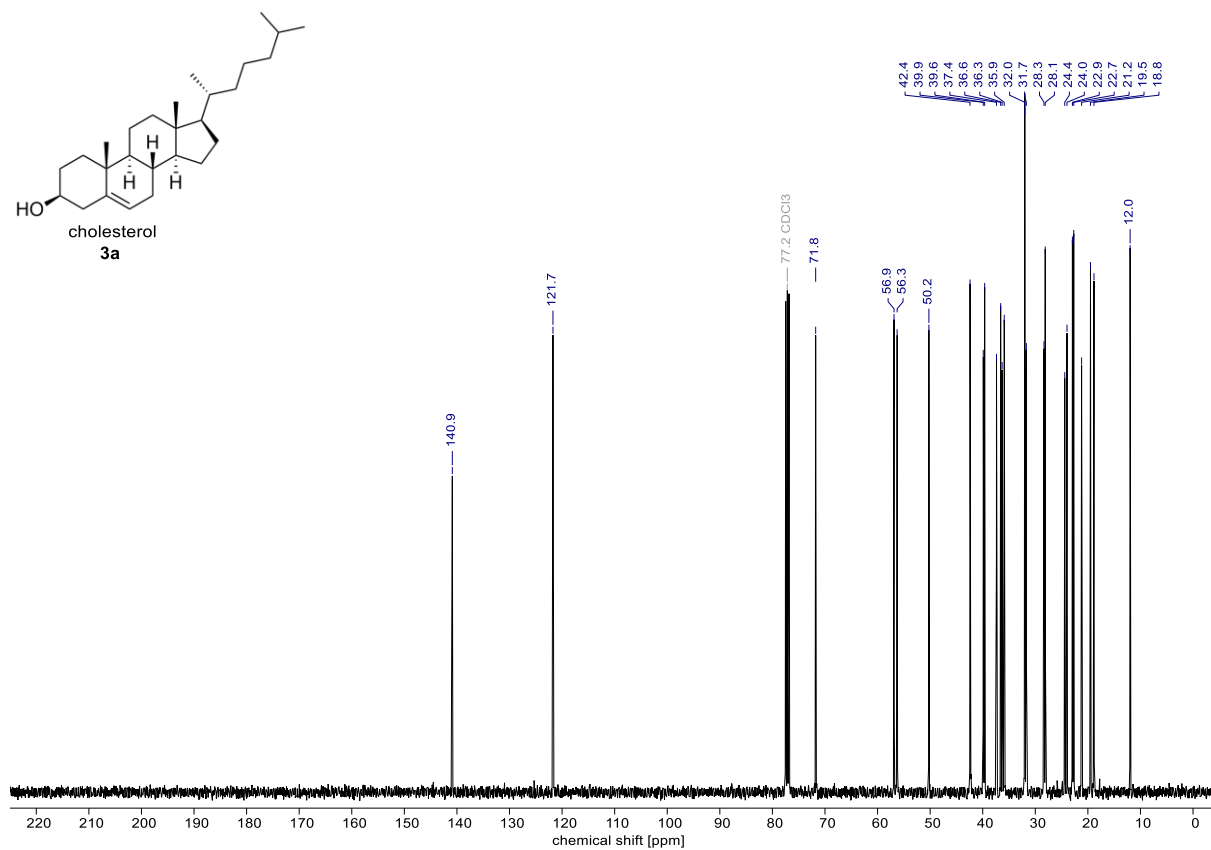


Figure S214. HMBC spectrum of starting material **1n**: (-)-α-cedrene.

10.17. Cholesterol

Figure S215. ¹H NMR spectrum (400 MHz) of starting material **3a**: cholesterol.Figure S216. ¹³C NMR spectrum (101 MHz) of starting material **3a**: cholesterol.

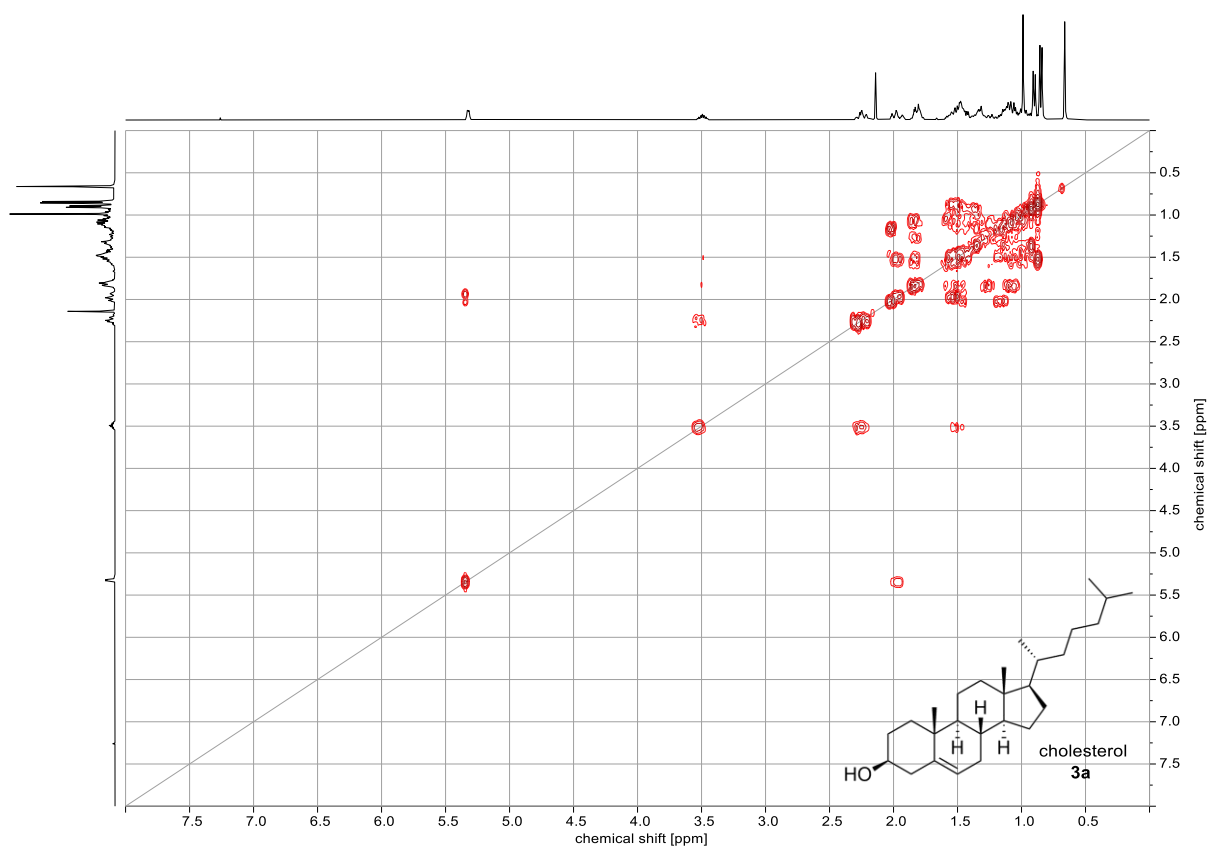


Figure S217. COSY spectrum of starting material **3a**: cholesterol.

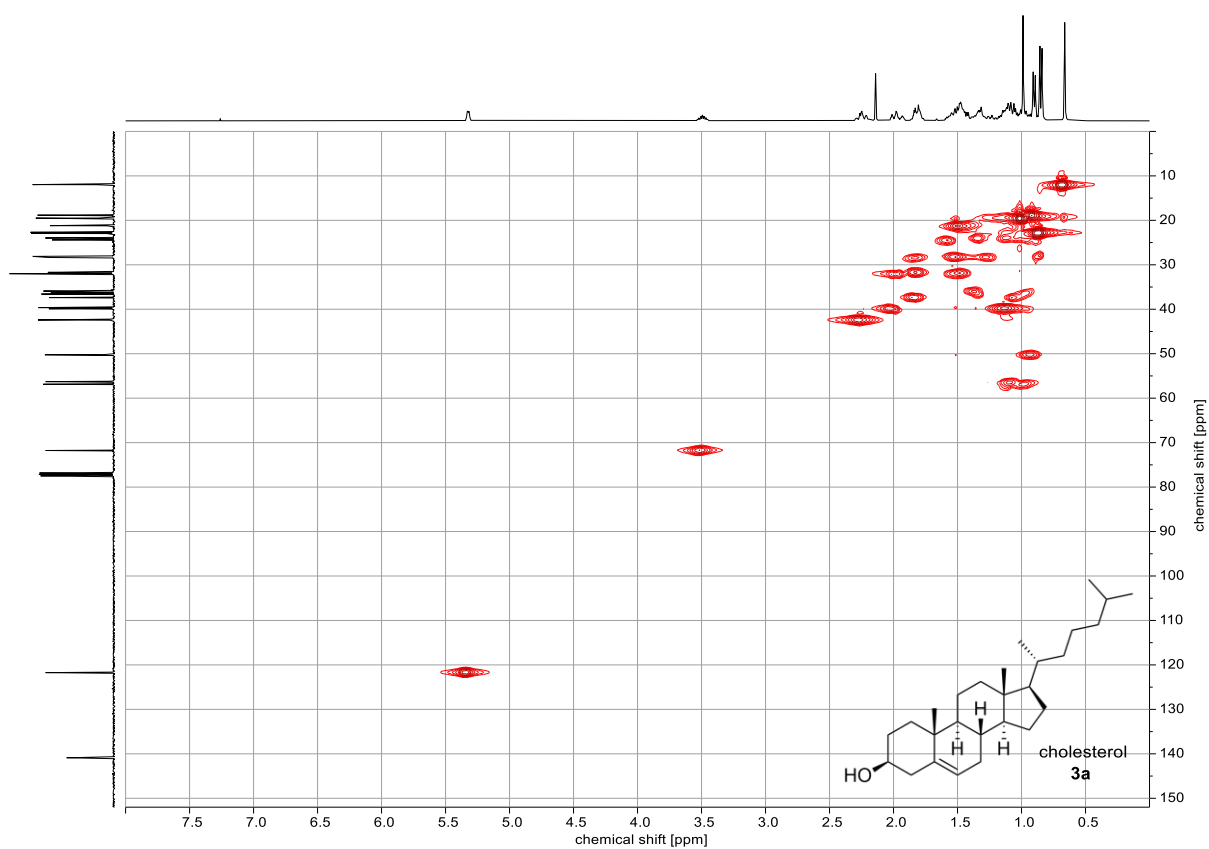


Figure S218. HSQC spectrum of starting material **3a**: cholesterol.

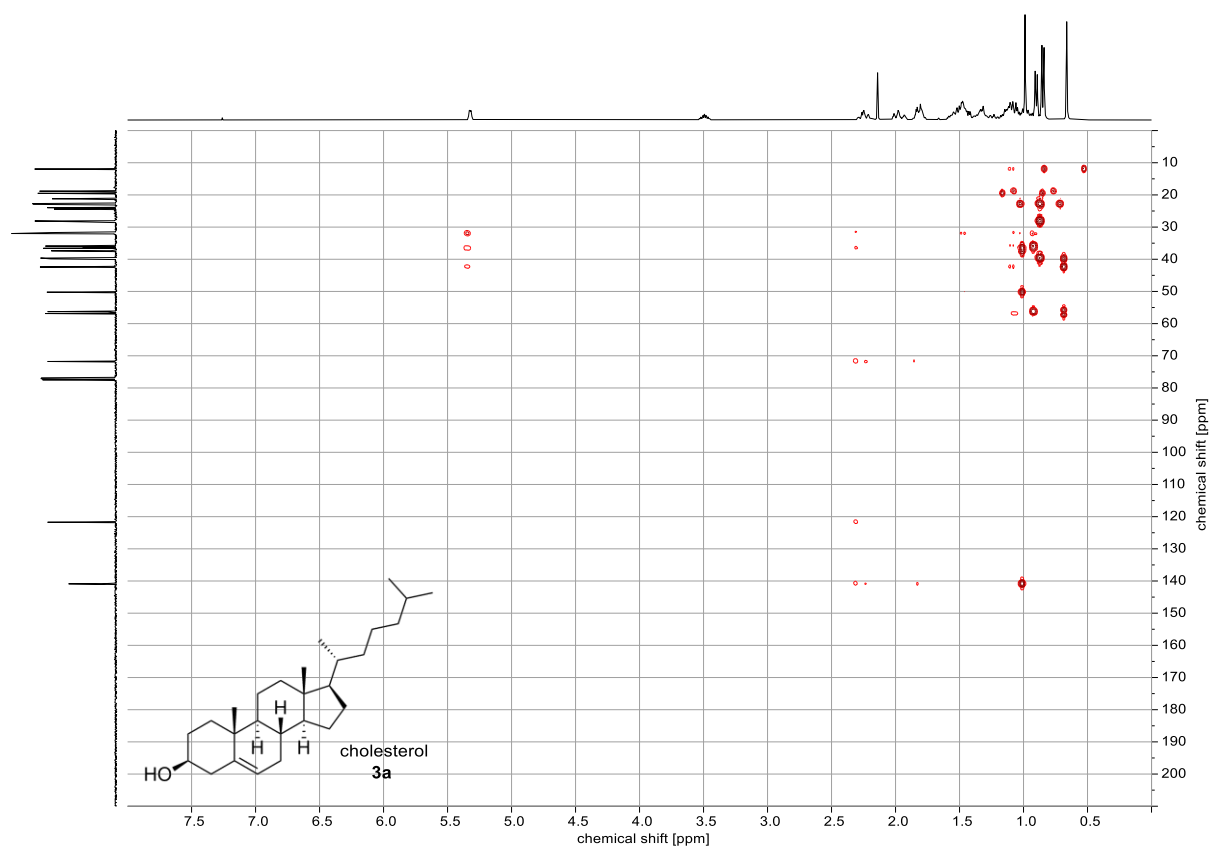


Figure S219. HMBC spectrum of starting material **3a**: cholesterol.

10.18. Cholesteryl acetate

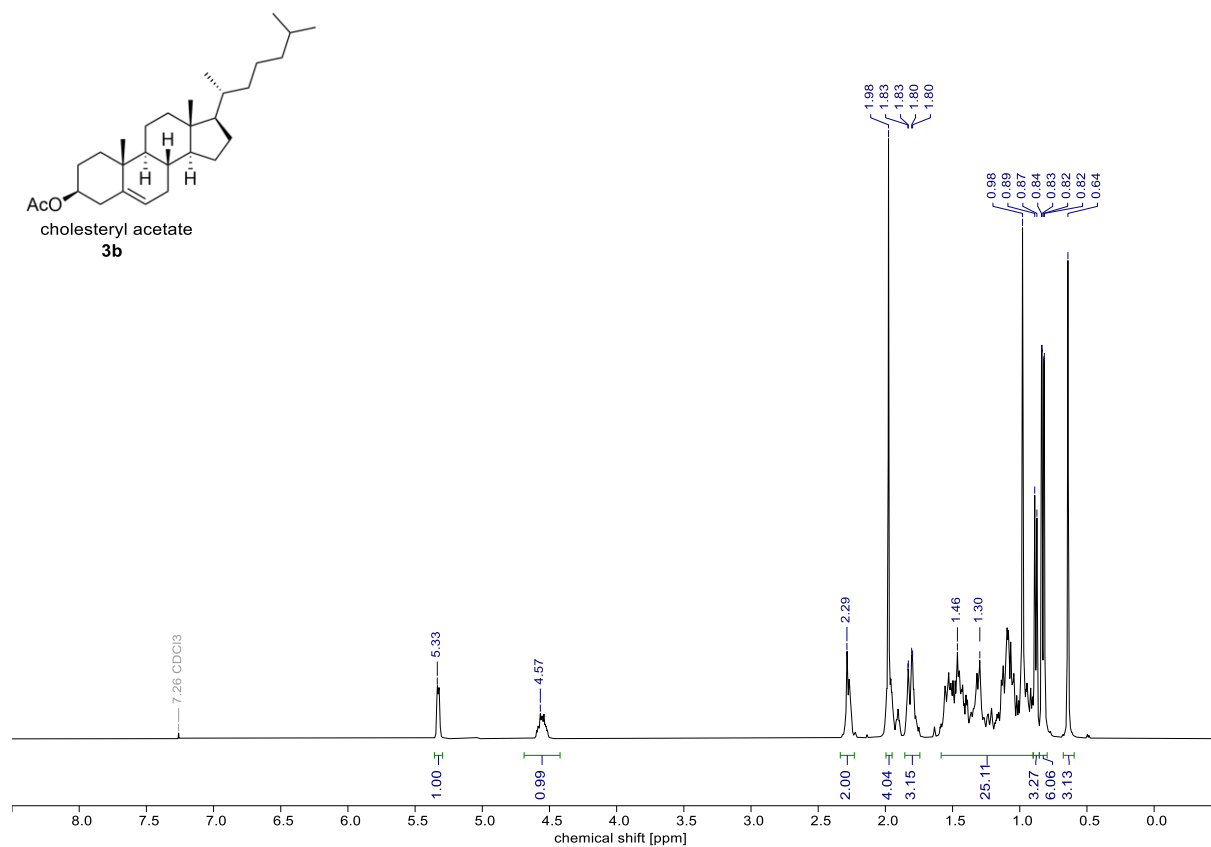


Figure S220. ^1H NMR spectrum (400 MHz) of starting material **3b**: cholesteryl acetate.

S127

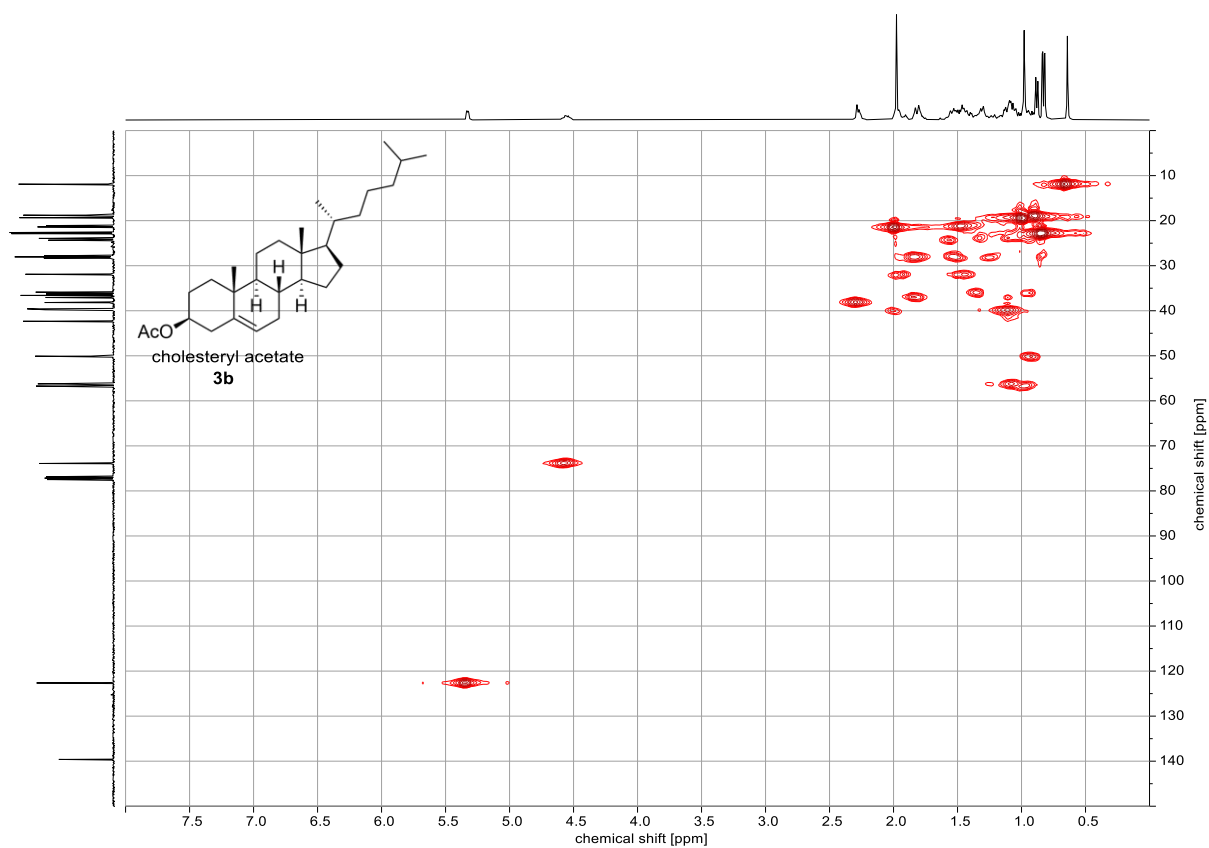


Figure S223. HSQC spectrum of starting material **3b**: cholesteryl acetate.

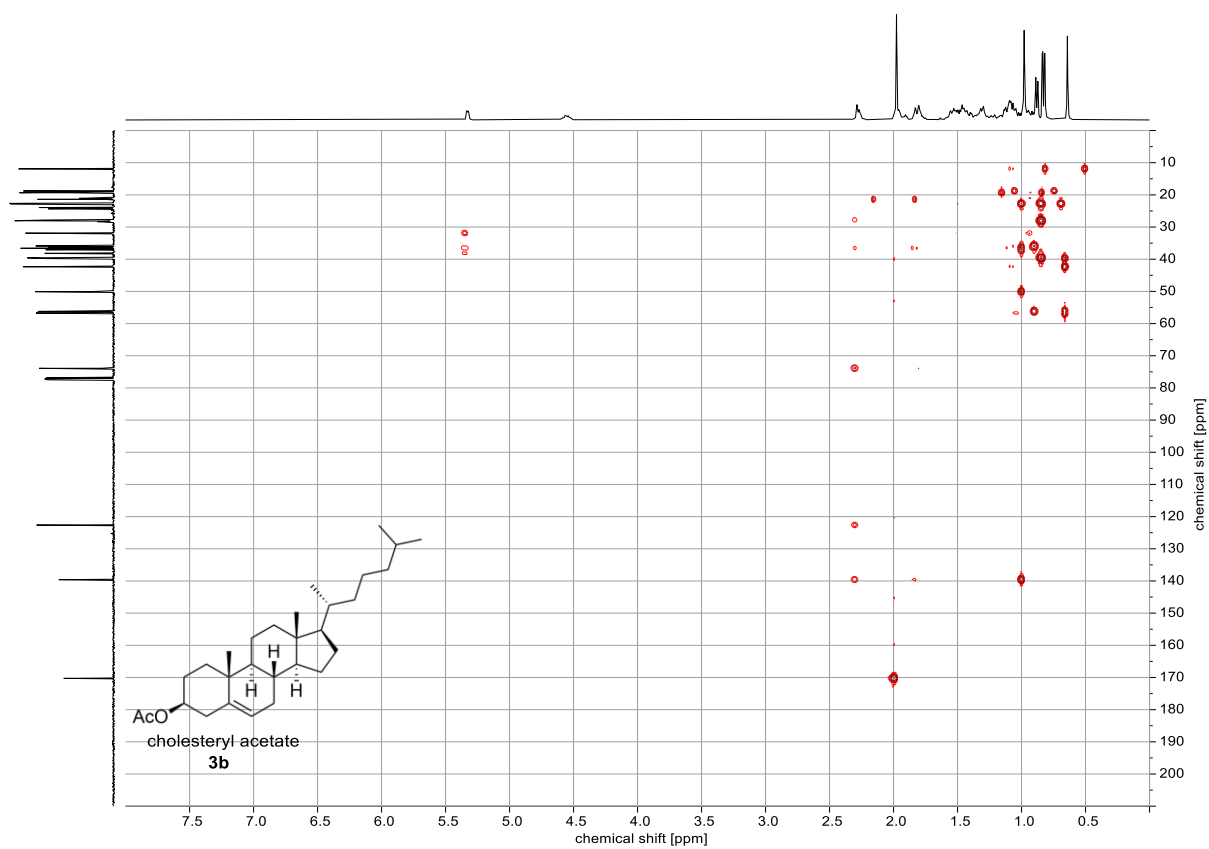
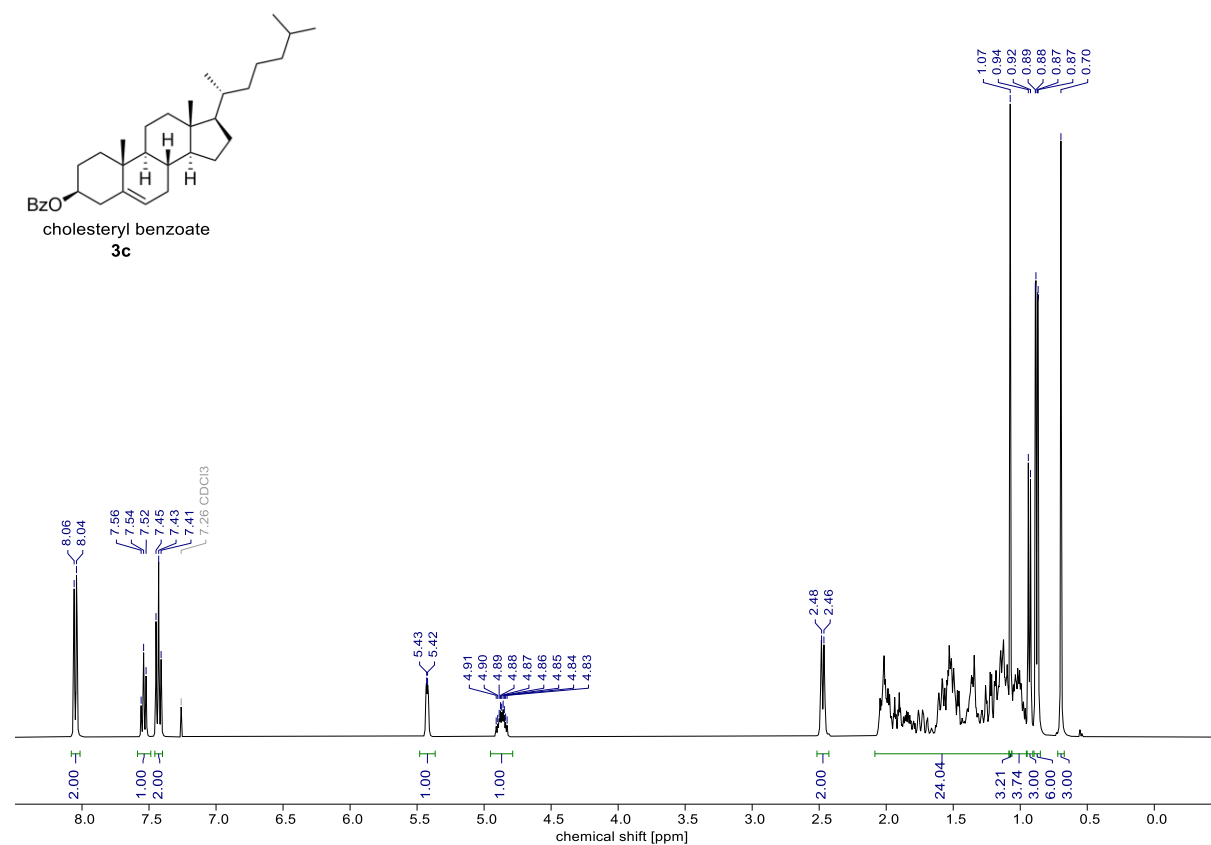
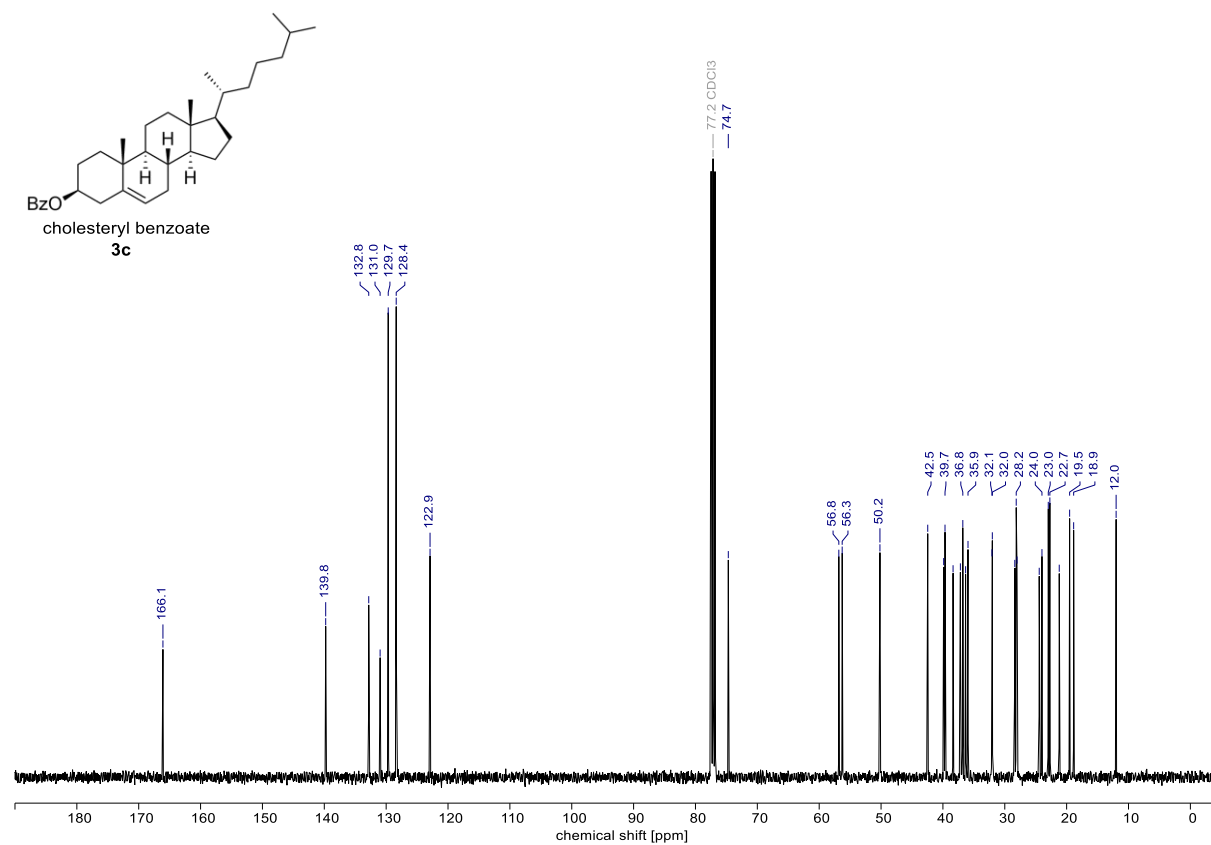


Figure S224. HSQC spectrum of starting material **3b**: cholesteryl acetate.

10.19. Cholesteryl benzoate

Figure S225. ¹H NMR spectrum (400 MHz) of starting material **3c**: cholesteryl benzoate.Figure S226. ¹³C NMR spectrum (101 MHz) of starting material **3c**: cholesteryl benzoate.

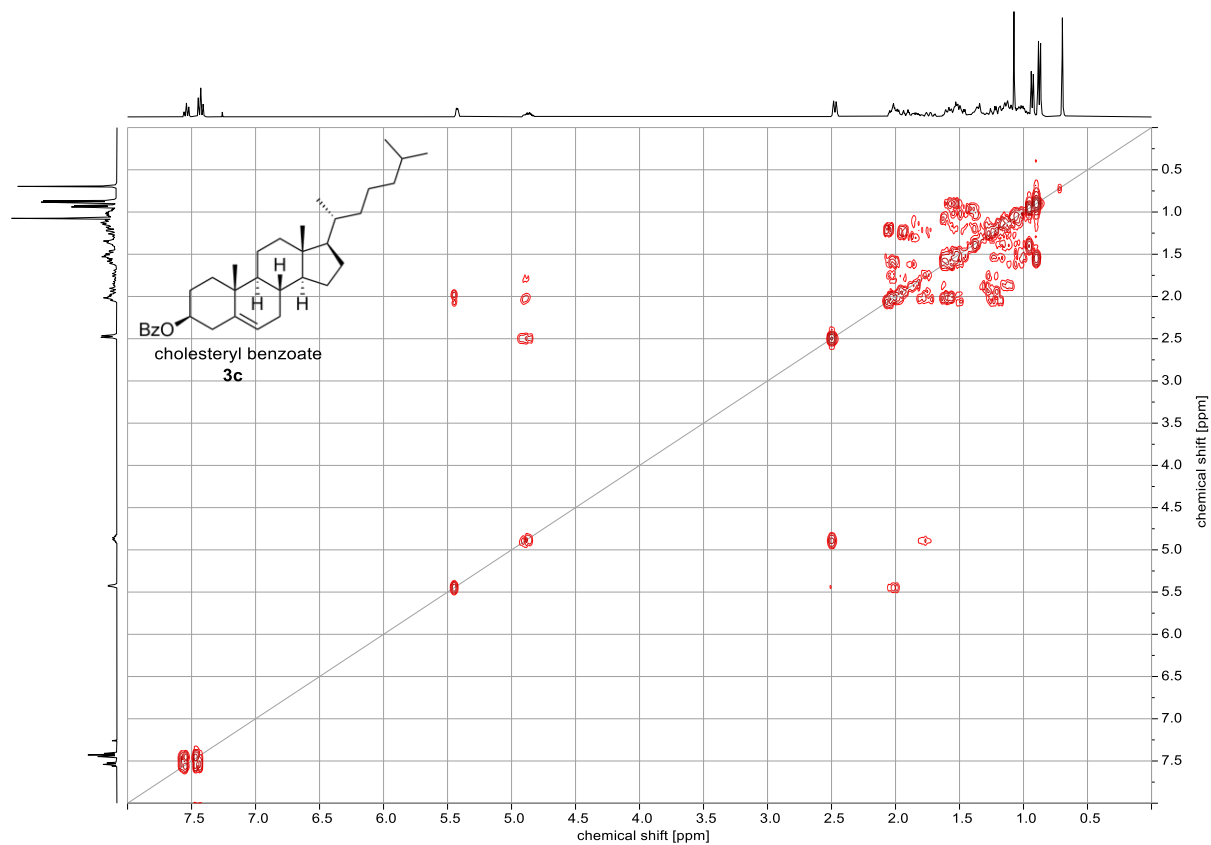


Figure S227. COSY spectrum of starting material **3c**: cholesteryl benzoate.

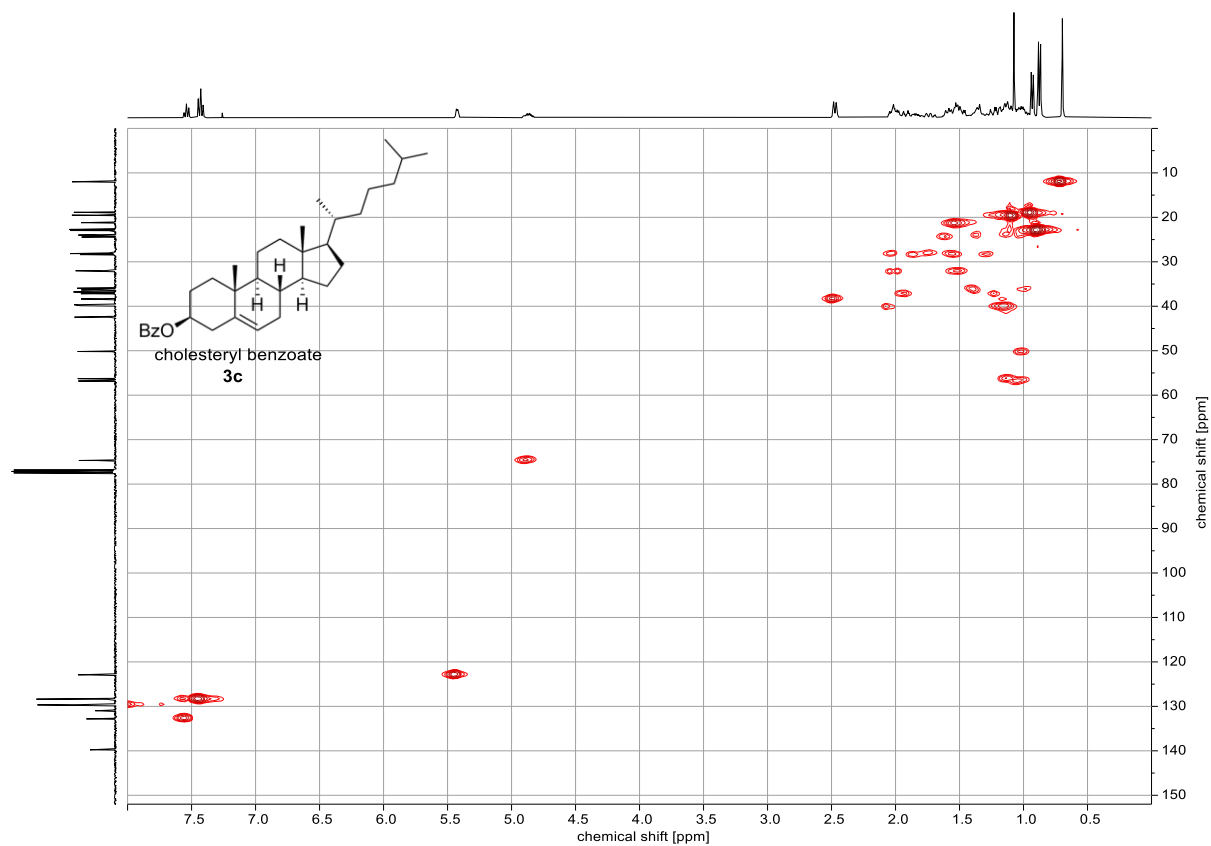


Figure S228. HSQC spectrum of starting material **3c**: cholesteryl benzoate.

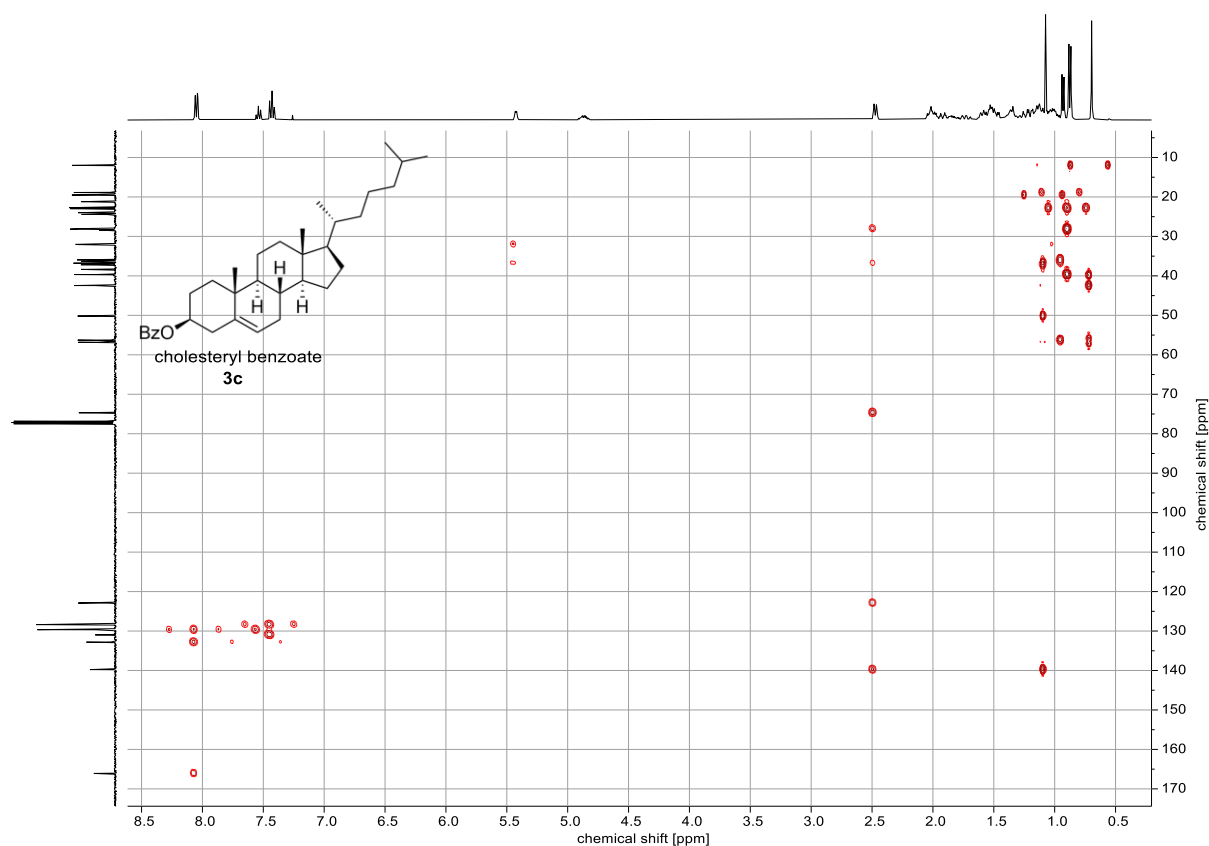


Figure S229. HMBC spectrum of starting material **3c**: cholesteryl benzoate.

10.20. Diosgenin acetate

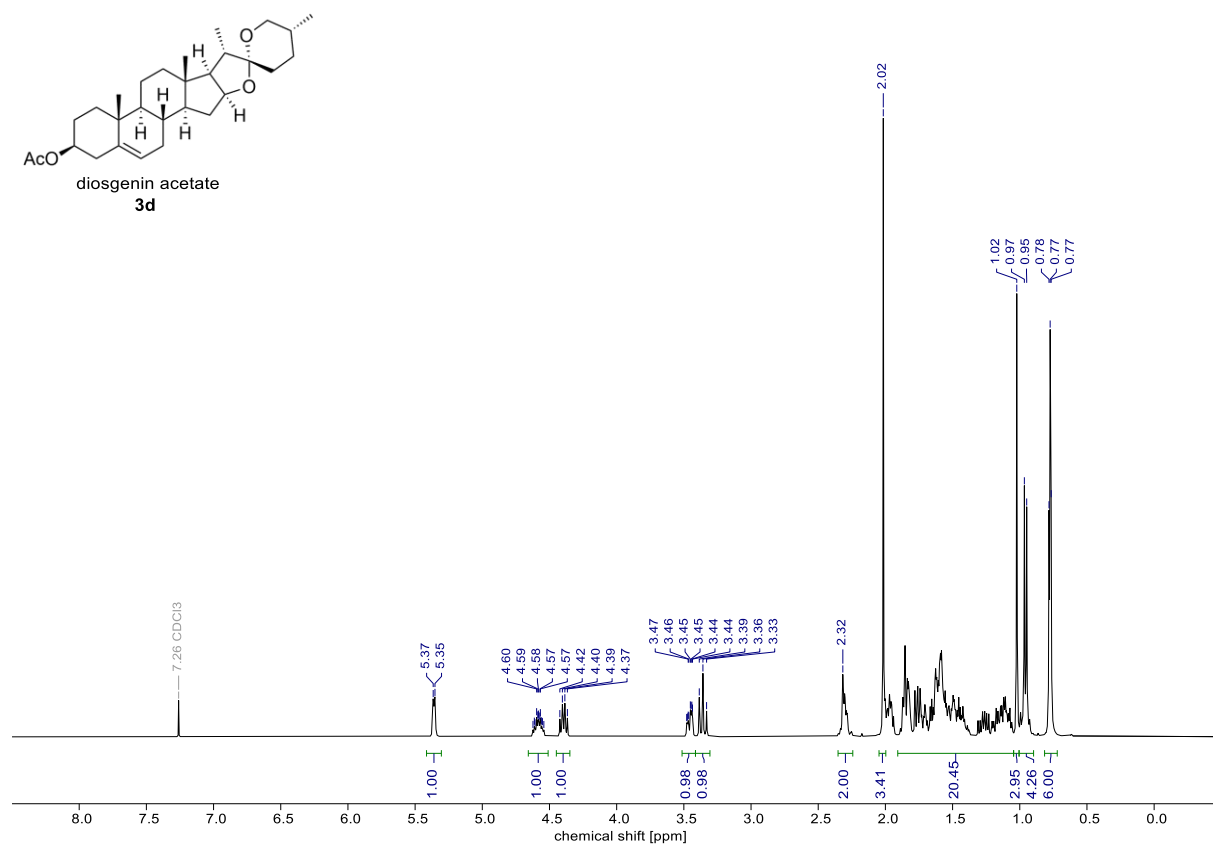


Figure S230. ¹H NMR spectrum (400 MHz) of starting material **3d**: diosgenin acetate.

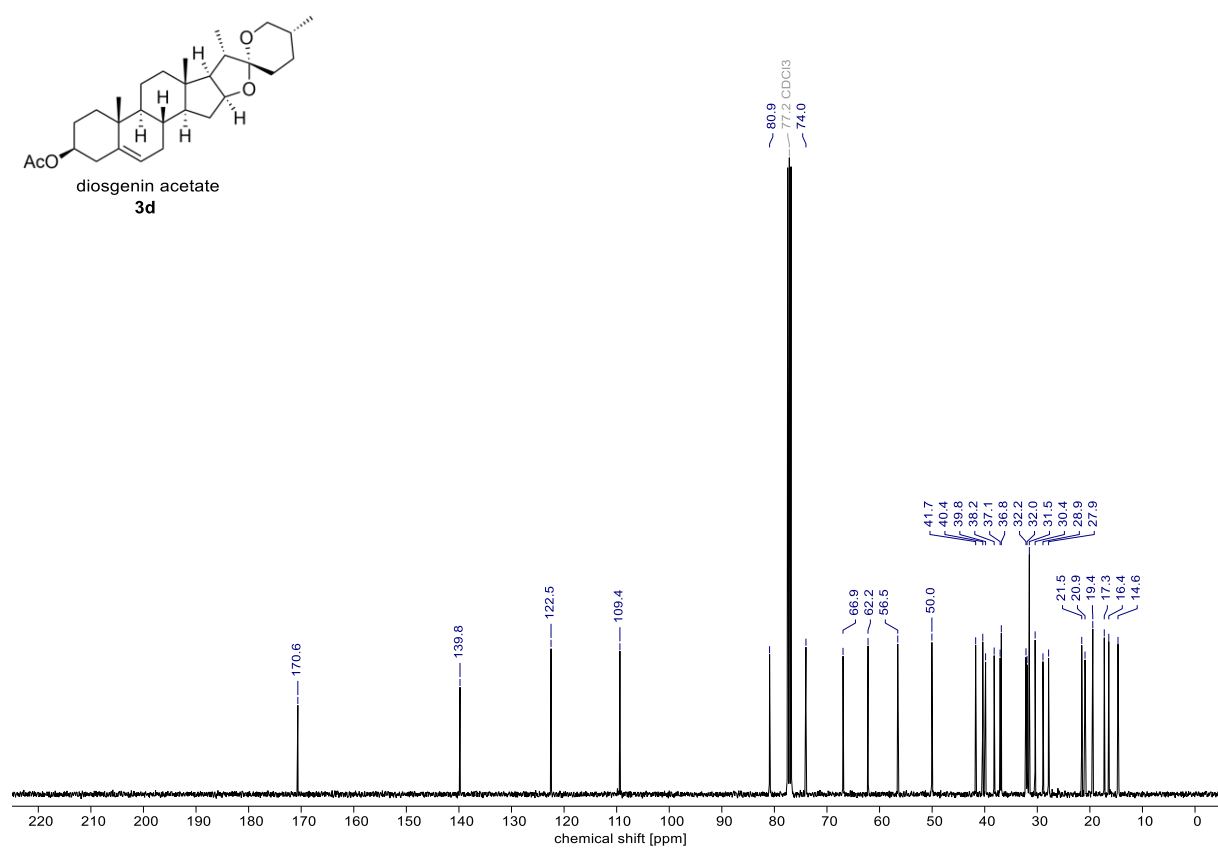


Figure S231. ¹³C NMR spectrum (101 MHz) of starting material **3d**: diosgenin acetate.

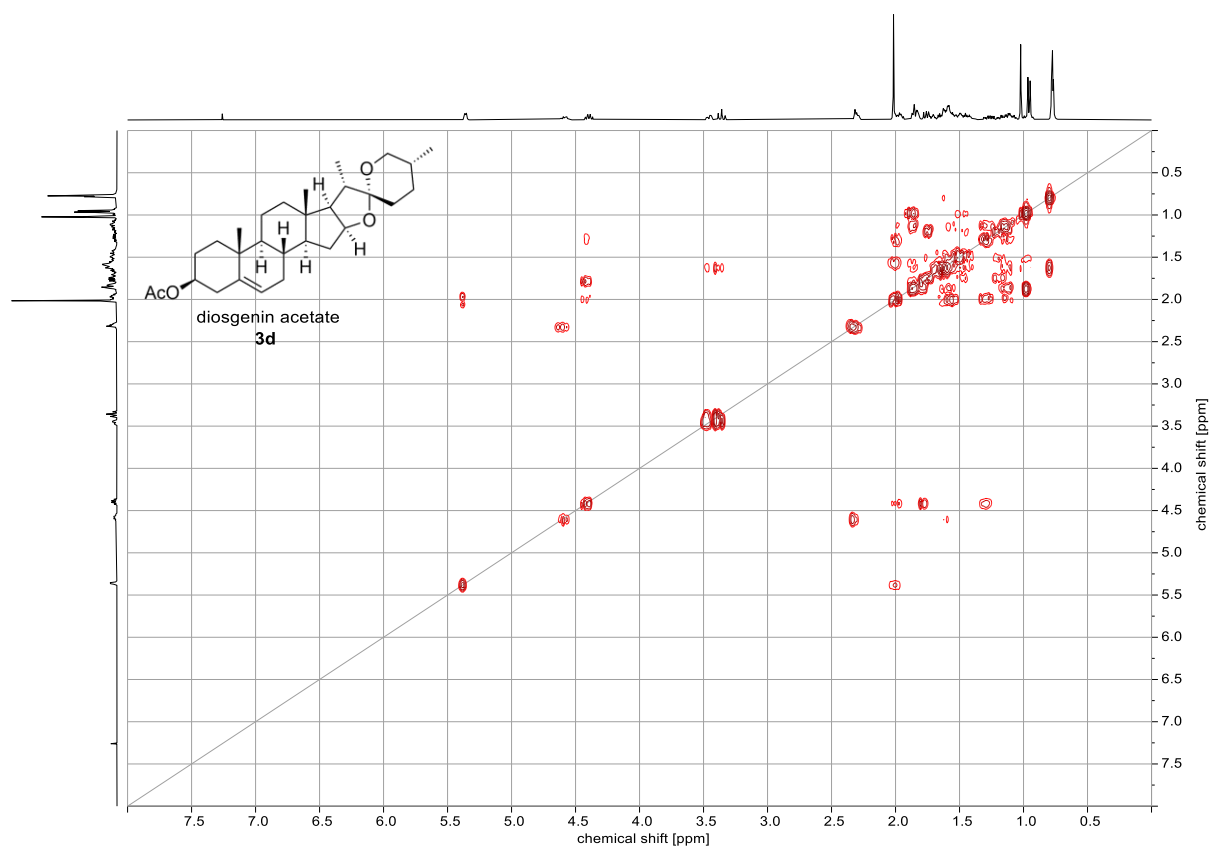


Figure S232. COSY spectrum of starting material **3d**: diosgenin acetate.

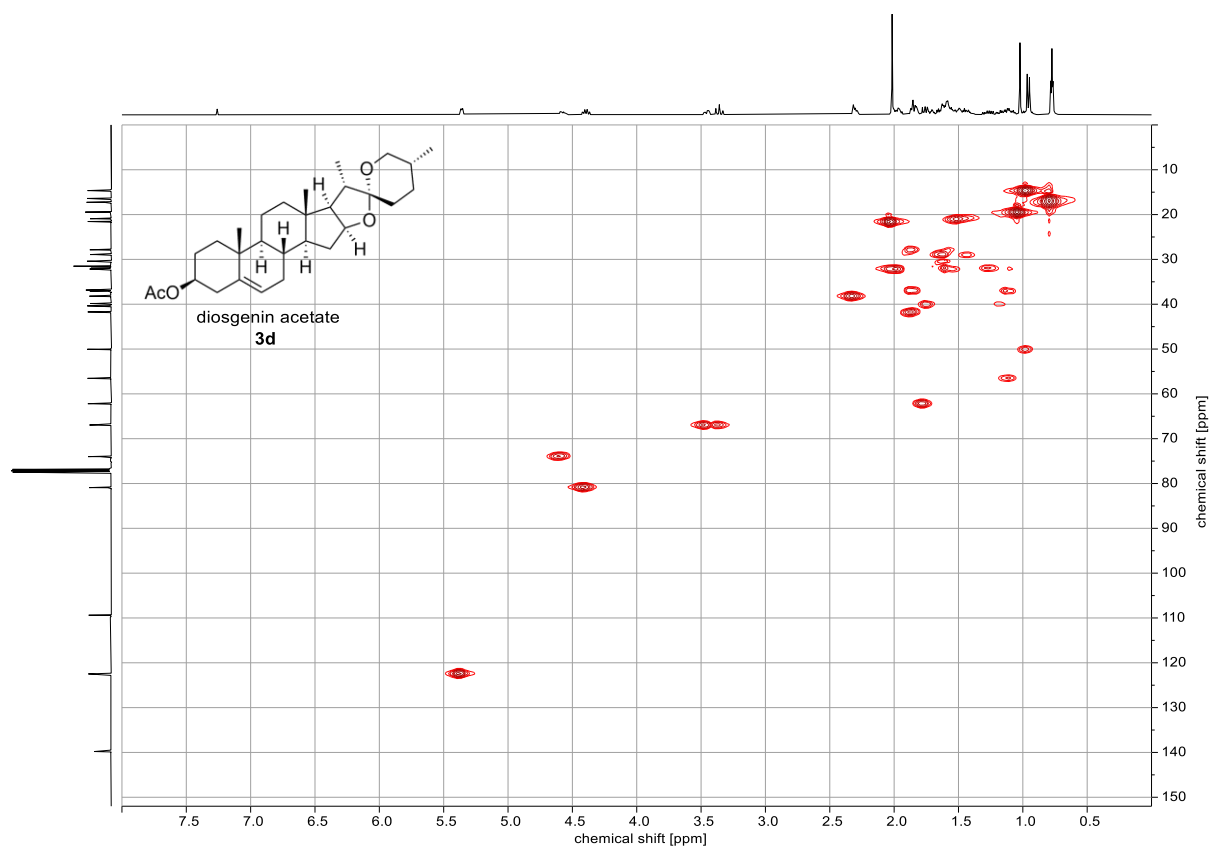


Figure S233. HSQC spectrum of starting material **3d**: diosgenin acetate.

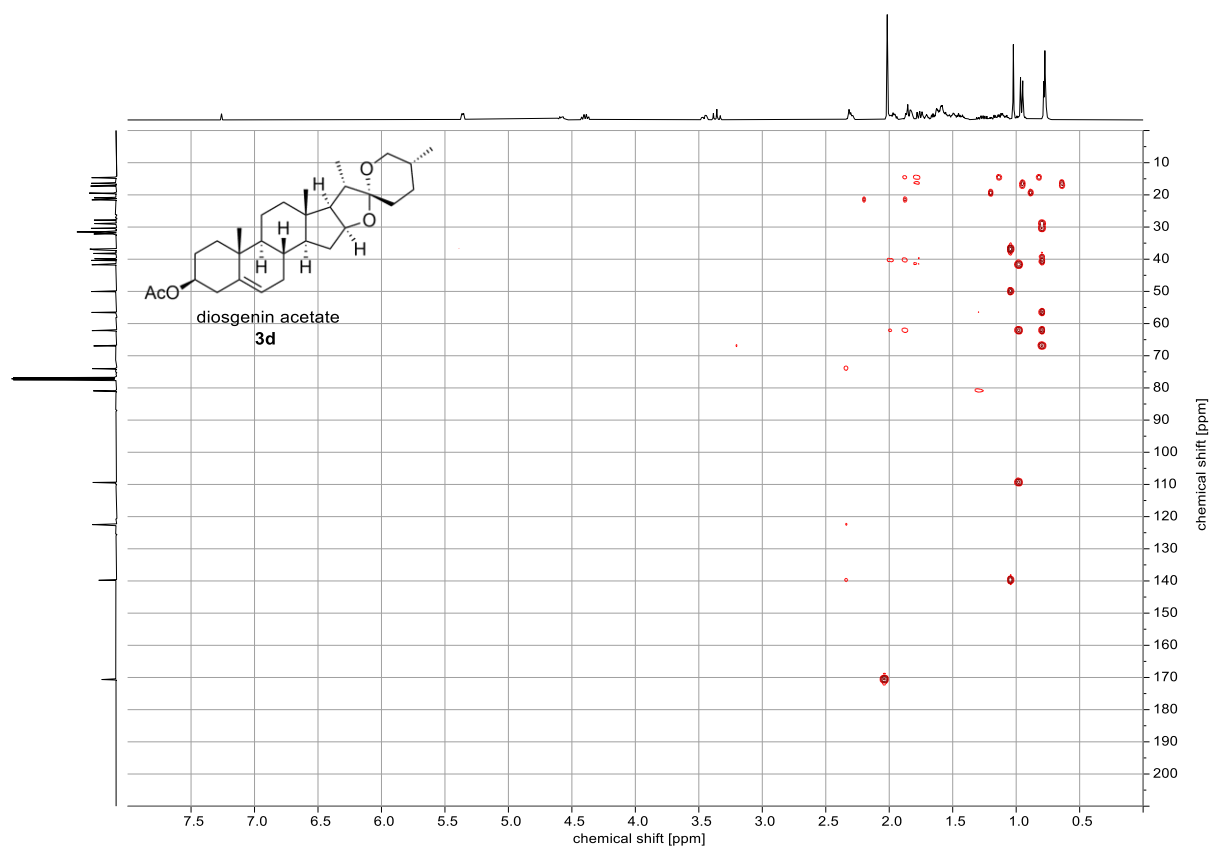
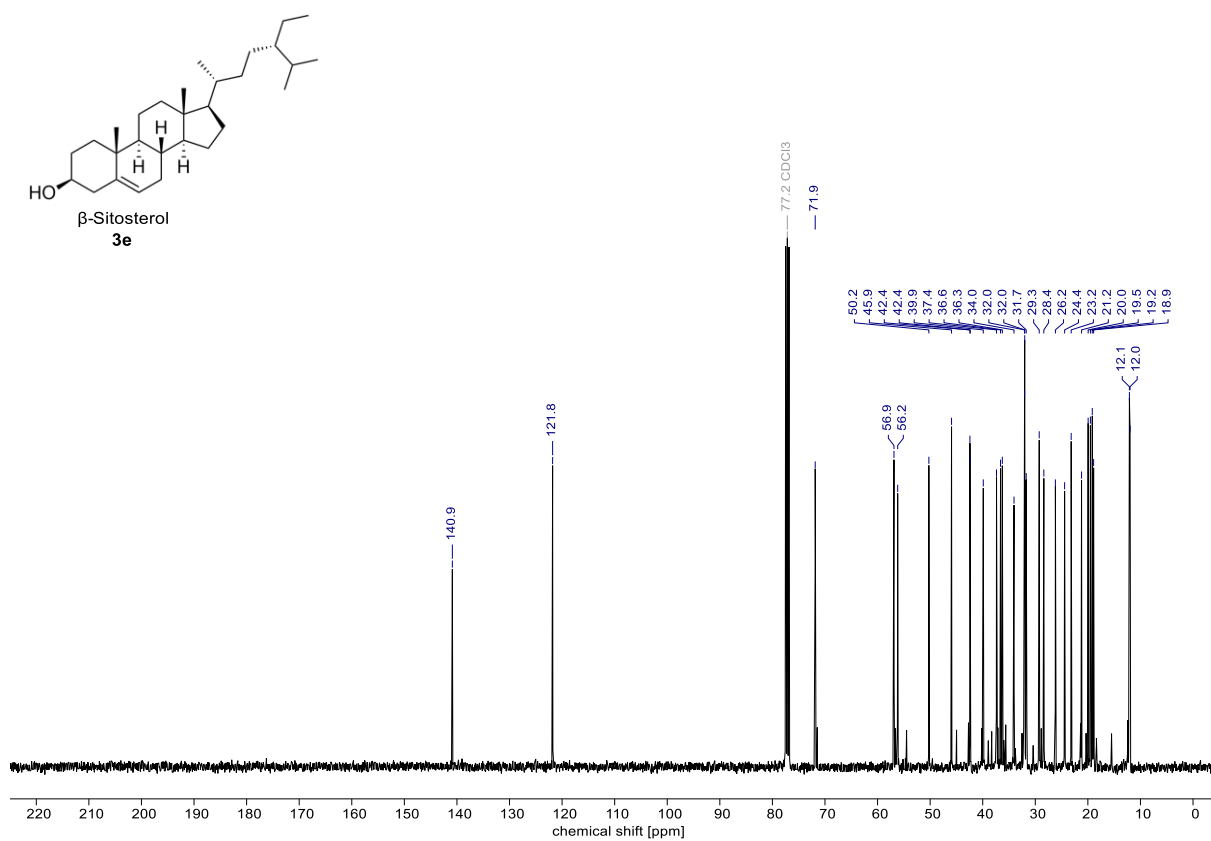
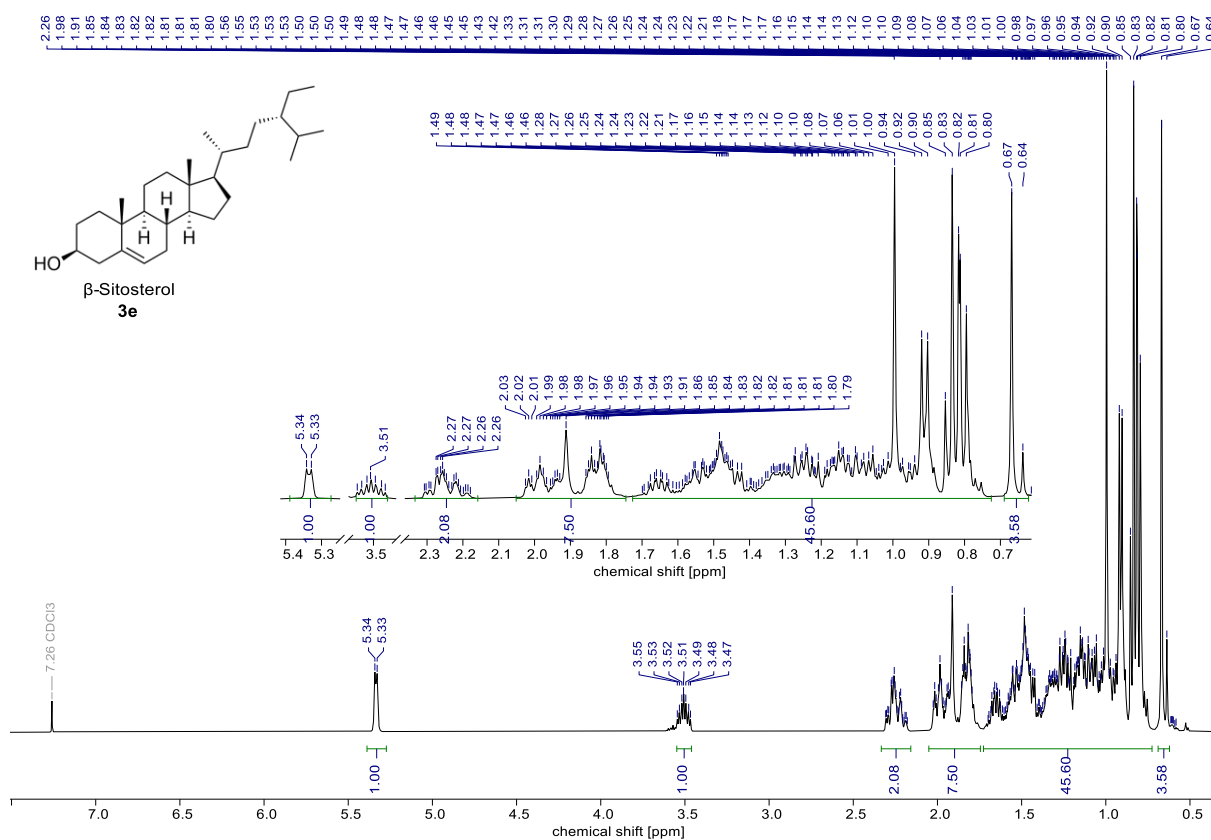


Figure S234. HMBC spectrum of starting material **3d**: diosgenin acetate.

10.21. β -Sitosterol

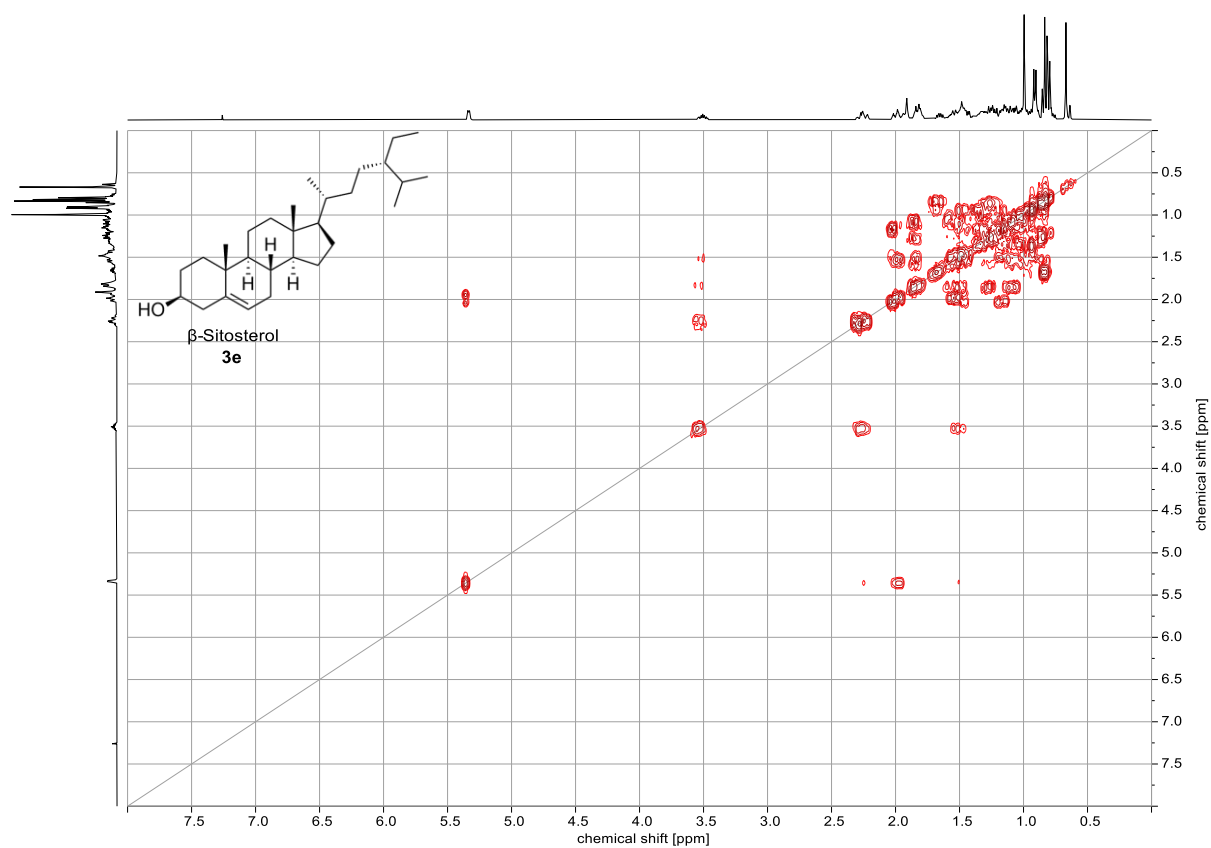


Figure S237. COSY spectrum of starting material **3e**: β -sitosterol.

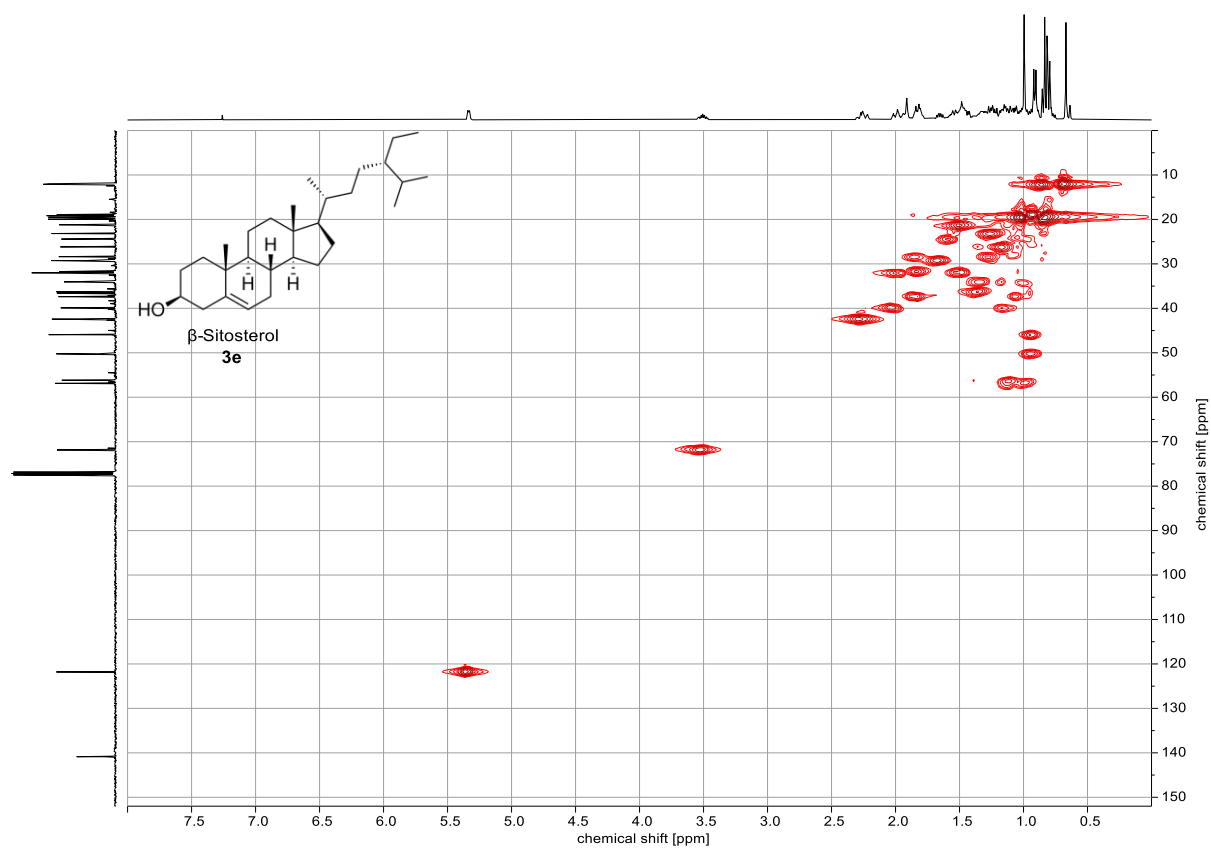
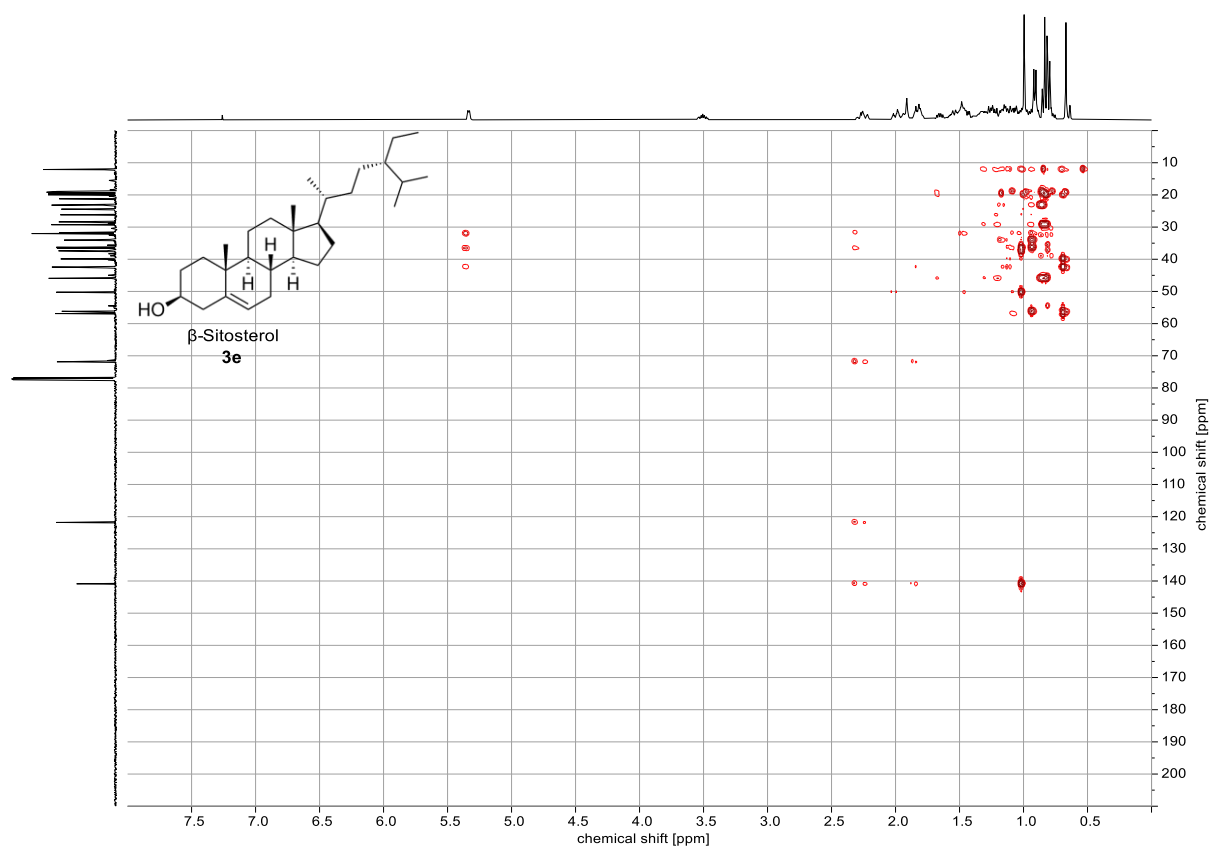
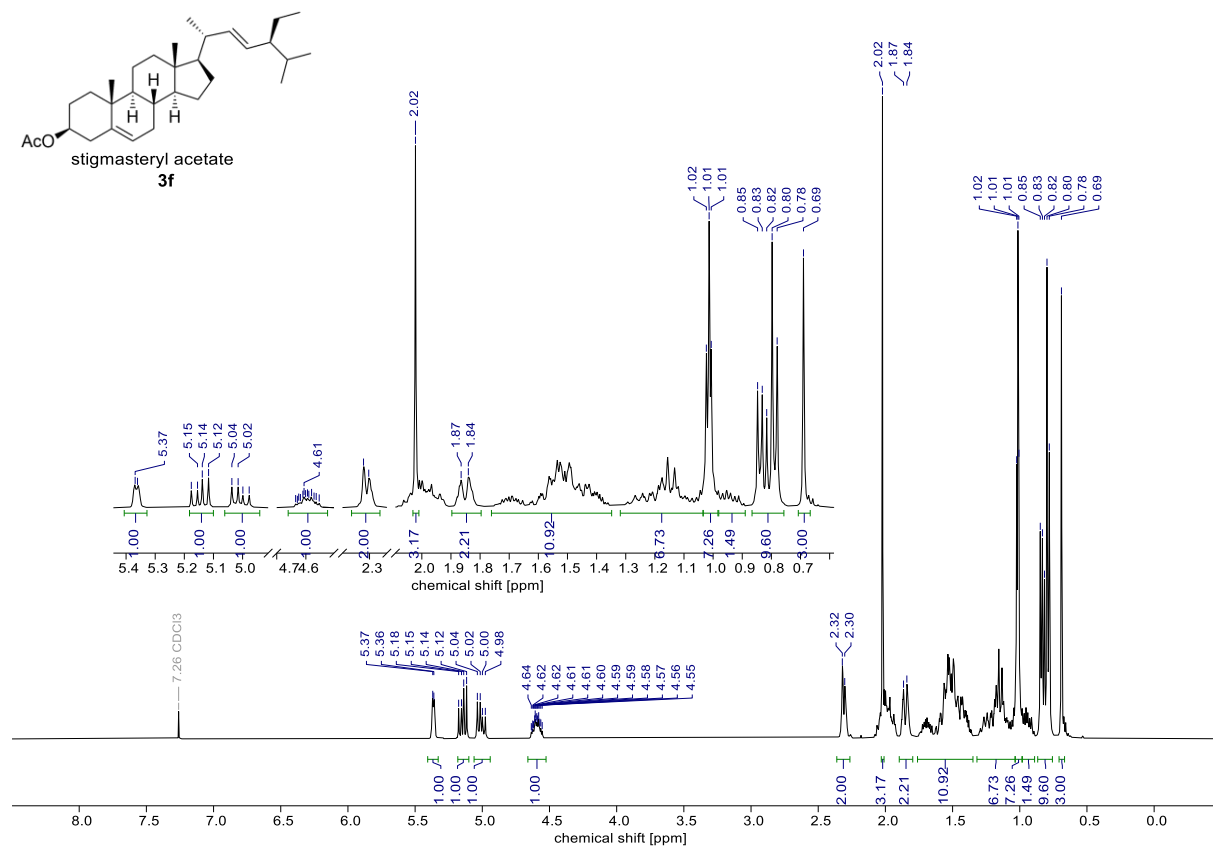


Figure S238. HSQC spectrum of starting material **3e**: β -sitosterol.



10.22. Stigmasteryl acetate



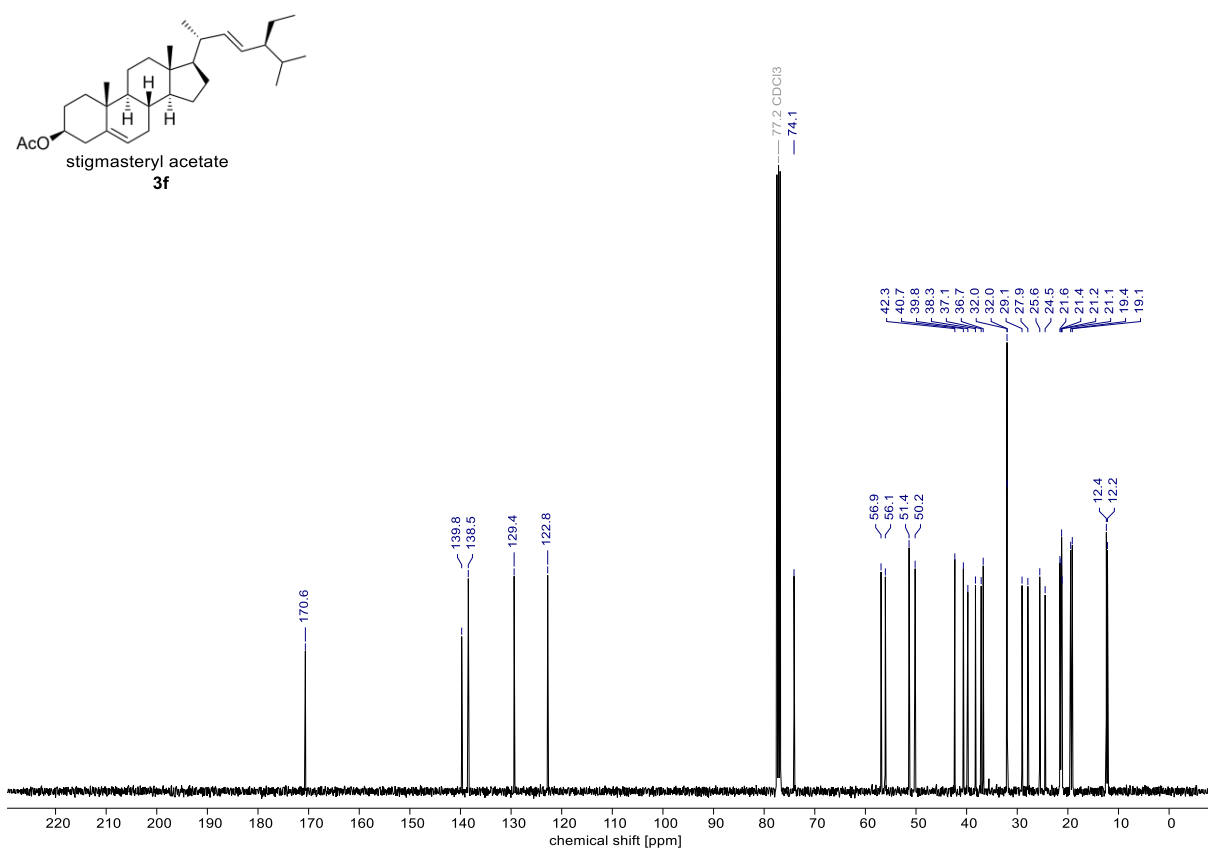


Figure S241. ¹³C NMR spectrum (101 MHz) of starting material **3f**: stigmasteryl acetate.

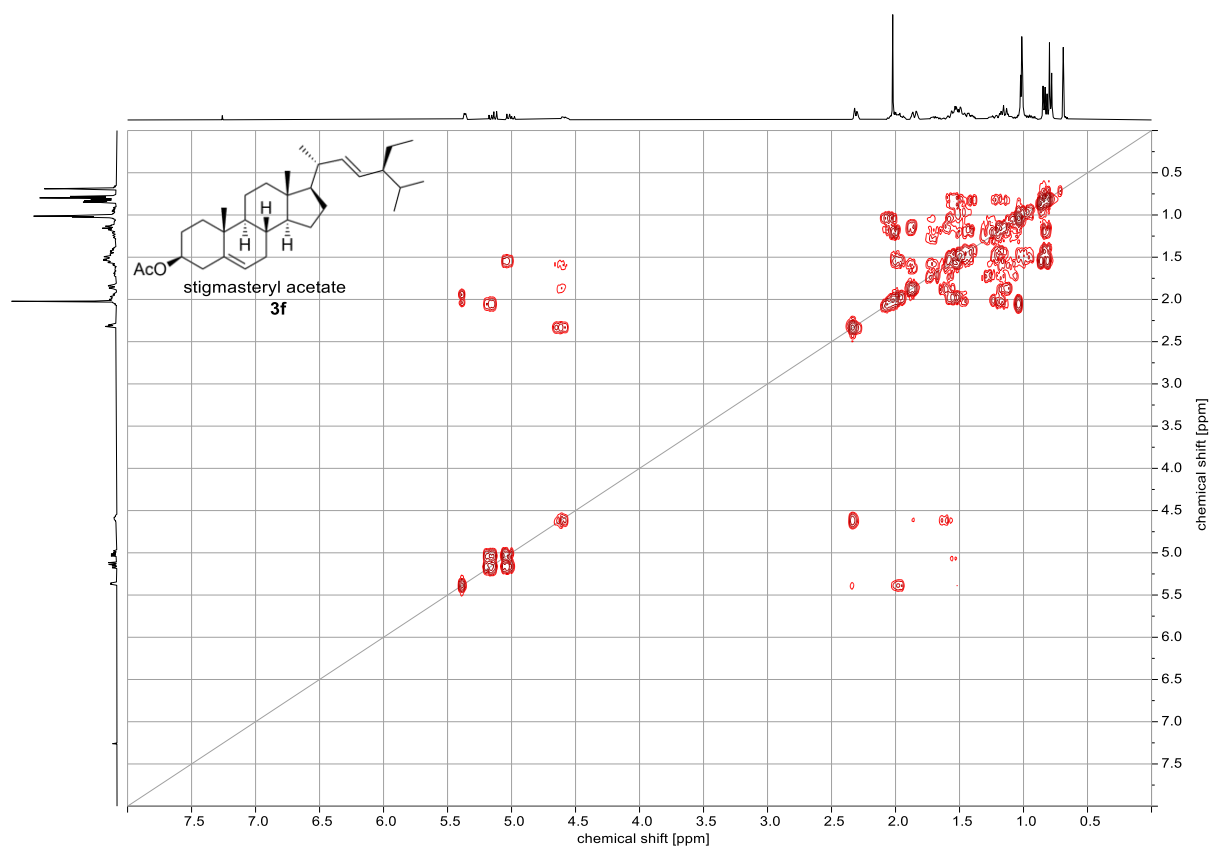


Figure S242. COSY spectrum of starting material **3f**: stigmasteryl acetate.

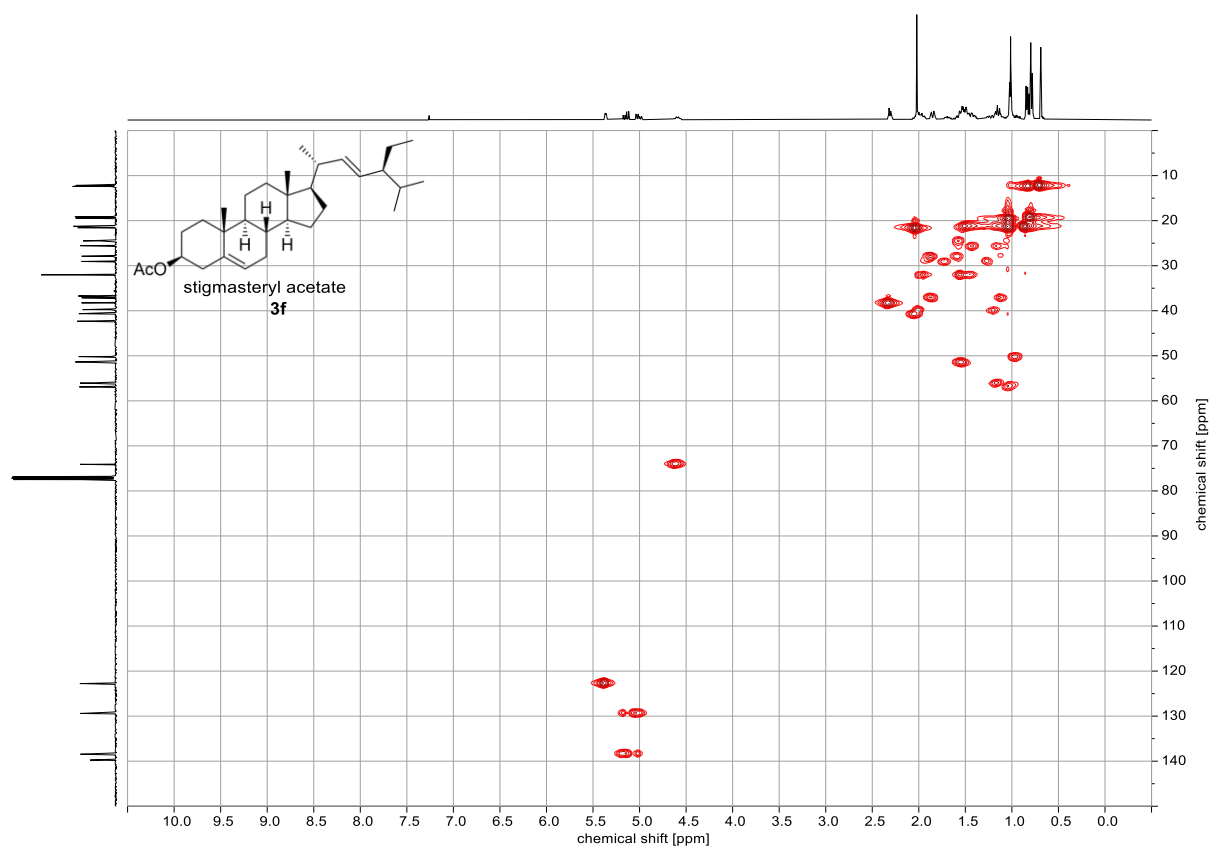


Figure S243. HSQC spectrum of starting material **3f**: stigmasteryl acetate.

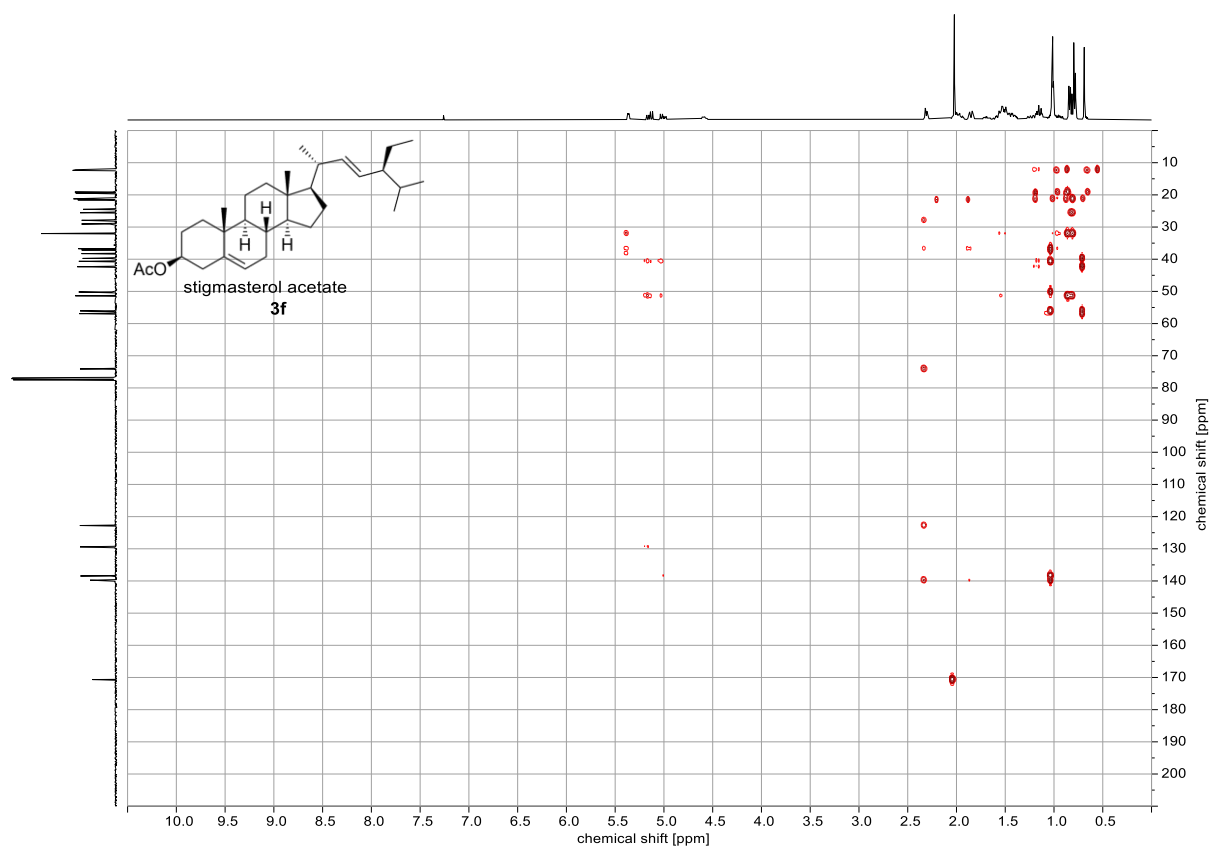
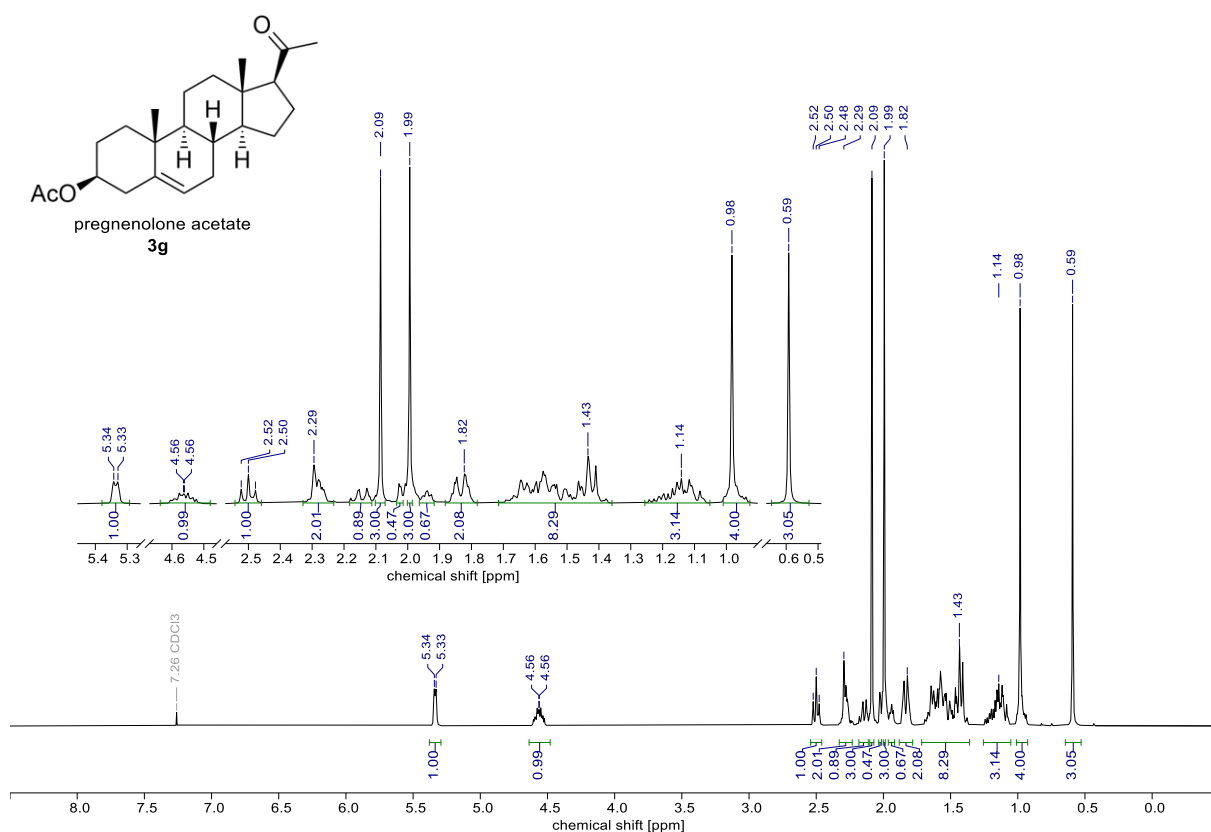
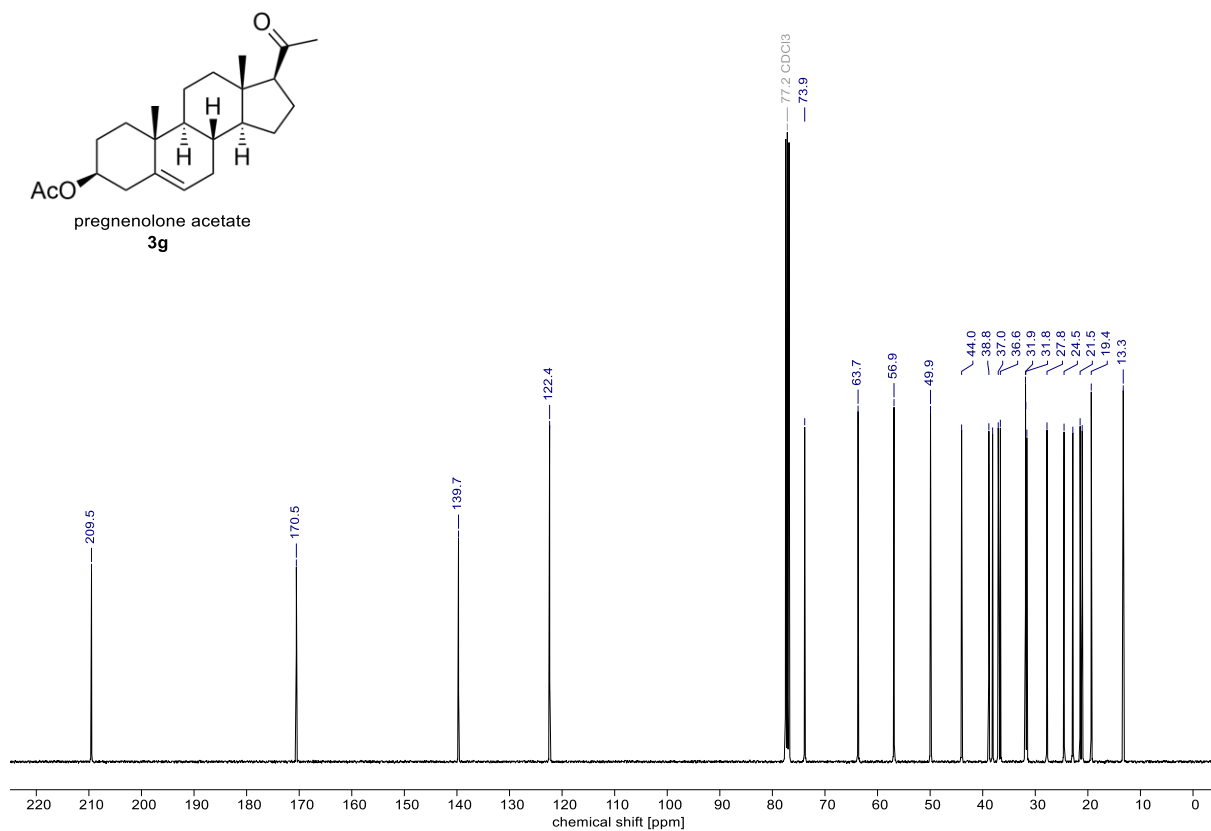


Figure S244. HMBC spectrum of starting material **3f**: stigmasteryl acetate.

10.23. Pregnenolone acetate

Figure S245. ¹H NMR spectrum (400 MHz) of starting material **3g**: pregnenolone acetate.Figure S246. ¹³C NMR spectrum (101 MHz) of starting material **3g**: pregnenolone acetate.

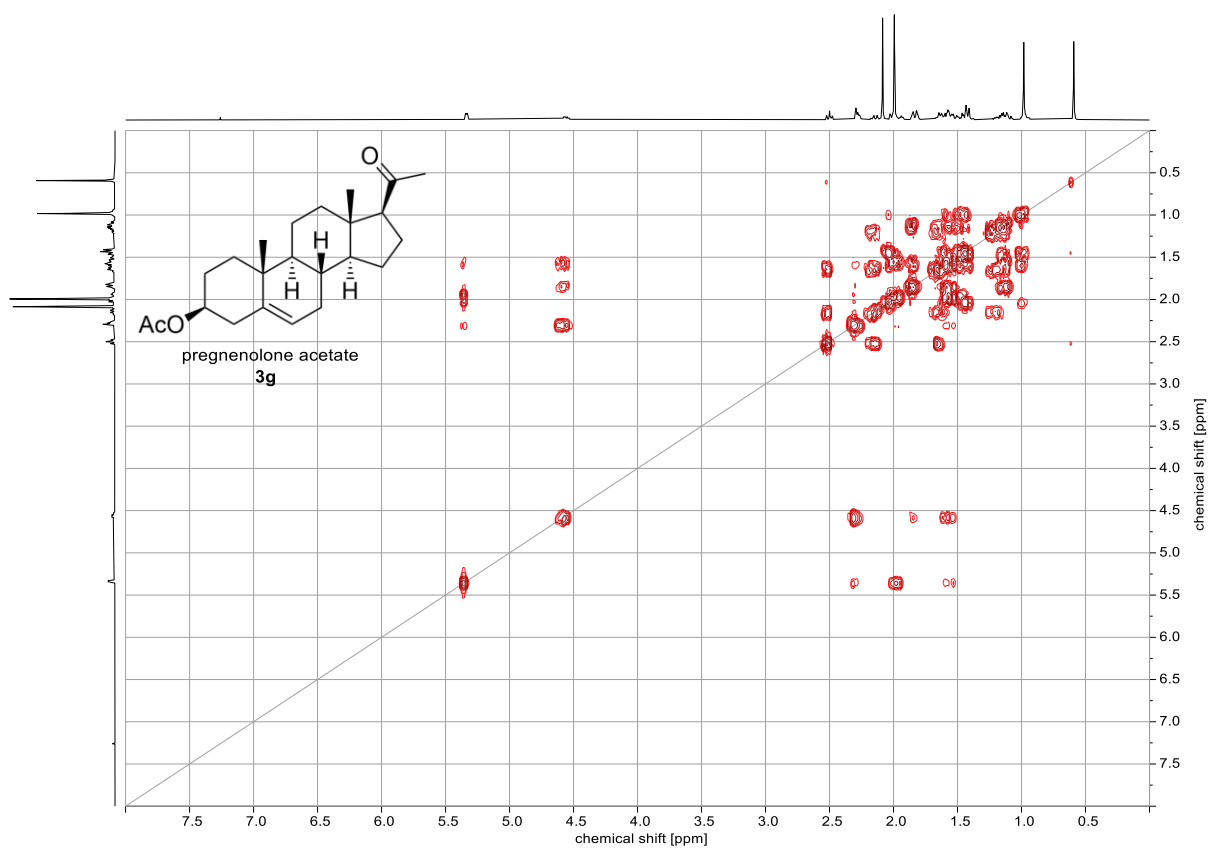


Figure S247. COSY spectrum of starting material **3g**: pregnenolone acetate.

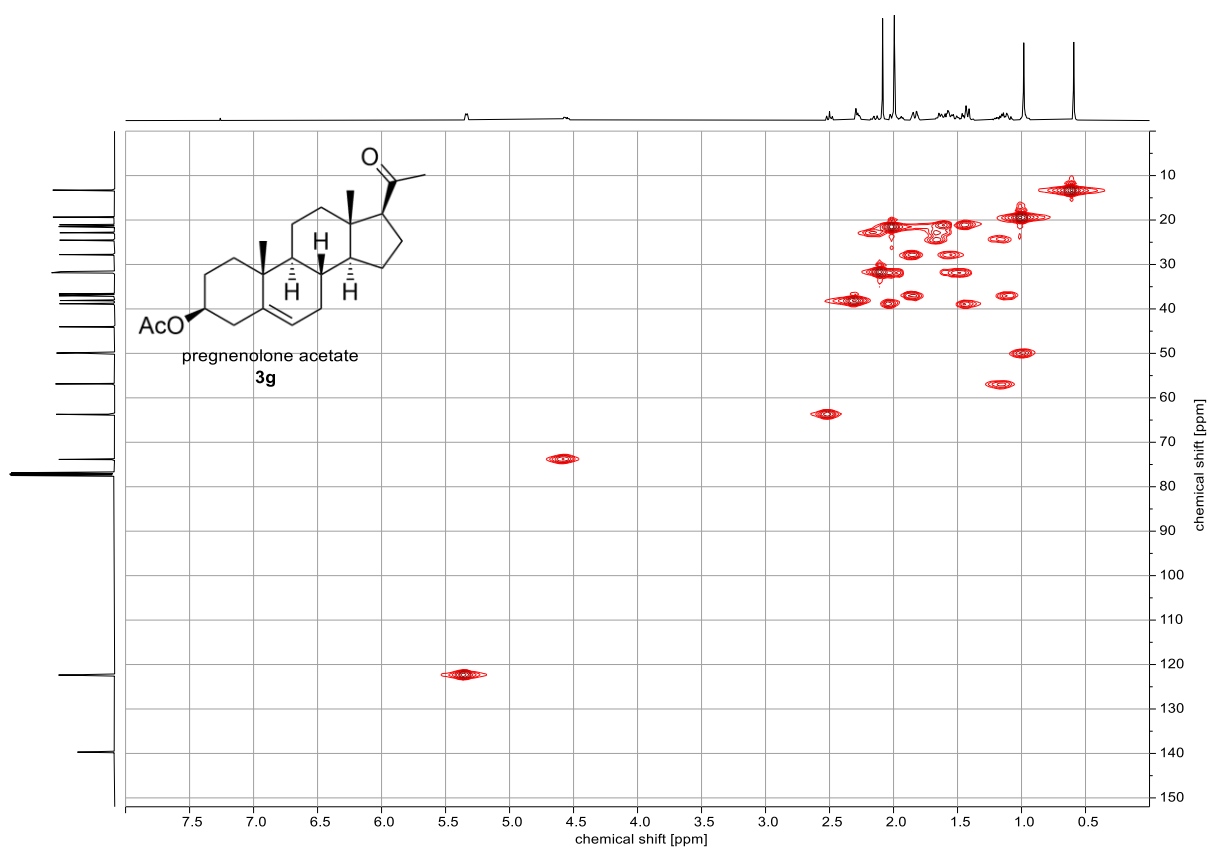


Figure S248. HSQC spectrum of starting material **3g**: pregnenolone acetate.

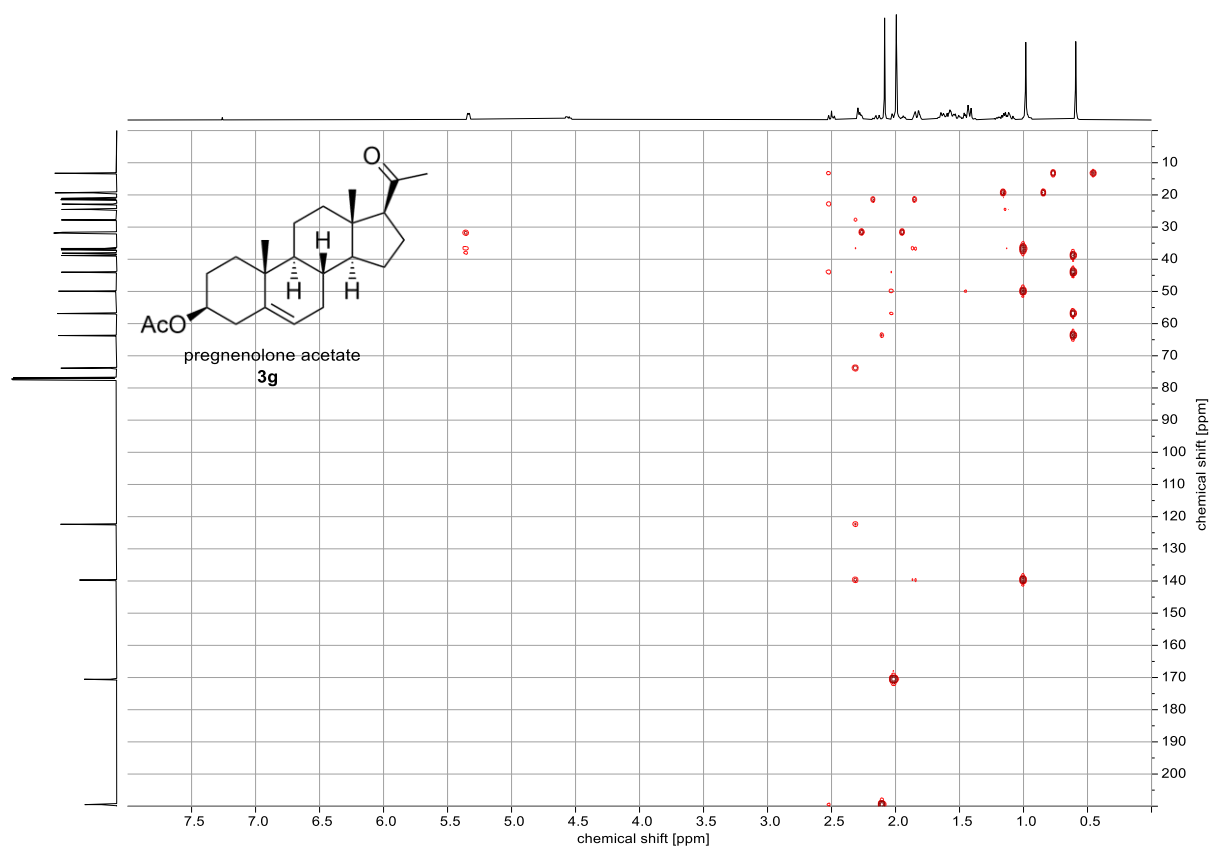


Figure S249. HMBC spectrum of starting material **3g**: pregnenolone acetate.

10.24. Dehydroepiandrosterone (DHEA) acetate

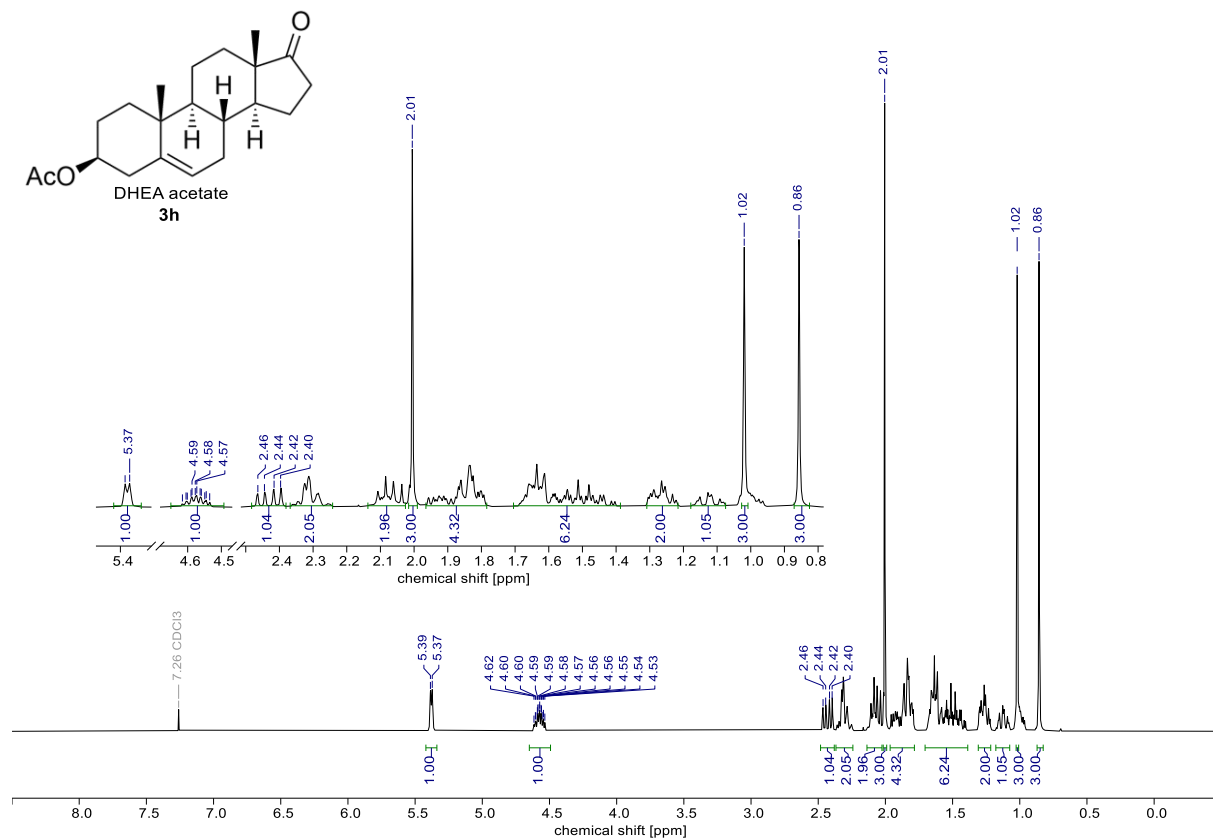


Figure S250. ^1H NMR spectrum (400 MHz) of starting material **3h**: dehydroepiandrosterone (DHEA) acetate.

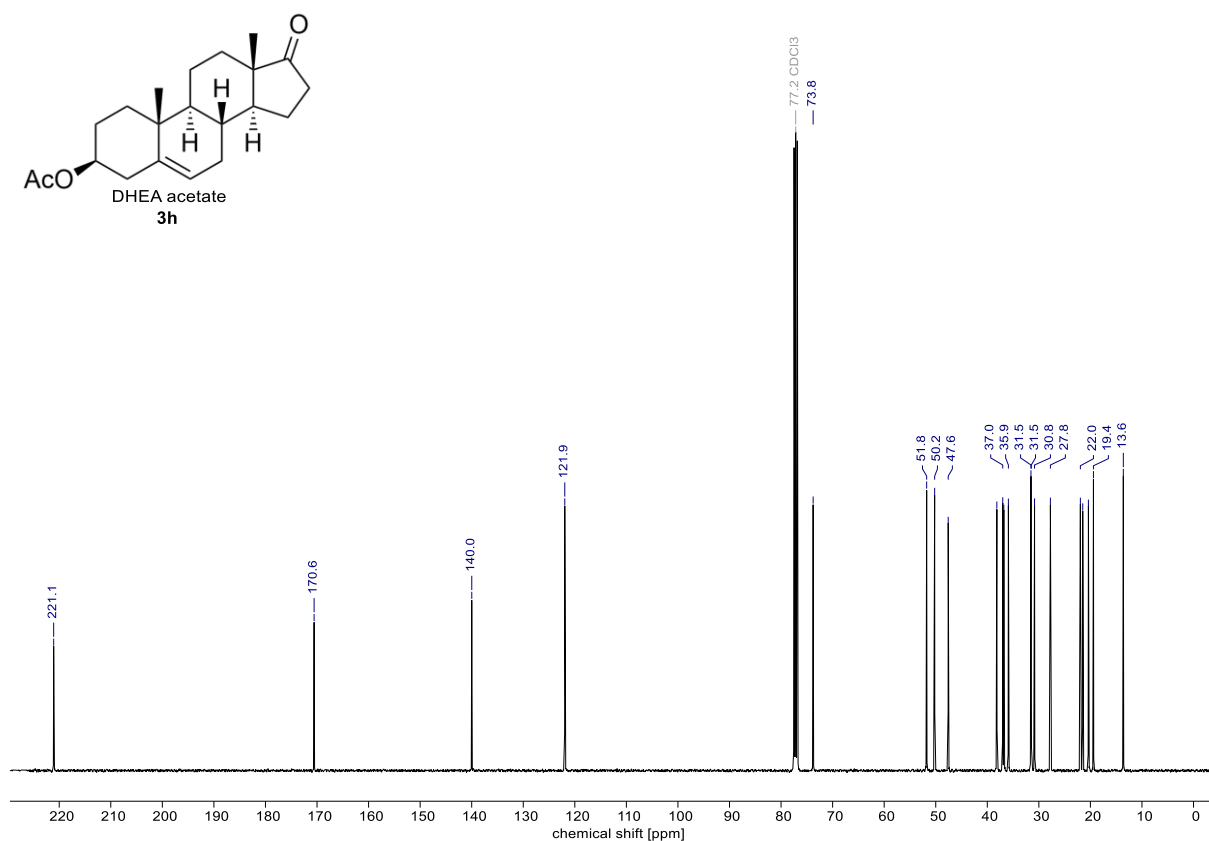


Figure S251. ¹³C NMR spectrum (101 MHz) of starting material **3h**: dehydroepiandrosterone (DHEA) acetate.

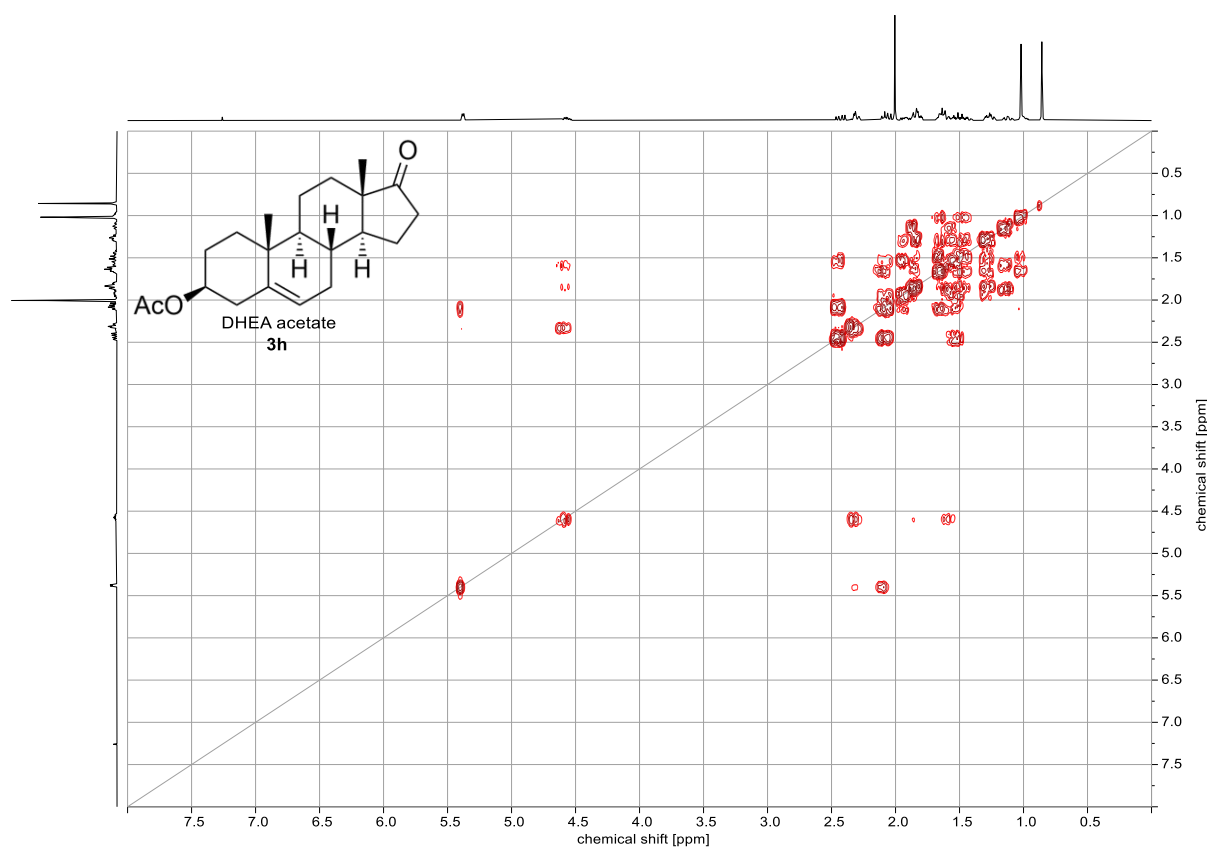


Figure S252. COSY of starting material **3h**: dehydroepiandrosterone (DHEA) acetate.

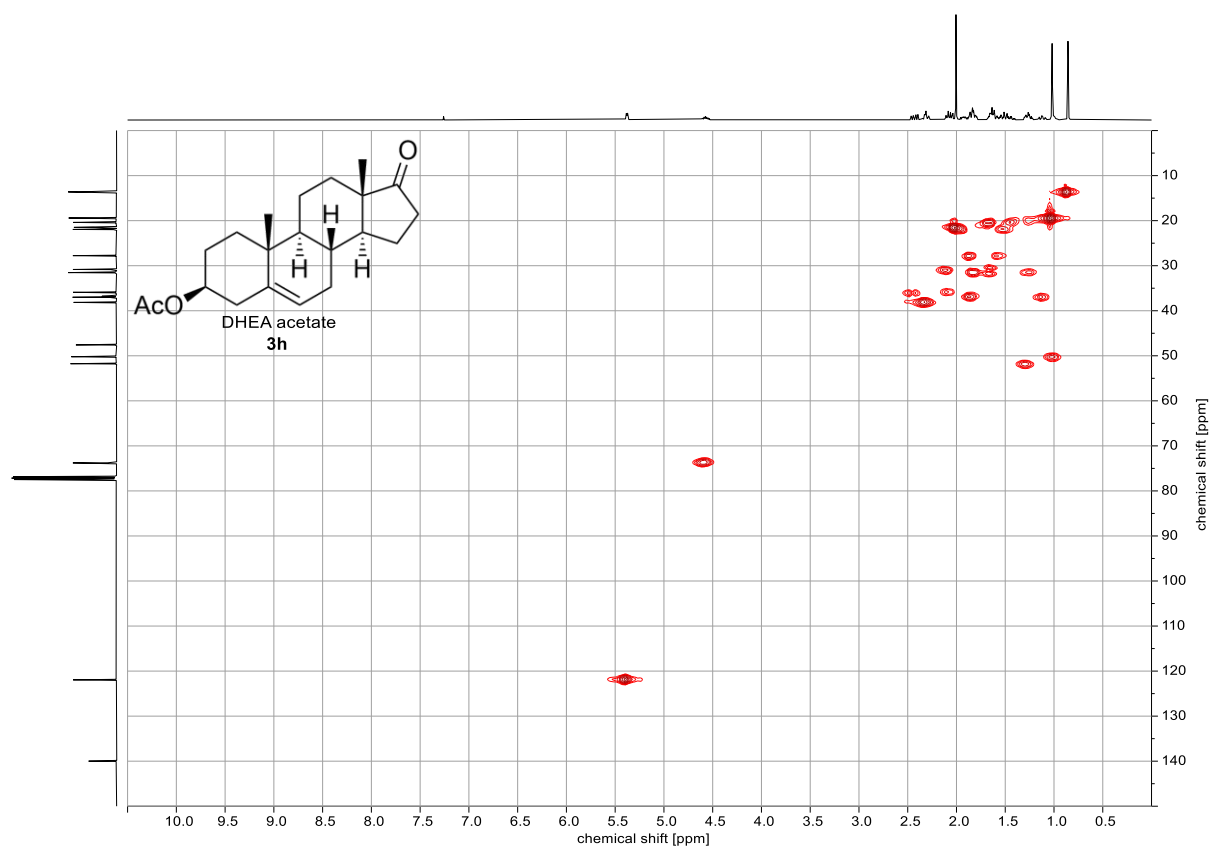


Figure S253. HSQC spectrum of starting material **3h**: dehydroepiandrosterone (DHEA) acetate.

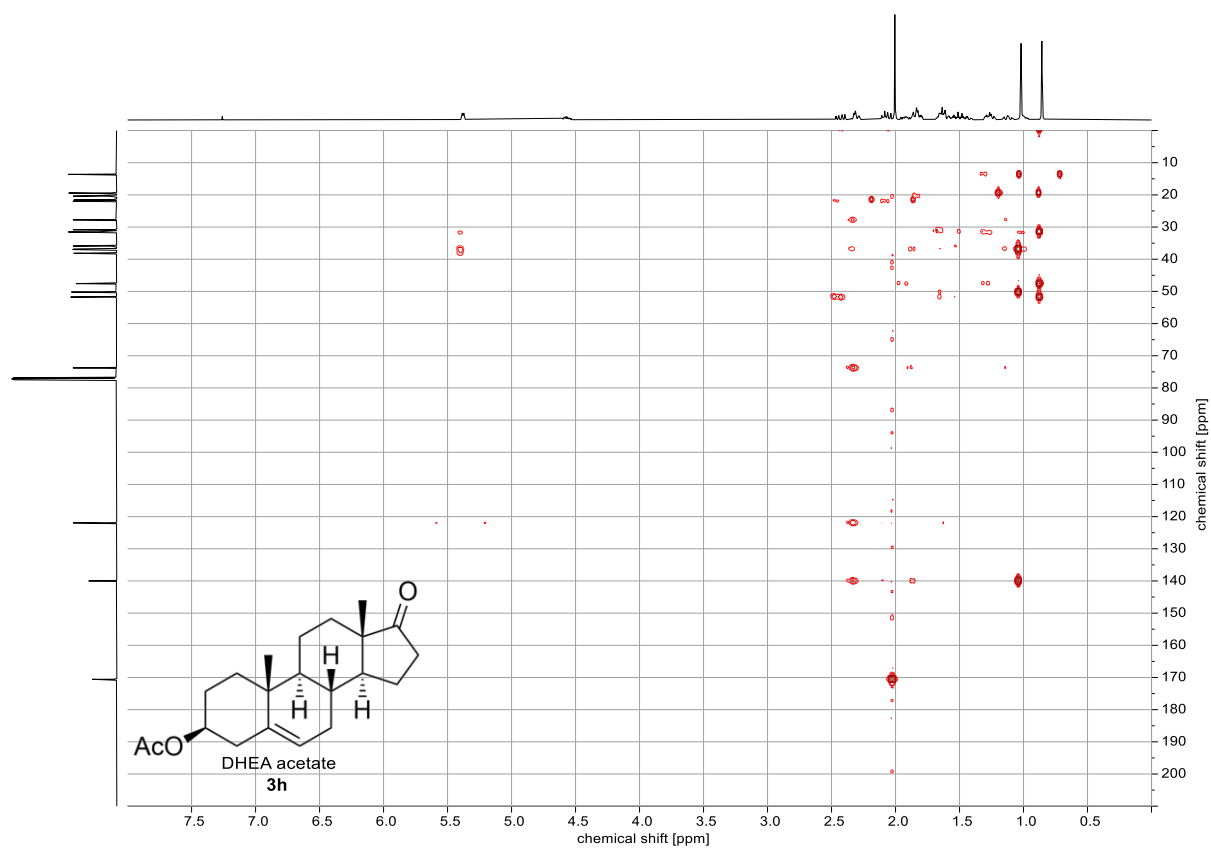
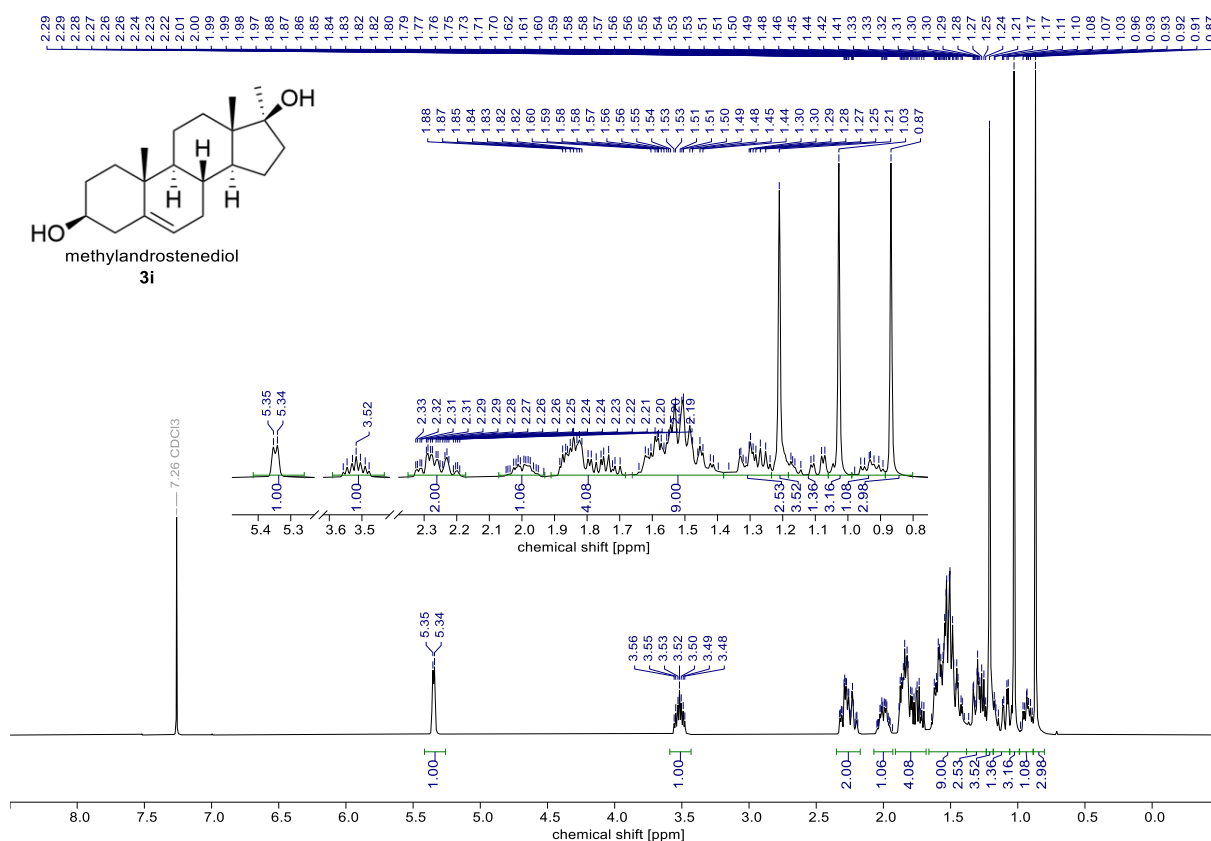


Figure S254. HMBC spectrum of starting material **3h**: dehydroepiandrosterone (DHEA) acetate.

10.25. Methylandrostenediol



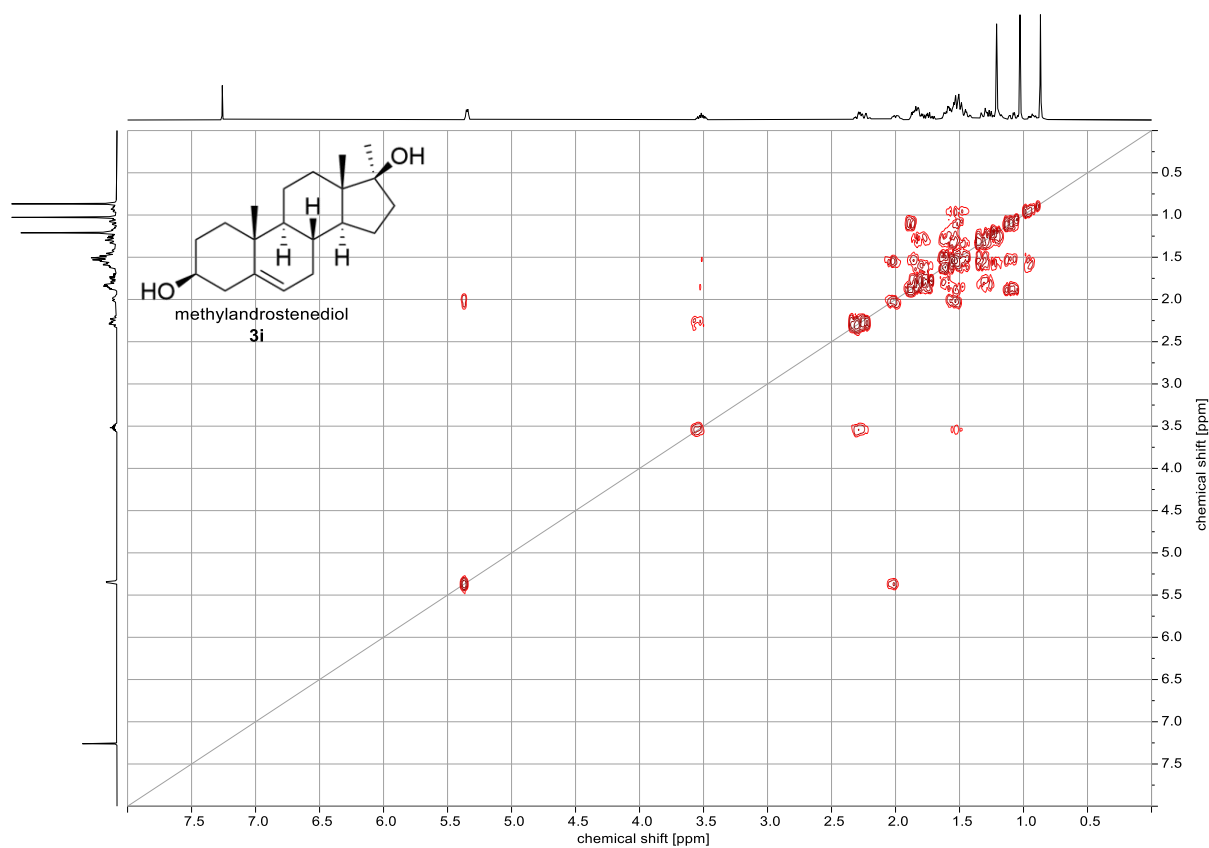


Figure S257. COSY spectrum of starting material **3i**: methylandrostenediol.

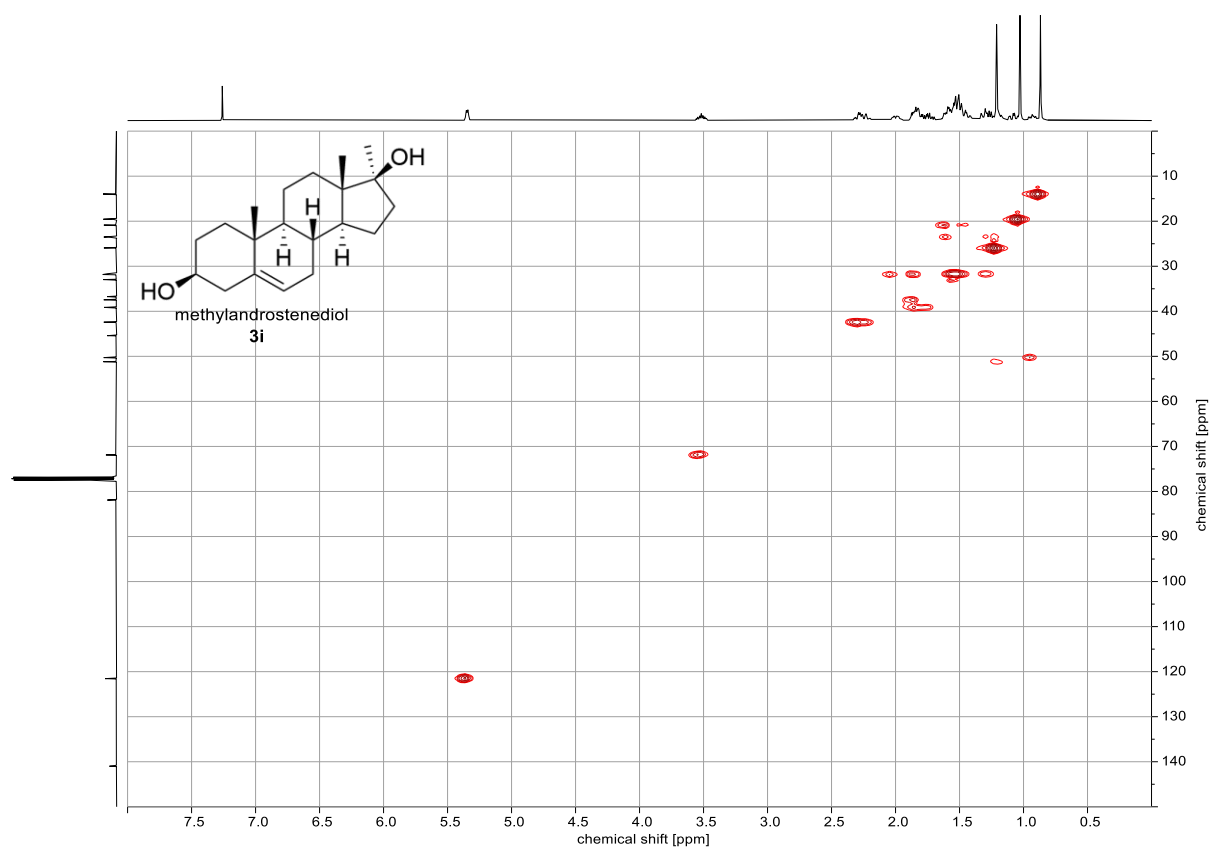
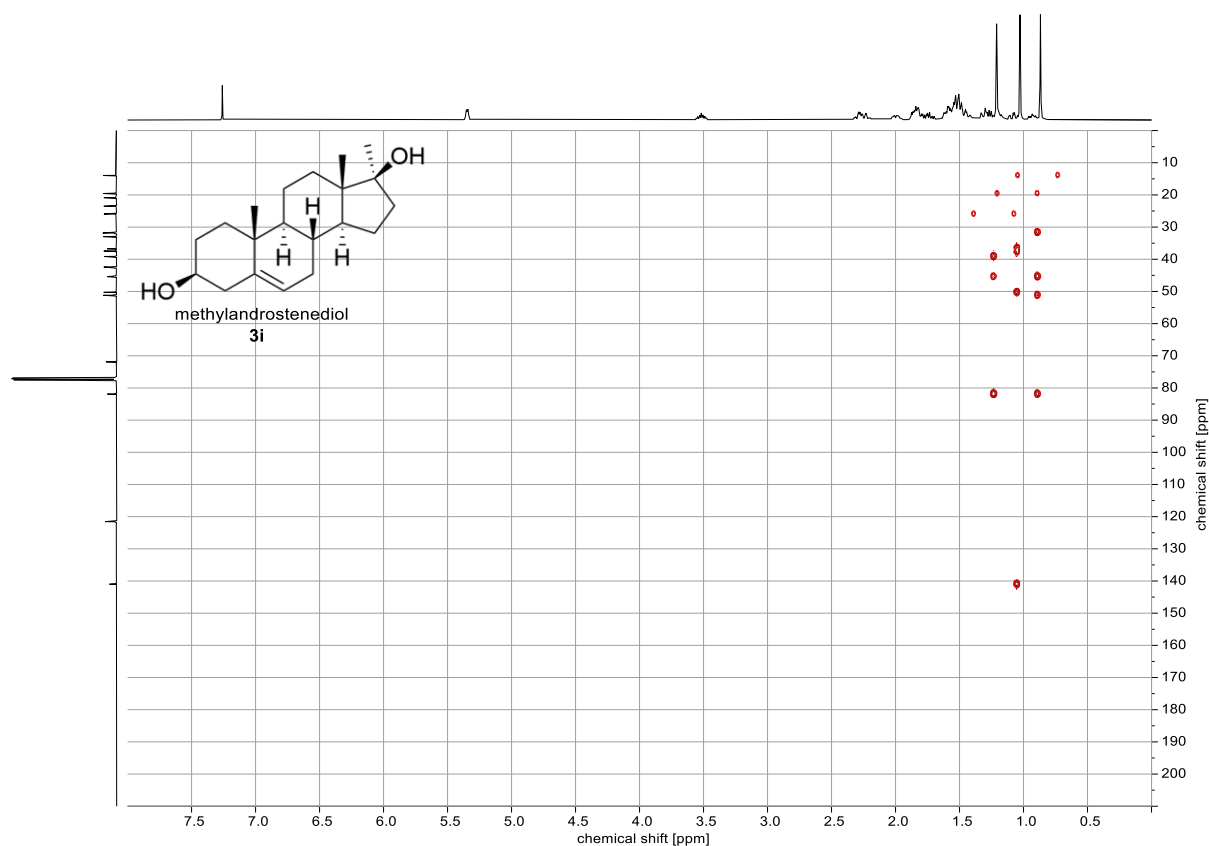
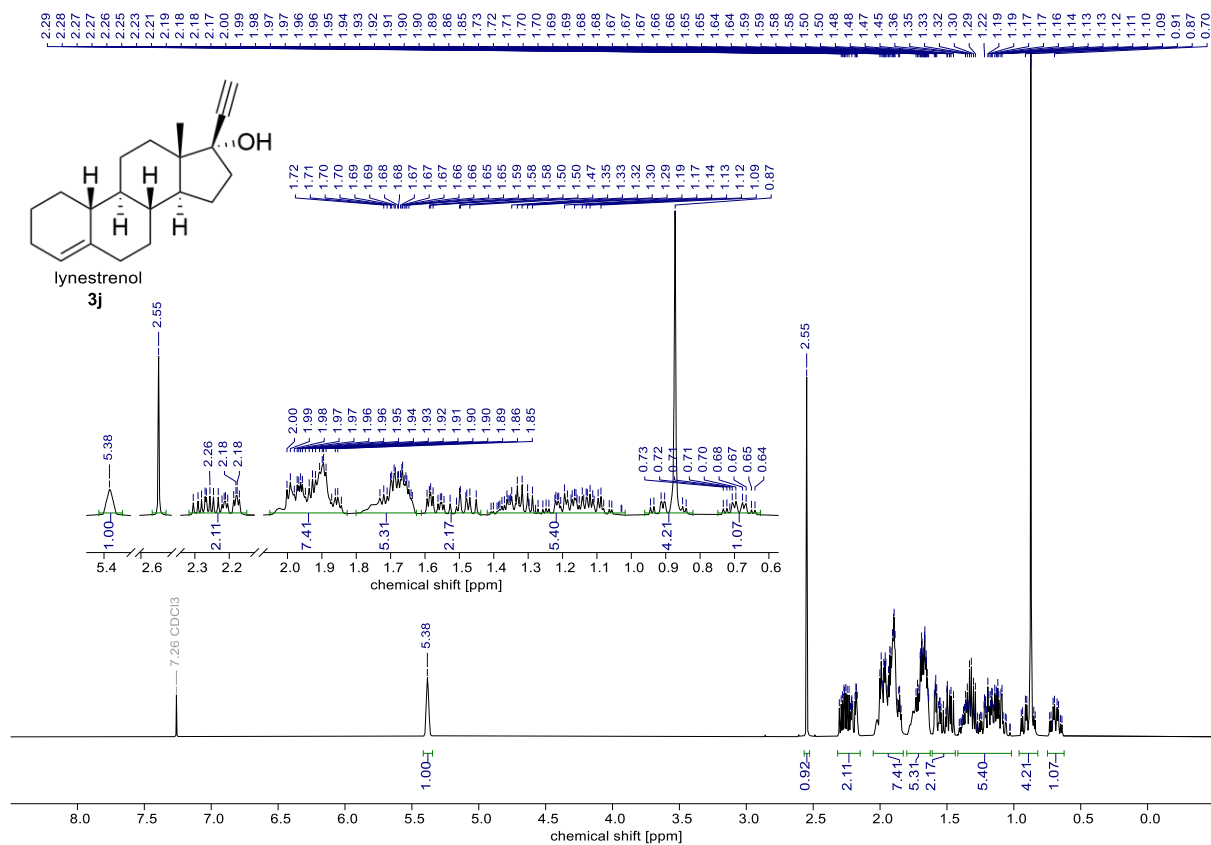
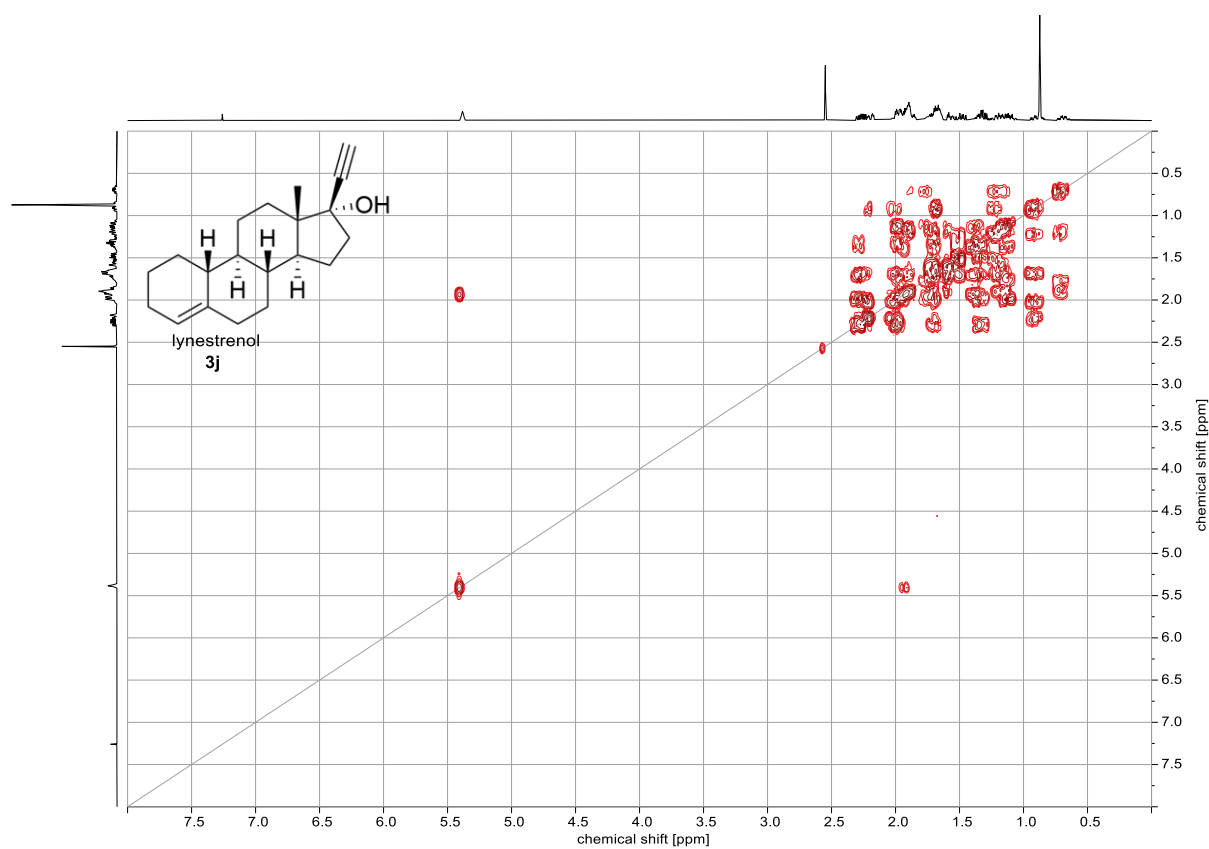
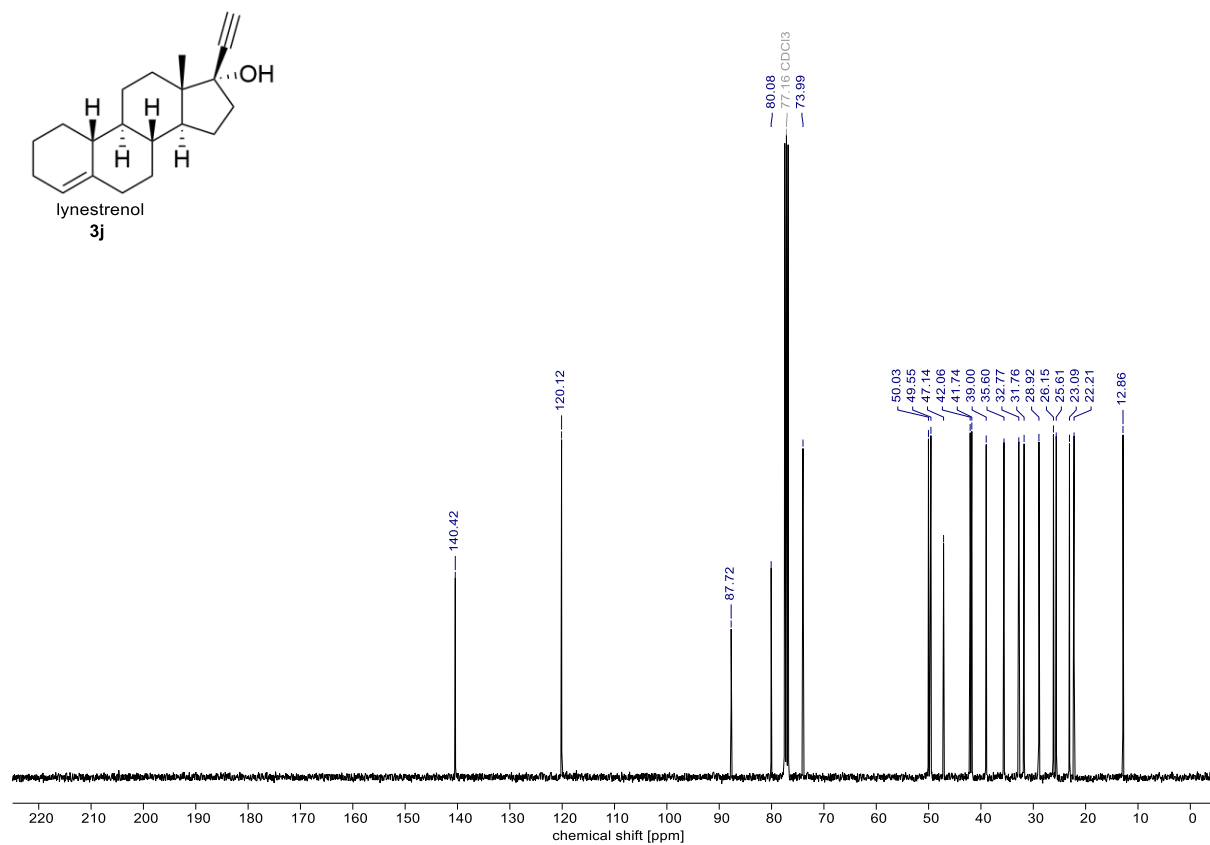


Figure S258. HSQC spectrum of starting material **3i**: methylandrostenediol.



10.26. Lynestrenol





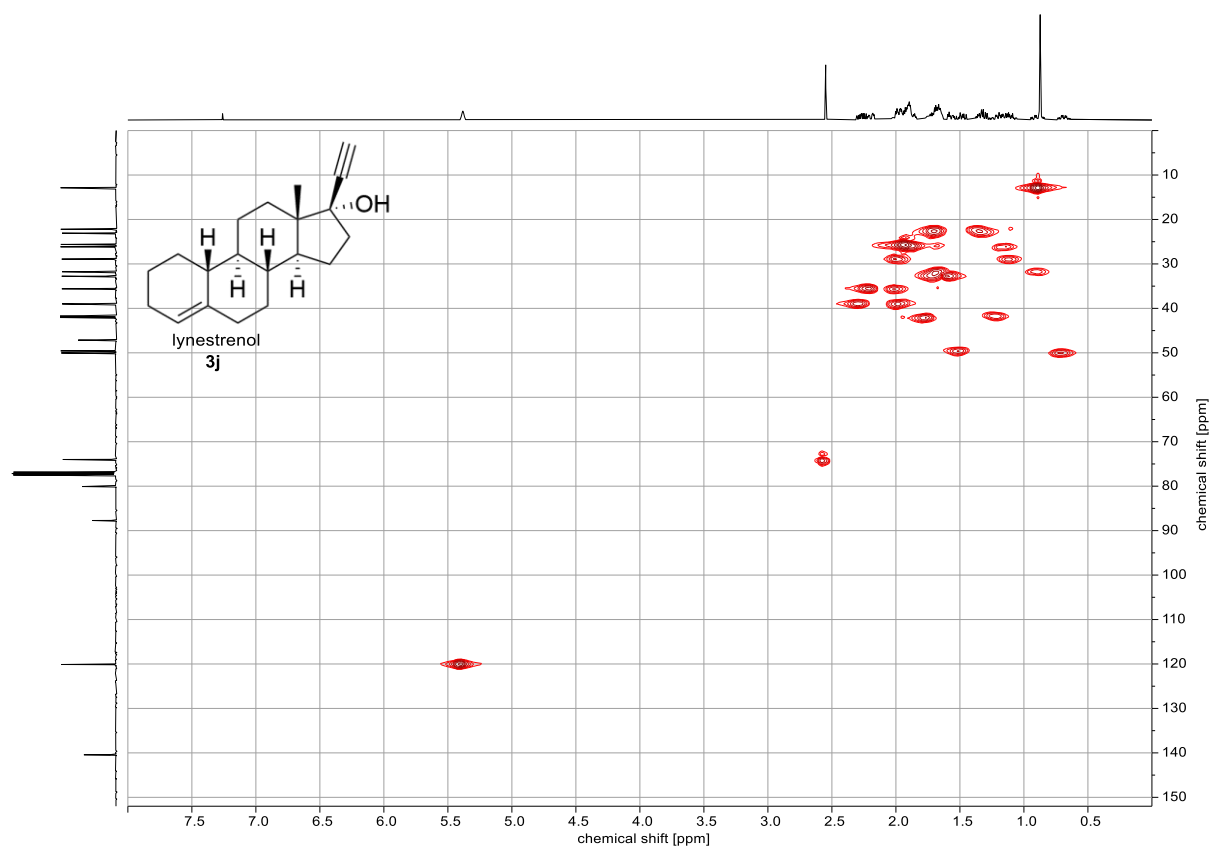


Figure S263. HSQC spectrum of starting material 3j: lyneestrenol.

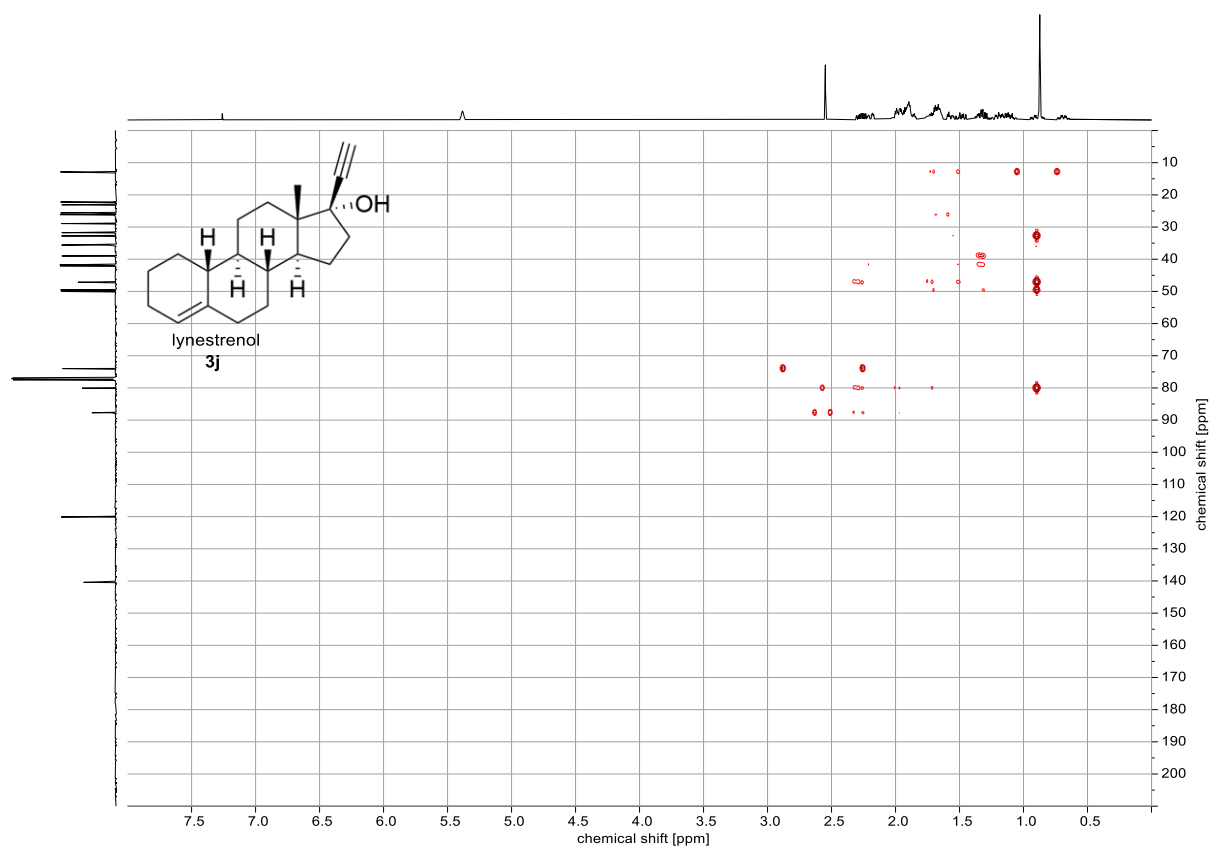


Figure S264. HMBC spectrum of starting material 3j: lyneestrenol.

11. Cyclic Voltammetry (CV)

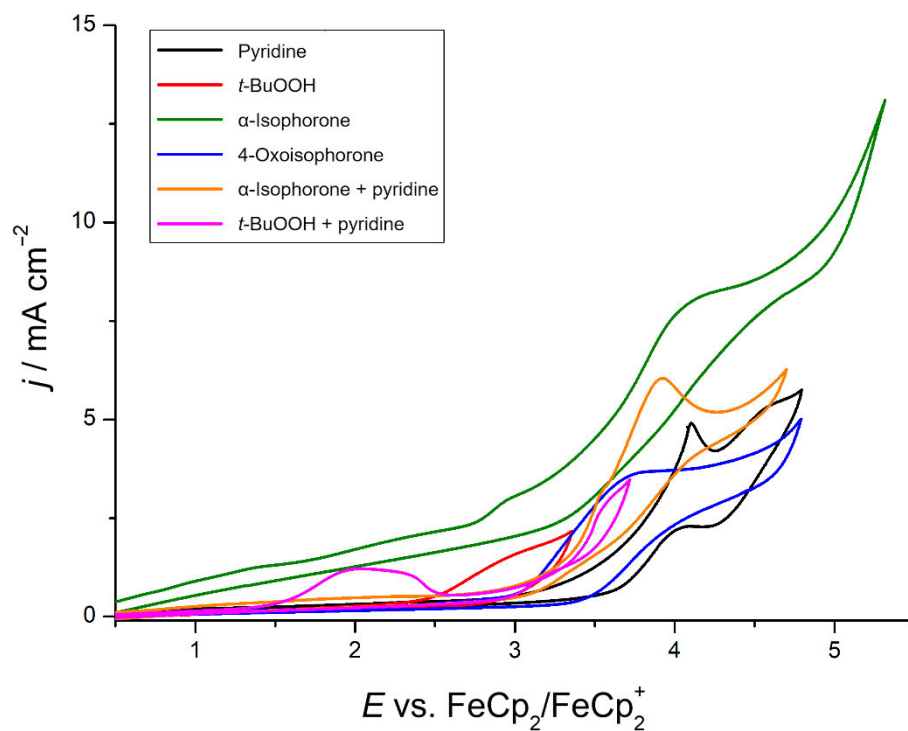


Figure S 265. Cyclic Voltammetry (CV) measurements of various combinations of substances. As mentioned in the main manuscript, it can be seen that the potential of *t*-BuOOH in the presence of pyridine is lower than the potential of *t*-BuOOH, making it more susceptible to oxidation. Each measurement was carried out in a solution of NEt_4BF_4 (0.1 mol L^{-1}) in MeCN with the substrate(s) in concentration of 0.01 mol L^{-1} .

12. References

- [1] W. L. F. Armarego, 'Purification of Laboratory Chemicals', Butterworth-Heinemann, Oxford, **2017**.
- [2] A. Saib, R. Goy, J. Medlock, B. Wüstenberg, G. Kociok-Köhn, C. L. Lyall, J. P. Lowe, U. Hintermair, 'Catalyst speciation and deactivation in the ruthenium-mediated transformation of ethynyl- β -ionol to α,β -unsaturated esters for vitamin A synthesis', *Catal. Sci. Technol.* **2025**, 15, 355–375.
- [3] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, 'NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist', *Organometallics* **2010**, 29, 2176–2179.
- [4] K. Izutsu, 'Electrochemistry in Nonaqueous Solutions', Wiley, Weinheim, **2002**.
- [5] N. Elgrishi, K. J. Rountree, B. D. McCarthy, E. S. Rountree, T. T. Eisenhart, J. L. Dempsey, 'A Practical Beginner's Guide to Cyclic Voltammetry', *J. Chem. Educ.* **2018**, 95, 197–206.
- [6] R. G. Compton, C. E. Banks, 'Understanding Voltammetry', World Scientific, New Jersey, **2025**.
- [7] T. Rundlöf, M. Mathiasson, S. Bekiroglu, B. Hakkarainen, T. Bowden, T. Arvidsson, 'Survey and qualification of internal standards for quantification by ^1H NMR spectroscopy', *J. Pharm. Biomed. Anal.* **2010**, 52, 645–651.
- [8] M. Tavanti, F. Parmeggiani, J. R. G. Castellanos, A. Mattevi, N. J. Turner, 'One-Pot Biocatalytic Double Oxidation of α -Isophorone for the Synthesis of Ketoisophorone', *ChemCatChem* **2017**, 9, 3338–3348.
- [9] V. B. Kharitonov, E. Podyacheva, D. Chusov, Y. V. Nelyubina, D. V. Muratov, D. A. Loginov, 'Planar Chiral Rhodium Complex Based on the Tetrahydrofluorenyl Core for Enantioselective Catalysis', *Org. Lett.* **2023**, 25, 8906–8911.
- [10] T. J. Kuczmara, P. Puylaert, B. J. Nachtsheim, 'Oxidation of benzylic alcohols to carbonyls using *N*-heterocyclic stabilized λ^3 -iodanes', *Beilstein J. Org. Chem.* **2024**, 20, 1677–1683.
- [11] T. Shen, J. Zhao, X. Ren, Z.-Q. Liu, S. Liu, 'Metal-Free Electrochemical Allylic C–H Aerobic Oxidation', *J. Org. Chem.* **2025**, 90, 1148–1158.
- [12] S. Serra, 'MnO₂/TBHP: A Versatile and User-Friendly Combination of Reagents for the Oxidation of Allylic and Benzylic Methylene Functional Groups', *Eur. J. Org. Chem.* **2015**, 6472–6478.
- [13] D. Clemente-Tejeda, A. López-Moreno, F. A. Bermejo, 'Non-heme iron catalysis in C=C, C–H, and CH₂ oxidation reactions. Oxidative transformations on terpenoids catalyzed by Fe(bpmen)(OTf)₂', *Tetrahedron* **2013**, 69, 2977–2986.
- [14] C. Zanato, A. Pelagalli, K. F. M. Marwick, M. Piras, S. Dall'Angelo, A. Spinaci, R. G. Pertwee, D. J. A. Wyllie, G. E. Hardingham, M. Zanda, 'Synthesis, radio-synthesis and in vitro evaluation of terminally fluorinated derivatives of HU-210 and HU-211 as novel candidate PET tracers', *Org. Biomol. Chem.* **2017**, 15, 2086–2096.
- [15] W. S. Grainger, E. J. Parish, 'Allylic oxidation of steroidal olefins by vanadyl acetylacetonate and tert-butyl hydroperoxide', *Steroids* **2015**, 101, 103–109.
- [16] V. Amountzias, D. Abatis, N. Aligiannis, 'Chemical Constituents from the Fruits of *Paliurus spina-christi*', *Chem. Nat. Compd.* **2024**, 60, 714–716.
- [17] Y. Zhao, Y.-Y. Yeung, 'An Unprecedented Method for the Generation of *tert*-Butylperoxy Radical Using DIB/TBHP Protocol: Solvent Effect and Application on Allylic Oxidation', *Org. Lett.* **2010**, 12, 2128–2131.
- [18] S. Nurfazilah Wan Yusop, S. Imran, M. Ilham Adenan, K. Ashraf, S. Sultan, 'Biocatalytic modifications of ethynodiol diacetate by fungi, anti-proliferative activity, and acetylcholinesterase inhibitory of its transformed products', *Steroids* **2021**, 171, 108832.

Supporting Information

Electrochemical Dehydration of Sulfonic Acids to their Anhydrides

Enrico Lunghi,^[a] Annemijn M. van Koten,^[a] Johannes Schneider,^[b] and Siegfried R. Waldvogel^{*[a,c]}

E-Mail: siegfried.waldvogel@cec.mpg.de

^[a] Max-Planck-Institute for Chemical Energy Conversion (MPI CEC), Stiftstraße 34–36, 45470 Mülheim an der Ruhr (Germany)

^[b] Department of Chemistry, Johannes Gutenberg University (JGU), Duesbergweg 10-14, 55128 Mainz

^[c] Karlsruhe Institute of Technology (KIT), Institute of Biological and Chemical Systems – Functional Molecular Systems (IBCS FMS), Kaiserstraße 12, 76131 Karlsruhe (Germany)

Table of Contents

GENERAL ASPECTS	S3
1.1 General Information	S3
1.2 Instruments and Analytical Methods	S3
1.3 Electrochemical Setup	S3
EXPERIMENTAL PROCEDURES	S5
1.4 General protocol for the synthesis of sulfonic anhydrides and their derivatives (GP1)	S5
1.5 General protocol for the optimization of reaction conditions (GP2)	S5
1.6 General protocol for scale-up	S6
OPTIMIZATION	S7
CONTROL EXPERIMENTS	S10
CYCLOVOLTAMMETRY STUDIES	S11
COMPOUND CHARACTERIZATION	S14
1.7 1-(Methylsulfonyl)pyrrolidine (2a)	S14
1.8 <i>N</i> -Phenyl methanesulfonamide (2b)	S14
1.9 4-(Methylsulfonyl)morpholine (2c)	S14
1.10 1-(Methylsulfonyl)imidazole (2d)	S14
1.11 1-(Methylsulfonyl)indole (2e)	S14
1.12 <i>N</i> -Butyl methanesulfonamide (2f)	S15
1.13 <i>N</i> -Ethyl- <i>N</i> -methyl methanesulfonamide (2g)	S15
1.14 <i>O</i> -Phenyl methanesulfonate (3a)	S15
1.15 <i>O</i> -Butyl methanesulfonate (3b)	S15
1.16 <i>O</i> -Cyclohexyl methanesulfonate (3c)	S16
1.17 Cyclohex-3-en-1-yl methanesulfonate (3d)	S16
1.18 1,1-Dimethylethyl-4-((methylsulfonyl)oxy)piperidine-1-carboxylate (3e)	S16
1.19 Methyl (S)-2-((methylsulfonyl)oxy)propanoate (3f)	S16
1.20 1-(Phenylsulfonyl)pyrrolidine (4a)	S16
1.21 1-Tosyl pyrrolidine (4b)	S17
1.22 1-((4-Bromophenyl)sulfonyl)pyrrolidine (4c)	S17
1.23 1-((4-Chlorophenyl)sulfonyl)pyrrolidine (4d)	S17
1.24 1-((4-Methoxyphenyl)sulfonyl)pyrrolidine (4e)	S17
1.25 <i>N</i> -Phenyl ethanesulfonamide (4f)	S18
1.26 <i>N</i> -Phenyl propanesulfonamide (4g)	S18
1.27 <i>N</i> -Phenyl-2,2,2-trifluoroethanesulfonamide (4h)	S18
1.28 4-Cyano- <i>N</i> -phenylbenzenesulfonamide (4i)	S18
1.29 <i>N</i> -Phenyl 1-methylethanesulfonamide (4j)	S18
1.30 <i>N</i> -Phenyl phenylmethanesulfonamide (4k)	S19
1.31 Limitations of the Scope/Unsuccessful Substrates	S19
NMR SPECTRA	S21
MASS SPECTRA	S45
RADICAL TRAPPING EXPERIMENT	S46
AUTHOR CONTRIBUTIONS	S47
REFERENCES	S48

General aspects

1.1 General Information

If not stated otherwise, all reactions were performed at ambient conditions and chemicals in analytical grade were used as purchased without further purification. Cyclohexane and ethyl acetate used for column chromatography were purchased in HPLC grade. Acetonitrile was commercially obtained in LCMS grade. These solvents were used without further treatment. The IUPAC nomenclature for the substances was checked using OPSIN parser.¹

1.2 Instruments and Analytical Methods

Chromatography

Thin layer chromatography (TLC) for reaction monitoring was performed using DC Kieselgel 60 F₂₅₄ on aluminium plates (*Merck KGaA*, Darmstadt, Germany). A UV lamp ($\lambda = 254$ nm, UV-4 S/L, *Herolab GmbH Laborgeräte*, Wiesloch, Germany) and potassium permanganate solution (3 g KMnO₄, 20 g K₂CO₃, 5 mL NaOH (5%), 300 mL H₂O) were used for staining of TLC plates. Preparative column chromatography was performed manually on 100-200 mesh silica gel.

Gas Chromatography coupled with Mass Spectrometry (GC/MS)

Analysis of crude reaction mixtures and purified products were performed using a GCMS QP2010SE (*Shimadzu*, Kyoto, Japan) equipped with an electron ionization (EI) source and a quadrupole mass analyzer. A quartz capillary column HI-5MS (*Avantor VWR*, Radnor, USA) with the following specification was used: length of 30 m, inner diameter of 0.25 mm and a stationary phase [(5%-phenyl)-dimethylsiloxane] of 0.25 μ m thickness. Helium was used as carrier gas with a constant velocity of 30 cm/s. The GC temperature ramp started at 50 °C (holding for 1 min) and heated to 300 °C (holding for 4.71 min) with a temperature ramp of 17.5 °C/min (total program time: 20.0 min). Measurements were performed at an injector temperature of 270 °C and a temperature of the EI source of 250 °C.

Nuclear Magnetic Resonance (NMR) Spectroscopy

¹H NMR and ¹³C{¹H} NMR spectra were recorded at 25 °C on a Bruker AVANCE III HD 400 MHz NMR spectrometer with a Bruker Prodigy probe (*Bruker BioSpin GmbH*, Rheinstetten, Germany) using CDCl₃ or DMSO as deuterated solvent. All chemical shifts are reported in δ -scale as parts per million [ppm] (multiplicity, coupling constant *J*, number of protons), relative to the solvent residual peaks as the internal standard.² Coupling constants *J* are given in Hertz [Hz]. The following abbreviations were used to describe the signals: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), sext (sextet), hept (heptet), m (multiplet), br (broad signal). The spectra obtained were evaluated with MestReNova 14 (*Mestrelab Research S.L.*, Spain).

High Resolution Mass Spectrometry

Mass spectra *via* electrospray-ionization (ESI+) were recorded using a Q Exactive™ mass spectrometer (*Thermo Fischer Scientific*™, Waltham, USA). Mass spectra *via* electron-ionization (EI) were recorded using a Q Exactive™ GC Orbitrap™ GC-MS/MS (*Thermo Fischer Scientific*™, Waltham, USA) equipped with an XTI-5 column (*Restek GmbH*, Bad Homburg v. d. Höhe, Deutschland).

Cyclic Voltammetry (CV) Measurements

Cyclic voltammetry was performed using a Metrohm 663 VA Stand equipped with an Autolab type III potentiostat (*Metrohm AG*, Herisau, Switzerland). WE: glassy carbon electrode (*d* = 2 mm); CE: glassy carbon rod; RE: Ag/AgNO₃; Scan rate ν = 100 mV/s. Electrolyte: NBu₄BF₄ (0.1 mol/L) in acetonitrile; *c*(substrate) = 10 mmol/L; *V* = 5 mL. All solutions have been deoxygenated by bubbling with argon for 10 min prior to measurement. Electrodes have been thoroughly rinsed before and after each measurement with acetone and acetonitrile. The glassy carbon working electrode was polished with alumina paste (1 μ m followed by 0.1 μ m) and sonicated for 5 min each in between measurements. All data is displayed against the half-wave potential of ferrocene/ferrocenium redox couple (FcH/FcH⁺; -0.10 V vs. Ag/AgNO₃) as internal reference. Oxidation potentials are marked and displayed as the half-wave potential of the respective peak.³

1.3 Electrochemical Setup

Galvanostat (DC power supply)

Electrochemical reactions were carried out using a multichannel galvanostat HMP4040 programmable power supply (4 channels per device; max. electric current per channel: 10 A; max. power per channel: 160 W; total output power per device: 384 W; upper terminal voltage limit per channel: 32 V; Rohde & Schwarz GmbH & Co. KG, Munich, Germany).

Screening and small-scale batch-type reactions

Screening reactions were carried out in undivided/quasi-divided Teflon™ cells with a volume of 5 mL equipped with two electrodes and a round, cross-shaped stirring bar. The described system is commercially available as IKA Screening System Package (*IKA*™ *Werke GmbH & Co. KG*, Staufen, Germany). Detailed description of these cells are reported in the literature.⁴

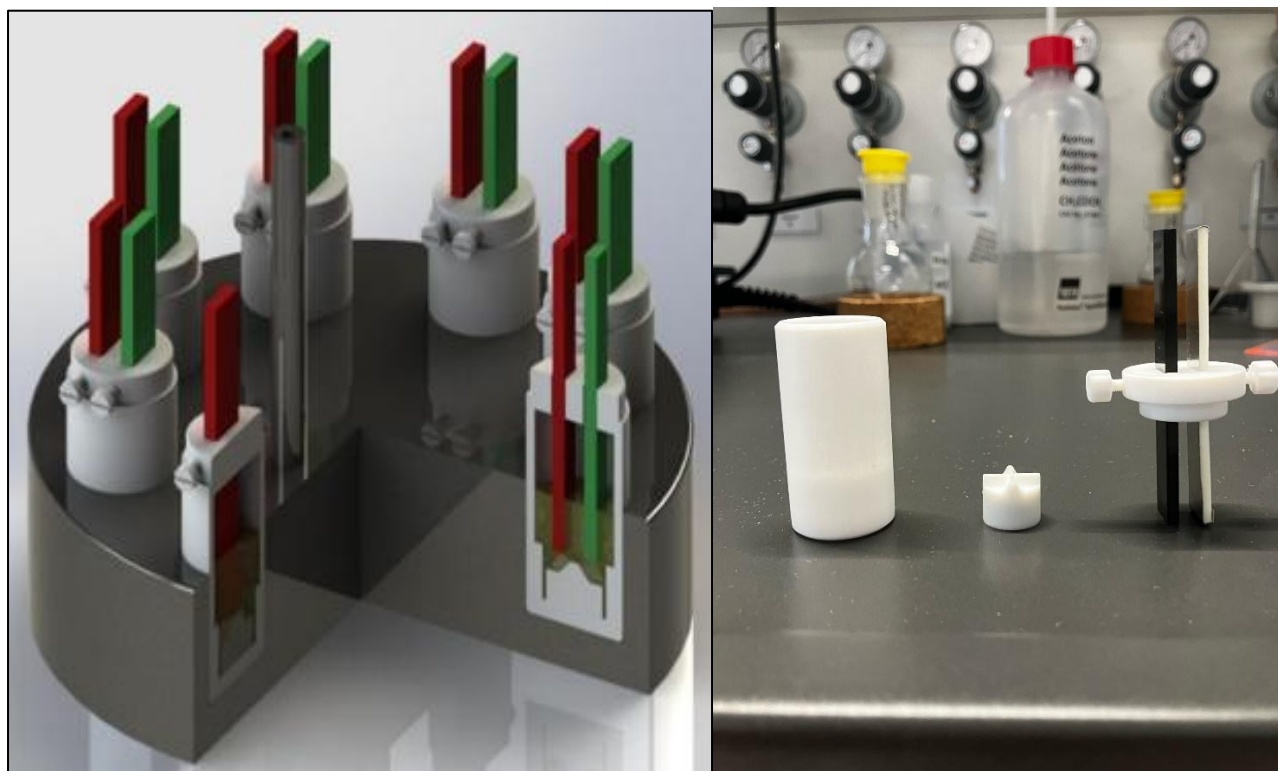


Figure S1: Undivided screening setup as available from IKA equipped with glassy carbon as anode and platinum as cathode (left) and undivided cell equipped with platinum foil and glassy carbon (right).⁵

The screening was carried out using various electrode materials (electrode size: 7 cm × 1 cm × 0.3 cm). Graphite electrodes were sanded using sandpaper of grit size 600, followed by grit size 1000, and cleaned with acetonitrile prior to use. BDD electrodes were electrochemically treated as anode ($j = 50 \text{ mA/cm}^2$) in 20% (v/v) sulfuric acid for 10 min before use. The anodes were immersed 1.8 cm into the electrolyte. This resulted in a geometric active electrode area of 1.8 cm^2 .

Table S1: Electrode materials, specification, and supplier.

Entry	Electrode Material	Specification	Supplier
1	Boron-doped diamond (BDD)	15 μm BDD on silicon carrier material	CONDIA GmbH, Itzehoe, Germany
2	Glassy Carbon	Sigradur G	HTW, Thierhaupten, Germany
3	Graphite	highly isostatic, V2100	SGL Carbon, Bonn, Germany
4	Graphite foil (Sigraflex™)	F02012Z	SGL Carbon, Meitingen, Germany
5	Platinum	99.9% Pt	ÖGUSSA, Vienna, Austria.

Scale-up

The scale-up experiment was performed in a double-walled undivided glass cell with no thermostat attached, with a volume of 100 mL equipped with a PTFE stopper and sleeve, electrodes, electrode holders and a cross-shaped stirring bar. The cell is commercially available via HWS Labortechnik (Mainz, Germany) as Sigma-Aldrich within the SynLectro™ series. The electrolysis was carried out using a TDK-Lambda Z+ series (TDK-Lambda UK Limited, Devon, United Kingdom) as power supply. The glassy carbon anode was held in place using a PTFE support frame. Its dimensions were 6 cm × 2 cm × 0.02 cm and was half submerged into the solution. This resulted in an active electrode area of 6 cm^2 . As cathode, a platinum foil (3 x 2 cm) was used and placed in front of the anode by a PTFE support frame. The interelectrode gap is 0.5 cm. The stoppers and electrode holders are available from Sigma-Aldrich within the SynLectro™ series.



Figure S2: 100 mL undivided cell with glassy carbon anode and platinum cathode and electrode holders used for the scale-up.

Experimental Procedures

1.4 General protocol for the synthesis of sulfonic anhydrides and their derivatives (GP1)

Caution! Methanesulfonic acid (CAS 75-75-2) and methanesulfonic anhydride (CAS 7143-01-3) are highly corrosive and cause severe skin burns and eye damage! They must be handled with extreme care!

The reactions are carried out using the undivided Teflon™ cells with a glassy carbon anode and a platinum foil as a cathode as described in the section before.

Electrolyte: An undivided Teflon™ cell is filled with a sulfonic acid (3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (0.5 mmol, 0.15 equiv.), and acetonitrile (5 mL).

The lid including a prefixed glassy carbon anode and a platinum cathode is attached to the cell, the electric current is set accordingly so that a current density of 75 mA/cm² is reached (172 mA with the setup described herein) and the amount of applied charge is set to 3 F (1143 C for 3.54 mmol of starting material). The electrolysis is carried out at room temperature under constant stirring (900 rpm) for ca. 1 h 50 min. After completion of the electrolysis, 5 equiv. of an amine (**2a**, **2b**, **2c**, **2f**, **2g**, **4a-k**) or 2 equiv. of triethylamine and 2 equiv. of amine (**2d**, **2e**) or 2 equiv. of triethylamine and 2 equiv. of an alcohol (**3a-f**) are added to the reaction mixture in the same reaction vessel and the solution is stirred overnight. The solvent is then removed under vacuum and the residue is dissolved in ethyl acetate, washed two times with aqueous HCl (1 mol/L, 2x10 mL), two times with saturated aqueous NaHCO₃ solution (2x10 mL) and one time with brine (1x10 mL). The organic layer is then dried over MgSO₄, filtered and concentrated under vacuum. The crude was then purified *via* column chromatography using cyclohexane and ethyl acetate.

1.5 General protocol for the optimization of reaction conditions (GP2)

The reactions are carried out using the undivided Teflon™ cells with a PTFE lid including the anode and a cathode as described in the section before.

Electrolyte: An undivided Teflon™ cell is filled with methanesulfonic acid (3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (0.5 mmol, 0.15 equiv.), and acetonitrile (5 mL).

The lid including the electrodes is attached to the cell, the electric current and amount of applied charge are set to the desired values, and the electrolysis was carried out at room temperature under constant stirring (900 rpm). After completion, 1,3,5-trichlorobenzene (60 mg) is added to the reaction mixture as an internal standard.² The solution is stirred for 5 min at room temperature and an aliquot (ca. 0.5 mL) is taken for qNMR measurement (¹H NMR, 400 MHz). The yield is calculated using the six protons of the product **2a** (Figure S3).

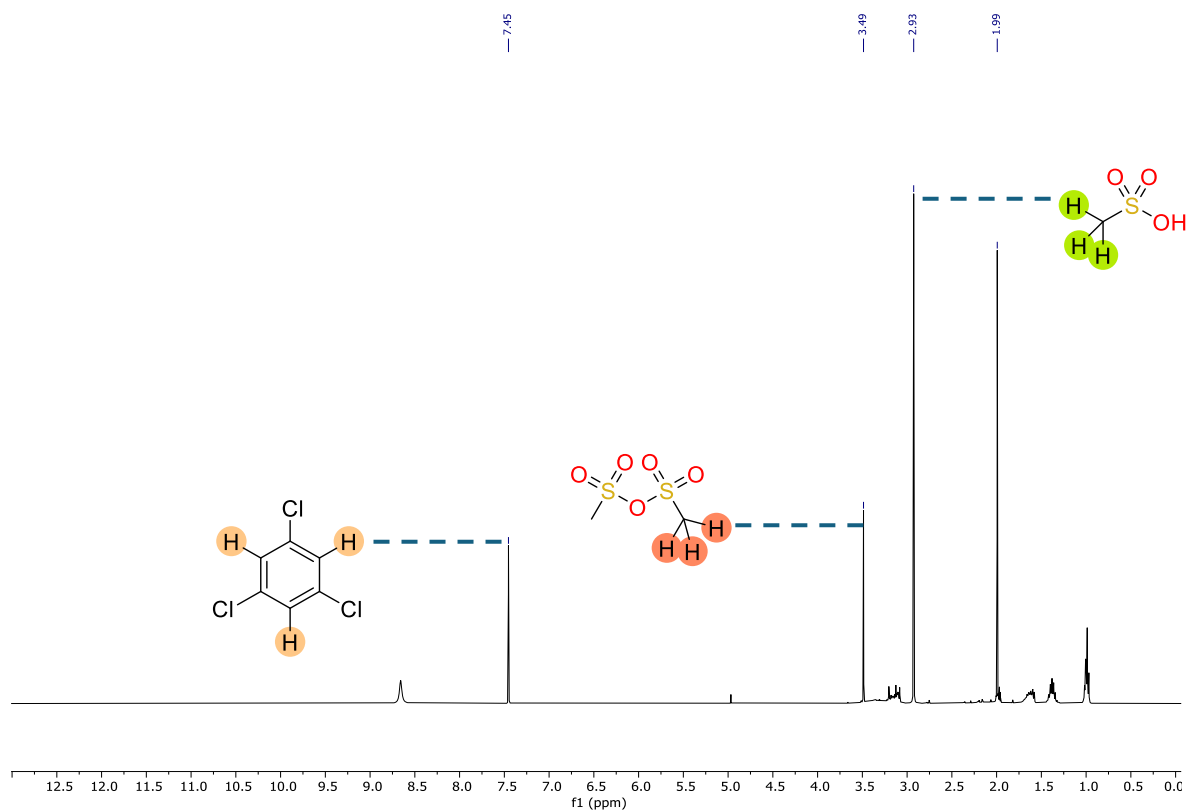


Figure S3: Typical ^1H NMR spectrum in CD_3CN of a reaction mixture used for quantification of product **2a**.²

1.6 General protocol for scale-up

The reaction is carried out using the undivided glass cell with a glassy carbon anode and a platinum foil as a cathode as described in the section above.

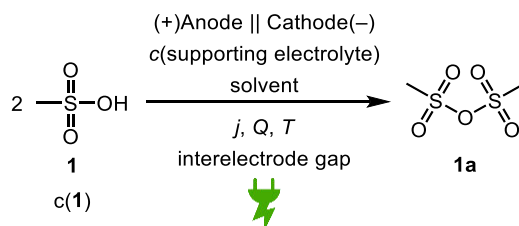
Electrolyte: The glass cell is filled with methanesulfonic acid (**1**, 2.25 mL, 35.4 mmol, 1 equiv.), NBu_4SCN (1.8 g, 5 mmol, 0.15 equiv.), and acetonitrile (50 mL).

The stopper including the electrodes and electrode holders is attached to the cell and connected to the power supply. The electric current is set accordingly so that a current density of 75 mA/cm^2 is reached (345 mA with the setup described herein) and the amount of applied charge is set to $3 F$ (corresponds to 11430 C when using 35.4 mmol of starting material). The electrolysis is carried out at room temperature under constant stirring (500 rpm) for ca. 9 h 35 min. After completion of the electrolysis, NMR yield was determined as described in **GP1**: 1,3,5-trichlorobenzene (600 mg) are dissolved in the reaction mixture. The solution was stirred for 5 min at room temperature and an aliquot (ca. 0.5 mL) was taken for qNMR measurement (^1H NMR, 400 MHz).

Spectroscopic data of the compound matched the one obtained from the small-scale reaction described in section “NMR Spectra”.

Optimization

Optimization of the reaction conditions was carried out by using a linear screening approach.⁴ Methanesulfonic acid (MsOH) was used as a test substrate according to **GP2**. Yields were determined by ¹H NMR spectroscopy in CD₃CN *via* the addition of 1,3,5-trichlorobenzene (60 mg) as an internal standard after the end of electrolysis.²



Initial experiments were carried out in an undivided Teflon™ cell with a planar glassy carbon anode and cathode (Table S2), with KSCN as supporting electrolyte.

Table S2: First experiments.

Entry	Anode	Cathode	Yield (¹ H NMR)
1	Graphite plate	Graphite plate	0%
2	Graphite plate	Stainless-steel plate	0%
3	Glassy carbon	Glassy carbon	11%

Conditions (GP2): KSCN (0.5 mmol, 0.15 equiv., 0.1 M), MeCN, $j = 50 \text{ mA cm}^{-2}$, 2 F, r.t., 5 mm interelectrode gap, 900 rpm.

Next, the current density was screened (Table S3). 75 mA cm^{-2} gave the best results, and screening was continued with this parameter. This is also beneficial because a higher current density decreases the electrolysis time.

Table S3: Screening of current densities.

$j \text{ [mA cm}^{-2}\text{]}$	1	1a
10	93%	5%
25	90%	8%
50	62%	11%
75	62%	34%
100	70%	26%

Conditions (GP2): KSCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), (+)GC||GC(-), MeCN, 2 F, r.t., 5 mm interelectrode gap, 900 rpm.

Screening of various interelectrode gaps (Table S4) showed no improvement to the previously used conditions, so the optimization was continued with 5 mm.

Table S4: Screening of interelectrode gap.

gap [mm]	1	1a
1	70%	28%
2	69%	28%
3	66%	32%
4	60%	34%
5	61%	34%

Conditions (GP2): KSCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), (+)GC||GC(-), $j = 75 \text{ mA cm}^{-2}$, MeCN, 2 F, r.t., 900 rpm.

Table S5: Screening of cathode materials.

Cathode	1	1a
GC	62%	34%
graphite	47%	49%
BDD	77%	22%
RVC	70%	27%
Pt	45%	51%

Conditions (GP2): KSCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, GC anode, MeCN, 2 F, r.t., interelectrode gap 5 mm, 900 rpm.
GC: glassy carbon, RVC: reticulated vitreous carbon foam, BDD: boron-doped diamond.

Table S6: Screening of anode materials.

Anode	1	1a
GC	45%	51%
Pt	56%	42%
Gr	60%	37%
Zn	-	-
Ni (foam)	-	-
BDD	56%	41%

Conditions (GP2): KSCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, MeCN, Pt cathode, 2 F, r.t., interelectrode gap 5 mm, 900 rpm.

Table S7: Screening of supporting electrolytes.

Supporting Electrolyte	1	1a
KSCN	45%	51%
EMIMSCN	90%	10%
NBu ₄ SCN	36%	62%

Conditions (GP2): supporting electrolyte (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, (+)GC||Pt(-), MeCN, 2 F, r.t., interelectrode gap 5 mm, 900 rpm.
EMIMSCN: 1-Ethyl-3-methylimidazolium thiocyanate.

Table S8: Screening of starting material concentrations.

$c(\text{CH}_3\text{SO}_3\text{H})$ [mol L ⁻¹]	1	1a
0.1	80%	17%
0.3	72%	26%
0.5	50%	44%
0.7	36%	62%
1.0	51%	44%

Conditions (GP2): NBu₄SCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), (+)GC||Pt(-), $j = 75 \text{ mA cm}^{-2}$ MeCN, 2 F, r.t., interelectrode gap 5 mm, 900 rpm.

Table S9: Screening of solvents.

Solvent	1	1a
DMSO	62%	0%
DMF	74%	0%
DMC	91%	7%
DMC/PC	84%	10%
MeCN	36%	62%

Conditions (GP2): NBu₄SCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, (+)GC||Pt(-), 2 F, r.t., interelectrode gap 5 mm, 900 rpm.
DMSO: dimethyl sulfoxide, DMF: dimethyl formamide, DMC: dimethyl carbonate, PC: propylene carbonate, MeCN: acetonitrile.

Table S10: Screening of the amount of applied charge.

$Q [F]$	1	1a
2.0	36%	62%
2.5	27%	70%
3.0	22%	74%
3.5	45%	51%

Conditions (GP2): NBu₄SCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, MeCN, (+)GC||Pt(-), r.t., interelectrode gap 5 mm, 900 rpm.

Table S11: Screening of concentrations of the supporting electrolyte NBu₄SCN.

$c(\text{NBu}_4\text{SCN})$ [mol L ⁻¹]	1	1a
0.07	42%	55%
0.1	22%	74%
0.3	52%	42%
0.5	58%	39%
0.7	75%	28%

Conditions (GP2): NBu₄SCN, $j = 75 \text{ mA cm}^{-2}$, MeCN, 3 F, (+)GC||Pt(-), r.t., interelectrode gap 5 mm, 900 rpm.

Table S12: Screening of temperatures.

T [°C]	1	1a
0	66%	29%
r.t.	22%	74%
50	50%	45%

Conditions (GP2): NBu₄SCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, MeCN, 3 F, (+)GC||Pt(-), interelectrode gap 5 mm, 900 rpm.

Table S13: Final optimized reaction conditions.

$c(\text{SM})$	Supporting Electrolyte (SE)	$c(\text{SE})$	j [mA cm ⁻²]	Cathode Material	Anode Material	T	Q [F]	Yield 1a (¹ H NMR)
0.7	NBu ₄ SCN	0.1	75	Pt	GC	r.t.	3	74%

Control Experiments

Several control experiments (Table S14) were performed using the optimized conditions (Table S13).

Table S14: Control experiments.

Entry	Deviation from the standard conditions ^[a]	Yield (¹ H NMR)
1	No electricity; stirred for 1.5 h at room temperature	0%
2	No SCN supporting electrolyte (0.1 mol/L NBu ₄ PF ₆ added for conductivity)	0%

[a]: Conditions (GP2): NBu₄SCN (0.5 mmol, 0.15 equiv., 0.1 mol/L), $j = 75 \text{ mA cm}^{-2}$, MeCN, 3 F, (+)GC||Pt(-), r.t., interelectrode gap 5 mm, 900 rpm.

Cyclic Voltammetry Studies

To investigate the interaction between the thiocyanate anion and methanesulfonic acid, we carried out cyclic voltammetry (CV) studies. When tetrabutylammonium thiocyanate was the only component in a solution in acetonitrile, a non-reversible oxidation peak was observed at +1.45 V (Figure S3, blue curve), indicating the oxidation of the SCN^- anion. A subsequent scan of the same solution decreased the oxidation peak, confirming that the oxidized species was neither fully consumed nor sequestered by another component. In contrast, upon the addition of methanesulfonic acid (MsOH), the first scan exhibited a broader oxidation peak at +1.45 V with a decreased current response, suggesting rapid trapping of the oxidation product by MsOH (Figure S3, orange curve). In the second scan, the oxidation peak was no longer detected, providing further evidence that the oxidized thiocyanate species had been effectively sequestered by MsOH.

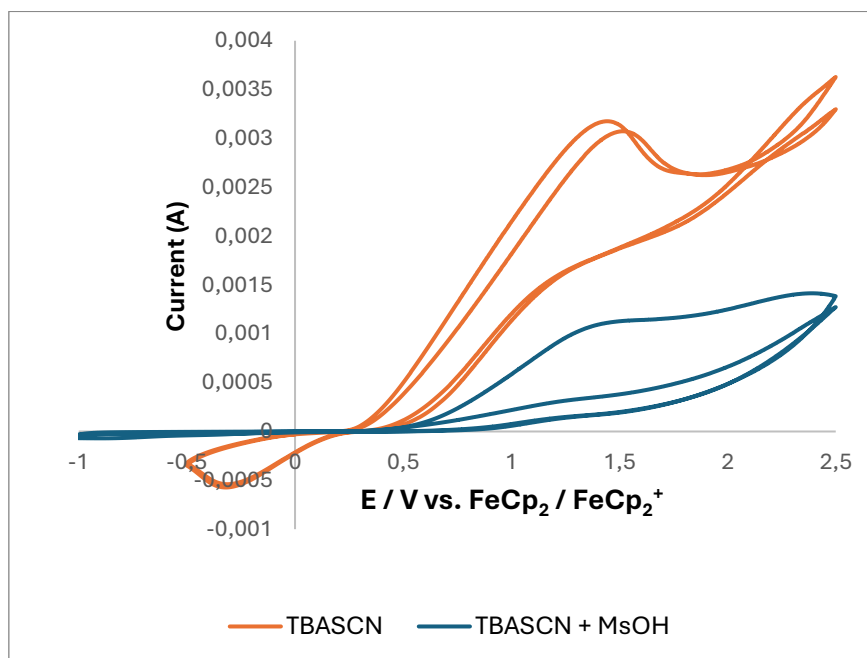


Figure S4: Cyclic voltammogram of 0.1 mol/L NBu_4SCN in MeCN (orange curve), addition of methanesulfonic acid 0.06 mol/L (blue curve), Ag^+/Ag reference electrode (RE), glassy carbon as working electrode (WE) and counter electrode (CE). All CV measurements were carried out under argon atmosphere. Each CV measurement was referenced against ferrocene. Oxidation potentials are marked and displayed as the half-wave potential of the respective peak (IUPAC convention). Scan has been taken in this direction: $0 \text{ V} \rightarrow +2.5 \text{ V} \rightarrow -0.5 \text{ V} \rightarrow 0 \text{ V}$.

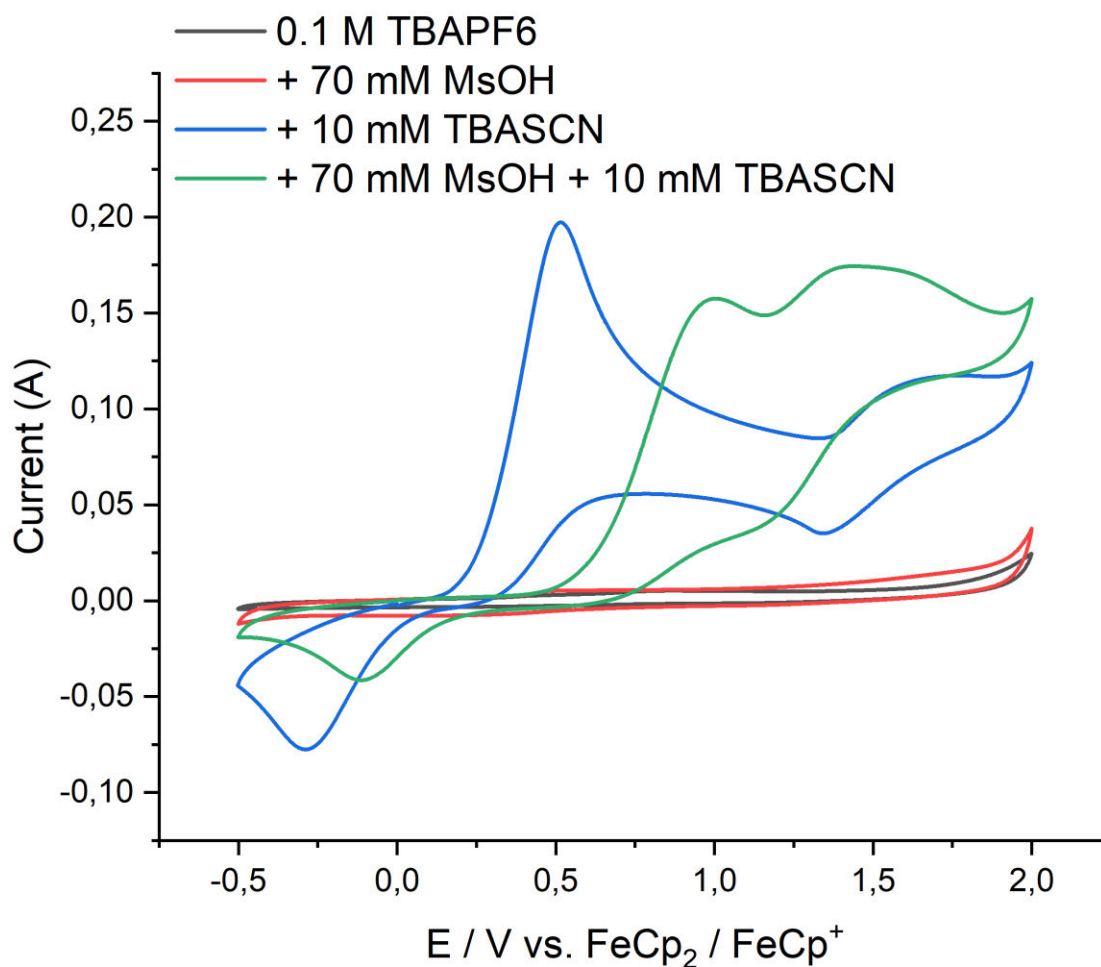


Figure S5: Cyclic voltammogram of 0.1 mol/L NBu_4PF_6 in MeCN (gray curve), addition of methanesulfonic acid 0.07 mol/L (red curve). CV of NBu_4SCN 10 mM in NBu_4PF_6 (blue curve), addition of methanesulfonic acid 70 mM (green curve). Ag^+/Ag reference electrode (RE), glassy carbon as working electrode (WE) and counter electrode (CE). All CV measurements were carried out under argon atmosphere. Each CV measurement was referenced against ferrocene. Oxidation potentials are marked and displayed as the half-wave potential of the respective peak (IUPAC convention). Scan has been taken in this direction: $0 \text{ V} \rightarrow +2.0 \text{ V} \rightarrow -0.5 \text{ V} \rightarrow 0 \text{ V}$.

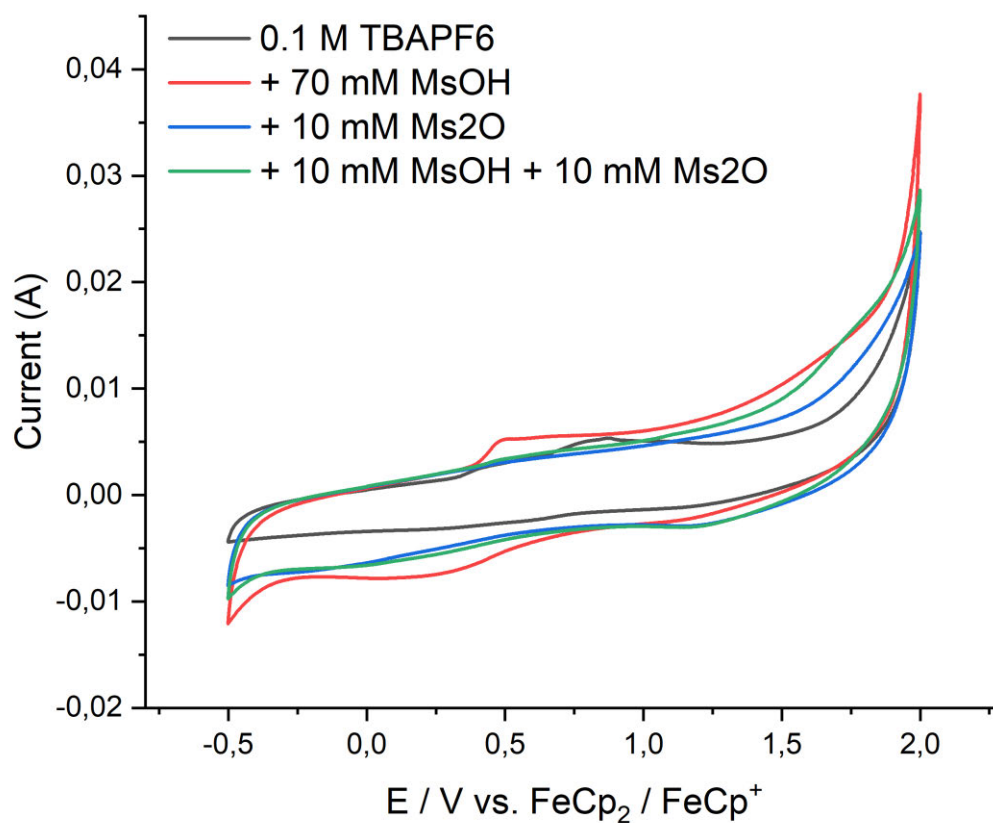
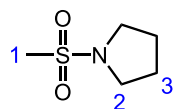


Figure S6: Cyclic voltammogram of 0.1 mol/L NBu_4PF_6 in MeCN (gray curve), addition of methanesulfonic acid 0.07 mol/L (red curve). CV of methanesulfonic anhydride 10 mM in NBu_4PF_6 (blue curve), addition of methanesulfonic acid 70 mM (green curve). Ag^+/Ag reference electrode (RE), glassy carbon as working electrode (WE) and counter electrode (CE). All CV measurements were carried out under argon atmosphere. Each CV measurement was referenced against ferrocene. Oxidation potentials are marked and displayed as the half-wave potential of the respective peak (IUPAC convention). Scan has been taken in this direction: $0 \text{ V} \rightarrow +2.0 \text{ V} \rightarrow -0.5 \text{ V} \rightarrow 0 \text{ V}$.

Compound Characterization

1.7 1-(Methylsulfonyl)pyrrolidine (2a)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and pyrrolidine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **2a** (181 mg, 1.2 mmol, 64%) was obtained as a yellow oil.



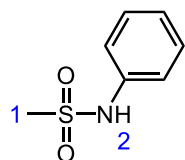
¹H NMR (400 MHz, CDCl₃) δ = 3.31 (t, *J* = 6.8 Hz, 4H, 2-*H*), 2.80 (s, 3H, 1-*H*), 1.99 – 1.86 (m, 4H, 3-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 48.0, 34.6, 25.8 ppm.

This NMR data agrees with the data previously reported in literature.⁶

1.8 N-Phenyl methanesulfonamide (2b)

According to GP1, methanesulfonic acid (MsOH) 340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **2b** (170 mg, 1 mmol, 56%) was obtained as a yellow oil.



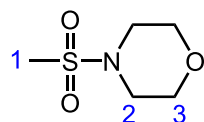
¹H NMR (400 MHz, DMSO) δ = 9.73 (s, 1H, 2-*H*), 7.40 – 7.26 (m, 2H, Ar-*H*), 7.26 – 7.16 (m, 2H, Ar-*H*), 7.15 – 7.04 (m, 1H, Ar-*H*), 2.97 (s, 3H, 1-*H*) ppm.

¹³C{¹H} NMR (101 MHz, DMSO) δ = 138.4, 129.4, 123.9, 119.8, 39.2 ppm.

This NMR data agrees with the data previously reported in literature.⁷

1.9 4-(Methylsulfonyl)morpholine (2c)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and morpholine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **2c** (174 mg, 1.05 mmol, 60%) was obtained as a yellow oil.

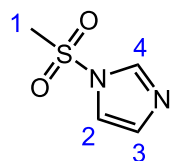


¹H NMR (400 MHz, CDCl₃) δ = 3.83 – 3.75 (m, 4H, 2-*H*), 3.25 – 3.17 (m, 4H, 3-*H*), 2.79 (s, 3H, 1-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 66.3, 45.9, 34.1, 29.7 ppm.

1.10 1-(Methylsulfonyl)imidazole (2d)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and imidazole (17.7 mmol, 1.2 g, 5 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 1/1 → 3/7), the desired product **2d** (160 mg, 1.1 mmol, 63%) was obtained as a white solid.



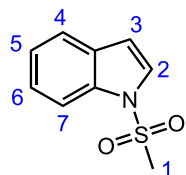
¹H NMR (400 MHz, CDCl₃) δ = 7.96 (m, 1H, 4-*H*), 7.32 (m, 1H, 2-*H*), 7.16 (m, 1H, 3-*H*), 3.27 (s, 3H, 1-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 136.6, 131.7, 117.4, 43.8 ppm.

This NMR data agrees with the data previously reported in literature.⁹

1.11 1-(Methylsulfonyl)indole (2e)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and indole (7.08 mmol, 828 mg, 2 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 1/1 → 4/6), the desired product **2e** (140 mg, 0.71 mmol, 41%) was obtained as a viscous colorless oil.



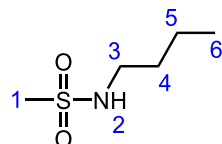
¹H NMR (400 MHz, CDCl₃) δ = 7.85 (dq, J = 8.3, 0.9 Hz, 1H, 7-*H*), 7.61 – 7.52 (m, 1H, 4-*H*), 7.37 (d, J = 3.7 Hz, 1H, 6-*H*), 7.30 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H, 2-*H*), 7.26 – 7.20 (m, 1H, 5-*H*), 6.64 (dd, J = 3.7, 0.9 Hz, 1H, 3-*H*), 3.02 (s, 3H, 1-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 134.7, 130.5, 125.9, 124.7, 123.4, 121.5, 112.8, 108.7, 40.5 ppm.

This NMR data agrees with the data previously reported in literature.¹⁰

1.12 *N*-Butyl methanesulfonamide (2f)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and 1-butylamine (17.7 mmol, 1.7 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **2f** (171 mg, 1.13 mmol, 64%) was obtained as a colorless oil.



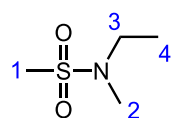
¹H NMR (400 MHz, CDCl₃) δ = 4.74 (s, 1H, 2-*H*), 3.09 (t, J = 7.1 Hz, 2H, 3-*H*), 2.93 (s, 3H, 1-*H*), 1.59 – 1.47 (m, 2H, 4-*H*), 1.43 – 1.29 (m, 2H, 5-*H*), 0.91 (t, J = 7.3 Hz, 3H, 6-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 43.1, 40.1, 32.1, 19.8, 13.7 ppm.

This NMR data agrees with the data previously reported in literature.¹¹

1.13 *N*-Ethyl-*N*-methyl methanesulfonamide (2g)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and methyl ethyl amine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **2g** (135 mg, 0.99 mmol, 56%) was obtained as colorless oil.



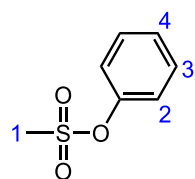
¹H NMR (400 MHz, CDCl₃) δ = 3.23 (q, J = 7.1 Hz, 2H), 2.85 (s, 3H), 2.79 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 44.8, 35.8, 33.9, 13.3 ppm.

HRMS (EI, m/z): [M]⁺ = calcd. For C₄H₁₁NO₂S⁺ : 137.050501, found: 137.050500.

1.14 *O*-Phenyl methanesulfonate (3a)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and phenol (7.08 mmol, 665 mg, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 7/3), the desired product **3a** (115 mg, 0.66 mmol, 50%) was obtained as a white crystalline solid.



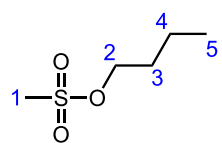
¹H NMR (400 MHz, CDCl₃) δ = 7.39 – 7.30 (m, 2H, 3-*H*), 7.28 – 7.17 (m, 3H, 2-4-*H*), 3.05 (s, 3H, 1-*H*) ppm.

This NMR data agrees with the data previously reported in literature.¹²

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 149.33, 130.1, 127.5, 122.0, 37.3 ppm

1.15 *O*-Butyl methanesulfonate (3b)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and 1-butanol (7.08 mmol, 0.65 mL, 2 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 8/2), the desired product **3b** (177 mg, 1.16 mmol, 66%) was obtained as a pale yellow oil.



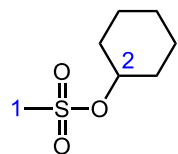
¹H NMR (400 MHz, CDCl₃) δ = 4.17 (t, J = 6.5 Hz, 2H, 2-*H*), 2.94 (s, 3H, 1-*H*), 1.67 (ddt, J = 8.9, 7.9, 6.5 Hz, 2H, 3-*H*), 1.45 – 1.27 (m, 2H, 4-*H*), 0.89 (t, J = 7.4 Hz, 3H, 5-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 70.0, 37.4, 31.2, 18.8, 13.6 ppm.

This NMR data agrees with the data previously reported in literature.¹³

1.16 O-Cyclohexyl methanesulfonate (3c)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and cyclohexanol (7.08 mmol, 0.74 mL, 2 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 8/2), the desired product **3c** (182 mg, 1.03 mmol, 58%) was obtained as a clear oil



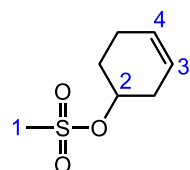
¹H NMR (400 MHz, CDCl₃) δ = 4.68 (tt, *J* = 9.1, 3.9 Hz, 1H, 2-*H*), 2.99 (s, 3H, 1-*H*), 2.03 – 1.91 (m, 2H, CyHex-*H*), 1.83 – 1.71 (m, 2H, CyHex-*H*), 1.69 – 1.57 (m, 2H, CyHex-*H*), 1.57 – 1.47 (m, 1H, CyHex-*H*), 1.46 – 1.14 (m, 4H, CyHex-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 81.5, 38.9, 32.8, 24.9, 23.6 ppm.

This NMR data agrees with the data previously reported in literature.¹³

1.17 Cyclohex-3-en-1-yl methanesulfonate (3d)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and cyclohexen-3-ol (7.08 mmol, 0.86 mL, 2 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 8/2), the desired product **3d** (202 mg, 1.15 mmol, 65%) was obtained as a colorless oil.



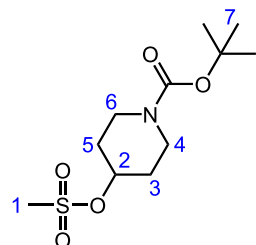
¹H NMR (400 MHz, CDCl₃) δ = 5.70 (ddt, *J* = 7.3, 3.5, 1.8 Hz, 1H, 3-*H*), 5.61 – 5.52 (m, 1H, 4-*H*), 4.96 (tq, *J* = 8.8, 3.2 Hz, 1H, 2-*H*), 3.02 (s, 3H, 1-*H*), 2.57 – 2.44 (m, 1H, CyHex-*H*), 2.40 – 2.10 (m, 3H, CyHex-*H*), 2.09 – 1.85 (m, 2H, CyHex-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 127.0, 122.8, 78.2, 38.9, 31.8, 28.5, 23.2 ppm.

HRMS (ESI, *m/z*): [M+Na]⁺ = calcd. For C₇H₁₃O₃SN⁺: 199.03994, found: 199.03999

1.18 1,1-Dimethylethyl-4-((methylsulfonyl)oxy)piperidine-1-carboxylate (3e)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and 1-Boc-4-hydroxypiperidine (7.08 mmol, 1.4 g, 2 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **3e** (331 mg, 1.18 mmol, 67%) was obtained as an off-white solid.



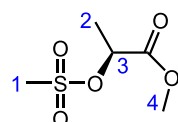
¹H NMR (400 MHz, CDCl₃) δ = 4.88 (tt, *J* = 7.8, 3.8 Hz, 1H, 2-*H*), 3.70 (ddd, *J* = 13.8, 7.0, 4.0 Hz, 2H, 3-*H*), 3.30 (ddd, *J* = 13.7, 8.1, 3.8 Hz, 2H, 5-*H*), 3.03 (s, 3H, 1-*H*), 1.96 (ddt, *J* = 10.9, 7.3, 3.9 Hz, 2H, 4-*H*), 1.81 (dtd, *J* = 12.3, 7.9, 4.0 Hz, 2H, 6-*H*), 1.46 (s, 9H, 7-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 154.7, 80.1, 77.8, 39.0, 31.8, 28.5 ppm.

This NMR data agrees with the data previously reported in literature.¹⁴

1.19 Methyl (S)-2-((methylsulfonyl)oxy)propanoate (3f)

According to GP1, methanesulfonic acid (MsOH) (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), triethylamine (1.5 mL, 10.6 mmol, 3 equiv.) and (–)-methyl L-lactate (7.08 mmol, 0.74 mL, 2 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 8/2), the desired product **3f** (201 mg, 1.11 mmol, 63%) was obtained as a clear oil.



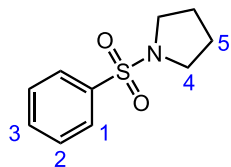
¹H NMR (400 MHz, CDCl₃) δ = 5.14 (q, *J* = 7.0 Hz, 1H, 3-*H*), 3.80 (s, 3H, 4-*H*), 3.15 (s, 3H, 1-*H*), 1.62 (d, *J* = 7.0 Hz, 3H, 2-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 170.1, 74.2, 53.0, 39.3, 18.5 ppm.

This NMR data agrees with the data previously reported in literature.¹⁵

1.20 1-(Phenylsulfonyl)pyrrolidine (4a)

According to GP1, benzenesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and pyrrolidine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 F. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4a** (82 mg, 0.39 mmol, 22%) was obtained as a pale yellow viscous foam.



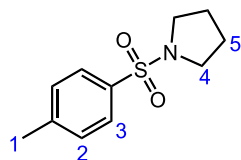
¹H NMR (400 MHz, CDCl₃) δ = 7.87 – 7.81 (m, 2H, 1-*H*), 7.64 – 7.57 (m, 1H, 3-*H*), 7.56 – 7.49 (m, 2H, 2-*H*), 3.31 – 3.19 (m, 4H, 4-*H*), 1.82 – 1.70 (m, 4H, 5-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 137.1, 132.7, 129.1, 127.6, 48.1, 25.4 ppm.

This NMR data agrees with the data previously reported in literature.^{6,8,16}

1.21 1-Tosyl pyrrolidine (4b)

According to GP1, p-toluensulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and pyrrolidine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4b** (31 mg, 0.14 mmol, 8%) was obtained as a pale yellow oil.



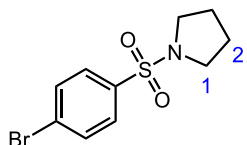
¹H NMR (400 MHz, CDCl₃) δ = 7.72 (d, *J* = 8.3 Hz, 2H, 3-*H*), 7.32 (d, *J* = 8.0 Hz, 2H, 2-*H*), 3.29 – 3.18 (m, 4H, 4-*H*), 2.43 (s, 3H, 1-*H*), 1.80 – 1.70 (m, 4H, 5-*H*) ppm.

¹³C NMR couldn't be measured because of the low quantity resulted in bad signal to noise ration in the spectrum

This NMR data agrees with the data previously reported in literature.^{6,17}

1.22 1-((4-Bromophenyl)sulfonyl)pyrrolidine (4c)

According to GP1, 4-bromobenzenesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and pyrrolidine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4c** (56 mg, 0.19 mmol, 11%) was obtained as a brown oil.



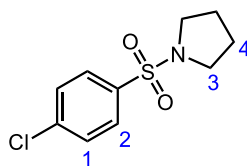
¹H NMR (400 MHz, CDCl₃) δ = 7.72 – 7.60 (m, 4H, Ar-*H*), 3.27 – 3.16 (m, 4H, 1-*H*), 1.82 – 1.69 (m, 4H, 2-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 136.1, 132.4, 129.0, 127.6, 48.0, 25.3 ppm.

This NMR data agrees with the data previously reported in literature.^{6,8}

1.23 1-((4-Chlorophenyl)sulfonyl)pyrrolidine (4d)

According to GP1, 4-chlorobenzenesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and pyrrolidine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4d** (65 mg, 0.26 mmol, 15%) was obtained as a pale yellow oil.



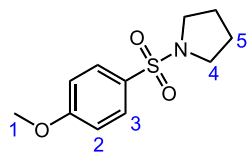
¹H NMR (400 MHz, CDCl₃) δ = 7.81 – 7.74 (m, 2H, 2-*H*), 7.54 – 7.48 (m, 2H, 1-*H*), 3.30 – 3.19 (m, 4H, 3-*H*), 1.85 – 1.72 (m, 4H, 4-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 139.2, 135.7, 129.5, 129.0, 48.1, 25.4 ppm.

This NMR data agrees with the data previously reported in literature.^{6,8}

1.24 1-((4-Methoxyphenyl)sulfonyl)pyrrolidine (4e)

According to GP1, 4-methoxybenzenesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and pyrrolidine (17.7 mmol, 1.5 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4e** (123 mg, 0.51 mmol, 29%) was obtained as a pale yellow oil.



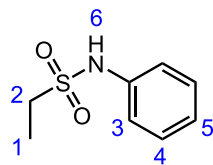
¹H NMR (400 MHz, CDCl₃) δ = 7.84 – 7.75 (m, 2H, 3-*H*), 7.06 – 6.97 (m, 2H, 2-*H*), 3.90 (s, 3H, 1-*H*), 3.34 – 3.18 (m, 4H, 4-*H*), 1.86 – 1.72 (m, 4H, 5-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 162.9, 129.6, 128.8, 114.1, 55.6, 47.9, 25.2 ppm.

This NMR data agrees with the data previously reported in literature.¹⁸

1.25 *N*-Phenyl ethanesulfonamide (**4f**)

According to GP1, ethanesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 7/3), the desired product **4f** (199 mg, 1.08 mmol, 61%) was obtained as a colorless viscous oil.



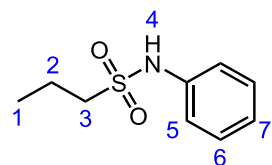
¹H NMR (400 MHz, CDCl₃) δ = 7.41 – 7.33 (m, 2H, 3-*H*), 7.30 – 7.22 (m, 2H, 4-*H*), 7.19 (td, *J* = 7.3, 1.2 Hz, 1H, 5-*H*), 6.82 (s, 1H, 6-*H*), 3.16 (q, *J* = 7.4 Hz, 2H, 2-*H*), 1.40 (t, *J* = 7.4 Hz, 3H, 1-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 137.0, 129.8, 125.3, 120.6, 46.0, 8.3 ppm.

This NMR data agrees with the data previously reported in literature.¹⁹

1.26 *N*-Phenyl propanesulfonamide (**4g**)

According to GP1, propanesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4g** (193 mg, 0.97 mmol, 55%) was obtained as a yellow oil.



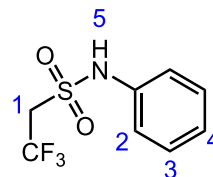
¹H NMR (400 MHz, CDCl₃) δ = 7.27 (dd, *J* = 8.5, 7.3 Hz, 2H, 5-*H*), 7.18 – 7.02 (m, 3H, 6-7-*H*), 6.69 (s, 1H, 4-*H*), 3.08 – 2.93 (m, 2H, 3-*H*), 1.88 – 1.71 (m, 2H, 2-*H*), 0.95 (t, *J* = 7.4 Hz, 3H, 1-*H*) ppm.

This NMR data agrees with the data previously reported in literature.²⁰

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 136.9, 129.7, 125.1, 120.4, 53.4, 17.3, 12.9 ppm.

1.27 *N*-Phenyl-2,2,2-trifluoroethanesulfonamide (**4h**)

According to GP1, 2,2,2-trifluoroethanesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4h** (215 mg, 0.90 mmol, 51%) was obtained as a colorless oil.



¹H NMR (400 MHz, CDCl₃) δ = 7.33 (dd, *J* = 8.7, 7.0 Hz, 2H, 2-*H*), 7.20 (ddd, *J* = 8.4, 7.3, 2.0 Hz, 3H, 3-4-*H*), 6.74 (s, 1H, 5-*H*), 3.73 (q, *J* = 8.9 Hz, 2H, 1-*H*) ppm.

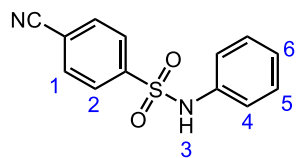
¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 134.9, 129.8, 126.5, 122.6, 121.7, 119.8, 52.3, 52.0, 51.7, 51.3 ppm.

¹⁹F NMR (376 MHz, CDCl₃) δ = -62.27 ppm.

HRMS (ESI, *m/z*): [*M*+*H*]⁺ = calcd. For C₈H₉F₃NO₂S⁺ : 240.0301, found: 240.0304

1.28 4-Cyano-*N*-phenylbenzenesulfonamide (**4i**)

According to GP1, 4-cyanobenzenesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4i** (100 mg, 0.39 mmol, 22%) was obtained as an off-white foam.



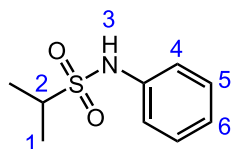
¹H NMR (400 MHz, CDCl₃) δ = 7.84 – 7.74 (m, 2H, 2-*H*), 7.66 (d, *J* = 8.5 Hz, 2H, 1-*H*), 7.20 (dd, *J* = 6.7, 1.4 Hz, 2H, 4-*H*), 7.16 – 7.07 (m, 1H, 6-*H*), 7.03 – 6.96 (m, 2H, 5-*H*), 6.78 (s, 1H, 3-*H*) ppm.

¹³C{¹H} NMR (101 MHz, CDCl₃) δ = 143.3, 135.5, 133.0, 129.8, 128.0, 126.6, 122.5, 117.3, 116.9 ppm.

This NMR data agrees with the data previously reported in literature.²¹

1.29 *N*-Phenyl 1-methylethanesulfonamide (**4j**)

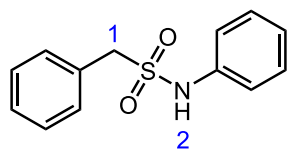
According to GP1, isopropanesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu₄SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 → 6/4), the desired product **4j** (225 mg, 1.13 mmol, 64%) was obtained as a yellow oil.



^1H NMR (400 MHz, CDCl_3) δ = 7.30 – 7.23 (m, 2H, 4-*H*), 7.18 – 7.12 (m, 2H, 5-*H*), 7.09 (td, J = 7.3, 1.3 Hz, 1H, 6-*H*), 3.23 (hept, J = 6.8 Hz, 1H, 2-*H*), 1.33 (d, J = 6.9 Hz, 6H, 1-*H*) ppm.
 $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 137.0, 129.7, 125.0, 120.3, 52.5, 16.5 ppm.
 This NMR data agrees with the data previously reported in literature.²²

1.30 *N*-Phenyl phenylmethanesulfonamide (**4k**)

According to GP1, phenylmethanesulfonic acid (340 mg, 3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (NBu_4SCN) (180 mg, 0.5 mmol, 0.15 equiv.), and aniline (17.7 mmol, 1.6 mL, 5 equiv.) were employed. The electrolysis was carried out using 3 *F*. After purification by column chromatography (cyclohexane/ethyl acetate = 9/1 $\rightarrow$ 6/4), the desired product **4k** (65 mg, 0.26 mmol, 15%) was obtained as a dark oil.



^1H NMR (400 MHz, CDCl_3) δ = 7.37 (ddd, J = 7.2, 5.0, 3.8 Hz, 5H, Ar-*H*), 7.31 – 7.24 (m, 2H, Ar-*H*), 7.23 – 7.14 (m, 3H, Ar-*H*), 6.60 – 6.46 (m, 1H, 2-*H*), 4.35 (s, 2H, 1-*H*) ppm.
 $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ = 137.1, 131.0, 129.8, 129.1, 129.0, 128.7, 125.0, 120.0, 57.6, 27.1 ppm.
 This NMR data agrees with the data previously reported in literature.²³

1.31 Limitations of the Scope/Unsuccessful Substrates

The following substrates were also employed, but the desired products could not be isolated in sufficient quantities.

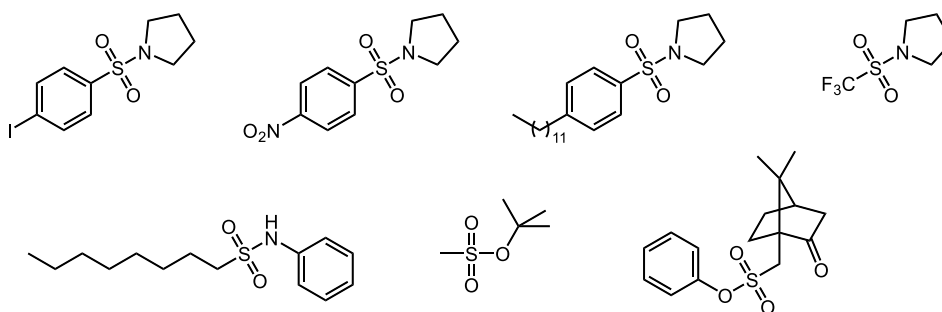
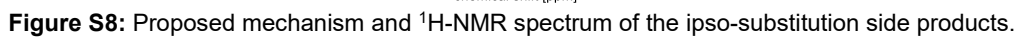
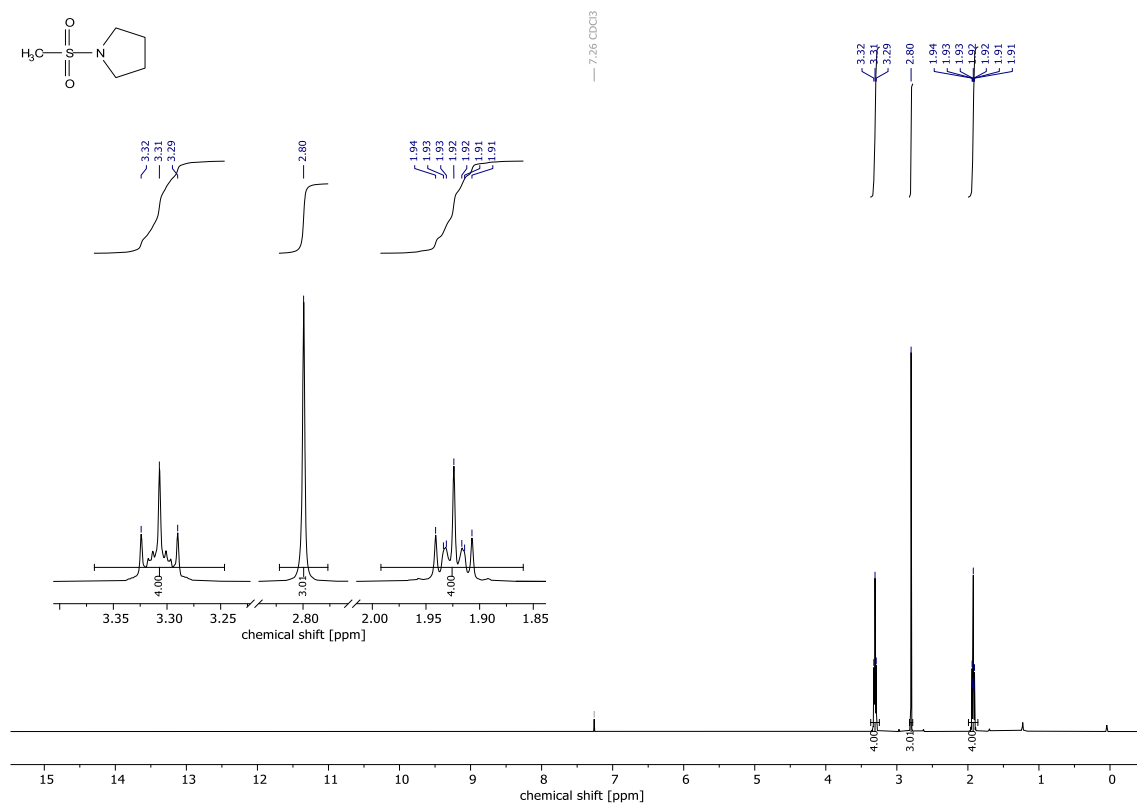
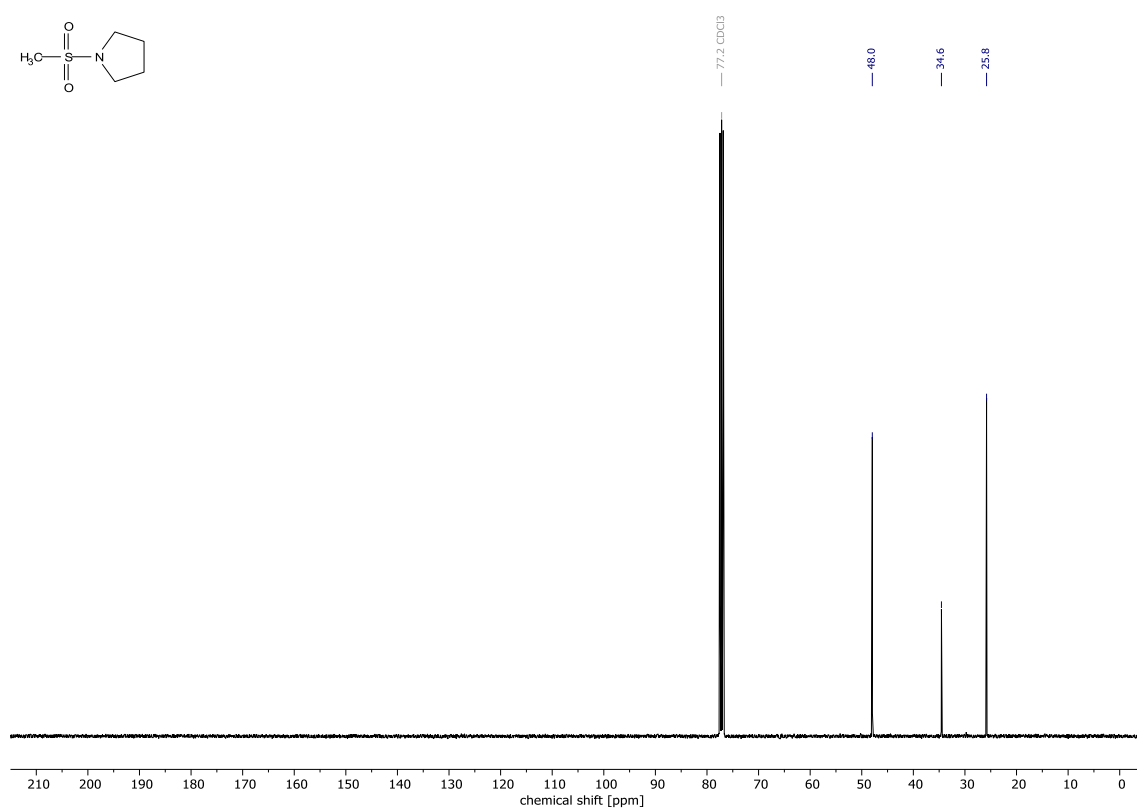


Figure S7 : Unsuccessful substrates.



NMR Spectra

Figure S9: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 2a.Figure S10: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 2a.

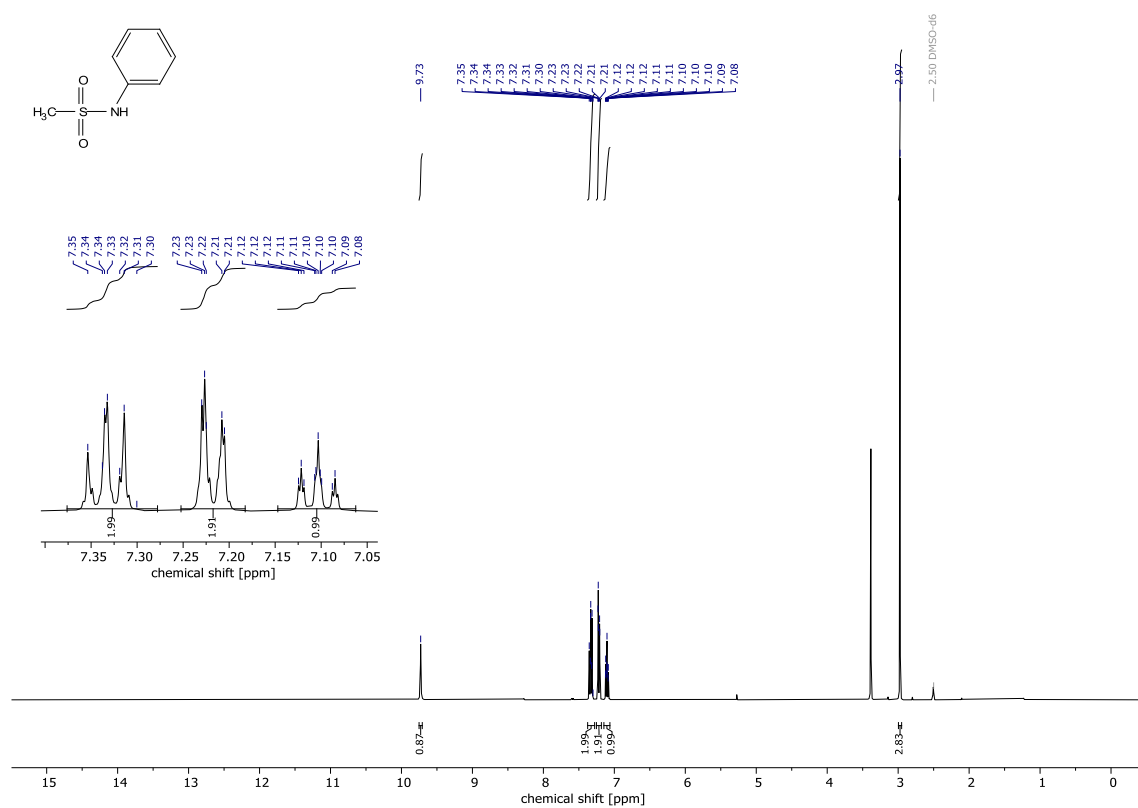


Figure S11: ¹H NMR spectrum (400 MHz, 25 °C, DMSO-d₆) of 2b.

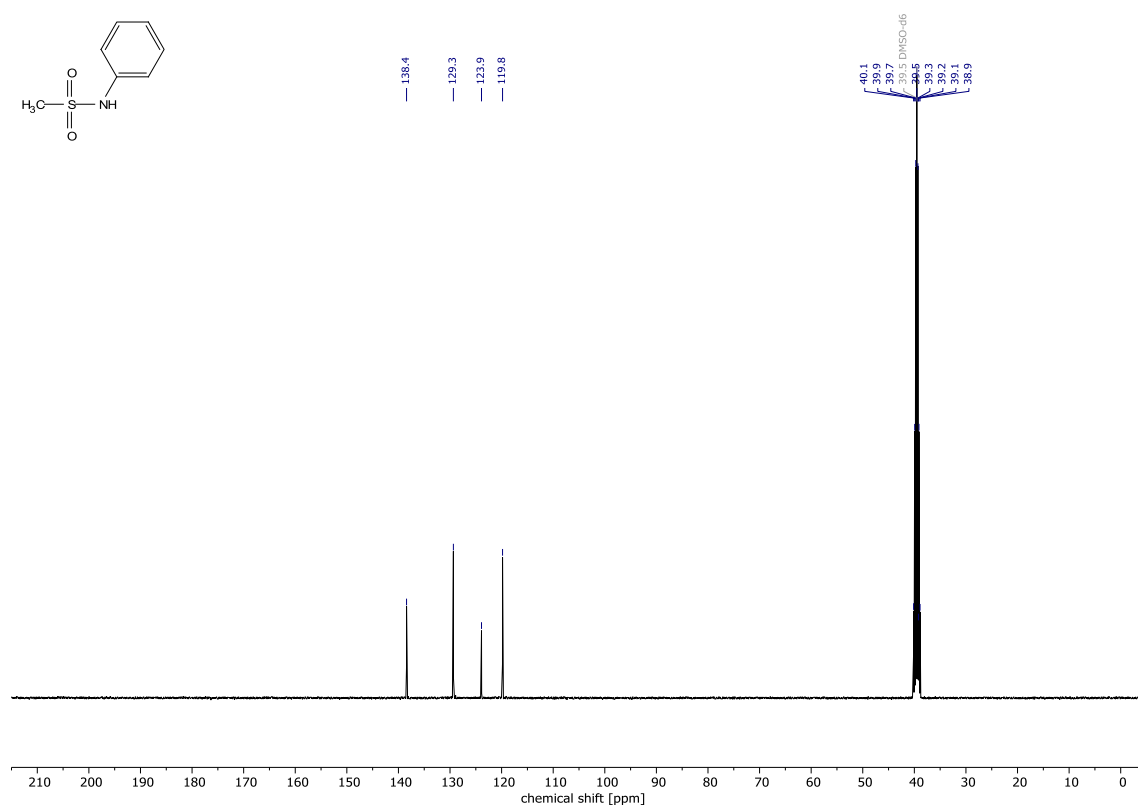


Figure S12: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, DMSO-d₆) of 2b.

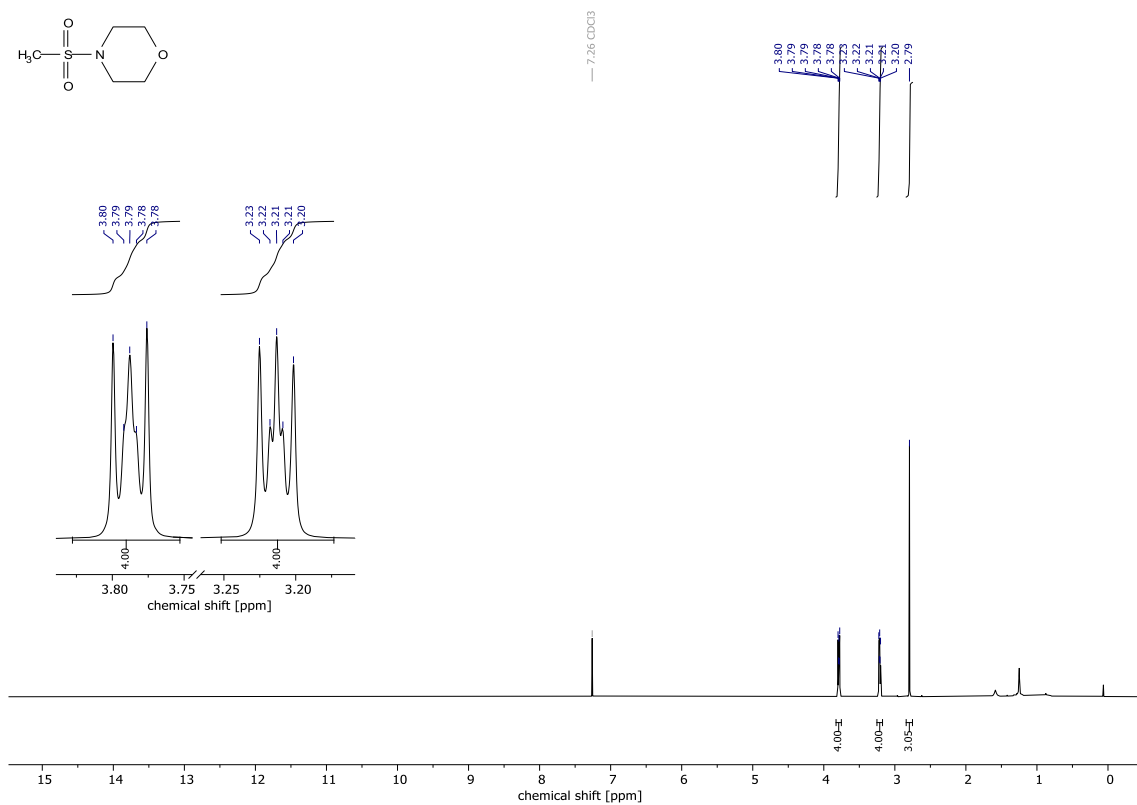


Figure S13: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **2c**.

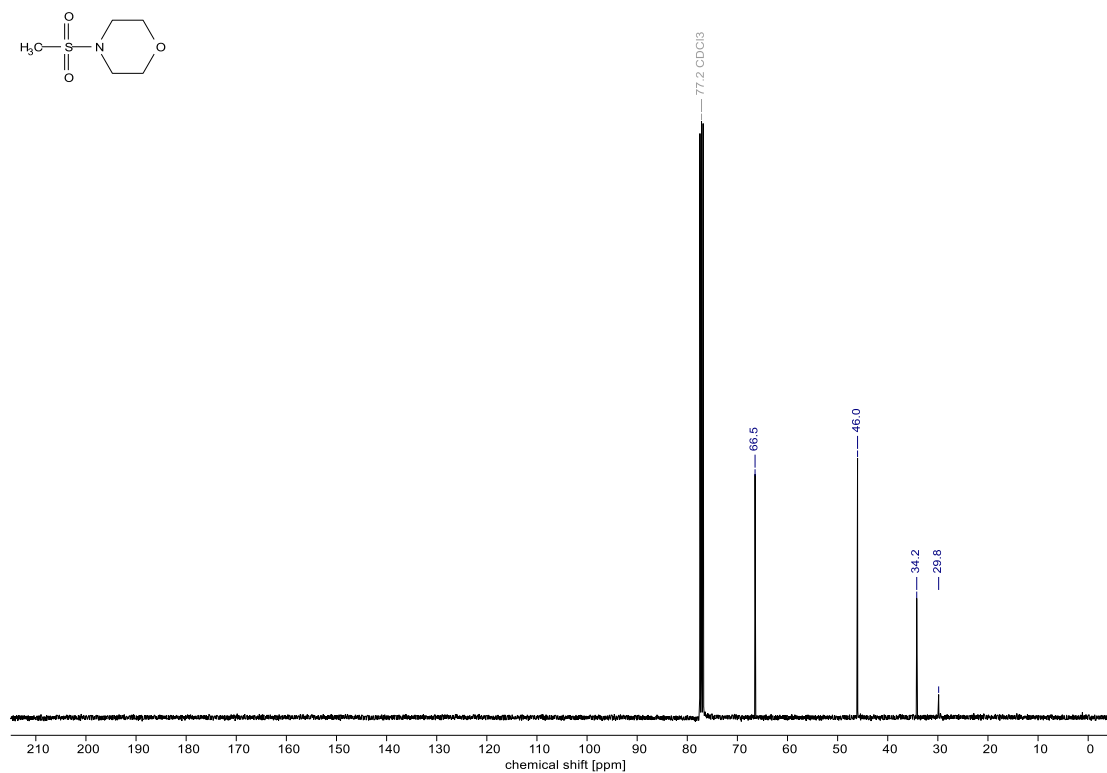


Figure S14: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **2c**.

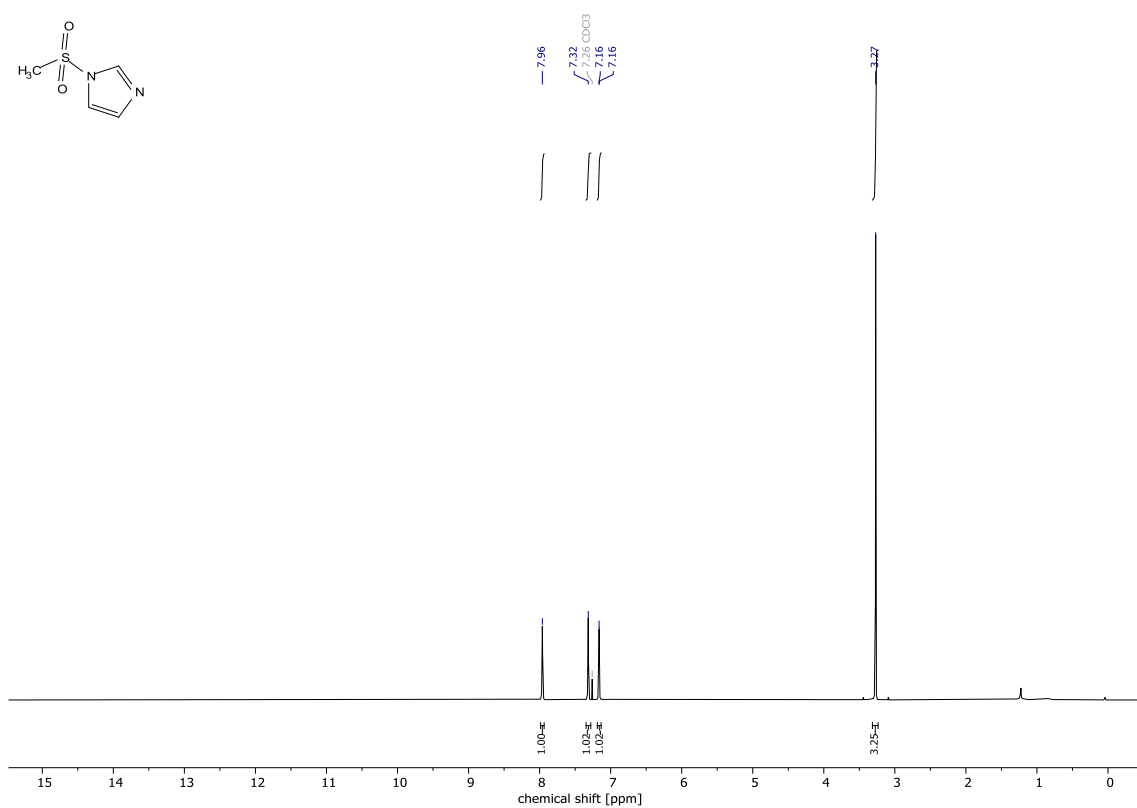


Figure S15: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 2d.

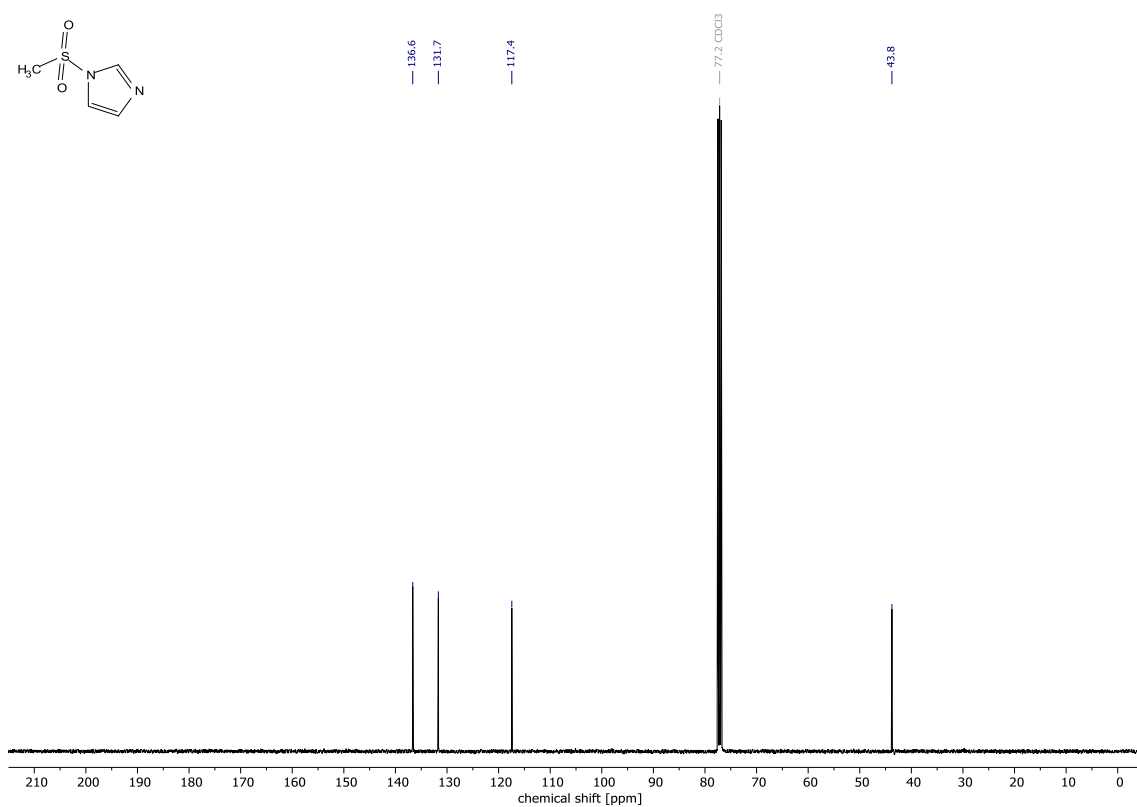


Figure S16: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 2d.

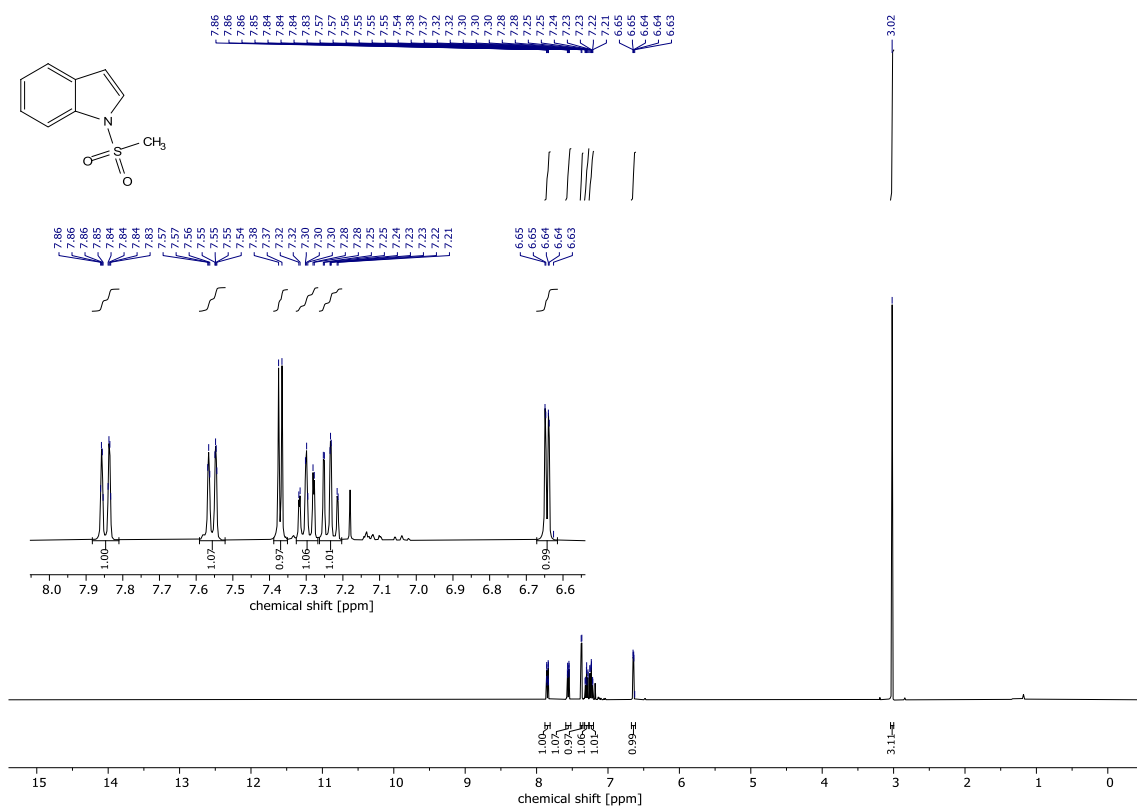


Figure S17: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **2e**.

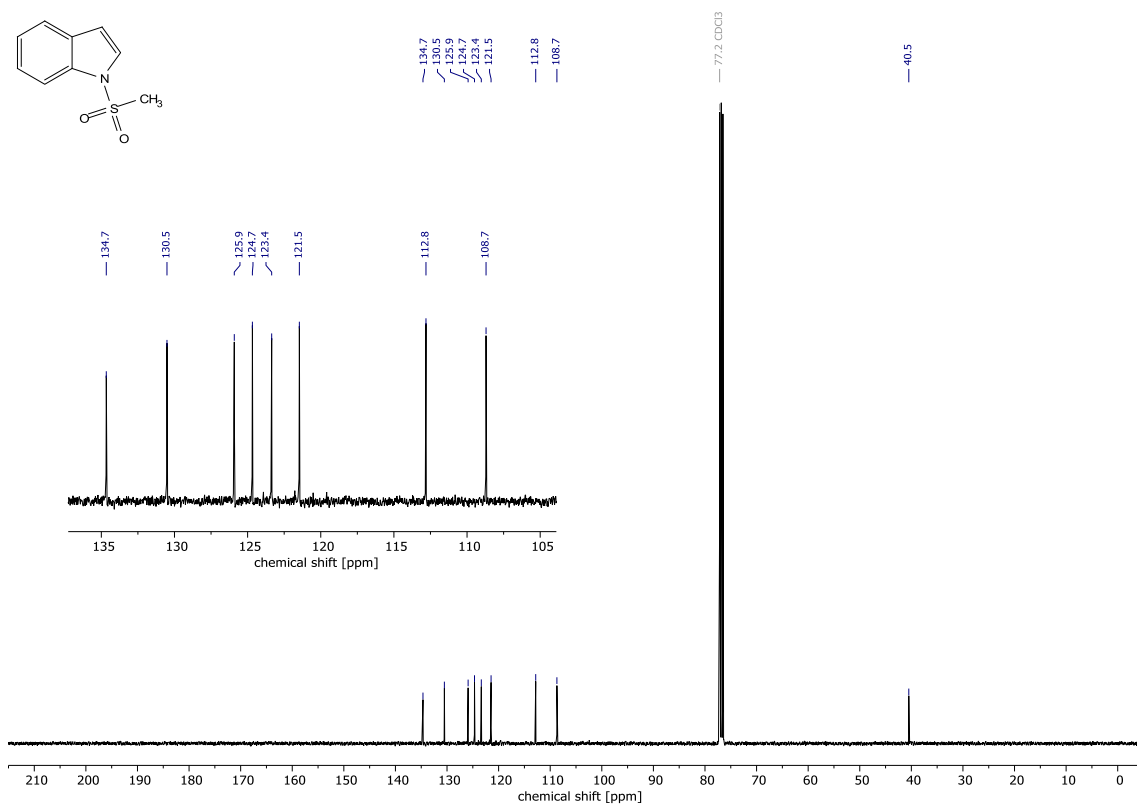
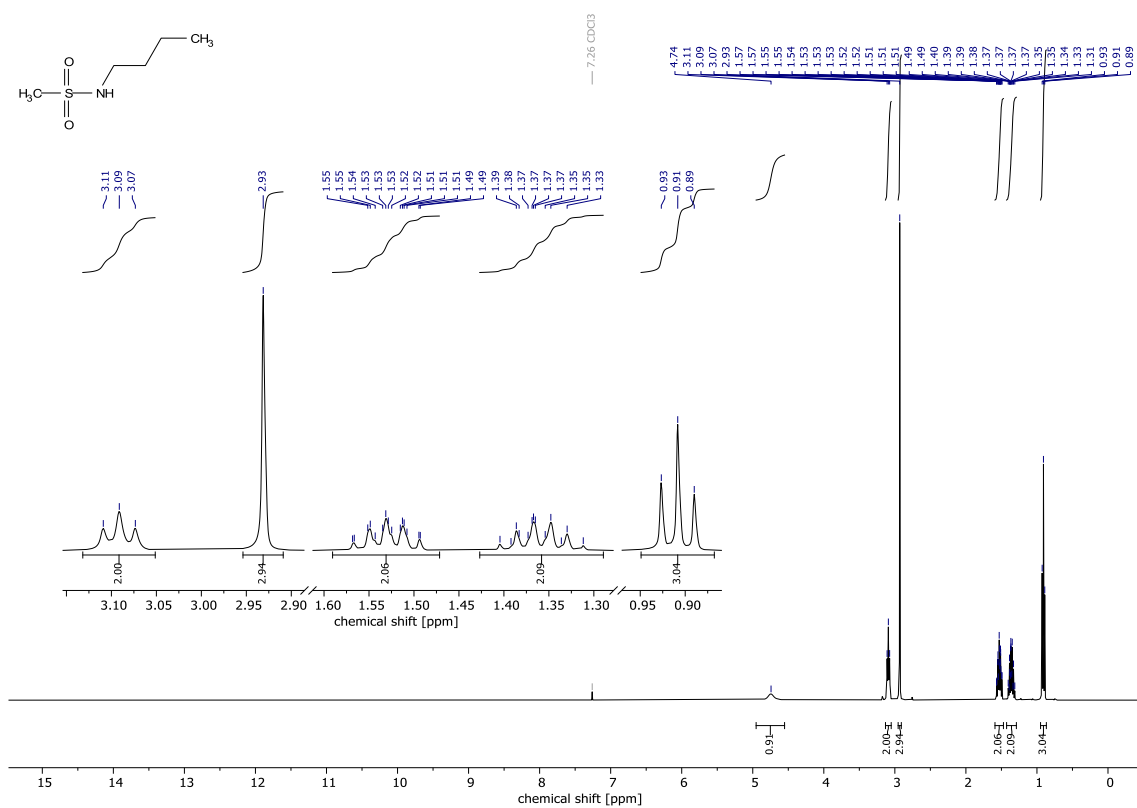
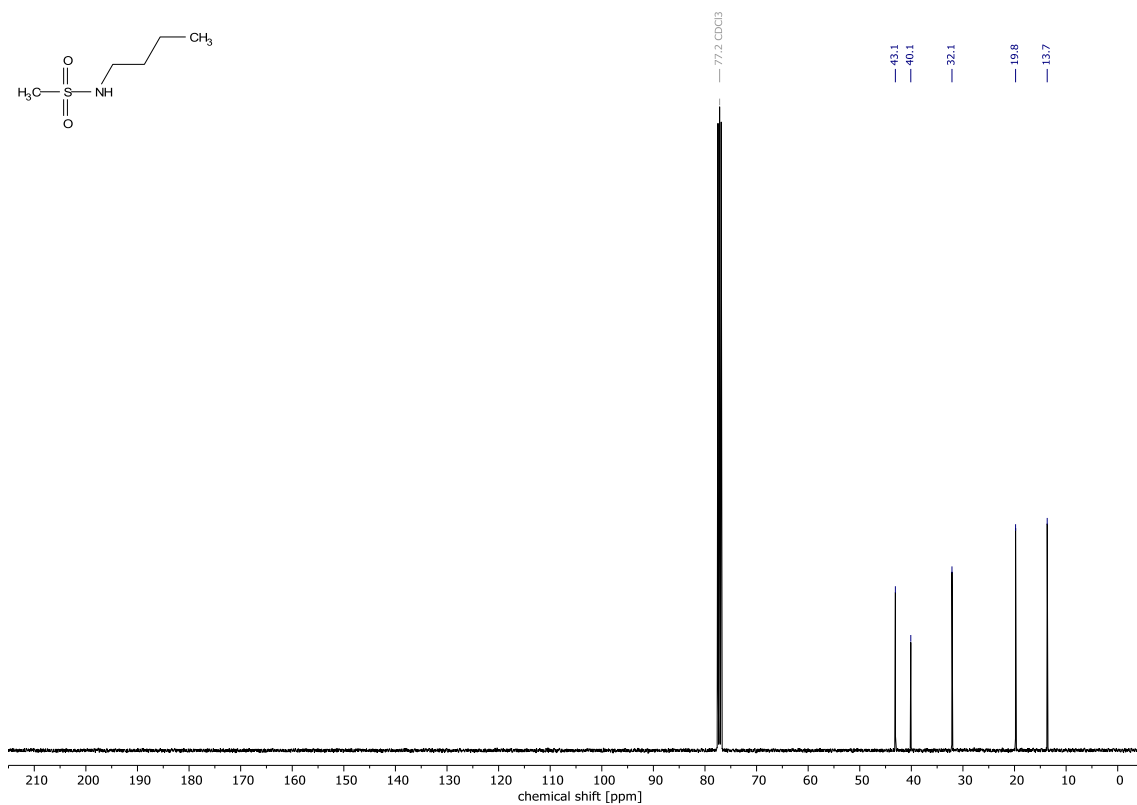


Figure S18: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **2e**.

Figure S19: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **2f**.Figure S20: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **2f**.

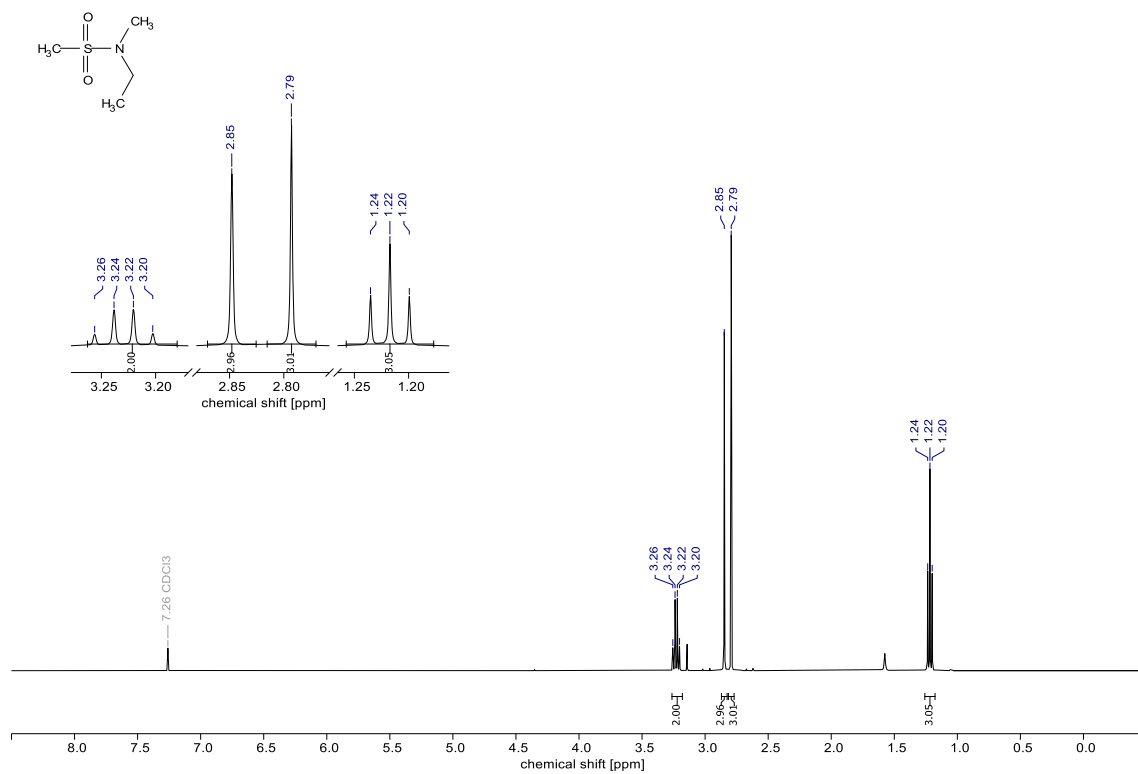


Figure S21: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **2g**.

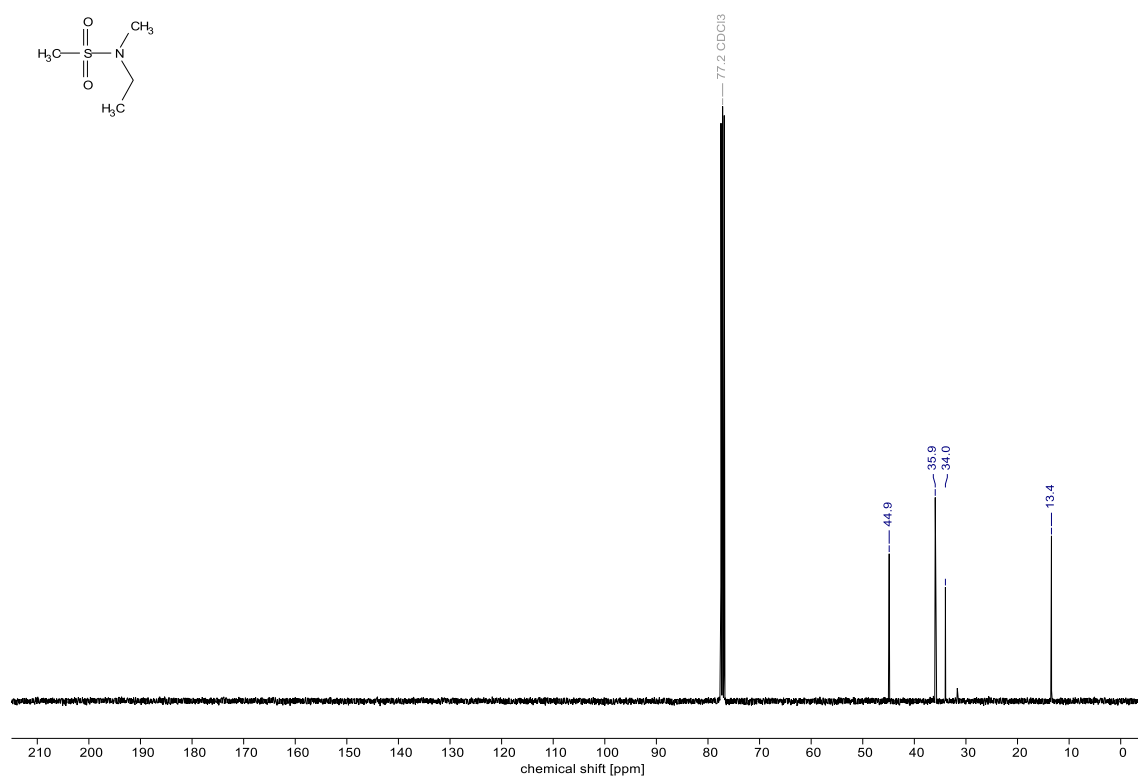


Figure S22: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **2g**.

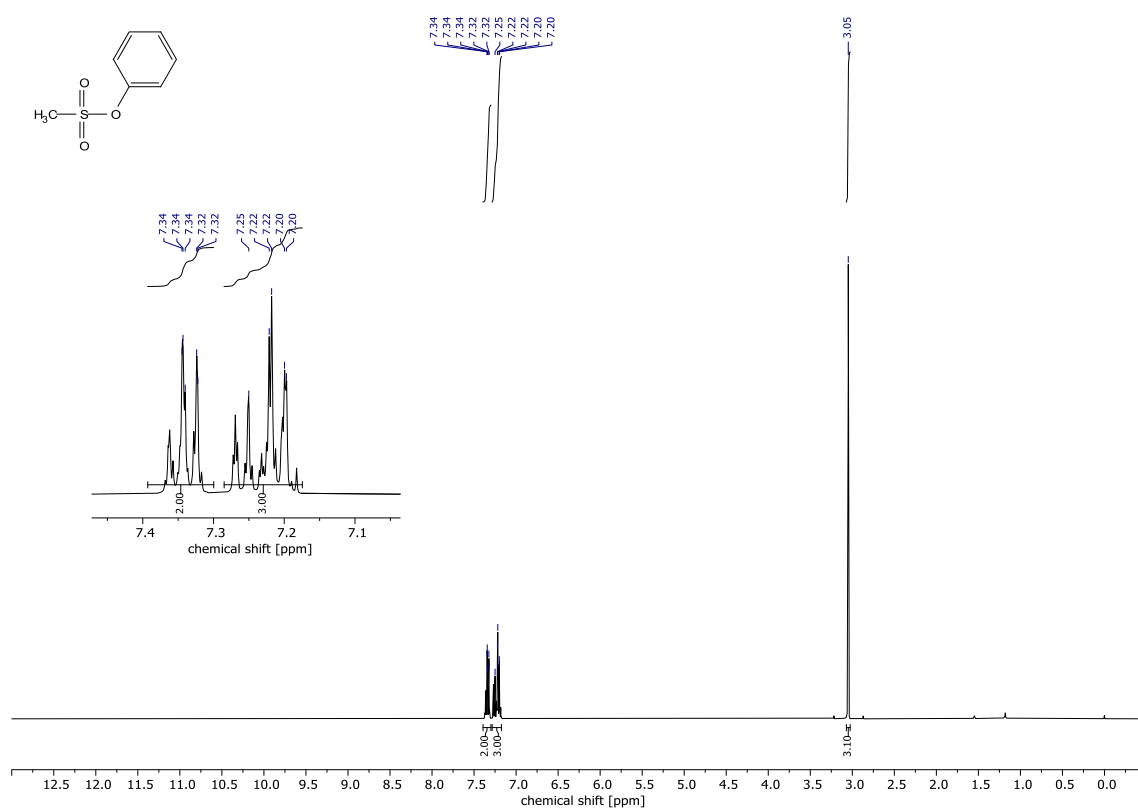


Figure S23: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 3a.

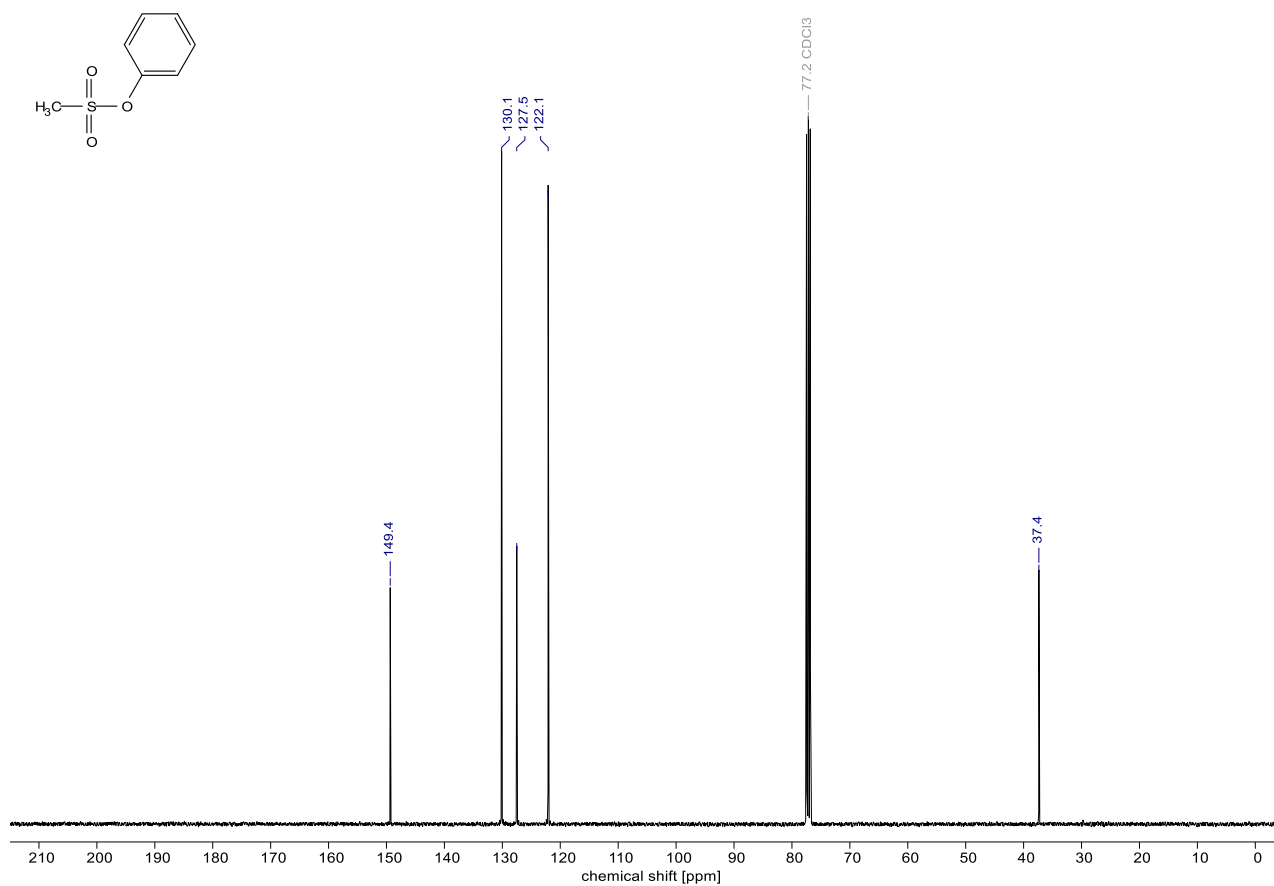


Figure S24: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 3a.

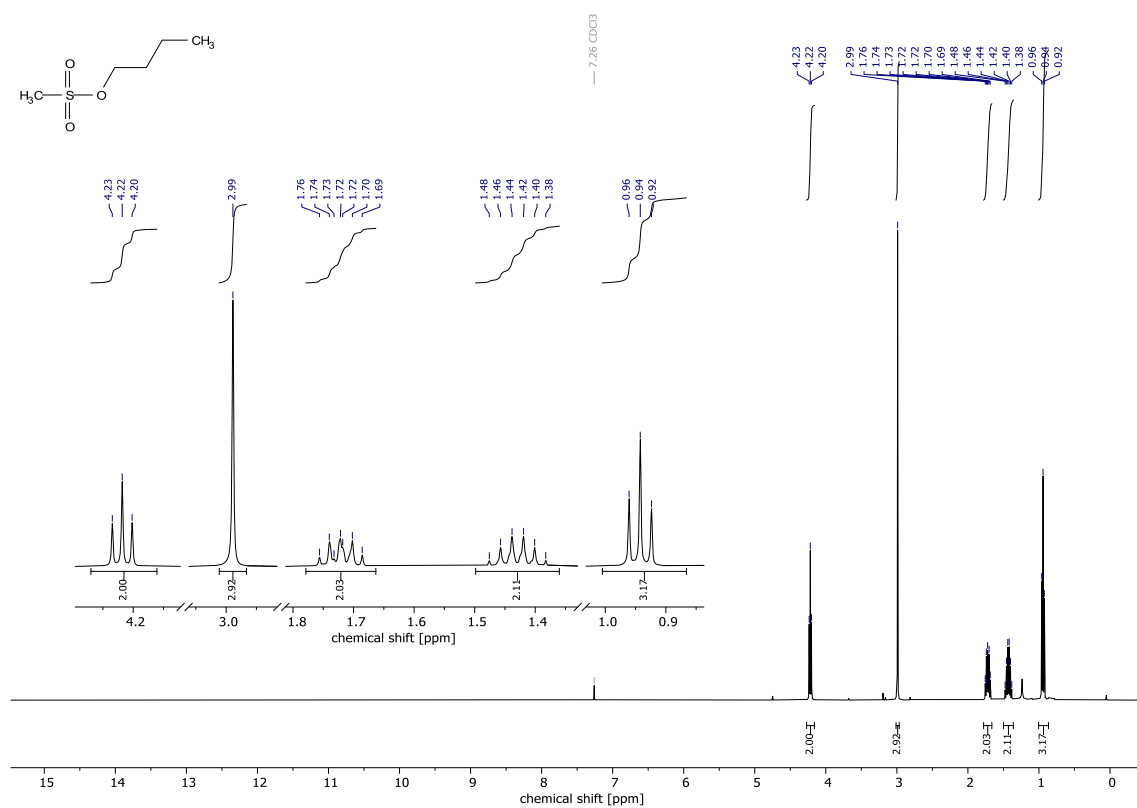


Figure S25: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 3b.

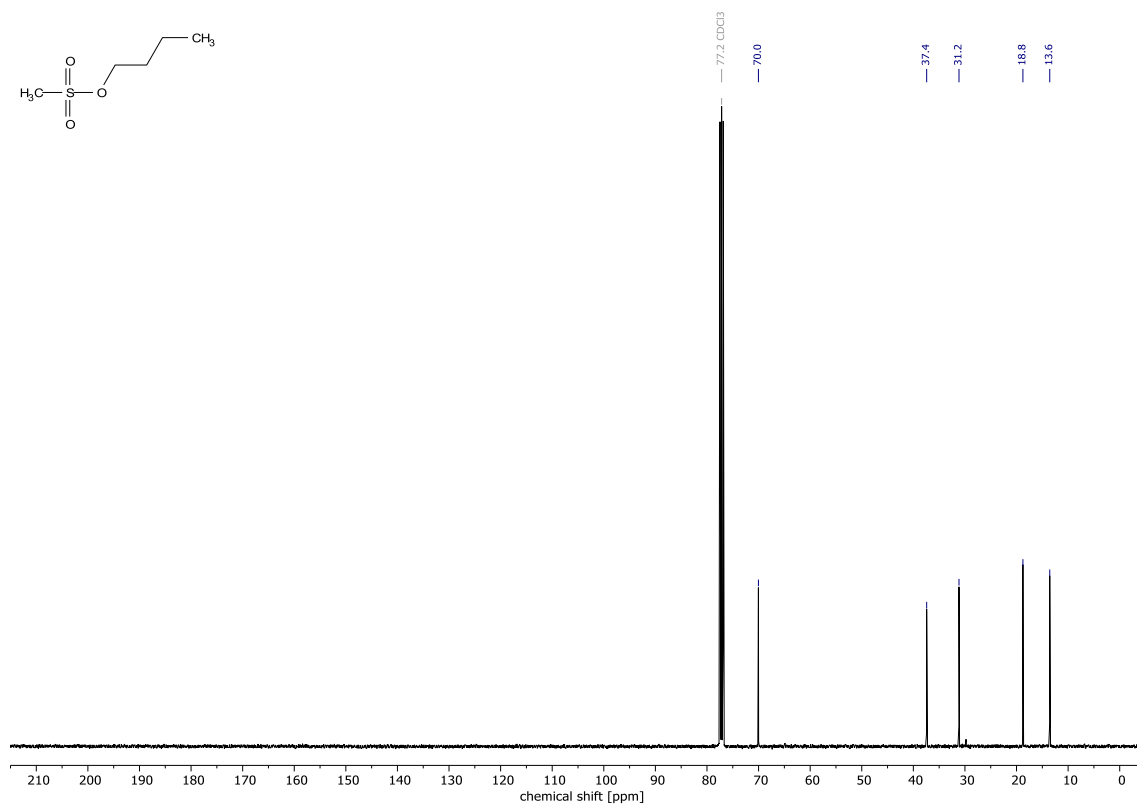
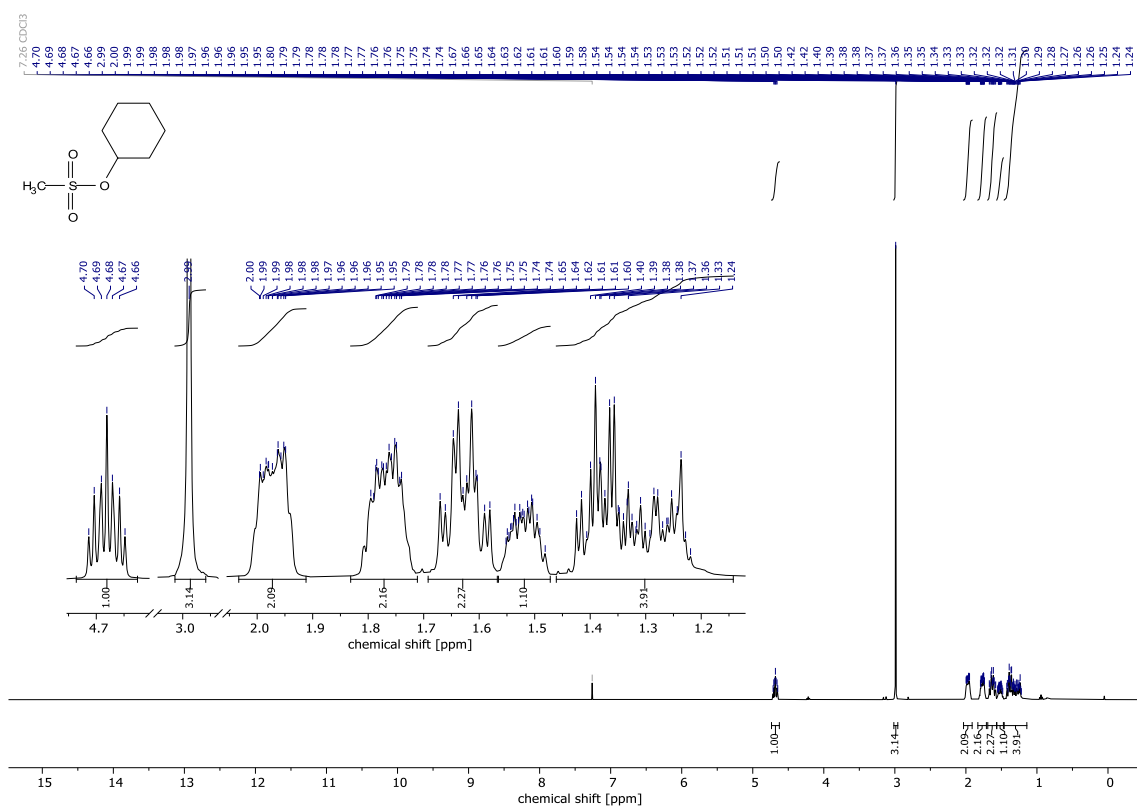
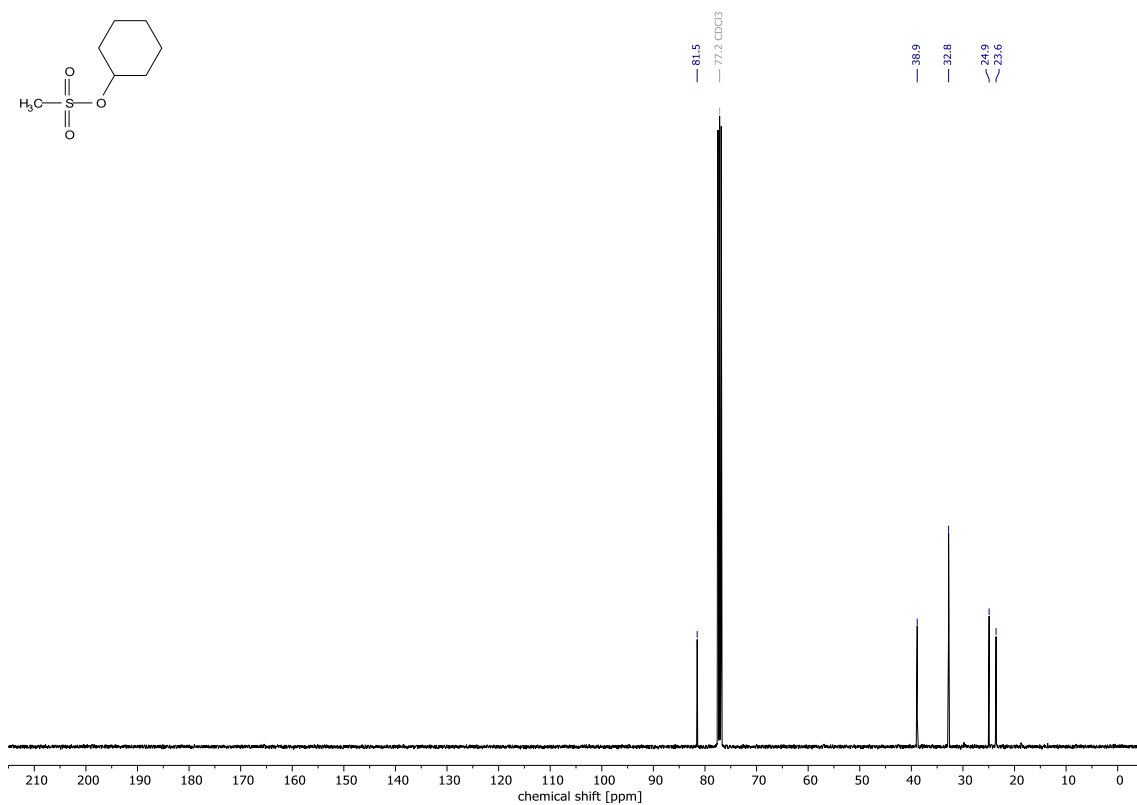


Figure S26: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 3b.

Figure S27: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 3c.Figure S28: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 3c.

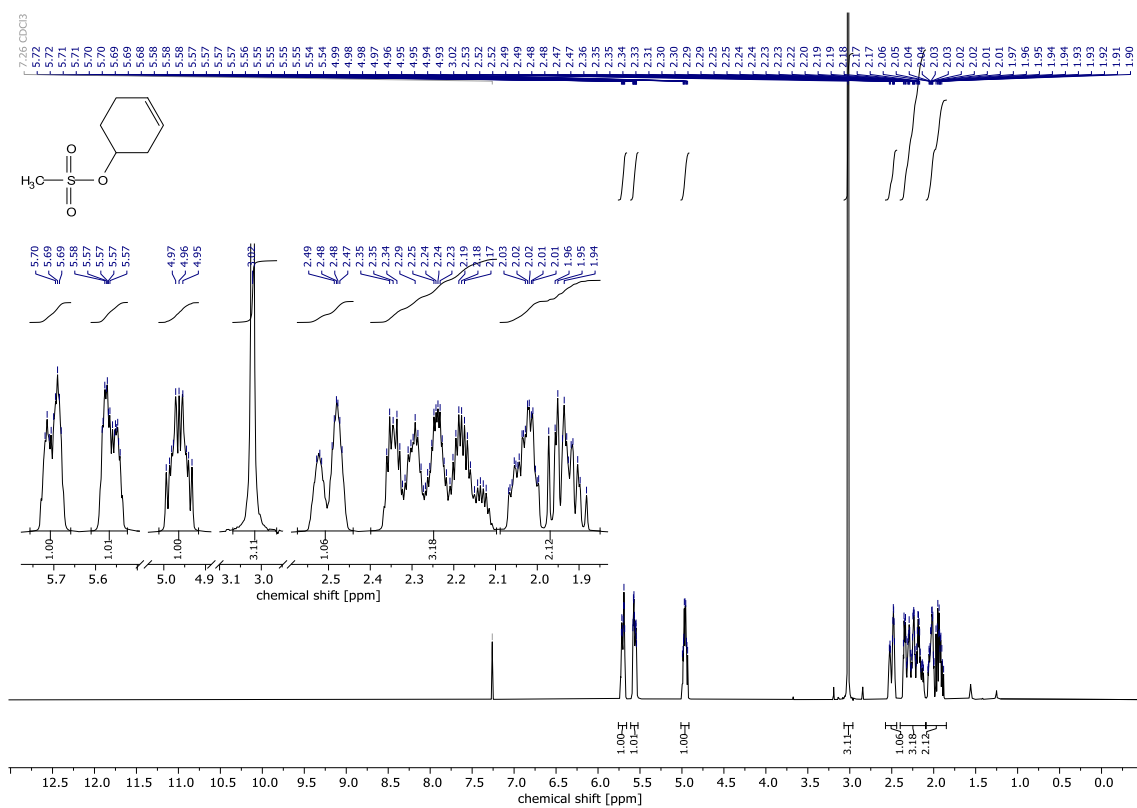


Figure S29: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 3d.

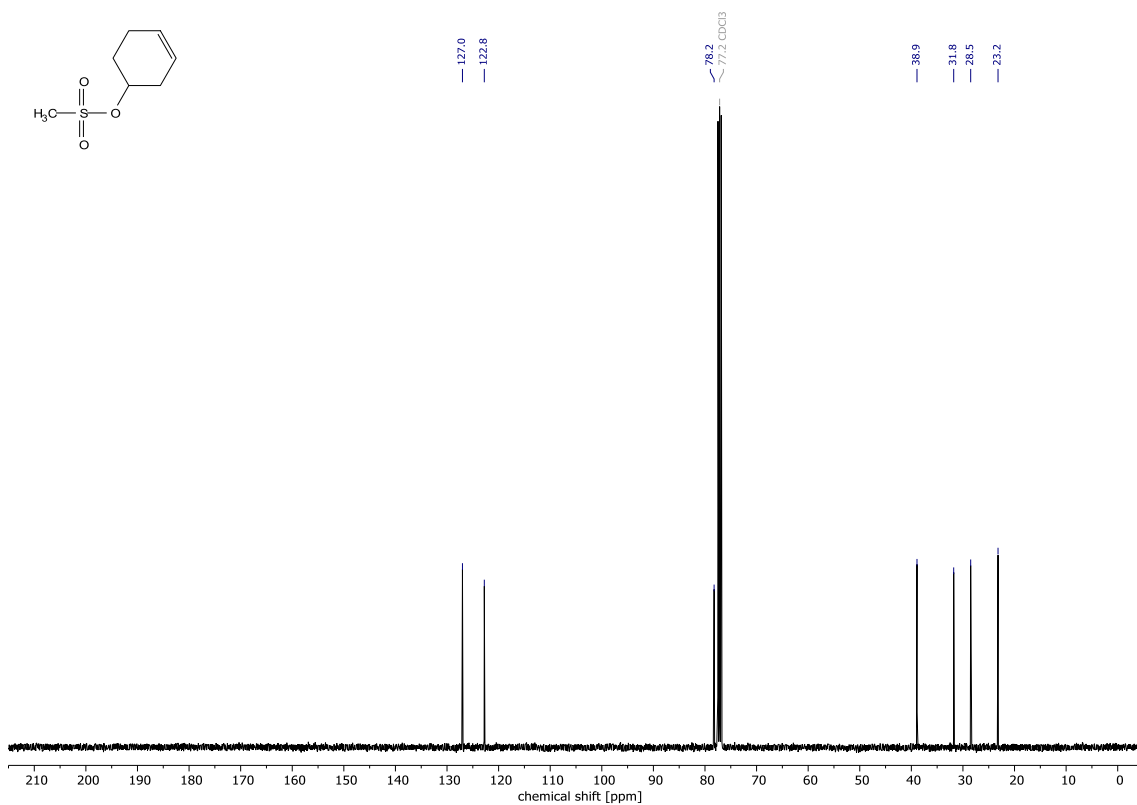
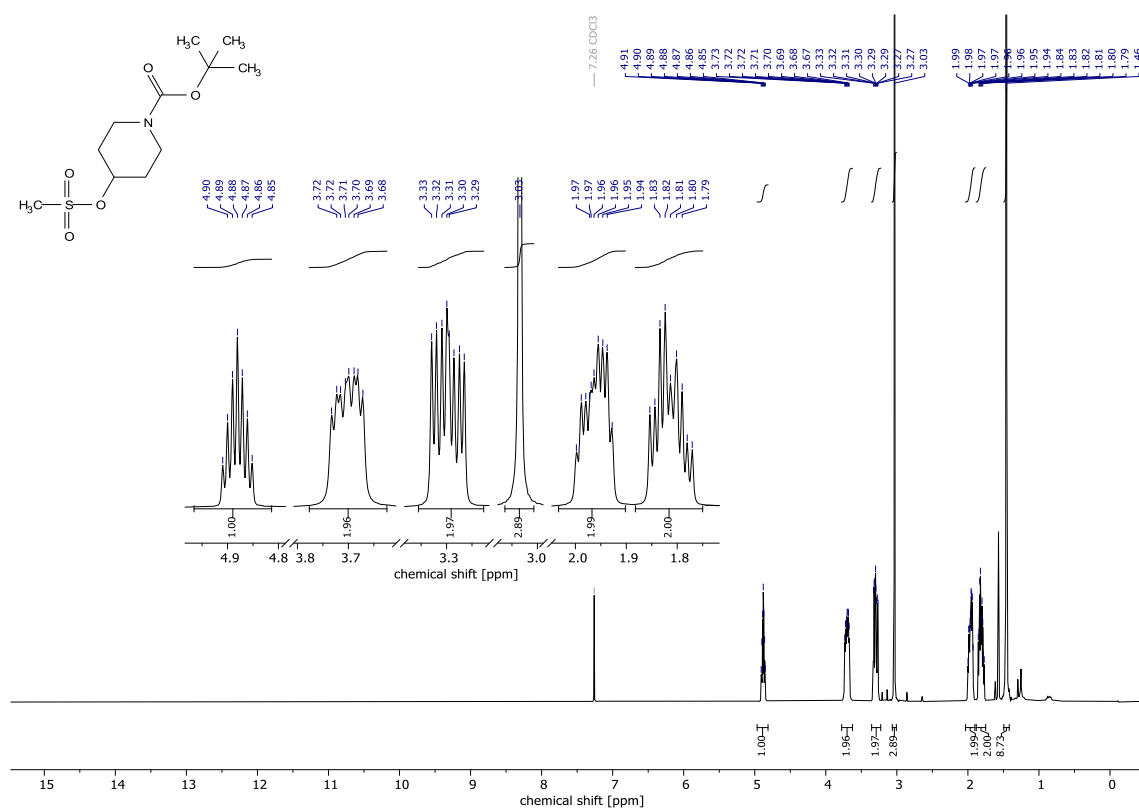
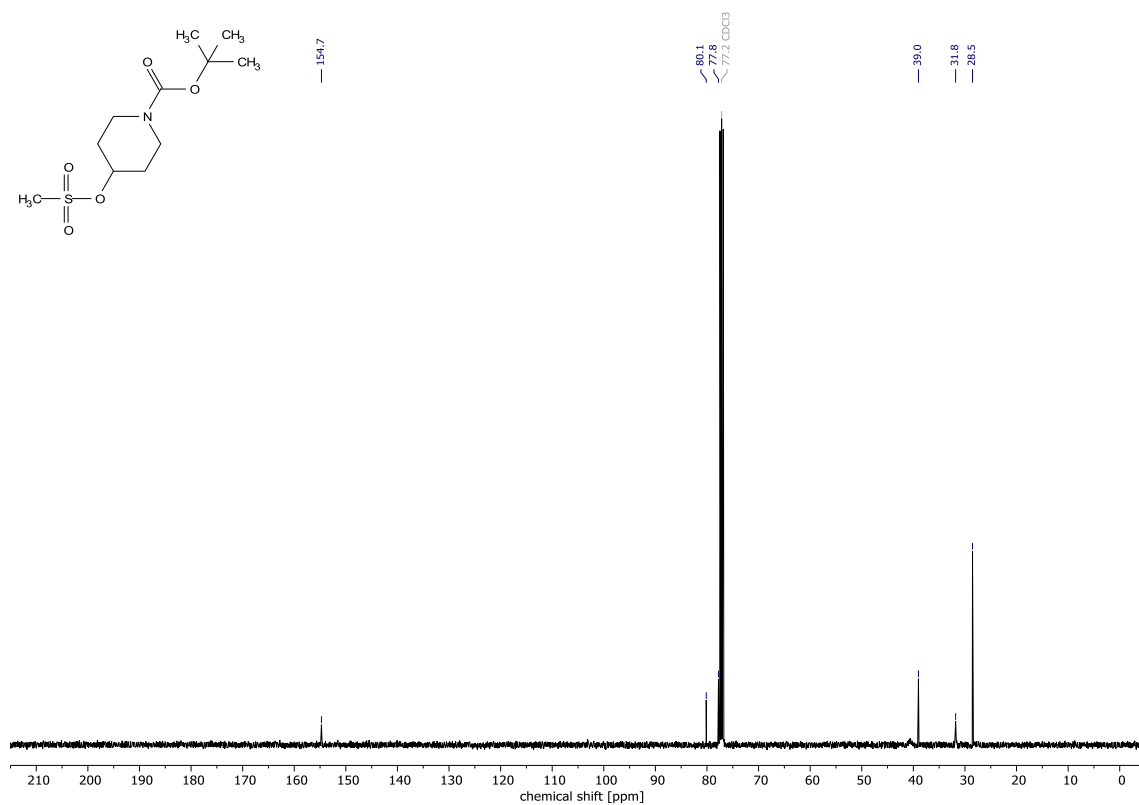
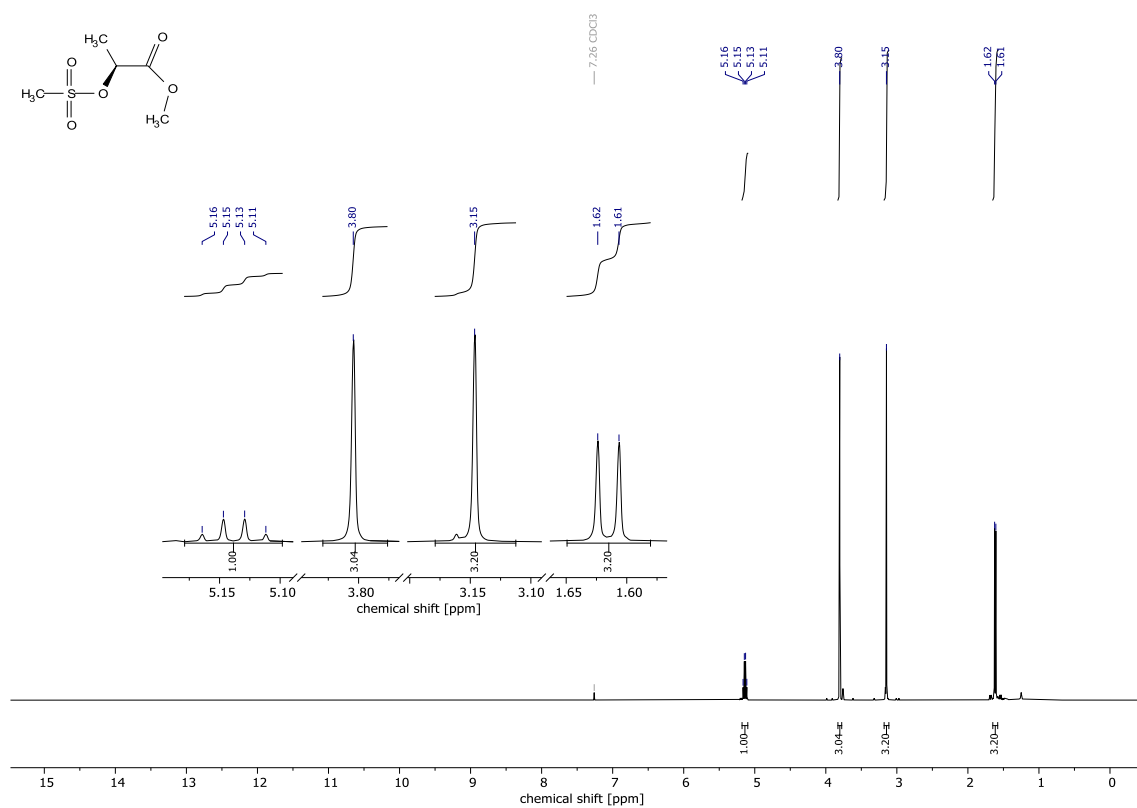
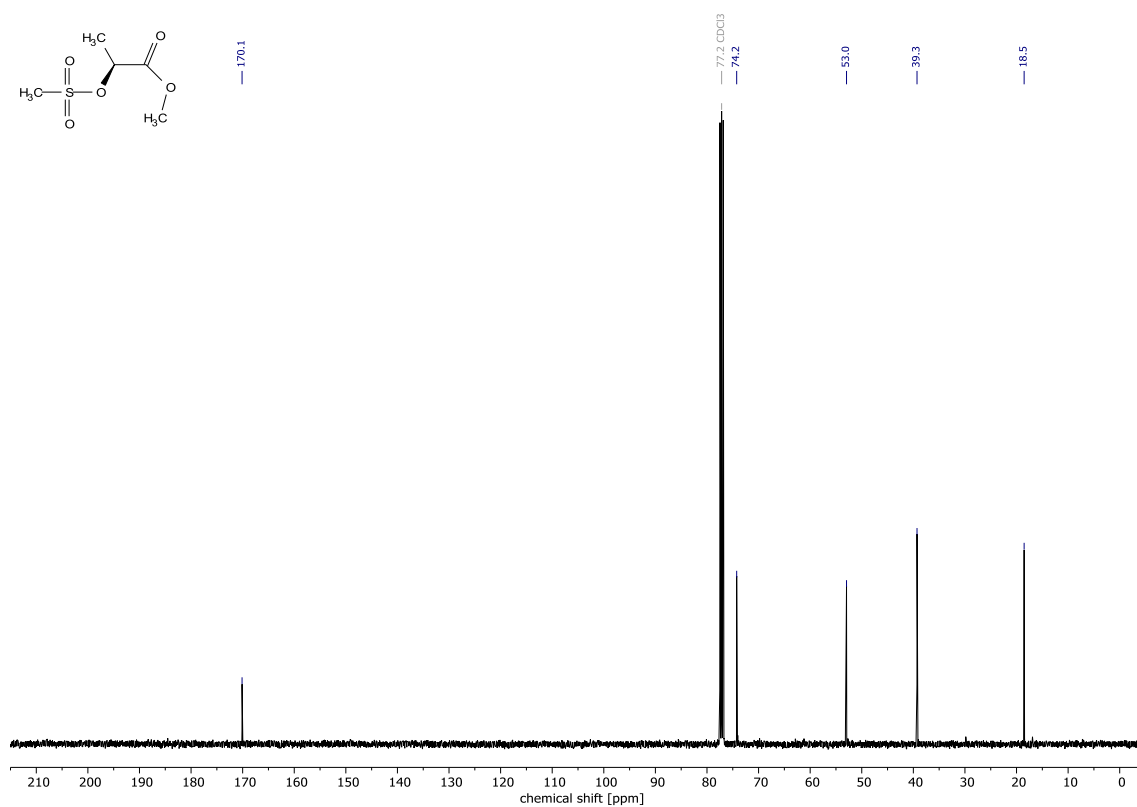
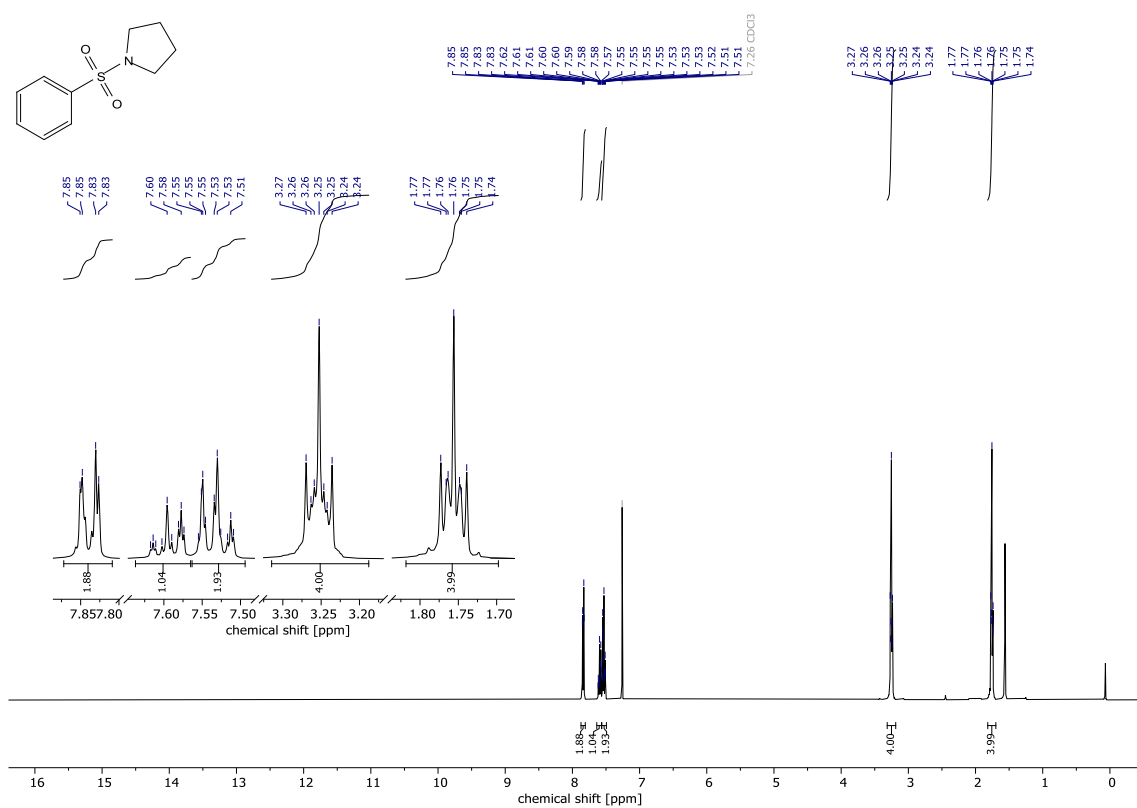
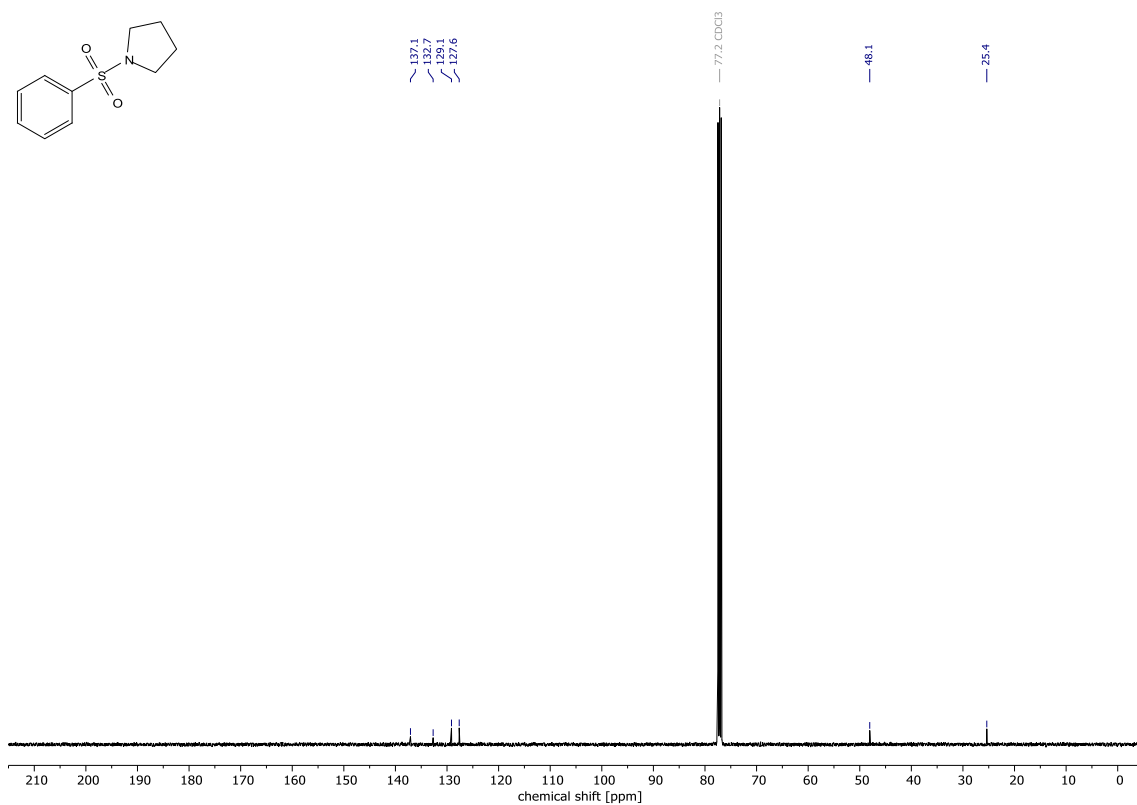
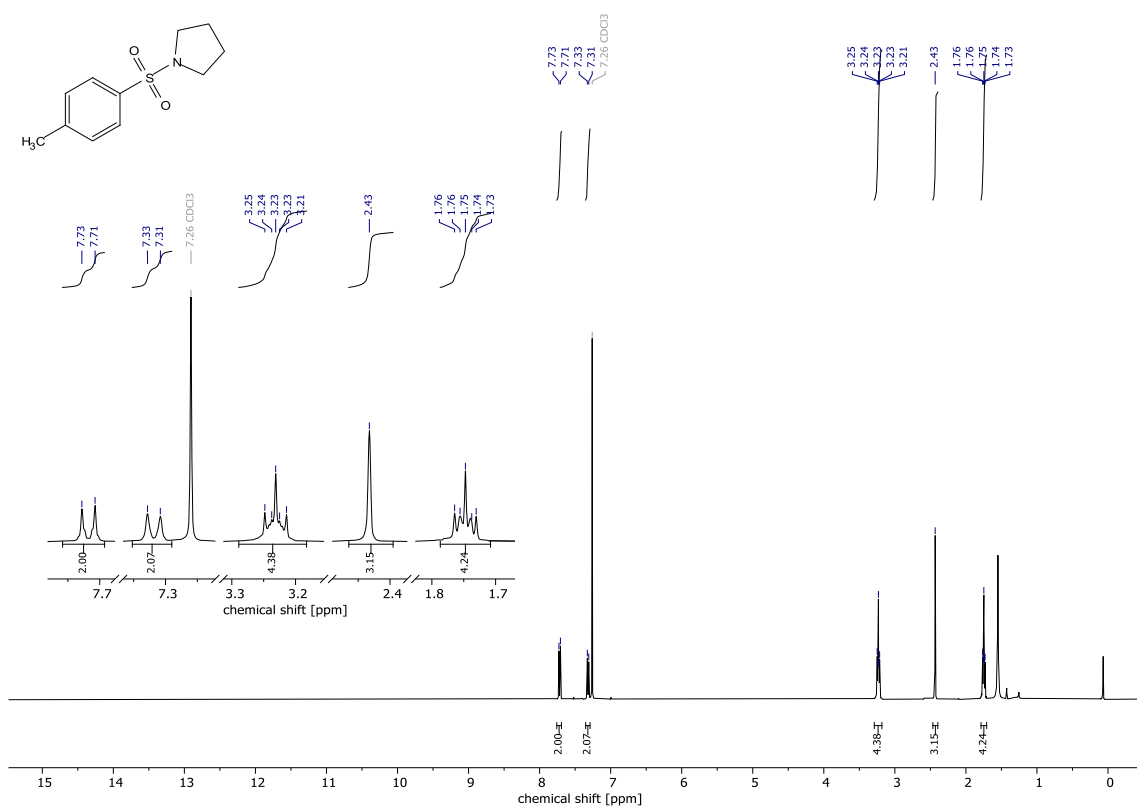
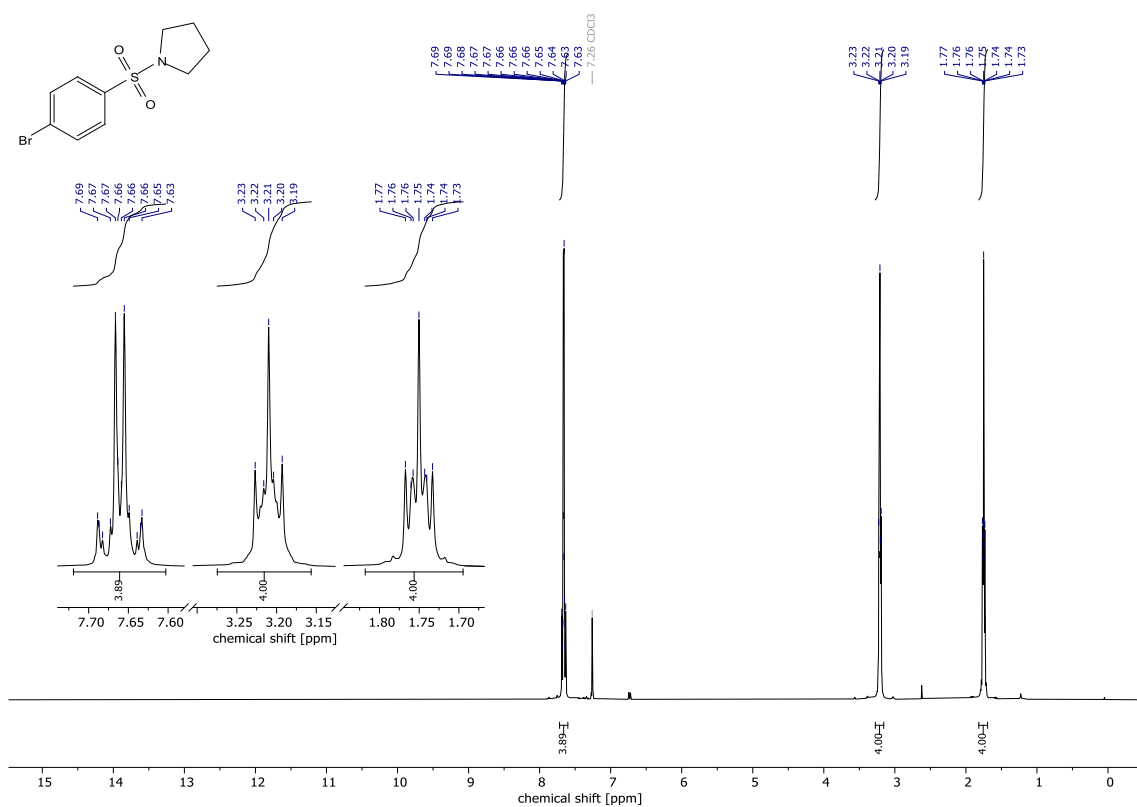


Figure S30: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 3d.

Figure S31: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **3e**.Figure S32: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **3e**.

Figure S33: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **3f**.Figure S34: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **3f**.

Figure S35: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **4a**.Figure S36: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **4a**.

Figure S37: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 4b.Figure S38: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 4c.

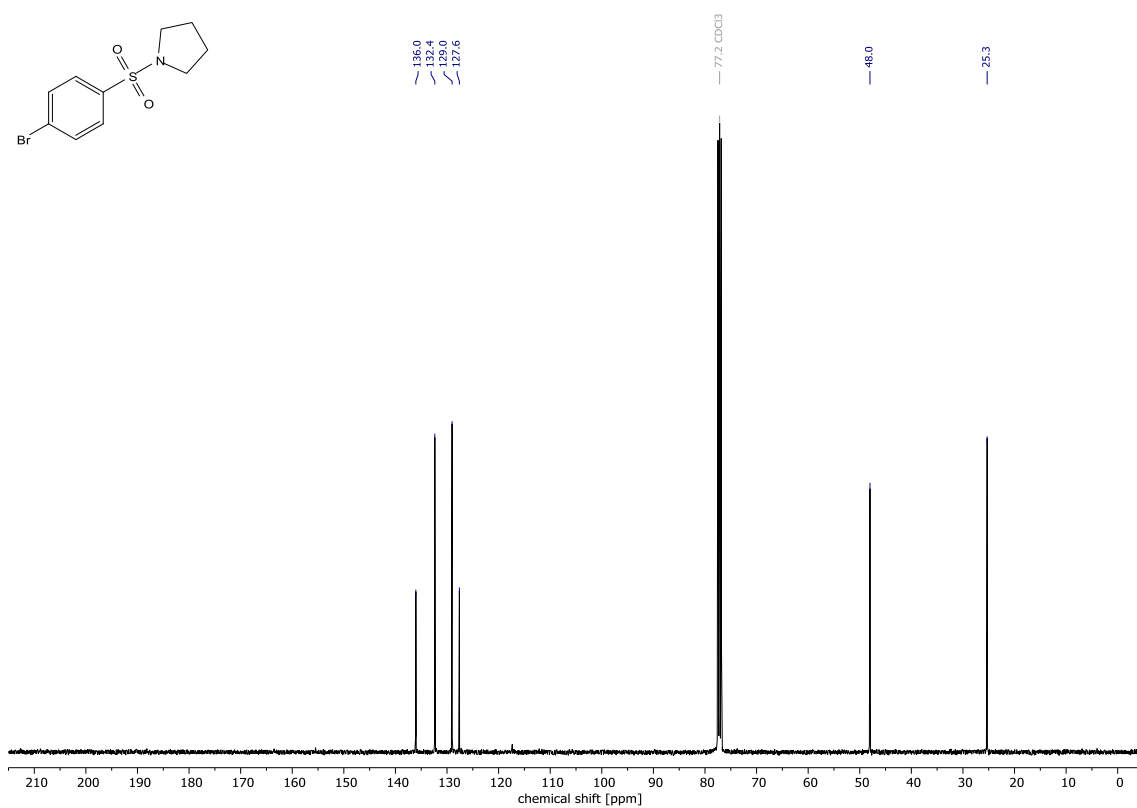


Figure S39: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (101 MHz, 25 °C, CDCl_3) of **4c**.

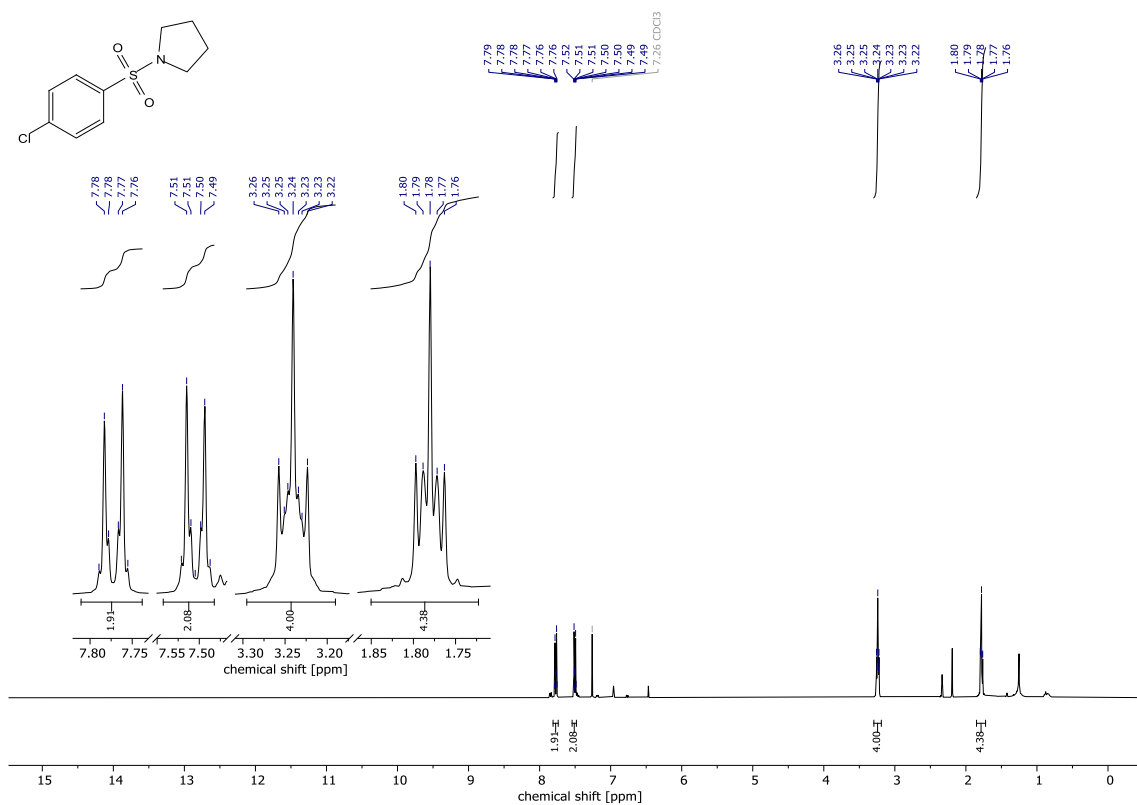
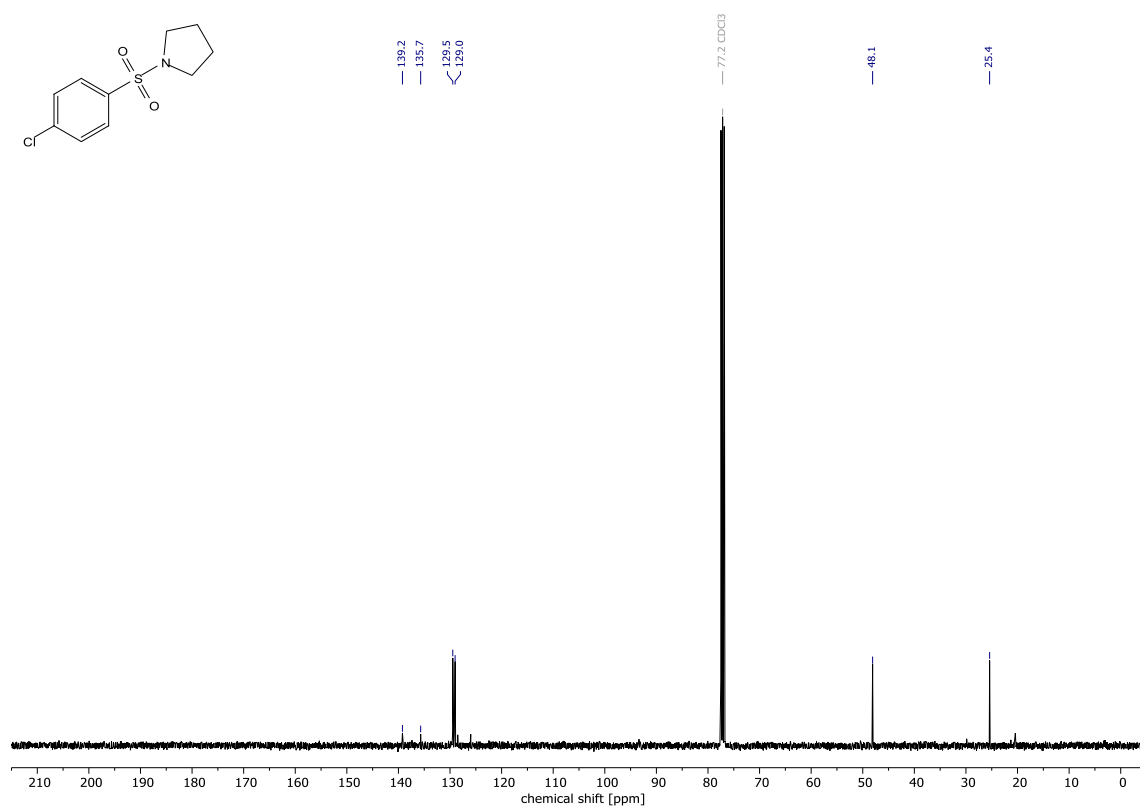
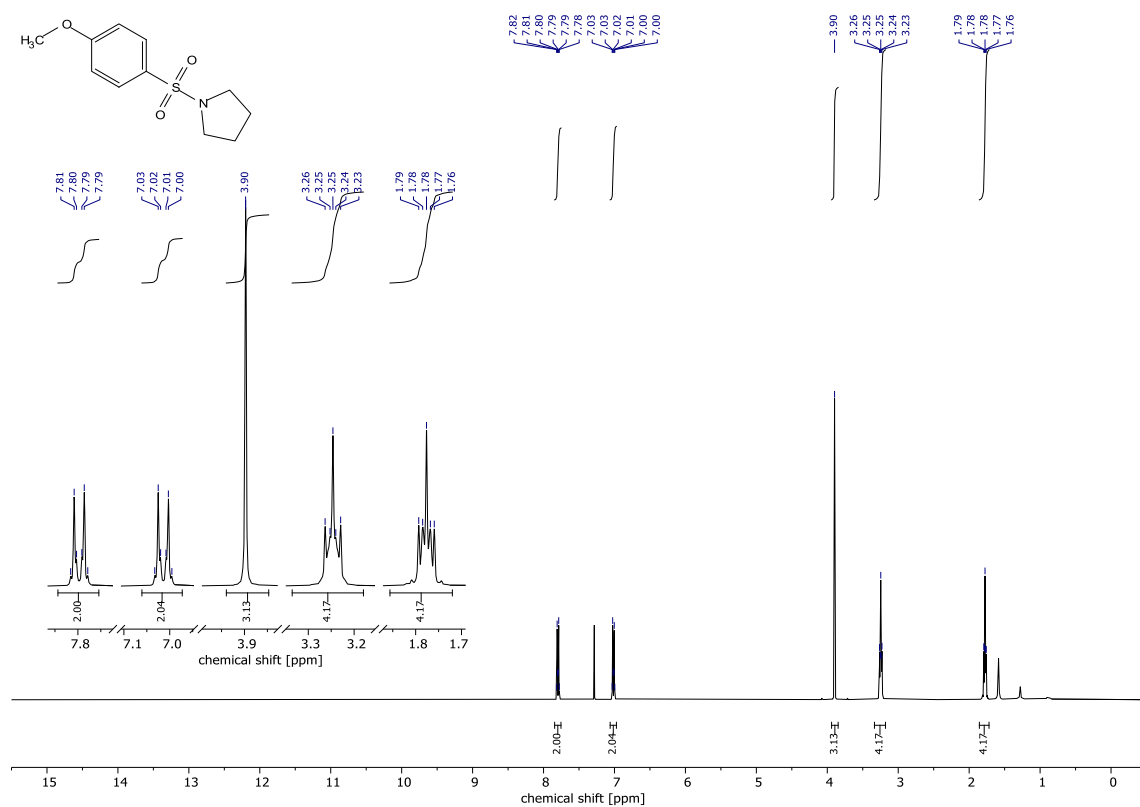


Figure S40: ^1H NMR spectrum (400 MHz, 25 °C, CDCl_3) of **4d**.

Figure S41: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (101 MHz, 25 °C, CDCl_3) of 4d.Figure S42: ^1H NMR spectrum (400 MHz, 25 °C, CDCl_3) of 4e.

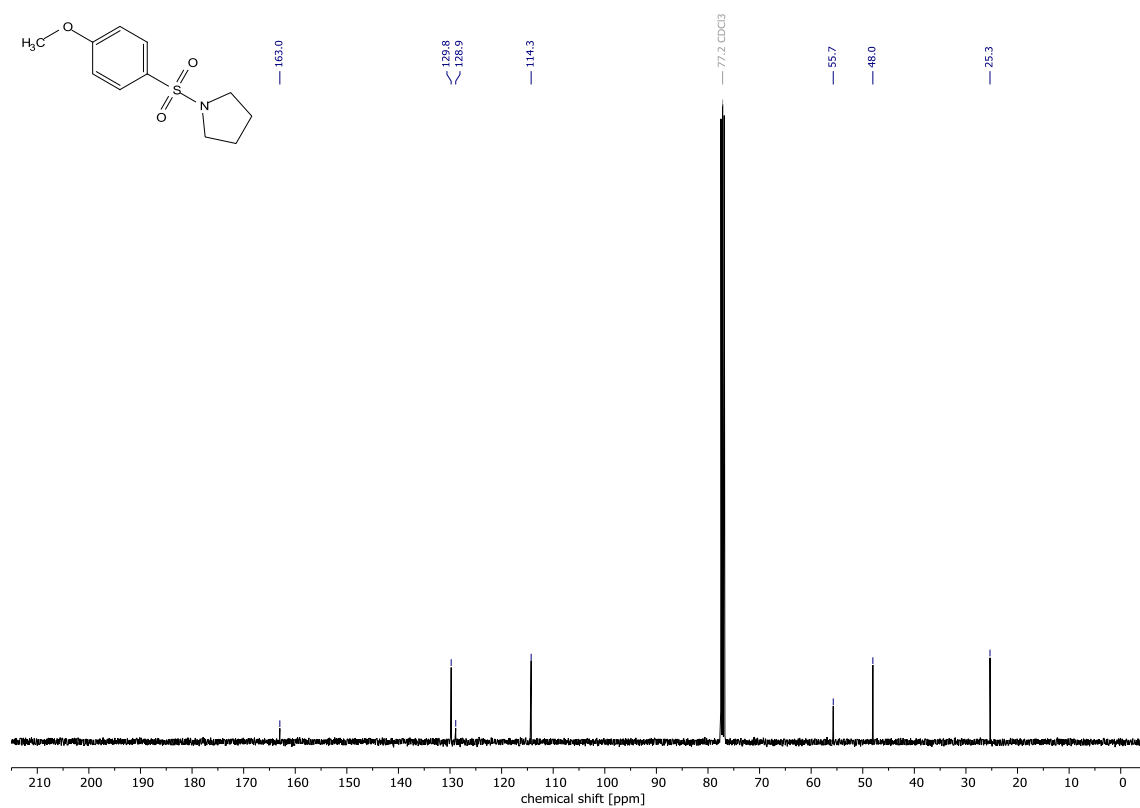


Figure S43: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (101 MHz, 25 °C, CDCl_3) of 4e.

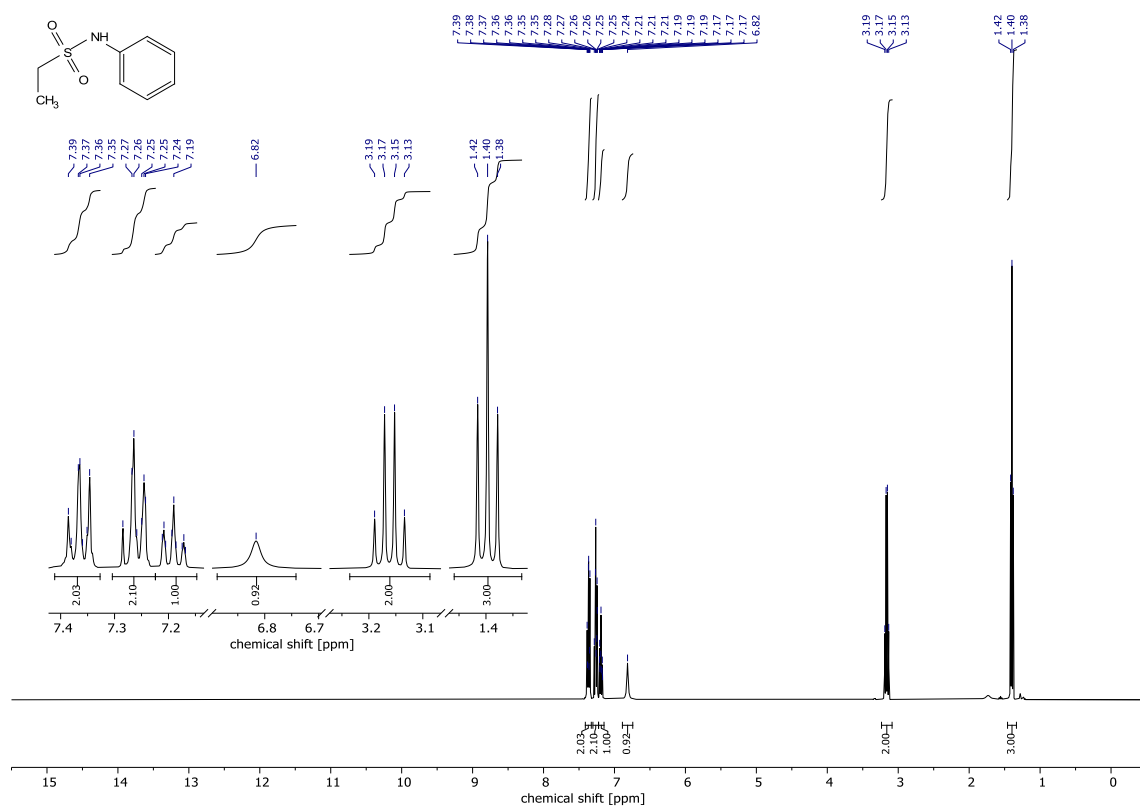


Figure S44: ^1H NMR spectrum (400 MHz, 25 °C, CDCl_3) of 4f.

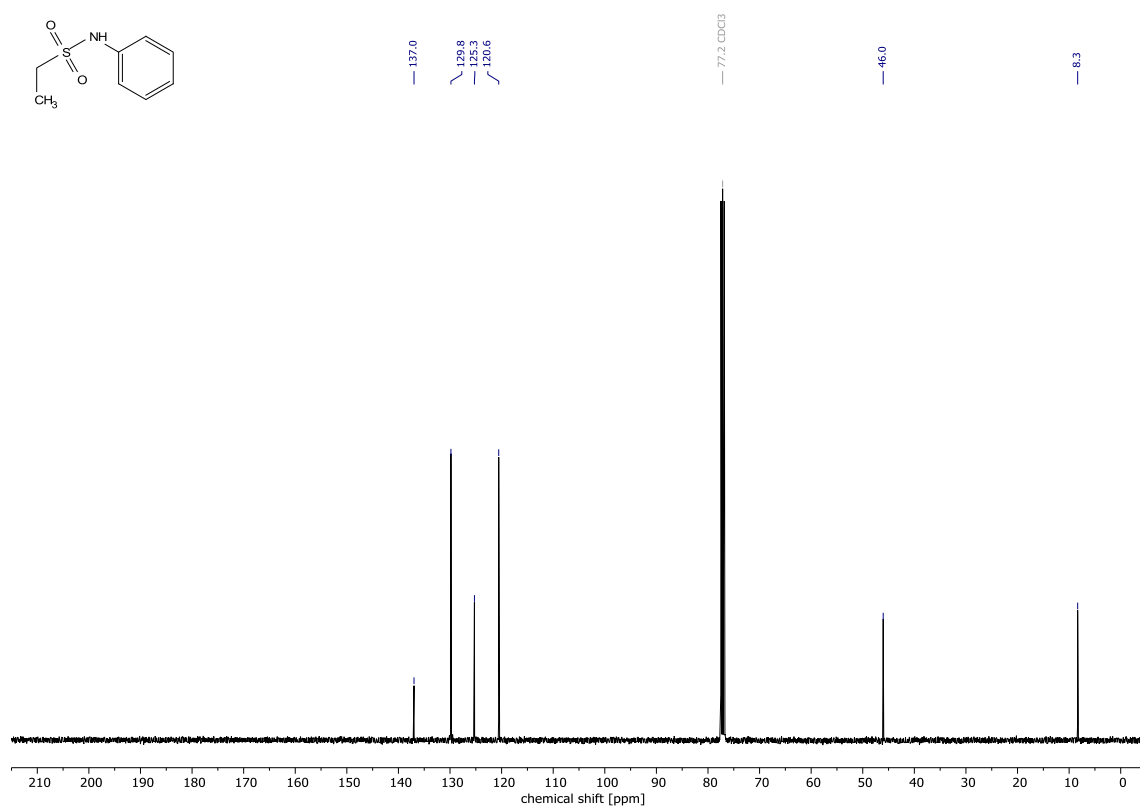


Figure S45: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (101 MHz, 25 °C, CDCl_3) of 4f.

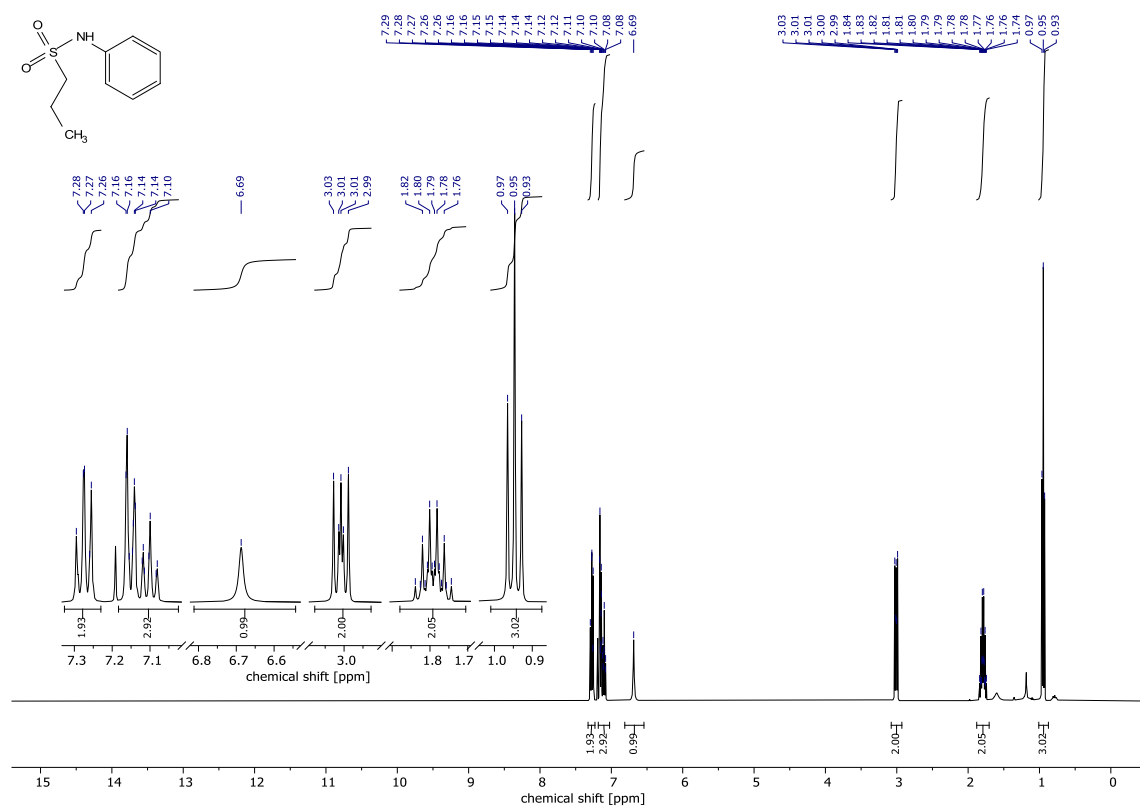


Figure S46: ^1H NMR spectrum (400 MHz, 25 °C, CDCl_3) of 4g.

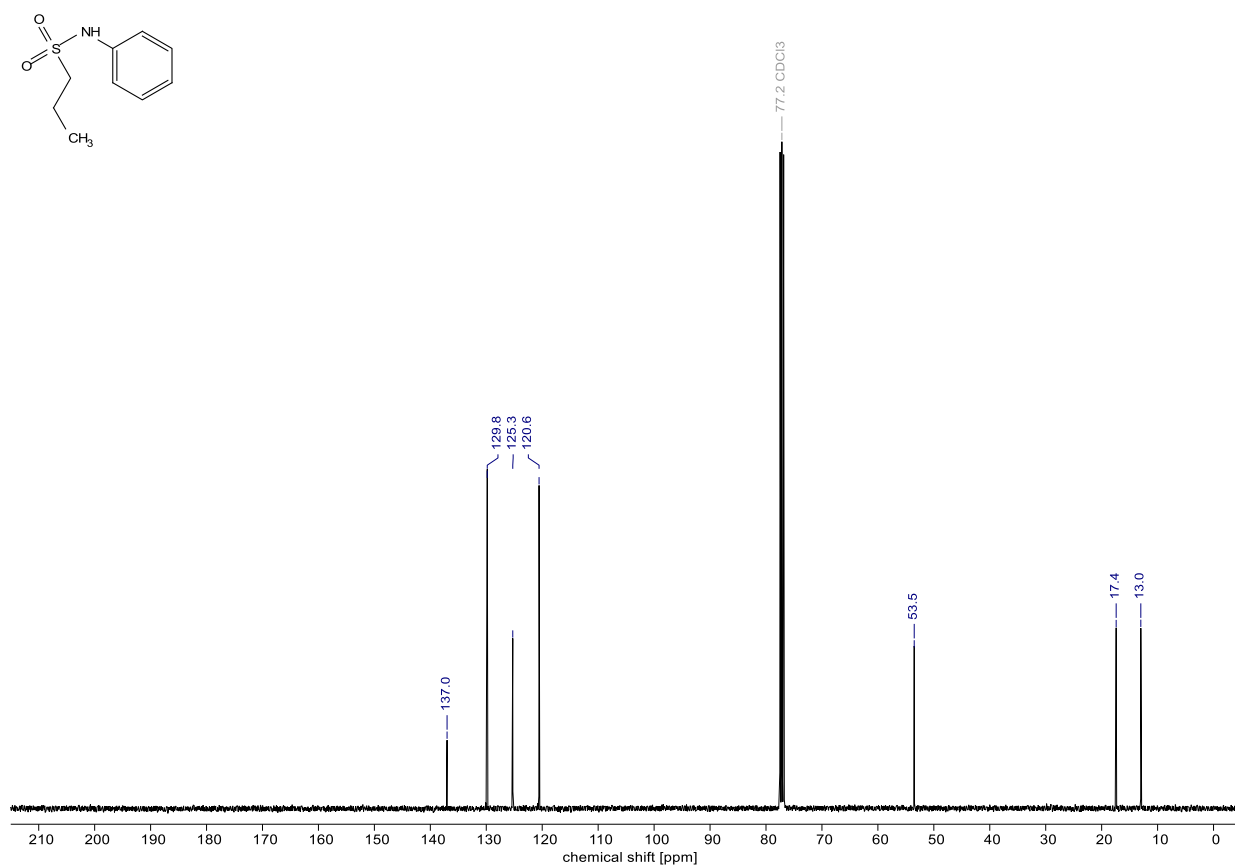


Figure S47: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **4g**.

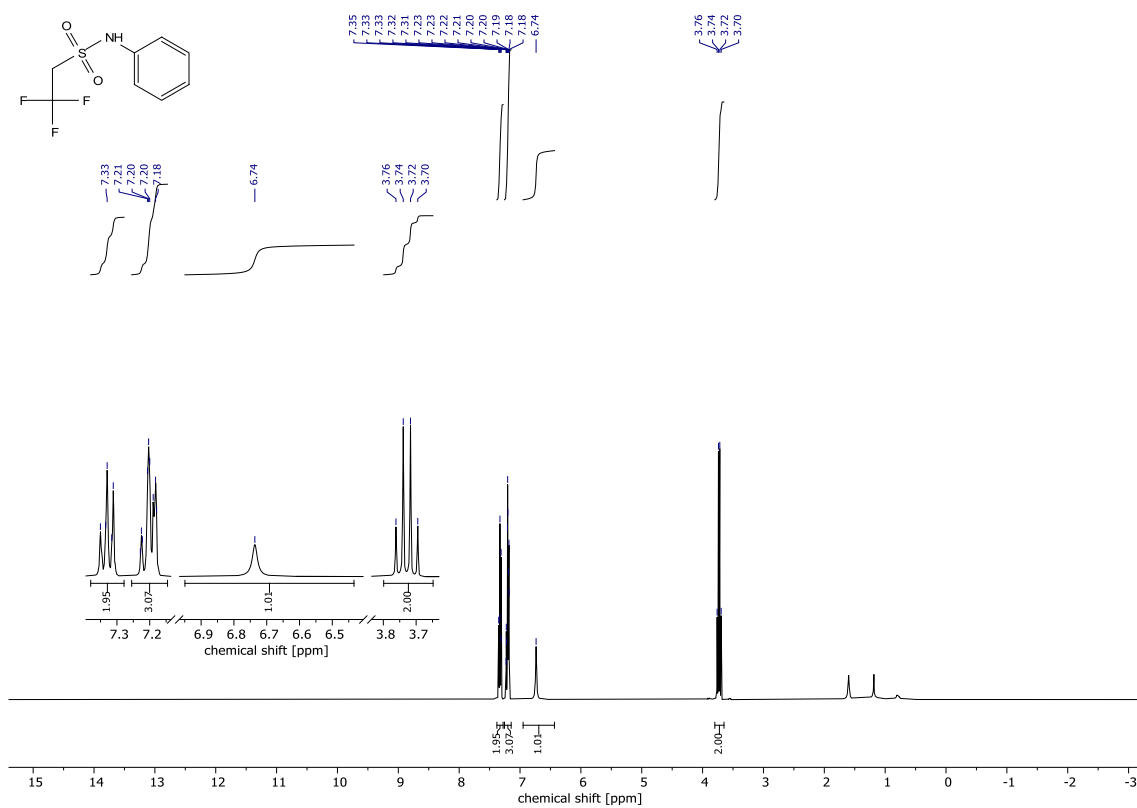


Figure S48: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **4h**.

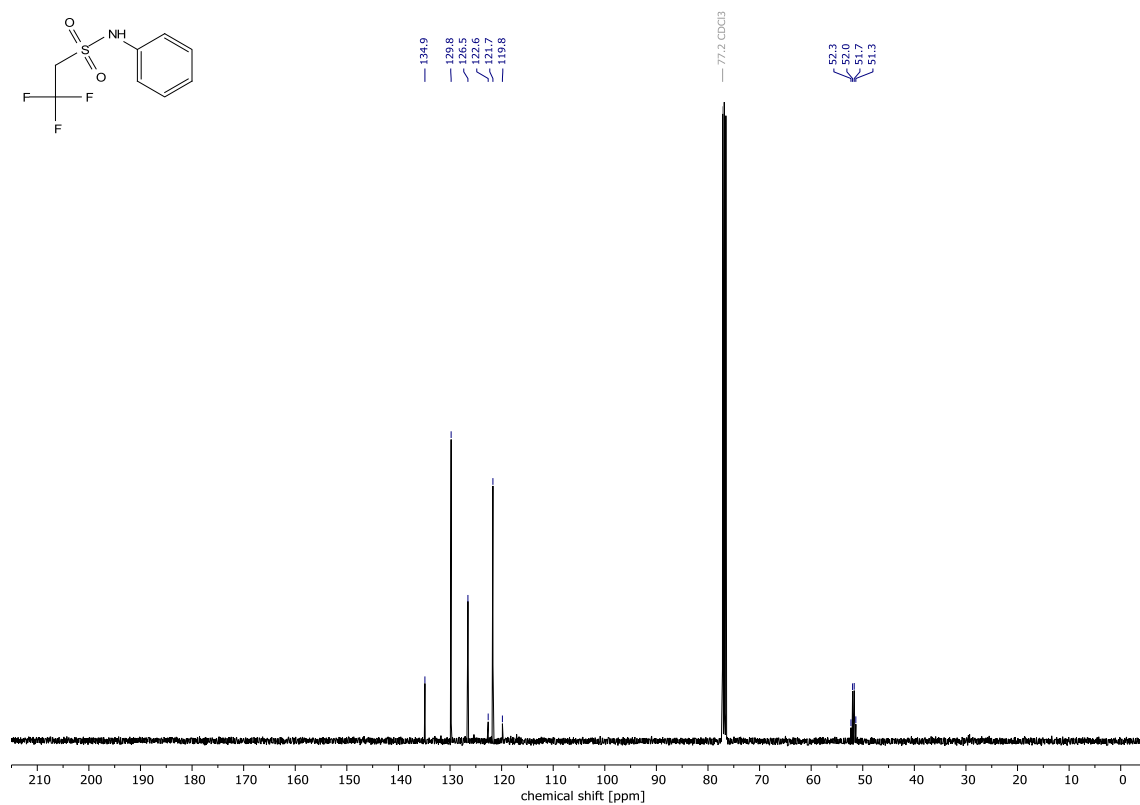


Figure S49: $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum (101 MHz, 25 °C, CDCl_3) of 4h.

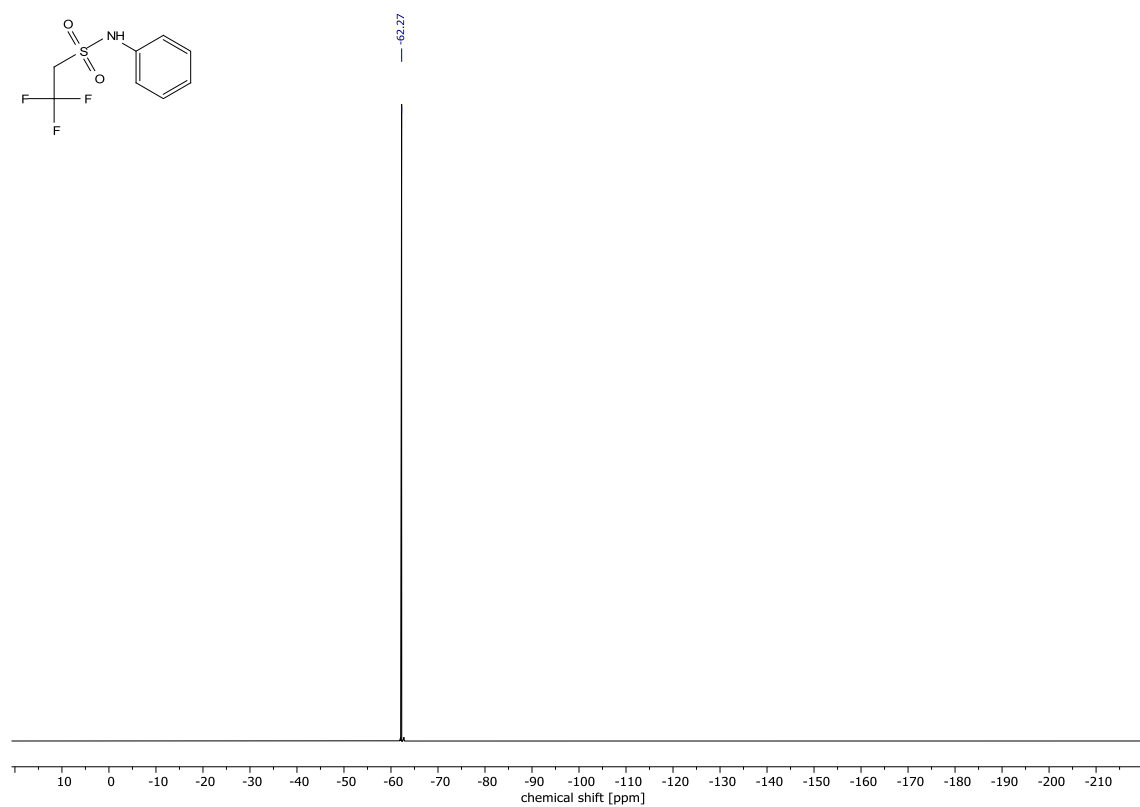


Figure S50: ^{19}F NMR (376 MHz, 25 °C, CDCl_3) of 4h.

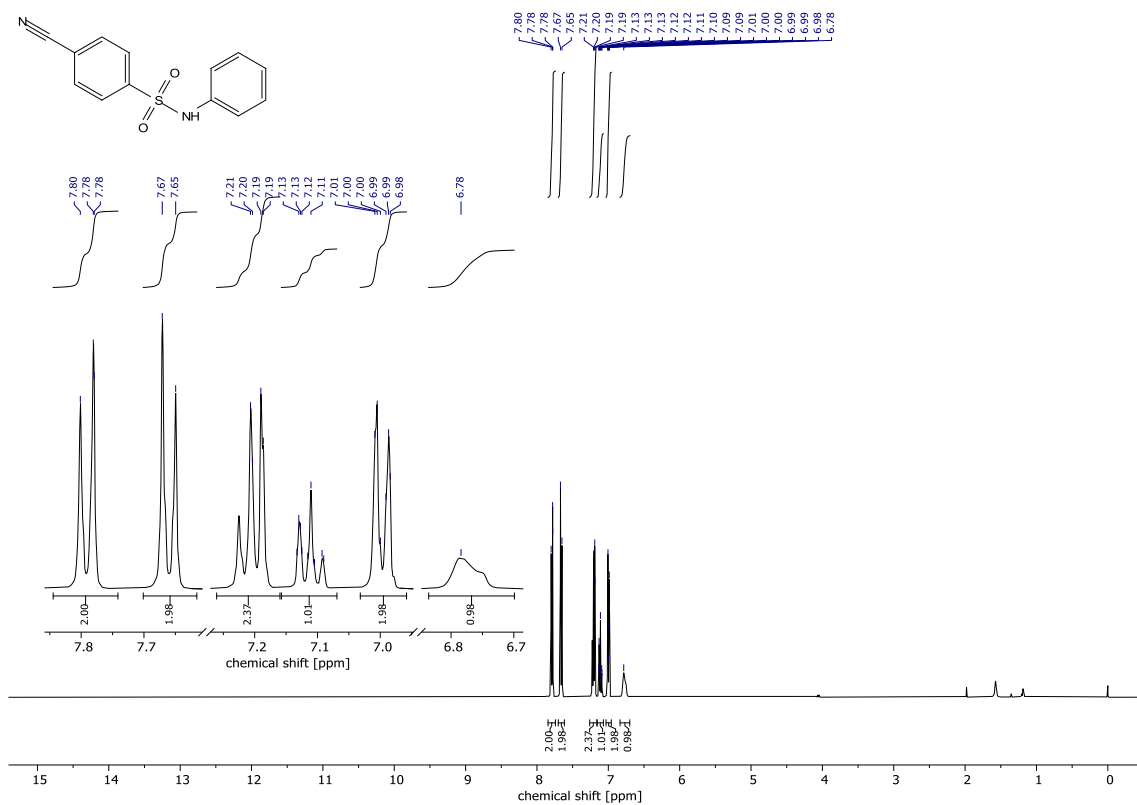


Figure S51: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **4i**.

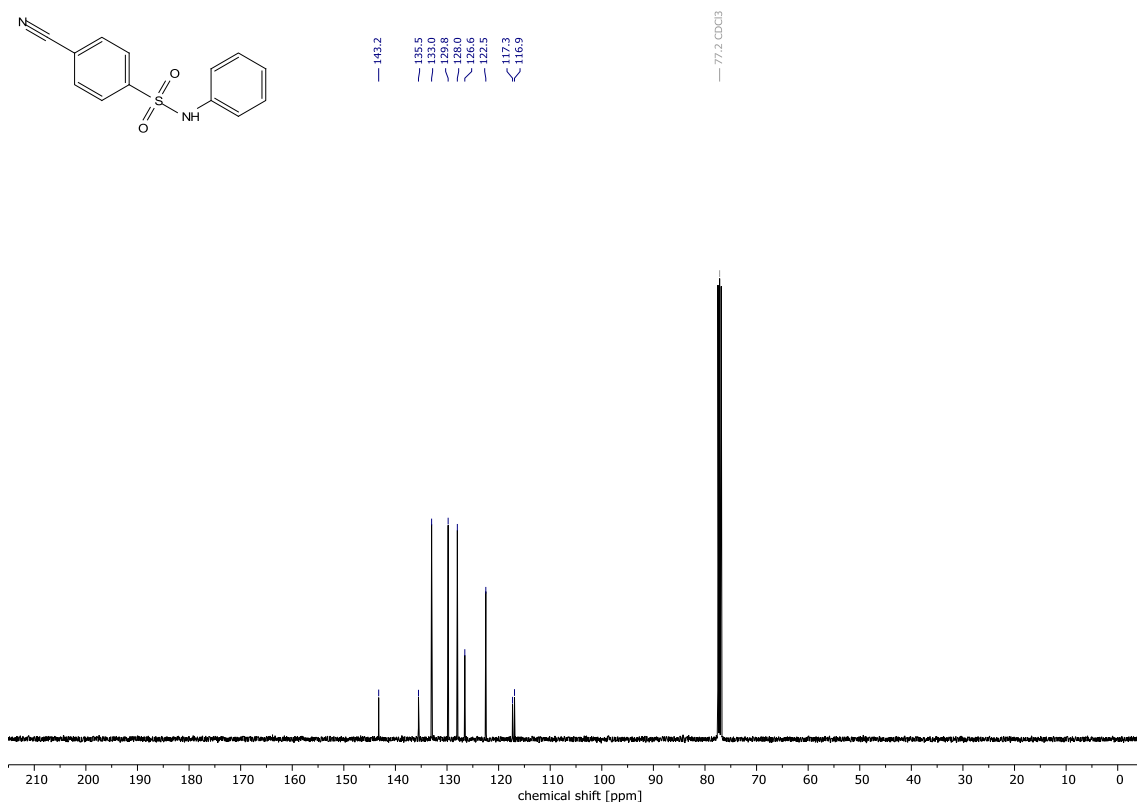


Figure S52: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **4i**.

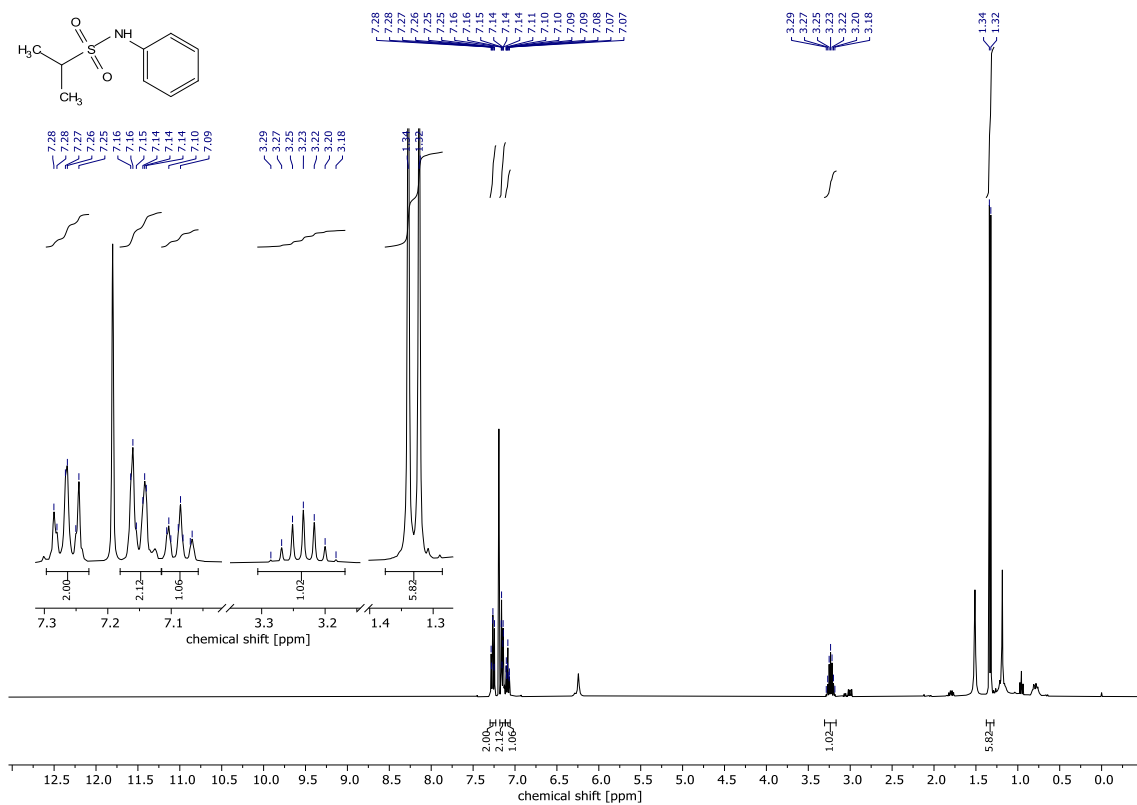


Figure S53: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of **4j**.

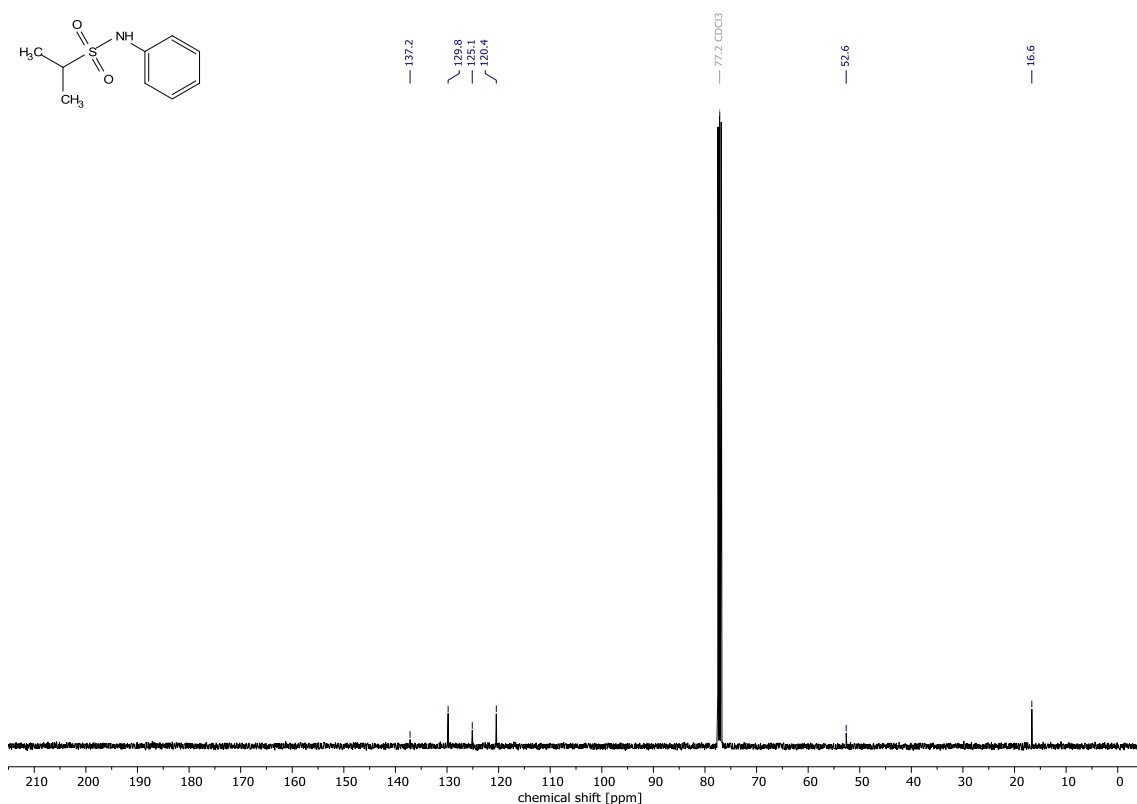
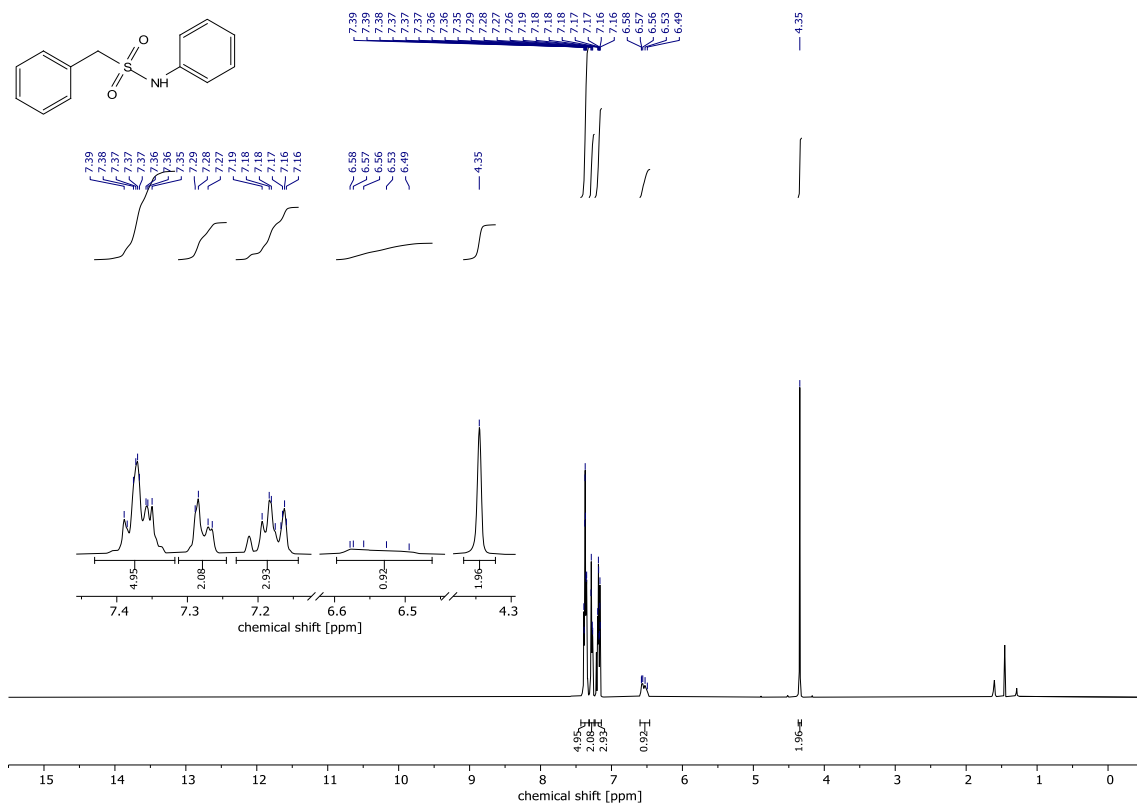
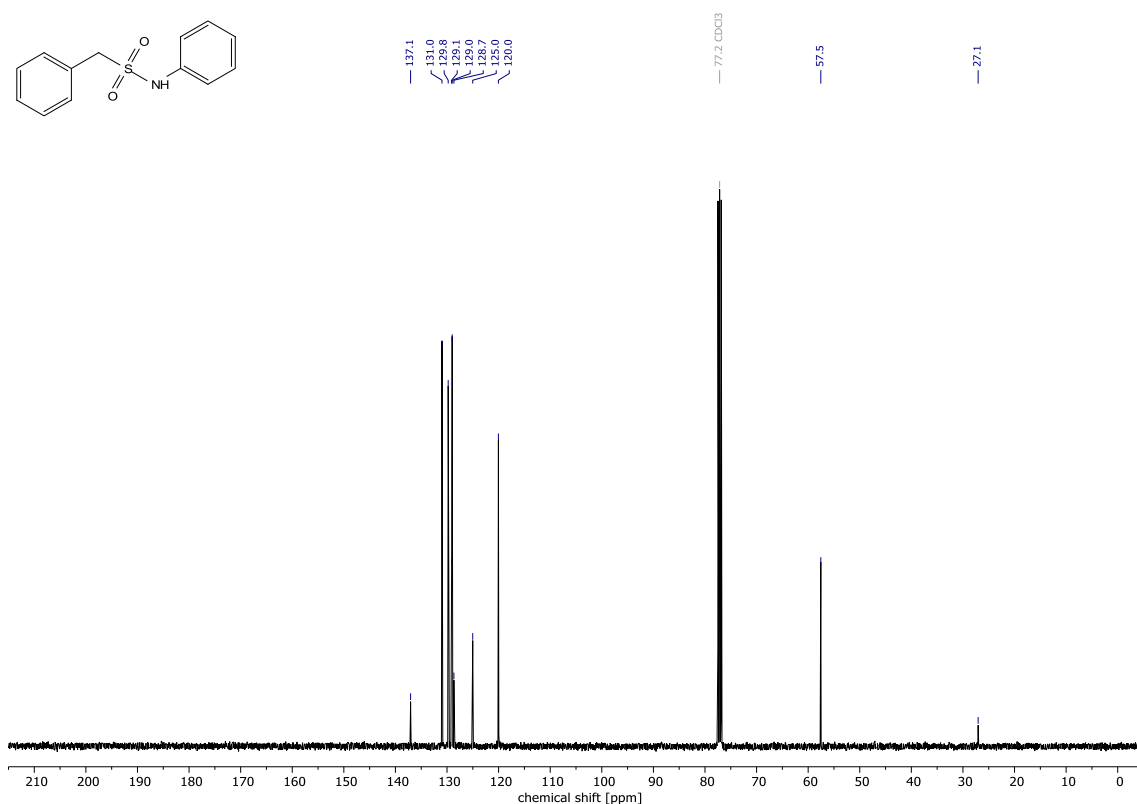


Figure S54: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of **4j**.

Figure S55: ¹H NMR spectrum (400 MHz, 25 °C, CDCl₃) of 4k.Figure S56: ¹³C{¹H} NMR spectrum (101 MHz, 25 °C, CDCl₃) of 4k.

Mass Spectra

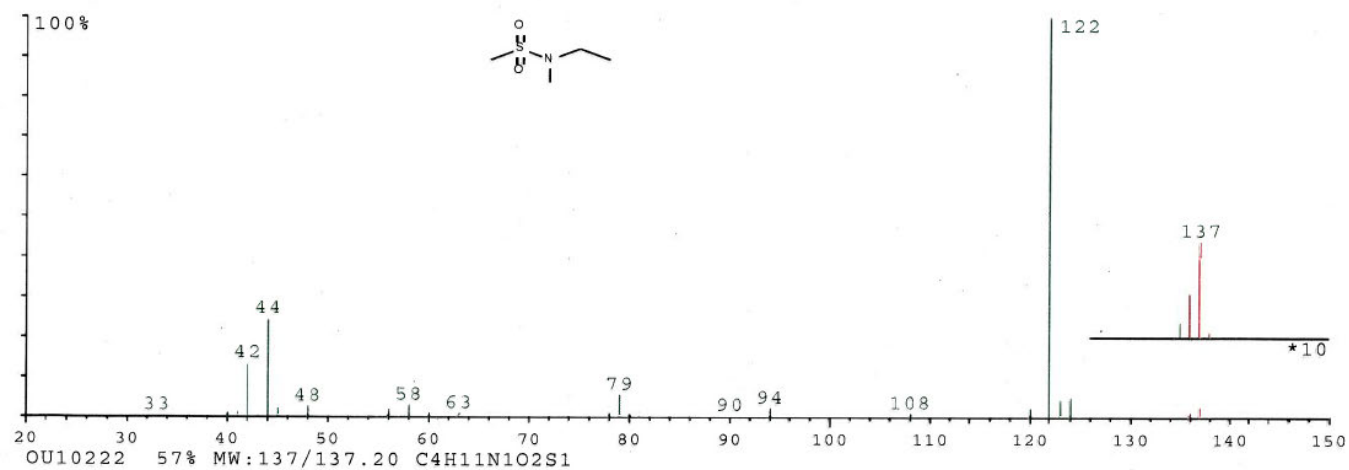
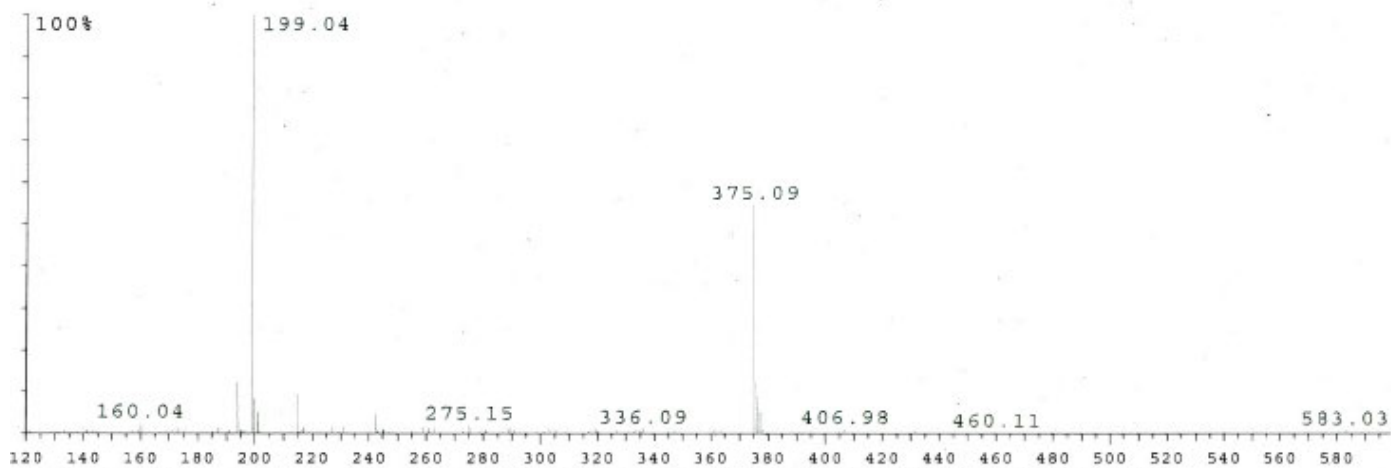


Figure S57: Mass Spectrum of product 2g.



Mass to be matched (m/z): 199.03999 charge: 1

Mass tolerance: ±0.005

restriction of atom numbers:

C 1-100 H 1-100 O 0-10 S 1-1 Na 1-1

Number of calculated formulas: 1

Formula C₇ H₁₂ Na₁ O₃ S₁ Diff. (ppm) -0.25 theor. m/z 199.03994

Figure S58: Mass Spectrum of product 3d.

Radical Trapping Experiment

Procedure:

The reaction was carried out using the undivided Teflon™ cells with a PTFE lid including the anode and a cathode as described in the General procedure GP2.

Electrolyte: An undivided Teflon™ cell is filled with methanesulfonic acid (3.54 mmol, 1 equiv.), tetrabutylammonium thiocyanate (0.5 mmol, 0.15 equiv.), 2,2,6,6-Tetramethylpiperidinyloxy (TEMPO, 1.77 mmol, 1 equiv.) and acetonitrile (5 mL).

The lid including the electrodes is attached to the cell, the electric current and amount of applied charge are set to 172 mA (75 mA cm⁻²), 3 F and the electrolysis was carried out at room temperature under constant stirring (900 rpm). After completion, the reaction mixture has been analyzed via GC-MS. No species other than TEMPO itself could be observed.

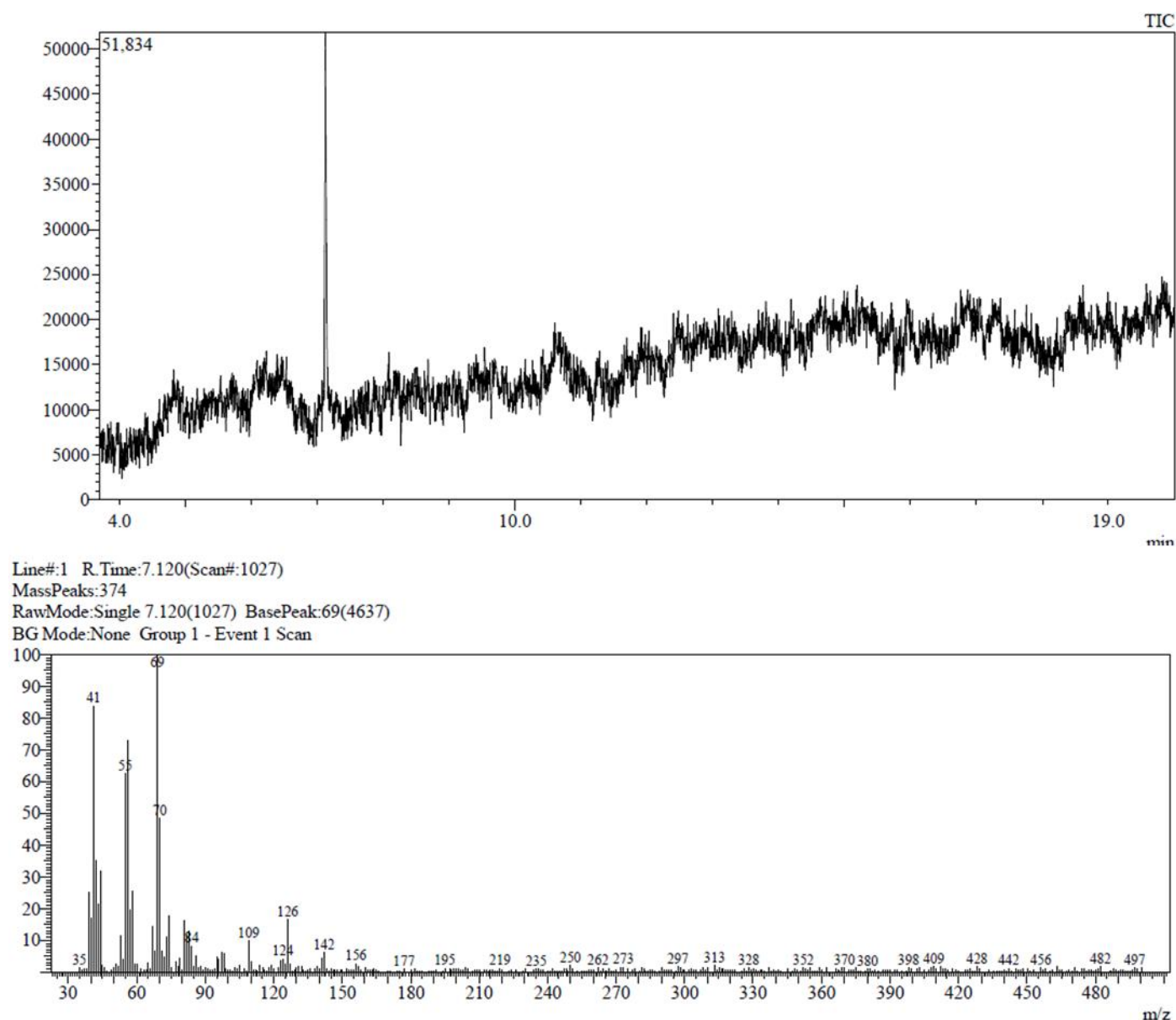


Figure S59: Result of the radical trapping experiment with TEMPO: No species other than TEMPO could be observed in GCMS.

Author contributions

E.L.:	conceptualization, investigation, methodology, data curation and analysis, writing the original draft.
A.V.K.:	supporting (part of the scope, cyclic voltammetry, scale up).
J.S.:	supporting (initial investigation, writing).
S.R.W.:	conceptualization, funding acquisition, project administration, resources, supervision, writing the original draft.

References

- (1) Lowe, D. M.; Corbett, P. T.; Murray-Rust, P.; Glen, R. C. Chemical name to structure: OPSIN, an open source solution. *J. Chem. Inf. Model.* **2011**, *51* (3), 739–753. DOI: 10.1021/ci100384d
- (2) Rundlöf, T.; Mathiasson, M.; Bekiroglu, S.; Hakkarainen, B.; Bowden, T.; Arvidsson, T. Survey and qualification of internal standards for quantification by ¹H NMR spectroscopy. *J. Pharm. Biomed. Anal.* **2010**, *52* (5), 645–651. DOI: 10.1016/j.jpba.2010.02.007
- (3) a) Izutsu, K. *Electrochemistry in Nonaqueous Solutions*; Wiley, 2002. DOI: 10.1002/3527600655#; b) Compton, R. G.; Banks, C. E. *Understanding voltammetry / Richard G Compton, Craig E Banks*; World Scientific, 2025; c) Elgrishi, N.; Rountree, K. J.; McCarthy, B. D.; Rountree, E. S.; Eisenhart, T. T.; Dempsey, J. L. A Practical Beginner's Guide to Cyclic Voltammetry. *J. Chem. Educ.* **2018**, *95* (2), 197–206. DOI: 10.1021/acs.jchemed.7b00361
- (4) Gütz, C.; Klöckner, B.; Waldvogel, S. R. Electrochemical Screening for Electroorganic Synthesis. *Org. Process Res. Dev.* **2016**, *20* (1), 26–32. DOI: 10.1021/acs.oprd.5b00377
- (5) Breitschaft, F. A.; Saak, A. L.; Krumbiegel, C.; Bartolomeu, A. d. A.; Weyhermüller, T.; Waldvogel, S. R. Multicomponent Electrosynthesis of Enaminy Sulfonates Starting from Alkylamines, SO₂, and Alcohols. *Org. Lett.* **2025**, *27* (5), 1210–1215. DOI: 10.1021/acs.orglett.4c04746
- (6) Shi, W.; Bai, C.-M.; Zhu, K.; Cui, D.-M.; Zhang, C. Brønsted acid-assisted N-alkylation of sulfonamides using ethers as the alkylation reagents. *Tetrahedron* **2014**, *70* (2), 434–438. DOI: 10.1016/j.tet.2013.11.036
- (7) Kloeckner, U.; Nachtsheim, B. J. Mild hypervalent iodine mediated oxidative nitration of N-aryl sulfonamides. *Chem. Commun.* **2014**, *50* (72), 10485–10487. DOI: 10.1039/C4CC04738A
- (8) Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H. Copper-catalyzed sulfonamides formation from sodium sulfinates and amines. *Chem. Commun.* **2013**, *49* (54), 6102–6104. DOI: 10.1039/C3CC41249K
- (9) Dabkowski, W.; Michalski, J.; Skrzypczyński, Z. A Convenient Synthesis Of Phosphorus And Sulfonyl Substituted N - Imidazoles (Triazoles) Using The Corresponding Acid Chlorides And N -Trimethylsilyl Imidazoles (Triazoles). *Phosphorus Sulfur Relat. Elem.* **1986**, *26* (3), 321–326. DOI: 10.1080/03086648608084586
- (10) Varela-Fernández, A.; Varela, J. A.; Saá, C. Ruthenium-Catalyzed Cycloisomerization of Aromatic Homo- and Bis-Homopropargylic Amines/Amides: Formation of Indoles, Dihydroisoquinolines and Dihydroquinolines. *Adv. Synth. Catal.* **2011**, *353* (11-12), 1933–1937. DOI: 10.1002/adsc.201100095
- (11) O'Sullivan, S.; Doni, E.; Tuttle, T.; Murphy, J. A. Metal-free reductive cleavage of C-N and S-N bonds by photoactivated electron transfer from a neutral organic donor. *Angew. Chem. Int. Ed.* **2014**, *53* (2), 474–478. DOI: 10.1002/anie.201306543
- (12) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A.-M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. Neopentylglycolborylation of aryl mesylates and tosylates catalyzed by Ni-based mixed-ligand systems activated with Zn. *J. Am. Chem. Soc.* **2010**, *132* (6), 1800–1801. DOI: 10.1021/ja910808x
- (13) Albrecht, S.; Defoin, A.; Tarnus, C. Simple Preparation of O-Substituted Hydroxylamines from Alcohols. *Synthesis* **2006**, *2006* (10), 1635–1638. DOI: 10.1055/s-2006-926440
- (14) Kuhne, S.; Kooistra, A. J.; Bosma, R.; Bortolato, A.; Wiltmans, M.; Vischer, H. F.; Mason, J. S.; Graaf, C. de; Esch, I. J. P. de; Leurs, R. Identification of Ligand Binding Hot Spots of the Histamine H1 Receptor following Structure-Based Fragment Optimization. *J. Med. Chem.* **2016**, *59* (19), 9047–9061. DOI: 10.1021/acs.jmedchem.6b00981
- (15) Curti, C.; Zanardi, F.; Battistini, L.; Sartori, A.; Rassu, G.; Pinna, L.; Casiraghi, G. Streamlined, asymmetric synthesis of 8,4'-oxyneolignans. *J. Org. Chem.* **2006**, *71* (22), 8552–8558. DOI: 10.1021/jo061521t
- (16) Laudadio, G.; Bampoutsis, E.; Schotten, C.; Struik, L.; Govaerts, S.; Browne, D. L.; Noël, T. Sulfonamide Synthesis through Electrochemical Oxidative Coupling of Amines and Thiols. *J. Am. Chem. Soc.* **2019**, *141* (14), 5664–5668. DOI: 10.1021/jacs.9b02266
- (17) Hu, L.; Liu, X.; Liao, X. Nickel-Catalyzed Methylation of Aryl Halides with Deuterated Methyl Iodide. *Angew. Chem. Int. Ed.* **2016**, *55* (33), 9743–9747. DOI: 10.1002/anie.201604406
- (18) Chen, J.; Han, X.; Mei, L.; Liu, J.; Du, K.; Cao, T.; Li, Q. Iodine-catalyzed sulfonylation of sulfonyl hydrazides with tert-amines: a green and efficient protocol for the synthesis of sulfonamides. *RSC Adv.* **2019**, *9* (54), 31212–31216. DOI: 10.1039/C9RA07361B
- (19) Moon, S.-Y.; Nam, J.; Rathwell, K.; Kim, W.-S. Copper-catalyzed Chan-Lam coupling between sulfonyl azides and boronic acids at room temperature. *Org. Lett.* **2014**, *16* (2), 338–341. DOI: 10.1021/ol403717f
- (20) Tan, B. Y.-H.; Teo, Y.-C.; Seow, A.-H. Low Catalyst Loadings for Ligand-Free Copper(II)-Oxide-Catalyzed N -Arylation of Methanesulfonamide in Water. *Eur. J. Org. Chem.* **2014**, *2014* (7), 1541–1546. DOI: 10.1002/ejoc.201301561
- (21) Holden, C. M.; Sohel, S. M. A.; Greaney, M. F. Metal Free Bi(hetero)aryl Synthesis: A Benzyne Truce–Smiles Rearrangement. *Angew. Chem.* **2016**, *128* (7), 2496–2499. DOI: 10.1002/ange.201510236
- (22) García Ruano, J.; Parra, A.; Yuste, F.; Mastranzo, V. Mild and General Method for the Synthesis of Sulfonamides. *Synthesis* **2008**, *2008* (2), 311–319. DOI: 10.1055/s-2007-1000850
- (23) Hill, B.; Liu, Y.; Taylor, S. D. Synthesis of alpha-fluorosulfonamides by electrophilic fluorination. *Org. Lett.* **2004**, *6* (23), 4285–4288. DOI: 10.1021/ol048249z