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Electrosynthesis 2.0 in 1,1,1,3,3,3-Hexafluoroisopropanol/Amine Mixtures

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In memory of Prof. Dr. Dennis G. Peters

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The intention of this review is to highlight the innovative electrolyte combination of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with tertiary nitrogen bases in electro-organic synthesis. This easy applicable and promising mixture is not yet well established in electro-organic synthesis, but expands the various possibilities in the latter. Combinations of fluorinated alcohols with nitrogen bases form highly conductive electrolyte systems, which can be evaporated completely. Consequently, no additional supporting electrolyte is required and work-up procedures are tremendously simplified. With this electrolyte mixture carbon-carbon homo- and cross-coupling reactions of arenes and phenols have been established with substrates that have not been previously susceptible to the anodic dehydrogenative coupling reaction. The intermediate installation of highly fluorinated alkoxy moieties can be exploited for subsequent conversions as well as various benzylic functionalization, including asymmetric transformations. These transformations show unique selectivity and functional group tolerance making them highly applicable to the synthesis of sophisticated structural motifs, including natural products.

1. Introduction

Fluorinated alcohols have emerged as excellent choices for a broad range of applications in organic chemistry, due to their high hydrogen-bond donor ability,[1,2] high polarity,[2,3] outstanding (electro-)chemical stability,[4,5] and micro-heterogeneity.[6–8] This is illustrated by their use as solvents, co-solvents or promoters in organic syntheses.[2,5,9,10] Several examples have showcased the utility of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in transition metal-catalyzed,[10,11] and metal-free reactions.[12] In combination with bases, HFIP promotes unusual transformations like the generation of aza-oxyallyl cationic intermediates from α-haloamides[13] or HFIP-promoted nucleophilic substitutions[9,14]. These unique features of HFIP make it particularly well-suited as a solvent for electrochemical reactions, especially its ability to stabilize radical intermediates.[15,16] HFIP has demonstrated superior effects compared to other solvents when it comes to improving selectivity and yield of various electrochemical transformations.[17–21] In particular, the solvate formation modulates nucleophilicity and oxidation potential.[7,17] The unusual electrochemical stability of HFIP is ensured as long as inert anodes are employed for direct electrode processes,[22] whereas hypervalent iodine mediators are capable to convert HFIP to highly toxic hexafluoroacetone.[23] HFIP is corrosive and a strong skin and respiratory irritant, but nevertheless easy to handle.[24] For a long time the biggest drawback of HFIP was its comparably high costs for a solvent. In past decades, general anesthesia, e.g. sevoflurane, became common in use, wherein HFIP is a synthetic precursor. Typical cost range from a 100 to 300 euros per kg and highly depend on the scale being bought.[25] Due to the low boiling point of 58 °C the recovery of HFIP by distillation is simple, thus overcoming the significant costs to a certain degree.[26] The melting point is −4 °C,[27] and HFIP has a high density of 1.517 g/mL while being miscible with water and most organic solvents.[24]

Electrochemistry has experienced a renaissance in recent years since it offers benefits over classical synthetic methodologies.[18–20,28] Electric current, as an inexpensive and inherently safe reagent, facilitates sustainable synthetic pathways, and is compatible with renewable energy sources.[29] A direct contribution for the stabilizing of the electric grid is provided, when the electro-conversions are robust and fluctuating electricity can be employed without loss of selectivity and reactivity. Here, HFIP based electrolytes seem to play an outstanding role.[30] The avoidance of chemical reagents minimizes the amount of reagent waste produced by the process. Thus, many of the "green chemistry" principles may be fulfilled by applying electro-organic methods.[30,31] A common drawback in electrochemistry is the need for supporting electrolytes, which are often salts with significant environmental impact.[32] The subsequent workup is complicated due to difficult removal or recovery of the salt. Noteworthy, perchlorates can lead to explosive events and symmetric tetraalkylammonium salts strongly affect the wastewater treatment.[33] When applying a combination of base with acidic HFIP ($pK_a = 9.3$[15]) to electro-organic synthesis, a supporting electrolyte is formed in-situ, eliminating the need for additional supporting electrolyte. Avoiding the use of salts simplifies the workup procedure, facilitating easy removal of the electrolyte by distillation, simplifying downstream processing and recycling of the electrolyte. Additionally, the lack of salts allows the coupling with mass spectrometry for real-time reaction monitoring in, for example, automated synthesis. In addition, the enhanced nucleophilicity of deprotonated HFIP allows trapping of reactive intermediates, which can be submitted to different coupling reactions to open new pathways in organic synthesis. For example, in 2013 Tajima et al. first described the use of a solid-supported base in HFIP in a one-pot sequence of alkoxylation followed by the reaction with allyltrimethylsilane (Scheme 1).[34] Subsequently, our group first used a simple tertiary amine base without additional salt or reagents in a formal benzyl-aryl cross-coupling reaction, demonstrating the potential of this approach (Scheme 3).[35] Many more seminal applications of this powerful combination have been recently published and will be discussed within this review.[36–40]

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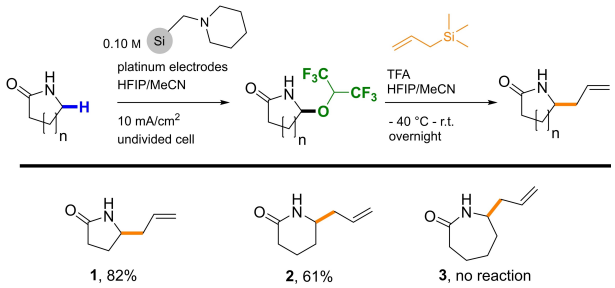
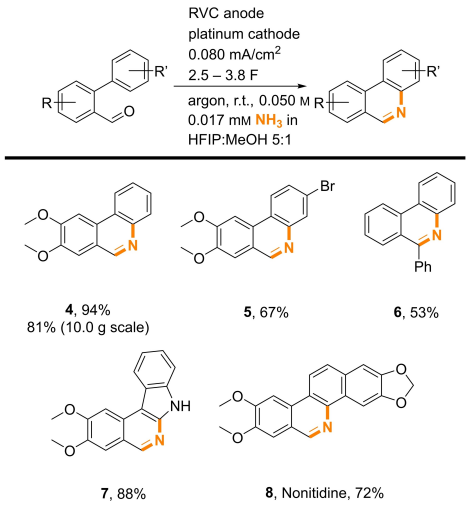


Scheme 1. One-pot sequence enabling allyl-substituted lactams utilizing a solid-supported amine base in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).

2. Anodic Alkoxylation Promoted by Solid-Supported Base as Part of a One-Pot Sequence

The Tateno group developed an elegant anodic alkoxylation of lactams followed by allylation in a one-pot sequence using HFIP in combination with a solid-supported amine base.[34] This gives rise to allylated five- and six-membered lactams (**1**) and (**2**) in yields up to 82% over both steps (Scheme 1). After electrolysis the silica-supported piperidine can be easily removed by filtration. In case of a 7-membered ring (**3**) the intermediate *N*-acyliminium ion was not formed and therefore no reaction took place.



Scheme 2. Electro-organic access to phenanthridines and related structures using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and ammonia.

3. Electro-organic Formation of Nitrogen Heterocycles using Ammonia in HFIP

The ubiquity of nitrogen moieties in natural products, pharmaceutically active compounds, and advanced materials highlights the necessity for sustainable formation of nitrogen heterocycles.[41] Several approaches have been described along with electro-organic C–N bond construction.[42] A regioselective

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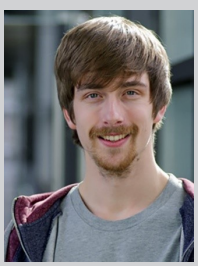

Maurice Dörr received his B.Sc. degree in chemistry from Johannes Gutenberg University Mainz (Germany) working on anodic C–C cross-coupling reactions in 2016 and his M.Sc. working on anodic C–N cross-coupling reactions in 2018 supervised by Prof. Dr. Siegfried R. Waldvogel. Currently, he is engaged in the application of Design of Experiments (DoE) towards electro-organic synthesis as a graduate student in the Waldvogel lab.

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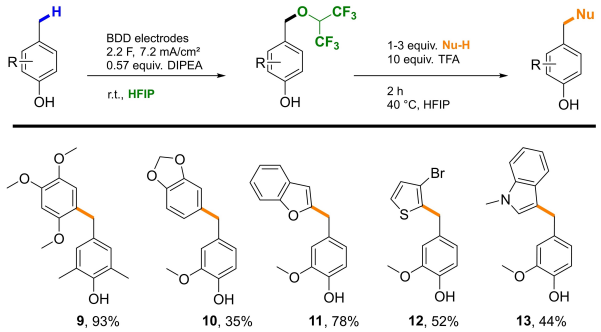


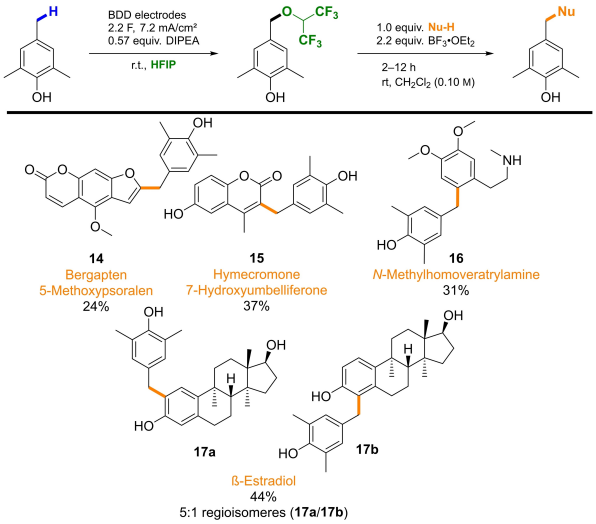
Scheme 3. Benzyl-aryl cross-coupling of phenols with various nucleophiles after anodic activation with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).

anodic approach towards phenanthridines and pyridine-fused polycyclic structures exploits ammonia as an inexpensive and stable nitrogen donor and base with high atom economy in HFIP (Scheme 2).[43] Ammonia ($pK_a(NH_4^+) = 9.2$)[44] is used as a reagent and additive for ensuring sufficient conductivity by an acid-base equilibrium with the solvent HFIP. This galvanostatic protocol was also performed in a decagram-scale towards **4** in 81% yield to highlight the utility in organic synthesis. In addition, access to the natural product nonitidine **8** could be accomplished in 72% yield.

4. Benzyl-Aryl Cross-Coupling Reaction via Anodic C–H Functionalization by HFIP

A selective dehydrogenative electrochemical functionalization of benzylic positions with HFIP has been developed by Waldvogel et al.[35] These electro-generated HFIP ethers are versatile intermediates for subsequent functionalization, as they act as masked benzylic cations, which can be easily activated. Best results were obtained in combination with *N,N*-diisopropylethylamine (DIPEA). Liberation of the benzylic cation was accomplished by acidic treatment. These cations can readily react with aromatic nucleophiles to provide valuable diarylmethanes. Overall, 28 examples in yields up to 93% (**9**) over both steps have been accessed (Scheme 3). Various heterocycles could be alkylated by this way, such as 1,3-benzodioxoles (**10**), benzo[*b*]furanes (**11**), thiophenes (**12**) and indoles (**13**) in high yields up to 78% over 2 steps.

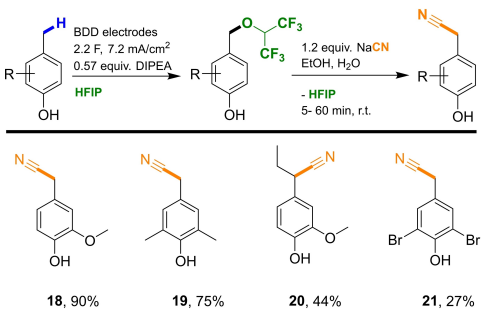
Even late-stage functionalization of a variety of natural products and pharmaceutically active ingredients was possible in yields up to 44% (**17a** and **17b**) with slight alteration of the protocol employing Lewis acids instead of 2,2,2-trifluoroacetic acid for HFIP ether cleavage (Scheme 4). Bergapten (**14**), hymecromone (**15**) and even phenylethylamines (**16**) could be converted in this reaction in yields up to 37%.



Scheme 4. Lewis acid-directed late-stage functionalization of natural products and pharmaceutically active compounds.

5. Benzylic Anodic C–H Functionalization with HFIP and Subsequent Cyanation to Generate 2-Phenylacetonitriles

The HFIP ether concept has been expanded to other valuable building blocks by the Waldvogel group. It was found that liberation of the benzylic cation is not necessary to achieve selective bond formation when stronger nucleophiles are used.[37] With cyanides, a direct substitution reaction is observed to yield 2-phenylacetonitriles, which represent important building blocks in organic synthesis. This structural feature is a precursor to many biologically active molecules such as 2-phenylethylamines[45] or pharmaceuticals, such as the calcium ion channel blocker verapamil or the fungicide mandipropamid.[46] This procedure allows a simple, sustainable, easily scalable, reagent- and metal-free electrochemical cyanation reaction (Scheme 5). It consists of a two-step sequence and the HFIP ether generated in-situ can be used without further purification. The reaction is selective with yields up to 90% over 2 steps and methoxy groups (**18**), multiple alkyl groups (**19**), propyl moieties (**20**) and halogens (**21**) being tolerated (Scheme 5). Phenols can be converted in a protective group-



Scheme 5. Scope of the benzylic anodic activation with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and subsequent cyanation reaction.

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free manner, shortening the usual synthetic route by one or two steps. Additionally, only a small excess of cyanide source is used and therefore less toxic reagent waste is generated. The HFIP released during the reaction can be recovered and redistilled, improving the sustainability of this reaction.

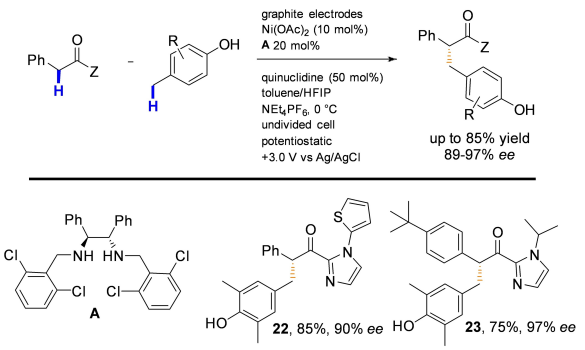
6. Asymmetric Lewis Acid-catalyzed Alkylation in a Toluene/HFIP/Quinuclidine Electrolyte

Inspired by the benzyl-aryl coupling via HFIP ethers by Waldvogel et al., the Guo group developed an outstanding asymmetric nickel-catalyzed electrochemical alkylation.[39] Asymmetric induction is achieved through the radical-radical coupling of a chiral Ni(II) complex chelated radical with an electrochemically formed benzylic radical. The resulting alkylation products could be isolated in yields up to 85% (**22**) and enantiomeric excess up to 97% (**23**) (Scheme 6). However, the well conductive nature of the HFIP/amine mixture was not exploited, since an additional supporting electrolyte was employed.

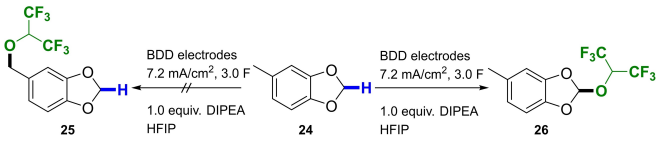
7. Anodic C–H Functionalization towards Fluorinated Orthoesters from 1,3-Benzodioxoles

In contrast to benzylic anodic oxidation of phenols, anisoles and anilides, 1,3-benzodioxoles were found to exhibit unexpected reactivity at complete conversion.[36] Functionalization of **24** occurred at position 2 (**26**), even in the presence of benzylic methyl groups. This is in contrast to previous work, wherein the benzylic position was functionalized (**25**) (Scheme 7).

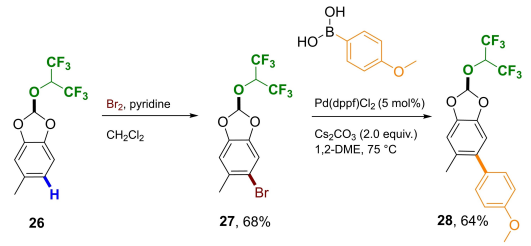
These orthoesters exhibit unusual and unique properties. Surprisingly, **26** proved to be extraordinarily stable towards acids and bases and does not undergo substitution reactions, even when transition metals are present within the reaction mixture. Therefore, it was possible to perform a bromination on **26**, followed by a Pd-catalyzed Suzuki coupling to give **28** in 64% yield, in the presence of the HFIP orthoester (Scheme 8).



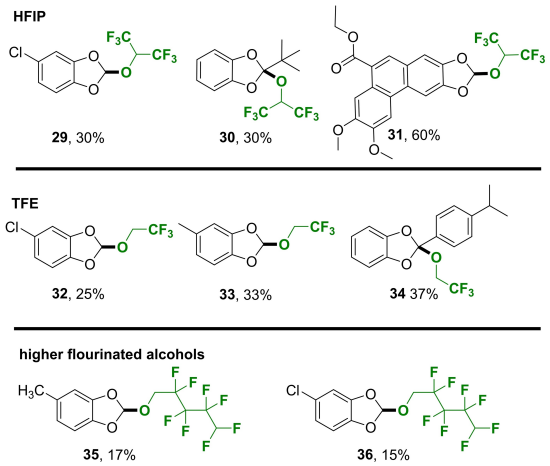
Scheme 6. Quinuclidine in toluene/1,1,1,3,3,3-hexafluoroisopropanol (HFIP) mixture as electrolyte in a Lewis acid-catalyzed asymmetric alkylation.



Scheme 7. Selectivity of the anodic C–H functionalization of 1,3-benzodioxoles with HFIP.



Scheme 8. Bromination reaction under acidic conditions followed by Suzuki coupling at elevated temperatures in the presence of fluorinated orthoesters.



Scheme 9. Scope of electrochemically accessible fluorinated orthoesters.

It was also possible to install various fluorinated alkoxy moieties, allowing the modulation of the bioactive properties of the pharmaceutically relevant 1,3-benzodioxole moiety in 28 examples in yields up to 60% (**31**) (Scheme 9).[47]

Higher yields and improved selectivity were observed with increasingly larger π-systems (**31** and **34**). This can be explained by stabilization of the respective cations after twofold oxidation and deprotonation. Halo substituents (**29**, **32**, **36**), as well as a substitution pattern in position 2 and 5 were tolerated (**33**, **34**, **35**). The log*P*-values of 1,3-benzodioxoles and the corresponding orthoesters were calculated and compared, to determine the lipophilicity of the orthoesters in comparison to the respective 1,3-benzodioxoles (see SI of Ref.[36]). Remarkably, these values increased by a factor of 1.5 to 2 when fluorinated side chains were installed. Such an enhancement of lipophilicity is very unusual. This transformation could boost the potency of bioactive compounds and impact target selectivity tremen-

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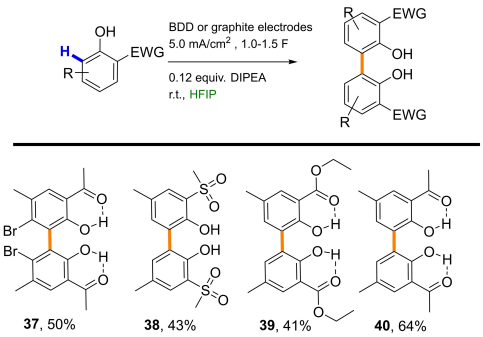
dously by influencing pK_a, modulating conformation, and hydrophobic interactions of the 1,3-benzodioxole moiety.[48]

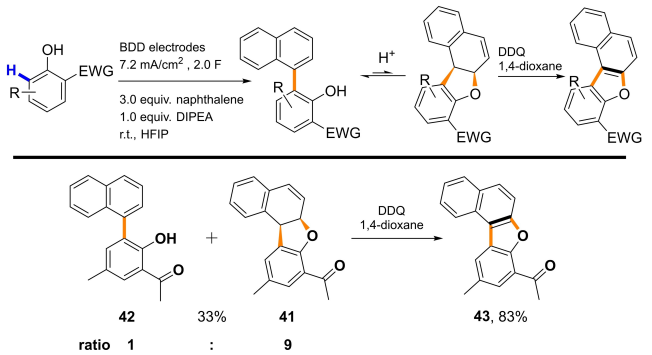
8. Dehydrogenative Anodic C–C Coupling of Phenols Bearing Electron-Withdrawing Groups

Electron-rich phenols and related substrates such as arenes, anilides or heterocycles could be selectively cross-coupled due to the solvent effect of HFIP.[6,17,49] However, the method failed when the components were not electron-rich enough. Interestingly, phenols carrying electron-withdrawing groups (EWG) in position 2 undergo dehydrodimerization reaction instead of HFIP ether formation. To the best of our knowledge, this represents the first selective electrochemical coupling of phenols bearing EWGs.[38] The reaction is highly selective and yields 2,2′-biphenols in up to 64% yield (Scheme 10). This reaction showed a high tolerance to functional groups like ketones (**37** and **40**), halogens (**37**), sulfoxides (**38**), as well as esters (**39**).

These types of structures are used as ligands in the synthesis of several binuclear boron[50] and aluminum complexes,[51] for application in optoelectronic devices and as catalysts in polymerization reactions[52] and most of them need sophisticated multi-step syntheses.[53] Cross-coupling reactions were also investigated in the HFIP/amine electrolyte system. Co-electrolysis with naphthalene unexpectedly yielded polycyclic structures (**41**), which were unequivocally analyzed by X-ray analysis, NMR and ESI/MS techniques (Scheme 11). The aromatic system was intercepted by the nucleophilic attack of the phenolic oxygen, which is quite unusual. It was also found that these are in equilibrium with the common cross-coupled products (**42**). This equilibrium is influenced by the pH, which poses a new type of isomerism. Further oxidation with DDQ provided dibenzofurans (**43**) in yields up to 83%. Therefore, it is possible to obtain both, the simple cross-coupled or polycyclic product selectively.



Scheme 10. First selective homo-coupling of phenols bearing electron-withdrawing groups.

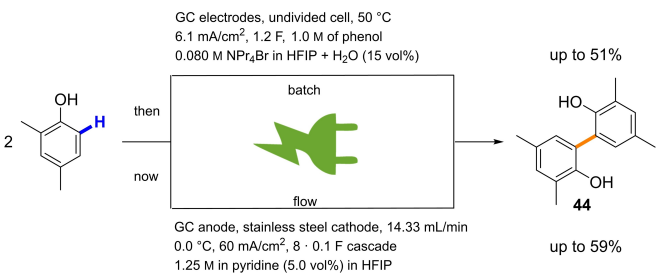


Scheme 11. Cross-coupling of phenols bearing electron-withdrawing groups with naphthalene – discovery of a new form of isomerism.

9. Scalable Synthesis of 2,2′-Biphenols using HFIP/Pyridine as Electrolyte

2,2′-Biphenols are important ligand building blocks for the transition metal-catalyzed hydroformylation as a major branch of transition metal catalysis.[54] The synthesis of this particular structural motif either requires economically and ecologically unfavorable transition metal catalysis or can be performed in an electro-organic transformation which requires supporting electrolytes.[55] The use of HFIP is vital to avoid undesired C–O coupling reactions and formation of polycyclic products.[56] The electrochemical synthesis of **44** was major research topic within the Waldvogel group[57] because of the technical relevance. A novel approach surmounting the laborious recovery of supporting electrolyte using a HFIP-pyridine system (Scheme 12) was established.[58]

The straightforward removal of HFIP and pyridine after electrolysis by simple distillation is a major advantage of this synthetic protocol. This is of particular interest when scalability of the electro-conversion in a technical range is intended. Scale-up in continuous flow-electrolysis cells[59] using a glassy carbon (GC) anode gives the desired ligand precursor in yields up to 58% in a 12 cm² and 59% in a 48 cm² flow-cell. High current densities of 60 mA/cm² and high flow rates in a cascade electrolysis result in a high time efficiency (Table 1). Numbering up of flow-cells and a simple work-up strategy make this process viable for a technical scale.



Scheme 12. Electro-organic synthesis of 3,3′,5,5′-tetramethyl-2,2′-biphenol using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)/supporting electrolyte and HFIP/pyridine system as electrolyte.

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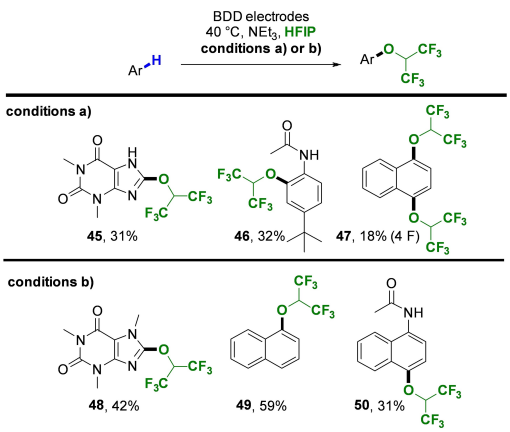
Table 1. Optimized parameters of the different flow cells and yields obtained. 2,4-Dimethylphenol c = 1.25 mol/L and pyridine (5 vol %) in HFIP, cathode: stainless steel, anode: glassy carbon, cascade electrolysis with 8 steps of 0.1 F, total applied charge: 0.8 F

	2×6 cm-flow cell	4×12 cm-flow cell
Anode surface	12 cm^2	48 cm^2
Current density	60 mA/cm^2	60 mA/cm^2
Flow rate	3.58 mL/min	14.33 mL/min
Temperature	20 °C	0 °C
Isolated yield (44)	**58%**	**59%**

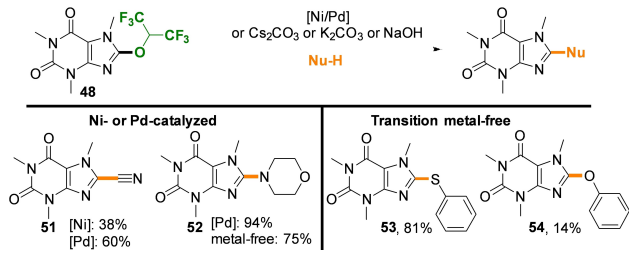
10. Anodic C–H Functionalization of Purine Derivatives and Subsequent Cross-Coupling Reaction (sp2)

After developing benzylic activation reactions and isolating aryl HFIP ethers as side components, it was considered to use the HFIP moiety attached to aryls as a leaving group in metal-catalyzed cross-coupling reactions. A selective, scalable, and sustainable electrochemical synthesis of HFIP aryl ethers was thus developed.[60] Of particular interest is the electrochemical modification of bioactive purine derivatives, such as theophylline (**45**) and caffeine (**48**) derivatives (Scheme 13). Anilides (**46, 50**) as well as naphthalene (**47** and **49**) could be converted successfully in yields up to 59%.

The optimization to increase the yield for the electrosynthesis of HFIP caffeyl ether (**48**) was conducted via a Design of Experiment (DoE) approach. Optimal reaction conditions were successfully applied to a variety of aryl substrates to extend the scope to non-purine derivatives. Furthermore, the HFIP caffeyl ether was successfully used as the electrophile in transition metal-catalyzed and transition metal-free reactions with cyanides (**51**) and amines with excellent yields up to 94% (**52**) (Scheme 14). Even under metal-free conditions most of the conversions worked, accessing thioethers (**53**) and ethers (**54**) in yields up to 81%.



Scheme 13. One variable at a time (OVAT) and Design of Experiment (DoE) optimized reaction conditions of the anodic oxidation of purines and other arenes to 8-(1,1,1,3,3,3-hexafluoro-2-propoxy)-arenes in the presence of a base. OVAT optimized a) 7.2 mA/cm^2, 2.0 F, 300 rpm (stirrer velocity), 0.25 M caffeine, 0.1 M NEt_3, yield of **48** 33%; DoE optimized b) 22.1 mA/cm^2, 2.61 F, 700 rpm (stirrer velocity), 0.2 M caffeine, 0.2 M NEt_3, yield of **48** 42%;



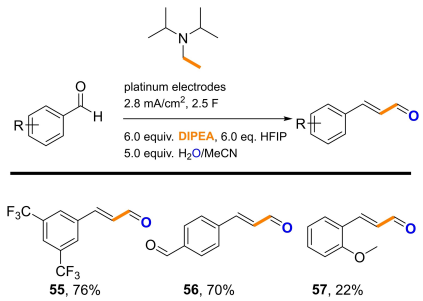
Scheme 14. Derivatization of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) caffeyl ether with various nucleophiles.

11. Anodic Formation of Cinnamaldehydes with DIPEA as Reagent

The Chiba group recently identified a novel mode of reactivity and reported a HFIP/DIPEA-based aldol reaction, whereby the ethyl group of DIPEA additionally serves as a C_2 source.[40] Mechanistic studies revealed that DIPEA and HFIP play a significant role within this reaction. DIPEA forms not only an electrolyte with HFIP, but also generates acetaldehyde in-situ. A broad scope of benzaldehyde derivatives and heteroarene-aldehydes could be employed in this reaction, forming the cinnamaldehydes in yields up to 76% (**55**) (Scheme 15). Even selective reaction of only one of two aldehyde groups was achieved in yield of 70% (**56**). Electron-releasing groups lowered the yield significantly down to 22%, as seen for a methoxy group in ortho position (**57**).

12. Electrosynthesis of Alkyl Arylsulfonates in a Multi-Component Reaction

The combination of DIPEA and HFIP has also been applied in the concise electrochemical synthesis of alkyl arylsulfonates by direct anodic oxidation of electron-rich arenes in a multi-



Scheme 15. *N,N*-Diisopropylethylamine (DIPEA) as C2 feedstock and base promoting conductivity in the anodic formation of cinnamaldehydes.

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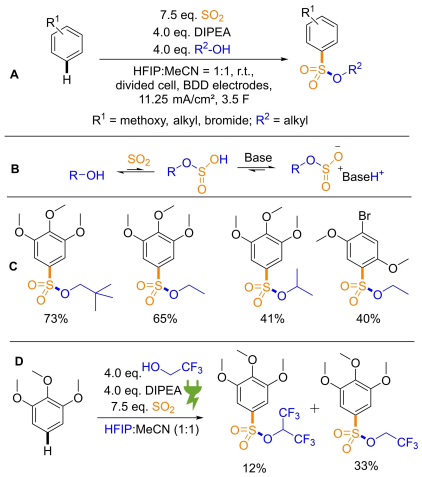

Scheme 16. Electrochemical synthesis of alkyl arylsulfonates in a multi-component reaction.

component reaction (Scheme 16, **A**). The combination of SO_2, an alcohol, and DIPEA leads to an in-situ generation of monoalkyl sulfites (**B**) with bifunctional purpose. Firstly, this species functions as nucleophile and secondly, excellent conductivity is provided. Several primary and secondary alcohols and electron-rich arenes are implemented in this reaction to generate the alkyl arylsulfonates in yields up to 73% with exquisite selectivity (**C**). A competition reaction was observed between 1,1,1-trifluoroethanol and HFIP resulting in a product mixture (**D**). BDD electrodes are employed in divided cells at galvanostatic conditions, separated by a simple commercially available glass frit.[61]

13. Summary and Perspectives

Within this review, the outstanding impact and unique reactivity of organic substrates in HFIP/amine electrolytes during electrolysis are surveyed. The important advantage of this approach in comparison to conventional electro-organic synthesis using additional salts as supporting electrolytes is the simple purification process, which can mostly be performed by distillation of the electrolyte. The direct evaporative recovery of the HFIP/amines mixtures and subsequent reuse diminishes the environmental footprint. Although, besides aryls several aliphatic compounds have been transformed and a large functional group tolerance has been demonstrated. Moreover, the scope of most electrosynthetic transformations is significantly expanded by using HFIP/amines instead of the traditional HFIP electrolytes. The successful conversion of and towards natural products and pharmaceutically active compounds is of exceptional importance and underlines the versatility for the application of this technique. This development will open a new field in electro-organic synthesis and should encourage scientists towards novel processes using these particular HFIP/amine mixtures in sustainable electrosynthesis protocols.

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Conflict of Interest

The authors declare no conflict of interest.

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