Novel Heterocycle Syntheses from Allylic Alcohols and Cyclobutanol Derivatives

Dissertation
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Synopsis

Over the course of the work presented herein, novel heterocycle syntheses from allylic alcohols and cyclobutanol derivatives were established. The introduced work is structured into three major and four minor research projects.

In the first major research project, a method for the synthesis of *O*-heterocycles through the desymmetrisation of 3-substituted oxetanols was developed. An electron deficient trifluoroacetophenone was identified to form stable hemi ketals, which act as transient nucleophiles in a cobalt catalysed ring-closing and ring-opening sequence towards dioxolanes through a dynamic kinetic resolution. Thereby, densely functionalised and uniquely stable *O*-heterocycles were provided with high degrees of enantio- and diastereoselectivity.

During the second major research project, a first proof-of-concept for an unprecedented allylic *C–H* oxidation *via* transient hemi ketals yielding dioxolanes was established. In this palladium catalysed approach, again, the special abilities of electron deficient carbonyls were harnessed. An initial optimisation of the employed palladium catalyst and additives was performed, revealing the dependency of *Lewis* acidic additives for a successful transformation.

The third major research endeavour dealt with the skeletal editing of cyclic alcohols with ambiphilic aminating reagents towards a variety of medicinally relevant *N*-heterocycles, including pyrrolidenes and indoles. High functional group tolerance was achieved by a mild activation method exploiting the exceptional properties of fluorinated alcoholic solvents. The developed atom insertion method was effectively applied to a range of small and medium sized rings. Moreover, in this project, the insertion of unsubstituted as well as substituted *N*-atoms was achieved.

Furthermore, a series of minor research works was concluded: Trifluoroacetophenones were examined as trifluoromethylating reagents, boronic acids were investigated as nucleophiles in ring-opening reactions of strained *O*-heterocycles, attempts towards *C–C* and allylic *C–H* functionalisation with trichloroacetimidates were undertaken and a first proof for the oxidative rearrangement of secondary amines towards *N*-heterocycles was furnished.

Zusammenfassung

Im Rahmen der vorliegenden Arbeit konnten neuartige Heterozyklensynthesen ausgehend von Allylalkoholen und Cyclobutanolderivaten verwirklicht werden. Die vorgestellte Forschungsarbeit ist in drei Hauptprojekte und vier untergeordnete Projekte gegliedert. Im ersten Hauptprojekt wurde eine Methode zur Synthese von *O*-Heterozyklen mittels Desymmetrisierung von 3-substituierten Oxetanolen entwickelt. Für ein elektronenarmes Trifluoracetophenon wurde die Bildung stabiler Halbketalen festgestellt, die als transiente Nucleophile in einer cobaltkatalysierten Ringschluss- und Ringöffnungssequenz zu Dioxolanen in einer dynamisch kinetischen Racematspaltung fungieren. Es konnten dadurch hochfunktionalisierte und einzigartig stabile *O*-Heterozyklen mit hoher Enantio- und Diastereoselektivität hergestellt werden. Während des zweiten Hauptprojektes wurde ein erster Nachweis über die Machbarkeit einer allylischen *C–H*-Oxidation transienter Halbketale erbracht. In diesem palladiumkatalysierten Ansatz wurden wieder die besonderen Eigenschaften elektronenarmer Carbonylverbindungen ausgenutzt, um Dioxolane herzustellen. Eine vorläufige Optimierung der Reaktionsbedingungen hinsichtlich der verwendeten Palladiumkatalysatoren und Additive deutete die Abhängigkeit einer erfolgreichen Reaktion vom Vorhandensein *Lewis*-saurer Additive an. Das dritte Hauptforschungsvorhaben befasste sich mit der Bearbeitung des Molekülgerüsts zyklischer Alkohole mit ambiphilen Aminierungsreagenzien für die Synthese einer Vielzahl medizinisch relevanter *N*-Heterozyklen, einschließlich Pyrrolidinen und Indolen. Eine hohe Toleranz funktioneller Gruppen wurde durch eine milde Aktivierungsmethode vermittels der besonderen Eigenschaften fluorierter alkoholischer Lösungsmittel erreicht. Die entwickelte Methode zur Atominsertion wurde erfolgreich bei einer Reihe kleinerer und mittlerer zyklischer Moleküle angewandt. Außerdem konnte innerhalb dieses Projekts die Insertion substituierter und unsubstituierter Stickstoffatome verwirklicht werden. In einer Reihe untergeordneter Projekte wurden Trifluoracetophenone als Trifluormethylierungsreagenzien und Boronsäuren als Nucleophile für die Ringöffnung gespannter *O*-Heterozyklen untersucht. Außerdem wurden Versuche zu *C–C*- und allylischen *C–H*-Funktionalisierungen mit Trichloracetimidaten unternommen, sowie eine erste Synthese von *N*-Heterozyklen durch oxidative Umlagerung sekundärer Amine gezeigt.

Publications

Parts of this thesis have been published in peer reviewed journals:

- **From Cycloalkanols to Heterocycles via Nitrogen Insertion**
  A. Sandvoß, J. M. Wahl,* *Org. Lett.* **2023**, *25*, 5795-5799.
  *Corresponding Author
- **Dynamic kinetic resolution of transient hemiketals: a strategy for the desymmetrisation of prochiral oxetanols**
  A. Sandvoß,* H. Maag, C. G. Daniliuc, D. Schollmeyer, J. M. Wahl,*
  Chem. Sci., **2022**, *13*, 6297-6302.
  *Corresponding Authors
- **Recent Advances in Enantioselective Desymmetrizations of Prochiral Oxetanes**
  A. Sandvoß, J. M. Wahl,* *Chem. Eur. J.* **2021**, *27*, 5871 –5879.
  *Corresponding Author

Poster presentations

Parts of this thesis have been presented at the following scientific conferences:

- 27th International symposium: Synthesis in organic chemistry; Oxford, United Kingdom; Topic: “**Strain-driven Transition Metal-free *N*-Insertion for Heterocycle Synthesis**”; 07/2023
- ORCHEM 2022 – 22nd Lecture Conference; Münster, Germany; Topic: “**Dynamic Kinetic Resolution of Transient Hemiketals: A Strategy for the Desymmetrisation of Prochiral Oxetanols**”; 09/2022
- 47th National Organic Chemistry Symposium; La Jolla, CA, USA; Topic: “**Dynamic Kinetic Resolution of Transient Hemiketals: A Strategy for the Desymmetrisation of Prochiral Oxetanols**”; 06/2022

Declaration on the work of others included herein

Throughout the research projects discussed in this thesis, other individuals participated in the work described herein. A detailed overview of the individual contribution of each collaborator can be found below.

In the first discussed research project (*cf.* Chapter 2), additional work has been done by [redacted] and [redacted] [redacted] prepared Co^{II}·salen complex **2.77**, which was used in the initial optimisation. [redacted] provided the Co^{II}·salen complexes *epi*-**2.78**, **2.79** and **2.106** which were used in the initial optimisation and the substrate scope of the developed reaction. The substrate for entry **2.113** was prepared by [redacted] Furthermore, [redacted] contributed to the scope of the reaction by testing alkynyl, and alkyl substituted substrates, such as **2.126** and **2.127**. Moreover, the starting material for the synthesis of **2.133** and **2.134** was provided by [redacted]

In the third discussed research project (*cf.* Chapter 4), [redacted] contributed to the scope of the reaction by providing the starting material for the entry of **4.83**.

In the seventh discussed research project (*cf.* Chapter 5.4), additional work has been done by [redacted] She contributed to this work by synthesising the acyl protected amine used for the initial optimisation (Table 15, entries 3 and 4).

The X-ray measurement and structure refinement of samples from the molecules **2.24** and **2.96** was performed by [redacted] [redacted] contributed with the X-ray measurement and structure refinement of dioxolane **2.117**.

Further research on the cyclisation of trichloroacetimidates based on the findings in the second discussed research project (*cf.* Chapter 3) has been conducted by [redacted] during her Bachelor thesis. [redacted] did further research on *N*-heterocycle syntheses by oxidation of amines as shown herein (*cf.* Chapter 5.4).

Index of abbreviations

2,5-DMBQ	2,5-dimethyl-1,4-benzoquinone
Ac	acetyl
acac	acetylacetonate
AMLA	ambiphilic metal ligand activation
ArSOX	aryl sulfoxide-oxazoline
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Bn-Box	bis((*R*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane
Boc	*tert*-butyloxycarbonyl
BQ	1,4-benzoquinone
Chloranil	2,3,5,6-tetrachloro-1,4-benzoquinone
CMD	concerted metalation deprotonation
dbu	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-4,5-dicyano-1,4-benzoquinone
DIPEA	*N,N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMAP	*N,N*-dimethylpyridin-4-amine
DMF	*N,N*-dimethylformamide
DMP	*Dess-Martin* periodinane
dmso	dimethyl sulfoxide
DNase	deoxyribonuclease
DNPH	2,4-dinitrophenylhydrazine
dppbz	1,2-bis(diphenylphosphino)benzene
dr	diastereomeric ratio
EA	elementary analysis
ELN	electronic lab notebook
eq.	equivalent
er	enantiomeric ratio
esp	α,α,α',α'-tetramethyl-1,3-benzene-dipropionic acid
EtOAc	ethyl acetate
EWG	electron-withdrawing group
EXSY	exchange spectroscopy
FC	flash chromatography
GP	general procedure
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared
LG	leaving group
m.p.	melting point
Mes	2,4,6-trimethylphenyl
MPLC	medium pressure liquid chromatography
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n.d.	not determined
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear *Overhauser* effect spectroscopy
Ns	4-nitrobenzenesulfonyl
Nu	nucleophile
OTf	trifluoromethanesulfonate
PBK	phosphate-buffered potassium chloride
PhBQ	2-phenyl-1,4-benzoquinone
phen	1,10-phenanthroline
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine(III) bis(trifluoroacetate)
ppm	parts per million
pTol	*p*-tolyl
RC	recrystallisation
*Re*LEH	*Rhodococcus erythropolis* limonene epoxide hydrolase
RP	reverse-phase
rr	regiomeric ratio
rt	room temperature
salen	bis(salicyliden)ethylendiamin type ligand
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
UV	ultraviolet
vis	visible

1 Introduction

Organic chemistry can be defined as the subdomain of the chemical sciences that is focused on carbon and its derived compounds. Notwithstanding its simplicity, this definition has some ambiguities, as the nature of certain compounds such as carbon monoxide or sodium acetate is not entirely distinct as either organic or inorganic. However, if one accepts this definition, there is a myriad of known organic compounds today, with an estimated number of 70 million organic molecules listed in public repositories.[1] This vast amount can undoubtedly be reasoned by the special nature of carbon to adapt structures with up to four other bound atoms and the possibility to build multiple bonds to the same atom. While deeper analysing the immense structural manifold of organic compounds, it is therefore intriguingly simple, yet misleading, to only focus on molecules containing mostly carbon atoms. Certainly, considering only hydrocarbons, carbocycles or polymers such as polyethylene or polypropylene as organic compounds would lead to immensely different numbers. What is it then, that offers this huge chemical space to explore for organic chemists? Answering this question is straightforward if one widens one's view and takes heteroatoms in regard. Including other atoms than carbon in a network, increases the structural variety extraordinarily as manifested in a combinatorial study by *Reymond* and coworkers.[2] They conceptualised a theoretical experiment to create molecular skeletons with a set of 17 atoms. If all of them were carbon atoms, more than five million hydrocarbons could possibly be formed, whereas introducing heteroelements, such as nitrogen or oxygen, would open a potential chemical space of over 166 billion molecules. Introducing heteroatoms is not only increasing the complexity of a given molecular scaffold, but also providing a functional handle for organic chemists to continuingly broaden the diversity of organic molecules. For instance, carbocyclic cyclopentane can be considered as inert towards most chemical transformations. Contrarily, its heterocyclic counterpart pyrrolidine is a *Brønsted* basic and nucleophilic compound which is readily interacting with other molecules, for example by hydrogen bond interactions (Figure 1). A more drastic difference can be observed for benzene and its heterocyclic analogue pyridine. Whilst benzene being a highly symmetric molecule and slightly nucleophilic in any position, pyridine on the contrary is nucleophilic only on the nitrogen atom and otherwise electrophilic in the 2- and 4-positions (Figure 1). Given this small selection of different properties caused by incorporating heteroatoms, it is not surprising that those sparked the interest of organic chemists in further exploring the chemical space of heterocyclic compounds.[3]

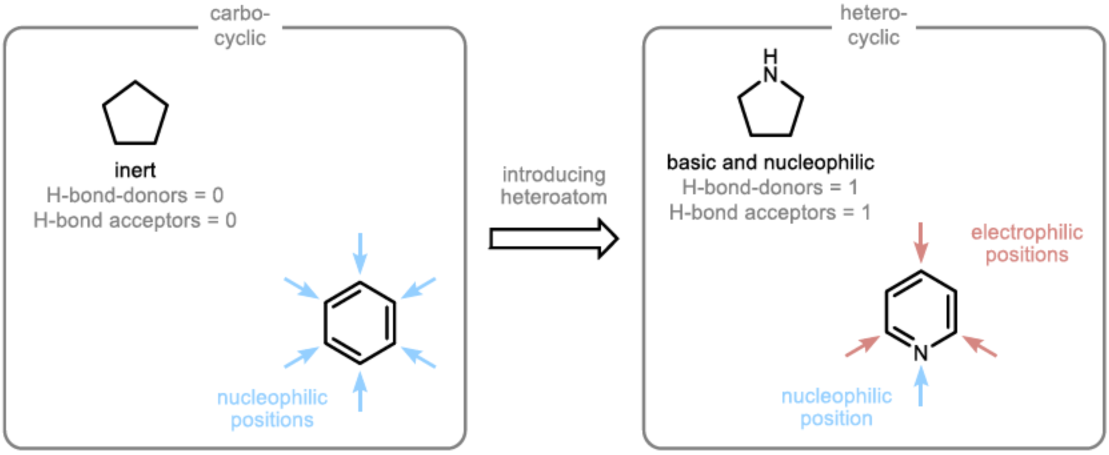


Figure 1: Overview of selected properties of heterocyclic compounds and their carbocyclic analogues.

1.1 Heterocycles in medicinal chemistry

The great significance of heterocyclic compounds is represented by their widespread use in medicinal chemistry. Early investigations on the structure of drug molecules indicate the prevalence of heteroatom containing cyclic frameworks in marketed drugs.[4] Recently, the group of *Njardarson* performed an analysis of 328 compounds which were approved as small molecule drugs by the United States *Food and Drug Administration* in a time span from 1940 to September 2018. This simple, yet very enlightening, structural analysis shows, that 58% are *N*-heterocyclic and another 19% are *O*-heterocyclic compounds,[5] thus highlighting the utmost importance of heterocyclic compounds.[6] On the contrary, other heteroatoms such as sulphur or phosphorous, play a less prominent role.[7] Furthermore, the number of approved drugs consisting of sheer hydrocarbons is insignificantly small.[8]

The apparent high abundance of heterocyclic compounds in medicinal chemistry can be explained when some major trends in drug discovery are further elucidated. First to mention is the famous “rule-of-five” by *Lipinski*.[9] Originally, formulated for orally active drug-like compounds, the rule defines four physicochemical parameters to influence the success of a structure in drug development. Namely, the molecular weight, the partitioning coefficient between water and 1-octanol (log P), and the amount of hydrogen bond acceptor and donor sites are supposed to have a critical effect on a compounds chance to pass the different phases in drug development (Figure 2).

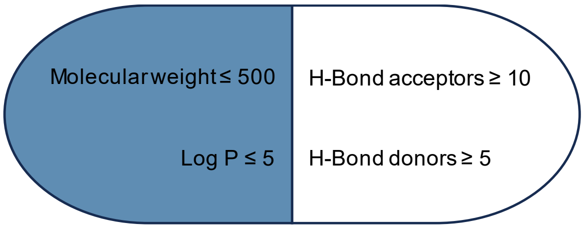


Figure 2: Graphic representation of *Lipinski's* "rule-of-five".

Naturally, heteroatoms, such as oxygen or nitrogen atoms, are electronically different to carbon atoms thereby a high count of such heteroatoms increase the polarity of a given structure and offer multiple sites for hydrogen bond-interactions. Thereby, the "rule-of-five" predicts a higher success rate of a heterocyclic compound compared to its parent carbocyclic compound.

Another aspect to be further discussed is the degree of molecular complexity, which often has a beneficial effect on the medicinal properties of a compound.[10] In this context, the trend to higher saturated compounds with a notable degree of *sp*^{3}-centres has to be emphasised.[11] The so-called "escape from flatland" describes the trend of exchanging benzene-derived or other flat structures for rigid *sp*^{3}-rich cyclic structures to improve the clinical success rate.[12] Again, heterocyclic compounds can offer improved abilities, such as higher water solubility and altered hydrogen bond interactions.[13]

1.2 Heterocycles in synthesis

Given the frequent occurrence of heterocycles in drug molecules, a major research interest for medicinal and organic chemists lies in their preparation. As a consequence thereof, a plethora of different methods for heterocycle synthesis exist. In the following, only selected reactions are discussed which exemplify general strategies for the preparation of heterocycles. Common approaches include cycloadditions, ring-closing reactions, rearrangements, and the manipulation of an already existing heterocyclic system (Figure 3).[14]

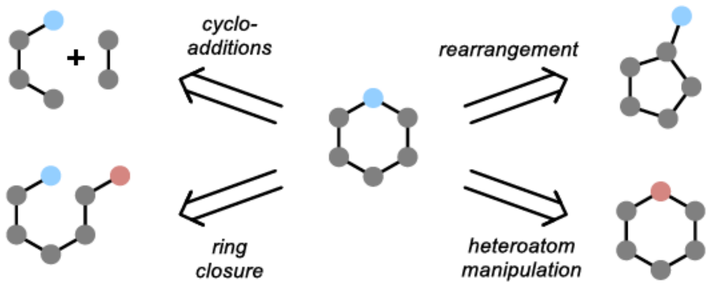
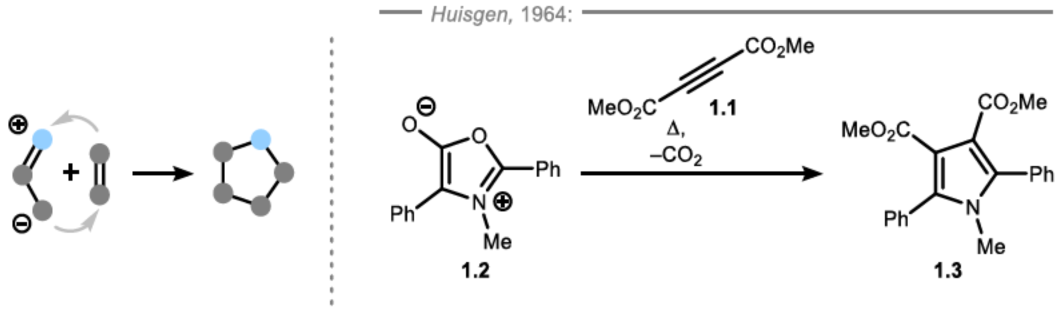


Figure 3: Major strategies in heterocycle synthesis.

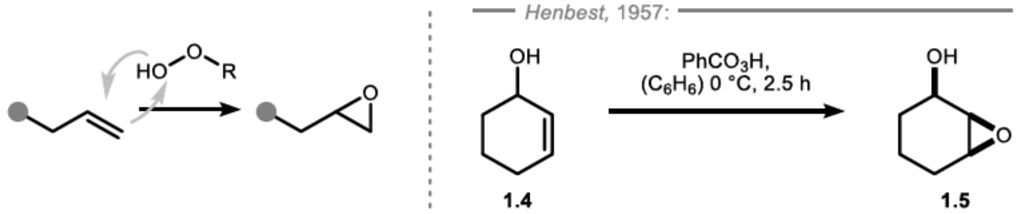
From the four showcased methodologies, cycloadditions of two or more unsaturated molecules, or parts of the same molecule, are discussed as first. Since at least two new bonds are formed in that process, consequently a cyclic product is formed stepwise or in a concerted fashion. The latter case renders the total transformation a pericyclic reaction.[15] Famous examples, in terms of heterocycle synthesis, are 1,3-dipolar cycloadditions, which were introduced to the chemical literature by *Huisgen* 60 years ago (Scheme 1).[16] In their seminal publication, they described the concerted addition of a double substituted alkyne **1.1** to a cyclic 1,3-dipolar compound **1.2**, referred to as Münchnone, which ultimately upon loss of carbon dioxide delivered a polysubstituted pyrrole **1.3**.



Scheme 1: Left: Schematic representation of a 1,3-dipolar cycloaddition. Right: Early example of a 1,3-dipolar cycloaddition by *Huisgen*.[16a]

The field of dipolar cycloadditions evolved ever since then,[17] and culminated in the bestowal of the nobel prize to *K. B. Sharpless, M. P. Meldal* and *C. Bertozzi* in 2022 for the development of click chemistry and bioorthogonal chemistry.[18] Another well-known cycloaddition in the context of heterocycle synthesis is the epoxidation reaction (Scheme 2, left). Whereas many variants without control over the stereochemical outcome of the epoxidation were long known, an initial example for a diastereoselective reaction was established by *Henbest* in 1957.

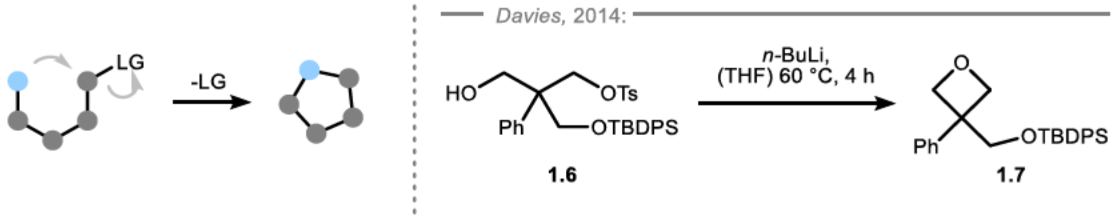
They found cyclohex-2-en-1-ol **1.4** to undergo epoxidation with perbenzoic acid in a diastereoselective fashion (Scheme 2, right).[19] Counterintuitively, the reaction proceeded from the sterically more hindered side to deliver *syn* oxirane **1.5**, due to substrate coordination to the peroxo compound through hydrogen bonds.



Scheme 2: Left: Schematic representation of an epoxidation. Right: Example of a diastereoselective epoxidation by *Henbest*.[19]

A multitude of different methods for epoxidations was developed over time and many challenges in terms of regio-, diastereo-, or enantioselectivity have been successfully overcome.[20] Thus, the formal (2+1)[a] cycloaddition of an alkene with a peroxo compound became widely applied in both research and industrial contexts.[21] Again, the extensive work on this transformation was awarded with the nobel prize for *K. B. Sharpless* in 2001, namely for his work on chirally catalysed oxidation reactions.[22]

Secondly, heterocycles can be formed through intramolecular ring-closing reactions, frequently proceeding *via* an attack of an internal nucleophile to a site of the same molecule bearing a leaving group (Scheme 3, left).[23]



Scheme 3: Left: Schematic representation of an intramolecular ring-closing reaction. Right: Example of an intramolecular oxetane synthesis.[24] LG = leaving group, TBDPS = *tert*-butyldiphenylsilyl, Ts = *p*-toluenesulfonyl.

For instance, oxetanes can be formed through *Williamson* ether synthesis according to *Davies et al.* (Scheme 3, right). After basic activation of the hydroxy group of the functionalised diol **1.6**, the strained 4-membered ether **1.7** can be formed *via* extrusion of the tosylate as a leaving group.[24] In agreement with the nomenclature established by *Baldwin* in his famous communication on the rules for ring-closing reactions,[25] this transformation is rendered a *4-exo-tet* reaction (Scheme 3). Not only providing a nomenclature to classify such ring-closing

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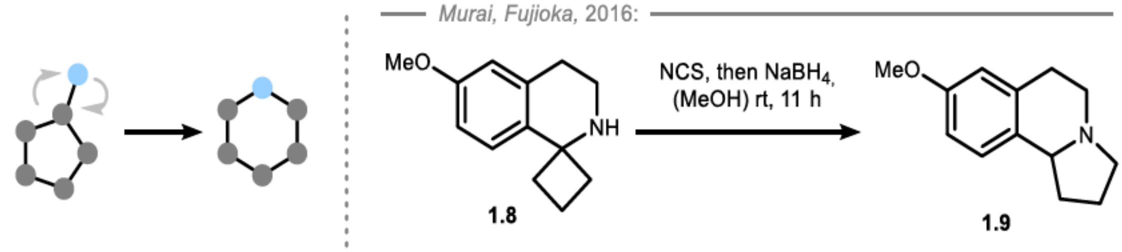
[a] Hereinafter, the preferred IUPAC terminology for cycloadditions will be used.[15].

reactions, but the *Baldwin* rules also enable the prediction of the outcome of ring-closing reactions to a certain extent.[26] Accordingly, the ring-closing towards oxetanes should be an allowed process. However, in contrast to oxiranes or aziridines, the ring-closing of 4-membered rings, such as oxetanes or azetidines is typically less effective. Although thermodynamically almost identical, there is a kinetic barrier which inhibits product formation.[27]

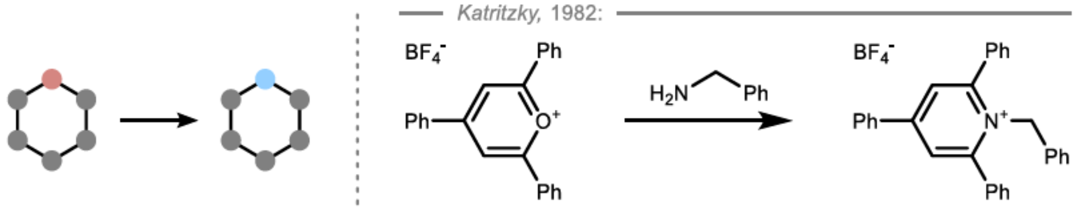
Molecular rearrangements represent the third major strategy in heterocycle synthesis. After sufficient activation, for instance through engagement of a leaving group, heteroatomic functional groups attached to a carbocyclic core can undergo rearrangement to heterocycles with a larger ring size (Scheme 4, left).



Scheme 4: Left: Schematic representation of a heteroatom rearrangement. Right: Example of an oxidatively triggered amine rearrangement by the groups of *Fujioka* and *Murai*.[28] NCS = *N*-chlorosuccinimide.

A simple way of triggering such a molecular rearrangement is the oxidation of a functional group. For example, amines are easily oxidised with electrophilic halogen sources such as *N*-chlorosuccinimide (NCS), resulting in a chlorine atom as a leaving group attached to the heteroatom. Subsequently a 1,2-carbon shift can occur, which forms the ring expanded heterocycle. The groups of *Fujioka* and *Murai* made use of this strategy in their synthesis of annulated heterocycles (Scheme 4, right). Starting from a spirocyclic cyclobutene derivative **1.8**, annulated tetrahydroisoquinoline **1.9** can be formed after reduction of an oxidised and rearranged intermediate. The *Wahl* group employed a similar strategy in the synthesis of γ-lactams. In their work on the desymmetrisation of prochiral cyclobutanones, a heteroatom was engaged to the carbocycle through transient formation of a hemi-aminal, followed by oxidation to deliver chiral γ-lactams.[29] Another oxidative heterocycle synthesis is displayed by the *Baeyer-Villiger* oxidation of cyclic ketones towards lactones.[30]

As the fourth strategy for heterocycle synthesis, the manipulation of an already existing heterocyclic system will be discussed at last. The distinct reactivity of heterocycles can be harnessed to manipulate the ring-size or to alter the type of heteroatom in the cyclic system (Scheme 5, left). In this regard, a prominent example is the formation of cyclic carbonates from oxiranes and carbon dioxide. This process is carried out worldwide on an industrial level in an annual multi ton scale due to the manifold of applications of organic carbonates reaching from fuel additives over polymer production to solvents for catalysis or electrolytes for electrochemical energy storage.[31] Furthermore, heterocycle manipulations are essential in research contexts. Initiated by the findings of *Katritzky*, that pyrylium salts, like **1.10**, undergo rearrangements to pyridines or pyridinium salts, such as **1.11**, when treated with ammonia or primary amines (Scheme 5, right),[32] a whole research area was established which made use of the so formed heterocyclic salts. Fuelled by the relative ease to break the bond between a charged pyridinium salt and the attached carbon chain, a plethora of methods was developed to exploit this reactivity in late stage functionalisation.[33]



1.10 **1.11**

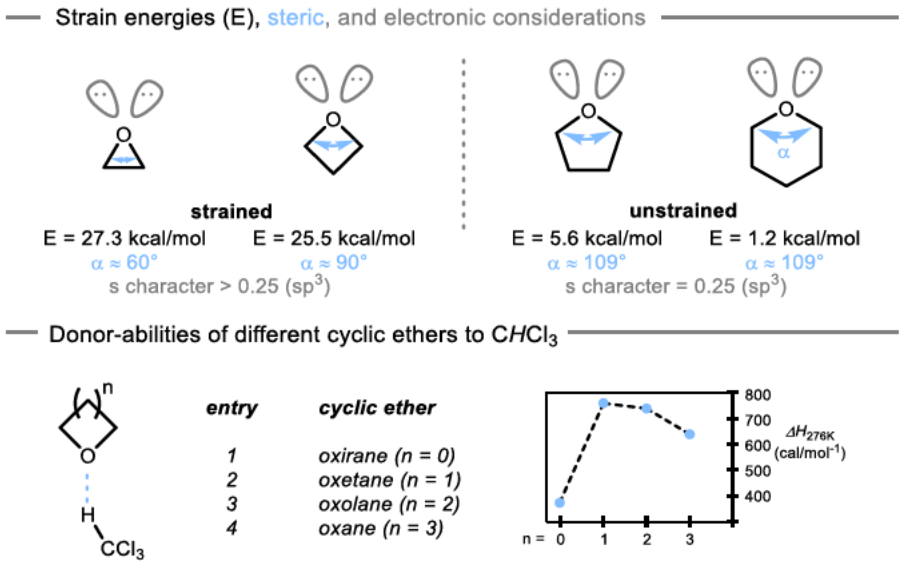
Scheme 5: Left: Graphical representation of a heterocycle manipulation. Right: Example for the displacement of the heteroatom in pyrilium salts to deliver pyridinium salts by *Katritzky*.[32]

2 Cyclic alcohols as platform for the synthesis of oxygen rich heterocycles

2.1 Introduction

2.1.1 Physical, chemical and medicinal properties of oxetanes

Among the discussed strategies in heterocycle synthesis, the manipulation of an already existing heterocycle can be of particular value. Especially, the exceptional reactivity of oxiranes can be turned to account as the release of the inherent ring strain energy of this small cyclic ether is favouring ring-opening reactions thermodynamically.[34] Thus, oxiranes can act as masked leaving groups in ring-closing reactions, which simultaneously open the three-membered ring resulting in larger heterocyclic compounds. Therefore, oxiranes are utilised prominently in industrial processes to prepare larger heterocycles.[31e,35] On the other hand, the use of oxetanes, although promising, is lesser explored.[36] Nevertheless, in terms of ring strain, oxiranes and oxetanes show similar properties (Figure 4, top). Both small cyclic ethers have a high ring strain energy, and their bond angles differ remarkably from the optimal values of a sp^3-hybridised carbon atom, whereas 5- or 6-membered cyclic ethers can be considered as unstrained.[37]



entry	*cyclic ether*
1	*oxirane (n = 0)*
2	*oxetane (n = 1)*
3	*oxolane (n = 2)*
4	*oxane (n = 3)*

Figure 4: Top: Overview of strain energies and other physical organic properties of cyclic ethers. Bottom: Survey on the heat of mixing of cyclic ethers with chloroform.

Furthermore, the oxygen lone pairs in 3- or 4-membered cyclic ethers have a high *s*-character, a trend which decreases to the larger rings.[38] On the contrary, the narrow *C–O–C* bond angle in the smaller cyclic systems increases the accessibility of the oxygen lone pairs. Those two contradictory effects determine the degree of *Lewis* basicity associated with the donor abilities of the cyclic ethers, which is therefore not following the ring-size. Oxetanes exhibit the strongest interactions with *Lewis* or *Brønsted* acids of the 3- to 6-membered cyclic ethers, since both opposing effects are advantageously balanced (Figure 4, bottom).[39]

Nonetheless, oxetanes are surprisingly stable compounds compared to oxiranes, as they require strong activation prior to ring-opening.[23] Their donor abilities compared with their steric size and relative stability led to an increased use as a bioisostere in medicinal chemistry.[40] For example, *gem*-dimethyl groups can be replaced by an oxetane ring, which has the same metabolic stability, while reducing the lipophilicity and further adding an additional hydrogen bond acceptor to a potential drug molecule.[41] Moreover, oxetanes can be utilised to replace carbonyl groups.[42] Although their steric size is different, both functional groups have the same orientation of the oxygen lone pairs, similar basicity and a comparable dipole moment,[43] which allow the oxetane bioisostere to interact with the same biological binding sites.[44] In contrast to oxetanes, carbonyl functional units are strongly polarising consequently increasing the acidity of protons in *α*-position. Thereby, the *α*-proton can be easily exchanged, eventually causing severe problems in the context of medicinal chemistry, if the *α*-position of a carbonyl is a stereogenic centre. In the 1950's such an racemisation of an α-stereocentre was observed for thalidomide **2.1**, which was prescribed as the drug Contergan.[45] During that time, the drug was used as a racemic mixture, whereas only the (*R*)-enantiomer is the eutomer which acts as a sedative. The (*S*)-enantiomer, on the other hand, has a high teratogenic potential causing malformations on unborn children. In fact, the application of enantiopure (*R*)-thalidomide would have led to the same fatal side effects, as the molecule undergoes rapid racemisation under physiological conditions and forms the teratogenic (*S*)-enantiomer. Recent studies indicate, that this problem can be overcome by the use of an oxetane ring as a bioisostere in oxetano-thalidomide **2.2**.[46]

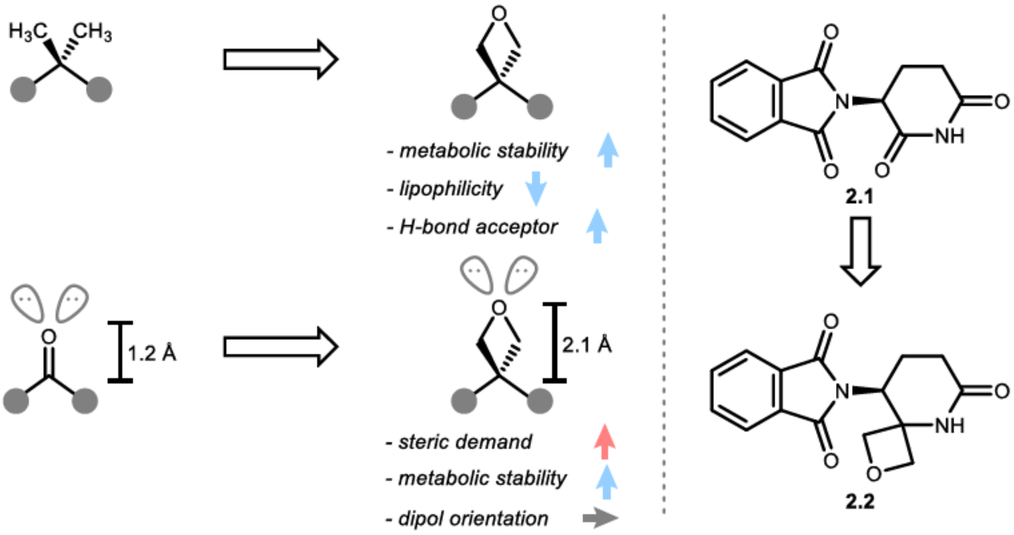


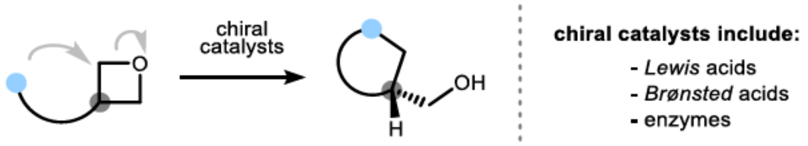
Figure 5: Overview of oxetane rings as bioisosteres in medicinal chemistry.

2.1.2 Oxetanes in synthesis

Besides the growing use as a bioisostere, oxetanes are utilised in various different synthetic transformations.[23,47] Especially, enantioselective reactions are of interest, because of the need for enantiopure molecules in drug discovery, showcased by the fatal racemisation of thalidomide. The enantioselective desymmetrisation of a prochiral compound is an especially elegant way for the preparation of enantiopure material.[48] Hence oxetanes are easily activated and the exothermic release of ring strain energy of the 4-membered ring is providing a strong driving force, desymmetrising reactions with oxetanes are an ongoing research interest.[49] The easiest way to release the ring strain energy in a desymmetrising fashion is the opening of the oxetane ring to deliver open chain products. For example, nucleophilic ring-opening with sulphur-,[50] carbon-,[51] or halogen-nucleophiles[52] were developed. Furthermore, the oxetane ring can be used as a platform for the asymmetric synthesis of other heterocycles. Many undertaken endeavours in this respect can be assigned to the four general principles of heterocycle synthesis discussed above (*cf.* Chapter 1.2, Figure 3).

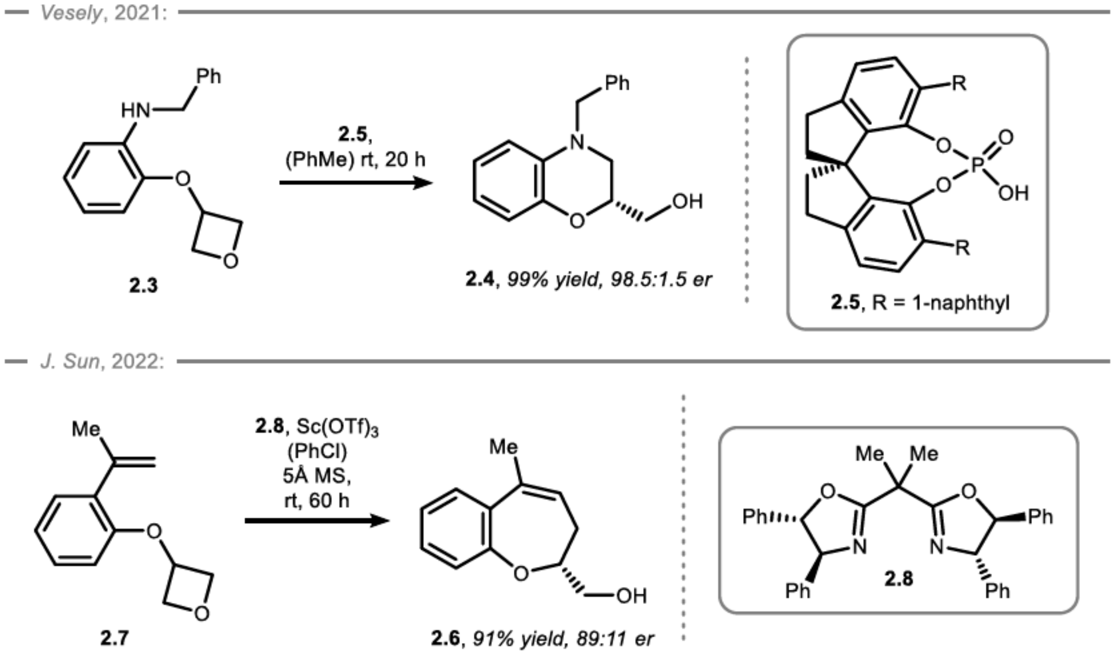
Strategies include the oxidative rearrangement of 3-substituted oxetanols by *Yin et al.* yielding 5-membered *O*-heterocycles,[53] and the *Lewis* or *Brønsted* acid catalysed rearrangement of 2,2-disubstituted oxetanes to dihydro-pyrans by *Njardarson*.[54] Furthermore, the manipulation of the existing heterocyclic core can be undertaken by transition metal catalysed atom insertions.[55]

Most frequently, the strategy of a combined ring-closing and ring-opening reaction is used for desymmetrising heterocycle syntheses based on oxetanes (Scheme 6).



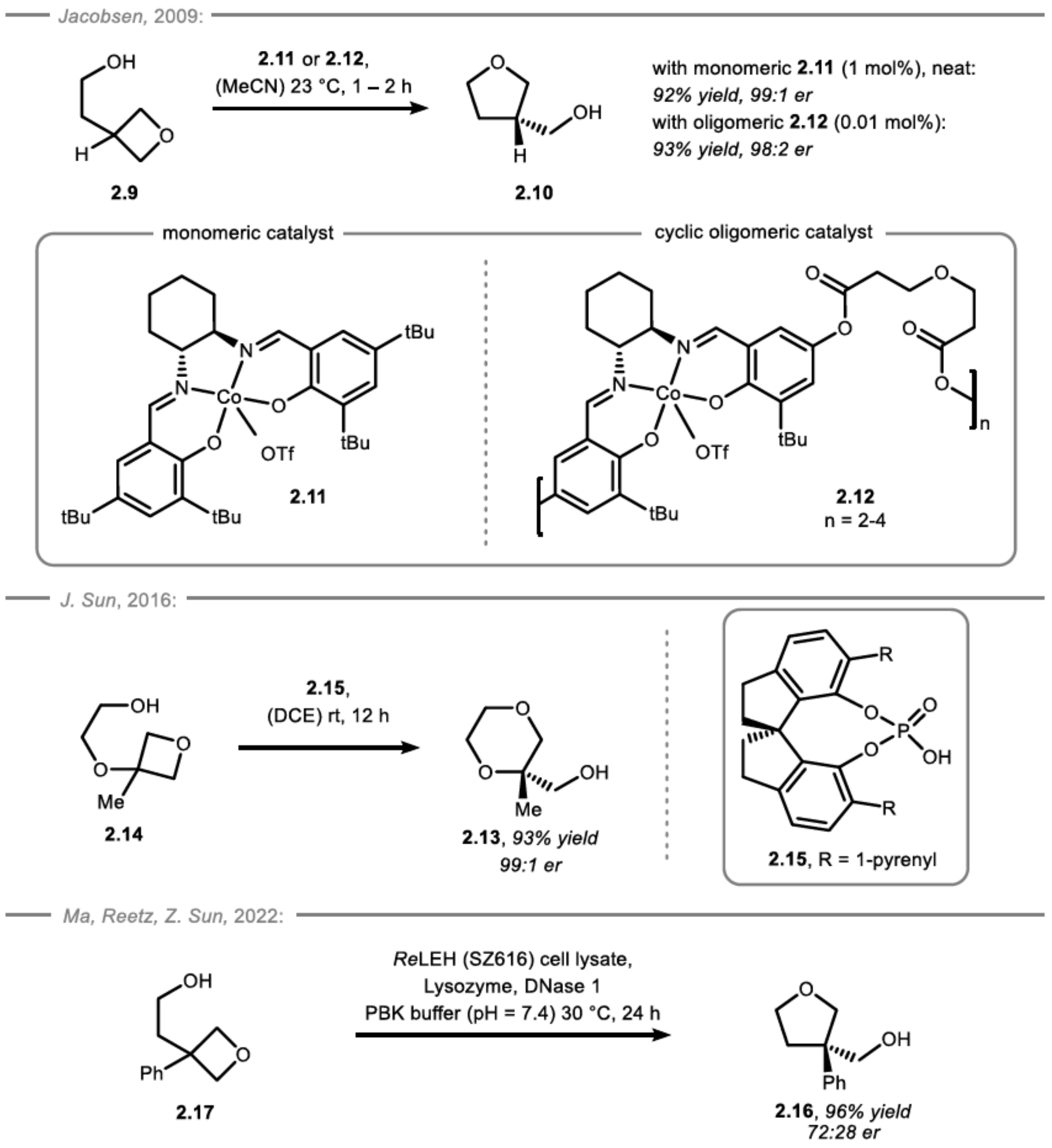
Scheme 6: Graphical representation of a ring-closing and ring-opening sequence for the enantioselective preparation of heterocycles from oxetanes.

As mentioned earlier, the effectiveness of such attempts is depending on the present leaving group. In the case of small, strained ethers, the leaving group is commonly a hydroxy functionality, usually regarded as a poor leaving group. Nevertheless, the release of ring-strain energy can provide enough enthalpic driving force for the overall transformation. To further improve the efficacy of the nucleophilic ring-opening, methods of enzymatic, *Brønsted* or *Lewis* acid catalysis can be applied. By exploiting asymmetric variants of the catalysts, additionally, high degrees of stereocontrol can be provided. For instance, the groups of *Houk* and *J. Sun* reported the enantioselective preparation of sulphur- and nitrogen containing heterocycles, by means of *Brønsted* acid catalysis starting from oxetanes.[56] Moreover, by rational design of the starting materials, *O*-heterocycles were prepared with the same strategy using a range of different nucleophiles, such as nitrogen- or carbon-based nucleophiles. Exemplarily, the *Vesely* group used the oxetane tethered aniline derivative **2.3** as a starting material for the intramolecular ring-opening and ring-closing sequence for the preparation of chiral 3,4-dihydro-1,4-benzoxazines **2.4** with a chiral phosphoric acid **2.5** as a catalyst (Scheme 7, top). Based on an initial proof of concept, the *J. Sun* group developed a method for the enantioselective formation of 2,3-dihydrobenzo[b]oxepines **2.6** through *Prins*-type reaction of styrene linked oxetanes **2.7**.[57] Enantioinduction was achieved by the combination of scandium triflate and a chiral bisoxazoline ligand **2.8** (Scheme 7, bottom).



Scheme 7: Top: Chiral *Brønsted* acid desymmetrisation of oxetanes by *Vesely*.[58] Bottom: Chiral *Lewis* acid catalysed *Prins* type reaction for the desymmetrisation of oxetanes by *J. Sun*.[57b] *er* = enantiomeric ratio, OTf = trifluoromethanesulfonate, MS = molecular sieves.

Furthermore, oxygen nucleophiles were employed, as reported by *Loy et al.,* for the asymmetric ring-opening of oxetanes **2.9** with an internal, tethered oxygen nucleophile towards oxolanes **2.10** (Scheme 8, top).[59] Either monomeric or oligomeric Co^{III}·salen (salen complexes **2.11** or **2.12** were found to catalyse the transetherication with high enantioselectivities. Additionally, the group of *J. Sun* reported the enantioselective formation of 1,4-dioxanes, such as **2.13**, from oxetanes **2.14** with a linked hydroxy group under *Brønsted* acid catalysis employing chiral phosphoric acid **2.15** (Scheme 8, middle).[60] The scope of this method was expanded to 1,4-benzodioxepines by the same group in 2020.[61]



Scheme 8: Top: Synthesis of oxolanes through cobalt(III) catalysed ring-opening of oxetanes by *Jacobsen*.[59] Middle: *O*-heterocycle synthesis starting from oxetanes through chiral phosphoric acid catalysed ring-opening reaction by *J. Sun*.[60] Bottom: Enzymatic synthesis of oxolanes through intramolecular ring-opening by *Ma, Reetz* and *Z. Sun*.[62] DCE = 1,2-dichloroethane, DNase = deoxyribonuclease, PBK = phosphate-buffered potassium chloride.

Recently, the groups of *Ma, Reetz*, and *Z. Sun* reported a variant for the enzyme catalysed enantioselective preparation of cyclic ethers, like oxolane **2.16,** from oxiranes and oxetanes, such as **2.17** (Scheme 8, bottom). Again, tethered hydroxy functionalities were used as nucleophiles. A high degree of enantioselectivity was achieved by the use of a limonene epoxide hydrolase from a mutated *Rhodococcus erythropolis* (*Re*LEH), which originally has a high selectivity for the formation of vicinal diols from oxiranes.[62]

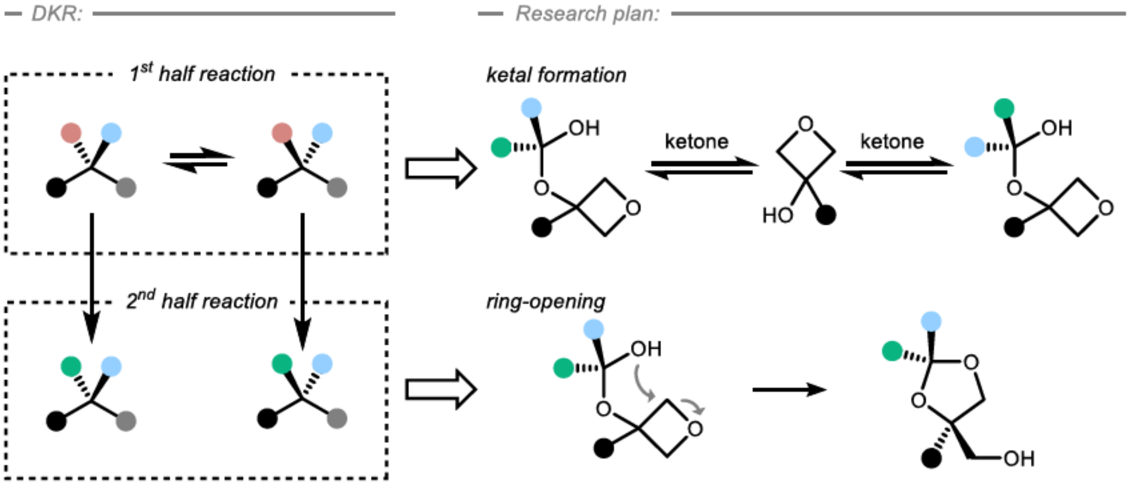
Despite their growing use in medicinal and organic chemistry, synthetic approaches for the construction of 4-membered cyclic ethers are developed to a lesser extent compared to 3-membered oxiranes. In the course of oxetane synthesis, *Paterno-Büchi* reactions (*cf.* Figure 3, cycloadditions) or *Williamson* ether syntheses (*cf.* Figure 3, ring-closures) are prevalent, although novel methods are developed recently.[23,63]

2.1.3 Motivation and aim

Combining techniques of heterocycle synthesis with the concept of desymmetrisation is particularly interesting, as the need for enantiopure material and the demand of novel heterocyclic compounds can be fulfilled at once. As discussed above, ring-closing reactions with an internal nucleophile is an auspicious way for the preparation of oxygen rich heterocycles. When small cyclic ethers are used in a ring-closing and ring-opening sequence, additional enthalpic driving force through strain-release can be harnessed to design new methodologies, without the necessity of installing a leaving group in a synthetic step. Thus, 3-substituted oxetanes come into focus. Since the preparation of oxetanes is a sometimes-tedious venture, 3-oxetanols were identified as a promising starting material, as they can be prepared by simple addition of a carbon nucleophile to commercially available 3-oxetanone.

For the intended enantioselective desymmetrisation of prochiral 3-oxetanols, a dynamic resolution was sought to be developed. Among the many available concepts in asymmetric synthesis, dynamic kinetic resolutions (DKRs) have a special position. Generally, transformations based on a DKR can be partitioned in two nearly independent half reactions.[64] A fundamental prerequisite for a DKR is the presence of a fast equilibrium, which interconverts two enantiomers of the same molecule in the first reaction step. While one enantiomer has a higher reaction rate in the second step, the other is almost not consumed (Scheme 9, left). Due to the fast racemisation in the first step, the more reactive enantiomer is constantly rebuilt at the expense of the concentration of the undesired enantiomer. Hence, a high selectivity for one enantiomer of the desired product can be achieved combined with a theoretically achievable quantitative conversion.

For the desymmetrising ring-opening and ring-closing sequence of 3-oxetanols, an internal nucleophile is needed. Accordingly, the formation of a hemi ketal was found to fulfil the criteria for both DKR and ring-opening, as a nucleophilic hydroxy functionality is transiently introduced to the molecule which is present in a fast equilibrium of its epimers. The subsequent diastereoselective ring-opening and ring-closing sequence from one hemi ketal enantiomer delivers 1,3-dioxolanes (Scheme 9, right), which can be regarded as a partially protected polyolic compound bearing a quaternary stereogenic centre.



Scheme 9: Left: General scheme of a dynamic kinetic resolution. Right: Envisioned desymmetrisation of 3-oxetanols through transient formation of a nucleophilic hemi ketal.

2.2 Preparation of starting materials

2.2.1 Preparation of 2,2,2-trifluoroacetophenones

For the outlined investigation on the formation of hemi ketals, a number of electronically differing ketones were prepared. As the electronic parameters of aromatic ketones can easily be altered, trifluoroacetophenones came into focus. Additionally, the trifluoromethyl group prevents the ketone from enolisation and thus from undesired side reactions. Principally, there are two possible ways to prepare varying examples of trifluoroacetophenones, either through derivatisation of the aromatic ring of 2,2,2-trifluoroacetophenone **2.18**, or through introduction of a trifluoromethyl group to an aromatic carbonyl compound (Figure 6). Such being the case, the former synthesis was done for ketones **2.19** and **2.20**, the latter for ketones **2.21**, **2.22** and **2.23**, respectively.

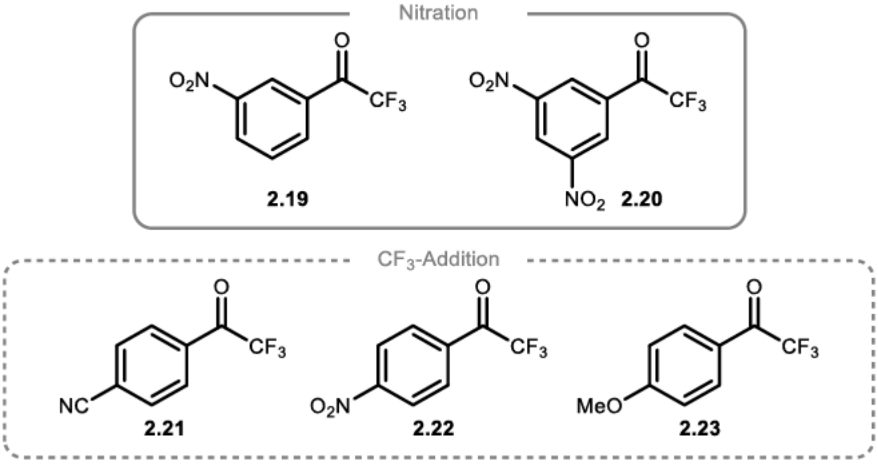
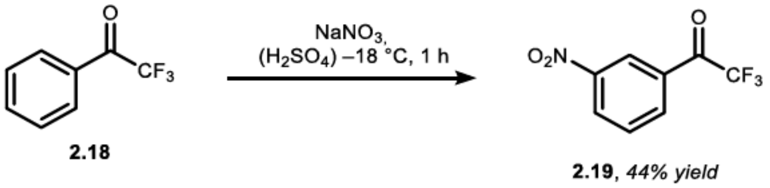


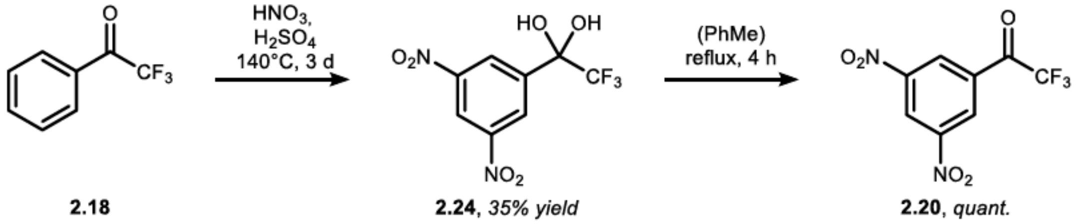
Figure 6: Trifluoroacetophenones synthesised for this project. Top: *Via* nitration of 2,2,2-trifluoroacetophenone 2.18. Bottom: *Via* addition of a CF_3-Group to an aromatic electrophile.

The introduction of a single nitro group to trifluoroacetophenone **2.18** was achieved by a method of *Otevrel et al.*, where sodium nitrate was used as a source of the electrophilic nitronium ion (Scheme 10).[65]



Scheme 10: Preparation of 3'-nitro-2,2,2-trifluoroacetophenone 2.19 according to *Otevrel et al.*[65]

To further decrease the electron density in the aromatic ring, another nitro group should be installed. As both, the ketone and the first nitro group are electron withdrawing thereby deactivating the aromatic ring towards electrophilic substitution, harsher conditions were needed. Therefore, concentrated nitric acid was used as a source for the nitronium ion, and the reaction was performed at elevated temperatures. Initial attempts to isolate the 3',5'-dinitro-2,2,2-trifluoroacetophenone **2.20** by means of column chromatography were not fruitful and distillation of the desired product was discarded due to the potentially high risk of the product being thermally instable reasoned by the high count of nitrogen and oxygen heteroatoms. Finally, the preparation and isolation of double nitrated trifluoroacetophenone **2.20** was achieved stepwise with the hydrate **2.24** as an isolable intermediate in medium yields after recrystallisation from water. The hydrated form **2.24** of the ketone **2.20** was dehydrated by an azeotropic distillation with toluene in a *Dean-Stark* apparatus to yield the ketone **2.20** quantitatively (Scheme 11).



Scheme 11: Stepwise preparation of 3'5'-dinitro-2,2,2-trifluoroacetophenone 2.20.

The structure of compound **2.24** as a hydrate was proven by nuclear magnetic resonance (NMR) spectroscopy, as the signals of the protons of the OH-groups were identified through ^1H,^1H-EXSY correlation (EXSY = exchange spectroscopy) to the signals of residual water. Another evidence for the proposed structure was the missing carbonyl valence band in the infrared spectroscopy. It was further possible to characterise the molecular structure unambiguously as a hydrate through X-ray diffraction (Figure 7, CCDC 2130259).

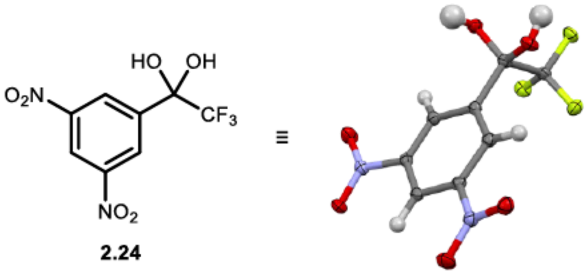
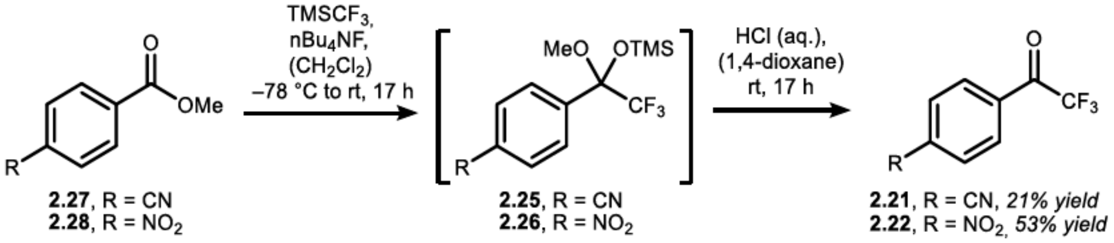


Figure 7: Molecular structure of hydrate 2.24 determined *via* x-ray diffraction, thermal ellipsoids are depicted at 50% probability. CCDC 2130259.

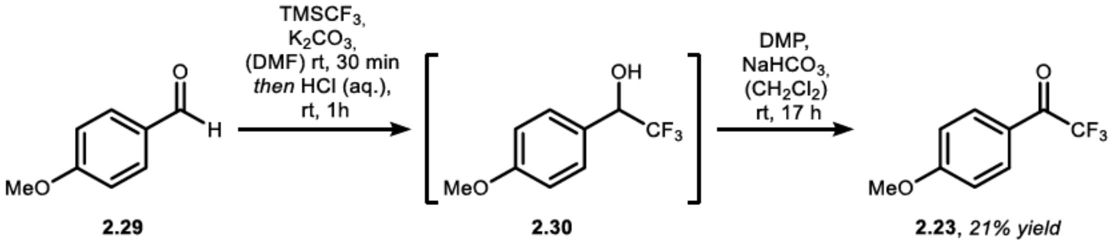
Due to the directing effect of the ketone functionality, electrophilic aromatic substitution of trifluoroacetophenone **2.18** was not feasible for the synthesis of 4-substituted aromatic ketones. For that reason, a procedure of *Prakash* and *Olah* was followed for the synthesis of 4-cyano and 4-nitro substituted trifluoroacetophenones **2.21** and **2.22** respectively (Scheme 12).[66]



Scheme 12: Preparation of 4-substituted trifluoroacetophenones from benzoic acid derivatives according to *Prakash* and *Olah*.[66] TMS = trimethylsilyl.

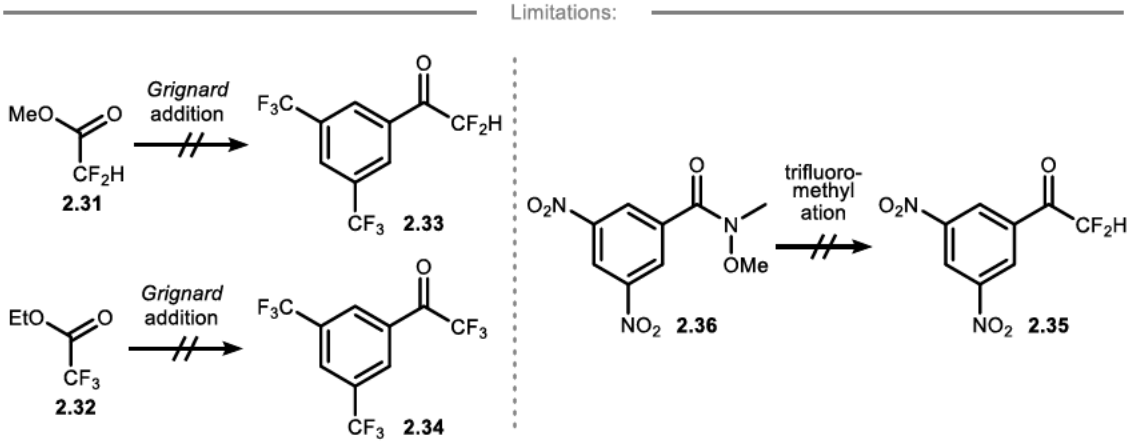
In a first reaction step the trimethylsilyl ethers **2.25** and **2.26** are formed after nucleophilic attack of a trifluoromethyl anion to esters **2.27** and **2.28**, generated through activation of trifluoromethyltrimethylsilane with a fluoride anion. The ethers **2.25** and **2.26** can be regarded as a ketal of the desired ketones **2.21** and

2.22, thereby the trimethylsilyl and methoxy groups were removed under acidic conditions, delivering the desired ketones in low but acceptable yields. The synthesis of a more electron-rich trifluoroacetophenone **2.23** was achieved with a similar strategy. According to a method of the *Gilmour* group,[67] 4-methoxybenzaldehyde **2.29** was reacted with trifluoromethyltrimethylsilane and a base to form the fluorinated alcohol **2.30**, which was oxidised with *Dess-Martin* periodinane (DMP) affording the desired product **2.23** in low yields (Scheme 13).



Scheme 13: Synthesis of 4'-methoxy-2,2,2-trifluoroacetophenone 2.23 according to *Fassbender* and *Metternich* et al.[67] DMF = *N*,*N*-dimethylformamide.

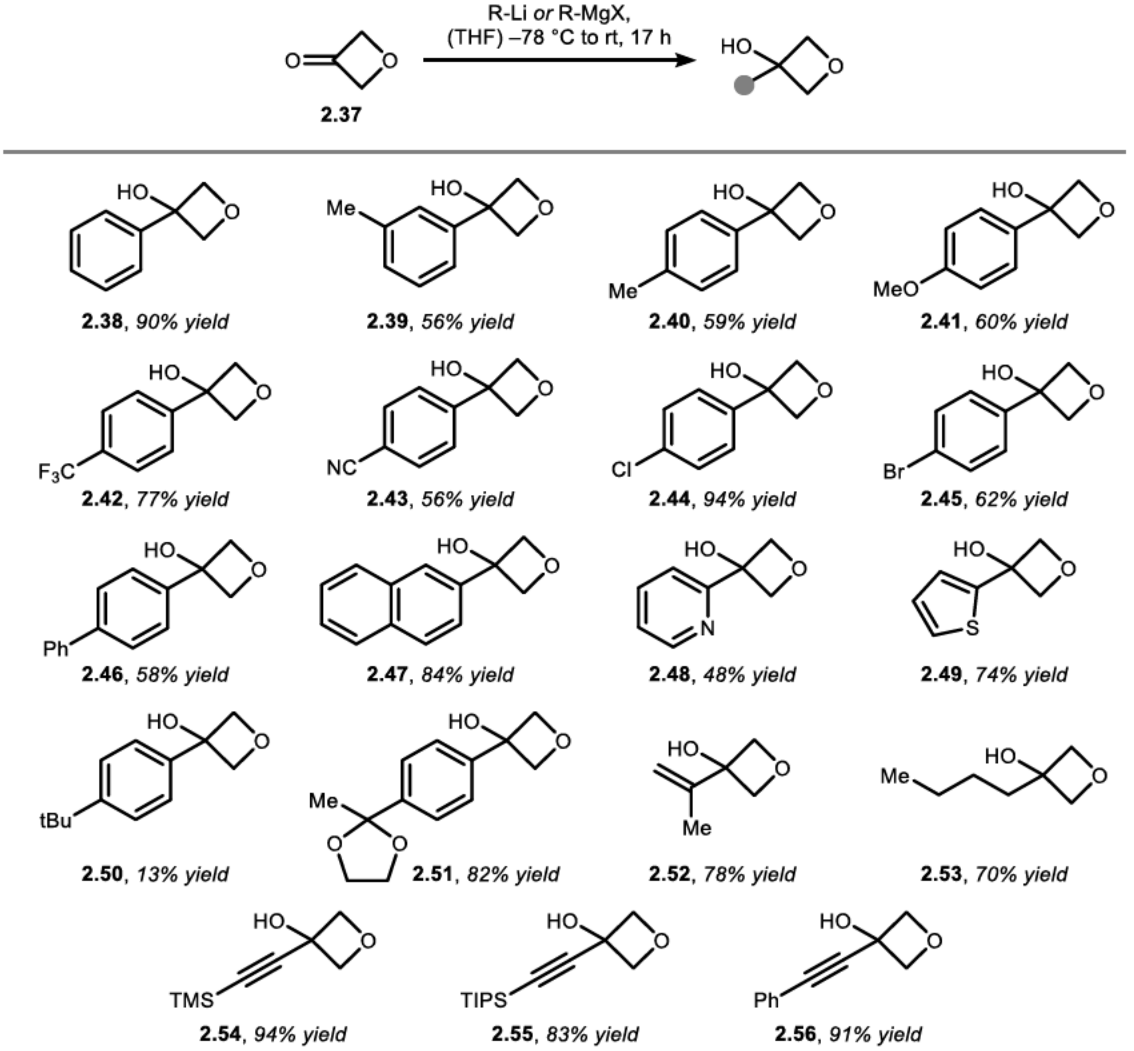
The preparation of other trifluoroacetophenone derivatives proved to be difficult if alternative methods were used. The addition of aromatic organomagnesium compounds to fluorinated esters **2.31** and **2.32** for instance was ineffective for the preparation of 3,5-bis-trifluoromethylated acetophenones **2.33** and **2.34** (Scheme 14, left). Even adapting known methods for difluoromethylation,[68] failed for the synthesis of the very electron-poor difluoroacetophenone **2.35** from *Weinreb* amide **2.36** (Scheme 14, right).



Scheme 14: Unsuccessful approaches for electron-poor acetophenone derivatives.

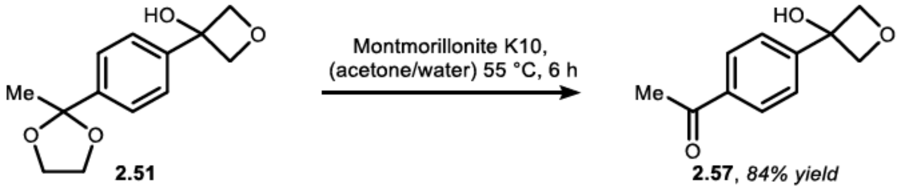
2.2.2 Preparation of 3-oxetanols

As outlined above, 3-oxetanols should be used as a platform for the synthesis of heterocycles in this project. A simple, yet very effective, method for their preparation is the addition of an organolithium or organomagnesium species to commercially available 3-oxetanone **2.37**. Thereby a manifold of differing 3-oxetanols (**2.38** to **2.56**) was prepared following either lab own protocols, or literature known procedures with minor alterations (Scheme 15). Organolithium or organomagnesium compounds were either commercially available or prepared through lithium-halogen exchange, magnesium-halogen exchange or deprotonation.[69] Typically, the shown oxetanols were obtained in yields greater than 50%. Thus, the differing methods for their synthesis were equally effective.



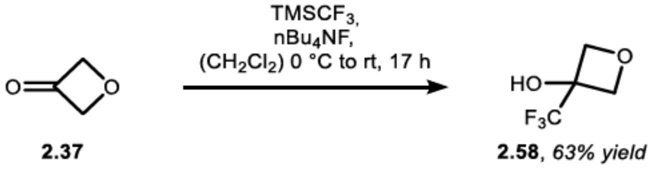
Scheme 15: Overview of prepared 3-oxetanols by addition of carbon nucleophiles. THF = tetrahydrofuran.

The oxetanol **2.51** bears a glycol protected ketone functionality, which was mildly deprotected with Montmorrilonite K10 following a protocol by *Li et al.* yielding oxetanol **2.57** with high efficiency (Scheme 16).[70]



Scheme 16: Heterogenous deprotection of dioxolane 2.51 to free acetophenone 2.57 according to *Li et al.*[70]

Furthermore, the more acidic fluorinated oxetanol **2.58** was prepared correspondent to a literature known protocol with minor alterations.[66] Again, a trifluoromethyl group is introduced to a carbonyl compound, namely 3-oxetanone **2.37**, with trifluoromethyltrimethylsilane (Scheme 17).

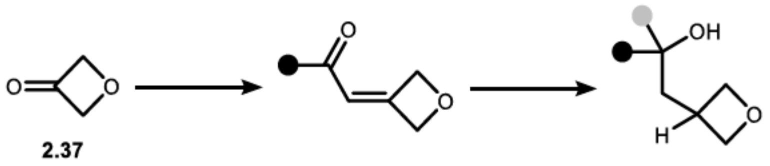


Scheme 17: Synthesis of trifluoromethylated oxetanol 2.58 according to *Prakash* and *Olah*.[66]

2.2.3 Other substrates

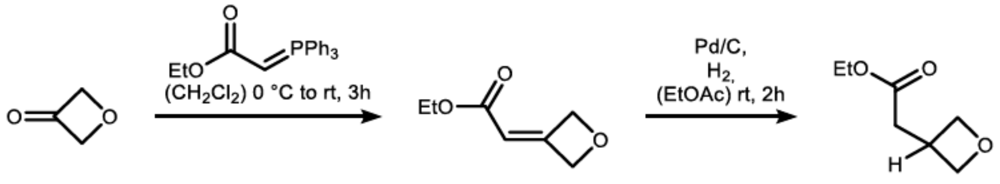
A number of other oxetane containing substrates were synthesised in order to investigate the mechanistic background of the transformation described below (*cf.* Chapter 2.5).

Therefore, oxetanes with a tethered nucleophile were prepared over multiple steps. As the *Wittig* olefination and related reactions are an easy way to install functional groups and prolong an existing carbon chain, it was used in the stepwise synthesis of such tethered oxetanes, starting from commercially available 3-oxetanone **2.37** (Scheme 18).



Scheme 18: General strategy for the synthesis of oxetanes bearing a tethered nucleophile.

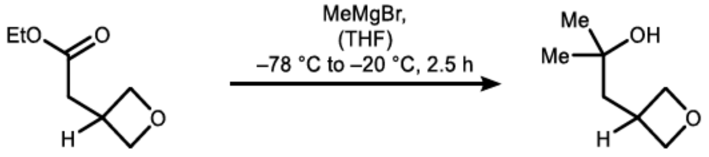
In a first approach, the α, β-unsaturated ester **2.59** was prepared in a *Wittig* reaction, followed by a reduction step to efficiently yield oxetane tethered ester **2.60** observing high yields in both reaction steps (Scheme 19).



2.37   **2.59**, *97% yield*   **2.60**, *93% yield*

Scheme 19: Synthesis of oxetane tethered ester 2.60 *via Wittig* olefination and hydrogenation.

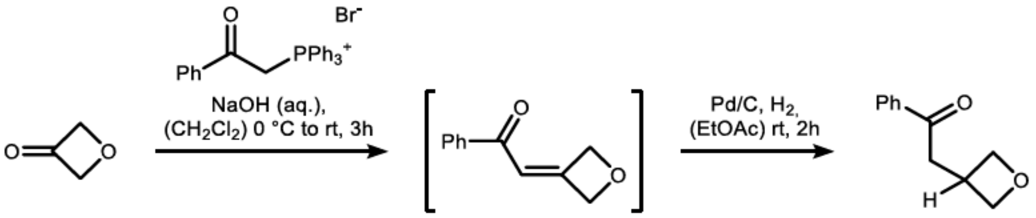
The ester **2.60** was further transformed into the prochiral tertiary alcohol **2.61** after double addition of a *Grignard* reagent (Scheme 20).



2.60   **2.61**, *33% yield*

Scheme 20: Preparation of tertiary alcohol 2.61 through *Grignard* addition.

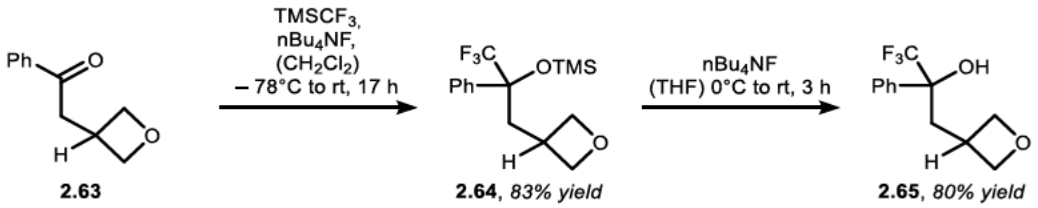
Furthermore, 3-oxetanone **2.37** was used in a similar approach affording the *α*,*β*-unsaturated ketone **2.62**. Since ketone **2.62** is known to facilely undergo rearrangement to a substituted furan,[71] it was used without being isolated and directly reduced to the stable oxetane **2.63** to circumvent the unwanted side reaction. Thus, oxetane **2.63** was obtained with an overall low yield of 27% over this two-step sequence (Scheme 21).



2.37   **2.62**   **2.63**, *27% yield*

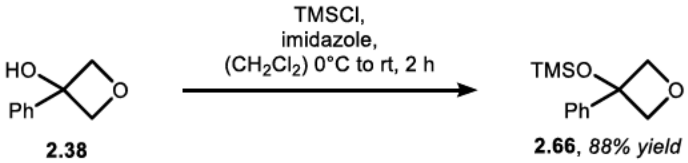
Scheme 21: Preparation of tethered oxetane 2.63 *via Wittig* olefination and hydrogenation.

Subsequently, a trifluoromethyl group was transferred to the ketone moiety.[66] After cleavage of the first formed trimethylsilyl ether **2.64**,[72] racemic trifluoromethylalcohol **2.65** was afforded in good yields.



Scheme 22: Stepwise synthesis of trifluoromethylated alcohol 2.65.[66,72]

In addition to the prepared tertiary alcohols, trimethylsilyl ether **2.66** was afforded following a slightly varied literature known procedure from phenyl oxetanol **2.38** in high yields (Scheme 23).[73]



Scheme 23: Silyl protection of phenyl oxetanol 2.38.

2.2.4 Preparation of catalysts

In order to find an appropriate catalyst for the method reported below (*cf.* Chapter 2.5), multiple salen type ligands were prepared and utilised to generate Co^{II} complexes. Generally, salen type ligands can be divided into two classes, firstly *Jacobsen* type ligands, which have up to two stereogenic centres solely in the amine backbone, secondly *Katsuki* type ligands, which have an additional stereoelement, as they consist of axially chiral binaphthyl units.[74]

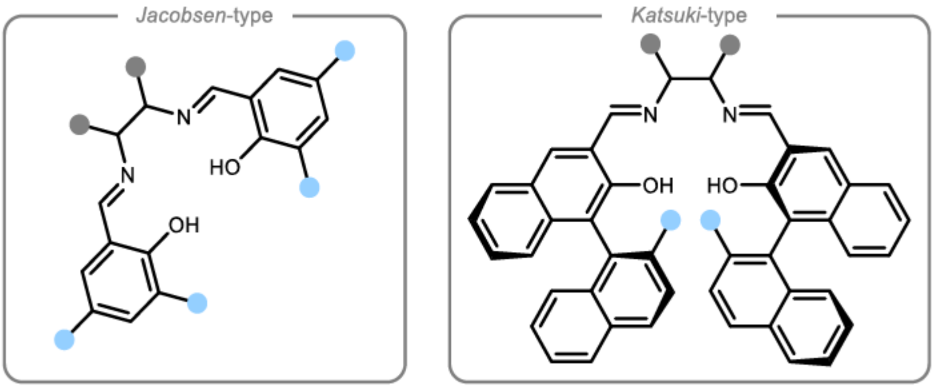
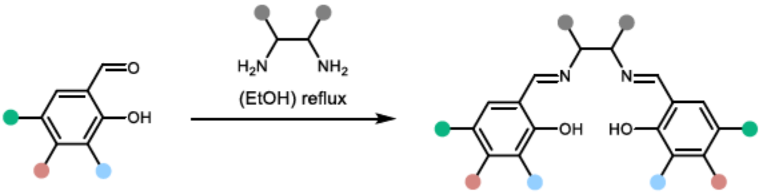
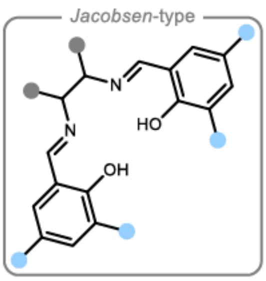
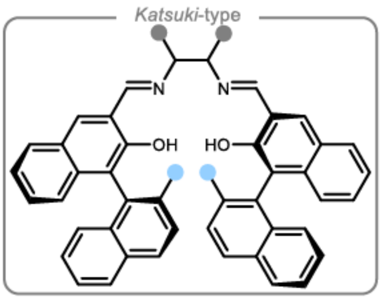
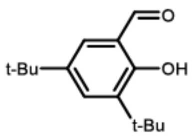
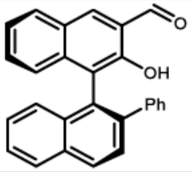
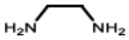
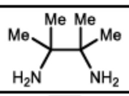
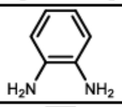
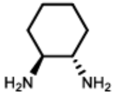
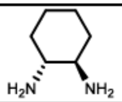
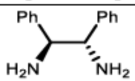
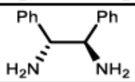


Figure 8: Typical structures of *Jacobsen* and *Katsuki* type salen ligands.

A standard method for the synthesis of salen type ligands is the condensation of an aromatic aldehyde with a diamine, thereby *Jacobsen* type ligands **2.67** to **2.70** and *Katsuki* type ligands **2.71** and **2.72** were afforded in medium to excellent yields (Table 1).[75]

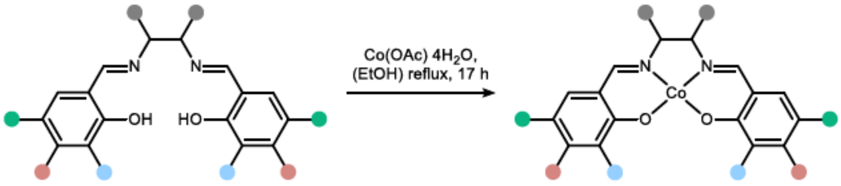
Table 1: Salen type ligands prepared in this project *via Schiff* base condensation.

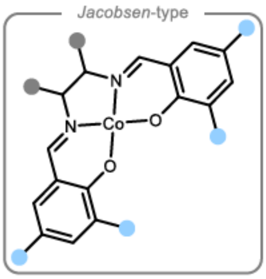
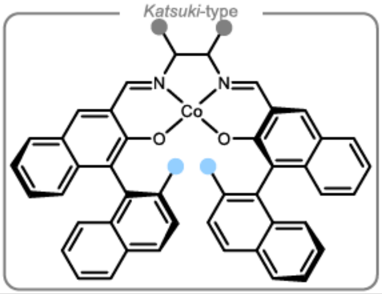
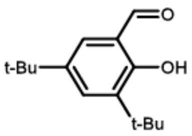
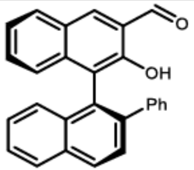
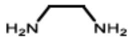
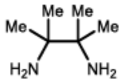
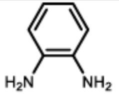
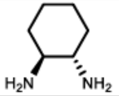
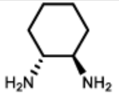
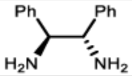
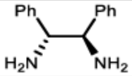


		
		
	**2.67**, *43% yield*	–
	**2.68**, *78% yield*	–
	**2.69**, *77% yield*	–
	–	**2.71**, *87% yield*
	**2.70**, *92% yield*	*epi*-**2.71**, *76% yield*
	–	–
	–	**2.72**, *50% yield*

With the ligands in hand, a variety of Co^{II}·salen complexes were synthesised in moderate to good yields according to a method by *Ebisawa et al.* such as the achiral *Jacobsen* type complexes **2.73** to **2.75**, the chiral *Jacobsen* type complexes *epi*-**2.76** and *epi*-**2.77**, and *Katsuki* type complexes **2.78** and *epi*-**2.79** (Table 2).[76] In cooperation with [redacted] and [redacted] Co^{II}·salen complexes **2.77**, *epi*-**2.78** and **2.79** were prepared (Table 2).

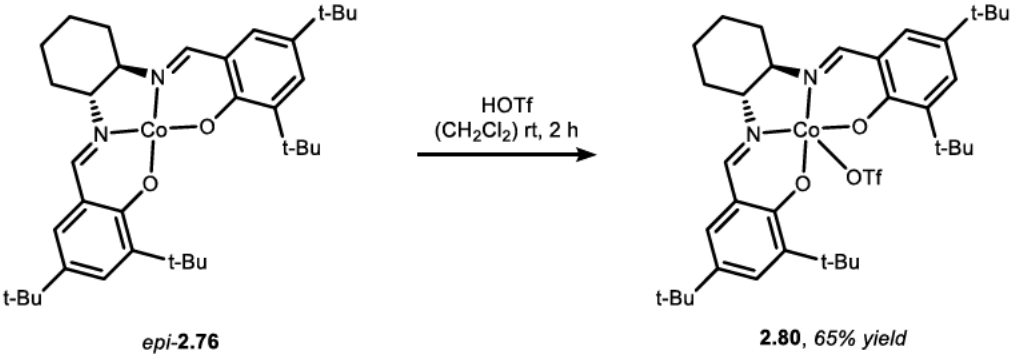
Table 2: Overview of prepared Co^{II}·salen complexes.



		
		
	**2.73**, 78% yield	–
	**2.74**, *41% yield*	–
	**2.75**, *68% yield*	–
	commercially available, **2.76**	**2.78**, *51% yield*
	*epi*-**2.76**, *51% yield*	*epi*-**2.78**[b]
	**2.77**[a]	**2.79**[b]
	*epi*-**2.77**, *73% yield*	*epi*-**2.79**, *43% yield*

[a] Prepared by [redacted] [b] Prepared by [redacted]

In addition to the Co^{II} complexes, a more *Lewis* acidic Co^{III} complex was prepared following a procedure by the *Jacobsen* group.[59] The aerobic oxidation of Co^{II}·salen *epi*-**2.76** was achieved through the addition of triflic acid as a *Brønsted* acid to a solution of the cobalt complex *epi*-**2.76** affording (TfO) Co^{III}·salen **2.80** in a moderate yield (Scheme 24).

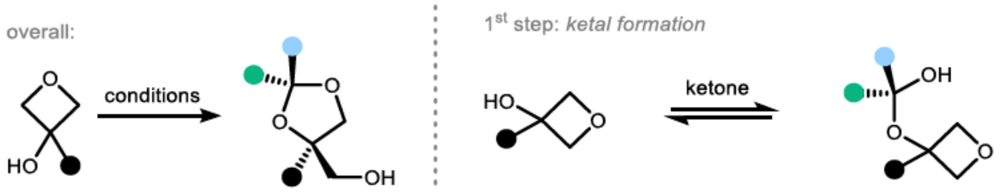


Scheme 24: Aerobic oxidation of Co^{II}·salen to Co^{III}·salen, according to *Loy et al.*[59]

2.3 Optimisation of reaction conditions

2.3.1 Hemi ketal formation

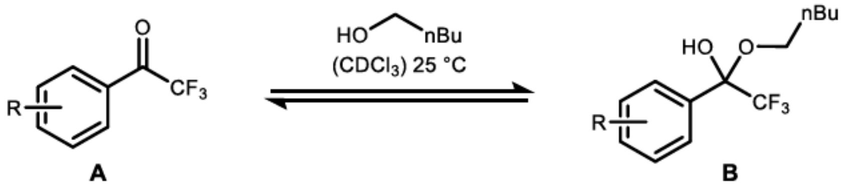
As delineated above (*cf.* Chapter 2.1, Scheme 9), the desired ring-opening and ring-closing sequence of oxetanes can be partitioned into two reaction steps. The first step includes the transient formation of a hemi ketal (Scheme 25). It was assumed, that the hemi ketal is in a fast equilibrium with the respective alcohol and ketone, and that the position of the equilibrium could be influenced by steric and electronic parameters of both the ketone and the alcohol.



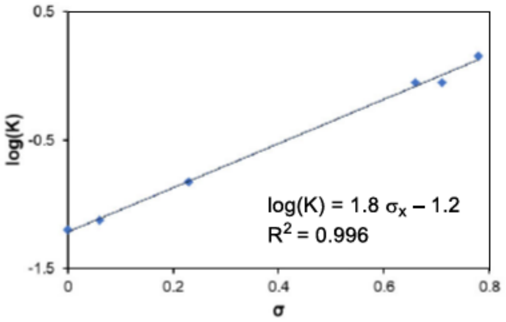
Scheme 25: Left: Graphical representation of the desired dioxolane synthesis. Right: First step for the planned overall dynamic kinetic resolution.

Initially, the influence of the electronic nature of the ketone was investigated. Therefore, 2,2,2-trifluoroacetophenones were chosen as ideal models, hence their trifluoromethyl group is a sensitive probe for changes in polarity of the molecule, which come along the formation of a hemi ketal. Even subtle changes of the chemical surrounding of the trifluoromethyl group can be monitored *via* ^{19}F NMR techniques, due to the high sensitivity and broad range of chemical shifts.

The reaction of *n*-pentanol with substituted trifluoroacetophenones was chosen as the model reaction for investigating, to what extent the equilibrium position is influenced by the electronic nature of the ketone. The reaction was monitored *via* NMR spectroscopy and the equilibrium constants were determined by integration of the signals in the corresponding ^{1}H NMR and ^{19}F NMR spectra. A systematic variation of the substituents on the aromatic ring was performed to analyse if the *Hammett* equation is applicable as a linear free-energy correlation (Scheme 26). The corresponding σ values of the altered functional groups can be found in literature.[77]



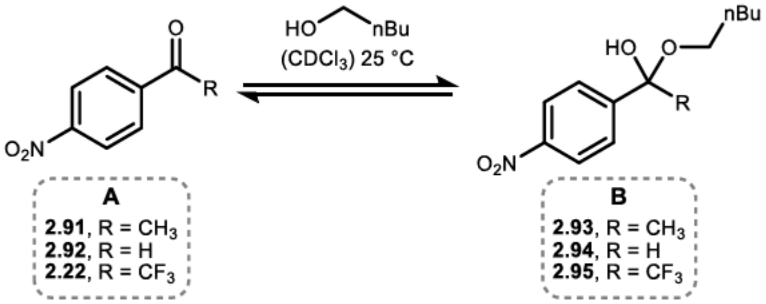
Entry	A	B	R	σ	Ratio (A:B)
1	**2.23**	**2.83**	4-MeO	−0.27	100:0
2	**2.18**	**2.84**	4-H	0.00	94:6
3	**2.81**	**2.85**	4-F	0.06	93:7
4	**2.82**	**2.86**	4-Br	0.23	87:13
5	**2.21**	**2.87**	4-CN	0.66	53:47
6	**2.19**	**2.88**	3-NO$_2$	0.71	53:47
7	**2.22**	**2.89**	4-NO$_2$	0.78	41:59
8	**2.20**	**2.90**	3,5-(NO$_2$)$_2$		12:88



Scheme 26: *Hammett* study for the ketone/hemi ketal equilibrium of trifluoroacetophenones and pentanol.

Whereas the electron-rich methoxy substituted ketone **2.23** is showing no ketal formation, the slightly electron-poor 4-fluoro substituted ketone **2.81** and 4-bromo substituted ketone **2.82** are providing a small but measurable ketal formation. Installing stronger electron withdrawing groups such as a nitro group in the 4-position on the aromatic ring was required to shift the equilibrium to the side of the hemi ketal. The performed *Hammett* study showed a strong correlation between the electronic nature of the substituents on the aromatic ring and the examined equilibrium towards hemi ketals **2.83** to **2.90**. It can be concluded, that the more electron-withdrawing the substituents are, the more partial positive charge is generated at the carbonyl carbon thus rendering it more electrophilic and accordingly more susceptible to nucleophilic attack of the alcohol. It was further deduced, that by adding two nitro groups, the equilibrium is mostly shifted to the side of the hemi ketal. Indeed, the reaction of ketone **2.20** with pentanol showed predominantly hemi ketal and only a little amount of unconsumed alcohol. As a consequence, 3',5'-dinitro-2,2,2-trifluoroacetophenone **2.20** was determined as the optimal reagent for the ring-opening and ring-closing sequence of oxetanols.

The influence of the trifluoromethyl group was reevaluated by comparing the reactivity of other 4-nitro substituted aromatic carbonyls, namely benzaldehyde **2.91** and acetophenone **2.92**, with trifluoroacetophenone **2.22** in the model reaction with *n*-pentanol towards hemi acetal **2.93** or hemi ketals **2.94** and **2.95** respectively. It was found that the CF_3 group is needed as an additional electron-withdrawing factor to form stable hemi ketals (Scheme 27).



Entry	A	B	Ratio (**A**:**B**)
1	**2.91**	**2.93**	100:0
2	**2.92**	**2.94**	84:16
3	**2.22**	**2.95**	41:59

Scheme 27: Comparison of aromatic carbonyl compounds in the reaction with *n*-pentanol.

During the investigations on the formation of hemi ketals with electron-deficient ketones, other alcohols were tested as nucleophiles. For example, benzyl alcohol was used as another primary alcohol, which delivered the hemi ketal **2.96** whose molecular structure was successfully determined *via* X-ray diffraction (Figure 9, CCDC 2130260). This structure displays a rare example of a stable acyclic hemi ketal, thus showcasing the extraordinary reactivity of trifluoroacetophenone derivatives.

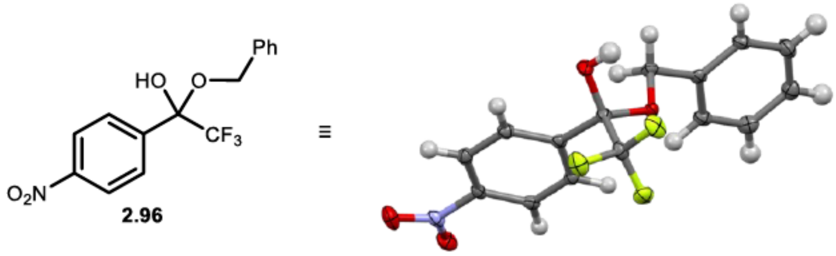
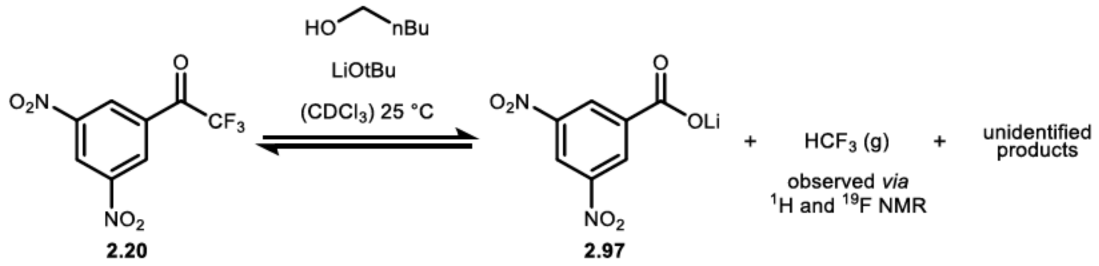


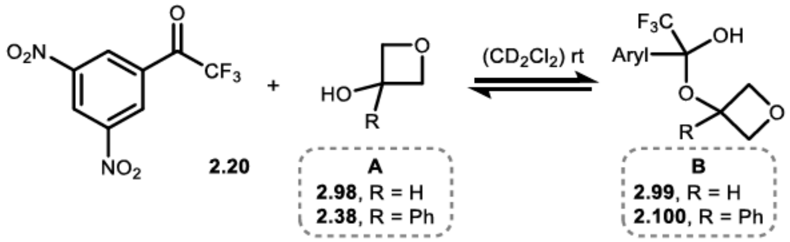
Figure 9: Molecular structure of hemi ketal 2.96 determined *via* x-ray diffraction, thermal ellipsoids are depicted at 50% probability. CCDC 2130260.

It was moreover examined whether the addition of *Brønsted* acids has an influence on the hemi ketal/ketone equilibrium. The addition of trifluoroacetic acid to the undertaken experiments shown earlier (Scheme 26) indicated no effect. The addition of *Brønsted* bases had also no beneficial effect on the equilibrium. Effectively, adding strong *Brønsted* bases such as lithium *tert*-butoxide led to fragmentation of the trifluoroacetophenone in a haloform-type reaction to deprotonated benzoic acid **2.97** and the formation of gaseous trifluoromethane. Despite its low boiling point, trifluoromethane was observed *via* ^{1}H and ^{19}F NMR techniques as it was partially dissolved. After the base induced fragmentation, not all the formed reaction products could be assigned to distinct structures by means of NMR analysis (Scheme 28).



Scheme 28: Haloform-type reaction of trifluoroacetophenone 2.20.

Nevertheless, 3',5'-dinitro-2,2,2-trifluoroacetophenone **2.20** was identified as the most reactive ketone in this study due to its high electrophilicity. The reactivity of ketone **2.20** with oxetanols **2.98** and **2.38** was therefore tested to probe if the hemi ketal is formed and can be employed in the desired combined ring-closing and ring-opening sequence of oxetanes to form bigger oxygen heterocycles. Indeed, the hemi ketal **2.99** derived from unsubstituted 3-oxetanol **2.98** was formed to a high degree, on the other hand, the hemi ketal **2.100** derived from phenyl substituted oxetanol **2.38** was hardly detectable (Scheme 29).

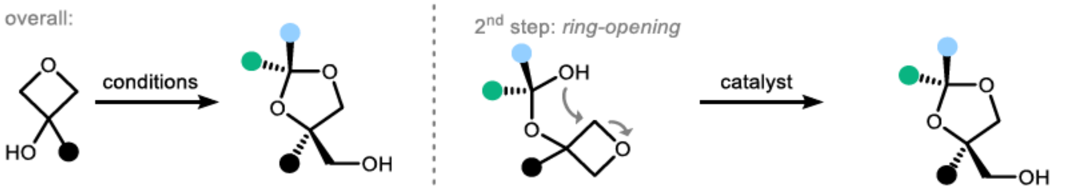


Entry	A	B	Ratio (**A**:**B**)
1	**2.98**	**2.99**	40:60
2	**2.38**	**2.100**	>99:1

Scheme 29: Hemi ketal/ketal equilibrium for selected 3-oxetanols and ketone 2.20.

2.3.2 Ring-opening

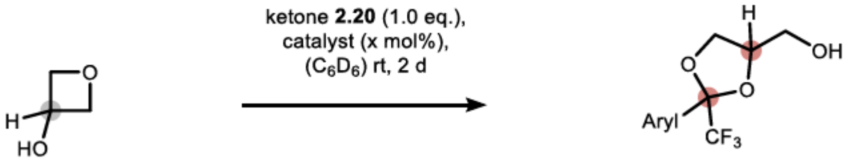
Finding a reactive ketone for the formation of hemi ketals was a first step towards the successful synthesis of 1,3-dioxolanes through a ring-opening and ring-closing sequence of oxetanes (Scheme 30). Although initial results of the hemi ketal formation with oxetanols were not fully positive in regard of the desired overall transformation (Scheme 29), they marked the outset for a deeper investigation on the envisioned two step transformation.



Scheme 30: Left: Graphical representation of the desired dioxolane synthesis. Right: Second step for the planned overall dynamic kinetic resolution.

As discussed in the literature, activation of the *Lewis* basic oxetane is needed to use these cyclic ethers in organic synthesis (*cf.* Chapter 2.1). It can further be presumed, that a proper catalyst for the ring-opening might also influence the hemi ketal formation in the first step. For instance, chiral phosphoric acids, which are known to catalyse ring-opening reactions of oxetanes, interact with substrate molecules in multiple modes and not solely as *Brønsted* acids.[78] For that reason, chiral phosphoric acids were tested as additives for the reaction of 3-oxetanol **2.98** to the dioxolane **2.101**, but failed to achieve the desired activity (Table 3, entries 1 to 3). Additionally, metal complexes were applied (Figure 10). For instance, Co^{III}·salen complex **2.80** was used in the desired reaction, inspired by the work of the *Jacobsen* group.[59] The catalyst showed activity and the dioxolane **2.101** was formed reproducibly in a small but detectable yield (entry 4), whereas another Co^{III} salt provided no reactivity (entry 5). Other chiral *Lewis* acids were tried, such as scandium triflate in combination with a chiral ligand, *Jacobsens* catalyst **2.102** or (Cl)Al·salen **2.103** but showed no improved product formation (entries 6 to 8). Since cobalt salen complexes are known to interact strongly with oxygen species,[79] alternative cobalt complexes were tested and found to enhance the product formation to almost full conversion of the starting material. Both, chiral and achiral Co^{II}·salen complexes **2.73** and **2.76** provided high reactivity (entries 9 and 10), whereas the absence of a salen ligand completely shut down the formation of the desired dioxolane **2.101** (entries 11 and 12).

Table 3: Initial findings for ring-opening reactions of oxetanes, conversion based on ^{19}F NMR experiments. Reactions were run in C_6D_6 on a 0.1 mmol scale.

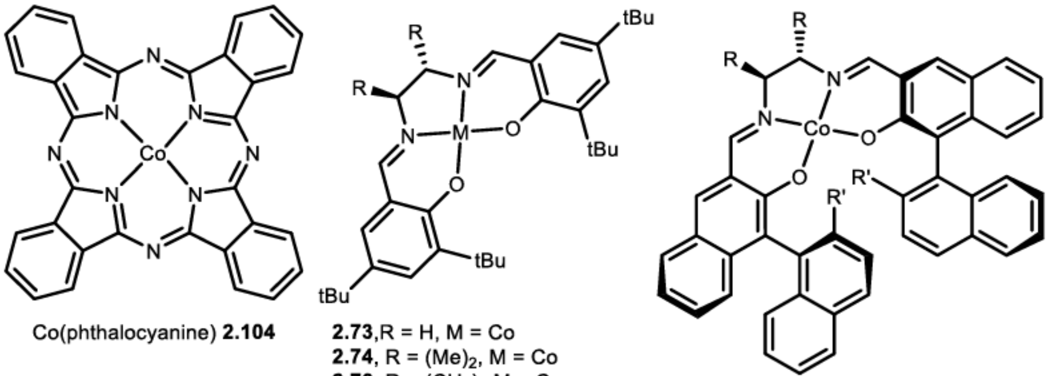


2.98

2.101, Aryl = 3,5-$(NO_2)_2$-C_6H_3

Entry	Catalyst	Equivalents	Conversion
1	(*R*)-3,3′-Bis-(9-anthracenyl)-1,1′-binaphthyl-2,2′-diyl-hydrogenphosphat	10 mol%	0%
2	(*R*)-3,3′-Bis-(2,4,6-triisopropyl-phenyl)-1,1′-binaphthyl-2,2′-diyl-hydrogenphosphat	5 mol%	0%
3	(*R*)-3,3′-Bis-(2,4,6-triethyl-phenyl)-1,1′-binaphthyl-2,2′-diyl-hydrogenphosphat	5 mol%	0%
4	(TfO)Co^{III} salen **2.80**	1 mol%	<5%
5	$Co(acac)_3$	1 mol%	0%
6	$Sc(OTf)_3$ premixed with 15 mol% Bn-Box ligand	10 mol%	0%
7	(Cl)Mn^{III}·salen **2.102**	1 mol%	<5%
8	(Cl)Al·salen **2.103**	1 mol%	<5%
9	Co^{II}·salen **2.73**	1 mol%	95%
10	Co^{II}·salen **2.76**	1 mol%	92%
11	Co^{II} (phthalocyanine) **2.104**	1 mol%	0%
12	$Co(acac)_2$	1 mol%	0%

Bn-Box = bis((*R*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane, acac = acetylacetonate.



Co(phthalocyanine) **2.104**

2.73,R = H, M = Co
2.74, R = $(Me)_2$, M = Co
2.76, R = $(CH_2)_4$,M = Co
2.80, R = $(CH_2)_4$,M = Co-OTf
2.77, R = Ph, M = Co
2.102, R = $(CH_2)_4$, M = Mn-Cl
2.103, R = $(CH_2)_4$, M = Al-Cl

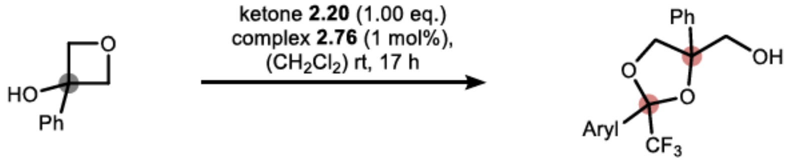
2.78, R = $(CH_2)_4$, R' = Ph
2.79, R = Ph, R' = Ph
2.106, R = $(CH_2)_4$, R' = 4-tBu-C_6H_4

Figure 10: Overview of the applied metal complexes in the optimisation of the ring-opening ring-closing sequence of oxetanols.

After the primary results, that cobalt catalysts furnish reactivity in the envisioned reaction by utilising unsubstituted oxetanol **2.98** as substrate, phenyl oxetanol **2.38** was applied next. It was assumed, that by finding a catalyst which is robust to this substrate, potentially, a generally applicable catalyst could be found, which tolerates a wide range of electronically and sterically differing oxetanols. Additionally, a catalyst should be found which is not only providing reactivity, but also allowing control over enantio- and diastereoselectivity in the envisaged reaction.

As a starting point, a short survey on the employed solvents was performed (Table 4, entries 1 to 4). Amending the solvent had no effect on the diastereo- or enantiocontrol, typically the product **2.105** was obtained in high yields of up to 98% with 80:20 *dr* (*dr* = diastereomeric ratio) and 60:40 *er*. Dichloromethane was proven best due to practical reasons as it provides the lowest melting point of the investigated solvents whereby offering the possibility of decreasing the temperature to further improve enantiocontrol. Changing the catalyst on the other hand had a strong impact on the overall reaction outcome. Expectably, the use of achiral complexes **2.73** and **2.75** led to product formation with minor changes in terms of diastereoselectivity (entries 5 and 6), whereas the use of the sterically more encumbered achiral catalyst **2.74** completely shut down the reaction (entry 7). An increased steric demand in the backbone of the *Jacobsen* type catalyst **2.77** also led to lower conversion to the desired product (entry 8). *Katsuki* type catalysts were applied next and the use of (*S*)-BINOL (BINOL = 1,1′-bi-2-naphthol) based catalyst **2.78** led to higher yield of 90% and an increased stereocontrol (90:10 *dr*, 75:25 *er*). When applying the corresponding epimer *epi*-**2.78** product formation and enantioselectivity was diminished while the diastereoselectivity was unchanged (entries 9 and 10). The sterically more demanding *Katsuki* type catalysts **2.79** and *epi*-**2.79** with a diphenylethane backbone were employed with the product almost not being formed (entries 11 and 12), thereby illustrating the sensitivity of the overall reaction towards steric bulk in the backbone of the utilised catalysts. As a consequence, the BINOL part of the catalyst was varied next and the steric demand of the phenyl group in 2'-position was increased by adding a *tert*-butyl group to the phenyl ring. Therefore, the *Katsuki type* Co^{II}·salen complex **2.106** was prepared by [redacted] and used in this optimisation. The thereby achieved change in steric size led to a maintained high yield of 88% with an increased sterocontrol, thus higher diastereo- and enantioselectivity (96:4 *dr*, and 86:14 *er*) was observed in the formation of 1,3-dioxolane **2.105** (entry 13).

Table 4: Solvent and catalyst optimisation, reactions were carried out on a 0.1 mmol scale in varying solvents [0.2M], NMR yield and *dr* based on ^{19}F NMR experiments using trifluorotoluene as an internal standard, *er* determined *via* high-performance liquid chromatography (HPLC) using chiral stationary phases.



2.38

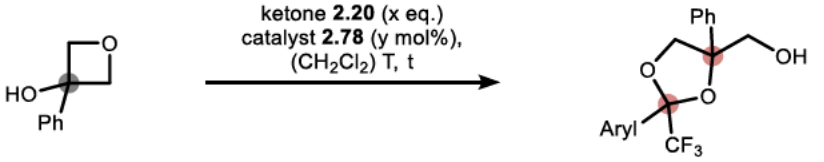
2.105, Aryl = 3,5-$(NO_2)_2$-C_6H_3

Entry	Changes from standard conditions	NMR yield	*dr*	*er*
1[a]	–	> 98%	79:21	60:40
2[a]	C_6D_6 used as solvent	92%	79:21	60:40
3[a]	CH_3CN used as solvent	> 98%	79:21	60:40
4[a]	MTBE used as solvent	50%	80:20	60:40
5	**2.73** used as catalyst	95%	76:24	–
6	**2.75** used as catalyst	93%	71:39	–
7	**2.74** used as catalyst	0%	–	–
8	**2.77** [b] used as catalyst	48%	78:22	60:40
9	**2.78** used as catalyst	90%	90:10	75:25
10	*epi*-**2.78**[c] used as catalyst	52%	90:10	58:42
11	**2.79**[c] used as catalyst	< 5%	n.d.	n.d.
12	*epi*-**2.79** used as catalyst	< 5%	n.d.	n.d.
13	**2.106**[c] used as catalyst	88%	96:4	86:14

MTBE = methyl *tert*-butyl ether. [a] Reaction was run with 2 mol% of catalyst. [b] Complex was prepared by [redacted]
[c] Complex was prepared by [redacted]

Changing other parameters, such as the equivalents of ketone **2.20** (Table 5, entries 1 to 3), or amending the concentration (entries 4 and 5), was only marginally affecting the overall reaction outcome. The biggest impact on the reaction rate was achieved by adding a higher amount of cobalt catalyst (entries 6 to 8). It has to be noted, that the 1,3-dioxolane **2.105** was still formed even with very low loadings of the Co^{II} catalst. Surprisingly, decreasing the temperature by 40 °C had no effect on the observed diastereoselectivity, while it immensely slowed down the whole reaction (entries 9 and 10). The enantiomeric ratios obtained under these conditions were not determined, since the massive decrease in yield rendered these conditions as synthetically not useful.

Table 5: Catalyst loading and temperature optimisation, reactions were carried out in CH_2Cl_2 on a 0.1 mmol scale in varying concentrations with catalyst 2.78, yield and *dr* based on ^{19}F NMR experiments using trifluorotoluene as an internal standard.



2.38

2.105, Aryl = 3,5-$(NO_2)_2$-C_6H_3

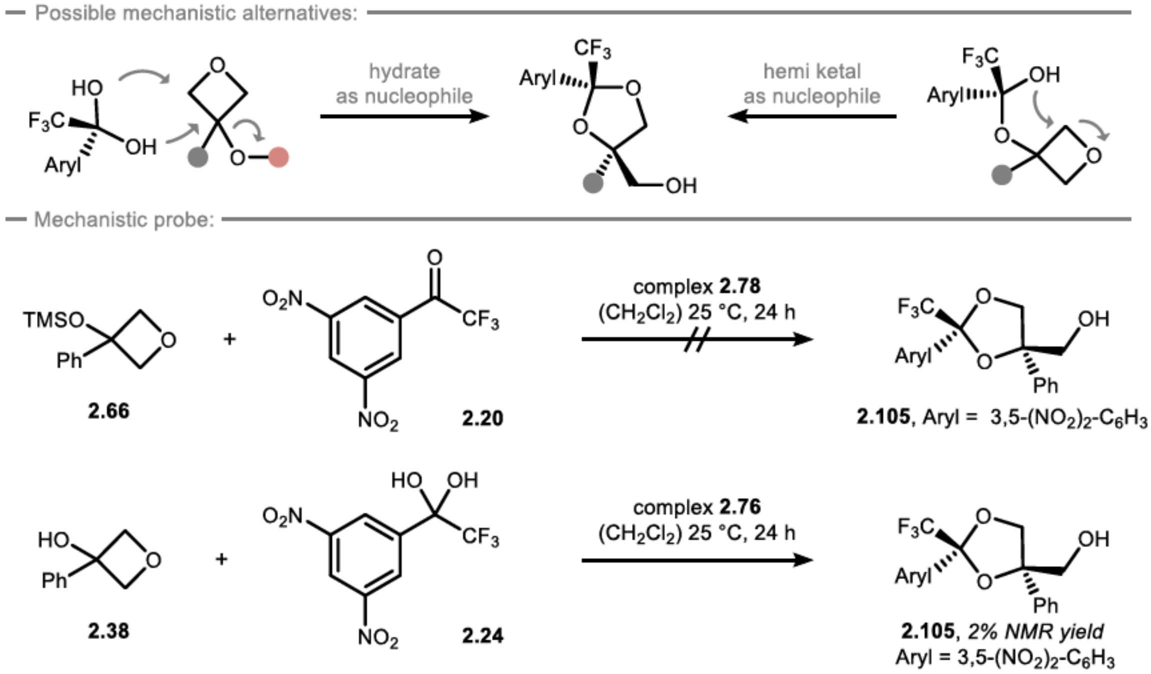
Entry	Equivalents of **2.20**	Catalyst loading	*T*	*t*	Concen-tration	NMR yield	*dr*
1	1.00	1 mol%	rt	2.5 h	0.2 M	26%	n.d.
2	1.20	1 mol%	rt	2.5 h	0.2 M	29%	n.d.
3	1.40	1 mol%	rt	2.5 h	0.2 M	34%	n.d.
4	1.00	1 mol%	rt	4 h	0.05 M	40%	n.d.
5	1.00	1 mol%	rt	4 h	0.8 M	49%	n.d.
6[a]	1.00	0.1 mol%	rt	3 d	0.2 M	67%	n.d.
7	1.00	2 mol%	rt	2.5 h	0.2 M	49%	n.d.
8	1.00	4 mol%	rt	2.5 h	0.2 M	87%	n.d.
9	1.00	1 mol%	5 °C	17 h	0.2 M	50%	96:4
10	1.00	1 mol%	−20 °C	17 h	0.2 M	23%	96:4

[a] Reaction was performed with 3-oxetanol **2.98** and catalyst **2.76**.

2.4 Mechanistic studies

2.4.1 Survey of nucleophiles in the ring-opening of 3-oxetanols

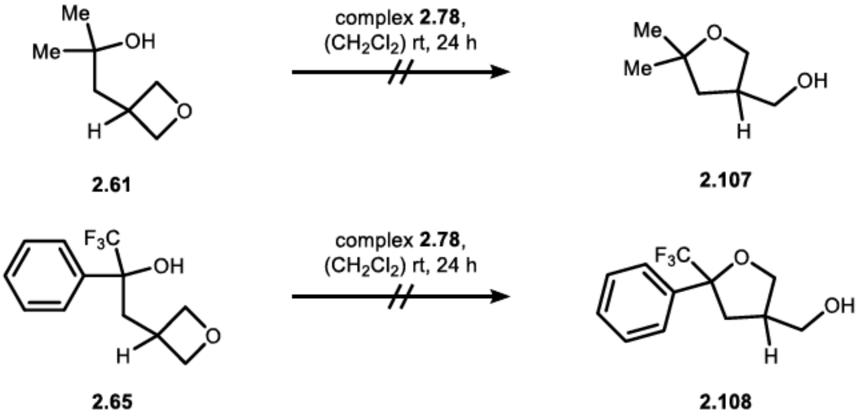
To get an insight on the fundamentals of the overall transformation of oxetanes to 1,3-dioxolanes, the present nucleophile for the ring-opening and ring-closing sequence was further investigated. To probe if a hemi ketal is the acting nucleophile or the hydrated form **2.24** of ketone **2.20** (Scheme 31, top), the desymmetrisation reaction was carried out under the same conditions shown above with silyl protected oxetanol **2.66** (Scheme 31, middle). No ring-opened product **2.105** was formed, leading to the conclusion, that a nucleophilic hemi ketal is needed for the desired synthesis of 1,3-dioxolanes.



Scheme 31: Mechanistic investigations on the nucleophile in the oxetane ring-opening.

Additionally, the role of hydrate **2.24** was analysed by interchanging ketone **2.20** with hydrate **2.24** and applying the standard conditions with phenyl oxetanol **2.38** and catalyst **2.76** (Scheme 31, bottom). Virtually no dioxolane **2.105** was formed under these conditions. The formation of the dioxolane product **2.105** was even inhibited, when hydrate **2.24** was formed *in situ* by adding one equivalent of water to ketone **2.20** under otherwise unchanged reaction conditions. It can therefore be deduced that the hydrate **2.24** is a thermodynamically stable form and not reactive towards ring-opening of 3-oxetanols.

In order to further examine the role of the nucleophile, the overall reaction was simplified to substrates with tethered hydroxy groups so no pre-equilibrium is required for the ring-opening. Therefore, substrates **2.61** and **2.65** were designed and applied to identical conditions which were successful for the 1,3 dioxolane synthesis with hemi ketals. Surprisingly, the oxolane products **2.107** and **2.108** were not formed (Scheme 32).

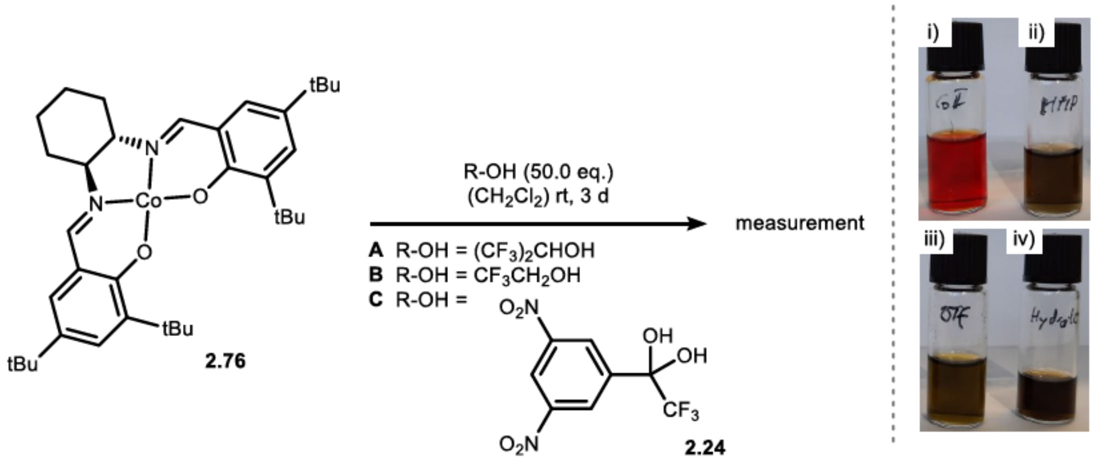


Scheme 32: Unsuccessful ring-opening of tethered model substrates 2.61 and 2.65.

This result can be interpreted by comparing the structure of the both simplified substrates **2.61** and **2.65** and the differing general structure of a hemi ketal derived from trifluoroacetophenone **2.20**. Hence, substrate **2.61** is completely lacking electron-withdrawing substituents on the alcohol and substrate **2.65** is only bearing one electron-withdrawing group, the acidity of their hydroxy groups is assumed to be lower compared to the hydroxy group of the hemi ketal. Therefore, their inherent nucleophilicity should be higher, which is contradictory to their observed reactivity. These findings led to a further elucidation of the role of the Co^{II} catalyst.

2.4.2 Investigations on the role of the cobalt catalysts

The role of the cobalt catalyst in the desymmetrisation of 3-oxetanols was deeper analysed to get a better understanding of the underlying mechanism of the synthesis of 1,3-dioxolanes. Based on the experiments discussed so far, it can be assumed, that the Co^{II}·salen catalyst interacts with the hemi ketal to enhance the nucleophilicity of the hemi ketal hydroxy group. It is known, that Co^{II} complexes undergo aerobic oxidation with acidic alcohols.[80] In the course of this oxidation process, the acidic group gets deprotonated and thus increased in its nucleophilicity. Typically, a pK_a value below 10 is required to effectively oxidise Co^{II} complexes with *Brønsted* acids under aerobic conditions.[81] Presumably, the pK_a value of hemi ketals derived from the electron-poor ketone **2.20** is in the same range, hence activation of the hemi ketals through oxidation of Co^{II}·salen complexes can be hypothesised. To further underpin this theory, the oxidation of commercially available Co^{II}·salen complex **2.76** with *Brønsted* acidic groups was studied (Scheme 33, left). As a reference, (OTf)Co^{III}·salen **2.80** was used, which was prepared by following a literature known protocol for the aerobic oxidation of cobalt complexes (*cf*. Chapter 2.2.4, Scheme 24).[59]



Scheme 33:Left: Oxidation of Co^{II}·salen 2.76 with weakly acidic alcohols. Right: Pictures of Co^{II}·salen 2.76 in solution from top left to bottom right: i) without additive, ii) with added hexafluoroisopropanol, iii) with added TfOH and iv) with added hydrate 2.24.

A change of colour was observed with the naked eye for the addition of either triflic acid, hexafluoroisopropanol or the hydrate **2.24** to Co^{II}·salen **2.76** (Scheme 33, right), hence implying an oxidation of the cobalt complex taking place. The hydrate **2.24** was used in this testing as a surrogate for the formed hemi ketals with trifluoroacetophenone **2.20**.

The oxidation was further monitored *via* UV/vis spectroscopy (UV= ultraviolet, vis = visible, Figure 11). In this course, Co^{II}·salen **2.76** and oxidised (OTf)Co^{III}·salen **2.80** were used as reference substances, the former shows an absorption maximum around 420 nm, whereas the latter, oxidised Co^{III} complex has no absorption maximum above 400 nm in the investigated spectral range. Treating Co^{II}·salen **2.76** with 2,2,2-trifluoroethanol (TFE), under the typical conditions (Scheme 33), was not shifting the absorption maxima, on the contrary the addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) changed the absorption spectra. The same holds true for the addition of hydrate **2.24**.

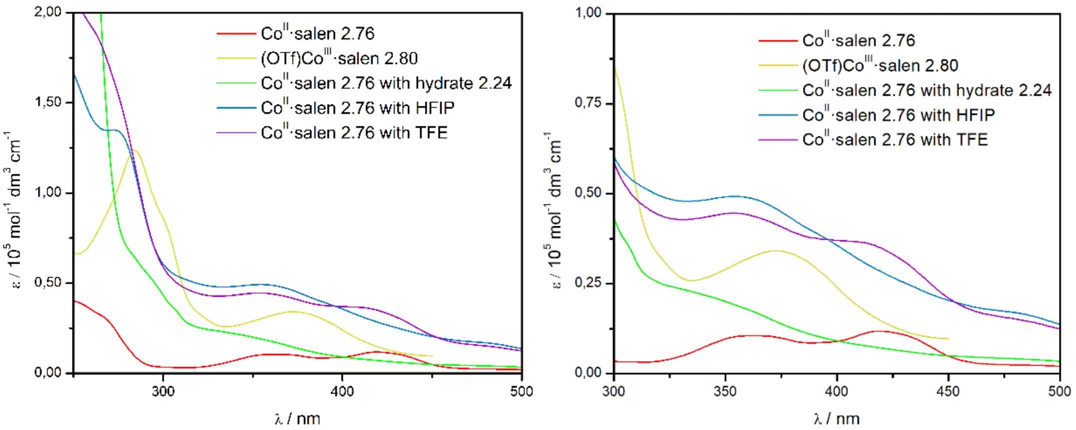
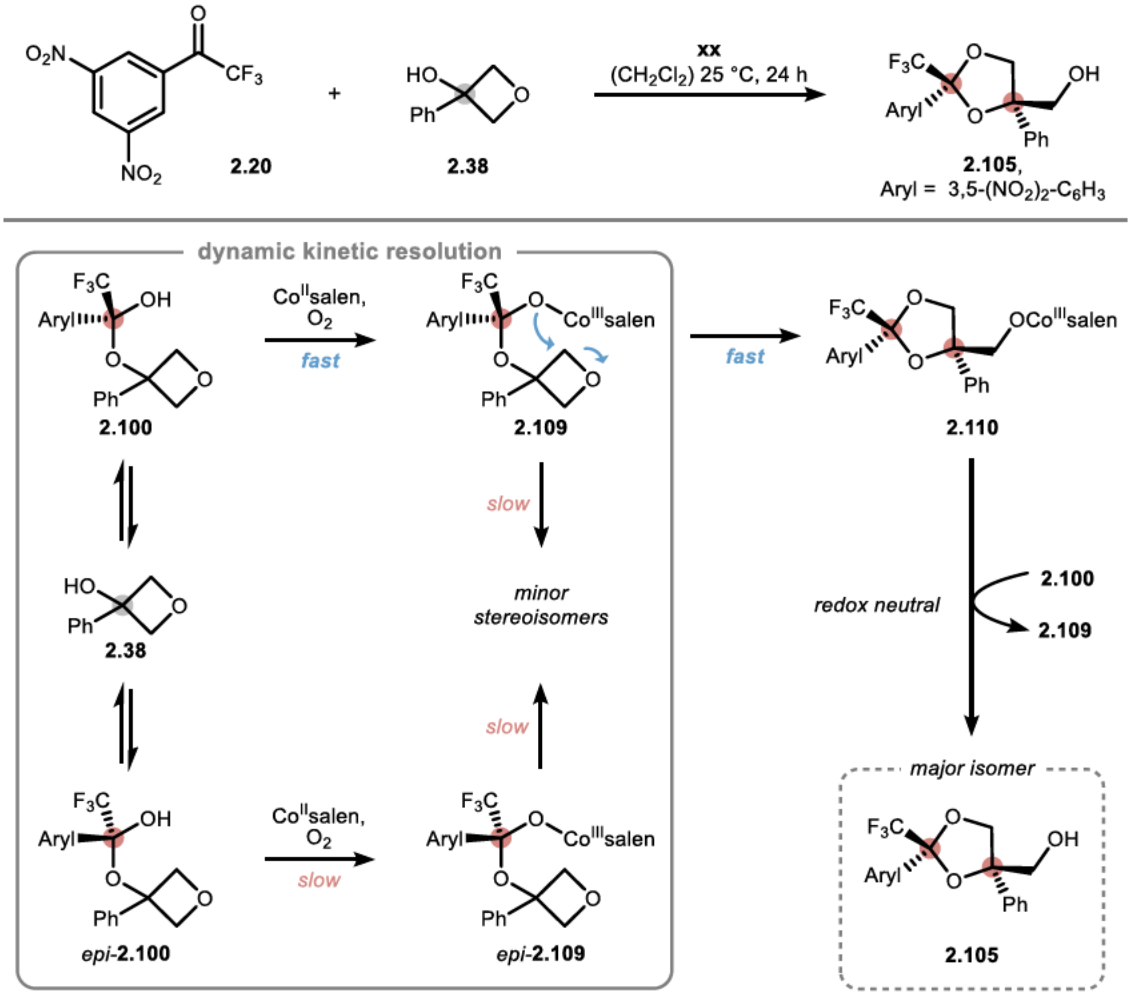


Figure 11: Left: UV/vis spectra of cobalt complexes after attempted oxidation with acidic alcohols, UV/vis spectrum of Co^{II}·salen 2.76 and (OTf)Co^{III}·salen 2.80 as references. Right: Extracted UV/vis spectra of cobalt complexes after attempted oxidation with acidic alcohols, UV/vis spectrum of Co^{II}·salen 2.76 and (OTf)Co^{III}·salen 2.80 as references.

Therefore, it can be concluded, that the hydrate **2.24** and the structurally related *in situ* formed hemi ketals are capable of oxidising Co^{II}·salen complexes under air thus being activated by deprotonation for nucleophilic ring-opening. Moreover, the unsuccessful formation of oxolanes from the tethered alcohols **2.61** and **2.65** can now be reasoned by their low acidity (*cf.* Chapter 2.3.2, Scheme 32).

2.4.3 Mechanistic picture for the DKR of hemi ketals for the desymmetrisation of 3-oxetanols

The above discussed findings can be compiled to a mechanistic picture which includes the transient formation of an acidic hemi-ketal as the first step of the dynamic kinetic resolution (Scheme 34).



Scheme 34: Mechanistic picture of the desymmetrisation of 3-oxetanols by dynamic kinetic resolution of hemi ketals.

The underlying equilibrium is swiftly epimerising the sterogenic centre of the hemi ketals **2.100** and *epi*-**2.100**. Based on the obtained data, an influence of the cobalt catalyst on the equilibrium can neither be confirmed nor excluded at this point. The next step includes the aerobic oxidation of the Co^{II} catalyst, which activates the internal nucleophile by deprotonation. Subsequently, the hemi ketalate **2.109** is opening the oxetane ring to form the cobalt alkoxide **2.110** by intramolecular nucleophilic attack to one side of the oxetane ring. Throughout this step, the desired product diastereoisomer is formed enantioselectively, presumably because of the steric bulk of the employed catalyst which blocks one side of the oxetane ring from the hemi ketalate **2.109**. Whereas the minor stereoisomers are formed slower by either nucleophilic ring-opening from the unfavoured side of the oxetane ring of hemi ketalate **2.109**, or by the ring-opening of hemiketalate *epi*-**2.109**. The role of the catalyst in the ring-opening step remains speculative, as the cobalt complex can act as an intermolecular as well as an intramolecular *Lewis* acid. However, a double interaction seems plausible to rationalise the high efficiency of the ring-opening, which usually requires activation of the oxetane ring. The active hemi ketalate Co^{III} species **2.109** is presumed to be regenerated by a redox neutral replacement of the more basic primary alkoxide **2.110** to the acidic hemi ketal **2.100** upon release of the major isomer **2.105**. This ligand exchange is assumed to proceed sluggish for pre-oxidised Co^{III} species, such as (OTf)Co^{III}·salen **2.80**, due to the differing basicities of the hemi ketalate **2.100** and the commonly present anionic ligand in those Co^{III}·salen complexes.

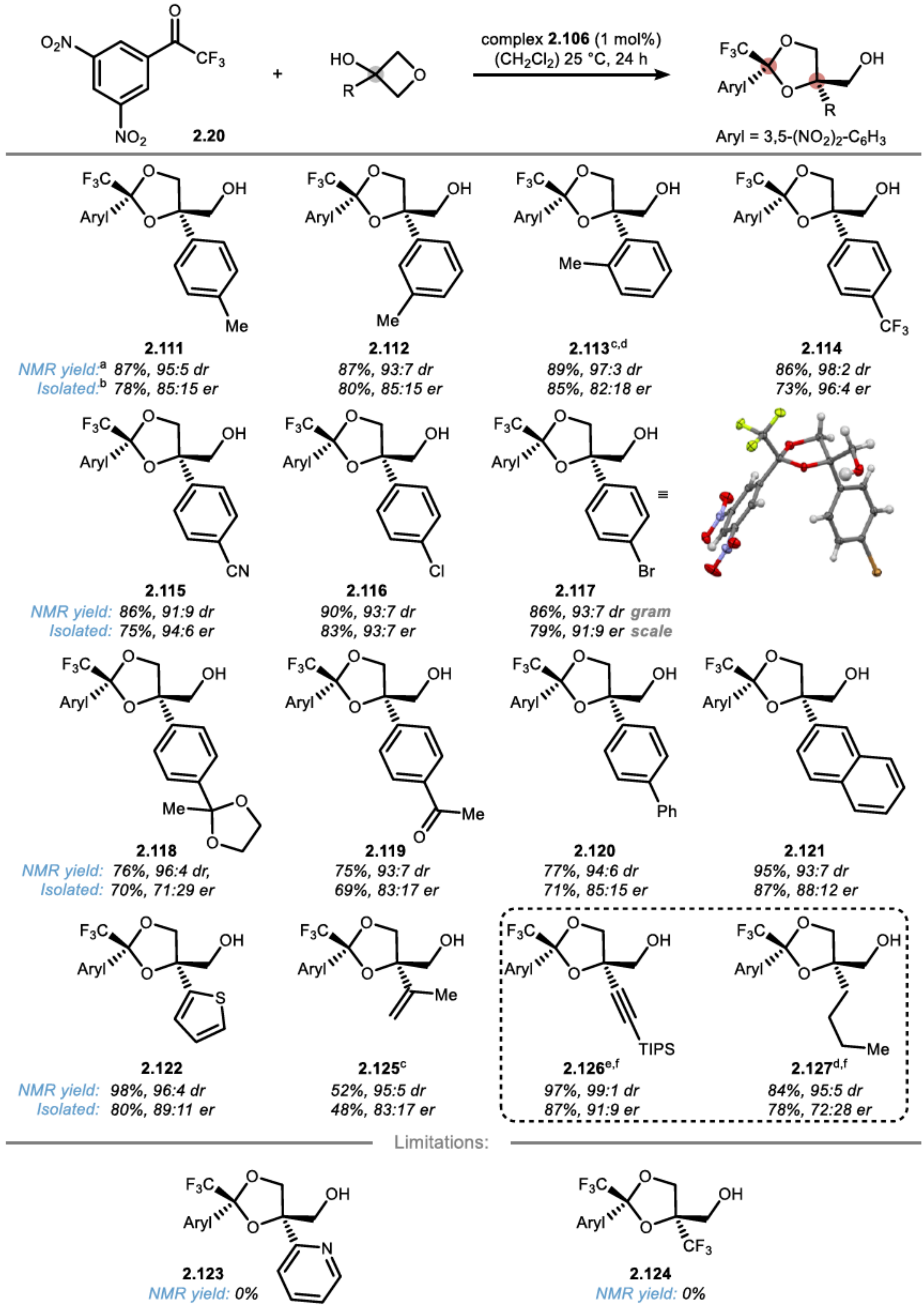
2.5 Scope

With optimised conditions in hand, a study on the applicability of the presented method was performed. On that account, Co^{II}·salen complex **2.106**, prepared by [redacted] was utilised in combination with trifluoroacetophenone **2.20** and the prepared oxetanols **2.38** to **2.56**. In this project, mainly *sp*^{2}-substituted oxetanols, different activated ketones and the limitations of the desired transformation were investigated.

A variety of substituted 1,3-dioxolanes were prepared with the optimised conditions (Scheme 35). For instance, tolyl substituted dioxolanes **2.111** to **2.113** were isolated in high yields. The observed diastereo- and enantioselectivites were comparably high and little to no negative effect of the increasing steric demand from *p*-tolyl over *m*-tolyl to *o*-tolyl substituted dioxolanes **2.111** to **2.113** was noted. From the *sp*^{2}-substituted oxetanols, the electron-poor trifluoromethylated dioxolane **2.114** was prepared with the highest sterocontrol with 98:2 *dr* and 96:4 *er*, respectively. Further, dioxolanes with other electron-withdrawing substituents such as nitril substituted dioxolane **2.115**, or halogenated dioxolanes **2.116** and **2.117** were synthesised. It was moreover possible to obtain dioxolane **2.117** in a gram scale synthesis. The molecular structure of bromo substituted dioxolane **2.117** was resolved *via* X-ray diffraction (CCDC 2141905). It was further possible to determine the absolute configuration of the two formed stereogenic centres by the same means. Accordingly, the structures of the remaining dioxolanes are represented likewise. Although comparably yielding, the protected ketone substituted dioxolane **2.118** was synthesised with a lower enantiomeric ratio in comparison to its unprotected counterpart **2.119**. The scope of arene substituted dioxolanes was further expanded to other aromatic systems such as biaromatic **2.120**, naphthyl substituted dioxolane **2.121**, or heteroaromatic

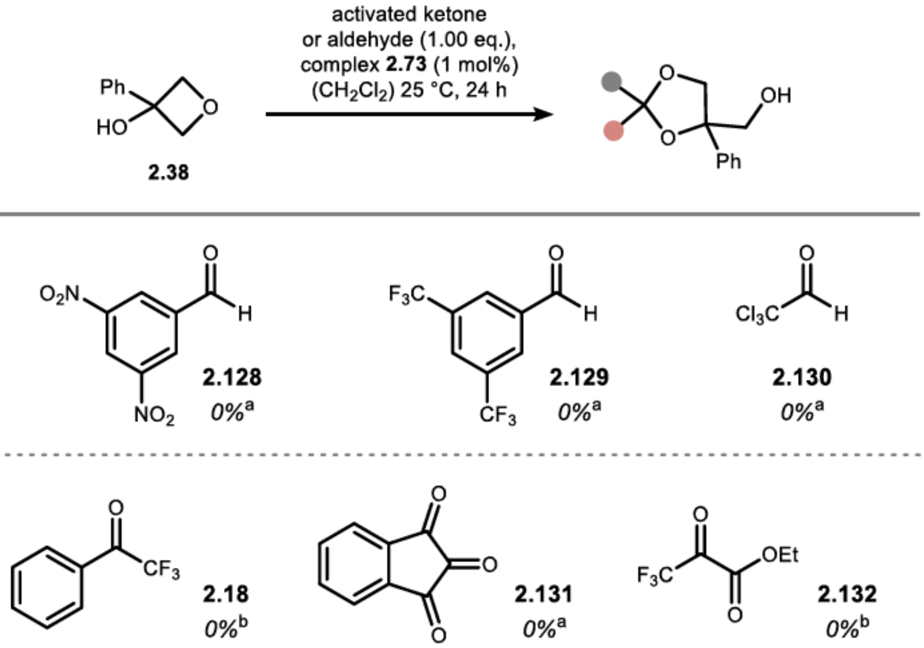
2.122, whereas pyridine substituted dioxolane **2.123** was not accessible. Supposedly, the pyridine ring is coordinating as an additional ligand to the cobalt centre consequently obstructing the hemi ketal to interact with the cobalt catalyst. The presented method is further limited as the trifluoromethyl substituted dioxolane **2.124** could not be prepared. Certainly, alkene substituted dioxolane **2.125** was formed with a medium yield of 52% albeit with comparable diastereo- and enantioselectivity to arene substituted dioxolanes.

The scope of the reaction was further studied by [redacted] thereby alkyne or alkyl substituted 1,3-dioxolanes were prepared with yields up to 97%. High degrees of enantio and diastereoselectivity of up to 92:8 *er* and 99:1 *dr* were achieved for those substrates. Alkyne and alkyl substituted dioxolanes **2.126** and **2.127** are shown exemplarily (Scheme 35). Thereby, it was shown, that the established method is as well applicable to *sp*- and *sp*^{3}-substituted oxetanols. The desymmetrisation of oxetanols proceeded with a comparable high degree of enantioselectivity for most of the shown substrates, only reactions with oxetanols with bulky substituents on the arene (see entry for **2.118**) or alkyl substituted oxetanols (see entry for **2.127** provided by [redacted] were less selective. Thus, a π interaction of the oxetanol with the catalyst is indicated, assisting the enantioselective ring-opening/ring-closing sequence.



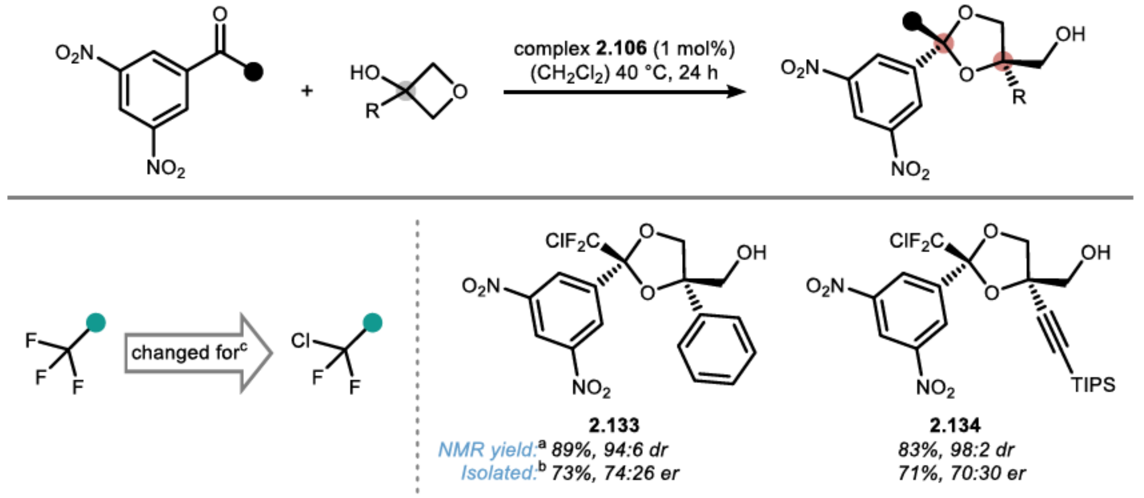
Scheme 35: Scope of the desymmetrisation of prochiral oxetanols. Reactions were run in CH_2Cl_2 [0.2 M] on a 0.2 mmol scale. [a] NMR yield and diastereomeric ratios were determined by ^{19}F NMR analysis of the crude reaction mixture using either trifluorotoluene or fluorobenzene as an internal standard. [b] Isolated yield and enantiomeric ratio correspond to the major isomer only, *er was* determined *via* HPLC using chiral stationary phases. [c] Oxetanol was prepared by [redacted] [d] Reactions were run at 40 °C instead of 25 °C. [e] Reactions run with catalyst 2.78 instead of 2.106. [f] Reactions were performed by [redacted] Molecular structure of 2.117 determined *via* x-ray diffraction, thermal ellipsoids are depicted at 50% probability. CCDC 2141905.

It was further investigated whether other electrophilic ketones could be used for the synthesis of dioxolanes through desymmetrisation of 3-oxetanols. In addition to the optimised trifluoroacetophenone (*cf.* Chapter 2.3.1), other activated ketones and aldehydes were applied to the established reaction conditions. Neither aldehydes **2.128** to **2.130**, nor electron deficient ketones **2.18**, **2.131** and **2.132** were reactive in the envisaged synthesis of substituted 1,3-dioxolanes from 3-oxetanols (Scheme 36). Consequently, the crucial role of the notably electron-poor trifluoroacetophenone **2.20** was further underpinned.



Scheme 36: Limitations for the synthesis of dioxolanes based on activated carbonyl compounds. Reactions were run in CH_2Cl_2 [0.2 M] on a 0.1 mmol scale. [a] Yield based on ^{1}H NMR experiments using mesitylene as internal standard. [b] Yield based on ^{19}F NMR experiments using trifluorotoluene as internal standard.

Certainly, by only marginally amending the optimised acetophenone **2.20**, the reactivity towards formation of dioxolanes from oxetanols was preserved. Therefore, the trifluoromethyl group was slightly altered by exchanging one fluorine for a chlorine atom. The corresponding chlorodifluoro-acetophenone was prepared by [redacted] Applying the otherwise unchanged optimal conditions, gave access to the *sp*- and *sp*^{2}-substituted dioxolanes **2.133** and **2.134** with high yields and diastereoselectivities (Scheme 37). However, the reaction with both oxetanols proceeded less selective in terms of enantioselectivity compared to the reaction with 3',5'-dinitro-trifluoroacetophenone **2.20** (*cf.* Scheme 35) most likely due to the increased steric size of the perhalogenated methyl group which hampers enantiofacial discrimination during the DKR.

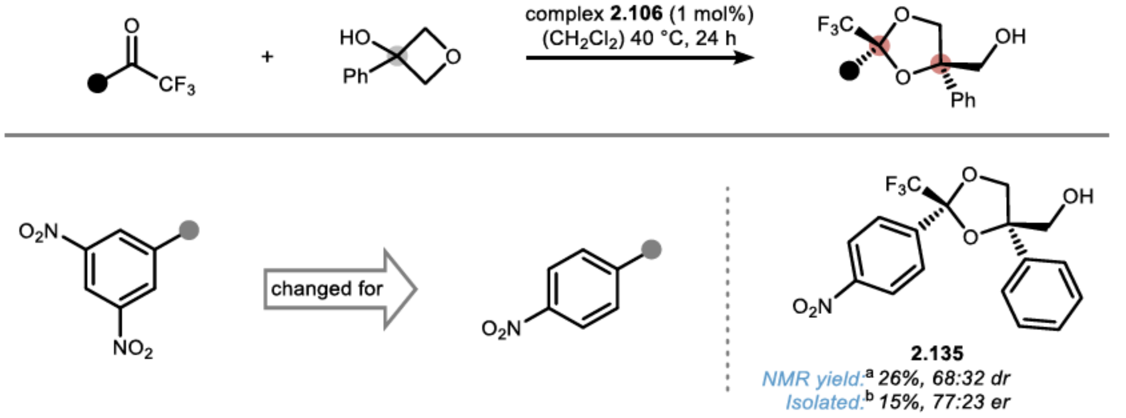


2.133
NMR yield:[a] 89%, 94:6 dr
Isolated:[b] 73%, 74:26 er

2.134
83%, 98:2 dr
71%, 70:30 er

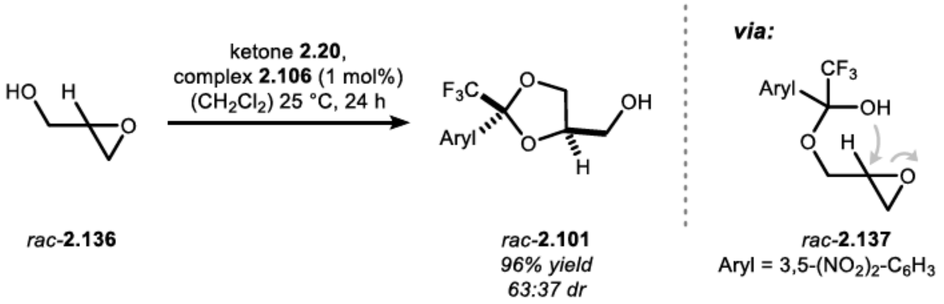
Scheme 37: Cobalt catalysed desymmetrisation of 3-oxetanols with chlorodifluoromethylated ketone. Reactions were run in CH_2Cl_2 [0.2 M] on a 0.2 mmol scale. [a] NMR yield and diastereomeric ratios were determined by ^{19}F NMR analysis of the crude reaction mixture using either trifluorotoluene as an internal standard. [b] Isolated yield and enantiomeric ratio correspond to the major isomer only, *er was* determined *via* HPLC using chiral stationary phases. [c] Applied chlorodifluoro-acetophenone derivative was prepared by [redacted]

Furthermore, 4-nitro-trifluoroacetophenone **2.22** was employed in the cobalt catalysed desymmetrisation of oxetanols affording 1,3-dioxolane **2.135** with low yields and poor stereocontrol (Scheme 38). As elaborated above, the interplay of the formed hemi ketals with the catalysts is depending on their acidity. Removing one nitro group clearly influences the electronic properties of the hemi ketal, hence lowering its acidity and decreasing the interdependencies with the chiral catalyst resulting in lower yields and enantiocontrol.



Scheme 38: Cobalt catalysed desymmetrisation of 3-oxetanols with 4-nitro-trifluoroacetophenone 2.22. Reaction was run in CH_2Cl_2 [0.2 M] on a 0.2 mmol scale. [a] NMR yield and diastereomeric ratios were determined by ^{19}F NMR analysis of the crude reaction mixture using trifluorotoluene as an internal standard. [d] Isolated yield and enantiomeric ratio correspond to the major isomer only, *er* was determined *via* HPLC using chiral stationary phases.

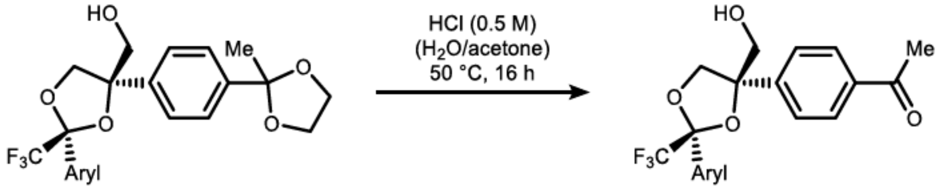
It was further surveyed if the preparation of oxygen heterocycles by a ring-closing ring-opening sequence is possible when different cyclic ethers were used as a platform. As smaller rings are estimated to provide alike enthalpic driving force through ring strain release, oxirane **2.136** was applied to the otherwise unchanged optimal conditions. Again, a 1,3-dioxolane was prepared *via* nucleophilic ring-opening of a transient hemi ketal **2.137** (Scheme 39). The formation of dioxolane **2.101** was high yielding albeit with low diastereoselectivity. The ring-opening of oxirane **2.136** was not proceeding enantioselectively and therefore racemic product was obtained, presumably because of the fast reaction rate which impedes a successful DKR.



Scheme 39: Preparation of dioxolane 2.101 using oxirane *rac*-2.136 as a platform. Reaction was run in CH_2Cl_2 [0.2 M] on a 0.2 mmol scale [a] Diastereomeric ratio was determined by ^{19}F NMR analysis of the crude reaction mixture.

2.6 Further transformations with 1,3-dioxolanes

The 1,3-dioxolanes obtained after desymmetrisation of 3-oxetanols can moreover be used as starting materials for further reactions. The dioxolane **2.118** consists of two protected ketones, one is the ketal of the trifluoroacetophenone **2.20** and one stems from the oxetanol **2.51**, which was used for the desymmetrisation in the first place. It was therefore investigated whether the ketals could be cleaved under acidic conditions. A chemoselective deprotection was achieved and the ketone **2.119** was formed under conservation of the stereogenic centres keeping the core dioxolane ring intact only deprotecting the latter ketone (Scheme 40).



2.118, Aryl = 3,5-$(NO_2)_2$-C_6H_3
71:29 er

2.119, Aryl = 3,5-$(NO_2)_2$-C_6H_3
94% yield
69:31 er

Scheme 40: Chemoselective hydrolysis of dioxolane 2.118, *er* was determined *via* HPLC using chiral stationary phases.

On the other hand, attempts to cleave the core dioxolane ring of cyclic ether **2.117** by hydrolysis under either acid or base catalysis were not fruitful (Table 6, entries 1 to 8). When extremely basic conditions were applied in an alcoholic solvent, NMR analysis of the crude reaction mixture implies a nucleophilic aromatic substitution of one nitro group for a methoxy group (entry 6). Common nucleophiles for the ring-opening of cyclic ethers were tried next but failed to deliver the substituted open chain product (entries 9 to 12). Furthermore, reductive and oxidative conditions were applied to either the silyl protected dioxolane **2.138** or unprotected dioxolane **2.117** without affecting the heterocyclic core. Effectively, either the nitro groups were reduced or the silyl protecting group was cleaved off under these conditions (entries 13 to 21). Additionally, a photochemical method for the cleavage of the aromatic ketone was employed but no deprotected triol was observed. Despite the multitude of varying conditions applied, the desired cleavage of the ketal was not observed throughout this study.

Table 6: Attempts for the cleavage of the prepared 1,3-dioxolanes to release open chain triol derived structures.

2.117, R = H
2.138, R = TIPS

X = OH,...

Entry		Conditions	Yield
1	hydrolytic	PPTS (20 mol%), (MeOH) rt ,17 h	0%
2		pTsOH (20 mol%), (MeOH) rt, 17 h	0%
3		HCl aq. (1N), (MeOH) rt, 17 h	0%
4		HCl aq. (6N), (MeOH) 60 °C, 4 h	0%
5		TfOH (1.00 eq.), (TFA) rt, 17h	0%
6		KOH aq. (2N), (MeOH) 60°C, 17 h	0%
7		KOH aq. (2N), (THF) 60°C, 17 h	0%
8		BBr_3 (6.00 eq.), (CH_2Cl_2) rt. 17 h	0%
9	nucleophilic	benzo[d]thiazole-2-thiol (2.00 eq.), $BF_3 \cdot OEt_2$ (1.00 eq.) (DCE), 60°C, 17 h	0%
10		EtSH (10.0 eq.), NaOMe (10.0 eq.), (PhMe) 80 °C, 16 h	0%
11		CH_2=CHMgBr (2.00 eq.), (THF) 0°C to rt, 17 h	0%
12		TMSI (1.00 eq.), (CH_2Cl_2) rt, 17 h	0%
13	reductive	Pd/C (5 mol%), H_2, (MeOH) rt, 1 h	0%
14		$LiBHEt_3$, (1.00 eq.), (THF) –20 °C to rt, 20 h	0%
15		DIBAL-H (4.00 eq.), (CH_2Cl_2) rt, 16 h	0%
16	oxidative	$[NH_4]_2[Ce(NO_3)_6]$ (1.00 eq.), (MeCN:H_2O, 1:1) rt, 17 h	0%
17		$RuCl_3 \cdot H_2O$ (0.20 eq.), $NaIO_4$ (4.00 eq.), (MeCN:H_2O:CCl_4, 1:1.5:1) 40 °C, 3d	0%
18		Cumene hydroperoxide (1.00 eq.), KO*t*Bu (9.00 eq.), (CH_2Cl_2) reflux, 24 h	0%
19		$K_3[Fe(CN)_6)]$ (10.0 eq.), ($NaHCO_3$ aq. sat.) 100 °C, 24 h	0%
20		$K_3[Fe(CN)_6)]$ (10.0 eq.), (NaOH aq., 2N) 100 °C, 24 h	0%
21		Mn_2O_7 (2.00 eq.), (EtOAc:CCl_4, 1:1) –40 °C, 30 min	0%
22	photo-chemical	*hν* (254 nm), (MeCN:H_2O, 95:5) rt, 16 h	0%

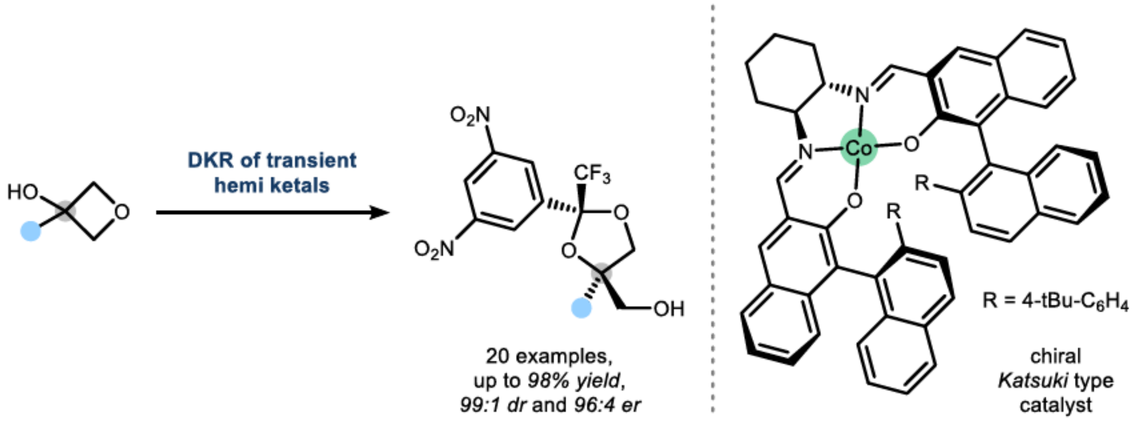
TFA = trifluoroacetic acid, EtOAc = ethyl acetate.

2.7 Summary and outlook

Throughout this project, a method for the synthesis of *O*-heterocycles, namely 1,3-dioxolanes, by DKR of transiently formed hemi ketals was established in cooperation with [redacted][82] Therefore, a variety of electron deficient ketones was prepared and employed in a thorough analysis of the hemi ketal formation with *n*-pentanol as a model substrate, revealing a strong correlation between the electronic nature of the ketone and the hemi ketal/ketone equilibrium which was visualised by a linear free-energy correlation to the *Hammett* parameters. Thereby, the strongly electrophilic 3',5'-dinitro trifluoroacetophenone **2.20** was assigned as an ideal reagent to form hemi-ketals. It was furthermore possible to determine the molecular structure of a stable acyclic hemi ketal by X-ray analysis (**2.96**, CCDC 2130260).

After an initial proof of concept for the intramolecular ring-closing and ring-opening of oxetanols with transient hemi ketals, a careful optimisation of the employed catalysts was undertaken, resulting in the identification of *Katsuki*-type Co^{II}·salen complexes as active catalysts providing high yields in combination with high diastereo- and enantioselectivity. Moreover, the underlying mechanistic background of the overall transformation was elucidated by the synthesis and use of tethered hydroxy oxetanes which indicated an activation of the nucleophile through interaction with the employed Co^{II} complexes to be necessary for a successful ring-closing and ring-opening sequence. The corresponding activation mode was disclosed by oxidising Co^{II}·salen complexes with acidic groups resembling the transiently formed hemi ketals. Thus, a mechanistic picture was provided for the desymmetristion of 3-oxetanols by cobalt catalysed DKR. A variety of 3-oxetanols with sterically and electronically differing aromatic and aliphatic groups was prepared and subsequently used in the established method for the DKR to yield 1,3-dioxolanes.

Generally, high conversion of the starting material for arene substituted oxetanols was observed with yields of the two formed diastereoisomers from 75 to 98% with diasteroselectivities of up to 91:9 *dr* and 96:4 *er* (*cf.* Chapter 2.5, Scheme 35 and Scheme 41). The relative configuration of the synthesised dioxolanes was ascertained by nuclear *Overhauser* effect spectroscopy (NOESY) experiments. Furthermore, it was feasible to determine the molecular structure and absolute configuration of dioxolane **2.117** *via* X-ray diffraction (CCDC 2141905).



20 examples,
up to *98% yield*,
99:1 dr and *96:4 er*

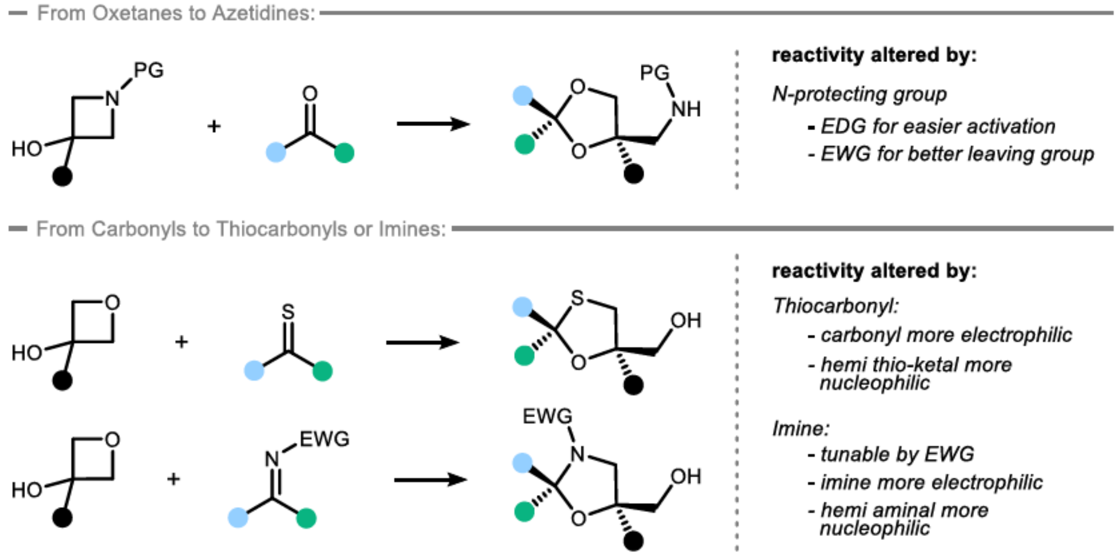
chiral
Katsuki type
catalyst

Scheme 41: Synthesis of 1,3-dioxolanes *via* dynamic kinetic resolution of transient hemi ketals.

Comparing the achieved enantioselectivities of arene substituted oxetanols with alkyl substituted starting materials indicates π interactions assisting a productive DKR. This hypothesis is further underlined by the results of glycidol **2.136** which only delivered the desired product as a racemic mixture. Furthermore, it was shown that a successful DKR crucially depends on the interplay of the hemi ketal with the catalyst. Increasing the hemi ketals steric demand through substituting the trifluoromethyl group or decreasing the acidity by removing a nitro group from the acetophenone impedes the DKR. Moreover, offering a strongly donating group, as in the case of pyridyl substituted oxetane, completely obstructs the reaction.

The presented desymmetrisation of 3-oxetanols delivered surprisingly stable cyclic ketals of 1,2,3-triols. The chemical stability of this heterocycle seems to hamper the potential of the presented method if the focus lies only on the preparation of 1,2,3-triolic structures. Nevertheless, if a wider field of applications is taken in regard, the presented method for the synthesis of stable trifluoromethylated dioxolanes might offer new opportunities in the context of medicinal chemistry, hence the stereocontrolled synthesis of fluorinated molecules is a major field for research especially in drug discovery.[83] Additionally, acetals or ketals stable towards hydrolysis under acidic conditions are important motifs in oral drug development as outlined by *Wu* and *Meanwell*.[84]

To further broaden the applicability of the developed method, there are two major handles that either simplify the ring-opening or enabling the cleavage of the formed heterocycles (Scheme 42).



Scheme 42: Outline for possible heterocycle syntheses based on the DKR of 3-oxetanols presented in this project.

Firstly, the substrates could be varied from oxetanols to azetidines. Hence, these *N*-heterocycles are similar strained, a ring-opening seems thermodynamically plausible. In addition to that, the attached functional groups on the nitrogen atom can be used to alter the reactivity of the heterocycle. Electron-donating groups are supposed to facilitate the activation for ring-opening reactions as they increase the donor abilities of the heteroatom, whereas electron-withdrawing groups increase the leaving group ability of the amine leaving group. Secondly, the carbonyl compound could be changed to either thiocarbonyls or imines. The tendency for hemi ketal formation is either intrinsically higher or tuneable by the protecting groups of the imine. In both cases, the transient species formed after nucleophilic attack of an alcohol, namely the hemi thioketal or hemi aminal, are more nucleophilic than their *O*-analogues, thus increasing the reactivity towards ring-opening forming *S*,*O*- and *N*,*O*-heterocycles. These heterocycles might offer new opportunities for their cleavage to yield 1,2,3-functionalised chiral open chain products.

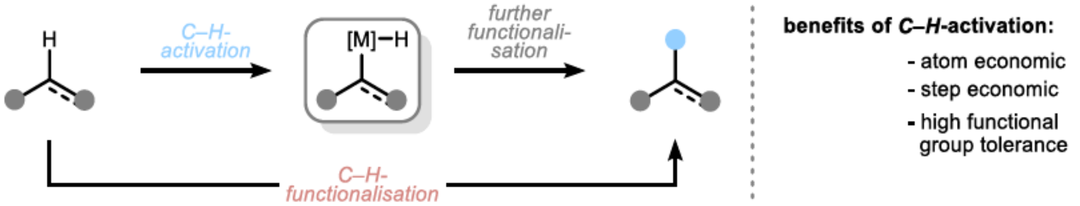
3 Acyclic alcohols as platform for the synthesis of oxygen rich heterocycles

3.1 Introduction

3.1.1 *C–H* activation as a tool in organic chemistry

One of the common approaches for intramolecular ring-closing reactions in heterocycle synthesis necessitates a leaving group to be present in the molecule. Classical examples of leaving groups include halogen atoms and functionalised alcohols, such as tosylates, showcased in the ring-closing reaction towards oxetane **1.7** (*cf.* Chapter 1.2, Scheme 3). Furthermore, halonium ions can act as pseudo leaving groups in alkene difunctionalisations such as iodolactonisations.[85] Other prominent ring-closing reactions with alkenes proceed through activation of the π-bonds with transition metal complexes in intramolecular nucleopalladations or *Wacker*-type cyclisations.[86] To circumvent the prerequisite of such highly functionalised starting materials, a plethora of methods for the direct functionalisation of "inert" *C–H* bonds were developed,[87] and came to maturity including electrochemical, photochemical, enzymatic or transition metal catalysed processes.[88] In this context, a concise terminology for the overall transformation was established in the literature.[89]

Whereas the term *C–H* activation should strictly be used for a specific mechanistic step including the cleavage of a *C–H* bond ensuing in a newly formed carbon-metal bond, the term *C–H* functionalisation, on the contrary, can be applied in a much wider sense. Thereby, the whole process of exchanging a *C–H* bond by another functional group or element, commonly including a *C–H* activation combined with a subsequent functionalisation, is defined as a *C–H* functionalisation (Scheme 43). Henceforth, reactions of *C–H* bonds are categorised *as per* the definitions provided herein.



Scheme 43: General scheme of a *C–H* activation reaction with subsequent functionalisation.

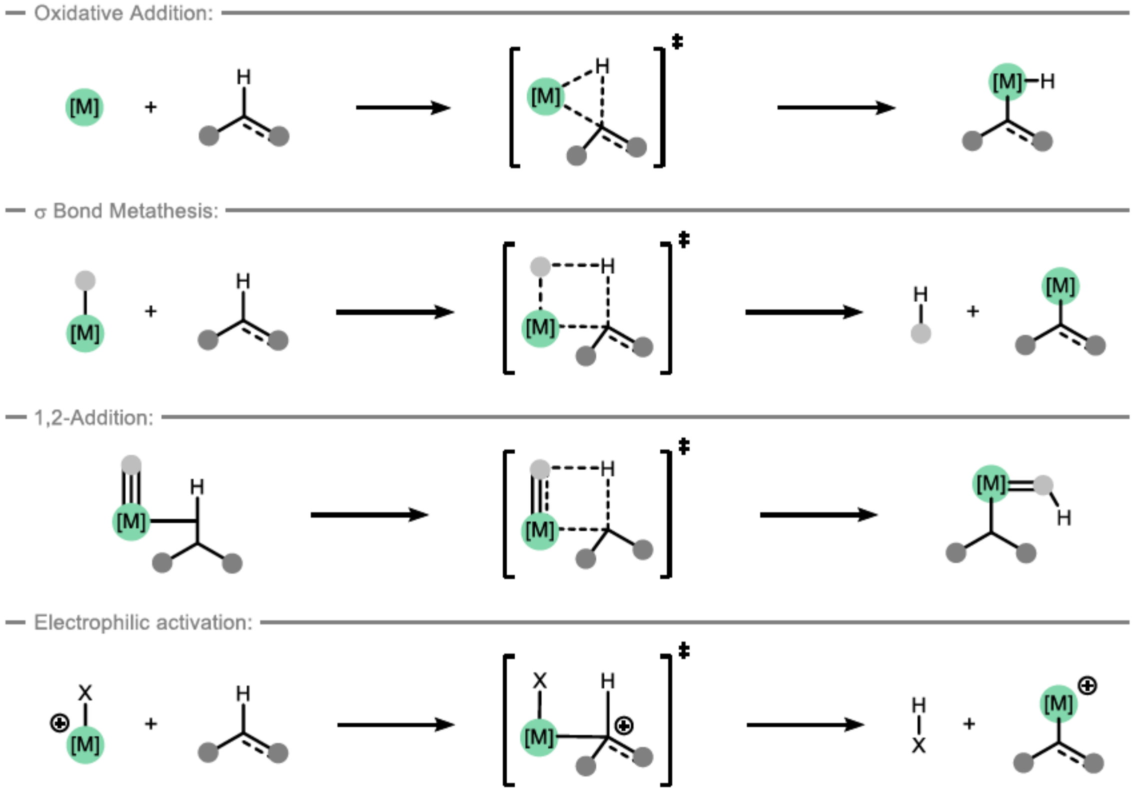
The direct functionalisation of a *C–H* bond, in contrast to classical methods like functional group interconversions, comes along with beneficial properties such as higher atom and step economy. Moreover, high functional group tolerance is typically achieved under the commonly applied reaction conditions.[90] Accordingly, *C–H*-activation and further functionalisation has become a relevant tool in organic synthesis, especially in late stage functionalisation or the modification of complex molecules.[88h,91]

A manifold of different metals have shown reactivity towards activation and further functionalisation of *C–H* bonds of both aliphatic and aromatic carbon centres.[92] Nonetheless, palladium has a pivotal role among the transition metals and is widely used in *C–H*-activation reactions.[91e,93] Therefore, the following discussion is mainly focussed on palladium catalysed reactions, whereas the reactivity of other transition metals such as iron or nickel will not be further elaborated. Detailed information thereof can be found elsewhere.[94]

3.1.2 Mechanistic background for *C–H* activation and functionalisation

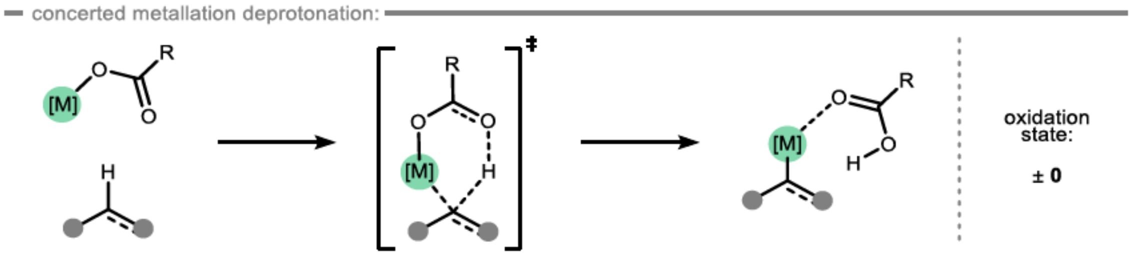
With the terminology fixed, the domain of *C–H* activation can now further be explored. Prior to the formation of the metalated carbon species, mainly two types of interdependencies set the stage for an effective *C–H* activation, *viz.*, agostic or σ-interaction.[95] Both proceed in a way that electron density from the σ_{C-H} bond is donated to empty *d* orbitals of the transition metal, thereby stabilising high energy metal species, weakening the *C–H* bond and facilitating the bond cleavage. Apart from the underlying similar electronic principles, the both differ in the connectivity of the molecules entering the interplay. In agostic complexes other primary metal-ligand interactions keep the *C–H* bond in a fixed position in the coordination sphere of the transition metal.[96] Thus, agostic interactions are considered intramolecular processes, whereas σ- interactions are intermolecular.[95]

For the subsequent mechanistic steps, which are subsumed as the concrete *C–H* activation, four main pathways are described in the literature, including σ-bond metathesis, oxidative addition, 1,2 additions, and electrophilic reactions (Scheme 44).[89,97] The four different pathways will be addressed briefly with a focus on the electrophilic activation mode.



Scheme 44: General scheme of the four major mechanistic pathways for *C–H* activation. [M] = Generic metal complex.

Typically, oxidative additions of *C–H* bonds through a three membered transition state occur with electron-rich late transition metals, although recent computational studies indicate this mechanism being active with certain electron-poor metal systems as well.[98] Usually, σ-bond metathesis is the active reaction mode with early transition metals or lanthanides on the one side, which are bound to hydrocarbyl or main group species, and a hydrocarbon on the other side proceeding through a four-membered transition state.[99] A similar four-membered transition state is reached in 1,2-additions. Therefore, early transition metal alkylidine, alkylidyne or imido complexes engage in strong σ-complexes with alkanes. After initial complexation, the alkyl *C–H* bond is weakened by a $\pi_{\mathrm{M-R}} - \sigma^*_{\mathrm{C-H}}$-interaction to such an extent, that the alkyl's hydrogen atom is subsequently transferred to the π-bonded substituent at the same time as the alkyl group to the metal centre.[100] Electrophilic activation of *C–H* bonds is the fourth major mechanistic pathway for *C–H* activation commonly observed with electropositive late transition metals, hence rendering this mode most relevant for the majority of palladium catalysed reactions. The general requirement for this mode is the presence of a neighbouring heteroatom next to the metal centre which can abstract the proton from the carbon group through interaction with its lone pair while traversing the transition state. In the literature, a whole mechanistic continuum from electrophilic substitution to concerted metalation is classified as electrophilic *C–H* activation.[101] From the set of possible electrophilic mechanisms, ambiphilic metal ligand activation (AMLA)[102] and concerted metalation deprotonation (CMD)[103] can arguably be considered as the most important for applications in late stage functionalisations. The both have the base assisted cleavage of a *C–H* bond as a common key feature, whereas the differences of both mechanisms are of a mere subtle nature. The two pathways mainly differ in the amount of transition states during the reaction, since the concerted metalation proceeds *via* a single transition state and the AMLA reaction requires two transition states.[104] However, the further discussion is centred around the CMD mechanism (Scheme 45).



Scheme 45: Mechanistic picture of a *C–H* activation *via* concerted metalation deprotonation.

Commonly, weak bases such as carboxylates, phosphates or carbonates are effective in CMD mechanisms. The apparent contradiction between the *C–H* bond acidity and the basicity of the applied bases can be resolved by reconsidering the initial σ-interactions. Hence, the acidity of the σ-complex is increased due to the primary attenuation of the *C–H* bond strength. Furthermore, no isolated deprotonation step is implied in a concerted mechanism, therefore the native *C–H* acidities are of only minor relevance. The deprotonation itself can conceivably proceed either intramolecularly or intermolecularly. Nevertheless, theoretical studies indicate, that the intramolecular concerted deprotonation metalation through a six-membered transition state with the base being coordinated to the metal centre is thermodynamically favoured.[105] Usually, the protonated base is only weakly coordinating, thus rapidly dissociating from the metal centre after the CMD step. Thereby, the coordination number of the metal centre is maintained after the overall activation. When proceeding through a CMD mechanism, the oxidation state of the metal centre throughout *C–H* activation will likewise stay unchanged.

In general, *C–H* functionalisations can be divided into non-directed and directed approaches.[106] Whereas undirected approaches often follow the “innate” reactivity dominated by the diverging bond strengths and electronic properties of different *C–H* bonds in a molecular skeleton,[107] installing a directing group, on the other hand, often overrides the innate reactivity. Furthermore, control over regio- or site-selectivity in aromatic or aliphatic *C–H* functionalisations can be gained by following a directing group approach.[108] Directing effects are attributed to either sterically demanding substituents, thereby decreasing the accessibility of certain *C–H* bonds in a molecule, or by substituents binding to the metal centre, thus locating the transition metal in a fixed position and allowing selective activation of *C–H* bonds. These diverging effects can be illustrated with the different approaches to control the active sites in the *C–H* activation of arenes (Figure 12). For instance, the *ortho* position, with respect to the directing group, of an arene can either be blocked through detrimental steric interactions or exposed for activation due to binding of the metal.

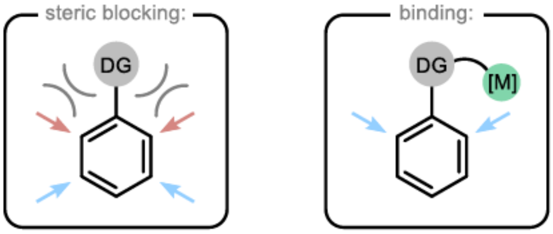
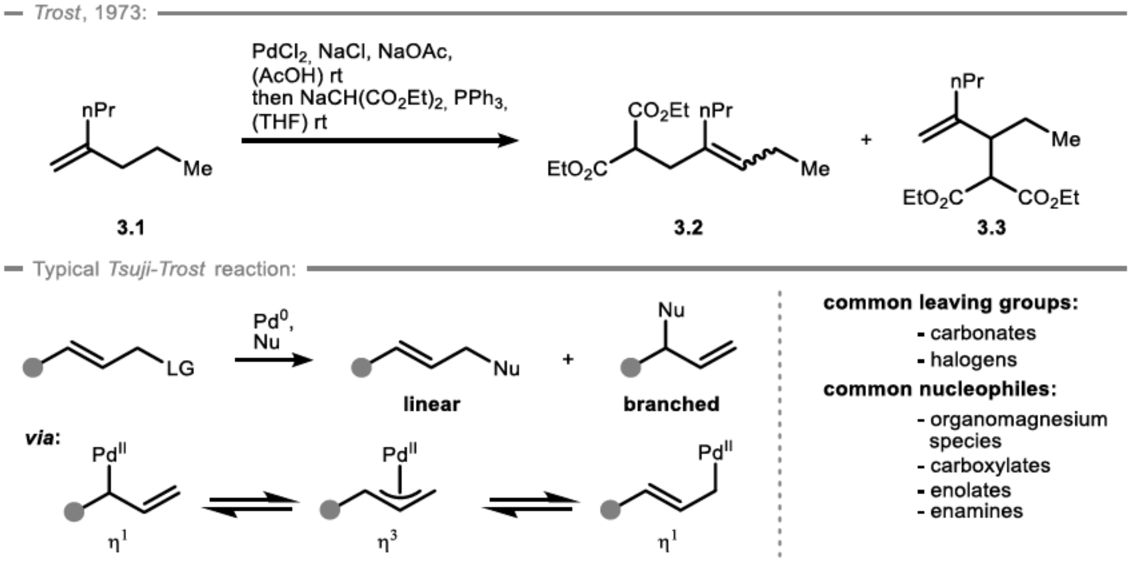


Figure 12: Principal directing group effects exemplified for *C–H* activation with arenes.

A more recent approach is the use of transient directing groups,[109] whereas commonly covalently bound groups such as carboxylic acids, amides or *N*-heteroaromatics have been used as directing groups.[110] Typical transient directing groups on the other hand are *in situ* formed imines,[111] or norbornene in the *Catellani* reaction and related transformations.[112] The former group has a directing effect by its intrinsic reactivity as a *Lewis* base. Furthermore, through *Schiff* base condensation additional functional groups acting as directing groups can be attached to the molecule. The latter directing group norbornene is inserting in existing carbon-metal bonds thereby translocating the metal centre to a different position and making formerly inaccessible *C–H* bonds amenable for activation.

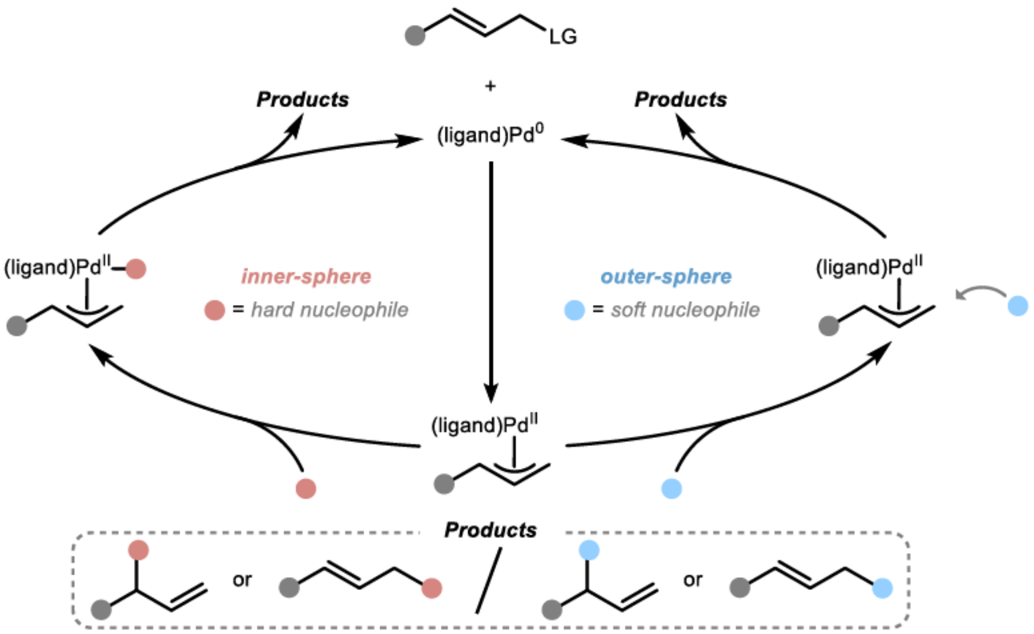
3.1.3 Palladium catalysed allylic *C–H*-oxidation

In *C–H* activation chemistry, a directing group, although frequently applied, is not a mandatory prerequisite.[113] Indeed it is possible to perform *C–H* activation only favoured by the electronic properties of the respective *C–H* bond and its chemical surrounding.[107] Exemplarily, the functionalisation of allylic positions is remarkably straightforward in contrast to functionalising unactivated C_{sp3}–*H* bonds. In addition to allylic functionalisations relying on selenium, chromium or radical chemistry,[114] palladium complexes are also known to facilitate such functionalisations *via C–H* activation. In fact, what has become the well-known *Tsuji-Trost* reaction was initially reported by *Trost et al.* as an allylic *C–H* activation of the terminal alkene **3.1** with subsequent functionalisation yielding a mixture of alkylated malonates **3.2** and **3.3** (Scheme 46, top).[115] Whilst nowadays, the substitution of an allylic leaving group with a nucleophile under palladium catalysis is typically considered as the *Tsuji-Trost* reaction in the chemical literature (Scheme 46, bottom).[116]



Scheme 46: Top: Seminal example for palladium catalysed allylation by *Trost*. [115] Bottom: Modern conception of the *Tsuji-Trost* reaction. Ac = acetyl, LG = leaving group, Nu = nucleophile.

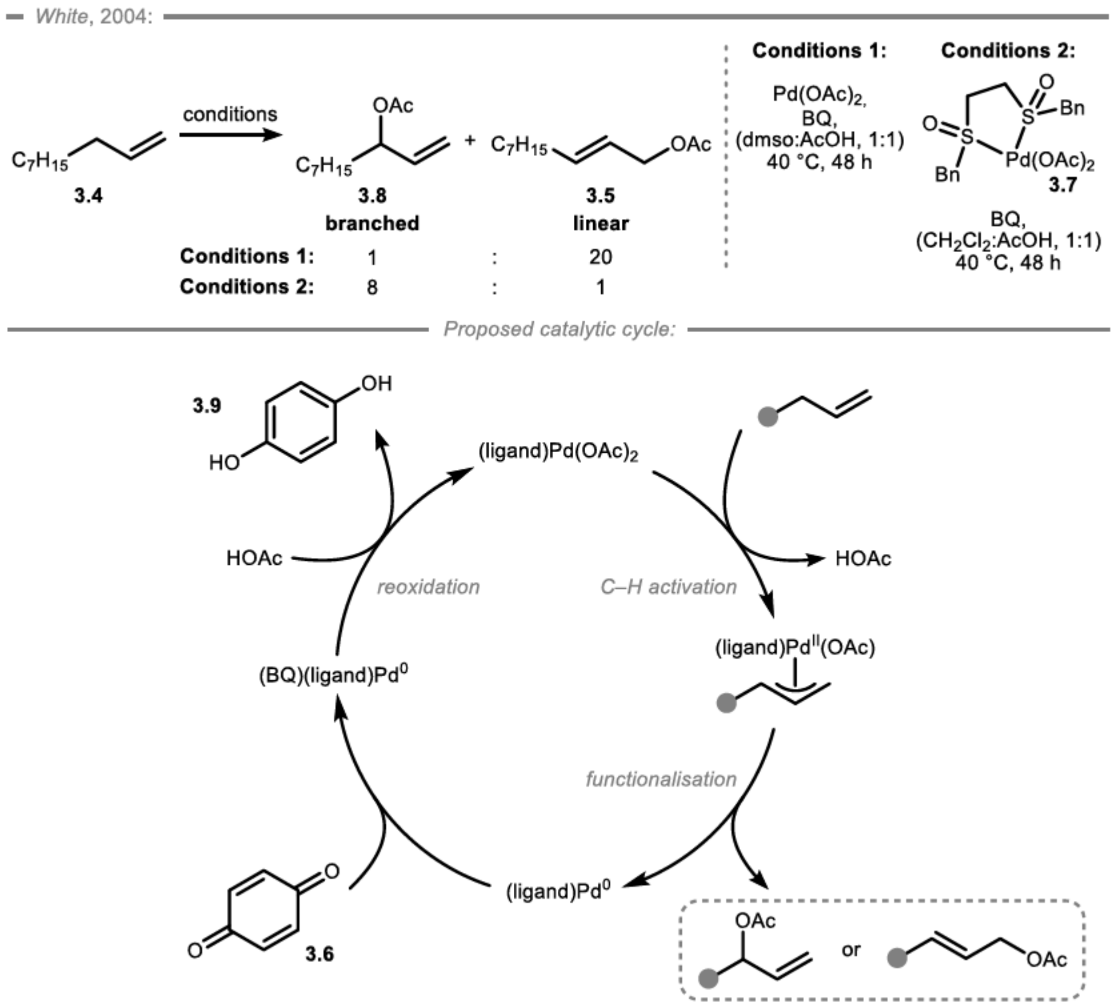
Nevertheless, throughout the archetypical and the contemporary *Tsuji-Trost* type reaction a η^3-palladium complex is formed which acts as the reactive species for further functionalisation with a nucleophile. In general, two modes for the allylic functionalisation can be discriminated depending on the nature of the employed nucleophile. Either the carbon functionalisation is proceeding *via* an inner-sphere mechanism through direct attachment of the nucleophile to the metal centre and subsequent reductive elimination releasing the desired products (Scheme 47, left), or through attacking the allyl unit outside the coordination sphere of the metal (Scheme 47, right). Typically, inner-sphere mechanisms are discussed for hard nucleophiles derived from conjugate acids with pK_a values above 25, whereas outer-sphere mechanisms are predominant for stabilised or soft nucleophiles whose corresponding acids have pK_a values below 25.[116b] It is noteworthy, that both mechanisms deliver a distribution of linear and branched products.



Scheme 47: Simplified graphical representation of the different modes for palladium catalysed allylic functionalisations with hard or soft nucleophiles.

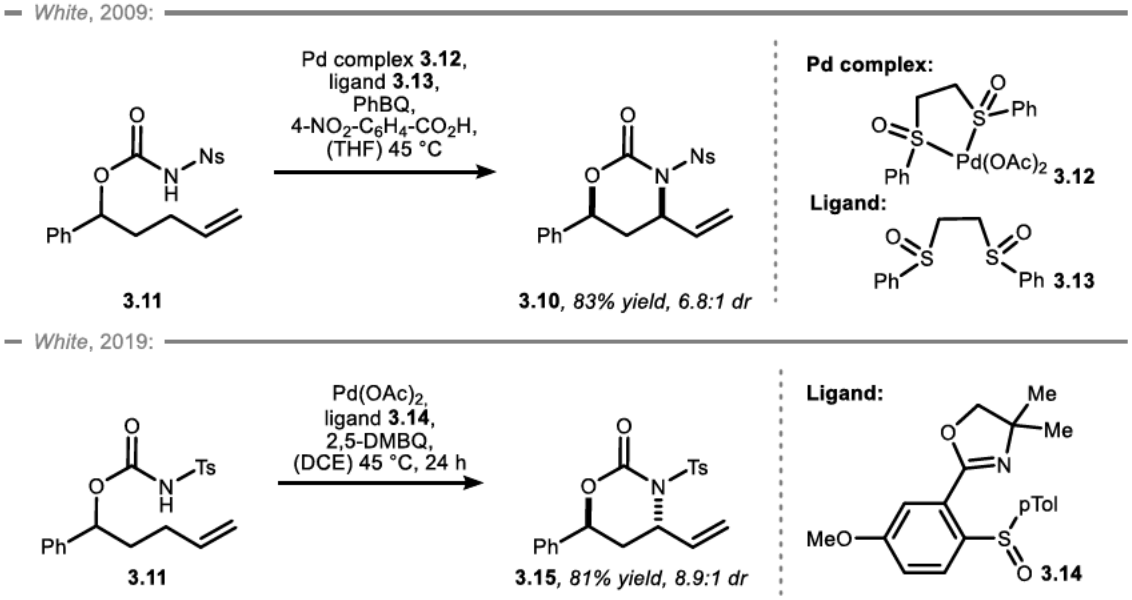
Interestingly, the reactive allyl palladium intermediate has been exploited earlier for allylic *C–H* oxidations as reported by *Hüttel*.[117] In their seminal reports a stoichiometric amount of palladium was necessary for a successful transformation of an allylic *C–H* bond. A drawback, which was overcome by *Haszeldine* and others.[118] Early contributions to the field of allylic oxidations made use of internal alkenes such as cyclopentene.[119] Hence, only branched products were formed in these approaches. On the contrary, if terminal alkenes are applied to the conventional reaction conditions, both linear and branched products are accessible from the internal or external η^1-complexes which are in an equilibrium with the η^3-palladium species (Scheme 46, bottom). Additionally, the *Wacker*-

Tsuji type reaction is a competing side reaction,[120] if terminal alkenes are oxidised as shown by the seminal work of *Rappoport* and *Åkermark*.[121] These synthetic problems were successfully addressed by *White* and coworkers in 2004 (Scheme 48).[122] In their pivotal report, the allylic oxidation of 1-decene **3.4** was feasible yielding selectively the linear product **3.5**. Key to the selective oxidation towards the linear product was the use of dimethyl sulfoxide (dmso) as a solvent additive in combination with 1,4-benzoquinone **3.6** as an oxidant. Applying other conditions with the bidentate sulfoxide ligated palladium complex **3.7** in a solvent mixture consisting out of dichloromethane and acetic acid altered the selectivity and the branched product **3.8** was afforded in a higher amount. The proposed catalytic cycle starts with a *C–H* activation step, likely *via* CMD mechanism, thereby an allyl palladium species is formed (for reasons of clarity only the η^3-palladium species is shown in Scheme 48). Subsequent functionalisation through reductive elimination delivers the desired linear or branched products and is resulting in a Pd^0 species. After association of benzoquinone **3.6**, the palladium catalyst can be reoxidised under acidic conditions, liberating hydroquinone **3.9**.



Scheme 48: Allylic oxidation of a terminal alkene by *White* and coworkers.[122] Bn = benzyl. BQ = 1,4-benzoquinone.

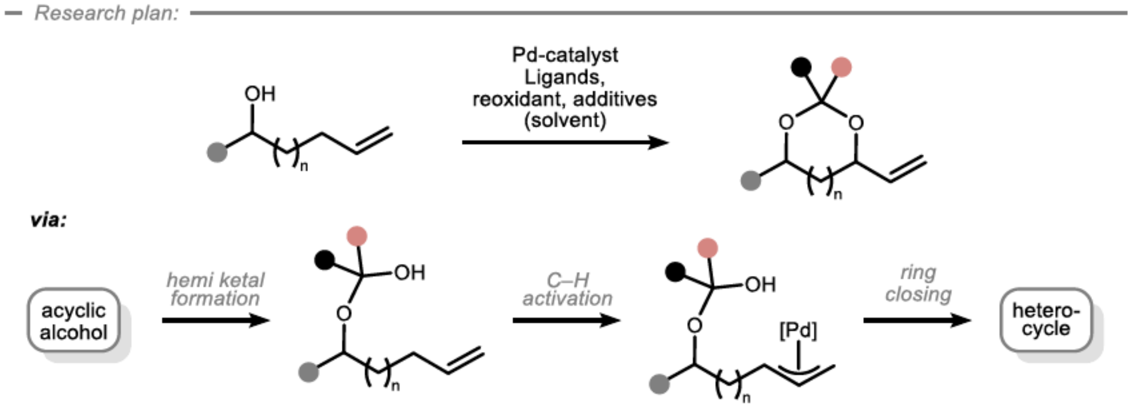
Incited by these fundamental results, a wide field of intermolecular palladium catalysed allylic functionalisations was established.[123] Furthermore, intramolecular cyclisations were equally realised. In a seminal example, a commonly challenging macrolactonisation was feasible.[124] Moreover, varying nucleophiles such as carbamates or benzylic alcohols were applied in intramolecular ring-closing reactions.[125] Thereby, a variety of heterocyclic compounds was prepared, as shown by the preparation of the cyclic *syn* 1,3-aminoalcohol **3.10** starting from carbamate **3.11** with the improved catalyst **3.12** in combination with a slight excess of the bis-sulfoxide ligand **3.13** (Scheme 49, top).[126] By employing the chiral aryl sulfoxide-oxazoline (ArSOX) ligand **3.14** high degrees of diastereoselectivity in the formation of cyclic carbamates such as **3.15** was obtained (Scheme 49, bottom). Interestingly, the selectivity towards either *syn* or *anti* products can be switched by employing electronically differing ArSOX ligands.[127] In general, the outcome of palladium catalysed allylic oxidations is immensely depending on the reaction conditions applied. The choice of the utilised solvents,[122] the benzoquinone reoxidants,[128] the sulfoxide ligands[129], additives, such as *Brønsted* bases and acids,[123f,130] *Lewis* acidic metal complexes[123e] or silver salts,[131] is heavily affecting the reactivity in palladium catalysed *C–H* functionalisations. Therefore, these factors have to be carefully balanced depending on the specific scientific problem to be solved.



Scheme 49: Top: *Syn*-selective formation of cyclic carbamate 3.11 with a bis-sulfoxide ligand.[126] Bottom: *Anti*-selective formation of cyclic carbamate 3.11 with the ArSOX ligand 3.14.[127] Ns = 4-nitrobenzenesulfonyl, PhBQ = 2-phenyl-1,4-benzoquinone, 2,5-DMBQ = 2,5-dimethyl-1,4-benzoquinone, pTol = *p*-tolyl.

3.1.4 Motivation and aim

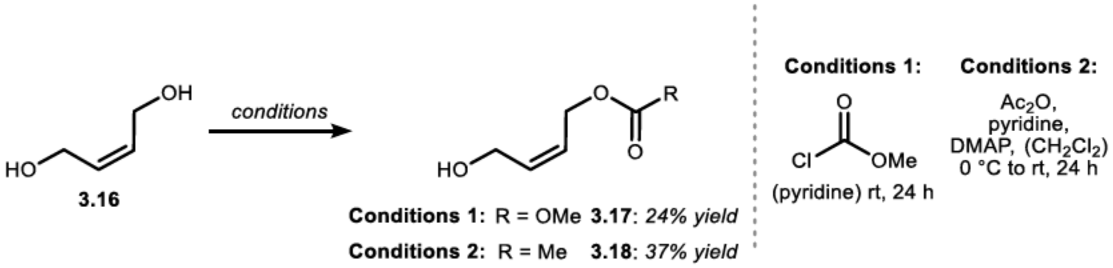
The benchmark publication of *White* and coworkers, concerning the allylic oxidation of terminal alkenes,[122] gave rise to a variety of different approaches for allylic oxidation with several nucleophilic groups being successfully employed. Both, intramolecular and intermolecular nucleophiles were harnessed. Thus, a manifold of different heterocyclic compounds is attainable from simple starting materials. Notwithstanding the achievable structural diversity, commonly applied methods for intramolecular *C–H* oxidation necessitate the formation of the internal nucleophile in an additional synthetic step, thereby decreasing the efficiency of the overall process. For instance, the frequently employed carbamates are formed by treating an alcohol with an isocyanate.[126] Despite the ease of preparing those compounds, the overall step economy is generally negatively affected. To further streamline the preparation of heterocycles from simple aliphatic alcohols, the development of a method deploying a transient nucleophilic group was aimed for in this project. It was envisioned that an *in situ* formed hemiketal can be employed in an allylic *C–H* oxidation yielding *O*-heterocycles through intramolecular cyclisation in a three-step process (Scheme 50). The feasibility of the overall process is substantiated by the existing literature precedent for the application of hemi ketals as internal nucleophiles in *Tsuji-Trost* type allylations.[132]



Scheme 50: Research plan for the formation of *O*-heterocycles through intramolecular *C–H* oxidation.

3.2 Preparation of starting materials

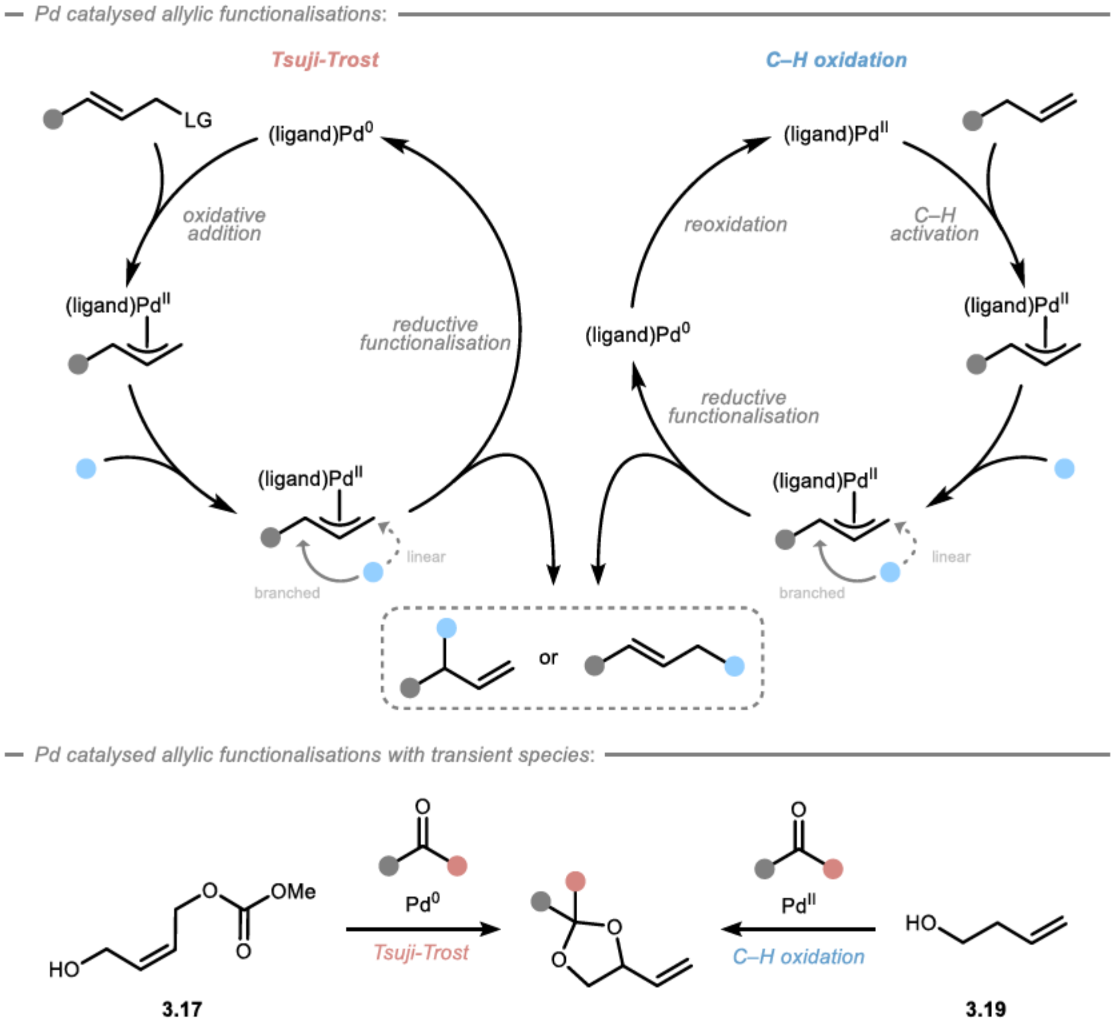
To investigate whether an intramolecular *C–H* oxidation with a transient nucleophile is feasible, allylic alcohols were differently functionalised. Starting from (*Z*)-but-2-ene-1,4-diol **3.16,** allylic carbonate **3.17** and allylic acetate **3.18** were prepared following literature known protocols.[133] The symmetric allylic diol **3.16** was selectively derivatised and both desired products were obtained in sufficient yields (Scheme 51).



Scheme 51: Synthesis of allylic carbonate 3.17 and acetate 3.18 from (*Z*)-but-2-ene-1,4-diol 3.16 following literature known procedures.[133]

3.3 Initial results and optimisation of reaction conditions

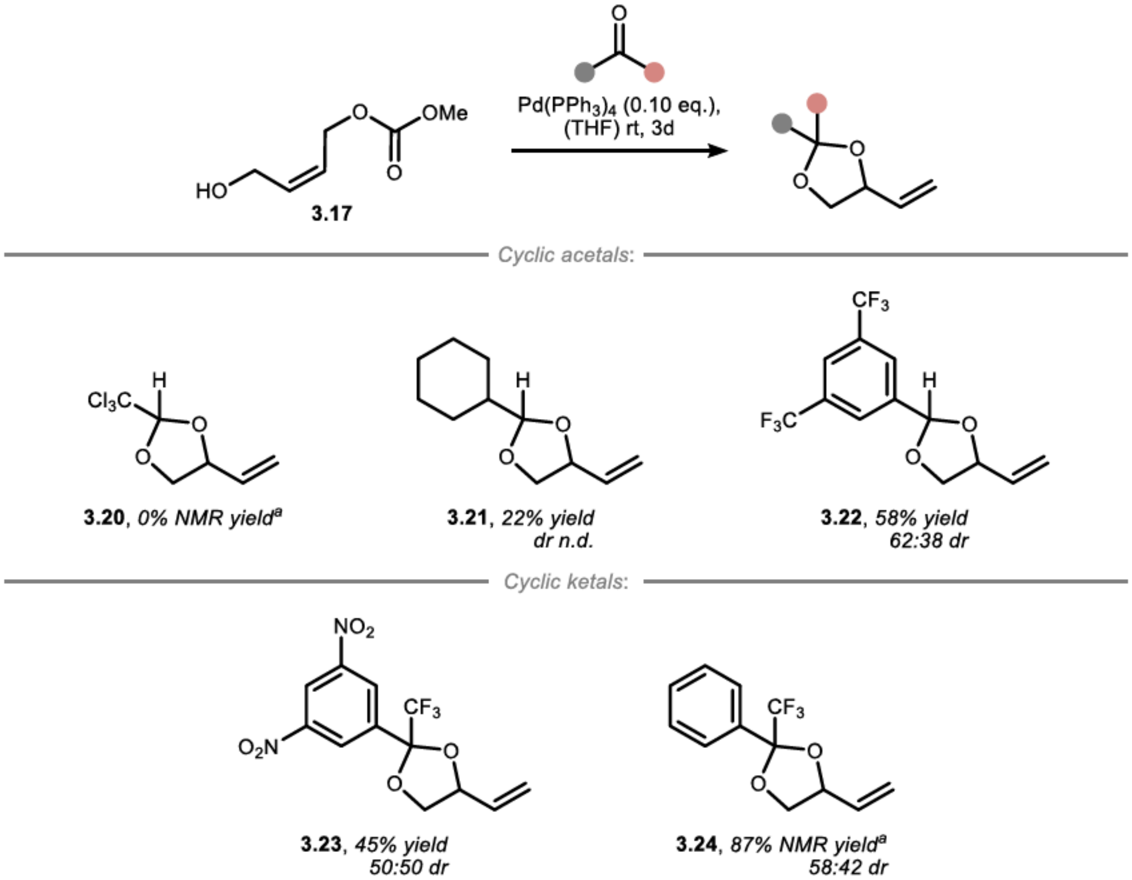
In the research plan for the aspired to *C–H* oxidation with a transient hemi ketal, three independent steps can be identified. Firstly, the hemi ketal has to be formed, secondly, a neighbouring *C–H* bond has to be activated and as a last step, the allyl palladium complex has to be attacked by the hemi ketal as an internal nucleophile to engage the ring-closing. The envisaged synthesis of oxygen containing heterocycles from simple and benign alcohols by means of *C–H* oxidation, as delineated above (*cf.* Chapter 3.1.4, Scheme 50), is therefore a difficult undertaking. As already outlined, the both, *Tsuji-Trost* type reactions and *C–H* oxidations, are historically and mechanistically related (Scheme 52, top). Such being the case, juxtaposing both palladium catalysed allylic functionalisations exhibits a facility for approaching the envisaged intramolecular *C–H* oxidation *via* transient hemi ketals. In both catalytic cycles, the same allyl palladium species is formed, either through oxidative addition or by *C–H* activation. Moreover, it is revealed that the same products can be formed in either of the above-mentioned reactions. Accordingly, allylic carbonate **3.17** can be transformed *via* hemi ketal formation and subsequent *Tsuji-Trost* type allylation to a 1,3-dioxolane species. The same dioxolane product can likewise be obtained by *C–H* functionalisation of homo allylic alcohol **3.19** after formation of a hemi ketal (Scheme 52, bottom). Given the moderate acidity of hemi ketals and acetals, it is likely, that the allylic functionalisation steps proceed *via* outer-sphere mechanisms.



Scheme 52: Top: Juxtaposition of simplified catalytic cycles of palladium catalysed allylic functionalisations through outer-sphere mechanisms with soft nucleophiles. Bottom: Representation of the general approaches for palladium catalysed allylic functionalisations leading to 1,3-dioxolanes.

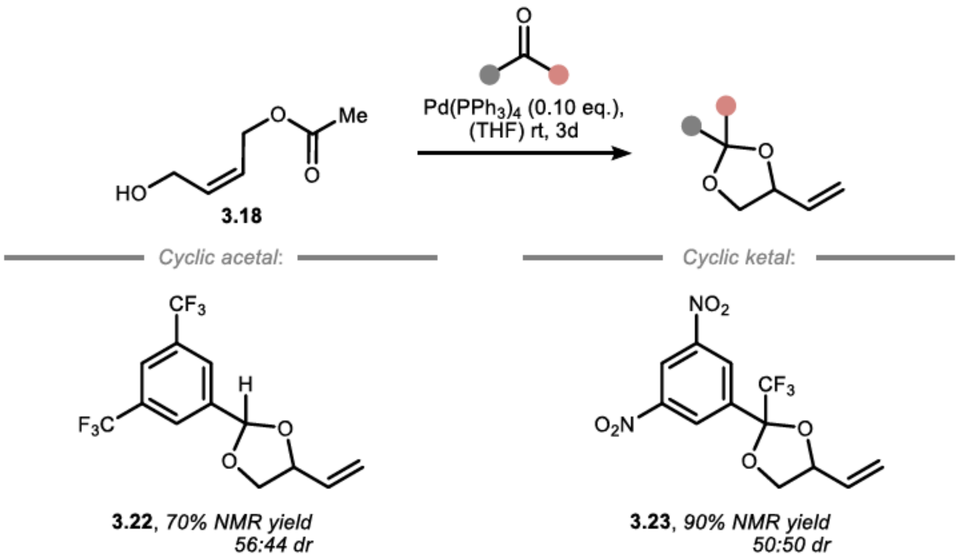
Inasmuch as both, *Tsuji-Trost* type reaction and allylic *C–H* oxidation, could deliver the same target molecules; the former was used to initially prepare the desired heterocyclic products. Allylic alcohol **3.17** was therefore submitted to common conditions for *Tsuji-Trost* type reactions with tetrakis triphenylphosphine palladium(0) as the catalyst. In total five different carbonyl compounds were tested for their reactivity. From the investigated aldehydes, only trichloroacetaldehyde failed to deliver the desired product **3.20**, whereas the acetals **3.21** and **3.22** were obtained by the chosen method. Aliphatic acetal **3.21** was isolated in low yield, without the diastereomeric ratio being determined. Dioxolane **3.22** was formed with a small but distinct diastereomeric excess. It was further examined, if ketones could similarly be used in this *Tsuji-Trost* type allylation. Therefore, again trifluoroacetophenones were used, as their trifluoromethyl group is a valuable probe for NMR scale experiments. Indeed, the cyclic ketals **3.23** and

3.24 were synthesised. Ketal **3.23** was isolated in an acceptable yield, while the diastereomeric ratio was determined prior to isolation with NMR techniques indicating no selectivity for one of the two possible stereoisomers. On the contrary, ketal **3.24** derived from trifluoroacetophenone **2.18** was obtained with a slight selectivity for one diastereomer.



Scheme 53: Preparation of 1,3-dioxolanes *via* intramolecular *Tsuji-Trost* type ring-closing with allyl carbonate 3.17. Reactions were run on a 0.1 mmol scale in THF [0.1 M]. Isolated yields are reported, *dr* was determined *via* ^{1}H NMR of the crude reaction mixture. ^{a} NMR yields were determined *via* ^{1}H NMR of the crude reaction mixtures using mesitylene as internal standard.

Additionally allylic acetate **3.18** was analysed as a precursor for the *Tsuji-Trost* type ring-closing. These attempts turned out to be high yielding and notably selective for the desired reaction as both dioxolanes **3.22** and **3.23** were formed with more than 70% yield without other side reactions occurring. (Scheme 54)

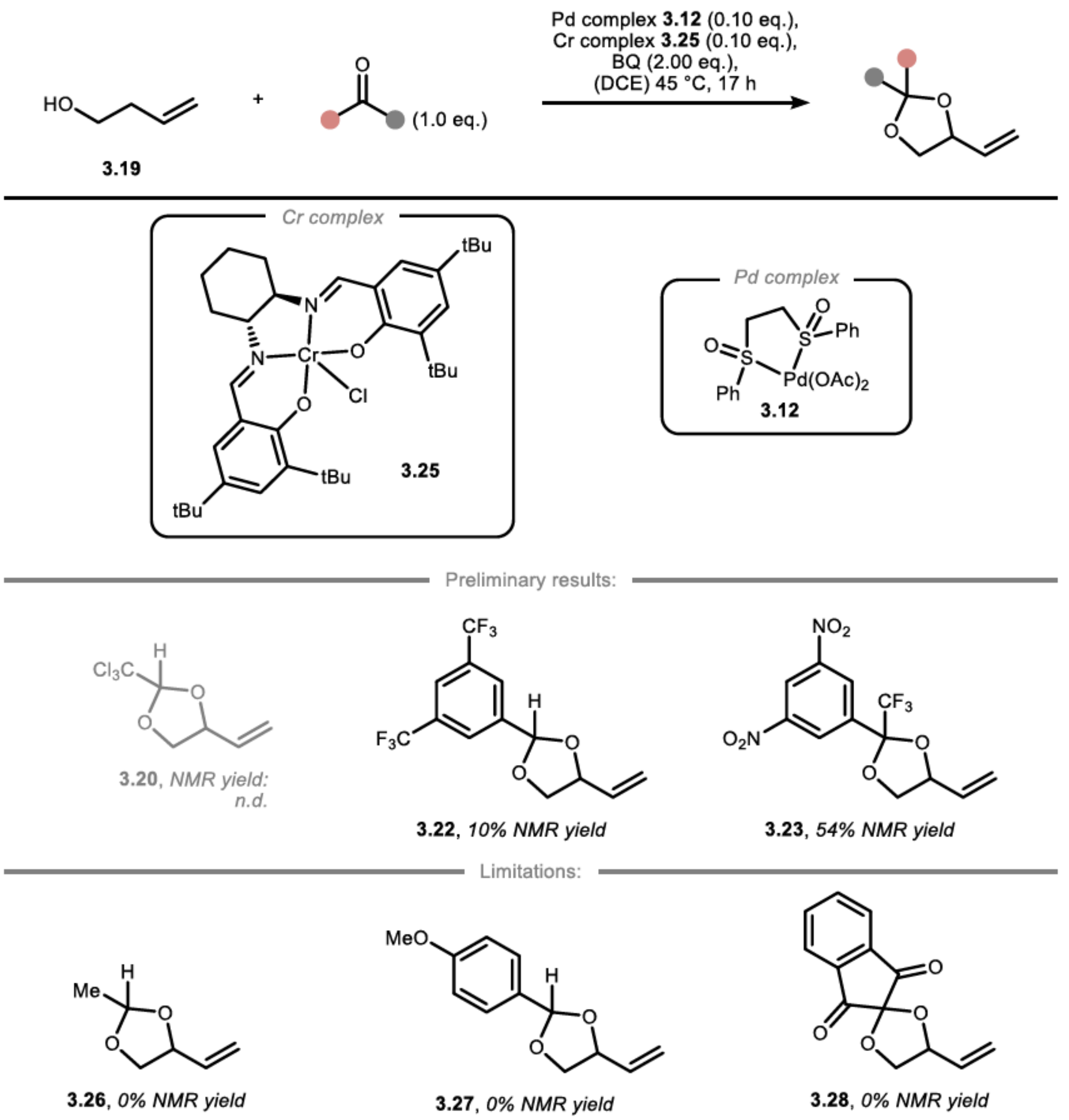


3.22, *70% NMR yield 56:44 dr*

3.23, *90% NMR yield 50:50 dr*

Scheme 54: Preparation of 1,3-dioxolanes *via* intramolecular *Tsuji-Trost* type ring-closing with allyl acetate 3.18. Reactions were run on a 0.1 mmol scale in THF [0.1 M]. NMR yields and *dr* were determined *via* ^{1}H NMR of the crude reaction mixtures using mesitylene as internal standard.

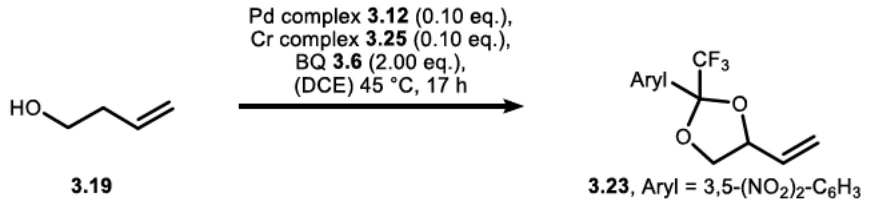
The differing measured yields for the synthesis of 1,3-dioxolanes through *Tsuji-Trost* type ring-closing starting from allylic carbonates or allylic acetates should only be compared to a limited extend due to the fact, that the latter ones were determined from the crude mixture with NMR techniques, whereas the former were isolated yields. Nevertheless, both delivered the desired product, thereby initiating a deeper analysis of the originally outlined synthetic goal. Again, a set of electronically differing carbonyl compounds was applied to typical reaction conditions of the *White* group for allylic aminations.[123e] A bimetallic catalytic system consisting out of the palladium complex **3.12** and the chromium complex **3.25** was therefore used (Scheme 55). The chromium complex is supposed to aid ligand dissociation to keep the palladium centre active in the desired transformation. Moreover, it was presumed, that by *Lewis* acid interactions the carbonyl compounds becoming more electrophilic, thus more susceptible for hemi acetal or ketal formation.



Scheme 55: Preliminary results for the intramolecular *C–H* oxidation with transient hemi acetals and ketals. Reactions were run on a 0.1 mmol scale in DCE [0.1 M]. Yields were determined *via* ^{1}H NMR of the crude reaction mixtures using mesitylene as internal standard. n.d. = not determined.

In a preliminary study, the cyclic acetal **3.22** derived from 3,5-bis(trifluoromethyl)benzaldehyde **2.129** and the cyclic ketal **3.23** derived from the electron-poor trifluoroacetophenone **2.20** were identified in the crude reaction mixtures. Acetal **3.20** is formed in a low but detectable yield, whereas ketal **3.23** was formed with 50% yield. In case of trichloroacetaldehyde as the carbonyl compound, the crude mixture showed broad peaks in the ^{1}H NMR spectrum, therefore the yield of **3.20** could not be determined *via* NMR techniques. However, it was qualitatively observed, that the starting material was consumed and a new species with proton signals resembling an allylic group was formed. The applied reaction conditions failed to deliver the cyclic acetals **3.26**, **3.27** and the cyclic ketal **3.28**. Based on these preliminary results, ketone **2.20** was identified as a promising carbonyl compound in the envisioned *C–H* oxidation of allylic alcohols. A further survey of the utilised reaction conditions was performed (Table 7, Figure 13).

Table 7: Optimisation of reaction conditions for the *C–H* oxidation with transient hemi ketals. Reactions were performed on a 0.1 mmol scale in DCE [0.1 M]. NMR yield was determined *via* ^{1}H NMR of the crude reaction mixtures using mesitylene as internal standard.



Entry	Changes from standard conditions	NMR yield
1	–	54%
2	No Pd complex used	0%
3	No oxidant used	7%
4	DDQ (2.00 eq.) used as oxidant	0%
5	Chloranil (2.00 eq.) used as oxidant	<5%
6	Ph-BQ (2.00 eq.) used as oxidant	55%
7	Mn complex **2.102** (0.10 eq.) used as additive	15%
8	Co complex **2.76** (0.10 eq.) used as additive	0%
9	Co complex **2.80** (0.10 eq.) used as additive	0%
10	EtN(*i*Pr)$_2$ (0.06 eq.) used as additive	0%

DDQ = 2,3-dichloro-4,5-dicyano-1,4-benzoquinone, Chloranil = 2,3,5,6-tetrachloro-1,4-benzoquinone.

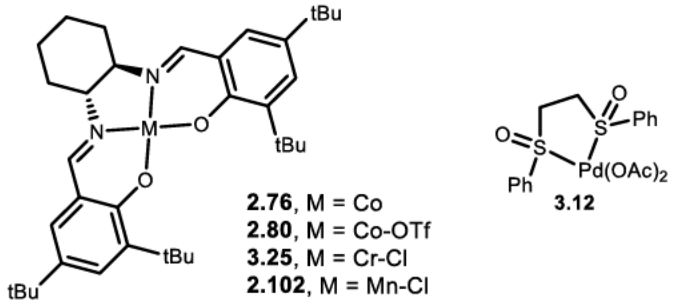


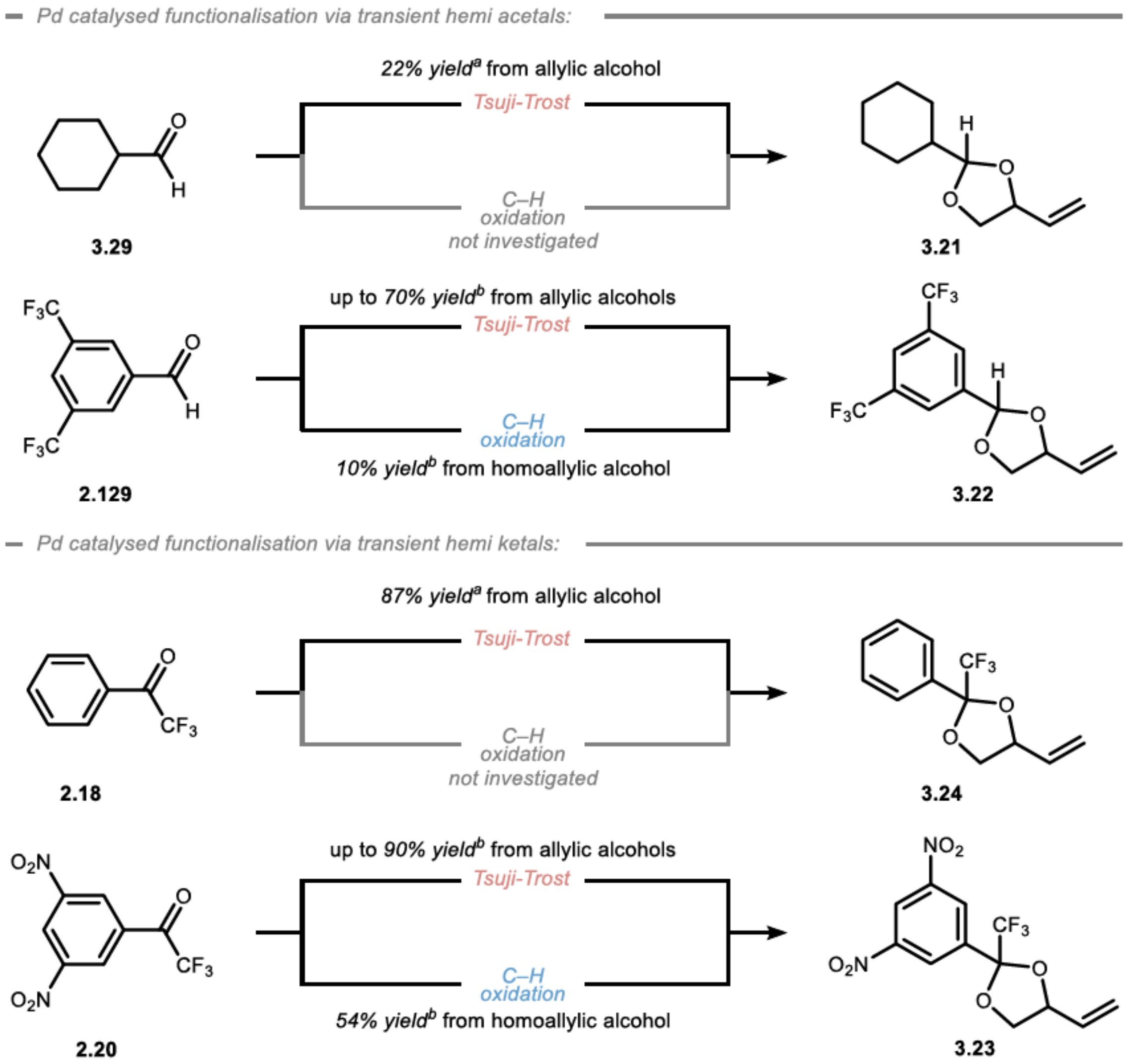
Figure 13: Utilised transition metal complexes in the attempted intramolecular allylic *C–H* oxidation of homoallylalcohol 3.19.

Omitting the palladium complex **3.12**, obstructed the product formation completely (entry 2). In the absence of benzoquinone, only a small amount of the desired product was obtained (entry 3), indicating the crucial role of the oxidant for catalyst turn-over. Utilising 2-phenyl-1,4-benzoquinone led to comparable results, while the use of other benzoquinone derivatives was not effectively yielding the cyclic ketal **3.23** (entries 4 to 6). Substituting the chromium complex with other transition metal salen complexes such as manganese complex **2.102** or cobalt complexes **2.76** or **2.80** had a likewise detrimental effect on the reaction outcome (entries 7 to 9). Apart from *Lewis* acid activation, another activation mode through *Brønsted* bases was probed, but the addition of *Hünig*'s base failed to promote the aspired *C–H* oxidation (entry 10).

3.4 Summary and outlook

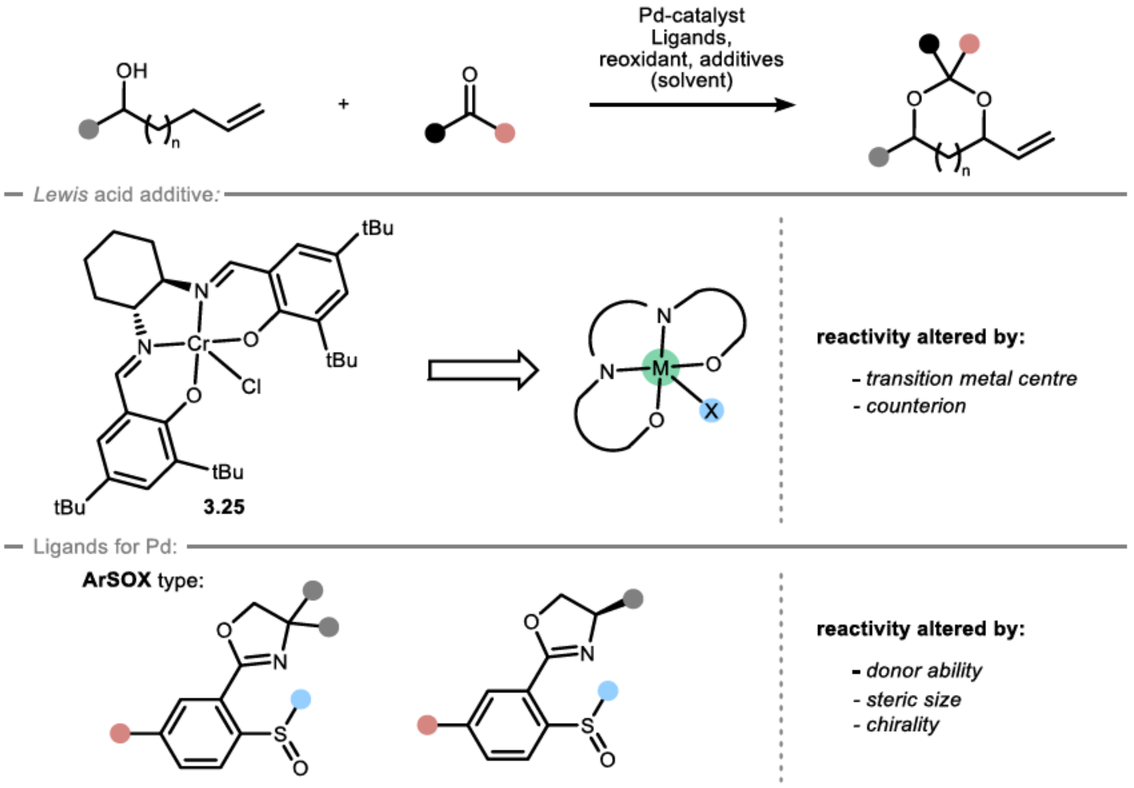
The envisaged *C–H* oxidation towards heterocyclic compounds from benign alcohols proved to be a difficult endeavour. This fact is reasoned by the three different reaction steps, namely hemi ketal formation, *C–H* activation and ring-closing, to be conducted consecutively. Nonetheless, it was shown that the formidable challenge of preparing highly substituted *O*-heterocycles from simple alcohols can be taken up with palladium catalysed allylic functionalisation strategies in hand.

The presented three-step problem (*cf.* Chapter 3.1.4, Scheme 50) was partially simplified through *Tsuji-Trost* type reactions, as the oxidative addition of a Pd^0 species into an allylic carbonate is a just as facile as reliable method for the generation of the essential allyl palladium species occurring in both *Tsuji-Trost* type reactions and allylic *C–H* functionalisations. Thereby, 1,3 dioxolanes **3.21** to **3.24** were prepared from allylic carbonates and allylic acetates, respectively, in good to high yields (Scheme 56). For the envisioned oxidative *C–H* functionalisation with a transient hemi ketal or acetal, a first proof of concept was established. Thereby, aldehyde **2.129** and ketone **2.20** both have proven their applicability in the desired intramolecular allylic *C–H* oxidation thus acetal **3.22** was obtained in 10% yield and ketal **3.23** in 54% yield, respectively.



Scheme 56: Results of the palladium catalysed allylic functionalisations with transient hemi acetals and ketals. [a] Isolated yields of the diastereomeric mixtures. [b] Yields were determined *via* ^1H NMR of the crude reaction mixtures using mesitylene as internal standard.

Furthermore, a preliminary evaluation of the reaction conditions has showcased the crucial role of the utilised oxidant and the *Lewis* acid. However, the initially used conditions were not outperformed throughout the optimisation in this project. Nevertheless, novel prospects for the synthesis of *O*-heterocycles from benign alcohols are opened by the shown proof of concept. Future endeavours possibly focus on the pivotal role of the deployed *Lewis* acid, as the counterion and the metal centre could be varied (Scheme 57). Additionally, altering the employed ligand is presumed to affect the reactivity by their donor abilities, and possibly enhance stereocontrol through their steric demand.



Scheme 57: Outline for possible handles to increase reactivity in the allylic *C–H* oxidation yielding *O*-heterocycles.

4 Cyclic alcohols as platform for the synthesis of *N*-heterocycles

4.1 Introduction

4.1.1 *N*-insertions in synthesis

From the manifold of heterocycles, the nitrogen analogues arguably represent the most important structural motifs. On that account, a plethora of methods exist, focussing on their synthesis mostly following the trends reviewed above (*cf.* Chapter 1.2.).[14d,134] Recently, the groups of *Sarpong* and *Levin* conceptualised the principles of "skeletal editing" for heterocycle synthesis emphasising molecular rearrangements as an elegant way of approaching heterocycles.[135] Additionally, insertions of single heteroatoms are depicted as desired transformations for heterocycle synthesis (Figure 14).[135,136]

Figure 14: Representation of the skeletal editing logic in heterocycle syntheses.

Generally, those two ways of introducing a heteroatom into a molecular framework can be differentiated by the origin of the added atom. Whilst ring-expanding rearrangements are occurring with endogenous groups, the insertion of a single atom proceeds with groups initially not bound to the molecular skeleton. Nevertheless, in this dichotomy, both strategies are not fully independent from each other, as the insertion of an atom is usually relying on the engagement of a functional group which is regularly ensued by a molecular rearrangement yielding the heterocyclic product (Figure 15).

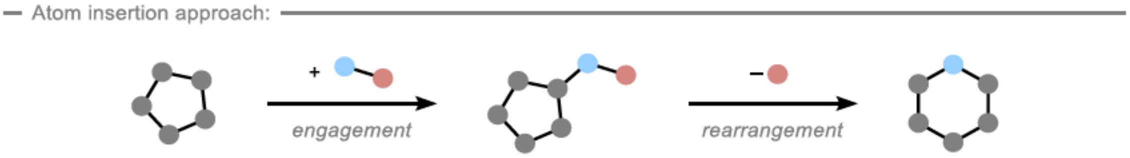


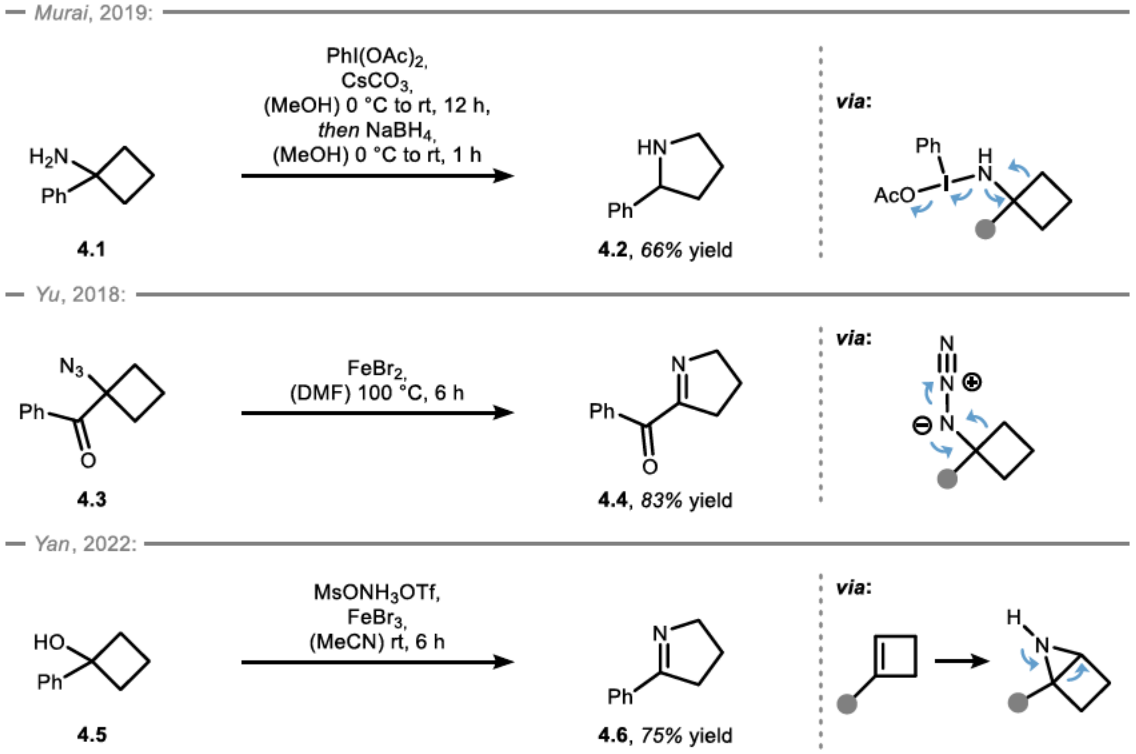
Figure 15: Schematic representation of an atom insertion approach for heterocycle synthesis.

To initiate a productive ring-expansion by rearrangement, the most important prerequisite is the engagement of a leaving group to the heteroatom, thus triggering the molecular skeleton to reorganise. Typically, potent leaving groups are therefore installed by oxidation of existing functional groups.[137] If an atom insertion strategy is pursued, the leaving group is commonly included in the *ab initio* engaged fragment. Besides additionally enhancing the leaving group abilities by *Brønsted* or *Lewis* acids interactions, a powerful thermodynamic driving force for the rearrangement is the release of ring-strain energy. Hence, small cyclic molecules such as cyclobutane derivatives came into focus, as the one atom expansion of the cyclic core is beneficial in terms of strain energy.

The following discussion will primarily focus on the preparation of *N*-heterocycles due to their given importance as structural motifs in medicinal chemistry or natural products. Accordingly, different methods for their synthesis starting from strained carbocyclic cores were developed following the principles of “skeletal editing”. For instance, the rearrangement of cyclobutane derivatives can be accomplished by the oxidation of amines. The *Murai* group has shown, that cyclobutyl amine **4.1** can be transformed to pyrrolidine **4.2** through oxidative rearrangement with a hypervalent iodine species and *in situ* reduction of the rearranged species (Scheme 58, top).[138] A similar oxidative approach with hypervalent iodine species was reported by the group of *Chang* through a reaction sequence including a *Hofmann* type rearrangement.[139]

Another way of initiating the molecular rearrangement of carbocycles is the decomposition of azides, which can be triggered either thermally, by *Brønsted* acid or by *Lewis* acid catalysis.[140] As to that, *Yu* and coworkers reported the iron catalysed denitrogenative rearrangement of cyclobutylazide **4.3** yielding the pyrrolidene **4.4** (Scheme 58, middle).[140e]

In addition to the discussed rearrangements *vide supra*, an atom insertion reaction into a cyclobutyl framework was reported by *Yan*. The alcohol **4.5** is supposedly reacting in a formal nitrene (2+1) cycloaddition after elimination forming a strained bicyclic system, which undergoes rapid rearrangement to pyrrolidene **4.6** (Scheme 58, bottom).[141]



Scheme 58: Top: Oxidative rearrangement of cyclobutalamines reported by *Murai*.[138] Middle: Iron catalysed azide decomposition of cyclobutylazides reported by *Yu*.[140e] Bottom: Iron catalysed synthesis of pyrrolidenes *via* nitrene addition reported by *Yan*.[141] Ms = methanesulfonyl.

In addition to the methods outlined above, molecular rearrangements and atom insertion reactions have found widespread use in the derivatisation and functionalisation of cyclobutanones. Reactions harnessing the reactivity of carbonyls are not further discussed herein and can be found elsewhere.[29,142] Transformations with different cyclic molecules are likewise discussed in other works.[143]

4.1.2 Hydroxylamine reagents

Hydroxylamines and related reagents have a long history of applications in heterocycle syntheses as they found use within the famous *Beckmann* rearrangement and akin reactions.[144] Especially, *O*-substituted hydroxylamines have proven to be potent *N*-donating agents in a multitude of different reactions.[145] Most frequently, *O*-sulfonyl, *O*-acyl, *O*-phosphinyl and *O*-aryl substituted hydroxylamines were utilised, with foremost significance lying on the *O*-sulfonyl substituted derivatives,[146] including hydroxylamine-*O*-sulfonic acid **4.7**, *O*-(mesitylsulfonyl)hydroxylamine **4.8**, furthermore the triflate salts **4.9** and **4.10** (Figure 16).

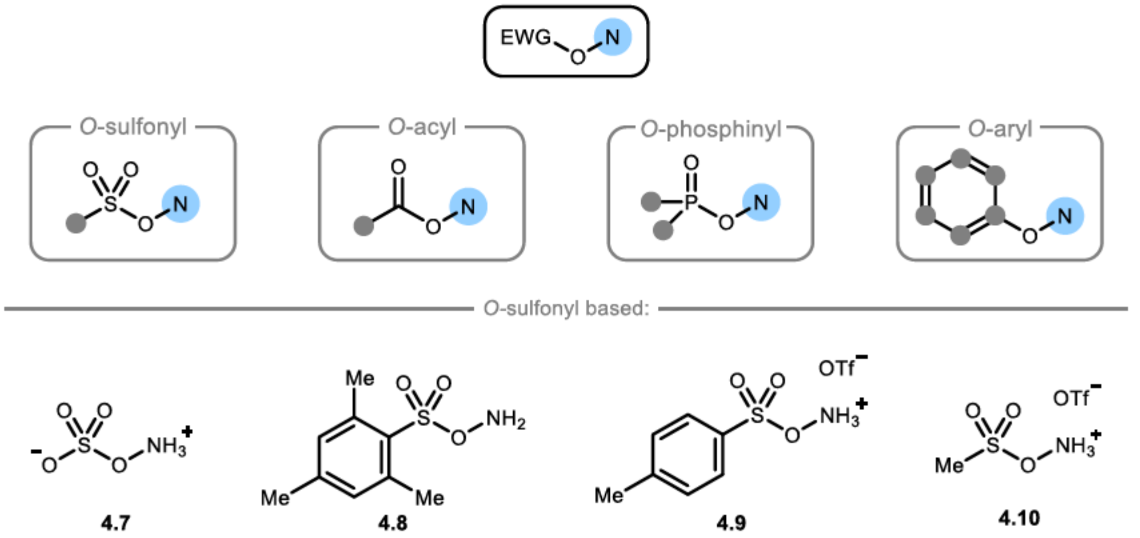
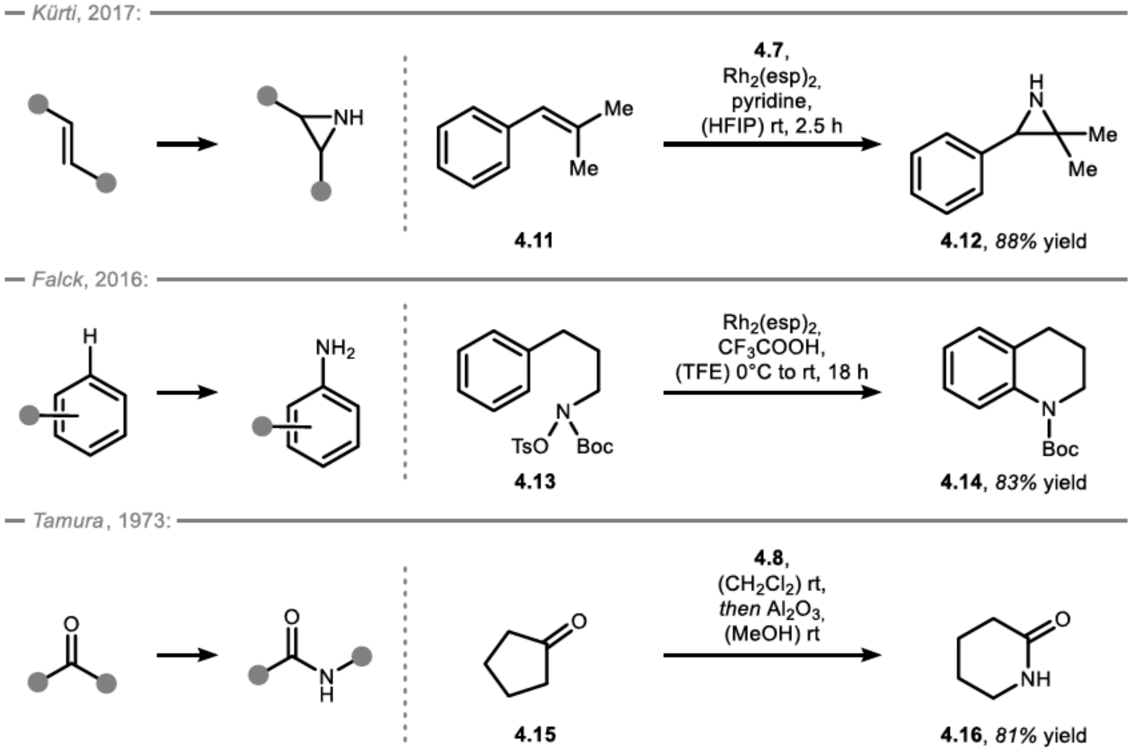


Figure 16: Overview of hydroxylamine based aminating reagents. EWG = electron-withdrawing group.

Due to the typically attached strongly electron withdrawing groups, the most hydroxylamine derivatives shown are commonly referred to as electrophilic reagents. However, typically ambiphilic behaviour of these hydroxylamine derivatives is observed in diverse applications of these reagents, showcased for instance in a series of heterocycle syntheses. Exemplarily, hydroxylamine-*O*-sulfonic acid **4.7** was used as a nitrene precursor by *Kürti* in the rhodium catalysed aziridination of unactivated alkenes such as styrene **4.11** yielding aziridine **4.12** (Scheme 59, top),[147] while *Falck* and coworkers used the same catalyst for the intramolecular *C–H* amination of arenes like **4.13** resulting in heterocycles such as tetrahydroquinoline **4.14** (Scheme 59, middle).[148] Earlier, *Tamura* reported the use of *O*-(mesitylsulfonyl)hydroxylamine **4.8** in a nitrogen insertion of cyclic ketone **4.15** yielding lactam **4.16** (Scheme 59, bottom).[149] A similar approach was followed by the *Wahl* group in their synthesis of γ-lactams.[142c]



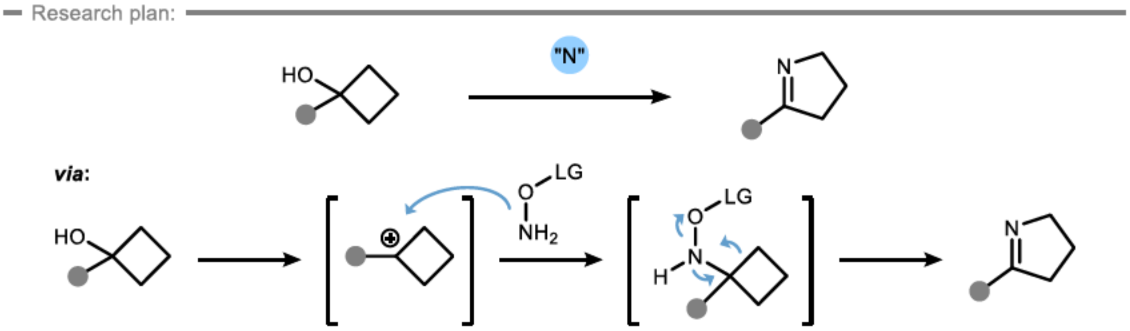
Scheme 59: Applications of hydroxylamine reagents in heterocycle syntheses. Top: Aziridation reported by *Kürti* and coworkers.[147] Middle: *C–H* functionalisation of arenes reported by *Falck* and coworkers.[148] Bottom: *N*-insertion for the preparation of lactams reported by *Tamura* and coworkers.[149] esp = α,α,α'α'-tetramethyl-1,3-benzene-dipropionic acid, Boc = *tert*-butyloxycarbonyl.

Besides the discussed *C–H* and *C–C* bond insertions, hydroxylamine derived reagents were utilised in several *C–X* bond functionalisations.[150] Furthermore, especially hydroxylamine salts such as **4.9** and **4.10** have been extensively studied in olefin difunctionalisations, those and other applications are reviewed elsewhere,[145b,145d,151] since this overview is focussing on heterocycle synthesis.

4.1.3 Motivation and aim

In contrast to molecular rearrangements, the direct insertion of a heteroatom, albeit a worthwhile endeavour, is developed to a lesser extent. The same holds true for transformations of cyclic molecules not depending on the reactivity of carbonyl compounds. As a consequence, a method for the preparation of *N*-heterocycles by means of atom insertion starting from simple cyclic alcohols should be developed (Scheme 60). Therefore, cyclobutanols were identified as ideal starting materials, since the insertion of an atom into their molecular framework partially releases the ring-strain energy consequently providing additional thermodynamic driving force for the overall transformation. In contrast to existing strategies for the preparation of pyrrolidenes through skeletal rearrangement of

4-membered carbocycles a protocol omitting the use of oxidants or transition metals should be established. Hence, a reaction pathway through mild ionisation of the cyclobutanol is envisaged followed by the engagement of a hydroxylamine derivative bearing a leaving group. Subsequently, a rearrangement is assumed to yield the desired pyrrolidene upon elimination of the leaving group.



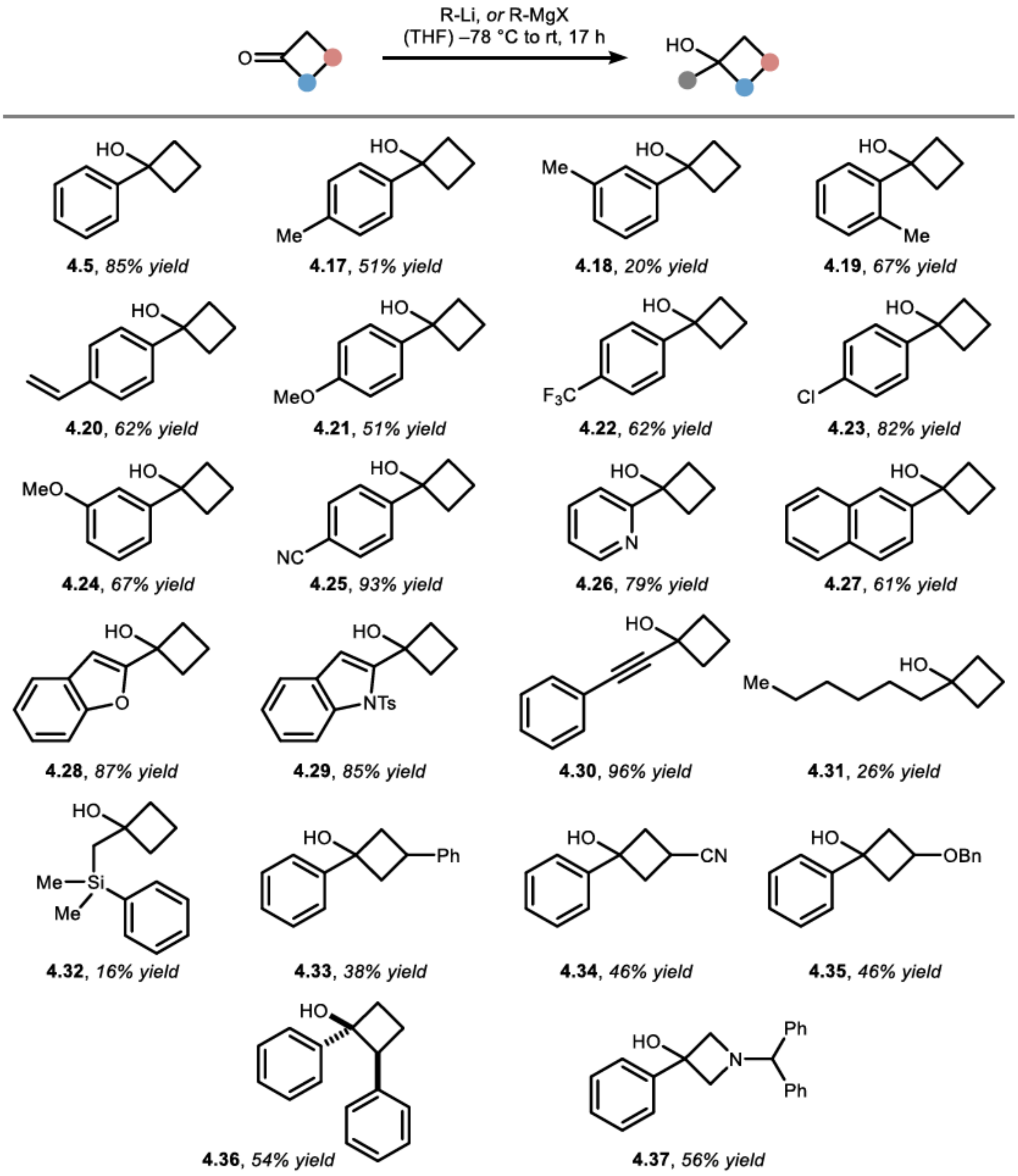
Scheme 60: Research plan for preparation of pyrrolidenes *via N*-insertion.

4.2 Preparation of starting materials

4.2.1 Preparation of cyclobutanols and benzannulated cyclic alcohols

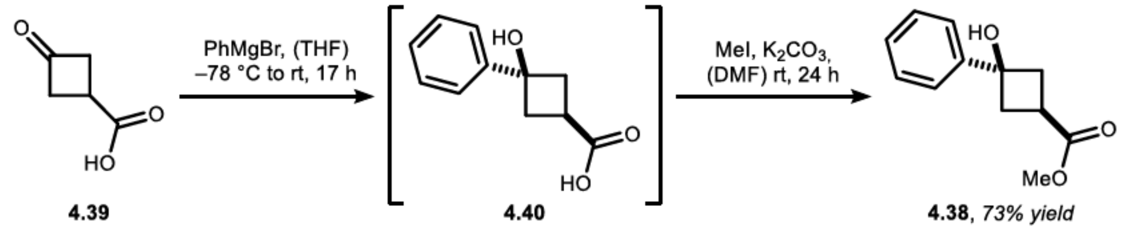
Over the course of this project, several cyclic alcohols for the investigation regarding their reactivity in *N*-insertion reactions were prepared.

A variety of sterically and electronically differing cyclobutanol derivatives were synthesised by addition of organolithium or organomagnesium species to commercially available cyclobutanones in a single step following literature known procedures (Scheme 61).[82,141,152] Thereby, the 1-substituted tertiary cyclic alcohols **4.5** and **4.17** to **4.32** were obtained. Furthermore, 1,3- and 1,2-disubstituted cyclobutanols **4.33** to **4.36** were prepared by the same method, adding phenylmagnesium bromide to the respective cyclobutanones. Additionally, azetidine derivative **4.37** was synthesised in the same manner. Again, the deployed organolithium or magnesium compounds were either commercially available or prepared through lithium-halogen exchange, magnesium-halogen exchange, or deprotonation.



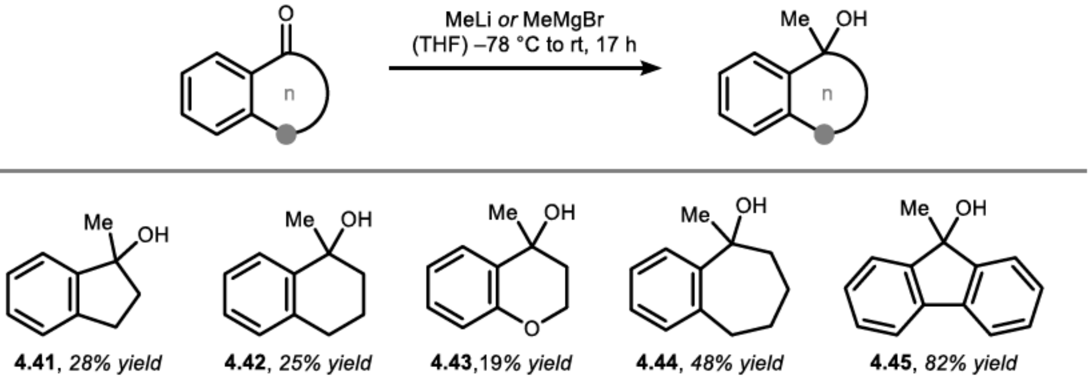
Scheme 61: Overview of the tertiary cyclobutanols prepared by the addition of carbon nucleophiles to cyclobutanones.

Moreover, ester **4.38** was prepared following a literature known protocol from 3-substituted cyclobutanone **4.39** and subsequent esterification of acid **4.40** in a two-step process.[153]



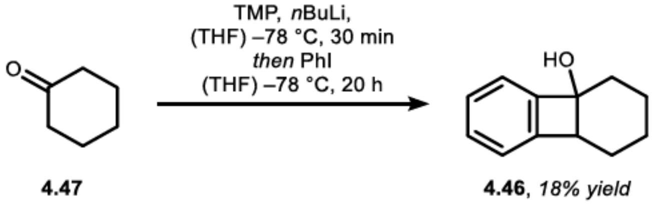
Scheme 62: Preparation of 1,3-disubstituted cyclobutanol 4.39 according to *Chernykh et al.*[153]

Besides the discussed cyclobutanols, benzannulated cyclic alcohols **4.41** to **4.45** were likewise prepared by addition of methyllithium or methylmagnesium bromide to the respective benzannulated cyclic ketones.[137a,154]



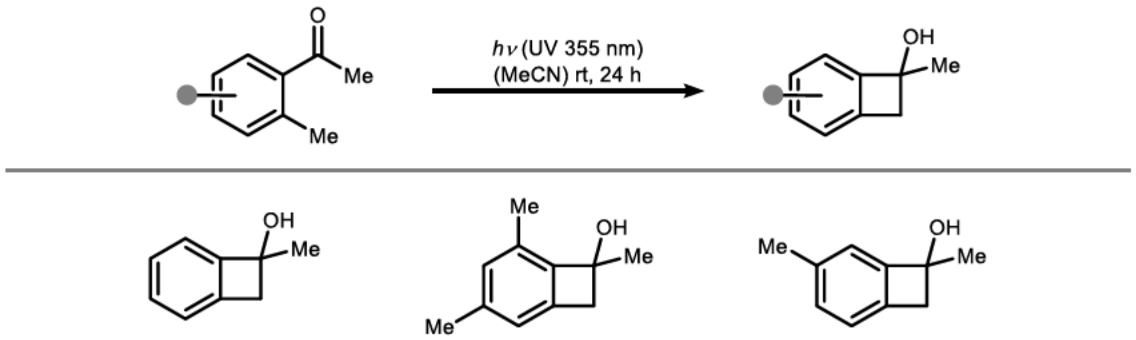
Scheme 63: Synthesis of benzannulated tertiary alcohols.

Additionally, the benzannulated cyclobutanol **4.46** was obtained through a formal aryne (2+2) cycloaddition with the *in situ* formed enolate of cyclohexanone **4.47** following a procedure by the groups of *Browne* and *Morrill*.[152d]



Scheme 64: Preparation of benzannulated cyclobutanol 4.46 by *in situ* aryne formation and cycloaddition according to *Browne* and *Morrill*.[152d] TMP = 2,2,6,6-tetramethylpiperidine.

Moreover, photochemical methods were exploited for the synthesis of benzannulated cyclobutanols.[155] Therefore, 2-methyl acetophenone derivatives were irradiated with UV light to initiate the photochemical cyclisation effectively yielding the benzannulated cyclobutanols **4.48** and **4.49**, respectively. On the contrary, cyclobutanol **4.50** was not formed under the applied conditions.



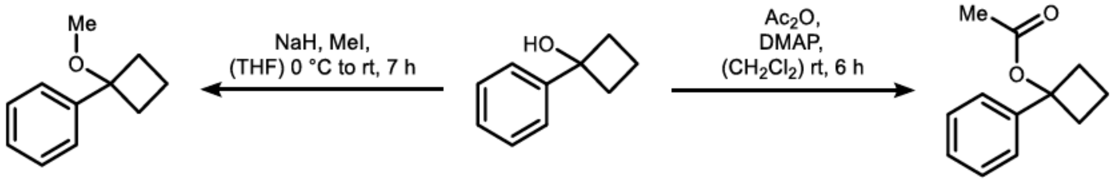
4.48, *16% yield* (*94% yield*)[a]

4.49, *15% yield* (*33% yield*)[a]

4.50, *0% yield*

Scheme 65: Photochemical approach for benzannulated cyclobutanols following protocols developed by *Wagner*.[155] [a] Yield in parentheses is based on recovered starting material.

In order to gain insight into the mechanistic background of the envisaged reaction, methylether **4.51** and acetate ester **4.52** were both prepared by functionalising cyclobutanol **4.5** following literature known protocols (Scheme 66).[152d,156]



4.51, *37% yield*

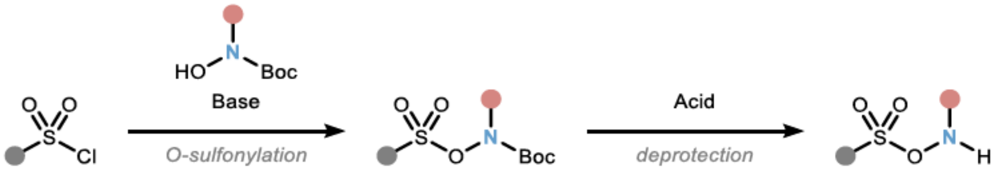
4.5

4.52, *85% yield*

Scheme 66: Functionalisation of cyclobutanol 4.5 yielding protected alcohols 4.51 and 4.52 following literature known procedures.[152d,156] DMAP = *N,N*-dimethylpyridin-4-amine.

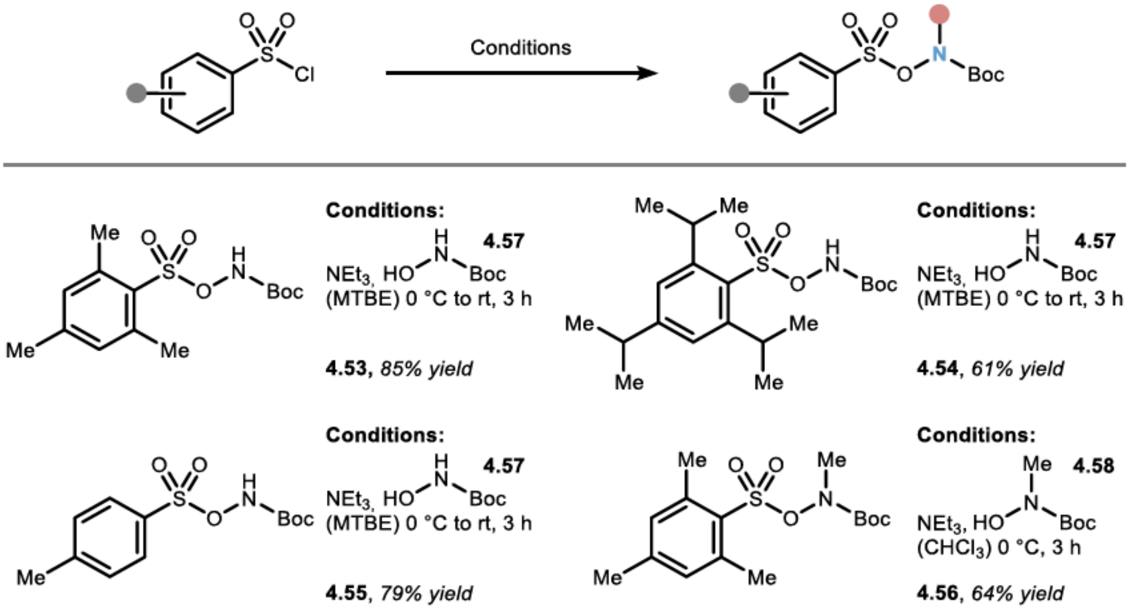
4.2.2 Preparation of hydroxylamine reagents

A series of *O*-substituted hydroxylamine reagents was prepared throughout this project. In general, ambiphilic *O*-sulfonyl hydroxylamine reagents should be prepared, following the typical synthetic route *via* *O*-sulfonylation of a Boc-group protected hydroxylamine with a substituted sulfonyl chloride. Subsequent removal of the protecting group affords the desired *O*-sulfonyl hydroxylamine reagents (Scheme 67).



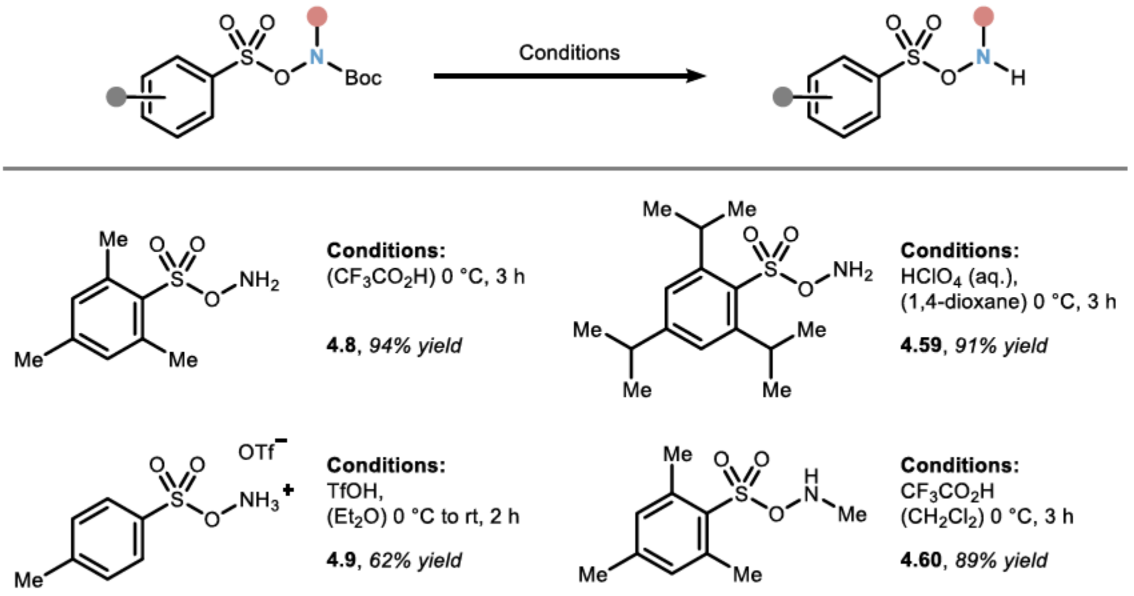
Scheme 67: General synthetic route towards *O*-sulfonyl hydroxylamines.

Accordingly, the Boc-protected hydroxylamines **4.53** to **4.56** were prepared in good to high yields adapting literature known procedures.[146c,157] Therefore, either *N*-Boc-hydroxylamine **4.57** or *N*-Boc-*N*-methyl-hydroxylamine **4.58** was used in combination with varying aryl sulfonyl chlorides.



Scheme 68: Preparation of *N*-Boc-*O*-sulfonyl hydroxylamines 4.53 to 4.56.[146c,157]

The following *Brønsted* acidic deprotection was performed according to literature known protocols with strong acids, such as trifluoroacetic acid, perchloric acid or triflic acid,[157] effectively yielding the sterically encumbered *O*-sulfonyl hydroxylamines **4.8** and **4.59**. The hydroxylamine salt **4.9** and *N*-methyl *O*-sulfonyl hydroxylamine **4.60** were likewise afforded.



Scheme 69: Boc-group deprotection for the preparation of *O*-sulfonyl hydroxylamines according to *Hashmi* and coworkers.[157]

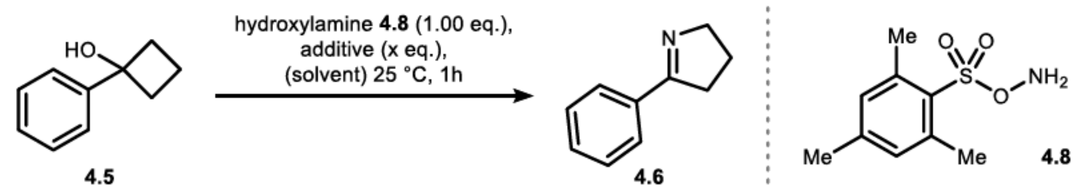
4.3 Optimisation of reaction conditions

Initially, a set of different reaction conditions was evaluated in order to achieve a successful *N*-insertion in agreement with the above-mentioned research outline (*cf.* Chapter 4.1.3, Scheme 60). At the beginning of the optimisation process, *O*-(mesitylsulfonyl)hydroxylamine **4.8** was presumed to serve as a nitrogen source in the outlined transformation, as it proved to be effective in related reactions.[157] Additionally, phenyl cyclobutanol **4.5** was chosen as the model substrate to gain insight into the reactivity of strained cyclic alcohols towards *N*-insertion, reasoned by the supposedly facile cation formation at the benzylic position. Since the assumed product, pyrrolidene **4.6**, is a literature known compound, the primary optimisation was analysed by quantitative ^{1}H NMR techniques.

Firstly, a set of different solvents was tested with a series of aprotic solvents reaching from apolar to polar without any proof of the desired product formed (Table 8, entries 1 to 4). Next, protic solvents were investigated. While using methanol was ineffective in the sought after reaction (entry 5), the application of fluorinated alcohols TFE and HFIP gave the desired pyrrolidene **4.6** in 57% and 65% yield, respectively (entries 6 and 7). Dilution with a less polar solvent had a detrimental effect on the reaction outcome, which was only partially counterbalanced by longer reaction times and the addition of an excess of hydroxylamine

4.8 (entries 8 and 9), thus highlighting the special properties of fluorinated alcohols as solvents.[158] Subsequently, the role of additives was investigated. Remarkably, adding a strong *Lewis* acid, such as boron trifluoride diethyl etherate, restored the reactivity in dichloromethane to some degree, while it has a marginal negative effect on the reactivity in HFIP (entries 10 and 11). On the contrary, the addition of a *Brønsted* acid, namely *rac*-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, turned out to have no beneficial effect on the reaction outcome in apolar dichloromethane, in addition a similar negative effect was observed in HFIP (entries 12 and 13). Interestingly, attempts to scavenge the leaving group as a salt with *Brønsted* bases, such as *N*,*N*-diisopropylethylamine or caesium carbonate, inhibited the entire reaction (entries 14 and 15). Unlike the addition of *Brønsted* acids or bases and *Lewis* acids, employing molecular sieves had a negligible effect on the formation of pyrrolidene **4.6**. Thereby, it was excluded, that trace amounts of water are affecting the desired transformation.

Table 8: Solvent optimisation and screening for additives. Reactions were carried out on a 0.1 mmol scale in 0.5 mL solvent, NMR yield based on ^1H NMR experiments using CH_2Br_2 as an internal standard.

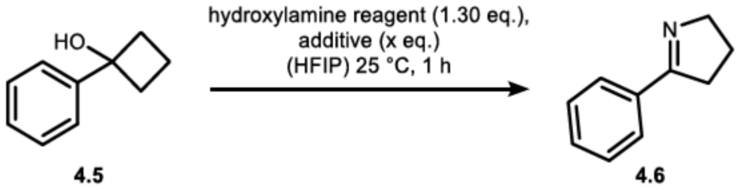


Entry	Additive (eq.)	Solvent	NMR yield
1	–	PhMe	0%
2	–	THF	0%
3	–	CH_2Cl_2	0%
4	–	DMF	0%
5	–	MeOH	0%
6	–	TFE	57%
7	–	HFIP	65%
8[a]	–	HFIP/CH_2Cl_2 (1:1)	65%
9[a]	–	HFIP/CH_2Cl_2 (1:4)	60%
10	$BF_3{\cdot}OEt_2$ (0.20 eq.)	CH_2Cl_2	63%
11	$BF_3{\cdot}OEt_2$ (0.20 eq.)	HFIP	63%
12	*rac*-BINOL PO_2H (0.20 eq.)	CH_2Cl_2	0%
13	*rac*-BINOL PO_2H (0.20 eq.)	HFIP	55%
14	DIPEA (1.00 eq.)	HFIP	0%
15	Cs_2CO_3 (1.00 eq.)	HFIP	0%
16	4Å MS	HFIP	66%

rac-BINOL PO_3H = 1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate, DIPEA = *N*,*N*-diisopropylethylamine, MS = molecular sieves. [a] Reaction was run with **4.8** (1.30 eq.) for 17 h.

Subsequently, differing *O*-substituted hydroxylamines were utilised to find the optimal aminating reagent in the intended reaction (Table 9). In this series of experiments, a slight excess of aminating reagent was applied. *O*-phosphinyl reagent **4.61** was less effective as the initially used *O*-sulfonyl reagent **4.8**. Intriguingly, again, adding a *Lewis* acid, enabled the product formation in an apolar solvent (entries 1 and 2). On the other hand, pyrrolidene **4.6** was not afforded by employing *O*-aryl substituted hydroxylamine **4.62** in neither HFIP or TFE (entries 3 and 4). It was therefore assumed, that a stronger leaving group is a key prerequisite for a productive *N*-insertion. Reverting to *O*-sulfonyl based reagents, substantiated this hypothesis, as the initially utilised *O*-(mesitylsulfonyl)hydroxylamine **4.8** proved to be superior (entry 5). Enhancing the electrophilicity of the applied reagent by using the triflate salt **4.9** had an adverse effect on the product formation (entry 6). Further increasing the steric demand on the aryl substituent similarly diminished the formation of pyrrolidene **4.6** (entry 7). It was additionally investigated whether the *N*-Boc protected hydroxylamine **4.53** can be employed as the *N*-donating agent. Notwithstanding the existing literature precedent for Boc-group removal solely by solvation in HFIP,[159] the desired product was not obtained (entry 8). Thus, the *in situ* deprotection of the hydroxylamine derivative **4.53** was not observed.

Table 9: Hydroxylamine reagent optimisation. Reactions were carried out on a 0.1 mmol scale in 0.5 mL solvent, NMR yield based on ^1H NMR experiments using CH_2Br_2 as an internal standard.



Entry	Additive (eq.)	Solvent	Hydroxylamine (1.30 eq.)	NMR yield
1	–	HFIP	*O*-phosphinyl **4.61**	35%
2	$BF_3\ OEt_2$ (0.20 eq.)	CH_2Cl_2	*O*-phosphinyl **4.61**	37%
3[a]	–	HFIP	*O*-aryl **4.62**	0%
4[a]	–	TFE	*O*-aryl **4.62**	0%
5	–	HFIP	*O*-sulfonyl **4.8**	88%
6[a]	–	HFIP	*O*-sulfonyl **4.9**	15%
7	–	HFIP	*O*-sulfonyl **4.59**	68%
8	–	HFIP	*N*-Boc-*O*-sulfonyl **4.53**	0%

[a] Reaction was run for 17 h instead of 1 h.

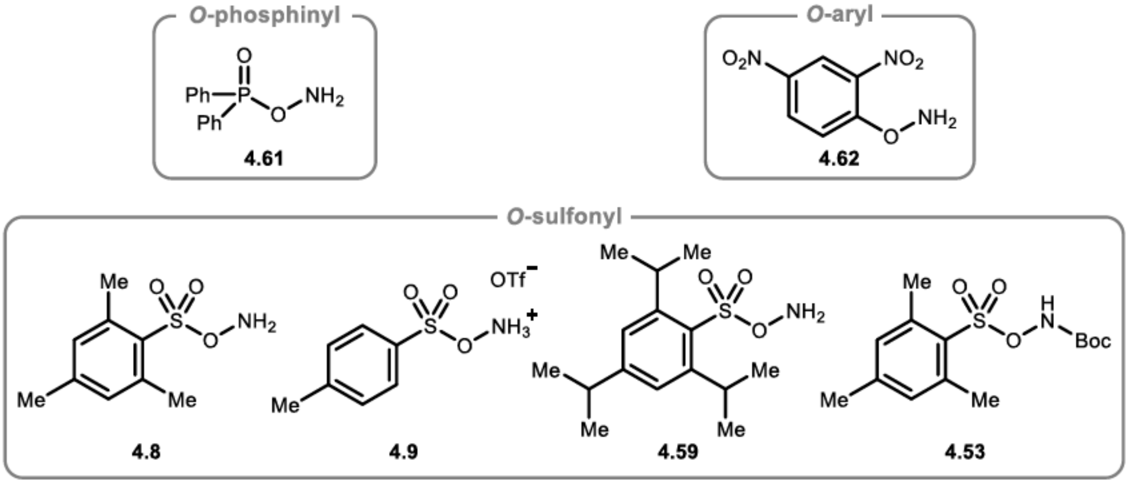
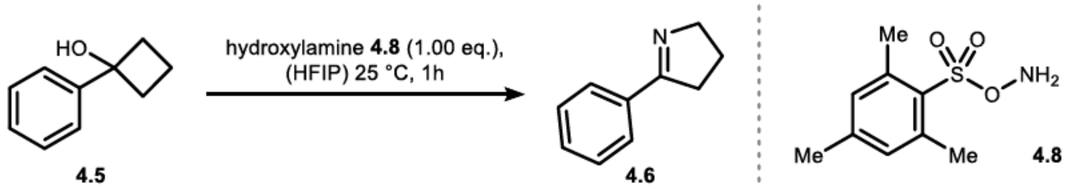


Figure 17: Overview of the applied *O*-substituted hydroxylamine reagents for the optimisation of the envisioned *N*-insertion.

In the following, differing concentrations of the reagents were tested. Carrying out the reaction at low concentrations led to an insignificant augmentation of product formation, whereas increasing the concentration slightly inhibited the formation of pyrrolidene **4.6** (Table 10, entries 1 to 3). Likewise, a variation of the reaction temperature led to a decline in yield (entries 3 and 4). Whilst conducting the reaction at low temperatures the conversion of cyclobutanol **4.5** is slowed down, elevating the temperature, on the other hand, led to partial decomposition of the hydroxylamine reagent **4.8**. Ultimately, the optimal reaction conditions were found, by amending the amount of hydroxylamine reagent applied (entries 5 to 9).

Table 10: Concentration and hydroxylamine reagent optimisation. Reactions were carried out on a 0.1 mmol scale in HFIP [0.2 M], NMR yield based on ^1H NMR experiments using CH_2Br_2 as an internal standard.

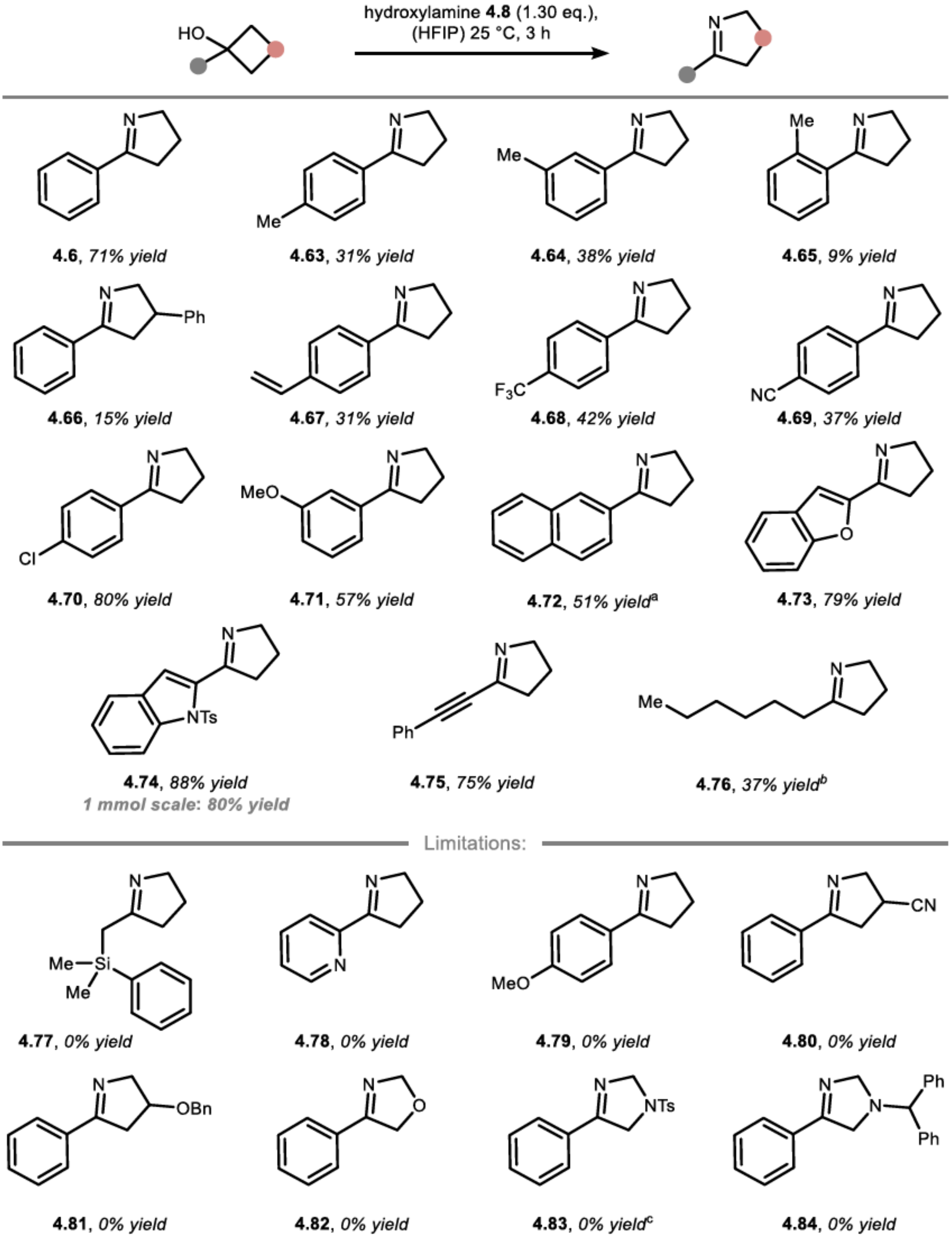


Entry	Changes from standard conditions	NMR yield
1	–	68%
2	Reaction performed in HFIP [0.05 M]	68%
3	Reaction performed in HFIP [0.8 M]	59%
4	Reaction performed at 0 °C	63%
5	Reaction performed at 50 °C	59%
6	1.10 eq. of aminating reagent **4.8** used	65%
7	1.30 eq. of aminating reagent **4.8** used	88%
8	1.50 eq. of aminating reagent **4.8** used	68%
9	2.00 eq. of aminating reagent **4.8** used	74%

4.4 Scope

In accordance with the research outline (*cf.* Chapter 4.1.3, Scheme 60), the title reaction is supposedly depending on the formation of a cationic intermediate. The stabilisation thereof is presumed to be facilitated by orbital interactions of the tertiary carbon centre of the employed alcohols. Therefore, to explore the scope and limitations of the envisaged *N*-insertion, a series of electronically differing tertiary cyclobutanol substrates was treated with *O*-(mesitylsulfonyl)hydroxylamine **4.8** as ambiphilic aminating reagent in HFIP. However, the optimised reaction conditions were altered, since the standard reaction was conducted on a bigger scale than the performed optimisation (Scheme 70).

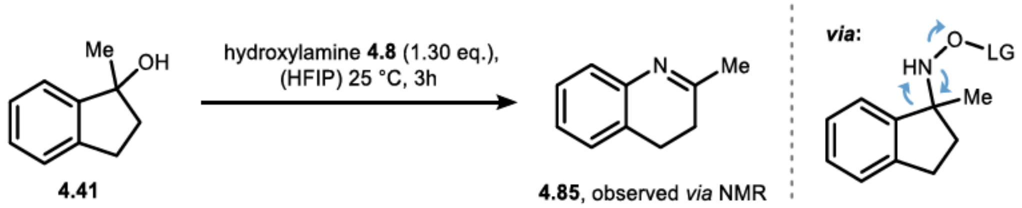
The substrate utilised in the seminal optimisation, phenyl cyclobutanol **4.5**, delivered phenyl pyrrolidene **4.6** in 71% yield. Moderately more electron-rich tolyl substituted pyrrolidenes **4.63** and **4.64** were afforded with diminished yields of 31% and 38%, respectively. When steric bulk was introduced by an *ortho*-substituted arene, the desired reaction was virtually shut down (See entry for **4.65**). The same holds true for the inefficient formation of 3,5-diphenyl pyrrolidene **4.66** from sterically more congested 1,3-disubstituted cyclobutanol **4.33**. Contrarily, alkenes were tolerated well, therefore the styrene derivative **4.67** was obtained under the standard conditions in a yield comparable to related electron-rich products. Additionally, electron-withdrawing substituents were surveyed, resulting in the isolation of trifluoromethylated pyrrolidene **4.68** and *para*-cyanophenyl pyrrolidene **4.69** in medium yields. Furthermore, halogenated pyrrolidene **4.70** was accessible in high yields. Although methoxy substituents generally increase the electron density in an aromatic system, introducing a methoxy group in *meta* position results in a decrease of negative charge in the benzylic position. Accordingly, *meta*-methoxy phenyl substituted cyclobutanol **4.24** was tested alongside other electron-poor substrates and resulted in the isolation of derivative **4.71** in comparable yields. Additionally, the influence of different aromatic systems was investigated by exposing naphthalene substituted cyclobutanol **4.27** to the standard reaction conditions. By employing TFE instead of HFIP, the π-extended derivative **4.72** was accessed. The scope was further expanded towards heterocyclic derivatives, hence benzofuran substituted pyrrolidene **4.73** and indole derivative **4.74** were both attained in high yields. Even upscaling the reaction was feasible, thus affording indole substituted pyrrolidene **4.74** with minor deviations in yield on a 1 mmol scale. The reactions dependence on benzylic stabilisation was examined by subjecting *sp*- and sp^3-substituted cyclobutanols to the standard reaction conditions. Interestingly, alkynyl substitution was not only tolerated but effectively delivered the desired product **4.75** in 75% yield. Moreover, alkyl substituted pyrrolidene **4.76** was achieved by amending the standard conditions inasmuch as a greater excess of aminating reagent was utilised and the reaction was allowed to run for 17 h. Stabilisation of the assumed cationic intermediate through a β-silyl group could not be harnessed, as cyclobutanol **4.32** was not stable under the standard reaction conditions. Consequently, silyl substituted pyrrolidene **4.77** was not formed. The shown method is further limited, hence nucleophilic heterocycles like pyridine or strong electron-donating substituents such as *para*-methoxy were not tolerated (See entries for **4.78** and **4.79**). Latent leaving groups attached to the cyclobutane core were similarly not tolerated (See entries for **4.80** and **4.81**). Likewise, the preparation of oxazole or imidazole derivatives **4.82** to **4.84** from 4-membered heterocyclic alcohols was not feasible with the developed method.



Scheme 70: Reactions were run in HFIP [0.2 M] on a 0.3 mmol scale, reported yields are of isolated products. [a] Reaction was run in TFE instead of HFIP. [b] Reaction was run for 17 h with 1.50 eq. of hydroxylamine 4.8. [c] The parent azetidinol was prepared by [redacted]

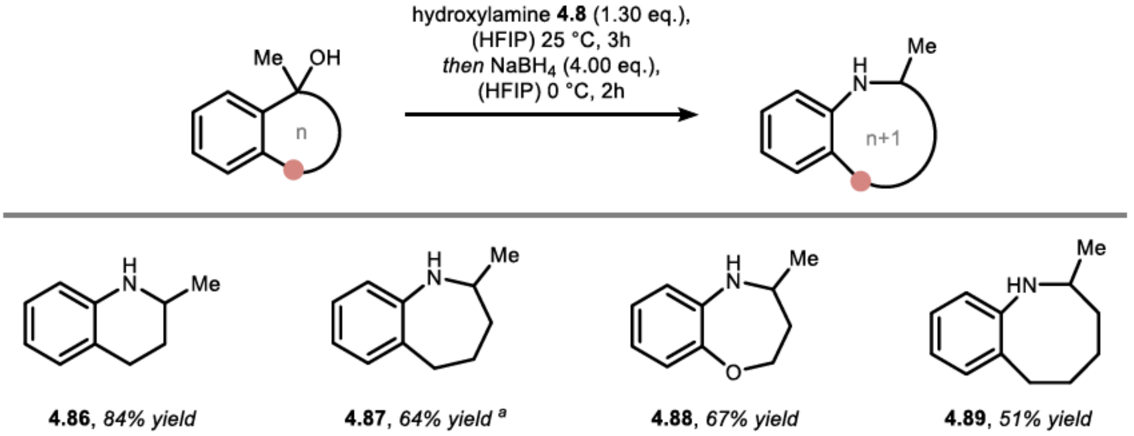
Encouraged by the shown results for the synthesis of pyrrolidenes *via* *N*-insertion into strained cyclobutanols, it was sought to extend the presented method for the synthesis of larger heterocycles. Therefore, benzannulated cyclic alcohols were envisioned to be promising starting materials due to benzylic stabilisation of the presumed cationic intermediate (*cf.* Chapter 4.1.3, Scheme 60).

Initially, benzannulated cyclopentanol **4.41** was subjected to the standard reaction conditions utilised for the preparation of pyrrolidenes. Indeed, a cyclic 6-membered imine was identified in the crude reaction mixture by ^{1}H NMR analysis (Scheme 71). However, attempts to isolate the presumably formed dihydroquinoline **4.85** derivative failed, as the imine turned out to be prone for hydrolysis and furthermore labile for oxidation.



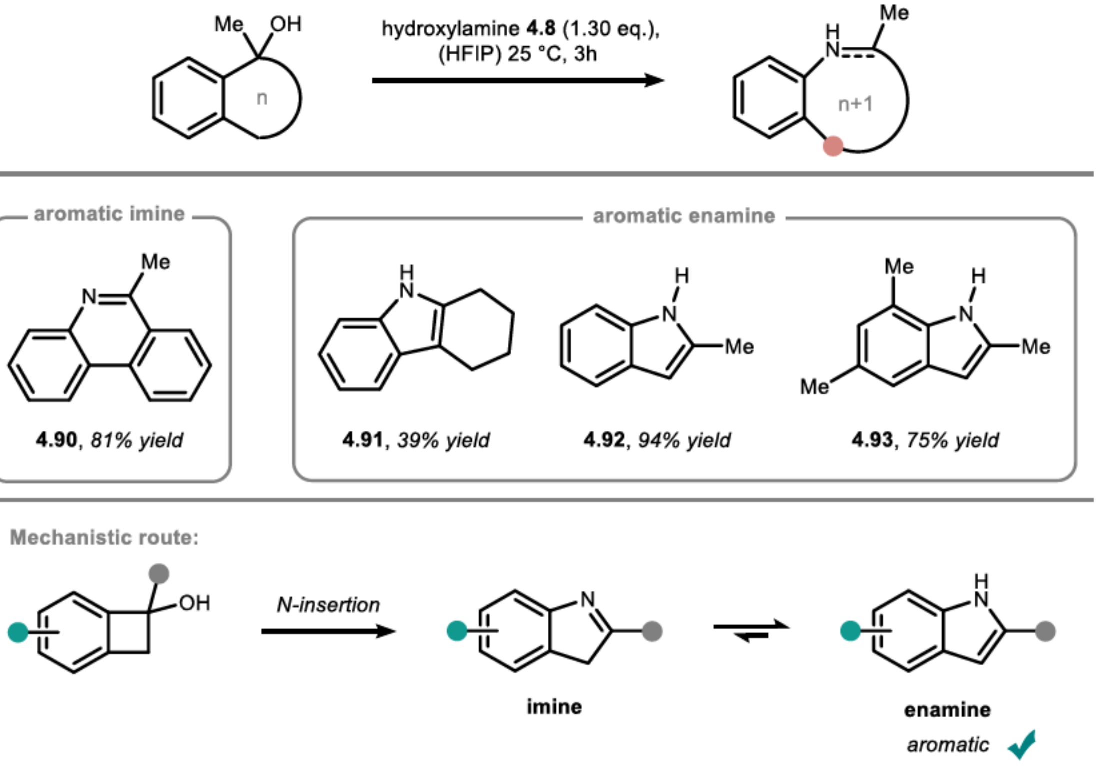
Scheme 71: Preliminary study for the *N*-insertion of benzannulated cyclic alcohols. Reaction was run in HFIP [0.2 M] on a 0.3 mmol scale.

Nevertheless, a ring-expanded product was isolated by simply adding a reducing agent to the crude reaction mixture after the proceeded atom insertion. With the modified reaction conditions in hand, a series of benzannulated cyclic alcohols was investigated regarding their reactivity towards *N*-insertions. Accordingly, the cyclic amines **4.86** to **4.89** were obtained in medium to good yields even tolerating other heteroatoms inside the ring. Interestingly, the obtained yields decreased with increasing ring size of the formed products, following the trends for the ring-strain energy (Scheme 72).



Scheme 72: *N*-insertion of benzannulated cyclic alcohols towards cyclic secondary amines, reactions were run in HFIP [0.2 M] on a 0.3 mmol scale, reported yields are of isolated products. ᵃ Reaction was run in TFE instead of HFIP as the solvent.

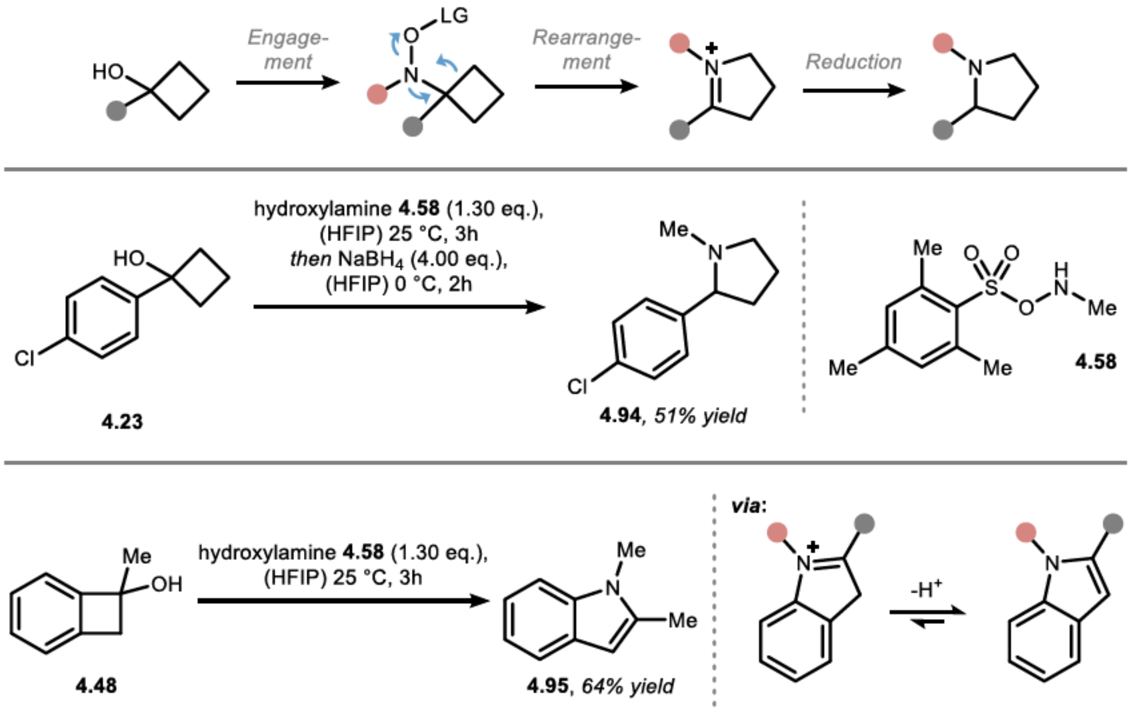
It was envisaged, that by careful design of the employed substrates, the gain of aromaticity can be exploited as an additional driving force in the desired *N*-insertion reactions. Therefore, fluorenol **4.45** was subjected to the standard reaction conditions initially applied for the synthesis of pyrrolidenes resulting in the formation of aromatic phenanthridine **4.90** (Scheme 73). Moreover, it was envisioned, that by means of atom insertion not only aromatic imines such as **4.90** could be formed. By using benzannulated cyclobutanols access towards indole motifs is possibly granted by *in situ* formation of a benzannulated 5-membered imine which subsequently tautomerises to the enamine structure thus gaining aromaticity (Scheme 73, bottom). Indeed, the *N*-insertion with such systems effectively yielded the respective tetrahydrocarbazol **4.91**, 2-methyl indole **4.92** and 2,5,7-trimethyl-indole **4.93**. The preparation of the latter indoles can be considered a build-and release strategy, since the starting material for their synthesis was prepared in a photochemical cyclisation step (*cf*. Chapter 4.2, Scheme 65).



Scheme 73: *N*-insertion of benzannulated cyclic alcohols towards heteroarenes, reactions were run in HFIP [0.2 M] on a 0.3 mmol scale, reported yields are of isolated products.

Inspired by the so far discussed insertions of an *NH*-group, it was investigated whether substituted nitrogen atoms could be transferred to the cyclic core of strained alcohols as well. If a pathway similar to the *NH*-insertion is assumed, a positively charged iminium ion is presumably formed. Thus, again, a reduction step is necessitated to form isolable products, namely *N*-substituted pyrrolidines (Scheme 74, top).

To probe the hypothesised reactivity, cyclobutanol **4.23** was put to reaction with *N*-methylated *O*-sulfonyl hydroxylamine **4.58** and a reducing agent. By doing so, *N*-methyl pyrrolidine **4.94** was isolated with 51% yield (Scheme 74, middle). Furthermore, *N*-methyl indole **4.95** was obtained in a medium yield by simply treating benzannulated cyclobutanol **4.48** with the *N*-methylated reagent **4.58**. Here, no reducing agent is needed, as the *in situ* formed iminium ion can rapidly undergo deprotonation hence affording the enamine structure of indole (Scheme 74, bottom).

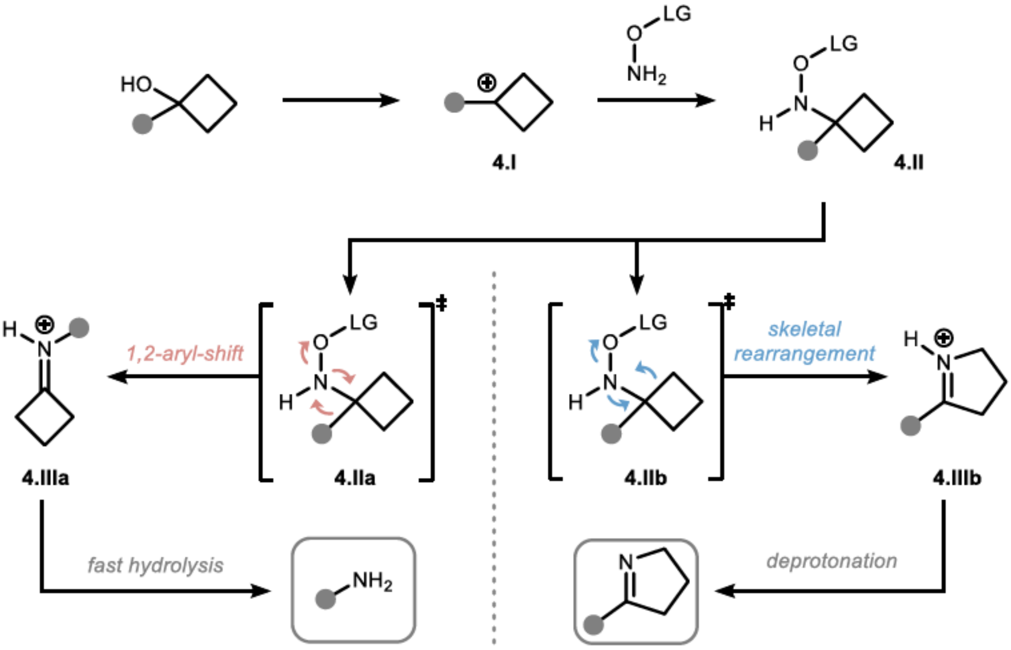


Scheme 74: *NMe*-insertion of cyclic alcohols towards *N*-substituted heterocycles, reactions were run in HFIP [0.2 M] on a 0.3 mmol scale, reported yields are of isolated products.

4.5 Mechanistic studies

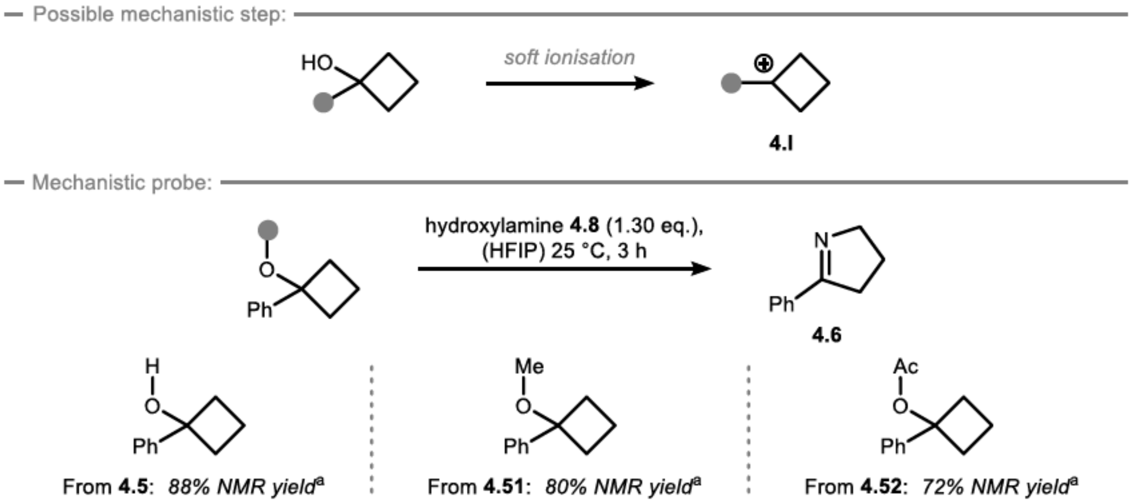
Hitherto, the applications of hydroxylamines in *N*-insertion reactions of cyclic alcohols were illustrated. The found conditions were widely applicable and generally productive in heterocycle syntheses, yet a deeper understanding of the underlying mechanistic principles is missing. Still, a hypothesis for the mechanistic background is postulated as follows (Scheme 75). The overall transformation is anticipated to proceed *via* nucleophilic substitution of the hydroxy group with the ambiphilic hydroxylamine reagent likely through an S_N1-type mechanism through intermediate **4.I**. The initial activation step is supposedly facilitated by the physicochemical properties, such as strong hydrogen bonds,[160] and high ionisation power,[161] of the perfluorinated protic solvents. After the successful engagement of the hydroxylamine and the formation of tetrahedral intermediate **4.II**, subsequently two different *Stieglitz*-type shifts are conceivably occurring.[162]

Thereby, either a 1,2-shift of the cyclobutanol's substituent or the desired skeletal rearrangement of the cyclic framework ensues from the transition states **4.IIa** and **4.IIb**, respectively. Consequently, two disparate iminium ions are formed. Exocyclic iminium **4.IIIa** is prone to hydrolysis, therefore ultimately affording amines, whereas endocyclic iminium **4.IIIb** is yielding the desired 5-membered pyrrolidine after deprotonation.



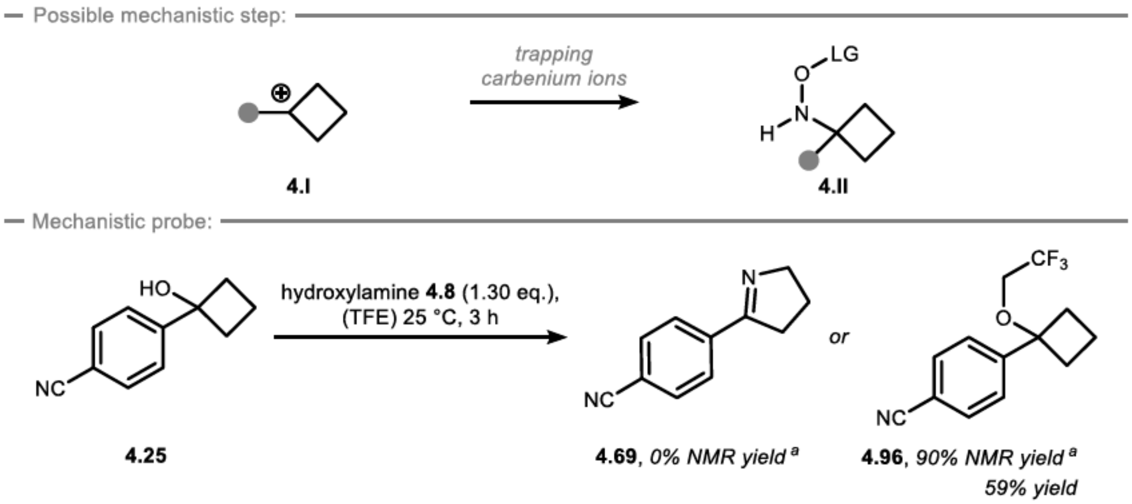
Scheme 75: Mechanistic picture for the *N*-insertion of hydroxylamines into cyclobutanols.

To corroborate the mechanistic hypothesis stated above, a set of experiments was designed. Firstly, the reactivity of phenyl cyclobutanol **4.5**, was compared to its derivatives, namely methyl ether **4.51** and acetate **4.52** (Scheme 76). When the optimised reaction conditions for the preparation of pyrrolidenes were applied, the desired cyclic imine **4.6** was formed in each case. Counterintuitively, the hydroxy group turned out to be most reactive, while the acetoxy group is presumed to be a stronger leaving group. Since the unsubstituted hydroxy functionality is more susceptible to engage in a hydrogen bond network, compared to the acetylated derivative, mild substrate activation through interaction with the fluorinated solvents is substantiated.



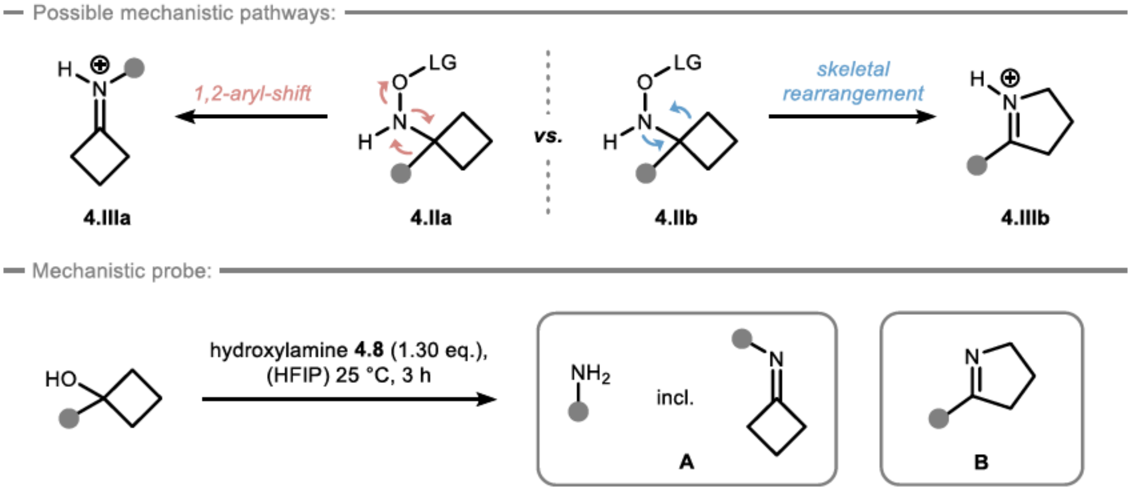
Scheme 76: Mechanistic probe for the substrate activation *via* soft ionisation. Reactions were run in HFIP [0.2 M] on a 0.1 mmol scale. ^aNMR yield was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.

Additionally, the influence of the perfluorinated solvents was reevaluated (Scheme 77). As already discussed, the effectiveness of the desired *N*-insertion is strongly dependent on the choice of solvent. Whilst *para*-cyano phenyl cyclobutanol **4.25** was transformed productively into pyrrolidene **4.69** through *N*-insertion in HFIP (*cf*. Scheme 70), a differing reactivity was observed in TFE, inasmuch as the trifluoromethyl ether **4.96** was almost exclusively formed. After initial activation by ionisation, TFE is outperforming aminating reagent **4.8** as a latent nucleophile, notwithstanding its low nucleophilicity.[163] This finding further underpins the importance of HFIP as a virtually non-nucleophilic solvent which stabilises carbocationic intermediates present in the reaction.



Scheme 77: Mechanistic probe for the trapping of reactive carbenium intermediates. Reaction was run in HFIP [0.2 M] on a 0.1 mmol scale. [a]NMR yield was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.

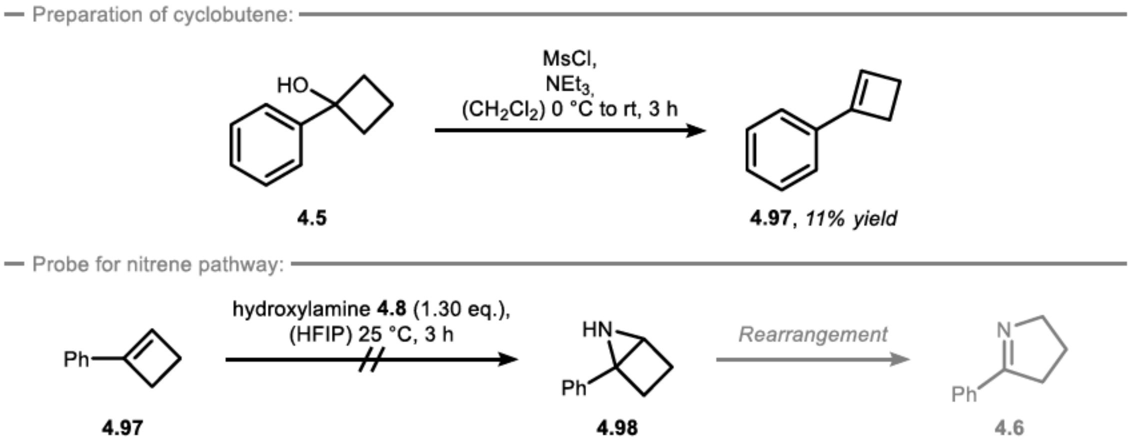
The crude product composition of the presented pyrrolidene synthesis *via* *N*-insertion was subjected to an in-depth analysis (Scheme 78), to gain insight into the two concurring pathways of the hypothetical *Stieglitz* type shifts (Scheme 75, left and right). Indeed, the electronic nature of the employed cyclobutanols had an impact on the reaction pathway. Consequently, Electron-rich substrates demonstrated an increased tendency for the undesired 1,2-aryl shift, which comes along with the formation of anilines, ultimately being formed by hydrolysis of *in situ* built cyclobutylimines. On the contrary, it was ascertained, that the less electron-rich the substrate molecule, the more pyrrolidine was formed by the desired skeletal rearrangement.



Entry	Substrate	NMR yield **A**^{a}	NMR yield **B**^{a}	Ratio **A**:**B**^{a}
1	● = 4-MeO-C_6H_4 (**4.21**)	66%	0%	100:0
2	● = 2-Me-C_6H_4 (**4.19**)	69%	9%	88:12
3	● = 4-Me-C_6H_4 (**4.17**)	23%	36%	38:62
4	● = C_6H_5 (**4.5**)	11%	80%	12:88
5	● = 4-Cl-C_6H_4 (**4.23**)	6%	89%	6:94

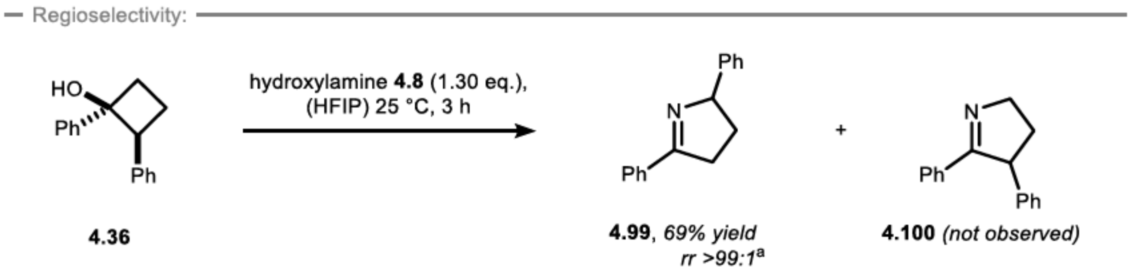
Scheme 78: Investigation of the diverging rearrangement pathways of tetrahedral intermediate 4.II. Reactions were run in HFIP [0.2 M] on a 0.3 mmol scale. ^{a}NMR yields were determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.

Only recently, *Yan* reported an alternative pathway for the synthesis of pyrrolidenes in a related study on iron catalysed *N*-insertions of cyclobutanols.[141] In their report of a transition metal catalysed reaction, a nitrene species is postulated to engage in a (2+1) cycloaddition with *in situ* formed cyclobutenes. To probe this mechanistic option, cyclobutene **4.97** was prepared from phenylcyclobutanol **4.5** and submitted to the standard reaction conditions, effectively resulting in the decomposition of the starting material (Scheme 79). Consequently, the aforementioned alternative mechanistic pathway through bicyclic aziridine **4.98** can be ruled out.



Scheme 79: Top: Synthesis of cyclobutene 4.97 by elimination of tertiary alcohol 4.5. Bottom: Survey of a concurring nitrene pathway for the *N*-insertion of cyclobutanols through *in situ* dehydration.

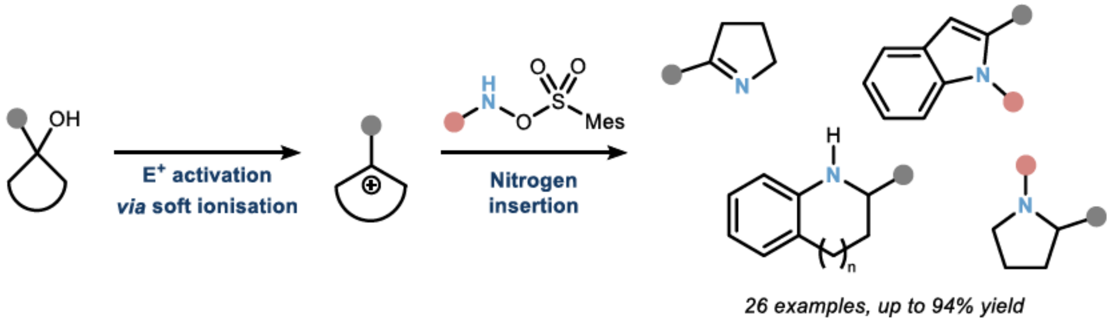
Additionally, the regioselectivity of the desired *N*-insertion towards pyrrolidenes was studied by subjecting unsymmetrical cyclobutanol **4.36** to the presented standard reaction conditions for the synthesis of pyrrolidenes (Scheme 80). As expected, only the higher substituted, thus the more electron-rich, carbon-atom underwent the desired skeletal rearrangement. Hence, the 5-membered heterocyclic product **4.99** was obtained, without any spectroscopic evidence of the corresponding regioisomer **4.100** being formed.



Scheme 80: Examination of the regioselectivity in the preparation of pyrrolidenes *via* *N*-insertion, reported yield is of isolated product. [a] Regiomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. *rr* = regiomeric ratio.

4.6 Summary and outlook

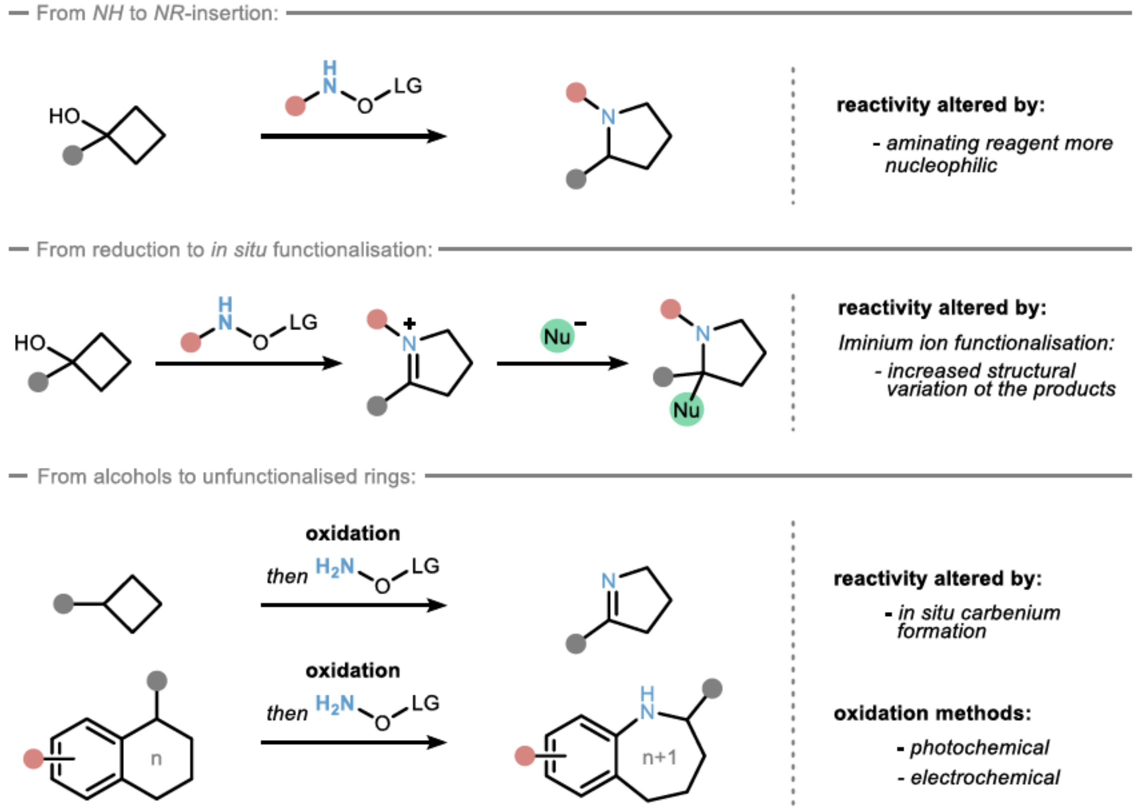
During the research endeavour delineated above, the atom insertion into cyclic alcohols was realised, thus yielding a variety of medicinally relevant *N*-heterocycles (Scheme 81).[164] A primary optimisation revealed the pre-eminence of *O*-sulfonyl hydroxylamine reagents in the envisioned reaction, which is initiated by an exceedingly mild ionisation of the starting materials by the chosen perfluorinated alcoholic solvents. By harnessing the special reactivity of the ambiphilic aminating reagent **4.8**, a productive method for the preparation of pyrrolidenes from cyclobutanols was developed. A broad range of functional groups was withal tolerated in this transition metal-free transformation, which is moreover not confined to aryl substituted cyclobutanols. Furthermore, the scope of the presented reaction was expanded towards the preparation of medium sized rings by utilising benzannulated cyclic alcohols. In order to investigate the scope and the limitations of the shown reaction, a range of cyclobutanol derivatives and benzannulated tertiary alcohols was prepared accordingly.



Scheme 81: Summarised results of the skeletal editing of cyclic alcohols through soft ionisation and nitrogen insertion. Mes = 2,4,6-trimethylphenyl.

Over the course of this investigation a novel entry to the manifold of indole syntheses was established by fruitfully combining a photochemical cyclisation step with the developed *N*-insertion method in a stepwise build-and-release strategy. Besides elaborating the synthetic applications, a preliminary mechanistic study was performed thus providing a mechanistic picture for the *N*-insertion. However, the mechanistic background is not fully understood yet and open for future research including kinetic measurements or quantum-chemical calculations.

In addition to the *NH*-group insertions an initial proof-of-concept for the insertion of an *NMe*-group into a molecular skeleton was achieved, which can mark the outset for future applications of the presented method (Scheme 82, top). Moreover, capturing iminium intermediates formed throughout the atom insertion reaction by differing nucleophiles can be a topic for future research (Scheme 82, middle). In lieu of an already oxidised cyclobutane derivative, such as cyclobutanol, ideally non-functionalised hydrocarbons should be addressed in future endeavours (Scheme 82, bottom). On that account, photochemical or electrochemical methods are promising approaches for the *in situ* formation of the crucial carbenium intermediate.



Scheme 82: Prospects for future research on the atom insertion of carbocycles towards the preparation of *N*-heterocycles.

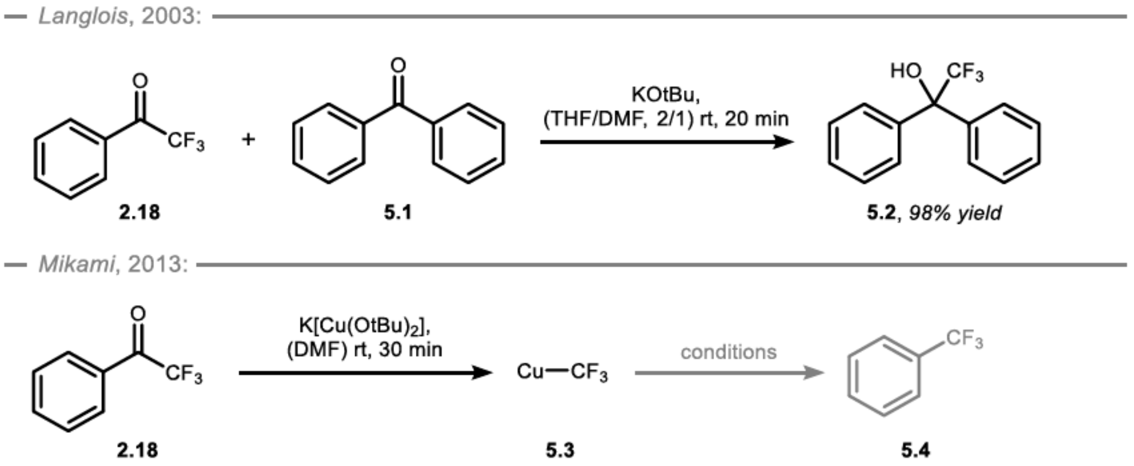
5 Miscellaneous reactions and proof-of-concept studies

Over the course of the projects delineated above, a few findings of mechanistic experiments, or observations made during the synthesis of substrate molecules, led to the development of new project areas, which go beyond the scope of the already discussed transformations. A number of mere serendipitous findings, which possibly mark the basis for new project ideas, are outlined briefly in the following.

5.1 Haloform reaction of trifluoroacetophenones and its applications

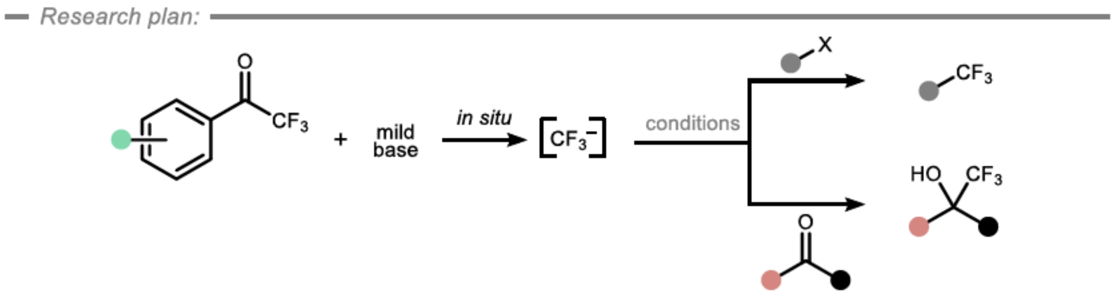
Motivated by the ubiquitous presence of fluorinated molecules in medicinal,[165] agrochemical[166] and material sciences[167] a variety of methods to install fluorinated groups into a molecular scaffold including radical,[168] nucleophilic,[169] electrophilic,[170] transition metal catalysed[171] or photochemical[172] approaches came to fruition. Employing fluoroform as an atom efficient source of a trifluoromethyl group is intriguing although careful measures have to be taken due to its huge potential as a greenhouse gas.[173] Nevertheless, its use is emerging in the chemical literature.[174] Handling gaseous trifluoromethane requires special equipment in the laboratory. Therefore, ways to circumvent the use of trifluoromethane in nucleophilic perfluoroalkylation reactions were established with a number of bench stable trifluoromethane sources reported to the literature with trimethylsilyltrifluoromethane as the most prominent representative.[66,175] Furthermore, perfluorinated sulfones,[176] substituted phosphonates,[177] acetals[178] and aminals[179] can be used. There is also literature precedent for the direct use of trifluoromethyl ketones for the trifluoromethylation of ketones through a haloform type fragmentation of the utilised trifluoromethylketones.[180] The haloform type fragmentation of trifluoroacetophenones is unlike slower compared to its heavier homologues trichloro- or tribromoacetophenone.[181]

However, this haloform type fragmentation can be synthetically used as shown by *Langlois* and *Mikami* independently.[180,182] *Langlois* and coworkers presented the trifluoromethylation of ketones with limited applicability as only non-enolisable benzophenones like **5.1** were applied to the reaction conditions thereby no more than four trifluoromethylated alcohols such as **5.2** were prepared as they reported initially (Scheme 83, top). *Mikami* and coworkers on the other hand have shown the direct synthesis of trifluoromethyl copper **5.3** as a highly reactive trifluoromethylating reagent by fragmentation of trifluoroacetophenone **2.18** (Scheme 83, bottom) which was used for instance in the preparation of trifluorotoluene **5.4**. Both approaches have the use of strong bases in common which drastically reduces the applicability of the presented methods.



Scheme 83: Applications of trilfuoroacetophenones in trifluoromethylation reactions. Top: Trifluoromethylation of benzophenones reported by *Langlois*.[180] Bottom: Preparation of Trifluoromethyl copper for transition metal catalysed trifluoromethylations by *Mikami*.[182]

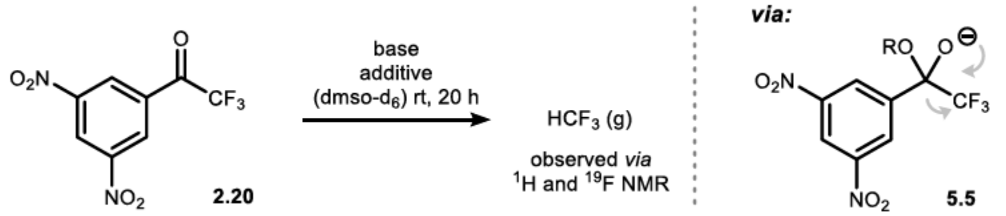
During the investigations on the formation of hemi ketals with electron-poor trifluoroacetophenones a similar fragmentation yielding fluoroform was observed (*cf.* Chapter 2.3.1, Scheme 28). The highly electrophilic ketones were assumed to facilely undergo fragmentation upon release of the trifluoromethyl anion initiated by adding a mild and nucleophilic base. Conditions to capture this reactive species either through cross-coupling or addition to carbonyl compounds were sought after (Scheme 84).



Scheme 84: Research plan for the mild *in situ* generation of trifluoromethyl anion by haloform type fragmentation of trifluoroacetophenones.

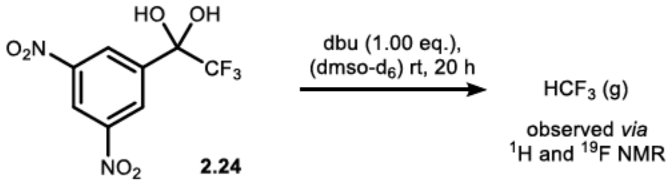
The behaviour of the prepared trifluoroacetophenones with bases was therefore analysed to a greater extent by adding varying *Brønsted* bases to a solution of the trifluoroacetophenone. In a series of NMR scale experiments, the fragmentation of dinitrotrifluoroacetophenone **2.20**, presumably *via* intermediate **5.5** was observed qualitatively after addition of *tert*-butoxide bases (Table 11, entries 1 to 4). Although careful measures were taken, the full absent of water in the reaction mixtures could not be guaranteed, so the presence of hydrate **2.24** as the actual trifluoromethyl-releasing agent cannot be excluded. Nevertheless, supposedly adding water had no qualitative influence on the fragmentation (Table 11, entry 3). Furthermore the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu) resulted in the fragmentation as well (entry 5), whereas weaker bases such as silver carbonate or silver oxide were ineffective (entries 6 and 7).

Table 11: Fragmentation of dinitrotrifluoroacetophenone 2.20 with strong bases. Reactions were performed in dmso-d_6 [0.1 M] on a 0.1 mmol scale and monitored *via* ^{1}H and ^{19}F NMR.



Entry	Base (1.00 eq.)	Additives (1.00 eq.)	Fragmentation
1	LiO*t*Bu	–	yes
2	NaO*t*Bu	–	yes
3	NaO*t*Bu	H_2O	yes
4	KO*t*Bu	–	yes
5	dbu	–	yes
6	Ag_2CO_3	H_2O	no
7	Ag_2O	H_2O	no

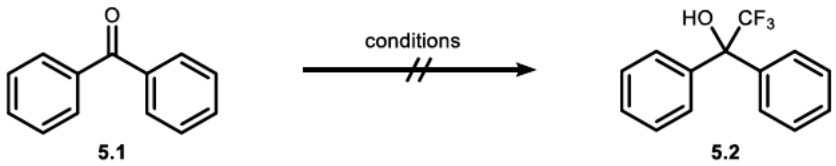
Supposedly, the fragmentation is proceeding *via* tetrahedral intermediate **5.5** which resembles the structure of the hydrated form **2.24** of ketone **2.20**. Consequently, it was investigated whether the hydrate **2.24** can be deprotonated resulting in the fragmentation to trifluoromethane. Indeed, trifluoromethane was obtained by adding dbu as a base to a solution of hydrate **2.24** (Scheme 85).



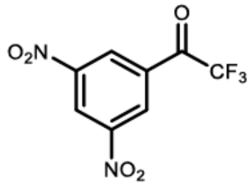
Scheme 85: Base induced trifluoromethane release from hydrate 2.24.

Attempts to capture the trifluoromethyl anion were made with conditions likewise to those reported by *Langlois*[180] but failed to deliver the desired trifluoromethylated alcohol **5.2** (Table 12).

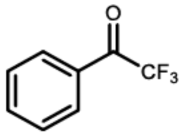
Table 12: Attempts for the trifluoromethylation of non-enolisable ketone 5.1 with conditions similar to *Langlois* and coworkers.[180]



Entry	Conditions
1	ketone **2.20** (1.00 eq.), LiO*t*Bu (1.00 eq.), (THF) rt, 24 h
2	ketone **2.20** (1.00 eq.), nBu$_4$NF (1.00 eq.), (THF) rt, 24 h
3	ketone **2.18** (1.00 eq.), LiO*t*Bu (1.00 eq.), (DMF/THF) rt, 30 min
4	ketone **2.18** (1.00 eq.), NaO*t*Bu (1.00 eq.), (DMF/dmso-d$_6$) rt, 30 min
5	ketone **2.18** (1.00 eq.), NaO*t*Bu (1.00 eq.), (DMF/THF) rt, 30 min
6	ketone **2.18** (1.00 eq.), KO*t*Bu (1.00 eq.), (DMF/THF) rt, 30 min
7	ketone **2.18** (1.00 eq.), KO*t*Bu (1.00 eq.), (DMF/THF) –40 °C, 30 min



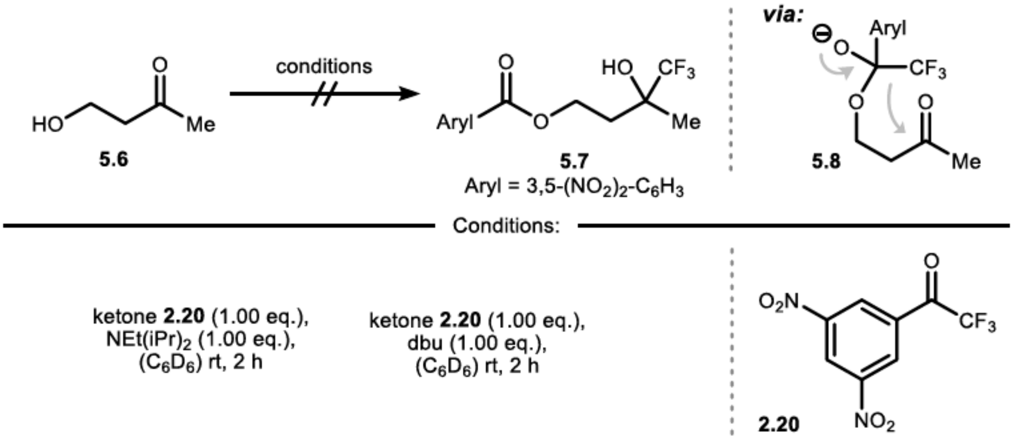
2.20



2.18

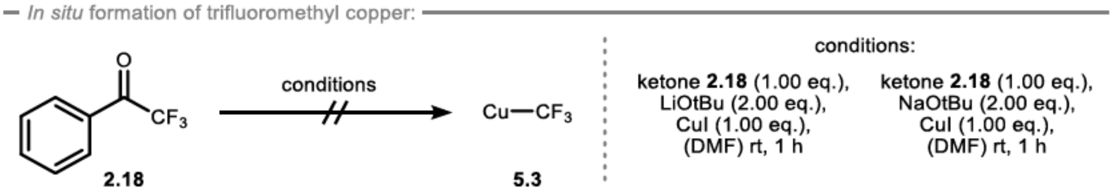
In addition to these attempts for intermolecular trifluoromethylation, it was investigated if the trifluoromethyl group can be transferred intramolecularly. It was hypothesised that a hemi ketal of a trifluoroacetophenone derivative could be formed with a hydroxy substituted electron-poor ketone which can undergo base triggered trifluromethyl group transfer from the acetophenone derivative to the other ketone resulting in the formation of a benzoic acid ester. (Scheme 86).

Therefore, β-hydroxy ketone **5.6** was treated with the electron-deficient trifluoroacetophenone **2.20**. Amine bases such as *Hünig's* base or dbu were used to trigger the trifluoromethyl transfer. In both cases no spectroscopic proof for the formation of the desired ester **5.7** was found. Certainly, the hemi-ketal **5.8** is not transferring its trifluoromethyl group, it rather acts as a leaving group. Thereby, elimination of the hydroxy group of ketone **5.6** was facilitated. The formally dehydrated product, methyl vinyl ketone, was observed *via* NMR spectroscopy as only reaction product besides the hemi ketal.



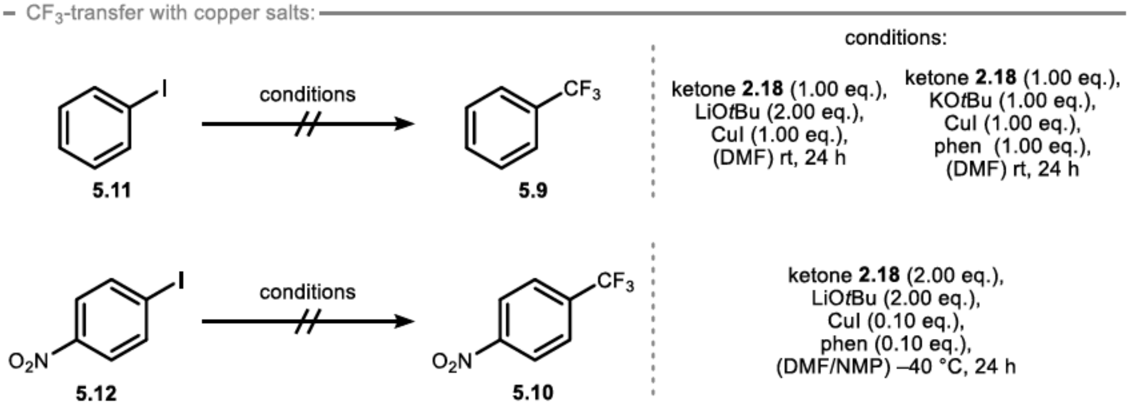
Scheme 86: Attempts for the intramolecular trifluoromethylation of enolisable ketones through a transient hemi-ketal.

Additionally, endeavours were undertaken to form trifluoromethylated transition metal species following methods reported by *Mikami*, *Amii* and *Grushin*.[182,183] Neither used conditions led to the formation of trifluoromethyl copper albeit proof for the haloform type fragmentation were found. Although known to the literature, the released gaseous trifluoromethane was not cuprated under the employed conditions (Scheme 87).



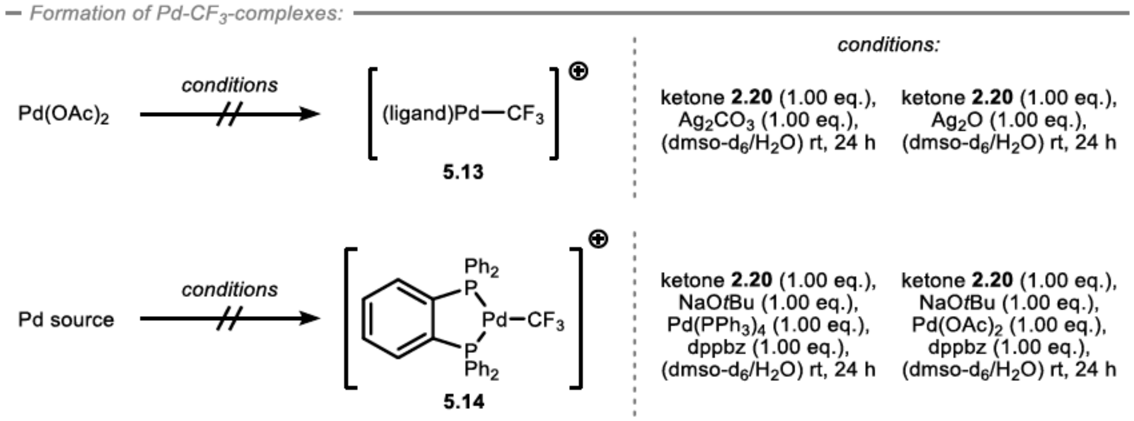
Scheme 87: Attempted trifluoromethylation of copper salts according to *Mikami* and *Grushin*.[182,184]

Notwithstanding the missing direct proof for the formation of a trifluoromethyl copper species, it is conceivable, that a cuprated trifluoromethyl species is transiently formed with a limited life time, therefore undergoing rapid degradation due to limited stability to the applied reaction conditions. To further prove this hypothesis and to find an indirect confirmation for the formation of cuprated trifluoromethane, literature known protocols for the trifluoromethylation of iodoarenes with organo copper species were followed. Again, the trifluoromethylated products **5.9** and **5.10** were not observed from neither iodobenzene **5.11** nor 4-nitro-iodobenzene **5.12** (Scheme 88).



Scheme 88: Attempted trifluoromethylation of iodoarenes according to *Mikami*, *Grushin* and *Amii*.[182,183] phen = 1,10-phenanthroline, NMP = *N*-methyl-2-pyrrolidone.

Moreover, it was examined whether trifluoromethylated palladium complexes could be formed after base induced fragmentation of trifluoroacetophenone **2.20**, as there is evidence in the literature that palladium complexes can scavenge trifluoromethyl anions.[185] Firstly, palladium acetate was treated with a mixture of silver bases and ketone **2.20** in wet dimethylsulfoxide. By doing so, no evidence for the formation of a trifluoromethylated palladium complex, such as **5.13**, was found (Scheme 89, top). It was further investigated if an added bidentate ligand facilitates the formation of a trifluoromethylated complex. Therefore, 1,2-bis(diphenylphosphino)benzene (dppbz), which is known to strongly stabilise trifluoromethylated palladium complexes,[186] was utilised. Additionally, a stronger alcoholate base was used to enhance the fragmentation of trifluoroacetophenone **2.20**. However, the formation of a trifluoromethylated complex, like **5.14**, could not be verified by that means. Furthermore, the reaction outcome was unaffected from the choice of palladium source as both, Pd^0 and Pd^{II} species, did not facilitate formation of the sought after complex (Scheme 89, bottom).



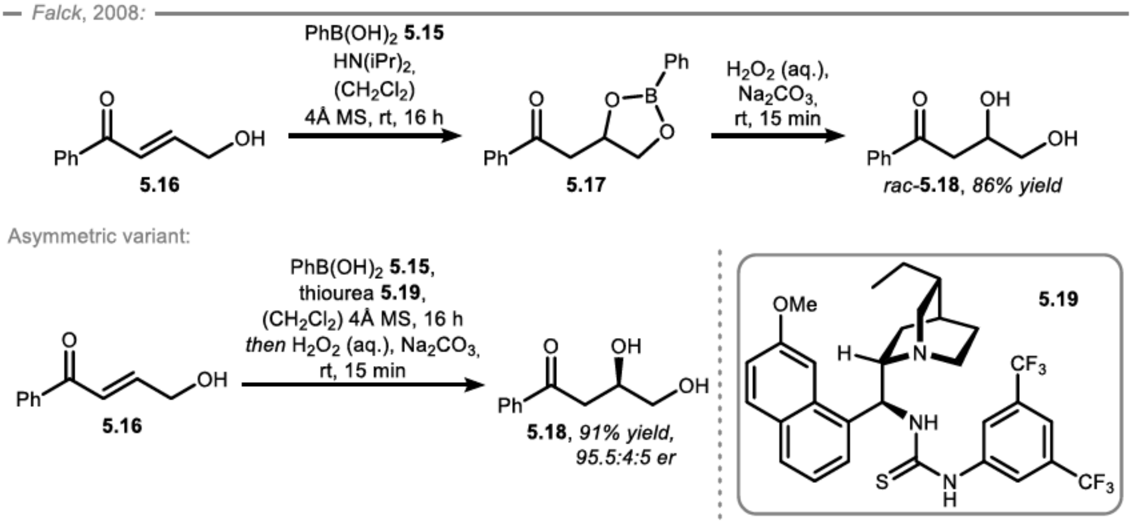
Scheme 89: Unsuccessful efforts for the preparation of trifluoromethylated palladium complexes. Displayed palladium complexes are only representative structures of the supposedly formed complexes without guarantee given for exactness in ligand surrounding and oxidation state.

In conclusion, it was shown that trifluoroacetophenones are a viable and benign source of trifluoromethane after treatment with a base, through haloform type fragmentation of a tetrahedral intermediate. The release of trifluoromethane from hydrate **2.24** triggered by the addition of dbu is an exceedingly mild example for the desired fragmentation as usually stronger alcoholate bases are required for related reactions. This finding offers room for future research with milder bases or nucleophilic bases such as morpholine. Furthermore, endeavours to transfer trifluoromethyl groups intra- or intermolecularly to electrophilic ketones were undertaken albeit no trifluoromethyl alcohols could be isolated. Additionally, transition metals were employed as trifluoromethyl scavenger. However, neither direct nor indirect evidence for the formation of trifluoromethylated metal complexes were found.

5.2 Boronic acids as *O*-nucleophiles in ring-opening reactions

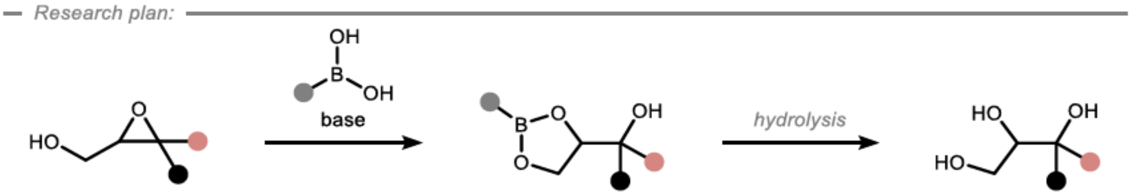
In addition to the outlined desymmetrisation of oxetanols with transient hemi ketals (*cf.* Chapter 2), it was investigated, if other transiently formed acidic species undergo a ring-opening and ring-closing sequence on strained ethers.

Therefore, boronic acids were investigated, due to their similar acidity compared to the estimated value of the already discussed hemi ketals.[187] Typically, boronic acids or boronic esters are used as *C*-nucleophiles for example in *Brown* type allylations or *Michael* additions.[188] Contrarily, examples of their use as *O*-nucleophiles remains scarce.[189] *Falck* and coworkers did pioneering work in this area and have shown, that phenylboronic acid **5.15** can be utilized in an intramolecular oxy-*Michael* addition with an alcohol directing group (Scheme 90). Crucial to the success of this ring-closing from allylic alcohol **5.16** was the addition of a nucleophilic amine base. Subsequent oxidative cleavage of the resulting dioxaborolane **5.17** afforded the corresponding diol **5.18**. A further improvement of their method was achieved by applying a quinine derived thiourea catalyst **5.19** which activates both, the *Michael* acceptor through *Brønsted* acidic and the nucleophile by *Lewis* basic interactions. Thereby, high degrees of enantiocontrol with maintained high yields were achieved.



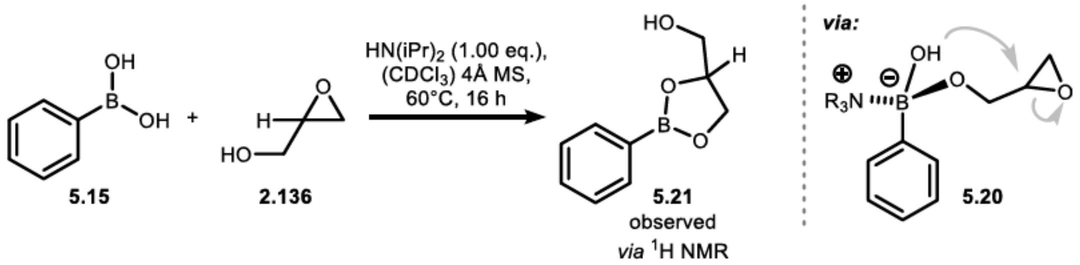
Scheme 90: Hydroxy group directed oxy-*Michael* addition of boronic acids reported by *Falck* and coworkers.[189b]

Inspired by the work of *Falck* and coworkers, boronic acids were identified to be promising substrates for the ring-opening and ring-closing sequence of strained ethers to yield polyolic compounds (Scheme 91).



Scheme 91: Research plan for the envisioned intramolecular ring-opening of oxiranes with boronic acids.

Therefore, phenyl boronic acid **5.15** and oxirane **2.136** were treated with an amine base (Scheme 92). Based on the results of *Falck* and coworkers, partial esterification of the boronic acid and the alcohol was assumed. Formation of a *Lewis* adduct **5.20** after addition of an amine base subsequently leads to the ring-opening of oxirane **2.136** (Scheme 92, right).



Scheme 92: Left: Initial results for the intramolecular ring-opening of strained oxiranes with boronic acids as *O*-nucleophiles. Reaction was run on a 0.1 mmol scale in $CDCl_3$ [0.15 M]. Right: Assumed mechanistic key step *via Lewis* adduct formation.

The reaction was monitored *via* ^{1}H NMR and dioxaborolane **5.21** was observed. First attempts to isolate the ring-opened product by column chromatography were not fruitful, as the boronic ester formed in the reaction tends to hydrolyse, notwithstanding the stabilisation through intramolecular interactions of the hydroxy group with the empty *p*-orbital of the boron atom.[190]

The reaction was deeper analysed by a series of NMR scale experiments (Figure 18). Therefore, oxirane **2.136** was treated with diisopropylamine and phenyl boronic acid independently. It was shown that the addition of base had an almost neglectable effect on the chemical shifts of the starting material, whereas the addition of phenyl boronic acid **5.15** shifted the original signals. This can be attributed to the partial formation of a boronic ester. When both, boronic acid and amine base, were added, a new set of signals was observed in the ^{1}H NMR which resembled the signals obtained for the structurally related dioxolane compound **2.137**, which was prepared by the intramolecular ring-closing and ring-opening of oxetanol **2.136**. Furthermore, the formation of exclusively one boron containing species was observed by ^{11}B NMR techniques with a signal shift of $\Delta\delta = 2$ ppm compared to phenylboronic acid (Figure 19). After this initial proof of concept, no further investigations were exercised. However, the *O*-nucleophilic ring-opening of strained ethers with boronic acids is a promising way for the preparation of polyolic compounds.

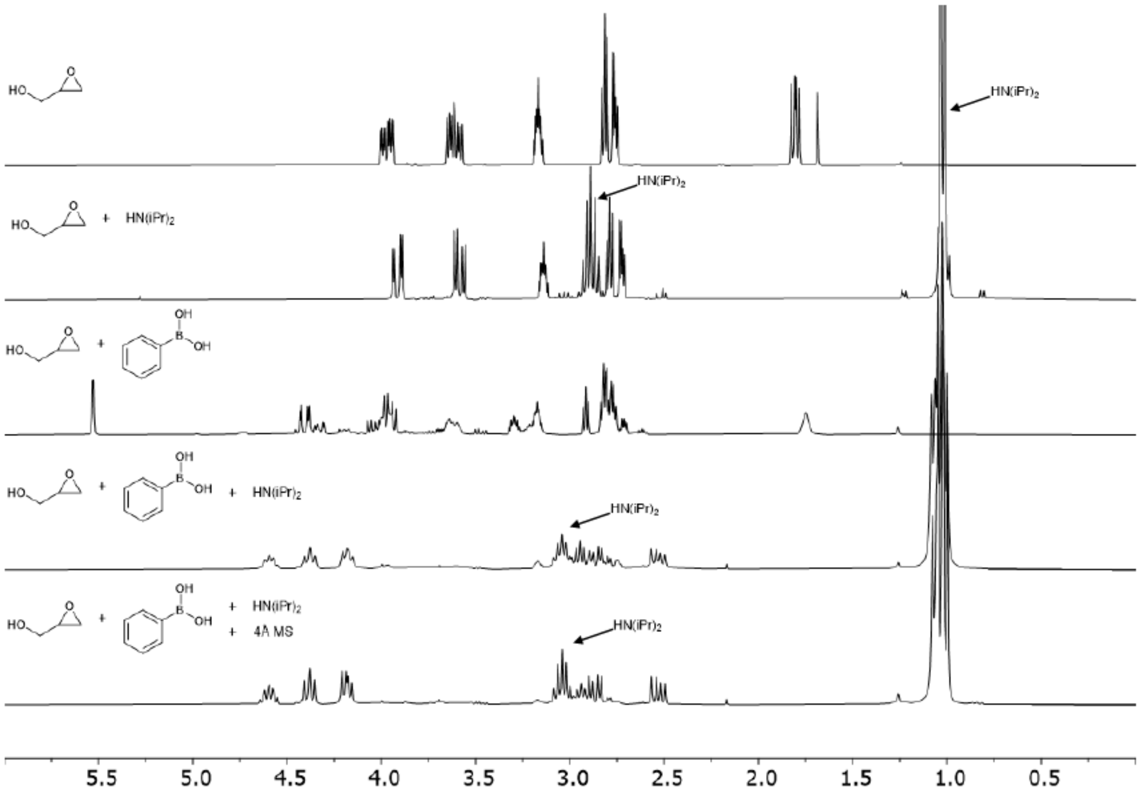


Figure 18: Overlay of ^{1}H NMR spectra recorded in $CDCl_3$ [0.1 M] for the reaction of oxirane 2.136 with boronic acid 5.15 on a 0.1 mmol scale. From top to bottom: Spectrum of oxirane 2.136. Spectrum of oxirane 2.136 with $HN(iPr)_2$. Spectrum of oxirane 2.136 with phenyl boronic acid 5.15. Spectrum of oxirane 2.136 with phenyl boronic acid 5.15 and diisopropylamine. Spectrum of oxirane 2.136 with phenyl boronic acid 5.15, diisopropylamine and molecular sieves.

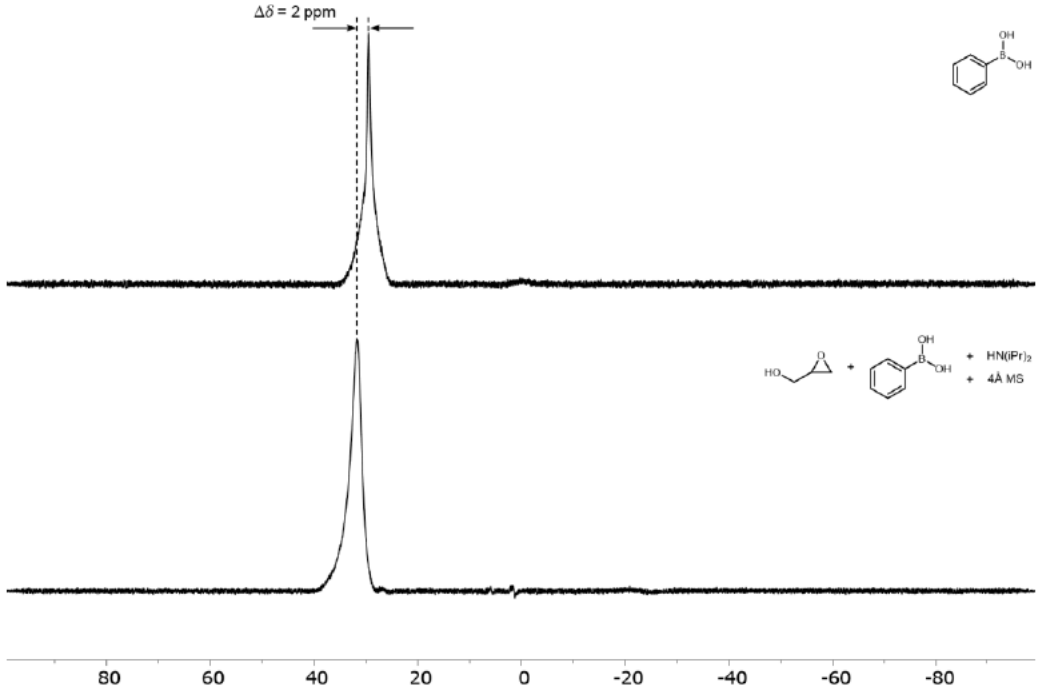
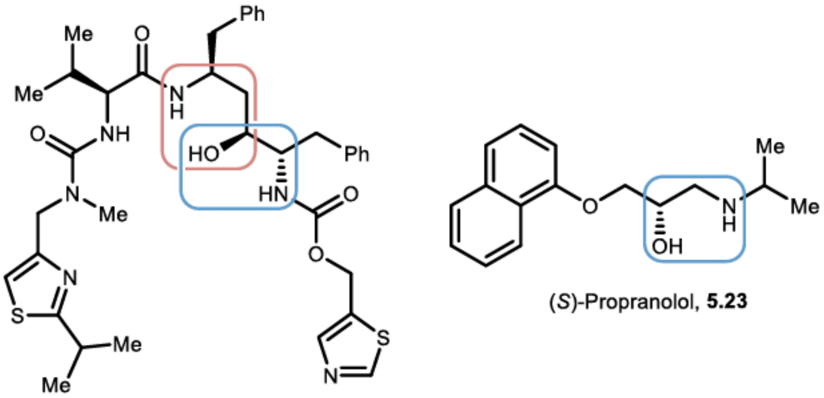


Figure 19: Overlay of ^{11}B NMR spectra recorded in $CDCl_3$ [0.1 M] on a 0.1 mmol scale. Top: Spectrum of phenylboronic acid 5.15. Bottom: Spectrum of oxirane 2.136 with phenyl boronic acid 5.15, diisopropylamine and molecular sieves.

5.3 *C–C* and *C–H* functionalisations with trichloro acetimidates

During the COVID pandemic the medicinal drug Ritonavir **5.22**, formerly used as an antiretroviral compound in the therapy of HIV/AIDS,[191] became famous as a possible treatment against the respiratory disease caused by the Corona virus.[192] From the perspective of an organic chemist, 1,2- and 1,3-amino alcohols were identified as important structural motifs in this compound (Figure 20). This core structure can additionally be found in other marketed drugs such as Propranolol **5.23**, a *β*-blocker which is listed in the World Health Organisation's List of Essential Medicines.[191a,193]

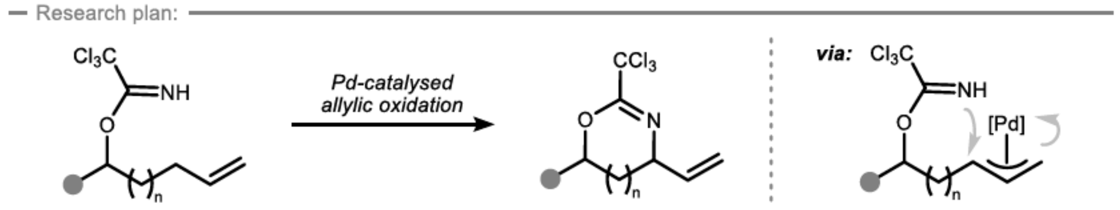


Ritonavir, **5.22**

(*S*)-Propranolol, **5.23**

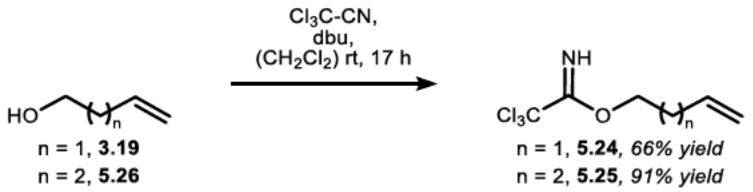
Figure 20: Chemical structures of Ritonavir 5.22 and Propanolol 5.23.

Due to their importance as a structural motif in drug-like compounds, there are multiple ways to engage their synthesis.[194] Incited by the work on allylic *C–H* oxidations (*cf*. Chapter 3) a method for the palladium catalysed allylic amination with trichloroacetimidates should be found within this project (Scheme 93). This class of compounds was identified as a promising starting material as their nucleophilic properties in ring-closing reactions were already studied in amino-halogenations.[195] Moreover, trichloroacetimidates have been successfully applied in *Tsuji-Trost* type cyclisations.[196]



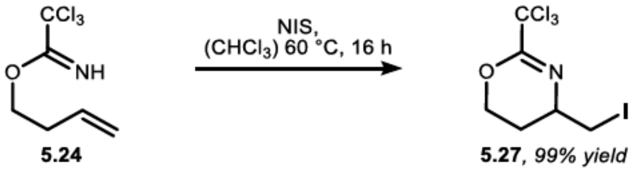
Scheme 93: Research plan for the synthesis of cyclic aminoalcohols by means of palladium catalysed *C–H* oxidation.

To study the outlined reactivity, trichloroacetimidates **5.24** and **5.25** were prepared in good to high yields following a literature known protocol from alcohols **5.26** and **3.19**, respectively.[197]



Scheme 94: Preparation of trichloroacetimidates 5.24 and 5.25 from primary alcohols 3.19 and 5.26 according to a literature known procedure.[197]

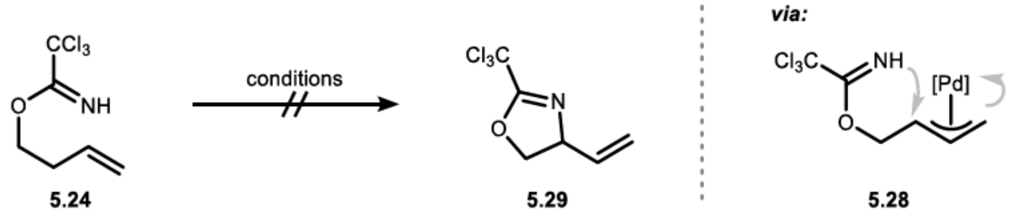
With those imidates in hand, at first their reactivity towards amino-halogenation was tested. By adding an electrophilic iodine source to the imidate **5.24**, the cyclic 1,3-amino alcohol **5.27** was synthesised. Further investigations on related amino-chlorinations were undertaken by [redacted]



Scheme 95: Amino-iodination of allylic alcohol 5.24.

Furthermore, the applicability of trichloroacetimidates in allylic *C–H* aminations through a palladium allyl complex, such as **5.28**, was tested by applying reaction conditions likewise to those reported by *White* and coworkers for the preparation of cyclic aminoalcohols (Table 13, entries 1 and 2).[126] Those catalytic conditions led to the consumption of the starting material **5.24**, without spectroscopic proof for the desired oxazole product **5.29**. Even increasing the catalyst loading of palladium catalyst **3.12**, from substoichiometric to stoichometric amounts (entries 3 to 5), was not facilitating product formation. Again, the starting material was consumed under the reaction conditions without the oxazole **5.29** being formed. Thereby, only a complex product mixture was obtained. Moreover, proof for catalyst degradation through ligand decomposition were found as phenyl vinyl sulfoxide was spectroscopically identified as a major product.

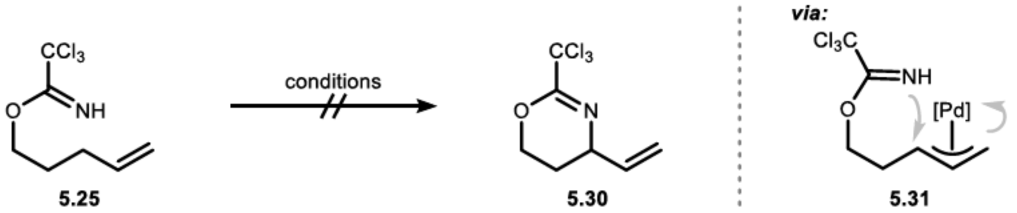
Table 13: Conditions for the attempted allylic oxidation of trichloroacetimidate 5.24. Reactions were run on 0.1 mmol or 0.05 mmol scale in various concentrations.



Entry	Catalyst (eq.)	Additives (eq.)	Solvent	*T*
1	Pd catalyst **3.12** (0.10 eq.)	BQ (2.00 eq.), 4-NO_2-C_6H_4-CO_2H (0.10 eq.)	$CDCl_3$	40 °C
2	Pd catalyst **3.12** (0.10 eq.)	BQ (2.00 eq.)	AcOH	40 °C
3	Pd catalyst **3.12** (0.50 eq.)	BQ (1.00 eq.)	CH_2Cl_2	40 °C
4	Pd catalyst **3.12** (1.00 eq.)	–	CD_2Cl_2	40 °C
5	Pd catalyst **3.12** (1.00 eq.)	–	AcOH	40 °C

In addition to the allylic trichloroacetimidate **5.24**, homoallylic imidate **5.25** was investigated. Again, substoichiometric amounts of a palladium salt did not lead to the desired 1,3-aminoalcohol **5.30** (Table 14, entry 1). Stoichiometric amounts of different palladium sources, including complex **3.12**, palladium(II) trifluoroacetate or allylpalladium(II) chloride dimer, were also not effective in the sought-after transformation (entries 2 to 5). When applying the latter, silver acetate was added to enhance the electrophilicity of the palladium centre by removing a chloride ligand. Through the resulting precipitation of silver chloride, additional space in the coordination sphere of the metal centre is granted. Nonetheless, this attempt was not fruitful at all. Varying the solvent (entries 6 to 8) or adding a *Brønsted* base (entry 9) had no beneficial effect on the reaction outcome as well. Again, the formation of a palladium allyl species, like **5.31**, could not be confirmed.

Table 14: Conditions for the attempted allylic oxidation of trichloroacetimidate 5.25. Reactions were run on a 0.1 mmol scale in varying solvents [0.14 M].



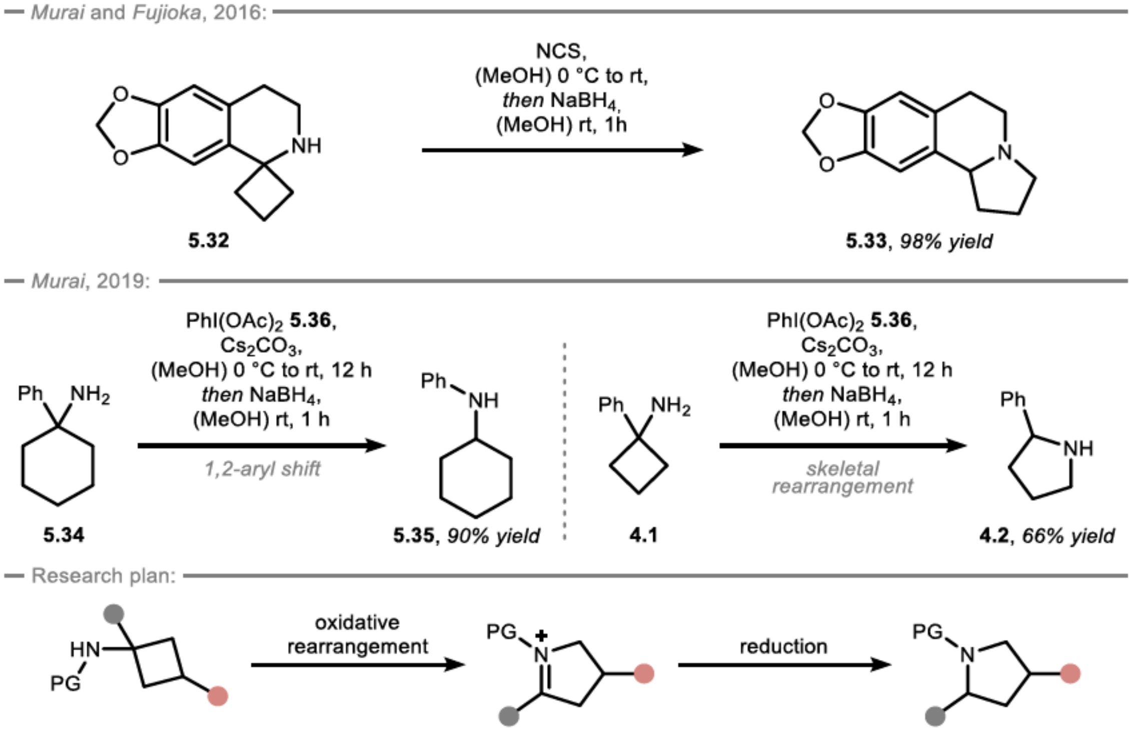
Entry	Catalyst (eq.)	Additives (eq.)	Solvent	*T*	*t*
1	$Pd(OAc)_2$ (0.20 eq.)	BQ (2.00 eq.)	dmso-d_6	40 °C	17 h
2	Pd complex **3.12** (1.00 eq.)	–	CD_2Cl_2	40 °C	17 h
3	$Pd(OAc)_2$ (1.00 eq.)		dmso-d_6	40 °C	17 h
4	$Pd(TFA)_2$ (1.00 eq.)		dmso-d_6	rt	1 h
5	$[Pd(allyl)Cl]_2$ (0.50 eq.)[a]	AgOAc (1.00 eq.)	dmso-d_6	40 °C	1 h
6	$Pd(OAc)_2$ (1.00 eq.)	–	CD_2Cl_2	40 °C	17 h
7	$Pd(TFA)_2$ (1.00 eq.)		CD_2Cl_2	40 °C	17 h
8	$Pd(TFA)_2$ (1.00 eq.)		$CDCl_3$	40 °C	1 h
9	$Pd(OAc)_2$ (1.00 eq.)	EtN(*i*Pr)$_2$ (1.00 eq.)	dmso-d_6	40 °C	17 h

[a] In total, 1.00 eq. of active Palladium species was applied.

In summary, it has to be noted, that although the chosen trichloroacetimidates were both consumed under the applied reaction conditions, no spectroscopic evidence for the formation of the desired amino alcohols was obtained. In this project only a limited number of additives and catalysts was screened, therefore it cannot be excluded, that intramolecular *C–H* amination with trichloroacetimidates is actually feasible. Nonetheless, the discussed results indicate such a transformation being unlikely.

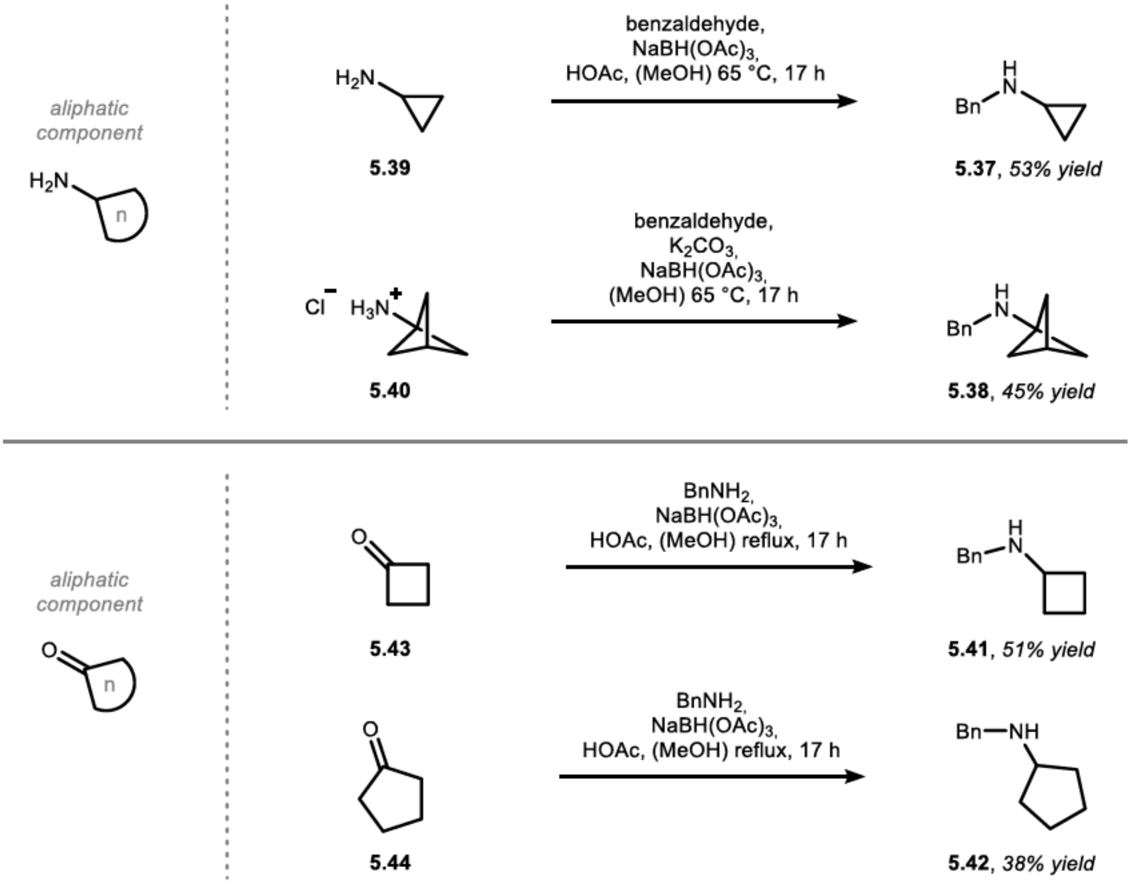
5.4 *N*-Heterocycle synthesis *via* oxidative rearrangement of secondary amines

Reasoned by the major importance of *N*-heterocycles in medicinal chemistry there is a constant demand of efficient methods for their preparation. In addition to the atom insertion strategy discussed *vide supra* (*cf.* Chapter 4), skeletal rearrangements are promising ways for the synthesis of nitrogen-containing cyclic systems (*cf.* Chapter 1.2, Figure 3). An illustrative example of the latter strategy was reported by *Murai* and *Fujioka* in their elegant synthesis of tetrahydroisoquinolines. In their seminal account,[142a] spirocyclic cyclobutane **5.32** was transformed into the fused tricyclic tetrahydroisoquinoline **5.33** under oxidative conditions (Scheme 96, top). The rearrangement is triggered by *N*-oxidation of the secondary amine with an electrophilic chlorine source. Thus, one of the bonds of the quaternary spiro atom in α-position migrates, resulting in the ring-expanded fused product. Initially, a cyclic iminium ion is formed, which is *in situ* reduced in a second reaction step. In following communications, the same group expanded their method by using diazomethanes as a trapping reagent for the iminium species, or by varying the oxidising conditions.[137b,198] Lately, *Murai* reported the oxidative rearrangement of primary amines like **5.34** with α-quaternary carbons in a *Stieglitz* type 1,2-aryl migration whereby affording secondary amines such as aniline **5.35** (Scheme 96, middle).[138] Interestingly, when cyclobutylamine **4.1** was treated under the same reaction conditions, with hypervalent iodine reagent phenyliodine(III) diacetate (PIDA) **5.36** in combination with a base, a skeletal rearrangement occurs ultimately resulting in the formation of pyrrolidine **4.2** (*cf.* Chapter 4.1.1, Scheme 58, top). Thereby, the influence of ring-strain relief is highlighted as a determining factor for steering chemical reactions. Inspired by the work of *Murai* and others on oxidative amine rearrangements,[29,142b] a general method for the skeletal editing of strained rings with adjacent protected amines should be developed. A strategy, including an oxidative rearrangement followed by a subsequent reduction step, is envisaged (Scheme 96, bottom). Therefore, a variety of cyclobutyl- and otherwise substituted amines should be prepared and tested for their reactivity towards oxidative heterocycle synthesis.



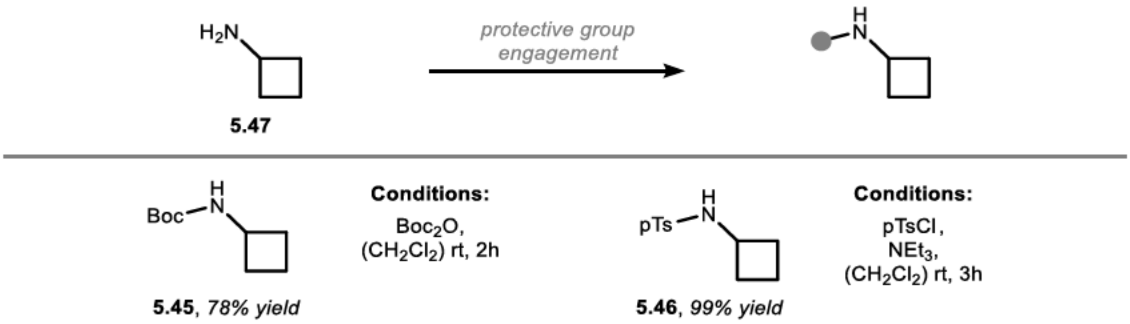
Scheme 96: Top: Seminal report from *Murai* and *Fujioka* for the oxidative rearrangement of spirocyclic amines.[142a] Middle: *Stieglitz*-type oxidative rearrangement of primary amines reported by *Murai*.[138] Bottom: Research outline for the oxidative rearrangement of strained amines.

According to literature known protocols, a series of benzyl protected amines was prepared.[199] Benzyl-protected amines **5.37** and **5.38** were synthesised through reductive amination of cyclopropylamine **5.39** and bicyclo[1.1.1]pentyl amine **5.40**, respectively (Scheme 97, top). On the contrary, amines **5.41** and **5.42** were afforded by the reaction of benzylamine with the respective 4- and 5-membered cyclic ketones **5.43** and **5.44** under likewise reductive conditions (Scheme 97, bottom)

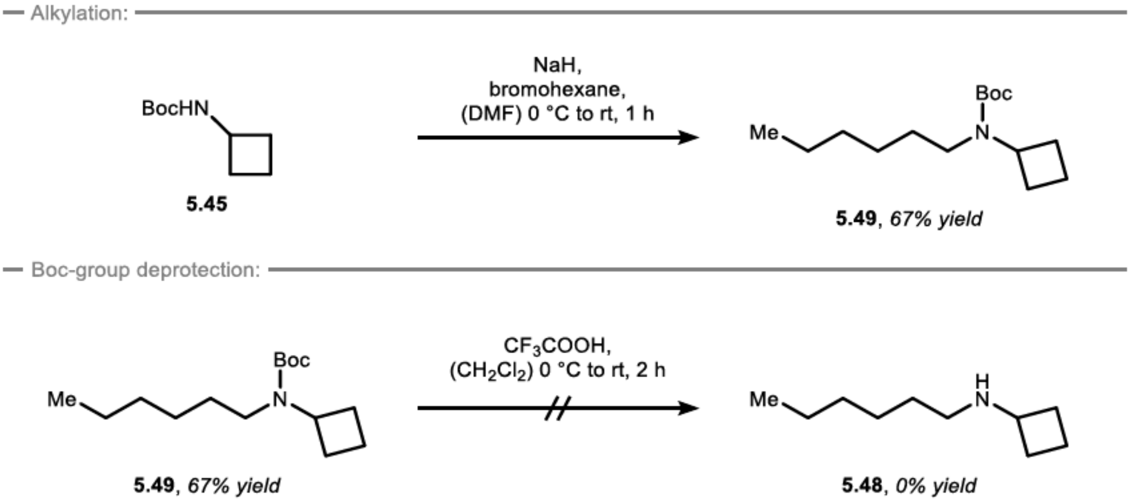


Scheme 97: Top: Reductive amination of benzaldehyde with strained aliphatic amines. Bottom: Reductive amination of cyclic ketones with benzylamine.[199]

Moreover, cyclobutylamines bearing a diverse array of protecting groups were prepared following literature known protocols.[200] On that account, Boc-group protected amine **5.45** and tosyl-protected amine **5.46** were both obtained in high yields in a single reaction step from cyclobutylamine **5.47** (Scheme 98).
On the contrary, an *N*-alkyl substituted cyclobutylamine **5.48** should be prepared in a two-step sequence from Boc-protected cyclobutylamine **5.45** to avoid exhaustive alkylation (Scheme 99). In a first step, Boc-protected cyclobutylamine **5.45** was treated with a base and bromohexane to yield tertiary amine **5.49**. The following envisioned acidic Boc-group removal was not fruitful utilising standard reaction conditions. Further research on the synthesis of protected cyclobutylamines has been conducted by [redacted]

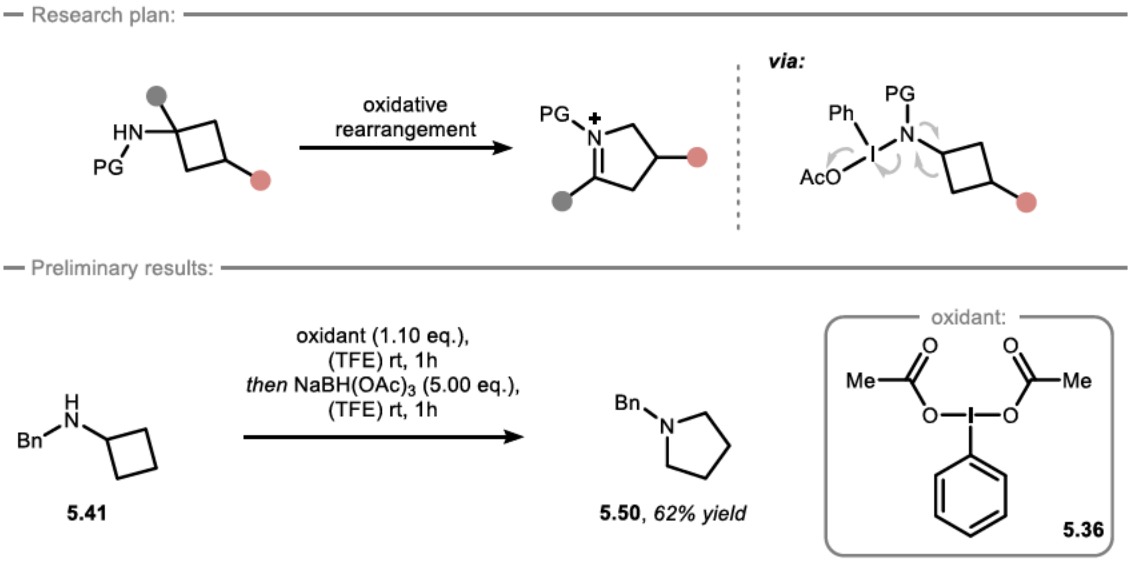


Scheme 98: Single reaction step protecting group attachment on cyclobutylamine 5.47.



Scheme 99: Attempted two step sequence for the synthesis of alkylated cyclobutylamine 5.48.

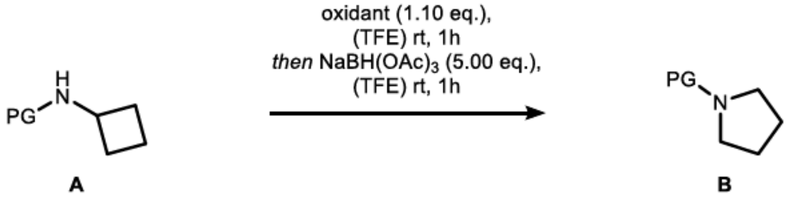
According to the research plan outlined above (Scheme 96), secondary amine **5.41** was treated with phenyliodine(III) diacetate **5.36**. Shortly afterwards, sodium triacetoxyborohydride was added as a reducing agent (Scheme 100). Analysing the crude reaction mixture with ^{1}H NMR techniques revealed the productive formation of the desired rearranged product, benzyl protected pyrrolidine **5.50**. Initially, the reaction was performed in a fluorinated alcohol, as those solvents are known to facilitate related oxidative rearrangement reactions.[158l,201]

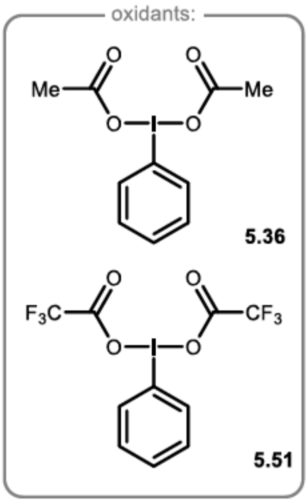


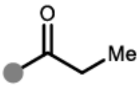
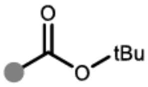
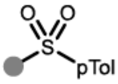
Scheme 100: Research outline for the oxidative rearrangement of cyclobutylamines and preliminary results for the envisaged reaction. Reaction was performed in TFE [0.2 M] on 0.1 mmol scale.

After this preliminary proof-of-concept, a set of electronically differing amines decorated with varying protective groups was tested under the initially used conditions (Table 15). In addition to hypervalent iodine compound **5.36**, phenyliodine(III) bis(trifluoroacetate (PIFA), **5.51**) was examined as an oxidant. In the case of benzyl-protected amine **5.41**, both hypervalent iodine oxidants were initialising the oxidative rearrangement, while it has to be noted, that the use of PIFA **5.51** is not as effective as employing PIDA **5.41** (entries 1 and 2). Furthermore, an acyl protected amine, prepared by [redacted] was treated under the same conditions without any formation of the rearranged product (entries 3 and 4). The same holds true for the Boc-group protected analogue **5.45** (entries 5 and 6) and likewise the tosyl-protected amine **5.46** (entries 7 and 8).

Table 15: Evalutation of protecting groups in the envisioned oxidative rearrangement of cyclobutylamines. Reactions were performed in TFE [0.2 M] on 0.1 mmol scale, NMR yields were determined *via* ^{1}H NMR with mesitylene as internal standard.



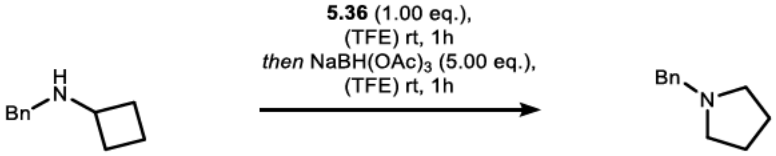


Entry	Protecting group	Oxidant	NMR yield **B**
1		**5.36**	62%
2		**5.51**	25%
3[a]		**5.36**	0%
4[a]		**5.51**	0%
5		**5.36**	0%
6		**5.51**	0%
7		**5.36**	0%
8		**5.51**	0%

[a] Substrate was prepared by [redacted]

Subsequently, the reactions conditions primarily applied were re-examined (Table 16, entry 1). Changing the reducing agent had a detrimental, yet small, influence on the amount of pyrrolidine obtained (entry 2). As already indicated, the choice of the oxidising reagent had an immense influence on reaction outcome. When PIFA **5.51** was applied, a decrease in yield was observed (entry 3). Whilst using either *N*-oxidised succinimides, including NCS, *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS), or electrophilic fluorine sources completely inhibited the desired reaction (entries 4 to 7). Furthermore, the pyrrolidine **5.50** was not formed in an apolar solvent or in non-fluorinated protic solvents (entries 8 and 9). On the contrary, conducting the reaction in HFIP led to an increase in yield (entry 10), thus underlining the special reactivity of fluorinated alcohols. Additionally, the conditions reported by *Murai* for the oxidative rearrangement of primary amines,[138] were applied in a futile attempt to form the desired pyrrolidine **5.50** (entry 11).

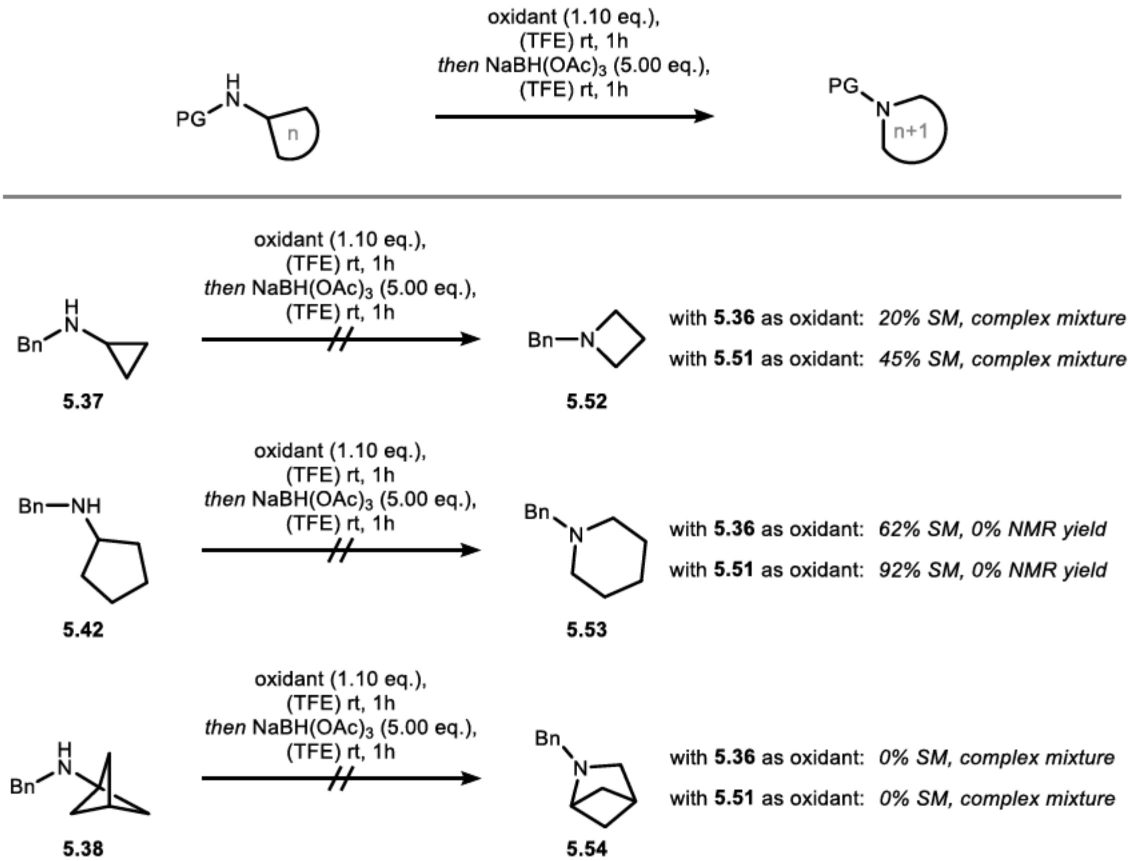
Table 16: Preliminary optimisation of the reaction conditions for the envisioned oxditave rearrangement of cyclobutylamines. Reactions were performed in TFE [0.2 M] on 0.1 mmol scale, NMR yields were determined *via* ^{1}H NMR with mesitylene as internal standard.



Entry	Changes from standard conditions	NMR yield
1	–	62%
2	$NaBH_4$ used as reductant	54%
3	$PhI(OCOCF_3)_2$ **5.51** (1.10 eq.) used as oxidant	25%
4	NCS (1.10 eq.) used as oxidant	0%
5	NBS (1.10 eq.) used as oxidant	0%
6	NIS (1.10 eq.) used as oxidant	0%
7	NFSI (1.10 eq.) used as oxidant	0%
8	reaction was run in CH_2Cl_2	0%
9	reaction was run in MeOH	0%
10	reaction was run in HFIP	82%
11	Cs_2CO_3 as additive in MeOH	0%

NFSI = *N*-fluorobenzenesulfonimide.

In a second set of experiments, the initially employed conditions were applied to amines bearing different carbocyclic substituents (Scheme 101). Therefore, cyclopropyl substituted amine **5.37**, was treated with both, PIDA **5.36** and PIFA **5.51**. In both cases, the starting material was consumed yielding a complex mixture of products. Attempts to isolate the formed products including the desired azetidine **5.52** were not fruitful. Cyclopentyl substituted amine **5.42** was studied next. Again, the desired product **5.53** was not obtained. Additionally, the bicyclic amine **5.38** was tested under the initial conditions. Although full conversion of the starting material was observed, neither the desired bicyclic **5.54** or other distinct products could be isolated from the complex reaction mixture.



Scheme 101: Attempts for the oxidative rearrangement of amines adjacent to different carbocyclic systems. Reactions were performed in TFE [0.2 M] on 0.1 mmol scale, NMR yields were determined *via* ^{1}H NMR with mesitylene as internal standard.

As has been demonstrated in this brief overview, the oxidative rearrangement of secondary amines adjacent to strained rings is a possible alternative for the synthesis of *N*-heterocycles. After an initial proof-of-concept, a short optimisation was performed. Thereby it was demonstrated, that cyclobutylamines can be productively transformed into pyrrolidines by utilising hypervalent iodine compounds as oxidants in fluorinated alcohols. Future endeavours in this field may be focussed on the synthesis of substituted strained rings and further optimising the conditions to find a broadly applicable method for the synthesis of heterocycles from strained rings.

6 Experimental part

6.1 General information

Analytical Methods: ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded by the analytical departments of the Organisch-Chemisches Institut at the Westfälische Wilhelms-Universität and of the Department Chemie at Johannes Gutenberg-Universität Mainz. Following spectrometers were used: An Avance II 400 (*Bruker*), a DD2 500 (*Agilent*), a DD2 600 (*Agilent*), an Avance III HD 300 (*Bruker*), an Avance III HD 400 (*Bruker*). Spectra were recorded at 26 °C (unless otherwise noted). Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H NMR $CHCl_3$: $\delta = 7.26$ ppm, $CHDCl_2$: $\delta = 5.32$ ppm, C_6HD_5: $\delta = 7.16$ ppm, $(CHD_2)(CD_3)CO = 2.05$ ppm, $(CHD_2)(CD_3)SO = 2.50$ ppm; ^{13}C NMR $CDCl_3$: $\delta = 77.16$ ppm, CD_2Cl_2: $\delta = 53.84$ ppm, C_6D_6 $\delta = 128.06$ ppm, $(CD_3)_2CO = 29.84$ ppm $(CD_3)_2SO = 39.5$ ppm). Chemical shifts of ^{19}F NMR are referenced to internal or external standards according to *Togni* and coworkers.[202] The data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet or combinations of these), coupling constants (Hz) and integration. In the reported ^{1}H NMR spectra, unless otherwise noted, multiplets are reasoned from *H,H* couplings. Apparent multiplicity, which occurs as a result of accidental equality of coupling constants to magnetically non-equivalent protons, is marked as *app*.

Infrared (IR) spectra were obtained either on a *Perkin-Elmer* 100 FT-IR spectrometer or on a Jasco FT/IR-4100 and are reported in wavenumbers (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w).

Melting points (m.p.) were measured on a *Büchi* B-540 melting-point apparatus and are reported uncorrected.

High Resolution Mass Spectrometry (HRMS) was performed by the analytical departments of the Organisch-Chemisches Institut at the Westfälische Wilhelms-Universität and of the Department Chemie at Johannes Gutenberg-Universität Mainz. Spectra were recorded on a *Bruker* Daltonics MicroTof, on a *Thermo-*

Fisher Scientific Orbitrap LTQ XL or an *Agilent* G6545AQ-ToF. Signals are reported as mass to charge ratio *m/z*.

Optical rotations were measured on a *Perkin-Elmer* 241 polarimeter at 589 nm wavelength (sodium D-line) using a standard 10 cm cell (1 mL). Specific rotations, $[\alpha]_D^{20}$, are reported in degree mL/(g·dm) at the specific temperature. Concentrations (*c*) are given in grams per 100 mL of the specific solvent.

UV/vis absorption spectra were recorded on a V-670 UV-Vis-NIR spectrometer from *Jasco* at ambient temperature in a 10 mm cell.

Elementary Analysis (EA) was performed by the analytical department of the Organisch-Chemisches Institut at the Westfälische Wilhelms-Universität using a *Elementar Analysensysteme Gmbh* - Vario EL III.

Analytical HPLC measurements were performed on the following system: *Knauer* HPLC Pump Smartline 1000 with degassing unit, *Knauer* Autosampler Smartline 3950, *Knauer* UV-detector Smartline 2550, *Knauer* RI-detector Smartline 2300. Separation was performed using Lux® i-Cellulose-5 (4.6 x 250 nm x 5 µm, *Phenomenex* Ltd.), Lux® Cellulose-1 (4.6 x 250 nm x 5 µm, *Phenomenex* Ltd.), Lux® Amylose-1 (4.6 x 250 nm x 5 µm, *Phenomenex* Ltd.), Lux® i-Amylose-3 (4.6 x 250 nm x 5 µm, *Phenomenex* Ltd.), or Reprosil Chiral-AMS (4.6 x 250 nm x 5 µm, *Dr Maisch* GmBH.).

Purification methods: Purification was performed either with standard column chromatography techniques using 60 M silica gel (0.04-0.063 mm, *MACHEREY-NAGEL*), on an automated flash chromatography system *Biotage Isolera One* utilizing *Biotage Sfär Silica D-Duo* 60 µm columns (5 g, 25 g, 100 g) or on an automated flash chromatography system *Teledyne Isco* with *Biotage Sfär Silica C18-Duo* 100 Å 30 µm columns (12 g). Glass silica gel plates 60 F254 (*Merck*) were used for thin layer chromatography (TLC) using UV light (254/366 nm), $KMnO_4$ (1.5 g $KMnO_4$, 5 g $NaHCO_3$ and 5 mL NaOH 10% in 200 mL H_2O), CAM (0.5g $Ce(NH_4)_2(NO_3)_6$ and 24.0 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 28 mL H_2SO_4 in 200 mL H_2O), DNPH (12 g 2,4-dinitrophenylhydrazine, 60 mL H_2SO_4, and 80 mL of H_2O in 200 mL EtOH), $FeCl_3$ (1 g in 2 mL HCl (conc.) and 50 mL of H_2O in 200 mL EtOH) for detection.

Reagents and solvents: Chemicals were purchased from *Alfa Aesar*, *Acros Organics*, *Sigma Aldrich*, *BLDpharm*, *FluoroChem*, *Carbolution* or *ABCR* and used as received. All work-up and purification procedures were carried out with pre-distilled technical grade solvents. EtOH was purified prior to use applying standard techniques (distilled over activated Mg turnings). Dry solvents were either dried with standard techniques (CH_2Cl_2 distilled over P_2O_5 and stored over activated 4Å molecular sieves), or collected from a *MBraun MB SPS-800* (CH_2Cl_2, Et_2O, THF). A positive argon pressure was used to pass the solvents through the following columns:

CH_2Cl_2:	2	x MB-KOL-A
Et_2O:	1	x MB-KOL-A and 1 x MB-KOL MT2-250
THF:	2	x MB-KOL MT2-150°C

Reaction set-up: All reactions involving air or moisture sensitive reagents were carried out in oven- (125 ^oC) and flame-dried glassware under nitrogen atmosphere using standard *Schlenk* techniques. Reactions requiring heating were conducted using aluminium blocks as heating source. Photochemical reactions were performed in a *Luzchem* LZC-ORG photoreactor with 10 x 8 Watt *Luzchem* LZC-355 mercury lamps or with a Pyrex filtered *Hanovia* medium pressure Hg-lamp (400 W).

X-Ray diffraction: Data sets for compounds **2.24** and **2.96** were collected with a *Bruker* D8 Venture PHOTON III diffractometer. Programs used: data collection: APEX3 V2016.1-0 [203] (*Bruker* AXS Inc., **2016**); cell refinement: SAINT V8.37A [203] (*Bruker* AXS Inc., **2015**); data reduction: SAINT V8.37A [203] (*Bruker* AXS Inc., **2015**); absorption correction, SADABS V2014/7 [203] (*Bruker* AXS Inc., **2014**); structure solution *SHELXT-2015* [204] (Sheldrick, G. M. *Acta Cryst.,* **2015**, *A71*, 3-8); structure refinement *SHELXL-2015* [205] (Sheldrick, G. M. *Acta Cryst.,* **2015**, *C71* (1), 3-8) and graphics, *XP* [206] (Version 5.1, *Bruker* AXS Inc., Madison, Wisconsin, USA, **1998**). *R*-values are given for observed reflections, and wR^2 values are given for all reflections.
Data sets for compounds **2.117** were collected with a STOE IPDS-2T Diffractometer system. Programs used: data collection: X-Area WinXpose 2.0.22.0 [207] (*X-RED* and *X-AREA*, Stoe & Cie, **2019**), cell refinement: X-Area Recipe 1.36.0 [207] (*X-RED* and *X-AREA*, Stoe & Cie, **2019**), data reduction: X-Area Integrate 1.78.3

[207] (*X-RED* and *X-AREA*, Stoe & Cie, **2019**), structure solution *SHELXT-2014* [204] (Sheldrick, G. M. *Acta Cryst.,* **2015**, *A71*, 3-8); structure refinement *SHELXL-2018/3* [205] (Sheldrick, G. M. *Acta Cryst.,* **2015**, *C71* (1), 3-8) and graphics Platon [208] (Spek, A. L. *Acta Cryst.,* **2009**, *D65*, 148-155). *R*-values are given for observed reflections, and wR^2 values are given for all reflections.

Documentation: The experimental work was partly documented using the electronic lab notebook (ELN) *Chemotion*. A respective sample number is indicated in the corresponding entries. Otherwise, the documentation was carried out using conventional lab notebooks in paper form.

6.2 Cyclic alcohols as platform for the synthesis of oxygen rich heterocycles

General procedures

General procedure A (GP-A) for the preparation of 3-substituted oxetanols from oxetan-3-one with lithium organyls:

3-substituted oxetanols were prepared following a lab-own protocol,[82] which was adapted from literature known procedures.[69] A halogenated arene (1.20 eq.) or monosubstituted alkyne (1.20 eq.) was dissolved in dry THF (0.1 M) under inert atmosphere and cooled to −78 °C at which temperature *n*-BuLi (2.5 M, 1.20 eq.) was added dropwise. After 1 h, oxetan-3-one (1.00 eq.) was added slowly and the mixture was stirred at −78 °C for 3 h, before it was slowly warmed up to room temperature (rt) for 17 h. The solution was diluted with Et_2O and NH_4Cl sat. aq. was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The products were isolated after FC or automated FC.

General procedure B (GP-B) for the preparation of Co^{II}·salen type complexes:

Following a literature known protocol with minor alterations,[76] EtOH was deaerated by purging with a flow of nitrogen for 10 min. $Co(OAc)_2{\cdot}4H_2O$ (1.00 eq.) was dissolved under inert atmosphere in the deaerated EtOH and stirred until complete solvation of the salt took place. Then salen-type ligand (1.00 eq.) was added and the mixture was heated to reflux for 17 h. The solution was cooled to −18 °C, the resulting precipitate was filtered off and washed with small portions of cold EtOH. The filtrate was concentrated, and the residue was recrystallised to gain a second crop of the complex.

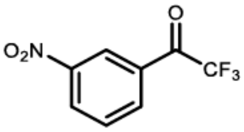
General procedure C (GP-C) for the desymmetrisation of 3-substituted oxetanols:

Ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}-salen complex **2.106**, prepared by [redacted] (1 mol%) were dissolved in dry CH_2Cl_2 (0.4 M) at room temperature. To this solution the corresponding 3-substituted oxetanol (0.20 mmol, 1.00 eq.) was added. The temperature was maintained for 24 h before silica gel was added and filtered off. The resulting silica gel plug was flushed with Et_2O, and the filtrate was concentrated. NMR yield and *dr* of the crude reaction mixture were determined by ^{19}F NMR using trifluorotoluene (0.10 mmol) as the internal standard. The product diastereomers were separated by silica gel column chromatography or RP-MPLC.

6.2.1 Synthesis of starting materials and complexes

6.2.1.1 Synthesis of trifluoroacetophenone derivatives

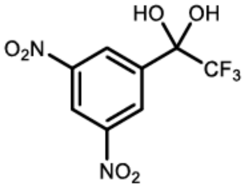
3'-Nitro-2,2,2-trifluoroacetophenone [2.19]



According to a literature known procedure[65] 2,2,2-trifluoroacetophenone (500 µL, 3.56 mmol, 1.00 eq.) was dissolved in H_2SO_4 conc. (35 mL) and $NaNO_3$ (317 mg, 3.74 mmol, 1.05 eq.) was added portionwise at −18 °C and stirred for 1 h before the reaction mixture was warmed up to rt. The mixture was poured on ice and treated with KOH aq. (1N) until the pH reached 10. The aqueous phase was extracted with CH_2Cl_2:*i*PrOH (4:1, 3x15 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was obtained after FC (pentane:EtOAc, 5:1) as a pale brown solid (347 mg, 1.58 mmol, 44%)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 8.58 (ddd, J = 8.2, 2.2, 1.1 Hz, 1H), 8.45 – 8.35 (m, 1H), 7.82 (*app* t, J = 8.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 135.4 (q, $J_{C,F}$ = 2.1 Hz), 131.3, 130.8, 129.8, 125.1 (q, $J_{C,F}$ = 2.4 Hz), 116.4 (q, $^1J_{C,F}$ = 290.5 Hz). Two signals missing. Obtained spectroscopic data are in agreement to those previously reported.[65]

3'5'-Dinitro-2,2,2-trifluoroacetophenone monohydrate [2.24]



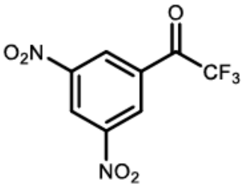
2,2,2-Trifluoroacetophenone (2.00 g, 11.5 mmol, 1.00 eq.) was dissolved in H_2SO_4 conc. (50 mL) and HNO_3 aq. (65%, 15 mL) was added slowly at 0 °C and stirred for 30 min before the reaction mixture was heated to 130 °C. After 4 h the reaction mixture was cooled down to rt before another portion of HNO_3 aq. (65%, 15 mL) was added. The solution was refluxed at 130 °C for 3 d before it was poured on ice. The aqueous phase was extracted with Et_2O (3x5 mL) and the organic phase was carefully washed with $NaHCO_3$ sat. aq. until no gas evolution was observed. The organic phase was dried over K_2CO_3 and the solvent was removed *in vacuo*. The crude product was recrystallised from H_2O to yield the hydrate as colourless crystals (1.12 g, 3.95 mmol, 34%).

m.p.: 84 – 85 °C. **IR (neat)**: $\tilde{\nu}$ = 3479 (w), 3107 (w), 2357 (w), 1632 (w), 1542 (s), 1345 (s), 1260 (w),1180 (s), 1153 (m), 1116 (m), 1075 (s), 972 (w), 916 (m), 773 (w), 732 (s), 712 (s), 678 (m). **^{1}H NMR (400 MHz, $(CD_3)_2SO$)**: δ = 8.91 (t, J = 2.1 Hz, 1H, C*H*$_{arom.}$), 8.67 (d, J = 2.1 Hz, 2H, C*H*$_{arom.}$), 8.45 (s, 2H, O*H*). **^{13}C NMR (101 MHz, $(CD_3)_2SO$)**: δ = 148.0 (*C*$_q$), 142.7 (*C*$_q$), 127.4 (*C*H), 122.8 (q, $^1J_{C,F}$ = 289.0 Hz), 119.7 (*C*H), 91.8 (q, $^2J_{C,F}$ = 32.0 Hz). **^{19}F NMR (376 MHz, $(CD_3)_2SO$)**: δ = –82.6 (s, *C*F_3). **HRMS (APCI)**: Calculated for $C_8H_4F_3N_2O_6$ [M-H]$^-$: 281.0021, Found: 281.0027.

The protons of the OH-groups were identified through ^{1}H,^{1}H-EXSY correlation to the signals of residual water.

A sample of hydrate **2.24** suitable for X-ray analysis was obtained after dissolving 3'5'-dinitro-2,2,2-trifluoroacetophenone **2.20** in $CDCl_3$ and slowly evaporating the solvent open to air.

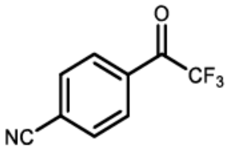
3'5'-Dinitro-2,2,2-trifluoroacetophenone [2.20]



3'5'-Dinitro-2,2,2-trifluoroacetophenone monohydrate **13** was refluxed with toluene in a *Dean-Stark* apparatus for 4 h. The water-free product was obtained as a light yellow solid (quantitative conversion of the hydrate)

m.p.: 70 – 71 °C. **IR (neat)**: $\tilde{\nu}$ = 3103 (w), 1741 (m), 1631 (m), 1545 (s), 1461 (w), 1345 (s), 1204 (s), 1149 (s), 1121 (s), 1079 (w), 1010 (s), 921 (m), 773 (w), 730 (s), 720 (s), 703(s). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 9.37 (t, J = 2.1 Hz, 1H, $CH_{arom.}$), 9.19 (dd, J = 2.0, 0.9 Hz, 2H, $CH_{arom.}$).**^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 177.4 (q, $^2J_{C,F}$ = 38.0 Hz, C_q), 149.3 (C_q), 132.6 (C_q), 129.6 (q, $^4J_{C,F}$ = 2.2 Hz, CH), 124.5 (CH), 116.0 (q, $^1J_{C,F}$ = 290.2 Hz, CF_3). **^{19}F NMR (377 MHz, $CDCl_3$)**: δ = −71.8 (s, CF_3). **HRMS (APCI)**: Calculated for $C_8H_3F_3N_2O_5$ $[M]^-$: 263.9994, Found: 263.9968.

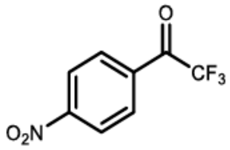
4'-Cyano-2,2,2-trifluoroacetophenone [2.21]



According to a literature known protocol with minor alterations,[66] methyl 4-cyanobenzoate (1.00 g, 6.21 mmol, 1.00 eq.) and trifluoromethyltrimethylsilane (1.53 mL, 10.3 mmol, 1.66 eq.) were dissolved in dry CH_2Cl_2 (60 mL) under Argon atmosphere and cooled to −78 °C. Tetrabutylammonium fluoride (1M in THF, 370 µL, 0.37 mmol, 6 mol%) was added slowly. After 1 h at −78 °C the solution was allowed to warm up to rt over 17 h. NH_4Cl sat. aq. was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting oil was redissolved in a mixture of 1,4-dioxane:HCl:H_2O (3:1:1, 6 mL) and stirred for 17 h at rt. After removal of the solvent *in vacuo* the product was obtained after FC (pentane:EtOAc, 10:1 to 4:1) as a pale yellow solid (263 mg, 1.32 mmol, 21%).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.39 – 7.31 (m, 2H), 6.81 – 6.75 (m, 2H). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 179.3 (q, $^{2}J_{C,F}$ = 35.8 Hz, C_q), 132.4, 132.2, 129.9 (q, $^{4}J_{C,F}$ = 2.2 Hz), 118.6, 117.4, 116.74 (q, $^{1}J_{C,F}$ = 291.1 Hz). **^{19}F NMR (377 MHz, C_6D_6)**: δ = −71.6 (*s*). Obtained spectroscopic data are in agreement to those previously reported.[209]

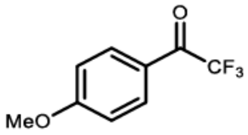
4'-Nitro-2,2,2-trifluoroacetophenone [2.22]



According to a literature known protocol with minor alterations,[66] methyl 4-nitrobenzoate (3.00 g, 16.6 mmol, 1.00 eq.) and trifluoromethyltrimethylsilane (4.07 mL, 27.5 mmol, 1.66 eq.) were dissolved in dry CH_2Cl_2 (150 mL) under Argon atmosphere and cooled to −78 °C. Tetrabutylammonium fluoride (1M in THF, 550 µL, 0.55 mmol, 6 mol%) was added slowly. After 1 h at −78 °C the solution was allowed to warm up to rt over 17 h. NH_4Cl sat. aq. was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (3x50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting oil was redissolved in a mixture of 1,4-dioxane:HCl:H_2O (3:1:1, 20 mL) and stirred for 17 h at rt. After removal of the solvent *in vacuo* the product was obtained after FC (pentane:EtOAc, 3:1 to 1:1) as a pale yellow solid (1.91 g, 8.81 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 – 8.37 (m, 2H), 8.30 – 8.23 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)**: δ = 179.5 (q, $^{2}J_{C,F}$ = 36.6 Hz), 151.7, 134.4, 131.4 (q, $^{4}J_{C,F}$ = 2.2 Hz), 124.4, 116.4 (q, $^{1}J_{C,F}$ = 290.8 Hz). **^{19}F NMR (376 MHz, $CDCl_3$)**: δ = −71.8 (*s*). Obtained spectroscopic data are in agreement to those previously reported.[210]

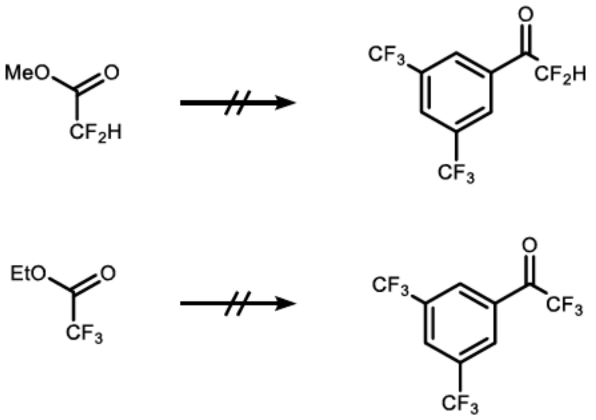
4'-Methoxy-2,2,2-trifluoroacetophenone [2.23]



4-Methoxy benzaldehyde (1.00 g, 7.34 mmol, 1.00 eq.), K_2CO_3 (10 mg, 73 µmol, 0.01 eq.) and trifluoromethyltrimethylsilane (1.30 mL µL, 8.81 mmol, 1.20 eq.) were dissolved in dry DMF (70 mL) according to a literature known procedure.[67] After 30 min at rt HCl aq. (1N, 30 mL) was added and the mixture was stirred for 1 h at rt before Et_2O (30 mL) was added. The organic phase was separated and the aqueous phase was extracted with Et_2O (3x30 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (70 mL) and *Dess-Martin* periodinane (7.47 g, 17.6 mmol, 2.40 eq.) and $NaHCO_3$ (2.47 g, 29.4 mmol, 4.00 eq.) were added. The mixture was stirred at rt for 17 h before $Na_2S_2O_3$ sat. aq. and $NaHCO_3$ sat. aq. were added. The mixture was filtered over celite. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3x30 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was obtained after FC (pentane:Et_2O, 10:1) as a colourless oil (263 mg, 1.32 mmol, 21%)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 – 8.01 (m, 2H), 7.07 – 6.95 (m, 2H), 3.92 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 179.1 (q, $^2J_{C,F}$ = 34.5 Hz), 165.6, 132.9 (q, $^4J_{C,F}$ = 2.2 Hz), 123.0, 117.1 (q, $^1J_{C,F}$ = 291.5 Hz), 114.6, 55.9. **^{19}F NMR (376 MHz, $CDCl_3$)**: δ = –70.9 (s). Obtained spectroscopic data are in agreement to those previously reported.[67]

Unsuccessful attempts



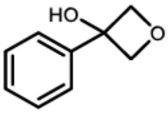
Magnesium turnings (1.05 eq.) were activated with iodine vapour prior to reaction. The activated magnesium was placed in a flask and dry THF (2 M) was added. 1-bromo-3,5-bis(trifluoromethyl)benzene (1.00 eq.) was added slowly to maintain exothermic reaction. The mixture was stirred for 1 h at 60 °C, cooled to –20 °C and diluted with dry THF (0.1 M). Either methyl 2,2-difluoroacetate

(2.00 eq.) or ethyl 2,2,2-trifluoroacetate (2.00 eq.) was added slowly and stirred for 3 h, before it was slowly warmed up to rt for 17 h. The solution was diluted with Et_2O and NH_4Cl sat. aq. was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*.
The desired products were not formed according to NMR and TLC analysis.

According to a literature known protocol with minor alterations,[68] *N*-methoxy-*N*-methyl-3,5-dinitrobenzamide (0.50 g, 1.96 mmol, 1.00 eq.) and trifluoro methyltrimethylsilane (530 µL, 3.92 mmol, 2.00 eq.) were dissolved in dry THF (20 mL) under Argon atmosphere. Potassium *tert*-butoxide (396 mg, 3.53 mmol, 1.80 eq.) was added portionwise at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 17 h. NH_4Cl sat. aq. was added to the reaction mixture and the aqueous phase was extracted with Et_2O (3x20 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*.
The desired product was not formed according to NMR and TLC analysis.

6.2.1.2 Synthesis of oxetanols

3-Phenyloxetan-3-ol [2.38]

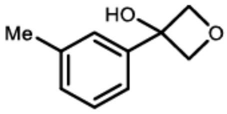


Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and bromobenzene (630 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after FC (Et_2O:pentane, 4:1) as a colourless solid (679 mg, 4.52 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 – 7.56 (m, 2H), 7.46 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 4.96 – 4.87 (m, 4H), 2.89 (br, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 142.4, 128.9, 128.1, 124.6, 85.8, 75.9.

Spectroscopic data was in agreement to those previously reported.[69c]

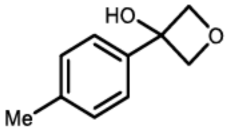
3-(*m*-Tolyl)oxetan-3-ol [2.39]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 3-methyl-iodobenzene (770 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc, 80:20 to 60:40) as a colourless solid (458 mg, 2.79 mmol, 56%).

m.p.: 41 – 43 °C. **IR (neat)**: $\tilde{\nu}$ = 3401 (m), 2959 (w), 2948 (w), 2820 (w), 2883 (w), 2874 (w), 2356 (w), 1610 (w), 1492 (w), 1455 (w), 1325 (w), 1284 (w), 1200 (m), 1178 (w), 1165 (m), 1143 (w), 1072 (w), 970 (s), 905 (m), 848 (m), 786 (m), 703 (s), 683 (w). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.44 – 7.37 (m, 2H, C$H_{\text{arom.}}$), 7.33 (app. t, J = 7.5 Hz, 1H, C$H_{\text{arom.}}$), 7.20 – 7.16 (m, 1H, C$H_{\text{arom.}}$), 4.92 (app. q, J = 6.8 Hz, 4H, CH_2), 3.05 (br, 1H, OH), 2.42 (s, 3H, CH_3). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 142.4 (C_q), 138.6 (C_q), 128.8 (CH), 128.7 (CH), 125.3 (CH), 121.6 (CH), 85.7 (CH$_2$), 75.9 (C_q), 21.7 (CH$_3$).

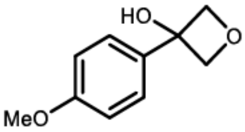
3-(*p*-Tolyl)oxetan-3-ol [2.40]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 4-methyl-bromobenzene (730 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc, 80:20 to 65:35) as a colourless solid (486 mg, 2.96 mmol, 59%).

m.p.: 66 – 68 °C. **IR (neat)**: $\tilde{\nu}$ = 3397 (m), 2955 (w), 2874 (w), 2360 (w), 2341 (w), 2329 (w), 1738 (w), 1516 (w), 1450 (w), 1417 (w), 1379 (w), 1328 (w), 1280 (w), 1231 (w), 1213 (w), 1173 (m), 1141 (w), 1114 (w), 1064 (w), 1022 (w), 971 (s), 879 (m), 816 (s), 720 (w). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.48 – 7.43 (m, 2H, C$H_{\text{arom.}}$), 7.25 – 7.21 (m, 2H, C$H_{\text{arom.}}$), 4.92 – 4.86 (m, 4H, CH_2), 2.90 (br, 1H, OH), 2.37 (s, 3H, CH_3). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 139.4 (C_q), 137.7 (C_q), 129.4 (CH), 124.5 (CH), 85.6 (CH$_2$), 75.7 (C_q), 21.1 (CH$_3$).

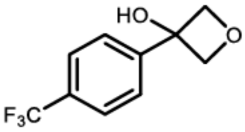
3-(4-Methoxyphenyl)oxetan-3-ol [2.41]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 4-methoxy-bromobenzene (751 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc, 80:20 to 70:30) as a colourless oil (542 mg, 3.01 mmol, 60%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 – 7.41 (m, 2H), 7.25 – 7.19 (m, 2H), 4.92 – 4.85 (m, 4H), 3.30 – 3.14 (br, 1H), 2.37 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 139.5, 137.8, 129.4, 124.6, 85.8, 75.7, 21.2.
Spectroscopic data was in agreement to those previously reported.[211]

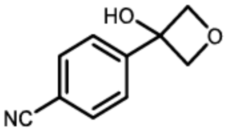
3-(4-(Trifluoromethyl)phenyl)oxetan-3-ol [2.42]



Following **GP-A**, with minor alterations using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.20 mL, 5.50 mmol, 1.10 eq.) and 4-trifluoromethyl-bromobenzene (770 µL, 6.00 mmol, 1.10 eq.), the desired product was obtained after automated FC (CyH:EtOAc, 80:20 to 70:30) as a colourless solid (838 mg, 3.84 mmol, 77%).

m.p.: 122 – 123 °C. **IR (neat)**: $\tilde{\nu}$ = 3380 (m), 2973 (m), 2891 (w), 2364 (w), 2331 (w), 1740 (w), 1380 (w), 1328 (s), 1166 (m), 1128 (s), 1107 (s), 1076 (m), 1016 (w), 951 (s), 913 (w), 844 (w), 817 (m), 734 (s). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.80 – 7.73 (m, 2H, $C\mathit{H}_{\text{arom.}}$), 7.66 – 7.70 (m, 2H, $C\mathit{H}_{\text{arom.}}$), 4.97 – 4.90 (m, 2H, $C\mathit{H}_2$), 4.91 – 4.85 (m, 2H, $C\mathit{H}_2$), 3.11 (s, 1H, O*H*). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 146.3 (C_q), 130.3 (q, $^2J_{C,F}$ = 32.6 Hz, C_q), 125.8 (q, $^3J_{C,F}$ = 3.7 Hz, *C*H), 125.0 (*C*H), 124.1 (q, $^1J_{C,F}$ = 272.0 Hz, *C*F$_3$), 86.1 (*C*H$_2$), 75.5 (C_q). **^{19}F NMR (377 MHz, CDCl$_3$)** δ = –62.5 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{10}H_8F_3O_2$ [M+H]$^-$: 217.0476, Found: 217.0476.

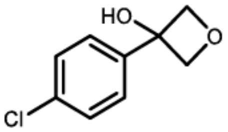
4-(3-Hydroxyoxetan-3-yl)benzonitrile [2.43]



According to a literature known protocol,[152d] 4-iodobenzonitrile (1.20 g, 5.00 mmol, 1.00 eq.) was dissolved in dry THF (20 mL) under inert atmosphere and cooled to –78 °C before iPrMgCl (2.0 M, 2.5 mL, 5.00 mmol, 1.00 eq.) was added slowly. The mixture was slowly warmed up to –20 °C and kept at this temperature for 1 h before it was cooled again to –78 °C. At which temperature oxetan-3-one (480 µL, 7.50 mmol, 1.50 eq.) was added. The temperature was raised to –20 °C and stirred for 1 h, then 1 h at 0 °C followed by 6 h at rt. The solvent was removed and the product was obtained *via* recrystallization (EtOAc:CyH, 95:5) as a colourless solid (489 mg, 2.79 mmol, 56%).

m.p.: 171 – 172 °C. **IR (neat)**: $\tilde{\nu}$ = 3338 (m), 3009 (w), 2964 (w), 2877 (w), 2225 (w), 1737 (w), 1721 (w), 1596 (w), 1547 (m), 1436 (m), 1405 (w), 1346 (m), 1325 (w), 1293 (w), 1237 (w), 1205 (m), 1178 (s), 1132 (w), 1108 (w), 1016 (w), 978 (s), 954 (m), 877 (s), 842 (m), 778 (w), 751 (w), 729 (m), 661 (w). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.84 – 7.78 (m, 2H, C$H_{\text{arom.}}$), 7.75 – 7.70 (m, 2H, C$H_{\text{arom.}}$), 4.97 – 4.92 (m, 2H, CH_2), 4.88 – 4.82 (m, 2H, CH_2), 2.74 (s, 1H, OH). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 147.6 (C_q), 132.6 (CH), 125.3 (CH), 118.7 (C_q), 111.9 (C_q), 86.1 (CH$_2$), 75.4 (C_q). **HRMS (APCI)**: Calculated for $C_{10}H_9NO_2$ [M+H]$^+$: 176.0712, Found: 176.0702.

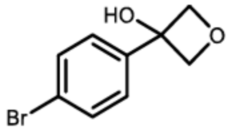
3-(4-Chlorophenyl)oxetan-3-ol [2.44]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-chloro-4-iodobenzene (1.43 g, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc 70:30 to 65:35) as a colourless solid (869 mg, 4.71 mmol, 94%).

m.p.: 71 – 72 °C. **IR (neat)**: $\tilde{\nu}$ = 3353 (m), 2969 (w), 2881 (w), 2368 (w), 1922 (w), 1663 (w), 1577 (w), 1544 (w), 1490 (w), 1437 (w), 1233 (w), 1181 (m), 1141 (w), 1100 (m), 1050 (w), 1012 (m), 971 (s), 953 (m), 908 (w), 876 (m), 824 (s), 731 (m). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.56 – 7.52 (m, 2H, C*H*$_{arom.}$), 7.41 – 7.36 (m, 2H, C*H*$_{arom.}$), 4.87 (app. q, *J* = 7.0 Hz, 4H, C*H*$_2$), 3.05 (br, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 140.9 (*C*$_q$), 133.9 (*C*$_q$), 128.9 (*C*H), 126.1 (*C*H), 85.9 (*C*H$_2$), 75.5 (*C*$_q$). **HRMS (APCI)**: Calculated for C_9H_8ClO [M-OH]$^+$: 167.0264, Found: 167.0255.

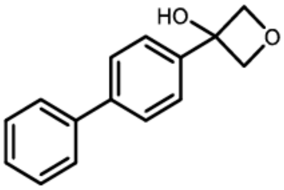
3-(4-Bromophenyl)oxetan-3-ol [2.45]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.20 mL, 5.50 mmol, 1.10 eq.) and 1-bromo-4-iodobenzene (1.70 g, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc 70:30 to 65:35) as a colourless solid (714 mg, 3.12 mmol, 62%).

m.p.: 82 – 83 °C. **IR (neat)**: $\tilde{\nu}$ = 3369 (m), 2957 (w), 2879 (w), 2332 (w), 2251 (w), 1593 (w), 1488 (w), 1411 (w), 1398 (w), 1265 (w), 1176 (w), 1138 (w), 1102 (w), 1071 (w), 1009 (m), 978 (m), 952 (w), 909 (m), 873 (w), 821 (m), 734 (s). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.58 – 7.53 (m, 2H, C*H*$_{arom.}$), 7.52 – 7.47 (m, 2H, C*H*$_{arom.}$), 4.92 – 4.89 (m, 2H, C*H*$_2$), 4.87 – 4.83 (m, 2H, C*H*$_2$), 2.70 (br, 1H, O*H*). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 141.5 (*C*$_q$), 131.9 (*C*$_q$), 126.4 (*C*H), 122.1 (*C*H), 85.9 (*C*H$_2$), 75.6 (*C*$_q$). **HRMS (APCI)**: Calculated for C_9H_8BrO [M-OH]$^+$: 210.9759, Found: 210.9749.

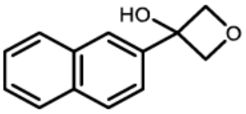
3-([1,1'-Biphenyl]-4-yl)oxetan-3-ol [2.46]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 4-iodo-1,1'-biphenyl (1.68 g, 6.00 mmol, 1.20 eq.), the desired product was obtained after recrystallization (CH_2Cl_2:petroleum ether) as a colourless solid (660 mg, 2.92 mmol, 58%).

m.p.: 140 – 141 °C. **IR (neat)**: $\tilde{\nu}$ = 3375 (m), 2366 (w), 2326 (w), 1543 (w), 1486 (w), 1423 (w), 1187 (w), 1093 (w), 966 (m), 909 (m), 877 (w), 831 (m), 764 (m), 731 (m), 699 (m), 668 (m), 660(m). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.72 – 7.62 (m, 4H, C$H_{\text{arom.}}$), 7.64 – 7.57 (m, 2H, C$H_{\text{arom.}}$), 7.50 – 7.42 (m, 2H, C$H_{\text{arom.}}$), 7.41 – 7.33 (m, 1H, C$H_{\text{arom.}}$), 5.01 – 4.92 (m, 4H, CH_2), 2.56 (br, 1H, O*H*). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 141.4 (C_q), 141.0 (C_q), 140.6 (C_q), 129.0 (*C*H), 127.7 (*C*H), 127.5 (*C*H), 127.2 (*C*H), 125.1 (*C*H), 85.8 (*C*H$_2$), 75.9 (C_q). **HRMS (APCI)**: Calculated for $C_{15}H_{13}O$ [M-OH]$^+$: 209.0966, Found: 209.0996.

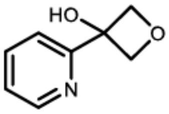
3-(Naphthalen-2-yl)oxetan-3-ol [2.47]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 2-bromonaphthalene (1.24 g, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc 70:30 to 65:35) as a colourless solid (836 mg, 4.18 mmol, 84%).

m.p.: 110 – 110 °C. **IR (neat)**: $\tilde{\nu}$ = 3341 (m), 3054 (w), 2965 (m), 2892 (w), 2358 (w), 2339 (w), 2332 (w), 2172 (w), 1721 (m), 1602 (w), 1421 (w), 1358 (w), 1314 (w), 1271 (s), 1250 (m), 1231 (m), 1192 (w), 1147 (w), 1127 (w), 1027 (w), 964 (s), 951 (m), 903 (w), 857 (s), 841 (s), 822 (s), 742 (m), 714 (m), 687 (w). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 8.01 (d, J = 1.9 Hz, 1H, C$H_{\text{arom.}}$), 7.93 (d, J = 8.6 Hz, 1H, C$H_{\text{arom.}}$), 7.90 – 7.84 (m, 2H, C$H_{\text{arom.}}$), 7.74 (dd, J = 8.6, 1.9 Hz, 1H, C$H_{\text{arom.}}$), 7.57 – 7.47 (m, 2H, C$H_{\text{arom.}}$), 5.07 – 4.96 (m, 4H, CH_2), 2.60 (br, 1H, O*H*). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 139.6 (C_q), 133.1 (C_q), 133.0 (C_q), 129.0 (*C*H), 128.4 (*C*H), 127.8 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 123.3 (*C*H), 122.8 (*C*H), 85.7 (*C*H$_2$), 76.1 (C_q). **HRMS (APCI)**: Calculated for $C_{13}H_{11}O$ [M-OH]$^+$: 183.0810, Found: 183.0802.

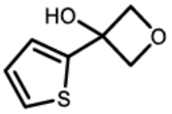
3-(pyridin-2-yl)oxetan-3-ol [2.48]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 2-bromopyridine (570 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc 80:20 to 60:40) as a yellow oil (363 mg, 2.40 mmol, 48%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.52 (ddd, *J* = 5.0, 1.7, 1.0 Hz, 1H, C*H*$_{\text{arom.}}$), 8.00 (app. dt, *J* = 8.1, 1.1 Hz, 1H, C*H*$_{\text{arom.}}$), 7.89 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H, C*H*$_{\text{arom.}}$), 7.33 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H, C*H*$_{\text{arom.}}$), 6.05 (br, 1H, O*H*), 5.13 – 5.07 (m, 2H, C*H*$_2$), 4.75 – 4.70 (m, 2H, C*H*$_2$). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 160.4 (*C*$_q$), 146.8 (*C*H), 138.5 (*C*H), 123.3 (*C*H), 119.2 (*C*H), 85.9 (*C*H$_2$), 74.2 (*C*$_q$).

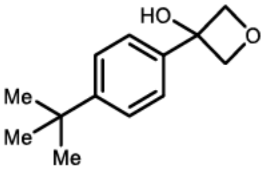
3-(Thiophen-2-yl)oxetan-3-ol [2.49]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 2-bromothiophene (978 mg, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc 70:30 to 60:40) as a colourless solid (575 mg, 3.68 mmol, 74%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.29 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.16 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.03 (dd, *J* = 5.0, 3.6 Hz, 1H), 4.91 – 4.84 (m, 4H), 3.50 (s, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 146.9, 127.4, 125.4, 123.7, 85.9, 74.5. Spectroscopic data was in agreement to those reported previously.[60]

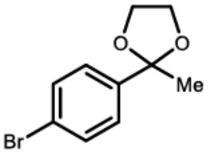
3-(4-(*tert*-Butyl)phenyl)oxetan-3-ol [2.50]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-bromo-4-(*tert*-butyl)benzene (1.28 g, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (CyH:EtOAc 70:30) as a colourless solid (139 mg, 0.67 mmol, 13%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.55 – 7.48 (m, 2H, C*H*$_{\text{arom.}}$), 7.48 – 7.41 (m, 2H, C*H*$_{\text{arom.}}$), 4.97 – 4.87 (m, 4H, C*H*$_2$), 2.63 (s, 1H, O*H*), 1.34 (s, 9H, C*H*$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 151.2 (*C*$_q$), 139.4 (*C*$_q$), 125.8 (*C*H), 124.4 (*C*H), 85.7 (*C*H$_2$), 75.9 (*C*$_q$), 34.7 (*C*$_q$), 31.4 (*C*H$_3$).

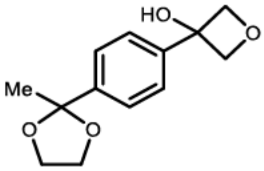
2-(4-Bromophenyl)-2-methyl-1,3-dioxolane [6.1]



Following a literature known protocol,[212] 4'-bromoacetophenone (3.00 g, 15.1 mmol, 1.00 eq.) and *para*-toluenesulfonic acid monohydrate (143 mg, 0.75 mmol, 5 mol%) were dissolved in toluene (30 mL) and ethylene glycol (22.6 mmol, 1.26 mL, 1.50 eq.) was added. The mixture was heated to reflux in a *Dean-Stark*-apparatus for 17 h. After cooling to rt, $NaHCO_3$ sat. aq. (15 mL) was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3x30 mL). The combined organic fractions were dried over $MgSO_4$, and the solvent was removed. The product was obtained as a colourless solid (3.40 g, 14.0 mmol, 93%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 – 7.44 (m, 2H), 7.38 – 7.33 (m, 2H), 4.06 – 4.01 (m, 2H), 3.78 – 3.73 (m, 2H), 1.63 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 142.5, 131.3, 127.2, 121.9, 108.5, 64.5, 27.5. Spectroscopic data was in agreement to those previously reported.[212]

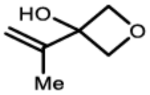
3-(4-(2-Methyl-1,3-dioxolan-2-yl)phenyl)oxetan-3-ol [2.51]



Following **GP-A**, with minor alterations using oxetan-3-one (340 µL, 5.33 mmol, 1.20 eq.), *n*-BuLi (2.50 M, 1.78 mL, 4.44 mmol, 1.00 eq.) and 2-(4-bromophenyl)-2-methyl-1,3-dioxolane (1.08 g, 4.44 mmol, 1.00 eq.), the desired product was obtained after recrystallization (petroleum ether:EtOAc) as a colourless solid (863 mg, 3.65 mmol, 82%).

m.p.: 128 – 129 °C. **IR (neat)**: $\tilde{\nu}$ = 3362 (m), 2891 (w), 1423 (w), 1373 (w), 1455 (w), 1226 (w), 1194 (m), 1097 (m), 1036 (s), 1013 (m), 963 (s), 952 (m), 873 (m), 830 (m), 656 (m). **^{1}H NMR (600 MHz, DMSO-d$_6$)**: δ = 7.60 – 7.56 (m, 2H, C$H_{arom.}$), 7.45 – 7.42 (m, 2H, C$H_{arom.}$), 6.35 (s, 1H, OH), 4.77 – 4.74 (m, 2H, CH_2), 4.69 – 4.65 (m, 2H, CH_2), 4.01 – 3.95 (m, 2H, CH_2), 3.71 – 3.64 (m, 2H, CH_2), 1.55 (s, 3H, CH_3). **^{13}C NMR (151 MHz, DMSO-d$_6$)**: δ = 143.8 (C_q), 142.2 (C_q), 125.0 (CH), 124.5 (CH), 108.1 (C_q), 85.3 (CH_2), 73.9 (C_q), 64.1 (CH_2), 27.4 (CH_3). **HRMS (APCI)**: Calculated for $C_{13}H_{17}O_4$ $[M+H]^+$: 237.1127, Found: 273.1123.

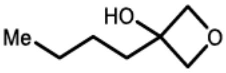
3-(Prop-1-en-2-yl)oxetan-3-ol [2.52]



Oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.) was dissolved in dry THF (20 mL), isopropenylmagnesium bromide (0.5 M, 12.0 mL, 6.00 mmol, 1.20 eq.) was added at –78 °C and stirred for 30 min before it was slowly warmed to rt over 1.5 h. Et_2O (25 mL) and NH_4Cl sat. aq. (20 mL) were added and the organic phase was separated. The aqueous phase was extracted with Et_2O (3x25 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed and the product was obtained as a colourless oil (446 mg, 3.91 mmol, 78%) after automated FC (CyH:EtOAc, 70:30).

IR (neat): $\tilde{\nu}$ = 3399 (m), 2954 (w), 2878 (w), 2360 (w), 2331 (w), 1732 (w), 1715 (w), 1650 (w), 1459 (w), 1447 (w), 1439 (w), 1375 (w), 1332 (w), 1267 (w), 1187 (s), 1141 (w), 1122 (m), 1060 (w), 1038 (w), 971 (s), 904 (s), 874 (m), 826 (w), 813 (w), 726 (w), 655 (w), 622 (m), 615 (m), 593 (m), 584 (m). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 5.10 (app. *t*, J = 0.9 Hz, 1H, CH_2), 5.02 (app. p, J = 1.4 Hz, 1H, CH_2), 4.82 – 4.76 (m, 2H, CH_2), 4.68 – 4.61 (m, 2H, CH_2), 2.26 (br, 1H, OH), 1.91 (dd, J = 1.4, 0.8 Hz, 3H, CH_3). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 144.5 (C_q), 111.9 (CH_2), 82.5 (CH_2), 18.0 (CH_3).[b] **HRMS (APCI)**: Calculated for $C_8H_{14}NO_2$ $[M+MeCN+H]^+$: 156.1025, Found: 156.1016.

3-Butyloxetan-3-ol [2.53]



Oxetan-3-one (500 µL, 7.77 mmol, 1.00 eq.) was dissolved in dry THF (8 mL), *n*-BuLi (2.50 M, 3.42 mL, 8.55 mmol, 1.10 eq.) was added at –78 °C. The mixture was stirred for 2 h before it was slowly warmed to rt over 2 h and stirred at rt for 1h. Et_2O (8 mL) and NH_4Cl sat. aq. (10 mL) were added. The organic phase was

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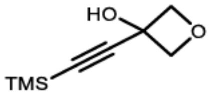
[b] One signal missing due to signal overlapping.

separated and the aqueous phase was extracted with Et_2O (3x8 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed. The desired product was obtained *via* automated FC (CyH:EtOAc, 80:20 to 50:50) as a colourless oil (706 mg, 5.42 mmol, 70%).

IR (neat): 3403 (m), 2954 (m), 2871 (m), 2358 (w), 1465 (w), 1240 (m), 1073 (m), 965 (s), 831 (m). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 4.56 (d, J = 6.7 Hz, 2H, CH_2), 4.53 – 4.48 (m, 2H, CH_2), 2.53 (s, 1H, OH), 1.87 – 1.76 (m, 2H, CH_2), 1.36 (dtd, J = 9.1, 4.6, 3.1 Hz, 4H, CH_2), 0.99 – 0.87 (m, 3H, CH_3). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 84.1 (CH_2), 74.8 (C_q), 37.6 (CH_2), 25.5 (CH_2), 23.0 (CH_2), 14.1 (CH_3). **HRMS (APCI):** Calculated for $C_9H_{18}O_2N$ $[M+MeCN+H]^+$: 172.1338, Found: 172.1334.

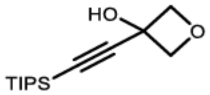
3-((Trimethylsilyl)ethynyl)oxetan-3-ol [2.54]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (1.60 M, 3.75 mL, 6.00 mmol, 1.20 eq.) and trimethylsilylacetylene (854 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained *via* FC (pentane:Et_2O, 80:20) as a colourless oil (802 mg, 4.70 mmol, 94%).

IR (neat): 3396 (w), 2953 (w), 2880 (w), 2180 (w), 1251 (m), 1134 (m), 978 (m), 921 (m), 839 (s). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 4.86 – 4.81 (m, 2H, CH_2), 4.71 – 4.66 (m, 2H, CH_2), 2.61 (s, 1H, OH), 0.19 (s, 9H, CH_3). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 104.2 (C_q), 91.7 (C_q), 84.6 (CH_2), 67.5 (C_q), -0.1 (CH_3). **HRMS (APCI):** Calculated for $C_8H_{15}O_2Si$ $[M+H]^+$: 171.0841, Found: 171.0836.

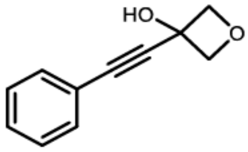
3-((Triisopropylsilyl)ethynyl)oxetan-3-ol [2.55]



Following **GP-A**, using oxetan-3-one (193 µL, 3.00 mmol, 1.00 eq.), *n*-BuLi (1.60 M, 2.25 mL, 3.60 mmol, 1.20 eq.) and 1-(triisopropylsilyl)-1-propyne (811 µL, 3.60 mmol, 1.20 eq.), the desired product was obtained *via* FC (pentane:Et_2O, 60:40) as a colourless oil (635 mg, 2.50 mmol, 83%).

IR (neat): 3394 (m), 2948 (s), 2866 (s), 2172 (w), 1464 (m), 1235 (m), 1135 (m), 988 (s), 920 (s), 883 (s), 838 (s), 772 (m). **^{1}H NMR (400 MHz, CDCl$_3$)** δ = 4.86 – 4.81 (m, CH_2), 4.74 – 4.70 (m, 2H, CH_2), 2.65 (s, 1H, OH), 1.08 (s, 21H, CH, CH_3). **^{13}C NMR (101 MHz, CDCl$_3$)** δ = 106.5 (C_q), 88.1 (C_q), 84.9 (CH$_2$), 67.5 (C_q), 18.7 (CH$_3$), 11.2 (CH). **HRMS (APCI):** Calculated for $C_{14}H_{27}O_2Si$ [M+H]$^+$: 255.1780, Found: 255.1771.

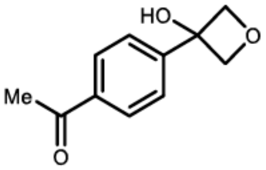
3-(Phenylethynyl)oxetan-3-ol [2.56]



Following **GP-A**, using oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and phenylacetylene (659 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained *via* FC (pentane:Et$_2$O, 70:30) as a colourless solid (791 mg, 4.54 mmol, 91%).

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.48 – 7.42 (m, 2H), 7.39 – 7.29 (m, 3H), 4.97 – 4.91 (m, 2H), 4.82 – 4.77 (m, 2H), 2.86 (s, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ = 131.8, 129.1, 128.6, 121.9, 88.0, 86.5, 84.8, 67.7. Spectroscopic data was in agreement to those previously reported.[50]

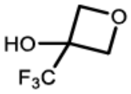
1-(4-(3-Hydroxyoxetan-3-yl)phenyl)ethan-1-one [2.57]



According to a literature known protocol,[70] 3-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)oxetan-3-ol **2.51** (150 mg, 0.635 mmol, 1.00 eq.) was dissolved in acetone (5 mL) and water (10 µL) before Montmorrilonite K10 (190 mg) was added. The mixture was stirred for 6 h at 55 °C. The mixture was filtered through celite and the solvent was removed. The product was obtained *via* automated FC (CyH:EtOAc, 70:30 to 60:40) as a colourless solid (102 mmg, 0.531 mmol, 84%).

m.p.: 131 – 132 °C. **IR (neat)**: $\tilde{\nu}$ = 3344 (m), 2954 (m), 2927 (m), 2853 (w), 2238 (w), 1678 (s), 1608 (m), 1428 (w), 1360 (m), 1307 (w), 1270 (s), 1183 (m), 1108 (m), 1014 (m), 976 (m), 960 (s), 910 (m), 874 (m), 833 (s), 809 (m), 734 (s), 704 (w), 661 (m), 646 (s). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.02 – 7.97 (m, 2H, C*H*$_{\text{arom.}}$), 7.76 – 7.72 (m, 2H, C*H*$_{\text{arom.}}$), 4.96 – 4.93 (m, 2H, C*H*$_2$), 4.89 – 4.86 (m, 2H, C*H*$_2$), 3.22 (br, 1H, O*H*), 2.62 (s, 3H, C*H*$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 198.0 (*C*$_q$), 147.6 (*C*$_q$), 136.6 (*C*$_q$), 128.9 (*C*H), 124.8 (*C*H), 86.0 (*C*H$_2$), 75.6 (*C*$_q$), 26.8 (*C*H$_3$). **HRMS (APCI)**: Calculated for $C_{11}H_{13}O_3$ [M+H]$^+$: 193.0865, Found: 193.0854.

3-(Trifluoromethyl)oxetan-3-ol [2.58]

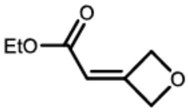


According to a literature known protocol with minor alterations,[66] oxetan-3-one (320 µL, 5.00 mmol, 1.00 eq) and trifluoromethyltrimethylsilane (1.04 mL, 7.00 mmol, 1.40 eq.) were dissolved in dry THF (25 mL) under Argon atmosphere and cooled to 0 °C. Tetrabutylammonium fluoride (1M in THF, 150 µL, 0.15 mmol, 3 mol%) was added slowly. After 1 h at 0 °C the solution was allowed to warm up to rt over 2 h. HCl aq. (1N, 15 mL) was added to the reaction mixture and stirred for 17 h. The aqueous phase was extracted afterwards with Et$_2$O (3x15 mL). The combined organic fractions were dried over MgSO$_4$ and the solvent was removed *in vacuo*. The product was obtained after FC (pentane:Et$_2$O, 50:50) as an off-white solid (449 mg, 3.16 mmol, 63%).

^{1}H NMR (500 MHz, CDCl$_3$) δ = 4.89 – 4.76 (m, 2H), 4.71 – 4.53 (m, 2H), 3.34 (s, 1H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ = 124.2 (q, $^1J_{C,F}$ = 280.7 Hz), 77.6 (q, $^3J_{C,F}$ = 2.6 Hz), 73.7 (q, $^2J_{C,F}$ = 33.0 Hz). **^{19}F NMR (470 MHz, CDCl$_3$)** δ = –84.1 (t, 3F, J = 1.6 Hz).
Spectroscopic data was in agreement to those previously reported.[50]

6.2.1.3 Synthesis of other carbinols

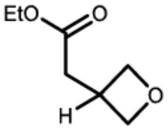
Ethyl 2-(oxetan-3-ylidene)acetate [2.59]



According to a literature known protocol with minor alterations,[41] ethyl (triphenylphosphoranylidene)acetate (6.50 g, 18.7 mmol, 1.20 eq.) was dissolved in CH$_2$Cl$_2$ (40 mL) and cooled to 0 °C before using oxetan-3-one (1.00 mL, 15.5 mmol, 1.00 eq.) was added slowly. The mixture was stirred for 2 h at rt before the solvent was removed *in vacuo*. The residue was taken up in a small portion of Et_2O and treated with pentane, the resulting precipitate was filtered off and washed with Et_2O: pentane (1:1). The filtrate was reduced and the desired product was obtained *via* automated FC (CyH: EtOAc, 90:10 to 70:30) as a colourless oil (2.14 g, 15.1 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.63 (app. t, *J* = 2.4 Hz, 1H), 5.53 – 5.47 (m, 2H), 5.34 – 5.27 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 165.4, 159.3, 111.3, 81.2, 78.6, 60.5, 14.4 (CH_3).
Spectroscopic data was in agreement to those previously reported.[41]

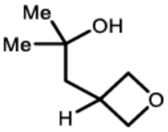
Ethyl 2-(oxetan-3-yl)acetate [2.60]



Ethyl 2-(oxetan-3-ylidene)acetate **2.59** (2.14 g, 15.1 mmol, 1.00 eq.) was dissolved in EtOAc (30 mL) under inert atmosphere, then Pd/C (5% w/w, 640 mg, 0.31 mmol, 2.00 mol%) was added. The atmosphere was changed to H_2 and H_2 was bubbled through the solution for 10 min. The mixture was stirred for 2 h at rt before the solids were filtered off. The solvent was removed and the product was obtained as a colourless oil (2.02 g, 14.0 mmol, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.85 (dd, *J* = 7.8, 6.2 Hz, 2H), 4.42 (t, *J* = 6.3 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.36 (app. pt, *J* = 7.9, 6.3 Hz, 1H), 2.71 (d, *J* = 7.9 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 171.9, 77.2, 60.7, 38.1, 31.6, 14.3.
Spectroscopic data was in agreement to those previously reported.[213]

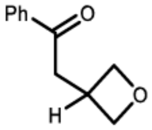
2-methyl-1-(oxetan-3-yl)propan-2-ol [2.61]



Ethyl 2-(oxetan-3-yl)acetate **2.60** (500 mg, 3.47 mmol, 1.00 eq.) was dissolved in dry THF (30 mL) and cooled to −78 °C at which temperature methylmagnesium bromide (3.00 M, 2.43 mL, 7.28 mmol, 2.10 eq.) was added slowly. The mixture was allowed to warm up to –20 °C and stirred at this temperature for 2.5 h before it was again cooled to –78 °C prior to addition of NH_4Cl sat. aq. The mixture was slowly warmed to rt and the aqueous phase was extracted afterwards with Et_2O (3x15 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was obtained after FC (Et_2O) as a colourless oil (147 mg, 1.13 mmol, 33%).

^{1}H NMR (400 MHz, C_6D_6) δ = 4.63 (dd, J = 8.0, 5.7 Hz, 2H, CH_2), 4.34 (dd, J = 7.0, 5.7 Hz, 2H, CH_2), 3.07 – 2.90 (m, 1H, CH), 1.57 – 1.51 (m, 1H OH), 1.44 (d, J = 7.2 Hz, 2H, CH_2), 0.88 (s, 6H, CH_3). **^{13}C NMR (101 MHz, C_6D_6)** δ = 78.1 (CH_2), 69.9 (C_q), 47.3 (CH), 32.1 (CH_2), 29.5 (CH_3). **HRMS (ESI)**: Calculated for $C_7H_{14}O_2$ $[M+Na]^+$: 153.0886, Found: 193.0886.

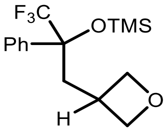
2-(oxetan-3-yl)-1-phenylethan-1-one [2.63]



Phenacyltriphenylphosphoniumbromide (5.07 g, 11.0 mmol, 1.10 eq.) was dissolved in CH_2Cl_2 (14 mL), NaOH (2N, 14 mL) was added and the mixture was stirred vigorously for 15 min. The organic phase was separated and cooled to 0 °C before a solution of 3-oxetanone (640 µL, 10.0 mmol, 1.00 eq.) in CH_2Cl_2 (5 mL) was added slowly. The mixture was stirred at rt after complete addition for 3 h, after which time the solvent was removed. The residue was taken up in Et_2O:petroleum ether (1:1, 15 mL) and the precipitate was filtered off and washed with Et_2O:petroleum ether (1:1). The filtrate was reduced and redissolved in EtOAc (10 mL) under inert atmosphere, then Pd/C (5% w/w, 213 mg, 0.10 mmol, 1.00 mol%) was added. The atmosphere was changed to H_2 and H_2 was bubbled through the solution for 10 min. The mixture was stirred for 2 h at rt before the solids were filtered off. The solvent was removed and the product was obtained as a colourless wax-like solid (482 mg, 2.74 mmol, 27%) after FC (EtOAc:CyH, 20:80)

m.p.: < 35 °C. **IR (neat)**: $\tilde{\nu}$ = 2968 (w), 2871 (w), 1474 (s), 1595 (w), 1449 (w), 1408 (w), 1350 (w), 1230 (w), 1212 (w), 965 (s), 949 (w), 859 (w), 762 (s), 690 (s), 671(w). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 7.73 – 7.66 (m, 2H, C$H_{arom.}$), 7.15 – 7.11 (m, 1H, C$H_{arom.}$), 7.07 – 7.02 (m, 2H, C$H_{arom.}$), 4.77 (dd, J = 7.8, 6.0 Hz, 2H, C*H*$_2$), 4.19 (t, *J* = 6.2 Hz, 2H, C*H*$_2$), 3.17 (pt, *J* = 7.7, 6.3 Hz, 1H, C*H*), 2.64 (d, *J* = 7.5 Hz, 2H, C*H*$_2$).**^{13}C NMR (101 MHz, C$_6$D$_6$)**: δ = 197.3 (*C*$_q$), 137.2 (*C*$_q$), 132.9 (*C*H), 128.6 (*C*H), 128.2 (*C*H), 76.9 (*C*H$_2$), 42.3 (*C*H$_2$), 31.3 (*C*H). **HRMS (ESI)**: Calculated for $C_{11}H_{13}O_2$ [M+H]$^+$: 177.0916, Found: 177.0911.

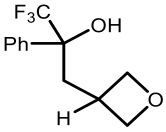
Trimethyl((1,1,1-trifluoro-3-(oxetan-3-yl)-2-phenylpropan-2-yl)oxy)-silane [2.64]



According to a literature known protocol with minor changes,[66] 2-(oxetan-3-ylidene)-1-phenylethan-1-one **2.63** (250 mg, 1.42 mmol, 1.00 eq.) and trifluoromethyltrimethylsilane (350 µL, 2.36 mmol, 1.66 eq.) were dissolved in dry CH_2Cl_2 (15 mL) and cooled to −78 °C before tetrabutylammonium fluoride (1M in THF, 43 µL, 0.43 mmol, 3.00 mol%) was added slowly. The mixture was stirred at −78 °C for 2 h and was warmed up to rt over 17 h. NH_4Cl sat. aq. (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3x15 mL). The combined organic fractions were dried over Na_2SO_4. The product was obtained after filtration through silica with CH_2Cl_2 as a colourless solid (374 mg, 1.17 mmol, 83%).

m.p.: 54–55 °C. **IR (neat)**: $\tilde{\nu}$ = 2968 (w), 1268 (w), 1256 (w), 1167 (s), 978 (w), 915 (w), 844 (s), 759 (w), 697 (w), 670 (m), 656 (m). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 7.48 – 7.43 (m, 2H, C*H*$_{arom.}$), 7.39 – 7.30 (m, 3H, C*H*$_{arom.}$), 4.62 (dd, *J* = 8.3, 5.9 Hz, 1H, C*H*$_2$), 4.47 (dd, *J* = 7.6, 5.9 Hz, 1H, C*H*$_2$), 4.13 (dd, *J* = 8.1, 6.1 Hz, 1H, C*H*$_2$), 4.02 (dd, *J* = 7.4, 6.1 Hz, 1H, C*H*$_2$), 3.16 – 3.00 (m, 1H, C*H*), 2.52 – 2.27 (m, 2H, C*H*$_2$), 0.21 (s, 9H, C*H*$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 137.9 (*C*$_q$), 128.5 (*C*H), 128.3 (*C*H), 126.3 (*C*H), 125.6 (q, $^1J_{C,F}$ = 287.4 Hz, *C*F$_3$), 79.9 (app. d, $^2J_{C,F}$ = 28.2 Hz, *C*$_q$), 77.7 (*C*H$_2$), 40.2 (*C*H$_2$), 30.6 (*C*H), 1.9 (*C*H$_3$).**^{19}F NMR (377 MHz, CDCl$_3$)** δ = −76.4 (s, 3F, C*F*$_3$). **HRMS (ESI)**: Calculated for $C_{15}H_{22}F_3O_2Si$ [M+H]$^+$: 319.1341, Found: 319.1328.

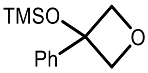
1,1,1-Trifluoro-3-(oxetan-3-yl)-2-phenylpropan-2-ol [2.65]



According to a literature known protocol,[72] trimethyl((1,1,1-trifluoro-3-(oxetan-3-yl)-2-phenylpropan-2-yl)oxy)silane **2.64** (250 mg, 0.785 mmol, 1.00 eq.) was dissolved in THF (10 mL) and cooled to 0 °C before tetrabutylammonium fluoride (1N in THF, 785 μL, 1.00 eq.) was added. The mixture was stirred for 1 h at 0 °C and for 2 h at rt before NH_4Cl sat. aq. (10 mL) was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3x10 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed. The product was obtained after FC (EtOAc:CyH, 20:80) as a slightly yellow solid (154 mg, 0.625 mmol, 80%).

m.p.: 87–88 °C. **IR (neat)**: $\tilde{\nu}$ = 3269 (w), 2968 (w), 1273 (w), 1164 (s), 1020 (w), 965 (w), 957 (w), 914 (m), 767 (w), 704 (s), 661 (s), 634 (s), 618 (s). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.50 – 7.45 (m, 2H, C$H_{\text{arom.}}$), 7.42 – 7.33 (m, 3H, C$H_{\text{arom.}}$), 4.64 (dd, J = 8.2, 6.1 Hz, 1H, CH_2), 4.49 (dd, J = 7.2, 6.1 Hz, 1H, CH_2), 4.29 (dd, J = 8.2, 6.1 Hz, 1H, CH_2), 4.10 (dd, J = 7.2, 6.1 Hz, 1H, CH_2), 3.12 – 3.03 (m, 1H, CH), 3.03 (s, 1H, OH), 2.48 – 2.34 (m, 1H, CH_2). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 136.4 (C_q), 128.8 (CH), 128.6 (CH), 125.8 (q, $^4J_{C,F}$ = 1.7 Hz, CH), 125.7 (q, $^1J_{C,F}$ = 286.0 Hz, CF$_3$), 77.9 (CH$_2$), 77.4 (CH$_2$), 77.2 (q, $^2J_{C,F}$ = 28.1 Hz, C_q), 39.3 (CH$_2$), 30.3 (CH). **^{19}F NMR (377 MHz, $CDCl_3$)** δ = −79.5 (s, 3F, CF_3).

Trimethyl((3-phenyloxetan-3-yl)oxy)silane [2.66]



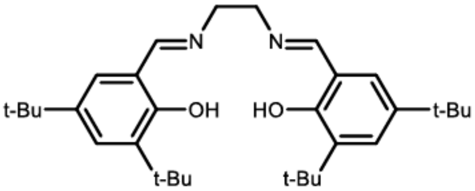
According to a literature known protocol,[30] 3-phenyloxetan-3-ol **2.38** (50.0 mg, 0.33 mmol, 1.00eq.) and imidazole (68.0 mg, 1.00 mmol, 3.00 eq.) were dissolved in CH_2Cl_2 (6 mL) and cooled to 0 °C before TMSCl (105 μL, 0.832 mmol, 2.50 eq.) was added slowly. The mixture was allowed to warm up to rt over 2 h before NH_4Cl sat. aq. (5 mL) and CH_2Cl_2 (5 mL) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3x5 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed. The crude material was filtered through silica with CH_2Cl_2 to yield the product as a colourless oil (65 mg, 0.292 mmol, 88%).

IR (neat): $\tilde{\nu}$ = 3057 (w), 2955 (w), 1448 (w), 1277 (w), 1254 (m), 1190 (m), 1079 (w), 985 (m), 916 (w), 845 (s), 758 (s), 700 (s), 657 (w), 641 (w), 624 (s).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.61 – 7.56 (m, 2H, C*H*$_{\text{arom.}}$), 7.43 – 7.38 (m, 2H, C*H*$_{\text{arom.}}$), 7.34 – 7.29 (m, 1H, C*H*$_{\text{arom.}}$), 5.05 – 4.99 (m, 2H, C*H*$_2$), 4.83 – 4.80 (m, 2H, C*H*$_2$), 0.09 (s, 9H, C*H*$_3$). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 144.0 (*C*$_q$), 128.6 (*C*H), 127.7 (*C*H), 124.9 (*C*H), 86.0 (*C*H$_2$), 76.9 (*C*$_q$), 1.6 (*C*H$_3$). **HRMS (ESI)**: Calculated for $C_{12}H_{19}O_2Si$ [M+H]$^+$: 223.1154, Found: 223.1141.

6.2.1.4 Ligand synthesis

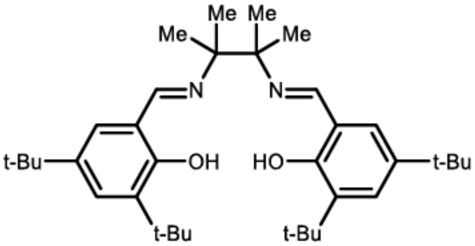
6,6'-((1*E*,1'*E*)-(Ethane-1,2-diylbis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-butylphenol) [2.67]



According to a literature known protocol with minor alterations,[75d] 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (2.34 g, 10.0 mmol, 2.00 eq.) was dissolved in MeOH (75 mL) before ethylenediamine (330 µL, 5.00 mmol, 1.00 eq.) was added and the mixture was heated to 75 °C for 24 h. The solvent was partially removed after cooling to rt. The concentrated mixture was cooled to 0 °C and the precipitate was filtered off and washed with cold MeOH to yield the product as yellow crystals (2.10 g, 4.26 mmol, 43%).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.39 (s, 2H), 7.37 (d, *J* = 2.5 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 2H), 3.93 (s, 4H), 1.44 (s, 18H), 1.29 (s, 18H). **^{13}C NMR (126 MHz, CDCl$_3$)**: δ = 167.7, 158.2, 140.2, 136.8, 127.2, 126.2, 118.0, 59.8, 35.2, 34.3, 31.6, 29.6. Spectroscopic data was in agreement to those previously reported.[214]

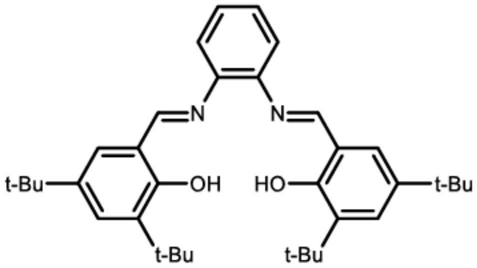
6,6'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-butylphenol) [2.68]



According to a literature known protocol with minor alterations,[75b] 2,3-dimethylbutane-2,3-diaminium oxalate (995 mg, 4.82 mmol, 1.00 eq.) was dissolved in EtOH:H_2O (25 mL, 80:20) with K_2CO_3 (1.33 g, 9.65 mmol, 2.00 eq.) and stirred for 15 min. After complete solvation, 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (2.26 g, 9.65 mmol, 2.00 eq.) was added and the mixture was heated to 90 °C for 4 h. The mixture was cooled to 0 °C, the precipitate was filtered off and washed with small portions of cold H_2O and EtOH. The residue was taken up in CH_2Cl_2 and filtered again. The filtrate was concentrated to yield the product as yellow crystals (2.06 g, 3.74 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 14.32$ (s, 2H), 8.40 (s, 2H), 7.36 (d, $J =$ 2.4 Hz, 2H), 7.10 (d, $J = 2.5$ Hz, 2H), 1.44 (s, 18H), 1.40 (s, 12H), 1.30 (s, 18H). **^{13}C NMR (101 MHz, $CDCl_3$)**: $\delta = 162.8$, 158.6, 139.9, 136.8, 126.9, 126.4, 118.1, 65.1, 35.2, 34.3, 31.7, 29.6, 23.4. Spectroscopic data was in agreement to those previously reported.[215]

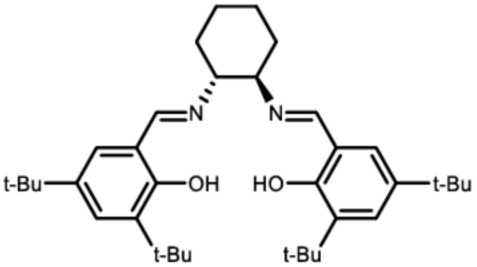
6,6'-((1*E*,1'*E*)-(1,2-Phenylenebis(azaneylylidene))bis(methaneylylidene))bis(2,4-di-*tert*-butylphenol) [2.69]



According to a literature known protocol with minor alterations,[75d] benzene-1,2-diamine (108 mg, 1.00 mmol, 1.00 eq.) was dissolved in EtOH (4 mL), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (500 mg, 2.14 mmol, 2.14 eq.) was added and the mixture was heated to 80 °C for 4 h. The mixture was cooled to −18 °C, the precipitate was filtered off and washed with small portions of cold EtOH to obtain the product as yellow crystals (415 mg, 0.77 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 14.03$ (s, 2H), 8.12 (s, 2H), 7.63 (d, $J =$ 2.5 Hz, 2H), 7.05 (d, $J = 2.4$ Hz, 2H), 6.99 (dt, $J = 7.3$, 3.6 Hz, 2H), 6.73 (dd, $J =$ 5.9, 3.4 Hz, 2H), 1.66 (s, 18H), 1.34 (s, 18H). **^{13}C NMR (101 MHz, $CDCl_3$)**: $\delta = 165.2$, 159.4, 143.1, 140.4, 137.7, 127.4, 127.3, 120.1, 119.1, 35.5, 34.3, 31.7, 29.8. Spectroscopic data was in agreement to those previously reported.[214]

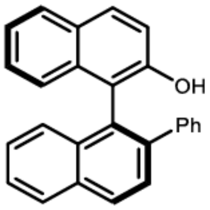
6,6'-((1*E*,1'*E*)-(((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(azaneylylidene))bis-(methaneylylidene))-bis(2,4-di-*tert*-butylphenol) [2.70]



According to a literature known procedure,[75c] (1*R*,2*R*)-(–)-1,2-cyclohexanediamine (2.00 g, 17.5 mmol, 1.00 eq.) was dissolved in EtOH (30 mL), and added to a solution of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (8.21 g, 35.0 mmol, 2.00 eq.) in EtOH (30 mL). The mixture was heated to 80 °C for 4 h and cooled to −18 °C afterwards. The resulting precipitate was filtered off and washed with small portions of cold EtOH to gain the product as a yellow solid (8.80 g, 16.1 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.72 (s, 2H), 8.31 (s, 2H), 7.31 (d, *J* = 2.5 Hz, 2H), 6.99 (d, *J* = 2.5 Hz, 2H), 3.38 – 3.27 (m, 2H), 1.99 – 1.91 (m, 2H), 1.88 (dq, *J* = 8.0, 2.8 Hz, 2H), 1.80 – 1.67 (m, 2H), 1.48 (dt, *J* = 9.7, 2.7 Hz, 2H CH_2), 1.42 (s, 18H), 1.24 (s, 18H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 166.0 (*C*HN), 158.1, 140.0, 136.5, 126.9, 126.2, 118.0, 72.6, 35.1, 34.2, 33.4, 31.6, 29.6, 24.5. Spectroscopic data was in agreement to those previously reported.[75c]

(*S*)-2'-Phenyl-[1,1'-binaphthalen]-2-ol [6.2]



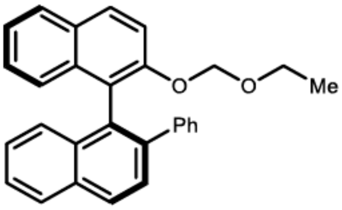
According to a literature known procedure,[216] (*S*)-BINOL (1.00 g, 3.49 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (40 mL) and *N*,*N*-diisopropylethylamine (650 µL, 3.84 mmol, 1.10 eq.) was added slowly. The solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (645 µL, 3.84 mmol, 1.10 eq.) was added dropwise and the reaction mixture was allowed to warm up to rt and was stirred for 17 h. NH_4Cl sat. aq. (40 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3x40 mL). The combined organic phases were washed with NaCl sat. aq. (3x50 mL) and were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was used without further purification.

Mg-turnings (848 mg, 34.9 mmol, 10.0 eq.) were activated with I_2 in a flame-dried Schlenk-flask under nitrogen atmosphere and dry THF (15 ml) was added. Bromobenzene (1.83 mL, 17.5 mmol, 5.00 eq.) was added dropwise at a rate to sustain constant reflux and the mixture was stirred 2 h at rt.

The crude product from the first step was dissolved in THF (15 mL) under nitrogen atmosphere and the freshly prepared Grignard-reagent was added as a solution at 0 °C *via* a transfer cannula and the mixture was stirred at 70 °C for 17 h. After cooling to rt, NH_4Cl sat. aq. (50 mL) was added, and the aqueous phase was extracted with Et_2O (3x30 mL). The combined organic fractions were washed with $NaHCO_3$ sat. aq. (30 mL), NaCl sat. aq. (30 mL), were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was obtained after FC (pentane:EtOAc, 95:5) as a colourless foam (975 mg, 2.81 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (d, J = 8.5 Hz, 1H), 7.99 (dt, J = 8.3, 1.1 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.52 (ddd, J = 8.1, 6.0, 2.0 Hz, 1H), 7.36 – 7.27 (m, 3H), 7.23 (ddd, J = 15.0, 6.6, 1.5 Hz, 2H), 7.18 – 7.11 (m, 3H), 7.12 – 7.02 (m, 4H), 4.84 (s, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 151.1, 141.7, 140.9, 134.3, 133.4, 133.3, 130.0, 129.6, 128.8, 128.7, 128.7, 128.6, 128.3, 128.2, 127.8, 127.3, 127.1, 126.7, 126.6, 126.5, 125.2, 123.3, 117.8, 117.3.[c] **HRMS (APCI)**: Calculated for $C_{26}H_{17}O$ $[M-H]^-$: 345.1279, Found: 345.1281. Spectroscopic data was in agreement to those previously reported.[217]

(*S*)-2-(Ethoxymethoxy)-2'-phenyl-1,1'-binaphthalene [6.3]



According to a literature known procedure,[218] (*S*)-2'-phenyl-[1,1'-binaphthalen]-2-ol **6.2** (975 mg, 2.81 mmol, 1.00 eq.) was dissolved in dry THF (30 mL) in

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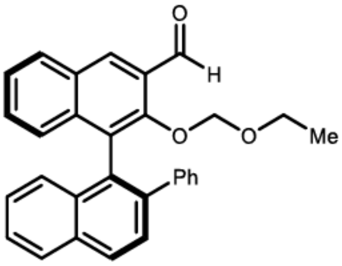
[c] Missing signals under solvent peak.

a flame-dried Schlenk-flask under nitrogen atmosphere and a dispersion of sodium hydride in mineral oil (60% NaH, 124 mg, 3.10 mmol, 1.10 eq.) was added portion wise at 0 °C and the mixture was stirred for 50 min at 0 °C. 2-Methoxyethoxymethylchlorid (310 µL, 3.38 mmol, 1.20 eq.) was added dropwise at 0 °C and the mixture was stirred for 20 min at 0°C and 1 h at rt. H_2O (50 mL) and Et_2O (50 mL) were added and the organic phase was extracted with Et_2O (3x50 mL). The combined organic fractions were washed with NaCl sat. aq. (50 mL) and were dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was used without further purification in the next step.

^{1}H NMR (400 MHz, C_6D_6) δ = 7.81 (d, J = 8.6 Hz, 1H, $CH_{arom.}$), 7.76 (d, J = 8.3 Hz, 1H, $CH_{arom.}$), 7.68 (d, J = 8.5 Hz, 1H, $CH_{arom.}$), 7.62 (d, J = 9.1 Hz, 1H, $CH_{arom.}$), 7.58 (d, J = 8.8 Hz, 1H, $CH_{arom.}$), 7.53 (d, J = 9.1 Hz, 1H, $CH_{arom.}$), 7.49 (dq, J = 8.5, 0.9 Hz, 1H, $CH_{arom.}$), 7.41 – 7.31 (m, 3H, $CH_{arom.}$), 7.24 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H, $CH_{arom.}$), 7.11 – 6.94 (m, 3H, $CH_{arom.}$), 6.92 – 6.84 (m, 2H, $CH_{arom.}$), 6.84 – 6.77 (m, 1H, $CH_{arom.}$), 4.74 (d, J = 7.2 Hz, 1H, CH_2), 4.61 (d, J = 7.2 Hz, 1H, CH_2), 3.24 – 2.96 (m, 2H, CH_2), 0.83 (t, J = 7.1 Hz, 3H, CH_3). **^{13}C NMR (101 MHz, C_6D_6)** δ = 153.7 (C_q), 142.7 (C_q), 140.6 (C_q), 135.1 (C_q), 133.9 (C_q), 133.5 (C_q), 132.7 (C_q), 129.9 (CH), 129.8 (CH), 129.3 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 126.0 (CH), 124.1 (CH), 123.3 (CH), 116.6 (CH), 93.6 (CH_2), 63.9 (CH_2), 15.1 (CH_3).

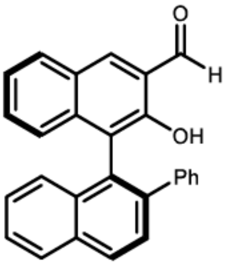
(*S*)-2-(Ethoxymethoxy)-2'-phenyl-[1,1'-binaphthalene]-3-carbaldehyde [6.4]



According to a literature known procedure,[216] (*S*)-2-(ethoxymethoxy)-2'-phenyl-1,1'-binaphthalene **6.3** (1.14 g, 2.81 mmol, 1.00 eq.) was dissolved in dry THF (15 mL) under nitrogen atmosphere. The reaction flask was cooled to –78 °C, *n*-BuLi (1.6 M, 2.10 mL, 3.37 mmol, 1.20 eq.) was added dropwise and the mixture was stirred at –78 °C for 30 min and for 90 min at rt. The flask was cooled to −78 °C and *N*,*N*-dimethylformamide (1.10 mL, 14.1 mmol, 5.00 eq.) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min and at rt for 14 h. NH_4Cl sat. aq. (25 mL) was added and the organic phase was extracted with EtOAc (3x25 mL). The combined organic fractions were washed with NaCl sat. aq. (25 mL) and were dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was obtained after FC (pentane:Et_2O, 90:10) as a colourless solid (736 mg, 1.70 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.34 (s, 1H), 8.42 (d, *J* = 0.8 Hz, 1H), 8.06 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.98 (dt, *J* = 8.2, 0.6 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.45 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.38 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.22 (m, 1H), 7.11 – 7.06 (m, 2H), 7.06 – 6.98 (m, 3H), 4.63 (d, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 1H), 3.27 (dq, *J* = 9.4, 7.0 Hz, 1H), 2.98 (dq, *J* = 9.4, 7.0 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 191.3, 153.5, 141.6, 140.9, 137.8, 133.3, 132.8, 131.2, 130.5, 130.4, 129.7, 129.4, 129.3, 129.0, 128.8, 128.6, 128.3, 127.7, 126.9, 126.8, 126.8, 126.6, 126.0, 125.9, 98.4, 65.4, 14.7.

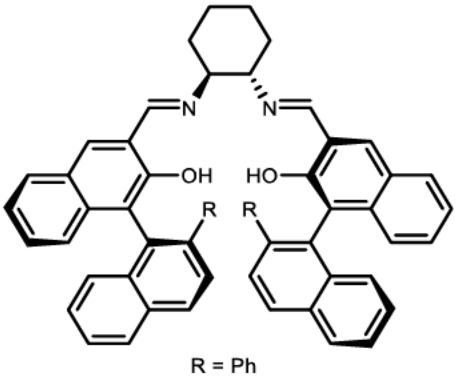
(*S*)-2-Hydroxy-2'-phenyl-[1,1'-binaphthalene]-3-carbaldehyde [6.5]



According to a literature known procedure,[216] (*S*)-2-(ethoxymethoxy)-2'-phenyl-[1,1'-binaphthalene]-3-carbaldehyde **6.4** (300 mg, 0.69 mmol, 1.00 eq.) was dissolved in 1,4-dioxane (3 mL) and conc. HCl (1 mL) was added dropwise at rt. The mixture was stirred for 2 h and water was added (10 mL). A yellow precipitate was formed, that was filtered off, was washed with water (3x20 mL) and was dried over P_4O_{10} for 17 h. The product was obtained as a bright yellow solid (242 mg, 0.65 mmol, 93%).

^{1}H NMR (400 MHz, CDCl$_3$) δ = 10.43 (s, 1H), 10.09 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 8.05 (dd, J = 8.5, 0.8 Hz, 1H), 7.98 (dt, J = 8.4, 1.0 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.48 (ddd, J = 8.2, 6.5, 1.4 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.27 – 7.24 (m, 1H), 7.23 – 7.19 (m, 2H), 7.13 (ddd, J = 7.7, 1.9, 0.8 Hz, 1H), 7.05 – 6.99 (m, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ = 196.9, 153.7, 142.0, 140.8, 138.0, 137.9, 133.1, 132.7, 130.5, 130.0, 129.8, 128.7, 128.7, 128.4, 128.4, 127.5, 127.2, 126.7, 126.6, 126.2, 126.0, 125.5, 124.3, 121.6, 121.4. Spectroscopic data was in agreement to those previously reported.[217]

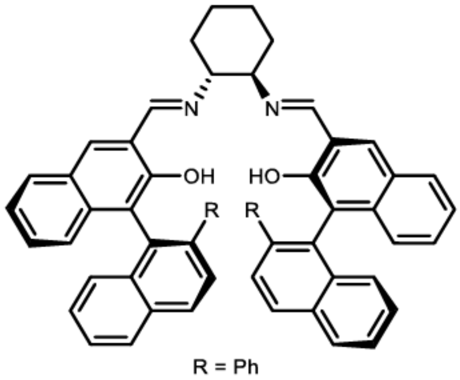
3-((*E*)-(((1*S*,2*S*)-2-(((*E*)-((*S*)-2-Hydroxy-2'-phenyl-[1,1'-binaphthalen]-3-yl)methylene)amino)cyclohexyl)imino)methyl)-2'-phenyl- [1,1'-binaphthalen]-2-ol [2.71]



According to a literature known procedure,[75a] (1*S*,2*S*)-(−)-1,2-cyclohexanediamine D-tartrate (60 mg, 0.23 mmol, 1.00 eq.) was stirred with K$_2$CO$_3$ (63.0 mg, 0.45 mmol, 2.00 eq.) in EtOH (5 mL) and H$_2$O (1 mL) for 15 min, before (*S*)-2-hydroxy-2'-phenyl-[1,1'-binaphthalene]-3-carbaldehyde **6.5** (170 mg, 0.45 mmol, 2.00 eq.) was added. The mixture was heated to reflux for 4 h. Water (10 mL) was added and the flask was cooled to −18 °C. A yellow precipitate was formed, that was filtered off, was washed with water (3x20 mL) and ice-cold EtOH (3x5 mL). The product was dried in-vacuo and was obtained as a pale yellow solid (164 mg, 0.20 mmol, 87%).

^{1}H NMR (400 MHz, CDCl$_3$) δ = 13.04 (s, 2H), 8.37 (s, 2H), 8.01 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.63 – 7.59 (m, 1H), 7.58 (s, 2H), 7.34 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 7.27 – 7.22 (m, 5H), 7.21 – 7.13 (m, 4H), 7.08 (d, J = 8.5 Hz, 2H), 6.99 (td, J = 6.2, 2.7 Hz, 8H), 6.78 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 3.32 – 3.21 (m, 2H), 1.94 (d, J = 13.4 Hz, 2H), 1.86 (d, *J* = 9.9 Hz, 2H), 1.76 – 1.61 (m, 2H), 1.44 (d, *J* = 10.1 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 165.1, 154.8, 142.3, 140.4, 135.3, 133.3, 133.1, 133.0, 131.4, 128.9, 128.8, 128.4, 128.3, 128.2, 128.2, 127.4, 127.1, 126.5, 126.4, 126.2, 125.8, 125.0, 123.1, 120.0, 119.9, 73.3, 32.9, 24.2.

(*S*)-3-((*E*)-(((1*R*,2*R*)-2-(((*E*)-((*R*)-2-hydroxy-2'-phenyl-[1,1'-binaphthalen]-3-yl)methylene)amino)cyclohexyl)imino)methyl)-2'-phenyl-[1,1'-binaphthalen]-2-ol [*epi*-2.71]

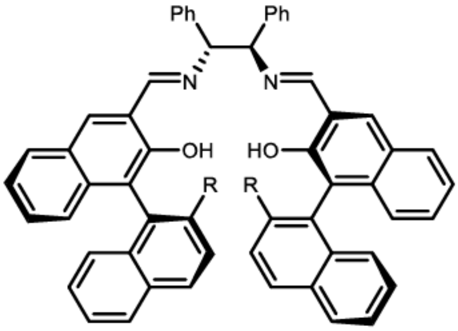


According to a literature known procedure with minor alterations,[75b] (1*R*,2*R*)-cyclohexane-1,2-diamine L-tartrate (25.0 mg, 94.5 µmol, 1.00 eq.) was stirred with K_2CO_3 (26.0 mg, 187 µmol, 2.00 eq.) in EtOH (5 mL) and H_2O (0.5 mL) for 15 min, before (S)-2-hydroxy-2'-phenyl-[1,1'-binaphthalene]-3-carbaldehyde **6.5** (70 mg, 187 µmol, 2.00 eq.) was added. The mixture was heated to reflux for 60 h. Water (10 mL) was added and the flask was cooled to −18 °C. The precipitate was filtered off, and washed with small portions of water and cold EtOH. The product was obtained as a pale yellow solid (59 mg, 71 µmol, 76%).

^{1}H NMR (400 MHz, C_6D_6) δ = 13.25 (s, 2H, C*H*N), 7.95 (s, 2H, CH_{arom}), 7.85 (d, *J* = 8.5 Hz, 2H, CH_{arom}), 7.78 (d, *J* = 8.5 Hz, 2H, CH_{arom}), 7.74 – 7.67 (m, 4H, CH_{arom}), 7.43 – 7.37 (m, 4H, CH_{arom}), 7.36 – 7.31 (m, 4H, O*H*, CH_{arom}), 7.24 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H, CH_{arom}), 7.15 – 7.13 (m, 2H, CH_{arom}), 7.07 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H, CH_{arom}), 6.90 (dqd, *J* = 8.0, 6.7, 1.5 Hz, 4H, CH_{arom}), 6.33 (t, *J* = 7.7 Hz, 4H, CH_{arom}), 6.23 – 6.16 (m, 2H, CH_{arom}), 2.92 – 2.79 (m, 2H, C*H*), 1.56 – 1.46 (m, 2H, CH_2), 1.47 – 1.39 (m, 2H, CH_2), 1.34 (d, *J* = 12.3 Hz, 2H, CH_2), 1.11 – 0.95 (m, 2H, CH_2). **^{13}C NMR (101 MHz, C_6D_6)** δ = δ 165.5 (*C*HN), 156.1 (C_q-OH), 142.5 (C_q), 140.8 (C_q), 135.4 (C_q), 133.9 (C_q), 133.8 (*C*H), 133.6 (C_q), 132.3 (C_q), 129.0 (C_q), 128.7 (*C*H), 128.7 (*C*H), 128.5 (*C*H), 128.5

(*C*H), 128.4 (*C*H), 128.0 (*C*H), 127.7 (C_q), 127.2 (C_q), 126.8 (*C*H), 126.0 (*C*H), 125.2 (*C*H), 123.4 (*C*H), 120.9 (*C*H), 120.4 (*C*H), 73.2 (*C*H), 32.6 (CH_2), 24.2 (CH_2).[d]

(*S*)-3-((*E*)-(((1*R*,2*R*)-2-(((*E*)-((*R*)-2-hydroxy-2'-phenyl-[1,1'-binaphthalen]-3-yl)methylene)amino)-1,2-diphenylethyl)imino)methyl)-2'-phenyl-[1,1'-binaphthalen]-2-ol [2.72]



R = Ph

According to a literature known procedure,[75d] (*S*)-2-hydroxy-2'-phenyl-[1,1'-binaphthalene]-3-carbaldehyde **6.5** (136 mg, 0.36 mmol, 2.00 eq.) was dissolved in EtOH (4 mL) and (1*R*,2*R*)-1,2-diphenylethylenediamine (39 mg, 0.18 mmol, 1.00 eq.) was added. The mixture was heated to 80 °C for 17 h before it was cooled to −18 °C. A yellow precipitate was formed, that was filtered off to yield a yellow solid (84 mg, 0.09 mmol, 50%).

m.p.: decomp. >250 °C. **IR (neat)**: 3060 (w), 2870 (w), 1953 (w), 1629 (s), 1495 (m), 1442 (w), 1346 (w), 1120 (w), 1029 (w), 942 (w), 822 (m), 762 (w), 735 (m), 698 (s). **^{1}H NMR (400 MHz, CDCl$_3$)** $\delta = 12.82$ (s, 2H, C*H*N), 8.26 (s, 2H, CH_{arom}), 8.07 (d, $J = 8.5$ Hz, 2H, CH_{arom}), 7.97 (d, $J = 8.3$ Hz, 2H, CH_{arom}), 7.69 (d, $J = 8.5$ Hz, 2H, CH_{arom}), 7.45 (ddd, $J = 8.1, 6.1, 1.8$ Hz, 2H, CH_{arom}), 7.32 (s, 2H, O*H*), 7.28 (d, $J = 6.8$ Hz, 2H, CH_{arom}), 7.23 (ddd, $J = 8.2, 3.3, 1.2$ Hz, 4H, CH_{arom}), 7.19 – 7.15 (m, 6H, CH_{arom}), 7.15 – 7.10 (m, 10H, CH_{arom}), 7.08 – 6.96 (m, 4H, CH_{arom}), 6.46 (t, $J = 7.7$ Hz, 4H, CH_{arom}), 6.38 – 6.29 (m, 2H, CH_{arom}), 4.60 (s, 2H, C*H*). **^{13}C NMR (101 MHz, CDCl$_3$)** $\delta = 166.5$ (*C*HN), 154.8 (C_q-OH), 142.1 (C_q), 140.7 (C_q), 138.6 (C_q), 135.4 (C_q), 134.1 (C_q), 133.1 (C_q), 133.0 (C_q), 131.2 (C_q), 128.8 (*C*H), 128.6 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 128.3 (*C*H), 128.3 (*C*H), 128.1 (*C*H), 127.9 (*C*H), 127.4 (*C*H), 127.2 (C_q), 126.6 (*C*H), 126.5 (*C*H), 126.4 (*C*H), 125.8 (*C*H), 124.9 (*C*H), 123.3 (*C*H), 120.3 (C_q),

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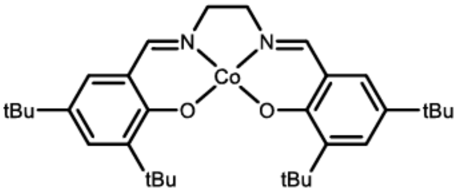
[d] Missing signals under solvent peak.

120.0 (*C*H), 81.5 (*C*H).[e] **HRMS (ESI)**: Calculated for $C_{68}H_{48}N_2O_2Na$ $[M+Na]^+$: 947.3619, Found: 947.3611.

6.2.1.5 Synthesis of cobalt complexes

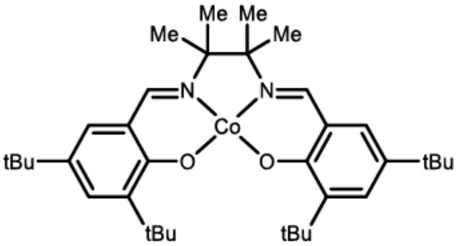
Co^{II}·salen [2.73]



Following **GP-B**, $Co(OAc)_2 \cdot 4H_2O$ (127 mg, 0.51 mmol, 1.00 eq.) was reacted with achiral salen ligand **2.67** (250 mg, 0.51 mmol, 1.00 eq.) to yield the dark red complex (219 mg, 0.398 mmol, 78%).

Elemental analysis calcd (%) for $C_{32}H_{46}CoN_2O_2$: C 69.92, H 8.44, N 5.10; found: C 69.55, H 8.23, N 5.00.

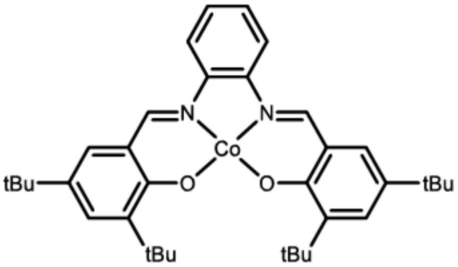
Co^{II}·salen [2.74]



Following **GP-B**, $Co(OAc)_2 \cdot 4H_2O$ (227 mg, 0.91 mmol, 1.00 eq.) was reacted with achiral salen ligand **2.68** (500 mg, 0.91 mmol, 1.00 eq.) to yield the dark red complex (226 mg, 0.373 mmol, 41%).

HRMS (ESI): Calculated for $C_{36}H_{54}CoN_2O_2$ $[M]^+$: 605.3512, Found: 605.3518.

Co^{II}·salen [2.75]



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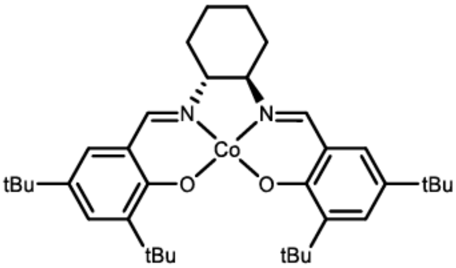
[e] Missing signals under solvent peak.

Following **GP-B**, $Co(OAc)_2·4H_2O$ (69 mg, 277 µmol, 1.00 eq.) was reacted with achiral salen ligand **2.69** (150 mg, 277 µmol, 1.00 eq.) to yield the dark red complex (102 mg, 198 µmol, 76%).

HRMS (ESI): Calculated for $C_{36}H_{46}CoN_2O_2$ $[M]^+$: 597.2886, Found: 597.2893.

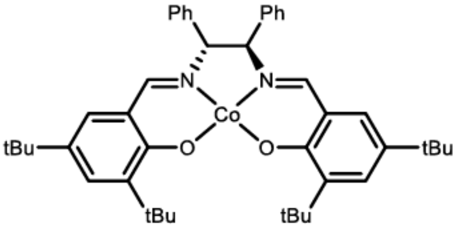
Co^{II}·salen [*epi*-2.76]



Following **GP-B**, $Co(OAc)_2·4H_2O$ (623 mg, 2.50 mmol, 1.00 eq.) was reacted with achiral salen ligand **2.70** (1.37 g, 2.50 mmol, 1.00 eq.) to yield the dark red complex (771 mg, 1.28 mmol, 51%).

Elemental analysis calcd (%) for $C_{36}H_{52}CoN_2O_2$: C 71.62, H 8.68, N 4.64; found: C 71.62, H 8.57, N 4.57.

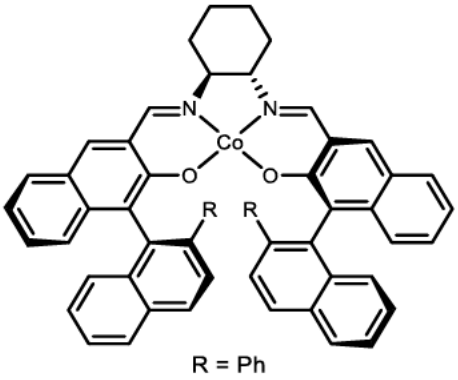
Co^{II}·salen [epi-2.77]



Following **GP-B**, $Co(OAc)_2·4H_2O$ (38.6 mg, 0.155 mmol, 1.00 eq.) was reacted with a chiral salen ligand (100 mg, 0.155 mmol, 1.00 eq.), to yield the dark red complex **2.77** (80 mg, 0.113 mmol, 73%).

Elemental analysis calcd (%) for $C_{44}H_{54}CoN_2O_2$: C 75.30, H 7.76, N 3.99; found: C 75.16, H 7.63, N 3.78.

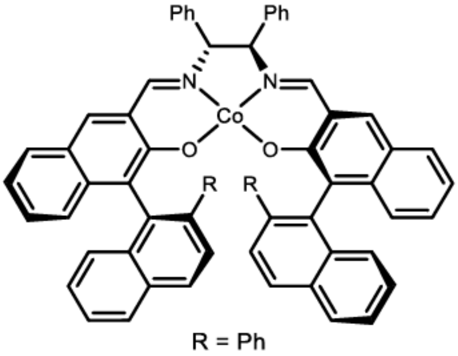
Co^{II}·salen [2.78]



Following **GP-B**, $Co(OAc)_2·4H_2O$ (36.1 mg, 145 µmol, 1.00 eq.) was reacted with chiral salen ligand **2.71** (120 mg, 145 µmol, 1.00 eq.) to yield the dark red complex (65 mg, 74 µmol, 51%).

IR (neat): 3058 (w), 2931 (w), 2331 (w), 1586 (s), 1548 (m), 1446 (m), 1413 (m), 1333 (s), 1148 (m), 820 (m), 759 (w), 735 (s). **HRMS (ESI):** Calculated for $C_{60}H_{44}CoN_2O_2$ [M]$^+$: 883.2735, Found: 883.2720.

Co^{II}·salen [*epi*-2.79]

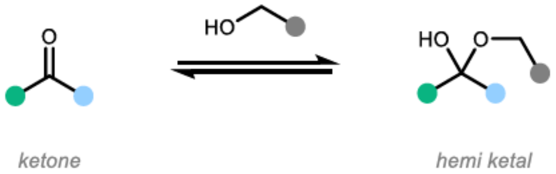


Following General procedure **B**, $Co(OAc)_2·4H_2O$ (17 mg, 0.07 mmol, 1.00 eq.) was reacted with the chiral BINOL-type ligand **2.72** (62 mg, 0.07 mmol, 1.00 eq.) to yield the orange-brown complex (32 mg, 0.03 mmol, 43%).

m.p.: decomp. >250 °C. **IR (neat)**: 3058 (w), 2931 (w), 2346 (w), 630(s), 1591 (m), 1495 (m), 1453 (m), 1347 (m), 1147 (m), 1028 (m), 822 (m), 738 (m), 700 (s). **HRMS (ESI):** Calculated for $C_{68}H_{47}CoN_2O_2$ [M+H]$^+$: 982.2969, Found: 982.2948.

6.2.2 Mechanistic experiments

6.2.2.1 Hammett-plot of the hemi-ketal formation



The hemi ketal/ ketone equilibrium of varying trifluoroacetophenone derivatives was examined by dissolving the corresponding trifluoroacetophenone (0.10 mmol, 1.00 eq.) in dry $CDCl_3$ (700 µL) and adding 1-pentanol (0.10 mmol, 1.00 eq.). The reaction towards the hemi ketal was monitored by ^1H NMR and ^{19}F NMR spectroscopy until no further conversion was observed.

Exemplarily, the spectra of 4'-nitro-2,2,2-trifluoroacetophenone **2.22** and its hemiketal **2.89** with 1-pentanol are shown below to demonstrate the typical chemical shifts of the trifluoroacetophenones and their respective hemiketals. In case of very electron-poor trifluoroacetophenone derivates a small amount, typically less than 2%, is converted to the hydrate due to a trace amount of water in the used solvent.

The equilibrium of other alcohols was determined likewise to the above outlined method. Accordingly, hemiketal **2.96** was prepared using 4'-nitro-2,2,2-trifluoroacetophenone **2.22** (0.10 mmol, 1.00 eq.) and benzyl alcohol (0.10 mmol, 1.00 eq.). By slow evaporation of the solvent, a sample suitable for X-ray analysis was obtained.

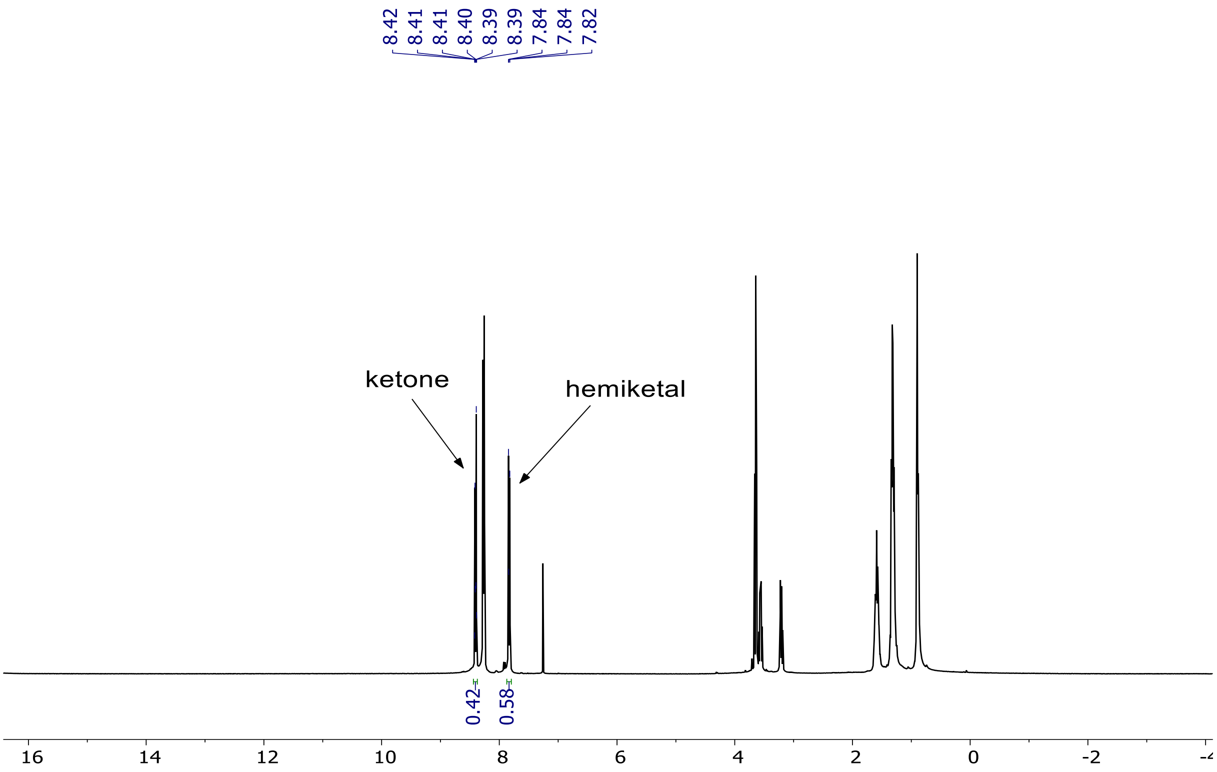


Figure 21: ^{1}H **NMR spectrum of 4'-nitro-2,2,2-trifluoroacetophenone 2.22 with 1-pentanol in** $CDCl_3$ **after 7 days.**

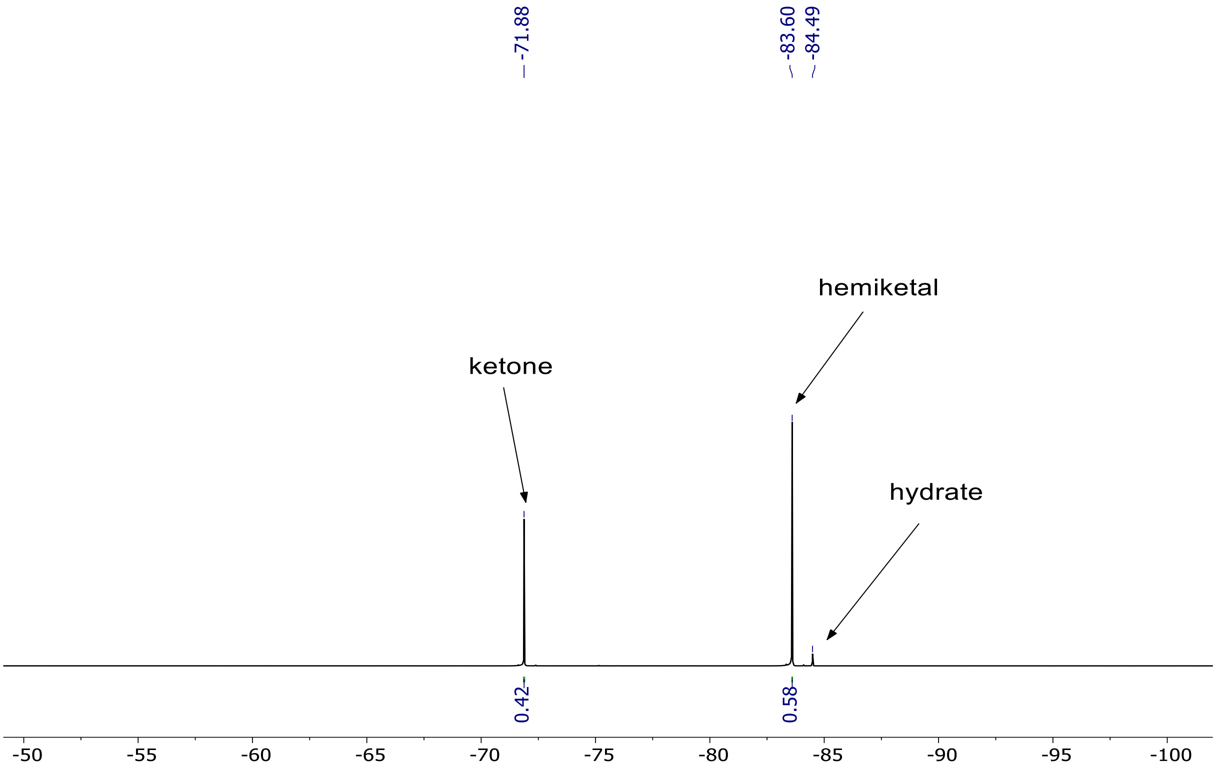


Figure 22: ^{19}F **NMR spectrum of 4'-nitro-2,2,2-trifluoroacetophenone 2.22 with 1-pentanol in** $CDCl_3$ **after 7 days.**

The equilibrium constants of the reactions were determined by simple integration of the corresponding signals in the ^{1}H NMR and ^{19}F NMR spectra (Eq. 6.1).

$$k = \frac{I(ketone)}{I(hemiacetal)} \tag{6.1}$$

For the corresponding substituents, the σ values used for the calculations in the *Hammett*-equation (Eq. 6.2) are tabulated in the literature.[77]

$$log\, k = \sigma \cdot \rho \tag{6.2}$$

Table 17: Equilibrium constants and *σ* values for the *Hammett*-plot of hemiketal formation of trifluoroacetophenone derivatives.

Entry	Substituent	*σ*	*I*(ketone)	*I*(hemiketal)	*k*	log *k*
1	4-OMe	-0.27	100	0	0.0000	n.d.
2	4-H	0.00	94	6	0.0638	-1.1950
3	4-F	0.06	93	7	0.0753	-1.1234
4	4-Br	0.23	87	13	0.1494	-0.8256
5	4-CN	0.66	53	47	0.8868	-0.0522
6	3-NO_2	0.71	53	47	0.8868	-0.0522
7	4-NO_2	0.78	41	59	1.4390	0.1581

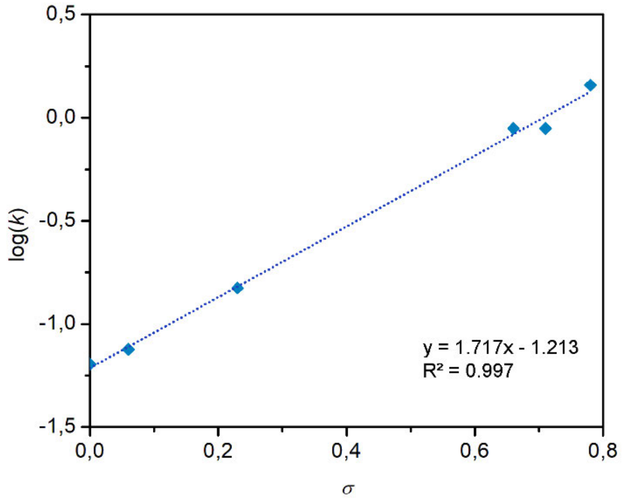
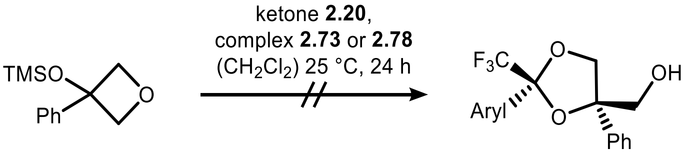


Figure 23: *Hammett*-plot of the hemiketal formation of trifluoroacetophenone derivatives with 1-pentanol.

6.2.2.2 Survey on the role of the nucleophile in the ring-opening of oxetanes

Investigating the role of hemi ketal and hydrate



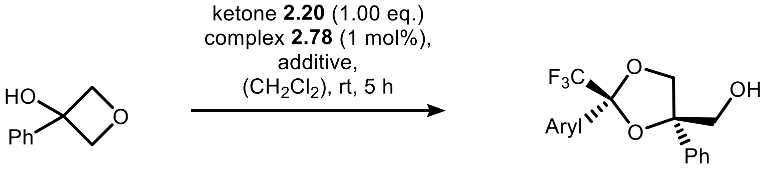
2.66 **2.105**, Aryl = 3,5-$(NO_2)_2$-C_6H_3

Following **GP-C**, using trimethyl((3-phenyloxetan-3-yl)oxy)silane **2.66** (22.2 mg, 0.10 mmol, 1.00 eq.) and Co^{II} catalyst **2.73** or **2.78** (1 mol%). The reaction was monitored through ^{19}F NMR with 0.1 mmol of trifluorotoluene as internal standard. No product was observed within 24 h of reaction time.

Deliberately adding water (up to 1.00 eq.) had no influence on the reaction outcome.

The role of the hydrate as a possible nucleophile was investigated by exchanging ketone **2.20** through its hydrate **2.24** and subjecting it to the reaction conditions of **GP-C** with 3-phenyl-oxetan-3-ol **2.38** (30.0 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.78** (1 mol%) in CH_2Cl_2.

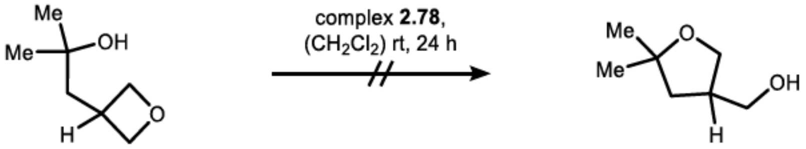
Table 18: Reactions were carried out on a 0.1 mmol scale in 0.5 mL solvent with catalyst 2.78, yield and *dr* based on ^{19}F NMR experiments using trifluorotoluene as an internal standard.



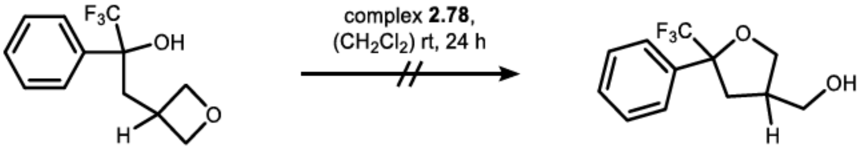
2.38 **2.105**, Aryl = 3,5-$(NO_2)_2$-C_6H_3

Entry	Equivalents of **2.20**	Additive	Catalyst loading	Yield
1	1.00	-	1 mol%	47%
2	0.50	0.50 eq. **2.24**	1 mol%	9%
3	0.00	1.00 eq. **2.24**	1 mol%	2%
4	1.00	1.00 eq. H_2O	1 mol%	7%

Tertiary tethered alcohols as model substrates



Following **GP-C** with minor alterations, the dimethyl substituted alcohol **2.61** (13.0 mg, 0.10 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (0.5 mL) and Co^{II} catalyst **2.73** or **2.78** (1 mol%) was added. The reaction was monitored through ^1H NMR with 0.1 mmol of mesitylene as internal standard. No product was observed within 24 h of reaction time.



Following **GP-C** with minor alterations, the trifluoromethyl substituted alcohol *rac*-**2.65** (24.6 mg, 0.10 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (0.5 mL) and Co^{II} catalyst **2.73** or **2.78** (1 mol%) was added. The reaction was monitored through ^{19}F NMR with 0.1 mmol of trifluorotoluene as internal standard. No product was observed within 24 h of reaction time.

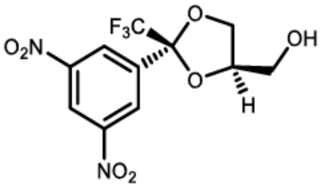
6.2.2.3 Measuring the UV/vis spectra of the applied cobalt complexes

The oxidation of (salen)Co^{II}-complexes by weakly acidic alcohols was achieved by dissolving commercial (salen)Co^{II} **2.76** (1.00 eq.) in CH_2Cl_2 and adding the corresponding alcohol (50.0 eq.). The solvent was removed to dryness after stirring for 3 d at rt. The residue was directly used for UV/vis-absorption measurements. Each spectrum was recorded as solutions of the corresponding Co-complexes in CH_2Cl_2 at rt with a concentration of $c = 5 \cdot 10^{-5}$ mol/L.

6.2.3 Synthesis of oxygen rich heterocycles *via* dynamic kinetic resolution

6.2.3.1 Substrate scope of the reaction

((2*S*,4*R*)-2-(3,5-dinitrophenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.101]



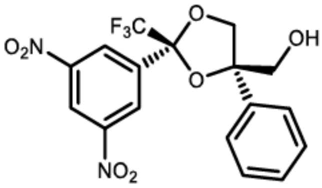
Following **GP-C**, using *rac*-glycidol **2.136** (13.4 µL, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the product was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless oil (65 mg, 0.192 mmol, 96%) and a diastereomeric mixture with 63:37 *dr*.

Mixture:
HRMS (APCI): Calculated for $C_{11}H_8F_3N_2O_7$ [M-H]$^-$: 337.0284, Found: 337.0265. Absolute stereochemistry determined through analogy with **2.117**.

Major diastereomer [2.101]:
^{1}H NMR (400 MHz, C_6D_6) δ = 8.56 (d, *J* = 2.1 Hz, 2H, C*H*$_{arom.}$), 8.40 (t, *J* = 2.1 Hz, 1H, C*H*$_{arom.}$), 3.67 – 3.58 (m, 2H, C*H*$_2$), 3.46 – 3.39 (m, 1H, C*H*), 3.27 – 3.17 (m, 2H, C*H*$_2$), 1.35 (s, 1H, O*H*). **^{13}C NMR (101 MHz, C_6D_6)** δ = 148.4 (*C*$_q$-NO$_2$), 138.8 (*C*$_q$), 126.9 (*C*H), 122.3 (q, $^1J_{C,F}$ = 287.9 Hz, *C*F$_3$), 120.3 (*C*H), 103.9 (q, $^2J_{C,F}$ = 33.3 Hz, *C*$_q$), 79.5 (*C*H), 68.8 (*C*H$_2$), 61.0 (*C*H$_2$). **^{19}F NMR (377 MHz, C_6D_6)** δ = −81.73 (s, 3F, C*F*$_3$).

Minor diastereomer:
^{1}H NMR (400 MHz, C_6D_6) δ = 8.63 (d, *J* = 2.1 Hz, 2H, C*H*$_{arom.}$), 8.34 (t, *J* = 2.1 Hz, 1H, C*H*$_{arom.}$), 3.99 (tt, *J* = 7.0, 3.9 Hz, 1H, C*H*), 3.74 – 3.67 (m, 1H, C*H*$_2$), 3.48 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H, C*H*$_2$), 3.10 (dd, *J* = 12.1, 3.8 Hz, 1H, C*H*$_2$), 2.84 (dd, *J* = 12.1, 3.8 Hz, 1H, C*H*$_2$), 1.03 (s, 1H, O*H*). **^{13}C NMR (101 MHz, C_6D_6)** δ = 148.3 (*C*$_q$-NO$_2$), 138.7 (*C*$_q$), 126.9 (*C*H), 122.9 (q, $^1J_{C,F}$ = 289.9 Hz, *C*F$_3$), 120.2 (*C*H), 104.1 (q, $^2J_{C,F}$ = 33.0 Hz, *C*$_q$), 80.4 (*C*H), 68.2 (*C*H$_2$), 60.8 (*C*H$_2$). **^{19}F NMR (377 MHz, C_6D_6)** δ = −81.78 (s, 3F, C*F*$_3$).

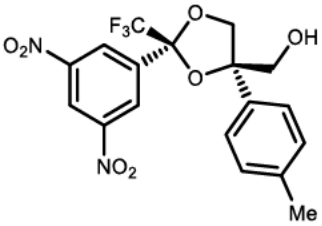
((2*S*,4*R*)-4-(Phenyl)-2-(3,5-dinitrophenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.105]



Following **GP-C**, using 3-phenyl-oxetan-3-ol **2.38** (30.0 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (68.0 mg, 0.164 mmol, 82%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.105]: IR (neat): $\tilde{\nu}$ = 3522 (w), 3112 (w), 2917 (w), 2280 (w), 1543 (s), 1346 (s), 1328 (w), 1200 (m), 1182 (m), 1135 (s), 1104 (m), 1070 (m), 1007 (m), 997 (m), 914 (m), 860 (w), 813 (w), 765 (w), 730 (s), 705 (s), 665 (w), 656 (w), 639 (w), 617 (m), 608 (m). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.56 (d, J = 2.1 Hz, 2H, C$H_{\text{arom.}}$), 8.10 (t, J = 2.1 Hz, 1H, C$H_{\text{arom.}}$), 6.93 – 6.88 (m, 2H, C$H_{\text{arom.}}$), 6.87 – 6.80 (m, 3H, C$H_{\text{arom.}}$), 4.42 (d, J = 8.6 Hz, 1H, CH_2), 3.86 (d, J = 8.6 Hz, 1H, CH_2), 3.57 (d, J = 12.0 Hz, 1H, CH_2), 3.28 (d, J = 12.0 Hz, 1H, CH_2), 1.64 – 1.37 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.1 (C_q), 139.0 (C_q), 138.5 (C_q), 128.7 (CH), 127.0 (CH), 126.0 (CH), 125.8 (CH), 122.3 (q, $^1J_{C,F}$ = 287.8 Hz, CF$_3$), 120.2 (CH), 104.5 (q, $^2J_{C,F}$ = 33.2 Hz, C_q), 89.7 (C_q), 72.4 (CH$_2$), 67.0 (CH$_2$). **^{19}F NMR (377 MHz, C_6D_6)** δ = –81.4 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{18}H_{14}F_3N_2O_9$ [M+HCOO]$^-$: 456.0651, Found: 456.0654. **Optical Rotation**: $[\alpha]_D^{25}$ = +20.6 (c = 1.00, CHCl$_3$) for an enantiomerically enriched sample of 86:14 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Amylose-3 column, 22 °C, 1 mL/min, 95:05 hexane:isopropanol, 254 nm, t_{minor} = 20.203 min, t_{major} = 17.186 min). Absolute stereochemistry determined through analogy with **2.117**.

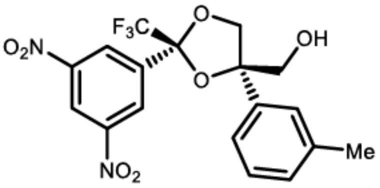
((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(*p*-tolyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.111]



Following **GP-C**, using 3-(*p*-tolyl)oxetan-3-ol **2.40** (32.8 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 μmol, 1.0 mol%), the major diastereomer (67.0 mg, 0.156 mmol, 78%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.111]: IR (neat): $\tilde{\nu}$ = 3512 (w), 2916 (w), 2281 (w), 1770 (w), 1544 (s), 1346 (s), 1246 (w), 1199 (m), 1185 (m), 1135 (s), 1104 (m), 1064 (m), 1013 (m), 998 (m), 914 (m), 815 (m), 759 (w), 729 (s), 709 (s), 657 (w), 638 (w). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.59 (d, J = 2.1 Hz, 2H, C$H_{arom.}$), 8.09 (t, J = 2.1 Hz, 1H, C$H_{arom.}$), 6.78 (*app*. q, J = 8.4 Hz, 4H, C$H_{arom.}$), 4.45 (d, J = 8.5 Hz, 1H, CH_2), 3.92 (d, J = 8.6 Hz, 1H, CH_2), 3.60 (d, J = 12.1 Hz, 1H, CH_2), 3.31 (d, J = 12.1 Hz, 1H, CH_2), 1.89 (s, 3H, CH_3), 1.34 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.1 (C_q), 138.6 (2xC_q), 136.1 (C_q), 129.3 (CH), 127.1 (CH), 125.8 (CH), 122.4 (q, $^1J_{C,F}$ = 287.9 Hz, CF$_3$), 120.1 (CH), 104.5 (q, $^2J_{C,F}$ = 33.2 Hz, C_q), 89.8 (C_q), 72.4 (CH$_2$), 67.1 (CH$_2$), 20.7 (CH$_3$). **^{19}F NMR (377 MHz, C_6D_6)** δ = −81.4 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{18}H_{15}F_3N_2O_7$ $[M]^-$: 428.0831, Found: 428.0836. **Optical Rotation**: $[\alpha]_D^{25}$ = +9.8 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 85:15 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5 column, 22 °C, 0.5 mL/min, 90:10 hexane:isopropanol, 254 nm, t_{minor} = 22.182 min, t_{major} = 18.659 min). Absolute stereochemistry determined through analogy with **2.117**.

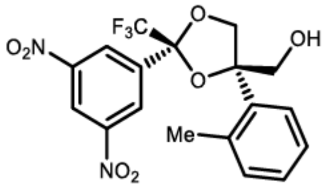
((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(*m*-tolyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.112]



Following **GP-C**, using 3-(*m*-tolyl)oxetan-3-ol **2.39** (32.8 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and $\mathrm{Co^{II}}$·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (68.0 mg, 0.159 mmol, 80%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.112]: IR (neat): $\tilde{\nu}$ = 3523 (w), 3096 (w), 2962 (w), 2917 (w), 2280 (w), 1544 (s), 1345 (s), 1328 (w), 1200 (m), 1183 (m), 1134 (s), 1104 (m), 1063 (w), 1009 (w), 998 (w), 914 (m), 786 (w), 730 (s), 708 (s), 656 (w), 637 (m), 623 (w), 615 (m). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.57 (d, J = 2.1 Hz, 2H, C$H_{\mathrm{arom.}}$), 8.10 (t, J = 2.1 Hz, 1H, C$H_{\mathrm{arom.}}$), 6.87 – 6.80 (m, 2H, C$H_{\mathrm{arom.}}$), 6.69 (d, J = 7.6 Hz, 1H, C$H_{\mathrm{arom.}}$), 6.64 (d, J = 7.8 Hz, 1H, C$H_{\mathrm{arom.}}$), 4.43 (d, J = 8.5 Hz, 1H, CH_2), 3.88 (d, J = 8.6 Hz, 1H, CH_2), 3.59 (d, J = 12.0 Hz, 1H, CH_2), 3.30 (d, J = 12.1 Hz, 1H, CH_2), 2.02 (s, 3H), 1.55 (br, 1H, O*H*). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.0 (C_q), 139.0 (C_q), 138.6 (C_q), 138.5 (C_q), 129.4 (*C*H), 128.7 (*C*H), 127.1(*C*H), 126.6 (*C*H), 122.8 (*C*H), 122.3 (q, $^1J_{C,F}$ = 287.8 Hz, *C*F_3), 120.1 (*C*H), 104.5 (q, $^2J_{C,F}$ = 33.3 Hz, C_q), 89.8 (C_q), 72.3 (*C*H_2), 67.2 (*C*H_2), 21.2 (*C*H_3). **^{19}F NMR (377 MHz, C_6D_6)** δ = −81.4 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{18}H_{15}F_3N_2O_7$ $[M]^-$: 428.0831, Found: 428.0834. **Optical Rotation**: $[\alpha]_D^{25}$ = +12.6 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 85:15 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5 column, 22 °C, 2 mL/min, 98:02 hexane:isopropanol, 254 nm, t_{minor} = 20.151 min, t_{major} = 17.331 min). Absolute stereochemistry determined through analogy with **2.117**.

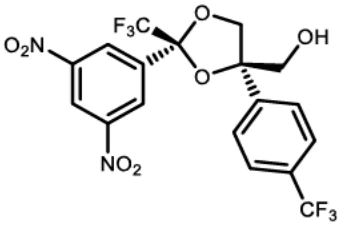
((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(*o*-tolyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.113]



Following **GP-C**, using 3-(*o*-tolyl)oxetan-3-ol, prepared by [redacted] (32.8 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and $\mathrm{Co^{II}}$·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (73.0 mg, 0.170 mmol, 85%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.113]: IR (neat): $\tilde{\nu}$ = 3581 (w), 3113 (w), 2917 (w), 2280 (w), 1544 (s), 1345 (s), 1330 (m), 1203 (m), 1183 (m), 1136 (s), 1105 (m), 1070 (m), 1012 (w), 998 (w), 914 (w), 812 (w), 765 (m), 729 (s), 707 (m), 669 (w), 659 (w), 638 (w). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.56 (d, J = 2.1 Hz, 2H, C$H_{arom.}$), 8.04 (t, J = 2.1 Hz, 1H, C$H_{arom.}$), 7.15 – 7.09 (m, 1H, C$H_{arom.}$), 6.94 – 6.89 (m, 1H, C$H_{arom.}$), 6.87 – 6.80 (m, 1H, C$H_{arom.}$), 6.78 – 6.73 (m, 1H, C$H_{arom.}$), 4.51 (d, J = 8.7 Hz, 1H, CH_2), 3.67 (d, J = 8.7 Hz, 1H, CH_2), 3.64 (d, J = 12.0 Hz, 1H, CH_2), 3.45 (d, J = 12.0 Hz, 1H, CH_2), 1.97 (s, 3H, CH_3), 1.53 – 1.28 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.2 (C_q), 138.3 (C_q), 137.1 (C_q), 134.4 (C_q), 132.4 (CH), 128.8 (CH), 128.6 (CH), 127.3 (CH), 127.0 (CH), 126.2 (CH), 122.1 (q, $^1J_{C,F}$ = 286.2 Hz), 120.4 (CH), 104.2 (q, $^2J_{C,F}$ = 33.5 Hz), 90.8 (C_q), 72.3 (CH$_2$), 66.8 (CH$_2$), 20.6 (CH$_3$). **^{19}F NMR (377 MHz, C_6D_6)** δ = –81.5 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{18}H_{15}F_3N_2O_7$ [M]$^-$: 428.0831, Found: 428.0833. **Optical Rotation**: $[\alpha]_D^{25}$ = –11.7 (c = 1.00, CHCl$_3$) for an enantiomerically enriched sample of 82:18 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5 column, 22 °C, 2 mL/min, 98:02 hexane:isopropanol, 254 nm, t_{minor} = 20.637 min, t_{major} = 18.968 min). Absolute stereochemistry determined through analogy with **2.117**.

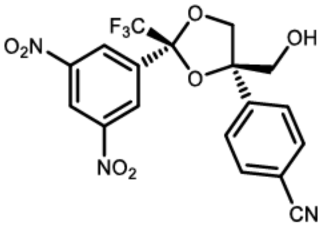
((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-2-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,3-dioxolan-4-yl)methanol [2.114]



Following **GP-C**, using 3-(4-(trifluoromethyl)phenyl)oxetan-3-ol **2.42** (43.6 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (70.0 mg, 0.145 mmol, 73%) was obtained *via* RP-MPLC (MeCN:H$_2$O, 50:50) as a colorless foam.

Major diastereomer [2.114]: IR (neat): $\tilde{\nu}$ = 3457 (w), 3110 (w), 2978 (w), 2280 1546 (s), 1346 (s), 1327 (s), 1241 (w), 1200 (m), 1168 (m), 1132 (s), 1067 (m), 1013 (m), 999 (m), 915 (w), 841 (w), 813 (w), 759 (w), 730 (s), 709 (m), 684 (w), 658 (w), 638 (w), 624 (w), 612 (m). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.51 (d, J = 2.0 Hz, 2H, C$H_{arom.}$), 8.11 (t, J = 2.1 Hz, 1H, C$H_{arom.}$), 7.22 – 7.17 (m, 2H, C$H_{arom.}$), 6.78 – 6.71 (m, 2H, C$H_{arom.}$), 4.30 (d, J = 8.7 Hz, 1H, CH_2), 3.65 (d, J = 8.8 Hz, 1H, CH_2), 3.44 (d, J = 11.8 Hz, 1H, CH_2), 3.19 (d, J = 11.8 Hz, 1H, CH_2), 1.23 (br, 1H, O*H*). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.2 (C_q), 143.1 (C_q), 138.0 (C_q), 130.9 (q, $^2J_{C,F}$ = 32.6 Hz, C_q), 126.8 (*C*H), 126.2 (*C*H), 125.6 (q, $^3J_{C,F}$ = 3.7 Hz, *C*H), 124.3 (*app.* d, $^1J_{C,F}$ = 272.0 Hz, *C*F$_3$), 122.2 (q, $^1J_{C,F}$ = 288.0 Hz, *C*F$_3$), 120.4 (*C*H), 104.7 (q, $^2J_{C,F}$ = 33.5 Hz, C_q), 89.1 (C_q), 72.5 (*C*H$_2$), 66.7 (*C*H$_2$). **^{19}F NMR (377 MHz, C_6D_6)** δ = –62.9 (s, 3F, CF_3), – 81.4 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{19}H_{13}F_6N_2O_9$ [M+HCOO]$^-$: 527.0525, Found: 527.0531. **Optical Rotation**: $[\alpha]_D^{25}$ = +19.0 (*c* = 1.00, CHCl$_3$) for an enantiomerically enriched sample of 96:4 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, 22 °C, 1 mL/min, 95:05 hexane:isopropanol, 254 nm, t_{minor} = 20.287 min, t_{major} = 13.878 min). Absolute stereochemistry determined through analogy with **2.117**.

4-((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(hydroxymethyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)benzonitrile [2.115]

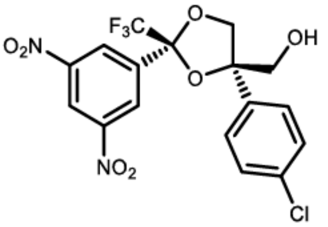


Following **GP-C**, using 4-(3-hydroxyoxetan-3-yl)benzonitrile **2.43** (35.0 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (66.0 mg, 0.150 mmol, 75%) was obtained *via* RP-MPLC (MeCN:H$_2$O, 50:50) as a colourless solid.

Major diastereomer [2.115]: m.p.: 196 – 198 °C. **IR (neat)**: $\tilde{\nu}$ = 3456 (w), 2917 (w), 2280 (w), 1544 (s), 1346 (s), 1326 (w), 1198 (m), 1188 (m), 1134 (m), 1103 (w), 1063 (w), 1013 (w), 994 (w), 915 (w), 836 (w), 813 (w), 730 (s), 709 (s), 693 (w), 668 (w), 650 (w). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.51 (d, J = 2.1 Hz, 2H, C$H_{arom.}$), 8.22 (t, J = 2.1 Hz, 1H, C$H_{arom.}$), 7.03 – 6.80 (m, 2H, C$H_{arom.}$), 6.74 – 6.48 (m, 2H, C$H_{arom.}$), 4.29 (d, J = 8.8 Hz, 1H, CH_2), 3.61 (d,

J = 8.8 Hz, 1H, CH_2), 3.45 (d, J = 11.7 Hz, 1H, CH_2), 3.22 (d, J = 11.7 Hz, 1H, CH_2), 1.57 (br, 1H, O*H*). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.3 (C_q), 143.8 (C_q), 138.0 (C_q), 132.1 (*C*H), 126.4 (*C*H), 122.1 (app. d, $^1J_{C,F}$ = 287.8 Hz, CF_3), 120.4 (*C*H), 117.9 (C_q), 112.8 (C_q), 104.7 (q, $^2J_{C,F}$ = 33.6 Hz, C_q), 89.0 (C_q), 72.4 (CH_2), 66.6 (CH_2). **^{19}F NMR (377 MHz, C_6D_6)** δ = –82.2 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{19}H_{12}F_3N_3O_9$ [M+HCOO]$^-$: 486.0604, Found: 486.0600. **Optical Rotation**: $[\alpha]_D^{25}$ = +1.8 (c = 0.50, acetone) for an enantiomerically enriched sample of 94:6 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Cellulose-5 column, 22 °C, 1 mL/min, 80:20 hexane:isopropanol, 254 nm, t_{minor} = 21.652 min, t_{major} = 13.880 min). Absolute stereochemistry determined through analogy with **2.117**.

((2*S*,4*R*)-4-(4-Chlorophenyl)-2-(3,5-dinitrophenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.116]

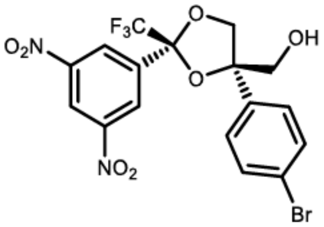


Following **GP-C**, using 3-(4-chlorophenyl)oxetan-3-ol **2.44** (36.9 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (75.0 mg, 0.167 mmol, 83%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.116]: IR (neat): $\tilde{\nu}$ = 3568 (w), 3093 (w), 2917 (w), 2280 (w), 1770 (w), 1544 (s), 1494 (w), 1346 (s), 1239 (w), 1199 (m), 1185 (m), 1135 (s), 1103 (m), 1063 (w), 1011 (m), 993 (w), 915 (w), 831 (w), 729 (s), 708 (m). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.52 (d, J = 2.1 Hz, 2H, $CH_{arom.}$), 8.14 (t, J = 2.1 Hz, 1H, $CH_{arom.}$), 6.96 – 6.89 (m, 2H, $CH_{arom.}$), 6.63 – 6.59 (m, 2H, $CH_{arom.}$), 4.34 (d, J = 8.7 Hz, 1H, CH_2), 3.71 (d, J = 8.7 Hz, 1H, CH_2), 3.48 (d, J = 11.9 Hz, 1H, CH_2), 3.20 (d, J = 11.9 Hz, 1H, CH_2), 1.34 (br, 1H, O*H*). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.2 (C_q), 138.3 (C_q), 137.5 (C_q), 134.8 (C_q), 128.8 (*C*H), 127.2 (*C*H), 126.9 (*C*H), 122.2 (q, $^1J_{C,F}$ = 287.9 Hz, CF_3), 120.3 (*C*H), 104.6 (q, $^2J_{C,F}$ = 33.4 Hz, C_q), 89.2 (C_q), 72.4 (CH_2), 66.8 (CH_2). **^{19}F NMR (377 MHz, C_6D_6)** δ = –81.4 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for

$C_{17}H_{12}ClF_3N_2O_7$ [M]⁻: 448,0285, Found: 448,0274. **Optical Rotation**: $[\alpha]_D^{25}$ = +1.7 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 93:7 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, 22 °C, 2 mL/min, 95:05 hexane:isopropanol, 254 nm, t_{minor} = 14.683 min, t_{major} = 9.490 min). Absolute stereochemistry determined through analogy with **2.117** .

((2*S*,4*R*)-4-(4-Bromophenyl)-2-(3,5-dinitrophenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.117]



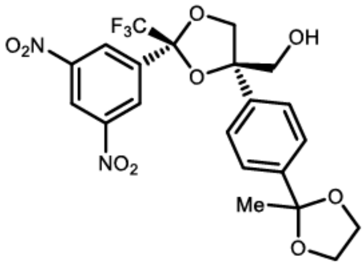
Following **GP-C**, using 3-(4-bromophenyl)oxetan-3-ol **2.45** (45.8 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (78.0 mg, 0.158 mmol, 79%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.117]: IR (neat): $\tilde{\nu}$ = 3556 (br), 3099 (w), 2920 (w), 2371 (w), 2279 (w), 1631 (w), 1596 (w), 1544 (s), 1490 (w), 1346 (s), 1330 (w), 1202 (m), 1185 (m), 1135 (s), 1104 (m), 1070 (w), 1007 (m), 914 (m), 828 (w), 729 (s), 710 (m), 680 (w), 663 (w), 655 (w). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.50 (d, J = 2.1 Hz, 2H, $CH_{arom.}$), 8.10 (t, J = 2.1 Hz, 1H, $CH_{arom.}$), 7.09 – 7.02 (m, 2H, $CH_{arom.}$), 6.53 – 6.46 (m, 2H, $CH_{arom.}$), 4.29 (d, J = 8.7 Hz, 1H, CH_2), 3.65 (d, J = 8.7 Hz, 1H, CH_2), 3.42 (d, J = 11.9 Hz, 1H, CH_2), 3.14 (d, J = 11.9 Hz, 1H, CH_2), 1.40 – 1.11 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.1 (C_q), 138.1 (C_q), 138.0 (C_q), 131.8 (CH), 128.6 (CH), 127.5 (CH), 126.8 (CH), 123.0 (C_q), 122.2 (q, $^1J_{C,F}$ = 287.9 Hz, CF$_3$), 120.3 (CH), 104.5 (q, $^2J_{C,F}$ = 33.2 Hz, C_q), 89.1 (C_q), 72.3 (CH$_2$), 66.7 (CH$_2$). **^{19}F NMR (282 MHz, C_6D_6)** δ = –81.4 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{17}H_{12}BrF_3N_2O_7$ [M]⁻: 491.9780, Found: 491.9776. **Optical Rotation**: $[\alpha]_D^{25}$ = –5.7 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 91:9 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, 22 °C, 1 mL/min, 90:10 hexane:isopropanol, 254 nm, t_{minor} = 24.101 min, t_{major} = 25.526 min).

A sample suitable for X-ray analysis was obtained after dissolving ((2*S*,4*R*)-4-(4-bromophenyl)-2-(3,5-dinitrophenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)-methanol **2.117** in C_6F_6 and slowly evaporating the solvent. Absolute stereochemistry determined through X-ray diffraction (*cf.* Chapter 6.2.4).

Gram scale:
Following **GP-C**, using 3'5'-dinitro-2,2,2-trifluoroacetophenone **2.20** (792 mg, 3.00 mmol, 1.00 eq.), 3-(4-bromophenyl)oxetan-3-ol **2.45** (687 mg, 3.00 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (30.0 mg, 30.0 µmol, 1.0 mol%), the major diastereomer (782 mg, 1.59 mmol, 53%) was obtained *via* automated FC (CyH:Et_2O, 75:25) as a colourless foam.

((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.118]

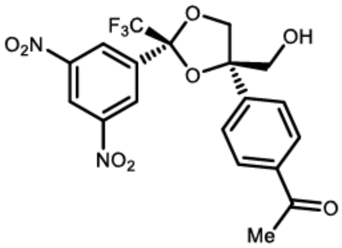


Following **GP-C**, using 3-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)oxetan-3-ol **2.51** (38.4 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (70.0 mg, 0.140 mmol, 70%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless solid.

Major diastereomer [2.118]: m.p.: 133 – 135 °C. **IR (neat)**: $\tilde{\nu}$ = 3457 (w), 3112 (w), 2987 (w), 2917 (w), 2362 (w), 2279 (w), 1546 (s), 1346 (s), 1200 (m), 1186 (m), 1135 (m), 1103 (w), 1040 (w), 1012 (w), 998 (w), 915 (w), 834 (w), 730 (s), 709 (m), 667 (w), 657 (w), 648 (w), 633 (m), 617 (s), 607 (s). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.56 (d, J = 2.1 Hz, 2H, C$H_{arom.}$), 8.08 (t, J = 2.1 Hz, 1H, C$H_{arom.}$), 7.47 – 7.39 (m, 2H, C$H_{arom.}$), 6.91 – 6.84 (m, 2H, C$H_{arom.}$), 4.43 (d, J = 8.6 Hz, 1H, CH_2), 3.87 (d, J = 8.6 Hz, 1H, CH_2), 3.58 (d, J = 12.0 Hz, 1H,

CH_2), 3.49 – 3.39 (m, 2H, CH_2), 3.31 (d, J = 11.9 Hz, 1H, CH_2), 3.25 – 3.14 (m, 2H, CH_2), 1.49 (s, 3H, CH_3), 1.34 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.1 (C_q), 145.1 (C_q), 138.7 (C_q), 138.4 (C_q), 127.0 (CH), 125.9 (CH), 125.7 (CH), 122.3 (q, $^1J_{C,F}$ = 287.8 Hz, CF_3), 120.1 (CH), 108.6 (C_q), 104.5 (q, $^2J_{C,F}$ = 33.2 Hz, C_q), 89.6 (C_q), 72.6 (CH_2), 67.1 (CH_2), 64.6 (2xCH_2), 28.0 (CH_3). **^{19}F NMR (377 MHz, C_6D_6)** δ = −82.1 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{21}H_{19}F_3N_2O_9$ $[M]^-$: 500.1043, Found: 500.1047. **Optical Rotation**: $[\alpha]_D^{25}$ = +5.0 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 71:29 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Cellulose-1 column, 22 °C, 1 mL/min, 90:10 hexane:isopropanol, 254 nm, t_{minor} = 46.432 min, t_{major} = 23.644 min). Absolute stereochemistry determined through analogy with **2.117**.

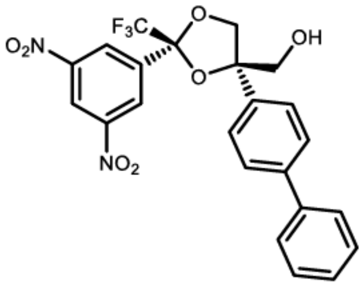
1-(4-((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(hydroxymethyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)phenyl)ethan-1-one [2.119]



Following **GP-C**, using 1-(4-(3-hydroxyoxetan-3-yl)phenyl)ethan-1-one **2.57** (38.4 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (60.0 mg, 0.131 mmol, 66%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless solid.

Major diastereomer [2.119]: m.p.: 135 – 137 °C. **IR (neat)**: $\tilde{\nu}$ = 3475 (w), 3113 (w), 2962 (w), 2924 (m), 2852 (w), 2343 (w), 1701 (s), 1609 (w), 1546 (s), 1462 (w), 1407 (w), 1347 (s), 1267 (m), 1248 (m), 1200 (m), 1183 (m), 1135 (s), 1103 (m), 1064 (m), 1005 (m), 958 (w), 913 (w), 834 (w), 801 (w), 729 (s), 708 (s), 683 (w). **^{1}H NMR (400 MHz, acetone-d6)**: δ = 8.96 (t, J = 2.1 Hz, 1H, $CH_{arom.}$), 8.75 (d, J = 2.0 Hz, 2H, $CH_{arom.}$), 7.84 – 7.81 (m, 2H, $CH_{arom.}$), 7.56 – 7.52 (m, 2H, $CH_{arom.}$), 4.89 (d, J = 8.9 Hz, 1H, CH_2), 4.65 (d, J = 8.8 Hz, 1H, CH_2), 4.62 (t, J = 6.2 Hz, 1H, OH), 4.05 (dd, J = 11.8, 6.3 Hz, 1H, CH_2), 3.90 (dd, J = 11.7, 6.3 Hz, 1H, CH_2), 2.48 (s, 3H, CH_3). **^{13}C NMR (101 MHz, acetone-d6)**: δ = 197.5 (C_q), 149.6 (C_q), 145.4 (C_q), 139.7 (C_q), 137.6 (C_q), 128.8 (CH), 128.0 (*C*H), 127.2 (*C*H), 122.9 (*app*. d, $^1J_{C,F}$ = 287.7 Hz, *C*F$_3$), 121.1 (*C*H), 104.9 (q, $^2J_{C,F}$ = 33.3 Hz, *C*$_q$), 90.9 (*C*$_q$), 74.2 (*C*H$_2$), 67.1 (*C*H$_2$), 26.6 (*C*H$_3$). **^{19}F NMR (377 MHz, acetone-d6)** δ = −82.9 (s, 3F, C*F*$_3$). **HRMS (APCI)**: Calculated for $C_{20}H_{16}F_3N_2O_{10}$ [M+HCOO]$^-$: 501.0757, Found: 501.0761. **Optical Rotation**: $[\alpha]_D^{25}$ = +2.1 (*c* = 1.00, acetone) for an enantiomerically enriched sample of 83:17 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® Amylose-1 column, 22 °C, 0.5 mL/min, 80:20 hexane:isopropanol, 254 nm, t_{minor} = 41.267 min, t_{major} = 24.111 min). Absolute stereochemistry determined through analogy with **2.117**.

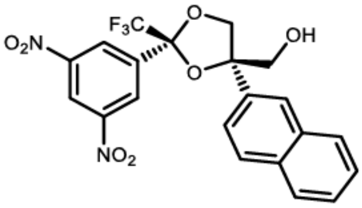
((2*S*,4*R*)-4-([1,1'-Biphenyl]-4-yl)-2-(3,5-dinitrophenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.120]



Following **GP-C**, using 3-([1,1'-biphenyl]-4-yl)oxetan-3-ol **2.46** (45.3 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (70.0 mg, 0.142 mmol, 71%) was obtained *via* RP-MPLC (MeCN:H$_2$O, 50:50) as a colourless solid.

Major diastereomer [2.120]: m.p.: 66 – 68 °C. **IR (neat)**: $\tilde{\nu}$ = 3401 (w), 3097 (w), 2939 (w), 2280 (w), 1543 (s), 1488 (w), 1345 (s), 1325 (w), 1203 (m), 1187 (m), 1135 (s), 1103 (w), 1068 (w), 1006 (w), 996 (w), 915 (w), 841 (w), 812 (w), 767 (m), 729 (s), 707 (m), 657 (w). **^{1}H NMR (400 MHz, C$_6$D$_6$)**: δ = 8.59 (d, *J* = 2.1 Hz, 2H, C*H*$_{arom.}$), 8.06 (t, *J* = 2.1 Hz, 1H, C*H*$_{arom.}$), 7.30 – 7.23 (m, 4H, C*H*$_{arom.}$), 7.14 – 7.03 (m, 3H, C*H*$_{arom.}$), 6.94 – 6.89 (m, 2H, C*H*$_{arom.}$), 4.44 (d, *J* = 8.6 Hz, 1H, C*H*$_2$), 3.88 (d, *J* = 8.6 Hz, 1H, C*H*$_2$), 3.60 (d, *J* = 11.9 Hz, 1H, C*H*$_2$), 3.31 (d, *J* = 12.0 Hz, 1H, C*H*$_2$), 1.36 (br, 1H, O*H*). **^{13}C NMR (101 MHz, C$_6$D$_6$)**: δ = 148.1 (*C*$_q$), 142.1 (*C*$_q$), 140.3 (*C*$_q$), 137.9 (*C*$_q$), 129.2 (*C*H), 127.5 (*C*H), 127.3 (*C*H), 127.0 (*C*H), 126.3 (*C*H), 122.3 (q, $^1J_{C,F}$ = 287.9 Hz, *C*F$_3$), 120.2 (*C*H), 104.6 (q, ${}^{2}J_{C,F}$ = 33.4 Hz, C_q). 89.6 (C_q), 72.5 (CH_2), 67.1 (CH_2).[f] **^{19}F NMR (377 MHz, C_6D_6)** $\delta = -82.3$ (s, 3F, CF_3). **HRMS (ESI)**: Calculated for $C_{23}H_{17}F_3N_2O_7Na$ $[M+Na]^+$: 513.0886, Found: 513.0883. **Optical Rotation**: $[\alpha]_D^{25} = -20.9$ (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 85:15 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, 22 °C, 1 mL/min, 95:5 hexane:isopropanol, 254 nm, t_{minor} = 31.619 min, t_{major} = 20.706 min). Absolute stereochemistry determined through analogy with **2.117** .

((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(naphthalen-2-yl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.121]



Following **GP-C**, using 3-(naphthalen-2-yl)oxetan-3-ol **2.47** (40.1 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (81.0 mg, 0.174 mmol, 87%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.121]: IR (neat): $\tilde{\nu}$ = 3434 (w), 2917 (w), 1543 (s), 1346 (s), 1328 (w), 1200 (m), 1185 (m), 1135 (s), 1103 (w), 1065 (w), 1008 (w), 996 (w), 914 (w), 815 (w), 730 (s), 707 (m), 683 (w), 655 (w). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.62 (d, J = 2.1 Hz, 2H, $CH_{arom.}$), 7.98 (t, J = 2.1 Hz, 1H, $CH_{arom.}$), 7.65 – 7.58 (m, 1H, $CH_{arom.}$), 7.51 (d, J = 1.9 Hz, 1H, $CH_{arom.}$), 7.40 (*app*. t, J = 8.1 Hz, 2H, $CH_{arom.}$), 7.20 – 7.17 (m, 1H, $CH_{arom.}$), 7.09 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H, $CH_{arom.}$), 6.92 (dd, J = 8.6, 1.9 Hz, 1H, $CH_{arom.}$), 4.52 (d, J = 8.6 Hz, 1H, CH_2), 4.02 (d, J = 8.6 Hz, 1H, CH_2), 3.67 (d, J = 12.1 Hz, 1H, CH_2), 3.40 (d, J = 12.1 Hz, 1H, CH_2), 1.65 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.0 (C_q), 136.2 (C_q), 133.2 (C_q), 133.1 (C_q), 128.7 (CH), 128.1 (CH), 127.2 (CH), 127.1 (CH), 127.1 (CH), 125.3 (CH), 123.2 (CH), 122.4 (q, ${}^{1}J_{C,F}$ = 287.8 Hz, CF_3), 120.1 (CH), 104.6 (q, ${}^{2}J_{C,F}$ = 33.3 Hz, C_q), 90.0 (C_q), 72.5

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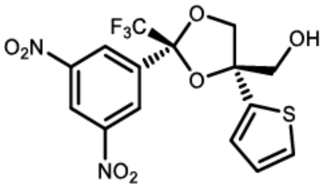
[f] Missing signals under solvent peak.

(CH_2), 67.1 (CH_2).[g] **^{19}F NMR (377 MHz, C_6D_6)** $\delta = -82.3$ (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{21}H_{15}F_3N_2O_7$ $[M]^-$: 464.0831, Found: 464.0828. **Optical Rotation**: $[\alpha]_D^{25} = -25.4$ ($c = 1.00$, $CHCl_3$) for an enantiomerically enriched sample of 88:12 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, 22 °C, 1 mL/min, 95:5 hexane:isopropanol, 254 nm, $t_{minor} = 37.407$ min, $t_{major} = 22.872$ min). Absolute stereochemistry determined through analogy with **2.117**.

((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(thiophen-2-yl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.122]



Following **GP-C**, using 3-(thiophen-2-yl)oxetan-3-ol **2.49** (31.2 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (67.0 mg, 0.159 mmol, 80%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.122]: IR (neat): $\tilde{\nu} = 3438$ (w), 3098 (w), 2918 (w), 2357 (w), 2273 (w), 1631 (w), 1543 (s), 1345 (s), 1327 (w), 1184 (m), 1152 (w), 1133 (s), 1105 (m), 1064 (m), 1005 (m), 997 (m), 914 (m), 849 (w), 813 (w), 729 (s), 707 (s), 679 (w). **^{1}H NMR (400 MHz, C_6D_6)**: $\delta = 8.60$ (d, $J = 2.1$ Hz, 2H, $CH_{arom.}$), 8.21 (t, $J = 2.1$ Hz, 1H, $CH_{arom.}$), 6.52 (dd, $J = 5.0$, 1.3 Hz, 1H, $CH_{arom.}$), 6.37 – 6.13 (m, 2H, $CH_{arom.}$), 4.35 (dd, $J = 8.6$, 1H, CH_2), 3.96 (dd, $J = 8.7$ Hz, 1H, CH_2), 3.65 (d, $J = 12.1$ Hz, 1H, CH_2), 3.34 (d, $J = 12.2$ Hz, 1H, CH_2), 1.56 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: $\delta = 147.7$ (C_q), 141.9 (C_q), 138.0 (C_q), 126.8 (CH), 126.7 (CH), 125.9 (CH), 124.9 (CH), 122.0 (q, $^1J_{C,F} = 288.5$ Hz, CF_3), 119.7 (CH), 104.3 (q, $^2J_{C,F} = 33.3$ Hz, C_q), 87.2 (C_q), 73.4 (CH_2), 65.9 (CH_2). **^{19}F NMR (377 MHz, C_6D_6)** $\delta = -82.3$ (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{15}H_{11}F_3N_2O_7S$ $[M]^-$: 420.0239, Found: 420,0240. **Optical Rotation**: $[\alpha]_D^{25} = +32.9$ ($c = 1.00$, $CHCl_3$) for an enantiomerically enriched sample of 89:11 *er*. The enantiomeric purity was established by HPLC analysis using a chi-

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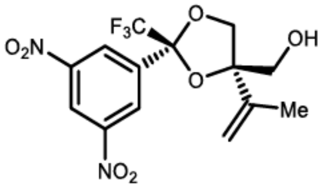
[g] Missing signals under solvent peak.

ral column (Reprosil Chiral-AMS column, 22 °C, 0.5 mL/min, 95:5 hexane:isopropanol, 254 nm, t_{minor} = 68.893 min, t_{major} = 47.824 min). Absolute stereochemistry determined through analogy with **2.117**.

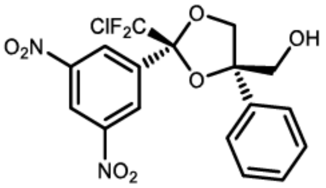
((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(prop-1-en-2-yl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.125]



Following **GP-C** with minor alterations, using 3-(prop-1-en-2-yl)oxetan-3-ol **2.52** (22.8 mg, 0.20 mmol, 1.00 eq.), ketone **2.20** (52.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%) the reaction was run at 40 °C for 24 h. The major diastereomer (81.0 mg, 0.174 mmol, 87%) was obtained *via* RP-MPLC (MeCN:H_2O, 50:50) as a colourless foam.

Major diastereomer [2.125]: IR (neat): $\tilde{\nu}$ = 3593 (w), 3100 (w), 1623 (w), 1543 (s), 1346 (s), 1197 (m), 1179 (m), 1135 (m), 1103 (m), 1063 (w), 996 (m), 914 (m), 811 (w), 729 (s), 708 (s). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 8.58 (d, J = 2.1 Hz, 2H, $CH_{arom.}$), 8.23 (t, J = 2.1 Hz, 1H, $CH_{arom.}$), 4.55 – 4.49 (m, 2H, CH_2), 3.96 (d, J = 8.7 Hz, 1H, CH_2), 3.56 (d, J = 8.7 Hz, 1H, CH_2), 3.38 (d, J = 12.0 Hz, 1H, CH_2), 3.27 (d, J = 12.0 Hz, 1H, CH_2), 1.30 (br, 1H, OH), 1.26 – 1.21 (m, 3H, CH_3). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 148.2 (C_q), 142.0 (C_q), 138.8 (C_q), 126.8 (CH), 122.3 (q, $^1J_{C,F}$ = 288.4 Hz, CF$_3$), 120.2 (CH), 114.3 (CH$_2$), 104.3 (q, $^2J_{C,F}$ = 33.3 Hz, C_q), 90.7 (C_q), 71.3 (CH$_2$), 64.2 (CH$_2$), 19.2 (CH$_3$). **^{19}F NMR (377 MHz, C_6D_6)** δ = −82.3 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{14}H_{13}F_3N_2O_7$ $[M]^-$: 378.0675, Found: 378.0677. **Optical Rotation**: $[\alpha]_D^{25}$ = +26.1 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 83:17 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS column, 22 °C, 1 mL/min, 95:5 hexane:isopropanol, 254 nm, t_{minor} = 18.835 min, t_{major} = 13.812 min). Absolute stereochemistry determined through analogy with **2.117**.

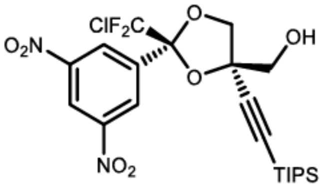
((2*S*,4*R*)-2-(chlorodifluoromethyl)-2-(3,5-dinitrophenyl)-4-phenyl-1,3-dioxolan-4-yl)methanol [2.133]



Following **GP-C** with minor alterations using 3-phenyl-oxetan-3-ol **2.38** (30.0 mg, 0.20 mmol, 1.00 eq.), 3'5'-dinitro-2,2-difluoro-2-chloroacetophenone, prepared by [redacted] (56.1 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (63.0 mg, 0.146 mmol, 73%) was obtained *via* RP-MPLC (MeCN:H$_2$O, 50:50) as a colourless foam.

Major diastereomer [2.133]: IR (neat): $\tilde{\nu}$ = 3341 (m), 3114 (m), 2927 (m), 1628 (w), 1545 (s), 1345 (s), 1232 (w), 1127 (m), 1061 (m), 1033 (m), 911 (m), 760 (m). **^{1}H NMR (400 MHz, C$_6$D$_6$)**: δ = 8.59 (d, J = 2.0 Hz, 2H, C$H_{\text{arom.}}$), 8.09 (t, J = 2.1 Hz, 1H, C$H_{\text{arom.}}$), 6.91 – 6.85 (m, 2H, C$H_{\text{arom.}}$), 6.84 – 6.78 (m, 3H, C$H_{\text{arom.}}$), 4.43 (d, J = 8.6 Hz, 1H, CH_2), 3.88 (d, J = 8.6 Hz, 1H, CH_2), 3.60 (d, J = 12.0 Hz, 1H, CH_2), 3.29 (d, J = 12.0 Hz, 1H, CH_2), 1.63 – 1.38 (br, 1H, OH). **^{13}C NMR (101 MHz, C$_6$D$_6$)**: δ = 147.8 (C_q), 139.0 (C_q), 138.9 (C_q), 128.6 (CH), 128.6 (CH), 127.7 (CH), 127.1 (t, $^1J_{C,F}$ = 301.9 Hz, CF$_2$Cl), 125.8 (CH), 120.0 (CH), 107.1 (t, $^2J_{C,F}$ = 28.1 Hz, C_q), 89.7 (C_q), 72.4 (CH$_2$), 67.2 (CH$_2$). **^{19}F NMR (377 MHz, C$_6$D$_6$)** δ = –67.5 (s, 2F, CF_2Cl). **HRMS (APCI)**: Calculated for C$_{18}$H$_{14}$ClF$_2$N$_2$O$_9$ [M+HCOO]$^-$: 475.0356, Found: 475.0363. **Optical Rotation**: $[\alpha]_D^{25}$ = +12.2 (c = 1.00, CHCl$_3$) for an enantiomerically enriched sample of 74:26 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux® i-Amylose-3 column, 22 °C, 1 mL/min, 95:05 hexane:isopropanol, 254 nm, t_{minor} = 20.097 min, t_{major} = 23.786 min). Relative configuration was determined *via* 2D-^{1}H,^{1}H NOESY experiments. Absolute stereochemistry determined through analogy with **2.117**.

((2*S*,4*R*)-2-(chlorodifluoromethyl)-2-(3,5-dinitrophenyl)-4-((triisopropylsilyl)ethynyl)-1,3-dioxolan-4-yl)methanol [2.134]

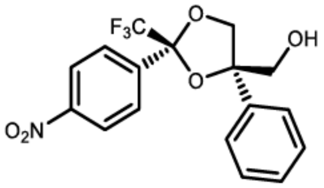


Following **GP-C** with minor alterations using 3-((triisopropylsilyl)ethynyl)oxetan-3-ol **2.55** (50.9 mg, 0.20 mmol, 1.00 eq.), 3'5'-dinitro-2,2-difluoro-2-chloroacetophenone, prepared by [redacted] (56.1 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (76.0 mg, 0.142 mmol, 71%) was obtained *via* RP-MPLC (MeCN:H$_2$O, 50:50) as a colourless foam.

Major diastereomer [2.134]: ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 8.82 (d, J = 2.1 Hz, 2H, C$H_{\text{arom.}}$), 8.65 (t, J = 2.1 Hz, 1H, C$H_{\text{arom.}}$), 4.15 (d, J = 7.9 Hz, 1H, C*H*), 3.75 (d, J = 7.9 Hz, 1H, C*H*), 3.58 (d, J = 12.4 Hz, 1H, C*H*), 3.33 (d, J = 12.4 Hz, 1H, C*H*), 0.73 (dd, J = 7.2, 2.7 Hz, 18H, CH_3), 0.68 – 0.54 (m, 3H, C*H*). **^{13}C NMR (101 MHz, C$_6$D$_6$)**: δ = 148.5 (C_q), 139.8 (C_q), 127.9 (*C*H), 127.1 (t, $^1J_{C,F}$ = 301.9 Hz, *C*F$_2$Cl), 120.0 (*C*H), 107.1 (t, $^2J_{C,F}$ = 28.5 Hz, C_q), 103.6 (C_q), 90.6 (C_q), 81.4 (C_q), 74.4 (*C*H$_2$), 64.1 (*C*H$_2$), 18.3 (*C*H$_3$), 10.9 (*C*H).**^{19}F NMR (377 MHz, C$_6$D$_6$)** δ = –67.5 (*app.* d, J = 43.3 Hz. 2F, CF_2Cl).

Relative configuration was determined *via* 2D-^{1}H,^{1}H NOESY experiments. Absolute stereochemistry determined through analogy with **2.117**.

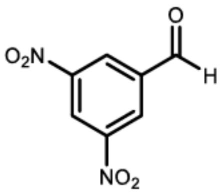
((2*S*,4*R*)-2-(4-nitrophenyl)-4-phenyl-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol [2.135]

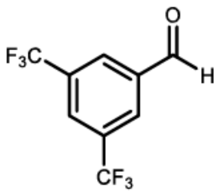


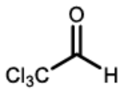
Following **GP-C** with minor alterations using 3-phenyl-oxetan-3-ol **2.38** (30.0 mg, 0.20 mmol, 1.00 eq.), 4'-nitro-2,2,2-trifluoroacetophenone **2.22** (43.8 mg, 0.20 mmol, 1.00 eq.) and Co^{II}·salen **2.106** (2.0 mg, 2.0 µmol, 1.0 mol%), the major diastereomer (11.0 mg, 0.030 mmol, 15%) was obtained *via* RP-MPLC (MeCN:H$_2$O, 50:50) as a colourless oil.

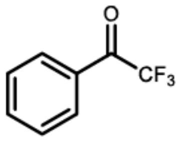
Major diastereomer [2.135]: IR (neat): $\tilde{\nu}$ = 3424 (m), 2986 (w), 2941 (m), 1527 (s), 1351 (s), 1189 (s), 1099 (s), 1068 (m), 851 (s), 759 (s), 727 (s), 703 (s). **^{1}H NMR (400 MHz, C_6D_6)**: δ = 7.61 – 7.55 (m, 2H, $CH_{\text{arom.}}$), 7.38 – 7.34 (m, 2H, $CH_{\text{arom.}}$), 6.94 – 6.83 (m, 5H, $CH_{\text{arom.}}$), 4.40 (d, J = 8.4 Hz, 1H, CH_2), 3.82 (d, J = 8.4 Hz, 1H, CH_2), 3.61 (d, J = 11.9 Hz, 1H, CH_2), 3.38 (d, J = 11.9 Hz, 1H, CH_2), 1.32 (br, 1H, OH). **^{13}C NMR (101 MHz, C_6D_6)**: δ = 149.0 (C_q), 140.7 (C_q), 139.6 (C_q), 128.4 (CH), 128.2 (CH), 127.9 (CH), 125.8 (CH), 123.3 (CH), 122.8 (q, $^1J_{C,F}$ = 288.0 Hz, CF_3), 105.4 (app. d, $^2J_{C,F}$ = 32.6 Hz, C_q), 89.1 (C_q), 72.7 (CH_2), 67.1 (CH_2). **^{19}F NMR (377 MHz, C_6D_6)** δ = –81.3 (s, 3F, CF_3). **HRMS (APCI)**: Calculated for $C_{18}H_{15}F_3NO_7$ [M+HCOO]$^-$: 414.0801, Found: 414.0806. **Optical Rotation**: $[\alpha]_D^{25}$ = +14.0 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 77:23 *er*. The enantiomeric purity was established by HPLC analysis using a chiral column (Reprosil Chiral-AMS, 22 °C, 1 mL/min, 95:05 hexane:isopropanol, 254 nm, t_{minor} = 20.203 min, t_{major} = 17.186 min). Absolute stereochemistry determined through analogy with **2.117**.

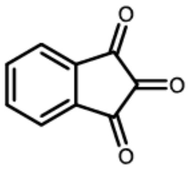
Limitations of the presented method

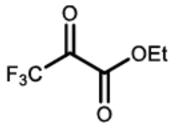












Following **GP-C** the above shown activated ketones or aldehydes (0.20 mmol, 1.00 eq.) were used with 3-phenyl-oxetan-3-ol **2.38** (30.0 mg, 0.20 mmol, 1.00 eq.) and Co^{II} catalyst **2.73** or **2.78** (1 mol%). The reaction was monitored through ^{1}H NMR and ^{19}F NMR with 0.1 mmol of mesitylene or 0.1 mmol of trifluorotoluene as internal standard. No product was observed within 24 h of reaction time.

Determination of the relative configuration of the 1,3-dioxolanes:

The both diastereotopic CH2-groups of the substrates **2.105** and **2.111** to **2.125** are unambiguously identified *via* HMBC or COSY experiments. The relative configuration of the major diastereoisomer of the formed 1,3-dioxolanes were determined *via* 2D-^{1}H,^{1}H NOESY experiments. Correlations between the signals of the protons in *ortho*-position of both aromatic rings were observed. It can therefore be concluded that the two aromatic substituents are positioned *syn* to each other. Typically, NOE contacts were likewise observed for the *ortho*-protons of one aromatic ring and the proton of the CH2-group protons inside the ring, which is oriented to the same face.

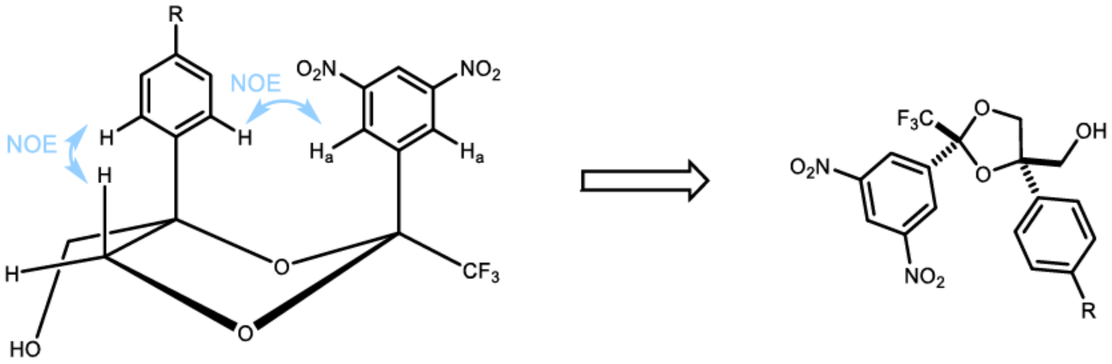
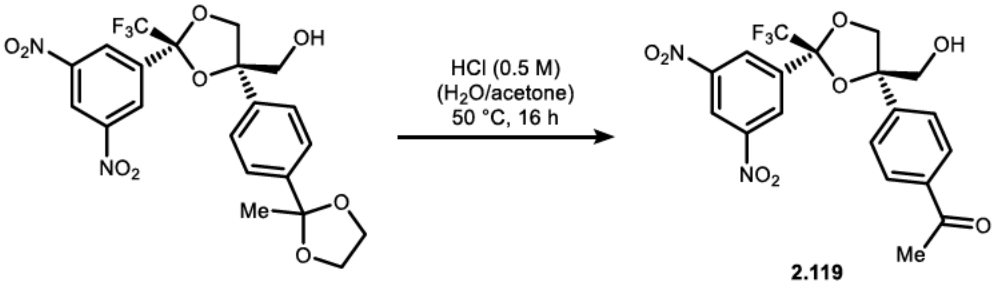


Figure 24: Summary of relevant NOE interactions and model of the relative configuration.

6.2.3.2 Further transformations with 1,3-dioxolanes

Chemoselective deprotection of [2.118] towards [2.119]



2.118
71:29 er

2.119
94% yield
69:31 er

((2*S*,4*R*)-2-(3,5-Dinitrophenyl)-4-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)-2-(trifluoromethyl)-1,3-dioxolan-4-yl)methanol **2.118** (50 mg, 0.10 mmol, 1.00 eq.) was dissolved in acetone (1mL) and HCl aq. (1N, 1 mL) was added. The mixture was heated to 50 °C for 17 h before EtOAc (4 mL) and $NaHCO_3$ sat. aq. (4 mL) were added. The aqueous phase was extracted with EtOAc (3x4 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed.

The crude mixture was analyzed by ^{1}H NMR with 0.1 mmol mesitylene as an internal standard. The product was isolated after RP-MPLC (MeCN:H_2O, 50:50) as a colourless solid (43 mg, 94%).

^{1}H NMR (300 MHz, acetone-d6): δ = 8.96 (t, *J* = 2.1 Hz, 1H, C*H*$_{\text{arom.}}$), 8.78 – 8.71 (m, 2H, C*H*$_{\text{arom.}}$), 7.86 – 7.80 (m, 2H, C*H*$_{\text{arom.}}$), 7.57 – 7.50 (m, 2H, C*H*$_{\text{arom.}}$), 4.89 (dd, *J* = 8.9, 0.9 Hz, 1H, C*H*$_2$), 4.67 – 4.61 (m, 1H, C*H*$_2$), 4.04 (d, *J* = 11.7 Hz, 1H, C*H*$_2$), 3.89 (d, *J* = 11.7 Hz, 1H, C*H*$_2$), 2.48 (s, 3H, C*H*$_3$). **^{19}F NMR (282 MHz, acetone-d6)** δ = – 82.7 (s, 3F, C*F*$_3$).
The obtained spectroscopic data were identical to those of dioxolane **2.119** prepared from oxetanol **2.57**.

Attempted deprotection of the ketal

Various conditions were applied in a manifold of attempts to cleave the formed ketals (Table 19, *cf.* Chapter 2.6, Table 6). Therefore, 1,3-dioxolane **2.117** or its TIPS protected variant was used as model substrates under either, hydrolytic, nucleophilic, reducing or oxidative conditions. For reducing conditions other than in Entry 19, solely the TIPS-protected variant of **2.117** was used. The desired cleavage of the cyclic ketal was not observed by TLC or NMR analysis of the crude reaction mixtures.

Table 19: Unsuccessful conditions for the deprotection of cyclic ketals.

Entry		Conditions	Yield
1	hydrolytic	PPTS (20 mol%), (MeOH), rt ,17 h	0%
2		pTsOH (20 mol%), (MeOH), rt, 17 h	0%
3		HCl aq. (1N), (MeOH), rt, 17 h	0%
4		HCl aq. (6N), (MeOH), 60 °C, 4 h	0%
5		TfOH (1.00 eq.), (TFA), rt, 17 hh	0%
6		KOH aq. (2N), (MeOH), 60°C, 17 h	0%
7		KOH aq. (2N), (THF), 60°C, 17 h	0%
8		BBr_3 (6.00 eq.), CH_2Cl_2, rt. 17 h	0%
9	nucleophilic	benzo[d]thiazole-2-thiol (2.00 eq.), $BF_3 \cdot OEt_2$ (1.00 eq.), (DCE), 60 °C, 17 h	0%
10		EtSH (10.0 eq.), NaOMe (10.0 eq.), (PhMe), 80 °C, 16 h	0%
11		CH_2=CHMgBr (2.00 eq.), 0°C to rt, 17 h	0%
12		TMSI (1.00 eq.), (CH_2Cl_2), rt, 17 h	0%

Table 19 (continued): Unsuccessful conditions for the deprotection of cyclic ketals.

Entry		Conditions	Yield
13	reducing	Pd/C (5 mol%), H_2, (MeOH), rt, 1 h	0%
14		$LiBHEt_3$, (1.00 eq.), (THF), – 20 °C to rt, 20 h	0%
15		DIBAL-H (4.00 eq.), (CH_2Cl_2), rt, 16 h	0%
16	oxidative	CAN (1.00 eq.), (MeCN:H_2O, 1:1), rt, 17 h	0%
17		$RuCl_3 \cdot H_2O$ (0.20 eq.), $NaIO_4$ (4.00 eq.), (MeCN:H_2O:CCl_4, 1:1.5:1), 40 °C, 3d	0%
18		Cumene hydroperoxide (1.00 eq.), KO*t*Bu (9.00 eq.), (CH_2Cl_2), reflux, 24 h	0%
19		$K_3[Fe(CN)_6)]$ (10.0 eq.), ($NaHCO_3$ sat. aq.) 100 °C, 24 h	0%
20		$K_3[Fe(CN)_6)]$ (10.0 eq.), (NaOH aq., 2N). 100 °C, 24 h	0%
21		Mn_2O_7 (2.00 eq.), (EtOAc:CCl_4, 1:1), – 40 °C, 30 min	0%
22	photo-chemical	*hv* (245 nm), (MeCN:H_2O, 95:5), rt, 16 h	0%

6.2.4 Crystallographic Data

X-ray crystal structure analysis of [2.24] (wie 9886):

The X-ray measurement and structure refinement was performed by [redacted]

A colourless plate-like specimen of $C_8H_5F_3N_2O_6$, approximate dimensions 0.049 mm x 0.101 mm x 0.197 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a *Bruker* D8 Venture PHOTON III Diffractometer system equipped with a micro focus tube Cu Ims (CuK_α, $\lambda = 1.54178$ Å) and a MX mirror monochromator. A total of 1609 frames were collected. The total exposure time was 14.90 hours. The frames were integrated with the *Bruker* SAINT software package using a wide-frame algorithm. The integration of the data using an monoclinic unit cell yielded a total of 16992 reflections to a maximum θ angle of 68.15° (0.83 Å resolution), of which 1797 were independent (average redundancy 9.456, completeness = 96.8%, R_{int} = 4.75%, R_{sig} = 2.59%) and 1736 (96.61%) were greater than $2\sigma(F^2)$.The final cell constants of of a = 6.15030(10) Å, b = 12.5829(3) Å, c = 13.1818(3) Å, β = 93.6830(10)°, volume = 1018.01(4) Å^3, are based upon the refinement of the XYZ-centroids of 9978 reflections above 20 σ(I) with 13.46° < 2θ < 136.3°. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.851. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7280 and 0.9200. The structure was solved and refined using the *Bruker* SHELXTL Software Package, using the space group $P2_1/c$ 1, with Z = 4 for the formula unit, $C_8H_5F_3N_2O_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 180 variables converged at R1 = 3.02%, for the observed data and wR2 = 7.53% for all data. The goodness-of-fit was 1.089. The largest peak in the final difference electron density synthesis was 0.273 e^-/Å^3 and the largest hole was -0.210 e^-/Å^3 with an RMS de*via*tion of 0.041 e^-/Å^3. On the basis of the final model, the calculated density was 1.841 g/cm^3 and F(000), 568 e^-. The hydrogen atoms at O1 and O2 were refined freely. CCDC Nr.: 2130259.

X-ray crystal structure analysis of [2.96] (wie 9750):

The X-ray measurement and structure refinement was performed by [redacted]

A colourless needle-like specimen of $C_{15}H_{12}F_3N_2O_4$, approximate dimensions 0.058 mm x 0.101 mm x 0.334 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1224 frames were collected. The total exposure time was 23.74 hours. The frames were integrated with the *Bruker* SAINT software package using a wide-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 22240 reflections to a maximum θ angle of 68.36° (0.83 Å resolution), of which 2578 were independent (average redundancy 8.627, completeness = 99.4%, R_{int} = 5.26%, R_{sig} = 3.99%) and 2349 (91.12%) were greater than $2\sigma(F^2)$.The final cell constants of a = 13.5889(3) Å, b = 9.9317(2) Å, c = 20.9678(4) Å, volume = 2829.83(10) $Å^3$, are based upon the refinement of the XYZ-centroids of 9928 reflections above 20 σ(I) with 8.434° < 2θ < 136.6°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.747. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.6900 and 0.9340. The structure was solved and refined using the *Bruker* SHELXTL Software Package, using the space group *P* b c a, with Z = 8 for the formula unit, $C_{15}H_{12}F_3N_2O_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 212 variables converged at R1 = 3.38%, for the observed data and wR2 = 8.27% for all data. The goodness-of-fit was 1.044. The largest peak in the final difference electron density synthesis was 0.275 $e^-/Å^3$ and the largest hole was -0.272 $e^-/Å^3$ with an RMS de*via*tion of 0.047 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.536 g/cm^3 and F(000), 1344 e^-. The hydrogen at O2 atom was refined freely. CCDC Nr.: 2130260.

X-ray crystal structure analysis of [2.117] (ass6091):

The X-ray measurement and structure refinement was performed by [redacted]

A colourless block-like specimen of $C_{17}H_{12}F_3N_2O_7$, approximate dimensions 0.080 mm x 0.260 mm x 0.280 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a STOE IPDS-2T Diffractometer system. CCDC number: 2141905

Table 20: Crystal data and structure refinement for [2.117] (ass6091).

Identification code	ass6091
Empirical formula	$C_{17}H_{12}BrF_3N_2O_7$
moiety formula	$C_{17}H_{12}BrF_3N_2O_7$
Formula weight	493.20
Temperature	120(2) K
Wavelength, radiation type	0.71073Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	Orthorhombic
Space group name, number	P $2_12_12_1$, (19)
Unit cell dimensions	a = 10.9727(5) Å b = 11.7950(4) Å c = 14.1878(7) Å
Volume	1836.23(14) $Å^3$
Number of reflections	9257
and range used for lattice parameters	2.87° <=θ<= 28.47°
Z	4
Density (calculated)	1.784 Mg/m^3
Absorption coefficient	2.314 mm^{-1}
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8306 and 0.5223
F(000)	984
Crystal size, colour and form	0.080 x 0.260 x 0.280 mm_3, colourless block
Theta range for data collection	2.871 to 27.957°.
Index ranges	-14<=h<=12, -13<=k<=15, -18<=l<=16
Number of reflections:	
collected	7188
independent	4369 [R(int) = 0.0314]
observed [I>2sigma(I)]	4002
Completeness to theta = 25.2°	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4369 / 0 / 317
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0778
R indices (all data)	R1 = 0.0425, wR2 = 0.0816
Absolute structure parameter	0.013(8)
Largest diff. peak and hole	0.605 and -0.319 $eÅ^{-3}$
Remark	hydrogen atoms localized and refined with isotropic thermal displacement parameters

6.3 Acyclic alcohols as platform for the synthesis of oxygen rich heterocycles

General procedures

General procedure D (GP-D) for the *Tsuji-Trost* type allylic functionalisation with transient hemi ketals:

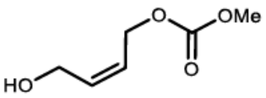
Allylic acetate or carbonate (0.10 mmol, 1.00 eq.) and the respective ketone (0.10 mmol, 1.00 eq.) were dissolved in dry THF (0.1 M) and $Pd(PPh_3)_4$ (0.01 mmol, 0.10 eq.) was added. The mixture was stirred for 3 d at rt and filtered through silica with EtOAc. The solvent was removed *in vacuo* and the products were isolated after FC or automated FC.
NMR yield and *dr* of the crude reaction mixture were determined by ^1H NMR using mesitylene (0.10 mmol) as internal standard, or by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard.

General procedure E (GP-E) for the allylic *C–H* oxidation with transient hemi ketals:

Similar to the reaction conditions for the allylic *C–H* amination reported by *White*,[123e] the ketone or aldehyde (0.10 mmol, 1.00 eq.) and but-3-en-1-ol (8.6 µL, 0.10 mmol, 1.00 eq.) were dissolved in 1,2-dichloroethane (0.1 M) and 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq), (Cl)Cr^{III}·salen **3.25** (6.3 mg, 0.01 mmol, 0.10 eq.) and 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate **3.12** (5.0 mg 0.01 mmol, 0.10 eq.) were added. The mixture was stirred for 17 h at rt and filtered through silica with EtOAc. The solvent was removed. NMR yield of the crude reaction mixture was determined by either ^1H NMR using mesitylene (0.10 mmol) as internal standard, or by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard.

6.3.1 Synthesis of starting materials

(*Z*)-4-Hydroxybut-2-en-1-yl methyl carbonate [3.17]

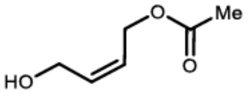


According to a literature known protocol,[133a] (*Z*)-but-2-ene-1,4-diol **3.16** (2.00 mL, 24.3 mmol, 1.00 eq.) was dissolved in pyridine (20.0 mL) and methyl chloroformiate (1.98 mL, 25.5 mmol, 1.05 eq.) was added slowly at 0 °C. The mixture was stirred for 24 h before it was diluted with EtOAc (40 mL) and $CuSO_4$ sat. aq. (20 mL) was added. The aqueous phase was extracted with EtOAc (3x40 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was obtained after automated FC (CyH:EtOAc 60:40 to 40:60) as a colourless oil (858 mg, 5.87 mmol, 24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 – 5.83 (m, 1H), 5.67 (dtt, J = 11.1, 7.1, 1.4 Hz, 1H), 4.77 – 4.70 (m, 1H), 4.32 – 4.21 (m, 2H), 3.78 (s, 3H).[h]
^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0, 134.2, 125.1, 63.4, 58.6, 55.0.
Spectroscopic data was in agreement to those previously reported.[133a]

Chemotion ELN sample number: ASS-9-56-A.

(*Z*)-4-Hydroxybut-2-en-1-yl acetate [3.18]



According to a literature known protocol,[133b] (*Z*)-but-2-ene-1,4-diol **3.16** (823 µL, 10.0 mmol, 1.00 eq.), *N*,*N*-dimethylpyridin-4-amine (12.2 mg, 100 µmol, 0.01 eq.) and pyridine (846 µL, 10.5 mmol, 1.05 eq.) were dissolved in CH_2Cl_2 (40.0 mL) and acetic anhydride (993 µL, 10.5 mmol, 1.05 eq.) was added slowly at 0 °C. The mixture was stirred for 4 h at rt before it was diluted with CH_2Cl_2 (40 mL) and NH4Cl sat. aq. (20 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3x40 mL). The combined organic fractions were washed with $NaHCO_3$ sat. aq. (2x40 mL), NaCl sat. aq. (40 mL). The organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The product was obtained after automated FC (CyH:EtOAc 80:20 to 60:40) as a colourless oil (476 mg, 3.66 mmol, 37%)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.92 – 5.79 (m, 1H), 5.68 – 5.57 (m, 1H), 4.67 (d, J = 7.1 Hz, 2H), 4.25 (d, J = 6.6 Hz, 2H), 2.06 (s, 3H).[i]

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[h] Signal of OH group not detectable due to rapid exchange with residual water.
[i] Signal of OH group not detectable due to rapid exchange with residual water.

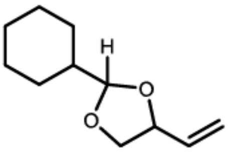
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 133.5, 125.7, 60.2, 58.5, 21.1. Spectroscopic data was in agreement to those previously reported.[133b]

Chemotion ELN sample number: ASS-9-41-A.

6.3.2 Palladium catalysed synthesis of oxygen rich heterocycles

6.3.2.1 *Tsuji-Trost* type allylation of transient hemi ketals

2-Cyclohexyl-4-vinyl-1,3-dioxolane [3.21]



Following **GP-D**, using [(*Z*)-4-hydroxybut-2-enyl] methyl carbonate **3.17** (14.6 mg, 0.10 mmol, 1.00 eq.), cyclohexanecarbaldehyde (11.2 mg, 0.10 mmol, 1.00 eq.), and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.10 eq.) the product was obtained as a diasteromeric mixture (>9:1 *dr*) *via* FC (pentane:EtOAc, 70:30) as a colourless oil (4.00 mg, 21.9 µmol, 22%).

Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (ddd, J = 17.6, 10.7, 5.7 Hz, 1H, C*H*), 5.39 – 5.23 (m, 3H, CH_2 and C*H*), 3.79 – 3.63 (m, 2H, CH_2), 2.37 (tt, J = 11.4, 3.6 Hz, 1H, C*H*), 1.94 (d, J = 12.9 Hz, 2H, CH_2), 1.82 – 1.72 (m, 2H, CH_2), 1.69 – 1.62 (m, 1H, CH_2), 1.46 (app. qd, J = 11.8, 7.1 Hz, 2H, CH_2), 1.36 – 1.16 (m, 4H, CH_2 and C*H*). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 133.1 (*C*H), 118.5 (*C*H_2), 75.1 (*C*H), 64.7 (*C*H_2), 43.4 (*C*H), 29.2 (*C*H_2), 29.1 (*C*H_2), 25.9 (*C*H_2), 25.6 (*C*H_2), 25.5 (*C*H_2).[j]

Chemotion ELN sample number: ASS-9-36-A.

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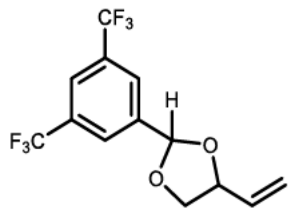
[j] One signal missing due to signal overlap.

2-(3,5-Bis(trifluoromethyl)phenyl)-4-vinyl-1,3-dioxolane [3.22]



Following **GP-D**, using [(*Z*)-4-hydroxybut-2-enyl] methyl carbonate **3.17** (14.6 mg, 0.10 mmol, 1.00 eq.), 3,5-bis(trifluoromethyl)benzaldehyde **2.129** (16.5 µL, 0.10 mmol, 1.00 eq.), and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.10 eq.) the product was obtained as a diasteromeric mixture (61:39 *dr*) *via* FC (pentane:CH_2Cl_2, 99.5:0.5 to 0:100) as a colourless oil (18.0 mg, 57.7 µmol, 58%)

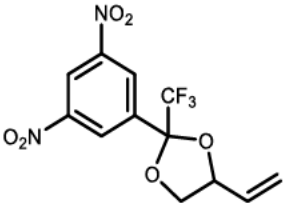
The same product was obtained by following **GP-D** using (*Z*)-4-hydroxybut-2-en-1-yl acetate **3.18** (13.0 mg, 0.10 mmol, 1.00 eq.), 3,5-bis(trifluoromethyl)benzaldehyde **2.129** (16.5 µL, 0.10 mmol, 1.00 eq.), and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.10 eq.).
NMR yield and *dr* of the crude reaction mixture were determined by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard.

Major diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (br, 2H, C$H_{arom.}$), 7.89 (br, 1H, C$H_{arom.}$), 6.06 (s, 1H, C*H*), 5.97 – 5.84 (m, 1H, C*H*), 5.32 (ddt, *J* = 10.4, 6.7, 1.0 Hz, 2H, CH_2), 4.69 – 4.62 (m, 1H, C*H*), 4.32 (dd, *J* = 8.3, 6.3 Hz, 1H, CH_2), 3.77 (dd, *J* = 8.4, 7.3 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 141.1 (C_q), 134.6 (*C*H), 131.9 (q, $^2J_{C,F}$ = 33.8 Hz, C_q), 126.9 (q, $^4J_{C,F}$ = 3.9 Hz, *C*H), 123.3 (q, $^1J_{C,F}$ = 272.6 Hz, *C*F_3), 123.1 (m, *C*H), 119.1 (*C*H_2), 102.0 (*C*H), 77.8 (*C*H), 70.7 (*C*H_2). **^{19}F NMR (377 MHz, $CDCl_3$)**: δ = −62.8 (s, CF_3).

Minor diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (br, 2H, C$H_{arom.}$), 7.89 (br, 1H, C$H_{arom.}$), 5.97 – 5.84 (m, 1H, C*H*), 5.96 (s, 1H, C*H*), 5.49 – 5.39 (m, CH_2), 4.70 (tdd, *J* = 7.0, 6.5, 0.9 Hz, 1H, C*H*), 4.22 (dd, *J* = 8.0, 6.8 Hz, 1H, CH_2), 3.78 (dd, *J* = 8.0, 6.9 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 140.6 (C_q), 134.7 (*C*H), 131.9 (q, $^2J_{C,F}$ = 33.8 Hz, C_q), 127.1 (q, $^4J_{C,F}$ = 3.8 Hz, *C*H), 123.3 (m, *C*H), 123.2 (q, $^1J_{C,F}$ = 272.6 Hz, *C*F_3), 119.5 (*C*H_2), 102.5 (*C*H), 79.0 (*C*H), 70.2 (*C*H_2). **^{19}F NMR (377 MHz, $CDCl_3$)**: δ = −62.8 (s, CF_3).

Chemotion ELN sample number: ASS-9-40-A.

2-(3,5-Dinitrophenyl)-2-(trifluoromethyl)-4-vinyl-1,3-dioxolane [3.23]



Following **GP-D**, using [(*Z*)-4-hydroxybut-2-enyl] methyl carbonate **3.17** (14.6 mg, 0.10 mmol, 1.00 eq.), 3'5'-dinitro-2,2,2-trifluoroacetophenone **2.20** (26.4 mg, 0.10 mmol, 1.00 eq.), and Pd(PPh_3)$_4$ (11.6 mg, 0.01 mmol, 0.10 eq.) the product was obtained as a diasteromeric mixture (61:39 *dr*) *via* FC (CH_2Cl_2:Et_2O 100:0 to 0:100) as a colourless oil (15.0 mg, 44.9 µmol, 45%)

The same product was obtained by following **GP-D** using (*Z*)-4-hydroxybut-2-en-1-yl acetate **3.18** (13.0 mg, 0.10 mmol, 1.00 eq.), 3'5'-dinitro-2,2,2-trifluoroacetophenone (26.4 mg, 0.10 mmol, 1.00 eq.), and Pd(PPh_3)$_4$ (11.6 mg, 0.01 mmol, 0.10 eq.).
NMR yield and *dr* of the crude reaction mixture were determined by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard.

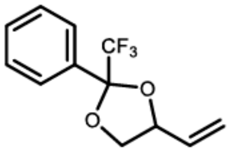
Major diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 – 9.10 (m. 1H, C$H_{\text{arom.}}$), 8.82 – 8.79 (m, 2H, C$H_{\text{arom.}}$), 5.74 – 5.62 (m, 1H, C*H*), 5.45 (d, *J* = 10.4 Hz, 1H, CH_2), 5.34 (dt, *J* = 10.3, 0.9 Hz, 1H, CH_2), 5.02 (app. q, *J* = 7.1 Hz, 1H, C*H*), 4.51 (dd, *J* = 8.1, 6.2 Hz, 1H, CH_2), 4.01 (ddd, *J* = 9.0, 8.1, 0.9 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 148.6 (C_q), 139.8 (C_q), 131.7 (CH), 127.7 (*C*H), 122.0 (q, $^1J_{C,F}$ = 288.3 Hz, *C*F$_3$), 121.5 (*C*H$_2$), 120.3 (*C*H), 103.8 (app. d, $^2J_{C,F}$ = 32.7 Hz, C_q). 80.5 (*C*H), 71.4 (*C*H$_2$). **^{19}F NMR (377 MHz, $CDCl_3$)**: δ = –81.5 (s, CF_3).

Minor diastereomer:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12 (app. td, *J* = 2.1, 1.3 Hz, 1H, C$H_{\text{arom.}}$), 8.81 (t, *J* = 1.9 Hz, 2H), C$H_{\text{arom.}}$, 5.99 – 5.87 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H, C*H*), 5.51 (dt, *J* = 17.3, 1.0 Hz, 1H, CH_2), 5.48 – 5.44 (m, 1H, CH_2), 4.66 – 4.57 (m, 1H, C*H*), 4.39 (ddd, *J* = 8.2, 6.0, 1.3 Hz, 1H, CH_2), 3.74 (td, *J* = 8.0, 0.9 Hz,

1H, CH_2). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 148.6 (C_q), 139.8 (C_q), 132.4 (CH), 127.6 (CH), 122.2 (q, $^1J_{C,F}$ = 289.3 Hz, CF$_3$), 121.5 (CH$_2$), 120.3 (CH), 103.8 (q, $^2J_{C,F}$ = 32.7 Hz, C_q), 81.5 (CH), 72.1 (CH$_2$). **^{19}F NMR (377 MHz, CDCl$_3$)**: δ = −81.5 (s, CF_3).

Chemotion ELN sample number: ASS-9-37-A.

2-Phenyl-2-(trifluoromethyl)-4-vinyl-1,3-dioxolane [3.24]



Following **GP-D**, using [(*Z*)-4-hydroxybut-2-enyl] methyl carbonate **3.17** (14.6 mg, 0.10 mmol, 1.00 eq.), 2,2,2-trifluoroacetophenone **2.18** (14.0 µL, 0.10 mmol, 1.00 eq.), and Pd(PPh$_3$)$_4$ (11.6 mg, 0.01 mmol, 0.10 eq.) the product was obtained as a diasteromeric mixture (61:39 *dr*, 87% NMR yield).

Major diastereomer:

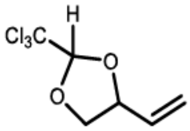
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68 – 7.59 (m, 2H, C$H_{arom.}$), 7.46 – 7.37 (m, 3H, C$H_{arom.}$), 5.77 – 5.64 (m, 1H, CH), 5.45 (dt, J = 13.5, 1.1 Hz, 1H, CH_2), 5.26 (dt, J = 10.2, 1.0 Hz, 1H, CH_2), 4.91 (app. q, J = 7.2 Hz, 1H, CH), 4.41 (dd, J = 8.0, 6.2 Hz, 1H, CH_2), 3.66 (td, J = 8.0, 0.9 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 135.1 (C_q), 133.8 (CH), 129.8 (CH), 128.2 (CH), 127.0 (CH), 123.0 (q, $^1J_{C,F}$ = 288.9 Hz, CF$_3$), 120.1 (CH$_2$), 105.2 (q, $^2J_{C,F}$ = 32.0 Hz, C_q), 79.5 (CH), 70.9 (CH$_2$). **^{19}F NMR (377 MHz, CDCl$_3$)**: δ = −81.7 (s, CF_3).

Minor diastereomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68 – 7.59 (m, 2H, C$H_{arom.}$), 7.44 – 7.38 (m, 3H, C$H_{arom.}$), 6.01 – 5.85 (m, 1H, CH), 5.41 (dt, J = 13.5, 1.1 Hz, 1H, CH_2), 5.36 (dt, J = 10.3, 1.0 Hz, 1H, CH_2), 4.63 – 4.50 (m, 1H, CH), 4.26 (ddd, J = 7.6, 6.2, 1.3 Hz, 1H, CH_2), 3.91 (ddd, J = 8.7, 7.8, 0.9 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 135.0 (C_q), 133.1 (CH), 129.8 (CH), 128.2 (CH), 127.0 (CH), 122.8 (q, $^1J_{C,F}$ = 288.0 Hz, CF$_3$), 120.5 (CH$_2$), 105.2 (q, $^2J_{C,F}$ = 32.4 Hz, C_q), 80.6 (CH), 71.5 (CH$_2$). **^{19}F NMR (377 MHz, CDCl$_3$)**: δ = −81.7 (s, CF_3).

Chemotion ELN sample number: ASS-14-45-A.

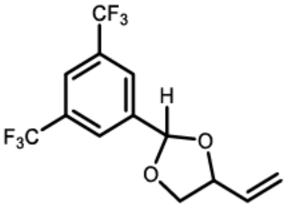
Limitations



Following **GP-D**, using [(*Z*)-4-hydroxybut-2-enyl] methyl carbonate **3.17** (14.6 mg, 0.10 mmol, 1.00 eq.), 2,2,2-trichloroacetaldehyde (14.7 mg, 0.10 mmol, 1.00 eq.) and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.10 eq.), no product formation was observed by ^1H NMR using mesitylene (0.10 mmol) as internal standard.

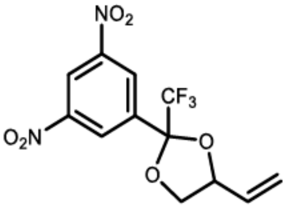
6.3.2.2 Allylic *C–H* oxidation with transient hemi ketals

2-(3,5-Bis(trifluoromethyl)phenyl)-4-vinyl-1,3-dioxolane [3.22]



By following **GP-E**, using 3,5-bis(trifluoromethyl)benzaldehyde **2.129** (16.5 µL, 0.10 mmol, 1.00 eq.), but-3-en-1-ol (8.6 µL, 0.10 mmol, 1.00 eq.), 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq), (Cl)Cr^{III}·salen **3.25** (6.3 mg, 0.01 mmol, 0.10 eq.) and palladium complex **3.12** (*White* catalyst) (5.0 mg 0.01 mmol, 0.10 eq.) the desired dioxolane was obtained in the crude reaction mixture (NMR yield: 10%).

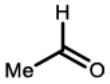
2-(3,5-Dinitrophenyl)-2-(trifluoromethyl)-4-vinyl-1,3-dioxolane [3.23]

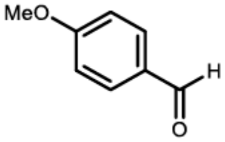


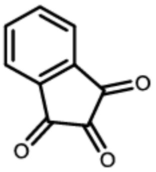
By following **GP-E**, using or 3'5'-dinitro-2,2,2-trifluoroacetophenone **2.20** (26.4 mg, 0.10 mmol, 1.00 eq.), but-3-en-1-ol (8.6 µL, 0.10 mmol, 1.00 eq.), 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq), (Cl)Cr^{III}·salen **3.25** (6.3 mg, 0.01 mmol, 0.10 eq.) and palladium complex **3.12** (*White* catalyst) (5.0 mg

0.01 mmol, 0.10 eq.) the desired dioxolane was obtained in the crude reaction mixture (NMR yield: 54%).

Limitations







By following **GP-E**, using the above shown aldehydes or ketones (0.10 mmol, 1.00 eq.) in combination with but-3-en-1-ol (8.6 µL, 0.10 mmol, 1.00 eq.), 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq), $(Cl)Cr^{III}$·salen **3.25** (6.3 mg, 0.01 mmol, 0.10 eq.) and palladium complex **3.12** (5.0 mg 0.01 mmol, 0.10 eq.) no product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard.

6.4 Cyclic alcohols as platform for the synthesis of *N*-heterocycles

General procedure F (GP-F) for the preparation of 3-substituted cyclobutanols from cyclobutanone with lithium organyls:

3-Substituted cyclobutanols were prepared following a lab-own protocol.[82] A halogenated arene (1.20 eq.) or monosubstituted alkyne (1.20 eq.) was dissolved in dry THF (0.1 M) under inert atmosphere and cooled to −78°C at which temperature *n*-BuLi (2.5 M, 1.20 eq.) was added dropwise. After 1 h, oxetan-3-one (1.00 eq.) was added slowly and the mixture was stirred at −78°C for 3 h, before it was slowly warmed up to rt for 17 h. The solution was diluted with Et_2O and NH_4Cl sat. aq. was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The products were isolated after FC or automated FC.

General procedure G (GP-G) for the preparation of 3-substituted cyclobutanols from cyclobutanone with magnesium organyls:

3-Substituted cyclobutanols were prepared following a lab-own protocol.[164] Grignard reagents were either commercially available or prepared as follows.

Magnesium turnings (1.20 eq.) were activated with iodine vapour prior to reaction. The activated magnesium was placed in a flask and dry THF (2 M) was added. Haloarene (1.30 eq.) was added slowly to maintain exothermic reaction. The mixture was stirred for 1 h at 60 °C, cooled to −20 °C and diluted with dry THF (0.1 M). Cyclobutanone (1.00 eq.) was added slowly and stirred for 3 h, before it was slowly warmed up to rt for 17 h. The solution was diluted with Et_2O and NH_4Cl sat. aq. was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The products were isolated after FC or automated FC.

General procedure H (GP-H) for the preparation of tertiary alcohols from benzannulated cyclic ketones:

Tertiary alcohols were prepared following a lab-own protocol.[82] A benzannulated cyclic ketone (1.00 eq.) was dissolved in dry THF (0.1 M) under inert atmosphere and cooled to −20°C at which temperature MeMgBr (3.0 M, 1.2 eq.) was added and stirred for 3 h, before it was slowly warmed up to rt for 17 h. The solution was diluted with Et_2O and NH_4Cl sat. aq. was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The products were isolated after FC or automated FC.

General procedure I (GP-I) for the preparation of Boc-protected sulfonylhydroxylamines:

Following a modified procedure of *Wang et al.*,[157] an arylsulfonyl chloride (1.00 eq.) and *tert*-butyl *N*-hydroxycarbamate (1.00 eq.) were dissolved in MTBE (0.25 M) and cooled to 0 °C. NEt_3 (1.10 eq.) was added slowly and the mixture was stirred for 1 h at 0 °C, the mixture was warmed to rt and stirred for 2 h. The mixture was filtered, and the residue was washed with small portions of cold MTBE. The filtrate was reduced to 1/10 of its original volume. Hexane (10-fold excess) was added, and the mixture was stirred until precipitation started. The precipitate was filtered off and washed with hexane. The residue was dried to yield Boc-protected sulfonylhydroxylamines as colourless solids. The products were either used without further purification or isolated after recrystallisation (RC) or FC.

General procedure J (GP-J) for the deprotection of Boc-protected sulfonylhydroxylamines:

Following a modified procedure of *Wang et al.*,[157] Boc-protected sulfonyl hydroxylamine (1.00 eq.) was dissolved in trifluoroacetic acid (0.8 M) at 0 °C and stirred for 3 h. The mixture was poured on ice water and stirred for another 30 min. The resulting colourless precipitate was filtered off and washed with cold water. The crude product was redissolved in a small portion of Et_2O and cooled to 0 °C at which temperature pentane (5-fold excess) was added and stirred for 30 min. The colourless precipitate was filtered off and dried under vacuum for a short period of time to yield the desired product. The products were either used without further purification or isolated after RC or FC.

General procedure K (GP-K) for the *N*-insertion of cyclic tertiary alcohols:

Cyclobutanol or other cyclic tertiary alcohol (300 µmol, 1.00 eq.) was dissolved in HFIP (0.2 M) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) was added at 0 °C. The mixture was immediately warmed to rt and stirred for 3 h before being cooled to 0 °C. NEt_3 (54.4 µL, 330 µmol, 1.30 eq.) was added and the solvent was removed. NMR yield of the crude reaction mixture was determined by ^1H NMR using CH_2Br_2 (7.0 µL, 0.10 mmol) as the internal standard. The product was separated by silica gel column chromatography or preparative TLC.

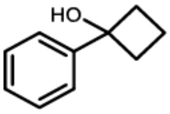
General procedure L (GP-L) for the *N*-insertion of benzannulated cyclic tertiary alcohols:

Cyclic tertiary alcohol (300 µmol, 1.00 eq.) was dissolved in HFIP (0.2 M) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) was added at 0 °C. The mixture was stirred for 3h at rt at which point sodium borohydride (45.4 mg, 1.20 mmol, 4.00 eq.) was added, and stirred for 2 h followed by the addition of NaOH aq. (2N, 2 mL). The aqueous phase was extracted with CH_2Cl_2 (3x4 mL). the combined organic fractions were dried over Na_2SO_4, and the solvent was removed. The residue was subjected to quantitative NMR. The desired product was obtained after automated FC.

6.4.1 Synthesis of starting materials

6.4.1.1 Synthesis of cyclobutanols and other cyclic alcohols

3-Phenylcyclobutanol [4.5]

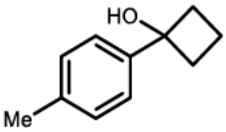


Following **GP-G**, using cyclobutanone (701 mg, 734 µL, 10.0 mmol, 1.00 eq.) and phenylmagnesiumbromide (7.50 mL, 12.0 mmol, 1.60 M, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85) as a colourless solid (1261 mg, 8.51 mmol, 85%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.54 – 7.49 (m, 2H), 7.42 – 7.35 (m, 2H), 7.32 – 7.26 (m, 1H), 2.65 – 2.52 (m, 2H), 2.44 – 2.31 (m, 2H), 2.10 – 1.94 (m, 1H), 1.78 – 1.61 (m, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 146.4, 128.6, 127.4, 125.1, 77.4, 37.0, 13.1. Spectroscopic data was in agreement to those previously reported.[141]

Chemotion ELN sample number: ASS-11-6-A and ASS-13-99.

1-(*p*-Tolyl)cyclobutan-1-ol [4.17]

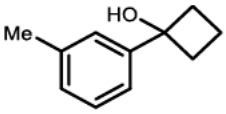


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-bromo-4-methyl-benzene (1.03 g, 738 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90) as a colourless solid (417 mg, 2.57 mmol, 51%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.43 – 7.36 (m, 2H), 7.22 – 7.16 (m, 2H), 2.63 – 2.49 (m, 2H), 2.43 – 2.30 (m, 5H), 2.08 – 1.92 (m, 1H), 1.88 (s, 1H), 1.66 (app. dtt, J = 11.2, 8.8, 7.6 Hz, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 143.4, 137.1, 129.3, 125.1, 77.0, 37.0, 21.2, 13.1. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-12-44-A.

1-(*m*-Tolyl)cyclobutan-1-ol [4.18]

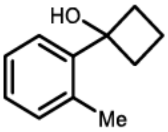


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-iodo-3-methylbenzene (1.31 g, 770 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90) as a colourless solid (166 mg, 1.02 mmol, 20%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.35 – 7.23 (m, 3H), 7.14 – 7.07 (m, 1H), 2.65 – 2.51 (m, 2H), 2.43 – 2.30 (m, 5H), 2.10 – 1.94 (m, 2H), 1.69 (app. dtt, *J* = 11.2, 8.8, 7.4 Hz, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 146.3, 138.2, 128.5, 128.1, 125.9, 122.1, 77.2, 36.9, 21.7, 13.2. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-12-57-B.

1-(o-Tolyl)cyclobutan-1-ol [4.19]

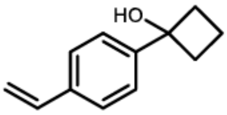


Following **GP-G**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.) and *o*-tolylmagnesium bromide (1.00 M, 6.00 mL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90) as a colourless solid (544 mg, 3.35 mmol, 67%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.33 – 7.27 (m, 1H), 7.20 – 7.16 (m, 3H), 2.78 – 2.60 (m, 2H), 2.46 – 2.34 (m, 5H), 2.27 – 2.11 (m, 1H), 1.83 – 1.65 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 143.0, 137.2, 131.9, 127.9, 125.6, 125.3, 79.2, 36.1, 20.3, 14.9. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-12-63-1.

1-(4-Vinylphenyl)cyclobutan-1-ol [4.20]

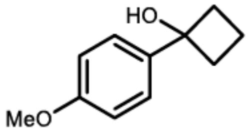


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.) *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-bromo-4-vinylbenzene (1.10 g, 784 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90) as a colourless oil (544 mg, 3.35 mmol, 67%).

IR (neat): $\tilde{\nu}$ = 3359 (w), 2985 (w), 2942 (w), 1629 (w), 1511 (w), 1423 (w), 1401 (w), 1285 (w), 1243 (m), 1137 (m), 1112 (m), 1015 (m), 989 (m), 904 (m), 843 (s), 529 (m). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 7.50 – 7.39 (m, 4H, C*H*$_{arom.}$), 6.73 (dd, *J* = 17.6, 10.9 Hz, 1H, C*H*), 5.76 (dd, *J* = 17.6, 1.0 Hz, 1H, C*H*$_2$), 5.26 (dd, *J* = 10.8, 1.0 Hz, 1H, C*H*$_2$), 2.62 – 2.49 (m, 2H, C*H*$_2$), 2.44 – 2.29 (m, 2H, C*H*$_2$), 2.13 (s, 1H O*H*), 2.10 – 1.93 (m, 1H, C*H*$_2$), 1.69 (app. dtt, *J* = 11.2, 8.8, 7.6 Hz, 1H, C*H*$_2$). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 145.9 (C_q), 136.7 (C_q), 136.5 (*C*H), 126.4 (*C*H), 125.3 (*C*H), 114.0 (*C*H$_2$), 76.9 (C_q), 37.0 (*C*H$_2$), 13.1 (*C*H$_2$). **HRMS (APCI)**: Calculated for $C_{12}H_{13}$ [M-OH]$^+$: 157.1012, Found: 157.1009.

Chemotion ELN sample number: ASS-13-43-B.

1-(4-Methoxyphenyl)cyclobutan-1-ol [4.21]

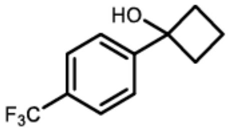


Following **GP-G** with minor alterations, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.) and *p*-methoxy-phenylmagnesium bromide (1.00 M, 6.00 mL, 5.25 mmol, 1.05 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85) as a colourless oil (458 mg, 2.57 mmol, 51%).

^{1}H NMR (300 MHz, C$_6$D$_6$): δ = 7.37 – 7.30 (m, 2H), 6.86 – 6.77 (m, 2H), 3.34 (s, 3H), 2.45 – 2.33 (m, 2H), 2.29 – 2.15 (m, 2H), 1.94 – 1.77 (m, 1H), 1.71 (s, 1H), 1.52 (app. dtt, *J* = 11.0, 8.8, 7.6 Hz, 1H). **^{13}C NMR (75 MHz, C$_6$D$_6$)**: δ = 158.9, 139.0, 126.3, 113.6, 76.2, 54.5, 37.2, 13.0. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-11-32-A.

1-(4-(Trifluoromethyl)phenyl)cyclobutan-1-ol [4.22]

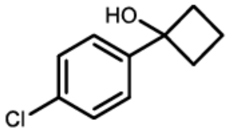


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.) *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-bromo-4-(trifluoromethyl)benzene (840 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a colourless solid (670 mg, 3.10 mmol, 62%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.66 – 7.58 (m, 4H), 2.62 – 2.50 (m, 2H), 2.45 – 2.33 (m, 2H), 2.15 – 2.00 (m, 2H), 1.82 – 1.68 (m, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 150.3, 129.5 (q, $^2J_{C,F}$ = 32.4 Hz), 125.5 (q, $^4J_{C,F}$ = 3.7 Hz), 125.4, 124.3 (q, $^1J_{C,F}$ = 271.8 Hz), 76.8, 37.3, 13.1. **^{19}F NMR (282 MHz, CDCl$_3$)**: – 62.4 (s, 3F). Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-11-67-A.

1-(4-Chlorophenyl)cyclobutan-1-ol [4.23]

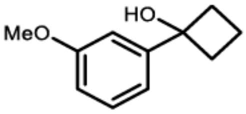


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.) *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-bromo-4-chlorobenzene (1.15 g, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a colourless oil (747 mg, 4.09 mmol, 82%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.47 – 7.40 (m, 2H), 7.36 – 7.30 (m, 2H), 2.60 – 2.46 (m, 2H), 2.43 – 2.30 (m, 2H), 2.11 – 1.95 (m, 2H), 1.78 – 1.61 (m, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 144.9, 133.1, 128.7, 126.6, 76.7, 37.2, 13.1. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-12-68-B.

1-(3-Methoxyphenyl)cyclobutan-1-ol [4.24]

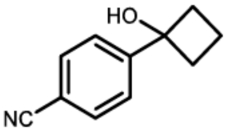


Following **GP-G**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), magnesium turnings (146 mg, 6.00 mmol, 1.20 eq.) and 1-bromo-3-methoxybenzene (823 µL, 6.50 mmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85 to 35:65) as a colourless solid (500 mg, 3.81 mmol, 56%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.30 (app. t, J = 7.9 Hz, 1H), 7.09 (ddd, J = 7.6, 1.7, 1.0 Hz, 1H), 7.05 (dd, J = 2.6, 1.7 Hz, 1H), 6.83 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 3.83 (s, 3H), 2.62 – 2.48 (m, 2H), 2.43 – 2.28 (m, 2H), 2.11 – 1.94 (m, 2H), 1.70 (app. dtt, J = 11.2, 8.8, 7.4 Hz, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 159.9, 148.2, 129.6, 117.4, 112.6, 111.0, 77.1, 55.4, 37.0, 13.2. Spectroscopic data was in agreement to those previously reported.[152e]

Chemotion ELN sample number: ASS-13-72-B.

4-(1-Hydroxycyclobutyl)benzonitrile [4.25]

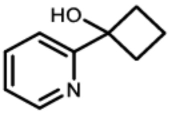


4-(1-Hydroxycyclobutyl)benzonitrile was prepared according to a literature known procedure.[152d] 4-Iodobenzonitrile (1.37 g, 6.00 mmol, 1.20 eq.) was dissolved in dry THF (20 mL) and isopropylmagnesium chloride lithium chloride complex (1.30 M, 4.62 mL, 6.00 mmol, 1.20 eq.) was added dropwise. The mixture was stirred for 4 h at 0°C prior to addition of cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.). The mixture was stirred for 1 h at 0 °C and for 2 h at rt before Et_2O (20 mL) and NH_4Cl sat. aq. (20 mL) were added. The aqueous phase was separated and extracted with Et_2O (3x20 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed. Automated FC (EtOAc:CyH, 20:80 to 30:70) delivered the product as a colourless solid (803 mg, 4.64 mmol, 93%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.68 – 7.57 (m, 4H), 2.58 – 2.46 (m, 2H), 2.45 – 2.32 (m, 2H), 2.26 (s, 1H), 2.16 – 2.00 (m, 1H), 1.76 (app. dtt, J = 11.5, 8.9, 7.3 Hz, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 151.7, 132.4, 125.8, 119.0, 110.9, 76.7, 37.4, 13.1. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-11-49-A.

1-(Pyridin-2-yl)cyclobutan-1-ol [4.26]

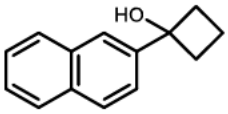


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.) *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 2-bromo-pyridine (570 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 20:80 to 40:60) as a yellow oil (589 mg, 3.95 mmol, 79%).

IR (neat): $\tilde{\nu}$ = 2939 (m), 1591 (s), 1473 (s), 1434 (m), 1296 (s), 1244 (m), 1143 (s), 1072 (s), 788 (m), 749 (s). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 8.51 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, C*H*$_{\text{arom.}}$), 7.75 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H, C*H*$_{\text{arom.}}$), 7.58 (dt, *J* = 8.0, 1.1 Hz, 1H, C*H*$_{\text{arom.}}$), 7.21 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H, C*H*$_{\text{arom.}}$), 2.64 – 2.42 (m, 4H, C*H*$_2$), 2.16 – 2.00 (m, 1H, C*H*$_2$), 1.97 – 1.78 (m, 1H, C*H*$_2$). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 164.5, 147.5, 137.4, 122.2, 118.6, 75.8, 37.6, 13.1. **HRMS (ESI)**: Calculated for $C_9H_{12}NO$ [M+H]$^+$: 150.0913, Found: 150.0913.

Chemotion ELN sample number: ASS-12-52-B.

1-(Naphthalen-2-yl)cyclobutan-1-ol [4.27]

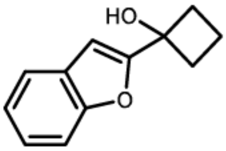


Following **GP-G**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), Magnesium turnings (146 mg, 6.00 mmol, 1.20 eq.) and 2-bromonaphthalene (823 µL, 6.50 mmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a colourless solid (606 mg, 3.06 mmol, 61%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.96 – 7.79 (m, 4H), 7.64 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.55 – 7.44 (m, 2H), 2.76 – 2.61 (m, 2H), 2.45 (app. tdd, *J* = 9.4, 7.5, 2.9 Hz, 2H), 2.15 (s, 1H), 2.13 – 1.99 (m, 1H), 1.84 – 1.66 (m, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 143.4, 133.2, 132.7, 128.6, 128.3, 127.7, 126.3, 126.1, 124.1, 123.1, 77.2, 36.8, 13.2. Spectroscopic data was in agreement to those previously reported.[152e]

Chemotion ELN sample number: ASS-13-48-B.

1-(Benzofuran-2-yl)cyclobutan-1-ol [4.28]

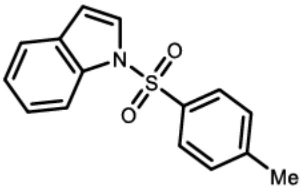


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and benzofuran (661 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95) as a colourless solid (822 mg, 4.37 mmol, 87%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.58 – 7.53 (m, 1H), 7.50 – 7.45 (m, 1H), 7.32 – 7.19 (m, 2H), 6.68 (d, J = 0.9 Hz, 1H), 2.70 – 2.58 (m, 2H), 2.49 – 2.35 (m, 2H), 2.05 – 1.90 (m, 1H), 1.88 – 1.70 (m, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 160.8, 155.2, 128.3, 124.3, 122.9, 121.2, 111.4, 101.7, 72.8, 35.7, 13.0. Spectroscopic data was in agreement to those previously reported.

Chemotion ELN sample number: ASS-13-17-B.

1-Tosyl-1*H*-indole [6.6]

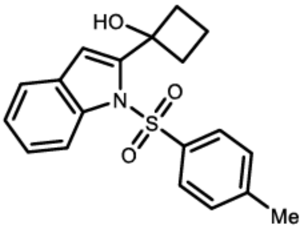


Following a literature known protocol,[219] 1*H*-Indole (937 mg, 8.00 mmol, 1.00 eq.) was dissolved in THF (40 mL) and cooled to 0 °C prior to addition of sodium hydride (60 m/m%, 480 mg, 12.0 mmol, 1.50 eq.). The mixture was stirred for 30 min at 0 °C before 4-methylbenzenesulfonyl chloride (1.68 g, 8.80 mmol, 1.10 eq.) was added. The mixture was warmed to rt and stirred for 3 h. Water (30 mL) was added and the aqueous phase was extracted with EtOAc (3x30 mL). The combined organic fractions were washed with NaHCO$_3$ sat. aq. (30 mL) and NaCl sat. aq. (30 mL). The organic extracts were dried over NaSO$_4$ and the solvent was removed. automated FC (EtOAc:CyH, 20:80) delivered a colourless solid (2.02 g, 7.43 mmol, 93%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.00 (dt, J = 8.3, 1.0 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.57 (d, J = 3.7 Hz, 1H), 7.53 (ddd, J = 7.7, 1.3, 0.8 Hz, 1H), 7.31 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.22 (ddd, J = 7.8, 7.2, 1.2 Hz, 3H), 6.66 (dd, J = 3.7, 0.8 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 145.0, 135.4, 134.9, 130.9, 130.0, 126.9, 126.5, 124.7, 123.4, 121.5, 113.7, 109.1, 21.7. Spectroscopic data was in agreement to those previously reported.[219]

Chemotion ELN sample number: ASS-12-69-A.

1-(1-Tosyl-1*H*-indol-2-yl)cyclobutan-1-ol [4.29]

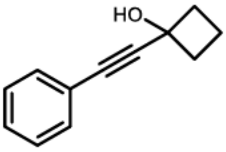


Following **GP-F**, using cyclobutanone (210 mg, 220 µL, 3.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and 1-tosyl-1*H*-indole **7.6** (977 mg, 3.60 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 20:80) as a colourless solid (873 mg, 2.56 mmol, 85%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.88 (ddd, J = 7.5, 1.8, 0.8 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.51 – 7.45 (m, 1H), 7.25 – 7.19 (m, 2H), 7.19 – 7.14 (m, 2H), 6.74 (d, J = 0.8 Hz, 1H), 2.75 – 2.63 (m, 2H), 2.57 – 2.48 (m, 2H), 2.31 (s, 3H), 2.17 – 2.03 (m, 1H), 1.74 (dtt, J = 11.0, 8.8, 7.0 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 145.9, 145.0, 137.5, 136.0, 129.9, 128.8, 126.6, 125.1, 123.9, 121.3, 114.8, 110.0, 73.2, 36.5, 21.7, 14.4. Spectroscopic data was in agreement to those previously reported.[152c]

Chemotion ELN sample number: ASS-12-81-A.

1-(Phenylethynyl)cyclobutan-1-ol [4.30]

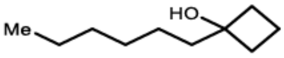


Following **GP-F**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), *n*-BuLi (2.50 M, 2.40 mL, 6.00 mmol, 1.20 eq.) and phenylacetylene (613 mg, 659 µL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85 to 20:80) as a colourless solid (829 mg, 4.81 mmol, 96%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 – 7.41 (m, 2H), 7.34 – 7.27 (m, 3H), 2.59 – 2.48 (m, 2H), 2.41 – 2.29 (m, 3H), 1.93 – 1.81 (m, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 131.7, 128.3, 128.3, 122.7, 92.5, 83.5, 68.3, 38.6, 13.0. Spectroscopic data was in agreement to those previously reported.[152b]

Chemotion ELN sample number: ASS-13-38-B.

1-Hexylcyclobutan-1-ol [4.31]

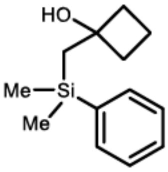


Following **GP-G**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), magnesium turnings (146 mg, 6.00 mmol, 1.20 eq.) and 1-bromohexane (909 µL, 6.50 mmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a colourless oil (207 mg, 1.32 mmol, 26%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.12 – 1.90 (m, 4H), 1.81 – 1.68 (m, 1H), 1.64 (d, J = 3.7 Hz, 1H), 1.62 – 1.44 (m, 3H), 1.41 – 1.21 (m, 8H), 0.94 – 0.83 (m, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 75.5, 39.7, 36.1, 32.0, 29.9, 23.5, 22.8, 14.2, 12.3. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-13-56-B.

1-((Dimethyl(phenyl)silyl)methyl)cyclobutan-1-ol [4.32]



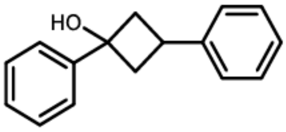
Following **GP-G**, using cyclobutanone (367 µL, 5.00 mmol, 1.00 eq.), magnesium turnings (146 mg, 6.00 mmol, 1.20 eq.) and chloromethyl-dimethylphenylsilane (1.17 mL, 6.50 mmol, 1.30 equiv), the desired product was obtained after automated FC (EtOAc:CyH, 20:80) as a colourless oil (175 mg, 0.79 mmol, 16%).

IR (neat): $\tilde{\nu}$ = 3416 (w), 2955 (m), 1427 (m), 1247 (m), 1217 (w), 1112 (m), 1058 (w), 998 (w), 961 (w), 833 (s), 805 (m), 732 (m), 699 (m), 468 (w). **^{1}H NMR**

(300 MHz, CDCl$_3$): δ = 7.61 – 7.53 (m, 2H, C*H*$_{arom.}$), 7.39 – 7.32 (m, 3H, C*H*$_{arom.}$), 2.02 (app. tq, *J* = 7.2, 2.0 Hz, 4H, C*H*$_2$), 1.79 – 1.65 (m, 1H, C*H*$_2$), 1.64 – 1.46 (m, 2H, C*H*$_2$), 1.38 (s, 2H, C*H*$_2$), 0.37 (s, 6H, C*H*$_3$). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 140.2 (*C*$_q$), 133.8 (*C*H), 129.0 (*C*H), 128.0 (*C*H), 76.3 (*C*$_q$), 39.8 (*C*H$_2$), 29.4 (*C*H$_2$), 12.4 (*C*H$_2$), -1.3 (*C*H$_3$). **HRMS (APCI)**: Calculated for $C_{13}H_{20}OSiNa^+$ [M+Na]$^+$: 243.1176, Found: 243.1167.

Chemotion ELN sample number: ASS-13-8-B.

1,3-Diphenylcyclobutan-1-ol [4.33]

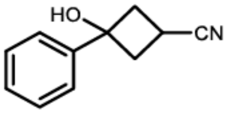


Following **GP-G**, using 3-phenylcyclobutanone[142c] (731 mg, 5.00 mmol, 1.00 eq.) and phenylmagnesium bromide (1.60 M, 3.44 mL, 5.50 mmol, 1.10 eq.), the desired product was obtained as a mixture of two diasteroisomers after automated FC (EtOAc:CyH, 10:90) as a colourless solid (430 mg, 1.92 mmol, 38%).

Major: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.72 – 7.65 (m, 2H), 7.52 – 7.44 (m, 2H), 7.42 – 7.31 (m, 5H), 7.30 – 7.22 (m, 1H), 3.18 – 3.03 (m, 3H), 2.67 – 2.54 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 145.3, 144.7, 128.7, 128.4, 127.7, 126.7, 126.2, 125.5, 72.5, 44.6, 30.0. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-11-48-A.

3-Hydroxy-3-phenylcyclobutane-1-carbonitrile [4.34]



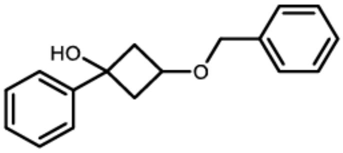
Following **GP-G**, using 3-oxocyclobutane-1-carbonitrile (475 mg, 5.00 mmol, 1.00 eq.) and phenylmagnesium bromide (1.60 M, 3.44 mL, 5.50 mmol, 1.10 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 30:70) as a colourless oil (401 mg, 2.32 mmol, 46%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 – 7.39 (m, 4H), 7.37 – 7.32 (m, 1H), 3.06 – 2.97 (m, 2H), 2.85 – 2.66 (m, 3H), 2.26 (s, 1H). **^{13}C NMR (101 MHz,**

$CDCl_3$): δ = 143.2, 129.1, 128.5, 125.1, 122.0, 74.1, 41.5, 13.9. Spectroscopic data was in agreement to those previously reported.[220]

Chemotion ELN sample number: ASS-13-39-B.

3-(Benzyloxy)-1-phenylcyclobutan-1-ol [4.35]

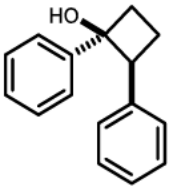


Following **GP-G**, using 3-(benzyloxy)cyclobutan-1-one (808 µL, 5.00 mmol, 1.00 eq.) and phenylmagnesium bromide (1.60 M, 3.44 mL, 5.50 mmol, 1.10 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 20:80) as a colourless oil (359 mg, 1.41 mmol, 28%).

IR (neat): $\tilde{\nu}$ = 3416 (w), 3030 (w), 2985 (w), 2937 (w), 1495 (w), 1448 (w), 1349 (w), 1238 (m), 1156 (m), 1095 (m), 1052 (s), 1027 (m), 913 (w), 752 (m), 697 (s), 554 (w). **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.52 – 7.45 (m, 2H, C$H_{arom.}$), 7.41 – 7.33 (m, 6H, C$H_{arom.}$), 7.33 – 7.27 (m, 2H, C$H_{arom.}$), 4.47 (s, 2H, CH_2), 3.86 (app. p, J = 6.7 Hz, 1H), 3.01 – 2.88 (m, 2H, CH_2), 2.53 – 2.40 (m, 2H, CH_2), 2.22 (s, 1H, OH). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 145.5 (C_q), 138.1 (C_q), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 125.3 (CH), 70.7 (CH$_2$), 70.5 (C_q), 65.5 (CH), 45.4 (CH$_2$). **HRMS (ESI)**: Calculated for $C_{17}H_{18}O_2Na^+$ $[M+Na]^+$: 277.1199, Found: 277.1200.

Chemotion ELN sample number: ASS-12-98-A.

trans 1,2-Diphenylcyclobutan-1-ol [4.36]

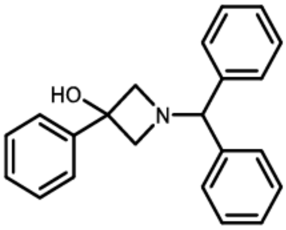


Following **GP-G**, using 2-phenylcyclobutanone[142c] (470 mg, 3.22 mmol, 1.00 eq.) and phenylmagnesium bromide (1.60 M, 2.41 mL, 3.86 mmol, 1.20 eq.), the desired product was obtained after automated FC (CH_2Cl_2) as a colourless oil (387 mg, 1.73 mmol, 54%)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.52 – 7.48 (m, 2H), 7.41 – 7.36 (m, 2H), 7.35 – 7.31 (m, 2H), 7.31 – 7.26 (m, 2H), 7.25 – 7.21 (m, 2H), 4.01 (m, 1H), 2.71 – 2.49 (m, 2H), 2.34 – 2.22 (m, 2H), 1.74 (s, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 146.6, 138.2, 128.6, 128.4, 127.0, 124.9, 79.8, 50.6, 33.9, 20.8.[k] Spectroscopic data was in agreement to those previously reported.[152a]

Chemotion ELN sample number: ASS-13-16-B.

1-Benzhydryl-3-phenylazetidin-3-ol [4.37]

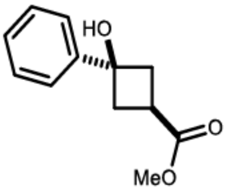


Following **GP-G**, using 1-benzhydrylazetidin-3-one (763 mg, 3.22 mmol, 1.00 eq.) and phenylmagnesium bromide (1.60 M, 2.41 mL, 3.86 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a colourless oil (568 mg, 1.80 mmol, 56%)

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.72 – 7.61 (m, 2H), 7.55 – 7.42 (m, 6H), 7.40 – 7.28 (m, 5H), 7.28 – 7.18 (m, 2H), 4.54 (s, 1H), 3.66 (d, J = 8.3 Hz, 2H), 3.47 (d, J = 8.5 Hz, 2H), 2.83 (s, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 144.2, 142.0, 128.6, 127.7, 127.6, 127.4, 125.1, 78.1, 71.6, 67.7.[l] Spectroscopic data was in agreement to those previously reported.[221]

Chemotion ELN sample number: ASS-13-28-B.

Methyl *trans* 3-hydroxy-3-phenylcyclobutane-1-carboxylate [4.38]



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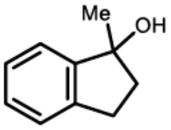
[k] Two signals missing due to signal overlap.
[l] One signal missing due to signal overlap.

According to a literature known protocol,[153] 3-oxocyclobutane-1-carboxylic acid (570 mg, 5.00 mmol 1.00 eq.) was dissolved in dry THF (0.1 M) under inert atmosphere and cooled to –78°C at which temperature PhMgBr (1.6 M, 6.88 mL, 11.0 mmol, 2.20 eq.) was added and stirred for 1 h, before it was slowly warmed up to rt for 17 h. The solution was diluted with Et_2O (20 mL) and NH_4Cl sat. aq. (20 mL) was added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3x20 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude material was used without further purification and was dissolved in DMF (5 mL) with K_2CO_3 (829 mg, 6.00 mmol, 1.20 eq.) and iodomethane (374 µL, 6.00 mmol, 1.20 eq.) was added slowly at rt. The mixture was stirred for 24 h before water (5 mL) was added. The aqueous mixture was extracted with EtOAc (3x10 mL). The combined organic fractions were washed with LiCl aq. (5% w/w, 20 mL) and dried over Na_2SO_4. The desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a colourless oil (751 mg, 3.64 mmol, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 – 7.47 (m, 2H), 7.42 – 7.35 (m, 2H), 7.33 – 7.27 (m, 1H), 3.73 (s, 3H), 3.13 (s, 1H), 2.94 – 2.77 (m, 3H), 2.71 – 2.57 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 176.7, 144.9, 128.7, 127.7, 125.1, 73.6, 52.3, 40.9, 29.7. Spectroscopic data was in agreement to those previously reported.[153]

Chemotion ELN sample number: ASS-13-5-A.

1-Methyl-2,3-dihydro-1*H*-inden-1-ol [4.41]



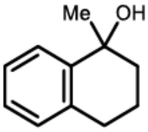
Following **GP-H** with minor alterations, using 2,3-dihydro-1*H*-inden-1-one (661 mg, 5.00 mmol, 1.00 eq.) and methyllithium (3.00 M, 1.83 mL, 5.50 mmol, 1.10 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85) as a colourless solid (210 mg, 1.42 mmol, 28%).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.28 – 7.22 (m, 1H), 7.13 – 7.08 (m, 2H), 7.06 – 7.01 (m, 1H), 2.80 – 2.66 (m, 1H), 2.51 (dddd, J = 15.9, 7.6, 6.9, 0.7 Hz, 1H), 1.90 (td, J = 6.6, 0.9 Hz, 2H), 1.44 (s, 1H), 1.38 (s, 3H). **^{13}C NMR (101 MHz,**

C_6D_6): δ = 149.3, 142.7, 128.2, 127.0, 125.0, 122.7, 80.9, 42.6, 29.6, 27.7. Spectroscopic data was in agreement to those previously reported.[154a]

Chemotion ELN sample number: ASS-12-6-A.

1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol [4.42]

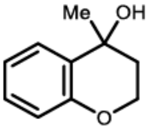


Following **GP-H** with minor alterations, using 3,4-dihydronaphthalen-1(2H)-one (665 µL, 5.00 mmol, 1.00 eq.) and methylmagnesium bromide (3.00 M, 1.83 mL, 5.50 mmol, 1.10 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85 to 20:80) as a colourless solid (201 mg, 1.24 mmol, 25%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 – 7.57 (m, 1H), 7.25 – 7.12 (m, 2H), 7.08 (app. ddt, J = 7.2, 1.4, 0.7 Hz, 1H), 2.92 – 2.68 (m, 2H), 2.11 – 1.78 (m, 4H), 1.76 (s, 1H), 1.57 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 143.0, 136.4, 129.0, 127.2, 126.5, 126.4, 70.7, 39.9, 30.9, 30.0, 20.5. Spectroscopic data was in agreement to those previously reported.[137a]

Chemotion ELN sample number: ASS-11-74-B.

4-Methylchroman-4-ol [4.43]

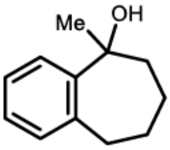


Following **GP-H** with minor alterations, using chroman-4-one (741 mg, 5.00 mmol, 1.00 eq.) and methylmagnesium bromide (3.00 M, 2.00 mL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85 to 25:75) as a colourless solid (155 mg, 944 µmol, 19%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (dd, J = 7.8, 1.7 Hz, 1H), 7.18 (ddd, J = 8.2, 7.2, 1.7 Hz, 1H), 6.94 (ddd, J = 7.8, 7.2, 1.3 Hz, 1H), 6.82 (dd, J = 8.2, 1.3 Hz, 1H), 4.34 – 4.18 (m, 2H), 2.12 – 2.04 (m, 2H), 1.89 (s, 1H), 1.63 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 154.0, 129.3, 128.5, 126.5, 120.9, 117.3, 66.5, 63.5, 38.2, 29.6. Spectroscopic data was in agreement to those previously reported.[137a]

Chemotion ELN sample number: ASS-13-63-A.

5-Methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol [4.44]

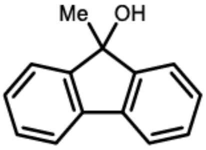


Following **GP-H** with minor alterations, using 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (801 mg, 748 µL, 5.00 mmol, 1.00 eq.) and methylmagnesium bromide (3.00 M, 2.00 mL, 6.00 mmol, 1.20 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a colourless oil (422 mg, 2.39 mmol, 48%)

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.68 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.21 (app. td, *J* = 7.4, 1.9 Hz, 1H), 7.14 (app. td, *J* = 7.3, 1.6 Hz, 1H), 7.11 – 7.05 (m, 1H), 3.04 – 2.82 (m, 2H), 2.03 – 1.75 (m, 6H), 1.70 (s, 1H), 1.60 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 147.3, 140.2, 131.0, 127.1, 126.3, 125.4, 75.9, 42.8, 37.0, 28.9, 28.1, 26.3. Spectroscopic data was in agreement to those previously reported.[137a]

Chemotion ELN sample number: ASS-12-70-B.

9-Methyl-9*H*-fluoren-9-ol [4.45]

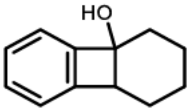


Following **GP-H** with minor alterations, using 9*H*-fluoren-9-one (367 µL, 5.00 mmol, 1.00 eq.) and methylmagnesium bromide (3.00 M, 1.83 mL, 5.50 mmol, 1.10 eq.), the desired product was obtained after recrystallisation from hot hexane as a colourless solid (806 mg, 4.11 mmol, 82%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.64 – 7.60 (m, 2H), 7.55 (ddd, *J* = 7.2, 1.4, 0.7 Hz, 2H), 7.39 – 7.29 (m, 4H), 1.98 (s, 1H) 1.73 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 149.9, 138.9, 129.0, 128.2, 123.4, 120.2, 79.7, 26.2. Spectroscopic data was in agreement to those previously reported.[154b]

Chemotion ELN sample number: ASS-11-60-A.

1,3,4,8b-Tetrahydrobiphenylen-4a(2H)-ol [4.46]

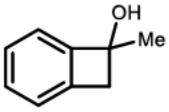


According to a literature known protocol,[152d] 2,2,6,6-tetramethylpiperidine (2.11 mL, 12.5 mmol, 2.50 eq.) was dissolved in THF (15 mL) and cooled to −78 °C at which temperature *n*-BuLi (2.5 M, 5.00 mL, 12.5 mmol, 2.50 eq.) was added dropwise over 10 min. The mixture was stirred for 30 min before cyclohexanone (517 µL, 5.00 mmol, 1.00 eq.) dissolved in THF (6 mL) was added followed by the addition of iodobenzene (560 µL, 5.00 mmol, 1.00 eq.). The mixture was stirred for 20 h at −78°C before it was diluted with Et_2O and NH_4Cl sat. aq. was added. The aqueous phase was extracted with Et_2O (3x) and the combined organic fractions were dried over Na_2SO_4. The solvent was removed and automated FC (EtOAc:CyH, 5:95 to 10:90) delivered a colourless solid (153 mg, 878 µmol, 18%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 – 7.21 (m, 2H), 7.16 (app. ddt, J = 7.1, 6.4, 1.2 Hz, 2H), 3.39 (t, J = 5.1 Hz, 1H), 2.11 – 1.92 (m, 3H), 1.87 – 1.74 (m, 1H), 1.67 – 1.41 (m, 3H), 1.38 – 1.23 (m, 1H), 1.22 – 1.05 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 149.5, 145.7, 129.3, 127.7, 123.3, 121.2, 79.2, 53.8, 31.7, 23.9, 18.0, 17.6. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-13-7-A.

7-Methylbicyclo[4.2.0]octa-1,3,5-trien-7-ol [4.48]

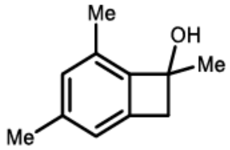


Similar to a literature known protocol,[155] 1-(*o*-tolyl)ethan-1-one (262 µL, 2.00 mmol, 1.00 eq.) was dissolved in acetonitrile (100 mL). A stream of N_2 was passed through the solution for 15 min. The solution was irradiated afterwards in a Luzchem photoreactor with UV-A light (355 nm) for 17 h. The solvent was removed, automated FC (EtOAc: CyH, 10:90 to 20:80) gave the starting material (224 mg, 1.67 mmol, 83%) and the desired product (43.0 mg, 320 µmol, 16%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31 – 7.26 (m, 1H), 7.23 (app. tq, J = 7.6, 0.9 Hz, 1H), 7.19 – 7.14 (m, 2H), 3.39 – 3.30 (m, 1H), 3.22 (d, J = 14.1 Hz, 1H), 2.47 (s, 1H) 1.66 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 151.2, 141.3, 129.4, 127.4, 124.2, 120.6, 78.4, 48.4, 25.8. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-11-81-A.

3,5,7-Trimethylbicyclo[4.2.0]octa-1,3,5-trien-7-ol [4.49]

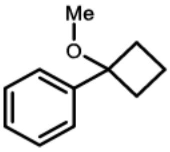


Similar to a literature known protocol,[155] 1-(*o*-tolyl)ethan-1-one (262 µL, 2.00 mmol, 1.00 eq.) was dissolved in acetonitrile (100 mL). A stream of N_2 was passed through the solution for 15 min. The solution was irradiated afterwards with a Pyrex filtered medium pressure Hg-lamp (400 W) for 17 h. The solvent was removed, automated FC (EtOAc: CyH, 5:95 to 10:90) gave the starting material (718 mg, 4.43 mmol, 55%) and the desired product (198 mg, 1.22 mmol, 15%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.83 (app. qd, J = 1.5, 0.7 Hz, 1H), 6.81 – 6.79 (m, 1H), 3.28 (d, J = 14.0 Hz, 1H), 3.13 (d, J = 14.1 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 1.69 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 146.0, 141.0, 139.3, 132.0, 129.3, 121.7, 78.2, 48.1, 25.0, 22.1, 16.6. Spectroscopic data was in agreement to those previously reported.[222]

Chemotion ELN sample number: ASS-13-25-B.

(1-Methoxycyclobutyl)benzene [4.51]

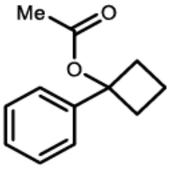


According to a literature known protocol,[152d] 1-phenylcyclobutan-1-ol **4.5** (296 mg, 2.00 mmol, 1.00 eq.) was dissolved in dry THF (10 mL) and NaH (60% w/w, 104 mg, 2.60 mmol, 1.30 eq.) was slowly added. Once gas evolution had ceased, the solution was cooled to 0 °C and methyl iodide (623 µL, 10.0 mmol, 5.00 eq.) was added slowly. The reaction mixture was stirred at rt for 7 h, before being cooled to 0 °C and water (15 mL) was added. The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 15 mL). The combined organic fractions were washed with water and NaCl sat. aq. and dried over $MgSO_4$, and the solvent was removed *in vacuo*. The product was isolated after automated FC (EtOAc:CyH, 5:95) as a colourless oil (119 mg, 734 µmol, 37%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.34 (m, 4H), 7.32 – 7.26 (m, 1H), 2.94 (s, 3H), 2.49 – 2.28 (m, 4H), 2.03 – 1.86 (m, 1H), 1.68 (app. dp, J = 11.1, 8.4 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 143.2, 128.4, 127.3, 126.4, 81.6, 50.6, 32.9, 13.1. Spectroscopic data was in agreement to those previously reported.[152d]

Chemotion ELN sample number: ASS-14-4-A.

1-Phenylcyclobutyl acetate [4.52]



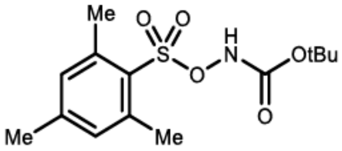
Similar to a literature known protocol,[156] 1-phenylcyclobutan-1-ol **4.5** (175 mg, 1.18 mmol, 1.00 eq.) and *N*,*N*-dimethylpyridin-4-amine (180 mg, 1.48 mmol, 1.25 eq.) were dissolved in dry CH_2Cl_2. Acetic anhydride (223 µL, 2.36 mmol, 2.00 eq.) was added and the mixture was stirred for 6 h at rt. The solvent was removed, and the residue was taken up into pentane (4 mL), the organic phase was washed with cold water (4 mL), dilute HCl (1N, 4 mL), water (4 mL), and $NaHCO_3$ sat. aq. (4 mL), and then dried over Na_2SO_4. The solvent was removed in vacuo leaving a colourless oil (191 mg, 1.00 mmol, 85%).

IR (neat): $\tilde{\nu}$ = 1737 (s), 1368 (m), 1237 (s), 1120 (w), 1107 (w), 1076 (w), 1062 (w), 1011 (w), 762 (w), 699 (m), 537 (w). **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.52 – 7.45 (m, 2H, $CH_{arom.}$), 7.36 (m, 2H, $CH_{arom.}$), 7.27 (m, 1H, $CH_{arom.}$), 2.77 – 2.50 (m, 4H, CH_2), 2.05 – 1.94 (m, 4H, CH_2 and CH_3), 1.84 – 1.64 (m, 1H, CH_2). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 169.6 (C_q), 142.8 (C_q), 128.4 (CH), 127.4 (CH), 125.7 (CH), 82.3 (C_q), 35.0 (CH_2), 21.8 (CH_3), 14.3 (CH_2). **HRMS (ESI)**: Calculated for $C_{12}H_{14}O_2Na^+$ $[M+Na]^+$: 213.0886, Found: 213.0881.

Chemotion ELN sample number: ASS-14-10-A.

6.4.1.2 Synthesis of *O*-sulfonylhydroxylamine reagents

tert-Butyl ((mesitylsulfonyl)oxy)carbamate [4.53]

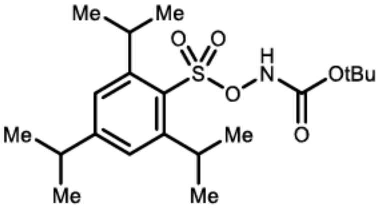


Following **GP-I**, using 2,4,6-trimethylbenzenesulfonyl chloride (10.9 g, 50.0 mmol, 1.00 eq.), *tert*-butyl *N*-hydroxycarbamate (6.66 g, 50.0 mmol, 1.00 eq.) and NEt_3 (7.67 mL, 55.0 mmol, 1.10 eq.), the desired product was obtained without further purification as a colourless solid (13.5 g, 42.7 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 6.99 (s, 2H), 2.67 (s, 6H), 2.32 (s, 3H), 1.31 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 154.3, 144.5, 142.1, 131.8, 128.6, 83.9, 27.8, 23.3, 21.2. Spectroscopic data was in agreement to those previously reported.[157]

Chemotion ELN sample number: ASS-13-73-A.

tert-Butyl (((2,4,6-triisopropylphenyl)sulfonyl)oxy)carbamate [4.54]

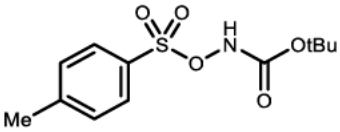


GP-I was followed with minor alterations, using 2,4,6-triisopropylbenzenesulfonyl chloride (1.59 g, 5.25 mmol, 1.05 eq.), *tert*-butyl *N*-hydroxycarbamate (666 mg, 5.00 mmol, 1.00 eq.) and NEt_3 (732 µL, 5.25 mmol, 1.05 eq.) in dry THF (20 mL). The organic phase was washed with HCl aq. (1N, 20 mL) and NaCl sat. aq. after filtration. The solvent was removed *in vacuo*. The desired product was obtained after automated FC (EtOAc:CyH, 5:95) as a colourless solid (1.22 g, 3.05 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.20 (s, 2H), 4.12 (hept, J = 6.8 Hz, 2H), 2.92 (hept, J = 6.9 Hz, 1H), 1.40 (s, 9H), 1.28 (d, J = 6.7 Hz, 12H), 1.25 (d, J = 6.9 Hz, 6H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 154.8, 154.4, 152.5, 127.8, 124.1, 83.9, 34.5, 30.2, 28.0, 24.9, 23.6. Spectroscopic data was in agreement to those previously reported.[157]

Chemotion ELN sample number: ASS-11-53-A.

tert-Butyl (tosyloxy)carbamate [4.57]

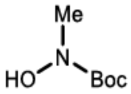


GP-I was followed with minor alterations, using 4-methylbenzenesulfonyl chloride (953 mg, 5.00 mmol, 1.00 eq.), *tert*-butyl *N*-hydroxycarbamate (699 mg, 5.25 mmol, 1.05 eq.) and NEt$_3$ (732 µL, 5.25 mmol, 1.05 eq.) in dry THF (20 mL). The mixture was stirred for 4 h. The resulting solids were filtered off and NaHCO$_3$ sat. aq. (10 mL) was added to the filtrate. The aqueous phase was extracted with CH$_2$Cl$_2$ (3x10 mL), and the combined organic fractions were dried over Na$_2$SO$_4$. The solvent was removed, and the residue was crystallised from hot hexane to yield a colourless solid (1.13 g, 3.94 mmol, 79%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.91 – 7.84 (m, 2H), 7.68 (s, 1H), 7.39 – 7.32 (m, 2H), 2.46 (s, 3H), 1.30 (s, 9H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 154.2, 146.1, 130.7, 129.8, 129.8, 84.0, 27.8, 21.9. Spectroscopic data was in agreement to those previously reported.[157]

Chemotion ELN sample number: ASS-11-7-A.

tert-Butyl hydroxy(methyl)carbamate [6.7]

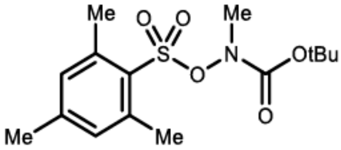


Following a literature known protocol,[146c] *N*-methylhydroxylamine hydrochloride (2.00 g, 23.9 mmol, 1.00 eq.) and K$_2$CO$_3$ (1.82 g, 13.2 mmol, 0.550 eq.) were dissolved in THF (20.0 mL) and water (2.00 mL). Di-*tert*-butyl dicarbonate (5.75 g, 26.3 mmol, 1.10 eq.) was added at 0 °C. The mixture was stirred for 1 h at 0 °C and for 2 h at rt. Before CH$_2$Cl$_2$ (10 mL) was added and the aqueous phase was separated and extracted with CH$_2$Cl$_2$ (3x10 mL). The combined organic fractions were dried over MgSO$_4$ and concentrated. The product was obtained after bulb-to-bulb distillation (120°C, 0.8 mbar) (3.02 g, 20.5 mmol, 86%). Spectroscopic data was in agreement to those previously reported.[223]

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.01 (s, 1H), 3.15 (s, 3H), 1.48 (s, 9H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 157.7, 82.1, 37.9, 28.4.

Chemotion ELN sample number: ASS-13-64-A.

tert-Butyl ((mesitylsulfonyl)oxy)(methyl)carbamate [4.56]

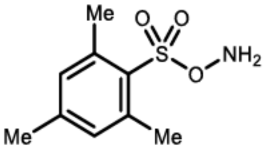


Following a literature known protocol,[146c] *tert*-butyl *N*-hydroxy-*N*-methylcarbamate **7.6** (736 mg, 5.00 mmol, 1.00 eq.) and NEt$_3$ (767 µL, 5.50 mmol, 1.10 eq.) were dissolved in chloroform (20.0 mL) and cooled to −10 °C. A solution of 2,4,6-trimethylbenzenesulfonyl chloride (1.09 g, 5.00 mmol, 1.00 eq.) in CHCl$_3$ (2 mL) was added slowly and the mixture was stirred for 1 h at −10 °C and 2 h at rt. The mixture was washed with NaHCO$_3$ sat. aq. (5 mL) and NaCl sat. aq. (5 mL) The organic phase was dried over Na$_2$SO$_4$, and the solvent was removed. The oily residue was crystallised from hot hexane to yield a colourless solid (1.05 g, 3.19 mmol, 64%).

IR (neat): $\tilde{\nu}$ = 2990 (w), 2361 (w), 1721 (m), 1603 (w), 1368 (s), 1332 (m), 1193 (s), 1179 (s), 1148 (s), 1058 (m), 846 (s), 750 (s), 663 (s), 647 (s). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 6.98 (s, 2H), 3.24 (s, 3H), 2.65 (s, 6H), 2.31 (s, 3H), 1.26 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 156.4, 144.3, 142.0, 131.8, 129.5, 83.5, 40.4, 27.8, 23.5, 21.2. **HRMS (ESI)**: Calculated for $C_{15}H_{23}NO_5SNa^+$ [M+Na]$^+$: 352.1189, Found: 352.1192. Spectroscopic data was in agreement to those previously reported.[146c]

Chemotion ELN sample number: ASS-11-9-A.

O-(Mesitylsulfonyl)hydroxylamine [4.8]

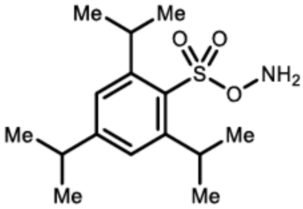


Following **GP-J**, using *tert*-butyl ((mesitylsulfonyl)oxy)-carbamate **4.53** (2.00 g, 6.34 mmol, 1.00 eq.), the desired product was obtained without further purification as a colourless solid (1.28 g, 5.97 mmol, 94%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.00 (s, 2H), 5.38 (br, 2H), 2.64 (s, 6H), 2.32 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 143.9, 141.1, 131.8, 129.2, 22.9, 21.2. Spectroscopic data was in agreement to those previously reported.[157]

Chemotion ELN sample number: ASS-11-37-A and ASS-13-94-A.

O-((2,4,6-Triisopropylphenyl)sulfonyl)hydroxylamine [4.59]

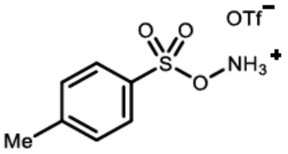


Following a literature known protocol, *tert*-butyl (((2,4,6-triisopropylphenyl)sulfonyl)oxy)carbamate **4.54** (500 mg, 1.25 mmol, 1.00 eq.) was dissolved in 1,4-dioxane (2 mL) and cooled to 0 °C before HClO$_4$ aq. (70%, 2.10 mL) was added. The mixture was stirred for 3 h at 0 °C. The mixture was poured on ice-water (20 mL) and stirred for 30 min. The precipitate was filtered off and washed with small portions of water. The desired product was obtained without further purification as a colourless solid (342 mg, 1.14 mmol, 91%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.21 (s, 2H), 4.12 (h, J = 6.9 Hz, 2H), 3.49 (br, 2H), 2.92 (hept, J = 7.0 Hz, 1H), 1.27 (*app.* dd, J = 6.8, 2.1 Hz, 18H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 154.4, 151.9, 127.8, 124.0, 34.4, 29.9, 24.9, 24.7, 23.7. **HRMS (ESI)**: Calculated for $C_{15}H_{26}NO_3S^+$ [M+H]$^+$: 300.1628, Found: 300.1627. Spectroscopic data was in agreement to those previously reported.[224]

Chemotion ELN sample number: ASS-12-42-A.

O-Tosylhydroxylammonium triflate [4.9]

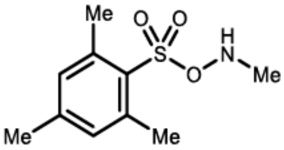


Following a literature known protocol,[157] *tert*-butyl (tosyloxy)carbamate **4.55** (287 mg, 1.00 mmol, 1.00 eq.) was dissolved in Et_2O (5 mL) at 0 °C and triflic acid (92.7 µL, 1.05 mmol, 1.05 eq.) was added slowly at 0 °C, the reaction was stirred for 1 h at room temperature before pentane (8 mL) was added to the mixture, and was stirred for 15 min. The mixture was filtered and the residue was washed with Et_2O:pentane (10:90) and dried under vacuum to afford a colourless solid (210 mg, 623 µmol, 62%).

^{1}H NMR (400 MHz, dmso-d6): δ =7.50 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.84 (br, 3H), 2.29 (s, 3H). **^{13}C NMR (101 MHz, dmso-d6)**: δ = 144.9, 138.3, 128.4, 125.6, 120.8 (q, $^1J_{C,F}$ = 322.2 Hz), 20.9. **^{19}F NMR (282 MHz, dmso-d6)**: – 77.6 (s, 3F). Spectroscopic data was in agreement to those previously reported.[157]

Chemotion ELN sample number: ASS-11-14-1.

O-(Mesitylsulfonyl)- *N*-methylhydroxylamine [4.60]



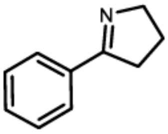
Following **GP-J** with minor alterations, using *tert*-butyl ((mesitylsulfonyl)oxy)(methyl)carbamate **4.56** (1.00 g, 3.04 mmol, 1.00 eq.), which was dissolved in CH_2Cl_2 (3 mL) and trifluoroacetic acid (3 mL) was added dropwise at 0 °C and stirred for 3 h. The mixture was poured on ice water and stirred for another 30 min. The aqueous phase was extracted with CH_2Cl_2 (3x5 mL). The combined organic fractions were washed with water and dried over Na_2SO_4. The solvent was removed and the product was obtained without further purification as a colourless solid (620 mg, 2.70 mmol, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 – 6.97 (m, 2H), 2.76 (s, 3H), 2.64 (s, 6H), 2.32 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 143.5, 140.9, 131.7, 130.4, 40.1, 22.9, 21.2. Spectroscopic data was in agreement to those previously reported.[146c]

Chemotion ELN sample number: ASS-11-19-A and ASS-14-5-A.

6.4.2 Substrate scope for the synthesis of *N*-heterocycles *via* *N*-insertion

5-Phenyl-3,4-dihydro-2*H*-pyrrole [4.6]

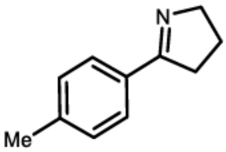


Following **GP-K**, using 3-phenylcyclobutanol **4.5** (367 µL, 5.00 mmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 15:85 to 20:80) as an orange oil (31.0 mg, 213 µmol, 71%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.95 – 7.75 (m, 2H), 7.54 – 7.34 (m, 3H), 4.07 (ddd, *J* = 7.4, 5.3, 2.0 Hz, 2H), 3.08 – 2.82 (m, 2H), 2.04 (app. dq, *J* = 9.1, 7.5 Hz, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.7, 134.5, 130.6, 128.6, 127.8, 61.4, 35.0, 22.7. Spectroscopic data was in agreement to those previously reported.[140f]

Chemotion ELN sample number: ASS-12-88-A.

5-(*p*-Tolyl)-3,4-dihydro-2*H*-pyrrole [4.63]

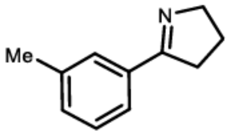


Following **GP-K**, using 1-(*p*-tolyl)cyclobutan-1-ol **4.17** (48.7 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after preparative TLC (EtOAc:pentane, 40:60) as a yellow oil (15.0 mg, 94.2 µmol, 31%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.78 – 7.69 (m, 2H), 7.24 – 7.17 (m, 2H), 4.05 (tt, *J* = 7.4, 2.0 Hz, 2H), 2.93 (ddt, *J* = 8.3, 7.2, 2.0 Hz, 2H), 2.38 (s, 3H), 2.11 – 1.95 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.4, 140.7, 132.0, 129.3, 127.7, 61.5, 35.0, 22.8, 21.6. Spectroscopic data was in agreement to those previously reported.[141]

Chemotion ELN sample number: ASS-13-53-A.

5-(*m*-Tolyl)-3,4-dihydro-2*H*-pyrrole [4.64]

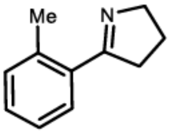


Following **GP-K**, using 1-(*m*-tolyl)cyclobutan-1-ol **4.18** (48.7 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after preparative TLC (EtOAc:pentane, 40:60) as a yellow oil (18.0 mg, 113 µmol, 38%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.74 – 7.70 (m, 1H), 7.62 (app. dt, *J* = 7.5, 1.8 Hz, 1H), 7.30 (app. t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 6.0 Hz, 1H), 4.07 (tt, *J* = 7.4, 2.0 Hz, 2H), 3.00 – 2.90 (m, 2H), 2.39 (d, *J* = 0.8 Hz, 3H), 2.04 (app. dq, *J* = 9.1, 7.5 Hz, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.9, 138.3, 134.3, 131.4, 128.5, 128.4, 125.1, 61.3, 35.1, 22.7, 21.5. Spectroscopic data was in agreement to those previously reported.[140f]

Chemotion ELN sample number: ASS-13-55-A.

5-(*o*-Tolyl)-3,4-dihydro-2*H*-pyrrole [4.65]



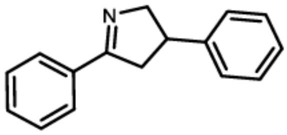
Following **GP-K**, using 1-(*o*-tolyl)cyclobutan-1-ol **4.19** (48.7 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product could not be separated by FC from the aniline side product.

Desired product: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.51 – 7.40 (m, 1H), 7.33 – 7.18 (m, 3H), 4.11 (tt, *J* = 7.5, 1.8 Hz, 2H), 2.95 (tt, *J* = 8.5, 2.0 Hz, 2H), 2.53 (s, 3H), 2.09 – 1.93 (m, 2H). Spectroscopic data was in agreement to those previously reported.[225]

Side product: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.10 – 7.00 (m, 2H), 6.76 – 6.65 (m, 2H), 2.17 (s, 3H). Spectroscopic data was in agreement to those previously reported.[226]

Chemotion ELN sample number: ASS-13-11.

3,5-Diphenyl-3,4-dihydro-2*H*-pyrrole [4.66]

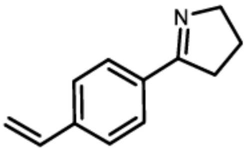


Following **GP-K**, using 1,3-diphenylcyclobutan-1-ol **4.33** (102 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 20:80 to 25:75) as a colourless oil (10.0 mg, 45 µmol, 15%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.93 – 7.84 (m, 2H), 7.50 – 7.37 (m, 3H), 7.36 – 7.28 (m, 2H), 7.25 – 7.16 (m, 3H), 4.54 (ddt, *J* = 16.3, 8.5, 1.8 Hz, 1H), 4.13 (ddt, *J* = 16.4, 6.1, 2.1 Hz, 1H), 3.68 (tt, *J* = 8.8, 6.3 Hz, 1H), 3.49 (dddd, *J* = 17.0, 9.7, 2.3, 1.4 Hz, 1H), 3.11 (ddt, *J* = 17.0, 6.6, 2.0 Hz, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 172.6, 145.0, 134.2, 130.7, 128.8, 128.6, 127.7, 126.8, 126.5, 69.5, 44.0, 42.9. Spectroscopic data was in agreement to those previously reported.[227]

Chemotion ELN sample number: ASS-13-97-B.

5-(4-Vinylphenyl)-3,4-dihydro-2*H*-pyrrole [4.67]

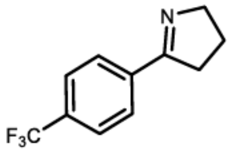


Following **GP-K**, using 1-(4-vinylphenyl)cyclobutan-1-ol **4.20** (52.3 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a yellow oil (16.0 mg, 93.4 µmol, 31%).

IR (neat): $\tilde{\nu}$ = 2953 (w), 2230 (w), 1609 (w), 1428 (m), 1277 (m), 1164 (m), 1118 (m), 967 (m), 843 (m), 732 (s), 689 (w). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 7.87 – 7.80 (m, 2H, C$H_{\text{arom.}}$), 7.49 – 7.41 (m, 2H, C$H_{\text{arom.}}$), 6.73 (dd, *J* = 17.6, 10.9 Hz, 1H, C*H*), 5.82 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.32 (dd, *J* = 10.9, 0.8 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.03 – 2.90 (m, 2H), 2.05 (dq, *J* = 9.1, 7.6 Hz, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.6 (C_q), 139.9 (C_q), 136.4 (CH), 133.5 (C_q), 128.2 (CH), 126.4 (CH), 115.5 (CH$_2$), 61.2 (CH$_2$), 35.0 (CH$_2$), 22.6 (CH$_2$). **HRMS (ESI)**: Calculated for $C_{12}H_{14}N^+$ [M+H]$^+$: 172.1121, Found: 172.1116.

Chemotion ELN sample number: ASS-13-50-B.

5-(4-(Trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyrrole [4.68]

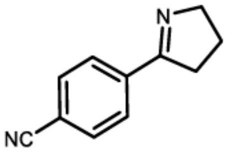


Following **GP-K**, using 1-(4-(trifluoromethyl)phenyl)cyclobutan-1-ol **4.22** (64.9 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (MeOH:CH_2Cl_2, 0:100 to 5:95) as an orange oil (27.0 mg, 127 µmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 – 7.93 (m, 2H), 7.69 – 7.64 (m, 2H), 4.11 (tt, J = 7.5, 2.2 Hz, 2H), 3.01 – 2.92 (m, 2H), 2.14 – 2.02 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 172.5, 137.7, 132.2 (q, $^2J_{C,F}$ = 32.5 Hz), 128.1, 125.6 (q, $^4J_{C,F}$ = 3.8 Hz), 124.0 (q, $^1J_{C,F}$ = 272.2 Hz), 61.8, 35.2, 22.8. **^{19}F NMR (282 MHz, $CDCl_3$)**: – 62.8 (s, 3F). Spectroscopic data was in agreement to those previously reported.[140f]

Chemotion ELN sample number: ASS-13-84-A.

4-(3,4-Dihydro-2*H*-pyrrol-5-yl)benzonitrile [4.69]



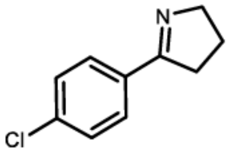
Following **GP-K** with minor alterations, using 4-(1-hydroxycyclobutyl)benzonitrile **4.25** (52.3 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (96.9 mg, 450 µmol, 1.50 eq.). The mixture was stirred for 17 h at rt. The desired product was obtained after automated FC (EtOAc:CyH, 40:60 to 70:30) as a yellow oil (19.0 mg, 112 µmol, 37%).

IR (neat): $\tilde{\nu}$ = 2923 (m), 2863 (w), 2229 (s), 1616 (s), 1409 (m), 1339 (s), 1289 (m), 1049 (m), 966 (m), 837 (s), 565 (s). **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.97 – 7.90 (m, 2H, C$H_{arom.}$), 7.72 – 7.66 (m, 2H, C$H_{arom.}$), 4.11 (tt, J = 7.5, 2.2 Hz, 2H, CH_2), 3.00 – 2.88 (m, 2H, CH_2), 2.15 – 2.00 (m, 2H, CH_2). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 172.0 (C_q), 138.6 (C_q), 132.4 (CH), 128.3 (CH), 118.7

(C_q), 113.8 (C_q), 62.0 (CH$_2$), 35.0 (CH$_2$), 22.8 (CH$_2$). **HRMS (ESI)**: Calculated for $C_{11}H_{11}N_2^+$ [M+H]$^+$: 171.0917, found 171.0920.

Chemotion ELN sample number: ASS-14-30-B.

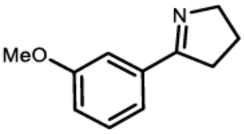
5-(4-Chlorophenyl)-3,4-dihydro-2*H*-pyrrole [4.70]



Following **GP-K**, using 1-(4-chlorophenyl)cyclobutan-1-ol **4.23** (54.8 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 40:60) as an orange oil (43.0 mg, 239 µmol, 80%).
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.80 – 7.72 (m, 2H), 7.39 – 7.33 (m, 2H), 4.05 (tt, J = 7.4, 2.1 Hz, 2H), 2.90 (ddt, J = 8.2, 7.3, 2.1 Hz, 2H), 2.10 – 1.96 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 172.3, 136.4, 133.1, 129.0, 128.7, 61.7, 35.0, 22.8. Spectroscopic data was in agreement to those previously reported.[140f]

Chemotion ELN sample number: ASS-13-54-A.

5-(3-Methoxyphenyl)-3,4-dihydro-2*H*-pyrrole [4.71]

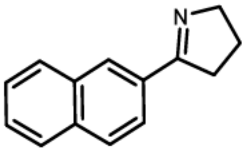


Following **GP-K**, using 1-(3-methoxyphenyl)cyclobutan-1-ol **4.24** (53.5 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after preparative TLC (EtOAc:pentane, 40:60) as a yellow oil (30.0 mg, 171 µmol, 57%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.45 (dd, J = 2.8, 1.5 Hz, 1H), 7.35 (app. dt, J = 7.6, 1.5 Hz, 1H), 7.29 (app. t, J = 7.7 Hz, 1H), 6.97 (ddd, J = 7.8, 2.7, 1.4 Hz, 1H), 4.05 (tt, J = 7.4, 2.1 Hz, 2H), 3.83 (s, 3H), 2.92 (ddt, J = 8.2, 7.3, 2.0 Hz, 2H), 2.09 – 1.94 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.4, 159.7, 136.0, 129.5, 120.5, 117.0, 111.8, 61.6, 55.4, 35.1, 22.8. Spectroscopic data was in agreement to those previously reported.[140f]

Chemotion ELN sample number: ASS-13-76-A.

5-(Naphthalen-2-yl)-3,4-dihydro-2*H*-pyrrole [4.72]

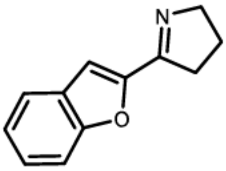


Following **GP-K** with minor alterations, using 1-(naphthalen-2-yl)cyclobutan-1-ol **4.27** (59.5 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.3 eq.) in TFE (1.5 mL), the desired product was obtained after FC (EtOAc:pentane, 20:80) as an orange oil (30.0 mg, 154 µmol, 51%)

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.20 (d, J = 1.7 Hz, 1H), 8.12 (dd, J = 8.6, 1.8 Hz, 1H), 7.94 – 7.81 (m, 3H), 7.57 – 7.46 (m, 2H), 4.14 (tt, J = 7.4, 2.0 Hz, 2H), 3.16 – 3.05 (m, 2H), 2.18 – 2.04 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.9, 134.6, 133.1, 131.7, 128.9, 128.7, 128.4, 127.9, 127.4, 126.6, 124.6, 61.4, 35.1, 22.7. Spectroscopic data was in agreement to those previously reported.[141]

Chemotion ELN sample number: ASS-13-59-A and ASS-13-79-B.

5-(Benzofuran-2-yl)-3,4-dihydro-2*H*-pyrrole [4.73]

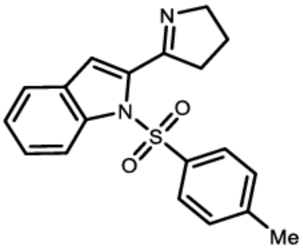


Following **GP-K**, using 1-(benzofuran-2-yl)cyclobutan-1-ol **4.28** (56.5 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as an orange solid (44.0 mg, 238 µmol, 79%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.61 (ddd, J = 7.8, 1.4, 0.8 Hz, 1H), 7.54 (app. dq, J = 8.3, 0.9 Hz, 1H), 7.35 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.28 – 7.20 (m, 1H), 7.08 (s, 1H), 4.12 (tt, J = 7.4, 2.1 Hz, 2H), 3.01 – 2.87 (m, 2H), 2.13 – 1.95 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 164.8, 155.5, 151.3, 127.9, 126.3, 123.3, 122.0, 112.0, 109.4, 62.0, 35.1, 22.5. Spectroscopic data was in agreement to those previously reported.[141]

Chemotion ELN sample number: ASS-13-22-B.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl)-1-tosyl-1*H*-indole [4.74]



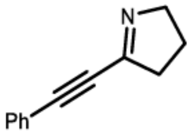
Following **GP-K**, using 1-(1-tosyl-1*H*-indol-2-yl)cyclobutan-1-ol **4.29** (102 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 60:40 to 80:20) as an orange solid (89.0 mg, 263 µmol, 88%).

1 mmol scale: The reaction was carried out following **GP-K**, using 1-(1-tosyl-1*H*-indol-2-yl)cyclobutan-1-ol **4.29** (341 mg, 1.00 mmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (280 mg, 1.30 mmol, 1.30 eq), the desired product was obtained after automated FC (EtOAc:CyH, 60:40 to 80:20) as an orange solid (271 mg, 801 µmol, 80%).

IR (neat): $\tilde{\nu}$ = 2953 (w), 2863 (w), 1626 (w), 1597 (w), 1495 (w), 1450 (w), 1370 (m), 1324 (w), 1245 (w), 1221 (w), 1189 (m), 1175 (s), 1149 (w), 1121 (w), 1090 (m), 1076 (w), 1021 (w), 987 (w), 963 (w), 902 (w), 814 (w), 752 (m), 704 (w), 684 (m), 654 (w), 583 (m), 570 (m), 543 (m), 500 (w), 451 (w). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 8.07 (app. dq, *J* = 8.4, 0.8 Hz, 1H, C*H*$_{\text{arom.}}$), 7.65 – 7.58 (m, 2H, C*H*$_{\text{arom.}}$), 7.42 (ddd, *J* = 7.7, 1.3, 0.8 Hz, 1H, C*H*$_{\text{arom.}}$), 7.32 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H, C*H*$_{\text{arom.}}$), 7.20 (app. td, *J* = 7.5, 1.0 Hz, 1H, C*H*$_{\text{arom.}}$), 7.12 – 7.07 (m, 2H, C*H*$_{\text{arom.}}$), 6.80 (d, *J* = 0.8 Hz, 1H, C*H*$_{\text{arom.}}$), 4.10 (tt, *J* = 7.4, 2.0 Hz, 2H, C*H*$_2$), 3.13 – 3.03 (m, 2H, C*H*$_2$), 2.25 (s, 3H, C*H*$_3$), 2.19 – 2.07 (m, 2H, C*H*$_2$). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 170.3 (*C*$_q$), 144.9 (*C*$_q$), 137.9 (*C*$_q$), 137.1 (*C*$_q$), 133.7 (*C*$_q$), 130.4 (*C*$_q$), 129.6 (*C*H), 127.2 (*C*H), 125.8 (*C*H), 124.5 (*C*H), 121.7 (*C*H), 115.7 (*C*H), 114.3 (*C*H), 61.5 (*C*H$_2$), 40.5 (*C*H$_2$), 23.5 (*C*H$_2$), 21.7 (*C*H$_3$). **HRMS (ESI)**: Calculated for $C_{19}H_{19}N_2O_2S^+$ [M+H]$^+$: 339.1162, found 339.1166.

Chemotion ELN sample number: ASS-13-90-B and ASS-14-33-A.

5-(Phenylethynyl)-3,4-dihydro-2*H*-pyrrole [4.75]

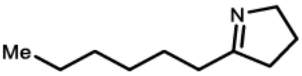


Following **GP-K**, using 1-(phenylethynyl)cyclobutan-1-ol **4.30** (51.7 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 40:60) as a yellow oil (38.0 mg, 225 µmol, 75%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.58 – 7.47 (m, 2H), 7.41 – 7.28 (m, 3H), 4.00 (tt, *J* = 7.5, 2.3 Hz, 2H), 2.73 (tt, *J* = 8.6, 2.3 Hz, 2H), 2.02 – 1.87 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 159.7, 132.3, 129.5, 128.5, 121.8, 92.6, 84.8, 62.1, 40.0, 22.5. Spectroscopic data was in agreement to those previously reported.[228]

Chemotion ELN sample number: ASS-13-92-A.

5-Hexyl-3,4-dihydro-2*H*-pyrrole [4.76]

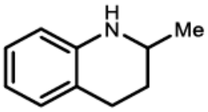


Following **GP-K** with minor alterations, using 1-hexylcyclobutan-1-ol **4.31** (46.9 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (96.9 mg, 450 µmol, 1.50 eq.). The mixture was stirred for 17 h at rt. The desired product was obtained after automated FC (EtOAc:CyH, 50:50 to 70:30) as a colourless oil (17.0 mg, 111 µmol, 37%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.78 (ddt, *J* = 9.2, 5.5, 1.8 Hz, 2H), 2.45 (tt, *J* = 8.7, 1.9 Hz, 2H), 2.38 – 2.29 (m, 2H), 1.92 – 1.77 (m, 2H), 1.56 (app. dq, *J* = 13.0, 5.5 Hz, 2H), 1.38 – 1.21 (m, 6H), 0.91 – 0.82 (m, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 179.2, 60.6, 37.2, 33.9, 31.7, 29.3, 26.5, 22.7, 22.6, 14.2. Spectroscopic data was in agreement to those previously reported.[229]

Chemotion ELN sample number: ASS-14-29-A.

2-Methyl-1,2,3,4-tetrahydroquinoline [4.86]

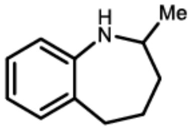


Following **GP-L**, using 1-methyl-2,3-dihydro-1*H*-inden-1-ol **4.41** (44.5 mg, 300 µmol, 1.00 eq.), *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) and sodium borohydride (45.4 mg, 1.20 mmol, 4.00 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a slightly orange solid (37.0 mg, 251 µmol, 84%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.03 – 6.95 (m, 2H), 6.63 (td, *J* = 7.4, 1.2 Hz, 1H), 6.49 (dd, *J* = 8.3, 1.2 Hz, 1H), 3.51 (br, 1H), 3.42 (dqd, *J* = 9.9, 6.3, 2.8 Hz, 1H), 2.96 – 2.67 (m, 2H), 1.95 (dddd, *J* = 12.8, 5.6, 3.5, 2.8 Hz, 1H), 1.61 (dddd, *J* = 12.9, 11.4, 9.9, 5.5 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 144.8, 129.4, 126.8, 121.2, 117.1, 114.1, 47.3, 30.2, 26.7, 22.7. Spectroscopic data was in agreement to those previously reported.[230]

Chemotion ELN sample number: ASS-13-91-A.

2-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine [4.87]

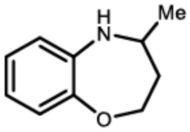


Following **GP-L** with minor alterations, using 1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol **4.42** (48.7 mg, 300 µmol, 1.00 eq.), *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) and sodium borohydride (45.4 mg, 1.20 mmol, 4.00 eq.) in TFE (1.5 mL), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a slight orange solid (31.0 mg, 192 µmol, 64%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.12 – 7.06 (m, 1H), 7.06 – 7.00 (m, 1H), 6.84 (td, *J* = 7.4, 1.3 Hz, 1H), 6.74 (dd, *J* = 7.7, 1.3 Hz, 1H), 3.27 (s, 1H), 2.94 (dqd, *J* = 9.8, 6.4, 2.0 Hz, 1H), 2.87 – 2.59 (m, 2H), 2.02 – 1.78 (m, 2H), 1.60 – 1.32 (m, 2H), 1.26 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 149.0, 134.0, 130.7, 126.7, 121.1, 120.0, 53.9, 39.4, 35.7, 26.4, 24.2. Spectroscopic data was in agreement to those previously reported.[138]

Chemotion ELN sample number: ASS-13-86-A.

4-Methyl-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine [4.88]

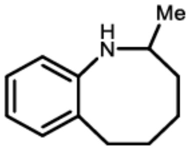


Following **GP-L**, using 4-methylchroman-4-ol **4.43** (49.3 mg, 300 µmol, 1.00 eq.), *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) and sodium borohydride (45.4 mg, 1.20 mmol, 4.00 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 20:80) as a colourless oil (33.0 mg, 202 µmol, 67%).

IR (neat): $\tilde{\nu}$ = 2961 (w), 1600 (w), 1485 (s), 1453 (w), 1379 (m), 1340 (w), 1304 (s), 1263 (s), 1211 (m), 1074 (m), 1052 (m), 754 (s). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 6.95 (dd, J = 7.7, 1.7 Hz, 1H, C$H_{\text{arom.}}$), 6.87 (td, J = 7.4, 1.7 Hz, 1H, C$H_{\text{arom.}}$), 6.78 (td, J = 7.5, 1.8 Hz, 1H, C$H_{\text{arom.}}$), 6.73 (dd, J = 7.6, 1.8 Hz, 1H, C$H_{\text{arom.}}$), 4.39 (ddd, J = 12.1, 6.3, 3.8 Hz, 1H, CH_2), 3.79 (ddd, J = 11.9, 8.2, 3.5 Hz, 1H, CH_2), 3.32 (app. dtd, J = 13.0, 6.5, 3.2 Hz, 1H, CH), 3.25 (br, 1H, NH), 1.97 (ddt, J = 13.9, 6.5, 3.3 Hz, 1H, CH_2), 1.79 (dddd, J = 14.0, 10.3, 8.2, 3.8 Hz, 1H, CH_2), 1.30 (d, J = 6.4 Hz, 3H, CH_3). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 150.5 (C_q), 140.9 (C_q), 123.4 (CH), 121.8 (CH), 121.1 (CH), 120.0 (CH), 70.7 (CH$_2$), 51.7 (CH), 39.5 (CH$_2$), 23.0 (CH$_3$). **HRMS (ESI)**: Calculated for $C_{10}H_{14}NO^+$ [M+H]$^+$: 164.1070, Found: 164.1071.

Chemotion ELN sample number: ASS-13-93-B.

2-Methyl-1,2,3,4,5,6-hexahydrobenzo[b]azocine [4.89]

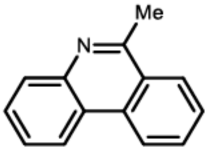


Following **GP-L**, using 5-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol **4.44** (52.9 mg, 300 µmol, 1.00 eq.), *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) and sodium borohydride (45.4 mg, 1.20 mmol, 4.00 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a slight yellow solid (27.0 mg, 154 µmol, 51%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.14 – 7.03 (m, 2H), 6.92 (td, J = 7.4, 1.4 Hz, 1H), 6.86 (dd, J = 7.7, 1.3 Hz, 1H), 3.44 (dddd, J = 13.0, 6.5, 5.0, 2.7 Hz, 1H), 2.99 (br, 1H), 2.85 (ddd, $J = 7.6, 4.9, 2.4$ Hz, 2H), 1.89 – 1.74 (m, 1H), 1.71 – 1.51 (m, 3H), 1.45 – 1.30 (m, 2H), 1.22 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: $\delta = 147.0$, 135.0, 130.6, 127.0, 123.5, 122.7, 55.7, 35.8, 32.3, 31.5, 23.3, 23.2. Spectroscopic data was in agreement to those previously reported.[138]

Chemotion ELN sample number: ASS-13-87-A.

6-Methylphenanthridine [4.90]

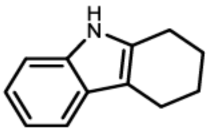


Following **GP-K** with minor alterations, using 9-methyl-9*H*-fluoren-9-ol **4.45** (58.9 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.) in TFE (1.5 mL). The mixture was stirred for 17 h at rt. The desired product was obtained after automated FC (EtOAc:CyH, 10:90 to 30:70) as a slight yellow solid (47.0 mg, 243 µmol, 81%).

^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 8.59 – 8.53$ (m, 1H), 8.49 (dd, $J = 8.2, 1.5$ Hz, 1H), 8.16 (ddd, $J = 8.2, 1.3, 0.6$ Hz, 1H), 8.11 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.79 (ddd, $J = 8.3, 7.0, 1.3$ Hz, 1H), 7.74 – 7.54 (m, 3H), 3.02 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: $\delta = 158.9$, 143.6, 132.6, 130.6, 129.3, 128.7, 127.4, 126.6, 126.4, 125.9, 123.8, 122.4, 122.0, 23.4. Spectroscopic data was in agreement to those previously reported.[231]

Chemotion ELN sample number: ASS-13-77-A.

2,3,4,9-Tetrahydro-1*H*-carbazole [4.91]



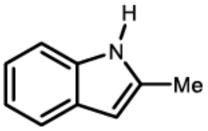
Following **GP-K**, using 1,3,4,8b-tetrahydrobiphenylen-4a(2H)-ol **4.46** (52.3 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95) as a slight yellow solid (20.0 mg, 117 µmol, 39%).

^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.63$ (br, 1H), 7.52 – 7.43 (m, 1H), 7.30 – 7.23 (m, 1H), 7.16 – 7.04 (m, 2H), 2.77 – 2.68 (m, 4H), 2.01 – 1.83 (m, 4H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 135.7, 134.2, 127.9, 121.1, 119.2, 117.8, 110.5, 110.3, 23.4, 23.4, 23.3, 21.0. Spectroscopic data was in agreement to those previously reported.[232]

Chemotion ELN sample number: ASS-13-18-B.

2-Methyl-1*H*-indole [4.92]

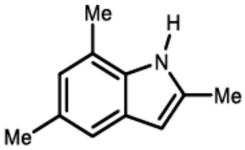


Following **GP-K**, using 7-methylbicyclo[4.2.0]octa-1,3,5-trien-7-ol **4.48** (40.3 mg, 300 µmol, 1.00 eq.), *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a colourless solid (37.0 mg, 282 µmol, 94%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.72 (br, 1H), 7.63 – 7.53 (m, 1H), 7.31 – 7.24 (m, 1H), 7.21 – 7.08 (m, 2H), 6.26 (d, J = 2.2 Hz, 1H), 2.44 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 136.1, 135.2, 129.1, 121.0, 119.7, 110.4, 100.4, 13.8. Spectroscopic data was in agreement to those previously reported.[233]

Chemotion ELN sample number: ASS-14-13-B.

2,5,7-Trimethyl-1*H*-indole [4.93]

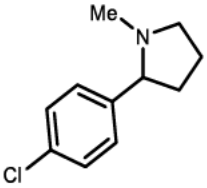


Following **GP-K**, using 7-methylbicyclo[4.2.0]octa-1,3,5-trien-7-ol **4.49** (40.3 mg, 300 µmol, 1.00 eq.) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 0.33 mmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a slight yellow solid (36.0 mg, 226 µmol, 75%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.70 (s, 1H), 7.21 (s, 1H), 6.81 (s, 1H), 6.19 (d, J = 1.1 Hz, 1H), 2.48 (s, 6H), 2.46 (s, 3H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 134.9, 134.0, 129.0, 129.0, 123.3, 119.1, 117.2, 100.6, 21.5, 16.7, 13.9. Spectroscopic data was in agreement to those previously reported.[234]

Chemotion ELN sample number: ASS-14-8-A.

2-(4-Chlorophenyl)-1-methylpyrrolidine [4.94]

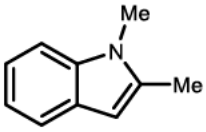


Following **GP-L** with minor alterations, 1-(4-chlorophenyl)cyclobutan-1-ol **4.23** (54.8 mg, 300 µmol, 1.00 eq.), *O*-(mesitylsulfonyl)-*N*-methylhydroxylamine (89.4 mg, 390 µmol, 1.30 eq.) and sodium borohydride (45.4 mg, 1.20 mmol, 4.00 eq.), the desired product was obtained after automated FC (MeOH:CH_2Cl_2, 5:95) as a slight orange solid (30.0 mg, 0.15 mmol, 51%).

IR (neat): $\tilde{\nu}$ = 2968 (w), 2943 (w), 2779 (m), 1489 (w), 1459 (s), 1219 (m), 1088 (s), 1045 (s), 1014 (s), 903 (m), 823 (s), 522 (s), 482 (s). **^{1}H NMR (300 MHz, $CDCl_3$)**: δ = 7.31 – 7.27 (m, 4H, C$H_{\text{arom.}}$), 3.25 (ddd, J = 9.4, 7.7, 2.1 Hz, 1H, CH_2), 3.04 (dd, J = 9.0, 7.6 Hz, 1H, CH), 2.30 (app. q, J = 9.0 Hz, 1H, CH_2), 2.23 – 2.08 (m, 4H, CH_2 and CH_3), 2.06 – 1.88 (m, 1H, CH_2), 1.88 – 1.63 (m, 2H, CH_2). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 141.7(C_q), 132.8 (C_q), 129.0 (CH), 128.7 (CH), 71.1 (CH), 57.1 (CH$_2$), 40.5 (CH), 35.3 (CH$_2$), 22.6 (CH$_2$). **HRMS (ESI)**: Calculated for $C_{11}H_{15}ClN^+$ [M+H]$^+$: 196.0888, Found: 196.0884.

Chemotion ELN sample number: ASS-14-12-B.

1,2-Dimethyl-1*H*-indole [4.95]

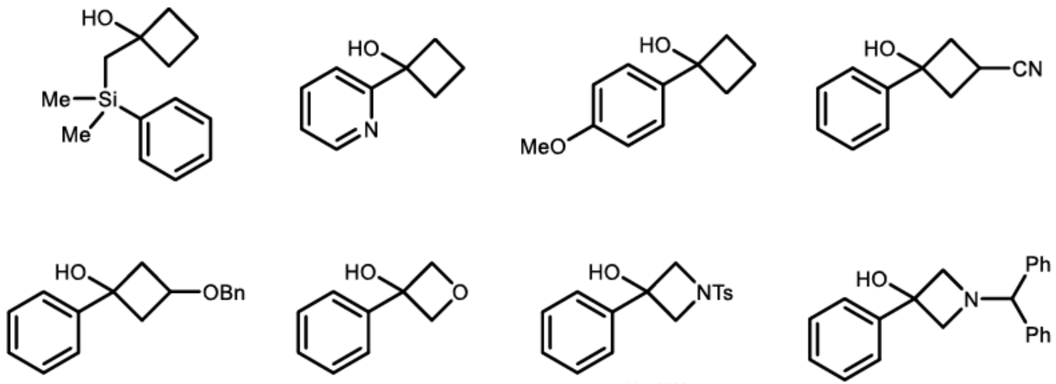


Following **GP-K** with minor alterations, using 7-methylbicyclo[4.2.0]octa-1,3,5-trien-7-ol **4.48** (40.3 mg, 300 µmol, 1.00 eq.), *O*-(mesitylsulfonyl)-*N*-methylhydroxylamine (89.4 mg, 330 µmol, 1.30 eq.), the desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 10:90) as a slight yellow solid (28.0 mg, 193 µmol, 64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 – 7.51 (m, 1H), 7.29 (app. dt, J = 8.1, 1.0 Hz, 1H), 7.22 – 7.14 (m, 1H), 7.10 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.27 (br, 1H), 3.68 (s, 3H), 2.45 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 137.4, 136.9, 128.0, 120.5, 119.7, 119.3, 108.8, 99.7, 29.5, 12.9. Spectroscopic data was in agreement to those previously reported.[235]

Chemotion ELN sample number: ASS-14-14-A.

Limitations of the presented method

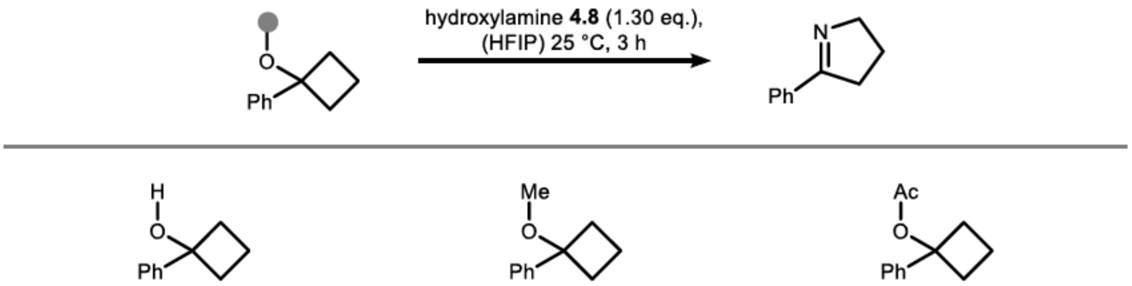


prepared by *H.Maag*

Following **GP-K**, the above shown cyclic tertiary alcohols (0.30 mmol, 1.00 eq.) were used with *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 330 µmol, 1.30 eq.). The reaction was monitored through ^{1}H NMR with CH_2Br_2 (0.1 mmol) as internal standard. No product was observed within 3 h of reaction time.

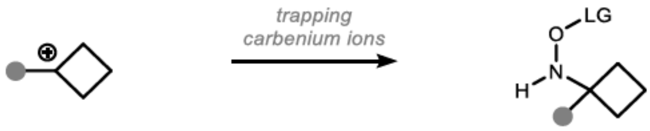
6.4.3 Mechanistic experiments

6.4.3.1 Investigations on substrate activation

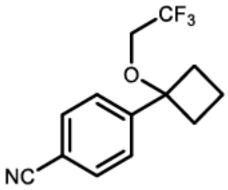


Cyclobutyl derivatives **4.5**, **4.51** or **4.52**, (0.10 mmol, 1.00 eq.) were dissolved in HFIP (0.2 M) and *O*-mesitylsulfonylhydroxylamine **4.8** (28.0 mg, 0.13 mmol, 1.30 eq.) was added at 0 °C. The mixture was immediately warmed to rt and stirred for 3 h before being cooled to 0 °C. NEt_3 (18.1 µL, 0.13 mmol, 1.3 eq.) was added and the solvent was removed. NMR yield of the crude reaction mixture was determined by ^1H NMR using CH_2Br_2 (7.0 µL, 0.10 mmol) as the internal standard.

6.4.3.2 Investigations on reactive carbenium intermediates



4-(1-(2,2,2-trifluoroethoxy)cyclobutyl)benzonitrile [4.96]



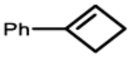
4-(1-Hydroxycyclobutyl)benzonitrile **4.25** (17.3 mg, 100 µmol, 1.00 eq.) was dissolved in TFE (0.5 mL) and *O*-mesitylsulfonylhydroxylamine **4.8** (28.0 mg, 0.13 mmol, 1.30 eq.) was added at 0 °C. The mixture was immediately warmed to rt and stirred for 3 h before being cooled to 0 °C. NEt_3 (18.1 µL, 0.13 mmol, 1.3 eq.) was added and the solvent was removed. NMR yield of the crude reaction mixture was determined by ^1H NMR using CH_2Br_2 (7.0 µL, 0.10 mmol) as the internal standard. The trifluoroethanol ether **4.96** was obtained after automated FC (EtOAc:CyH, 5:95 to 20:80) as a yellow oil (15.0 mg, 58.8 µmol, 59%).

IR (neat): $\tilde{\nu}$ = 2953 (m), 2230 (m), 1609 (w), 1428 (w), 1277 (s), 1164 (s), 1118 (s), 967 (m), 843 (m), 732 (m), 689 (m). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 7.73 – 7.68 (m, 2H, $CH_{arom.}$), 7.58 – 7.54 (m, 2H, $CH_{arom.}$), 3.38 (q, J = 8.6 Hz, 2H, CH_2), 2.55 – 2.34 (m, 4H, CH_2), 2.10 – 1.97 (m, 1H, CH_2), 1.72 (app. dp, J = 11.4, 8.5 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 147.3 (C_q), 132.8 (CH), 126.9 (CH), 123.9 (d, $^1J_{C,F}$ = 277.4 Hz, CF_3), 118.7 (C_q), 112.0 (C_q), 82.1 (C_q), 62.0 (q, $^2J_{C,F}$ = 34.6 Hz, CH_2), 32.8 (CH_2), 32.8 (CH_2), 12.8 (CH_2). **^{19}F NMR (282 MHz, $CDCl_3$)**: – 74.0 (s, 3F, CF_3).

Chemotion ELN sample number: ASS-11-52-B.

6.4.3.3 Investigations on alternative reaction pathways *via* nitrene formation

Cyclobut-1-en-1-ylbenzene [4.97]

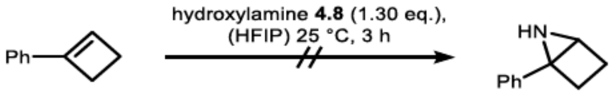


Following a literature known protocol,[152e] 1-phenylcyclobutanol **4.5** (296 mg, 2.00 mmol, 1.00 eq.) and NEt_3 (1.67 mL, 12.0 mmol, 6.00 eq.) were dissolved in CH_2Cl_2 (10 mL) and methanesulfonyl chloride (372 µL, 4.80 mmol, 2.40 eq.) was added at 0 °C. The mixture was stirred for 1 h at 0°C and 3 h at rt. Water (10 mL) and Et_2O (20 mL) were added. The aqueous phase was separated and extracted with Et_2O (3x20 mL). The combined organic fractions were washed with NH_4Cl sat. aq. (20 mL) $NHCO_3$ sat (20 mL), NaCl sat. aq. (20 mL) and dried over $MgSO_4$ and the solvent was removed *in vacuo*. Bulb-to-bulb distillation (10 mbar, 100 °C) afforded a colourless oil which was passed through a plug of SiO_2 (pentane) leaving a colourless oil (28.0 mg, 215 µmol, 11%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 – 7.19 (m, 5H), 6.30 (t, J = 1.3 Hz, 1H), 2.83 – 2.79 (m, 2H), 2.55 – 2.51 (m, 2H). Spectroscopic data was in agreement to those previously reported.[152e]

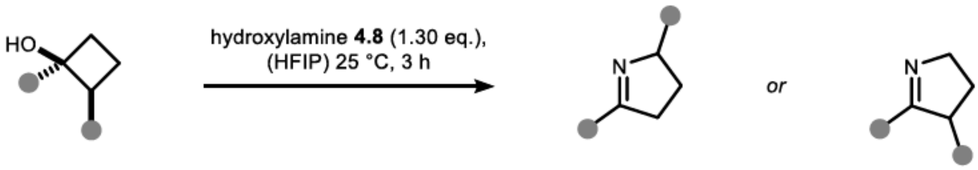
Chemotion ELN sample number: ASS-14-22.

Probe for nitrene pathway

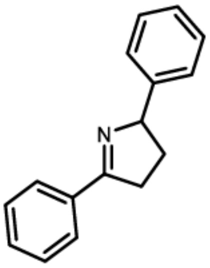


Cyclobut-1-en-1-ylbenzene **4.97** (13.0 mg, 100 µmol, 1.00 eq.) was dissolved in HFIP (0.2 M) and *O*-mesitylsulfonylhydroxylamine **4.8** (28.0 mg, 130 µmol, 1.30 eq.) was added at 0 °C. The mixture was immediately warmed to rt and stirred for 3 h before being cooled to 0 °C. NEt_3 (18.1 µL, 0.13 mmol, 1.3 eq.) was added and the solvent was removed. No product formation was observed by ^1H NMR using mesitylene (0.10 mmol) as internal standard.

6.4.3.4 Investigations on regioselectivity



2,5-diphenyl-3,4-dihydro-2*H*-pyrrole [4.99]



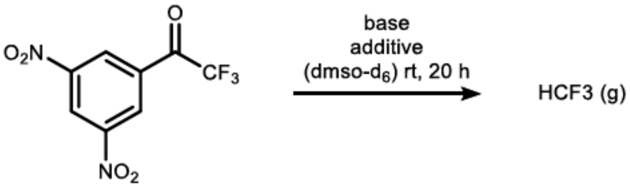
trans 1,2-Diphenylcyclobutan-1-ol **4.36** (67.3 mg, 300 µmol, 1.00 eq.) was dissolved in HFIP (1.5 mL) and *O*-mesitylsulfonylhydroxylamine **4.8** (84.0 mg, 0.39 µmol, 1.30 eq.) was added at 0 °C. The mixture was immediately warmed to rt and stirred for 3 h before being cooled to 0 °C. NEt_3 (54.4 µL, 330 µmol, 1.3 eq.) was added and the solvent was removed. NMR yield and regiomeric ratio of the crude reaction mixture was determined by ^1H NMR using CH_2Br_2 (7.0 µL, 0.10 mmol) as the internal standard. The desired product was obtained after automated FC (EtOAc:CyH, 5:95 to 15:85) as a yellow solid (46.0 mg, 208 µmol, 69%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.02 – 7.91 (m, 2H), 7.52 – 7.40 (m, 3H), 7.39 – 7.30 (m, 4H), 7.30 – 7.21 (m, 1H), 5.33 (app. tt, *J* = 7.7, 2.1 Hz, 1H), 3.19 (dddd, *J* = 16.5, 9.8, 4.5, 2.0 Hz, 1H), 3.02 (dddd, *J* = 17.0, 9.4, 8.0, 2.1 Hz, 1H), 2.61 (dddd, *J* = 12.7, 9.4, 8.1, 4.5 Hz, 1H), 1.92 (dddd, *J* = 12.8, 9.7, 8.0, 7.3 Hz, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 173.8, 144.7, 134.5, 130.7, 128.6, 128.0, 126.9, 126.7, 76.2, 35.7, 32.6. Spectroscopic data was in agreement to those previously reported.[236]

Chemotion ELN sample number: ASS-14-21-B.

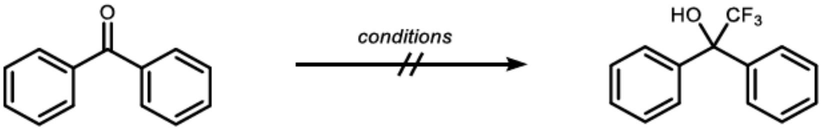
6.5 Haloform reaction of trifluoroacetophenones and its applications

Base induced fragmentation of trifluoroacetophenones



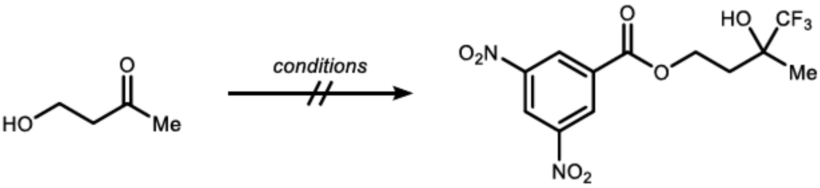
3'5'-Dinitro-2,2,2-trifluoroacetophenone **2.20** (26.4 mg, 0.10 mmol, 1.00 eq.) or a related trifluoroacetophenone derivative (0.10 mmol, 1.00 eq.) was dissolved in dmso-d_6 (0.15 M) followed by the addition of a base (0.10 mmol, 1.00 eq.) at rt. The reaction was monitored by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard (*cf.* Chapter 5.1, Table 11).

Intermolecular base induced trifluoromethylation of ketones



According to a literature known protocol with minor alterations,[180] 3'5'-Dinitro-2,2,2-trifluoroacetophenone **2.20** (1.00 eq.) or 2,2,2-trifluoroacetophenone **2.18** (1.00 eq.) was dissolved with benzophenone (1.00 eq.) in varying solvents (0.15 M) before adding a base (1.00 eq.) at rt. No product formation was observed by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard (*cf.* Chapter 5.1, Table 12).

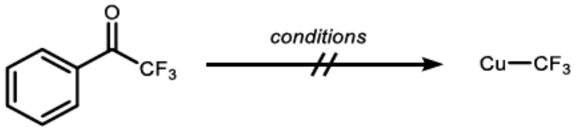
Intramolecular base induced trifluoromethylations of ketones



3'5'-Dinitro-2,2,2-trifluoroacetophenone **2.20** (26.4 mg, 0.10 mmol, 1.00 eq.) and 4-hydroxybutan-2-one (10.1 µL, 0.10 mmol, 1.00 eq.) were dissolved in C_6D_6

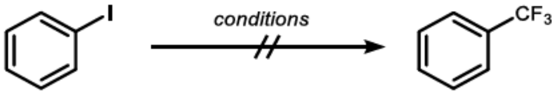
(0.15 M) and a base (1.00 eq.) was added at rt. No product formation was observed by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard (*cf.* Chapter 5.1, Scheme 86).

Base induced trifluoromethylation of copper salts



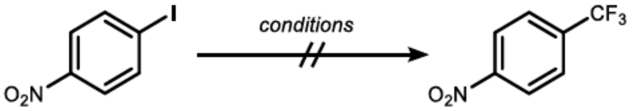
According to a literature known protocol with minor alterations,[182,184] 2,2,2-trifluoroacetophenone **2.18** (7.0 µL, 0.05 mmol, 1.00 eq.) was dissolved in dmso-d$_6$:DMF (0.1 M, 1:1) with CuCl (5.0 mg, 0.05 mmol, 1.00 eq.) and a base (2.00 eq.) was added. The reaction was monitored by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard and no product formation was observed (*cf.* Chapter 5.1, Scheme 87).

Base induced trifluoromethylation of arenes with copper salts



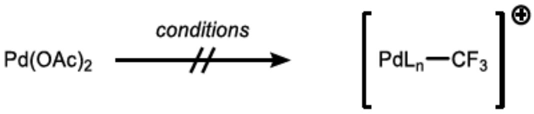
According to a literature known protocol with minor alterations,[182,183] 2,2,2-trifluoroacetophenone **2.18** (7.0 µL, 0.05 mmol, 1.00 eq.), iodobenzene (5.6 µL, 0.05 mmol, 1.00 eq.) and CuCl (5.0 mg, 0.05 mmol, 1.00 eq.) were dissolved in DMF (0.05 M). Lithium *tert*-butoxide (8.0 mg, 0.10 mmol, 2.00 eq.) was added at rt and the mixture was stirred for 24 h. No product formation was observed by ^{19}F NMR using fluorobenzene (0.10 mmol) as internal standard (*cf.* Chapter 5.1, Scheme 88).

According to a literature known protocol with minor alterations,[182,183] 2,2,2-trifluoroacetophenone **2.18** (14.0 µL, 0.10 mmol, 1.00 eq.), iodobenzene (11.2 µL, 0.10 mmol, 1.00 eq.), CuCl (9.9 mg, 0.10 mmol, 1.00 eq.) and 1,10-phenanthroline (18.0 mg, 0.10 mmol, 1.00 eq.) were dissolved in DMF (0.05 M). Potassium *tert*-butoxide (11.2 mg, 0.10 mmol, 1.00 eq.) was added at rt and the mixture was stirred for 24 h. No product formation was observed by ^{19}F NMR using fluorobenzene (0.10 mmol) as internal standard (*cf.* Chapter 5.1, Scheme 88).

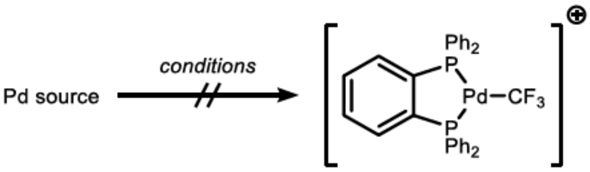


According to a literature known protocol with minor alterations,[182,183] 2,2,2-trifluoroacetophenone **2.18** (28.1 µL, 0.20 mmol, 2.00 eq.), 4-nitro-iodobenzene (24.9 mg, 0.10 mmol, 1.00 eq.), CuCl (1.9 mg, 0.01 mmol, 0.10 eq.) and 1,10-phenanthroline (1.8 mg, 0.01 mmol, 0.10 eq.) were dissolved in DMF:*N*-methylpyrrolidinone (0.05 M, 1:1). Potassium *tert*-butoxide (11.2 mg, 0.10 mmol, 1.00 eq.) was added at −40 °C and stirred for 20 min before it was heated to 60 °C for 24 h. No product formation was observed by ^{19}F NMR using trifluorotoluene (0.10 mmol) as internal standard (*cf.* Chapter 5.1, Scheme 88).

Base induced trifluoromethylation of palladium complexes



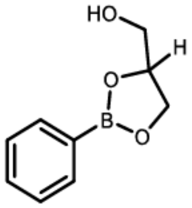
3'5'-Dinitro-2,2,2-trifluoroacetophenone **2.20** (13.2 mg, 0.05 mmol, 1.00 eq.), water (0.9 µL, 0.05 mmol, 1.00 eq.) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 1.00 eq.) were dissolved in dmso-d_6 (0.1 M) and basic silver salts were added (1.00 eq.). No product formation was observed by ^{1}H NMR or by ^{19}F NMR (*cf.* Chapter 5.1, Scheme 89).



3'5'-Dinitro-2,2,2-trifluoroacetophenone **2.20** (26.4 mg, 0.10 mmol, 1.00 eq.), water (1.8 µL, 0.10 mmol, 1.00 eq.), 1,2-bis(diphenylphosphaneyl)benzene (44.7 mg, 0.10 mmol, 1.00 eq.) and either $Pd(OAc)_2$ (22.5 mg, 0.10 mmol, 1.00 eq.) or $Pd(PPh_3)_4$ (115.6 mg, 0.10 mmol, 1.00 eq.) were dissolved in dmso-d_6 (0.1 M) and sodium *tert*-butoxide (9.6 mg, 0.10 mmol, 1.00 eq.) was added (1.00 eq.). No product formation was observed by ^{1}H NMR or by ^{19}F NMR (*cf.* Chapter 5.1, Scheme 89).

6.6 Boronic acids as *O*-nucleophiles in ring-opening reactions

(2-Phenyl-1,3,2-dioxaborolan-4-yl)methanol [5.21]



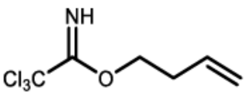
Oxiran-2-ylmethanol (6.7 µL, 0.10 mmol, 1.00 eq.) was dissolved in $CDCl_3$ with 4Å molecular sieves (50 mg/mmol) and phenylboronic acid (12.2 mg, 0.10 µmol, 1.00 eq.) and *N,N*-diisopropylamine (14.1 µL, 0.10 mmol, 1.00 eq.) was added. The mixture was stirred at 60 °C for 16 h. The reaction mixture was subjected to quantitative NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 – 7.79 (m, 2H), 7.53 – 7.43 (m, 1H), 7.40 – 7.31 (m, 2H), 4.68 – 4.52 (m, 1H), 4.38 (dd, *J* = 9.2, 7.7 Hz, 1H), 4.18 (dd, *J* = 9.2, 6.6 Hz, 1H), 2.87 (dd, *J* = 13.9, 5.3 Hz, 1H), 2.53 (dd, *J* = 13.9, 7.7 Hz, 1H). **^{11}B NMR (128 MHz, $CDCl_3$)**: δ = –31.7 (br).

Chemotion ELN sample number: ASS-9-09, ASS-14-38.

6.7 *C–C* and *C–H* functionalisations with trichloro acetimidates

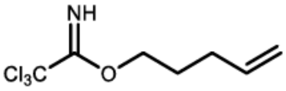
But-3-en-1-yl 2,2,2-trichloroacetimidate [5.24]



According to a literature known protocol with minor alterations,[197] but-3-en-1-ol (0.84 mL, 10.0 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C before trichloroacetonitrile (1.10 mL, 11.0 mmol, 1.10 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (150 µL, 1.00 mmol, 0.10 eq.) were added. The mixture was warmed up to rt and stirred for 15 h. The solvent was removed *in vacuo*. The product was obtained after FC (hexane:NEt_3, 97:3) as a colourless oil (1.44 g, 6.63 mmol, 66%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.27 (s, 1H), 5.86 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.23 – 5.07 (m, 2H), 4.34 (t, J = 6.7 Hz, 2H), 2.54 (qt, J = 6.7, 1.4 Hz, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 163.0, 133.8, 117.6, 91.7, 68.6, 32.7. Spectroscopic data was in agreement to those previously reported.[197]

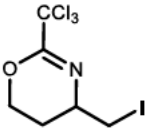
Pent-4-en-1-yl 2,2,2-trichloroacetimidate [5.25]



According to a literature known protocol with minor alterations,[197] pent-4-en-1-ol (1.00 mL, 10.0 mmol, 1.00 eq.) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C before trichloroacetonitrile (1.10 mL, 11.0 mmol, 1.10 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (150 µL, 1.00 mmol, 0.10 eq.) were added. The mixture was warmed up to rt and stirred for 15 h. The solvent was removed *in vacuo*. The product was obtained after FC (hexane:NEt_3, 97:3) as a colourless oil (2.09 g, 9.07 mmol, 91%).

IR (neat): $\tilde{\nu}$ = 3346 (w), 2953 (w), 1664 (s), 1308 (m), 1093 (m), 1084 (m), 997 (m), 913 (m), 826 (m), 797 (s), 736 (w). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 8.24 (s, 1H, N*H*), 5.83 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, C*H*), 5.06 (dq, J = 17.1, 1.7 Hz, 1H, CH_2), 5.01 (ddt, J = 10.2, 2.1, 1.2 Hz, 1H, CH_2), 4.30 (t, J = 6.4 Hz, 2H, CH_2), 2.28 – 2.13 (m, 2H, CH_2), 1.96 – 1.80 (m, 2H, CH_2). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 163.1 (C_q), 137.5 (*C*H), 115.7 (CH_2), 91.7 (C_q), 68.9 (CH_2), 30.0 (CH_2), 27.6 (CH_2).

4-(Iodomethyl)-2-(trichloromethyl)-5,6-dihydro-4*H*-1,3-oxazine [5.27]

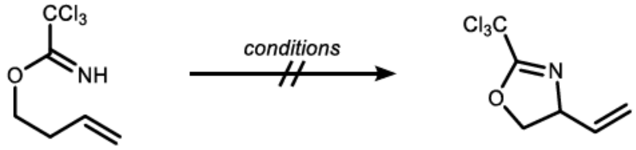


But-3-en-1-yl 2,2,2-trichloroacetimidate **5.24** (21.6 mg, 0.10 mmol, 1.00 eq.) was dissolved in $CHCl_3$ (1 mL) and *N*-iodosuccinimide (33.8 mg, 0.15 mmol, 1.50 eq.) was added and the mixture was stirred for 16 h. The solvent was removed *in vacuo*. The product was obtained after automated FC (CyH:EtOAc, 95:5 to 90:10) as a colourless oil (34.0 mg, 0.099 mmol, 99%)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 4.51 (ddd, J = 11.1, 4.7, 3.6 Hz, 1H, CH_2), 4.33 (td, J = 11.0, 3.3 Hz, 1H, CH_2), 3.72 – 3.63 (m, 1H, CH), 3.50 (dd, J = 10.0, 4.2 Hz, 1H, CH_2), 3.24 (dd, J = 10.0, 8.0 Hz, 1H, CH_2), 2.23 (ddt, J = 14.1, 4.9, 3.5 Hz, 1H, CH_2), 1.84 (dddd, J = 14.0, 11.0, 9.2, 4.6 Hz, 1H, CH_2). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 154.2 (C_q), 92.1 (C_q), 66.3 (CH$_2$), 53.1 (CH), 26.8 (CH$_2$), 10.8 (CH$_2$).

Chemotion ELN sample number: ASS-9-57-A.

Allylic *C–H*-amination with trichloroacetimidates



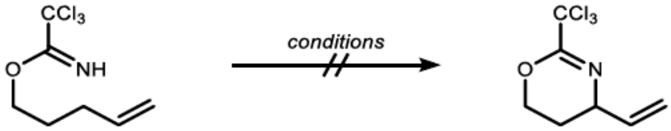
According to a literature known protocol with minor alterations,[126] but-3-en-1-yl 2,2,2-trichloroacetimidate **5.24** (21.6 mg, 0.10 mmol, 1.00 eq.), 4-nitro benzoic acid (1.7 mg, 0.01 mmol, 0.10 eq.) and 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq.) were dissolved in CDCl$_3$ (700 µL). Palladium complex **3.12** (*White* catalyst) (5.0 mg, 0.01 mmol, 0.10 eq.) was added and the mixture was stirred at 40 °C for 17 h. The solvent was removed *in vacuo*. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 13, entry 1).

According to a literature known protocol with minor alterations,[126] but-3-en-1-yl 2,2,2-trichloroacetimidate **5.24** (21.6 mg, 0.10 mmol, 1.00 eq.) and 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq.) were dissolved in AcOH (700 µL). Palladium complex **3.12** (*White* catalyst) (5.0 mg, 0.01 mmol, 0.10 eq.) was added and the mixture was stirred at 40 °C for 17 h. The mixture was diluted with Et$_2$O (2 mL) and water (2 mL). The aqueous phase was treated with NaHCO$_3$ until pH = 7 was reached. The aqueous phase was extracted with Et$_2$O (3x2 mL), the combined organic fractions were dried over Na$_2$SO$_4$, and the solvent was removed *in vacuo*. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 13, entry 2).

But-3-en-1-yl 2,2,2-trichloroacetimidate **5.24** (21.6 mg, 0.10 mmol, 1.00 eq.) and 1,4-benzoquinone (10.8 mg, 0.10 mmol, 1.00 eq.) were dissolved in CH$_2$Cl$_2$ (500 µL). Palladium complex **3.12** (*White* catalyst) (25.1 mg, 0.05 mmol, 0.50 eq.) was added and the mixture was stirred at 40 °C for 17 h. The solvent was removed *in vacuo*. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 13, entry 3).

But-3-en-1-yl 2,2,2-trichloroacetimidate **5.24** (10.8 mg, 0.05 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (500 µL). Palladium complex **3.12** (*White* catalyst) (25.1 mg, 0.05 mmol, 1.00 eq.) was added and the mixture was stirred at 40 °C for 17 h. The solvent was removed *in vacuo*. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 13, entry 4).

But-3-en-1-yl 2,2,2-trichloroacetimidate **5.24** (10.8 mg, 0.05 mmol, 1.00 eq.) was dissolved in AcOH (700 µL). Palladium complex **3.12** (*White* catalyst) (25.1 mg, 0.05 mmol, 1.00 eq.) was added and the mixture was stirred at 40 °C for 17 h. The mixture was diluted with Et_2O (2 mL) and water (2 mL). The aqueous phase was treated with $NaHCO_3$ until pH = 7 was reached. The aqueous phase was extracted with Et_2O (3x2 mL), the combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 13, entry 5).



According to a literature known protocol with minor alterations,[126] pent-4-en-1-yl 2,2,2-trichloroacetimidate **5.25** (23.1 mg, 0.10 mmol, 1.00 eq.) and 1,4-benzoquinone (21.6 mg, 0.20 mmol, 2.00 eq.) were dissolved in dmso-d_6 (700 µL). $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.20 eq.) was added and the mixture was heated to 40 °C for 17 h. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 14, entry 1).

Pent-4-en-1-yl 2,2,2-trichloroacetimidate **5.25** (23.1 mg, 0.10 mmol, 1.00 eq.) was dissolved in dmso-d_6 (700 µL) or CD_2Cl_2 (700 µL). Varying Pd^{II} complexes (1.00 eq. of Pd^{II}) were added. If additives were applied, then (1.00 eq.) was used. The mixture was heated to 40 °C. No product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard (*cf.* 5.3, Table 14, entries 2 to 9).

6.8 *N*-Heterocycle synthesis *via* oxidative rearrangement of secondary amines

General procedure M (GP-M) for the reductive amination of aldehydes and ketones:

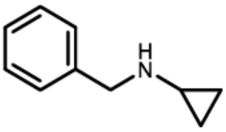
According to a literature known protocol with minor alterations,[199a] aldehyde (1.00 eq.) or ketone (1.00 eq.) was dissolved in methanol (0.25 M) and stirred at 65 °C for 3 h. After cooling to rt, sodium triacetoxyborohydride (2.00 eq.) was added portionwise, and the mixture was heated to 65 °C for 17 h. The solvent was removed to 1/3 of its original volume and NaOH (2N) was added until pH = 14 was reached. The aqueous mixture was extracted with CH_2Cl_2 (3x), the combined organic fractions were washed with NaCl sat. aq. and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the products were isolated *via* FC or automated FC.

General procedure N (GP-N) for the oxidative rearrangement of secondary amines:

Secondary amine (0.10 mmol, 1.00 eq.) was dissolved in TFE (0.2 M) and phenyliodine(III) diacetate (0.11 mmol, 1.10 eq.) was added at 0 °C. The mixture was stirred for 1 h at rt before sodium triacetoxyborohydride (0.50 mmol, 5.00 eq.) was added, and stirred for 1 h followed by the addition of NaOH aq. (2N). The aqueous phase was extracted with CH_2Cl_2 (3x). the combined organic fractions were dried over Na_2SO_4, and the solvent was removed. The residue was subjected to quantitative NMR.

6.8.1 Synthesis of secondary amines

N-Benzylcyclopropanamine [5.37]

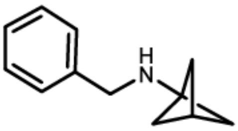


Following **GP-M**, using benzaldehyde (500 µL, 5.00 mmol, 1.00 eq.), cyclopropanamine (350 µL, 5.00 mmol, 1.00 eq.) and sodium triacetoxyborohydride (2.12 g, 10.0 mmol, 2.00 eq.), the desired product was obtained after FC (CH_2Cl_2:MeOH, 98:2) as a colourless oil (774 mg, 5.26 mmol, 53%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.36 – 7.31 (m, 4H), 7.30 – 7.21 (m, 1H), 3.85 (s, 2H), 2.52 (s, 1H), 2.21 – 2.12 (m, 1H), 0.49 – 0.41 (m, 4H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 140.5, 128.5, 128.4, 127.0, 53.8, 30.1, 6.5. Spectroscopic data was in agreement to those previously reported.[237]

Chemotion ELN sample number: ASS-10-61-A.

N-Benzylbicyclo[1.1.1]pentan-1-amine [5.38]

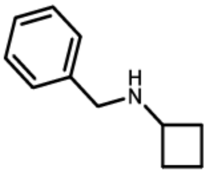


Following **GP-M** with minor alterations, bicyclo[1.1.1]pentan-1-amine hydrochloride (150 mg, 1.25 mmol, 1.00 eq.) and K_2CO_3 (173 mg, 1.25 mmol, 1.00 eq.) were dissolved in MeOH (5 mL) and stirred for 15 min at rt. The suspension was filtered and the filtrate was diluted with MeOH (10 mL). Benzaldehyde (130 µL, 1.25 mmol, 1.00 eq.) was added to the mixture and stirred at 65 °C for 1 h. After cooling to rt, sodium triacetoxyborohydride (2.00 eq.) was added portionwise, and the mixture was heated to 65 °C for 17 h. The solvent was removed to 1/3 of its original volume and NaOH (2N) was added until pH = 14 was reached. The aqueous mixture was extracted with CH_2Cl_2 (3x), the combined organic fractions were washed with NaCl sat. aq. and dried over Na_2SO_4. the desired product was obtained after automated FC (CyH:EtOAc, 10:90 to 20:80) as a colourless oil (98.0 mg, 0.57 mmol, 45%).

IR (neat): $\tilde{\nu}$ = 2961 (s), 2906 (m), 2871 (m), 1454 (m), 1307 (s), 1194 (m), 1061 (m), 738 (s), 699 (s). **^{1}H NMR (300 MHz, CDCl$_3$)**: δ = 7.35 – 7.28 (m, 4H, C*H*$_{\text{arom.}}$), 7.26 – 7.20 (m, 1H, C*H*$_{\text{arom.}}$), 3.78 (s, 2H, C*H*$_2$), 2.39 (s, 1H, C*H*), 1.85 (s, 1H, N*H*), 1.80 (s, 6H, C*H*$_2$). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 140.7 (C_q), 128.5 (*C*H), 128.1 (*C*H), 127.0 (*C*H), 56.7 (C_q), 51.1 (*C*H$_2$), 50.0 (*C*H$_2$), 22.8 (*C*H). **HRMS (ESI)**: Calculated for $C_{12}H_{16}N$ [M+H]$^+$: 174.1277, Found: 174.1275.

Chemotion ELN sample number: ASS-416.

N-Benzylcyclobutanamine [5.41]

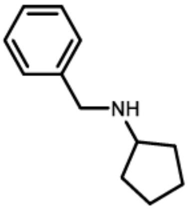


Following **GP-M**, using cyclobutanone (370 µL, 5.00 mmol, 1.00 eq.), benzylamine (550 µL, 5.00 mmol, 1.00 eq.) and sodium triacetoxyborohydride (2.12 g, 10.0 mmol, 2.00 eq.), the desired product was obtained after FC (CH_2Cl_2:MeOH, 98:2) as a colourless oil (412 mg, 2.56 mmol, 51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 – 7.29 (m, 4H), 7.29 – 7.20 (m, 1H), 3.71 (s, 2H), 3.37 – 3.24 (m, 1H), 2.30 – 2.14 (m, 2H), 1.81 – 1.55 (m, 5H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ = 140.3, 128.5, 128.4, 127.1, 53.6, 51.1, 31.1, 14.9. Spectroscopic data was in agreement to those previously reported.[238]

Chemotion ELN sample number: ASS-10-51-A.

N-Benzylcyclopentanamine [5.42]

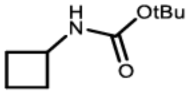


Following **GP-M**, using cyclopentanone (440 µL, 5.00 mmol, 1.00 eq.), benzylamine (550 µL, 5.00 mmol, 1.00 eq.) and sodium triacetoxyborohydride (2.12 g, 10.0 mmol, 2.00 eq.), the desired product was obtained after FC (CH_2Cl_2:MeOH, 98:2) as a colourless oil (412 mg, 2.56 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.29 (m, 4H), 7.28 – 7.21 (m, 1H), 3.78 (s, 2H), 3.12 (p, J = 6.7 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.77 – 1.64 (m, 2H), 1.60 – 1.46 (m, 2H), 1.44 – 1.32 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 140.6, 128.5, 128.4, 127.0, 59.2, 52.8, 33.2, 24.2. Spectroscopic data was in agreement to those previously reported.[239]

Chemotion ELN sample number: ASS-339.

tert-Butyl cyclobutylcarbamate [5.45]

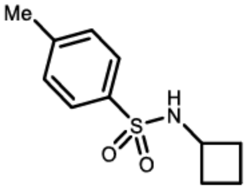


According to a literature known protocol with minor alterations,[200a] cyclobutanamine (854 µL, 10.0 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) and di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol, 1.10 eq.) dissolved in dichloromethane (5 mL) was added at 0 °C. The mixture was stirred for 2 h at rt before HCl aq. (1N) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3x10 mL). The combined organic fractions were washed with NaOH aq. (1N), NaCl sat. aq., dried over Na_2SO_4 and the solvent was removed *in vacuo*. The desired product was obtained after filtration through silica with EtOAc:CyH (15:85) as a colourless solid (1.33 g, 7.77 mmol, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (s, 1H), 4.18 – 3.96 (m, 1H), 2.29 (*app.* q, J = 7.9 Hz, 2H), 1.88 – 1.71 (m, 2H), 1.69 – 1.53 (m, 2H), 1.43 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 154.9, 79.3, 45.9, 31.7, 28.5, 14.9. Spectroscopic data was in agreement to those previously reported.[240]

Chemotion ELN sample number: ASS-388.

N-Cyclobutyl-4-methylbenzenesulfonamide [5.46]

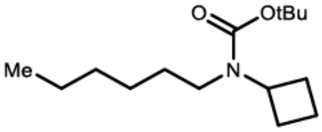


According to a literature known protocol with minor alterations,[241] cyclobutanamine (430 µL, 5.00 mmol, 1.00 eq.) and NEt_3 (1.05 mL, 7.50 mmol, 1.50 eq.) were dissolved in dichloromethane (25 mL) and *p*-toluenesulfonyl chloride (1.05 g, 5.50 mmol, 1.10 eq.) was added. The mixture was stirred for 3 h at rt, before NaOH aq. (1N, 10 mL) was added and the aqueous phase was extracted with EtOAc (3x25 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was obtained after FC (EtOAc:CyH, 10:90 to 30:70) as a colourless solid (1.12 g, 4.97 mmol, 99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 – 7.71 (m, 2H), 7.31 – 7.27 (m, 2H), 4.78 (d, J = 8.9 Hz, 1H), 3.87 – 3.69 (m, 1H), 2.42 (s, 3H), 2.19 – 2.04 (m, 2H), 1.85 – 1.67 (m, 2H), 1.65 – 1.44 (m, 2H). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ = 143.5, 138.0, 129.8, 127.2, 48.3, 31.9, 21.7, 15.1. Spectroscopic data was in agreement to those previously reported.[242]

Chemotion ELN sample number: ASS-10-92-A.

tert-Butyl cyclobutyl(hexyl)carbamate [5.49]



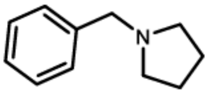
According to a literature known protocol with minor alterations,[243] *tert*-butyl *N*-cyclobutylcarbamate **5.45** (250 mg, 1.46 mmol, 1.00 eq.) was dissolved in DMF (14 mL) and sodium hydride (60%, 64.2 mg, 1.61 mmol, 1.10 eq.) was added at 0°C. The mixture was warmed to rt and stirred for 30 min before 1-bromohexane (310 µL, 2.19 mmol, 1.50 eq.) was added. The mixture was stirred for 17 h before NH_4Cl sat. aq. (10 mL) was added and the aqueous phase was extracted with Et_2O (3x15 mL). The combined organic fractions were washed with LiCl aq. (5% w/w, 50 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The product was obtained after FC (EtOAc:Cy, 0:100 to 10:90) as a colourless oil (250 mg, 0.98 mmol, 67%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.24 (s, 1H), 3.20 – 3.08 (m, 2H), 2.20 – 1.96 (m, 4H), 1.70 – 1.50 (m, 4H), 1.45 (s, 9H), 1.28 (app. p, J = 5.4 Hz, 6H), 0.93 – 0.82 (m, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 155.5, 79.2, 51.0, 43.7, 31.8, 30.0, 29.4, 28.7, 26.8, 22.8, 14.9, 14.2. **HRMS (ESI)**: Calculated for $C_{15}H_{29}NO_2Na$ [M+Na]$^+$: 278.2091, Found: 278.2097

Chemotion ELN sample number: ASS-10-87-A.

6.8.2 Oxidative rearrangement of secondary amines

1-Benzylpyrrolidine [5.50]

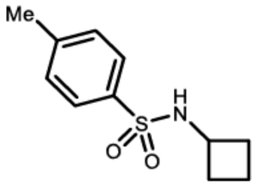


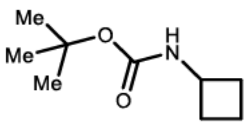
By following **GP-N**, using *N*-benzylcyclobutanamine **5.41** (16.1 mg, 0.10 mmol, 1.00 eq.), phenyliodine(III) diacetate **5.36** (35.4 mg, 0.11 mmol, 1.10 eq.) and sodium triacetoxyborohydride (106 mg, 0.50 mmol, 1.00 eq.) the product was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard.

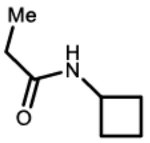
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.39 – 7.28 (m, 5H), 3.69 (s, 2H), 2.65 – 2.55 (m, 4H), 1.87 – 1.77 (m, 4H). Spectroscopic data was in agreement to those previously reported.[244]

Chemotion ELN sample number: ASS-14-44.

Limitations

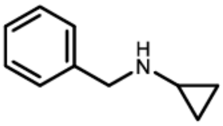


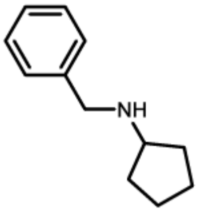


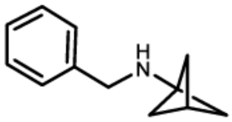


Prepared by K. Sellmann

By following **GP-N**, using the above shown amines (0.10 mmol, 1.00 eq.) in combination with phenyliodine(III) diacetate **5.36** (0.11 mmol, 1.10 eq.), or (bis(trifluoroacetoxy)iodo)benzene **5.51** (0.11 mmol, 1.10 eq.), and sodium triacetoxyborohydride (0.50 mmol, 5.00 eq.) no product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard.







By following **GP-N**, using the above shown secondary amines (0.10 mmol, 1.00 eq.) in combination with phenyliodine(III) diacetate **5.36** (0.11 mmol, 1.10 eq.) and sodium triacetoxyborohydride (0.50 mmol, 5.00 eq.) no product formation was observed by ^{1}H NMR using mesitylene (0.10 mmol) as internal standard.

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