DISSERTATION | DOCTORAL THESIS

Titel | Title

Harnessing Carbocations for the Remote Functionalization of Alkenes and Silyl Enol Ethers

verfasst von | submitted by

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Slow, but I'm getting there!

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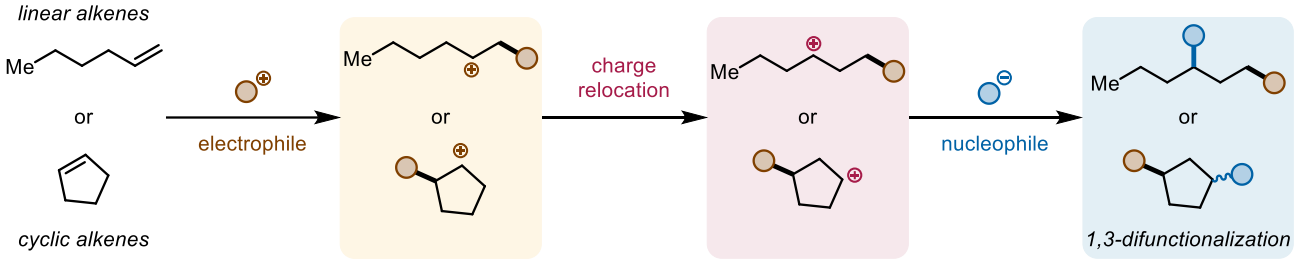
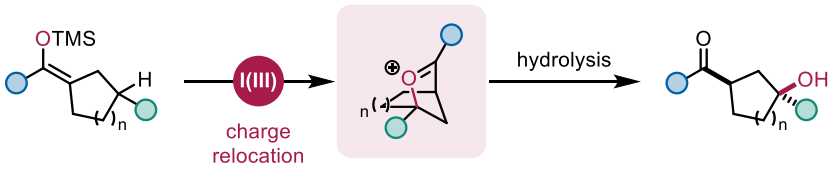
Abstract

The first chapter of this thesis describes our efforts to develop a method for the 1,3-difunctionalization of unbiased linear and cyclic alkenes using acyl chlorides and silver salts, generating oxocarbenium intermediates after a selective charge migration to a controlled position: a process we termed *charge relocation*. Treatment of these carbocationic species with a variety of suitable nucleophiles has resulted in the development of a stereodivergent synthesis of ketoalcohols, dicarbonyls compounds and various difunctionalized products, as well as biologically active molecules.

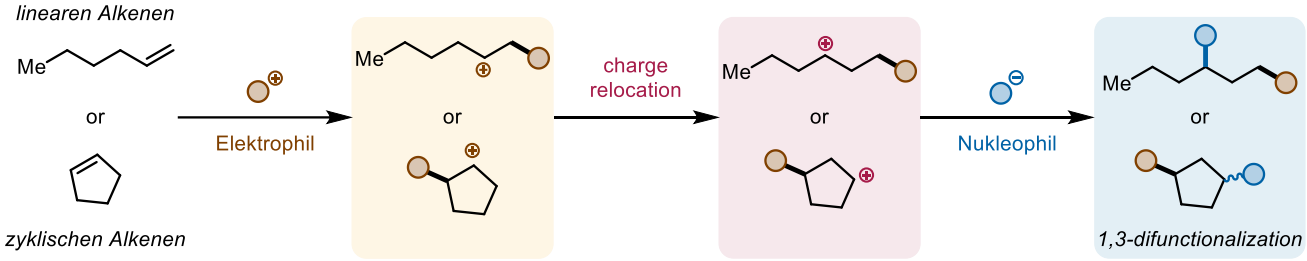


The second chapter of this thesis details mechanistic insights gained from treating silyl enol ethers with preactivated hypervalent iodine reagents. This reaction results in remote oxidation of unreactive C–H bonds in cyclic hydrocarbons via a directed cationic rearrangement similar to the previously described *charge relocation*.

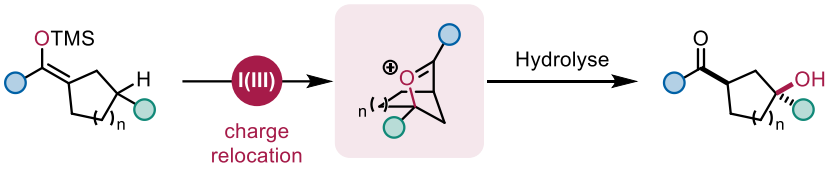


Kurzzusammenfassung

Das erste Kapitel dieser Arbeit beschreibt unsere Bemühungen, eine Methode zur 1,3-Difunktionalisierung von linearen und zyklischen Alkenen unter Verwendung von Acylchloriden und Silbersalzen zu entwickeln, wobei nach einer selektiven Ladungswanderung an eine kontrollierte Position Oxocarbenium-Zwischenprodukte entstehen: ein Prozess, den wir im Englischen als *charge relocation* bezeichnen. Die Behandlung dieser carbokationischen Spezies mit einer Vielzahl geeigneter Nukleophile hat zur Entwicklung einer stereodivergenten Synthese von Ketoalkoholen, Dicarbonylen und verschiedenen difunktionalisierten Produkten, sowie biologisch aktiven Molekülen, geführt.



Im zweiten Kapitel dieser Arbeit werden Einblicke in den Mechanismus der Reaktion von Silylenolethern mit aktivierten hypervalenten Iodreagenzien beschrieben. Diese führt zu einer Oxidation entfernter, unreaktiver C–H-Bindungen in zyklischen Kohlenwasserstoffen über eine gerichtete kationische Umlagerung ähnlich der zuvor beschriebenen *charge relocation*.



Abbreviations

°C	degrees Celsius
Ac	acetyl
Ad	adamantyl
Ar	aryl
BDE	bond dissociation energy (at 298.15 K)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
br	broad
Bu	butyl
cf.	confer (*latin for:* "compare")
d	doublet
δ	chemical shif
ΔG	Gibbs free energy change
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine; Hünig's base
	DMAP 4-dimethylaminopyridine
DMF	dimethylformamide
EDCI	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide
EDG	electron-donating group
ee	enantiomeric excess; e.g. exempli gratia (*latin for:* "for example")
er	enantiomeric ratio
Et	ethyl
et al.	et alia (latin for: "and others")
etc.	et cetera (latin for: "and other things")
EtOAc	ethyl acetate eq. equivalents
EWG	electron-withdrawing group
GC-MS	gas chromatography – mass spectrometry
h	hour(s)
HFIP	hexafluoroisopropanol; 1,1,1,3,3,3-hexafluoropropan-2-ol
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
i.e.	id est (latin for: "that is to say")
IR	infrared
K	Kelvin
L	litre(s)
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	metre; multiplet
m	meta
M	molar, mol*L−1
***m*CPBA**	meta-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	Megahertz, 1·106 s−1
mm	millimetre(s)
MOM	methoxymethyl
Ms	mesyl, methanesulfonyl
N	normal
Nm	nanometre(s)
NMR	nuclear magnetic resonance
o	ortho
p	para
p	pentet
Ph	phenyl

ppm parts per million

Pr propyl

py pyridine

q quartet quant. quantitative

rac racemic

s singlet

SOMO singly occupied molecular orbital

T triplet

TBDPS tert-butyldiphenylsilyl

TBS tert-butyldimethylsilyl

tert, t tertiary

TES triethylsilyl

Tf triflyl, trifluoromethanesulfonyl

TFA trifluoroacetic acid

THF tetrahydrofuran

TIPS tri-iso-propylsilyl

TLC thin layer chromatography

TMS trimethylsilyl

Tol tolyl

Trt trityl, triphenylmethyl

Ts toluenesulfonyl

TsOH p-toluenesulfonic acid

vide

infra latin for: “see below”

vide

supra latin for: “see above”

xs excess

1 Electrophilic Functionalization of Alkenes

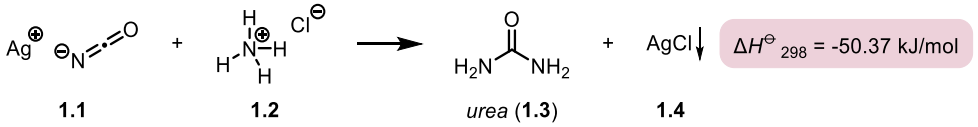
The work described was conducted in collaboration with Dr. Giulia Iannelli, Dr. Margaux Riomet and Dr. Daniel Kaiser. The results of this project have, in parts, been published.[1]

1.1 Introduction

This chapter will focus on alkene functionalization using electrophilic species, with emphasis on acylium ions paired with non-coordinating and non-basic counter ions.

1.1.1 The Genesis of Organic Chemistry

The dawn of organic chemistry was kickstarted in 1828 by Friedrich Wöhler's urea synthesis.[2] Not only was this the first synthesis of an organic molecule from simple inorganic substances, particularly silver cyanate (**1.1**) and ammonium chloride (**1.2**) (Scheme 1.1),[3] it contributed towards a shift in the established world view at the time by challenging the concept of *vitalism*. The belief of vitalism was rooted in the premise that there are non-physical elements that distinguish living organisms from non-living ones.[4] The driving force of this particular reaction is the formation of the slightly more thermodynamically stable urea [$(NH_2)_2CO$] (**1.3**), when compared to **1.1** (difference in standard enthalpy of formation of 18.76 kJ/mol), as well as the precipitation of silver chloride (AgCl, **1.4**), by removing it from the system and pushing the equilibrium towards reactants in accordance with Le Chatelier's principle).[5] Aside from representing the first synthesis of an organic compound, the use of all four classical organogen elements—C, H, N and O—adds to the beauty of the reaction.[a] While this process has most often been highlighted for giving rise to the field of *organic chemistry*, the impact of using formation of silver chloride as a driving force has been used by organic chemists ever since.

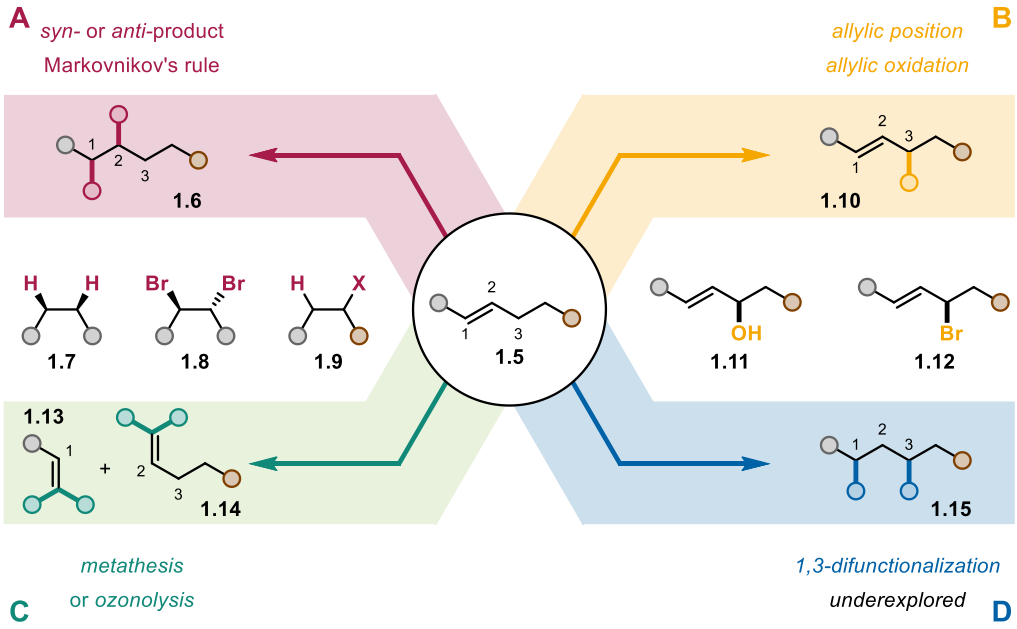


Scheme 1.1: First synthesis of an organic compound by Friedrich Wöhler.

[a] The definition according to Merriam-Webster dictionary has been updated over time to also include sulfur and phosphor

1.1.2 Current Paradigm of Alkene Functionalization

Alkenes or olefins, are the simplest unsaturated hydrocarbons. They contain a functional handle, the carbon-carbon double bond which opens up endless possibilities for further derivatization. Among the current, well-established paradigms in chemistry text-books are three types of functionalization. The first is 1,2-addition—addition of two fragments across a double bond with concomitant cleavage of the π-bond, while maintaining the C–C σ-bond connectivity.[6] [7] Notably, these 1,2-additions (**1.6**) (Scheme 1.2A), resulting in the formation of *syn*- (**1.7**) or *anti*-configured products (**1.8**), follow Markovnikov's rule.[8] There are however a plethora of reports on the synthesis of *anti*-Markovnikov products. Such is the case for hydroboration,[9] where, rather than addition of a proton and a nucleophile, a hydride and electrophilic boron species are added; in this case the boron atom assumes the role of the proton and stabilization of the resulting positive charge dictates regioselectivity. Additionally, other factors, such as steric hindrance, can play a role. The second type of functionalization of alkene-containing structures is allylic functionalization. While in most cases preserving the original C=C bond, the allylic position (**1.10**) can lend itself to functionalization reactions such as oxidation (**1.11**), radical functionalization (such as halogenation, **1.12**) or even more complex transition-metal-catalyzed processes (Scheme 1.2B)[10] [11] [12] [13] The third established mode of alkene functionalization involves C=C bond-cleavage reactions, such as metathesis (**1.13** and **1.14**) or ozonolysis (Scheme 1.2C).[14]



Scheme 1.2: Functionalization of alkenes. A) 1,2-Difunctionalization of alkenes. B) Allylic functionalization of alkenes. C) Bond-breaking of the alkene double bond. D) Underexplored 1,3-difunctionalization of alkenes.

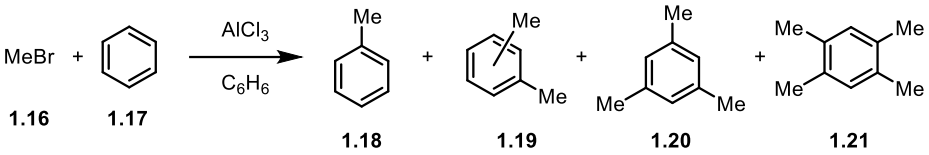
The field of remote functionalization has gained popularity in the last decades and aims to divert reactivity away from the initial double bond and towards a distal position, resulting in 1,n-functionalization

transforms (**1.15**, n > 2).[15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] However this field is still underexplored and usually requires adjuvant elements to overcome selectivity and reactivity challenges (Scheme 1.2D).

In some of the above highlighted cases, double bonds fulfill the role of a nucleophile, using their π-electrons for electrophilic addition (A_E), thereby forming a carbon-centered cation (carbocation). This type of reactivity is also particularly well described for aromatic rings, giving rise to electrophilic aromatic substitution (S_EAr), where one of the classical examples is the Friedel–Crafts reaction.

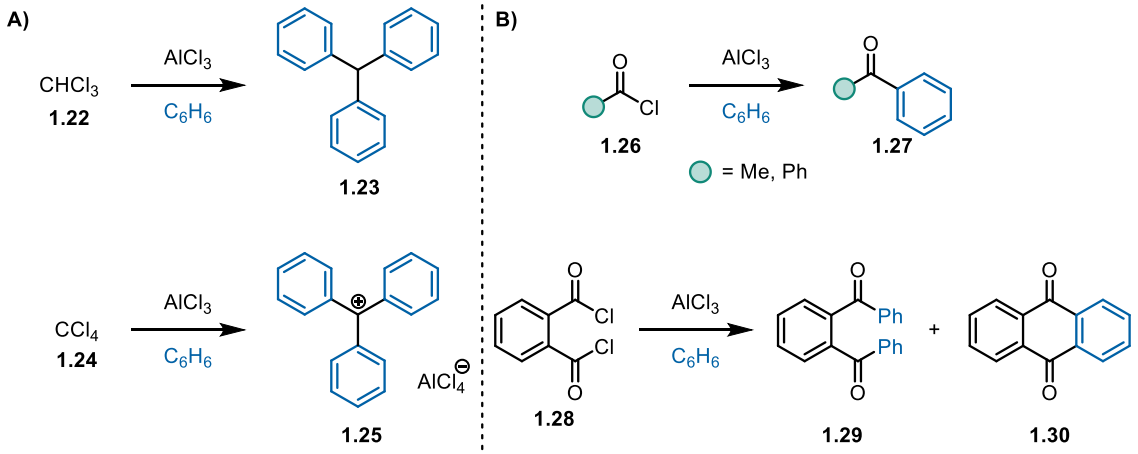
1.1.3 Friedel–Crafts Reactions

Over the course of five years (1877–1881), Friedel and Crafts published nine papers together on the reaction that would later carry their name. In their first paper, they reported the alkylation of benzene with different electrophiles such as methylbromide (Scheme 1.3).[26] [27] They showcased the unselective nature of alkylation with a primary halide (**1.16**), leading to mixtures of polysubstituted products (**1.18**-**1.21**). This lack of selectivity is a direct result of the inductive effect of the methyl groups, leading to increased nucleophilicity of alkylated benzenes (**1.18**-**1.21**), compared to non-substituted benzene itself (**1.17**). Thus, these products are more reactive towards electrophiles and generate di-, tri- and tetra-substituted arenes (while penta- and fully-substituted ones could in theory be achievable, the steric hindrance of *ortho*-substituents reduces the likelihood of such processes). Therefore, a mixture of compounds is inevitable in the classical Friedel–Crafts alkylation protocol.



Scheme 1.3: First joint paper of Friedel and Crafts: alkylation of benzene.

The following articles expanded the range of electrophiles from alkyl mono-halides to polyhalogenated reactants such as chloroform (**1.22**) and carbon tetrachloride (**1.24**) (Scheme 1.4A),[28] and even acyl chlorides (**1.26** and **1.28**) (Scheme 1.4B).[29]

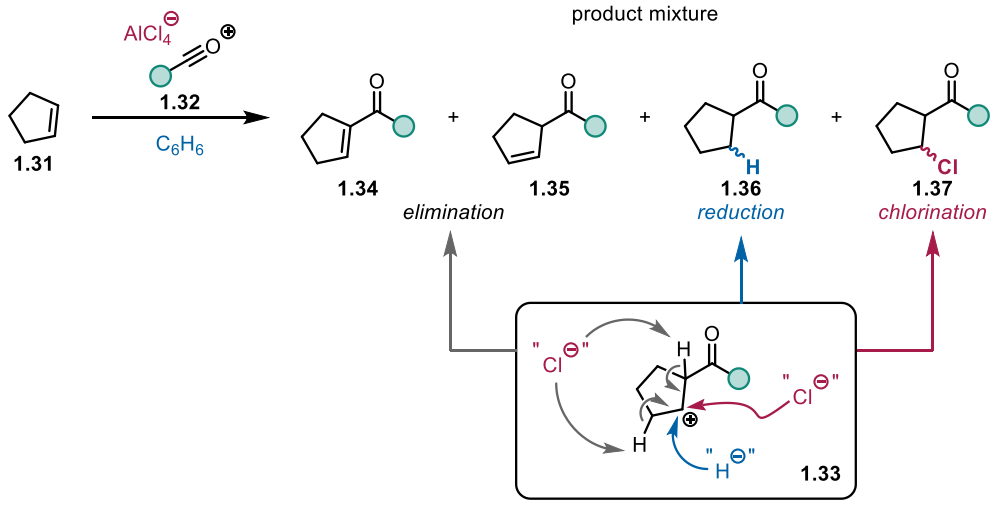


Scheme 1.4: A) Second alkylation report by Friedel and Crafts. B) First acylation report by Friedel and Crafts.

While in their investigation with CCl_4 (**1.24**), tetraphenylmethane was suggested as the product, it was later shown to be in fact the tritylium salt $[Ph_3C][AlCl_4]$ (**1.25**). Later reports show that the acylation reaction, in contrast to its predecessor, has an increased selectivity. In most cases it leads to mono-substituted arenes, thanks to the reduced electron density of the aromatic ring bearing a deactivating substituent (acyl). However,

rate differences between intra- and inter-molecular processes, as well as varying stoichiometry can still influence the outcome of the process, as shown by the reaction of phthaloyl dichloride (**1.28**) with benzene, leading to both 1,2-phenylenebis(phenylmethanone) (**1.29**) and anthraquinone (**1.30**), the latter resulting from intramolecular acylation following the first, intermolecular reaction.

Importantly, Friedel–Crafts-type reactions are not limited to arene substrates. An extensive body of nucleophilic additions of alkenes (**1.31**) to acylium ions (**1.32**) is known.[30] However, the reported processes are unselective, leading to mixtures of elimination products such as α,β- and β,γ-enones (**1.34** and **1.35**), depending on which proton is abstracted by the conjugated base (Cl^- or $AlCl_4^-$). Reduction is also possible to form **1.36**, the hydride source being the solvent itself (cyclohexane). Additionally, chlorination reactions to form **1.37**, relying on the chloride sources present in the reaction mixtures (Cl^-, $AlCl_4^-$ or even unreacted acyl chloride) are also observed (Scheme 1.5). Generally, product distributions for such processes were found to be reliant on a variety of factors, including the nature of the substrate, the precise choice of reagents and the properties of the solvent used.

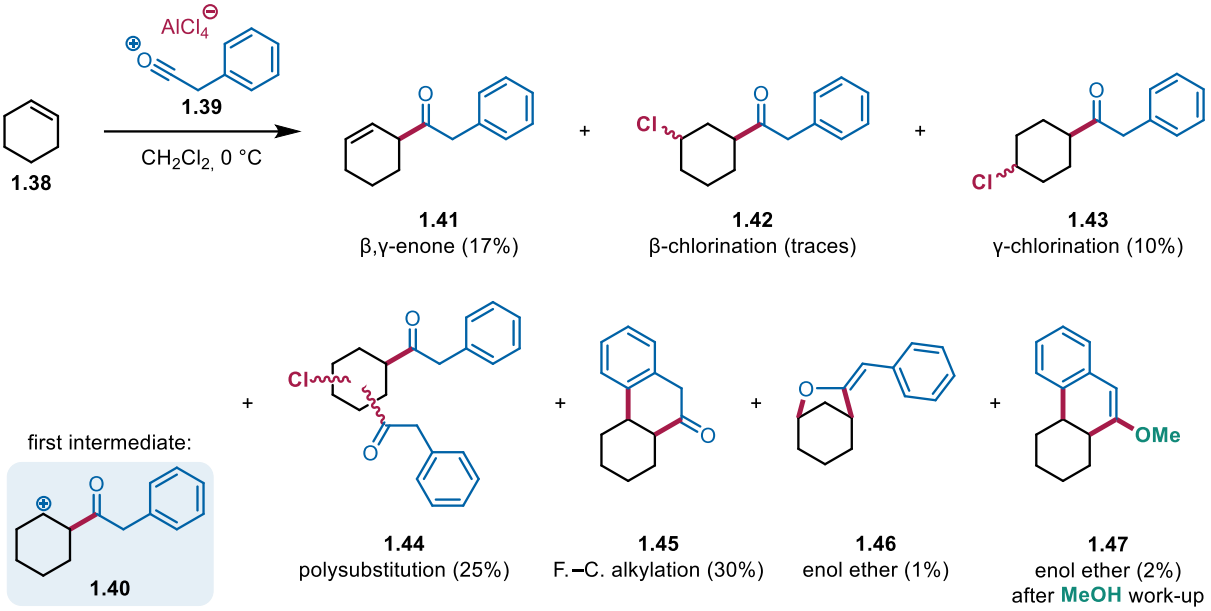


Scheme 1.5: Friedel–Crafts-type reactions of alkenes are generally unselective, leading to product mixtures.

In addition to monofunctionalization (formation of **1.34**) and 1,2-funtionalization using acyl chlorides in a Friedel–Crafts fashion, remote functionalization of alkenes is also possible. The mechanism by which these products are formed with be discussed later (section 1.3.2).

Due to the high reactivity of the carbocationic intermediate **1.40** formed upon alkene double-bond addition to an electrophile (in this case the acylium ion **1.39**), most reports resort to reporting mixtures of products resulting from unselective 1,2- and 1,3-difunctionalization.[31] [32] [33] [34] One particular case was shown by Wolinsky in 1979, where treatment of phenylacetyl chloride with cyclohexene in the presence of $AlCl_3$ in dichloromethane at 0 °C, led to the formation of a mixture of no less than seven distinct products:

β,γ-enone **1.41** (17%), β- and γ-chlorinated **1.42** (traces) and **1.43** (10%), Friedel–Crafts product **1.45** (30%), polysubstituted **1.44** (25%) and enol ethers **1.47** (2%) and **1.46** (1%) (Scheme 1.6).[31]

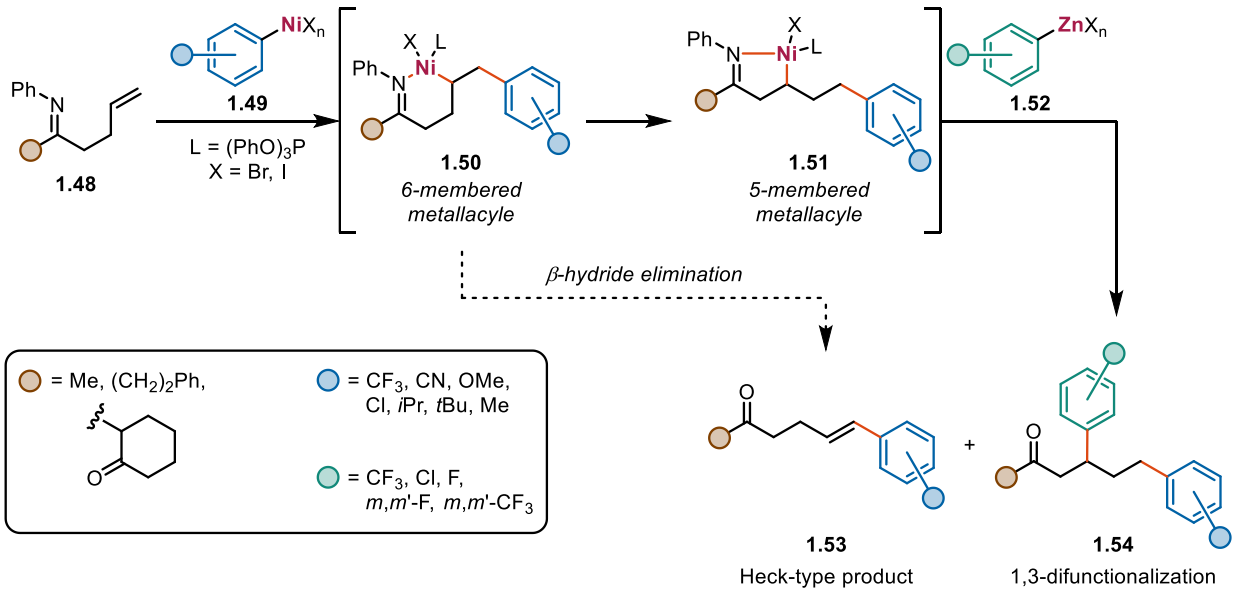


Scheme 1.6: Friedel–Crafts-type reactions of alkenes are unselective, leading to product mixtures.

1.1.4 State of the Art of Remote Functionalization of Alkenes

Several methods for the 1,3-difuntionalization of alkenes have been reported. However, they usually require transition-metal catalysts and prefunctionalized substrates (biased alkenes). Such prefunctionalized substrates often bear a deliberately installed directing group, such as an arene, alcohol, ketone or hydrazone, employed to terminate the migration of the transition metal at a certain position, for example through coordination. One major downside to these methods is the tendency of the metallacycles (carbocyclic compound wherein a metal has replaced at least one carbon center) formed through such coordination to undergo β-hydride (β-H) elimination, forming Heck-type products.[7] [35] [36] [37] [38] [39] Additionally, the field of photochemistry has bloomed over the past decades thanks to considerable advancements in the area.[40] [41] [42] [43] [44] Therefore it comes as no surprise that, complementary to transition-metal catalysis, photocatalysis can facilitate remote functionalization processes.

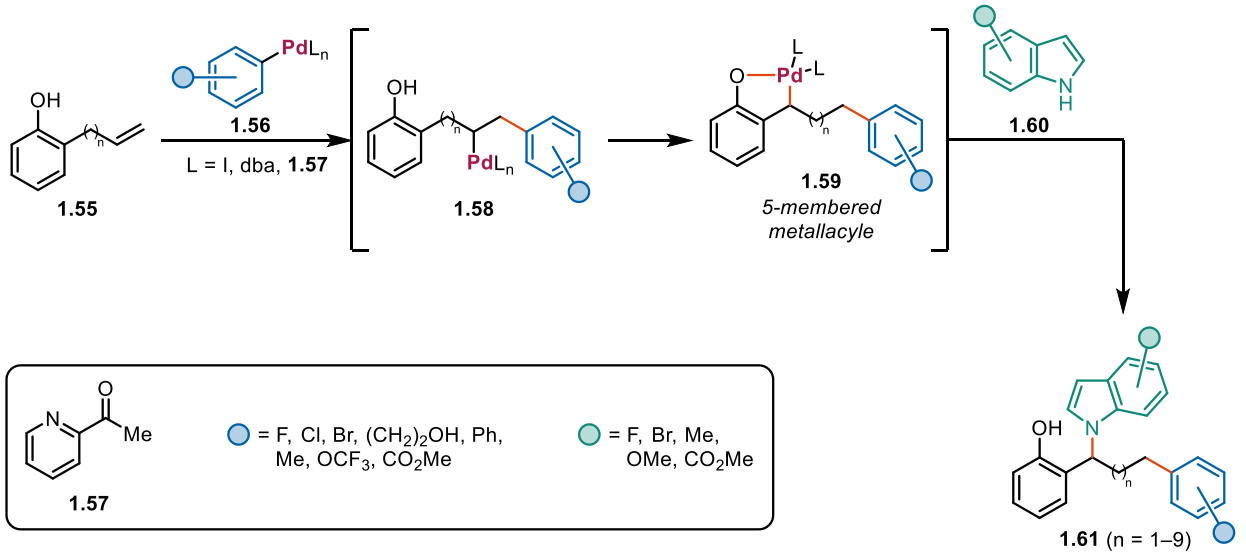
One such example of transition-metal catalysis is the 1,3-difunctionalization of alkenes bearing a ketimine group (**1.48**) under nickel catalysis (Scheme 1.7).[39] The driving force, as well as the feature determining the regioselectivity of this reaction is the formation of a 5-membered metallacycle (**1.50**) that, after transmetalation with aryl zincates (**1.52**), can lead to the formation of β,δ-disubstituted ketones (**1.54**) upon hydrolysis of the ketimine. The main disadvantages of this method are the use of transition metals such as catalytic nickel and excess of zinc (1.5 eq. aryl zincate) and the required prefunctionalized ketone (**1.48**, in this case a ketimine). As described above, β-hydride elimination, leading to formation of Heck-type products **1.53**, was found to be the main competing pathway to this process.



Scheme 1.7: Ni-catalyzed regioselective 1,3-difuntionalization of alkenes using ketimines as directing groups.

In addition to nickel, there are also reports using palladium as a catalyst to promote chain walking (defined as an iterative series of consecutive 1,2- or 1,3-hydride transfer steps of a metal complex along a

single hydrocarbon chain),[45] ending the sequence in a 5-membered metallacycle (**1.59**) (Scheme 1.8).[37] In this case, the authors report remote 1,3- up to 1,11-diarylaminations of alkenes (**1.55**) with excellent regio- and chemoselectivity. The main drawback of this method is, as in the case of most transition-metal-based protocols, the mandatory use of functionalized alkenes bearing a directing group (**1.55**). Without this feature, Heck-type products or other β-hydride elimination mixtures are most likely to be formed.

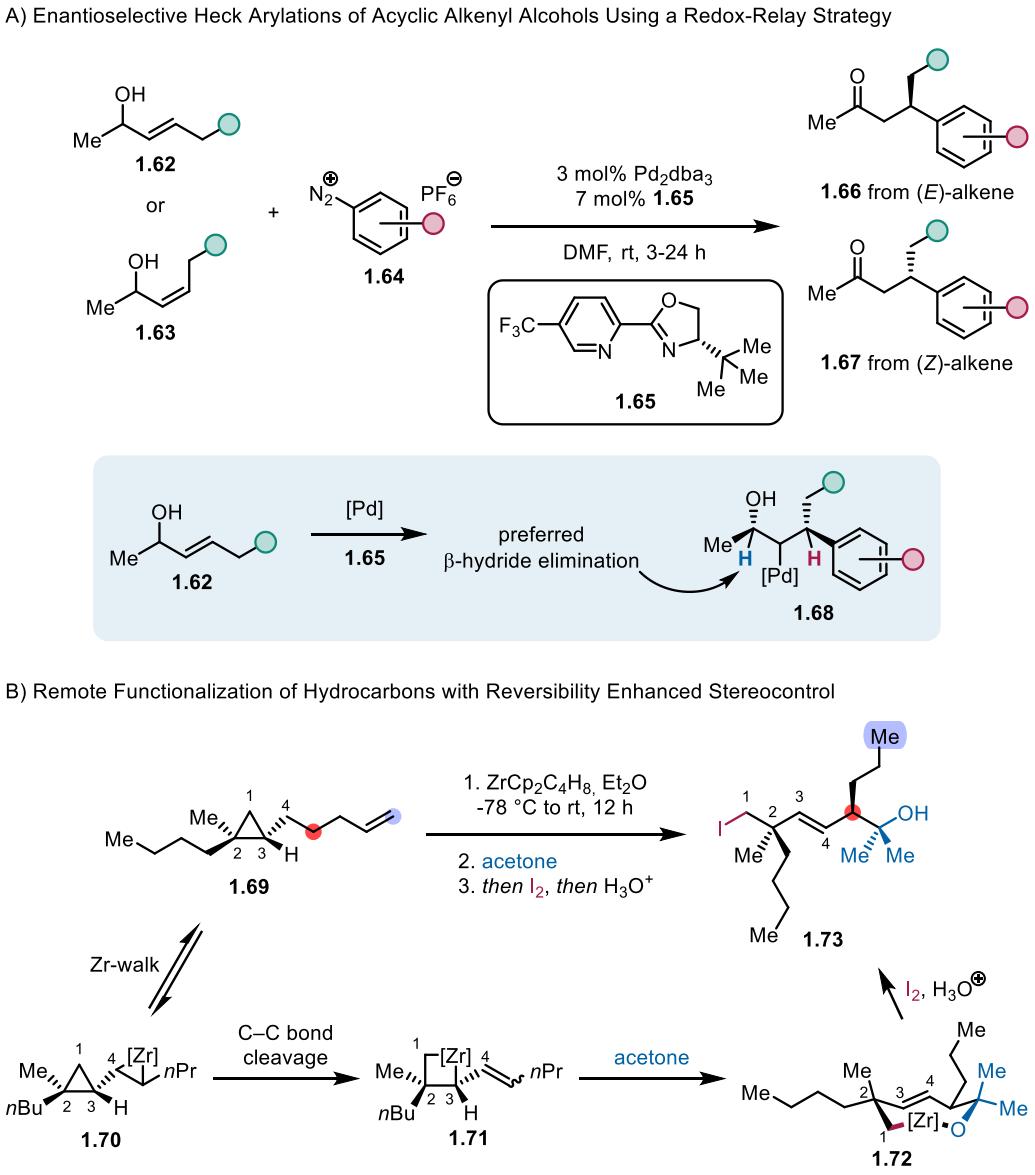


Scheme 1.8: Pd-catalyzed regioselective 1,n-difuntionalization of alkenes using decorated phenols as directing groups.

In 2012, Sigman *et al.* reported an enantioselective Heck arylation using allylic alcohols (Scheme 1.9A),[7] where they combined several concepts: the substrate-biased nature of Heck reactions,[46] [47] [48] [49] [50] redox-relay processes of allylic alcohols (preferred insertion into terminal alkenes)[51] [52] and chain-walking capabilities of palladium species (through sequential β-hydride eliminations/migratory insertions).[53] [54]

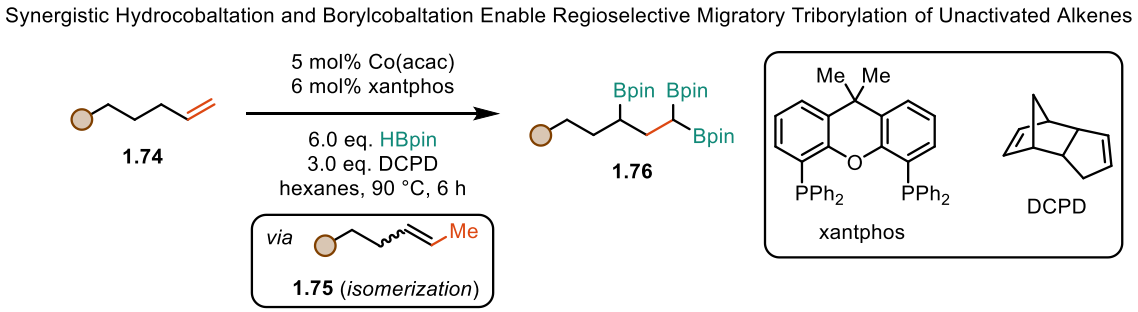
In this protocol, aryldiazonium salts (**1.64**) were used as the arene source in combination with (*E*)- or (*Z*)-configured allylic alcohols (**1.62** or **1.63**) to give enantiopure products (**1.66** or **1.67**). Based on the configuration of the double bond, the authors were able to obtain the two corresponding enantiomers (**1.66** and **1.67**) using the same catalyst (Pd_2dba_3) and chiral ligand (**1.65**). The process relies on several key components: a directing group (allylic alcohols, 2 step synthesis), control of the double-bond geometry (**1.62** or **1.63**), the use of diazonium salts (**1.64**) (not commercially available) and transition-metal catalyst (Pd_2dba_3).

Similarly to palladium chain-walking,[45] zirconocene-mediated allylic C–H bond activation followed by selective C–C bond cleavage (Scheme 1.9A) can also lead to remote functionalization of alkenes. The method enables the functionalization of alkenes in a 1,4-fashion (highlighted) with high diastereocontrol, relying on enantiomerically enriched cyclopropane starting materials,[55] [56] [57] which enable the formation of products bearing enatiomerically enriched tertiary and quaternary carbon centers.



Scheme 1.9: Remote functionalization – literature highlights (I): A) Enantioselective Heck arylation of allylic alcohols. B) Zirconocene-mediated allylic C–H bond activation.

A further example showcasing the recent variety of remote functionalization reactions is the triborylation of unactivated alkenes (Scheme 1.10).[22] In the initial step, cobalt-catalyzed isomerization of the terminal double bond (**1.74**) shifts the double bond one methylene group away to form **1.75**. The internal alkene subsequently undergoes a Boryl-Heck reaction, introducing the internal pinacolatoboryl moiety (Bpin) at the allylic position of the concomitantly reformed terminal double bond. Finally, 1,1-diborylation of the substrate yields the desired 1,1,3-triborylalkanes (**1.76**). While this methodology employs unfunctionalized alkenes, a sacrificial alkene, namely dicyclopentadiene (DCPD), is required as a hydrogen acceptor, in order to prevent further isomerization of the alkene substrate **1.75**.



Scheme 1.10: Remote functionalization – literature highlights (II): Triborylation of unactivated alkenes.

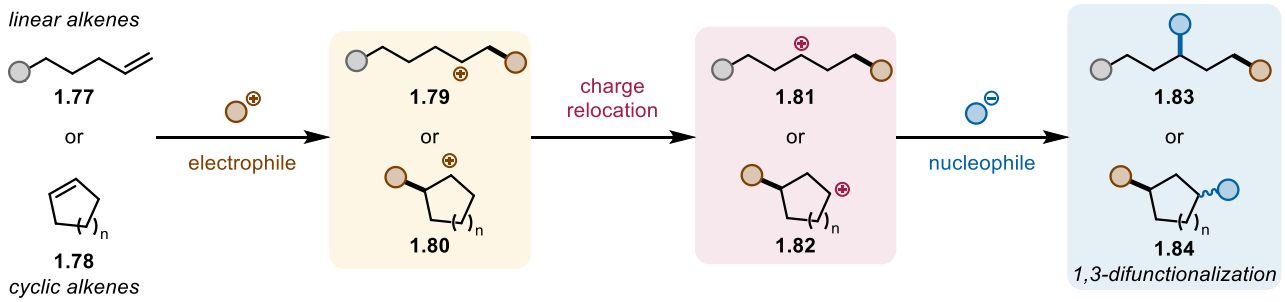
In conclusion, remote functionalization of alkenes has garnered substantial interest over the past decades, highlighted by the plethora of research articles and new creative ways of manipulating highly reactive species generated either by transition-metal catalysis or photochemical methods. However, the development of transformations effecting distal functionalization of simple, commercially available molecules, free of functional handles or directing groups, still requires further investigation. Such methods not only have the potential to redefine the reactivity and synthetic limitations of alkenes, but also exponentially increase the number of possible substrates. Therefore, a method which brings deeper understanding towards which factors govern reactivity as well as a method to increase chemo-, regio- and stereoselectivity is highly desirable. These methods could also have applications beyond academic interest potentially enabling the development of more efficient industrial procedures.

1.2 Aim of the Project

While established methods of alkene functionalization are among the first textbook organic chemistry reactions learned, 1,3-difuntionalization is still a relatively new reactivity staple. Modern methods mostly rely on transition-metal catalysed processes employing prefunctionalized substrates or the use of substrates bearing directing groups as stoppers, dictating the final site of bond formation.

This work aimed to develop a method for the 1,3-difunctionalization of unbiased alkenes (**1.77** or **1.78**), both terminal and internal, as well as cyclic olefins. Inspired by the reports of the Friedel–Crafts reactions of alkenes, we set out to generate an electrophilic species that can be attacked by an alkene without further leading to divergent reactivity (e.g., halogenation, elimination) of the resulting carbocation (**1.79** or **1.80**). Rather, we anticipated that, given appropriate reaction conditions, such intermediate carbocations would equilibrate—through a synthetic device we termed *charge relocation*—to a predetermined distal position (**1.81** or **1.82**) through a 1,2-hydride transfer step. We set out to demonstrate the validity of this idea by investigating reliable ways to generate an acylium ion, starting from acyl chlorides, with a non-nucleophilic and non-basic counteranion. Therein, the acylium ion would be attacked by a double bond and form the initial carbocation **1.79** or **1.80**, which would relocate to a predetermined position and form intermediate **1.81** or **1.82**. Finally, upon subsequent addition of a suitable nucleophile, the overall reaction would result in the formation of products of 1,3-alkene difunctionalization **1.83** or **1.84** (Scheme 1.11).

The work described was conducted in collaboration with Dr. Giulia Iannelli, Dr. Margaux Riomet and Dr. Daniel Kaiser. The results of this project have, in parts, been published.[1]



Scheme 1.11: Proposed 1,3-difuntionalization of alkenes.

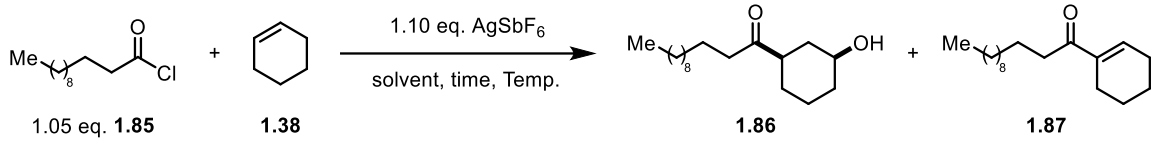
1.3 Results and Discussion

1.3.1 Optimization Studies

At the outset of this project, cyclohexene (**1.38**) and lauroyl chloride (**1.85**) were chosen as our standard substrates and acylium-ion formation was ensured by addition of a silver salt (or other Lewis acid, L.A.) bearing a range of non-coordinating anions. In addition to the nature of the silver salt/Lewis acid, a range of other parameters, including temperature, time and solvent, were explored (Table 1.1).

Our initial optimization attempts revealed dichloromethane (CH_2Cl_2) as the optimal solvent. In all other cases ($CHCl_3$ and 1,2-difluorobenzene, as well as cyclohexane and 1,2-dichloroethane, not shown), significant amounts of elimination product **1.87** were observed. Notably, the absence of a silver salt (Entry 7) led to no observable conversion, underlining the need for activation of the acyl chloride to form an acylium ion. We next investigated alternative acylium-ion forming reagents, such as other silver salts and Lewis acids. Our initial choice, $AgSbF_6$ (Entry 4), was found to be the optimal promoter, likely owing to the highly non-coordinating, non-basic counter anion SbF_6^-. Other silvers salts (Entries 8-10), as well as Lewis acids (Entries 11-15) invariably lead to increased amounts of elimination product **1.87** (relative to the desired product **1.86**), as well as reduced levels of conversion and significant amounts of decomposition. Pleasingly, we were able to achieve an isolated yield of 70% of keto-alcohol **1.86** by reacting 1.00 eq. cyclohexene **1.38**, 1.05 eq. lauroyl chloride **1.85** and 1.10 eq. silver hexafluoroantimonate ($AgSbF_6$) in dichloromethane (CH_2Cl_2, 1 mL/mmol alkene), at 35 °C for 10 minutes, followed by workup with a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$).

Table 1.1: Optimization of the reaction conditions for the alkene 1,3-functionalization.



1.05 eq. **1.85** **1.38** **1.86** **1.87**

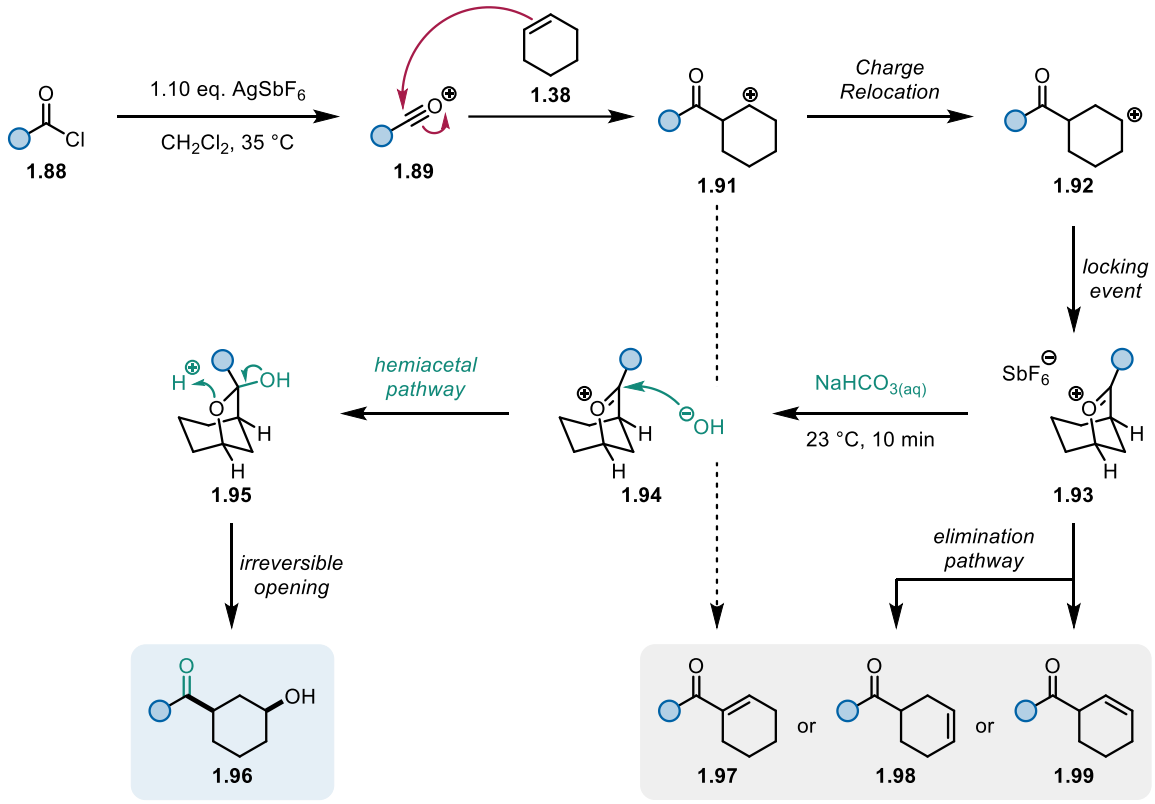
Entry	Silver salt or L.A.	Time	Temp.	Solvent	Yield 1.86	Yield 1.87
1	$AgSbF_6$	10 min	23 °C	CH_2Cl_2	60%[a]	25%[b]
2	$AgSbF_6$	60 min	23 °C	CH_2Cl_2	35%[a]	35%[b]
3	$AgSbF_6$	10 min	0 °C	CH_2Cl_2	52%[a]	46%[b]
4	**$AgSbF_6$**	**10 min**	**35 °C**	**CH_2Cl_2**	**70%[a]**	**30%[b]**
5	$AgSbF_6$	10 min	35 °C	$CHCl_3$	22%[a]	62%[b]
6	$AgSbF_6$	10 min	35 °C	1,2-difluorobenzene	12%[a]	58%[b]
7	no silver salt	10 min	35 °C	CH_2Cl_2	no observable products	
8	AgOTf	10 min	35 °C	CH_2Cl_2	24%[b]	49%[b]
9	$AgBF_4$	10 min	35 °C	CH_2Cl_2	11%[b]	<5%[b]
10	$AgPF_6$	10 min	35 °C	CH_2Cl_2	13%[b]	5%[b]
11	$SnCl_4$	10 min	35 °C	CH_2Cl_2	n.d.	<5%[b]
12	$FeCl_3$	10 min	35 °C	CH_2Cl_2	n.d.	14%[b]
13	$BF_3 \bullet Et_2O$	10 min	35 °C	CH_2Cl_2	no observable products	
14	$AlCl_3$	10 min	35 °C	CH_2Cl_2	n.d.	<5%[b]
15	$InCl_3$	10 min	35 °C	CH_2Cl_2	n.d.	6%[b]

[a]isolated yield, [b]NMR yield using mesitylene as internal standard, n.d. – not detected

In general, commercially available acyl chlorides were used, due to their availability and reduced cost when compared to their highly reactive, unstable and demanding synthetic counterparts, namely acyl fluorides and bromides. Any synthesized acyl chloride will be briefly mentioned in the following sections.

1.3.2 Synthesis of *syn*-Ketoalcohols

Having determined, the parameters influencing the feasibility of the initially proposed transformation, we became confident in formulating a mechanistic proposal, which is described in Scheme 1.12. Addition of silver hexafluoroantimonate ($AgSbF_6$) to a mixture containing cyclohexene **1.38** and an acyl chloride **1.88** swiftly forms the corresponding acylium ion **1.89** that is attacked by the alkene (in this case cyclohexene (**1.38**)), forming carbocation **1.91**. From here, two mechanistic pathways are conceivable: 1) abstraction of a proton, leading to formation of an α,β-unsaturated enone (**1.97**) through elimination, or 2) charge relocation (1,2-hydride transfer) towards the γ-position. The use of SbF_6^- as the counter anion, due to its non-basic and non-nucleophilic character, largely avoids formation of the elimination products. However, small amounts of elimination products **1.97**, **1.98** or sometimes even **1.99** can still be observed, likely stemming from side reactions of later intermediates.



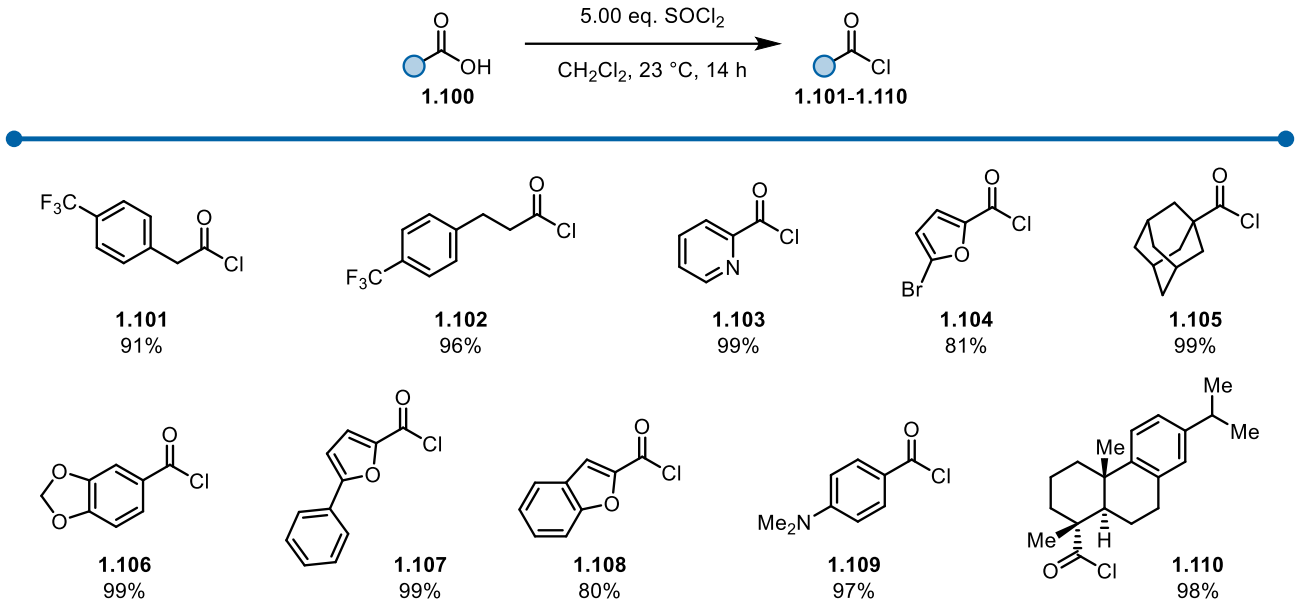
Scheme 1.12: Proposed mechanism for formation of oxocarbenium intermediate **1.93** and synthesis of 1,3-*syn*-ketoalcohol **1.96**.

Following relocation of the positive charge to the γ-position, the resulting intermediate **1.92** is suited for what we have termed a *locking event*. Therein, the carbocation experiences stabilization through interaction with a lone pair of the carbonyl and formation of an oxocarbenium ion (**1.93**).[24] [25] [58] [59] [60] [61] Notably, while relocation of the positive charge to the γ-position had a slight inherent driving force (i.e., the positive charge moving away from the electron-withdrawing carbonyl), any further charge relocation is

thwarted by the now-stabilizing effect of the carbonyl oxygen. This cyclic oxocarbenium ion **1.93** can in theory suffer the same elimination fate under harsh basic conditions, and could form detectable amounts of β,γ- and β,δ-elimination products **1.98** and **1.99**. However, its stability (**1.94**) enables survival under the mild reaction medium. Detailed studies investigating the stability of oxocarbenium ion **1.93** will be elaborated in section 1.3.9 of this thesis.

The formation of a bridged bicyclic intermediate relies on another key feature of this transformation: through this locking event, the two newly formed bonds are fixed in a *syn*-relationship, with both substituents adopting an axial conformation (**1.93**).

Following formation of the oxocarbenium intermediate **1.93**, hydrolysis under mildly basic conditions leads to the obtention of *syn*-ketoalcohol **1.96**, presenting 1,3-*syn*-configuration. This high diastereoselectivity is proposed to be a result of the nature of hydrolysis, where the oxocarbenium ion is likely attacked at its sp^2-hybridized carbon, forming a hemiacetal, which further collapses to yield the final product.



Scheme 1.13: Synthesis of acyl chlorides from carboxylic acids.

In order to investigate the mechanism and limitations of such a transformation, a plethora of commercially available as well as several synthetic acyl chlorides (see Scheme 1.13) were used throughout this project.

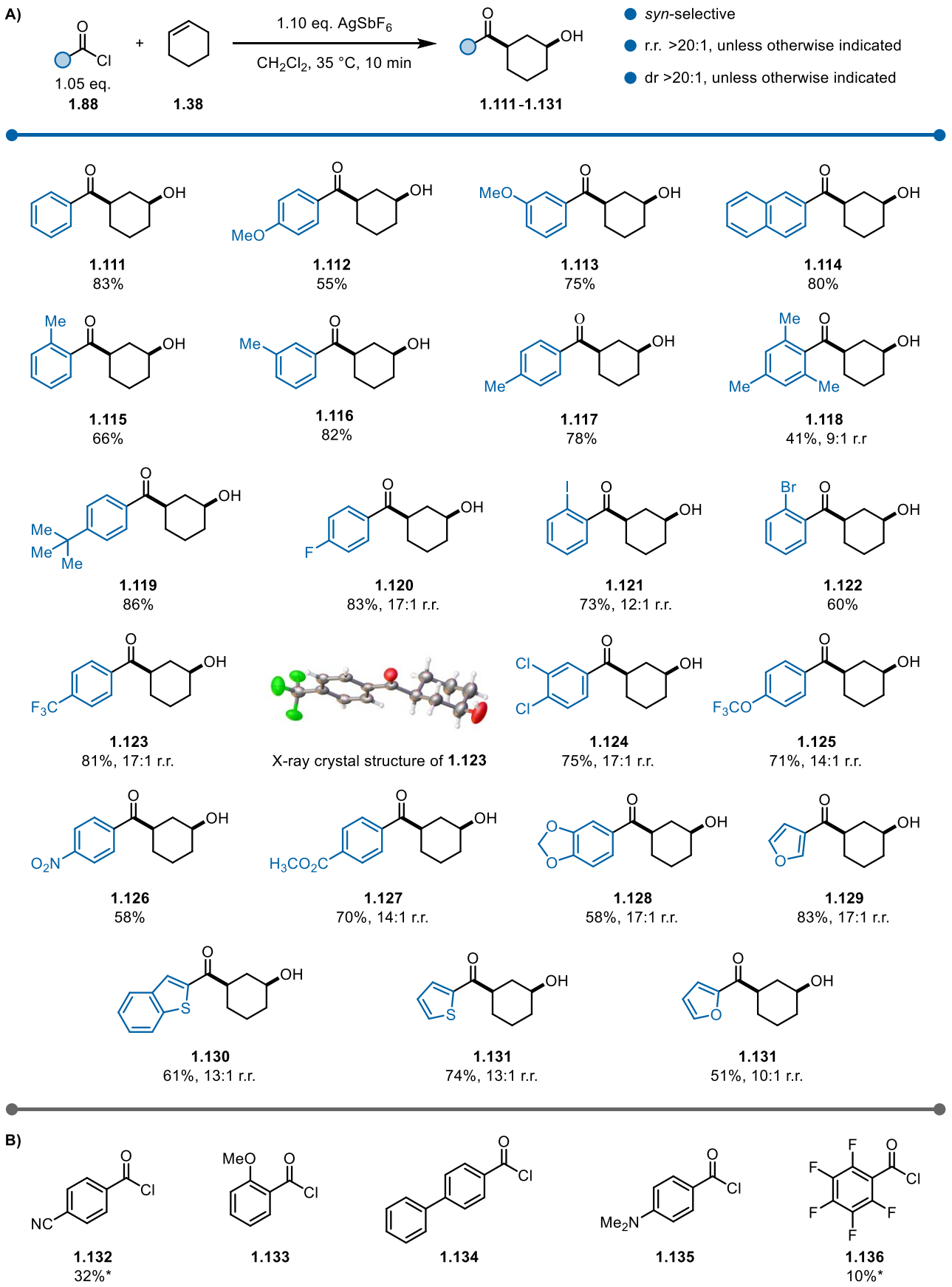
With a wide range of both commercial and home-made acyl chlorides in hand, we set out to explore the scope of our alkene 1,3-difunctionalization reaction, initially with respect to the scope of aromatic acyl chlorides **1.88** using cyclohexene **1.38** (Scheme 1.14A).

We were pleased to find that benzoyl chloride allowed the formation of the corresponding the *syn*-ketoalcohol **1.111** in 83% yield (Scheme 1.14B)—formally, this product can be seen as stemming from a

hydroxyacylation (addition of a hydroxyl and acyl group). Traces of elimination products were observed, but due to their straightforward separation by column chromatography, they will only be highlighted when significant amounts were formed. Endowing the aromatic with an electron-donating group, specifically a *para*-methoxy substituent, reduced the amount of product **1.112** that was obtained (55%). The increased amount of elimination products (30%) observed in the crude reaction mixture could be due to the increased stability of the formed acylium ion, as well as decrease of electrophilicity of the oxocarbenium, favoring elimination through abstraction of a neighboring proton, when compared to the default phenyl substituent **1.111**. The increased stability stems from the positive mesomeric effect (+M) and inductive effect (-I) of the methoxy group compared to the "neutral" proton.[62] This is further supported by the increase in yield to 75% (**1.113**) when the methoxy-group is placed in *meta*-position, disabling any stabilizing mesomeric effects. Of note, the reduced yield of **1.115** could be the result not of electronics, but rather of steric effects. This is further supported by a 41% yield of **1.118** when both *ortho*-positions are decorated with methyl substituents. This product also represents the first example where two regioisomers were observed. While the γ-alcohol was still the major component of the product mixture, a regioisomeric δ-alcohol was also observed (9:1 regioisomeric ratio (r.r.), compared to >20:1 observed for most products. While no unified explanation for regioisomeric distribution is conceivable, it is possible that the increased steric demand of the two *ortho*-substituents in **1.118** prevent efficient locking and enable a second 1,2-hydride transfer, relocating the carbocation to the δ-position. Aryl rings decorated with halide substituents also afforded medium to high yields (**1.120**-**1.124**), however with slightly reduced regiomeric ratios (**1.120** and **1.121**). Electron-withdrawing groups also showed promising results, as illustrated by products bearing *p*-CF_3 (**1.123**) and *p*-OCF_3 (**1.125**) substitution. An X-ray crystal structure of a *p*-CF_3-substituted arene (**1.123**) could be obtained, confirming the *syn*-configuration of the product. The nitro compound **1.126** was obtained in lower yield (58%), most likely due to the difficulty in generating the acylium ion itself. Pleasingly, esters were tolerated in this reaction protocol, as highlighted by ketoalcohol **1.127**.

Several reagents bearing heterocycles were investigated, and pleasingly acyl chlorides of furan (**1.129**), benzothiophene (**1.130**) and thiophene (**1.131**) were appropriate candidates for this transformation.

As for the more challenging examples showcased in Scheme 1.14B, *p*-nitrile-substituted acyl chloride **1.132** gave only 32% of product, as determined by NMR analysis. Other examples such as the fully fluorinated benzoylium ion could only form the desired product in 10% NMR yield. More strikingly, substrates such as **1.133**, **1.134**, and **1.135** did not deliver any product. In the case of **1.136**, it comes as no surprise as both steric hindrance and positive mesomeric effects (+M) have shown to be detrimental for this transformation. Nevertheless, a broad range of functional groups are tolerated for this reaction, specifically halides (F, Cl, Br, I), nitro (NO_2), methoxy (OMe), ester (COOMe), trifluoromethyl ethers (OCF_3) and several heteroaromatic compounds.



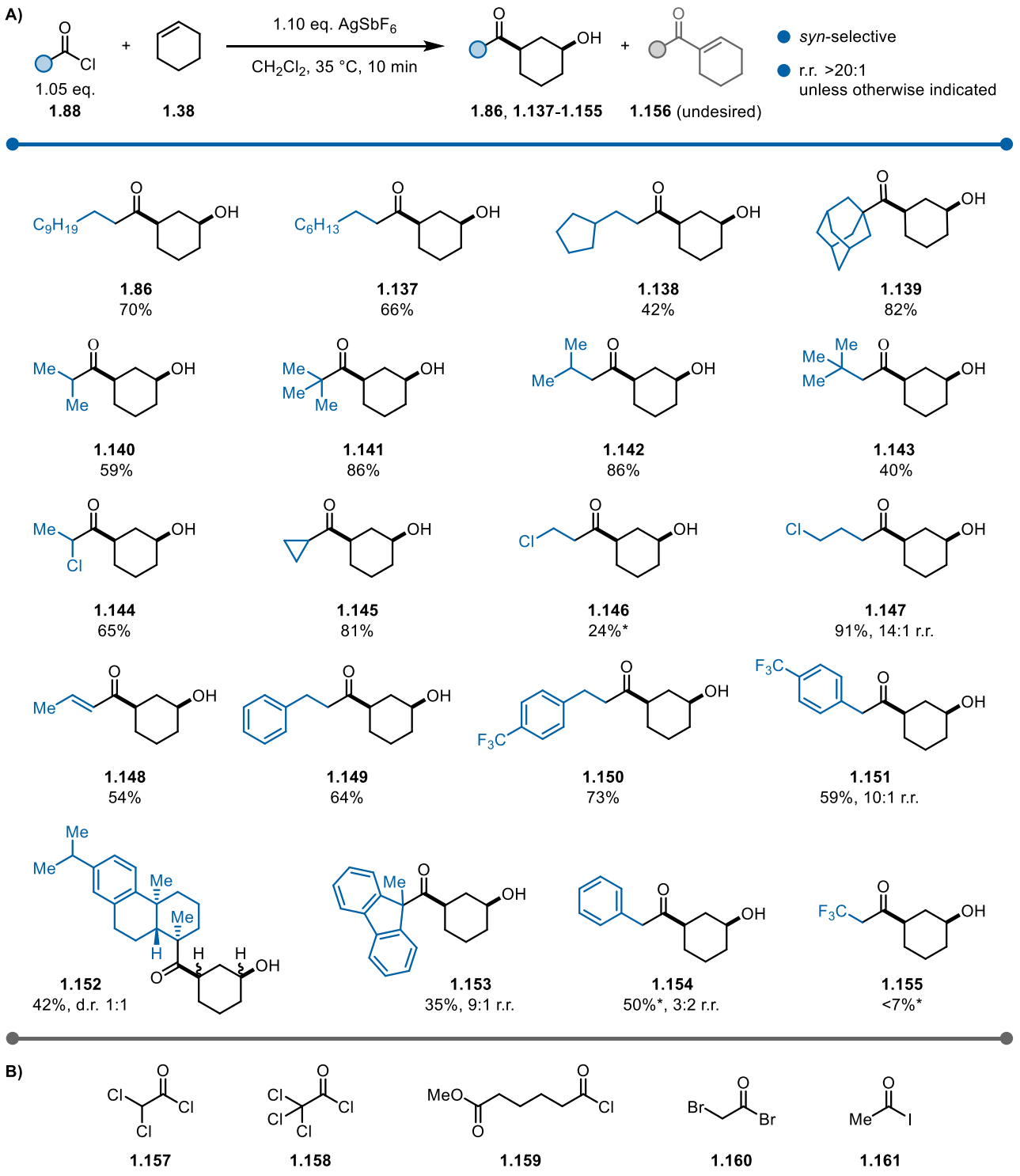
Scheme 1.14: A) 1,3-Hydroacylation of cyclohexene with aromatic acyl chlorides. B) Failed aromatic acyl chlorides.

*NMR yield calculated using mesitylene as the internal standard.

We next turned our attention to the exploration of suitable aliphatic acyl chlorides **1.88** (Scheme 1.15A). A particular challenge we observed early on in our optimization of the reaction conditions, was the propensity of acyl chlorides decorated with protons in the α-position to produce significant amounts of α,β-elimination product **1.156**. Despite this side reaction, the desired 1,3-*syn*-ketoalcohols were consistently obtained as the major products with high selectivity.

With these observations in mind, we started investigating simple, long-chained acyl chlorides and isolated the desired products in moderate to high yields (**1.86** and **1.137**) as showcased in Scheme 1.15B. When no α-protons are present, such as in the case of an adamantyl substrate (**1.138**), an 82% isolated yield was obtained. Further supporting the observations of the influence of α-protons on the reaction outcome, we obtained 59% and 86% of ketoalcohols **1.140** and **1.141** when acyl chlorides bearing one and no α-protons, respectively, were used. In general, acyl chlorides bearing α-primary, secondary and tertiary alkyl groups were found to be amenable to the reaction conditions. An interesting trend was observed between **1.142** and **1.143**, where the acyl chloride decorated with more methyl groups only gave 40% ketoalcohol **1.143**, in contrast to **1.142**, where up to 86% isolated yield was obtained. α-Chloro substituents (**1.144**) as well as a cyclopropyl moiety (**1.145**) were well suited for this reaction. Pleasingly, an acryloyl chloride was also a suitable electrophile for this transformation (**1.146**). Aliphatic chains bearing halides or aryl groups were moderately competent substrates (**1.149**, **1.150** and **1.151**) as long as the substituents were far enough from the electrophilic carbon. Interestingly, in the case of **1.146** and **1.147** one methylene group was enough to increase the yield from 24% (NMR) to one of the highest yielding products (91%), further emphasizing the delicate balance between steric hindrance and electrophilicity. Another outlier was the product **1.149** when compared to the *p*-CF_3-substituted version **1.150**. While the yield only increased by 9% when the *p*-CF_3-group was added, a drop of regioselectivity from 10:1 to 3:2 was puzzling. In this case steric hindrance could not be the culprit, but rather the electronics must play a determining role. To further understand this phenomenon, calculations would be a suitable tool.

Hoping to exert control of absolute stereochemistry by using an enantioenriched reagent, the acyl chloride of dehydroabietic acid was employed. The obtained diastereomeric ratio of 1:1, however, showed that control of absolute stereochemistry is a challenging endeavor in this manner (**1.152**). A fluorene-derived acyl chloride gave ketoalcohol **1.153** in only 35% isolated yield, with the majority of substrate undergoing non-specific decomposition. Several acyl chlorides proved to be unsuitable for this transformation: poly-α-halogenated acyl chlorides (**1.157** and **1.158**), ester-bearing **1.159**, as well as acyl bromides (**1.160**) and acyl iodides (**1.161**) were found to not deliver the desired products. In most of these cases decomposition was observed, most likely due to the reduced stability of the generated acylium ions.

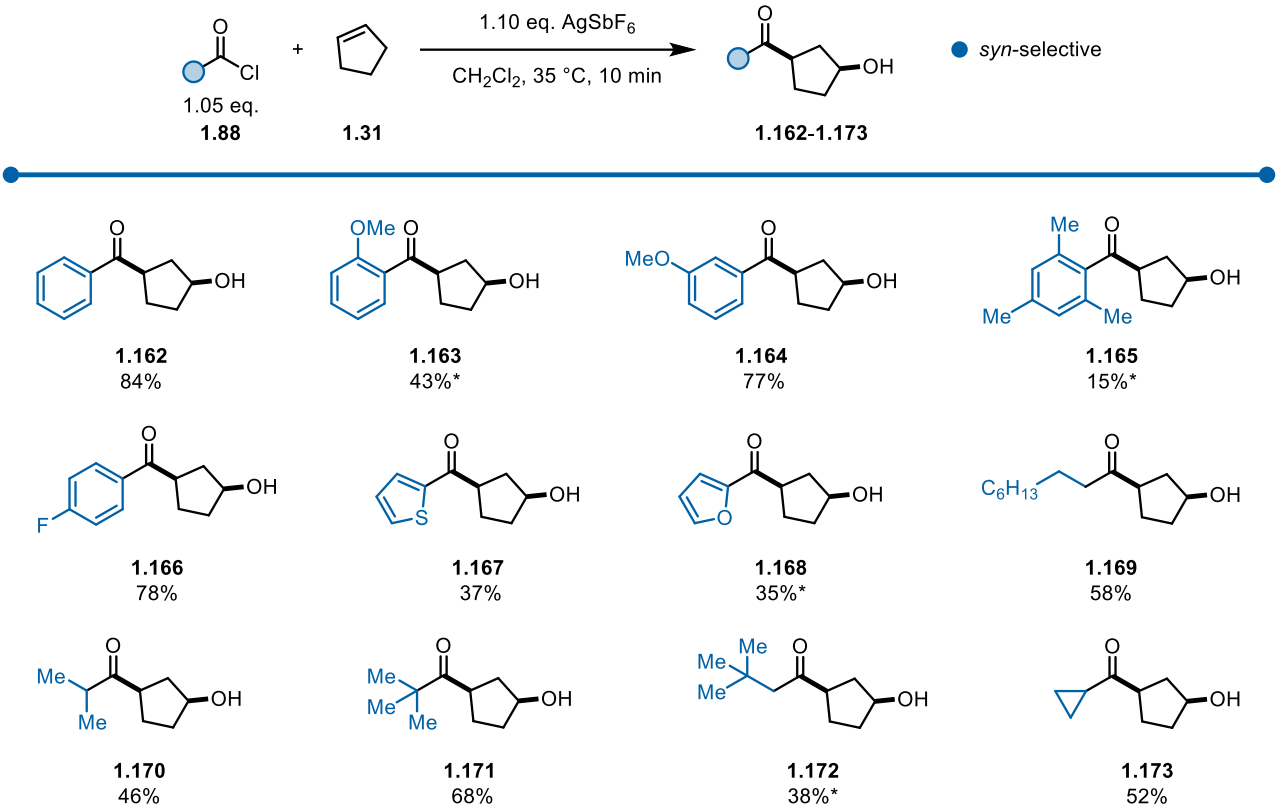


Scheme 1.15: A) 1,3-Hydroacylation of cyclohexene with aliphatic acyl chlorides. B) Failed aliphatic acyl halides.

*NMR yield calculated using mesitylene as the internal standard.

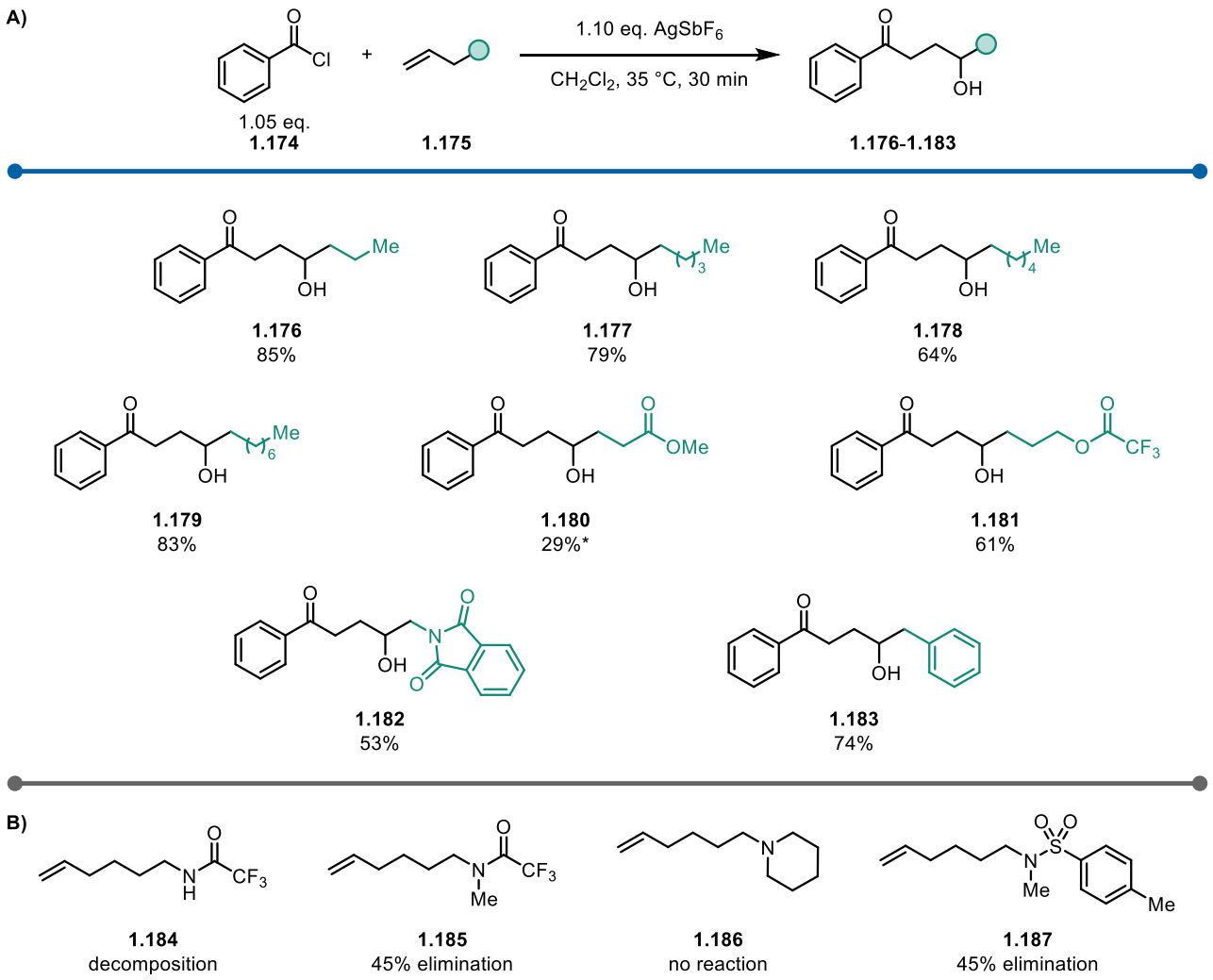
Having thoroughly explored the scope of acyl chlorides using cyclohexene, we shifted our attention towards cyclopentene (Scheme 1.16). Notably, while cyclohexene, in some cases, led to the formation of regioisomers, within a 5-memebred ring, a further charge relocation step would—due to symmetry—not result in an isomeric product.

Drawing from knowledge gained during previous investigations (Schemes 1.14-1.15), we started with benzoyl chloride, *o*-methoxy- /*m*-methoxy-containing substrates and 2,4,6-trimethylbenzoyl chloride as the electrophiles (Scheme 1.16). The results presented below corroborate our previous observations. *Ortho*-substituents proved to also be problematic for this adapted system, reducing the overall yield of the transformation (**1.163** and **1.165**). Aryl compounds bearing neutral (**1.162**) or electron-withdrawing substituents (**1.166**) delivered the desired products in high yields. Heteroaromatic acyl chlorides can lead to product formation, albeit in modest amounts (37% for **1.167** and 35% NMR yield for **1.168**). Additionally, a variety of products derived from aliphatic acyl chlorides could also be synthesized (**1.169**-**1.173**).



Scheme 1.16: 1,3-Hydroacylation of cyclopentene. *NMR yield calculated using mesitylene as the internal standard.

The next step in our endeavors was the escape from cyclic structure towards linear alkenes. For this purpose, a further round of optimization was necessary (not shown herein), revealing that linear alkenes require a slightly prolonged reaction time (30 minutes, rather than 10 minutes) in order to give reproducible results (Scheme 1.17A).



Scheme 1.17: A) 1,3-Hydroacylation of terminal linear alkenes. B) Failed terminal linear alkene substrates. *NMR yield calculated using mesitylene as the internal standard.

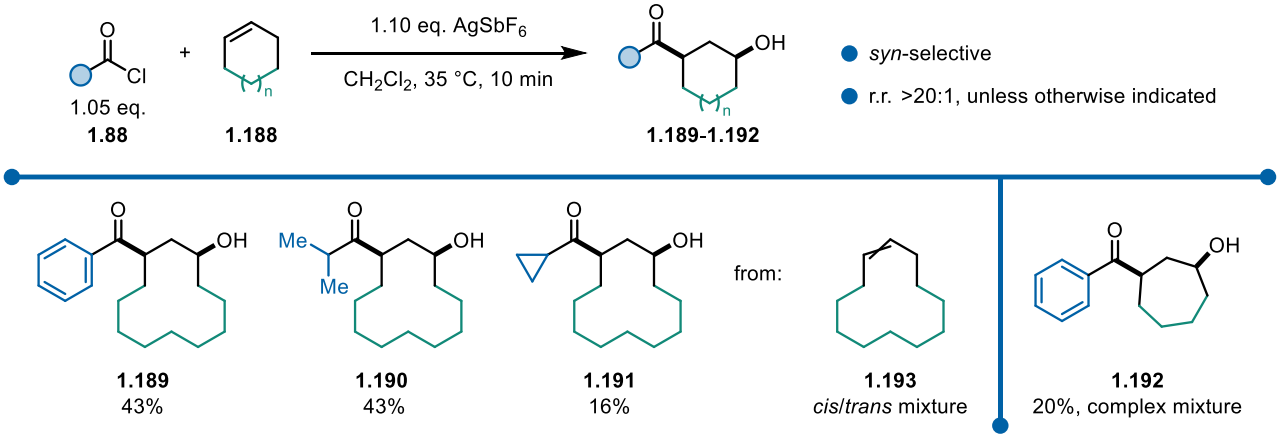
Pleasingly, terminal alkenes of varying chain lengths, delivered the 1,3-hydroacylated products (**1.176**-**1.183**). Of course, in the case of linear functionalized products resulting from terminal alkenes, the only concern is regioselectivity, as no diastereomers can be formed. An interesting problem arose when we employed an alkene bearing an ester. In this case, we only could detect 29% NMR yield of alcohol **1.180**. Most likely the basicity of the distant ester group is responsible for an increased amount of elimination products, before the reaction is quenched.

Next, we designed a substrate bearing a trifluoroacetate substrate and obtained functionalized alcohol **1.181** in 61% yield. The reduced basicity, alleviated when using trifluoroacetate, more than doubled the yield of **1.181** when compared to **1.180**. Additionally, an alkene bearing a protected amine (phthalimide) was able to be functionalized towards product **1.182** (53%). One of the most intriguing results obtained throughout this project was the reaction of benzoyl chloride and 4-phenyl-1-butene, where the major product obtained was ketoalcohol **1.183** (74%). While the two stabilizing forces (the benzylic position and the 5-membered

oxocarbenium ion) could potentially compete with each other, this not the case. One would expect the γ-carbocation to easily end up in the δ-position (benzylic), however in this case, no 1,4-functionalized product was observed, crowning the oxocarbenium formation as the fastest and presumably more thermodynamically stable player.

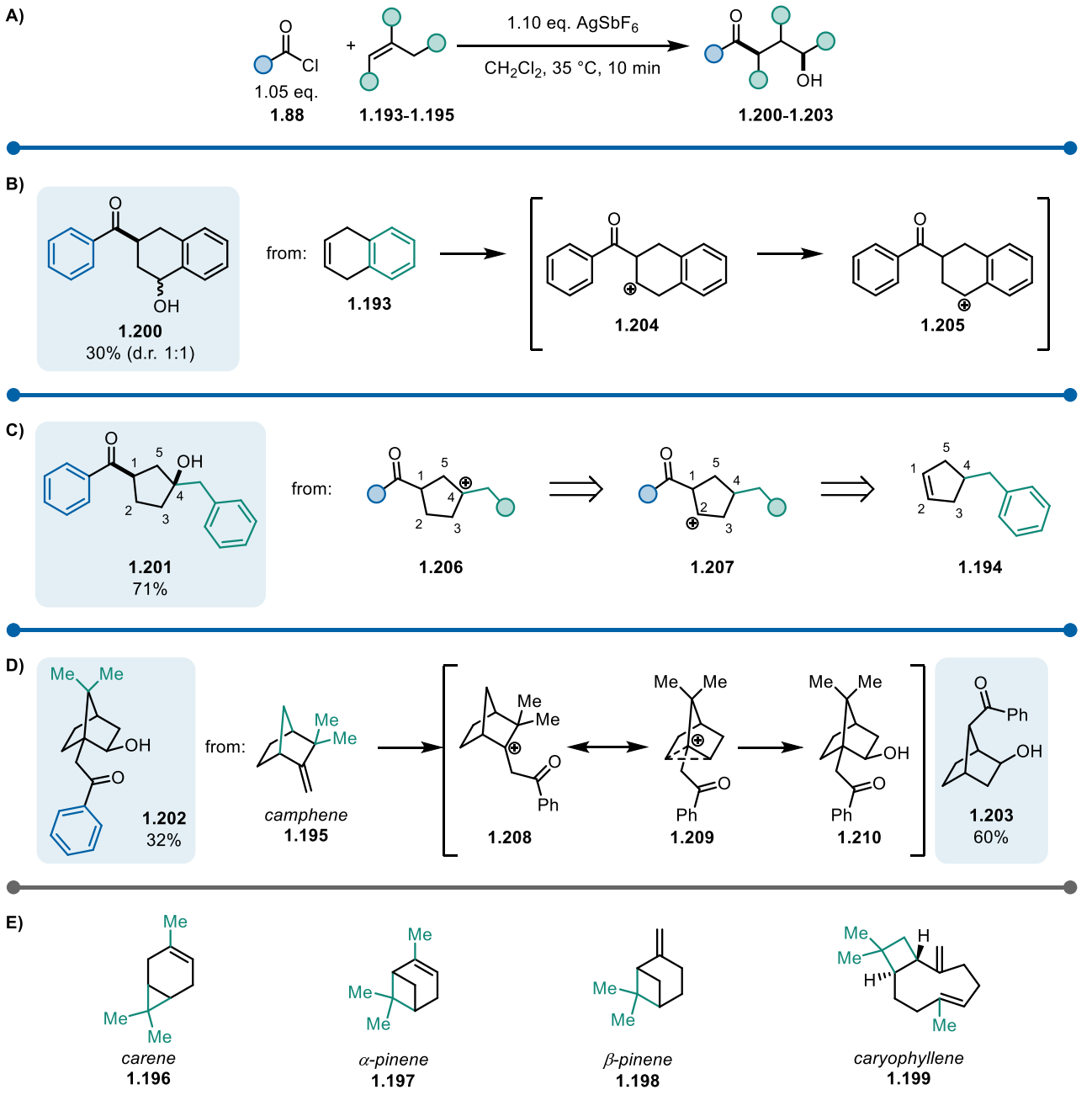
Inspired by the positive result when using protected alcohols (**1.181**), several electron-deficient amides (**1.184** and **1.185**), and amines (**1.186** and **1.187**) were probed. However, these substrates proved to be too basic for this version of alkene 1,3-functionalization.

We next moved to larger ring systems (Scheme 1.18). Initially, cyclododecene **1.193** (*cis*/*trans* mixture) was evaluated as a substrate using different acyl chlorides. In the case of benzoyl chloride or isobutyryl chloride, we were able to obtain both desired products in 43% yield (**1.189** and **1.190**). However, when cyclopropanecarbonylchlorid was employed, only 16% of ketoalcohol **1.191** was isolated. The products were obtained with excellent diastereoselectivity and regioselectivity (>20:1). Compared to these results, the increased ring strain of cycloheptane significantly influenced the outcome of this reaction.[63] Therefore, we could not isolate a single pure product, but rather 20% of a complex mixture containing different regioisomers (**1.192**).



Scheme 1.18: Investigation of alkenes of medium- and large-sized rings.

The following section of this chapter will explore more challenging, yet intriguing examples ranging from unsymmetrical alkenes to natural products such as camphene, carene and pinenes (Scheme 1.19).



Scheme 1.19: A-D) Selected examples of rearrangements and natural product substrates for the 1,3-difunctionalization of alkenes. E) Failed substrates.

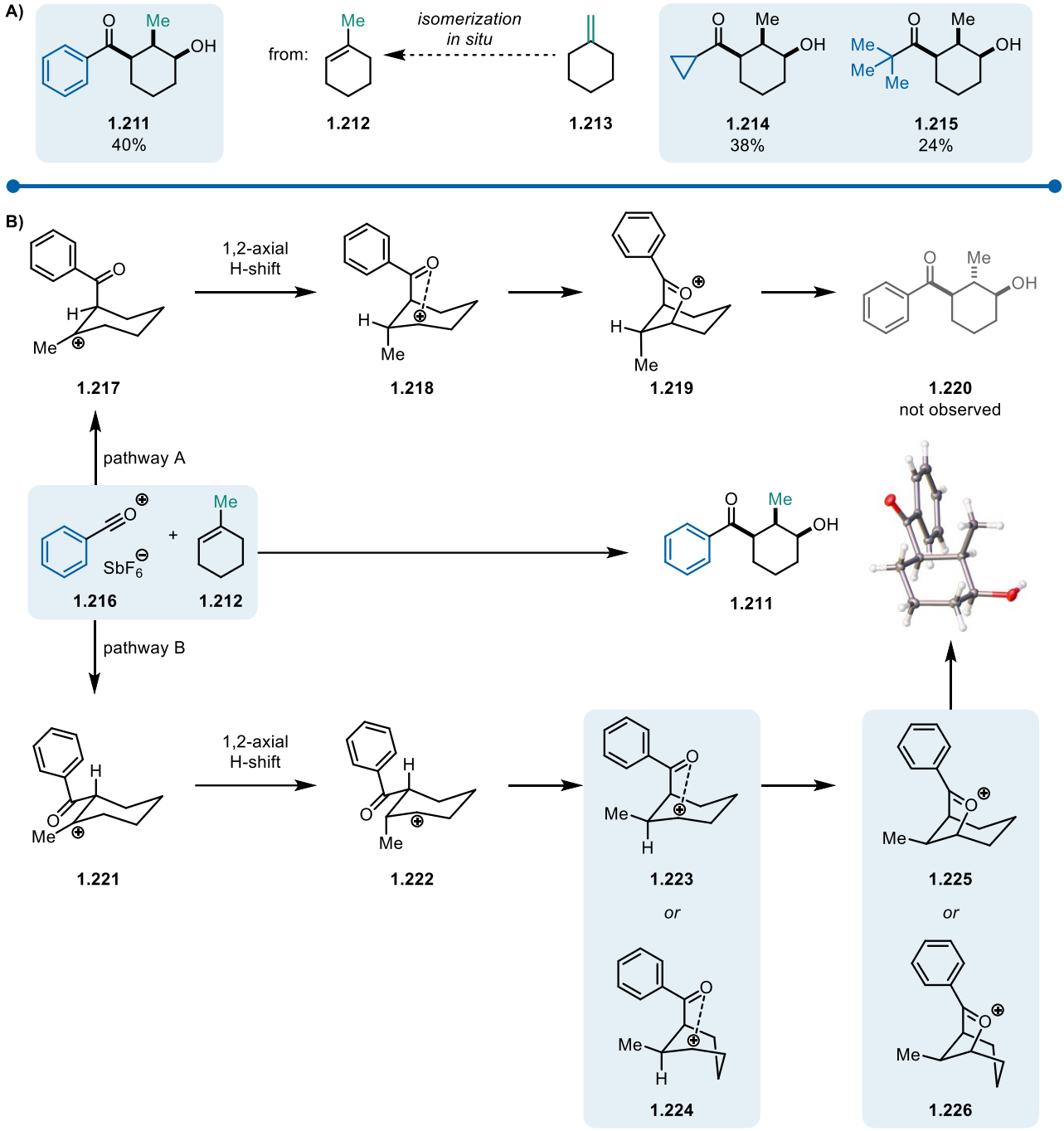
The first example highlighted in Scheme 1.19B is the reaction between benzoyl chloride and 1,4-dihydronaphthalene. The intermediate formed after alkene attack of the acylium ion and first charge relocation (1,2-hydride transfer) is a carbocation that is both benzylic and in a 1,3-relationship to the electrophilic carbon of the ketone formed. While two possible stabilizing forces are present (benzylic position and oxocarbenium ion formation), the nucleophilic attack of hydroxide occurs predominantly on the "naked" benzylic carbocation. While the corresponding oxocarbenium ion might be formed, due to strong benzylic stabilization, the cyclic form is most likely not the preferred resting state. The product obtained after hydrolysis (**1.200**) is 1:1 mixture between the *syn*- and *anti*-isomer.

To better understand what would govern such an additional hydride shift, we engineered a symmetrical substrate **1.194**, synthesized in four steps from a commercially available carboxylic acid (see experimental section). Notably, upon exposure of **1.194** to benzoyl chloride and Ag^+, product **1.201** was exclusively formed. This outcome, while at first glance resembling a 1,3-difunctionalization, highlights the propensity of additional pronounced stabilizing factors (such as generation of a tertiary cation) to trigger a further hydride transfer step and effect 1,4-functionalization. Therefore, our classical understanding of carbocation stability (tertiary>secondary>primary), owed to the inductive effect of neighboring groups (hyperconjugation), is a determining factor to be considered then predicting the outcome of such transformations (Scheme 1.19C).

Two more examples highlighted here are the products of non-classical carbocation chemistry,[64] [65] [66] [67] [68] specifically **1.202** (originating from camphene **1.195**), and **1.203** (from norbornene). Upon treatment with an acylium ion, camphene is proposed to initially form intermediate **1.208** and, after a methylene shift, result in **1.209**. Finally, a capture by newly placed ketone would form the corresponding oxocarbenium ion and, after hydrolysis, product **1.202** (Scheme 1.19D). These observations were also confirmed by an X-ray crystal structure of **1.202**.

In contrast to camphene and norbornene, several other terpenoids, such as carene (**1.196**), α-pinene (**1.197**), β-pinene (**1.198**) and caryophyllene (**1.199**) were found not to undergo the desired transformation, instead leading to non-specific decomposition (Scheme 1.19E).

Another intriguing example is formation of the all-*syn*-substituted ketoalcohol **1.211** (Scheme 1.20A). Interestingly, this product was formed upon treatment of either methylene cyclohexane or 1-methylcyclohexene (**1.213** and **1.212**) with an acylium ion, pointing towards *in-situ* isomerization to the thermodynamically favored alkene. The stereochemical outcome, with all substituents showing a *syn*-relationship, is explained by the stability of the corresponding oxocarbenium ion intermediate (**1.225** or **1.226**, Scheme 1.20B), where the methyl substituent adopts an equatorial orientation.



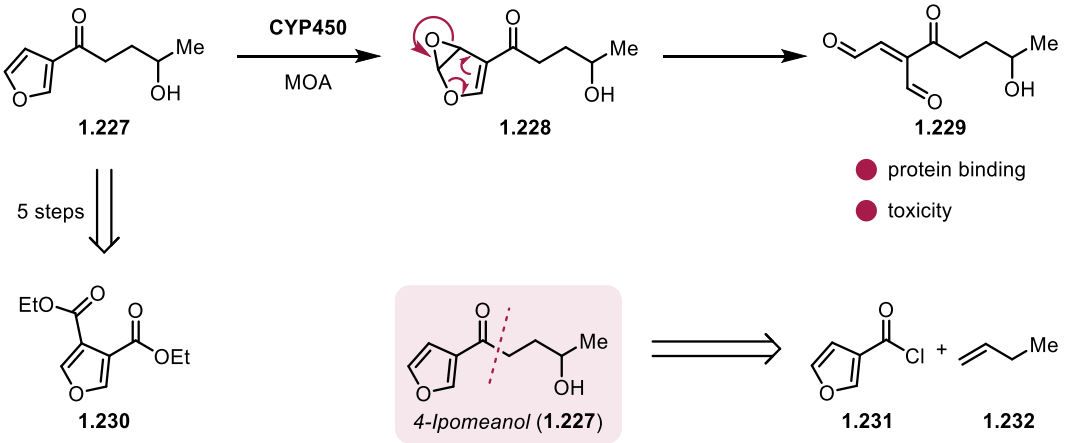
Scheme 1.20: Complete stereocontrol for the formation of a 1,2,3-trisubstituted cyclohexane.

There are two possible reaction pathways. Pathway A would place the benzoyl substituent in an axial position after attack of the alkene (**1.212**). A 1,2-axial hydride transfer step from the top face of **1.217** would place the methyl group axial and the newly formed carbocation is in a favorable position to be coordinated by the ketone (**1.218**) and form oxocarbenium intermediate **1.219**. Hydrolysis of this intermediate would deliver an *anti*,*anti*-configured product **1.220**, which was however never detected. Pathway B places the benzoyl substituent in an equatorial position next to the methyl rest (**1.221**). In this case, a 1,2-axial hydride transfer would produce intermediate **1.222**, that can now flip into two possible forms (**1.223** and **1.224**), where the

ketone is in proximity to the carbocation and can coordinate it. Finally, capture of the positive charge would form oxocarbenium ion **1.225**or **1.226**, that after hydrolysis delivers the all-*syn*-substituted ketoalcohol **1.211**. These observations were confirmed by an X-ray crystal structure of **1.211**. In addition, two more substrates using different acyl chlorides gave the same all-*syn*-outcome (**1.214** and **1.215**).

During investigation into potential biological applications of our 1,3-difunctionalization protocol through charge relocation, we encountered the naturally occurring pulmonary toxin 4-Ipomeanol **1.227** (4-IPO) shown below. 4-Ipomeanol **1.227** was the first agent to be developed by the National Cancer Institute based on biochemical/biological rationale as an anticancer agent targeted specifically against lung cancer. However, due to its metabolization into a highly reactive furan-epoxide by specific CYP450 (found in pulmonary Clara cells and type II pneumocytes, which share biochemical features with bronchogenic carcinoma), it was found to exhibit pulmonary toxicity in several mammalian species. (Scheme 1.21).[69] [70] [71] 4-IPO also underwent clinical trials (phase I and II), however some studies highlighted possible hepato-toxicity in humans which limited its future perspectives. The typical mode of action (MOA) involves an oxidation to epoxide **1.228**, which can undergo opening to the di-aldehyde **1.229**, capable of binding to proteins and the primary reason for the toxicity of this pre-drug. It has been previously synthesized in five steps from the symmetrical furan derivative **1.230**.[72]

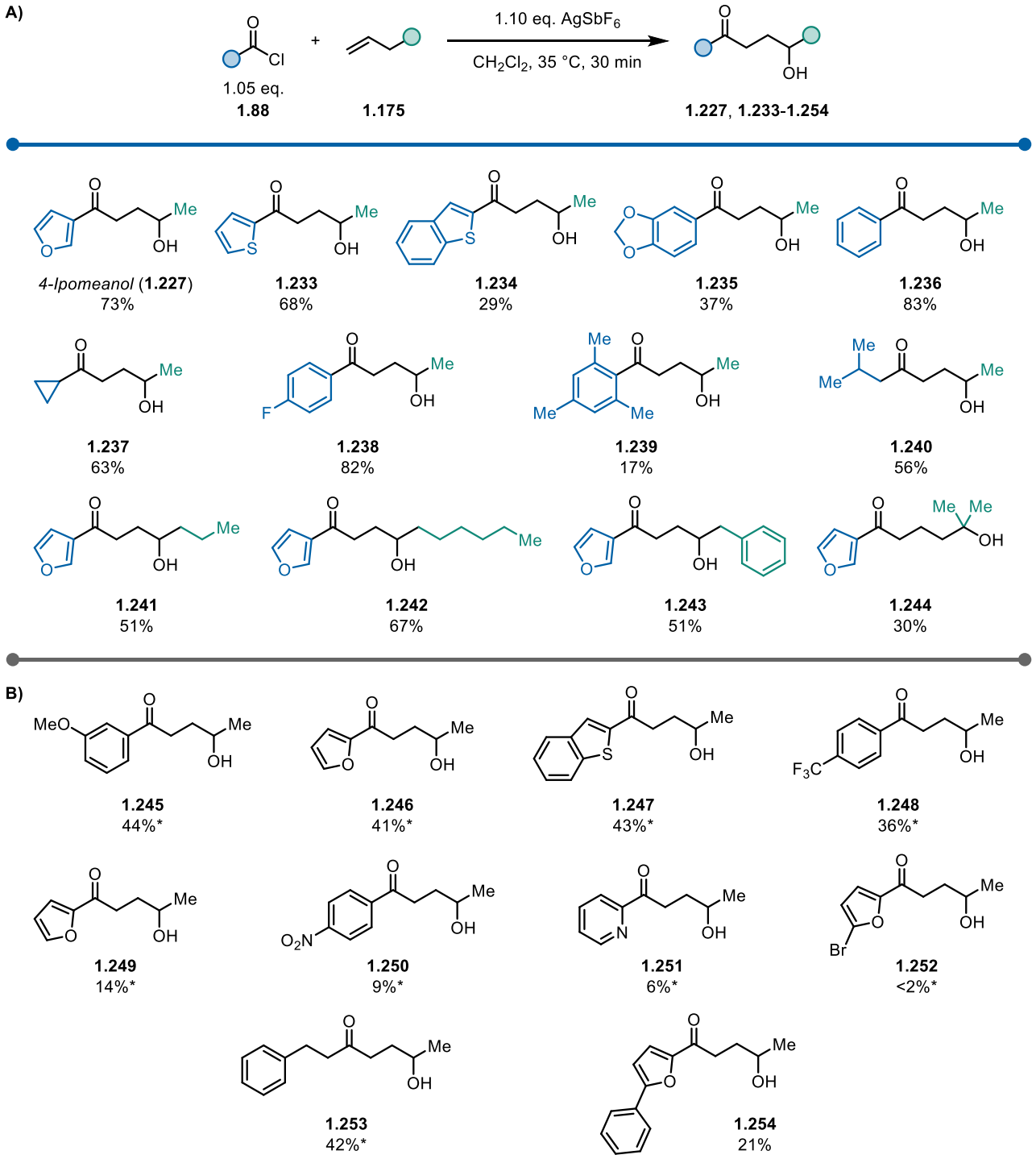
Given the 1,4-relationship of the ketone- and alcohol-substituent and based on our knowledge gained from this project, we proposed a direct synthesis of **1.227** from 3-furoyl chloride **1.231** and 1-butene **1.232** (Scheme 1.21).



Scheme 1.21: 4-Ipomeanol mode of action and mechanism.

If successful, not only would this approach significantly reduce the number of steps towards **1.227**, but it would also establish a general and straightforward single-step procedure for the synthesis of potential 4-IPO analogs that could be studied by our collaborators at CeMM (Research Center for Molecular Medicine of the Austrian Academy of Sciences).

Gratifyingly, combing a solution of 1-butene in hexanes and 3-furoyl chloride in dichloromethane (CH_2Cl_2) and treating the resulting solution with silver hexafluoroantimonate ($AgSbF_6$) gave us the biologically active 4-Ipomeanol **1.227** in 73% yield (Scheme 1.22A). We then moved to other acyl chlorides and successfully obtained 4-IPO analogs containing heterocycles (**1.233** and **1.234**), aromatic moieties (**1.235**, **1.236**, **1.238** and **1.239**) and aliphatic groups (**1.237** and **1.240**).



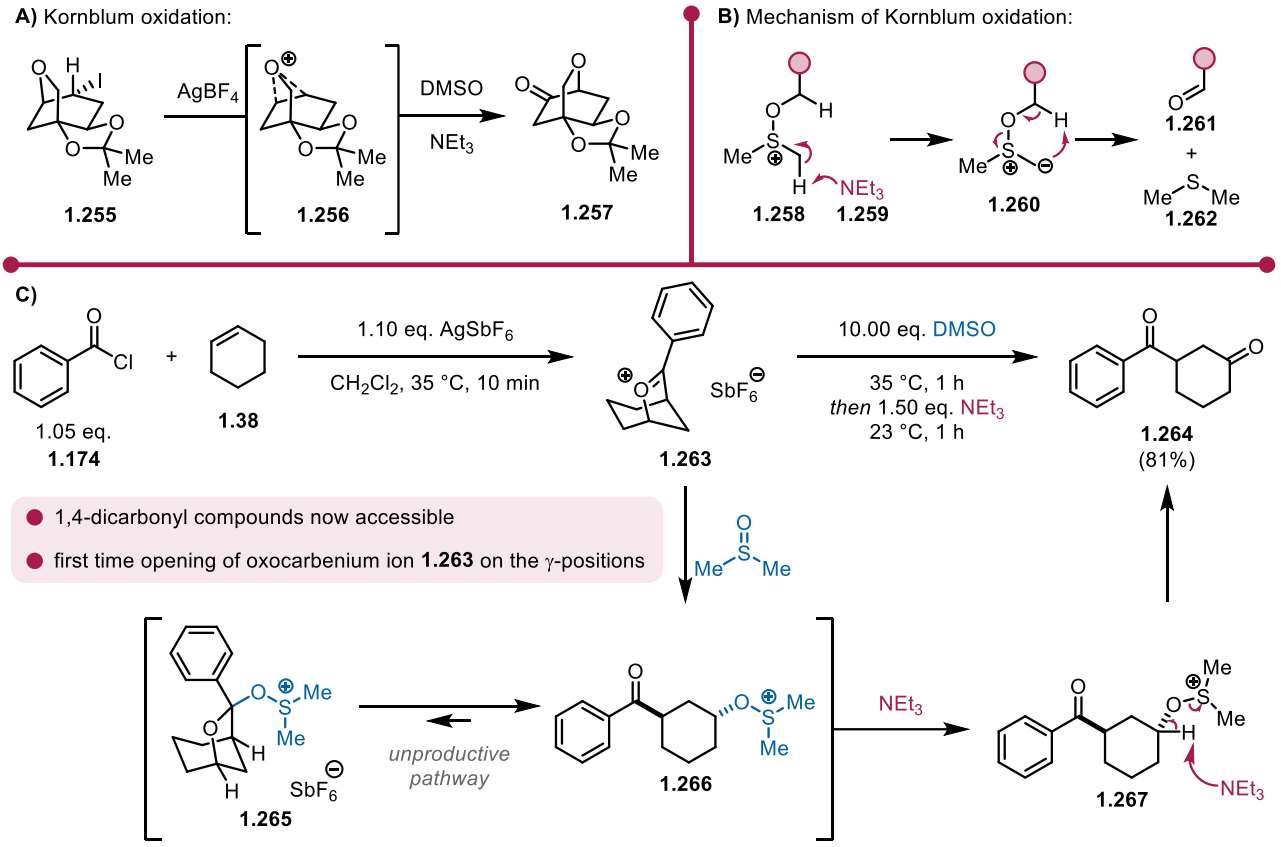
Scheme 1.22: A) Synthesis of 4-Ipomeanol and other analogs. B) Lower yielding substrates. *NMR yield calculated using mesitylene as the internal standard.

The sidechain length was also extended (**1.241** and **1.242**) and decorated with a phenyl ring (**1.243**). Finally, the hydroxyl group was also pushed one methylene group further, towards a tertiary position (**1.244**). Several substrates (**1.245**-**1.254**) were less successful and the lower NMR yields prompted us to pause their isolation until we receive promising data from our collaborators. If any would present interest, ideally a scale-up of the reaction would deliver enough material for biological testing even with these reduced yields. The investigation of their activity is still ongoing.

1.3.3 Synthesis of 1,4-Dicarbonyls

After intense screening and being inspired by a report in the literature,[73] we proposed that the standard oxocarbenium ion **1.263** could be opened at the γ-position by suitable nucleophiles, such as dimethyl sulfoxide (DMSO). The report by Lou (Scheme 1.23A)[73] showcased a cyclic oxonium ion **1.256** that could be generated by treating lactone **1.255** with silver tetrafluoroborate ($AgBF_4$) and addition of DMSO. Addition of triethylamine (NEt_3) delivered the ketone **1.257** through the classical Kornblum oxidation mechanism (Scheme 1.23B).

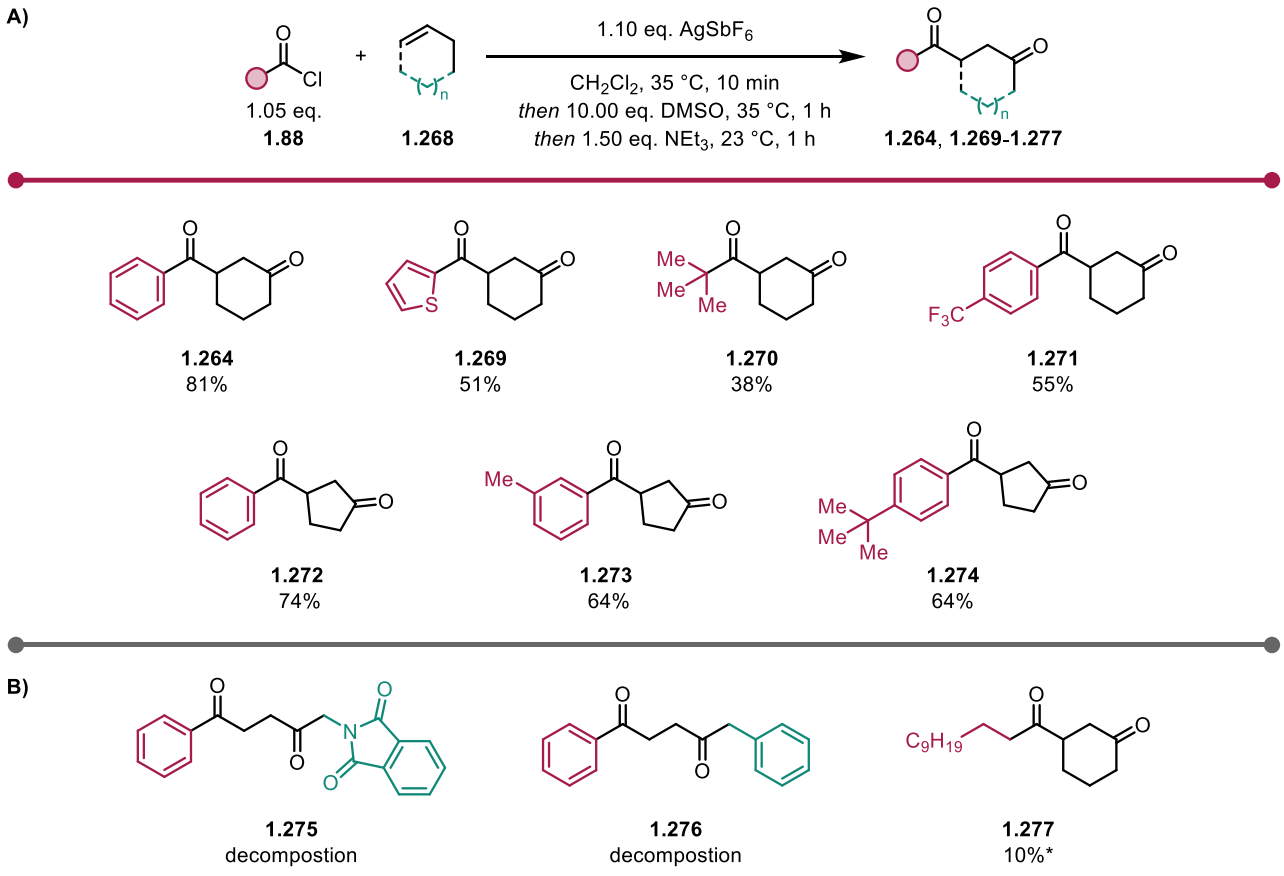
Our proposed mechanism would involve generation of the standard oxocarbenium ion **1.263** from benzoyl chloride **1.174**, cyclohexene **1.38** and $AgSbF_6$, followed by addition of DMSO to open the oxocarbenium ion **1.263** in an *anti*-fashion to generate sulfonium ion **1.266**. Even though DMSO could also attack the carbonyl-carbon and form intermediate **1.267**, this step should be reversible. Addition of triethylamine would trigger the oxidation of **1.267** through elimination of dimethyl sulfide to afforded the 1,4-diketone **1.264.** Indeed, when this transformation was attempted, **1.264** was formed in 81% yield. Methods for accessing such products are of interest.[70]



Scheme 1.23: A) Opening of a cyclic oxocarbenium ion **1.263** with DMSO. B) Mechanism of the classic Kornblum oxidation of alcohols to aldehydes. C) Proposed mechanism for the synthesis of 1,4-dicarbonyls and the initial observations.

We started with a short optimization of reaction conditions (time, temperature and DMSO stoichiometry), but quickly realized that the initial conditions already delivering the highest possible yield (81% yield of **1.264**). Therefore, we moved on with exploration of the scope of this transformation (Scheme 1.24).

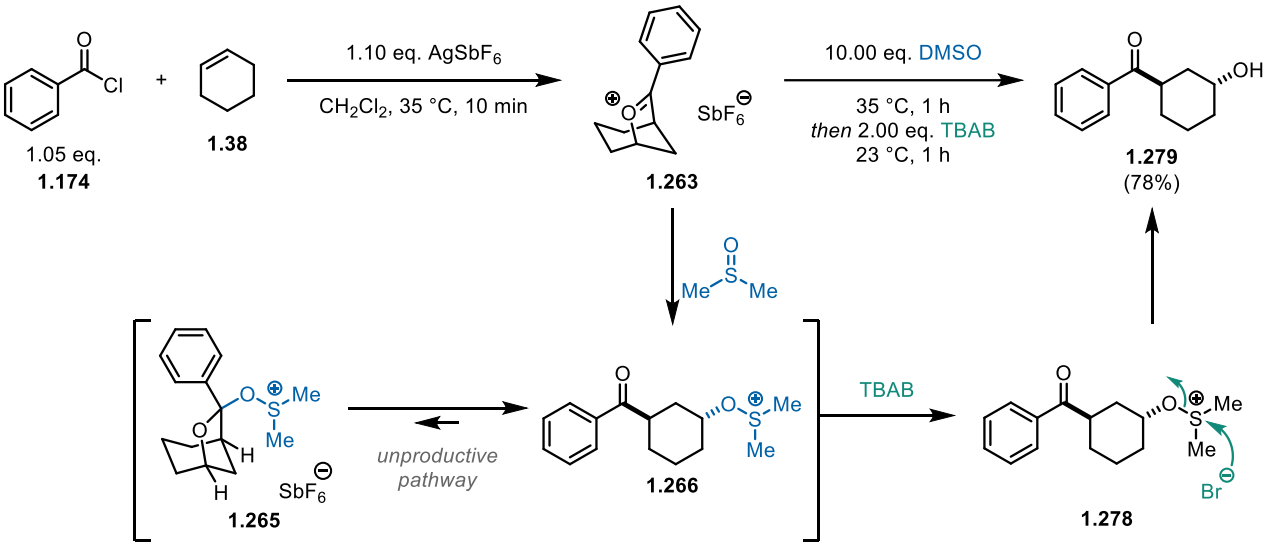
As was the case for previous endeavors, reactions between aromatic acyl chlorides and cyclohexene behaved similarly, delivering 1,4-dicarbonyl compounds **1.265**, **1.269**, **1.270** and **1.271** in moderate to high yields (Scheme 1.24A). Cyclopentene also lends itself to this transformation when paired with aromatic acyl chlorides to access compounds **1.272**, **1.273** and **1.274** in 74%, 64% and 64% yield, respectively. Linear alkenes led to decomposition and no products could be isolated, most likely to the reduced stability of the cyclic oxocarbenium ion when subjected to the several additional reaction steps (Scheme 1.24B). Another major challenge for this protocol proved to be aliphatic acyl chlorides. Product **1.277** was only detected at 10% NMR yield, while the corresponding 1,3-ketoalcohol **1.86** was isolated in 70% yield (cf. Scheme 1.15).



Scheme 1.24: Synthesis of 1,4-diketones. *NMR yield calculated using mesitylene as the internal standard.

1.3.4 Synthesis of *anti*-Ketoalcohols

Building on the knowledge from previous chapters, we wondered whether treatment of the sulfonium intermediate **1.263** with a different nucleophile, such as bromide, would cleave the S-O bond of intermediate **1.278** (Scheme 1.25). After aqueous work-up we would then obtain the *anti*-1,3-ketoalcohol **1.279**. The *anti*-orientation would come from the initial backwards attack of DMSO on oxocarbenium ion **1.263**. As before, DMSO could also attack the carbonyl-carbon, this step should be reversible. If any traces of *syn*-ketoalcohol are observed in the crude mixture, it could stem from this unproductive pathway. Sulfonium **1.266** should irreversibly convert to intermediate **1.278** by addition of tetrabutylammonium bromide (TBAB).

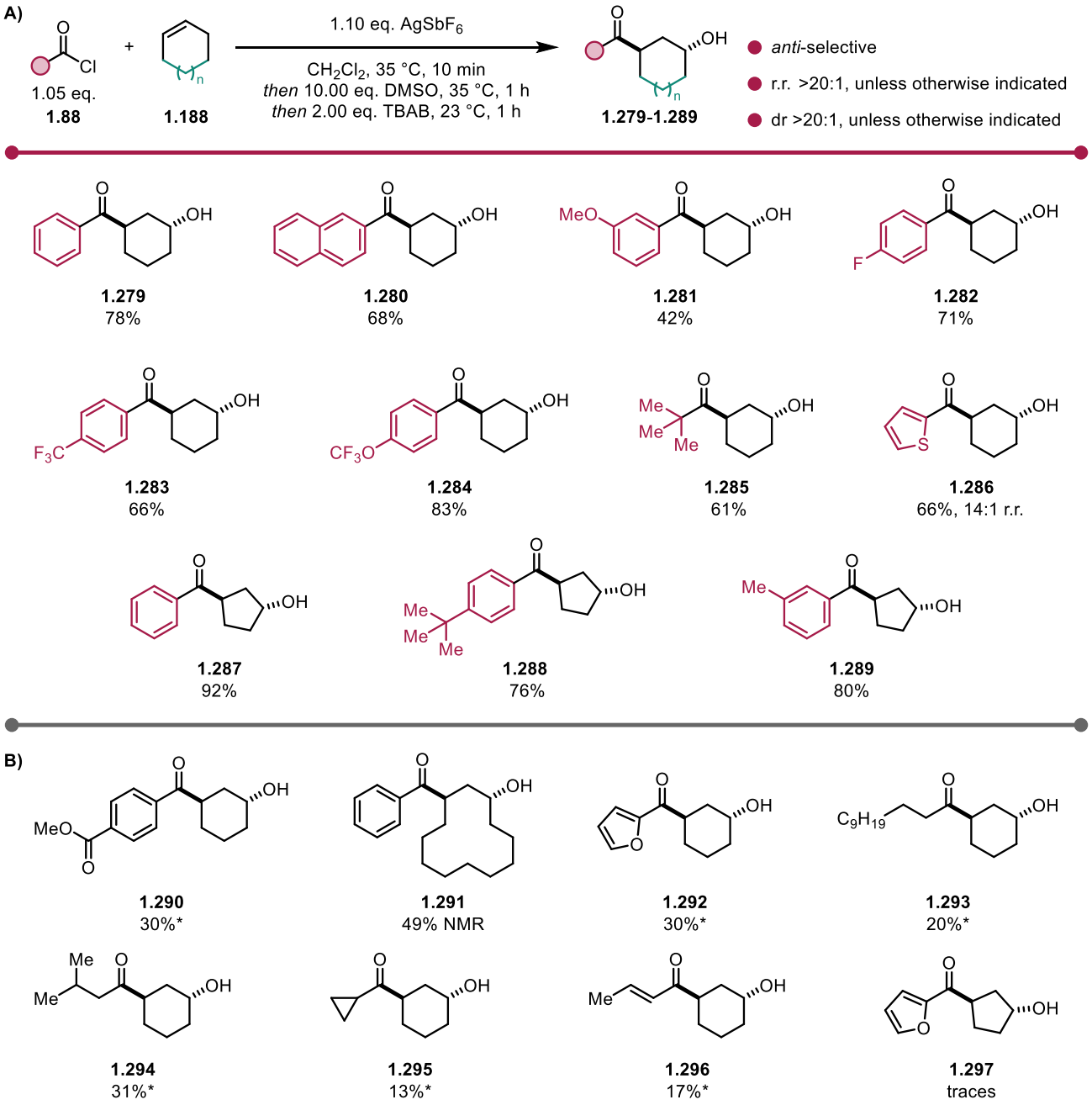


Scheme 1.25: Proposed mechanism for the synthesis of *anti*-ketoalcohols.

Pleasingly, our first attempts led to formation of the desired products containing aromatic substituents in moderate to high yields. Electron-neutral (**1.279** and **1.280**) and electron-poor substituents (**1.283** and **1.284**) were well tolerated. Electron-rich substituents led to an overall decrease in yield, as seen with *anti*-1,3-ketoalcohol **1.281** (42%). Aliphatic acylium-derived and heterocyclic products (**1.285** and **1.286**, repsectively) were tolerated, with a slight reduction of regioisomeric selectivity (16:1) for the latter substrate. Additionally, 5-memberd rings were well suited for this transformation (**1.287**, **1.288** and **1.289**).

Given the increased number of sequential steps in this methodology, it comes as no surprise that some substrates were lower yielding (**1.290**-**1.297**). Among them are mostly aliphatic acyl chlorides bearing α-protons (**1.293**-**1.295**) and 2-furoyl chloride (**1.287**).

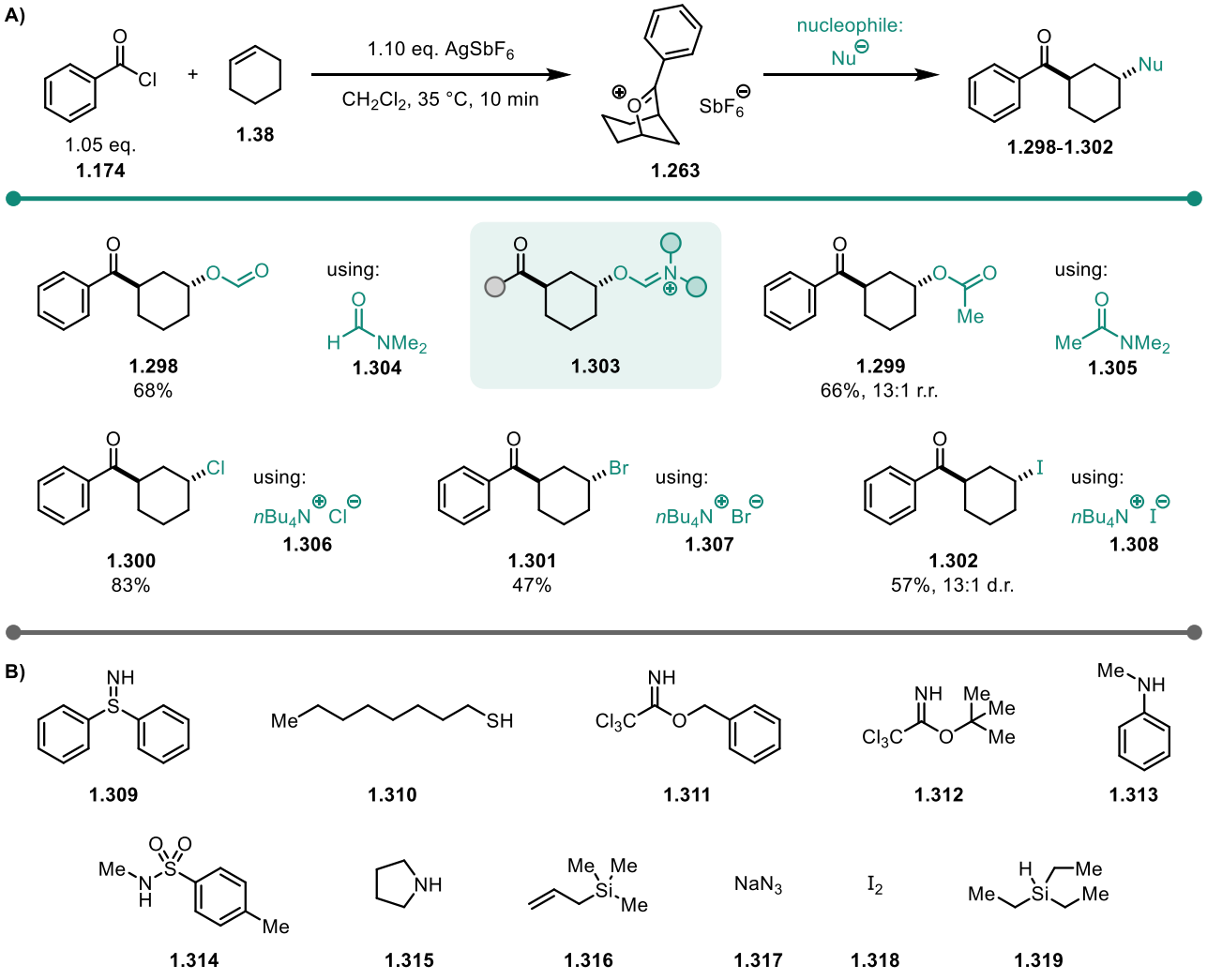
Nevertheless, this results of Scheme 1.26 showcase the stereodivergent nature of our transformation,[75] [76] [77] [78] [79] allowing access to both the *syn*- and *anti*-configured isomers in an elegant manner. Notably, these transformations do not the need a directing group or substrate-dependant features, rather using unactivated, unbiased alkenes.



Scheme 1.26: A) Scope of *anti*-1,3-ketoalcohols. B) Lower yielding and failed substrates. *NMR yield calculated using mesitylene as the internal standard.

1.3.5 Opening Oxocarbenium Ions with Different Nucleophiles

Encouraged by our breakthrough in opening oxocarbenium ions both at the original carbonyl carbon as well as at the γ-position, we explored a plethora of nucleophilic candidates (Scheme 1.27). Scheme 1.27A shows the results obtained. Since DMSO proved to be a suitable nucleophile to perform a backside attack on the γ-carbon, we investigated dimethylformamide (DMF). Pleasingly, after treatment of oxocarbenium ion **1.263** with a slight excess of DMF, and after hydrolysis of the Vilsmeier-type intermediate **1.303**, formate **1.298** was obtained in good yield. Similarly, by exchanging DMF for dimethylacetamide (DMA), we accessed the acetate products **1.299** (13:1 regioisomeric ratio). Both products presenting an *anti*-configuration supports the proposed mechanism of an S_N2-type attack of the same nature as DMSO.



Scheme 1.27: Investigation on the opening of oxocarbenium ions with additional nucleophiles. NMR yield calculated using mesitylene as the internal standard.

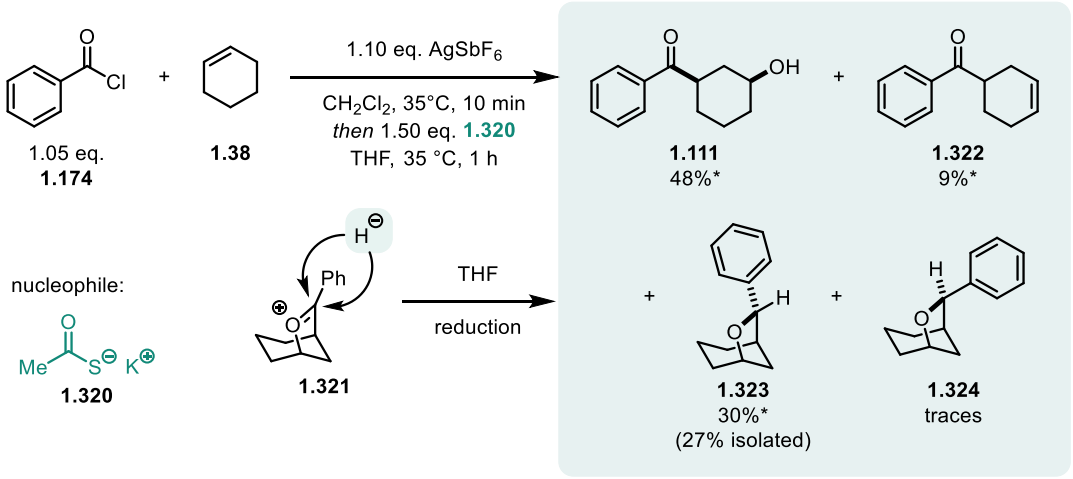
We then decided to move away from oxygen-based nucleophiles towards halides. After intensive screening of nucleophiles, the tetrabutylammonium salts **1.306** (TBAC) **1.307** (TBAB) and **1.308** (TBAI)

produced the corresponding *anti*-chloro-, *anti*-bromo- and *anti*-iodo-substituted products **1.301**, **1.302** and **1.303** respectively.

While several different fluoride sources, such as potassium fluoride (KF), tetrabutylammonium fluoride (TBAF) and boron trifluoride (BF_3), were investigated, only hydrolysis products could be observed in all of these reactions.

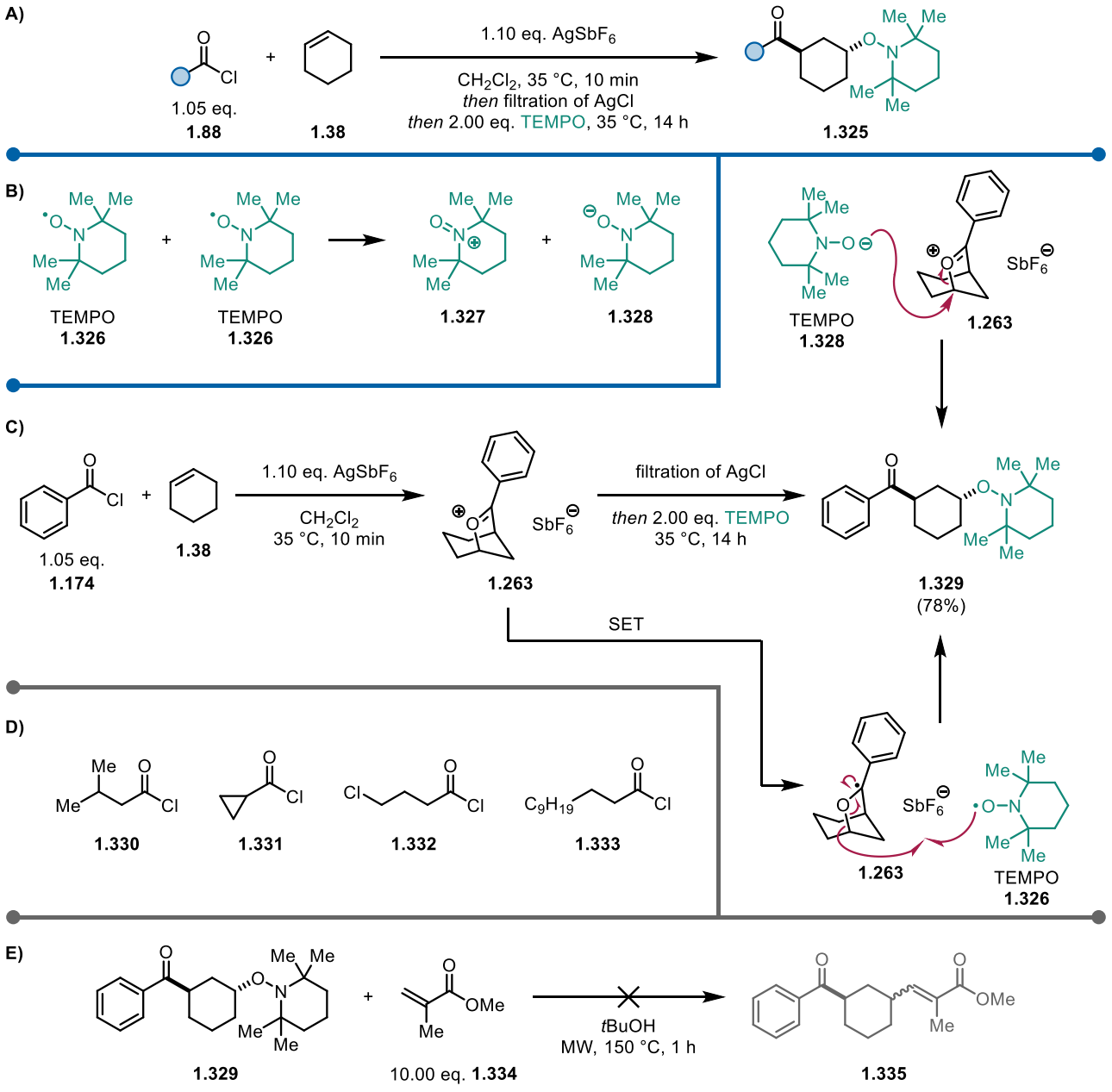
The key to successfully using tetrabutylammonium salts was found in the removal of any potential residual chloride source (particularly precipitated AgCl), by transferring the supernatant to a separate oven-dried vial. This branch of the scope proved to be the most challenging so far, as most nucleophiles were either not nucleophilic enough or proved to be too basic, leading to either hydrolysed products (*syn*-ketoalcohol) or non-negligible amounts of elimination products. The following nucleophiles (Scheme 1.27B) were investigated, but did not prove competent for this type of transformation: sulfilimines (**1.309**), thiols (**1.310**), 2,2,2-trichloroacetimidates (**1.311** and **1.312**), amines (**1.313** and **1.315**), sulfonamides (**1.314**), silanes (**1.316** and **1.319**), sodium azide (NaN_3, **1.317**) and iodine (I_2, **1.318**).

While acetates are too basic and would lead to elimination products, a softer nucleophile, such as potassium thioacetate **1.320**, was an intriguing candidate (Scheme 1.28). Adding a solution of **1.320** in tetrahydrofuran (THF) resulted in a mixture composed of the standard hydrolysis product **1.111** (48% NMR yield), γ,δ-enone **1.322** (9% NMR yield) and, for the first time observed in this project, the reduction products **1.323** (30% NMR yield and 27% isolated yield). No thioacetate adduct could be detected by NMR or mass spectrometry. The genesis of the tetrahydrofuran derivatives **1.323** and **1.324** was puzzling at first, but could be explained once the reaction had been repeated without the addition of **1.320**, and only using THF as an additive. Indeed, THF was hydridic enough to reduce the cyclic oxocarbenium ion.



Scheme 1.28: Reaction of oxocarbenium ions and potassium acetate. *NMR yield calculated using mesitylene as the internal standard.

While charged species and neutral molecules were investigated, no radicals had yet been submitted to the reaction conditions. We chose as our candidate the stable aminoxyl radical (2,2,6,6-tetramethylpiperidin-1-yl)oxyl **1.326** (TEMPO) (Scheme 1.29). Initial investigations using 1.00 eq. of TEMPO yielded the *anti*-OTMP product **1.325** in 44% yield. Doubling the amount of TEMPO **1.326** increased the yield to 80% (Scheme 1.29A). This suggests that a possible mechanism of this transformation involves a single-electron transfer (SET) to the oxocarbenium ion **1.263**, followed up by an attack of the second equivalent of TEMPO **1.326** (Scheme 1.29C). Alternatively, TEMPO could disproportionate to form the corresponding nucleophilic anion that can attack on the γ-position of the oxocarbenium ion and yield the product **1.329** after aqueous work-up (Scheme 1.29B).

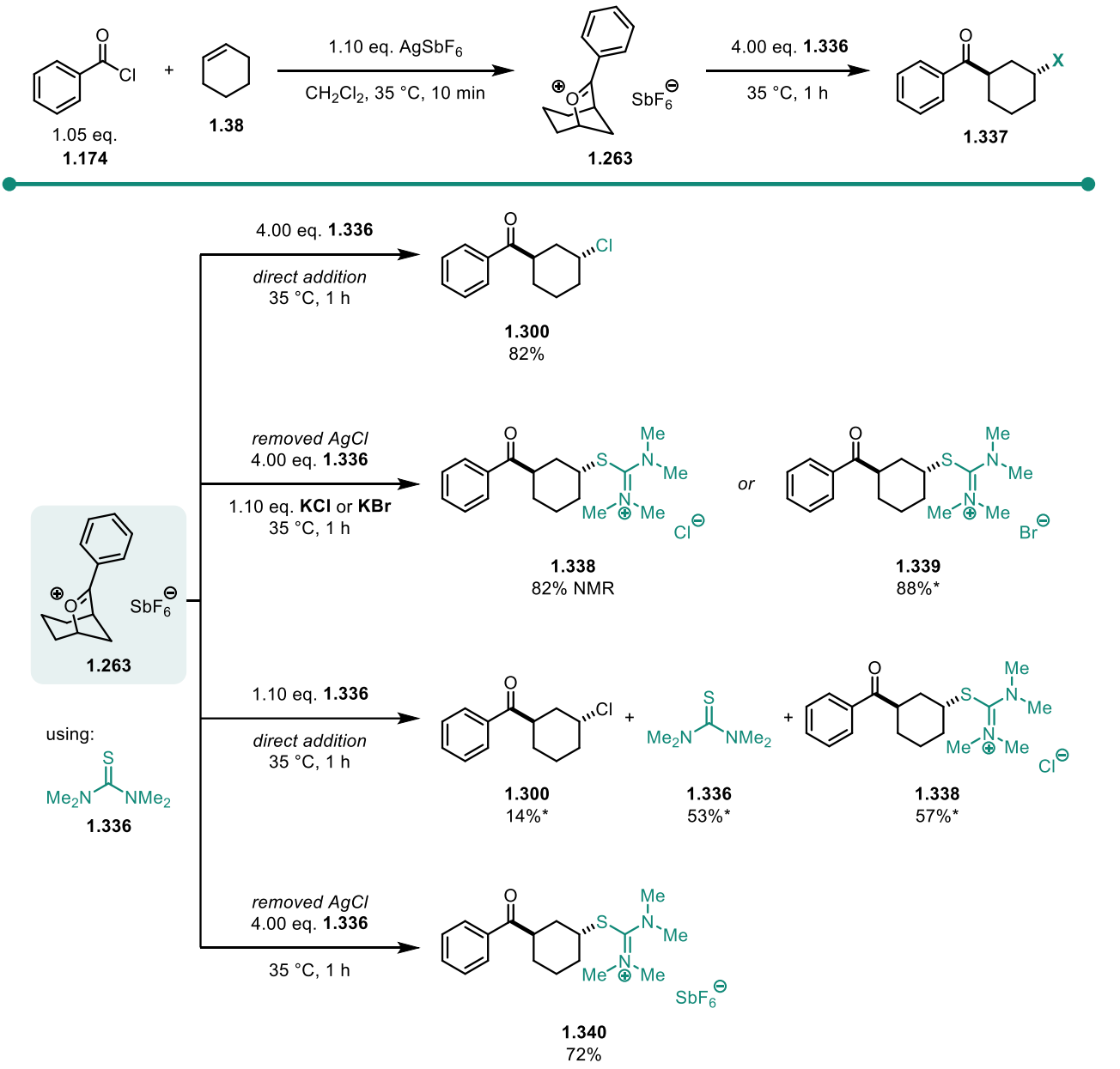


Scheme 1.29: Investigations of reactivity of oxocarbenium ions with TEMPO.

Several additional acyl chlorides (**1.330**-**1.333**) were investigated, but proved to be unsuitable for this multi-step process (Scheme 1.29D).

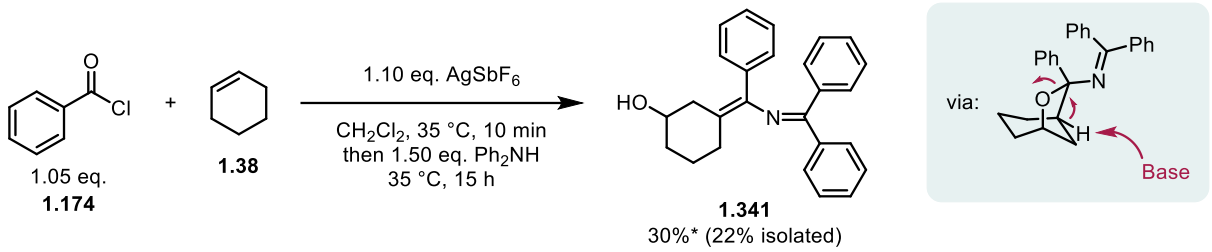
With a reliable method to form *anti*-OTMP-products, we then investigated potential further functionalization methods, particularly microwave-induced homolytic cleavage in the presence of acrylates **1.334** (Scheme 1.29E). While only one reaction is highlighted above, several unfruitful attempts were carried out. A closer literature search showcases the limitations of such transformations, since most examples involving radical conditions require substrates bearing OTMP-substituents in an allylic or benzylic position, or rely on intramolecular processes.[80] [81] [82]

Based on previous unpublished results from our group, tetramethylthiourea **1.336** (TMTU) was selected as a potential nucleophile that could open up the oxocarbenium ion **1.263** (Scheme 1.30). The initial attempt featured direct addition of 4.00 equivalents of TMTU and, surprisingly, delivered **1.300** as the major product. With precipitated silver chloride (AgCl) being the sole possible chloride source, the question remained, how solubilization of the chloride occurred? We developed the hypothesis that TMTU is able of coordinate the silver cation (Ag^+), thereby liberating the chloride from its grip. In order to probe this hypothesis, in a follow-up experiment, the oxocarbenium ion **1.263** was first generated, followed by transfer of the supernatant to a separate reaction vessel, before adding TMTU and subsequently potassium bromide (KBr) or potassium chloride (KCl). Interestingly, the products observed by proton NMR suggest adduct formation, likely by opening of the oxocarbenium ion with TMTU, to yield the thiouronium salts **1.338** and **1.339** with their corresponding counteranions. When only 1.10 equivalents of TMTU were added directly (no AgCl filtration), a mixture of chlorinated product **1.300** (14% NMR yield), unreacted TMTU **1.336** (53% NMR yield) and thiouronium salt **1.338** (57% NMR yield) was observed. Finally, when silver chloride was removed and excess of tetramethylthiourea was added, we were able to isolate by column chromatography the thiouronium salt **1.338** as the major product (72%). The succeeding investigations using hydrolysis conditions with different bases did not, however, deliver a thiol product. Further optimization and investigations are required and will most likely be the subject of future research projects within our group.



Scheme 1.30: Investigations of tetramethylthiourea as a nucleophile. *NMR yield calculated using mesitylene as the internal standard.

Moving towards nitrogen-containing nucleophiles, we added diphenylmethanimine to the standard oxocarbenium ion (Scheme 1.31). Interestingly, we did not observe significant amounts of products resulting from elimination or hydrolysis, but rather a new compound **1.341** (30% NMR yield, 22% isolated). This product is most likely formed by an initial attack of the imine on the carbonyl-carbon, followed by an elimination reaction catalyzed most likely by excess of imine. The structure of **1.341** was confirmed by 2D NMR analysis and by Prof. H. Kählig.



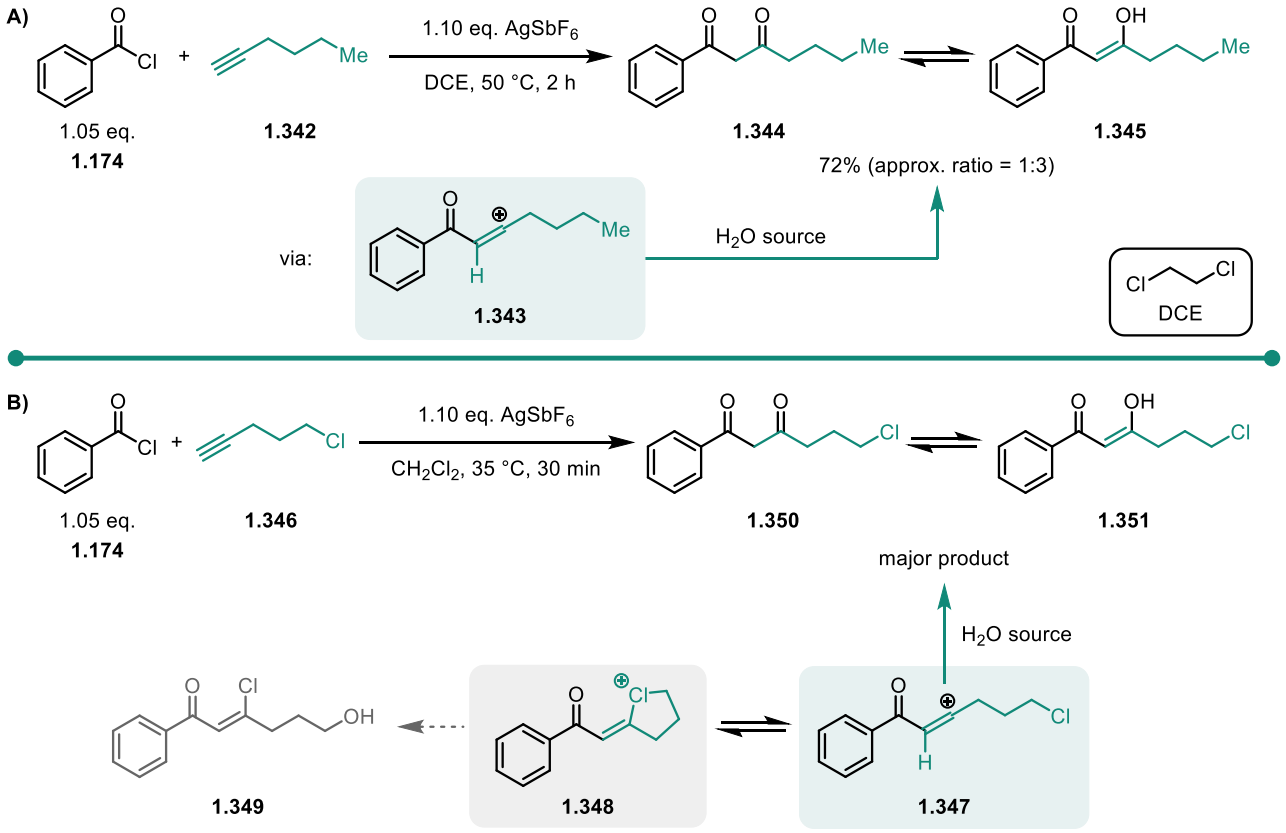
Scheme 1.31: Addition of diphenylmethanimine to the standard oxocarbenium ion. *NMR yield calculated using mesitylene as the internal standard.

To summarize, several nucleophiles have shown promise and could be suitable for opening the oxocarbenium ion. However, in most explored cases, further optimization of reaction parameters is necessary.

1.3.6 Dienes, Alkynes and Other Partners

After thoroughly exploring unbiased and unactivated alkene substrates, we increased the unsaturation and probed alkynes (Scheme 1.32). Submitting the simple, terminal alkyne **1.342** and benzoyl chloride **1.174** to the standard reaction conditions at elevated temperature led to a lower conversion. Therefore, the reaction was repeated at elevated temperature (50 °C in 1,2-dichloroethane, DCE), resulting in the formation of the 1,3-dicarbonyl compound **1.344** after aqueous work-up. Most likely, the initial step of this transformation is the formation of a highly reactive vinyl carbocation **1.343** that can readily react with traces of water. The 1,3-dicarbonyl **1.344** was shown to be in equilibrium with its tautomeric form **1.345** (Scheme 1.32A).

We considered whether adding a chloride to the other end of the alkyne would facilitate the formation of a chloronium ion **1.348**, that upon hydrolysis could potentially produce vinylchloride **1.349** (Scheme 1.32B). However, no such chloride-shifted product was observed, but rather, similarly to the previous example, a 1,3-dicarbonyl **1.350** was found to be the major product. Further studies on the reactivity of alkynes are currently ongoing in our work group.



Scheme 1.32: Studies on alkyne substrates.

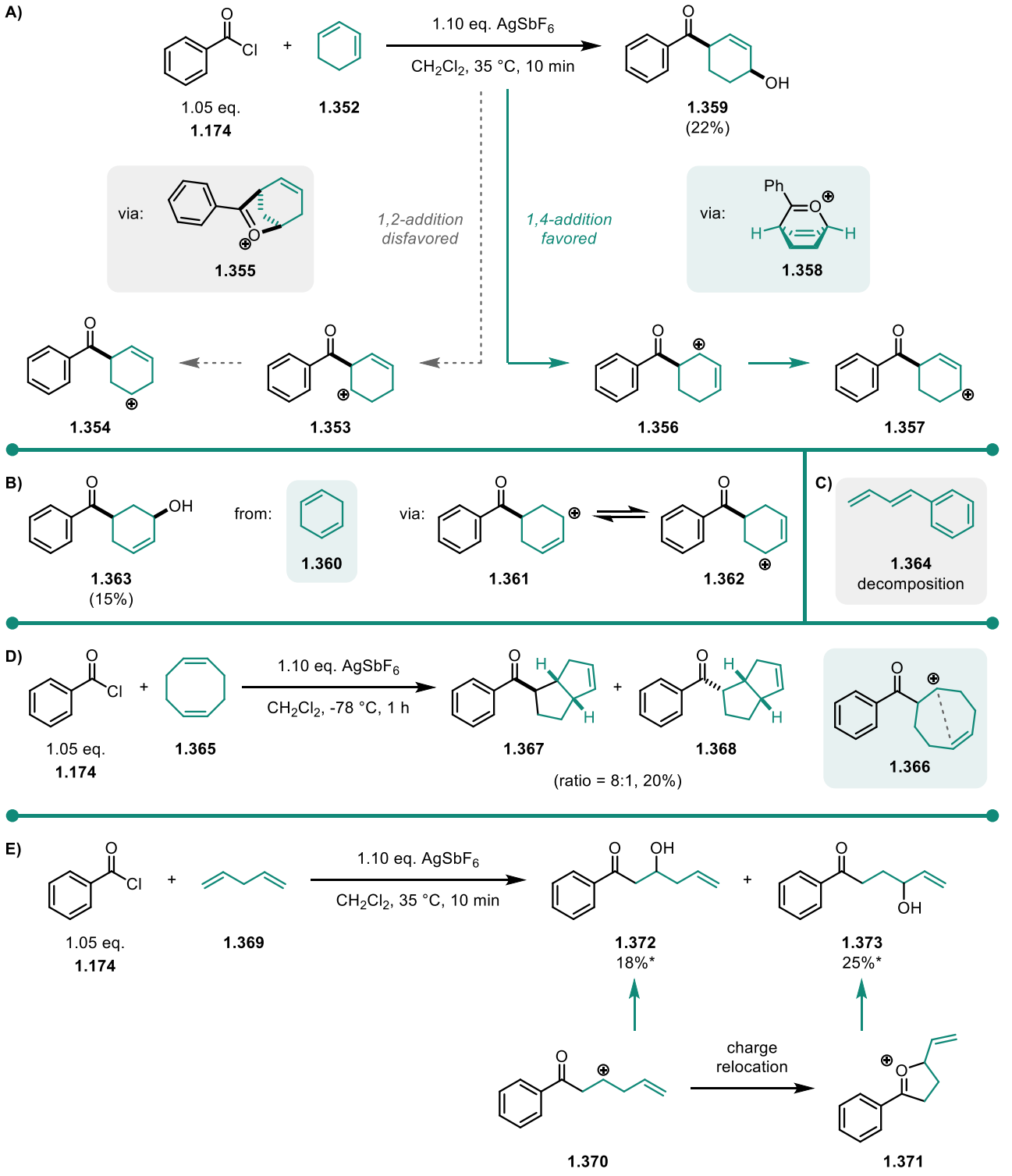
We were also interested in the reactivity of dienes, for which regioselectivity becomes a topic of interest. In the case of 1,3-cyclohexadiene **1.352**, a conjugated diene, two possible outcomes can be formulated *a priori*: 1,2-addition and 1,4-addition. In the first case, we can envision an initial carbocation (**1.353**) in the homo-allylic position, which could undergo 1,2-hydride transfer towards intermediate **1.354**, followed by attack of the ketone to generate the oxocarbenium ion **1.355** (Scheme 1.33A, left side). However, this intermediate is disfavored given the intrinsic polarity of the double bond system. Indeed, the major product isolated was the allylic alcohol **1.359** (Scheme 1.33B, right side). This is the result of a formal 1,4-addition, forming the allylic carbocation **1.356** that, instead of performing the usual 1,2-hydride shift, would mesomerize in an allylic fashion to intermediate **1.357**, that, after adopting a boat conformation, can be captured by the ketone and presumably form oxocarbenium ion **1.358**. The intermediate **1.358** is most likely the source of product **1.359**, which was isolated in 22% yield.

When the isolated diene **1.360** was treated with the standard acylium ion, **1.363** was isolated as the major product, albeit still in low yield (15%). While the carbocation intermediate **1.361** could presumably mesomerize to the equivalent version **1.362** could lead to significant amount of side-reactions and decomposition (Scheme 1.33B). Diene **1.364** was a more ambitious substrate that also led to mostly decomposition, likely due to the proximity of the benzyl ring as part of the π-system (Scheme 1.33C).

1,5-Octadiene (**1.365**) also sparked our interest. Following its treatment with an acylium ion, we anticipated the formation of intermediate **1.366**, which indeed led a mixture of the fused cyclopentane products **1.367** and **1.368** in 20% yield and an 8:1 ratio (Scheme 1.33D). For this transformation, we observed that a reduced reaction temperature (-78 °C) was required to reduce the amount of side-reactions and supress decomposition pathways.

The final diene explored in this chapter was 1,4-pentadiene **1.369** (Scheme 1.33E). The main fraction that was isolated contained an inseparable mixture of allylic alcohol **1.373** and homo-allylic alcohol **1.372**. The first product could easily be explained by the intermediate **1.371**, however **1.372** would require an intermediate such as **1.370**. Due to the difficulties in isolating the individual products, absolute confirmation is a challenge reserved for future endeavours in this project.

In general, the results present herein are a step stone towards a comprehensive understanding of acylium chemistry and a more detailed study of varying alkynes and dienes is still required.



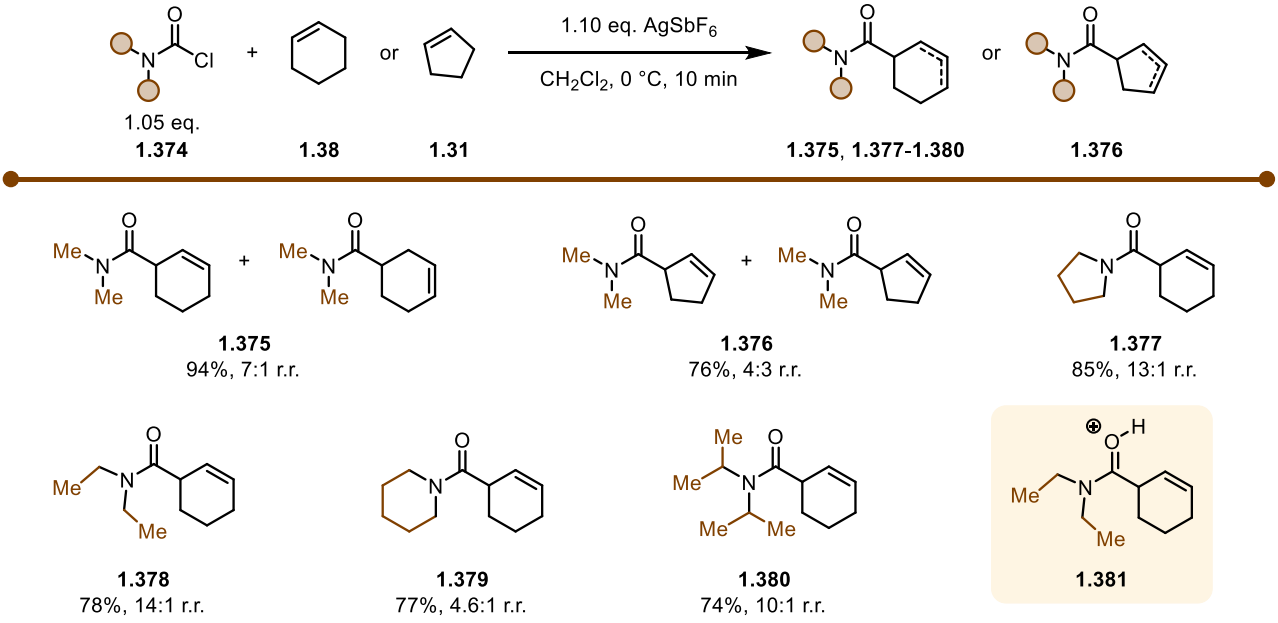
Scheme 1.33: Investigation of dienes under acylium conditions. *NMR yield calculated using mesitylene as the internal standard.

1.3.7 Different Electrophiles

Given the main body of work in the previous sub-chapters, one more element remains to be varied on a fundamental level: the nature of the initial electrophile. Therefore, for purpose of this section, we moved away from acyl chlorides towards carbamoyl chlorides (Scheme 1.34). Of note, chloroformates were initially investigated, but halide abstraction using silver hexafluoroantimonate ($AgSbF_6$) was never observed.

A series of commercially available carbamoyl chlorides were paired with cyclohexene or cyclopentene, and the initial results are showcased below. Treating a mixture of dimethyl carbamoyl chloride and cyclohexene **1.38** with silver hexafluoroantimonate gave an almost quantitative yield of a mixture of β,γ- and γ,δ-unsaturated amides **1.375** in a 7:1 regioisomeric ratio (94% isolated yield). While we had hoped for a 1,3-difunctionalized hexane, we were only able to obtain the so-called desaturation products. Further screening using cyclopentene **1.31** gave an even less selective mixture **1.376** (76%, 4:3 r.r.). More sterically hindered carbamoyl chlorides presented an increase in regioselectivity of the double bond of 13:1 and 14:1 for **1.377** and **1.378**, respectively. However, 1-piperidine carbonyl chloride gave a less selective reaction, affording a 4.6:1 regioisomeric mixture of **1.379**. Increasing the steric demand further landed in the middle of our results so far, a 10:1 ratio for compound **1.380**. An additional NMR experiment indicated a protonated amide prior to reaction work up, suggesting that the products are formed during the reaction due to the increased basicity of the amide (compared to ketones).

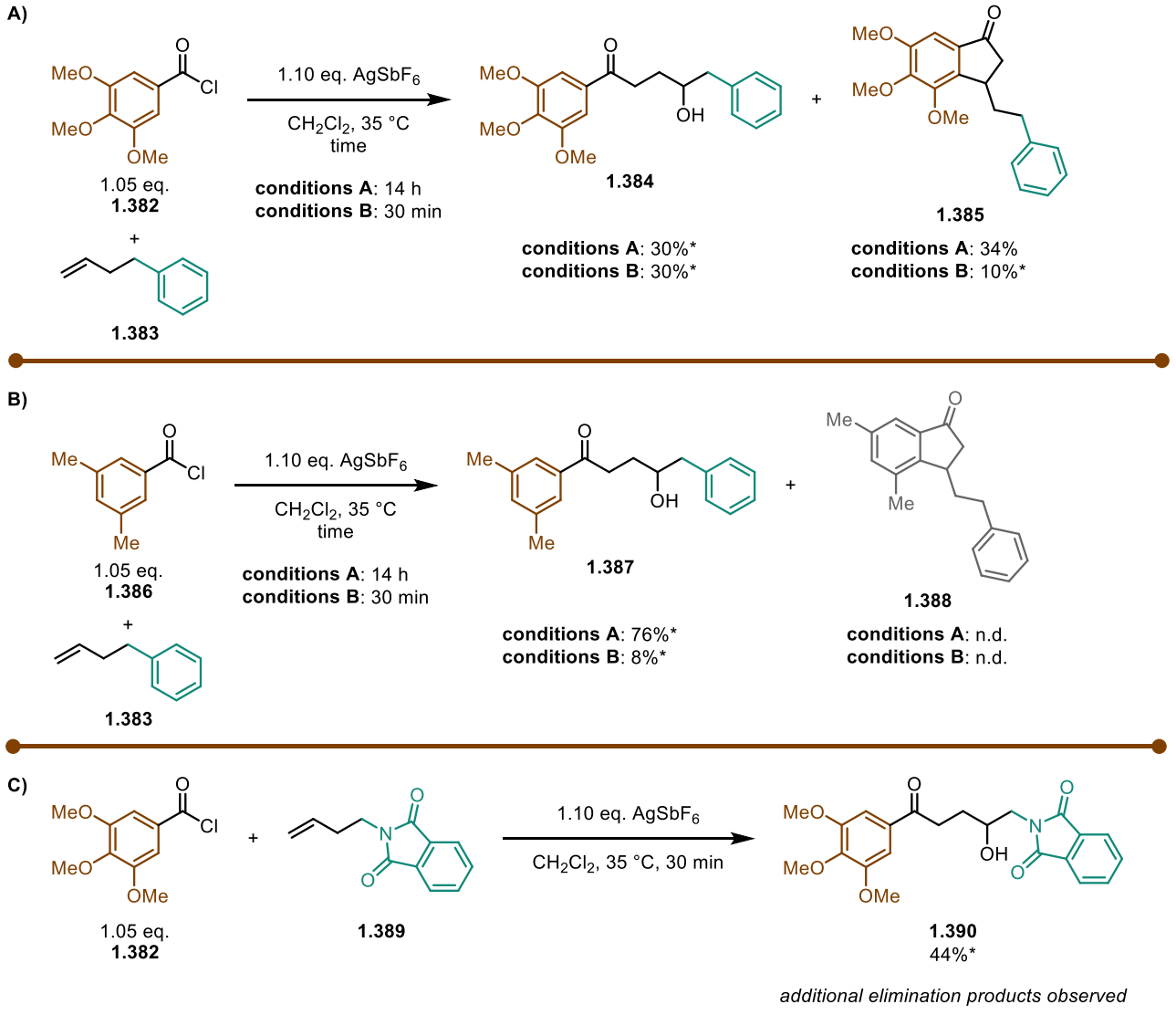
The detailed study of carbamoyl chlorides will be further explored by our team in the future, with emphasis on substituents that reduce the basicity of the amide, aiming at a 1,3-difunctionalization protocol and hoping to avoid the formation of elimination products.



Scheme 1.34: Initial screening of carbamoyl chlorides.

1.3.8 Miscellaneous Reactions

Acyl chlorides decorated with electron-donating groups on the aromatic part have shown do be challenging substrates (cf. Scheme 1.14), however, we postulated that an increase in electron density on the aromatic ring could be harnessed towards a Friedel–Crafts type transformation (Scheme 1.35). In the event, reaction of 3,4,5-trimethoxybenzoyl chloride **1.382** with 4-phenylbutene **1.383** formed a mixture of the 1,3-difunctionalized ketoalcohol **1.384** (30% NMR yield) as well as the desired Friedel–Crafts adduct **1.385** (34% isolated yield) after 14 hours at 35 °C. An additional experiment with a reduced reaction time (30 minutes) showed a lower proportion of Friedel–Crafts product **1.385** and the same amount of 1,3-difunctionalized product **1.384** (Scheme 1.35A).

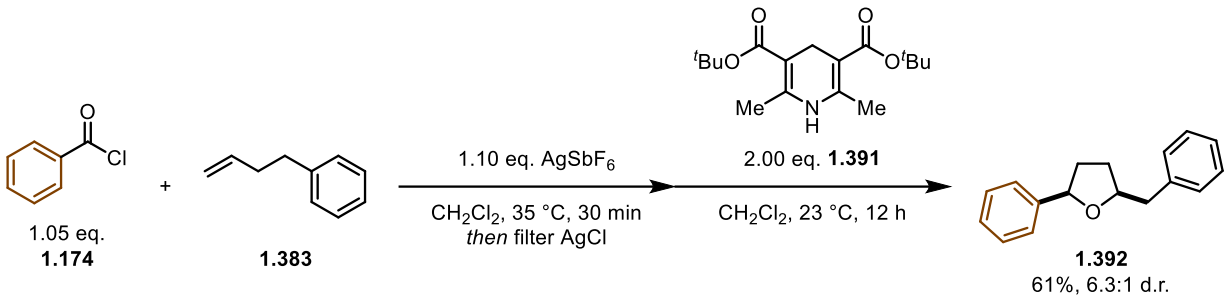


Scheme 1.35: Friedel–Crafts attempts. *NMR yield calculated using mesitylene as the internal standard.

A *m*,*m*'-dimethyl-substituted benzoyl chloride gave exclusively the standard 1,3-difunctionalized alkene **1.383** and no traces of Friedel–Crafts-type product **1.388** were detected. In addition, a significant

amount of elimination product was observed when the reaction time was shortened from 14 hours to 30 minutes, and only 8% of functionalized alkene **1.387** was formed (Scheme 1.35B). Additionally, when we changed the alkene substrate to **1.389**, our previously promising acyl chloride **1.382** yielded the 1,3-ketoalcohol **1.390** (44% NMR yield) as the major product and small amounts of elimination products (Scheme 1.35C).

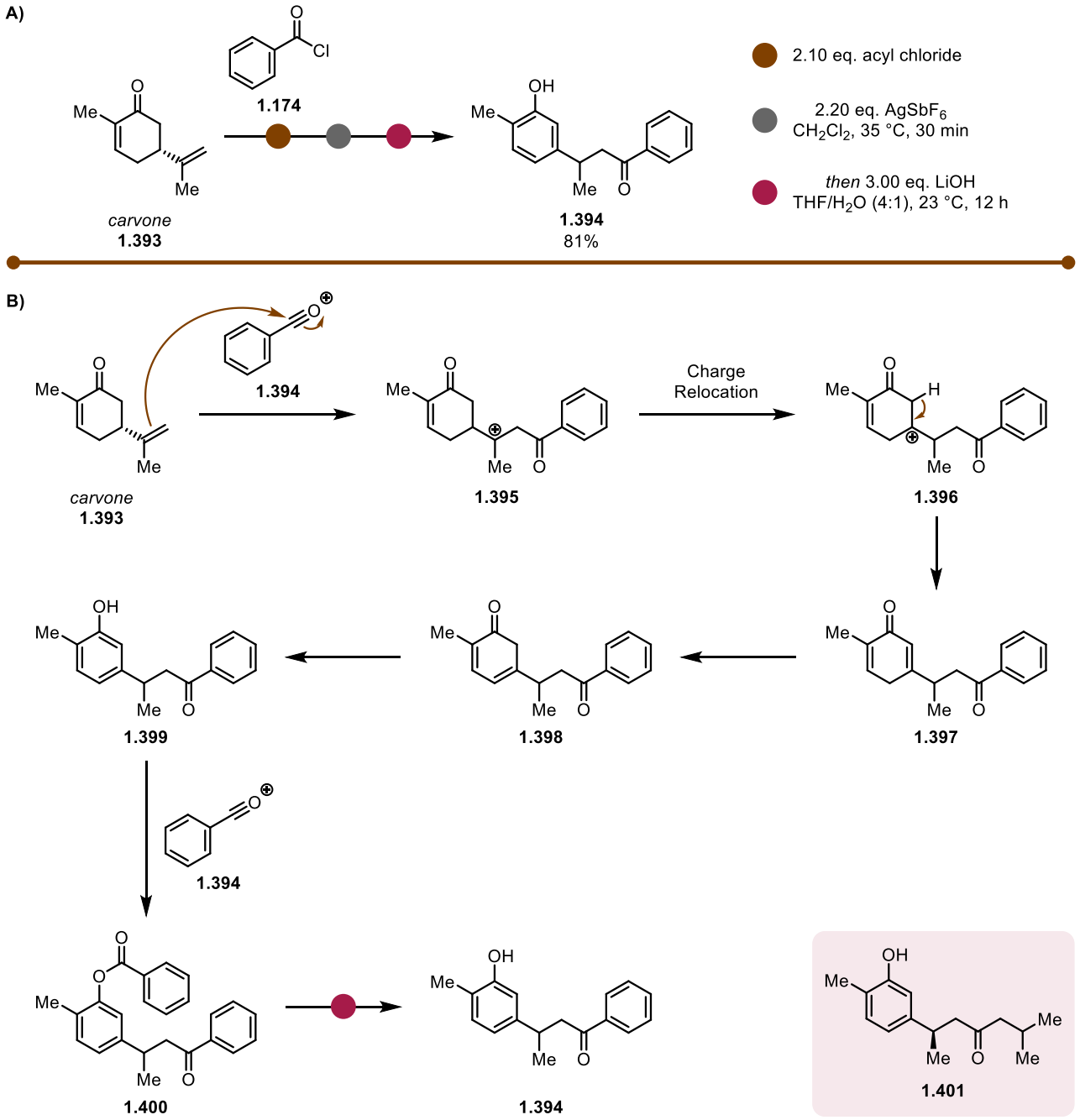
Inspired by a previous subchapter, we also investigated the reduction of the oxocarbenium ion formed from benzoyl chloride **1.174** and alkene **1.383** using a Hantzsch ester **1.391** as a reducing agent (Scheme 1.36). Among our initial screening, we observed formation of the *syn*-2,5-disubstituted tetrahydrofuran **1.392** in a good initial yield (61%) and with a 6.3:1 diastereomeric ratio. Further optimization of this reaction is currently being explored in our group.



Scheme 1.36: Reduction of oxocarbenium ions with Hantzsch ester **1.391**.

Two final examples highlighted in this chapter are the compounds **1.394** and **1.403**, derived from *carvone* **1.393**. By reacting an excess of benzoyl chloride **1.174** (2.10 eq.) with carvone **1.393** under charge relocation conditions, we obtained phenol **1.394** after basic hydrolysis (Scheme 1.37A). The proposed mechanism is explored below (Scheme 1.37B). In the first step, the exocyclic-double bond of carvone **1.393** attacks the generated acylium ion **1.394**, forming the initial carbocation **1.395**. After a 1,2-hydride transfer, intermediate **1.396** is generated, followed by abstraction of proton to form either **1.397** or **1.398**. It is feasible that both would tend to tautomerize to the phenol **1.399**, gaining increased stability from aromaticity. During initial investigations, we realized that excess of acylium reagent could further react with phenol **1.399** to form the benzoate **1.400**. Upon hydrolysis with lithium hydroxide (LiOH), the ester is converted back to phenol **1.394**.

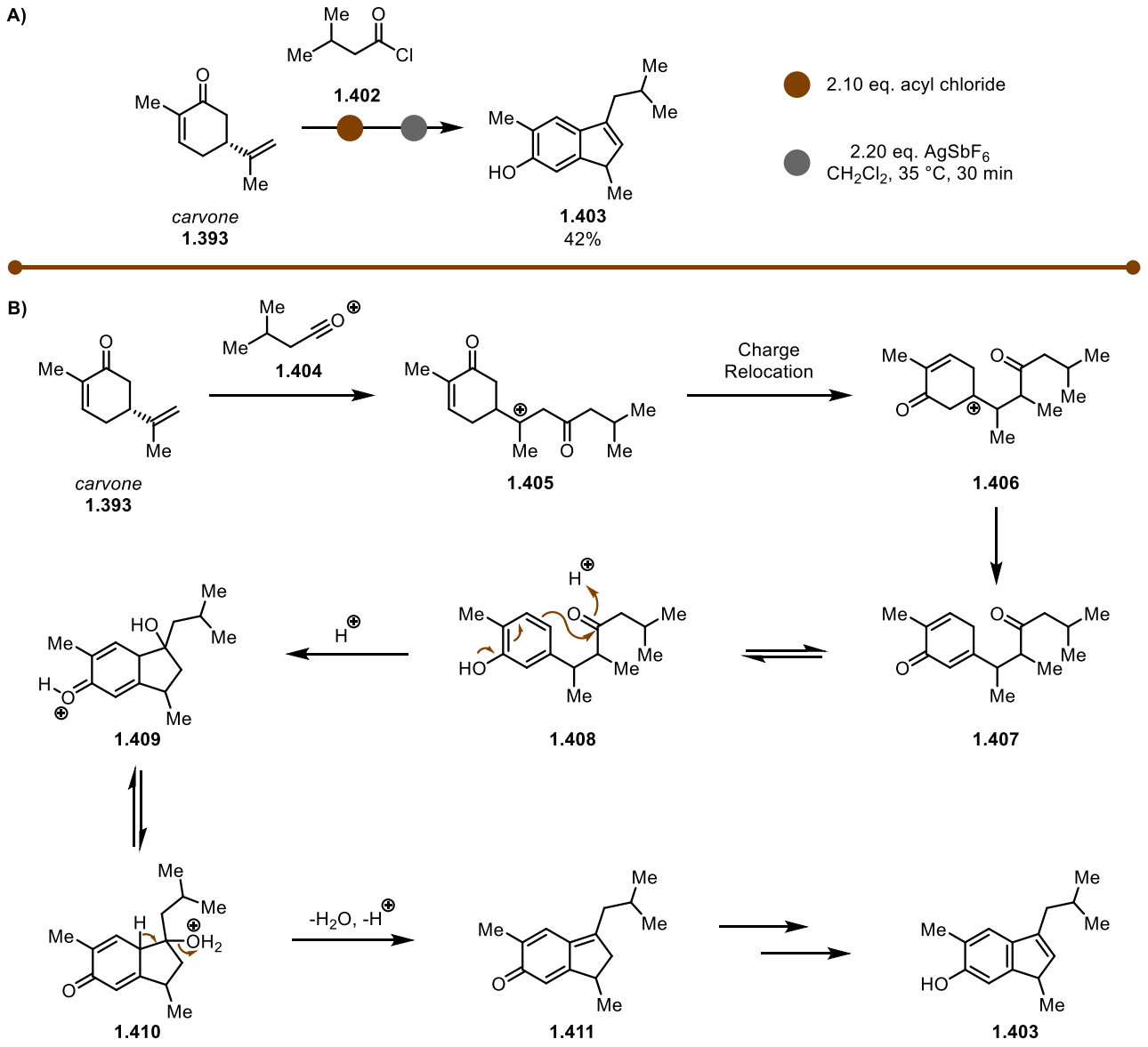
While the product itself is not reported to be biologically active, during literature surveys, we discovered that if, instead of benzoyl chloride **1.174**, isovaleryl chloride **1.402** was used as the reagent, compound **1.401**, with potential anti-Alzheimer's disease (AD) activity, could be synthesized in racemic fashion (Scheme 1.37B, bottom right).[83]



Scheme 1.37: A) Reactivity of carvone with benzoyl chlorides. B) Proposed reaction mechanism.

We subjected isovaleryl chloride **1.402** and carvone **1.393** to the reaction conditions, however we obtained indene **1.403** (Scheme 1.38A, right side) in 42% yield due to decomposition during purification. Adjusting the reaction time and increasing the excess of isovaleryl chloride **1.402** did not have any significant impact on the outcome of this protocol. We were unable to stop at the desired racemic version of **1.401**. A plausible mechanism for the formation of the indene is described in Scheme 1.38B. Similarly, to Scheme 1.37, the reaction is initiated by formation of carbocation **1.405**, which undergoes a charge relocation to form intermediate **1.406** and is most likely deprotonated swiftly to form compound **1.407**. After tautomerization to the phenol **1.408**, nucleophilic attack of the electron-rich arene on the carbonyl (more electrophilic than the

corresponding aryl-substituted congener) leads to **1.409**. After proton transfer to **1.410**, a simple deprotonation/elimination process delivers indene **1.411**. Of note, indenes are often unstable compounds, highlighted by our difficulties during purification and the need for several iterations of chromatographic purification. Attempts to stop at substrate **1.407** were unfruitful, even when carvone **1.393** was used in slight excess.



Scheme 1.38: Proposed reaction mechanism for the synthesis of indene product **1.403**.

1.3.9 Mechanistic Studies

The following section will cover several mechanistic experiments conducted, and the insights gained throughout this project.

1.3.9.1 React IR

Aiming to further investigate oxocarbenium ions, we set up a sequence of react IR experiments to attempt a study of the individual components of this transformation (Figure 1.1). Firstly, the background solvent (dichloromethane, CH_2Cl_2) and individual starting materials (turquoise and amber) were measured to determine characteristic peaks. Then, in two additional experiments, the IR spectra of both the acylium ion (red) and the oxocarbenium ion (turquoise, lower intensity). The main take away from overlapping theses IR spectra was the vanishing of characteristic signals for benzoyl chloride and cyclohexene in the 1750–1100 cm^{-1} range. However, we were not able to clearly identify characteristic signals for any of the cationic intermediates.

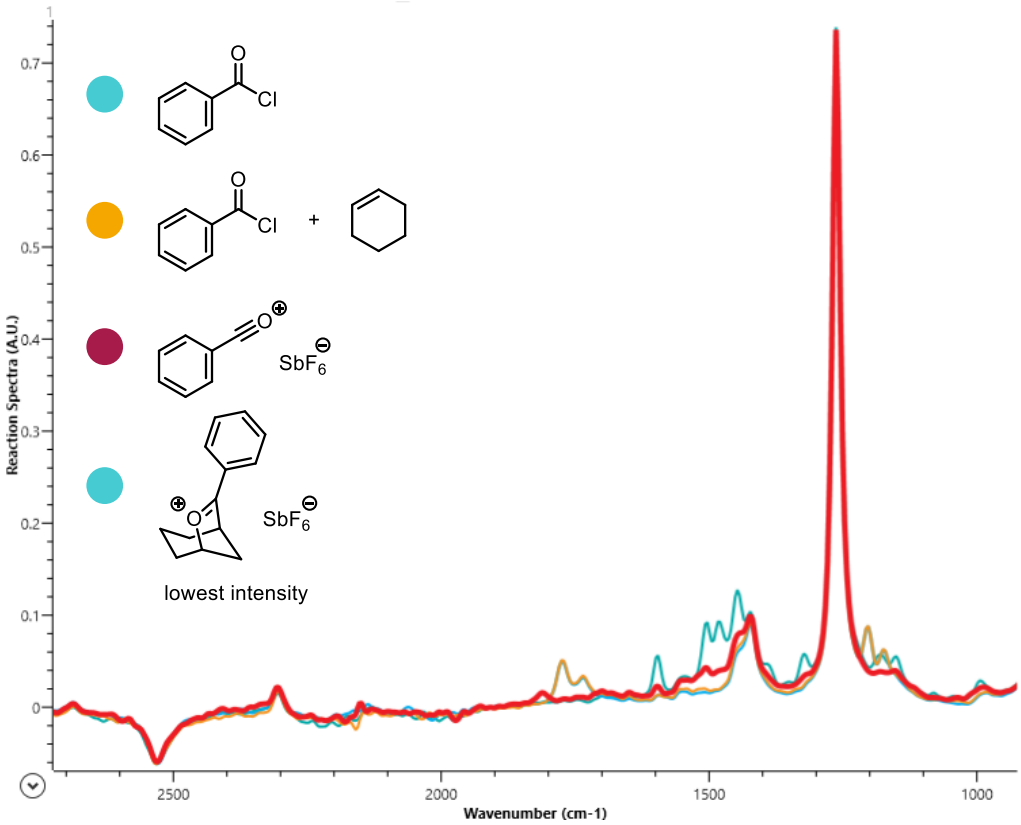


Figure 1.1: React IR experiment: Absorption bands of starting materials and persistent cationic intermediates.

We then explored a time-dependent measurement by first generating the acylium ion and monitoring the IR spectrum after addition of cyclohexene at ambient temperature (23 °C) (Figure 1.2).

Several observations were made. Firstly, the intensity of the characteristic peaks of the acylium ions, above 1900 cm^{-1}, shows a significant drop after cyclohexene addition. Secondly, a signal above 1800 cm^{-1} seems to start growing immediately after alkene addition and reaches a constant value in less than one minute. We were aware of the fast reaction times of the 1,3-difuntionalization of alkenes through charge relocation. While these results do not offer more insights and no other intermediates were detected (and would require computationally generated IR spectra for a proper picture), given more time and additional studies, react IR measurements could still prove insightful for following reaction kinetics and will be the subject of further studies.

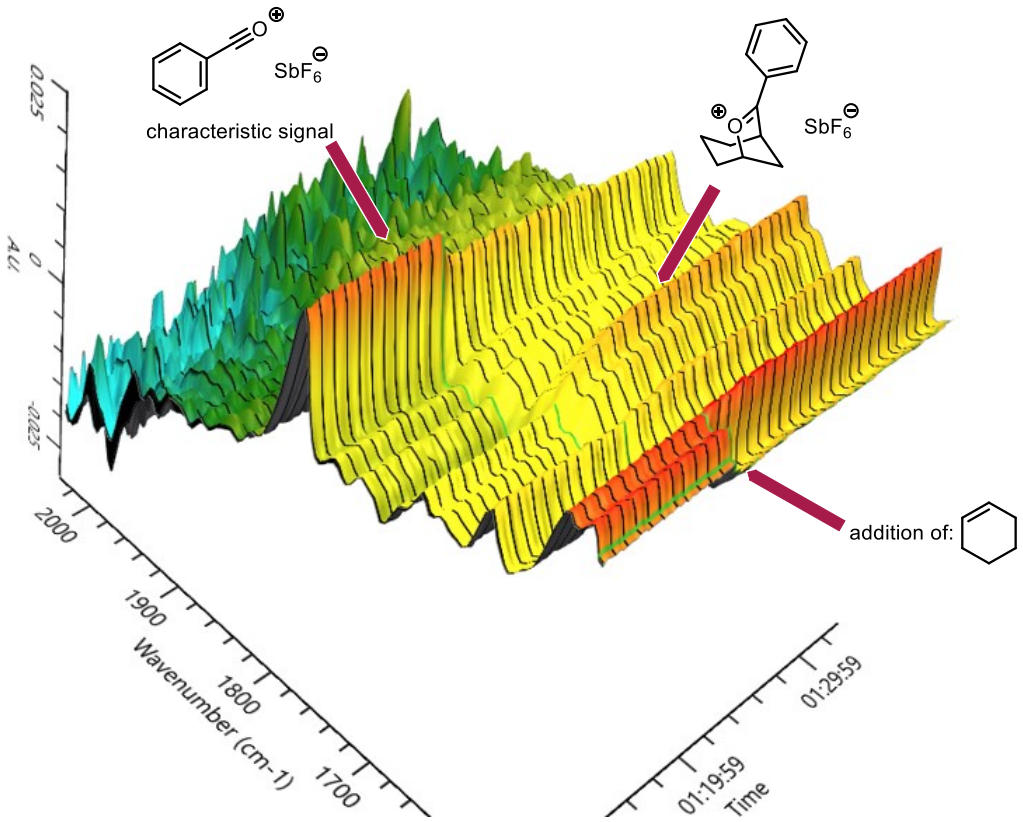


Figure 1.2: React IR experiments.

1.3.9.2 Protonation Studies

Early in our studies, we observed that the standard cyclic oxocarbenium ion **1.263** can survive extended periods of time in the reaction mixture, even at ambient temperature (23 °C). Additionally, if the reaction is performed in deuterated dichloromethane (CD_2Cl_2), both ^{1}H-NMR (Figure 1.3, blue) and ^{13}C-NMR spectra can be measured. While some amounts of elimination products can accumulate over time, they are mostly negligible and do not affect the studies presented herein. To probe the potential reversibility of the reaction and whether protonation/deprotonation reactions, or ene-type pathways are involved, the ^{1}H-NMR spectrum of the α,β-enone **1.412** (Figure 1.3, green) was measured and compared to a mixture of enone/fluoroantimonic acid hexahydrate **1.413** ($HSbF_6 \bullet 6H_2O$, Figure 1.3, violet) and a 1:1 mixture of enone starting material/triflic acid **1.414** (Figure 1.3, red). The amount of water present in the commercially available fluoroantimonic acid did not interfere significantly with our measurements.

The addition of triflic acid greatly shifts the NMR signals in the aromatic region, which indicates the formation of a protonated ketone **1.414**, with the double bond proton from the β-position significantly deshielded, when compared to the starting material **1.412**. The $HSbF_6$ adduct **1.413** seems to have almost no impact on the aromatic protons and moved the β-proton slightly downfield. This could be due to the presence of excess of water molecules ($HSbF_6 \bullet 6H_2O$).

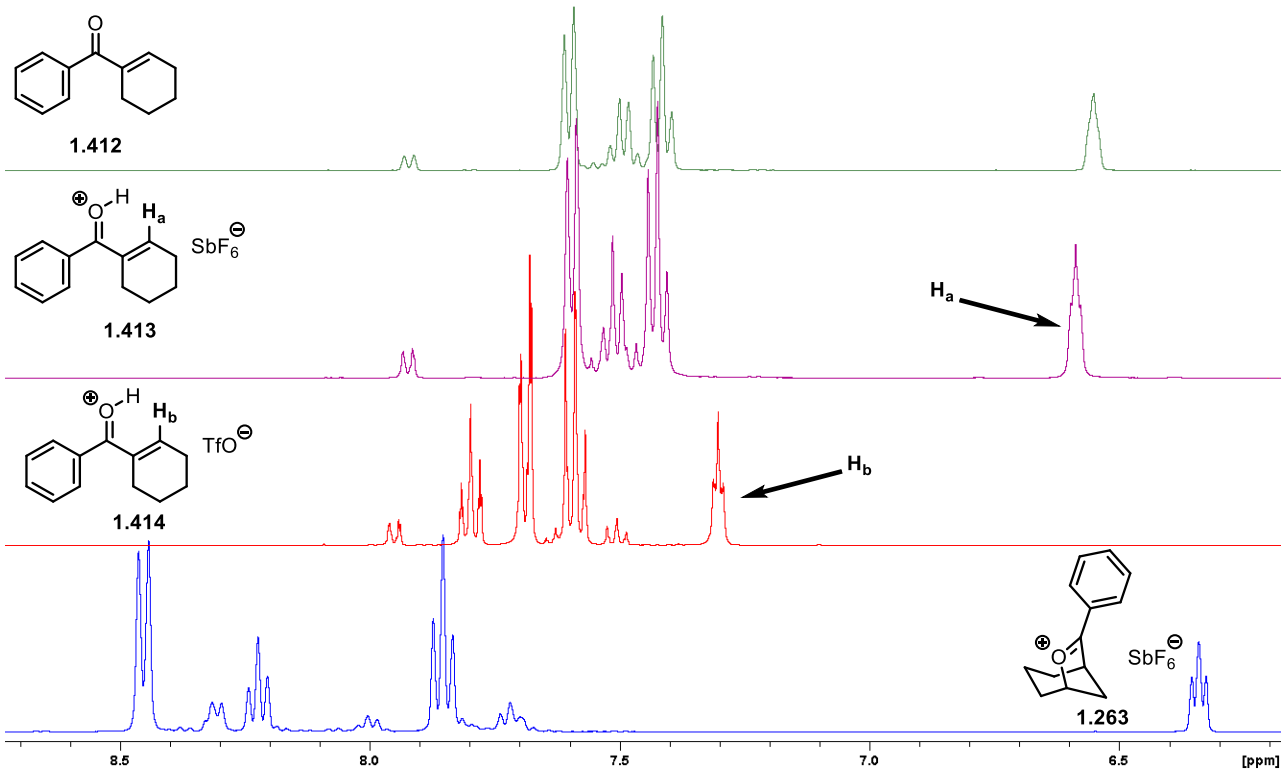
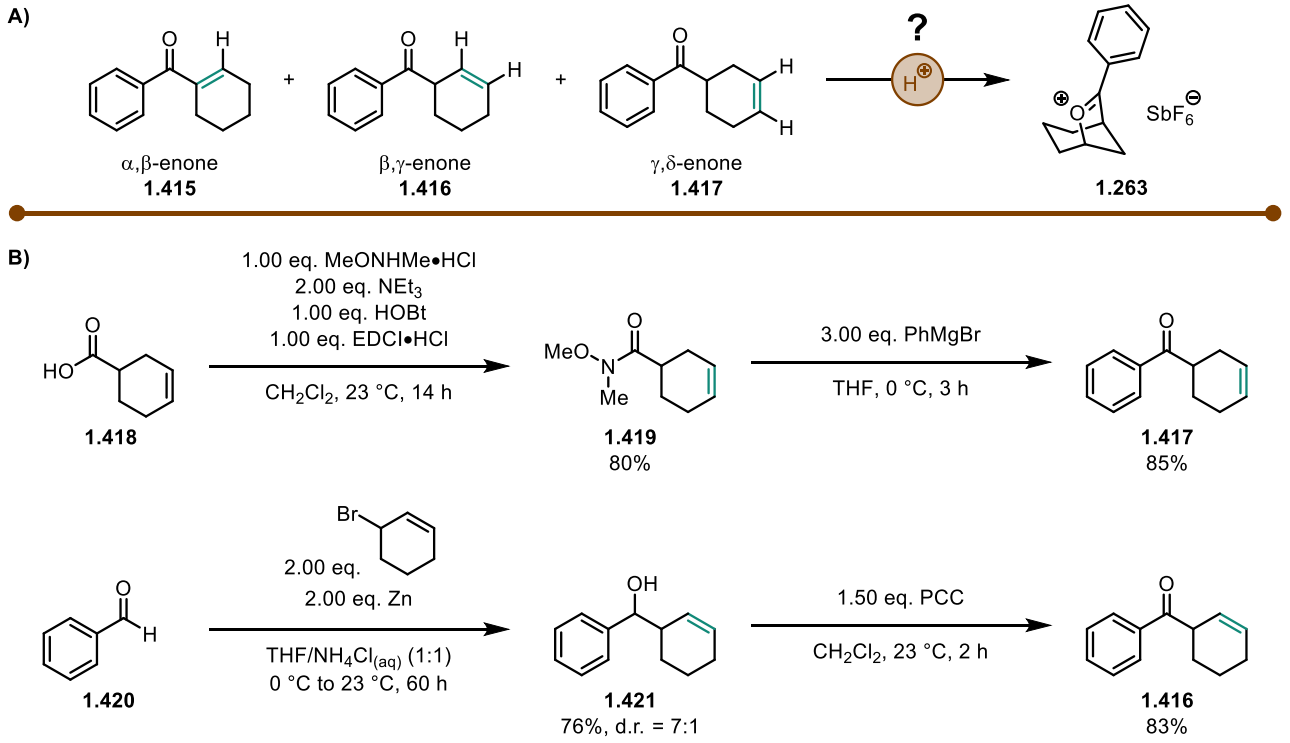


Figure 1.3: NMR protonation studies.

These results suggest the need for a more detailed study of triflic acid in combination with enones, however the α,β-enone **1.412** does not seem to convert to the oxocarbenium ion **1.263** by protonation. Therefore, if an α,β-unsaturated ketone would be formed during our alkene 1,3-difuntionalization protocol, it would most likely be a dead-end.

With this knowledge in hand, we wanted to study the reaction of all three alkene regiosiomers (**1.415**, **1.416**, **1.412**) showcased in Scheme 1.39A and whether they can convert into one another and/or lead to formation of oxocarbenium ion **1.263** when treated with a strong Brønsted acid. Towards this goal, the corresponding β,γ-unsaturated ketone **1.416** was synthesized by converting commercially available carboxylic acid **1.418** into the corresponding Weinreb amide **1.419**, followed by Grignard addition. γ,δ-Unsaturated ketone **1.416** was obtained by treating benzaldehyde **1.420** with the zincate of 3-bromo-cyclohexene, followed by pyridinium chlorochromate (PCC) oxidation (Scheme 1.39B).

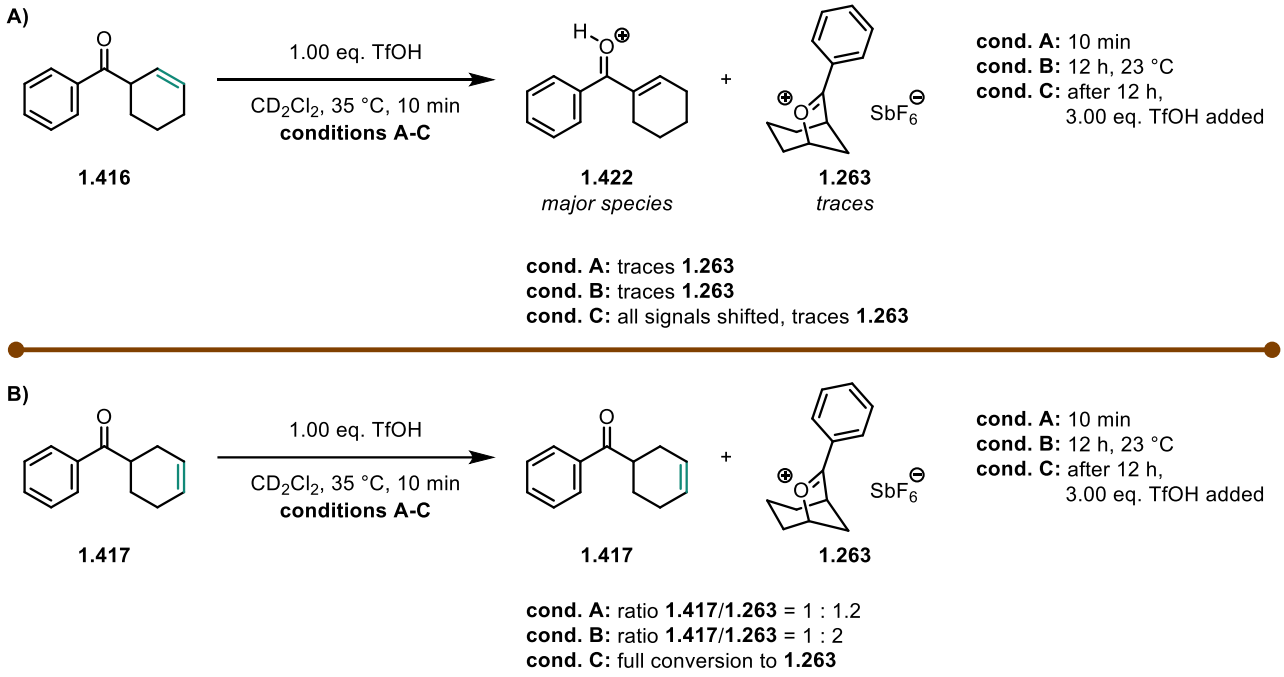


Scheme 1.39: A) Potential generation of an oxocarbenium ion through protonation of different enones. B) Synthesis of β,γ- and γ,δ-unsaturated ketones.

With the two new double bond regioisomers at our disposal, we proceeded to treat them with 1.00 eq. TfOH (Scheme 1.40) and measure an aliquot of each solution after 10 minutes (Conditions A) and 12 hours (Conditions B) at ambient temperature (23 °C). To push the reaction to completion, excess triflic acid was added also after 12 hours (Conditions C). The results of these NMR experiments are presented in Scheme 1.40. When β,γ-unsaturated ketone **1.416** was treated with the acid, trace amount of oxocarbenium ion **1.263** could be observed in all three cases (Conditions A-C) and the protonated α,β-unsatured ketone **1.422** as the major

product. Using excess of the Brønsted acid had no influence on the outcome of the reaction and only shifted the signals downfield (Scheme 1.40A). We can therefore presume that in addition to the α,β-unsatured ketone **1.415**, **1.422** is also a dead-end for our transformation, yet yields the potential to for the oxocarbenium ion **1.263**.

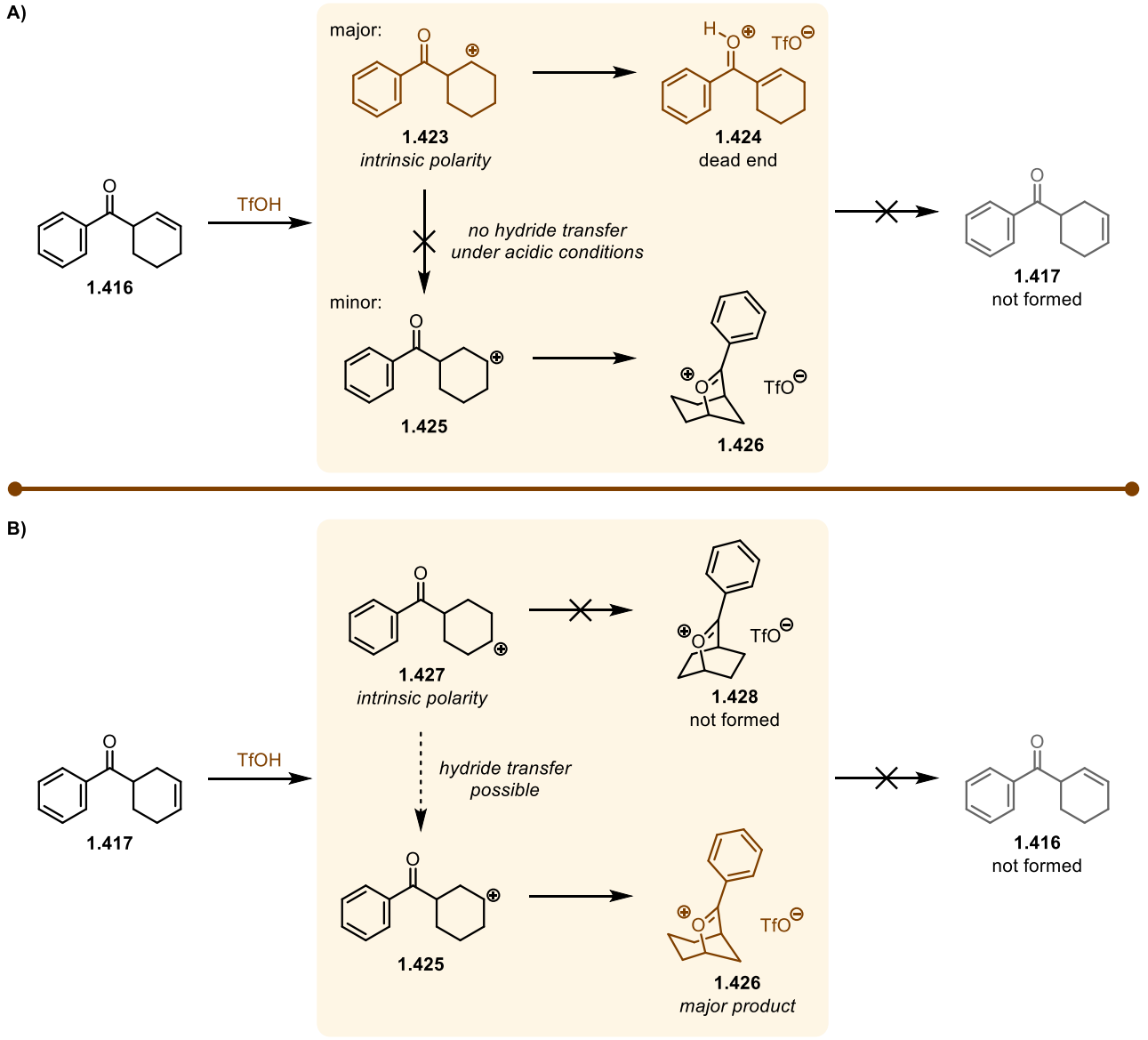
Complementary, γ,δ-unsaturated ketone **1.417** showed traces of oxocarbenium ion **1.263** formation. After only 10 minutes, a 1:1.2 mixture between unreacted starting material an oxocarbenium ion **1.263** was visible by proton NMR in deuterated dichloromethane (Scheme 1.40B, Conditions A). By increasing the reaction time to 12 hours (Conditions B) or the equivalents of triflic acid (Conditions C), we were able to increase the amount of **1.263** and even obtain full conversion.



Scheme 1.40: A) Protonation of β,γ-unsaturated ketone with triflic acid. B) Protonation of γ,δ-unsaturated ketones with triflic acid.

Taking a closer look at the mechanistic pathways involved in these transformations, two possible initial protonation products of alkene **1.416** can be proposed. Protonation at the γ-position leads to intermediate **1.423**, bearing the positive charge in β-position (Scheme 1.41A). One would expect this product to eliminate the α-proton and form a dead-end intermediate **1.424**, which is indeed the major species detected. If, however, the β-position is protonated, carbocation **1.425**, which is one ketone capture away from yielding the standard oxocarbenium ion **1.426**, is formed. However, as shown previously in Scheme 1.40A, this intermediate is only present in small amounts. Additionally, the γ,δ-unsaturated ketone **1.417** is never observed. These results put together suggest no possibility for required hydride transfer processes under such acidic conditions and both double bond isomers (α,β- and β,γ-) seem to funnel towards an

unproductive/dead-end pathways (**1.424**). Furthermore, protonation/deprotonation pathways, if at all present, seem to not equilibrate towards the oxocarbenium ion **1.426**.



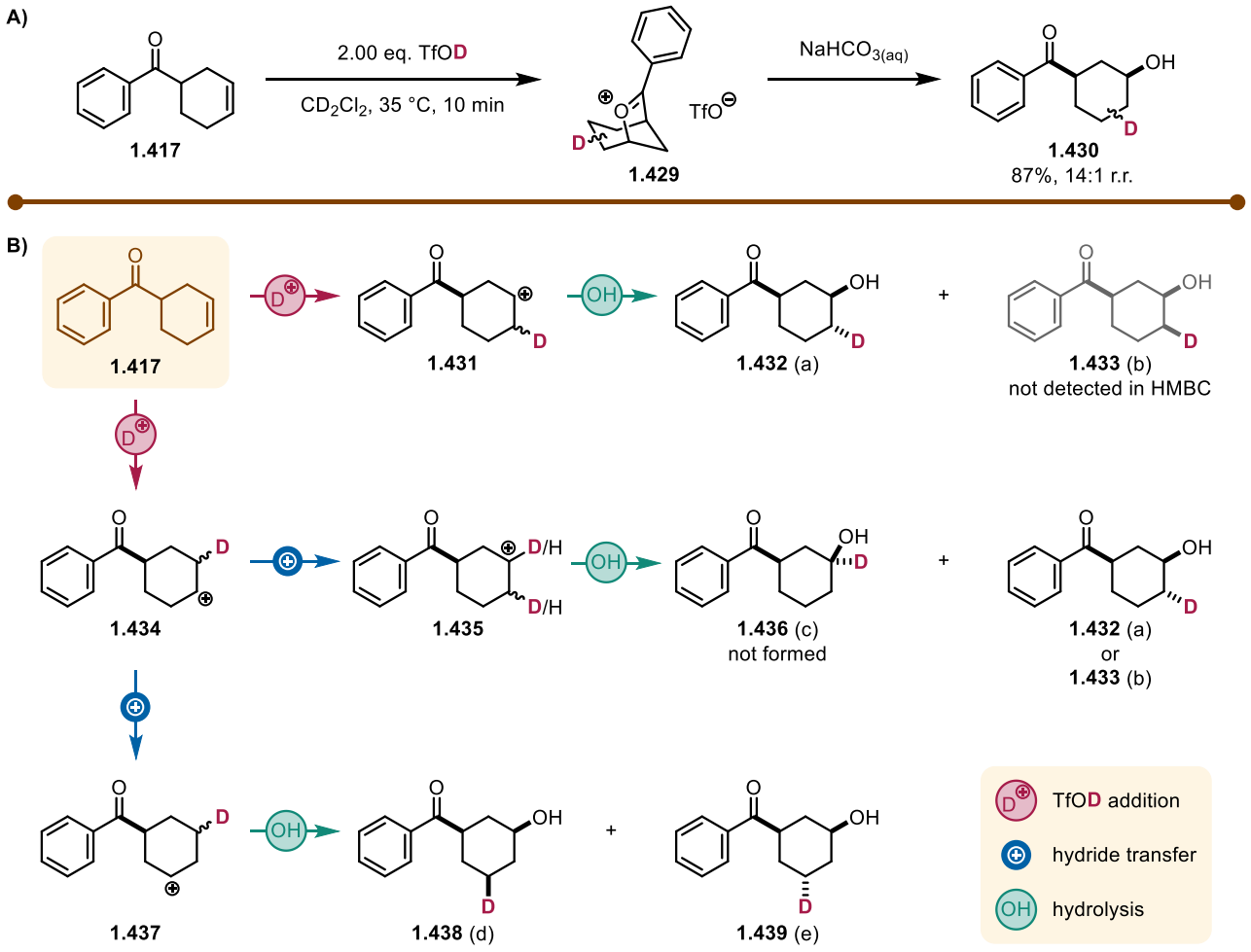
Scheme 1.41: Mechanistic proposal to support protonation of enones.

In the case of alkene **1.417**, again two possible protonation pathways are presented (Scheme 1.41B). If the symmetrical intermediate **1.427** were formed, one would expect capture of the positive charge by the ketone to form the symmetric oxocarbenium ion **1.428**. Such an intermediate, while interesting and responsible for 1,4-functionalizations starting from acyl chlorides and alkenes, was never observed. Instead, the major intermediate detected, stems from carbocation **1.425**, and is our known oxocarbenium ion **1.426**. In the case of regioisomer **1.417**, it appears that formation of the less likely protonation isomer **1.425** (when taking into account intrinsic polarity of the molecule) is either favored or, if not the case, the other regioisomer **1.427** is unable to form a bridged structure **1.428**, but rather does a hydride shift towards **1.425**. Additionally, no conversion of **1.417** to its regioisomer **1.416** was observed.

These results strongly suggest that no protonation/deprotonation pathway or ene-type mechanism is involved in the formation of oxocarbenium ions and it is indeed a hydride-transfer dominated process. The only option to overcome this, would be, as highlighted in this sub-chapter, to generate the carbocation that can directly form the desired oxocarbenium ion in one single protonation step from the appropriate double bond isomer.

1.3.9.3 Isotope Labeling Studies

Protonation studies delivered insights into the nature of oxocarbenium ion formation and in order to wrap-up these investigations a final experiment using **deuterated** triflic acid (TfO**D**) was performed (Scheme 1.42A). The isolated product after hydrolysis with saturated aqueous sodium bicarbonate solution ($NaHCO_3$) was shown to be a mixture of deuterium regioisomers **1.430**.



Scheme 1.42: Deuterium studies.

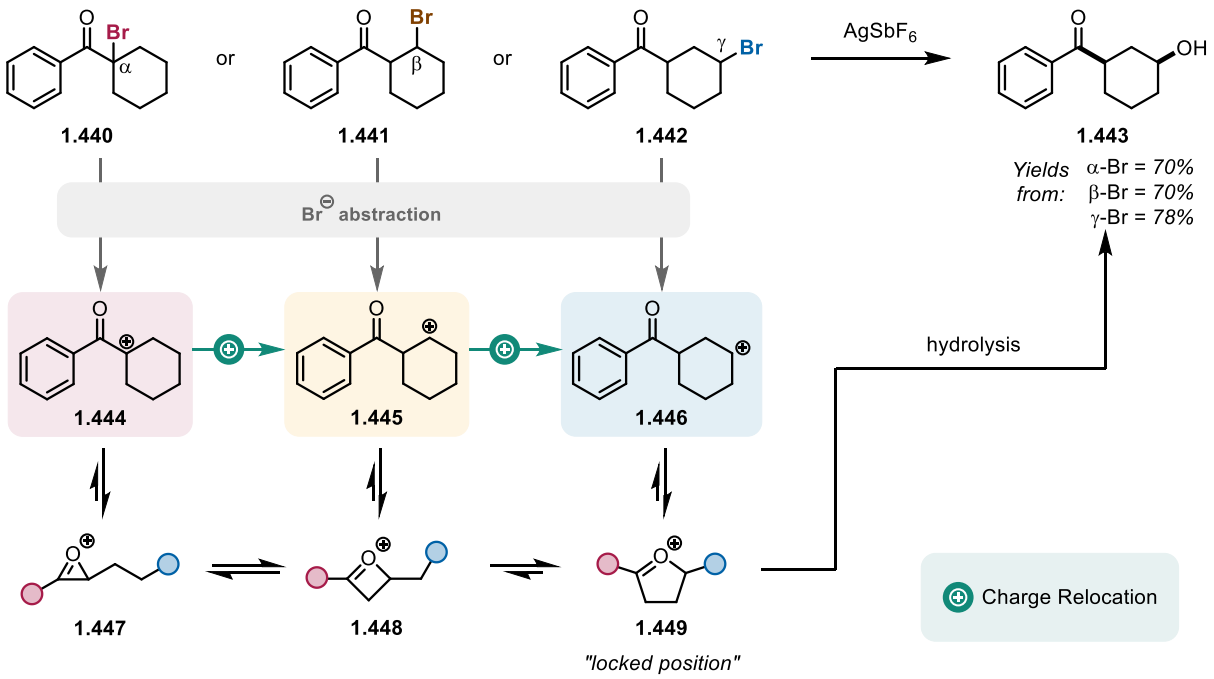
We know from previous endeavours, that the double bond can attack a deuterium cation from both ends. In the first case, carbocation **1.429** is formed (deuterium can be either axial or equatorial) and after

hydrolysis two possible diastereomers (a and b) would be obtained (Scheme 1.42B). However, HMBC analysis could not identify product **1.433** (b) and only **1.432** (a) was observed in NMR. If no hydride shift events could take place **1.432** (a) would be the only obtained product. The reality is often more complex and we noticed several additional species. If the other carbocation regioisomer **1.434** is formed, it also has two possible pathways to follow. Firstly, a hydride or deuteride shift would form the mixed intermediate **1.435**, that upon hydrolysis would again form product **1.432** (a), **1.433** (b) or **1.436** (c). We established previously that **1.433** (b) is not formed, and, in this case, **1.436** (c) could also not be detected. This pathway is rather inconclusive, as it provides the same observed results as the first one. Finally, a pathway involving a hydride shift on the other side of the molecule towards intermediate **1.437** is hypothesized. In this final case, hydrolysis would yield a mixture of products **1.438** (d) and **1.439** (e), which were indeed identified in the inseparable product mixture.

To summarize the deuterium studies, the main product **1.432** (a) is formed by deuterium cation trapping on the less hindered side of the cycle (relatively speaking: γ-equatorial position if the ketone is equatorial, γ-axial position if the ketone is axial) and forms the expected oxocarbenium ion as the main intermediate. If the protonation occurs on the other side (δ-position), it is either a minor event (leading to products d and e) or it quickly converts through hydride transfer to the major intermediate and sequentially to the major product (a).

1.3.9.4 Bromide Abstraction

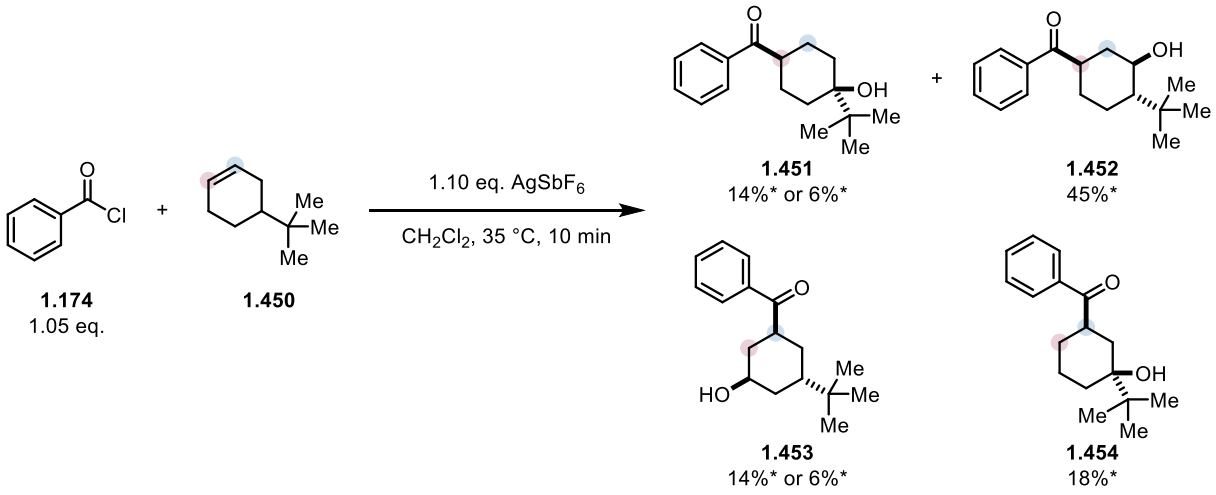
The previous studies provided a broader picture of the mechanism guiding the generation of oxocarbenium ions, however certain complementary pieces of information were required. The main disadvantage is the use of a different counteranion, specifically triflate (TfO^-). We therefore synthesized all three regioisomeric bromides (α-**1.440**, β-**1.441** and γ-**1.442**) and subjected them to bromide abstraction with silver hexafluoroantimonate ($AgSbF_6$). We postulated that the 1,3-difunctionalization presented in this thesis relies on rapid isomerization of carbocations. Regardless of where the initial charge is formed (α, β or γ), it should always follow the same trajectory: from α-**1.444** to β-**1.445** and from β-**1.445** to γ-**1.446**, respectively, through consecutive *charge relocation* events drawn below (Scheme 1.43). We reasoned that an increase in stability, showcased by the different cyclic oxocarbenium ions (**1.447**, **1.448** and **1.449**) could serve as the driving force of this isomerization. Once the cation has relocated to the γ-position, it is trapped and not allowed to pursue more distal locations. After hydrolysis, all three bromo-ketones were found to yield the same major product **1.443** in 70-78% yield, with no traces of other regioisomeric products detected in either case. Of course, perceivable amounts of elimination products were observed, yet they were all consistent with precious results, supporting our mechanistic proposal.



Scheme 1.43: Studies of bromide abstraction.

1.3.9.5 Regioselectivity

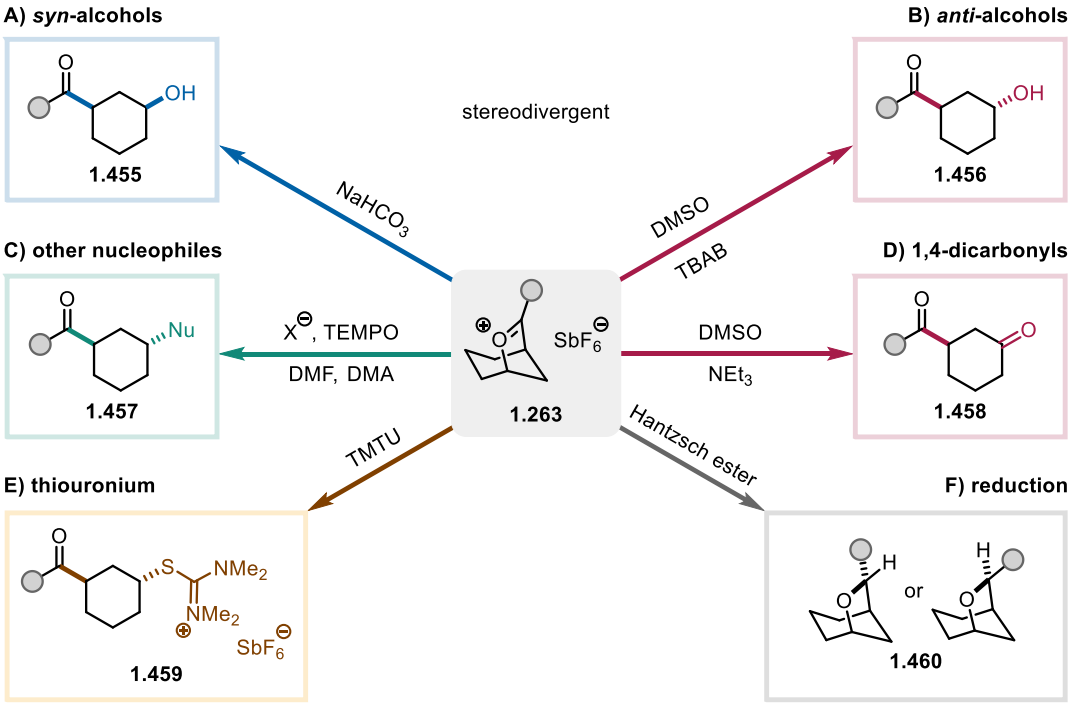
Lastly, the question of the determining factors with regard to regioselectivity remained unanswered. As we learned, it can play a role even when the smallest substituents, such as proton and deuterium, are involved. To lay this issue to rest, we synthesized an unsymmetrical, *tert*-butyl-substituted cyclohexene substrate (**1.450**) and subjected it to the reaction conditions with benzoyl chloride **1.174** (Scheme 1.44). The product mixture obtained was composed of a total of four 1,3- and 1,4-difunctionalized products. Ketoalcohols **1.451** and **1.452** are derived from the addition to the less sterically hindered carbon of the double bond (pink) and are the result of one and two hydride transfer steps, respectively. Ketoalcohols **1.453** and **1.454** stem from addition to the more sterically hindered carbon (blue) of the double bond of **1.450**, as seen by their lower combined yield when compared to the other two isomers. An exact yield for **1.452** and **1.453** could not be determined due to overlapping signals in the NMR of these inseparable products. Nevertheless, these two isomers (**1.452** and **1.454**) again showcase one and two hydride transfer steps, respectively. Therefore, unsymmetrical, cyclic alkenes seem to be an open challenge for future studies.



Scheme 1.44: Regioselectivity studies. *NMR yield calculated using mesitylene as the internal standard.

1.4 Conclusion

The goals of this project were successfully achieved. We developed a method for the remote 1,3-difunctionalization of unbiased alkenes (both terminal and internal/cyclic) by generating an acylium ion that could, after attack by the double bond of the alkene and charge relocation, form stable cyclic oxocarbenium ions **1.263**, largely circumventing elimination reactions (Scheme 1.45). A plethora of functionalization protocols were established, ranging from the stereodivergent synthesis of both *syn*- and *anti*-ketoalcohols (**1.455** and **1.456**, A and B), opening of oxocarbenium ion **1.263** with a variety of nucleophiles **1.457** (C), and access to 1,4-dicarbonyls **1.458** (D) to thiouronium salt synthesis **1.459** (E) and reduction towards tetrahydrofuran products **1.460** (F). A lwide range of investigations shined light onto the proposed mechanism of this reaction and broadened our understanding of carbocation chemistry. All individual side-branches of this project that have only been briefly mentioned in this thesis, are currently under development in the Maulide lab.

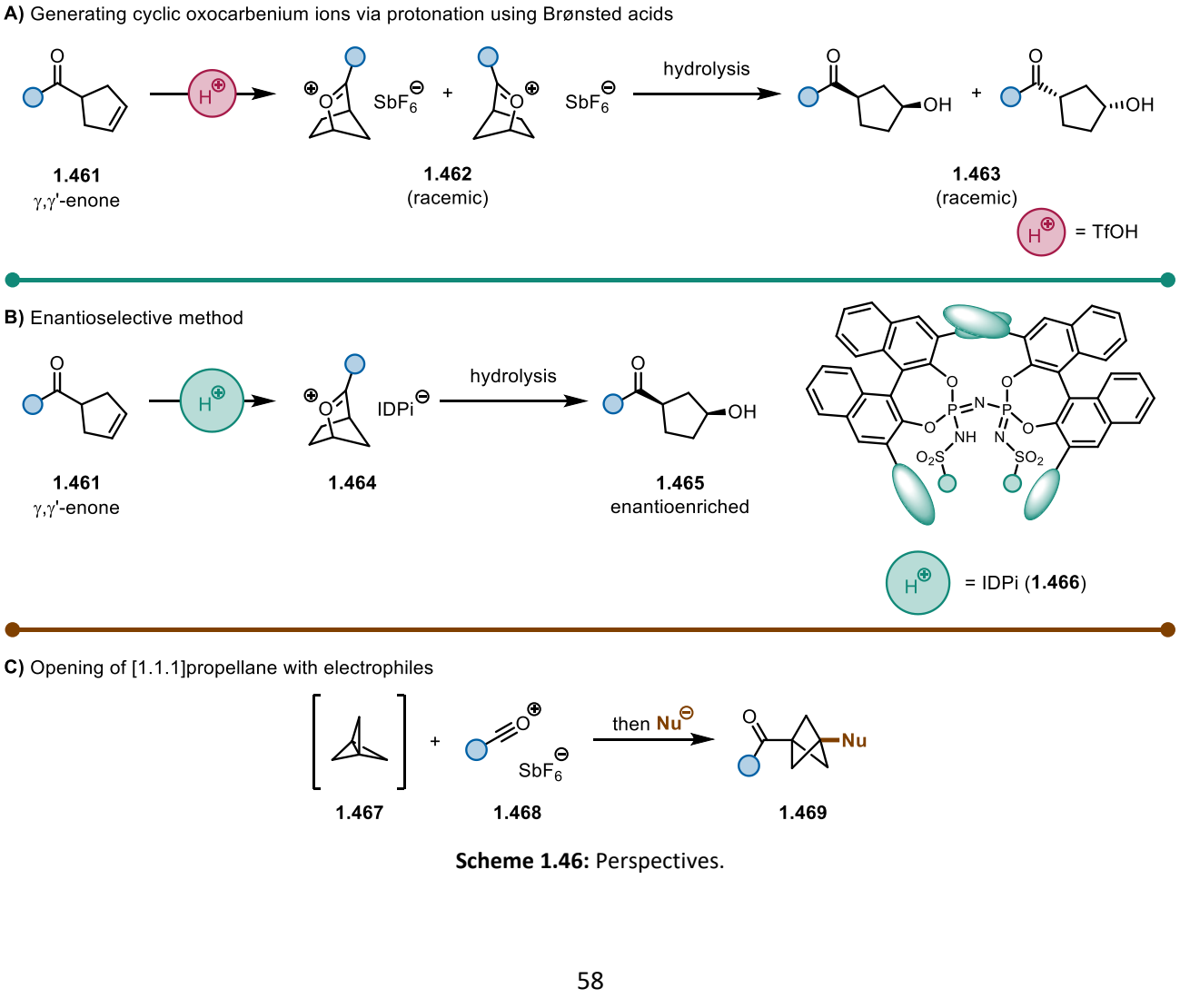


Scheme 1.45: Overview of oxocarbenium ion chemistry applications

1.5 Perspectives

During our studies, we explored ways of generating racemic oxocarbenium ions in a reliable and reproducible method from appropriate acyl chlorides, alkenes and silver salts. Complementary to these methodologies, protonation of aptly placed double bonds with triflic acid (TfOH) was shown to be an intriguing way of accessing these reactive intermediates (**1.462**) in a racemic fashion (Scheme 1.46A). However, an enantioselective method remains to be developed. Such a transformation would require a chiral proton source such as IDPi (**1.466**), a class of chiral acids explored in a substantial body of work with regard to their applications as organocatalysts (Scheme 1.46B).[84] [85] If achievable, a catalytic method would need to be developed to account for atom economy.[86]

An alternative project would be the opening of [1.1.1]propellane with acylium ions (Scheme 1.46C). Bicyclo[1.1.1]propane products (BCPs, **1.467**) have gained significant attention recently as surrogates for arenes in medicinal chemsistry.[87] [88] [89] [90] [91] [92] [93] However, most reports open [1.1.1]propellanes (**1.467**) with nucleophiles or nucleophilic radicals, in part due to orbital geometry and overlap of BCPs. Therefore, a methodology using highly reactive electrophilic species partnered with non-nucleophilic/non-basic counteranions would have a positive impact on the field as a whole.



Scheme 1.46: Perspectives.

2 Remote Functionalization of Inert C–H bonds in Cyclic Hydrocarbons Mediated by Hypervalent Iodine

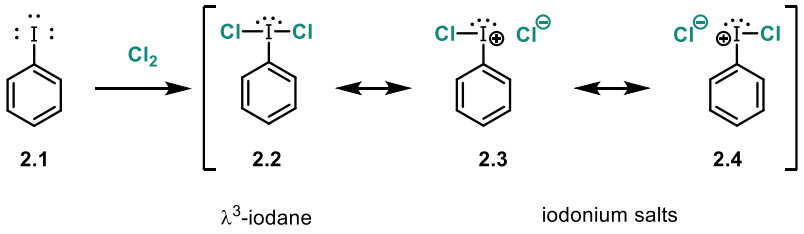
The work described was conducted in collaboration with Dr. Nicolas G.-Simonian, Dr. Daniel Kaiser, Ricardo Meyrelles, MSc and Maria Zazirna, BSc. Parts of the results have been submitted to Angewandte Chemie.

2.1 Introduction

2.1.1 Structure and Properties of Hypervalent Iodine Reagents

Iodine is the heaviest non-radioactive halogen with an atomic number of 53 and can be found in a variety of oxidation states. Its unique position in the periodic table among non-metals dictates its characteristic properties such as the tendency to form longer, yet weaker covalent bonds.[94] [95] [96] Therefore, iodide is both an excellent leaving group and a competent nucleophile.[97] Due to the size and polarizability of iodine bonds with other organogen elements, a plethora of polyvalent iodine compounds have been synthesized and their reactivity has been extensively exploited. To further illustrate these features, the bond dissociation energy (BDE) of the C–I bond in H_3C–I (55.9 kcal mol^{-1}) shows that it is almost half as strong as the C–H bond present in H_3C–H (104.9 kcal mol^{-1}).[98] All these features taken together, have led to the synthesis and isolation of so called λ^3-Iodanes or "hypervalent" iodine reagents. When Lewis structures of these molecules are drawn, they seem to defy the octet-rule.

The first report of a hypervalent iodine reagent was achieved by Conrad Willgerodt in 1885 where the synthesis of the T-shaped (dichloroiodo)benzene **2.2** was achieved by oxidizing iodobenzene **2.1** with chlorine gas (Cl_2) (Scheme 2.1).[99]

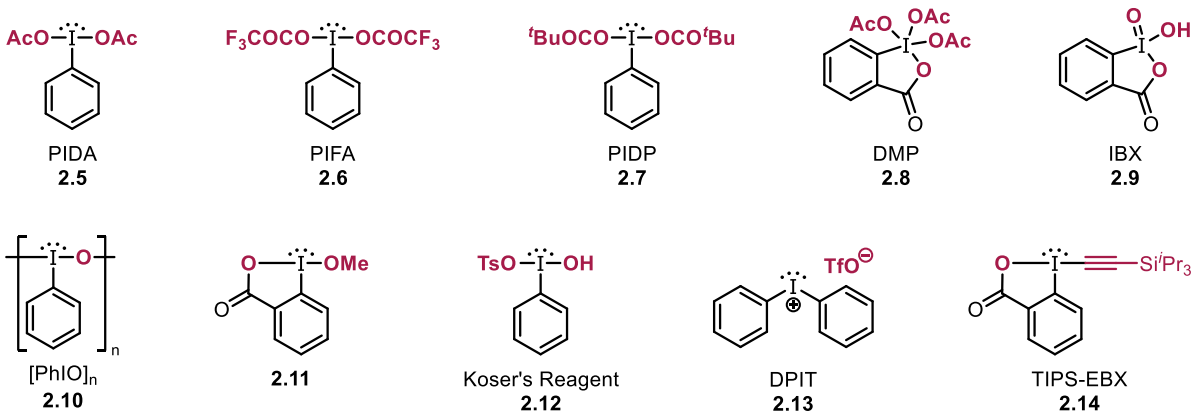


Scheme 2.1: First synthesis of a hypervalent iodine reagent reported by Conrad Willgerodt in 1885.

In general, when referring to hypervalent iodine compounds, two main forms are accepted. The previously mentioned λ^3-iodane **2.2** where both chlorine atoms are *trans*-positioned to each other and the overall T-shape of the compound leaves a side of the molecule substituent free, the space being occupied by the non-bonding electrons of iodine. Alternatively, **2.2** can displace a chloride and form iodonium salts **2.3** and

2.4, which highlight the electrophilic nature of these reagents and give a hint towards the reactivity features and potential applications.

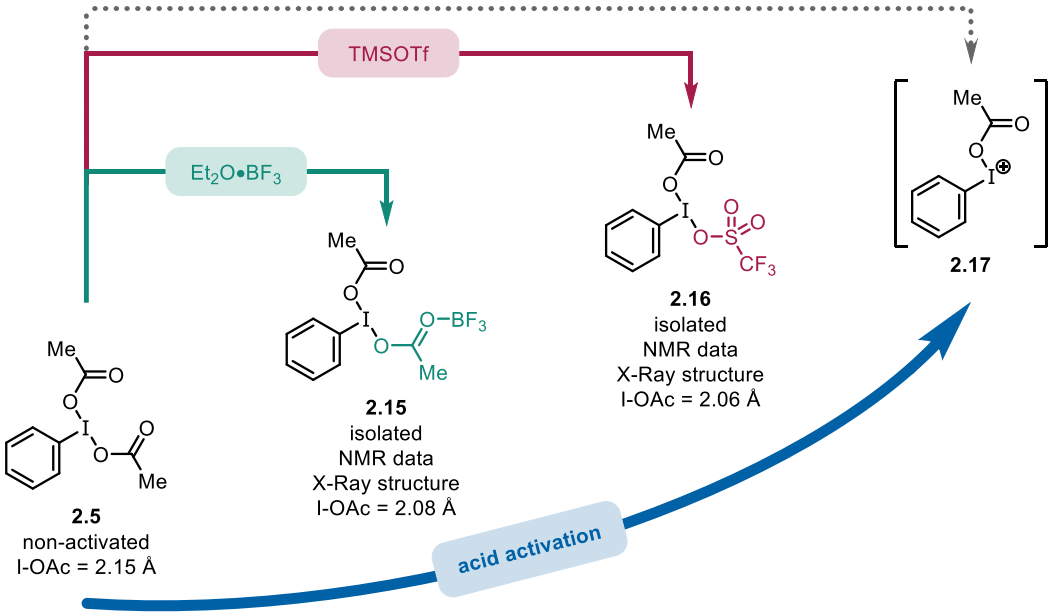
Building on these inherent traits, as well as their low toxicity, ready availability and ease of handling, a plethora of hypervalent iodine reagents have been synthesized, isolated and featured in an abundance of literature reports (Scheme 2.2).[100] Textbook examples include (diacetoxyiodo)benzene **2.5** (PIDA), its more electrophilic variant [bis(trifluoroacetoxy)iodo]benzene **2.6** (PIFA) and phenyliodine(III) dipivaloate **2.7** (PIDP). Among these frequently employed oxidants, cyclic versions such as the well-established Dess–Martin periodinane **2.8** (DMP), 2-Iodoxybenzoic acid **2.9** (IBX) and reagent **2.11** have also found success in chemical synthesis. Iodosobenzene **2.10** (PhIO) has an oligomeric structure and is used as an oxo-transfer reagent by releasing iodobenzene as a leaving group. Koser's Reagent **2.12** (hydroxy(tosyloxy)iodobenzene, HTIB) has found applications as a phenyliodinating and oxytosylating reagent. Diphenyliodonium triflate **2.13** (DPIT) is part of a class of arylating reagents in palladium-catalyzed cross coupling transformations. Finally, 1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one **2.14** (TIPS-EBX) has recently found application as an alkynylating reagent. Most reagents highlighted in Scheme 2.2 are used as a green alternative to transition metals. However, they are routinely used in stoichiometric amounts.[101] Recent efforts have produced methods where hypervalent iodine reagents are used in a catalytic fashion as well as in flow-chemistry.[102] [103] [104] [105]



Scheme 2.2: Frequently used Iodine (III) reagents for α-functionalization and oxidation of ketones and silyl enol ethers.

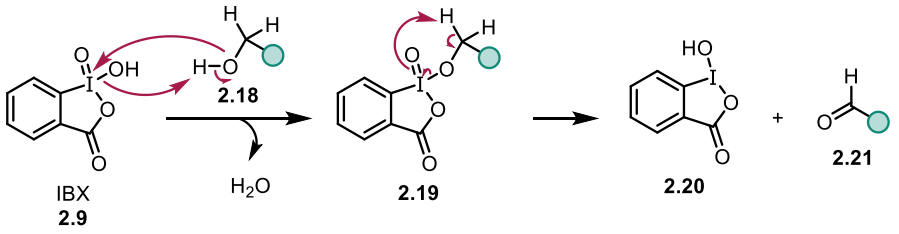
To further understand the unique behavior of iodonium species, a deeper look at halogen bonding and σ-holes is warranted.[106] A σ-hole is usually located on the surface of an atom bearing a σ-bond and is a region of positive electrostatic potential. It can also play a role as a force in crystal packing or in the formation of supramolecular chains as well as association of molecules in the solid phase.[107] Therefore, a suitable nucleophile or solvent molecule can interact on the I-Ar-axis (z-axis). Additionally, the orbitals in the x- and y-axis are fully occupied and can act as a shield, characterized by a negative electrostatic potential. Taking this into account, iodine (III) reagents are usually employed as electrophilic oxidants.

The electrophilicity of λ^3-iodanes can be increased by activation in acidic media (Lewis or Brønsted acids) with activators such as boron trifluoride etherate ($Et_2O{\bullet}BF_3$), trifluoromethanesulfonic acid (TfOH), trimethylsilyl trifluoromethanesulfonate (TMSOTf) or bromotrimethylsilane (TMSBr). By replacing one or two of the ligands with a less basic leaving group, the hypervalent iodine reagent becomes more "activated".[108] Treating PIDA **2.5** with $Et_2O{\bullet}BF_3$ forms a PIDA$\bullet BF_3$ **2.15** complex (Scheme 2.3). Both compounds (PIDA and **2.15**) have been isolated and characterized by X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy. One key characteristic is the reduced bond length between the non-participating acetate ligand ($^-$OAc) and the iodine atom from 2.15 Å to 2.08 Å. Further treatment of **2.15** with TMSOTf (or direct treatment of **2.5**) leads to formation of hypervalent iodine reagent **2.16**, where an acetate ligand is fully replaced by a triflate ($^-$OTf). In this case, **2.16** was fully characterized by NMR spectroscopy and X-ray crystallography. Compound **2.16** showcases a further reduction of the I-OAc bond length to 2.06 Å. This species is now even more reactive.[108] Notably, treating hypervalent iodine reagent **2.16** with $Et_2O{\bullet}BF_3$ does not form back reagent **2.15**. Therefore, the activation axis is unidirectional. The authors highlight in this report that the reaction mechanism and type can also influence the role of the acid additives by influencing other phenomena such as substrate activation, radical caging, catalysis and fluoride transfer. As for the DFT calculated LUMO energies of the four different species shown in Scheme 2.3, a steady drop can be showcased in the expected order: from **2.5** (OAc, -1.90 eV), **2.15** (OAc$\bullet BF_3$, -2.59 eV), **2.16** (OTf, -2.77 eV) and **2.17** (+, -4.19 eV). In this sequence, the most reactive species should theoretically be the most electrophilic one **2.17**, having a formal positive charge on the iodine atom and missing one acetate ligand.



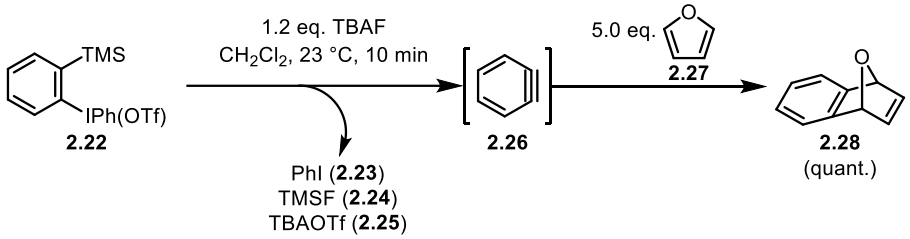
Scheme 2.3: Increasing electrophilic character of hypervalent iodine reagents facilitated by acid activation.

Due to their electrophilic nature, iodine (III) reagents are excellent oxidants. A textbook example is the IBX oxidation of alcohols to aldehydes (Scheme 2.4).[109] In the first step of the reaction mechanism, IBX **2.9** interacts with a primary alcohol **2.18**, forming **2.19** (Scheme 2.4) after ligand exchange (loss of water). The concerted elimination process forms **2.20** and the aldehyde **2.21** through a 5-membered cyclic transition state. The newly generated iodonium species **2.20** can easily be reoxidized to regenerate IBX.



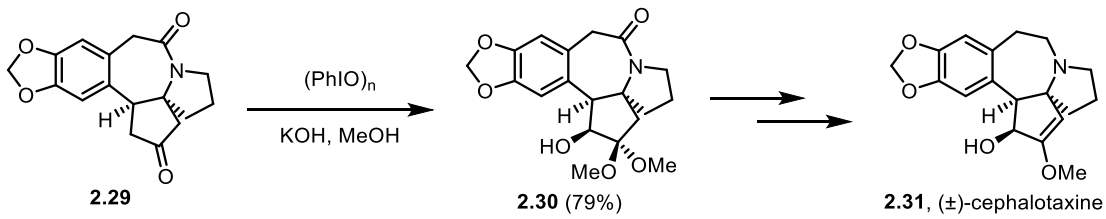
Scheme 2.4: Mechanism of IBX oxidation of primary alcohols to aldehydes.

Hypervalent Iodine reagents can generate arynes from (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate **2.22** under mild conditions by treatment with tetra-*n*-butylammonium fluoride (TBAF) at 23 °C.[110] The driving force for this transformation is the formation of TMSF **2.24**, iodobenzene **2.23** and TBAOTf salt **2.25**. The aryne **2.26** can be easily captured e. g. by excess of furan **2.27** yielding the [4+2]-cycloaddition product **2.28** (Scheme 2.5).



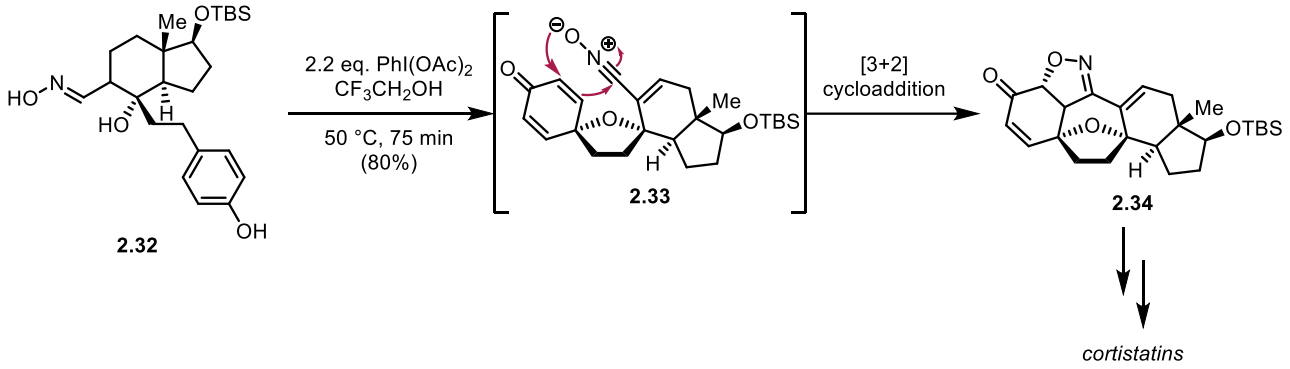
Scheme 2.5: Iodonium reagents as mild precursors for arynes generation.

Iodine (III) reagents have also been successfully applied in total synthesis.[111] For example, in the total synthesis of (±)-cephalotaxine **2.31** (Scheme 2.6), iodosobenzene was successfully employed for the functionalization of the ketone moiety in the key intermediate step **2.30**. In combination with potassium hydroxide (KOH) and methanol (MeOH), iodosobenzene afforded α-hydroxy, dimethyl acetal intermediate **2.30** in a diastereoselective fashion, in part due to the steric congestion inherent in substrate **2.29**.



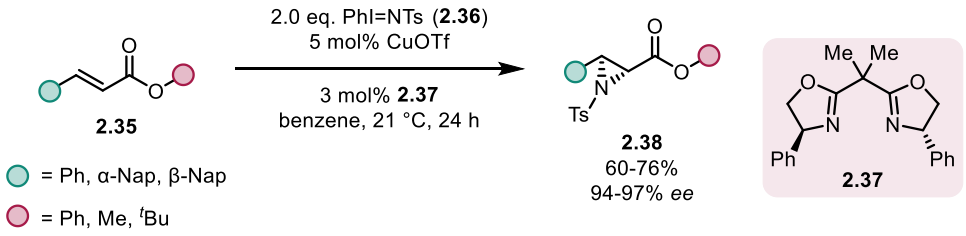
Scheme 2.6: Application of hypervalent iodine reagents in the total synthesis of (±)-cephalotaxine.

The, oxidative dearomatization of phenols with hypervalent iodine reagent is a popular reaction in total synthesis of natural products.[112] Hypervalent iodine reagents can also be used in combination with 1,3-dipolar cycloadditions to form complex scaffolds such as the pentacyclic core structure of the *cortistatins* (Scheme 2.7). Treating aldoxime **2.32** with PIDA in 2,2,2-trifluoroethanol (TFE) led to the simultaneous oxidation of both the oxime to the corresponding nitrile oxide and the phenol to the quinone of **2.33**, positioned to undergo a [3+2]-cycloaddition delivering the hexacyclic intermediate **2.34**, *en route* to the *cortistatins*.



Scheme 2.7: Oxidative dearomatization of phenols with PIDA enables 1,3-dipolar cycloadditions to access key intermediate **2.34** toward the total synthesis of cortistatins.

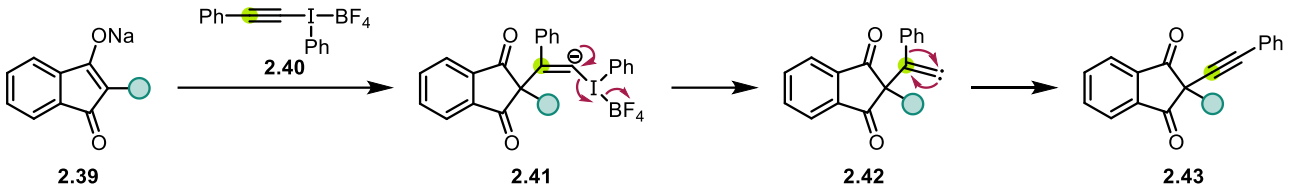
Hypervalent iodine reagents bearing nitrogen were successfully employed in nitrogen insertion transformations.[113] [114] Evans and co-workers reported the use of [*N*--(*p*-Toluenesulfonyl)imino]phenyliodinane (PhI=NTs **2.36**) in the enantioselective conversion of α,β-unsaturated esters (**2.35**) to aziridines **2.38** under Cu catalysis. Aziridines **2.38** were afforded in good yields and excellent enantioselectivities (Scheme 2.8). However, a limitation of this method is underlined by the lack of functional group tolerance.



Scheme 2.8: Enantioselective aziridination of α,β-unsaturated esters with PhI=NTs **2.36** under Cu catalysis.

As previously mentioned, hypervalent iodine reagents are not limited to oxidation protocols, and have also found applications as alkynylating agents. In a study using ^{13}C-labeled phenylethynyl-λ^3-iodane **2.40** (green highlighted in scheme 2.9), annulation of cyclopentenes showed an unexpected phenyl shift.[115] In the first step of the reaction mechanism, deprotonated indene **2.39** is reacted with phenylethynyl-λ^3-iodane **2.40**. The electrophilic λ^3-iodane **2.40** is attacked by the nucleophile **2.39** on the ^{13}C-labeled position to form vinyl

carbanion **2.41**. Finally, extrusion of iodobenzene (PhI) and tetrafluoroborate (BF_4^-), followed up by the phenyl shift of **2.42**, leads to annulation product **2.43**.

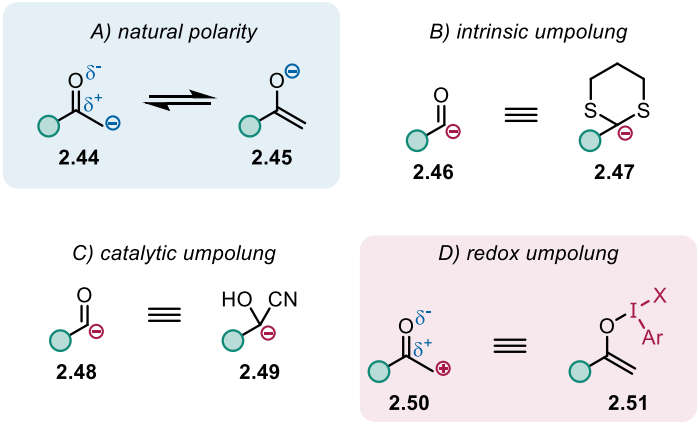


Scheme 2.9: ^{13}C-labeled studies of alkynylation with alkynyl(aryl) iodonium salts.

2.1.2 Umpolung with Hypervalent Iodine Reagents

In the following section, the ability of iodine (III) reagents to promote umpolung reactions with emphasis on the α-carbon position of carbonyl compounds will be discussed.[116]

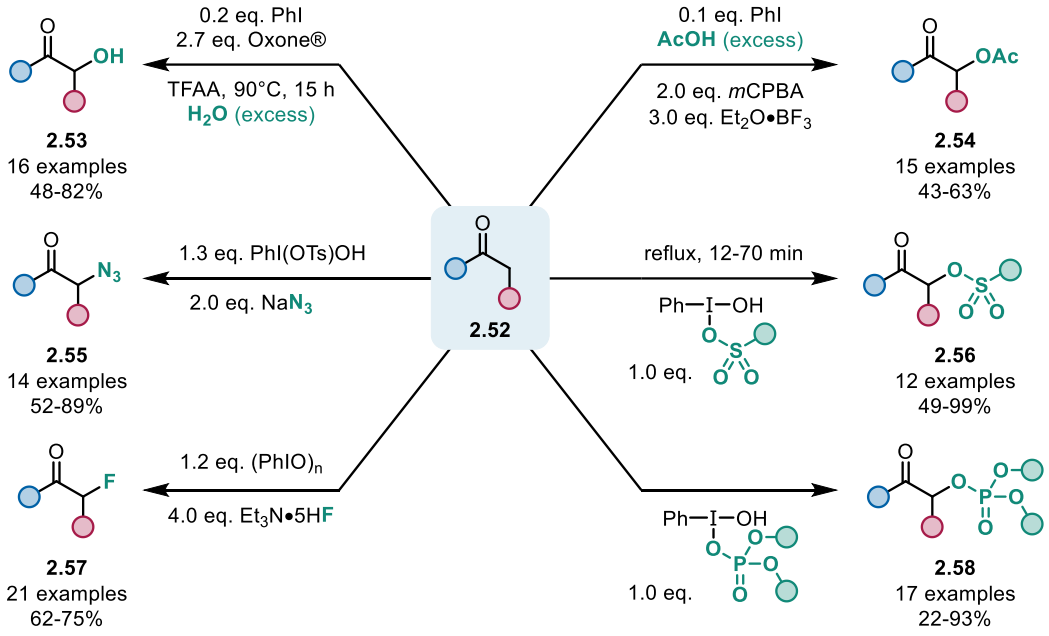
The term "umpolung" or polarity inversion (*from German Umpolung*) was popularized by D. Seebach and E. J. Corey and refers to the transformation of a functional group by reversing the polarity of said group.[117] The natural polarity of a carbonyl bond is textbook material and can be represented by a partial positive charge on the carbon atom of the carbonyl group and a partial negative charge on the oxygen atom. This representation dictates reactivity towards nucleophiles and electrophiles respectively. If the system is extended, it comes as no surprise that the α-position of the carbonyl bond would possess a partial negative charge. If a ketone is converted to a silyl enol ether, the corresponding synthon **2.44** elegantly showcases the α-positioned negative charge and its reactivity towards electrophiles (Scheme 2.10A).[97] A facile way to convert the partial positive charge of the carbonyl-carbon of **2.46** to a formal negative one has been reported by Corey and Seebach using 1,3-dithianes and sequentially deprotonating them (Scheme 2.10B).[118] Catalytic umpolung is also feasible when using cyanide ions generating **2.48** (Scheme 2.10C).[119] Hypervalent iodine reagents can perform a so-called redox umpolung. It is presumed that it involves an enolonium species **2.50** that can increase the electrophilic character of the α-position and enables it to react with a variety of nucleophiles (Scheme 2.10D).[120] In the following part of this thesis, we will focus on the latter type of umpolung.



Scheme 2.10: Types of Umpolung reactivity: A) Natural polarity of carbonyls. B) inversion of polarity through dithiane chemistry. C) Umpolung-reactivity through catalysis. D) Redox umpolung by an external reagent.

Ketones are often chosen as substrates for hypervalent iodine-mediated umpolung reactions. Scheme 2.11 depicts several key examples of α-functionalization of ketones (**2.52**). Firstly, there are well-established protocols for α-hydroxylation (**2.53**),[121] and acetoxylation (**2.54**).[122] Azidations using [hydroxy (*p*-nitrobenzenesulfonyloxy]iodo]benzene (HNIB) and sodium azide (NaN_3) to deliver α-azido ketones (**2.55**) have also been reported.[123] Additionally, α-mesylated and α-tosylated derivatives (**2.56**) can

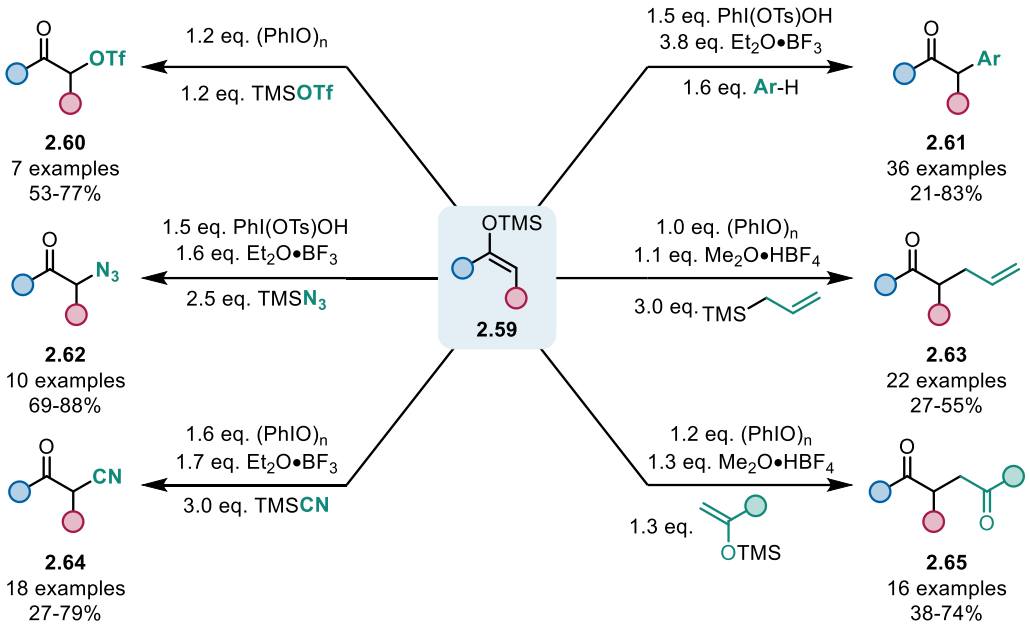
also be synthesized.[124] [125] Kitamura has reported fluorination of the α-position to directly form α-fluoro derivatives (**2.57**) in good yields.[126] Finally, an α-oxyphosphorylation protocol can deliver a variety of functionalized ketones and esters (**2.58**).[127]



Scheme 2.11: Overview of α-functionalization of ketones using iodine (III) reagents.

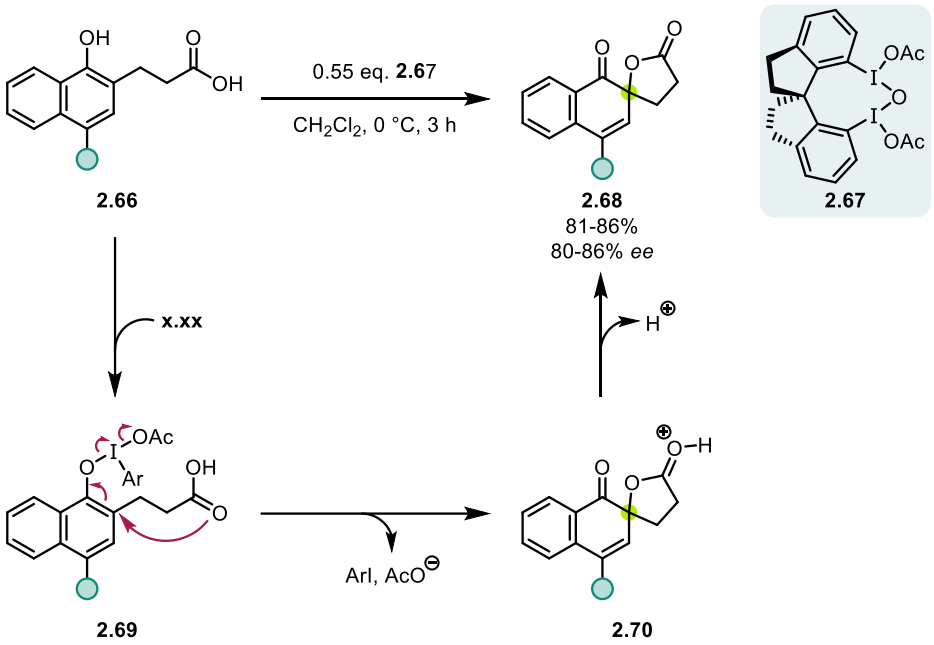
In most cases, when ketone substrates are used, an adjuvant reagent to catalyze the keto-enol tautomerization is required. Given that the enol form is most likely the main reaction partner for hypervalent iodine-mediated processes it comes as no surprise that silyl enol ethers have shown to be remarkable substrates in similar transformations. The increased α-nucleophilic character of silyl enol ethers when compared to ketones plays a crucial role.[128]

Similarly to ketones (Scheme 2.12), silyl enol ethers (**2.59**) can undergo α-functionalization reactions where α-trifloxy ketones (**2.60**) can be synthesized and even isolated.[129] More recently, α-arylation (**2.61**) with mainly electron-rich arenes has led to an increase in transition-metal free procedures.[130] Employing trimethylsilyl azide ($TMSN_3$) under similar reaction conditions, azidation products (**2.62**) were obtained.[131] More interestingly, carbon-based nucleophiles such as allyl silanes are excellent coupling partners, generating after TMS-cleavage allylic-decorated products **2.63**.[132] Additionally, boron trifluoride etherate ($Et_2O•BF_3$) activated iodosobenzene ($[PhIO]_n$) can facilitate cyanation yielding β-ketonitriles (**2.64**).[133] One common undesired side-reaction of the generated electrophilic enol species is attack by unreacted or relative excess amounts of silyl enol ethers (homo coupling). However, over the past decades, this disadvantage has been elegantly used and reports of transition metal-free intermolecular cross-coupling reactions of silyl enol ethers have been cemented for the synthesis of 1,4-dicarbonyl compounds (**2.65**, Scheme 2.12).[134]



Scheme 2.12: Overview of cross-nucleophile coupling of silyl enol ethers with hypervalent iodine reagents and a variety of nucleophiles.

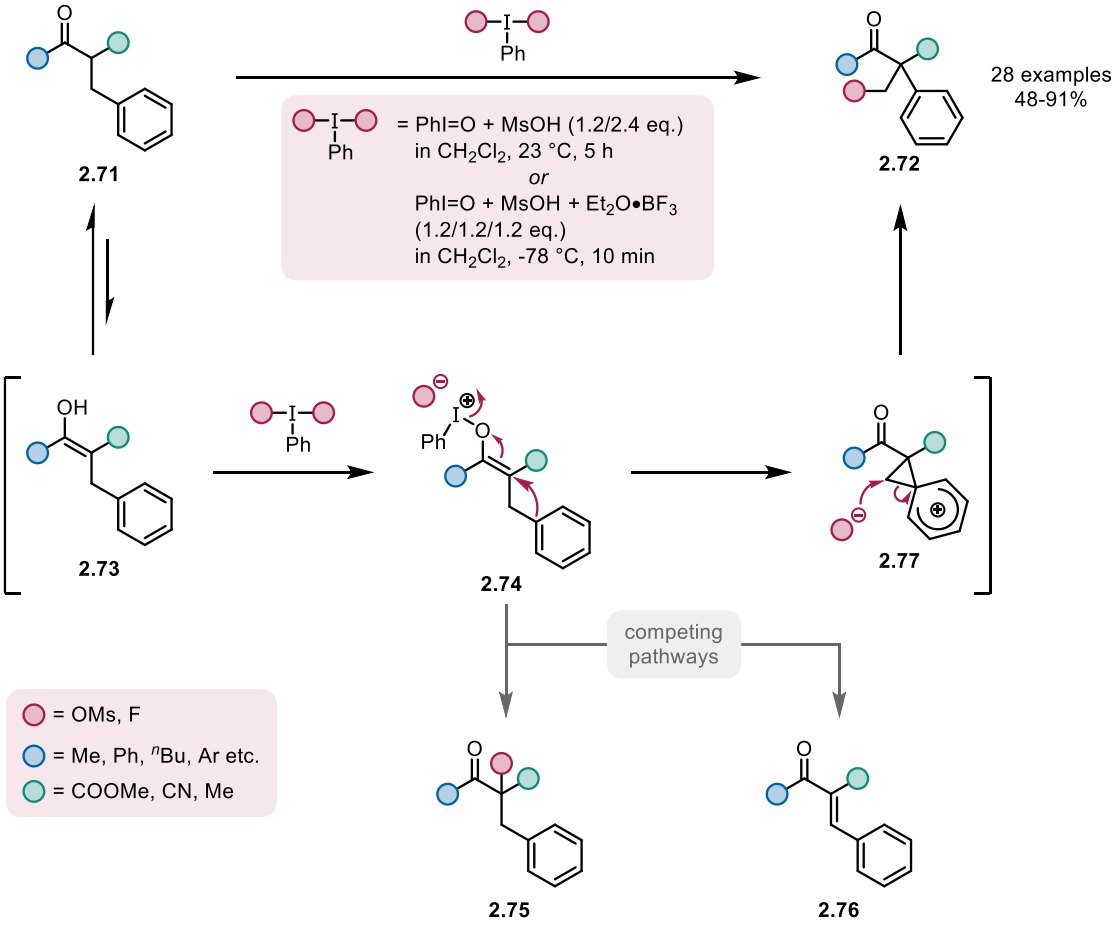
Recently, chiral iodine (III) reagents have been more explored.[135] In a study by Kita *et al.*, chiral 1,1'-spirobiindane iodine(III) reagent **2.67** was successfully employed in the enantioselective dearomatization of phenols **2.66** (Scheme 2.13). The first step involves a ligand transfer between the C_2-symmetric reagent **2.67** and the phenolate of **2.66**. The presumably formed phenoxy-λ^3-iodane species **2.69** can now extrude the reduced iodine reagent and one acetate ligand, generating an intermediate **2.70**. *Spiro*-products **2.68** are formed in high yields (81-86%) and elevated enantiomeric excesses (80-86% *ee*) after proton elimination.



Scheme 2.13: Enantioselective dearomatization of phenols **2.66** to form spiro lactones **2.68** with chiral iodine (III) reagent **2.67**.

2.1.3 State of the Art Hypervalent Iodine (III)-Mediated Functionalization Reactions

Recently, the structure and use of hypervalent iodine reagents and their applications in cross-nucleophile coupling reactions have been explored by our group.[128] [136] The α-arylation of carbonyl compounds through oxidative C–C bond activation, relying on an unusual 1,2-aryl shift mechanism was disclosed in 2019 (Scheme 2.14).[137] In this particular instance, an α-disubstituted ketone or 1,3-dicarbonyl compound (**2.71**) is treated with an *in situ* activated hypervalent iodine reagent. The reagent is formed by treating iodosobenzene ($[PhIO]_n$) with excess methanesulfonic acid (MsOH) or a methanesulfonic acid/boron trifluoride etherate ($MsOH/Et_2O•BF_3$) mixture. The ketone substrate (**2.71**) is in equilibrium with the key enol form **2.73**. Nucleophilic attack and ligand exchange with the generated hypervalent iodine reagent forms intermediate **2.74**.

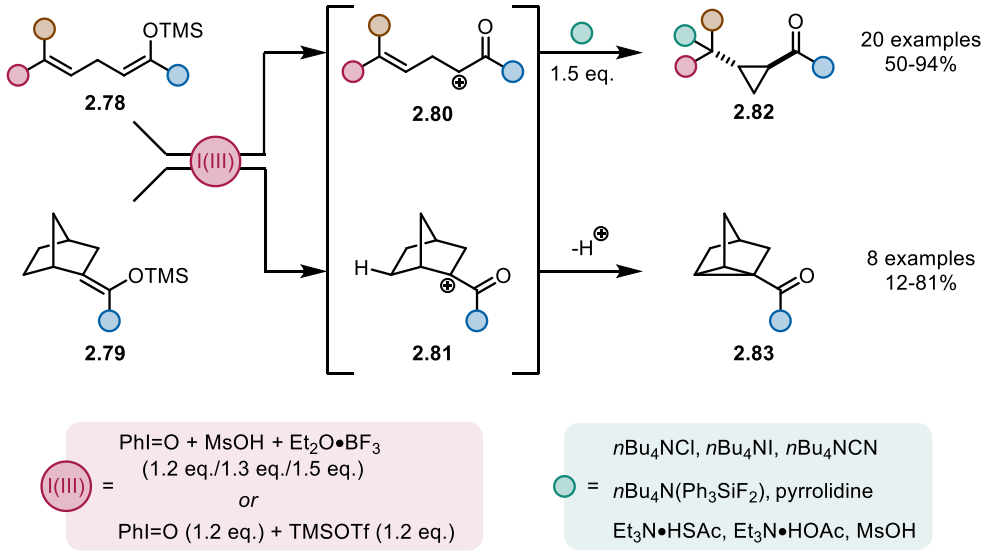


Scheme 2.14: α-Arylation of ketones **2.71** with hypervalent iodine through oxidative C-C bond activation and 1,2 aryl-shift.

The key intermediate **2.74** is faced with three competing and irreversible pathways. Two of the undesired routes are direct nucleophilic attack in an intermolecular fashion to form a tertiary substituted product **2.75** or elimination towards the α,β-enone **2.76**. Pleasingly, the proximity of the phenyl group enables a faster intramolecular process extruding iodobenzene and forming a three-membered ring-bearing Wheland intermediate **2.77** in a concerted fashion.[138] [139] The newly formed arenium ion **2.77** can be opened by the

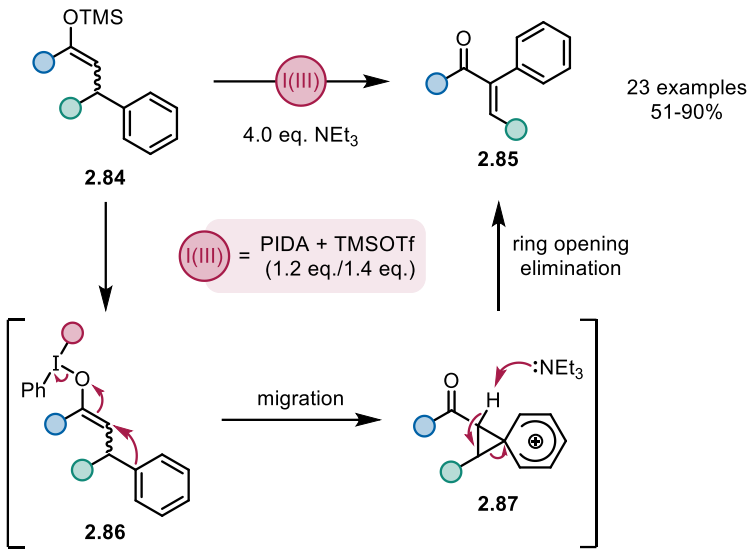
released mesylate nucleophile/ligand and the resulting 1,2-aryl shifted product **2.72** is obtained in moderate to high yields.

In a follow-up study, allylic silyl enol ethers (**2.78**) and norbornane-bearing silyl enol ethers **2.79** were subjected to iodine (III) reagents and underwent α-cyclopropanation (Scheme 2.15).[117] The proposed oxidative umpolung proceeds through a non-classical cyclopropylcarbinyl cation leading to formation of a single diastereomer of *trans*-cyclopropane **2.82** after nucleophilic capture. A plethora of nucleophiles such as tetrabutylammonium chloride/iodie/cyanide/difluorotriphenylsilicate, pyrrolidine, triethylammonium thioacetate and triethylammonium acetate (nBu$_4$NCl, nBu$_4$NI, nBu$_4$NCN, nBu$_4$N(Ph$_3$SiF$_2$), Et$_3$N•HSAc and Et$_3$N•HOAc) can be employed in this transformation. Additionally, when norbornane-type silyl enol ethers were employed, the non-classical 2-norbornyl cation (**2.81**) is formed and after rapid proton elimination nortricyclane **2.83** was obtained as the major product. In this case the external nucleophile acts presumably as a base and does not intercept the non-classical carbocation. Interestingly, no α,β-unsaturated products were detected.



Scheme 2.15: α-Cyclopropanation of carbonyl derivatives by oxidative umpolung with hypervalent iodine reagents.

Additionally, the skeletal rearrangement of aryl-containing silyl enol ethers **2.84**, lacking however a second substituent in the α-position, was disclosed (Scheme 2.16).[140] When silyl enol ether **2.84** was treated with an activated iodine (III) reagent (PIDA + TMSOTf), enolonium species **2.86** was generated. Similar to previous reports, the arene can now attack the highly electrophilic position and extrude iodobenzene in a concerted fashion. The newly formed Wheland intermediate **2.87** has now a highly acidic proton in the α-position, that can be easily deprotonated by addition of an external base, in this case triethylamine (NEt$_3$), yielding after ring opening and elimination, a formal α-arylated enone **2.85**.



Scheme 2.16: Formal enone α-arylation via I(III)-mediated aryl migration/elimination.

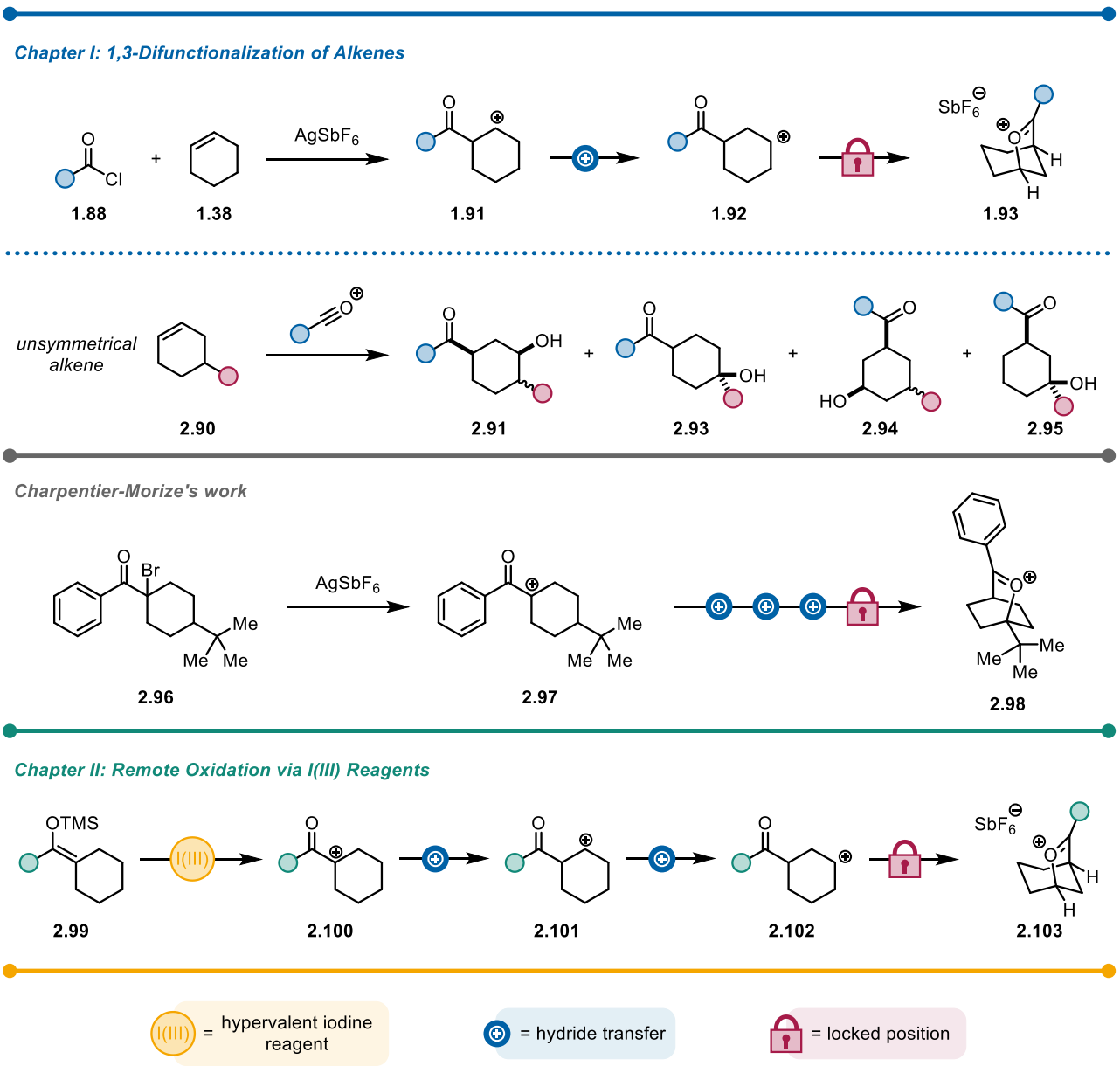
2.2 Aim of the Project

The efforts discussed in the first chapter of this thesis have shown how to generate oxocarbenium ions **1.93** through *charge relocation* (Scheme 2.17, blue section).[1] However, employing unsymmetrical alkenes resulted in an inseparable product mixture **2.91**-**2.95**, due to the unspecific attack of alkene **2.90** on an acylium ion(Scheme 2.17). Therefore, we became interested in investigating an intramolecular alternative, circumventing such limitations.

An alternative to generating α-carbocations is bromide abstraction. While exploring the literature, we came across the pioneering work of Charpentier-Morize, where starting from α-bromoketones **2.96** a bromide abstraction forms the α-carbocation **2.97** (Scheme 2.17, grey section).[141] [142] [143] [144] Stepwise hydride transfers going through the β-, γ- and terminating in the δ-position was reported to form a tertiary carbocation that can be trapped by the ketone to form a 6-membered oxocarbenium ion **2.98**. Additionally, the final carbocation required further stabilization by being a tertiary one.

Given our group's endeavors into generation of highly reactive intermediates starting from silyl enol ethers and using hypervalent iodine reagents, we wondered if we could harness such reactivity to form cyclic oxocarbenium ions **2.103** (Scheme 2.17, green section). We proposed that treating a silyl enol ether **2.99** with an appropriate cationic iodonium reagent could give the α-keto-carbocation **2.100**, which after two hydride shift steps (**2.101**-**2.102**) would lead to the most stable oxocarbenium ion **2.103**. The first essential step would be identifying suitable hypervalent iodine reagents that bear non-nucleophilic and non-basic ligands, to allow formation and manipulation of the desired oxocarbenium ion **2.103**.

The work described was conducted in collaboration with Dr. Nicolas G.-Simonian, Dr. Daniel Kaiser, Ricardo Meyrelles, MSc and Maria Zazirna, BSc. Parts of the results have been submitted to Angewandte Chemie.



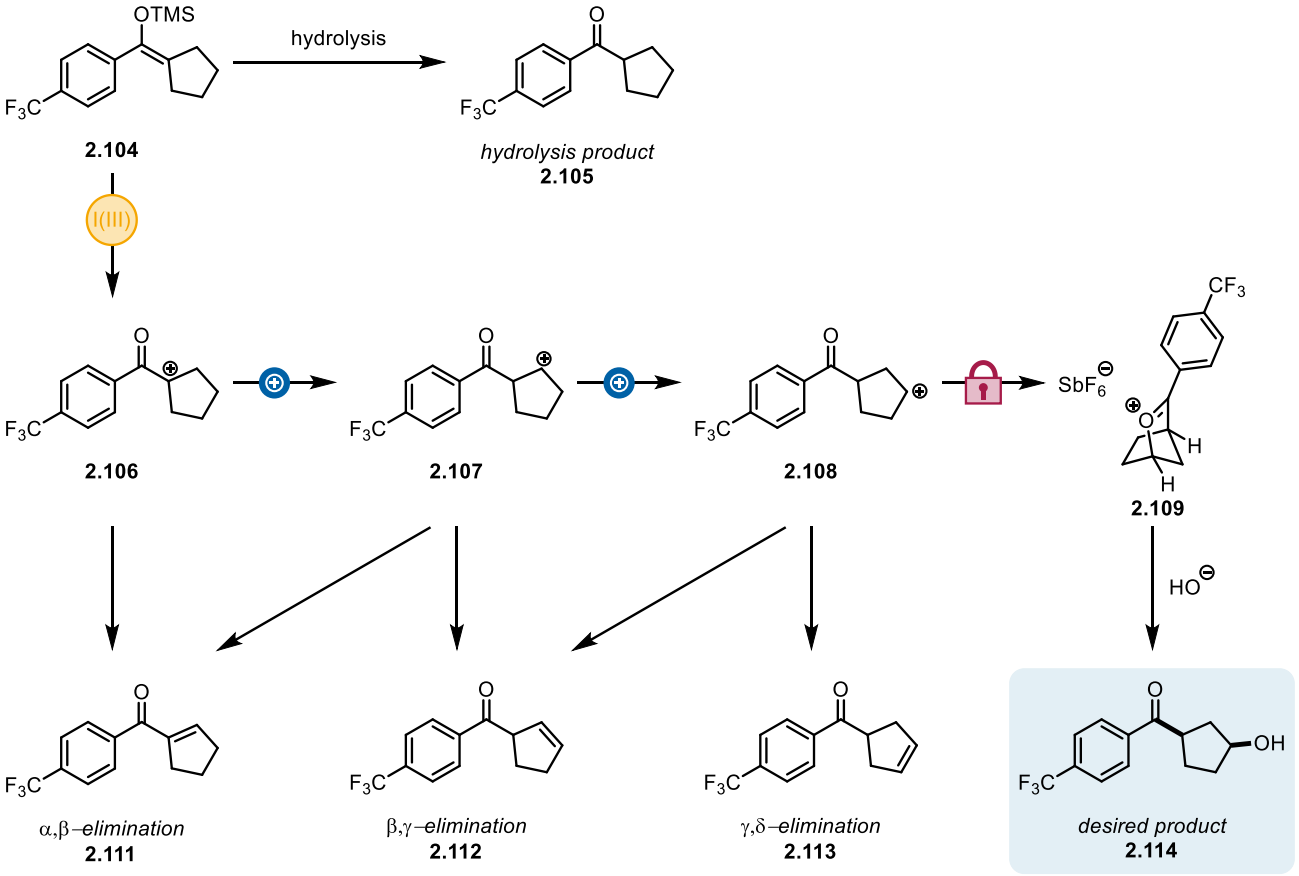
Scheme 2.17: Chapter I – 1,3-difunctionalization of alkenes through charge relocation: unsymmetrical alkenes lead to inseparable product mixtures. Chapter II – Remote oxidation of silyl enol ethers with hypervalent iodine reagents: selectivity issues can be overcome by transitioning from an intermolecular process to an intramolecular one.

2.3 Results and Discussion

2.3.1 Optimization Studies

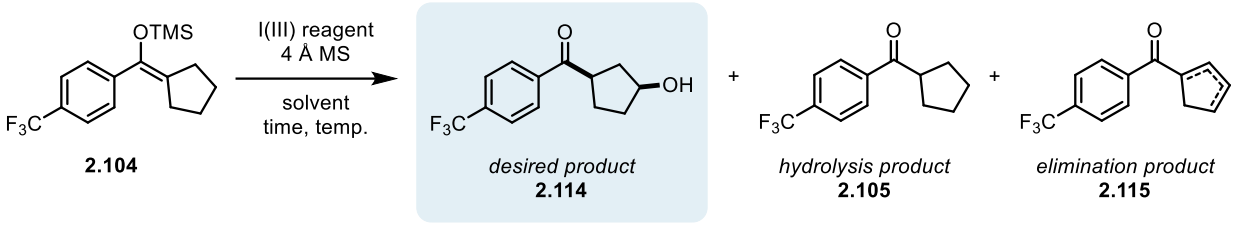
At the onset of this project, we wanted to explore the generation of α-keto-carbocations from silyl enol ethers using hypervalent iodine reagents. We chose **2.104** as a model substrate (Scheme 2.18) equipped with the electron withdrawing group *p*-CF_3. The substituents can influence the ketone intermediates (**2.106**-**2.108**), by reducing basicity and destabilizing the positive charge in the α-position of **2.106**. Important to mention, 4 side products could be obtained from this reaction. A general hydrolysis product **2.105** (could also result at the end of the reaction from the unreacted starting material) and 3 different elimination products (**2.111**-**2.113**) which we will refer to in a combined yield, as separation of these products was generally not possible (Table **2.1**). While the desired product **2.11** would be obtained after hydrolysis of the oxocarbenium intermediate **2.109**, the possible carbocationic intermediates **2.106**-**2.108**, formed during the reaction, can lead to several elimination products **2.111**-**2.113**, as shown below.

In our preliminary studies, we determined that water could interfere with our reaction mixture and lead to significant amount of hydrolysis product **2.105**. Therefore, we used 4 Å molecular sieves as additives throughout the optimization process.



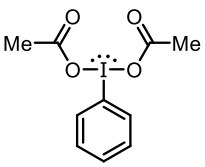
Scheme 2.18: Overview of possible oxidation products by treating silyl enol ether **2.104** with hypervalent iodine reagents.

Table 2.1: Optimization of reaction conditions for the remote oxidation of silyl enol ethers.

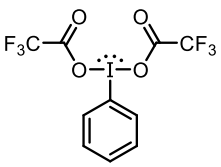


Entry	I(III) reagent	Eq.	Time	Temp.	Solvent	Yield 2.115	Yield 2.105	Yield 2.114
1	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	PhMe	11%[a]	63%[b]	7%[b]
2	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	$PhCF_3$	7%[a]	27%[b]	27%[b]
3	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	$MeNO_2$	2%[a]	31%[b]	25%[b]
4	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	EtOAc	32%[a]	<5%[b]	<5%[b]
5	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	$CHCl_3$	<5%[a]	19%[b]	40%[b]
6	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	CH_2Cl_2	<5%[a]	19%[b]	45%[b]
7	PIDA/Me_3SiOTf	1.2/1.4	60 min	-78 °C	CH_2Cl_2	48%[c]	n.d.	n.d.
8	PIFA/Me_3SiOTf	1.2/1.4	60 min	-78 °C	CH_2Cl_2	35%[c]	10%[b]	n.d.
9	$PhI(^tBuCOO)_2$/ Me_3SiOTf	1.2/1.4	60 min	-78 °C	CH_2Cl_2	75%[c]	n.d.	n.d.
10	$[PhIO]_n/Tf_2O$	2.4/2.2	60 min	-15 °C	CH_2Cl_2	40%[c]	25%[b]	n.d.
11	$(PhI)_2O(BF_4)_2$	1.0	60 min	-15 °C	CH_2Cl_2	complex mixture	11%[b]	5%[b]
12	$(PhI)_2O(ClO_4)_2$	1.0	60 min	-15 °C	CH_2Cl_2	15%[c]	38%[b]	n.d.
13	$(^tBuPhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	CH_2Cl_2	28%[c]	56%[b]	n.d.
14	$(PhI)_2O(SbF_6)_2$	1.0	60 min	-15 °C	CH_2Cl_2	6%[c]	23%[b]	53%[b]
15	**$(PhI)_2O(SbF_6)_2$**	**1.0**	**10 min**	**-15 °C**	**CH_2Cl_2**	**9%[c]**	**29%[b]**	**79%[b] (74%)[d]**

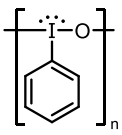
[a]combined NMR yield of elimination products **2.115** (mixture of **2.111**-**2.113**), [b]NMR yield, [c]NMR yield of **2.111** (using mesitylene as internal standard), [d]isolated yield, n.d. – not detected



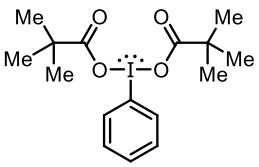
PIDA
2.5



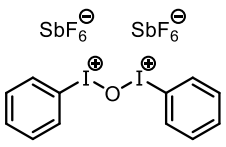
PIFA
2.6



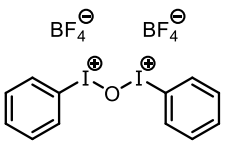
$[PhIO]_n$
2.10



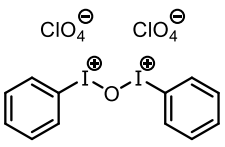
PIDP
2.7



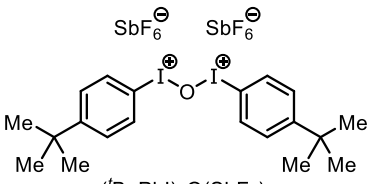
$(PhI)_2O(SbF_6)_2$
2.116



$(PhI)_2O(BF_4)_2$
2.117



$(PhI)_2O(ClO_4)_2$
2.118

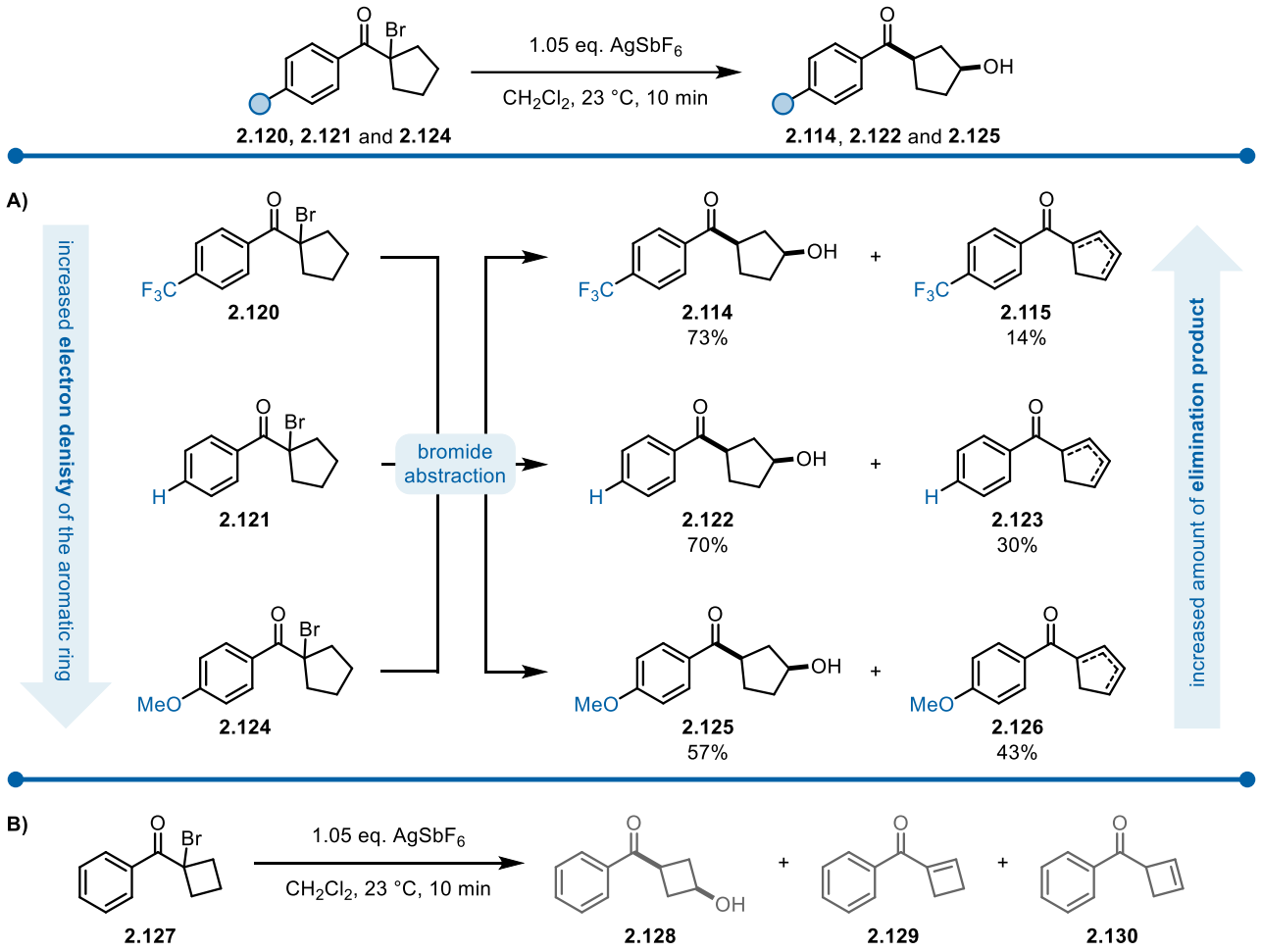


$(^tBuPhI)_2O(SbF_6)_2$
2.119

Our optimization attempts revealed oxybis(phenyliodonium) bis(hexafluoroantimonate) **2.116** ($(PhI)_2O(SbF_6)_2$) as an ideally suitable oxidizing agent. The presence of non-nucleophilic, non-basic ligands/counteranions would be an ideal match for our proposed carbocationic reaction pathway, thus hindering formation of undesired elimination products **2.115**. We investigated several solvents. While solvents such as toluene (PhMe, Entry 1) led to hydrolyzed product **2.105** in 63% yield (regenerating the original ketone), only 7% of the desired oxidized product **2.114** could be detected. *α*,*α*,*α*-Trifluorotoluene ($PhCF_3$, Entry 2), nitromethane ($MeNO_2$, Entry 3) and ethyl acetate (EtOAc, Entry 4) proved too basic and led to significant amounts of elimination products. Pleasingly, halogenated solvents such as chloroform ($CHCl_3$, Entry 6) and dichloromethane (CH_2Cl_2, Entry 7) were best suited for such a transformation, leading to **2.115** as the major product (40-45% yield) with an overall selectivity in the range of 63-65%. Next, we investigated a plethora of commercial and synthesized hypervalent iodine reagents; however, in most cases (Entries 8-14), $(PhI)_2O(SbF_6)_2$ proved to be most suitable. Finally, reducing reaction time to 10 minutes from 1 h had a positive effect on the outcome of this transformation, yielding up to 79% NMR yield of **2.114** (74% isolated yield) with only 9% elimination products and the rest of the material being converted back to the original ketone.

2.3.2 Bromide Abstraction Studies

Throughout this project, α-bromo ketones were synthesized in order to probe reactivity limits of previous reports by Charpentier-Morize,[142] [143] [144] and improve our understanding of the reactive intermediates formed during the reaction.



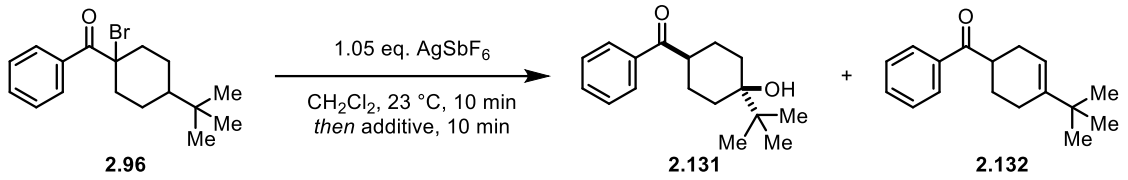
Scheme 2.19: A) Effect of electron withdrawing and electron donating substituents on bromide abstraction. B) Application of this method on a more challenging cyclobutane substrate.

When α-bromo-ketones **2.120**, **2.121** and **2.124** bearing electron withdrawing, neutral and electron donating groups (*p*-CF_3, *p*-H and *p*-OMe), were treated with silver hexafluoroantimonate ($AgSbF_6$), a trend was observed (Scheme 2.19A). Firstly, regardless of electronics, 1,3-ketoalcohols **2.114**, **2.122** and **2.125** were obtained together with elimination products **2.115**, **2.123** and **2.126** and in all cases, full conversion was observed. Secondly, increasing the electron density on the aromatic ring resulted in lower yields of desired keto-alcohols (73%→70%→57%). While the drop from an electron withdrawing group to a neutral substituent is only 3%, changing to an electron donating group had a significant effect on the outcome of this process (23%). Thirdly, this decrease in yield was complemented by an increase in elimination products **2.115**, **2.123** and **2.126** (14%→30%→43%). These findings are supported by our previous endeavors in Chapter 1. However,

in this case the initial carbocation is formed in the α-position, whereas in the case of 1,3-alkene functionalization, it was always generated in the β-position. This additional required hydride transfer step could pose a challenge and a source of additional elimination products. The increased instability due to proximity to the ketone may facilitate a faster [1,2]-hydride transfer process. This could be one of the reasons why ketones bearing electron withdrawing groups such as **2.120** seem to lead to higher amounts of desired ketoalcohol **2.114**. Finally, the basicity of the ketone is known to play a role in the elimination process, being partially responsible for products **2.115**, **2.123** and **2.126**. Therefore, an increase in yield can also be attributed to the reduced basicity of ketone **2.120**, by reducing the electron density thanks to the *p*-CF_3 group. We also investigated a more challenging, cyclobutane-bearing, substrate **2.127** (Scheme 2.19B). However, we did not observe any keto-alcohol **2.128** and only reduced amounts of elimination products **2.129** and **2.130** accompanied by unspecific decomposition products.

2.3.3 Investigation of Oxocarbenium Ions in the Presence of Additives

Having studied, in section 2.3.2, the effect of substituents on the aromatic ring on carbocation formation and oxocarbenium ion generation, we wanted to investigate further the effect of additives. In order to simplify the system, we propose several experiments where we treat α-bromo ketone **2.96** with $AgSbF_6$, then add an additive and after quench observe the ratio between oxidation product **2.131** and undesired elimination **2.132** (Scheme 2.20). Our aim was to evaluate if oxocarbenium ion can survive classical hypervalent iodine reaction conditions. As displayed in the introduction of this chapter, PIDA (**2.10**) can be converted to its more electrophilic counterpart **2.16** by displacing one acetate (OAc) ligand with a triflate (OTf), using TMSOTf (Scheme 2.3). Therefore, we chose TMSOTf as our first additive to be investigated. Secondly, since iodosobenzene **2.10** is a common side-product of such transformations, we decided to also investigate its effect on oxocarbenium ion **2.98**.



Scheme 2.20: Generation of oxocarbenium ions from α-bromo ketone and influence of additives on product formation.

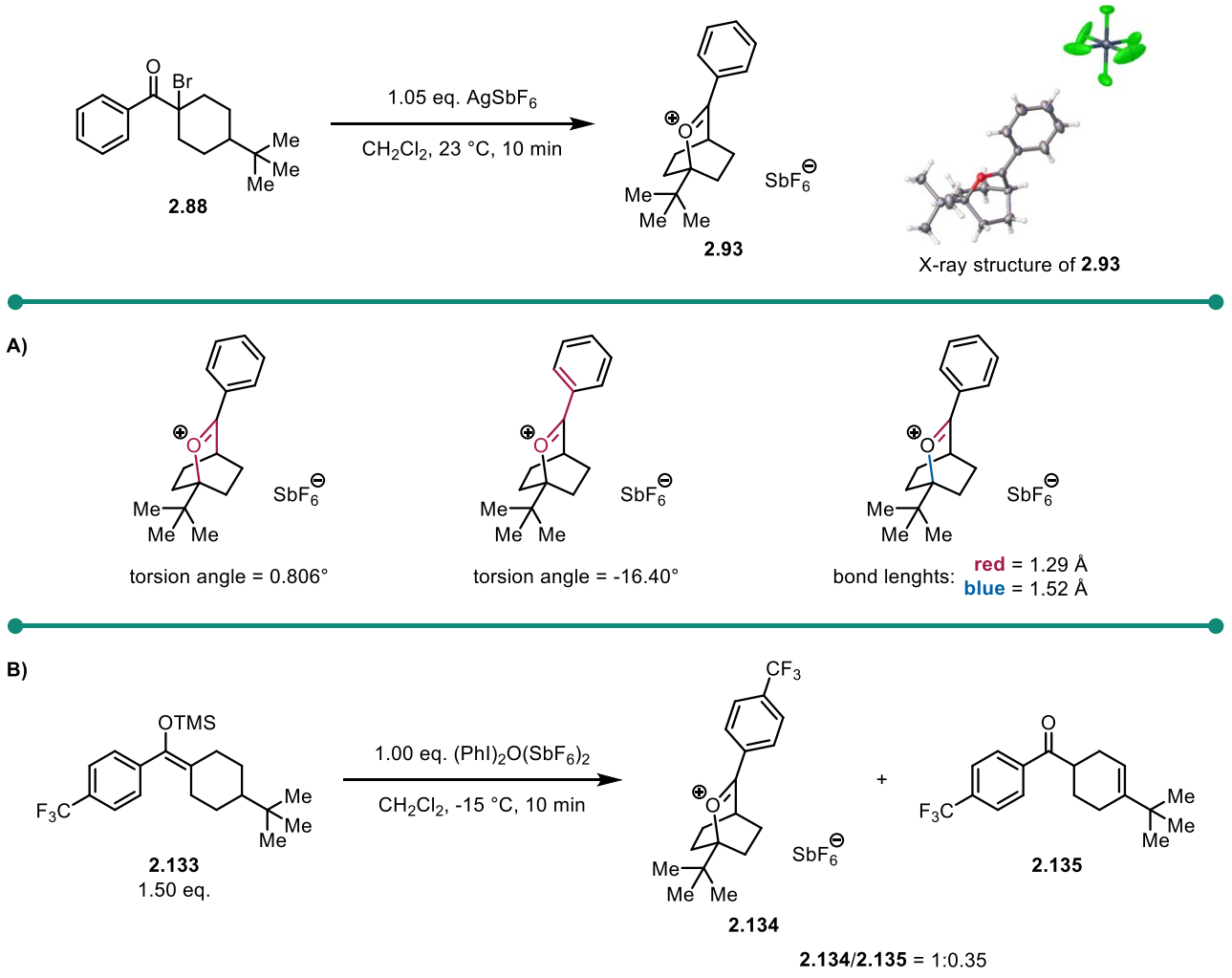
As shown in Table **2.2**, both iodosobenzene **2.10** and TMSOTf were responsible for a reduction in yield of ketoalcohol **2.131** and a significant increase in elimination product **2.132**. Iodosobenzene **2.10** had a greater influence, resulting in an almost 1:1 ratio of **2.131** and **2.132**, slightly favoring the undesired elimination product. TMSOTf led to a 2:1 ratio of **2.131** and **2.132**. Therefore, we moved away early on in our studies from Lewis Acid activated iodonium species, while also being aware that any iodosobenzene **2.10** generated throughout the reaction, can have a negative effect on the outcome of this process

Entry	Additive	Yield of 2.131	Yield of 2.132
1	-	75%	10%
2	PhIO **2.10**	35%	37%
3	TMSOTf	50%	25%

Table 2.2: Effect of additives on product ratio.

2.3.4 X-Ray Crystallographic Investigation of Oxocarbenium Ion 2.93

With the experience gained from generating and handling oxocarbenium ions, we attempted to isolate and fully characterize such species. While there have been ^{1}H-NMR and ^{13}C-NMR reports of oxocarbenium species,[142] [143][144] we aimed to obtain an X-ray crystal structure of oxocarbenium ions. Pleasingly, we were able, after significant efforts, to convert bromide **2.88** to oxocarbenium ion **2.93** and obtain an X-ray crystal structure (Scheme 2.21). Interestingly, oxocarbenium ion **2.93** does not seem to be fully symmetrical and the phenyl substituent is slightly tilted (**2.93**, torsion angle = -16.40°) and therefore not in conjugation with the drawn C=O double bond (Scheme 2.21A). Additionally, when looking at the distance between the oxygen atom and the two carbon atoms connected to it, they are deviated from the typical lengths. The carbon-oxygen double bond (C=O, red) of the oxocarbenium ion **2.93** is shown to be stretched to 1.29 Å instead of 1.24 Å.[145] As for the carbon-oxygen single bond (C–O, blue) a distance of 1.52 Å was measured, a length above the average range of 1.38–1.42 Å.[145]



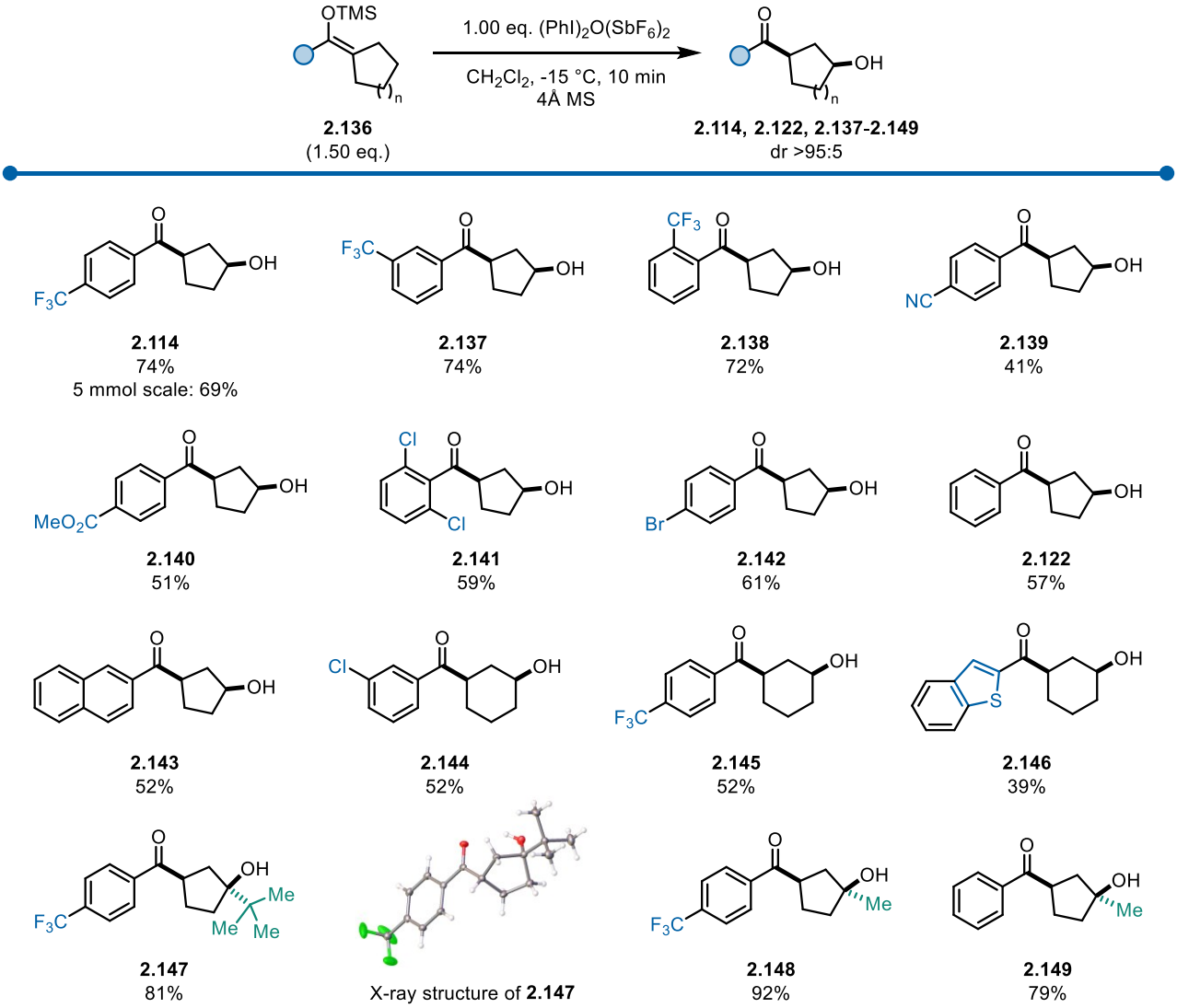
Scheme 2.21: A) Synthesis and X-ray structure of oxocarbenium ion **2.93**. B) Oxocarbenium ion **2.93** obtained as a mixture with inseparable elimination product **2.135**.

Isolation of such an intermediate from the hypervalent iodine protocol outlined in this chapter has so far proven more challenging (Scheme 2.21B). NMR analysis of **2.93** has shown it to be accompanied by significant amounts of inseparable elimination product **2.135**.

2.3.5 Reaction of Silyl Enol Ethers with Hypervalent Iodine Reagents

With optimized conditions in hand we set out to explore the scope and limitations of this procedure to funnel remote hydroxylation.

Firstly, we will take a look at cyclopentylidene- and cyclohexylidene-containing silyl enol ethers **2.136** (Scheme 2.22). A plethora of 1,3-difuntionalized ketoalcohols (**2.114**, **2.122**, **2.137**-**2.149**) were obtained in good yields. In most cases, full conversion was achieved and the remaining material was isolated as the hydrolyzed ketone as previously described in section 2.3.1 along low amounts of elimination products (not shown).

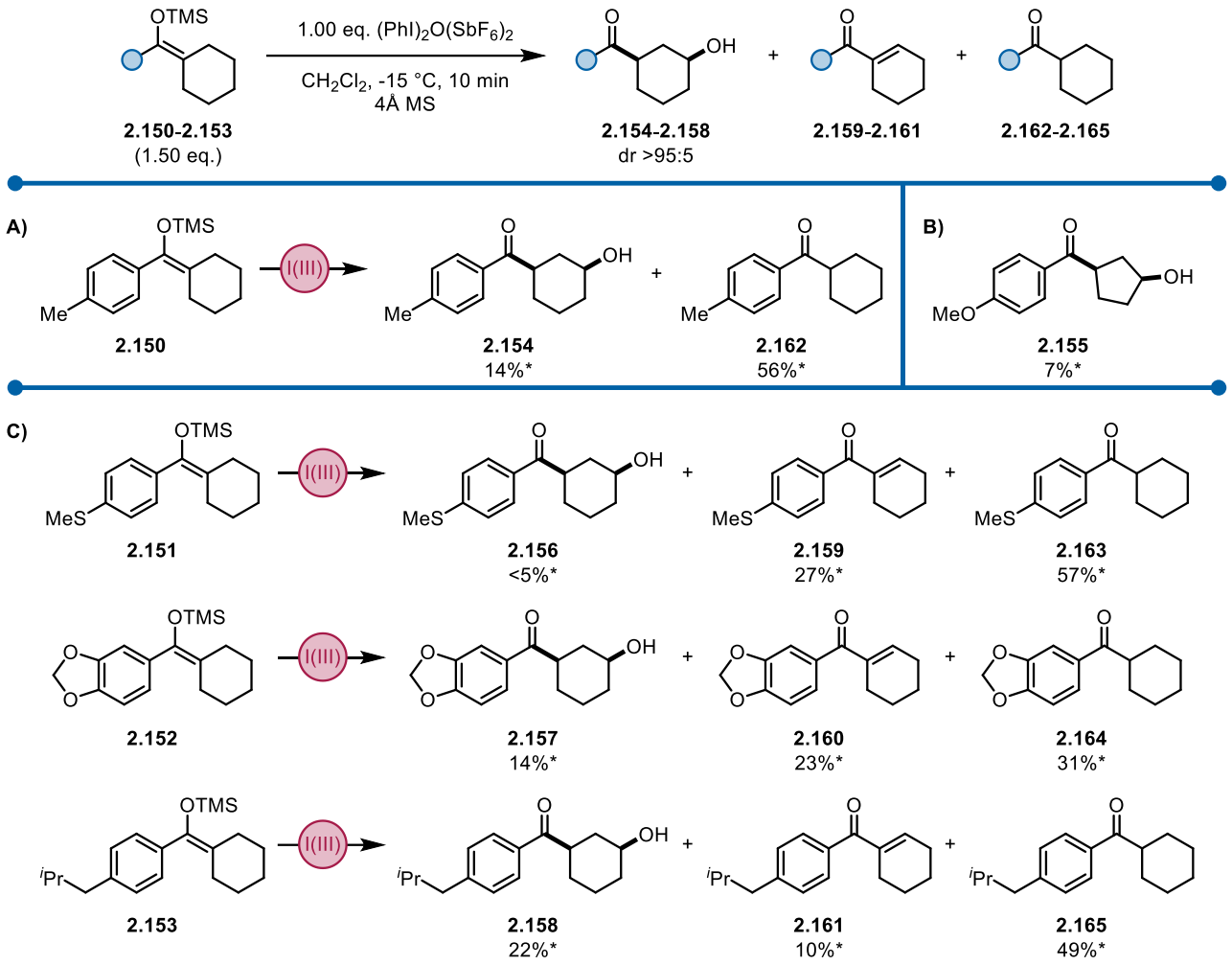


Scheme 2.22: Substrate scope of γ-Selective oxidation of silyl enol ethers. Yields calculated based on hypervalent iodine reagent.

As previously observed, aromatic substituents bearing electron withdrawing groups such as trifluoromethyl groups (CF_3) led to over 70% isolated yield of the desired oxidation products **2.114**, **2.137** and

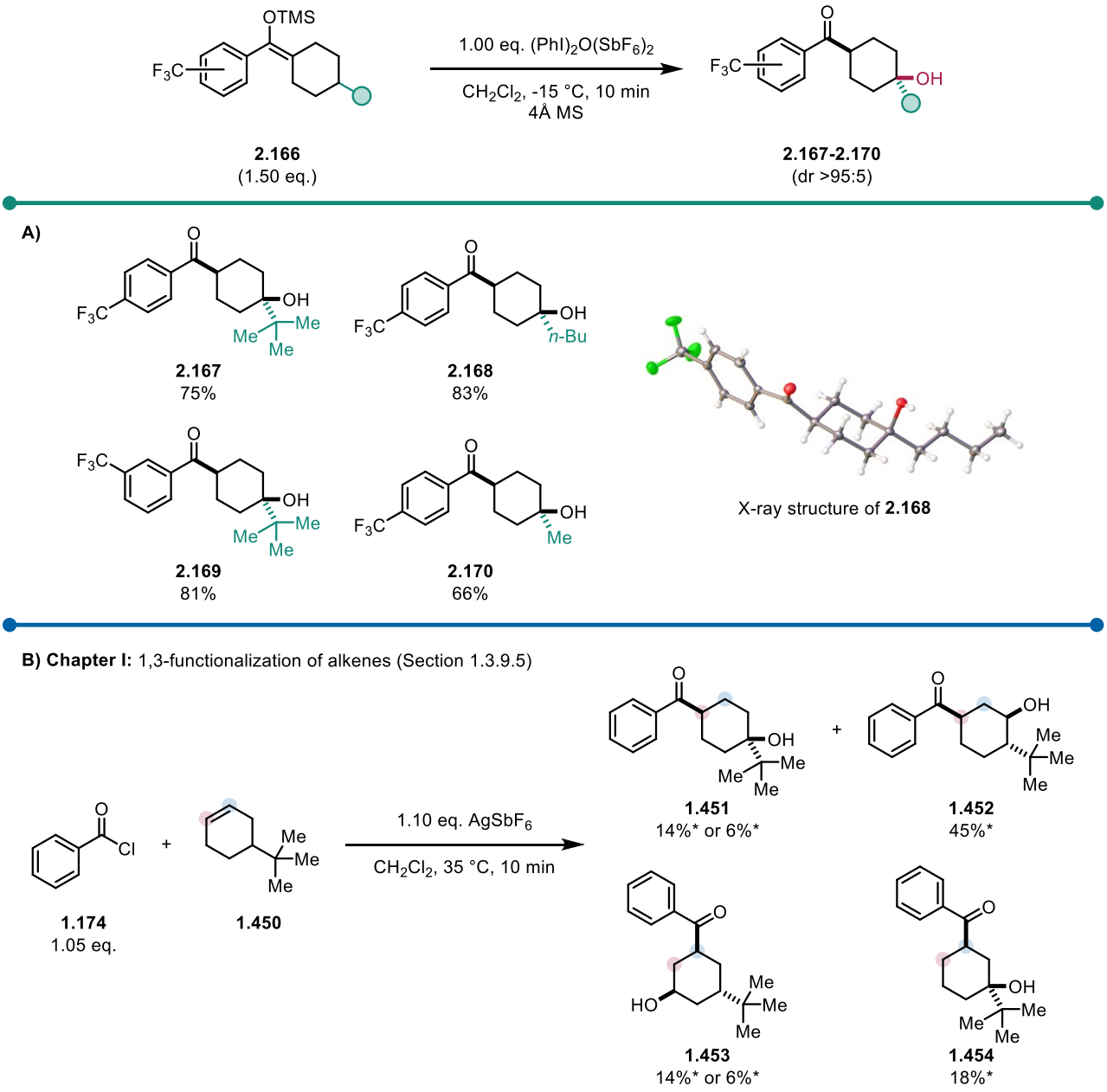
2.138. In the case of **2.114**, the reaction was scaled up to 5 mmol of silyl enol ether, with a comparable yield of 69%. Substrates decorated with other electron withdrawing groups such as nitrile (CN) and methyl ester (COOMe) led to formation of **2.139** and **2.140** in 41% and 51% yield respectively. Halide substituents were also tolerated in this reaction as showcased by **2.141** (Cl) and **2.142** (Br). Electronic neutral aromatic substrates such as phenyl and 2-naphthyl were also suitable for this transformation, leading to **2.122** (57%) and **2.143** (52%) respectively. Cyclohexyl ketoalcohols **2.144** and **2.145** were also synthesized in 52% yield. A 2-benzo[*b*]thiophenyl ketone substrate was obtained, albeit only in 41% yield. When the γ-position of the silyl enol ether contained an additional substituent, a significant increase in yield was observed as showcased by **2.147**, **2.148** and **2.149**. In the case of **2.147**, an X-ray crystal structure confirmed the *syn*-configuration of **2.147**. A positive change in yield can be explained by the increased stability of the γ-carbocation being tertiary, as opposed to the previous cases where it was mostly secondary.

Next, we investigated the effect of electron-donating groups on the aryl moiety of silyl enol ethers (Scheme 2.23). As previously mentioned, we expect certain amounts of elimination products **2.159**-**2.161** as well as hydrolysis towards ketone **2.162**-**2.165**. Silyl enol ether **2.150** having a *p*-methyl (*p*-Me) substituent delivered as the major product ketone **2.154** (57%) alongside 14% of ketoalcohol **2.162** (Scheme 2.23A). In this case, no elimination products were observed, suggesting the hydrolysis step being faster than the carbocation generation through the hypervalent iodine reagent. A substrate bearing a *p*-methoxy (*p*-OMe) group led only to 7% yield of the corresponding ketoalcohol **2.155** (Scheme 2.23B), the rest of the starting material being hydrolyzed/deprotected under the reaction conditions. Scheme 2.23C shows a trend where hydrolysis towards ketones **2.163**-**2.165** was the main reaction pathway of silyl enol ethers **2.151**-**2.153**.



Scheme 2.23: A) Remote oxidation of silyl enol ethers bearing electron rich substituted arenes. *NMR yield using mesitylene as an internal standard

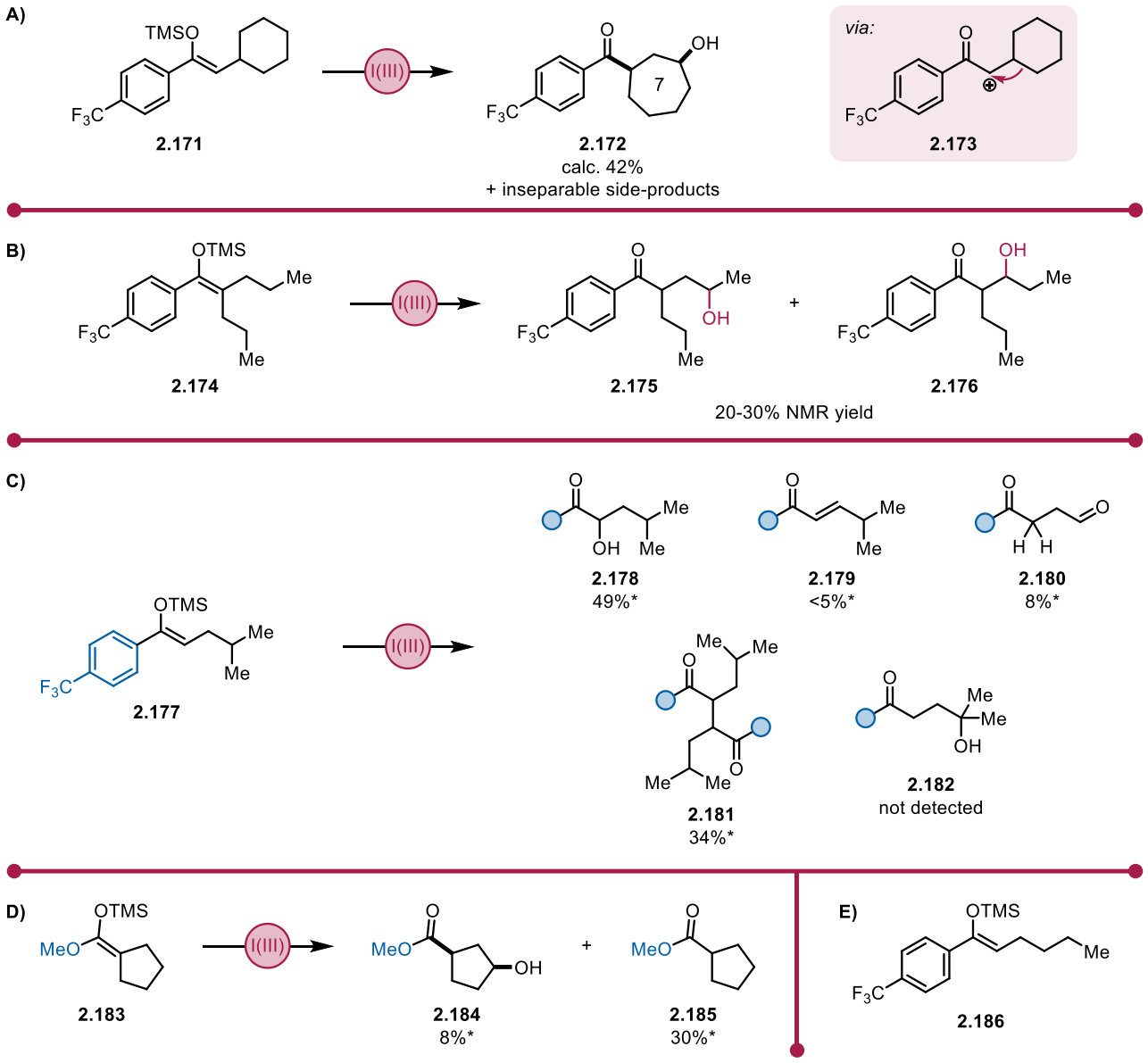
Building on the results of Scheme 2.22, we proposed that δ-substituted silyl enol ethers such as **2.166** could help direct the carbocation intermediate an additional [1,2]-hydride transfer step further (from the γ-position) towards the δ-position and after hydrolysis yield the δ-functionalized alcohol **2.167**-**2.170**. Indeed, the corresponding ketoalcohol **2.167** was obtained in excellent yield and diastereomeric ratio (dr >95:5, 75% yield) as shown in Scheme 2.24A. Similar results were obtained when the *tert*-butyl (^{t}Bu) substituent of **2.167** was replaced with *n*-butyl (*n*-Bu), forming **2.168** in 83%. Pleasingly, an X-ray structure could also be obtained for ketoalcohol **2.168**. Two additional scope entries **2.169** and **2.170** are shown below. These type of δ-functionalized ketoalcohols would be unachievable using our previous intermolecular protocol (Chapter I: 1,3-funtionalization of alkenes, section 1.3.9.5).



Scheme 2.24: A) δ-Selective oxidation of silyl enol ethers with hypervalent iodine reagents. Yields calculated based on hypervalent iodine reagent. B) Regioselectivity issues of intermolecular protocol.

When a linear substrate bearing a cyclic substituent **2.171** was subjected to the reaction conditions, among unidentifiable side products, a product **2.172** resulting from ring expansion was observed (Scheme 2.25A). Presumably, the initial carbocation **2.173** would undergo a methylene shift, followed by a [1,2]-hydride transfer to place the positive charge in the γ-position. After oxocarbenium formation and hydrolysis, as we have seen numerous times throughout this thesis, ketoalcohol **2.172** was obtained at approximatively 42% NMR yield. Additionally, non-cyclic substrates resulted in poor yields and regioselectivity issues. When symmetrical silyl enol ether **2.174** was treated with the standard hypervalent iodine reagent, the only distinguishable products were γ-alcohol **2.175** and β-alcohol **2.176** in 20-30% NMR yield (Scheme 2.25B).

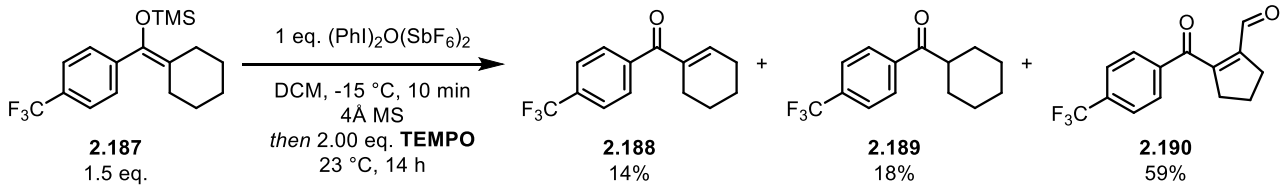
Due to overlapping signals and products resulting from decomposition, an accurate yield could not be determined. Silyl enol ether **2.177** proved to be even less selective, resulting in a mixture containing α-hydroxyketone **2.178** (49%), α,β-unsaturated ketone **2.179** (<5%), dimerization product **2.181** (34%) and rearranged and overoxidized product **2.181** (8%). No amount of desired ketoalcohol **2.182** could be detected (Scheme 2.25C). A more exotic substrate was silyl ketene acetal **2.183** (Scheme 2.25D). Due to low stability of the starting material **2.183** and increased basicity of the carbonyl group, the reaction favored hydrolysis towards **2.184** (30%) and only 8% of oxidation product **2.185** was observed.



Scheme 2.25: Additional silyl enol ether substrates: A) Ring expansion product observed starting from a linear substrate bearing a cyclic substituent. B-C) Non-cyclic substrates have poor yields and regioselectivity. D) Increased basicity of silyl ketene acetal substrate unfavorable for remote oxidation. E) Linear substrate **2.186** leads to unidentifiable decomposition products and hydrolysis product.

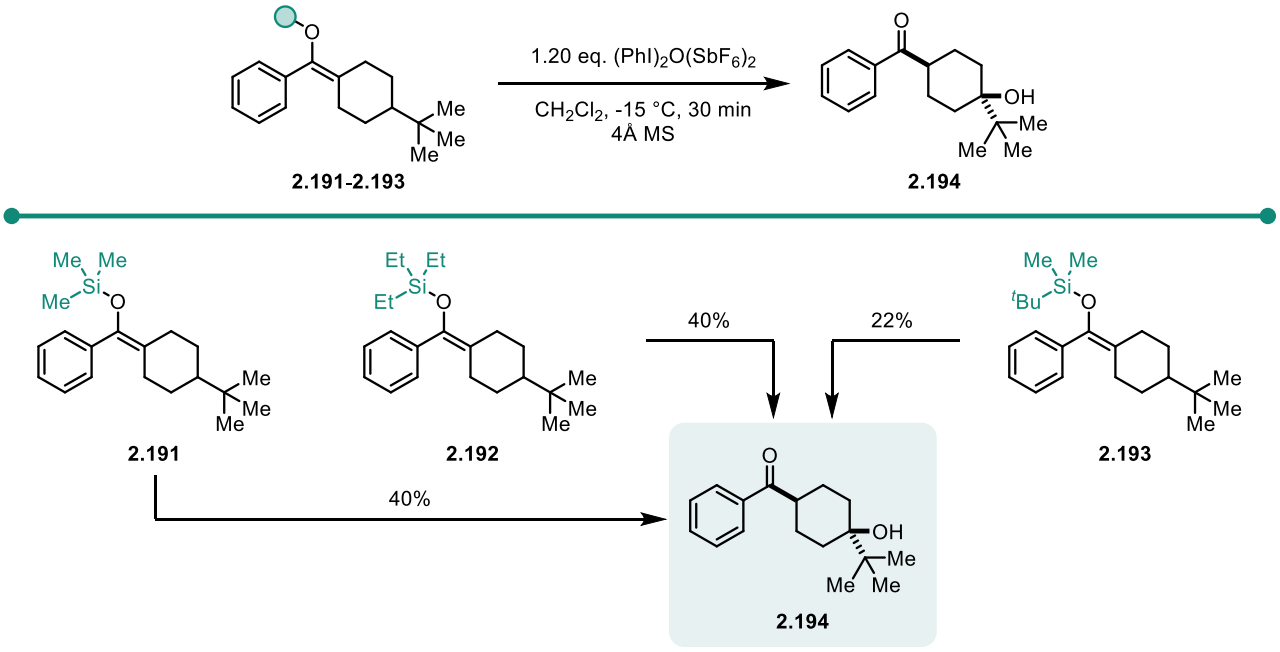
As for linear silyl enol ether **2.186**, we observed mostly elimination product mixtures alongside non-specific decomposition products and 32% of identifiable hydrolysis (Scheme 2.25E).

Since oxocarbenium ions can survive the reaction conditions to a certain extent, we wondered whether addition of (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) would result in further functionalization (Scheme 2.26). In this case, we isolated α,β-unsaturated ketone **2.188** (14%) and hydrolyzed ketone **2.189** (18%) together with 59% of what seems to be a 1,4-dicarbonyl compound **2.190**. Further studies are currently ongoing to explore this intriguing observation.



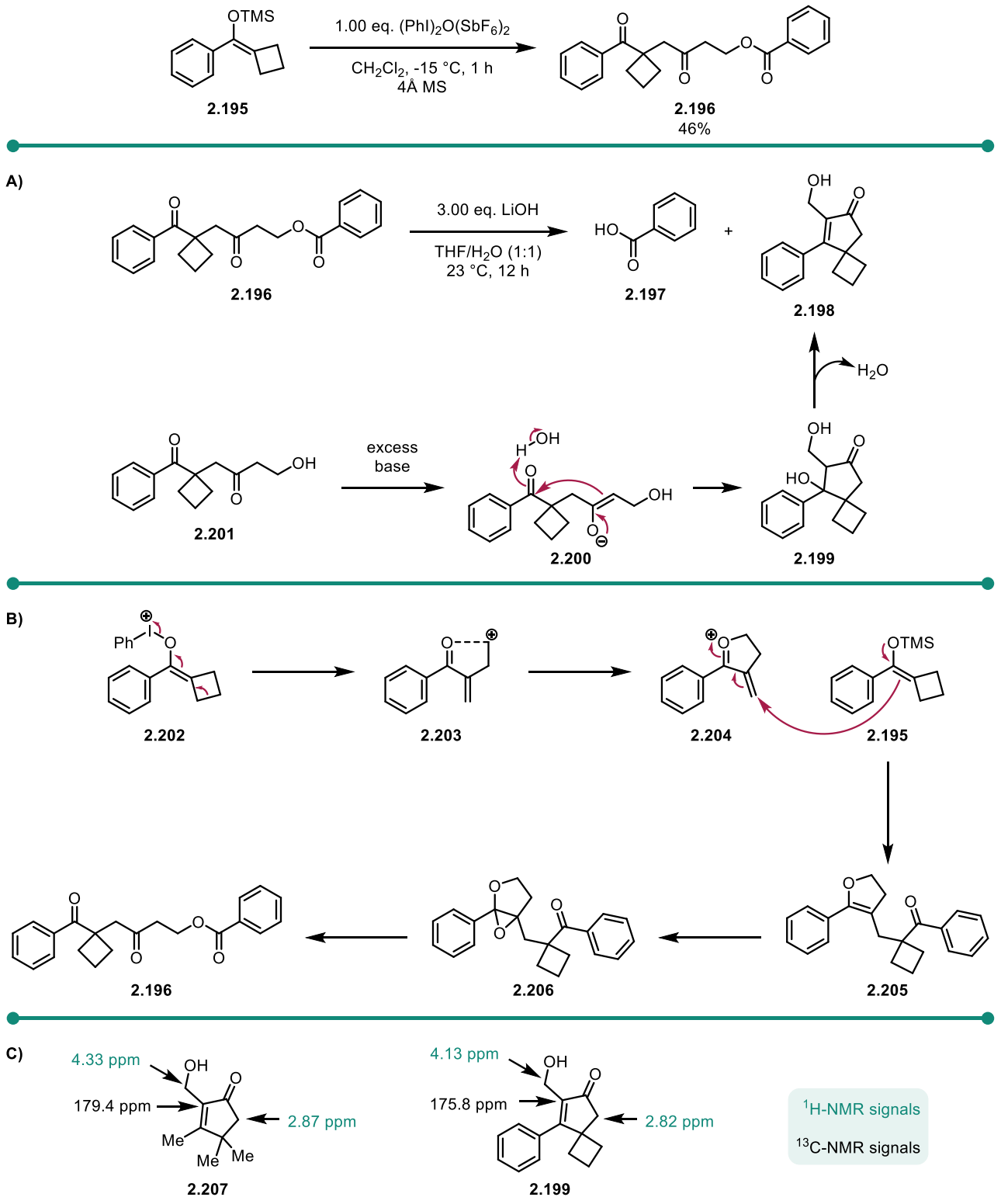
Scheme 2.26: TEMPO enables overoxidation and rearrangement processes.

While in most cases, trimethylsilyl (TMS) was selected as the protecting group of choice, substrates **2.192** and **2.193** bearing triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBDMS) protecting groups were also submitted to an earlier iteration of the reaction conditions (Scheme 2.27). No significant change in yield of **2.194** was observed between **2.191** (TMS) and **2.192** (TES), both leading to 40% of 1,4-ketoalcohol **2.194**. Surprisingly, *tert*-butyldimethylsilyl ether **2.193** (TBDMS) gave only 22% of the desired product. Most likely, the increased steric demand of **2.193** resulted in a more challenging attack on the hypervalent iodine reagent. The remaining material was hydrolyzed to the corresponding ketone.



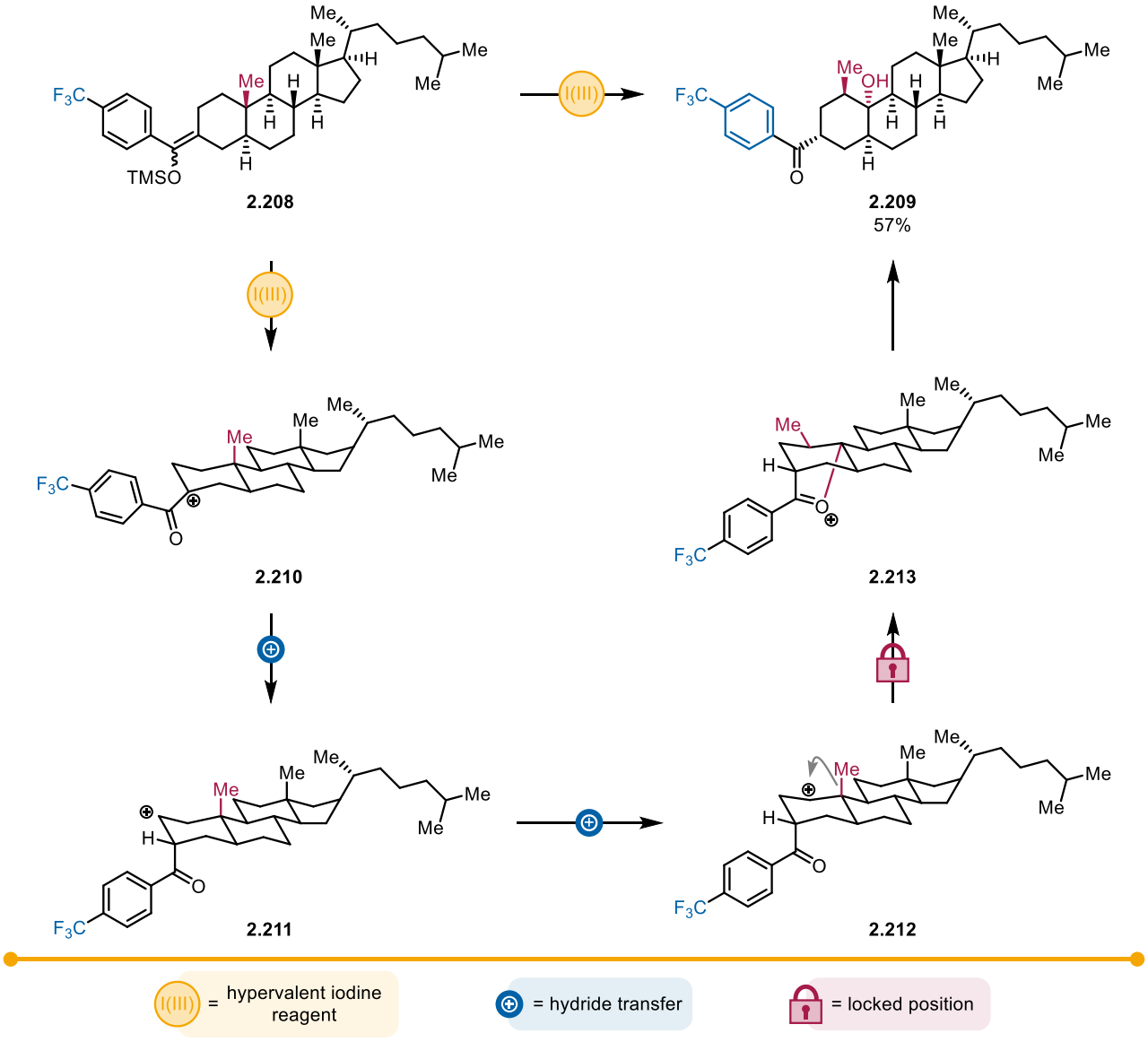
Scheme 2.27: Varied silyl protecting groups and their influence on the reaction outcome.

When (cyclobutylidene(phenyl)methoxy)trimethylsilane **2.195** was submitted to the reaction conditions, a rearranged oligomerized product **2.196** was identified (Scheme 2.28). To confirm the structure of **2.196**, a hydrolysis step employing an excess of lithium hydroxide (LiOH) was performed and led to formation of benzoic acid **2.197** and enone **2.198** (Scheme 2.28A). The enol form **2.200** could attack the remaining ketone in an intramolecular fashion, leading to aldol **2.199** followed by a dehydration step resembling the crotonization product of **2.198**. The reaction mechanism could involve a strain release process in which enolonium species **2.202** forms oxocarbenium intermediate **2.204**. An attack of a second equivalent of silyl enol ether **2.195** would lead to formation of 4,5-dihydrofuran **2.205**. Epoxidation towards **2.206** and further oxidation would deliver the isolated product **2.196** (Scheme 2.28B). However, exploration of a simplified version of **2.206** under the reaction conditions are required to gain further insights into this unusual transformation. The structure of **2.199** was confirmed by comparison to a similar literature reported compound **2.207** (Scheme 2.28C).[146]



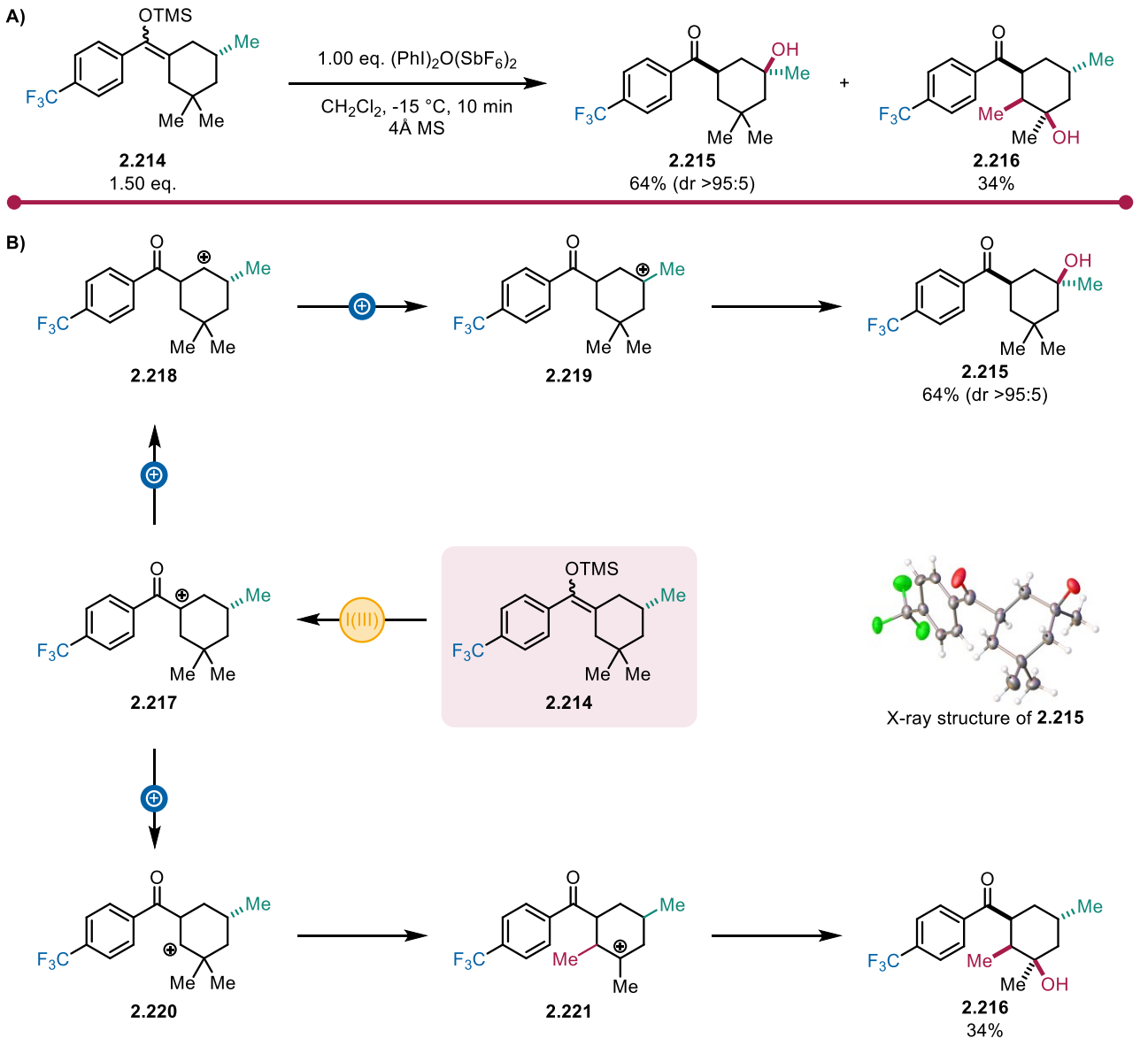
Scheme 2.28: Rearrangement product of silyl enol ether **2.195**. A) Proposed reaction mechanism. B) Hydrolysis of product **2.196** gives further insights into its structure. C) Comparison of **2.199** with a literature reported compound **2.200**.

The steroid derivative **2.208** gave a Wagner–Meerwein-type rearranged product **2.209** when submitted to the reaction conditions (Scheme 2.29).[147] [148][149][150] The proposed mechanism involves generation, as has been the case so far, of α-carbocationic species **2.210**. This intermediate has two reaction pathways through an axial-[1,2]-hydride transfer step. According to the isolated product **2.211**, it seems to prefer a pathway closer to the axial methyl group and form carbocation **2.212**. At this stage, an axial-[1,2]-methyl shift would form a δ-carbocation that is immediately captured by the ketone and stabilized (locked) in the form of oxocarbenium ion **2.213**. Basic work-up delivers **2.209** as a single diastereomer in 57% yield.



Scheme 2.29: Late-stage steroid modification proceeds with unexpected methyl shift.

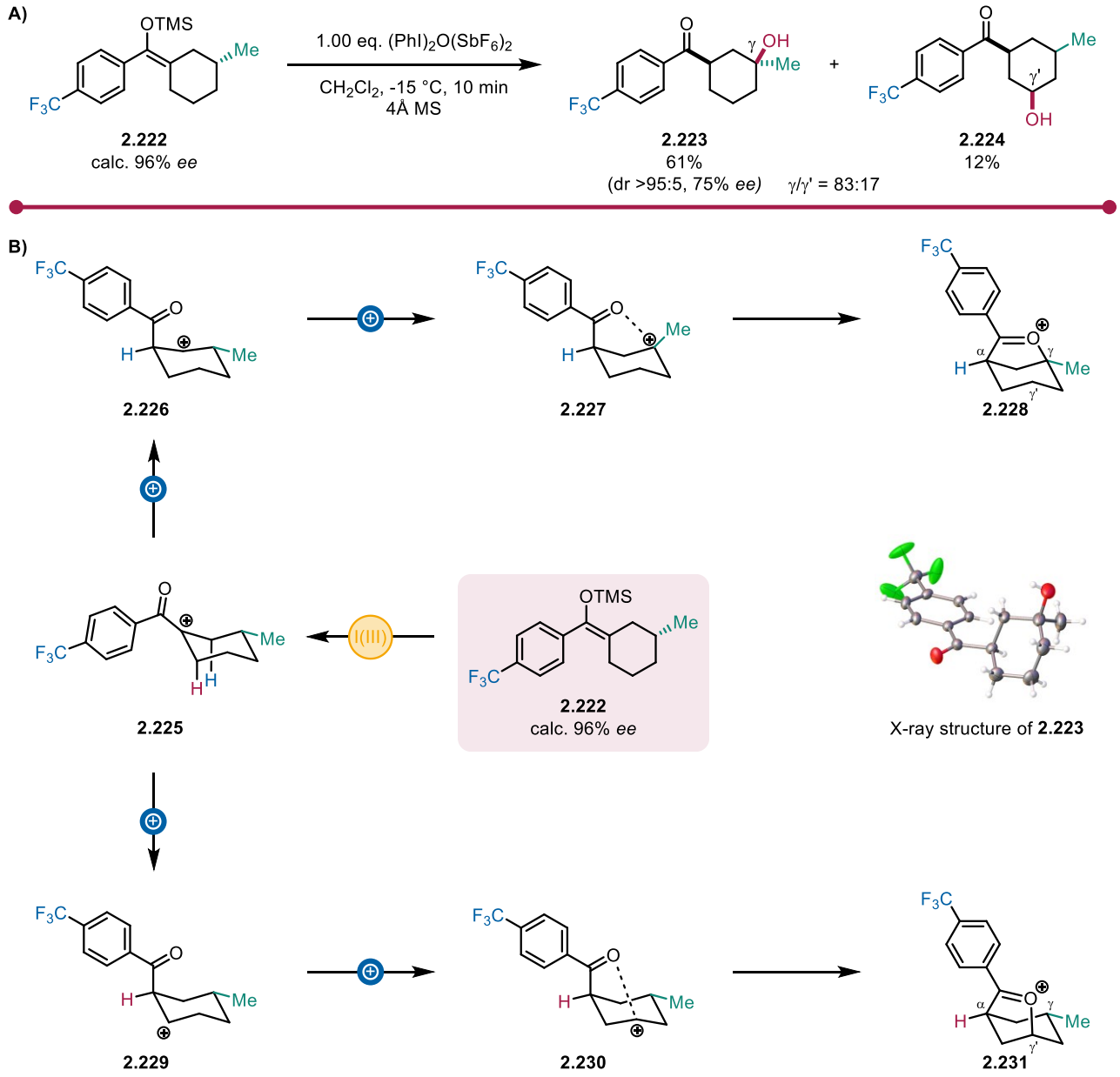
In addition, we tested the presence of a substituent in the γ-position (Scheme 2.30A). Surprisingly, treating **2.214** with the hypervalent iodine reagent of choice gave a mixture of 2:1 ratio between the predicted ketoalcohol **2.215** and its methyl-regioisomer **2.216**. Silyl enol ether **2.214** (Scheme 2.30B, center) would form, after treatment with the highly electrophilic species $(PhI)_2O(SbF_6)_2$, α-carbocation **2.217**. Given that one neighboring position is blocked by two methyl groups and presents no available hydrogen atoms, the most likely scenario is that a [1,2]-hydride transfer occurs, forming intermediate **2.218**. An additional hydride shift to the tertiary position would yield the more stable carbocation **2.219**. Finally, capture by the ketone and hydrolysis yields ketoalcohol **2.215** (64%) with an excellent diastereomeric ratio (dr >95:5). Additionally, the structure of **2.215** was confirmed by its X-ray crystal structure. However, there was another isolated ketoalcohol **2.216** (34%). Looking back at intermediate **2.220**, if one of the methyl groups were to perform a methyl shift instead of a hydride shift, we would land at carbocation **2.221**. Since intermediate **2.221** has its positive charge at an appropriate distance from the oxygen atom of the ketone and is a tertiary carbocation, a capture is feasible. After hydrolysis of the newly formed oxocarbenium ion, product **2.216** is obtained. This process showcases that methyl shifts are indeed possible even in simpler systems and not just in steroid-derived substrates.



Scheme 2.30: Methyl shift on a simplified substrate **2.214**. A) Silyl enol ether **2.214** leads to a mixture of ketoalcohol **2.215** and a methyl-shifted isomer **2.216** after treatment with hypervalent iodine reagent. B) Proposed reaction pathway.

The final example displayed in this sub-chapter is the enantioenriched silyl enol ether **2.222** (Scheme 2.31A). Subjecting **2.222** to the reaction conditions gave an 83:17 mixture of γ- and γ'-alcohols **2.223** and **2.224** respectively. The silyl enol ether **2.222** would initially form carbocation **2.225**, where the methyl group is placed equatorial and the ketone in a pseudo-equatorial position (Scheme 2.31B). There are two vicinal axial hydrogen atoms (red and blue) that could perform a [1,2]-hydride transfer. If the blue hydride shifts, we would end up at carbocation **2.226**. An additional hydride shift would form intermediate **2.227**. Capture of the positive charge by ketone **2.227** would lead to oxocarbenium ion **2.228**, that is the source of the main γ-functionalized product **2.223** (61%, dr >95:5, 75% *ee*). The structure of **2.223** was confirmed by and X-ray crystal structure as well. If the red hydrogen atom shifts, we land at intermediate **2.229**. As before, a

second hydride shift and capture of the newly formed positive charge results in oxocarbenium ion **2.230**, the intermediate responsible for γ'-functionalized product **2.224** (12%).



Scheme 2.31: A) Stereospecific oxidation by conformation control. B) Proposed reaction pathway for the formation of the enantioenriched product **2.223**.

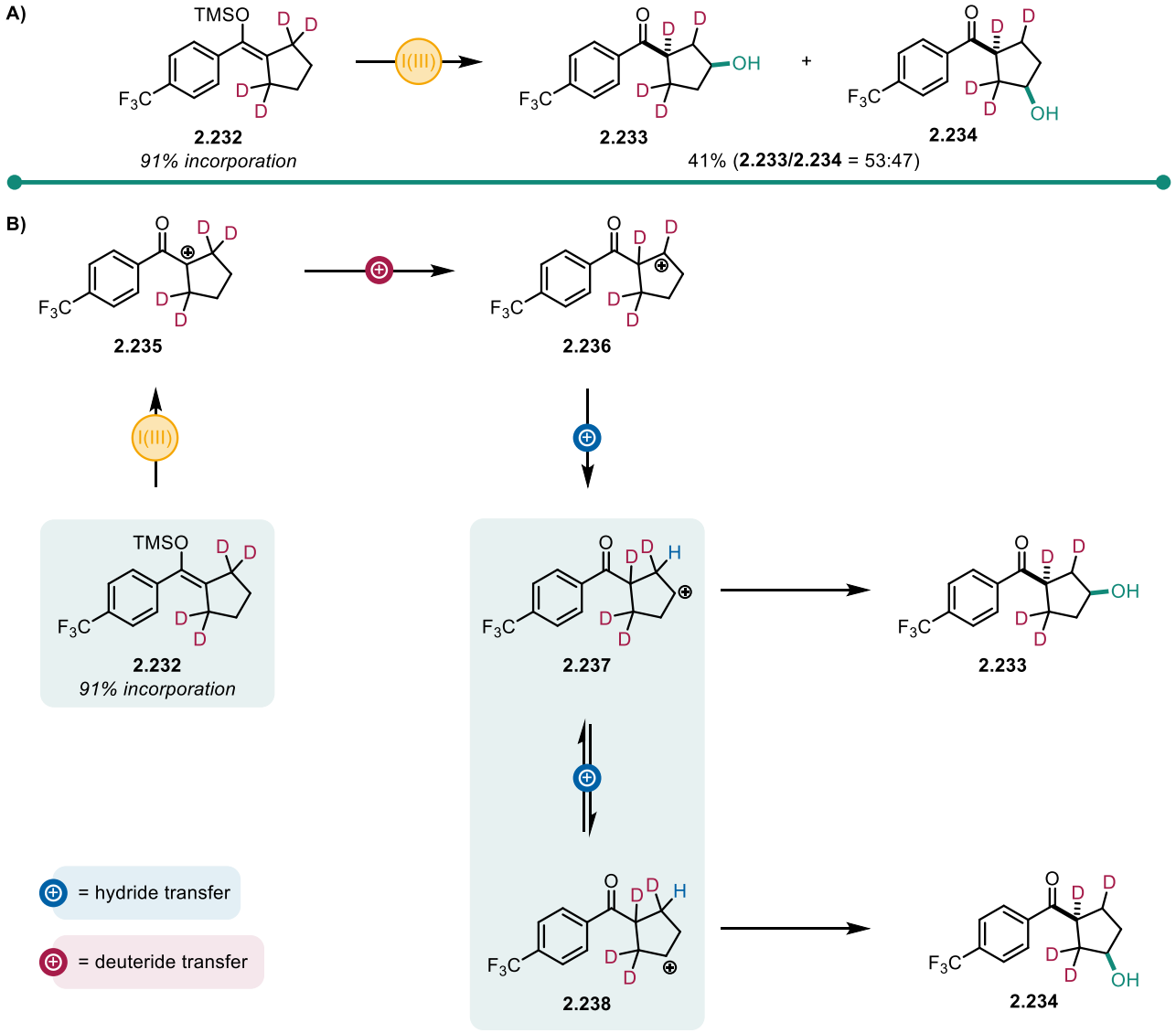
There are several intriguing observations derived from this transformation (Scheme 2.31A). Firstly, the absolute configuration of **2.226**, where the substituent is placed axial, is set after the first axial-[1,2]-hydride transfer. Secondly, the following hydride shift from **2.226** to **2.227** erases the initial stereocenter adjacent to the methyl substituent. Capture from the top face of **2.227** by the ketone locks oxocarbenium ion **2.228** in its drawn conformation and re-establishes the absolute configuration of the γ-position of **2.228**. A slight erosion of *ee* is observed in this process. There are two main possibilities to account for this. Firstly, the precise

enantiomeric ratio of the starting silyl enol ether could not be determined by chiral HPLC analysis, due to it being a mixture between *E*/*Z*-double bond isomers. All previous synthetic steps should not lead to loss of enantiomeric excess: therefore, if we presume the enantiomeric ratio remains unchanged, it should be the same as the starting 3-methylcyclohexan-1-one (calc. 96% *ee*).

Finally, while axial-[1,2]-hydride transfer should be favored, one cannot exclude the possibility of the equatorial hydrogen atoms performing the hydride transfer, therefore leading to formation of the enantiomer of oxocarbenium ion **2.231**.

2.3.6 Deuteration Studies

Deuterium-labeled silyl enol ether **2.232** (91% average deuterium incorporation) was submitted to the reaction conditions and resulted in a 53:47 mixture of γ-oxidized ketones **2.233** and **2.234** (Scheme 2.32A). The first step of the reaction mechanism is generation of α-carbocation **2.235** (Scheme 2.32B). Since carbocation **2.235** is fully flanked by deuterium atoms, it can either eliminate or perform a [1,2]-deuteride transfer to form β-carbocation **2.236**. Next, a [1,2]-hydride transfer process from **2.236** would lead to intermediate **2.237**. As we have seen numerous times in previous sections of this thesis, γ-carbocation **2.237** is further stabilized by formation of an oxocarbenium ion and after basic work-up leads to ketoalcohol **2.233**.

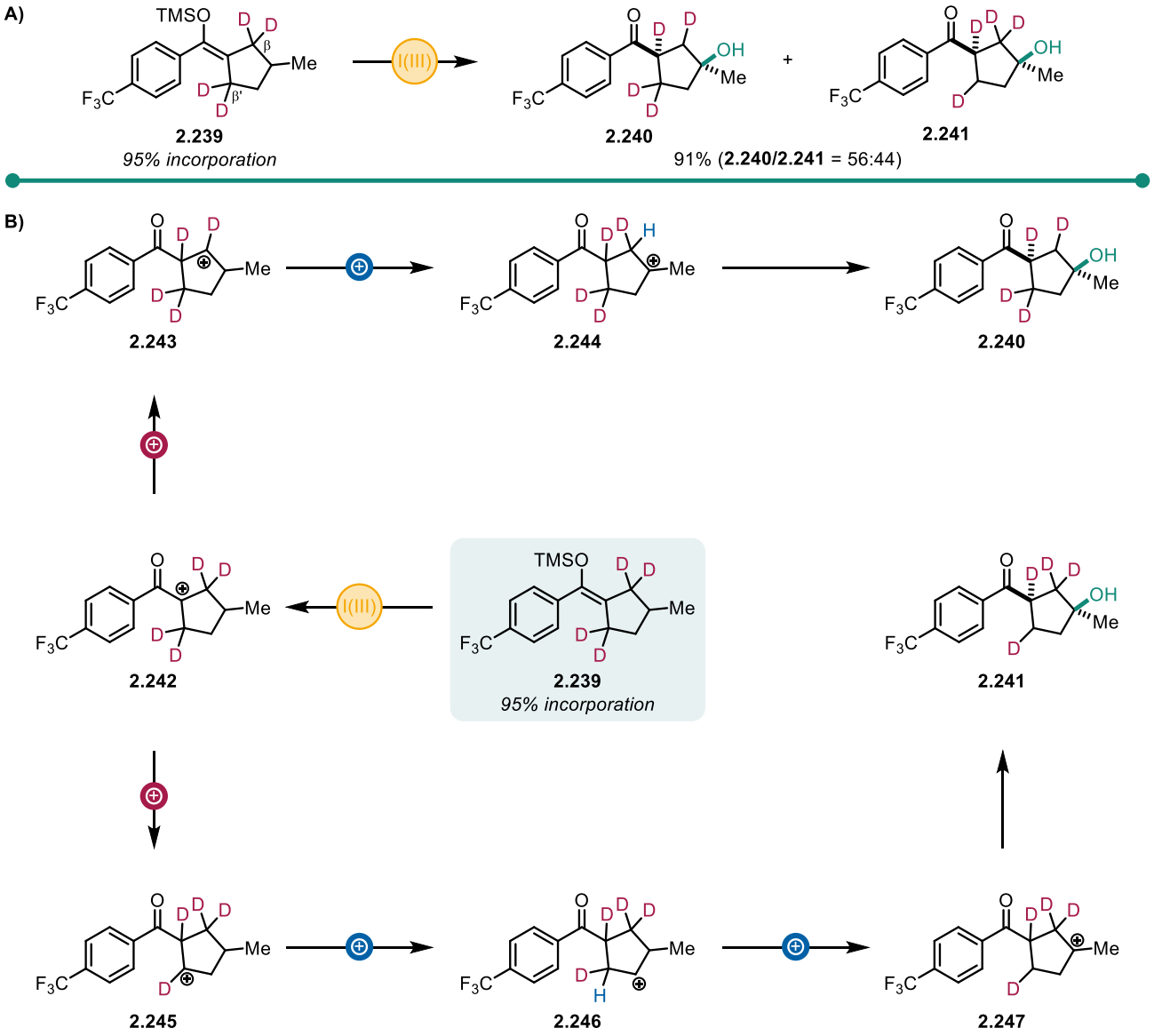


Scheme 2.32: Mechanistic studies of deuterated silyl enol ether **2.232**.

Interestingly, **2.233** is not the sole product of this transformation. Regioisomer **2.234** is also obtained in an almost 1:1 ratio with **2.233**. Such an observation could be explained by a second and rapid hydride shift step from **2.237** to **2.238**, or rather, an equilibration process between the two γ-carbocations **2.237** and **2.238**. An

equilibrium process of this nature would need to have a similar reaction speed to the ketone capture itself, since, to the best of our knowledge, oxocarbenium ion formation is not a reversible process. This would explain the formal "deuterium scramble" between the two products **2.233** and **2.234**. Since only these two products were observed, we can presume that no elimination/protonation processes are involved, in which case we would see a plethora of deuterated products.

In order to break away from the symmetry of γ-carbocations **2.237** and **2.238** and push back the equilibrium towards the initial γ-carbocation **2.237**, silyl enol ether **2.239** (95% average deuterium incorporation) was synthesized and tested under the reaction conditions (Scheme 2.33A).

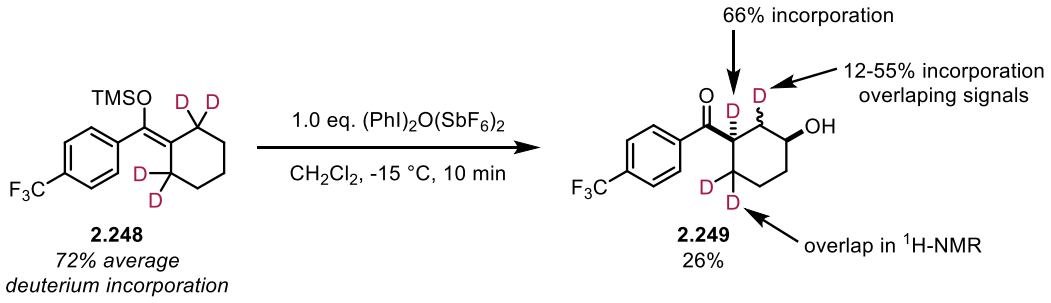


Scheme 2.33: Studies of unsymmetrical deuterated silyl enol ether **2.239**.

When silyl enol ether **2.239** was submitted to the reaction conditions, again a mixture of deuterated ketoalcohols **2.240** and **2.241** was isolated in a 56:44 ratio and 91% yield. Carbocation **2.242**, originating from

silyl enol ether **2.239** (Scheme 2.33B, center), should perform a deuteride shift, similar to its unsubstituted analogue described before. In the case of a deuteride shift performed by one of the two α-deuterium atoms, we would form intermediate **2.243**. A [1,2]-hydride transfer would form the tertiary carbocation **2.244** and then after basic work-up, tertiary alcohol **2.240** would be produced. However, if one of the two α'-deuterium atoms are transferred, we would arrive at carbocation **2.245**. An additional hydride transfer step would lead to **2.246**. While intermediate **2.246** is at an appropriate distance from the ketone and could be captured and form an oxocarbenium ion, the neighboring hydride is faster and formation of a tertiary carbocation **2.247** is preferred, due to stability. Oxocarbenium formation and hydrolysis delivers tertiary alcohol **2.241**, a deuterium-regioisomer of **2.240**.

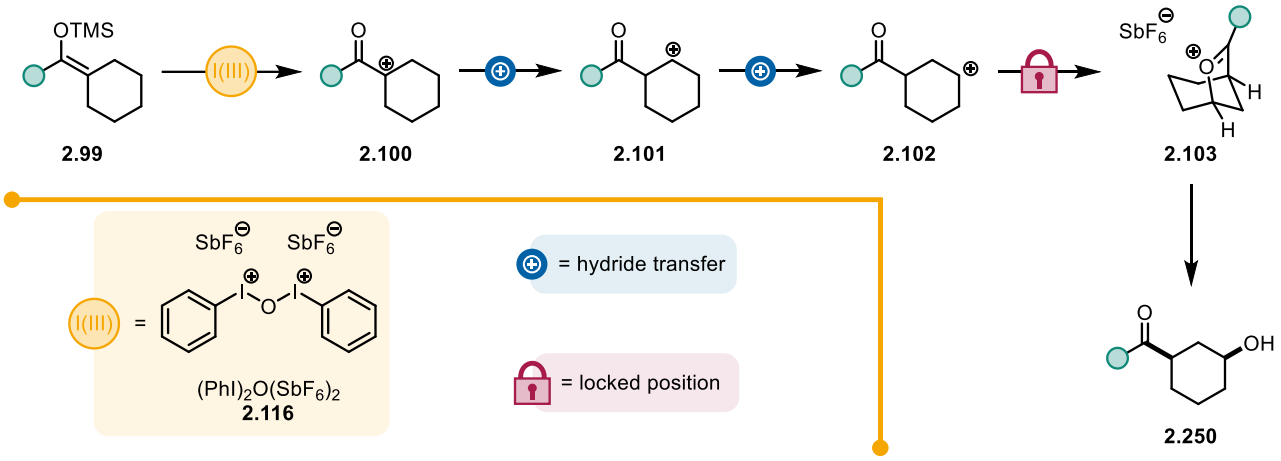
The final deuterated substrate we synthesized and investigated was a cyclohexylidene silyl enol ether **2.248** (Scheme 2.34). In this case we observed in addition to the expected product **2.249**, a plethora of compounds containing varying amounts of deuterium atoms. Of note, the initial starting material **2.248** had an average of 72% deuterium incorporation over four α-positions. A total of 5-6 compounds could be counted in the ^{13}C-NMR spectrum. Their structure could not be fully characterized given the plethora of overlapping signals. For a more precise and accurate investigation, silyl enol ether **2.248** should be resynthesized with a higher deuterium incorporation. Nevertheless, we still wanted to see what knowledge can be gained from such a substrate. The main takeaway being the increased complexity when changing from a 5-memered ring system to a 6-membred one, most likely due to the potential conformational changes (boat/chair) involved.



Scheme 2.34: Deuterium-labelled experiment using a *d*$_4$-cyclohexyl silyl enol ether **2.248**.

2.4 Conclusion

The goals of this project were successfully achieved. We developed a novel strategy for the formal oxidation of inert C–H bonds by generating highly reactive carbocationic species through hypervalent iodine reagents (Scheme 2.35). By designing an intramolecular reaction process, we were able to circumvent certain regioselectivity issues from the previous chapter. Unsymmetrically substituted cyclic substrates were studied as well as late-stage modification of a steroid. Finally, an enantiospecific transformation, starting from enantioenriched substrates and deuterated silyl enol ethers gave additional mechanistic insights into carbocation mediated remote functionalization reactions.



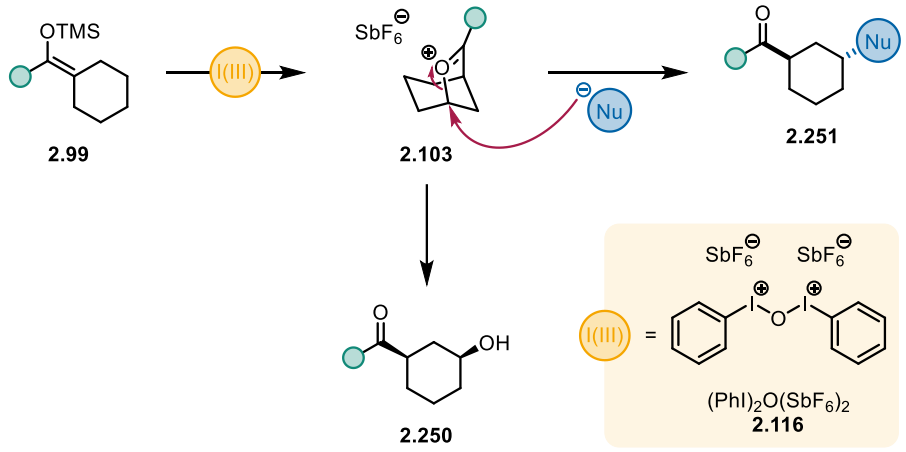
Scheme 2.35: Remote oxidation of inert C–H bonds through highly reactive carbocationic species generated by hypervalent iodine reagents.

2.5 Perspectives

During our studies, we explored ways to generate oxocarbenium ion **2.103** from silyl enol ethers (**2.99**) using a hypervalent iodine reagent **2.116** (Scheme 2.36). However, given the nature of the iodine reagent, a catalytic version could theoretically be feasible by identifying suitable activating agents to regenerate the reactive electrophilic reagent *in situ*. This would be a significant advancement and greatly improve the atom economy of the reaction.

A more challenging project would be the functionalization of oxocarbenium ion **2.103** with suitable nucleophiles that could open up the intermediate in an *anti*-fashion leading to 1,3-disubstituted products **2.251**, similarly to our results from Chapter 1. While we have gained insights regarding species that are detrimental to intermediate **2.103**, so far, most cases led to an increased amount of elimination and hydrolysis products.

Finally, development of a novel chiral iodine (III) reagent analog of **2.116**, also bearing non-basic, non-coordinating counteranions could be a useful tool and significant scientific leap in the repertoire of iodine (III) reagents.



Scheme 2.36: Remote functionalization using hypervalent iodine reagents and suitable nucleophiles remain a challenge.

3 Experimental Section

3.1 General Information

Unless otherwise stated, all glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. All solvents were distilled from appropriate drying agents prior to use. All reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.).

Neat infrared spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (ν_{max}) are reported in cm^{-1}. Optical rotations were measured on a Perkin Elmer 341 polarimeter using a 100 mm path-length cell at 589 nm (c given in g/100 ml). Chiral HPLC was performed using AGILENT Infinity 1260 with Chiralpak I, Chiralpak IC, or Lux-3 Cellulose-3 columns. Details on chromatographic conditions are indicated under each compound.

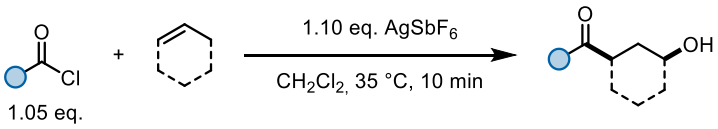
All ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded using a Bruker AV-400, AV-500, AV-600 or AV-700 spectrometer at 300 K. Chemical shifts are given in parts per million (ppm, δ), referenced to the solvent peak of $CDCl_3$, defined at δ = 7.26 ppm (^{1}H NMR) and δ = 77.16 ppm (^{13}C NMR). Spectra of iodonium reagents were recorded in $CDCl_3$/DMSO-d_6 (8:2 mixture), in which case the chemical shifts were referenced to the residual peak of DMSO-d_6, defined at δ = 2.50 ppm (^{1}H NMR) and δ = 39.52 ppm (^{13}C NMR).[151] Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) as they appeared in the spectrum. If the appearance of a signal differs from the expected splitting pattern, the observed pattern is designated as apparent (app). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Protons and carbons were assigned whenever unambiguously possible—atoms that could not be assigned are denoted as H_{Ar} or C_{Ar} (aryl) for aromatic protons and carbons, H_{Alk} or C_{Alk} (alkyl) for aliphatic protons and carbons or similar. ^{13}C shifts that were not detected by ^{13}C NMR but showed a crosspeak in the HSQC are denoted as HSQC in parentheses.

Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV), an Agilent 5973 (70 eV) or a Bruker maXis UHR-TOF spectrometer, using electrospray ionisation (ESI). For cases in which mass was not detected with ESI ionisation, an Agilent 7200B GC/Q-TOF Spectrometer with electron impact (EI) ionisation and a TOF mass analyser was used. Infra-red (IR) spectra were obtained using Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers ($\nu_{max} = 1/\lambda$) are reported in cm^{-1}. Melting points were determined on a capillary apparatus and are uncorrected.

3.2 Stereodivergent 1,3-Difunctionalization of Alkenes by Charge Relocation

3.2.1 1,3-Hydroxyacylation of Alkenes with Acylium Ions

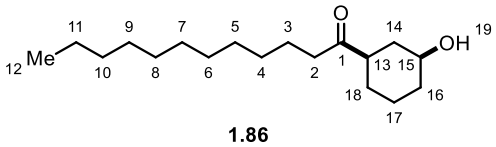
3.2.1.1 General Procedure 1: Synthesis of *syn*-1,3-Ketoalcohols



In an oven-dried vial at 23 °C, a solution of alkene (0.200 mmol, 1.00 eq.) and acyl chloride (0.21 mmol, 1.05 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) was treated with silver hexafluoroantimonate ($AgSbF_6$, 0.22 mmol, 1.10 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C. After vigorously stirring the reaction mixture at the same temperature for 10 min, the reaction vial was removed from the oil bath and a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 2 mL) was added, followed by vigorous stirring for 10 min. After this time, the phases were separated, the aqueous phase was extracted with dichloromethane three times (3 × 3.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding *syn*-ketoalcohol.

Note: *For linear alkene substrates, the reaction time is increased from 10 minutes to 30 minutes in order to have more reproducible results.*

1.86 – *syn*-1-(3-Hydroxycyclohexyl)dodecan-1-one



1.86

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), lauroyl chloride (48.6 µL, 45.9 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.22 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.86** (>20:1 r.r., 46.6 mg, 0.170 mmol, 83%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.32).

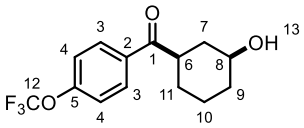
^{1}H NMR (400 MHz, $CDCl_3$): δ (m, 1H, H_{15}), 2.43 (t, J = 7.4 Hz, 3H, H_{2+13}), 2.07 (d, J = 12.4 Hz, 1H, H_{14}), 1.94 (d, J = 12.1 Hz, 1H, H_{14}), 1.87 – 1.74 (m, 2H, H_{16}), 1.57 – 1.49 (m, 2H, H_{18}), 1.38 – 1.18 (m, 21H, H_{Alk}), 0.87 (t, J = 6.6 Hz, 3H, H_{12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 213.2 (C_1), 70.0 (C_{15}), 49.3 (C_{13}), 40.9 (C_2), 37.0 (C_{14}), 35.2 (C_{16}), 32.0 (C_{Alk}), 29.7 (2C, C_{Alk}), 29.6 (C_{Alk}), 29.6 (C_{Alk}), 29.5 (C_{Alk}), 29.4 (C_{Alk}), 27.6 (C_{Alk}), 23.9 (C_{Alk}), 23.3 (C_{Alk}), 22.8 (C_{Alk}), 14.2 (C_{12}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{34}O_2Na^+$) requires *m/z* 305.2451, found *m/z* 305.2450.

IR (neat) ν_{max}: = 3397, 2958, 2922, 2853, 1710, 1466, 1450, 1406, 1377, 1361, 1295, 1269, 1229, 1197, 1146, 1127, 1071, 1053, 964, 741 cm^{-1}.

1.125 – *syn*- (3-Hydroxycyclohexyl)[4-(trifluoromethoxy)phenyl]methanone



1.125

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 4-(trifluoromethoxy)benzoyl chloride (33.2 µL, 47.2 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.125** (40.9 mg, 0.14 mmol, 71%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.20).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.8 Hz, 2H, H_3), 7.28 (d, J = 8.4 Hz, 2H, H_4), 3.81 – 3.66 (m, 1H, H_8), 3.32 (tt, J = 11.2, 3.4 Hz, 1H, H_6), 2.17 – 2.08 (m, 1H, H_7), 2.06 – 1.95 (m, 2H, H_{7+9}), 1.93 – 1.76 (m, 2H, $H_{9\text{ or }11}$), 1.58 – 1.36 (m, 3H, $H_{10\text{ or}11}$), 1.29 (ddd, J = 22.7, 12.3, 3.6 Hz, 1H, $H_{10\text{ or }11}$) ppm.

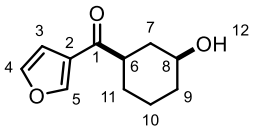
^{13}C NMR (101 MHz, $CDCl_3$): δ 201.0 (C_1), 152.7 (C_5), 134.3 (C_2), 130.5 (2C, C_3), 120.6 (2C, C_4), 120.4 (C_{12}, q, J = 258.8 Hz), 70.1 (C_8), 44.2 (C_6), 37.7 (C_7), 35.3 (C_9), 28.6 (C_{11}), 23.5 (C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -57.63 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}O_3F_3^+$) requires *m/z* 289.1046, found *m/z* 289.1040.

IR (neat) ν_{max}: = 3361, 2937, 2862, 2361, 1681, 1602, 1505, 1451, 1413, 1362, 1254, 1207, 1165, 1113, 1062, 1014, 956, 927, 883, 859, 816, 796 cm^{-1}.

1.129 – *syn*-Furan-3-yl(3-hydroxycyclohexyl)methanone



1.129

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 3-furoyl chloride (20.7 µL, 27.4 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.129** (31.7 mg, 17.0 µmol, 83%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.31).

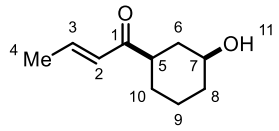
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 7.93 (m, 1H, H_5), 7.49 – 7.36 (m, 1H, H_3), 6.75 (dd, J = 1.9, 0.8 Hz, 1H, H_4), 3.71 (tt, J = 10.3, 4.2 Hz, 1H, H_8), 2.92 (ddd, J = 14.6, 7.3, 3.6 Hz, 1H, H_6), 2.19 – 2.05 (m, 2H, H_7), 2.05 – 1.93 (m, 1H, H_9), 1.92 – 1.79 (m, 2H, H_{9+11}), 1.53 (ddd, J = 12.6, 11.4, 10.7 Hz, 1H, H_{11}), 1.47 – 1.35 (m, 2H, H_{10+12}), 1.35 – 1.22 (m, 1H, H_{10}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 197.5 (C_1), 147.3 (C_5), 144.4 (C_4), 126.7 (C_2), 109.1 (C_3), 69.8 (C_8), 47.0 (C_6), 37.5 (C_7), 35.2 (C_9), 28.6 (C_{11}), 23.3 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{11}H_{15}O_3^+$) requires *m/z* 195.1016, found *m/z* 195.1012.

IR (neat) ν_{max}: = 3410, 3136, 2936, 2860, 1715, 1668, 1561, 1511, 1450, 1396, 1364, 1326, 1284, 1158, 1066, 926, 873, 772 cm^{-1}.

1.148 – *syn*-(*E*)-1-(3-Hydroxycyclohexyl)but-2-en-1-one



1.148

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), isobutyryl chloride (22.0 µL, 22.4 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.148** (18.6 mg, 0.11 mmol, 55%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.20).

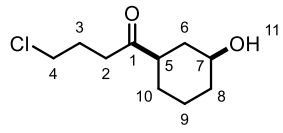
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (dq, *J* = 13.7, 6.9 Hz, 1H, H_3), 6.19 (dd, *J* = 15.6, 1.6 Hz, 1H, H_2), 3.66 (ddd, *J* = 14.2, 10.0, 4.1 Hz, 1H, H_7), 2.65 (tt, *J* = 11.0, 3.5 Hz, 1H, H_5), 2.08 – 1.91 (m, 2H, H_6), 1.89 (dd, *J* = 6.9, 1.5 Hz, 3H, H_4), 1.85 – 1.69 (m, 2H, $H_{8\text{-}11}$), 1.46 – 1.16 (m, 5H, $H_{8\text{-}11}$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 202.0 (C_1), 143.2 (C_3), 130.1 (C_2), 70.0 (C_7), 47.0 (C_5), 37.1 (C_6), 35.2 (C_8), 27.8 (C_{10}), 23.2 (C_9), 18.4 (C_4) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{10}H_{17}O_2^+$) requires *m/z* 169.1223, found *m/z* 169.1219.

IR (neat) ν_{max}: = 3408, 2934, 2858, 2360, 1688, 1662, 1626, 1444, 1361, 1294, 1199, 1150, 1058, 969, 934, 889, 869, 844, 787 cm^{-1}.

1.147 – *syn*-4-Chloro-1-(3-hydroxycyclohexyl)butan-1-one



1.147

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 4-chlorobutyryl chloride (23.7 µL, 29.6 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.147** (37.3 mg, 0.180 mmol, 91%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.14).

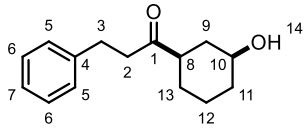
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 – 3.60 (m, 1H, H_7), 3.56 (t, *J* = 6.2 Hz, 2H, H_4), 2.70 – 2.60 (m, 2H, H_2), 2.44 (tt, *J* = 11.4, 3.5 Hz, 1H, H_5), 2.12 – 2.07 (m, 1H, H_3), 2.07 – 1.99 (m, 2H, H_{3+6}), 1.96 (dd, *J* = 9.0, 3.6 Hz, 1H, H_6), 1.89 – 1.78 (m, 3H, H_{8+10}), 1.41 – 1.15 (m, 4H, $H_{9\text{-}11}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.7 (C_1), 70.0 (C_7), 49.5 (C_5), 44.6 (C_4), 37.3 (C_2), 37.0 (C_6), 35.1 (C_8), 27.6 (C_{10}), 26.3 (C_3), 23.4 (C_9) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{17}ClO_2Na^+$) requires *m/z* 227.0809, found *m/z* 227.0806.

IR (neat) ν_{max}: = 3398, 2934, 2858, 1703, 1466, 1449, 1408, 1378, 1361, 1319, 1293, 1270, 1251, 1230, .1199, 1142, 1063, 1046, 956, 929, 906, 889, 872, 847, 830, 794 cm^{-1}.

1.149 – *syn*-1-(3-Hydroxycyclohexyl)-3-phenylpropan-1-one



1.149

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), hydrocinnamoyl chloride (31.8 µL, 36.1 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.149** (>16:1 r.r, 29.7 mg, 0.130 mmol, 64%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67;33, R_f = 0.26).

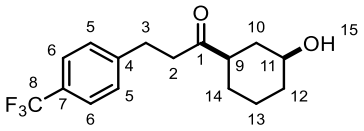
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 2H, H_6), 7.22 – 7.14 (m, 3H, H_{5+7}), 3.67 – 3.53 (m, 1H, H_{10}), 2.94 – 2.83 (m, 2H, H_3), 2.82 – 2.74 (m, 2H, H_2), 2.39 (tt, *J* = 11.3, 3.5 Hz, 1H, H_8), 2.11 – 2.00 (m, 1H, H_9), 2.00 – 1.90 (m, 1H, H_9), 1.90 – 1.67 (m, 3H, H_{11+14}), 1.39 – 1.09 (m, 4H, H_{12+13}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.9 (C_1), 141.3 (C_4), 128.6 (2C, C_6), 128.4 (2C, C_5), 126.2 (C_7), 70.0 (C_{10}), 49.5 (C_8), 42.4 (C_2), 36.9 (C_9), 35.1 (C_3), 29.8 (C_{11}), 27.5 (C_{13}), 23.3 (C_{12}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O_2^+$) requires *m/z* 233.1536, found *m/z* 233.1531.

IR (neat) ν_{max}: = 3464, 3086, 3062, 3027, 2934, 2857, 1740, 1704, 1604, 1495, 1451, 1405, 1364, 1327, 1301, 1269, 1229, 1220, 1200, 1142, 1130, 1111, 1069, 1055, 1031, 966, 952, 928, 906, 850, 818, 748 cm^{-1}.

1.150 – *syn*-(3-Hydroxycyclohexyl)-3-[4-(trifluoromethyl)phenyl]propan-1-one



1.150

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 3-(4-(trifluoromethyl)phenyl)propanoyl chloride (49.7 mg, 0.21 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.150** (>20:1 r.r., 43.7 mg, 0.150 mmol, 73%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.30).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.1 Hz, 2H, H_6), 7.28 (d, J = 8.0 Hz, 2H, H_5), 3.66 – 3.57 (m, 1H, H_{11}), 2.94 (t, J = 7.4 Hz, 2H, H_3), 2.79 (dd, J = 11.1, 4.2 Hz, 2H, H_2), 2.39 (ddd, J = 11.4, 7.4, 3.5 Hz, 1H, H_9), 2.13 – 2.02 (m, 1H, H_{10}), 2.00 – 1.91 (m, 1H, H_{10}), 1.89 – 1.71 (m, 3H, H_{12+15}), 1.42 – 1.10 (m, 4H, H_{13+14}) ppm.

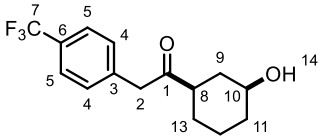
^{13}C NMR (101 MHz, $CDCl_3$): δ 211.2 (C_1), 145.5 (C_4), 129.1 (C_7),128.46 (2C, C_5), 127.10 (d, J = 273.2 Hz, C_8).128.46, 125.52 (q, J = 3.7 Hz, 2C, C_6), 69.9 (C_{11}), 49.4(C_9), 41.9 (C_2), 36.9 (C_{12}), 35.1 (C_3), 29.5 (C_5), 27.5 (C_{14}), 23.3 (C_{13}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -62.37 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{16}H_{20}F_3O_2^+$) requires *m/z* 301.1410, found *m/z* 301.1409.

IR (neat) ν_{max}: = 3341, 2934, 2858, 1710, 1667, 1618, 1467, 1451, 1418, 1364, 1323, 1269, 1230, 1191, 1162, 1122, 1109, 1067, 1018, 967, 952, 853, 830, 737 cm^{-1}.

1.151 – *syn*-1-(3-Hydroxycyclohexyl)-2-[4-(trifluoromethyl)phenyl]ethan-1-one



1.151

Synthesized following **GP-1**, using cyclohexene (46.7 mg, 0.200 mmol, 1.00 eq.), 2-(4-(trifluoromethyl)phenyl)acetyl chloride (20.7 µL, 27.4 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.151** (33.9 mg, 0.12 mmol, 59%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.26).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.1 Hz, 2H, H_5), 7.29 (d, J = 8.0 Hz, 2H, H_4), 3.82 (s, 2H, H_2), 3.71 – 3.54 (m, 1H, H_{10}), 2.54 (tt, J = 11.4, 3.6 Hz, 1H, H_8), 2.17 – 2.05 (m, 1H, H_9), 2.01 – 1.92 (m, 1H, H_9), 1.90 – 1.60 (m, 3H, H_{11+13}), 1.44 – 1.16 (m, 4H, H_{12-14}) ppm.

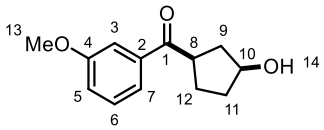
^{13}C NMR (101 MHz, $CDCl_3$): δ 208.9 (C_1), 138.2 (C_3), 130.0 (2C, C_4), 129.5 (q, J = 32.3 Hz, 2C, C_5), 128.3 (C_6), 125.7 (q, J = 3.8 Hz, C_7), 70.0 (C_{10}), 49.1 (C_8), 47.4 (C_2), 37.0 (C_9), 35.1 (C_{11}), 27.6 (C_{13}), 23.3 (C_{12}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.53 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}F_3O_2^+$) requires *m/z* 287.1253, found *m/z* 287.1245.

IR (neat) ν_{max}: = 3324, 2936, 2904, 2859, 1711, 1667, 1617, 1467, 1451, 1419, 1372, 1359, 1322, 1269, 1252, 1232, 1190, 1161, 1123, 1107, 1065, 1049, 1019, 998, 963, 916, 899, 852, 833, 815, 786 cm^{-1}.

1.164 – *syn*-1-(3-Hydroxycyclopentyl)(3-methoxyphenyl)methanone



1.164

Synthesized following **GP-1**, using cyclopentene (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), 3-methoxybenzoyl chloride (30.1 µL, 36.6 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.164** (34.1 mg, 0.160 mmol, 77%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.14).

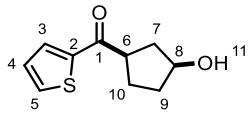
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.7 Hz, 1H, H_7), 7.53 – 7.48 (m, 1H, H_6), 7.38 (t, J = 7.9 Hz, 1H, H_3), 7.12 (dd, J = 8.0, 2.3 Hz, 1H, H_5), 4.43 – 4.32 (m, 1H, H_{10}), 3.94 – 3.87 (m, 1H, H_8), 3.85 (s, 3H, H_{13}), 3.09 (s, 1H, H_{14}), 2.18 – 2.04 (m, 3H, H_{9+11}), 2.03 – 1.92 (m, 1H, H_{9+11}), 1.88 – 1.78 (m, 2H, H_{12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.7 (C_1), 160.0 (C_4), 137.6 (C_2), 129.8 (C_3), 121.4 (C_6), 119.9 (C_7), 113.1 (C_5), 73.9 (C_{10}), 55.6 (C_{13}), 44.6 (C_8), 38.3 (C_9), 36.4 (C_{11}), 29.1 (C_{12}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}O_3Na^+$) requires *m/z* 243.0992, found *m/z* 243.0988.

IR (neat) ν_{max}: = 3404, 2942, 2837, 1677, 1595, 1581, 1486, 1464, 1450, 1430, 1349, 1316, 1286, 1257, 1200, 1170, 1082, 1045, 994, 960, 878, 797 cm^{-1}.

1.167 – *syn*-(3-Hydroxycyclopentyl)(thiophen-2-yl)methanone



1.167

Synthesized following **GP-1**, using cyclopentene (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), thiophene-2-carbonyl chloride (22.7 µL, 31.1 mg, 0.21 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.22 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.167** (14.5 mg, 70.0 µmol, 37%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.40).

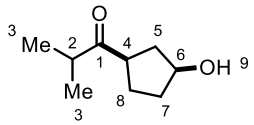
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 3.7 Hz, 1H, H_5), 7.69 (d, J = 4.9 Hz, 1H, H_3), 7.16 (t, J = 4.3 Hz, 1H, H_4), 4.36 (s, 1H, H_8), 3.80 (dq, J = 9.3, 6.2 Hz, 1H, H_6), 3.22 (s, 1H, H_{11}), 2.24 – 1.98 (m, 4H, H_{7+9}), 1.84 (ddd, J = 13.2, 8.7, 4.4 Hz, 2H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1 (C_1), 143.6 (C_5), 134.7 (C_3), 132.9 (C_4), 128.5 (C_2), 73.8 (C_8), 45.9 (C_6), 38.5 (C_7), 36.6 (C_9), 29.6 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{10}H_{12}O_2SNa^+$) requires *m/z* 219.0450, found *m/z* 219.0446.

IR (neat) ν_{max}: = 3399, 3093, 2955, 2362, 1737, 1653, 1518, 1414, 1353, 1239, 1080, 1059, 986, 844, 810, 728 cm^{-1}.

1.170 – *syn*-1-(3-Hydroxycyclopentyl)-2-methylpropan-1-one



1.170

Synthesized following **GP-1**, using cyclopentene (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), isobutyryl chloride (22.0 µL, 22.4 mg, 0.21 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.22 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.170** (27.7 mg, 0.11 mmol, 55%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.34).

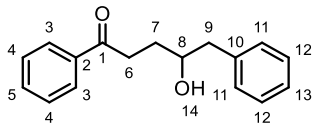
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28 (d, J = 2.6 Hz, 1H, H_6), 3.25 (tdd, J = 9.4, 5.8, 3.6 Hz, 1H, H_2), 3.11 (d, J = 7.8 Hz, 1H, H_4), 2.74 (hept, J = 6.9 Hz, 1H, H_5), 2.04 – 1.88 (m, 2H, H_{5+7}), 1.87 – 1.78 (m, 3H, H_{5+7+8}), 1.78 – 1.65 (m, 1H, H_8), 1.12 (dd, J = 6.9, 3.5 Hz, 6H, H_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 220.3 (C_1), 73.8 (C_6), 46.9 (C_4), 40.8 (C_2), 38.2 (C_5), 36.5 (C_7), 28.4 (C_8), 18.4 (C_3), 18.2 (C_3) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_9H_{16}O_2Na^+$) requires *m/z* 179.1043, found *m/z* 179.1037.

IR (neat) ν_{max}: = 3404, 2966, 2936, 2874, 1701, 1467, 1383, 1364, 1291, 1207, 1179, 1075, 1051, 960, 739 cm^{-1}.

1.183 – 4-Hydroxy-1,5-diphenylpentan-1-one



1.183

Synthesized following **GP-1**, using phenyl-1-butene (30.0 µL, 26.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.183** (>20:1 r.r., 37.6 mg, 0.120 mmol, 63%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.28).

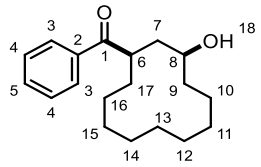
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.96 (m, 2H, H_3), 7.57 (*d*, J = 7.4 Hz, 1H, H_5), 7.48 (d, *J* = 7.8 Hz, 2H, H_4), 7.37 – 7.30 (m, 2H, H_{11}), 7.29 – 7.19 (m, 3H, H_{12+13}), 4.04 – 3.83 (m, 1H, H_8), 3.28 – 3.09 (m, 2H, H_9), 2.90 (dd, *J* = 13.5, 4.6 Hz, 1H, H_6), 2.77 (dd, *J* = 13.5, 8.2 Hz, 1H, H_6), 2.09 (dtd, *J* = 10.6, 7.3, 3.3 Hz, 1H, H_7), 1.96 – 1.84 (m, 2H, H_{7+14}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.8 (C_1), 138.4 ($C_{2\text{ or }10}$), 137.1 ($C_{2\text{ or }10}$), 133.2 ($C_{5\text{ or }13}$), 129.6 (2C, $C_{3,4,11\text{ or}12}$), 128.8 (2C, $C_{3,4,11\text{ or}12}$), 128.7 (2C, $C_{3,4,11\text{ or}12}$), 128.2 (2C, $C_{3,4,11\text{ or}12}$), 126.7($C_{5\text{ or }13}$), 72.3 (C_8), 44.6 (C_9), 35.1 (C_6), 30.9 (C_7) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}O_2Na^+$) requires *m/z* 277.1199, found *m/z* 277.1193.

IR (neat) ν_{max}: = 3062, 3029, 2925, 1715, 1602, 1584, 1494, 1451, 1315, 1271, 1176, 1111, 1069, 1026, 748 cm^{-1}.

1.189 – *syn*-(3-Hydroxycyclododecyl)(phenyl)methanone



1.189

Synthesized following **GP-1**, using cyclododecene (*E*/*Z* mixture, 193 µL, 166 mg, 1.00 mmol, 1.00 eq.), benzoyl chloride (122 µL, 148 mg, 1.05 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 378 mg, 1.10 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 10.0 mL) afforded compound **1.189** (124 mg, 0.430 mmol, 43%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 80:20, R_f = 0.34).

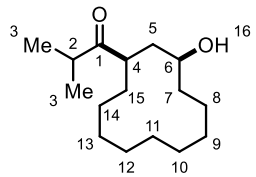
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (dd, *J* = 8.2, 1.1 Hz, 2H, H_3), 7.59 – 7.53 (m, 1H, H_5), 7.46 (dd, *J* = 10.7, 4.7 Hz, 2H, H_4), 3.97 (dd, *J* = 9.0, 4.3 Hz, 1H, H_8), 3.62 (ddt, *J* = 10.2, 7.0, 3.5 Hz, 1H, H_6), 2.27 (ddd, *J* = 14.9, 6.7, 5.2 Hz, 1H, H_7), 2.21 (s, 1H, H_{18}), 1.77 (dt, *J* = 15.0, 3.6 Hz, 1H, H_7), 1.70 (ddd, *J* = 13.8, 9.0, 4.3 Hz, 2H, H_9), 1.54 (ddd, *J* = 15.5, 9.8, 5.2 Hz, 3H, $H_{10\text{ to }17}$), 1.49 – 1.33 (m, 13H, $H_{10\text{ to }16}$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.3 (C_1), 136.7 (C_2), 133.0 (C_5), 128.8 (2C, C_4), 128.5 (2C, C_3), 68.0 (C_8), 40.1 (C_6), 33.4 (C_7), 32.6 (C_9), 28.9 (C_{17}), 24.8 ($C_{11\text{ to }16}$), 24.3 ($C_{11\text{ to }16}$), 23.9 ($C_{11\text{ to }16}$), 23.6 ($C_{11\text{ to }16}$), 23.2 ($C_{11\text{ to }16}$), 22.9 ($C_{11\text{ to }16}$), 21.9 ($C_{11\text{ to }16}$) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{28}O_2Na^+$) requires *m/z* 311.1982, found *m/z* 311.1976.

IR (neat) ν_{max}: = 3429, 2933, 2861, 2361, 1733, 1681, 1596, 1580, 1469, 1446, 1332, 1235, 1210, 1157, 1078, 1046, 1027, 989, 962, 784 cm^{-1}.

1.190 – *syn*-(3-Hydroxycyclododecyl)-2-methylpropan-1-one



1.190

Synthesized following **GP-1**, using cyclododecene (*E*/*Z* mixture, 38.5 µL, 33.3 mg, 0.200 mmol, 1.00 eq.), isobutyryl chloride (22.0 µL, 22.4 mg, 0.21 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.22 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.190** (21.8 mg, 90.0 µmol, 43%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.30).

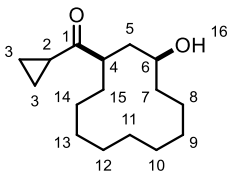
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (dd, J = 8.7, 4.1 Hz, 1H, H_6), 2.94 – 2.76 (m, 2H, H_{2+4}), 2.18 (s, 1H, H_{16}), 2.03 (ddd, J = 14.8, 6.5, 5.2 Hz, 1H, H_5), 1.70 – 1.51 (m, 3H, H_{5+7}), 1.48 – 1.16 (m, 18H, $H_{8\text{-}15}$), 1.09 (t, J = 6.6 Hz, 6H, H_3) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 219.6 (C_1), 67.9 (C_6), 43.7 (C_4), 39.9 (C_2), 33.5 (C_5), 32.5 (C_7), 27.8 (C_{15}), 24.7 ($C_{9\text{-}14}$), 24.1 ($C_{9\text{-}14}$), 23.9 ($C_{9\text{-}14}$), 23.4 ($C_{9\text{-}14}$), 23.1 ($C_{9\text{-}14}$), 23.1 ($C_{9\text{-}14}$), 21.9 ($C_{9\text{-}14}$), 19.2 (C_3), 18.7 (C_3) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{30}O_2Na^+$) requires m/z 277.2138, found m/z 277.2126.

IR (neat) ν_{max}: = 3444, 2934, 2864, 2361, 1704, 1469, 1446, 1383, 1345, 1267, 1189, 1158, 1080, 1026, 1004, 741 cm^{-1}.

1.191 – *syn*-Cyclopropyl(3-hydroxycyclododecyl)methanone



1.191

Synthesized following **GP-1**, using cyclododecene (*E*/*Z* mixture, 38.5 µL, 33.3 mg, 0.200 mmol, 1.00 eq.), isobutyryl chloride (22.0 µL, 22.4 mg, 0.21 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.191** (7.8 mg, 0.03 mmol, 16%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.20).

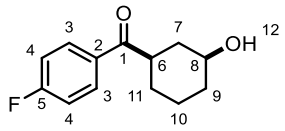
^{1}H NMR (700 MHz, $CDCl_3$): δ 3.88 (d, J = 4.2 Hz, 1H, H_6), 2.86 (d, J = 3.0 Hz, 1H, H_4), 2.58 (s, 1H, H_2), 2.09 (dt, J = 11.3, 5.4 Hz, 1H, H_5), 2.00 (dt, J = 12.1, 4.1 Hz, 1H, H_5), 1.79 (t, J = 9.2 Hz, 1H, H_7), 1.63 (dd, J = 13.8, 10.1 Hz, 2H, H_{7+15}), 1.47 (ddd, J = 28.1, 13.0, 6.8 Hz, 1H, H_{15}), 1.31 (m, 15H, $H_{8\text{-}14,\ 16}$), 1.05 (d, J = 6.1 Hz, 1H, H_3), 1.00 (d, J = 5.8 Hz, 1H, H_3), 0.90 (d, J = 7.6 Hz, 2H, H_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 216.0 (C_1), 67.7 (C_6), 46.8 (C_4), 32.7 (2C, C_{5+7}), 28.0 (C_{15}), 24.7 ($C_{8\text{-}14}$), 24.1 ($C_{8\text{-}14}$), 24.1 ($C_{8\text{-}14}$), 23.5 ($C_{8\text{-}14}$), 23.4 ($C_{8\text{-}14}$), 23.0 ($C_{8\text{-}14}$), 21.9 ($C_{8\text{-}14}$), 20.0 (C_2), 11.6 (C_3), 11.5 (C_3) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{28}O_2Na^+$) requires m/z 275.1982, found m/z 275.1973.

IR (neat) ν_{max}: = 3446, 3008, 2934, 2861, 2361, 1691, 1469, 1446, 1388, 1267, 1195, 1160, 1047, 1020, 889, 818, 741 cm^{-1}.

1.120 – *syn*-(4-Fluorophenyl)(3-hydroxycyclohexyl)methanone



1.120

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.20 mmol, 1.00 eq.), 4-fluorobenzoyl chloride (24.8 µL, 33.3 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.120** (>14:1 r.r., 22.1 mg, 0.100 mmol, 50%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.32).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 – 7.936 (m, 2H, H_3), 7.18 – 7.06 (m, 2H, H_4), 3.85 – 3.71 (m, 1H, H_8), 3.32 (tt, J = 11.3, 3.5 Hz, 1H, H_6), 2.12 (m, 1H, H_7), 2.06 – 2.00 (m, 1H, H_7), 1.94 – 1.87 (m, 2H, H_9), 1.87 – 1.81 (m, 1H, H_{11}), 1.52 (dd, J = 23.6, 11.2 Hz, 1H, H_{11}), 1.49 – 1.37 (m, 2H, H_{10+12}), 1.34 – 1.26 (m, 1H, H_{10}) ppm.

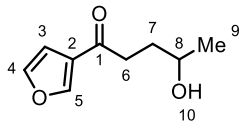
^{13}C NMR (151 MHz, $CDCl_3$): δ 200.9 (C_1), 166.7 (C_5), 164.3 (C_2), 131.1 (d, J = 9.3 Hz, 2C, C_3), 115.9 (d, J = 21.8 Hz, 2C, C_4), 70.1 (C_8), 44.1 (C_6), 37.8 (C_7), 35.3 (C_9), 28.6 (C_{11}), 23.5 (C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -105.29 (F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}FO_2^+$) requires *m/z* 223.1129, found *m/z* 223.1127.

IR (neat) ν_{max}: = 3399, 2936, 2859, 1677, 1596, 1505, 1466, 1450, 1410, 1374, 1359, 1319, 1298, 1262, 1230, 1205, 1185, 1156, 1136, 1105, 1057, 1013, 956, 944, 930, 883, 857, 843, 821, 777 cm^{-1}.

1.227 – 4-Ipomeanol



1.227

Synthesized following **GP-1**, using a 9% solution of 1-butene in hexane (185 µL, 0.200 mmol, 1.00 eq.), 3-furoyl chloride (20.7 µL, 27.4 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.227** (24.1 mg, 0.15 mmol, 73%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.36).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 7.96 (m, 1H, H_5), 7.48 – 7.39 (m, 1H, H_3), 6.77 (dd, J = 1.9, 0.8 Hz, 1H, H_4), 3.87 (dqd, J = 12.3, 6.2, 3.9 Hz, 1H, H_8), 2.91 (t, J = 7.1 Hz, 2H, H_6), 1.98 – 1.74 (m, 3H, H_{7+10}), 1.24 (d, J = 6.2 Hz, 3H, H_9) ppm.

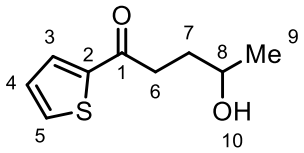
^{13}C NMR (101 MHz, $CDCl_3$): δ 195.6 (C_1), 147.4 (C_5), 144.4 (C_4), 127.8 (C_2), 108.8 (C_3), 67.6 (C_8), 36.8 (C_6), 33.1 (C_7), 24.0 (C_9) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_9H_{13}O_3^+$) requires *m/z* 169.0859, found *m/z* 169.0854.

IR (neat) ν_{max}: = 3425, 3135, 2967, 2928, 1718, 1671, 1562, 1510, 1455, 1394, 1376, 1349, 1306, 1243, 1156, 1132, 1046, 1019, 995, 955, 932, 903, 873, 821, 795 cm^{-1}.

Note: *the concentration of the commercially available 1-butene in hexane was determined by 1H NMR using mesitylene as an internal standard.*

1.233 – 4-Hydroxy-1-(thiophen-2-yl)pentan-1-one



1.233

Synthesized following **GP-1**, using a 9% solution of 1-butene in hexane (185 µL, 0.200 mmol, 1.00 eq.), 2-thenoyl chloride (20.7 µL, 27.4 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.233** (>20:1 r.r., 25.2 mg, 0.140 mmol, 68%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.39).

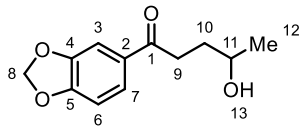
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 3.8, 1.1 Hz, 1H, H_5), 7.63 (dd, *J* = 5.0, 1.1 Hz, 1H, H_3), 7.12 (dd, *J* = 4.9, 3.8 Hz, 1H, H_4), 3.98 – 3.81 (m, 1H, H_8), 3.07 (t, *J* = 7.1 Hz, 2H, H_6), 1.95 (dtd, *J* = 11.2, 7.3, 3.9 Hz, 2H, H_{7+10}), 1.83 (ddt, *J* = 14.2, 8.2, 7.0 Hz, 1H, H_7), 1.24 (d, *J* = 6.2 Hz, 3H, H_9) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.8 (C_1), 144.3 (C_2), 133.8 (C_5), 132.2 (C_3), 128.3 (C_4), 67.6 (C_8), 35.8 (C_6), 33.5 (C_7), 23.9 (C_9) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_9H_{12}O_2SNa^+$) requires *m/z* 207.0450, found *m/z* 207.0449.

IR (neat) ν_{max}: = 3422, 3105, 3088, 2966, 2927, 2871, 2847, 1712, 1662, 1649, 1642, 1517, 1455, 1413, 1374, 1355, 1284, 1268, 1235, 1210, 1180, 1128, 1094, 1081, 1058, 1037, 1017, 980, 953, 929, 901, 851, 794 cm^{-1}.

1.235 – 1-(Benzo[*d*][1,3]dioxol-5-yl)-4-hydroxypentan-1-one



1.235

Synthesized following **GP-1**, using a 9% solution of 1-butene in hexane (185 µL, 0.200 mmol, 1.00 eq.), piperonyloyl chloride (38.8 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.235** (>10:1 r.r., 16.4 mg, 0.070 mmol, 37%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.46).

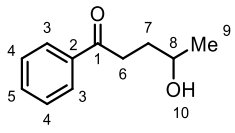
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (dd, J = 8.2, 1.7 Hz, 1H, H_7), 7.45 (d, J = 1.6 Hz, 1H, H_3), 6.85 (d, J = 8.2 Hz, 1H, H_6), 6.04 (s, 2H, H_8), 3.97 – 3.81 (m, 1H, H_{11}), 3.06 (td, J = 7.1, 1.6 Hz, 2H, H_9), 1.98 – 1.74 (m, 3H, H_{10+13}), 1.25 (d, J = 6.2 Hz, 3H, H_{12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.0 (C_1), 151.9 (C_5), 148.3 (C_4), 131.9 (C_2), 124.5 (C_7), 108.1 (C_3), 108.0 (C_6), 102.0 (C_8), 67.8 (C_{11}), 34.9 (C_9), 33.4 (C_{10}), 24.0 (C_{12}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}O_4Na^+$) requires *m/z* 245.0784, found *m/z* 245.0781.

IR (neat) ν_{max}: = 3341, 2968, 2923, 2852, 1740, 1712, 1677, 1671, 1616, 1603, 1505, 1487, 1441, 1376, 1352, 1326, 1281, 1260, 1242, 1202, 1164, 1129, 1110, 1069, 1037, 988, 961, 933, 899, 877, 856, 810, 783 cm^{-1}.

1.236 – 4-Hydroxy-1-phenylpentan-1-one



1.236

Synthesized following **GP-1**, using a 9% solution of 1-butene in hexane (185 µL, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.236** (29.7 mg, 0.17 mmol, 83%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.27).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 – 7.91 (m, 2H, H_3), 7.55 (t, J = 7.4 Hz, 1H, H_5), 7.45 (t, J = 7.6 Hz, 2H, H_4), 4.00 – 3.74 (m, 1H, H_8), 3.22 – 2.97 (m, 2H, H_6), 1.95 (dtd, J = 11.1, 7.3, 4.1 Hz, 2H, H_{7+10}), 1.92 – 1.70 (m, 1H, H_7), 1.25 (d, J = 6.2 Hz, 3H, H_9) ppm.

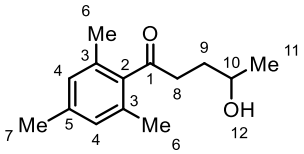
^{13}C NMR (101 MHz, $CDCl_3$): δ 200.9 (C_1), 137.0 (C_2), 133.2 (C_5), 128.7 (2C, C_3), 128.2 (2C, C_4), 67.7 (C_8), 35.1 (C_6), 33.2 (C_7), 24.0 (C_9) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{11}H_{15}O_2^+$) requires *m/z* 179.1067, found *m/z* 179.1051.

IR (neat) ν_{max}: = 3422, 3059, 2969, 2929, 1716, 1683, 1598, 1581, 1492, 1448, 1377, 1314, 1273, 1207, 1177, 1111, 1068, 1025, 911, 848, 759 cm^{-1}.

Note: *the concentration of the commercially available 1-butene in hexane was determined by 1H NMR using mesitylene as an internal standard.*

1.239 – 4-Hydroxy-1-mesitylpentan-1-one



1.239

Synthesized following **GP-1**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 2,4,6-trimethylbenzoyl chloride (35.0 µL, 38.4 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.239** (>20:1 r.r., 7.4 mg, 0.03 mmol, 17%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.40).

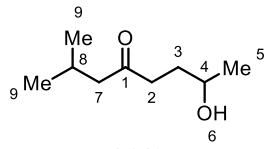
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 2H, H_4), 3.90 (dq, *J* = 12.3, 6.1 Hz, 1H, H_{10}), 2.85 (t, *J* = 7.0 Hz, 2H, H_9), 2.27 (s, 3H, H_7), 2.19 (s, 6H, H_6), 1.98 – 1.71 (m, 2H, H_9), 1.25 (d, *J* = 6.2 Hz, 4H, H_{11+12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.5 (C_1), 139.8 (C_5), 138.5 (C_2), 132.6 (2C, C_3), 128.6 (2C, C_4), 67.6 (C_{10}), 41.4 (C_8), 32.5 (C_9), 24.0 (C_{11}), 21.2 (C_7), 19.2 (2C, C_6) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}O_2Na^+$) requires *m/z* 243.1356, found *m/z* 243.1346.

IR (neat) ν_{max}: = 3460, 3233, 2968, 2956, 2919, 2850, 2568, 2499, 2370, 2332, 2273, 2235, 2191, 2163, 2114, 2037, 1944, 1739, 1715, 1698, 1612, 1576, 1540, 1453, 1378, 1351, 1326, 1263, 1231, 1218, 1130, 1111 cm^{-1}.

1.240 – 7-Hydroxy-2-methyloctan-4-one



1.240

Synthesized following **GP-1**, using a 9% solution of 1-butene in hexane (185 µL, 0.200 mmol, 1.00 eq.), isovaleryl chloride (25.6 µL, 25.3 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.240** (>20:1 r.r., 17.7 mg, 0.11 mmol, 56%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.29).

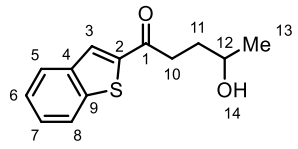
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 1H, H_4), 2.54 (t, J = 7.0 Hz, 2H, H_2), 2.31 (d, J = 7.0 Hz, 2H, H_7), 2.20 – 2.08 (m, 1H, H_8), 1.77 (dtd, J = 14.2, 7.2, 4.1 Hz, 2H, H_{3+6}), 1.66 (dt, J = 21.4, 7.0 Hz, 1H, H_3), 1.20 (d, J = 6.2 Hz, 3H, H_5), 0.91 (d, J = 6.6 Hz, 6H, H_9) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.8 (C_1), 67.7 (C_4), 52.1 (C_2), 39.8 (C_7), 32.7 (C_3), 24.8 (C_8), 23.9 (C_5), 22.7 (2C, C_9) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_9H_{18}O_2Na^+$) requires *m/z* 181.1199, found *m/z* 181.1197.

IR (neat) ν_{max}: = 3506, 3398, 2959, 2929, 2872, 1712, 1467, 1406, 1368, 1290, 1267, 1224, 1170, 1144, 1131, 1100, 1064, 1044, 1019, 962, 934, 740 cm^{-1}.

1.247 – 1-(Benzo[*b*]thiophen-2-yl)-4-hydroxypentan-1-one



1.247

Synthesized following **GP-1**, using a 9% solution of 1-butene in hexane (185 µL, 0.200 mmol, 1.00 eq.), benzo[*b*]thiophene-2-carbonyl chloride (42.1 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.247** (>10:1 r.r., 13.6 mg, 0.060 mmol, 29%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.46).

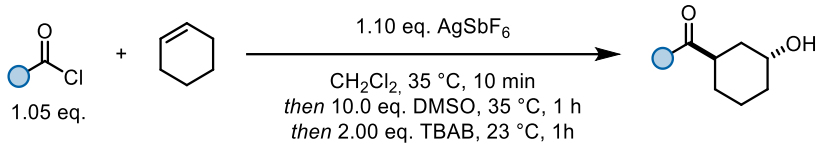
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H, H_3), 7.88 (t, J = 8.1 Hz, 2H, H_{5+8}), 7.51 – 7.43 (m, 1H, $H_{6\text{ or }7}$), 7.44 – 7.37 (m, 1H, $H_{6\text{ or }7}$), 3.99 – 3.83 (m, 1H, H_{12}), 3.23 – 3.10 (m, 2H, H_{10}), 2.00 (dtd, J = 11.2, 7.3, 3.7 Hz, 1H, H_{11}), 1.87 (dt, J = 21.3, 7.1 Hz, 1H, H_{11}), 1.76 (br s, 1H, H_{14}), 1.27 (d, J = 6.2 Hz, 3H, H_{13}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.2 (C_1), 143.7 (C_2), 142.7 (C_9), 139.3 (C_4), 129.3 ($C_{6\text{ or }7}$), 127.6 ($C_{6\text{ or }7}$), 126.1 ($C_{5\text{ or }8}$), 125.2 ($C_{5\text{ or }8}$), 123.2 (C_3), 67.6 (C_{12}), 35.7 (C_{10}), 33.5 (C_{11}), 24.0 (C_{13}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{14}O_2SNa^+$) requires *m/z* 257.0607, found *m/z* 257.0605.

IR (neat) ν_{max}: = 3392, 2966, 2925, 2870, 2852, 1711, .1665, 1652, 1594, 1514, 1457, 1429, 1408, 1375, 1349, 1329, 1282, 1269, 1254, 1234, 1215, 1171, 1157, 1127, 1079, 1066, 1017, 958, 940, 923, 902, 884, 866, 839 cm^{-1}.

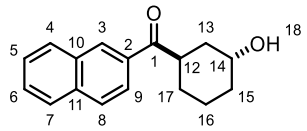
3.2.1.2 General Procedure 2: Synthesis of *anti*-1,3-Ketoalcohols



In an oven-dried vial at 23 °C, a solution of alkene (0.200 mmol, 1.00 eq.) and acyl chloride (0.21 mmol, 1.05 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) was treated with silver hexafluoroantimonate ($AgSbF_6$, 0.220 mmol, 1.10 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C. After vigorously stirring the reaction mixture at the same temperature for 10 min, dimethyl sulfoxide (DMSO, 2.00 mmol, 10.0 eq.) was added and the reaction mixture was stirred for 1 h at 35 °C. Then the reaction vial was removed from the oil bath and tetrabuthylammonium bromide (TBAB, 0.400 mmol, 2.00 eq.) dissolved in a minimum amount of dichloromethane was added and the reaction mixture was stirred for an additional 1 h at 23 °C. The reaction was stopped by addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL/0.10 mmol alkene substrate initially used), followed by vigorous stirring for 10 min. Then, the mixture was transferred to a separation funnel, diluted with dichloromethane (3.00 mL) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (3 × 5.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding *anti*-ketoalcohol.

Note: *For linear alkene substrates, the reaction time is increased from 10 minutes to 30 minutes in order to have more reproducible results.*

1.280 – *anti*-(3-Hydroxycyclohexyl)(naphthalen-2-yl)methanone



1.280

Synthesized following **GP-2**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 2-naphthoyl chloride (40.0 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142.0 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129 mg, 0.40 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.280** (34.6 mg, 0.140 mmol, 68%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.19).

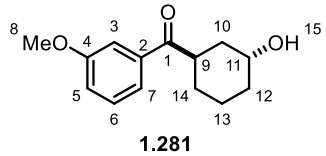
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H, H_3), 8.02 (dd, J = 8.6, 1.6 Hz, 1H, H_8), 7.96 (d, J = 8.0 Hz, 1H, $H_{(4\text{ or }7)}$), 7.92 – 7.81 (m, 2H, $H_{(4\text{ or }7)+9}$), 7.64 – 7.45 (m, 2H, H_{5+6}), 4.28 (d, J = 2.6 Hz, 1H, H_{14}), 3.97 (tt, J = 10.9, 3.5 Hz, 1H, H_{12}), 2.07 – 1.82 (m, 4H, H_{13+15}), 1.76 (ddd, J = 26.4, 16.0, 8.7 Hz, 2H, H_{17}), 1.69 – 1.49 (m, 3H, H_{16+18}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9 (C_1), 135.6 (C_2), 133.5 ($C_{10\text{ or }11}$), 132.7 ($C_{10\text{ or }11}$), 130.0 (C_3), 129.7 (C_4), 128.6 (C_6), 128.5 (C_8), 127.8 (C_7), 126.8 (C_9), 124.4 (C_5), 66.4 (C_{14}), 39.8 (C_{12}), 35.7 (C_{13}), 32.8 (C_{15}), 29.2 (C_{17}), 19.9 (C_{16}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{17}H_{19}O_2^+$) requires *m/z* 255.1380, found *m/z* 255.1379.

IR (neat) ν_{max}: = 3421, 3058, 2930, 2859, 2247, 1667, 1626, 1595, 1577, 1507, 1467, 1449, 1434, 1378, 1350, 1279, 1251, 1228, 1173, 1117, 1054, 974, 942, 907, 862, 821, 790 cm^{-1}.

1.281 – *anti*-(3-Hydroxycyclohexyl)(3-methoxyphenyl)methanone



1.281

Synthesized following **GP-2**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 3-methoxybenzoyl chloride (30.1 µL, 36.6 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142.0 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129 mg, 0.40 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.281** (19.5 mg, 0.080 mmol, 42%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.16).

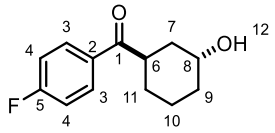
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.7 Hz, 1H, H_7), 7.50 – 7.46 (m, 1H, H_3), 7.36 (t, J = 7.9 Hz, 1H, H_6), 7.15 – 7.02 (m, 1H, H_5), 4.24 (d, J = 2.6 Hz, 1H, H_{11}), 3.85 (s, 3H, H_8), 3.77 (tt, J = 10.9, 3.5 Hz, 1H, H_9), 1.96 – 1.69 (m, 5H, $H_{10\text{-}15}$), 1.68 – 1.58 (m, 2H, $H_{10\text{-}15}$), 1.57 – 1.45 (m, 2H, $H_{10\text{-}15}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.8 (C_1), 160.0 (C_4), 137.7 (C_2), 129.7 (C_3), 121.1 (C_6), 119.4 (C_7), 112.9 (C_5), 66.3 (C_{11}), 55.6 (C_8), 39.9 (C_9), 35.7 (C_{10}), 32.8 (C_{12}), 29.1 (C_{14}), 19.9 (C_{13}) ppm.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}O_3^+$) requires *m/z* 235.1329, found *m/z* 235.1325.

IR (neat) ν_{max}: = 3413, 2933, 2860, 2362, 1674, 1596, 1581, 1487, 1450, 1430, 1373, 1315, 1287, 1255, 1197, 1168, 1120, 1035, 975, 885, 826, 784 cm^{-1}.

1.282 – *anti*-(4-Fluorophenyl)(3-hydroxycyclohexyl)methanone



1.282

Synthesized following **GP-2**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 4-fluorobenzoyl chloride (24.3 µL, 33.3 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129.0 mg, 0.400 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.282** (>20:1 r.r., 32.1 mg, 0.140 mmol, 72%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.27).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J = 8.5, 5.6 Hz, 2H, H_3), 7.11 (t, J = 8.6 Hz, 2H, H_4), 4.25 (s, 1H, H_8), 3.76 (ddd, J = 10.9, 7.0, 3.7 Hz, 1H, H_6), 1.95 – 1.68 (m, 5H, H_{7+9+12}), 1.67 – 1.44 (m, 4H, H_{11+10}) ppm.

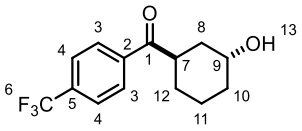
^{13}C NMR (151 MHz, $CDCl_3$): δ 200.8 (C_1), 166.7 (C_2), 132.5 (C_5), 131.09 (d, J = 9.0 Hz, 2C, C_3), 115.94 (d, J = 21.8 Hz, 2C, C_4)., 70.1 (C_8), 44.1 (C_6), 37.8 (C_7), 35.4 (C_9), 28.7 (C_{11}), 23.5 (C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -105.69 (F) ppm.

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{15}O_2FNa^+$) requires *m/z* 245.0948, found *m/z* 245.0948.

IR (neat) ν_{max}: = 3489, 2930, 2861, 1713, 1680, 1668, 1595, 1505, 1450, 1433, 1409, 1376, 1336, 1315, 1298, 1285, 1268, 1229, 1202, 1180, 1156, 1121, 1101, 1056, 1029, 1012, 984, 966, 926, 907, 889, 855, 842, 817 cm^{-1}.

1.283 – *anti*-(3-Hydroxycyclohexyl)[4-(trifluoromethyl)phenyl]methanone



1.283

Synthesized following **GP-2**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 4-(trifluoromethyl)benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142.0 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129 mg, 0.40 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.283** (27.3 mg, 0.10 mmol, 50%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.22).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.1 Hz, 2H, H_4), 7.71 (d, J = 8.2 Hz, 2H, H_3), 4.25 (d, J = 2.6 Hz, 1H, H_9), 3.79 (tt, J = 11.0, 3.5 Hz, 1H, H_7), 1.97 – 1.85 (m, 2H, H_8), 1.85 – 1.71 (m, 2H, H_{10}), 1.69 – 1.43 (m, 4H, H_{11+12}) ppm.

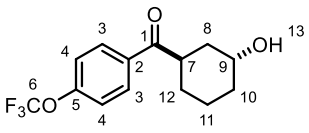
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.0 (C_1), 139.0 (C_2), 134.3 (q, J = 32.7 Hz, C_5), 128.8 (2C, C_3), 125.8 (q, J = 3.7 Hz, 2C, C_4), 123.8 (q, J = 545.7, 272.5 Hz, C_6), 66.2 (C_9), 40.2 (C_7), 35.4 (C_8), 32.8 (C_{10}), 28.8 (C_{12}), 19.8 (C_{11}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.11 (3F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_3O_2^+$) requires *m/z* 273.1097, found *m/z* 273.1096.

IR (neat) ν_{max}: = 3422, 2935, 2863, 1682, 1580, 1511, 1450, 1409, 1322, 1235, 1166, 1123, 1065, 1016, 967, 908, 890, 846, 807, 783 cm^{-1}.

1.284 – *anti*-(3-Hydroxycyclohexyl)[4-(trifluoromethoxy)phenyl]methanone



1.284

Synthesized following **GP-2**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 4-(trifluoromethoxy)benzoyl chloride (33.2 µL, 47.2 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129 mg, 0.400 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.284** (>20:1 r.r., 47.9 mg, 0.170 mmol, 83%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.39).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.6 Hz, 2H, H_3), 7.27 (d, J = 8.7 Hz, 2H, H_4), 4.25 (s, 1H, H_9), 3.76 (tt, J = 11.1, 3.3 Hz, 1H, H_7), 2.00 – 1.70 (m, 5H, $H_{8+10+12}$), 1.68 – 1.57 (m, 3H, $H_{11+12+13}$), 1.51 (ddd, J = 24.6, 12.8, 3.6 Hz, 1H, H_{11}) ppm.

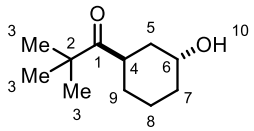
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4 (C_1), 152.6 (C_5), 134.5 (C_2), 130.5 (2C, C_3), 120.6 (2C, C_4), 120.4 (q, J = 258.9 Hz, C_6), 66.2 (C_9), 39.9 (C_7), 35.5 (C_8), 32.8 (C_{10}), 28.9 (C_{12}), 19.8 (C_{11}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -57.63 (3F) ppm.

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}O_3F_3Na^+$) requires *m/z* 311.0866, found *m/z* 311.0865.

IR (neat) ν_{max}: = 3427, 2935, 2863, 1713, 1682, 1602, 1587, 1505, 1451, 1434, 1413, 1377, 1312, 1302, 1254, 1204, 1154, 1120, 1107, 1056, 1032, 1016, 967, 925, 907, 890, 861, 844, 813, 795 cm^{-1}.

1.285 – *anti*-1-(3-Hydroxycyclohexyl)-2,2-dimethylpropan-1-one



1.285

Synthesized following **GP-2**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), pivaloyl chloride (25.9 µL, 25.3 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129.0 mg, 0.400 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.285** (22.4 mg, 0.120 mmol, 61%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.25).

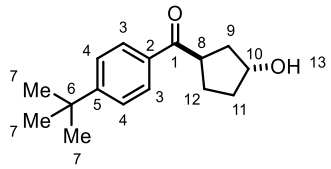
^{1}H NMR (700 MHz, $CDCl_3$): δ 4.18 (dd, J = 5.9, 2.9 Hz, 1H, H_6), 3.42 – 3.27 (m, 1H, H_4), 1.75 – 1.68 (m, 2H, H_5), 1.67 – 1.61 (m, 3H, H_7), 1.59 – 1.51 (m, 2H, H_9), 1.50 – 1.42 (m, 1H, H_8), 1.43 – 1.35 (m, 1H, H_{10}), 1.14 (s, 9H, H_3) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 219.0 (C_1), 66.2 (C_6), 45.0 (C_2), 38.5 (C_4), 36.0 (C_5), 32.4 (C_7), 29.5 (C_9), 26.1 (3C, C_3), 19.5 (C_8) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}O_2^+$) requires *m/z* 185.1536, found *m/z* 185.1536.

IR (neat) ν_{max}: = 3424, 2930, 2865, 1689, 1478, 1450, 1394, 1366, 1314, 1269, 1225, 1180, 1129, 1072, 1014, 981, 887, 857, 822, 789 cm^{-1}.

1.288 – *anti*-[4-(*tert*-Butyl)phenyl](3-hydroxycyclopentyl)methanone



1.288

Synthesized following **GP-2**, using cyclopentene (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), 4-*tert*-butylbenzoyl chloride (41.3 µL, 41.3 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129 mg, 0.400 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.288** (37.3 mg, 0.140 mmol, 71%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.22).

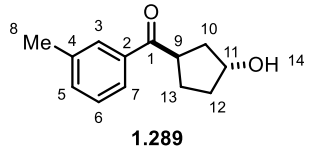
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 – 7.89 (m, 2H, H_4), 7.58 – 7.39 (m, 2H, H_3), 4.52 (dt, J = 7.1, 2.3 Hz, 1H, H_9), 4.04 (qd, J = 8.6, 6.0 Hz, 1H, H_7), 2.65 (s, 1H, H_{12}), 2.28 – 2.13 (m, 2H, H_8), 2.03 – 1.83 (m, 3H, H_{10+11}), 1.82 – 1.68 (m, 1H, H_{11}), 1.34 (d, J = 2.4 Hz, 9H, H_6) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.0 (C_1), 156.8 (C_5), 134.1 (C_2), 128.6 (2C, C_3), 125.7 (2C, C_4), 74.2 (C_{10}), 44.2 (C_8), 39.0 (C_9), 35.3 (C_{11}), 35.2 (C_6), 31.2 (3C, C_7), 27.8 (C_{12}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}O_2^+$) requires *m/z* 247.1693, found *m/z* 247.1690.

IR (neat) ν_{max}: = 3420, 2963, 2870, 2248, 1673, 1604, 1565, 1462, 1408, 1363, 1299, 1268, 1226, 1190, 1109, 1009, 974, 909, 847, 779 cm^{-1}.

1.289 – *anti*-(3-Hydroxycyclopentyl)(m-tolyl)methanone



1.289

Synthesized following **GP-2**, using cyclopentene (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), *m*-toluoyl chloride (27.7 µL, 32.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129 mg, 0.40 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.289** (32.5 mg, 0.150 mmol, 74%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.23).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.73 (m, 2H, H_{3+7}), 7.40 – 7.32 (m, 2H, H_{5+6}), 4.51 (td, *J* = 4.8, 2.4 Hz, 1H, H_{11}), 4.12 – 3.93 (m, 1H, H_9), 2.40 (s, 3H, H_8), 2.26 – 2.13 (m, 2H, H_{10}), 1.99 – 1.87 (m, 3H, H_{12+13}), 1.83 (s, 1H, H_{14}), 1.77 – 1.67 (m, 1H, H_{33}) ppm.

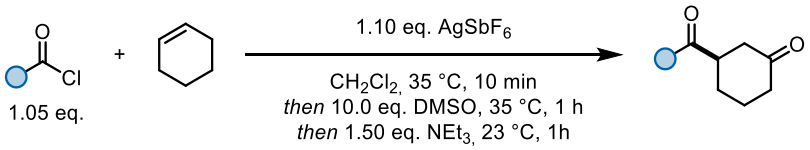
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.7 (C_1), 138.5 (C_4), 136.8 (C_2), 133.8 (C_5), 129.1 (C_6), 128.6 (C_3), 125.8 (C_7), 74.1 (C_{11}), 44.3 (C_9), 39.0 (C_{10}), 35.2 (C_{12}), 27.8 (C_{13}), 21.5 (C_8) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}O_2^+$) requires *m/z* 205.1223, found *m/z* 205.1219.

IR (neat) ν_{max}: = 3408, 3047, 2938, 2868, 1675, 1602, 1584, 1485, 1432, 1354, 1306, 1249, 1165, 1017, 976, 938, 914, 842, 796 cm^{-1}.

3.2.2 Synthesis of 1,4-Dicarbonyl Compounds

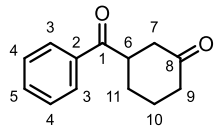
3.2.2.1 General Procedure 3: Synthesis of 1,4-Dicarbonyl Compounds



In an oven-dried vial at 23 °C, a solution of alkene (0.200 mmol, 1.00 eq.) and acyl chloride (0.21 mmol, 1.05 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) was treated with silver hexafluoroantimonate ($AgSbF_6$, 0.220 mmol, 1.10 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C. After vigorously stirring the reaction mixture at the same temperature for 10 min, dimethyl sulfoxide (DMSO, 2.00 mmol, 10.0 eq.) was added and the reaction mixture was stirred for 1 h at 35 °C. Then the reaction vial was removed from the oil bath and triethyl amine (NEt_3, 0.300 mmol, 1.50 eq.) was added and the reaction mixture was stirred for an additional 1 h at 23 °C. The reaction was stopped by addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL/0.100 mmol alkene substrate initially used), followed by vigorous stirring for 10 min. Then, the mixture was transferred to a separation funnel, diluted with dichloromethane (3.00 mL) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (3 × 5.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding 1,4-dicarbonyl compounds.

Note: *In the cases where regioisomeric mixtures were formed, this has been indicated.*

1.264 – 3-Benzoylcyclohexan-1-one



1.264

Synthesized following **GP-3**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), triethyl amine (NEt_3, 41.8 µL, 30.4 mg, 0.400 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.264** (32.7 mg, 0.160 mmol, 81%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.28).

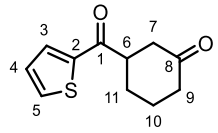
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.86 (m, 2H, H_3), 7.59 (t, J = 7.4 Hz, 1H, H_5), 7.48 (t, J = 7.7 Hz, 2H, H_4), 3.81 (ddd, J = 14.2, 6.9, 3.6 Hz, 1H, H_6), 2.69 (s, 1H, H_7), 2.48 (dd, J = 14.7, 4.3 Hz, 1H, H_7), 2.45 – 2.34 (m, 2H, H_9), 2.18 – 1.98 (m, 2H, H_{11}), 1.93 – 1.73 (m, 2H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.4 (C_8), 200.5 (C_1), 135.5 (C_2), 133.6 (C_5), 129.0 (2C, C_4), 128.5 (2C, C_3), 45.3 (C_6), 43.3 (C_7), 41.1 (C_9), 28.5 (C_{10}), 25.0 (C_{11}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_2^+$) requires *m/z* 203.1067, found *m/z* 203.1066.

IR (neat) ν_{max}: = 2944, 2868, 1709, 1676, 1596, 1580, 1448, 1420, 1375, 1346, 1315, 1262, 1220, 1178, 1106, 1011, 987, 959, 907, 883, 852, 754 cm^{-1}.

1.269 – 3-(Thiophene-2-carbonyl)cyclohexan-1-one



1.269

Synthesized following **GP-3**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 2-thenoyl chloride (22.7 µL, 31.1 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), triethyl amine (NEt_3, 41.8 µL, 30.4 mg, 0.400 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.269** (21.3 mg, 0.100 mmol, 51%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.18).

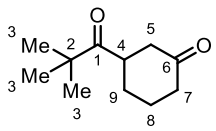
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 3.6 Hz, 1H, H_5), 7.68 (d, J = 4.9 Hz, 1H, H_3), 7.17 – 7.12 (m, 1H, H_3), 3.63 (tt, J = 10.7, 3.9 Hz, 1H, H_6), 2.72 (dd, J = 14.5, 11.0 Hz, 1H, H_7), 2.48 (dd, J = 14.7, 4.3 Hz, 1H, H_9), 2.44 – 2.32 (m, 2H, $H_{7,\,9\text{ or }11}$), 2.21 – 2.05 (m, 2H, $H_{9\text{ or }11}$), 2.02 – 1.76 (m, 2H, H_{11}) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 210.1 (C_1), 193.3 (C_8), 142.8 (C_2), 134.7 (C_3), 132.3 (C_5), 128.5 (C_4), 47.0 (C_6), 43.3 (C_7), 41.1 (C_9), 28.9 (C_{10}), 25.0 (C_{11}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{11}H_{13}O_2S^+$) requires m/z 209.0631, found m/z 209.0630.

IR (neat) ν_{max}: = 3090, 2946, 2869, 2361, 1710, 1656, 1518, 1449, 1414, 1375, 1352, 1316, 1265, 1239, 1223, 1201, 1180, 1146, 1106, 1081, 1059, 1040, 942, 896, 859, 842, 826, 757 cm^{-1}.

1.270 – 3-Pivaloylcyclohexan-1-one



1.270

Synthesized following **GP-3**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), pivaloyl chloride (25.9 µL, 25.3 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), triethyl amine (NEt_3, 41.8 µL, 30.4 mg, 0.400 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.270** (13.7 mg, 0.08 mmol, 38%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 83:17, R_f = 0.30).

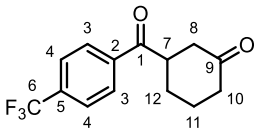
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (dtd, J = 10.3, 8.1, 4.0 Hz, 1H, H_4), 2.65 – 2.49 (m, 1H, H_5), 2.45 – 2.30 (m, 2H, H_{5+7}), 2.24 (ddd, J = 12.8, 3.9, 1.9 Hz, 1H, H_7), 2.11 (ddd, J = 13.9, 7.7, 4.2 Hz, 1H, H_9), 1.92 – 1.61 (m, 3H, H_{8+9}), 1.14 (s, 9H, H_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 215.8 (C_1), 210.6 (C_6), 44.5 (C_2), 44.9 (C_4), 44.4 (C_5), 41.1 (C_7), 28.8 (C_9), 26.0 (3C, C_3), 25.4 (C_8) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{11}H_{19}O_2^+$) requires m/z 183.1380, found m/z 183.1379.

IR (neat) ν_{max}: = 2956, 2871, 1703, 1479, 1367, 1225, 1064, 971, 739 cm^{-1}.

1.271 – 3-[4-(Trifluoromethyl)benzoyl]cyclohexan-1-one



1.271

Synthesized following **GP-3**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), 4-(trifluorometyl)benzoyl chloride (32.2 µL, 45.2 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), triethyl amine (NEt_3, 41.8 µL, 30.4 mg, 0.400 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.271** (30.0 mg, 0.110 mmol, 56%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.22).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.2 Hz, 2H, H_3), 7.75 (d, *J* = 8.2 Hz, 2H, H_4), 3.90 – 3.75 (m, 1H, H_7), 2.71 (dd, *J* = 14.6, 10.6 Hz, 1H, H_8), 2.54 – 2.45 (m, 1H, H_{10}), 2.45 – 2.35 (m, 2H, $H_{8,\ 10\ or\ 12}$), 2.18 – 2.02 (m, 2H, $H_{8,\ 10\ or\ 12}$), 1.95 – 1.75 (m, 2H, H_{11}) ppm.

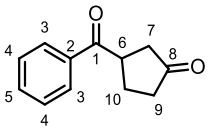
^{13}C NMR (101 MHz, $CDCl_3$): δ 209.7 (C_1), 199.7 (C_9), 138.2 (C_2) 134.9 (q, *J* = 32.8 Hz, C_5), 128.9 (2C, C_3), 126.1 (q, *J* = 3.7 Hz, 2C, C_4), 123.6 (q, *J* = 272.7 Hz, C_6), 45.6 (C_7), 43.0 (C_8), 41.1 (C_{10}), 28.3 (C_{12}), 24.8 (C_{11}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -63.20 (3F) ppm.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{14}F_3O_2^+$) requires *m/z* 271.0940, found *m/z* 271.0940.

IR (neat) ν_{max}: = 3071, 2948, 2872, 2363, 1713, 1686, 1580, 1511, 1451, 1410, 1323, 1264, 1222, 1167, 1126, 1113, 1066, 1036, 1014, 989, 961, 908, 846, 794 cm^{-1}.

1.272 – 3-3-benzoylcyclopentan-1-one



1.272

Synthesized following **GP-3**, using cyclopentene (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), triethyl amine (NEt_3, 41.8 µL, 30.4 mg, 0.400 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.272** (27.7 mg,

0.150 mmol, 74%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.22).

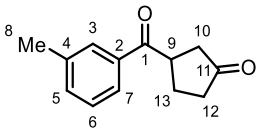
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.3 Hz, 2H, H_3), 7.61 (t, J = 7.4 Hz, 1H, H_5), 7.50 (t, J = 7.6 Hz, 2H, H_4), 4.13 (p, J = 7.5 Hz, 1H, H_6), 2.71 (dd, J = 18.4, 7.9 Hz, 1H, H_7), 2.50 – 2.24 (m, 4H, $H_{7,\,9\text{ and }10}$), 2.23 – 2.06 (m, 1H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 217.0 (C_1), 200.4 (C_8), 135.7 (C_2), 133.7 (C_5), 129.0 (2C, C_4), 128.6 (2C, C_3), 43.2 (C_6), 41.1 (C_6), 37.5 (C_9), 27.1 (C_{10}) ppm.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{12}H_{13}O_2^+$) requires *m/z* 189.0910, found *m/z* 189.0908.

IR (neat) ν_{max}: = 3061, 2969, 2363, 1737, 1673, 1596, 1579, 1448, 1403, 1365, 1264, 1221, 1158, 1133, 1074, 1005, 980, 950, 909, 883, 807, 777 cm^{-1}.

1.273 – 3-(3-Methylbenzoyl)cyclopentan-1-one



1.273

Synthesized following **GP-3**, using cyclopente (17.7 µL, 13.6 mg, 0.200 mmol, 1.00 eq.), m-toluoyl chloride (22.7 µL, 31.1 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), triethyl amine (NEt_3, 41.8 µL, 30.4 mg, 0.400 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.273** (25.9 mg, 0.130 mmol, 64%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.29).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 9.2 Hz, 2H, H_{3+7}), 7.45 – 7.32 (m, 2H, H_{5+6}), 4.12 (dd, J = 15.1, 7.6 Hz, 1H, H_9), 2.70 (dd, J = 18.4, 7.9 Hz, 1H, H_{10}), 2.47 (d, J = 8.0 Hz, 1H, H_{10}), 2.43 (s, 3H, H_8), 2.42 – 2.23 (m, 3H, H_{12+13}), 2.21 – 2.10 (m, 1H, H_{13}) ppm.

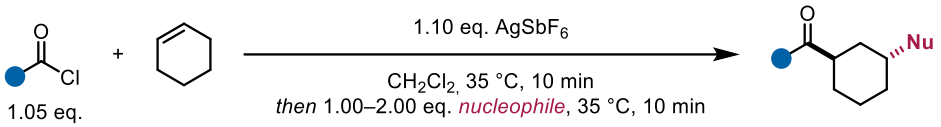
^{13}C NMR (101 MHz, $CDCl_3$): δ 217.1 (C_1), 200.6 (C_{11}), 138.9 (C_4), 135.8 (C_2), 134.4 (C_5), 129.1 (C_6), 128.8 (C_3), 125.8 (C_7), 43.2 (C_9), 41.2 (C_{10}), 37.5 (C_{12}), 27.2 (C_{13}), 21.5 (C_8) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_2^+$) requires *m/z* 203.1067, found *m/z* 203.1065.

IR (neat) ν_{max}: = 3049, 2961, 2922, 1738, 1674, 1602, 1585, 1485, 1458, 1426, 1404, 1363, 1264, 1249, 1177, 1154, 1088, 1033, 1015, 981, 954, 912, 845, 805, 777 cm^{-1}.

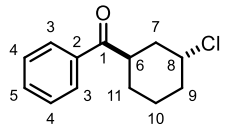
3.2.3 Reaction of Oxocarbenium Ions with Different Nucleophiles

3.2.3.1 General Procedure 4: Synthesis using different nucleophiles



In an oven-dried vial at 23 °C, a solution of alkene (0.200 mmol, 1.00 eq.) and acyl chloride (0.21 mmol, 1.05 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) was treated with silver hexafluoroantimonate ($AgSbF_6$, 0.220 mmol, 1.10 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C. After vigorously stirring the reaction mixture at the same temperature for 10 min, dimethyl sulfoxide (DMSO, 2.00 mmol, 10.0 eq.) was added and the reaction mixture was stirred for 1 h at 35 °C. Then the reaction vial was removed from the oil bath and the corresponding nucleophile (0.20–0.40 mmol, 1.00–2.00 eq.) was added and the reaction mixture was stirred for an additional 10 min at 23 °C. The reaction was stopped by addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL/0.10 mmol alkene substrate initially used), followed by vigorous stirring for 10 min. Then, the mixture was transferred to a separation funnel, diluted with dichloromethane (3.00 mL) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (3 × 5.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding 1,3-functionalized product.

1.300 – *anti*-(3-Chlorocyclohexyl)(phenyl)methanone



1.300

Synthesized following **GP-4**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) dimethylsulfoxide (DMSO, 142 µL, 2.00 mmol, 10.0 eq.), tetrabutylammonium bromide (TBAB, 129.0 mg, 0.400 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.300** (37.9 mg, 0.170 mmol, 83%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 95:5, R_f = 0.35).

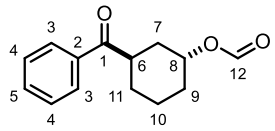
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 – 7.93 (m, 2H, H_3), 7.61 – 7.53 (m, 1H, H_5), 7.47 (t, *J* = 7.7 Hz, 2H, H_4), 4.65 (dd, *J* = 6.8, 3.4 Hz, 1H, H_8), 3.89 (tt, *J* = 11.1, 3.3 Hz, 1H, H_6), 2.21 – 2.13 (m, 1H, H_7), 2.08 – 1.92 (m, 4H, $H_{7,\ 9,\ 10\ and\ 11}$), 1.86 – 1.78 (m, 1H, H_9), 1.74 – 1.66 (m, 1H, H_{10}), 1.58 – 1.47 (m, 1H, H_{11}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 203.0 (C_1), 136.0 (C_2), 133.2 (C_5), 128.9 (2C, C_4), 128.5 (2C, C_3), 59.4 (C_8), 39.8 (C_6), 36.8 (C_7), 33.7 (C_9), 28.8 (C_{11}), 20.0 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}ClO^+$) requires *m/z* 223.0884, found *m/z* 223.0884.

IR (neat) ν_{max}: = 3060, 2940, 2862, 1677, 1596, 1579, 1447, 1430, 1375, 1339, 1322, 1268, 1224, 1201, 1175, 1138, 1098, 1076, 1020, 1001, 968, 910, 862, 818, 791 cm^{-1}.

1.298 – *anti*-3-Benzoylcyclohexyl formate



1.298

Synthesized following **GP-4**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.), *N*,*N*-dimethylformamide (DMF, 155 µL, 146 mg, 2.00 mmol, 10.0 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.298** (31.6 mg, 0.140 mmol, 68%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 83:17, R_f = 0.46).

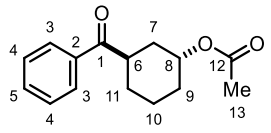
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.14 (s, 1H, H_{12}), 7.94 (d, J = 7.4 Hz, 2H, H_3), 7.56 (t, J = 7.4 Hz, 1H, H_5), 7.46 (t, J = 7.7 Hz, 2H, H_4), 5.37 (s, 1H, H_8), 3.70 (tt, J = 11.5, 3.4 Hz, 1H, H_6), 2.03 (d, J = 14.4 Hz, 1H, H_7), 1.95 (dd, J = 21.4, 11.2 Hz, 2H, H_{7+9}), 1.90 – 1.83 (m, 1H, H_9), 1.79 – 1.67 (m, 2H, H_{11}), 1.62 – 1.55 (m, 1H, H_{10}), 1.51 (ddd, J = 25.0, 12.6, 3.9 Hz, 1H, H_{10}) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 202.9 (C_1), 160.6 (C_{12}), 136.0 (C_2), 133.2 (C_5), 128.8 (2C, C_4), 128.4 (2C, C_3), 69.8 (C_8), 40.1 (C_6), 32.5 (C_7), 29.6 (C_9), 29.0 (C_{11}), 20.3 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}O_3Na^+$) requires *m/z* 255.0992, found *m/z* 255.0980.

IR (neat) ν_{max}: = 2939, 2863, 1716, 1679, 1597, 1579, 1448, 1378, 1283, 1242, 1175, 1110, 1026, 1002, 975, 937, 885, 822, 792 cm^{-1}.

1.299 – *anti*-3-Benzoylcyclohexyl acetate



1.299

Synthesized following **GP-4**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.), *N*,*N*-dimethylacetamide (DMA, 186 µL, 175 mg, 1.00 mmol, 10.0 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.299** (32.4 mg, 0.130 mmol, 66%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.28).

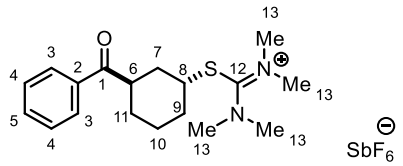
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H, H_3), 7.58 – 7.53 (m, 1H, H_5), 7.50 – 7.43 (m, 2H, H_4), 5.28 – 5.22 (m, 1H, H_8), 3.67 (tt, *J* = 11.5, 3.5 Hz, 1H, H_6), 2.12 (s, 3H, H_{13}), 2.01 (dddd, *J* = 14.3, 5.7, 3.8, 2.0 Hz, 1H, H_7), 1.97 – 1.93 (m, 1H, H_7), 1.93 – 1.88 (m, 1H, H_9), 1.83 (ddd, *J* = 14.3, 11.6, 2.8 Hz, 1H, H_{11}), 1.78 – 1.65 (m, 2H, H_{9+11}), 1.57 – 1.45 (m, 2H, H_{10}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 203.1 (C_1), 170.5 (C_{12}), 136.2 (C_2), 133.1 (C_5), 128.8 (2C, C_4), 128.4 (2C, C_3), 69.6 (C_8), 40.3 (C_6), 32.6 (C_7), 29.6 (C_9), 29.1 (C_{11}), 21.6 (C_{10}), 20.5 (C_{13}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}O_3Na^+$) requires *m/z* 269.1148, found *m/z* 269.1146.

IR (neat) ν_{max}: = 2939, 2862, 1733, 1680, 1597, 1580, 1448, 1375, 1236, 1207, 1180, 1146, 1113, 1018, 977, 960, 887, 830, 792 cm^{-1}.

1.340 – *anti*-2-(3-Benzoylcyclohexyl)-1,1,3,3-tetramethylisothiouronium hexafluoroantimonate



1.340

Synthesized following **GP-4**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.), tetramethylthiourea (TMTU, 106 mg, 0.800 mmol, 4.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.340** (79.9 mg, 0.140 mmol, 72%) as a white solid after purification by column chromatography (dichlormethane/methanol = 95:5, R_f = 0.48).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.3 Hz, 2H, H_3), 7.56 (t, J = 7.3 Hz, 1H, H_5), 7.47 (t, J = 7.5 Hz, 2H, H_4), 3.99 – 3.88 (m, 1H, H_8), 3.81 – 3.70 (m, 1H, H_6), 3.30 (s, 12H, H_{13}), 2.14 (dd, J = 9.4, 4.0 Hz, 1H, H_7), 1.93 (dd, J = 13.9, 8.0 Hz, 1H, H_9), 1.91 – 1.78 (m, 3H, H_{7+11}), 1.71 (dd, J = 10.3, 3.9 Hz, 1H, H_{10}), 1.51 (ddd, J = 13.6, 11.3, 3.2 Hz, 2H, H_{10+11}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 203.3 (C_1), 174.6 (C_{12}), 135.7 (C_2), 133.4 (C_5), 129.0 (2C, C_4), 128.4 (2C, C_3), 45.7 (C_8), 44.0 (4C, C_{13}), 41.6 (C_6), 34.3 (C_7), 31.7 (C_9), 27.7 (C_{11}), 22.2 (C_{10}) ppm.

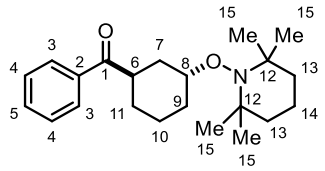
^{19}F NMR (565 MHz, $CDCl_3$): δ -114.8, -117.3, -121.7, -125.3, -129.7, -132.1 (SbF_6) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M\text{-}SbF_6]^+$ ($C_{18}H_{27}N_2OS^+$) requires *m/z* 319.1839, found *m/z* 319.1837.

HRMS (ESI$^-$): exact mass calculated for $[SbF_6]^-$ requires *m/z* 234.8946, found *m/z* 234.8948.

IR (neat) ν_{max}: = 2942, 2860, 1734, 1676, 1593, 1505, 1449, 1395, 1340, 1321, 1255, 1226, 1208, 1165, 1140, 1113, 1077, 1057, 1017, 994, 968, 910, 870, 817, 793 cm^{-1}.

1.329 – *anti*-Phenyl{3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]cyclohexyl}methanone



1.329

Synthesized following **GP-4**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 63.8 mg, 0.400 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.329** (54.7 mg, 0.160 mmol, 80%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 95:5, R_f = 0.24).

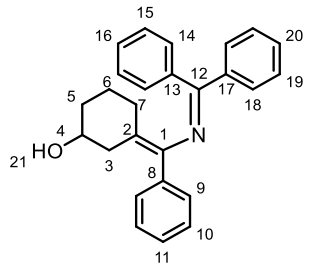
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 – 7.91 (m, 2H, H_3), 7.55 (t, J = 7.3 Hz, 1H, H_5), 7.46 (t, J = 7.5 Hz, 2H, H_4), 4.13 – 4.00 (m, 1H, H_8), 3.72 (tt, J = 10.9, 3.4 Hz, 1H, H_6), 2.16 (d, J = 13.5 Hz, 1H, H_7), 2.12 – 2.03 (m, 1H, H_9), 1.93 – 1.81 (m, 1H, H_{10}), 1.80 – 1.51 (m, 5H, $H_{7, 9\text{-}11}$), 1.47 (s, 4H, H_{13}), 1.43 – 1.34 (m, 2H, H_{14}), 1.20 (s, 6H, H_{15}), 1.15 (s, 6H, H_{15}) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 204.2 (C_1), 136.5 (C_2), 132.9 (C_5), 128.7 (2C, C_4), 128.5 (2C, C_3), 78.1 (C_8), 59.4 (2C, C_{12}, according to HMBC), 40.9 (C_6), 40.5 (2C, C_{13}), 34.6 (2C, C_{15}, according to HSQC), 34.1 (C_7), 30.3 (C_9), 29.1 (C_{11}), 20.9 (C_{10}), 20.1 (2C, C_{15}, according to HSQC), 17.3 (C_{14}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{22}H_{34}NO_2^+$) requires *m/z* 344.2584, found *m/z* 344.2572.

IR (neat) ν_{max}: = 3058, 3000, 2970, 2930, 2867, 2359, 2339, 1717, 1681, 1597, 1580, 1541, 1447, 1374, 1360, 1337, 1299, 1279, 1258, 1237, 1209, 1180, 1158, 1132, 1117, 1082, 1044, 1028, 1001, 908, 879, 820, 792 cm^{-1}

1.341 – (*E*)-3-{[(Diphenylmethylene)amino](phenyl)methylene}cyclohexan-1-ol



1.341

Synthesized following **GP-4**, using cyclohexene (20.3 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.21 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.22 mmol, 1.10 eq.), benzophenone imine (50.3 µL, 54.4 mg, 0.30 mmol, 1.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.341** (16.4 mg, 0.04 mmol, 22%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.25). The compound **1.341** was isolated as 10:1 stereoisomeric mixture.

^{1}H NMR (400 MHz, $CDCl_3$): (*major isomer*) δ 7.71 (d, J = 7.5 Hz, 2H, H_{18}), 7.42 (t, J = 7.3 Hz, 1H, H_{20}), 7.37 – 7.32 (m, 3H, H_{16+19}), 7.30 – 7.24 (m, 2H, H_{15}), 7.18 – 7.09 (m, 3H, H_{10+11}), 7.02 (d, J = 6.7 Hz, 2H, H_9), 6.97 – 6.90 (m, 2H, H_{14}), 3.65 – 3.60 (m, 1H, H_4), 2.48 (dd, J = 13.2, 3.1 Hz, 1H, H_3), 2.36 – 2.27 (m, 1H, H_7), 2.03 (dd, J = 13.4, 8.7 Hz, 1H, H_3), 1.94 (ddd, J = 13.8, 9.6, 4.4 Hz, 1H, H_7), 1.85 – 1.76 (m, 1H, H_5), 1.61 – 1.52 (m, 1H, H_6), 1.49 – 1.40 (m, 1H, H_5), 1.32 (d, J = 12.9 Hz, 1H, H_{21}), 1.28 (ddd, J = 14.0, 9.6, 6.0 Hz, 1H, H_6) ppm.

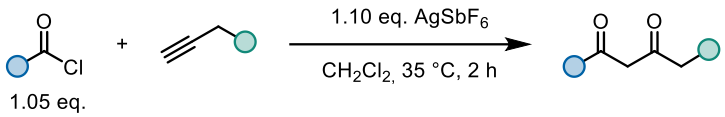
^{13}C NMR (151 MHz, $CDCl_3$): (*major isomer*) δ 167.9 (C_{12}), 143.3 (C_1), 139.6 (C_{17}), 139.4 (C_8), 137.7 (C_{13}), 130.6 (C_{20}), 129.2 (2C, C_9), 129.1 (2C, C_{18}), 128.7 (C_{16}), 128.2 (2C, C_{19}), 128.1 (2C, C_{14}), 127.9 (2C, C_{15}), 127.7 (2C, C_{10}), 126.7 (C_{11}), 117.2 (C_2), 70.3 (C_4), 38.8 (C_3), 34.7 (C_5), 28.4 (C_7), 22.6 (C_6) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{26}H_{26}NO^+$) requires *m/z* 368.2009, found *m/z* 368.2009.

IR (neat) ν_{max}: = 3368, 3056, 2928, 2857, 2360, 1739, 1597, 1574, 1489, 1445, 1316, 1290, 1229, 1206, 1180, 1109, 1044, 1023, 1000, 953, 915, 851, 775 cm^{-1}.

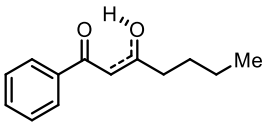
3.2.4 Reaction of Oxocarbenium Ions with Alkynes and Dienes

3.2.4.1 General Procedure 5: Reactions of Alkynes and Dienes



In an oven-dried vial at 23 °C, a solution of alkene (0.200 mmol, 1.00 eq.) and acyl chloride (0.210 mmol, 1.05 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) was treated with silver hexafluoroantimonate (AgSbF6, 0.220 mmol, 1.10 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C and vigorously stirred at this temperature for 2 h. The reaction was stopped by addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL/0.100 mmol alkene substrate initially used), followed by vigorous stirring for 10 min. Then, the mixture was transferred to a separation funnel, diluted with dichloromethane (3.00 mL) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (3 × 5.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding 1,3-functionalized product.

1.344-1.345 – 1-Phenylheptane-1,3-dione

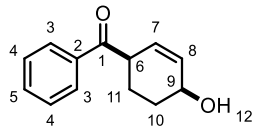


1.344

Synthesized following **GP-5**, using 1-hexyne (23.0 µL, 16.4 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.344**-**1.345** (29.5 mg, 0.140 mmol, 72%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.64). Spectroscopic data were in accordance with literature.[152]

^{1}H NMR (400 MHz, $CDCl_3$): δ 16.2 (s, 1H), 8.14 – 7.78 (m, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.17 (s, 1H), 2.50 – 2.38 (m, 2H), 1.68 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.41 (dq, *J* = 14.6, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm.

1.359 – *syn*-(4-Hydroxycyclohex-2-en-1-yl)(phenyl)methanone



1.359

Synthesized following **GP-5**, using 1,3-cyclohexadiene (19.6 µL, 16.5 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.359** (8.9 mg, 0.040 mmol, 22%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.41).

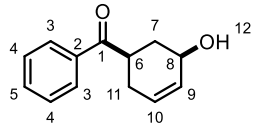
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 7.4 Hz, 2H, H_3), 7.58 (t, J = 7.4 Hz, 1H, H_5), 7.49 (t, J = 7.6 Hz, 2H, H_4), 6.07 – 5.98 (m, 1H, $H_{7\text{ or }8}$), 5.92 (dd, J = 10.1, 2.2 Hz, 1H, $H_{7\text{ or }8}$), 4.21 (d, J = 3.4 Hz, 1H, H_9), 4.03 (s, 1H, H_6), 2.12 – 1.70 (m, 4H, H_{10+11}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.9 (C_1), 136.1 (C_2), 133.3 (C_5), 132.2 ($C_{7\text{ or }8}$), 128.9 (2C, C_3), 128.7 (2C, C_4), 128.4 ($C_{7\text{ or }8}$), 64.5 (C_9), 43.9 (C_6), 30.2 (C_{10}), 22.0 (C_{11}) ppm.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_2^+$) requires *m/z* 203.1067, found *m/z* 203.1062.

IR (neat) ν_{max}: = 3403, 3060, 3029, 2927, 2868, 1678, 1596, 1580, 1448, 1403, 1379, 1328, 1309, 1267, 1214, 1181, 1150, 1106, 1059, 1001, 982, 973, 942, 870, 814, 803, 766 cm^{-1}.

1.363 – *syn*-(5-Hydroxycyclohex-3-en-1-yl)(phenyl)methanone



1.363

Synthesized following **GP-5**, using 1,4-cyclohexadiene (19.6 µL, 16.5 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.363** (6.0 mg, 0.030 mmol, 15%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.23).

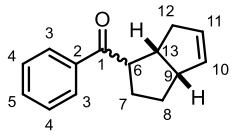
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, J = 27.1, 7.8 Hz, 2H, H_3), 7.58 (t, J = 7.3 Hz, 1H, H_5), 7.48 (t, J = 7.6 Hz, 2H, H_4), 5.93 – 5.60 (m, 2H, H_{9+10}), 4.40 (s, 1H, H_8), 3.72 (dt, J = 9.2, 6.2 Hz, 1H, H_6), 2.34 (ddd, J = 21.9, 18.4, 5.5 Hz, 4H, $H_{10+11+12}$), 1.90 – 1.75 (m, 1H, H_{11}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5 (C_1), 135.9 (C_2), 133.4 (C_5), 131.1 (C_{10}), 128.9 (2C, C_3), 128.6 (2C, C_4), 127.0 (C_9), 66.3 (C_8), 40.3 (C_6), 34.6 (C_7), 28.0 (C_{11}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{15}O_2^+$) requires *m/z* 203.1065, found *m/z* 203.1062 ppm.

IR (neat) ν_{max}: = 3388, 3058, 3028, 2925, 2856, 1675, 1596, 1579, 1488, 1448, 1375, 1302, 1247, 1203, 1183, 1159, 1142, 1104, 1061, 1039, 1003, 951, 919, 867, 811, 781 cm^{-1}.

1.367-**1.368 – (1,2,3,3a,6,6*a*-Hexahydropentalen-1-yl)(phenyl)methanone**



1.367-1.368

Synthesized following **GP-5**, using 1,5-cyclooctadiene (24.6 µL, 21.6 mg, 0.200 mmol, 1.00 eq.), benzoyl chloride (24.4 µL, 29.5 mg, 0.210 mmol, 1.05 eq.), silver hexafluoroantimonate ($AgSbF_6$, 75.6 mg, 0.220 mmol, 1.10 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.367**-**1.368** (8.60 mg, 0.040 mmol, 20%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.48). Relative stereochemistry at C_6 could not be determined.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 16.3, 7.6 Hz, 2H, H_3), 7.56 (t, *J* = 7.3 Hz, 1H, H_5), 7.47 (dd, *J* = 14.8, 7.3 Hz, 2H, H_4), 5.68 (dd, *J* = 5.4, 2.0 Hz, 1H, H_{10}), 5.01 (dd, *J* = 5.4, 2.2 Hz, 1H, H_{11}), 3.73 (ddd, *J* = 10.9, 9.1, 5.7 Hz, 1H, H_{13}), 3.63 (t, *J* = 8.0 Hz, 1H, H_6), 2.89 (q, *J* = 8.4 Hz, 1H, H_9), 2.67 (ddd, *J* = 17.0, 9.3, 1.5 Hz, 1H, H_{12}), 2.08 (d, *J* = 17.2 Hz, 1H, H_{12}), 2.01 (ddd, *J* = 18.7, 12.2, 6.2 Hz, 1H, H_7), 1.86 – 1.79 (m, 1H, H_7), 1.75 – 1.66 (m, 1H, H_8), 1.63 – 1.59 (m, 1H, H_8) ppm.

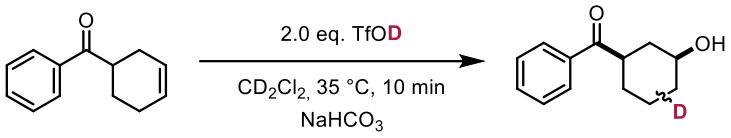
^{13}C NMR (151 MHz, $CDCl_3$): δ 201.0 (C_1), 137.7 (C_2), 133.2 (C_5), 132.9 ($C_{10\text{ or }11}$), 128.9 ($C_{10\text{ or }11}$), 128.8 (2C, C_3), 128.4 (2C, C_4), 54.7 (C_6), 52.5 ($C_{9\text{ or }13}$), 41.9 (C_{12}), 40.7 ($C_{9\text{ or }13}$), 33.9 (C_7), 26.2 (C_8) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}O^+$) requires *m/z* 213.1274, found *m/z* 213.1272.

IR (neat) ν_{max}: = 3050, 2939, 2866, 2846, 1675, 1619, 1598, 1579, 1447, 1357, 1309, 1278, 1242, 1198, 1177, 1127, 1072, 1022, 974, 939, 909, 887, 850, 815, 765 cm^{-1}.

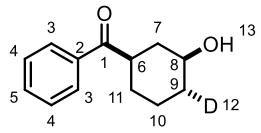
3.2.5 Additional Compounds

3.2.5.1 General Procedure 6: Deterium Studies



To a flame-dried Schlenk flask was added under inert atmosphere the corresponding alkene (0.200 mmol, 1.00 eq.), anhydrous deuterated dichloromethane (CD_2Cl_2, 2.00 ml) and deuterated triflic acid (TfOD, 35.4 µL, 0.400 mmol, 2.00 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C and vigorously stirred at this temperature for 10 min. The reaction was stopped by addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL/0.10 mmol alkene substrate initially used), followed by vigorous stirring for 10 min. Then, the mixture was transferred to a separation funnel, diluted with dichloromethane (3.00 mL) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (3 × 5.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding deuterated product.

1.433 – d_1-*syn*-(3-Hydroxycyclohexyl)(phenyl)methanone



1.433

Synthesized following **GP-6**, using cyclohex-3-en-1-yl(phenyl)methanone (37.3 mg, 0.200 mmol, 1.00 eq.), deuterated triflic acid (TfOD, 35.4 µL, 60.4 mg, 0.400 mmol, 2.05 eq.) and deuterated dichloromethane (CD_2Cl_2, 2.00 mL) afforded compound **1.433** (>15:1 r.r., 35.7 mg, 0.170 mmol, 87%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.24).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.99 – 7.89 (m, 2H, H_3), 7.61 – 7.51 (m, 1H, H_5), 7.46 (t, *J* = 7.8 Hz, 2H, H_4), 4.02 (d, *J* = 2.3 Hz, 0.06H, H_6), 3.82 – 3.70 (m, 0.89H, H_6), 3.37 (tt, *J* = 10.8, 3.2 Hz, 0.97H, H_8), 3.30 (ddd, *J* = 13.8, 7.0, 3.6 Hz, 0.08H, H_8), 2.18 – 2.06 (m, 1H, H_7), 2.06 – 1.93 (m, 1.7H, $H_{7+9/11}$), 1.87 (dddd, *J* = 15.0, 11.2, 6.8, 4.3 Hz, 2H, $H_{7/9/11}$), 1.74 – 1.65 (m, 0.3H, $H_{7/9/11}$), 1.52 (dd, *J* = 23.3, 11.5 Hz, 1H, $H_{7/9/11}$), 1.49 – 1.38 (m, 2H, H_{10+13}), 1.34 – 1.22 (m, 1H, H_{10}) ppm.

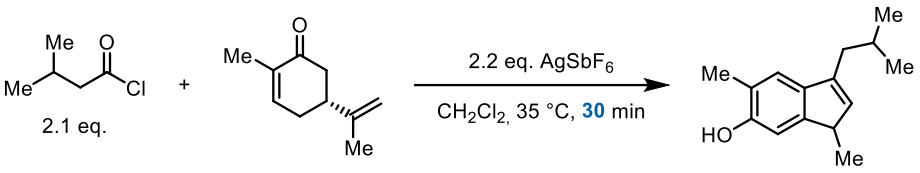
^{13}C NMR (176 MHz, $CDCl_3$): δ 202.6 (*major*, C_1), 136.1 (*major*, C_2), 133.2 (*major*, C_5), 132.9 (*minor*, C_5), 128.8 (2C, *major*, C_4), 128.7 (2C, *minor*, C_4), 128.4 (2C, *major*, C_3), 128.4 (2C, *minor*, C_3), 70.1 (*minor*, C_8), 70.0 (*major*, C_8), 44.1 (*major*, C_6), 37.8 (d, *J* = 2.3 Hz, *major*, C_6), 37.7 (*minor*, C_7), 35.3 (*major*, C_7), 35.2 (d, *J* = 2.8 Hz, *major*, C_9), 35.1 – 34.7 (m, *minor*, C_9), 32.2 (d, *J* = 3.6 Hz, *major*, C_{11}), 32.0 – 31.6 (m, *minor*, C_{11}), 23.7 (d, *J* = 17.8 Hz, *minor*, C_{10}), 23.5 (d, *J* = 16.9 Hz, *major*, C_{10}), 23.1 (d, *J* = 19.1 Hz, *minor*, C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}DO_2^+$) requires *m/z* 206.1286, found *m/z* 206.1284.

IR (neat) ν_{max}: = 3429, 2937, 2859, 1742, 1679, 1670, 1597, 1579, 1448, 1374, 1356, 1319, 1267, 1252, 1229, 1202, 1180, 1148, 1104, 1058, 1013, 992, 970, 942, 918, 872, 836, 804 cm^{-1}.

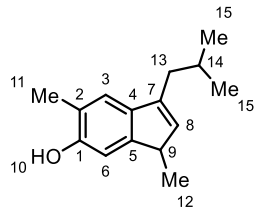
Note: In some cases, certain minor signals could not be identified due to overlap with other signals.

3.2.5.2 General Procedure 7: Synthesis of Indenes



In an oven-dried vial at 23 °C, a solution of alkene (0.200 mmol, 1.00 eq.) and acyl chloride (0.210 mmol, 1.05 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) was treated with silver hexafluoroantimonate ($AgSbF_6$, 0.440 mmol, 2.20 eq.) and the resulting suspension was immediately placed in a preheated oil bath at 35 °C. After vigorously stirring the reaction mixture at the same temperature for 30 min, the reaction vial was removed from the oil bath and a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 2 mL) was added, followed by vigorous stirring for 10 min. After this time, the phases were separated, the aqueous phase was extracted with dichloromethane three times (3 × 3.00 mL) and the combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding product.

1.403 – d_1-*syn*-(3-Hydroxycyclohexyl)(phenyl)methanone



1.403

Synthesized following **GP-7**, using (*R*)-(−)-carvone (31.3 µL, 30.0 mg, 0.200 mmol, 1.00 eq.), izovaleryl chloride (51.2 µL, 50.6 mg, 0.420 mmol, 2.10 eq.), silver hexafluoroantimonate ($AgSbF_6$, 151 mg, 0.440 mmol, 2.20 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **1.403** (18.0 mg, 0.080 mmol, 41%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.27).

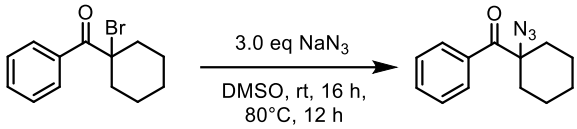
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H, H_3), 6.86 (s, 1H, H_6), 5.96 (s, 1H, H_8), 4.55 (s, 1H, H_{10}), 3.39 – 3.27 (m, 1H, H_9), 2.34 (d, J = 7.0 Hz, 2H, H_{13}), 2.29 (s, 3H, H_{11}), 1.99 (dt, J = 13.3, 6.7 Hz, 1H, H_{14}), 1.25 (d, J = 7.6 Hz, 3H, H_9), 0.96 (d, J = 6.6 Hz, 6H, H_{15}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.8 (C_1), 149.8 (C_5), 141.3 (C_4), 138.2 (C_2), 134.4 (C_8), 121.4 (C_3), 121.1 (C_7), 110.4 (C_6), 43.4 (C_9), 37.4 (C_{13}), 27.2 (C_{14}), 23.0 (C_{15}), 23.0 (C_{15}), 17.0 (C_9), 16.2 (C_{11}) ppm.

HRMS (ESI$^+$): *HRMS could not be recorded for this compound*.

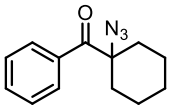
IR (neat) ν_{max}: = 3398, 2961, 2930, 2871, 1744, 1708, 1653, 1629, 1613, 1584, 1564, 1501, 1467, 1449, 1419, 1382, 1365, 1310, 1267, 1218, 1180, 1150, 1117, 1095, 1057, 1037 cm^{-1}.

3.2.5.4 General Procedure 8: Synthesis of α-Azides



In an oven dried round bottom flask was added at 23 °C, a solution of bromide **3.1** (1.00 mmol, 1.00 eq.) in dimethyl sulfoxide (DMSO, 3.00 mL), followed up by a portion-wise addition of sodium azide (NaN_3, 3.00 mmol, 3.00 eq.) and the resulting suspension was stirred vigorously at 23 °C for 16 hours. Then the mixture was poured into distilled water (H_2O, 20.0 mL). Then, the mixture was transferred to a separation funnel and diluted with ethyl acetate (EtOAc, 10.0 mL). The organic phase was separated, the aqueous phase was extracted two more times with ethyl acetate (EtOAc, 2 × 10.0 mL) and the combined organic phases were washed six time with brine (6 × 20.0 mL), then dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding α-azides.

3.1 – (1-Azidocyclohexyl)(phenyl)methanone



1.470

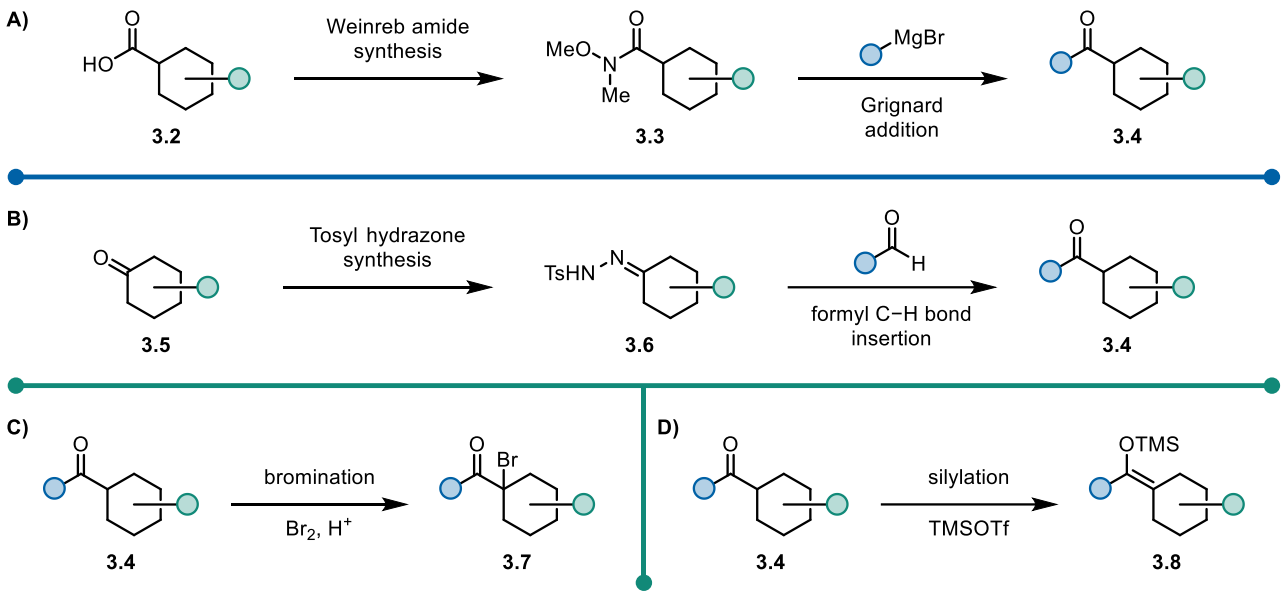
Synthesized following **GP-8**, using bromide **3.1** (267 mg, 1.00 mmol, 1.00 eq.), sodium azide (195 mg, 3.00 mmol, 3.00 eq.) and dimethyl sulfoxide (DMSO, 3.00 mL) afforded compound **3.1** (85.0 mg, 0.370 mmol, 37%) as a pale-yellow oil after purification by column chromatography (heptanes/ethyl acetate = 95:5, R_f = 0.41). Spectroscopic data were in accordance with literature.[153]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 7.4 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 2.03 – 1.87 (m, 4H), 1.77 – 1.55 (m, 5H), 1.42 – 1.23 (m, 1H) ppm.

3.3 Synthesis of 1,3-Ketoalcohols via Carbocation-Mediated, Directed Diastereoselective Oxidation of Inert C–H Bonds

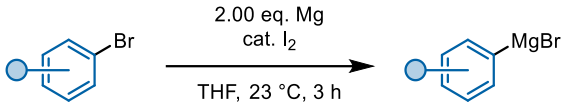
3.3.1 Synthesis of Silyl Enol Ethers

We followed several strategies to obtain the ketone precursors as shown below (Scheme 3.1). In the first route, Weinreb amides **3.3** were synthesized from the corresponding carboxylic acid **3.2**. Then, addition of Grignard reagents delivered ketones **3.4** (Scheme 3.1A). A second strategy involved synthesis of tosyl hydrazones **3.6** from ketones (**3.5**). Treatment with aldehydes in the presence of caesium carbonate (Cs_2CO_3) resulted in a formyl C–H bond insertion yielding ketones **3.4** (Scheme 3.1B). To support our mechanistic studies, selected examples of ketones **3.4** were converted to the corresponding α-bromoketones **3.7** (Scheme 3.1C). Finally, ketones from both synthetic routes were converted to silyl enol ethers **3.8** through silylation (Scheme 3.1D).



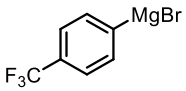
Scheme 3.1: Overview of synthetic routes: A) Synthesis of ketones starting from carboxylic acids. B) Synthesis of ketones through tosyl hydrazones and formyl C−H bond insertion. C) α-Bromination of ketones. D) Silylation of ketones.

3.3.1.1 General Procedure 9: Synthesis of Grignard Reagents



To a flame-dried Schlenk containing Magnesium turnings (2.00 eq.) in dry, unstabilized tetrahydrofuran (THF, 2.00 mL/mmol of Mg) was added, under argon atmosphere, a crystal of iodine. The mixture was stirred until a homogenous coloration was obtained. Without stirring, a few drops of the pure aryl bromide were added (5 drops). Upon discoloration, indicating initiation of the reaction, the rest of the bromide (1.00 eq.) was added dropwise (over 10 min). The resulting mixture was left stirring for 3 h and the resulting solution of Grignard reagent was titrated according to the procedure described by B. E. Love.[154]

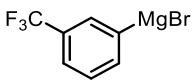
3.9 – Phenylmagnesium bromide



3.9

Synthesized following **GP-9**, using 4-bromobenzotrifluoride (6.36 mL, 45.0 mmol, 1.00 eq.) and magnesium (1.64 g, 67.5 mmol, 1.50 eq.). The resulting solution of **3.9** (70.0 mL, 0.46 M in THF, 32.0 mmol, 72%) was immediately used in the next step.

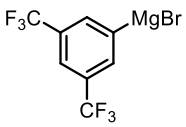
3.10 – [3-(Trifluoromethyl)phenyl]magnesium bromide



3.10

Synthesized following **GP-9**, using 3-bromobenzotrifluoride (1.67 mL, 12.0 mmol, 1.00 eq.) and magnesium (438 g, 18.0 mmol, 1.50 eq.). The resulting solution of **3.10** (17.0 mL, 0.49 M in THF, 8.30 mmol, 69%) was immediately used in the next step.

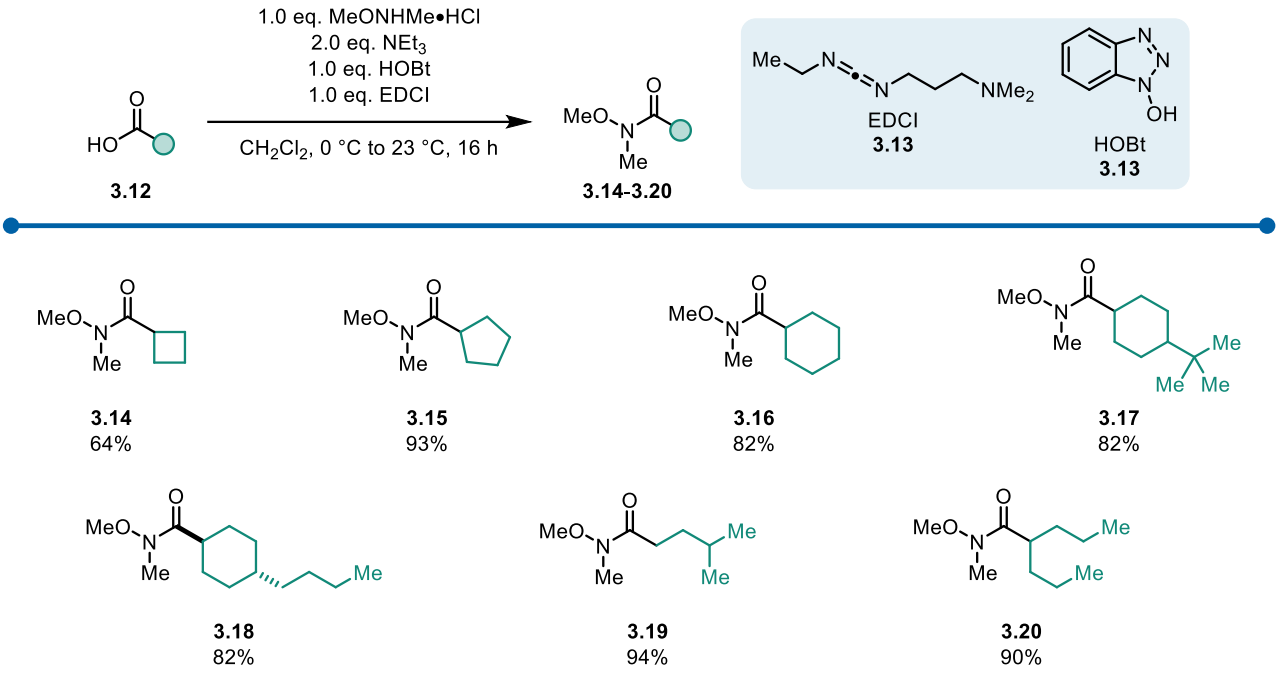
3.11 – [3,5-Bis(trifluoromethyl)phenyl]magnesium bromide



3.11

Synthesized following **GP-9**, using 1,3-bis(trifluoromethyl)-5-bromobenzene (1.20 mL, 7.00 mmol, 1.00 eq.) and magnesium (255 mg, 10.5 mmol, 1.50 eq.). The resulting solution of **3.11** (11.0 mL, 0.60 M in THF, 6.42 mmol, 92%) was immediately used in the next step.

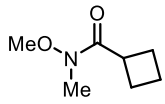
3.3.1.2 General Procedure 10: Synthesis of Weinreb Amides from Carboxylic Acids



Scheme 3.2: Scope of Weinreb Amides.

To a solution of carboxylic acid (10.0 mmol, 1.00 eq.) in dichloromethane (CH_2Cl_2, 0.5 M) were added *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 10.0 mmol, 1.05 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl, 10.0 mmol, 1.20 eq.), 1-hydroxybenzotriazole hydrate (HOBt, 10.0 mmol, 1.00 eq.) and triethyl amine (NEt_3, 20.0 mmol, 2.00 eq.) in sequence and the resulting mixture was left stirring at 23 °C for 16 h. The reaction was stopped by addition of an aqueous solution of hydrochloric acid (HCl, 1 M, 20.0 mL) and transferred to a separation funnel. The organic phase was separated then washed twice with a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 2 × 20.0 mL) and brine (20.0 mL). The organic phase was dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was removed under reduced pressure to yield the Weinreb amide, which was used in the next step without further purification.

3.14 – *N*-Methoxy-*N*-methylcyclobutanecarboxamide

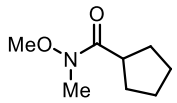


3.14

Synthesized following **GP-10**, using cyclobutanecarboxylic acid (1.01 g, 10.0 mmol, 1.00 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 975 mg, 10.0 mmol, 1.00 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl, 1.92 g, 10.0 mmol, 1.00 eq.), 1-hydroxybenzotriazole hydrate (HOBt, 1.35 g, 10.0 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 20.0 mL) afforded compound **3.14** (911 mg, 6.36 mmol, 64%) as a colourless oil. Spectroscopic data were in accordance with literature.[155]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.47 (s, 1H), 3.16 (s, 3H), 2.39 – 2.24 (m, 2H), 2.22 – 2.06 (m, 2H), 2.03 – 1.93 (m, 1H), 1.92 – 1.80 (m, 1H) ppm.

3.15 – *N*-Methoxy-*N*-methylcyclopentanecarboxamide

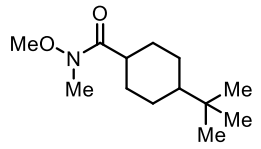


3.15

Synthesized following **GP-10**, using cyclopentanecarboxylic acid (2.28 g, 20.0 mmol, 1.00 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 1.95 g, 20.0 mmol, 1.00 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl, 3.84 g, 20.0 mmol, 1.00 eq.), 1-hydroxybenzotriazole hydrate (HOBt, 2.70 g, 20.0 mmol, 1.00 eq.), triethyl amine (NEt_3, 5.58 mL, 4.05 g, 40.0 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 40.0 mL) afforded compound **3.15** (2.94 g, 18.7 mmol, 93%) as a colourless oil. Spectroscopic data were in accordance with literature.[156]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.19 (s, 3H), 3.09 (s, 1H), 1.95 – 1.66 (m, 6H), 1.66 – 1.50 (m, 2H) ppm.

3.18 – 4-(*tert*-Butyl)-*N*-methoxy-*N*-methylcyclohexane-1-carboxamide

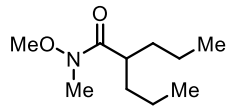


3.18

Synthesized following **GP-10**, using 4-*tert*-butylcyclohexanecarboxylic acid (2.76 g, 15.0 mmol, 1.00 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 1.46 g, 15.0 mmol, 1.00 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl, 2.88 g, 15.0 mmol, 1.00 eq.), 1-hydroxybenzotriazole hydrate (HOBt, 2.03 g, 15.0 mmol, 1.00 eq.), triethyl amine (NEt_3, 4.18 mL, 3.04 g, 30.0 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 30.0 mL) afforded compound **3.18** (3.08 g, 13.5 mmol, 90%) as a colourless oil. Spectroscopic data were in accordance with literature.[157]

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.17 (s, 3H), 2.60 (s, 1H), 1.91 – 1.77 (m, 4H), 1.57 – 1.45 (m, 2H), 1.11 – 0.97 (m, 3H), 0.85 (s, 9H) ppm.

3.20 – *N*-Methoxy-*N*-methyl-2-propylpentanamide

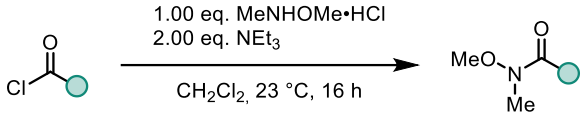


3.20

Synthesized following **GP-10**, using 2-propylpentanoic acid (2.88 g, 20.0 mmol, 1.00 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 1.95 g, 20.0 mmol, 1.00 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl, 3.84 g, 20.0 mmol, 1.00 eq.), 1-hydroxybenzotriazole hydrate (HOBt, 2.70 g, 20.0 mmol, 1.00 eq.), triethyl amine (NEt_3, 5.58 mL, 4.05 g, 40.0 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 40.0 mL) afforded compound **3.20** (3.36 g, 17.90 mmol, 90%) as a colourless oil. Spectroscopic data were in accordance with literature.[158]

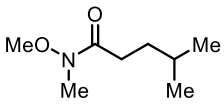
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (d, *J* = 1.3 Hz, 3H), 3.18 (s, 3H), 2.86 (s, 1H), 1.67 – 1.42 (m, 2H), 1.44 – 1.34 (m, 2H), 1.34 – 1.20 (m, 4H), 0.89 (dt, *J* = 8.4, 4.1 Hz, 6H) ppm.

3.3.1.3 General Procedure 11: Synthesis of Weinreb Amides from Acyl Chlorides



To a solution of the corresponding acyl chloride (1.00 eq. 10.0 mmol) in dichloromethane (CH_2Cl_2, 0.5 M) were added *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 10.0 mmol, 1.00 eq.) and triethyl amine (NEt_3, 20.0 mmol, 2.00 eq.) in sequence and the resulting mixture was left stirring at 23 °C for 16 h. The reaction was stopped by addition of an aqueous solution of hydrochloric acid (HCl, 1 M, 10.0 mL) and transferred to a separation funnel. The organic phase was washed with an aqueous solution of hydrochloric acid (HCl, 1 M, 10.0 mL), twice with a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 2 × 20.0 mL) and brine (20.0 mL). The organic phase was dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was removed under reduced pressure to yield the corresponding Weinreb amide, which was used in the next step without further purification.

3.19 – *N*-Methoxy-*N*,4-dimethylpentanamide

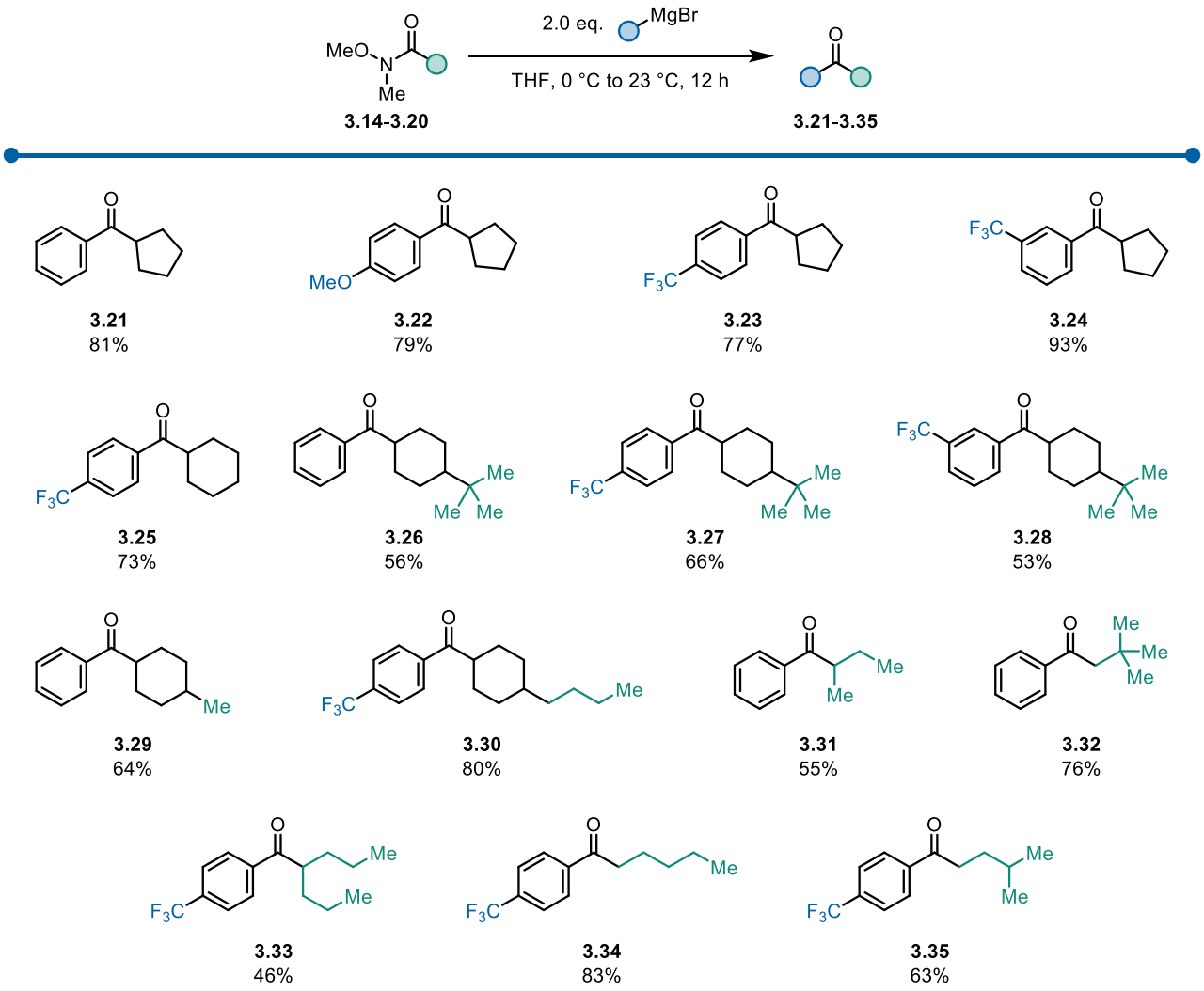


3.19

Synthesized following **GP-11**, using 4-methylvaleryl chloride (1.35 g, 10.0 mmol, 1.00 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (MeNHOMe•HCl, 975.0 mg, 10.0 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 2.00 eq.) and dichloromethane (CH_2Cl_2, 20.0 mL) afforded compound **3.19** (1.50 g, 9.40 mmol, 94%) as a colourless oil. Spectroscopic data were in accordance with literature.[159]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.17 (s, 3H), 2.48 – 2.31 (m, 2H), 1.68 – 1.45 (m, 3H), 0.91 (d, J = 6.4 Hz, 6H) ppm.

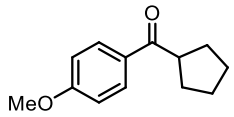
3.3.1.4 General Procedure 12: Synthesis of Ketones from Weinreb Amides



Scheme 3.3: Scope of Ketones.

To a solution of the corresponding Weinreb amide (10.0 mmol, 1.00 eq.) in tetrahydrofuran (THF, 0.25 M) was added a solution of Grignard reagent (20.0 mmol 2.00 eq.) at 0 °C. The resulting solution was left to warm-up to 23 °C over 12 h under stirring. The reaction was stopped by addition of a saturated aqueous solution of ammonium chloride (NH_4Cl, 20.0 mL) and transferred to a separation funnel. The organic phase was separated and the aqueous phase was extracted three times with diethyl ether (Et_2O, 3 × 20.0 mL). The combined organic phases were washed with brine (30.00 mL), dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/ethyl acetate = 100:0 to 90:10 or toluene/CH_2Cl_2 = 90:10 to 50:50) to afford the pure ketone.

3.22 – Cyclopentyl(4-methoxyphenyl)methanone

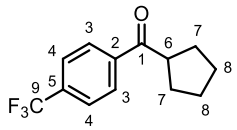


3.22

Synthesized following **GP-12**, using Weinreb amide **3.15** (786 mg, 5.00 mmol, 1.00 eq.), *p*-methoxy-phenylmagnesium bromide (10.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 10.0 mL) afforded compound **3.22** (809 mg, 3.96 mmol, 79%) as a colourless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.15). Spectroscopic data were in accordance with literature.[160]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.66 (p, *J* = 7.9 Hz, 1H), 1.98 – 1.80 (m, 4H), 1.80 – 1.57 (m, 4H) ppm.

3.23 – Cyclopentyl[4-(trifluoromethyl)phenyl]methanone



3.23

Synthesized following **GP-12**, using Weinreb amide **3.15** (314 mg, 2.00 mmol, 1.00 eq.), Grignard reagent **3.9** (4.00 mmol, 2.00 eq.) and tetrahydrofuran (THF, 4.00 mL) afforded compound **3.23** (373 mg, 1.54 mmol, 77%) as a colourless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.68).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.1 Hz, 2H, H_3), 7.73 (d, *J* = 8.2 Hz, 2H, H_4), 3.81 – 3.59 (m, 1H, H_6), 2.01 – 1.84 (m, 4H, H_7), 1.80 – 1.60 (m, 4H, H_8) ppm.

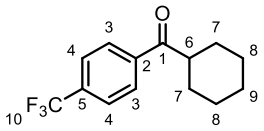
^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9 (C_1), 139.8 (C_2), 134.4 (C_5), 134.0 (C_9), 128.9 (2C, C_3), 125.7 (q, *J* = 3.7 Hz, 2C, C_4), 46.8 (C_6), 30.0 (2C, C_7), 26.4 (2C, C_8) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.07 (3F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{14}F_3O^+$) requires *m/z* 243.0991, found *m/z* 243.0996.

IR (neat) ν_{max}: = 2960, 2871, 1686, 1581, 1511, 1451, 1409, 1323, 1217, 1166, 1125, 1108, 1065, 1016, 999 cm^{-1}.

3.25 – Cyclohexyl[4-(trifluoromethyl)phenyl]methanone



3.25

Synthesized following **GP-12**, using Weinreb amide **3.16** (856 mg, 5.00 mmol, 1.00 eq.), Grignard reagent **3.9** (10.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 10.0 mL) afforded compound **3.25** (936 mg, 3.65 mmol, 73%) as a colourless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.23).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.1 Hz, 2H, H_4), 7.72 (d, J = 8.2 Hz, 2H, H_3), 3.25 (tt, J = 11.4, 3.2 Hz, 1H, H_6), 1.94 – 1.82 (m, 4H, H_7), 1.75 (ddd, J = 12.6, 4.6, 2.4 Hz, 1H, H_9), 1.58 – 1.21 (m, 5H, H_{8+9}) ppm.

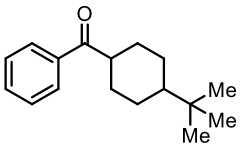
^{13}C NMR (151 MHz, $CDCl_3$): δ 203.0 (C_1), 139.3 (C_2), 134.2 (q, J = 32.7 Hz, C_5), 128.7 (2C, C_3), 125.8 (q, J = 3.7 Hz, 2C, C_4), 123.8 (q, J = 272.6 Hz, C_{10}), 46.1 (C_6), 29.4 (2C, C_7), 26.0 (C_9), 25.9 (2C, C_8) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.08 (3F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_3O^+$) requires *m/z* 257.1148, found *m/z* 257.1149 ppm.

IR (neat) ν_{max}: = 2933, 2857, 1687, 1510, 1451, 1409, 1322, 1249, 1206, 1167, 1128, 1111, 1066, 1016, 975 cm^{-1}.

3.26 – [4-(*tert*-Butyl)cyclohexyl](phenyl)methanone

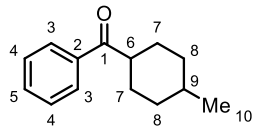


3.26
(*cis*/*trans* ratio = 1:1)

Synthesized following **GP-12**, Weinreb amide **3.17** (2.27 g, 10.0 mmol, 1.00 eq.), phenylmagnesium bromide (20.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 50.0 mL) afforded compound **3.26** (1.37 g, 5.60 mmol, 56%) as a white solid after purification by column chromatography (toluene/CH_2Cl_2 = 90:10, R_f = 0.69). Spectroscopic data were in accordance with literature.[161]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 – 7.82 (m, 2H), 7.61 – 7.50 (m, 1H), 7.45 (dt, J = 8.5, 7.6 Hz, 2H), 3.52 (t, J = 5.6 Hz, 0.5H, *cis* isomer), 3.19 (tt, J = 12.0, 3.3 Hz, 0.5H, *trans* isomer), 2.23–2.12 (m, 1H), 2.01–1.87 (m, 2H), 1.69–1.42 (m, 3H), 1.33–0.94 (m, 3H), 0.88 (s, J = 5.9 Hz, 4H, *trans* isomer), 0.83 (s, 5H, *cis* isomer) ppm.

3.29 – (4-Methylcyclohexyl)(phenyl)methanone



3.29
(*cis*/*trans* ratio = 66:33)

Synthesized following **GP-12**, using the corresponding Weinreb amide (1.48 g, 8.00 mmol, 1.00 eq.), phenylmagnesium bromide (16.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 45.0 mL) afforded compound **3.29** (1.03 g, 5.10 mmol, 64%) as a white solid after purification by column chromatography (toluene/CH_2Cl_2 = 83:17, R_f = 0.72).

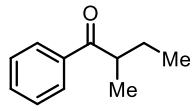
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.88 (m, 2H, H_3), 7.61 – 7.51 (m, 1H, H_5), 7.45 (td, J = 7.2, 3.5 Hz, 2H, H_4), 3.44 – 3.30 (m, 0.7H, $H_{6\text{-cis}}$), 3.20 (tt, J = 11.9, 3.3 Hz, 0.3H, $H_{6\text{-trans}}$), 2.00 – 1.79 (m, 2H, $H_{7\text{-}8}$), 1.79 – 1.54 (m, 4H, $H_{7\text{-}8}$), 1.44 (ddd, J = 13.8, 7.2, 3.7 Hz, 2H, $H_{7\text{-}8}$), 1.07 (ddd, J = 25.1, 13.3, 3.3 Hz, 1H, H_9), 0.94 (dd, J = 13.4, 6.7 Hz, 3H, H_{10}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.3 ($C_{1\text{-cis}}$), 204.2 ($C_{1\text{-trans}}$), 136.8 ($C_{2\text{-trans}}$), 136.6 ($C_{2\text{-cis}}$), 132.9 ($C_{5\text{-trans}}$), 132.7 ($C_{5\text{-cis}}$), 128.7 (2C, $C_{3\text{-trans}}$), 128.7 (2C, $C_{3\text{-cis}}$), 128.4 (2C, $C_{4\text{-trans}}$), 128.4 (2C, $C_{4\text{-cis}}$), 45.6 ($C_{6\text{-cis}}$), 43.6 ($C_{6\text{-trans}}$), 34.7 (2C, $C_{8\text{-trans}}$), 32.4 ($C_{9\text{-cis}}$), 31.3 (2C, $C_{8\text{-cis}}$), 29.6 (2C, $C_{7\text{-trans}}$), 29.6 ($C_{9\text{-trans}}$), 25.6 (2C, $C_{7\text{-cis}}$), 22.8 ($C_{10\text{-trans}}$), 19.9 ($C_{10\text{-cis}}$) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}O^+$) requires *m/z* 203.1430, found *m/z* 203.1428.

IR (neat) ν_{max}: = 2946, 2925, 2858, 2361, 2341, 1682, 1653, 1597, 1580, 1448, 1376, 1350, 1305, 1283, 1249, 1229, 1215, 1205, 1178, 1001, 992, 965, 949, 769 cm^{-1}.

3.31 – 2-Methyl-1-phenylbutan-1-one

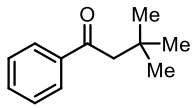


3.31

Synthesized following **GP-12**, using the corresponding Weinreb amide (726 mg, 5.00 mmol, 1.00 eq.), phenylmagnesium bromide (10.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 10.0 mL) afforded compound **3.31** (449 mg, 2.77 mmol, 55%) as a colourless oil after purification by column chromatography (pentane/diethyl ether = 95:5, R_f = 0.43). Spectroscopic data were in accordance with literature.[159]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.93 (m, 2H), 7.59 – 7.52 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.40 (h, *J* = 6.8 Hz, 1H), 1.92 – 1.76 (m, 1H), 1.49 (tt, *J* = 14.1, 7.2 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H) ppm.

3.32 – 3,3-Dimethyl-1-phenylbutan-1-one

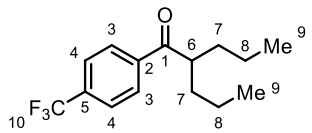


3.32

Synthesized following **GP-12**, using the corresponding Weinreb amide (318 mg, 2.00 mmol, 1.00 eq.), phenylmagnesium bromide (4.00 mmol, 2.00 eq.) and diethyl ether (Et_2O, 4.00 mL) afforded compound **3.32** (335 mg, 2.77 mmol, 76%, 80% purity) as a colourless oil after purification by column chromatography (pentane/diethyl ether = 95:5, R_f = 0.63). Spectroscopic data were in accordance with literature.[162]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.88 (m, 2H), 7.55 (dd, *J* = 10.5, 4.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 2.86 (s, 2H), 1.07 (s, 9H) ppm.

3.33 – 2-Propyl-1-[4-(trifluoromethyl)phenyl]pentan-1-one



3.33

Synthesized following **GP-12**, using Weinreb amide **3.20** (983 mg, 5.00 mmol, 1.00 eq.), Grignard reagent **3.9** (10.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 10.0 mL) afforded compound **3.33** (622 mg, 2.28 mmol, 46%) as a colourless oil after column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.18).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.1 Hz, 2H, H_4), 7.73 (d, *J* = 8.2 Hz, 2H, H_3), 3.43 (tt, *J* = 7.8, 5.5 Hz, 1H, H_6), 1.75 (ddd, *J* = 15.7, 13.5, 7.8 Hz, 2H, H_7), 1.66 – 1.42 (m, 2H, H_7), 1.38 – 1.22 (m, 4H, H_8), 0.88 (t, *J* = 7.3 Hz, 6H, H_9) ppm.

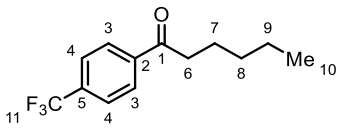
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9 (C_1), 140.6 (C_2), 134.1 (C_5), 128.6 (2C, C_3), 125.9 (q, *J* = 3.7 Hz, 2C, C_4), 125.2 (C_{10}), 46.4 (C_6), 34.7 (2C, C_7), 20.9 (2C, C_8), 14.4 (2C, C_9) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.09 (3F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}F_3O^+$) requires *m/z* 273.1461, found *m/z* 245.1457.

IR (neat) ν_{max}: = 2960, 2934, 2875, 1686, 1582, 1510, 1466, 1409, 1381, 1323, 1243, 1207, 1168, 1129, 1066, 1015, 997, 948, 911, 850, 790 cm^{-1}.

3.34 – 1-[4-(Trifluoromethyl)phenyl]hexan-1-one



3.34

Synthesized following **GP-12**, using the corresponding Weinreb amide (796 mg, 5.00 mmol, 1.00 eq.), Grignard reagent **3.9** (10.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 10.0 mL) afforded compound **3.34** (1.01 g, 4.14 mmol, 83%) as a colourless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.25).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.1 Hz, 2H, H_4), 7.72 (d, J = 8.2 Hz, 2H, H_3), 2.98 (dd, J = 9.2, 5.6 Hz, 2H, H_6), 1.80 – 1.69 (m, 2H, H_7), 1.36 (dq, J = 7.2, 3.6 Hz, 4H, $H_{8\text{-}9}$), 1.03 – 0.75 (m, 3H, H_{10}) ppm.

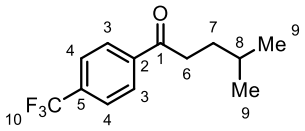
^{13}C NMR (101 MHz, $CDCl_3$): δ 199.6 (C_1), 139.9 (C_2), 134.3 (q, J = 32.6 Hz, C_5), 128.5 (2C, C_3), 125.8 (q, J = 3.7 Hz, 2C, C_4), 123.8 (q, J = 272.6 Hz, C_{11}), 39.0 (C_6), 31.6 (C_7), 24.0 (C_8), 22.6 (C_9), 14.1 (C_{10}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.12 (3F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}F_3O^+$) requires *m/z* 245.1148, found *m/z* 245.1149.

IR (neat) ν_{max}: = 2960, 2932, 2862, 1683, 1581, 1511, 1469, 1459, 1409, 1372, 1323, 1247, 1201, 1165, 1127, 1109, 1065, 1015, 978, 902, 864, 850, 828, 758 cm^{-1}.

3.35 – 4-Methyl-1-[4-(trifluoromethyl)phenyl]pentan-1-one



3.35

Synthesized following **GP-12**, using Weinreb amide **3.19** (796 mg, 5.00 mmol, 1.00 eq.), Grignard reagent **3.9** (10.0 mmol, 2.00 eq.) and tetrahydrofuran (THF, 10.0 mL) afforded compound **3.35** (773 mg, 3.17 mmol, 63%) as a colourless oil after column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.17).

Note: *Following column chromatography,* ***3.35*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.35*** *was subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.1 Hz, 2H, H_4), 7.73 (d, J = 8.2 Hz, 2H, H_3), 3.02 – 2.89 (m, 2H, H_6), 1.76 – 1.55 (m, 3H, H_{7+8}), 0.95 (d, J = 6.2 Hz, 6H, H_9) ppm.

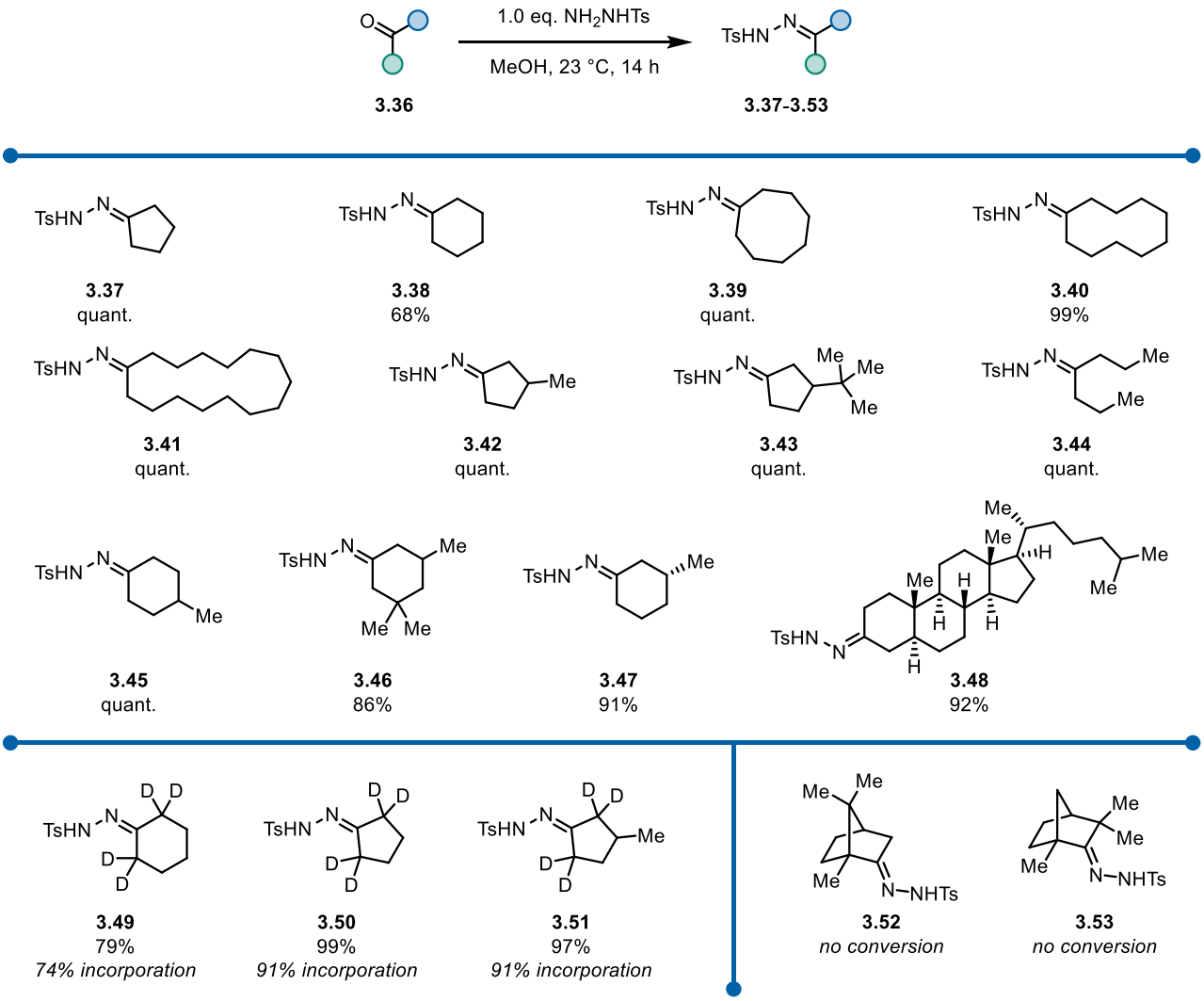
^{13}C NMR (101 MHz, $CDCl_3$): *as is the case for some of these ketones, no clean data can be obtained*.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.10 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}F_3O^+$) requires *m/z* 245.1149, found *m/z* 245.1148.

IR (neat) ν_{max}: = 2956, 2930, 2872, 1692, 1582, 1511, 1468, 1410, 1387, 1369, 1322, 1272, 1206, 1167, 1128, 1110, 1066, 1016, 991, 847, 835, 793 cm^{-1}.

3.3.1.5 General Procedure 13: Synthesis of Hydrazones



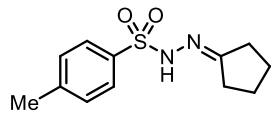
Scheme 3.4: Scope of Hydrazones.

Prepared according to a procedure previously described in the literature.[163]

To a flame-dried flask containing the corresponding ketone (10.0 mmol, 1.00 eq.) in methanol (MeOH, 0.5 M) was added 4-methylbenzenesulfonylhydrazide (NH_2NHTs, 10.0 mmol, 1.00 eq.) and the mixture was left stirring at 23 °C for 14 h. Then, the solvent was evaporated under reduced pressure to afford the crude hydrazone which was used in the next step without further purification.

Note: *In the case of unreacted starting material still detectable by NMR analysis in the crude product, a wash with cold pentane, followed up by removal of residual solvent under reduced pressure, afforded cleaner hydrazine which was used for the next step without further purification.*

3.37 – *N*'-cyclopentylidene-4-methylbenzenesulfonohydrazide

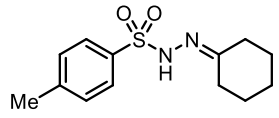


3.37

Synthesized following **GP-13**, using cyclopentanone (841 mg, 10.0 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (1.86 g, 10.0 mmol, 1.00 eq.) and methanol (MeOH, 20.0 mL) afforded compound **3.37** (2.52 g, 9.99 mmol, 99%) as a white solid. Spectroscopic data were in accordance with literature.[164]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.05 (s, 1HN), 2.43 (s, 3H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.14 (d, *J* = 6.7 Hz, 2H), 1.90 – 1.76 (m, 2H), 1.76 – 1.64 (m, 2H) ppm.

3.38 – *N*'-Cyclohexylidene-4-methylbenzenesulfonohydrazide

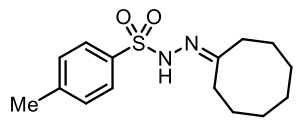


3.38

Synthesized following **GP-13**, using cyclohexanone (1.96 g, 20.0 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (3.73 g, 20.0 mmol, 1.00 eq.) and methanol (MeOH, 40.0 mL) afforded compound **3.38** (3.61 g, 13.6 mmol, 68%) as a white solid. Spectroscopic data were in accordance with literature.[165]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.15 (s, 1H), 2.43 (s, 3H), 2.29 – 2.14 (m, 4H), 1.75 – 1.51 (m, 6H) ppm.

3.39 – *N*'-Cyclooctylidene-4-methylbenzenesulfonohydrazide



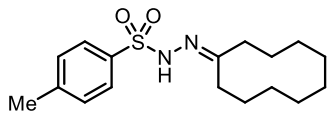
3.39

Synthesized following **GP-13**, using cyclooctanone (1.26 g, 10.0 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (1.86 g, 10.0 mmol, 1.00 eq.) and methanol (MeOH, 40.0 mL) afforded

compound **3.39** (2.96 g, 10.0 mmol, quant.) as a white solid. Spectroscopic data were in accordance with literature.[166]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.41 (s, 3H), 2.30 (dd, *J* = 7.6, 4.9 Hz, 2H), 2.28 – 2.16 (m, 2H), 1.76 – 1.56 (m, 4H), 1.51 – 1.29 (m, 4H), 1.28 – 1.02 (m, 2H) ppm.

3.40 – *N*'-Cyclodecylidene-4-methylbenzenesulfonohydrazide

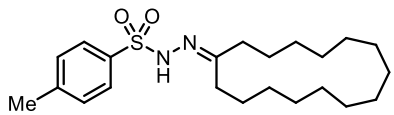


3.40

Synthesized following **GP-13**, using cyclodecanone (309 mg, 2.00 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (372 mg, 2.00 mmol, 1.00 eq.) and methanol (MeOH, 5.00 mL) afforded compound **3.40** (646 mg, 1.99 mmol, 99%) as a white solid. Spectroscopic data were in accordance with literature.[167]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.79 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 1H), 2.41 (s, 3H), 2.39 – 2.31 (m, 2H), 2.25 – 2.15 (m, 2H), 1.74 – 1.60 (m, 4H), 1.33 – 1.23 (m, 2H), 1.19 (dd, *J* = 5.9, 3.5 Hz, 4H), 1.15 – 1.07 (m, 2H), 1.03 – 0.91 (m, 2H) ppm.

3.41 – *N*'-Cyclopentadecylidene-4-methylbenzenesulfonohydrazide

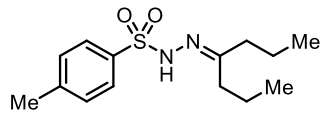


3.41

Synthesized following **GP-13**, using cyclopentadecanone (2.24 g, 10.0 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (1.86 g, 10.0 mmol, 1.00 eq.) and methanol (MeOH, 40.0 mL) afforded compound **3.41** (3.94 g, 10.0 mmol, quant.) as a white solid. Spectroscopic data were in accordance with literature.[168]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.41 (s, 3H), 2.18 (t, *J* = 7.4 Hz, 2H), 2.12 (t, *J* = 7.4 Hz, 2H), 1.55 – 1.36 (m, 4H), 1.36 – 1.02 (m, 20H) ppm.

3.44 – *N*'-(heptan-4-ylidene)-4-methylbenzenesulfonohydrazide

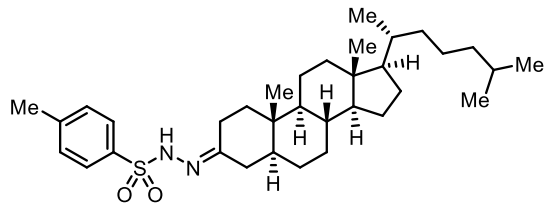


3.44

Synthesized following **GP-13**, using 4-heptanone (1.18 g, 10.0 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (1.86 g, 10.0 mmol, 1.00 eq.) and methanol (MeOH, 20.0 mL) afforded compound **3.44** (2.83 g, 10.0 mmol, quant.) as a white solid. Spectroscopic data were in accordance with literature.[169]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.77 (m, 2H), 7.29 (d, J = 8.0 Hz, 3H – includes NH), 2.42 (s, 3H), 2.19 – 2.09 (m, 2H), 2.09 – 2.00 (m, 2H), 1.54 – 1.36 (m, 4H), 0.89 (t, J = 7.3 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H) ppm.

3.48 – *N*'-{(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*,*E*)-10,13-Dimethyl-17-[(*R*)-6-methylheptan-2-yl]hexadecahydro-3*H*-cyclopenta[*a*]phenanthren-3-ylidene}-4-methylbenzenesulfonohydrazide

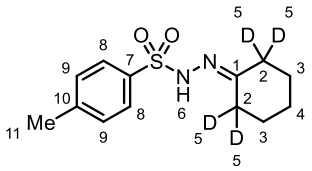


3.48

Synthesized following **GP-13**, using 5α-cholestan-3-on (1.93 g, 5.00 mmol, 1.00 eq.), 4-methylbenzenesulfonhydrazide (931 mg, 5.00 mmol, 1.00 eq.) and methanol (MeOH, 10.0 mL) afforded compound **3.48** (2.54 g, 4.58 mmol, 92%) as a white solid. Spectroscopic data were in accordance with literature.[170]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.03 (bs, 1H), 2.54 (d, J = 16.3 Hz, 1H), 2.43 (s, 3H), 2.34 – 2.25 (m, 1H), 2.23 – 2.08 (m, 1H), 2.06 – 1.76 (m, 4H), 1.66 (s, 2H), 1.61 – 1.41 (m, 4H), 1.41 – 0.93 (m, 20H), 0.89 (d, J = 6.5 Hz, 3H), 0.88 – 0.82 (m, 9H), 0.64 (s, 3H) ppm.

3.49 – *N*'-(Cyclohexylidene-2,2,6,6-d_4)-4-methylbenzenesulfonohydrazide



3.49

Synthesized following **GP-13**, using a solution of cyclohexan-1-one-2,2,6,6-d_4 **3.55** in diethyl ether (1.11 g, 6.11 mmol, 56% purity in Et_2O, 1.00 eq.), 4-methylbenzenesulfonhydrazide (977 mg, 6.11 mmol, 1.00 eq.) and methanol (MeOH, 12.0 mL) afforded compound **3.49** (1.31 g, 4.83 mmol, 79%, 74% average deuterium incorporation) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.3 Hz, 2H, H_8), 7.31 (d, J = 8.1 Hz, 2H, H_9), 7.19 (s, 1H, H_6), 2.44 (d, J = 10.8 Hz, 3H, H_{11}), 2.26 – 2.15 (m, 1H, H_2), 1.68 – 1.49 (m, 6H, H_{3+4}) ppm.

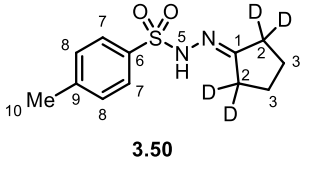
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C_1), 144.1 (C_7), 135.5 (C_{10}), 129.6 (2C, C_9), 128.3 (2C, C_8), 35.4 (C_4), 26.8 (dd, J = 8.9, 2.1 Hz, C_2), 25.7 (d, J = 7.5 Hz, C_2), 25.4 (2C, C_3), 21.8 (C_{11}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}O_2D_3N_2S^+$) requires *m/z* 270.1350, found *m/z* 270.1350.

IR (neat) ν_{max}: = 3248, 2934, 2853, 1706, 1596, 1491, 1445, 1397, 1331, 1289, 1208, 1179, 1163, 1120, 1092, 1029, 915, 851, 813, 748 cm^{-1}.

Note: *cyclohexan-1-one-2,2,6,6-d_4* ***3.55*** *was prepared according to a reported literature procedure*.[171]

3.50 – *N*'-(Cyclopentylidene-2,2,5,5-d_4)-4-methylbenzenesulfonohydrazide



3.50

Synthesized following **GP-13**, using a solution of cyclopentan-1-one-2,2,5,5-d_4 **3.54** in diethyl ether (700 mg, 5.24 mmol, 66% purity in Et_2O, 1.00 eq.), 4-methylbenzenesulfonhydrazide (977.0 mg, 5.24 mmol, 1.00 eq.) and methanol (MeOH, 16.00 mL) afforded compound **3.50** (1.33 g, 5.19 mmol, 99%, 91% average deuterium incorporation) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.3 Hz, 2H, H_7), 7.31 (d, J = 8.1 Hz, 2H, H_8), 7.02 (s, 1H, H_5), 2.43 (s, 3H, H_{10}), 1.79 (t, J = 6.5 Hz, 2H, H_3), 1.70 (q, J = 6.4 Hz, 2H, H_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9 (C_1), 144.2 (C_6), 135.6 (C_9), 129.7 (2C, C_7), 128.2 (2C, C_8), 24.7 (t, *J* = 10.0 Hz, 2C, C_3), 21.8 (C_{10}), 21.8 (2C, C_2) ppm.

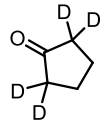
HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{12}H_{13}D_4N_2O_2S^+$) requires *m/z* 257.1256, found *m/z* 257.1256.

IR (neat) ν_{max}: = 3213, 2967, 2876, 1597, 1403, 1337, 1267, 1163, 1091, 1063, 1002, 917, 814, 740 cm^{-1}.

Note: *cyclopentan-1-one-2,2,5,5-d_4* ***3.54*** *was prepared according to a reported literature procedure*.[171]

Note: *Total and average deuterium incorporation was determined from ^{1}H NMR analysis by comparison to its non-deuterated compound and by the integration (intensity) of the (H_2)-protons in relatively the intact (H_3)-proton of the ketone.*

3.54 – **Cyclopentan-1-one-2,2,5,5-*d_4***



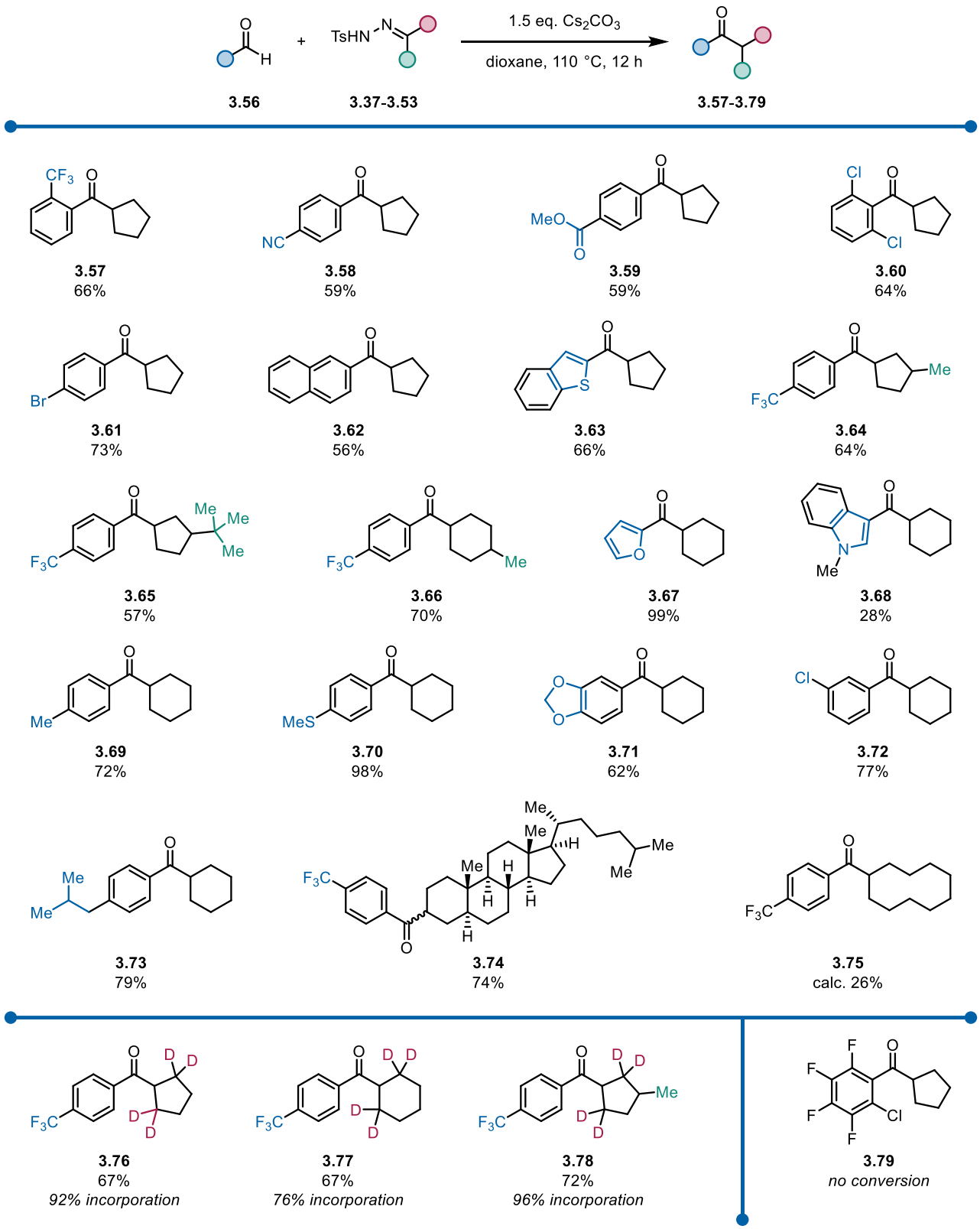
96% average incorporation

3.54

To an oven-dried vial charged with a magnetic stir bar, cyclopentanone (841 mg, 10.0 mmol, 1.00 eq.), heavy water (D_2O, 1.09 mL, 60.0 mmol, 6.00 eq.) and sodium carbonate (Na_2CO_3, 17.0 mg, 0.16 mmol, 0.16 eq.) were added. The reaction mixture was stirred at 50 °C for 12 h. The organic layer was extracted with anhydrous diethyl ether (Et_2O, 3 x 1.00 mL), and the organic layer was transferred to an oven-dried vial, dried with anhydrous magnesium sulfate ($MgSO_4$) and filtered over cotton to a second oven-dried vial. The ether solution was carefully evaporated at 800 mbar. An ^{1}H NMR sample was taken to check the total deuterium incorporation. After this, the same amount of sodium carbonate (Na_2CO_3) and heavy water (D_2O) as above was added to the ether solution and another 12 h reaction cycle was performed (3 x cycles in total). The reaction afforded **3.54** (700 mg, 5.24 mmol, 52%, 66% purity in ether, 96% average deuterium incorporation) as a solution in ether. The highly volatile compound was used for the next step as a solution in diethyl ether and without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 4H) ppm.

3.3.1.6 General Procedure 14: Synthesis of Ketones from Hydrazones



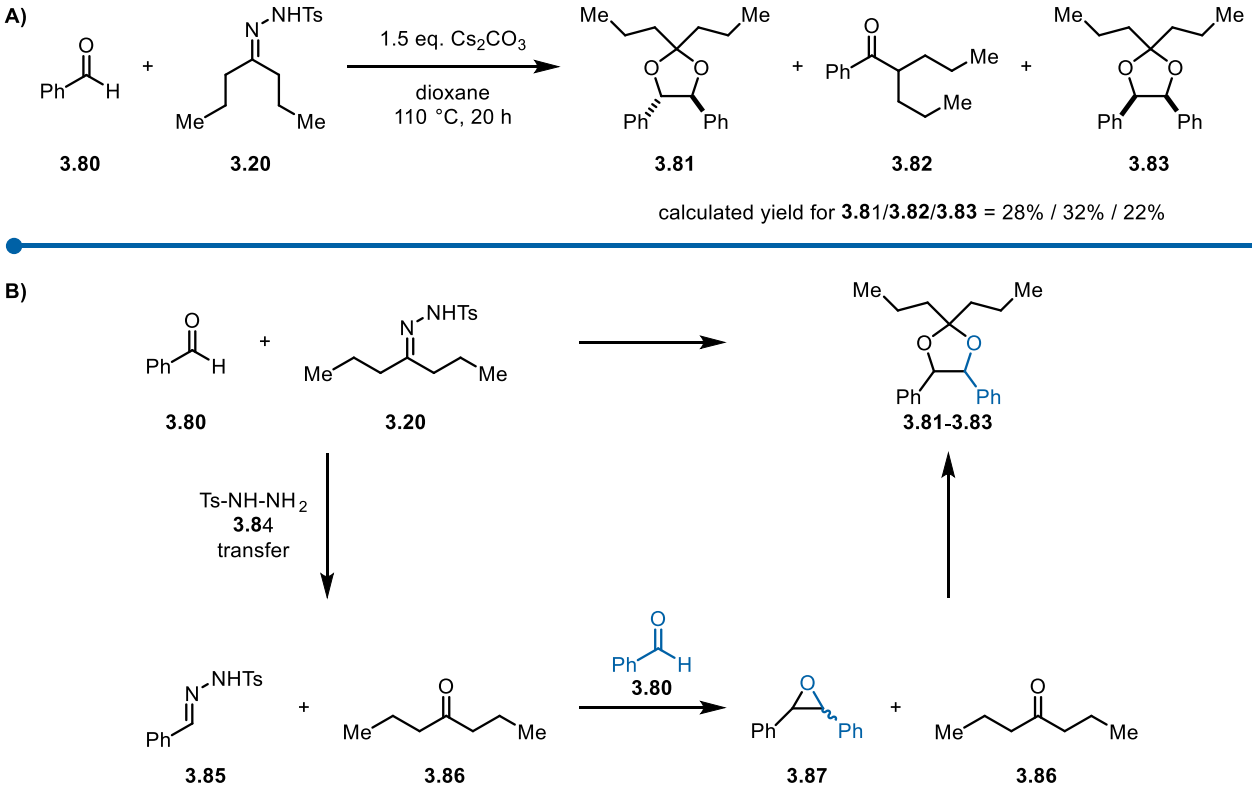
Scheme 3.5: Scope of Ketones from Hydrazones.

Prepared according to a procedure previously described in the literature.[156]

To a mixture of hydrazone (2.00 mmol, 1.00 eq.) and cesium carbonate (Cs_2CO_3, 3.00 mmol, 1.50 eq.) in 1,4-dioxane (0.2 M) was added the corresponding aldehyde (2.00 mmol, 1.00 eq.) and the mixture was refluxed for 14 h (oil batch temperature set at 110 °C). After cooling to 23 °C, the reaction was stopped by addition of a saturated aqueous solution of ammonium chloride (NH_4Cl, 10.0 mL) and transferred to a separation funnel, followed up by addition of dichloromethane (CH_2Cl_2, 10.0 mL). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (CH_2Cl_2, 3 × 10.0 mL). The combined organic phases were washed with brine (30.0 mL), dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/ethyl acetate = 100:0 to 50:50) to afford the corresponding ketone.

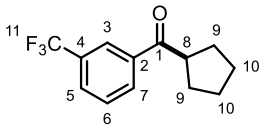
Note: *In some cases, ketones were obtained with other undefined impurities of similar polarity. Despite these contaminants, the ketones were subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

Non-cyclic and branched substrate **3.20** was paired with benzaldehyde **3.80** and delivered an inseparable product mixture containing the desired ketone **3.82**, *anti*- and *syn*-1,3-dioxolane products **3.81** and **3.83** in a ratio of 1.5:1.3:1 (Scheme 3.6). Presumably during the reaction, a *p*-toluenesulfonyl hydrazide **3.84** (Ts-NH-NH_2) exchange takes place, forming the hydrazone **3.85** of benzaldehyde **3.80** and regenerating heptan-4-one **3.86**. Hydrazone **3.85** has been known to react with benzaldehyde **3.80** and form epoxide **3.87**.[165] Finally, according to several literature reports, the newly formed ketone **3.86** can convert 2,3-phenyl-substituted opeoxide **3.87** into 2,2-propyl-1,3-dioxolane **3.81**-**3.83**.[174] [176]



Scheme 3.6: A) Unexpected product mixture. B) Proposed reaction pathway.

3.24 – Cyclopentyl[3-(trifluoromethyl)phenyl]methanone



3.24

Synthesized following **GP-14**, using **3.37** (505 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 3-(trifluoromethyl)benzaldehyde (268 µL, 348 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.24** (322 mg, 1.33 mmol, 67%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.23).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H, H_3), 8.15 (d, J = 7.8 Hz, 1H, H_7), 7.80 (dd, J = 7.8, 0.5 Hz, 1H, H_5), 7.61 (t, J = 7.8 Hz, 1H, H_6), 3.79 – 3.59 (m, 1H, H_8), 1.99 – 1.86 (m, 4H, H_9), 1.81 – 1.62 (m, 4H, H_{10}) ppm.

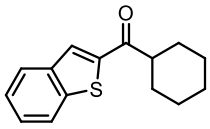
^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5 (C_1), 137.6 (C_2), 131.7 (C_7), 131.3 (q, J = 32.8 Hz, C_4), 129.33 (q, J = 32.8 Hz, C_6), 129.27 (q, J = 3.7 Hz, C_5), 125.4 (q, J = 3.8 Hz, C_3), 123.9 (q, J = 271.8 Hz, C_{11}), 46.6 (C_8), 30.0 (2C, C_9), 26.4 (2C, C_{10}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.77 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{13}F_3ONa^+$) requires *m/z* 265.0811, found *m/z* 265.0811.

IR (neat) ν_{max}: = 2957, 2934, 2872, 2208, 2111, 1691, 1658, 1645, 1616, 1575, 1466, 794 cm^{-1}.

3.63 – Benzo[*b*]thiophen-2-yl(cyclohexyl)methanone

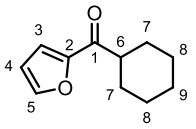


3.63

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), benzo[*b*]thiophene-2-carboxaldehyde (331 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.63** (322 mg, 1.32 mmol, 66%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.38). Spectroscopic data were in accordance with literature.[172]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.88 (t, J = 8.2 Hz, 2H), 7.43 (dtd, J = 14.8, 7.1, 1.2 Hz, 2H), 3.24 (tt, J = 11.6, 3.4 Hz, 1H), 1.97 (d, J = 13.5 Hz, 2H), 1.93 – 1.83 (m, 2H), 1.76 (ddd, J = 12.7, 4.9, 2.5 Hz, 1H), 1.66 – 1.55 (m, 2H), 1.49 – 1.36 (m, 2H), 1.36 – 1.22 (m, 1H) ppm.

3.67 – Cyclohexyl(furan-2-yl)methanone



3.67

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), furfural (166 µL, 192 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.67** (357 mg, 1.99 mmol, 99%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.31).

Note: *Following column chromatography,* ***3.67*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.67*** *was subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

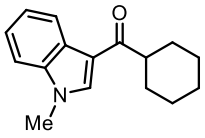
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.55 (m, 1H, H_5), 7.18 (d, *J* = 3.5 Hz, 1H, H_3), 6.52 (dd, *J* = 3.5, 1.7 Hz, 1H, H_4), 3.06 (tt, *J* = 11.7, 3.2 Hz, 1H, H_6), 1.91 – 1.79 (m, 4H, H_7), 1.72 (d, *J* = 12.4 Hz, 1H, H_8), 1.57 – 1.45 (m, 2H, H_8), 1.44 – 1.20 (m, 3H, H_9) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{14}O_2Na^+$) requires *m/z* 201.0886, found *m/z* 201.0894.

IR (neat) ν_{max}: = 3134, 2928, 2854, 1674, 1608, 1566, 1467, 1450, 1396, 1376, 1314, 1293, 1263, 1226, 1157, 1137, 1116, 1086, 1056, 1011, 980, 938, 911, 884, 828, 800 cm^{-1}.

3.68 – Cyclohexyl(1-methyl-1*H*-indol-3-yl)methanone



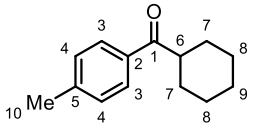
3.68

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-(methylthio)benzaldehyde (318 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.68** (133 mg, 0.55 mmol, 28%) as a colorless oil after purification by column

chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.59). Spectroscopic data were in accordance with literature.[173]

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.52 – 8.37 (m, 1H), 7.75 (s, 1H), 7.44 – 7.28 (m, 3H), 3.85 (s, 3H), 3.02 (tt, *J* = 11.8, 3.3 Hz, 1H), 1.96 – 1.85 (m, 4H), 1.78 – 1.71 (m, 1H), 1.69 – 1.57 (m, 2H), 1.47 – 1.15 (m, 3H) ppm.

3.69 – Cyclopentyl(*p*-tolyl)methanone



3.69

Synthesized following **GP-14**, using **3.38** (505 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-methylbenzalde (237 µL, 240 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.69** (290 mg, 1.43 mmol, 72%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 95:5, R_f = 0.36).

Note: *Following column chromatography,* ***3.69*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.69*** *was subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

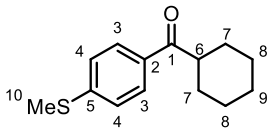
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.85 (d, *J* = 8.2 Hz, 2H, H_4), 7.25 (d, *J* = 6.6 Hz, 2H, H_3), 3.23 (ddd, *J* = 11.4, 7.4, 3.2 Hz, 1H, H_6), 2.41 (s, 3H, H_{10}), 1.93 – 1.80 (m, 4H, H_7), 1.55 – 1.20 (m, 6H, H_{8+9}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}O^+$) requires *m/z* 203.1430, found *m/z* 203.1437.

IR (neat) ν_{max}: = 3029, 2929, 2854, 1722, 1677, 1607, 1572, 1514, 1449, 1408, 1372, 1332, 1314, 1290, 1252, 1201, 1173, 1134, 1116, 1072, 1039, 1020, 973, 893, 825, 792 cm^{-1}.

3.70 – Cyclohexyl[4-(methylthio)pheny]methanone



3.70

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-(methylthio)benzaldehyde (266 µL, 304 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.70** (460 mg, 1.96 mmol, 98%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.28).

Note: *Following column chromatography,* ***3.70*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.70*** *was subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

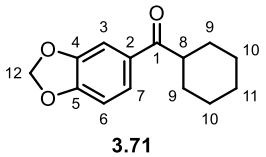
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.78 (m, 2H, H_4), 7.27 (dd, J = 6.8, 1.8 Hz, 2H, H_3), 3.21 (tt, J = 11.4, 3.2 Hz, 1H, H_6), 2.52 (s, 3H, H_{10}), 1.94 – 1.81 (m, 4H, H_7), 1.81 – 1.65 (m, 1H, H_8), 1.55 – 1.18 (m, 5H, H_{8+9}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

HRMS (ESI^+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}OSNa^+$) requires *m/z* 257.0971, found *m/z* 257.0975.

IR (neat) ν_{max}: = 3310, 3075, 3029, 2986, 2922, 2854, 2658, 2564, 1723, 1660, 1587, 1556, 1492, 1460, 1449, 1433, 1402, 1376, 1334, 1318, 1302, 1280, 1259, 1213, 1187, 1172, 1138, 1121, 1093, 1054, 1037, 1028, 1013, 977, 926, 894, 857, 845, 825, 815, 785 cm^{-1}.

3.71 – Benzo[*d*][1,3]dioxol-5-yl(cyclohexyl)methanone



3.71

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), piperonal (300 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.71** (289 mg, 1.24 mmol, 62%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.37).

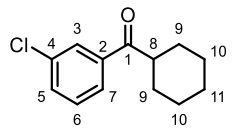
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, J = 8.2, 1.7 Hz, 1H, H_7), 7.43 (d, J = 1.7 Hz, 1H, H_3), 6.85 (d, J = 8.2 Hz, 1H, H_6), 6.04 (s, 2H, H_{12}), 3.16 (tt, J = 11.4, 3.1 Hz, 1H, H_8), 1.91 – 1.79 (m, 4H, H_9), 1.79 – 1.68 (m, 1H, H_{10}), 1.54 – 1.45 (m, 2H, H_{10}), 1.45 – 1.35 (m, 2H, H_{10+11}), 1.35 – 1.20 (m, 1H, H_{11}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.1 (C_1), 151.6 (C_5), 148.4 (C_4), 131.3 (C_2), 124.4 (C_7), 108.4 (C_3), 108.0 (C_6), 101.9 (C_{12}), 45.6 (C_8), 29.8 (2C, C_9), 26.1 (C_9), 26.1 (2C, C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}O_3Na^+$) requires *m/z* 255.0992, found *m/z* 255.0991.

IR (neat) ν_{max}: = 2929, 2854, 2781, 1671, 1604, 1504, 1488, 1441, 1367, 1347, 1313, 1248, 1191, 1165, 1130, 1098, 1066, 1035, 986, 932, 901, 869, 850, 808, 798 cm^{-1}.

3.72 – (3-Chlorophenyl)(cyclohexyl)methanone



3.72

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 3-chlorobenzaldehyde (227 µL, 281 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.72** (341 mg, 1.53 mmol, 77%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 96:4, R_f = 0.35).

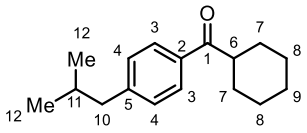
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 1.8 Hz, 1H, H_3), 7.81 (d, J = 7.8 Hz, 1H, H_7), 7.52 (ddd, J = 7.9, 2.0, 1.0 Hz, 1H, H_5), 7.40 (t, J = 7.9 Hz, 1H, H_6), 3.20 (tt, J = 11.3, 3.1 Hz, 1H, H_8), 1.99 – 1.80 (m, 4H, H_9), 1.75 (dd, J = 8.4, 5.3 Hz, 1H, H_{10}), 1.59 – 1.33 (m, 4H, H_{10+11}), 1.33 – 1.13 (m, 1H, H_{11}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.7 (C_1), 138.1 (C_2), 135.1 (C_4), 132.8 (C_5), 130.1 (C_6), 128.5 (C_3), 126.5 (C_7), 45.9 (C_8), 29.5 (2C, C_9), 26.0 (C_{11}), 25.9 (2C, C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}OCl^+$) requires *m/z* 223.0884, found *m/z* 223.0881.

IR (neat) ν_{max}: = 3068, 2929, 2854, 1682, 1596, 1571, 1473, 1449, 1423, 1370, 1332, 1312, 1289, 1265, 1246, 1203, 1175, 1167, 1135, 1113, 1077, 1041, 999, 980, 952, 906, 893, 877, 867, 850, 829, 784 cm^{-1}.

3.73 – Cyclohexyl(4-isobutylphenyl)methanone



3.73

Synthesized following **GP-14**, using **3.38** (533 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-isobutylbenzaldehyde (338 µL, 324 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.73** (384 mg, 1.57 mmol, 79%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.42).

Note: *Following column chromatography,* ***3.73*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.73*** *was subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

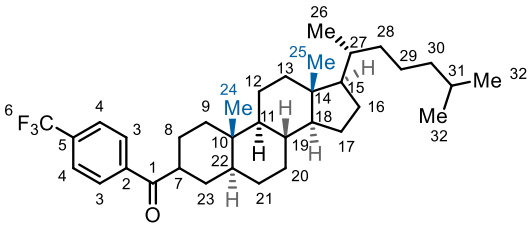
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.76 (m, 2H, H_4), 7.22 (d, J = 8.3 Hz, 2H, H_3), 3.25 (tt, J = 11.5, 3.2 Hz, 1H, H_6), 2.53 (d, J = 7.2 Hz, 1H, H_{10}), 1.96 – 1.83 (m, 5H, $H_{7+10+11}$), 1.79 – 1.68 (m, 1H, H_8), 1.59 – 1.19 (m, 6H, H_{7+8+9}), 0.91 (d, J = 6.6 Hz, 6H, H_{12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

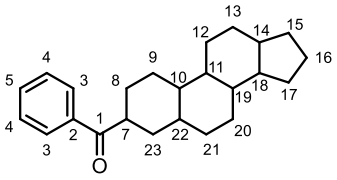
HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}O^+$) requires *m/z* 245.1900, found *m/z* 245.1898.

IR (neat) ν_{max}: = 2932, 2866, 2854, 1680, 1606, 975, 740 cm^{-1}.

3.74 – {(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-[(*R*)-6-methylheptan-2-yl]hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl}[4-(trifluoromethyl)phenyl]methanone



3.74



skeleton of **3.74**

Synthesized following **GP-14**, using **3.48** (1.11 g, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-(trifluoromethyl)benzaldehyde (274 µL, 348 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.74** (802 mg, 1.47 mmol, 74%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.55).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.1 Hz, 2H, H_4), 7.72 (d, *J* = 8.3 Hz, 2H, H_3), 3.29 (dt, *J* = 20.6, 7.8 Hz, 1H, H_7), 1.98 (dd, *J* = 12.5, 3.5 Hz, 1H, $H_{16\text{ or }17}$), 1.91 – 1.78 (m, 2H, H_{16+17}), 1.78 – 1.63 (m, 3H, $H_{16\text{ or }17+8\text{ or }23}$), 1.61 – 1.55 (m, 1H, $H_{8\text{ or }23}$), 1.53 – 1.44 (m, 3H, $H_{12\text{ or }20\text{ or }12}$), 1.40 – 1.20 (m, 10H, H_{Alk}), 1.19 – 0.97 (m, 10H, H_{Alk}), 0.91 (d, *J* = 6.5 Hz, 3H, H_{26}), 0.87 (d, *J* = 1.8 Hz, 3H, H_{32}), 0.86 (d, J = 1.8 Hz, 3H, H_{32}). 0.84 (s, 3H, H_{25}), 0.75 – 0.67 (m, 1H, H_{Alk}), 0.66 (s, 3H, H_{24}) ppm.

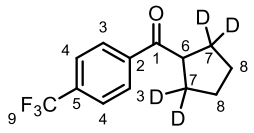
^{13}C NMR (101 MHz, $CDCl_3$): *δ* 203.0 (C_1), 137.4 (C_2), 132.2 (C_5), 128.7 (2C, C_3), 125.8 (2C, C_4), 122.8 (C_6), 56.7 (C_{18}), 56.5 (C_{15}), 54.7 (C_{11}), 46.7 ($C_{7\text{ or }22}$), 46.6 ($C_{7\text{ or }22}$), 42.8 (C_{13}), 40.2 (C_{30}), 39.7 (C_{14}), 38.1 (C_{28}), 36.3 (C_9), 36.2, (C_{10}) 35.9 (C_{27}), 35.6 (C_{19}), 32.2 (C_{20}), 31.7 (C_8), 28.9 (C_{21}), 28.4 (C_{29}), 28.2 (C_{31}), 24.9 (C_{23}), 24.3 (C_{16}), 24.0 (C_{17}), 23.0 (C_{32}), 22.7 (C_{32}), 21.2 (C_{12}), 18.8 (C_{26}), 12.5 ($C_{24\text{ or }25}$), 12.2 ($C_{24\text{ or }25}$) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.07 (3F) ppm.

HRMS (ESI$^+$): *HRMS could not be recorded for this compound.*

IR (neat) ν_{max}: 2951, 2929, 2867, 2846, 1688, 1620, 1582, 1512, 1467, 1445, 1410, 1383, 1323, 1265, 1245, 1213, 1166, 1130, 1109, 1067, 1016, 993, 975, 954, 931, 854, 819, 771 cm^{-1}.

3.76 – (Cyclopentyl-2,2,5,5-*d*$_4$)[4-(trifluoromethyl)phenyl]methanone



92% average incorporation

3.76

Synthesized following **GP-14**, using **3.50** (513 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-(trifluoromethyl)benzaldehyde (274 µL, 348 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.76** (331 mg, 1.34 mmol, 67%, 92% average deuterium incorporation) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.20).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.1 Hz, 2H, H_3), 7.73 (d, J = 8.2 Hz, 2H, H_4), 3.68 (s, 1H, H_6), 1.78 – 1.63 (m, 4H, H_8) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9 (C_1), 139.8 (C_2), 134.2 (q, J = 32.6 Hz, C_5), 128.9 (2C, C_3), 125.7 (q, J = 3.7 Hz, 2C, C_4), 123.8 (q, J = 272.6 Hz, C_9), 46.5 (C_6), 29.3 (2C, C_7), 26.2 (2C, C_8) ppm.

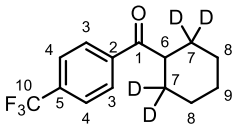
HRMS (QTOF, EI$^+$, 70 eV): exact mass calculated for $[M]^+$ ($C_{13}H_9D_4F_3O^+$) requires *m/z* 246.1164, found *m/z* 246.1159.

Note: *HRMS could not be recorded for this compound.*

IR (neat) ν_{max}: = 2956, 2874, 2229, 2115, 1726, 1686, 1620, 1582, 1511, 1466, 1450, 1409, 1321, 1212, 1165, 1126, 1108, 1065, 1014, 980, 964, 909, 866, 850, 833, 781 cm^{-1}.

Note: *Total and average deuterium incorporation was determined from ^{1}H NMR analysis by comparison to the non-deuterated compound and by the integration (intensity) of the β-protons in relatively the intact α-proton of the ketone.*

3.77 – (Cyclohexyl-2,2,6,6-*d*$_4$)[4-(trifluoromethyl)phenyl]methanone



76% incorporation

3.77

Synthesized following **GP-14**, using **3.49** (541 mg, 2.00 mmol, 1.00 eq.), cesium carbonate (Cs_2CO_3, 977 mg, 3.00 mmol, 1.50 eq.), 4-(Trifluoromethyl)benzaldehyde (274 µL, 348 mg, 2.00 mmol, 1.00 eq.) and 1,4-dioxane (10.0 mL) afforded compound **3.77** (350 mg, 1.34 mmol, 67%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.33).

Note: *Following column chromatography,* ***3.77*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.77*** *was subjected to the subsequent step, silyl enol ether formation. The corresponding silyl enol ether, being less polar, was then easily separable from the aforementioned impurities due to the change in the relative polarities.*

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 2H, H_4), 7.72 (d, J = 8.4 Hz, 2H, H_3), 3.22 (s, 1H, H_6), 2.01 – 1.79 (m, 2H, H_{7+8}), 1.78 – 1.69 (m, 1H, H_8), 1.56 – 1.35 (m, 3H, H_{8+9}), 1.35 – 1.08 (m, 1H, H_9) ppm.

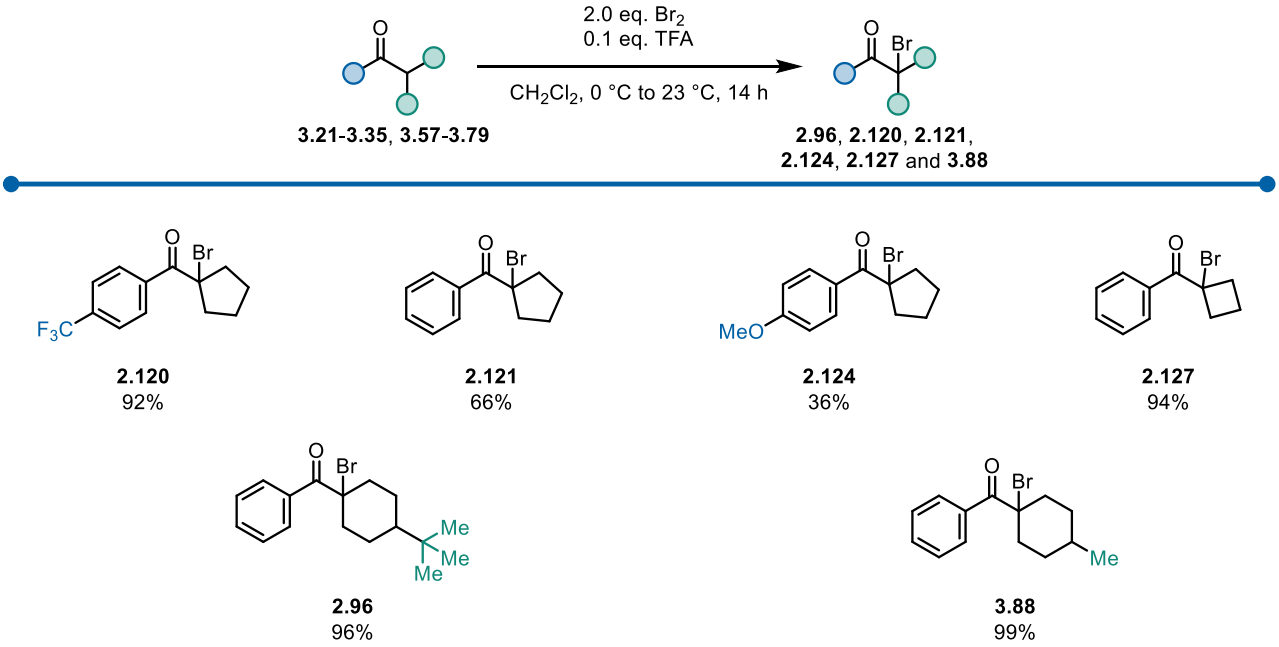
^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.08 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{14}H_{12}D_4F_3O^+$) requires *m/z* 261.1399, found *m/z* 261.1398.

IR (neat) ν_{max}: = 2928, 2856, 1685, 1618, 1581, 1510, 1447, 1408, 1321, 1253, 1214, 1165, 1126, 1066, 1016, 975, 946, 850, 817, 761 cm^{-1}.

3.3.1.7 General Procedure 15: Synthesis of α-Bromoketones from Ketones



2.120
92%

2.121
66%

2.124
36%

2.127
94%

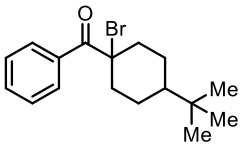
2.96
96%

3.88
99%

Scheme 3.7: Scope of α-Bromoketones.

To a mixture of ketone (1.00 mmol, 1.00 eq.) dry dichloromethane (CH_2Cl_2, 0.5 M) was added bromine (Br_2, 2.00 mmol, 2.00 eq.) and 5 drops of glacial acetic acid (AcOH), and the mixture was stirred at 23 °C for 14 h. The reaction was stopped by addition of a saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$, 2.00 mL) and transferred to a separation funnel, followed up by addition of dichloromethane (CH_2Cl_2, 2.00 mL). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (CH_2Cl_2, 3 × 5.00 mL). The combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/ethyl acetate = 100:0 to 80:20) to afford the corresponding ketone.

2.96 – (1-Bromo-4-(*tert*-butyl)cyclohexyl)(phenyl)methanone

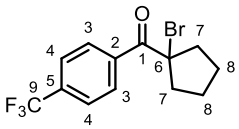


2.96

Synthesized following **GP-15**, using **3.26** (489 mg, 2.00 mmol, 1.00 eq.), bromine (Br_2, 205 µL, 320 mg, 4.00 mmol, 2.00 eq.), 5 drops acetic acid (AcOH) and dichloromethane (CH_2Cl_2, 4.00 mL) afforded compound **2.88** (619 mg, 1.92 mmol, 96%) as a colorless oil after purification by column chromatography (heptanes/toluene = 90:10, R_f = 0.32). Spectroscopic data were in accordance with literature.[143]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 – 7.99 (m, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 2.99 (dd, *J* = 13.5, 2.9 Hz, 2H), 2.13 (td, *J* = 13.2, 3.5 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.15 (tt, *J* = 12.3, 3.3 Hz, 1H), 1.01 – 0.87 (m, 2H), 0.76 (s, 9H) ppm.

2.120 – <u>(1-Bromocyclopentyl)[4-(trifluoromethyl)phenyl]methanone</u>



2.120

Synthesized following **GP-15**, using **3.23** (101 mg, 1.00 mmol, 1.00 eq.), bromine (Br_2, 53 µL, 160 mg, 1.00 mmol, 2.00 eq.), 5 drops acetic acid (AcOH) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.120** (150 mg, 0.47 mmol, 92%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.69).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.2 Hz, 2H, H_3), 7.71 (d, *J* = 8.3 Hz, 2H, H_4), 2.62 – 2.36 (m, 4H, H_7), 2.25 – 2.01 (m, 2H, H_8), 1.98 – 1.74 (m, 2H, H_8) ppm.

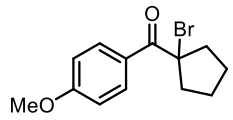
^{13}C NMR (101 MHz, $CDCl_3$): δ 194.5 (C_1), 138.0 (C_2), 134.0 (C_5), 130.6 (2C, C_3), 125.4 (q, *J* = 3.7 Hz, 2C, C_4), 125.1 (C_9), 70.9 (C_6), 41.0 (2C, C_7), 23.7 (2C, C_8) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.20 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}BrF_3O^+$) requires *m/z* 321.0096, found *m/z* 321.0096.

IR (neat) ν_{max}: = 2968, 1682, 1601, 1409, 1327, 1261, 1171, 1132, 1067, 1015, 855, 766 cm^{-1}.

2.124 – (1-Bromocyclopentyl)(4-methoxyphenyl)methanone

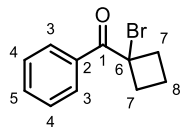


2.124

Synthesized following **GP-15**, using **3.21** (204 mg, 1.00 mmol, 1.00 eq.), bromine (Br_2, 102 µL, 320 mg, 2.00 mmol, 2.00 eq.), 5 drops acetic acid (AcOH) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.124** (103 mg, 0.36 mmol, 36%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.39). Spectroscopic data were in accordance with literature.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 – 8.02 (m, 2H), 6.98 – 6.84 (m, 2H), 3.88 (s, 3H), 2.63 – 2.36 (m, 4H), 2.11 – 1.98 (m, 2H), 1.86 – 1.73 (m, 2H) ppm.

2.127 – (1-Bromocyclobutyl)(phenyl)methanone



2.127

Synthesized following **GP-15**, using cyclobutyl(phenyl)methanone (169 mg, 1.00 mmol, 1.00 eq.), bromine (Br_2, 102 µL, 320 mg, 2.00 mmol, 2.00 eq.), 5 drops acetic acid (AcOH) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.127** (225 mg, 0.94 mmol, 94%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 90:10, Rf = 0.64).

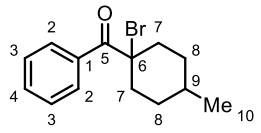
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05 (d, J = 8.0 Hz, 2H, H_3), 7.56 (t, J = 7.3 Hz, 1H, H_5), 7.46 (t, J = 7.7 Hz, 2H, H_4), 3.26 – 3.03 (m, 2H, H_7), 2.85 – 2.70 (m, 2H, H_7), 2.50 – 2.30 (m, 1H, H_8), 1.96 – 1.80 (m, 1H, H_8) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 194.7 (C_1), 133.4 (C_5), 132.4 (C_2), 130.3 (2C, C_3), 128.5 (2C, C_4), 59.8 (C_6), 37.2 (2C, C_7), 16.6 (C_8) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{11}BrNa^+$) requires *m/z* 260.9885, found *m/z* 260.9886.

IR (neat) ν_{max}: = 2996, 2954, 1677, 1597, 1580, 1448, 1423, 1318, 1281, 1249, 1209, 1182, 1140, 1075, 1027, 959, 900, 854, 798 cm^{-1}.

3.88 – (1-Bromo-4-methylcyclohexyl)(phenyl)methanone



3.88

cis/trans mixture

Synthesized following **GP-15**, using **3.29** (101 mg, 1.00 mmol, 1.00 eq.), bromine (Br_2, 102 µL, 320 mg, 2.00 mmol, 2.00 eq.), 5 drops acetic acid (AcOH) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.88** (139 mg, 0.50 mmol, 99%) as a colorless oil after filtering over a short pad of silica and washing with EtOAc.

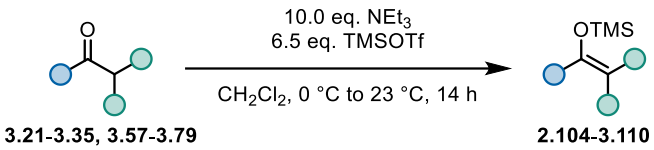
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 – 8.02 (m, 2H, H_2), 7.59 – 7.49 (m, 1H, H_4), 7.42 (tt, *J* = 7.7, 1.9 Hz, 2H, H_3), 2.85 (d, *J* = 12.7 Hz, 1H, H_7), 2.57–2.41 (m, 1H, H_7), 2.17 (td, *J* = 13.2, 3.8 Hz, 1H, H_7), 1.81–1.58 (m, 3H, H_{7+8}), 1.58 – 1.31 (m, 2H, H_8), 0.99 (d, *J* = 6.5 Hz, 1H, H_{10a}), 0.92 (td, *J* = 13.8, 2.9 Hz, 1H, H_9), 0.81 (d, *J* = 6.6 Hz, 2H, $_{10b}$) ppm

^{13}C NMR (126 MHz, $CDCl_3$): δ 197.6 ($C_{5a\text{ or }5b}$), 197.5 ($C_{5a\text{ or }5b}$), 136.2 ($C_{1a\text{ or }1b}$), 135.9 ($C_{1a\text{ or }1b}$), 132.2 ($C_{4a\text{ or }4b}$), 132.2 ($C_{4a\text{ or }4b}$), 130.0 (2C, $C_{2a\text{ or }2b}$), 129.8 (2C, $C_{2a\text{ or }2b}$), 128.3 (2C, $C_{3a\text{ or }3b}$), 128.2 (2C, $C_{3a\text{ or }3b}$), 69.5 (C_6), 39.2 ($C_{7a\text{ or }7b}$), 37.2 ($C_{7a\text{ or }7b}$), 33.7 ($C_{8a\text{ or }8b}$), 31.5 ($C_{9a\text{ or }9b}$), 31.2 ($C_{9a\text{ or }9b}$), 30.7 ($C_{8a\text{ or }8b}$), 22.0 ($C_{10a\text{ or }10b}$), 21.6 ($C_{10a\text{ or }10b}$) ppm.

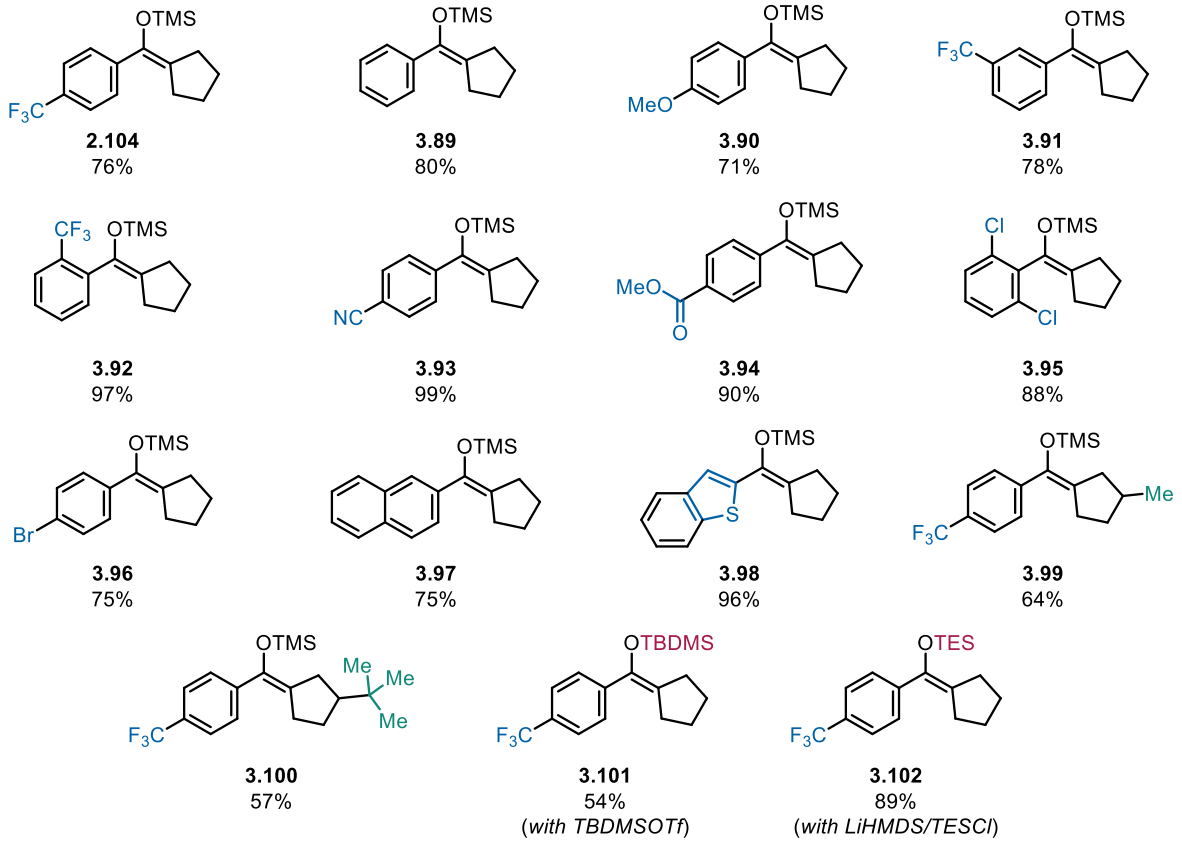
HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{17}OBrNa^+$) requires *m/z* 303.0355, found *m/z* 303.0354.

IR (neat) ν_{max}: = 2950, 2924, 2858, 1675, 1597, 1578, 1450, 1279, 1253, 1218, 1183, 1134, 1078, 1060, 1020, 1002, 950, 938, 860, 817, 811, 787 cm^{-1}.

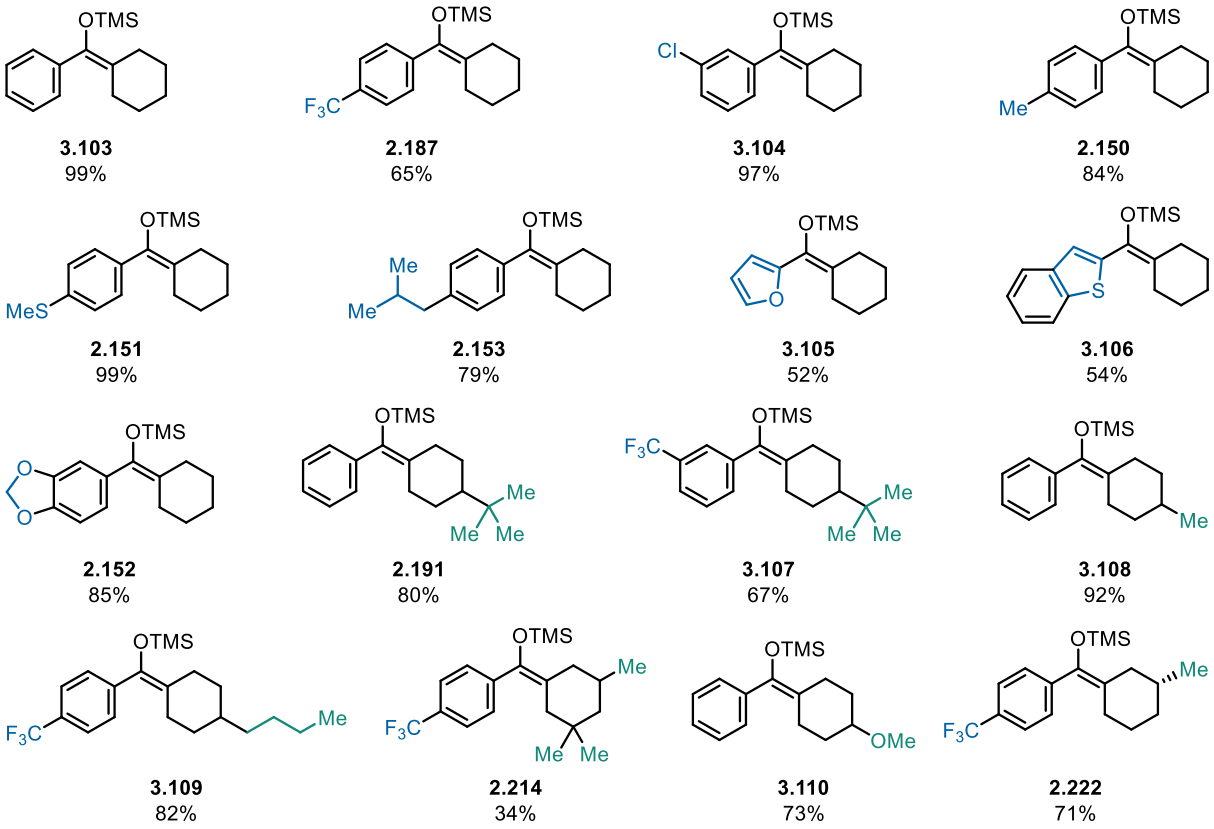
3.3.1.8 General Procedure 16: Synthesis of Silyl Enol Ethers from Ketones



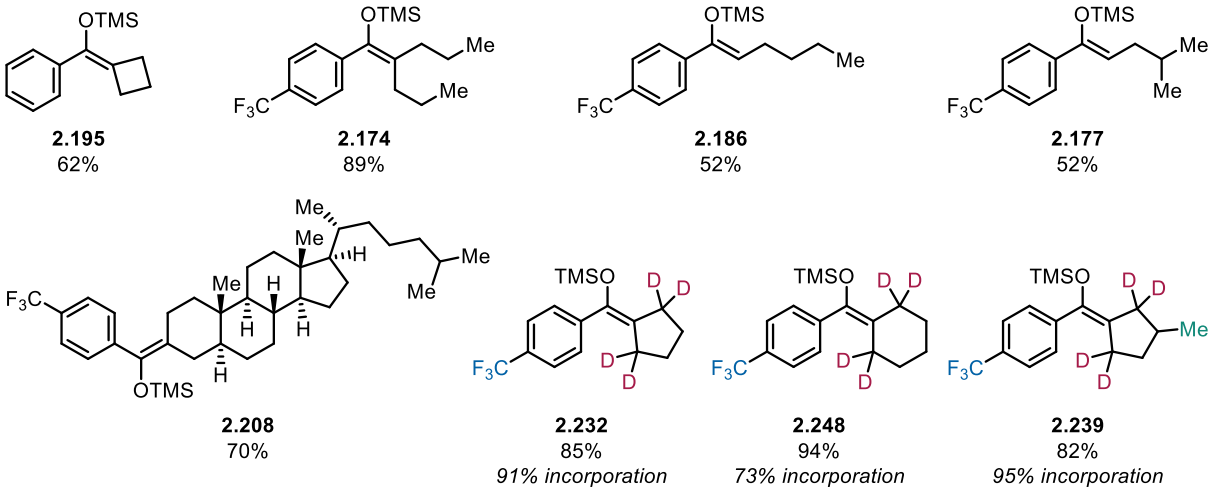
To a solution of the ketone (2.00 mmol, 1.00 eq.) and NEt_3 (20.0 mmol, 10.0 eq.) in dichloromethane (CH_2Cl_2, 0.5 M) at 0 °C Me_3SiOTf (13.0 mmol, 6.50 eq.) was added dropwise and the mixture was subsequently allowed to slowly warm to 23 °C over 14 h. After cooling to 0 °C, the reaction was stopped by slow addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 10.0 mL) and transferred to a separation funnel, followed up by addition of dichloromethane (CH_2Cl_2, 10.0 mL). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (CH_2Cl_2, 3 × 10.0 mL). The combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50 or pentane/diethyl ether EtOAc = 100:0 to 50:50) to afford the corresponding ketone.



Scheme 3.8: Silylation of cylopentyl-bearing ketones.

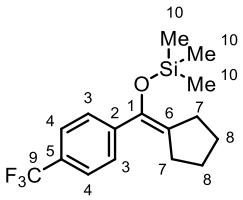


Scheme 3.9: Silylation of cyclohexyl-bearing ketones.



Scheme 3.10: Silylation of mechanistically interesting ketone substrates.

2.104 – {cyclopentylidene[4-(trifluoromethyl)phenyl]methoxy}trimethylsilane



2.104

Synthesized following **GP-16**, using **3.23** (242.0 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.104** (238.0 mg, 0.76 mmol, 76%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.91).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (q, J = 8.4 Hz, 4H, H_{3+4}), 2.41 (ddd, J = 10.0, 8.4, 4.4 Hz, 4H, H_7), 1.68 (qd, J = 7.4, 5.2 Hz, 4H, H_8), 0.06 (s, 9H, H_9) ppm.

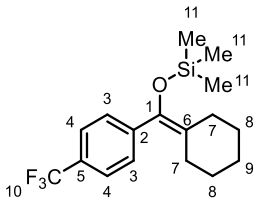
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.2 (C_1), 139.9 (C_2), 128.7 (C_6), 128.6 (q, J = 32.5 Hz, C_5), 127.7 (2C, C_3), 124.8 (q, J = 4.0 Hz, 2C, C_4), 124.4 (q, J = 271 Hz, C_9), 31.4 (C_7), 30.8 (C_7), 27.8 (C_8), 25.9 (C_8), 0.75 (3C, C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -62.40 (3F) ppm.

HRMS (ESI^+): *HRMS could not be recorded for this compound*.

IR (neat) ν_{max}: = 2958, 2869, 2839, 1659, 1616, 1437, 1408, 1323, 1276, 1252, 1163, 1124, 1096, 1066, 1015, 957, 916, 872, 841, 829, 763, 748 cm^{-1}.

2.187 – {Cyclohexylidene[4-(trifluoromethyl)phenyl]methoxy}trimethylsilane



2.187

Synthesized following **GP-16**, using **3.25** (394 mg, 2.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 2.40 mL, 2.95 g, 13.0 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 4.00 mL) afforded compound **2.187** (427 mg, 1.30 mmol, 65%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.34).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.1 Hz, 2H, H_4), 7.41 (d, J = 8.0 Hz, 2H, H_3), 2.34 (t, J = 5.8 Hz, 2H, H_7), 2.20 – 2.07 (m, 2H, H_7), 1.68 – 1.55 (m, 4H, H_8), 1.49 (d, J = 5.7 Hz, 2H, H_9), -0.03 (s, 9H, H_{11}) ppm.

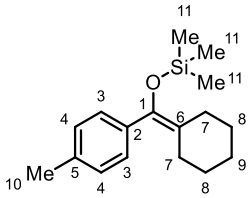
^{13}C NMR (101 MHz, $CDCl_3$): δ 142.7 (C_1), 140.0 (C_2), 129.6 (2C, C_3), 127.8 (C_5), 126.11 (q, J = 3.7 Hz, C_{10}), 124.9 (q, J = 3.8 Hz, 2C, C_4), 122.9 (C_6), 29.9 (C_7), 28.2 (C_7), 28.0 (C_8), 27.5 (C_8), 26.9 (C_9), 0.5 (3C, C_{11}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.45 (3F) ppm.

HRMS (ESI$^+$): *HRMS could not be recorded for this compound.*

IR (neat) ν_{max}: = 2930, 2856, 1728, 1688, 1581, 1511, 1451, 1409, 1323, 1252, 1207, 1168, 1129, 1066, 1018, 975, 946, 913, 879, 842, 765 cm^{-1}.

2.150 – [Cyclohexylidene(*p*-tolyl)methoxy]trimethylsilane



2.150

Synthesized following **GP-16**, using **3.69** (202 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.150** (231 mg, 0.84 mmol, 84%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.41).

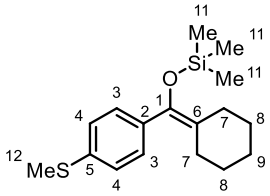
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.15 (m, 2H, H_4), 7.10 (d, J = 7.9 Hz, 2H, H_3), 2.34 (s, 3H, H_{10}), 2.34 – 2.30 (m, 2H, H_7), 2.17 – 2.09 (m, 2H, H_7), 1.66 – 1.52 (m, 4H, H_8), 1.51 – 1.42 (m, 2H, H_9), -0.04 (s, 9H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.3 (C_1), 136.9 (C_5), 136.1 (C_2), 129.3 (2C, C_3), 128.5 (2C, C_4), 120.7 (C_6), 30.1 (C_7), 28.3 (C_7), 27.9 (C_8), 27.6 (C_8), 27.0 (C_9), 21.4 (C_{10}), 0.5 (3C, C_{11}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{17}H_{27}OSi^+$) requires m/z 275.1826, found m/z 275.1820.

IR (neat) ν_{max}: = 3024, 2958, 2923, 2852, 1661, 1510, 1447, 1405, 1289, 1250, 1234, 1219, 1180, 1128, 1110, 1079, 1022, 989, 929, 915, 870, 842, 786 cm^{-1}.

2.151 – {cyclohexylidene[4-(methylthio)phenyl]methoxy}trimethylsilane



2.151

Synthesized following **GP-16**, using **3.70** (234 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.151** (303 mg, 0.99 mmol, 99%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.33).

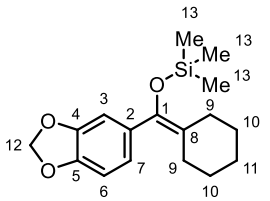
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.15 (m, 4H, H_{3+4}), 2.49 (s, 3H, H_{10}), 2.32 (t, J = 5.7 Hz, 2H, H_7), 2.19 – 2.05 (m, 2H, H_7), 1.63 – 1.51 (m, 4H, H_8), 1.47 (d, J = 5.0 Hz, 2H, H_9), -0.03 (s, 9H, H_{11}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.8 (C_1), 137.3 (C_5), 135.8 (C_2), 129.8 (2C, C_4), 125.8 (2C, C_3), 121.3 (C_6), 30.0 (C_7), 28.3 (C_7), 28.0 (C_8), 27.6 (C_8), 27.0 (C_9), 15.9 (C_{10}), 0.5 (3C, C_{11}) ppm.

HRMS (QTOF, EI$^+$, 70 eV): exact mass calculated for $[M]^+$ ($C_{17}H_{26}SiOS^+$) requires *m/z* 306.1474, found *m/z* 306.1460.

IR (neat) ν_{max}: = 3023, 2957, 2921, 2851, 1716, 1657, 1595, 1491, 1446, 1396, 1348, 1333, 1319, 1286, 1250, 1233, 1216, 1183, 1127, 1110, 1095, 1075, 1016, 989, 967, 928, 913, 867, 838, 752 cm^{-1}.

2.152 – [Benzo[*d*][1,3]dioxol-5-yl(cyclohexylidene)methoxy]trimethylsilane



2.152

Synthesized following **GP-16**, using **3.71** (116 mg, 0.50 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.70 mL, 506 mg, 5.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.70 mL, 737 mg, 3.25 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.152** (130.0 mg, 0.43 mmol, 85%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 95:5, R_f = 0.36).

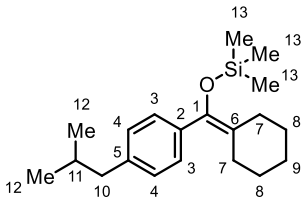
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (dd, J = 1.3, 0.7 Hz, 1H, H_7), 6.75 (dd, J = 1.6, 1.1 Hz, 2H, H_{3+6}), 5.95 (s, 2H, H_{12}), 2.30 (t, J = 5.7 Hz, 2H, H_9), 2.19 – 2.06 (m, 2H, H_9), 1.56 (dd, J = 6.1, 3.0 Hz, 4H, H_{10}), 1.47 (d, J = 3.3 Hz, 2H, H_{11}), -0.01 (s, 9H, H_{13}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.1 (C_1), 146.7 (C_5), 140.8 (C_4), 133.0 (C_2), 123.0 (C_7), 120.7 (C_8), 109.9 (C_3), 107.7 (C_6), 101.0 (C_{12}), 30.1 (C_9), 28.3 (C_9), 27.9 (C_{10}), 27.6 (C_{10}), 27.0 (C_{11}), 0.5 (3C, C_{13}) ppm.

HRMS (QTOF, EI$^+$, 70 eV): exact mass calculated for $[M]^+$ ($C_{17}H_{24}O_3Si^+$) requires m/z 314.1489, found m/z 314.1482.

IR (neat) ν_{max}: = 2958, 2922, 2851, 2775, 1658, 1606, 1503, 1485, 1434, 1344, 1333, 1286, 1250, 1233, 1205, 1147, 1135, 1120, 1101, 1063, 1039, 991, 934, 901, 869, 838, 817, 805, 752 cm^{-1}.

2.153 – <u>[Cyclohexylidene(4-isobutylphenyl)methoxy]trimethylsilane</u>



2.153

Synthesized following **GP-16**, using **3.73** (122 mg, 0.50 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.70 mL, 506 mg, 5.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.70 mL, 737 mg, 3.25 mmol, 6.50.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.153** (250 mg, 0.79 mmol, 79%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 95:5, R_f = 0.62).

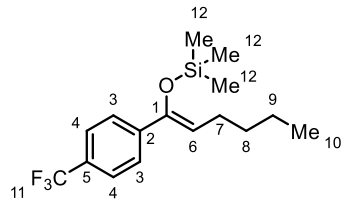
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.16 (m, 2H, H_4), 7.06 (d, J = 8.2 Hz, 2H, H_3), 2.46 (d, J = 7.2 Hz, 2H, H_{10}), 2.33 (t, J = 5.8 Hz, 2H, H_7), 2.13 (d, J = 6.0 Hz, 2H, H_7), 1.88 (dd, J = 13.6, 6.7 Hz, 1H, H_{11}), 1.66 – 1.52 (m, 4H, H_8), 1.48 (d, J = 5.0 Hz, 2H, H_9), 0.89 (d, J = 6.6 Hz, 6H, H_{12}), -0.05 (s, 9H, H_{13}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.3 (C_1), 140.8 (C_5), 136.4 (C_2), 129.1 (2C, C_3), 128.6 (2C, C_4), 120.6 (C_6), 45.4 (C_{10}), 30.4 (C_{11}), 30.0 (C_7), 28.3 (C_7), 27.9 (C_8), 27.6 (C_8), 27.0 (2C, C_{12}), 22.5 (C_9), 0.4 (3C, C_{13}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{20}H_{32}OSi^+$) requires m/z 316.2217, found m/z 316.2220.

IR (neat) ν_{max}: = 3023, 2955, 2922, 2868, 2851, 1718, 1665, 1611, 1510, 1465, 1447, 1409, 1384, 1366, 1334, 1319, 1287, 1250, 1234, 1217, 1180, 1167, 1128, 1078, 1021, 990, 914, 869, 839, 752 cm^{-1}.

2.186 – (*Z*)-trimethyl({1-[4-(trifluoromethyl)phenyl]hex-1-en-1-yl}oxy)silane



2.186

Synthesized following **GP-16**, using **3.34** (489 mg, 2.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 2.40 mL, 2.95 g, 13.0 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 4.00 mL) afforded compound **2.186** (326 mg, 1.03 mmol, 52%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 96:4, R_f = 0.41).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.45 (m, 4H, H_{3+4}), 5.36 (t, *J* = 7.2 Hz, 1H, H_6), 2.21 (dd, *J* = 14.4, 7.2 Hz, 2H, H_7), 1.51 – 1.30 (m, 4H, H_{8+9}), 1.13 – 0.85 (m, 3H, H_{10}), 0.14 (s, 9H, H_{12}) ppm.

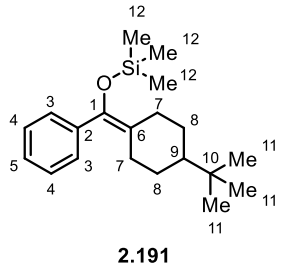
^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8 (C_1), 142.9 (C_2), 129.3 (q, *J* = 33.4 Hz (C_5), 125.5 (2C, C_3), 125.2 (q, *J* = 3.8 Hz, 2C, C_4), 123.0 (C_{11}), 114.1 (C_6), 31.9 (C_7), 26.2 (C_8), 22.7 (C_9), 14.1 (C_{10}), -0.7 (3C, C_{12}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.42 (3F) ppm.

HRMS (ESI$^+$): *HRMS could not be recorded for this compound.*

IR (neat) ν_{max}: = 2959, 2928, 2858, 1690, 1646, 1617, 1466, 1409, 1379, 1324, 1288, 1253, 1166, 1127, 1110, 1069, 1015, 977, 934, 880, 843, 750 cm^{-1}.

2.191 – {[4-(tert-butyl)cyclohexylidene](phenyl)methoxy}trimethylsilane



2.191

Synthesized following **GP-16**, using **3.26** (147 mg, 0.60 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.84 mL, 607 mg, 6.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.72 mL, 885 mg, 3.90 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **2.191** (151 mg, 0.48 mmol, 80%) as a colorless oil after purification by column chromatography (heptanes/toluene = 50:50, Rf = 0.88).

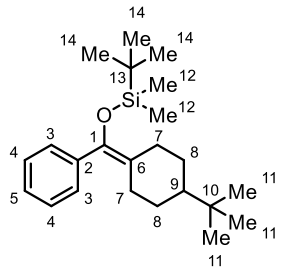
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.12 (m, 5H, $H_{3\text{-}5}$), 3.05 (dd, J = 13.6, 2.3 Hz, 1H, H_7), 2.62 – 2.47 (m, 1H, H_7), 1.96 – 1.69 (m, 4H, H_{7+8}), 1.21 – 1.05 (m, 2H, H_8), 1.04 – 0.95 (m, 1H, H_8), 0.89 (s, 9H, H_{11}), 0.00 (s, 9H, H_{12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.0 (C_1), 139.0 (2C, C_3), 129.4 (2C, C_4), 127.8 (C_2), 127.3 (C_5), 121.0 (C_6), 48.5 (C_9), 32.6 (C_{10}), 30.0 (C_7), 29.0 (C_7), 28.2 (C_8), 27.9 (C_8), 27.8 (3C, C_{11}), 0.48 (3C, C_{12}) ppm.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{33}OSi^+$) requires *m/z* 317.2295, found *m/z* 317.2292.

IR (neat) ν_{max}: = 2941, 2865, 1718, 1682, 1597, 1579, 1478, 1467, 1448, 1393, 1365, 1346, 1314, 1282, 1241, 1214, 1176, 1143, 1109, 1071, 1026, 1002, 973, 930, 859, 841, 768 cm^{-1}.

2.193 – *tert*-Butyl((4-(tert-butyl)cyclohexylidene)(phenyl)methoxy)dimethylsilane



2.193

Synthesized following **GP-16**, using **3.26** (122 mg, 0.50 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.70 mL, 506 mg, 5.00 mmol, 10.0 eq.), *tert*-butyldimethylsilyl triflate (TBDMSOTf, 0.77 mL, 0.89 g, 3.25 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **2.193** (109 mg, 0.30 mmol, 61%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.71).

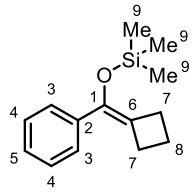
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 – 7.24 (m, 4H, $H_{2\text{-}4}$), 7.24 – 7.18 (m, 1H, $H_{2\text{-}4}$), 3.06 (ddd, J = 13.4, 5.7, 3.1 Hz, 1H, H_7), 2.45 (ddd, J = 13.4, 5.7, 3.1 Hz, 1H, H_7), 1.91 – 1.84 (m, 1H, H_7), 1.82 – 1.62 (m, 3H, H_{7+8}), 1.16 – 1.02 (m, 2H, H_8), 1.00 – 0.91 (m, 1H, H_9), 0.87 – 0.85 (m, 9H, H_{14}), 0.83 (s, 9H, H_{11}), -0.23 (s, 3H, H_{12}), -0.21 (s, 3H, H_{12}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.2 (C_1), 139.2 (C_2), 129.5 (2C, C_3), 127.8 (2C, C_4), 127.3 (C_5), 120.5 (C_6), 48.5 (C_9), 32.6 (C_{10}), 30.1 (C_{13}), 29.0 (2C, C_8), 28.1 (2C, C_7), 27.8 (3C, C_{11}), 26.0 (3C, C_{14}), -4.2 (C_{12}), -4.3 (C_{12}) ppm.

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{23}H_{38}OSiNa^+$) requires *m/z* 381.2584, found *m/z* 381.2580.

IR (neat) ν_{max}: = 2954, 2937, 2857, 1472, 1463, 1444, 1391, 1364, 1291, 1250, 1218, 1174, 1109, 1072, 1029, 1006, 988, 959, 928, 881, 849, 836, 816, 777 cm^{-1}.

2.195 – [Cyclobutylidene(phenyl)methoxy]trimethylsilane



2.195

Synthesized following **GP-16**, using cyclobutyl(phenyl)methanone (169 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.195** (145 mg, 0.62 mmol, 62%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.87).

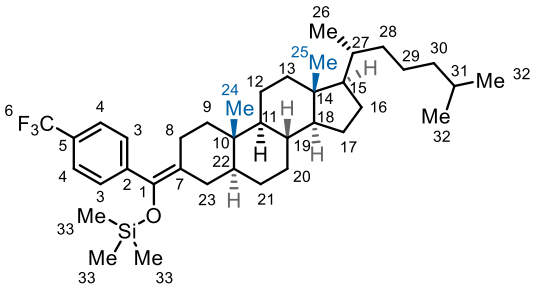
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (d, J = 7.9 Hz, 2H, H_3), 7.30 (t, J = 7.6 Hz, 2H, H_4), 7.19 (t, J = 7.3 Hz, 1H, H_5), 3.02 – 2.91 (m, 2H, H_7), 2.91 – 2.77 (m, 2H, H_7), 2.03 (p, J = 7.7 Hz, 2H, H_8), 0.12 (s, 9H, H_9) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 140.8 (C_1), 137.9 (C_2), 128.0 (2C, C_3), 126.6 (C_5), 125.8 (2C, C_4), 123.2 (C_6), 31.2 (C_7), 29.7 (C_7), 18.3 (C_8), 0.7 (3C, C_9) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}OSi^+$) requires *m/z* 233.1356, found *m/z* 233.1353.

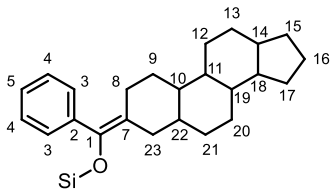
IR (neat) ν_{max}: = 3057, 2954, 2901, 2830, 1706, 1683, 1599, 1493, 1446, 1312, 1290, 1278, 1250, 1213, 1169, 1134, 1116, 1074, 1023, 991, 968, 912, 874, 836, 752 cm^{-1}.

2.208 – {[(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-3*H*-cyclopenta[*a*]phenanthren-3-ylidene][4-(trifluoromethyl)phenyl]methoxy}trimethylsilane



2.208

E/*Z* ratio = 1:1



skeleton of **2.208**

Synthesized following **GP-16**, using **3.74** (163 mg, 0.30 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.42 mL, 304.0 mg, 3.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.36 mL, 438 mg, 1.95 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.208** (131 mg, 0.21 mmol, 71%, *E*/*Z* = 1:1) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 100:0 to 96.4, R_f = 0.25 in 100% heptane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.0 Hz, 2H, H_4), 7.41 (d, *J* = 8.0 Hz, 2H, H_3), 2.83 (d, *J* = 14.5 Hz, 0.5H, $H_{8\ or23}$), 2.57 (d, *J* = 12.7 Hz, 0.5H, $H_{8\ or23}$), 2.25 (s, 0.5H, $H_{8\ or23}$), 2.05 (d, *J* = 18.8 Hz, 0.5H, $H_{8\ or23}$), 2.02 – 1.58 (m, 7H, H_{Alk}), 1.51 – 0.94 (m, 22H, H_{Alk}), 0.92 – 0.89 (m, 3H, H_{26}), 0.88 – 0.86 (m, 6H, H_{32}), 0.85 (d, *J* = 1.6 Hz, 3H, H_{25}), 0.63 (d, *J* = 17.1 Hz, 3H, H_{24}), -0.03 (s, 9H, H_{33}) ppm.

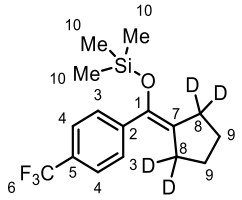
^{13}C NMR (101 MHz, $CDCl_3$): δ 147.4 (C_1), 142.8 (C_2), 130.6 (C_5), 129.6 (C_3), 129.5 (C_3), 124.84 (C_4), 124.81 (C_4), 122.8 (C_7), 122.6 (C_6), 83.6 (C_{33}), 56.6 (C_{18}), 56.4 (C_{15}), 54.5 (C_{11}), 47.8 (C_{22a}), 47.2 (C_{22b}), 42.8 (C_{13}), 40.2 (C_{30}), 39.7 (C_{14}), 38.9 (C_{28}), 36.3 (C_9), 36.0 (C_{27}), 35.6 (C_{10}), 32.3 (C_{19}), 30.4 (C_{20}), 29.0 (C_{21}), 28.4 (C_{29}), 28.2 (C_{31}), 24.4 (C_{23}), 24.0 (C_{16}), 23.5 (C_{17}), 23.0 (C_{32}), 22.7 (C_{32}), 21.3 (C_{12}), 18.8 (C_{26}), 12.2 ($C_{24\ or\ 25}$), 11.9 ($C_{24\ or\ 25}$), 0.5 (3C, C_{34}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{38}H_{60}F_3OSi^+$) requires *m/z* 617.4360, found *m/z* 617.4359.

IR (neat) ν_{max}: = 2955, 2928, 2868, 2848, 1325, 1267, 1251, 1164, 1128, 1105, 1089, 1067, 883, 866, 844, 746 cm^{-1}.

2.232 – {(Cyclopentylidene-2,2,5,5-*d*$_4$)[4-(trifluoromethyl)phenyl]methoxy}trimethylsilane



2.232

Synthesized following **GP-16**, using **3.76** (74.0 mg, 0.30 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.42 mL, 304 mg, 3.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.36 mL, 438 mg, 1.95 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.232** (81.5 mg, 0.26 mmol, 85%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 96:4, R_f = 0.74).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.56 (d, J = 8.3 Hz, 2H, H_3), 7.51 (d, J = 8.3 Hz, 2H, H_4), 1.73 – 1.62 (m, 4H, H_9), 0.06 (s, 9H, H_{10}) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 143.2 (C_1), 140.0 (C_2), 128.7 (C_5), 128.6 (C_7), 127.7 (2C, C_3), 124.8 (q, J = 3.8 Hz, 2C, C_4), 124.4 (q, J = 239.8 Hz, C_6), 31.1 (ap t, C_8), 30.5 (ap t, C_8), 27.6 (C_9), 25.7 (C_9), 0.7 (3C, C_{10}) ppm.

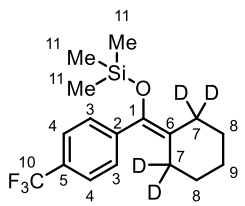
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.40 (3F) ppm.

HRMS (QTOF, EI$^+$, 70 eV): exact mass calculated for $[M]^+$ ($C_{16}H_{17}D_4F_3OSi^+$) requires *m/z* 318.1559, found *m/z* 318.1547.

Note: *HRMS could not be recorded for this compound.*

IR (neat) ν_{max}: = 2957, 2934, 2872, 2208, 2111, 1691, 1658, 1645, 1616, 1575, 1466, 1450, 1407, 1323, 1274, 1251, 1222, 1205, 1165, 1151, 1124, 1106, 1086, 1066, 1035, 1016, 979, 958, 912, 882, 866, 839, 794 cm^{-1}.

2.248 – {(Cyclohexylidene-2,2,6,6-*d*$_4$)[4-(trifluoromethyl)phenyl]methoxy}trimethylsilane



73% average incorporation

2.248

Synthesized following **GP-16**, using **3.77** (130 mg, 0.50 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.70 mL, 506 mg, 5.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.70 mL, 737 mg, 3.25 mmol, 6.50.) and dichloromethane

(CH_2Cl_2, 2.00 mL) afforded compound **2.248** (155 mg, 0.47 mmol, 94%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 96:4, R_f = 0.48).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.0 Hz, 2H, H_4), 7.41 (d, J = 7.9 Hz, 2H, H_3), 2.33 (dd, J = 14.6, 8.8 Hz, 0.5H, H_7), 2.23 – 2.00 (m, 0.6H, H_7), 1.57 (dd, J = 9.8, 3.5 Hz, 4H, H_8), 1.48 (d, J = 3.4 Hz, 2H, H_9), -0.03 (s, 9H, H_{11}) ppm.

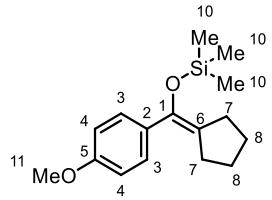
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.8 (C_1), 140.0 (C_2), 129.5 (2C, C_3), 129.2 (q, J = 32.3 Hz, C_5), 124.9 (q, J = 3.7 Hz, 2C, C_4), 124.4 (q, J = 271.9 Hz, C_{10}), 122.8 (C_6), 29.8 – 29.3 (m, C_9), 28.5 – 27.9 (m, C_1), 27.8 – 27.5 (m, C_7), 27.4 (d, J = 14.2 Hz, C_8), 26.9 – 26.75 (m, C_8), 0.5 (3C, C_{11}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.45 (3F) ppm.

HRMS (GC-QTOF): exact mass calculated for $[M]^+$ ($C_{17}H_{19}D_4F_3OSi^+$) requires *m/z* 332.1716, found *m/z* 332.1703.

IR (neat) ν_{max}: = 2928, 2854, 2364, 1325, 1265, 1253, 1166, 1129, 1106, 1068, 878, 847, 742 cm^{-1}.

3.90 – [Cyclopentylidene(4-methoxyphenyl)methoxy]trimethylsilane



3.90

Synthesized following **GP-16**, using **3.22** (394 mg, 2.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 2.40 mL, 2.95 g, 13.0 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.90** (394 mg, 1.43 mmol, 71%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.74).

Note: *Following column chromatography,* ***3.90*** *was obtained contaminated with other undefined impurities of similar polarity. Despite these contaminants,* ***3.90*** *was subjected to the subsequent step.*

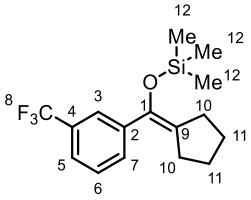
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.32 (m, 2H, H_3), 6.94 – 6.71 (m, 2H, H_4), 3.81 (s, 3H, H_9), 2.48 – 2.38 (m, 2H, H_7), 2.35 (td, J = 5.6, 2.7 Hz, 2H, H_7), 1.73 – 1.60 (m, 4H, H_8), 0.05 (s, 9H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}O_2Si^+$) requires *m/z* 277.1618, found *m/z* 277.1613.

IR (neat) ν_{max}: = 3001, 2954, 2894, 2866, 2836, 1661, 1608, 1575, 1509, 1465, 1439, 1412, 1314, 1298, 1275, 1244, 1165, 1133, 1094, 1036, 1010, 957, 916, 873, 832, 791 cm^{-1}.

3.91 – {Cyclopentylidene[3-(trifluoromethyl)phenyl]methoxy}trimethylsilane



3.91

Synthesized following **GP-16**, using **3.24** (242.0 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.91** (246k mg, 0.78 mmol, 78%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.45).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H, H_3), 7.58 (d, *J* = 7.5 Hz, 1H, H_5), 7.43 (dt, *J* = 15.3, 7.8 Hz, 1H, H_{6+7}), 2.48 – 2.32 (m, 4H, H_{10}), 1.74 – 1.63 (m, 4H, H_{11}), 0.06 (s, 9H, H_{12}) ppm.

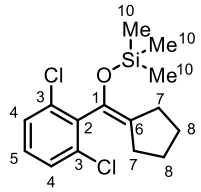
^{13}C NMR (101 MHz, $CDCl_3$): δ 140.4 (C_2), 139.7 (C_4), 130.6 (C_7), 128.2 (C_6), 128.0 (C_9), 124.3 (d, *J* = 4.0 Hz, C_5), 123.4 (d, *J* = 3.7 Hz, C_3), 31.3 (C_{10}), 30.7 (C_{10}), 27.8 (C_{11}), 25.9 (C_{11}), 0.7 (3C, C_{12}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -62.75 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}F_3OSiNa^+$) requires *m/z* 337.1206, found *m/z* 337.1206.

IR (neat) ν_{max}: = 2957, 2934, 2872, 2208, 2111, 1691, 1658, 1645, 1616, 1575, 1466, 794 cm^{-1}.

3.95 – [Cyclopentylidene(2,6-dichlorophenyl)methoxy]trimethylsilane



3.95

Synthesized following **GP-16**, using **3.60** (146.0 mg, 0.60 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.84 mL, 608 mg, 6.01 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.72 mL, 885 mg, 3.90 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.95** (166 mg, 0.53 mmol, 88%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 96:4, R_f = 0.74).

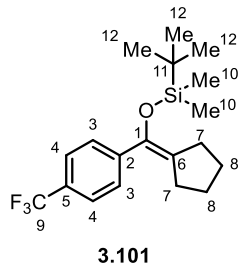
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2H, H_4), 7.14 (dd, J = 8.5, 7.6 Hz, 1H, H_5), 2.43 (dd, J = 10.1, 4.3 Hz, 2H, H_7), 1.94 (dd, J = 7.6, 6.3 Hz, 2H, H_7), 1.73 – 1.66 (m, 2H, H_8), 1.66 – 1.57 (m, 2H, H_8), 0.03 (s, 9H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2 (C_1), 135.6 (2C, C_3), 135.2 (C_2), 129.4 (C_5), 128.2 (2C, C_4), 127.8 (C_6), 29.4 (C_7), 29.0 (C_7), 27.2 (C_8), 26.5 (C_8), 0.7 (3C, C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}Cl_2OSi^+$) requires *m/z* 315.0733, found *m/z* 315.0737.

IR (neat) ν_{max}: = 2956, 2891, 2867, 2839, 1687, 1647, 1580, 1556, 1426, 1312, 1298, 1267, 1249, 1191, 1169, 1123, 1087, 1064, 1014, 955, 914, 896, 871, 839, 773 cm^{-1}.

3.101 – *tert*-Butyl{cyclopentylidene[4-(trifluoromethyl)phenyl]methoxy}dimethylsilane



3.101

Synthesized following **GP-16**, using **3.23** (90.0 mg, 0.37 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.52 mL, 376 mg, 3.72 mmol, 10.0 eq.), *tert*-butyldimethylsilyl triflate (TBDMSOTf, 0.57 mL, 658 mg, 2.41 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.101** (193 mg, 0.20 mmol, 54%, 37% purity) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.72).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 2H, H_3), 7.48 (d, J = 8.2 Hz, 2H, H_4), 2.45 (t, J = 7.0 Hz, 2H, H_7), 2.33 (t, J = 6.8 Hz, 2H, H_7), 1.76 – 1.56 (m, 4H, H_8), 0.94 (s, 9H, H_{12}), -0.11 (s, 6H, H_{10}) ppm.

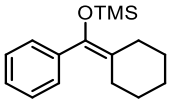
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5 (C_1), 140.0 (C_2), 128.1 (2C, C_3), 128.0 (C_5), 124.7 (2C, q, J = 3.8 Hz, C_4), 123.9 (C_9), 123.1 (C_6), 31.3 (C_7), 30.5 (C_7), 27.6 (C_8), 26.0 (C_8), 25.9 (3C, C_{12}), 18.4 (C_{11}), -3.9 (2C, C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.39 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{27}F_3OSiNa^+$) requires *m/z* 379.1675, found *m/z* 379.1675.

IR (neat) ν_{max}: = 2958, 2931, 2858, 1690, 1618, 1472, 1410, 1326, 1258, 1168, 1129, 1068, 1017, 893, 838, 783 cm^{-1}.

3.103 – [Cyclohexylidene(phenyl)methoxy]trimethylsilane

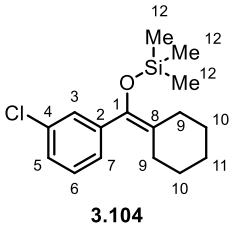


3.103

Synthesized following **GP-16**, using benzoylcyclohexane (389 µL, 377 mg, 2.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 2.35 mL, 2.89 g, 13.0 mmol, 10.0 eq.) and dichloromethane (CH_2Cl_2, 4.00 mL) afforded compound **3.103** (519 mg, 1.99 mmol, quant.) as a colorless oil after purification by column chromatography (heptanes/toluene = 90:10, Rf = 0.90). Spectroscopic data were in accordance with literature.[177]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.27 (m, 3H), 7.27–7.19 (m, 2H), 2.33 (d, J = 5.6 Hz, 2H), 2.23–2.08 (m, 2H), 1.56 (d, J = 15.2 Hz, 4H), 1.48 (d, J = 4.4 Hz, 2H), -0.04 (s, 9H) ppm.

3.104 – [(3-chlorophenyl)(cyclohexylidene)methoxy]trimethylsilane



3.104

Synthesized following **GP-16**, using **3.72** (111 mg, 0.50 mmol, 1.00 eq.), triethyl amine (NEt_3, 0.70 mL, 506 mg, 5.00 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 0.70 mL, 737 mg, 3.25 mmol, 6.50.) and dichloromethane

(CH_2Cl_2, 2.00 mL) afforded compound **3.104** (143 mg, 0.49 mmol, 97%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 96:4, R_f = 0.66).

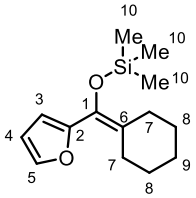
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, *J* = 1.7 Hz, 1H, H_3), 7.24 – 7.20 (m, 2H, H_{5+7}), 7.18 (ddd, *J* = 6.5, 2.6, 1.5 Hz, 1H, H_6), 2.32 (t, *J* = 5.7 Hz, 2H, H_9), 2.22 – 2.04 (m, 2H, H_9), 1.66 – 1.52 (m, 4H, H_{10}), 1.48 (d, *J* = 5.2 Hz, 2H, H_{11}), -0.02 (s, 9H, H_{12}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9 (C_1), 140.0 (C_4), 133.7 (C_2), 129.4 (C_6), 129.1 (C_5), 127.5 (C_3), 127.4 (C_7), 122.2 (C_8), 29.9 (C_9), 28.2 (C_9), 27.9 (C_{10}), 27.5 (C_{10}), 26.9 (C_{11}), 0.5 (3C, C_{12}).

HRMS (GC-QTOF): exact mass calculated for $[M]^+$ ($C_{16}H_{23}ClOSi^+$) requires *m/z* 294.1201, found *m/z* 294.1202.

IR (neat) ν_{max}: = 2958, 2924, 2852, 1656, 1593, 1562, 1472, 1447, 1411, 1332, 1282, 1250, 1234, 1214, 1130, 1096, 1070, 1023, 995, 921, 893, 865, 838, 794 cm^{-1}.

3.105 – [Cyclohexylidene(furan-2-yl)methoxy]trimethylsilane



3.105

Synthesized following **GP-16**, using **3.67** (178 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.105** (231 mg, 0.84 mmol, 84%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.33).

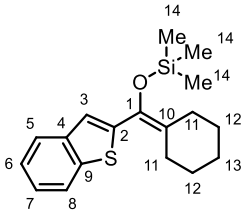
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 1.7, 0.7 Hz, 1H, H_5), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H, H_3), 6.29 – 6.14 (m, 1H, H_4), 2.32 (dd, *J* = 11.2, 6.1 Hz, 4H, H_7), 1.55 (ddt, *J* = 8.4, 4.9, 2.5 Hz, 6H, H_{8+9}), 0.07 (s, 9H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.4 (C_1), 141.0 (C_5), 132.5 (C_2), 124.9 (C_6), 110.5 (C_4), 109.1 (C_3), 29.5 (C_7), 28.1 (C_7), 28.1 (C_8), 27.5 (C_8), 26.9 (C_9), 0.2 (3C, C_{10}) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}O_2Si^+$) requires *m/z* 251.1462, found *m/z* 251.1457.

IR (neat) ν_{max}: = 3447, 3134, 2931, 2855, 1727, 1670, 1566, 1465, 1450, 1395, 1334, 1313, 1292, 1263, 1226, 1157, 1138, 1086, 1057, 1014, 980, 912, 884, 872, 843, 800 cm^{-1}.

3.106 – [Benzo[*b*]thiophen-2-yl(cyclohexylidene)methoxy]trimethylsilane



3.106

Synthesized following **GP-16**, using **3.106** (178 mg, 1.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 1.39 mL, 1.01 g, 10.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 1.20 mL, 1.48 g, 6.50 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **3.106** (231 mg, 0.84 mmol, 84%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.33).

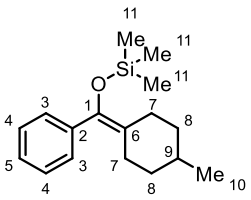
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.79 (m, 1H, H_5), 7.74 (dd, *J* = 7.0, 1.5 Hz, 1H, H_8), 7.38 – 7.27 (m, 2H, H_{6+7}), 7.16 (s, 1H, H_3), 2.47 – 2.33 (m, 4H, H_{11}), 1.59 (ddd, *J* = 10.6, 5.7, 2.7 Hz, 6H, H_{12+13}), 0.11 (s, 9H, H_{14}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): *a clean ^{13}C NMR could not be measured for this compound.*

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}SiSO^+$) requires *m/z* 317.1390, found *m/z* 317.1388.

IR (neat) ν_{max}: = 3058, 2925, 2852, 1659, 1528, 1457, 1447, 1436, 1348, 1335, 1304, 1249, 1195, 1177, 1155, 1120, 1073, 1049, 1024, 1015, 976, 929, 906, 865, 841, 786 cm^{-1}

3.108 – Trimethyl[(4-methylcyclohexylidene)(phenyl)methoxy]silane



3.108

Synthesized following **GP-16**, using **3.29** (405 mg, 2.00 mmol, 1.00 eq.), triethyl amine (NEt_3, 2.79 mL, 2.02 g, 20.0 mmol, 10.0 eq.), trimethylsilyl triflate (TMSOTf, 2.40 mL, 2.95 g, 13.0 mmol, 6.50 eq.) and dichloromethane (CH_2Cl_2, 4.00 mL) afforded compound **3.108** (506 mg, 1.84 mmol, 92%) as a colorless oil after purification by column chromatography (heptanes/toluene = 90:10, Rf = 0.90).

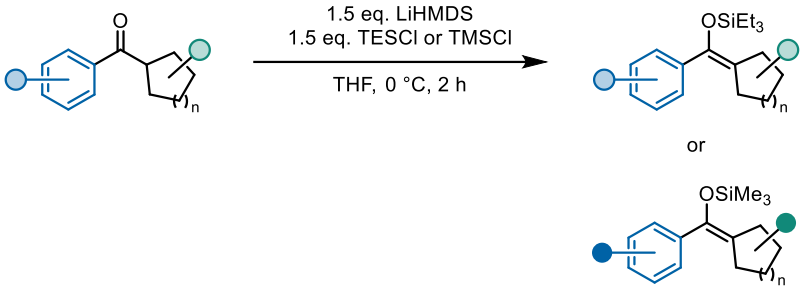
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (dt, *J* = 15.4, 4.5 Hz, 5H, $H_{3\text{-}5}$), 2.89 (dd, *J* = 8.4, 6.5 Hz, 1H, H_7), 2.40 (dd, *J* = 13.8, 1.6 Hz, 1H, H_7), 1.88 – 1.69 (m, 3H, H_{7+8}), 1.69 – 1.58 (m, 1H, H_8), 1.57 – 1.40 (m, 1H, H_9), 1.09 – 0.90 (m, 2H, H_8), 0.88 (d, *J* = 6.6 Hz, 3H, H_{10}), -0.07 (s, 9H, H_{11}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.3 (C_1), 139.1 (C_2), 129.4 (2C, C_3), 127.8 (2C, C_4), 127.3 (C_5), 120.6 (C_6), 36.6 (C_9), 35.9 (C_8), 32.9 (C_8), 29.4 (C_7), 27.3 (C_7), 22.3 (3C, C_{10}), 0.5 (3C, C_{11}) ppm.

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{27}OSi^+$) requires *m/z* 275.1826, found *m/z* 275.1824.

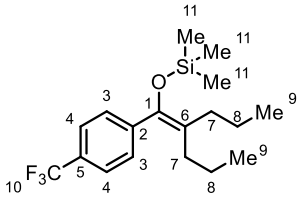
IR (neat) ν_{max}: = 2953, 2910, 2844, 1455, 1444, 1292, 1279, 1250, 1221, 1197, 1132, 1084, 1072, 1028, 1005, 951, 933, 910, 876, 859, 838, 798 cm^{-1}.

3.3.1.9 General Procedure 17: Synthesis of additional Silyl Enol Ethers from Ketones



To a solution of lithium bis(trimethylsilyl)amide (LiHMDS, 1.00 M in THF, 1.50 mmol, 1.50 eq.) was added dropwise a solution of ketone (1.00 mmol, 1.00 eq.) in tetrahydrofuran (THF, 0.5 M) and the mixture was stirred at 0 °C for 30 min. Then, triethylsilyl chloride (TESCl, 1.50 mmol, 1.50 eq.) or trimethylsilyl chloride (TMSCl, 1.50 mmol, 1.50 eq.) was added dropwise and the reaction was allowed to warm up to 23 °C over 2 h. After cooling to 0 °C, the reaction was stopped by slow addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL) and transferred to a separation funnel, followed up by addition of diethyl ether (Et_2O, 5.00 mL). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (CH_2Cl_2, 3 × 5.00 mL). The combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50 or pentane/diethyl ether EtOAc = 100:0 to 50:50) to afford the corresponding silyl enol ether.

2.174 – Trimethyl({2-propyl-1-[4-(trifluoromethyl)phenyl]pent-1-en-1-yl}oxy)silane



2.174

Synthesized following **GP-17**, using **3.33** (210 mg, 0.77 mmol, 1.00 eq.), lithium bis(trimethylsilyl)amide solution (LiHMDS, 1.00 M in THF, 1.16 mL, 1.16 mmol, 1.50 eq.), trimethylsilyl chloride (TMSCl, 147 µL, 1.16 mmol, 1.50 eq.) and tetrahydrofuran (THF, 3.00 mL) afforded compound **2.174** (237 mg, 0.69 mmol, 89%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.44).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 2H, H_4), 7.40 (d, J = 8.0 Hz, 2H, H_3), 2.23 – 2.07 (m, 2H, H_7), 2.03 – 1.87 (m, 2H, H_7), 1.54 – 1.43 (m, 2H, H_8), 1.43 – 1.33 (m, 2H, H_8), 0.96 (t, J = 7.3 Hz, 3H, H_9), 0.79 (t, J = 7.3 Hz, 3H, H_9), -0.04 (s, 9H, H_{11}).

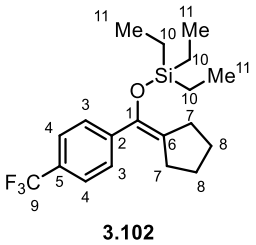
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.3 (C_1), 143.1 (C_2), 129.6 (2C, C_3), 126.2 (C_5), 125.7 (C_{10}), 124.9 (q, J = 3.8 Hz, 2C, C_4), 123.2 (C_6), 32.4 (C_7), 30.8 (C_7), 22.0 (C_8), 21.2 (C_8), 14.6 (C_9), 14.1 (C_9), 0.6 (3C, C_{11}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.44 (3F) ppm.

HRMS (ESI$^+$): *HRMS could not be recorded for this compound.*

IR (neat) ν_{max}: = 2960, 2933, 2872, 1691, 1655, 1616, 1466, 1406, 1324, 1265, 1253, 1232, 1203, 1166, 1129, 1106, 1080, 1066, 1018, 899, 880, 844, 750 cm^{-1}

3.102 – {Cyclopentylidene[4-(trifluoromethyl)phenyl]methoxy}triethylsilane



3.102

Synthesized following **GP-17**, using **3.23** (90.0 mg, 0.37 mmol, 1.00 eq.), lithium bis(trimethylsilyl)amide solution (LiHMDS, 1.00 M in THF, 0.56 mL, 0.56 mmol, 1.50 eq.), triethylsilyl chloride (TESCl, 93.5 µL, 84.0 mg, 0.56 mmol, 1.50 eq.) and tetrahydrofuran (THF, 1.00 mL) afforded compound **3.102** (118 mg, 0.33 mmol, 89%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 98:2, R_f = 0.69).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.3 Hz, 2H, H_3), 7.50 (d, J = 8.4 Hz, 2H, H_4), 2.47 (t, J = 6.9 Hz, 2H, H_7), 2.34 (t, J = 6.8 Hz, 2H, H_7), 1.67 (ddd, J = 15.1, 12.6, 7.0 Hz, 4H, H_8), 0.90 (t, J = 7.9 Hz, 9H, H_{11}), 0.53 (q, J = 7.9 Hz, 6H, H_{10}) ppm.

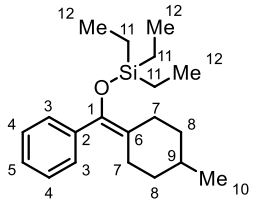
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.4 (C_1), 140.1 (C_2), 128.6 (C_5), 128.0 (C_9), 127.8 (2C, C_3), 124.7 (2C, C_4) (q, J = 3.7 Hz), 123.1 (C_6), 31.4 (C_7), 30.5 (C_7), 27.7 (C_8), 26.0 (C_8), 6.8 (3C, C_{11}), 5.5 (3C, C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$): δ -62.40 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{19}H_{27}F_3OSiNa^+$) requires m/z 379.1675, found m/z 379.1675.

IR (neat) ν_{max}: = 2956, 2913, 2877, 2837, 1655, 1616, 1462, 1408, 1323, 1275, 1239, 1164, 1125, 1097, 1066, 1016, 1003, 975, 958, 915, 891, 850, 809, 772 cm^{-1}.

3.111 – Triethyl[(4-methylcyclohexylidene)(phenyl)methoxy]silane



3.111

Synthesized following **GP-17**, using **3.29** (101 mg, 0.50 mmol, 1.00 eq.), lithium bis(trimethylsilyl)amide solution (LiHMDS, 1.00 M in THF, 0.75 mL, 0.75 mmol, 1.50 eq.), triethylsilyl chloride (TESCl, 126 µL, 113 mg, 0.75 mmol, 1.50 eq.) and tetrahydrofuran (THF, 1.00 mL) afforded compound **3.111** (213 mg, 0.73 mmol, 73%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 90:10, Rf = 0.54).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 4.2 Hz, 4H, H_{3+4}), 7.28 – 7.19 (m, 1H, H_5), 2.98 (dd, J = 8.7, 6.5 Hz, 1H, H_7), 2.43 – 2.25 (m, 1H, H_7), 1.82 (dt, J = 20.2, 7.5 Hz, 3H, H_{7+8}), 1.64 (dd, J = 8.7, 3.7 Hz, 1H, H_8), 1.59 – 1.41 (m, 1H, H_8), 1.13 – 0.93 (m, 2H, H_9), 0.90 (d, J = 6.5 Hz, 3H, H_{10}), 0.85 (t, J = 7.9 Hz, 9H, H_{12}), 0.51 – 0.35 (m, 6H, H_{11}) ppm.

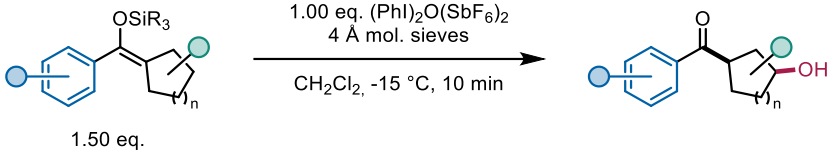
^{13}C NMR (101 MHz, $CDCl_3$): δ 141.5 (C_1), 139.2 (C_2), 129.4 (2C, C_3), 127.8 (2C, C_4), 127.3 (C_5), 119.9 (C_6), 36.5 (C_9), 35.7 (C_8), 32.9 (C_8), 29.5 (C_7), 27.1 (C_7), 22.4 (C_{10}), 6.8 (3C, C_{11}), 5.3 (3C, C_{12}) ppm.

HRMS (ESI+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{33}OSi^+$) requires m/z 317.2295, found m/z 317.2293.

IR (neat) ν_{max}: = 2952, 2910, 2876, 2844, 1456, 1443, 1413, 1291, 1279, 1255, 1238, 1220, 1198, 1133, 1085, 1072, 1003, 973, 960, 951, 934, 918, 908, 872, 821, 782 cm^{-1}.

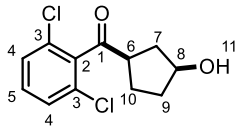
3.3.2 Remote Oxidation of Silyl Enol Ethers

3.3.2.1 General Procedure 18: Remote Oxidation of Silyl Enol Ethers using Hypervalent Iodonium Reagents



To a flame-dried Schlenk flask charged with 4 Å molecular sieves (4-5 beads) with was added the hypervalent iodine reagent ($(PhI)_2O(SbF_6)_2$, 1.00 eq.) under inert atmosphere. The Schlenk flask was cooled to –15 °C (using a NaCl/ice mixture), and dry dichloromethane (CH_2Cl_2, 0.1 M) was added. The resulting mixture was vigorously stirred for 5 minutes, after which a solution of silyl enol ether in CH_2Cl_2 (0.15 M, 1.50 equiv.) was added dropwise, and the mixture was left stirring at –15 °C for 10 minutes. The reaction was stopped by slow addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL/0.1 mmol of iodonium reagent) and after 10 minutes the reaction mixture was transferred to a separation funnel, followed up by addition of dichloromethane (CH_2Cl_2, 2.00 mL/0.1 mmol of iodonium reagent) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 2.00 mL/0.1 mmol of iodonium reagent). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (CH_2Cl_2, 3 × 5.00 mL/0.1 mmol of iodonium reagent). The combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding ketoalcohol.

2.141 – *syn*-(2,6-Dichlorophenyl)(3-hydroxycyclopentyl)methanone



2.141

Synthesized following **GP-18**, using **3.95** (28.3 mg, 0.10 mmol, 1.50 eq.), iodonium reagent $((PhI)_2O(SbF_6)_2$, 59.7 mg, 0.07 mmol, 1.00 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.141** (13.9 mg, 0.06 mmol, 63%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.18).

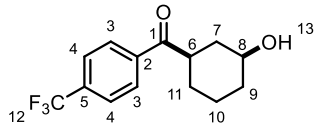
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J = 7.9, 1.3 Hz, 2H, H_4), 7.23 (dd, J = 5.8, 3.5 Hz, 1H, H_5), 4.34 (app s, 1H, H_8), 3.50 (tdd, J = 8.9, 7.2, 5.7 Hz, 1H, H_6), 2.37 (br s, 1H, H_{11}), 2.26 – 2.04 (m, 3H, $H_{7\text{ and }9}$), 1.95 (ddt, J = 13.0, 8.8, 6.3 Hz, 1H, H_9), 1.82 (ddd, J = 8.6, 6.4, 4.7 Hz, 2H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.7 (C_1), 140.0 (C_2), 130.9 (2C, C_3), 130.8 (C_5), 128.5 (2C, C_4), 73.7 (C_8), 50.8 (C_6), 38.5 (C_7), 36.2 (C_9), 27.9 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}Cl_2O_2Na^+$) requires *m/z* 281.0107, found *m/z* 281.0106.

IR (neat) ν_{max}: = 3559, 3393, 3072, 2967, 2941, 2871, 1741, 1704, 1692, 1661, 1578, 1559, 1466, 1427, 1352, 1328, 1298, 1265, 1241, 1213, 1191, 1152, 1105, 1085, 1067, 1007, 984, 956, 919, 880, 852, 777 cm^{-1}.

2.145 – *syn*-(3-Hydroxycyclohexyl)[4-(trifluoromethyl)phenyl]methanone



2.145

Synthesized following **GP-18**, using **2.187** (49.3 mg, 0.15 mmol, 1.50 eq.), iodonium reagent $((PhI)_2O(SbF_6)_2$, 89.6 mg, 0.10 mmol, 1.00 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.145** (10.8 mg, 0.04 mmol, 40%) as a colorless oil after purification by column chromatography (heptanes/ethyl acetate = 70:30, R_f = 0.19).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.2 Hz, 2H, H_4), 7.74 (d, J = 8.2 Hz, 2H, H_3), 3.78 (ddd, J = 14.7, 10.5, 4.2 Hz, 1H, H_8), 3.35 (tt, J = 11.3, 3.4 Hz, 1H, H_6), 2.24 – 2.10 (m, 1H, H_7), 2.05 (d, J = 12.5 Hz, 1H, H_7), 2.00 – 1.78 (m, 2H, H_9), 1.69 (brs, 1H, H_{13}), 1.60 – 1.24 (m, 4H, H_{10+11}) ppm.

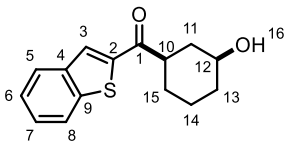
^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5 (C_1), 139.0 (C_2), 134.5 (q, J = 32.7 Hz, C_5), 128.8 (2C, C_3), 125.9 (q, J = 3.6 Hz, 2C, C_4), 123.7 (q, J = 272.7 Hz, C_{12}), 70.1 (C_8), 44.5 (C_6), 37.7 (C_7), 35.3 (C_9), 28.5 (C_{11}), 23.5 (C_{10}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.13 (3F) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_3O_2^+$) requires *m/z* 271.1940, found *m/z* 271.1939.

IR (neat) ν_{max}: = 3352, 2932, 2858, 1686, 1451, 1409, 1324, 1262, 1207, 1168, 1129, 1112, 1067, 1014, 976, 956, 946, 882, 849, 813, 767cm^{-1}.

2.146 – *syn*-Benzo[*b*]thiophen-2-yl(3-hydroxycyclohexyl)methanone



2.146

Synthesized following **GP-18**, using **3.106** (47.5 mg, 0.15 mmol, 1.50 eq.), iodonium reagent ($(PhI)_2O(SbF_6)_2$, 89.6 mg, 0.10 mmol, 1.00 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.146** (10.8 mg, 0.04 mmol, 40%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.30).

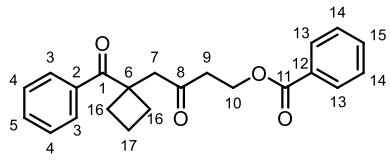
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H, H_3), 7.88 (t, J = 7.5 Hz, 2H, H_{5+8}), 7.52 – 7.44 (m, 1H, $H_{6\text{ or }7}$), 7.44 – 7.38 (m, 1H, $H_{6\text{ or }7}$), 3.83 – 3.71 (m, 1H, H_{12}), 3.34 (ddd, J = 11.3, 7.3, 3.3 Hz, 1H, H_{10}), 2.22 (dd, J = 12.6, 3.8 Hz, 1H, H_{11}), 2.05 (d, J = 7.6 Hz, 1H, H_{11}), 2.00 – 1.89 (m, 2H, H_{13}), 1.73 (s, 1H, H_{15}), 1.70 – 1.42 (m, 4H, H_{14}), 1.41 – 1.20 (m, 2H, H_{15}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.8 (C_1), 143.0 (C_2), 139.3 (C_9), 129.0 ($C_{6\text{ or }7}$), 127.6 ($C_{6\text{ or }7}$), 126.1 (C_5), 125.2 (C_8), 123.2 (C_3), 122.8 (C_4), 70.1 (C_{12}), 45.8 (C_{10}), 38.0 (C_{11}), 35.3 (C_{13}), 29.0 (C_{15}), 23.6 (C_{14}) ppm.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}O_2S^+$) requires *m/z* 261.0944, found *m/z* 261.0944.

IR (neat) ν_{max}: = 3277, 2928, 2853, 2359, 2207, 2196, 2175, 2162, 2121, 2066, 2001, 1713, 1665, 1594, 1516, 1447, 1376, 1291, 1220, 1096, 1048, 1009, 918, 871, 815, 727 cm^{-1}.

2.196 – 4-(1-Benzoylcyclobutyl)-3-oxobutyl benzoate



2.196

Synthesized following **GP-18**, using **2.195** (23.2 mg, 0.10 mmol, 1.50 eq.), iodonium reagent ($(PhI)_2O(SbF_6)_2$, 59.7 mg, 0.07 mmol, 1.00 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.196** (8.1 mg, 0.02 mmol, 46%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.46).

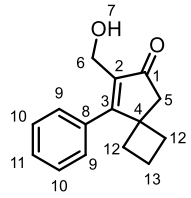
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, J = 7.8 Hz, 2H, H_{13}), 7.69 (d, J = 7.7 Hz, 2H, H_3), 7.55 (t, J = 7.4 Hz, 1H, H_{15}), 7.45 (t, J = 7.4 Hz, 1H, H_5), 7.41 (t, J = 7.7 Hz, 2H, H_{14}), 7.37 (t, J = 7.6 Hz, 2H, H_4), 4.45 (t, J = 6.3 Hz, 2H, H_{10}), 3.31 (s, 2H, H_7), 2.86 – 2.77 (m, 2H, H_{16}), 2.72 (t, J = 6.3 Hz, 2H, H_9), 2.14 – 2.03 (m, 3H, H_{16+17}), 1.99 – 1.83 (m, 1H, H_{17}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.5 (C_{12}), 203.8 (C_2), 166.4 (C_{11}), 136.3 (C_2), 133.2 (C_5), 131.9 (C_{15}), 130.0 (C_{12}), 129.7 (2C, C_{13}), 128.5 (2C, C_3), 128.5 (2C, C_{14}), 128.4 (2C, C_4), 59.8 (C_{10}), 51.9 (C_7), 50.1 (C_9), 42.1 (C_6), 30.7 (2C, C_{16}), 16.0 (C_{17}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{22}O_4Na^+$) requires *m/z* 373.1410, found *m/z* 373.1408.

IR (neat) ν_{max}: = 2990, 2955, 2930, 1717, 1678, 1600, 1581, 1449, 1403, 1383, 1315, 1276, 1248, 1223, 1177, 1156, 1118, 1095, 1074, 1026, 1003, 980, 970, 934, 897, 783 cm^{-1}.

2.198 – 7-(hydroxymethyl)-8-phenylspiro[3.4]oct-7-en-6-one



2.198

To a vial containing **2.196** (10.5 mg, 0.03 mmol, 1.00 eq.) in a tetrahydrofuran/water mixture (THF/H_2O ratio = 1:1, 1.00 mL) was added lithium hydroxide monohydrate (LiOH•H_2O, 3.8 mg, 0.09 mmol, 3.00 eq.) at 0 °C under stirring. The reaction mixture was left to warm-up to 23 °C over 12 h. The reaction was stopped by dilution with diethyl ether (Et_2O, 2 mL) and transferred to a separation funnel, followed up by addition of diethyl ether (Et_2O, 3.00 mL) and saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated and the aqueous phase was extracted two times with diethyl ether (Et_2O, 2 × 5.00 mL). The combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude compound **2.198** (4.1 mg, 0.02 mmol, 56%) was obtained as a white solid.

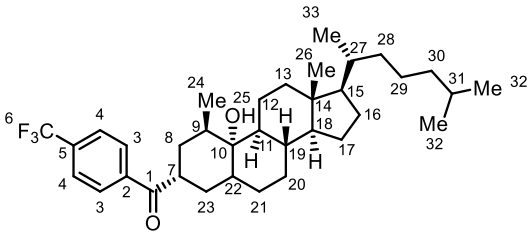
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (t, J = 7.3 Hz, 2H, H_{10}), 7.47 – 7.42 (m, 1H, H_{11}), 7.23 (d, J = 7.6 Hz, 2H, H_9), 4.13 (s, 2H, H_6), 2.82 (s, 2H, H_5), 2.42 (dd, J = 20.1, 9.0 Hz, 2H, H_{12}), 2.11 – 2.02 (m, 2H, H_{12}), 1.98 – 1.88 (m, 1H, H_{13}), 1.55 (dtd, J = 13.9, 9.1, 4.6 Hz, 2H, H_{13+7}) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.1 (C_1), 175.8 (C_3), 138.9 (C_8), 134.4 (C_2), 128.8 (C_{11}), 128.7 (2C, C_9), 127.5 (2C, C_{10}), 56.6 (C_6), 51.0 (C_5), 48.8 (C_4), 32.1 (2C, C_{12}), 16.8 (C_{13}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}O_2Na^+$) requires *m/z* 251.1043, found *m/z* 251.1042.

IR (neat) ν_{max}: = 3397, 3057, 2983, 2956, 2931, 2871, 2853, 1704, 1689, 1631, 1597, 1571, 1492, 1464, 1442, 1404, 1348, 1286, 1242, 1203, 1173, 1128, 1071, 1020, 986, 919, 804, 752 cm^{-1}.

2.209 – {(1*R*,3*R*,8*S*,9*S*,10*S*,13*R*,14*S*,17*R*)-10-hydroxy-1,13-dimethyl-17-[(*R*)-6-methylheptan-2-yl]hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl}[4-(trifluoromethyl)phenyl]methanone



2.209

Synthesized following **GP-18**, using **2.208** (61.7 mg, 0.10 mmol, 1.50 eq.), iodonium reagent ($(PhI)_2O(SbF_6)_2$, 59.7 mg, 0.07 mmol, 1.00 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.209** (24.3 mg, 0.04 mmol, 65%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 90:10, R_f = 0.18).

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.03 (d, J = 8.1 Hz, 2H, H_3), 7.74 (d, J = 8.2 Hz, 2H, H_4), 3.62 (tt, J = 12.6, 2.6 Hz, 1H, H_7), 2.29 (td, J = 13.3, 5.7 Hz, 1H, H_{Alk}), 2.23 (td, J = 13.1, 5.0 Hz, 1H, H_{Alk}), 2.08 (tt, J = 6.6, 4.6 Hz, 2H, H_{Alk}), 1.93 – 1.76 (m, 4H, H_{Alk}), 1.69 – 1.46 (m, 8H, H_{Alk}), 1.39 (d, J = 7.6 Hz, 3H, H_{24}), 1.37 – 0.95 (m, 15H, H_{Alk}), 0.92 (d, J = 6.5 Hz, 3H, H_{33}), 0.87 (d, J = 3.3 Hz, 3H, H_{32}), 0.86 (d, J = 3.2 Hz, 3H, H_{32}), 0.74 (s, 3H, H_{26}) ppm.

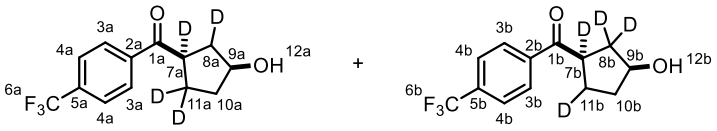
^{13}C NMR (176 MHz, $CDCl_3$): δ 202.8 (C_1), 139.3 (C_2), 134.2 (q, J = 32.6 Hz, C_5), 128.7 (2C, C_3), 125.9 (2C, q, J = 3.6 Hz C_4), 123.8 (q, J = 273 Hz, C_6), 74.3 (C_{10}), 57.7 ($C_{15\text{ or }18}$), 56.6 ($C_{15\text{ or }18}$), 56.2 (C_{11}), 45.3 (C_{22}), 43.1 (C_{14}), 40.1 ($C_{13\text{ or }30}$), 39.7 ($C_{13\text{ or }30}$), 38.1 (C_{19}), 36.6 (C_{27}), 36.3 (C_{28}), 36.1 (C_7), 36.0 (C_9), 34.1 (C_{20}), 31.7 (C_{21}), 31.4 (C_{17}), 29.8 (C_{16}), 28.4 (C_{23}), 28.2 (C_{31}), 24.3 (C_{29}), 24.0 (C_{12}), 23.0 (C_{32}), 22.7 (C_{32}), 20.1 (C_8), 19.3 (C_{24}), 18.8 (C_{33}), 12.9 (C_{26}) ppm.

^{19}F NMR (659 MHz, $CDCl_3$) δ -63.08 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{35}H_{51}F_3O_2Na^+$) requires *m/z* 583.3733, found *m/z* 583.3723.

IR (neat) ν_{max}: = 3536, 3501, 2950, 2929, 2868, 2846, 1690, 1582, 1467, 1443, 1409, 1382, 1324, 1279, 1244, 1208, 1169, 1132, 1110, 1068, 1016, 984, 959, 913, 888, 852, 832, 773 cm^{-1}.

2.233/2.234 – *syn*-(3-Hydroxycyclopentyl-1,2,5,5-d_4)[4-(trifluoromethyl)phenyl]methanone



2.233/2.234 ratio = 53:47

Synthesized following **GP-18**, using **2.232** (31.8 mg, 0.10 mmol, 1.50 eq.), iodonium reagent ($(PhI)_2O(SbF_6)_2$, 59.7 mg, 0.07 mmol, 1.00 eq.), and dichloromethane (CH_2Cl_2, 2.00 mL) afforded compound **2.233/2.234** (11.0 mg, 0.04 mmol, 42%, 53:47 mixture of 2 regioisomers) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.30).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.1 Hz, 2H, H_{3a+3b}), 7.75 (d, *J* = 8.2 Hz, 2H, H_{4a+4b}), 4.39 (t, *J* = 3.6 Hz, 1H, H_{9a+9b}), 2.69 (br s, 1H, $H_{12a+12b}$), 2.17 – 2.05 (m, 1H, H_{8a+11b}), 1.86 (dd, *J* = 11.4, 5.6 Hz, 2H, $H_{10a+10b}$) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ [203.53 and 203.52] (C_{1a} and C_{1b}), 139.0 (C_{2a} and C_{2b}), 134.7 (q, *J* = 32.7 Hz, C_{5a} and C_{5b}), 129.1 (2C, C_{3a} and C_{3b}), 125.9 (q, *J* = 3.7 Hz, 2C, C_{4a} and C_{4b}), 123.7 (q, *J* = 272.7 Hz, 2C, C_{6a} and C_{6b}), [73.81 and 73.76] (C_{9a} and C_{9b}), 44.8 (C_{7a} and C_{7b}), 37.7 (ap t, C_{8a} and C_{8b}), [36.22, 36.13] (C_{10a} and C_{10b}), 28.3 (app t, C_{11a} and C_{11b}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) *δ* -63.15 (3F) ppm.

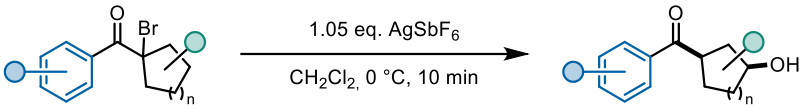
HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_9D_4F_3O_2Na^+$) requires *m/z* 285.1011, found *m/z* 285.1016.

IR (neat) ν_{max}: 3518, 3363, 2940, 1689, 1409, 1328, 1311, 1271, 1241, 1169, 1129, 1111, 1067, 1016, 935, 910, 854, 769 cm^{-1}.

Note: *The signals at 37.7 ppm and 28.3 ppm in ^{13}C-NMR appear as apparent triplets due to the overlap of the CDH-signals (triplet) and CD_2-signals (quintet) of carbon atom pairs (C_{8a} and C_{8b}) and (C_{11a} and C_{11b}) respectively.*

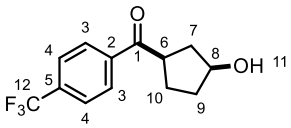
3.3.3 Synthesis of 1,3-Ketoalcohols from α-Bromoketones for Mechanistic Studies

3.3.3.1 General Procedure 19: Synthesis of 1,3-Ketoalcohols from α-Bromoketones



To a solution of the α-bromoketone (0.20 mmol, 1.00 eq.) in dichloromethane (CH_2Cl_2, 0.1 M) at 0 °C, under inert atmosphere, was added silver hexafluoroantimonate ($AgSbF_6$, 0.21 mmol, 1.05 eq.). The reaction was allowed to stir for 10 min and was afterwards stopped by addition of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 1.00 mL) and transferred to a separation funnel, followed up by addition of dichloromethane (CH_2Cl_2, 5.00 mL) and a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$, 5.00 mL). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (CH_2Cl_2, 3 × 5.00 mL). The combined organic phases were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (typical eluent: heptanes/EtOAc = 100:0 to 50:50) to afford the corresponding ketoalcohol.

2.114 – *syn*-(3-Hydroxycyclopentyl)[4-(trifluoromethyl)phenyl]methanone



2.114

Synthesized following **GP-19**, using **2.120** (33.9 mg, 0.11 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 38.1 mg, 0.11 mmol, 1.05 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **2.114** (20.0 mg, 0.08 mmol, 73%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 50:50, R_f = 0.37).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.1 Hz, 2H, H_3), 7.74 (d, J = 8.2 Hz, 2H, H_4), 4.40 (app s, 1H, H_8), 3.89 (ddd, J = 14.5, 8.4, 6.3 Hz, 1H, H_6), 2.68 (s, 1H, H_{11}), 2.20 – 2.07 (m, 3H, H_{7+9}), 2.07 – 1.96 (m, 1H, H_9), 1.87 (dt, J = 12.0, 6.2 Hz, 2H, H_{10}) ppm.

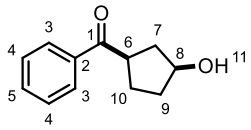
^{13}C NMR (101 MHz, $CDCl_3$): δ 203.2 (C_1), 138.9 (C_2), 134.6 (d, J = 32.7 Hz, C_5), 129.0 (2C, C_3), 125.8 (q, J = 3.7 Hz, 2C, C_4) 123.6 (d, J = 272.7 Hz, C_{12}), 73.7 (C_8), 44.9 (C_6), 38.0 (C_7), 36.1 (C_9), 28.5 (C_{10}) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -63.15 (3F) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{13}F_3NaO_2^+$) requires *m/z* 281.0760, found *m/z* 281.0751.

IR (neat) ν_{max}: = 3536, 3515, 3461, 3429, 3374, 2963, 2940, 2871, 1687, 1581, 1512, 1466, 1445, 1410, 1323, 1278, 1222, 1165, 1126, 1109, 1065, 1014, 988, 958, 909, 881, 854, 834, 767 cm^{-1}.

2.122 – *syn*-(3-Hydroxycyclopentyl)(phenyl)methanone



2.122

Synthesized following **GP-19**, using **2.121** (25.7 mg, 0.10 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 36.6 mg, 1.07 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **2.122** (10.7 mg, 0.06 mmol, 55%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.21).

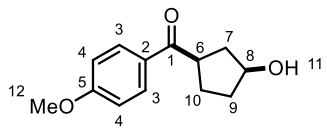
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 8.3, 1.1 Hz, 2H, H_3), 7.62 – 7.57 (m, 1H, H_5), 7.52 – 7.45 (m, 2H, H_4), 4.38 (app s, 1H, H_8), 3.99 – 3.85 (m, 1H, H_6), 3.08 (s, 1H, OH), 2.20 – 2.05 (m, 3H, H_{7+10}), 2.05 – 1.93 (m, 1H, H_7), 1.85 (ddd, *J* = 8.9, 6.8, 3.9 Hz, 2H, H_9) ppm.

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.0 (C_1), 136.2 (2C, C_2), 133.5 (C_5), 128.9 (2C, C_3), 128.8 (C_4), 73.9 (C_8), 44.5 (C_6), 38.2 (C_7), 36.5 (C_9), 29.1 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}O_2Na^+$) requires *m/z* 213.0886, found *m/z* 213.0879.

IR (neat) ν_{max}: = 3394, 2955, 2870, 1677, 1596, 1579, 1448, 1361, 1280, 1225, 1180, 1160, 1079, 1052, 1002, 993, 958, 932, 882, 842, 790 cm^{-1}.

2.125 – *syn*-(3-Hydroxycyclopentyl)(4-methoxyphenyl)methanone



2.125

Synthesized following **GP-19**, using **2.124** (28.3 mg, 0.10 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 36.1 mg, 1.05 mmol, 1.05 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **2.125**

(13.9 mg, 0.06 mmol, 63%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 67:33, R_f = 0.31).

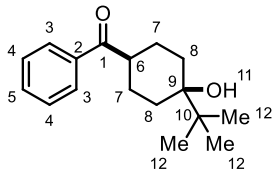
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.88 (m, 2H, H_3), 7.05 – 6.88 (m, 2H, H_4), 4.37 (d, J = 2.6 Hz, 1H, H_{11}), 4.01 – 3.90 (m, 1H, H_8), 3.89 (d, J = 5.8 Hz, 3H, H_{12}), 3.34 (d, J = 8.0 Hz, 1H, H_6), 2.20 – 1.91 (m, 4H, H_{7+9}), 1.89 – 1.77 (m, 2H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.9 (C_1), 163.9 (C_2), 131.2 (2C, C_3), 129.1 (2C, C_5), 114.0 (C_4), 73.9 (C_8), 55.7 (C_{12}), 44.1 (C_8), 38.3 (C_7), 36.6 (C_9), 29.4 (C_{10}) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}NaO_3^+$) requires *m/z* 243.0992, found *m/z* 243.0999.

IR (neat) ν_{max}: = 3537, 3511, 3429, 3403, 3369, 3324, 2962, 2936, 2903, 2870, 2840, 1670, 1653, 1596, 1573, 1510, 1463, 1441, 1419, 1365, 1310, 1261, 1230, 1166, 1115, 1081, 1052, 1028, 988, 957, 919, 902, 877, 840, 813, 797 cm^{-1}.

2.131 – *syn*-[4-(*tert*-Butyl)-4-hydroxycyclohexyl](phenyl)methanone



2.131

Synthesized following **GP-19**, using **2.96** (97.0 mg, 0.30 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 108.0 mg, 1.05 eq.) and dichloromethane (CH_2Cl_2, 3.00 mL) afforded compound **2.131** (58.4 mg, 0.22 mmol, 75%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 83:17, R_f = 0.31).

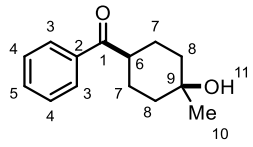
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 7.3 Hz, 2H, H_3), 7.55 (t, J = 7.3 Hz, 1H, H_5), 7.46 (t, J = 7.5 Hz, 2H, H_4), 3.16 (ddd, J = 11.9, 8.6, 3.2 Hz, 1H, H_6), 2.03 – 1.74 (m, 6H, $H_{7\text{ or }8}$), 1.71 – 1.55 (m, 2H, $H_{7\text{ or }8}$), 0.97 (s, 9H, H_{12}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.6 (C_1), 136.4 (C_2), 133.0 (C_5), 128.8 (2C, C_3), 128.4 (2C, C_4), 74.4 (C_9), 45.4 (C_6), 37.8 (C_{10}), 30.6 (2C, C_8), 25.2 (C_{11}), 25.0 (2C, C_7) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}O_2Na^+$) requires *m/z* 283.1669, found *m/z* 283.1677.

IR (neat) ν_{max}: = 3553, 3540, 3522, 3502, 2957, 2872, 2360, 2341, 1678, 1597, 1580, 1471, 1448, 1394, 1370, 1338, 1321, 1259, 1223, 1198, 1181, 1119, 1001, 989, 954, 928 cm^{-1}.

3.111 – *syn*-(4-hydroxy-4-methylcyclohexyl)(phenyl)methanone



3.111

Synthesized following **GP-19**, using **3.88** (28.1 mg, 0.10 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 36.1 mg, 1.05 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **3.111** (15.0 mg, 0.07 mmol, 63%) as a white solid after purification by column chromatography (heptanes/ethyl acetate = 75:25, R_f = 0.20).

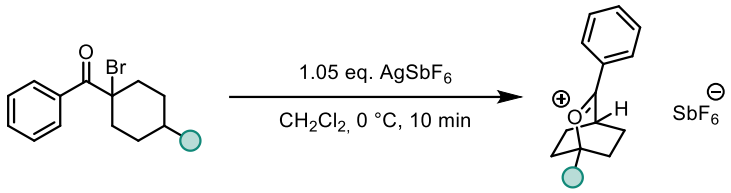
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.89 (m, 2H, H_3), 7.55 (t, J = 7.3 Hz, 1H, H_5), 7.46 (t, J = 7.5 Hz, 2H, H_4), 3.20 (tt, J = 11.6, 3.3 Hz, 1H, H_6), 1.89 (ddd, J = 16.5, 13.4, 3.9 Hz, 2H, H_8), 1.83 – 1.72 (m, 2H, H_8), 1.66 – 1.38 (m, 4H, H_7), 1.28 (s, 3H, H_{10}) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.5 (C_1), 136.5 (C_2), 133.0 (C_5), 128.8 (2C, C_3), 128.4 (2C, C_4), 68.8 (C_9), 45.0 (C_6), 38.2 (2C, C_8), 31.3 (C_{10}), 24.9 (2C, C_7) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}O_2Na^+$) requires *m/z* 241.1199, found *m/z* 241.1201.

IR (neat) ν_{max}: = 3503, 3481, 2958, 2927, 2865, 1676, 1597, 1580.4, 1447, 1375, 1335, 1318, 1286, 1263, 1209, 1181, 1157, 1120, 1030, 1019, 1003, 951, 933, 910, 826, 770 cm^{-1}.

3.3.3.2 General Procedure 20: Synthesis of Oxocarbenium Ions from α-Bromoketones



To a solution of the α-bromoketone (0.20 mmol, 1.00 eq.) in dry dichloromethane (CH_2Cl_2, 0.1 M) at 0 °C, under inert atmosphere, was added silver hexafluoroantimonate ($AgSbF_6$, 0.21 mmol, 1.05 eq.). The reaction was allowed to stir for 10 minutes. Then the stirring was stopped and the supernatant was transferred under inert atmosphere to a flame-dried round-bottom flask. The solvent was removed under reduced pressure (water bath temperature = 20 °C) and then dry diethyl ether was added, and then the flask was cooled to 0 °C using an ice bath. The oxocarbenium ion crashed out after 15 min and the supernatant was removed using a syringe. The flask was placed under reduced pressure for 20 minutes and then stored under argon at –20 °C.

Note: *If no precipitate is formed after cooling for 15 min on an ice bath, the flask is sonicated in an ultrasound bath for 1 minute at 23 °C. Then the oxocarbenium ion crashes out.*

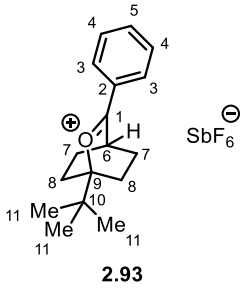
Note: *The brown coloring of the supernatant is due to formation of elimination products, specifically, γ,δ-alkenes.*

Note: *If the crystallin oxocarbenium ions present slightly brown coloration, addition dry diethyl ether washes were performed until the crystals appear white/colorless.*

Note: *A suitable X-ray sample was prepared by dissolving 20 mg of oxocarbenium ion in dry chloroform (CH_3Cl, 0.50 mL) in a small 2 mL vial that was placed inside a larger 8 mL vial under inert atmosphere. Then dry diethyl ether (Et_2O, 1.00 mL) was added to the larger vial (next to the small vial), and the vials were place in a fridge (4 °C). Slow diffusion of the diethyl ether into the chloroform solution resulted in formation of oxocarbenium crystals after 2 days. The X-ray structure was measured by immersing the crystals in oil to prevent air and water exposure.*

Note: *The oxocarbenium ions are air, moisture and temperature sensitive and exposure to these factors leads to elimination products.*

2.134 – 1-(*tert*-Butyl)-3-phenyl-2-oxabicyclo[2.2.2]oct-2-en-2-ium hexafluoroantimonate



2.93

Synthesized following **GP-20**, using **2.88** (32.3 mg, 0.10 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 36.1 mg, 1.05 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **2.134** (28 mg, 0.06 mmol, 58%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, J = 7.9 Hz, 2H, H_3), 8.12 (t, J = 7.0 Hz, 1H, H_5), 7.79 (t, J = 7.5 Hz, 2H, H_4), 4.49 (s, 1H, H_6), 2.52 (s, 2H, H_7), 2.28 (t, J = 12.1 Hz, 2H, H_8), 2.14 (t, J = 13.7 Hz, 2H, H_7), 2.02 (d, J = 11.5 Hz, 2H, H_8), 1.25 (s, 9H, H_{11}) ppm.

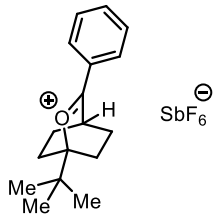
^{13}C NMR (176 MHz, $CDCl_3$): 143.7 (2C, C_3), 133.8 (C_5), 131.1 (2C, C_4), 127.7 (C_1), 107.3 (C_2), 36.8 (C_9), 35.4 (C_6), 28.7 (C_9), 26.0 (3C, C_{11}), 25.3 (2C, C_8), 25.1 (2C, C_7) ppm.

^{19}F NMR (659 MHz, $CDCl_3$): δ -116.35, -122.56, -126.08, -128.02, -129.35, -131.30, -156.20, -161.44. (SbF_6) ppm.

HRMS (ESI$^+$): exact mass calculated for $[M\text{-}SbF_6]^+$ ($C_{17}H_{23}O^+$) requires *m/z* 243.1743, found *m/z* 243.1741.

IR (neat) ν_{max}: = 2975, 1598, 1489, 1472, 1444, 1405, 1375, 1352, 1315, 1299, 1285, 1258, 1223, 1186, 1108, 1076, 1037, 1014, 1000, 879, 854, 809, 777 cm^{-1}.

X-ray Structure of 2.93



2.93

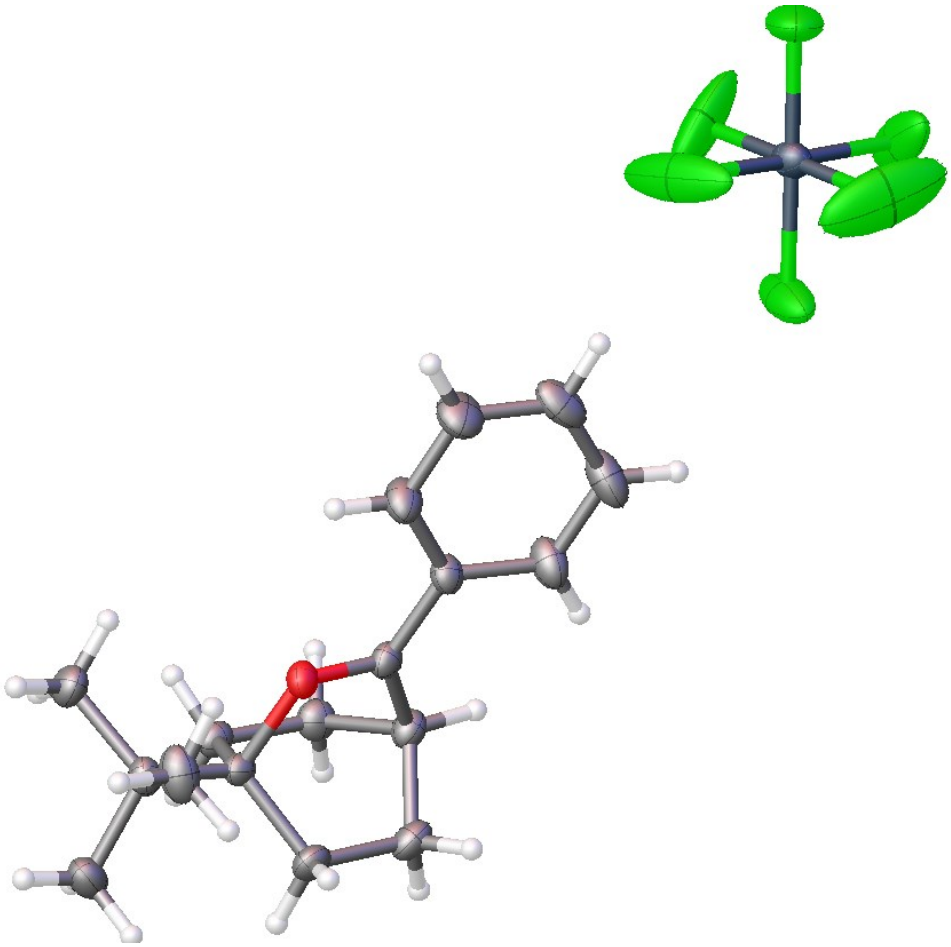


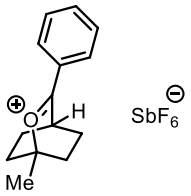
Figure 3.1: X-ray structure of oxocarbenium ion **2.93**.

X-ray Structure of 2.93 (XYZ Coordinates)

54 atoms							
Sb	71.479	37.446	82.228	C	165.941	57.047	18.110
F	74.934	42.018	99.564	H	158.972	51.559	22.276
O	146.245	68.891	37.671	H	174.437	52.163	18.204
C	153.859	77.345	27.654	H	163.425	59.047	0.8852
C	167.494	70.190	25.956	C	177.051	79.401	18.285
F	65.629	20.565	87.285	H	172.797	82.309	0.9949
C	154.685	91.295	33.915	H	185.309	74.547	16.217
H	158.939	97.541	27.520	H	179.155	87.234	23.784
H	160.306	90.935	42.057	C	108.014	62.794	64.874
F	77.920	54.253	77.365	H	100.494	66.496	69.346
C	130.184	85.698	34.128	C	122.928	44.194	61.004
H	121.012	88.454	37.008	H	125.380	35.174	62.699
C	140.716	96.432	37.564	F	67.634	33.386	64.679
H	138.789	104.739	32.535	F	88.214	30.033	79.802
H	140.339	98.513	47.236	F	54.716	44.532	84.078
C	134.463	73.150	40.725	C	111.564	49.552	66.938
C	130.863	83.091	18.897	H	106.150	44.064	72.489
H	123.857	76.603	16.286	C	173.767	66.923	39.607
H	129.268	91.530	13.973	H	174.700	75.164	44.829
C	126.877	65.195	50.08	H	182.597	62.891	38.263
C	130.624	51.982	52.667	H	168.003	60.634	44.430
H	138.480	48.386	48.718	Q	71.631	37.675	88.873
C	144.775	77.492	15.306	Q	76.557	33.312	67.660
H	143.831	68.290	11.778	Q	64.547	38.702	99.963
H	148.875	83.088	0.8243	Q	86.291	30.050	90.119
C	115.550	70.586	56.216	Q	88.089	29.410	76.705
H	113.021	79.581	54.500	Q	68.949	42.306	79.604

Table 3.1: XYZ coordinates of oxocarbenium ion **2.93**.

3.113 – 1-Methyl-3-phenyl-2-oxabicyclo[2.2.2]oct-2-en-2-ium hexafluoroantimonate

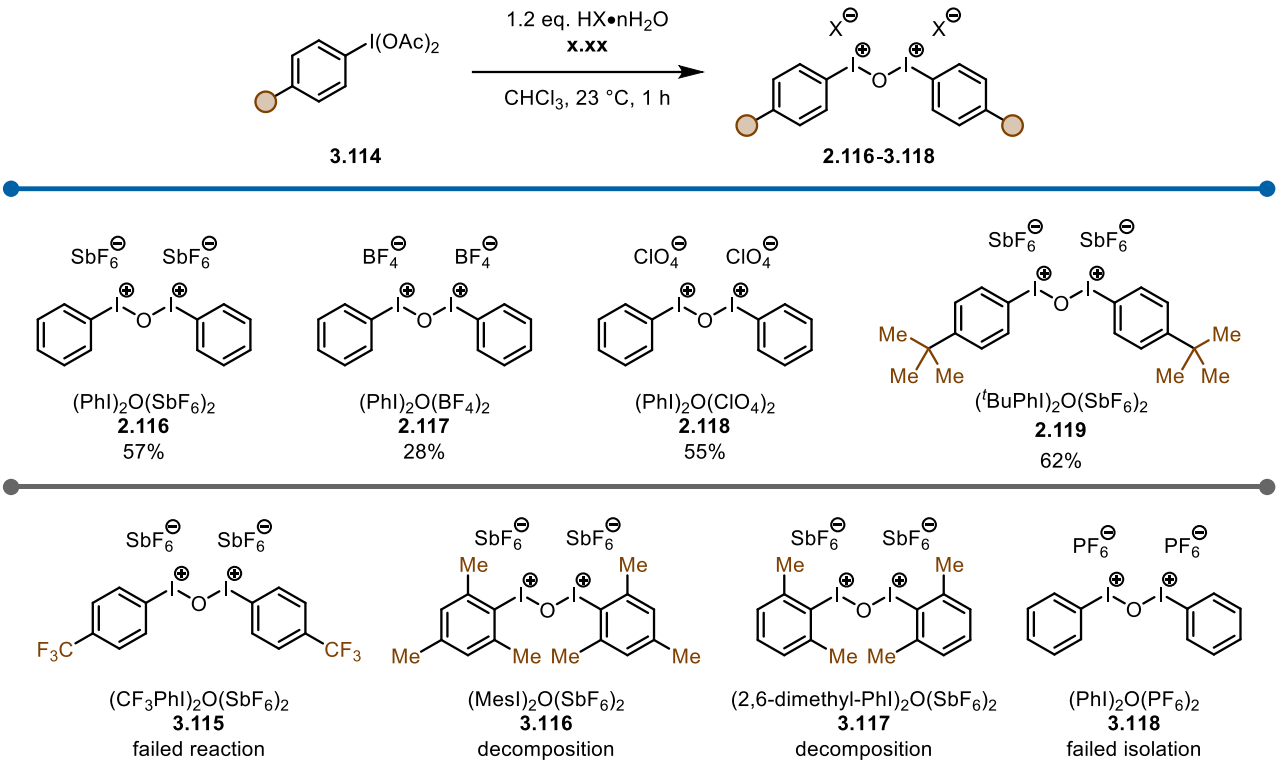


3.112

Synthesized following **GP-20**, using **3.88** (28.1 mg, 0.10 mmol, 1.00 eq.), silver hexafluoroantimonate ($AgSbF_6$, 36.1 mg, 1.05 eq.) and dichloromethane (CH_2Cl_2, 1.00 mL) afforded compound **3.113** (33 mg, 0.08 mmol, 76%). Spectroscopic data were in accordance with literature.[144]

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.48 (d, J = 7.5 Hz, 2H), 8.12 (t, J = 7.5 Hz, 1H), 7.78 (t, J = 8.0 Hz, 2H), 4.48 (d, J = 2.4 Hz, 1H), 2.49 (dd, J = 13.7, 6.9 Hz, 2H), 2.35 – 2.26 (m, 2H), 2.08 – 2.00 (m, 4H), 1.96 (s, 3H) ppm.

3.3.4 General Procedure 21: Synthesis of Iodonium Reagents

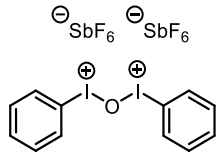


Scheme 3.11: Synthesis of Iodonium Reagents.

Adapted from a literature procedure.[178]

To an ice-bath cooled (0 °C) solution of diacetoxyiodobenzene (PIDA, 1.00 eq.) in chloroform ($CHCl_3$, 2 M) was added slowly hexaluoroantimonic acid hexahydrate ($HSbF_6 \bullet 6H_2O$, 1.20 eq.), and the resulting mixture was allowed to warm to 23 °C. After 1 h, water (1.00 mL for 1.00 mmol of diacetoxyiodobenzene) was added, and the mixture was cooled to 0 °C. After 1 h at 0 °C, a precipitate was formed and the mixture was filtered. The precipitate was washed with chloroform ($CHCl_3$), distilled water (H_2O) and pentane. The obtained solid was crushed to a powder and the washing steps were repeated in the same order twice. The resulting solid was dried under reduced pressure for 3 h to afford the dicationic iodonium reagent **2.116** as a bright-yellow powder.

2.116 – $(PhI)_2O(SbF_6)_2$ – Oxybis(phenyliodonium) bis[hexafluorostilbate(V)



2.116

Synthesized following **GP-21**, using diacetoxyiodobenzene (3.32 g, 10.0 mmol, 1.00 eq.), hexaluoroantimonic acid hexahydrate ($HSbF_6 \bullet 6H_2O$, 4.22 g, 12.0 mmol, 1.20 eq.) and chloroform (CH_3Cl, 5.00 mL) afforded compound **2.116** (2.60 g, 2.90 mmol, 58% - average yield over 8 runs) as a bright yellow solid. Spectroscopic data were in accordance with literature.[178]

^{1}H NMR (400 MHz, 8:3 $CDCl_3$/DMSO-*d_6*): δ 7.74 – 7.53 (m, 4H), 7.47 – 7.35 (m, 2H), 7.32 – 7.14 (m, 4H) ppm.

4 References

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