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DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

„Carbocationic Intermediates in Redox Processes

&

a Catalytic Cross-Coupling of Carbene Precursors“

verfasst von / submitted by

Adriano Bauer

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TO MY BLOODLINE

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The work presented in this doctoral thesis was conducted between March 2016 and February 2020 at the University of Vienna (Austria) under the supervision of Univ.-Prof. Dr. Nuno Maulide

Referees:

Prof. Dr. Benjamin List

Mag. Dr. Roman Lichtenecker, Privatdoz.

Herewith I would like to authenticate that I have written this thesis on my own.

I have not used other resources, tools or assistance than those reported in this thesis.

Adriano Bauer, February 2020

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PERSONAL FOREWORD

THE ABBREVIATION PHD STANDING FOR *philosophiae doctor* (Latin for "doctor of philosophy") does not necessarily imply philosophical training, and this work (including the foreword) is by no means meant to reach philosophical standards. However, the meaning of the degree "PhD" may be interpreted in a more literal sense: as a love for knowledge ("φιλο" (philo) - ancient Greek for "love" or "affinity" and "σοφία" – (Sophia) for "wisdom" or "knowledge"): science, and fundamental research in particular, is motivated by curiosity, fascination and the desire to understand the unknown. Indeed the academic title "PhD" stands in contrast to other degrees that are granted for studies in fields which are readily applicable in the "real world" such as medicinal doctor or doctor of business administration. Yet scientists claim that they have the instruments and the culture to measure objective truth; a general valid interpretation of what is real. But is it not already a paradox that the search for objective truth is driven by subjective emotions like curiosity or desire for knowledge? Although, objective truth is meant to carry a certain general validity, it stands in contrast to the fact that the most certain truth is subjective existence ("*cogito ergo sum*") and that this consciousness (*i.e.* subjective experience) cannot be explained by scientific means. Sometimes I have the feeling that science is an expensive form of art which provides something practically useful only in rare cases but is more regularly done to please the human mind. Nevertheless, I also believe that science is deeply associated to progress, technological development and human control over the chaos of nature's uncertainty which we have to face since we were expelled from the Garden of Eden. Maybe eating the fruits from the tree of knowledge stands for what Yuval Harari calls "cognitive revolution" (*i.e.* paleolithic revolution) or the "dawn of men" in Stanley Kubrick's odyssey: the ability to perceive things as objects rather than subjective impressions. Cursed with this divine knowledge we are able to find subjective pleasure in destruction but we are also capable to create beautiful things, with or without practical utility and find satisfaction in creation and creativity. This is what I believe distinguishes us from other animals.

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TABLE OF CONTENT

ABSTRACT

THE WORK PRESENTED HEREIN DESCRIBES the development of new synthetic methodologies in organic synthesis.

The first chapter depicts the investigation of a one-pot procedure in which a Hosomi-Sakurai reaction is coupled to a regio- and stereoselective internal reduction of the generated homoallylic double bond *via* an non-sigmatropic 1,5 hydride transfer. In doing so, 1,3-substituted alcohols are formed preferentially in the *anti*-configuration.

In the second chapter, the development of a ruthenium-catalyzed olefination is illustrated in which two different carbene-precursors are coupled to each other. The generated alkenes show generally a high selectivity for the *Z*-isomer.

In the third chapter, novel one-pot functionalization reactions of tertiary-amides are explored, which are based on electrophilic amide activation and further oxidation steps. Therein, α,β-epoxiamides, β-thioamides, α-ketoamides, β-ketoamides and furanones are generated in moderate to excellent yields. Moreover, in the course of the study, several unexpected side reactions were discovered and investigated which led to previously difficult to obtain heterocyclic rings.

In the fourth and final chapter, iodine(III) reagents are used on ketone-derivatives to trigger rearrangements typically associated to classical and non-classical carbocations. The first method describes an oxidative 1,2-aryl transfer of β-aryl ketone derivatives leading to α-aryl-β-mesylate ketones. An asymmetric variant of this reaction has also been successfully studied. The second method uses γ,δ-dehydrogenated ketone derivatives to generate cyclopropylcarbinyl cations. These cations are then trapped by several nucleophiles to furnish a disubstituted *trans*-cyclopropanes.

ABSTRAKT (GERMAN)

DIESE ARBEIT BESCHREIBT DIE ENTWICKLUNG neuer Synthesemethoden in der organischen Chemie.

Das erste Kapitel schildert ein Eintopfverfahren, in welchem eine Hosomi-Sakurai Reaktion mit einer regio- sowie stereoselektiven internen Reduktion der generierten homoallylischen Doppelbindungen durch eine nicht sigmatrope 1,5 Hydridverschiebung, gekoppelt wird. Hierbei werden 1,3-disubstituierte Alkohole vorzugsweise als *anti*-Diastereoisomere gewonnen.

Im zweiten Kapitel wird die Entwicklung einer Ruthenium-katalysierten Olefinierungsreaktion erörtert, in der Carbenvorstufen miteinander gekuppelt werden. Die Alkene, welche als Produkt anfallen, werden dabei in hoher *Z*-Selektivität gebildet.

Das dritte Kapitel setzt sich mit neuartigen Funktionalisierungsreaktionen von tertiären Amiden auseinander. Diese Reaktionen basieren auf der elektrophilen Aktivierung von Amiden, welche mit weiteren Oxidationschritten kombiniert wird. α,β-Epoxyamide, β-Thioamide α-Ketoamide, β-Ketoamide sowie Furanone können dabei in moderaten bis exzellenten Ausbeuten gewonnen werden. Desweitern wurden im Laufe der Studie mehrere unerwartete Nebenreaktionen entdeckt und erforscht. Diese Reaktionen führten zur Bildung heterocyclischer Verbindungen deren Darstellung zuvor schwierig war.

Im vierten und letzten Kapitel wird der Gebrauch von Iod(III) Reagenzien zur Oxidation von Keton-derivativen beschrieben, um Umlagerungen, welche typischerweise in klassischen und nicht-klassischen Carbokationen beobachtet werden, hervorzurufen. Die erste Methode beschäftigt sich mit einer oxidativen 1,2-Aryl Verschiebung in β-Aryl Ketonderivaten, welche zur Bildung von α-Aryl-β-Mesylat-Ketonen führt. Eine asymmetrische Variante dieser Reaktion wurde ebenfalls erfolgreich untersucht. Die zweite Methode nutzt hingegen γ,δ-ungesättigte Ketonderivative als Startmaterialien, welche durch Oxidation in Cyclopropylcarbinylkationen überführt werden. Diese Kationen können dann mit verschiedenen Nukleophilen eingefangen werden, was zur Bildung von disubstituierten *trans*-Cyclopropanen führt.

HOW TO READ THIS THESIS

THIS THESIS IS COMPOSED OF 4 chapters

I) A reductive Hosomi-Sakurai reaction
II) A catalytic cross-coupling of carbene precursors
III) α,β,γ-Functionalization and formation of heterocycles *via* amide activation
IV) Iodine(III) mediated carbocationic rearrangements

Each chapter starts with an INTRODUCTION (**subchapter 1**) where the basic principles and the state of the art are described which are both a necessity to understand a) the fundamentals of our hypotheses and b) why the questions we ask are desirable to be investigated.

Thereafter the central hypothesis of the work is expressed in the OBJECTIVE SECTION (**subchapter 2**), where the pivotal questions are described in a few lines.

The RESULTS AND DISCUSSION are presented afterwards (**subchapter 3**). These lines are mostly constituted of original discoveries and interpretation of the observed data which is followed by

a CONCLUSION AND OUTLOOK SECTION (**subchapter 4**) where the results are summarized in a concise manner. Moreover, comments on unexpected emerged observations, which are yet to be investigated, will be found therein.

The SUPPORTING INFORMATION (**subchapter 5**) describes the experiments and the synthesis of starting material, while the CHARACTERIZATION OF NEW COMPOUNDS (**subchapter 6**) is found thereafter.

Yields are generally reported as isolated yields of the pure material. If the yield is followed by the abbrevation "(NMR)" (*e.g.* 76% (NMR)) it refers to the yield determined by analysis of the ^{1}H NMR spectrum of the crude mixture with mesitylene as the internal standard.

The bibliography is organized in the style of *Angewandte Chemie International Edition* and can be found at the very end of the thesis.

LIST OF ABBREVIATIONS

2-Cl Py	2-CHLOROPYRIDINE
2-F Py	2-FLUOROPYRIDINE
2-I Py	2-IODOPYRIDINE
9-BBN	9-BORABICYCLO[3.3.1]NONANE
δ	CHEMICAL SHIFT
σ	SUBSTITUTION CONSTANT (HAMMETT SCALE)
σ^+	SUBSTITUTION CONSTANT (BROWN SCALE)
°C	DEGREES CELSIUS
Å	ÅNGSTRÖM (= $1 \bullet 10^{-10}$ meters)
A	ANTISYMMETRIC
aq.	AQUEOUS SOLUTION
ATR	ATTENUATED TOTAL REFLECTION
Ac	ACETYL
acac	ACETYLACETONATE
Ar	ARYL
BDE	BOND DISSOCIATION ENERGY
BDSI	BENZENEDISULFONIMIDE
BCS	BÜCHNER-CURTIUS-SCHLOTTERBECK
BINAP	2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL
Bn	BENZYL ($C_6H_5CH_2$-)
brsm	BASED ON RECOVERED STARTING MATERIAL
Bs	PARA-BROMOPHENYLSULFONYL (BROSYL/*p*-$BrC_6H_4SO_2$-))
Bu	BUTYL (C_4H_9-)
Bz	BENZOYL ($C_6H_5C(O)$-)
c	CONVERSION
c	CISOID
ca.	CIRCA
cal	CALORIES
cat.	CATALYST
cf.	CONFER/CONFERATUR
COD	CYCLOOCTADIENE
Cp	CYCLOPENTADIENYL
Cp*	PENTAMETHYLCYCLOPENTADIENYL
CSA	CAMPHORSULFONIC ACID
Cy	CYCLOHEXYL
d.r.	DIASTEREOMERIC RATIO
DAST	DIETHYLAMINOSULFUR TRIFLUORIDE
DBU	1,8-DIAZABICYCLO[5.4.0]UNDEC-7-EN
DCM	DICHLOROMETHANE
DCE	1,2-DICHLOROETHANE
DEAD	DIETHYL AZODICARBOXYLATE
DIPA	DIISOPROPYLAMINE

DMF	*N,N*-DIMETHYLFORMAMIDE
DFT	DENSITY FUNCTIONAL THEORY
DMP	DESS-MARTIN-PERIODINANE
dmpe	1,2-BIS(DIMETHYLPHOSPHINO)ETHANE
DMSO	DIMETHYLSULFOXIDE
DMAP	*N,N*-DIMETHYLPYRIDIN-4-AMINE
DNBA	2,4-DINITROBENZENSULFONIC ACID
dppf	1,1'-BIS(DIPHENYLPHOSPHINO)FERROCENE
DSI	DISULFONIMIDES
DTBP	2,6-DITERTBUTYLPYRIDINE
E	ENTHALPY
E^+	ANY ELECTROPHILE
e.g.	EXEMPLI GRATIA
E_a	ACTIVATION ENERGY
EDA	ETHYL DIAZOACETATE
EDG	ELECTRON-DONATING GROUP
EDTA	ETHYLENEDIAMINETETRAACETIC ACID
ee	ENATIOMERIC EXCESS
EI	ELECTRON IMPACT IONISATION
eq.	EQUATION
equiv.	EQUIVALENT(S)
ESI	ELECTRON SPRAY IONIZATION
esp	α,α,α′,α′-TETRAMETHYL-1,3-BENZENEDIPROPIONIC ACID
Et	ETHYL
et al.	ET ALIA/ET ALII/ET ALIBI
etc.	ET CETERA
eV	ELECTRON VOLT
EWG	ELECTRON-WITHDRAWING GROUP
FTIR	FOURIER-TRANSFORM INFRARED SPECTROSCOPY
G	FREE GIBBS ENERGY
GC	GAS CHROMATOGRAPHY
h	HOUR(S)
HOMO	HIGHEST OCCUPIED MOLECULAR ORBITAL
HMDS	HEXAMETHYLDISILAZIDE
HMPA	HEXAMETHYLPHOSPHORAMIDE
HRMS	HIGH RESOLUTION MASS SPECTROMETRY
Hz	HERTZ
i.e.	ID EST
IC_{50}	HALF MAXIMAL INHIBITORY CONCENTRATION
IDP	IMIDODIPHOSPHATES
IDPi	IMIDODIPHOSPHORIMIDATES
IPR	NHC-LIGAND WITH CAS NUMBER 244187-81-3
IUPAC	INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY
K	KELVIN
k	REACTION RATE
KIE	KINETIC ISOTOPE EFFECT
L.A.	LEWIS ACID
LDA	LITHIUM DIISOPROPYLAMIDE

LG	LEAVING GROUP
LUMO	LOWEST UNOCCUPIED MOLECULAR ORBITAL
M	MOLAR (mol/L)
*m*CPBA	META-CHLOROPEROXYBENZOIC ACID
Me	METHYL (CH_3-)
MEP	MOLECULAR ELECTROSTATIC POTENTIAL
Mes	MESYTYL
Min	MINUTE(S)
MO	MOLECULAR ORBITAL
MPV	MEERWEIN-PONNDORF-VERLEY
Ms	METHANESULFONYL (MESYL/CH_3SO_2-)
MS	MOLECULAR SIEVES
MTO	METHYLTRIOXORHENIUM
N	NUCLEOPHILICITY (MAYR SCALE)
n	PRINCIPLE QUANTUM NUMBER
$NaBAr^F_4$	SODIUM TETRAKIS(3,5-BIS(TRIFLUOROMETHYL)PHENYL)BORATE
NADH	NICOTINAMIDE ADENINE DINUCLEOTIDE
N.B.	NOTA BENE
N.D.	NOT DETECTED
NMR	NUCLEAR MAGNETIC RESONANCE
NOESY	NUCLEAR OVERHAUSER ENHANCEMENT SPECTROSCOPY
~~*O*~~	OXOPHILICITY (KEPP SCALE)
PA	PROTON AFFINITY
PES	POTENTIAL ENERGY SURFACE
pH	POTENTIA HYDROGENII
Ph	PHENYL
Phen	PHENANTROLINE
Pht	PHTALYL
PIDA	PHENYLIODINE(III) DIACETATE
PIFA	PHENYLIODINE(III) BIS(TRIFLUOROACETATE)
Piv	PIVOYL
pK_a	ACID DISSOCIATION CONSTANT
PMB	PARAMETHOXYBENZYL
PNO	PYRIDINE-*N*-OXIDE
ppm	PARTS PER MILLION
Pr	PROPYL (C_3H_7-)
*p*Tol	PARATOLYL
*p*TSA	PARA-TOLUENESULFONIC ACID
Py	PYRIDINE
r.t.	ROOM TEMPERATURE
RCM	RING-CLOSING METATHESIS
S	SYMMETRIC
S	OVERLAP
s, sec	SECOND(S)
T	TEMPERATURE
t	TIME
t	TRANSOID
TBAB	TETRABUTYLAMMONIUM BROMIDE

TBAC	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium flouride
TBAI	Tetrabutylammonium iodide
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TCE	1,1,2-Trichloroethane
TES	Triethylsilyl (Et_3Si-)
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TIPS	Triisopropylsilyl ($i Pr_3Si$-)
Tf	Trifluoromethyanesulfonyl (Triflyl/CF_3SO_2-)
TLC	Thin layer chromatography
TMS	Trimethylsilyl (Me_3Si-)
Ts	Para-toluolsulfonyl (Tosyl /*p*-$MeC_6H_4SO_2$-)
v/v%	Volume percent
VB	Valence bond
w/w%	Weight percent

CHAPTER I

A reductive Hosomi-Sakurai reaction

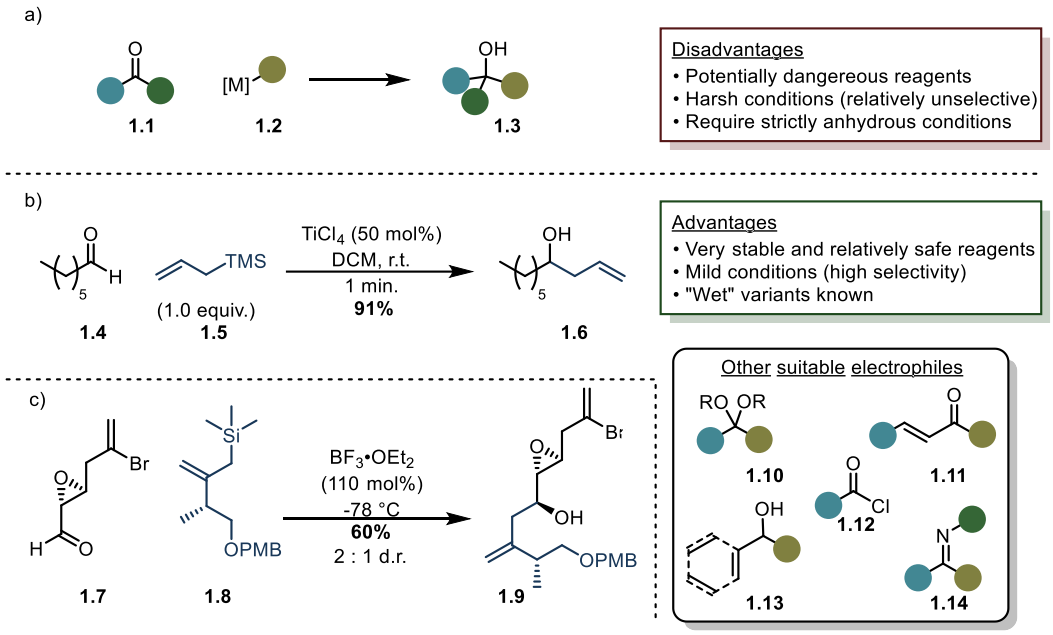
The results of this work are published in *Org. Lett.* **2018**, 20, 1461 – 1464,[1] and *Tetrahedron* **2018**, 6883 – 6889.[2] Dr. P. Aillard and M. Radic (B.Sc.) are acknowledged for preliminary results on the 1,5-hydride transfer, J. Sprachmann (M.Sc.) is acknowledged for the synthesis of several allylsilanes and Dr. B. Maryasin is acknowledged for the assistance in the computational study.

1.1. Introduction

1.1.1. The Hosomi-Sakurai reaction

1.1.1.1. *Overview*

THE FORMATION OF C-C BONDS has always been at the heart of organic chemistry. A historical breakthrough was achieved, when Philippe Barbier and his student, Victor Grignard, discovered the addition of organometallic reagents onto carbonyl functionalities (*Scheme 1.1a*).[3] Although such organometallic reactions have been used for copious syntheses in industry and in academic research,[4–6] their main limitations include their high reactivity, which is closely associated with their notorious lack of functional group tolerance, their need for strictly anhydrous conditions and their potentially pyrophoric nature. In 1976 Hosomi and Sakurai reported allylsilanes as milder cognates of the aforementioned organometallic reagents which react readily with aldehydes and ketones in the presence of a Lewis acid (*Scheme 1.1b*).[7] The mildness of this method has been showcased by its use in many total syntheses.[3]



Scheme 1.1 - a) General reaction of organometallic reagents with carbonyl functionalities. b) The originally reported Hosomi-Sakurai reaction. c) Selected application of the Hosomi-Sakurai reaction in total synthesis.

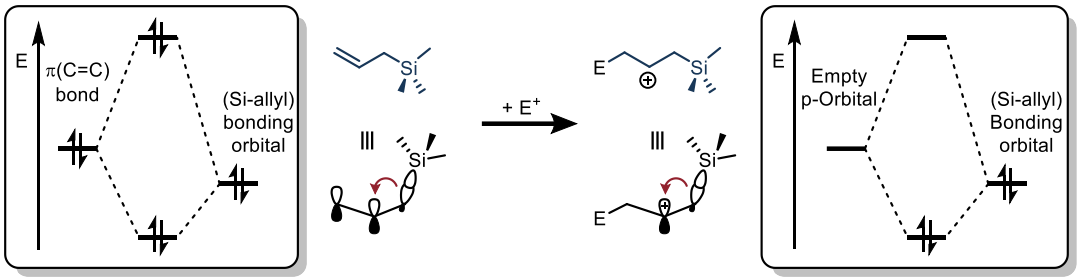
In one example, the allylsilane **1.8** was used in combination with $BF_3 \bullet OEt_2$ as the Lewis acid, and reacted with a highly electrophilic α,β-epoxy aldehyde **1.7**, which also contained a vinyl bromide (*Scheme 1.1c*). The reaction proceeded smoothly and demonstrated good functional group tolerance.[8] In comparison, classical organometallic reagents struggle to compete with such selectivity.

Over the years, the Hosomi-Sakurai reaction has unsurprisingly enjoyed considerable attention, and many useful variants have since been developed. Shortly after their initial discovery, Hosomi and Sakurai showed that enones (**1.11**),[9] ketals and acetals (**1.10**) were also suitable electrophiles (*Scheme 1.1b – box*).[10,11] Other electrophiles that have been utilized in this chemistry include *in situ* generated iminium ions by the groups of Grieco[12,13] and Overman,[14] isolated imines (**1.14**)[15,16] as well as acylchlorides (**1.12**) allowing to access to β,γ-unsaturated amines and ketones respectively.[17,18] Interestingly, Fleming and Pearce used vinylsilanes as nucleophiles in reactions with acylchlorides under Lewis acidic conditions (furnishing enones), before the allylation by Hosomi and Sakurai was reported.[19] These reactions are likely to involve acylium ions as the electrophile.[17–19] *In situ* generated allylic,[20,21] benzylic,[21] and propargylic[22] cations (starting from the corresponding alcohols (**1.13**)) have all been reacted with allylsilanes to generate 1,5-dienes, allylarenes and 1,5-enynes respectively.

1.1.1.2. *Mechanism and state of the art of the Hosomi-Sakurai reaction*

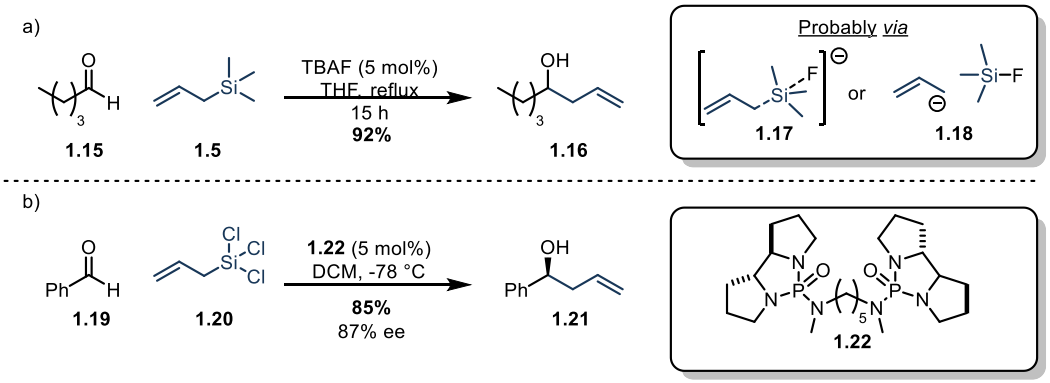
Although alkylsilanes are not very nucleophilic because the electrons of the sp^3-sp^3 carbon-silicon bond are energetically on a relatively low level, these electrons can interact effectively with an adjacent π-systems *via* hyperconjugation to enhance the energetic level of the π-electrons (*Scheme 1.2 - left*).[23,24] During nucleophilic attack a positive charge develops on the β-carbon of the silane reagent. This cation is supported by the aforementioned hyperconjugation, which now stabilizes the vacant p-orbital (β-silicon effect – *Scheme 1.2/right*).[25] In this regard, organosilanes that carry either alkenyl, alkynyl or allylic substituents on the silicon atom show an enhanced nucleophilicity (with respect to simple alkenes or

alkylsilanes) because in these structures hyperconjugation can operate.[23] Due to the β-silicon effect, allylsilanes react usually on the γ-carbon, while alkenyl- and alkynyl-silanes react on the α-carbon.



Scheme 1.2 – Hyperconjugation of the silicon with π-systems (β-silicon effect).

Allylsilanes are nevertheless only moderately nucleophilic (Mayr scale): the nucleophilicity of trimethylallylsilane (*N* = 1.68)[26] lies in the range of furan (*N* = 1.33)[26] and 4-methylstyrene (*N* = 1.70)[27] (all values measured in DCM). The nucleophilicity can be enhanced by additives that have a high affinity towards the silicon atom[28] (*e.g.* fluorides,[16,29–31] amides,[32] phosphoramides,[33,34] and pyridine-*N*-oxides[35–37]), either to form a silicate complex or an allylic carbanion (*Scheme 1.3a*).[28] In most cases, electron-withdrawing groups on the silicon atom are used to enhance its affinity to the Lewis base. This strategy can also be extended to chiral catalysts,[28,30,31,33–37] which enable enantioselective versions of the Hosomi-Sakurai reaction (*Scheme 1.3b*).



Scheme 1.3 – a) First Lewis base-promoted Hosomi-Sakurai reaction. b) Enantioselective Lewis base-promoted Hosomi-Sakurai reaction.

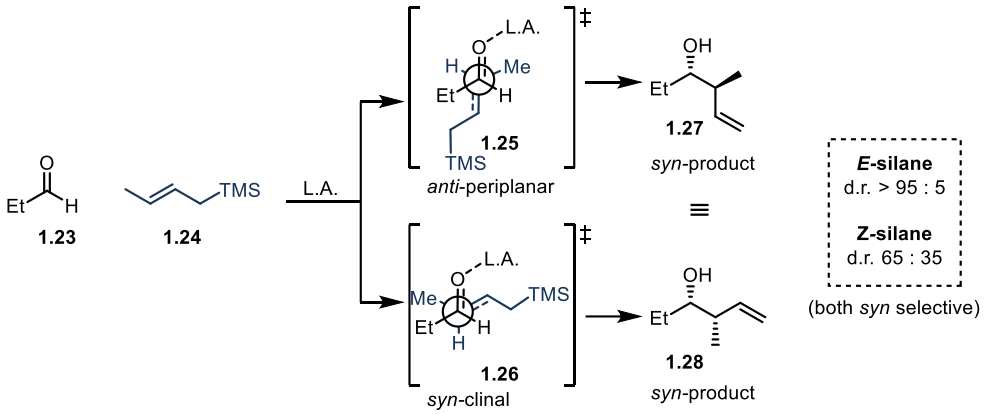
Yet, most of the approaches using allylsilanes as nucleophiles follow the strategy of enhancing reactivity of the electrophile by the use of an acid, as in the case of the classical Hosomi-Sakurai reaction.

Typical Lewis acids used for the Hosomi-Sakurai reaction are $TiCl_4$, $BF_3{\bullet}OEt_2$, $AlCl_3$, $SnCl_4$ or $EtAlCl_2$.[3] These acids are often used in stoichiometric amounts, although some catalytic versions with low catalyst loading have also been discovered. $InCl_3$ in combination with TMSCl (5 mol% of each) is ,for instance, an effective catalyst for this classical transformation.[38] Furthermore, $Sc(OTf_3)$ is reported to be a very active catalyst for the allylation of aldehydes.[39]

Lewis acids and bases are not the only possible reagents to promote this reaction; the use of the strong Brønsted acid *bis*(trifluoromethanesulfonyl)imide (Tf_2NH) in only 0.5 mol% amounts can afford an excellent yield of the allylic alcohol, when starting from the aldehyde.[40] It is noteworthy that, Tf_2NH is only the pre-catalyst, since it is transformed to TMS-NTf_2 after reacting once with the silane. Some Brønsted acids have recently been shown to be excellent pre-catalysts for the enantioselective allylation of aldehydes using allylsilanes (see also chapter 1.1.1.3.).[41,42]

The reaction mechanism of a typical Hosomi-Sakurai reaction (*Scheme 1.4*) shows that, in contrast with allylborane reagents,[43] the transformation proceeds predominantly through a non-cyclic transition state.[43–45] This is due to the weak Lewis acidic character exhibited by the silyl moiety of allylsilanes, which is unable to effectively coordinate to the carbonyl moiety.[23] Exceptions to this rule can be found in electron-depleted allylsilanes such as trichloro-[32,33] or trifluorosilanes[46,47], which are superior Lewis acids. The open transition state has important implications on the stereochemical outcome of the reaction (*Scheme 1.4*). Allylsilanes are oriented either *syn*-clinal **1.26** or *anti*-periplanar **1.25** to the carbonyl moiety.[45] Both transition states are considered to be feasible and often lead to the same product, although the *syn*-clinal arrangement **1.26** is energetically preferred.[44] Usually, *E*-allylsilanes give very high *syn* selectivity for the addition on aldehydes, while *Z*-allylsilanes are only moderately selective for the *syn* product.[48] Computational studies suggest that the transition state is cyclic to some extent when $BF_3{\bullet}OEt_2$ is used as the Lewis Acid, since the fluorine in BF_3 can weakly coordinate to the silicon atom.[44] Aldehydes

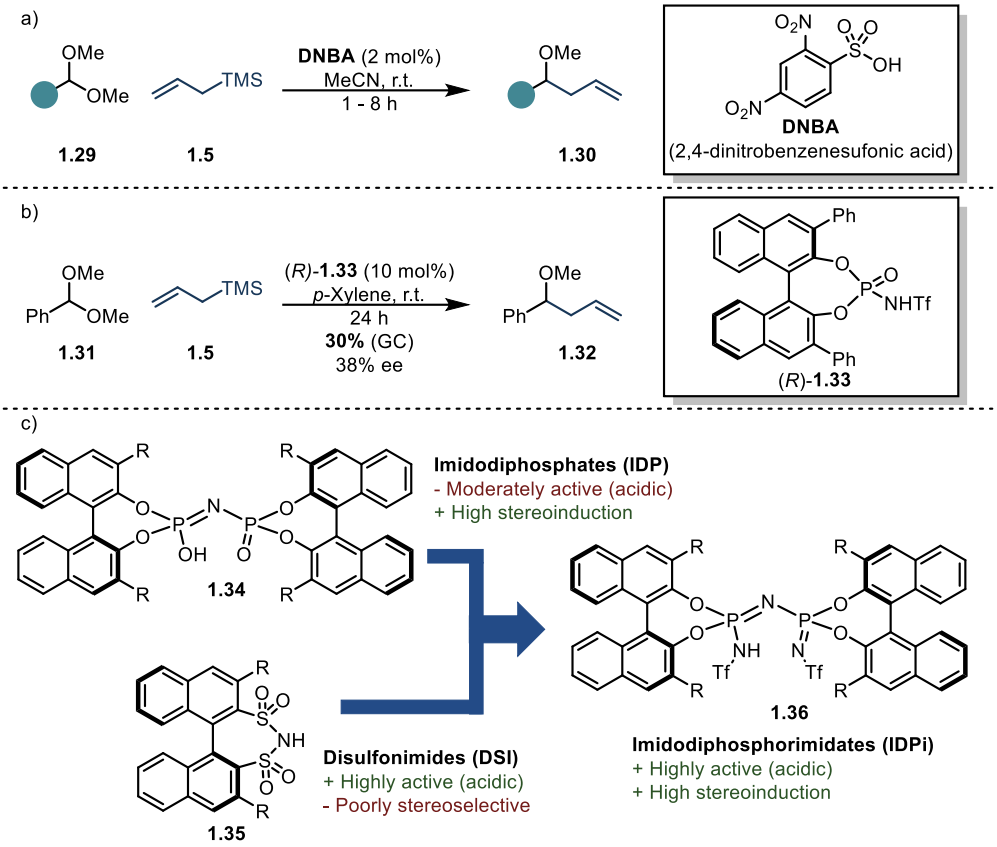
with a stereogenic center in the α-position show some diastereoselectivity towards addition, which can be predicted by Felkin-Anh [49] or Cram chelate models depending on the nature of the substituent.[50]



Scheme 1.4 – Stereochemical model of the open transition state in the Hosomi-Sakurai reaction.

1.1.1.3. *The Hosomi-Sakurai reaction with acetals as substrates*

Ketals and acetals are suitable alternatives to aldehydes in the Hosomi-Sakurai reaction. They generally react with a cleaner and smoother reaction profile when compared to their unprotected counterparts. Similarly to the addition on aldehydes and ketones, stoichiometric amounts of Lewis acids such as $TiCl_4$,[11] BF_3•OEt_2,[51] $AlCl_3$,[51] liquid SO_2[52] or CuBr[53] are typically used to promote the reaction of acetals with allylsilanes. Catalytic variants have also been developed, with substoichiometric amounts of TMS-iodide successfully promoting the reaction between allylsilanes and acetals.[10] Conversely, aldehydes require a co-catalyst for a similar reaction to occur (*c.f.* section 1.1.1.2).[38] A large variety of Lewis acid catalysts has been explored in substoichiometric amounts for this reaction including $AlBr_3$/CuBr,[54] $NbCl_5$/$AgClO_4$,[55] $FeCl_3$,[56] TMSOTf,[57,58] $Sc(OTf)_3$,[59] $Bi(OTf)_3$,[60] $BiBr_3$,[61] $TMSNTf_2$,[62] $TMSN(SO_2F)_2$,[63] $TiCp_2(OTf)_2$,[64] $TrClO_4$,[65] and Ph_2BOTf.[65] Ghosez and coworkers reported a reaction where certain simple alkenes were added similarly onto oxocarbenium ions, which were generated by a Lewis acid from the corrisponding acetals.[66] The Brønsted acid-catalyzed allylsilane addition to acetals has been pioneered by the group of Denmark.[67] However, it was the group of List that has made significant contributions towards the generalization of this approach (*Scheme 1.5a*).[68]



Scheme 1.5 – a) Brønsted acid catalyzed Hosomi-Sakurai reaction on acetals. b) Enantioselective version. c) Development of IDPi catalysts.

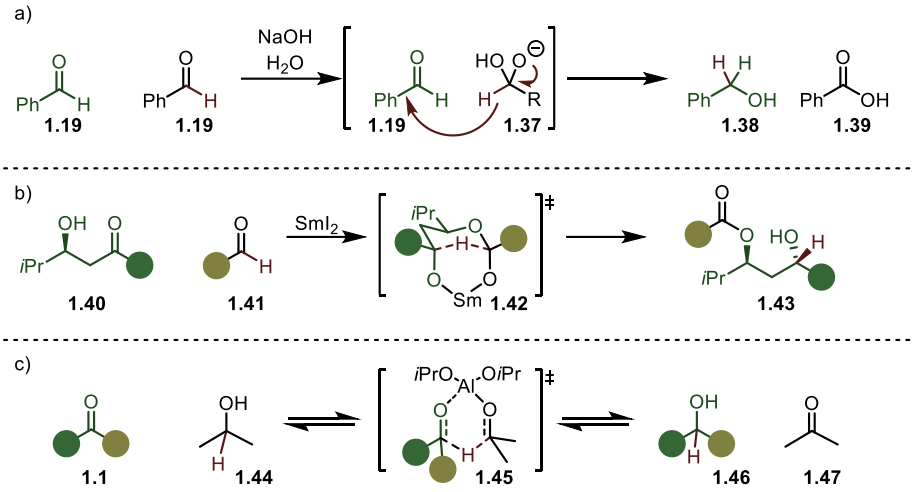
In a communication by List *et al.*, the use of 2,4-dinitrobenzenesulfonic acid (DNBA) as a Brønsted acidic catalyst was reported (this acid was utilized for most of our work on the reductive Hosomi-Sakurai reaction). In 2008, the concept was extended by List to the *in situ* formation of the acetals, starting from the corresponding aldehyde.[69] Dughera *et al.* reported that benzenedisulfonimide (BDSI) can be used similarly as the catalyst.[70] Enantioselective allylation of acetals using phosphorus-based Brønsted acids as chiral catalysts has shown promising potential, although only modest enantioselectivities have yet been observed. The *N*-triflylphosphoramide **1.33**, for instance, has demonstrated appreciable enantioselectivies in this transformation (*Scheme 1.5b*).[71] Acetals derived from sterically unhindered alcohols have proven to be the most suitable partners for this enantioselective reaction. Recently, structural changes to the catalysts, designed to overcome electronic- and sterical flaws, were made and involved combining the high acidity of chiral disulfonimides (DSI -**1.35**) and the excellent stereoselectivity

of imidodiphosphates (IDP – **1.34**), allowing for the development of the imidodiphosphor imidate (IDPi – **1.36**) catalysts.[42] These remarkably active catalysts have not only been used for the highly enantioselective allylation of aldehydes, but have also demonstrated their usefulness in the enantio- and diastereoselective synthesis of 1,5-disubstituted tetrahydrofurans.[41,42,72][72] However, IDPi catalysts have not to date been used in the enantioselective Hosomi-Sakurai reaction using acetals as electrophiles.

1.1.2. Hydride transfers

1.1.2.1. *Overview*

The reduction of organic functionalities by negatively charged hydrogen atoms (hydride or 'H^-') is a widely used transformation in organic synthesis. Asides from common inorganic hydride reagents, such as $NaBH_4$ and $LiAlH_4$,, organic hydride sources have been well explored over the past century. Several of these reactions, which exploit the transfer of an organic H^- onto an electrophilic atom of an organic molecule were named after their discoverers. In the middle of the 19th century, Cannizzaro discovered the base-mediated disproportionation of two molecules of benzaldehyde (*Scheme 1.6a*), which presumably proceeds *via* hydride transfer step, although radical based mechanisms have also been suggested.[3,73] More than half a century later, Tishchenko discovered a related reaction,[74] which was later modified by Evans and coworkers, using SmI_2 and an aldehyde (the source of the hydride) to effect the reduction of β-hydroxy aldehydes *via* a cyclic transition state (*Scheme 1.6b*).[75] In the so called Meerwein-Ponndorf-Verley reduction (*MPV – Scheme 1.6c*)[76–78] and its retro-reaction (Oppenauer oxidation),[79] a reversible six-membered hydride transfer from an alcohol onto a carbonyl compound takes place. Other commonly used organic hydride sources include formic acid such as in the Eschweiler-Clarke reductive amination reaction,[80,81] and the Hantzsch-ester, which resembles NADH in biological systems, and which is popularly used in mild hydride reductions.[82] Intramolecular hydride transfers have been likewise explored extensively and summed up in several reviews.[83–86]



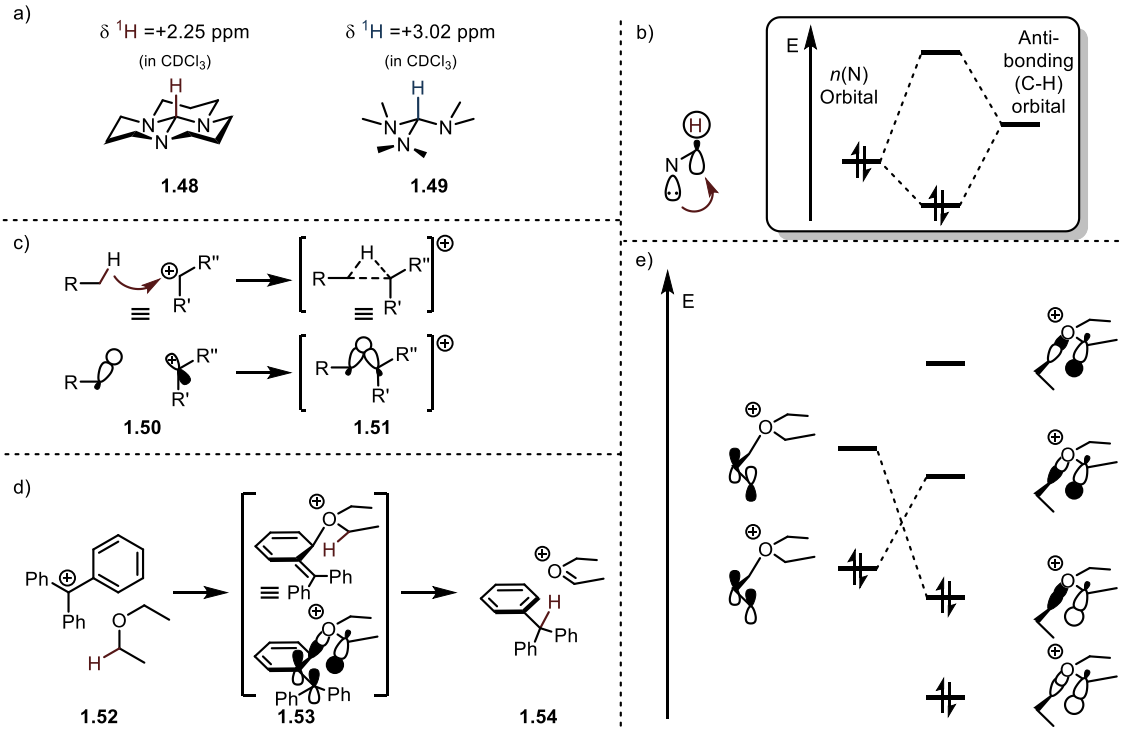
Scheme 1.6 – a) Cannizzaro reaction. b) Evans-Tishchenko reaction. c) MPV reaction.

1.1.2.2. *Mechanism of intramolecular hydride transfer reactions*

Intramolecular hydrogen shifts are typically categorized into two groups: sigmatropic rearrangements and non-sigmatropic hydride transfers. The former proceeds *via* a strictly concerted cyclic transition state, in which a fully conjugated π-system interacts with the orbital of a C-H bond.[87,88] The orbitals of these two fragments contribute to a transition state in which all the electrons are delocalized and the hydrogen atom is transferred to the distal terminus of the π-system.[89] Conventionally, the hydrogen shift is said to be a sigmatropic change of order [1, *j*], where *j* numbers the position in which the new C-H bond is formed (relative to the broken bond).[87–89] Due to the high degree of concertedness, the categorization of the fragments into "nucleophile" and "electrophile" is often inappropriate.

Conversely, non-sigmatropic hydride transfers consist of the intra- or intermolecular transfer of a nucleophilic hydrogen atom (hydride) from an organic molecule to an electrophilic carbon. Fully conjugated π-systems may connect the two termini, but do not interact with the hydride transfer event in such a way that a fully conjugated cyclic transition state is established. Consequently, a distinction of non-sigmatropic and sigmatropic shift is not always obvious at first glance and might require detailed mechanistic studies.

Hydride transfers are often reversible reactions. However, in most cases, a *quasi* irreversible reaction is desired as it is coupled to a suitable thermodynamic driving force. The hydridic nature of given moieties can be rationalized either by the stability of the formed carbocation after the transfer, or by the partially occupied antibonding orbital of the C-H bond. An interesting example is the orthoamide **1.48** (*Scheme 1.7a*).[90,91]



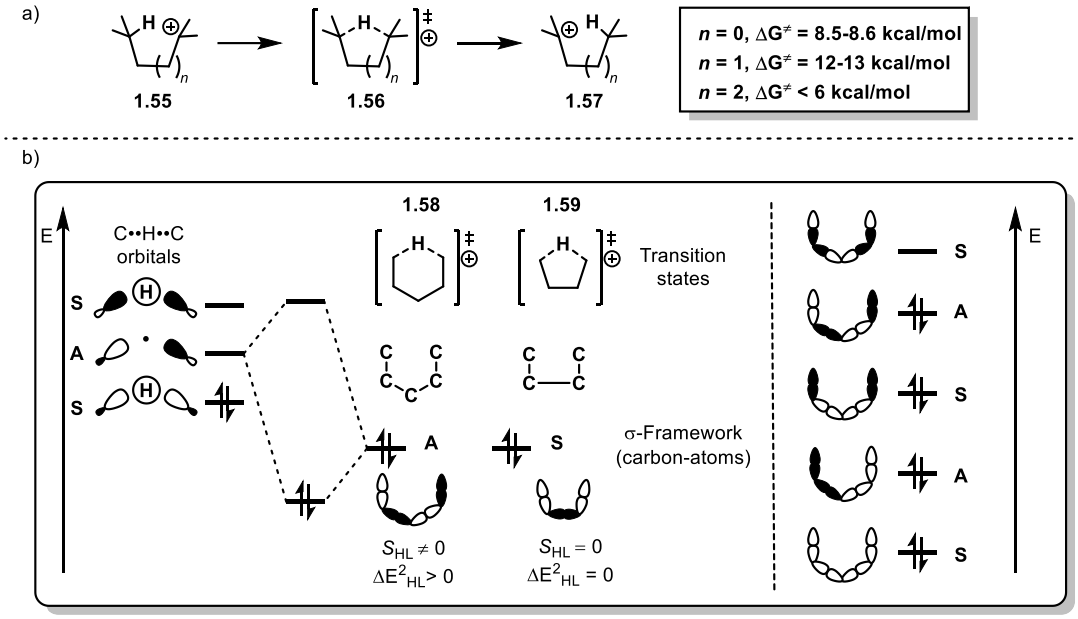
Scheme 1.7 – a) Orthoamides as hydridic organic molecules. b) Explanation of the hydridic nature by hyperconjugation effects. c) Orbital approaches in non-sigmatropic hydride transfer reactions. d) Olah's mechanism of hydride transfer reactions onto sterically congested benzylic cations. e) Orbital interpretation of this effect on a simplified model.

This compound produces H_2 and the guanidinium salt when treated with a Brønsted acid upon heating. The chemical shift of the methine proton in the ^{1}H NMR spectrum appears at δ = 2.25 ppm and thus considerably more shielded than its floppy cognate **1.49**.[92] This indicates that a relatively high amount of electron-density is located on the hydrogen atom, which is caused by the efficient electron-donation of the *N*-lone pairs to the antibonding C-H orbital. This stabilizing orbital interaction is highlighted in *Scheme 1.7b* and is known as the "gauche effect", "heteroatom hyperconjugation" or the "anomeric effect".[89]

Hydride transfer reactions from a hydridic organic compound bear many interesting mechanistic implications that are not immediately obvious. Olah *et al.* showed that the geometry of a hydride transfer between two alkyl species is not linear but rather reassembles a tricyclic structure in a 3-center-2-electron bond fashion (*Scheme 1.7c*).[93,94] In other words, the empty p-orbital of the carbocation approaches the σ-bond at the position where most of the electrons are located, reminiscent of an σ-complex in coordination chemistry.[95] Such structures are often transition states, but can also be intermediates, as shown below.

In a subsequent study, Olah and Svoboda showed that a hydride transfer from an ether to the stabilized trityl cation goes by way of a stepwise mechanism (*Scheme 1.7d*).[96,97] The ether may attack the *ortho* position of the benzene ring to form an oxonium intermediate **1.53**, which undergoes a fragmentation reminiscent of a retro ene-reaction (**1.53** to **1.54**). If we consider the fragmental frontier orbitals of the alkene (HOMO) and the two σ-bonds involved (LUMO) of this rearrangement we can see the symmetry allowed orbital interaction, which are typically observed in ene-reactions (*Scheme 1.7e*).[98] The implication of this mechanism is such hydride shifts could also be interpreted as pericyclic reactions.

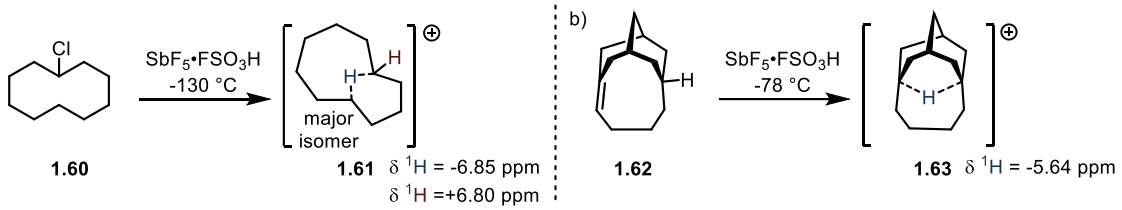
Although cyclopentadienes easily undergo [1,5] hydride shifts at low temperatures,[99] such reactions typically require harsh conditions in order to occur in non-cyclic diene systems.[83,100] In stark contrast, non-sigmatropic 1,5-hydride transfer reactions have a rather low reaction barrier, because they lack the rigidity of conjugated systems, and can easily achieve a favorable conformation. In a study by the group of Saunders, the activation energies for 1,3-, 1,4- and 1,5-hydride transfer reactions of aliphatic compounds have been measured (*Scheme 1.8a*). The Gibbs free energy of activation ($\Delta G^{\ddagger}$) for the hydride transfer follows the decreasing order 1,4 > 1,3 > 1,5 ranging from 12–13 kcal/mol for the 1,4-shift down to <6 kcal/mol for the 1,5-shift at -95 °C[101].



Scheme 1.8 – Orbital symmetry stabilization of intramolecular 1,n-hydride transfer, where n is an odd natural number.

Indeed, the 4 methyl groups in the cation **1.55**/**1.57** appear as a single peak in the ^{1}H NMR spectra, suggesting that the reaction is very fast on the NMR timescale. In a separate study they found that the [1,2]-hydride shift has an even lower reaction barrier (3.1 kcal/mol at -138 °C).[102] However, it has to be noted that the [1,2]-hydride transfer is often interpreted to be a sigmatropic rearrangement[103] with an aromatic transition state and thus its comparison with other non-sigmatropic hydride transfer reactions might not be appropriate. The 1,5-relationship for the hydride transfer reaction not only profits from a favorable conformation during the transition state, but also benefits from a symmetrically allowed interaction between the σ-carbon framework and the C-H-C three-center two-electron bond during the transition state (*Scheme 1.8b*).[97,104,105] While transition states with an odd number of atoms in the carbon framework have a HOMO which is *anti*symmetric to a mirror plane in between the molecule (pentane **1.58**), the HOMO of a transition state with an even number of carbons in the framework is symmetric with respect to the mirror plane (butane **1.59**). Only the *anti*symmetrical HOMO of the carbon framework is able to interact effectively with the LUMO of the C-H-C fragment, because they share the same symmetry. This interaction imparts significant stabilization.[104]

The relative stability of the transition state for a 1,5-hydride transfer is showcased by the characterization of several stable hydrogen-bridged cations bearing this relationship (*Scheme 1.9*). Similar to the non-classical 2-norbornyl carbocation,[106] these structures benefit from a very rigid framework: they do not have to compensate for the loss of entropy during the hydrogen atom transfer event, thus the hydrogen-bridged cation structure, which is typically associated with a transition state, becomes an intermediate. When the cyclic chloroalkane **1.60** (*Scheme 1.9*), for instance, was dissolved in strongly acidic media, the ^{1}H NMR spectra indicated the presence of hydrogen-bridged cyclic compound (**1.61**).[107,108] The very low value of the chemical shift for the bridged hydrogen atom suggests that it carries more negative charge when compared to the hydrogen atoms in tetramethylsilane and therefore reassembles a "real" hydride. The sophisticated tricyclic alkane **1.63** presents a more pronounced example of this effect.[109]



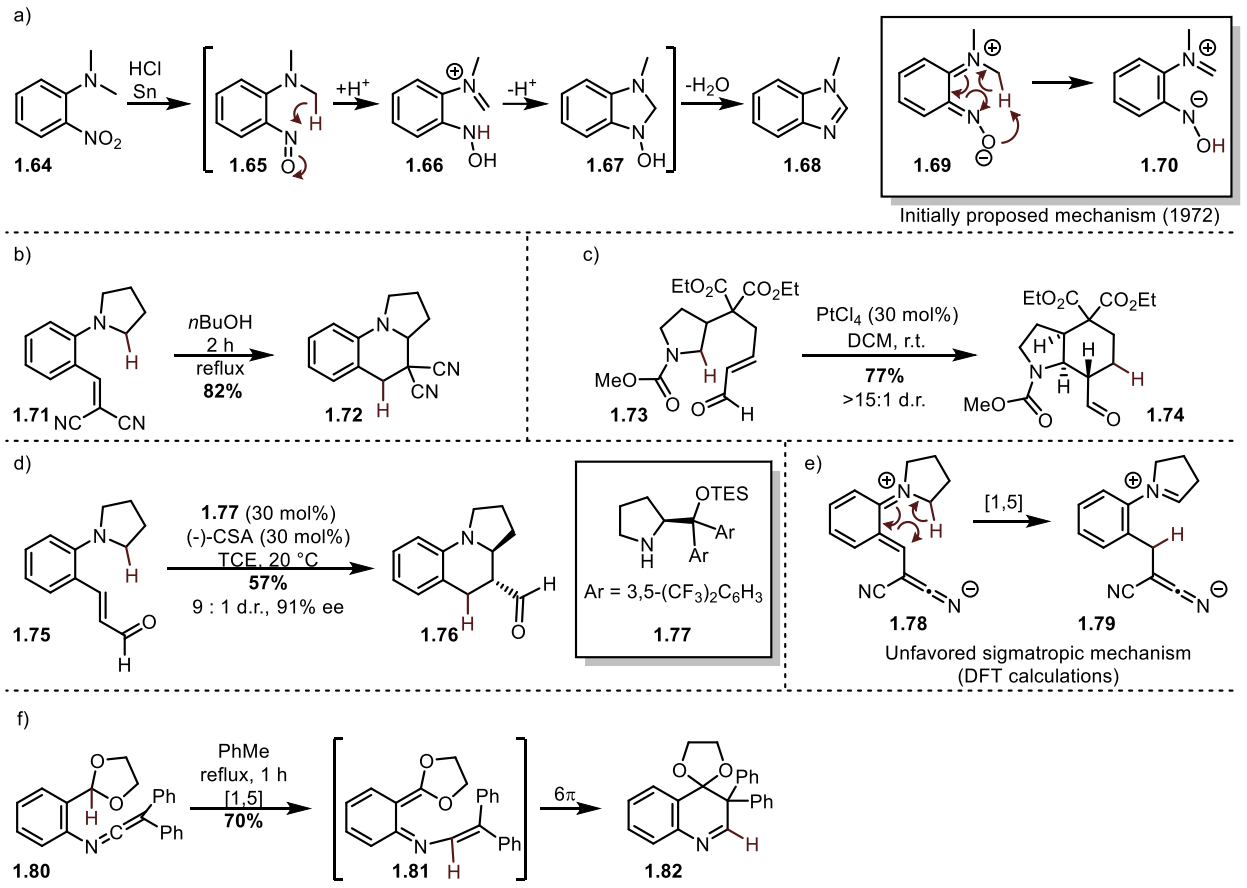
1.60 **1.61** $\delta\ ^{1}H$ = -6.85 ppm, $\delta\ ^{1}H$ =+6.80 ppm **1.62** **1.63** $\delta\ ^{1}H$ = -5.64 ppm

Scheme 1.9 – Stable hydrogen-bridged carbocations.

1.1.2.3. *The "tert-Amino effect"*

One of the earliest non-sigmatropic intramolecular 1,5-hydride transfer reaction was reported as early as 1895 by Pinnow.[110] The structure of the product was elucidated two years later,[111] and the mechanistic details of the reaction were explained in 1901.[112][110] Pinnow noticed that during the reduction of *o*-Nitro-*N,N*-dimethylaniline **1.64**, *N*-methyl benzimidazole **1.68** was formed (*Scheme 1.10a*) and argued that the reaction must result from an "intramolecular oxidation" of the intermediate **1.65**. The mechanism has initially been depicted to proceed through a deprotonation of the α-amino hydrogen by the nitroso group or by the nitro group in a zwitterionic resonance structure (*Scheme 1.10* – black box).[113] However, this seems unlikely; it is indeed more plausible that a 1,5-hydride transfer onto the

electrophilic nitrogen of the nitroso group takes place as depicted in *Scheme 1.10a*, although some authors prefer a 1,6 hydride transfer onto the more electronegative oxygen atom of the nitroso-group.[114] This type of hydride transfer is sometimes named "*tert*Amino effect", because the *tertiary* amine makes the adjacent hydrogen atom hydridic (*cf. Scheme 1.7a*).



Scheme 1.10 – a) Early example of non-sigmatropic 1,5-hydride transfer reaction. b) The tert-amino effect in anilines. c) The tert-amino effect on carbamates. d) An organocatalytic enantioselective 1,5-hydride transfer reaction. e) Disproven sigmatropic mechanism of the reaction in scheme 10c. f) Sigmatropic [1,5]-rearrangement.

The aforementioned effect has since been extended to include numerous other internal electrophiles. The group of Reinhoudt has systematically studied the formation of 6-membered rings using, electron-depleted alkenes attached to an aniline (*Scheme 1.10b*).[115] Also aldehydes,[116,117] *in situ* formed iminium ions,[118] α,β-desaturated aldehydes (*Scheme 1.10c*)[119,120] and α,β-desaturated sulfoximines[121] have been utilized as internal hydride acceptors. This approach has further been exploited such that an enantioselective organocatalytic version has been realized, allowing for the

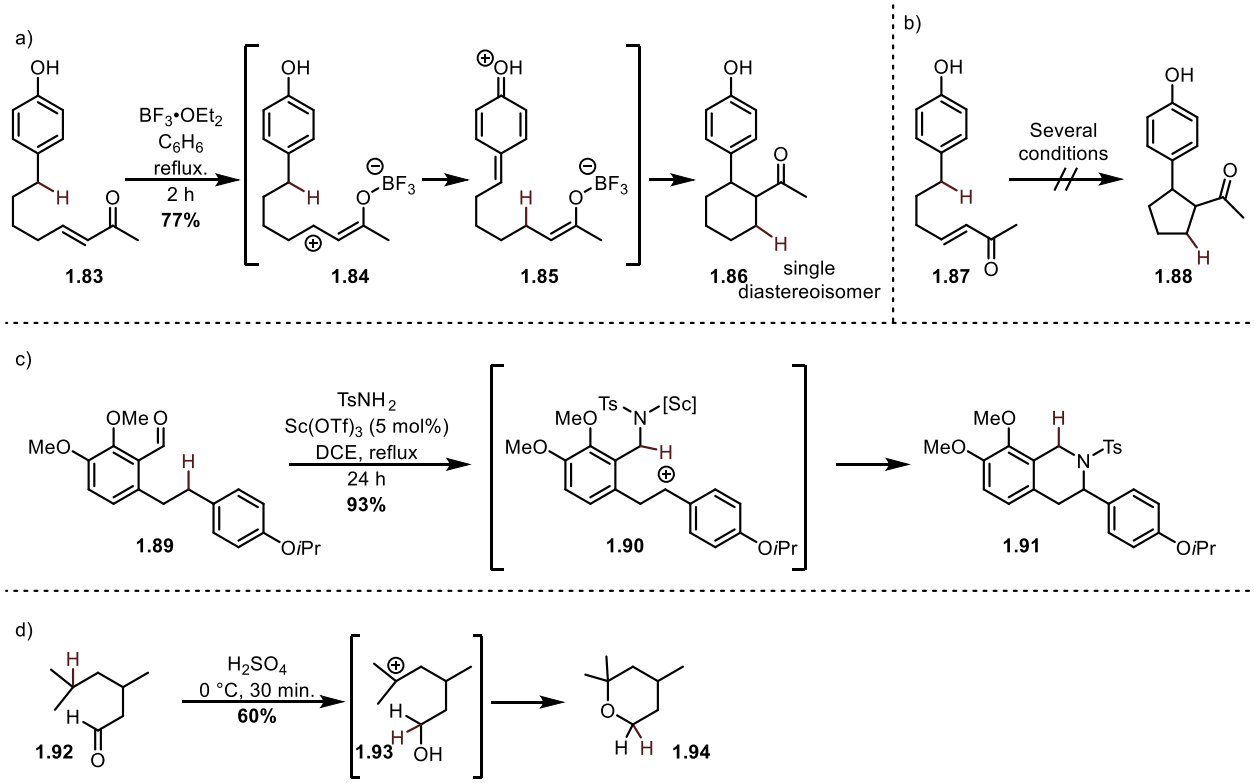
asymmetric synthesis of tetrahydroquinolines (*Scheme 1.10d*),[120] with the reaction involving an intriguing annulation cascade reaction.[122] The reader is directed to a recent review on this topic for further examples.[84]

In many of the cases discussed here, both a sigmatropic and a non-sigmatropic rearrangement can be formulated, however the former has been ruled out by computational studies for at least one of the cases (*Scheme 1.10e*).[123] As mentioned before, sigmatropic [1,5]-hydride shifts in acyclic arrays require typically harsh conditions. Even those systems bearing very hydridic hydrogen atoms and sterically unhindered acceptors such as in acetal **1.80**, require temperatures above 100 °C (*Scheme 1.10f*).[124]

1.1.2.4. *1,5-hydride transfer reaction without nitrogen*

In 1969, Atkinson showed that a nitrogen atom is not necessary to enable a 1,5-hydride transfer.[125] In the reaction examined, the benzylic hydride of an electron-rich arene served as the hydride donor and was able to migrate onto α,β-unsaturated ketone **1.83**, which was activated using a Lewis acid (*Scheme 1.11a*). Given that there is no requirement for nitrogen atoms, these reactions were alternatively categorized as being a "1,5-hydride transfer/shift", "redox neutral C-H functionalization" or an "intramolecular redox process".[84] Several reviews have been published on this area.[83,85] A few years later, a full account of Atkinsons's 1,5-hydride transfer was released,[126] providing compelling evidence for the proposed mechanism following analysis of a deuterium labeling study. They observed that the analogous reaction involving a 1,4-hydride transfer in α,β-unsaturated ketone **1.87** did not take place under several conditions (*Scheme 1.11b*). The use of electron-rich benzylic hydrogen atoms have since been used as hydride-donors by several other groups. An example by Akiyama and coworkers showcases the utility of these transformations in natural product synthesis (*Scheme 1.11c*), whereby the group reported a formal total synthesis of (±)-Tetrahydropalmatine using a 1,5-hydride transfer in the key step.[127] Intramolecular 1,5-hydride transfers from benzylic positions onto iminium ions have also been

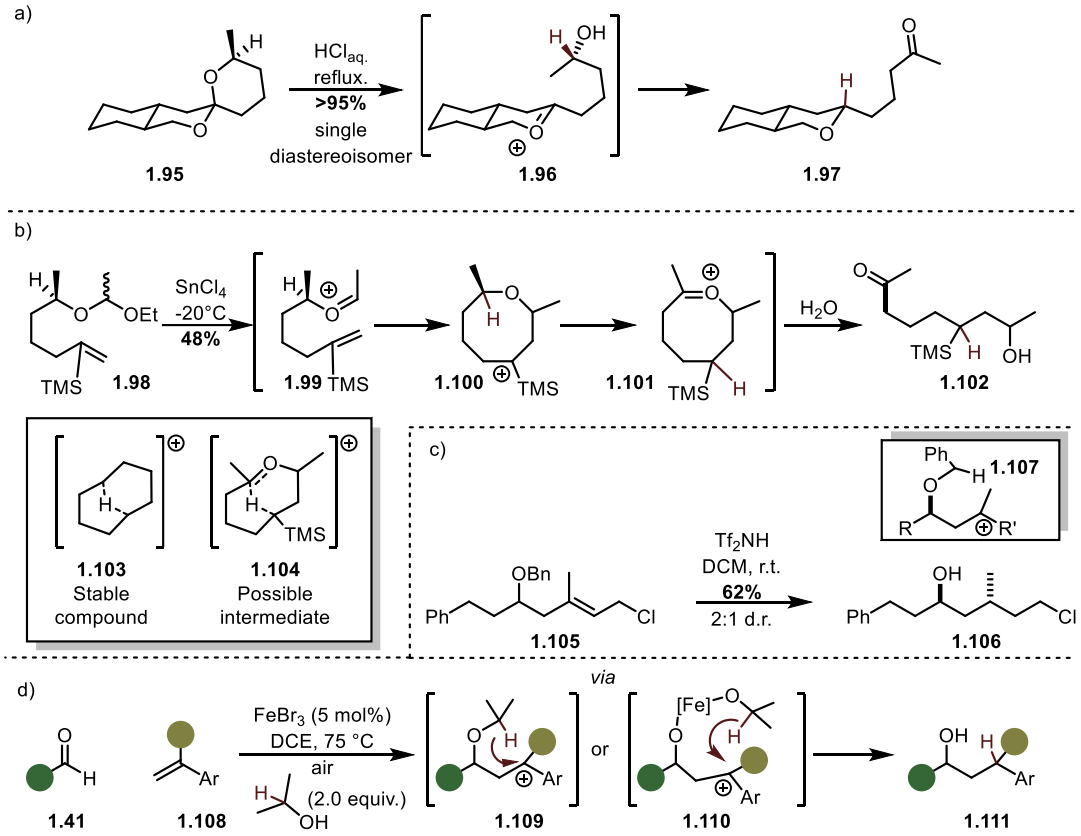
observed in steroidal polycyclic systems.[128] Furthermore, it was found early on that an all-carbon tertiary alkane can be sufficiently hydridic: In 1978, Schulz and Onopchenko synthesized a tetrahydropyran by the intermolecular reduction of aldehyde **1.92** (*Scheme 1.11d*).[129]



Scheme 1.11- a) Atkinson's observed 1,5-hydride transfer reaction. b) Follow up study on non-occurring 1,4-hydride transfers. c) A similar reaction used in the formal total synthesis of Tetrahydropalmatine. d) A tertiary alkane as the internal hydride sources in a 1,5-hydride transfer reaction.

The hydridic potential of α-oxygen C-H bonds has been recognized since the discovery of the Cannizzaro reaction.[73] Also historically important is the reduction of highly stabilized carbocations by alcohols in acidic media, as reported in 1956.[130] Two years later Woodward *et al.* reported the elegant isomerization of Sapogenins with an alcohol as the intramolecular hydride source.[131] An equivalent transformation, albeit on a less complex system, was reported in 1981 when spiroketal **1.95** underwent ring-opening to the corresponding alcohol *via* formation of an oxocarbenium ion intermediate (*Scheme 1.12a*). The α-hydrogen of the alcohol was subsequently transferred to furnish the tetrahydropyranyl

ketone **1.97**.[132] Interestingly, other diastereoisomers gave the same product under the reaction conditions, suggesting that the products are formed through a common intermediate.



Scheme 1.12 – a) A tetrahydropyrane synthesis with an alcohol as the internal hydride donor. b) Overman's observation of an 1,5-hydride transfer reaction within an 8-membered ring. c) Taylor's and Stefan's observation of a 1,5-hydride transfer in a protonated homoallylic ether. d) Ye's reductive addition of styrenes to aldehydes.

Overman's group later discovered that upon treatment of acetal **1.98** with a mild Lewis acid, the keto-alcohol **1.102** was formed (*Scheme 1.12b*).[133] The authors expected a Prins-type addition to form the 8-membered cycle **1.100**. This product then eliminated only partially to the expected vinylsilane. Instead, driven by the stability of the oxocarbenium ion **1.101**, a 1,5-hydride transfer took place. Hydrolysis then furnished the observed keto-alcohol **1.102**. It could be argued that the reaction might not undergo a classical 1,5-hydride transfer but might rather procced *via* an intermediate with a bridged hydrogen atom (**1.104** - *Scheme 1.12b/box*) as a similar stable compound has been previously characterized as discussed in the previous lines (**1.103** see also *Scheme 1.9*).[107] The mechanism has been

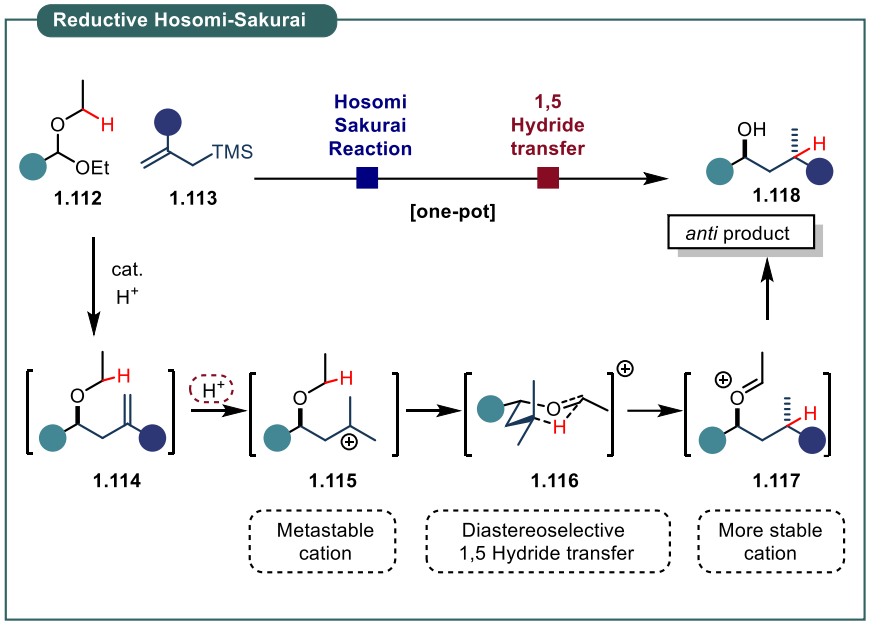
studied by Kataoka *et al.* [134] and was later elegantly exploited by the group of Maulide in a chirality transfer reaction.[135,136]

At the beginning of the 21th century, 1,5-hydride transfer reactions from ethers onto α,β-unsaturated carbonyl compounds were extensively studied by Sames *et al.*[119,137,138] It was later shown that protonated alkenes can also function as hydride-acceptors. As reported by Taylor and Stefan, the homoallylic ether **1.105** underwent a smooth 1,5-hydride transfer upon treatment with a strong Brønsted acid (*Scheme 1.12c*).[139] The basis for this reactivity follows from early mechanistic studies on the reduction of stabilized carbocations by alcohols and ethers.[130] Relatively recently, (after our findings were already published), a set of similar studies were reported.[140,141]

1,5-hydride transfer events have also been observed in the reaction of activated alkenes with *N,N*-dimethylmethyleneiminium salts. In this reaction, the nucleophilic attack of the alkene onto the iminium salt was followed by a 1,5-hydride transfer to the resulting carbocation. After hydrolysis the secondary amine was formed. The approach (which effectively results in a hydroamino methylation of alkenes) was only successful with certain activated alkenes and was accompanied by problematic side reactions.[142] Very recently, this approach has been made more general by Maulide *et al.*[143] Similarly, the iron-catalyzed addition of activated alkenes onto aldehydes with *iso*propanol as the reductant was developed by the group of Ye (*Scheme 1.12d*).[144] This reaction is believed to proceed either *via* an *iso*propyl oxocarbenium **1.109**, with subsequent intramolecular 1,5-hydride transfer, or *via* coordination of the aldehyde, the alkene and *iso*propanol to the iron(III) catalyst (**1.110**). The latter mechanism is somewhat similar to the MPV reaction. Unactivated alkenes gave generally poor yields in this reaction, even when a large excess of the alkene was employed (3 equiv.).

1.2. Objectives

The objective of this study was to investigate whether the acidic conditions of a Hosomi-Sakurai reaction involving an acetal (**1.112**) and an allylsilane (**1.113**), would initiate a subsequent non-sigmatropic 1,5-hydrogen transfer in a one-pot fashion to give the desired alcohol in a diastereoselective manner (*Scheme 1.13*).



Scheme 1.13 – Plan for a reductive Hosomi-Sakurai reaction.

During the first step, which follows the chemistry reported by List *et al.,* the Brønsted acid catalyzed C-C bond formation is expected to take place to give homoallylic ether **1.114** as the product.[68,69,71] The same acid is then hypothetically capable of protonating the double bond of **1.114**. Under these conditions, the resulting carbocation **1.115** is then expected to undergo a non-sigmatropic 1,5-hydrogen transfer in a defined six-membered transition state.[139] Thermodynamically driven by the formation of the more stable oxocarbenium ion **1.117**, the chair-like transition state **1.116** would then lead preferentially to one of the two possible diastereoisomers, due to a significant difference in the Gibbs free energy of activation of the two diastereomeric conformers. More specifically, a transition state with the more sterically congested substituents in the *pseudo*-axial position is expected to be energetically

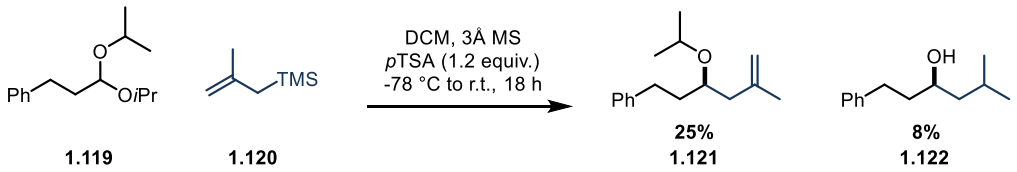
unfavored, due to 1,3 diaxial strain. After hydrolysis of the oxocarbenium ion, during aqueous workup, the alcohol **1.118** would be formed with a diastereomeric excess of the *anti* product.

There are many advantages associated with this new method when compared to conventional approaches: a) While diastereoselectivity for β-substituents of the formed alcohol is commonly observed in the Hosomi-Sakurai reaction (*c.f.* chapter 1.1.1.2.), γ-diastereoselectivity in the formation of γ-branched alcohols has rarely been achieved. Whilst such products can be synthesized by the diastereoselective hydrogenation of an homoallylic alcohol, these approaches are not general.[145,146] b) The reaction conditions are relatively mild, especially when compared to organometallic reagents, which are commonly used to form similar products. c) A classical Hosomi-Sakurai reaction with a subsequent reduction of the double bond moiety by *e.g.* palladium-catalyzed hydrogenation is incompatible with many other functional groups, including double bonds, triple bonds, benzyl-protected ethers or CBz-protected amines. d) The approach presented herein was expected to be more general than the method developed by the group of Ye[144] (*c.f. Scheme 1.12d*), given the enhanced nucleophilicity of allylsilanes compared to simple alkenes. Indeed, and as discussed in the introduction, allylsilanes are as nucleophilic as styrenes and are thus expected to react with similar ease.

1.3. Results and Discussion

1.3.1. Preliminary results (Proof of principle)

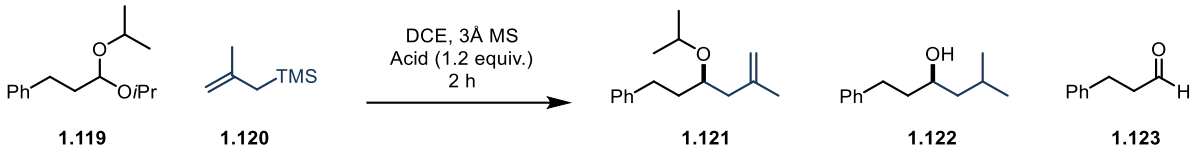
Initially, the di*iso*propyl acetal **1.119** and the allylsilane **1.120** were dissolved in DCM with a superstoichiometric amount of dry *p*-toluenesulfonic acid (*p*TSA). The reaction showed full conversion of the starting material but was rather messy. The main product was the homoallylic ether **1.121**, as expected from a classical Hosomi-Sakurai reaction. Interestingly, we were also able to isolate the desired alcohol **1.122**, albeit in a poor yield (8%), which was most likely formed by the postulated 1,5-hydride transfer of the homoallylic ether intermediate.



Scheme 1.14 – Initial experiment on the reductive Hosomi-Sakurai reaction.

Encouraged by this preliminary result, we began looking towards the optimization of this process in order to obtain the alcohol as the main product. During the first screening (*Table 1.1*) we explored different Brønsted acids and we observed that trifluoroacetic acid (pK_a(TFA)= 0.23 in water[147]) was unable to promote the 1,5-hydride transfer event. Increasing the temperature to 50 °C did not furnish the alcohol **1.122** and with the homoallylic ether being the main product. Trifluoromethansulfonic acid (pK_a(TfOH) = -12 in water[148]) on the other hand, seemed to be too reactive: the reaction was unselective and many unidentified products were obtained. Analysis of this complex mixture did however reveal that there was none of the homoallylic alcohol **1.121** present amongst the inseparable products. Although the Brønsted acid induced 1,5-hydride transfer from an homoallylic ether was reported to be compatible with TfOH,[139] it has been shown that allylsilanes protodesilylate readily at room temperature in the presence of this strong acid.[149,150] This might be one of the reasons for the uncontrolled reaction. Returning to *p*TSA, we

found that increasing the temperature enabled us to isolate the desired alcohol in a slightly higher yield compared to our first attempt.



1.119 **1.120** **1.121** **1.122** **1.123**

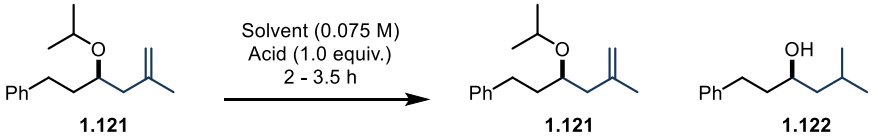
Entry	Acid	Temperature	Comment
1	TFA	0 °C to 50 °C	No **1.122**. Main products: **1.121** and **1.123**
2	TfOH	0 °C to r.t.	Messy reaction. No **1.121** observed
3	*p*TSA	0 °C to 50 °C	**14% of 1.122 isolated**. Aldehyde and ether not observed

Table 1.1 – Screening of Brønsted acids. Observation based on the ^{1}H NMR analysis of the crude mixtures.

1.3.2. Optimization of the 1,5-Hydride-transfer

At this point we considered independently optimizing the 1,5-hydride transfer step of the isolated homoallylic ether by again using various Brønsted acids. The reactivity of 2,4-dinitrobenzenesulfonic acid (**DNBA**), benzene disulfonimide (**BDSI**) and *p*TSA were directly compared in two different solvents (*Table 1.2*). All acids were dried azeotropically with toluene prior to use (see supporting information). A low reaction concentration (0.075 M) used in order to prevent unwanted intermolecular side reactions of the formed carbocation intermediate. Overall, DNBA lead to a higher yield of the desired product in all cases. Indeed, it was the only acid to give full conversion of the homoallylic ether at room temperature. In the other cases, starting material was still present after 3 h and the reaction had to be heated to 50 °C. However, the starting material was still the major compound in the mixture when BDSI was used. At higher temperatures, *p*TSA was almost as efficient as DNBA, but nevertheless traces of starting material was still observable by ^{1}H NMR analysis of the crude reaction mixture. Aside from the improved reaction profile, another advantage of DNBA is that it is less hygroscopic than *p*TSA and can be stored for months under argon, without deterioration of its quality.

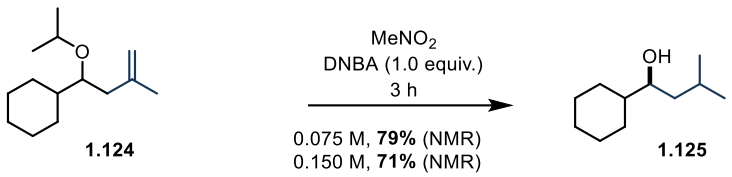
The efficiency of the process was improved by using a solvent with a higher relative permittivity (MeCN instead of DCM). Thereafter, some other polar solvents were investigated (*Table 1.2*). Much to our surprise, THF and DMF gave only trace amounts of the alcohol. Methanol, lead to no product formation at all. Nitromethane ($MeNO_2$) on the other hand was by far the most efficient solvent for the 1,5-hydride transfer reaction. This might be due to its high relative permeability in combination with its low nucleophilicity.



Entry	Acid	Solvent	Temperature	Time	Conversion	Yield (NMR) **1.121**	Yield (NMR) **1.122**
1	DNBA	DCE	r.t. to 50 °C	3.5 h	>95%	<5%	25%
2	*p*TSA	DCE	r.t. to 50 °C	3.5 h	>95%	<5%	21%
3	BDSI	DCE	r.t. to 50 °C	3.5 h	68%	32%	14%
4	DNBA	MeCN	r.t.	3 h	>95%	0%	40%
5	*p*TSA	MeCN	r.t. to 50 °C	3 h	>95%	<5%	34%
6	BDSI	MeCN	r.t. to 50 °C	3 h	65%	35%	26%
7	DNBA	DMF	r.t.	2 h	38%	62%	<5%
8	DNBA	THF	r.t.	2 h	21%	79%	<5%
9	DNBA	MeOH	r.t.	2 h	90%	90%	0%
10	DNBA	$MeNO_2$	r.t.	2 h	>95%	0%	79%

Table 1.2 – Screening of Brønsted acids for the 1,5-hydride transfer step in different solvents.

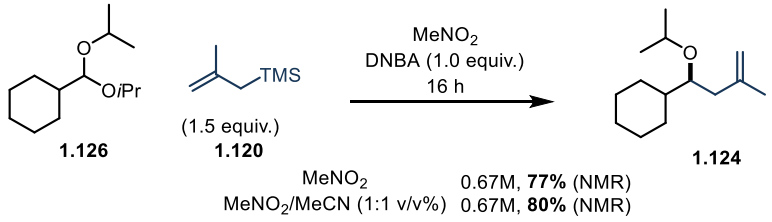
Afterwards, we confirmed the suspected effect of the concentration on the 1,5-hydride-transfer (*Scheme 1.15*). The NMR yield was indeed lower when the concentration was doubled. This result was in good agreement with experiments conducted by one of our Bachelor students (Mitar Radić).



Scheme 1.15 – Effects of the concentration on the 1,5-hydride transfer reaction.

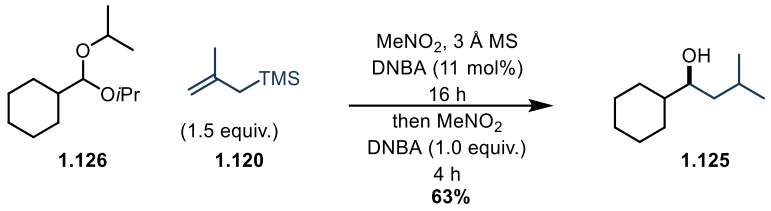
1.3.3. Combination of the two reaction steps

Since nitromethane enabled a smooth 1,5-hydride transfer, we then investigated the solvent in the Brønsted acid catalyzed Hosomi-Sakurai reaction. To our delight, the reaction proceeded smoothly in nitromethane or in a $MeNO_2$/MeCN mixture (*Scheme 1.16*). We found that high concentrations were beneficial for the C-C bond formation event resulting in higher yields. Moreover, relatively long reaction times were required for complete conversion. Both of these modifications (high concentration and long reaction times) are in strong contrast to the optimal conditions for conversion of the homoallylic ether to the alcohol *via* 1,5-hydride transfer.



Scheme 1.16 – Nitromethane as the solvent for the Brønsted acid catalyzed Hosomi-Sakurai reaction.

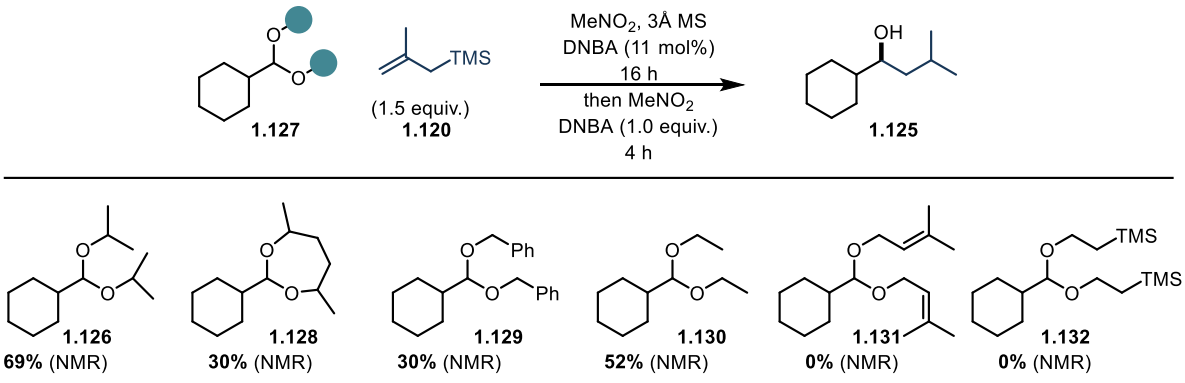
Due to these strongly opposing conditions, we concluded that the one-pot procedure might be most successful by altering the setup during the reaction itself. In practice, this meant the first step needed to be carried out at high concentration with substoichiometric amounts of the acid, and with longer reaction times, followed by diluted conditions, superstoichiometric amounts of the acid, and shorter reaction times with no change in solvent. Upon making these adjustment, the reaction proceeded smoothly to afford the desired product in over 60% yield (*Scheme 1.17*). 1.5 Equivalents of the allylsilane seemed to be optimal: the reaction did not improve with 2.0 equivalents and the yield considerably deteriorated when less than 1.5 equivalents were used. Pleasingly, the reaction profile for this one-pot transformation is typically very clean. Iindeed we were never able to identify any side products, probably due to insolubility or volatility.



Scheme 1.17 – The first successful one-pot reductive Hosomi-Sakurai reaction.

1.3.4. Acetal screening

Since the acetal moiety was expected to have the most pronounced influence on the 1,5-hydride transfer event, acetals other than *di*isopropyl-acetal were studied next (*Scheme 1.18*). Cyclic acetals were relatively unreactive, with acetal **1.128** which was used as a mixture of diastereoisomers, giving the best results with only 30% of the desired product by ^{1}H NMR analysis of the crude reaction mixture. An acetal derived from an electron-rich allylic alcohol (**1.131**), did not lead to any formation of the desired product. The dibenzyl-acetal **1.129** was surprisingly not very efficient in promoting the one-pot reaction. Interestingly, the diethyl acetal **1.130** was found to give higher yields than most of the other acetals, highlighting that the stability of the corresponding oxocarbenium ion is not necessarily the most decisive element of a 1,5-hydride transfer reaction.[151] Conclusively, the di*iso*propyl-acetal **1.126** remained the acetal of choice as it displayed the highest yield for the desired transformation.



Scheme 1.18 – First acetal screening for the reductive Hosomi-Sakurai reaction.

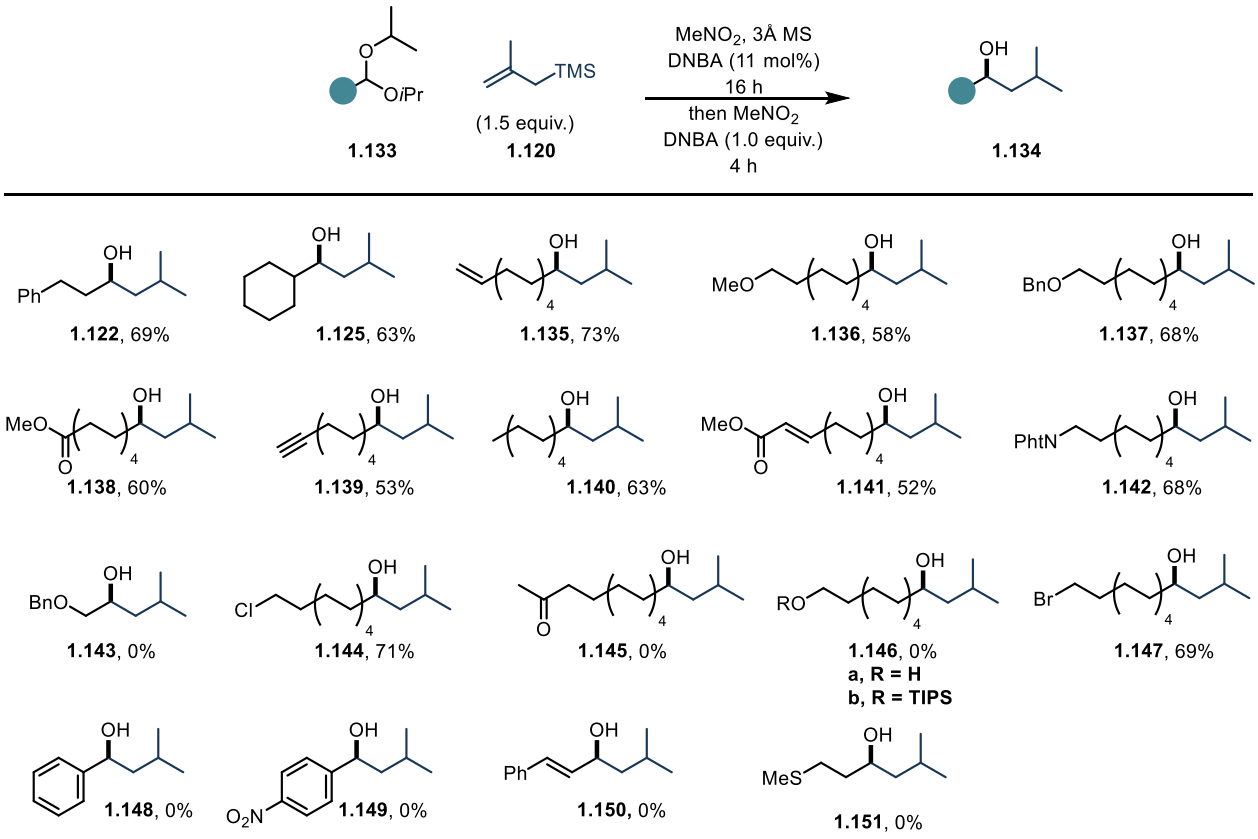
1.3.5. Reproducibility

During the optimization of the reaction conditions, we encountered some reproducibility issues but were successfully able to identify their cause. The results are highly reproducible when two conditions are ensured: 1) the acid (**DNBA**) must be dried azeotropically using toluene under reduced pressure (70 — 100 mbar). Although azeotropes are a function of the pressure and can sometimes disappear by its alternation, the composition of the azeotrope can be expected to be in the range of 47:53 mol/mol% under these conditions.[152] 2) The solid acid needs to be finely grinded, since its solubility seems to be relatively low in $MeNO_2$. A detailed procedure for the drying of DNBA is provided in the supporting information. Using azeotropic drying with toluene at ambient pressure, with a Dean-Stark apparatus, leads to melting of the insoluble compound, which after cooling leads to a black dense block of partially decomposed material. With this material, the results are typically not reproducible. Furthermore, extensive heating of a few grams (5-10 g) of the neat compound under vacuum caused a violent explosion. Indicative of low quality DNBA is the hydrolysis of the acetal to the unreactive aldehyde under the reaction conditions of the reductive Hosomi-Sakurai protocol, which is not observed when high quality DNBA is used.

1.3.6. Acetal scope

With the optimized conditions in hand, we planned to investigate the scope of several di*iso*propylacetals. In this regard, we were especially interested in the tolerance of functional groups and the variation of electronic properties of the acetals. The scope is depicted in *Scheme 1.19*. Additional unsaturation, such as alkene (**1.135**) or alkyne (**1.139**) on the substrate molecule did not interfere with the internal redox-process. Moreover, the benzyl-protected alcohol (**1.137**) was well tolerated, as well as functional groups, which are perceived as incompatible with LiR or Grignard additions, such as a bromide (**1.147**), a chloride (**1.144**) or ester functionality (**1.138**). A highly reactive α,β—unsaturated ester (**1.141**) was well tolerated under the reaction conditions. The reaction was also carried out on a 6 mmol scale

(**1.125**), with only a little corrosion of the yield (57% compared to 65 % on small scale) when the reaction vessel was neither flame dried nor kept under inert gas. Despite all of these encouraging results, a few functional groups were unable to withstand the strongly acidic conditions. Free or silyl-protected alcohols (**1.146**), ketones (**1.145**) and sulfides (**1.151**) did not give any of the desired products. Functional groups which are generally tolerated might prevent the reaction if they are in close proximity to the reaction center (**1.143**). Moreover, unstable aromatic acetals (**1.148**/**1.150**) did not lead to formation of the alcohol. Instead, additional double bonds were observed by ^{1}H NMR spectra, suggesting that elimination to the styrene was occuring. This challenge was not circumvented by using strongly electron-depleted aromatic rings (**1.149**).



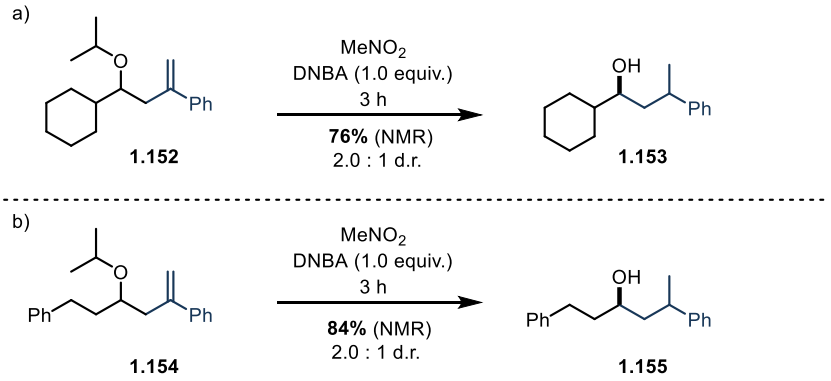
Scheme 1.19 – Acetal scope for the reductive Hosomi-Sakurai reaction. See supporting information for more details.

Despite these unexpected drawbacks, our expectations regarding chemoselectivity were met and, to some extent, exceeded. Moreover, we could prove that purely aliphatic groups could be attached to the carbonyl derivative in relatively high yields, which was not possible by the method of Ye *et al.*[144]

1.3.7. Diastereoselectivity

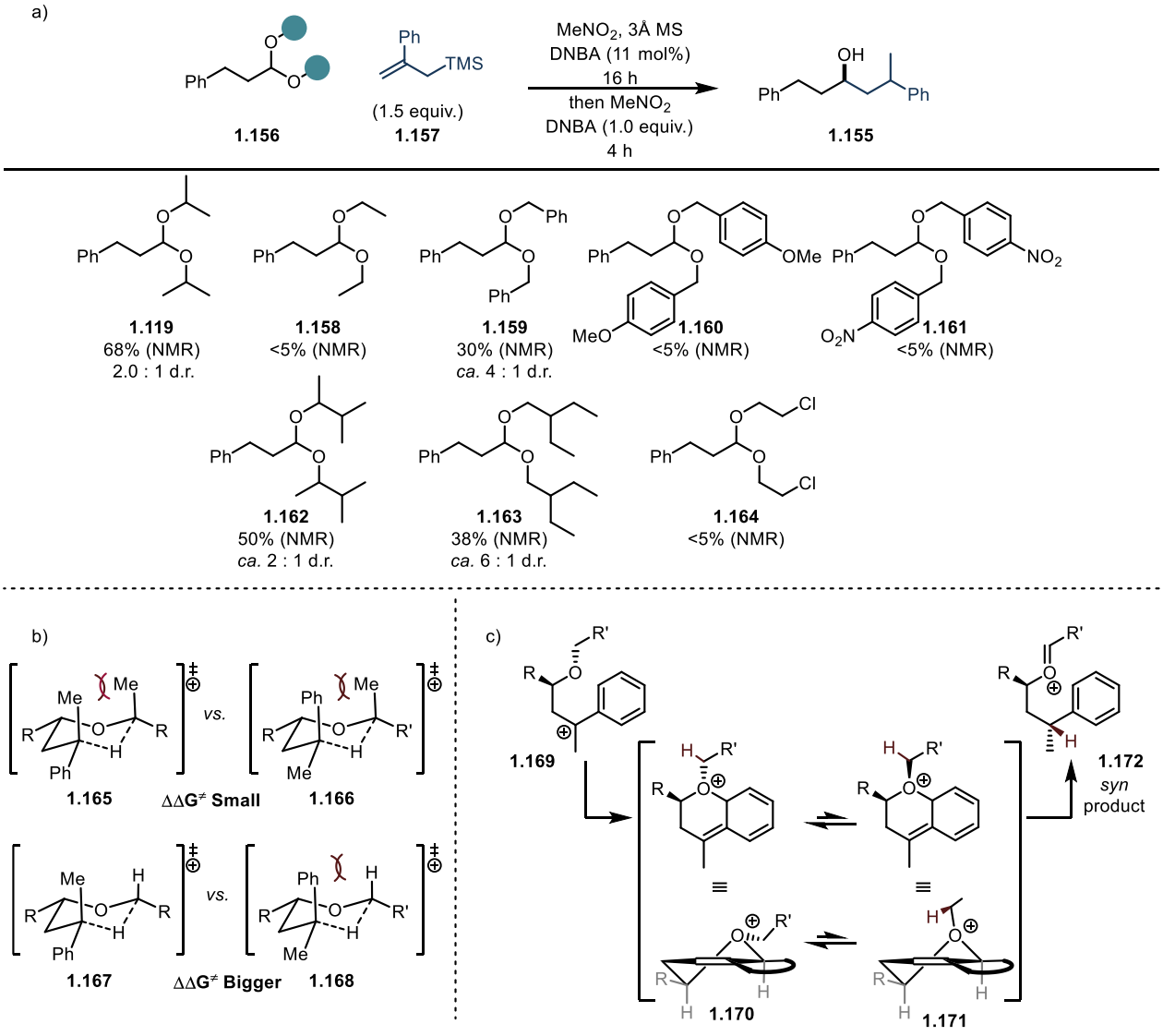
1.3.7.1. *Influence of the acetal*

One of our hypotheses was that the reaction would be diastereoselective due to the cyclic 6-membered transition state, although in some reported cases the diastereoinduction for similar processes seemed to be low.[139] In one of our first trials where a phenyl substituted homoallylic ether was investigated, a rather low diastereoselectivty for the 1,5-hydride transfer step was observed (*Scheme 1.20*). The selectivity is comparable to those observed by Ye *et al.* for similar substrates, suggesting that a similar mechanism might be operative.[144] Unfortunately, diastereoselectivity could not be enhanced by external parameters such as solvents, temperature or the acid. Toluene, MeCN, Et_2O, DMF, DCM and 2-nitropropane were investigated as solvents or as co-solvents with $MeNO_2$, but there was little to no altering of the diastereoisomeric ratio. Moreover, a temperature range from -25 °C to 50 °C was explored and although some interesting insights about the reaction rate could be gained (the acid-promoted 1,5-hydride transfer is rather slow at lower temperatures), the diastereoisomeric ratio remained unaffected.



Scheme 1.20 – First investigation on the diastereoselective 1,5-hydride transfer.

The only loophole we could identify for this challenge was the steric and electronic modulation of the acetal moiety (*Scheme 1.21*). Indeed, we quickly identified that the nature of the acetal moiety was of considerable importance. Interestingly, acetals derived from secondary alcohols lead to a relatively low diastereoselectivity of d.r. = 2 : 1 (**1.119**, **1.162**), while acetals derived from primary alcohols (**1.159**, **1.163**) were found to be much more selective in the reductive Hosomi-Sakurai reaction.



Scheme 1.21 – a) Second acetal screening in order to enhance diastereoselectivity. b) Explanation for the relatively low stereoselectivity with acetals derived from secondary alcohols. c) Olah's model for a stepwise hydride transfer on benzylic cations.

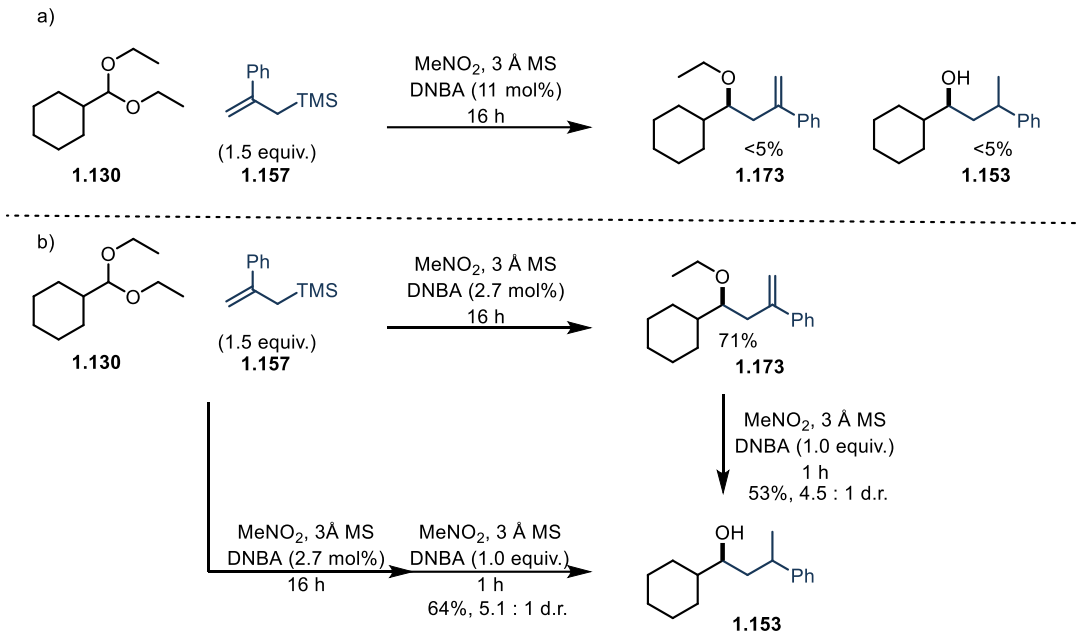
We therefore concluded that the substitution pattern at the α-position of the acetal is greatlyinfluencing the selectivity (*Scheme 1.21b*). If one considers two pairs of the diastereoisomeric 6-

membered transition states for the 1,5-hydride transfer event (**1.165** *vs*. **1.166** and **1.167** *vs*. **1.168**), it is evident that the 1,3-diaxial repulsion in **1.165** and **1.166** are similarly unfavorable. As a consequence, the difference in Gibbs free energy of activation ($\Delta\Delta G^{\ddagger}$) for the two transition state is small and thus stereoselectivity is low. Conversely, the 1,3-diaxial repulsion in the isomer **1.167** is less severe than in its diastereoisomeric cognate **1.168**. Thus, the two transition states **1.167** and **1.168** are energetically less similar, which leads to a more pronounced diastereoselectivity.

In benzyl-cationic systems the mechanism suggested by Olah's group (*Scheme 1.21c*) with an active participation of the aromatic moiety should be also taken into account (chapter 1.1.2.2.).[96] Interestingly, this mechanism would favor the *syn* product and thus could be accountable for the appearance of the undesired isomer. The mechanism seems however unlikely because the cyclohexene intermediate would need to be in the unfavorable conformer as shown in **1.171** with the aliphatic moiety in the axial position and the lone pair in the equatorial position. However, the possibility for such a route should be kept in mind for following investigations.

As the yields were not deemed satisfactory, we investigated the stepwise reaction again. It was especially surprising that the diethyl acetal gave a good yield when it was reacted with a purely aliphatic allylsilane (*cf. Scheme 1.18* – ***1.130***), but only traces were obtained when the aromatic allylsilane **1.157** was used instead (*Scheme 1.21*). We recognized that under the typical conditions, the Hosomi-Sakurai step was rather messy and only traces of the homoallylic ether were detected by ^{1}H NMR (*Scheme 1.22a*). The relatively high nucleophilicity/basicity of the styrene-derived allylsilane was probably accountable for side reactions in the acidic reaction medium. Indeed, when the catalyst loading was reduced from 11 mol% to 2.7 mol% the homoallylic ether was obtained in a much cleaner fashion. The isolated ether was then submitted to an equimolar suspension of DNBA in $MeNO_2$, and the desired product was observed in a fair yield of 53% and a diastereoisomeric ratio of 4.5 : 1. These conditions were then quickly applied to the one-pot procedure and gratifyingly we isolated the alcohol in more than 60% yield with a d.r. > 5:1.

The stereoselectivities are in good accordance with those reported by Chiba *et al.* for similar systems, where only the acid-promoted hydride transfer was investigated.[140,141]

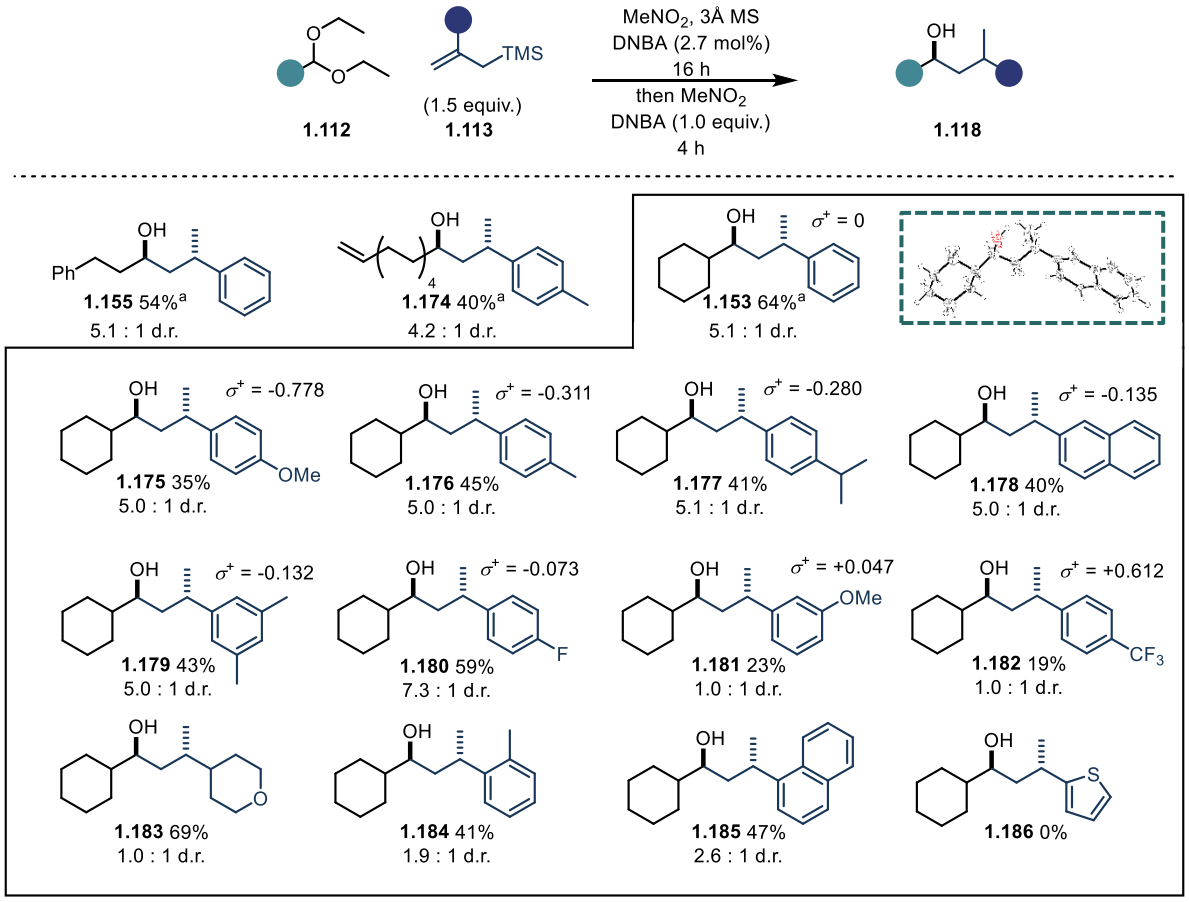


Scheme 1.22 – a) Unsuccessful reaction of a diethylacetal with an electron-rich allylsilane. b) Stepwise investigation of electron-rich allylsilanes.

1.3.7.2. *Allylsilane scope*

The optimized conditions for the stereoselective variant of the reductive Hosomi-Sakurai reaction were successfully applied to a large variety of allylsilanes (*Scheme 1.23*). Interestingly, stereoselectivities up to d.r. >7:1 could be reached using these conditions. The relative configuration (*anti*) was confirmed by an X-ray diffraction-study of compound **1.178**. We observed an interestring trend concerning the stereoselectivity: when electron-rich arenes were used, the stereoselectivity obtained was generally high (>5:1 d.r). Conversely, when an electron-poor or a purely aliphatic allylsilane was submitted to the same reaction conditions, both diastereoisomers were observed in (nearly) equimolar amounts. This is further exemplified by the modified Hammett substitution constants for benzylic cations (σ^+),[153] which are written above the structures of each arene. These numbers are didactically interesting, because it uncovers a few common misconceptions: the *m*-OMe group is electron-withdrawing ($\sigma^+ = +0.047$), while

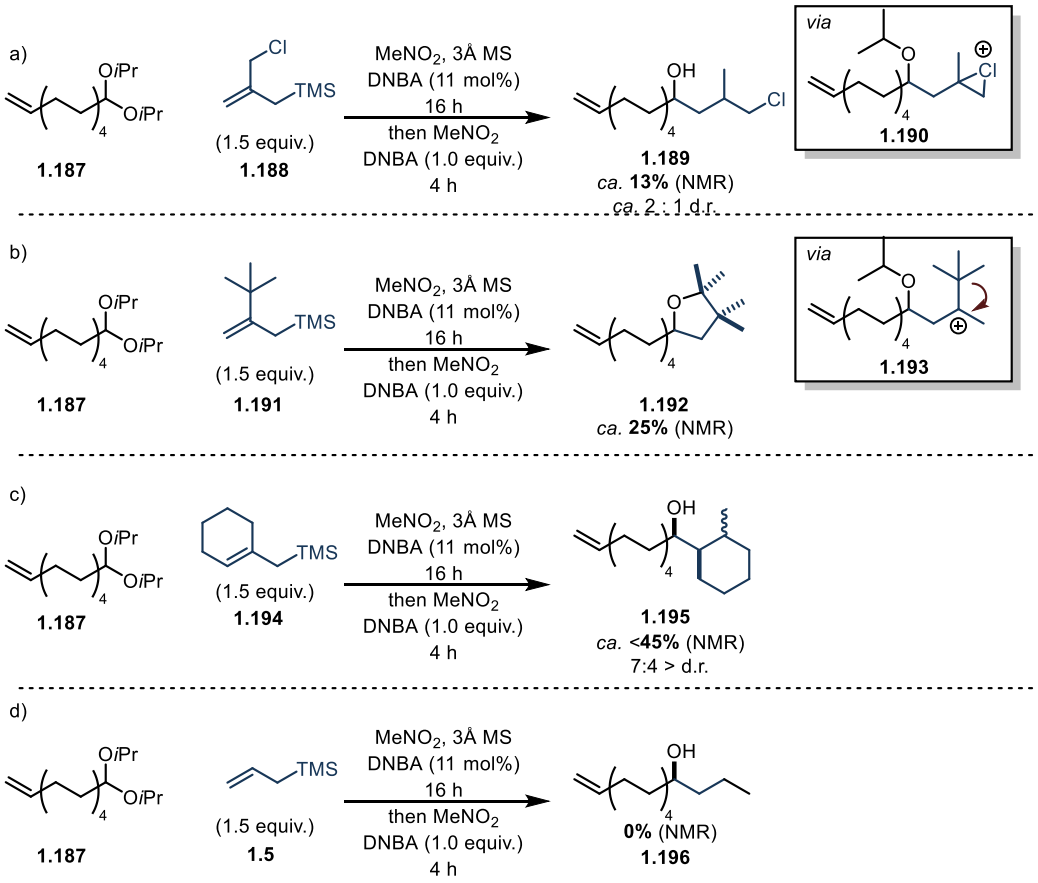
the *p*-F substituent is electron-donating (σ^+ = -0.073). It seems that substituents, which are less electron-donating than a phenyl ring will give an unselective transformation under these conditions. This issue will be further discussed in the mechanistic section (chapter 1.3.8.). An *ortho*-substituents also showed lower diastereoselectivity: this is most likely due to sterical reasons where congestion allows multiple conformers of the 6-membered transition state to be energetically similar. This might be analogous to the cases where acetals derived from secondary alcohols were used (chapter 1.3.7.1.).



Scheme 1.23 – Allylsilane scope. See supporting information for more details.

The absence of stereoselectivity with purely aliphatic allylsilanes was found not to be in accordance with the results by Taylor and Stefan.[139] There is, however, a plausible explanation for the observed selectivity in their cases. The homoallylic alkene which they investigated also had a terminal chloride in the β-position to the formed carbocation. This chloride might participate actively by stabilizing

the carbocation through the formation of a chloronium ion. The mechanism of the hydride transfer could thus be changed significantly by this interaction. Indeed, when allylsilane **1.188** was used in our reaction, a complex crude reaction mixture with only 13% of the desired product were observed by ^{1}H NMR spectrometry. The diastereoselectivity for this reaction was measured to be *ca.* 2:1 d.r. and was found to be in good agreement with the literature. A likewise complex reaction was observed, when the *t*butyl-substituted allylsilane **1.191** was used as a reaction partner. We were indeed not able to isolate a clean alcohol from this mixture. One of the products, which was isolated in sufficient purity was deduced to be the sterically congested tetrahydrofuran **1.192**, according to ^{1}H NMR analysis, suggesting that a [1,2] methyl shift (Wagner-Meerwein rearrangement) took place.

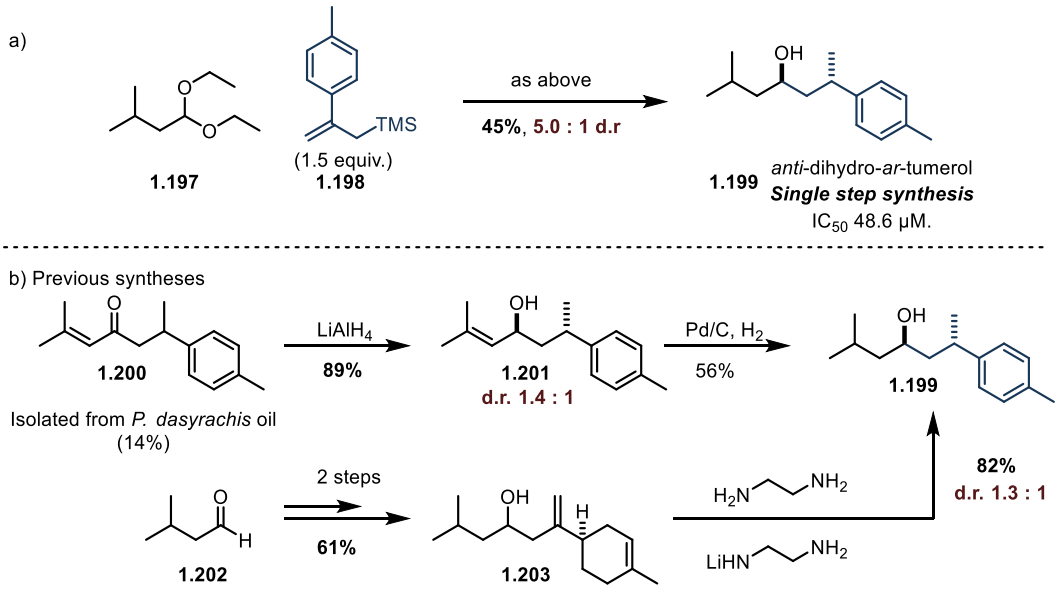


Scheme 1.24 – a) Moderate diastereoselectivity observed while using a chloro-allylsilane. b) Side product formation involving a [1,2] methyl shift. c) Investigation of a cyclic trisubstituted allylsilane. d) Investigation of an unsubstituted allylsilane.

The cyclic allylsilane **1.194** afforded the desired product in less than 45% NMR yield. Isolation of the pure product failed, but we observed two different diastereoisomers. Since the Hosomi-Sakurai step is expected to yield the *syn* product with high selectivity, it is likely that these two isomers are epimeric at the tertiary carbon atom where the hydride transfer occurred.

The unsubstituted allylsilane (**1.5**) lead predominantly to the formation of the Hosomi-Sakurai product (homoallylic ether). Unfortunately, the acid induced 1,5-hydride transfer was not observed. The acid was likely too weak to protonate the *vicinal* disubstituted double bond.

Subsequently, the reductive Hosomi-Sakurai protocol was applied in the one-step synthesis of a known acetylcholinesterase inhibitor (*Scheme 1.25*).[154] The product was isolated with an observed 5.0 : 1 d.r. Although the yield is modest, the conciseness of our approach and the relatively high diastereoselectivity has not been matched by prior approaches (*Scheme 1.25b*).[154,155]

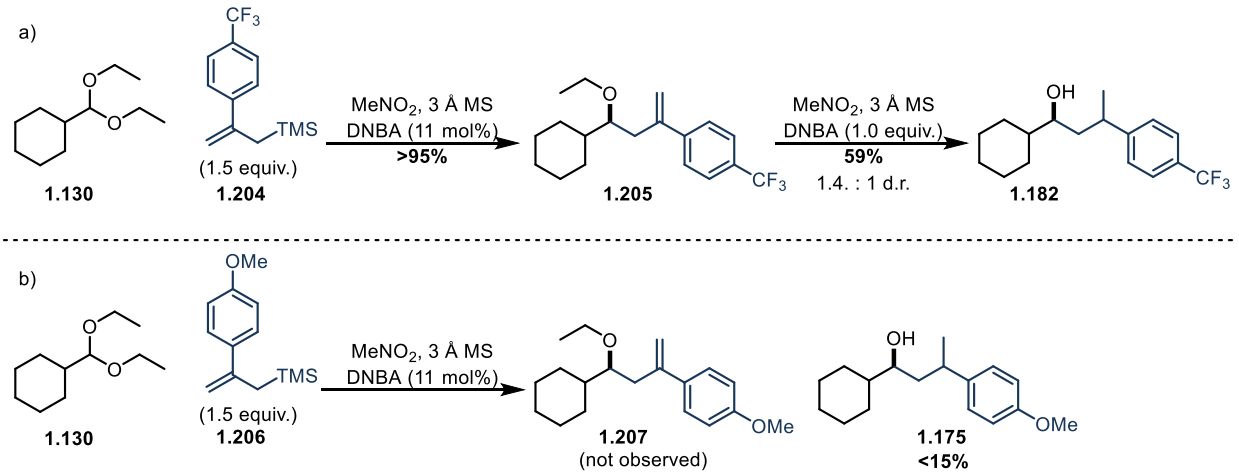


Scheme 1.25 – One-step synthesis of an acetylcholinesterase inhibitor.

1.3.8. Mechanistic investigation

When the stepwise reaction of the aromatic allylsilanes was studied (on one electron-rich and one electron-poor substrates) we observed the following: The electron-poor allylsilane **1.204**, which

afforded a poor yield in the one-pot protocol, gave a quantitative yield for the Hosomi-Sakurai step under the usual conditions. The corresponding isolated homoallylic ether was then submitted to the conditions to promote the 1,5-hydride transfer and much to our surprise the product was formed in a fair yield of 59% without significant diastereoselectivity. The electron-rich allylsilane **1.206** on the other hand did not afford any of the desired homoallylic ether under catalytic Hosomi-Sakurai conditions. Instead, the alcohol with the reduced double bond was observed in small amounts. Conclusively, the one-pot reaction is clearly beneficial for some substrates, while for others better results are obtained using a stepwise protocol. This tendency goes in hand with the strong difference in stereoselectivity for electron-poor and electron-rich substituted allylsilanes.



Scheme 1.26 – a) Stepwise investigation of the Hosomi-Sakurai reaction followed by a 1,5-hydride transfer step using an electron-poor allylsilane. b) Using an electron-rich allylsilane.

These two effects can be explained by the operation of two different mechanisms: the carbocationic intermediates formed by protonation of the double bond, can be stabilized to a different extent, depending on substitution pattern. Electron-rich aromatic rings can stabilize such carbocations very effectively. Thus, the latter are expected to be formed quickly and their lifetime is expected to be increased. The enhanced stability results in a (relatively) slow hydride transfer step. Since the hydride transfer is the stereoselectivity-determining step, it is likely that the relative reaction rate of this step might have a dramatic effect on the stereoselective outcome of the reaction. In this case, a Curtin-

Hammett scenario might come into play,[156] in which a relatively fast equilibrium between the two possible conformers of the formed carbocation, leading to either the *syn*- or to the *anti*-product, operates. The conformer leading to the *anti*-product reacts faster in the rate-determining step (the hydride transfer), since less steric congestion is built up during the transition state. Conversely, when electron-withdrawing groups are attached to the arene or the arene is displaced by an aliphatic substituent, the carbocation becomes less stable and the molecule undergoes the 1,5-hydride transfer (relatively) promptly. The highly reactive, weakly stabilized carbocation might not have the possibility of establishing an equilibrium, but rather the two possible conformers reacts fast and indiscriminately. In other words, there is a random distribution of different conformers directly after the protonation of the double bond. According to the principle of least motion,[157] both possible transition states are reached by the conformers, which resemble them more.

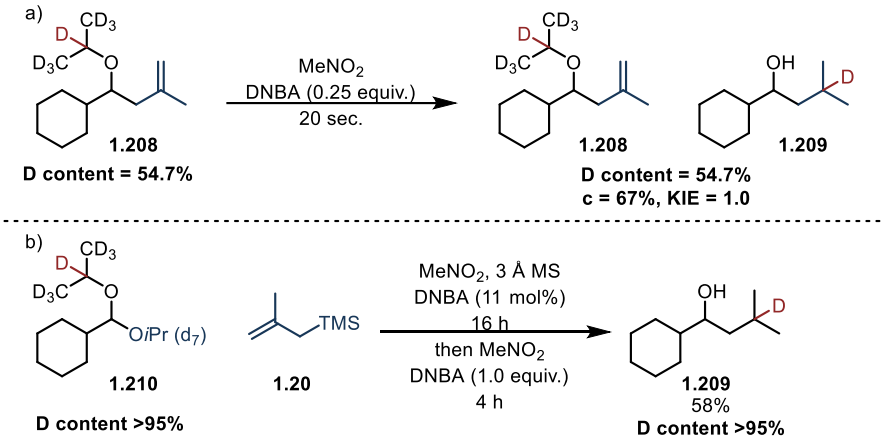
This hypothesis is supported by a kinetic isotope effect experiment. Allylsilanes with purely aliphatic substituents showed virtually no stereoselectivity for the 1,5-hydride transfer. When a mixture of the homoallylic silane **1.208**, with its isotopically labeled analogue was only partly converted *via* a Brønsted acid-promoted 1,5-hydrogen transfer under the usual conditions, the recovered starting material contained the same percentage of both isotopologues as the initial starting material (*Scheme 1.27a*). Conclusively, the kinetic isotope effect (KIE) which is defined as[158]

$$KIE = \frac{k_L}{k_H} \qquad \text{(eq. 1.1)}$$

$k_L = reaction\,rate\ of\ the\ light\ isotopologue$, $k_H = reaction\,rate\ of\ the\ heavy\ \ isotopologue$

is equal to unity. Since deuteride is expected to be transferred slower than hydride (by bond breaking and bond forming), we would expect that the C-D/C-H cleavage enriches the starting material in the heavy isotopologue, if the C-D/C-H cleavage is involved in the rate-determining step. While the observation of a KIE ≠ 1 in this experimental setup does not necessarily indicate that the rate-determining step occurs

during the C-H/C-D cleavage, the absence of an accumulation of one of the heavy isotopologue (KIE = 1 is a clear indicator that the rate-determining step does not coincide with the C-H/C-D transfer.[159]



Scheme 1.27 – a) Kinetic isotope effect study of the acid-promoted 1,5-hydride transfer. b) Deuterium labeling effect of the reductive Hosomi-Sakurai reaction.

There is additional computational support for this assumption. A study on a hydrotriflated alkene was performed in implicit DCM using DFT with dispersion correction (using B3LYP-D3-SMD/6-31+G(d,p) level of theory). The most stable conformer of this molecule **A** was calculated to form the carbocation **B** by departure of the triflate anion (*Figure 1.1*). No transition state for the hydride transfer onto the triflate could be found (S_N2-type). The most stable conformer of the carbocation is slightly more unstable than the starting triflate (+3.2 kcal/mol). Interestingly, there is an even less stable conformer (+6.1 kcal/mol), which is connected almost barrierless to the transition state. Not only does the conformer resemble the transition state by the position of the atoms, but also by the appearance of its frontier orbitals. Overall, the transition state for the 1,5-hydride transfer lies only 3 kcal/mol (Gibbs free energy) above the energetical level of the most stable conformer of the carbocation. This kinetic barrier is in good agreement with the NMR experiments for other systems.[101] The Gibbs free energy of activation is in the same range of energy that is required for the dehydral rotation around the central C-C bond of ethane. The hydrogen transfer reaction is quite exothermic: more than 13 kcal/mol are released when the oxocarbenium ion is formed with respect of the neutral triflate **A**. Interesting is also that the cation **B** has a long C^1-C^2 bond

(1.64 Å), which is due to the overlap of its bonding-orbital with the vacant p-orbital of the cation (hyperconjugation). Although, the substrate, the solvent, and the acid differ from the reactions performed in the lab, this calculation suggests that the hydride transfer to unstabilized carbocations is likely to be very rapid.

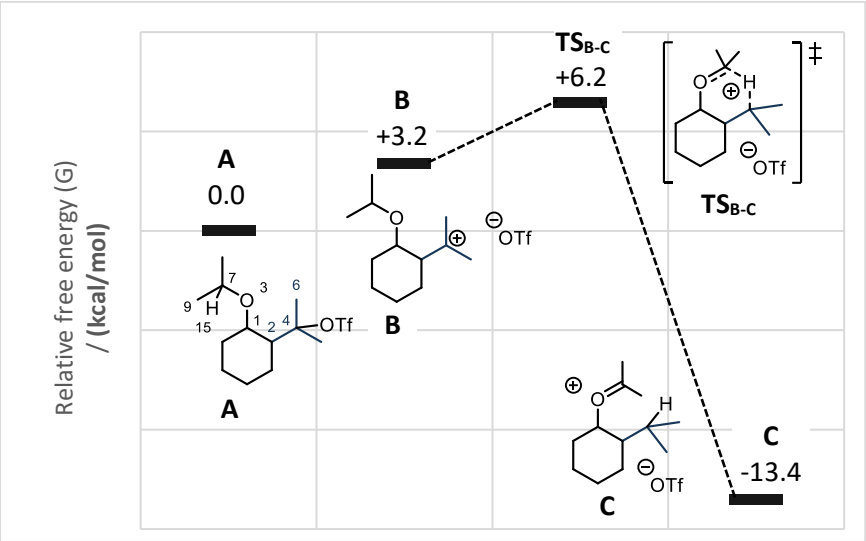
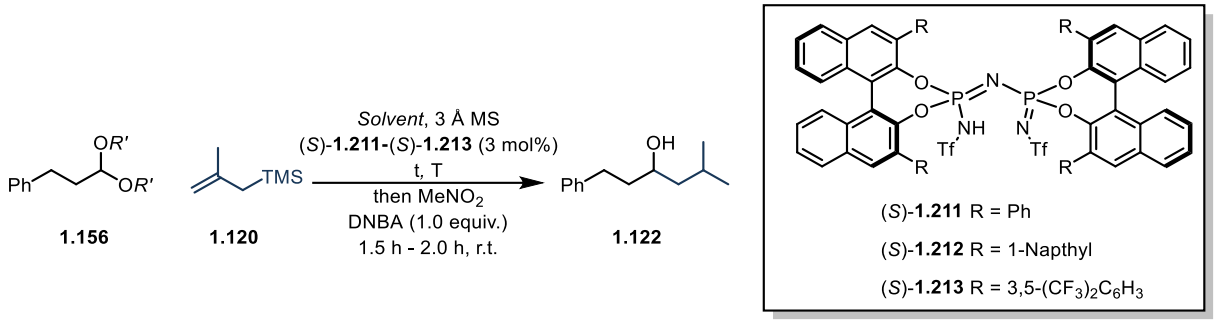


Figure 1.1 – Computational study on a 1,5-hydride transfer from a protonated homoallylic ether.

1.3.9. Enantioselective study

Shortly after our manuscripts on the reductive Hosomi-Sakurai reaction were published[1,2], Prof. List contacted and offered us to investigate an enantioselective version of the reductive Sakurai using his IDPi catalysts.[42] Th List group subsequently sent us a few samples of these very valuable compounds.

In a first attempt, the acetal and the allylsilane were submitted under the usual reaction conditions but using one of the IDPi catalysts. The acetal was completely converted completed to the homoallylic ether within minutes (by TLC analysis). Subsequently, a stoichiometric amount of DNBA was added to promote the hydride transfer step. Both reactions gave a respectable yield of over 60% overall, however the product was unfortunately found to be racemic.

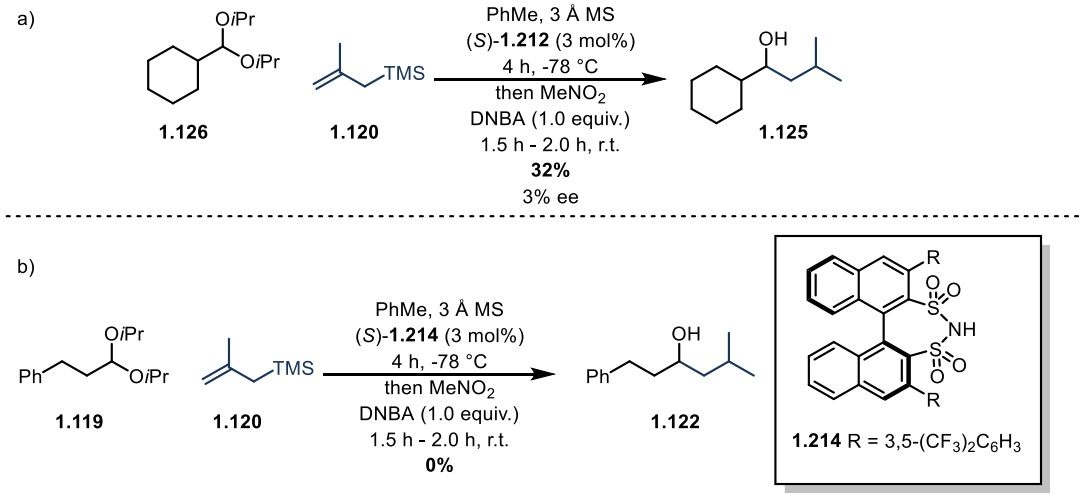


Entry	Catalyst	R'	Solvent	Temperature	Time	Isolated yield	ee
1	(*S*)-**1.212**	*i*Pr	$MeNO_2$	r.t.	14 h	**67%**	**0%**
2	(*S*)-**1.211**	*i*Pr	$MeNO_2$	r.t.	14 h	**63%**	**0%**
3	(*S*)-**1.212**	*i*Pr	DCM	-78 °C	3 h	**73%**	**12%**
4	(*S*)-**1.211**	*i*Pr	DCM	-78 °C	3 h	**61%**	**9%**
5	(*S*)-**1.212**	*i*Pr	Toluene	-78 °C	3 h	**63%**	**33%**
6	(*S*)-**1.211**	*i*Pr	Toluene	-78 °C	3 h	**36%**	**25%**
7	(*S*)-**1.213**	*i*Pr	Toluene	-78 °C	3 h	**44%**	**17%**
8	(*S*)-**1.211**	Et	Toluene	-78 °C	3 h	**31%**	**21%**
9	(*S*)-**1.211**	*i*Pr	Pentane	-78 °C	3 h	**/**	**/**
10	(*S*)-**1.211**	*i*Pr	Pentane : Toluene	-78 °C	3 h	**/**	**/**

Table 1.3 – IDPi catalysts as enantioselective promoters for the reductive Hosomi-Sakurai reaction.

In a second attempt the temperature was lowered substantially and the solvent for the Hosomi-Sakurai step was changed to the relatively apolar and less dissociative solvent DCM. Similar isolated yields were observed for the transformation, although on this occasion we were able to measure a small but significant enantiomeric excess. When the solvent polarity was decreased even more by switching to toluene, an ee of 33% was observed with the bulky 1-napthyl derivative **1.212** as the catalyst. Ultimately, the phenyl and the *bis*(trifluoromethyl)benzene IDPi-derivatives were less stereoselective and less efficient as catalysts. Decreasing the polarity of the reaction medium by using pentane or pentane-toluene mixtures inhibited the reaction completely, most likely because the catalyst was not soluble at the low temperature. The ethyl acetal showed a similar yield but lower enantioselectivity. This is in contrast with observations from the List group, where less bulky acetals showed higher ee's.[71] However, in those cases *N*-Triflylphosphoramides were primarily investigated since the IDPi catalysts were unknown at this time.

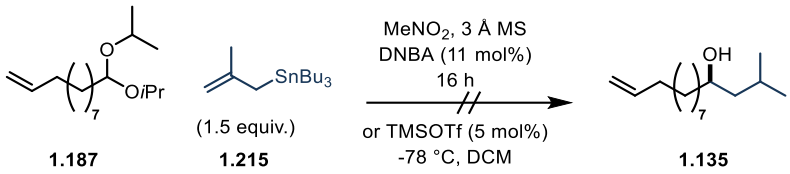
Interestingly, when the steric congestion of the starting material was further increased (**1.126** – *Scheme 1.28a*), the stereoselectivity dropped completely to almost 0% ee. This might be due to the steric similarity of the *iso*propyl group with the cyclohexylmoiety of the acetal. An enantiopure disulfonimide was also investigated as a promoter for the allylation step, however the starting material was fully recovered in this instance. This is in accordance with our previous observation, where a sulfonimide (BDSI) was found to be a poor catalyst for this reaction.



Scheme 1.28 – a) The cyclohexyl acetal as an alternative substrate for the enantioselective reductive Hosomi-Sakurai reaction. b) A chiral disulfonimide as an unactive catalyst for the reductive Hosomi-Sakurai reaction.

1.3.10. Other results

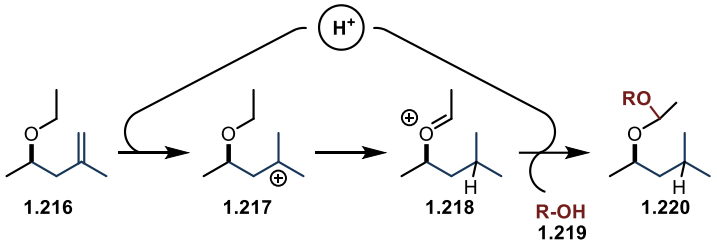
The addition of an analogous allylstannane to the *iso*propylacetal did not take place using Brønsted acid catalysis or by the use of a strong Lewis acid at low temperatures. The latter conditions have previously been used successfully to add tributylallylstannane **1.215** onto a benzylacetal.[160]



Scheme 1.29 – Allylstannanes as alternative allylation partners (not successful).

Theoretically the reductive Hosomi-Sakurai reaction should be operable with substoichiometric amounts of Brønsted acid (*i.e.* fully catalytic system) since the formed oxocarbenium intermediate **1.218** is a

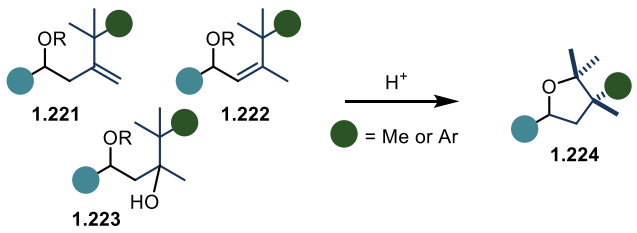
potential source of an acid (*Scheme 1.30*). However, several attempts to exploit the aforementioned cation as a proton-source by adding a protic nucleophile did not lead to the desired catalytic cycle. Instead the homoyallylic ether was always observed. Protic nucleophiles that were investigated included water, MeOH, *i*PrOH and EtOH but they were not successful in the one-pot protocol. Chiba *et al.* used trifluoroethanol as a solvent to regain the proton under equivalent conditions.[140] However, the compatibility of this solvent with the Hosomi-Sakurai step is expected to be problematic.



Scheme 1.30 – Fully catalytic version of the reductive Hosomi-Sakurai reaction.

1.4. Conclusions and perspective

In conclusion we were able to demonstrate that a one-pot protocol for a reductive Hosomi-Sakurai reaction in combination with an acid induced 1,5-hydride transfer brings not only many synthetic advantages, but also reveals intriguing mechanistic insights about the chemistry involved. Good diastereoselectivity was observed for a variety of different substrates. Trisubstituted allylsilanes were only marginally investigated. A follow-up study is necessary to determine whether these allylsilanes are suitable, particularly given that the diastereoselective 1,5-hydride transfer has been observed to be more diastereoselective in the corresponding homoallylic ethers.[140] The one-pot protocol developed is compatible with enantioselective organocatalysis, although only moderate enantioselectivities have been observed in our preliminary investigations. This might be further investigated by screening of other catalysts and/or conditions. Due to the carbocationic nature of the mechanism, interesting side products associated with this chemistry have been identified, for example the isolation of the sterically congested tetrahydrofuran (*Scheme 1.24b*). This reaction might be generalized in the near future to provide an alternative strategy for the synthesis of this important structural motif.[161] Moreover, the chemistry might be combined with other carbocationic rearrangements, such as a 1,2-phenyl-shift.[162]



Scheme 1.31 – Perspective for the observed sterically congested tetrahydrofuran.

1.5. Supporting information

1.5.1. General

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. 2,4-Dinitrobenzenesulfonic acid was purified as described below. All reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum 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}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300K. Chemical shifts were 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 (^{13}C-NMR). Coupling constants are quoted in Hz (J). 1H-NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br).

1.5.2. Purification of 2,4-dinitrobenzenesulfonic acid (DNBA)

DNBA was grinded thoroughly with a pestle and suspended in dry Toluene (6 mL / g DNBA – typically 5 - 10 g). The solvent was evaporated under reduced pressure (60-80 mbar, 40 °C) afterwards the

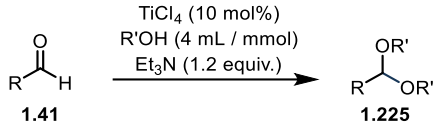
aperture was filled with argon. DNBA was quickly scratched from the round bottom flask and further dried at *ca*. $1.0*10^{-2}$ mbar at room temperature for 1 hour. This procedure was repeated three times to get sufficiently dry DNBA. Dry DNBA is a fine beige powder, which should be stored under argon at room temperature. Typically DNBA get friable when water it absorbed, which can take months if stored properly. Dry DNBA seems to be less hygroscopic then dry *p*-Toluenesulfonic acid (*p*TSA), which is why it can be handled with ease once it is dried.

1.5.3. Starting material synthesis

1.5.3.1. *Synthesis of acetals*

1.5.3.1.1. General methods

Method A[163]

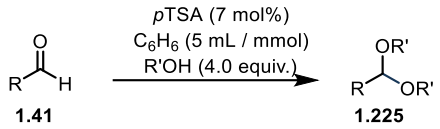


1.41 **1.225**

Scheme 1.32

The aldehyde **1.41** (1.0 equiv.) was placed in a Schlenk tube with freshly activated 3 Å molecular sieves. The alcohol was added (4 mL / mmol aldehyde) and cooled to 0 °C. Thereafter, $TiCl_4$ was added (1 M in DCM, 0.1 equiv.) and stirred for 25 minutes. Then Et_3N (1.25 equiv.) was added slowly, the reaction mixture was warmed up to room temperature and the reaction mixture was stirred for further 120 minutes. The reaction was carefully quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (typically Et_2O : heptanes - 1.5 : 98.5 v/v%) to obtain the corresponding acetal **1.225**.

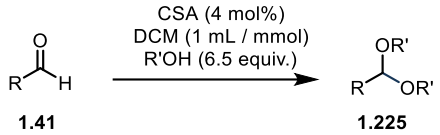
Method B



Scheme 1.33

The aldehyde **1.41** (1.0 equiv.) was dissolved in benzene (5 mL / mmol) in a round-bottom flask and pTSA was added (7 mol%). The flask was attacked to a Dean-Stark trap and refluxed for 16 hours. Then the reaction mixture was cooled to room temperature and washed with water. The organic layer was dried over Na_2SO_4, the solvent was evaporated and the crude product was purified by silica gel column chromatography (typically Et_2O : heptanes - 1.5 : 98.5 v/v%) to obtain the corresponding acetal **1.225**.

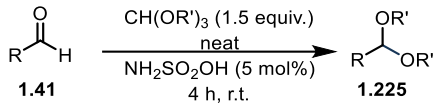
Method C[164]



Scheme 1.34

The aldehyde **1.41** (1.0 equiv.) was placed in a Schlenk tube and dissolved in DCM (1 mL / mmol). Camphor sulfonic acid (CSA) was added (7 mol%) and the reaction mixture was refluxed for 5 hours. The mixture was cooled down to room temperature and freshly activated 3 Å molecular sieves were added. The reaction was stirred for 16 h at room temperature, then quenched with saturated aqueous $NaHCO_3$ and afterwards further stirred for 45 minutes. The two phases were separated and the aqueous phase was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4, the solvent was evaporated and the crude product was purified by silica gel column chromatography (typically Et_2O : heptanes - 1.5 : 98.5 v/v%) to obtain the corresponding acetal **1.225**.

Method D[165]

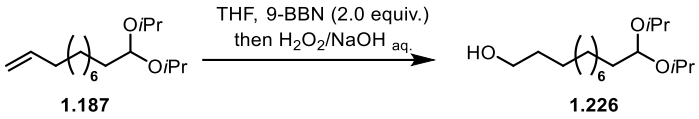


Scheme 1.35

The aldehyde **1.41** (1.0 equiv.) was dissolved in trialkyl Orthoformate (1.5 equiv.) and amidosulfonic acid (5 mol%) was added. The reaction mixture was stirred at room temperature for 4 hours. The mixture was filtrated and the solid residue was washed with Et_2O. The highly volatile compounds were removed under reduced pressure and the crude product was purified by silica gel column chromatography (typically Et_2O : heptanes – 1.5 : 98.5 v/v%) to obtain the corresponding acetal **1.225.**

1.5.3.1.2. Specific syntheses

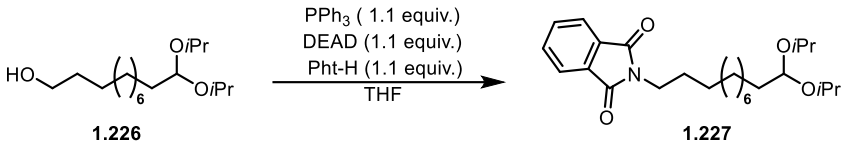
Synthesis of alcohol intermediate



Scheme 1.36

The acetal **1.187** (7.5 mmol, 1.0 equiv., 2038 mg) was dissolved in THF (1.5 mL) and cooled to 0 °C. Thereafter, 9-Borabicyclo[3.3.1]nonane was added (0.5 M in THF, 30 mL) slowly. The reaction mixture was warmed up to room temperature and stirred for 3 h. Then water (0.3 mL), aqueous NaOH solution (3 M, 5.5 mL) and aqueous H_2O_2 solution (35 w/w%, 5.5 mL) were added carefully at -15 °C and the mixture was further stirred for 2 hours at room temperture. Afterwards the reaction was diluted with Et_2O (20 mL) and and washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by silica gel column chromatography (heptanes : Et_2O - 80 : 20 v/v%) to obtain the desired product as a colorless liquid. (yield 1812 mg, 84%).

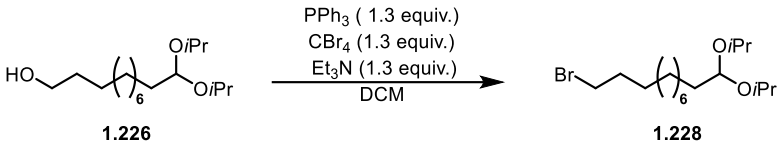
Synthesis of Phtalimide substrate



Scheme 1.37

The alcohol **1.226** (1.0 mmol, 1.0 equiv., 288 mg) was dissolved in THF (8 mL) and cooled to 0 °C. Then, Phthalimide (1.1 mmol, 1.1 equiv., 162 mg), triphenylphosphine (1.1 mmol, 1.1 equiv., 289 mg) and diethyl azodicarboxylate (1.1 mmol, 1.1 equiv., 200 µL) were added. The reaction was warmed to room temperature and stirred for 16 h. Then the reaction was diluted with Et_2O (10 mL), filtered and washed with water (10 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (heptanes : Et_2O – 95 : 5 v/v%) to obtain **1.227** as a yellow solid (yield 317 mg, 76%).

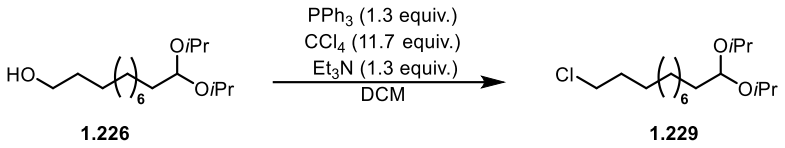
Synthesis of the bromide substrate



Scheme 1.38

The alcohol **1.226** (1.0 mmol, 1.0 equiv., 288 mg), triethylamine (1.3 mmol, 1.3 equiv., 181 µL) and tetrabromomethane (1.3 mmol, 1.3 equiv., 431 mg) were dissolved in DCM (1.2 mL). A solution of Triphenylphosphine was added (1.3 mmol, 1.3 equiv., 341 mg) in DCM (1 mL) was added dropwise to the mixture and the reaction was stirred at room temperature until no starting material was observed by TLC (4 h). The reaction was diluted with a pentane/Et_2O mixture (1 : 1, 17 mL), filtered, and the clear solution was washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (heptanes : Et_2O – 98 : 2 v/v%) to obtain **1.228** as a colorless to yellowish oil (yield 268 mg, 76%).

Synthesis of the chloride substrate

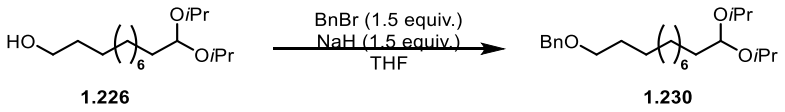


1.226 **1.229**

Scheme 1.39

The alcohol **1.226** (1.0 mmol, 1.0 equiv., 288 mg), triethylamine (1.3 mmol, 1.3 equiv., 181 µL) and tetrachloromomethane (11.7 mmol, 11.7 equiv., 1125 µL) were dissolved in DCM (1.2 mL). A solution of Triphenylphosphine was added (1.3 mmol, 1.3 equiv., 341 mg) in DCM (1 mL) was added dropwise to the mixture and the reaction was stirred at room temperature. After 5 h only starting material was observed by TLC. More tetrachloromethane was added (10.4 mmol, 10.4 eq., 1 mL) and the reaction was heated to 40 °C for 2 h. The reaction was diluted with a pentane/Et_2O mixture (1 : 1, 17 mL), filtered, and the clear solution was washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (heptanes : Et_2O – 98 : 2 v/v%) to obtain **1.229** as a colorless to yellowish oil (yield 204 mg, 67%).

Synthesis of the benzyl ether substrate

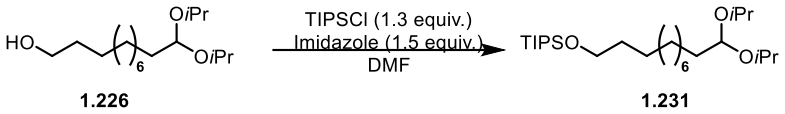


1.226 **1.230**

Scheme 1.40

The alcohol **1.226** (0.7 mmol, 1.0 eq., 200 mg) was dissolved in THF (1.75 mL). Benzylbromide (1.04 mmol, 1.5 eq., 124 µL) and NaH (1.04 mmol, 68 wt.% dispersion in paraffin, 42 mg) was added. The reaction was stirred at room temperature for 20 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and extracted with DCM (3 x 5 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (heptanes : Et_2O – 99 : 1 v/v%) to obtain **1.230** as a yellowish oil (yield 200 mg, 76%).

Synthesis of the TIPS ether substrate

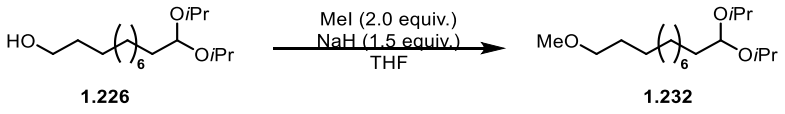


1.226 **1.231**

Scheme 1.41

The alcohol **1.226** (1.0 mmol, 1.0 equiv., 288 mg) has been dissolved in DMF (1 mL) and the solution was cooled to 10 °C. Thereafter imidazole (1.5 mmol, 1.5 equiv., 102 mg) and TIPSCl (1.3 mmol, 1.3 equiv., 278 µL) were added. The reaction mixture was stirred for 30 minutes at the same temperature, then diluted with Et_2O, washed with brine and dried over Na_2SO_4. After filtration, the volatiles were removed under reduced pressure, and the crude product was purified by column chromatography (Heptanes : Et_2O – 98 : 2 v/v%). The product **1.231** was obtained as a yellowish oil (yield 160 mg, 36%).

Synthesis of the methyl ether substrate

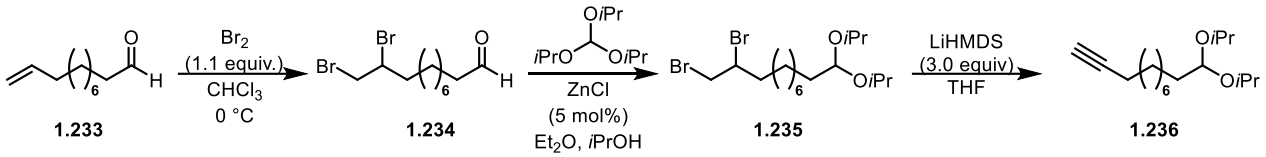


1.226 **1.232**

Scheme 1.42

The alcohol **1.226** (0.42 mmol, 1.0 eq., 120 mg) was dissolved in THF (1.0 mL). MeI (0.83 mmol, 2.0 eq., 52 µL) and NaH (0.62 mmol, 68 wt.% dispersion in paraffin, 25 mg) was added. The reaction was stirred at room temperature for 20 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and extracted with DCM (3 x 5 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (heptanes : Et_2O – 99 : 1 v/v%) to obtain **1.232** as a colorless oil (yield 108 mg, 86%).

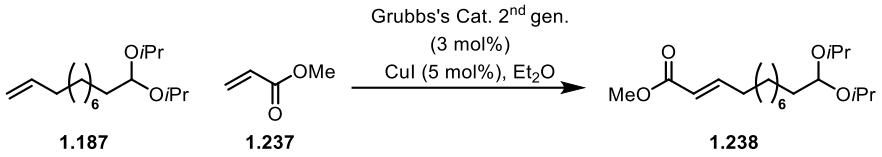
Synthesis of the alkyne substrate



Scheme 1.43

Aldehyde **1.233** (5.0 mmol, 1.0 equiv., 841 mg) was dissolved in $CHCl_3$ (12 mL) and cooled to 0 °C. Bromine (5.4 mmol, 1.1 equiv., 274 µL) was added and the reaction was stirred at the same temperature for 2 h. Then the mixture was quenched with a saturated aqueous thiosulfate solution (10 mL) and stirred for 15 minutes at room temperature. The aqueous layer was extracted with chloroform (2 x 10 mL), the combined organic layer dried over Na_2SO_4 and finally the solvent was evaporated under reduced pressure. The resulting dibromide **1.234** was dissolved in Et_2O (1.5 mL) with tri*iso*propyl orthoformate (7.5 mmol, 1.5 equiv., 1.66 mL), isopropanol (55 µL) and $ZnCl_2$ (0.05 equiv., 0.25 mmol, 34 mg). The reaction was stirred 4 hours at room temperature and then poured into water (1.8 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic layer dried over Na_2SO_4. Purification by column chromatography yielded acetal **1.235**. The acetal **1.235** was dissolved in THF (2.3 mL) and added slowly to a solution of LiHMDS (9.6 mmol, 1.61 g, 3.0 equiv.) in THF (6.9 mL). After 13 hours of stirring at room temperature, the solution was heated to 50 °C and further stirred for 8 h. Then the reaction was cooled to room temperature and diluted with Et_2O (10 mL). The organic layer was repeatedly washed with water until the aqueous phase remained neutral. The organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by column chromatography (Heptanes : Et_2O – 98 : 2 v/v%) to yield **1.236** as a colorless oil (overall yield 1.01 g, 48%).

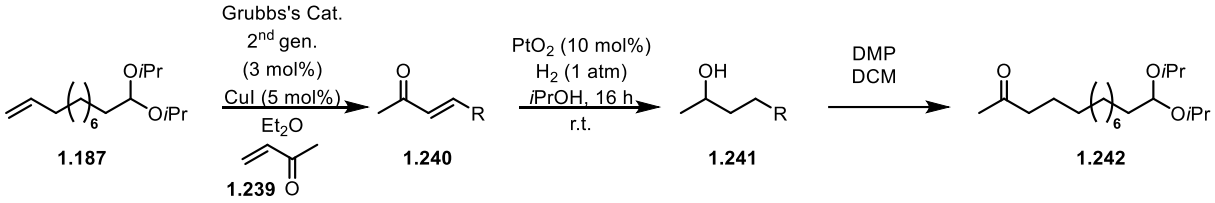
Synthesis of α,β-unsaturated ester substrate[166]



Scheme 1.44

The acetal **1.187** (1.0 mmol, 1.0 equiv., 270 mg), methyl acrylate (1.5 mmol, 1.5 equiv., 135 µL) Copper-(I)-Iodide (0.05 mmol, 0.05 equiv., 9.5 mg) and Grubbs' second generation catalyst (0.03 mmol, 0.03 eq., 26 mg) were dissolved in Et_2O (10 mL) and stirred at 35 °C for 16 hours. The reaction was cooled down to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (heptanes : Et_2O – 98 : 2 v/v%) to obtain **1.238** as a colorless liquid (yield 220 mg, 67%).

Synthesis of α,β-unsaturated ketone substrate



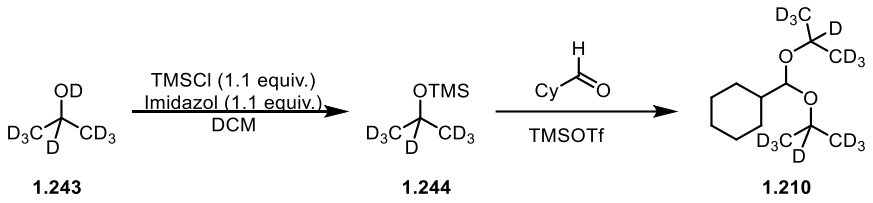
Scheme 1.45

The acetal **1.187** (2.0 mmol, 1.0 equiv., 541 mg), methyl vinyl ketone (3.0 mmol, 1.5 equiv., 243 µL) Copper-(I)-Iodide (0.1 mmol, 0.05 equiv., 19 mg) and Grubbs' second generation catalyst (0.06 mmol, 0.03 eq., 51 mg) were dissolved in Et_2O (20 mL) and stirred at 35 °C for 16 hours. The reaction was cooled down to room temperature and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (heptanes : Et_2O – 98 : 2 v/v%) to obtain **1.240** as a colorless liquid (yield 324 mg, 52%). The resulting enone **1.240** (0.64 mmol, 1.0 equiv., 200 mg) was dissolved in *i*PrOH (2 mL) and PtO_2 was added (0.06 mmol, 10 mol%, 15 mg). Air was removed from the flask and exchanged with H_2 (balloon – *ca.* 1 atm). The reaction was stirred for 16 h at room temperature, and

filtered over Celite®. The pad was washed with EtOAc and the volatiles were removed under reduced pressure to obtain the alcohol **1.241** in quantitative yield as a colorless liquid (yield 197 mg, >95%).

The alcohol **1.241** (0.62 mmol, 1.0 equiv. 197 mg) was dissolved in DCM (7 mL) and pyridine (1 mL) and Dess-Martin-Periodinane was added (1.87 mmol, 3.0 equiv., 792 mg). The reaction was stirred at room temperature for 3 h. The mixture was quenched with water, extracted with DCM, dried over Na_2SO_4 and filtered. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (Heptanes : Et_2O – 98 : 2 v/v%). The desired ketone **1.242** was obtained as a colorless oil. (yield 192 mg, 98 mg)

Synthesis of the deutorated starting material[167]



1.243 **1.244** **1.210**

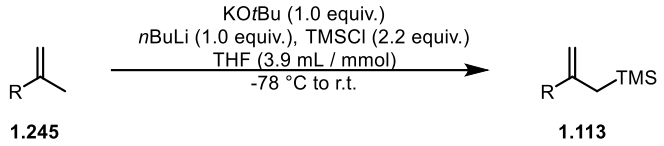
Scheme 1.46

D_8-Isopropanol (1.0 equiv., 20 mmol, 1.7 mL) was dissolved in DCM (20 mL) and imidazole (1.1equiv., 22 mmol, 1.50 g) was added and the system was cooled to 0 °C. Then freshly distilled TMSCl (1.1 equiv., 22 mmol, 2.79 mL) was added dropwise. The ice bath was removed and the mixture was stirred 30 minutes at room temperature. The precipitate was filtered off and washed with DCM (2 x 5 mL). Distillation of the solution gave no separation (the product came over at about 40 °C with DCM). Concentration of the product under moderately reduced pressure, gave a clean solution of the desired product in DCM (1.7 mL, about 6 M). The solution was placed into a Schlenk flask, which was cooled down to -78 °C. TMSOTf (0.09 equiv., 0.14 mmol, 25 µL) and cyclohexanecarboxaldehyde (1.0 equiv., 1.6 mmol, 194 µL) were added slowly. The reaction mixture was stirred for 3 h at the same temperature. The reaction was quenched with a few drops of dry pyridine, aqueous saturated $NaHCO_3$ solution was added and the mixture was then warmed to room temperature. The solution was extracted with Et_2O (3 x 5 mL) and the combined organic layer was dried over Na_2SO_4. The solvent was evaporated and the crude product was

purified by column chromatography (heptanes : Et_2O – 99 : 1 v/v%) to obtain **1.210**. (Overall yield 110 mg, 5%)

1.5.3.2. *Synthesis of allylsilanes*

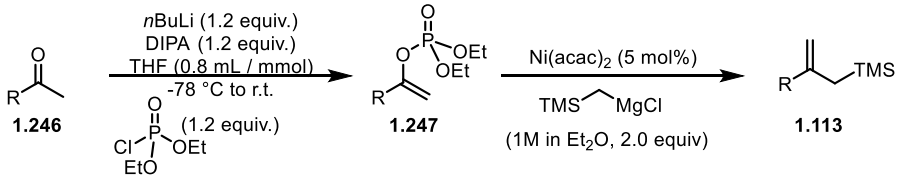
Method I[168,169]



Scheme 1.47

KO*t*Bu (1.0 equiv.) and the olefin (1.0 equiv.) were dissolved in THF (3 mL / mmol olefine) and the resulting solution cooled to –78°C. Subsequently *n*BuLi (2.5M in hexane, 1.0 equiv.) was added over a period of 5-10 minutes at this temperature. The solution was warmed to –50°C and stirred at this temperature for 5 h. The resulting solution was then added to a solution of freshly distilled chlorotrimethylsilane (2.2 equiv.) in THF (0.9 mL / mmol olefin) at –78°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue taken up in *n*-pentane. The resulting suspension was filtered through a pad of celite® and concentrated under reduced pressure. The residue was purified by column chromatography on silica using pentane as the eluent to obtain the allylsilane.

Method II[169–171]



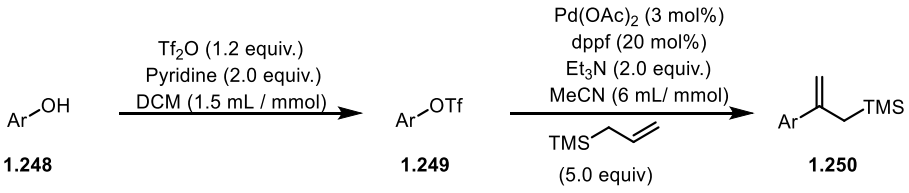
Scheme 1.48

A solution of *i*Pr_2NH (1.18 equiv.) in THF (0.8 mL / mmol ketone) was cooled to 0°C and *n*BuLi (1.18 equiv.) was added dropwise. The resulting solution of LDA was cooled to –78°C and the ketone (1.0 eq.) was added dropwise over approximately 10 minutes. The reaction mixture was stirred at –78 °C for 30 minutes followed by the dropwise addition of diethyl phosphorochloridate (1.24 equiv.) over a period of

5 minutes. The resulting mixture was allowed to slowly warm to room temperature and stirred for 1 h. The reaction mixture was diluted with Et_2O and successively washed with H_2O and an aqueous saturated NaHCO3-solution. Drying over Na_2SO4 and evaporation of the solvents under reduced pressure gave the crude enol phosphate, which was purified by column chromatography (typically Heptanes : EtOAc – 90 : 10 v/v%).

The resulting enol phosphate was added to a mixture of $Ni(acac)_2$ (5 mol%) and trimethylsilylmethylmagnesium chloride (ca. 1 M solution in Et_2O, 2 mL/mmol enolphosphate) and the resulting reaction mixture stirred at r.t. for 16 hours. The reaction was quenched by addition of water at 0°C. The phases were separated, the aqueous phase extracted with Et_2O and the combined organic phases were washed successively with aqueous saturated $NaHCO_3$ solution and brine and dried over Na_2SO_4. The solvents were evaporated under reduced pressure, the residue taken up in pentane and filtered through a short chromatography column (described more accurately in the characterization section) to yield α-aromatic allylsilane AAS.

Method III[172]



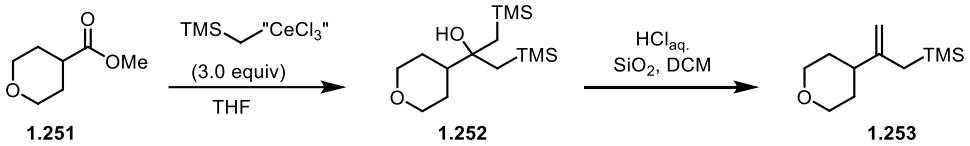
1.248 **1.249** **1.250**

Scheme 1.49

The phenol (1.0 equiv.) was dissolved in non-dry DCM (30 mL) with pyridine (2.0 equiv.). The solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (1.2 equiv.) was added dropwise. The reaction mixture was stirred for 2 hours at room temperature. The reaction was then quenched with aqueous saturated NH_4Cl and the aqueous phase was extracted three times with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica using heptanes and EtOAc as eluent (typically 90 : 10 v/v%).

The quantitatively generated triflated phenol **1.249** (1.0 equiv.) was then dissolved in MeCN (6 mL / mmol) and $Pd(OAc)_2$ (3 mol%), 1,1'-Bis(diphenylphosphino)ferrocene (dppf - 20 mol%), Et_3N (2.0 equiv.) and allylTMS (5.0 equiv.) were added to the solution. The reaction mixture was stirred for 14 hours at 60 °C. The system was cooled to room temperature, diluted with Et_2O and water was added. The aqueous phase was extracted three times with Et_2O and the combined organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (described more accurately in the characterization section) to yield the desired α-aromatic allylsilane **1.250**.

Method IV[173]



Scheme 1.50

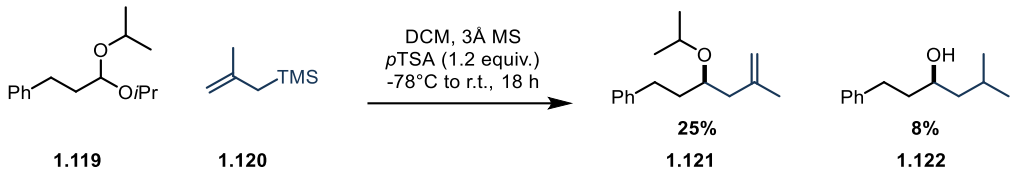
$CeCl_3 \bullet 7H_2O$ (12 mmol, 3.0 equiv., 4.47 g) was grinded with a pestle in a mortar and placed in a 250 mL three-necked round bottom flask connected to a cooling trap (-78 °C) and attached to a vacuum pump. The flask was evacuated (0.01 mbar - 0.1 mbar) and heated to 95 °C for 2.5 hours with intermittent shaking. The flask was then filled with argon and cooled to room temperature. The solid was further grinded with an appropriate glass rod in the flask and a dry rugby-shaped magnet stirring bar was added. Warming to 95 °C and evacuating (0.01 mbar – 0.1 mbar) again for 2 hours leads to the formation of the monohydrate, which is then further heated to 135 °C and then gently stirred for 2 hours at the same temperature. While the flask is still hot, the area that is not immersed in the oil bath is heated by the use of a heat gun in order to remove traces of water[174].The flask containing the free flowing fine white powder (anhydrous $CeCl_3$) was filled with argon and cooled to room temperature. Then THF was added (18 mL) and the white, milky suspension was stirred for 16 h.

Magnesium (12 mmol, 3 equiv., 292 mg) was added to a separate 50 mL three-necked round bottom flask fitted with a condenser. A solution of (chloromethyl)trimethylsilane (12.0 mmol, 3.0 equiv., 1.67 mL) in THF (8 mL) was added dropwise and stirred until most of the magnesium was dissolved (3 hours).

The $CeCl_3$ suspension was cooled to -78 °C and the prepared Grignard solution was added to the mixture. After 2 hours of stirring at the same temperature a solution of the ester **1.251** (4.0 mmol, 1.0 equiv., 534 µL) in THF (2.4 mL) was added dropwise over 5 minutes. The mixture was warmed to room temperature and the process of the reaction was followed by TLC. After completion (3 hours) the solution was cooled to 0 °C and quenched with aqueous saturated NH_4Cl (9 mL) and diluted with Et_2O (10 mL). The aqueous phase was extracted (3 x 20 mL) and the combined organic layer was washed with brine (2 x 20 mL) and dried over Na_2SO_4. The solvent was removed and the residue (**1.252**) was dissolved in non-dry DCM (30 mL). Silica gel (5 g) and two drops of $HCl_{aq.}$ (1 wt.%) were added and the reaction was stirred at room temperature until no starting material was observed by TLC. The mixture was filtered and the silica was washed with DCM (3 x 10 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica using pentane as eluent. The desired allylsilane **1.253** was obtained as a colorless liquid (yield 891 mg, 90 %).

1.5.4. Experimental section

1.5.4.1. *Preliminary results*

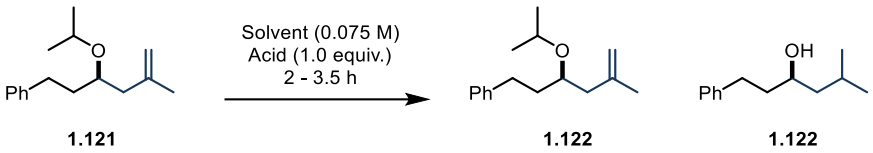


Scheme 1.51

Allylsilane **1.120** (1.1 mmol, 1.1 eq., 193 µL) was dissolved in DCM (0.6 mL) in a Schlenk tube containing freshly activated 3 Å molecular sieves and pTSA (0.2 mmol, 0.2 eq., 35 mg). The reaction

mixture was cooled to -78 °C and acetal **1.119** (1.0 mmol, 1.0 eq., 236 mg) in DCM (0.5 mL) was added. After 1 h of stirring at the same temperature more pTSA was added (1.0 mmol, 1.0 eq., 173 mg) and the reaction mixture was warmed to room temperature and the reaction was stirred for further 16 h. The reaction was carefully quenched with saturated aqueous $NaHCO_3$ (ca. 1-2 mL), the aqueous phase extracted with Et_2O (3 x 5 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (gradient from heptanes : Et_2O - 98 : 2 v/v% to heptanes : Et_2O - 80 : 20 v/v%) to obtain 16 mg of **1.121** (8% yield) and 58 mg of **1.122** (25%), both as a yellowish oil. The experiments in table 1.1 were conducted equivalently.

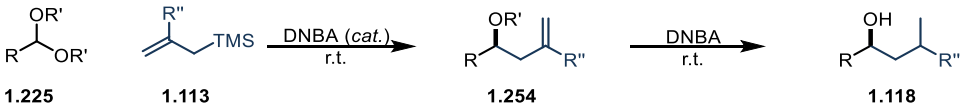
1.5.4.2. *General procedure for the optimization of the 1,5-hydride transfer*



Scheme 1.52

Homoallylic ether **1.121** (0.3 mmol, 1.0 eq., 70 mg) was dissolved in the solvent (2 mL) at room temperature. Thereafter, the acid was added (0.3 mmol, 1.0 eq.) and the reaction was stirred for the indicated time at the indicated temperature. All reactions were stirred for 2 h at room temperature at the beginning. Higher temperatures (*i.e.* 50 °C) were applied for the remaining time. The reaction was carefully quenched with saturated aqueous $NaHCO_3$ (ca. 2-3 mL), the aqueous phase extracted with DCM (3 x 5 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and mesitylene (0.3 mmol, 1.0 eq., 41.7 µL) was added to the reaction flask as an internal standard. The ^1H NMR spectrum was measured and the yield was determined by integration of the signal of the proton in alpha to the oxygen atom. Conversion was measured by integration of the olefin signal.

1.5.4.3. *General procedure for stepwise investigations*

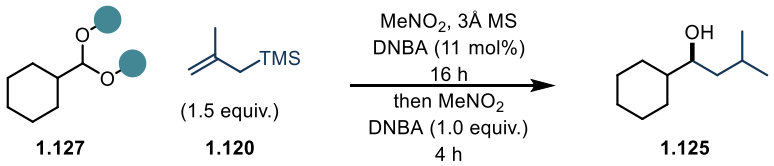


Scheme 1.53

DNBA (0.03 or 0.01 mmol, 0.11 or 0.03 eq.) was poured into a Schlenk tube with freshly activated 3 Å molecular sieves. Nitromethane was added (1.0 mL) and the reaction was cooled to 0 °C. Thereafter, allylsilane (0.45 mmol, 1.5 eq.) and the acetal were added (0.3 mmol, 1.0 eq.). The reaction was warmed up to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (ca. 5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (typically first pure heptanes, then heptanes : Et_2O - 98 : 2 v/v%) to obtain the homoallylic ether.

The isolated homoallylic ether was dissolved in a Schlenk tube in $MeNO_2$ (0.2 M) and DNBA was added (1.0eq.) and stirred for 60 minutes at room temperature and then quenched with saturated aqueous $NaHCO_3$ (ca. 5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (typically heptanes : Et_2O - 85 : 15 v/v%) to obtain the alcohol.

1.5.4.4. *General procedure for the acetal screening*

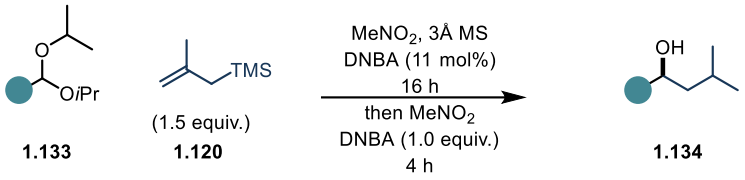


Scheme 1.54

DNBA (0.03 mmol, 0.11 eq., 8 mg) was poured into a Schlenk tube with freshly activated 3 Å molecular sieves. Nitromethane was added (1.0 mL) and the reaction was cooled to 0 °C. Thereafter, allylsilane **1.120** (0.45 mmol, 1.5 eq., 79 µL) and the acetal was added (0.3 mmol, 1.0 eq.). The reaction

was warmed up to room temperature and stirred for 16 h. Afterwards, more nitromethane (2.45 mL) and DNBA (0.3 mmol, 1.0 eq., 76 mg) were added at once. The reaction was stirred for further 4 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ (ca. 5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude was analyzed by ^1H NMR with mesitylene as an internal standard.

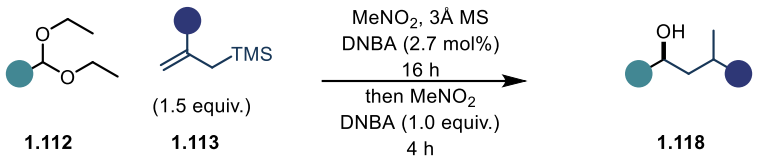
1.5.4.5. *General procedure for the product scope*



Scheme 1.55

DNBA (0.03 mmol, 0.11 eq., 8 mg) was poured into a Schlenk tube with freshly activated 3 Å molecular sieves. Nitromethane was added (1.0 mL) and the reaction was cooled to 0 °C. Thereafter, allylsilane **1.120** (0.45 mmol, 1.5 eq., 79 µL) and the acetal **1.133** was added (0.3 mmol, 1.0 eq.). The reaction was warmed up to room temperature and stirred for 16 h. Afterwards, more nitromethane (2.45 mL) and DNBA (0.3 mmol, 1.0 eq., 76 mg) were added at once. The reaction was stirred for further 4 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ (ca. 5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (typically heptanes : Et_2O - 85 : 15 v/v%) to obtain **1.134**.

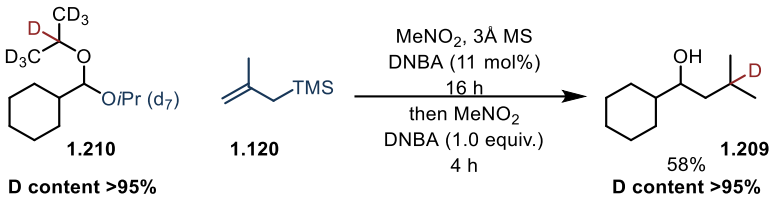
1.5.4.6. *General procedure or the allylsilane scope*



Scheme 1.56

DNBA (0.01 mmol, 0.03 eq., 2 mg) was poured into a Schlenk tube with freshly activated 3 Å molecular sieves. Nitromethane was added (1.0 mL) and the reaction was cooled to 0 °C. Thereafter, allylsilane **1.113** (0.45 mmol, 1.5 eq.) and the acetal **1.112** was added (0.3 mmol, 1.0 eq.). The reaction was warmed up to room temperature and stirred for 16 h. Afterwards, more nitromethane (2.45 mL) and DNBA (0.3 mmol, 1.0 eq., 76 mg) were added at once. The reaction was stirred for further 60 minutes at room temperature and then quenched with saturated aqueous $NaHCO_3$ (ca. 5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (typically heptanes : Et_2O - 85 : 15 v/v%).

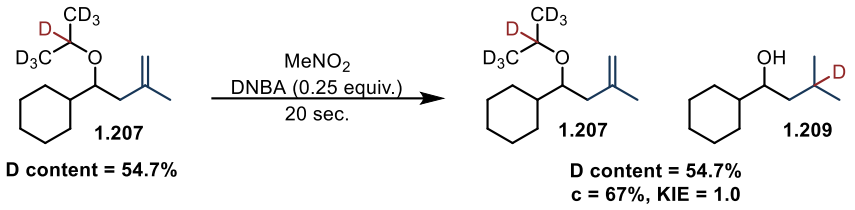
1.5.4.7. *Deuterium experiments*



Scheme 1.57

DNBA (0.015 mmol, 0.11 eq., 4 mg) was poured into a Schlenk tube with freshly activated 3 Å molecular sieves. Nitromethane was added (0.5 mL) and the reaction was cooled to 0 °C. Thereafter, allylsilane **1.120** (0.23 mmol, 1.5 eq., 39 µL) and the acetal **1.210** (0.15 mmol, 1.0 eq., 34.2 mg) was added. The reaction was warmed up to room temperature and stirred for 16 h. Afterwards, more nitromethane (1.25 mL) and DNBA (0.15 mmol, 1.0 eq., 38 mg) were added at once. The reaction was stirred for further

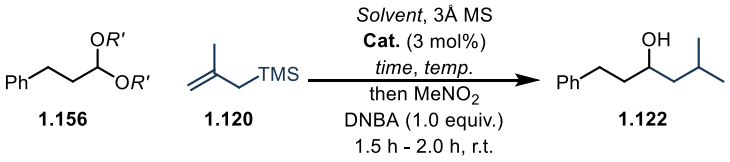
4 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ (ca. 2 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by silica gel column chromatography (heptanes : Et_2O - 80 : 20 v/v%) to obtain **10ba** as a colorless oil (yield 15 mg, 58%).



Scheme 1.58

The homoallylic ether **1.207** (0.10 mmol, 1.0 eq., 22 mg), which deuterium content was measured before by ^1H NMR was dissolved in $MeNO_2$ (0.5 mL) in a dram vial. Under stirring DNBA (0.026 mmol, 0.25 eq., 6.5 mg) was added. After 20 seconds of stirring the reaction was quenched with saturated aqueous $NaHCO_3$ (ca. 5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic layer dried over Na_2SO_4. The solvent was evaporated and the crude product was analyzed by ^1H NMR. For an accurate integration of the recovered starting material the crude was purified by silica gel column chromatrography (first pure heptanes, then heptanes : Et_2O – 98: 2 v/v%).

1.5.4.8. *Enantioselective experiments*



Scheme 1.59

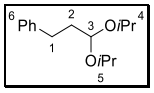
A flame dried Schlenk flask was charged with the chiral catalyst (3 mol% - 0.003 mmol) under argon and dissolved in the solvent (0.3 mmol). After cooling the reaction mixture for at least 10 minutes in an appropriate cooling bath (acetone, $CO_{2\,(s)}$), the allylsilane (1.5 equiv. – 0.15 mmol) and the starting material (1.0 equiv. – 0.1 mmol) were added subsequently under stirring. The reaction was stirred at the

same temperature and followed by TLC: the tip of a Pasteur pipette was inserted into the reaction mixture under argon counterflow and was quenched immediately with a few drops of water and mixed in a small vial with either Et_2O or EtOAc. The organic layer was then used for TLC samples. When no acetal and/or aldehyde were observed by TLC the conversion towards the homoallylic ether was assumed to be completed. The mixture was then warmed to room temperature. Nitromethane (0.8 mL) and 2,4-dinitrobenzenesulfonic acid (DNBA) were added to the reaction mixture and stirred until the homoallylic ether was not observable by TLC. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution and extracted three times with Et_2O. The combined organic layer was dried over Na_2SO_4, filtrated and solvent was removed under reduced pressure. Purification through column chromatography (typical eluent : Et_2O : Heptanes – 10 : 90 v/v%) afforded the desired alcohol as a yellowish oily liquid.

1.6. Characterization

1.6.1. Cyclohexanecarb- or dihydro-cinnamyl-acetals

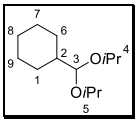
(3,3-di*iso*propoxypropyl)benzene (**1.119**)



Synthesized by using general **method C** for the synthesis of acetals.

Isolated yield: 2.17 g, 46%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H, Ar), 7.22 – 7.16 (m, 3H, Ar), 4.56 (t, *J* = 5.5 Hz, 1H, C3), 3.86 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 2.71 – 2.67 (m, 2H, C1), 1.95 – 1.89 (m, 2H, C2), 1.20 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.97 (Ar), 128.37 (Ar), 128.30 (Ar), 125.72 (Ar), 99.61 (C3), 67.71 (*i*Pr(C-H)), 36.91 (C2), 31.05 (C1), 23.43 (*i*Pr(CH_3)), 22.61 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 259.1674 found 259.1669. **ATR-FTIR** (cm^{-1}): 3063, 3028, 2971, 2870, 1604, 1496, 1455, 1379, 1276, 1261, 1173, 1127, 1033, 990, 912, 763, 750, 699.

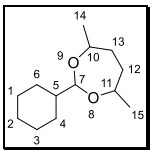
(Di*iso*propoxymethyl)cyclohexane (**1.126**)



Synthesized by using general **method C** for the synthesis of acetals.

Isolated yield: 1.71 g, 40%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.24 (d, *J* = 6.2 Hz, 1H, C3), 3.84 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 1.82 – 1.77 (m, 2H, Cy), 1.74 – 1.70 (m, 2H, Cy), 1.66 – 1.61 (m, 1H, Cy), 1.52 – 1.45 (m, 1H, Cy), 1.19 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)), 1.04 – 0.95 (m, 2H, Cy). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 103.83 (C3), 68.16 (*i*Pr(C-H), 42.36 (C2), 28.35 (Cy), 26.68 (Cy), 26.17 (Cy), 23.59 (*i*Pr(CH_3)), 22.75 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 237.1830 found 237.1822. **ATR-FTIR** (cm^{-1}): 2970, 2922, 2852, 1451, 1378, 1323, 1262, 1238, 1178, 1122, 1079, 1062, 1020, 967, 943, 943, 891, 873, 844, 789, 751.

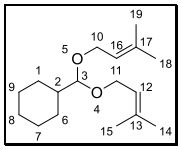
As 2-cyclohexyl-4,7-dimethyl-1,3-dioxepane (**1.128**)



Synthesized by using general **method B** for the synthesis of acetals.

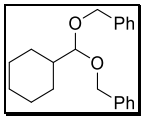
Isolated yield: 960 mg, 45%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.35 (d, *J* = 7.3 Hz, 0.5H, C7), 4.19 (d, *J* = 6.6 Hz, 0.5H, C7), 4.07 – 3.97 (m, 0.5H, C10/C11), 3.87 – 3.77 (m, 1H, C10/C11), 3.75 – 3.64 (m, 0.5H, C10/C11), 1.90 – 1.80 (m, 4H, CH), 1.78 – 1.60 (m, 13H, CH), 1.54 – 1.41 (m, 4H, CH), 1.32 – 1.06 (m, 19H, CH), 1.04 – 0.90 (m, 4H, CH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 106.94 (C7), 103.78 (C7), 75.58 (C10/C11), 75.25 (C10/C11), 68.60 (C10/C11), 43.10 (C5), 41.84 (C5), 36.20 (C12/C13), 36.16 (C12/C13), 33.66 (C12/C13), 28.84 (C4/C6), 28.75(C4/C6), 28.55(C4/C6), 26.70 (C1/C2/C3), 26.62 (C1/C2/C3), 26.00 (C1/C2/C3), 25.95 (C1/C2/C3), 22.82 (C14/C15), 22.71 (C14/C15), 22.49 (C14/C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 235.1674 found 235.1665. **ATR-FTIR** (cm^{-1}): 2969, 2921, 2851, 1448, 1373, 1327, 1303, 1262, 1237, 1175, 1156, 1137, 1122, 1101, 1079, 1038, 1005, 970, 930, 893, 876, 853, 764, 750, 655.

(*bis*((3-methylbut-2-en-1-yl)oxy)methyl)cyclohexane (**1.141**)

 Synthesized by using general **method A** for the synthesis of acetals.

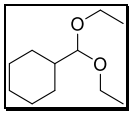
Compound isolated, no yield determined. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.40 – 5.32 (m, 2H, C12/C16), 4.19 (d, *J* = 7.5 Hz, 1H, C3), 4.08 (dd, *J* = 11.4, 6.8 Hz, 2H, C10/C11), 3.99 (dd, *J* = 11.4, 7.1 Hz, 2H, C10/C11), 1.85 – 1.78 (m, 2H, C1/C6), 1.74 (s, 6H, CH_3), 1.72 – 1.70 (m, 1H, C2), 1.68 (s, 6H, CH_3), 1.66 – 1.58 (m, 2H, Cy), 1.28 – 1.07 (m, 3H, Cy), 1.04 – 0.92 (m, 2H, Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.68 (C13/C17), 121.36 (C12/C16), 105.92 (C3), 62.28 (C10/C11), 40.60 (C2), 28.54 (CH_3), 26.58 (Cy), 25.95 (CH_3), 18.14 (Cy). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 289.2143 found 289.2435. **ATR-FTIR** (cm^{-1}): 2971, 2921, 2852, 1676, 1448, 1378, 1349, 1324, 1264, 1201, 1186, 1160, 1124, 1074, 1022, 917, 890, 843, 781, 765, 750.

(((cyclohexylmethylene)bis(oxy))*bis*(methylene))dibenzene (**1.129**)

 Synthesized by using general **method A** for the synthesis of acetals.

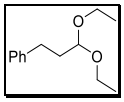
Isolated yield: 2.1 g, 68%. Spectroscopic properties match with the literature.[56]

(diethoxymethyl)cyclohexane (**1.130**)

 Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 1.4 g, 75%. Spectroscopic properties match with the literature.[175]

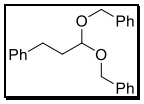
(3,3-diethoxypropyl)benzene (**1.158**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 1.3 g, 63%. Spectroscopic properties match with the literature.[175]

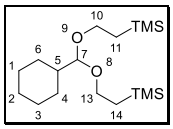
(((3-phenylpropane-1,1-diyl)*bis*(oxy))*bis*(methylene))dibenzene (**1.159**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 750 mg, 45%. Spectroscopic properties match with the literature.[176]

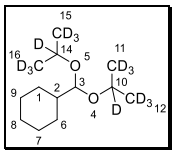
6-cyclohexyl-2,2,10,10-tetramethyl-5,7-dioxa-2,10-disilaundecane (**1.132**)



Synthesized by using general **method C** for the synthesis of acetals.

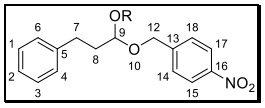
Compoud isolated, no yield determined. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (d, *J* = 6.8 Hz, 1H, C7), 3.71 – 3.61 (m, 2H, C10/C13), 3.56 – 3.42 (m, 2H, C10/C13), 1.84 – 1.68 (m, 4H, Cy), 1.68 – 1.51 (m, 2H, Cy), 1.28 – 1.20 (m, 3H, Cy), 1.06 – 0.96 (m, 2H, Cy), 0.93 (ddd, *J* = 9.8, 6.6, 3.0 Hz, 4H, C11/C14), 0.02 (s, 18H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 106.58 (C7), 63.64 (C10/C13), 41.13 (C5), 28.39 (Cy), 26.67 (Cy), 26.04 (Cy), 18.52 (C11/C13), -1.23 (TMS). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 353.2308 found 353.2297. **ATR-FTIR** (cm^{-1}): 2951, 2922, 2853, 1450, 1345, 1246, 1202, 1123, 1080, 1046, 972, 938, 913, 890, 856, 831, 752, 692, 665.

(*bis*((propan-2-yl-d7)oxy)methyl)cyclohexane (**1.210**)

 Synthesized by using the **specific** procedure.

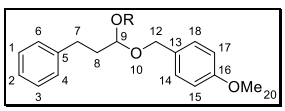
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 6.2 Hz, 1H, C3), 1.84 – 1.76 (m, 2H, Cy), 1.76 – 1.69 (m, 2H, Cy), 1.54 – 1.43 (m, 1H, Cy), 1.27 – 1.11 (m, 3H, Cy), 1.09 – 0.95 (m, 2H, Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 103.83 (C3), 42.42 (C2), 28.38 (C1/C6), 26.72 (C8), 26.20 (C7/9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 251.2709 found 251.2701. **ATR-FTIR** (cm^{-1}): 2923, 2852, 2227, 1451, 1242, 1222, 1167, 1122, 1087, 1029, 1001, 961, 893.

4,4'-(((3-phenylpropane-1,1-diyl)*bis*(oxy))bis(methylene))*bis*(nitrobenzene) (**1.161**)

 Synthesized by using general **method B** for the synthesis of acetals.

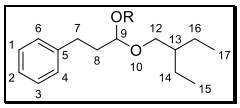
Isolated yield: 1.2 mg, 58%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 4H, C15/C17), 7.48 (d, *J* = 8.8 Hz, 4H, C14/C16), 7.29 (t, *J* = 7.3 Hz, 2H, Ph), 7.24 – 7.16 (m, 3H, Ph), 4.83 (t, *J* = 5.7 Hz, 1H, C9), 4.76 (d, *J* = 13.2 Hz, 2H, C12), 4.66 (d, *J* = 13.2 Hz, 2H, C12), 2.80 – 2.73 (m, 2H, C7), 2.18 – 2.09 (m, 2H, C8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.58 (C16), 145.60 (C13), 141.03 (C15/C17), 128.70 (C14/C18), 128.47 (Ph), 127.80 (Ph), 126.33 (Ph), 123.83 (Ph), 102.53 (C9), 66.20 (C12), 34.71 (C8), 31.08 (C7). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 445.1376 found 445.1373. **ATR-FTIR** (cm^{-1}): 2926, 2859, 1604, 1518, 1495, 1454, 1393, 1343, 1296, 1277, 1261, 1178, 1126, 1110, 1042, 1014, 906, 860, 842, 801, 727, 699, 648.

4,4'-(((3-phenylpropane-1,1-diyl)*bis*(oxy))*bis*(methylene))*bis*(methoxybenzene) (**1.160**)

 Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 1.4 g, 73%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 6H, Ar), 7.24 – 7.14 (m, 3H, Ar), 6.93 – 6.85 (m, 4H, C13/C15/C17/C18), 4.73 (t, *J* = 5.7 Hz, 1H, C9), 4.62 (d, *J* = 11.4 Hz, 2H, C12), 4.52 (d, *J* = 11.4 Hz, 2H, C12), 3.84 (s, 6H, C20), 2.77 – 2.69 (m, 2H, C7), 2.13 – 2.04 (m, 2H, C8). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.35 (Ar), 141.77 (Ar), 130.49 (Ar), 129.60 (Ar), 128.56 (Ar), 128.51 (Ar), 125.98 (Ar), 114.00 (Ar), 101.20 (C9), 67.12 (C12), 55.44 (C20), 35.13 (C8), 31.17 (C7). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 415.1885 found 415.1884. **ATR-FTIR** (cm^{-1}): 3027, 3002, 2923, 2853, 2836, 1612, 1586, 1512, 1456, 1381, 1350, 1301, 1245, 1173, 1118, 1090, 1031, 908, 847, 819, 729, 699, 648.

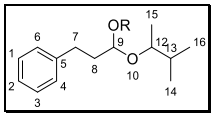
(3,3-*bis*(2-ethylbutoxy)propyl)benzene (**1.163**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 1.1 g, 70%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H, Ar), 7.23 – 7.14 (m, 3H, Ar), 4.46 (t, *J* = 5.7 Hz, 1H, C9), 3.51 (dd, *J* = 9.3, 5.4 Hz, 2H, C12), 3.30 (dd, *J* = 9.3, 5.5 Hz, 2H, C12), 2.72 – 2.64 (m, 2H, C7), 1.99 – 1.91 (m, 2H, C8), 1.47 – 1.29 (m, 10H, C13/C14/C16), 0.90 (dt, *J* = 7.3, 3.6 Hz, 12H, C15/C17). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.13 (Ar), 128.54 (Ar), 128.49 (Ar), 125.91 (Ar), 102.88 (C9), 67.98 (C12), 41.58 (C13), 35.25 (C8), 31.26 (C7), 23.57 (C14/C16), 23.55 (C14/C16), 11.31 (C15/C17). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 343.2613. found 343.2621. **ATR-FTIR** (cm^{-1}): 3028, 2960, 2929, 2874, 1604, 1595, 1458, 1380, 1238, 1124, 1041, 908, 824, 779, 734, 698.

(3,3-*bis*((3-methylbutan-2-yl)oxy)propyl)benzene (**1.162**)

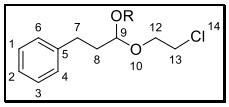


Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 830 mg, 57%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.5 Hz, 2H, Ar), 7.23 – 7.15 (m, 3H, Ar), 4.57 – 4.51 (m, 1H, C9), 3.51 – 3.46 (m, 1H, C12), 3.45 – 3.40 (m, 1H, C12), 2.78 – 2.64 (m, 2H, C7),

1.94 – 1.88 (m, 2H, C8), 1.81 – 1.72 (m, 2H, C13), 1.12 (dd, *J* = 10.5, 6.3 Hz, 3H, C15), 1.06 – 1.02 (m, 3H, C15), 0.94 – 0.87 (m, 12H, C14/C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.49 (Ar), 142.48 (Ar), 128.55 (Ar), 128.51 (Ar), 128.47 (Ar), 128.47 (Ar), 128.45 (Ar), 128.42 (Ar), 125.83 (Ar), 125.81 (Ar), 125.78 (Ar), 102.13 (Ar), 100.59 (C9), 99.55 (C9), 77.50 (C12), 77.47 (C12), 76.40 (C12), 75.95 (C12), 37.78 (C8), 37.45 (C8), 37.36 (C13), 33.71 (C13), 33.68 (C13), 33.03 (C13), 32.89 (C7), 31.23 (C7), 18.90 (C15), 18.87 (C15), 18.79 (C15), 18.78 (C15), 17.71 (C14/C16), 17.62 (C14/C16), 17.30 (C14/C16), 17.10 (C14/C16), 16.72 (C14/C16), 16.50 (C14/C16), 16.21 (C14/C16), 16.12 (C14/C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 315.2300 found 315.2303. **ATR-FTIR** (cm^{-1}): 3028, 2960, 2931, 2874, 1604, 1496, 1455, 1379, 1337, 1185, 1116, 1030, 909, 888, 820, 766, 750, 734, 698, 648, 592.

(3,3-*bis*(2-chloroethoxy)propyl)benzene (**1.164**)

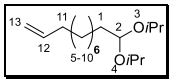


Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 692 mg, 50%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H, Ar), 7.22 – 7.18 (m, 3H, Ar), 4.64 (t, *J* = 5.8 Hz, 1H, C9), 3.89 – 3.84 (m, 2H, C12), 3.79 – 3.73 (m, 2H, C12), 3.65 (t, *J* = 5.6 Hz, 4H, C13), 2.76 – 2.70 (m, 2H, C7), 2.00 (m, 2H, C8). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.34 (Ar), 128.59 (Ar), 128.56 (Ar), 126.16 (Ar), 102.57 (Ar), 65.52 (C12), 43.43 (C13), 34.61 (C8), 30.98 (C7). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 299.0580 found 229.0582. **ATR-FTIR** (cm^{-1}): 3027, 2958, 2926, 2867, 1603, 1495, 1454, 1430, 1384, 1353, 1299, 1256, 1200, 1179, 1128, 1083, 1033, 994, 964, 909, 839, 807, 774, 731, 699, 665, 598.

1.6.2. Other acetals

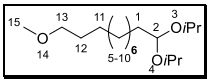
2-methyltetradec-13-en-4-ol (**1.187**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 6.3 g, 58%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, C12), 4.99 (ddd, *J* = 16.9, 3.6, 1.6 Hz, 1H, C13), 4.92 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H, C13), 4.53 (t, *J* = 5.6 Hz, 1H, C2), 3.86 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 2.06 – 2.00 (m, 2H, C11), 1.59 – 1.53 (m, 2H, C1), 1.39 – 1.31 (m, 4H, C5-10), 1.27 (s, 9H, C5-C10), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.2 Hz, 6H, *i*Pr (CH_3)). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.41 (C12), 114.24 (C13), 100.49 (C2), 67.59 (*i*Pr(C-H)), 35.58 (C1), 33.96 (C11), 29.70 (C5-10), 29.66 (C5-10), 29.57(C5-10), 29.25 (C5-10), 29.06 (C5-10), 25.05 (C5-10), 23.61 (*i*Pr(CH_3)), 22.75 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for 293.2457 $[M+Na]^+$ 293.2451 found. **ATR-FTIR** (cm^{-1}): 2971, 2925, 2855, 1641, 1464, 1379, 1368, 1327, 1276, 1261, 1128, 1021, 908, 764, 750, 724.

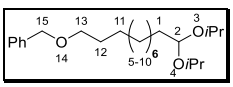
1,1-di*iso*propoxy-11-methoxyundecane (**1.232**)



Synthesized starting as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.5 Hz, 1H, C2), 3.86 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 3.36 (t, *J* = 6.7 Hz, 2H, C13), 3.33 (s, 3H, C15), 1.60 – 1.52 (m, 4H, C1/C12), 1.38 – 1.25 (m, 14H, C5-C11), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 100.59 (C2), 73.14 (C13), 67.62 (*i*Pr(C-H)), 58.67 (C15), 35.61 (C1), 29.81 (C12), 29.74 (C5-11), 29.71 (C5-11), 29.69 (C5-11), 29.67 (C5-11), 29.64 (C5-11), 26.30 (C5-11), 25.06 (C5-11), 23.62 (*i*Pr(CH_3)), 22.78 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 325.2719 found 325.2708. **ATR-FTIR** (cm^{-1}): 2971, 2925, 2855, 1463, 1380, 1327, 1276, 1261, 1120, 1019, 763, 750.

(((11,11-di*iso*propoxyundecyl)oxy)methyl)benzene (**1.230**)

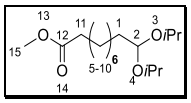


Synthesized as described in the **specific procedure**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H, Ar), 7.30 – 7.26 (m, 1H, Ar), 4.53 (t, *J* = 5.6 Hz, 1H, C2), 4.50 (s, 2H, C15), 3.86 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 3.46 (t, *J* = 6.7 Hz, 2H, C13), 1.64 – 1.59 (m, 2H, C1), 1.59

– 1.54 (m, 2H, C12), 1.37 – 1.31 (m, 4H, C5-11), 1.26 (bs, 10H, C5-11), 1.19 (d, *J* = 6.1 Hz, 3H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.1 Hz, 3H, *i*Pr(CH_3)). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.84 (Ar), 128.49 (Ar), 127.77 (Ar), 127.61 (Ar, 100.50 (C2), 72.99 (15), 70.67 (C13), 67.59 (*i*Pr(C-H)), 35.59 (C1), 29.92 (C12), 29.75 (C5-11), 29.72 (C5-11), 29.69 (C5-11), 29.62 (C5-11), 26.34 (C5-11), 25.07 (C5-11), 23.62 (*i*Pr(CH_3)), 22.76 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 401.3032 found 401.3036. **ATR-FTIR** (cm^{-1}): 2970, 2925, 2853, 1495, 1455, 1378, 1366, 1327, 1276, 1261, 1204, 1104, 1018, 911, 799, 764, 749, 697, 612.

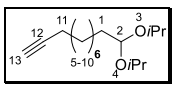
Methyl 4,4-di*iso*propoxybutanoate (**1.255**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 376 mg, 50%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.52 (t, *J* = 5.5 Hz, 1H, C2), 3.85 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 3.66 (s, 3H, C15), 2.29 (t, *J* = 7.6 Hz, 2H, C11), 1.65 – 1.58 (m, 3H, C1/C5-10), 1.57 – 1.53 (m, 2H, C5-10), 1.36 – 1.24 (m, 10H, C5-10), 1.18 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.52 (C12), 100.47 (C2), 67.61 (*i*Pr(C-H)), 51.61 (C15), 35.56 (C1), 34.25 (C11), 29.60 (C5-10), 29.54 (C5-10), 29.33 (C5-10), 29.26 (C5-10), 25.07 (C5-10), 25.01 (C5-10), 23.60 (*i*Pr(CH_3)), 22.75 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 235.2355 found 235.2352. **ATR-FTIR** (cm^{-1}): 2918, 2929, 2857, 1742, 1464, 1437, 1380, 1368, 1368, 1326, 1275, 1260, 1172, 1128, 1023, 764, 750.

11,11-di*iso*propoxyundec-1-yne (**1.236**)

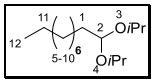


Synthesized as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.5 Hz, 1H), 3.86 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 2.20 – 2.14 (m, 2H, C11), 1.93 (t, *J* = 2.6 Hz, 1H, C13), 1.60 – 1.48 (m, 4H, C5-10), 1.41 – 1.27 (m, 10H, C5-10), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 100.55 (C2), 84.92 (C12),

68.18 (C13), 67.62 (*i*Pr(C-H)), 35.60 (C1), 29.63 (C5-10), 29.59 (C5-10), 29.18 (C5-10), 28.88 (C5-10), 28.63 (C5-10), 25.02 (C5-10), 23.62 (*i*Pr(CH_3)), 22.77 (*i*Pr(CH_3)), 18.54 (C11). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 291.2300 found 291.2287. **ATR-FTIR** (cm^{-1}): 3313, 2971, 2929, 2857, 1738, 1464, 1379, 1368, 1328, 1217, 1128, 1024, 756, 723, 677, 629.

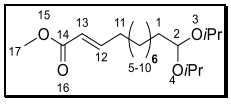
1,1-di*iso*propoxydecane (**1.256**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 240 mg, 19%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.6 Hz, 1H, C2), 3.86 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 1.59 – 1.53 (m, 2H, C1), 1.36 – 1.22 (m, 14H, C5-11), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 0.87 (t, *J* = 7.0 Hz, 3H, C12). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 100.34 (C2), 67.42 (*i*Pr(C-H)), 35.41 (C1), 31.87 (C5-11), 29.60 (C5-11), 29.54 (C5-11), 29.52 (C5-11), 29.29 (C5-11), 24.91 (C5-11), 23.44 (C5-11), 22.67 (*i*Pr(CH_3)), 22.58 (*i*Pr(CH_3)), 14.11 (C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 281.2457 found 281.2450. **ATR-FTIR** (cm^{-1}): 2969, 2924, 2855, 1465, 1379, 1327, 1174, 1129, 1016, 923, 722.

methyl (*E*)-12,12-di*iso*propoxydodec-2-enoate (**1.238**)

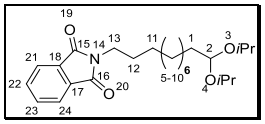


Synthesized starting as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.6, 7.2 Hz, 1H, C12), 5.81 (dt, *J* = 15.6, 1.5 Hz, 1H, C13), 4.53 (t, *J* = 5.5 Hz, 1H, C2), 3.85 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 2.19 (qd, *J* = 7.2, 1.5 Hz, 2H, C11), 1.60 – 1.53 (m, 2H, C1), 1.48 – 1.40 (m, 2H, C5-10), 1.36 – 1.25 (m, 10H, C5-10), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.34 (C14), 149.93 (C12), 120.97 (C13), 100.55 (C2), 67.63 (*i*Pr(C-H)), 51.50 (C17), 35.59 (C1), 32.35 (C11), 29.64 (C5-10), 29.61(C5-10), 29.45 (C5-10), 29.24 (C5-10), 28.15 (C5-10), 25.01 (C5-10), 23.61 (*i*Pr(CH_3)), 22.77 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated

for $[M+Na]^+$ 351.2511 found 351.2501. **ATR-FTIR** (cm^{-1}): 3594, 2971, 2928, 2856, 1728, 1658, 1437, 1368, 1271, 1216, 1176, 1129, 1026, 913, 750.

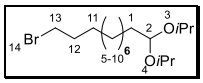
2-(11,11-di*iso*propoxyundecyl)isoindoline-1,3-dione (**1.227**)



Synthesized as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar), 4.53 (t, *J* = 5.6 Hz, 1H, C2), 3.85 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 3.70 – 3.65 (m, 2H, C13), 1.71 – 1.63 (m, 2H, C1), 1.58 – 1.53 (m, 2H, C12), 1.35 – 1.24 (m, 14H, C5-11), 1.18 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.61 (C16), 133.96 (C22/C23), 132.38 (C17/C18), 123.29 (C21/24), 100.58 (C2), 67.61 (*i*Pr(C-H)), 38.24 (C13), 35.60 (C1), 29.71 (C5-12), 29.66 (C5-12), 29.64 (C5-12), 29.60 (C5-12), 29.33 (C5-12), 28.75 (C5-12), 27.02 (C5-12), 25.06 (C5-12), 23.62 (*i*Pr(CH_3)), 22.78 *i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 440.2777 found 440.2765. **ATR-FTIR** (cm^{-1}): 2971, 2926, 2854, 1773, 1712, 1466, 1437, 1395, 1367, 1332, 1276, 1261, 1127, 1013, 764, 750, 720.

11-bromo-1,1-di*iso*propoxyundecane (**1.228**)

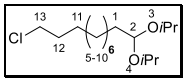


Synthesized as described in the **specific procedure**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.6 Hz, 1H), 3.86 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 3.40 (t, *J* = 6.9 Hz, 2H, C13), 1.89 – 1.81 (m, 2H, C12), 1.59 – 1.53 (m, 2H, C5-11), 1.45 – 1.38 (m, 2H, C5-11), 1.37 – 1.23 (m, 12H, C5-11), 1.19 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 100.49 (C2), 67.60 (*i*Pr(C-H)), 35.58 (C1), 34.27 (C13), 32.97 (C12), 29.70 (C11), 29.66 (C5-10), 29.60 (C5-10), 29.55 (C5-10), 28.89 (C5-10), 28.31 (C5-10), 25.04 (C5-10), 23.61 (*i*Pr(CH_3)), 22.76 (*i*Pr(CH_3)). **HRMS**

(ESI) m/z calculated for $[M+Na]^+$ 375.1675 found 375.1698. **ATR-FTIR** (cm^{-1}): 3394, 3031, 2926, 2854, 1675, 1496, 1456, 1365, 1276, 1261, 1204, 1101, 1029, 764, 750, 698, 617.

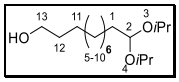
11-chloro-1,1-di*iso*propoxyundecane (**1.229**)



Synthesized as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.5 Hz, 1H, C2), 3.86 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 3.53 (t, *J* = 6.8 Hz, 2H, C13), 1.81 – 1.71 (m, 2H, C12), 1.61 – 1.53 (m, 2H, C1), 1.46 – 1.39 (m, 2H, C5-11), 1.38 – 1.24 (m, 12H, C5-11), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 100.57 (C2), 67.63 (*i*Pr(C-H)), 45.32 (C13), 35.61 (C1), 32.81 (C12), 29.70 (C5-11), 29.67 (C5-11), 29.60 (C5-11), 29.57 (C5-11), 29.02 (C5-11), 27.04 (C5-11), 25.04 (C5-11), 23.62 (*i*Pr(CH_3)), 22.77 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 329.2223 found 329.2210. **ATR-FTIR** (cm^{-1}): 2971, 2926 ,2855, 1464, 1379, 1326, 1276, 1261, 1128, 1016, 764, 750.

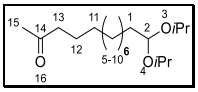
11,11-di*iso*propoxyundecan-1-ol (**1.226**)



Synthesized as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.5 Hz, 1H, C2), 3.86 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 3.66 – 3.60 (m, 2H, C13), 1.59 – 1.52 (m, 4H, C1/C12), 1.39 – 1.26 (m, 14H, C5-11), 1.19 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 100.57 (C2), 67.62 (*i*Pr(C-H)), 63.24 (C13), 35.60 (C1), 32.97 (C12), 29.72 (C5-11), 29.71 (C5-11), 29.68 (C5-11), 29.65 (C5-11), 29.55 (C5-11), 25.88 (C5-11), 25.05 (C5-11), 23.62 (*i*Pr(CH_3)), 22.77 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated 311.2562 for $[M+Na]^+$ found 311.2556. **ATR-FTIR** (cm^{-1}): 3390, 2971, 2923, 2854, 1464, 1379, 1368, 1327, 1276, 1261, 1125, 1010, 926.

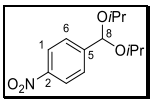
13,13-di*iso*propoxytridecan-2-one (**1.242**)



Synthesized as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (d, *J* = 5.5 Hz, 1H, C2), 3.85 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 2.49 – 2.37 (m, 2H, C13), 2.12 (s, 3H, C15), 1.59 – 1.51 (m, 4H, C1/C12), 1.35 – 1.25 (m, 14H, C5-11), 1.18 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.13 (d, *J* = 6.1 Hz, 5H, *i*Pr(CH_3)). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 209.53 (C14), 100.54 (C2), 67.61 (*i*Pr(C-H)), 43.97 (C13), 35.59 (C1), 29.99 (C15), 29.72 (C5-11), 29.67 (C5-11), 29.66 (C5-11), 29.57 (C5-11), 29.52 (C5-11), 29.32 (C5-11), 25.05 (C15), 24.02 (C12), 23.61 (*i*Pr(CH_3)), 22.76 (*i*Pr(CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 337.2719 found 337.2719. **ATR-FTIR** (cm^{-1}): 2972, 2925, 2855, 1715, 1463, 1367, 1327, 1276, 1261, 1161, 1127, 1014, 914, 731, 647.

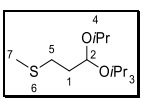
1-(di*iso*propoxymethyl)-4-nitrobenzene (**1.257**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 581 mg, 58%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 – 8.14 (m, 2H, C1), 7.71 – 7.60 (m, 2H, C6), 5.61 (s, 1H, C8), 3.92 (hept, *J* = 6.2 Hz, 2H, *i*Pr(C-H)), 1.21 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.18 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.02 (C2), 147.72 (C5), 127.91 (C6), 123.56 (C1), 98.27 (C8), 68.81 (*i*Pr(C-H)), 23.26 (*i*Pr(CH_3)), 22.60 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 276.1212 found 276.1208. **ATR-FTIR** (cm^{-1}): 2973, 2928, 1607, 1521, 1465, 1380, 1345, 1317, 1290, 1202, 1179, 1122, 1076, 1029, 966, 645, 910, 854, 748, 716, 699.

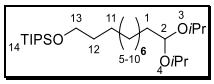
(3,3-di*iso*propoxypropyl)(methyl)sulfane (**1.258**)



Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 542 mg, 53%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.68 (t, *J* = 5.4 Hz, 1H, C2), 3.85 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 2.57 – 2.50 (m, 2H, (C5)), 2.09 (s, 3H, C7), 1.88 – 1.80 (m, 2H, C1), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 99.11 (C2), 68.28 (*i*Pr(C-H)), 35.10 (C5), 29.67 (C7), 23.51 (C1), 22.71 (*i*Pr(CH_3)), 15.61 (*i*Pr(CH_3)). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 229.1238 found 229.1238. **ATR-FTIR** (cm^{-1}): 2970, 2918, 1437, 1379, 1326, 1225, 1170, 1123, 1029, 981, 914, 888, 733.

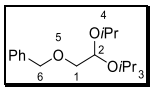
((11,11-di*iso*propoxyundecyl)oxy)tri*iso*propylsilane (**1.231**)



Synthesized as described in the **specific procedure**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (t, *J* = 5.5 Hz, 1H, C2), 3.94 – 3.81 (m, 2H, C13), 3.66 (t, *J* = 6.6 Hz, 2H, *i*Pr(C-H)), 1.61 – 1.49 (m, 4H, C1/C12), 1.39 –1.25 (m, 14H, C5-11), 1.19 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.14 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.10 – 1.02 (m, 21H, TIPS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 100.59 (C2), 67.61 (*i*Pr(C-H)), 63.69 (C13), 35.61 (C1), 33.22 (C2), 29.76 (C5-12), 29.70 (C5-12), 29.63 (C5-12), 25.99 (C5-12), 25.08 (C5-12), 23.62 (*i*Pr(CH_3)), 22.78 (*i*Pr(CH_3)), 18.19 (TIPS), 12.20 (TIPS). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 467.3896 found 467.3893. **ATR-FTIR** (cm^{-1}): 2968, 2924, 2863, 1463, 1380, 1367, 1327, 1276, 1260, 1104, 1069, 1014, 919, 882, 789, 763, 750, 721, 681, 657.

((2,2-di*iso*propoxyethoxy)methyl)benzene (**1.259**)



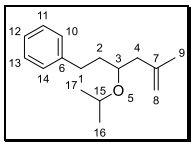
Synthesized by using general **method A** for the synthesis of acetals.

Isolated yield: 869 mg, 69%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H, Ar), 4.74 (t, *J* = 5.2 Hz, 1H, C2), 4.58 (s, 2H, C6), 3.90 (hept, *J* = 6.1 Hz, 2H, *i*Pr(C-H)), 3.48 (d, *J* = 5.2 Hz, 2H, C1), 1.21 (d, *J* = 6.2 Hz, 6H, *i*Pr(CH_3)), 1.17 (d, *J* = 6.1 Hz, 6H, *i*Pr(CH_3)). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.34 (Ar), 128.30 (Ar), 127.63 (Ar), 127.51 (Ar), 98.66 (C2), 73.40 (C6), 72.20 (C1), 68.70 (*i*Pr(C-H)), 23.27 (*i*Pr(CH_3)), 22.50 (*i*Pr(CH_3)).

HRMS (ESI) m/z calculated for $[M+Na]^+$ 275.1623 found 275.1626. **ATR-FTIR** (cm^{-1}): 2973, 2927, 2870, 1497, 1454, 1380, 1327, 1247, 1181, 1098, 1045, 984, 909, 818, 730, 647, 647, 618.

1.6.3. Intermediates

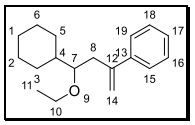
As (3-*iso*propoxy-5-methylhex-5-en-1-yl)benzene (**1.121**)



Synthesized as described in the **Stepwise investigations**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H, Ar), 7.22 – 7.15 (m, 3H, Ar), 4.83 – 4.76 (m, 1H, C8), 4.75 – 4.70 (m, 1H, C8), 3.66 (hept, *J* = 6.1 Hz, 1H, C15), 3.53 – 3.44 (m, 1H, C3), 2.81 (ddd, *J* = 13.8, 10.5, 5.5 Hz, 1H, C1), 2.61 (ddd, *J* = 13.8, 10.5, 6.0 Hz, 1H, C1), 2.31 (dd, *J* = 13.6, 5.5 Hz, 1H, C4), 2.17 (ddd, *J* = 13.6, 7.2, 0.8 Hz, 1H, C4), 1.87 – 1.78 (m, 1H,C2), 1.74 (s, 3H, C9), 1.73 – 1.65 (m, 1H,C2), 1.16 (d, *J* = 6.1 Hz, 6H, C16/C17). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.04 (Ar), 142.74 (C8), 128.54 (Ar), 128.44 (Ar), 125.79 (Ar), 112.86 (C8), 75.05 (C3), 69.87 (C15), 43.85 (C4), 36.50 (C2), 32.27 (C1), 23.26 (C15), 23.13 (C17), 22.80 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 255.1725 found 255.1717. **ATR-FTIR** (cm^{-1}): 3065, 3027, 2970, 2933, 1648, 1603, 1495, 1453, 1376, 1333, 1276, 1261, 1173, 1123, 1083, 1057, 1031, 989.

1-(4-cyclohexyl-4-ethoxybut-1-en-2-yl)-4-(trifluoromethyl)benzene (**1.121**)

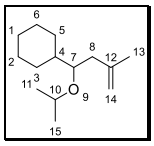


Synthesized as described in the **Stepwise investigations**. (**1.173**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H, C16/C18), 7.51 (d, *J* = 8.1 Hz, 2H, C16/C19), 5.38 (d, *J* = 1.3 Hz, 1H, C14), 5.26 (d, *J* = 1.0 Hz, 1H, C14), 3.42 – 3.25 (m, 2H, C10), 3.07 – 3.00 (m, 1H, C7), 2.74 (ddd, *J* = 14.5, 4.0, 0.9 Hz, 1H, C4), 2.59 (ddd, *J* = 14.5, 8.6, 0.9 Hz, 1H, C4), 1.80 – 1.71 (m, 3H, Cy), 1.70 – 1.62 (m, 2H, Cy), 1.50 – 1.40 (m, 1H, Cy), 1.31 – 1.06 (m, 5H, Cy), 1.03 (t, *J* = 7.0 Hz, 3H, C11). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.78 (C13), 145.44 (C12), 129.27 (q, *J* = 32.5 Hz, C17) 126.72 (C15/C19), 125.36 (q, *J* = 3.8

Hz, C16/C18), 124.38 (q, *J* = 273.34 Hz, C20), 116.66 (C14), 82.83 (C7), 66.20 (C10), 42.24 (C4), 38.04 (C8), 29.27 (Cy), 28.58 (Cy), 26.79 (Cy), 26.56 (Cy), 26.54 (Cy), 15.60 (C11). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 349.1755 found 349.1749. **ATR-FTIR** (cm^{-1}): 2927, 2854, 1617, 1450, 1405, 1323, 1165, 1167, 1066, 1015, 906, 847, 732, 648, 590.

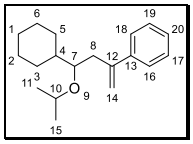
(1-*iso*propoxy-3-methylbut-3-en-1-yl)cyclohexane (**1.124**)



Synthesized as described in the **Stepwise investigations**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 7.2, 1.1 Hz, 2H, C14), 3.58 (hept, *J* = 6.1 Hz, 1H, C10), 3.26 – 3.17 (m, 1H, C7), 2.16 (qd, *J* = 13.9, 6.1 Hz, 2H, C8), 1.85 – 1.58 (m, 8H ,C13), 1.46 – 1.33 (m, 1H, Cy), 1.29 – 1.13 (m, 4H, Cy), 1.12 (d, *J* = 6.1 Hz, 3H, C11), 1.10 (d, *J* = 6.1 Hz, 3H, C15), 1.08 – 0.80 (m, 1H, Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.81 (C12), 112.49 (C14), 79.96 (C7), 70.40 (C10), 41.87 (C13), 40.77 (C8), 29.60 (Cy), 28.28 (Cy), 26.90 (Cy), 26.73 (Cy), 26.67 (Cy), 23.26 (C4), 23.11 (C11), 22.81 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 219.1719 found 219.1717. **ATR-FTIR** (cm^{-1}): 2928, 2852, 1619, 1447, 1401, 1327, 1165, 1167, 1066, 1015, 906, 847, 732, 648, 590.

(4-cyclohexyl-4-*iso*propoxybut-1-en-2-yl)benzene (**1.152**)

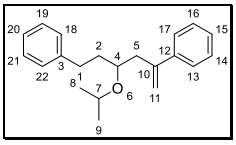


Synthesized as described in the **Stepwise investigations**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 3.3, 1.9 Hz, 2H, Ar), 7.36 – 7.30 (m, 2H, Ar), 7.29 – 7.22 (m, 1H, Ar), 5.31 (d, *J* = 1.7 Hz, 1H, C14), 5.15 (d, *J* = 1.3 Hz, 1H, C14), 3.45 (hept, *J* = 6.1 Hz, 1H, C10), 3.14 (dt, *J* = 7.9, 4.6 Hz, 1H, C7), 2.76 (ddd, *J* = 14.3, 4.8, 1.0 Hz, 1H, C8), 2.55 (ddd, *J* = 14.3, 7.8, 0.7 Hz, 1H, C8), 1.81 – 1.60 (m, 5H, Cy), 1.41 (ddd, *J* = 15.4, 7.8, 3.7 Hz, 1H, C4), 1.30 – 1.06 (m, 5H, Cy), 1.02 (d, *J* = 6.1 Hz, 3H,

C11), 0.98 (d, *J* = 6.1 Hz, 3H, C15). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.43 (Ar), 141.55 (Ar), 128.42 (Ar), 127.40 (Ar), 126.46 (C12), 114.97 (C14), 79.87 (C7), 70.64 (C10), 42.33 (C8), 38.59 (C4), 29.37 (Cy), 28.41 (Cy), 26.89 (Cy), 26.76 (Cy), 26.71 (Cy), 23.05 (C11), 22.89 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 295.2032 found 295.2025.

(3-*iso*propoxyhex-5-ene-1,5-diyl)dibenzene (**1.154**)

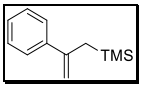


Synthesized as described in the **Stepwise investigations**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H, Ar), 7.36 – 7.28 (m, 3H, Ar), 7.25 – 7.10 (m, 5H, Ar), 5.30 (d, *J* = 1.6 Hz, 1H, C11), 5.13 (d, *J* = 1.3 Hz, 1H, C11), 3.56 (hept, *J* = 6.1 Hz, 1H, C7), 3.45 – 3.35 (m, 1H, C4), 2.84 (ddd, *J* = 14.1, 6.1, 1.0 Hz, 1H, C5), 2.75 (ddd, *J* = 13.9, 10.6, 5.5 Hz, 1H, C5), 2.66 – 2.50 (m, 2H, C1), 1.89 – 1.78 (m, 1H, C2), 1.78 – 1.70 (m, 1H, C2), 1.08 (d, *J* = 6.1 Hz, 3H, C8), 1.06 (d, *J* = 6.1 Hz, 3H, C9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.93 (Ar), 142.64 (Ar), 141.39 (Ar), 128.50 (Ar), 128.48 (Ar), 128.42 (Ar), 127.56 (Ar), 126.41 (Ar), 125.77 (C10), 115.20 (C11), 75.14 (C4), 70.12 (C7), 41.71 (C5), 36.55 (C2), 31.80 (C1), 23.18 (C8), 22.84 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 317.1876 found 317.1881.

1.6.4. Allylsilanes

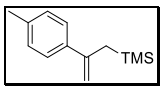
Trimethyl(2-phenylallyl)silane (**1.157**)



Synthesized by using general **method I** for the synthesis of allylsilanes.

Isolated yield: 2.6 g, 68%. Spectroscopic properties match with the literature.[169]

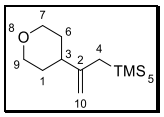
trimethyl(2-(p-tolyl)allyl)silane (**1.198**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent. Protodesilylation if Et_3N is not used, and rearrangement to vinylsilane on aluminiumoxide (active basic or neutral).

Isolated yield: 320 mg, 54%. Spectroscopic properties match with the literature.[169]

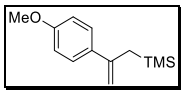
trimethyl(2-(tetrahydro-2H-pyran-4-yl)allyl)silane (**1.253**)



Synthesized starting from the corresponding ester described in the **method IV**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.61 (t, *J* = 1.2 Hz, 1H, C10), 4.56 (d, *J* = 0.8 Hz, 1H, C10), 4.05 – 3.97 (m, 2H, C7/C9), 3.38 (td, *J* = 12.2, 1.7 Hz, 2H, C7/C9), 1.89 (tt, *J* = 11.8, 3.2 Hz, 1H, C3), 1.71 – 1.65 (m, 2H, C1/C6), 1.54 (d, *J* = 0.8 Hz, 2H, C1/C6), 1.53 – 1.45 (m, 2H, C4), 0.02 (s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.15 (C2), 105.78 (C10), 68.62 (C7/C9), 42.75 (C3), 32.29 (C1/C6), 25.61 (C4), -1.10 (TMS). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 199.1518 found 199.1507. **ATR-FTIR** (cm^{-1}): 3084, 2953, 2917, 2837, 2755, 2692, 1630, 1467, 1442, 1419, 1385, 1279, 1246, 1158, 1137, 1121, 1096, 1085, 1041, 1012, 980, 969, 905, 837.

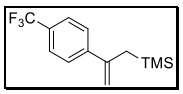
(2-(4-methoxyphenyl)allyl)trimethylsilane (**1.206**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on active basic aluminiumoxide with heptanes as the eluent. Protodesilylation on silica.

Isolated yield: 480 mg, 47%. Spectroscopic properties match with the literature.[172]

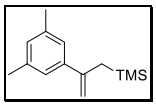
trimethyl(2-(4-(trifluoromethyl)phenyl)allyl)silane (**1.204**)



Synthesized by using general **method III** for the synthesis of allylsilanes. Purification on silica with heptanes as the eluent.

Isolated yield: 710 mg, 55%. Spectroscopic properties match with the literature.[177]

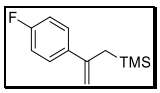
(2-(3,5-dimethylphenyl)allyl)trimethylsilane (**1.260**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent.

Compound isolated, no yield determined. Spectroscopic properties match with the literature.[178]

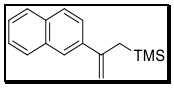
(2-(4-fluorophenyl)allyl)trimethylsilane (**1.261**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent.

Isolated yield: 670 mg, 80%. Spectroscopic properties match with the literature.[179]

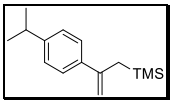
trimethyl(2-(naphthalen-2-yl)allyl)silane (**1.262**)



Synthesized by using general **method III** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent.

Isolated yield: 120 mg, 10%. Spectroscopic properties match with the literature.[172]

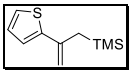
(2-(4-isopropylphenyl)allyl)trimethylsilane (**1.263**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent.

Isolated yield: 110 mg, 10%. Spectroscopic properties match with the literature.[180]

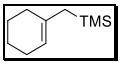
trimethyl(2-(thiophen-2-yl)allyl)silane (**1.264**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent.

Isolated yield: 85 mg, 23%. Spectroscopic properties match with the literature.[181]

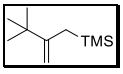
(cyclohex-1-en-1-ylmethyl)trimethylsilane (**1.194**)



Synthesized by using general **method II** for the synthesis of allylsilanes. Purification on silica with heptanes containing 1% Et_3N as the eluent.

Isolated yield: 792 mg, 47%. Spectroscopic properties match with the literature.[171]

(3,3-dimethyl-2-methylenebutyl)trimethylsilane (**1.190**)

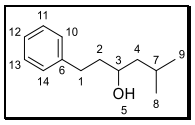


Synthesized by using general **method I** for the synthesis of allylsilanes. Purification on silica with pentanes containing 1% Et_3N as the eluent.

Compound isolated, no yield determined. Spectroscopic properties match with the literature.[182]

1.6.5. Products

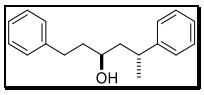
5-methyl-1-phenylhexan-3-ol (**1.122**)



Synthesized by using the **general procedure for the product scope**.

Isolated yield: 36 mg, 63%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H, Ar), 7.25 – 7.18 (m, 3H, Ar), 3.78 – 3.71 (m, 1H, C3), 2.82 (ddd, *J* = 13.8, 10.1, 5.7 Hz, 1H, C1), 2.70 (ddd, *J* = 13.8, 10.1, 6.4 Hz, 1H, C1), 1.86 – 1.71 (m, 3H, C2/C7), 1.49 – 1.41 (m, 1H), 1.36 – 1.26 (m, 2H, C4), 0.94 (d, *J* = 6.6 Hz, 3H, C8), 0.93 (d, *J* = 6.6 Hz, 3H, C9). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.22 (Ar), 128.41 (Ar), 128.22 (Ar), 125.81 (Ar), 69.49 (C3), 46.84 (C4), 39.72 (C2), 32.10 (C1), 24.65 (C7), 23.49 (C9), 22.11 (8). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 215.1412 found 215.1405. **ATR-FTIR** (cm^{-1}): 3325, 3027, 2953, 2925, 2867, 1603, 1495, 1454, 1384, 1367, 1276, 1170, 1138, 1085, 1054, 1031, 998, 919, 845, 748, 698.

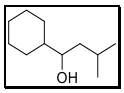
(3*RS*,5*RS*)-1,5-diphenylhexan-3-ol (**1.155**)



Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 41 mg, 54%. 5.1 : 1 d.r. Spectroscopic properties match with the literature.[183]

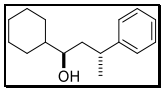
1-cyclohexyl-3-methylbutan-1-ol (**1.125**)



Synthesized by using the **general procedure for the product scope.**

Isolated yield: 35 mg, 69%. Spectroscopic properties match with the literature.[184]

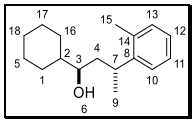
(*1RS*,3*SR*)-1-cyclohexyl-3-phenylbutan-1-ol (**1.153**)



Synthesized by using the **general procedure for the allylsilane scope** on a 0.15 mmol scale.

Isolated yield: 23 mg, 64%. 5.1 : 1 d.r. Spectroscopic properties match with the literature.[185]

1-cyclohexyl-3-(*o*-tolyl)butan-1-ol (**1.184**)

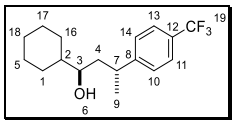


Synthesized by using the **general procedure for the allylsilane scope.**

Isolated yield: 30 mg, 41%. 1.9 : 1 d.r. **Major isomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 4H, Ar), 3.56 (bs, 1H, C3), 3.35 – 3.25 (m, 1H, C7), 2.43 (s, 3H, C15), 1.98 – 1.66 (m, 7H, Cy/C4), 1.41 – 0.93 (m, 10H, Cy/C9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.23 (C14), 135.21 (C8), 130.53 (Ar), 126.39 (Ar), 125.79 (Ar), 125.57 (Ar), 74.49 (C3), 44.42 (C2), 42.59 (C4), 31.23 (C7), 29.38 (Cy), 27.83 (Cy), 26.71 (Cy), 26.50 (Cy), 26.38 (Cy), 20.76 (C9), 19.65 (C18).

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 4H, Ar), 3.46 – 3.36 (m, 1H, C3), 3.15 (bs, 1H, C7), 2.44 (s, 3H, C18), 1.98 – 1.66 (m, 7H, C4/Cy), 1.41 – 0.93 (m, 10H, Cy/C9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.07 (C14), 136.05 (C8), 130.42 (Ar), 126.34 (Ar), 125.66 (Ar), 125.48 (Ar), 74.18 (C3), 44.49 (C2), 41.86 (C4), 31.23 (C7), 29.18 (Cy), 27.83 (Cy), 26.68 (Cy), 26.46 (Cy), 26.33 (Cy), 23.32 (C9), 19.81 (C18). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 269.1881 found 269.1865. **ATR-FTIR** (cm^{-1}): 2924, 2852, 1489, 1450, 1377, 1292, 1178, 1088, 1033, 977, 907, 834, 759, 727, 648.

As 1-cyclohexyl-3-(4-(trifluoromethyl)phenyl)butan-1-ol (**1.182**)



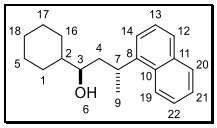
Synthesized by using the **general procedure for the allylsilane scope.**

Isolated yield: 17 mg, 19%. 1.0 : 1 d.r. **Major isomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H, C11/C13), 7.32 (t, *J* = 8.0 Hz, 2H, C10/C14), 3.50 – 3.44 (m, 1H, C3), 3.09 – 3.01 (m, 1H, C7), 1.82 – 1.57 (m, 7H, C4/Cy), 1.36 – 0.98 (m, 10H, C9/Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.46 (C8), 128.24 (q, *J* = 32.2 Hz,

C12) 127.38 (Ar), 125.53 (p, *J* = 3.8 Hz, Ar), 124.33 (q, *J* = 271.7 Hz, C18), 74.09 (C3), 44.26 (C2), 42.94 (C4), 36.47 (C7), 29.41 (Cy), 27.71 (Cy), 26.66 (Cy), 26.47 (Cy), 26.33 (Cy), 21.10 (C9).

Minor isomer: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H, C11/C13)), 7.32 (t, *J* = 8.0 Hz, 2H, C10/C14), 3.17 – 3.09 (m, 1H, C3), 3.03 – 2.96 (m, 1H, C7), 1.82 – 1.57 (m, 7H, C4/Cy), 1.36 – 0.98 (m, 10H, C9/Cy). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 151.18 (C8), 128.29 (q, *J* = 32.2 Hz, C12), 127.71 (Ar), 125.53 (p, *J* = 3.8 Hz, Ar), 124.35 (q, *J* = 271.7 Hz, C18), 73.78 (C3), 44.45 (C2), 42.34 (C4), 36.66 (C7), 29.13 (Cy), 27.86 (Cy), 26.62 (Cy), 26.39 (Cy), 26.27 (Cy), 23.54 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 323.1599 found 323.1593. **ATR-FTIR** (cm^{-1}): 2926, 2854, 1619, 1451, 1420, 1324, 1324, 1163, 1121, 1068, 1016, 978, 907, 838, 731, 648, 607.

1-cyclohexyl-3-(naphthalen-1-yl)butan-1-ol (**1.185**)



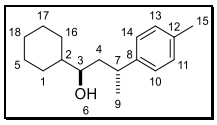
Synthesized by using the **general procedure for the allylsilane scope.**

Isolated yield: 40 mg, 47%. 2.6 : 1 d.r. **Major isomer:** ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 11.8 Hz, 1H, Ar), 7.86 (d, *J* = 9.5 Hz, 1H, Ar), 7.72 (d, *J* = 7.7 Hz, 1H, Ar), 7.57 – 7.34 (m, 5H, Ar), 4.04 – 3.86 (m, 1H, C3), 3.69 – 3.53 (m, 1H, C7), 1.95 – 1.58 (m, 6H, C4/Cy), 1.44 (d, *J* = 6.8 Hz, 3H, C9), 1.38 – 0.86 (m, 8H, Cy). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 144.32 (Ar), 134.13 (Ar), 131.47 (Ar), 129.03 (Ar), 126.53 (Ar), 125.96 (Ar), 125.70 (Ar), 125.46 (Ar), 123.48 (Ar), 122.63 (Ar), 74.43 (C3), 44.59 (C2), 43.04 (C4), 30.20 (C7), 29.32 (Cy), 28.00 (Cy), 26.68 (Cy), 26.44 (Cy), 26.34 (Cy), 20.49 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 305.1876 found 305.1881. **ATR-FTIR** (cm^{-1}): 2925, 2852, 1510, 1450, 1395, 1061, 1024, 996, 977, 905, 798, 778, 726, 648, 588.

Minor isomer: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 11.8 Hz, 1H, Ar), 7.86 (d, *J* = 9.5 Hz, 1H, Ar), 7.72 (d, *J* = 7.7 Hz, 1H, Ar), 7.57 – 7.34 (m, 5H, Ar), 4.04 – 3.86 (m, 1H, C3), 3.23 – 3.05 (m, 1H, C7), 1.95 – 1.58 (m,

7H, C4/Cy), 1.41 (d, *J* = 7.0 Hz, 3H, C9), 1.38 – 0.86 (m, 8H, Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.33 (Ar), 132.23 (Ar), 129.05 (Ar), 126.45 (Ar), 125.93 (Ar), 125.78 (Ar), 125.49 (Ar), 123.39 (Ar), 74.10 (C3), 44.46 (C2), 42.14 (C4), 30.20 (C7), 29.21 (Cy), 27.84 (Cy), 26.68 (Cy), 26.44 (Cy), 26.32 (Cy), 23.90 (C9).

1-cyclohexyl-3-(p-tolyl)butan-1-ol (**1.176**)

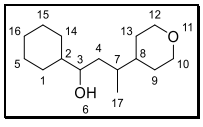


Synthesized by using the **general procedure for the allylsilane scope.**

Isolated yield: 33 mg, 45%. 5.0 : 1 d.r. **Major diastereoisomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (s, 4H, Ar), 3.46 (dt, *J* = 7.9, 4.9 Hz, 1H, C3), 2.94 – 2.84 (m, 1H, C7), 2.32 (s, 3H, C15), 1.82 – 1.72 (m, 3H, C1/Cy), 1.72 – 1.58 (m, 4H, C4/Cy), 1.25 (d, *J* = 6.9 Hz, 3H, C9), 1.44 – 0.86 (m, 10H, C4/Cy). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.01 (C8), 135.69 (C12), 129.38 (C11/C13), 126.88 (C10/C14), 74.56 (C3), 44.10 (C2), 43.29 (C4), 36.51 (C7), 29.36 (C1), 27.62 (C16), 26.70 (C18), 26.51 (C17), 26.37 (C5), 21.74 (C9), 21.13 (C15).

Minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 4H, Ar), 3.08 (ddd, *J* = 10.0, 5.3, 2.5 Hz, 1H, C3), 3.02 – 2.94 (m, 1H, C7), 2.32 (s, 3H, C15), 1.82 – 1.72 (m, 3H), 1.72 – 1.58 (m, 4H, C4/Cy), 1.25 (d, *J* = 6.9 Hz, 3H, C9), 1.44 – 0.86 (m, 10H, C4/Cy). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.80 (C8), 135.56 (C12), 129.27 (C11/C13), 127.18 (C10/C14), 73.86 (C3), 44.30 (C2), 42.44 (C4), 36.21 (C7), 29.13 (C1), 27.85 (C16), 26.66 (C18), 26.44 (C17), 26.32 (C5), 23.97 (C9), 21.16 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 269.1881 found 269.1868. **ATR-FTIR** (cm^{-1}): 3358, 3018, 2921, 2851, 2668, 1514, 1449, 1374, 1305, 1276, 1262, 1183, 1109, 1088, 1062, 1042, 1017, 978, 943, 892, 842, 815.

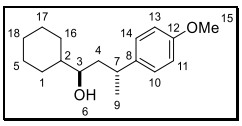
1-cyclohexyl-3-(tetrahydro-2H-pyran-4-yl)butan-1-ol (**1.183**)



Synthesized by using the **general procedure for the allylsilane scope** on a 0.15 mmol scale.

Isolated yield: 15 mg, 69%. 1.0 : 1 d.r. The characterization is reported as a 1:1 mixture of the two diastereoisomers. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.05 – 3.91 (m, 2H, C10/C12), 3.50 – 3.41 (m, 1H, C10), 3.40 – 3.28 (m, 2H, C12/C3), 1.86 – 1.71 (m, 3H, sp^3-C-H), 1.70 – 1.37 (m, 9H, sp^3-C-H), 1.36 – 1.07 (m, 7H, sp^3-C-H), 1.07 – 0.94 (m, 1H, sp^3-C-H), 0.90 (d, *J* = 6.6 Hz, 1.5H, C17), 0.87 (d, *J* = 6.8 Hz, 1.5H, C17). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 74.53 (C3), 73.76 (C3), 68.69 (C12), 68.65 (C12), 68.61 (C10), 68.58 (C10), 44.72 (C2), 43.62 (C2), 41.26 (C4), 39.20 (C4), 38.37 (C8), 38.33 (C8), 34.53 (C7), 33.88 (C7), 30.93 (C9), 30.49 (C9), 29.62 (C13), 29.39 (C13), 29.29 (C1), 28.16 (C1), 28.10 (C14), 27.04 (C14), 26.68 (16), 26.54 (C16), 26.44 (C15), 26.33 (C15), 26.33 (C5), 16.82 (C17), 15.62 (C17). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 263.1987 found 263.1974. **ATR-FTIR** (cm^{-1}): 3433, 2920, 2848, 1448, 1380, 1308, 1275, 1263, 1238, 1182, 1145, 1034, 1064, 1043, 1016, 980, 945, 911, 892, 873, 839.

(1*RS*,3*SR*)-1-cyclohexyl-3-(4-methoxyphenyl)butan-1-ol (**1.175**)



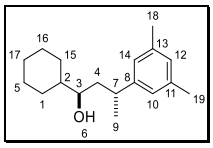
Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 28 mg, 35%. 5.0 : 1 d.r. **Major diastereoisomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 – 7.08 (m, 2H, C10/C14), 6.88 – 6.81 (m, 2H, C11/C13), 3.79 (s, 3H, C15), 3.50 – 3.41 (m, 1H, C3), 2.93 – 2.82 (m, 1H, C7), 1.82 – 1.70 (m, 3H, C4/Cy), 1.69 – 1.54 (m, 4H, C4/Cy), 1.24 (d, *J* = 6.9 Hz, 3H, C9), 1.36 – 0.89 (m, 7H, Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.03 (C12), 140.17 (C8), 127.89 (C14), 114.11 (C10), 74.61 (C3), 55.40 (C15), 44.15 (C2), 43.43 (C4), 36.15 (C7), 29.41 (C15), 27.66 (C1), 26.73 (C17), 26.54 (C5), 26.40 (C16), 21.92 (C9).

Minor diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.08 (m, 2H, C10/C14), 6.88 – 6.81 (m, 2H, C11/C13), 3.79 (s, 3H, C15), 3.13 – 3.02 (m, 1H, C3), 3.02 – 2.93 (m, 1H, C7), 1.82 – 1.70 (m, 3H, C4/Cy), 1.69 – 1.54 (m, 4H, C4/Cy), 1.24 (d, *J* = 6.9 Hz, 3H, C9), 1.36 – 0.89 (m, 7H, Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.98 (C12), 138.97 (C8), 128.16 (C14), 113.99 (C10), 73.90 (C3), 55.40 (C15), 44.35 (C2), 42.72 (C4),

35.84 (C7), 29.19 (C15), 27.92 (C1), 26.69 (C17), 26.46 (C5), 26.34 (C16), 23.97 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 285.1830 found 285.1814. **ATR-FTIR** (cm^{-1}): 3394, 2921, 2850, 1611,1583, 1511, 1449, 1374, 1300, 1244, 1177, 1087, 1038, 978, 944, 892, 828, 808.

1-cyclohexyl-3-(3,5-dimethylphenyl)butan-1-ol (**1.179**)

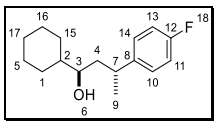


Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 33 mg, 43%. 5.0 : 1 d.r. **Major diastereoisomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.86 – 6.80 (m, 3H, Ar), 3.51 – 3.42 (m, 1H, C3), 2.88 – 2.80 (m, 1H, C7), 2.30 (s, 6H, C18/C19), 1.82 – 1.70 (m, 3H, Cy), 1.70 – 1.58 (m, 4H, Cy/C4), 1.35 – 1.28 (m, 1H, Cy), 1.24 (d, *J* = 6.9 Hz, 3H, C9), 1.22 – 0.86 (m, 6H, Cy). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.02 (C8), 138.17 (C11/C13), 127.93 (C12), 124.82 (C10/C14), 74.63 (C3), 44.17 (C2), 43.29 (C4), 36.86 (C7), 29.34 (C1), 27.70 (C15), 26.70 (C17), 26.51 (C16), 26.38 (C5), 21.65 (C28/C19), 21.51 (C9).

Minor diastereoisomer: ^{1}H NMR (600 MHz, CDCl3) δ 6.86 – 6.80 (m, 3H, Ar), 3.14 – 3.05 (m, 1H, C3), 2.97 – 2.89 (m, 1H, C7), 2.30 (s, 6H, C18/C19), 1.82 – 1.70 (m, 3H, Cy), 1.70 – 1.58 (m, 4H, Cy/C4), 1.35 – 1.28 (m, 1H, Cy), 1.24 (d, *J* = 6.9 Hz, 3H, C9), 1.22 – 0.86 (m, 6H, Cy). **^{13}C NMR** (151 MHz, CDCl3) δ 146.86 (C8), 137.95 (C11/13), 127.83 (C12), 125.11 (C10/C14), 73.85 (C3), 44.25 (C2), 42.37 (C4), 36.53 (C7), 29.15 (C1), 27.76 (C15), 26.67 (C17), 26.46 (C16), 26.34 (C5), 23.96 (C28/C19), 21.54 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 283.2038 found 283.2030. **ATR-FTIR** (cm^{-1}): 3365, 3014, 2920, 2731, 1727, 1604, 1449, 1374, 1219, 1183, 1122, 1087, 1063, 1039, 978, 944, 892, 846, 773, 707.

1-cyclohexyl-3-(4-fluorophenyl)butan-1-ol (**1.180**)

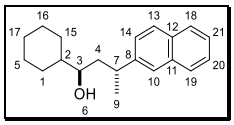


Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 44 mg, 59%. 7.3 : 1 d.r. **Major diastereoisomer: ^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H, Ar), 6.98 (t, *J* = 8.7 Hz, 2H, Ar), 3.48 – 3.43 (m, 1H, C3), 2.97 – 2.90 (m, 1H, Cy), 1.81 – 1.70 (m, 3H, Cy/C4), 1.69 – 1.56 (m, 4H, Cy), 1.33 – 1.27 (m, 1H, Cy), 1.24 (d, *J* = 6.9 Hz, 3H, C9), 1.22 – 0.86 (m, 6H, Cy). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 162.04 (Ar), 143.84 (d, *J* = 3.1 Hz, Ar), 128.32 (d, *J* = 7.8 Hz, Ar), 115.32 (d, *J* = 20.9 Hz, Ar), 74.29 (C3), 44.15 (C2), 43.27 (C4), 35.97 (C7), 29.40 (C1), 27.65 (C15), 26.68 (C17), 26.49 (C5), 26.35 (C16), 21.64 (C9).

Minor diastereoisomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H, Ar), 6.98 (t, *J* = 8.7 Hz, 2H, Ar), 3.04 – 2.98 (m, 1H, C3), 2.97 – 2.90 (m, 1H, C7), 1.81 – 1.70 (m, 3H, Cy), 1.69 – 1.56 (m, 4H, C4/Cy), 1.33 – 1.27 (m, 1H, Cy), 1.24 (d, *J* = 6.9 Hz, 3H, C9), 1.22 – 0.86 (m, 6H, Cy). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 160.65 (Ar), 142.51 (*J* = 3.1 Hz, Ar), 128.62 (d, *J* = 7.9 Hz, Ar), 115.27 (d, *J* = 21 Hz, Ar), 73.81 (C3), 44.36 (C2), 42.67 (C4), 35.97 (C7), 29.14 (C1), 27.87 (C15), 26.63 (C17), 26.40 (C5), 26.28 (C16), 23.87 (C9). **HRMS (ESI)** m/z calculated for $[M+Na]^+$ 273.1631 found 273.1621. **ATR-FTIR** (cm^{-1}): 3367, 2924, 2852, 1603, 1509, 1449, 1417, 1375, 1297, 1158, 1121, 1087, 1062, 1014, 977, 946, 893, 831, 772, 667.

1-cyclohexyl-3-(naphthalen-2-yl)butan-1-ol (**1.178**)

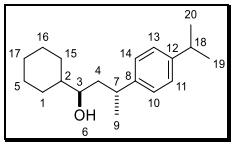


Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 34 mg, 40%. 5.0 : 1 d.r. **Major diastereoisomer: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 3H, Ar), 7.66 (s, 1H, Ar), 7.48 – 7.35 (m, 3H, Ar), 3.56 – 3.47 (m, 1H, C3), 3.15 – 3.08 (m, 1H, C7), 1.90 – 1.57 (m, 7H, C4/Cy), 1.35 (d, *J* = 6.9 Hz, 3H, C9), 1.31 – 0.86 (m, 7H, Cy). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.58 (Ar), 133.77 (Ar), 132.29 (Ar), 128.27 (Ar), 127.72 (Ar), 127.68 (Ar), 126.06 (Ar), 125.92 (Ar), 125.33 (Ar), 125.00 (Ar), 74.43 (C3), 44.12 (C2), 43.04 (C4), 36.90 (C7), 29.39 (C1), 27.62 (C15), 26.68 (C17), 26.49 (C16), 26.36 (C5), 21.58 (C9).

Minor diastereoisomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 3H, Ar), 7.65 (s, 1H, Ar), 7.48 – 7.35 (m, 3H, Ar), 3.25 – 3.17 (m, 1H, C3), 3.08 – 3.03 (m, 1H, C7), 1.90 – 1.57 (m, 7H, C4/Cy), 1.35 (d, *J* = 6.9 Hz, 3H, C9), 1.31 – 0.86 (m, 7H, Cy). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.34 (Ar), 133.72 (Ar), 132.34 (Ar), 128.24 (Ar), 127.72 (Ar), 127.68 (Ar), 126.01 (Ar), 125.85 (Ar), 125.69 (Ar), 125.30 (Ar), 73.85 (C3), 44.33 (C2), 42.35 (C4), 36.81 (C7), 29.11 (C1), 27.85 (C15), 26.62 (C17), 26.40 (C16), 26.28 (C5), 23.79 (C9). **HRMS (ESI)** m/z calculated for $[M+Na]^+$ 305.1881 found 305.1874. **ATR-FTIR** (cm^{-1}): 3367, 3052, 2921, 2850, 1633, 1600, 1555, 1507, 1449, 1380, 1270, 1219, 1183, 1143, 1128, 1087, 1062, 1019, 978, 950, 891, 854, 837, 817, 773, 745, 661, 623.

1-cyclohexyl-3-(4-isopropylphenyl)butan-1-ol (**1.177**)



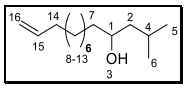
Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 43 mg, 41%. 5.1 : 1 d.r. **Major diastereoisomer:** ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 4H, Ar), 3.51 – 3.43 (m, 1H, C3), 2.93 – 2.84 (m, 2H, C7/C18), 1.81 – 1.71 (m, 3H, Cy), 1.71 – 1.59 (m, 4H. C4/Cy), 1.34 – 1.28 (m, 1H ,Cy), 1.25 (d, *J* = 7.0 Hz, 3H, C9), 1.24 (d, *J* = 6.9 Hz, 6H, C19/C20), 1.22 – 0.88 (m, 6H, Cy). ^{13}C NMR (176 MHz, $CDCl_3$) δ 146.69 (C12), 145.33 (C8), 126.90 (C11/C13), 126.71 (C10/C14), 74.62 (C3), 44.21 (C2), 43.40 (C4), 36.55 (C7), 33.80 (C18), 29.38 (C1), 27.71 (C15), 26.73 (C17), 26.54 (C16), 26.40 (C5), 24.20 (C19), 24.17 (C20), 21.65 (C9).

Minor diastereoisomer: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 4H, Ar), 3.12 – 3.07 (m, 1H, C3), 3.00 – 2.94 (m, 1H, C7), 2.93 – 2.84 (m, 1H, C18), 1.81 – 1.71 (m, 3H, Cy), 1.71 – 1.59 (m, 4H, C4/Cy), 1.34 – 1.28 (m, 1H, Cy), 1.25 (d, *J* = 7.0 Hz, 3H, C9), 1.24 (d, *J* = 6.9 Hz, 6H, C19/C20), 1.22 – 0.88 (m, 6H, Cy). ^{13}C NMR (176 MHz, $CDCl_3$) δ 146.52 (C12), 144.10 (C8), 127.13 (C11/C13), 126.58 (C10/C14), 73.88 (C3), 44.30 (C2), 42.50 (C4), 36.26 (C7), 33.80 (C18), 29.20 (C1), 27.81 (C15), 26.70 (C17), 26.48 (C16), 26.36 (C5), 24.20

(C19), 24.17 (C20), 23.90 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 267.2194 found 297.2186. **ATR-FTIR** (cm^{-1}): 3366, 3022, 2957, 2923, 2852, 1674, 1604, 1510, 1450, 1419, 1376, 1299, 1220, 1180, 1087, 1055, 1016, 978, 944, 892, 828, 773, 700.

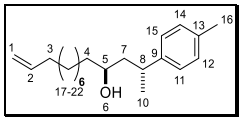
2-methyltetradec-13-en-4-ol (**1.135**)



Synthesized by using the **general procedure for the product scope**.

Isolated yield: 50 mg, 73%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.86 – 5.77 (m, 1H, C15), 4.99 (dd, *J* = 17.1, 1.7 Hz, 1H, C16), 4.93 (dd, *J* = 10.2, 0.8 Hz, 1H, C16), 3.67 (s, 1H, C1), 2.04 (dd, *J* = 14.4, 7.0 Hz, 2H, C14), 1.81 – 1.72 (m, 1H, C4), 1.47 – 1.33 (m, 6H, C8-13/C2/C7), 1.28 (bs, 9H, C8-13), 1.25 – 1.20 (m, 2H, C8-13/C2), 0.92 (d, *J* = 7.0 Hz, 3H, C6), 0.91 (d, *J* = 7.0 Hz, 3H, C5). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.40 (C15), 114.26 (C16), 70.12 (C1), 46.94 (C2), 38.22 (C7), 33.96 (C14), 29.83 (C8-13), 29.72 (C8-13), 29.58 (C8-13), 29.49 (C8-13), 29.06 (C8-13), 25.76 (C8-13), 24.76 (C4), 23.68 (C6), 22.20 (C5). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 249.2194 found 249.2194. **ATR-FTIR** (cm^{-1}): 3332, 2953, 2924, 2853, 1641, 1465, 1384, 1366, 1276, 1169, 1139, 992, 950, 908, 834, 764, 750, 723, 636.

2-(p-tolyl)tetradec-13-en-4-ol (**1.174**)



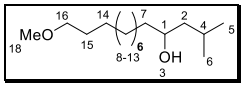
Synthesized by using the **general procedure for the allylsilane scope**.

Isolated yield: 36.4 mg, 40%. 4.1 : 1 d.r. **Major diastereoisomer: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 4H, Ar), 5.92 – 5.72 (m, 1H, C2), 5.08 – 4.87 (m, 2H, C1), 3.73 – 3.53 (m, 1H, C5), 2.93 – 2.82 (m, 1H, C8), 2.32 (s, 3H, C16), 2.08 – 1.99 (m, 2H, C3), 1.78 – 1.61 (m, 2H, C7), 1.50 – 1.33 (m, 5H, C4/C17-22), 1.32 – 1.19 (m, 12H, C17-22). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.65 (C9), 139.38 (C2), 135.73 (C13), 129.40

(C12/C14), 126.89 (C11/C15), 114.26 (C1), 70.51 (C5), 46.47 (C7), 37.90 (C3), 36.61 (C8), 33.95 (C17-22), 29.79 (C17-22), 29.68 (C17-22), 29.57 (C17-22), 29.26 (C17-22), 25.60 (C17-22), 22.26 (C10/C16).

Minor diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 4H, Ar), 5.92 – 5.72 (m, 1H, C2), 5.08 – 4.87 (m, 2H, C1), 3.38 – 3.28 (m, 1H, C5), 3.06 – 2.93 (m, 1H, C8), 2.32 (s, 3H, C16), 2.08 – 1.99 (m, 2H , C3), 1.78 – 1.61 (m, 2H, C7), 1.50 – 1.33 (m, 5H, C4/C17-22), 1.32 – 1.19 (m, 12H, C17-22). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.65 (C9), 139.38 (C2), 135.73 (C13), 129.31 (C12/C14), 127.14 (C11/C15), 114.26 (C1), 69.97 (C5), 45.94 (C7), 38.28 (C3), 36.16 (C8), 33.95 (C17-22), 29.79(C17-22), 29.68 (C17-22), 29.26 (C17-22), 29.08 (C17-22), 25.67 (C17-22), 23.60 (C8), 21.11 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 325.2507 found 325.2492. **ATR-FTIR** (cm^{-1}): 3345, 2923, 2853, 1641, 1514, 1456, 1373, 1305, 1276, 1261, 1184, 1108, 1079, 1019, 993.

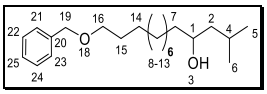
14-(methoxy)-2-methyltetradecan-4-ol (**1.136**)



Synthesized by using the **general procedure for the product scope** but on a 0.15 mmol scale.

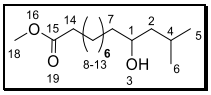
Isolated yield: 22 mg, 58%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.66 (s, 1H. C1), 3.36 (t, *J* = 6.7 Hz, 2H, C16), 3.33 (s, 3H, C18), 1.82 – 1.73 (m, 1H, C4), 1.61 – 1.51 (m, 2H, C15), 1.46 – 1.35 (m, 4H, C7/C14), 1.27 (s, 12H, C2/C8-13), 1.26 – 1.21 (m, 2H, C8-13), 0.92 (d, *J* = 7.3 Hz, 3H, C5), 0.91 (d, *J* = 7.0 Hz, 3H, C6). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 73.12 (C16), 70.11 (C1), 58.70 (C18), 46.93 (C2), 38.23 (C7), 29.90 (C15), 29.83 (C8-13), 29.80 (C8-13), 29.75 (C8-13), 29.63 (C8-13), 29.56 (C14), 26.28 (C8-13), 25.75 (C8-13), 24.75 (C6), 23.68 (C5), 22.19 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 281.2457 found 281.2451. **ATR-FTIR** (cm^{-1}): 3397, 2925, 2854, 1674, 1464, 1385, 1367, 1324, 1276, 1261, 1119, 1068, 764, 750, 618.

14-(benzyloxy)-2-methyltetradecan-4-ol (**1.137**)

 Synthesized by using the **general procedure for the product scope**.

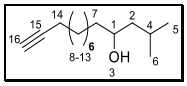
Isolated yield: 68 mg, 68%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H, Ar), 7.30 – 7.26 (m, 1H, Ar), 4.50 (s, 2H, C19), 3.68 – 3.63 (m, 1H, C1), 3.46 (t, *J* = 6.7 Hz, 2H, C16), 1.80 – 1.73 (m, 1H, C4), 1.63 – 1.58 (m, 2H, C15), 1.46 – 1.39 (m, 3H, C7/C14), 1.38 – 1.33 (m, 3H, C7/C2), 1.27 (bs, 10H, C8-13), 1.24 – 1.20 (m, 2H, C8-13), 0.92 (d, *J* = 7.2 Hz, 3H, C5), 0.91 (d, *J* = 7.2 Hz, 3H, C6). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.84 (Ar), 128.49 (Ar), 127.77 (Ar), 127.61 (Ar), 73.00 (C19), 70.67 (C16), 70.12 (C1), 46.94 (C2), 38.23 (C7), 29.92 (C15), 29.84 (C14), 29.76 (C8-13), 29.72 (C8-13), 29.68 (C8-13), 29.62 (C8-13), 26.33 (C8-13), 25.76 (C8-13), 24.76 (C4), 23.68 (C5), 22.20 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 357.2770 found 357.2768. **ATR-FTIR** (cm^{-1}): 3392, 3068, 3031, 2926, 2854, 1674, 1496, 1456, 1365, 1309, 1205, 1102, 1028, 734, 697, 631.

Methyl 10-hydroxy-12-methyltridecanoate (**1.138**)

 Synthesized by using the **general procedure for the product scope**.

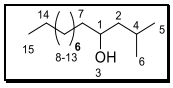
Isolated yield: 46 mg, 60%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.66 (s, 4H, C1/C18), 2.30 (t, *J* = 7.6 Hz, 2H, C14), 1.81 – 1.72 (m, 1H, C4), 1.65 – 1.58 (m, 2H, C2), 1.47 – 1.34 (m, 4H, C7/C8-13), 1.29 (s, 9H, C8-13), 1.26 – 1.20 (m, 2H, C8-13), 0.92 (d, *J* = 6.8 Hz, 3H, C5), 0.90 (d, *J* = 6.8 Hz, 3H, C6). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.51 (C15), 70.08 (C1), 51.62 (C18), 46.94 (C2), 38.19 (C7), 34.24 (C14), 29.75 (C8-13), 29.54 (C8-13), 29.32 (C8-13), 29.25 (C8-13), 25.72 (C8-13), 25.07 (C8-13), 24.75 (C4), 23.67 (C5), 22.19 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 281.2093 found 281.2087. **ATR-FTIR** (cm^{-1}): 3452, 2928, 2856, 1741, 1438, 1367, 1260, 1216, 1173, 1108, 1014, 750.

2-methyltetradec-13-yn-4-ol (**1.139**)

 Synthesized by using the **general procedure for the product scope**.

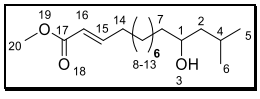
Isolated yield: 35 mg, 52%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.66 (s, 1H, C1), 2.18 (td, *J* = 7.1, 2.6 Hz, 2H, C14), 1.94 (t, *J* = 2.6 Hz, 1H, C16), 1.80 – 1.72 (m, 1H, C4), 1.55 – 1.49 (m, 2H, C13), 1.46 – 1.38 (m, 5H, C2/C8-12), 1.36 – 1.33 (m, 1H, C2), 1.30 (s, 7H, C8-12), 1.25 – 1.20 (m, 2H, C8-12), 0.92 (d, *J* = 6.8 Hz, 3H, C5), 0.91 (d, *J* = 6.7 Hz, 3H, C6).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 84.92 (C15), 70.11 (C1), 68.20 (C16), 46.95 (C2), 38.21 (C7), 29.78 (C8-13), 29.61 (C8-13), 29.19 (C8-13), 28.87 (C8-13), 28.60 (C8-13), 25.74 (C8-13), 24.76 (C4), 23.68 (C5), 22.20 (C6), 18.54 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 247.2038 found 247.2029. **ATR-FTIR** (cm^{-1}): 3313, 2924, 2856, 1740, 1466, 1367, 1276, 1261, 1231, 1136, 1061, 764, 750, 629.

2-methyltridecan-4-ol (**1.140**)

 Synthesized by using the **general procedure for the product scope**.

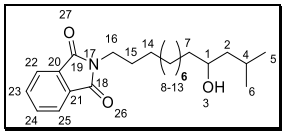
Isolated yield: 40 mg, 63%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (s, 1H, C1), 1.84 – 1.71 (m, 1H, C4), 1.48 – 1.41 (m, 2H, C7), 1.40 – 1.33 (m, 2H, C7-C14), 1.32 – 1.24 (m, 13H, C2/C7-C14), 1.23 – 1.19 (m, 1H, C2), 0.93 (d, *J* = 7.0 Hz, 3H, C5), 0.91 (d, *J* = 5.2 Hz, 3H, C15), 0.87 (d, *J* = 7.0 Hz, 3H, C6). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 70.13 (C1), 46.93 (C2), 38.23 (C7), 32.05 (C7-C13), 29.86 (C7-C13), 29.80 (C7-C13), 29.73 (C7-C13), 29.48 (C7-C13), 25.77 (C7-C13), 24.76 (C4), 23.68 (C5), 22.84 (C6), 22.20 (C14), 14.28 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 237.2194 found 237.2190. **ATR-FTIR** (cm^{-1}): 3343, 2955, 2922, 2854, 1465, 1367, 1276, 1262, 1170, 1144, 1064, 1014, 948, 840, 764, 750, 722, 658.

methyl (*E*)-12-hydroxy-14-methylpentadec-2-enoate (**1.141**)

 Synthesized by using the **general procedure for the product scope**.

Isolated yield: 52 mg, 52%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.6, 7.0 Hz, 1H, C15), 5.81 (d, *J* = 15.6 Hz, 1H, C16), 3.72 (s, 3H, C20), 3.66 (s, 1H, C1), 2.22 – 2.16 (m, 2H, C14), 1.80 – 1.73 (m, 1H, C4), 1.49 – 1.41 (m, 4H, C7/C8-13), 1.40 – 1.33 (m, 2H, C8-13), 1.29 (s, 9H, C8-13), 1.26 – 1.21 (m, 2H, C2), 0.92 (d, *J* = 7.2 Hz, 3H, C5), 0.91 (d, *J* = 7.2 Hz, 3H, C6). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.39 (C17), 150.02 (C15), 120.93 (C16), 70.10 (C1), 51.56 (C20), 46.95 (C2), 38.19 (C7), 32.35 (C14), 29.78 (C8-13), 29.62 (C8-13), 29.45 (C8-13), 29.23 (C8-13), 28.12 (C8-13), 25.73 (C8-13), 24.76 (C4), 23.67 (C5), 22.20 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 307.2249 found 3072245. **ATR-FTIR** (cm^{-1}): 3444, 2926, 2855, 1726, 1657, 1464, 1436, 1366, 1314, 1272, 1198, 1174, 1132, 1041, 981, 920, 842, 750, 721.

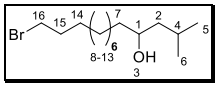
2-(11-hydroxy-13-methyltetradecyl)isoindoline-1,3-dione (**1.142**)



Synthesized by using the **general procedure for the product scope**.

Isolated yield: 77 mg, 69%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 2H, Ar), 7.72 – 7.69 (m, 2H, Ar), 3.69 – 3.65 (m, 3H, C1/C16), 1.80 – 1.72 (m, 1H, C4), 1.69 – 1.62 (m, 2H, C15), 1.48 – 1.33 (m, 3H, C7), 1.34 – 1.29 (m, 5H, C8-14), 1.28 – 1.19 (m, 10H, C8-14), 0.92 (d, *J* = 7.2 Hz, 3H, C2, C8-14), 0.90 (d, *J* = 7.2 Hz, 3H, C). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.65 (C18/C19), 133.99 (C23/24), 132.31 (C20/21), 123.30 (C22/25), 70.10 (C1), 46.92 (C2), 38.23 (C16), 38.21 (C7), 29.79 (C8-14), 29.69 (C8-14), 29.60 (C8-14), 29.57 (C8-14), 29.29 (C8-14), 28.73 (C15), 26.98 (C8-14), 25.74 (C8-14), 24.75 (C4), 23.68 (C5), 22.20 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 396.2515 found 396.2517. **ATR-FTIR** (cm^{-1}): 3469, 2923, 2853, 1772, 1706, 1615, 1466, 1437, 1396, 1366, 1276, 1188, 1172, 1142, 1053, 890, 793, 750, 719, 622.

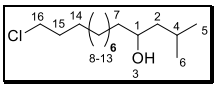
14-bromo-2-methyltetradecan-4-ol (**1.147**)



Synthesized by using the **general procedure for the product scope**.

Isolated yield: 63 mg, 69%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.66 (s, 1H, C1), 3.41 (t, *J* = 6.9 Hz, 2H, C16), 1.88 – 1.82 (m, 2H, C15), 1.80 – 1.72 (m, 1H, C4), 1.46 – 1.38 (m, 5H, C7-14), 1.38 – 1.33 (m, 1H, C8-14), 1.28 (bs, 10H, C8-14), 1.25 – 1.21 (m, 2H, C2), 0.92 (d, *J* = 7.5 Hz, 3H, C5), 0.91 (d, *J* = 6.9 Hz, 3H, C6). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 70.12 (C1), 46.95 (C2), 38.22, (C7) 34.27 (C16), 32.97 (C15), 29.82 (C14), 29.72 (C8-13), 29.67 (C8-13), 29.56 (C8-13), 28.90 (C8-13), 28.31 (C8-13), 25.75 (C8-13), 24.76 (C4), 23.68 (C5), 22.20 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 329.1456 found 329.1450. **ATR-FTIR** (cm^{-1}): 3728, 3352, 2926, 1465, 1367, 1217, 1136, 1055, 1032, 750, 646.

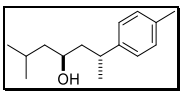
14-chloro-2-methyltetradecan-4-ol (**1.144**)



Synthesized by using the **general procedure for the product scope**.

Isolated yield: 56 mg, 71%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.71 – 3.63 (m, 1H, C1), 3.53 (t, *J* = 6.8 Hz, 2H, C16), 1.80 – 1.73 (m, 3H, C4/C15), 1.46 – 1.34 (m, 6H, C7-C14), 1.28 (s, 10H C7-C14), 1.26 – 1.19 (m, 2H, C2), 0.92 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 70.12 (C1), 46.95 (C2), 45.38 (C16), 38.22 (C7), 32.78 (C15), 29.83 (C8-C13), 29.73 (C14), 29.62 (C8-C13), 29.59 (C8-C13), 29.02 (C8-C13), 27.02 (C8-C13), 25.76 (C8-C13), 24.76 (C4), 23.68 (C5), 22.20 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 285.1961 found 285.1953. **ATR-FTIR** (cm^{-1}): 3345, 2926, 2855, 1465, 1367, 1276, 1262, 1136, 1054, 764, 750, 653.

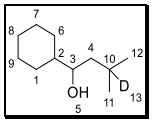
(4*RS*,6*RS*)-2-methyl-6-(p-tolyl)heptan-4-ol (**1.199**)



Synthesized by using the **general procedure for the allylsilane scope.**

Isolated yield: 30 mg, 45%. 5.0 : 1 d.r. Spectroscopic properties match with the literature.[154]

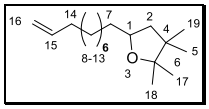
1-cyclohexyl-3-methylbutan-3-d-1-ol (**1.209**)



Synthesized by using the **deuterium experiment** procedure.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.46 – 3.41 (m, 1H, C3), 1.81 – 1.73 (m, 3H), 1.69 – 1.63 (m, 2H, C4/Cy), 1.31 – 1.18 (m, 5H, Cy), 1.17 – 0.96 (m, 3H, C4/Cy), 0.92 (s, 3H, C11), 0.88 (s, 3H, C12). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 74.17 (C3), 44.24 (C2), 43.43(C4), 29.39 (Cy), 27.72 (Cy), 26.74 (Cy), 26.54 (Cy), 26.39 (Cy), 24.34 (t, *J* = 19.4 Hz, C10), 23.89 (C11), 21.76 (C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 194.1631 found 194.1324. **ATR-FTIR** (cm^{-1}): 3351, 2921, 2852, 1676, 1450, 1384, 1364, 1324, 1249, 1187, 1163, 1135, 1088, 1047, 964, 926, 892, 868, 844, 794, 630.

5-(dec-9-en-1-yl)-2,2,3,3-tetramethyltetrahydrofuran (**1.202**)



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, C15), 5.04 – 4.88 (m, 2H, C16), 4.00 – 3.86 (m, 1H, C1), 2.08 – 1.99 (m, 2H, C14), 1.84 (dd, *J* = 12.4, 7.3 Hz, 1H, C2), 1.60 – 1.52 (m, 2H, C2/C8-13), 1.41 – 1.27 (m, 13H, C8-13), 1.10 (s, *J* = 1.3 Hz, 3H, C17), 1.09 (s, 3H, C18), 0.98 (s, 3H, C19), 0.96 (s, 3H, C5).

CHAPTER II

A catalytic cross-coupling of carbene precursors

The results of this work are published in *Angew. Chem. Int. Ed.* **2018**, 57, 16215 – 16218.[186] This work has been realized in collaboration with Dr. J. D. Neuhaus and Dr. A. Pinto. C. Bold (M.Sc.) is acknowledged for the synthesis of selected starting materials and products.

2.1. Introduction

2.1.1. Carbenes and Carbenoids

THE WORD CARBENOID IS A combination of the words carbene and the ancient Greek word *εἶδος* ("eidos" English for "appearance" or "shape"). It consequently refers to a molecule or a fragment with the reactivity akin to that of a carbene, though it is not one.[187] Unfortunately the terms (carbene/carbenoid) are used rather imprecisely in the literature, although there is a clear IUPAC definition which will be followed throughout the text: a carbene is "the electrically neutral species H_2C: and its derivatives, in which the carbon is covalently bonded to two univalent groups of any kind or a divalent group and bears two nonbonding electrons, which may be spin-paired (singlet state) or spin-non-paired (triplet state)."[188] By this definition, metal-carbene complexes themselves are not carbenes but carbenoids.

In order to understand the chemistry of carbene and carbenoids we will take a brief look at the simplest carbene: methylene. This neutral compound, which only exist at low temperatures and high dilution as a gas, consists of only three atoms (CH_2).[189] Therefore, the molecular orbitals can be easily drawn (*Scheme 2.1a*).[19,103,190] The orbitals are graphically depicted as expected for the bent triplet ground state of carbene with two non-degenerate single-occupied orbitals. This highly reactive compound tends to dimerize in a barrierless fashion to ground state ethylene.[191,192] The generated ethylene decomposes quickly to acetylene, most likely because it is promoted to an excited state under the reaction conditions.[193,194] Conversely, the dimerization of (non-radical) singlet methylene is disfavored as it must result in ethylene in an energetically high lying singlet excited state (Rydberg state).[192,195] Strikingly, the orbitals of ethylene are literally the combination of the orbitals found in two methylene molecules. It stands to reason then, that the union of two different carbenes (or carbenoids) is a potentially appealing synthetic route to access olefins.

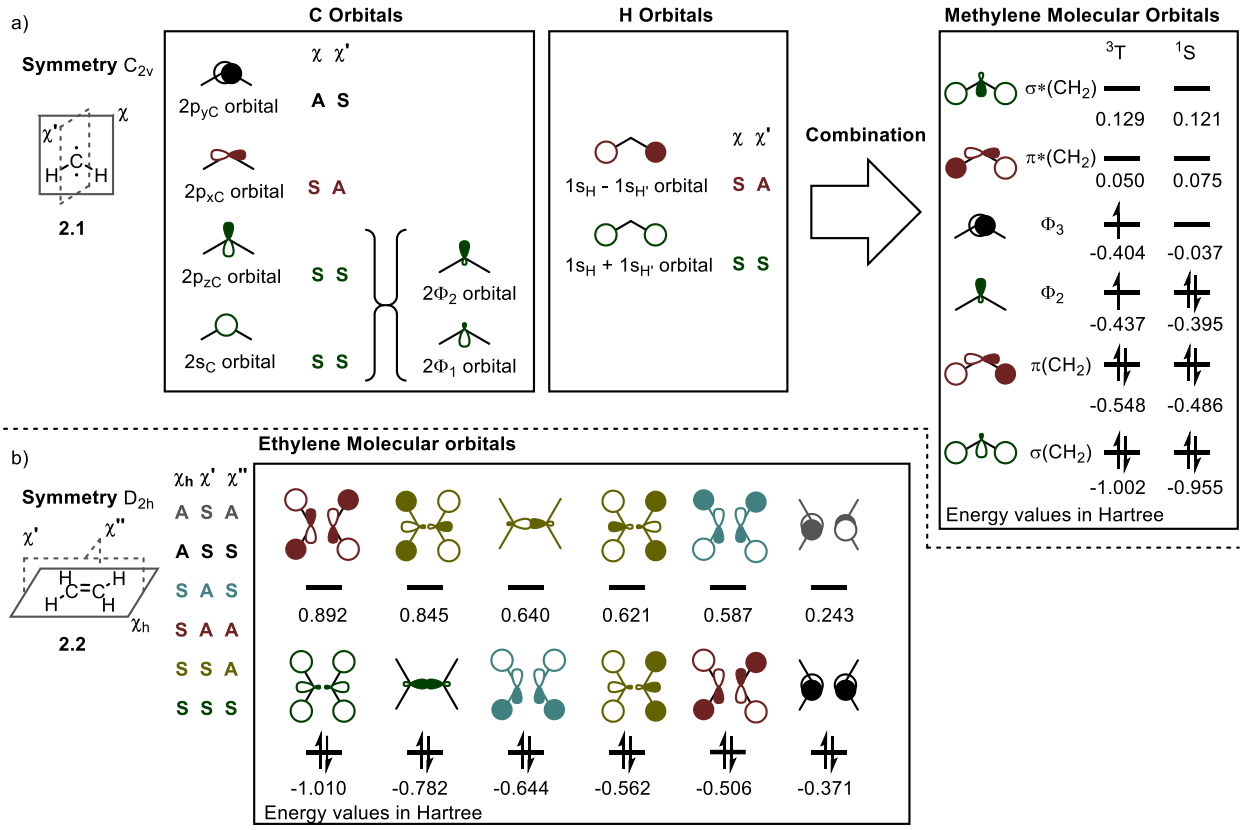
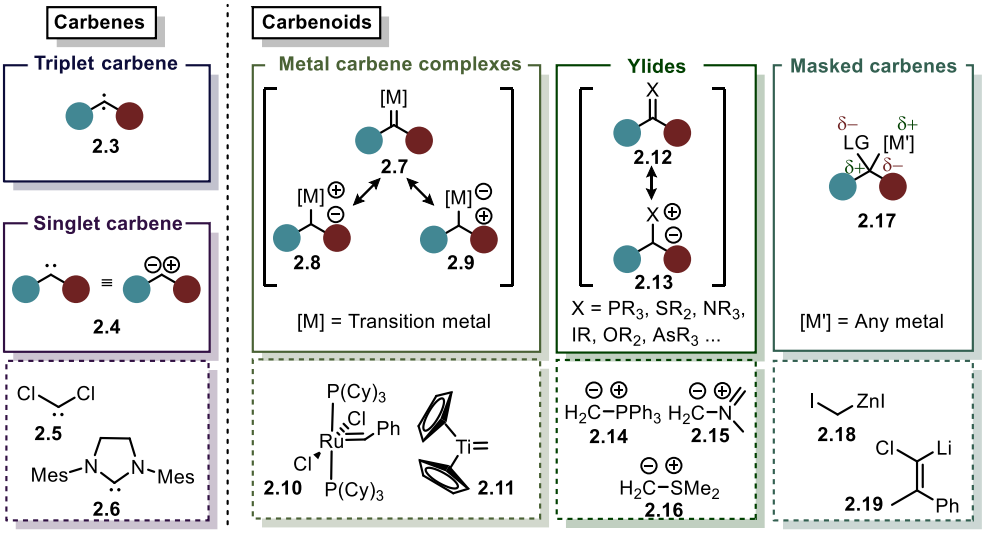


Figure 2.1 – a) Molecular orbitals of methylene with corresponding energies in Hartree.[190] The symmetry of the orbitals is described as symmetric (S) or antisymmetric (A) to a mirror plane (χ) of the molecule. b) Molecular orbitals for ethylene with corresponding energies of the orbitals in Hartree.[190]

Triplet methylene has been observed to be slightly more stable (9 kcal/mol) than its singlet spin-isomer.[196] However, electron-donating substituents lower this triplet-singlet gap considerably (by hyperconjugation or mesomeric effects), such that dimethylcarbene exists in the singlet ground state.[197] Moreover, the electronic structure of a carbene is not only dependent on the substituents it carries, but also on how the carbene is prepared. When diazomethane is irradiated with UV light for instance, it decomposes to nitrogen and singlet methylene. [198,199] Conversely, when benzophenone is used as a sensitizer under the same reaction conditions triplet methylene is observed.[199] The stereoselectivity in cyclopropanation reactions can be used as a test for the involvement of singlet or triplet carbene: if the carbene reacts with an olefin stereospecifically in a retentive manner, the carbene can be suspected to be in the singlet state. When the reaction lacks this stereospecificity, it is a clear indicator that the processinvolves a carbene as its triplet spin-isomer.[200] The reason for this behavior is that singlet

carbenes react in a pericyclic, and therefore strictly concerted, cycloaddition mode (*i.e.* cheletropic reaction).[103] In contrast, triplet carbenes react in a stepwise manner because a spin-flip is required in the open chain intermediate to close the ring.[200] This showcases that the reactivity of the two spin-isomers is (similar to triplet and singlet O_2) utterly different.

The chemistry of a triplet carbene can be mostly ascribed to its diradical character. In the reaction with saturated hydrocarbons for instance, it tends to abstract hydrogen atoms. The reactivity of singlet carbenes, on the other hand, is in good accordance with a divalent carbon atom carrying a positive and a negative charge: it tends to inserts into C-H bonds of the same hydrocarbon.[200] Since free carbenes are (mostly) highly reactive species, their use in organic synthesis is rather limited. Usually their precursors are commonly utilized instead. Most of these so-called carbenoids are in a singlet ground state and often follow "two-electron logic". Thus, they resemble mostly singlet carbene in its reactivity. Typically, the major families of carbenoids are carbene metal-complexes, ylides, or tetravalent carbon atoms with an electropositive element and a potential leaving group attached (masked carbenes) (*Scheme 2.1*).



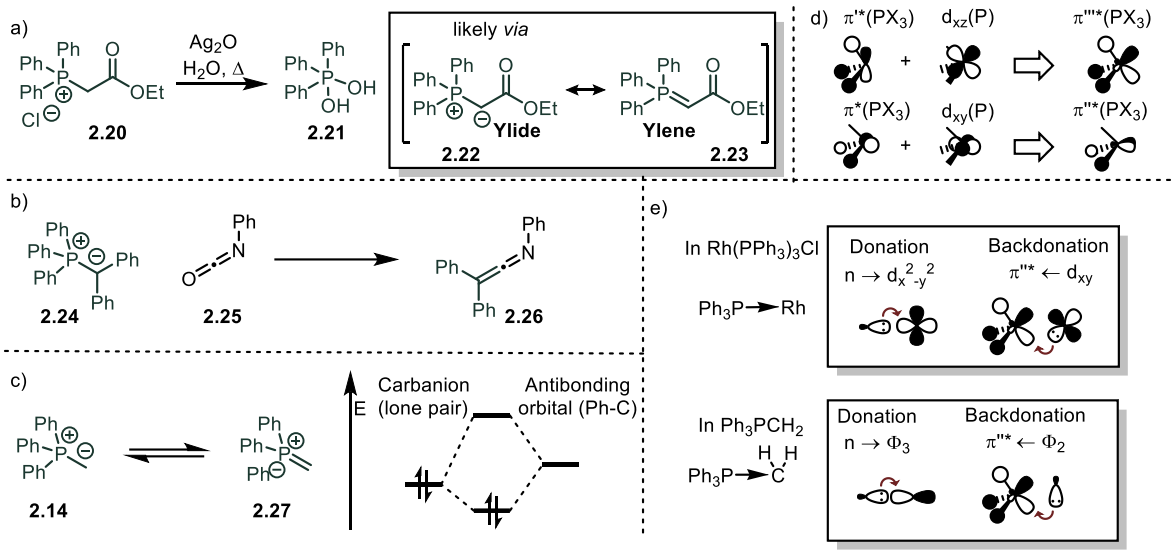
Scheme 2.1 – Left) Carbenes can be divided in singlet and triplet carbenes. The dashed box contains examples of relatively stable singlet carbenes (long living triplet carbenes are more exceptional).[201] *Right) Carbenoids divided in metal carbene complexes, ylides and masked carbenes. The dashed boxes below contain a few examples of each subgroup.*

2.1.2. Ylides

2.1.2.1. *General structural features*

Ylides have a long history in organic chemistry. Their first synthesis was believed to have occurred at the end of the 19th century, when Michaelis and Gimborn treated the phosphonium salt **2.20** with silver oxide in water (*Scheme 2.1a*).[202] They observed that under these conditions the hydrated form of triphenylphosphine oxide was formed, presumably following the aqueous decomposition of the corresponding ylide **2.22**.[203,204] Shortly after the first world war, Staudinger and Meyer reported the first isolated phosphonium ylides.[205] Indeed, they were the first to use them in an olefination reaction, more than 30 years before Wittig's report (*Scheme 2.1b*).[206]

The term ylide originates from the property of two adjacent atoms sharing a covalent (-yl) and an ionic bond (-ide).[207] This definition was coined by Wittig and has been later recognized by IUPAC.[208] For many ylides an alternative resonance structure, where a double bond connects the aforementioned atoms, can be drawn (*Scheme 1a* – **2.23**). This resonance structure is called an 'ylene'. The question of which resonance structure is the principal contributor, has been a point of discussion.[89] However, the ylene-form of phosphonium and sulfoxonium ylides has been found to be of subordinate importance, since stabilization is primarily a result of polarization and not of conjugative effects.[89,209] Direct participation of the d-orbitals has been excluded,[209,210] and instead hyperconjugation of the carbanion into antibonding S-C/P-C orbitals is believed to account for the shorter S-C/P-C bond of sulfur- and phosphorus-based ylides (*Scheme 2.2c*).[210–212] Yet, d-functions (*not* d-orbitals) are often included in calculations to polarize the antibonding π* and π'*-orbitals of PX_3 systems in order to describe the bonding situation in a more realistic way (*Scheme 2.2d*).[210,213] The thus generated orbitals π''* and π'''* are the orbitals involved in the aforementioned hyperconjugation and also responsible for π-backbonding in metal-phosphine complexes.[213]



Scheme 2.2 – a) The first ylide synthesis. b) Very first example of an olefination using a phosphonium ylide. c) Anomeric effect causing the shortening of the P-C bond in a phosphonium ylide. d) Polarization of the phosphine P-X_3 π-orbitals..

The stability of ylides is largely enhanced by electron-withdrawing substituents. While the phosphonium ylide **2.14** is only stable in solution, its electron-poor cognate **2.22** can be purified by column chromatography and is commercially available. This showcases that most of the negative charge can be expected to reside on the carbon atom, further supporting the zwitterionic description of these compounds.[210]

Another interpretation of the bonding situation in ylides has led to the picture of ylides being compounds in which donating heteroatoms can coordinate to the carbon atom of a carbene in a captodative manner similar to a metal.[214,215] The similarity can be best showcased in the classical Dewar-Chatt-Duncanson-model (DCD), which classically describes the bonding situation of metals and ligands.[216,217] In *Scheme 2.2e* a DCD-model for the interaction of a triphenylphosphine ligand with the central atom (Rh) in $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) is shown. The lone-pair of electrons of the phosphine are donated into the $d_{x^2-y^2}$ orbital of the metal to form a coordinative bond. At the same time the electrons of the filled, non-bonding d_{xy} orbital on the metal are delocalized into the empty π* orbital of the phosphine.[218] Similarly, in the phosphonium ylide **2.27**, the lone pair of triphenylphospine, is donated into the empty Φ_3-orbital of methylene (see *Figure 2.1*), while the HOMO of singlet carbene (Φ_2

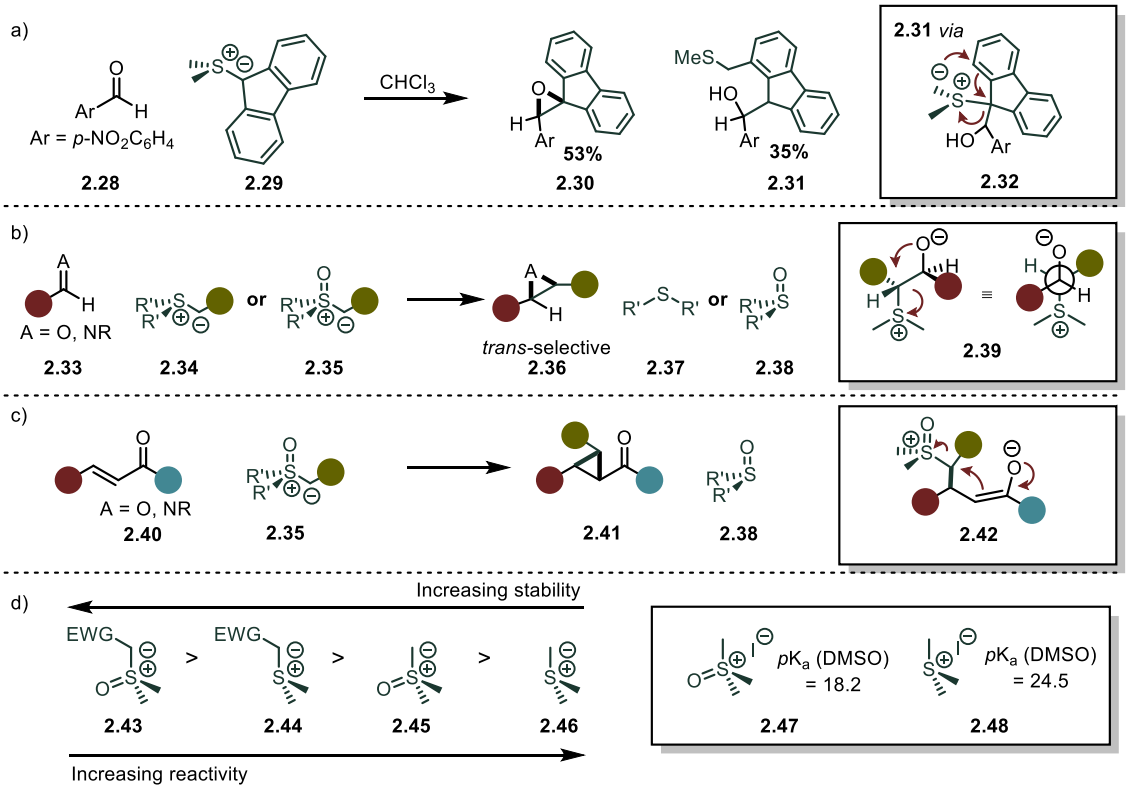
– *Figure 2.1*) pushes its electrons into the π''*-orbitals of the phosphine. This is equivalent to what we described in hyperconjugation earlier in the text (*Scheme 2.2c*).[214] This model has also been used to explain the stability and the reactivity of bisylides (X^+-C^{2-}-X^+), which are commonly interpreted as carbon^0 complexes.[219]

2.1.2.2. *Sulfonium- and Sulfoxonium ylides*

Sulfur-based ylides have been known and acknowledged for a long time in organic chemistry.[220,221] Most famously, epoxidation of aldehydes is readily achieved when a sulfonium salt is deprotonated and reacted with an aldehyde. This was inadvertently discovered by Johnson and LaCount, who hoped to generate an olefin but observed the epoxide **2.30** instead *(Scheme 2.3a*).[222] Corey and Chaykovsky expanded this reaction and developed it into a widely utilized protocol for the epoxidation of aldehydes (*Scheme 2.3b*). Moreover, they proved that sulfoxonium ylides (**2.35**) react similarly on ketones or aldehydes.[223,224] Aldimines showed an analogous reactivity and gave aziridines as products.[223] However, when α,β-unsaturated carbonyl compounds (**2.40**) were reacted with sulfoxonium ylides, epoxides were not observed but rather cyclopropanes were formed (*Scheme 2.3c*). These small rings are formed by a Michael addition of the strongly nucleophilic ylide, followed by an S_N2-displacement of the sulfoxonium moiety by the intermediate enolate **2.42**. Sulfoxonium ylides are the reagents of choice for such cyclopropanations. Conversely, sulfonium ylides are quite selective for epoxide formation, although in some cases cyclopropanation has also been reported.[225]

Both reactions have been acknowledged in copious total syntheses in the past,[3,226–228] particularly in part because the epoxidation is a highly diastereoselective transformation, generally favoring the *trans* isomer. This is due to the stepwise mechanism involved in which the formation of an *anti*-betain intermediate is preferred (**2.39**).[229] Enantioselective versions of the epoxidation have been established by using stoichiometric chiral ylides,[230,231] or by using an enantioenriched sulfide catalyst in

substoichiometric amounts.[232–236] Current research on the catalytic, enantioselective epoxidation and cyclopropanation involves stoichiometric sulfur-based ylides in reactions promoted by chiral organocatalysts or Lewis acids.[237]

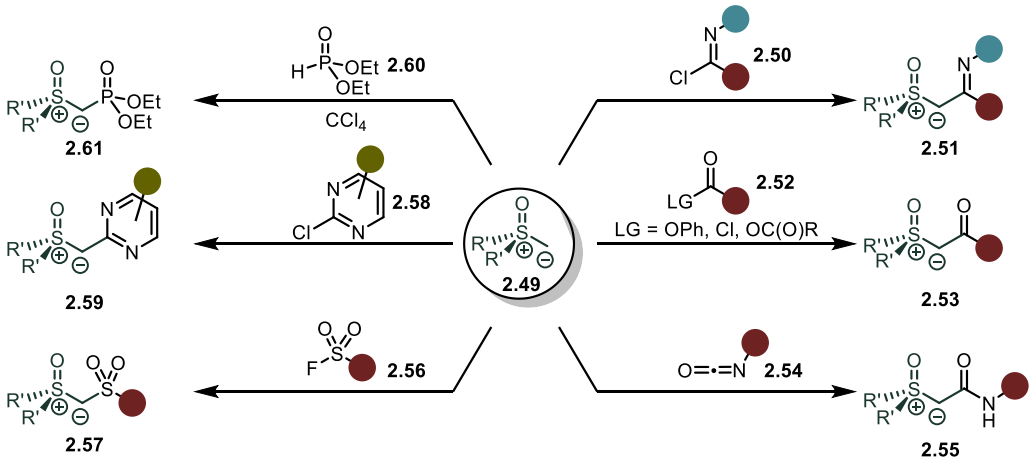


Scheme 2.3 – a) First observed epoxidation of an aldehyde by a sulfonium ylide. b) The Johnson-Corey-Chaykovsky epoxidation. c) The Johnson-Corey-Chaykovsky cyclopropanation. d) Reactivity/Stability scale for sulfoxonium ylides.

Non-stabilized sulfoxonium ylides (such as **2.45** – *Scheme 2.3d*) can be stored in solution at room temperature for several days.[223] Due to their relative stability, they are usually used at higher temperatures than their less stable sulfonium cognates (**2.46**), which are typically used *in situ* at low temperature. The different stabilization is also showcased by the pK_a values of the corresponding iodide salts (*Scheme 2.3d – box*).[221] Even more stable (thus less reactive) are ylides with an electon-withdrawing group directly attached to the formally negatively charged carbon atom (*Scheme 2.3d* – **2.43**, **2.44**). The stability of electron-poor sulfoxonium ylides **2.43** is such that they can often be purified by column chromatography. Indeed, in most of the cases, they are insensitive to shock and can be stored at room temperature under air without acknowledgeable decomposition. Their extraordinary polarity is due to

their zwitterionic nature and should be taken carefully into account during extraction and purification, illustrating again how the ylene-mesomeric structure plays a minor role.

The chemistry of sulfoxonium ylides is ruled by their relatively strong nucleophilicity and their basicity. For instance, ylide **2.45** has a nucleophilicity of *N* = 21.29 in DMSO (Mayr scale)[238] and is thus more nucleophilic than the anion of diethyl malonate (*N* = 20.22 in DMSO).[239] This reactivity enables transformations well beyond the classical Johnson-Corey-Chaykovsky reaction. Interestingly, a parent ylide (a disubstituted sulfoxonium methylide **2.49** - *Scheme 2.4*) can be used as a precursor in order to synthesize a large variety of electron-poor ylides. Acyl chlorides,[240–243] carboxylic anhydrides,[240,242] phenyl esters,[243] ketenes,[244] isocyanates,[241,242] imidoyl chlorides,[245] chloro-pyrimidines,[240,245] sulfonylfluorides,[246] halides of the phosphorus acids[247,248] and *in situ* generated dialkylchlorophosphites[249] (*via* an Atherton-Todd reaction[250]) react readily as electrophiles with the parent ylide to form the corresponding stabilized zwitterion.[221,251] The formation of α-sulfone ylides by reacting ylide **2.49** with sulfonylchlorides is also possible in some cases, although this reaction is not general, probably because the nucleophilic attack occurs on the chlorine atom.[246] Most of the sulfoxonium ylides we used as starting materials in our studies were synthesized following this approach.



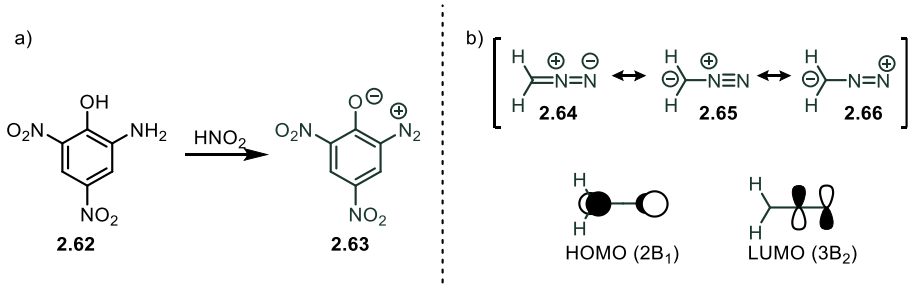
Scheme 2.4 – Synthesis of several stabilized sulfoxonium ylides, by the reaction of a non-stabilized sulfoxonium ylide with electrophiles.

Sulfoxonium ylides undergo many reactions which are characteristic of carbenes and carbenoids. Formal O-H[252], C-X[253] (X = halogen), C-H,[251] S-H[254,255] and N-H insertion[252] can be observed directly without the use of a catalyst. There is convincing evidence that sulfoxonium ylides are transformed into their free carbene derivatives when irradiated with UV-light.[221,243,256] A vast majority of recently reported transformations involving sulfoxonium ylides uses metal complexes as catalysts. Some of these reactions will be further discussed in section 2.1.4.3 and 2.1.5.1.

2.1.3. Diazocompounds

2.1.3.1. *Structural features*

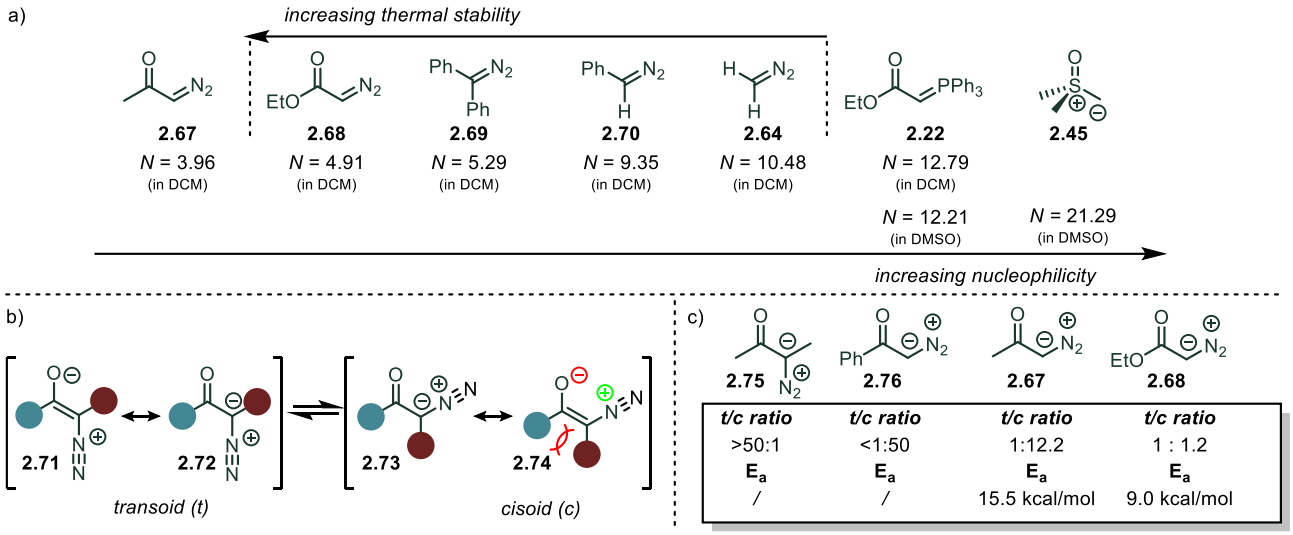
Diazocompounds have been known for more than 160 years: Peter Griess synthesized diazodinitrophenol, by the reaction of picrimic acid with nitrous acid in 1858 (*Scheme 2.5a*).[257,258] Nevertheless, the structure of these molecules has been the subject of a long debate. Curtius, who discovered ethyl diazoacetate (EDA)[259] preferred the cyclic diazirine over the open constitutional isomer.[260] In 1935 an electron diffraction study suggested that the open-chain arrangement is more realistic.[261] 22 years later an ^{15}N isotopologue experiment of EDA finally confirmed the linear structure.[262]



Scheme 2.5 – The first synthesis of a diazocompound (1858). b) Resonance structure of diazomethane and frontier orbitals.

These molecules are not readily described by Lewis structures. Diazomethane, the parent compound of this class, can be only drawn as a zwitterionic species in three mesomeric resonance structures. Those are in accordance with the description of the frontier MOs (*Scheme 2.5b*).[263] A possible mesomeric form with a positively charged carbon atom can be neglected in many cases. Although these

compounds are less polar and much less nucleophilic than comparable phosphonium or sulfonium ylides (*Scheme 2.6a*), an electronically neutral Lewis structure is not accessible unless the central nitrogen atom is drawn with 5 bonds. Some theoretical chemists indeed support such an "outlawed" structure, because it represents the chemical properties accurately and is in accordance with modern valence bond theory.[264,265] The resonance form **2.65** (*Scheme 2.5b*) reveals that diazocompounds can be also interpreted as ylides. However, they are often treated as a separate class because of their structural and reactivity peculiarities.



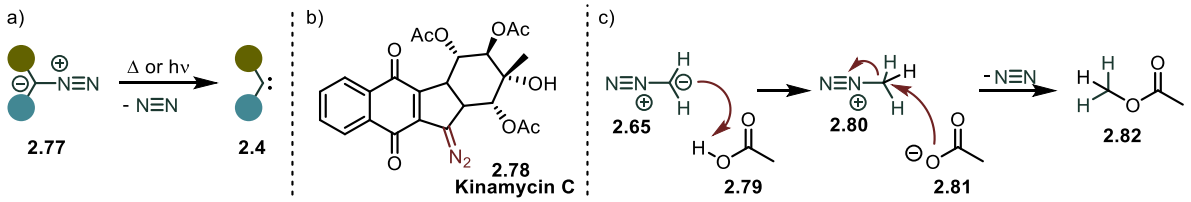
*Scheme 2.6 a) Stability/nucleophilicity scale for diazocompounds. The nucleophilicity is also compared with some ylides. N.B.: Nucleophilicity and thermal stability of diazocompounds is not strictly correlated.[258,266] Compound **2.67** for instance is less stable than EDA (**2.68**) but also less nucleophilic. b) Transoid and cisiod isomerism in α-carbonyl diazocompounds. c) Transiod/cisiod Isomerism measured for diazocompounds. E_a is the activation energy for the isomerization.*

Similar to sulfoxonium ylides, diazocompounds can also be greatly stabilized by electron-withdrawing groups. Ethyl diazoacetate (EDA – **2.68**) for instance, is indefinitely stable at refrigerating temperature and at 100 °C it has a half-life of >100 h.[258,266] To some extent stabilization can also be achieved by conjugation without the involvement of electronegative elements; diphenyl diazomethane **2.69** for example can be readily isolated, although it decomposes on standing.[267] The mesomeric structures of α-diazocarbonyl compounds suggest that both a *transoid* (**2.71**/**2.72**) and *cisoid* (**2.73**/**2.74**) form are possible. Indeed, they are in equilibrium with each other (*Scheme 2.6b*). The equilibrium is fast

(on an NMR timescale) at room temperature but is decisively slower at temperatures below -40 °C. The *transoid/cisoid* ratio, on the other hand, is barely dependent on the temperature.[258] The rotation barrier is much lower for α-diazoesters than for α-diazoketones (9 – 12 kcal/mol *vs.* 15 – 18 kcal/mol) probably because of alternative resonance structures involving the ester moiety (*Scheme 2.6c*).[258] It has been shown that Coulombic attraction of the negatively charged oxygen and the positively charged nitrogen in the *cisoid* structure has a stabilizing effect.[268] Therefore, most monosubstituted α-diazocarbonyl compounds in solution favor the *cisoid* configuration (*Scheme 2.6c*). However, the attractive force can be overshadowed by sterical 1,2 repulsion of the two vicinal substituents. Strikingly, disubstituted α-diazocarbonyl compounds are often found exclusively in the *transoid* form in solution.[258]

2.1.3.2. *Reactivity*

As indicated before, diazocompounds can be readily converted into their free carbenes by light irradiation or by heat (*Scheme 2.7a*).[23,198,199,258] Thus, they have been widely acknowledged as carbene precursors in organic chemistry, although it should be noted that they are considerably hazardous. Many diazocompounds are not only potentially explosive, but also carcinogenic and acutely toxic. Because of these potential dangers they are often produced *in situ* by *e.g.* the basic decomposition of sulfonyl-hydrazones,[269] or by thermal isomerization of sulfonyl-1,2,3-triazoles.[270] Remarkably some organisms, produce molecules containing diazo functionalities to protect themselves by using it as a "chemical weapon" (*Scheme 2.7b*).[271–273]

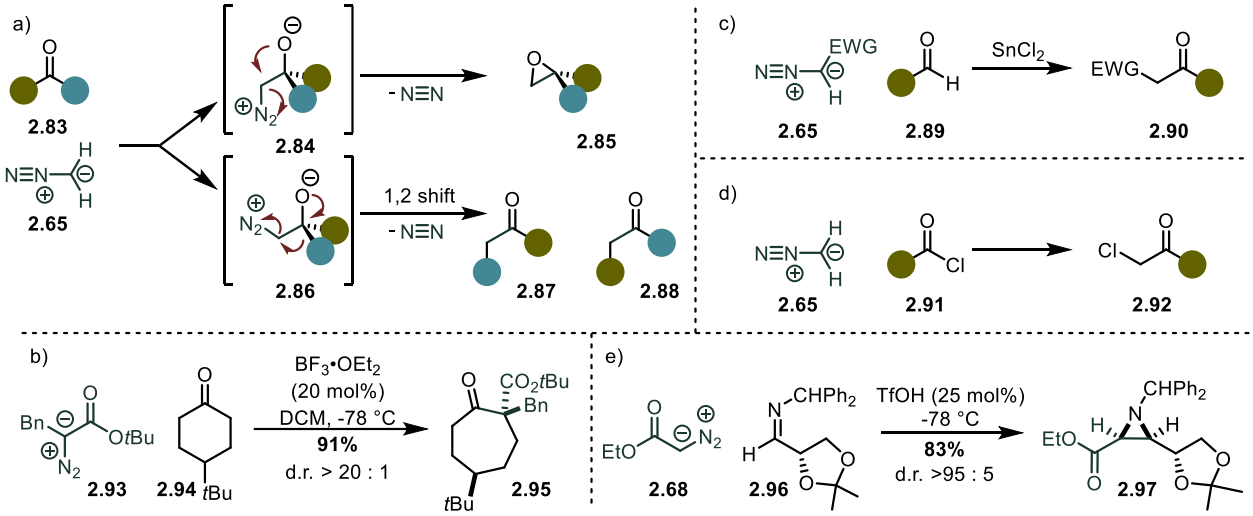


Scheme 2.7 – Photolytical decomposition of a diazocompound into its free carbene. b) Kinamycin C a bacterial metabolite containing a diazo "warhead". c) Methylation of an carboxylic acid by diazomethane.

The reactivity of most diazocompounds can be compared to that of the previously discussed sulfoxonium ylides. Due to their basicity they undergo (formal) insertions into acidic X-H bonds. Indeed diazomethane is a popular and mild reagent for the methylation of carboxylic acids (*Scheme 2.7c*),[274] phenols[275], phosphonic acids,[276] sulfonic acids[277] and 1,3 dicarbonyls.[278]. Its relatively stable and commercially available derivative $TMSCHN_2$ can be similarly used.[279] For the latter reagent, the use of methanol as the co-solvent is advisable to enable a different reaction mechanism.[280,281] Less acidic compounds, which do not react easily with diazomethane, can be methylated with the assistance of an acid. The methylation of alcohols with diazomethane is typically promoted by $HBF_4 \bullet OEt_2$.[282,283] BF_3, on the other hand, is often used as activator for the methylation of amines by H_2CN_2.[284]

Diazocompounds are mild nucleophiles[285] and can react analogously to sulfur-ylides in the Johnson-Corey-Chaykovsky reaction, forming epoxides, when reacted with ketones or aldehydes (*Scheme 2.8d*). The epoxidation is described as part of the Büchner-Curtius-Schlotterbeck (BCS) reaction, [286–288] which is accompanied by many competing side reactions (*Scheme 2.8a*). Most importantly, 1,2-alkyl, aryl or hydrogen shifts can be observed: the rearrangement of **2.86** is reminiscent of the Tiffeneau-Demjanov reaction and generally yields a mixture of two ketones (**2.87** and **2.88**).[3,289–291]. Due to its poor selectivity, the BCS reaction has only limited synthetic utility. However, homologation is often more selective in cyclic ketones and is commonly used in ring expansion strategies (*Scheme 2.8b*).[285,292] A synthetically more general but closely related transformation is the Roskamp reaction (*Scheme 2.8c*).[293,294] Here a stabilized diazocompound with an electron-withdrawing group at the α-position reacts with aldehydes undergoing a selective H-migration with extrusion of N_2 after the nucleophilic attack. A Lewis acid, typically $SnCl_2$, is required to enable the nucleophilic attack. Diastereo-[295] and enantioselective[296,297] versions of this transformation have been developed. Another variation of the BCS reaction was developed by Nierenstein, where the migrating substituents is a chloride (*Scheme 2.8d*).[298] The reaction-conditions for this transformation have to be carefully controlled, since the α-diazoketone is a common side product.

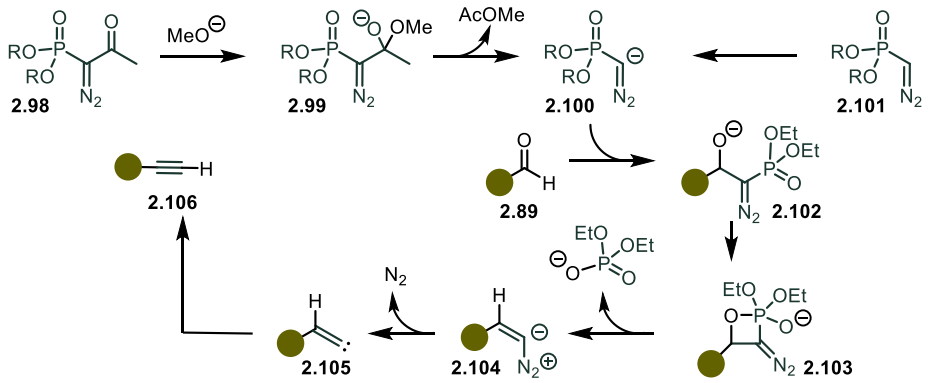
Aziridines can be selectively generated by a BCS-approach under Brønsted acid-catalysis (*Scheme 2.9e*).[299,300] These approaches are mechanistically reminiscent of the Johnson-Corey-Chaykovsky protocol. Diazocompounds can also be readily reacted with thioketones, which react more readily than ketones, to furnish thiiranes. The reaction mechanism actually involves a (3+2) cycloaddition and is thus different to that of a BCS reaction.[301] This reactivity has been exploited in the synthesis of olefins (Barton-Kellogg olefination).[302–304]



Scheme 2.8 – a) The Büchner-Curtius-Schlotterbeck reaction (BCS). b) The BCS reaction applied for a selective ring-expansion. c) The Roskamp reaction. d) The Nierenstein reaction. e) A variation of the BCS-reaction with selective formation of an azerine.

As mentioned previously, diazocompounds are only modestly nucleophilic. In the reactions of *Scheme 2.8* we saw how the electrophilicity of the reaction partner often has to be enhanced by acids. Another approach to increase the reaction rate is to deprotonate the diazocompound. This has been applied most famously in the Seyferth-Gilbert reaction, which was pioneered by Colvin and Hamill,[305,306] improved by the group of Gilbert,[307] and modified by Ohira[308] and the group of Bestmann (*Scheme 2.9*).[309] The reaction relies upon the generation of the conjugate base of a dialkylphosphonodiazomethane, either by deprotonation (**2.101** → **2.100**), or by a retro-Claisen condensation (**2.98** → **2.100** - Ohira-Bestmann modification). The anion **2.100** attacks the carbonyl compound in a stepwise formal (2+2) cycloaddition to form the oxaphosphetane **2.103**. After a formal retro-(2+2) cycloaddition, the diazocompound **2.104** is formed. This species is expected to be bent (*ca.*

120° - C-C-N angle) and to behave like a diazonium salt, thus having a pronounced ylidic character.[310,311] Carbenoids of this type are prone to undergo a Fritsch–Buttenberg–Wiechell rearrangement:[311–314] they decompose to the alkylidene carbene **2.105**, which rearranges readily through a 1,2-migration to furnish the alkyne **2.106**. In some cases the migration may be concerted, without formation of the alkylidene carbene.[311]



Scheme 2.9 - The Seyferth-Gilbert reaction as an example for enhancing the nucleophilicity of the diazocompound by deprotonation.

2.1.4. Transition metal carbenoids

2.1.4.1. *The structure of metal complexes*

The chemistry of transition metals (TMs) is governed by the properties of d-orbitals. Indeed a transition metal is defined (by IUPAC) as an element, which has an incomplete d-subshell or which can give rise to cations of the same element with partially empty d-orbitals.[315] Thus, elements of the groups 3-11 are generally accepted as transition metals and elements of the group 12 (Zn, Cd, Hg, Cn) are excluded by this definition.[316] Interestingly, there is one example where a group 12 element forms a d^8 complex (HgF_4). This compound is highly unstable and was only observed at 4K in a solid matrix.[317] However, in an essay Jensen made clear that 99.9% of mercury's accessible chemistry and 100% of the known chemistry of Zn and Cd follows non-transition metal behavior and thus it is misleading to call group 12 elements transition metals.[318] Moreover, the observation of HgF_4 has been questioned.[319]

Transition metals form complexes upon the the coordination of ligands. There are two different models to count the involved electrons in a complex: in the covalent model the electrons of a non-coordinative bond are formally shared between the metal and the ligand, while the ionic model assumes charge separation in which the ligands gains both binding electrons. In this regard, ligands are usually divided into L (neutral, lone pair donors) and X ligands. X ligands are described as radicals in the covalent model and as anions in the ionic model. A list of ligands and their electron count is found in *table 1*.[218]

Entry	Ligand	Type	Covalent count	Ionic count
1	Me, Ph, **Cl**, η^1-allyl, NO (bent)	X	1 e^-	2 e^-
2	CO, NH_3, η^2-C_2H_4, H_2, **M-Cl**, **$^1CH_2$**	L	2 e^-	2 e^-
3	η^3-allyl, κ^2-acetate	LX	3 e^-	4 e^-
4	NO (linear)		4 e^-	2 e^-
5	=O, **$^3CH_2$**	X_2	2 e^-	4 e^-
6	η^5-Cp	L_2X	5 e^-	6 e^-
7	**η^6-benzene**	L_3	6 e^-	6 e^-

Table 2.1 – Common ligands and their description as X and L ligands. Electron count for the covalent and the ionic model are provided.

Usually the bonding situation is described either by ligand field theory or more precisely by molecular orbitals.[320] If we consider 6 L-type ligands and a $3d^5 4s^1$-metal (chromium), we can combine the HOMO-orbitals of these ligands according to the O_h symmetry of an octahedron (*Figure 2.2 - left*). As a result, we form 6 new orbitals in 3 different symmetry-classes (A_{1g}, T_{1u} and E_g). These new combined orbitals can now interact with either 3d, 4s or 4p orbitals of chromium according to their symmetry. Only the d_{xy}, d_{xz} and d_{yz} orbitals are not able to recombine with the σ-electrons of the ligands because their symmetry does not match.[320] Often the non-bonding electrons (T_{2g}-symmetry) are further stabilized by their donation into a π*-orbital of the ligands as we have seen previously in the Dewar-Chatt-Duncanson model (*Figure 2.2 – right*). Note how the stabilization increases the gap between the two frontier orbitals in *Figure 2.2* (*right*).[320] This relatively simple MO model explains the spectrochemical series, in which ligands with strong σ-electron-donor- and π-electron-acceptor-properties have the most pronounced effect on the HOMO-LUMO gap of complexes.[321] The qualitative MO diagram for σ-donor, π-acceptor complexes shows also that these octahedral compounds are most stable with 18 valence electrons

because all bonding orbitals are filled (18-electron rule). Indeed, many exceptions to the 18-electron rule are found when the ligands are poor π-acceptors because the non-bonding electrons are not stabilized and the system does not gain (or sometimes loses) energy when the t_{2g} orbitals are filled. Other important exceptions are found in complexes which are not octahedral, such as square-planar or linear arrangements (16-electron rule).[320] Half sandwich complexes with a total of 4 ligands can also be interpreted as octahedral complexes where the arene occupies three coordination sides.

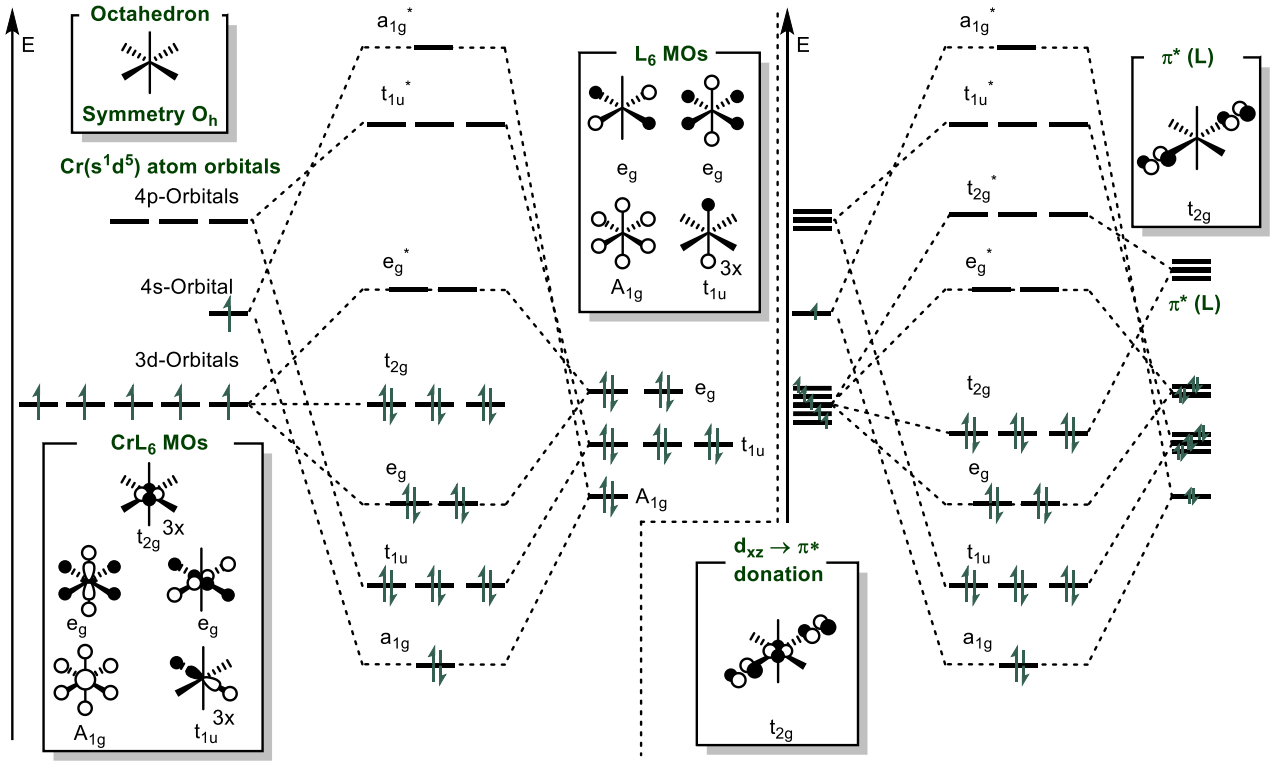
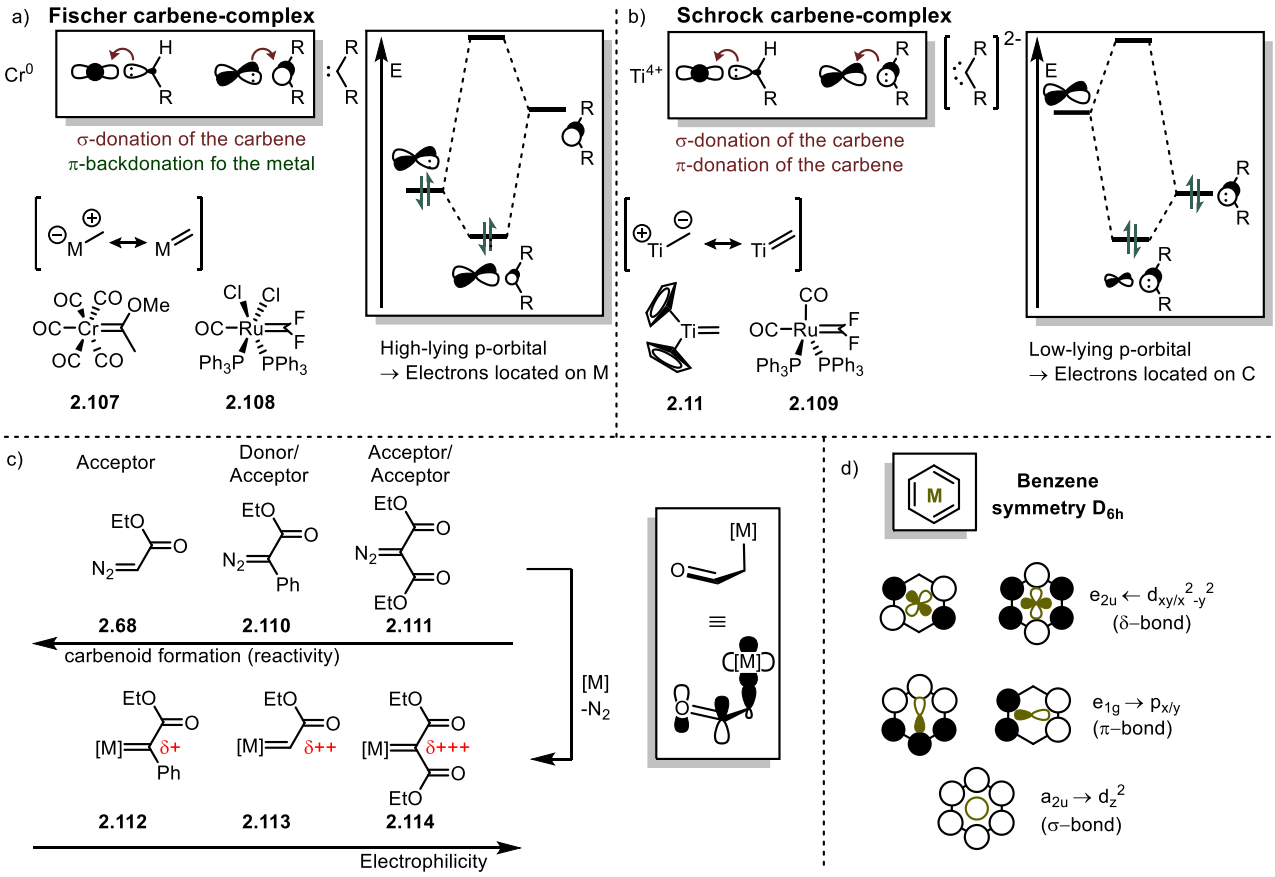


Figure 2.2 – MO diagram for the octrahedral complex $(CO)_6Cr$. Left without π-interactions. Right with π-backdonation.

2.1.4.2. *The structure of metal carbenoids*

Because carbenes are thermodynamically labile, they form rather strong bonds to metals. These metal carbene complexes are divided into Schrock-carbene- and Fischer-carbene complexes.[218,322] Fischer carbenoids (*Scheme 2.10a*) react with nucleophiles on the carbon atom. They are typically described as a singlet carbene, bound to a metal in a capto dative manner (L-type ligand). The lone pair of the carbene forms a coordinative bond (σ-donation), while the metal donates electrons back into the

empty p orbital of the carbene (π-backdonation).[323] The Fischer reactivity is enhanced by conditions where backdonation is subdued: electronegative metals ("late" TMs), strong electron-withdrawing groups on the metal (π-acceptors) and electron-donors on the carbon atom.[218,323] These are all features that lower the energy of the d-orbitals of the metal relative to the empty p-orbital of the carbene. Consequently, the M=C π-bond of the complex is more similar to the metal-d orbital and has thus more electron density located at the metal center (*Scheme 2.10a - right box)*.[324]



Scheme 2.10 – a) Fischer-carbene complexes, DCD-model and examples. b) Schrock-carbene complexes, DCD model and examples. c) Scale for the reactivity of acceptor diazocompounds and scale for the electrophilicity of their corresponding metal-carbene complexes. The box shows the 3D-structure of acceptor carbenoids and the hyperconjugation of the M-C bond and the LUMO of the carbonyl moiety. d) DCD-model for the σ/π and δ-interaction of aromatic rings with metal centers in half-sandwich complexes.

Conversely, Schrock carbenoids react with electrophiles on the carbon atom. They are often interpreted as having two formally covalent M-C bonds, where the carbene is seen as a dianion in the ionic model or as diradical in the covalent model (X_2-type ligand).[218,322] Alternatively, they can be seen as Fischer-carbene complexes with strong π-backdonation.[323] Schrock-reactivity is enhanced by

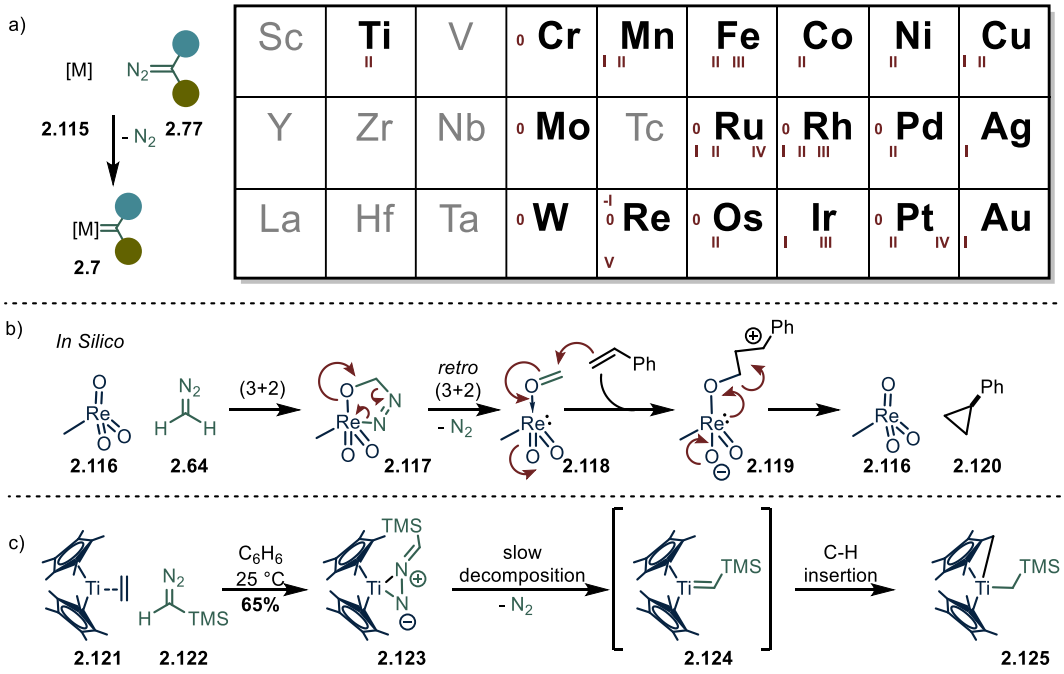
electropositive metals ("early" TMs) without electron-withdrawing groups as ligands. In this case, the d-orbitals lie high in energy (relative to the empty p-orbital of the carbene) and consequently more electron density is expected on the carbon atom (*Scheme 2.10b - right box)*. Sometimes the classification is in a shallow equilibrium. While the Ru^0 complex **2.109** is nucleophilic, the corresponding Ru^{2+} complex **2.108** is electrophilic on the carbon atom.[218,323] Metal carbene-complexes derived from diazocompounds are categorized into 5 different groups: acceptor, acceptor/acceptor, acceptor/donor, donor/donor and donor-carbenoids.[325–327] The acceptor carbenoids are compared in *Scheme 2.10c*. Acceptor substituents render the carbenoid generally electrophilic (Fischer-reactivity). This is seemingly a contradiction since Fischer-reactivity is typically enhanced by electron-donating groups on the carbon. Consequently, an EWG should favor Schrock-reactivity. The solution to this paradox is that the EWG is perpendicular to the carbene π-bond.[328] As a consequence, the π-backdonation is unaffected by this group, but the σ-donation from the carbene to the metal is influenced *via* hyperconjugation (*Scheme2.10c - box*).[329]

Expectedly, there is a major influence by the metal and its ligands not only on the reactivity of the carbenoid but also on its formation from the corresponding diazocompound. Half-sandwich complexes seem to be a privileged class in this regard since they are often used in reactions where a metal carbenoid is generated from a diazocompound.[328,330,339,331–338] This is probably due their strong σ-/π-donor and δ-acceptor abilities (*Scheme 2.10d*),[340] which may fine tune the reactivity of such complexes.

2.1.4.3. *Metal carbenoid formation from diazocompounds and sulfur ylides*

Metal-carbenoids are commonly generated *in situ* by the reaction of transition metals with diazocompounds. The requirements for carbenoid formation are a free coordination site and a certain degree of electrophilicity of the metal center. Rhodium(II) [326,341–349] and copper(I)[326,344,350–355] are most prominently used, although many other transition metals have been proven or are believed to form metal-carbene complexes including Cr(0),[356] Mn(I),[357] Mn(II),[358] Fe(II),[359–361] Fe(III),[360,362] Co(II),[363,364]

Ni(0),[365] Cu(II),[366–370] Mo(0),[371] Ru(0),[341,372] Ru(I),[373] Ru(II),[331,332,375–378,333–339,374] Ru(IV),[379] Rh(0),[380] Rh(I),[381] Rh(III),[328,330,382–384] Pd(0),[385,386] Pd(II),[386–388] Ag(I),[353,389,390] W(0),[391] Re(-I),[392] Re(V),[393] Os(0),[394] Os(II),[395] Ir(I),[327,396] Ir(III),[330,397] Pt(0)[398–401], Pt(II)[399], Pt(IV)[399] and Au(I)[402–406] (*Scheme 2.11a*). Early transition metals (Groups 3-5) are rarely encountered. This is possibly because they are often found in a d^0-electron configuration. This suppresses metal-carbene complexes formation because there is no possibility of backbonding in order to extrude N_2. Re(VII) for instance, a d(0) metal, catalyzes the cyclopropanation of alkenes and other reactions typical of carbenoids, but not by a metal-carbene complex mechanism (*Scheme 2.11b*).[407] Instead, a computational study suggests that a diazometallocycle is formed, which decomposes to a Re(V) species (**2.118**) under extrusion of N_2. This species then reacts in a reductive cyclopropanation to regain the Re(VII) catalyst without the involvement of a metal carbenoid.[408]

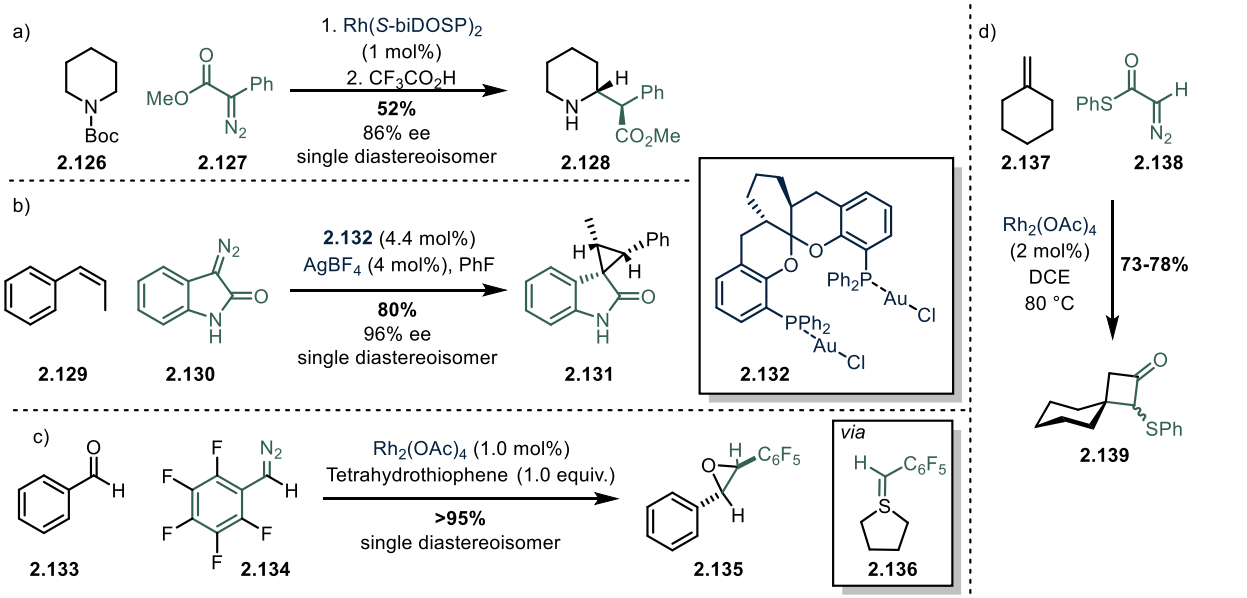


Scheme 2.11 – A selection of transition metal elements, which were observed in carbenoid reactions in combination with diazocompounds and are believed to go via a metal-carbene complex formation. Oxidation states of the metals prior to the reaction with the diazocompound are highlighted. b) Carbenoid reactivity of a Re(VII) catalyst without the formation of a metal-carbene complex. c) Formation of a Titanium diazomethane complex with a subsequent carbenoid formation.

Metals can generally form complexes with diazocompounds without losing N_2.[409,410] These complexes usually have distinct reactivities and can occasionally be difficult to convert into their

corresponding metal carbenoids.[409,411,412] An interesting example is provided in *Scheme 2.11c*). The Ti(II) TMS-diazomethane complex **2.123** decomposes slowly to the corresponding metal-carbene complex.[411] The resulting species undergoes a spontaneous C-H insertion with one of the methyl groups on its Cp* ligand. Sterically congested complexes or bulky diazocompounds such as Ph_2CN_2 are occasionally reported to form diazo-complexes (without the loss of N_2) including elements very prone to carbenoid formation (such as Rh(I)).[412–415]

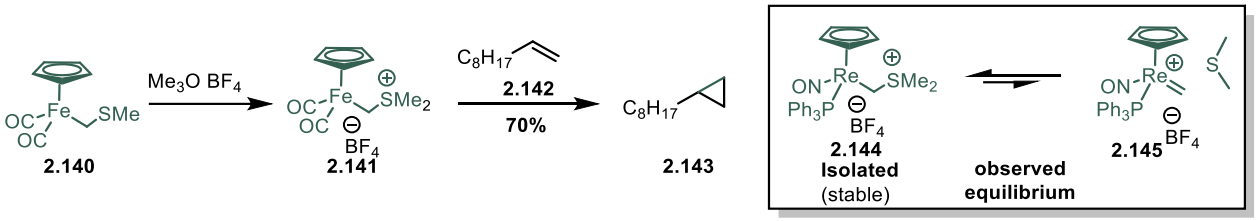
Metal-carbene complexes generated from diazocompounds generally behave like singlet carbenes, thus reacting in X-H insertions,[344,348,360,416] cyclopropanations[344,360,404,417], ylide formation[344,346,418,419] or rearrangements (*Scheme 2.12*).[326,420] Interestingly, the reactivity of some cobalt(II) carbenoids differs significantly from other carbene complexes, because they have a distinct radical character, reminiscent of the reactivity of triplet carbenes.[363,364]



Scheme 2.12 – a) Typical C-H insertion of a Rh-carbene complex into a C-H bond. b) Enantioselective cyclopropanation of a styrene enabled by a stabilized diazocompound and a gold(I) catalyst. c) Epoxidation of an aldehyde via a Johnson-Corey-Chaykovsky reaction. The ylide was produced in situ by a Rh-carbene complex. d) Wolff rearrangement of an α-diazothioester enabled by Rh(II). The formed ketene was captured in a formal (2+2) cycloaddition with a simple alkene.

Sulfur ylides can be also used as metal carbenoid precursors. However, such ylides are known to act as ligands on transition metals rather than to form metal complexes (*e.g.* Cu(I),[421] Pd(II),[422,423]

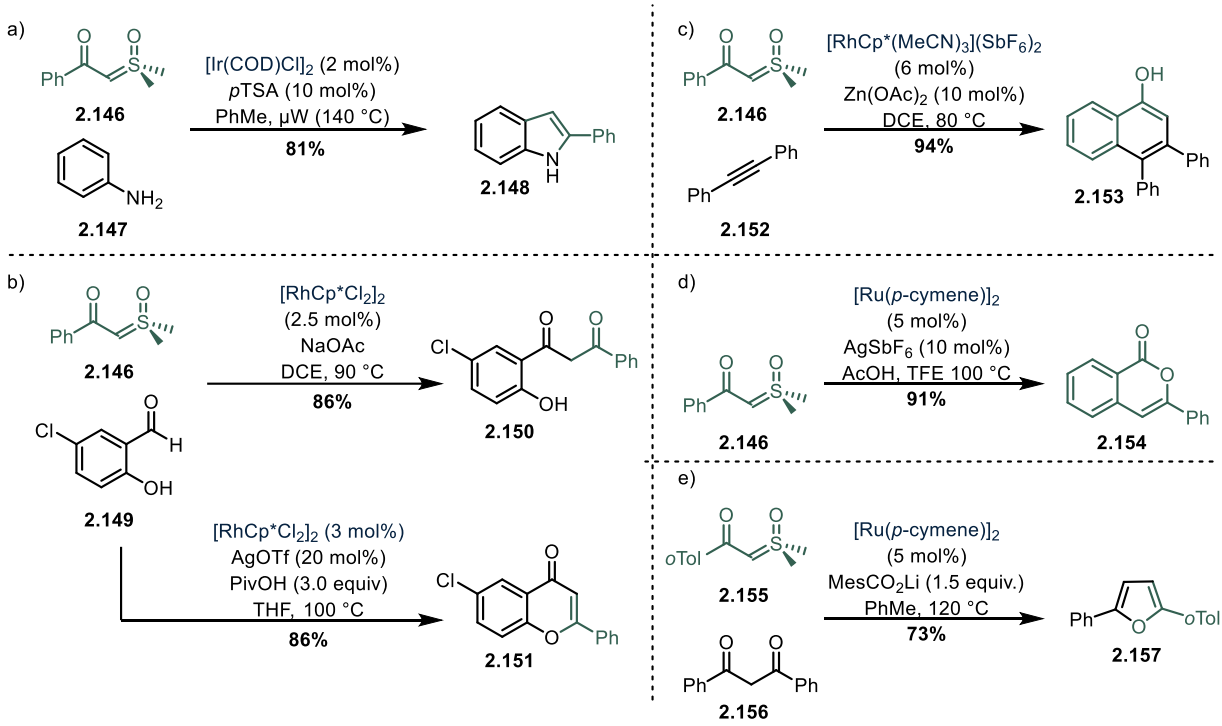
Ag(I)[421]).[424] Interestingly, sulfur ylide-metal complexes have been occasionally observed to undergo reactions typical of carbenes (*Scheme 2.13*).[425] However, this reactivity has been attributed to an equilibrium with the metal carbenoid (*Scheme 2.13 – box*).[426]



Scheme 2.13 – Sulfonium ylides as ligands in complexes. Some of those complexes show carbenoid reactivities, probably due to an equilibrium with the corresponding metal-carbene complex.

It should be noted that it is the formation of sulfur ylides from metal carbenoids which is generally favored from a thermodynamic viewpoint and not the generation of the carbenoid from the ylide (see also *scheme 2.12c*).[419,427] This emphasizes that the use of those ylides as metal-carbenoid precursors is challenging and typically requires harsh conditions (high temperatures). Yet there are many examples in the recent literature, where this reactivity has been exploited (*Scheme 2.14*). The group of Vaitla used an Ir(I) catalyst in combination with stabilized sulfoxonium ylides in an intriguing indole and pyrrole synthesis (*Scheme 2.14a*).[428] The first step of the pyrrole synthesis is particularly interesting and involves the C-H insertion of the metal carbenoid onto a secondary enamine, while anilines undergo N-H insertion, followed by cyclization to furnish the corresponding indole.

A reaction reminiscent of the previously discussed Roskamp reaction was disclosed by the group of Huang (*Scheme 2.14b top*).[429] An insertion into the C-H bond of the aldehyde by the Rh(III) catalyst is followed by the formation of the metal carbenoid by decomposition of the sulfoxonium ylide. The acyl-ligand undergoes a migratory insertion onto the carbene to form a β-diketone. A few months later the group of Lin and Yao published a very similar reaction, in which the generated β-diketone cyclizes to the corresponding chromone under the reaction conditions (*Scheme 14b - bottom*).[430]



Scheme 2.14 – a) Indole synthesis using anilines, sulfoxonium ylides and Ir(I) as the catalyst. b) Roskamp-type reactivity of sulfoxonium ylides mediated by Rh(III) catalysis. c) Naphthol synthesis using sulfoxonium ylides alkynes and a cationic rhodium catalyst. d) Formal dimerization of the carbenes derived from sulfoxonium ylides by Ru(II) catalysis. e) Furan synthesis by the reaction of sulfoxonium ylides, β-diketones and a ruthenium(II) catalyst.

Naphthols have been synthesized using a cationic Rh(II) catalyst on sulfoxonium ylides and disubstituted acetylenes (*Scheme 2.14c*).[431] A 5-membered rhodacycle, resulting from nucleophilic attack of the ylide onto the metal with subsequent C-H insertion into the aromatic *ortho* position of the ylide, is the key intermediate. The carbenes derived from sulfoxonium ylides can also be formally dimerized to isocoumarins by ruthenium(II) catalysis (*Scheme 2.14d*).[432] The reaction is mechanistically similar to the aforementioned napthol synthesis. Last but not least, furans can be synthesized by the reaction of β-diketones with sulfoxonium ylides using Ru(II) as the catalyst. Again, a migratory insertion of the Ru-carbenoid is the mechanistic keystep.[433]

2.1.5. Transition metal-mediated olefination reactions

2.1.5.1. *Overview*

Olefins are among the most studied functional groups in organic synthesis. Their intriguing properties were already under study in 1795 by Dutch researchers. They observed that ethene and

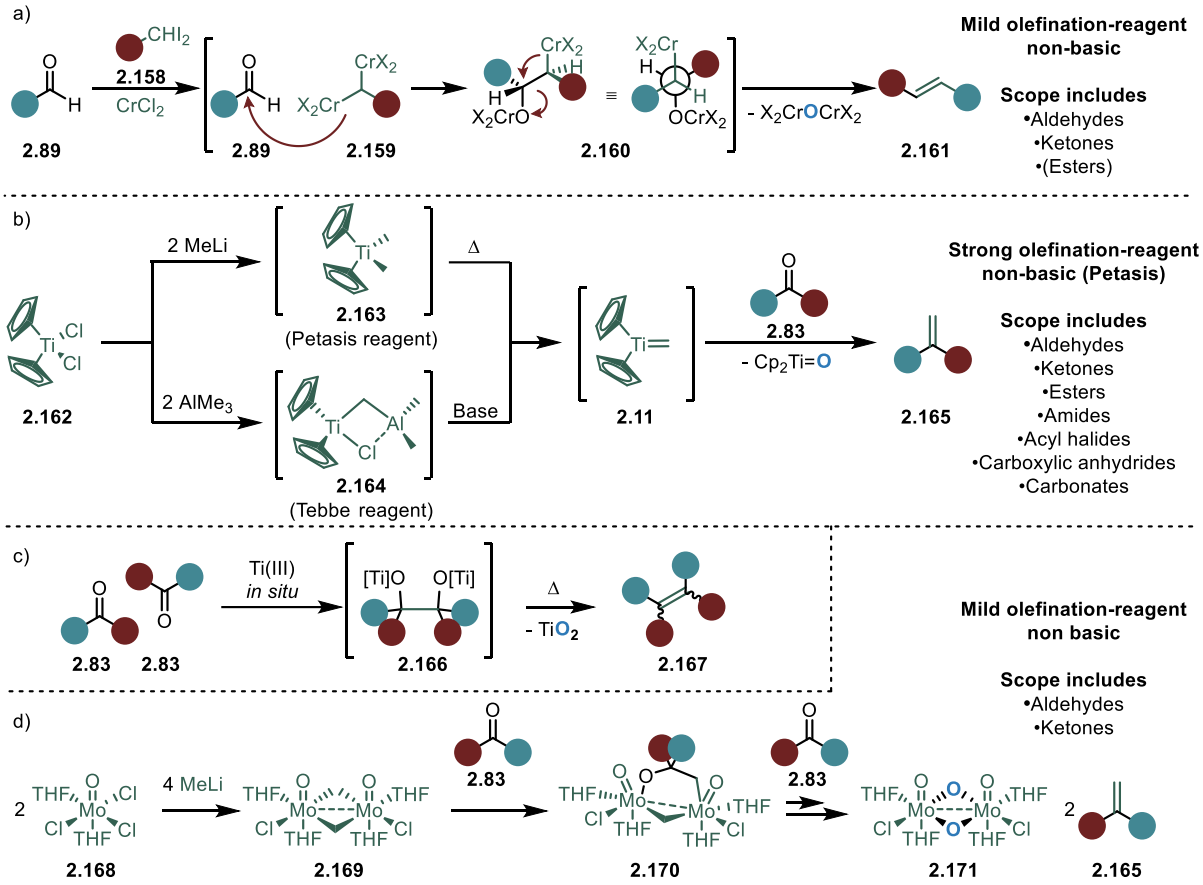
chlorine react together to form a colorless liquid. This reaction persuaded the scientists of the time to name ethylene “gaz heileux” (*i.e.* oil-forming gas), which was soon changed to “gaz oléfiant”.[434] 200 Years later, the heritage of these scientists is still preserved in the term “olefin”, probably the most common description of molecules that carry a C-C double bond. The importance of olefins has been the driving force for the development of many reactions in which C-C double bonds are formed. Many of them were named after their discoverers. Arguably, the most prominent reaction remains the Wittig-olefination,[205,206] which was acknowledged with the Nobel Prize in Chemistry in 1979. Besides the aforementioned named reaction, many other classical olefinations exist, which likewise do not rely on transition metals *e.g.* Horner-Wadsworth-Emmons,[435–437] Julia,[438] Peterson,[439] and the Ramberg-Bäcklund[440] reaction. To add to this, the azine-based olefination developed in our laboratories is also transition metal free.[441] Nevertheless, an impressive number of transition metals are able to promote the formation of double bonds, as we will discuss in the next subchapters.

2.1.5.2. *Metals as reagents in olefination reactions*

The majority of olefination reactions involving metals as stoichiometric reagents are based on organometallic compounds which carry an oxophilic metal. These complexes exchange their organic ligand with the oxygen of a carbonyl group to eventually form a C-C double bond. Also the non-transition metal based Wittig-, HWE-(oxophilicity of phosphorus (Kepp scale)[442] Θ(P) = 0.7) and Peterson-reaction (Θ(Si) = 0.8) use this principle as the thermodynamic driving force.

Cr(II) (Θ(Cr) = 0.6) is used in the Takai-Utimoto olefination (*Scheme 2.15a*).[443–445] The authors propose two oxidative additions to form a *bis*Cr(III) organometallic species. The Lombardo-modification uses weakly-oxophilic zinc(0) (Θ(Zn) = 0.2) for the oxidative addition but the organometal is then likely transmetallated with highly oxophilic titanium(IV) (Θ(Ti) = 1.0).[446,447] Both reactions are usually selective for aldehydes and ketones and, unlike the Wittig reaction, they tolerate a large variety of base-sensitive

functional groups. However, when TMEDA is added to the Lombardo conditions, olefination of carboxylic esters and amides can be observed.[448]

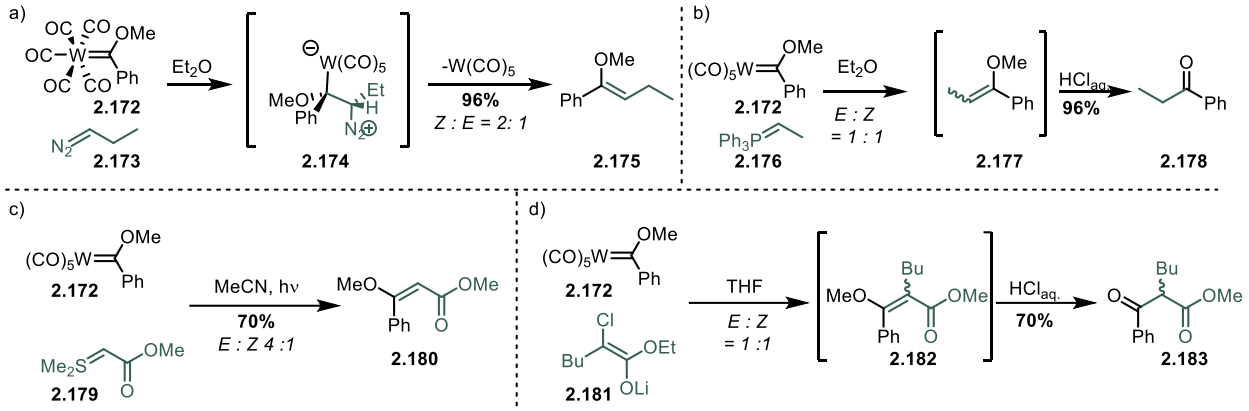


Scheme 2.15 – a) The Takai-Utimoto olefination. b) The Tebbe-Petasis reaction. c) The McMurry coupling of two ketones. d) The Kauffmann olefination.

Titanium is applied as a carbene complex in the Tebbe[449]-Petasis[450]-olefination, which proceeds *via* a C=O, Ti=C → C=C, Ti=O metathesis reaction (*Scheme 2.15b*). The carbene complex intermediate is highly reactive and able to olefinate almost all carbonyl functionalities.[3] Because the carbene complex **2.11** can also act as a catalyst for ring-closing metathesis (RCM), domino reactions involving olefination and RCM have been reported.[451]The same Ti-O affinity is exploited in the McMurry coupling where chemically inert TiO_2 is formed (*Scheme 2.15c*).[3,452] Intermolecular cross-couplings are also possible with modest selectivity.[453]

The group of Knochel showed that Zr(IV) (Θ(Zr) = 0.8) in combination with Zn(II) is also very effective in the olefination of aldehydes.[454] Molybdenum (Θ(Mo) = 0.6) or Tungsten (Θ(W) = 0.8) are used in the very mild and synthetically useful Kauffmann olefination, which operates *via* the exchange of two Mo-Mo methylene bridges with oxygen atoms (*Scheme 2.15d*).[455] The reagent is so mild that it is compatible with the Grubbs II catalyst in one-pot.[456] Similarly, a rather exotic oxophilic uranium complex (Θ(U) = 1.0) can also be applied in a general $CH_2 \leftrightarrow O$ exchange by the same mechanism.[457]

Early observations describe the tendency of stable metal carbenoids to decompose into homocoupling products (alkenes) under heating.[357,458] Since the 1970's those metal-carbene complexes have served as precursors for olefins. The W(0) complex **2.172** (*Scheme 2.16a*) reacts for instance in quantitative yield with aliphatic diazoalkenes, although the *Z : E* selectivity is very modest.[459] Similarly, phosphonium-ylides can be used for olefination (*Scheme 2.16b*). The reaction in this case shows no stereoselectivity and is not compatible with Fischer-carbenoids carryings α-protons, since the Wittig-reagent is basic enough to deprotonate them.[459,460] Sulfonium-ylides show a similar reactivity (*Scheme 2.16c*). Stereoselectivity which is usually observed is sometimes absent on other substrates.[461] The reactions were carried out under light irradiation, but the authors show that they worked similarly under thermal conditions (with prolonged reaction times). Masked carbenes, such as α-chloro lithium enolates, can also be used in similar olefination reactions, but again with the absence of stereoselectivity (*Scheme 2.16d*). Due to the high basicity of the lithium enolate, enolizable Fischer-carbenes cannot be used.[462] The reaction works analogously with α-bromo enolates.

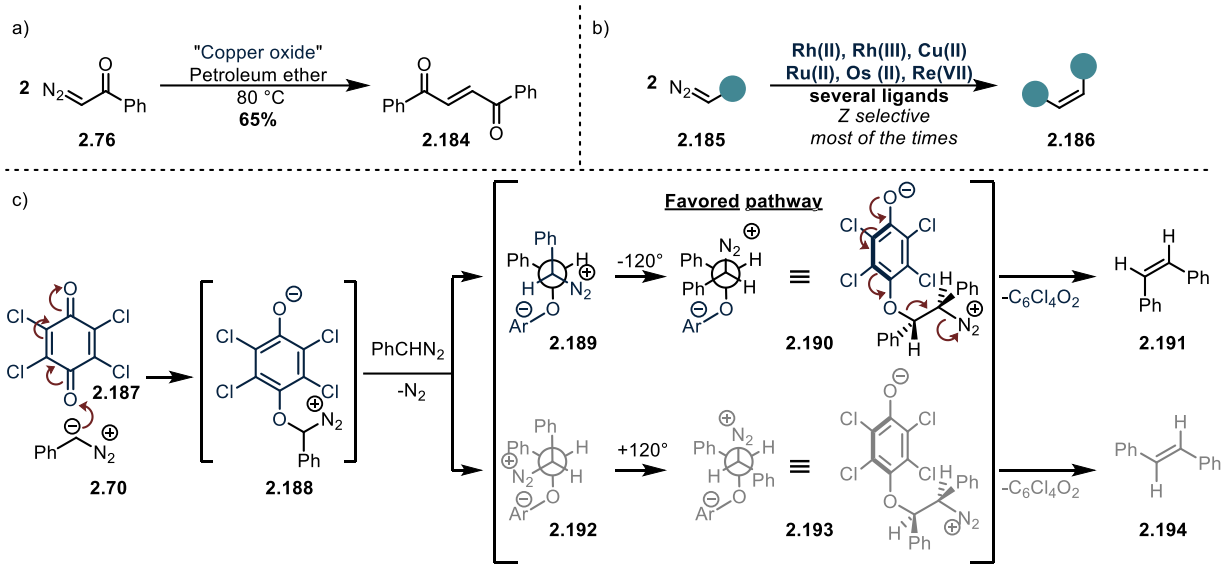


Scheme 2.16 – a) Fischer-tungsten-carbene complexes react with diazoalkanes to form enolethers. b) Phosphonium ylides show a similar reactivity. c) Sulfonium ylides display some stereoselectivity for the same reaction, which is promoted by light irradiation. d) α-Chloro enolates are used as masked carbenes in the same manner.

2.1.5.1. *Metals as catalysts in intermolecular olefination reactions*

The formal dimerization of carbenes derived from diazocompounds (*quasi*-dimerization) has been known since 1906. In that year, Silberrad and Roy described diethylfumarate (or diethylmaleate) as an intermediate when they treated EDA with copper dust.[463] Similarly, in 1938 Grundmann noticed that "*trans*-α,β-Dibenzoyl-äthylen" was formed when diazoacetophenone was reacted with "copper oxide" (*Scheme 2.17a*).[464] Later on, equivalent *quasi*-dimerizations have been observed with other monosubstituted α-diazoketones,[333,335,354,370,377] aryldiazocompounds,[369,383,465] lactams[466] α-diazomalonate[336] and several α-diazoesters.[333,335,349,376,391,395] It is interesting that, in most of these cases, the *Z*-isomer was preferentially formed, although very different metals (Rh(II), Rh(III), Cu(II), Os(II), Ru(II)) and a variety of different ligands were used (*Scheme 2.17b*). The few *E*-selective examples were either copper catalyzed or a Pt(0) phosphine complex was involved.[400] Even $MeReO_3$, which does not form metal-carbene complexes (as previously discussed) generates *Z*-olefins selectively from diazocompounds.[407] The same *Z*-preference has been strikingly observed in the formation of stilbene from the reaction of two molecules of phenyldiazomethane without the use of a metal, but *via* organocatalysis.[467] The authors propose the following mechanism (*Scheme 2.17c*): chloranil (**2.187**) reacts with phenyl diazomethane to form the masked carbene **2.188** which reacts irreversibly with another molecule of $PhCHN_2$ under nitrogen extrusion. Two diastereoisomers can be preferentially

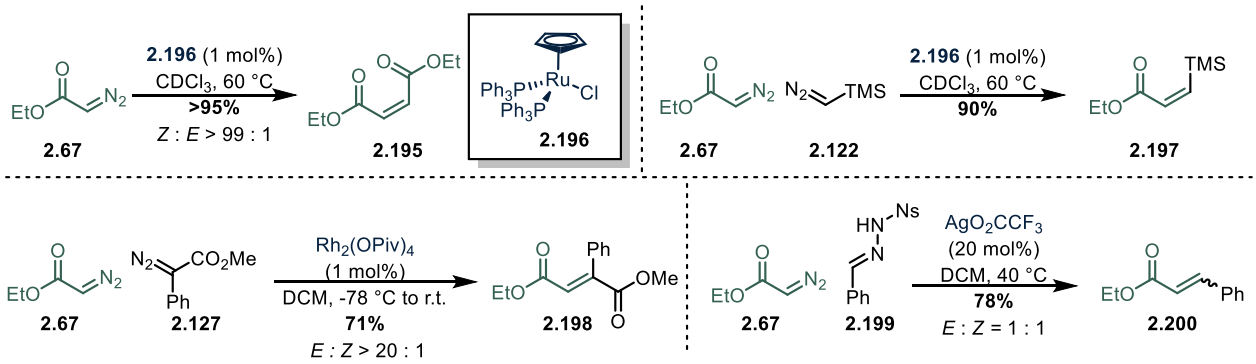
formed in this addition event (**2.189** and **2.192**) due to attractive Coulombic interactions. The authors argue that **2.189** is preferred due to steric reasons (H rather than N_2^+ in the sterically most congested position). After rotation around the central C-C axis the antiperiplanar arrangement **2.190** enables an elimination reaction to give the *Z* isomer as the major product. The same mechanism was later adapted for the metal-catalyzed *quasi*-dimerization of diazocompounds.[369,375,383]



Scheme 2.17 – a) First observed quasi-dimerization of diazocompounds. b) Several other metals catalyze the same reaction with similar stereoselectivity. c) Model for the selective formation of the Z-product

Rigo *et al.* found a Ruthenium(II) half-sandwich complex delivered almost complete *Z*-selectivity (*Scheme 2.18a*).[333,335] In a follow up paper, they noticed that the carbenes derived from two different diazocompounds dimerize in a non-statistical manner (in favor of the cross-coupling), when the two reaction partners differed sufficiently in their electronic features. Most notably, TMS-diazomethane reacted with almost complete selectivity with EDA to form the β-TMS enoate (*Scheme 2.18b*).[334] A few years later, respectable cross-coupling selectivities were achieved by steric discrimination.[375,378] In 2011, the principle of electronic discrimination was further pursued by Davies *et al.*, when they used a Rh(II) catalyst for the cross-coupling of donor-acceptor diazocompounds with α-diazocarbonyls.[347] The reaction showed to be highly cross-coupling- and stereoselective and afforded the alkene products in high yields. Similar reactions have been later studied with silver(I) and copper(I) catalysts.[353] The group of Sun used

a similar strategy for the stereoselective synthesis of tetrasubstituted alkenes by using gold(I) or Cu(II).[368,405] Wu, Bi and coworkers rendered this approach more general by coupling acceptor diazocompounds with unstable *in situ* generated diazoalkanes (*Scheme 2.18c*). However, stereoselectivity was practically absent.[390] Diazocompounds have also been cross-coupled by using blue light irradiation without the need of a metal.[468]

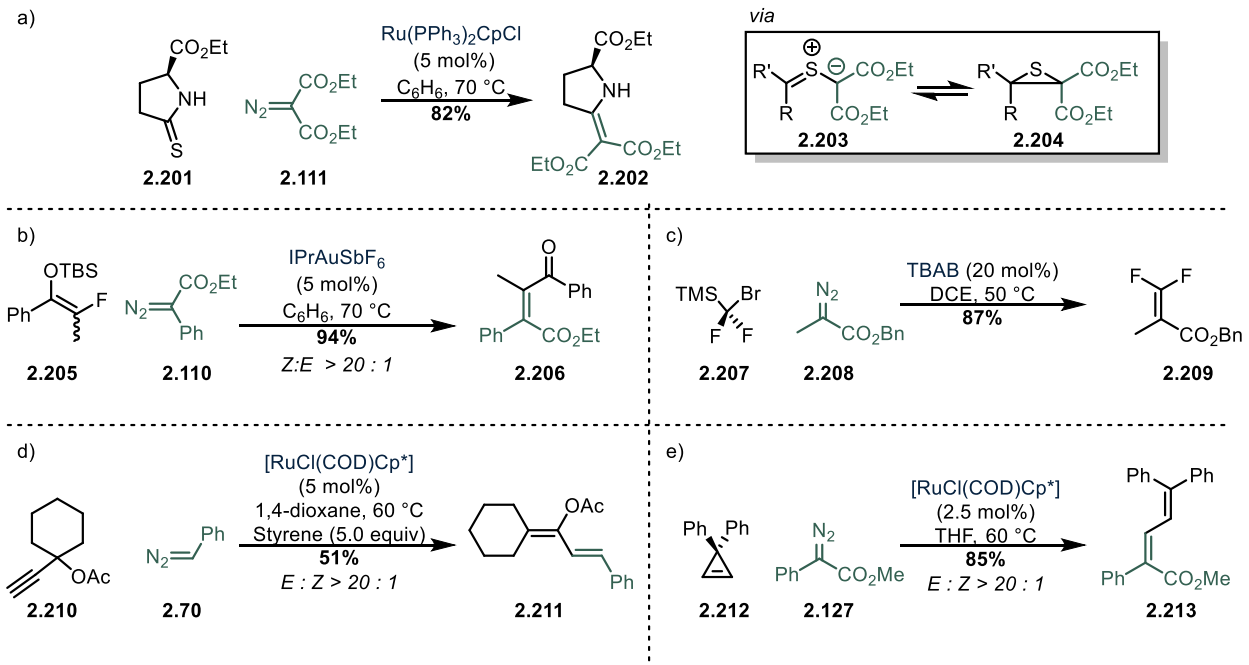


Scheme 2.18 – a) Highly stereoselective quasi-dimerization of diazoesters. b) Highly cross-coupling selective quasi-dimerization of diazocompounds. c) Stereoselective cross-coupling of donor-acceptor diazocompounds with acceptor diazocompounds. d) Cross-coupling of acceptor-diazocompounds with in situ generated diazoalkanes.

Diazocompounds have been also transformed into olefins by metal-catalysis in the presence of other coupling partners. Thioamides have been shown to react smoothly with the metal carbenoid formed by a diazocompound and the aforementioned half-sandwich ruthenium complex to give an ylide (*Scheme 2.19a*). This ylide cyclizes to the thiirane and gives the enamine after sulfur extrusion.[336] The reaction is reminiscent of the Barton-Kellogg olefination (see Chapter 2.1.3.2.). Olefination using α-fluoro silyl enolethers and donor/acceptor diazocompounds under Au(I) catalysis has also been studied (*Scheme 2.19b*). The mechanism involves either the cyclopropanation of the enol ether, or a simple nucleophilic attack onto the electrophilic metal carbenoid.[406] Interestingly, a very similar reaction has been published two years before without the use of a catalyst by using free difluroro-carbenes (*Scheme 2.19c*).[469] An analogous reaction employing α-deprotonated sulfones *via* copper(I) catalysis has also been reported. The sulfone moiety mimics the role of the α-halogen since it can act as a leaving group (sulfite).[355]

Conceptually similar but with the use of superstoichiometric amounts of a metal is the homocoupling of formal carbenes derived from dichlorides by using elementary copper.[470]

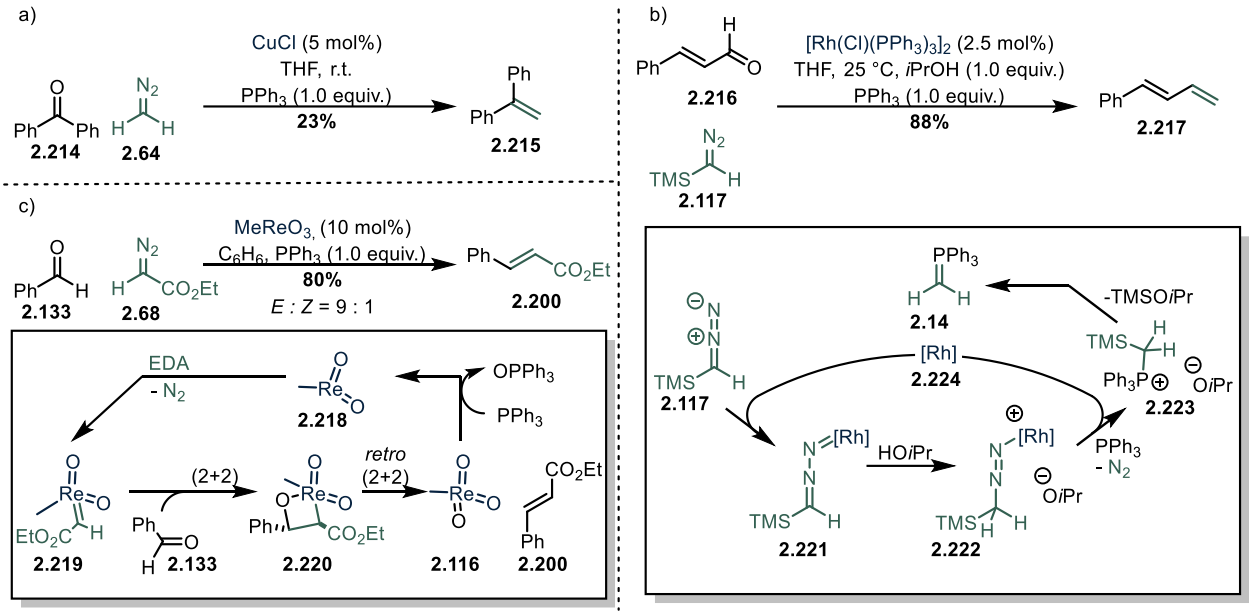
A Ru(II) half-sandwich complex has been used in an olefination reaction with non-stabilized diazocompounds and propargylic esters (*Scheme 2.19d*).[337,338] It is intriguing that in the mechanism of this reaction two different ruthenium carbenoids are proposed, one derived from the propargylic ester and the other one from the diazocompound. This chemistry has been later extended to the olefination of plain alkynes with diazocompounds by the same group.[339] Very recently cyclopropenes were used in a similar fashion to form 1,3-dienes (*Scheme 2.19e*).[332]



Scheme 2.19 – Barton-Kellogg-type olefination using acceptor-acceptor diazocompounds and thiolactams under ruthenium catalysis. b) Masked carbenes as olefin coupling partners with donor-acceptor diazocompounds under gold catalysis. c) A similar metal-free approach. d) Interesting olefination by using propargylic esters and non-stabilized diazocompounds. e) Olefination using donor-acceptor diazocompounds and cyclopropenes under ruthenium catalysis.

Another common strategy in metal-catalyzed olefinations is to combine a diazocompound with a carbonyl compound under loss of N_2 and oxygen. The requirement for such a reaction is the use of a reductant, since the carbonyl compound must formally gain two electrons. Most commonly, phosphines are used, because their oxophilicity is a thermodynamic sinkhole for the overall transformation. The

earliest example was pioneered by Wittig and Schlosser in 1962, in the decomposition of diazomethane with Cu(I) in presence of triphenylphosphine and benzophenone (*Scheme 2.20a*). The desired product was observed in 23% yield.[471] The more efficient methylation of aldehydes by Rh(I) catalysis in combination with TMS-diazomethane has been reported in 2001 by Lebel and co-workers (*Scheme 2.20b*). The reaction relies on the *in situ* formation of phosphonium ylides under nitrogen extrusion with the assistance of the catalyst. The use of an equimolar amount of isopropanol accelerated the reaction significantly. Intriguingly, the reaction does not proceed *via a metal*-carbene complex but rather an S_N2 displacement of the N_2^+ moiety by the phosphine, explaining the strong acceleration effect of the protic additive (*Scheme 2.20b – box*).[418,472]

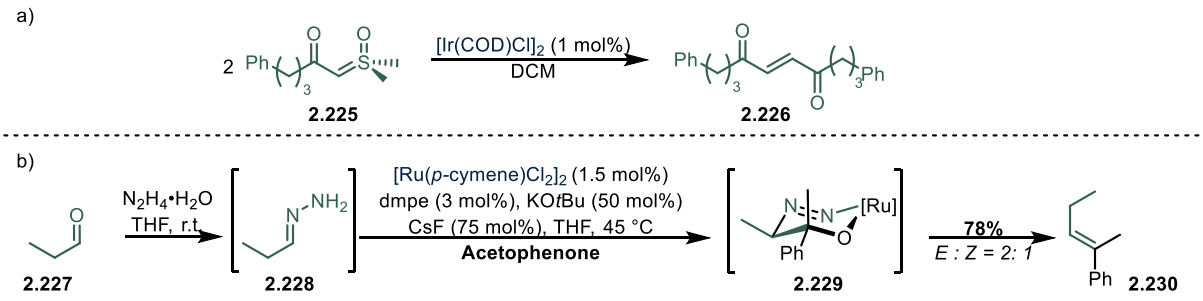


Scheme 2.20 – The first metal catalyzed Wittig-type olefination with diazocompounds. b) A similar but more efficient approach. c) Re(VII) in a similar transformation.

Stabilized diazocompounds such as EDA were not effective. Similar approaches by using other catalysts,[361,419,473] and/or other reductants such as dibutyltelluride,[346] or triphenylarsine have been studied as well.[474] All of these approaches were perhaps inspired by a paper from Herrmann and Wang, where methyltrioxorhenium (MTO) was applied in a similar reaction (*Scheme 2.20c*). The mechanism is believed to be different, and was spectulated to proceed without the formation of an ylide. It is more

likely that a Re(V) species is generated (**2.218**), which forms a carbenoid with the diazocompound.[393] A similar reaction was reported by Lu *et al.* with the use of Mo(IV) in 1989, two years before the report of Herrmann.[475]

Sulfoxonium ylides have been observed to undergo *quasi*-dimerization with the loss of two sulfoxide molecules. In an iridium(I)-catalyzed reaction, Mangion and coworkers expected a C-H insertion but observed almost quantitative olefination with full stereocontrol (*Scheme 2.21a*). Unfortunately, they did not explicitly specify which isomer they found.[476] A similar reaction was observed when a sulfoxonium ylide was irradiated with UV-light. The product was not isolated because a subsequent cyclopropanation took place to generate a symmetric trimer.[256] Li, Jang and coworkers disclosed an olefination by coupling ketones with aldehydes in a McMurry-type disconnection (*Scheme 2.21b*). The aldehyde is *in situ* converted to the hydrazone, which attacks the ketone *via* assistance of the half-sandwich Ruthenium catalyst, in an Umpolung-fashion, to form a proposed 6-membered ruthenacycle. Following loss of water and N_2, the desired olefin is generated in good yield.[477] The work is based on the findings by the groups of Schwartz[478] (stoichiometric Zr-complex) and Baldwin (metal free).[479]

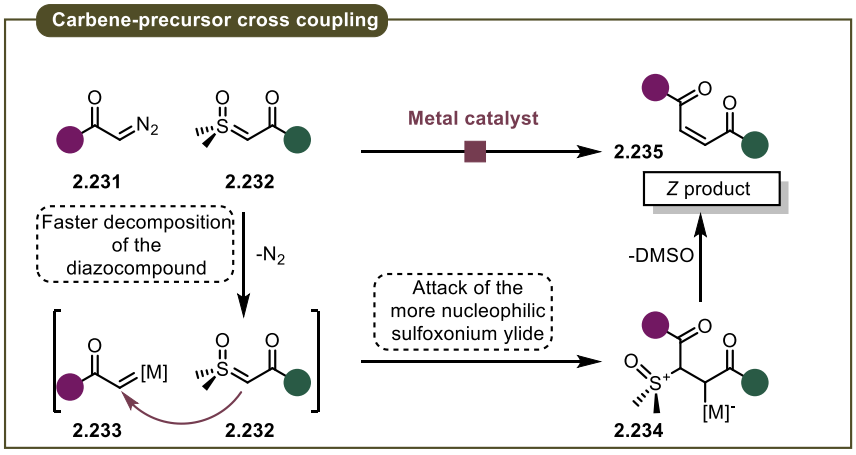


Scheme 2.21 a) Quasihomodimerization as a side reaction. b) Cross-olefination of two carbonyl compounds (McMurry type) by using hydrazine and a Ru(II) catalyst.

2.2. Objectives

As discussed in the introduction, the nucleophilicity of sulfoxonium ylides is generally higher than that of diazocompounds. Conversely, metal-carbene complexes are formed easily under extrusion of nitrogen with diazocompounds, whereas sulfoxonium ylides react analogously only under relatively harsh reaction conditions. The generated acceptor metal-carbene complexes react as electrophiles and have been observed to form dimers (as olefins) of the carbene derivative in a stereoselective manner, often favoring the *Z*-isomer.

The central hypothesis of this work is that a metal-catalyzed, selective cross-olefination of sulfoxonium ylides and diazocompounds should be possible. This is because the metal might react faster with the diazocompound to form a Fischer-type carbenoid, which should then be preferentially attacked by the more nucleophilic sulfoxonium ylide (*Scheme 2.22*). This approach would resemble the formal dimerization of carbenes from their precursors. Furthermore, drawing on the known results in the literature, we expect that the *Z*-isomer of a 1,2-disubstituted olefin should be preferentially formed. An obvious pitfall for this reaction would be the cyclopropanation of the alkene product, either by a Johnson-Corey-Chaykovsky cyclopropanation or by the metal-carbene complex.

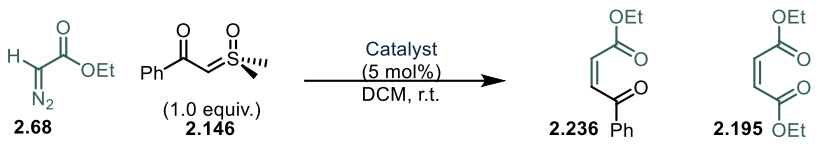


Scheme 2.22 – Central hypothesis of the project

2.3. Results and discussion

2.3.1. Proof of principle

In order to test our hypothesis, ethyl diazomethane (EDA) and a stabilized sulfoxonium ylide **2.146** were dissolved in DCM at room temperature with one of three selected catalysts (*Table 2.3.*). Gratifyingly, the Ru(II) half-sandwich complex [Ru(*p*-cymene)Cl_2]$_2$ showed a respectable 31% NMR-yield for the cross-coupled product **2.236** with a low *Z : E* ratio (1.9 : 1) in the first experiment. *Quasi*-homodimerization of the diazocompound **2.195** prevailed and was identified from the beginning as the major competing pathway (42% NMR yield). Conversely, the analogous homodimer derived from the sulfoxonium ylide was only detected in trace amounts. Dirhodium(II) tetraacetate on the other hand was surprisingly less effective; only 15% of an equimolar mixture of the *E* and the *Z* product was observed. The square planar d^8 complex [IrCOD)Cl]$_2$ showed similar reactivity to the rhodium catalyst. These preliminary results were nevertheless encouraging, particularly as the desired product was observed in a clean reaction profile with the expected *Z*-selectivity. Moreover, the feared cyclopropanation of the product was absent and was pleasingly never observed in the course of this study. This is quite surprising given that substrates which resemble our product have been used in Johnson-Corey-Chaykovsky reactions using stabilized sulfoxonium ylides, even at low temperature.[480]



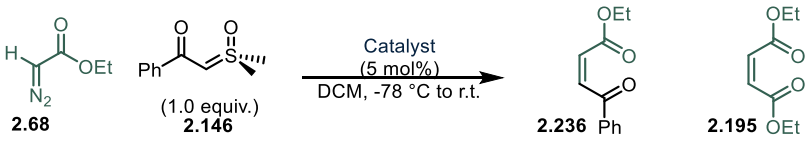
Entry	Catalyst	Yield (NMR) **2.236**	*Z : E* **2.236**	Yield (NMR) **2.195**	*Z : E* **2.195**
1	[Ru(*p*-cymene)Cl_2]$_2$	31%	2 : 1	42%	1 : 1
2	$Rh_2(OAc)_4$	15%	1 : 1	25%	1 : 1
3	[Ir(COD)Cl]$_2$	13%	1 : 1	15%	1 : 1

Table 2.2 – First trial of the cross-olefination reaction

2.3.2. Optimization of the reaction conditions

We recognized early that higher yields were obtained when the reaction was set up at -78 °C and then gradually warmed up to room temperature (*Table 2.3*). The [Ru(*p*-cymene)Cl_2]$_2$ catalyst delivered, under these conditions, a yield of over 50% by NMR, with the undesired homodimer only being observed in low amounts (*Entry 1*). Moreover, the *Z : E* ratio was enhanced to 8 : 1. At this point, a second screening of the catalyst was undertaken. Unfortunately, the preliminary results obtained with the aforementioned Ru(II) dimer was not improved: other Ru(II) half-sandwich complexes such as [RuCp*(MeCN)$_3$]SbF_6 or [Ru(indenyl)(PPh_3)$_2$Cl] were either almost inactive or favored the *quasi*-homodimerization of the diazocompound (*Entry 2/3*). When the *p*-cymene ligand of the dimeric Ru-compound was exchanged with benzene or mesitylene a deteriorating effect (in yield and in stereoselectivity) was observed (*Entry 4/5*). Moreover, the catalyst [RuCp(PPh_3)$_2$Cl], which was used in high efficiency by Rigo *et al.* (*Scheme 2.18a/b*), seemed to be a sluggish promoter under these conditions (*Entry 6*).[333,335] Indeed, in the reported reaction much higher temperatures were required to release one of the phosphine ligands from the 18e$^-$ complex.

With Fe(II) and Fe(III) based catalysts no reaction took place and the starting material was fully recovered (*Entry 8/9*). Cu(I) was slightly better: the desired product was obtained but in a low yield and without significant stereoselectivity (*Entry 10*). When phenanthroline was added as ligand, the yield for the cross-coupled product improved slightly, although the homo-coupled product (derived from the diazocompound) was the major product (*Entry 11*). Moreover, the *E*-isomer was favored, which has been reported in the literature when Cu catalysts were used (see section 2.1.5.1). Rh(II)-acetate was seemingly not catalytically active at low temperatures; only trace amounts of the homodimer derived from diazoethylacetate were observed (*Entry 12*). The Rh(III) compound [Cp*$RhCl_2$]$_2$ showed similar results (*Entry 13*), and [IrCOD)Cl]$_2$ appeared to promote the reaction only at very low rates. While several Pd(II) species were totally inactive as a catalyst (*e.g. Entry 15*), a Pd(0) complex showed traces of the product with *E*-selectivity (*Entry 14*). Echavarren's Au(I) catalyst was also seemingly inert (*Entry 16*).



2.68 **2.146** **2.236** **2.195**

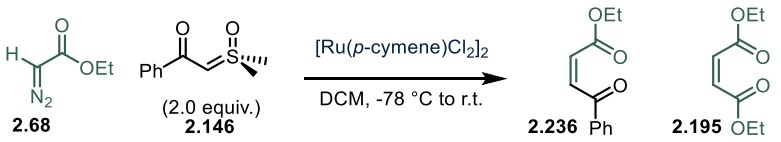
Entry	Catalyst	Yield (NMR) **2.236**	*Z : E* **2.236**	Yield (NMR) **2.195**	*Z : E* **2.195**
1	$[Ru(p\text{-cymene})Cl_2]_2$	53%	8 : 1	5%	>25 : 1
2	$[RuCp^*(MeCN)_3]SbF_6$	3%	4 : 1	N.D.	/
3	$[Ru(indenyl)(PPh_3)_2Cl]$	18%	8 : 1	41%	>25 : 1
4	$[Ru(benzene)Cl_2]_2$	38%	4 : 1	<3%	/
5	$[Ru(mesityelene)Cl_2]_2$	25%	3 : 1	14%	4 : 1
6	$[RuCp(PPh_3)_2Cl]$[a]	13%	1 : 1	6%	2 : 1
7	Cp_2Ru	N.D.	/	N.D.	/
8	FeI_2	N.D.	/	N.D.	/
9	$[FeCp(CO)_2THF]BF_4$	N.D.	/	N.D.	/
10	CuBr	3%	1 : 1	6%	1 : 2
11	CuBr/Phenantroline	9%	2 : 7	33%	1 : 7
12	$Rh_2(OAc)_4$	N.D.	/	<3%	/
13	$[Cp^*RhCl_2]_2$	<3%	/	10%	3 : 2
14	$Pd(dba)_2$	4%	1 : 3	6%	1 : 6
15	$Pd(MeCN)_2Cl_2$	N.D.	/	N.D.	/
16	Echavarren's catalyst	N.D.	/	N.D.	/

Table 2.3 – Second screening of the catalyst [a] 2.0 equiv. of sulfoxonium ylide used.

The yield was later further improved by using 2 equivalents of the sulfoxonium ylide (*Table 2.4*). Gratifyingly, the geometrical isomers (*E/Z*) of **2.236** were readily separable by column chromatography. In addition, the reaction was insensitive to moisture and/or air. However, lower catalyst loading (2.5 mol% and 1.25 mol%) diminished the yield considerably and non-chlorinated solvents were unsuitable, often because they could not dissolve the ylide to an acceptable extent. The concentration of the reaction was optimal at 0.08 M: while molarities of ≤0.05 M diminished the yield considerably, the use of less solvent was incompatible with the moderate solubility of the sulfoxonium ylide and the catalyst at low temperatures.

Unsurprisingly, catalysis was inhibited by a variety of ligands (Me_2S, PPh_3, pyridine, pyrimidine or phenantroline). Pyridines, phosphines, phosphites and arsines are reported to generate stable monomeric $18e^-$ complexes when mixed with $[Ru(p\text{-cymene})Cl_2]_2$.[481] This information could be used to our benefit:

pyridine was subsequently chosen as quencher of the reaction. When PPh_3 was used instead, full isomerization into the thermodynamically preferred *E*-isomer was observed. This will be discussed later in more detail (see section 2.3.4.4.). Dimethyl sulfide (DMS) was similarly a very strong inhibitor. Indeed, when sulfonium ylides were used instead of sulfoxonium ylides, the reaction ceased after 11% conversion. This corresponds roughly to one "catalytic cycle" and can be explained by the release of DMS when sulfonium ylides are reacted. Interestingly, DMSO (which is released during the reaction with sulfoxonium ylides) also slowed down the reaction. DMF, a less coordinative solvent, did not affect the outcome of the reaction to a strong degree. In addition, the use of halophilic additives such as AgOTf or $NaBAr_F$ as co-catalysts lowered the yield and the stereoselectivity.



Entry	Additive	Catalyst loading	Yield (NMR) **2.236**	*Z : E* **2.236**	Yield (NMR) **2.195**	*Z : E* **2.195**
1	/	5 mol%	71%[a]	9 : 1	9%	>25 : 1
2	/	2.5 mol%	50%	5 : 1	12%	5 : 1
3	/	1.3 mol%	48%	3 : 1	12%	5 : 1
4	Me_sS (2.0 equiv.)	5 mol%	N.D.	/	N.D.	/
5	Pyridine (2.0 equiv)	5 mol%	N.D.	/	N.D.	/
6	PPh_3 (10 mol%)	5 mol%	N.D.	/	N.D.	/
7	PPh_3 (10 mol%)	5 mol%	N.D.	/	N.D.	/
8	Phen (10 mol%)	5 mol%	7%	5 : 2	8%	3 : 1
9	DMSO (5.0 equiv)	5 mol%	19%	>25 : 1	17%	2 : 1
10	DMF (2.0 equiv.)	5 mol%	68%	8 : 1	16%	>25 : 1
11	AgOTf (10 mol%)	5 mol%	33%	3 : 1	25%	5 : 1
12	$NaBAr^F_4$ (10 mol%)	5 mol%	26%	3 : 1	25%	7 : 1

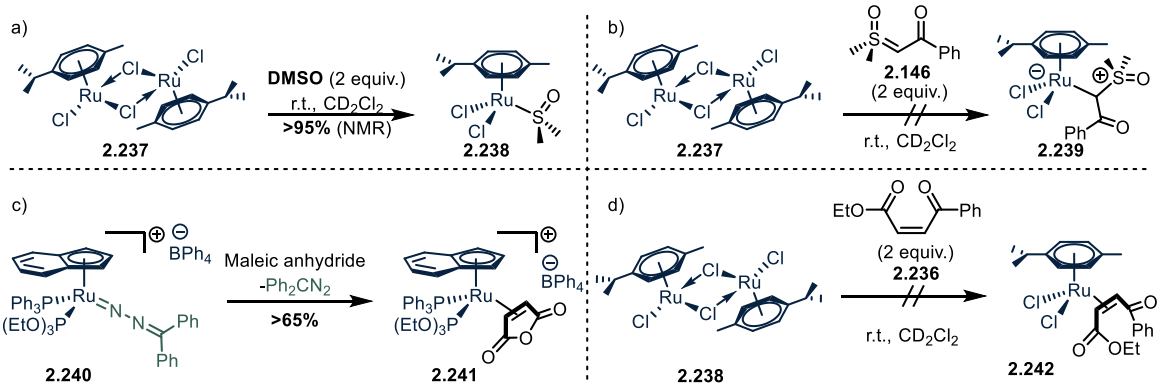
Table 2.4 – Effects of additives and catalyst loading on the cross-olefination reaction. [a] isolated yield.

2.3.3. NMR experiments and mechanistic elucidation

An NMR experiment revealed that the $18e^-$ dimer dissociated completely in the presence of two equivalents of DMSO into the $18e^-$ complex [Ru(*p*-cymene)(DMSO)Cl_2] (**2.239** - *Scheme 2.2.3a*). This compound has been characterized and synthesized by dissociation of the dimer before[482,483] and has been

reported to form a coordinative bond *via* the sulfur atom of the sulfoxide.[484] The coordination of DMSO to the complex was strong enough to displace several pyridine ligands and questioned the result of several medicinal chemistry studies, which used a pyridine complex in DMSO.[482] Ruthenium is slightly more thiophilic than oxophilic (Θ(Ru) = 0.4, S(Ru) = 0.6).[442] However, sulfoxides can bond either *via* oxygen or *via* sulfur to the ruthenium center depending on several features. When the electron density at the metal is high enough to enable π-backdonation into the antibonding orbitals at sulfur, S-coordination is generally favored. Thus, the coordination mode can also be interpreted as evidence for the ruthenium atom being relatively electron-rich.[485]

As mentioned in the introduction, several metals tend to form complexes with sulfoxonium ylides. However, this seems not be the case in our system: when the dimeric complex **2.238** was mixed with an ylide, there was no change in the chemical shifts of the catalyst in the ^{1}H NMR spectrum (*Scheme 2.23b*). Addition of DMSO to this mixture led again to the formation of [Ru(*p*-cymene)(DMSO)Cl_2] (**2.239**), whereas the NMR resonances ascribed to the ylide were unaltered.



Scheme 2.23 – a) Dissociation of the dimeric Ru-complex by DMSO. b) Sulfoxonium ylides were not observed to dissociate the dimer. c) Example of a π-acidic olefin as a ligand in a half-sandwich ruthenium complex. d) Dissociation of the Ru-dimer by the product was not observed.

Inhibition of the catalysis could also be caused by one of the products. 2-Ene-1,4-diones have been observed to form relatively strong coordinative bonds with certain half-sandwich Ru(II) species (*Scheme 2.23c*). The diazo ligand was completely dissociated from **2.240** by a maleic anhydride molecule

to form **2.241**. The complex was stable enough to be isolated and fully characterized.[415] Moreover, diethylfumarate has also been reported as a stable ligand on an isolated Ruthenium complex.[486] However, when mixing the dimeric complex **2.237** with 2 equivalents of the product **2.236** in d_2-DCM, the chemical shifts of both species were unaltered suggesting that coordination of the formed olefin, if at all existent, is rather weak. When the catalyst was dissolved in the presence of the diazocompound, the reaction was so fast that the removal of the mixture from the dry ice bath was sufficient to promote its complete *quasi*-dimerization.

In conclusion, these results indicate that the complex [Ru(*p*-cymene)(DMSO)Cl_2] (**2.239**) is formed after one "catalytic" cycle in the cross-olefination reaction, and thus the [Ru(*p*-cymene)Cl_2]$_2$ is actually the precatalyst. Since more DMSO is generated over the course of the reaction, its dissociation from the catalyst can be expected to become thermodynamically increasingly unfavored (Le Chatelier's principle).

Monitoring of the cross-coupling reaction by NMR revealed that the reaction does not take place at the starting temperature (*Figure 2.3*). First traces of products (and byproducts) were detected at -45 °C, suggesting that significant reaction rates are first encountered at temperatures >-65 °C. The rate of formation of the undesired diastereoisomer seems to increase at higher temperature. The *Z : E* ratio at -25 °C, for instance, was >25 : 1. Attempts were made to take advantage of this observation. However although in some cases the *Z : E* ratio was higher, the overall yield for the desired isomer was lower.

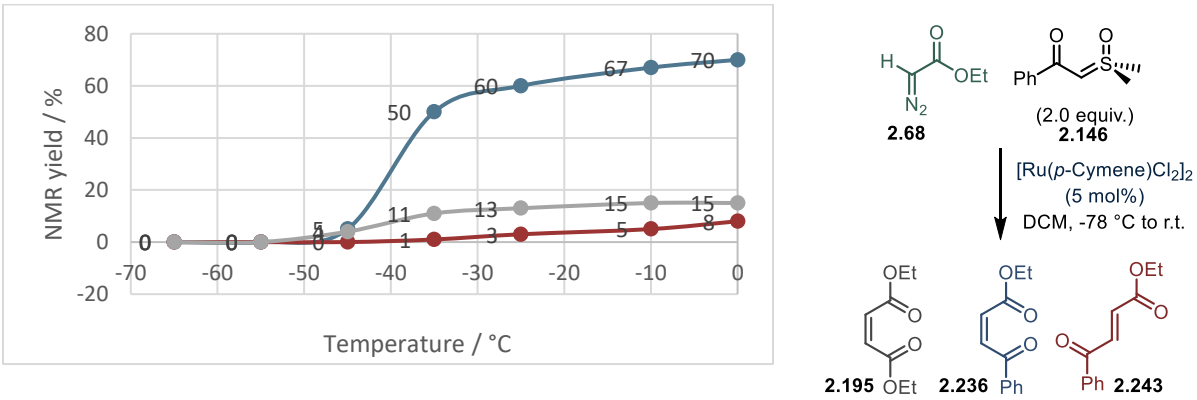
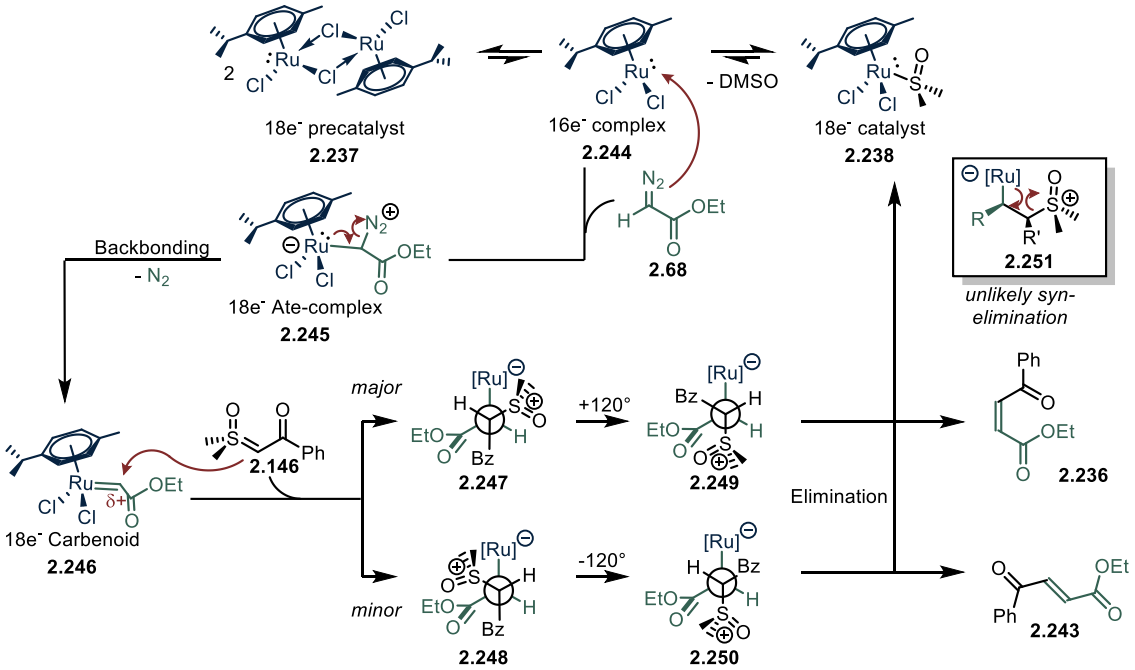


Figure 2.3 – Yields of three different (by)products at different temperatures.

Considering the literature precedence (see section 2.1.5.1) and the aforementioned NMR experiments, we can propose a mechanism for the reaction (*Scheme 2.24*). The dimeric 18e$^-$ precatalyst **2.237** is either in a biased equilibrium with the corresponding monomer **2.244**, or the bridging chloride-ligand is displaced in an S_N2-type reaction by the nucleophilic carbon atom of the diazocompound to form the ate-complex **2.245**. The 18 e$^-$ ate-complex decomposes spontaneously to the metal-carbene complex **2.246** under nitrogen extrusion, by π-backdonation of the ruthenium atom into the antibonding orbital of the C-N_2^+ bond. The Fischer-type carbenoid is attacked by the nucleophilic sulfoxonium ylide to form the diasteroisomers **2.247** and **2.248** of a second ate-complex. Due to steric constraints, the diastereoisomer **2.247** is favored (over **2.248**). After a rotation of 120° the *anti*periplanar complexes undergo an elimination reaction to form the observed alkenes (**2.249**/**2.250**) and regenerate the catalyst **2.238**. A *syn* elimination of the second ate-complex (**2.251**) can be excluded, since a free coordination site is required for such a pathway.[218]



Scheme 2.24 – Proposed mechanism for the cross olefination reaction.

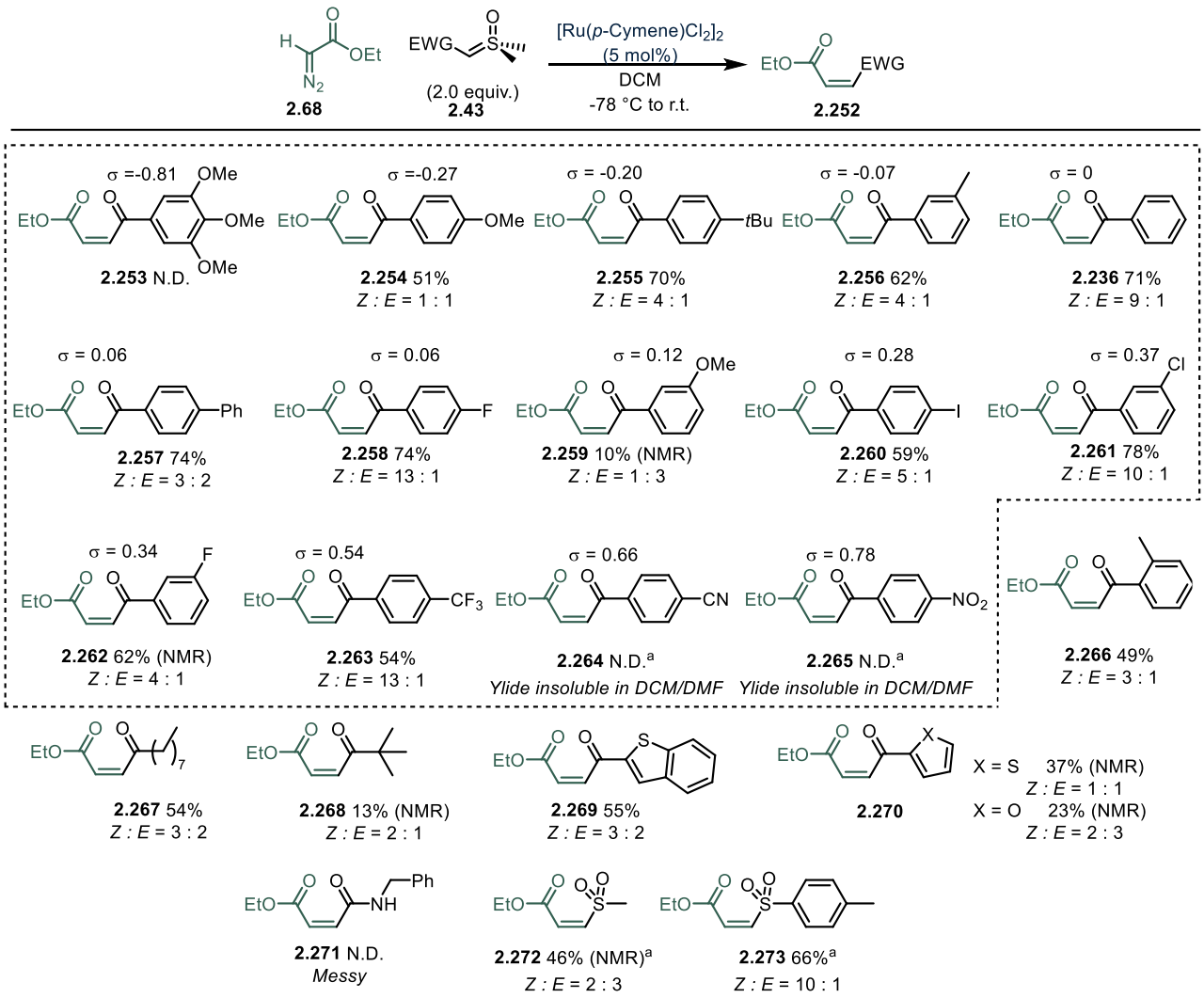
2.3.4. Scope of the reaction

2.3.4.1. *Sulfoxonium ylide scope*

With the optimized conditions in hands, we investigated the scope of the reaction regarding the sulfoxonium ylide partner (*Scheme 2.25*). The ylides can be prepared in one or two steps from commercially available starting materials. The substitution pattern of the aromatic ring was varied and the electronic effects were parameterized by the Hammett substitution constants (σ), since the negatively charged atom is attached to a benzoyl moiety, similar to a benzoate.[487] Electron-donating groups (**2.254** and **2.255**) and electron-withdrawing groups (**2.257** to **2.258**, **2.260** to **2.263**) were both tolerated with *Z : E* ratios up to 13 : 1. There seems to be no clear trend in the correlation between stereoselectivity/yield and substitution pattern of the ring. MeO groups were not tolerated for unknown reasons and nitro- and cyano-substituted substrates were not compatible with the reaction conditions due to their low solubility in DCM and DCM/DMF mixtures. Moreover, *ortho*-substitution of the aromatic ring had a deleterious effect on yield and stereoselectivity. Pleasingly, iodide and other halides were tolerated, without competing oxidative addition, which is known to occur in some Ru(II) half-sandwich complexes with allylic halides.[488] These products are potentially valuable as precursors for further modifications. Some of the products listed are biologically active and show useful medicinal properties.[489,490] The *para-tert*butyl substituted compound **2.255**, for instance, shows antimicrobial activity against *M. tubercolosis* with a minimal inhibitory concentration of only 0.8 µg/mL.[490]

The stereoselectivity of an aliphatic-substituted ylide was low, but the yield was acceptable (**2.267**). Heteroaromatic sulfoxonium ylides gave mostly poor yields and/or poor stereoselectivity. An α-amido ylide (theoretically leading to **2.271**) was also investigated but resulted in a messy reaction profile without providing evidence for the formation of the desired product. The scope was however not restricted to ketones since an ylidic sulfone was converted to **2.272** in an appreciable yield of almost 70%

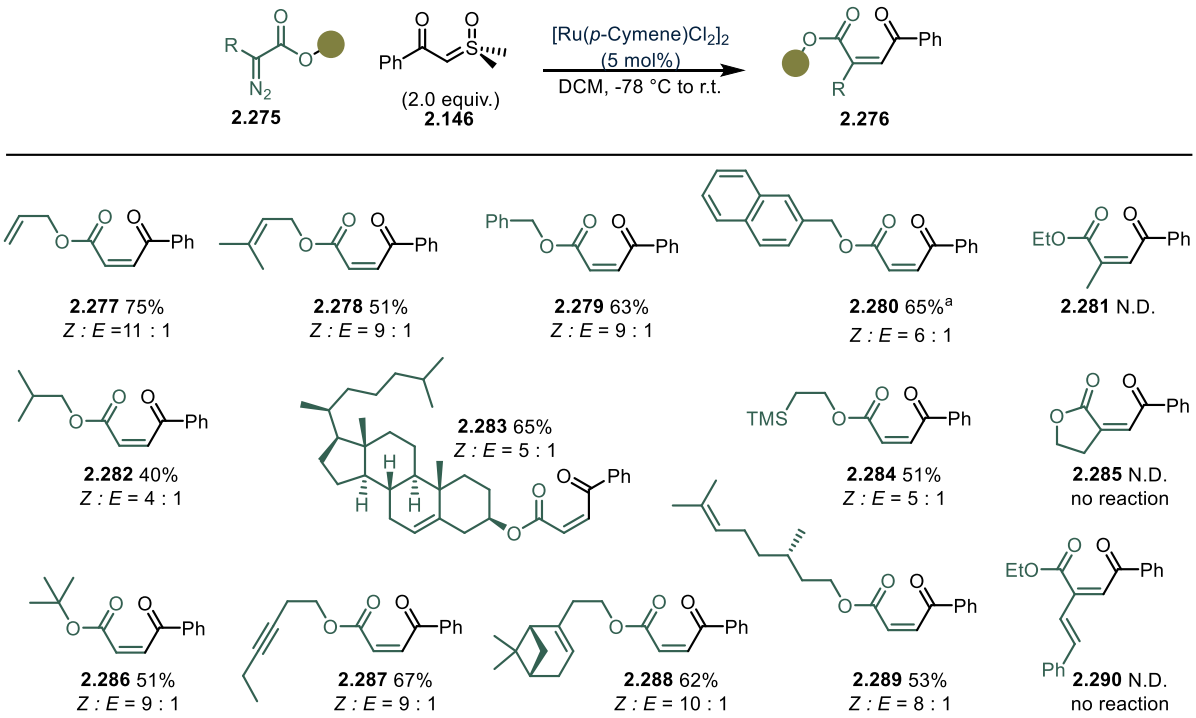
and high stereoselectivity. The solubility of the ylide in DCM was rather low, so that DMF had to be used as a co-solvent. Again the aromatic ring seemed to be crucial to achieve a high *Z : E* ratio (see **2.272**).



Scheme 2.25 – Sulfoxonium ylide scope for the cross-olefination reaction. [a] DMF used as cosolvent. See supporting information for more details. The isolated yields refer to the separated isomers and are cumulative.

2.3.4.2. *Acceptor diazocompound scope*

We then investigated several monosubstituted α-diazoesters and were delighted to find a wide range of tolerated substituents on the ester moiety (*Scheme 2.26*). Interestingly, allylic and benzylic esters were widely tolerated (**2.277** to **2.280**). This is noteworthy because oxidative addition of Ru(0) and Ru(II) to allylic esters has been reported in the literature.[491,492] The internal alkyne **2.287** was similarly tolerated and did not undergo any undesired reaction with the potentially π-acid catalyst.

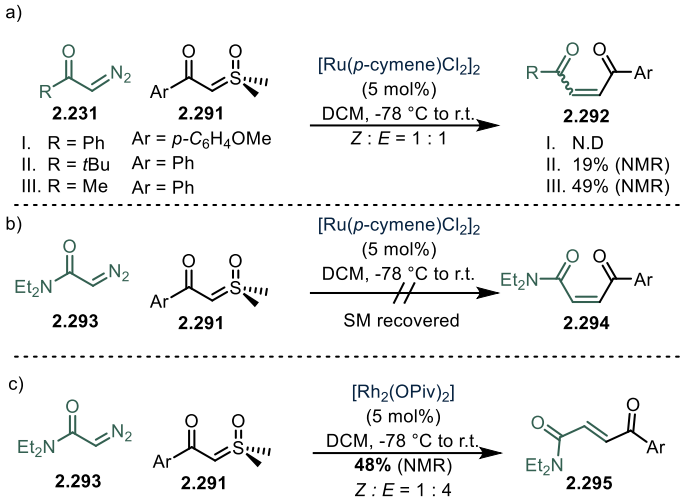


Scheme 2.26 – Diazoester scope for the cross-olefination reaction. The isolated yields refer to the separated isomers and are cumulative.

Olefins containing esters of terpenoid alcohols, such as cholesterol (**2.283**), a β-pinene derivative (**2.288**) or citronellol (**2.289**) were formed without unexpected side reactions. Disubstituted α-diazoesters on the other hand were not compatible. The use of diazoethyl-2-diazopropionate led to a rather messy NMR spectrum of the crude material with no unambiguously identifiable product (**2.281**). These types of diazocompounds are known to undergo several side reactions, particularly involving 1,2-hydride shifts onto the electrophilic carbenoid.[326] The lactone-derivative theoretically leading to **2.285** and donor-acceptor diazocompounds (**2.290**) did not appear to form a metal carbenoid under these conditions; the diazocompounds were recovered in these cases (see *Scheme 2.10c*).

Monosubstituted α-diazoketones typically reacted with no selectivity and, in some cases, they were mostly recovered from the crude reaction mixture (reaction I and II in *Scheme 2.27a*). These compounds are considerably less nucleophilic than their ester counterparts (*Scheme 2.6a*), which may be one of the reasons for the observed lower yields. However, diazoacetone, which is much less sterically

congested than the other two diazoketones investigated, showed a decent yield of 49% by NMR (reaction III – *Scheme 2.27 a*).



Scheme 2.27 – Reactions of diazoketones (a) and diazoamides (b,c) with sulfoxonium ylides and a metal catalyst.

The contrasting reactivity of these diazoketones might be due to differences in their conformational preferences (*cisoid*/*transoid* - *Scheme 2.6b*). Diazoacetone favors the *cisoid* conformer, although, the *transoid*-form can be observed in about 8% at -45°C in solution and is in fast equilibrium with the *cisoid* diazocompound at room temperature (*Scheme 2.6b*). Diazoacetophenone, on the other hand, can be exclusively found in the *cisoid* arrangement and, due to the bulky *t*butyl group of *t*BuCOCHN$_2$, it is reasonable to assume that this compound is similarly biased for the *cisoid* form. The conformational arrangement might be decisive for the reactivity of these nucleophiles because the two possible conformers likely differ in dipolar momentum and other electronic properties.

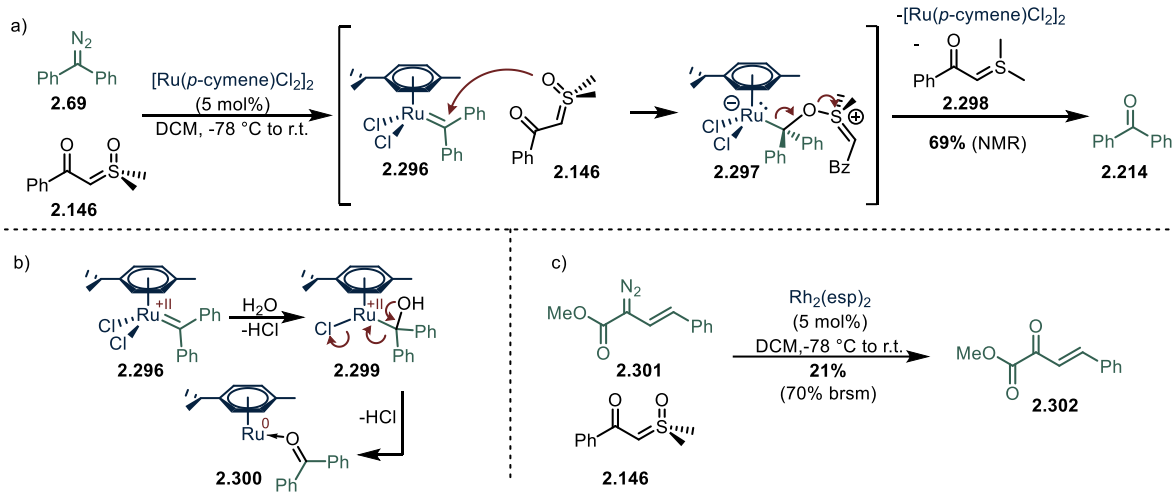
Diethyl α-diazoacetamide **2.293** (*Scheme 2.27b*) was not converted into the metal carbenoid by the ruthenium catalyst, since it was recovered unreacted from the reaction mixture. Carboxamides are commonly perceived to have a weaker electron-withdrawing effect than carboxylic esters or ketones. This leads to the assumption that diazoamides are more nucleophilic (*i.e.* reactive) than other carbonyl diazocompounds. However, little is known about the preferred conformation of these compounds. It is possible that the Coulomb-effect, which favors the *cisoid* conformer is enhanced due to the high partial

charge on the oxygen of the amide. Interestingly, when a Rh(I) catalyst was used, the desired cross-coupling took place in a fair NMR yield of 48% with a decent preference for the *E* isomer. This preference is unusual for the employed catalyst, since dirhodium(II)tetracarboxylates have been reported to yield mainly *Z* products in the *quasi*-dimerization of diazo compounds.[383]

2.3.4.3. *Donor diazo scope*

To investigate the cross-olefination of electron-rich diazocompounds with electron-poor sulfoxonium ylides, the relatively stable diphenyldiazomethane was synthesized. In a first trial under the usual reaction conditions, benzophenone was observed as the major product in 66% NMR yield (*Scheme 2.28a*). Moreover, 6% of the *quasi*-dimerization product of the sulfoxonium ylide was found in the crude NMR spectrum. Interestingly, when the reaction was carried out in the absence of the ylide, benzophenone was still observed in *ca.* 10% by NMR. The oxidation to benzophenone is probably due to the nucleophilic *O*-attack of the sulfoxonium ylide to the carbenoid (*Scheme 2.28a*). Interestingly, the same oxidation is known to occur with DMSO (as the oxidant and the solvent) without the assistance of a metal at elevated temperatures.[493] The occurrence of benzophenone in the absence of the ylide can be explained by an oxidation of the diazocompound by Ru(II) to Ru(IV) (*Scheme 2.28b*). This is suggested by the amount of the formed benzophenone, which is equimolar to the ruthenium content.

A very similar reaction occurred when the donor-acceptor diazocompound **2.301**, which did not react under Ru(II) catalysis, was reacted with the ylide and a dirhodium tetracarboxylate catalyst (*Scheme 2.28c*). Interestingly, these diazocompounds do not oxidize in DMSO without a metal catalyst because the elevated temperature needed for the conversion causes the compound **2.301** to cyclize to a pyrazole.[493]

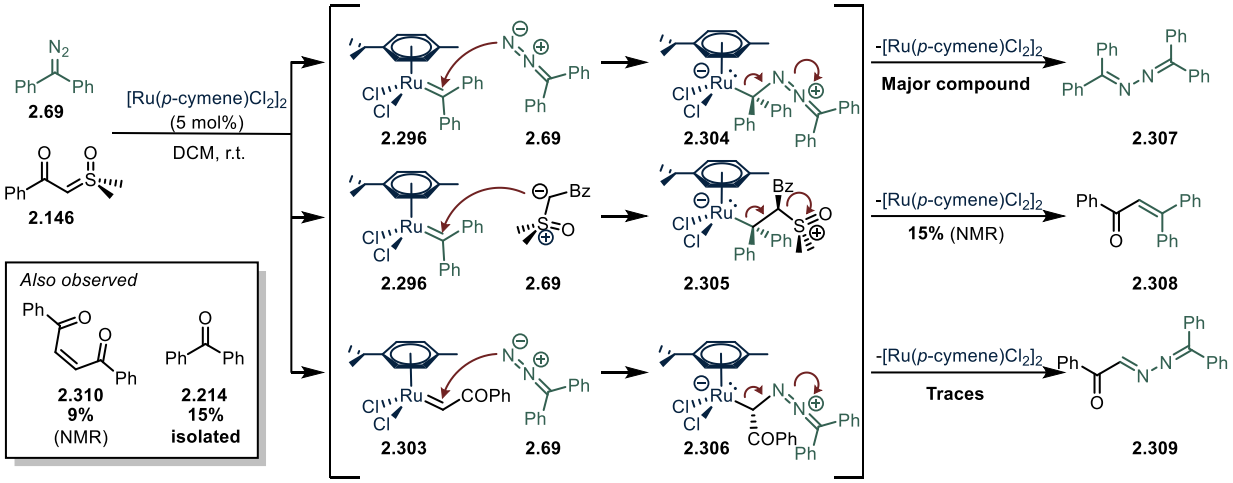


Scheme 2.28 – a) Reaction of diphenyldiazomethane under the usual reaction conditions of the cross-olefination reaction. b) Proposed mechanism for the formation of benzophenone in the absence of an ylide. c) Reaction of a donor-acceptor diazocompound with a stabilized sulfoxonium ylide under Rh(II) catalysis.

The desired olefin formed from the cross-coupling of the sulfoxonium ylide and diphenyldiazomethane was observed for the first time when the reaction was carried out at room temperature (*Scheme 2.29*). The yield was albeit very low (15% NMR yield), and benzophenone was isolated in an equimolar amount. The major product was interestingly the azine **2.307**, which was detected by NMR and could be isolated in low purity. The accompanying impurities were likely the unsymmetrical azine **2.309**, and the desired product **2.308**, which were both detected by mass spectrometry. While NMR data of the olefin **2.308** is available and matches the peaks found in the ^{1}H NMR spectra, the unsymmetrical azine is unknown in the literature, so that its proposed formation remains speculative. A similar result can be obtained by the *in situ* formation of the diazocompound by oxidation of the hydrazone generated from benzophenone and hydrazine with an equimolar amount of $PhI(O_2CCF_3)_2$.

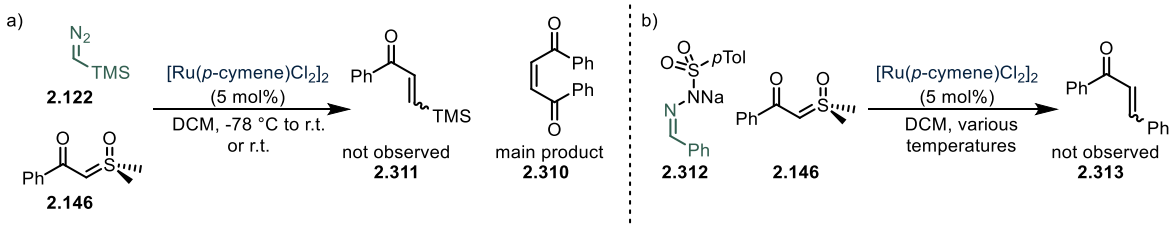
Azine formation is a known phenomenon; the proposed mechanism goes *via* a *N*-terminal nucleophilic attack of the diazocompound **2.296** onto the metal-carbenoid.[384,401] The trace formation of the formed unsymmetrical azine can be explained by generation of a metal-carbene complex from the

sulfoxonium ylide (**2.303**). This is also in accordance with the formation of the symmetric olefin **2.310**, derived from a *quasi*-dimerization of the sulfoxonium ylide in 9% NMR yield under these conditions.



Scheme 2.29 – Reaction of diphenyldiazomethane with a stabilized sulfoxonium ylide under Ru(II) catalysis at room temperature.

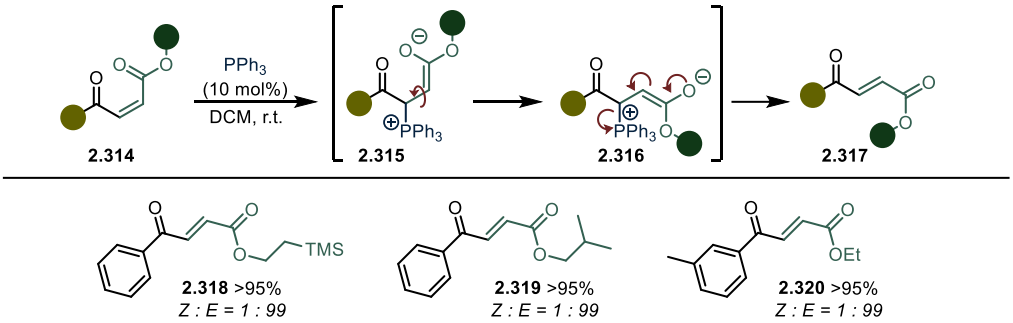
When TMS-diazomethane was submitted to the reaction conditions (at -78 °C or at room temperature), no desired product was observed (*Scheme 2.30a*). The main product was the *quasi*-dimer of the sulfoxonium ylide (**2.310**), which was formed in a low NMR yield. The formation of non-stabilized diazocompounds *in situ*, either by the oxidation of hydrazones or the thermal decomposition of a tosyl-hydrazone sodium salt, typically resulted in very messy reaction profiles. The tosyl-hydrazone sodium salt was practically insoluble in the mixture. A commonly used phase-transfer catalyst (Et_3NBnCl) and/or the *in situ* deprotonation of the corresponding hydrazone gave the same result or led to recovery of the starting material.



Scheme 2.30 – a) TMS-diazomethane under the optimized reaction conditions. b) In situ formation of phenyldiazomethane in presence of a stabilized sulfoxonium ylide and a ruthenium(II) precatalyst.

2.3.4.4. *Isomerization by triphenylphosphine*

As mentioned previously, PPh_3 was able to completely isomerize the *Z* isomer of several olefins synthesized by our cross-olefination approach to the *E* isomer. Interestingly, substoichiometric amounts were sufficient to catalyze this reaction (10 mol%) (*Scheme 2.32*). The isomerization of these electron-deficient olefins by using nucleophilic catalysts has precedence in the literature and likely proceeds *via* reversible Michael addition elimination of the nucleophilic catalyst.[494–496] Several of our products were isomerized in this way, with *Z : E* ratios of 1 : 99 for all cases.

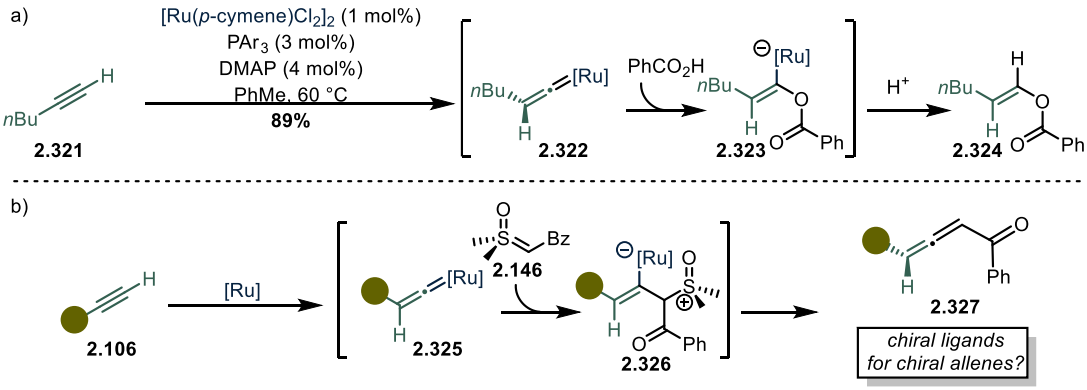


Scheme 2.31 – Isomerization to E olefins by using a phosphine catalyst. See supporting information for more details.

2.4. Conclusion and outlook

The central hypothesis was verified by our study. Indeed, the reaction was general for stabilized sulfoxonium ylides and α-monosubstituted diazoesters, with the products displaying a strong preference for the *Z* isomer. Other diazocompounds, more specifically those lacking a stabilizing group, were generally not suitable substrates under the optimal reaction conditions, although a α-monosubstituted diazoamide did show the desired reactivity under Rh(II) catalysis, albeit with *E* stereoselectivity. We further demonstrated that this approach can be used for the synthesis of biologically active compounds. The reactions proceed with good atom-economy, since only N_2 and DMSO are released.

In future work, the metal-carbenoids could be generated without the use of diazocompounds: ruthenium complexes are known to form vinylidene-complexes with terminal alkynes (*Scheme 2.31a*).[497] Indeed this has been exploited widely in the field of ruthenium catalysis.[498] The vinylidene complexes react as Fischer-carbene-complexes with nucleophiles. We could similarly envisage those vinylidene-complexes to be attacked by a sulfoxonium ylide in order to synthesize allenes (*Scheme 2.31b*). The use of chiral ligands could theoretically enable the synthesis of enantioenriched products. A competing pathway, which might be a pitfall for this reaction, would be the generation of the carbenoid the sulfoxonium ylide since, higher temperatures are required.



Scheme 2.32 a) Alkynes as ruthenium-vinylidene precursors. b) Possible application in the enantioselective synthesis of allenes.

2.5. Supporting information

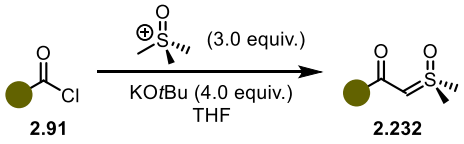
2.5.1. General

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 aluminum 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}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300K. Chemical shifts were 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 (^{13}C-NMR). Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Compounds, which were synthesized and characterized by coworkers can be found either in the SI of the published article or in the leaving reports.

2.5.2. Synthesis of starting material

2.5.2.1. *Synthesis of sulfoxonium ylides*

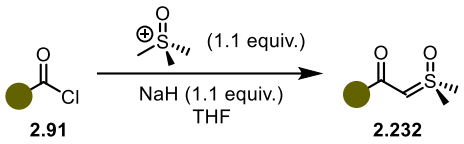
General method A



Scheme 2.33

The reaction was carried out under air. Potassium *tert*-butoxide (4.0 equiv.) was suspended in THF (1 mL/1 mmol KO*t*Bu) and trimethylsulfoxonium iodide (3.0 equiv.) at once in a three-necked flasked fitted with a condenser. The mixture was refluxed for 2 hours resulting in a yellow cloudy suspension. The reaction was cooled down to 0 °C and acyl chloride was added dropwise as a solution in THF (1.0 equiv., 1 M). After warming up to room temperature the mixture was stirred for 3 h. Afterwards, volatiles were removed under reduced pressure and the residue was dissolved in equal amounts of EtOAc and Water. After extracting the aqueous phase with EtOAc (3 x the volume of the aqueous phase) the combined organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (typical eluent – acetone : heptanes - 50 : 50 to 75 : 25 v/v%).

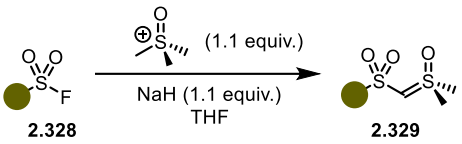
General method B



Scheme 2.34

The reaction was carried out under air. Trimethylsulfoxonium iodide (1.1 equiv.) was suspended in THF (4.0 mL / mmol Acylchloride) in a three-necked flasked fitted with a condenser and sodium hydride (1.1 equiv., 60% dispersion in mineral oil) was added portionwise. The mixture was refluxed for 2 hours resulting in a yellow cloudy suspension. The reaction was cooled down to 0 °C and acyl chloride was added dropwise as a solution in THF (1.0 equiv., 1 M). After warming up to room temperature the mixture was stirred for 3 h. Afterwards volatiles were removed under reduced pressure and the residue was dissolved in equal amounts of EtOAc and Water. After extracting the aqueous phase with EtOAc (3 x the volume of the aqueous phase) the combined organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (typical eluent – acetone : heptanes - 50 : 50 to 75 : 25 v/v%).

General method C

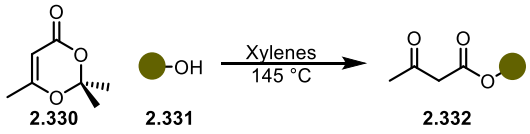


Scheme 2.35

Trimethylsulfoxonium iodide (1.1 equiv.) was suspended in THF (1.5 mL / mmol sulfonyl fluoride) in a three-necked flask fitted with a condenser and sodium hydride (1.1 equiv., 60% dispersion in mineral oil) was added portionwise. The mixture was stirred at room temperature for 30 minutes. The reaction was cooled down to 0 °C and sulfonyl fluoride was added dropwise as a solution in THF (1.0 eq. – 2 mol/L). After warming up to room temperature the mixture was stirred for 30 minutes. Then the mixture was stirred for further 3 h at 55 °C. Afterwards volatiles were removed under reduced pressure and the residue was dissolved in equal amounts of EtOAc and Water. After extracting the aqueous phase with EtOAc (3 x the volume of the aqueous phase) the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (typical eluent – acetone : heptanes - 50 : 50 to 75 : 25 v/v%).

2.5.2.2. *Synthesis of diazocompounds*

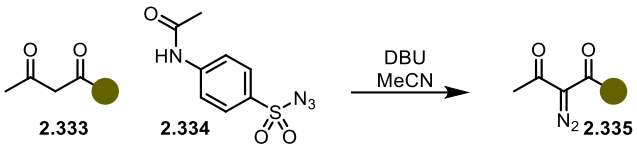
General method I[499]



Scheme 2.36

The reaction was carried out under air. 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.0 equiv.) and the alcohol (1.0 equiv.) were dissolved in xylenes (0.5 mL/mmol) in an Erlenmeyer flask. The mixture was stirred and heated to 145 °C. After 30 minutes the mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (typical eluent - Et_2O : heptanes - 10 : 90 to 40 : 60 v/v%).

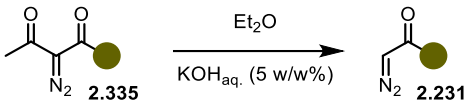
General method II[500]



Scheme 2.37

The reaction was carried out under air. The β-keto carbonyl compound (1.0 equiv.) and 4-acetamidobenzenesulfonyl azide (1.1 equiv.) were dissolved in MeCN (3 mL / mmol) in a round bottom flask. The mixture was cooled to 0 °C and DBU (1.4 equiv.) was added dropwise. The mixture was stirred until starting material disappeared (TLC). The solvent was evaporated after the mixture was filtered through celite®. Purification of the crude by column chromatography gave the desired product (typical eluent - EtOAc : heptanes - 5 : 95 to 20 : 80 v/v%).

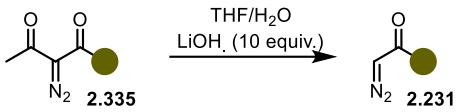
General method III[501]



Scheme 2.38

The reaction was carried out under air. The diazoacetoacetate ester was dissolved in Et_2O (5 mL /mmol) and $KOH_{aq.}$ (5 w/w%, 5 mL / mmol) was added. The mixture was allowed to stir vigorously for 6 h at room temperature. The aqueous phase was extracted with Et_2O (3 x the volume of the aqueous phase), the combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by a short column chromatography (typical eluent - EtOAc : heptanes - 10 : 90 to 30 : 70 v/v%). or a silica plug. (Note: The α-diazocarbonyl compounds synthesized for this report are stable on silica)

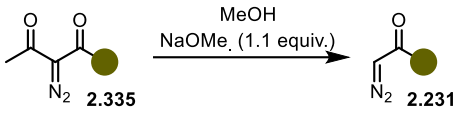
General method IV[500]



Scheme 2.39

The reaction was carried out under air. The diazoacetoacetate ester was dissolved in THF (4 mL / mmol) and H_2O (6 mL / mmol) was added. Under stirring LiOH (10.0 equiv.) was added and the mixture was allowed to stir vigorously for 14 h at room temperature. The aqueous phase was extracted with Et_2O (3 x the volume of the aqueous phase), the combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by a short column chromatography (typical eluent - EtOAc : heptanes - 10 : 90 to 30 : 70 v/v%) or a silica plug. (Note: The α-diazoesters synthesized for this report are stable on silica)

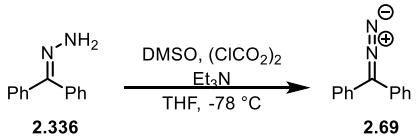
General method V[502]



Scheme 2.40

The reaction was carried out under air. The diazoacetoacetate ester was dissolved in MeOH (0.5 mL / mmol). Under stirring NaOMe (1.1 equiv.) was added and the mixture was allowed to stir vigorously for 6 h at room temperature. The aqueous phase was extracted with Et_2O (3 x the volume of the aqueous phase), the combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by a short column chromatography (typical eluent - EtOAc : heptanes - 10 : 90 to 30 : 70 v/v%) or a silica plug. (Note: The α-diazoesters synthesized for this report are stable on silica)

Synthesis of diphenydiazomethane[267]

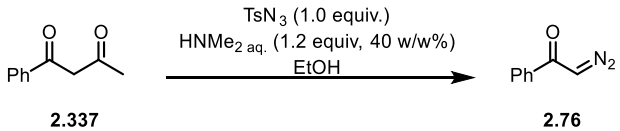


2.336 **2.69**

Scheme 2.41

The reaction was carried out behind a blast shield. DMSO (2.8 mmol, 1.1 equiv., 200 µL) was dissolved in THF (25 mL) at -55 °C. Oxalyl chloride (2.7 mmol, 1.1 equiv., 230 µL) were added dropwise and the reaction was stirred until the evolution of gas seized (*ca.* 30 min). The reaction was then cooled further to -78 °C and a solution of **2.xxx** (2.6 mmol, 1.0 equiv., 500 mg), Et_3N (5.4 mmol, 2.1 equiv., 750 µL) in THF (2.5 mL) was added dropwise to give a deeply red solution with a white precipitate. The reaction was stirred for further 60 minutes at the same temperature, thereafter the mixture was filtered under argon (Schlenk-frit) and the precipitate was washed with dry THF (20 mL). The solvent was removed under reduced pressure to give the crude product, which was used as such as a deep purple-red crystalline solid, which tends to melt at room temperature. The product is relatively stable on Al_2O_3 coated TLC plates (yield 405 mg, 82%).

Synthesis of α-diazoacetophenone



2.337 **2.76**

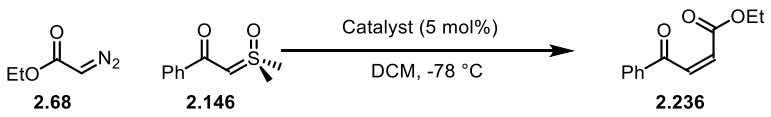
Scheme 2.42

1-Phenyl-1,3-butanedione (2.0 mmol, 1.0 equiv., 300 µL) was dissolved at room temperature in EtOH (2 mL) and Tosylazide (2.0 mmol, 1.0 equiv., 394 mg) was added at once under stirring. Thereafter a solution of methylamine in water was added dropwise (40 w/w%, 1.2 equiv., 266 µL). The reaction was stirred for 60 minutes at room temperature. The reaction was diluted with Et_2O (5 mL) and water (2 mL). The aqueous phase was extracted with Et_2O (3 x the volume of the aqueous phase), the combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product

was purified by a short column chromatography (eluent EtOAc : heptanes - 10 : 90 to 30 : 70 v/v%) to yield the product as a yellow liquid (yield 286 mg, >95%).

2.5.3. Experimental section

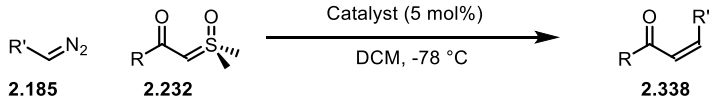
NMR experiments



Scheme 2.43

The reaction was carried out under air. In a microwave vial the sulfoxonium ylide (0.2 mmol, 2.0 equiv., 39.2 mg) and the diazocompound (0.1 mmol, 1.0 equiv., 21 µL) were dissolved in d_2-DCM (2 mL). In a separate microwave vial the $[Ru(p\text{-cymene})Cl_2]_2$ (5 µmol, 5 mol%, 3.1 mg) was dissolved in d_2-DCM (0.01 M). Both solutions were cooled to -78 °C in a dry ice bath for 5 - 10 minutes. Thereafter, the catalyst solution was added dropwise to the solution containing the ylide and the diazocompound. The vial was kept in the dry ice bath and stirred until it reached a certain temperature. At this point pyridine (0.2 mmol, 2.0 equiv., 32 µL) was added at once and the solution was stirred for 10 minutes at the same temperature. Then mesitylene (0.1 mmol, 1.0 equiv., 14 µL) was added and the mixture was warmed up to room temperature. The mixture was then transferred to an NMR tube and the ^{1}H spectrum was measured.

General procedure α

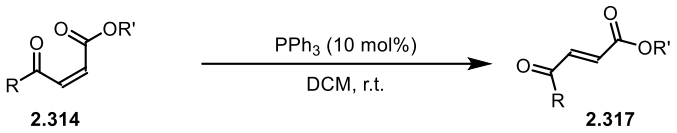


Scheme 2.44

The reaction was carried out under air. In a microwave vial the sulfoxonium ylide (2.0 equiv.) and the diazocompound (1.0 equiv.) were dissolved in DCM (5 mL/mmol of the diazocompound). In a separate microwave vial the catalyst (5 mol%) was dissolved in DCM (0.01 M). Both solutions were cooled to -78 °C in a dry ice bath for 5 - 10 minutes. Thereafter, the catalyst solution was added dropwise to the solution

containing the ylide and the diazocompound. The vial was kept in the dry ice bath for 16 h and was allowed to warm up slowly to room temperature. Afterwards, the reaction mixture was filtered through a short silica plug, which was washed several times with DCM. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (typical eluent - Et_2O : heptanes - 5 : 95 to 20 : 80 v/v%).

General procedure β



2.314 **2.317**

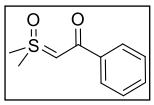
Scheme 2.45

The reaction was carried out under air. The *Z* olefin was dissolved in DCM (10 mL/mmol) in a dram vial with PPh_3 (10 mol%) and stirred for 15 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (typical eluent - Et_2O : heptanes 5 : 95 to 20 : 80 v/v%).

2.6. Characterization

2.6.1. Sulfoxonium ylides

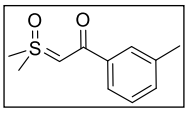
2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-phenylethan-1-one (**2.146**)



Synthesized following the general procedure **A.**

Isolated yield: 490 mg, 75%. Spectroscopic properties match with the literature.[503]

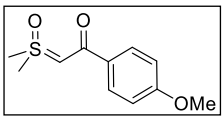
2-(dimethyl(oxo)- λ^6-sulfanylidene)-1-(*m*-tolyl)ethan-1-one (**2.339**)



Synthesized by following the general procedure **A.**

Isolated yield: 546 mg, 78%. Spectroscopic properties match with the literature.[504]

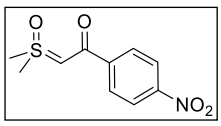
2-(dimethyl(oxo)- λ^6-sulfaneylidene)-1-(4-methoxyphenyl)ethan-1-one (**2.340**)



Synthesized by following the general procedure **A.**[505]

Spectroscopic properties match with the literature.

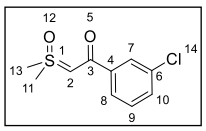
2-(dimethyl(oxo)- λ^6-sulfaneylidene)-1-(4-nitrophenyl)ethan-1-one (**2.341**)



Synthesized by following the general procedure **A.**

Spectroscopic properties match with the literature.[503]

2-(dimethyl(oxo)- λ^6-sulfanylidene)-1-(3-chlorophenyl)ethan-1-one (**2.342**)

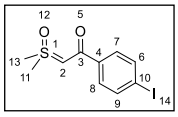


Synthesized following the general procedures **A**.

Isolated yield: 359 mg, 52%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (t, *J* = 1.8 Hz, 1H, C7), 7.74 (dt, *J* = 7.8, 1.8 Hz, 1H, C10), 7.41 – 7.39 (m, 1H, C8), 7.32 (t, *J* = 7.8 Hz, 1H, C9), 4.95 (s, 1H, C2), 3.52 (s, 6H, C11/C13). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 180.6 (C3), 140.7 (C4), 134.3 (C6), 130.6 (C10), 129.5 (C9), 126.9 (C8), 124.7 (C8), 68.8 (C2), 42.4 (C11/C13). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 231.0247 found: 231.0233. **ATR-FTIR** (cm^-

[1]): 3089, 3068, 3013, 2922, 2855, 1703, 1580, 1535, 1425, 1375, 1303, 1177, 1069, 1026, 877, 856, 801, 740.

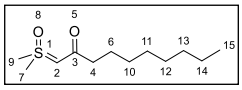
2-(dimethyl(oxo)- λ^6-sulfanylidene)-1-(4-fluorophenyl)ethan-1-one (**2.343**)



Synthesized following the procedure **A** using the corresponding methylester instead of the acyl chloride**.**

Isolated yield: 250 mg, 23%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H, C8/7), 7.51 (d, *J* = 8.4 Hz, 2H, C6/C9), 4.94 (s, 1H, C2), 3.50 (s, 6H, C11/C13). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 181.3 (C3), 138.4 (Ar), 137.5 (C7/C8), 128.4 (C6/C9), 97.7 (C10), 68.7 (C2), 42.6 (C11/C13). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 344.9422 found 344.9414. **ATR-FTIR** (cm^{-1}): 3007, 2921, 1698, 1580, 1481, 1395, 1267, 1177, 1142, 1057, 1005, 950, 830, 787, 757.

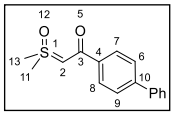
1-(dimethyl(oxo)- λ^6-sulfanylidene)decan-2-one (**2.344**)



Synthesized following the general procedure **A.**

Isolated yield: 428 mg, 56%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.34 (s, 1H, C2), 3.37 (s, 6H, C7/9), 2.22 – 2.08 (m, 2H, C4), 1.61 – 1.50 (m, 2H), 1.38 – 1.19 (m, 10H, C5-C14), 0.86 (t, *J* = 6.9 Hz, 3H, C15). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.5 (C3), 68.79 (C2), 42.5 (C7/C9), 41.2 (C4), 32.0 (C5), 29.6 (C10-14), 29.3 (C10-14), 26.3 (C10-14), 22.7(C10-14), 14.2 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 255.1395 found 255.1392. **ATR-FTIR** (cm^{-1}): 3389, 3063, 3026, 2957, 2920, 2852, 1554, 1466, 1391, 1309, 1174, 1032, 856, 761, 617.

1-([1,1'-biphenyl]-4-yl)-2-(dimethyl(oxo)- λ^6-sulfanylidene)ethan-1-one (**2.345**)

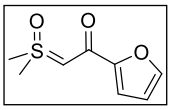


Synthesized following the general procedure **B.** (50%)

Isolated yield: 453 mg, 50%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H, Ar), 7.65 – 7.59 (m, 4H, Ar), 7.48 – 7.41 (m, 2H, Ar), 7.40 – 7.33 (m, 1H, Ar), 5.02 (s, 1H, C2), 3.53 (s, 6H, C11/C13). **^{13}C NMR** (151 MHz,

$CDCl_3$) δ 182.0 (C3), 143.6 (Ar), 140.54 (Ar), 137.8 (Ar), 129.0 (Ar), 128.0 (Ar), 127.3 (Ar), 127.2 (Ar), 127.0 (Ar), 68.4 (C2), 42.7 (C11/C13). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 295.0769 found 295.0762. **ATR-FTIR** (cm^{-1}): 3078, 3054, 3020, 2994, 2964, 1602, 1567, 1518, 1405, 1380, 1304, 1163, 1145, 1084, 1031, 1005, 993, 865, 846, 737, 690, 639, 568, 501, 443.

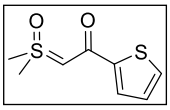
2-(dimethyl(oxo)- λ^6-sulfaneylidene)-1-(furan-2-yl)ethan-1-one (**2.346**)



Synthesized following the general procedure **A**.

Spectroscopic properties match with the literature.[506]

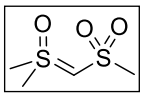
2-(dimethyl(oxo)- λ^6-sulfaneylidene)-1-(thiophen-2-yl)ethan-1-one (**2.347**)



Synthesized following the general procedure **A**.

Spectroscopic properties match with the literature.[503]

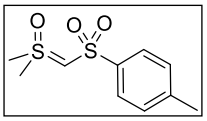
(dimethyl(oxo)- λ^6-sulfaneylidene)(methylsulfonyl)methane (**2.348**)



Synthesized following the general procedure **C**.

Spectroscopic properties match with the literature.[246]

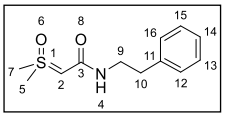
1-(((dimethyl(oxo)- λ^6-sulfanylidene)methyl)sulfonyl)-4-methylbenzene (**2.349**)



Synthesized following the general procedure **C.**

Isolated yield: 1012 mg, 41%. Spectroscopic properties match with the literature.[246]

2-(dimethyl(oxo)-l6-sulfaneylidene)-N-phenethylacetamide (**2.350**)



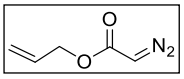
Synthesized following the general procedure **B** starting from Phenethyl isocyanate.

^{1}H NMR (400 MHz, DMSO) δ 6.45 (t, J = 7.4 Hz, 2H, C13/C14), 6.40 – 6.26 (m, 3H, C12/C14/C16), 5.58 (bs, 1H, C2), 3.03 (s, 1H, NH), 2.53 (s, 6H, C5/C7), 2.40 – 2.30 (m, 2H, C9), 1.83 (t, J = 7.5 Hz, 2H, C10). **^{13}C NMR**

(151 MHz, DMSO) δ 167.43 (C3), 140.02 (C11), 128.59 (C13/C15), 128.26 (C12/C16), 125.88 (C14), 56.53 (C2), 41.54 (C5/C7), 36.37 (C10). **HRMS** (ESI) m/z calculated for [M+H]+ 240.1058 found 240.1047. **ATR-FTIR** (cm^{-1}): 1580, 1525, 1454, 1382, 1351, 1276, 1261, 1148, 1031, 914, 764, 750, 703.

2.6.2. Diazocompound

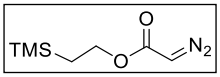
Allyl 2-diazoacetate (**2.351**)



1c was prepared by following the general procedures **II** and **III**.

Isolated yield: 287 mg, 83% over 2 steps. Spectroscopic properties match with the literature.[507]

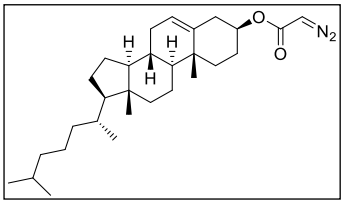
2-(trimethylsilyl)ethyl 2-diazoacetate (**2.352**)



Synthesized following the general procedures **I**, **II** and **IV**.

Isolated yield: 215 mg, 51% over 3 steps. Spectroscopic properties match with the literature.[508]

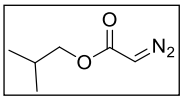
Cholesteryl diazoacetate (**2.353**)



Synthesized following the general procedures **I**, **II** and **IV**. The diazotransfer reaction has to be carried out in THF instead of MeCN.

Isolated yield: 665 mg, 78% over 3 steps. Spectroscopic properties match with the literature.[509]

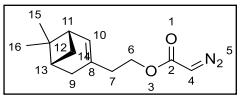
Isobutyl 2-diazoacetate (**2.354**)



Synthesized following the general procedures **II** and **III**.

Isolated yield: 573 mg, 90% over two steps. Spectroscopic properties match with the literature.[499]

2-((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)ethyl 2-diazoacetate (**2.355**)

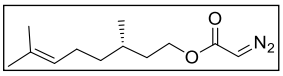


Synthesized following the general procedures **I**, **II** and **IV**.

Isolated yield: 280 mg, 49%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.29 (dq, *J* = 4.2, 1.4 Hz, 1H, C10), 4.70 (s, 1H, C4), 4.25 – 4.09 (m, 2H, C6), 2.36 (dt, *J* = 8.5, 5.6 Hz, 1H, C11), 2.33 – 2.26 (m, 2H, C7), 2.25 – 2.14 (m, 2H,

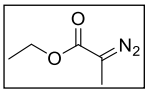
C12/C13), 2.10 – 2.02 (m, 2H, C9), 1.27 (s, 3H, C15/C16), 1.14 (d, *J* = 8.5 Hz, 1H, C12), 0.82 (s, 3H, C15/C16). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2 (C8), 119.1 (C10), 63.3 (C6), 45.8 (C4), 40.9 (C11), 38.1 (C12), 36.2 (C13), 31.8 (C7), 31.5 (C14), 26.4 (C9), 21.2 (C15/C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 217.1266 found 217.1254. **ATR-FTIR** (cm^{-1}): 2914, 2833, 2105, 1691, 1469, 1469, 1393, 1355, 1237, 1179, 1027, 958, 886, 789, 739.

(*S*)-3,7-dimethyloct-6-en-1-yl 2-diazoacetate (**2.356**)

 Synthesized following the general procedures **II** and **V**.

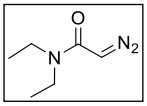
Isolated yield: 432 mg, >95% over two steps. Spectroscopic properties match with the literature.[510]

ethyl 2-diazopropanoate (**2.357**)

 Synthesized following the general procedures **II**. The intermediate deformylates spontaneously.

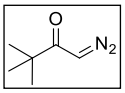
Isolated yield: 568 mg, 78%. Spectroscopic properties match with the literature.[511]

2-diazo-N,N-diethylacetamide (**2.293**)

 Synthesized following the general procedures **II** and **IV**.

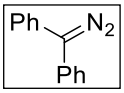
Isolated yield: 396 mg, 59% over two steps. Spectroscopic properties match with the literature.[512]

1-diazo-3,3-dimethylbutan-2-one (**2.358**)

 Synthesized following the general procedures **II** starting from the symmetric β-diketone. The intermediate depivylates spontaneously.

Isolated yield: 620 mg, >95%. Spectroscopic properties match with the literature.[513]

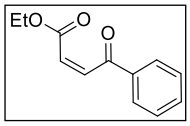
Diphenydiazomethane (**2.69**)

 Synthesized following the procedure for diphenyldiazomethane.

Spectroscopic properties match with the literature.[267]

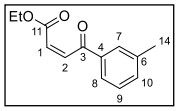
2.6.3. Products

Ethyl (*Z*)-4-oxo-4-phenylbut-2-enoate (**2.236**)

 Synthesized following the general procedure **α**. (0.2 mmol scale)

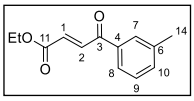
Isolated yield: 29.1 mg, 71% (*Z* : *E* = 9 : 1). Spectroscopic properties match with the literature.[334]

Ethyl (*Z*)-4-oxo-4-(m-tolyl)but-2-enoate (**2.256**)

 Synthesized following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 28.2 mg, 62% (*Z* : *E* = 4 : 1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 1.3 Hz, 1H, C7), 7.74 – 7.70 (m, 1H, C9), 7.42 – 7.32 (m, 2H, C8/C10), 6.87 (d, *J* = 12.2 Hz, 1H, C1), 6.26 (d, *J* = 12.2 Hz, 1H,C2), 4.05 (q, *J* = 7.1 Hz, 2H, CH_2O), 2.41 (s, 3H, C14) 1.08 (t, *J* = 7.1 Hz, 3H, Et-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.4 (C3), 165.0 (C11), 141.3 (C2), 138.7 (C4), 136.1 (C6), 134.6 (C10), 129.2 (C1), 128.7(C7-C9), 126.3(C7-C9), 126.1 (C7-C9), 61.2 (C14), 21.5 (CH_2O), 13.9 (Et-CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 241.0841 found 241.0835. **ATR-FTIR** (cm^{-1}): 3039, 2982, 2929, 2908, 2869, 1719, 1670, 1602, 1585, 1396, 1382, 1286, 1264, 1208, 1154, 1022, 952, 832, 773, 694, 668, 550, 457.

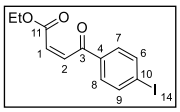
Ethyl (*E*)-4-oxo-4-(m-tolyl)but-2-enoate (**2.320**)

 Synthesized by following the general procedure **β**. (0.2 mmol scale)

Isolated yield: 43.6 mg, >95% (*Z* : *E* = 1 : 99). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 15.6 Hz, 1H, C2), 7.80 (d, *J* = 12.5 Hz, 2H, C7/C8), 7.43 (d, *J* = 7.5 Hz, 1H, C10), 7.40 (t, *J* = 7.5 Hz, 1H, C9), 6.88 (d, *J* = 15.6 Hz, 1H, C1), 4.31 (q, *J* = 7.1 Hz, 2H, CH_2O), 2.44 (s, 3H, C14), 1.35 (t, *J* = 7.1 Hz, 3H, Et-CH_3). **^{13}C NMR** (151 MHz,

$CDCl_3$) δ 189.9 (C3), 165.8 (C11), 139.0 (C4), 136.8 (C6), 134.8 (C2), 132.6 (C10), 129.5 (C1), 129.0 (C7), 128.9 (C9), 126.3 (C8), 61.5 (CH_2O), 21.5 (C14), 14.3 (Et-CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 241.0841 found 241.0833. **ATR-FTIR** (cm^{-1}): 2983, 2929, 2359, 2179, 1723, 1673, 1604, 1586, 1447, 1383, 1296, 1266, 1214, 1159, 1095, 1027, 782, 615, 590.

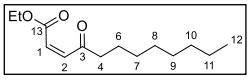
Ethyl (*Z*)-4-(4-iodophenyl)-4-oxobut-2-enoate (**2.260**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 77.9 mg, 59% (*Z* : *E* = 5 : 1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H, C6/C9), 7.67 – 7.62 (m, 2H, C7/8), 6.82 (d, *J* = 12.1 Hz, 1H, C2), 6.28 (d, *J* = 12.1 Hz, 1H, C1), 4.06 (q, *J* = 7.1 Hz, 2H, CH_2O), 1.11 (t, *J* = 7.1 Hz, 3H, Et-CH_3). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 193.7 (C3), 164.8 (C11), 140.7 (C2), 138.2 (C6/C9), 135.3 (C4), 130.1 (C7/C8), 126.5 (C1), 102.0 (C10), 61.4 (CH_2O), 13.9 (Et-CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 352.9651 found 352.9641. **ATR-FTIR** (cm^{-1}): 3078, 3054, 3020, 2994, 2964, 2927, 2915, 2890, 1602, 1567, 1518, 1405, 1380, 1304, 1163, 1145, 1084, 1031, 1005, 993, 865, 846, 737, 690, 639, 568, 501, 443.

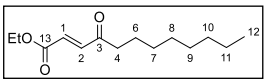
Ethyl (*Z*)-4-oxododec-2-enoate (**2.267**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

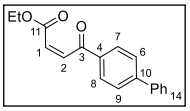
Isolated yield: 26.2 mg, 54% (*Z* : *E* = 3 : 2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 12.1 Hz, 1H, C2), 6.00 (d, *J* = 12.1 Hz, 1H, C1), 4.21 (q, *J* = 7.1 Hz, 2H, CH_2O), 2.59 (dd, *J* = 9.6, 5.3 Hz, 2H, C4), 1.70 – 1.59 (m, 2H, C6), 1.37 – 1.22 (m, 13H, C7-C11, Et-CH_3), 0.88 (t, *J* = 6.9 Hz, 3H , C12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.0 (C3), 166.0 (C13), 141.7 (C2), 124.9 (C1), 61.3 (CH_2O), 42.9 (C4), 32.0 (C6-C11), 29.5 (C6-C11), 29.3 (C6-C11), 29.3 (C6-C11), 23.5 (C6-C11), 22.8 (C6-C11), 14.2 (C12, Et-CH_3), 14.2 (C12, Et-CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 263.1623 found 263.1616. **ATR-FTIR** (cm^{-1}): 3443, 3334, 3059, 3028, 2982, 2913, 2832, 1719, 1670, 1598, 1581, 1448, 1396, 1382, 1286, 1200, 1161, 1004, 810, 755, 729, 704, 688, 543.

Ethyl (*E*)-4-oxododec-2-enoate (**2.359**)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 16.0 Hz, 1H ,C2), 6.66 (d, *J* = 16.0 Hz, 1H, C1), 4.27 (q, *J* = 7.1 Hz, 2H, CH_2O), 2.62 (t, *J* = 7.4 Hz, 2H, C4), 1.69 – 1.59 (m, 2H, C6), 1.31 – 1.23 (m, 13H, C7-C11, Et-CH_3), 0.90 – 0.82 (m, 3H, C12). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200 (C3), 165.8 (C13), 139.5 (C2), 130.8 (C1), 61.5 (CH_2O), 41.7 (C4), 31.9 (C6), 29.5 (C7-C11), 29.3 (C7-C11), 29.3 (C7-C11), 23.9 (C7-C11), 22.8 (C7-C11), 14.3 (C12, Et-CH_3), 14.2 (C12, Et-CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 263.1623 found 263.1618. **ATR-FTIR** (cm^{-1}): 2924, 2855, 1727, 1702, 1464, 1369, 1278, 1181, 1031, 981, 750.

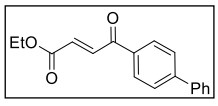
Ethyl (*Z*)-4-([1,1'-biphenyl]-4-yl)-4-oxobut-2-enoate (**2.257**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

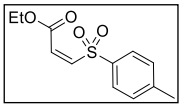
Isolated yield: 39.5 mg, 70% (*Z* : *E* = 3 : 2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H, Ar), 7.74 – 7.68 (m, 2H, Ar), 7.68 – 7.61 (m, 2H, Ar), 7.51 – 7.45 (m, 2H, Ar), 7.44 – 7.38 (m, 1H, Ar), 6.91 (d, *J* = 12.2 Hz, 1H, C2), 6.30 (d, *J* = 12.2 Hz, 1H, C1), 4.07 (q, *J* = 7.1 Hz, 2H, CH_2O), 1.10 (t, *J* = 7.1 Hz, 3H, Et-CH_3). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 194.0 (C3), 165.0 (C11), 146.5 (Ar), 141.3, 140.0 (C2), 134.7 (Ar), 129.5 (Ar), 129.1 (Ar), 128.5 (Ar), 127.6 (Ar), 127.5 (Ar), 126.2 (C1), 61.3 (CH_2O), 13.9 (Et-CH_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 303.0997 found 303.0987. **ATR-FTIR** (cm^{-1}): 3055, 3032, 2977, 2956, 2937, 2902, 2873, 2853, 1715, 1664, 1602, 1560, 1400, 1382, 1363, 1252, 1218, 1167, 1022, 1005, 942, 823, 756, 691, 559, 499, 457.

Ethyl (*E*)-4-([1,1'-biphenyl]-4-yl)-4-oxobut-2-enoate (**2.360**)



Spectroscopic properties match with the literature.[489]

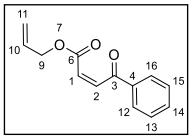
Ethyl (*Z*)-3-tosylacrylate (**2.274**)



Synthesized by following the general procedure **α**. (0.2 mmol scale) A mixture of DCM and DMF was used as the solvent (50 : 50 v/v%).

Isolated yield: 33.6 mg, 66% (*Z* : *E* = 10 : 1). Spectroscopic properties match with the literature.[514]

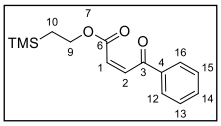
Allyl (*Z*)-4-oxo-4-phenylbut-2-enoate (**2.277**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 32.5 mg, 75% (*Z* : *E* = 11 : 1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.88 (m, 2H C12/C16), 7.63 – 7.54 (m, 1H, C14), 7.52 – 7.44 (m, 2H, C13/C15), 6.91 (d, *J* = 12.2 Hz, 1H, C2), 6.31 (d, *J* = 12.2 Hz, 1H, C1), 5.82 – 5.64 (m, 1H, C10), 5.23 – 5.11 (m, 2H, C11), 4.50 (t, *J* = 1.3 Hz, 1H, C9), 4.48 (t, *J* = 1.3 Hz, 1H, C9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.1 (C3), 164.6 (C6), 141.5 (C2), 136.0 (C4), 133.8 (C14), 131.5 (C1), 128.9 (C10), 128.9(C13/C15), 125.9 (C12/16), 118.9 (C11), 65.9. **HRMS** (ESI) m/z calculated for $[M+H]^+$ 217.0865 found 217.0860. **ATR-FTIR** (cm^{-1}): 3084, 3059, 3028, 2982, 2944, 2886, 1719, 1670, 1598, 1581, 1448, 1391, 1235, 1200, 1161, 983, 929, 810, 755, 729, 704, 488, 543.

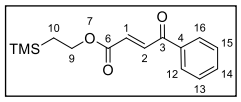
Benzyl (*Z*)-4-oxo-4-phenylbut-2-enoate (**2.284**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 28.4 mg, 51% (*Z* : *E* = 5 : 1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H, C12/C16), 7.58 (ddd, *J* = 8.7, 4.7, 2.0 Hz, 1H, C14), 7.52 – 7.41 (m, 2H, C13/C15), 6.86 (d, *J* = 12.1 Hz, 1H, C2), 6.27 (d, *J* = 12.1 Hz, 1H, C1), 4.11 – 4.04 (m, 2H, C9), 0.86 – 0.75 (m, 2H, C10), -0.03 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3 (C3), 165.1 (C6), 140.9 (C2), 136.1 (C4), 133.7 (C14), 128.9 (C13/C15), 128.8 (C12/C16), 126.5 (C1), 63.6 (C9), 17.1 (C10), -1.5 (TMS). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 299.1079 found 299.1077. **ATR-FTIR** (cm^{-1}): 3442, 3334, 3084, 3059, 3028, 2953, 2898, 1719, 1670, 1598, 1581, 1448, 1391, 1248, 1218, 1200, 1161, 1039, 1015, 967, 934, 834, 755, 729, 704, 688, 547.

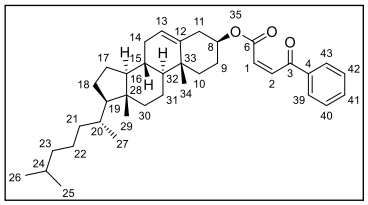
Benzyl (*E*)-4-oxo-4-phenylbut-2-enoate (**2.318**)



Synthesized by following the general procedure **β**. (0.2 mmol scale)

Isolated yield: 55.2 mg, >95% (*Z* : *E* = 1 : 99) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (dt, *J* = 8.5, 1.6 Hz, 2H, C12/C15), 7.90 (d, *J* = 15.6 Hz, 1H, C2), 7.66 – 7.57 (m, 1H, C14), 7.55 – 7.49 (m, 2H, C13/C15), 6.87 (d, *J* = 15.6 Hz, 1H, C1), 4.38 – 4.29 (m, 2H, C9), 1.12 – 1.05 (m, 2H, C10), 0.08 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.8 (C3), 165.9 (C6), 136.8 (C4), 136.4 (C2), 134.0 (C14), 133.0 (C12/C16), 129.0 (C13/C15), 129.0 (C1), 63.9 (C9), 17.5 (C10), -1.3 (TMS). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 299.1079 found 299.1081. **ATR-FTIR** (cm^{-1}): 2954, 1722, 1675, 1598, 1450, 1396, 1250, 1220, 1166, 1063, 1041, 1016, 937, 860, 838, 758, 691.

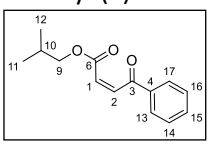
(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl-(*Z*)-4-oxo-4-phenylbut-2-enoate (**2.283**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 60.2 mg, 65% (*Z* : *E* = 5 : 1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 2H, C39/C43), 7.52 – 7.44 (m, 1H, C41), 7.43 – 7.33 (m, 2H, C40/C42), 6.75 (d, *J* = 12.2 Hz, 1H, C2), 6.15 (d, *J* = 12.2 Hz, 1H, C1), 5.19 – 5.13 (m, 1H, C13), 4.45 – 4.36 (m, 1H, C8), 2.01 (ddd, *J* = 13.0, 5.0, 2.2 Hz, 1H, C11), 1.94 – 1.78 (m, 3H, C14), 1.78 – 1.69 (m, 1H ,C11), 1.69 – 1.61 (m, 1H), 1.59 – 1.51 (m, 1H), 1.46 – 0.84 (m, 21H), 0.83 – 0.72 (m, 12H, C15/C16/C27/C34), 0.55 (s, 3H, C29). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3 (C3), 164.2 (C6), 140.7 (C2), 139.5 (C12), 136.2 (C4), 133.8 (41), 129.0 (C39/C43), 128.9 (C40/C32), 126.6 (C1), 122.9 (C13), 75.3 (C8), 56.8 (C16), 56.3 (C19), 50.1 (C32), 42.4 (C28), 39.8, 39.7, 37.6, 36.9, 36.6, 36.3, 35.9, 32.0, 32.0, 28.6, 28.2, 27.3, 24.4, 24.0 23.0, 21.0, 21.1, 19.3, 18.9, 12.0. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 567.3795 found 567.3814. **ATR-FTIR** (cm^{-1}): 2935, 2903, 2889, 2866, 2850, 1719, 1670, 1598, 1581, 1448, 1396, 1375, 1310, 1286, 1212, 1168, 1162, 1039, 1004, 958, 755, 729, 704, 688, 546.

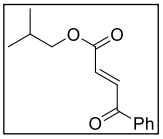
Isobutyl (*Z*)-4-oxo-4-phenylbut-2-enoate (**2.278**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 18.5 mg, 40% (*Z* : *E* = 4 : 1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H, C13/C17), 7.63 – 7.55 (m, 1H, C15), 7.51 – 7.42 (m, 2H, C14/C16), 6.88 (d, *J* = 12.2 Hz, 1H, C2), 6.28 (d, *J* = 12.2 Hz, 1H, C1), 3.77 (d, *J* = 6.6 Hz, 2H, C9), 1.86 – 1.66 (m, 1H, C10), 0.77 (d, *J* = 6.7 Hz, 6H, C11/C12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.2 (C3), 165.0 (C6), 141.2 (C2), 135.9 (C4), 133.8 (C15), 129.0 (C13/C17), C 128.9 (C14/C16), 126.1 (C1), 71.5 (C9), 27.6 (C10), 19.1 (C11/C12). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 233.1178 found 233.1173. **ATR-FTIR** (cm^{-1}): 3084, 3059, 3028, 2961, 2935, 2894, 2875, 1719, 1670, 1598, 1581, 1469, 1448, 1401, 1385, 1369, 1285, 1208, 1161, 1017, 993, 810, 755, 729, 704, 688, 529.

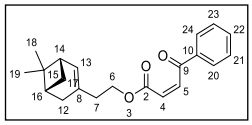
Isobutyl (*E*)-4-oxo-4-phenylbut-2-enoate (**2.319**)



Synthesized by following the general procedure **β**. (0.2 mmol scale)

Isolated yield: 18.4 mg, >95% (*Z : E* = 1 : 99). Spectroscopic data matches that previously reported.[515]

2-((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)ethyl (*Z*)-4-oxo-4-phenylbut-2-enoate (**2.288**)

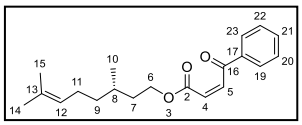


Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 40.0 mg, 62% (*Z* : *E* = 10 : 1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (t, *J* = 5.7 Hz, 2H, C20/C24), 7.62 – 7.54 (m, 1H, C22), 7.51 – 7.44 (m, 2H, C21/C23), 6.87 (d, *J* = 12.1 Hz, 1H, C5), 6.26 (d, *J* = 12.1 Hz, 1H, C4), 5.20 – 5.11 (m, 1H, C13), 4.05 – 3.95 (m, 2H, C6), 2.34 – 2.27 (m, 1H, C14), 2.24 – 2.16 (m, 1H, C7), 2.16 – 2.08 (m, 3H, C7/C16), 2.07 – 2.02 (m, 1H, C17), 1.93 (td, *J* = 5.6, 1.5 Hz, 1H, C12), 1.23 (s, 3H, C19), 1.07 (d, *J* = 8.6 Hz, 1H, C12), 0.76 (s, 3H, C18). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.2 (C9), 164.9 (C2), 143.8 (C10), 141.3 (C5), 136.0 (C13), 133.8 (C22), 128.9 (C20/C24), 128.9 (C21/C23), 126.1 (C13), 119.0 (C4), 63.5 (C6), 45.7 (C15), 40.8 (C14), 38.1 (C16), 35.6 (C7), 31.7 (C17), 31.4 (C12), 26.4 (C18/C19), 21.2 (C18/C19). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 347.1623 found 347.1617. **ATR-FTIR** (cm^{-1}): 3442, 3334, 3059,

3028, 2982, 2913, 2832, 1719, 1670, 1598, 1581, 1448, 1396, 1382, 1286, 1200, 1161, 1004, 810, 755, 729, 704, 688, 543.

(*S*)-3,7-dimethyloct-6-en-1-yl (*Z*)-4-oxo-4-phenylbut-2-enoate (**2.289**)



Synthesized by following the general procedure **α**. (0.2 mmol scale)

Isolated yield: 33.2 mg, 53% (*Z* : *E* = 8 : 1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H, C19/C23), 7.58 (ddd, *J* = 8.7, 4.7, 2.0 Hz, 1H, C21), 7.51 – 7.44 (m, 2H, C20/C22), 6.87 (d, *J* = 12.2 Hz, 1H, C5), 6.27 (d, *J* = 12.2 Hz, 1H, C4), 5.09 – 5.00 (m, 1H, C12), 4.09 – 3.94 (m, 2H, C6), 1.97 – 1.80 (m, 2H, C11), 1.68 (d, *J* = 1.0 Hz, 3H, C14/C15), 1.58 (s, 3H, C14/C15), 1.50 – 1.41 (m, 1H, C7), 1.40 – 1.31 (m, 1H, C7), 1.27 – 1.18 (m, 2H, C9), 1.13 – 1.01 (m, 1H, C8), 0.79 (d, *J* = 6.6 Hz, 3H, C10).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.2 (C16), 165.0 (C2), 141.1 (C5), 136.00 (C17), 133.8 (C21), 131.4 (C13), 128.9 (C19/C23), 128.9 (C20/22), 126.2 (C12), 124.7 (C4), 63.8 (C6), 37.0 (C7), 35.1 (C9), 29.4 (C8), 25.8 (C14/C15), 25.4 (C11), 19.3 (C10), 17.8 (C14/C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 337.1780 found 337.1765. **ATR-FTIR** (cm^{-1}): 3028, 2960, 2912, 2872, 2853, 1719, 1670, 1598, 1581, 1448, 1399, 1375, 1285, 1230, 1205, 1163, 1015, 813, 755, 729, 704, 688, 547.

CHAPTER III

α,β,γ-Functionalization of amides and formation of heterocycles *via* amide activation

The results of this work are published in *Chem. Sci.*, **2019**,10, 9836 – 9840,[516] and *Eur. J. Org. Chem.* **2019**, 5230–5233.[517] This work has been realized in collaboration with E. Spinozzi (M.Sc.) and E. Borsos (B.Sc.)

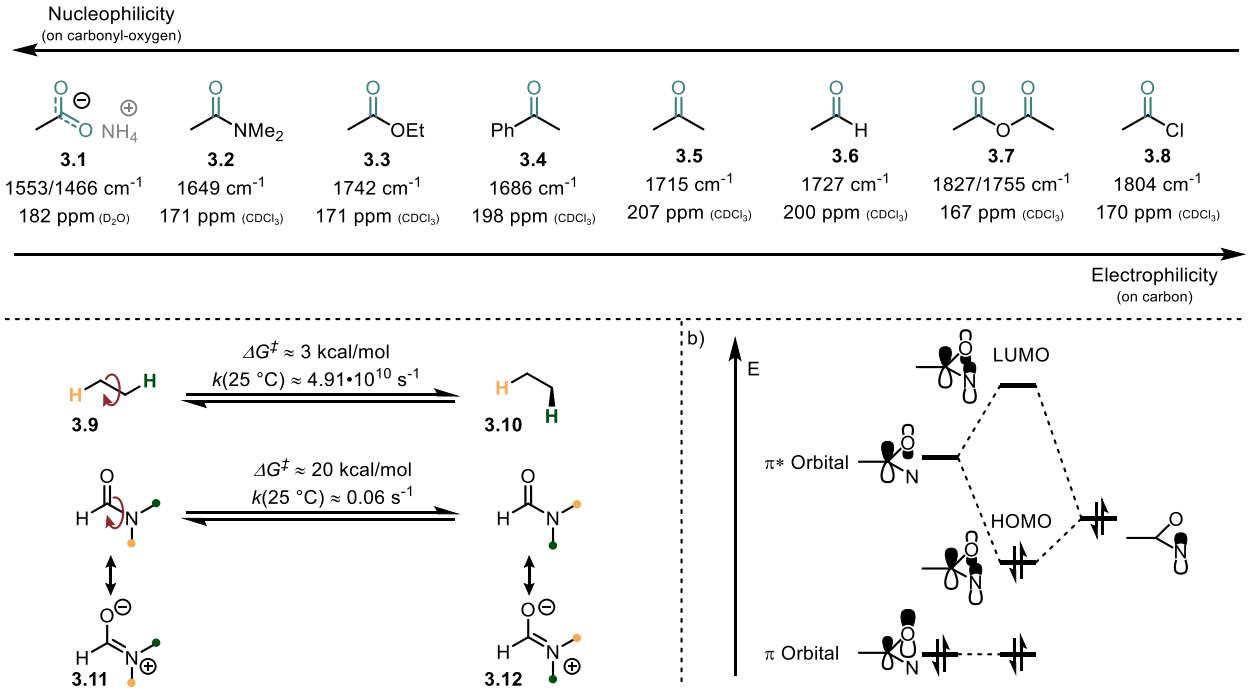
3.1. Introduction

3.1.1. Amide activation

3.1.1.1. *Classical activation*

THE CARBONYL FUNCTIONALITY IS ARGUABLY one of the most important functional group in organic synthesis. Due to the energetically low lying unoccupied π*-orbital and a partial positive charge on the carbon atom, the carbonyl often serves as a carbon-electrophile.[518] The chemistry of the carbon atom is governed by the substituents adjacent to the C=O bond. Mesomeric, inductive, strain and steric effects may influence the reactivity. Generally speaking, the electrophilicity of carbonyl compounds decreases when adjacent π-electrons are donated effectively into the aforementioned π*-orbital, due to the increase of its energetic state. This interaction weakens the C=O bond and is thus correlated with the C=O stretching wavenumber in the infrared spectrum (*Scheme 3.1a*). The acetate anion represents an extreme case of this interaction: a doubly filled lone pair of the O^- atom donates both of its electrons into the π*-orbital of the carbonyl moiety so that these electrons are delocalized on the three involved atoms. The interaction of these two orbitals (the C=O LUMO and the appropriate lone pair of O^-) is so effective because they have similar energetic values (*cf.* Klopman-Salem equation).[519] Due to this interaction the two oxygen atoms become equivalent and as a consequence the carbonyl stretching mode disappears. Instead, an antisymmetric (1553 cm^{-1}) and a symmetric stretching mode (1466 cm^{-1}) of the O-C-O fragment shows up.[520,521] The low wavenumber (compared to a carbonyl group) showcases that there is no "full" double bond anymore. Conversely, the chlorine atom in acetyl chloride **3.8** is a far less effective π-electron donor to the carbonyl, although acetyl chloride is isoelectronic to the acetate anion and in spite of chlorine's lower electronegativity (compared to oxygen – Pauling scala).[522] This is because its valence electrons are in 3s and 3p atomic-orbitals, which differ not only significantly in energy but also in their radial extent (the "size" of the orbitals) making the overlap less efficient.[523] Indeed, the C=O stretching of acyl chlorides requires more energy (higher wavenumbers) than the corresponding vibration in ketones

or aldehydes. Electron-donation of the carbonyl-oxygen into the antibonding C-Cl (σ*) orbital is accounted for this partial triple bond character.[518]

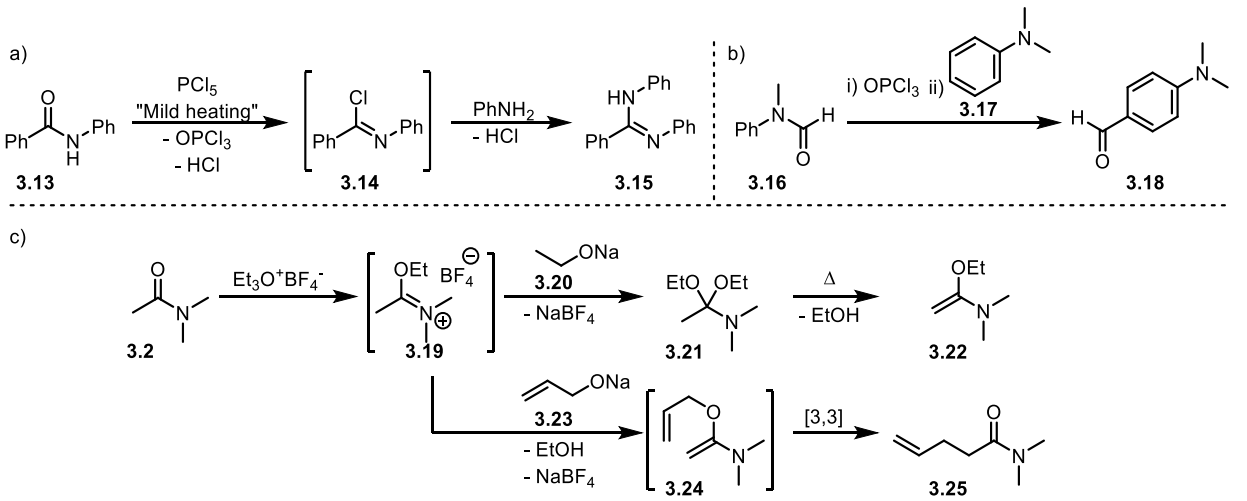


Scheme 3.1 – a) Philicity of several carbonyl compounds, with ^{13}C NMR shifts and IR vibration wavenumbers. b) C-C bond rotation of ethane and of DMF. c) Orbital interaction of a nitrogen lone pair and unoccupied antibonding π-orbital.*

Amides show a relatively weak C=O vibration mode, reminiscent of acetate anions. Again, π-electron donation is responsible for the low wavenumber, because the nitrogen lone pair electrons are delocalized effectively into the π*-orbital. This donation is also responsible for a partial double bond character of the amide C-N bond, which causes a relatively slow rotation (at room temperature) around this bond (*Scheme 3.1b*).[518] If we consider the frontier orbitals of an unfunctionalized carbonyl compound (the π and the π* orbitals respectively), the interaction of the high lying nitrogen lone pair with the unoccupied antibonding C=O orbital give rise to a new LUMO which is higher in energy and thus less accessible to nucleophiles. On the other hand, a new HOMO is also formed, which lies higher in energy than the occupied π-orbital of the unfunctionalized carbonyl compound. As a consequence, amides are not only less electrophilic but also better nucleophiles. This is showcased by the fact that amides react

readily with a range of electrophiles which leave aldehydes and alcohols untouched. Primary amides, for instance, can be dehydrated under mild conditions with thionyl chloride[524] or trifluoroacetic anhydride.[525] Moreover, tertiary amides, such as DMF, can act as catalysts for the formation of acyl chlorides when applying oxalyl chloride to organic acids, demonstrating that amides react faster with electrophiles than carboxylic acids.[518] These (tertiary) amides are also weakly basic; DMF for instance has a higher proton affinity than NH_3 or aniline (PA(DMF) = 211.3 kcal/mol, PA(NH_3) = 204.1 kcal/mol, PA($PhNH_2$) = 209.6 kcal/mol).[526]

The enhanced nucleophilicity of amides has been an asset in organic synthesis, since it can be exploited for chemoselective reactions in which other carbonyl functionalities do not react. The dehydration of primary amides with various agents was already known in the 19th century. Attempted dehydration of secondary and tertiary amides however usually resulted in unidentified decomposition reactions. In 1877 however, Wallach discovered that upon mild heating of a secondary amide (**3.13**) in presence of PCl_5 with a subsequent addition of a primary aniline, the amidine **3.15** was formed.[527] This can be reasonably called the first report of an amide activation reaction, in which the low reactivity of the amide towards nucleophiles was enhanced by an electrophilic activator (*Scheme 3.2a*).[528]

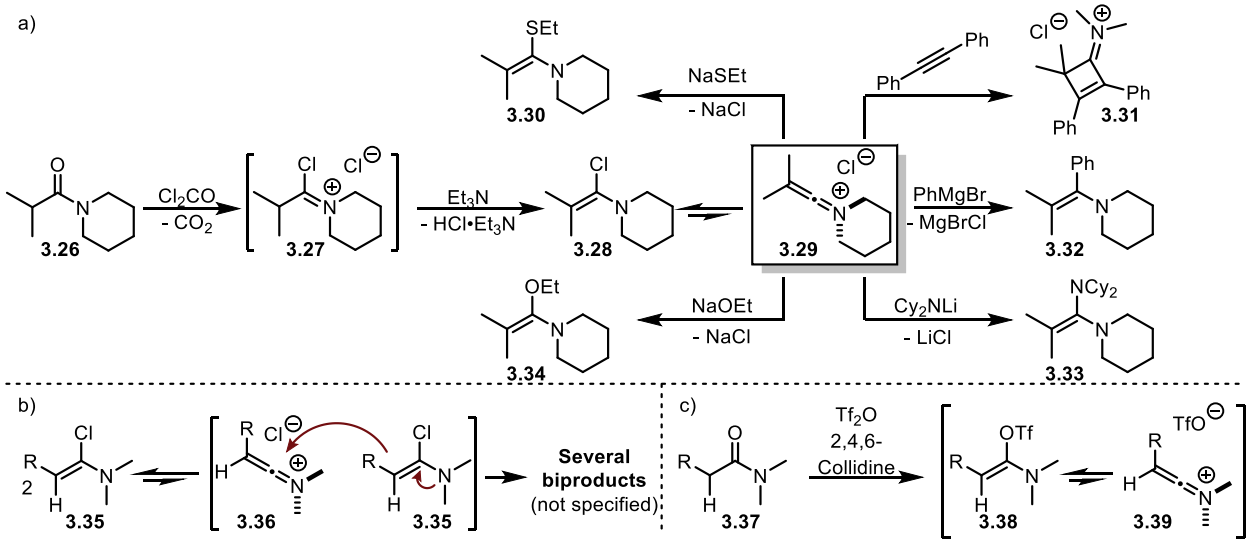


Scheme 3.2 – a) Earliest reported electrophilic amide activation. b) Original Vilsmeier-Haack reaction. c) Electrophilic amide activation by the use of Meerwein's salt.

This reactivity was famously applied in the Vilsmeier-Haack reaction, which was discovered 50 years later (*Scheme 3.2b*).[529] Moreover, in 1956 it has been noticed that DMF reacts (very slowly) even with alkylhalides at room temperature showcasing the relatively high nucleophilicity of this carbonyl functionality.[530] Just five years later, Meerwein and coworkers used triethyloxonium tetrafluoroborate ("Meerwein's salt")[531] to ethylate several tertiary amides on the oxygen atom (*Scheme 3.2c*).[532] The *in situ* generated α-ethoxy iminium salt has been used to synthesize "acetals" of amides (**3.21**) and ketene hemiaminal ethers (**3.322**). Moreover, the authors showed that treatment with an allylic alkoxide paved the way for a [3,3]-sigmatropic rearrangement resulting in the formation of a γ,δ-unsaturated amide **3.25**, a reaction which has been later investigated in an diastereoselective setting using a chiral auxiliary on the amide moiety.[533] Both reactions were probably inspired by an analogous transformation, in which an ynamine was activated by a Lewis acid and treated with an allylic alcohol, leading to the same sigmatropic rearrangement and a similar product.[534,535]

In 1969 Ghosez, Haveaux and Viehe reported that when tertiary amides are first treated with phosgene and then with a base the corresponding α-chloroenamine is formed (**3.28** – *Scheme 3.3a*).[536] They proposed that this species is in equilibrium with a keteniminium ion **3.29**, an intermediate postulated previously to explain the reactivity of some ynamines.[537] Although the putative keteniminium was not observed by any spectroscopic means at this time, the associated reactivity has been witnessed when the α-chloro enamine was treated with several nucleophiles, or with diphenyl acetylene to undergo a formal (2+2) cycloaddition reaction. However, just one year later Weingarten was able to measure the ^{1}H NMR spectrum of a keteniminium salt, which he generated by treating an α-chloroenamine with $AgPF_6$.[538] Research on keteniminium chemistry was long dominated by cycloaddition reactions, which are often higher yielding than the corresponding reactions of analogous ketenes.[539] However, since keteniminium salts are highly electrophilic, nucleophilic moieties may interfere with the cycloadditon,[540] which is most likely not a concerted pericyclic reaction but rather a stepwise process.[541]

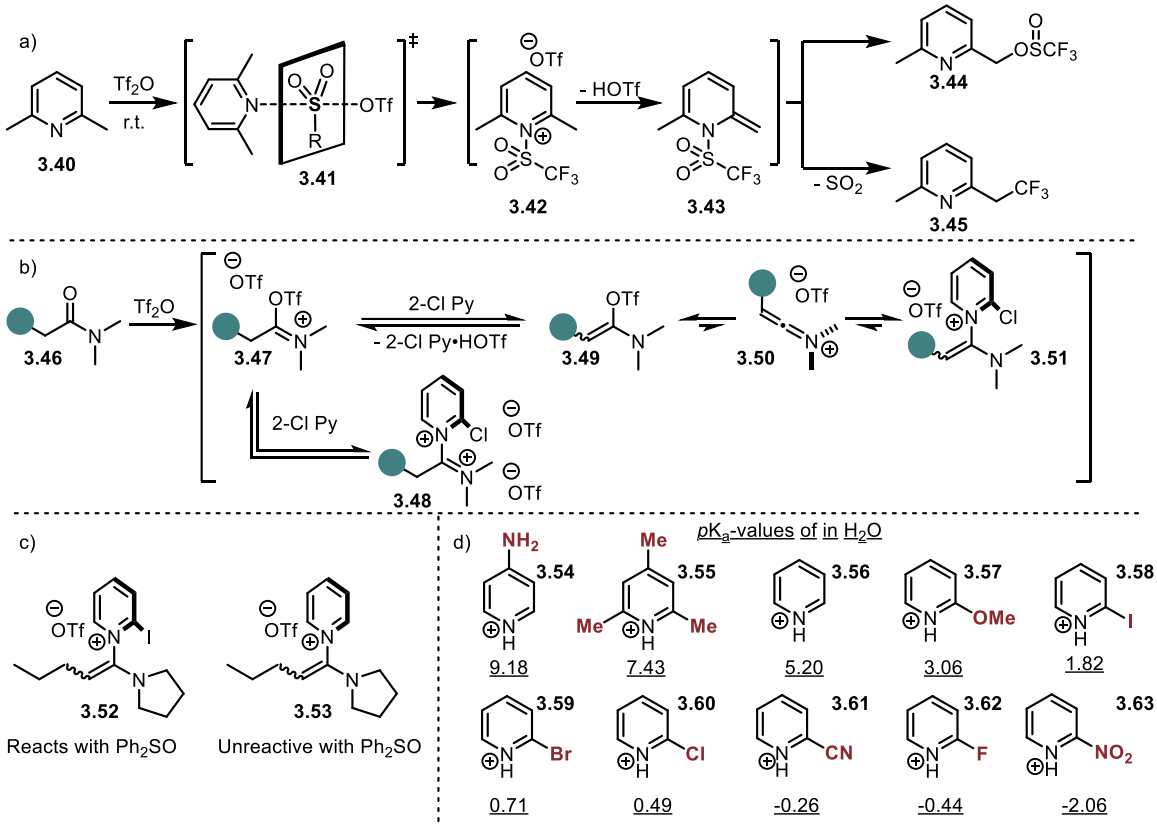
The use of phosgene for the activation of tertiary amides is problematic due to the former's high toxicity. Moreover, α-chloro enamines such as **3.35** are nucleophilic and may react with *in situ* formed keteniminium ions, in particular when they are monosubstitued on carbon (so-called "aldo" keteniminium ions) (*Scheme 3.3b*). Both issues have been overcome by the use of trifluoromethanesulfonic anhydride (triflic anhydride) in combination with a sterically congested pyridine base (*Scheme 3.3c*). In this reaction, the amide is converted first into a vinyl triflate which mimics the reactivity of the α-chloro enamine. This mode of activation has been applied to many synthetic challenges and is now a very common way to enhance the electrophilicity of tertiary amides.[528,542] Tf_2O is a potent electrophile; it does not only react with amides but also with ketones at room temperature[543] and decomposes moderately nucleophilic solvents such as THF or 1,4-dioxane.[544,545] However, chemoselectivity is usually achieved because amides are competitively more reactive than ketones and most ethers react with Tf_2O reversibly. Moreover, Tf_2O acts sometimes as an oxidant.[546]



Scheme 3.3 – a) Tertiary amide activation using phosgene and subsequent nucleophilic trapping of the putative keteniminium ion. b) Reaction of a α-chloro enamine with itself. c) More convenient activation by the use of triflic anhydride and a pyridine base.

The reaction pathway towards the vinyl triflate **3.38** is not as simple as it seems at first glance: nitrogen bases in general and pyridine bases in particular react very fast with sulfonylating agents to form *N*-sulfonyl pyridinium ions (*cf.* **3.42**)[547] and can be therefore used as sulfonylation catalysts (*Scheme*

3.4a).[548–550] Although dissociative (S_N1) and associative (S_AN) mechanisms were suggested earlier,[551] modern experimental and computational data points towards a mechanism in which the nucleophilic attack on the electrophilic O_2SR^+-synthon is an asynchronous S_N2 reaction (*Scheme 3.4a*).[552,553] It has been demonstrated by O^{18} labeling experiments that the two oxygen atoms and the R substituent of the sulfonylating agent undergo a Walden inversion.[554] When the attacking nucleophile carries a proton, deprotonation may occur during the transition state in an S_N3 reaction (general base catalysis).[555,556]

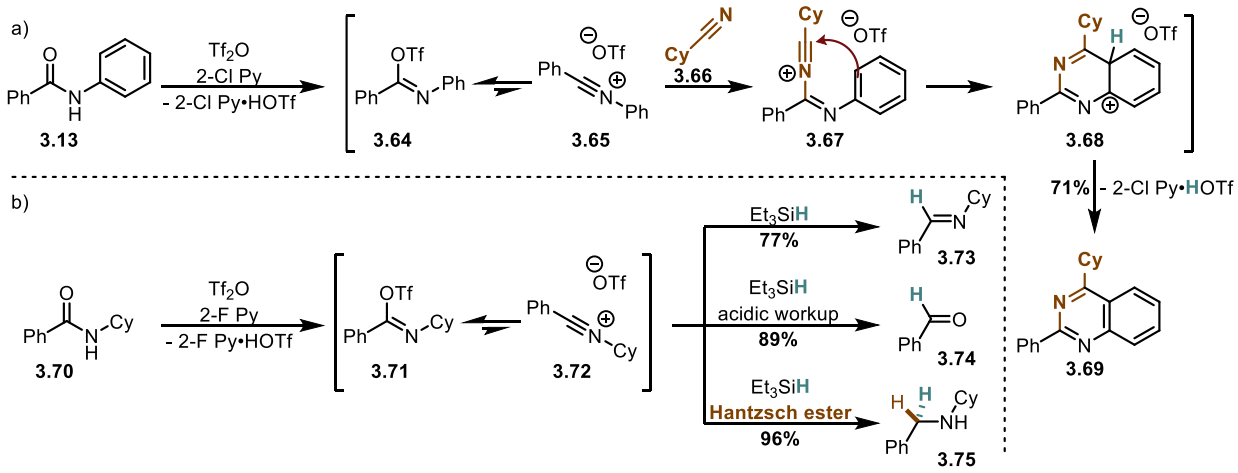


Scheme 3.4 – a) Reaction of a hindered pyridine base with triflic anhydride with subsequent decomposition. b) Equilibria of a keteniminium ion and its precursor with a pyridine bases. c) Two vinylpyridinium ions with different reactivity. d) pK_a values of several protonated pyridines in water.

The asynchronicity is dependent on many factors, but electron-withdrawing R-groups generally favor a "tight" transition state, in which the leaving group departs after initial approach of the nucleophile without forming a stabile intermediate. Notably, even sterically hindered bases such as 2,6-lutidine and 2,4,6-collidine undergo such a reaction at room temperature with triflic anhydride.[557] Moreover, it has been reported that these intermediates can react further to either the sulfinate **3.44** or to trifluoromethyl-

substituted lutidine **3.45** (*Scheme 3.4a*).[558] However, electron-poor pyridines undergo such a reaction only very slowly or not at all: 2-chloropyridine (2-Cl Py), for instance, seems not to react with Tf_2O in DCM solution at room temperature and other 2-halopyridine cognates react only at low rates under the same conditions.[559] Those 2-halopyridines are indeed most commonly used in electrophilic amide activation using triflic anhydride, because they are believed not to interfere in the first step of the activation. They have a low basicity and low nucleophilicity due to steric and electronic effects. Nevertheless, these pyridines may still act as nucleophiles (reversibly) on α-iminium triflates or on keteniminium ions to form cationic adducts (*Scheme 3.4c*).[560,561] These adducts are usually not problematic, as displacement by other nucleophiles is possible if the pyridine in question is a sufficiently good leaving group; however, it has been reported that plain pyridine does not conform to this.[562] There are no measurements on the nucleophilicity of electron-poor pyridine bases in the literature; however, the pK_a values of protonated pyridines in aqueous solution might be a valuable parameter in this regard although steric effects are obviously underestimated (*Scheme 3.4d*). The use of *in situ* generated keteniminium salts *via* triflic anhydride and pyridine bases is part of several reviews, and has been applied in many total syntheses.[528,542]

This electrophilic activation can also be used for secondary amides. In these cases, an *O*-triflyl imidate is generated (*cf.* **3.64** - *Scheme 3.5a*) which is in equilibrium with the corresponding, highly electrophilic, nitrilium ion (*cf.* **3.65**). This species has been often used in interesting and appealing methodologies, for instance in the synthesis of heteroarenes such as the pyrimidine synthesis of Movassaghi (*Scheme 3.5a*) [563–566] or in a tetrazole[567] and tetrazolium[568] syntheses when the electrophilic intermediate is trapped with azide salts or organic azides respectively. Alternatively, the nitrilium ion can be captured by simple nucleophiles. One useful and frequently cited example is the flexible reduction of the amide to either an amine, the imine or the aldehyde reported by Charette's group (*Scheme 3.5b*).[569]



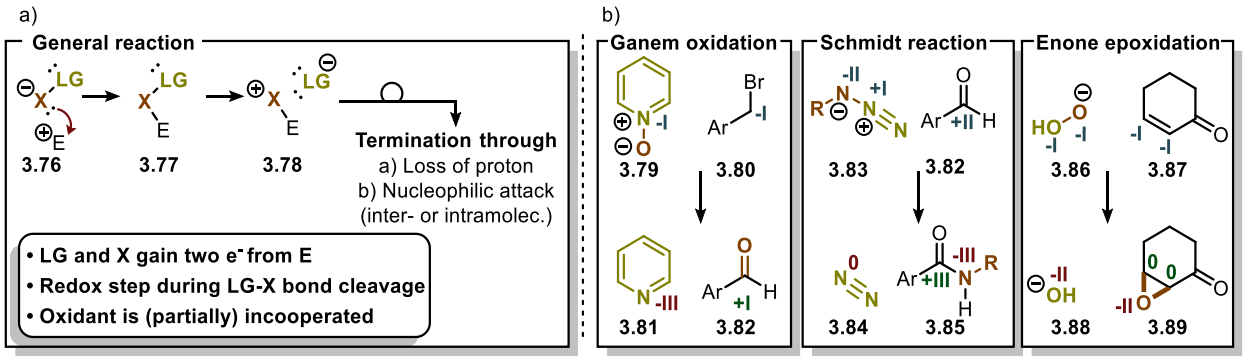
Scheme 3.5 – a) Activation of N-aryl substituted secondary amides lead to the formation of pyrimidines. b) Flexible reduction of secondary amides via the generation of a nitrilium ion.

3.1.1.2. *Nucleophilic oxidant addition to keteniminium ions*

Oxidants are generally electron-poor species, which can accept electrons from a reactant. Therefore, reagents that act as oxidants are intuitively perceived as electrophiles. Indeed, many oxidants such as activated DMSO (Swern oxidation), Cr(VI) compounds or λ-^{3} and λ^5-iodanes (as we shall see in the next chapter) commonly react with nucleophiles.

However, oxidants which comprise two heteroatoms of the second (or third) period directly bound to each other may show nucleophilic behavior. This nucleophilicity is often enhanced by the α-effect:[452,570,571] two adjacent lone pairs (or other π-electron containing orbitals) of the heteroatoms overlap to form a set of two new filled orbitals (π and π*) in which the antibonding orbital is higher in energy than the isolated lone pairs and more effective in interacting with vacant orbitals of an electrophile. On the other hand, the two electronegative elements withdraw electrons from each other through inductive effects (in the σ-framework) making them less reactive towards electrophiles which interact mainly through electrostatic interactions.[571] This explains why HO_2^- is much more nucleophilic than the hydroxyl anion yet more than 100 times less basic. Similarly, pyridine-*N*-oxide is a better nucleophile than pyridine,[548,550] but the pK_a of its corresponding acid is only 0.79 in water.[572]

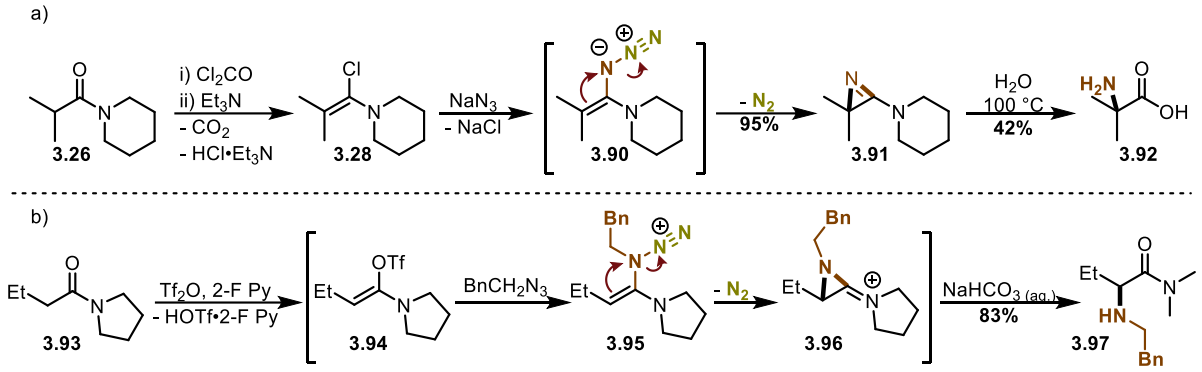
A nucleophilic oxidant reacts usually by attacking an electrophile through one of its aforementioned heteroatoms (mostly N or O), followed by the cleavage of the bond between the attacking heteroatom and the heteroatom which is directly attached to it (the nucleofuge) (*Scheme 3.6a*). During this bond cleavage, which is accompanied by the loss of a proton or a nucleophilic attack to quench the oxidized species **3.77**, the leaving group gains (formally) one or two electrons. The quenching of **3.78** can occur simultaneously during the departure of the leaving group or may take place after rearrangement reactions of the oxidized species. Consequently, the nucleophilic oxidant is partially incorporated into the oxidized molecule. A few examples are given in *Scheme 3.6*: the Ganem oxidatation,[573] the Boyer-variant[574] of the Schmidt reaction,[575] and a general enone oxidation promoted by deprotonated hydrogen peroxide.[576]



Scheme 3.6 – a) General reaction of an electrophile with a nucleophilic oxidant. b) Several examples of reactions where nucleophilic oxidants are used.

A few of these oxidants have been explored as nucleophiles in amide activation reactions. Ghosez's research group was arguably the leading pioneer in the 1970's and 1980's in this regard.[577,578] His group found early on that the nucleophilic attack of sodium azide on an α-chloroenamine, generated from the corresponding amide, leads to a vinyl azide which decomposes spontaneously at room temperature to the azirine *via* extrusion of nitrogen gas (*Scheme 3.7a*).[578] The azide reacts as the nucleophilic oxidant, somewhat reminiscent to hydrogen peroxide in the enone epoxidation in *Scheme 3.6* or hydroxylamine in the Neber rearrangement.[579] The thermally labile azirine can be hydrolyzed in boiling water to the α-amino acid **3.92**. This reaction, which had a rather limited scope at that time, has

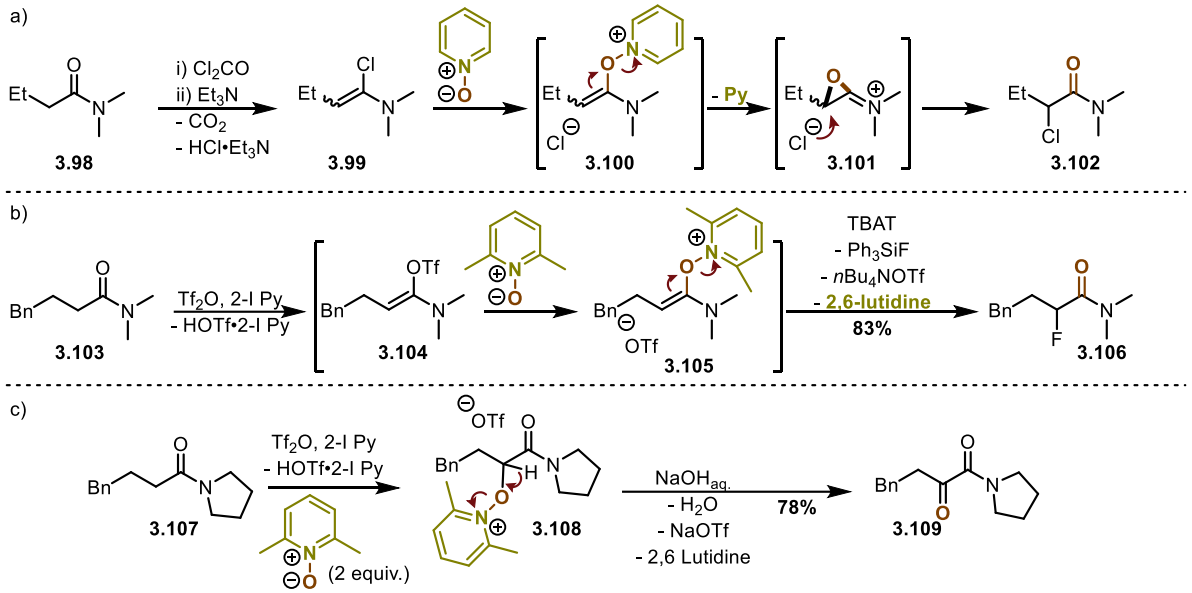
been later studied in more detail and generalized by the group of Maulide.[580] Instead of inorganic azide salts, organic azides were used as mild nucleophilic oxidants on *in situ* generated keteniminium salts, which were generated using triflic anhydride and a pyridine base. In doing so, azirinium salts (**3.96**) could be generated, which were hydrolyzed mildly during the aqueous workup to finally yield α-amino amides in good yields (*cf.* **3.97**).



Scheme 3.7 – a) Azerine generation by the reaction of sodium azide with a keteniminium salt. b) A keteniminium species is here oxidized directly to the α-amino amide by a similar mechanism.

The use of pyridine-*N*-oxide as nucleophilic oxidant for keteniminium intermediates has also been pioneered by the group of Ghosez (*Scheme 3.8a*).[577] The N-O binding situation of these oxidants has been described as being partially a double bond, although this strongly depends on the substituents on the aromatic ring.[581] The adduct **3.100** is believed to decompose, similarly to the organic azide adduct **3.90**, to the cation **3.101**. This intermediate represents a stabilized form of the α-carbocationic amide, where the nucleophilic amide-carbonyl stabilizes the positive charge by bridging (see chapter 4.1.1.6. for more details).[582–584] This cation is then attacked by the chloride anion on the electrophilic α-position to furnish the observed α-chloro amide. This reactivity has been later generalized by the group of Maulide where the amides were directly used: several nucleophiles such as fluorides (*Scheme 3.8b*),[585] enolates,[586] aromatic rings,[587] halides,[588] nitriles[589] or salts of heteroatomic compounds[588] can be added probably by displacing the *in situ* generated α-triflate *via* a nucleophilic substitution in intermolecular reactions. Intramolecular reactions may instead trap a short living cationic intermediated directly. Moreover, the

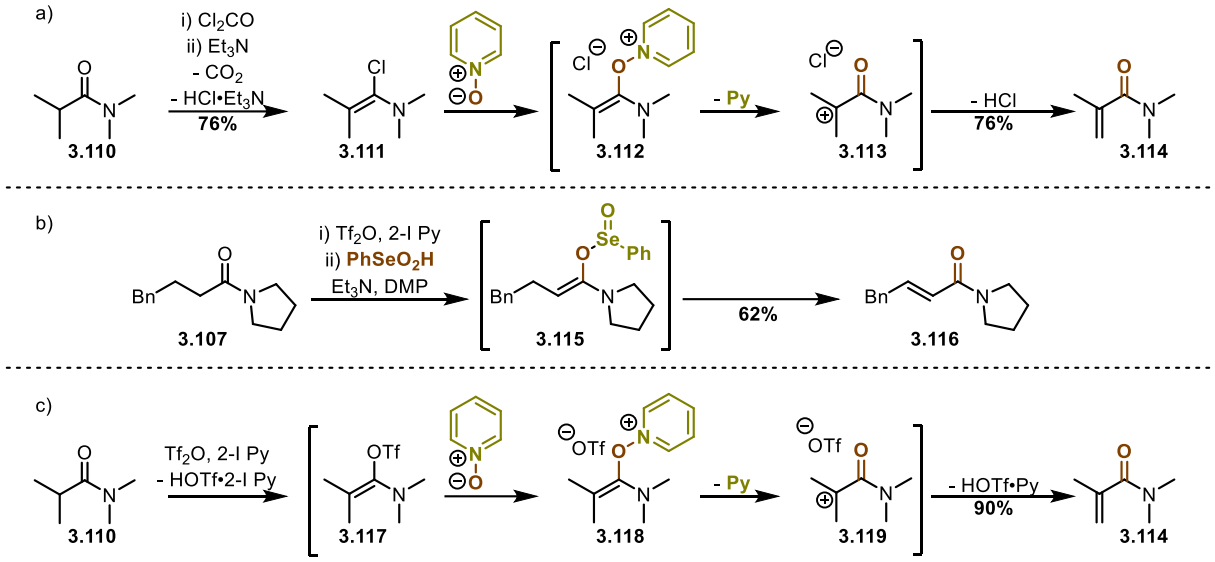
pyridine-*N*-oxide itself can act as a nucleophile on the electrophilic intermediate (*Scheme 3.8c*). In doing so, deprotonation of the α-proton leads to a further oxidation yielding an α-keto amide (as in the aforementioned Ganem oxidation).[590]



Scheme 3.8 – a) Reaction of PNO with a keteneiminium ion yields the α-chloroamide. b) By the use of triflic anhydride and a base in combination with lutidine-N-oxide the reaction is generalized so that several nucleophiles can be attached to the α-position. c) Lutidine-N-oxide itself can react as a nucleophile and may lead efficiently to a further oxidation.

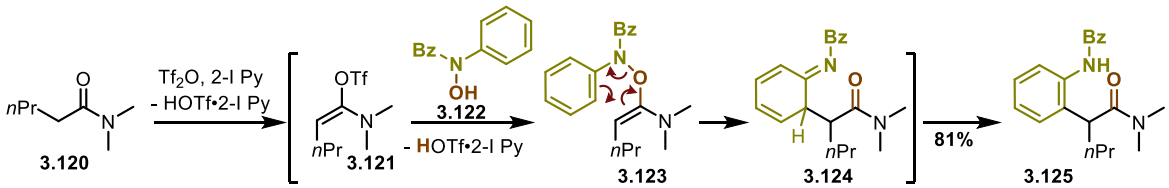
Interestingly, α-branched tertiary amides seem to react very differently when compared to their non-branched cognates; the α-chloride has never been observed for such substrates, instead they are oxidized cleanly to the α,β-dehydrogenated amide **3.114** (*Scheme 3.9a*).[577] α-branched cationic carbonyl compounds are indeed known to have a different reactivity due to the hyperconjugation of the substituents. Carbonyl-bridging seems to be disfavored in such species, thus they behave much like "real" carbocations (see chapter 4.1.1.6 for more details).[582–584] This α,β-dehydrogenation-reaction has been recently extended to amides which are not branched in the α-position, by the use of a nucleophilic selenium containg oxidant in combination with iodine(V) (*Scheme 3.9b*).[591] Dr. Jing Li, a former postdoctoral researcher of the Maulide group, discovered that the dehydrogenation of α-branched amides is similarly observed when the amide is treated with triflic anhydride and 2-iodopyridine with a

subsequent addition of pyridine-*N*-oxide (*Scheme 3.9c*). This observation is the base for most of the results presented in this chapter.



Scheme 3.9 – a) α-Chloroenamines derived from α-branched amides do not react with nucleophiles under those Umpolung conditions to yield α-functionalized amides, instead dehydrogenation is observed. b) The dehydrogenation reaction was extended to non-branched amides by the use of a selenium-based oxidant. c) α-Branched amides can be directly oxidized to the α,β-dehydrogenation amide by the use of triflic anhydride, a base and PNO.

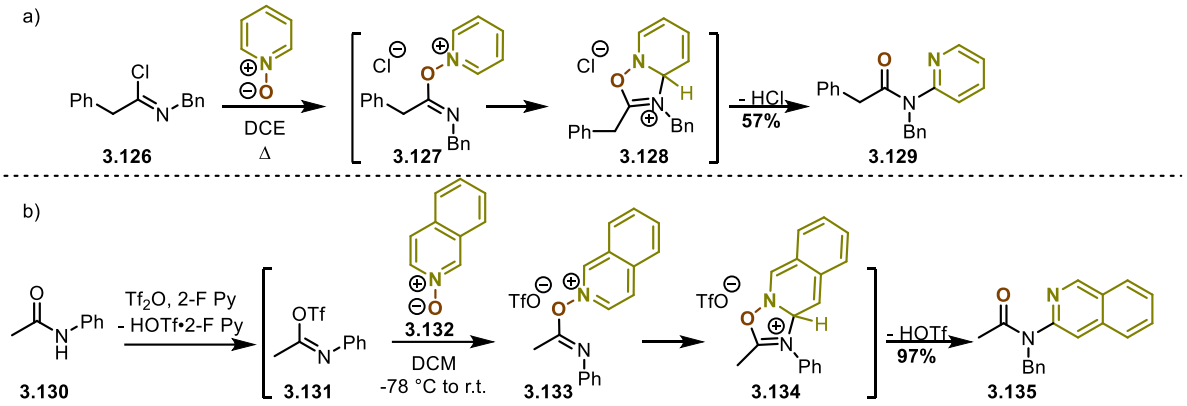
Somewhat similar to the addition of pyridine-*N*-oxides to activated amides is the nucleophilic attack of hydroxamic acids or sulfoxides to keteniminium ions (*Scheme 3.10*). In these cases the oxidation is accompanied by a [3,3]-sigmatropic rearrangement leading to the α-arylated amide.[592] Since sulfoxides carry potentially a stereogenic center on the sulfur-atom, they can also transfer their stereogenic information into the α-arylated product when the keteniminium is generated from ynamides.[593,594]



Scheme 3.10 – Hydroxamic acids act as oxidative nucleophiles on keteniminium ions paving the way for a [3,3]-sigmatropic rearrangement.

The addition of pyridine-*N*-oxides to activated secondary amides has been pioneered by Abramovitch and Singer at the end of the 1960's.[595] The addition of the nucleophilic oxidant onto imidoyl chlorides results in *N*-pyridinylized amides (*Scheme 3.11a*). This reaction has been later generalized

(starting directly from the amide) and mechanistically elucidated by Movassaghi *et al*. 40 years later (*Scheme 3.10b*).[596]



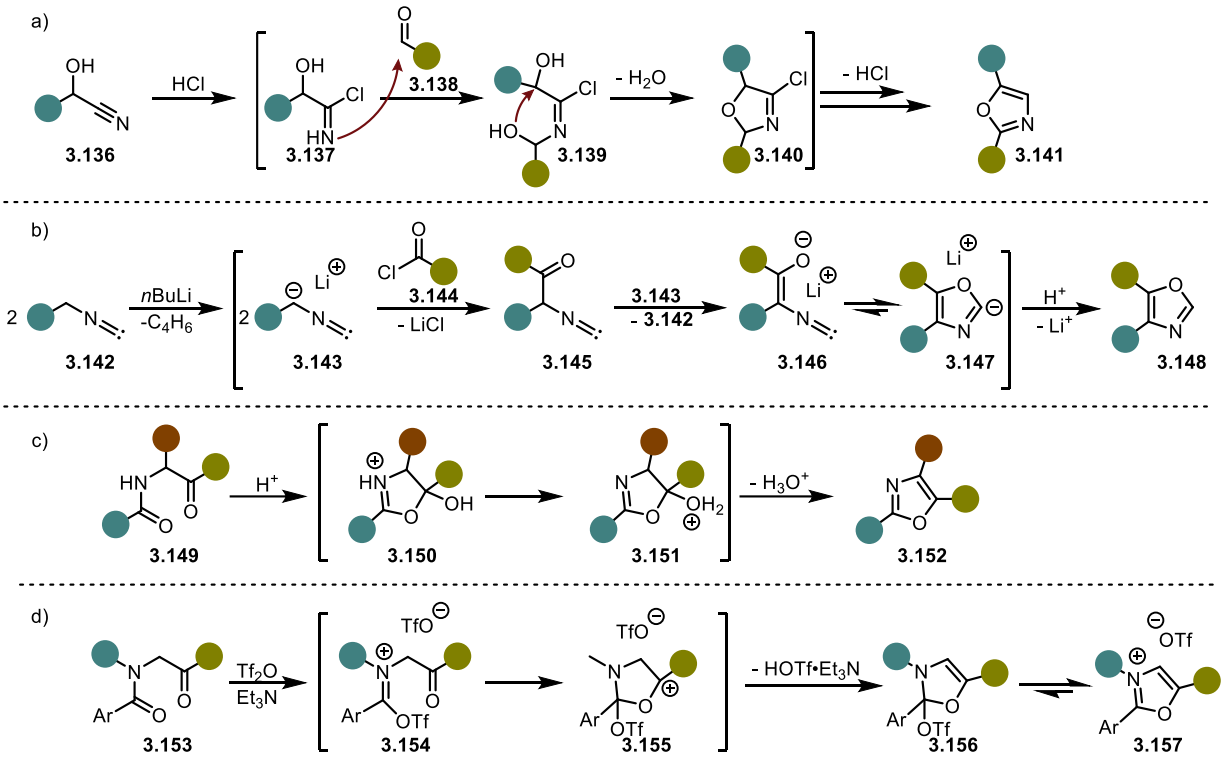
Scheme 3.11 – a) Nucleophilic oxidation of an α-chloroimine gives an N-pyridyl amide. b) A more convenient procedure uses triflic anhydride a base and arylic N-oxides on secondary amides.

3.1.2. Oxazolium salts – synthesis and reactivity

The formation of oxazolium salts and 7-membered rings were originally not part of this project. However, interesting side reactions were observed and led to the investigation of those reactions. A brief introduction will be discussed in the following lines.

Oxazoles are small heteroaromatic compounds, which can be generated in several ways. One of the earlier syntheses was the Fischer-oxazole synthesis reported at the end of the 19th century (*Scheme 3.12a*).[597,598] In this reaction, which is classically promoted by gaseous HCl, a cyanohydrin reacts with an aldehyde to furnish a 2,5-disubstituted oxazole. Ethereal HCl solution is a practical substitute for the corrosive gas. The reaction goes *via* the formation imidoyl chloride **3.137**, which attacks the aldehyde as a *N*-nucleophile. More than a decade earlier, Japp and Wilcock discovered another oxazole synthesis, which has a rather limited substrate scope.[599,600] In the early 1970's Schöllkopf and Schröder discovered a base-promoted oxazole synthesis were a deprotonated isonitrile reacts with an electrophilic carboxylic acid derivative (commonly acyl chlorides but also weaker electrophiles, such as carboxylic esters, are compatible).[598,600,601] Usually, two equivalents of the deprotonated isonitrile are used, because one equivalent acts as the base to deprotonate the α-position of the ketone **3.145**. The enolate **3.146** is in

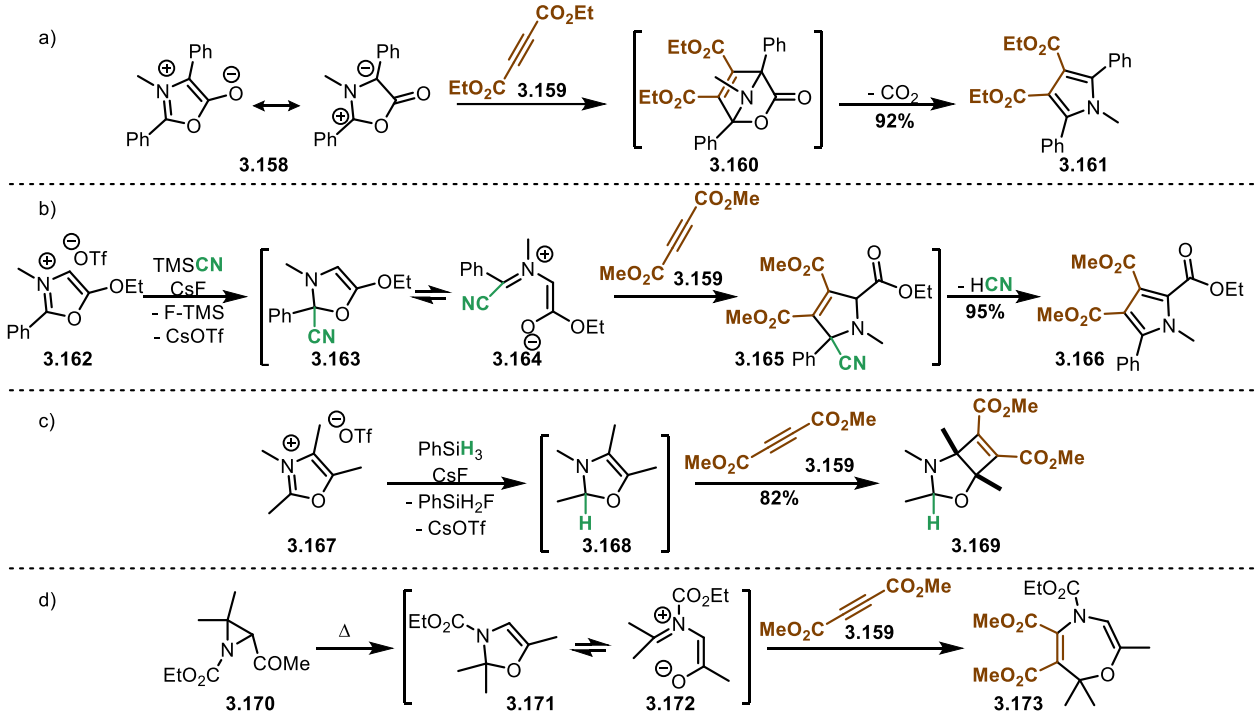
equilibrium with the deprotonated oxazole, which is converted to the desired product during the aqueous workup. Another important oxazole synthesis is the Robinson-Gabriel synthesis, where an acylated α-aminoketone is dehydrated under acidic conditions to furnish the oxazole (*Scheme 3.12c*).[602–604] In the Davidson variant of the reaction the acylated α-hydroxyketone and an ammonium salt are used instead.[598,605]



Scheme 3.12 – a) Generation of oxazoles by an acid-promoted reaction using cynohydrines as substrates. b) Isocyanides may react to similar products when treated with a base and an acylating agent. c) Acylated α-aminoketones are dehydrated under acidic conditions to oxazoles. d) Generation of oxazolium salts by the use of triflic anhydride and a base.

Oxazolium salts can be simply prepared by the alkylation of an oxazole.[606,607] A more direct approach consists in the dehydration of tertiary acylated α-aminoketones (*Scheme 3.12d*).[608,609] This approach is a variant of the Robinson-Gabriel reaction. However, it has been limited by the necessity of aromatic (non-enolizable) acyl substituents on the nitrogen atom, likely due to the formation of vinyl triflates/keteniminium salts, which may block the reactivity. The structural similarity of certain oxazolium salts and münchnones[610] has been noted in the literature. Interestingly, the reactivity of the later has been mimicked by the former: while münchnones react directly with dipolarophiles and extrude CO_2

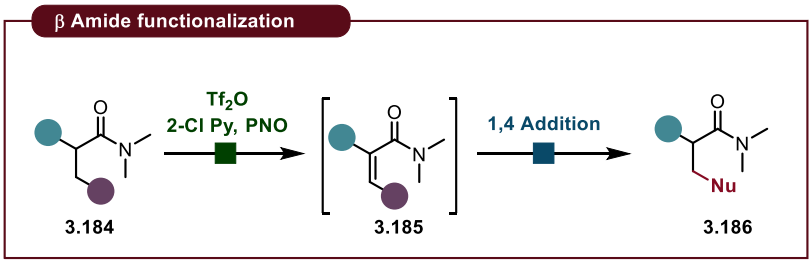
during the reaction to yield pyroles (*Scheme 3.13a*),[611] oxazolium salts behave similarly when activated with cyanide (*Scheme 3.13b*).[606] Other nucleophiles may activate the oxazolium salt but lead to a different reactivity. When a hydride is used, for instance, the generated oxazoline may undergo a (2+2) cycloadditon with an electron-poor alkyne (*Scheme 3.31c*).[612] Oxazolines react not only in (3+2) cycloadditions to give pyrroles as in *Scheme 3.13b*, but may undergo (5+2) cycloadditions with electron-poor alkynes (*Scheme 3.13d*).[613]



Scheme 3.13 – a) Cycloaddition reaction of a münchnone with an electron-poor alkyne generating a pyrrol. b) Oxazolium salts may also lead to the formation of pyrroles, when activated with a cyanide anion. c) Oxazolium salts can also react in formal (2+2) cycloaddition reactions. d) The open form of an oxazoline may react in a (5+2) manner instead of a (3+2) cycloadditon.

3.2. Objectives

The original aim of this work was to investigate if the α,β-dehydrogenation of α-branched tertiary amides can be used in a one-pot fashion to functionalize the β-position *via* a simple Michael addition. Other one-pot functionalizations shall also be explored. Importantly, the chemistry of the α,β-dehydrogenation has to be understood and eventually adapted to settings which allow a further functionalization of the intermediate. In this regard, it is crucial to explore the regio- and the stereoselectivity of the oxidation event.

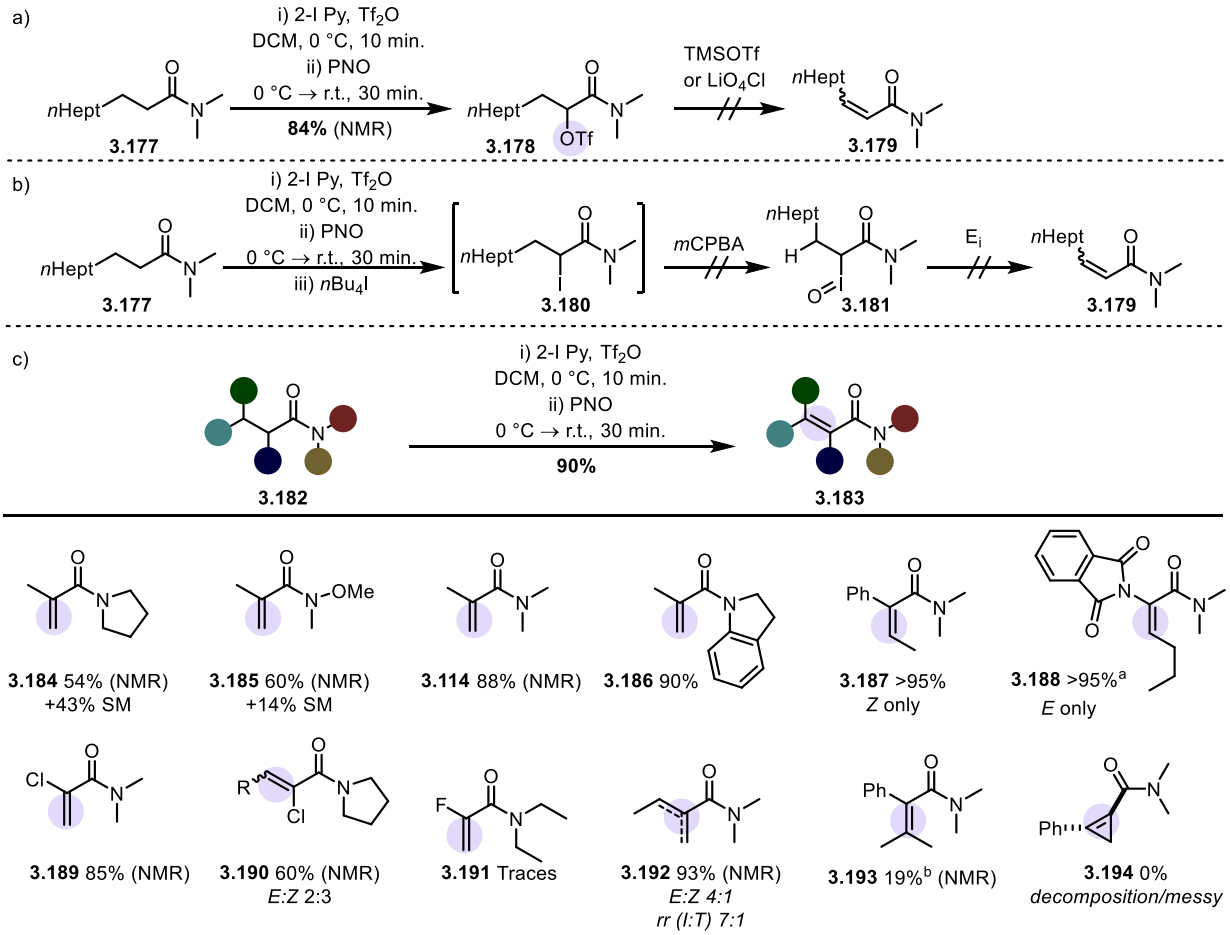


Scheme 3.14 – General objective for the β-functionalization of amides in a one-pot fashion.

3.3. Results and discussion

3.3.1. α,β-dehydrogenation of amides

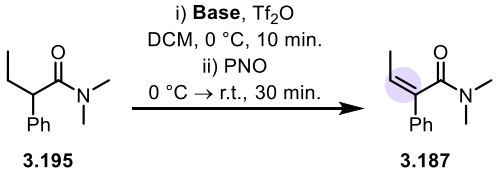
First we investigated the scope of the α,β-dehydrogenation reaction. As suspected, the reaction was strongly limited to α-secondary (*i.e.* branched) tertiary amides. All amides with a CH_2 substituent in α-position underwent the known Umpolung reactivity, mostly resulting in the formation of the α-triflate (*cf.* **3.178**, *Scheme 3.15a*). Attempts to overcome this limitation by adding lithium-salts or strong Lewis acids were not successful. Moreover, iodide displacement of the triflate followed by oxidation did not lead to the expected E_i-reaction of the iodoso-intermediate.[614]



Scheme 3.15 – a) Observation of the α-triflate in non-branched amides. b) Unsuccessful attempt to dehydrogenate non-branched amides by an internal elimination of an in situ formed iodoso compound. c) Scope of the dehydrogenation reaction of α-branched amides. [a] Reaction carried out at 60 °C. [b] Reaction carried out at 60 °C for 15 h.

However, when the amide was branched in α-position several substituents on the amide moiety were compatible with the protocol, although the best yields were observed when dimethyl- or indoline based amides were used. The Weinreb-amide **3.185** was only formed in a fair yield of 60%, possibly due to retro-ene type side reactions.[615] The low yield of the pyrrolidine amide **3.184** was surprising since it is a common motif in high yielding amide activation substrates. Notably, the aforementioned α-triflate has never been observed, even when the reaction was carried out in deuterated solvent and a ^{1}H NMR spectrum was measured immediately after the addition of PNO. α-Phenyl amides yielded the desired olefin in quantitative yield as a single *Z* isomer (**3.187**). In addition, an α-Phtalimide (an α-amino acid derivative) showed the same reactivity and selectivity but the reaction had to be promoted by heating.

α-Chloro amides on the other hand underwent dehydrogenation smoothly but with a low preference for the *Z*-isomer (*i.e.* with the aliphatic chain in *trans* to the amide). Interestingly, the fluoro-amide leading to **3.191** seems to form a very stable vinyl triflate intermediate, which does not further react to yield the desired α,β-dehydrogenated amide in significant amounts, even when heated for a prolonged period. Moreover, amides with two different aliphatic substituents showed the appropriate reactivity, but yielded a mixture of 3 isomers (two of those are *E:Z*-isomers), which are unfortunately not separable. The selectivity of the process is highly dependent on the amount and the nature of the oxidant (other pyridine-*N*-oxides have been used), the base and the temperature. These reaction parameters have to be controlled very strictly in order to give reproducible results. Tetrasubstituted olefins were only observed in low yields by using this approach (*cf.* **3.193**).



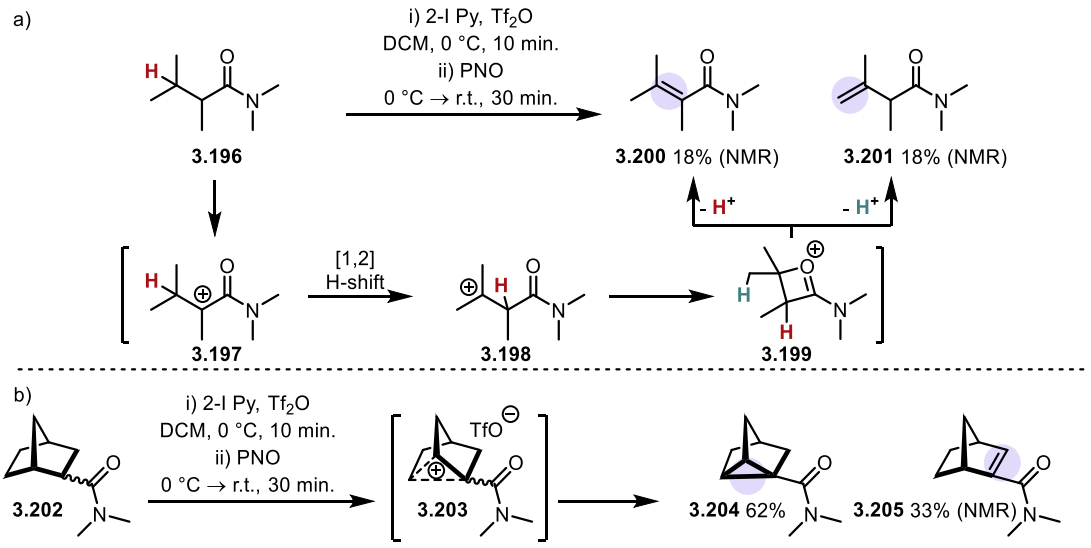
3.195 **3.187**

Table 3.1 – Screening of several bases for the dehydrogenation reaction.

Entry	Base	Yield **3.187** (NMR)	Yield **3.195** (NMR)
1	1-Methylpyrazole	63%	37%
2	1,5 Dimethylpyrazole	/	100%
3	Pyrimidine	5%	95%
4	2-Chloropyridine	98%	2%
5	2-Bromopyridine	97%	2%
6	2-Methoxypyridine	83%	16%
7	2-Nitropyridine	25%	73%

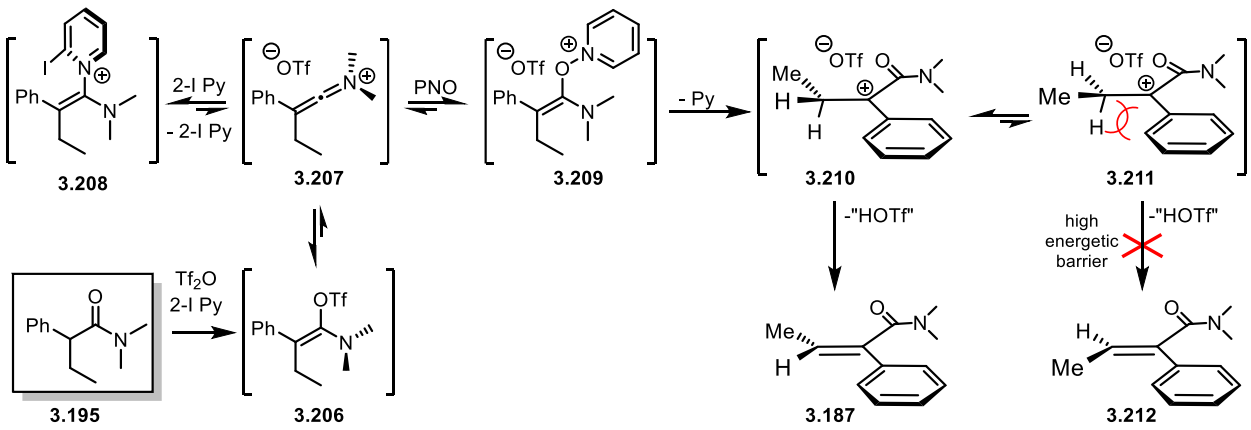
Although 2-iodopyridine was used initially, a range of other aromatic nitrogen bases promotes the reaction in the same fashion (*Table 3.1*). 2-Chloro- and 2-bromopyridine gave again a quantitative yield of the *Z*-isomer **3.187**. 2-Methoxypyridine and 1-methylpyrazole showed the same selectivity but with an incomplete conversion. Very low conversions were obtained when 2-fluoropyridine, 2-nitropyridine or pyrimidine were used.

Notably, the α,β–branched amide **3.196** lead only partially to the expected α,β-dehydrogenated product (*Scheme 3.16a*). An equimolar amount of the β,γ-isomer **3.200** was observed. The β,γ-alkene was easily separable from the α,β-desaturated product but unfortunately not from the starting material. This reactivity suggests that the α-carbocationic intermediate **3.197** is involved and undergoes a [1,2]-hydride shift to give the more stable tertiary carbocation **3.198**. This carbocation might be further stabilized by β-bridging of the amide moiety. Similarly, when the norbornyl-amide **3.202** was submitted to the usual reaction conditions the nortricyclene product **3.204** was observed (*Scheme 3.16b*), a reaction typical for the non-classical norbornyl carbocation. These carbocationic rearrangements are discussed in more detail in chapter 4.



Scheme 3.16 – a) Unexpected formation of a β,γ-dehydrogenated product probably via a cationic mechanism. b) Unexpected formation of a nortricyclene.

To conclude, we propose the following mechanism for the dehydrogenation reaction (*Scheme 3.17*): first triflic anhydride reacts, either directly or promoted by the pyridine base, with the amide to afford a vinyl triflate, which is in equilibrium with the reactive keteniminium species. This species may reversibly form adducts with the pyridine base. The electrophilic species is then attacked by pyridine-*N*-oxide, which leads to the enolonium species **3.209**. This unstable intermediate decomposes to pyridine and the carbocation **3.210**. Bridging of the amide-carbonyl to form a 3-membered heterocycle and stabilize the carbocation is unlikely but possible.[582] A perpendicular arrangement of the phenyl substituent and the empty p-orbital, on the other hand, should stabilize the system considerably, restricting the rotation of the arene substituent. This disfavors a possible conformer **3.211** due to steric congestion. This congestion actually increases during formation of the double bond, kinetically favoring elimination to **3.187** the thermodynamically more stable conformer.



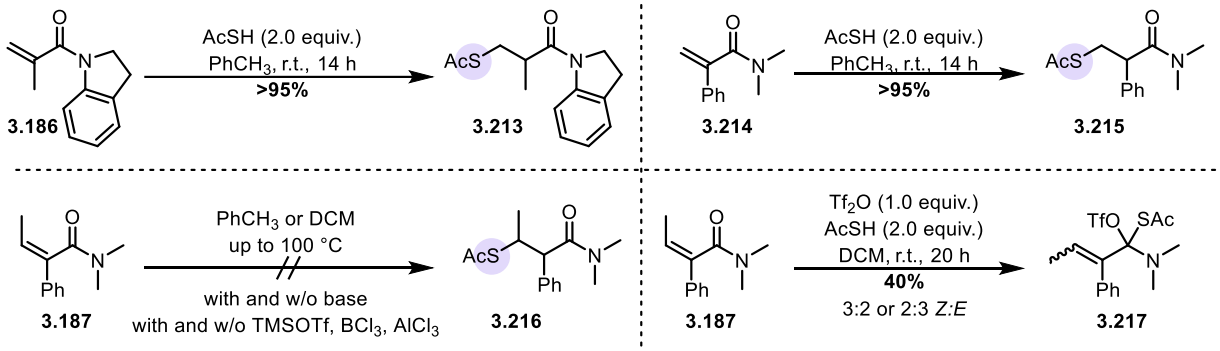
Scheme 3.17 – Proposed mechanism of the α,β-dehydrogenation of amides.

3.3.2. Reactivity of α-phenyl-α,β-dehydrogenated amides

Next we wanted to investigate the reactivity of the α-phenyl-α,β-dehydrogenated amide **3.187**, in order to explore potentially useful one-pot protocols.

Thioacetic acid undergoes 1,4-addition to the α,β-dehydrogenated amide **3.186** smoothly at room temperature (*Scheme 3.18a*).[616] Indeed, no catalyst or promoter was needed. This is somewhat in accordance with the fact that thioacetic acid reacts in a concerted mechanism with Michael-acceptors (a

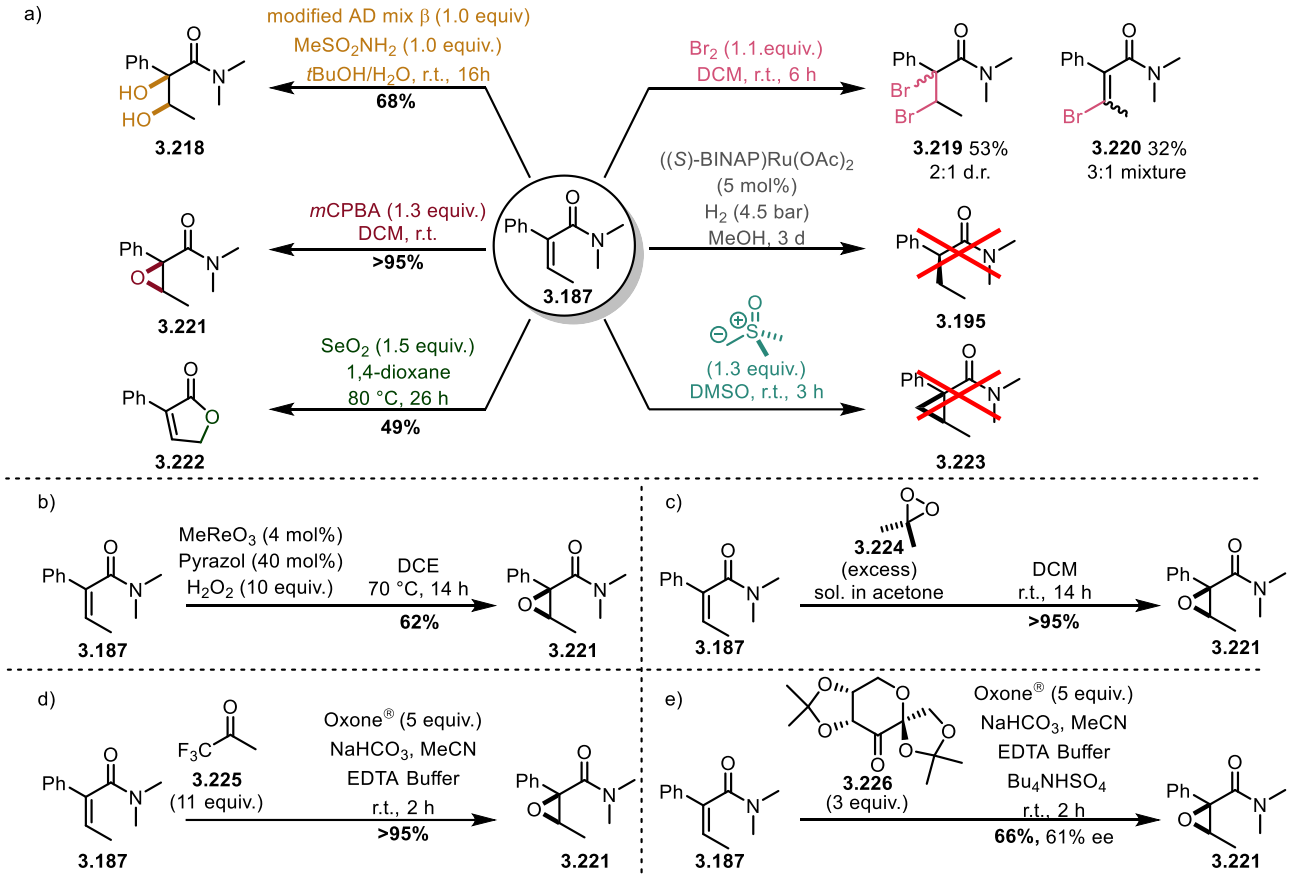
literal 1,4-addition).[617] The α-phenyl substituted product **3.214** was also very prone to undergo this reaction (*Scheme 3.18b*). Interestingly, the tri-substituted analogues alkene **3.187** did not react at all with thioacetic acid (or other strong nucleophiles such as the sulfoxonium ylide Me_2SOCH_2). A variety of promoters has been investigated to force the reaction (for instance TMSOTf, $AlCl_3$, BCl_3 or Et_3N in stoichiometric and substoichiometric amounts, at temperatures up to 100°C) but without notable success (*Scheme 3.18c*). The only activator which had a substantial effect on the substrate was Tf_2O. Interestingly the reaction did not go *via* a Michael addition but afforded 40% of the alkene **3.217** instead. The product is surprisingly stable and can be purified by column chromatography.



Scheme 3.18 – a/b) 1,4 addition on α,β-dehydrogenated amides. c) Unsuccessful Michael addition on a tri-substituted alkene. d) Unexpected 1,2 addition of thioacetic acid on an activated amide.

These results point towards an uneffective conjugation of the alkene with the carbonyl group. Indeed, the 3D-structure of the starting material shows that allylic strain of the methyl group in combination with the bulky phenyl substituent in α-position makes co-planarity of the olefin with the C=O practically impossible. The lack of carbonyl conjugation is furthermore revealed by the chemical reactivity of the seemingly electron-poor alkene in other reactions (*Scheme 3.19a*). Dihydroxylation can be achieved by using AD-mix α.[626] However the AD-mixture has to be slightly modified (the catalyst loading and the ligand loading have to be increased) since such substrates are known to react sluggishly.[627] When the alkene was reacted with elemental bromine, the dibromide was formed along with the vinyl bromide **3.220**. Interestingly, the reaction shows only very low stereoselectivity. We suspect that the bromonium ion is formed but might be in an equilibrium with an open carbocation, which is stabilized by the adjacent

aromatic ring. This carbocation might then lead directly to the formation of the vinyl bromide (by E_1 elimination), or to the formation of dibromide adduct.



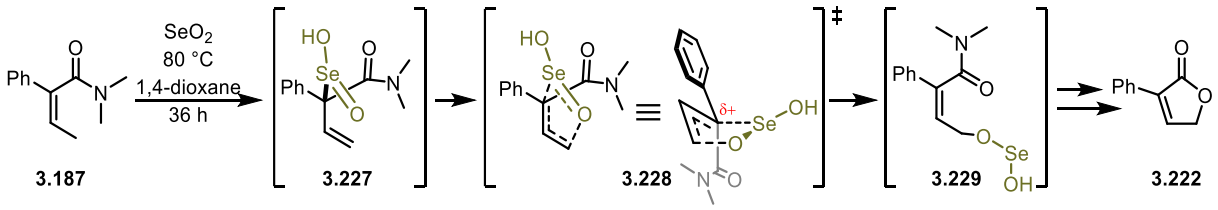
Scheme 3.19 – a) Reactivity of the α,β-desaturated amide. b) Epoxidation by the use of Re(VII) and hydrogen peroxide. c-d) Epoxidation by the use of several dioxiranes.

A few chiral hydrogenation catalysts were investigated in order to obtain the saturated amide enantioselectively. However, even working at high hydrogen pressure (>5 bar) and long reaction times (48 h) no conversion was observed. We believe that the steric congestion around the alkene is again at fault.

Oxidation with *m*CPBA resulted in a clean, stereospecific and quantitative formation of the epoxide at room temperature in a few hours, although this reaction requires typically high temperatures to occur on other electron-poor alkenes. The same epoxidation can be achieved with methyltrioxorhenium (MTO) and hydrogen peroxide (*Scheme 3.19b*).[618–620] Dioxiranes (prepared *in situ*[621] or purified by low temperature distillation[622,623]) are also effective in epoxidizing these alkenes

(*Scheme 3.19c-e*). Shi epoxidation[624,625] gave the epoxide in 66% yield and a moderate ee of 61% (*Scheme 3.19e*).

The alkene is also susceptible to SeO_2-promoted allylic oxidation (*Scheme 3.20*).[628,629] This reaction is coupled to lactonization likely by displacing $^-$OSeOH. Catalytic versions of this reaction (with peroxides as stoichiometric oxidants) did not provide the desired product in significant amounts.[630,631] It is remarkable that the reaction is at least highly stereoselective: the first intermediate of the allylic oxidation could, in principle rotate around the allylic C-C axis and enable the formation of the *Z* and the *E* allylic alcohol derivative (*Scheme 3.20*). However, high stereoselectivity in this regard has been noticed previously in similar reactions,[632,633] and can be explained by a more detailed look onto the mechanism (*Scheme 3.20*).[634,635] In the ene-step of the reaction, the SeO_2 approaches the alkene in an *endo* conformation (meaning that the two oxygen atoms are pointing towards the olefin).[636] The Se(IV) intermediate **3.227** undergoes [2,3]-sigmatropic rearrangement in an envelope-type cyclic transition state (**3.228**). Importantly, bulkier substituents favor a *pseudo*-equatorial arrangement.[636,637] Moreover, the coordination of the amide moiety towards the Se atom might also play an important role.



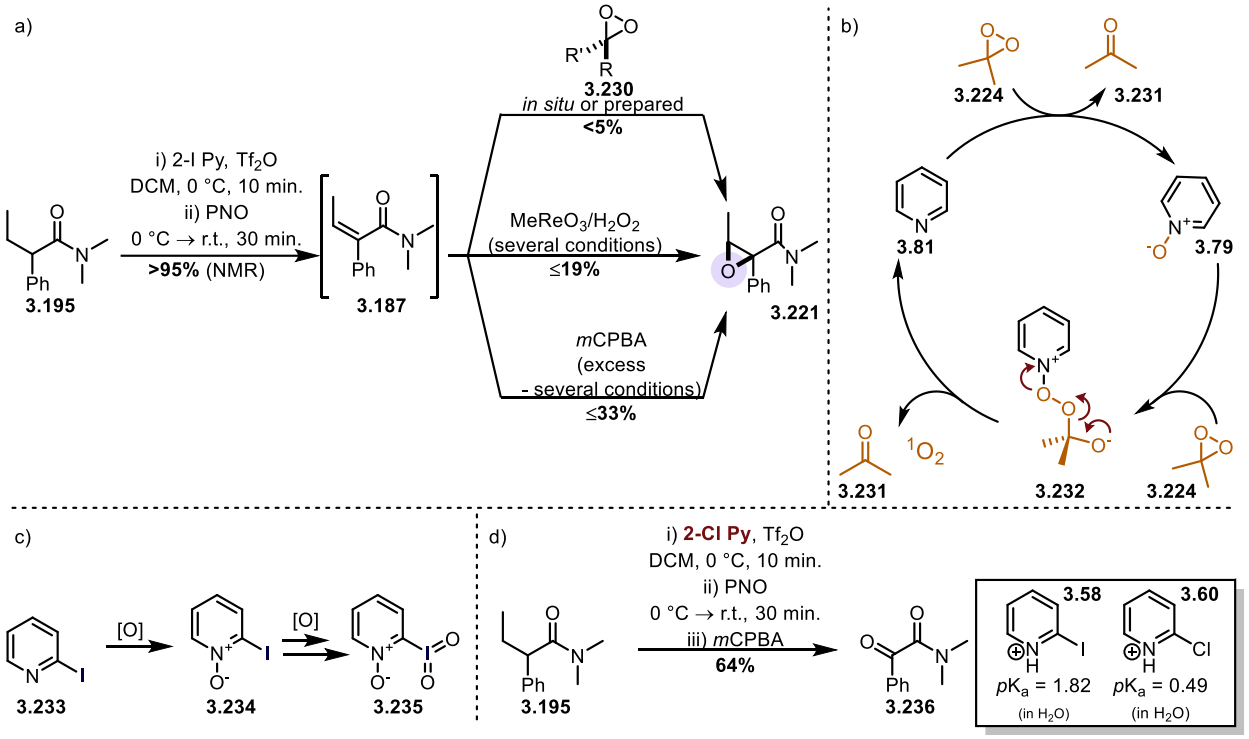
Scheme 3.20 – Mechanism of the allylic oxidation with SeO_2.

3.3.3. One-pot epoxidation

3.3.3.1. *Optimization*

After the initial results on the reactivity of the dehydrogenated product, we were encouraged to leverage the high *E:Z* selectivity into a stereoselective one-pot epoxidation reaction. Notably, these oxidations, which were highly efficient on the isolated alkene, were not compatible with the one-pot reaction due to different reasons (*Scheme 3.21a*). Pyridines are very efficient catalyst for the

decomposition of dioxiranes into acetone and singlet oxygen (*Scheme 3.21b*).[638] Thus the desired epoxide was only detected in traces in the crude mixture when dioxirane was added or produced *in situ* in the crude mixture of the dehydrogenated product. MTO-catalyzed oxidations gave only a poor yield of the desired epoxide under several conditions.

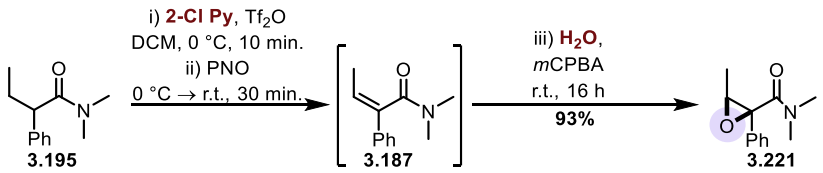


Scheme 3.21 – a) Unsuccessful one-pot α,β-epoxidation of a simple amide. b) Catalytic decomposition of dioxiranes by pyridine. c) Oxidation of 2-iodo pyridine. d) Unexpected formation of an α-keto amide due to the high acidity of the reaction medium.

The reaction of MTO follows complicated kinetics, especially because the setup is usually biphasic.[639,640] Non-coordinating bases tend to decompose the catalyst into methanol and perrhenate, while coordinating bases such as pyridine prevent the disintegration at higher concentrations.[640] The reaction is accelerated by those ligands *via* coordination and ultimately a "transfer catalysis effect" enhancing the solubility of the catalyst in organic solvents.[641,642] These nitrogen-based ligands are oxidized (usually faster than the alkene substrate itself) *in situ* to the *N*-oxides, which are then transferred to the aqueous phase due to their high hydrophilicity. The oxidation of the base is particularly fast when the competing alkene is electron-poor.[640] The ligands therefore must be used in large excess due to their

quick consumption. However, 2-halopyridines seem not to bind at all to the Re central atom. Moreover, thermal decomposition of the catalyst may occur at temperatures higher than 55 °C under epoxidation conditions.[643] All these factors make it difficult to steer the reactivity towards a higher yield in the one-pot procedure.

Initially, Prilezhaev oxidation was similarly very inefficient in a one-pot procedure. Even with a large excess of *m*CPBA and elevated temperatures, most of the formed alkene did not convert to the epoxide. The iodine atom of 2-iodopyridine, which can be easily oxidized (as well as the nitrogen atom of the pyridine ring) was accounted for the low conversion (*Scheme 3.21c*).[644] Changing the base in the amide activation step to 2-chloropyridine lead to the formation of the α-keto amide **3.236** (*Scheme 3.21d*). We will discuss that case in more detail later; it is, however, caused by the high acidity of the solution: protonated 2-chloropyridine (which is generated in the course of the reaction) has an acidity (in aqueous solution) similar to trifluoroacetic acid (pK_a (2-chloropyridine) = 0.49,[645] pK_a (TFA) = 0.23[147]). Indeed, when the reaction mixture was extracted with an equal volume of water, the pH of the aqueous phase was measured to be ≤1. Gratifyingly, the addition of water followed by 5 minutes of vigorous stirring lowered the acidity of the organic phase sufficiently to enable a smooth epoxidation of the alkene in a one-pot reaction (*Scheme 3.22*).



Scheme 3.22 – Successful one-pot α,β-epoxidation of a simple amide.

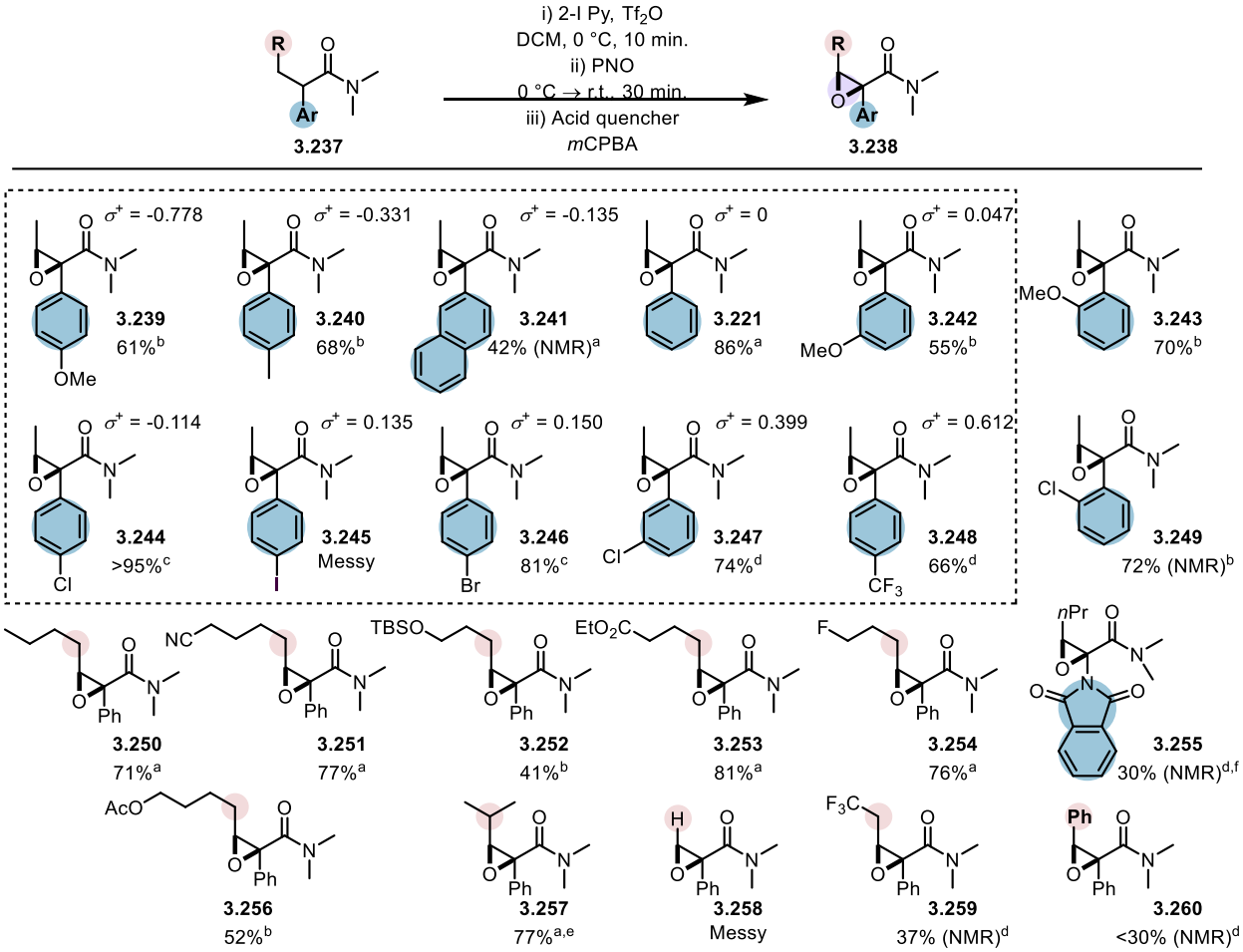
3.3.3.2. *Scope of the reaction*

With optimized conditions in hand, we investigated the scope of the epoxidation reaction, first by varying the aromatic ring in α-position (Parametrization of the electronic effects by Brown's modified substitution constant σ^+).[153] Electron-withdrawing and electron-donating groups do not form the epoxide

under the standard conditions seen in *Scheme* 3.22 due to two reasons. Electron-poor arenes render the generated alkene less susceptible towards electrophilic epoxidation, thus the reaction mixture has to be slightly heated (40-60 °C) to yield satisfactory conversions. Electron-rich arenes, on the other hand, yield epoxides which are very sensitive to acidic media. Therefore, a more basic acid scavenger than water is needed to prevent product decomposition. In our case, the use of aqueous saturated sodium bicarbonate solution was sufficient. By slightly modifying the reaction conditions, a variety of electron-poor and electron-rich substrates underwent the desired one-pot epoxidation. Also *ortho*-substituted α-aryl amides are suitable substrates and provide the epoxide in good yields, although purification of the chloride **3.249** was not successful. An electron-poor phtalimide (*cf.* **3.255**) shows only little conversion even at elevated temperatures. Other strongly electron-withdrawing groups seem to have a similar effect and yield mostly unreacted alkene intermediate (**3.259**). Iodo-arenes (*cf.* **3.245**) are expectably also not compatible with the oxidizing conditions.

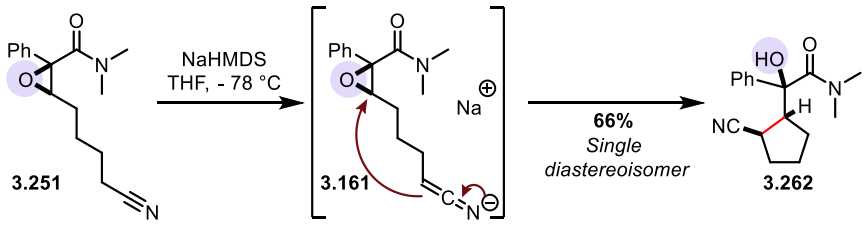
Several functional groups on the side chain of the amide were tolerated, including a nitrile (**3.251**) or an ester (**3.253**). Acid-labile functionalities have to be safeguarded from the acidic conditions of the reaction medium by using saturated aqueous $NaHCO_3$ instead of water as the acid scavenger. In doing so, the reaction becomes suitable also for protected alcohols (*cf.* **3.252** and **3.256**).

The stereoselectivity of the reaction was excellent in all cases. The only substrate in which traces of the undesired *trans* isomer were detected (<4%) was the *iso*propyl substituted precursor of **3.257**. *In situ* generated, geminal, disubstituted alkenes were not susceptible to epoxidation (*cf.* **3.258**), probably because the conjugation of the alkene with the carbonyl moiety is much more effective, lowering the electron-density of the olefin considerably.



Scheme 3.23 – Substrate scope of the direct α,β-epoxidation of simple amides. [a] Acid scavenger = water, epoxidation at r.t.. [b] Acid scavenger = sat. $NaHCO_{3\,aq.}$, epoxidation at r.t., [c] Acid scavenger = water, epoxidation at 40 °C. [d] Acid scavenger = water, DCE instead of DCM as the solvent, epoxidation at 60 °C. [f] Dehydrogenation at 60 °C.

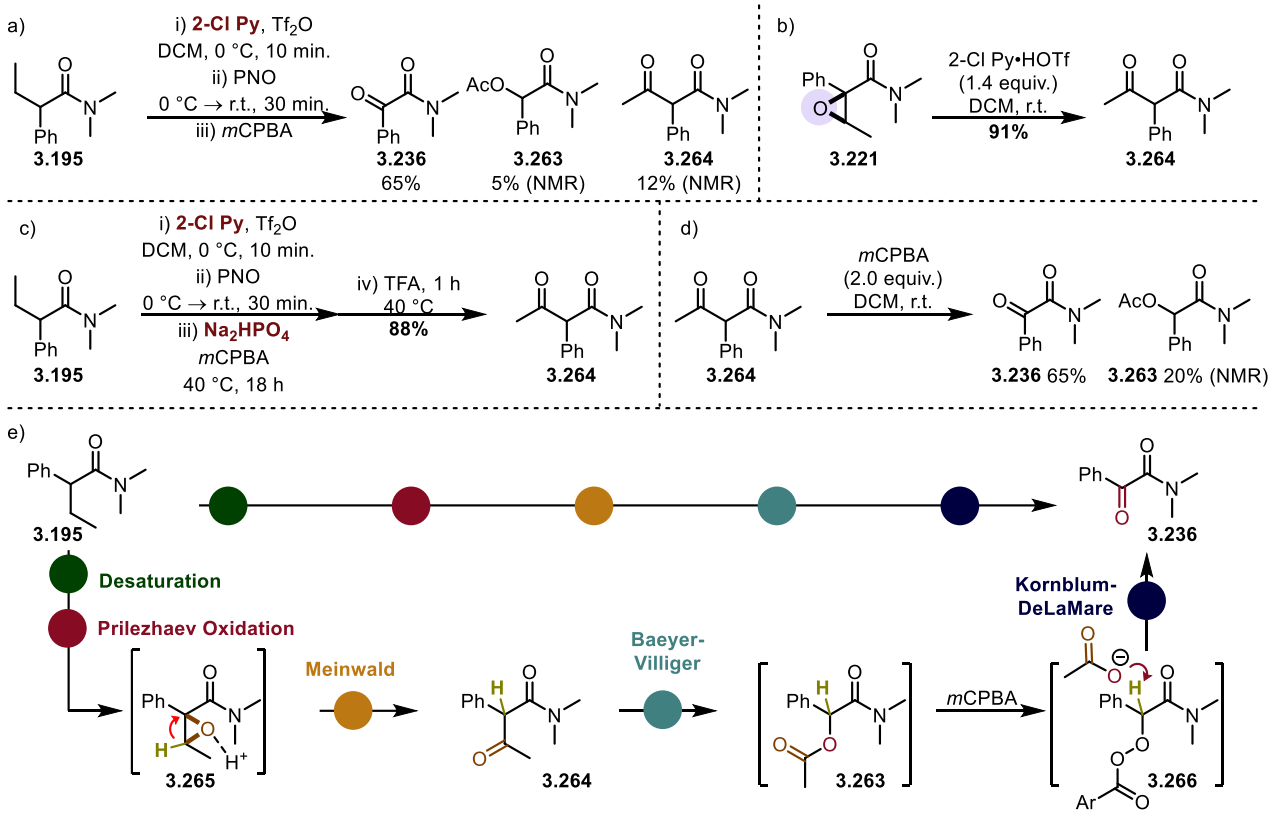
These epoxides can function as forerunners for much more elaborate carbon-scaffolds (*Scheme 3.24*). The nitrile **3.251** for instance can be deprotonated with NaHMDS to yield the cyclopentane derivative **3.262** in a fair yield, as a single diastereoisomer carrying 3 contiguous stereogenic centers.



Scheme 3.24 – Intramolecular functionalization of a generated epoxide.

3.3.3.3. *β-Oxidation and oxidative C–C bond cleavage*

As mentioned previously, the use of an acid scavenger was crucial to yield the epoxide in the one-pot procedure. However, the acid catalyzes an interesting cascade reaction to finally yield the aforementioned α-keto amide accompanied by the β-ketoamide **3.264** and the α-acetoxy amide **3.263** (*Scheme 3.25a*).



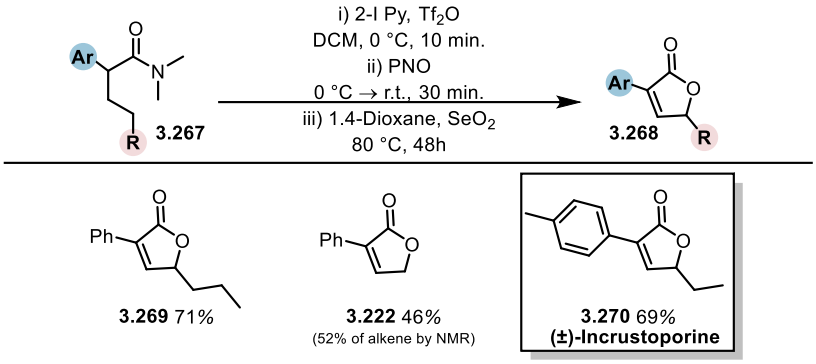
Scheme 3.25 – a) Unexpected formation of the aforementioned α-ketoamide with several side product. b) Acid-promoted Meinwald rearrangement of the formed epoxide. c) Direct β-oxidation of a simple amide to form the β-ketoamide selectively. d) Reaction of the β-ketoamide to the α-ketoamide by the use of mCPBA. e) Proposed mechanism of the overall transformation.

The β-ketoamide can be generated by treating the epoxide **3.221** with a Brønsted acid and proceeds *via* a Meinwald rearrangement (*Scheme 3.25b*).[646,647] Thus, selectivity in the one-pot reaction can be steered towards the β-ketoamide by adding first a non-aquous inorganic base (Na_2HPO_4) followed by the addition of trifluoroacetic acid (*Scheme 3.25c*). When the isolated ketone **3.264** was treated with *m*CPBA in DCM, the α-ketoamide was observed along with the acetoxy amide as the side product (*Scheme 3.25d*). Considering these results, we propose the following mechanism for this unusual cascade reaction

(*Scheme 3.25e*): the generated epoxide undergoes an acid-induced Meinwald rearrangement to form the β-ketoamide **3.264**. Then, the excess of *m*CPBA makes the ketone susceptible towards a Baeyer-Villiger oxidation (with a preferential migration of the benzylic substituent) to generate the observed α-acetoxy amide **3.263**.[648,649] Finally, a nucleophilic displacement of the acetate by the nucleophilic peroxide affords the peroxy ester **3.266**, which is prone to yield the α-keto amide *via* a Kornblum-DeLaMare oxidation.[650]

3.3.4. One-pot synthesis of 2-furanones

As shown in chapter 3.3.2., α-aryl-α,β-dehydrogenated amides react with SeO_2 to form furanones. Thus, we investigated the one-pot procedure in which the alkene was generated *in situ* under the aforementioned contions and then oxidized by the Selenium(IV) reagent. The carboxamides can be indeed transformed into butenolides using amide activation in combination with allylic oxidation promoted by SeO_2 (*Scheme 3.26*).[628,629] By this approach, several biologically active compounds can be synthesized directly. For instance, the antifungal natural product Incrustoporine is obtained in 69% isolated yield.

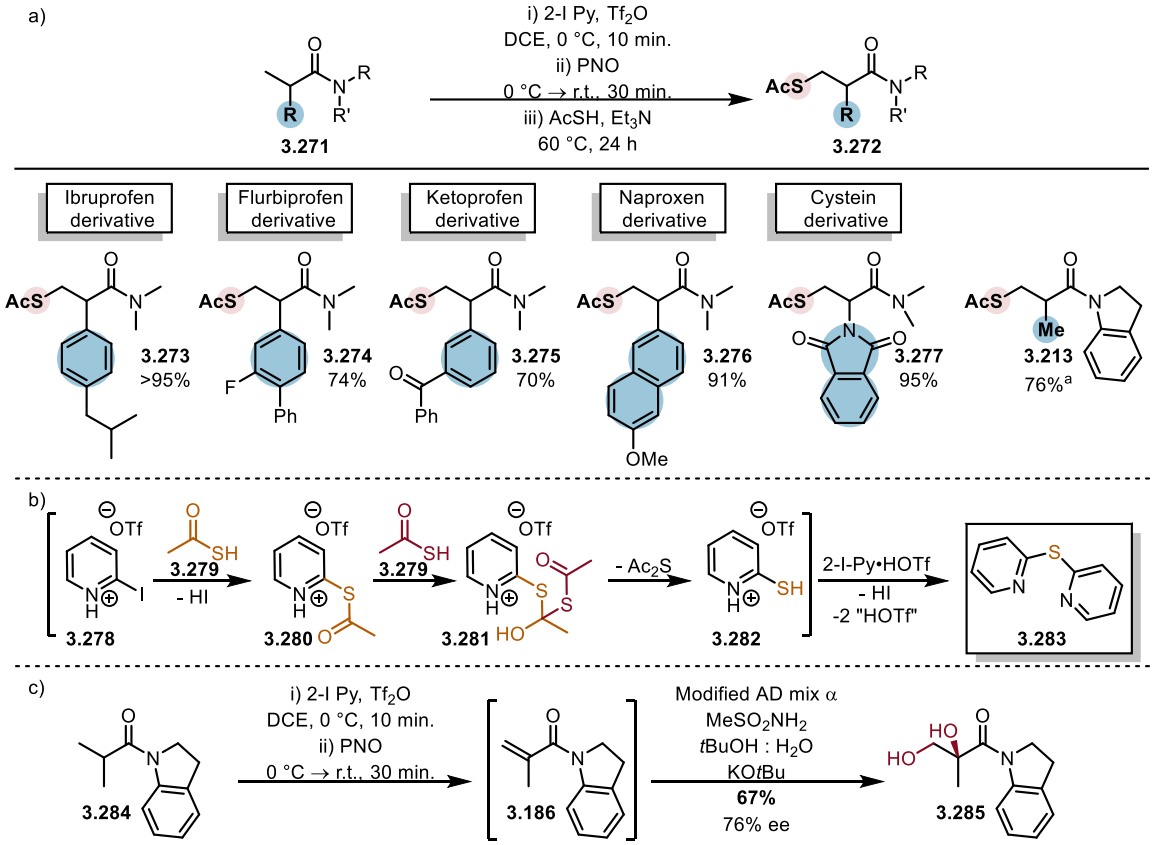


Scheme 3.26 – Scope of the 2-furanone synthesis starting from a simple amide.

3.3.5. One-pot β-thiolation

While the Michael addition to the geminal disubstituted alkene proceeded smoothly (see *Scheme 3.18*a/b), more forcing conditions were necessary to yield similar results in a procedure where the amide was dehydrogenated in α,β-position in the same pot. Best results were obtained when the dehydrogenated product was treated with an excess of thioacetic acid and triethylamine and stirred for

24 h at 60 °C (*Scheme 3.27a*). The major stoichiometric side product was the sulfide **3.283**, presumably formed by a nucleophilic aromatic substitution of the protonated 2-iodopyridine (*Scheme 3.27b*). The β-thiolation protocol was applied to derivatives of biologically active compounds such as Ibuprofen or Naproxen and was high yielding in most of the cases.

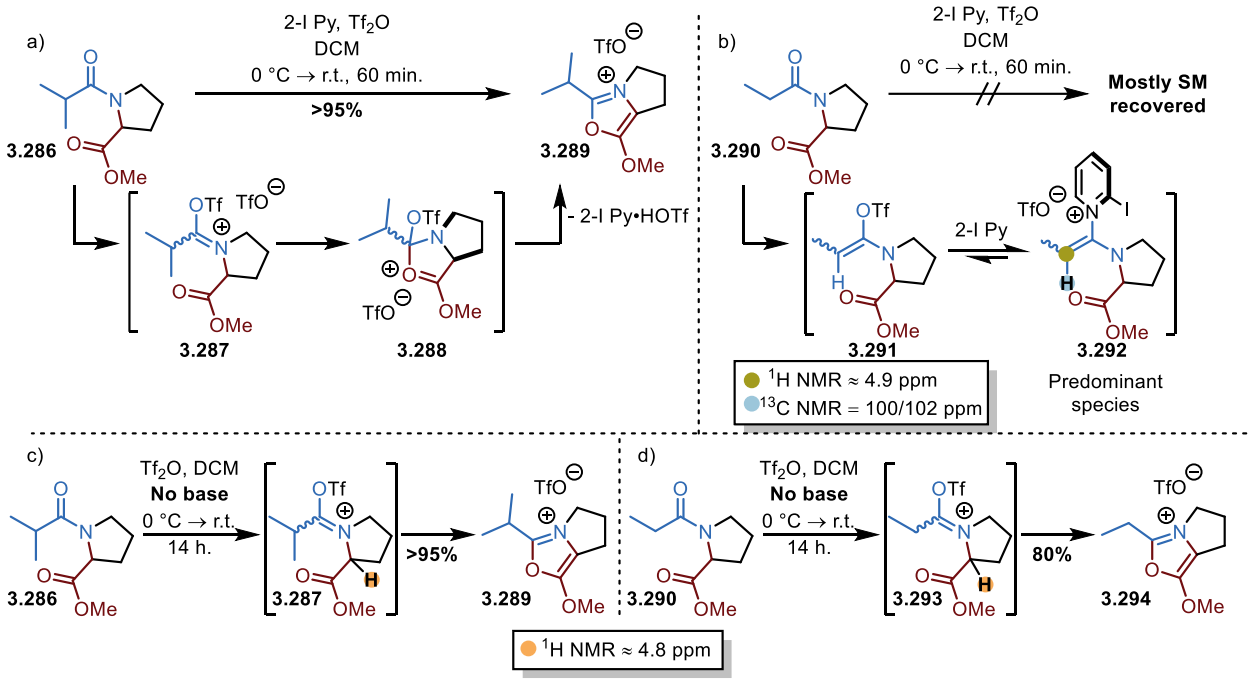


Scheme 3.27 – a) Scope of the β-thiolation of simple amides in a one-pot oxidation/Michael addition reaction. [a] No trimethylamine used. b) Side product formation. c) Enantioselective bishydroxylation of an in situ generated alkene.

Moreover, an alanine derivative was converted into a cysteine derivative by this approach (*cf.* **3.277**), demonstrating that proteogenic aminoacids can be potentially interconverted. The unfunctionalized amide **3.284** which was thiolated to **3.213** under the aforementioned reaction conditions has been also subjected to an enantioselective one-pot α,β-dehydrogenation-dihydroxylation reaction by using a modified AD-mix α (*Scheme 3.27c*).[651] The desired diol was isolated in almost 70% and an enantiomeric excess of 76% has been measured for the sample. This showcases that there is indeed room for further enantioselective one-pot α,β functionalizations of these simple amides.

3.3.6. Oxazolium salt formation

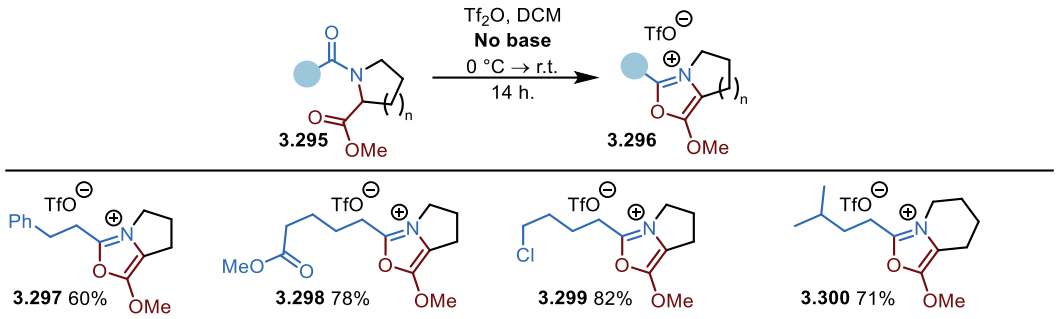
During our initial investigations, we tried to form the α,β-dehydrogenated amide from the proline-derivative **3.286**. Interestingly, the reaction did not afford an alkene but an oxazolium triflate instead in quantitative yield (*Scheme 3.28*). This orange ionic liquid was indefinitely stable under air and did not crystallize. The use of pyridine-*N*-oxide was not necessary for the reaction to proceed. Oxazolium salts have been previously synthesized by using Tf_2O and bases. However, the synthesis of alkyl-substituted oxazolium salts by this approach has no precedence in the literature as mentioned in the introduction (chapter 3.1.2). The reason why those products were probably not accessible is showcased by the result of the following experiment (*Scheme 3.28b*): when the isopropyl side chain was exchanged with an ethyl moiety, the reaction did not proceed at all under the original reaction conditions and the starting material was mostly recovered.



Scheme 3.28 – a) Unexpected oxazolium salt formation. b) The analogous reaction does not take place in α-linear amides. c) Oxazolium formation in absence of a base. d) The absence of base enables the reaction to proceed also on non-branched amides.

The reaction mixtures of the two amides do not only differ strongly in appearance but also the two ^{1}H NMR spectra of those mixtures (in d_2-DCM) are strikingly different. While the α-branched amide

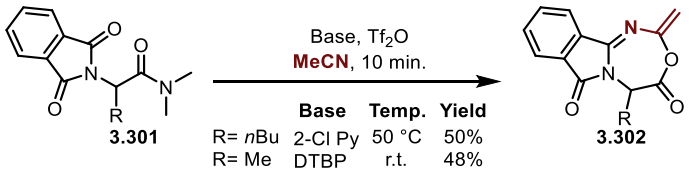
shows a clean (and exclusive) formation of the observed oxazolium salt, the non-branched cognate generates a complicated and messy spectrum with little amount of the desired product. The mechanism proceeds likely *via* an interception of the activated amide **3.287** by the ester with a subsequent (formal) extrusion of trifluoromethanesulfonic acid. In the spectrum of the non-branched amide, the predominant species is the pyridinium enamine **3.292**. As discussed in the introduction, these 2-halopyridine adducts of keteniminium ions are common intermediates in electrophilic amide activation reactions. We assume that the intermediate **3.292** is a "dead end" and is not able to react further to the desired product. Instead, it is ultimately hydrolyzed upon workup to refurnish the starting material. In contrast, the ^{1}H NMR spectrum of the reaction mixture of **3.286** shows not even traces of that species. Indeed, it is likely that a vinylic species has not been formed due to the inaccessibility of the α-proton in the branched substrate and the associated retardation of a hypothetical deprotonation event. In the absence of deprotonation, the ester attacks the electrophilic carbon atom of the activated amide to form eventually the observed oxazolium salt. This explains why in previous reports alkyl-substituted oxazolium salts were not formed by dehydration and led us to explore whether the reaction of non-branched amides can be promoted by omitting the base and quenching the reaction with water-saturated DCM. Indeed, this simple modification allowed us to isolate the oxazolium salt **3.294** in more than 80% yield (*Scheme 3.28 d*). The ^{1}H NMR spectrum of the reaction mixture did not show any vinylic C-H resonance, but a characteristic signal of the α-iminium triflate **3.293**. Both observations are in accordance with our rationale. Several bicyclic alkoxyoxazolium salts carrying a range of functional groups have been synthesized by this approach, which were all liquids. A selection of examples is depicted in *Scheme* 3.29. Interestingly, a second ester, which was distal to the reaction center, was tolerated and did not interfere with the process.



Scheme 3.29 – Scope of the oxazolium salt formation (selected examples).

3.3.7. 7-Membered heterocycle formation

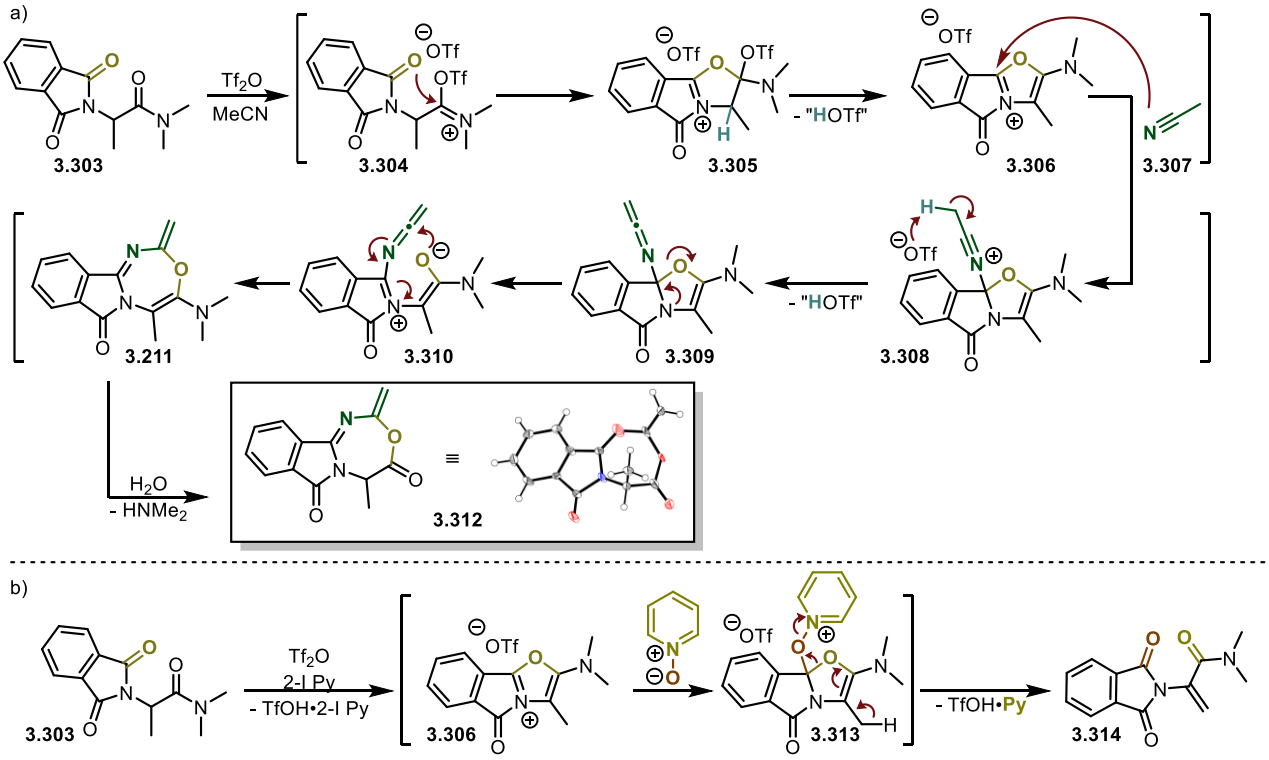
Another interesting side reaction was observed when the α-phtalimide was activated in the usual manner by triflic anhydride in acetonitrile (*Scheme 3.30*). Apparently, the solvent was incorporated in the final product. The structure of this unusual molecule was confirmed by 2D NMR and single-crystal X-ray analysis. The product was not particularly stable (probably due to the exocyclic, electron-rich double bond) although it can be purified by silica column chromatography without considerable decomposition. There were no side reactions but roughly, 50% of the starting material was recovered.



Scheme 3.30 – Unexpected formation of a 7-membered heterocyclic ring.

We later found that the reaction proceeds with excess of triflic anhydride and in absence of a base. Several reaction conditions were tested, but the yield of approximately 50% has been never exceeded. 2,6-di*tert*butylpyridine gave the best reproducible results. 2,6-lutidine gave a similar result, while pyridine, 2-fluoropyridine or $CsHCO_3$ showed no formation of the product. The proposed mechanism, which is still under investigation, is outlined in *Scheme 3.31a.* The activated amide is attacked intramolecularly by one of the carbonyl oxygen atoms of the imide. Thereafter, triflic acid is formally eliminated to give the acyl-substituted oxazolium ion. The addition of acetronitrile with a subsequent deprotonation of the nitrilium ion gives the ketene intermediate **3.309**, which rearranges in a 5 to 7 ring

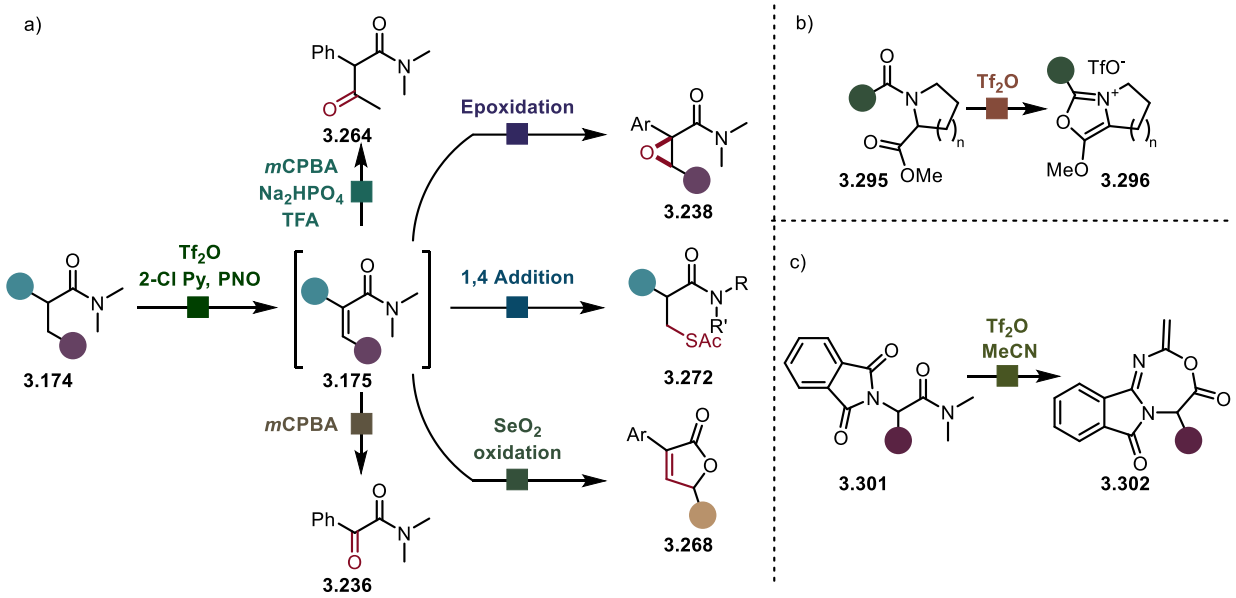
enlargement. The fully conjugated 7-membered ring containing 8π-electrons is likely non-planar to avoid antiaromatic destabilization. Hydrolysis of this enamine yields then the observed product. According to this mechanism, a number of deprotonation steps are necessary, in particular the deprotonation of acetonitrile moiety in its α-position. To some extent the solvent (MeCN) can be accounted for this. Indeed, acetonitrile has a higher proton affinity than H_2O (PA(MeCN) = 188.3 kcal/mol, PA(H_2O) = 166.6 kcal/mol)[526] and thus it can be reasonably expected to act as a base or a proton-shuttle in the reaction when the pyridine base is omitted. Notably, the mechanism also suggests that the α,β-dehydrogenation of the substrate under the usual conditions (in DCM and with PNO as the oxidant) may occur through a different mechanism providing an explanation for the elevated temperatures needed to yield the desired alkene. The intermediate **3.306** (*Scheme 3.31b*) may be attacked by PNO instead of acetonitrile. A rearrangement would then lead to the α,β-dehydrogenated product but the oxygen of PNO would be incorporated on the pthalimide moiety and not on the amide-carbonyl.



Scheme 3.31 – a) Proposed mechanism for the 7-membered ring formation and X-ray single crystal structure. b) Possible mechanism of the α,β-dehydrogenation of the same substrate under amide activation conditions using DCM as the solvent and PNO as the oxidant.

3.4. Conclusion and outlook

The initial goal (*i.e.* the β-functionalization of α-branched amides) has been successfully reached. More specifically, the mild conditions of the dehydrogenation were not only compatible with a β-functionalization of the amide but also with an epoxidation of the alkene and an allylic oxidation. Moreover, an interesting cascade reaction was observed leading to oxidative cleavage of alkylic substituents in the α-position of the amide, furnishing the corresponding α-ketoamide. The cascade was furthermore tamed in order to provide a synthetically useful intermediate, the β-ketoamide resulting from an *in situ* Meinwald rearrangement. Several substrates did not produce the anticipated products. However, a few of those missed targets led to the discovery of two new reactions: a general oxazolium salt formation and a 7-membered ring formation from aminoacid derivatives, which is still under investigation.



Scheme 3.32 – Summary of the study.

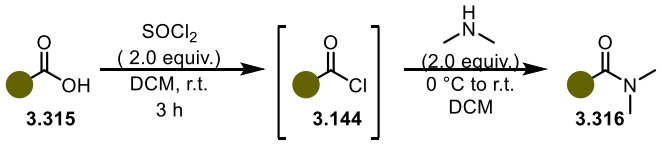
3.5. Supporting information

3.5.1. General

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 aluminum 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}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300K. Chemical shifts were 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 (^{13}C-NMR). Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Compounds which were synthesized and characterized by other coworkers can be found in the SI of the published articles.

3.5.2. Synthesis of starting material

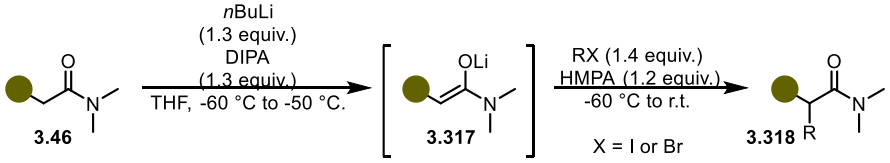
General procedure A[652]



Scheme 3.33

The reaction was carried out under air atmosphere. Typical scale was 5-10 mmol. The carboxylic acid was dissolved in DCM (ca. 0.3 M) and $SOCl_2$ (2.0 equiv.) was added. The reaction was stirred at room temperature for 3 h. Afterwards, the solvent and excess of $SOCl_2$ were removed under reduced pressure (rotary evaporator) to yield the crude acyl chloride. The crude acyl chloride was dissolved in DCM (ca. 0.3 M), cooled to 0 °C and dimethylamine in THF (1.0 M, 2.0 equiv.) was added dropwise. The mixture was stirred for another 2 h at room temperature. After quenching the reaction with an equal volume of aqueous saturated $NaHCO_3$ solution, the aqueous phase was extracted once with DCM. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (typical eluent – EtOAc: heptanes - 15 : 85 to 40 : 60 v/v%).

General procedure B[653]

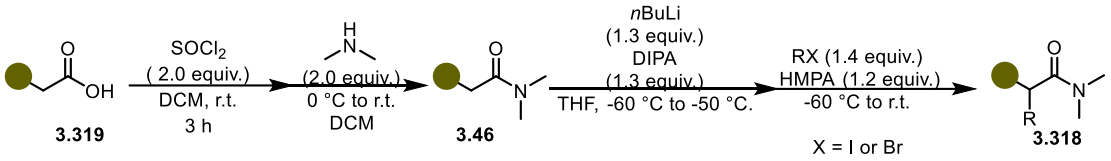


Scheme 3.34

Typical scale was 2-5 mmol. Di*iso*propylamine (1.3 equiv.) was dissolved in THF (ca. 0.5 M) and cooled to 0 °C. *n*BuLi (1.2 equiv., 2.5 M in hexanes) was added dropwise and the reaction was stirred for 15 min at the same temperature. The LDA solution was cooled to -60°C and hexamethylphosphoramide (HMPA - 1.2 equiv.) was added. A solution of the carboxamide (1.0 equiv.) in THF (ca. 0.8 M) was added dropwise to the mixture. The temperature was increased to -50 °C over 60 min and then cooled down again to -60°C. A solution of the alkylbromide or alkyliodide in THF (1.4 equiv., 1 M) was added dropwise. Afterwards, the reaction mixture was warmed up to r.t. and stirred for 16 h. After quenching with saturated aqueous NH_4Cl solution, the mixture was diluted with EtOAc. After extraction of the separated aqueous layer with more EtOAc, the combined organic layer was dried over Na_2SO_4, filtered and the

solvent was removed under reduced pressure. The crude was purified by column chromatography. The addition of HMPA is generally not necessary when primary iodides are used. (Typical eluent – EtOAc: Heptane - 10 : 90 to 35 : 65 v/v%).

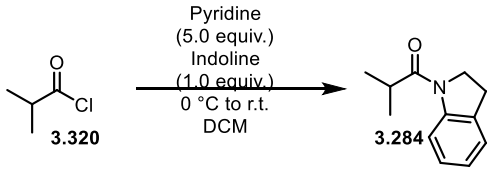
General procedure C



Scheme 3.35

More sophisticated amides where synthesized from the acid in two steps, by combining General procedure A and B. (Typical eluent – EtOAc: Heptane – 10 : 90 to 35 : 65 v/v%).

Procedure D – Indoline-amide starting material[654]



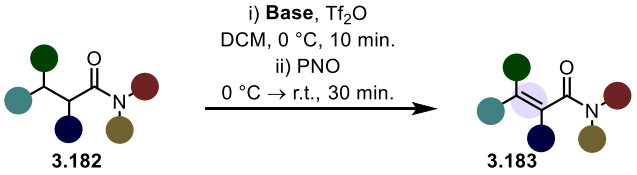
Scheme 3.36

Indoline (12.5 mmol, 1.0 equiv., 1.40 mL) was dissolved in DCM (5 mL) and pyridine (62.5 mmol, 5.0 equiv., 5.1 mL,). Thereafter, isobutyryl chloride (15 mmol, 1.2 equiv., 1.57 mL) was added dropwise at 0 °C and the reaction was diluted with more DCM (5 mL). The reaction was stirred for 120 min at room temperature. Afterwards, the mixture was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), aqueous HCl (50 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered and purified by column chromatography (Eluent - EtOAc: Heptane – 20 : 80 v/v%), to yield the desired compound as a brown solid (yield 2160 mg, 76%).

3.5.3. Experimental section

3.5.3.1. *Desaturation experiment*

General procedure E



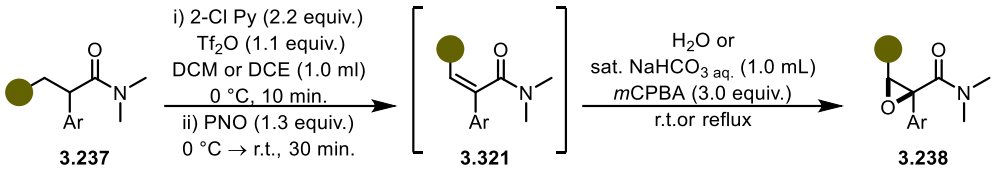
Scheme 3.37

The carboxamide (1.0 equiv., 0.20 mmol) was dissolved in DCM (1 mL) and the base (2.2 equiv., 0.44 mmol) was added. The clear solution was cooled to 0 °C and under stirring trifluoromethane sulfonic anhydride (37 µL, 1.1 equiv., 0.22 mmol) was added dropwise. The reaction was stirred for 10 min at the same temperature. Then, a pyridine-*N*-Oxide solution in DCM (25 mg in 250 µL, 1.3 eq., 0.26 mmol) was added at once resulting in a strong change in color of the solution. The ice bath was removed and the reaction was stirred at room temperature for a further 60 min. The progress of the reaction is usually trackable by TLC. The reaction was quenched with H_2O (*ca.* 5 mL), the aqueous phase was extracted with DCM (3 x 10 mL) and the combined organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure and the crude product was analyzed by ^1H NMR spectroscopy. The crude was (optionally) purified by column chromatography (Typical eluent – EtOAc: Heptane - 10 : 90 to 35 : 65 v/v%).to give the desired product.

The configuration of the double bond was determined by ^1H-^1H NOESY spectroscopy of a purified sample of **3.187**, where a distinct coupling between the vinylic and an aromatic proton was observed.

3.5.3.2. *Oxidations with mCPBA*

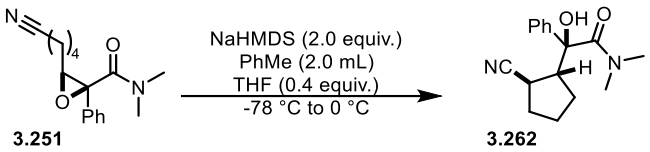
General procedure F



Scheme 3.38

The carboxamide (1.0 equiv., 0.20 mmol) was dissolved in DCM or 1,2-Dichloroethane (1,2DCE) (1.0 mL) and 2-chloropyridine (2.2 equiv., 0.44 mmol, 42 µL) was added. The clear solution was cooled to 0 °C and under stirring trifluoromethane sulfonic anhydride (1.1 equiv., 0.22 mmol, 37 µL) was added dropwise. The reaction was stirred for 10 min at the same temperature. Then, a pyridine-*N*-Oxide solution in DCM (0.26 mmol, 1.3 eq., 25 mg in 250 µL) was added at once resulting in a strong change in color of the solution. The ice bath was removed and the reaction was stirred at room temperature for further 60 min. The progress of the reaction is readily trackable by TLC. Water (1.0 mL) or saturated aqueous $NaHCO_3$ solution (1.0 mL) was added to the mixture as an acid scavenger, which was then vigorously stirred for 5 min. Thereafter, *m*CPBA (0.60 mmol, 70-77 w/w%, 3.0 equiv, 148 mg) was added at once. The reaction mixture was stirred for 18 h at a given temperature. After cooling to room temperature, the reaction was diluted with DCM (3-4 mL) and quenched with saturated $Na_2S_2O_3$ solution (24 mL). After separating the organic from the aqueous phase, the aqueous phase was extracted with DCM (10 mL) and the combined organic layer was washed once with aqueous saturated $NaHCO_3$ (10 mL). Thereafter, the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography. (Typical eluent – EtOAc: Heptane - 10 : 90 to 35 : 65 v/v%). While the dehydrogenated amides are visible under the UV lamp, the epoxides stain typically very well on TLC with "magic stain".[655]

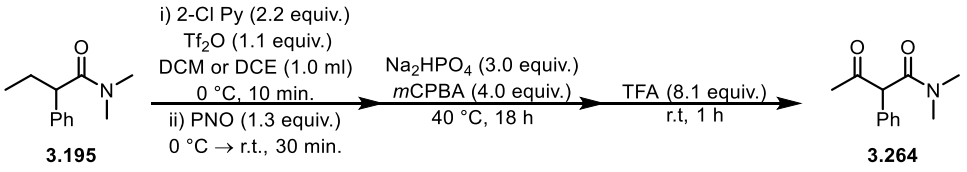
Procedure G – Cyclization of the epoxynitrile[656,657]



Scheme 3.39

The epoxynitrile (0.20 mmol, 1.0 equiv., 55 mg) was dissolved in Toluene (2.0 mL) and THF (0.2 mL) and the solution was cooled to -78 °C. Then a solution of NaHDMS in THF (2.0 equiv., 2 M, 0.2 mL) was added dropwise. The reaction was stirred for 30 min at the same temperature, then warmed up to 0 °C and stirred for 2.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (3-4 mL), diluted with EtOAc (3-4 mL) and warmed to room temperature. The separated aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (eluent – EtOAc: Heptane - 15 : 85 v/v%).to yield a colorless oil (36 mg, 66%). The crude ^1H NMR shows only one diastereoisomer, and also the purified compound's ^{13}C and ^1H NMR spectra provide a similar result, which implies the absence of another diastereoisomer. The configuration stereogenic centers were determined by ^1H-^1H NOESY spectroscopy.

Procedure H – β-Ketoamide synthesis

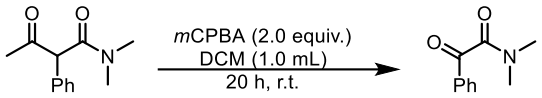


Scheme 3.40

The carboxamide (0.20 mmol, 1.0 equiv., 38 mg) was dissolved in DCM (1.0 mL) and 2-chloropyridine (0.44 mmol, 2.2 equiv., 42 µL) was added. The clear solution was cooled to 0 °C and under stirring trifluoromethane sulfonic anhydride (0.22 mmol, 1.1 equiv., 37 µL) was added dropwise. The reaction was stirred for 10 min at the same temperature. Then, a pyridine-*N*-Oxide solution in DCM (25 mg in 250 µL, 1.3 equiv.) was added at once resulting in a strong change in color of the solution. The ice

bath was removed and the reaction was stirred at room temperature for further 60 min. Thereafter, Na_2HPO_4 (0.6 mmol, 3.0 equiv., 85 mg) was added and the mixture was stirred vigorously for 5 min. Then, *m*CPBA (0.8 mmol, 70-77w/w%, 4.0 equiv., 197 mg) was added and the mixture was heated to 40 °C. After stirring for 18 h at the same temperature the reaction was cooled to room temperature and trifluoroacetic acid was added (1.62 mmol, 8.1 equiv., 120 µL). After 1 h the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (2-3 mL) and diluted with DCM (3-4 mL). The separated aqueous phase was extracted with DCM (5 mL) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (Eluent – EtOAc: Heptanes - 10 : 90 to 35 : 65 v/v%) to yield a colorless oil (yield 36 mg, 88%).

Procedure I – α-Ketoamide synthesis from β-ketoamide

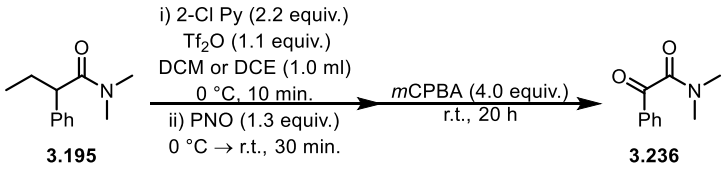


3.264 **3.236**

Scheme 3.41

The β-ketoamide (0.20 mmol, 1.0 equiv., 41 mg,) was dissolved in DCM (1.0 mL) and *m*CPBA was added (0.4 mmol, 70-77 w/w%, 2.0 equiv., 98 mg) and stirred for 20 h at room temperature. The mixture was quenched with saturated $Na_2S_2O_3$ solution (2-3 mL) and diluted with DCM (2-3 mL). After separating the organic from the aqueous phase, the aqueous phase was extracted with DCM (5 mL) and the combined organic layer was washed once with saturated aqueous solution of $NaHCO_3$ (5 mL). Thereafter, the combined organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (Eluent – EtOAc: Heptane – 15 : 85 v/v%) to yield the α-Ketoamide as a colorless oil (yield 23 mg, 65%).

Procedure J – α-Ketoamide synthesis from β-ketoamide

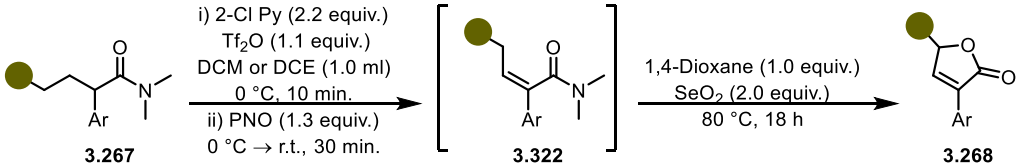


Scheme 3.42

The carboxamide (0.20 mmol, 1.0 equiv., 38 mg) was dissolved in DCM (1.0 mL) and 2-chloropyridine (0.44 mmol, 2.2 equiv., 42 µL) was added. The clear solution was cooled to 0 °C and under stirring trifluoromethane sulfonic anhydride (0.22 mmol, 1.1 equiv., 37 µL) was added dropwise. The reaction was stirred for 10 min at the same temperature. Then a pyridine-*N*-Oxide solution in DCM (25 mg in 250 µL, 1.3 eq.) was added at once resulting in a strong change in color of the solution. The ice bath was removed and the reaction was stirred at room temperature for further 60 min. Then *m*CBPA was added (0.8 mmol, 70-77 w/w%, 4.0 equiv., 196 mg) and the mixture was stirred for 20 h at room temperature. After quenching with saturated $Na_2S_2O_3$ solution (2-3 mL) the mixture was diluted with DCM (2-3 mL). After separating the organic from the aqueous phase, the aqueous phase was extracted with DCM (5 mL) and the combined organic layer was washed once with saturated aqueous solution of NaHCO3 (5 mL). Thereafter, the combined organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by column chromatography (eluent – EtOAc: Heptane - 15 : 85).to yield the α-Ketoamide as a colorless oil (yield 23 mg, 65%).

3.5.3.3. *2-Furanone synthesis*

General procedure K



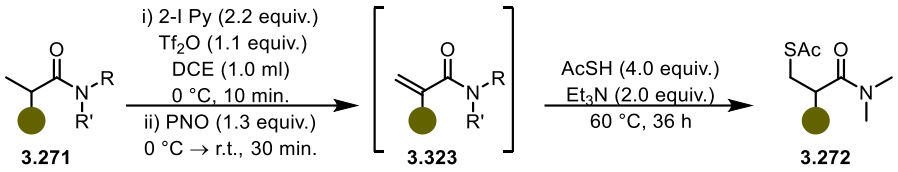
Scheme 3.43

The carboxamide (0.20 mmol, 1.0 equiv.) was dissolved in 1,2-dichloroethane (1.0 mL) and 2-Iodo pyridine (0.44 mmol, 2.2 equiv., 47 µL) was added. The clear solution was cooled to 0 °C and under stirring

trifluoromethane sulfonic anhydride (0.22 mmol, 1.1 equiv., 37 µL) was added dropwise. The reaction was stirred for 10 min at the same temperature. Then a pyridine-*N*-Oxide solution in DCM (25 mg in 250 µL, 1.3 eq.) was added at once resulting in a strong change in color of the solution. The ice bath was removed and the reaction was stirred at room temperature for further 60 min. The mixture was diluted with 1,4-dioxane (1.0 mL), SeO_2 (0.4 mmol, 2.0 equiv., 44 mg) was added and the resulting suspension was stirred at 80 °C for 18 h. After cooling down to room temperature, the mixture was quenched with water (1.0 mL), diluted with DCM (5 mL) and filtered through a pad of Celite®. The organic phase was washed with water, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was then purified by column chromatography (Eluent – EtOAc: Heptane – 15 : 85 v/v%) to yield the desired furanone.

3.5.3.4. *β-Functionalization via in situ 1,4 addition*

General procedure L



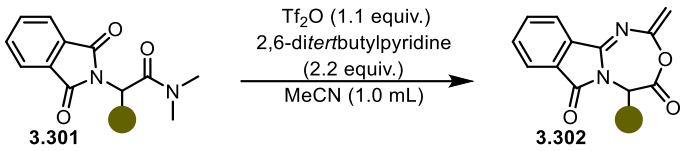
Scheme 3.44

The carboxamide (0.20 mmol, 1.0 equiv., 38 mg) was dissolved in 1,2-dichloroethane (1.0 mL) and 2-Iodopyridine (0.44 mmol, 2.2 equiv., 47 µL) was added. The clear solution was cooled to 0 °C and under stirring trifluoromethane sulfonic anhydride (0.22 mmol, 1.1 equiv., 37 µL) was added dropwise. The reaction was stirred for 10 min at the same temperature. Then a pyridine-*N*-oxide solution in DCM (25 mg in 250 µL, 1.3 equiv.) was added at once resulting in a strong change in color of the solution. The ice bath was removed and the reaction was stirred at room temperature for further 60 min. Then Et_3N (0.44 mmol, 2.0 equiv., 56 µL) and AcSH (0.8 mmol, 4.0 equiv., 57 µL) was added and the mixture was stirred at 60 °C for 36 h. The reaction was quenched with water (3-4 mL), diluted with DCM (3-4 mL) and the separated aqueous phase was extracted with DCM (3 x 5 mL). The combined organic layer was dried over Na_2SO_4,

filtered and the solvent was removed under reduced pressure. The crude was then purified by column chromatography to yield the desired product. (Typical eluent – EtOAc: Heptane - 10 : 90 to 35 : 65 v/v%). The synthesis of *S*-(3-(indolin-1-yl)-2-methyl-3-oxopropyl) ethanethioate (**3.xxx**) only proceeds without the use of Et_3N.

3.5.3.5. *7-membered ring formation*

General procedure M

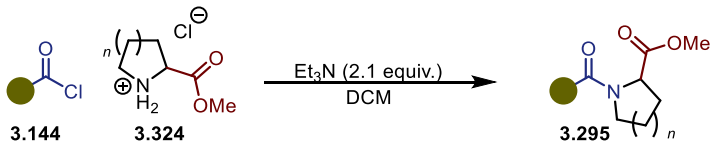


Scheme 3.45

The amide (0.2 mmol, 1.0 equiv.) was dissolved in MeCN (1.0 mL). Then 2,6-di-*tert*-butylpyridine (0.44 mmol, 2.2 equiv.) was added. The stirred reaction mixture was cooled down to 0 °C with an ice bath and (0.22 mmol, 1.1 equiv., 37 µl) distilled triflic anhydride was added. After stirring at 0 °C for 10 minutes, the mixture was warmed to room temperature and stirred for 30 minutes. The reaction was then quenched with water, the aqueous phase was extracted with DCM (3x 3 mL), the united organic phase was dried over $MgSO_4$, filtered and then volatiles were evaporated under reduced pressure. The crude mixture was purified *via* column chromatography (typical eluent – EtOAc: Heptane - 15 : 85 to 35 : 65 v/v%) to give the desired product.

3.5.3.6. *Oxazolium salt formation*

General procedure N

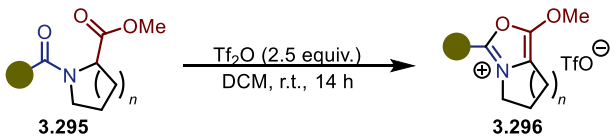


Scheme 3.46

To a solution of the amine hydrochloride (1.0 equiv.) and triethylamine (2.1 equiv.) in DCM (0.5 M) at r.t. a solution of the corresponding acyl chloride (1.0 equiv.) in DCM was added dropwise and the resulting reaction mixture was stirred 1 h at the same temperature. After this time, a saturated aqueous

solution of sodium bicarbonate was added and the biphasic system was separated. The aqueous phase was extracted with DCM (3 ×), the organic phases were combined and then washed with HCl (1 N). The organic layer was then dried over anhydrous Na_2SO_4. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography (typical eluent – heptanes: EtOAc - 30:70 v/v%) to afford the desired compound.

General procedure O



Scheme 3.47

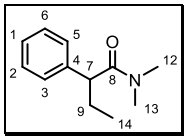
To a solution of the amide (1.0 equiv., 0.4 mmol) in DCM (0.1 M, 4 mL) at r.t. was added trifluoromethanesulfonic anhydride (2.5 equiv., 1.0 mmol) and the reaction was stirred 14 h at the same temperature. After this time DCM saturated with water (3 mL) was added to the reaction mixture and the reaction was stirred for 1 h at the same temperature. Then the organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified by silica gel column chromatography; first EtOAc (100 v/v% - ca. 40 mL) and then isopropanol (100 v/v%), to obtain the product typically as a yellow oil.

3.6. Characterization

3.6.1. Desaturation, epoxidation and furanone synthesis

3.6.1.1. *Starting material*

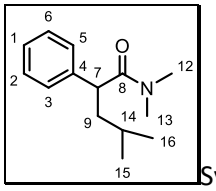
N,*N*-dimethyl-2-phenylbutanamide (**3.195**)



Synthesized following the general procedure **A.**

Isolated yield: 1874 mg, 68%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H, C2/C3/C4/C5), 7.27 – 7.17 (m, 1H, C1), 3.61 (t, *J* = 7.3 Hz, 1H, C7), 2.94 (s, 3H, C12), 2.94 (s, 3H, C13), 2.18 – 2.04 (m, 1H, C9), 1.83 – 1.68 (m, 1H, C9), 0.87 (t, *J* = 7.3 Hz, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.22 (C8), 140.28 (C4), 128.70 (C3/C5), 128.02 (C2/C6), 126.82 (C1), 50.81 (C7), 37.20 (C12), 35.91 (C13), 28.24 (C9), 12.50 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 214.1208 found 214.1205. **ATR-FTIR** (cm^{-1}): 3027, 3005, 2964, 2929, 2873, 2358, 1637, 1602, 1583, 1490, 1453, 1393, 1334, 1275, 1261, 1146, 1097, 1068, 1031, 964, 906, 850, 764, 749, 700, 634, 607.

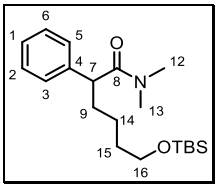
N,*N*,4-trimethyl-2-phenylpentanamide (**3.324**)



Synthesized following the general procedure **C.**

Isolated yield: 331 mg, 60%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H, C2/C3/C4/C5), 7.24 – 7.16 (m, 1H, C1), 3.82 (t, *J* = 7.1 Hz, 1H, C7), 2.96 (s, 3H, C12), 2.93 (s, 3H, C13), 2.07 – 1.93 (m, 1H, C9), 1.61 – 1.53 (m, 1H, C9), 1.52 – 1.38 (m, 1H, C14), 0.91 (d, *J* = 6.5 Hz, 3H, C15), 0.87 (d, *J* = 6.6 Hz, 3H, C16). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.34 (C8), 140.59 (C4), 128.78 (C3/C5), 128.05 (C2/C6), 126.83 (C1), 46.51 (C7), 44.31 (C9), 37.27 (C13), 36.07 (C12), 25.83 (C14), 22.81 (C15), 22.71 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 242.1521 found 242.1519. **ATR-FTIR** (cm^{-1}): 2953, 2933, 2906, 2869, 2855, 1631, 1602, 1584, 1493, 1457, 1412, 1393, 1262, 1171, 1142, 1109, 1072, 750, 722, 703, 633.

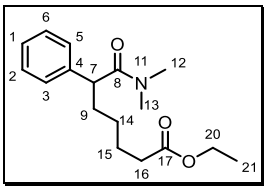
6-((*tert*-butyldimethylsilyl)oxy)-*N,N*-dimethyl-2-phenylhexanamide (**3.325**)



Synthesized following the general procedure **C.**

Isolated yield: 605 mg, 69%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H, C2/C3/C4/C5), 7.24 – 7.19 (m, 1H, C1), 3.69 (t, *J* = 7.3 Hz, 1H, C7), 3.60 – 3.52 (m, 2H, C16), 2.93 (s, 6H, C12/C13), 2.12 – 2.00 (m, 1H, C9), 1.78 – 1.67 (m, 1H, C9), 1.58 – 1.40 (m, 2H, C15), 1.36 – 1.14 (m, 2H, C14), 0.86 (s, 9H, TBS), 0.01 (d, *J* = 1.2 Hz, 6H, TBS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.29 (C8), 140.39 (C4), 128.81 (C3/C5), 128.07 (C2/C6), 126.91 (C1), 63.22 (C15), 49.06 (C7), 37.30 (C12), 36.04 (C13), 35.00 (C15), 32.94 (C9), 26.12 (TBS-Me_2), 24.18 (C14), 18.50 (TBS-qC), -5.13 (TBS, Me_3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 372.2335 found 372.2231. **ATR-FTIR** (cm^{-1}): 2929, 2857, 1643, 1603, 1493, 1471, 1462, 1393, 1361, 1275, 1258, 1140, 1094, 1032, 1006, 976, 939, 903, 833, 814, 765, 749, 700, 663, 633, 588.

Ethyl 7-(dimethylamino)-7-oxo-6-phenylheptanoate (**3.326**)

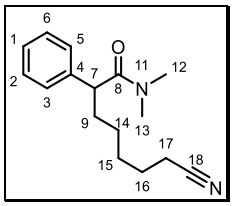


Synthesized following the general procedure **C.**

Isolated yield: 270 mg, 37%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 4H, C2/C3/C4/C5), 7.24 – 7.18 (m, 1H, C1), 4.08 (q, *J* = 7.1 Hz, 2H, C20), 3.68 (t, *J* = 7.3 Hz, 1H, C7), 2.92 (s, 3H, C12), 2.91 (s, 3H, C13), 2.25 (t, *J* = 7.5 Hz, 2H, C16), 2.12 – 2.03 (m, 1H, C9), 1.75 – 1.67 (m, 1H, C9), 1.67 – 1.57 (m, 2H, C15), 1.36 – 1.27 (m, 1H, C14), 1.21 (t, *J* = 7.1 Hz, 3H, C21), 1.24 – 1.15 (m, 1H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.87 (C8), 173.10 (C17), 140.24 (C4), 128.83 (C3/C5), 127.98 (C2/C6), 126.95 (C1), 60.28 (C20), 48.86 (C7), 37.26 (C12), 36.02 (C13), 34.84 (C16), 34.28 (C9), 27.41 (C14), 24.98 (C15), 14.34 (C21). **HRMS** (ESI) m/z

calculated for $[M+Na]^+$ 314.1732 found 314.1725. **ATR-FTIR** (cm^{-1}): 3026, 2933, 2864, 1730, 1642, 1493, 1454, 1395, 1374, 1348, 1304, 1260, 1181, 1151, 1091, 1066, 1031, 922, 855, 757, 735, 702, 633, 607, 587, 578, 537.

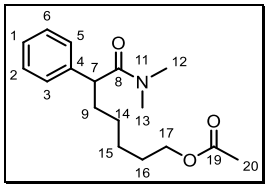
7-cyano-*N,N*-dimethyl-2-phenylheptanamide (**3.327**)



Synthesized following the general procedure **C.**

Isolated yield: 390 mg, 61%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H, C1-C6), 3.67 (t, 1H, C7), 2.93 (s, 3H, C12), 2.91 (s, 3H, C13), 2.29 (t, *J* = 7.0 Hz, 2H, C17), 2.13 – 2.04 (m, 1H, C9), 1.73 – 1.58 (m, 3H, C9/C16), 1.51 – 1.15 (m, 4H, C14/C15). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.96 (C18), 140.20 (C4), 128.89 (C3/C5), 127.92 (C2/C6), 127.02 (C1), 119.87 (C18), 49.00 (C7), 37.25 (C12), 36.03 (C13), 34.85 (C9), 28.58 (C15), 27.01 (C14), 25.19 (C16), 17.09 (C17). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 281.1628 found 281.1630. **ATR-FTIR** (cm^{-1}): 3007, 2932, 2861, 2244, 1638, 1062, 1583, 1492, 1453, 1394, 1329, 1276, 1261, 1132, 1093, 1066, 1031, 916, 850, 765, 754, 745, 701, 634, 617, 607, 591.

7-(dimethylamino)-7-oxo-6-phenylheptyl acetate (**3.328**)

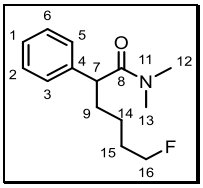


Synthesized following the general procedure **C.**

Isolated yield: 200 mg, 28%. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 4H, C2/C3/C4/C5), 7.23 – 7.19 (m, 1H, C1), 4.00 (t, *J* = 6.7 Hz, 2H, C17), 3.66 (t, *J* = 7.2 Hz, 1H, C7), 2.92 (s, 3H, C12), 2.91 (s, 3H, C13), 2.12 – 2.04 (m, 1H, C9), 2.00 (s, 3H, C20), 1.72 – 1.66 (m, 1H, C9), 1.57 (p, *J* = 7.0 Hz, 2H, C16), 1.38 – 1.15 (m, 4H, C14/C15). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.17 (C8), 171.33 (C19), 140.39 (C4), 128.85 (C3/C5), 128.00

(C2/C6), 126.95 (C1), 64.63 (C17), 49.12 (C1), 37.28 (C12), 36.05 (C13), 35.18 (C9), 28.57 (C16), 27.65 (C14), 26.06 (C15), 21.12 (C20). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 314.1732 found 314.1729. **ATR-FTIR** (cm^{-1}): 3026, 2935, 2858, 2366, 2335, 1733, 1640, 1602, 1583, 1492, 1454, 1392, 1365, 1328, 1233, 1141, 1104, 1033, 968, 800, 750, 729, 700, 634, 608.

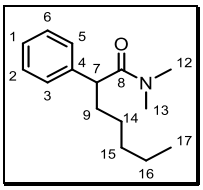
6-fluoro-*N,N*-dimethyl-2-phenylhexanamide (**3.329**)



Synthesized following the general procedure **C.**

Isolated yield: 448 mg, 76%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H, C2/C3/C4/C5), 7.25 – 7.19 (m, 1H, C1), 4.40 (dt, *J* = 47.3, 6.1 Hz, 2H, C16), 3.69 (t, *J* = 7.2 Hz, 1H, C7), 2.93 (s, 3H, C12), 2.92 (s, 3H, C13), 2.17 – 2.07 (m, 1H, C9), 1.80 – 1.61 (m, 3H, C9/C15), 1.45 – 1.36 (m, 1H, C14), 1.34 – 1.23 (m, 1H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.02 (C8), 140.18 (C4), 128.89 (C3/C5), 127.98 (C2/C6), 127.02 (C1), 84.09 (d, *J* = 164 Hz, C16), 49.13 (C7), 37.26 (C12), 36.03 (C13), 34.89 (C9), 30.55 (d, *J* = 20 Hz, C15), 23.71 (d, *J* = 6 Hz, C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 260.1427 found 260.1422. **ATR-FTIR** (cm^{-1}): 2939, 1637, 1602, 1493, 1454, 1394, 1252, 1218, 1141, 1101, 1058, 1031, 1003, 980, 938, 852, 754, 700, 665, 633, 593.

N,N-dimethyl-2-phenylheptanamide (**3.310**)

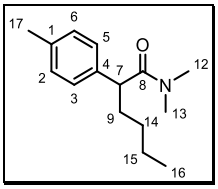


Synthesized following the general procedure **C.**

Isolated yield: 275 mg, 47%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H, C2/C3/C4/C5), 7.24 – 7.19 (m, 1H, C1), 3.68 (d, *J* = 7.3 Hz, 1H, C7), 2.93 (s, 6H, C12/C13), 2.14 – 2.03 (m, 1H, C9), 1.75 – 1.65 (m, 1H, C9),

1.36 – 1.12 (m, 6H, C14-16), 0.85 (t, *J* = 6.9 Hz, 3H, C17). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.38 (C8), 140.59 (C4), 128.78 (C3/C5), 128.06 (C2/C6), 126.86 (C1), 49.09 (C7), 37.30 (C12), 36.04 (C13), 35.26 (C9), 31.95 (C14), 27.70 (C15), 22.67 (C16), 14.20 (C17). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 256.1678 found 256.1682. **ATR-FTIR** (cm^{-1}): 2953, 2925, 2857, 2357, 1640, 1602, 1583, 1493, 1453, 1393, 1327, 1275, 1261, 1143, 1103, 1071, 1058, 1032, 763, 751, 726, 700, 633, 617, 606, 587.

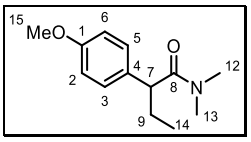
N,N-dimethyl-2-(p-tolyl)hexanamide (**3.331**)



Synthesized following the general procedure **C.**

Isolated yield: 325 mg, >95%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.8 Hz, 2H, C3/C5), 7.11 (d, *J* = 7.8 Hz, 2H, C2/C6), 3.64 (t, *J* = 7.2 Hz, 1H, C1), 2.94 – 2.92 (m, 6H, C12/C13), 2.31 (s, 3H, C17), 2.11 – 2.01 (m, 1H, C9), 1.74 – 1.62 (m, 1H, C9), 1.35 – 1.21 (m, 3H, C14/C15), 1.20 – 1.11 (m, 1H, C15), 0.85 (t, *J* = 7.0 Hz, 3H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.57 (C8), 137.53 (C4), 136.41 (C1), 129.46 (C3/C5), 127.91 (C2/C6), 48.63 (C7), 37.28 (C12), 36.01 (C13), 35.01 (C17), 30.20 (C9), 22.83 (C14), 21.16 (C15), 14.12 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 256.1677 found 256.1678. **ATR-FTIR** (cm^{-1}): 2954, 2926, 2859, 1640, 1511, 1491, 1457, 1393, 1341, 1263, 1144, 1113, 1096, 1057, 1023, 811.

2-(4-methoxyphenyl)-*N,N*-dimethylbutanamide (**3.332**)

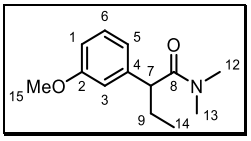


Synthesized following the general procedure **C.**

Isolated yield: 422 mg, 68%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H, C3/C5), 6.88 – 6.80 (m, 2H, C2/C6), 3.78 (s, 3H, C15), 3.54 (t, *J* = 7.3 Hz, 1H, C7), 2.93 (s, 3H, C12), 2.93 (s, 3H, C13), 2.11 – 2.00 (m, 1H, C9), 1.71 – 1.64 (m, 1H, C9), 0.87 – 0.81 (m, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.66 (C8), 158.54

(C1), 132.40 (C4), 129.07 (C3/C5), 114.14 (C2/C6), 55.36 (C15), 49.92 (C7), 37.28 (C12), 35.98 (C13), 28.28 (C9), 12.51 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 244.1313 found 244.1308. **ATR-FTIR** (cm^{-1}): 3006, 2963, 2932, 2873, 1634, 1583, 1510, 1461, 1394, 1337, 1301, 1275, 1257, 1178, 1147, 1112, 1087, 1033, 910, 850, 823, 788, 763, 750, 728, 645, 619, 559, 529.

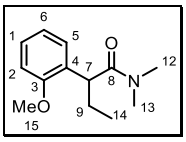
2-(3-methoxyphenyl)-*N,N*-dimethylbutanamide (**3.333**)



Synthesized following the general procedure **C.**

Isolated yield: 510 mg, 92%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.9 Hz, 1H, C6), 6.88 – 6.82 (m, 2H, C3/C5), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1H, C1), 3.79 (s, 3H, C15), 3.56 (t, *J* = 7.3 Hz, 1H, C7), 2.93 (s, 6H, C12/C13), 2.12 – 2.03 (m, 1H, C9), 1.78 – 1.70 (m, 1H, C9), 0.86 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.13 (C8), 159.98 (C2), 141.91 (C4), 129.66 (C6), 120.61 (C3), 113.59 (C1), 112.29 (C5), 55.34 (C15), 50.92 (C7), 37.31 (C12), 36.03 (C13), 28.23 (C9), 12.59 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 244.1313 found 244.1307. **ATR-FTIR** (cm^{-1}): 2962, 2931, 2874, 1637, 1598, 1583, 1485, 1455, 1436, 1393, 1320, 1296, 1258, 1143, 1087, 1047, 996, 939, 867, 847, 780, 754, 702, 627, 572, 551, 532.

2-(2-methoxyphenyl)-*N,N*-dimethylbutanamide (**3.334**)

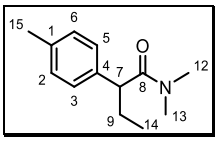


Synthesized following the general procedure **C.**

Isolated yield: 420 mg, 40%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.5, 1.7 Hz, 1H, C5), 7.19 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H, C1), 6.91 (td, *J* = 7.5, 1.0 Hz, 1H, C6), 6.86 (d, *J* = 8.2 Hz, 1H, C2), 4.18 (dd, *J* = 7.7, 6.8 Hz, 1H, C7), 3.85 (s, 3H, C15), 2.91 (s, 3H, C12), 2.87 (s, 3H, C13), 2.07 – 1.99 (m, 1H, C9), 1.69 – 1.59 (m, 1H, C9), 0.86 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.90 (C8), 156.06 (C3), 128.79 (C5),

127.95 (C4), 127.62 (C1), 121.10 (C6), 110.15 (C2), 55.42 (C15), 41.64 (C7), 36.62 (C12), 35.66 (C13), 27.29 (C9), 12.30 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 244.1313 found 244.1310. **ATR-FTIR** (cm^{-1}): 3006, 2964, 2931, 2873, 1639, 1599, 1491, 1462, 1439, 1394, 1329, 1276, 1261, 1241, 1172, 1150, 1107, 1082, 1052, 1026, 914, 792, 760, 746, 701, 616.

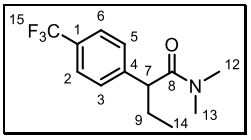
N,N-dimethyl-2-(*p*-tolyl)butanamide (**3.335**)



Synthesized following the general procedure **C.**

Isolated yield: 210 mg, 28%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.0 Hz, 2H, C5/C3), 7.10 (d, *J* = 8.0 Hz, 2H, C2/C6), 3.55 (t, *J* = 7.3 Hz, 1H, C7), 2.92 (s, 6H, C12/C13), 2.31 (s, 3H, C15), 2.14 – 2.02 (m, 1H, C9), 1.78 – 1.66 (m, 1H, C9), 0.85 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.48, 137.29, 136.43, 129.44, 127.94, 77.48, 77.16, 76.84, 50.46, 37.26, 35.96, 28.27, 21.14, 12.55. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 228.1364 found 228.1363. **ATR-FTIR** (cm^{-1}): 3006, 2964, 2925, 2873, 1638, 1512, 1490, 1457, 1393, 1276, 1261, 1146, 1113, 1089, 1056, 810, 764, 748, 722, 688.

N,N-dimethyl-2-(4-(trifluoromethyl)phenyl)butanamide (**3.336**)

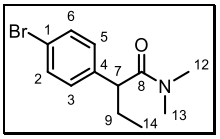


Synthesized following the general procedure **C.**

Isolated yield: 490 mg, 76%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 2H, C2/C6), 7.42 (d, *J* = 8.1 Hz, 2H, C2/C5), 3.68 (t, *J* = 7.3 Hz, 1H, C7), 2.95 (s, 6H, C12/C13), 2.21 – 2.01 (m, 1H, C9), 1.84 – 1.68 (m, 1H, C9), 0.87 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.53 (C8), 144.36 (C4), 129.32 (d, *J* = 33 Hz, C1), 128.50 (C3/C5), 125.74 (q, *J* = 4 Hz, C2/C6), 50.58 (C7), 37.32 (C12), 36.09 (C13), 28.28 (C9), 12.49 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 282.1082 found 282.1076. **ATR-FTIR** (cm^{-1}): 2967, 2935,

1641, 1618, 1493, 1460, 1396, 1322, 1276, 1261, 1161, 1112, 1087, 1066, 1018, 966, 859, 826, 764, 750, 711, 642, 630, 600.

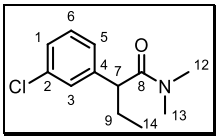
2-(4-bromophenyl)-*N,N*-dimethylbutanamide (**3.337**)



Synthesized following the general procedure **C.**

Isolated yield: 435 mg, 64%. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H, C2/C6), 7.19 – 7.14 (m, 2H, C3/C5), 3.57 (t, *J* = 7.3 Hz, 1H, C7), 2.93 (s, 6H, C12/C13), 2.10 – 2.01 (m, 1H, C9), 1.75 – 1.67 (m, 1H, C9), 0.85 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 172.83 (C8), 139.27 (C4), 131.88 (C3/C5), 129.85 (C2/C6), 120.84 (C1), 50.18 (C7), 37.31 (C12), 36.06 (C13), 28.20 (C9), 12.48 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 292.0313 found 292.0312. **ATR-FTIR** (cm^{-1}): 2963, 2930, 2873, 1736, 1639, 1589, 1487, 1462, 1393, 1373, 1325, 1240, 1189, 1146, 1106, 1083, 0173, 1046, 1010, 846, 813, 751, 724, 712, 637, 626.

2-(3-chlorophenyl)-*N,N*-dimethylbutanamide (**3.338**)

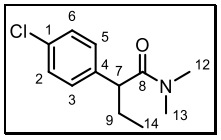


Synthesized following the general procedure **C.**

Isolated yield: 486 mg, 52%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 1H, C3), 7.25 – 7.15 (m, 3H, C1/C5/C6), 3.58 (t, *J* = 7.3 Hz, 1H, C7), 2.94 (s, 6H, C12/C13), 2.15 – 2.03 (m, 1H, C9), 1.86 – 1.66 (m, 1H, C9), 0.86 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.62 (C8), 142.32 (C4), 134.57 (C2), 130.02 (C3), 128.21 (C5), 127.20 (C6), 126.32 (C1), 50.43 (C7), 37.34 (C12), 36.07 (C13), 28.26 (C9), 12.51 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 248.0818 found 248.0813. **ATR-FTIR** (cm^{-1}): 3005, 2966, 2932,

2874, 1637, 1594, 1572, 1473, 1430, 1395, 1336, 1276, 1261, 1217, 1192, 1147, 1100, 1085, 890, 786, 747, 696, 677, 665, 634, 617.

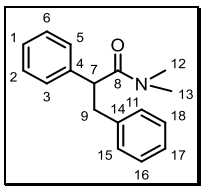
2-(4-chlorophenyl)-*N,N*-dimethylbutanamide (**3.339**)



Synthesized following the general procedure **C.**

Isolated yield: 561 mg, 66%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H, C2/C6), 7.22 (d, *J* = 8.4 Hz, 2H, C3/C5), 3.58 (t, *J* = 7.3 Hz, 1H, C7), 2.93 (s, 6H, C12/C13), 2.16 – 2.01 (m, 1H, C9), 1.84 – 1.64 (m, 1H, C9), 0.85 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.92 (C8), 138.77 (C4), 132.77 (C1), 129.48 (C3/C5), 128.93 (C2/C6), 50.11 (C7), 37.31 (C12), 36.05 (C13), 28.25 (C9), 12.48 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 248.0812 found 248.0818. **ATR-FTIR** (cm^{-1}): 2966, 2932, 2875, 1636, 1490, 1461, 1395, 1336, 1263, 1216, 1190, 1147, 1089, 1059, 1015, 965, 914, 848, 816.

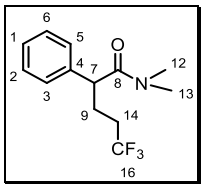
N,N-dimethyl-2,3-diphenylpropanamide (**3.340**)



Synthesized following the general procedure **C.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H, Ar), 7.24 – 7.19 (m, 5H, Ar), 7.18 – 7.14 (m, 1H, Ar), 7.08 (d, *J* = 7.2 Hz, 2H, Ar), 3.97 (t, *J* = 7.3 Hz, 1H, C7), 3.48 (dd, *J* = 13.6, 7.9 Hz, 1H, C9), 2.94 (dd, *J* = 13.6, 6.7 Hz, 1H, C9), 2.92 (s,3H, C12), 2.81 (s, 3H, C13). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.63 (C8), 140.22 (C4), 139.71 (C1), 129.29 (Ar), 128.77 (Ar), 128.26 (Ar), 128.17 (Ar), 127.08 (Ar), 126.17 (Ar), 51.32 (C7), 41.34 (C9), 37.22 (C12), 36.05 (C13). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 276.1364 found 276.1358. **ATR-FTIR** (cm^{-1}): 3059, 3027, 2925, 2357, 1641, 1602, 1583, 1494, 1453, 1395, 1276, 1261, 1134, 1072, 1031, 750, 699, 637.

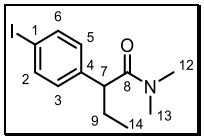
5,5,5-trifluoro-*N,N*-dimethyl-2-phenylpentanamide (**3.341**)



Synthesized following the general procedure **C.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H, C3/C5), 7.29 – 7.24 (m, 3H, C1/C2/C6), 3.79 – 3.74 (m, 1H, C7), 2.95 (s, 3H, C12), 2.89 (s, 3H, C13), 2.36 – 2.24 (m, 1H, C9), 2.21 – 2.09 (m, 1H, C9), 2.08 – 1.88 (m, 2H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.95 (C8), 138.98 (C4), 129.20 (C3/C5), 127.93 (C2/C6), 127.51 (C1), 47.78 (C7), 37.18 (C12), 36.08 (C13), 31.88 (q, *J* = 29 Hz, C14), 27.57 (d, *J* = 3 Hz, C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 282.1082 found 282.1076. **ATR-FTIR** (cm^{-1}): 2941, 1638, 1603, 1584, 1493, 1452, 1387, 1335, 1316, 1303, 1256, 1231, 1191, 1130, 1104, 1057, 1041, 996, 984, 943, 917, 864, 826, 769, 750, 701, 658, 635, 607, 596.

2-(4-iodophenyl)-*N,N*-dimethylbutanamide (**3.342**)

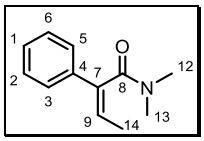


Synthesized following the general procedure **C.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H, C2/C6), 7.08 – 7.00 (m, 2H, C3/C5), 3.55 (t, *J* = 7.4 Hz, 1H, C7), 2.93 (s, 3H, C12), 2.93 (s, 3H, C13), 2.10 – 2.00 (m, 1H, C9), 1.75 – 1.65 (m, 1H, C9), 0.85 (t, *J* = 7.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.77 (C8), 139.98 (C4), 137.86 (C2/C6), 130.17 (C3/C5), 92.32 (C1), 50.29 (C7), 37.31 (C12), 36.05 (C13), 28.18 (C9), 12.49 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 340.0174 found 340.0167**. ATR-FTIR** (cm^{-1}): 2962, 2928, 2872, 1736, 1637, 1585, 1483, 1461, 1392, 1324, 1241, 1186, 1145, 1105, 1083, 1061, 1005, 964, 913, 844, 810, 751, 722, 710, 637, 622.

3.6.1.2. *Products*

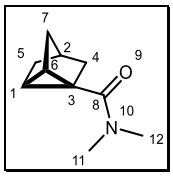
(*Z*)-*N,N*-dimethyl-2-phenylbut-2-enamiden (**3.187**)



Synthesized following the general procedure **E.**

Isolated yield: 37 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 2H, C3/C5), 7.33 – 7.28 (m, 2H, C2/C6), 7.26 – 7.22 (m, 1H, C1), 6.13 (q, *J* = 7.0 Hz, 1H, C9), 3.10 (s, 3H, C12), 2.91 (s, 3H, C13), 1.82 (d, *J* = 7.0 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.32 (C8), 138.52 (C7), 136.36 (C4), 128.83 (C2/C6), 127.73 (C1), 125.45 (C3/C5), 124.09 (C9), 37.70 (C12), 34.35 (C13), 15.44 (C14). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 190.1228 found 190.1226. **ATR-FTIR** (cm^{-1}): 2988, 2925, 1622, 1496, 1441, 1395, 1333, 1275, 1261, 1147, 1113, 1076, 1057, 1033, 980, 872, 751, 744, 709, 693, 66

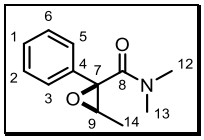
N,N-dimethyltricyclo[2.2.1.$0^{2,6}$]heptane-1-carboxamide (**3.204**)



Synthesized following the general procedure **E.**

^{1}H NMR (700 MHz, $CDCl_3$) δ 3.05 (bs, 6H, C11/C12), 2.11 (s, 1H, C2), 1.59 (s, 2H, C4), 1.53 (d, *J* = 1.4 Hz, 2H, C1/C6), 1.46 (d, *J* = 10.7 Hz, 2H, C5/C7 exo), 1.32 (d, *J* = 10.2 Hz, 2H, C5/C7 endo). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 172.87 (C8), 36.39 (C11/C12), 33.54 (C5/7), 31.64 (C4), 26.87 (C6), 18.54 (C3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 188.1051 found 188.1045. **ATR-FTIR** (cm^{-1}): 2981, 2943, 2865, 2356, 1624, 1501, 1447, 1397, 1367, 1290, 1274, 1196, 1177, 1119, 1071, 1053, 922, 884, 833, 764, 731, 691, 643.

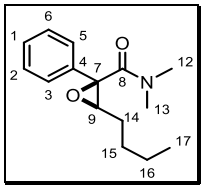
N,N,3-trimethyl-2-phenyloxirane-2-carboxamide (**3.221**)



Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at r.t.

Isolated yield: 38 mg, 93%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H, C3/C5), 7.37 – 7.28 (m, 3H, C1/C2/C6), 3.15 (q, *J* = 5.3 Hz, 1H, C9), 2.99 (s, 3H, C12), 2.98 (s, 3H, C13), 1.45 (d, *J* = 5.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.11 (C8), 136.28 (C4), 128.75 (C2/C6), 128.40 (C1), 125.14 (C3/C5), 64.51 (C9/C7), 37.02 (C12), 35.22 (C13), 16.85 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 228.1000 found 228.0993. **ATR-FTIR** (cm^{-1}): 2930, 2243, 1639, 1495, 1448, 1402, 1270, 1172, 1126, 1043, 1029, 980, 956, 907, 857, 797, 756, 727, 697, 646, 626, 583, 553.

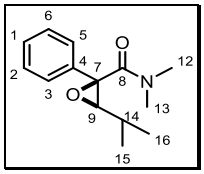
3-butyl-*N,N*-dimethyl-2-phenyloxirane-2-carboxamide (**3.250**)



Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at r.t.

Isolated yield: 35 mg, 71%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H, C3/C5), 7.37 – 7.27 (m, 3H, C1/C2/C6), 3.02 – 2.98 (m, 1H, C9), 2.97 (s, 6H, C12/C13), 1.94 – 1.84 (m, 1H, C14), 1.59 – 1.48 (m, 2H, C15), 1.39 (td, *J* = 14.6, 7.3 Hz, 3H, C14/C16), 0.92 (t, *J* = 7.3 Hz, 3H, C17). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.19 (C8), 136.53 (C4), 128.72 (C2/C6), 128.31 (C1), 125.11 (C3/C5), 68.72 (C9), 64.47 (C7), 37.00 (C12), 35.25 (C13), 31.11 (C14), 28.67 (C15), 22.63 (C16), 14.08 (C17). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 270.1470 found 270.1465. **ATR-FTIR** (cm^{-1}): 2958, 2932, 2872, 2366, 1643, 1495, 1450, 1400, 1267, 1158, 1124, 1092, 1062, 1031, 973, 937, 906, 760, 733, 698, 687, 627, 612.

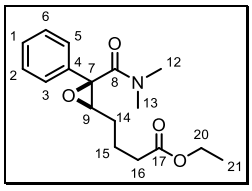
3-isopropyl-*N,N*-dimethyl-2-phenyloxirane-2-carboxamide (**3.257**)



Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at r.t.

Isolated yield: 36 mg, 77%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 2H, C3/C5), 7.31 – 7.17 (m, 3H, C1/C2/C6), 2.91 (s, 3H, C12), 2.89 (s, 3H, C13), 2.59 (d, *J* = 9.1 Hz, 1H, C9), 1.54 – 1.34 (m, 1H, C14), 1.06 (d, *J* = 6.7 Hz, 3H, C15), 1.02 (d, *J* = 6.7 Hz, 3H, C16). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.13 (C8), 136.79 (C4), 128.71 (C2/C6), 128.25 (C1), 125.05 (C3/C5), 73.87 (C9), 65.43 (C7), 37.01 (C12), 35.31 (C13), 30.68 (C14), 19.90 (C15), 18.50 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 256.1305 found 256.1313. **ATR-FTIR** (cm^{-1}): 2961, 2869, 1643, 1495, 1471, 1448, 1400, 1383, 1364, 1266, 1244, 1161, 1125, 1093, 1076, 1061, 1032, 986, 953, 934, 908, 886, 867, 827, 760, 733, 698, 628, 611.

Ethyl 4-(3-(dimethylcarbamoyl)-3-phenyloxiran-2-yl)butanoate (**3.254**)

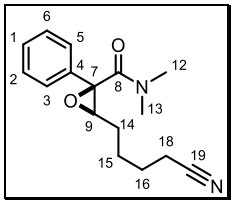


Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at r.t.

Isolated yield: 49 mg, 81%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H, C3/C5), 7.38 – 7.28 (m, 3H, C1/C2/C6), 4.12 (q, *J* = 7.1 Hz, 2H, C20), 3.02 – 2.99 (m, 1H, C9), 2.97 (s, 3H, C12), 2.97 (s, 3H, C13), 2.43 – 2.37 (m, 2H, C16), 1.98 – 1.83 (m, 3H, C14/C15), 1.52 – 1.40 (m, 1H, C14), 1.24 (t, *J* = 7.1 Hz, 3H, C21). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.37 (C17), 167.03 (C8), 136.26 (C4), 128.78 (C2/C6), 128.43 (C1), 125.09 (C3/C5), 68.11 (C9), 64.44 (C7), 60.43 (C20), 37.00 (C12), 35.27 (C13), 34.05 (C16), 30.80 (C14), 21.95 (C15), 14.37 (C21). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 328.1525 found 328.1509. **ATR-FTIR** (cm^{-1}): 2934,

1730, 1643, 1496, 1449, 1400, 1375, 1300, 1248, 1165, 1113, 1060, 1029, 971, 935, 906, 852, 800, 760, 732, 699, 626, 578, 528.

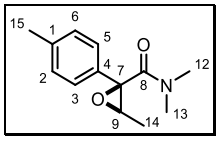
3-(4-cyanobutyl)-*N,N*-dimethyl-2-phenyloxirane-2-carboxamide (**3.251**)



Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at r.t.

Isolated yield: 42 mg, 77%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H, C3/C5), 7.37 – 7.27 (m, 3H, C1/C2/C6), 2.99 – 2.98 (m, 1H, C9), 2.97 (s, 3H, C12), 2.96 (s, 3H, C13), 2.39 – 2.33 (m, 2H, C18), 1.94 – 1.84 (m, 1H, C14), 1.81 – 1.67 (m, 4H, C15/C16), 1.54 – 1.44 (m, 1H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.94 (C8), 136.07 (C4), 128.79 (C2/C6), 128.47 (C1), 124.97 (C3/C5), 119.63 (C19), 68.01 (C9), 64.43 (C7), 36.97 (C12), 35.25 (C13), 30.46 (C14), 25.57 (C15), 25.21 (C16), 17.12 (C18). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 295.1422 found 295.1419. **ATR-FTIR** (cm^{-1}): 2946, 1643, 1496, 1449, 1402, 1265, 1154, 1115, 1061, 979, 935, 908, 730, 699, 648, 626.

N,N,3-trimethyl-2-(*p*-tolyl)oxirane-2-carboxamide (**3.240**)

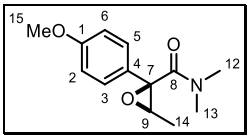


Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_3$ $_{aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 30 mg, 68%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 2H, C3/C5), 7.15 (d, *J* = 8.2 Hz, 2H, C2/C6), 3.13 (q, *J* = 5.4 Hz, 1H, C9), 2.98 (s, 3H, C12), 2.97 (s, 3H, C13), 2.33 (s, 3H, C15), 1.43 (d, *J* = 5.4 Hz, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.26 (C8), 138.21 (C1), 133.30 (C4), 129.44 (C2/C6), 125.10 (C6), 64.53 (C7), 64.31 (C9), 37.01 (C12), 35.19 (C13), 16.81 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$

242.1153 found 242.1157 **ATR-FTIR** (cm^{-1}): 2928, 2873, 2363, 2341, 1642, 1511, 1450, 1419, 1399, 1268, 1251, 1171, 1124, 1040, 1022, 981, 954, 917, 862, 815, 728, 712, 675, 591.

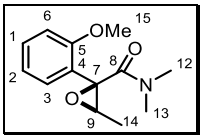
2-(2-methoxyphenyl)-*N,N*,3-trimethyloxirane-2-carboxamide (**3.239**)



Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_{3\ aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 29 mg, 61%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H, C3/C5), 6.86 (d, *J* = 8.7 Hz, 2H, C2/C6), 3.79 (s, 3H, C15), 3.13 (q, *J* = 5.4 Hz, 1H, C9), 2.98 (s, 3H, C12), 2.98 (s, 3H, C13), 1.42 (d, *J* = 5.4 Hz, 3H, C14). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 167.34 (C8), 159.78 (C1), 128.22 (C4), 126.52 (C3/C5), 114.16 (C2/C6), 64.40 (C7), 64.16 (C9), 55.42 (C15), 37.02 (C12), 35.20 (C13), 16.77 (C14). ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.34, 159.78, 128.22, 126.52, 114.16, 64.40, 64.16, 55.42, 37.02, 35.20, 16.77. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 258.1106 found 258.1104. **ATR-FTIR** (cm^{-1}): 2933, 1640, 1612, 1580, 1511, 1460, 1400, 1303, 1275, 1247, 1169, 1125, 1030, 981, 912, 829, 793, 750, 729, 675, 646, 591, 573.

2-(2-methoxyphenyl)-*N,N*,3-trimethyloxirane-2-carboxamide (**3.243**)

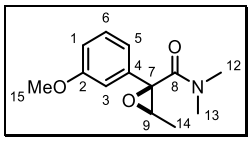


Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_{3\ aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 33 mg,70%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H, C3), 7.31 – 7.27 (m, 1H, C1), 6.96 – 6.91 (m, 1H, C2), 6.87 (d, *J* = 8.3 Hz, 1H, C6), 3.83 (s, 3H, C15), 3.54 (q, *J* = 5.4 Hz, 1H, C9), 3.16 (s, 3H, C12), 2.93 (s, 3H, C13), 1.42 (d, *J* = 5.4 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.10 (C8), 157.85 (C5), 130.19 (C1), 130.12 (C4), 125.15 (C3), 120.93 (C2), 111.36 (C6), 63.07 (C7), 60.02 (C9), 55.72

(C15), 37.08 (C12), 35.84 (C13), 15.47 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 258.1106 found 258.1102. **ATR-FTIR** (cm^{-1}): 2936, 2361, 2243, 2335, 1639, 1602, 1585, 1495, 1461, 1438, 1398, 1253, 1168, 1117, 1055, 1036, 1025, 982, 917, 756, 679.

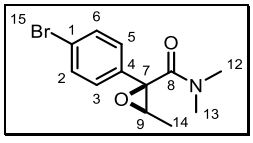
2-(3-methoxyphenyl)-*N,N*,3-trimethyloxirane-2-carboxamide (**3.242**)



Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_{3\,aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 26 mg, 55%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H, C6), 7.00 – 6.94 (m, 1H, C3), 6.93 – 6.90 (m, 1H, C5), 6.77 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H, C1), 3.73 (s, 3H, C15), 3.06 (q, *J* = 5.4 Hz, 1H, C9), 2.91 (s, 6H, C12/C13), 1.37 (d, *J* = 5.4 Hz, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.00 (C8), 160.09 (C2), 137.98 (C4), 129.82 (C6), 117.55 (C5), 114.14 (C3), 110.37 (C1), 64.44 (C7/C9), 55.40 (C15), 36.99 (C12), 35.22 (C13), 16.81 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 258.1106 found 258.1105. **ATR-FTIR** (cm^{-1}): 2934, 1642, 1601, 1583, 1487, 1455, 1434, 1400, 1318, 1285, 1257, 1218, 1184, 1157, 1124, 1035, 958, 929, 861, 812, 782, 750, 725, 696, 628, 567, 555, 534.

2-(4-bromophenyl)-*N,N*,3-trimethyloxirane-2-carboxamide (**3.246**)

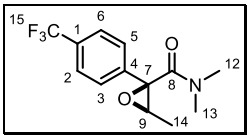


Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at 40 °C.

Isolated yield: 46 mg, 81%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H, C2/C6), 7.34 – 7.28 (m, 2H, C3/C5), 3.07 (q, *J* = 5.4 Hz, 1H, C9), 2.96 (s, 3H, C12), 2.95 (s, 3H, C13), 1.41 (d, *J* = 5.4 Hz, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.65 (C8), 135.46 (C4), 131.87 (C2/C6), 126.92 (C3/C5), 122.47 (C1), 64.54 (C9),

64.11 (C7), 36.93 (C12), 35.25 (C13), 16.76 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 306.0106 found 306.0101. **ATR-FTIR** (cm^{-1}): 2933, 1644, 1488, 1397, 1262, 1125, 1072, 1040, 1011, 984, 918, 821, 757.

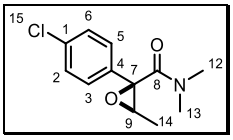
N,N,3-trimethyl-2-(4-(trifluoromethyl)phenyl)oxirane-2-carboxamide (**3.248**)



Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at 60 °C.

Isolated yield: 36 mg, 66%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 – 7.53 (m, 4H, Ar), 3.10 (q, *J* = 5.3 Hz, 1H, C9), 2.99 (s, 3H, C12), 2.97 (s, 3H, C13), 1.44 (d, *J* = 5.3 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.43 (C8), 140.45 (C4), 130.61 (q, *J* = 33 Hz, C1) 125.59 (m, C2/C3/C5/C6), 124.09 (q, *J* = 272 Hz, C15), 64.87 (C9), 64.12 (C7), 36.94 (C12), 35.30 (C13), 16.82 (C14). ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.67. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 296.0874 found 296.0873. **ATR-FTIR** (cm^{-1}): 2934, 1644, 1504, 1456, 1403, 1323, 1274, 1164, 1121, 1109, 1067, 1039, 1017, 986, 959, 921, 865, 834, 794, 764, 750, 727, 690, 649, 606, 574.

2-(4-chlorophenyl)-*N,N*,3-trimethyloxirane-2-carboxamide (**3.246**)

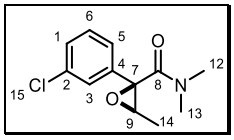


Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at 40 °C.

Isolated yield: 46 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H, C2/C6), 7.33 – 7.29 (m, 2H, C3/C5), 3.09 (q, *J* = 5.3 Hz, 1H, C9), 2.98 (s, 3H, C12), 2.97 (s, 3H, C13), 1.43 (d, *J* = 5.3 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.72 (C8), 134.94 (C1), 134.36 (C4), 128.97 (C2/C6), 126.63 (C3/C5), 64.64 (C9), 64.12 (C7), 36.98 (C12), 35.28 (C13), 16.82 (C14).. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 262.0611 found

262.0608. **ATR-FTIR** (cm^{-1}): 2360, 2343, 2335, 1648, 1492, 1461, 1420, 1399, 1126, 1091, 1040, 1015, 984, 918, 824, 750, 661.

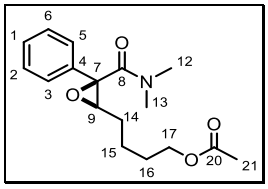
2-(3-chlorophenyl)-*N,N*,3-trimethyloxirane-2-carboxamide (**3.247**)



Synthesized following the general procedure **F** with DCM as the solvent, water as the scavenger and epoxidation at 40 °C.

Isolated yield: 35 mg, 74%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 1H, C3), 7.31 – 7.26 (m, 1H, C1), 7.23 – 7.17 (m, 2H, C5/C6), 3.03 (q, *J* = 5.3 Hz, 1H, C9), 2.92 (s, 3H, C12), 2.92 (s, 3H, C13), 1.37 (d, *J* = 5.3 Hz, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.52 (C8), 138.54 (C2), 134.93 (C4), 130.07 (C6), 128.63 (C1), 125.24 (C5), 123.47 (C3), 64.72 (C9), 63.99 (C7), 37.00 (C12), 35.30 (C13), 16.81 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 262.0611 found 262.0609. **ATR-FTIR** (cm^{-1}): 2930, 1642, 1597, 1572, 1503, 1474, 1400, 1244, 1172, 1126, 1079, 1043, 985, 931, 891, 864, 786, 749, 706, 691, 674, 629.

4-(3-(dimethylcarbamoyl)-3-phenyloxiran-2-yl)butyl acetate (**3.256**)

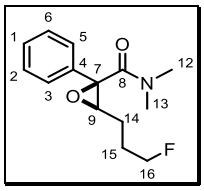


Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_{3\,aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 32 mg, 52%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H, C3/C5), 7.37 – 7.27 (m, 3H, C1/C2/C6), 4.08 (t, *J* = 6.5 Hz, 2H, C17), 3.01 – 2.99 (m, 1H, C9), 2.98 (s, 3H, C12), 2.97 (s, 3H, C13), 2.04 (s, 3H, C21), 1.96 – 1.89 (m, 1H, C14), 1.75 – 1.68 (m, 2H, C16), 1.67 – 1.59 (m, 2H, C15), 1.49 – 1.41 (m, 1H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.34 (C20), 167.06 (C8), 136.30 (C4), 128.78 (C2/C6), 128.42 (C1), 125.06 (C3/C5), 68.43 (C9), 64.46 (C7), 64.40 (C17), 37.02 (C12), 35.27 (C13), 31.04 (C16), 28.49 (C14),

23.04 (C15), 21.13 (C21). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 328.1525 found 328.1522. **ATR-FTIR** (cm^{-1}): 2938, 1734, 1643, 1496, 1450, 1400, 1239, 1157, 1118, 1034, 975, 934, 908, 840, 763, 730, 699, 646, 627, 609, 583, 534.

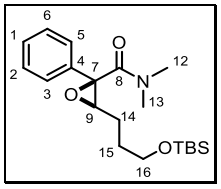
3-(3-fluoropropyl)-*N,N*-dimethyl-2-phenyloxirane-2-carboxamide (**3.254**)



Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_{3\ aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 38 mg, 76%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H, C3/C5), 7.37 – 7.28 (m, 3H, C1/C2/C6), 4.51 (dt, *J* = 47.0, 5.7 Hz, 2H, C16), 3.05 – 3.03 (m, 1H, C9), 2.98 (s, 3H, C12), 2.97 (s, 3H, C12), 2.07 – 1.87 (m, 3H, C15/C14), 1.65 – 1.53 (m, 1H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.93 (C8), 136.16 (C4), 128.78 (C2/C6), 128.46 (C1), 125.06 (C3/C5), 83.67 (d, *J* = 165 Hz, C16), 67.89 (C9), 64.62 (C7), 36.98 (C12), 35.25 (C13), 27.50 (d, *J* = 5 Hz, C14), 27.32 (d, *J* = 20 Hz, C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 274.1219 found 274.1214. **ATR-FTIR** (cm^{-1}): 3007, 2988, 1642, 1497, 1449, 1399, 1276, 1261, 1157, 1117, 1062, 1041, 996, 975, 936, 908, 750, 699, 626.

3-(3-((tert-butyldimethylsilyl)oxy)propyl)-*N,N*-dimethyl-2-phenyloxirane-2-carboxamide (**3.252**)

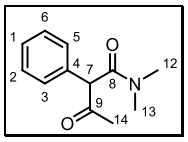


Synthesized following the general procedure **F** with DCM as the solvent, sat. $NaHCO_3$ $_{aq.}$ as the scavenger and epoxidation at r.t.

Isolated yield: 31 mg, 41%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H, C3/C5), 7.37 – 7.28 (m, 3H, C1/C2/C6), 3.67 (t, *J* = 6.3 Hz, 2H, C16), 3.11 – 3.02 (m, 1H, C9), 2.98 (s, 3H, C12), 2.97 (s, 2H, C13), 1.96 –

1.85 (m, 1H, C14), 1.84 – 1.72 (m, 2H, C15), 1.60 – 1.41 (m, 1H, C14), 0.92 – 0.83 (m, 9H, TBS-Me_3), 0.04 (d, *J* = 1.5 Hz, 6H TBS-Me_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.00 (C8), 136.33 (C4), 128.59 (C2/C6), 128.21 (C1), 125.02 (C3/C5), 68.31 (C9), 64.48 (C7), 62.65 (C16), 36.88 (C12), 35.11 (C13), 29.49 (C14), 27.94 (C15), 25.92 (TBS-Me_3), 18.27 (TBS-qC), -5.31 (TBS-Me_2). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 386.2127 found 386.2124 **ATR-FTIR** (cm^{-1}): 2952, 2928, 2894, 2856, 2365, 1649, 1496, 1471, 1462, 1450, 1400, 1361, 1252, 1157, 1094, 1031, 1006, 979, 957, 936, 907, 834, 809, 774, 733, 698, 687, 662, 627, 614.

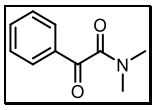
N,N-dimethyl-3-oxo-2-phenylbutanamide (**3.264**)



Synthesized following the general procedure **H.**

Isolated yield: 36 mg, 88%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H, C3/C5), 7.35 – 7.30 (m, 1H, C1), 7.30 – 7.27 (m, 2H, C2/C6), 4.78 (s, 1H, C7), 2.99 (s, 3H, C12), 2.88 (s, 3H, C13), 2.19 (s, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.69 (C9), 168.95 (C8), 133.77 (C4), 129.25 (C3/C5), 128.99 (C2/C6), 128.16 (C1), 64.13 (C7), 37.74 (C12), 35.84 (C13), 29.07 (C14). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 220.1000 found 220.0990. **ATR-FTIR** (cm^{-1}): 3006, 2936, 2360, 2342, 1727, 1713, 1634, 1584, 1496, 1454, 1396, 1354, 1276, 1261, 1161, 1134, 1077, 1060, 1033, 763, 750, 701, 700, 633.

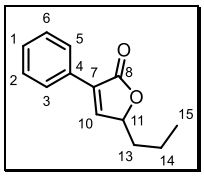
N,N-dimethyl-2-oxo-2-phenylacetamide (**3.236**)



Synthesized following the general procedure **I** or **J.**

Spectroscopic properties match with the literature.[658]

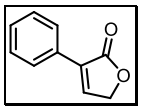
3-phenyl-5-propylfuran-2(5H)-one (**3.269**)



Synthesized following the general procedure **K.**

Isolated yield: 29 mg, 71%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.78 (m, 2H, C2/C6), 7.55 (d, *J* = 1.8 Hz, 1H, C10), 7.47 – 7.30 (m, 3H, C1/C3/C5), 5.05 (m, 1H, C11), 1.89 – 1.65 (m, 2H, C13), 1.61 – 1.40 (m, 2H, C14), 1.00 (t, *J* = 7.4 Hz, 3H, C15). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.88 (C8), 148.13 (C10), 131.68 (C4), 129.74 (C7), 129.39 (C1), 128.76 (C2/C6), 127.15 (C3/C5), 80.48 (C11), 35.72 (C13), 18.62 (C14), 13.98 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 225.0891 found 225.0892. **ATR-FTIR** (cm^{-1}): 3072, 2961, 2934, 2874, 2349, 1745, 1689, 1598, 1493, 1449, 1381, 1328, 1304, 1246, 1183, 1117, 1069, 1028, 965, 937, 901, 865.

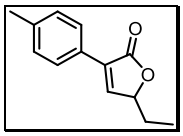
3-phenylfuran-2(5H)-one (**3.222**)



Synthesized following the general procedure **K.**

Isolated yield: 15 mg, 46%. Spectroscopic properties match with the literature.[659]

Incrustoprine (**3.270**)



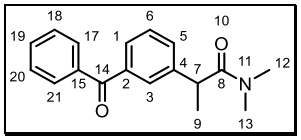
Synthesized following the general procedure **K.**

Isolated yield: 28 mg, 69%. Spectroscopic properties match with the literature.[660]

3.6.2. β-functionalization

3.6.2.1. *Starting material*

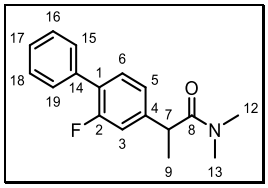
2-(3-benzoylphenyl)-*N,N*-dimethylpropanamide (**3.343**)



Synthesized following the general procedure **A.**

Isolated yield: 810 mg, 87%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 2H, Ar), 7.71 (s, 1H, Ar), 7.64 (d, *J* = 7.6 Hz, 1H, Ar), 7.59 (t, *J* = 7.4 Hz, 1H, Ar), 7.55 (d, *J* = 7.8 Hz, 1H, Ar), 7.48 (t, *J* = 7.7 Hz, 2H, Ar), 7.43 (dd, *J* = 9.6, 5.8 Hz, 1H, Ar), 3.99 (q, *J* = 6.9 Hz, 1H, C7), 2.96 (s, 3H, C12), 2.94 (s, 3H, C13), 1.48 (d, *J* = 6.9 Hz, 3H, C9). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.72 (C14), 173.32 (C8), 142.40 (C15), 138.19 (C2), 137.67 (C4), 132.69 (Ar), 131.42 (Ar), 130.22(Ar), 129.22 (Ar), 128.96 (Ar), 128.89 (Ar), 128.46 (Ar), 43.08 (C7), 37.40 (C12), 36.13 (C13), 20.70 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 304.1313 found 304.1303. **ATR-FTIR** (cm^{-1}): 2976, 2932, 1641, 1597, 1579, 1482, 1447, 1395, 1372, 1317, 1280, 1198, 1178, 1149, 1073, 999, 958, 939, 825, 783, 720, 699, 646, 604.

2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N,N*-dimethylpropanamide (**3.344**)

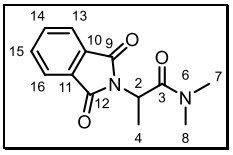


Synthesized following the general procedure **A.**

Isolated yield: 820 mg, 92%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H, Ar), 7.43 (t, *J* = 7.7 Hz, 2H, Ar), 7.41 – 7.33 (m, 2H, Ar), 7.15 – 7.08 (m, 2H, Ar), 3.94 (q, *J* = 6.9 Hz, 1H, C7), 2.98 (s, 3H, C12), 2.97 (s, 3H, C13), 1.48 (d, *J* = 6.9 Hz, 3H, C9). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.23 (C8), 159.99 (d, *J* = 249 Hz, C2), 143.44 (d, *J* = 8 Hz, C1), 135.66 (C14), 131.14 (C 17), 129.07 (d, *J* = 3 Hz, C6), 128.58 (C15/C19), 127.58 (d, *J* = 14 Hz, C4), 123.49 (d, *J* = 3 Hz, C5), 115.22 (d, *J* = 23 Hz, C3), 42.73 (C7), 37.39 (C12), 36.15 (C13), 20.62 (C9). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 294.1254 found 294.1270. **ATR-FTIR** (cm^{-1}): 3034, 2976,

2933, 1645, 1581, 1562, 1484, 1451, 1417, 1396, 1266, 1223, 1141, 1074, 1011, 949, 914, 878, 834, 766, 752, 724, 699, 643, 618, 595.

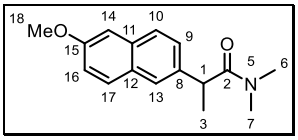
2-(1,3-dioxoisoindolin-2-yl)-*N,N*-dimethylpropanamide (**3.345**)



Synthesized following the general procedure **A.**

Isolated yield: 1501 mg, 92%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 2H, C13/C16), 7.76 – 7.69 (m, 2H, C14/C15), 5.13 (q, *J* = 7.2 Hz, 1H, C2), 2.97 (s, 3H, C7), 2.96 (s, 3H, C8), 1.71 (d, *J* = 7.2 Hz, 3H, C4). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.14 (C9/C12), 167.87 (C3), 134.25 (C14/C15), 131.92 (C10/C11), 123.57 (C13/C16), 47.31 (C2), 37.11 (C7), 36.36 (C8), 15.57 (C4). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 269.0902 found 269.0888. **ATR-FTIR** (cm^{-1}): 2938, 2363, 2343, 1777, 1713, 1657, 1611, 1500, 1468, 1386, 1361, 1260, 1174, 1130, 1084, 1052, 1018, 896, 881, 776, 721.

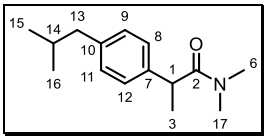
2-(6-methoxynaphthalen-2-yl)-*N,N*-dimethylpropanamide (**3.346**)



Synthesized following the general procedure **A.**

Isolated yield: 830 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (t, *J* = 8.4 Hz, 2H, C10/C17), 7.61 (s, 1H, C9), 7.38 (dd, *J* = 8.4, 1.7 Hz, 1H, C13), 7.16 – 7.09 (m, 2H, C14/C16), 4.00 (q, *J* = 6.9 Hz, 1H, C1), 3.90 (s, 3H, C18), 2.97 (s, 3H, C6), 2.90 (s, 3H, C7), 1.50 (d, *J* = 6.9 Hz, 3H, C3). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.87 (C2), 157.67 (C15), 137.21 (C8), 133.56 (C11), 129.28 (C17), 129.20 (C12), 127.55 (C10), 126.38 (C10), 125.67 (C13), 119.09 (C16), 105.72 (C14), 55.43 (C18), 43.36 (C1), 37.30 (C6), 36.05 (C7), 20.91 (C3). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 280.1313 found 280.1303. **ATR-FTIR** (cm^{-1}): 2934, 1638, 1606, 1505, 1485, 1464, 1393, 1264, 1229, 1213, 1195, 1151, 1122, 1075, 1060, 1032, 922, 893, 855, 813.

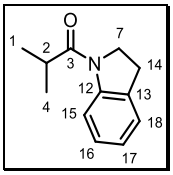
2-(4-isobutylphenyl)-*N,N*-dimethylpropanamide (**3.347**)



Synthesized following the general procedure **A.**

Isolated yield: 1167 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.0 Hz, 2H, C12/C8), 7.07 (d, *J* = 8.0 Hz, 2H, C9/C11), 3.85 (q, *J* = 6.9 Hz, 1H, C1), 2.95 (s, 3H, C6), 2.89 (s, 3H, C17), 2.43 (d, *J* = 7.2 Hz, 2H, C13), 1.89 – 1.79 (m, 1H, C14), 1.42 (d, *J* = 6.9 Hz, 3H, C3), 0.89 (d, *J* = 6.6 Hz, 6H, C15/C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 174.04 (C2), 140.22 (C10), 139.25 (C7), 129.64 (C9/C11), 127.15 (C8/C12), 45.17 (C13), 43.00 (C1), 37.30 (C17), 36.04 (6), 30.32 (C14), 22.54 (C16), 22.52 (C15), 20.89 (C3). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 234.1854 found 234.1854. **ATR-FTIR** (cm^{-1}): 2954, 2927, 2868, 2359, 1643, 1509, 1462, 1393, 1368, 1308, 1275, 1262, 1146, 1119, 1061, 1022, 1001, 848, 805, 765, 750, 695, 645, 612, 588.

1-(indolin-1-yl)-2-methylpropan-1-one (**3.284**)

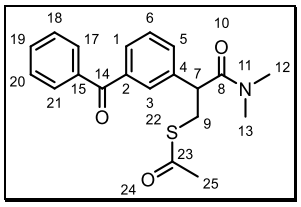


Synthesized following the general procedure **D.**

Isolated yield: 2160 mg, 76%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.8 Hz, 1H, C16), 7.22 – 7.15 (m, 2H, C15/C17), 7.00 (t, *J* = 7.4 Hz, 1H, C18), 4.12 (t, *J* = 8.5 Hz, 2H,C7), 3.19 (t, *J* = 8.2 Hz, 2H, C14), 2.73 –2.83 (m, 1H, C2), 1.23 (d, *J* = 6.7 Hz, 6H, C1/C4). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 175.75 (C3), 143.39 (C12), 131.28 (C13), 127.63 (C16), 124.56 (C18), 123.62 (C17), 117.42 (C15), 47.92 (C7), 33.54 (C14), 28.19 (C2), 19.26 (C4). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 212.1051 found 212.1053. **ATR-FTIR** (cm^{-1}): 2968, 2934, 2875, 2352, 1732, 1656, 1599, 1481, 1462, 1407, 1363, 1337, 1308, 1266, 1228, 1164, 1105, 1081, 926.

3.6.2.2. *Products*

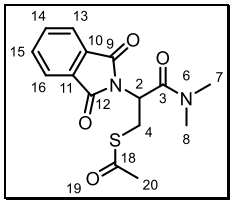
S-(2-(3-benzoylphenyl)-3-(dimethylamino)-3-oxopropyl) ethanethioate (**3.275**)



Synthesized following the general procedure **L.**

Isolated yield: 50 mg, 70%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 – 7.75 (m, 2H, Ar), 7.72 – 7.69 (m, 1H, Ar), 7.69 – 7.65 (m, 1H, Ar), 7.60 – 7.54 (m, 2H, Ar), 7.49 – 7.41 (m, 3H, Ar), 4.05 (dd, *J* = 8.8, 5.7 Hz, 1H, C7), 3.40 (dd, *J* = 13.4, 8.8 Hz, 1H, C9), 3.28 (dd, *J* = 13.4, 5.7 Hz, 1H, C9), 2.95 (s, 3H, C12), 2.86 (s, 3H, C13), 2.30 (s, 3H, C25). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.34 (C14), 196.33 (C23), 171.05 (8), 138.60 (C2), 138.34 (C4), 137.39 (C15), 132.76 (Ar), 131.76 (Ar), 130.17 (Ar), 129.67 (Ar), 129.45 (Ar), 129.12 (Ar), 128.43 (Ar), 49.07 (C7), 37.25 (C12), 36.05 (C13), 33.64 (C9), 30.67 (C28). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 378.1140 found 378.1140. **ATR-FTIR** (cm^{-1}): 2933, 2249, 1687, 1640, 1597, 1579, 1493, 1447, 1398, 1354, 1318, 1354, 1318, 1279, 1261, 1223, 1197, 1133, 1055, 1001, 963, 950, 908, 867, 819, 717, 699, 646, 628.

S-(3-(dimethylamino)-2-(1,3-dioxoisoindolin-2-yl)-3-oxopropyl) ethanethioate (**3.277**)

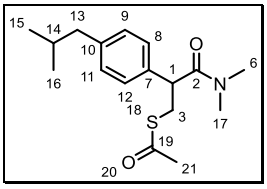


Synthesized following the general procedure **L.**

Isolated yield: 64 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 2H, C13/C16), 7.74 – 7.71 (m, 2H, C14/C15), 5.19 (dd, *J* = 10.4, 5.1 Hz, 1H, C2), 3.79 (dd, *J* = 14.2, 10.4 Hz, 1H, C4), 3.66 (dd, *J* = 14.2, 5.1 Hz, 1H, C4), 3.10 (s, 3H, C7), 2.95 (d, *J* = 5.5 Hz, 3H, C8), 2.28 (s, 3H, C20). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.97 (C18), 167.91 (C3), 167.23 (C12/C9), 134.38 (C13/C16), 131.62 (C10/C11), 123.69 (C14/C15), 51.39 (C2), 37.15 (C7), 36.34 (C8), 30.52 (C4), 28.47 (C20). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 343.0728 found

343.0718. **ATR-FTIR** (cm^{-1}): 1773, 1714, 1691, 1655, 1613, 1495, 1468, 1379, 1356, 1300, 1275, 1261, 1134, 1099, 1086, 1063, 960, 940, 912, 890, 764, 749, 716, 699, 646, 621.

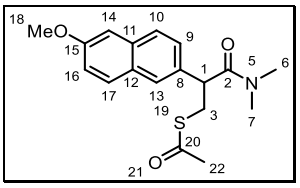
S-(3-(dimethylamino)-2-(4-isobutylphenyl)-3-oxopropyl) ethanethioate (**3.273**)



Synthesized following the general procedure **L.**

Isolated yield: 61 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H, C8/C12), 7.09 (d, *J* = 8.0 Hz, 2H, C9/C11), 3.93 (dd, *J* = 9.5, 5.1 Hz, 1H, C1), 3.33 (dd, *J* = 13.3, 9.5 Hz, 1H, C3), 3.26 (dd, *J* = 13.3, 5.1 Hz, 1H, C3), 2.95 (s, 3H, C6), 2.82 (s, 3H, C17), 2.43 (d, *J* = 7.2 Hz, 2H, C13), 2.30 (s, 3H, C21), 1.83 (hept, *J* = 6.6 Hz, 1H, C14), 0.88 (dd, *J* = 6.6, 0.7 Hz, 6H, C15/C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.74 (C19), 171.74 (C2), 141.14 (C10), 135.57 (C7), 129.79 (C9), 127.65 (C8), 49.27 (C1), 45.14 (C13), 37.17 (C17), 35.99 (C6), 33.80 (C3), 30.70 (21), 30.27 (C14), 22.48 (C16), 22.47 (C15). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 330.1504 found 330.1497. **ATR-FTIR** (cm^{-1}): 3007, 2989, 2955, 1686, 1639, 1507, 1464, 1398, 1354, 1276, 1261, 1135, 968, 908, 764, 751, 727, 629, 558, 540.

S-(3-(dimethylamino)-2-(6-methoxynaphthalen-2-yl)-3-oxopropyl) ethanethioate (**3.276**)

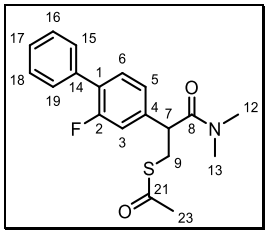


Synthesized following the general procedure **L.**

Isolated yield: 60 mg, 91%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H, C10/C13), 7.66 (s, 1H, C17), 7.42 (dd, *J* = 8.4, 1.8 Hz, 1H, C16), 7.15 (dd, *J* = 8.9, 2.5 Hz, 1H, C9), 7.11 (d, *J* = 2.5 Hz, 1H, C14), 4.10 (dd, *J* = 9.4, 5.2 Hz, 1H, C1), 3.91 (s, 3H, C18), 3.42 (dd, *J* = 13.4, 9.4 Hz, 1H, C3), 3.34 (dd, *J* = 13.4, 5.2 Hz, 1H, C3), 2.98 (s, 3H, C6), 2.84 (s, 3H, C7), 2.33 (s, 3H, C22). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.84 (C20), 171.68

(C2), 157.97 (C15), 133.99 (C11), 133.49 (C8), 129.45 (C17), 129.10 (C12), 127.78 (C10), 126.58 (C9), 126.47 (C13), 119.33 (C16), 105.72 (C14), 55.46 (C18), 49.58 (C1), 37.23 (C6), 36.04 (C7), 33.84 (C3), 30.76 (C22). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 354.1140 found 354.1134. **ATR-FTIR** (cm^{-1}): 2938, 1683, 1636, 1604, 1503, 1483, 1461, 1392, 1352, 1264, 1231, 1213, 1172, 1134, 1053, 1029, 962, 926, 894, 853, 813, 764, 732, 701, 671, 628, 575, 525.

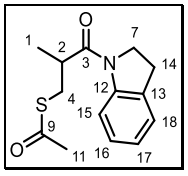
S-(3-(dimethylamino)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)-3-oxopropyl) ethanethioate (**3.274**)



Synthesized following the general procedure **L.**

Isolated yield: 51 mg, 74%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H, Ar), 7.46 – 7.39 (m, 3H ,Ar), 7.38 – 7.35 (m, 1H, Ar), 7.16 (ddd, *J* = 12.9, 9.6, 1.7 Hz, 2H, Ar), 4.03 (dd, *J* = 9.3, 5.3 Hz, 1H, C7), 3.40 (dd, *J* = 13.4, 9.3 Hz, 1H, C9), 3.30 (dd, *J* = 13.4, 5.3 Hz, 1H, C9), 3.00 (s, 3H, C12), 2.91 (s, 3H, C13), 2.34 (s, 3H, C23). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.70 (C21), 171.04 (C8), 160.00 (d, *J* = 249 Hz, C2), 139.65 (d, *J* = 8 Hz, C4), 135.41 (C14), 131.35 (d, *J* = 4 Hz, C6), 129.08 (C18/C16), 128.62 (C17), 128.46 (d, *J* = 14 Hz, C1), 127.93 (C15/19), 124.08 (d, *J* = 3 Hz, C5), 115.72 (d, *J* = 24 Hz, C3), 48.88 (C7), 37.32 (C13), 36.15 (C12), 33.68 (C9), 30.79 (C23). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 368.1096 found 368.1081. **ATR-FTIR** (cm^{-1}): 2935, 1687, 1643, 1581, 1562, 1483, 1451, 1416, 1397, 1354, 1319, 1264, 1232, 1131, 1077, 1051, 1011, 959, 910, 881, 837, 765, 750, 725, 698, 625.

S-(3-(indolin-1-yl)-2-methyl-3-oxopropyl) ethanethioate (**3.213**)



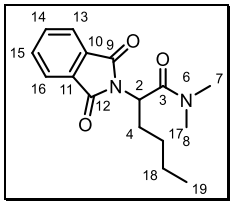
Synthesized following the general procedure **L** in absence of the base (Et_3N).

Isolated yield: 40 mg, 76%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H, C16), 7.19 (t, *J* = 8.0 Hz, 2H, C15/C17), 7.02 (t, *J* = 7.4 Hz, 1H, C18), 4.20 (td, *J* = 10.0, 7.1 Hz, 1H, C7), 4.05 (td, *J* = 10.0, 7.1 Hz, 1H, C7), 3.27 – 3.15 (m, 3H,C2/C14), 3.00 (dd, *J* = 13.5, 6.5 Hz, 1H, C4), 2.99 – 2.90 (m, 1H, C4), 2.33 (s, 3H, C11), 1.29 (d, *J* = 6.8 Hz, 3H, C1). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.43 (C8), 173.09 (C3), 143.04 (C12), 131.49 (C13), 127.67 (C16), 124.66 (C18), 124.01 (C17), 117.53 (C15), 48.11 (C7), 39.63 (C2), 32.78 (C4), 30.77 (C11), 28.14 (C14), 17.25 (C1). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 286.0878 found 286.0883. **ATR-FTIR** (cm^{-1}): 2970, 1688, 1651, 1598, 1481, 1461, 1411, 1372, 1338, 1313, 1283, 1136, 1103, 1025, 957.

3.6.3. 7-membered ring formation

3.6.3.1. *Starting material*

2-(1,3-dioxoisoindolin-2-yl)-*N,N*-dimethylhexanamide (**3.348**)

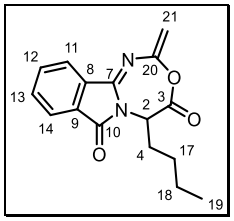


Synthesized following the general procedure **L.**

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.91 – 7.76 (m, 2H, C13/C16), 7.76 – 7.69 (m, 2H, C14/ C15), 5.02 (dd, *J* = 10.6, 4.8 Hz, 1H, C2), 3.00 (s, 3H, C7), 2.95 (s, 3H, C8), 2.52 – 2.43 (m, 1H, C4), 2.07 – 1.97 (m, 1H, C4), 1.42 – 1.21 (m, 4H, C17/C18), 0.87 (t, *J* = 6.8 Hz, 3H, C19). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 169.04 (C3), 168.21 (C9/C12), 134.21 (C14/C15), 131.83 (C10/C11), 123.56 (C13/C16), 52.02 (C2), 37.17 (C7), 36.29 (C8), 28.82 (C4), 28.48 (C17), 22.33 (C18), 14.04 (C19). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 311.3368 found 311.3360. **ATR-FTIR** (cm^{-1}): 2956, 2930, 2860, 1777, 1709, 1654, 1612, 1495, 1467, 1381, 1358, 1336, 1288, 1261, 1191, 1171, 1129, 1111, 1070, 951, 882, 791, 718, 698, 622.

3.6.3.2. *Products*

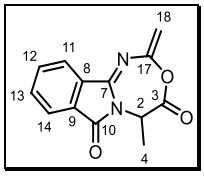
5-butyl-2-methylene-[1,3,5]oxadiazepino[4,5-*a*]isoindole-4,7(2*H*,5*H*)-dione (**3.349**)



Synthesized following the general procedure **M.**

Isolated yield: 28 mg, 50%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.97 – 7.93 (m, 1H, C11), 7.90 – 7.87 (m, 1H, C14), 7.76 – 7.72 (m, 1H, C12), 7.72 – 7.68 (m, 1H, C13), 5.21 (dd, *J* = 8.7, 8.2 Hz, 1H, C2), 4.88 (d, *J* = 1.6 Hz, 1H, C21), 4.83 (d, *J* = 1.6 Hz, 1H, C21), 2.12 – 1.98 (m, 1H, C4), 1.95 – 1.83 (m, 1H, C4), 1.40 – 1.32 (m, 4H, C17/C18), 0.89 – 0.85 (m,3H, C19). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.11 (C10), 164.46 (C3), 150.14 (C20), 147.95 (C7), 134.75 (C9), 134.22 (C12), 133.09 (C13), 129.63 (C8), 124.20 (C14), 122.85 (C11), 97.08 (C21), 56.39 (C2), 32.43 (C4), 27.64 (C17), 22.08 (C18), 13.79 (C19). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 307.1059 found 307.1054. **ATR-FTIR** (cm^{-1}): 2924, 2854, 1742, 1716, 1658, 1469, 1389, 1357, 1295, 1227, 1175, 1142, 1062, 1017, 1006, 978, 930, 917, 895, 881, 848, 778, 704, 653, 633.

5-methyl-2-methylene-[1,3,5]oxadiazepino[4,5-*a*]isoindole-4,7(2*H*,5*H*)-dione (**3.311**)



Synthesized following the general procedure **M.**

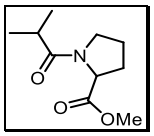
Isolated yield: 23 mg, 48%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 – 7.86 (m, 1H, C11), 7.81 (dd, *J* =6.4, 1.0 Hz, 1H, C14), 7.72 – 7.60 (m, 2H, C12/C13), 5.30 (q, *J* = 7.4Hz, 1H, C2), 4.81 (d, *J* = 1.5 Hz, 2H, C18), 1.62 (d, *J* = 7.4 Hz, 3H, C4). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 165.69 (C10), 164.77 (C3), 150.03 (C17), 147.73 (C7), 134.65 (C9), 134.09 (C12), 132.95 (C13), 129.60 (C8), 123.99 (C14), 122.72 (C11), 97.15 (C21), 51.73 (C2), 18.51 (C4). HRMS (ESI): m/z Calculated for $[M+H]^+$: 243.0770; found 243.0761. ATR-FTIR (cm^{-1}): 2924, 2853,

1768, 1742, 1657, 1626, 1611, 1471, 1452, 1388, 1353, 1293, 1264, 1227, 1174, 1141, 1062, 1017, 1006, 977, 932, 917, 895, 854, 797, 778, 730, 703, 674, 655, 610.

3.6.4. Oxazolium salt

3.6.4.1. *Starting material*

Methyl isobutyrylprolinate (**3.286**)

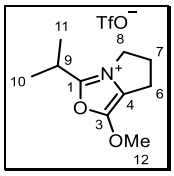


Synthesized following the general procedure **N**.

Isolated yield: 998 mg, >95%. Spectroscopic properties match with the literature.[661]

3.6.4.2. *Products*

3-isopropyl-1-methoxy-6,7-dihydro-5H-pyrrolo[1,2-c]oxazol-4-ium trifluoromethanesulfonate (**3.289**)



Synthesized following the general procedure **O.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.41 (t, *J* = 7.4 Hz, 2H, C8), 4.12 (s, 3H, C12), 3.41 (hept, *J* = 7.0 Hz, 1H, C9), 3.09 – 2.96 (m, 2H, C6), 2.85 – 2.74 (m, 2H, C7), 1.46 (d, *J* = 7.0 Hz, 6H, C10/C11). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.55 (C3), 152.45 (C1), 114.31 (C4), 61.98 (C8), 47.99 (C6), 28.92 (C7), 28.01 (C9), 20.92 (C10), 18.77 (C11). **HRMS** (ESI) m/z calculated for $[M\text{-}OTf]^+$ 182.1177 found 182.1176. **ATR-FTIR** (cm^{-1}): 2984, 1704, 1613, 1453, 1359, 1252, 1225, 1152, 1084, 1030, 913, 830, 757, 716, 636.

CHAPTER IV

Iodine(III) mediated carbocationic rearrangements

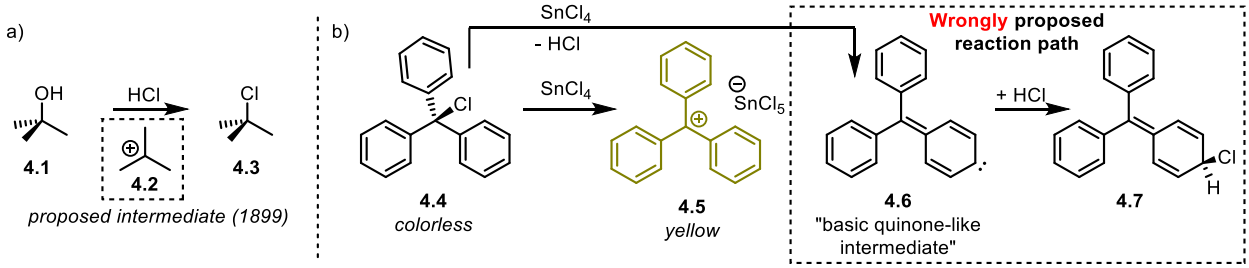
The results of this work are partially published in *Angew. Chem. Int. Ed* **2019**, *58*, 9816 – 9816.[662] This work has been realized in collaboration with Dr. J. Li and G. Di Mauro (M.Sc.).

4.1. Introduction

4.1.1. Carbocations

4.1.1.1. *History of early proposed cations*

THE NATURE OF POSITIVELY CHARGED carbon atoms has fascinated chemists since 1891, when Merling observed the first isolated carbocation (tropylium bromide). However, he was not able to elucidate the structure of this unusual compound.[663] 8 years later, at the end of the 19th century, Julius Stieglitz proposed the intermediacy of a trivalent, positively charged carbon atom in organic reactions (*Scheme 4.1a*):[664] he explained the transformation of *tert*-butanol into *tert*-butylchloride in the presence of HCl with the formation of a carbocationic *tert*-butylium ion (**4.2**). The publication which contained this revolutionary assumption unfortunately did not gain the deserved attention.



Scheme 4.1 – a) First mentioning of a carbocation. Here as a reaction intermediate. b) Observation of the triphenylmethylcation in the early 20th century.

Only two years later, several chemists were confronted with the unexpected behavior of triphenylmethanol and triphenylmethylhalides in the presence of Lewis or Brønsted acids (*Scheme 4.1b*).[665,666] They observed that these colorless compounds were transformed into a yellow dye, which was quite reactive but relatively stable. Trapped by the paradigms of that time, they had difficulties to describe the structure of what they called "a double compound". They proposed the formation of a carbene by loss of HCl (**4.6**), which would react with the formed hydrogenchloride to form the adduct **4.7**. This hypothesis was disproven shortly after by Baeyer and Villiger,[667] who recognized that the observed color was caused by the formation of a salt. This was described as "halochromy" *i.e.* formation of color by

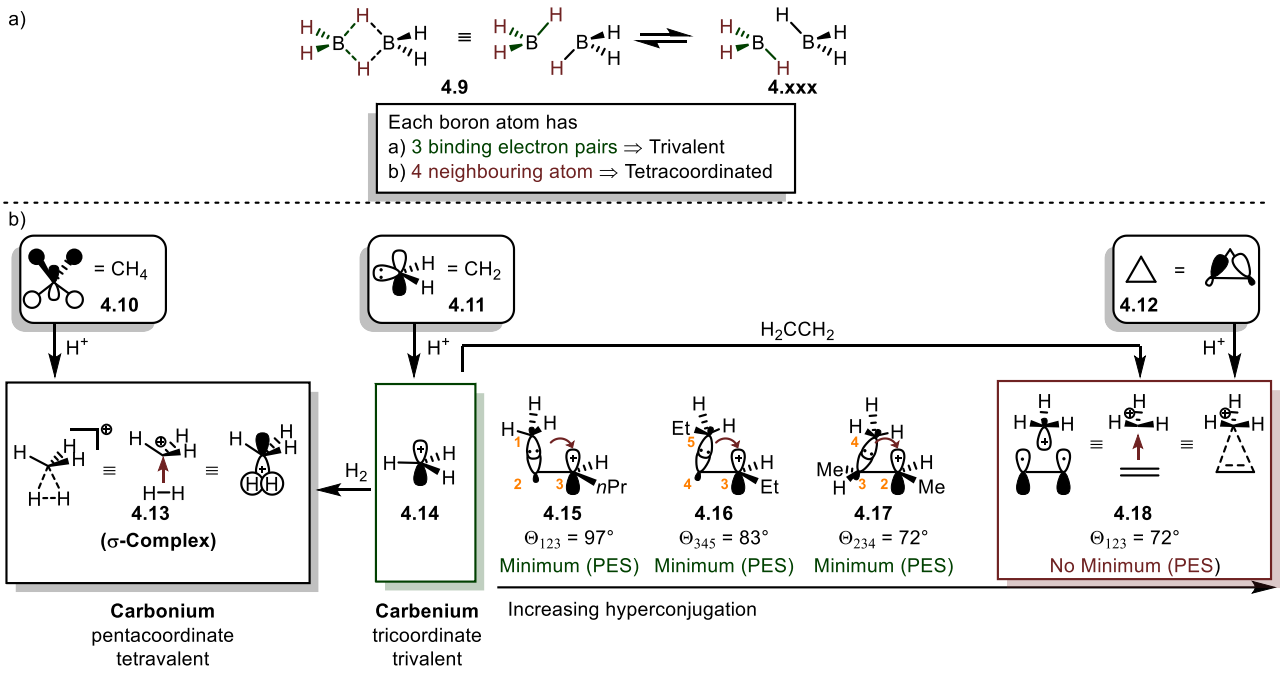
generation of a salt (ἅλς (háls) ancient Greek for "salt" and *χρῶμα* (khrôma) ancient Greek for "color"). In the same year, Walden undertook a study on the electric conductivity of these salts and their precursors. He concluded that an ion-pair with a positively charged cation $(Ph_3C)^+$ must have been formed.[668] Gomberg came to the same conclusion a few weeks earlier.[669] In 1922 Meerwein and van Emster readopted the idea of carbocationic intermediates in chemical reactions, interestingly with one of the most controversial carbocationic systems as we shall see in chapter 4.1.1.3.[670,671]

4.1.1.2. *Definitions and general aspects of carbocations*

The description of bonding in carbocations is not consistent in the literature probably because IUPAC does not offer a clear definition. However, the term "carbocation" was officially recognized to represent all cations with an excess of positive charge on a carbon atom.[672] In the course of the discussion, we will use the nomenclature coined by Olah.[673,674] Valence has been defined as the number of bonding electron-pairs used by an atom. This has to be strictly divided from the number of neighboring atoms, which has been named coordination number. As an illustrative example, we can take diborane (B_2H_6 – *Scheme 4.2a*). Each boron atom has 3 bonding electron-pairs and is thus trivalent. However, it is surrounded by 4 hydrogen atoms and has therefore a coordination number of 4.

By using these definitions, carbocations can be divided in two categories: carbenium ions and carbonium ions. A carbenium ion is trivalent, tricoordinated and typically sp^2 hybridized. The descriptor "carbenium" follows the common nomenclature because the parent ion CH_3^+ (**4.14** - *Scheme 4.2b*) can be considered a protonated singlet carbene. Carbonium ions on the other hand, are tetravalent, hypercoordinated species, which can be only described by multicenter-2-electron bonds in valence-bond theory (in MO theory almost every bond is a multicenter bond). This category includes the so-called "*non-classical*-carbocations" and the ion CH_5^+ (**4.13**) may be regarded as the parent of this class. Spectral[675] and computational[676] data suggest that the structure of this highly fluctuating ion is a CH_3-tripod with a

3-center-2-electron bond to H_2. Thus, the structure of CH_5^+ has been compared to metal σ-H_2-complexes,[677] where CH_3^+ plays the role of the metal.[678,679]



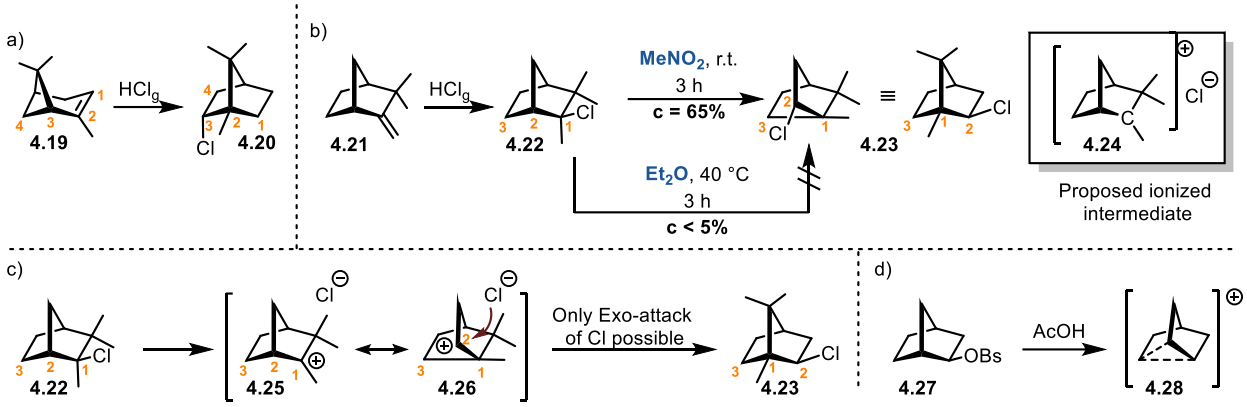
Scheme 4.2 – a) Diborane as an example for describing the definition of valency and coordination number by Olah. b) Carbenium and carbonium ions as extremes in a continuum of the same phenomenon.

Similar to other concepts, these two classes are just the extreme cases in a continuum (*Scheme 4.2b – right)*. If we consider the conformer **4.15** of the hexane-3-ylium cation in the gas-phase (a minimum on the potential energy surface (PES)) for instance, calculations show that the C^1-C^2-C^3 angle is only 97° (more than 10° off the ideal tetrahedral angle).[680] This distortion is due to a significant electron-donation of the C^1-C^2 σ-orbital into the empty p-orbital of the carbon atom (hyperconjugation), which is also responsible for a shortening of the C^2-C^3 bond. *N.B.* that this interaction can already be described as a 3-center-2-electron bond. A slightly more stable conformer (-2.4 kcal/mol with respect to **4.15**) of the same carbocation has a bond angle of just 83° (**4.16**), illustrating that hyperconjugation is a dynamic process. Other compounds such as 3-methylbutan-2-ylium (**4.17**) have been calculated to prefer even narrower arrangements (72°).[681] In this conformation the distances of C^2-C^4 (1.851 Å) and C^3-C^4 (1.722 Å) are comparable so that atom C^4 can be described as hypercoordinate (while it is still a tetravalent atom).

However, there is no defined borderline for the label “hypercoordinate”. Indeed hyperconjugation and hypercoordination can be often regarded to be different points in a continuum of the same phenomenon. In an extreme scenario, the electrons are equally shared between the three atoms involved (**4.18** – *Scheme 4.2b*). The bonding situation can be then interpreted as an olefin coordinated to a carbenium ion (similar to the σ-complex **4.13**) or as a corner-protonated cyclopropane. These symmetrical structures have however been calculated to be generally not located on minima along the PES, with some interesting exceptions (see next subchapter).[682] Caution must be taken when calculating such arrangements, since some functionals in DFT (*e.g.* MP2) appear to overestimate the stability of bridged structures.[683]

4.1.1.3. *The 2-norbornyl cation*

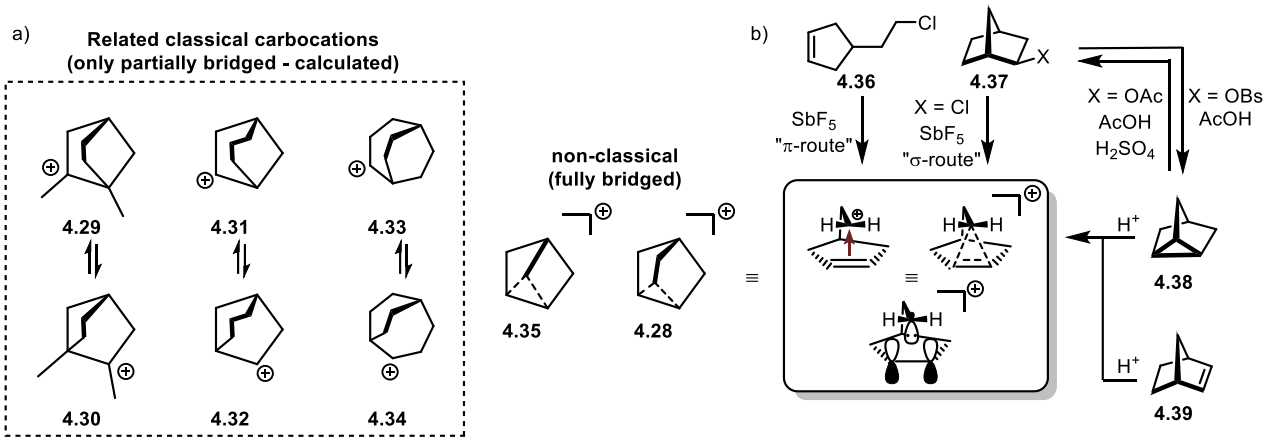
In 1899 Wagner and Brickner reported that α-pinene **4.19** rearranges to bornyl chloride **4.20** when treated with gaseous HCl (*Scheme 4.3a*).[684] These pioneers of carbocation chemistry were puzzled by this rearrangement and struggeled to propose a reasonable mechanism. In 1914 Meerwein, intrigued by the aforementioned results, started to investigate similar systems[685] and in 1922 van Emster and him observed that camphene hydrochloride **4.22** rearranged easily to isobornyl chloride **4.23** (*Scheme 4.3b*).[670,671] The rearrangement was not only promoted by acid or by heat, but even by standing in certain solvents. The authors recognized that the rate of this reaction was highly dependent on the solvents’s relative permittivity: in nitromethane conversion was 65% after 3 hours at room temperature, while in the same time the reaction proceeded only to less than 5% at 40 °C in diethylether. The authors concluded that this monomolecular reaction had to proceed *via* an ionic dissociation of the chloride atom and proposed a cationic intermediate (**4.24**). This study has often been considered the foundation of modern carbocation chemistry.[686] Moreover, it was also the basis for a long controversy in organic chemistry.[687]



Scheme 4.3 – a) Wagner's and Bricker's first observation of a skeletal rearrangement promoted by an acid. b) Meerwein's and van Emster's observation on the fast isomerization of camphene hydrochloride in polar solvents, with a proposed ionized intermediate. c) Wilson et al. proposed the non-classical cation for the first time by describing it in two mesomeric limiting structures. d) Winstein's proposed structure of the 2-norbornyl cation with dotted lines.

Wilson and coworkers agreed on the cationic nature of the intermediate and were the first to propose a mesomerism (not an equilibrium!) between the norbornyl and the camphenyl cation (*Scheme 4.3c* – **4.25**/**4.26**).[687,688] They used this model to explain the kinetics of the reaction and its unpredicted stereochemical outcome (namely that only the *exo*-isomer was formed). Winstein picked up the interpretation of Wilson, and continued the investigations. He was the first to propose a delocalized,three-membered ring structure **4.28** for the 2-norbornyl cation, which is just another way of drawing Wilson's mesomerism (*Scheme 4.3d*).[689] This cation was named "non-classical" in 1951 by Roberts and Lee,[690] a term which earned much criticism because it was considered a trendy word, with little scientific value.[687] Moreover, many scientists were not convinced of the existence of such intermediates, with the Nobel laureate H. C. Brown as the main front-runner. Between the late 1970's and the early 1980's the spectroscopical data (mostly provided by Olah and coworkers) led to the conclusion that the non-classical structure is the better descriptor for the 2-norbornyl cation.[686,691] Interestingly, H. C. Brown was not convinced by the evidence but questioned the results.[692] The "seal" of this controversy has been finally published in 2013, when Krossing, Meyer and Coworkers were able to measure the X-ray structure of a 2-norbornyl cation.[106] The structure was almost C_s-symmetric in the solid state and resembles the extreme case in *Scheme 4.2* (**4.18**), with the full delocalization of two electrons on 3 centers. There are apparently three structural features which enable the non-classical nature: 1) The rigidity of the cyclopentyl-base, 2)

the short bridge (*cf.* **4.31** *versus* **4.29**) and 3) the 1,2,3-trisubstitution on the same side of the "protonated cyclopropane" face (*cf.* **4.30** - *Scheme 4.4a*).[682,693] Indeed, small variations on these structural features (*e.g.* by extending the methylene bridge by another CH_2 - **4.31**) result in the loss of the non-classical nature of the cation. Shortening of the bridge on the other hand seems not to disfavor the non-classical geometry (**4.35**).[694,695] Apparently the non-classical nature is not restricted to carbocations: also norbornyl cations with bridgehead atoms (XH_2^+) of the heavier elements of group 14 (Si, Ge, Sn, Pb) were observed to be non-classical.[696]



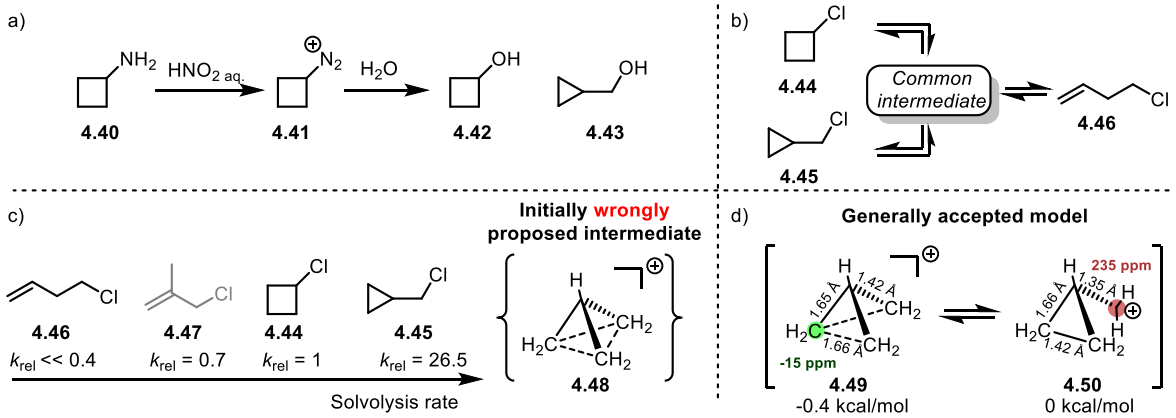
Scheme 4.4 – a) Classical and non-classical structures in derivatives of the 2-norbornyl cation. b) Different routes to the 2-norbornyl cation and interconversion of precursors via the cationic intermediate.

As discussed previously the binding situation of the symmetrically bridged non-classical cation can be described in many ways (*Scheme 4.2.*). This is not only a matter of representation, because it implies that the same carbocation can be accessed by various reaction routes (*Scheme 4.4b*). The 2-norbornyl cation can be indeed prepared not only by treatment of 2-norbornyl chloride **4.37** with a Lewis acid (the so-called "σ-route"), but also by protonation of the nortricyclene (**4.38**) or norbornene (**4.39**). In addition, dehalogenation of the primary chloride **4.36** leads to the formation of the same cation (the so-called "π-route").[691] Interestingly, the 2-norbornyl cation could also be generated from other chloro-norbornane regioisomers (1- & 7-) probably *via* a cascade of rearrangements.[697] The interconversion of the different precursors *via* the non-classical cation intermediate is a consequence of this interesting pattern of reactivity. 2-Norbornyl brosylate for instance converts to the nortricyclene derivative when treated with

acetic acid (*Scheme 4.4b*).[698] Similar reactions have been pioneered already in the 1950's.[699–701] The retro-reaction (*i.e.* the protonation of a nortricyclene with acetic acid to form 2-bornyl acetate), has been known since 1907[702] although the structures of the molecules in this transformation were elucidated more than 20 years later.[703]

4.1.1.4. *The cyclopropylcarbinyl cation ($C_4H_7^+$)*

The Demjanov rearrangement is widely known for its ability to enlarge cycloalkane rings by a methylene group.[3] However, in 1907 Demjanov noticed that under the typical reaction conditions cyclobutylamine reacted to cyclobutanol and cyclopropyl carbinol, revealing the unusual reactivity of cyclobutanols in acidic media (*Scheme 4.5a*).[704]



Scheme 4.5 – a) Ring contraction observed in the early 20th century. b) Observed isomerization of cyclobutyl chloride and cyclopropylcarbinylchloride. c) Solvolysis rate with firstly proposed common intermediate (except for the allyl chloride). d) Generally accepted model for the $C_4H_7^+$ cation. Bond length's and relative energies calculated by Olah et al., ^{13}C NMR shifts measured in the solid state by Mhyre and Webb.

More than 40 years later Mazur and Roberts observed that cyclobutyl chloride (**4.44**) and cyclopropylcarbinyl chloride (**4.45**) isomerize both to homoallyl chloride (**4.46**) and recognized the facile interconversion of the compounds (*Scheme 4.5b*).[705–707] In addition, they noticed that the reactivity of cyclopropylcarbinyl halides in solvolysis reactions was higher than analogously constituted allyl halides and concluded that the positive charge in cyclopropylcarbinyl cations must be highly stabilized (*Scheme 4.5c*). Indeed, the positive charge adjacent to a cyclopropyl has been later shown to be usually better stabilized than by a non-fused phenyl ring (the aromatic ring often requires a sterically unfavorable

conformation for an efficient stabilization).[708,709] Shortly after their discovery they proposed a C_{3v} symmetric cationic intermediate with a 3-center-2-electron bond (**4.48**).[710] However, carbocation formation from a ^{14}C-labeled cyclopropyl carbamine showed an unequal share of the ^{14}C-labeled cyclobutanol after aqueous quenching, suggesting that there is no such intermediate.[711] Moreover, the C_{3v} symmetry would cause the molecule to be a triplet in its ground state, and thus it is expected to be distorted due to a Jahn-Teller effect in the corresponding singlet state.[712,713] The current consensus on the structure of the cyclopropyl carbinyl cation is a very fast and shallow equilibrium between a non-classical bicyclobutonium **4.49** and a classical bisected cyclopropylcarbinyl cation **4.50** with a very low lying isomerization barrier.[714] This equilibrium has been observed to operate very quickly ($\leq 10^{-10}$ s) in the gas phase at 300 K[715] and the calculated NMR spectra of the two species (**4.49** and **4.50**) matched the results of the experimental measurement.[714,716] Calculations show that the non-classical structure **4.49** is 0.4 kcal/mol more stable than the classical isomer **4.50**.[716] The ^{13}C NMR spectrum (solid state) of the fluctuating $C_4H_7^+$ cation is worthy of mention, especially the incredible difference in shifts of the two isomeric forms. While the classical cation has a chemical shift of almost 235 ppm (calculated 227 ppm) on the carbenium atom, the pentacoordinated carbon in the non-classical structure **4.49** has a negative shift (-15 ppm, calculated -14 ppm).[717,718] This model was also supported by IR data.[715,719]

There is a relatively simple molecular-orbital picture for the structure and the fast equilibrium between the two species. The molecular orbitals of cyclopropane can be simply constructed by the combination of the MOs of three methylene molecules (*Figure 4.1*a – Walsh orbitals – see *Figure 2.1a* for the construction of the MOs of methylene).[103,190,720]

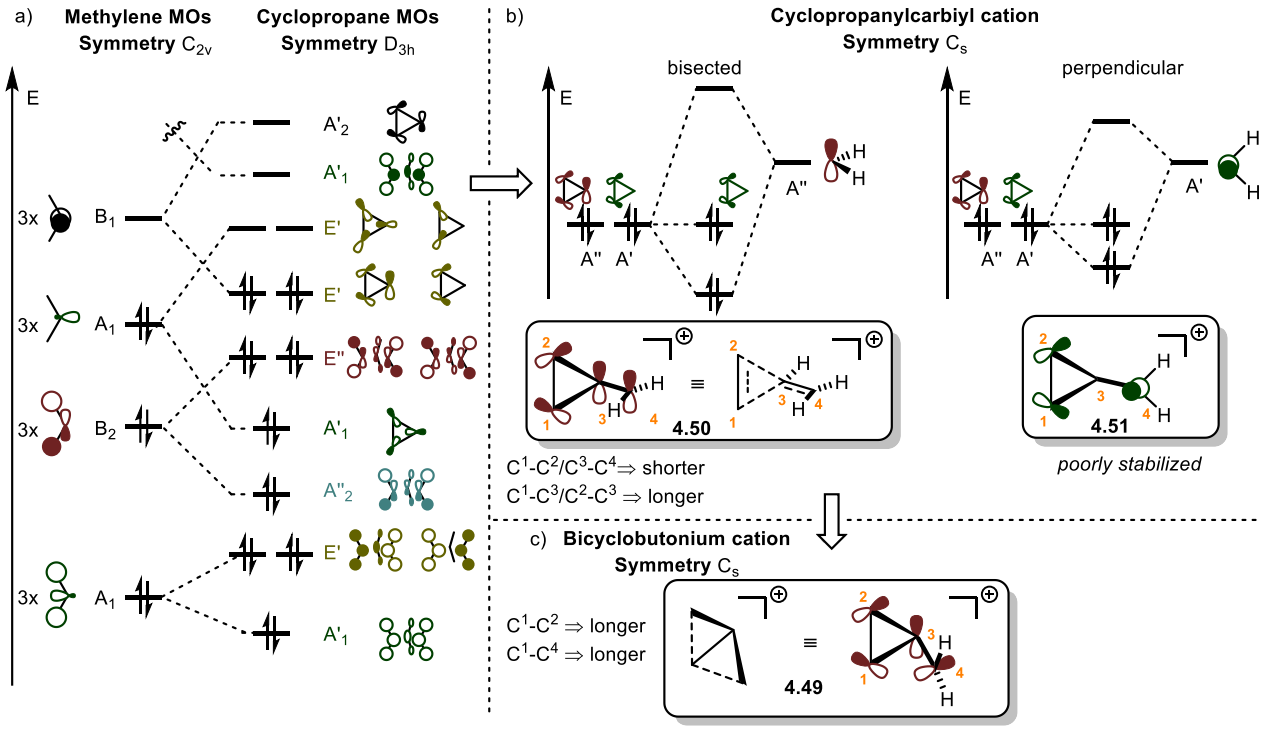
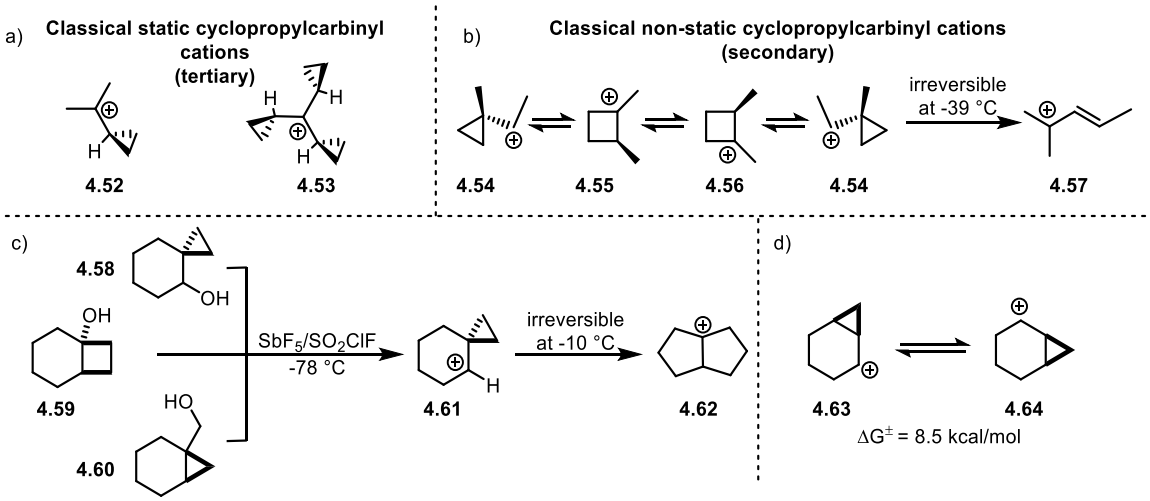


Figure 4.1 – a) Combination of 3 methylene MOs to construct the MOs of cyclopropane. b) Interaction of a cyclopropyl moiety with a CH_2^+ substituent. c) The relationship of the cyclopropylcarbinyl cation and the bicyclobutonium cation.

The two degenerate HOMOs of cyclopropane share E' symmetry in the D_{3h} point group. However, if the system is pertubated by a single CH_2^+ substituent, the molecule becomes C_s-symmetric. In this case the aforementioned orbitals do not share the same symmetry and thus lose their degeneracy.[190] If we now consider two conformers of the cyclopropylcarbinyl cation, one in which the CH_2^+ substituent "bisects" the cyclopropane (**4.50**) and the other conformer with a perpendicular substituent (**4.51**), we will observe two different interactions. In the former case, the empty p orbital has A'' symmetry (antisymmetric to the mirror plane of the molecule) and can therefore only interact with the HOMO of the cyclopropyl moiety, which shares the same symmetry. The overlap of the two fragments is quite effective, so that there is a large stabilization energy. Consequently, the C^3-C^4 bond shortens because the hyperconjugation endours it with double bond character (see also *Scheme 4.2*). Moreover, the C^1-C^2 bond shortens as well because the antibonding lobes of the two atoms are less populated with electron density. In contrast, the C^2-C^3/ C^1-C^3 distances increase because they lose electron density for the bonding interaction. The "perpendicular" CH_2^+, on the other hand, can only interact with the symmetric (A') HOMO.

The interaction is weak and indeed this conformation is usually not observed.[190,721] As discussed in section 4.1.1.2., hyperconjugation is just one part of a continuum: the overlap of the cyclopropanyl HOMO and the empty p-orbital can be indeed maximized when the CH_2^+ moiety flips in between C^3 and C^2. This heavy distortion of the molecular geometry will eventually yield the bicyclobutonium cation which also has C_s-symmetry.[716]

It is important to note that, unlike the $C_4H_7^+$ cation, tertiary cyclopropyl carbinyl cations are rather static in the classical bisected conformer (*Scheme 4.6a*).[674] Most secondary cyclopropylcarbinyl cations, on the other hand, participate in fast degenerate equilibria without the formation of non-classical intermediates at temperatures >-100 °C (*Scheme 4.6b*).[722,723] However, some cyclic secondary cations are more static. **4.61** for instance is not in equilibrium with other isomers at temperatures <-10 °C.[724] However, other cyclic cyclopropylcarbinyl cations may undergo fluctuating equilibria (*Scheme 4.6d*).

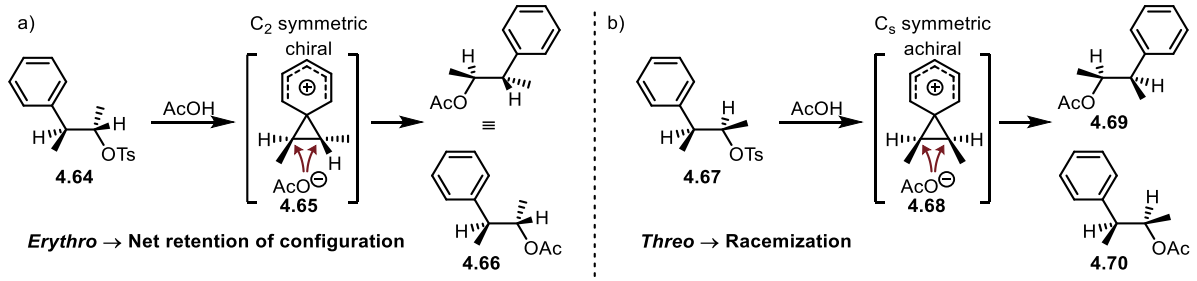


Scheme 4.6 – a) Tertiary cyclopropylcarbinyl cations are not in equilibrium with other forms. b) Secondary cyclopropylcarbinyl cations rearrange fast (often irreversibly). The data suggests that there is not a non-classical carbocations in this rearrangement. c) Static cyclic secondary cyclopropyl carbinyl cation. d) Non-static secondary cyclic cyclopropyl carbinyl cation.

4.1.1.5. *The spirocyclic phenonium cation*

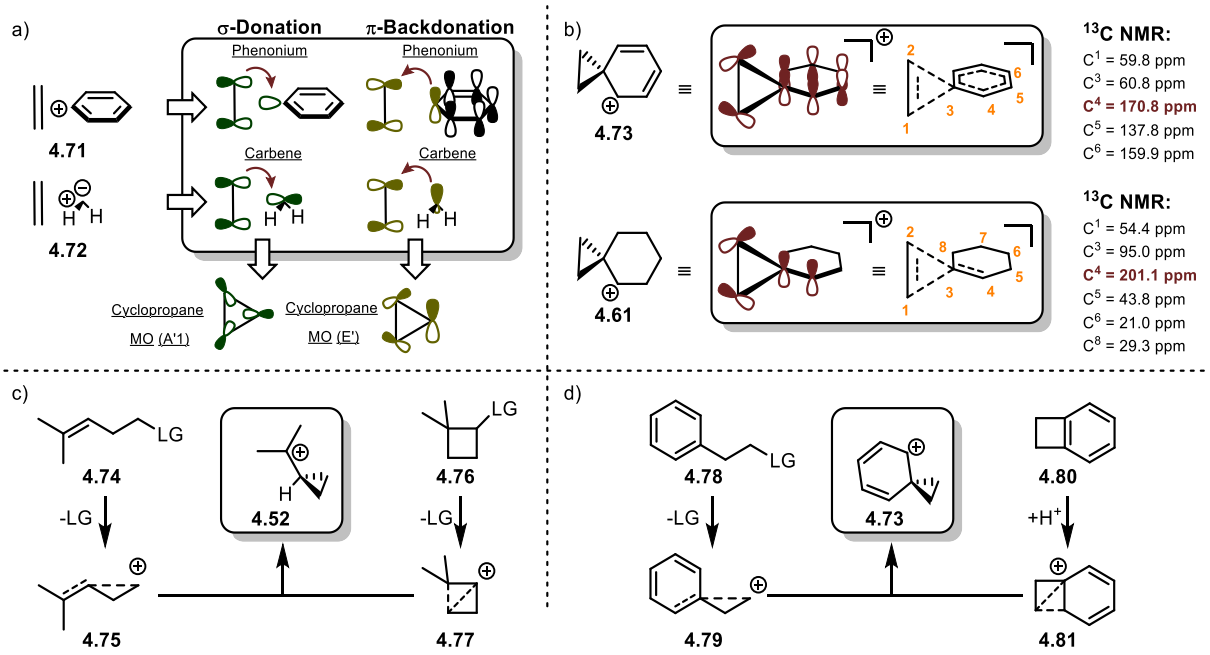
In 1927 Freundenberg studied cationic 1,2-phenyl migrations and proposed a spirocyclic intermediate, where he used molecular orbitals to describe a 3-center-2-electron bond of this intermediate.[725] Later, Cram re-proposed the spirocyclic phenonium intermediate in a series of articles:[726–728] When the *erythro*

3-phenyl-2-butyl tosylate **4.64** was solvolyzed in acetic acid the enantiopure acetate was formed mostly with retention of configuration (*Scheme 4.7a*). The *threo* isomer **4.67** on the other hand gave the *threo* acetate as a racemate. This unusual result was explained as the following: the racemization in the *threo* tosylate is due to the formation of an achiral C_s-symmetric phenonium ion **4.68**. The *erythro* diastereoisomer on the other hand goes through a chiral C_2 intermediate **4.65**, where the stereogenic information is retained.[729,730]



Scheme 4.7- Solvolysis of a) erythro and b) threo 3-phenyl-2-butyl tosylate.

The chemical community consented early that the cation is of classical nature. It is most commonly described as a monosubstituted cyclopropyl carbinyl cation, where the positive charge is delocalized by the cyclopropyl and a diene in a cyclic array (like in *Scheme 4.7*).[731] The phenonium cation has been also described as a phenylcation coordinated to an alkene (**4.71** – *Scheme 4.8a*).[732,733] This interpretation has led to the generation of the phenonium ion by the intermolecular reaction of Ph^+ (in a triplet state) with alkenes and a nucleophile,[734–736] and can be explained by a Dewar-Chatt-Duncanson model (DCD - *Scheme 4.8a*): in a perpendicular arrangement of the two reaction partners (Ph^+ and C_2H_4), the empty σ-orbital of Ph^+ interacts with the HOMO of ethylene to form a σ-bond. This σ-donation can be also used to describe the interaction of singlet methylene and ethylene, which eventually leads to one of the bonding A'1 orbitals in cyclopropane (See also *Figure 4.1*). At the same time, the π-system of the aromatic ring donates electron density into the LUMO of ethane. Again, there is a corresponding interaction of the lone pair of singlet CH_2 with ethene. This interaction is equivalent to one of the HOMOs in cyclopropane.



Scheme 4.8 – a) DCD-model for the phenonium cation in comparison with the interaction of singlet methylene with ethylene. b) The phenonium ion in comparison with a tertiary bisected cyclopropane carbinyl cation. c/d) Comparison of the generation of a tertiary cyclopropane carbinyl cation and the spirocyclic phenonium ion.

The phenonium cation can also be considered a classical bisected cyclopropane carbinyl cation (like **4.50** in *Figure 4.1.*), benefiting from further stabilization by the adjacent diene (*Scheme 4.8b*). When compared to the analogous system with a cyclohexyl substituent, the ^{13}C NMR peaks of the two species show some similarities (*Scheme 4.8b*). However, C^4 and C^3 are much more deshielded in compound **4.61** because the positive charge is located mostly between those two atoms. **4.73** on the other hand, has the possibility of delocalizing the charge into the adjacent diene. As a consequence of these considerations, electron-poor arenes participate less in phenonium ion formation, as documented by the kinetic data in solvolysis studies.[737]

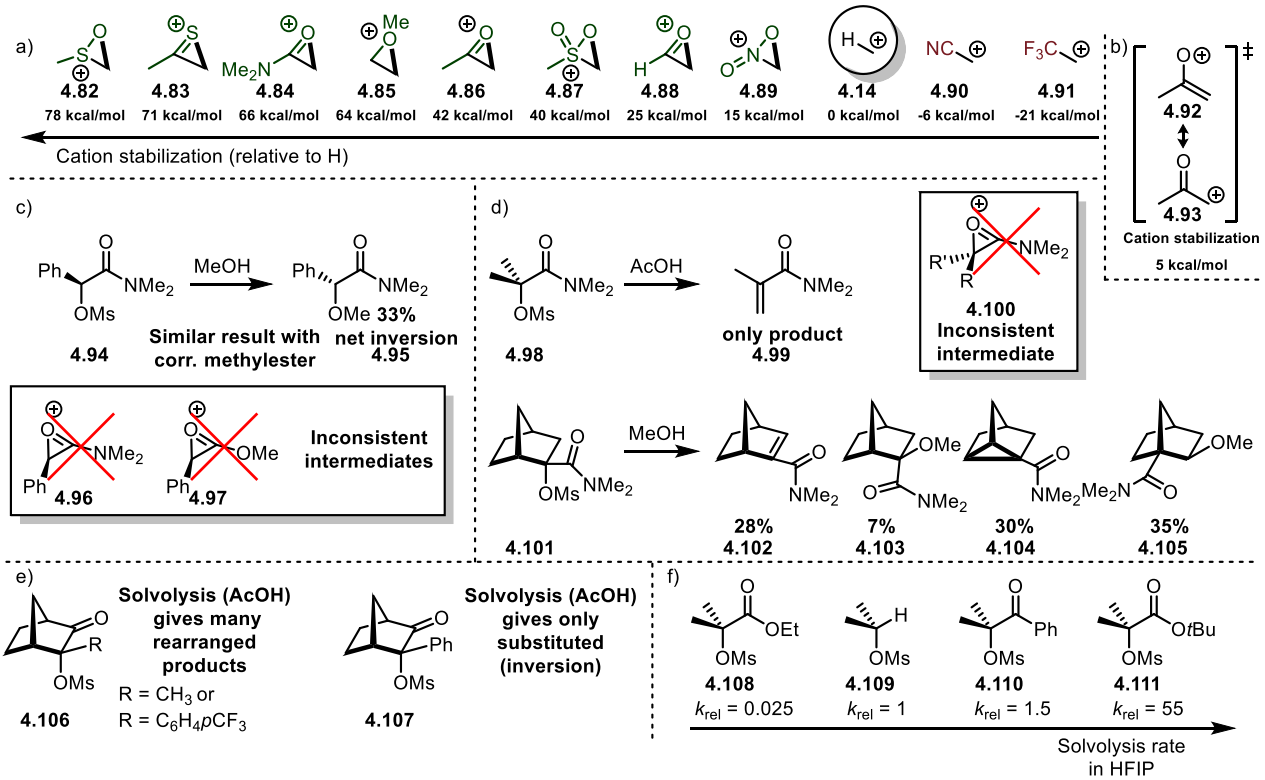
It is noteworthy to consider the close chemical relationship between the spirocyclic phenonium ion and the cyclopropylcarbinyl cations (*Scheme 4.8c/d*). By considering the orbitals in *Scheme 4.8b* and with regard to the previously discussed nature of cyclopropyl carbinyl cations, it is easy to deduce a rationale why the formation of **4.73** is preferred over its cyclobutyl isomer **4.81**.

4.1.1.6. *Carbocations in proximity to carbonyl groups*

Carbenium ions in α-position to a carbonyl group (and other electron-withdrawing groups) have long been considered particularly unstable. However, it has been shown that these cations cannot only be generated, but physico-chemical experiments and calculations demonstrated that they are less unstable than initially assumed.[582] Compounds which formed carbenium ions in α-position to an electron-withdrawing group showed higher reaction rates in solvolysis reactions than what was expected from the σ_p^+-values (which are based on the solvolysis of *para*-substituted cumyl chlorides).[582] Modern calculations showed that the reaction $CH_3^+ + H_3C\text{-EWG} \rightarrow CH_4 + (H_2C\text{-EWG})^+$ is exothermic in most of the cases (*Scheme 4.9a*) , showcasing that these substituents are more stabilizing than an hydrogen atom in these cases.[583] The stabilization is mostly a result of bridging by the electron-rich heteroatom (σ-donation). Two important exceptions are the cyano- (**4.90**) and the trifluoromethyl-group (**4.91**), which are both destabilizing the α-carbocation. The non-bridged cations were calculated to be transition states but even these energetically high-lying conformers, where bridging effects cannot operate, allow a subtle stabilizing effect probably owning to π-conjugation (*Scheme 4.9b*).

These results are, however, only valid for monosubstituted carbeniumions ($EWG\text{-}CH_2^+$). Substituents may have pronounced electronic and steric effects with dramatic consequences on the structure, the stability and the reactivity of these ions. Indeed, calculations from the late 1980's suggest that dimethyl- and phenyl- substituted carbenium ions are slightly destabilized by electron-withdrawing groups. Moreover, these structures were calculated to be more stable in open (not bridged) conformers because classical hyperconjugation outcompetes the bridging.[584] This is in accordance with experimental observations in the solvolysis of certain mesylates, which showed partial inversion of the stereocenter (*Scheme 4.9c*).[738,739] This contradicts the intermediacy of a bridged conformer (**4.96** and **4.97** (similar results were obtained with esters)), since a net retention of configuration would be expected in that case. Similarly, when the amide **4.98** was subjected to solvolysis in acetic acid only the product of an elimination

reaction was observed. The authors argue that if a bridged intermediate (**4.100**) would operate, mainly the α-acetylated amide had to be expected, because analogous bromonium and episulfonium ions evolve mainly by addition of the solvent with only traces of elimination.[739] In the same article, the norbornane derivative **4.101** was submitted to solvolysis and the outcome of the reaction was again not consistent with the bridged intermediate, since it would not react as a non-classical carbocation. The dramatic substituent effect is further showcased by the solvolysis reaction of **4.106** and **4.107** (*Scheme 4.9e*). While the methyl and *p*$CF_3C_6H_4$ groups in α-position to the ketone lead to the typical rearrangement of the cation, compound **4.107** underwent exclusively a nucleophilic substitution with the solvent, no rearranged products being observed.[740]



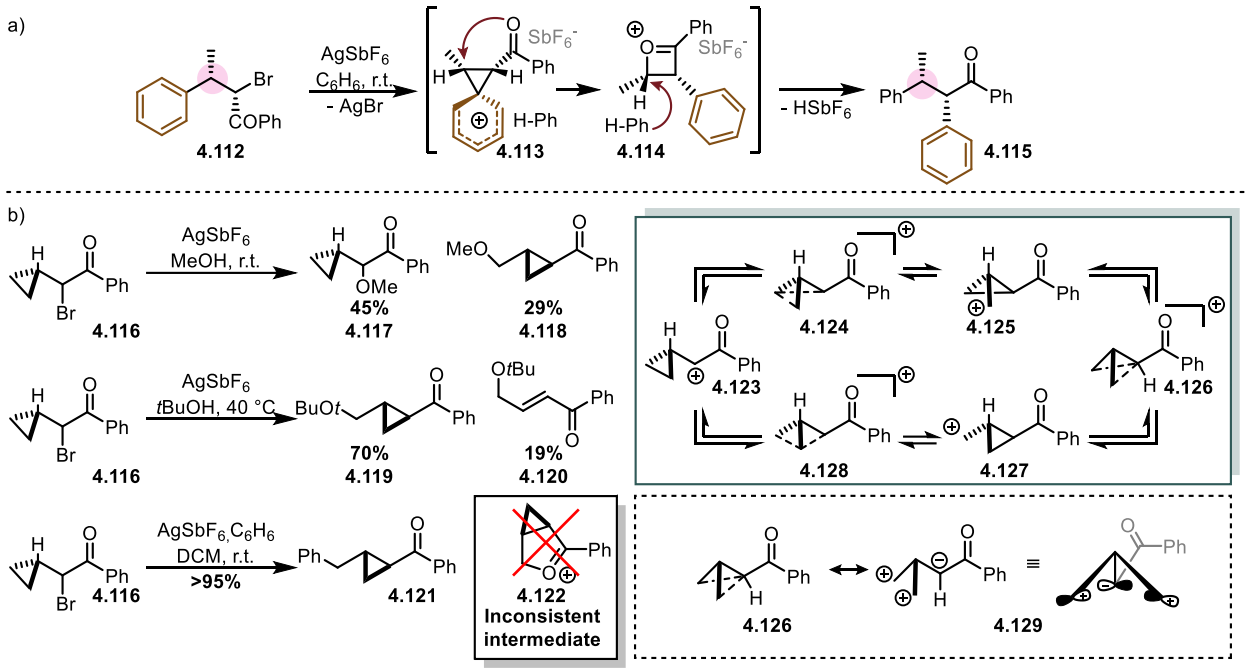
Scheme 4.9 – a) Stabilization energies of the CH_3^+ by EWG. b) π-Donation of the carbonyl group into the vacant carbenium ion. c/d) Solvolysis reactions inconsistent with a bridged intermediate. e) Effects of the substituent on the reactivity of a keto-α-carbenium ion. f) Steric effects on the solvolysis rates in HFIP of certain mesylates.

The rate of formation of carbocations *via* solvolysis is, moreover, greatly influenced by steric factors. In *Scheme 4.9f* the solvolysis rates of several mesylates are depicted. While the ethylester **4.108**

underwent solvolysis 40 times slower than isopropylmesylate (**4.109**), the solvolysis of the corresponding *t*butylester was more than 50 times faster (**4.111**). Strain-release effects of the congested tertiary mesylates were proposed to rationalize the enhanced reactivity.[741]

The carbonyl group may have a pronounced effect on carbocationic rearrangements. When the α-bromo ketone **4.112** (*Scheme 4.10*) was treated with a silver salt, the stereogenic center highlighted in red was retained (formally inverted according to the CIP-rules), upon nucleophilic attack. This is unexpected because a direct attack of the nucleophile on the phenonium ion (**4.113**) would lead to the C3-epimer of **4.115**. Carbonyl bridging might account for this observation (**4.114**), which is much more effective in 4- than in 3-membered rings.[742] Another, interesting effect was observed when the cyclopropane derivative **4.116** was dehalogenated (*Scheme 4.10b*).[743] In methanol, 45% of the expected substitution product **4.117** was observed. However, another cyclopropane (**4.118**) was formed in 29% yield exclusively as the *trans* isomer. With benzene as the nucleophile (and the cosolvent) the latter product was generated in quantitative yield. Bridging of the carbonyl group can be excluded (**4.122**), because such an intermediate would necessary lead to the *cis* product. Instead, the generated cation **4.123** can be written in an equilibrium consisting of three classical cyclopropyl carbinyl cations (**4.123**, **4.125**, **4.127**) and three non-classical bicyclobutonium ions (**4.124**, **4.126**, **4.128**) (the *pseudo-endo* conformers are neglected due to steric effects). The carbonyl group will likely not participate in 3-membered ring bridging, because the hyperconjugation (or hypercoordination) of the cyclopropyl moiety will outcompete such an effect. Arguably, the most stable isomer is **4.126** and its localized forms **4.125** and **4.127**: we saw that the ^{13}C NMR spectrum of the bicyclobutonium ion indicates a high electron density on the pentacoordinated atom (*Scheme 4.5d*).This can be interpreted formally as a carbanion, whose sp^2-hybrdized lone pair participates in a 3-center-2-electron bond with two adjacent carbenium ions (*Scheme 4.10b – dotted box*). The anion is further stabilized by a conjugation with the adjacent electron poor π-system. The stability of **4.126** may explain the regio- and stereoselectivity of the nucleophilic attack.

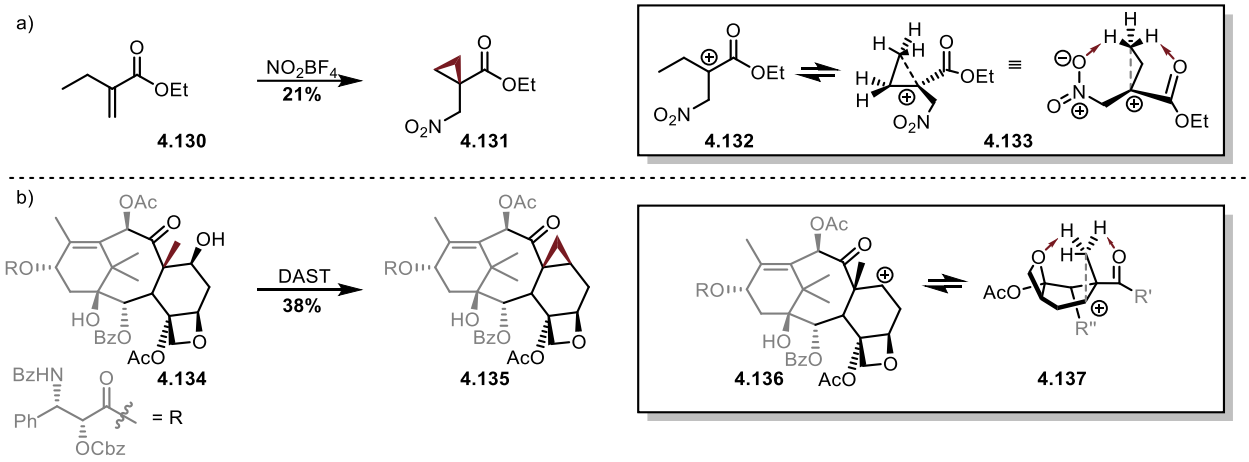
Similar reactions have been published very recently with TMS-substituted cyclopropanes and cyclobutanes.[744]



Scheme 4.10 – a) Stereochemical effect of the carbonyl moiety in a phenonium rearrangement. b) Silver(I)-promoted cyclopropyl rearrangement.

Some α-carbonyl carbocations undergo cyclopropanation reactions resulting from insection along an alkyl chain. When the α,β-dehydrogenated ester **4.130** was treated with nitronium tetrafluoroborate, 21% of the cyclopropanated product (**4.131**) was observed in low yield (*Scheme 4.11 a*). [745,746] The authors propose the deprotonation of a protonated cyclopropane intermediate. This corresponds to the deprotonation of the 2-nornbornyl non-classical cation, which results in the formation of nortricyclene (*Scheme 4.4*). As discussed previously, the existence of non-classical carbocations is bound to specific structural features. Stabilization is usually achieved through a rigid framework. However, biosynthesis non-classical carbocations seem to be more general.[747–749] It has been shown by calculations that this generality might result from hydrogen-bonding towards the protonated cyclopropane, which was calculated to be a good hydrogen-bond donor.[750] This provides a cogent interpretation of the result in *Scheme 4.11a*. The two electron-withdrawing groups might 1) enhance hyperconjugation and make the

CH_3 more "bridging" and 2) stabilize a non-classical carbocation *via* hydrogen bonding (**4.133**). Similarly,when the Taxol derivative **4.134** was treated with DAST, cyclopropane formation was observed.[751] The rigid framework of Taxol most likely plays a decisive role. When the structure of Taxol is represented in 3D the close proximity of two oxygen atoms to the methyl group becomes evident (**4.137**).[752] These two hydrogen-bonding interactions may, again, have a stabilizing effect on a non-classical carbocation.



Scheme 4.11 – a) Cyclopropanation during the reaction of an α,β-unsaturated ester with a nitronium salt. b) Similar cyclopropanation during the dehydration promoted by the fluorinating agent DAST.

4.1.2. Iodine(III) in organic chemistry

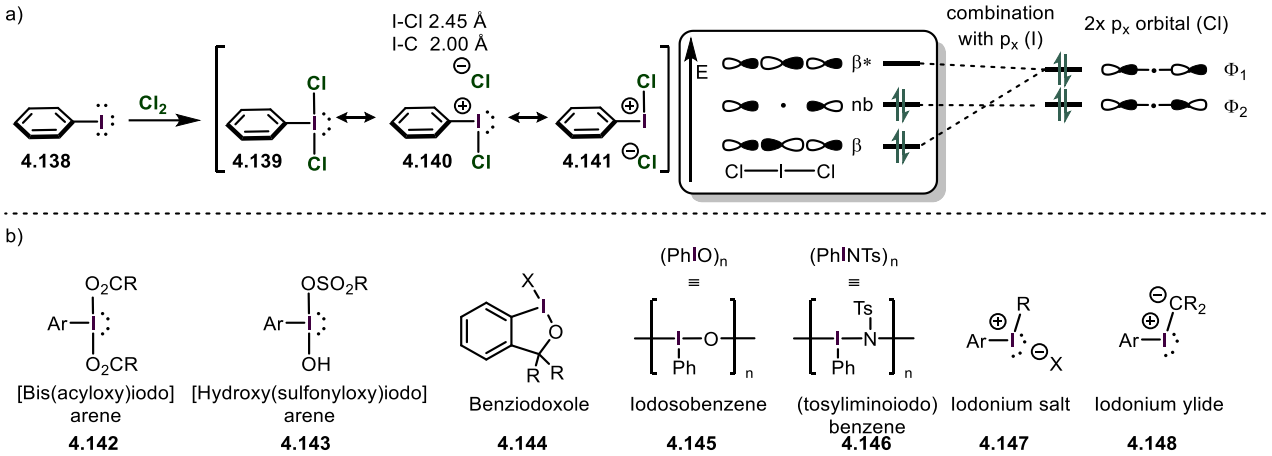
4.1.2.1. *General aspects and structure*

Iodine was discovered by Courtois in 1811 and was named after its beautiful violet color in the gas phase by Gay Lussac in 1813 (ἰοειδής (ioeidēs), ancient Greek for "violet").[753,754] The chemical properties of iodine are determined by its relatively low electronegativity and its high polarizability compared to the lighter halogen elements. It is the heaviest non-metallic element with stable isotopes. Iodine is mostly found as iodide in nature and forms weak bonds with organic molecules, due to weak orbital interactions. The bond dissociation energy (BDE) of the C-I bond in H_3C-I for instance is only 55.9 kcal/mol, and thus almost half as strong as the H_3C-H bond (104.9 kcal/mol).[755] Iodine and carbon have comparable electronegativities, which makes it occasionally ambiguous to assign the oxidation state of those

compounds, especially because the electronegativity depends on the hybridization of the carbon atom.[103] By convention iodine is considered less electronegative than carbon (although most commonly used electronegativity scales show the opposite relationship), so that PhI is considered an iodine(I) compound. We will follow this convention in the further discussion. In this regard, it might be important to remember that heavier p-block elements ($n > 2$ – including iodine) have a low tendency to form hybridized orbitals (sp^x), because the higher s and the p orbitals do not have a comparable radial extent (they are different in "size").[523,756,757] Consequently, they form bonds by using orbitals with large p-character while the s-orbital takes mostly the role of the lone pair ("inert pair effect").[523] When fully oxidized however, they are forced to use the s-orbital for bonding, which has dramatic effects on the chemical behavior, especially when the heavy atom is attached to electronegative elements.[523]

Because of iodine's low electronegativity, organoiodine(I) compounds can be oxidized relatively easily. The first isolated organoiodine compound with a higher oxidation state than (I) was the T-shaped (dichloroiodo)benzene in 1885 (**4.139** – *Scheme 4.12a*).[758] Neutral tricoordinated Iodine(III) molecules like **4.139** are called λ^3-iodanes, whereas positively charged iodine(III) compounds are called iodonium salts (**4.147** - *Scheme 4.12b*).[759,760] λ^3-iodanes seem to violate the octet-rule because they are drawn with more than 8 electrons in their outer shell. Thus they are often described as "hypervalent" species. It has been argued by many scholars that the term is misleading because the octet rule is still satisfied in most systems.[523,756,761–764] This goes along with the conclusion that empty d(n+1)-orbitals of a given element are usually too high in energy to be accessed.[765,766] Some iodine(III) and iodine(V) compounds (including $PhI(OAc)_2$, $PhIF_2$, DMP and IBX) are actually hypovalent on the iodine atom.[764] However, it was demonstrated that subtle hypervalency and d-orbital participation in bonding (to a small but significant extent) has to be expected in some fully oxidized systems (*e.g.* SF_6).[523,767,768] Conclusively, the topic remains under debate and studies and consensual statements might be reevaluated in the near future.

The term “hypervalent” is, in spite of its controversy, overwhelmingly used and accepted in the recent literature.



Scheme 4.12 – a) The first synthesis of a λ^3-iodane. The bonding situation can be described accurately by the VB (left) and the MO model (right). b) Typical iodine(III) compounds.

The bonding situation in electrically neutral I(III) compounds is accurately described as an ionic pair in two mesomeric forms in the valence bond model (*Scheme 4.12a*).[523] The equivalent commonly accepted molecular orbital picture combines the two p_x orbitals of Cl^- according to the C_{2v} symmetry of $PhICl_2$. One of those combined orbitals (Φ_1) has the right symmetry to interact with the p_x orbital of the iodine atom in PhI^{2+} to form a filled bonding (β) and an empty antibonding orbital (β*). The orbital Φ_2 does not have the appropriate symmetry for an interaction and remains unaltered (*Scheme 4.12a*).[769–772] This model is in accordance with the ionic mesomers **4.140** and **4.141**, because the two electrons of the non-bonding orbital are mostly localized on the chlorine atoms.[523] It also explains the preference of the two axial ligands to be electron-withdrawing and the relatively long bonds.

Iodine (III) compounds usually react as electrophilic oxidants. An important aspect of this reactivity is the so-called σ-hole, which often occurs in compounds of the main-group elements and plays a key role in halogen bonding.[773] A σ-hole is a region of a positive electrostatic potential, which is caused by a σ bond. Iodine in H_3C-I for instance, is bonded *via* a half-filled p_z-orbital to CH_3 and its electron will be localized mostly in the interatomic region in order to build up the single-bond (*Figure 4.2*). This causes a

depletion in electron density at the outer lobe on the z-axis. At the same time the lone pairs in x and y directions are double filled and act as a shield of high negative electrostatic potential.[773] The existence of a σ-hole has consequences not only on the reactivity, but also in the association of molecules in the solid phase (*e.g.* H_3C-I).[774] This phenomenon is especially intriguing because it contradicts the common approximation that an atom in a molecule has a net atomic charge (*e.g.* by assigning a "δ-" to an atom). Generally speaking, the electrostatic potential of an atom in a molecule (the "charge") is an anisotropic quantity, *i.e.* it is dependent on the physical location and can be usually illustrated as a surface around the atom on the van-der-Waals radius.[773]

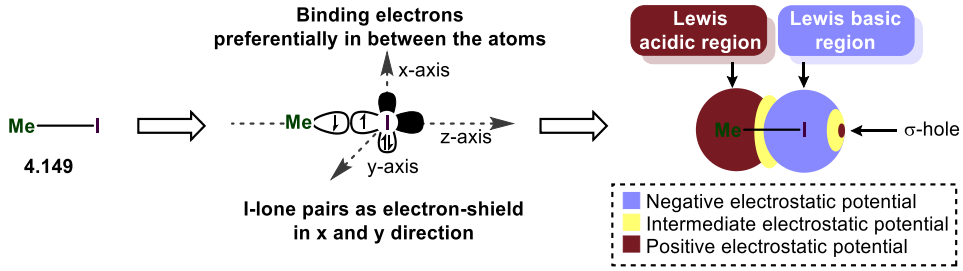
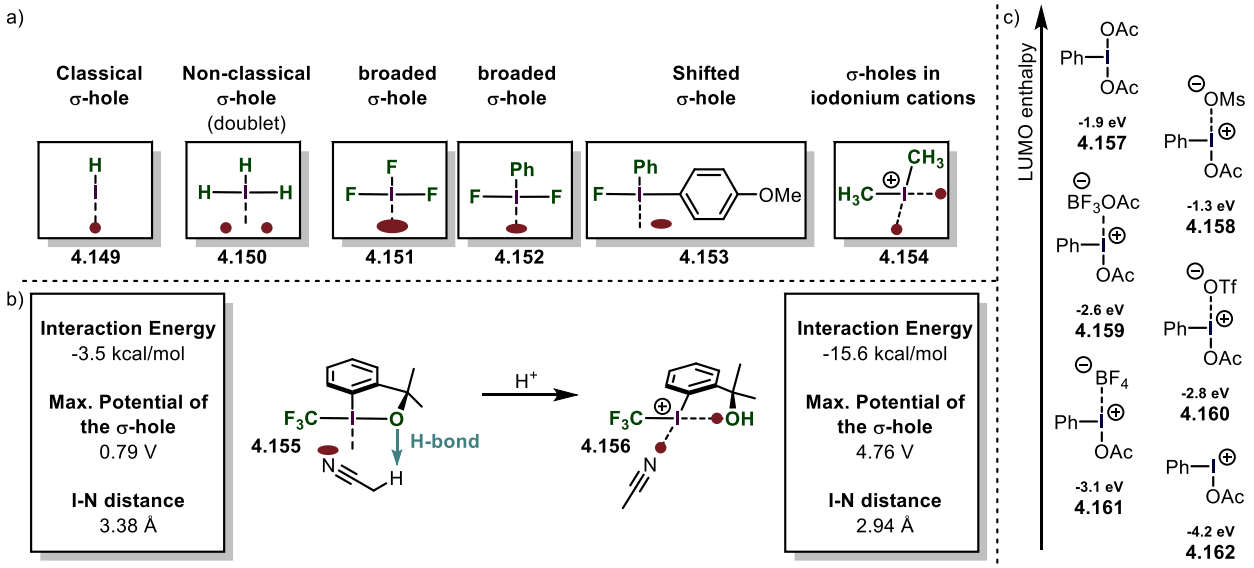


Figure 4.2 –The approximate molecular electrostatic potential (MEP) shows the σ-hole in iodomethane.

The σ-hole in iodine(III) species is caused by the classical 2-center-2-electron bond between the equatorial ligand and the iodine atom. The nature of this bond determines the strength of the σ-hole. Interestingly, the orthogonal 3-center-4-electron bond pertubates the shape of the σ-hole, so that two distinct maxima of positive electrostatic potential are observed (**4.150**) (*i.e.* the σ-hole forms a doublet – *Scheme 4.13*).[775] This phenomenon was termed a "non-classical σ-hole". The coupling seems to be more pronounced when electron-neutral ligands are attached (IH_3), while strongly electronegative atoms such as fluorine (IF_3 – **4.151**) make the σ-hole just appear broader. This broadening however is actually caused by the appearance of two distinct maxima. When the two axial ligands are different, the σ-hole becomes an apparent singlet again, but is shifted towards one of the ligands. Iodonium cations, which are bond to the ligands by two classical 2-center-2-electron bonds, have two distinct classical σ-holes along the prolonged axes of the C-I-bonds (**4.154**). Importantly, electron-rich species (*e.g.* nucleophiles) will form

coordinative bonds to the σ-hole (σ-hole bonding).[775] Acetonitrile, for example, was calculated to interact with the shifted σ-hole of Togni's reagent to form the adduct **4.155** (*Scheme 4.13b*). The I-N distance (3.38 Å) is typical for such an interaction. The non-classical σ-hole may also explain why the iodine atom in $PhI(O_2CR)_2$ is usually coordinated to 5 atoms in a planar pentagonal arrangement.[776,777]



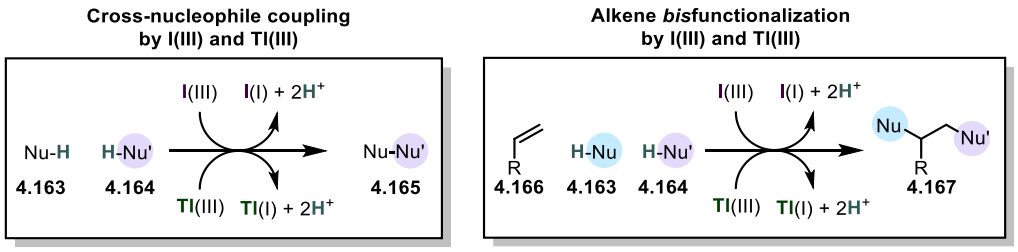
Scheme 4.13 – a) σ-Holes in different iodine compounds. b) Interaction of a non-classical σ-hole with acetonitrile. c) LUMO energies of several activated iodine(III) compounds).

λ^3-iodanes can be activated (*i.e.* they become more electrophilic) in acidic media if one of the ligands has sufficient basicity ($PhI(O_2CCF_3)_2$ for instance cannot be activated by $BF_3{\bullet}OEt_2$).[778] After protonation, one of the ligands is detached from the iodine atom so that an iodonium species is formed (**4.156** - *Scheme 4.13b*). The former ligand however remains in relative close proximity due its coordination to the new σ-hole in the iodonium species. Moreover, the strength of the σ-hole *trans* to the phenyl ring is enhanced significantly and consequently the interaction energy of the iodine compound with the ligand (MeCN) gets stronger. These results are in accordance with the fact that activated iodine(III) compounds like PhI(OH)(OTs)•HOTs have been described as Lewis acids.[779] In addition, X-ray crystal structures of several activated iodine (III) compounds have been interpreted as iodonium species with a weak coordination to the activated ligand.[778] The same article provides also a nice comparison of the LUMO energies of different activated iodine(III) compounds (*Scheme 4.13c*).

4.1.2.2. *Reactivity of iodine(III)*

The chemistry of iodine(III) compounds is incredibly versatile. A small selection of their chemistry will be outlined in this subchapter. This topic has recently been extensively reviewed and a more complete discussion can be found in selected articles and books.[759,760,780–787]

Many reactions which utilize iodine(III) compounds can be categorized as cross-coupling of nucleophilic species by oxidation of one of the partners (*Scheme 4.14 - left*). This type of reaction can be called "cross-nucleophile coupling" (in analogy to the "cross electrophile coupling" in metal catalysis).[788] The coupling is accompanied by the formal loss of two protons or an equivalent electrofuge (*e.g.* TMS^+). A common variant of the cross-nucleophile coupling is the *bis*functionalization of alkenes (which involves 3 formal nucleophiles – *Scheme 4.14 right*). Interestingly, these general transformations are not only accessible *via* iodine(III) compounds, but can be also accomplished with Tl(III). Indeed, the reactivities of iodine(III) and thallium(III) in organic chemistry are closely related (the chemistry of Pb(IV) has also some similarities).[789–796] However, due to its high toxicity and its environmental impact Tl(III) is seldom used in modern synthesis, especially because iodine(III) compounds are much safer, readily tunable and environmentally benign.

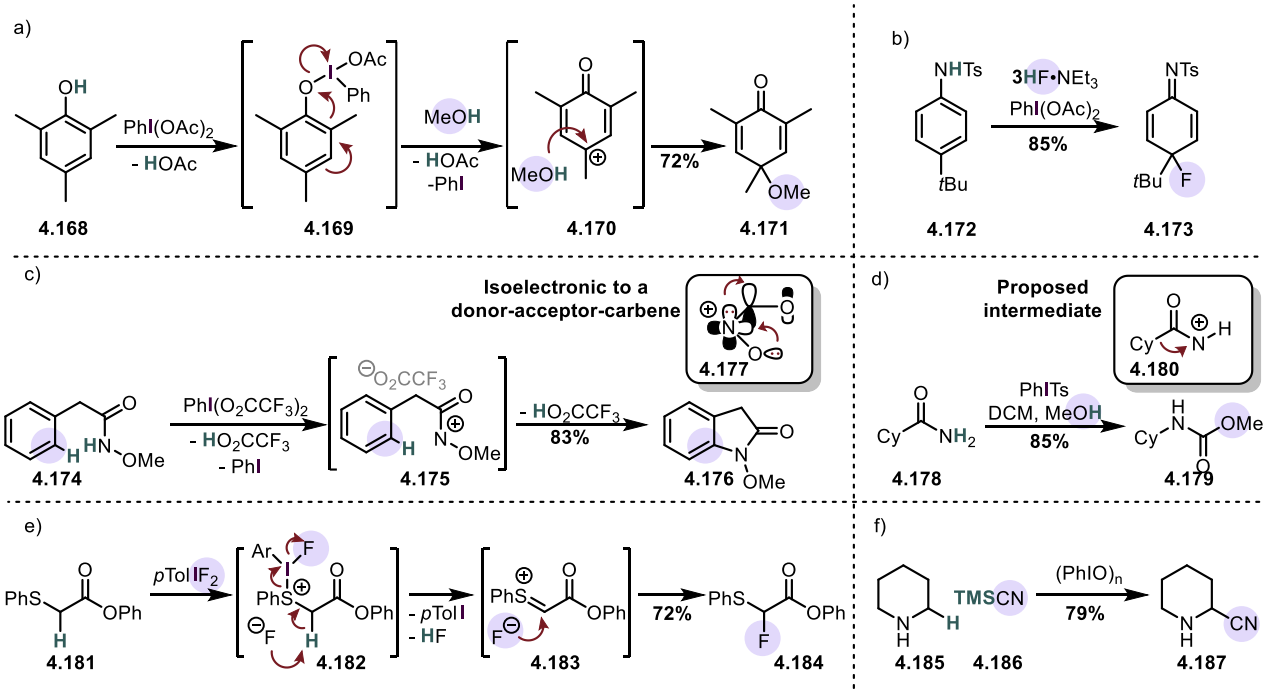


Scheme 4.14 – Cross-nucleophile coupling and alkene bisfunctionalization promoted by I(III) and Tl(III).

Phenols are typical substrates in cross-nucleophile coupling reactions (*Scheme 4.15a*). They were classically proposed to coordinate to iodine(III) *via* the oxygen-atom to form an electrophilic adduct, which converts into a phenoxonium intermediate (**4.170**).[797] The intermediate is then trapped by a second nucleophile.[798] However, the mechanism is still under debate; in fact, a more recent study found that the

iodine(III) is most likely attacked by the carbon atom of the phenol, which enables both dissociative (S_N1-type) and (S_N2-type) associative mechanisms.[799] There is nevertheless a consensus that coordination by the phenol-oxygen atom on the iodine(III) atom enables only dissociative mechanisms. Analogous reactions, where the iodine species is used catalytically with a secondary oxidant are known,[800,801] including enantioselective versions.[802,803] Similar reactions have been widely employed onto secondary anilines (*Scheme 4.15b*),[804] although the products usually rearomatize by the loss of an electrofuge (*e.g.* *t*Bu, H).[782] Phenol ethers follow a radical cation mechanism, in which the iodine(III) species act as single electron oxidant. The nucleophile is installed on the phenol without dearomatization.[805,806] A thallium(III)-promoted phenol dearomatization is also known.[807]

Carboxamides are also popularly used as oxidizable nucleophiles, especially *O*-methyl *N*-hydroxylamides (*Scheme 4.15c*).[808] The reaction mechanism involves the formation of an electrophilc nitrenium ion, which benefits from the electron-donating group in proximity (OMe). As depicted in **4.177** the oxidized *N*-methoxyamide is isoelectronic to a donor-acceptor carbene. The structural similarity is also showcased by the fact that unstabilized acylnitrenium ions generated by iodine(III) often rearrange to isocyanates (*Scheme 4.15d – Hoffmann-type rearrangement*),[809] and undergo C-H insertions,[810] reminiscent of carbene-reactivity. Indeed the intermediate **4.175** may undergo either a classical Friedel-Crafts-type mechanism with the arene, or a C-H insertion reaction to yield the observed product. The nitrenium ion can be attached to a variety of nucleophiles, although the majority of the reports involves arenes, alkenes and alkynes.[782] Some creative transformations have been developed using this approach, for instance a catalytic oxidative annulation of benzamides with alkynes.[811]

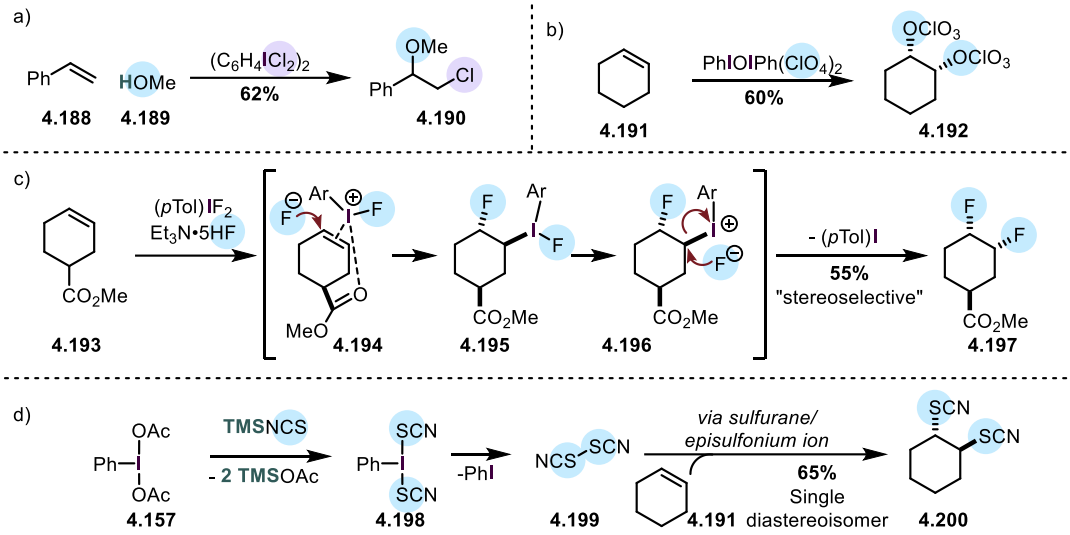


Scheme 4.15 – a) Cross-nucleophilic coupling of a phenol with methanol. b) A Tl(III)-promoted phenol dearomatization. c) Intramolecular cross-nucleophilic coupling of an arene with an amide promoted by I(III). d) Hoffmann-type rearrangement of an amide promoted by iodine(III). e) Pummerer-type reaction promoted by I(III) on a sulfide and f) on an amine.

Another common type of iodine(III) mediated nucleophilic coupling mimics the Pummerer-reaction:[812] the α-functionalization of sulfides has been achieved in good yields by using *p*TolIF$_2$ (*Scheme 4.15e*),[813] or PhIO in combination with TMSN$_3$.[814] The advantage of this reaction is that the isolation of an oxidated intermediate is not required. The chemistry can be similarly applied onto selenides[815] and amines (*Scheme 4.15*f).[816,817] α-Tertiary amines may undergo an 1,2-alkyl migration onto the partially positively charged nitrogen atom.[818]

The *bis*functionalization of alkenes is seemingly remiscient of a nucleophilic attack on an *in situ* generated halonium/episulfonium ion at first glance (*Scheme 4.16a/b*).[819] In cyclic alkenes vicinal *syn* substitution is often observed stereospecifically, in stark contrast to the usual *trans* selectivity in halonium ions.[820,821] However, neighboring group participation might alter the stereochemical outcome.[822,823] Intriguingly, the generated intermediates are so electrophilic that they can be trapped even by perchlorate anions (*Scheme 4.16b*).[824] Moreover, Lewis basic groups (like esters) can direct the oxidant by coordination as shown in *Scheme 4.16c*.[825] The mechanism is believed to proceed *via* an iodonium π-

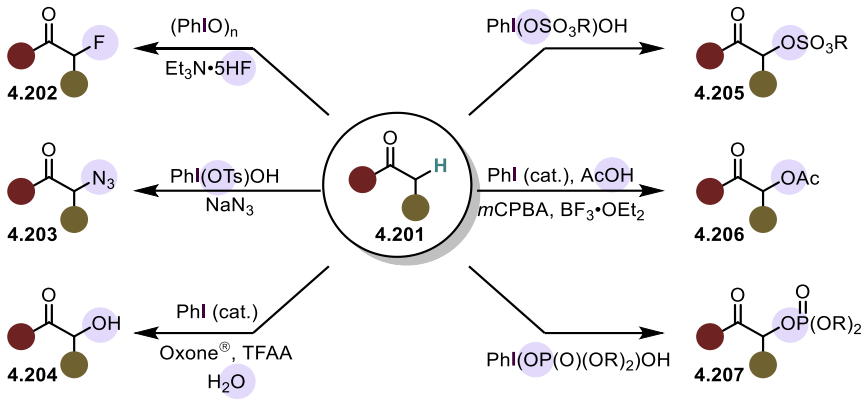
complex (**4.194**), which enables nucleophilic attack onto the alkene by the first fluoride (*Scheme 4.16c*). Thereafter, the iodine(III) species undergoes a formal reductive elimination, by departure of one of its substituents (**4.196**), which then attacks the backside of the C-I bond. Interestingly, classical *trans*-selectivity is sometimes observed for the *bis*functionalization even when neighboring group participation can be excluded. This may arise from an alternative mechanism, in which the two ligands of the I(III) species are oxidatively coupled (*Scheme 4.16d*).[826] For instance, the *in situ* generated thiocyanogen (**4.199**) in *Scheme 4.16*, undergoes a classical *trans* addition *via* a episulfonium/sulfurane species.[827]



Scheme 4.16 – a) Bisfunctionalization of a styrene. b) Cis-selectivity is often observed when I(III) is used. c) Diastereoselective difluorination of a cyclohexene, with CO_2Me as the directing group. d) Trans-selectivity from an alternative mechanism.

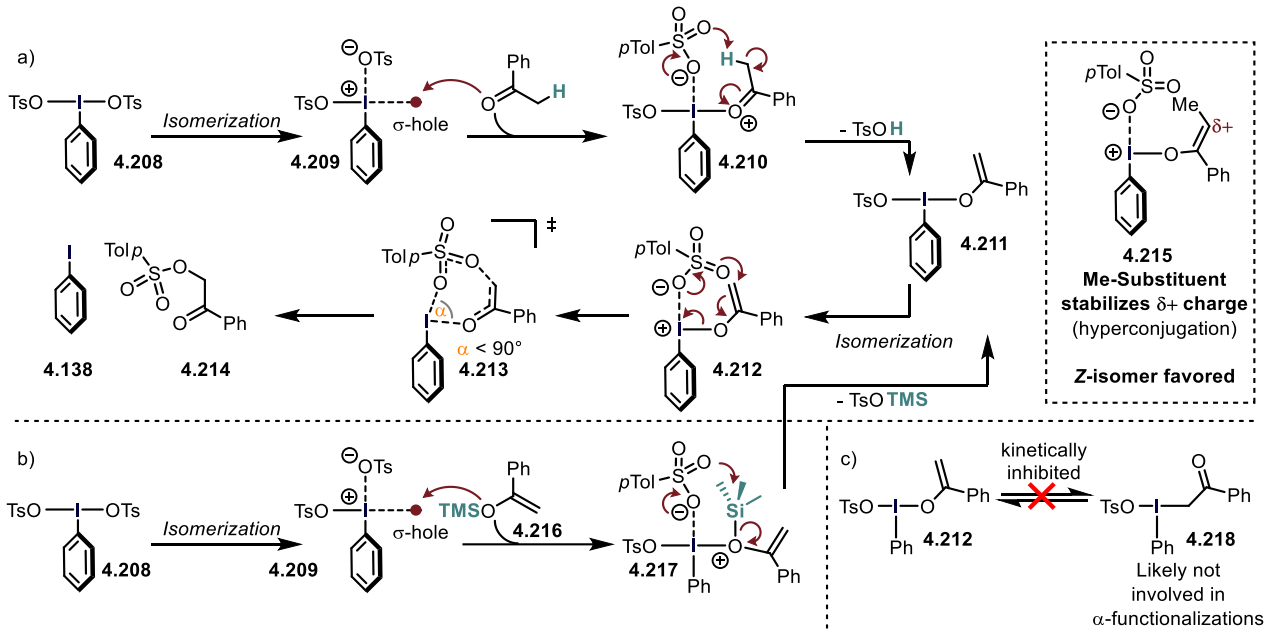
The cross-nucleophile coupling is also frequently used for the α-functionalization of ketones and their derivatives (*Scheme 4.17*).[786,787] One of the early reports by Mizukami *et al.* in 1978 describes the α-acetoxylation of acetophenones with $PhI(OAc)_2$. The reaction was generally low-yielding and a mixture of acetic acid and acetic anhydride had to be used as the solvent.[828] However, in the last decade major developments were accomplished in the direct α-functionalization of ketones including (*Scheme 4.17*) hydroxylations,[829–832] tosylations,[833–837] mesylations,[838] phosphoryloxylations,[839,840] fluorinations,[841] azidations[842–844] and acetoxylation.[845] Some of these transformations are catalytic in iodine(III)[831,834,835,845] and also enantioselective versions are known.[832,835–837] However, intermolecular

enantioselective α-functionalizations of ketones by the use of chiral iodine(III) compounds usually give low to modest ees (<60%). Acid-induced racemization of the product seems not to be the cause of the low stereoinduction.[779,837]



Scheme 4.17 – α-functionalization of ketones by iodine(III) compounds.

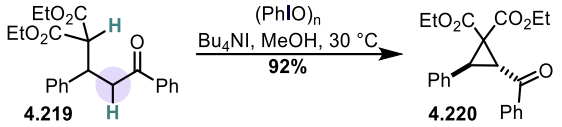
Legault and Beaulieu conducted a computational study on the α-tosylation of acetophenones (*Scheme 4.18*).[779] The reaction proceeds *via* inital activation of the iodine (III) reagent PhI(OH)OTs by an acid to form $PhI(OTs)_2$ (**4.208**). This compound must isomerize to an energetically high lying species, in which the two electron-withdrawing groups are in *cis*-relationship to further react (**4.209**). This requirement has been also found in other calculations for similar systems.[778] In this isomer, the TsO-ligand *trans* to the arene is only loosely bonded so that the species can also be described as an intimate ion pair. Due to this partial departure, the σ-hole becomes sufficiently strong to act as a Lewis acid on the ketone so that the adduct **4.210** is formed. The high acidity of the coordinated ketone leads to deprotonation, which releases TsOH and the enolate **4.211**. Again, an isomerization to the energetically high lying isomer **4.212** takes place, which decomposes to the products *via* a seven-membered transition state (**4.213**).



Scheme 4.18 – a) Mechanism for the α-tosylation of acetophenone. b) Reasonable mechanism for the α-tosylation of the silyl enolether of acetophenone. c) Calculated high barrier of O-C isomerization of the iodine(III)-enol intermediate.

Although the ring size of the transition state is rather large, a narrow O-I-O angle (α<90°) was calculated deviating considerably from the heptagonal angle (*ca.* 128.5°). This narrow angle has also been observed in calculations of other transition states in I(III) reductive elimination reactions going through 6-,[846] or 5-memberd rings.[847,848] Another important structural feature is that the I-O bond is almost perpendicular to the enol moiety. The last reaction step has been found to be the rate- and stereochemistry-determining step in the overall reaction, despite the small the reaction barrier from **4.212** to **4.213** (*ca*. 3 kcal/mol). Most of the energy is required for the enolization and for the formation of the *cis* isomer **4.212**. The authors conclude that the low stereoinduction in tosylation reactions of ketones is due to the great distance between the forming stereogenic center and the iodoarene. The overall reaction barrier was significantly lowered when an α-substituted acetophenone was used. The authors accounted hyperconjugation into the electron-poor enol-species for this stabilization. Moreover, they found that the *Z*-enol species (**4.215**) reacted much faster than the corresponding *E*-isomer. Because the enolization is a rather unfavored process, ketones which have a biased preference for the enol-tautomer are popular substrates for this kind of chemistry. β-diketones are commonly used:[849] Michael

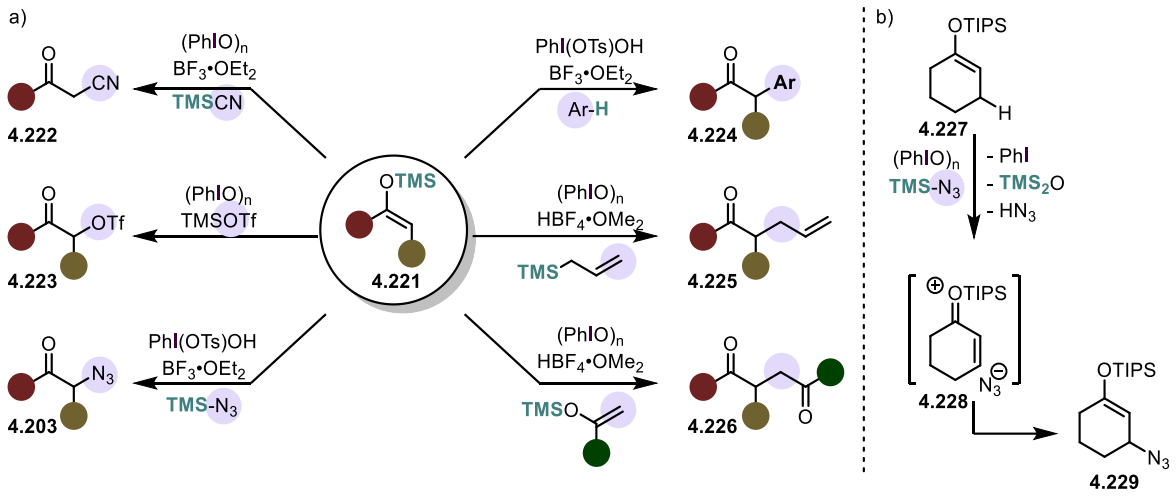
adducts, for instance, can be oxidatively cyclized to cyclopropanes by using PhIO in methanol (*Scheme 4.19*).[850]



Scheme 4.19 – β-Dicarbonyls are often used in iodine(III) oxidations because they are biased for the reactive enol form.

Another similar strategy is to derivatize ketones into silyl enolethers. In this case, the enolether presumably attacks through its oxygen atom and loses the electrofuge (TMS^+) to form **4.208** (*Scheme 4.18b*). This is in accordance with the NMR data provided by the group of Szpilman, where only the enol-iodine form (**4.211**) was detected when silyl enolethers were used[851] and with the fact that the C-O-isomerization (*Scheme 4.18c*) is kinetically inhibited for such systems.[779] Diaryl-enol iodine(III) species on the other hand may undergo such an isomerization.[848]

By using silyl enolethers as starting materials, the electrophilic enolate **4.211** can be generated under mild reaction conditions (due to their enhanced reactivity of the former). This opens up the possibility to use rather weak secondary nucleophiles for the cross-nucleophilic coupling (*Scheme 4.20a*). It has already been demonstrated in the 1980's, that electrophilic enol-species (like **4.211**), can be attacked by other silyl enolethers (in homo- and cross-coupling reactions – **4.226**), allyl silanes (**4.225**) and even some plain alkenes.[852–854] Moreover, it was demonstrated that α-trifloxy ketones (**4.223**) can be synthesized and isolated by this approach, showcasing the carbocationic character of iodine(III) mediated transformations.[855,856] In more recent years α-arylation (**4.224**),[857–860] azidation (**4.203**)[859,861] and cyanation (**4.222**)[862] have been accomplished. The cyanation is however limited to unsubstituted silyl enolethers. In other approaches the nucleophile was attached onto the silane-moiety during the starting material synthesis.[863] Cyclic TIPS enol ethers (**4.227**) may not react directly with the nucleophile but are rather oxidized to the α,β-unsaturated oxocarbenium **4.228**, which can then undergo a Michael addition (*Scheme 4.20b*).[864]

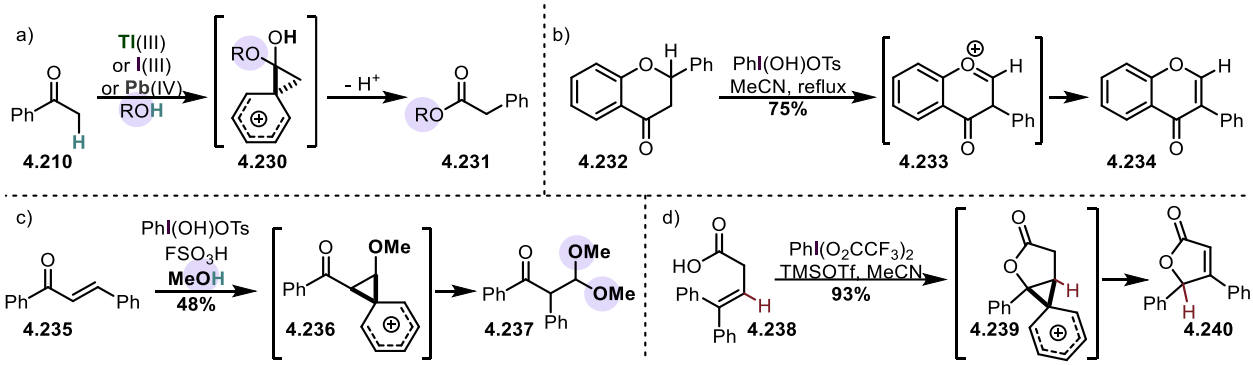


Scheme 4.20 – a) α-Functionalization of silyl enolethers. b) β-Functionalization of a cyclic silyl enolether.

4.1.2.3. *Cationic rearrangements promoted by iodine(III)*

The cationic oxidative 1,2-migration of arenes in aryl ketones has been appreciated for a long time in organic chemistry. This reaction is classically promoted by halogenation of the α-position with a subsequent treatment with Ag(I).[742] Direct approaches have been accomplished with Tl(III)[791] or Pb(IV)[795] and later with I(III)[865,866] in order to synthesize carboxylic acids and esters from ketones (*Scheme 4.21a*). The oxidative β → α migration has been similarly explored by using iodine(III). The interconversion of flavanones to isoflavones works smoothly with Koser's reagent (PhI(OH)OTs – *Scheme 4.21b*).[867] The outcome of the reaction is highly dependent on the conditions: when methanol was used as solvent, α,β-dehydrogenation was observed exclusively.[868] Using trimethylorthoformate as the solvent resulted instead in the migration of the fused benzene ring to yield a dihydrobenzofuran.[869] β-phenyl-α,β-dehydrogenated ketones are known to rearrange *via* a Michael-addition-oxidation sequence since the 1980's and were used to afford acetals (*Scheme 4.21c*).[796] An enantioselective version (by use of a stoichiometric iodine(III) oxidant) has been published in 2013.[870] This approach has been similarly used three years later in an catalytic asymmetric difluorination reaction of α,β-dehydrogenated carbonyl compounds. In this case the acetal is replaced by a geminal difluoride.[823] If the conditions are varied the acetal product (**4.237**) may be further oxidized to yield the α-aryl-α-keto carbonyl compound.[871] Arene

shifts were also reported during the iodine(III)-promoted functionalizations of alkenes. An interesting example is showcased in *Scheme 4.21d*. The alkene first coordinates to the iodine(III) compound and is then attacked by the pendant carboxylic acid. After dissociation of iodine(I) the homobenzylic cation rearranges first *via* a 1,2 phenyl shift (**4.239**) and second *via* a 1,2-hydride migration to yield the furanone **4.240** after elimination of H^+.[872] Alternatively, the phenyl and the hydride might migrate simultaneously (dyotropic reaction).



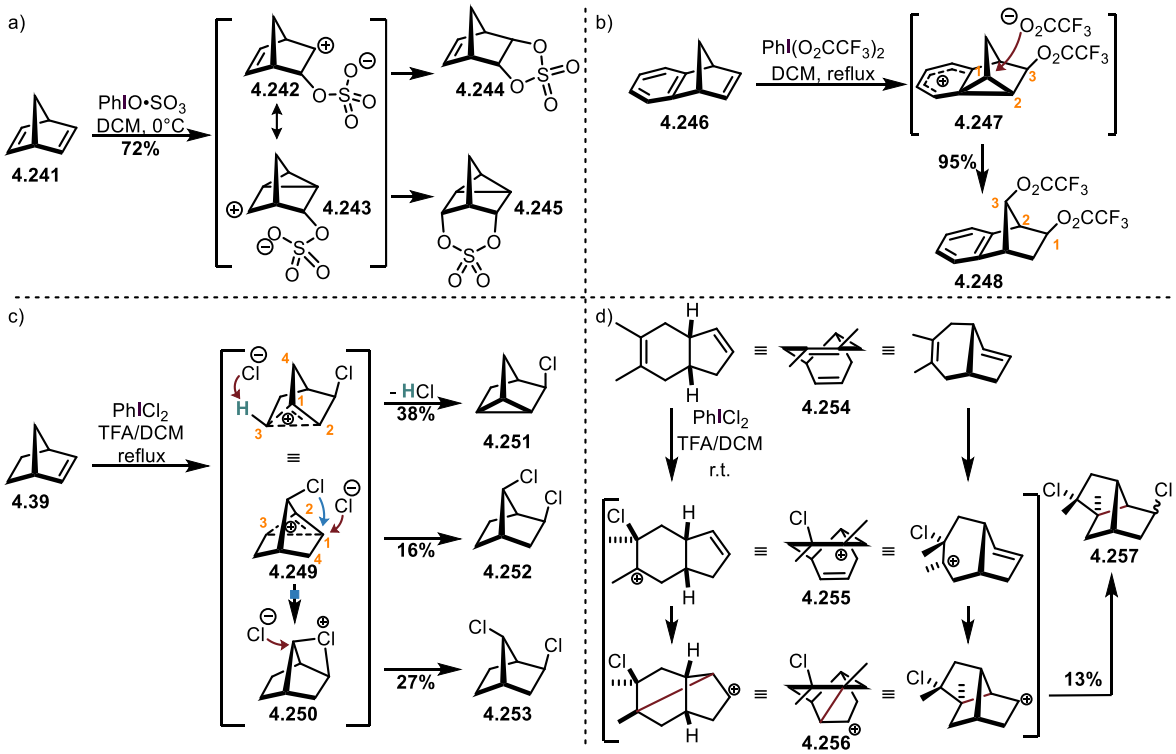
Scheme 4.21 – a) Oxidative 1,2-phenyl migrations in acetophenones promoted by Tl(III), I(III) or Pb(IV) to afford carboxylic acids and esters. b) Flavanone to isoflavone interconversion by the use of I(III). c) Michael-addition-oxidation cascade to promote a 1,2-phenyl migration on enones. d) Interesting 1,2-phenyl migration in the reaction of iodine(III) with an alkene.

Bornane-systems are generally known to undergo skeletal rearrangements under several conditions. Iodine(III) compounds have been described as promoters of those rearrangements in several contexts (*Scheme 4.22*).

Norbonadiene (**4.241**) reacted smoothly with PhIO•SO_3 to yield a mixture of the sulfate **4.244** and the nortricyclene **4.245**.[759,873] This reaction shows how cyclopropanes can be generated by nucleophilic attack onto a homoallylic cation. A similar cyclopropanation is observed with 1,4-cyclohexadiene as the starting material.[820]

The Benzonorbornane **4.246** rearranged in almost quantitative yield when reacted with $PhI(O_2CCF_3)_2$ (*Scheme 4.22b*).[820] The reaction presumably proceeds *via* a bridged classical phenonium ion **4.247**. Norbornene on the other hand, reacts *via* a non-classical cation with $PhICl_2$ (*Scheme 4.22c*).[874] The major product obtained was the chloronortricyclene **4.251**, which was formed by a deprotonation of the non-

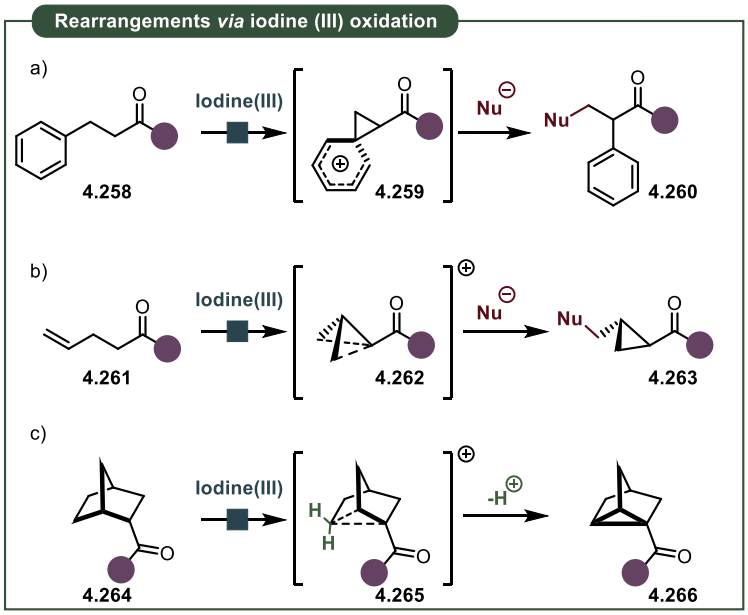
classical carbocation **4.249**. The reaction of the same substrate with $PhI(O_2CCF_3)_2$ on the other hand did not lead to any cyclopropanation.[820] Another very interesting case is the formation of norbornane-type structures *via* the bicycle **4.254**. When drawn by conventional means, there is little resemblance with bornanes. However, other perspectives reveal that there is just one bond missing. Oxidation with $PhICl_2$ yielded indeed the norbornane-type structure, however in poor yield.[875]



Scheme 4.22 – a) Intramolecular cyclopropanation promoted by I(III) on a cyclic compound. b) Rearrangement in the bisfunctionalization of a benzonorbornene with iodine(III). c) Typical products of a non-classical carbocation in the reaction of norbornene with $PhICl_2$. d) Synthesis of a norbornene-type structure via an interesting disconnectivity in low yield.

4.2. Objectives

Iodine(III) compounds are generally known to a) oxidize ketone-derivatives and b) promote cationic rearrangements in several substrate classes. The objective of this work is to investigate if previously unreported cationic rearrangements can be promoted by such oxidants. Namely, the β → α migration of simple β-aryl ketones (*Scheme 4.23a*) by the generation of a phenonium ion, and cyclopropanation reactions by the generation of non-classical carbocations are at the heart of our investigations (*Scheme 4.22b/c*). The β →α migration in simple ketones is reminiscent of a few examples discussed in the introduction. However, there is a decisive pitfall, which was circumvented by the choice of the starting material in the previously reports: a very favorable α,β-dehydrogenation to form the enone. Iodine(III)-promoted cyclopropanation reactions are not totally unprecedented in the literature. However, a general approach as depicted in *Scheme 4.23b* has never been explored. Similarly, a reaction in which a 2-norbornyl cation is generated by iodine(III) and leads selectively to a nortricyclene derivative (*Scheme 4.23c*) has also been explored as a synthetically interesting approach.



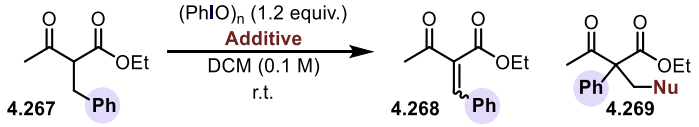
Scheme 4.23 – a) Synthesis of α-phenyl-β-functionalized ketones via the generation of a phenonium ion. b) Cyclopropanation of γ,δ-dehydrogenated ketone derivatives .c) General nortricyclenization of norbornyl derivatives.

4.3. Results and discussion

4.3.1. Iodine(III) induced β → α aryl migration on saturated ketones

4.3.1.1. *Optimization*

Our first investigation on the β → α aryl migration on saturated ketones was undertaken on β-keto esters due to their bias for the enol-tautomer (*Table 4.1*). Submitting the standard substrate **4.267** to *in situ* generated $PhI(OTs)_2$ by mixing iodosobenzene and *para*-toluenesulfonic anhydride gave 10% of the desired product **4.269**. The major product (80% isolated) was the α,β-dehydrogenated compound **4.268**, which was anticipated to be the major pitfall of the reaction. TsOH and TFA showed similar undesired results, while the use of TfOH gave a messy reaction with only trace amounts of both the desired and the dehydrogenated product. The use of 2.4 equivalents of MsOH as the activator for iodosobenzene was much more selective towards the desired product. Indeed, the desired mesylated product was isolated in more than 80% yield and easily separated from the enone side product. The scope of the reaction using active methylene compounds has been accomplished completely by Dr. Jing Li and will not be further discussed. For more information, we reference to our published manuscript.[662]

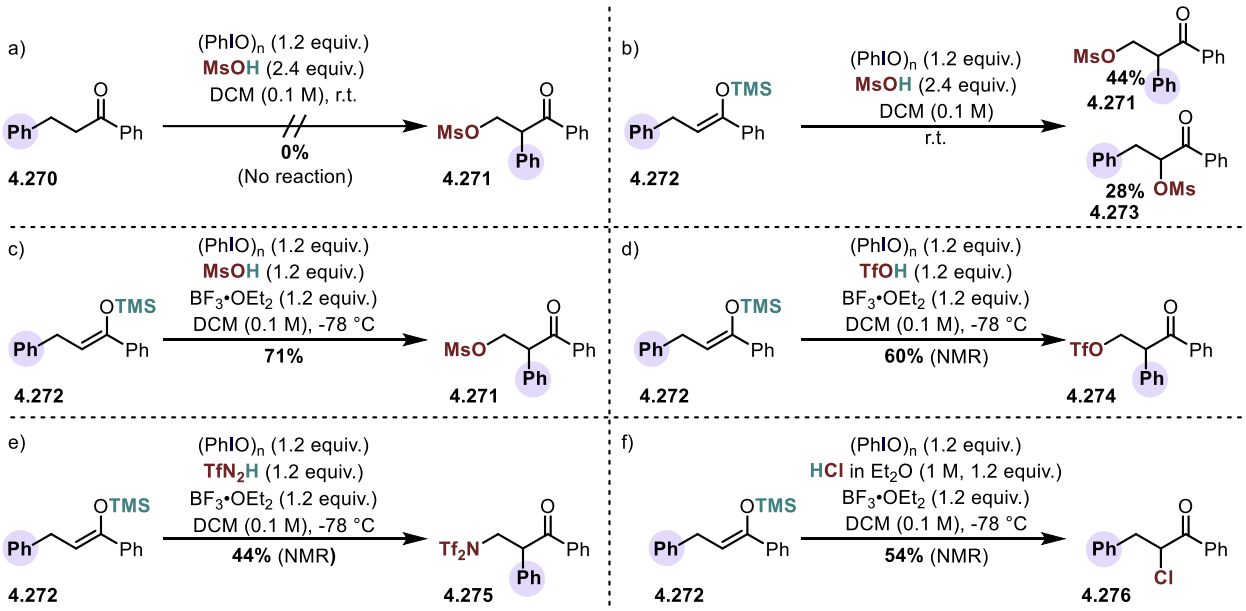


Entry	Additive	Time	Yield **4.268**	Yield **4.269**
1	Ts_2O (1.2 equiv.)	24 h	80%	10%
2	TsOH (1.2 equiv.)	24 h	81%	11%
3	TFA (2.4 equiv.)	24 h	70%	20%
4	TfOH (2.4 equiv.)	5 h	Trace	Trace
5	**MsOH (2.4 equiv.)**	**5 h**	**12%**	**81%**

Table 4.1 – Optimization of the β → α-aryl shift with subsequent functionalization of the β-position.

At the same time, we investigated simple ketones as substrates for the aforementioned transformation. Unfortunately, β-aryl substituted ketones did not react under the usual conditions and most of the starting material was recovered (*Scheme 4.24a*). This is likely due to their low tendency to

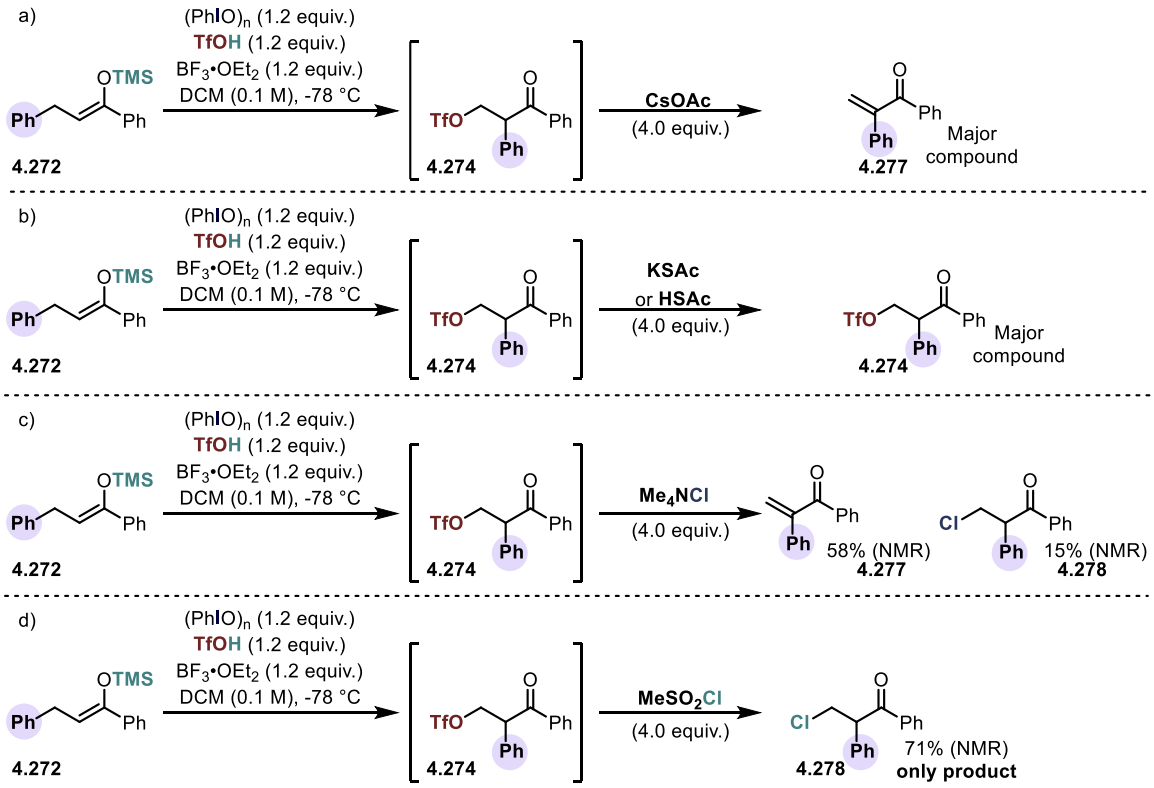
form the enol-tautomer. On the other hand, the trimethyl silyl enolether **4.272** exhibited the sought reactivity under those conditions (*Scheme 4.24b*). However, the undesired α-mesylate **4.273** (resulting from a functionalization in absence of a rearrangement) was formed in significant quantities and was difficult to separate from the desired β-mesylate. This challenge was circumvented by using a mixture of MsOH and BF_3•OEt_2 at low temperature in order to lower the nucleophilicity of the mesylate (*Scheme 4.24c*). Indeed, such a strategy has been similarly applied by Szpilman *et al.*[876] In doing so, **4.271** was isolated in more than 70% yield.



Scheme 4.24 – a) Simple ketones are too unreactive to undergo the oxidative β → α migration. b) Trimethyl silyl enolethers as reactive ketone-derivatives. c) Selectivity for the aryl-shift can be achieved by using an additional acid to tame the nucleophilicity of the mesylate. TfOH (d) and Tf_2NH (e) can be similarly used. f) Dry HCl yields only the α-chlorinated ketone, without rearrangement.

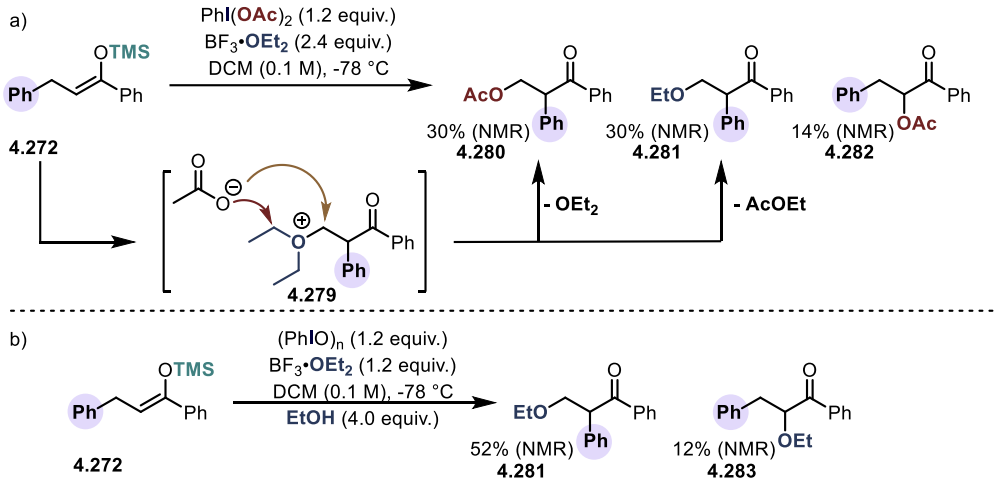
Other strong Brønsted acids in combination with BF_3•OEt_2 showed similar results. Trifluoromethanesulfonic acid (TfOH) for instance gave the triflate **4.274** in 60% NMR yield (*Scheme 4.24d*). Similarly *bis*(trifluoromethane)sulfonamide (Tf_2NH) yielded the *bis*sulfonamide **4.275** (*Scheme 4.24e*). Ethereal HCl on the other hand, led only to modest α-chlorination (*Scheme 4.24f*). The same α-chlorination was observed when PhIO was activated by BCl_3 only.

The β-triflate **4.274** was synthetically attractive because it could theoretically be displaced *in situ* by several nucleophiles under mild conditions. However, this compound is prone to eliminate TfOH (*Scheme 4.25a*): treatment of the β-triflate with CsOAc gave mostly the α,β-dehydrogenated compound **4.277**. Surprisingly, strongly nucleophilic thioacetic acid or potassium thioacetate did not react with the triflate, even in large excess (*Scheme 4.25b*). Tetramethylammonium chloride on the other hand, was basic enough to yield the enone together with the desired chloride as an inseparable mixture (*Scheme 4.25c*). However, elimination can be prevented by using an entirely non-basic chloride source: when the crude triflate was treated with MsCl in one pot, the chloride was formed exclusively in a good NMR yield (*Scheme 4.25d*). Unfortunately, this compound is not stable on silica and eliminates to the aforementioned enone. However, this could be circumvented by basifying the silica or using basic Al_2O_3 as the stationary phase.



Scheme 4.25 – In situ nucleophilic substitution of the triflate. a) CsOAc favors majorly elimination. b) Thioacetate or thio acetic acid do not react with the triflate. c) An ammonium chloride salt yields an inseparable mixture of the desired β-chloride and the enone. d) The use of an "acidic" chloride salt afforded the desired β-chloride as the only product.

When $PhI(OAc)_2$ was activated solely by $BF_3{\bullet}OEt_2$ and reacted with the silyl enolether **4.272**, a mixture of 3 different compounds was obtained (*Scheme 4.26a*). The desired product was formed in 30% NMR yield along with its unrearranged isomer **4.282**. Moreover, the rearranged ethyl ether **4.281** was generated in significant amounts. This product is most likely formed from the nucleophilic attack of Et_2O on the phenonium ion to yield the secondary intermediate **4.279**. The Et_2O moiety is then either displaced by the acetate or reacts *via* a cleavage of the EtO-linkage to form ethyl acetate and the observed product **4.281**. The yield for the formation of the ethyl ether could be improved by using PhIO instead of $PhI(OAc)_2$ in combination with ethanol as the quenching reagent (*Scheme 4.26*b).

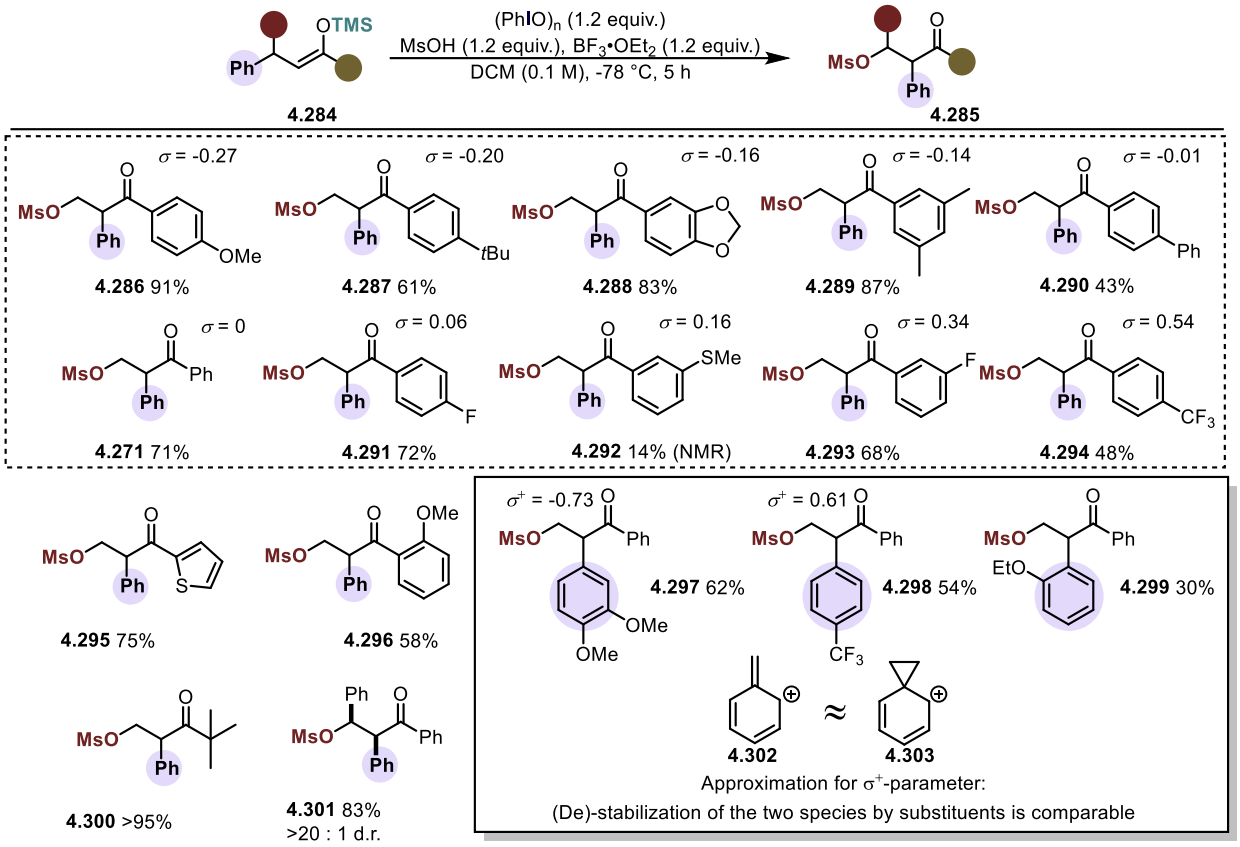


Scheme 4.26 – a) Diethylether as a nucleophile . b) Optimized synthesis for the ethyl ether.

4.3.1.2. *Scope on silyl enolethers of simple ketones*

Next, several silyl enolethers derived from simple ketones were submitted to the optimized reaction conditions for β-mesylate formation (*Scheme 4.27*). The non-migrating aryl group can be parametrized by using Hammett's substituent constants.[487] Large variations on the non-migrating aryl group were tolerated, although the yield seemed to be dependent on the substitution pattern. The substrate carrying the strongly electron-withdrawing CF_3 moiety (**4.294**) gave one of the lowest yields, while the highest yield was observed with the electron-rich *p*OMe containing silyl enolether (**4.286**). It seems that electron-donating substituents have a generally beneficial effect, in spite of the apparent

inconsistent results obtained with some substrates (difficulties during purification led sometimes to decreased yields). The thioether **4.292** was probably formed only in low yield due to its Lewis basicity. *Ortho*-substitution (**4.296**) had a detrimental effect but the product was nevertheless isolated in a fair yield. A heteroaromatic (**4.295**), and an aliphatic ketone (**4.300**) were converted into the mesylate in good yields.

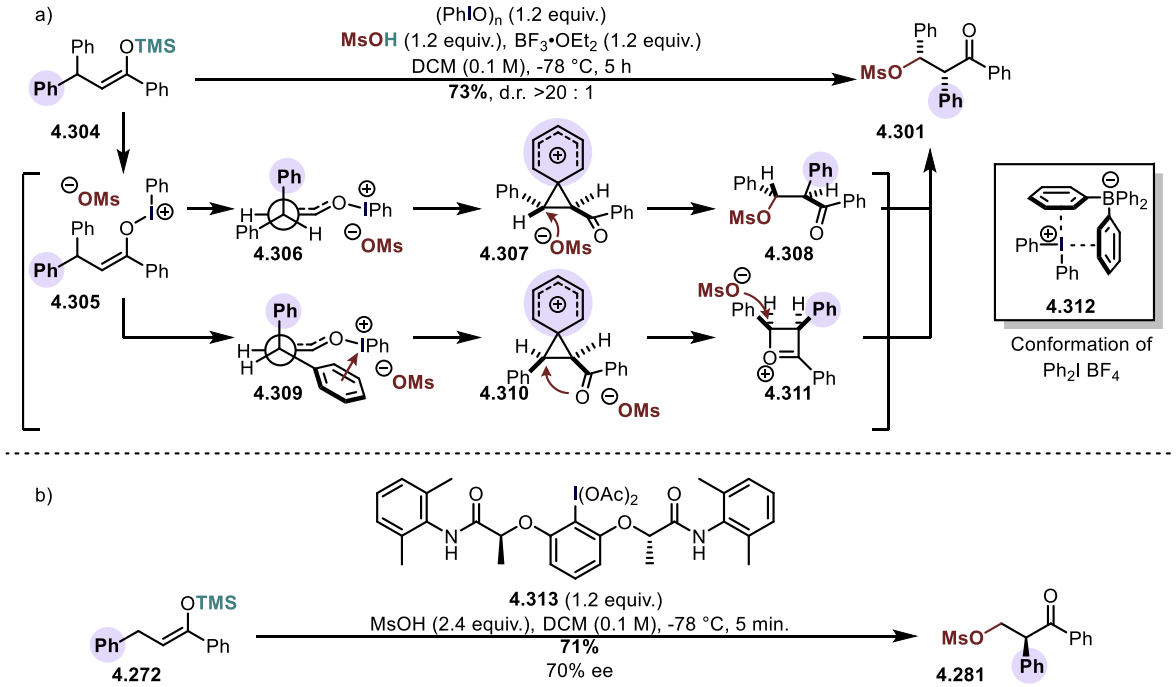


Scheme 4.27 – Substrate scope of the oxidative β → α aryl migration with subsequent β-functionalization. See supporting information for more details.

The electronic effects of the substituents on the migrating aryl moiety are more difficult to parametrize. However, if we assume that the electronic influence of substituents on a phenonium ion **4.303** and a benzylic cation **4.302** are similar, the modified substituent constants by Brown (σ^+) are appropriate parameters.[153] Both strongly electron-donating (**4.297**), and electron-withdrawing groups (**4.298**) seem to be compatible with the iodine(III)-promoted aryl migration. The smooth conversion of the CF_3-containing silyl enolether shows that even electron-poor arenes are prone to aryl migration. This

is not obvious from the kinetic data on aryl migration in solvolysis reactions (chapter 4.1.1.5). The use of *ortho* substituents on the migrating arene seems to lower the yield considerably (**4.299**).

A 3,3-diphenyl substituted silyl enolether **4.304** leading to **4.301** gave the desired product in more than 80% yield and as a single diastereoisomer under the usual reaction conditions. The stereochemical outcome is unexpected. In *Scheme 4.10a* we saw that the bromide **4.112** underwent a double inversion at the β-carbon atom due to the participation (bridging) of the carbonyl group. The bridging effect seems to be either absent (**4.306 → 4.308** - *Scheme 4.*28a) or a coordination of one of the phenyl groups to the iodonium ion favors the formation of the *cis* phenonium cation **4.310**. π-coordination of aromatic rings on iodonium species has been observed, for instance in the X-ray single crystal structure of $Ph_2I\ BPh_4$ (**4.312** – *Scheme 4.28a – box*).[877,878]



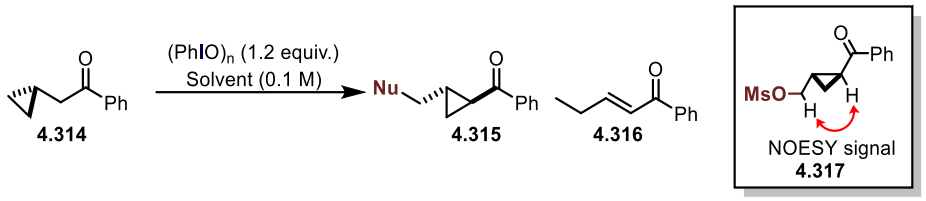
*Scheme 4.228 – a) Proposed reaction mechanism for the high diastereoselectivity observed in the rearrangement of **4.304**. b) Successful enantioselective variant with a stoichiometric chiral oxidant.*

The use of the chiral enantiopure iodine(III) compound **4.313** in a modified reaction procedure gave the desired product in over 70% yield and with an enantiomeric excess of 70%, showcasing that a highly enantioselective version might be developed.

4.3.2. Cyclopropanation

4.3.2.1. *Optimization*

Inspired by the work of Pardo and Charpentier-Morize (*Scheme 4.10b*), we investigated if similar rearrangements can be observed in a setting where ketones are oxidized in α-position by an iodine(III) compound.[743] After a few initial trials we found that the ketone **4.314** can be indeed rearranged in low yield (37%) to the internal cyclopropane **4.315**, exclusively as the *trans* isomer. The relative configuration was confirmed by 2D NMR where a unique NOE coupling can be observed between the α-proton of the ketone and the exocyclic methylene (**4.317**).

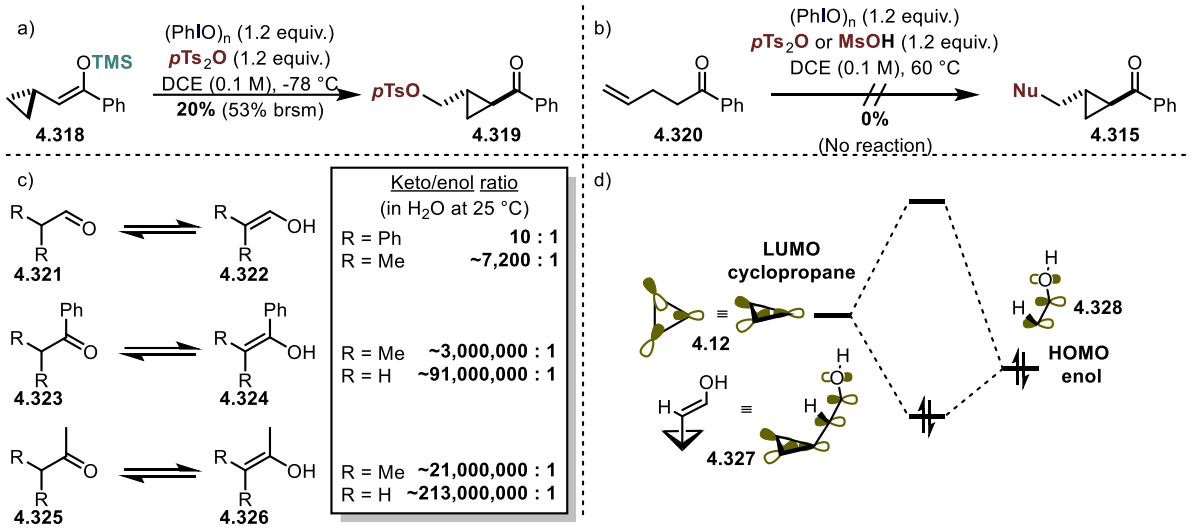


Entry	Additive	Solvent	Time	Temp.	Yield **4.314**	Yield **4.315**
1	**MsO**H (2.0 equiv.)	DCE	1 h	60 °C	45%	25%
2	**MsO**H (2.0 equiv.)	DCE	4 h	60 °C	7%	37%
3	**MsO**H (2.0 equiv.)	DCE	14 h	r.t.	2%	32%
4	**MsO**H (2.0 equiv.)	DMF	4 h	60 °C	77%	N.D.
5	**MsO**H (2.0 equiv.)	Et_2O	4 h	35 °C	84%	N.D.
6	**MsO**H (2.4 equiv.)	THF	4 h	60 °C	75%	N.D.
7	**MsO**H (2.0 equiv.)	$MeNO_2$	14 h	60 °C	N.D.	N.D.
8	***p*Ts$_2$O** (1.1 equiv.)	DCE	4 h	60 °C	26%	41%
9	***p*Ts$_2$O** (1.1 equiv.)	DCE	14 h	60 °C	26%	43%
10	***p*Ts$_2$O** (2.0 equiv.)	DCE	4 h	60 °C	24%	39%
11	***p*Ts$_2$O (2.0 equiv.)**	**DCE**	**14 h**	**60 °C**	**N.D.**	**52%**
12	**Tf$_2$O** (1.1 equiv.)	DCE	4 h	60 °C	N.D.	N.D.
13	***p*TsO**H (1.2 equiv.)	DCE	4 h	60 °C	10%	35%

Table 4.2 – Optimization for the oxidative cyclopropyl rearrangement.

The reaction has to be heated to 60 °C to afford reasonable amounts of product within 4 hours, but can also be stirred at room temperature overnight (14 h) to give similar results. The major side product was identified as the enone **4.316** although it was formed in relatively small amounts. This enone is the product of an acid catalyzed rearrangement: when **4.314** is submitted to a solution of MsOH in DCE at 60

°C for 4 h, it completely isomerizes to **4.316**. Ethereal solvents (Et_2O, THF), DMF and nitromethane did not allow any formation of the desired product. Varying the activator and the equivalents of the stoichiometric species gave us finally a maximum of 52% yield of **4.315**. *p*-Toluenesulfonic anhydride (*p*Ts_2O) showed a cleaner reaction profile than its corresponding acid, probably because it does not catalyze the undesired isomerization of the starting material. In order to improve the efficiency of the reaction, we used the corresponding trimethylsilyl enolether **4.318** at low temperature but observed only 20% of the product (by NMR - *Scheme 4.29a*).



Scheme 4.29 – Unproductive cyclopropyl rearrangement starting from a silyl enolether. b) γ,δ-Enones are unreactive under the usual reaction conditions. c) Keto-enol tautomer ratio in aqueous solution of different carbonyl compound. d) Rational for an enhanced enol-content in α-cyclopropyl carbonyl compounds.

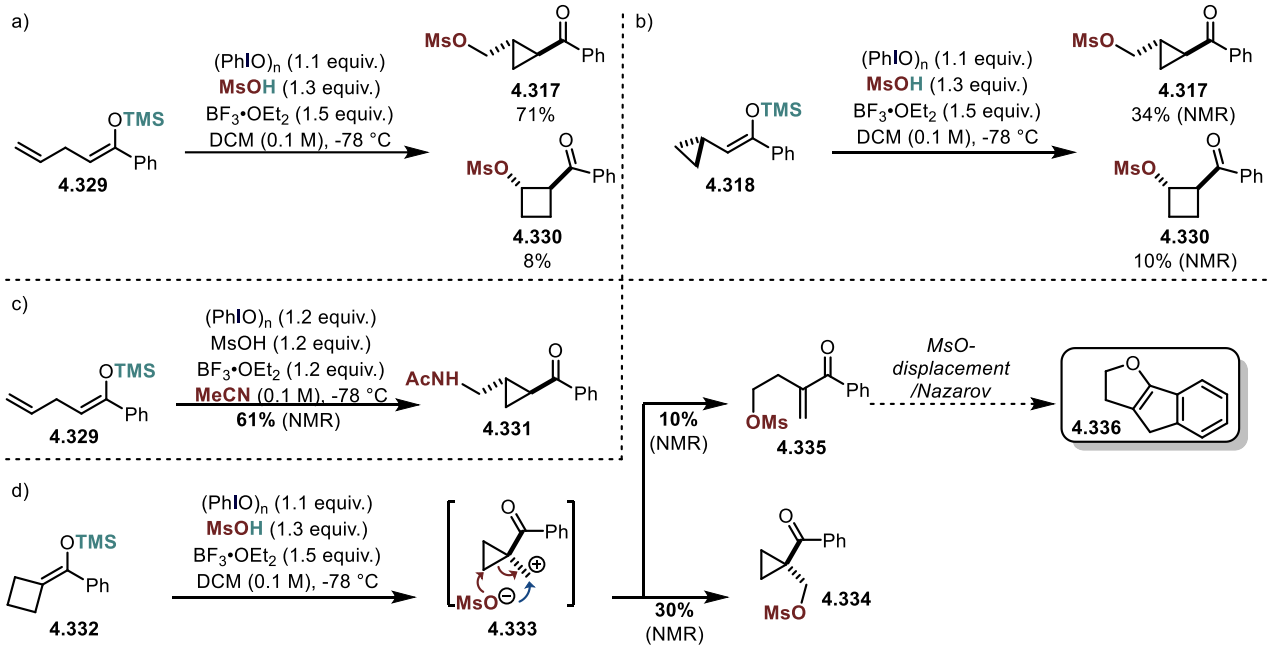
Drawing on the fleeting nature of the generated carbocation, we speculated that the oxidation of other ketones would lead to the same intermediate; namely, the α-oxidation of the ketone **4.320** (*Scheme 4.29b*). However, this ketone seems to be unreactive under the reaction conditions. This is probably due to a marginal population of its reactive enol tautomer (*Scheme 4.29c/d*)[879] while cyclopropyl-acetophenone might have a biased equilibrium, due to a stabilizing interaction of the π-system of the enol with the LUMO of the cyclopropyl moiety (**4.327** – *Scheme 4.29d*). We could not find any data on the equilibrium of α-cyclopropyl substituted carbonyl compounds with their enol tautomers, but it has been

shown by NMR experiments that α-deuterium exchange in the α-position of such compounds is 3 – 7 times faster than in acyclic analogs.[880]

The low reactivity of the ketone **4.320** can be circumvented by using its trimethylsilyl enolether derivative **4.329**. Indeed, by using conditions slightly different from those employed for the β→α phenyl migration, we observed the desired product exclusively as the *trans* diastereoisomer in more than 70% yield (*Scheme 4.30a*). Commercially available $PhI(OAc)_2$ can also be used as the oxidant but gives the mesylate product **4.317** in slightly lower yields. The reaction of the cyclopropylacetophenone-derivative **4.318** under the same conditions on the other hand was rather messy, although the product was detected in 34% NMR yield (*Scheme 4.30b*). Interestingly, we were able to isolate another structural isomer of the product; the cyclobutane **4.330** in the reaction described in *Scheme 4.30a*. This product was also formed as a single diastereoisomer, most likely (but not certain) in a *trans* configuration (suggested by 2D NMR and J^3 H-H coupling constants). The formation of similar products following a similar mechanism was reported notably the groups of Chang, Park and Baik in which aryl-substituted cyclobutanes were synthesized exclusively in *cis* configuration from homoallylic alcohols using Lewis acid catalysis.[881,882]

The reaction of the homoallylic silyl enolether **4.329** seems to be very fast: the substrate is consumed within a fraction of a minute (by TLC), not only at -78 °C but even at -100 °C (both of which lead to the same outcome). The use of DCM (or other chlorinated solvents) was again a requirement for a productive transformation. While the reaction lead mainly to α-functionalization (in absence of a rearrangement) in THF, very low yields were observed in $EtNO_2$ or toluene. Acetonitrile reacted as a nucleophile to give the desired disubstituted cyclopropane as the acetamide in more than 60% NMR yield at 0 °C (*Scheme 4.30c*). As discussed in the introduction, cyclopropyl carbinyl cations can be alternatively generated from cyclobutylcation precursors. When the cyclobutane **4.332** was submitted to the usual conditions, the expected cyclopropane **4.334** was observed in 30% yield,[883] together with an enone side product **4.335**. Interesting is that under slightly different conditions the heterocyclic compound **4.336** was

likely formed (suggested by ^{1}H NMR and MS data of partially purified fractions), which may have been generated *via* an intramolecular activation of the ketone by departure of the mesylate followed by a Nazarov cyclization

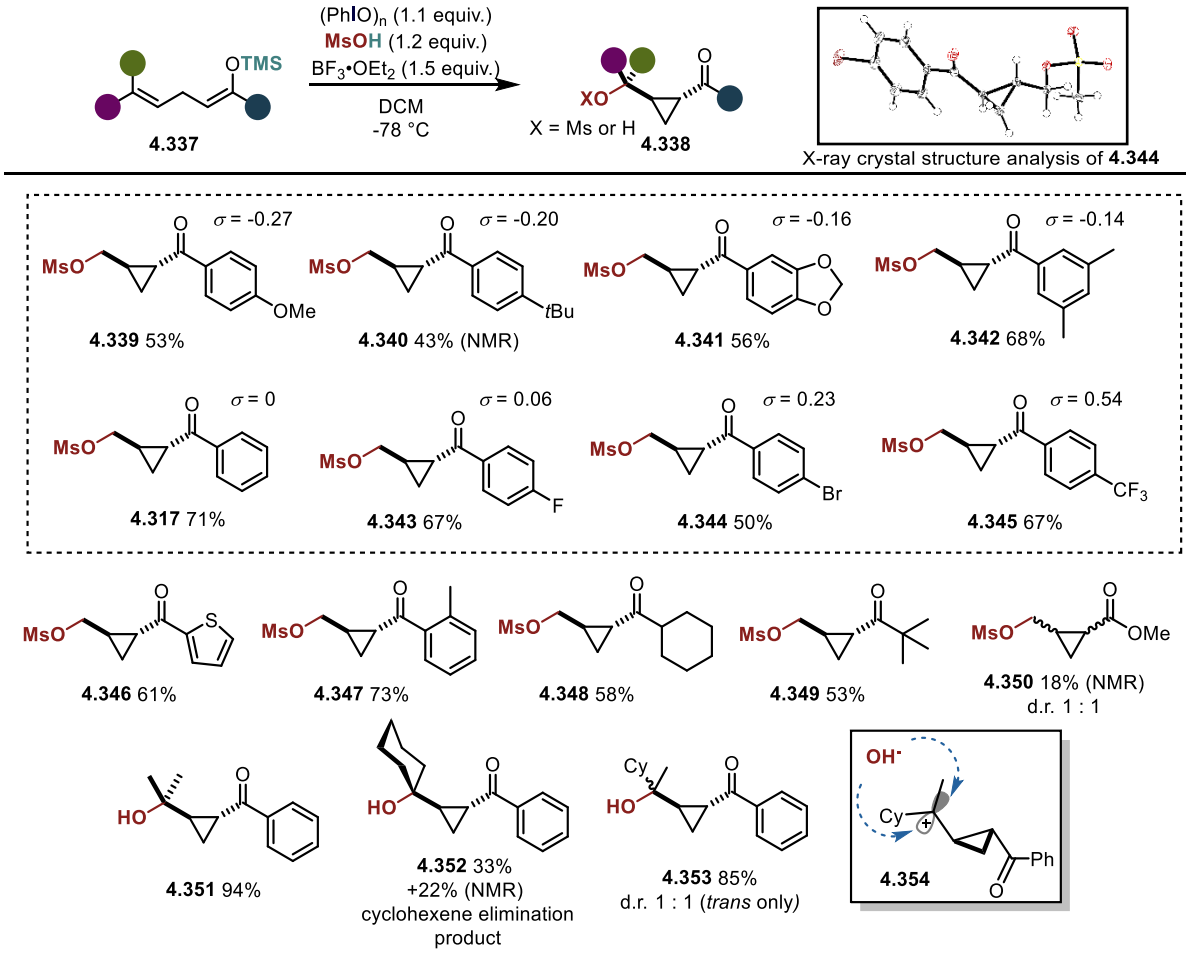


Scheme 4.3023 – a) Silyl enolethers as reactive ketone-derivatives. b) α-Cyclopropyl silyl enolethers react less efficiently under the same reaction conditions. c) The electrophilic intermediate can be trapped by nucleophilic solvents. d) Similar but less productive reactivity leading to geminal substituted cyclopropanes and α,β-enones.

4.3.2.2. *Substrate scope*

Several aryl ketones are compatible with the reaction conditions, ranging from those carrying strongly electron-donating (**4.339**) to strongly electron-withdrawing (**4.345**) groups (*Scheme 4.31*). The parametrization of the electron effects can be again achieved by using Hammett's substituent constants.[487] Observable decrease in yield is not caused by *ortho* substituents. The structure of **4.344** was studied by x-ray crystallography and shows the expected features, such as the carbonyl group bisecting the cyclopropane. Pleasingly, not only a hetereoaromatic ketone (**4.346**) but also a set of purely aliphatic cyclopropyl ketones (**4.348**/**4.349**) were formed in fair yields and as single diastereoisomers. However, in some cases traces of the corresponding alcohol were formed, which were difficult to separate from the mesylate. Most of the silyl enolethers were synthesized as *Z*-isomers (*Z:E* >20:1). However, the precursor

of **4.348** was obtained as a 1:1 *E:Z* mixture and used as such. The comparable outcome of the reaction suggests that the configuration of the enol plays a minor role. Ketene acetals seem not to be suitable substrates (**4.350**). Only little cyclopropanation was observed in a messy reaction and interestingly devoid of stereoselectivity. A rationale for the low yield might be the high reactivity of **4.350**, while the lack of stereoselectivity can be either explained by a possible bridging of the nucleophilic ester moiety, which might compete with other reaction routes or with the low steric demand of the methoxy group.



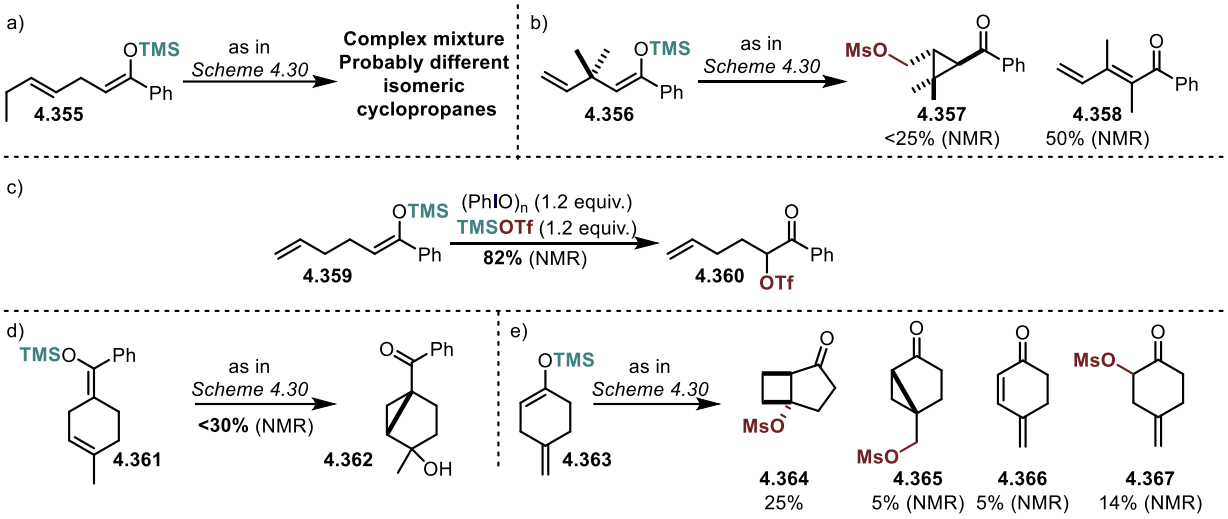
Scheme 4.241 – Substrate scope of the oxidative diastereoselective cyclopropanation reaction by using γ,δ-enone derivatives. See supporting information for more details.

A silyl enolether containing a trisubstituted alkene did not give the expected mesylate product but the alcohol **4.351** instead. This is likely due to the different nature of tertiary cyclopropyl carbinyl cations. The cation is probably so stable that it is not (irreversibly) attacked by the mesylate. Instead, it is quenched by H_2O during the aqueous workup. Cyclic tertiary cations, on the other hand, were prone to

elimination and yielded a mixture of the tertiary alcohol (**4.352**) and the corresponding cyclohexene derivative. When two different aliphatic substituents were attached to the terminal position of the alkene a 1 : 1 mixture of the two possible *trans* isomers was observed (**4.353**). This is because the two faces of the cation are only distinguished by the distal benzoyl moiety (**4.354**).

The vicinal disubstituted alkene **4.355** gave a messy mixture (*Scheme 4.32a*), from which no single compound could be isolated. The NMR spectra suggest several isomeric cyclopropanes. This is in accordance with the high fluxionality of secondary cyclopropyl carbinyl cations. Complete decomposition into a variety of identified products was observed when the terminal ethyl-group of **4.355** was exchanged with a phenyl group. When the central methylene (β-position) was substituted with one methyl group, similar observations were made. The analogous dimethylated species **4.356** on the other hand, was prone to an oxidative [1,2]-methyl shift, with a subsequent elimination (*Scheme 4.32b*). The desired cyclopropane was observed in less than 25% NMR yield. Importantly, the nucleophilic attack of the alkene did not take place when the olefin was placed one CH_2 further away (*Scheme 4.32c*). Instead, the α-triflate **4.360** was formed in a clean reaction. This result suggests that the interaction of the alkene with the "enolonium" species is indeed not a generic intramolecular nucleophilic attack and that the reactivity of γ,δ-unsaturated silyl enolethers is closely bound to the formation of a relatively stable cyclopropyl carbinyl cation.

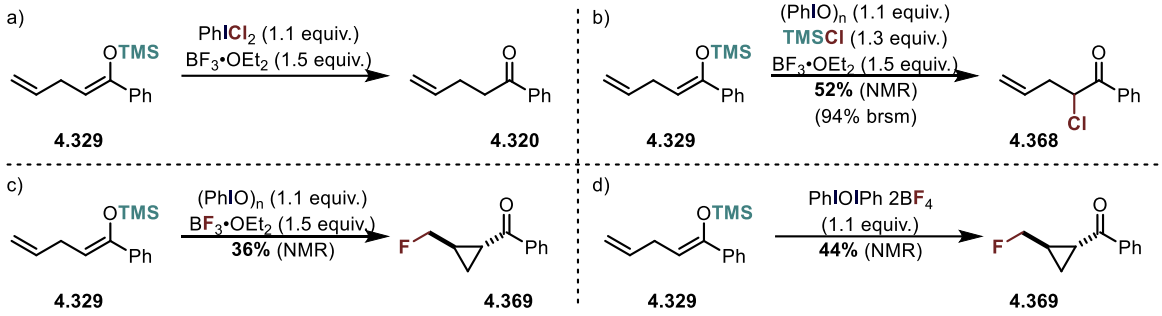
Transannular cyclopropanations of cyclohexane-derivatives were unfortunately unproductive. The cyclic substrate **4.363**, for instance, gave a mixture of several products (*Scheme 4.32e*): while the desired cyclopropane was formed in *ca.* 5% NMR yield, the [3.2.0] bicycloheptane **4.364** was isolated in 25% yield as the major product.[884]



Scheme 4.252 – a) Unproductive reaction of vicinal disubstituted alkenes. b) [1,2]-Methyl shifts seem to be favored in β-disubstituted derivatives. c) Increasing the distance of the silyl enolether to the alkene by one CH_2 group leads to a different reactivity. d/e) Cyclic substrates seem to react in a messy reaction profile.

4.3.2.3. *Nucleophile scope*

After the exploration of the substrate scope, we investigated the use of different nucleophiles to either trap the electrophilic intermediate or displace the mesylate *in situ.* In our first attempts the ligands on the iodine(III) species were varied, since they can act as nucleophiles in the course of the reaction. While $PhICl_2$ gave only the unoxidized, deprotected ketone, activation of iodosobenzene with TMSCl and BF_3•OEt_2-promoted the α-chlorination of the ketone-derivative (*Scheme 4.33 a/b*).

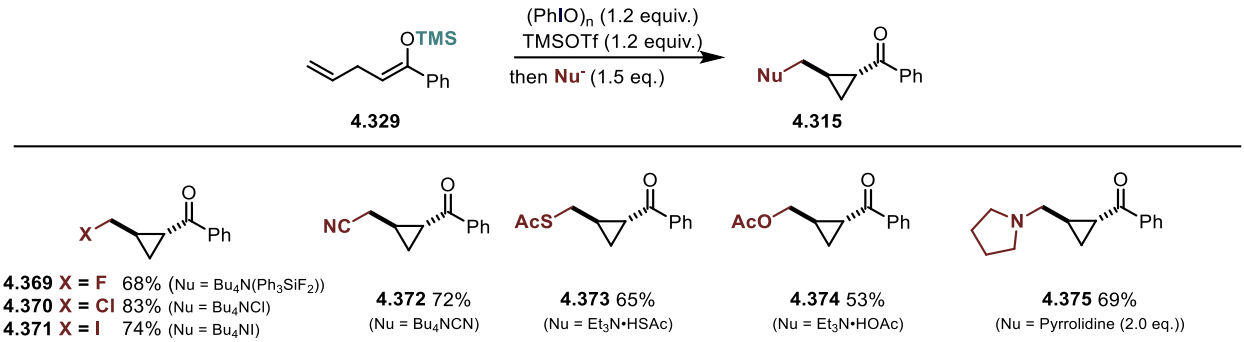


Scheme 4.263 – Initial trials on the nucleophile scope a) $PhICl_2$ lead only to the formation of the unprotected ketone. b) Activation of iodosobenzene with TMSCl and BF_3•OEt_2 lead to the α-chlorinated γ,δ-enone in a clean reaction. c) Low yielding fluorination of the intermediate with BF_3 as the fluoride source. d) Similar reaction with BF_4^- as the fluoride source.

Using weakly coordinating anions with a subsequent addition of the external nucleophile did also not land on fruitful ground. The cationic intermediate is so electrophilic that it abstracts fluorides from BF_4^- and other borates (*Scheme 4.33c/d*). This anion surprisingly outcompetes Et_2O, which is present in the mixture. This suggests indeed that a charged species (a "real" cation) is formed, as it is typical that

weakly nucleophilic anions (*i.e.* nucleofugal ions such as ClO_4^- or FSO_3^-) competitively bind to cationic atoms in the presence of other nucleophilic species.[885,886] Zefirov for instance showed that the perchlorate anion can act as a nucleophile on carbocations in presence of chloride anions and large excess of AcOH.[886]

Nucleophilic substitution of primary mesylates is generally feasible, but requires typically elevated temperatures and polar solvents,[887,888] which is not compatible with the reaction conditions for the oxidative cyclopropanation. Much more promising was an *in situ* displacement of a triflate, which can be theoretically formed when using TfOH instead of MsOH as the activator. However, by using TfOH we encountered reproducibility issues, associated with the formation of a sticky precipitate. It is indeed known that the activation of iodosobenzene with TfOH may cause unusual reaction pathways such as the formation of biaryl species from two molecules of iodosobenzene.[889]. The use of TMSOTf was much more reliable and usually resulted in a relatively clean formation of the cyclopropyl carbinyl triflate. However, this triflate is highly unstable and decomposes into several unidentified compounds when warming up to room temperature or quenching with an aqueous solution. At -78 °C however, it seems to be rather stable and can be smoothly and quickly displaced by a variety of nucleophiles in fair to good yields (*Scheme 4.34*). Several halides, including fluoride, were installed by using either the tetrabutylammonium salts (I^- and Cl^-) or the silicate salt TBAT (F^-). Nitrogen-, oxygen-, and sulfur nucleophiles also smoothly led to the expected product without further complications. While an amine can be used directly (**4.375**), the acetate **4.374** and the thioacetate **4.373** are cleanly formed when *in situ* generated trimethylamine salts of (thio)acetic acid are added. Also tetrabutylammonium cyanide was used and yielded the desired product in a good yield (**4.372**). However, weaker nucleophiles, such as a second trimethylsilyl enolether, could not be successfully applied yet.

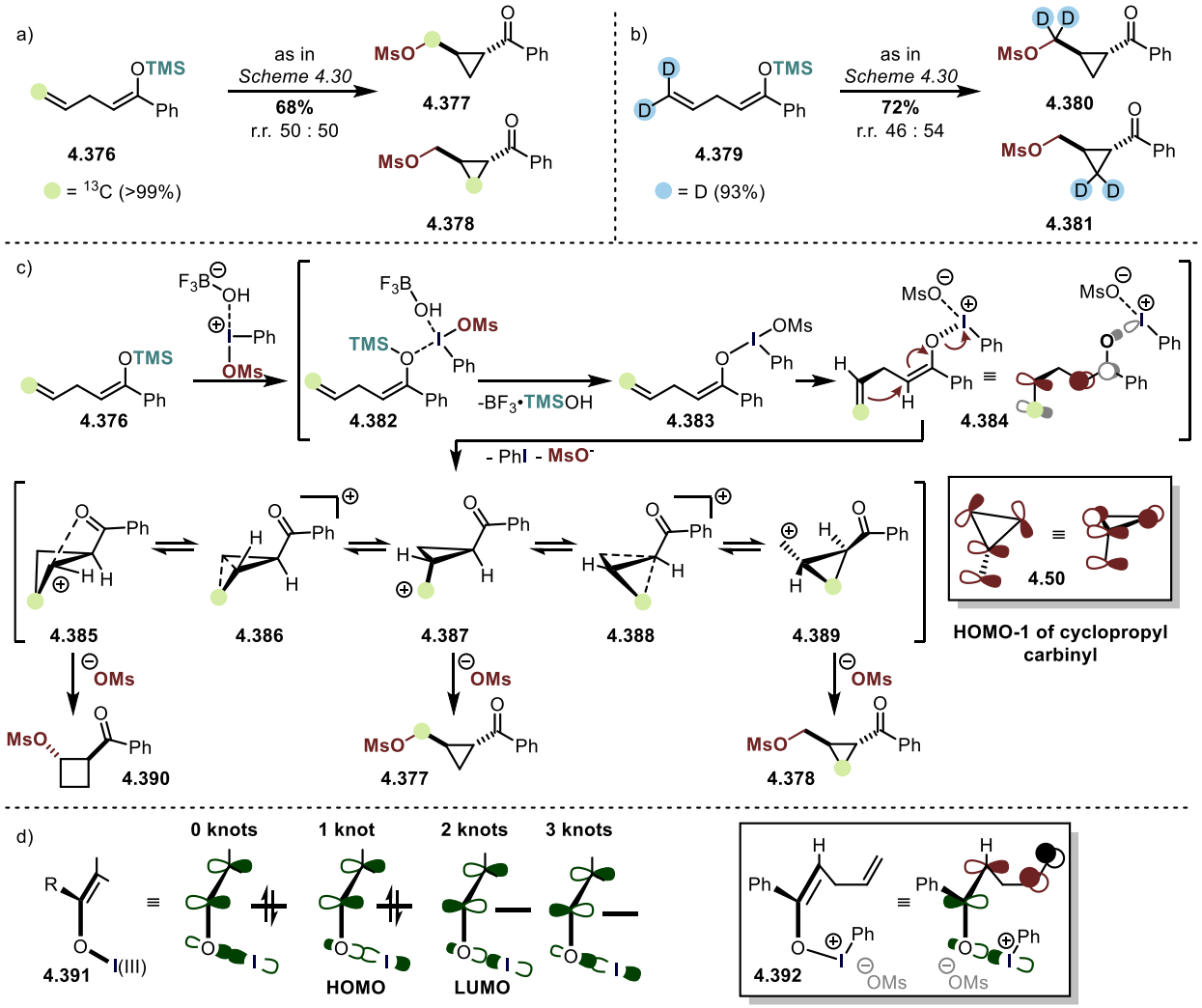


Scheme 4.274 – Nucleophile scope of the oxidative diastereoselective cyclopropanation reaction by using γ,δ-enone derivatives. See supporting information for more details.

4.3.2.4. *Mechanistic study*

In order to understand the reaction mechanism, we synthesized two different isotopically labeled compounds (*Scheme 4.35a/b*): the ^{13}C labeled **4.376** and the *bis*deuterated isotopologue **4.379**. Both compounds showed that the labeled atoms were equally shared in two different positions during the intramolecular cyclopropanation reaction. 50% of the labeled carbon atoms were found in the exocyclic methylene moiety (**4.377**) and the other 50% in the endocyclic methylene group (**4.378**). The deuterated species showed a slight excess of endocyclic deuterium (**4.381**), probably due to a secondary isotope effect. The scrambling of the isotopically labeled methylene group confirms the high fluxionality of the reactive species, but it is not definite proof for a non-classical carbocationic intermediate. Strong evidence for the non-classical nature might be challenging to obtain (it took more than 60 years to close the case on the 2-norbornyl cation). However, the results from the literature suggest that such an intermediate is likely formed, thus we propose it as a possibility in the following reaction mechanism: the silyl enolether attacks the electrophilic activated iodine(III) compound to form the complex **4.382**, which loses BF_3 and TMSOH and generates the enol-iodine species **4.383**. After isomerization of the compound, the HOMO of the alkene interacts intramolecularly with the LUMO of the enol-iodine species **4.384.** The π-orbitals of a general enol-iodine(III) species (including the LUMO) can be constructed analogously to the ones of butadiene and the facility of the interaction can be visualized by a simple molecular plastic model (*Scheme 4.34d*). Notably, the interaction of the two moieties reassembles the HOMO-1 of the cyclopropyl carbinyl

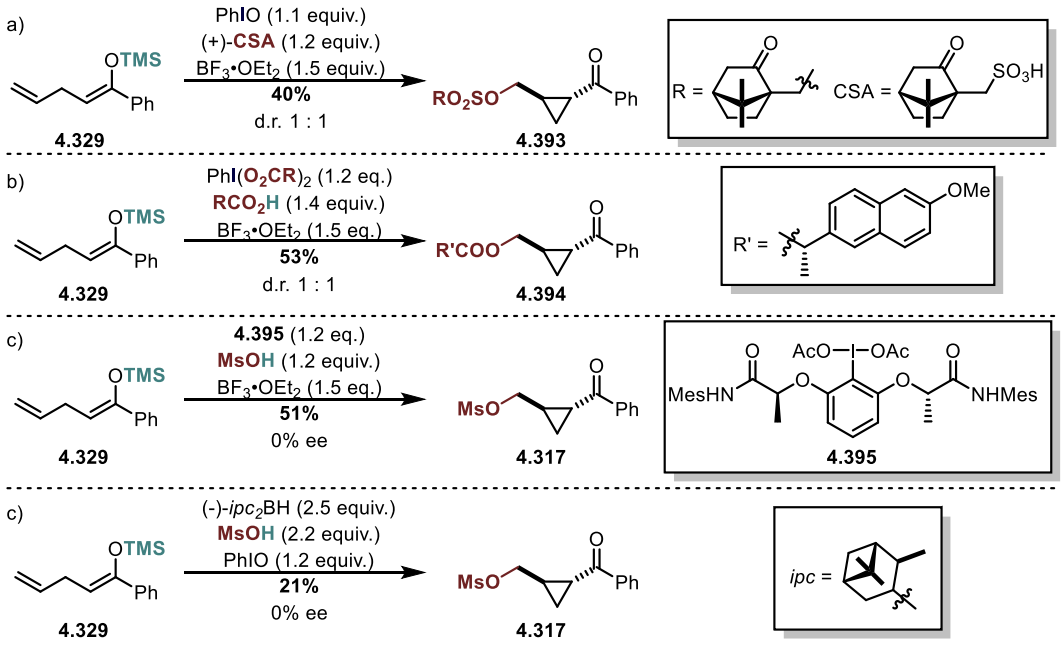
cation **4.50** (*Scheme 4.35c box – see also Figure 4.1b*) and promotes the decomposition of **4.384** into PhI and the carbocationic fluxional intermediate **4.387**. The isotopical isomers **4.387** and **4.389** form the two observed isomers **4.377** and **4.378**, when attacked by mesylate anion. Alternatively, the non-classical carbocation **4.388** might be attacked in a similar fashion on one of the two endocyclic methylene positions. The observed cyclobutane side-product is formed by the nuclophilic attack of MsO^- on either the bridged classical carbocation **4.385** or the non-classical carbocation **4.386**.



Scheme 4.35 – a) ^{13}C labeling experiment. b) Deuterium labeling experiment. c) Proposed reaction mechanism. d) Approximate π-molecular orbitals of an iodine(III)-enol species.

4.3.2.5. *Study on enantioselectivity*

Since the reactive species is apparently C_s symmetric (at least on the reaction time scale), a chiral desymmetrization of the cation should be theoretically feasible. Very recently, Ben List *et al.* showed that precursors of the 2-norbornyl carbocation can be indeed deracemized.[890] In our first investigation, we used several enantiopure acids as nucleophiles and speculated that a diastereoisomeric excess should be observed, due to a discrimination of one of the two enantiotopic methylene groups in the cationic intermediate. Unfortunately camphorsulforic acid (*Scheme 4.36a*), or Naproxen (*Scheme 4.*36b) did not show any diastereoselectivity. The use of a chiral iodine(III) compound lead to the formation of a racemic product (*Scheme 4.36c*) and the i*n situ* formation of the enantiopure Lewis acid (-)*ipc*$_2$BOMs similarly did not lead to any measurable enantioinduction (*Scheme 4.36d*).

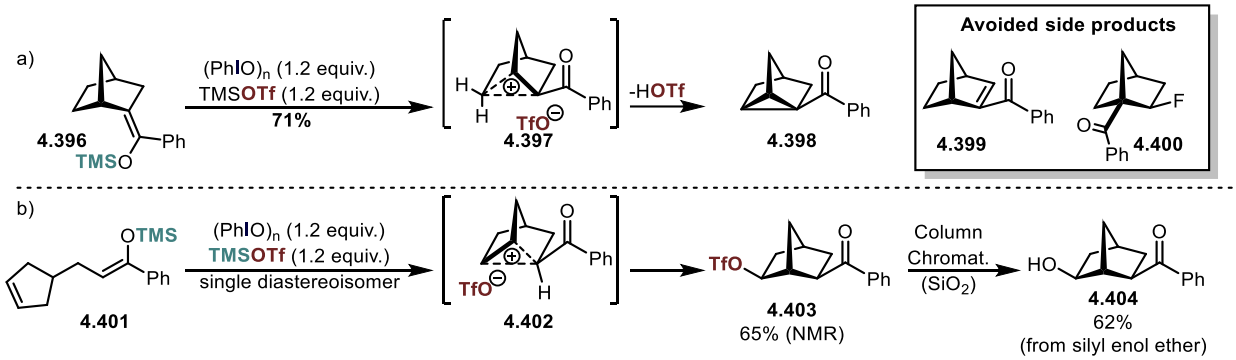


Scheme 4.3628 – Several diastereoselective and enantioselective approaches to desymmetrize the C_s-symmetric intermediate.

4.3.2.6. *Tricyclanization*

The α-oxidation of silyl enolethers attached to norbornyl-type structures gives rise to non-classical cations, which can rearrange and react in different ways. However, by applying a mixture of PhIO and TMSOTf at low temperatures to those substrates, the nortricyclane product is selectively formed, by

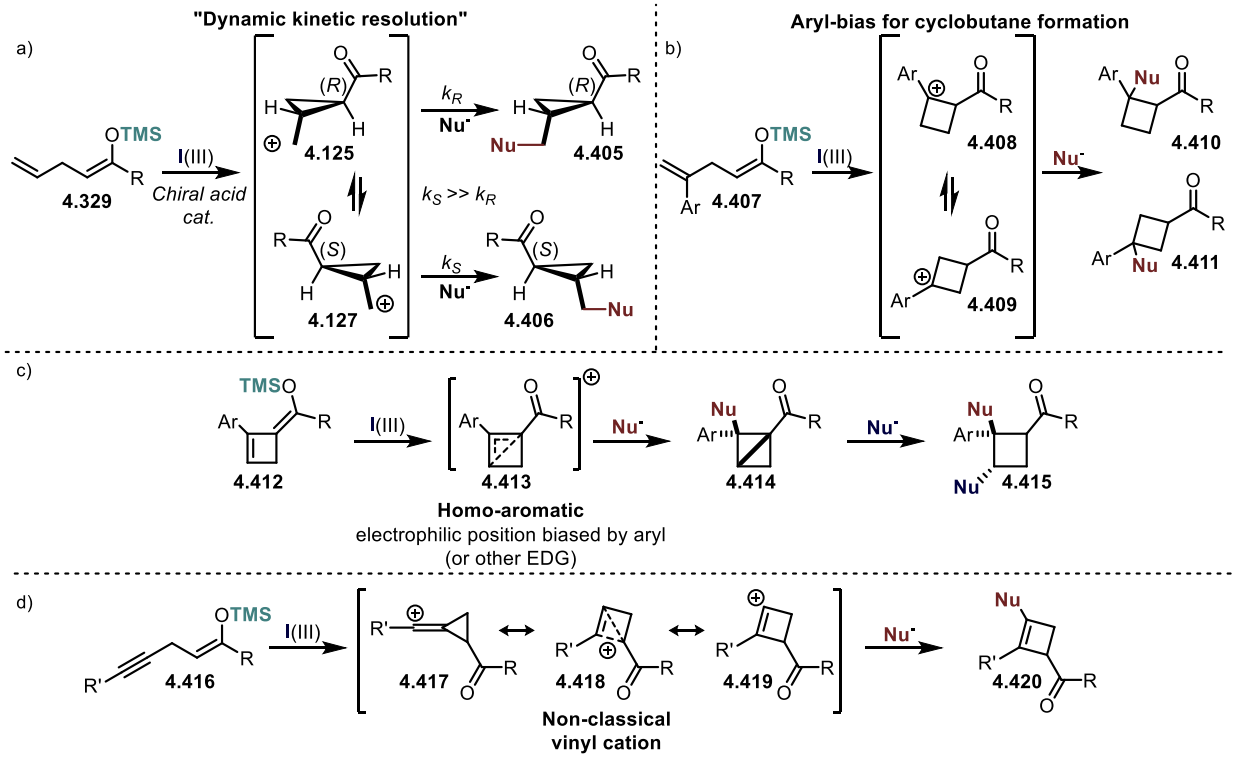
deprotonation of the "protonated cyclopropane" intermediate **4.397** (*Scheme 4.37a*). Previous attempts by using PhIO and BF_3•OEt_2 gave large amounts of inseparable α,β-desaturation product **4.399**, and/or the fluoride **4.400**. Later, we wanted to investigate if the so-called "π-route" (*see Scheme 4.4*) leads to the same product. The silyl enolether **4.401** however, does not lead to the non-classical carbocation **4.397** but to its isomer **4.402**. We hypothesized that the deprotonation of this species would be facilitated, because an electron-withdrawing group is attached to the hypercoordinated carbon atom. However, submitting the silyl enolether to the usual reaction conditions resulted in the clean formation of the 2-norbornyl triflate **4.403**, which hydrolyzed smoothly during purification to the corresponding norborneol. The addition of a relatively weak base (DIPEA) to the triflate did not afford the expected tricyclane. When the *bis*iodonium compound PhIOIPh $2BF_4^-$ was mixed with a solution of **4.401** the corresponding fluoride of **4.404** was observed as the major product.



Scheme 4.37 – a) Selective tricyclenization of a 2-benzoyl-norbornane silyl enolether. The box depicts products which are usually formed but were avoided by this approach. b) The "π-route" towards a non-classical carbocation does not yield a nortricyclene but a norbornyl triflate instead.

4.4. Conclusion and Outlook

We have demonstrated 1) that the oxidative β→α phenyl migration on simple saturated ketones can be synthetically exploited for the synthesis of α-arylated-β-functionalized ketones and 2) that the α-oxidation of γ,δ-unsaturated ketone-derivatives leads to a very fast *trans*-selective cyclopropanation reaction. The latter reaction proceeds *via* a symmetrical intermediate (on the reaction time scale) and can be thus theoretically desymmetrized in a chiral environment. This goal however, has not been achieved so far and may be continued in further investigations. Especially catalytic systems (asymmetric counteranion directed catalysis) would be attractive for such a "dynamic kinetic resolution" (*Scheme 4.38a*).



Scheme 4.298 – a) Potential for a "dynamic kinetic resolution" of the two classical carbocations towards enantiopure cyclopropanes. b) Biased substrate for the synthesis of cyclobutanes. c) Synthesis of bicyclo[1.1.0]butanes by the generation of a homoaromatic cation. d) Synthesis of cyclobutenes by generation of a non-classical vinyl cation.

The selectivity of the cyclopropanation reaction might be shifted towards the cyclobutane by-product by the use of biased substrates. γ-aryl-γ,δ-desaturated silyl enolethers might be appropriate candidates in this regard (*Scheme 4.38b*). Moreover, iodine(III) chemistry might be utilized for the generation of other

interesting carbocations, such as homoaromatic cyclobutenyl cation **4.413**.[891] This cation is potentially electrophilic at three distinct carbon atoms. The regioselectivity of a nucleophilic attack could be also biased by the use of an aryl substituent (*Scheme 4.38c*). The bicyclo[1.1.0]butane product **4.414** could be further functionalized in subsequent reaction steps, in order to afford highly substituted cyclobutanes.[892] "Non-classical" vinyl cations, could also be attractive targets (*Scheme 4.38d*).[893]

4.5. Supporting information

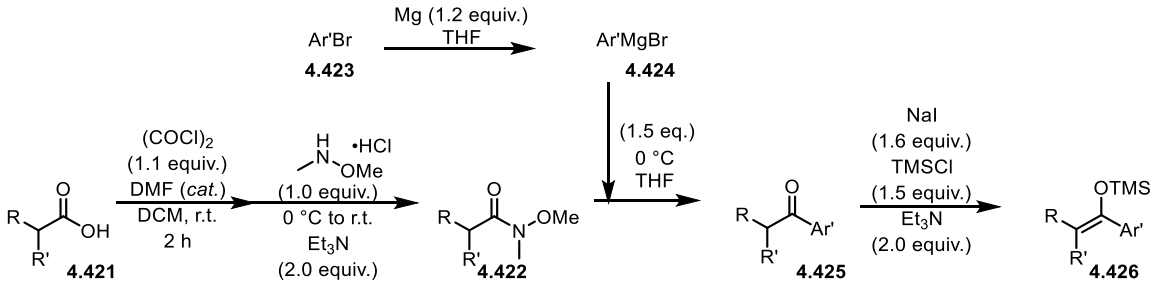
4.5.1. General

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 aluminum 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}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300K. Chemical shifts were 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 (^{13}C-NMR). Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Compounds, which were synthesized and characterized by coworkers can be found either in the SI of the published article or in the leaving reports.

4.5.2. Starting material synthesis

4.5.2.1. *Phenonium ion*

General procedure A



Scheme 4.309

This reaction step was carried out under air atmosphere. The carboxylic acid **4.421** was dissolved in DCM (0.3 M) and one drop of DMF was added. Then oxallylchloride (1.1 equiv.) was added quickly. After 2 h of stirring, the solvent was evaporated to yield the crude acyl chloride. The hydrochloride salt of *N*-methoxy-*N*-methylamine (1.0 equiv.) was dissolved in DCM (0.3 M) and cooled to 0 °C. Et_3N (2.0 equiv.) was added dropwise and stirred for 5 minutes at the same temperature. Then, the neat acyl chloride was added dropwise to the solution. The flask containing the acyl chloride was rinsed with DCM (5-10 mL). The solution was warmed up to room temperature and stirred for 2 h. Then, the reaction was quenched with $HCl_{aq.}$ (1 M) and transferred into a seperatory funnel. After washing with the aforementioned HCl solution, the organic layer was washed with saturated aqueous $NaHCO_3$, and with water. After drying the combined organic phases over Na_2SO_4, they were filtered and volatiles were removed under reduced pressure. The obtained Weinreb-amide was used without further purification.

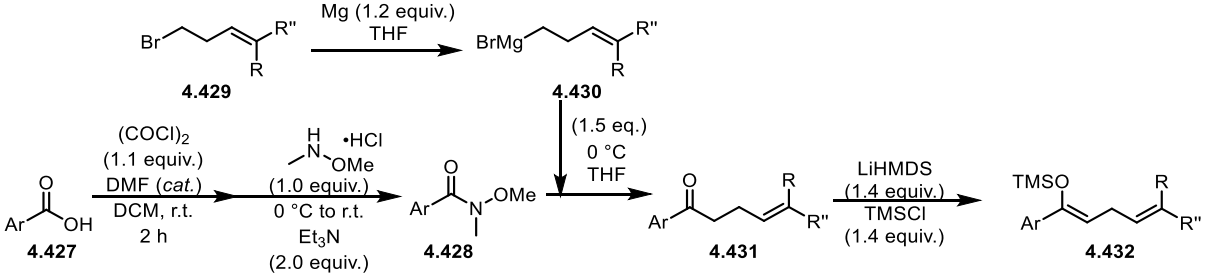
Magnesium turnings (1.2 equiv.) were suspended in THF (1/2 of the total volume) and a solution of the bromoarene **4.423** in THF (1/2 of the volume) was added slowly *via* a dropping funnel under vigorous stirring (Concentration of the bromide after the addition was 0.5 M). The reaction was stirred until most of the magnesium dissolved. A quantitative formation of the Grignard-reagent was assumed and used as such. The previously obtained amide was dissolved in THF (0.4 M) and cooled to 0 °C. Then, a THF solution of the arylmagnesium bromide **4.424** in THF (0.5 M) was added dropwise. The reaction was

stirred for 3 h at 0 °C. Then the reaction was quenched with saturated aqueous NH_4Cl and extracted with diethylether (2 x). The combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvent gave the crude ketone **4.425**, which was purified by column chromatography. (typical eluent - Heptanes : EtOAc, 98 : 2 → 60 : 40 v/v%).[894]

A flame-dried round bottom flask was charged with the ketone **4.425** (1.0 equiv.), CH_3CN (0.5 M with respect to the ketone) and NaI (1.6 equiv.), followed by the addition of TMSCl (1.5 equiv.). The reaction mixture was stirred for 10 minutes, then NEt_3 (20 mmol, 2.0 equiv.) was slowly added and the reaction was further stirred for 12 h at room temperature. The reaction mixture was poured into aqueous *sat.* $NaHCO_3$ (100 mL) solution, and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (100 mL), dried with $MgSO_4$, concentrated and purified *via* column chromatography (typical eluent - Heptanes : Toluene, 98 : 2 → 50 : 50 v/v%) to afford the desired silyl enolether **4.426**.[895]

4.5.2.2. *Cyclopropanation*

General procedure I



Scheme 4.40

The first reaction step was carried out under air atmosphere. The benzoic acid **4.427** was dissolved in DCM (0.3 M) and one drop of DMF was added. Then oxallylchloride (1.1 equiv.) was added quickly. After 2 h of stirring, the solvent was evaporated to yield the crude acyl chloride.

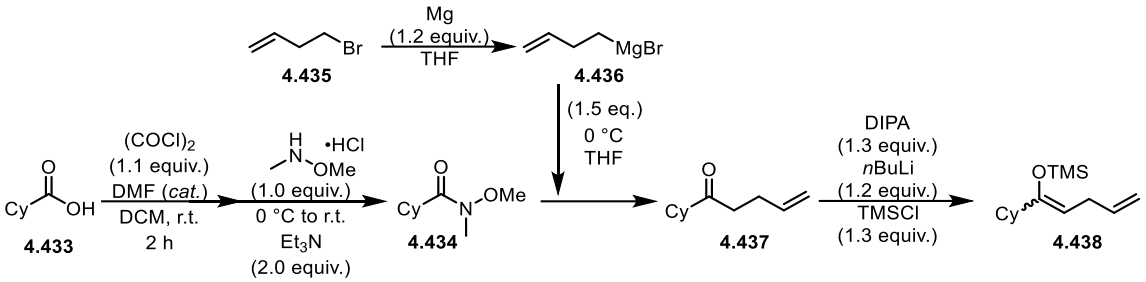
The hydrochloride salt of *N*-methoxy-*N*-methylamine (1.0 equiv.) was dissolved in DCM (0.3 M) and cooled to 0 °C. Et_3N (2.0 equiv.) was added dropwise and stirred for 5 minutes at the same temperature. Then the neat acyl chloride was added dropwise to the solution. Afterwards, the flask containing the acyl chloride was rinsed with DCM (5-10 mL). The solution was warmed up to room temperature and stirred for 2 h. Then the reaction was quenched with $HCl_{aq.}$ (1 M) and transferred into a seperatory funnel. After washing with the aforementioned HCl solution, the organic layer was washed with saturated aqueous $NaHCO_3$, and with water. After drying the organic phase over Na_2SO_4 the layer was filtered and volatiles were removed under reduced pressure. The Weinreb-amide (**4.428**) obtained without further purification.

Magnesium turnings (1.2 equiv.) were suspended in THF (1/2 of the total volume) and a solution of 1-bromo-3-pentene (**4.429**) in THF (1/2 of the volumne) was added slowly *via* a dropping funnel under vigorous stirring (Concentration of the bromide after the addition was 0.5 M). The reaction was stirred until most of the magnesium dissolved. A quantitative formation of the Grignard-reagent was assumed and used as such. The amide obtained was dissolved in THF (0.4 M) and cooled to 0 °C. Then a THF solution of 3-butene-1-magnesium bromide in THF (0.5 M) was added dropwise. The reaction was stirred for 3 h at 0 °C. Then the reaction was quenched with saturated aqueous NH_4Cl and extracted with diethylether (2 x). The combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvent gave the crude ketone **4.431**, which was purified by column chromatography. (Typical eluent - Heptanes : EtOAc, 98 : 2 → 60 : 40 v/v%).[894]

A solution of LiHMDS in THF (0.5 M, 1.4 equiv.) was cooled to 0 °C and a solution of the ketone **4.431** in THF (1 M, 1.0 equiv.) was added dropwise. The mixture was stirred for 30 minutes at the same temperature. Afterwards, TMSCl (1.4 equiv.) was added dropwise, the cooling bath was removed and the reaction was stirred for 2 h. Conversion was checked by TLC. Volatiles were removed under reduced pressure. The crude was purified by column chromatography. Most of the materials were very stable and

apolar and were eluated with pure heptanes. Electron-rich silyl enolethers had to be filtered quickly through a silica plug to yield the desired product **4.432** (Typical eluent - Heptanes : Et_2O, 96 : 4).[896]

Procedure II

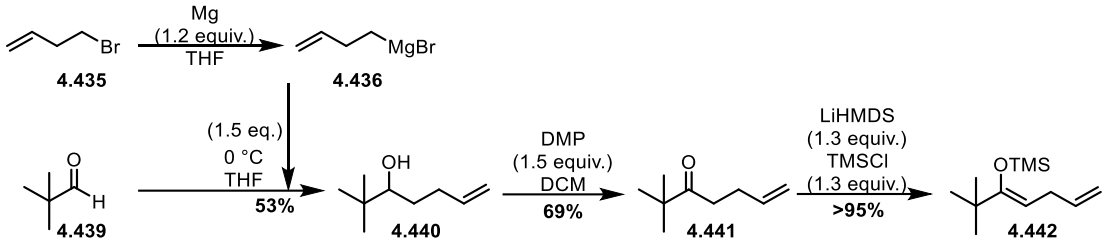


Scheme 4.311

The ketone **4.437** was obtained by the same route described in general procedure I in 84% yield as a colorless liquid (see S*cheme 4.40*).

Distilled di*iso*propylamine (1.3 equiv., 1.3 mmol, 182 µL) was dissolved in THF (1 mL) at 0 °C and *n*BuLi in hexanes (2.5M, 1.2 equiv., 1.2 mmol, 0.48 mL) was added dropwise. The mixture was stirred for 15 minutes at the same temperature and then cooled to -78 °C. A THF solution of the ketone (1M, 1.0 equiv., 1.0 mmol, 166 mg) was added dropwise. The mixture was warmed to room temperature over 30 minutes and TMSCl (1.3 equiv., 1.3 mmol, 330 µL) was added. The reaction was stirred for 5 h at room temperature. The volatiles were removed under reduced pressure and the residue was dissolved in a minimal amount of chloroform. The dissolved crude was loaded on a silica plug, which was rinsed quickly with heptanes (ca. 200 mL). After evaporating the solvent the product was obtained as a colorless liquid. (yield 235 mg, >95%).[897]

Procedure III



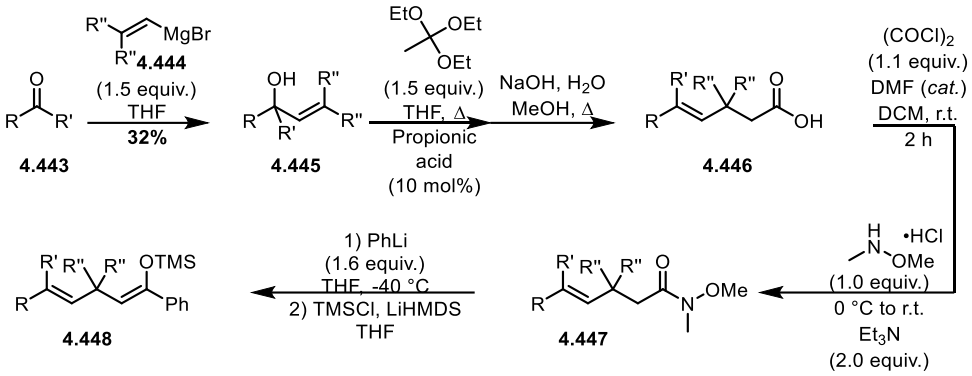
Scheme 4.322

Pivalaldehyde was dissolved in THF (0.5 M, 5.0 mmol, 0.54 mL) at 0 °C and a THF solution of 3-butene-1-magnesium bromide in THF (0.5 M, 15 mL, 1.5 equiv.) was added dropwise. The reaction was stirred for 3 h at the same temperature. Afterwards, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethylether (2x) and the combined organic phase was dried over Na_2SO_4 and filtered. Volatiles were removed under reduced pressure from the organic phase under reduced pressure and the crude was purified by column chromatography (Eluent - Heptanes : EtOAc, 90 : 10 → 50 : 50 v/v%) to yield the alcohol **4.440** as a yellow liquid (yield 380 mg, 53%).[898]

The alcohol (2.67 mmol, 380 mg) was dissolved in DCM (0.2 M, 13.5 mL) and Dess-Martin-Periodinane was added at once (1.5 equiv., 4.0 mmol, 1700 mg). The reaction was stirred 3 h at room temperature and quenched with aqueous saturated $Na_2S_2O_3$ solution. The mixture was extracted with diethylether (3 x), dried over Na_2SO_4 and filtered. The volatiles were removed under reduced pressure and the crude was purified by column chromatography (Eluent - Heptanes : EtOAc, 100 : 0 → 70 : 30 v/v%) to yield the ketone **4.441** as a yellow liquid (yield 259 mg, 69%).[899]

A solution of LiHMDS in THF (0.5 M, 1.3 equiv., 2.4 mmol, 4.8 mL) was cooled to 0 °C and a solution of the ketone in THF (1 M, 1.0 equiv., 1.85 mmol, 259 mg) was added dropwise. The mixture was stirred for 30 minutes at the same temperature. Afterwards, TMSCl (1.4 equiv., 2.4 mmol, 305 µL) was added dropwise, the cooling bath was removed and the reaction was stirred for 2 h. Volatiles were removed under reduced pressure. The crude was purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 70 : 30 v/v%) to yield the silyl enolether **4.442** as a colorless liquid. (385 mg, >95%).[896]

General Procedure IV



Scheme 4.333

The ketone **4.443** (1.0 equiv.) was dissolved in THF (0.5 M) at 0 °C. A THF solution of vinylmagnesium bromide **4.444** (1 M, 1.5 equiv) was added dropwise. The reaction was stirred at room temperature for 4 h before the mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc and the product was purified by vacuum distillation to yield the alcohol **4.445**.

The alcohol **4.445** (1.0 equiv.) was dissolved in triethyl orthoacetate (13.3 equiv.) and propionic acid (10 mol%) was added as the catalyst. The reaction was heated to 140 °C for 12 h. Afterwards most of the orthoacetate was distilled off, and a solution of $NaOH_{.}$ (2.5M) in a H_2O-MeOH mixture was added (1:9 v/v%, equal volume of the used orthoacetate). The mixture was heated to 100 °C for 1 h. After cooling down to room temperature, the mixture was diluted with $NaOH_{aq.}$ (1 M, equal volume of the used orthoacetate) and the aqueous phase was extracted with DCM. The aqueous layer was acidified to pH<1 by adding $HCl_{aq.}$ (4 M) and extracted again with DCM (5x). The combined organic layer was dried over Na_2SO_4, filtered and volatiles were removed. The crude was purified by column chromatography (Eluent - heptanes : EtOAc : AcOH, 93 : 5 : 2 → 60 : 38 : 2 v/v%) to yield the desired acid **4.446**.[900]

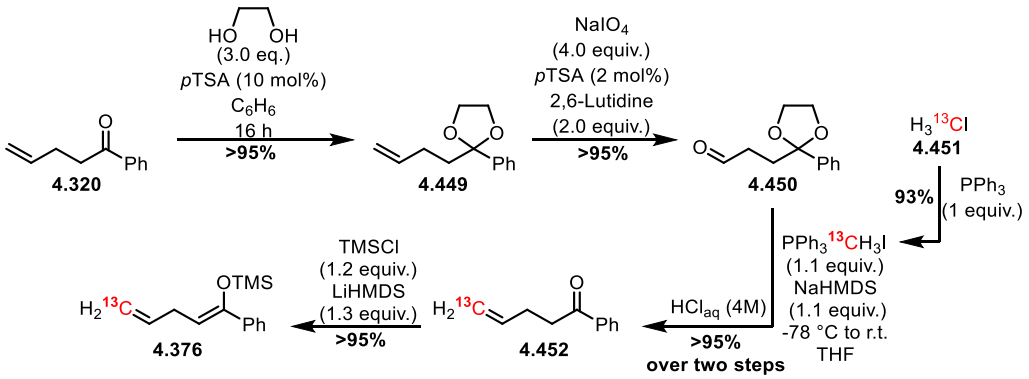
The acid **4.446** (1.0 equiv.) was dissolved in DCM (0.19 M) and two drops of DMF were added with a Pasteur pipette. Oxalyl chloride was added (1.1 equiv.) and the reaction was stirred 2 h at room temperature. Thereafter, volatiles were removed to afford the crude acyl chloride. The hydrochloride salt of *N*-Methoxy-*N*-methyl amine (1.1 equiv.) was dissolved in DCM (0.20 M) at 0 °C. Then triethylamine (2.2

equiv.) was added dropwise. Then the neat acyl chloride was added dropwise, and the ice bath was removed thereafter. The reaction was stirred for 2 h before it was quenched with HCl_{aq} (1 M), transferred to a separatory funnel and washed with the acidic solution. The organic phase was further washed with saturated aqueous $NaHCO_3$ and with water. After drying the solution over Na_2SO_4, the organic phase was filtered and volatiles were removed to give the amide **4.447**, which was used without further purification.

The Weinreb amide **4.447** (1.0 equiv.) was dissolved in THF (0.25 M) and cooled to -40 °C. A solution of phenyllithium in dibutylether (1.9M, 1.5 equiv.) was added over 10 minutes. After stirring the mixture for further 10 minutes at the same temperature, MeOH was added dropwise (10 equiv.) and the reaction was warmed up to room temperature. Saturated aqueous NH_4Cl was added, and the aqueous phase was extracted with diethylether (3x). The combined organic layer was dried over Na_2SO_4 and filtered. Volatiles were removed and the residue was purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 70 : 30 v/v) to give the desired pure ketone.[901]

A solution of LiHMDS in THF (0.5 M, 1.3 equiv.) was cooled to 0 °C and a solution of the ketone in THF (1 M, 1.0 equiv.) was added dropwise. The mixture was stirred for 30 minutes at the same temperature. Afterwards, TMSCl (1.4 equiv.) was added dropwise, the cooling bath was removed and the reaction was stirred for 2 h. Volatiles were removed under reduced pressure. The crude was purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 70 : 30 v/v%) to yield the silyl enolether **4.448**.[896]

Procedure V



Scheme 4.44

1-phenylpent-4-en-1-one was synthesized according to the general procedure A.

1-phenylpent-4-en-1-one (1.0 equiv., 10.7 mmol, 1720 mg) and ethlyeneglycol (3.0 equiv., 32.2 mmol, 1.8 mL) were dissolved in benzene (60 mL). *Para*-Toluenesulfonic acid monohydrate (10mol%, 1.1 mmol, 207 mg) was added to the solution, and the mixture was refluxed using a Dean-stark-apparatus and a condenser. After 11 h, the reaction was cooled down to room temperature and aqueous saturated $NaHCO_3$ was added. The separated aqueous layer was extracted with Et_2O (1x) and the combined organic layer was dried over Na_2SO_4 and filtered. After removing the solvent under reduced pressure, the ketal was obtained as a colorless liquid (2121 mg, >95% yield).[902] An analogous reaction in toluene gave a low yield and purification was troublesome.

The acetal (1.0 equiv., 5.0 mmol, 1021 mg) was dissolved in a mixture of 1,4-dioxane (37.5 mL) and water (12.5 mL). Lutidine (2.0 equiv., 10.0 mmol, 1.16 mL), sodium periodate (4.0 equiv., 20 mmol, 4278 mg) and last a solution of OsO_4 in water (2mol%, 4 *w*/w%, 640 µL) was added and the solution was stirred until the starting material was not observable by TLC anymore (3 h). The reaction was quenched with water (10 mL) and aqueous saturated $Na_2S_2O_4$ solution (10 mL). DCM was added and the aqueous layer was extracted with further DCM (3x). The combined organic layer was dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure. The crude mixture was purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 50 : 50 v/v%) to yield the aldehyde as a yellow liquid. (1006 mg, >95%)[903]

Triphenylphosphine (1.0 equiv., 2.0 mmol, 525 mg) in THF (3 mL) was added to a solution of methyliodide in MTBE (1.0 equiv., 2M, 1 mL, ^{13}C content >99%). The mixture was refluxed for 2 h and then cooled down to room temperature. The Wittig-salt was filtrated and thoroughly washed with diethylether. After drying under *vacuum*, the pure Wittig-salt was obtained as a white powder (yield 749 m, 93%).[904]

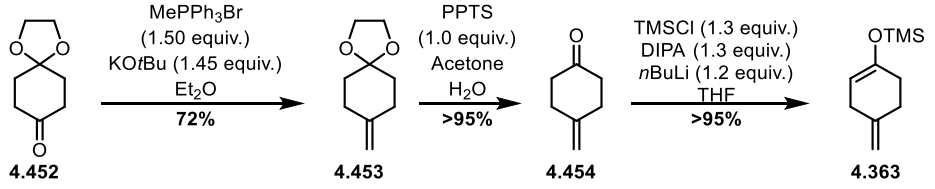
The Wittig-Salt (1.1 equiv., 1.85 mmol, 749 mg) was dispensed in THF (11 mL) and cooled to 0 °C. A solution of NaHMDS in THF (1.1 equiv., 2M, 920 µL) was added dropwise and stirred until the solution

became clear. Then the mixture was cooled to -78 °C and a solution of the aldehyde in THF was added (1.68M, 1.68 mmol, 347 mg). The mixture was warmed to room temperature and stirred until no aldehyde was observable by TLC. Thereafter, aqueous saturated NH_4Cl (*ca*. 3 mL) and aqueous HCl (4M, *ca.* 10 mL) were added. The reaction was stirred for 30 minutes, the deprotection of the ketal was observed by TLC, before the mixture was diluted with diethylether. Then the aqueous phase was extracted with more diethylether (3x), the combined organic layer was dried over Na_2SO_4, filtered, and the volatiles were removed under reduced pressure. Column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 60 : 40 v/v%), gave the ketone as a colorless liquid (260 mg, >95%)[905]

A THF solution of LiHMDS (1.25 equiv., 0.33M, 2.0 mmol) was cooled to 0 °C and a THF solution of the ketone (1.00 equiv., 1.6 mmol, 260 mg) was added dropwise. The solution was stirred for 30 minutes, before TMSCl (1.20 equiv., 1.9 mmol, 246 µL) was added. The reaction was stirred for 1 h at room temperature and quenched with aqueous saturated $NaHCO_3$. The aqueous layer was extracted with diethylether (3x) and the combined organic layer was dried over Na_2SO_4 and filtered. Evaporation of the volatiles under reduced pressure gave the crude silyl enolether, which was purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 80 : 20 v/v%) to give the pure compound as a colorless liquid (yield 361 mg, >95%).[896]

The same procedure was used to synthesize the dideutorated compound **4.379** with D_3CI.

Procedure VI



Scheme 4.345

$MePPh_3Br$ (1.50 equiv., 11.9 mmol, 4.25 g) was suspended in Et_2O (30 mL) and KO*t*Bu (1.45 equiv, 11.5 mmol, 1.33 g) was added at once. Then a solution of 1,4-Cyclohexanedione monoethylene acetal (1.00 equiv., 7.9 mmol, 1.24 g) was added and the reaction was refluxed for 90 minutes. The reaction was

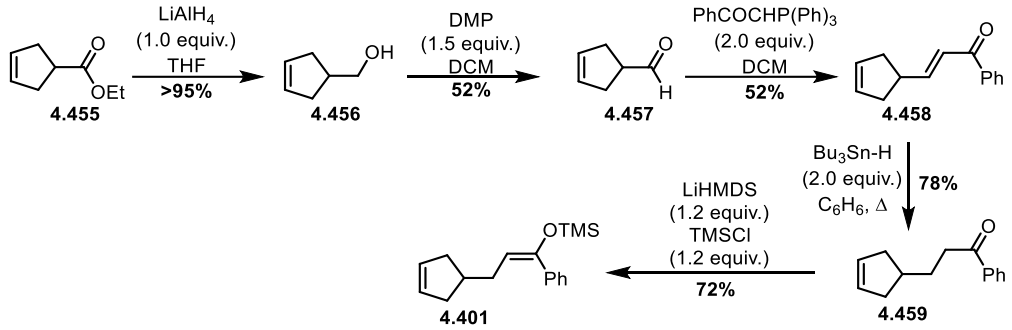
further stirred for 18 h at room temperature. Then the solution was washed with brine and the aqueous layer was extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, the volatiles evaporated under reduced pressure and the residue purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 80 : 20 v/v%) to yield the product as colorless liquid (yield 891 mg, 72%).[906]

The ketal (1.0 equiv, 5.7 mmol, 879 mg) was dissolved in acetone (45 mL) and water was added (5 mL). Then PPTS (1.0 equiv., 5.7 mmol, 1432 mg) was added and the reaction was refluxed for 6 h. The acetone was removed under reduced pressure and EtOAc was added to the biphasic mixture. The aqueous layer was extracted with EtOAc. The united organic phase was dried over Na_2SO_4, filtered and the volatiles were removed, to give the analytically pure enone as a yellowish liquid (yield 625 mg, >95%).[906]

Di*iso*propylamine (1.3 equiv., 2.6 mmol, 282 mg) was dissolved in THF (2 mL) and cooled to 0 °C. Then *n*-butyllithium (2.4 M, 1.2 equiv., 1 mL) was added and the reaction was stirred for 30 minutes at the same temperature. The reaction was cooled to -78 °C and a solution of the enone (1.0 equiv., 2.0 mmol, 220 mg) in THF (2 mL) was added dropwise. The mixture was warmed to room temperature over 30 minutes and then TMSCl (1.3 equiv., 2.6 mmol, 330 µL) was added dropwise. The mixture was stirred for 5 h at room temperature and then the volatiles were removed under reduced pressure. The residue was suspended in Et_2O, and filtered through a silica pad using heptanes as the eluent to yield the pure silyl enolether as a colorless liquid (yield 351 mg, >95%). [897]

4.5.2.3. *"π-route" towards the norbornane derivative*

Procedure VII



Scheme 4.46

Ethyl 3-Cyclopentene-1-carboxylate (1.0 equiv., 35.7 mmol, 5.0 mL) was dissolved in THF (90 mL) at -78 °C. A THF solution of $LiAlH_4$ (1.0 equiv., 1 M, 35.7 mL) was added slowly under stirring. The reaction mixture was stirred for further 4 h at the same temperature and then warmed to 0 °C. The reaction was quenched carefully and very slowly by the addition of H_2O (5 mL), aqueous NaOH (15 w/w%, 5 mL) and H_2O again (1.5 mL). Thereafter the cooling bath was removed and the reaction was filtered through Celite® 545. The Celite®-pad was washed with hot EtOAc and the resulting filtrate was washed with aqueous NaOH (0.1 M) and brine. The organic phase was then dried over Na_2SO_4, filtered and the volatiles were removed under reduced pressure to yield the desired alcohol as a sufficiently clean yellowish liquid (yield 3.50 g, >95%).

This reaction step was carried out under air atmosphere. The alcohol **4.456** (1.0 equiv., 10 mmol, 981 mg) was dissolved in DCM (50 mL) and Dess-Martin-Periodinane (DMP – 1.5 equiv., 15 mmol, 6.36 g) was added at once. The reaction was stirred until the starting material disappeared by TLC (*ca.* 4 h). Afterwards, the reaction was diluted with Et_2O and quenched with a saturated aqueous $Na_2S_2O_3$ solution and vigorously stirred for 5 minutes. The aqueous phase was extracted with Et_2O and the united organic phase was washed with H_2O, dried over Na_2SO_4, filtered and the solvent was removed under reduced

pressure (≥ 100 mbar). The residue was distilled using a Kugelrohr apparatus to yield the aldehyde as a colorless liquid (yield 496 mg, 52%).[899]

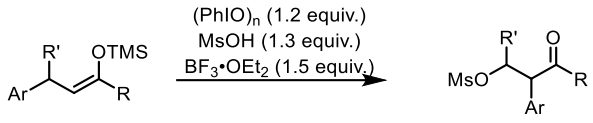
The aldehyde **4.457** (1.0 equiv., 3.0 mmol, 288 mg) was dissolved in $CHCl_3$ (10 mL) and $PhCOCHP(Ph)_3$ (2.0 equiv., 6.0 mmol, 2.283 g) was added at once and the reaction mixture was stirred at room temperature for 14 h. The solvent was removed under reduced pressure, the residue re-dissolved in EtOAc and the mixture filtered. The volatiles were removed again under reduced pressure and the residue was purified by column chromatography (eluent - heptanes : EtOAc, 100 : 0 → 60 : 40 v/v%) to yield the enone **4.458** as a yellowish liquid (Yield 310 mg, 52%).[907]

The enone **4.458** (1.0 equiv., 0.70 mmol, 140 mg) was dissolved in benzene (2.3 mL) and tri-*n*-butyltin hydride (2.0 equiv., 1.41 mmol, 411 mg) was added dropwise. The reaction was refluxed for 3 h and after cooling down the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (eluent - heptanes : EtOAc, 100 : 10 → 60 : 40 v/v%) to yield the enone **4.459** as a colorless liquid (Yield 110 mg, 78%).[908]

A THF solution of LiHMDS (1.20 equiv., 0.33M, 0.66 mmol) was cooled to 0 °C and a THF solution of the ketone (1.00 equiv., 0.55 mmol, 110 mg) was added dropwise. The solution was stirred for 30 minutes, before TMSCl (1.20 equiv., 0.66 mmol, 86 µL) was added. The reaction was stirred for 1 h at room temperature and quenched with aqueous saturated $NaHCO_3$. The aqueous layer was extracted with diethylether (3x) and the combined organic layer was dried over Na_2SO_4 and filtered. Evaporation of the volatiles under reduced pressure gave the crude silyl enolether, which was purified by column chromatography (Eluent - heptanes : EtOAc, 100 : 0 → 80 : 20 v/v%) to give the pure compound as a colorless liquid (108 mg, 72%).[896]

4.5.3. Experimental section

General procedure B

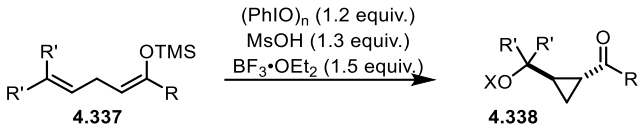


4.284 **4.285**

Scheme 4.47

Iodosobenzene (0.24 mmol, 1.2 equiv., 52.8 mg) was added to a flame dried flask, and DCM (2 mL) was added. Then MsOH (0.26 mmol, 1.3 equiv., 16.9 µL) was slowly added and further stirred until all the yellow solid was dissolved. Then the flask was cooled in a dry ice-acetone bath, and $BF_3{\cdot}Et_2O$ (0.3 mmol, 1.5 equiv., 37 µL) was slowly added and the mixture was further stirred for 5 minutes. Finally, the silyl enolether **4.284** was added at once and the mixture was further stirred for 10 minutes at the same temperature. Then sat. aqueous $NaHCO_3$ solution was added to quench the reaction, the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, then brine. The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel with AcOEt/ hexanes (1:3) to provide desired products.

General procedure VIII



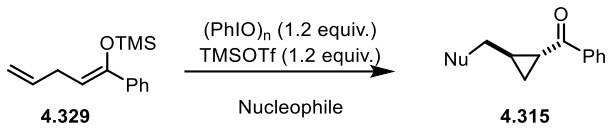
4.337 **4.338**

Scheme 4.48

Iodosobenzene (1.2 equiv, 0.24 mmol, 52.8 mg) was dispersed in DCM (2 mL) and methanesulfonic acid was added (1.3 equiv., 0.26 mmol, 16.9 µL) to get a clear yellow solution. The mixture was cooled to -78 °C, resulting in a less clear solution (precipitation). $BF_3{\bullet}OEt_2$ (1.5 equiv., 0.30 mmol, 37 µL) was added and the solution became clear again, and the yellow color intensified. The mixture was stirred for 15 minutes at the same temperature before the silyl enolether (1.0 equiv., 2.0 mmol) was added quickly at once. Alternatively, the substrate can be added as a DCM solution leading to the same

results. The reaction changed color immediately (usually to brown, depending on the substrate) and a precipitate can be observed. After stirring for further 15 minutes, the flask was removed from the cooling-bath and immediately quenched with water (*ca.* 4 mL) and diluted with DCM (*ca.* 4 mL). The mixture was transferred to a separatory funnel and the aqueous phase was extracted with DCM (3x), and the united organic layer was dried over Na_2SO_4 and filtered. After removal of the volatiles under reduced pressure, the crude was purified by column chromatography (typical eluent - heptanes : EtOAc, 90 : 10 → 50 : 50 v/v%) to give the pure cyclopropane. In most of the cases the product was eluated when the eluent was composed as follows: heptanes : EtOAc, 75 : 25 v/v%.

General procedure IX



4.329 **4.315**

Scheme 4.4935

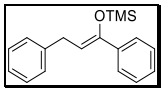
Iodosobenzene (1.2 equiv, 0.24 mmol, 52.8 mg) was dispersed in DCM (2 mL) and trimethylsilyltriflate was added (1.2 equiv., 0.24 mmol, 43 µL) at 0 °C to get a clear yellow solution. The mixture was cooled to -78 °C. Then the silyl enolether (1.0 equiv., 2.0 mmol, 46.5 mg) was added quickly at once. Alternatively, the substrate can be added as a DCM solution leading to the same results. The reaction changed color immediately (usually to brown, depending on the substrate) and a precipitate can be observed. After stirring for 5 minutes, the nucleophile was added (see characterization section for more details) and the reaction was stirred for further 10 minutes at -78 °C. Then the reaction was warmed up to room temperature and stirred 10 more minutes. The mixture was quenched with water (*ca.* 4 mL), diluted with DCM (*ca.* 4 mL) and transferred to a separatory funnel. The aqueous phase was extracted with DCM (3x), and the united organic layer was dried over Na_2SO_4 and filtered. After removal of the volatiles under reduced pressure, the crude was purified by column chromatography (typical eluent - heptanes : EtOAc, 90 : 10 → 50 : 50 v/v%) to give the pure cyclopropane.

4.6. Characterization

4.6.1. Starting material

4.6.1.1. *Aryl migration*

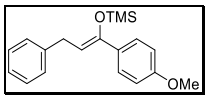
(*Z*)-((1,3-diphenylprop-1-en-1-yl)oxy)trimethylsilane (**4.272**)



Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 568 mg, 63% from the acyl chloride. Spectroscopic properties match with the literature. [909]

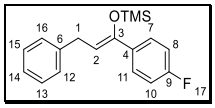
(*Z*)-((1-(4-methoxyphenyl)-3-phenylprop-1-en-1-yl)oxy)trimethylsilane (**4.460**)



Synthesized by using the **General procedure A.**

Isolated yield: 771 mg, 45% from the acyl chloride. Spectroscopic properties match with the literature. [910]

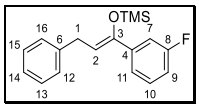
(*Z*)-((1-(4-fluorophenyl)-3-phenylprop-1-en-1-yl)oxy)trimethylsilane (**4.461**)



Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 640 mg, 39% from the acyl chloride. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 2H, Ar), 7.18 – 6.95 (m, 5H, Ar), 6.93 – 6.71 (m, 2H, Ar), 5.19 (t, *J* = 7.2 Hz, 1H, C2), 3.40 (d, *J* = 7.2 Hz, 2H, C1), -0.08 (m, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.8 (d, *J* = 300 Hz), 148.3 (C3), 140.7 (C6), 134.6 (C4), 127.8 (C13/C15), 127.8 (C7/11), 126.6 (C12/C16), 125.3 (C14), 114.3 (d, *J* = 28 Hz), 109.0 (C2), 31.7 (C1), -0.0 (TMS).**HRMS** (ESI): m/z calculated for $[M+H]^+$ 301.1418; found: 301.1421. **AT-FTIR** (cm^{-1}): 1647, 1604, 1506, 1453, 1342, 1279, 1252, 1220, 1157, 1101, 1072, 1037, 837, 775, 697.

(*Z*)-((1-(3-fluorophenyl)-3-phenylprop-1-en-1-yl)oxy)trimethylsilane (**4.462**)

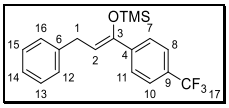


Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 661 mg, 81% from the acyl chloride. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 6H, Ar), 7.23 – 7.18 (m, 2H, Ar), 6.98 – 6.93 (m, 1H, C9), 5.47 (t, *J* = 7.2 Hz, 1H, C2), 3.57 (d, *J* = 7.2 Hz, 2H, C1), 0.18

(s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 162.8 (d, *J* = 245 Hz, C8), 148.6 (d, *J* = 3 Hz, C3), 141.4 (d, *J* = 7.5 Hz, C4), 141.1 (C6), 129.53 (d, *J* = 8 Hz, C10), 128.41 (d, *J* = 7 Hz, C11), 126.0 (C12/C13/C15/C16), 121.0 (C14), 114.38 (d, *J* = 21 Hz, C9), 112.4 (d, *J* = 23 Hz, C7), 110.9 (C2), 32.4 (C1), 0.6 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$ 301.1418; found: 301.1421. **AT–FTIR** (cm^{-1}): 1615, 1611, 1485, 1438, 1342, 1252, 1220, 1156, 1096, 1071, 1040, 965, 916, 839, 765, 696.

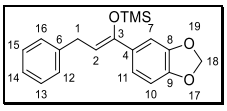
(*Z*)-trimethyl((3-phenyl-1-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)oxy)silane (**4.463**)



Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 764 mg, 57% from the acyl chloride. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.67 – 7.48 (m, 4H, Ar), 7.37 – 7.12 (m, 5H, Ar), 5.54 (t, *J* = 7.2 Hz, 1H, C2), 3.58 (d, *J* = 7.2 Hz, 2H, C1), 0.19 – 0.16 (m, 9H, TMS).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.5 (C3), 142.4 (C4), 140.9 (C5), 128.5 (Ar), 128.4(Ar), 126.0 (Ar), 125.6 (Ar), 125.1 (q, *J* = 4.0 Hz, C7/C11), 112.1 (C2), 32.4 (C1), 0.6 (TMS).**HRMS** (ESI): m/z calculated for $[M+H]^+$ 351.1387; found: 351.1383. **ATR-FTIR** (cm^{-1}): 1644, 1616, 1409, 1322, 1220, 1164, 1123, 1108, 1067, 1038, 839, 776, 896.

(*Z*)-((1-(benzo[*d*][1,3]dioxol-5-yl)-3-phenylprop-1-en-1-yl)oxy)trimethylsilane (**4.464**)

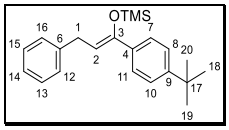


Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 687 mg, 76% from the acyl chloride.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 – 7.11 (m, 5H, C12-16), 7.04 – 6.93 (m, 2H, C7/11), 6.76 (dd, *J* = 13.7, 8.1 Hz, 1H, C10), 5.96 (d, *J* = 9.4 Hz, 2H, C18), 5.29 (t, *J* = 7.2 Hz, 1H, C2), 3.54 (d, *J* = 7.2 Hz, 2H, C1), 0.16 (s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 149.4 (C9), 147.4 (C8), 147.2 (C3), 141.5 (C6), 133.5 (C13/C15), 128.4 (C14), 128.4 (C12/C16), 125.8 (C14), 119.3 (C11), 108.7(C7), 107.8 (C10), 106.2 (C2), 101.0 (C8), 32.3 (C1), 0.6 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$

327.1411; found: 327.1408. **ATR-FTIR** (cm^{-1}): 1646, 1486, 1438, 1357, 1288, 1248, 1220, 1141, 1107, 1069, 1035, 937, 839, 772, 697 cm^{-1}.

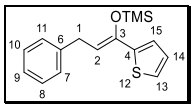
(*Z*)-((1-(4-(tert-butyl)phenyl)-3-phenylprop-1-en-1-yl)oxy)trimethylsilane (**4.465**)



Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 420 mg, 66% from the acyl chloride. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H, Ar), 7.17 – 6.98 (m, 7H, Ar), 5.23 (t, *J* = 7.2 Hz, 1H, C2), 3.41 (dd, *J* = 14.5, 6.7 Hz, 2H, C1), 1.15 (s, 9H, C18-20), 0.00 (s, 9H, TMS).**^{13}C NMR** (101 MHz, $CDCl_3$) δ = 156.6 (C9), 146.8 (C3), 141.5 (C6), 129.8 (C13/15), 128.6 (Ar), 128.0 (Ar), 127.8 (Ar), 125.2 (Ar), 119.7 (Ar), 112.0 (Ar), 110.4 (C2), 54.9 (C1), 31.5 (C18-20), -0.0 (TMS).**HRMS** (ESI): m/z calculated for $[M+H]^+$ 339.2139; found: 339.2130. **ATR-FTIR** (cm^{-1}): 1644, 1494, 1453, 1405, 1328, 1251, 1220, 1113, 1071, 1038, 1014, 837, 778 697.

(*Z*)-trimethyl((3-phenyl-1-(thiophen-2-yl)prop-1-en-1-yl)oxy)silane (**4.466**)

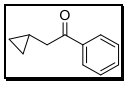


Synthesized by using the **General procedure A.** (*Z/E* > 20: 1).

Isolated yield: 723 mg, 70% from the acyl chloride. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H, C7/C11), 7.26 (t, *J* = 3.4 Hz, 2H, C8/C10), 7.21 (t, *J* = 7.2 Hz, 1H, C9), 7.15 – 7.11 (m, 1H ,C13), 7.09 (dd, *J* = 3.6, 1.1 Hz, 1H, C15), 6.95 (dd, *J* = 5.0, 3.6 Hz, 1H, C14), 5.44 (t, *J* = 7.3 Hz, 1H, C2), 3.54 (d, *J* = 7.3 Hz, 2H, C1), 0.25 (s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 144.6 (C3), 143.3 (C6), 141.0 (C4), 128.4 (C13/C8/C10), 127.1 (C7/C11), 125.9 (C14), 124.1 (C9), 123.3 (C15), 109.0 (C2), 32.2 (C1), 0.7 (TMS). **HRMS** (ESI): m/z calculated for $[M]^+$ 288.1004; found: 288.0941. **ATR-FTIR** (cm^{-1}): 1640, 1495, 1434, 1359, 1341, 1251, 1220, 1095, 1070, 1025, 839, 772, 693.

4.6.1.2. *Cyclopropanation*

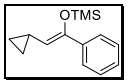
(*Z*)-2-cyclopropyl-1-phenylethan-1-one (**4.314**)



Synthesized by using the **General procedure I.**

Isolated yield: 287 mg,74% from the carboxylic acid. Spectroscopic properties match with the literature [911]

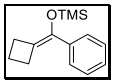
(*Z*)-((2-cyclopropyl-1-phenylvinyl)oxy)trimethylsilane (**4.318**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 120 mg, 73% from the carboxylic acid. Spectroscopic properties match with the literature.[912]

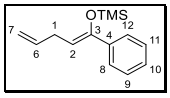
(*Z*)-(cyclobutylidene(phenyl)methoxy)trimethylsilane (**4.332**)



Synthesized by using the **General procedure I.**

Isolated yield: 354 mg, 82% from the carboxylic acid. Spectroscopic properties match with the literature.[913]

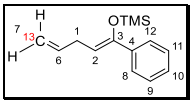
(*Z*)-trimethyl((1-phenylpenta-1,4-dien-1-yl)oxy)silane (**4.329**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 1065 mg, 69% from the carboxylic acid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 – 7.45 (m, 2H, C8/C12), 7.32 (dd, *J* = 10.3, 4.7 Hz, 2H, C9/C11), 7.29 – 7.23 (m, 1H, C10), 5.91 (ddt, *J* = 16.6, 10.1, 6.1 Hz, 1H, C6), 5.28 (t, *J* = 7.3 Hz, 1H, C7), 5.13 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H, C7), 5.07 – 4.99 (m, 1H, C2), 2.99 (td, *J* = 6.2, 1.4 Hz, 2H, C1), 0.15 (s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.89 (C3), 139.19 (C4), 137.33 (C6), 128.19 (C10), 127.72 (C9/11), 125.63(C8/C12), 114.80 (C7), 108.55 (C2), 30.52 (C1), 0.70 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$ 233.1356; found: 233.1356. **ATR-FTIR** (cm^{-1}): 2960, 1647, 1493, 1446, 1334, 1302, 1279, 1251, 1117, 1074, 1040, 1020, 993, 948, 900, 869, 839, 754, 695, 635, 526 cm^{-1}.

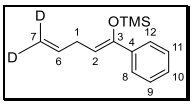
(*Z*)-trimethyl((1-phenylpenta-1,4-dien-1-yl-5-^{13}C)oxy)silane (**4.376**)



Synthesized by using the **General procedure V.** (*Z/E* > 20: 1).

Isolated yield: 361 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 2H, C8/C12), 7.32 (dd, *J* = 10.3, 4.7 Hz, 2H, C9/C11), 7.29 – 7.23 (m, 1H, C10), 5.91 (ddt, *J* = 16.6, 10.1, 6.1 Hz, 1H, C6), 5.29 – 4.97 (m, 2H, C7), 5.03 (ddd, *J* = 157.6, 10.1, 1.3 Hz, 1H, C7), 2.99 (q, *J* = 6.5 Hz, 2H, C1), 0.15 (s, 9H, TMS). **^{13}C NMR** (151 MHz, CDC_{l3}) δ 128.20 (C10), 127.72 (C9/C11), 125.64 (C8/C12), 114.80 (C7!), 30.53 (C1), 0.70 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$ 234.1390; found: 234.1392.

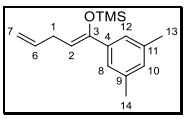
(*Z*)-trimethyl((1-phenylpenta-1,4-dien-1-yl-5,5-d_2)oxy)silane (**4.379**)



Synthesized by using the **General procedure V.** (*Z/E* > 20: 1).

Isolated yield: 363 mg, >95%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H), 7.33 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 5.93 – 5.81 (m, 1H), 5.26 (t, J = 7.3 Hz, 1H), 2.97 (t, J = 6.7 Hz, 2H), 0.13 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl^3$) δ 149.90 (C3), 139.22 (C4), 137.13 (C6), 128.19 (C10), 127.71 (C9/C11), 125.64 (C8/C12), 108.57 (C2), 30.43 (C1), 0.70 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$ 235.1482; found: 235.1486.

(*Z*)-((1-(3,5-dimethylphenyl)penta-1,4-dien-1-yl)oxy)trimethylsilane (**4.467**)

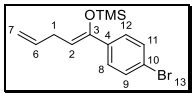


Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 496 mg, 62%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 (s, 2H, C8/C12), 6.89 (s, 1H, C10), 5.88 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H, C6), 5.23 (t, *J* = 6.9 Hz, 1H, C2), 5.22 – 4.96 (m, 2H, C7), 2.95 (ddt, *J* = 7.7, 6.2, 1.6 Hz, 2H, C1), 2.30 (s, 6H, C13/14), 0.14 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.07 (C3), 139.05 (C9/C11), 137.55 (C4), 137.46 (C6), 129.36 (C10), 123.56 (C8/C12), 114.69 (C7), 108.13 (C2), 30.53 (C1),

21.48 (C13/C14), 0.73 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$ 261.1669; found: 261.1678. **ATR-FTIR** (cm^{-1}): 2959, 1649, 1601, 1330, 1251, 1222, 1190, 1117, 1090, 992, 962, 903, 885, 839, 753, 706, 650, 545, 534.

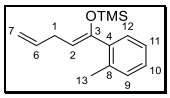
(*Z*)-((1-(4-bromophenyl)penta-1,4-dien-1-yl)oxy)trimethylsilane (**4.468**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 602 mg, 62%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H, C9/C11), 7.39 – 7.31 (m, 2H, C8/C12), 5.96 – 5.80 (m, 1H, C6), 5.25 (t, *J* = 7.3 Hz, 1H, C2), 5.18 – 4.96 (m, 2H, C7), 2.94 (ddt, *J* = 7.7, 6.2, 1.6 Hz, 2H, C1), 0.13 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.95 (C3), 138.22 (C4), 136.99 (C6), 131.34 (C9/C11), 127.19 (C8/C12), 121.59 (C10), 115.01 (C7), 109.22 (C2), 30.53 (C1), 0.70 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 311.0461 found: 311.0450. **ATR-FTIR** (cm^{-1}): 3080, 2958, 1645, 1589, 1485, 1394, 1335, 1304, 1279, 1251, 1210, 1179, 1118, 1073, 1027, 1007, 993, 950, 910, 863, 840, 721 cm^{-1}.

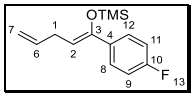
(*Z*)-trimethyl((1-(o-tolyl)penta-1,4-dien-1-yl)oxy)silane (**4.469**)



Synthesized by using the **General procedure I.** (*Z/E* = 5: 1).

Isolated yield: 328 mg, 28%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H, C12), 7.22 – 7.12 (m, 3H, C9-11), 5.97 – 5.71 (m, 1H, C6), 5.21 – 4.97 (m, 2H, C7), 4.95 – 4.75 (m, 1H, C2), 2.96 (ddt, *J* = 7.7, 6.2, 1.6 Hz, 2H, C1), 2.37 (s, 3H, C13), -0.01 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.50 (C3), 139.62 (C8), 137.72 (C6), 136.38 (C4), 130.32 (C9), 129.23 (C10), 127.90 (C11), 125.44 (C12), 114.40 (C7), 110.67 (C2), 30.04 (C1), 20.46 (C13), 0.38 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 247.1513 found: 247.1513. **ATR-FTIR** (cm^{-1}): 2960, 1657, 1639, 1326, 1300, 1251, 1195, 1121, 1076, 1022, 993, 952, 907, 873, 754, 728.

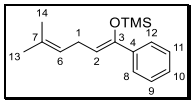
(*Z*)-((1-(4-fluorophenyl)penta-1,4-dien-1-yl)oxy)trimethylsilane (**4.470**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 485 mg, 77%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.39 (m, 2H, C8/C12), 7.05 – 6.90 (m, 2H, C9/C11), 5.88 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H, C6), 5.18 (t, *J* = 7.3 Hz, 1H, C2), 5.16 – 4.88 (m, 2H, C7), 3.02 – 2.91 (m, 2H, C1), 0.13 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.53 (d, *J* = 247 Hz, C10), 149.05 (C3), 137.21 (C4), 135.43 (C6), 127.31 (d, *J* = 8 Hz, C8/C12), 115.06 (d, *J* = 22 Hz, C9/C11), 114.86 (C7), 108.36 (C2), 30.51 (C1), 0.68 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 251.1262 found: 251.1270. **ATR-FTIR** (cm^{-1}): 2960, 1650, 1604, 1506, 1409, 1336, 1300, 1279, 1252, 1225, 1157, 1118, 1082, 1027, 1013, 993, 951, 909, 871, 837, 753, 725, 688, 643, 578.

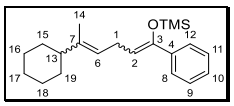
(*Z*)-trimethyl((5-methyl-1-phenylhexa-1,4-dien-1-yl)oxy)silane (**4.471**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 411 mg, 47%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H, C8/C12), 7.32 – 7.26 (m, 2H, C9/C11), 7.26 – 7.21 (m, 1H, C10), 5.26 – 5.09 (m, 2H, C2/C6), 2.91 (t, *J* = 7.1 Hz, 2H, C1), 1.73 (d, *J* = 1.1 Hz, 3H, C13), 1.69 (s, 3H, C14), 0.15 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.81 (C3), 139.16 (C4), 131.99 (C7), 127.98 (C10), 127.35 (C9/C11), 125.38 (C8/C12), 122.78 (C6), 110.21 (C2), 25.67 (C13), 25.28 (C1), 17.80 (C14), 0.57 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$ 261.1669; found: 261.1673. **ATR-FTIR** (cm^{-1}): 2962, 1645, 1493, 1445, 1331, 1281, 1251, 1095, 1075, 1041, 1026, 877, 839, 752.

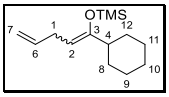
((5-cyclohexyl-1-phenylhexa-1,4-dien-1-yl)oxy)trimethylsilane (**4.472**)



Synthesized by using the **General procedure IV.** (Mixture of stereoisomers)

Isolated yield: 361 mg, 4%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (ddd, *J* = 7.2, 3.2, 1.8 Hz, 2H, C8/C10), 7.29 (ddd, *J* = 7.5, 6.8, 1.5 Hz, 2H, C9/C11), 7.25 – 7.19 (m, 1H, C10), 5.25 – 5.09 (m, 2H, C2/C6), 2.97 – 2.84 (m, 2H, C1), 1.92 – 1.61 (m, 8H, Cy, C14), 1.52 – 1.08 (m, 6H ,Cy), 0.16 – 0.13 (m, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.87 (C3), 141.24 (C4), 139.36 (C7), 128.13 (C10), 127.47 (C10), 125.53 (C9/C11), 125.51 (C8/C12), 122.25 (C6), 120.75 (C6'), 110.69 (C2), 110.66 (C2'), 47.45 (C13), 39.92 (C13'), 32.13 (C15/C19), 31.23 (C15/C19), 26.95 (C17), 26.85 (C16/C18), 26.60 (C16/C18), 26.46 (C16'/C18'), 25.21 (C1), 24.60 (C1'), 19.77 (C14), 14.69 (C14'), 0.71 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 329.2295 found: 329.2296. **ATR-FTIR** (cm^{-1}): 2961, 2927, 2854, 2363, 2349, 2338, 2327, 1738, 1726, 1689, 1449, 1367, 1270, 1229, 1218, 774, 698, 550.

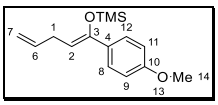
((1-cyclohexylpenta-1,4-dien-1-yl)oxy)trimethylsilane (**4.438**)



Synthesized by using the **Procedure II.** (*E/Z* ≈ 1: 1).

Isolated yield: 235 mg, 83%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.80 (ddtd, *J* = 16.0, 10.1, 6.0, 1.5 Hz, 1H, C6), 5.06 – 4.99 (m, 1H, C7), 4.96 – 4.92 (m, 1H, C7), 4.46 (t, *J* = 7.4 Hz, 1H, C2), 2.78 – 2.66 (m, 2H, C1), 2.73 – 2.21 (m, 2H, C1), 1.93 – 1.62 (m, 5H), 1.45 – 1.34 (m, 1H), 1.31 – 1.08 (m, 5H), 0.19 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 157.20 (C3), 156.05 (C3'), 138.49 (C6), 138.18 (C6'), 114.08 (C7), 113.93 (C7'), 103.14 (C2), 101.86 (C2'), 44.61 (C4), 39.23 (C4'), 31.39 (C1), 30.70 (C1'), 30.22 (C8/C12), 29.86 (C8'/C12'), 26.62 (C9/C11), 26.55 (C9'/C11'), 26.46 (C10), 26.17 (C10'), 0.85 (TMS), 0.68 (TMS'). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 239.1826 found: 239.1829. **ATR-FTIR** (cm^{-1}): 2927, 2854, 1656, 1450, 1250, 1176, 1136, 1115, 1041, 1014, 992, 977, 930, 904, 838, 752, 687.

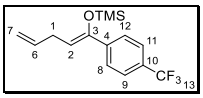
(*Z*)-((1-(4-methoxyphenyl)penta-1,4-dien-1-yl)oxy)trimethylsilane (**4.473**)



Synthesized by using the **General procedure I.** (*Z/E* = 17: 1).

Isolated yield: 504 mg, 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 2H, C8/C12), 6.97 – 6.77 (m, 2H, C9/C11), 5.88 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H, C6), 5.18 – 4.95 (m, 3H, C2/C7), 3.81 (s, 3H, C14), 2.98 – 2.91 (m, 2H, C1), 0.13 (s, 9H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.36 (C10), 149.64 (C3), 137.57 (C6), 131.96 (C4), 126.93 (C8/C12), 114.63 (C7), 113.55 (C9/C11), 106.92 (C2), 55.40 (C14), 30.52 (C1), 0.71 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 263.1462 found: 263.1463. **ATR-FTIR** (cm^{-1}): 2958, 16890, 1648, 1601, 1576, 1509, 1462, 1442, 1416, 1335, 1293, 1246, 1211, 1172, 1111, 1081, 1030, 1009, 994, 951, 911, 872, 835, 754, 688, 632, 588.

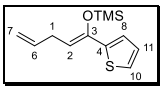
(*Z*)-trimethyl((1-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)oxy)silane (**4.474**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 574 mg, 68%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 4H, Ar), 5.88 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H, C6), 5.37 (t, *J* = 7.3 Hz, 1H, C2), 5.17 – 5.01 (m, 2H, C7), 3.02 – 2.95 (m, 2H, C1), 0.14 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.72 (C3), 142.67 (C4), 136.76 (C6), 129.64 (q, *J* = 32 Hz, C10), 125.68 (C8/C12), 125.26 (q, *J* = 4 Hz, C9/C11), 115.21 (C7), 110.80 (C2), 30.57 (C1), 0.69 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 301.1230 found: 301.1232. **ATR-FTIR** (cm^{-1}): 1646, 1617, 1410, 1322, 1282, 1253, 1165, 1123, 1109, 1067, 1014, 993, 951, 912, 869, 839, 753.

(*Z*)-trimethyl((1-(thiophen-2-yl)penta-1,4-dien-1-yl)oxy)silane (**4.475**)

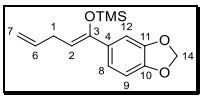


Synthesized by using the **General procedure I.** (*Z/E* = 10: 1).

Isolated yield: 430 mg, 59%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 5.1, 1.2 Hz, 1H, C10), 7.06 (dd, *J* = 3.6, 1.2 Hz, 1H, C8), 6.94 (dd, *J* = 5.1, 3.6 Hz, 1H, C11), 5.93 – 5.81 (m, 1H, C6), 5.26 (t, *J* = 7.4 Hz, 1H, C2), 5.15 – 4.99 (m, 2H, C7), 2.93 (ddt, *J* = 7.6, 6.2, 1.6 Hz, 2H, C1), 0.22 (s, 9H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.73 (C3), 143.53 (C4), 136.91 (C6), 127.19 (C10), 124.13 (C11), 123.32 (C8), 115.05 (C7), 107.85 (C2),

30.38 (C1), 0.70 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 239.0920 found: 239.0918. **ATR-FTIR** (cm^{-1}): 2960, 1643, 1434, 1414, 1359, 1338, 1296, 1251, 1224, 1199, 1112, 1085, 1073, 1018, 992, 911, 842, 754.

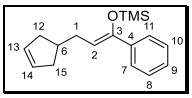
(*Z*)-((1-(benzo[d][1,3]dioxol-5-yl)penta-1,4-dien-1-yl)oxy)trimethylsilane (**4.476**)



Synthesized by using the **General procedure I.** (*Z/E* = 15: 1).

Isolated yield: 529 mg, 71%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 – 6.94 (m, 2H, C12, C9), 6.76 – 6.72 (m, 1H, C8), 5.95 (s, 2H, C14), 5.87 (ddt, *J* = 16.3, 10.1, 6.1 Hz, 1H, C6), 5.15 – 4.97 (m, 3H, C2/C7), 3.03 – 2.88 (m, 2H, C1), 0.13 (s, 9H, TMS). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.55 (C10), 147.60 (C11), 147.28 (C3), 137.40 (C6), 133.78 (C4), 119.42 (C8), 114.72 (C7), 107.96 (C12), 107.46 (C9), 106.33 (C2), 101.17 (C14), 30.51 (C1), 0.70 (TMS). **HRMS** (ESI): m/z calculated for $[M+H]^+$; 277.1254 found: 277.1254. **ATR-FTIR** (cm^{-1}): 1649, 1503, 1487, 1438, 1357, 1318, 1295, 1284, 1248, 1230, 1144, 1101, 1073, 1039, 994, 960, 938, 910, 891, 806, 753, 727, 689, 638, 571, 552.

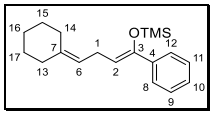
(*Z*)-((3-(cyclopent-3-en-1-yl)-1-phenylprop-1-en-1-yl)oxy)trimethylsilane (**4.401**)



Synthesized by using the **Procedure VII.** (*Z/E* > 20: 1).

Isolated yield: 110 mg, 15%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 2H, C7/C11), 7.30 (t, *J* = 7.6 Hz, 2H, C8/C10), 7.23 (t, *J* = 7.3 Hz, 1H, C9), 5.70 – 5.66 (m, 2H, C13/C14), 5.26 (t, *J* = 7.0 Hz, 1H, C2), 2.51 (dd, *J* = 14.0, 8.4 Hz, 2H, C1), 2.41 – 2.34 (m, 1H, C6), 2.28 (t, *J* = 7.1 Hz, 2H, C12/C15), 2.07 (dt, *J* = 17.5, 8.8 Hz, 2H, C12/C15), 0.13 (s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.72 (C3), 139.45 (C4), 130.00 (C9), 128.16 (C8/C10), 127.50 (C13/C14), 125.52 (C7/C11), 110.38 (C2), 38.90 (C12/C15), 37.58 (C6), 32.90 (C1), 0.77 (TMS). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 273.1669 found 273.1661. **ATR-FTIR** (cm^{-1}): 3054, 2957, 2921, 2842, 1646, 1492, 1446, 1355, 1330, 1277, 1251, 1100, 1061, 1025, 898, 870, 838, 753, 694.

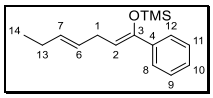
(*Z*)-((4-cyclohexylidene-1-phenylbut-1-en-1-yl)oxy)trimethylsilane (**4.477**)



Synthesized by using the **General procedure IV.** (*Z/E* > 20: 1).

Isolated yield: 489 mg, 8%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H, C8/C12), 7.33 – 7.19 (m, 3H, C9-11), 5.18 (t, *J* = 7.2 Hz, 1H, C6), 5.12 (t, *J* = 7.2 Hz, 1H, C2), 2.90 (t, *J* = 7.2 Hz, 2H, C1), 2.24 – 2.17 (m, 2H, C13), 2.11 – 2.03 (m, 2H, C14), 1.58 – 1.49 (m, 6H, C15-17), 0.14 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.84 (C3), 140.33 (C4), 139.35 (C7), 128.13 (C10), 127.49 (C9/C11), 125.53 (C8/C12), 119.49 (C6), 110.78 (C2), 37.24 (C16), 28.92 (C15), 28.76 (C17), 27.93 (C13), 27.09 (C1), 24.47 (C14), 0.73 (TMS). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 301.1982 found 301.1978. **AT-FTIR** (cm^{-1}): 2929, 2855, 1644, 1446, 1335, 1281, 1251, 1216, 1178, 1100, 1073, 1052, 1024, 977, 877, 838, 755, 695, 653, 546.

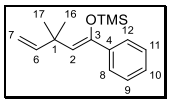
(*Z*)-trimethyl(((1Z,4E)-1-phenylhepta-1,4-dien-1-yl)oxy)silane (**4.455**)



Synthesized by using the **General procedure I.** (*Z/E* > 20: 1).

Isolated yield: 498 mg, 44%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H, C8/C12), 7.29 (t, *J* = 7.5 Hz, 2H, C9/C11), 7.24 (t, *J* = 7.3 Hz, 1H, C10), 5.55 (dt, *J* = 13.9, 6.2 Hz, 1H, C6), 5.49 – 5.42 (m, 1H, C7), 5.25 (t, *J* = 7.3 Hz, 1H, C2), 2.93 – 2.88 (m, 2H, C1), 2.05 – 1.99 (m, 2H, C13), 1.03 – 0.93 (m, 3H, C14), 0.15 – 0.10 (m, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.25 (C3), 139.27 (C4), 132.61 (C7), 128.15 (C10), 127.58 (C9/C11), 127.50 (C6), 125.55 (C8/C12), 109.75 (C2), 29.39 (C1), 25.74 (C13), 14.01 (C14), 0.70 (TMS). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 261.1669 found 261.1678.

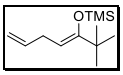
(*Z*)-((3,3-dimethyl-1-phenylpenta-1,4-dien-1-yl)oxy)trimethylsilane (**4.456**)



Synthesized by using the **General procedure IV.** (*Z/E* > 20: 1).

Isolated yield: 519 mg, 17%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H, C8/C12), 7.33 – 7.18 (m, 3H,C9-11), 6.08 (dd, *J* = 17.4, 10.5 Hz, 1H, C6), 5.06 – 4.88 (m, 2H, C7), 4.82 (s, 1H, C2), 1.27 (s, 6H, C16/C17), 0.05 (s, 9H, TMS). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.68 (C3), 146.94 (C6), 139.90 (C4), 126.81 (C8/C12), 126.54 (C10), 125.96 (C9/C11), 117.66 (C2), 108.04 (C7), 36.67 (C1), 27.17 (C16/C17), -0.00 (TMS). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 261.1669 found 261.1670. **ATR-FTIR** (cm^{-1}): 2961, 1643, 1337, 1263, 1251, 1075, 886, 836, 754, 698, 646.

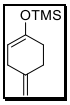
(*Z*)-((2,2-dimethylhepta-3,6-dien-3-yl)oxy)trimethylsilane (**4.442**)



Synthesized by using the **Procedure III.** (*Z/E* > 20: 1).

Isolated yield: 385 mg, 37%.Spectroscopic properties match with the literature.[914]

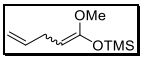
trimethyl((4-methylenecyclohex-1-en-1-yl)oxy)silane (**4.363**)



Synthesized by using the **Procedure VI.**

Isolated yield: 351 mg, 72%.Spectroscopic properties match with the literature.[915]

((1-methoxypenta-1,4-dien-1-yl)oxy)trimethylsilane (**4.478**)



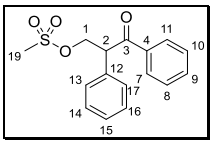
Synthesized by using the silylation step of **Procedure II. *N.B.* the compound is moisture sensitive and must be distilled for purification (no column).** (*Z/E* ≈ 1: 1).

Isolated yield: 6.2 g, 84%. Spectroscopic properties match with the literature.[916]

4.6.2. Products

4.6.2.1. *Aryl migration*

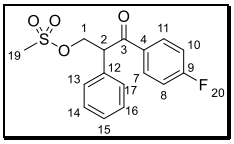
3-oxo-2,3-diphenylpropyl methanesulfonate (**4.271**)



Synthesized by using the **General procedure B.**

Isolated yield: 863 mg, 71%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 12.6, 6.1 Hz, 2H, C7/C11), 7.58 – 7.47 (m, 1H, C9), 7.47 – 7.25 (m, 7H, C8/C9/C13-17), 5.05 (dd, *J* = 9.1, 5.0 Hz, 1H, C1), 4.99 – 4.90 (m, 1H, C1), 4.45 (dd, *J* = 9.7, 5.0 Hz, 1H, C2), 2.99 (s, 3H, C19). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 196.3 (C3), 135.7 (C4), 134.1 (C12), 133.6 (C9), 129.5 (C14/C16), 128.8 (C13/C17), 128.7 (C7/C11), 128.5 (C15), 128.4 (C8/C10), 70.4 (C1), 52.8 (C2), 37.1 (C19). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 327.0662; found: 327.0667. **ATR-FTIR** (cm^{-1}): 1680, 1450, 1345, 1268, 1219, 1171, 979, 957, 917, 88, 828, 772, 696.

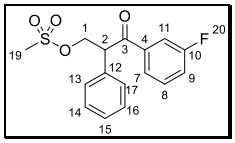
3-(4-fluorophenyl)-3-oxo-2-phenylpropyl methanesulfonate (**4.291**)



Synthesized by using the **General procedure B.**

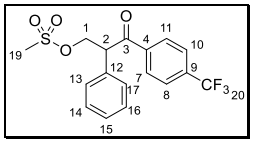
Isolated yield: 46.9 mg, 72%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.00 – 7.89 (m, 2H, C7/C11), 7.35 (dd, *J* = 10.4, 4.4 Hz, 2H, C8/C10), 7.33 – 7.28 (m, 3H, C13/C15/C17), 7.11 – 7.03 (m, 2H, C14/C16), 4.97 (dd, *J* = 9.1, 5.0 Hz, 1H, C1), 4.91 (t, *J* = 9.4 Hz, 1H, C1), 4.42 (dd, *J* = 9.7, 5.0 Hz, 1H, C2), 2.98 (s, 3H, C19). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 194.8 (C3), 166.1 (d, *J* = 256.3 Hz, C9), 134.0 (C12), 132.2 (C4), 132.2 (C16/C14), 131.7 (d, *J* = 10 Hz, C7/C11), 129.7 (C13/C17), 128.7 (C15), 116.1 (d, *J* = 22.0 Hz, C8/C10), 70.4 (C1), 53.0 (C2), 37.3 (C19). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 345.0567; found: 345.0567. **ATR-FTIR** (cm^{-1}): 1686, 1588, 1486, 1442, 1354, 1264, 1220, 1173, 956, 779, 700 674.

3-(3-fluorophenyl)-3-oxo-2-phenylpropyl methanesulfonate (**4.293**)

 Synthesized by using the **General procedure B.**

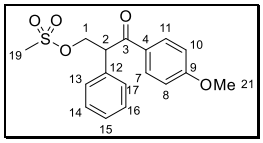
Isolated yield: 43.7 mg, 68%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 1H. C11), 7.66 – 7.58 (m, 1H, C7), 7.45 – 7.14 (m, 7H, Ar), 4.97 (dd, *J* = 9.1, 4.7 Hz, 1H, C1), 4.91 (t, *J* = 9.1 Hz, 1H, C1), 4.42 (dd, *J* = 9.5, 4.7 Hz, 1H, C2), 2.97 (s, 3H, C19). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.1 (C3), 162.8 (d, *J* = 249 Hz, C10), 137.8 (d, *J* = 6 Hz, C4), 133.6 (C12), 130.4 (d, *J* = 8 Hz, C8), 129.6 (C14/C16), 128.6 (C13/C17), 128.4 (C15), 124.6 (d, *J* = 3 Hz, C7), 120.7 (d, *J* = 22 Hz, C9), 115.5 (d, *J* = 22.5 Hz, C11), 70.2 (C1), 53.1 (C12), 37.1 (C19). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 345.0567; found: 345.0568. **ATR-FTIR** (cm^{-1}): 1685, 1588, 1486, 1442, 1354, 1264, 1220, 1173, 956, 881, 820, 773, 700, 674.

3-oxo-2-phenyl-3-(4-(trifluoromethyl)phenyl)propyl methanesulfonate (**4.294**)

 Synthesized by using the **General procedure B.**

Isolated yield: 36.1 mg, 48%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 2H, C7/C11), 7.66 (d, *J* = 8.3 Hz, 2H, C8/C10), 7.38 – 7.27 (m, 5H, C13-17), 5.02 (dd, *J* = 9.1, 5.1 Hz, 1H, C1), 4.92 (t, *J* = 9.6 Hz, 1H, C1), 4.44 (dd, *J* = 10.0, 5.1 Hz, 1H, C2), 2.99 (s, 3H, C19). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 195.5 (C3), 138.4 (C4), 134.9 (q, *J* = 33 Hz, C9), 133.5 (C12), 129.9 (C14/C16), 129.3 (C13/C17), 128.9 (C15), 128.6 (C7/C11), 125.9 (q, *J* = 4 Hz, C8/C9), 123.5 (q, *J* = 273 Hz, C20), 70.1 (C1), 53.4 (C2), 37.3 (C19). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 395.0535; found: 395.0537. **ATR-FTIR** (cm^{-1}): 1691, 1359, 1324, 1220, 1173, 1130, 1067, 956, 775.

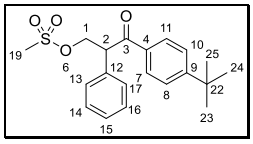
3-(4-methoxyphenyl)-3-oxo-2-phenylpropyl methanesulfonate (**4.286**)



Synthesized by using the **General procedure B.**

Isolated yield: 61.2 mg, 91%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 2H, C7/C11), 7.30 – 7.13 (m, 5H, C13-17), 6.86 – 6.68 (m, 2H, C8/C10), 4.89 (dd, *J* = 9.0, 4.5 Hz, 1H, C1), 4.87 – 4.80 (m, 1H, C1), 4.33 (dd, *J* = 9.1, 4.5 Hz, 1H, C2), 3.73 (s, 3H, C21), 2.88 (s, 3H, C19). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.8 (C3), 164.0 (C9), 134.7 (C12), 131.3 (C7/C11), 129.5 (C14/C16), 128.8 (C4), 128.5 (C13/C17), 128.4 (C15), 114.1 (C8/C10), 70.8 (C1), 55.59 (C21), 52.6 (C2), 37.2 (C19).**HRMS** (ESI): m/z calculated for $[M+Na]^+$ 357.0767; found: 357.0769. **ATR-FTIR** (cm^{-1}): 1672, 1599, 1511, 1455, 1260, 1220, 1170, 1028, 954, 876, 816, 773, 702.

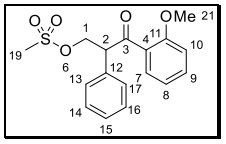
3-(4-(tert-butyl)phenyl)-3-oxo-2-phenylpropyl methanesulfonate (**4.287**)



Synthesized by using the **General procedure B.**

Isolated yield: 44.1 mg, 61%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 2H, C7/C11), 7.46 – 7.39 (m, 2H, C13/C17), 7.37 – 7.26 (m, 5H, Ar), 5.01 (dd, *J* = 9.2, 5.0 Hz, 1H, C1), 4.96 – 4.90 (m, 1H, C1), 4.42 (dd, *J* = 9.6, 5.0 Hz, 1H, C2), 2.96 (s, 3H, C19), 1.29 (s, 9H, C23-25). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.0 (C3), 157.6 (C9), 134.4 (C12), 133.3 (C4), 129.6 (C7/C11), 129.0 (C14/C16), 128.6 (C13/C17), 128.5 (C15), 125.9 (C8/C10), 70.7 (1), 52.80 (C2), 37.2 (C19), 35.3 (C22), 31.1 (C23-25). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 383.1288; found: 383.1288. **ATR-FTIR** (cm^{-1}): 2963, 1676, 1604, 1455, 1409, 1356, 1267, 1220, 1173, 1110, 953, 890, 812, 773.

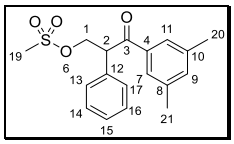
3-(2-methoxyphenyl)-3-oxo-2-phenylpropyl methanesulfonate (**4.296**)



Synthesized by using the **General procedure B.**

Isolated yield: 38.6 mg, 58%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.8 Hz, 1H, C7), 7.34 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1H, C9), 7.25 – 7.13 (m, 5H, C13-17), 6.87 (td, *J* = 7.7, 0.9 Hz, 1H, C8), 6.80 (d, *J* = 8.4 Hz, 1H, C10), 5.13 (dd, *J* = 8.8, 5.6 Hz, 1H, C1), 4.91 – 4.74 (m, 1H, C1), 4.31 (dd, *J* = 9.8, 5.6 Hz, 1H, C2), 3.76 (s, 3H, C21), 2.86 (s, 3H, C19). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.5 (C3), 158.6 (C11), 134.5 (C12), 134.4 (C9), 131.3 (C7), 129.0 (C14/C16), 129.0 (C13/C17), 128.1 (C15), 127.0 (C4), 120.9 (C8), 111.8 (C10), 71.2 (C1), 56.6 (C2), 55.5 (C21), 37.2 (C19). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 357.0767; found: 357.0769. **ATR-FTIR** (cm^{-1}): 1673, 1599, 1456, 1260, 1220, 1028, 954, 876, 816, 773, 701.

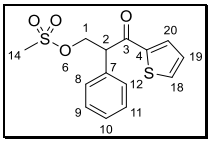
3-(3,5-dimethylphenyl)-3-oxo-2-phenylpropyl methanesulfonate (**4.289**)



Synthesized by using the **General procedure B.**

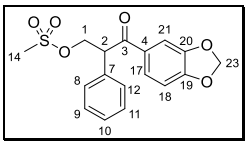
Isolated yield: 58.0 mg, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (s, 2H, C7/C11), 7.30 – 7.15 (m, 5H, C13-17), 7.10 – 7.06 (m, 1H, C9), 4.94 (dd, *J* = 9.2, 5.0 Hz, 1H, C1), 4.89 – 4.81 (m, 1H, C1), 4.34 (dd, *J* = 9.7, 5.0 Hz, 1H, C2), 2.89 (s, 3H, C19), 2.24 (s, 3H, C20/C21), 2.24 (s, 3H, C20/C21). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.8 (C3), 138.5 (C8/C10), 136.0 (C4), 135.5 (C9), 134.3 (C12), 129.6 (C14/C16), 128.6 (C13/17), 128.5 (C15), 126.8 (C7/C11), 70.7 (C1), 52.8 (C2), 37.2 (C19), 21.4 (C20/C21). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 355.0975; found: 355.0974. **ATR-FTIR** (cm^{-1}): 1676, 1601, 1493, 1454, 1355, 1297, 1220, 1174, 1047, 957, 889, 815 772, 701.

3-oxo-2-phenyl-3-(thiophen-2-yl)propyl methanesulfonate (**4.295**)

 Synthesized by using the **General procedure B.**

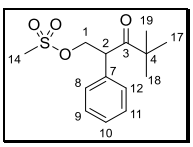
Isolated yield: 47.0 mg, 75%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 3.9, 1.0 Hz, 1H, C20), 7.63 (dd, *J* = 4.9, 1.0 Hz, 1H, C18), 7.42 –7.28 (m, 5H, C8-12), 7.07 (dd, *J* = 4.9, 3.9 Hz, 1H, C19), 4.95 – 4.76 (m, 2H, C1), 4.41 (dd, *J* = 9.3, 4.5 Hz, 1H, C2), 2.98 (s, 3H, C14). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.3 (C3), 143.0 (C4), 134.8 (C20), 134.3 (C7), 133.4 (C18), 129.6 (C9/C11), 128.7 (C8/12), 128.5 (C10), 128.5 (C19), 70.2 (C1), 54.2 (C2), 37.3 (C14). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 333.0226; found: 333.0226. **ATR-FTIR** (cm^{-1}): 1657, 1413, 1355, 1220, 1174, 958, 815, 773.

3-(benzo[d][1,3]dioxol-5-yl)-3-oxo-2-phenylpropyl methanesulfonate (**4.288**)

 Synthesized by using the **General procedure B.**

Isolated yield: 57.5 mg, 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 1H, C21), 7.25 (d, *J* = 1.7 Hz, 1H, C17), 7.21 – 7.09 (m, 5H, C8-12), 6.62 (d, *J* = 8.2 Hz, 1H, C18), 5.84 (s, 2H, C23), 4.79 – 4.69 (m, 2H, C1), 4.30 – 4.18 (m, 1H, C2), 2.80 (s, 3H, C14). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 194.4 (C3), 152.3 (C19), 148.4 (C20), 134.5 (C7), 130.6 (C4), 129.6 (C9/C11), 128.5 (C8/C12), 128.5 (C10), 125.6 (C17), 108.6 (C21), 108.2 (C18), 102.1 (C23), 70.7 (C1), 52.7 (C2), 37.2 (C14). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 371.0560; found: 371.0561. **ATR-FTIR** (cm^{-1}): 1671, 1604, 1490, 1443, 1355, 1260, 1220, 1174, 1037, 957, 894, 808, 773.

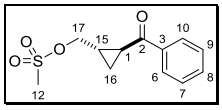
4,4-dimethyl-3-oxo-2-phenylpentyl methanesulfonate (**4.300**)

 Synthesized by using the **General procedure B.**

Isolated yield: 55.0 mg, >95%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 5H, C8-12), 4.68 (t, *J* = 9.8 Hz, 1H, C1), 4.58 (dd, *J* = 9.8, 4.9 Hz, 1H, C1), 4.22 (dd, *J* = 9.6, 4.9 Hz, 1H, C2), 2.92 (s, 3H, C14), 1.09 (s, 9H, C17-19). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 212.4 (C3), 133.7 (C7), 129.4 (C9/C11), 128.6 (C8/C12), 128.4 (C10), 71.3 (C1), 51.9 (C2), 45.3 (C4), 37.2 (C14), 26.5 (C17-19). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 307.0975; found: 307.0977. **ATR-FTIR** (cm^{-1}): 2971, 1704, 1358, 1220, 1175, 953, 684, 816, 773.

4.6.2.2. *Cyclopropanation*

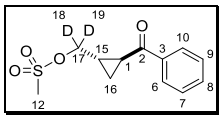
((1*S**,2*S**)-2-benzoylcyclopropyl)methyl methanesulfonate (**4.317**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 36.2 mg, 71%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H, C6/C10), 7.63 – 7.56 (m, 1H, C8), 7.55 – 7.45 (m, 2H, C7/C9), 4.40 (dd, *J* = 11.1, 6.0 Hz, 1H, C17), 4.12 (dd, *J* = 11.1, 8.1 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.84 – 2.75 (m, 1H, C1), 2.11 – 1.99 (m, 1H, C15), 1.56 (dt, *J* = 9.1, 4.7 Hz, 1H, C16), 1.19 – 1.10 (m, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.19 (C2), 137.41 (C3), 133.36 (C8), 128.79 (C6/C10), 128.30 (C7/C9), 71.77 (C17), 38.15 (C12), 23.29 (C1), 23.23 (C15), 15.89 (C16). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 277.0505 found: 277.0510. **ATR-FTIR** (cm^{-1}): 1725, 1667, 1598, 1580, 1451, 1414, 1352, 1332, 1264, 1224, 1172, 1061, 1039, 1025, 974, 948, 816, 786, 746.

((1*S**,2*S**)-2-benzoylcyclopropyl)methyl-d_2 methanesulfonate (**4.380**)

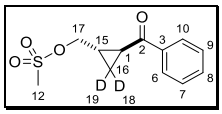


Synthesized by using the **General procedure VIII.**

Isolated yield: 29.8 mg, 72%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H, C6/C10), 7.59 (t, *J* = 7.4 Hz, 1H, C8), 7.49 (t, *J* = 7.8 Hz, 2H, C7/C9), 3.02 (s, 3H, C12), 2.83 – 2.77 (m, 1H, C1), 2.09 – 2.02 (m, 1H, C15), 1.58 – 1.54 (m, 1H, C16), 1.18 – 1.12 (m, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.22 (C2), 137.43 (C3), 133.37 (C8), 128.81 (C6/C10), 128.31 (C7/C9), 38.77 – 37.66 (m, C1), 23.79 – 22.82 (m, C15), 15.88 (C16).

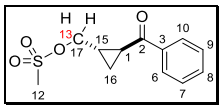
HRMS (ESI): m/z calculated for $[M+Na]^+$ 279.0631 found: 279.0632. **ATR-FTIR** (cm^{-1}): 1739, 1668, 1598, 1451, 1410, 1354, 1335, 1225, 1174, 1041, 1018, 973, 943, 828, 703, 527 cm^{-1}.

((1*S**,2*S**)-2-benzoylcyclopropyl-3,3-d_2)methyl methanesulfonate (**4.381**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 7.99 (m, 2H, C6/C10), 7.59 (t, *J* = 7.4 Hz, 1H, C8), 7.49 (t, *J* = 7.8 Hz, 2H, C7/C9), 4.41 (dd, *J* = 11.1, 6.0 Hz, 1H, C8), 4.12 (dd, *J* = 10.8, 7.8 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.83 – 2.77 (m, 1H, C1), 2.09 – 2.02 (m, 1H, C15). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.22 (C2), 137.43 (C3), 133.37 (C8), 128.81 (C6/C10), 128.31 (C7/C9), 71.72 (C17), 38.77 – 37.66 (m, C1), 23.79 – 22.82 (m, C15).

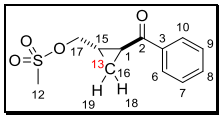
((1*S**,2*S**)-2-benzoylcyclopropyl)methyl-^{13}C methanesulfonate (**4.377**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 34.8 mg, 68%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 2H, C6/C10), 7.62 – 7.55 (m, 1H, C8), 7.51 – 7.46 (m, 2H, C7/C9), 4.40 (ddd, *J* = 150.9, 11.1, 6.0 Hz, 1H, C17), 4.11 (ddd, *J* = 150.3, 11.1, 8.1 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.83 – 2.77 (m, 1H, C1), 2.10 – 2.03 (m, 1H, C15), 1.59 – 1.54 (m, 1H, C16), 1.17 – 1.11 (m, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.22 (C2), 137.42 (C3), 133.37 (C8), 128.80 (C6/C10), 128.31 (C7/C9), 71.76 (C17!), 38.17 (C12), 34.12 (C1), 29.8 (C15), 15.91 (C16). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 278.0539 found: 278.0540. **ATR-FTIR** (cm^{-1}): 1666, 1597, 1580, 1451, 1412, 1349, 1329, 1263, 1222, 1170, 1107, 1057, 1037, 1023, 972, 931, 911, 809, 785, 757 cm^{-1}.

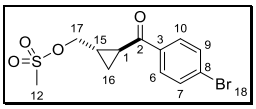
((1*S**,2*S**)-2-benzoylcyclopropyl-3-^{13}C)methyl methanesulfonate (**4.378**)



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 2H, C6/C10), 7.62 – 7.55 (m, 1H, C8), 7.51 – 7.46 (m, 2H, C7/C9), 4.41 (ddd, *J* = 11.1, 6.0, 1.5 Hz, 1H, C17), 4.12 (ddd, *J* = 11.4, 8.1, 3.6 Hz, 1H, C17), 3.02 (s, 3H, C12),

2.83 – 2.77 (m, 1H, C1), 2.10 – 2.03 (m, 1H, C15), 1.56 (d, *J* = 168.5, Hz, 1H, C16), 1.15 (d, J = 163.8, Hz, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.22 (C2), 137.42 (C3), 133.37 (C8), 128.80 (C6/C10), 128.31 (C7/C9), 71.76 (C17), 38.17 (C12), 34.12 (C1), 29.8 (C15), 15.91 (C16!).

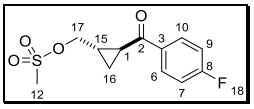
((1*S**,2*S**)-2-(4-bromobenzoyl)cyclopropyl)methyl methanesulfonate (**4.344**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 33.5 mg, 50%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H, C6/C10), 7.63 (d, *J* = 8.5 Hz, 2H, C7/C9), 4.42 (dd, *J* = 11.2, 5.8 Hz, 1H, C17), 4.09 (dd, *J* = 11.2, 8.2 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.79 – 2.71 (m, 1H, C1), 2.17 – 2.00 (m, 1H, C15), 1.57 (dt, *J* = 9.0, 4.7 Hz, 1H, C16), 1.19 – 1.10 (m, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.21 (C2), 136.12 (C3), 132.11 (C7/C9), 129.85 (C6/C10), 128.59 (C8), 71.58 (C17), 38.17 (C12), 23.60 (C1), 23.33 (C15), 16.00 (C16). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 354.9610 found: 354.9610. **ATR-FTIR** (cm^{-1}): 1669, 1585, 1415, 1397, 1352, 1267, 1221, 1173, 1070, 1038, 1009, 974, 948, 837, 812, 735.

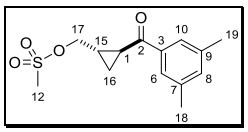
((1*S**,2*S**)-2-(4-fluorobenzoyl)cyclopropyl)methyl methanesulfonate (**4.343**)



Synthesized by using the **General procedure VIII.**

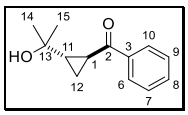
Isolated yield: 35.6 mg, 67%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 2H, C6/C10), 7.21 – 7.11 (m, 2H, C7/C9), 4.42 (dd, *J* = 11.1, 5.8 Hz, 1H, C17), 4.09 (dd, *J* = 11.1, 8.2 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.79 – 2.71 (m, 1H, C1), 2.10 – 1.97 (m, 1H, C15), 1.56 (dt, *J* = 9.1, 4.7 Hz, 1H, C16), 1.14 (ddd, *J* = 20.0, 11.1, 7.8 Hz, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.62 (C2), 166.00 (d, *J* = 255 Hz, C8), 133.84 (d, *J* = 2.9 Hz, C3), 130.97 (d, *J* = 9 Hz, C6/C10), 115.90 (d, *J* = 22 Hz, C7/C9), 71.68 (C17), 38.15 (C12), 23.38 (C1), 23.26 (C15), 15.83 (C16). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 295.0411 found: 295.0416. **ATR-FTIR** (cm^{-1}): 1667, 1597, 1507, 1417, 1350, 1329, 1265, 1221, 1171, 1157, 1111, 1061, 1036, 1013, 973, 943, 915, 845, 808, 758, 739.

((1*S**,2*S**)-2-(3,5-dimethylbenzoyl)cyclopropyl)methyl methanesulfonate (**4.342**)

 Synthesized by using the **General procedure VIII.**

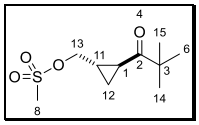
Isolated yield: 38.1 mg, 68%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (s, 2H, C6/C10), 7.21 (s, 1H, C8), 4.39 (dd, *J* = 11.0, 6.1 Hz, 1H, C17), 4.12 (dd, *J* = 11.0, 8.0 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.79 – 2.73 (m, 1H, C1), 2.38 (s, 6H, C18/C19), 2.09 – 2.00 (m, 1H, C15), 1.58 – 1.50 (m, 1H, C16), 1.16 – 1.10 (m, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 198.52 (C2), 138.45 (C7/9), 137.55 (C3), 134.99 (C8), 126.11 (C6/C10), 71.92 (C17), 38.17 (C12), 23.41 (C1), 23.00 (C15), 21.36 (C18/C19), 15.81 (C16). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 305.0818 found: 305.0824. **ATR-FTIR** (cm^{-1}): 1666, 1604, 1450, 1415, 1351, 1330, 1292, 1207, 1172, 1077, 1047, 972, 930, 864, 840, 816, 738, 711, 678.

((1*S**,2*S**)-2-(2-hydroxypropan-2-yl)cyclopropyl)(phenyl)methanone (**4.351**)

 Synthesized by using the **General procedure VIII.**

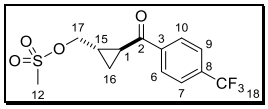
Isolated yield: 38.5 mg, 94%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 2H, C6/C10), 7.58 – 7.52 (m, 1H, C8), 7.46 (dt, *J* = 7.5, 4.2 Hz, 2H, C7/C9), 2.79 (dt, *J* = 8.3, 4.6 Hz, 1H, C1), 1.77 (ddd, *J* = 9.1, 6.8, 4.4 Hz, 1H, C11), 1.41 – 1.36 (m, 1H, C12), 1.32 (s, 3H, C14/C15), 1.31 (s, 4H, C14/C15/OH), 1.20 (ddd, *J* = 8.2, 6.8, 3.6 Hz, 1H, C12). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 200.35 (C2), 137.95 (C3), 132.90 (C8), 128.63 (C6/C10), 128.21 (C7/C9), 68.82 (C13), 36.92 (C1), 29.90 (C14/C15), 29.61 (C14/C15), 21.14 (C11), 14.54 (C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 227.1048 found 227.1045. **ATR-FTIR** (cm^{-1}): 3429, 2970, 1719, 1655, 1597, 1580, 1450, 1398, 1371, 1331, 1221, 1180, 1158, 1115, 1072, 1052, 1037, 1012, 1002, 954, 913, 873, 839, 794, 756, 729, 713, 693, 652.

((1*S**,2*S**)-2-pivaloylcyclopropyl)methyl methanesulfonate (**4.349**)

 Synthesized by using the **General procedure VIII.**

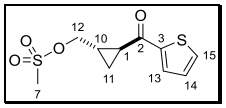
Isolated yield: 22.1 mg, 53%.**^{1}H NMR** (400 MHz, CDCl3) δ 4.31 (dd, J = 11.0, 6.1 Hz, 1H, C13), 3.98 (dd, J = 11.0, 8.2 Hz, 1H, C13), 3.01 (s, 3H, C8), 2.28 – 2.18 (m, 1H, C1), 1.83 – 1.68 (m, 1H, C11), 1.35 – 1.26 (m, 1H, C12), 1.20 (s, 9H, C6/C14/C15), 1.00 – 0.87 (m, 1H, C12). **^{13}C NMR** (101 MHz, CDCl3) δ 213.13 (C2), 71.92 (C13), 38.06 (C8), 26.27 (C6/C14/C15), 22.65 (C1), 21.95 (C11), 15.35 (C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 227.1048 found 227.1045. **ATR-FTIR** (cm^{-1}): 2970, 1690, 1479, 1415, 1396, 1353, 1201, 1174, 1092, 1044, 945, 951, 929, 812, 784.

((1*S**,2*S**)-2-(4-(trifluoromethyl)benzoyl)cyclopropyl)methyl methanesulfonate (**4.345**)

 Synthesized by using the **General procedure VIII.**

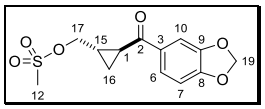
Isolated yield: 43.3 mg, 67%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.12 (d, J = 8.1 Hz, 2H, C6/10), 7.75 (d, *J* = 8.2 Hz, 2H, C7/9), 4.46 (ddd, *J* = 16.9, 9.7, 4.8 Hz, 1H, C17), 4.09 (dd, *J* = 11.2, 8.3 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.80 (dt, *J* = 8.7, 4.5 Hz, 1H, C1), 2.16 – 2.01 (m, 1H, C15), 1.66 – 1.50 (m, 1H, C16), 1.27 – 1.17 (m, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.45 (C2), 140.08 (C3), 134.56 (q, J = 33 Hz, C8), 128.66 (C6/C10), 125.84 (q, J = 4 Hz, C7/9), 123.70 (q, J = 273 Hz, C18), 71.46 (C17), 38.10 (12), 24.01 (C1), 23.73 (C15), 16.24 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 345.0379 found 345.0379. **ATR-FTIR** (cm^{-1}): 1675, 1513, 1415, 1353, 1319, 1268, 1222, 1167, 1124, 1065, 1040, 1015, 973, 946, 914, 851, 833, 811, 734, 698, 674, 649, 592.

((1*S**,2*S**)-2-(thiophene-2-carbonyl)cyclopropyl)methyl methanesulfonate (**4.346**)

 Synthesized by using the **General procedure VIII.**

Isolated yield: 31.5 mg, 61%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 3.8, 1.1 Hz, 1H, C13), 7.66 (td, *J* = 4.6, 1.2 Hz, 1H, C15), 7.17 (dd, J = 4.9, 3.8 Hz, 1H, C14), 4.38 (dd, *J* = 11.1, 6.0 Hz, 1H, C12), 4.10 (dd, *J* = 11.1, 8.0 Hz, 1H, C12), 3.02 (s, 3H, C7), 2.68 – 2.60 (m, 1H, C1), 2.12 – 1.99 (m, 1H, C10), 1.57 (dt, *J* = 9.1, 4.7 Hz, 1H, C11), 1.18 – 1.08 (m, 1H, C11). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 190.50 (C2), 144.46 (C3), 134.17 (C13), 132.43 (C15), 128.48 (C14), 71.58 (C12), 38.18 (C7), 24.16 (C1), 22.95 (C10), 15.50 (C11). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 283.0069 found 283.0070. **ATR-FTIR** (cm^{-1}): 1643, 1518, 1446, 1417, 1347, 1328, 1262, 1238, 1227, 1169, 1082, 1065, 1018, 971, 939, 895, 844, 808, 721.

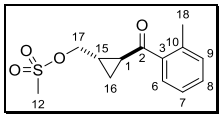
((1*S**,2*S**)-2-(benzo[*d*][1,3]dioxole-5-carbonyl)cyclopropyl)methyl methanesulfonate (**4.341**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 33.3 mg, 56%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 1H, C6), 7.47 (d, *J* = 1.7 Hz, 1H, C10), 6.88 (d, *J* = 8.2 Hz, 1H, C7), 6.04 (s, 2H, C19), 4.40 (dd, *J* = 11.1, 6.0 Hz, 1H, C17), 4.10 (dd, *J* = 11.1, 8.1 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.72 – 2.64 (m, 1H, C1), 2.06 – 1.95 (m, 1H, C15), 1.52 (ddd, *J* = 9.0, 4.9, 4.4 Hz, 1H, C16), 1.10 (ddd, *J* = 8.4, 6.1, 4.3 Hz, 1H, C16). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.04 (C2), 152.10 (C8), 148.41 (C9), 132.30 (C3), 124.72 (C6), 108.10 (C7/C10), 102.05 (C19), 71.86 (C17), 38.21 (C12), 23.11 (C1), 22.94 (C15), 15.56 (C1). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 321.0403 found 321.0412. **ATR-FTIR** (cm^{-1}): 1658, 1603, 1504, 1490, 1440, 1415, 1349, 1246, 1170, 1140, 1113, 1099, 1032, 973, 923, 883, 807, 762, 732, 647, 574.

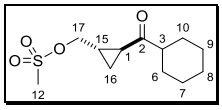
((1*S**,2*S**)-2-(2-methylbenzoyl)cyclopropyl)methyl methanesulfonate (**4.347**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 38.9 mg, 73%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 1.2 Hz, 1H, C6), 7.42 – 7.36 (m, 1H, C8), 7.32 – 7.23 (m, 2H, C7/C9), 4.36 (dd, *J* = 11.0, 6.2 Hz, 1H, C17), 4.10 (dd, *J* = 11.0, 7.9 Hz, 1H, C17), 3.02 (s, 3H, C12), 2.59 – 2.51 (m, 1H, C1), 2.48 (s, 3H, C18), 2.12 – 1.99 (m, 1H, C15), 1.55 (ddd, *J* = 9.0, 4.9, 4.4 Hz, 1H, C16), 1.13 (ddd, *J* = 8.4, 6.1, 4.3 Hz, 1H, C16). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.03 (C2), 138.69 (C10), 137.59 (C3), 131.83 (C8), 131.50 (C9), 128.78 (C6), 125.91 (C7), 71.76 (C17), 38.09 (C12), 26.46 (C18), 23.33 (C1), 21.01 (C15), 16.20 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 291.0662 found 291.0660. **ATR-FTIR** (cm^{-1}): 1669, 1456, 1413, 1350, 1288, 1260, 1219, 1171, 1060, 1031, 972, 943, 917, 810, 731, 649, 563, 527.

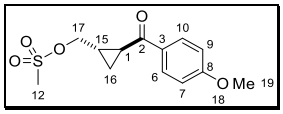
((1*S**,2*S**)-2-(cyclohexanecarbonyl)cyclopropyl)methyl methanesulfonate (**4.348**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 30.0 mg, 58%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 11.0, 6.2 Hz, 1H, C17), 3.99 (dd, *J* = 11.0, 8.0 Hz, 1H, C17), 3.01 (s, 3H, C12), 2.56 – 2.44 (m, 1H, C1), 2.12 – 2.04 (m, 1H, C3), 1.95 – 1.87 (m, 2H, C6/C10), 1.84 – 1.73 (m, 3H, C6/C10/Cy), 1.71 – 1.63 (m, 1H, C15), 1.43 – 1.17 (m, 6H, Cy), 0.93 (ddd, *J* = 8.4, 6.0, 4.3 Hz, 1H, C16). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 211.37 (C2), 71.87 (C17), 51.72 (C3), 38.07 (C12), 28.40 (C6), 28.39 (C10), 26.00 (C8), 25.71 (C7/9), 24.93 (C1), 22.30 (C15), 15.14 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 283.0975 found 283.0980. **ATR-FTIR** (cm^{-1}): 3062, 3005, 2958, 1665, 1597, 1580, 1449, 1396, 1333, 1309, 1225, 1174, 1070, 1017, 913, 867, 799, 775, 753, 701, 671, 664, 654, 573, 546.

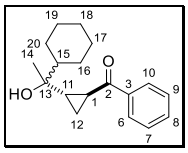
((1*S**,2*S**)-2-(4-methoxybenzoyl)cyclopropyl)methyl methanesulfonate (**4.339**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 30.1 mg, 53%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.90 (m, 2H, C6/C10), 7.00 – 6.92 (m, 2H, C7/C9), 4.39 (dd, *J* = 11.1, 6.0 Hz, 1H, C17), 4.11 (dd, *J* = 11.1, 8.1 Hz, 1H, C17), 3.87 (s, 3H, C19), 3.01 (s, 3H, C12), 2.80 – 2.70 (m, 1H, C1), 2.07 – 1.97 (m, 1H, C15), 1.57 – 1.50 (m, 1H, C16), 1.14 – 1.04 (m, 1H, C16). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.46 (C2), 163.82 (C8), 130.60 (C6/C10), 130.47 (C3), 113.97 (C7), 113.86 (C9), 71.99 (C17), 55.63 (C19), 38.20 (C12), 22.91 (C1), 22.81 (C15), 15.47 (C16). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 307.0611 found 307.0611. **ATR-FTIR** (cm^{-1}): 1658, 1598, 1574, 1511, 1461, 1422, 1351, 1331, 1257, 1227, 1167, 1120, 1061, 1025, 793, 943, 913, 840, 809, 750, 692, 667, 632, 565, 526.

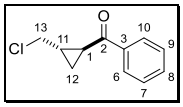
((1*S**,2*S**)-2-(1-cyclohexyl-1-hydroxyethyl)cyclopropyl)(phenyl)methanone (**4.353**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 46.5 mg, 85%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 – 7.94 (m, 2H, C6/C10), 7.59 – 7.53 (m, 1H, C8), 7.50 – 7.43 (m, 2H, C7/C9), 2.88 – 2.72 (m, 1H, C1), 1.92 – 1.59 (m, 6H, C11/Cy), 1.46 – 1.33 (m, 2H, Cy), 1.29 – 1.18 (m, 6H, C14, Cy), 1.16 – 0.96 (m, 4H, C12/Cy). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.81 (C2), 200.46 (C2'), 138.09 (C3), 132.86 (C8), 132.85 (C8'), 128.63 (C6/C10), 128.24 (C7/C9), 128.20 (C7'/C9'), 72.69 (C13), 72.41 (C13'), 49.51 (C15), 49.47 (C15'), 34.50 (C1), 33.95 (C1'), 27.80 (Cy), 27.64 (Cy), 27.61 (Cy), 27.55 (Cy), 26.80 (Cy), 26.78 (Cy), 26.77 (Cy), 26.76 (Cy), 26.60 (Cy), 26.56 (Cy), 25.68 (C14), 24.57 (C14'), 21.19 (C12), 20.37 (C12'), 15.44, 14.34. **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 295.1669 found .295.1670. **ATR-FTIR** (cm^{-1}): 3462, 2926, 2852, 1653, 1598, 1580, 1450, 1397, 1374, 1332, 1308, 1221, 1179, 1160, 1114, 1073, 1053, 1034, 1026, 1008, 935, 915, 893, 872, 857, 843, 731, 702, 671, 655, 546.

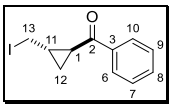
((1*S**,2*S**)-2-(chloromethyl)cyclopropyl)(phenyl)methanone (**4.370**)



Synthesized by using the **General procedure XI.** Nucleophile: Bu_4NCl (1.5. equiv.).

Isolated yield: 32.1 mg, 83%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H, C6/C10), 7.61 – 7.55 (m, 1H, C8), 7.51 – 7.45 (m, 2H, C7/C9), 3.75 (dd, *J* = 11.4, 6.1 Hz, 1H, C13), 3.48 (dd, *J* = 11.4, 7.8 Hz, 1H, C13), 2.76 – 2.68 (m, 1H, C1), 2.09 – 1.98 (m, 1H, C11), 1.67 – 1.57 (m, 1H, C12), 1.17 – 1.09 (m, 1H, C12) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.53 (C2), 137.74 (C3), 133.15 (C8), 128.72 (C6/C10), 128.28 (C7/9), 47.48 (C13), 27.06 (C1), 24.87 (C11), 17.83 (C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 217.0391 found 217.0393. **ATR-FTIR** (cm^{-1}): 1666, 1597, 1580, 1449, 1400, 1338, 1312, 1266, 1227, 1216, 1178, 1135, 1105, 1077, 1051, 1033, 1021, 949, 909, 867, 778, 758, 731, 697, 650, 627.

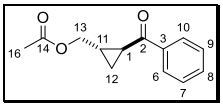
((1*S**,2*S**)-2-(iodomethyl)cyclopropyl)(phenyl)methanone (**4.371**)



Synthesized by using the **General procedure XI.** Nucleophile: Bu_4NI (1.5. equiv.).

Isolated yield: 42.6 mg, 74%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H, C6/C10), 7.58 (t, *J* = 7.3 Hz, 1H, C8), 7.49 (t, *J* = 7.6 Hz, 2H, C7/C9), 3.33 (dd, *J* = 10.1, 7.3 Hz, 1H, C13), 3.22 (dd, J = 10.0, 8.0 Hz, 1H, C13), 2.68 – 2.61 (m, 1H, C1), 2.14 – 2.04 (m, 1H, C11), 1.78 (dt, J = 8.9, 4.6 Hz, 1H, C12), 1.15 – 1.06 (m, 1H, C12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.28 (C2), 137.68 (C3), 133.17 (C8), 128.74 (C6/C10), 128.36 (C7/C9), 29.89 (C1), 29.28 (C11), 22.81 (C12), 8.93 (C13). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 308.9752 found 308.9745. **ATR-FTIR** (cm^{-1}): 2956, 2931, 1738, 1726, 1681, 1596, 1580, 1509, 1493, 1447, 1366, 1272, 1217, 1182, 1098, 1073, 1047, 1025, 1001, 764, 701, 674.

((1*S**,2*S**)-2-benzoylcyclopropyl)methyl acetate (**4.374**)

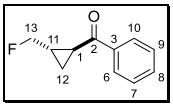


Synthesized by using the **General procedure XI.** Nucleophile: Et_3NHOAc (1.5. equiv.).

Isolated yield: 23.0 mg, 53%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 2H, C6/C10), 7.63 – 7.54 (m, 1H, C8), 7.48 (t, *J* = 7.6 Hz, 2H, C7/C9), 4.22 (dd, *J* = 11.7, 5.9 Hz, 1H, C13), 3.99 (dd, *J* = 11.7, 7.9 Hz, 1H, C13),

2.73 – 2.66 (m, 1H, C1), 2.06 (s, 3H, C16), 2.00 – 1.88 (m, 1H, C11), 1.56 – 1.46 (m, 1H, C12), 1.11 – 1.03 (m, 1H, C12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.86 (C2), 171.16 (C14), 137.79 (C3), 133.11 (C8), 128.72 (C6/C10), 128.24 (C7/C9), 66.46 (C13), 23.96 (C1), 23.43 (C16), 21.04 (C11), 15.70 (C12). HRMS (ESI) m/z calculated for $[M+Na]^+$ 241.0841 found 241.0836. **ATR-FTIR** (cm^{-1}): 1727, 1666, 1597, 1580, 1450, 1412, 1364, 1329, 1220, 1178, 1056, 1024, 973, 915, 888, 868, 810, 784, 754, 702, 654, 605, 546.

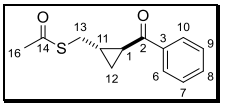
((1*S**,2*S**)-2-(fluoromethyl)cyclopropyl)(phenyl)methanone (**4.369**)



Synthesized by using the **General procedure XI.** Nucleophile: $Bu_4NPh_3SiF_2$ (1.5. equiv.).

Isolated yield: 24.3 mg, 68%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 – 8.00 (m, 2H, C6/C10), 7.60 – 7.55 (m, 1H, C8), 7.52 – 7.45 (m, 2H, C7/C9), 4.61 (ddd, *J* = 48.4, 9.9, 5.5 Hz, 1H, C13), 4.27 (ddd, *J* = 47.6, 9.9, 7.4 Hz, 1H, C13), 2.77 – 2.71 (m, 1H, C1), 2.07 – 1.99 (m, 1H, C11), 1.57 – 1.52 (m, 1H, C12), 1.13 – 1.07 (m, 1H, C12). **^{13}C NMR** (151 MHz, CDCl3) δ 198.78 (C2), 137.75 (C3), 133.18 (C8), 128.74 (C6/C10), 128.27 (C7/C9), 85.18 (d, *J* = 169 Hz, C13), 24.50 (d, *J* = 24 Hz, C11), 22.61 (d, *J* = 5 Hz, C11), 14.83 (d, *J* = 7.7 Hz, C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 201.0692 found 201.0682. **ATR-FTIR** (cm^{-1}): 1666, 1597, 1580, 1451, 1416, 1370, 1330, 1311, 1256, 1221, 1178, 1074, 1058, 1037, 1023, 976, 917, 892, 872, 849, 811, 784, 754, 700, 753, 618, 582.

S-(((1*S**,2*S**)-2-benzoylcyclopropyl)methyl) ethanethioate (**4.373**)

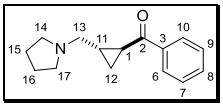


Synthesized by using the **General procedure XI.** Nucleophile: Et_3NHOAc (1.5. equiv.).

Isolated yield: 30.3 mg, 65%.**^{1}H NMR** (600 MHz, CDCl3) δ 8.02 – 7.97 (m, 2H, C6/C10), 7.57 (dd, *J* = 15.7, 8.4 Hz, 1H, C8), 7.48 (t, *J* = 7.7 Hz, 2H, C7/C9), 3.08 (dd, *J* = 13.9, 6.5 Hz, 1H, C13), 2.98 (dd, *J* = 13.9, 7.6 Hz, 1H, C13), 2.70 – 2.62 (m, 1H, C1), 2.34 (s, 3H, C16), 1.86 – 1.78 (m, 1H, C11), 1.57 – 1.52 (m, 1H, C12), 1.13

– 1.05 (m, 1H, C12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.94 (C2), 195.62 (C14), 137.80 (C3), 133.00 (C8), 128.67 (C6/C10), 128.21 (C7/C9), 32.58 (C13), 30.65 (C1), 25.73 (C16), 25.30 (C11), 18.59 (C12). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 257.0612 found 257.0607. **ATR-FTIR** (cm^{-1}): 1688, 1666, 1597, 1580, 1450, 1398, 1338, 1227, 1178, 1135, 1107, 1049, 1033, 1022, 960, 776, 759, 701, 652, 627.

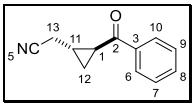
Phenyl((1*S**,2*S**)-2-(pyrrolidin-1-ylmethyl)cyclopropyl)methanone (**4.375**)



Synthesized by using the **General procedure XI.** Nucleophile: Pyrrolidine (2.0 equiv.).

Isolated yield: 31.4 mg, 69%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 – 7.96 (m, 2H, C6/C10), 7.55 (t, *J* = 7.4 Hz, 1H, C8), 7.46 (t, *J* = 7.7 Hz, 2H, C7/C9), 2.57 – 2.51 (m, 7H, C13/C14/C17/C1), 1.85 – 1.79 (m, 1H, C11), 1.79 – 1.74 (m, 4H, C15/C16), 1.54 – 1.48 (m, 1H, C12), 1.01 – 0.95 (m, 1H, C12). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 199.66 (C2), 138.08 (C3), 132.85 (C8), 128.62 (C5/C10), 128.19 (C7/C9), 59.53 (C13), 54.32 (C14/C17), 54.20 (C14/C17), 25.14 (C1), 24.28 (C16/C15), 23.53 (C11), 17.84 (C12). **HRMS** (ESI) m/z calculated for $[M+H]^+$ 230.1539 found 230.1540. **ATR-FTIR** (cm^{-1}): 3370, 2959, 2923, 2574, 2479, 1663, 1596, 1579, 1450, 1413, 1380, 1349, 1302, 1225, 1179, 1160, 1063, 1037, 1022, 984, 910, 877, 818, 785, 762, 705, 654, 588, 571, 534.

2-((1*R**,2*S**)-2-benzoylcyclopropyl)acetonitrile (**4.372**)

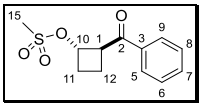


Synthesized by using the **General procedure XI.** Nucleophile: Bu_4NCN (1.5. equiv.).

Isolated yield: 26.6 mg, 72%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 2H, C6/C10), 7.63 – 7.56 (m, 1H, C8), 7.54 – 7.47 (m, 2H, C7/C9), 2.78 – 2.69 (m, 2H, C13), 2.61 (dd, *J* = 17.4, 6.0 Hz, 1H, C1), 2.02 – 1.78 (m, 1H, C11), 1.58 – 1.51 (m, 1H, C12), 1.23 – 1.13 (m, 1H, C12). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.19 (C2), 137.44 (C3), 133.40 (C8), 128.83 (C6/C10), 128.27 (C7/9), 117.37 (C5), 23.65 (C1), 20.56 (C13), 19.14 (C11),

17.28 (C2). HRMS (EI) m/z calculated for $[M]^{+\bullet}$ 185.0835 found 185.0834. **ATR-FTIR** (cm^{-1}): 2295, 1666, 1597, 1580, 1450, 1402, 1347, 1295, 1239, 1219, 1179, 1074, 1055, 1036, 1023, 962, 945, 751, 701, 654.

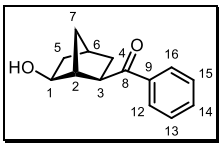
(1*S**,2*S**)-2-benzoylcyclobutyl methanesulfonate (**4.330**)



Synthesized by using the **General procedure VIII.** (Side product).

Isolated yield: 4.0 mg, 8%.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H, C5/C9), 7.62 – 7.59 (m, 1H, C7)), 7.49 (t, *J* = 7.8 Hz, 2H, C6/C8), 5.37 – 5.28 (m, 1H, C10), 4.25 – 4.16 (m, 1H, C1), 3.04 (s, 3H, C11/C12), 2.51 – 2.32 (m, 3H, C15), 1.87 – 1.79 (m, 1H, C12). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 197.45 (C2), 135.12 (C3), 133.95 (C7), 129.01 (C5/C9), 128.65 (C6/C8), 73.04 (C10), 49.91 (C1), 37.75 (C15), 27.86 (C11), 19.34 (C12). **HRMS** (ESI): m/z calculated for $[M+Na]^+$ 277.0505 found: 277.0512.

((1*R**,2*R**,4*S**,6*S**)-6-hydroxybicyclo[2.2.1]heptan-2-yl)(phenyl)methanone (**4.404**)



Synthesized by using the **General procedure VIII.**

Isolated yield: 30.5 mg, 62%.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dt, *J* = 8.5, 1.7 Hz, 2H, C12/C16), 7.59 – 7.53 (m, 1H, C14), 7.49 – 7.42 (m, 2H, C13/C15), 4.04 (d, *J* = 6.8 Hz, 1H, C1), 3.06 (dd, *J* = 8.7, 5.9 Hz, 1H, C3), 2.47 (s, 1H, C6), 2.40 (s, 1H, C2), 1.95 (dddd, *J* = 12.2, 5.5, 3.8, 3.0 Hz, 1H, C5), 1.83 (ddd, *J* = 13.4, 6.8, 2.4 Hz, 1H, C4), 1.60 – 1.49 (m, 2H, C4/C5), 1.45 – 1.41 (m, 1H, OH), 1.41 – 1.34 (m, 2H, C7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.59 (C2), 136.50 (C9), 133.01 (C14), 128.73 (C12/C16), 128.57 (C13/C15), 74.72 (C1), 48.64 (C3), 45.11 (C2), 42.18 (C5), 35.55 (C4), 32.83 (C7), 32.71 (C6). **HRMS** (ESI) m/z calculated for $[M+Na]^+$ 239.1043 found 239.1056. **ATR-FTIR** (cm^{-1}): 3490, 3456, 3432, 3402, 3373, 2959, 2872, 1727, 1679, 1597, 1581, 1448, 1356, 1311, 1272, 1227, 1180, 1083, 1030, 1002, 931, 916, 771, 739, 697, 671, 664, 654, 631.

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