universität wien

DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

„Amide activation: a tool for unprecedented transformations / Acid-mediated transformation of feedstock alkenes into valuable amines“

verfasst von / submitted by

Carlos Rafael Costa Gonçalves

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Doktor der Naturwissenschaften (Dr. rer. nat.)

Wien, 2022 / Vienna 2022

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 796 605 419
Dissertationsgebiet lt. Studienblatt / field of study as it appears on the student record sheet:	Chemie
Betreut von / Supervisor:	Univ.-Prof. Dr. Nuno Maulide

Ao meu Camarada

The work presented in this doctoral thesis was conducted between March 2018 and June 2022 at the University of Vienna (Austria) under the supervision of Prof. Dr. Nuno Maulide.

Referees: Prof. Dr. Virginie Vidal

Prof. Davide Bonifazi, PhD

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 the thesis.
Carlos R. Gonçalves, September 2022

Foreword

In my bachelor's studies, when I first got introduced to the world of organic chemistry, I was full of unrealistic expectations. In my eyes, it was like discovering a new language, full of novel signs and ethereal beautiful shapes that I hoped I could once master. I remember feeling like an architect that could build anything I could ever imagine. Better yet, I remembered thinking how architects needed chemists to build their art. You can build a molecule without architecture but you can't build a house without chemistry.

During my bachelor thesis, from a metaphorical point of view, it felt like I was entering a small pool, warmed by all the new things I learned each day. The same feeling persisted in my master's studies, and at the same time, I felt the pool increasing, stroke by stroke, as I learned the intricacies of reactions and the secrets of the lab.

At the start of the PhD, the edge of the pool already touched the horizon, and it felt that no matter how much I tried, it kept eluding me. Now, looking back, I see myself in the middle of the lukewarm ocean, looking around not for help but for direction instead.

How ruthless can science be? Can you drink from the fountain of curiosity without feeling endless thirst?

For me, the crux of the matter, lies not in the ability to swim, but in the capacity to cherish the people around you. A large ocean is a cosy place when having a good discussion, or better yet, a silly conversation.

Value the people around you, because despite not keeping in touch forever, pieces of them will always follow you.

The weeps of a lucky silly Goose,

R.

Acknowledgements

Foi uma bela aventura..

Obrigado à Ana por me sempre ter apoiado, e me ter tornado uma pessoas milhões de vezes melhor. Obrigado, decerteza que não estaria onde estou se não fosses tu.

Ao pessoal em PT, a toda a famelga, um grande obrigado e desculpa por ser tão desnaturado. Dizem que a sorte faz-se mas eu não faço nada e sou um grande sortudo. Oh minha mãe, como conseguiste mandar mensagens todos os dias!? Amo-te

Um grande obrigado ao Professor Nuno por ter acreditado em mim. Sei que não fui o aluno mais facil, mas fiz o que prometi, dei o meu melhor.

Oi, oi, where to begin. Obviously not gonna write everything... always thought it diluted things too much. To all of that helped, shouted, hugged, kissed, touched my private parts, listened, cried, danced, laughed, played, sang with me, a huge thank you. I'll probably not be in touch much, but you are my family, and there is no bigger praise than that 😊.

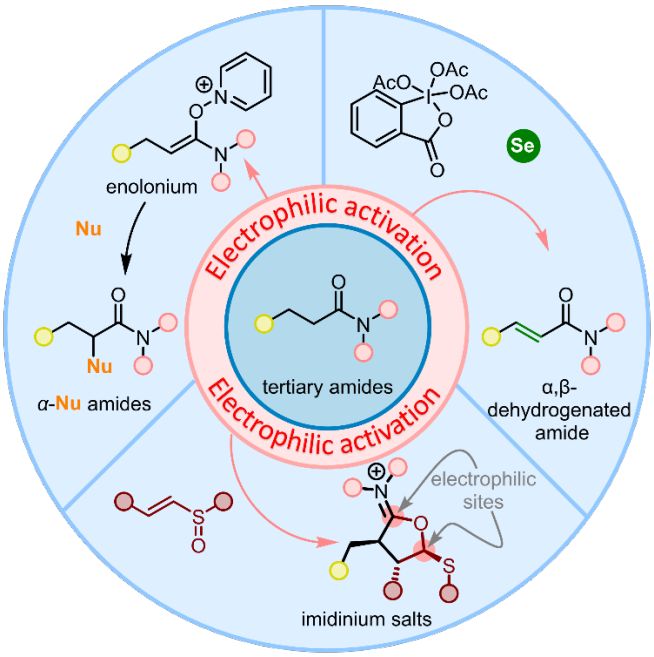
Gsi ghoco jsdojd pajos wpore üapisd üaipe ncfs souache bizsle apfrl oajer almc lompa bonga, kdeo lsdeo, eoj aaee si, george michael, luv gsi sevu loit - I know my Vorarlbergisch is a little bit rusty but im trying.

YES, you!

Thanks minha Mia. Thank you for the relentless motivation, laughing and talking. We have accomplished quite a lot recently, and this is only the beginning. Thank you for Lili, thank you for being my guiding light.

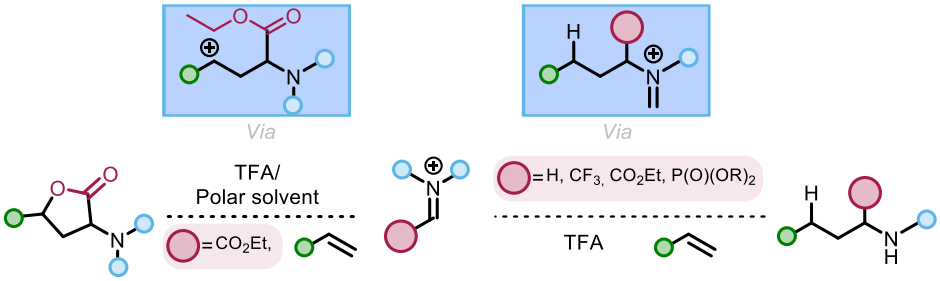
Abstract

The first chapter of this thesis describes our recent efforts on amide functionalisation through electrophilic activation. The first subchapter focuses on the investigation of amide-derived enolonium ions, formed by the addition of *N*-oxides to keteniminium ions. Harnessing these intermediates allowed for the development of a unified approach for the α-functionalization of amides, using halides, as well as, N-, S-, and O-centred nucleophiles to functionalise the α-position of amides.



The second part of this chapter revolves around the metal-free α,β-dehydrogenation of saturated amides using a simple, selenium-based protocol. This method directly transforms keteniminium ions into the desired α,β-dehydrogenated amides.

The third, and final, part of this chapter describes the combination of the keteniminium ions with vinyl sulfoxides, which results in charge-accelerated sulfonium rearrangement. The highly nucleophilic nature of the amide moiety not only facilitated its initial electrophilic activation, but also enabled capture of the subsequently formed thionium intermediate, generating a unique cyclic imidinium ion. Such species could by selectively transformed into an array of products.

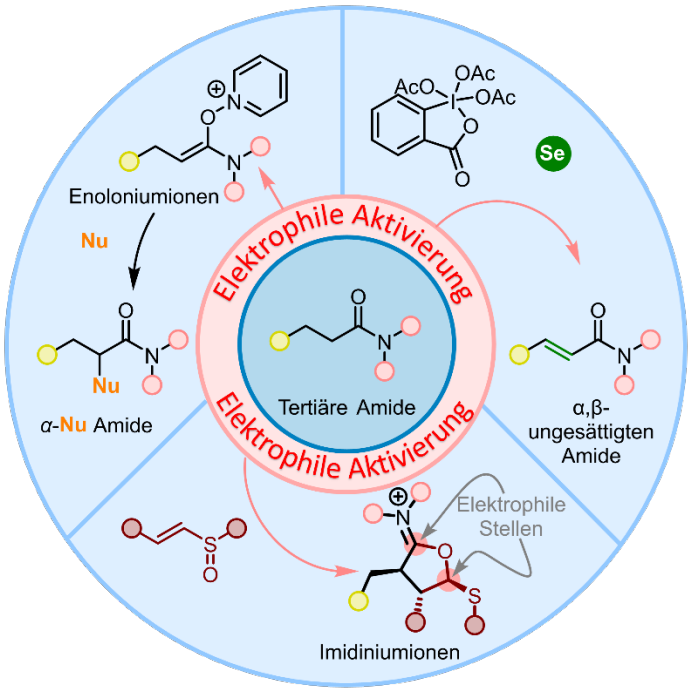


Chapter 2 outlines our recent efforts in the transformation of feedstock alkenes into valuable amine scaffolds through an acid-mediated reaction called hydroaminomethylenation/hydroaminoalkylation. By using electron-deficient iminium salts, biologically relevant α-amino acids, α-amino phosphonates and α-trifluoromethyl amines could be synthesised.

Finally, this chapter also describes how iminium salts were used to synthesise valuable α-aminolactones in a process resembling a (3+2)-cycloaddition.

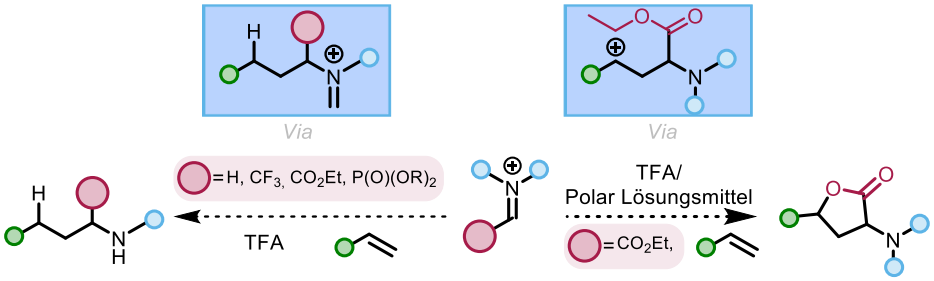
Kurzzusammenfassung

Das erste Kapitel dieser Arbeit behandelt neue Ergebnisse zur Funktionalisierung von Amiden mittels elektrophiler Aktivierung. Das erste Unterkapitel befasst sich mit unseren Untersuchungen der Reaktivität von, von Amiden stammenden, Enoloniumionen. Diese nützlichen Intermediate, die durch die Zusammenführung von N-Oxiden mit Keteniminiumionen entstehen, ermöglichten die Entwicklung eines allgemeinen Ansatzes zur α-Funktionalisierung von Amiden sowohl mit Halogeniden, als auch mit N-, S- und O-basierten Nukleophilen.



Im zweiten Teil dieses Kapitels geht es um die metallfreie α,β-Dehydrogenierung von gesättigten Amiden durch ein einfache Methode basierend auf Selenium. Darin werden Keteniminiumionen direkt in die erwünschten α,β-ungesättigten Amide überführt.

Der dritte und letzte Teil dieses Kapitel beschreibt die Kombination von Keteniminiumionen mit Vinylsulfoxiden, wodurch eine ladungsbeschleunigte Sulfoniumumlagerung ermöglicht wird. Die hohe Nukleophilie von Amiden ermöglicht hierin nicht nur die anfängliche elektrophile Aktivierung, sondern fängt in einem weiteren Schritt auch das entstehende Thioniumion ab, wodurch zyklische Imidiniumionen entstehen. Diese Spezies lassen sich nachfolgend selektiv in eine Reihe weiterer Produkte überführen.



Kapitel 2 handelt von der Umsetzung von simplen Alkenen zu nützlichen Amingerüsten durch eine Säure-vermittelte Hydroaminomethylenierungs oder –alkylierungsreaktion. Hierbei kommen elektrophile Iminiumsalze zum Einsatz, mit deren Hilfe biologisch relevante α-Aminosäuren, α-Aminophosphonate sowie α-Trifluoromethylamine zugänglich sind.

Zuletzt beinhaltet dieses Kapitel noch einen, an eine (3+2)-Zykloaddition erinnernden Prozess, in dem Iminiumsalze eingesetzt werden, um wertvolle α-Aminolactone zu erhalten.

Table of contents

	(unless stated otherwise)
2-F-Py	2-Fluoropyridine
2-Cl-Py	2-Chloropyridine
2-I-Py	2-I-Pyridine
A	generic activator
Å	Ångström
Ac	acetyl
Alk	alkyl
app	apparent
aq.	aqueous
Ar	aryl or arene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
c-	*cyclo*-
cf.	*confer* (Latin for: compare)
cm	centimetre
cod	cycloocta-1,5-diene
d	doublet
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DAG	diacetone-D-glucose (1,2:5,6-Di-O-isopropylidene-alpha-D-glucofuranose)
DBU	1,8-diazabicyclo[5.4.0]undec7-ene
DFT	density functional theory

DIAD	diisopropyl azodicarboxylate
DIBAL–H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMA	Solution of CH_2Cl_2, methanol and saturated ammonium hydroxide solution
DMAP	dimethylaminopyridine
DME	1,2-dimethoxythane
DMF	dimethylformamide
DMP	Dess Martin Periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNP	dynamic nuclear polarization
E	entgegen
E	generic electrophile
EDG	electron donating group
ee	enantiomeric excess
equiv.	equivalents
ESI	electrospray ionisation
et al.	Latin for: and others
Et	ethyl
EWG	electron withdrawing group
FG	generic functional group
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
gem	geminal
h	hour(s)
HAA	Hydroaminoalkylation

HAM	Hydroaminomethylenation
HFIP	hexafluoroisopropanol
HFPDSI	1,1,2,2,3,3-hexafluoropropane-1,3-disulfonimide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSAB	'hard' or 'soft', and 'acid' or 'base' to chemical species
Hz	Hertz
hν	irradiation
i	*iso*
i.e.	*id est* (Latin for: that is)
IBX	2-Iodoxybenzoic acid
J	coupling constant
Josyphos	(R-1- SP-2-ferrocenyl ethyldicyclohexylphosphine)
L	litre or generic ligand
LA	generic Lewis acid
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LED	light-emitting diode
LG	leaving group
LHMDS	lithium bis(trimethylsilyl)amide
LNO	Lutidine *N*-oxide
LUMO	Lowest Unoccupied Molecular Orbital
M	mega or generic metal
M	molar
m	multiplet or milli
m/z	mass to charge ratio

max	maximum
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
MNBA	2-Methyl-6-nitrobenzoic anhydride
mol	mole
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
MW	microwave
n	normal or generic integer
n.a.	not applicable
n.d.	not determined or not detected
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NHC	*N*-heterocyclic carbene
NMP	*N*-Methyl-2-Pyrrolidone
NMR	nuclear magnetic resonance
n-Oct	*n*-octyl
NOESY	Nuclear Overhauser and Exchange Spectroscopy
Nu	generic nucleophile
o-	*ortho*-
p-	*para*-
p	pentet
PA	Phosphoric acid

Ph	phenyl
Phth	phthaloyl
ppm	parts per million
Pr	propyl
q	quartet
quant.	quantitative
R	generic group
r.t.	room temperature
s	secondary
s	singlet
SAR	Structure-Activity Relationship
SEAr	Electrophilic aromatic substitution
sept	septet
SET	Single electron transfer
S_N	nucleophilic substitution
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
T	temperature
t	tertiary
t	time or triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBME	methyl *tert*-butyl ether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl

TCBC	2,4,6-Trichlorobenzoyl chloride
Tf	triflyl (trifluoromethanesulfonyl)
Tf_2NH	triflimide (bis(trifluoromethane)sulfonamide)
Tf_2O	triflic anhydride (trifluoromethanesulfonic anhydride)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFBA	4-(Trifluoromethyl)benzoic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TM	generic transition metal
TMDAM	tetramethyldiaminomethane
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethyl piperidine
TMS	trimethylsilyl
TOF	Time-of-flight mass spectrometr
TPP	Thiamine pyrophosphate
Ts	tosyl (4-toluenesulfonyl)
UV	ultraviolet
X	halogen or generic counteranion
Xantphos	(9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)
Y	generic heteroatom
Z	zusammen
δ	chemical shift
Δ	heat
ν	wavenumber

1 AMIDE ACTIVATION: A TOOL FOR UNPRECEDENTED TRANSFORMATIONS

1.1 GENERAL METHOD FOR THE α-FUNCTIONALISATION OF AMIDES USING HETEROATOM NUCLEOPHILES

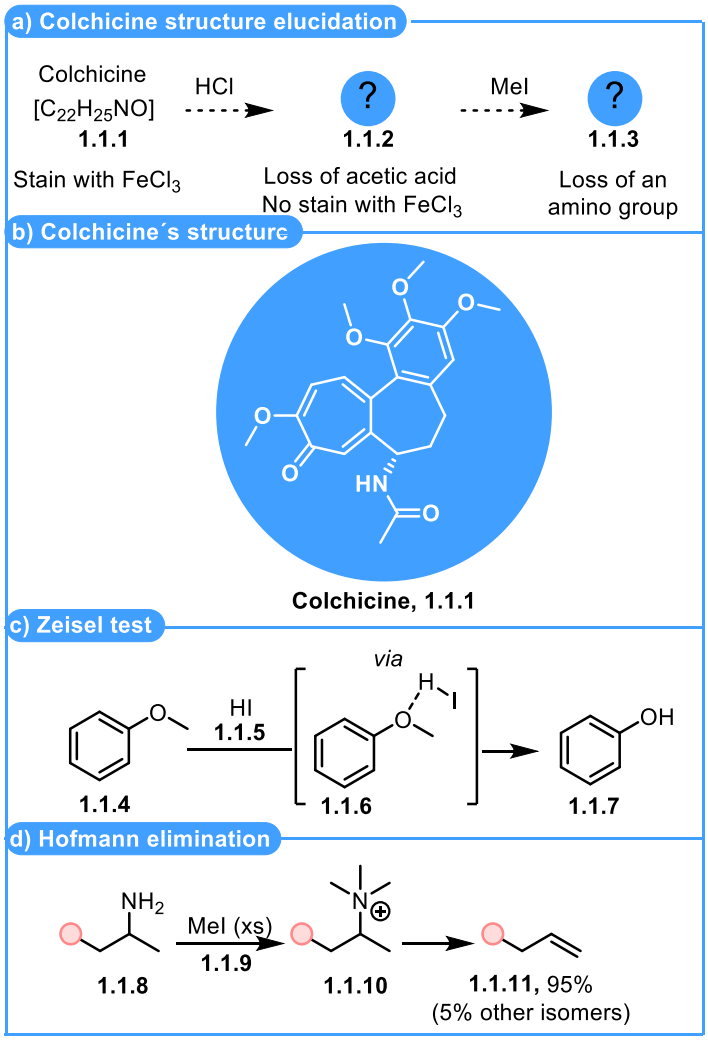
1.1.1 Introduction

1.1.1.1 Structural elucidation of colcichine.

In the ever-shifting field of chemistry, many things can be learned by studying the annals of organic synthesis. One of the most glaring changes concerns the occupation of the synthetic chemist, which has gone through many adaptations throughout the years.

Due to the broad spectrum of tools at the synthetic chemist´s disposal, it is easy to forget that today´s job description greatly differs from that of previous centuries. In the inception of modern chemistry, fields such as organic, physical, analytical and even material chemistry were intertwined - in fact - merged into one. Before researching elaborate strategies to synthesise molecules, chemists had first to elucidate their structure, [1,2] without access to today's powerful analytical and spectroscopic methods.

One of the most impactful utensils chemists had to tackle this problem was to qualitatively gauge molecules by conducting chemical tests (Scheme 1a)[3]– most of which resulted in fragmentation into (hopefully known) compounds. One example of such a process occurred during the initial structural elucidation of colchicine (**1.1.1**, Scheme 1b) – the bio-active component of a*utumn crocus* leaves[4] that has been used for centuries to treat gout-related symptoms. Throughout the years this molecule was the target of various synthetic efforts.[5–8]



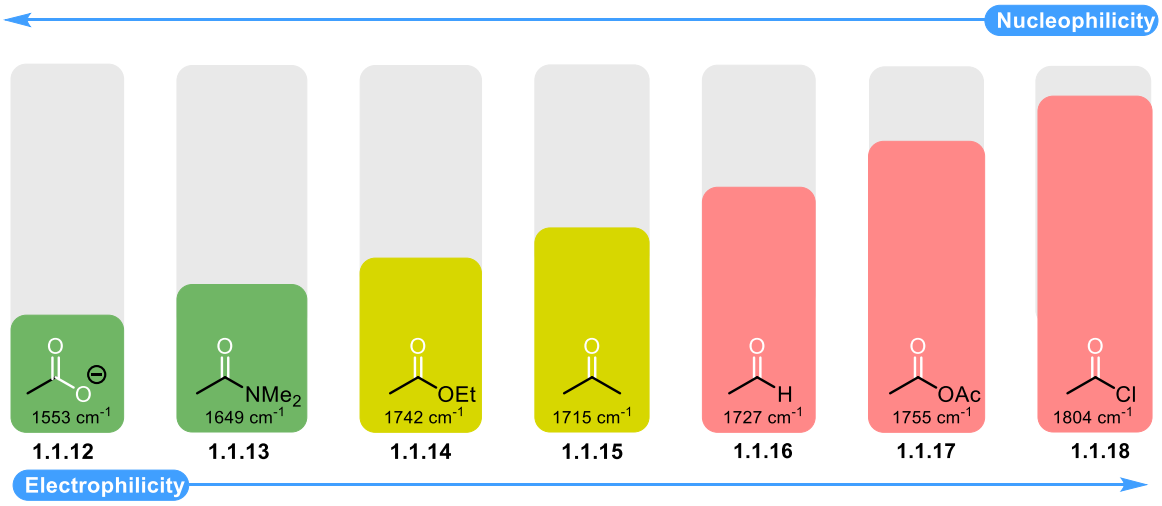
Scheme 1.1 – a) Structure elucidation of Colchicine, b) Structure of Colchicine, c) Zeisel test based on demethylation, d) Hofmann elimination of quaternary ammonium salts (1.1.10).

When Zeisel first tried to establish the structure, he made several interesting observations (Scheme 1c).[9–11] At first, he discovered a new method to quantify the number of methyl ether bonds by cleavage using HI (**1.1.5**)[12,13] – nowadays an eponymous method to cleave such functional groups (Scheme 1c). He also observed that, after treatment of colchicine with concentrated hydrochloric acid, acetic acid was formed, initially inferring that an acetate ester moiety was present in the molecule (**1.1.2**, Scheme 1a). An observation contrasting this deduction was that, unlike colchicine, the product of hydrolysis did not stain with $FeCl_3$ – a known staining agent for phenol and enols.[14] It would take more than a decade for Windaus[15] and Zeisel himself to revisit these studies. A sequence of experiments that solved the enigma at hand was the addition of MeI (**1.1.9**) and subsequent elevation of the temperature: It was then observed that a Hoffman-type elimination took place (Scheme 1d),[16,17] thus confirming the presence of an aliphatic amine **(1.1.3)**, which in term proved that an acetamide group was present in colchicine. In hindsight, the observed

characteristic chemical resilience pointed to the existence of an amide bond.[18] Indeed, this is one of the many intriguing characteristics this functional group possesses, and we will devote the following chapter to identifying and showcasing them in detail.

1.1.1.2 Carbonyl compounds – the amide bond.

Carbonyls are one of the most versatile and intensively studied motifs in organic chemistry.[19] This fact can be substantiated by numerous books and name reactions that are specifically devoted to this class of compounds.



Scheme 1.2 – Carbonyl compounds and their relative reactivity

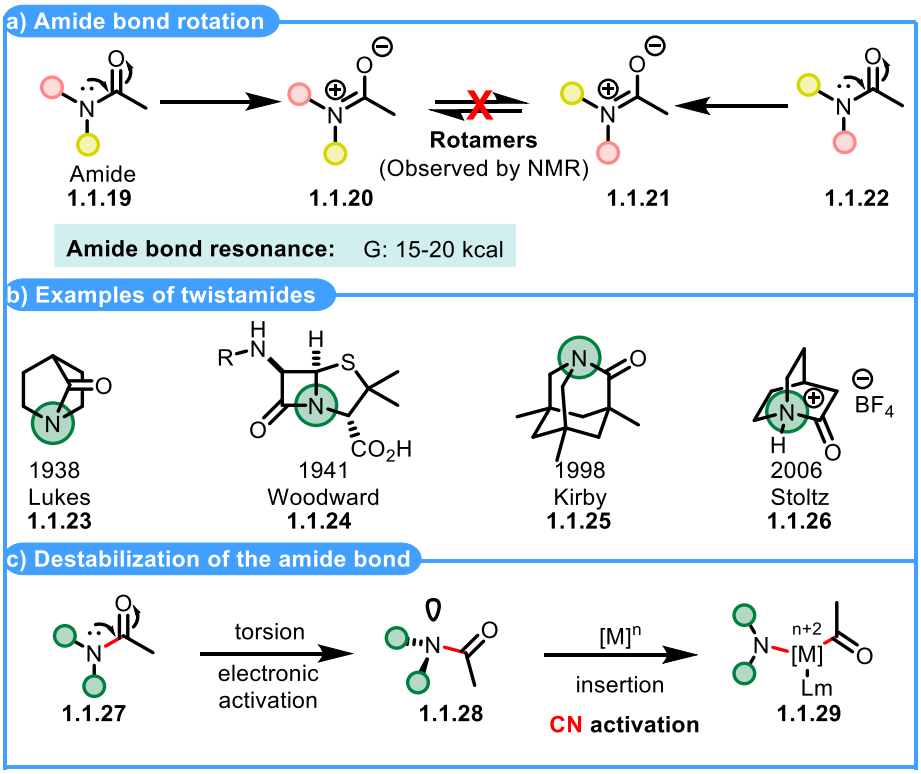
The reactivity of this amphiphilic species is directly connected to the substituents around its C=O bond, electronics and steric effects playing a key role in its modulation. A rudimentary way to evaluate the aforementioned effects is by IR spectroscopy,[20] where the C=O bond stretch can easily be distinguished. Despite no perfect correlation, exists, in general a higher C=O vibration implies higher electrophilicity at the carbon atom, such as in the case of acetyl chloride (**1.1.18**, Scheme 1.2).[21]

At the opposite end of this spectrum is the amide (**1.1.13,** Scheme 1.2)– the focal point of this chapter. Here, a much lower vibration is observed and, by applying the same logic, one can conclude that its carbonyl is less electron-deficient.[22,23] The key contributor to this effect is the donation by the neighbouring nitrogen atom to the π* orbital of the C=O bond (due to its sp^2 hybridisation).[24] This effect has considerable repercussions on the nature of the C–N bond, with a bond order between 1 and 2 and a consequent decrease of

the C=O double bond character. This generates a uniquely nucleophilic (at *O*) carbonyl moiety[25] which importantly can be found in about 20 % of all pharmaceutical compounds.[26]

1.1.1.3 Unique characteristcs of the amide bond.

Many special physical features emanate from this phenomenon of partial C=N character. Perhaps the clearest one, observable by NMR spectroscopy, is the existence of rotamers resulting from slow rotation around the C–N bond (Scheme 1.3a).[27]



Scheme 1.3 – Characteristics of the amide bond and examples of twistamides. a) Amide bond rotation, b) Destabilisation of the amide bond, c) Examples of twistamides

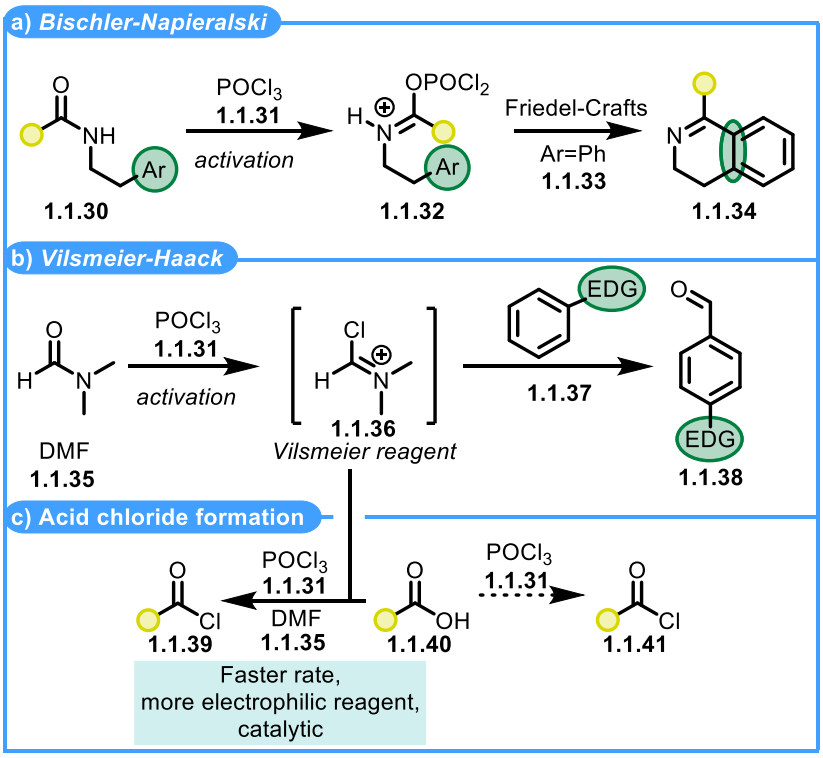
Exceptions to this general reactivity rule are so-called twistamides[28]- amides with inhibited C–N bond overlap, by having an enforced sp^3 hybridized nitrogen (Scheme 1.3b).[29,30] One of the first examples of such compounds was the antibiotic family of the Penicillins (**1.1.24**), whose structure elucidation was awarded the Nobel Prize owing to its importance and relative difficulty.[31] The proposition of a **1.2.24** β-lactam by Woodward was initially challenged by many. [32] Nevertheless, Woodward had shown interest in such motifs during its synthesis of Quinine (not shown)[33] – an alkaloid that shares a quinuclidine core, which might be accessed by reduction from the corresponding amide (**1.1.23**). Initial efforts to synthesize the quinuclidone by amide coupling were unsuccessful; this target

would be achieved much later by Stoltz in 2006 by Schmidt rearrangement,[34,35] and isolated in a salt form, confirming the amine-like nature (sp^3 nitrogen) of the compound (**1.1.26,** Scheme 1.3b). [36–38]

More recently, chemists have come across novel ways to take advantage of the aforementioned structures. Since the C-N bond is considerably weakened in twistamides, an opportunity arose to exploit transition-metal catalysed functionalisation by insertion (Scheme 1.3c). [39–41]

1.1.1.4 Electrophilic amide activation – A powerful chemoselective method.

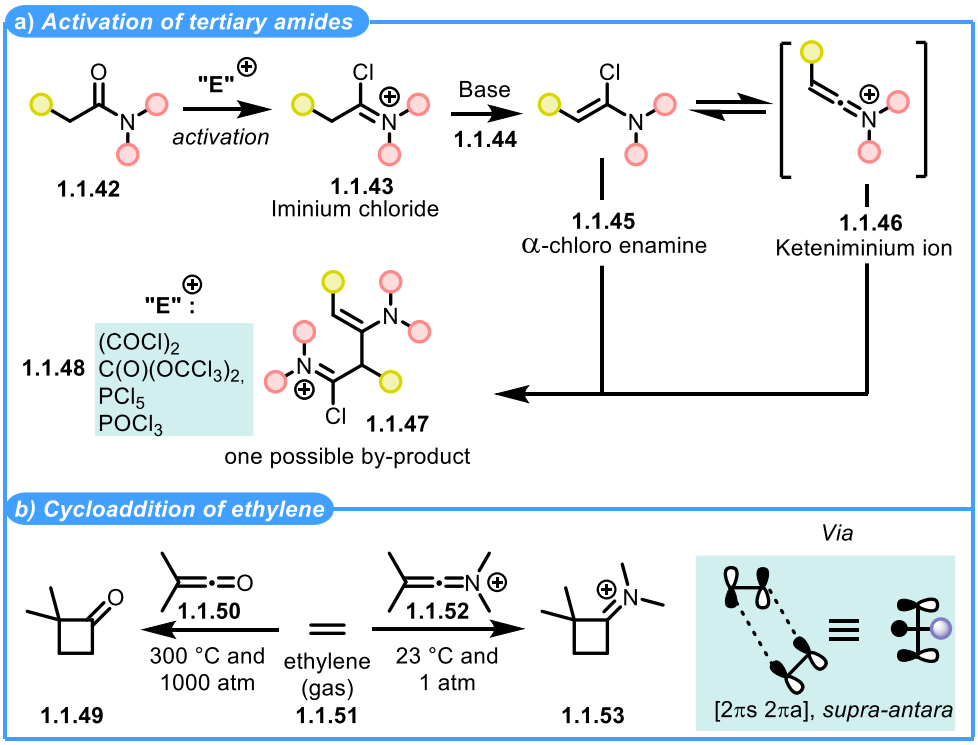
Conventional amides can be activated with potent electrophiles.[42,43] In general, electrophilic activation has seen numerous applications, with species such as Lewis acids and Brønsted acids playing key roles.[44] Concerning amides, first efforts date back to 1877 where attempts towards dehydration were successful albeit limited in scope and mechanistic understanding.[45] Considerable effort was devoted to studying the activation process (N or O attack) – a particularly challenging task considering the available spectroscopic tools at the time. [46]



Scheme 1.4 – Reactions using amide functionalities. a) Bischler-Napieralski, b) Vielsmeier-Haack, c) Acid chloride formation.

Such transformations can be showcased by e.g. the Bischler – Napieralski[47,48] or Vilsmeier – Haack (Scheme 1.4a, b).[49,50]A more recent and widely used example is typified by use of catalytic dimethylformamide (**1.1.35**, DMF), to help catalyse the formation of acid chlorides with oxalyl or phosphoryl chloride (**1.1.31**, Scheme 1.4c).[51]

Similar electrophilic reagents were used more generally in the electrophilic activation of other tertiary amides.[52] Importantly, it was observed that the addition of a base (**1.1.44**, Scheme 1.5a) leads to the formation of α-chloro enamines (**1.1.45**) – precursors for keteniminium ions (**1.1.46**).[53] These cationic nitrogen analogues of ketenes[54] showed enhanced reactivity, especially towards [2+2]-cycloadditions (Scheme 1.5b).[55] This effect was so dramatic that no harsh conditions were required.[56] Instead, the cycloaddition reactions occurred at room temperature (**1.1.53**, Scheme 1.5b). [57,58]



Scheme 1.5 – a) Electrophilic activation of tertiary amides and b) cycloaddition of ethylene with different ketene derivatives.

Wider adoption of such transformations was hampered by problems concerning their high reactivity. The use of hazardous reagents such as triphosgene (**1.1.48**, Scheme 1.5a),[59,60] and the observation of aldol-type reactions between the two initial intermediates were also quite problematic features (**1.1.47**, Scheme 1.5a).[61]

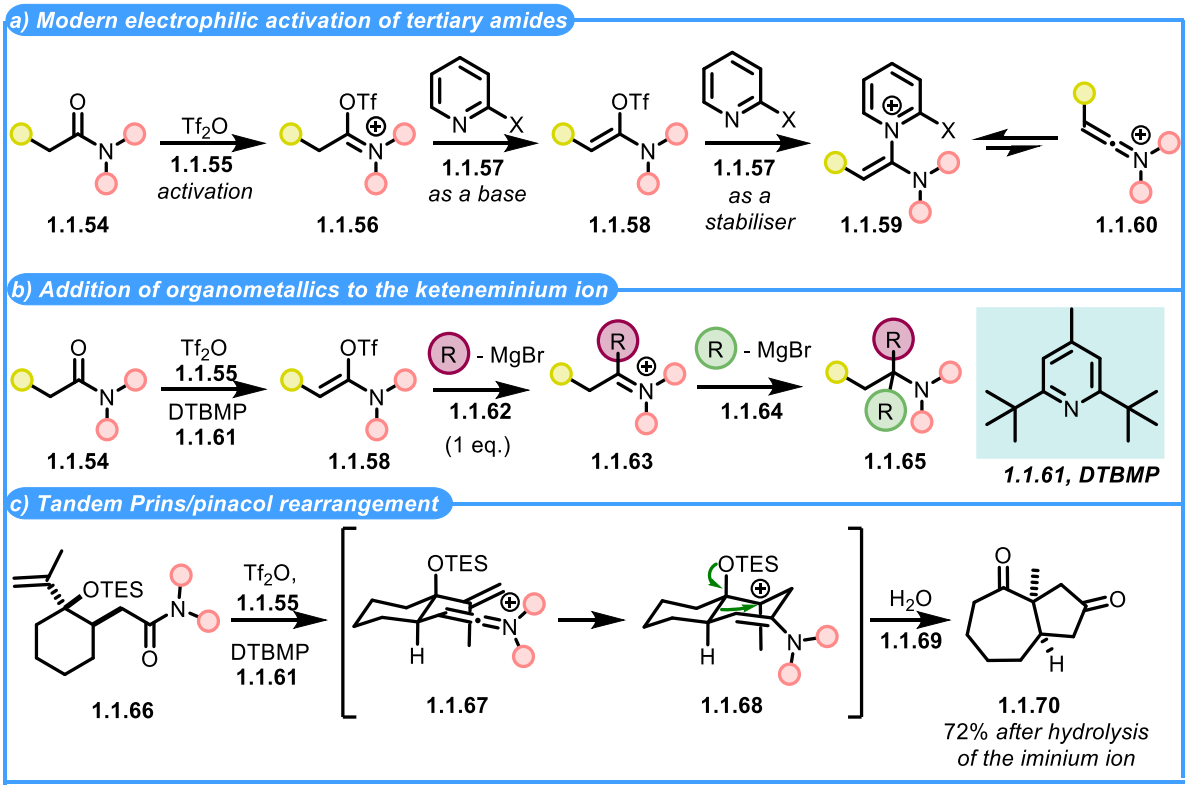
1.1.1.5 A new paradigm in electrophilic activation of amides – triflic anhydride and pyridine bases.

The solution came in the form of a novel combination of reagents - trifluoromethanesulfonic anhydride (**1.1.55**, Scheme 1.6a) as an electrophile and a pyridine base (**1.1.57**) which crucially stabilises the keteniminium intermediate (**1.1.60**).[62,63] While the use of unsubstituted pyridine completely halts reactivity, due to formation of a surprisingly stable adduct,[64,65] modulation of the electronics, sterics of the base enables a useful equilibrium to be established between the stabilised adduct (**1.1.59**) and the reactive keteniminium species (**1.1.60**, Scheme 1.6a).

1.1.1.6 C-C bond formation using the keteniminium intermediate.

It would be shown that the use of organometallic reagents[66–68] can result in different functionalised tertiary amines by sequential addition (**1.1.65**, Scheme 1.6b).[69] The high chemoselectivity of amide activation stands out in this case, whereby different organometallics can discern the more electrophilic keteniminium ion from other, sensitive functional groups.

An elegant domino example of C–C bond formation enabled by amide activation was reported by Overman.[70] In this case, the pendant olefin (**1.1.67**, Scheme 1.6c) undergoes a Prins-type reaction, reminiscent of the work presented in chapter II, instead of the predicted [2+2] cycloaddition – most likely due to ring strain (Scheme 1.6c). The formed carbocation then collapses in a pinacol-type rearrengement[71] to generate a bicyclic system.

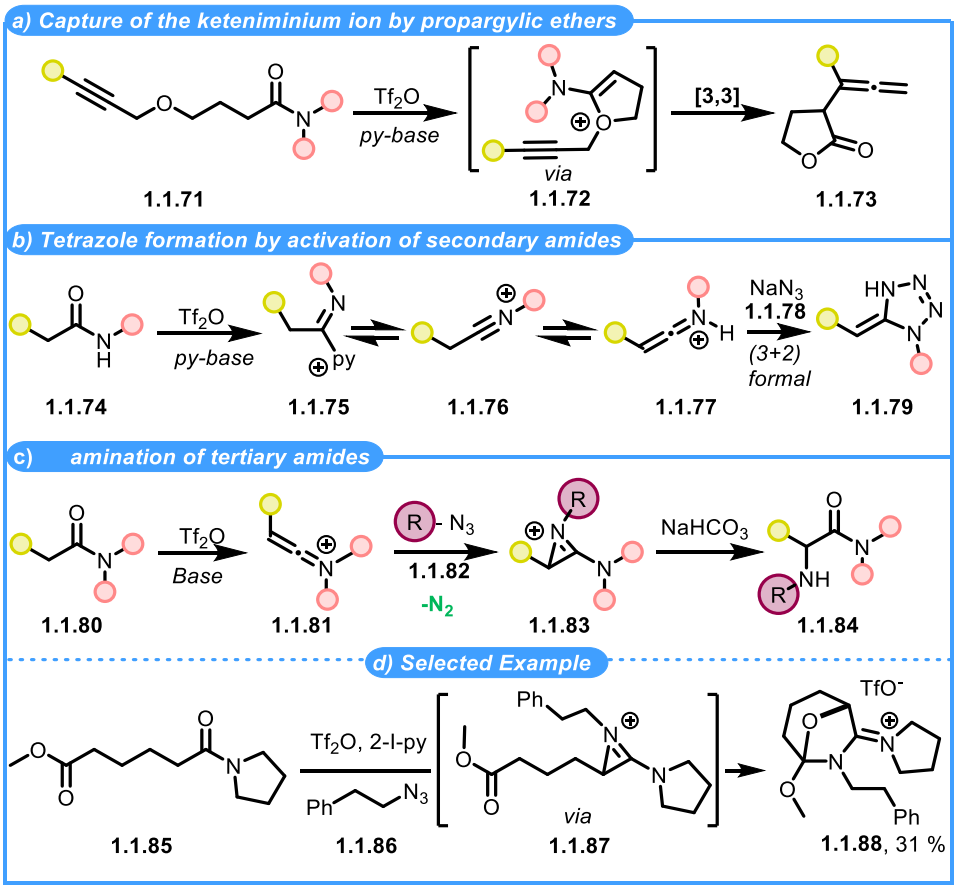


Scheme 1.6 – a) Contemporary activation of tertiary amides using triflic anhydride and pyridine bases. b) electrophilic activation of tertiary amides and addition of organometallic reagents, c) Activation of tertiary amides triggered C-C bond formation event by tandem Prins/Pinacol rearrangement.

1.1.1.7 Trapping the keteniminium intermediate with heteroatom nucleophiles

Other classes of nucleophiles, e.g. composed of heteroatoms, can also be used in conjunction with the keteniminium ion. For example, the use a tethered propargylic ether (**1.1.71**, Scheme 1.7a) leads to the formation of alkynyl lactones (**1.1.73**) – a motif as challenging as synthetically appealing (Scheme 1.7a).[72] In addition to showing that these types of reactions can occur in an intramolecular manner, it also presents that sigmatropic rearrangements can be evolved simultaneously.[73]

The reaction of nitrogen-derived nucleophiles, particularly azides (**1.1.78**, Scheme 1.7b), was an important stepping-stone for the further understanding of the reactivity of the keteniminium ion (**1.1.77**, Scheme 1.7b).[74,75] In initial findings, activated secondary amides reacted to form tetrazoles (**1.1.79**), through a nitrilium intermediate (**1.1.76**). However, in the context of tertiary amide activation, the reaction with organic azides (**1.1.82**, Scheme 1.7c) was only explored almost 40 years later and led to the formation of α-amino amides (**1.1.84**).[76,77] It was also found that α-amination occurred by formation of an aziridinium salt (**1.1.83**) and subsequent hydrolysis. A specific example stood out: when a tethered ester moiety (**1.1.85**, Scheme 1.7d) was present on the substrate, it reacted intramolecularly with the alkyl azide adduct (**1.1.87**), resulting in the formation of a bicyclic acetal (**1.1.88**).



Scheme 1.7 – Capture of the keteniminium ion using heteroatom nucleophiles. a) Intramolecular capture by propargylic ethers, b) and c) capture with azides. d) Selected example leading to the capture of 1.1.87 with a remote ester group.

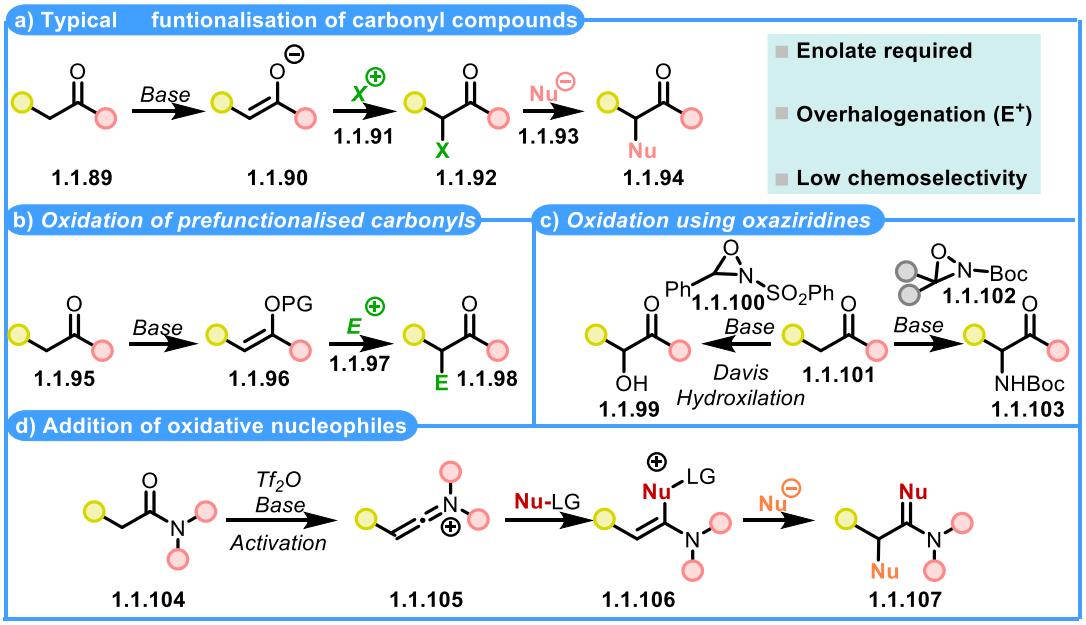
1.1.1.8 Strategies for the α-Funtionalisation of amides.

The chemical stability of amides can be seen as detrimental when we aim for functionalization. This is especially true when comparing them to other classes of carbonyl compounds. Most methods for the α-functionalisation rely on the deprotonation of the α-position, which is comparatively difficult in amides (high pKa, **1.1.90**, Scheme 1.8a), leading to problems of chemoselectivity when more acidic moieties are present (Scheme 1.8a). In the specific case of α-hydroxylation (**1.1.99**), a specific *N*-sulfonyloxaziridine (**1.1.100**, Scheme 1.8c) – known as Davis reagent,[78–80] is one of the most commonly used reagents. In fact, by changing the electronic configuration, oxaziridines can also present themselves as an electrophilic amination agent (**1.1.102**).[81,82]

An alternative strategy, often out of reach for amides,[83] is the prefunctionalisation of the carbonyl compounds (Scheme 1.8b). This can be achieved by formation of silyl enol ethers (**1.1.96**) that readily undergo oxidation with electrophilic agents, due to the electron rich nature character of the double bond. The most prominent example is the reaction with

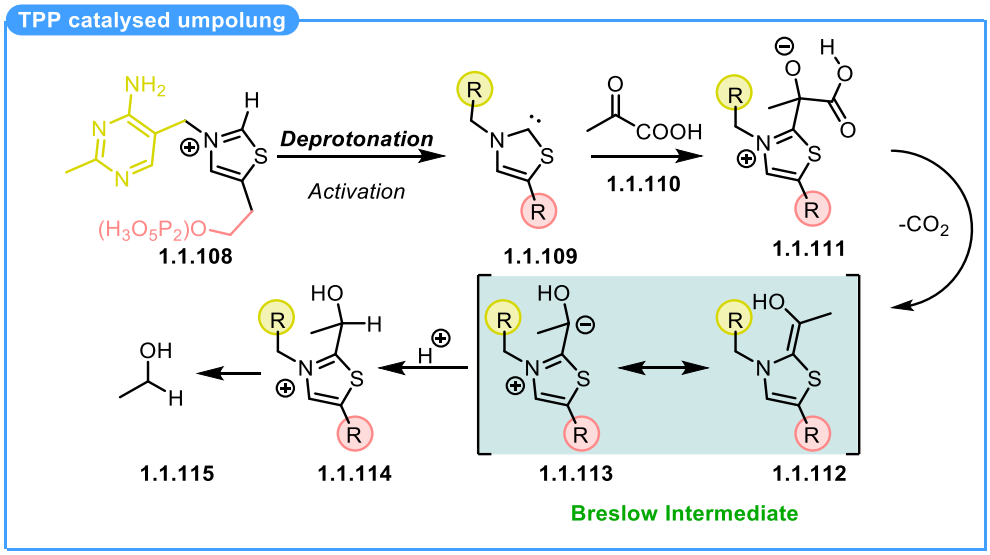
peracids, termed Rubottom oxidation,[84] which was interestingly simultaneously discovered by two other research groups (Scheme 1.8b).[85,86] Alternatively, the α-position can also be decorated with halogens or pseudohalogens (**1.1.98**)[87,88] to be subsequently substituted by various nucleophiles. The major problem with this strategy is the known oversubstitution due to an increase of reactivity after the initial halogenation takes place. [89,90]

One intriguing and arguably less explored alternative is the use of oxidising nucleophiles (Scheme 1.8d). Usually, such species are electron-rich and possess an additional leaving group, the departure of which formally oxidises the substrate (**1.1.106**). An example of such a reaction was shown earlier, in the α-amination using organic azides, where N_2 acted as a leaving group (Scheme 1.7c).[82]



Scheme 1.8 – a) general strategies for the α-Functionalisation of amides. b) Oxidation of prefunctionalised carbonyl compounds, c) Oxidation using oxaziridines, d) oxidation using oxidative nucleophiles.

An important concept that is used to describe this phenomenon is *Umpolung* [91,92] – a German term introduced by chemist Dieter Seebach, refeering to the inversion of polarity of a functional group into one. There are numerous specific examples of such events, many of which play a huge role in the modern organic synthesis toolbox. [93–95] One of the most relevant example is the cofactor thiamine pyrophosphate (**1.1.108**, TPP)[96] which catalyses many processes in our cells,[97] one of them being the decarboxylation of pyruvate (**1.1.100**, Scheme 1.9).[98]



Scheme 1.9 – Umpolung catalysed by TPP (Thiamine pyrophosphate)

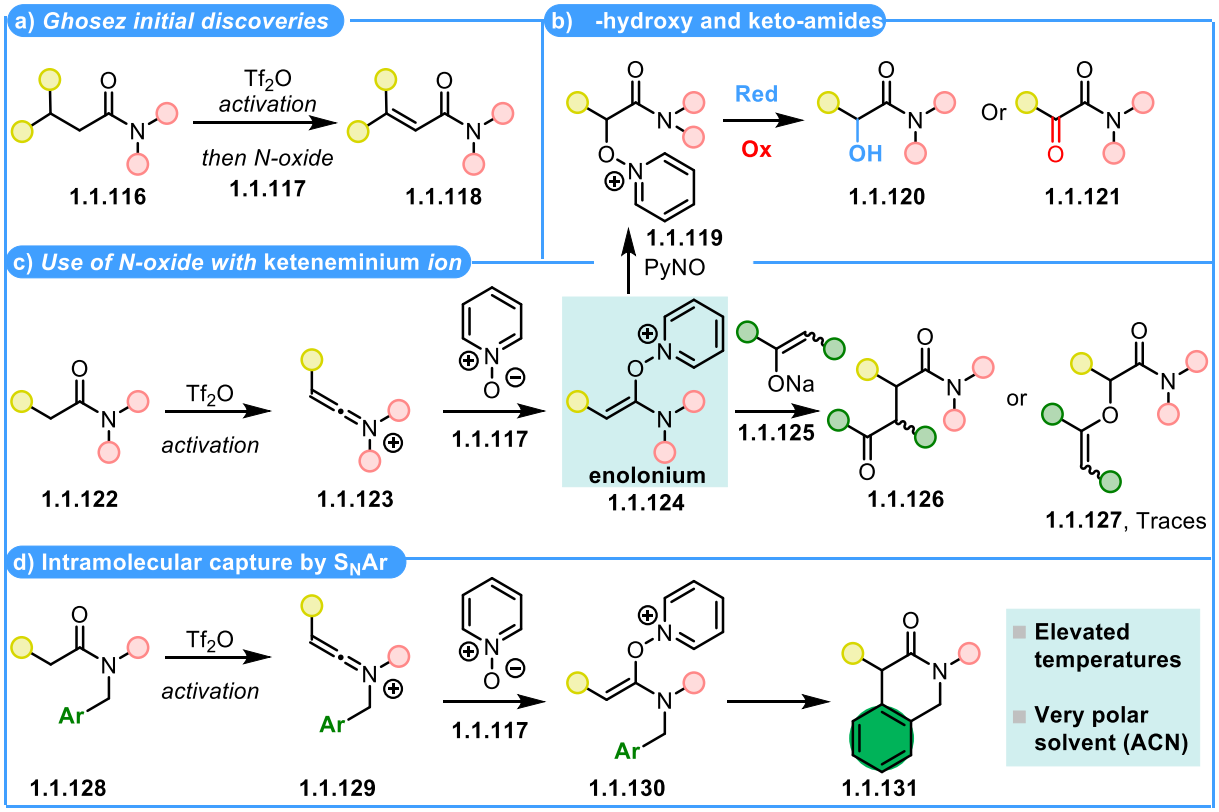
The accepted mechanism proceeds by an activated carbenic TPP molecule (deprotonated, **1.1.109**, Scheme 1.9) that adds nucleophilically to the carbonyl compound (**1.1.110**), generating an O-centred anion (**1.1.111**) that regenerates (deprotonates) another equivalent of TPP (**1.1.108**). This fleeting intermediate undergoes decarboxylation (**1.1.112**), generating an anion on the former electrophilic position of the carbonyl group (**1.1.113**) – thus deserving its name as a "*Umpoled*" species. Said species are commonly called Breslow intermediates[99] and are, known to react with a wide range of electrophiles, after which the catalyst is regenerated. This process is reminiscent of the Stetter reaction[100] – one of the main instruments for C–C bond formation.

1.1.1.9 Oxidation of the keteniminium intermediate

In the context of amide activation, the use of nucleophilic oxidants was pioneered by Leon Ghosez (Scheme 1.10a).[76] Pyridine *N*-oxides were reagents of choice (**1.1.117**), with the proposed mechanism consisting of the addition of the *N*-oxide to the keteneminum ion (**1.1.123**, Scheme 1.10c), generating a postulated enolonium intermediate (**1.1.124**) – the "Umpoled" derivative of the enolate ion. As it suggests, such an intermediate is susceptible to reaction with nucleophiles, or, in the specific case of α-branched amides, elimination (**1.1.118**, Scheme 1.10a). This result was quite surprising as no intermediates or by-products were found in this reaction, only the α,β-dehydrogenated products, a limitation of the methodology.[101]

Almost 40 years later, this type of oxidative event was extensively studied by the Maulide group. One of the initial attempts showed that the use of an excess of oxidant could enable the generation of the pyridine *N*-oxide adduct (**1.1.119**, Scheme 1.10a).[102] This versatile intermediate could then be reductively cleaved to generate the α-hydroxyl amide (**1.1.120**). Alternatively, this product can be formely oxidised *via* a mechanism closely resembling the Ganem oxidation,[103] thus affording the α-keto amide (**1.1.121**).

The intramolecular capture of the enolonium intermediate was achieved by employing different aromatic compounds that reacted in a Friedel-Crafts manner (Scheme 1.10d), yielding dihydroisoquinolinones (**1.1.131**). A point that raised some scepticism was that the yield benefited from high temperatures, a fact that will be discussed in detail later.[104]



Scheme 1.10 – Versatility of the enolonium intermediate. a) initial observation of the intermediate by Ghosez, b) synthesis of α-hydroxi and keto amides, c) synthesis of 1,4 dicarbonyl using the enolonium intermediate, d) capture of the enolonium intermediate by aromatic nucleophiles.

Analogously, intermolecular addition of enolates (**1.1.125**, Scheme 1.10c) to this enolonium intermediate successfully enable access to 1,4-dicarbonyl compounds (**1.1.126**, Scheme 1.10c),[105] a class of compounds that is challenging to construct,[106–109] despite being common in numerous natural products and drug scaffolds.[110,111]

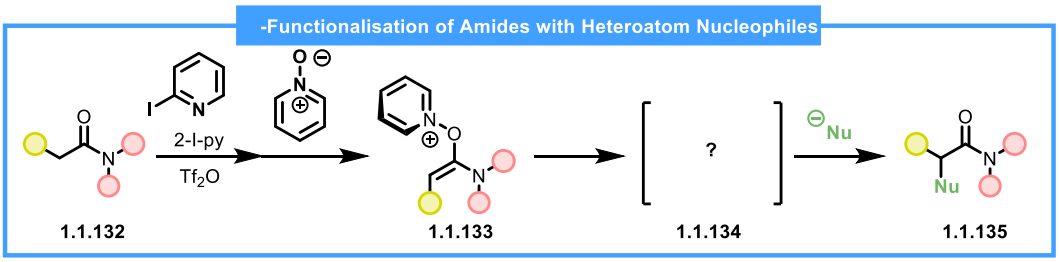
In the context of C–C bond formation, the only examples that have been discussed here describe the use of an aromatic ring which reacted in a S_EAr fashion or of an enolate. Nevertheless, organometallic reagents are very versatile nucleophilic sp^3 carbon synthons. Their use as nucleophiles in this synthetic strategy would greatly enhance its utility by allowing more general Csp^3–Csp^3 bond formation. Unfortunately, when this reactivity was assessed, a substantial amount of halogenation products was formed and with Grignard reagents, no alkylation product was detected. This result triggered efforts to fully elucidate the mechanism of the reaction.

1.1.2 Objective

This work aimed to elucidate the mechanism of oxidation of keteniminiun ions using *N*-oxides (Scheme 1.11).

As an additional objective, the limitations concerning the use of heteroatom based nucleophiles was to be explored. In this regard, the functionalisations using sulfonamides, and all subsequent transformations were carried out by PhD student Miran Lemmerer, Msc.

The work described was conducted in colloboration with Miran Lemmerer, Msc Dr. Christopher J. Teskey, Dr. Pauline Adler, Dr. Daniel Kaiser, Dr. Boris Maryasin, Prof. Leticia González and was published.[112]



Scheme 1.11 – Objectives – elucidation of the mechanism and develop a general method for the α-functionalisation of amides

1.1.3 Results and discussion

1.1.3.1 Investigation on the enolonium intermediate

The first logical step was to investigate the mechanism of the reaction. One of the most important tools at our disposal was NMR spectroscopy, which allowed us to detect most intermediates in solution. As reported, the pyridine adduct of the keteniminiumion could be identified.[62,63] After addition of the pyridine *N*-oxide, a new species was formed quantitatively, but could not be assigned unequivocally to the enolonium ion. ^{19}F NMR helped to identify two species, one of which being undoubtedly the triflate counter anion.

Initial attempts to isolate the intermediate by flash column chromatography proved unfruitful. Fast chromatographical separation in a cooled column (-30 °C) ultimatelly allowed isolation of the α-trifloxy amide (**1.1.137**, Figure 1.1). Additionally, and despite being quite sensitive, the high-resolution mass spectra also corroborated the existence of this intermediate.

To fully prove the formation of **1.1.137** *in situ (*Figure 1.1*)*, the α-trifloxy intermediate was independently synthesised. By reaction of an α-hydroxy amide (**1.1.139**) with triflic anhydride in the presence of a sterically hindered pyridine. The comparison between the spectral information showed, without any doubt, that the α-trifloxy was the "resting state" after oxidation of the keteniminium ion with pyridine *N*-oxides (Figure 1.1).

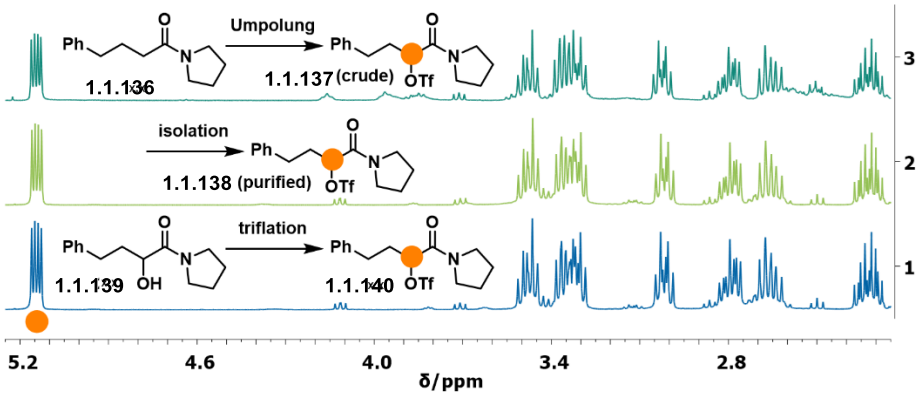
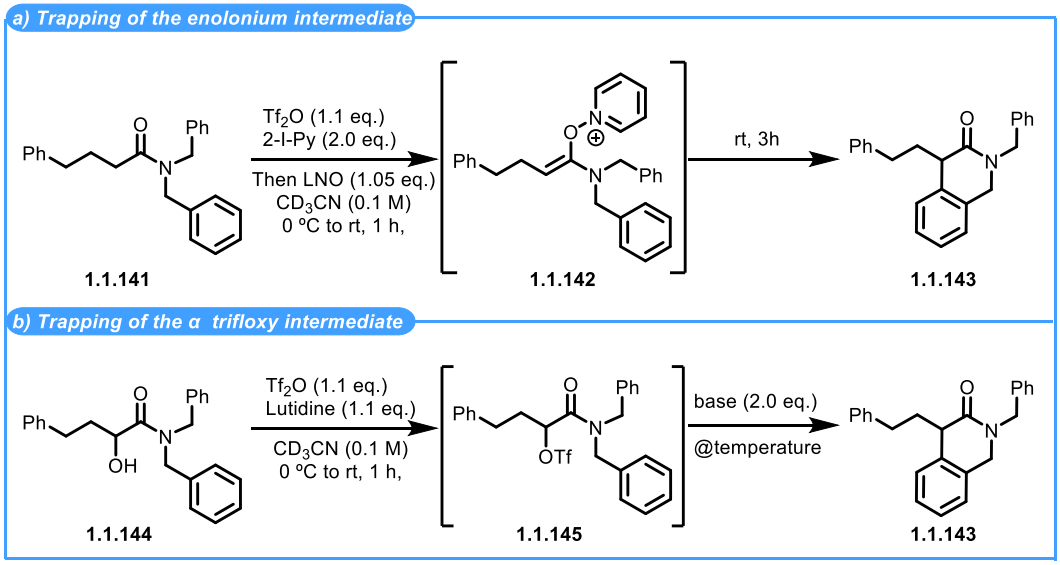


Figure 1.1 - ^{1}H-NMR overlap of the α-trifloxy species.

This species also underwent quantitive substitution when reacted with nucleophiles, such as enolates. Of the plethora of different nucleophiles tried, only aromatic

compounds seemed to be unable to displace the trifloxy (Scheme 1.12b). Indeed, when α-trifloxy dibenzyl substituted amides (**1.1.145**, Scheme 1.12b) were heated no product was conversion was observed, even with harsh conditions (110 °C, as in the original conditions, Table 1.1, entry 2).

At this point, the biggest question remained: was the enolonium a real intermediate, or did it collapse immediately to the trifloxy under the reaction conditions? To solve this, we aimed to mimic the reaction conditions of the Friedel-Crafts addition by adding the 2-I-pyridine base (Scheme 1.12) to the *in situ*-generated α-trifloxy (**1.1.145**). This result indicates that several pathways seemed to be at play. One possibilitity was the reaction proceeded but not to a large extent (entry 6), which would indicate that the pyridine adduct (Scheme 1.13b), in the case of 2-I-py, could be displaced by the aromatic compounds to give the desired product.



Scheme 1.12 – α-Triflation of N, N Dibenzyl amide (1.1.141) and subsequent S_NAR product (1.1.143).

Table 1.1 – Formation of the SEAr product (1.1.143). Reaction time 14h. [a]-reaction time: 3 hours

Entry	*Base*	*Temperature (°C)*	*Yield (NMR)*
1	2,6-lutidine	0	-
2	2,6-lutidine	110	-
3	2-I-pyridine	0	-
4	2-I-pyridine	80	-
5	2-I-pyridine	110[a]	18
6	2-I-pyridine	110	47

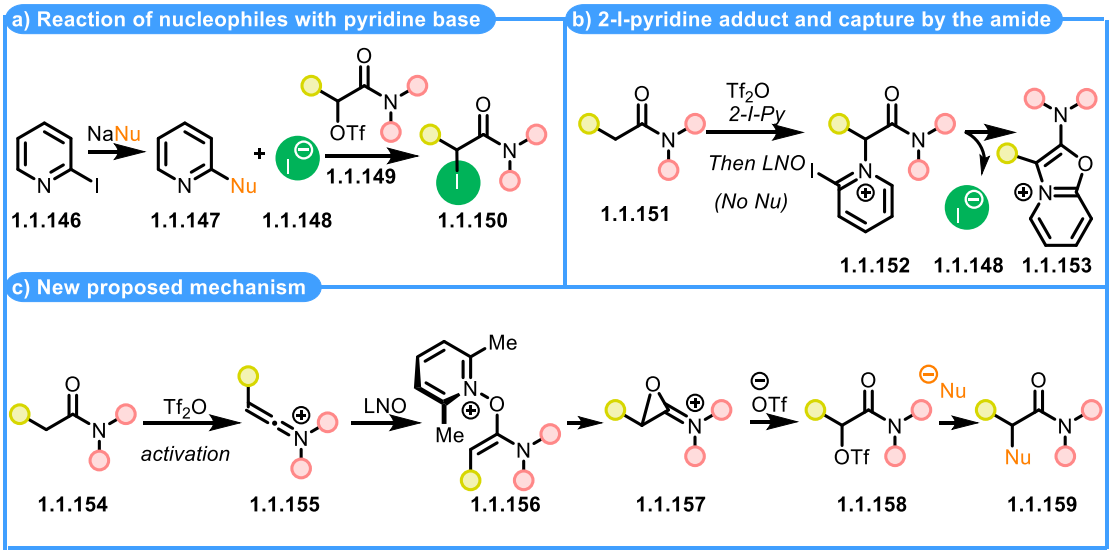
By following the amide activation of the dibenzyl substituted amide with ^{1}HNMR (**1.1.141**), the major product observed was indeed the expected Friedel-Crafts product (**1.1.143**), a finding which indirectly substantiates the formation of an enolonium intermediate (**1.1.142**, Scheme 1.12a). By heating this very same reaction we could observe full conversion, similar to what originally reported (81 % yield, Scheme 1.12a), indicating that high temperatures are necessary.

The repercussions of this discovery were quite significant, mainly because some findings now found new explanations. For example, the substitution of α-trifloxy with organometallic reagents is known to undergo substantial halogenation,[113] hence Lewis acids are usually used in combination with the organomettalic reagents.

1.1.3.2 Understanding the oxidation of the keteniminium ion with *N*-oxides – A new mechanism.

One of the main by-products that are usually found in this type of reaction is the product of α-halogenation (Scheme 1.13a). It is likely that the pyridine base (**1.1.146**) is dehalogenated by addition of a nucleophile, releasing one equivalent of halogen into solution (**1.1.148**) to itself act as a nucleophile (**1.1.150**). When using 2-I-pyridine in the absence of a further nucleophile, we identified an α-pyridinium adduct (**1.1.152**), which undergoes further substitution by the amide moiety (**1.1.153**), in turn releasing a halogen equivalent (iodine, **1.1.148**) - this process can therefore be seen as an alternative to that mentioned above. Such a hypothesis was additionally substantiated by computational experiments that found that such a pathway is, indeed, very plausible (not shown).

We opted to use that same tool to elucidate the mechanism of oxidation of the keteniminium ion, a work performed by Dr. Boris Maryasina and Prof. Leticia González. In summary, the quantum calculations of the proposed enolonium intermediates (**1.1.156**, Scheme 1.13c) indicate that fragmentation to give the α-trifloxy (**1.1.158**) is entirely plausible. Additionally, it was also observed that the enolonium intermediate would first collapse into an epoxide (**1.1.157**), releasing a lutidine molecule.



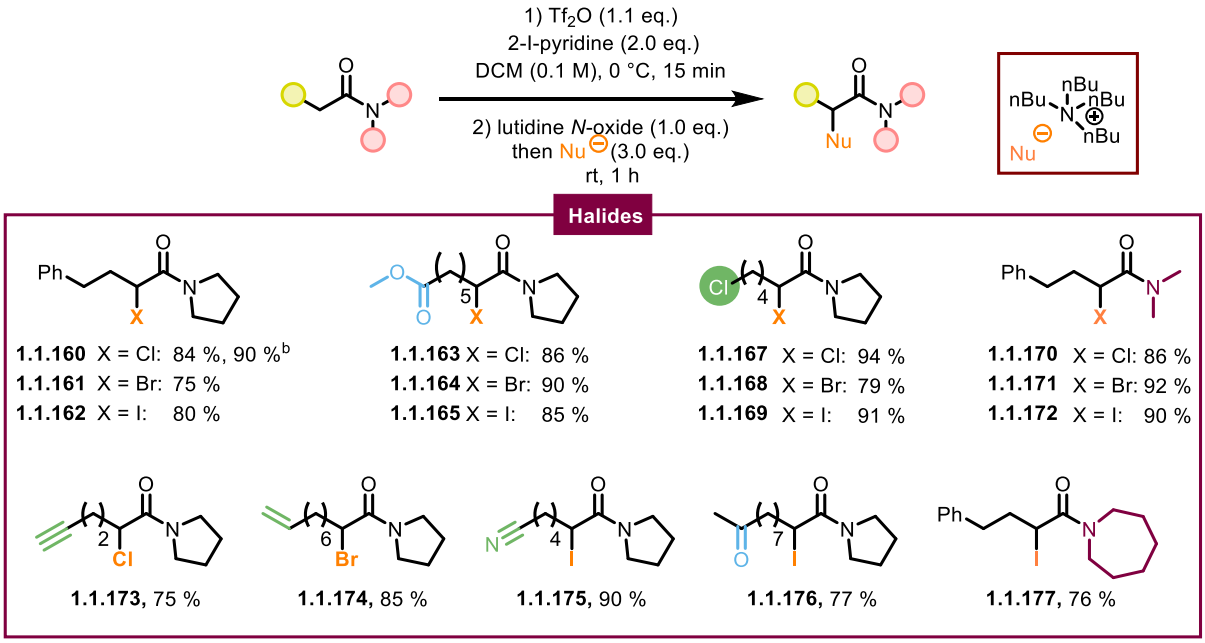
Scheme 1.13 – a) Interaction between nucleophiles and pyridine bases, b) Influence of the pyridine base in the reaction in in the absence of a nucleophile, c) New proposed mechanism based on computacional calculations.

1.1.3.3 α-Functionalisation of amides by nucleophilic halogenation.

With a clearer mechanistic picture in hands, we decided to focus on establishing a protocol for the α-functionalisation of amides by using heteroatom nucleophiles. We started to explore the scope of the reaction with chloride anion, since we had multiple a wide range of counter cation at our disposal. The reaction proceeded quite well, with marginal differences in the isolated yields for different counter cations (not shown). Even traditional table salt, which is known to have variant degrees of water, worked in good yield (**1.1.160**, Scheme 1.14). The best result was obtained using the tetrabutylammonium counter cation, which is known to catalyse several substitution reactions.[114] With these results in hand, we decided to try other halogen salts to assess if the reaction was indeed general.

In regards to other reactional parameters, we decided to use a very similar protocol to the ones presented in previous iterations of α-functionalisation of amides, in the use of enolates, *N*-oxides and S_EAr. The solvent of choice was DCM and the prefered oxidant was lutidine *N*-oxide (LNO). With the use of 2-I-Py, we observed high amounts of conversion with all amides.

One of the outstanding characteristics of electrophilic amide activation is its chemoselectivity. The possibility to functionalise amides in the presence of other functional groups greatly enhances the applicability of the method. This fact could be observed in our halogenation of amides, with substrates containing distal ester functionalities giving the corresponding α-halo amides in high yields (**1.1.163. 1.1.164, 1.1.165,** Scheme 1.14), regardless of the halogen salt used. Similarly, an amide containing a ketone (**1.1.176**) was also iodinated in high yields without the formation of by-products, ilustrating the chemoselectivity of amide activation toward amide carbonyls.



Scheme 1.14 – α-Halogenation of tertiary amides.

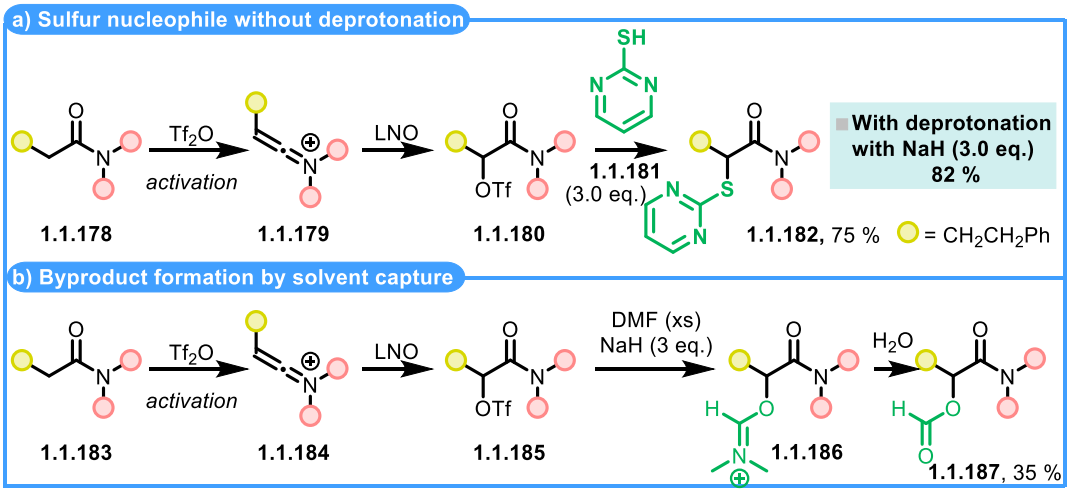
Primary chlorides (**1.1.167, 1.1.168, 1.1.169**) were also shown to be tolerated under the reaction conditions, with no apparent halogen exchange. The use of amides containing alkynes (**1.1.173**) and alkenes (**1.1.174**) also proceeded nicely, affording the corresponding α-halo amides in good yields, and no interactions such as halogenation being observed.[115,116] In regards to different *N*-substitutions (**1.1.170, 1.1.171, 1.1.172, 1.1.177,** Scheme 1.14), the yield remained excellent, even though the activation process depends on the nature of the amide bond.

Overall, this method proved to be tolerant of various functional groups, with yields constantly high. No major byproducts were observed, except for residual iodination from the formation of the aforementioned capture of the pyridine base. In theory, employing a pyridine base containing the halogen of choice would prevent the formation of any noticeable by-products.

1.1.3.4 α-Functionalisation of amides using O- and S-nucleophiles

When we first turned to on the use of other atom nucleophiles, we knew that deprotonation was most likely required for the reaction to succeed due to the existence of pyridinium acid that could deactivate the nucleophile. One exception to this fact was the

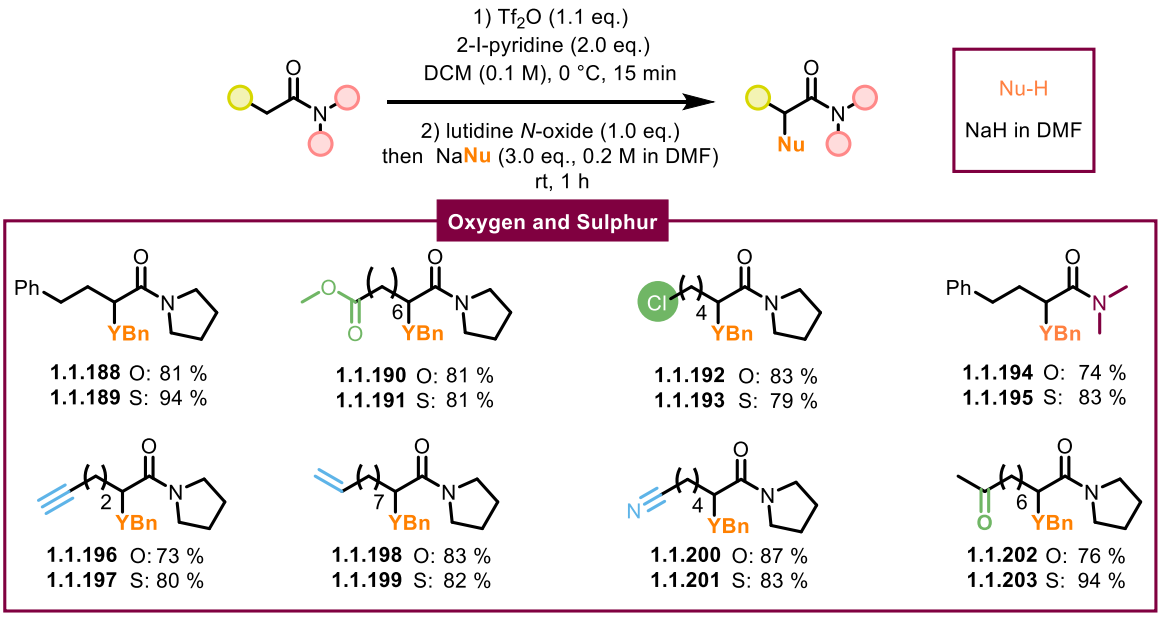
use of mercaptopyridine (**1.1.181**, Scheme 1.15a) which afforded the desired product in very good yields (**1.1.182**). We also observed that by deprotonation higher, and more reproducible yields could be reached. Concerning the other examples, we observed that strong bases were necessary to fully deprotonate the nucleophiles. For that reason, it was important to use a solvent that could solubilise these types of salts. The two main possibilities were DMF and DMSO with the latter being known to be deprotonated by NaH,[117] which could compete as a nucleophile.



Scheme 1.15 – a) Addition of sulfur nucleophilie (1.1.181) without deprotonation, b) Byproduct formation by attack of the solvent (DMF).

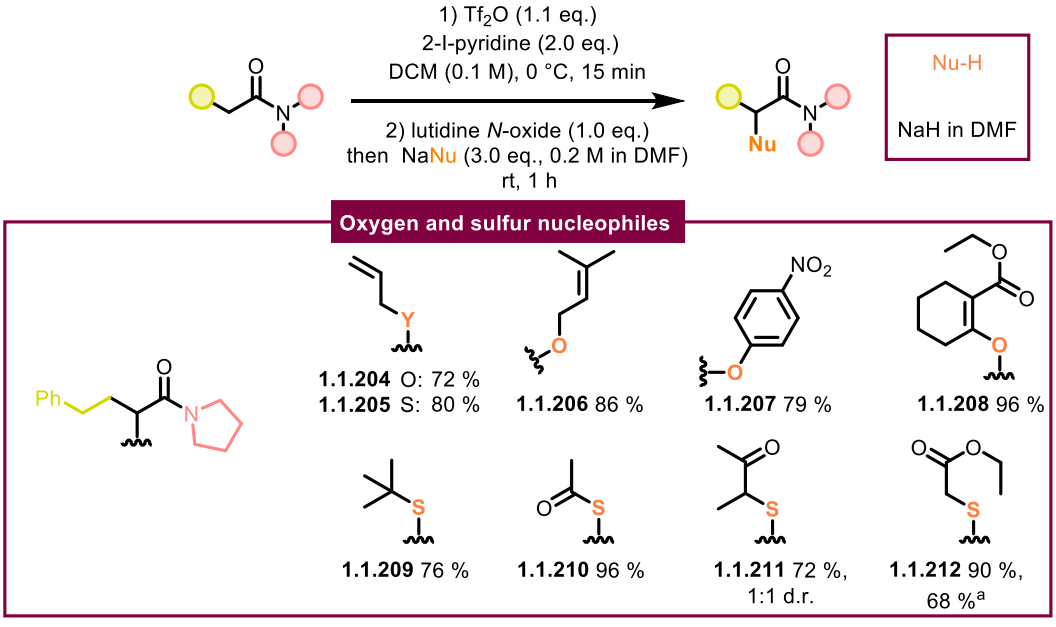
At that point, another byproduct besides the aforementioned halogenation that stemmed from the pyridine base was the attack of DMF (**1.1.186**, Scheme 1.15b). This result was not entirely unforeseen, and in some way even desired, as it led to an interesting formic acid adduct.

With the optimised conditions at hand, we decided to investigate several different amides, as in the halogenation case. The reaction with benzylic alcohols and the corresponding sulfur species, showed to have surprisingly good functional group tolerance. As is common with amide activation, carbonyl compounds such as esters (**1.1.190, 1.1.191**, Scheme 1.16), and ketones (**1.1.202, 1.1.203**) afforded the desired α-functionalised amides in good yields. Over all, no indication of deprotonation of sensitive moeities such as nitriles (**1.1.200**, **1.1.201,** Scheme 1.16) was found.



Scheme 1.16 – α-Functionalisation of amides using oxygen and sulfur nucleophiles (amide scope).

A remote alkyne (**1.1.196**, **1.1.197**, Scheme 1.16) also remained intact, regardless of which heteroatom nucleophile was used. The most surprising and interesting result was the tolerance of an alkyl chloride (**1.1.192, 1.1.193**) that was not substituted by the highly nucleophilic thiolate and alkoxide reagents.

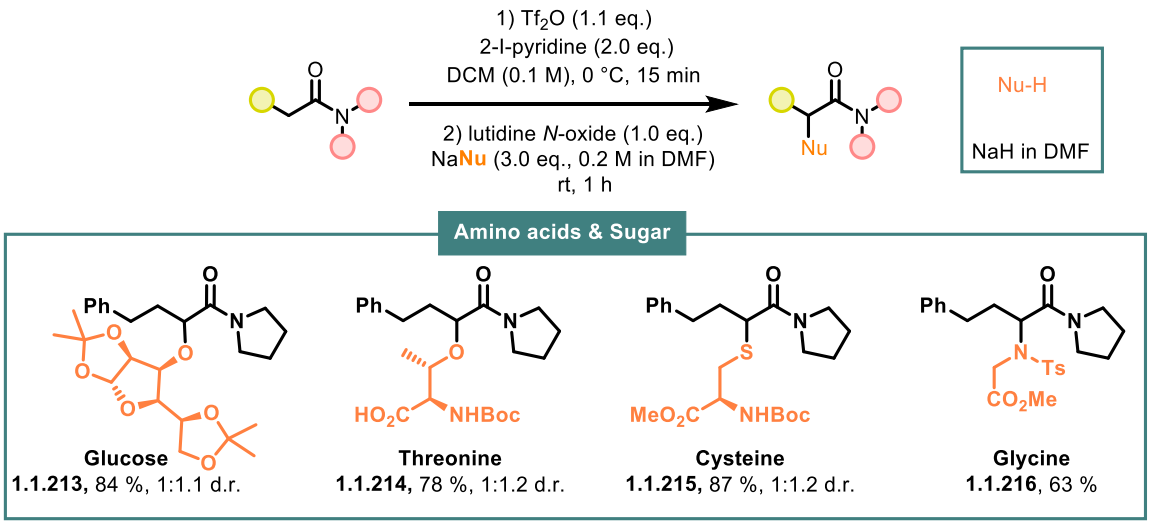


Scheme 1.17 - α-Functionalisation of amides using oxygen and sulfur nucleophiles (nucleophile scope). [a]without NaH deprotonation.

The successful use of different alcohols and thiols demonstrated the high applicability of this reaction. Primary (**1.1.205**, Scheme 1.17), secondary (**1.1.211**) and

even tertiary thiols (**1.1.209**) afforded the expected product in good yields. Additionally, different functional groups such as esters (**1.1.212**) and nitro moieties (**1.1.207**) were untouched in the reaction conditions. Interestingly, the use of a keto ester (**1.1.208**) gave exclusively the *O*-substitution, most likely because of increased steric hindrance from the enolate position. Additionally, one could also rationalise by using HSAB theory, in which by using a polar solvent, *O*-alkylation should be favoured due to a higher separation of charges, resulting in a more naked oxyanion.[118,119] Thioacetic acid also gave a single product (**1.1.210**), being that is the preferred position for the negative charge to be stabilised.[120]

1.1.3.5 α-functionalisation of amides with of biorelevant molecules



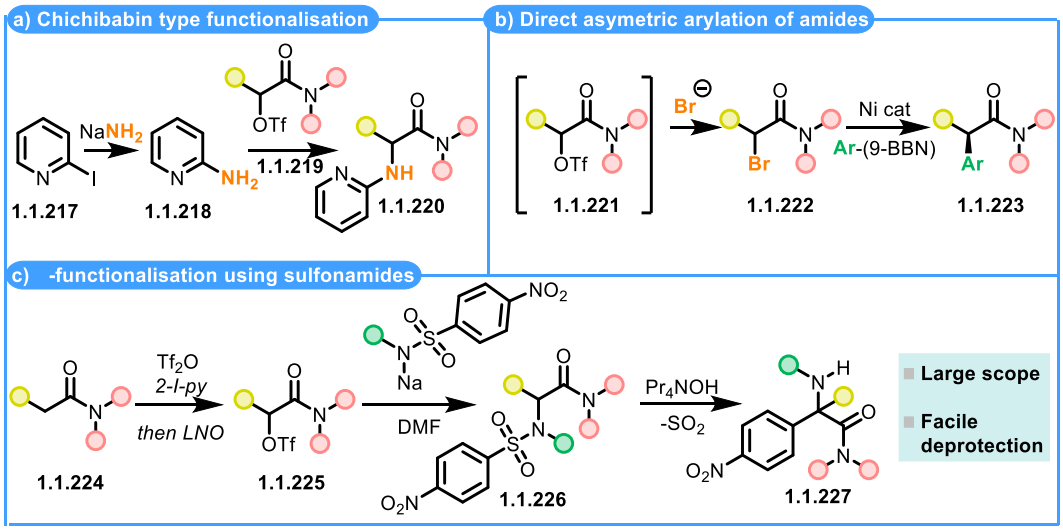
Scheme 1.18 - α-Functionalisation of amides using protected sugars and amino acids.

In order to assess the limits of the methodology, different relevant biomolecules were subjected to the reaction. The coupling was successful, however, no diastereocontrol was observed under the standard reaction conditions. These results point towards a lack of stereochemical differentiation in the formation of the α-trifloxy species. Using this approach glucose derivative (**1.1.213,** Scheme 1.18) could be easily synthesised, in higher yields. Analogously, protected amino acids with different heteroatom handles could also be attached. In the case of threonine, it was also observed that the ester group was hydrolysed during the work-up (**1.1.214**). The other amino acid examples showed no such reactivity (**1.2.215** and **1.1.216,** Scheme 1.18). Overall the reactions proceeded in high yields and with extraordinary functional group tolerance.

1.1.4 Conclusion

The goals of this project were successfully reached. We were able to establish a general protocol for the α-functionalisation of amides using different heteroatom nucleophiles. The yields of the transformation are exquisitely high, as is the functional group tolerance. The sucessfully coupling biomeolcules to the amide scaffold, one could extrapolate that this method might be amenable to broad use.

With respect to nitrogen-derived nucleophiles, it was observed that the amide reacted preferentially with the pyridine base, in a manner closely resembling the chichababin transformation (**1.1.220**, Scheme 1.19a).[121] For that reason, sulfonamides were used as amine surrogates which could undergo facile deprotection. Additionally, the sulfonamide products were also found to undergo Smile-type rearrangement, affording highly substituted amides (**1.1.227**, Scheme 1.19c). The bulk of this work was performed by Miran Lemmerer, MSc. And is therefore not presented in this thesis.

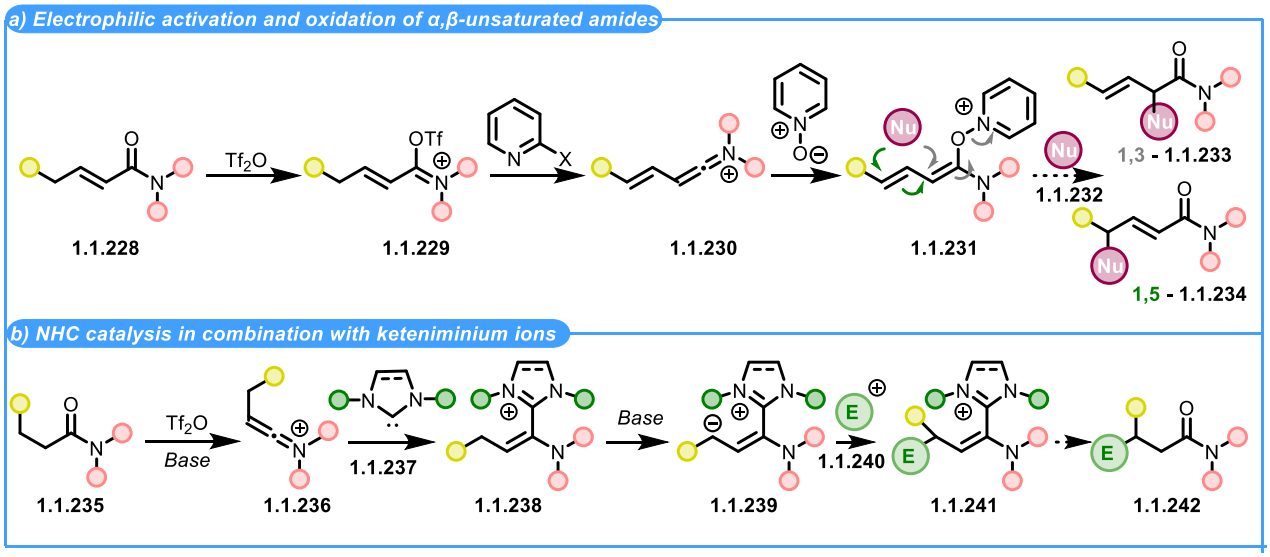


Scheme 1.19 – Final implications stemming from the elucidation of the mechanism. a) Chichibabin type functionalisation of the pyridine base (1.1.220), b) Asymetric arylation of amides using α-trifloxy amide (1.1.221), c) α-amination using sulphonamides as nucleophiles.

In regards to the mechanism, empirical data supports the suggested hypothesis, which is well substantiated by computational data. More importantly, this sort of information is crucial for the further understanding of future projects involving similar intermediates. More specifically, work on the cross-coupling of α-trifloxy amides (**1.1.221,** Scheme 1.19b) was only possible after the complete elucidation of the mechanism (Scheme 1.19b).[122]

1.1.5 Future prospects

As presented before, the formation of a keteniminium ion by electrophilic activation of amides using Tf_2O and pyridine base is a well-established concept, nonetheless, the use of α,β–unsaturated amides as substrates is limited (**1.1.228**, Scheme 1.20a). We are particularly interested by the prospect of achieving γ–functionalisation using an Umpolung strategy. This β,γ–unsaturated enolonium (**1.1.231**) would be electrophilic in both α–and γ–positions. Even known transformations could yield interesting new structures if applied to this intermediate in regioselective fashion. The intermolecular attack of a nucleophile can also proceed in a 1,3-(**1.1.233**) or a 1,5-fashion (**1.1.234**). Hence, it is reasonable to assume that the selectivity might correlate with the "soft/hard" character of the employed nucleophile, in analogy to the well-known 1,2- versus 1,4-addition.[123]



Scheme 1.20 – a) Electrophilic activation and Umpolung of α,β-unsaturated amides, b) NHC catalysis in combination with keteniminium ions to achieve 1.4-functionalisation

N-heterocyclic carbenes (**1.1.237**, Scheme 1.20b) are bench stable electron-rich ligands commonly used in catalysis.[124–127] As mentioned before, they can be used as organocatalysts, facilitating *Umpolung*-like reactivity in conjunction with carbonyl compounds (*cf*. Stetter reaction). Additionally, they have been used to generate homo-enolates from the α,β-unsaturated systems.[128,129]

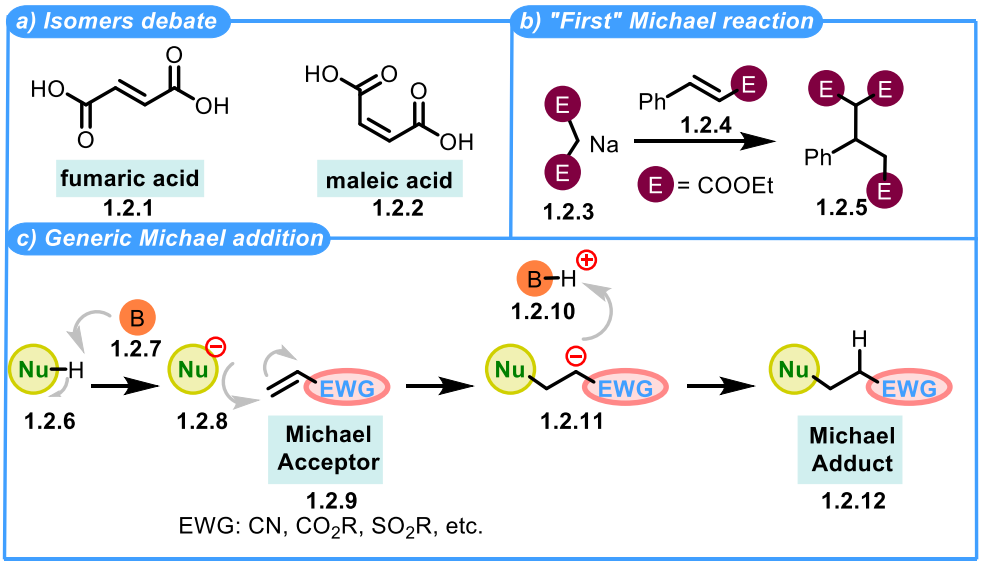
Trapping keteneminium ion (**1.1.236**, Scheme 1.20b) with **1.1.237** should lead to the formation of enamine-like intermediate (**1.1.238**), which under basic conditions should enable electrophilic functionalisation of the γ position. Similar type of reactivity should also be compatible with α,β-unsaturated systems (**1.1.228**, Scheme 1.20a), enabling remote functionalisation.

1.2 CHEMOSELECTIVE α,β DEHYDROGENATION OF TERTIARY AMIDES

1.2.1 Introduction

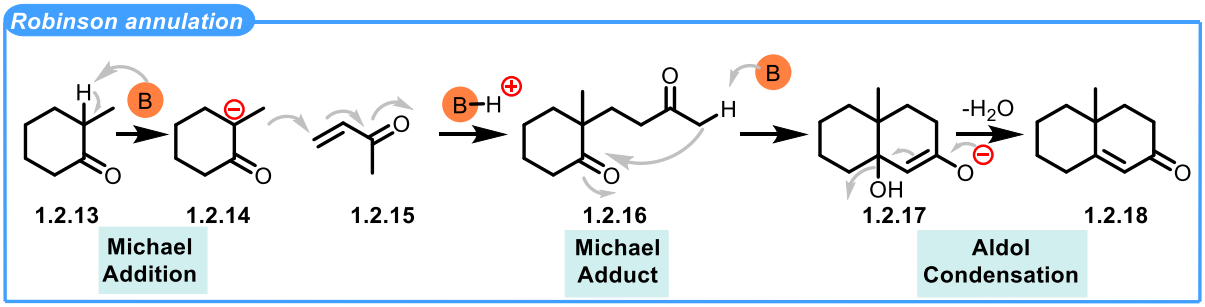
1.2.1.1 The discovery of the Michael addition

In the late 19th century, the understanding of key aspects in chemistry was at an incipient stage. A focal point was "Chemistry in space", better known to us as "stereochemistry".[130,131] To put things into perspective, significant debate was taking place regarding the structures of fumaric (**1.2.1**, Scheme 1.21a) and maleic (**1.2.2**) acid, now known to be structural isomers. By conducting degradation experiments, usually addition reactions, chemists tried to uncover the stereochemical nature of both compounds. At the time, common scientific consensus proposed that addition reactions occurred exclusively in a *cis* manner (Wislicenus theory).[132] However, Arthur Michael, a young chemist, assuredly disagreed with such generalisation of reactivity. His slant allowed him to formulate competing arguments, substantiated by empirical data, that helped shape the structural theory at the time.[133] By conducting close work with such aforementioned conjugated species, Michael first described an addition reaction between diethyl sodiomalonate (**1.2.3**, Scheme 1.21b) and ethyl cinnamate (**1.2.4**), resulting in the formation of a covalent bond between both reactants (Scheme 1.21b). Nowadays, the notorious term "Michael addition" encompasses all addition reactions to conjugated unsaturated systems adjacent to electron-withdrawing groups, colloquially described as "Michael acceptors" (**1.2.9,** Scheme 1.21c).[134–136]



Scheme 1.21 –a) Debate around geometrical isomers, fumaric and maleic acid (1.2.1 and 1.2.2), b) First reported addition reaction by Arthur Michael, c) Base-catalysed reactivity between Michael acceptors and Nucleophiles.

Robinson harnessed the synthetic utility of this concept in his eponymous annulation reaction (Scheme 1.22),[137] a tandem Michael addition/aldol condensation that was successfully deployed in the synthesis of various natural products, including steroids.[138,139] Nowadays, stereo-controlled C–C bond forming reactions based on Michael additions are a particular focus of the scientific community, with various methodologies utilising chiral catalysts to produce enantioselective versions,[140–144] Additionally, the described transformations are also being applied in the context of bioconjugation, providing a particularly valuable tool for the investigation of cell processes.[145]

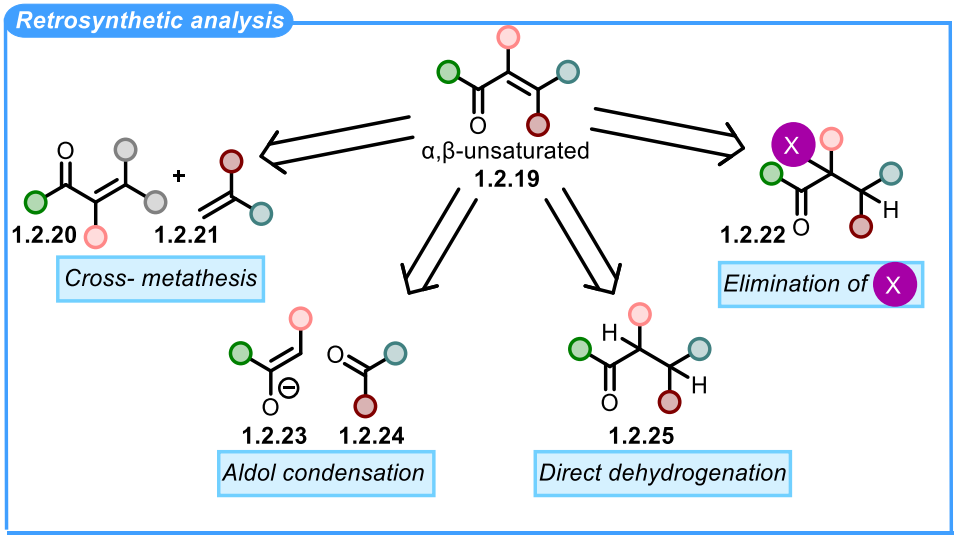


Scheme 1.22 - Detailed mechanism for Robinson annulation as one of successful examples of Michael addition reactions.

1.2.1.2 Methods for the synthesis of α,β-unsaturated systems

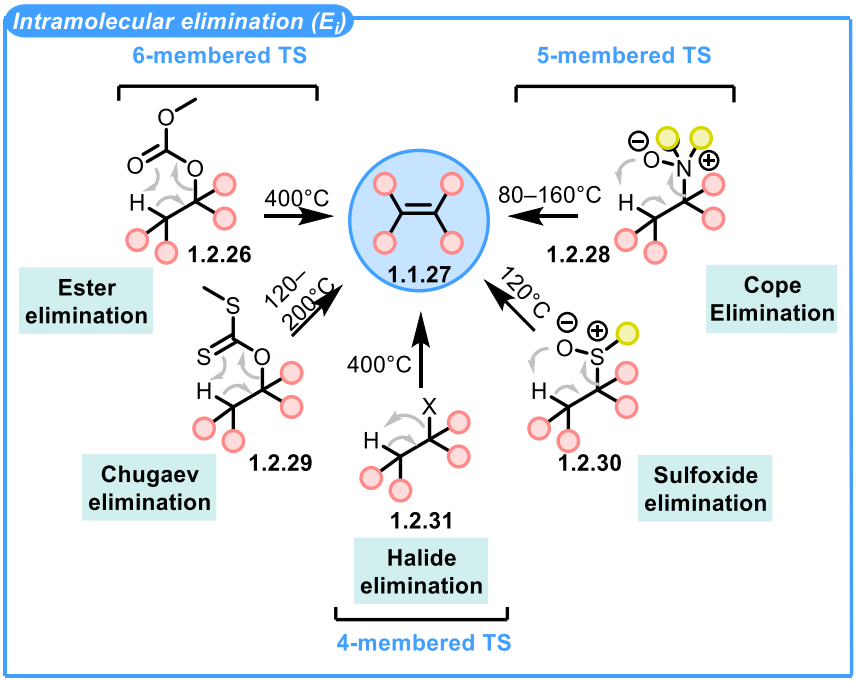
The development of novel methods for the formation of α,β-unsaturated systems continue to be of high interest to synthetic chemists (Scheme 1.23). Useful strategies

relying on cross-metathesis with unactivated alkenes can be successfully achieved in a stereoselective manner (Scheme 1.23).[146–148] Another common synthetic approach is the aldol condensation,[149,150] although, it usually relies on strong bases. Direct oxidation from the parent carbonyl derivative has become a well-established method (**1.2.25**). Inspiration for the syntheses of α,β-unsaturated species can be also drawn from simple elimination reactions, in particular thermal *syn* elimination (E_I) (**1.2.22**, Scheme 1.23).



Scheme 1.23 - Retrosynthetic approaches for the synthesis of α,β-unsaturated carbonyls.

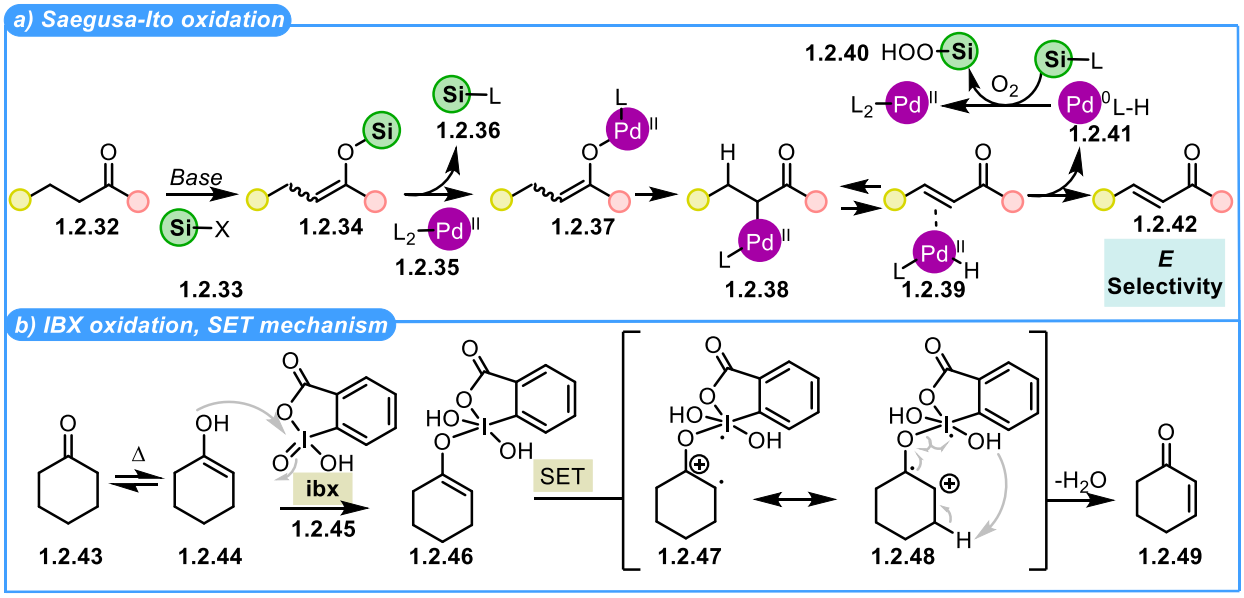
Elimination reactions to access alkenes have been well-studied. It was observed that alkenes could be obtained *via* thermolysis of various functional groups such as esters (**1.2.26**, Scheme 1.24),[151] xanthates (**1.2.29**),[152,153] halides (**1.2.31**),[154] *N*-oxides (Cope elimination, **1.2.28**)[155] and sulfoxides (**1.2.30**).[155–157]



Scheme 1.24 –Different thermal intramolecular elimination approaches (E_i).

1.2.1.3 Methods for the synthesis of α,β-unsaturated systems by dehydrogenation

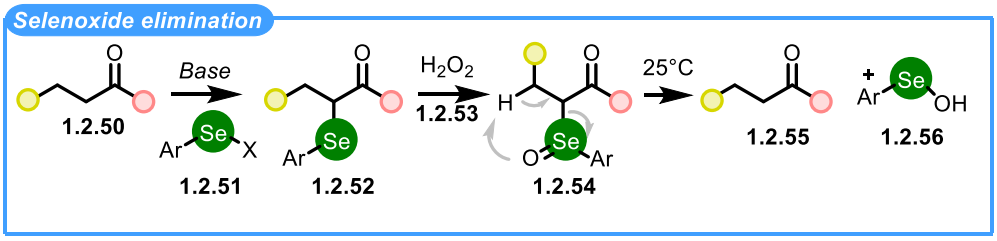
However, the use of drastic thermal conditions limits the applicability of some of these methods to access α,β-unsaturated systems (**1.2.27**, Scheme 1.25). A more versatile strategy would be to directly transform saturated systems into their α,β-unsaturated congeners. One notable strategy in this context is the Saegusa-Ito oxidation (Scheme 1.25a). The reaction is catalysed by Pd (II) species to promote a β-hydride elimination (**1.2.38**). The carbonyl moiety is transformed into a silyl enol ether (**1.2.34**), enabling the trapped enol tautomer to form oxoallyl-palladium complex **1.2.37**. Subsequent β-hydride elimination furnishes α,β-unsaturated ketones **1.2.42**. Interestingly, when linear silyl enol ethers are applied, the reaction predominantly affords the *E*-isomer even when a mixture of silyl enol ether stereoisomers is used.[158] This is attributed to reversible coordination of the Pd^{II}–H species to the enone after the elimination step (**1.2.39**).[32–36]



Scheme 1.25 – Selected well-established methods for the synthesis of α,β-unsaturated ketones via direct oxidation: a) Pd-catalyzed Saegusa-Ito oxidation, b) IBX-mediated oxidation of enones.

Despite its synthetic utility, the Segussa-Ito oxidation suffers from high catalyst loadings, as a result of the strong π-coordination of the catalyst system by the reaction product (**1.2.39,** Scheme 1.25).

Nicolaou and co-workers described an alternative strategy employing IBX (**1.2.45**, Scheme 1.25b) as an oxidant in a metal-free approach (Scheme 1.25b).[159,160] It was proposed that the enol tautomer (**1.2.44**) could participate in the formation of iodine-enolate intermediate **1.2.46**. Upon SET, the radical cation **1.2.47** is formed. Subsequent elimination then takes place furnishing α,β-unsaturated ketones (**1.2.49**).[161–164] However, harsh reaction conditions limited the applicability of this method, and resulted in poor chemoselectivity in some cases. Furthermore, the formation of tautomer (**1.2.44**) is crucial for the outcome of the transformation, hence most methods rely on ketones and rarely esters.



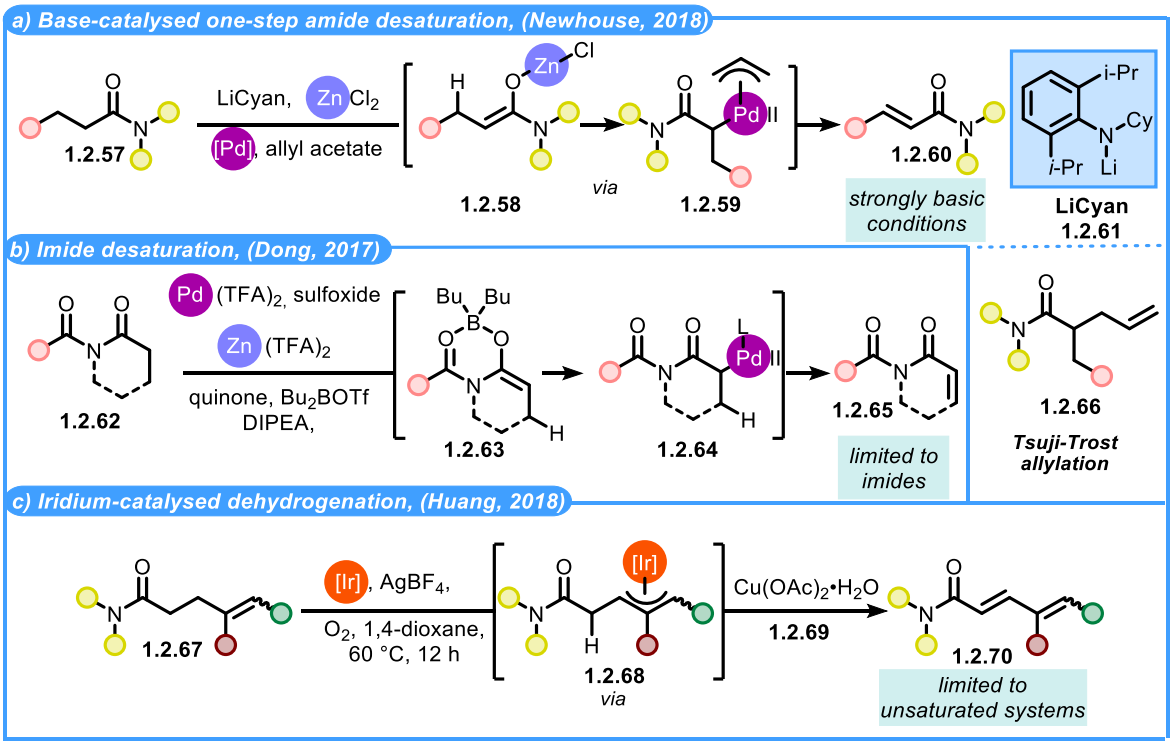
Scheme 1.26 – a) Selenoxide elimination of carbonyl compounds.

Sharpless investigated the elimination of aromatic selenoxides (**1.2.54**, Scheme 1.26),[165] resulting from oxidation of the corresponding selenides (**1.2.52**), usually with

hydrogen peroxide (**1.2.53**). An important feature was the facile elimination that occurs at room temperature, which contrasts well with the previously mentioned E_i methods (Scheme 1.24). The premise of this reaction was also incorporated in other processes such as the venerable Grieco elimination,[166] which achieves the elimination of primary alcohols[167–169] in a similar fashion.

1.2.1.4 Recent methods for the dehydrogenation of saturated carbonyl systems

The reliance on α-carbonyl acidity in the synthesis of α,β-dehydrogenated compounds, led to the development of novel methods that focused on problematic functional groups such as esters, nitriles and carboxyamides. In 2018, Newhouse and co-workers reported a zinc enolate-mediated (**1.2.58**, Scheme 1.27a) dehydrogenation of amides (Scheme 1.27a),[170] which has been shown to tolerate *O*-H and *N-H* moieties.[171] One key feature of the reaction is the use of allyl acetate as an oxidant. The postulated mechanism involves intermediate **1.2.59**, which preferably undergoes ß-hydride elimination in the presence of zinc salts, which have showed experimentally to prevent the traditional Tsuji-Trost type allylation products (**1.2.66**).[172–175] Furthermore, this methodology has been applied to the dehydrogenation of carboxylic acids[176] and the total synthesis of natural products.[177,178] In the specific case of imides (**1.2.62**, Dong *et al.* developed a desaturation procedure by using acyl groups to enable facile enolization.[170] The method hinged on a boron enolate intermediate (**1.2.63**, Scheme 1.27b) that interacts with the palladium catalyst under mild conditions, with the zinc salt being again crucial for the outcome of the transformation.



Scheme 1.27 – Recent metal-catalysed, one-step amide dehydrogenation methods.

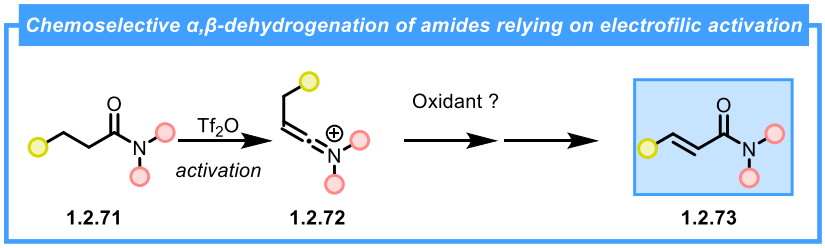
In the specific case of γ,β-unsaturated systems (**1.2.67**, Scheme 1.27c), Huang found that dehydrogenation was possible in the presence of an iridium catalyst, that enabled a facile deprotonation of the α-position.[179] The copper co-cocatalyst (**1.2.69**) acts as an oxidant as was found to be crucial for the turnover of the iridinium catalyst under air.[180,181]

Nevertheless, a general method for the α,β-dehydrogenation of amides is not yet available. The most efficient methods rely either on strong bases or substrate engineering to facilitate the deprotonation of the α-position of the carboxamide. Consequently, we decided to investigate chemoselective dehydrogenation methodology of amides employing electrophilic activation.

1.2.2 Objectives

The aim of this project was the development of a chemoselective method for the synthesis of α,β-unsaturated amides starting from their saturated congeners (Scheme 1.28).

The work in question was initiated by Dr. Paulide Adler and Dr. Christopher Teskey, and both worked on the optimisation of the reaction and the development of the scope. Carlos Goncalves focused on the last part of optimisation, extension of the scope and all further functionalisation including the synthesis of the natural product. Part of this work has been published.[182]

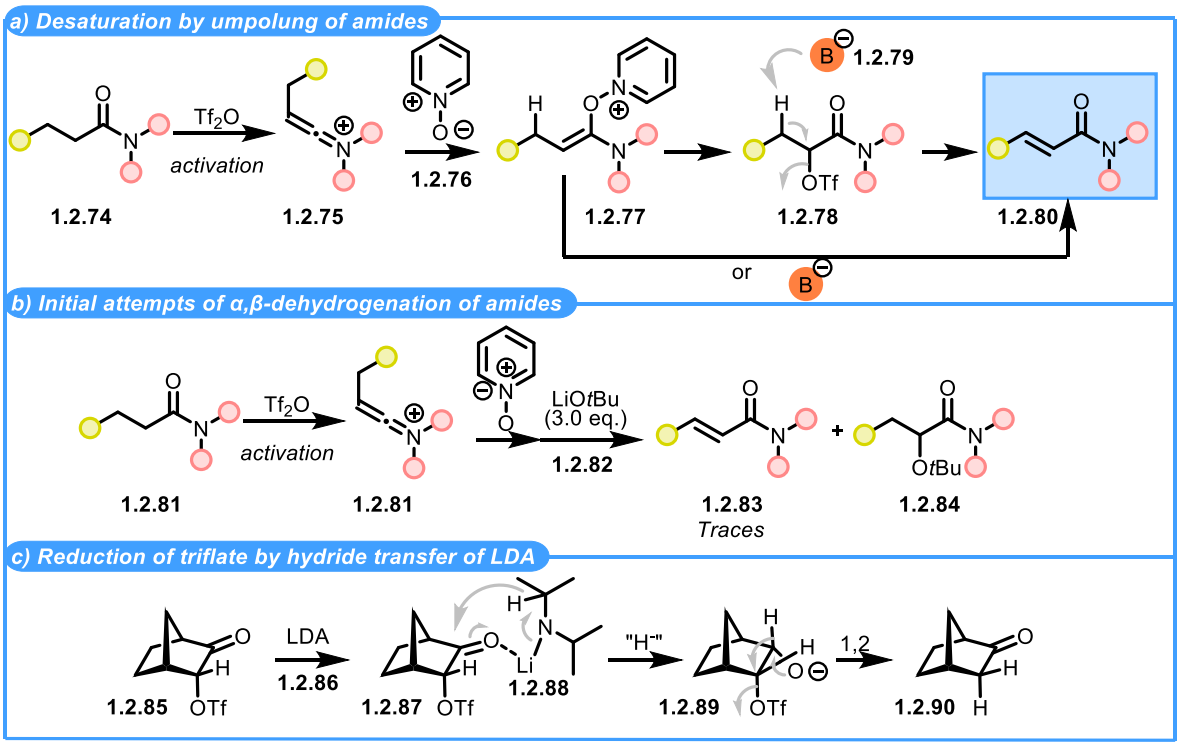


Scheme 1.28 – Objective: Chemoselective, metal-free approach for the α,β-dehydrogenation of amides.

1.2.3 Results and discussion

1.2.3.1 Initial attemps of α,β-dehydrogenation of amides

Our approach was predicated on electrophilic activation *via* of the previously described keteniminium intermediate (**1.2.75**, Scheme 1.29a). Oxidation to the α-triflyloxy amide **1.2.78** *via* the enolonium species (**1.2.77**) could also be seen as a potential pathway towards desaturation (**1.2.80**, Scheme 1.29a).



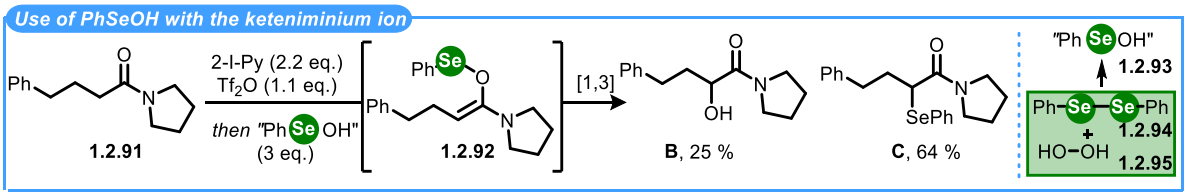
*Scheme 1.29 – a) Umpolung approach to the desaturation of amides. b) Initial attempts of desaturation with LiO*t*Bu. c) Reduction of α-triflyloxy ketone (1.2.85) with LDA.*

What initially seemed like a simple extension proved to be a challenging task. Applying LiO*t*Bu (**1.2.82**) as a base resulted in the formation of the correspondent ether (**1.2.84**, Scheme 1.29b) and only traces of the dehydrogenated amide was observed. The same outcome was observed when stronger base such as LDA was used in combination with the α-triflyloxy amide. It is important to mention that LDA (**1.2.86,** Scheme 1.29c) could also act as a hydride donor when reacted with α-triflyloxyketone **1.2.85**.[183,184] In a similar report by Creary *et al.*, treatment of α-triflyloxy ketone **1.2.87** with LDA resulted in the formation of the starting ketone **1.2.90** (Scheme 1.29c).[185,186]

Thus, we turned our focus into an alternative approach, whereby selenium intermediates akin the Sharpless selenoxide methods would be generated.

1.2.3.2 Selenium based approach for the α,ß-dehydrogenation of amides

As seen in Scheme 1.30, initial results were highly promising and addition of an *in situ* generated phenylselenol (**1.2.93**, PhSeOH, Scheme 1.30), by oxidative cleavage of diphenyl diselenide (**1.2.94**), afforded the corresponding α-selenide species **C** in 64 % yield albeit accompanied by α-hydroxy amide **B**. The underlying reaction mechanism remained elusive as it appeared that a [1,3]-rearrangement had taken place (**1.2.92**). Further oxidation of **C** should trigger the elimination step and furnish the α,ß-dehydrogenated amide. Our aim was the development of a one-pot procedure, selenium species in a higher oxidation state was used to favour the elimination directly.



Scheme 1.30 - Initial attempt for the desaturation of amide 1.2.91 with in situ generated "PhSeOH" by oxidative cleavage of diphenyldiselenide.

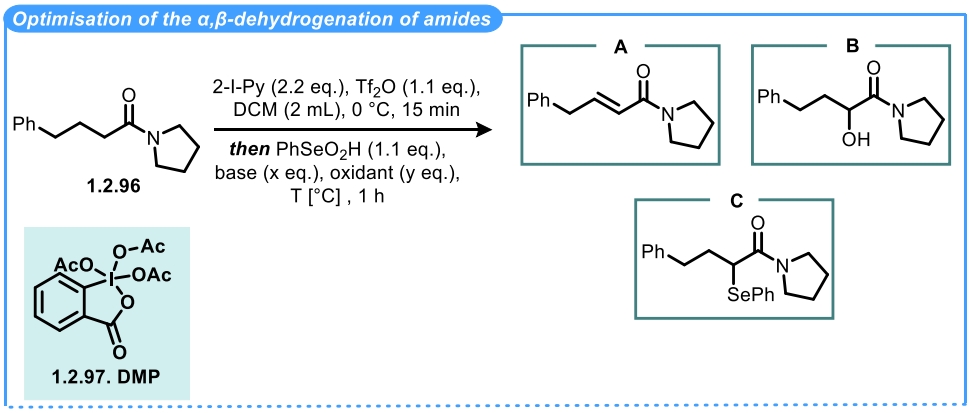


Table 1.2 - Optimisation of the one-pot desaturation of amide 1.2.96 with $PhSeO_2H$. "-": Not detected

Entry	*$PhSeO_2H$ (eq.)*	*Base*	*Oxidant/Add.*	*T [°C]*	***1.2.96*** *[%]*	***A*** *[%]*	***B*** *[%]*	***C*** *[%]*
1	(3.0 eq.)	–	–	–	–	–	38	–
2	(1.0 eq.)	Et_3N (1.1 eq.)	–	–	–	–	21	50
3	(1.0 eq.)	Ag_2CO_3 (1.1 eq.)	–	23	18	47	16	–
4	(2.0 eq.)	Ag_2CO_3 (2.2 eq.)	–	23	15	40	15	–
5	(2.0 eq.)	Ag_2CO_3 (2.2 eq.)	–	23	15	40	15	–
6	(1.0 eq.)	NEt_3 (2.2 eq.)	IBX (2.2 eq.)	23	21	29	45	–
7	(1.0 eq.)	NEt_3 (2.2 eq.)	DMP (2.2 eq.)	23	17	71	–	–
8	(1.0 eq.)	NEt_3 (2.2 eq.)	DMP (2.2 eq.)	-78	10	80	–	–

When phenyl seleninic acid ($PhSeO_2H$) was used under our standard reaction conditions, we did not observe the desaturation product **A**. Instead, *α*-hydroxylation (**B**) resulted in moderate yield (Table 1.2, entry 1). In order to facilitate the attack of the selenium species, phenyl seleninic acid was treated with a base, prior to addition to the reaction mixture (Table 1.2, entry 2). However, *α*-selenated amide (**C**) was found to be the major product. Interestingly, the use of Ag_2CO_3 in stoichiometric amounts (Table 1.2, entry 3) led to the formation of desired product **A** in 47 % yield. Increasing the amount of base and selenium species led to negligible differences in yields (Table 1.2, entries 4 and 5). It is important to note that Ag_2CO_3 can have a dual role in this reaction. Besides acting as a base, Ag_2CO_3 can also act as an oxidant (Fetizon reaction). [187–189]

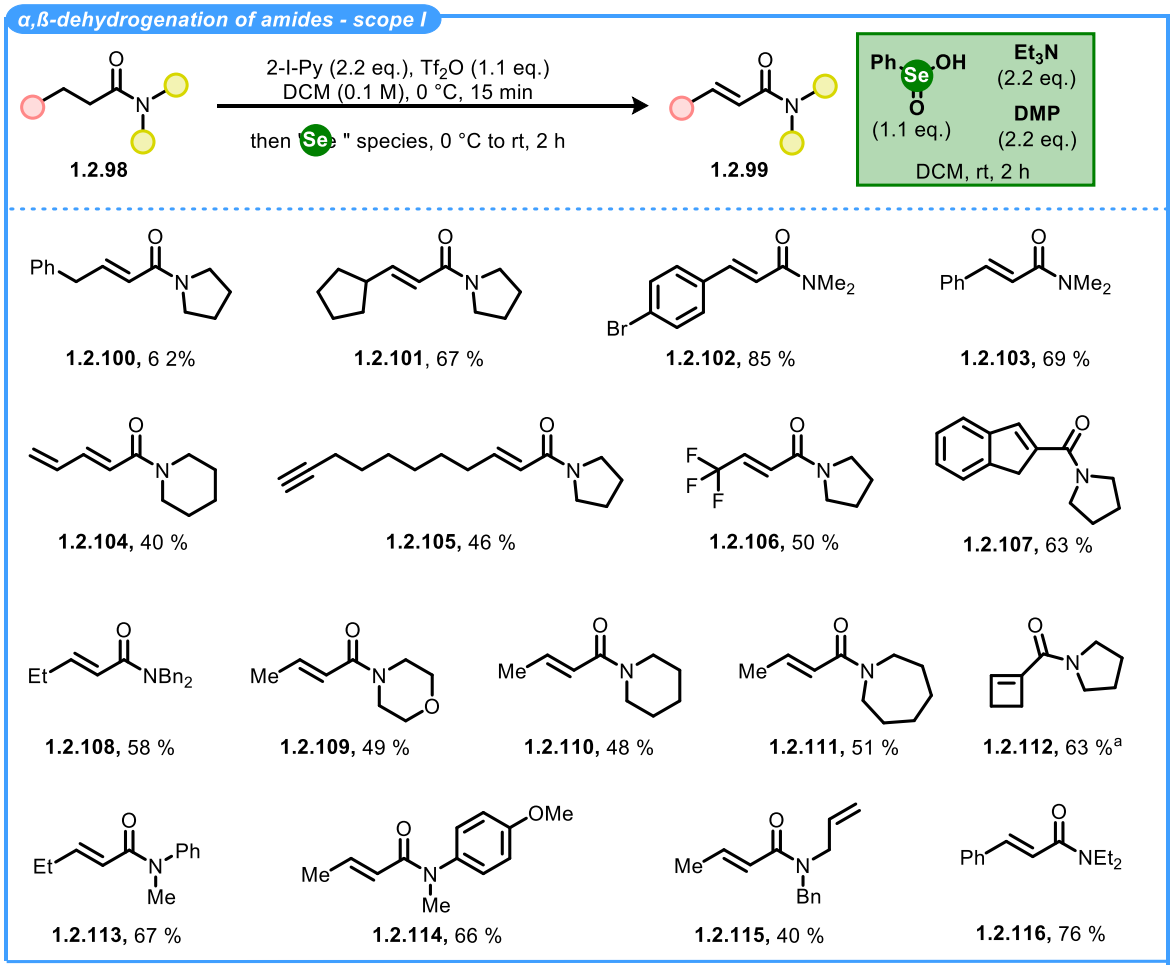
Thus, we screened different oxidants in combination with Et_3N as a base (Table 1.2, entries 6-8). IBX resulted in the formation of significant amounts of **B** (45 %), but importantly 20 % of **A** was also observed. Finally, DMP yielded the dehydrogenated product **A** in 71 % (Entry 7). Higher yield was observed when lower temperature was

applied (Table 1.2, entry 8). However, to make this method more user-friendly, we chose to run the reaction at room temperature. In both cases, small amount of the starting amide was observed.

1.2.3.3 Scope of the α,β-dehydrogenation of amides

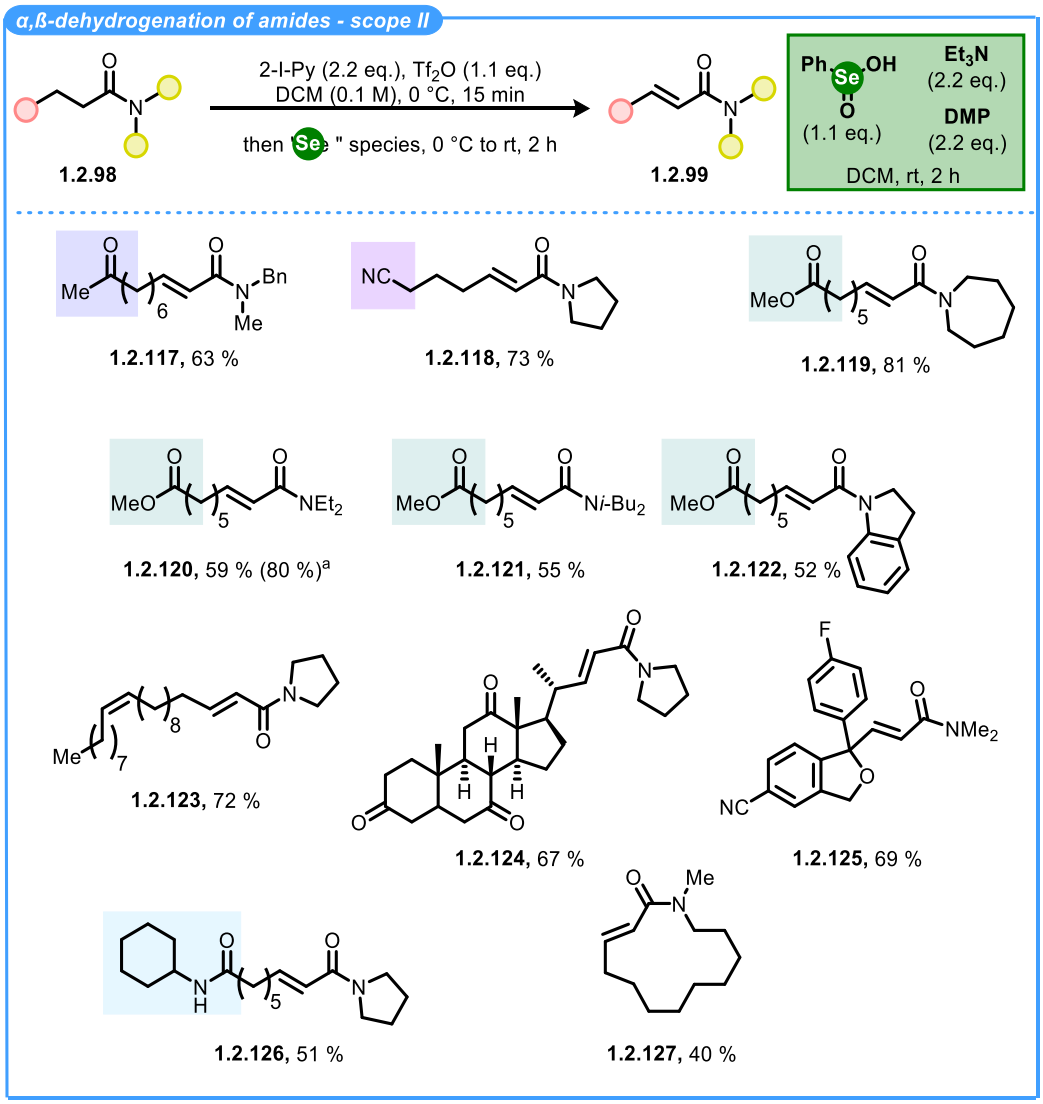
With optimised reaction conditions in hand, we proceeded to explore the limits of this transformation. Generally, separation of the starting materials and the dehydrogenated reaction products by column chromatography was challenging., Therefore, we explored different purification stationary phases besides "normal" flash silica. Basic alumina led to isomerisation of the double bond.[190] A particularly appealing alternative involved the use of silver-impregnated silica, with which sufficient separation could be achieved.[191–193]

Applying our developed procedure, we observed that the reaction proceeded with a wide range of tertiary amides (Scheme 1.31). Different cinnamyl derivatives (**1.2.102, 1.2.103**) could be formed in good yields. Additionally, a diene (**1.2.104**) was obtained in acceptable yields. The use of a trifluoromethyl-substituted amide gave access to the desired product **1.2.106** in 50 % yield. The reaction also proceeded with α-branched amides, namely affording indene (**1.2.107**.) in good yields. The substitution on the nitrogen of the amide moiety had little influence on the reaction outcome. Dibenzyl (**1.2.108**), morpholine (**1.2.109**), pyrrolidine (**1.2.100**) and azepine (**1.2.101**) analogues were formed in acceptable yields. Notably, also a strained cyclobutene ring (**1.2.112)** successfully gave the desired product in 63 %. Finally, anilines were shown to be suitable reaction partners and **1.2.113** and **1.2.114** were isolated in 66 and 67 % yield respectively.



Scheme 1.31 –Scope of substrates for the one-pot α,ß-dehydrogenation of amides. [a] yield based on the recovery of starting material.

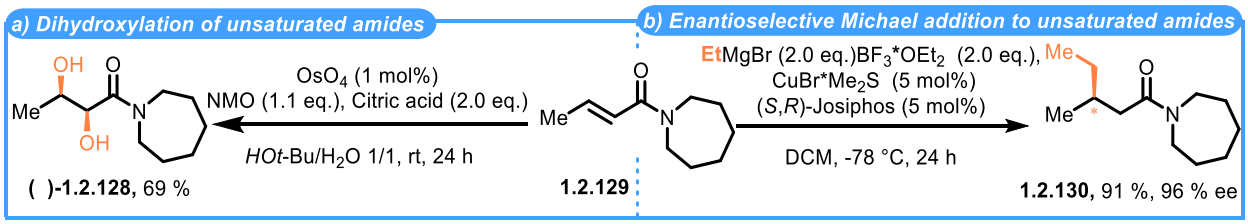
We subsequently investigated the functional group tolerance of our methodology (Scheme 1.32). Notably, ketones (**1.2.117**), nitriles (**1.2.118**), and esters (**1.2.119**) were well-tolerated and underwent the desired dehydrogenation chemoselectively. Moreover, natural product-derived substrates **1.2.123** and **1.2.124** (originating from dehydrocholic and oleic acid) also afforded the desired products in 67 and 72 % yield, respectively. Additionally, citalopram-based derivative **1.2.125** was successfully transformed into the α,β-unsaturated amide. Finally, we could selectively react a tertiary amide in the presence of a secondary carboxamide, yielding **1.2.126** in 51 % yield.



Scheme 1.32 - Scope of substrates with respect to functional group tolerance in the direct dehydrogenation of amides. [a] yield based on the recovery of starting material.

1.2.3.4 Applications using α,ß-dehydrogenated amides

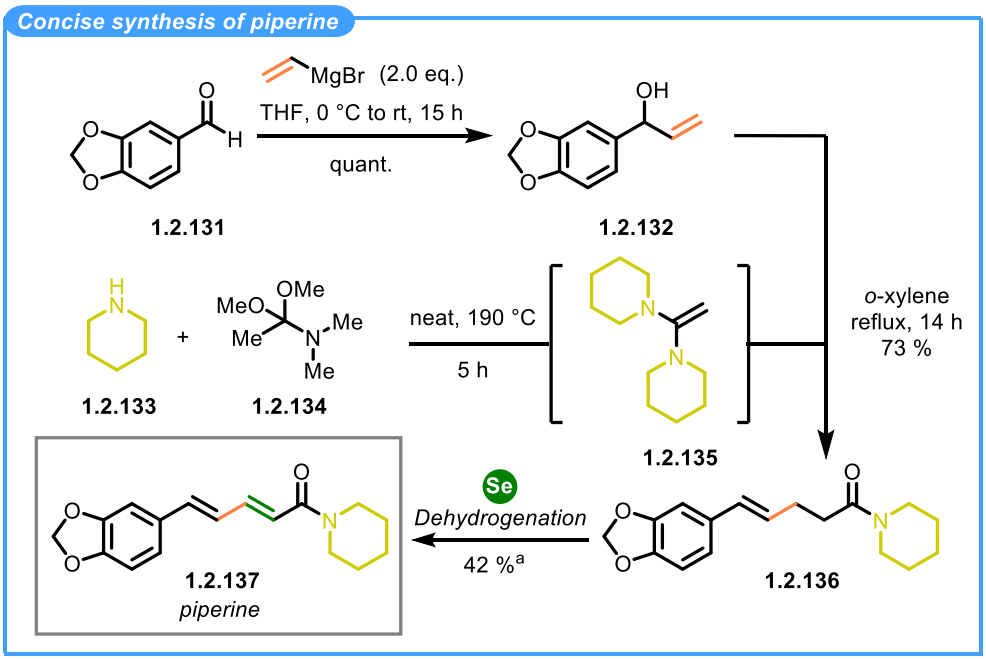
We conducted a few post-functionalisation experiments. Employing catalytic Sharpless dihydroxylation, we synthesised diol (**1.2.128**, Scheme 1.33a) in 69% yield.[194] Similarly, enantioselective cuprate addition was accomplished furnishing **1.2.30** in high yield and enantioselectivity (Scheme 1.33b).[195]



Scheme 1.33 – Derivatisation of the product (1.2.129) by hydroxylation and enantioselective Michael addition.

1.2.3.5 Synthesis of piperine using our method for α,β-dehydrogenation of amides

Furthermore, we applied our method to the synthesis of piperine (**1.2.137**, Scheme 1.34), an alkaloid in black pepper that reportedly enhances the bioavailability of other compounds in food and dietary supplements (Scheme 1.34).[196] The short synthetic route consisted on the synthesis of allylic alcohol (**1.2.131**), which subsequently underwent a Claisen-Eschenmoser sigmatropic rearrangement,[197–199] affording the dehydrogenation precursor (**1.2.136**). By applying our protocol, the target compound piperine (**1.2.137**) was synthesised in 42 % yield over three steps.



Scheme 1.34 –Concise synthesis of piperine(1.2.137) via direct dehydrogenation of the amide 1.2.136 [a]Based on recovery of starting material.

1.2.3.6 Mechanistic elucidation of the transformation

With respect to the mechanism of the transformation, we established several competing pathways that could explain the formation of the product (Scheme 1.36). As described before, the use of phenyl seleninic acid led primarily to the α-selenyl product (**1.2.139**, Scheme 1.39a), which could be oxidised with DMP to the desired product (**1.2.140**, Scheme 1.35a). This was not high yielding, suggesting that other pathways could be converging in the formation of the product.

The required pre-mixture of the selenium species (Scheme 1.35b) with DMP hinted at the formation of a new species (**B**, Figure 1.2). We attempted to monitor the corresponding reaction product by ^{1}HNMR and ^{77}SeNMR. However, all attempts remained unsuccessful. Nevertheless, ^{77}SeNMR proved to be particularly useful as it allowed identification of several other species in the reaction mixture. By conducting NMR experiments on the premixture process and the reaction itself, we observed that different selenium species were most likely disproportioning, leading, for example to the formation of diphenyl diselenide (**C**) in high quantities. We also putatively assigned an intermediate Se species (**B**) that was formed, likely interacting with the DMP (**B**, Figure 1.2). We have concluded it to be chemically similar to seleninic anhydride – despite not matching the literature shifts.

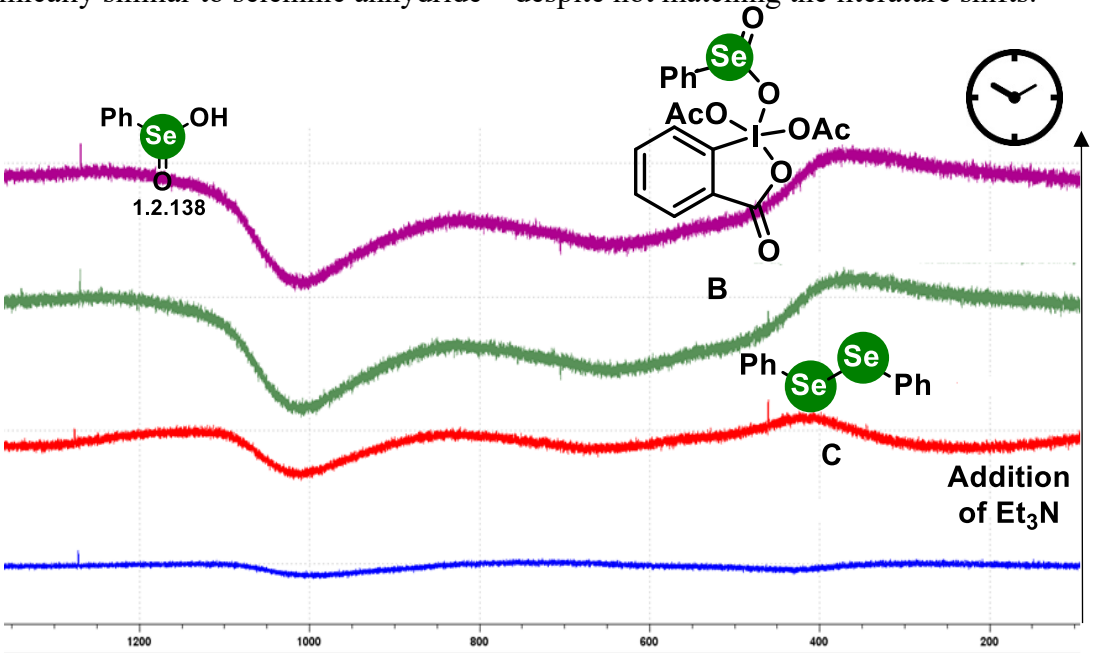
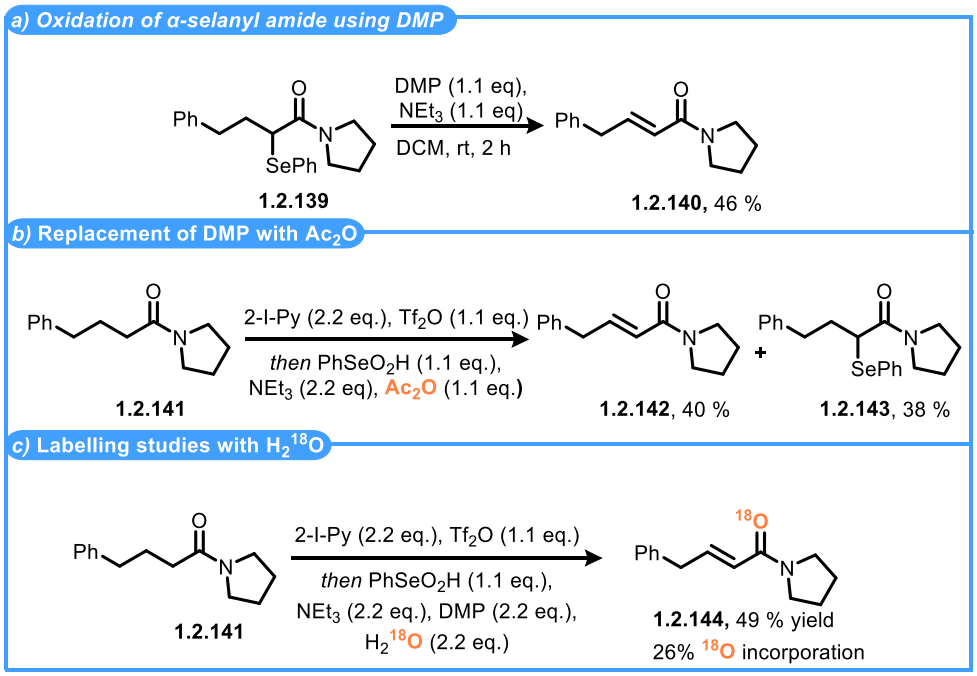


Figure 1.2 – ^{77}Se-NMR studies of the premixture of the selenium species. Red line– addition of Et_3N

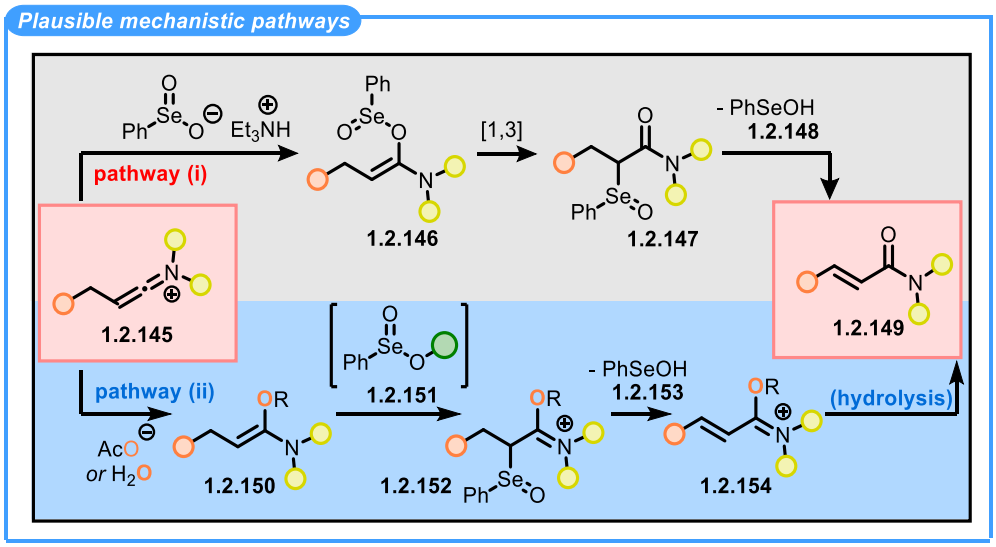
The second pathway is directly connected to the DMP species and its components. During the premixture, we assume that acetate is released from DMP, which can

subsequently interact with the keteniminium ion to generate an enolate-like intermediate (**1.2.150**, Scheme 1.35b), subsequently reacting with an electrophilic selenium species (**1.2.151**). In addition, when using commercially available DMP, which contains substantial amounts of acetic acid, better and more reproducible results were obtained in comparison to material synthesised in our laboratories according to literature procedures.[200,201] This indicates that the acetate ion indeed has an effect on the reaction. It should be noted that similar effects have been described before in DMP oxidations, where commonly known impurities such as water appeared to facilitate the oxidative process.[202] Additionally, the use of acetic anhydride in combination with the selenium mixture also afforded the desired product in 40 %, again suggesting involvement of acetate species (Scheme 1.35b). When we added ^{18}O-labelled water to our reaction mixture, we observed partial ^{18}O-incorporation into the final reaction product, eluding to the replacement of the oxygen in the starting amide (**1.2.144**, Scheme 1.35c).



Scheme 1.35 - a) Oxidation of α-selenyl using DMP, b) using Ac_2O instead of DMP in the standard conditions, c) ^{18}O-Labelling study.

Isotopic labelling of the selenium species would be helpful, however its synthesis involves the use of ^{18}O-labelled hydrogen peroxide, which was unfeasible due to practical aspects.[203,204] Finally, by conducting the aforementioned NMR studies, we observed that the reaction was quite fast, with no intermediates being successfully characterised.



Scheme 1.36 – Plausible mechanistic pathways.

In retrospect, pathway **(i)** relies on the nucleophilic attack of seleninic acid and subsequent undergoes a [1,3]-shift to afford **1.2.147**, prone to elimination (Scheme 1.36). The important role of DMP in the outcome of the transformation implied an alternative, concurrent pathway **(ii)**, in which the keteniminium can be transformed into a umpolulled species **1.2.150**. that can react with an electrophilic selenium species, which we postulate is attached to the DMP core (**1.2.151**). Species **1.2.152** should then afford the α,β-unsaturated imidate **1.2.154** species, subsequently hydrolysed to product (**1.2.149**, Scheme 1.36)

Due to the known disproportionation of selenium derivatives,[205,206] multiple pathways could be in play. Despite being difficult to ascertain at this juncture the exact mechanism of the transformation, a combination of both suggest pathways seems to be a plausible statement.

1.2.4 Conclusion

In this work we reported a chemoselective dehydrogenation of amides to the corresponding α,β-unsaturated analogues with exceptional functional group tolerance. Despite not fully uncovering the mechanism, we suggested different pathways using electrophilic selenium species.

We highlighted the versatility of the obtained α,β-unsaturated amide by several post-functionalisation reactions. The protocol also enabled the straightforward synthesis of natural product piperine in three linear steps.

1.2.5 Future Prospects

One of the most enticing features of this transformation is the underlining mechanistic riddle. Due to the fast nature of the transformation, few options remain for total comprehension of the process. A possibility is to use direct IR to follow the transformation,[207] although monitoring is likely hampered by the fleeting nature of the intermediates.

The most likely candidate for the elucidation of the mechanism is NMR technique. More specifically, an NMR experiment that deals with very small-time scales and is able to detect immediately after addition. In order to suppress the low sensitivity of NMR, in elements of interest i.e. H, C,[208] an experiment has been specially developed called DNP-Dynamic nuclear polarisation- which enhances the polarisation of the electron spins, which in term can be transferred to the surrounding. One of the nuclei to enhance is ^{77}Se, which could prove to crucial in our case (Figure 1.2).

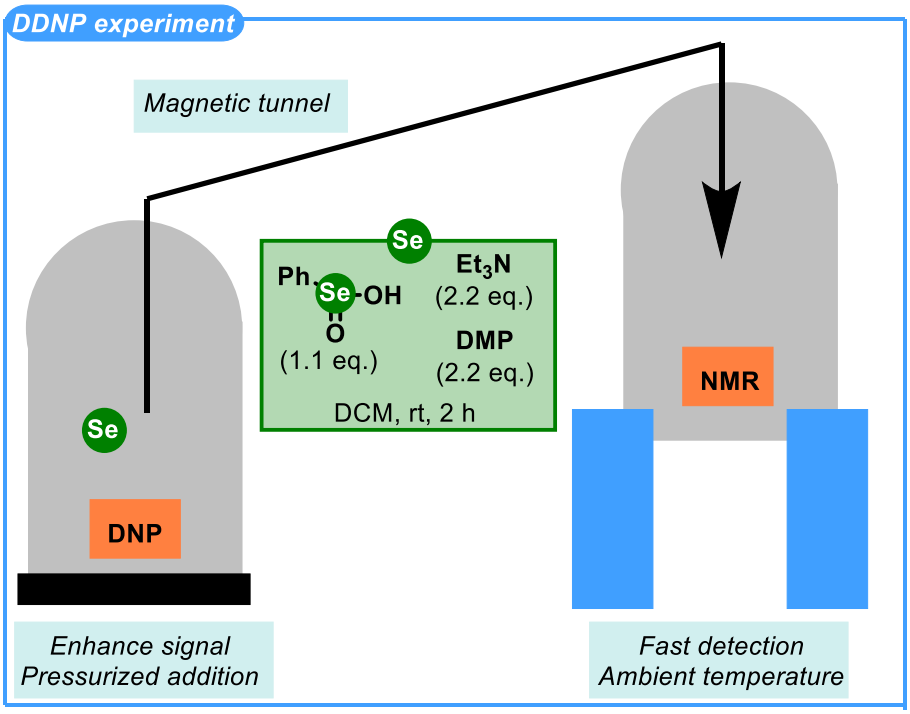


Figure 1.2 – dDNP experiment. Picture has been adapted for better understanding.

Most common solvents that are used in this type of experiment are water and glycerol, although other solvents such as toluene and CCl_4 can also be employed.[209] In general, these experiments could help shed the light on the intermediates involved in this process, and

perhaps, ultimately provide tips and hints that would enable the conceptualisation of a new selenium-based oxidant.

1.3 Synthesis and reactivity of imidinium salts – unexplored charged intermediates

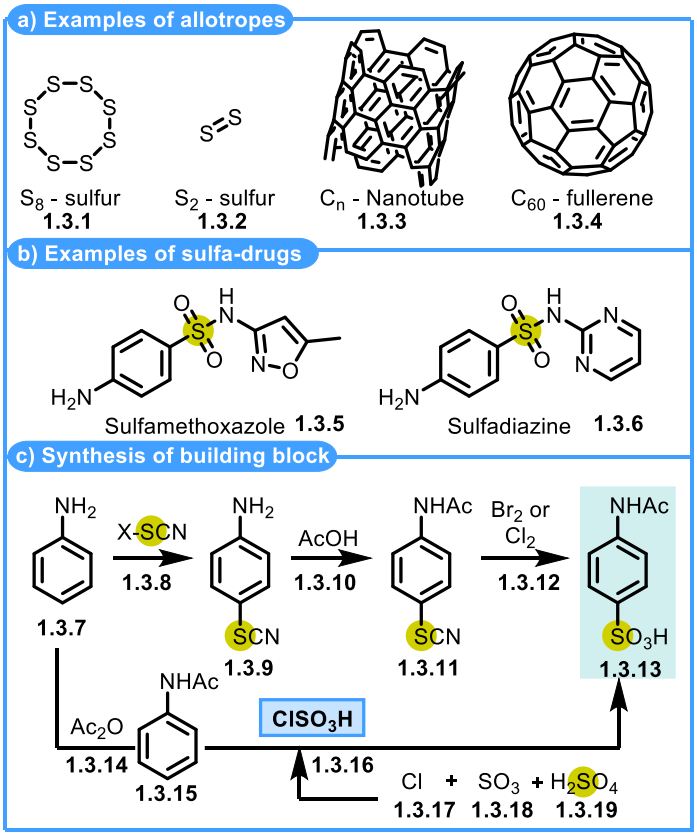
1.3.1 Introduction

1.3.1.1 The unique members of the Chalcogen family

As shown in the previous chapter, the use of elements such as selenium can offer a solution to problems that would otherwise require forcing conditions or the use of metals. Selenium is a chalcogen, a class also including sulfur and tellurium. The versatility of sulfur, for example, can be illustrated by the fact that it has as many as 20 known allotropes,[210] a number only matched by carbon.[211] Allotropes are substances that, despite existing in the same physical state, possess inherently different forms and therefore characteristics,[212] *e.g.* carbon nanotubes[213] and fullerene[214] (**1.3.3**, **1.3.4**, Scheme 1.37a).

1.3.1.2 Sulfur – An important chemical element

Sulfur also serves important roles in pharmaceutical chemistry and is the name-giving constituent of one of the most important drug classes, which paved the way for the antibiotic revolution in the 1930s: sulfa-drugs (Scheme 1.37b).[215] These compounds provided a solution to the surge of bacterial infections around the world, possibly saving millions of lives.[216] During wartime, while pneumonia levels reached a record high, a shortage of sulfa-drugs impaired treatment,[217] as chlorosulfuric acid (**1.3.16**, Scheme 1.37c),[218] required for the synthesis of sulfa-drugs, grew scarce due to its precursors, sulfuric acid (**1.3.19**) or sulfur trioxide (**1.3.18**), being devoted exclusively to war efforts. Consequently, alternative synthetic pathways had to be discovered in order to meet the high demand. Shortly after the war, Shigeru Oae, known for his expertise in the chemistry of sulfur, offered a route[219] bypassing the scarce chlorosulfuric acid (**1.3.16**). Therein, thiocyanation of aniline (**1.3.7**),[220] followed by acetylation (**1.3.9**) and subsequent oxidation with Br_2 or Cl_2 (**1.3.12**, Scheme 1.37c) yields sulfonic acids (**1.3.13**) as precursors for **1.3.5** and **1.3.6** (Scheme 1.37b). However, this process never found large-scale application, as the market equalised after the strenuous war efforts, leading to the resume of sulfuric acid use.[221]



Scheme 1.37 – a) Examples of sulfur and carbon allotropes, b) Examples of early Sulfa-drugs (1.3.5 and 1.3.6), c) Synthesis of the precursor for sulfa-drugs.

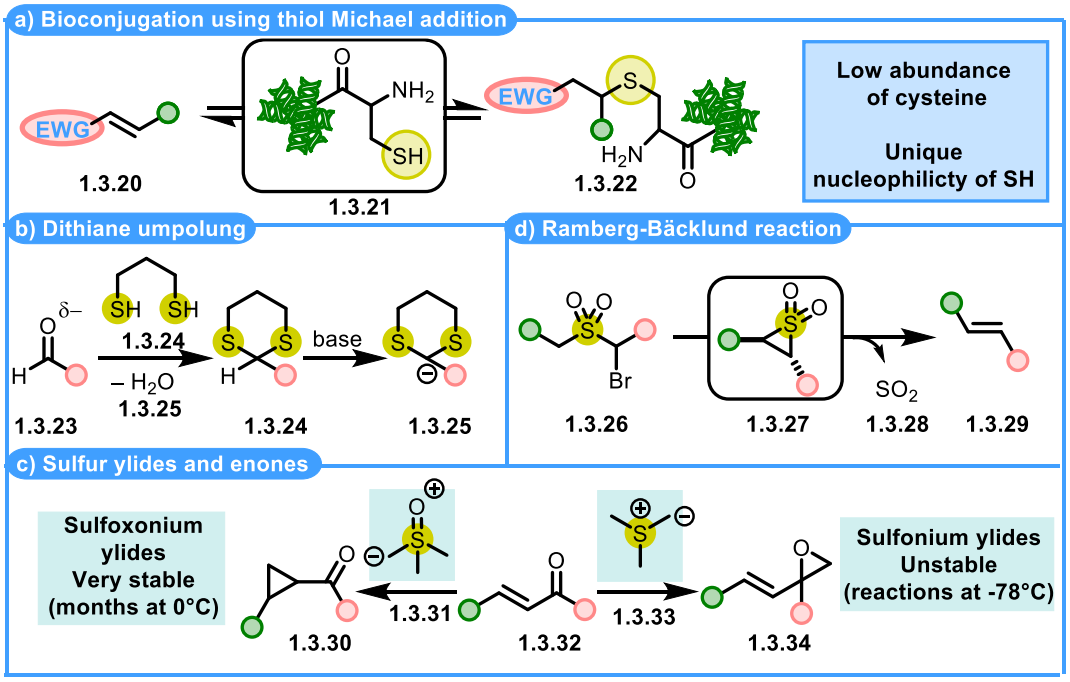
The rich chemistry of sulfur is also illustrated by the wide range of sulfur-related named reactions and reagents associated with highly useful transformations.[222,223]

1.3.1.3 The crucial role of sulfur in chemical biology

Examples of sulfur's rich chemistry include bioconjugation, mostly by Michael addition (or thiol-ene reaction) of cysteine-containing motifs (**1.3.21**, Scheme 1.38a) to unsaturated reagents (**1.3.20**). This is a particularly chemoselective process in which cysteins residues can be functionalised selectively in the presence of all other amino acids (**1.3.22**, Scheme 1.38a).[224–226]

Sulfur also enables reactivity uncommon to any other element. For example, dithianes (**1.3.24**, Scheme 1.38b), containing two C–S bonds to the same carbon atom, played a key role in the development of the concept of *Umpolung*. While initially employing dithianes as protecting groups for aldehydes, Corey and Seebach observed that structures such as **1.3.24** can be deprotonated by strong bases (**1.3.24**, Scheme 1.38b). [227]

The resulting formation of an acyl anion equivalent (*cf.* **1.3.25**)[228] and its application to retrosynthesis and new possible disconnections helped establish the concept of *Umpolung*.



Scheme 1.38 – Sulfur: versatile reactivity, a) Bioconjugation using Michael addition, b) Dithiane Umpolung, c) Ramberg-Bäcklund reaction, d) Divergent reactivity of different sulfur ylides with enones.

1.3.1.4 Uses of high oxidation sulfur species – Sulfones and Ylides

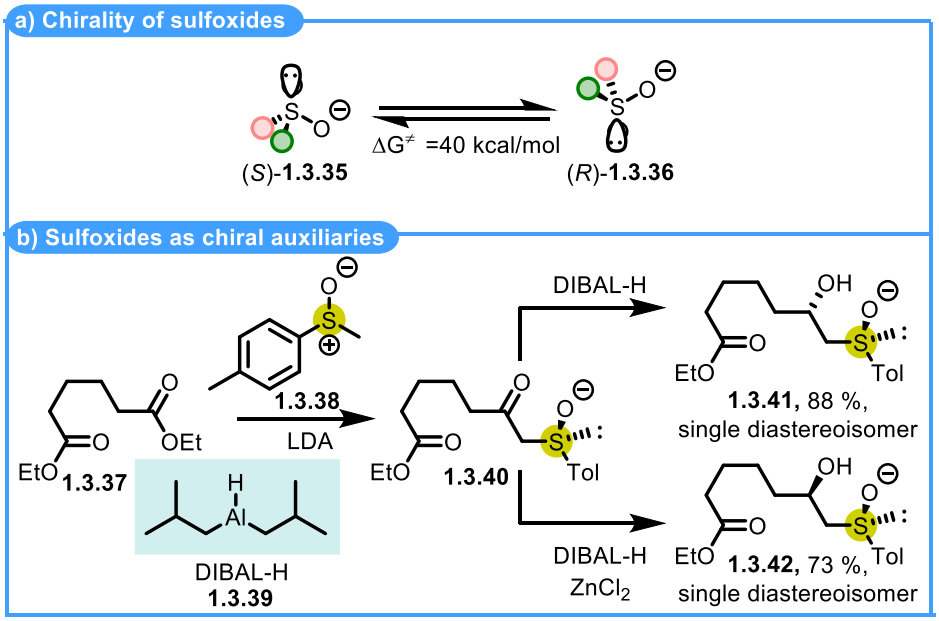
Another representative example of the versatile chemistry of sulfur is the reaction of α,β-unsaturated systems (**1.3.32**, Scheme 1.38c) with sulfur ylides, zwitterionic molecules (**1.3.31** and **1.3.33**) that are able to generate small ring systems.[229] Depending on the nature of the ylide, two distinct reaction pathways dominate: while sulfonium ylides (**1.3.33**) react preferentially with the carbonyl group to form oxiranes (**1.3.34**) in the so-called Johnson–Corey–Chaykovsky reaction, sulfoxonium ylides (**1.3.31**), lead instead to cyclopropanation (**1.3.30**, Scheme 1.38c).[230–234]

The chameleonic nature of sulfur is even more evident when looking at its higher oxidation states.[235] Sulfones, for example, can be engaged in single-electron chemistry as well as in two-electron processes where they can display either nucleophilic or electrophilic behaviour. In the case of α-halo sulfones, (**1.3.26**, Scheme 1.38d) SO_2-extrusion can occur from a three-membered episulfone (**1.3.27**) formed *in situ* under basic conditions affording

the alkene (**1.3.29**).[236] This skeleton editing process, resulting in a formal fragment coupling, is usually referred to as the Ramberg-Bäcklund reaction (Scheme 1.38d).[237–239]

1.3.1.5 Sulfoxides – An important chiral functional group

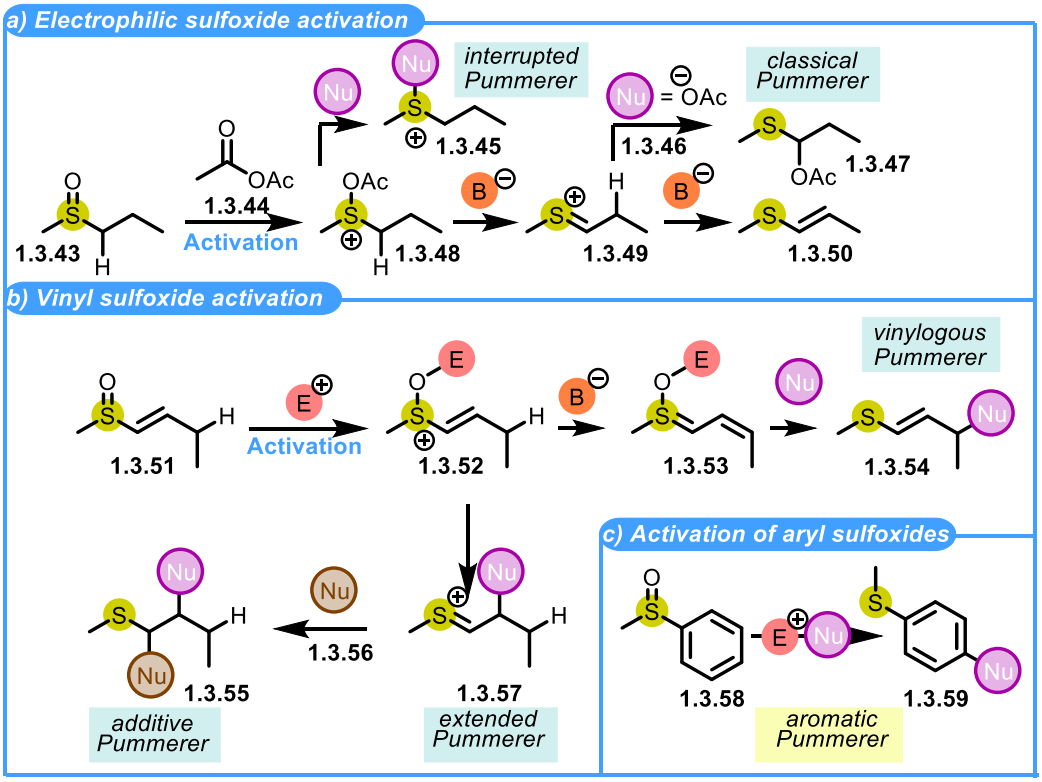
Sulfoxides are a class of compounds encompassing a large span of particularly interesting reactivity. One of the key features of this functional group is the fact that the electron pair on sulfur renders sulfoxides chiral if the two carbon substituents are non-equivalent (**1.3.35** and **1.3.36**, Scheme 1.39a), with high racemisation barriers (Scheme 1.39a).[240–242] One could describe sulfoxides as "chiral carbonyl groups", with the electrophilic sulfur attached to the nucleophilic oxygen (Scheme 1.39a). Sulfoxides have found many applications over the years, one of the most prominent ones being their use as chiral auxiliaries (Scheme 1.39b).[243,244] The diastereoselective reduction of ketone **1.3.37** using DIBAL–H (**1.3.39**) serves as an ideal example of a sulfoxide asserting stereocontrol through coordination, leading to the preferential formation of one product (**1.3.41**, Scheme 1.39b). In contrast, the use of zinc chloride prevents this complexation and, as a result, leads to the opposite diastereoisomer upon reduction (**1.3.42**, Scheme 1.39b).[245]



Scheme 1.39 – Sulfoxide chirality and use of sulfoxides as chiral auxiliaries.

It would be remiss to talk about the reactivity of sulfoxides without highlighting the Pummerer reaction,[246–248] a process involving electrophilic activation of a sulfoxide (Scheme 1.40a). In the classical Pummerer reaction,[249] treatment of a sulfoxide (**1.3.43**) with acetic anhydride (**1.3.44**) leads to the formation of an electrophilic sulfonium

intermediate (**1.3.48**), followed by an elimination event to reveal a thionium species (**1.3.49**), which is now no longer electrophilic at sulfur, but rather at the α-carbon (Scheme 1.40). This thionium ion has two possible, sometimes competing, pathways for further reaction: on the one hand, capture by a nucleophile (such as acetate, **1.3.46**) can lead to the formation of a hemithioacetal species (**1.3.47**), while, on the other hand, an elimination reaction can occur, affording the vinyl sulfide **1.3.50**. Depending on the nature of the sulfonium intermediate (**1.3.48**), divergent reaction pathways are known that lead to a plethora of other pathways Besides the aforementioned addition of a nucleophile α- to the sulfoxide (*cf.* **1.3.47**, Scheme 1.40a), the nucleophile can also add directly onto the sulfur atom **1.3.45**, resulting in a process which has been widely used in combination with transition metals and photocatalysis and is generally referred to as an interrupted Pummerer reaction.[250–252]



Scheme 1.40 – Pummerer reaction and the different pathways. Electrophilic activation of vinyl and aryl sulfoxides and subsequent reactivity.

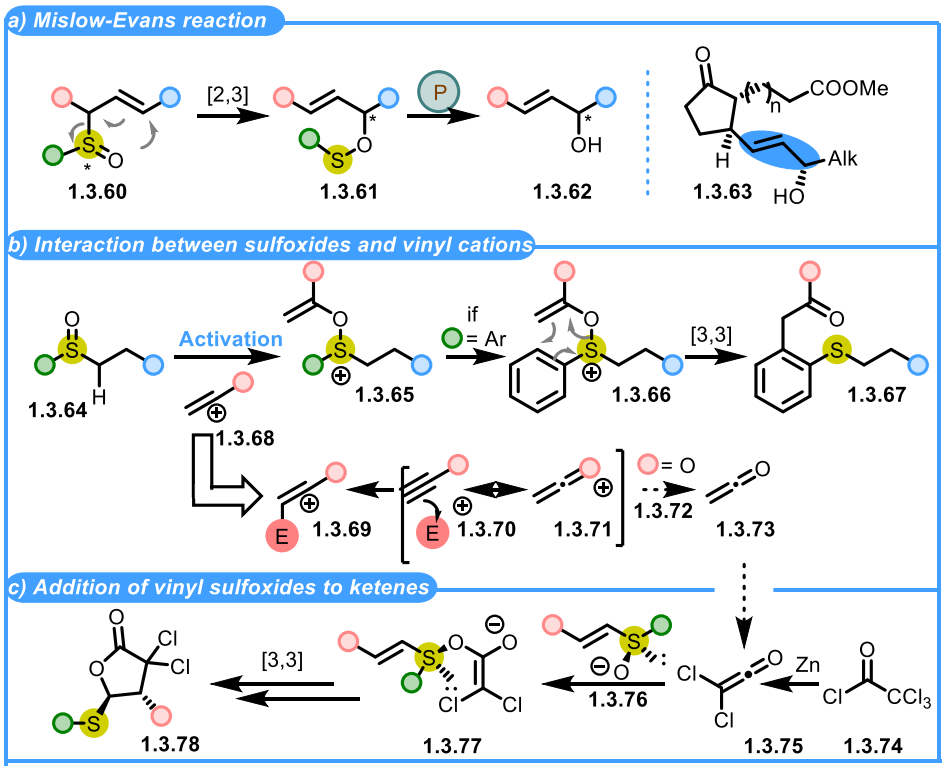
With varying substitution and functionality around the sulfoxide, new reaction pathways also become available. In particular, the use of vinyl sulfoxides (**1.3.51**, Scheme 1.40b) allows once again for diverting modes of the reaction: while the interrupted Pummerer pathway is of course still accessible (not shown), involvement of the carbon–carbon double bond significantly extends the scope of reactivity. For example, attack by a

nucleophile on the double bond initiates a so-called extended Pummerer reaction, in which functionalisation α to sulfur takes place (**1.3.57**, Scheme 1.40b). In fact, the resulting thionium ion **1.3.55** can be captured by another nucleophile (**1.3.56**) in a process referred to as the additive Pummerer reaction (**1.3.55**). A different pathway involves the elimination of the γ-proton from the sulfonium ion **1.3.52**, generating a conjugated thionium ion (**1.3.53**). Subsequent 1,4-addition completes a transformation known as the vinylogous Pummerer reaction (*cf.* **1.3.54**).[253] Related reactions can also be applied to aryl sulfoxides (aromatic Pummerer reaction, **1.3.58**), allowing a direct nucleophilic addition to the ring system with concomitant net reduction of the sulfur atom (**1.3.59**, Scheme 1.40c). [254–256]

1.3.1.6 Sigmatropic rearrangements - An important tool in the organic synthesis toolbox

Sigmatropic rearrangements are a highly coveted way to access complex structures through non-intuitive disconnections.[257] They encompass the formation of a sigma bond, by rupturing of a different sigma bond with concurrent relocation of a π-system in an intramolecular setting.[258,259] Many examples include sulfur-containing reactions, such as textbook rearrangements named Morin-,[260] Doyle–Kirmse,[261–263] Thia-Sommelet-Hauser,[264–266] and the Stevens reaction.[267-268]

A prominent example of sigmatropic rearrangements of sulfoxides was discovered independently by Evans and Mislow (Scheme 1.41a),[269–271] who observed formation of an allylic alcohol (**1.3.62**, revealed following S–O bond cleavage after treatment with a phosphite) from allylic sulfoxides (**1.3.60**) at elevated reaction temperatures (Scheme 1.41a). This seemingly simple transposition, proceeding through a [2,3]-sigmatropic rearrangement, carries an important feature: chirality of the sulfur atom is transferred to the allylic alcohol.[272] This remarkable fact has been repeatedly used in the synthesis of natural products,[273,274] amongst them the prostaglandins (**1.3.63**, Scheme 1.41a).[275]



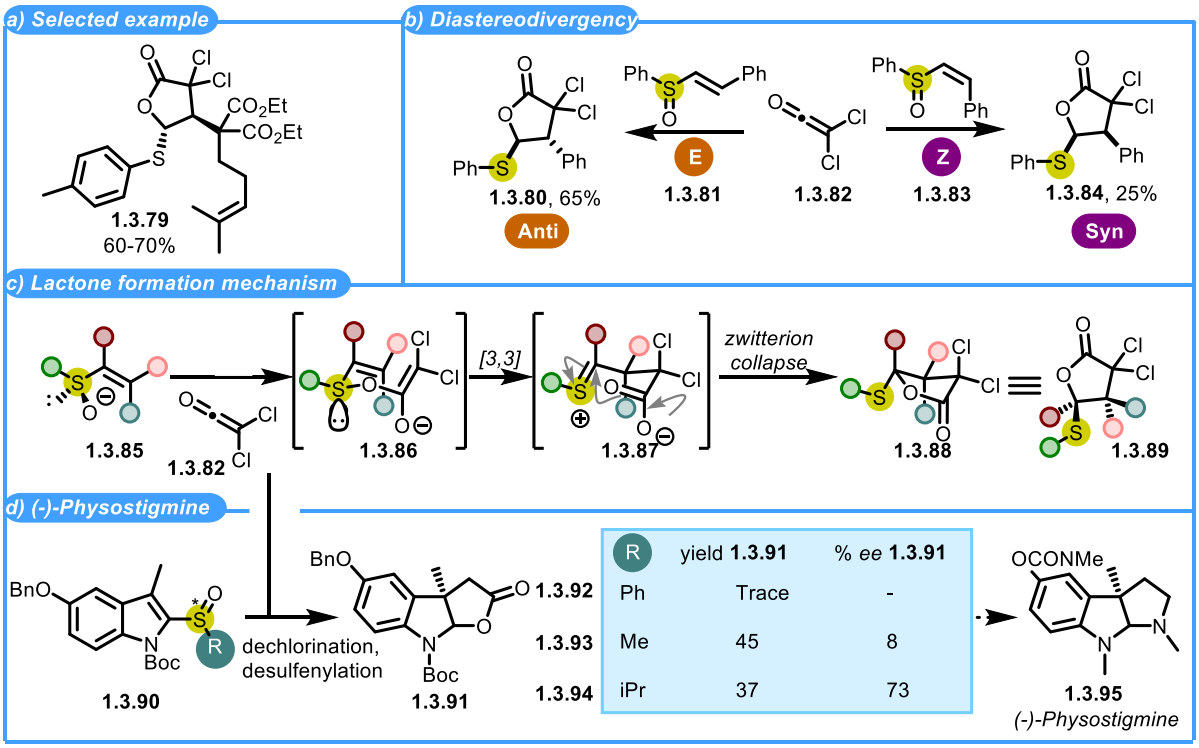
Scheme 1.41 – Sigmatropic rearrangements involving sulfoxides, a) Mislow-Evans reaction and its use in the synthesis of prostaglandins (1.3.63), b) Addition of sulfoxides to vinyl cations, c) Addition of vinyl sulfoxides to ketene derivatives (1.3.75).

1.3.1.7 Addition of sulfoxides to vinyl cations

While Scheme 1.40 has shown that sulfonium intermediates such as **1.3.65** (Scheme 1.41) can be formed by electrophilic activation this can in a broader sense occur by addition of a sulfoxide (**1.3.64**) to a vinylic cation (*vide supra*, **1.3.68**).[276–281] Different methods can be used to generate such vinyl cation species, many of which include activation of alkyne derivatives (**1.3.70**) with strong electrophiles such as gold (I) complexes or Brønsted acids (**1.3.69**, Scheme 1.41b).[282] Upon the formation of the adduct **1.3.65**, different pathways become accessible. In the case of an aryl substituent **1.3.66**, [3,3]-sigmatropic rearrangement can take place, resulting in an *ortho*-functionalisation of the aromatic sulfoxide which itself is reduced to the sulfide in the process (**1.3.67**, Scheme 1.41b).[283]

Ketene derivatives such as **1.3.73** can be employed as vinyl cation surrogates in such a process (Scheme 1.41c). This was first developed by Marino, who utilised the highly reactive dichloroketene (**1.3.75**, *in situ* generated by addition of zinc to trichloroacetyl chloride (**1.3.74**).[284,285] Using an optically pure, geometrically defined vinyl sulfoxide (**1.3.76**), an α,α-dichloro-lactone product was formed with high enantio– and diastereoselectivity (**1.3.78**, Scheme 1.41b and **1.3.79**, Scheme 1.42a). Importantly, it was

found that the geometric and optical configuration of the parent vinyl sulfoxide directly influenced the stereochemical identity of the product (**1.3.80** from **1.3.81** and **1.3.84** from **1.3.83**, Scheme 1.42a).[286–288]



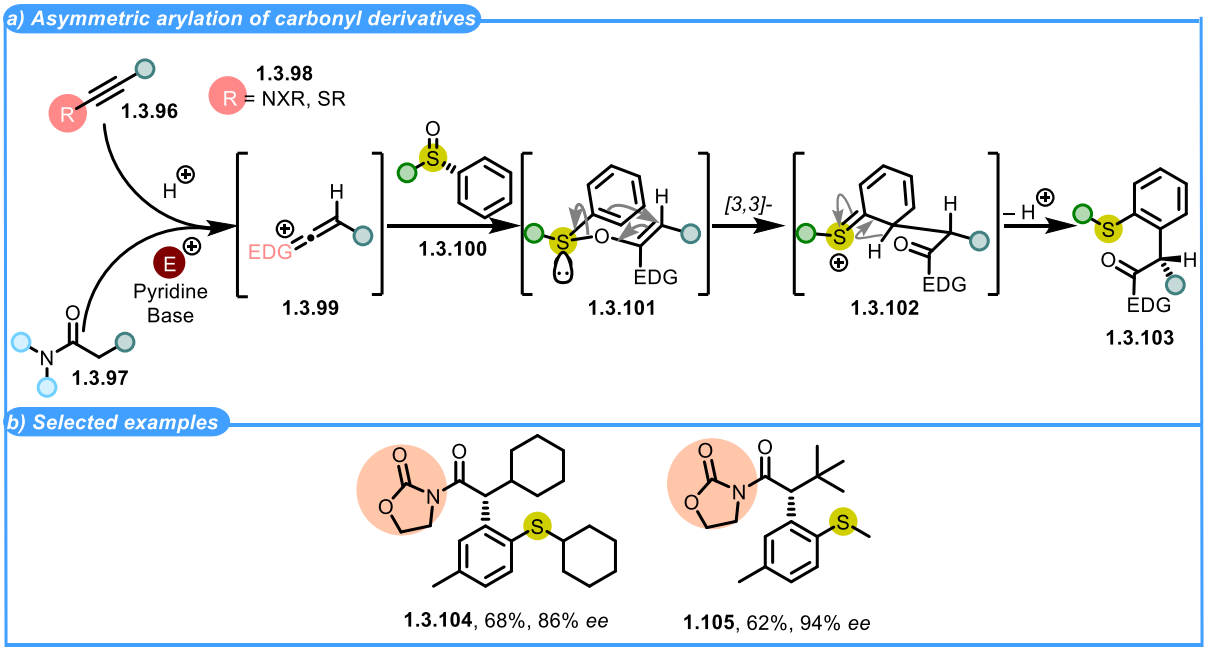
Scheme 1.42 – a) Selected example on the Marino´s lactone formation, b) Diastereodivergency of the method by employing different vinyl sulfoxides, c) mechanism of the lactone formation, d) Efforts towards the total synthesis of Physostigmine (1.3.95).

1.3.1.8 Marino´s studies on the formation of lactones

The chirality transfer observed was explained by a typical chair like transition state (**1.3.86**, Scheme 1.42b). The lone pair on sulfur is preferentially placed in pseudoaxial arrangement. Interestingly, different substituents at sulfur play a crucial role in the outcome of the transformation. In the specific example shown (**1.3.91**, Scheme 1.42d), *en route* to the synthesis of Physostigmine, the methyl sulfoxide moiety (**1.3.93**) gave a satisfying yield of 45% whilst the corresponding phenyl sulfoxide (**1.3.92**) only afforded trace amounts of product (**1.3.91**). In addition, the enantioselectivity was very low both with the methyl and the phenyl analogue (**1.3.92** and **1.3.93**). Finally, the transformation with an isopropyl sulfoxide (**1.3.94**) gave satisfactory results and afforded the product in 73% enantiomeric excess.[289,290] Despite this reaction being applied in multiple total syntheses, its translation

to complex molecules proved difficult, with the reaction conditions, such as temperature and solvents, having to be extensively reoptimised.[288,291]

Moreover, the limitation to the α,α-dichloro substitution pattern on the lactone product meant that extensive manipulations were required in order to obtain the desired valuable scaffolds,[292–294] with different reductive conditions in some cases only affording low yields and leading to side-product formation.[295]



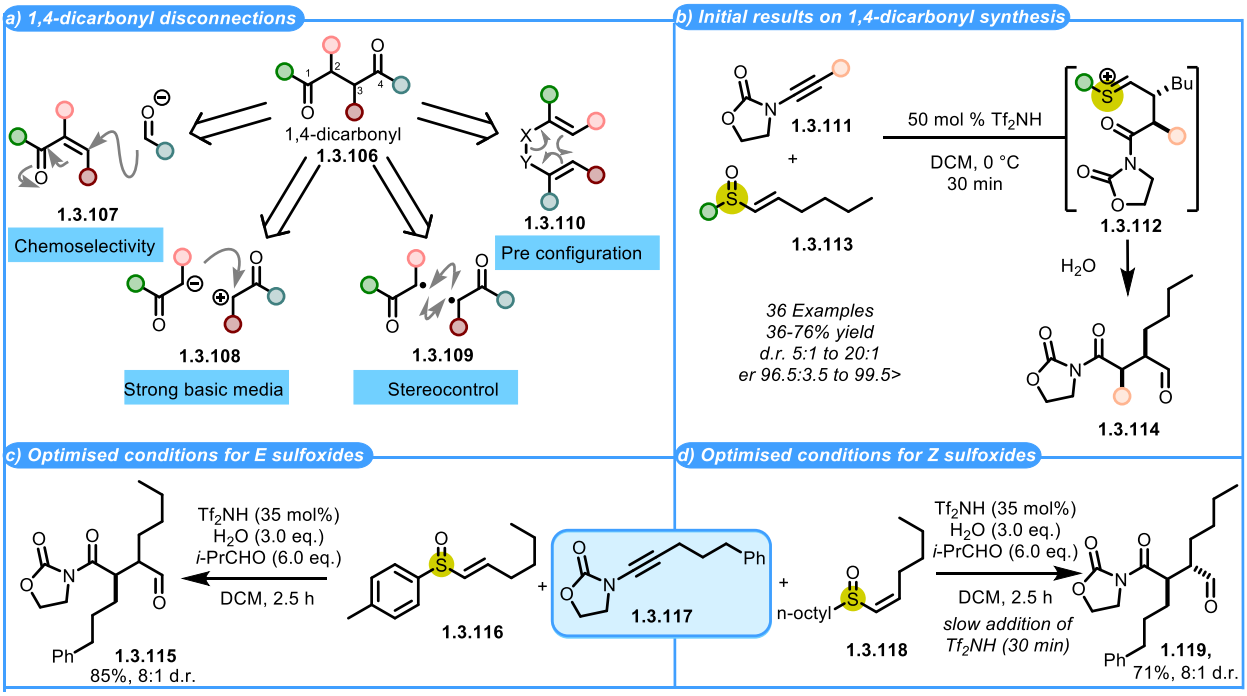
Scheme 1.43 – Asymmetric arylation of alkynes via chirality transfer from aryl sulfoxides.

1.3.1.9 Stereodivergent synthesis of 1,4 dicarbonyl by sulfonium rearrangements

Chronologically, the Maulide group successfully applied a related strategy to aryl sulfoxides and keteniminium ions (**1.3.99**, Scheme 1.43a) derived from amides (**1.3.97**) or activated alkynes (**1.3.96**, Scheme 1.43a). Herein, the use of chiral aryl sulfoxides (**1.3.100**) with activated alkynes (ynamides or thioalkynes **1.3.98**) resulted in α-arylated products (**1.3.103**) with high level of *S*-to-*C* chirality transfer (**1.3.104** and **1.3.105,** Scheme 1.43b).[296]

The 1,4 dicarbonyl motif is one of the most challenging dicarbonyl framework to prepare, due to the "unnatural" disconnections required (**1.3.106**, Scheme 1.44a). Retrosynthetically, any disconnection reveals carbonyl synthons with reversed polarity, e.g. cleavage of the central C–C bond reveals an α-carbonyl cation (**1.3.108**). Different

solutions reported in the literature have struggled to control the stereochemical orientation between the two carbons.[297–300] Evidently, the use of vinyl sulfoxides in this rearrangement reaction (**1.3.110**)[301,302] offered a new potential solution to this longstanding synthetic problem. In 2018, Maulide *et al.* successfully achieved the asymmetric synthesis of 1,4-dicarbonyl derivatives by combining vinyl sulfoxides (**1.3.113**, Scheme 1.44b) with ynamides (**1.3.111**, Scheme 1.44b).[303] Under acidic catalysis, the reaction led to the formation of a wide array of 1,4-dicarbonyl derivatives with excellent levels of ee and dr (**1.3.114**). Importantly, complete chirality transfer from sulfur to carbon was observed in all cases.

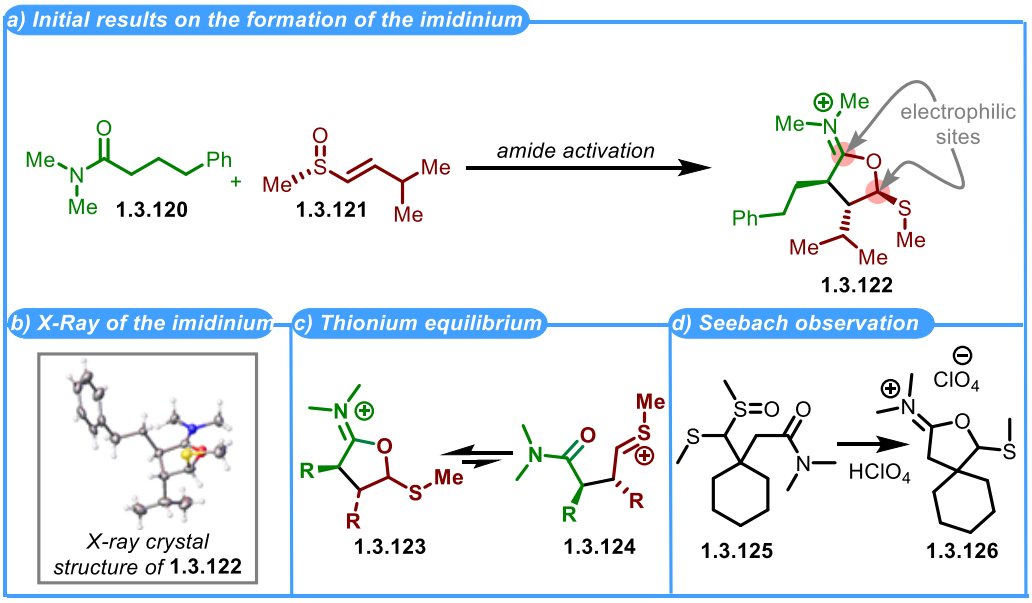


Scheme 1.44 – a) Disconnections towards 1,4 dicarbonyl compounds, b) Initial results on the synthesis of 1,4 dicarbonyls, c) and d) Optimisation condtions depending on the configuration of the sulfoxide in the synthesis of 1,4 dicarbonyls.

Notably, *p*-tolyl moiety was the preferred substituent on sulfur for *E*-vinyl sulfoxides (**1.3.116**, Scheme 1.44c), providing good diastereoselectivities (8:1 d.r. for **1.3.115,** Scheme 1.44c), whilst in the case of *Z*-vinyl sulfoxides, the preferred sulfur substituent was an *n*-octyl group (*cf.* **1.3.118**, Scheme 1.44d).

1.3.1.10 Vinyl sulfoxide in combination with activated amides

The successful results on the use of vinyl sulfoxides in combination with activated ynamides prompted us to test the reaction with amides instead. Under standard conditions, the major product was assigned to be **1.3.122** (Scheme 1.45a), from 4 different diastereoisomers. This appears to result from an internally captured thionium intermediate (**1.3.123**, Scheme 1.45c). We will refer to these species hereinafter as imidinium ions. The structure of **1.3.122** was further confirmed by X-ray analysis (Scheme 1.45b), revealing that the major diastereomer has an *anti-anti* configuration on the three newly formed stereogenic centres. However, after purification by column chromatography, only two out of four possible diastereomers were isolated, which suggests an equilibrium between the closed imidinium salt (**1.3.123**, Scheme 1.45b) and its open form **1.3.124** (Scheme 1.45d), resulting in an epimerisation of the sulfur-bearing stereocenter. To the best of our knowledge, such a species was only ever observed once in the literature, namely by Seebach *et al.* (**1.3.126**, Scheme 1.45b), but no study about its stability or reactivity has been reported.[304]



Scheme 1.45 – a) Initial studies on the formation of Imidinium salts, b) X-Ray of the proposed imidinium salt (1.3.122), c) equilibrium of the thionium species, d) Seebach's observation

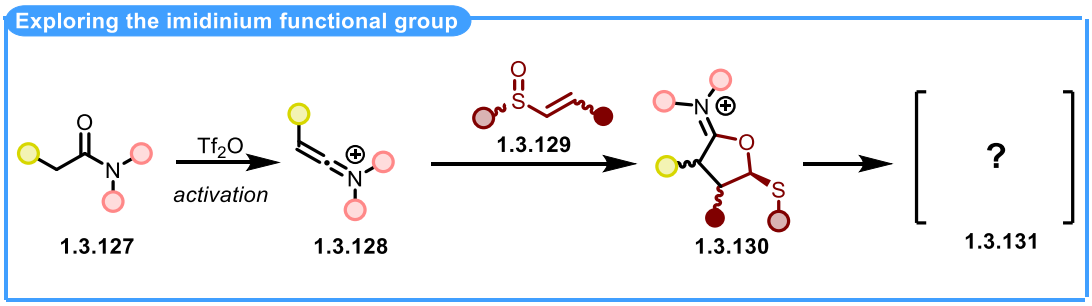
The discovery of this intriguing imidinium species prompted us therefore to investigate it further, with hopes of fully harnessing its synthetic potential.

1.3.2 Objectives

The aim of this project can be divided into two sub-goals. First, we were eager to explore and optimise the formation of the imidinium ion.

Second, we wanted to investigate the nature of the newly found imidinium ion including a closer understanding of its reactivity in different chemical environments. This would include attempts to convert these imidinium intermediates into e.g. aldehydes and lactones (Scheme 1.46).

This work was performed in collaboration with by Dr. Immo Klose, Dr. Bruna Simoes Martins, Dr. Simone Placidi and Laurin Pollesböck.



Scheme 1.46 – Studies on the formation and reactivity of the imidinium ion (1.3.130).

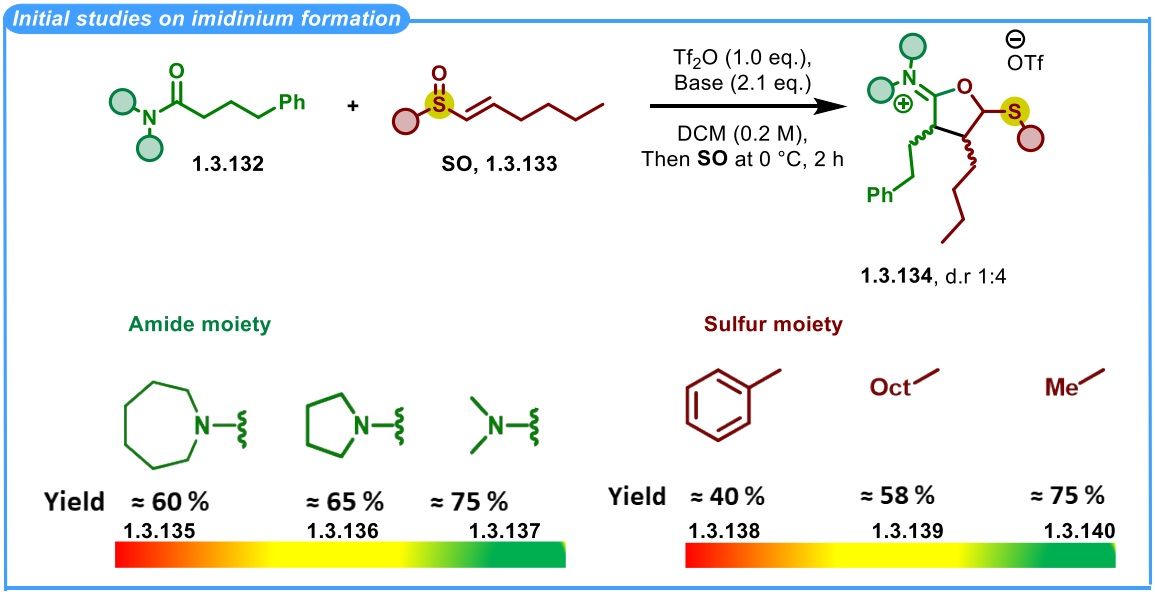
1.3.3 Results and Discussion

1.3.3.1 Initial studies on the formation of imidinium salts

Some initial caveats should be outlined at the start of this section. Generally, the diastereomeric ratio was determined by ^{1}HNMR. However, due to the nature of the products (4 different stereoisomers), occasionally the complexity of the spectra prevented us from assigning all of the stereoisomers. In addition, often times the minor diastereomers overlapped with other signals in the ^{1}HNMR spectrum thus complicating accurate determination of the d.r. We could putatively assign the different diastereoisomers by literature comparison and by isolation of the two major diastereoisomers.

In regard to the purification process, normal flash chromatography afforded the desired imidinium salt after a solvent switch from a conventional ethyl acetate/heptane mixture to acetone/heptane. While crude mixtures were soluble in halogenated solvents such as deuterated chloroform, after purification, their solubility in these solvents decreases significantly, which is why their NMR spectra were recorded in deuterated acetonitrile or acetone. With protic solvents such as deuterated water or methanol, decomposition or non-selective product formation was observed. A commonly found impurity during purification were pyridinium salts that coelute with the desired imidinium salts.

In our initial attempts of optimisation, we probed different substrates – amides and vinyl sulfoxides to deduce advantageous substitution patterns for the optimisation of yield and diastereoselectivity (Scheme 1.47). From the different amides at our disposal, we focused on the influence of the nitrogen moieties. Pyrrolidine (**1.3.135**) and azepane (**1.3.136**) gave similar results whilst a substantial increase in yield was observed when using the dimethyl amide (**1.3.137**, Scheme 1.47). On the side of the vinyl sulfoxides, the yield was also highly dependent on the sulfur substituent with the methyl sulfoxide **1.3.140** giving the best results compared to the respective *p*-tolyl (**1.3.138**) and *n*-octyl sulfoxides (**1.3.139**).



Scheme 1.47 – Initial substrate optimisation on the formation of imidinium salt (1.3.134).

1.3.3.2 Optimisation studies on the formation of the imidinium ion

Optimisation of amide activation processes usually includes an investigation of different halo-pyridine bases. An initial screening did not show any particular outliers – most yields remained fairly constant, only marginally higher yields were observed in the case of 2-I-Py (71 %, entry 1, Table 1.3).

An important parameter to describe this reaction is the ratio (A+B)/(C+D) (Table 1.3), which accurately portrays the ratio of diastereoisomers formed along the C–C bond forming event. While only moderate diastereoselectivity was observed for this reaction, we focused on improving this aspect of the transformation. Different spectator moieties at the sulfur atom of the vinyl sulfoxide partner, showed no significant change in yield and diastereoselectivity (Table 1.3, Entry 2-4). On the other hand, temperature revealed to play a key role in the transformation (Table 1.3, Entry 5-8), with -78 °C providing a considerable increase in the stereochemical outcome. The best conditions were found when 2-F-Py was used, generating the desired imidinium intermediate in high diastereoselectivity and yield. (Table 1.3, Entry 5).

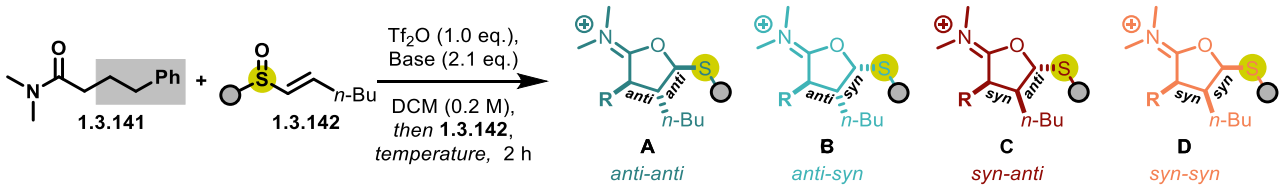
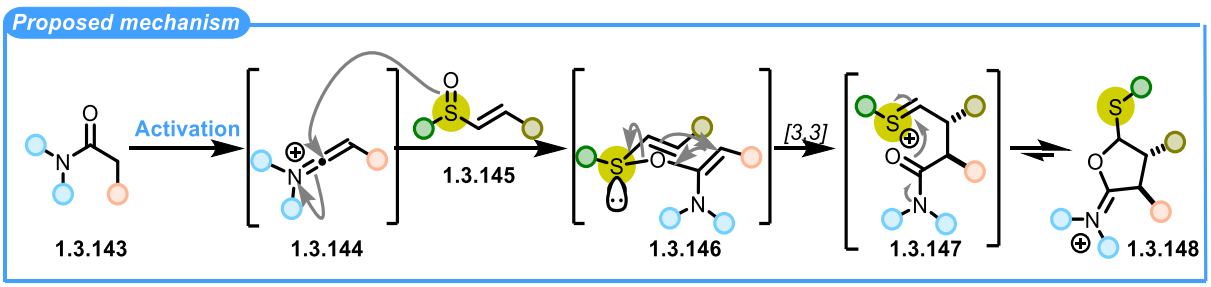


Table 1.3 – Optimisation table for the diastereomeric formation of imidinium ion. [a]Module of the ratio

Entry	Temperature °C	Base	Sulfoxide	double bond geometry	NMR yield	diasteromeric ratio *absolute*	(A+B)/(C+D)
1	0	2-I-Py	Me	*E*	71 %	71 : 17	3.7
2	0	2-I-Py	*n*-Oct	*E*	61 %	68 : 19	3.3
3	0	2-I-Py	*n*-Oct	*Z*	58 %	17 : 68 : 13	[4.3][a]
4	0	2-F-Py	Me	*E*	62 %	71 : 6 : 20	2.8
5	–78	2-F-Py	Me	*E*	85 %	83 : 9	13.4
6	–78	2-F-Py	*p*-Tolyl	*E*	65 %	82 : 7 : 7	8.9
7	–78	2-I-Py	Me	*E*	56 %	77 : 12	[6.1[a]]
8	–78	2-F-Py	Me	*Z*	76 %	72 : 18	8.2

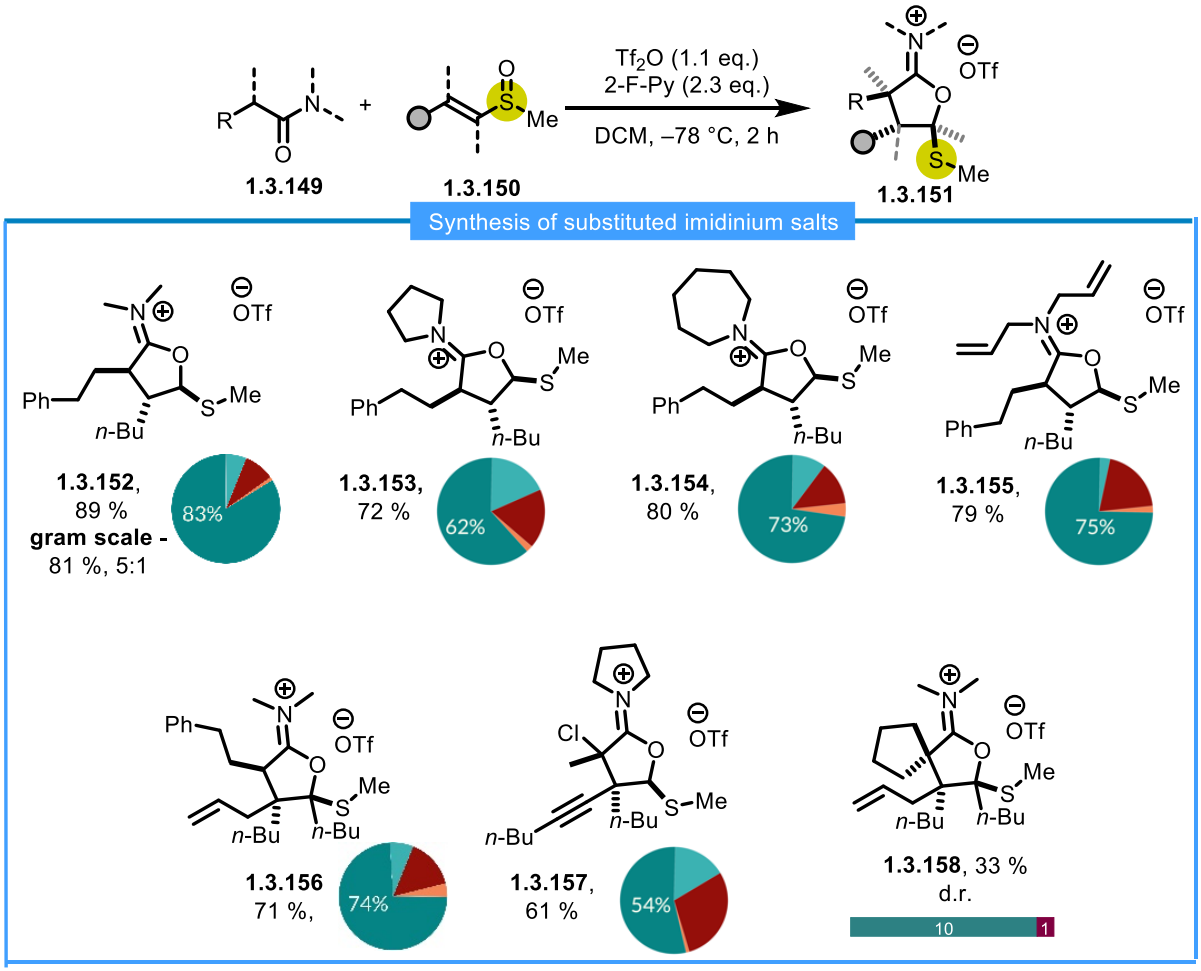
In regards to the mechanism of the transformation, we postulate that it proceeds analogously to the one proposed in the synthesis of 1,4 dicarbonyls *via* a chair-like transition state (intermediate **1.3.146**, Scheme 1.48), with the lone pair on sulfur occupying the pseudoaxial orientation (Scheme 1.48). After [3,3]-sigmatropic rearrangement, the third stereo-centre is formed during intramolecular capture by the nucleophilic amide to generate the imidinium salt **1.3.148**. Additionally, we propose that the imidinium **1.3.148** can be in equilibrium with the thionium species (**1.3.147**) under certain conditions such as higher temperatures, polar solvents or purification on silica gel.



Scheme 1.48 – Proposed mechanism of the imidinium salt formation (1.3.148) and subsequent stability.

1.3.3.3 Scope of the formation of imidinium salts

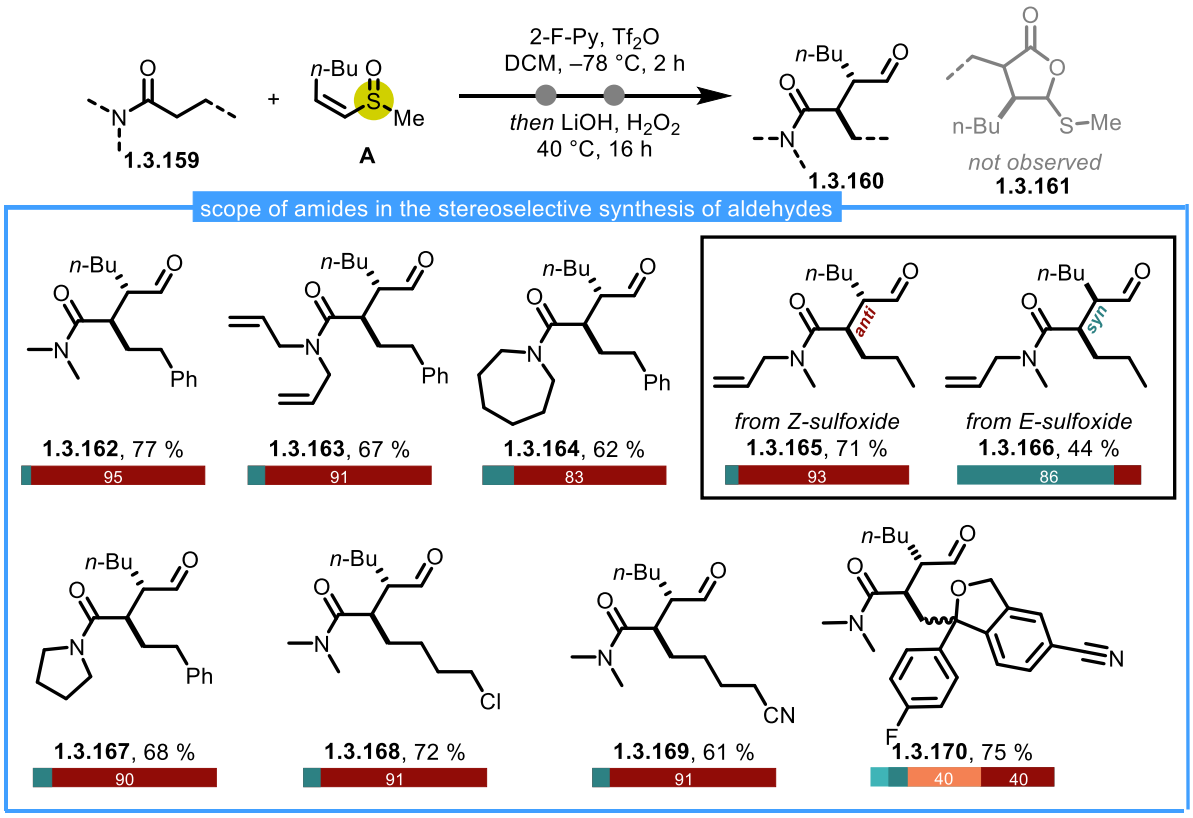
Then we moved into exploring the scope of this transformation transformation (Scheme 1.49). Several amides acyclic (**1.3.155**) and cyclic derivatives (**1.3.153** and **1.3.154**) were successfully coupled with different *E* sulfoxides to afford the desired imidinium ion, with good diastereoselectivities. Using the dimethyl substituted amide, we that the reaction was amenable to gram scale (**1.3.152**, Scheme 1.49). Substituted vinyl sulfoxides, including β,β-disubstituted also lead to good results (**1.3.156**). The coupling of tetrasubstituted reactants with a α-chloro amide gave rise to an imidinium ion bearing adjacent quaternary stereocenters (**1.3.157**), in one step, albeit with low diastereoselectivty. Finally, the combination of a cyclopentyl amide and a tetrasubstituted vinyl sulfoxide led to exhaustively substituted imidinium species **1.3.158**, carrying three contiguous (two of which all-carbon) quaternary centres, in moderate yield. When using branched amides, dehydrogenation was found to be the main by-product.[305,306]



Scheme 1.49 – Scope of imidinium salts using different substituted amides and vinyl sulfoxides.

1.3.3.4 Functionalisation of the imidinium salt - Basic oxidative work-up for the synthesis of amidoaldehydes

Subsequently, we then turned our attention towards the reactivity of the imidinium species. Our initial attempts to hydrolyse the intermediate, resulted in two different products, a sulfenyl lactone **1.3.160** and the aldehyde **1.3.161** (Scheme 1.50). A wide range of different conditions were tried, including using a long list of buffers, acids and bases, and water surrogates,[307–309] however, all of these conditions led to mixtures of the two products. After several attempts to selectively afford one of the products, we observed that lithium hydroxide in conjunction with hydrogen peroxide – commonly used conditions to remove the chiral auxiliary oxazolidinone – resulted in the selective formation of 1,4-amidoaldehydes in good yields.



Scheme 1.50 – Scope using different sulfoxides to afford amidoaldehydes derived from basic workup.

In this transformation, the use of *Z*-vinyl sulfoxides afforded significantly better yields and diastereomeric values. Since the optimised reaction conditions require elevated temperatures, we hypothesise that *trans*-1,4 dicarbonyl compounds are thermodynamically more stable, hence preferentially formed. We next focussed on exploring the scope of this reaction with a wide range of cyclic (**1.3.164** and **1.3.167,** Scheme 1.50) and acyclic amides

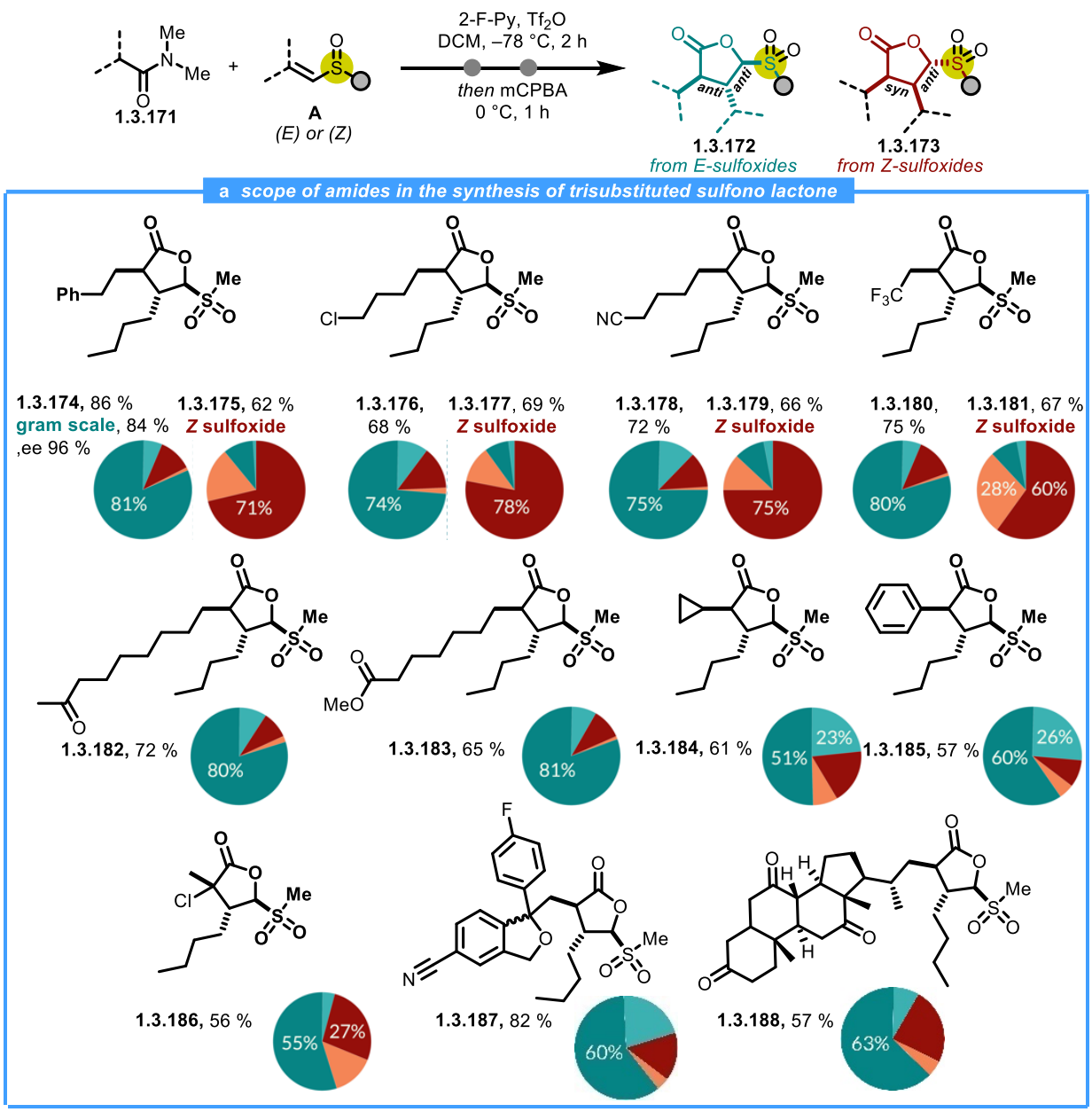
(**1.3.162** and **1.3.163**) which all led to the expected product in high yields (Scheme 1.50). Sensitive functional groups such as a terminal chloride (**1.3.168**) and a nitrile (**1.3.169**) did not influence the reaction outcome, even at elevated temperatures. Drug-like amide derived from citalopram® was also transformed into its aldehyde derivative (**1.3.170**), in a reaction that resembles the result of a coupling to the drug scaffold. The use of *N*-allylmethyl amide (**1.3.165**) gave excellent diastereomeric ratios with *Z*-vinyl sulfoxide, whilst the *E*-vinyl sulfoxide, gave the respective *syn*-aldehyde albeit in lower yields and slightly decrease diastereomeric ratio (**1.3.166**, Scheme 1.50).

1.3.3.5 Functionalisation of the imidinium salt – acidic oxidative work-up for the synthesis of sulfonolactones

Alternatively, we found that acidic oxidative conditions cleanly converted the imidinium salts into the corresponding sulfonolactones **1.3.172** and **1.3.173** (Scheme 1.51). The reagent of choice was *m*CPBA which contains water in its commercial form, therefore both mediating the hydrolysis and concomitantly oxidising the intermediate. This transformation was found to be amenable to gram scale, resulting in high isolated yields of the sulfonolactone intermediate (**1.3.174**, 84 %, Scheme 1.51).

We were also eager to test whether sulfur to carbon chirality transfer was possible. By employing a chiral *E*-vinyl sulfoxide, the sulfonolactone (**1.3.174**, Scheme 1.51) was formed with near perfect enantiomeric excess (97 % *ee*), thus showcasing one key feature of the method – control over the absolute of relative stereo outcome.

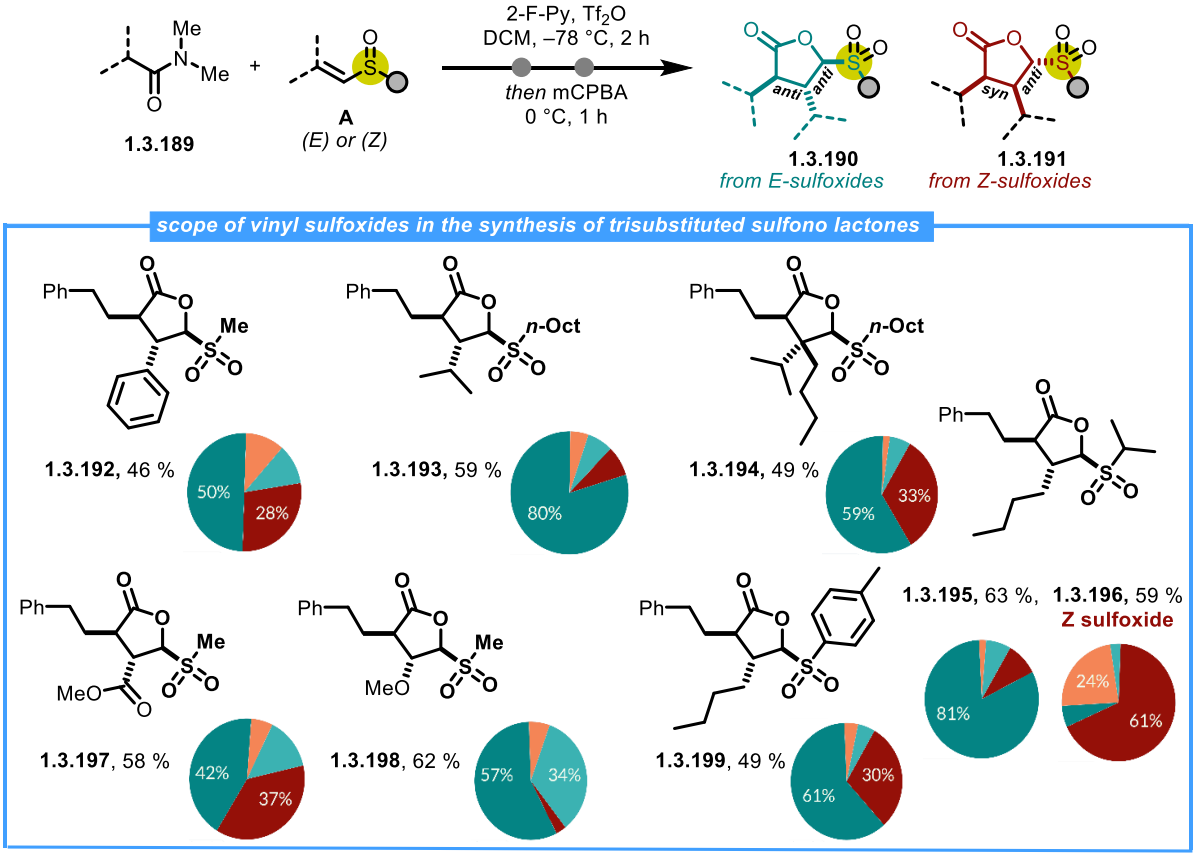
Sensitive synthetic handles such as alkyl chlorides (**1.3.176**, Scheme 1.51), ketones (**1.3.182**), and esters (**1.3.183**) were preserved and the respective products formed with high diastereomeric ratios. The use of both *E*- and *Z*-isomers of the vinyl sulfoxide resulted in complementary pairs of diastereomers with slightly inferior yields in the case of *Z*-vinyl sulfoxides (**1.3.175**, **1.3.177**, **1.3.179** and **1.3.181**). α-Branched amides were also found to be amenable to oxidative hydrolysis, resulting in the formation of branched lactone **1.3.186**. Dehydrocholic acid (**1.3.188**) and citalopram scaffolds (**1.3.187,** Scheme 1.51) were also successfully decorated with the sulfonolactone moiety in good yields but moderate diastereomeric values.



Scheme 1.51 – Scope of sulfonal lactones obtained after oxidative workup (mCPBA).

Exploring the scope of vinyl sulfoxides, different sterically demanding moieties such as a phenyl (*cf.* **1.3.192**, Scheme Scheme 1.52) or an isopropyl moiety (**1.3.193**) could be attached to the vinyl sulfoxide to afford the respective lactones in good yields. In a similar fashion, all-carbon quaternary centres could also be generated by using a β,β-disubstituted vinyl sulfoxide (*cf.* **1.3.194**). Gratifyingly, even challenging substrates that contain strongly electron-donating (**1.3.198**) or -withdrawing substituents (**1.3.197**), gave the expected product with no observed by-products. Different sulfoxide moieties such as the tolyl– (*cf.* **1.3.199**) or isopropyl sulfoxide (*cf.* **1.3.195**) also resulted in the respective imidinium salts with good diastereomeric ratios. The latter was also efficient when using

the respective *Z*-isomer to afford the product with opposite configuration (**1.3.196**) which was only slightly inferior compared to the reaction with the corresponding methyl sulfoxide (**1.3.175**, Scheme 1.51).[310–312]



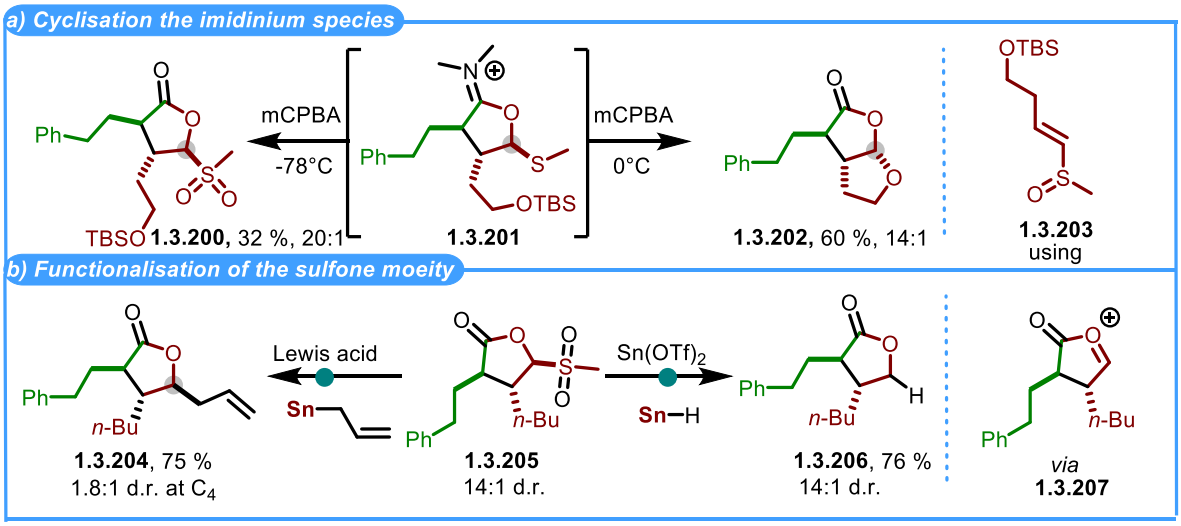
Scheme 1.52 – Scope of sulfono lactones derived from different sulfoxides after oxidative workup (mCPBA).

Using a vinyl sulfoxide bearing a silyl protected alcohol moiety (**1.3.203**, Scheme 1.53a), we unexpectedly observed the formation of a cyclic ether **1.3.202**. in which the sulfenyl moiety was cleaved after treatment with *m*CPBA. Interestingly, when the oxidation was conducted at lower temperatures (–78 °C), the initially anticipated sulfono lactone was the major product (**1.3.200**), suggesting that cyclisation to **1.3.202** only occurs at higher temperatures.

1.3.3.6 Functionalisation of sulfono-lactones

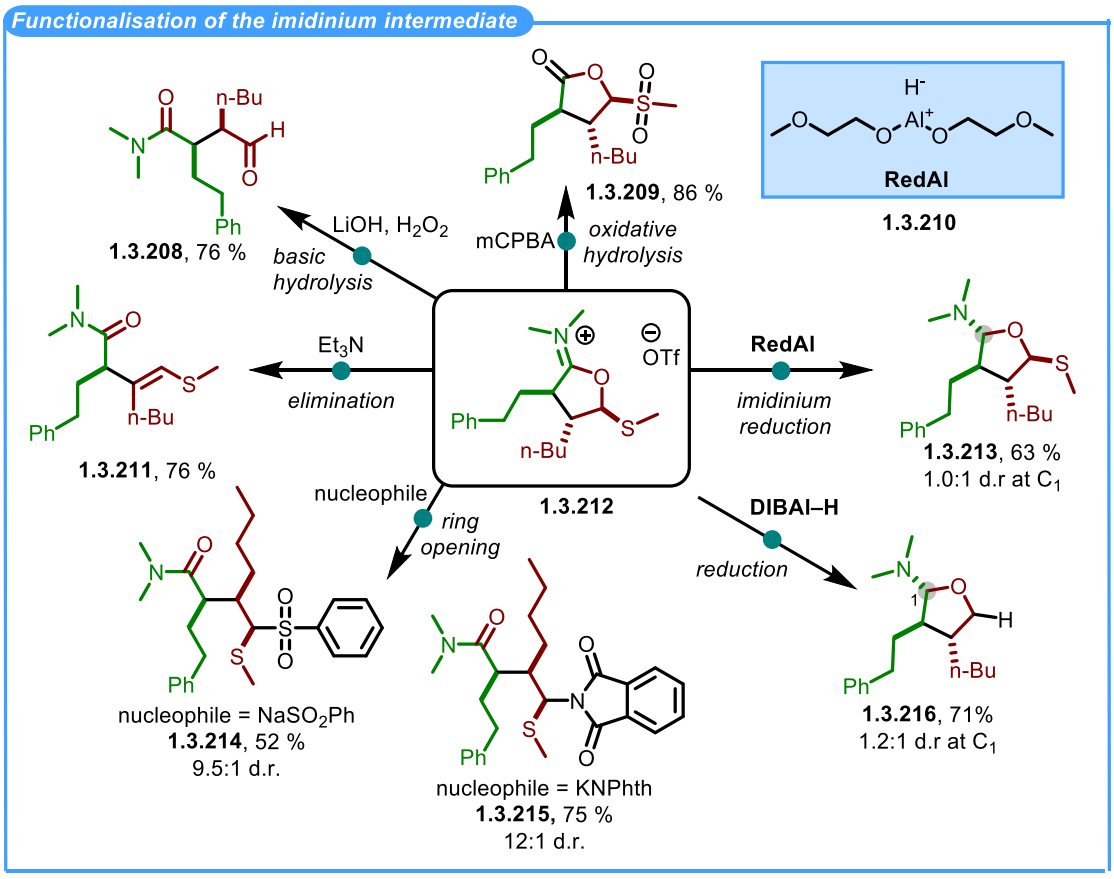
To demonstrate the utility of the sulfone moiety, we decided to displace it using different nucleophiles (Scheme 1.53b). The use of tin triflate ($SnOTf_2$) as a Lewis acid in combination with allyl nucleophiles afforded the substituted lactone **1.3.204**. with moderate diastereoselectivity likely *via* a cationic intermediate (**1.3.207**). Reductive cleavage of the sulfone moiety with tributyl tin hydride led to a single product (**1.3.206**). This lends support

to our proposal diastereometic ratio of the starting material, due to the exact diastereomeric ratio being found after the reaction (Scheme 1.53b).



Scheme 1.53 – a) Divergent conditions for imidinium cyclisation; b) Functionalisation of sulfono lactones with Allyltributylstannane

1.3.3.7 Versatility of the imidinium intermediate - An array of possibilities



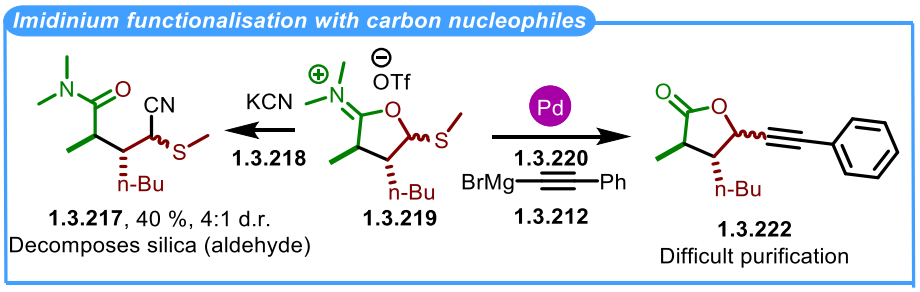
Scheme 1.54 – Functionalisation of the imidinium intermediate

We also had an interest in exploring different reductive protocols. In the event, we found that the use of Red-Al led to a partial reduction of the intermediate and afforded a cyclic hemiaminal **1.3.213**, still carrying the native sulfenyl moiety. Conversely, employing DIBAL as the reducing agent additionally excised the sulfur appendage, delivering hemiaminal **1.3.216** in 71 % yield (Scheme 1.54).

The direct addition of nucleophiles to the imidinium ion has a high potential for increasing molecular complexity. A substitution reaction that would trigger a ring-opening in analogy to the observed aldehydes with basic H_2O_2 would lead to three contiguous stereogenic centres in a linear product. Indeed, nucleophiles such as phthalimide and sulfinate salts cleanly opened the imidinium species to the corresponding amide derivatives **1.3.215** and **1.3.214** respectively with excellent diastereoselectivities.

1.3.3.8 Miscellaneous results on the functionalisation of the imidinium intermediate

On the other hand, some preliminary results during the functionalisation of the imidinium salts deserves additional efforts. Various carbon nucleophiles were used in combination with the imidinium ion, for one of which, namely potassium cyanide, we observed that the addition product **1.3.217** decomposed during flash chromatography (Scheme 1.55). Efforts could be focused on purifying this intermediate with deactivating silica or alumina to potentially avoid its decomposition. Alternatively, we attempted to directly perform a cross-coupling reaction on the imidinium ion (**1.3.219**) using palladium catalysis and an alkynyl Grignard reagent **1.3.212**. The product of sulfur displacement by the Grignard reagent was detected by mass spectroscopy (**1.3.222**), however, purification proved challenging and the desired product was not isolated. The direct use of these charged intermediates in cross-coupling reactions would enable an easy way to introduce complexity in these systems and in turn bringing it closer to accessing chemical space of biologically relevant molecules.



Scheme 1.55 – Functionalisation of the imidinium intermediate using carbon nucleophiles.

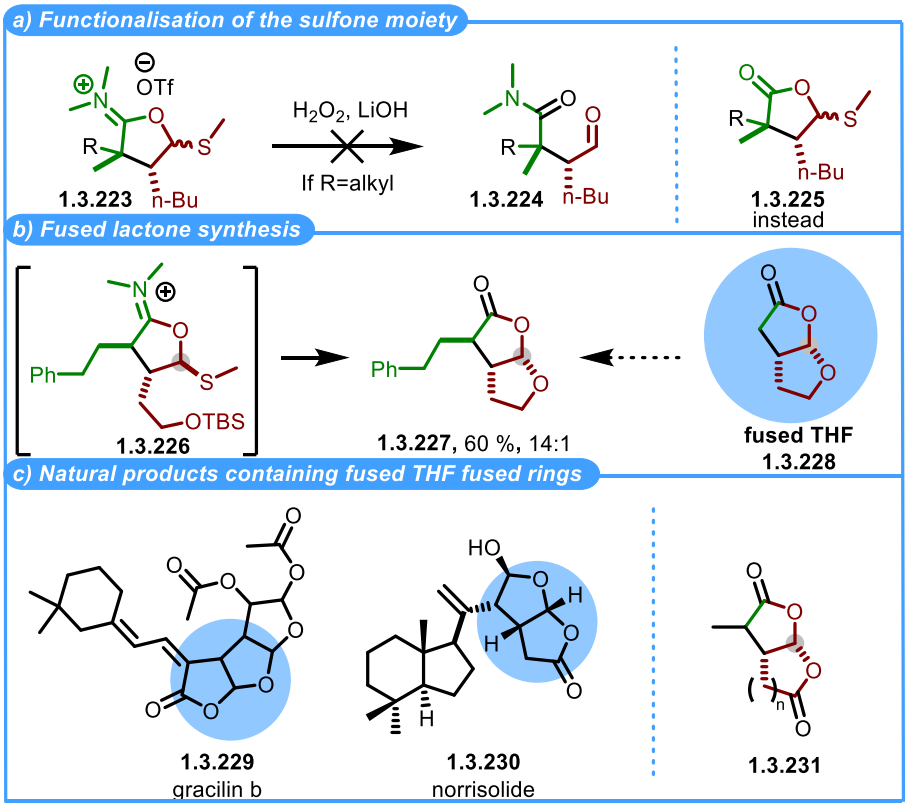
1.3.4 Conclusion

We have successfully achieved most of the aims of this project. The serendipitously observed imidinium intermediate was successfully transformed into valuable 1,4-aldehydes with high diastereoselectivities. On the other hand, valuable sulfono lactones were obtained in high yields from *E*-vinyl sulfoxides as demonstrated by a large scope of highly substituted products.

With this work, we have showcased the high synthetic applicability of the imidinium ion and believe it might find utility in the context of natural product synthesis of congested carbon frameworks.

1.3.5 Future prospects

We came across various interesting observations that are worth a closer look, potentially leading to new projects. One of these would be the synthesis of sterically congested sulfenyl lactones from branched amides (**1.3.225**, Scheme 1.56). Using basic oxidative conditions, the expected aldehyde **1.3.224** was not formed, but instead the sulfenyl lactone **1.3.225** was generated as major product without oxidation at sulfur atom (Scheme 1.56a). The fully substituted α-position of the carbonyl is crucial as it provides an opportunity to greatly expand the accessible molecular complexity. Thus far, a quaternary centre in the α-position of the carbonyl is not accessible by other methods that utilise keteniminium ions.



Scheme 1.56 – Future projects revolving around C-C bond formation. Potential natural products that could be synthesised with this methodology.

As it was briefly mentioned before, a key stepping stone for this methodology would be its implementation in the synthesis of a natural products. One particular case which highlights this possibility is the cyclisation when using tethered alcohol on the sulfoxide moiety, which upon oxidation, cyclizes to afford the fused lactone (**1.3.227**, Scheme 1.56b). Such motifs, more specifically the THF-fused γ-lactone (**1.3.228**), has been found in several natural occurring products (**1.3.229** and **1.3.230**, Scheme 1.56c) and is recognised as a

privileged scaffold.[313–315] Importantly, its synthesis is known to be challenging.[316–319] A suitable combination of vinyl sulfoxides could swiftly construct such promising scaffolds. Last but not least, we can also envision other remote groups undergoing said cyclisation – generating different motifs and ring sizes (**1.3.231**, Scheme 1.56).

2 Amine synthesis from alkenes – Acid mediated hydroaminomethylenation and hydroaminoalkylation of alkenes

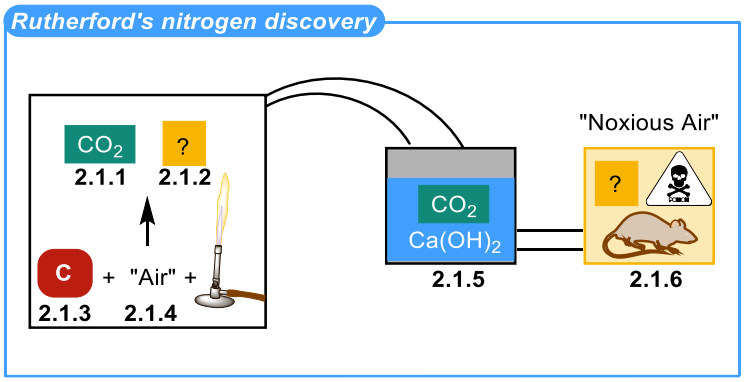
2.1 Synthesis of valuable amines from feedstock alkenes

The results presented in this section were obtained in collaboration with Dr. Alberto Oppedisano, Dr. Veronica Tona, Dr. Daniel Kaiser, Dr. Saad Shaaban, Dr. Che-Sheng Hsu, Dr. Amandine Pons.[320,321]

2.1.1 Introduction

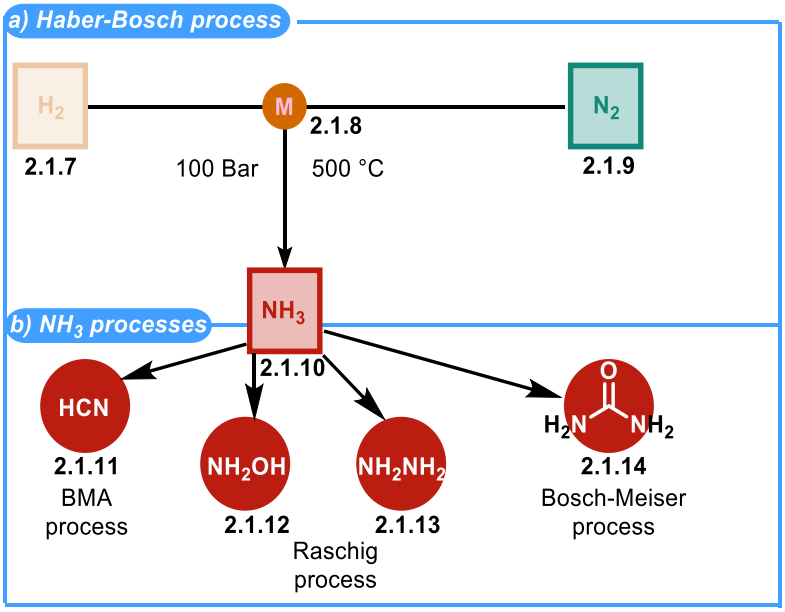
2.1.1.1 Discovery of nitrogen and related compounds.

Nitrogen-containing compounds see widespread use in pharmaceutical and agrochemical contexts. The discovery of nitrogen gas was first credited to Rutherford[322] despite being simultaneously reported by Scheele and Cavendish.[323,324] By igniting carbon in a closed vessel (**2.1.3**, Scheme 2.57), and removing the newly formed CO_2 (**2.1.1**) with limewater (**2.1.5**, $Ca(OH)_2$), Rutherford isolated what he called "noxious air"(**2.1.6**), after realising that exposing animals to it led to death.[325] Etymologically, Lavoisier adopted the word *azote*, stemming from "no life" in Greek, or in German *Stickstoff*, due to its apparent asphyxiating proprieties. Concurrently, the name nitrogen was proposed in 1790 by Jean-Antoine Chaptal, after discovering that elemental nitrogen (air) was also present in nitrates and nitric acid.



Scheme 2.57 – Adapted depiction of Rutherford's initial discovery of nitrogen gas.

An important discovery that altered the perception of nitrogen-related compounds from a purely academic curiosity to an industry of itself was the Haber-Bosch process (Scheme 2.58a).[326–328] By employing high pressures of nitrogen (**2.1.9**) and hydrogen gas (**2.1.7**), in combinations with various heterogeneous catalysts (**2.1.8**), high amounts of ammonia could be efficiently synthesised, [329] which in term enabled the industrial and agricultural revolution.[330-331]

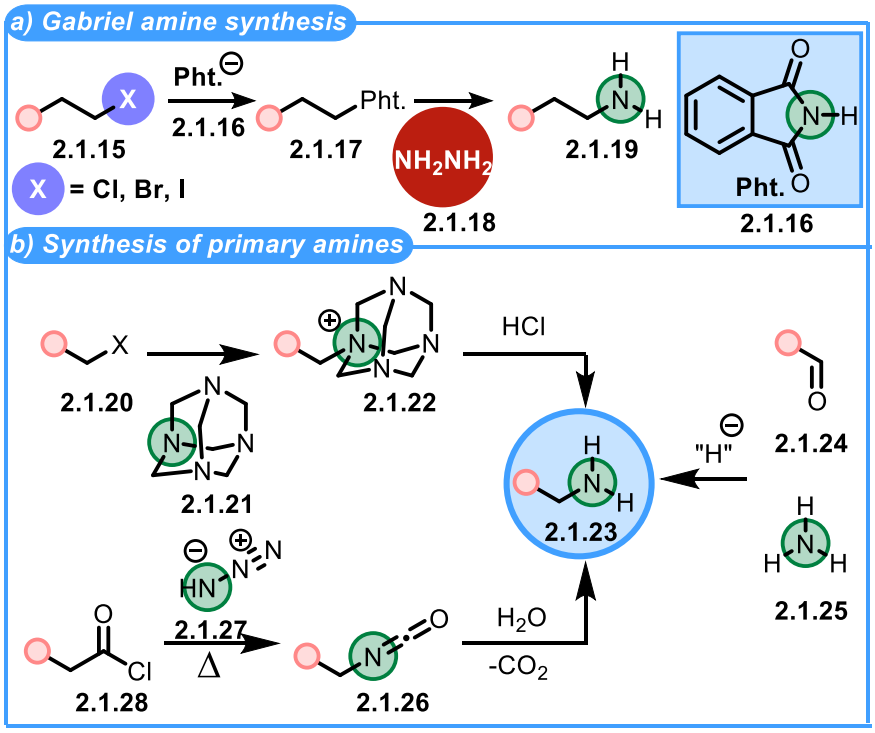


Scheme 2.58 – Synthesis and uses of ammonia (2.1.10). a) Haber-Bosch process, b) Products stemming from ammonia (2.1.10).

2.1.1.2 Ramifications of the Haber Bosch process. Synthesis of amines.

Despite around 80 % of ammonia being devoted to the synthesis of fertilisers, this important building block is also used in other crucial endeavours (Scheme 2.58b). Namely,

compounds such as hydrogen cyanide (**2.1.11**),[332] hydroxylamine (**2.1.12**, Raschig process),[333] urea (**2.1.14**, Bosch-Meiser),[334,335] and hydrazine (**2.1.13**)[336,337] are commonly synthesised by their own named processes. The latter compound, hydrazine (**2.1.13** or **2.1.18,** Scheme 2.59a),[338] which serves various roles[339,340] was found to be a mild deprotecting agent for phthalimide (**2.1.17,** Scheme 2.59a), an important intermediate in the so-called Gabriel amine synthesis (Scheme 2.59a), devoted to the synthesis of primary amines[341–344] (**2.1.19**) from alkyl halides (**2.1.15**). The harsh conditions required for the direct substitution using ammonia, coupled with overalkylation problems, led to the development of complementary methods that could tackle these hurdles (Scheme 2.59b).



Scheme 2.59 – a) Gabriel synthesis of primary amines, b) alternative methods for the synthesis of primary amines.

An analogous approach to synthesise primary amines is by using hexamethylenetetramine (**2.1.21**, Scheme 2.59b) to generate the correspondent quaternary ammonium salt (**2.1.22**), which can be hydrolysed to the desired amine (**2.1.23**). Another example of a hydrolysis-prone intermediate is the isocyanate (**2.1.26**), a functional group that can be generated from a plethora of starting materials (**2.1.28**) and readily affords the primary amine moiety upon hydrolysis.[345–357] The favoured method, especially in an industrial context, is reductive amination, a reliable transformation that combines

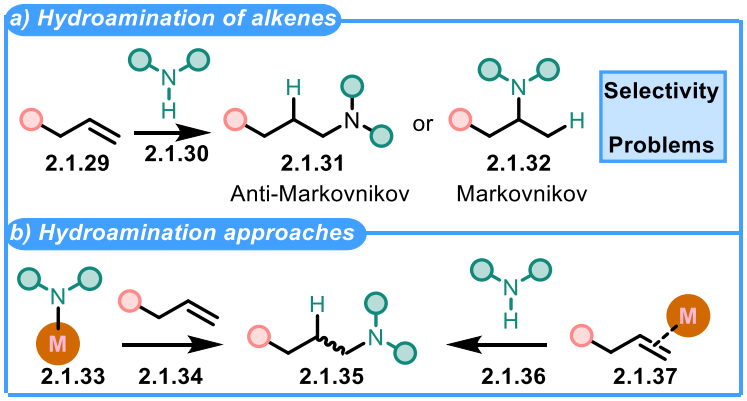
aldehydes (**2.1.24**) with a wide range of amines (**2.1.25**) with concomitant reduction of the imine/iminium intermediate.[358,359]

2.1.1.3 Alkenes as valuable building blocks for the synthesis of amines.

Alkenes are undoubtedly valuable feedstock materials for the chemical industry. Such compounds are usually sourced from the steam cracking of hydrocarbons, hence often referred to as olefins (derived from oil). They are considered by industry as prime targets[360–362] due to their high abundance, polymerisation ability and ease of manipulation.

Despite their inherently high chemical stability,[363] alkenes are known to be involved in a wide range of addition reactions, interacting with a wide range of electrophiles[364–368] or radical species.[369–373]

In the context of amine synthesis, hydroamination (Scheme 2.60a), constitutes a prime method to use the high availability of alkenes (**2.1.29,** Scheme 2.60a).[374]



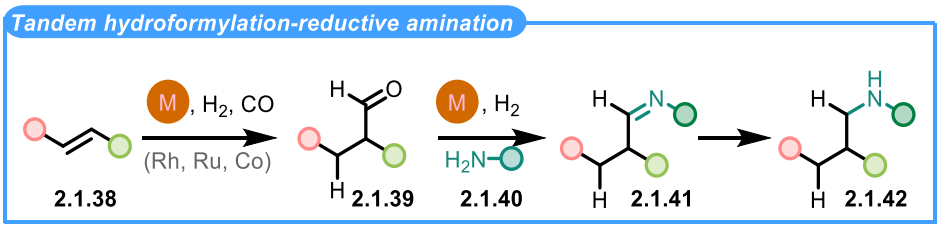
Scheme 2.60 – a) Hydroamination of alkenes and b) Metal-catalysed approaches for hydroamination of alkenes.

Different strategies have been developed to enable what is a challenging reaction between two electron rich partners. One approach focuses on enhancing the nucleophilicity of the N–M bond (**2.1.33**, Scheme 2.60a), e.g. using rare earth metals such as Li and Na, which nevertheless require high pressures and temperatures (usually 200°C and 900 bar, Scheme 2.60b).[375] Alternatively, by using late transition metals (Rh, Ir, Ru, Pd, Pt) the π system of the double bond can be activated (**2.1.37)** to favour nucleophilic attack of the nitrogen (**2.1.36**, Scheme 2.60b).[376–385] Other catalysts based on Brønsted acids can also be used, albeit with lower generality.[386] Overall, the main caveat of hydroamination is its

underlying substrate dependency, with different classes of alkenes requiring specific catalytic systems.

2.1.1.4 Tandem Hydroaminomethylenation.

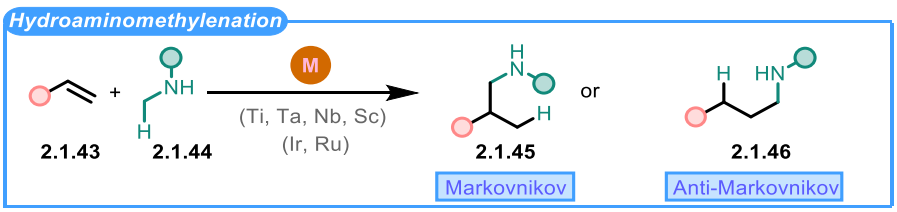
An enticing possibility to achieve the synthesis of amines from alkenes utilises the formal insertion of a carbon subunit between the C-H bond of the amine and the alkene, a reaction called "hydroaminoalkylation". This would result in native connectivity between the two fragments, hypothetically solving the aforementioned synthetic problems. In its simplest iteration, this approach uses a methylene subunit to bind the two different fragments, hence called hydroaminomethylenation (HAM). In early reports, hydroaminomethylenation was accomplished as a domino hydroformylation[387,388]/ reductive amination (Scheme 2.61).[389]



Scheme 2.61 – TM-catalysed step-wise hydroaminomethylenation of alkenes.

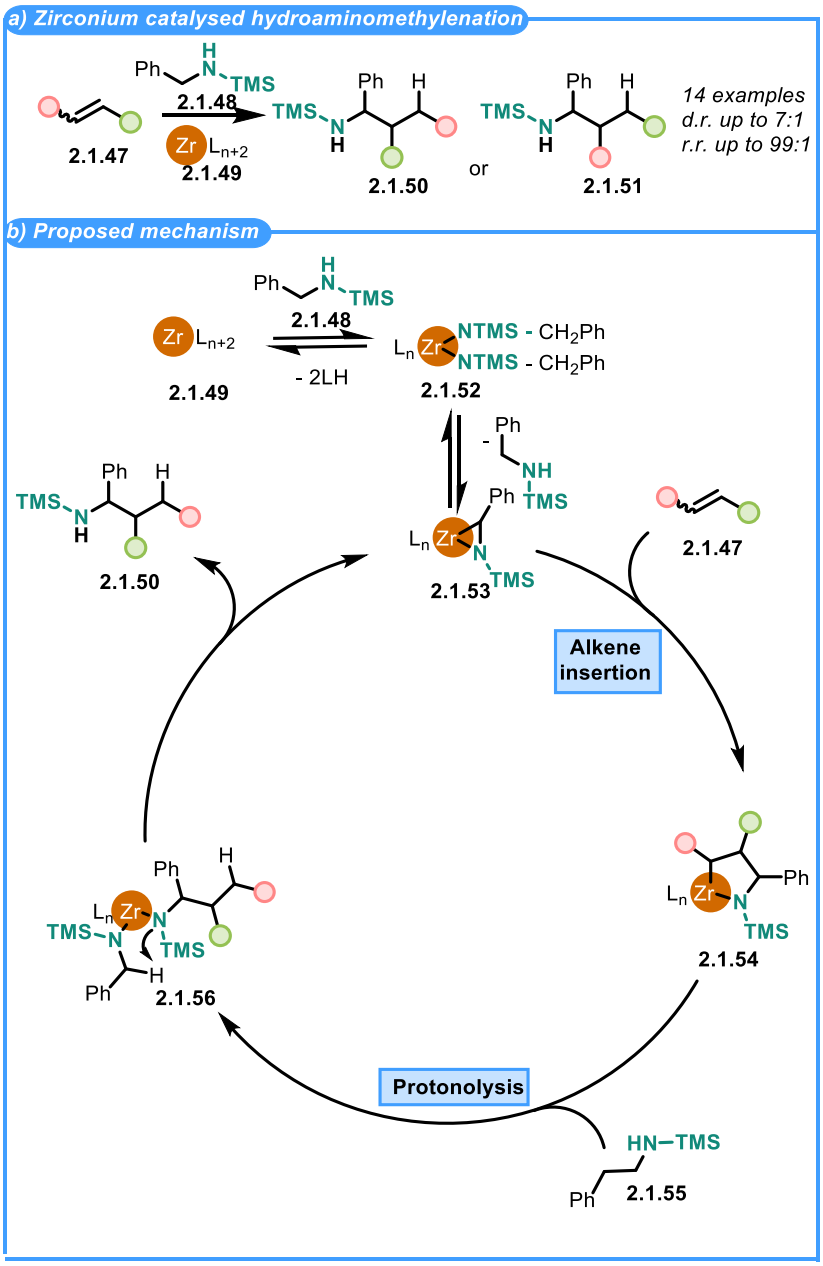
More specifically, the hydroformylation process entails the addition of a carbon monoxide unit in the presence of synthesis gas (H_2 and CO) and TM-catalyst (Ru, Rh or Co),[390–392] usually affording the Markovnikov addition adduct[393,394] likely due to steric effects (**2.1.39**, Scheme 2.61).[395] In this context, the main additional challenge consists of the careful tuning of the reducing agent, to prevent the reduction of the aldehyde intermediate (**2.1.39**).[396,397] This process has been applied industrially in the synthesis of various pharmaceuticals,[398] with more recent iterations resorting to flow chemistry.[399]

2.1.1.5 State of the art of Hydroaminomethylenation.



Scheme 2.62 - Direct metal-catalysed hydroaminomethylenation of alkenes

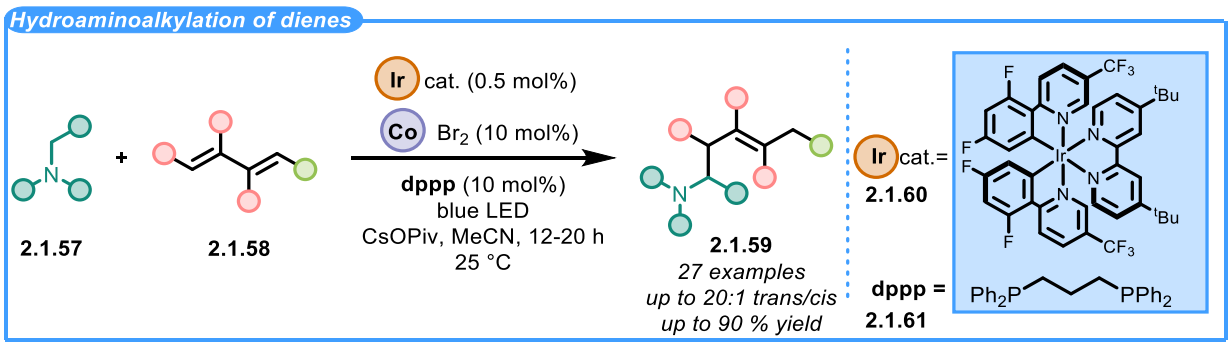
The two main issues associated with direct hydroaminomethylenation pertain to low chemo- and regioselectivity,[400] owing to the use of late transition metals under harsh conditions (Scheme 2.62). One of the most recent efforts was reported by Schafer *et al.* in 2019 (Scheme 2.63a).[401] Employing a zirconium catalyst (**2.1.49**), good results were obtained in the synthesis of benzylated amines (**2.1.50**, Scheme 2.63a). The method uses *N*-TMS amines (**2.1.48**) to stabilise the zirconaziridine intermediate (**2.1.53**, Scheme 2.63b), facilitating the formation of the linear product due to the steric bulk of the amine (Scheme 2.63b). Despite not showcasing perfect selectivity, this method can be seen as a conceptual leap from previous metal-catalysed entries on this field.[402–404] Limitations such as a narrow scope and a need for super-stoichiometric amounts of alkene remain to be answered in future work.



Scheme 2.63 –a) Zirconium-catalysed hydroaminoalkylation of alkenes with N-silylbenzylamine (2.1.48), b) proposed mechanism for the aforementioned trasnformation.

One of the pressing issues of most metal-catalysed hydroaminomethylenation methods is their reliance on high temperatures, with the obvious repercussion in the inability to tolerate many functional groups. Photoredox catalysis offers a solution, by presenting a milder alternative based on the formation of an α-amino radical intermediate. One of the first reports of such reactivity in the context of hydroaminoalkylation was described by Rovis *et al.* in 2017 (Scheme 2.64).[405] By employing a low valent cobalt catalyst in combination with an iridium photocatalyst in basic media, the authors observed coupling of conjugated dienes **2.1.58** to tertiary amines **2.1.57** (Scheme 2.64).[406] The

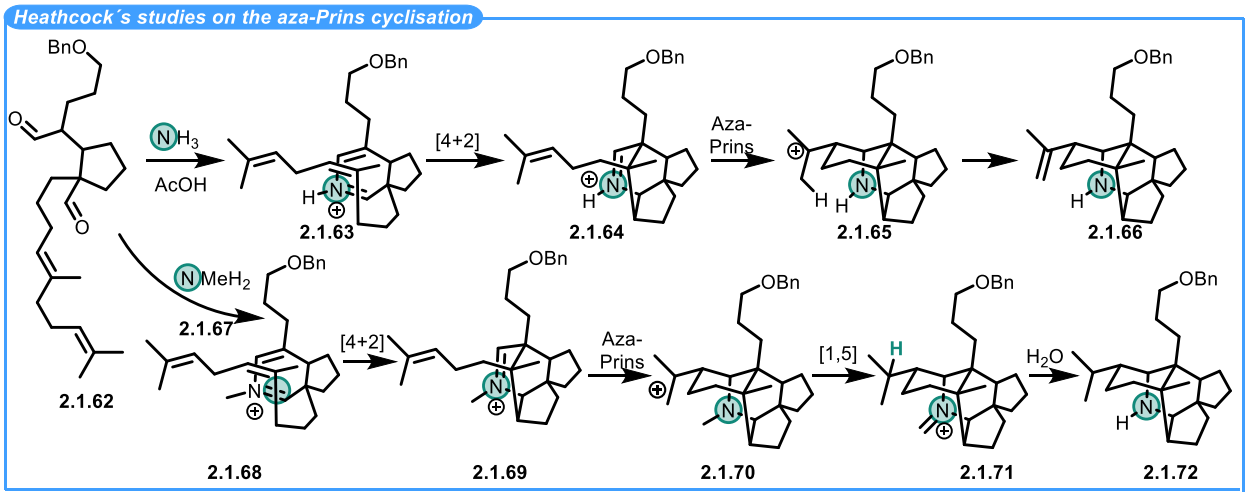
reaction afforded a wide scope of homo-allyl amines (**2.1.59**) with excellent regioselectivity. Such processes, however, are applicable only to alkene substrates which are matched in polarity to the intrinsically nucleophilic α-aminoradical, i.e. electron-poor alkenes or conjugated dienes.



Scheme 2.64 – Hydroaminoalkylation of dienes using tertiary amines under cobalt and photoredox catalysis.

2.1.1.6 Prins reaction – alkenes as nucleophiles.

An important methylene donor for the hydroaminomethylenation reaction is the iminium ion. This electrophilic species[407–409] can be used in conjunction with alkenes in a Prins-type reaction.[410–413] The Aza-Prins reaction remains a powerful method for the synthesis of amine scaffolds in complex natural products,[414–416] a notable example by Heathcock,[417,418] in shown in Scheme 2.65. The *in-situ* generated azadiene (**2.1.63**) engages in a [4+2][419,420] reaction, swiftly (**2.1.64**) setting the stage for subsequent aza-Prins cyclisation to generate the complex secondary amine scaffold (**2.1.66**, Scheme 2.65).

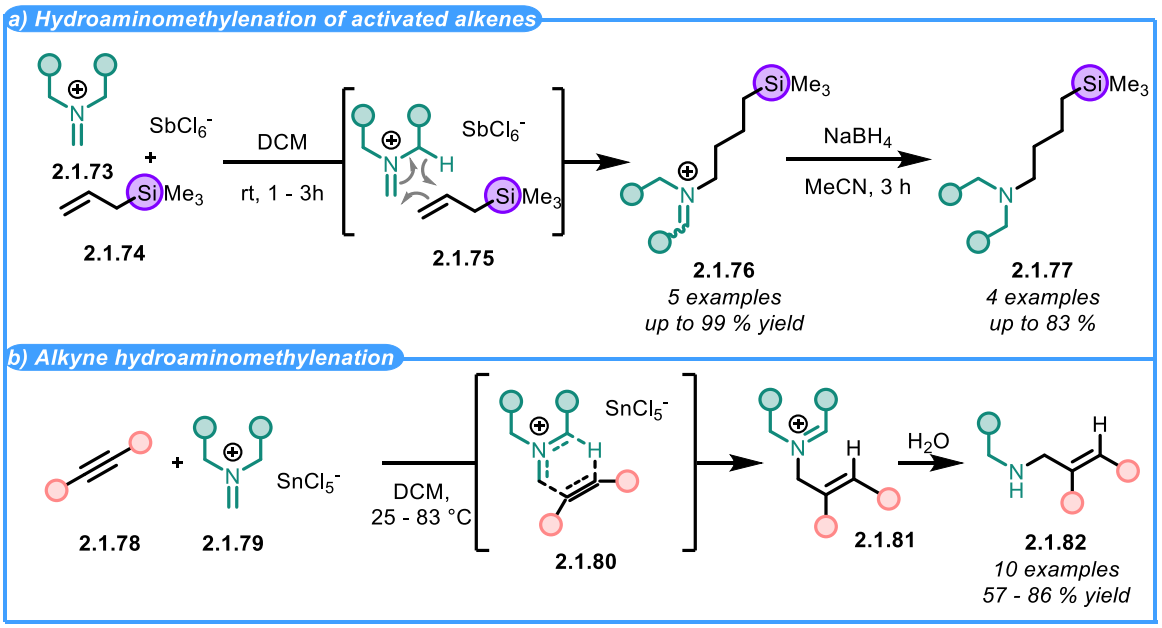


Scheme 2.65 – Heathcock´s serendipitous discoveries on the aza-Prins cyclisation

Remarkably, years after this protocol had been reported, the repetition of the reaction revealed a different product (**2.1.72**, Scheme 2.65), a secondary amine, without the unsaturation (**2.1.66**). Puzzled by this result, the co-workers investigated every possibility including contaminants, reanalysing all NMR spectra, and reagents alike. The origins of this "impossible" product came in a way of necessity. Upon setting up the reaction, the chemists borrowed the ammonia bottle from a neighbouring group (Vollhardt), unsuspected that it was *N*-methyl amine instead (**2.1.67**). A possible explanation then arose: a [1,5]-hydride transfer, resulting in an iminium ion (**2.1.71**, scheme 9), subsequently hydrolysed. Serendipitously, Heathcock and co-workers came across an enticing transformation, in which the apparent addition of alkyl amine triggered a cyclisation that reduced the substrate (**2.1.72**).

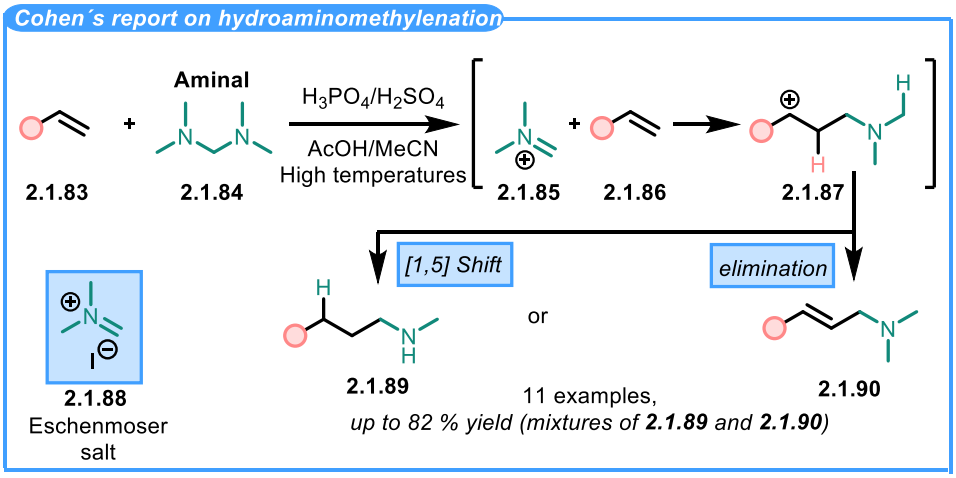
2.1.1.7 Hydroaminomethylenation of iminium ions.

Analogously, iminium ions (**2.1.73**, Scheme 2.66a) have been known to react with a plethora of different π-nucleophiles, as deeply investigated by Mayr in the '90s (Scheme 2.66a). Initially, the preferred nucleophiles were allyl silanes (**2.1.74**), which reacted similarly to the aforementioned Heathcock observations. The authors claim that an inverse electron demand-ene reaction took place (**2.1.75**), offering no comment on the exact mechanism. It is important to note that, in this case, the iminium ion requires a non-nucleophilic counterion ($SbCl_5^-$) for the reaction to take place,[421,422] with the authors inferring that the "naked" iminium ion is crucial for this transformation. Additionally, for the first time, alkynes (**2.1.78**, Scheme 2.66b) were also found to react in a similar fashion, generating *E*-allylamines in good yields (**2.1.82**, Scheme 2.66b).



Scheme 2.66 –Hydroaminomethylenation of a) activated alkenes (2.1.74, allyl silanes) b) alkynes to afford E-allyl amines

Another important report was published by Cohen in 1983.[423] Initially correcting earlier literature results,[424] instead of the reported tertiary amines (**2.1.90**, Scheme 2.67), the reaction of *in situ* generated iminium ions (**2.1.85**) in combination with alkenes (**2.1.86**) afforded secondary amines (**2.1.89**). One of the major differences between the aforementioned reactions is the origin of the iminium ion. In this case, aminals (**2.1.84**) are used as an iminium source[425] in conjunction with a strong acid. In the same article, different iminium sources were also explored, most prominently the so-called Eschenmoser´s salt (**2.1.88**, Scheme 2.67), initially developed as a regent for the methylenation of carbonyls.[426,427]

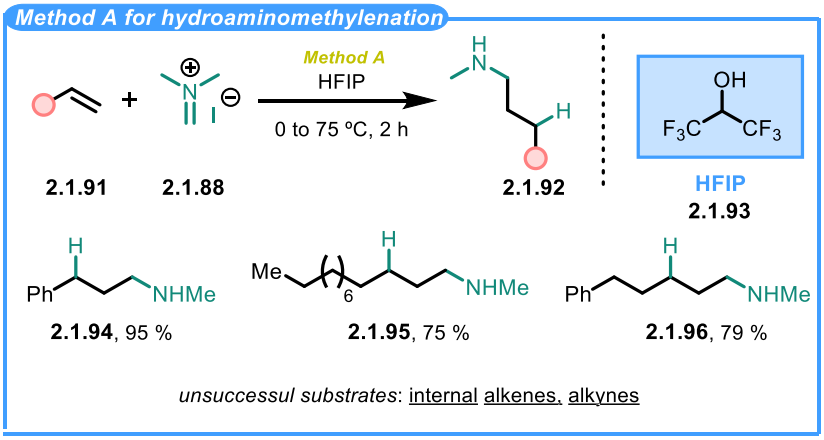


Scheme 2.67 – Cohen´s hydroaminomethylenation of alkenes using aminals

Limitations on the method included a generally low yield (below 50 %) and limited scope of substrates, mostly activated alkenes (**2.1.83**, norbornene or styrene derivatives, Scheme 2.67). A notorious feature of this method is the anti-Markovnikov selectivity, a highly pursued motif in industrial context and described as one of the top 10 challenges for catalysis.[428] By revisiting these results, the Maulide group aimed to develop a general method for the hydroaminomethylenation of unactivated alkenes.

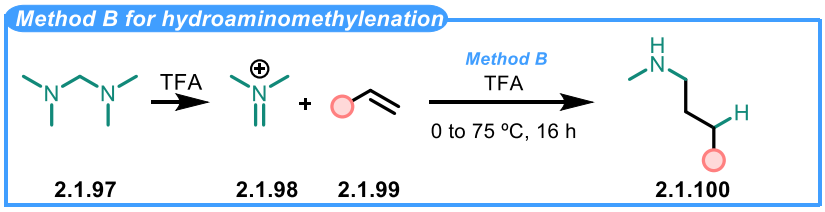
2.1.1.8 Initial studies on the acid-mediated hydroaminomethylenation of alkenes.

After substantial optimisation, our investigation revealed two useful methods to achieve this transformation.



Scheme 2.68 – Hydroaminomethylenation of alkenes using Eschenmoser salt in HFIP (method A)

HFIP (**2.1.93**, Scheme 2.68), a polar solvent with strong hydrogen-bonding proprieties was demonstrated to facilitate the reaction between Eschenmoser iodide (**2.1.88**) and various alkenes (method **A**, **2.1.94**, **2.1.95**, **2.1.96**, Scheme 2.68). The reaction afforded the products in elevated yields (75 - 95 %), however, whilst being limited to terminal alkenes.

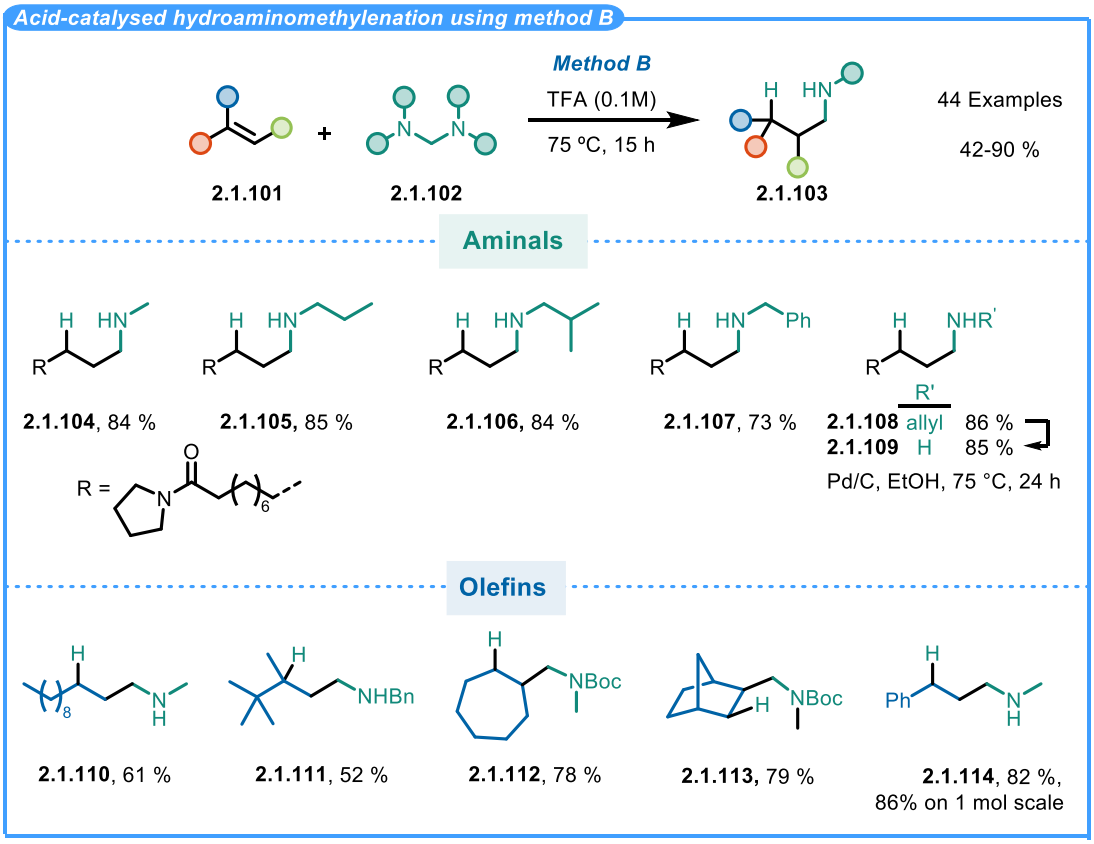


Scheme 2.69 – Method B for the acid-mediated hydroaminomethylenation of alkenes

By investigating different acids in combination with tetramethyldiaminomethane (**2.1.97**, TMDAM, Scheme 2.69), to generate the iminium ion (**2.1.98**) *in situ*, TFA was found to give the best results (Scheme 2.69). In comparison to the above conditions, this different set of conditions was found to be applicable to a wide range of substrates, from unactivated alkenes to complex scaffolds. As displayed by the selected examples, internal alkenes were also suitable subtrates.

2.1.1.9 Scope and limitations of method B for the hydroaminomethylenation of alkenes.

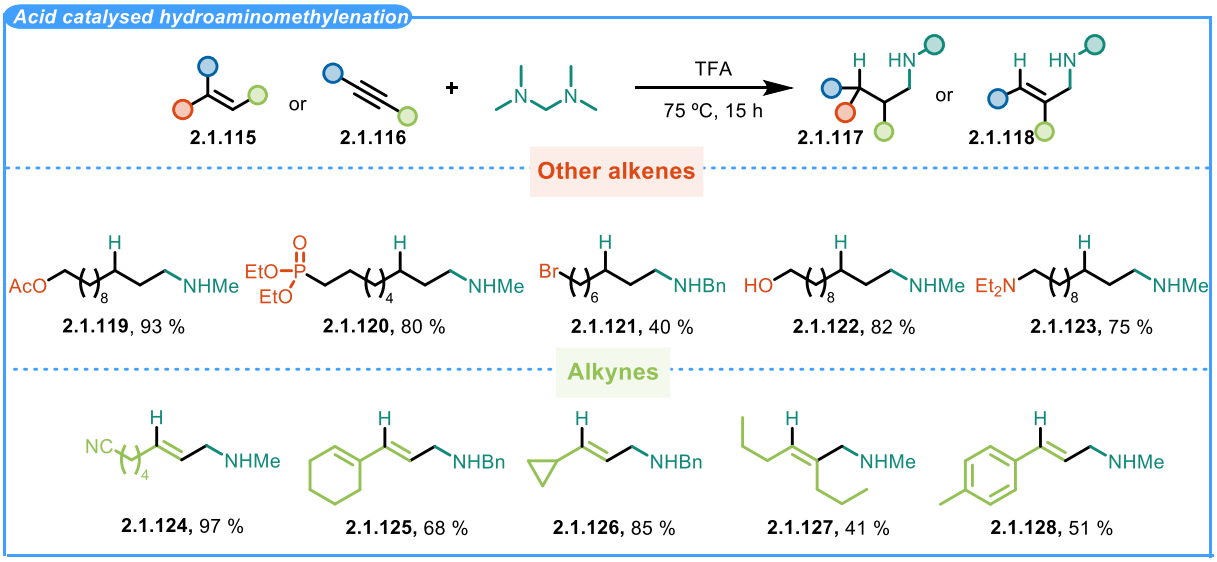
The reaction tolerated a wide range of aminals, from *n*-butyl to benzyl derivatives (**2.1.105** and **2.1.107** in Scheme 2.70). The use of a tetraallylaminal (**2.1.108**) allowed formation of the primary amine, following facile Pd-catalysed deallylation (**2.1.109**).[429]



Scheme 2.70 – Selected examples on the hydroaminomethylenation of alkenes with aminals using method B

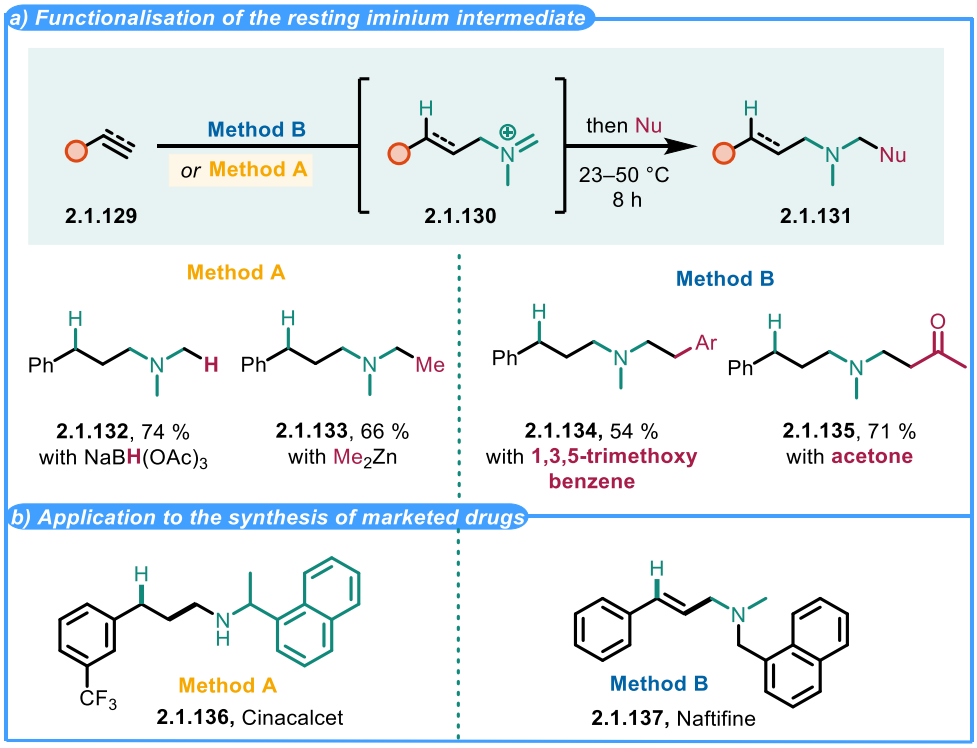
Notably, good functional tolerance was observed, with functional groups such as amines (**2.1.122**, Scheme 2.71) and halides (**2.1.121**) not interfering in the reaction outcome (Scheme 2.15). The use of other sensitive moieties such as acetates (**2.1.119**) and phosphonates (**2.1.120**) also gave the desired amines in high yield. When alkynes (**2.1.116**)

were subjected to the reaction conditions, selective formation of *E*-allyl amines was observed (**2.1.118**). The reaction showed selectivity towards the terminal alkyne when enynes were employed as substrates (**2.1.125,** Scheme 2.71).



Scheme 2.71 – Selected examples showing the FG-tolerance of this hydroaminomethylenation on alkenes and alkynes

One of the key features of this process is the possible functionalisation of the resulting iminium intermediate (**2.1.130**, Scheme 2.72a), instead of simple hydrolysis. Using method **B**, different nucleophiles were directly introduced, namely ketones, resulted in the formation of β-amino carbonyls (such as **2.1.135**). Electron-rich aromatic compounds were also employed in a one-pot procedure (**2.1.134**).



Scheme 2.72 – a) Functionalisation of the resting iminium ion, b) Application of the method in the synthesis of marketed drugs.

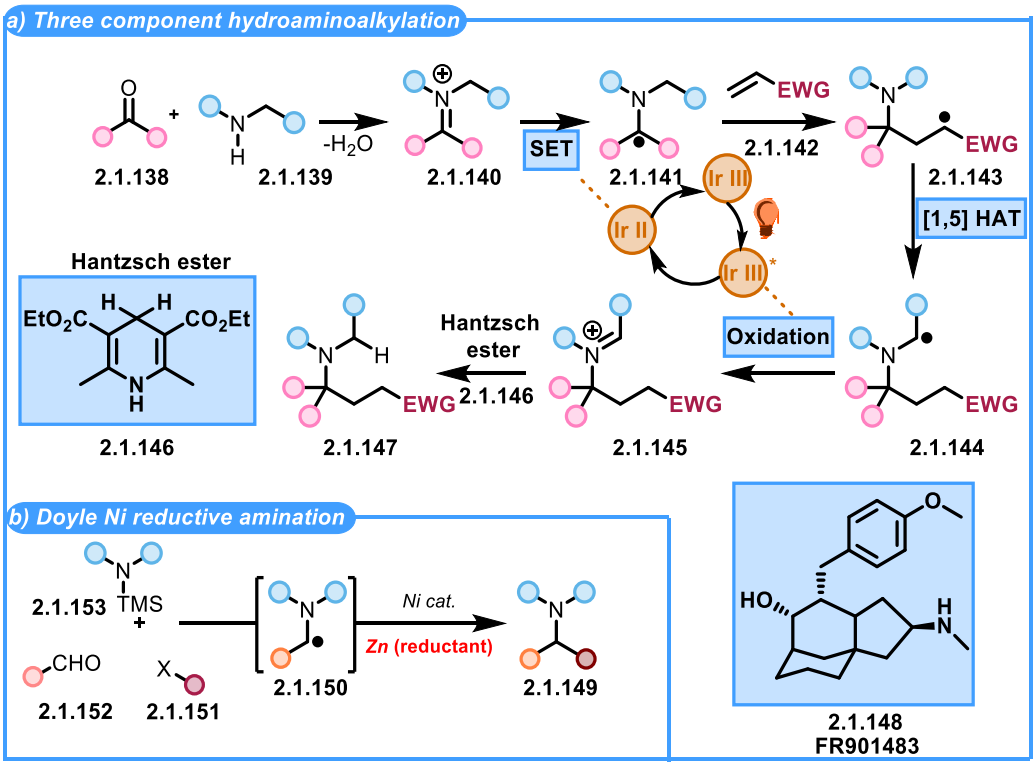
Finally, this method was successfully applied to the synthesis of marketed drugs such as Cinacalcet (**2.1.136**, Scheme 2.72b) and Naftifine (**2.1.137**).

We then turned our attention to extend this chemistry into the synthesis of α-branched amines, in a process that would be termed hydroaminoalkylation.

2.1.1.10 State of the art of the hydroaminoalkylation of alkenes.

In 2018, Gaunt and co-workers published a multicomponent photocatalytic method for the synthesis of amines from alkenes (Scheme 2.73a).[430] This powerful hydroaminoalkylation method relied on the formation of an α-amino-radical intermediate (**2.1.140**) from the corresponding iminium ion (**2.1.141**) by single-electron reduction (SET). The radical is subsequently captured by a Michael acceptor (**2.1.142**) to generate the complex amine scaffold (**2.1.147**). Mechanistically, one of the most interesting observations was that the final radical (**2.1.143**) can undergo multiple pathways. Besides being directly reduced *via* HAT by the stoichiometric reductant (Hantzsch-ester, **2.1.146**), it can also be involved in a 1,5-HAT event, again generating an α-amino radical (**2.1.144**) which can be oxidised to the corresponding iminium (**2.1.145,** Scheme 2.73). The

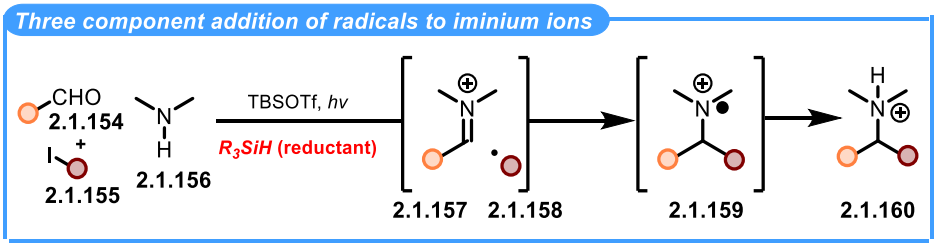
subsequent reduction by Hantzsch-ester (**2.1.146**) terminates the reaction. The methodology was successfully applied to the synthesis of complex natural products such as FR901483 (**2.1.148**).



Scheme 2.73 –Three component hydroaminoalkylation using: a) photocatalysis. b) Nickel catalysis.

Similarly, Doyle *et al.* reported that α-amino radicals (**2.1.150**, Scheme 2.73b) can be coupled with aryl halides (**2.1.151**) using a nickel catalyst (Scheme 2.73b).[430] The mechanism is not yet fully understood, but it the method affords a wide range of tertiary amines (**2.1.149**).

In 2020, the Gaunt group disclosed an alternative method for the synthesis of tertiary amines (**2.1.160**, Scheme 2.74), once again utilising iminium species as a key, *in situ* generated intermediate **2.1.157** (Scheme 2.74).[431] Instead of the formation of an α-amino radical by iminium reduction, addition of a radical (**2.1.158**) to the iminium species, triggers formation of an aminium radical cation (**2.1.158**), swiftly trapped by HAT furnishing the corresponding ammonium salt (**2.1.160**).



Scheme 2.74 – Three component addition of radicals to iminium ions

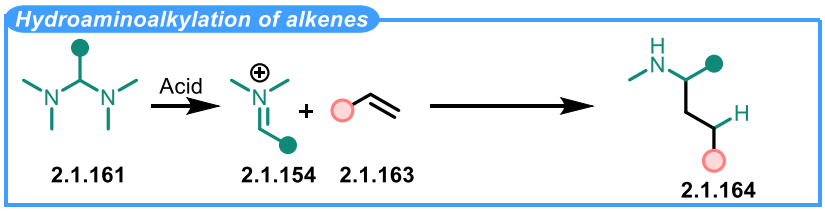
A wide variation of all components of the transformation was showcased, mostly by utilising commercially available compounds. One of the pitfalls associated is related to the stability of the radical intermediate, which is limited by the rate of its formation. Adjacent groups such as esters, nitriles or other electron-withdrawing groups are not easily incorporated using this method.

This motivated us to establish a method of hydroaminoalkylation that could address these problematic issues.

2.1.2 Objectives:

Our aim was to develop a method that fills a gap in the synthetic landscape. Our premise was based on the use of 1,1 disubstituted aminals (**2.1.161**, Scheme 2.75) that could afford amines (**2.1.164**) upon reaction with the correspondent alkene (**2.1.163**). As showed in our previous work, acid usually catalyses this transformation. The possibility to use a wide range of aminals, derived from unstable aldehydes, was a highly enticing feature of this project, due to their products being inaccessible to previously mentioned state of the art methods.

This work was performed in collaboration with Dr. Che-Sheng Hsu, Dr. Veronica Tona and Dr. Amandine Pons.[320]

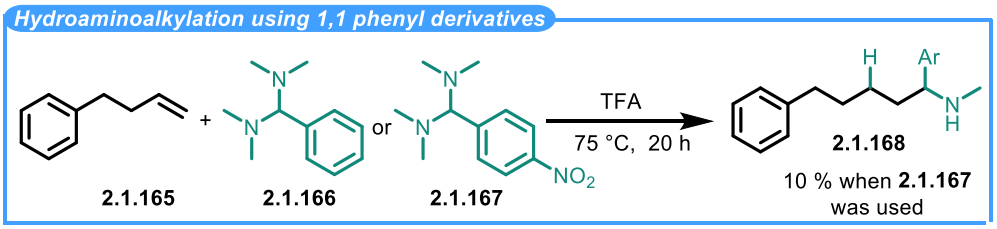


Scheme 2.75 – Acid-mediated hydroaminoalkylation of alkenes

2.1.3 Results and discussion

2.1.3.1 Initial studies on the acid-mediated hydroaminoalkylation of alkenes.

Our first strategy to tackle this problem, was to use different 1,1-substituted aminals (**2.1.166** and **2.1.167**, Scheme 2.76). Specifically, the use of phenyl derivatives did not lead to the formation of the desired product (**2.1.168**). However, a small amount of product **2.1.168** (~10 %) was observed when with *p*-nitrophenyl aminal derivative was employed (**2.1.167**, Scheme 2.76).



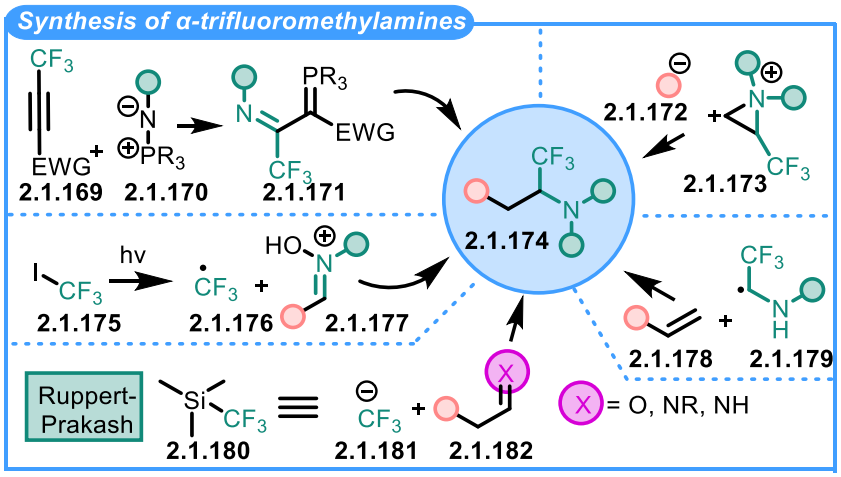
Scheme 2.76 – Initial attempts of the hydroaminoalkylation with 1,1aryl-substituted aminals

Despite not achieving acceptable yields, the use of a more electrodeficient iminium ion precursor (**2.1.167**, Scheme 2.76) seemed to aid the reaction progression. Therefore, we hypothesised that the addition of electron withdrawing groups to the iminium should render it more susceptible to attack by alkenes. The main problem of this hypothesis is the lack of stability of such electrodeficent species. In the case of CF_3, the corresponding aldehyde is stabilised in form of a hemiacetal, rendering it incompatible to methodologies that rely on *in-situ* formation of the iminium ion. However, the incorporation of a trifluoromethyl functionality could prove to be valuable in the context of medicinal chemistry,[432–434] especially given its use as methyl and amide bond bioisosteres.[435,436]

2.1.3.2 Methods for the synthesis of α-trifluoromethylamines.

The state of the art for α-trifluoromethylation of amines (**2.1.174**, Scheme 2.77) usually involves multiple-step procedures,[437] resorting to [2+2] of azadiene (**2.1.170**, Scheme 2.77) and fluorinated alkynes (**2.1.169**),[438] or the indirect trifluoromethylation of nitroalkenes (**2.1.177**, Scheme 2.77).[439] A common denominator in most strategies is the use of the Ruppert-Prakash reagent (**2.1.180**),[440–442] that adds to a wide range of electrophiles such as imines, aldehydes and aldimines (**2.1.182**, Scheme 2.77).[443,444]

Unfortunately, its use is sometimes associated with the formation of undesired by-products due to its oxidative nature. Alternatively, radical addition to olefins (**2.1.178**),[445] or opening of aziridine intermediate (**2.1.173**)[446] have also been investigated in the synthesis α-trifluoromethylamines (**2.1.174**).



Scheme 2.77 – Different approaches for the synthesis of α-trifluoromethylated amines.

2.1.3.3 Development of a method for the synthesis of α-trifluoromethylamines from alkenes.

Motivated by the interesting characteristics of the trifluoromethyl group, we decided to use the aminal (**A**, **2.1.184**) as benchmark to test our hypothesis. When applying the conditions of the aforementioned hydroaminomethylenation (Table 2.4, entry 1), full conversion was observed, however in moderate yield. Surprisingly, a similar outcome was observed when the reaction was performed at ambient temperature (Entry 2). At lower temperatures, the desired product was obtained in higher yields (entries 3 and 4). In fact, limited only by the melting point of the solvent (TFA), we found that -10 °C gave the best results. Further screening of concentration and reaction time (entries 5-7) led to the formation of the desired product in excellent yield (**2.1.185**, entry 7).

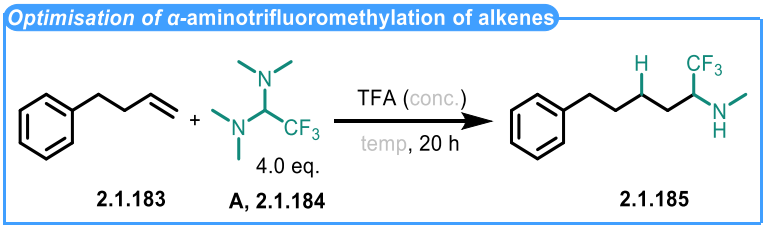
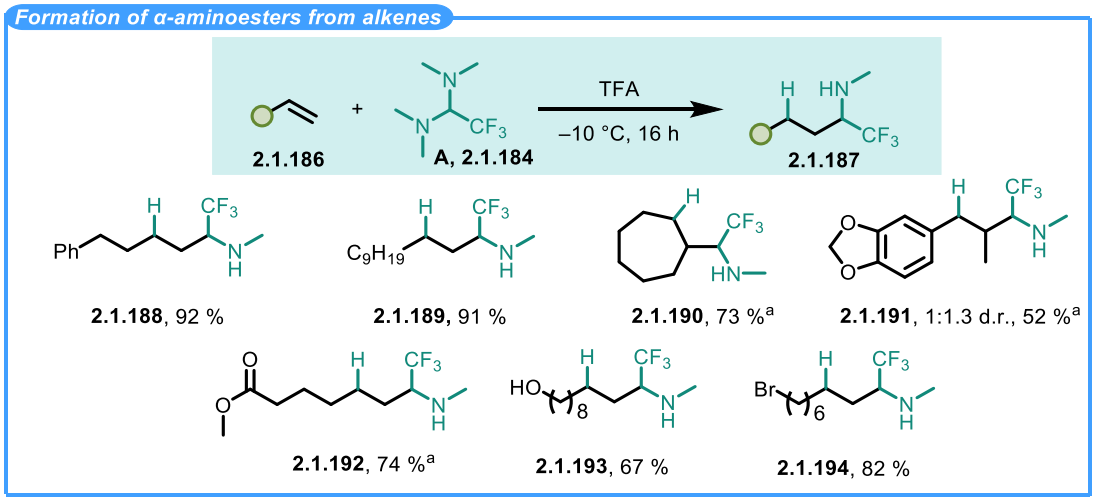


*Table 2.4 – Optimisation of hydroaminoalkylation using CF_3-substituted aminal A (2.1.184). *Mesitylene was used as an internal standard.*

Entry	*Temperature (°C)*	*Time (h)*	*Conc. (M)*	*NMR yield **2.1.185** (%)*
1	75	10	0.6	57
2	20	10	0.6	53
3	0	10	0.6	61
4	-10	10	0.6	64
5	-10	15	0.6	70
6	-10	13	0.1	80*
7	-10	16	0.1	92*

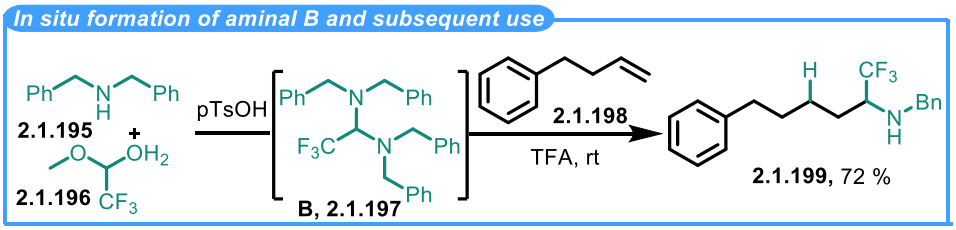
2.1.3.4 Scope of the α-aminotrifluoromethylation of alkenes.

With optimised conditions in hand, we started to investigate different substrates. Despite employing milder conditions, the transformation showed similarly broad scope to the previously developed hydroaminomethylenation (Scheme 2.78). Halides (**2.1.194**, Scheme 2.78) and free alcohols were tolerated (**2.1.193**). Styrene and cyclic derivatives (**2.1.191** and **2.1.190**) gave the desired product in good yield, with room temperature being a deciding factor to prevent elimination.



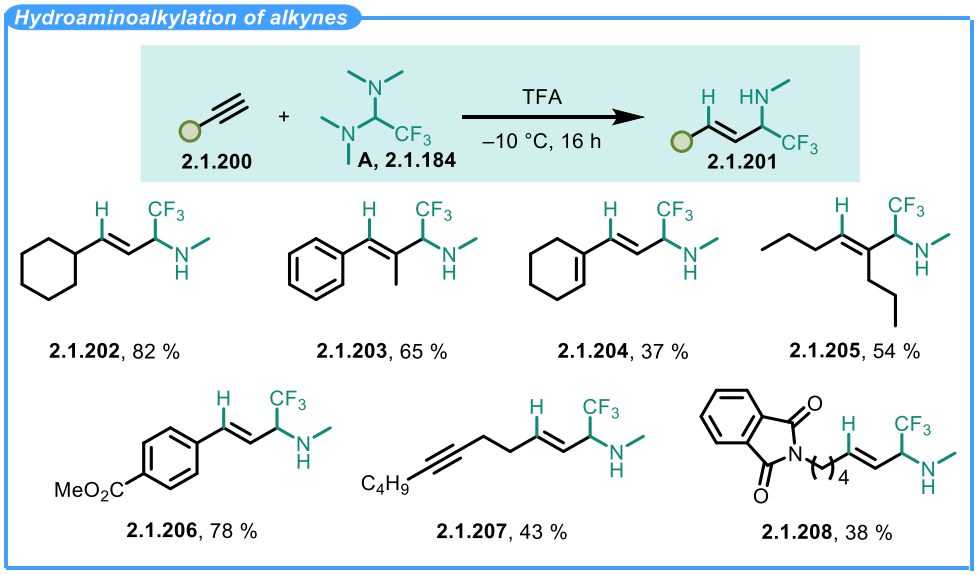
Scheme 2.78 – Scope of α-trifluromethylamines by hydroaminoalkylation of alkenes. [a]reaction conducted at ambient temperature (20 °C)

Notably, the use of an *in situ* generated tetrabenzyltrifluoromethyl aminal (**B, 2.1.197,** Scheme 2.79) led to the desired trifluorobenzyl amine **2.1.199** (Scheme 2.79), a potential precursor for the free primary amine.



Scheme 2.79 – In situ formation of tetrabenzyltrifluoromethyl aminal B (2.1.197) and use in the hydroaminoalkylation reaction to afford α-trifluoromethylbenzylamines (2.1.199).

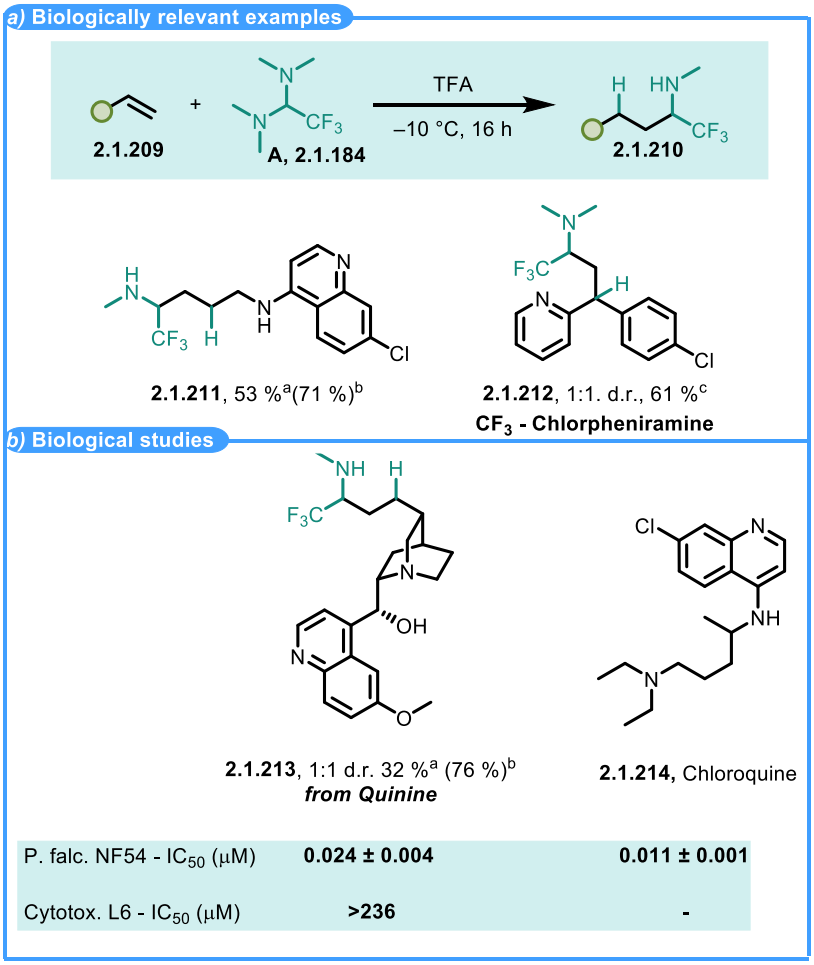
Good yields were also found with terminal (**2.1.202**, **2.1.206** and **2.1.208,** Scheme 2.80) and internal alkynes (**2.1.203** and **2.1.205**), leading selectively to the formation of *E*-allyl amines (Scheme 2.80). Once again, a substrate containing two potential reactive sites, proved to react preferentially at the alkyne moiety over an alkene (**2.1.204**). Additionally, we were able to establish that terminal alkynes react more readily than internal ones (**2.1.207**).



Scheme 2.80 – Scope of alkynes in the synthesis of α-trifluoromethyl E-allyl amines (2.1.201)

2.1.3.5 Synthesis of biologically relevant α-trifluoromethylamines and their biological evaluation.

Using a tandem hydroaminoalkylation/Eschweiler-Clarke type reduction with formic acid,[447,448] the 1st generation anti-histaminic chlorpheniramine could be swiftly prepared (**2.1.212**, Scheme 2.81). In a similar way, an analogue closely resembling chloroquine was also successfully synthesised (**2.1.211**) from the corresponding allyl amine. Interestingly, in prior studies allyl amine substrates were unresponsive to this protocol, presumably due to protonation of the nitrogen and resultingly decrease in nucleophilicity of the alkene.



Scheme 2.81 – a) Synthesis of biologically-relevant trifluoromethyl amine derivatives (2.1.211 and 2.1.212). b) Biological studies on the CF_3-quinine analogue. [a]reaction conducted at 75 °C, [b]yield based on recovery of starting material. [c]with addition of paraformaldehyde and formic acid

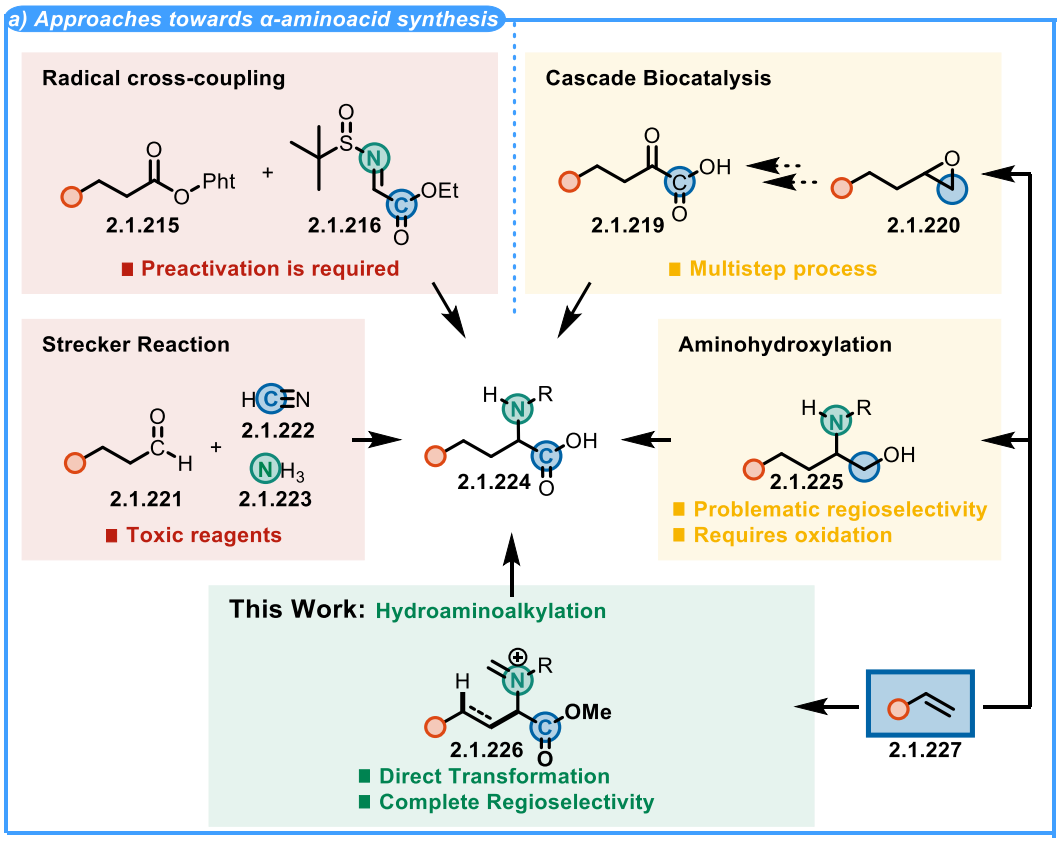
The natural product quinine was also successfully converted into α-trifluoromethyl-amine **2.1.213** (Scheme 2.81), demonstrating an interesting example of a late-stage functionalisation. Our collaborators at the Swiss tropical institute (Basel, Prof. Marcel Kaiser) conducted preliminary biological tests on the aforementioned analogue (**2.1.213**) in two distinct cell-lines: the first one containing *P. falciparum* parasite and the second L6 rat cells, to check its biological activity and cytotoxicity, respectively (Scheme 2.81b).

The results were very encouraging – **2.1.213** was found to be non-cytotoxic with high antimalarial activity (IC_{50} = 24 nM). When compared to other compounds targeting malaria, **2.1.213** exhibited similar potency to chloroquine sulphate (**2.1.214,** Scheme 2.81), a drug used to treat similar diseases, which recently saw controversy as a possible treatment for COVID-19. [449]

2.1.3.6 State of the art on the synthesis of α-aminoacids from alkenes.

We then turned our attention towards different types of functionalised aminals which could enable acid-mediated hydroaminoalkylation. In particular, we were interested in the use of α-(carboxyalkyl) derivatives (**2.1.228**, Scheme 2.82a). This would result in an appealing, direct formation of α-amino-acid derivatives from alkenes (**2.1.227**, **2.1.224**, Scheme 2.82b). Dominant alternatives to afford this motif are, the Strecker reaction (**2.1.221** – **2.1.223**)[450] or radical cross-coupling reactions (**2.1.215** and **2.1.216**, Scheme 2.82a).[451] These prevalent approaches display some disadvantages such as the use of toxic reagents or complex starting materials.[452]

The direct use of alkenes (**2.1.227**, Scheme 2.82a) as feedstocks to prepare α-aminoacids is a valuable approach. Despite important efforts in this regard, most strategies have considerable pitfalls. One of the simplest ways to directly assemble α-aminoacids derivatives from alkenes is by aminohydroxylation and subsequent oxidation (**2.1.225**, Scheme 2.82a).[453,454] However, due to issues of regioselectivity, its use in a broad context is limited. An interesting alternative relies on multistep, high yielding biocatalytic transformations (**2.1.119** – **2.1.220**).[455–457]



Scheme 2.82 – a) Different strategies for the synthesis of α-amino acids (2.1.224), Synthesis of α-amino acids from alkenes (2.1.227) via hydroaminoalkylation (2.1.226).

2.1.3.7 Initial studies on the acid-catalysed synthesis of α-amino acids from alkenes.

Using our established methodology, we envisioned that an aminal containing an ester group could be employed in the direct synthesis of amino acids from alkenes (**C**, **2.1.229**, Table 2.5). The aminal in question (**C, 2.1.229**) had already been used previously in Ti-catalysed Mannich-type reactions.[458,459] In the optimisation process, we found that aminal **C** behaved differently from the trifluoromethyl derivative (**2.1.184**, Aminal **A** and **2.1.197**, Aminal **B**). At low temperatures, almost no conversion was observed (Table 2.5, entry 1), and only traces were observed at room temperature (entry 2). Further increase in the temperature ultimately led to full conversion (entry 3), albeit in only moderate yield. We surmised that the products could be somewhat temperature sensitive, and lowered the temperature to 35 °C (entry 4), which in turn only decreased the yield slightly, as well as the conversion. At higher concentration, we observed improvement in the yield. Finally,

the best conditions were found at 50 °C using a 0.6 M concentration, affording the product in 63 % isolated yield (entry 6).

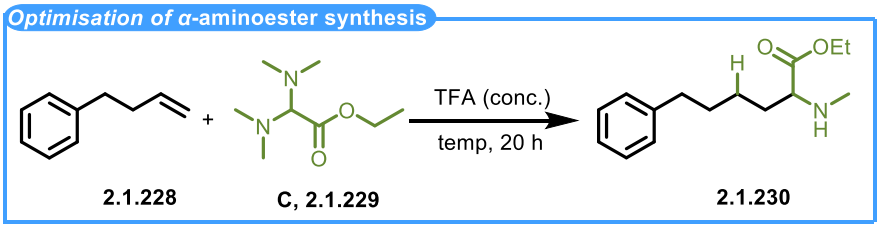
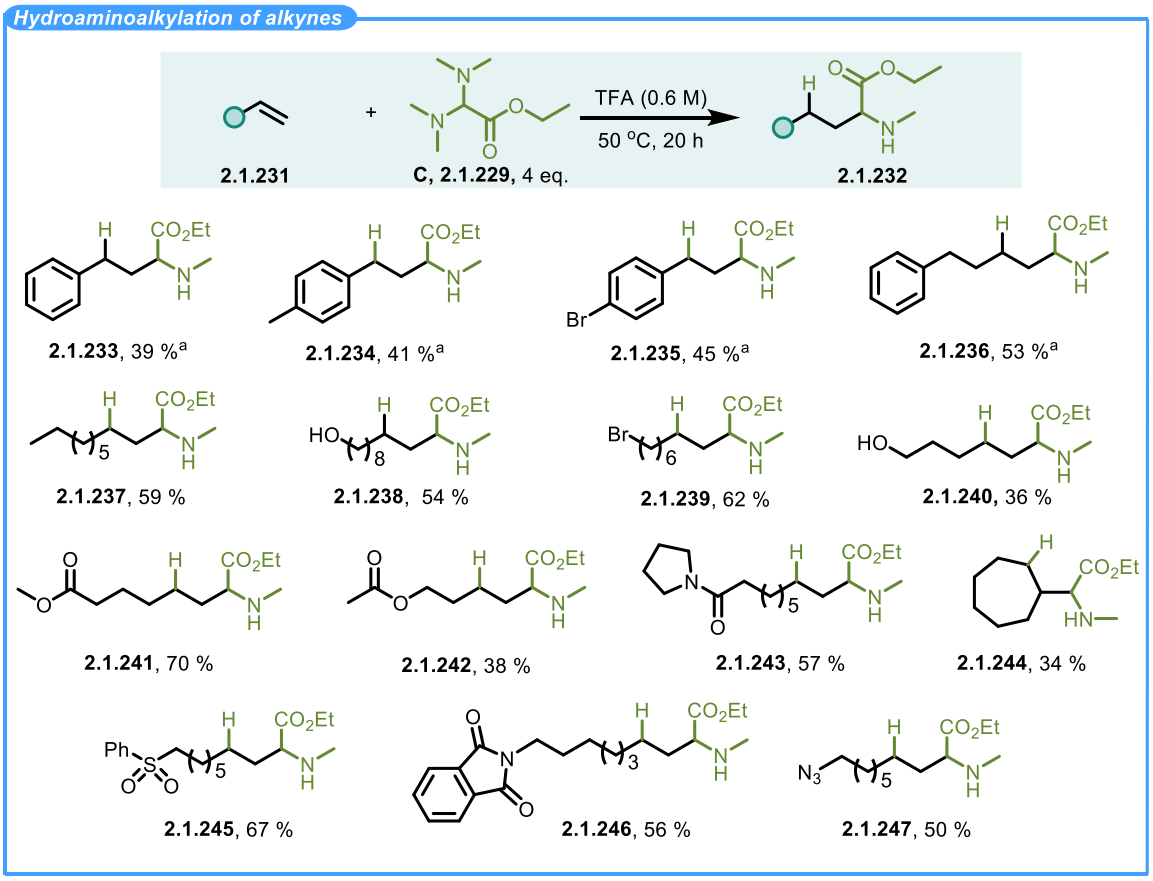


Table 2.5 – Optimisation of conditions for the synthesis of α-amino acid derivatives by hydroaminoalkylation

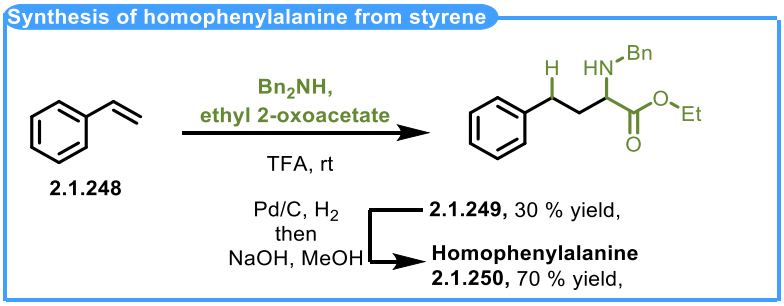
Entry	*Temperature*	*Conc. (M)*	*Conversion %*	*Product (**2.1.230**) %*
1	-10	0.1	-	-
2	20	0.1	50	5
3	50	0.1	100	45
4	35	0.1	35	20
5	35	0.6	65	33
6	50	0.6	100	63

We then proceeded to explore the reaction with different alkenes (**2.1.231**, Scheme 2.83). Styrenes with variable electronic properties (**2.1.233**, **2.1.234** and **2.1.235**) performed comparably well and were converted to the corresponding α-amino acid derivatives. Once again, the high functional group tolerance of the process was showcased, and it was possible to obtain α-amino esters bearing a hydroxyl (**2.1.238,** Scheme 2.83), ester (**2.1.241**) or sulfone (**2.1.245**) moiety along the aliphatic chain. Even a primary bromide (**2.1.239**) did not undergo solvolysis or nucleophilic substitution under the reported conditions, whilst an azide (**2.1.247**) remained untouched.



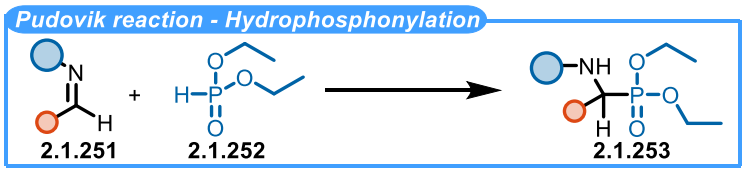
Scheme 2.83 – Scope of α-amino ester synthesis via hydroaminoalkylation of alkenes with aminal C (2.1.229). [a] Reaction conducted at 20 °C.

As a sample application (Scheme 2.84), the presented method enabled a straightforward synthesis of the unnatural α-amino acid 'homophenylalanine' in only three steps from styrene (**2.1.250**, Scheme 2.84). The hydroaminalkylation can, in this case, be conducted as a 3-component coupling of a secondary amine, a glyoxalate and an olefin.



Scheme 2.84 – Application of the method in direct synthesis of homophenylalanine (2.1.250) from styrene using a one pot procedure for the in-situ formation of the aminal.

2.1.3.8 State of the art on the synthesis of α-aminophosphonates.



Scheme 2.85 – Hydrophosphonylation of imines (2.1.251). The Pudovik reaction

In the spirit of designing amines carrying biorelevant functional groups in α-position, we set our sights on a phosphonate-containing hemiaminal (**D**, **2.1.255,** Scheme 2.86). The hypothetical products, α-aminophosphonates (**2.1.253**, Scheme 2.85 or **2.1.256**, Scheme 2.86), have well-documented biological proprieties,[460,461] and are sought-after synthetic targets. Most methods rely on hydrophosphonylation, a type of reaction which heavily depends on the nature of the amine partner (Scheme 2.85).[462] Prominent methods are the Pudovik addition of a phosphite (**2.1.252**) to an imine intermediate (**2.1.251**), which is generated *in situ* in the Kabachnik-Fields variant.[463]

2.1.3.9 Initial studies on the synthesis of α-aminophosphonates from alkenes

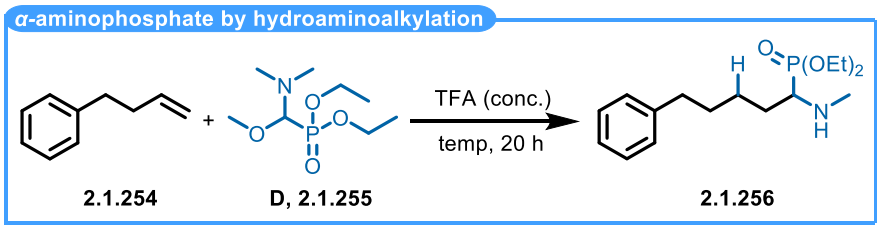
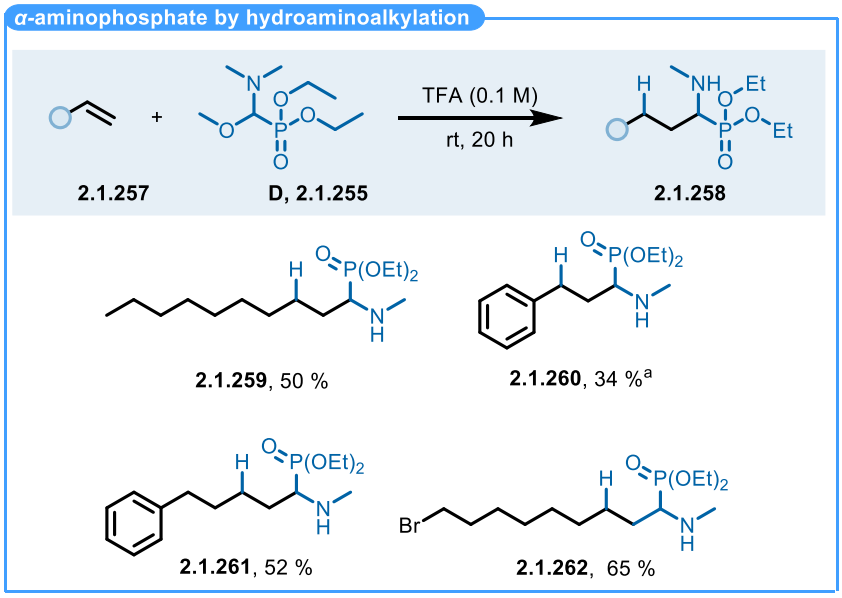


Table 2.6 – Optimisation of the synthesis of α-phosphonate amines (2.1.256) by hydroaminoalkylation using aminal D (2.1.255).

Entry	*Temperature (°C)*	*Conc. (M)*	*Conversion **2.1.254** %*	*Product (**2.1.256**) %*
1	-10	0.1	70	15
2	20	0.1	100	52
3	20	0.6	100	-
4	50	0.1	100	33

Instead of using an aminal to reductively couple the iminium surrogate to the alkene, we explored to correspondent hemiaminal (**D**, **2.1.255,** Table 2.6), previously characterised and isolated.[458] In the optimisation process we observed that this compound exhibits comparatively intermediate reactivity, being less reactive than aminal **A (2.1.184)** and more reactive than **C (2.1.229)**. At -10 °C only average conversion was observed (Table 2.6, entry 1). Under warmer reaction conditions, full conversion was observed, with 50 % of the product isolated under those conditions (entry 2). A more concentrated solution led to non-selective decomposition (entry 3). The postulated instability of the product (**2.1.258**) was confirmed when the reaction was conducted at 50 °C, leading to substantial decrease in yield (entry 4).



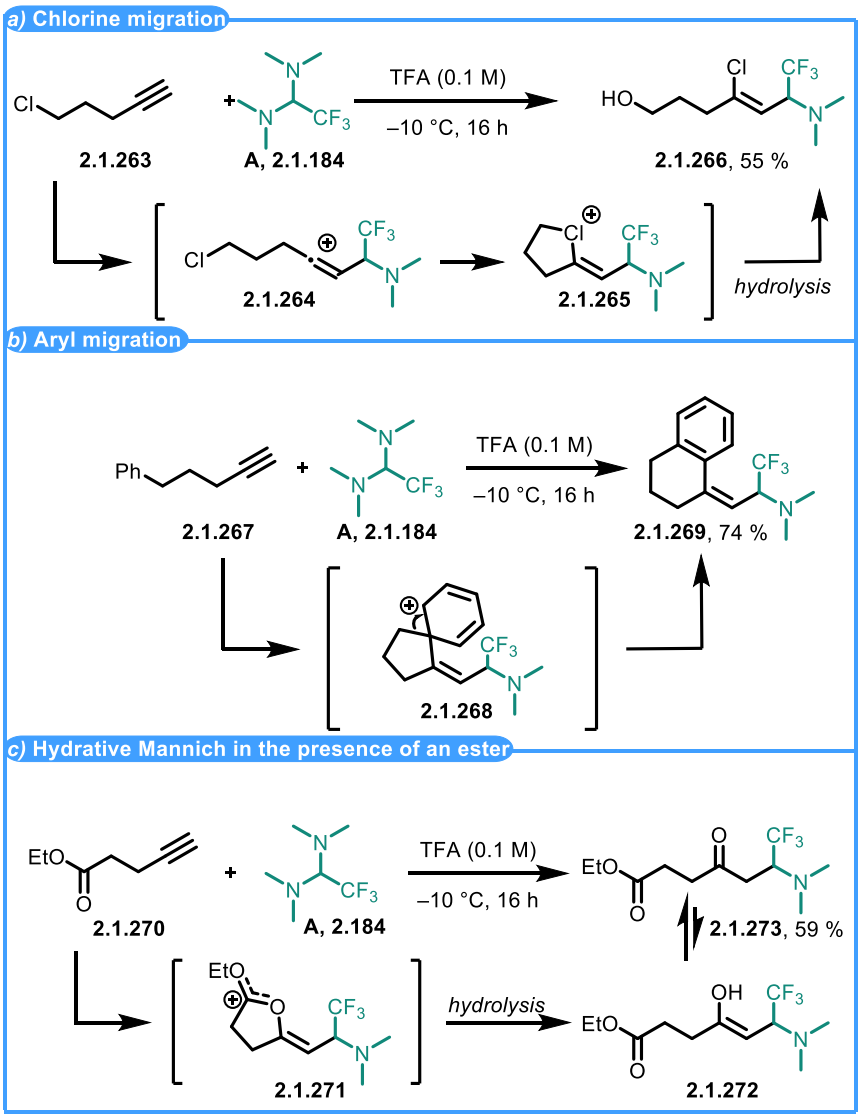
Scheme 2.86 – Scope of α-aminophosphates synthesised via hydroaminoalkylation of alkenes with hemiaminal D (2.1.255). [a] Reaction conducted at -15 °C

As shown in Scheme 2.86, acidolysis of the hemiaminal **D** (**2.1.255**) resulted in the selective formation of an iminium reagent able to deliver the α-aminophosphonate product by redox-neutral coupling to an alkene. As for the preceding cases, both styrenes (**2.1.260** and **2.1.261**) and aliphatic alkenes (**2.1.259** and **2.1.262,** Scheme 2.86) afforded the desired adducts in good yields.

2.1.3.10 Mechanistic considerations of the acid-catalysed hydroaminoalkylation of alkenes.

In terms of the mechanism, some unexpected observations suggested the intermediacy of defined carbocations (Scheme 2.87). [464–466]

Employing 5-chloropent-1-yne (**2.1.263**, Scheme 2.87a) as a starting material afforded chloro-alcohol **2.1.266** in 55 % yield (Scheme 2.87a). The chlorine migration observed in the product likely results from the formation of a 5-membered chloronium intermediate (**2.1.265**). This undergoes ring-opening either by trifluoroacetate or by adventitious water, to account for the observed product.[467]



Scheme 2.87 – Domino functionalisation from the formation of a vinyl carbocation: a) Chlorine migration, b) Phenyl migration, c) Hydrative Mannich in the presence of an ester.

In a similar fashion (Scheme 2.87b), the presence of a remote phenyl group (**2.1.267**) resulted in an aryl migration with formation of the tetralin **2.1.269** in 74 % yield. This can be explained by a domino Prins/Friedel-Crafts process followed by an alkyl shift of the spirocyclic intermediate **2.1.268**.

Finally, the presence of an ester was able to arrest the hydride shift event (**2.1.270**, Scheme 2.87c), resulting in the formation of interesting ketone **2.1.273** (Scheme 2.87). Instead, this intriguing observation, explained in a similar fashion to the aforementioned results, delivers the equivalent to a hydrative Mannich reaction of a terminal alkyne.

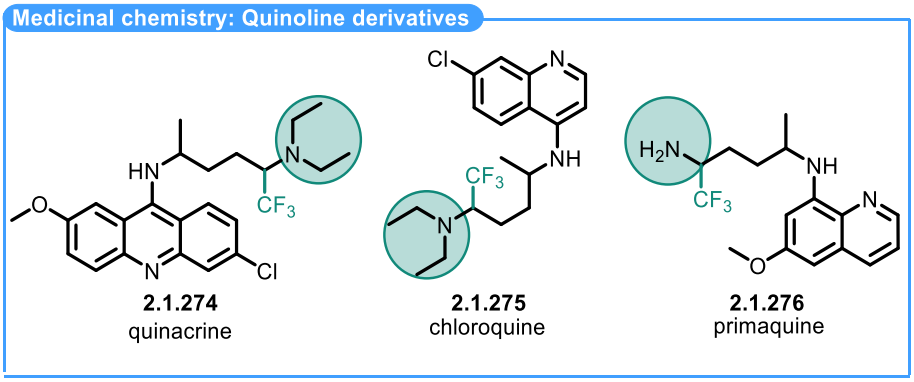
2.1.4 Conclusion

In conclusion, we developed a general acid-mediated hydroaminoalkylation of alkenes and alkynes for the synthesis of highly functionalised amine derivatives. This work enables the direct synthesis of trifluoromethylated amines, aminoesters and aminophosphonates through a direct, reductive coupling of simple alkenes/alkynes. Our approach can be readily generalised to obtain a wide range of structurally valuable amine scaffolds, including antihistaminic, druglike scaffolds, in good yields.

Given the extensive interest of the scientific community in the building blocks prepared here, allied with simplicity of the method reported, we envisage that the reactions described herein will find broad application.

2.1.5 Future prospects

The developed hydroaminoalkylation method has high synthetic potential, especially in the realm of medicinal chemistry. The ability to swiftly generate scaffolds such as amino acids, amino phosphonates or amino trifluoromethyl derivatives in a direct fashion from an unactivated alkene, should enable the synthesis of various important derivatives.



Scheme 2.88 – Syntheses of new bio-active quinoline derivatives

Quinolines are biologically important scaffolds that combat a multitude of diseases, from cancer to malaria (Scheme 2.88). Their syntheses have been targeted by many groups in the last few years, considering their medicinal value. A wide range of quinoline alkaloids could be targeted, leading for the possibility to explore the mechanism of action of such compounds by SAR studies (**2.1.274**, **2.1.275**, **2.1.276**, Scheme 2.88). Additionally, we could also expand this method to include other fluorinated scaffolds, such as CF_2H, that are known to possess biologically relevant proprieties.[468,469]

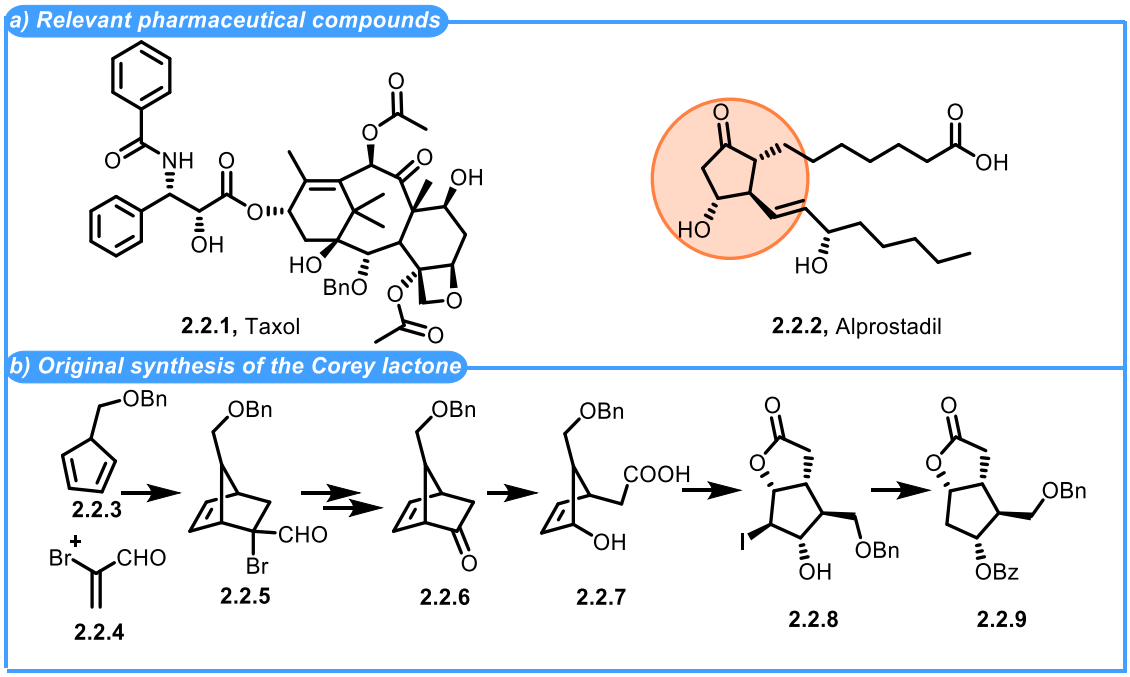
2.2 AMINOLACTONISATION OF ALKENES

2.2.1 Introduction

2.2.1.1 Total synthesis of natural products, a healthy competition?

The biological activity, combined with natural scarcity, as well as challenging structural complexity of certain drug scaffolds or groups of compounds have motivated synthetic chemists to construct them artificially, sometimes resulting in races to first synthesise said targets. An important example of such a target is Taxol (**2.2.1**, Paclitaxel©, Scheme 2.89a), a compound originally shown to have promising antitumoral activity,[470–474] and which later became the most profitable anti-cancer drug of the 2000´s.[475] In 1992, 15 years after the report of its antitumoral activity, over 40 synthetic research groups were targeting Taxol, a "race"[476] won simultaneously by Nicolaou[477] and R. A. Holton.[478,479] Notably, the published syntheses spawned multiple different strategies for the synthesis of a wide array of analogues.[480,481]

Another earlier example of this pursuit towards a family of molecules with biological relevance was the prostaglandins, a group of ubiquitous lipid-containing compounds that possess important biological activity, such as the vasodilator Alprostadil (**2.2.2.**, Scheme 2.89a).[482–484] For the elucidation of the structure of these molecules and their role in the human body, Bergström was jointly awarded the Nobel prize for physiology and medicine in 1982.[485]



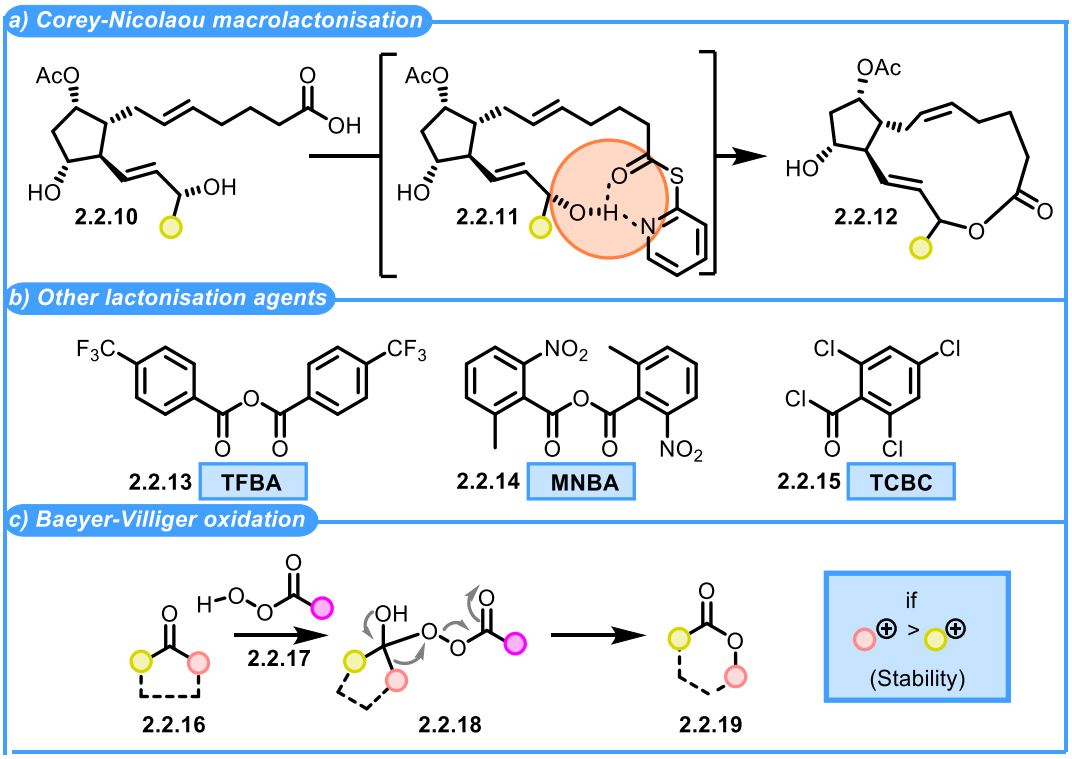
Scheme 2.89 – a) Pharmaceutically relevant complex natural products Taxol (2.2.1) and Alprostadil (2.2.2), b) Original synthesis of the Corey lactone (2.2.9).

In order to easily construct this heterogeneous family of molecules, synthetic chemists tried to reach a common precursor that would enable a divergent and facile synthesis of different analogues. This feat was first accomplished by Corey, developing a lactone so vital to all following synthetic efforts towards prostaglandins that it is widely referred to as the Corey lactone (**2.2.9**, Scheme 2.89b).[486–490] Notably, this versatile intermediate can be formed stereoselectively *via* a Diels-Alder [4+2]-cycloaddition (**2.2.3** and **2.2.4**), with the crucial lactone subsequently built by iodolactonisation (**2.2.8**).[491–494] In time, alternative methodologies, involving three-component reactions[495] and organocatalysed cyclisations[496–499]—one of which assembling the Corey lactone in a one-pot procedure lasting less than 3 hours [500] —, were developed.

2.2.1.2 Synthesis of lactones – important and versatile building blocks.

In addition to being synthetically versatile, lactones are important chemical moieties, with studies suggesting their presence in around 10 % of all natural products,[501] mostly containing 5- and 6-membered lactones.[502] In terms of biological activity, macrocyclic lactones have shown to have particularly promising effects, and have hence been the subject of various synthetic efforts.[503,504] In pursuit of these targets, several

methodologies have been developed to access this highly coveted chemical moiety. One of the most common approaches for the synthesis of large lactones is macrocyclic esterification, termed macrolactonisation. The so-called Corey-Nicolaou lactonisation, curiously initially developed for the synthesis of prostaglandins (Scheme 2.90a), involves the cyclisation of a hydroxy acid (**2.1.10**) by formation of a thio ester (**2.1.11**). This reaction proceeds with concomitant activation of the hydroxyl group by H-Bonding, increasing its nucleophilic character, and the thioester, rendering it a better electrophile (**2.2.11**, orange circle).[505–507] Other methodologies also employ a similar activation of the acid moiety, namely the procedures developed by Shiina, relying on electrophilic anhydrides, such as TFBA (**2.2.13**. Scheme 2.90b) under acid catalysis or MNBA (**2.2.14**) in combination with a nucleophilic catalyst (Scheme 2.90b) [508–510] to generate the desired mixed anhydride. Alternatively, the Yamaguchi cyclisation uses halobenzoyl acid chlorides such as TCBC (**2.2.15**),[511,512] to facilitate the cyclisation step.



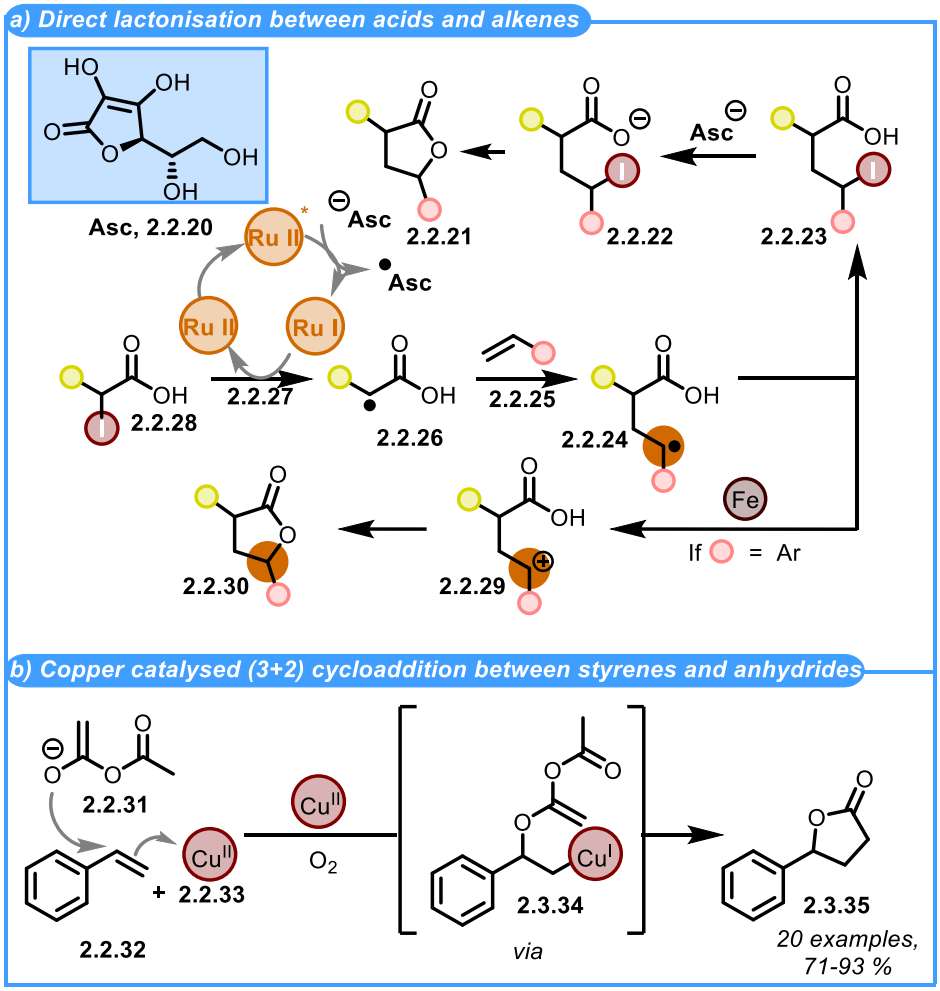
Scheme 2.90 – a) Nicolaou-Corey macrocyclisation of 2.2.10 to afford 2.2.12, b) Macrolactonisation methods using electrophilic agents (2.1.13 – 2.1.15), c) Baeyer-Villiger oxidation of cyclic ketones (2.2.16).

An important transformation which combines cyclic ketones (**2.2.16**, Scheme 2.90c) with peroxy acids to afford the corresponding lactones (**2.2.19**) is the Baeyer-Villiger reaction (Scheme 2.90c).[513] Mechanistically, the reaction proceeds *via* protic activation of the carbonyl (by **2.2.17**), which is subsequently attacked by the nucleophilic

peroxide anion, generating a Criegee-type intermediate (**2.2.18**). In a concerted fashion, one of the substituents of the former ketone migrates from carbon to oxygen, expelling a carboxylic acid.[514–516] It is thought that the ability to stabilise incipient positive charge determines the order of migration, which is also known to occur with retention of the configuration.[517,518]

2.2.1.3 Synthesis of lactones using alkenes.

Complementary methods on the synthesis of lactones rely on the addition of a radical (**2.2.26**, Scheme 2.91a), stemming from an α-halocarboxylic acid derivative (**2.2.28**), to alkenes (**2.2.25**), generating the lactone scaffold by ultimate cyclisation of the carboxylic acid (**2.2.21**, Scheme 2.91a). Such methods rely on the use of photocatalysts to generate the radical species by homolytic scission of a C–I bond (**2.2.26**), usually in combination with a base that facilitates the photocatalytic cycle.[519,520] One of the preferred examples uses ascorbate (**2.2.20**) as a base. Upon addition of the radical species to the alkene, the subsequent radical (**2.2.24**) can undergo propagation to generate a new C–I bond (**2.2.23**). Displacement of the iodide by the carboxylic acid then furnishes the desired lactone (**2.2.21**). A similar strategy, albeit limited to styrenes (**2.2.25**, aromatic substituents, orange circle), relies on the nature of these particular alkenes to generate a benzylic radical (**2.2.24**) which can be oxidised to the corresponding cation (**2.2.29**, for example using iron), and subsequently cyclised (**2.2.30**, Scheme 2.91a).[521–526527–535]

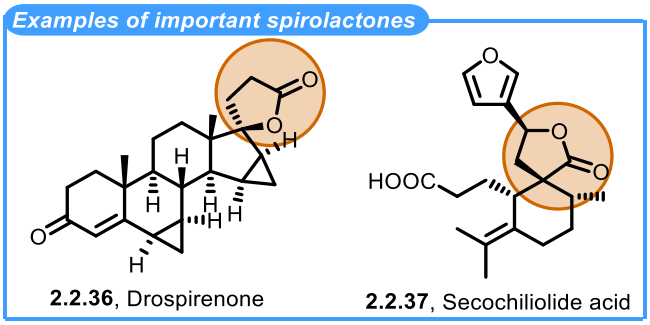


Scheme 2.91 – a) Direct lactonisation from alkenes using α-halo carboxylic acids (2.2.28), b) Copper catalysed (3+2) cycloaddition of styrenes (2.2.32) with anhydrides (2.2.31).

Alternatively, it is also possible to catalyse (3+2)-oxidative cycloadditions between alkenes (**2.2.32**, Scheme 2.91b) and anhydrides, (**2.2.31**) using copper salts that activate the alkene under an oxygen atmosphere.[536] An important limitation of this methodology is the reliance on styrene derivatives, (Scheme 2.91b) rendering it unable to access important families of lactones.

2.2.1.4 Important family of γ-lactones – Spirolactones and their synthesis.

A relevant family of γ-lactones (Scheme 2.92) are spirolactones, which, as the name suggests, are connected to another cycle by a single common carbon atom.[537] This important group possess a range of intriguing proprieties, with e.g. numerous examples of steroids containing spirolactones,[538,539] (**2.2.36** and **2.2.37**, Scheme 2.92) with the spirocenter located at different position of the lactone framework.

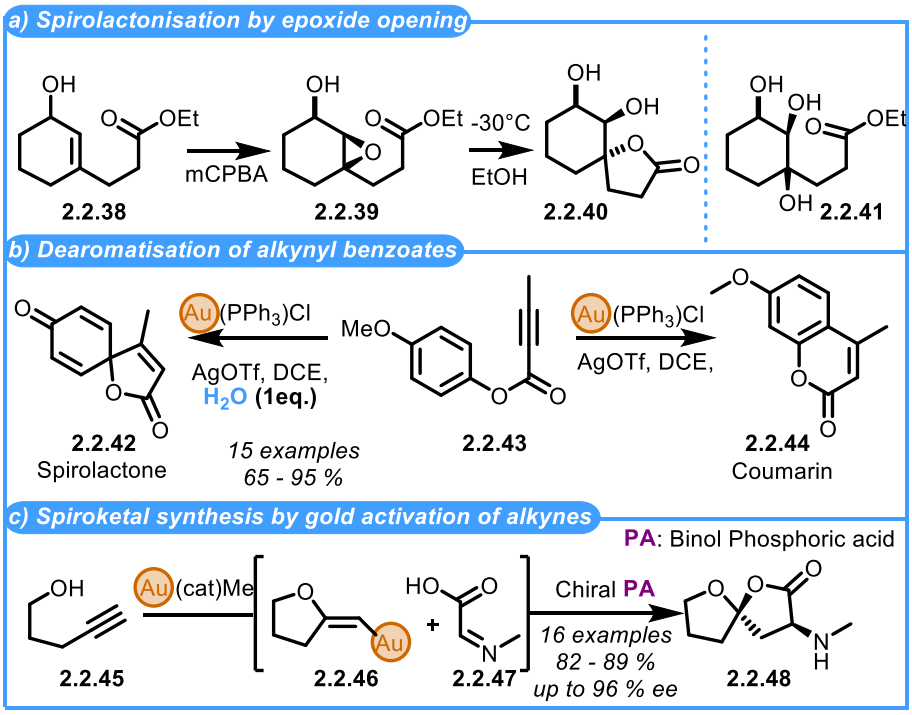


Scheme 2.92 – Important families of Spirolactones. Secochiliolide acid (2.2.36) possessing anti-carcinogenic and trypanocidal activities [540]

State of the art protocols for the synthesis of such spirolactones utilise electrophiles to facilitate the spirocyclisation of allylic systems, (**2.2.39**, Scheme 2.93a) usually stemming from the corresponding allylic alcohols (**2.2.38**). Such cyclisation can also be promoted by strong acids and the corresponding alcohols (**2.2.41**, Scheme 2.93a).[541]

Gold catalysis also proved successful in triggering spirolactonisation events. One example utilises phenolic dearomatisation to trigger the cyclisation event of gold-activated ynoates (**2.2.43**, Scheme 2.93b)[542–544], a process also possible using activation with an electrophilic halogen source.[545–550] Curiously, when the reaction is conducted in anhydrous conditions, a coumarin core was formed instead (**2.2.44**). The rationale for this finding is that water was responsible for demethylation of the activated anisole, which is exclusive to spirolactone formation.

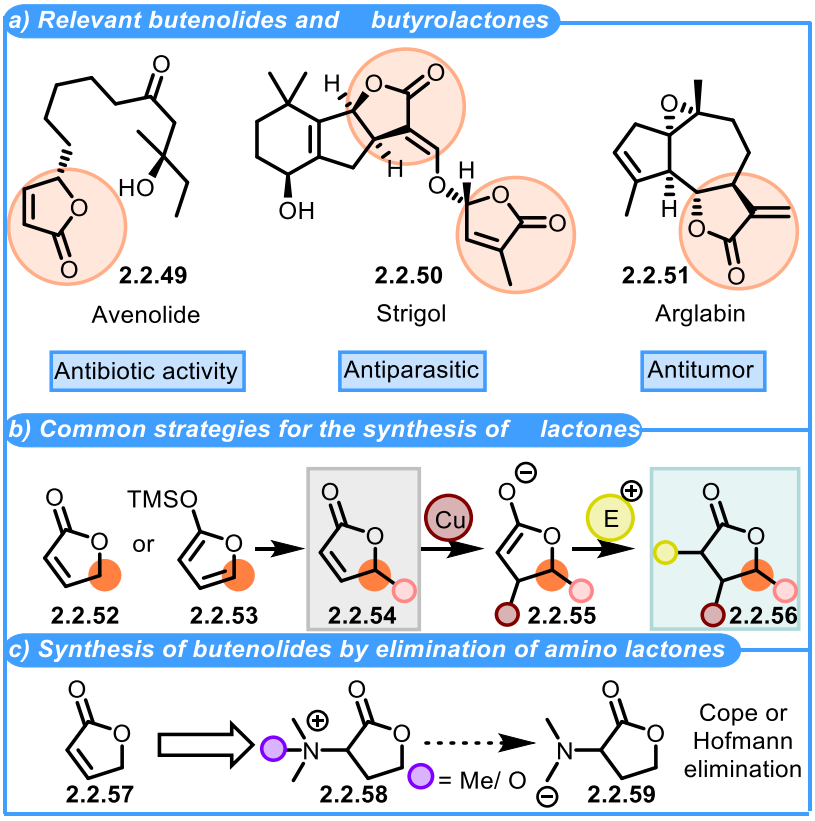
A very interesting example involves the reaction between gold-activated alkynols (exo, **2.2.46,** Scheme 2.93c) and imines derived from glyoxylic acid (**2.2.47**),[551] which react in a (3+2)-cycloaddition to generate spiroketals (**2.2.48**),[552,553] yet another biologically important lactone-containing moiety.[554] Importantly, stereoselective cyclisation was achieved by using chiral phosphoric acids (PA – derived from Binol).[555]



Scheme 2.93 – a) Spirolactonisation by intramolecular epoxide opening (2.2.39, b) Synthesis of spiroketals by alkyne activation (2.2.43) using gold catalyst, c) Dearomatisation of aryl alkynoate esters (2.2.45) to afford spiroketals (2.2.48).

2.2.1.5 Butenolides and butyrolactones – Enticing chemical targets.

One of the main motivations for the development of new lactonisation methods, is the existence of natural products containing this privileged framework (**2.2.49**, **2.2.50** and **2.2.51**, Scheme 2.94a). Two of the most important examples are γ-butyrolactones (**2.2.56**, Scheme 2.94b) and their unsaturated congeners, the butenolides (**2.2.54**).[556–564] From a biological point of view, these families exhibit a wide range of effects,[565] ranging from antibiotic (**2.2.49**),[566–568] and antiparasitic (**2.2.50**)[569] to antitumor (**2.2.51**, scheme xa).[570] Synthetically, the route towards butenolides (**2.2.54**) involves the enantioselective functionalisation of the γ-position (orange circle) of furanones (**2.2.52** or **2.2.53**). This scaffold (**2.2.54**) can be then functionalised by addition of cuprates, and quenched with an electrophile to build fully substituted γ-butyrolactones (**2.2.56**, blue square, Scheme 2.94b).

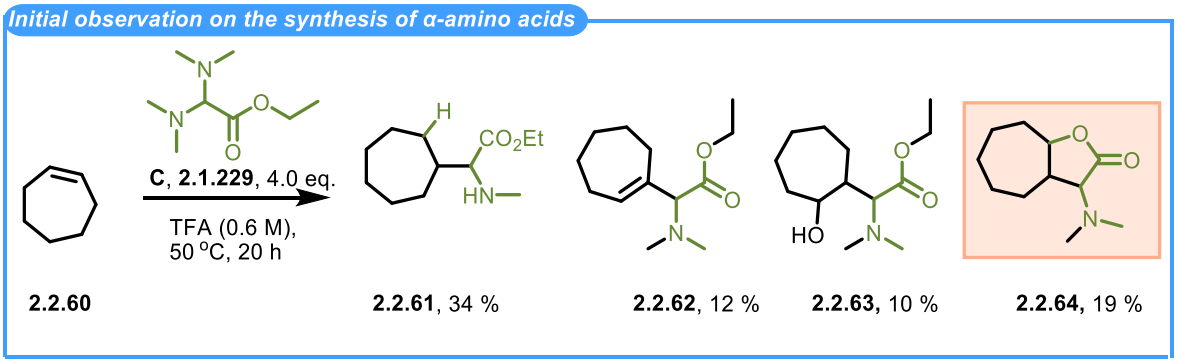


Scheme 2.94 - a) Relevant butenolides and γ-butyrolactones – Avenolide (2.2.49), Strigol (2.2.50), Arglabin (2.2.51) b) Common strategies for the synthesis of substituted γ-lactones (2.2.56), c) Synthesis of butenolides (2.2.57) by elimination of α-amino lactones (2.2.59)

2.2.1.6 Revisiting the aminoacids synthesis from alkenes – An interesting side product.

As mentioned in the previous chapter, during our investigation on the synthesis of α-amino esters by hydroaminoalkylation (Scheme 2.95), we observed the formation of a lactone product bearing an α-amino group. Apart from being interesting products by their own right, one can envisage a straightforward butenolide synthesis from these α-amino

lactones (**2.2.64**, Scheme 2.95 or **2.2.59**, Scheme 2.94b) through either Cope or Hofmann elimination of the amine (**2.2.58**).



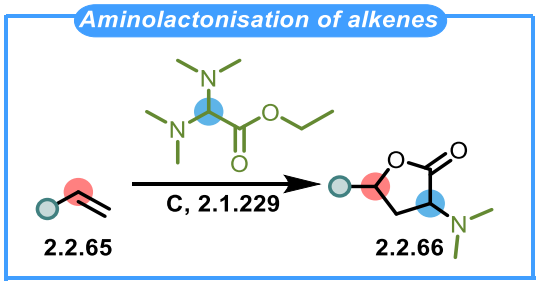
Scheme 2.95 - Initial observation on the synthesis of α-aminoacids by hydroaminoalkylation. Formation of multiple side products including fused lactone 2.2.64.

A closer look at our initial results showcases the challenging nature of this transformation, with side-products (**2.2.61**) including those resulting from elimination (**2.2.62**, Scheme 2.95) or capture of the carbocation by adventitious water/TFA (**2.2.63**). Nevertheless, we decided to explore this method for the synthesis of lactones (**2.2.64**), as it would constitute a formal overall cycloaddition, if general applicability could be demonstrated. These efforts form the content of the next section.

2.2.2 Objectives

The aim of this project is to develop a method for the direct aminolactonisation of alkenes (**2.2.65**, Scheme 2.96), resulting in the formation of γ-lactones bearing an α-amino group (**2.2.66**), and to investigate their chemistry (e.g. as precursors to butenolides).

The results described herein were obtained in collaboration with Dr. David Just, Dr. Sheng-Hsu, Sergio Armentia Matheu and Laurin Pollesböck.



Scheme 2.96 – Objective –Proposed amino lactonisation of alkenes

2.2.3 Results and discussion

2.2.3.1 Initial studies on the aminolactonisation of alkenes

During an initial screening of different alkenes in the hydroaminoalkylation reaction, we observed low yields when using cyclic substrates containing exo-methylene groups. Specifically, the use of methylene cyclohexane (**2.2.67**, Table 2.7) under our standard hydroaminoalkylation conditions (cf section 2.1) afforded the lactone product in 57 % ^{1}HNMR yield.

With this encouraging result, we sought to optimise other reaction parameters such as solvent, concentration and reaction temperature (Table 2.7). The use of NMP (*N*-methyl-2-pyrrolidone) as a co-solvent led to an increase in yield (entry 2). However, the presence of NMP rendered isolation challenging, leading us to the pursue alternative solvents. In comparison, ethyl acetate gave slight worse yields at the same temperature (50 °C, entry 3), while, surprisingly, a decrease in temperature afforded better results (20 °C, entry 4). At 20 °C, DME also gave satisfactory results as co-solvent (entry 5), and a mixture of DME and TFA, heated to the latter solvent's boiling point (72.5 °C), also led to good yields. Due to concerns about the stability of the aminal at 75 °C, we decided to lower the temperature, providing **2.2.68** in 75 % isolated yield (entry 8). Variation of other reaction parameters, such as concentration, aminal stoichiometry and reaction time, did not seem to have noticeable effects on the reaction outcome (not shown).

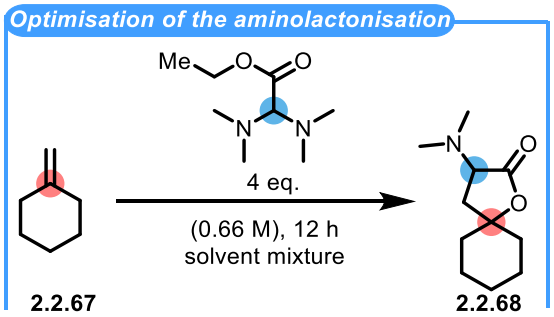
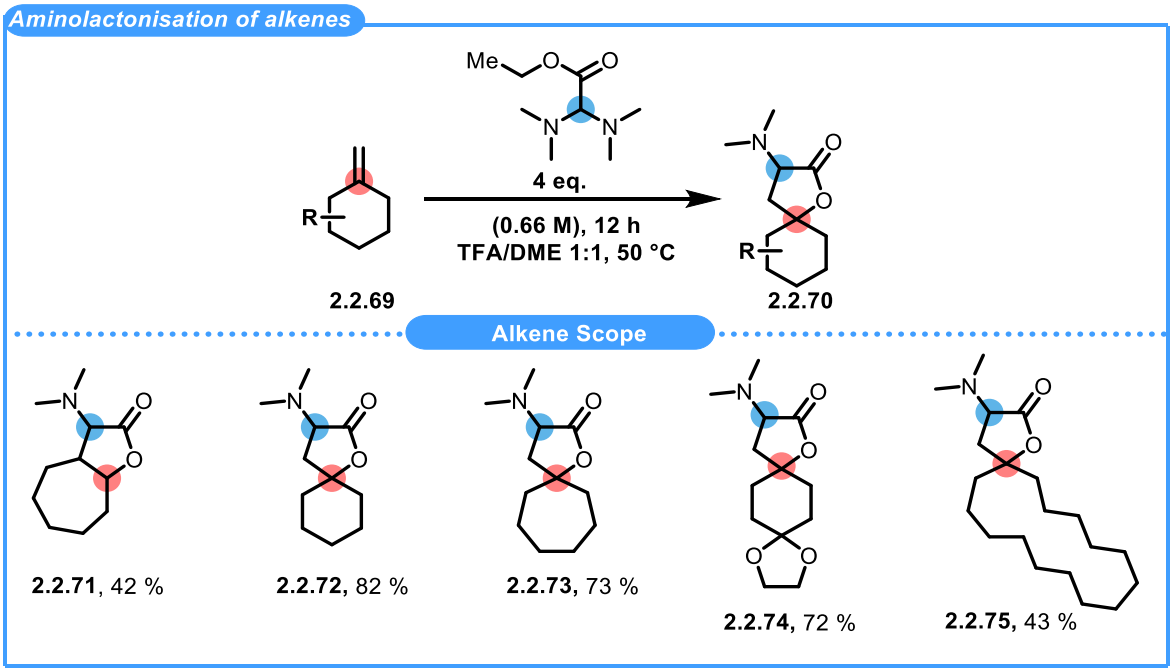


Table 2.7 – Selected experiments in the optimisation of the aminolactonisation of alkenes. [a]isolated yield.

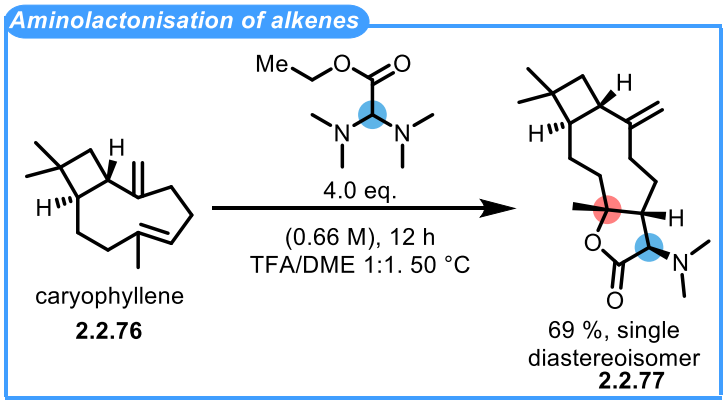
Entry	*Temperature (°C)*	*Solvent*	*NMR yield **2.2.68** (%)*
1	50	TFA	57
2	50	TFA/NMP	75
3	50	TFA/EtOAC	63
4	20	TFA/EtOAC	80
5	20	TFA/DME	63
7	75	TFA/DME	78
8	50	TFA/DME	85 (75 %)[a]

2.2.3.2 Aminolactonisation of alkenes – Scope of the transformation.

With the optimised conditions in hand, we set out to uncover the limitations of this methodology by performing experiments with a range of alkenes. As shown in Scheme 2.97, cyclic alkene resulted in a fused lactone in modest yield (**2.2.71**). Other exocyclic alkenes, namely methylene cycloheptane and -cyclopentadecane, also afforded the desired products **2.2.73** and **2.2.75**. In terms of functional group tolerance, we surprisingly observed that ketal (**2.2.74**) survived the reaction conditions, despite the use of TFA.

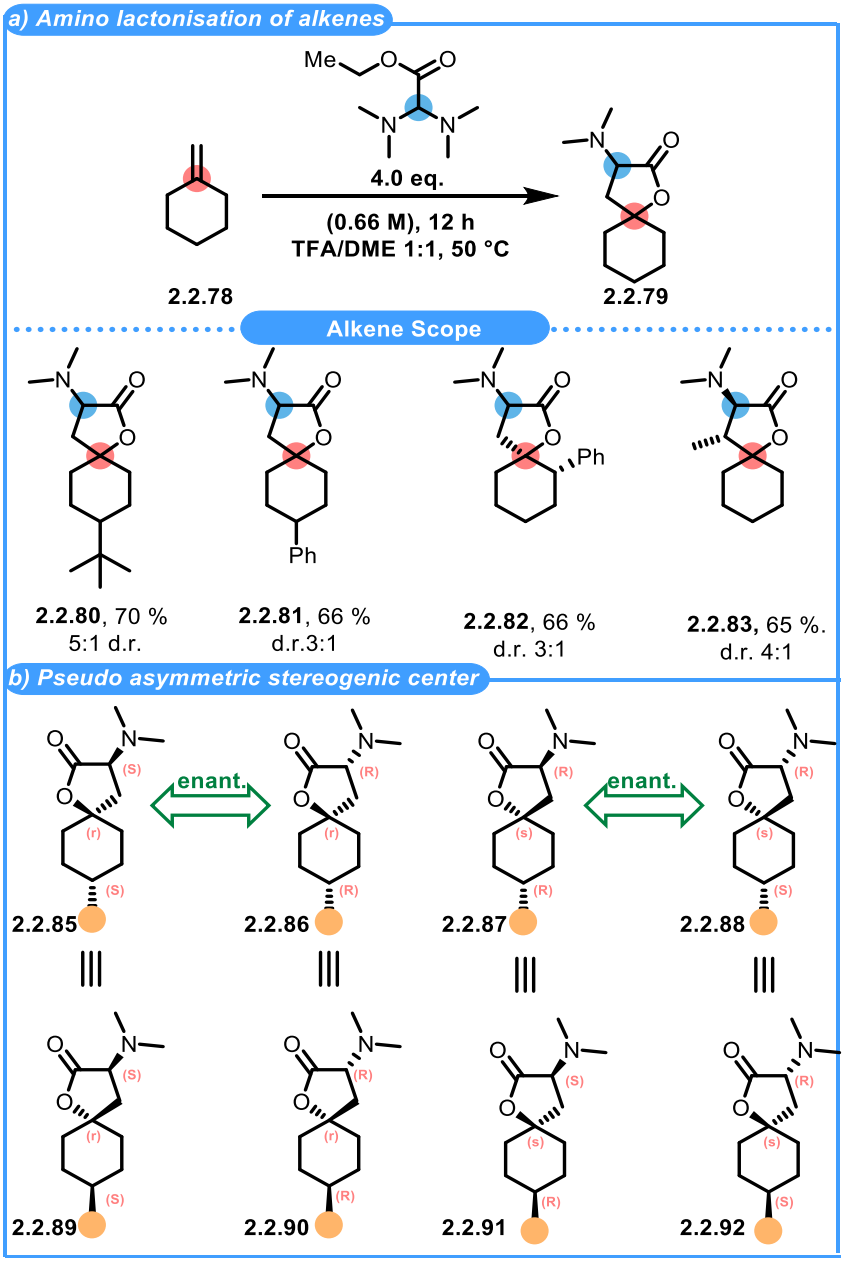


Scheme 2.97 – Aminolactonisation of different ring-sized exocyclic alkenes (2.2.69).



Scheme 2.98 - Opposite selectivity on the aminolactonisation of caryophyllene

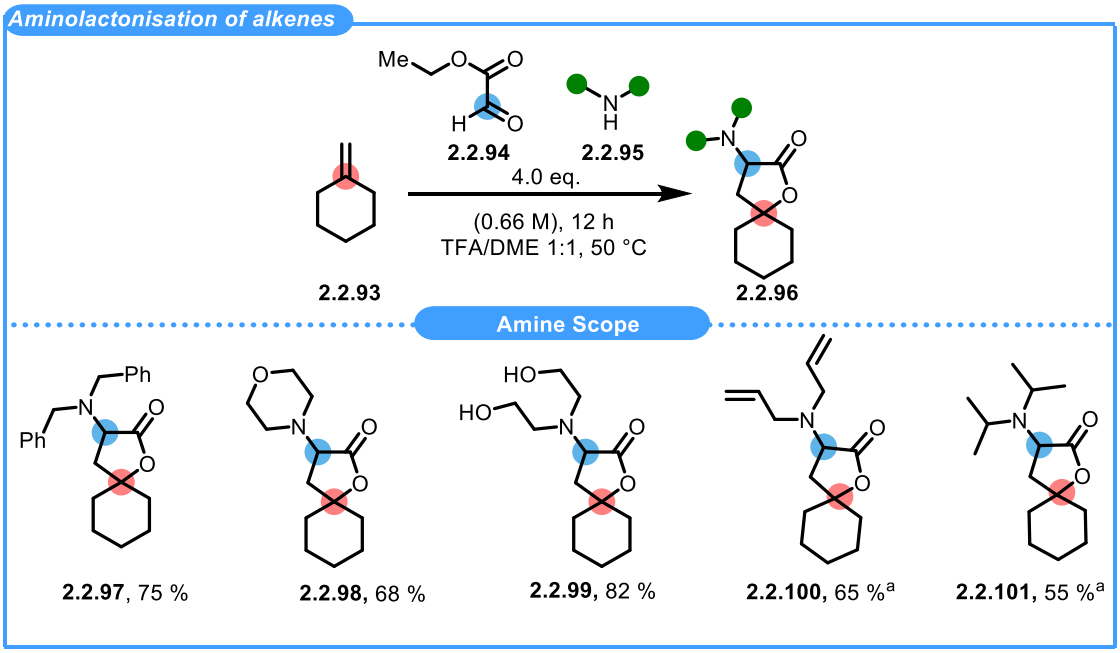
When subjecting caryophyllene (**2.2.76**, Scheme 2.98), possessing both an exo-methylene group and an endocyclic, trisubstituted double bond, to our reaction conditions, we observed diverging reactivity (Scheme 2.98). Instead of reaction with the exocyclic alkene, we observed conversion of the endocyclic trisubstituted alkene affording **2.2.77**. The high strain of this *E*-endocyclic alkene, along with the steric hindrance at the exocyclic methylene moiety, could justify the observed reactivity.[571,572]



Scheme 2.99 - Methylenecyclohexane scope on the aminolactonisation of alkenes substitution. b) Pseudo asymmetric stereogenic center found on the products of aminolactonisation

We then decided to study a range of substituted methylenecyclohexane derivatives, anticipating that the typical chair-like nature of these substrates would have an effect on the diastereomeric ratios obtained (Scheme 2.99a). *Tert*-butyl (**2.2.80**) and phenyl (**2.2.81**) substitution at position 4 of the cyclohexane induced moderate diastereoselectivity, while the yield remained high. A phenyl substituent at position 2 led to similar results, with a diastereomeric ratio of 3:1 (**2.2.82**). The use of an exocyclic substituted alkene also afforded the desired product in good yield, affording the lactone with a trans:cis ratio of 4:1 (**2.2.83**). It is important to mention that 1,4 substituted spirocyclohexanes contain a

spiro pseudo asymmetric stereogenic center which, is the reason why only two diastereoisomers can be found in our experiments instead of 4 (e.g. **2.2.85** is the same as **2.2.89**, Scheme 2.99b).



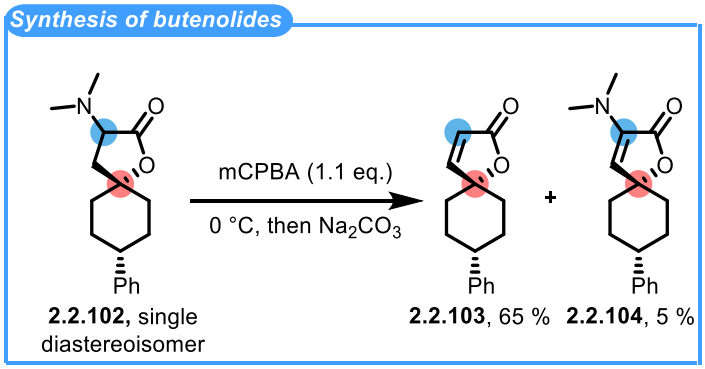
Scheme 2.100 –Scope for the aminolactonisation reaction using different amines (2.2.95).[a] ^{1}HNMR yield using mesitylene as an internal standard.

To our delight, the use of different aminals formed *in situ* also resulted in aminolactonisation products (**2.2.96**, Scheme 2.100). A range of secondary amines (**2.2.95**, Scheme 2.100) could be employed in this manner, including dibenzyl amine (**2.2.97**) or diallyl amine (**2.2.100**), both of which might lend themselves to facile downstream deprotection. Unfortunately, purification issues prevented the isolation of the products, due to elevated amounts of amine impurities (**2.2.101**). Other amines, including morpholine (**2.2.98**) and diethanol amine (**2.2.99**), gave the desired lactone products in good yields, with purification being facilitated by the water solubility of the free amines.

2.2.3.3 Initial studies on the synthesis of butenolides from α-amino lactones.

We then focused on the synthesis of butenolides by elimination from the correspondent α-amino lactones (**2.2.102**, Scheme 2.101). Cope elimination was found to afford the desired butenolides in high yield (**2.2.103**), with low amounts of the undesired unsaturated amine (**2.2.104**), which stemmed from the tautomerisation of the iminium

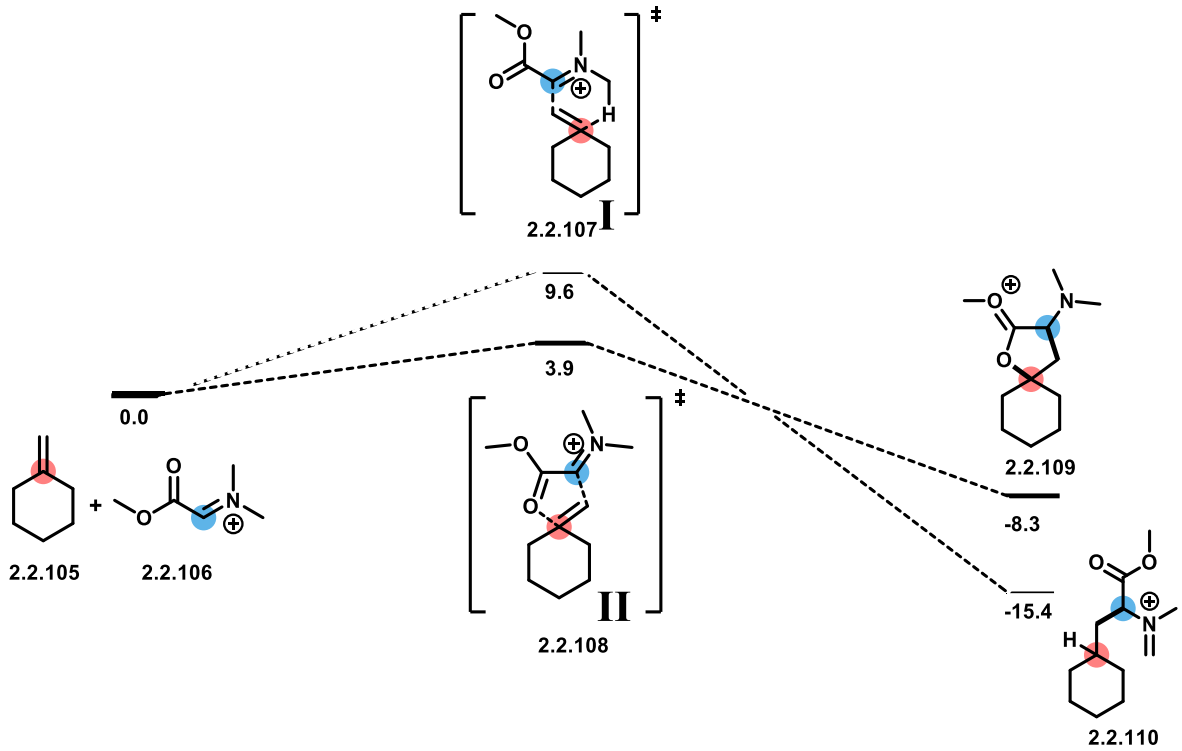
intermediate. Low temperature was found to be crucial in achieving a high ratio of the butanolide product.



Scheme 2.101 – Cope elimination of α-amino lactones to afford butenolides

2.2.3.4 Aminolactonisation vs Hydroaminoalkylation: a competing mechanism.

As shown previously, the reaction of aminals with alkenes readily affords the products of hydroaminomethylation and hydroaminoalkylation (Scheme 2.102). It is therefore worth noting that the substrates shown in this section react almost exclusively along the aminolactonisation pathway, with almost no hydroaminoalkylation product detected in the crude mixtures. Hoping to pinpoint the reason for this selectivity. We undertook computational calculations with our collaboration partners (Prof. Leticia Gonzalez, Dr. Boris Maryasin and Laurin Pollesböck) (Scheme 2.102). For exocyclic alkenes such as those used within this study, preliminary data showed that there are substantial energetic differences in the transition states associated with the two competing pathways.



Scheme 2.102 – Competing pathways on the reaction between aminals and alkenes. Hydroaminoalkylation vs aminolactonisation of alkenes.

The formation of each product involves a single step. The transition state for the hydroaminoalkylation (**2.2.107**, profile **I**) involves a C–C bond formation concerted with a proton transfer, while the transition state for the aminolactonisation (**2.2.108**, profile **II**) is akin to a [3+2] cycloaddition. In contrast to experimental observations, the obtained energy profile shows that the path for the hydroaminoalkylation (profile **I**) is thermodynamically favoured even though both pathways are exergonic (ΔGI = -15.4 kcal/mol, while ΔGII = -8.3 kcal/mol). Notably, an activation energy of 3.9 kcal/mol for the aminolactonisation pathway (TS **II**) is considerably lower than the barrier obtained for the hydroaminoalkylation process (9.6 kcal/mol, TS **I**). The obtained results thus suggest that the studied reaction occurs under kinetic control. This fact also helps to rationalise the reason why exocyclic alkenes are favoured.

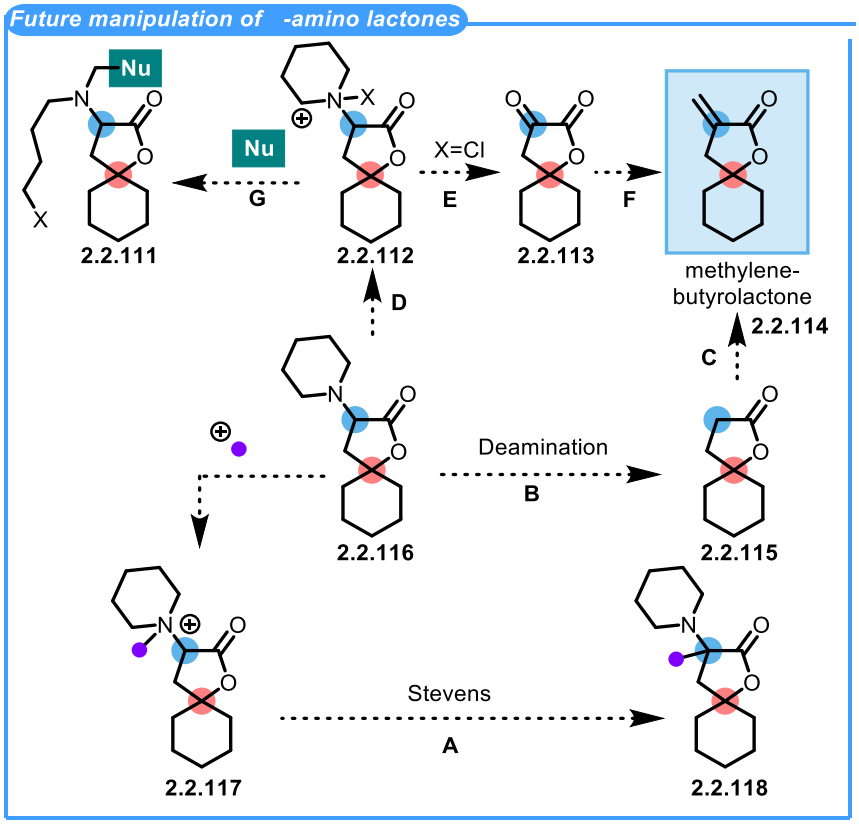
2.2.4 Conclusions

In summary, we have developed a novel approach to the construction of α-amino lactones. The reaction is applicable to a wide range of substrates and different olefinic substitution patterns. While some diastereoselectivity is observed, the nature of the diastereomeric ratio, as well as the factors controlling diastereoselectivity, are not yet fully understood. We also showed that this method tolerates a wide range of aminals, even when these are generated *in situ*.

The high potential of this reaction motivates us to continue our studies, with the goal of achieving the synthesis of relevant natural products and gaining a complete understanding of the reaction mechanism.

2.2.5 Future prospects

In expanding this chemistry and the utility of the reaction, there are multiple avenues worth pursuing (**Fehler! Verweisquelle konnte nicht gefunden werden.**). B esides the enhancement of the substrate scope to include alkenes bearing various functional groups or different substitution patterns, this project and following studies could focus on the synthesis of drug-like structural motifs, namely different γ-butyrolactones and butenolides. In terms of product manipulation, one could envision that using the ammonium salt (**2.2.117**, **Fehler! Verweisquelle konnte nicht gefunden werden.**), one could trigger S tevens rearrangement[573] (**A, 2.2.118**), leading to the formation of complex α-tertiary amines.



Scheme 2.103 - Functionalisation of the amino lactone core.

On the other hand, methylene γ-butyrolactones (**2.2.114**, Scheme 2.103) can be synthesised in various ways. One of the most straightforward approaches involves initial deamination[574] **(B, 2.2.115)**, followed by an Eschenmoser methylenation **(C, 2.2.114)**.[575–577] Additionally, chlorination of the tertiary amine[578] **(D, 2.2.112)** should also be feasible, leading to the formation of the iminium ion (not shown) that can be readily hydrolysed **(E, 2.2.113)** and methylenated (**F, 2.2.114**). An interesting point of this pathway is the

formation of the halogenonium amine (**2.2.112**), which in theory can also undergo different types of transformation such as deconstructive functionalisations using different nucleophiles (**G, 2.2.111**).[579]

Overall, several intriguing further developments can be envisaged, as a range of valuable and potentially biologically interesting structures are closely related to the amino lactones generated through our approach.

3 EXPERIMENTAL SECTION

3.1 GENERAL INFORMATION

General procedures. All reactions were performed in round bottom flasks or vials fitted with rubber septa with magnetic stirring, unless otherwise stated. Liquids and solutions were transferred via syringe. All reactions were performed using anhydrous solvents from Acros Organics or Sigma-Aldrich unless stated otherwise. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F_{254} with 0.2 mm thickness. Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate or vanillin. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck and co.).

Materials. All reagents were used as received from commercial suppliers and stored under an atmosphere of argon, unless otherwise stated.

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400, AV-500, AV-600 or AV-700 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 ppm (^{13}C NMR). Coupling constants (*J*) are reported in Hertz (Hz). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept). Splitting patterns that could not be interpreted or easily visualised were designated as multiplet (m) or broad (br). Protons and carbons were assigned whenever unambiguously possible - atoms that could not be assigned are denoted as H_{Ar} or C_{Ar} (aryl) for aromatic protons and carbons, H_{Alk} or C_{Alk} (alkyl) for aliphatic protons and carbons or similar. ^{13}C shifts that were not detected by ^{13}C NMR but showed a crosspeak in the HSQC are denoted as HSQC in parentheses.

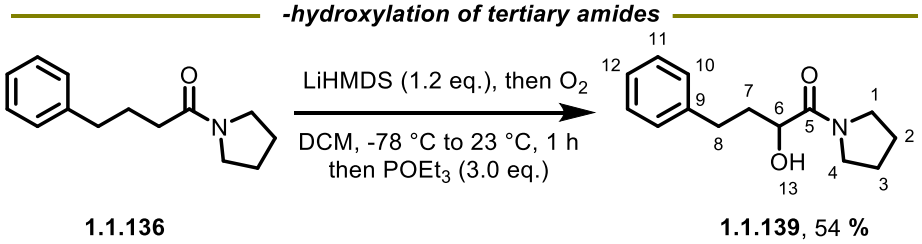
Mass spectra were obtained using a Finnigan MAT 8200 (70 eV), or an Agilent 5973 (70 eV) or a Bruker maXis UHR-TOF spectrometer, using electrospray ionisation (ESI). For cases in which mass was not detected with ESI ionisation, an Agilent 7200B GC/Q-TOF Spectrometer with electron impact (EI) ionisation and a TOF mass analyser was used. Infra-red (IR) spectra were obtained using Perkin-Elmer Spectrum 100 FT-IR

spectrometer. Wavenumbers (ν_{max}= 1/λ) are reported in cm^{-1}. Melting points were determined on a capillary apparatus and are uncorrected.

Given the difficulty of separating the dehydrogenated products from the starting materials, we have reported R_f values in a solvent system which we found best provided some separation between the starting materials and products.

3.2 Experimental Section Chapter 1.1

3.2.1.1 Synthesis of the materials for the mechanistic studies



2-hydroxy-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.139)

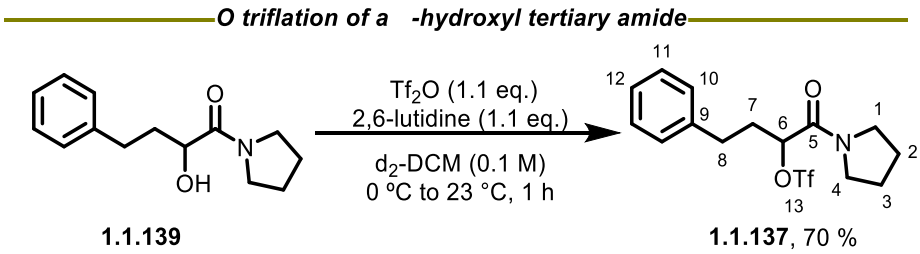
A flamed-dried Schlenk tube containing 4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (**1.1.136**, 0.43 g, 2.0 mmol) in 25.0 mL of DCM was cooled down to -78 °C for 15 min before the addition of 1.20 eq. of LiHMDS (2.1 mL, 1.0 M in DCM). The mixture was stirred for 1 h before the solution was saturated with oxygen gas. After stirring for 3 h at -78 °C, the reaction was allowed to slowly warm up to 23 °C. At this point, triethylphosphite (1.0 g, 6.0 mmol, 3.0 eq.) was added. After 1 h the mixture was quenched with saturated NH_4Cl and washed with DCM (3x). The combined organic phases were dried using $MgSO_4$ and evaporated. Purification by column chromatography on silica gel (EtOAc: heptane = 2:1) yielded the product as a yellow oil (0.251 g, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 - 7.27 (m, 3H, H_{Ar}), 7.24 - 7.16 (m, 2H, H_{Ar}), 4.17 - 4.14 (m, 1H, H_6), 3.71 (d, J = 7.2 Hz, 1H, H_5), 3.55 - 3.52 (m, 1H, $H_{1/4}$), 3.43 - 3.39 (m, 1H, $H_{1/4}$), 3.31 - 3.26 (m, 1H, $H_{1/4}$), 3.19 - 3.14 (m, 1H, $H_{1/4}$), 2.89 - 2.77 (m, 2H, H_8), 1.95 - 1.79 (m, 6H, $H_{2/3/7}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9 (C_5), 141.6 (C_{Ar}), 128.7 (2C, C_{Ar}), 128.6 (2C, C_{Ar}), 126.2 (C_{Ar}), 68.6 (C_6), 46.4 ($C_{1/4}$), 45.9 ($C_{1/4}$), 36.2 (C_8), 31.4 (C_7), 26.2 ($C_{2/3}$), 24.0 ($C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{14}H_{19}NO_2$ $[M+H]^+$ *m/z* : 256.1313, found: 256.1316;

IR (neat) ν_{max}: 3400, 3059, 2936, 1645.



Independent formation and isolation of the α-trifloxy amide. (1.1.137)

To a solution of the amide (**1.1.139**, 1.0 eq., 0.2 mmol) and distilled lutidine (0.2 mmol, 1.0 eq.) in d_2-DCM (0.1 M, 2.0 mL) at 0 °C, triflic anhydride (1.1 eq., 35.0 µL) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring for 1 h. After this time, the reaction mixture was quickly purified by column chromatography (ethyl acetate/heptane 1:1 - 3:1) at -30 °C (cryostat / isopropanol) to afford the α-trifloxy amide in 70 % yield (**1.1.137**, 50.0 mg) as a yellow oil.

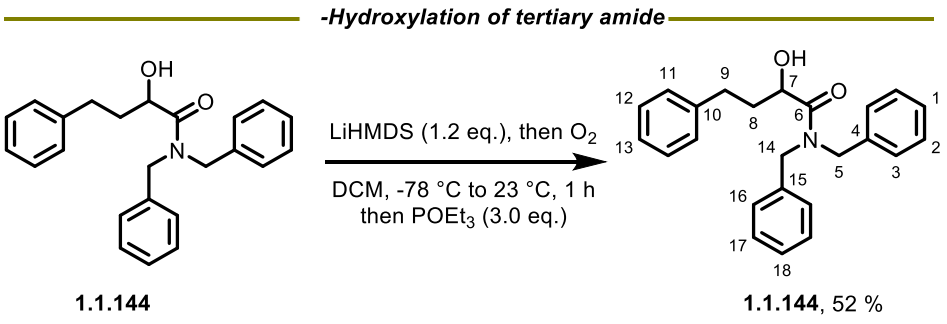
1-Oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl trifluoromethanesulfonate (1.1.137)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.28 (m, *J* = 8.5, 1.5 Hz, 2H, H_{11}), 7.25 - 7.17 (m, 3H, $H_{10/12}$), 5.21 (dd, *J* = 8.7, 4.4 Hz, 1H, H_6), 3.62 - 3.48 (m, 1H, $H_{1/4}$), 3.48 - 3.36 (m, 2H, $H_{1/4}$), 3.14 - 3.04 (m, 1H, $H_{1/4}$), 2.91 - 2.80 (m, 1H, H_8), 2.78 - 2.67 (m, 1H, H_8), 2.46 - 2.33 (m, 1H, H_7), 2.24 - 2.14 (m, 1H, H_7), 1.94 - 1.79 (m, 4H, $H_{2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.5 (C_5), 139.3 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 126.9 (C_{Ar}), 118.6 (q, *J*= 320 Hz, C_{13}), 83.1 (C_6), 46.6 ($C_{1/4}$), 46.2 ($C_{1/4}$), 33.4 (C_8), 30.8 (C_8), 26.2 ($C_{2/3}$), 23.9 ($C_{2/3}$);

^{19}F NMR (565 MHz, $CDCl_3$): δ -75.4, -78.9 (free OTf^-);

HRMS (ESI^+): calculated for $C_{15}H_{19}F_3NO_4S$ $[M+H]^+$ *m/z* : 366.0981, found: 366.0969.



_N_,_N_-Dibenzyl-2-hydroxy-4-phenylbutanamide (1.1.144)

A flamed-dried Schlenk tube containing *N,N*-dibenzyl-4-phenylbutanamide (**1.1.144**., 0.69 g, 2.0 mmol) in 25.0 mL of DCM was cooled down to -78 °C for 15 min before the addition of LiHMDS (1.2 eq., 2.1 mL, 1.0 M in DCM). The mixture was stirred for 1 h before being saturated with oxygen gas. After stirring for 1 h at -78 °C, the reaction was allowed to slowly warm up to 23 °C. At this point, triethylphosphite (1.0 mL, 6.0 mmol, 3.0 eq.) was added. After 1 h the mixture was quenched with saturated NH_4Cl and washed with DCM (3x). The combined organic phases were dried using $MgSO_4$ and evaporated. Purification by column chromatography on silica gel (EtOAc: heptane = 2:1) yielded the product as a yellow oil (**1.1.144**, 0.373 g, 52 %).

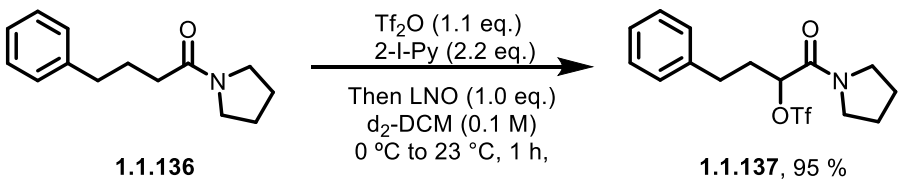
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 - 7.26 (m, 6H, H_{Ar}), 7.25 - 7.23 (m, 2H, H_{Ar}), 7.17 - 7.15 (m, 3H, H_{Ar}), 7.12 - 7.11 (m, 2H, H_{Ar}), 7.04 - 7.03 (m, 2H, H_{Ar}), 4.98 (d, J = 14.8 Hz, 1H, H_7), 4.39 (dd, J = 8.6, 2.6 Hz, 1H, $H_{5/14}$), 4.27 (d, J = 16.6 Hz, 1H, $H_{5/14}$), 4.21 (d, J = 14.8 Hz, 1H, $H_{5/14}$), 4.10 (d, J = 16.6 Hz, 1H, $H_{5/14}$), 3.92 - 3.53 (br., 1H, OH), 2.87 - 2.76 (m, 2H, H_9), 1.97 - 1.92 (m, 1H, H_8), 1.92 - 1.82 (m, 1H, H_8);

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 (C_6), 141.3 (C_{Ar}), 136.6 (C_{Ar}), 135.4 (C_{Ar}), 129.2 (C2, C_{Ar}) , 128.9 (C2, C_{Ar}) , 128.7 (C2, C_{Ar}) , 128.6 (C2, C_{Ar}), 128.4 (C2, C_{Ar}) , 128.1 (C_{Ar}), 127.9 (C_{Ar}), 126.8 (2C, C_{Ar}), 126.2 (C_{Ar}), 67.5 (C_7), 48.9 ($C_{5/14}$), 48.4 ($C_{5/14}$), 37.5 (C_9), 31.4 (C_8);

HRMS (ESI$^+$): calculated for $C_{24}H_{25}NONa$ $[M+Na]^+$ *m/z* : 366.1834, found: 366.1823;

IR (neat) ν_{max}: 3062, 3032, 2928, 1644, 1494, 1452.

Isolation of the -triflate amide from an umpolung reaction



1.1.136 **1.1.137**, 95 %

To a mixture of amide 4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (**1.1.136**, 0.2 mmol, 1.0 eq.), 2-iodopyridine (2.2 eq., 0.44 mmol) in DCM (2 mL) was added triflic anhydride (37 µL, 1.1 eq., 0.22 mmol) dropwise under argon at 0 °C. After stirring for 15 min at 0 °C,

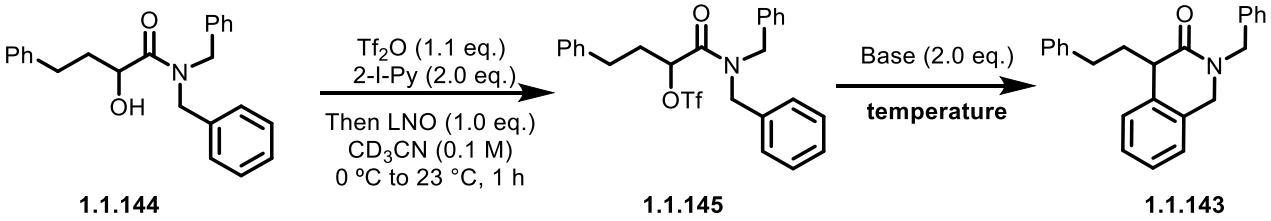
lutidine *N*-oxide (22.4 μL, 1.0 eq., 0.20 mmol) was added and the reaction stirred for a further 5 min at 0 °C. After 1 h the reaction was quenched with water and extracted with DCM (2x). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude mixture was quickly columned at -30 °C (cryostat / isopropanol) to afford the desired compound in 95 % yield (**1.1.137**, 69.0 mg) as a yellow oil.

Important information about the NMR experiments

One important fact to disclose was that the formation of the α-triflate from the corresponding α-hydroxyamide proved to proceed in consistently higher yields when 2,6-lutidine was used as a base. For instance, when 2-I-pyridine was used the yield was significantly lower and the ^{1}H-NMR spectra was too complex to be fully analysed.

In order to access whether the intermediate (α-trifloxy) could undertake the intramolecular Fridel-Crafts, we attempted a wide array of conditions. We soon realised that forcing conditions, such as the one encountered previously in the literature[104] were ideal. After careful examination we became aware that 2-I-Pyridine as a base, combined with high temperatures (110 °C) in acetonitrile were crucial for the reaction to take place (*vide infra*).

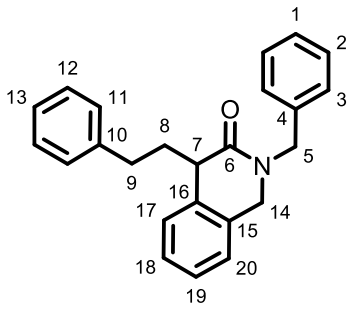
Elucidation of the Fridel-Crafts product



1.1.144 **1.1.145** **1.1.143**

Entry	Base	Temperature (ºC)	NMR yield **1.1.143** (%)
1	2,6-lutidine	0	-
2	2,6-lutidine	110	-
3	2-I-Pyridine	0	-
4	2-I-Pyridine	80	-
5	2-I-Pyridine	110 (3 h)	18
6	2-I-Pyridine	110 (14 h)	47

2-Benzyl-4-phenethyl-1,4-dihydroisoquinolin-3(2H)-one (1.1.143)



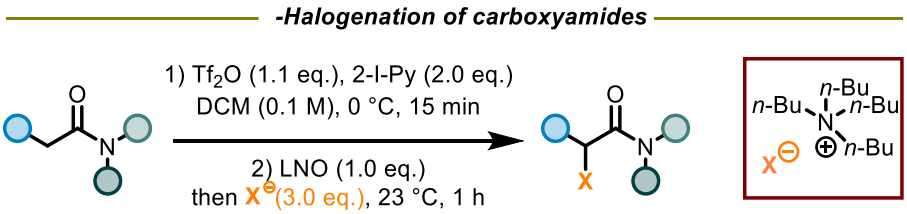
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 - 7.26 (m, 7H, H_{Ar}), 7.25 - 7.19 (m, 2H, H_{Ar}), 7.17 (dd, *J* = 14.0, 7.0 Hz, 4H, H_{Ar}), 7.09 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 4.88 (d, *J* = 14.8 Hz, 1H, $H_{5/14}$), 4.64 (d, *J* = 14.8 Hz, 1H, $H_{5/14}$), 4.54 (d, *J* = 15.9 Hz, 1H, $H_{5/14}$), 4.21 (d, *J* = 15.9 Hz, 1H, $H_{5/14}$), 3.70 (t, *J* = 6.8 Hz, 1H, H_7), 2.70 - 2.64 (m, 2H, H_9), 2.25 - 2.14 (m, 1H, H_8), 2.14 - 2.01 (m, 1H, H_8);

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7 (C_6), 141.5 (C_{Ar}), 137.0 (C_{Ar}), 136.6 (C_{Ar}), 131.2 (C_{Ar}), 128.9 (2C, C_{Ar}) , 128.6 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 128.1 (2C, C_{Ar}) , 127.7 (2C, C_{Ar}) , 127.6 (C_{Ar}), 126.8 (C_{Ar}), 126.1 (C_{Ar}), 125.6 (C_{Ar}), 50.4 ($C_{5/14}$), 50.0 ($C_{5/14}$), 47.6 (C_7), 35.7 (C_9), 33.0 (C_8);

HRMS (ESI$^+$): calculated for $C_{24}H_{23}NO$ $[M+H]^+$ *m/z*: 342.1852 found: 342.1854;

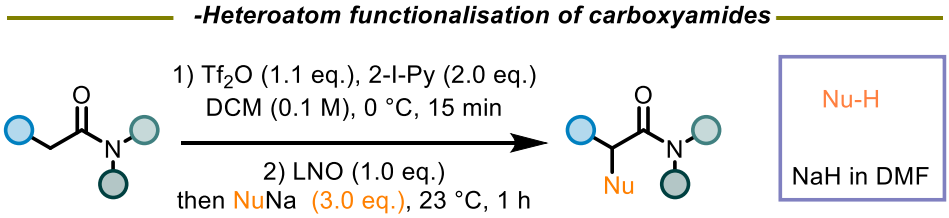
IR (neat) ν_{max}: 3060, 3034, 2932, 1655, 1495, 1452.

3.2.2 General procedures for the α-functionalisation of amides



3.2.2.1 General procedure **1.1** - Procedure for the α-halogenation of amides

To a mixture of amide (0.20 mmol), 2-iodopyridine (2.0 eq., 42.5 µL, 0.44 mmol) in DCM (2.0 mL) was added triflic anhydride (1.1 eq., 37.0 µL, 0.22 mmol) dropwise under Ar at 0 °C. After stirring for 15 min at 0 °C, 2,6-lutidine *N*-oxide (1.0 eq., 22.4 µL, 0.20 mmol,) was added and the reaction stirred for a further 5 min at 0 °C. Then a *tetra*-butylammonium halide was added in one portion (3.0 eq.). The reaction mixture was stirred at room temperature for 3 h before being quenched with a saturated solution of NH_4Cl. The layers were separated and the aqueous extracted with DCM (3x). The combined organic layers were washed with brine before being dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure.

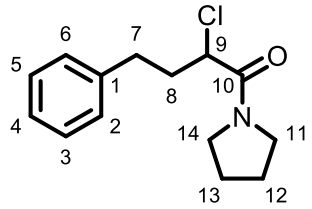


3.2.2.2 General procedure **1.2** - Procedure for the α-functionalisation of amides using *O*- and *S*-Nucleophiles

To a mixture of amide (0.20 mmol), 2-iodopyridine (2.0 eq., 42.5 µL, 0.44 mmol) in DCM (2.0 mL) was added triflic anhydride (1.1 eq., 37 µL, 0.22 mmol) dropwise under argon at 0 °C. After stirring for 15 min, 2,6-lutidine *N*-oxide (1.0 eq., 22.4 µL, 0.20 mmol) was added and the reaction stirred for a further 5 min at 0 °C. Then, a solution of the deprotonated nucleophile -generated from addition of the nucleophile (0.60 mmol) to a

suspension of NaH (3.0 eq., 0.60 mmol) in DMF (3.0 mL) was added. The reaction mixture was stirred at room temperature for 3 h before being quenched with NH_4Cl solution. The layers were separated and the aqueous extracted with DCM. The combined organic layers were washed with brine before being dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure.

2-Chloro-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.160)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (42.0 mg, 84%). When NaCl (95%, purity) was used as the halide source, the reaction was stirred for 20 h instead and yielded the product as a yellow oil (45.1 mg, 90 %).

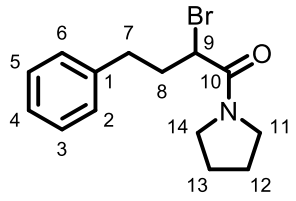
^{1}HNMR (700 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.5 Hz, 1H, $H_{3/5}$), 7.21 - 7.17 (m, 2H, $H_{2/4/6}$), 4.14 (t, *J* = 7.3 Hz, 1H, H_9), 3.52 - 3.46 (m, 3H, $H_{11/14}$), 3.14 (dt, *J* = 9.8, 7.0 Hz, 1H, H_{14}), 2.76 (t, *J* = 7.3 Hz, 2H, H_7), 2.47 - 2.45 (m, 1H, H_8), 2.37 - 2.35 (m, 1H, H_8), 1.95 - 1.93 (m, 2H, $H_{12/13}$), 1.88 - 1.85 (m, 2H, $H_{12/13}$);

^{13}CNMR (176 MHz, $CDCl_3$): δ 167.0 (C_{10}), 140.4 (C_1), 128.7 (2C, $C_{3/5}$), 128.6 ($C_{2/6}$), 126.4 (C_4), 46.5 ($C_{11/C14}$), 44.9 (C_9), 36.0 (C_8), 33.4 (C_7), 26.1 ($C_{12/13}$), 24.4 ($C_{12/13}$);

HRMS (ESI^+): calculated for $C_{14}H_{18}ClNO$ $[M+Na]^+$ *m/z*: 274.0969, found: 274.0971;

IR (neat) ν_{max}: 3025, 2950, 2874, 1643, 1495, 1433, 1340, 1189.

2-Bromo-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.161)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (44.2 mg, 75 %).

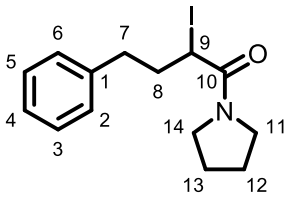
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.26 (m, 2H, $H_{3/5}$), 7.22 - 7.18 (m, 3H, $H_{6/4/2}$), 4.18 (dd, *J* = 7.9, 6.4 Hz, 1H, H_9), 3.55 - 3.47 (m, 3H, $H_{11/14}$), 3.21 - 3.18 (m, 1H, H_{14}), 2.80 - 2.77 (m, 2H, H_7), 2.39 - 2.29 (m, 2H, H_8), 1.95 - 1.83 (m, 4H, $H_{12/13}$).

^{13}C NMR (176 MHz, $CDCl_3$): δ 166.9 (C_{10}), 140.5 (C_1), 128.7 ($C_{3/5}$), 128.7 ($C_{2/6}$), 126.4 (C_4), 55.0 (C_9), 46.5 ($C_{11/14}$), 46.4 ($C_{11/14}$), 35.6 (C_8), 32.3 (C_7), 26.2 ($C_{12/13}$), 24.3 ($C_{12/13}$);

HRMS (ESI$^+$): calculated for $C_{14}H_{18}BrNO$ $[M+Na]^+$ *m/z:* 318.0464, found: 318.0462;

IR (neat) ν_{max}: 2972, 2875, 1651, 1438, 752, 700.

2-Iodo-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.162)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography as a yellow oil (58.0 mg, 80 %).

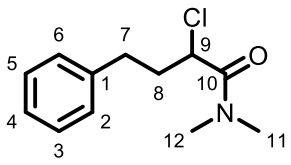
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 - 7.28 (m, 2H, $H_{2/5}$), 7.21 (t, *J* = 7.3 Hz, 1H, H_4), 7.17 (d, *J* = 7.4 Hz, 2H, $H_{2/6}$), 4.15 (t, *J* = 7.4 Hz, 1H, H_9), 3.46 (t, *J* = 6.9 Hz, 2H, $H_{11/14}$), 3.35 (dt, *J* = 9.7, 6.7 Hz, 1H, H_{14}), 3.05 - 3.01 (m, 1H, H_{14}), 2.73 - 2.69 (m, 2H, H_8), 2.44 (td, *J* = 14.2, 7.5 Hz, 1H, H_7), 2.36 (td, *J* = 14.5, 7.3 Hz, 1H, H_7), 1.98 - 1.91 (m, 2H, $H_{12/13}$), 1.89 - 1.81 (m, 2H, $H_{12/13}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.5 (C_{10}), 140.3 (C_1), 128.7 ($C_{3/5}$), 128.7 ($C_{2/6}$), 126.4 (C_4), 46.8 (C_9), 46.7 (2C, $C_{11/14}$), 37.7 (C_8), 35.2 (C_7), 26.1 ($C_{12/13}$), 24.4 ($C_{12/13}$).

HRMS (ESI$^+$): calculated for $C_{14}H_{18}INO$ $[M+Na]^+$ *m/z*: 366.0325, found: 366.0331;

IR (neat) ν_{max}: 2969, 2928, 2873, 1642, 1430, 1341, 750, 700.

2-Chloro-*N*,*N*-dimethyl-4-phenylbutanamide (1.1.170)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (38.7 mg, 86 %).

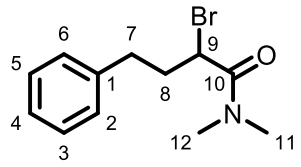
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 - 7.28 (m, 2H, $H_{3/5}$), 7.22 - 7.18 (m, 3H, $H_{2/4/6}$), 4.32 (t, *J* = 7.0 Hz, 1H, H_9), 2.98 (s, 3H, $H_{11/12}$), 2.97 (s, 3H, $H_{11/12}$), 2.78 (t, *J* = 7.3 Hz, H2, H_7), 2.38 - 2.26 (m, 2H, H_8);

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.4 (C_{10}), 140.5 (C_1), 128.6 ($C_{3/5}$), 128.6 ($C_{2/6}$), 126.4 (C_4), 53.0 (C_9), 37.3 (C_{11}), 36.3 (C_{12}), 35.8 (C_8), 32.3 (C_7);

HRMS (ESI$^+$): calculated for $C_{12}H_{16}ClNO$ $[M+Na]^+$ *m/z*: 248.0818, found: 248.0812;

IR (neat) ν_{max}: 2933, 2867, 1656, 1495, 1545, 1401.

2-Bromo-*N*,*N*-dimethyl-4-phenylbutanamide (1.1.171)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (49.5 mg, 92 %).

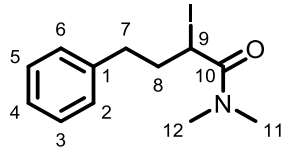
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 - 7.29 (m, 2H, $H_{3/5}$), 7.22 - 7.19 (m, 3H, $H_{2/4/6}$), 4.32 (t, *J* = 7.0 Hz, 1H, H_9), 2.99 (s, 3H, $H_{12/11}$), 2.99 (s, 3H, $H_{12/11}$), 2.78 (t, *J* = 7.3 Hz, 2H, H_7), 2.38 - 2.26 (m, 2H, H_8);

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.5 (C_{10}), 140.5 (C_1), 128.7 ($C_{2/6}$), 128.7 ($C_{3/5}$), 126.4 (C_4), 53.0 (C_9), 37.3 (C_{11}), 36.3 (C_{12}), 35.9 (C_8), 32.3 (C_7);

HRMS (ESI$^+$): calculated for $C_{12}H_{16}BrNO$ $[M+Na]^+$ *m/z:* 292.0313, found: 292.0303;

IR (neat) ν_{max}: 3026, 2929, 2859, 1652, 1494, 1453, 1400, 1135.

2-Iodo-*N*,*N*-dimethyl-4-phenylbutanamide (1.1.172)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (57.0 mg, 90 %). **(Rotamers present in a 1:3 ratio at room temperature).**

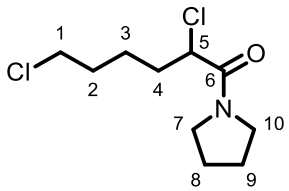
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 - 7.28 (m, 2H, $H_{3/5}$), 7.22 - 7.16 (m, 3H, $H_{6/4/2}$), 4.32 (t, *J* = 7.3 Hz, 1H, H_9), 2.97 (s, 3H, H_{12}); 2.87 (s, 3H, H_{11}), 2.70 - 2.65 (m, 2H, H_7), 2.45 - 2.30 (m, 2H, H_8);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.1 (C_{10}), 140.3 (C_1), 128.7 (2C, $C_{2/6}$), 128.6 ($C_{3/5}$), 126.4 (C_4), 53.0 (minor, C_9), 38.1 (major, C_9) , 37.8 (major, C_{11}), 37.3 (minor, C_{11}), 36.6 (major, C_{12}) , 36.3 (minor, C_{12}), 35.9 (minor, C_8) , 35.2 (major, C_8) , 32.4 (minor, C_7) , 19.9 (major, C_7);

HRMS (ESI$^+$): calculated for $C_{12}H_{16}INO$ $[M+Na]^+$ *m/z*: 340.0174, found: 340.0170;

IR (neat) ν_{max}: 2927, 2857, 1645, 1494, 1453, 1399.

2,6-Dichloro-1-(pyrrolidin-1-yl)hexan-1-one (1.1.167)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (44.6 mg, 94 %).

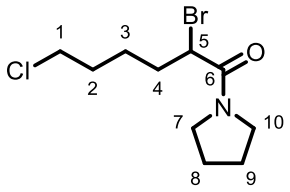
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29 - 4.26 (m, 1H, H_5), 3.69 - 3.67 (m, 1H, H_{10}), 3.54 - 3.44 (m, 5H, $H_{1/7/10}$), 2.12 - 2.06 (m, 1H, H_4), 2.03 - 1.93 (m, 3H, $H_{4/8/9}$), 1.91 - 1.88 (m, 2H, $H_{8/9}$), 1.83 - 1.81 (m, 2H, H_2), 1.66 - 1.64 (m, 1H, H_3), 1.51 - 1.49 (m, 1H, H_3);

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.9 (C_6), 55.8 (C_5), 46.6 ($C_{7/10}$), 46.5 ($C_{7/10}$), 44.8 (C_1), 33.5 (C_4), 32.2 (C_2), 26.2 (C_3), 24.3 ($C_{8/9}$), 23.9 ($C_{8/9}$);

HRMS (ESI$^+$): calculated for $C_{10}H_{17}Cl_2NO$ $[M+Na]^+$ *m/z:* 260.0585, found: 260.0570**;**

IR (neat) ν_{max}: 2954, 2875, 1650, 1440, 1314.

2-Bromo-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one (1.1.168)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (44.5 mg, 79 %).

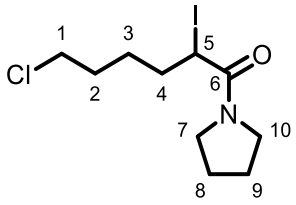
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.29 - 4.27 (m, 1H, H_5), 3.71 - 3.67 (m, 1H, H_{10}), 3.57 - 3.43 (m, 5H, $H_{1/7/10}$), 2.12 - 2.06 (m, 1H, H_4), 2.01 - 1.98 (m, 3H, $H_{4/9}$), 1.91 - 1.87 (m, 2H, H_8), 1.83 - 1.80 (m, 2H, H_2), 1.68 - 1.60 (m, 2H, H_3), 1.54 - 1.47 (m, 1H, H_3);

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.9 (C_6), 55.8 (C_5), 46.6 ($C_{7/10}$), 46.5 ($C_{7/10}$), 44.8 (C_1), 33.6 (C_4), 32.2 (C_2), 26.2 (C_3), 24.3 ($C_{8/9}$), 23.9 ($C_{8/9}$);

HRMS (ESI$^+$): calculated for $C_{10}H_{17}BrClNO$ $[M+H]^+$ *m/z* :282.0260, found: 282.0250;

IR (neat) ν_{max}: 2954, 2874, 1674, 1438, 1340, 1311, 736, 648.

2-Iodo-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one (1.1.169)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (59.8 mg, 91 %). **(Rotamers present with a ratio of 3/2 at room temperature)**

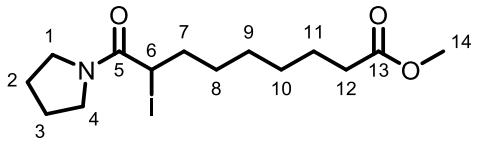
^{1}H NMR (700 MHz, $CDCl_3$): δ 4.27 (t, *J* = 7.4 Hz, 1H, H_5), 3.69 - 3.66 {minor}(m, 0.4H, $H_{7/10}$), 3.57 - 3.50 (m, 3H, $H_{7/10}$), 3.49 - 3.42 (m, 2H, H_1), 3.33 - 3.29 {major}(m, 0.6H, $H_{7/10}$), 2.10 - 2.06 (m, 2H, H_4), 2.03 - 1.99 (m, 2H, H_2), 1.91 - 1.79 (m, 4H, $H_{8/9}$), 1.67 - 1.56 (m, 1H, H_3), 1.51 - 1.40 (m, 1H, H_3);

^{13}C NMR (176 MHz, $CDCl_3$): δ 168.6 (major, C_6), 166.8 (minor, C_6), 55.8 (minor, C_5), 47.0 (C_{10}), 46.8 (C_7), 44.8 (C_1), 35.6 (C_4), 32.0 (C_2), 27.1 (C_3), 26.2 ($C_{8/9}$), 24.4 ($C_{8/9}$), 22.9 (major, C_5);

HRMS (ESI$^+$): calculated for $C_{10}H_{17}ClINO$ $[M+Na]^+$ *m/z*: 351.9941, found: 351.9936;

IR (neat) ν_{max}: 2951, 2872, 1642, 1431, 1341.

Methyl 8-iodo-9-oxo-9-(pyrrolidin-1-yl)nonanoate (1.1.165)



The product was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (64.8 mg, 85 %). **(Rotamers present with a ratio of 1/2 at room temperature using ^{13}C NMR).**

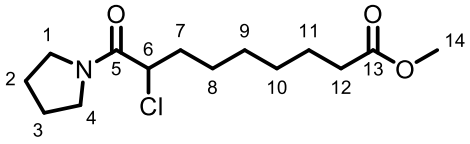
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 (t, *J* = 7.3 Hz, 1H, H_6), 3.66 (s, 3H, H_{14}), 3.51 - 3.48 (m, 1H, H_1), 3.45 - 3.43 (m, 2H, $H_{1/4}$), 3.32 - 3.28 (m, 1H, H_1), 2.30 - 2.27 (m, 2H, H_{12}), 2.03 - 1.99 (m, 4H, $H_{2/3}$), 1.90 - 1.85 (m, 2H, H_7), 1.61 - 1.59 (m, 2H, H_{11}), 1.35 - 1.25 (m, 6H, $H_{8/9/10}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_{13}), 168.8 (major, C_5), 167.2 (minor, C_5), 56.1 (minor, C_6), 51.7 (C_{14}), 46.9 (major, 2C, $C_{1/4}$), 46.7 (major, $C_{1/4}$), 46.6 (minor, $C_{1/4}$), 46.5 (minor, $C_{1/4}$), 36.2 (C_7), 34.2 (major, C_{12}), 34.1 (minor, C_{12}), 29.5 (major, C_{Alk}), 29.0 (minor, C_{Alk}), 28.9 (major, C_{Alk}), 28.7 (minor, C_{Alk}), 26.3 (major, $C_{2/3}$), 26.2 (minor, 2C, $C_{2/3/Alk}$), 24.9 (minor, $C_{2/3}$), 24.4 (major, $C_{2/3}$), 24.3 (major, C_6);

HRMS (ESI$^+$): calculated for$C_{14}H_{24}INO_3$ $[M+Na]^+$ *m/z*: 404.0693, found: 404.0693;

IR (neat) ν_{max}: 2924, 2854, 1734, 1642, 1431, 1340, 1249.

Methyl 8-chloro-9-oxo-9-(pyrrolidin-1-yl)nonanoate (1.1.163)



The product was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (49.7 mg, 86 %). **(Rotamers present).**

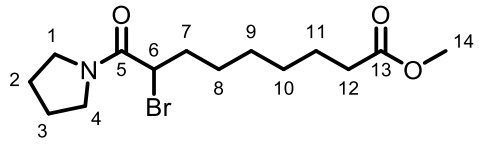
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.28 - 4.25 (m, 1H, H_6), 3.66 (s, 3H, H_{14}), 3.54 - 3.48 (m, 3H, H1/4), 3.47 - 3.42 (m, 1H, $H_{1/4}$), 2.30 (t, *J* = 7.5 Hz, 2H, H_{12}), 2.04 - 1.97 (m, 3H, $H_{2/3/7}$), 1.94 - 1.86 (m, 3H, $H_{2/3/7}$), 1.64 - 1.60 (m, 2H, H_{11}), 1.48 – 1.44 (m, 1H, H_8), 1.37 - 1.32 (m, 5H, $H_{8/9/10}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_{13}), 167.2 (C_5), 56.1 (C_6), 51.7 (C_{14}), 46.6 ($C_{1/4}$), 46.5 ($C_{1/4}$), 34.2 (C_7), 34.1 (C_{12}), 29.0 ($C_{2/3}$), 28.9 ($C_{2/3}$), 26.3 (C_9), 26.2 (C_{10}), 24.9 (C_{11}), 24.3 (C_8);

HRMS (ESI$^+$): calculated for $C_{14}H_{24}ClNO_3$ $[M+Na]^+$ *m/z*: 312.1337, found: 312.1338;

IR (neat) ν_{max}: 2927, 2856, 1735, 1651, 1436, 1341, 1170.

Methyl 8-iodo-9-oxo-9-(pyrrolidin-1-yl)nonanoate (1.1.164)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (59.9 mg, 90 %). **(Rotamers present with a ratio of 1:3 at room temperature using ^{13}CNMR).**

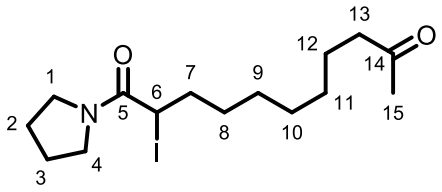
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 (t, *J* = 7.2 Hz, 1H, H_6), 3.72 - 3.63 (m, 4H, $H_{14/1}$), 3.55 - 3.36 (m, 3H, $H_{1/4}$), 2.30 (t, *J* = 7.5 Hz, 2H, H_{12}), 2.01 - 1.87 (m, 6H, $H_{7/4/2}$), 1.65 - 1.60 (m, 2H, H_{11}), 1.36 -1.33 (m, 6H, $H_{8/9/10}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_{13}), 167.3 (minor, C_5), 167.2 (major, C_5), 56.1 (C_6), 51.7 (C_{14}), 46.7 (major, C_1), 46.6 (major, C_4), 46.5 (minor, $C_{1/4}$), 46.5 (minor, $C_{1/4}$), 46.1, 34.6, 34.2 (minor, C_7), 34.1 (major, C_7), 29.0 (minor, C_{12}), 28.9 (major, C_{12}), 28.9 (major, C_{Alk}), 27.5 (minor, C_{Alk}), 26.3 (minor, major, 2C, C_{Alk}), 26.2 (major, $C_{2/3}$), 24.9 (major, $C_{2/3}$), 24.4 (minor, $C_{2/3}$), 24.3 (minor, $C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{14}H_{24}BrNO_3$ $[M+Na]^+$ *m/z*: 356.0832, found: 356.0832;

IR (neat) ν_{max}: 2930, 2858, 1734, 1649, 1434, 1340, 1193, 1169.

2-Iodo-1-(pyrrolidin-1-yl)undecane-1,10-dione (1.1.176)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-3:2) yielded the product as a yellow oil (64.8 mg, 85 %). **(Rotamers present with a ratio of 1:2 at room temperature using ^{13}CNMR).**

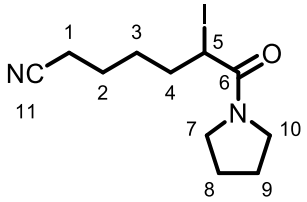
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 (t, *J* = 7.3 Hz, 1H, H_6), 3.68 - 3.66 (m, 0.7H, major, $H_{1/4}$), 3.53 - 3.42 (m, 3H, $H_{1/4}$), 3.32 - 3.30 (m, 0.4H, minor, $H_{1/4}$), 2.41 (t, *J* = 7.4 Hz, 2H, H_{13}), 2.13 (s, 3H, H_{15}), 2.03 - 2.00 (m, 3H, $H_{7/2/3}$), 1.92 - 1.84 (m, 2H, $H_{2/3}$), 1.56 - 1.54 (m, 2H, H_{12}), 1.35 - 1.19 (m, 8H, $H_{8/9/10/11}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.5 (C_{14}), 168.8 (major, C_5), 167.2 (minor, C_5), 56.2 (C_6), 46.9 (major, $C_{1/4}$), 46.7 (minor, $C_{1/4}$), 46.6 (minor, $C_{1/4}$), 46.5 (major, $C_{1/4}$), 43.9 (C_{13}), 36.3 (C_7), 34.3 (C_6), 30.1 (C_{15}), 29.6 (major, C_{Alk}), 29.3 (major, minor, 2C, C_{Alk}), 29.1 (major, minor, 2C, C_{Alk}), 28.9 (minor, C_{Alk}), 26.4 (major, C_{Alk}), 26.2 (major, $C_{2/3}$), 24.4 (minor, $C_{2/3}$), 24.3 (major, $C_{2/3}$), 23.9 (minor, $C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{15}H_{26}INO$ $[M+Na]^+$ *m/z*: 402.0906, found: 402.0897;

IR (neat) ν_{max}: 2926, 2855, 1721, 1648, 1433, 1358, 1167.

6-Iodo-7-oxo-7-(pyrrolidin-1-yl)heptanenitrile (1.1.175)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:1-20:1) yielded the product as a yellow oil (57.6 mg, 90 %). **(Rotamers present with a ratio of 4/1 at room temperature using ^{13}C NMR).**

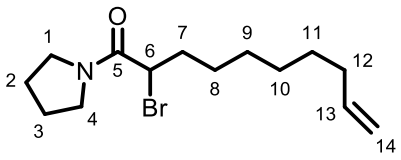
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 - 4.25 (m, 1H, H_5), 3.70 – 3.66 (m, 0.2H, minor, $H_{7/10}$), 3.51 - 3.43 (m, 3H, $H_{7/10}$), 3.32 - 3.28 (m, major, 0.8H, $H_{7/10}$), 2.39 - 2.34 (m, 2H, H_1), 2.10 - 1.99 (m, 4H, $H_{4/8/9}$), 1.91 - 1.85 (m, 2H, $H_{8/9}$), 1.72 - 1.67 (m, 2H, H_2), 1.58 - 1.53 (m, 1H, H_3), 1.47 – 1.44 (m, 1H, H_3);

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.4 (major, C_6), 168.7 (minor, C_6), 119.6 (C_{11}), 55.4 (minor, C_5), 47.0 (major, $C_{7/10}$), 46.8 (major, $C_{7/10}$), 46.6 (minor, $C_{7/10}$), 46.5 (minor, $C_{7/10}$), 35.5 (major, C_4), 33.4 (minor, C_4), 28.8 (C_{Alk}), 26.2 (2C, C_{Alk}), 24.8 ($C_{8,9}$), 24.4 ($C_{8,9}$), 22.3 (major, C_5), 17.20 (major, minor, 2C, C_1);

HRMS (ESI$^+$): calculated for $C_{11}H_{17}ClNO$ $[M+Na]^+$ *m/z:* 343.0283, found: 343.0271;

IR (neat) ν_{max}: 3362, 2955, 2923, 2853, 2334, 1640, 1432, 1342, 748.

2-Bromo-1-(pyrrolidin-1-yl)undec-10-en-1-one (1.1.174)



The product was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:3-2:1) yielded the product as a yellow oil (53.5 mg, 85 %).

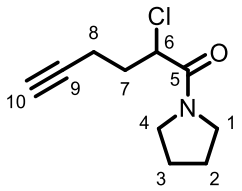
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.82 - 2.76 (m, 1H, H_{13}), 4.99 - 4.91 (m, 2H, H_{14}), 4.28 - 4.26 (m, 1H, C_6), 3.68 - 3.65 (m, 1H, H_1), 3.51 - 3.42 (m, 3H, $H_{1/4}$), 2.04 - 1.96 (m, 5H, $H_{2/3/7/12}$), 1.93 - 1.86 (m, 3H, $H_{2/3/7/12}$), 1.37 - 1.29 (m, 10H, $H_{8/9/10/11}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.2 (C_5), 139.3 (C_{13}), 114.3 (C_{14}), 56.2 (C_6), 46.6 ($C_{1/4}$), 46.5 ($C_{1/4}$), 34.3 (C_7), 33.9 (C_{12}), 29.4 (C_{Alk}), 29.2 (C_{Alk}), 29.1 (C_{Alk}), 29.0 (C_{Alk}), 26.5 (C_{Alk}), 26.2 ($C_{2/3}$), 24.3 ($C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{15}H_{26}BrNO$ $[M+Na]^+$ *m/z:* 338.1095, found: 338.1073;

IR (neat) ν_{max}: 2924, 2853, 1738, 1651, 1435, 909.

2-Chloro-1-(pyrrolidin-1-yl)hex-5-yn-1-one (1.1.173)



The title compound was prepared according to general procedure **1.1**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (29.8 mg, 75 %). **(Rotamers present with a ration of 1:10 in ^{13}CNMR).**

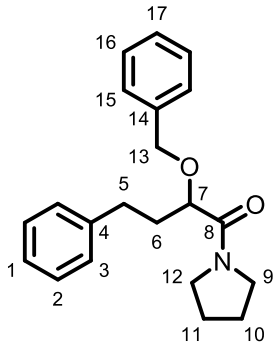
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.59 - 4.56 (m, 1H, H_6), 3.71 - 3.67 (m, 1H, $H_{1/4}$), 3.55 - 3.47 (m, 3H, $H_{1/4}$), 2.47 - 2.42 (m, 1H, H_7), 2.39 - 2.35 (m, 1H, H_7), 2.27 - 2.22 (m, 1H, H_8), 2.03 - 1.98 (m, 2H, H_8), 1.94 - 1.86 (m, 5H, $H_{2/3/10}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.6 (C_5), 69.8 (C_{10}), 54.4 (C_6), 46.6 ($C_{1/4}$), 32.8 ($C_{1/4}$), 29.9 (C_7), 26.2 ($C_{2/3}$), 24.4 ($C_{2/3}$), 15.6 (C_8); (C_9 - not shown)

HRMS (ESI$^+$): calculated for $C_{10}H_{14}ClNO$ $[M+Na]^+$ *m/z*: 222.0662, found: 222.0648;

IR (neat) ν_{max}: 3296, 3239, 2972, 2877, 1737, 1646, 1440, 1342.

2-(Benzyloxy)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.188)



The product was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (52.3 mg, 81 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 - 7.26 (m, 4H, H_{Ar}), 7.22 - 7.21 (m, 1H, H_{Ar}), 7.17 - 7.15 (m, 2H, H_{Ar}), 7.09 - 7.06 (m, 1H, H_{Ar}), 7.05 - 7.03 (m, 2H, H_{Ar}), 4.57 - 4.55 (m, 1H, H_{13}), 4.29 - 4.27 (m, 1H, H_{13}), 3.91 - 3.89 (m, 1H, H_7), 3.41 - 3.36 (m, 2H, $H_{9/12}$) 3.15 -

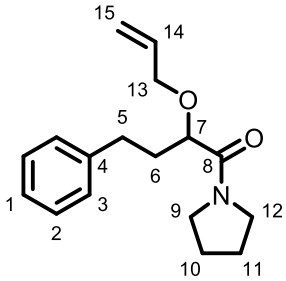
3.11 (m, 2H, $H_{9/12}$), 2.77 - 2.76 (m, 1H, H_5), 2.61 - 2.58 (m, 1H, H_5), 2.08 - 2.03 (m, 1H, H_6), 1.86 - 1.81 (m, 1H, H_6), 1.74 - 1.67 (m, 4H, $H_{10/11}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.5 (C_8), 141.5 (C_{Ar}), 137.8 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 128.0 (2C, C_{Ar}), 126.1 (2C, C_{Ar}), 77.7 (C_7), 71.5 (C_{13}), 46.3 ($C_{12/9}$), 45.9 ($C_{12/9}$), 33.8 (C_5), 31.9 (C_6), 26.5 ($C_{10/11}$), 23.8 ($C_{10/11}$);

HRMS (ESI$^+$): calculated for $C_{21}H_{25}NO_2$ $[M+Na]^+$ *m/z*: 346.1783, found: 346.1777;

IR (neat) ν_{max}: 3060, 3027, 2950, 2926, 2871, 1641, 1495, 1433.

2-(Allyloxy)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.204)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (39.3 mg, 72 %).

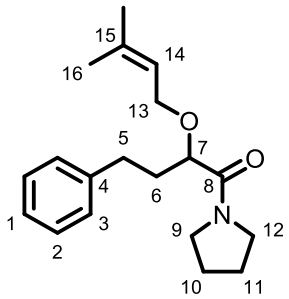
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 - 7.32 (m, 2H, C_{Ar}), 7.26 - 7.25 (m, 3H, C_{Ar}), 6.01 - 5.97 (m, 1H, H_{14}), 5.35 - 5.32 (m, 1H, H_{15}), 5.25 - 5.23 (m, 1H, H_{15}), 4.16 - 4.13 (m, 1H, H_{13}), 4.04 - 4.02 (m, 1H, H_{13}), 3.93 - 3.90 (m, 1H, H_7), 3.56 - 3.52 (m, 2H, $H_{9/12}$), 3.48 - 3.45 (m, 1H, $H_{9/12}$), 3.38 - 3.35 (m, 1H, $H_{9/12}$), 2.92 - 2.88 (m, 1H, H_5), 2.80 - 2.75 (m, 1H, H_5), 2.16 - 2.13 (m, 1H, H_6), 2.01 - 1.97 (m, 1H, H_6), 1.96 - 1.93 (m, 2H, $H_{10/11}$), 1.87 - 1.83 (m, 2H, $H_{10/11}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6 (C_8), 141.5 (C_{Ar}), 134.6 (C_{14}), 128.7 (2C, C_{Ar}) , 128.5 (2C, C_{Ar}), 126.1 (C_{Ar}), 117.6 (C_{15}), 78.1 (C_7), 70.6 (C_{13}), 46.4 ($C_{9/12}$), 46.0 ($C_{9/12}$), 33.7 (C_6), 31.8 (C_5), 26.5 ($C_{10/11}$), 23.8 ($C_{10/11}$);

HRMS (ESI$^+$): calculated for $C_{17}H_{23}NO_2$ $[M+Na]^+$ *m/z:* 296.1626, found: 296.1622;

IR (neat) ν_{max}: 3025, 2952, 2927, 2873, 1637, 1495, 1434.

2-((3-Methylbut-2-en-1-yl)oxy)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.206)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (51.8 mg, 86 %).

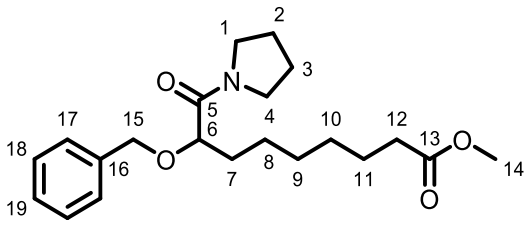
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.26 (m, 2H, H_{Ar}), 7.20 - 7.19 (m, 2H, H_{Ar}), 7.19 - 7.17 (m, 1H, H_{Ar}), 5.38 - 5.35 (m, 1H, H_{14}), 4.04 - 4.02 (m, 1H, H_{13}), 3.96 - 3.94 (m, 1H, H_{13}), 3.90 - 3.88 (m, 1H, H_7), 3.50 - 3.47 (m, 2H, $H_{9\text{-}12}$), 3.39 - 3.37 (m, 1H, $H_{9\text{-}12}$), 3.34 - 3.31 (m, 1H, $H_{9\text{-}12}$), 2.85 - 2.82 (m, 1H, H_5), 2.73 - 2.70 (m, 1H, H_5), 2.10 - 2.06 (m, 1H, H_6), 1.94 - 1.92 (m, 1H, H_6), 1.88 - 1.86 (m, 2H, $H_{10\text{-}11}$), 1.85 - 1.81 (m, 2H, $H_{10\text{-}11}$), 1.75 (s, 3H, H_{16}), 1.64 (s, 3H, H_{16});

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9 (C_8), 141.6 (C_{Ar}), 137.6 (C_{15}), 128.7 (2C, C_{Ar}) , 128.5 (2C, C_{Ar}) , 126.1 (C_{Ar}), 120.9 (C_{14}), 77.9 (C_7), 65.9 (C_{13}), 46.4 ($C_{9/12}$), 46.0 ($C_{9/12}$), 33.7 (C_6), 31.9 (C_5), 26.6 ($C_{10/11}$), 26.0 ($C_{10/11}$), 23.8 (C_{16}), 18.2 (C_{16});

HRMS (ESI$^+$): calculated for $[M+Na]^+$ $C_{19}H_{27}NO_2$ *m/z:* 324.1939, found: 324.1934;

IR (neat) ν_{max}: 3025, 2952, 2930, 2878, 1639, 1495, 1436.

Methyl 8-(benzyloxy)-9-oxo-9-(pyrrolidin-1-yl)nonanoate (1.1.190)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (58.5 mg, 81 %).

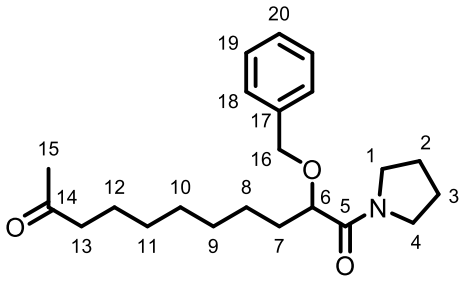
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.25 (m, 4H, H_{Ar}), 7.22 - 7.19 (m, 1H, H_{Ar}), 4.57 - 4.55 (m, 1H, H_{15}), 4.32 - 4.30 (m, 1H, H_{15}), 3.95 - 3.93 (m, 1H, H_6), 3.59 (s, 3H, H_{14}), 3.44 - 3.42 (m, 2H, $H_{1/4}$), 3.34 - 3.31 (m, 2H, $H_{1/4}$), 2.22 (t, *J* = 7.8 Hz, 2H, H_{12}), 1.82 - 1.80 (m, 2H, $H_{2/3}$), 1.75 - 1.69 (m, 3H, $H_{2/3,Alk}$), 1.47 - 1.42 (m, 1H, H_{Alk}), 1.54 - 1.51 (m, 1H, H_{Alk}), 1.47 - 1.42 (m, 1H, H_{Alk}), 1.28 - 1.18 (m, 6H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_{13}), 170.8 (C_5), 137.9 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 79.0 (C_6), 71.4 (C_{15}), 66.2 (C_{14}), 51.6 , 46.4 (C_{Alk}), 46.1 (C_{Alk}), 34.2 (C_{Alk}), 32.1 (C_{Alk}), 29.1 (C_{Alk}), ($C_{2/3}$), 29.1 ($C_{2/3}$), 25.6 (C_{Alk}), 25.0 (C_{Alk}), 23.8 (C_{Alk});

HRMS (ESI$^+$): calculated for $C_{21}H_{31}NO_4$ $[M+Na]^+$ *m/z*: 384.2151, found: 384.2150;

IR (neat) ν_{max}: 3029, 2932, 2860, 1736, 1646, 1495, 1435.

2-(Benzyloxy)-1-(pyrrolidin-1-yl)undecane-1,10-dione (1.1.202)



The product was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (54.5 mg, 76 %).

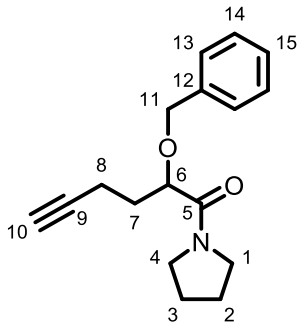
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.25 (m, 4H, H_{Ar}), 7.22 - 7.20 (m, 1H, H_{Ar}), 4.57 - 4.55 (m, 1H, H_{16}), 4.32 - 4.30 (m, 1H, H_{16}), 3.95 (m, 1H, H_6), 3.46 - 3.43 (m, 2H, $H_{1/4}$), 3.41 - 3.32 (m, 2H, $H_{1/4}$), 2.35 - 2.32 (t, *J* = 7.8 Hz, 2H, H_{13}), 2.06 (s, 3H, H_{15}), 1.82 - 1.80 (m, 2H, H_{12}), 1.75 - 1.71 (m, 3H, $H_{2/3}$), 1.60 - 1.57 (m, 1H, $H_{2/3}$), 1.48 - 1.43 (m, 2H, H_{Alk}), 1.26 - 1.18 (m, 8H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.6 (C_{14}), 170.8 (C_5), 137.9 (C_{Ar}), 128.5 (2C, C_{Ar}) , 128.1 (2C, C_{Ar}) , 127.9 (C_{Ar}), 79.1 (C_6), 71.4, (C_{16}), 46.4 ($C_{1/4}$), 46.1 ($C_{1/4}$), 43.9 (C_{13}), 32.1 (C_7), 30.0 (C_{15}), 29.3 (2C, C_{Alk}), 29.2 (C_{Alk}), 26.5 ($C_{2/3}$), 25.7 ($C_{2/3}$), 23.9 (C_{Alk}), 23.8 (C_{Alk});

HRMS (ESI$^+$): calculated for $C_{22}H_{33}NO_3$ $[M+Na]^+$ *m/z:* 382.2358, found: 382.2357;

IR (neat) ν_{max}: 2928, 2856, 1712, 1647, 1435, 1342.

2-(Benzyloxy)-1-(pyrrolidin-1-yl)hex-5-yn-1-one (1.1.196)



The product was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-2:1) yielded the product as a yellow oil (40.0 mg, 73 %).

(Rotamers present with a ratio of 1:3 at room temperature using ^{13}CNMR).

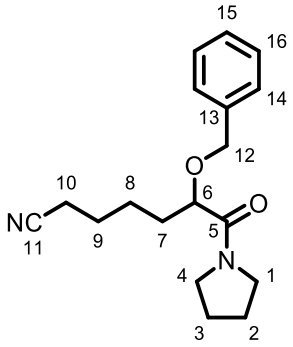
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 - 7.32 (m, 3H, H_{Ar}), 7.30 - 7.27 (m, 2H, H_{Ar}), 4.66 (d, *J* = 11.7 Hz, 1H, H_{11}), 4.42 (d, *J* = 11.7 Hz, 1H, H_{11}), 4.24 (dd, *J* = 9.3, 4.0 Hz, 1H, H_6), 3.61 - 3.54 (m, 1H, H_{10}), 3.52 - 3.44 (m, 2H, $H_{1/4}$), 3.44 - 3.35 (m, 2H, $H_{1/4}$), 2.46 - 2.33 (m, 2H, H_8), 2.04 - 2.00 (m, 1H, H_7), 1.98 - 1.92 (m, 1H, H_7), 1.90 - 1.86 (m, 2H, $H_{2/3}$), 1.84 - 1.80 (m, 2H, $H_{2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.1 (C_5), 137.8 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 128.0 (C_{Ar}), 83.6 (C_9), 78.5 (C_6), 71.6 (major, C_{10}) , 69.1 (major, C_{11}) 69.0 (minor, C_{10}), 68.0 (minor, C_{11}), 46.4 ($C_{1/4}$), 46.1 ($C_{1/4}$), 33.6 (minor, C_7), 31.0 (major, C_7), 26.5 (major, $C_{1/4}$), 26.2 (major, $C_{1/4}$), 25.9 (major, $C_{1/4}$), 24.0 (minor, $C_{1/4}$), 15.0 (major, C_8), 14.7 (minor, C_8);

HRMS (ESI$^+$): calculated for $C_{17}H_{21}NO_2$ $[M+Na]^+$ *m/z* :294.1470, found: 294.1459;

IR (neat) ν_{max}: 3061, 3028, 2938, 2871, 1632, 1492, 1429.

6-(Benzyloxy)-7-oxo-7-(pyrrolidin-1-yl)heptanenitrile (1.1.200)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:1-20:1) yielded the product as a yellow oil (52.2 mg, 87 %).

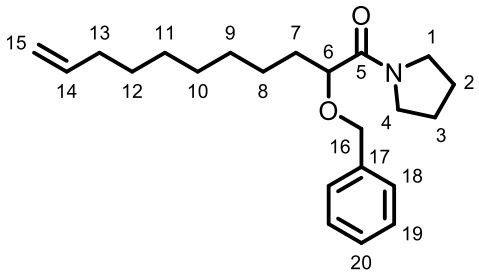
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 - 7.26 (m, 5H, H_{Ar}), 4.64 (d, *J* = 11.8 Hz, 1H, H_{12}), 4.39 (d, *J* = 11.8 Hz, 1H, H_{12}), 4.03 (dd, *J* = 8.5, 4.3 Hz, 1H, H_6), 3.57 - 3.43 (m, 3H, $H_{1/4}$), 3.41 (t, *J* = 6.7 Hz, 1H, $H_{1/4}$), 2.33 (t, *J* = 6.7 Hz, 2H, H_{10}), 1.94 - 1.86 (m, 2H, H_7), 1.86 - 1.78 (m, 3H, $H_{Alk/2/3}$), 1.77 - 1.59 (m, 5H, $H_{Alk/2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.2 (C_5), 137.7 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 128.1 (C_{Ar}), 119.7 (C_{11}), 78.5 (C_6), 71.5 (C_{12}), 46.5 ($C_{1/4}$), 46.2 ($C_{1/4}$), 31.2 (C_7), 26.6 (C_9), 25.3 ($C_{2/3}$), 25.0 ($C_{2/3}$), 23.8 (C_8), 17.2 (C_{10});

HRMS (ESI$^+$): calculated for $C_{18}H_{24}N_2O_2$ $[M+Na]^+$ *m/z*: 323.1735, found: 323.1722;

IR (neat) ν_{max}: 3023, 3010, 2933, 2845, 1640, 1491, 1430.

2-(Benzyloxy)-1-(pyrrolidin-1-yl)undec-10-en-1-one (1.1.198)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:1) yielded the product as a yellow oil (56.9 mg, 83 %).

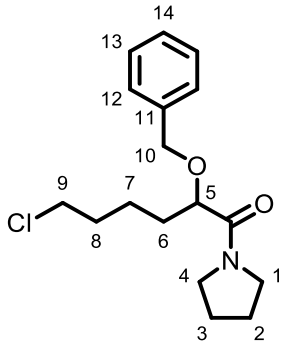
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.22 (m, 4H; H_{Ar}), 7.21 - 7.19 (m, 1H, H_{Ar}), 5.76 - 5.70 (m, 1H, H_{14}), 4.93 - 4.85 (m, 2H, H_{15}), 4.57 - 4.55 (m, 1H, H_{16}), 4.33 - 4.31 (m, 1H, H_{16}), 3.96 - 3.94 (m, 1H, H_6), 3.47 - 3.41 (m, 2H, $H_{1/4}$), 3.35 - 3.32 (m, 2H, $H_{1/4}$), 1.97 - 1.94 (m, 2H, H_{13}), 1.82 - 1.80 (m, 2H, H_7), 1.75 - 1.71 (m, 2H, H_{Alk}), 1.61 - 1.58 (m, 1H, H_{Alk}), 1.44 - 1.43 (m, 1H, H_{Alk}), 1.29 - 1.28 (m, 3H, $H_{Alk/2/3}$), 1.20 - 1.18 (m, 7H, $H_{Alk/2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9 (C_5), 139.3 (C_{14}), 138.0 (C_{Ar}), 128.5 (2C, C_{Ar}) , 128.1 (2C, C_{Ar}), 127.9 (C_{Ar}), 114.3 (C_{15}), 79.2 (C_{16}), 71.4 (C_6), 46.4 ($C_{1/4}$), 46.1 ($C_{1/4}$), 33.9 (C_{13}), 32.2 (C_7), 29.5 (2C, $C_{Alk/2/3}$), 29.2 ($C_{Alk/2/3}$), 29.0 ($C_{Alk/2/3}$), 26.6 (C_{Alk}), 25.8 (C_{Alk}), 23.8 (C_{Alk});

HRMS (ESI$^+$): calculated for $C_{22}H_{33}NO_2$ $[M+Na]^+$ *m/z*: 366.2409, found: 366.2404;

IR (neat) ν_{max}: 3072, 3030, 2971, 2925, 2855, 1639, 1434.

2-(Benzyloxy)-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one (1.1.192)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (51.3 mg, 83 %).

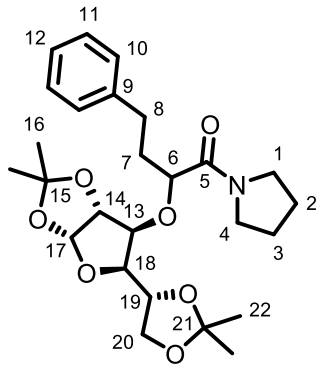
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 - 7.26 (m, 4H, H_{Ar}), 7.23 - 7.19 (m, 1H, H_{Ar}), 4.57 - 4.55 (m, 1H, H_{10}), 4.32 - 4.30 (m, 1H, H_{10}), 3.96 - 3.95 (m, 1H, H_5), 3.47 - 3.40 (m, 4H, $H_{1,4}$), 3.34 - 3.32 (m, 2H, H_9), 1.81 - 1.77 (m, 2H, H_6), 1.76 - 1.72 (m, 3H, $H_{Alk,\,2,\,3}$), 1.71 - 1.67 (m, 2H, $H_{Alk,\,2,\,3}$), 1.63 - 1.61 (m, 2H, $H_{Alk,\,2,\,3}$), 1.45 - 1.42 (m, 1H, $H_{Alk,\,2,\,3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.5 (C_{Ar}), 137.8 (C_{Ar}), 128.5 (2C, C_{Ar}) , 128.1 (2C, C_{Ar}) , 128.0 (C_{Ar}), 78.7 (C_5), 71.4 (C_{10}), 46.4 ($C_{1/4}$), 46.2 ($C_{1/4}$), 44.9 (C_9), 32.4 ($C_{6,8}$), 31.3 ($C_{6,8}$), 26.5 ($C_{2,3}$), 23.8 ($C_{2,3}$), 23.2 (C_7);

HRMS (ESI$^+$): calculated for $C_{17}H_{24}ClNO_2$ $[M+Na]^+$ *m/z*: 332.1393, found: 332.1388;

IR (neat) ν_{max}: 2942, 2888, 1640, 1494, 1450.

2-(((3aR,5R,6S,6aR)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.213)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:2-7:1) as a yellow oil (87.4 mg, 92 %, d.r 1:1, determined by crude ^{1}H NMR).

^{1}H NMR (600 MHz, $CDCl_3$): Diastereoisomers are present δ 7.28 - 7.26 (m, 2H, H_{Ar}), 7.24 - 7.23 (m, 1H, H_{Ar}), 7.20 - 7.17 (m, 2H, H_{Ar}), 5.77 (d, *J* = 3.8 Hz, 0.5H, d1, H_{14}), 5.67 (d, *J* = 3.5 Hz, 0.5H, d2, H_{14}), 4.57 - 4.54 (m, 1H), 4.40 - 4.38 (m, 0.5H, d1), 4.26 - 4.23 (m, 1.5H), 4.18 - 4.16 (m, 0.5H, d2), 4.09 - 4.07 (m, 0.5H, d1), 4.05 - 3.98 (m, 2H), 3.85 - 3.79 (m, 1.5H), 3.53 - 3.49 (m, 0.5H, d1), 3.47 - 3.30 (m, 3H), 2.87 - 2.81 (m, 1H), 2.77 - 2.74 (m, 0.5H, d1), 2.71 - 2.67 (m, 0.5H, d2), 2.16 - 2.05 (m, 1.5H), 1.99 - 1.96 (m, 0.5H, d1), 1.91 - 1.85 (m, 2H), 1.83 - 1.78 (m, 2H), 1.59 (bs, 1.5H, d1), 1.55 (bs, 1.5H, d2), 1.45 (bs, 1.5H, d1), 1.44 (bs, 1.5H, d2), 1.35 (bs, 4.5H), 1.31 (bs, 1.5H, d1);

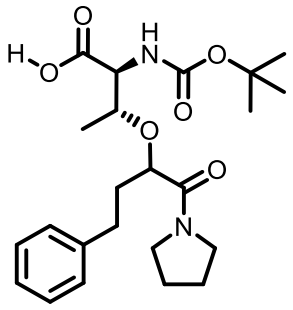
^{13}C NMR (151 MHz, $CDCl_3$): δ 169.9 (d1), 169.5 (d2), 141.8 (d1), 141.5 (d2), 128.7, 128.6, 128.5, 128.5, 128.4, 126.2 (d1), 126.1 (d2), 113.0 (d1), 113.0 (d2), 109.8 (d1), 109.6

(d2), 104.5 (d1), 103.7 (d2), 82.0, 80.3, 78.9, 78.4, 78.1, 77.6, 76.7, 76.5, 75.5, 75.4, 65.7, 65.0, 46.7, 46.3, 45.9, 45.9, 33.6, 33.3, 31.9, 31.6, 27.1, 27.1, 27.0 (2C), 26.7, 26.5 (2C), 26.4, 26.4, 25.6, 25.2, 23.9, 23.8;

HRMS (ESI$^+$): calculated for $C_{26}H_{37}NO_7$ $[M+Na]^+$ *m/z*: 498.2468, found: 498.2460;

IR (neat) ν_{max}: 2982, 2933, 2875, 1635, 1631, 1452.

***N*-(*tert*-butoxycarbonyl)-*O*-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)-L-threonine (1.1.214)**



The title compound was prepared according to general procedure **1.2** using *N*-(*tert*-Butoxycarbonyl)-L-threonine methyl ester (commercialy available) as a nucleophile. Product Isolated as the free carboxylic Acid. Purification by flash column chromatography (EtOAc: heptane = 1:2-5:1) as a yellow oil (72.0 mg, 83 %, 1:1.1 d.r. determined by crude ^{1}HNMR).

^{1}H NMR (600 MHz, $CDCl_3$) Diastereoisomers present: δ 7.32 - 7.29 (m, 2H), 7.19 - 7.17 (m, 3H), 5.56 (d, *J* = 8.4 Hz, 0.5H, d1), 5.26 (d, *J* = 8.4 Hz, 0.5H, d2), 5.06 - 5.04 (m, 0.5H, d1), 4.99 - 4.98 (m, 0.5H, d2), 4.87 (bs, 0.5H, d1), 4.68 (bs, 0.5H, d2), 4.43 - 4.42 (m, 0.5H, d2), 4.29 (bs, 0.5H), 4.22 (m, *J* = 6.0 Hz, 0.5H), 4.09 (d, *J* = 9.0 Hz, 0.5H, d1), 3.53 - 3.47 (m, 1H), 3.41 - 3.29 (m, 2H), 3.13 - 3.06 (m, 1H), 2.90 - 2.84 (m, 1H), 2.74 - 2.67 (m, 1H), 2.24 - 2.17 (m, 1H), 2.02 - 1.76 (m, 5H), 1.47 (bs, 4.5H), 1.46 (bs, 4.5H), 1.28 (d, *J*= 6.6 Hz, 1.5H), 1.25 (d, *J*= 6.6 Hz, 1.5H);

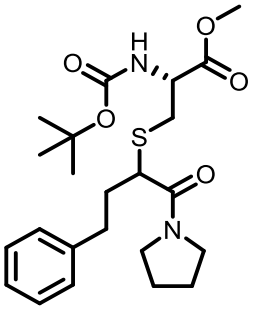
^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (d1), 172.1 (d2), 169.1 (d1), 169.0 (d2), 156.5 (d1), 156.4 (d2), 140.4 (d1), 140.3 (d2), 128.8 (2C, d1), 128.8 (2C, d2), 128.7 (2C, d1), 128.6 (2C, d2) , 126.6, 80.0 (d1), 79.8 (d2), 72.3 (d1), 72.0 (d2), 68.5 (d1), 68.0 (d2), 60.2 (d1),

59.4 (d2), 46.5, 45.9, 32.1 (d1), 32.0 (d2), 31.6 (d1), 31.4 (d2), 28.5 (3C, d1), 28.5 (3C, d2), 26.2 (d1), 26.2 (d2), 23.9 (d1), 23.9 (d2), 19.5 (d1), 18.6 (d2);

HRMS (ESI$^+$): calculated for $C_{23}H_{34}N_2O_6$ $[M+Na]^+$ *m/z:* 457.2315, found: 457.2299;

IR (neat) ν_{max}: 3359, 2975, 2931, 2882, 1745, 1712, 1635, 1496, 1453.

Methyl *N*-(*tert*-butoxycarbonyl)-S-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)-L-cysteinate (1.1.215)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:1-4:1) as a yellow oil (78.3 mg, 87 %, d.r. 1:1, determined by crude ^{1}H NMR).

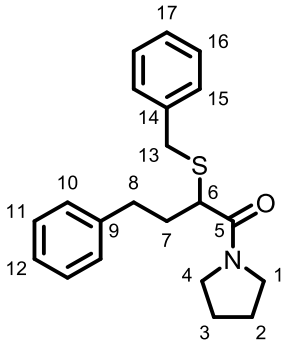
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 - 7.36 (m, 2H), 7.29 - 7.25 (m, 3H), 5.48 - 5.44 (m, 1H), 4.58 - 4.56 (m, 0.5H, d1), 4.50 - 4.47 (m, 0,5H, d2), 3.82 (s, 1.5H, d1), 3.81 (s, 1.5H, d2), 3.64 - 3.58 (m, 3H), 3.29 - 3.28 (m, 1H), 3.20 - 3.17 (m, 2H), 3.11 - 3.07 (m, 1H), 2.85 - 2.83 (m, 1H), 2.76 - 2.73 (m, 1H), 2.46 - 2.43 (m, 1H), 2.11 - 2.08 (m, 1H), 2.03 - 1.91 (m, 4H), 1.53 (s, 4.5H), 1.52 (s, 4.5H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.6, 169.1 (d1), 168.7 (d2), 155.5 (d1), 155.3 (d2), 141.0 (d1), 141.0 (d2), 128.6, 128.6, 128.4, 126.2, 125.9, 80.1, 53.8 (d1), 53.3 (d2), 52.6, 46.6, 46.3, 46.2, 46.2, 45.7, 43.3 (d1), 43.3 (d2), 39.1 (d1), 38.8 (d2), 35.4 (d1), 34.0 (d2), 33.3, 33.2, 33.2, 30.9 (d1), 30.3 (d2), 28.4, 26.4 (d1), 26.2 (d2), 26.1, 24.5, 24.4 (d1), 24.4 (d2), 22.8, 14.3;

HRMS (ESI$^+$): calculated for $C_{23}H_{34}N_2O_5S$ $[M+Na]^+$ *m/z:* 473.2086, found: 473.2080;

IR (neat) ν_{max}: 3289, 2973, 2929, 2875, 1745, 1711, 1628, 1517, 1435.

_N_-(_tert_-butoxycarbonyl)-O-(1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)-L-threonine (1.1.189)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (63.7 mg, 94 %).

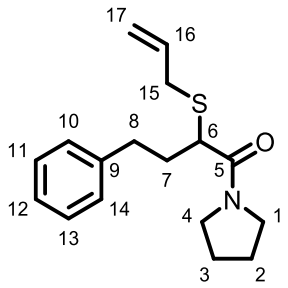
^{1}H NMR (600 MHz, MeOD): δ 7.31 - 7.28 (m, 2H, H_{Ar}), 7.27 - 7.21 (m, 4H, H_{Ar}), 7.19 (d, J = 7.2 Hz, 2H, H_{Ar}), 7.15 (d, J = 7.8 Hz, 2H, H_{Ar}), 3.75 (s, 2H, H_{13}), 3.45 - 3.35 (m, 2H, $H_{1/4}$), 3.30 - 3.28 (m, 1H, H_6), 3.18 - 3.16 (m, 1H, $H_{1/4}$), 2.86 - 2.82 (m, 1H, $H_{1/4}$), 2.78 - 2.72 (m, 2H, H_8), 2.61 - 2.56 (m, 1H, H_7), 2.35 - 2.29 (m, 1H, H_7), 2.09 - 2.03 (m, 1H, $H_{2/3}$), 1.91 - 1.87 (m, 1H, $H_{2/3}$), 1.80 - 1.74 (m, 2H, $H_{2/3}$);

^{13}C NMR (151 MHz, MeOD): δ 171.5 (C_5), 142.3 (C_{Ar}), 139.7 (C_{Ar}), 130.2 (2C, C_{Ar}), 129.7 (2C, C_{Ar}), 129.6 (2C, C_{Ar}), 129.5 (2C, C_{Ar}), 128.1 (C_{Ar}), 127.2 (C_{Ar}), 47.2 (C_6), 47.0 ($C_{1/4}$), 44.6 ($C_{1/4}$), 35.5 (C_7), 34.7 (C_{13}), 34.3 (C_8), 26.7($C_{2/3}$), 25.1 ($C_{2/3}$);

HRMS (ESI^{+}): calculated for $C_{21}H_{25}NOS$ $[M+Na]^{+}$ *m/z*: 362.1555, found: 362.1549;

IR (neat) ν_{max}: 3026, 2949, 2872, 1635, 1494, 1428.

2-(Allylthio)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.205)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (46.2 mg, 80 %).

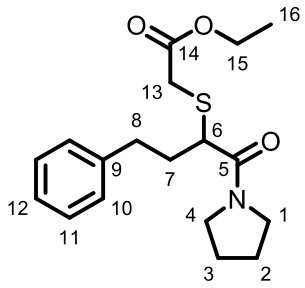
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.26 (m, 2H, H_{Ar}), 7.19 - 7.15 (m, 3H, H_{Ar}), 5.80 - 5.74 (m, 1H, H_{16}), 5.03 - 5.00 (m, 2H, H_{17}), 3.52 - 3.46 (m, 3H, $H_{1/4}$), 3.23 – 3.20 (m, 2H, H_{15}), 3.18 - 3.16 (m, 1H, H_6), 3.10 - 3.08 (m, 1H, $H_{1/4}$), 2.79 - 2.75 (m, 1H, H_8), 2.66 - 2.61 (m, 1H, H_8), 2.44 - 2.38 (m, 1H, H_7), 2.05 - 1.99 (m, 1H, H_7), 1.91 - 1.89 (m, 2H, $H_{2/3}$), 1.86 - 1.83 (m, 2H, $H_{2/3}$);

^{13}C NMR (176 MHz, $CDCl_3$): δ 169.1 (C_5), 141.3 (C_{Ar}), 134.5 (C_{16}), 128.7 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 126.1 (C_{Ar}), 117.4 (C_{17}), 46.3 (C_{174}), 46.2 ($C_{1/4}$), 43.5 (C_6), 33.5 (C_{15}), 33.4 (C_7), 32.7 (C_8), 26.2 ($C_{2/3}$), 24.4 ($C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{17}H_{23}NOS$ $[M+Na]^+$ *m/z*: 312.1398, found: 312.1396;

IR (neat) ν_{max}: 3060, 3024, 2948, 2871, 1633, 1494, 1423, 1340.

Ethyl 2-((1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)thio)acetate (1.1.212)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-2:3) yielded the product as a yellow oil (60.3 mg, 90 %).

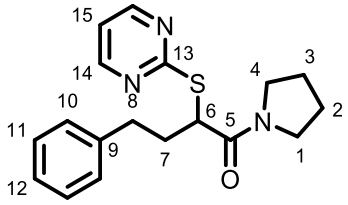
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.26 (m, 2H, H_{Ar}), 7.19 - 7.16 (m, 3H, H_{Ar}), 4.14 (q, J = 7.2 Hz, 2H, H_{15}), 3.58 - 3.55 (m, 1H, $H_{1/4}$), 3.48 - 3.46 (m, 2H, $H_{1/4}$) 3.44 - 3.34 (m, 1H, $H_{1/4}$), 3.34- 3.33 (m, 2H, H_{13}) , 3.11 - 3.08 (m, 1H, H_6), 2.78 - 2.75 (m, 1H, H_8), 2.69 - 2.65 (m, 1H, H_8), 2.37 - 2.34 (m, 1H, H_7), 2.06 - 2.03 (m, 1H, H_7), 1.93 - 1.80 (m, 4H, $H_{2/3}$), 1.25 (t, J = 7.2 Hz, 3H, H_{16});

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.5 (C_{14}), 168.5 (C_5), 141.1 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 126.2 (C_{Ar}), 61.5 (C_{15}), 46.3 ($C_{1/4}$), 46.2 ($C_{1/4}$), 43.6 (C_6), 33.3 (C_{13}), 33.0 (C_8), 31.2 (C_7), 26.1 ($C_{2/3}$), 24.4 ($C_{2/3}$), 14.2(C_{16});

HRMS (ESI$^+$): calculated for $C_{18}H_{25}NO_3S$ $[M+Na]^+$ *m/z*: 358.1453, found: 358.1448;

IR (neat) ν_{max}: 2971, 2927, 2874, 1734, 1637, 1432.

4-Phenyl-2-(pyrimidin-2-ylthio)-1-(pyrrolidin-1-yl)butan-1-one (1.1.182)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-3:1) yielded the product as a yellow oil (49.3 mg, 81 %).

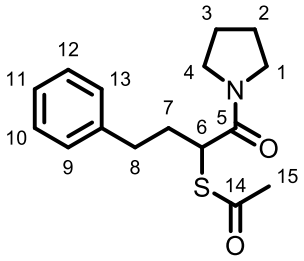
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4.8 Hz, 2H, $H_{14/16}$), 7.32 (d, *J* = 7.5 Hz, 2H, H_{10}), 7.28 - 7.23 (m, 3H, $H_{11\text{-}12}$), 7.02 (t, *J* = 4.8 Hz, 1H, H_{15}), 4.76 - 4.73 (m, 1H, H_6), 3.68 - 3.64 (m, 1H, $H_{1/4}$), 3.61 - 3.51 (m, 2H, $H_{1/4}$), 3.33 - 3.31 (m, 1H, $H_{1/4}$), 2.91 - 2.78 (m, 2H, H_8), 2.55 - 2.47 (m, 1H, H_7), 2.35 - 2.23 (m, 1H, H_7), 1.98 - 1.92 (m, 2H, $H_{2/3}$), 1.92 - 1.88 (m, 2H, $H_{2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7 (C_5), 169.3 (C_{13}), 157.4 (2C, C_{14}), 141.2 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 126.1 (C_{Ar}), 116.8 (C_{15}), 46.6 ($C_{1/4}$), 46.3 ($C_{1/4}$), 45.6 (C_6), 34.1 (C_8), 33.4 (C_7), 26.2 ($C_{2,'/3}$), 24.4 ($C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{18}H_{21}N_3OS$ $[M+Na]^+$ *m/z*: 350.1303, found: 350.1301;

IR (neat) ν_{max}: 3112, 3018, 2929, 2855, 1712, 1564, 1547, 1431, 1379, 1186, 748.

S-(1-Oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl) ethanethioate (1.1.210)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-1:1) yielded the product as a yellow oil (55.9 mg, 96 %).

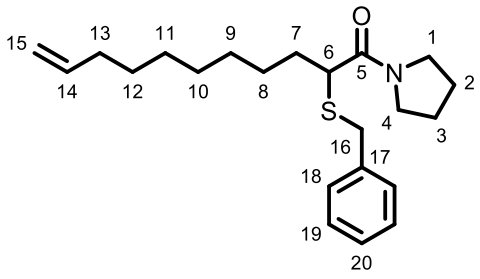
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 - 7.28 (m, 2H, H_{Ar}), 7.20 - 7.17 (m, 3H, H_{Ar}), 4.29 (t, *J* = 7.5 Hz, 1H, $H_{1/4}$), 3.50 - 3.41 (m, 3H, $H_{1/4}$), 3.20 - 3.18 (m, 1H, H_6), 2.70 - 2.68 (t, *J* = 7.7 Hz, 2H, H_8), 2.35 (s, 3H, H_{15}), 2.30 - 2.27 (m, 1H, H_7), 2.07 - 2.01 (m, 1H, H_7), 1.91 - 1.86 (m, 2H, $H_{2/3}$), 1.85 - 1.78 (m, 2H, $H_{2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 195.2 (C_{14}), 169.0 (C_5), 140.8 (C_{Ar}), 128.5 (4C, C_{Ar}), 126.3 (C_{Ar}), 46.6 ($C_{1/4}$), 46.3 ($C_{1/4}$), 44.4 (C_6), 34.1 (C_{15}), 33.3 (C_8), 30.4 (C_7), 26.1 ($C_{2/3}$), 24.4 ($C_{2/3}$);

HRMS (ESI^+): calculated for $C_{16}H_{21}NO_2S$ $[M+Na]^+$ *m/z*: 314.1191, found: 314.1182;

IR (neat) ν_{max}: 2950, 2926, 2874, 1689, 1639, 1428, 1353, 1128.

2-(benzylthio)-1-(pyrrolidin-1-yl)undec-10-en-1-one (1.1.199)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (58.8 mg, 82 %).

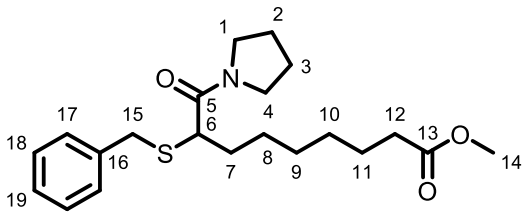
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 - 7.22 (m, 4H, H_{Ar}), 7.18 - 7.16 (m, 1H, H_{Ar}), 5.79 - 5.72 (m, 1H, H_{14}), 4.91 (m, 2H, H_{15}), 3.75 (s, 2H, H_{16}), 3.43 - 3.33 (m, 2H, $H_{1/4}$), 3.25 - 3.22 (m, 1H, H_6), 3.18 - 3.12 (m, 2H, $H_{1/4}$), 1.99 - 1.92 (m, 3H, H_{Alk}), 1.83 - 1.77 (m, 2H, H_{Alk}), 1.76 - 1.73 (m, 2H, H_{Alk}), 1.70 - 1.65 (m, 1H, H_{Alk}), 1.31 - 1.21 (m, 10H, $H_{Alk/2/31}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.4 (C_5), 139.3 (C_{14}), 138.4 (C_{Ar}), 129.1 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 127.1 (C_{Ar}), 114.3 (C_{15}), 46.2 ($C_{1/4}$), 46.1 ($C_{1/4}$), 45.2 (C_6), 34.0 (C_{16}), 33.9 (C_{13}), 31.9 (C_{Alk}), 29.4 (C_{Alk}), 29.4 (C_{Alk}), 29.1 (C_{Alk}), 29.0 (C_{Alk}), 27.6 ($C_{2/3}$), 26.1 ($C_{2/3}$), 24.3 (C_{Alk});

HRMS (ESI$^+$): calculated for $C_{22}H_{33}NOS$ $[M+Na]^+$ *m/z*: 382.2181, found: 382.2177;

IR (neat) ν_{max}: 3027, 2971, 2853, 2362, 1736, 1639, 1425.

Methyl 8-(benzylthio)-9-oxo-9-(pyrrolidin-1-yl)nonanoate (1.1.191)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-2:3) yielded the product as a yellow oil (61.0 mg, 81 %).

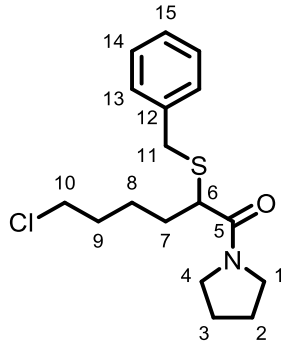
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 - 7.23 (m, 4H, H_{Ar}), 7.18 - 7.16 (m, 1H, H_{Ar}), 3.77 - 3.72 (m, 2H, H_{15}), 3.61 (s, 3H, H_{14}), 3.41 - 3.39 (m, 1H, $H_{1/4}$), 3.37 - 3.34 (m, 1H, $H_{1/4}$), 3.26 - 3.24 (m, 1H, H_6), 3.17 - 3.13 (m, 2H, $H_{1/4}$), 2.25 - 2.22 (m, 2H, H_{12}), 1.97 - 1.95 (m, 1H, H_{Alk}), 1.82 - 1.80 (m, 2H, H_{Alk}), 1.76 - 1.74 (m, 2H, H_{Alk}), 1.67 - 1.65 (m, 1H, H_{Alk}), 1.56 - 1.53 (m, 2H, H_{Alk}), 1.28 - 1.21 (m, 6H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.3 (C_{13}), 169.3 (C_5), 138.4 (C_{Ar}), 129.1 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 127.1 (C_{Ar}), 51.6 (C_{14}), 46.2 ($C_{1/4}$), 46.1 ($C_{1/4}$), 45.2 (C_6), 34.1 (C_{15}), 34.0 (C_{12}), 31.8 (C_{Alk}), 29.1 (C_{Alk}), 29.0 (C_{Alk}), 27.4 (C_{Alk}), 26.1 ($C_{2/3}$), 24.9 ($C_{2/3}$), 24.3(C_{Alk});

HRMS (ESI$^+$): calculated for $C_{21}H_{31}NO_3S$ $[M+Na]^+$ *m/z*: 400.1922, found: 400.1912;

IR (neat) ν_{max}: 2930, 2876, 1736, 1639, 1431.

2-(Benzylthio)-6-chloro-1-(pyrrolidin-1-yl)hexan-1-one (1.1.193)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (51.3 mg, 79 %).

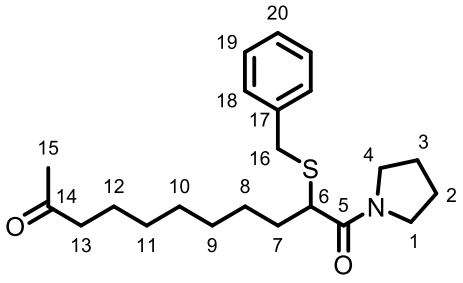
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 - 7.28 (m, 4H, H_{Ar}), 7.23 - 7.21 (m, 1H, H_{Ar}), 3.82 - 3.76 (m, 2H, H_{11}), 3.54 - 3.31 (m, 5H, $H_{1,4,6}$), 3.21 - 3.17 (m, 2H, H_{10}), 2.06 - 2.00 (m, 1H, H_{Alk}), 1.90 - 1.84 (m, 2H, H_{Alk}), 1.79 - 1.68 (m, 5H, $H_{Alk/2/3}$), 1.56 - 1.49 (m, 1H, $H_{2/3}$), 1.45 - 1.38 (m, 1H, $H_{2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.0 (C_5), 138.3 (C_{Ar}), 129.2 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 127.2 (C_{Ar}), 46.2 ($C_{1/4}$), 46.1 ($C_{1/4}$), 45.0 (2C, $C_{6/10}$), 34.0 (C_{11}), 32.4 (C_9), 31.1 (C_7), 26.1 (C_8), 25.0 ($C_{2/3}$), 24.3 ($C_{2/3}$);

HRMS (ESI$^+$): calculated for $C_{17}H_{24}ClNOS$ $[M+Na]^+$ *m/z:* 348.1165, found: 348.1152;

IR (neat) ν_{max}: 2951, 2871, 1634, 1493, 1428.

2-(Benzylthio)-1-(pyrrolidin-1-yl)undecane-1,10-dione (1.1.203)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:4-1:1) yielded the product as a yellow oil (70.5 mg, 94 %).

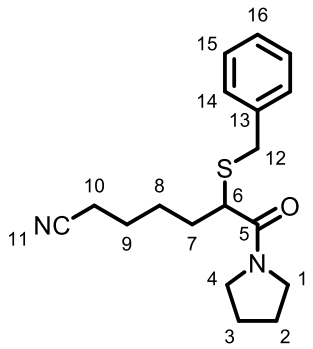
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.23 (m, 4H, H_{Ar}), 7.19 - 7.17 (m, 1H, H_{Ar}), 3.75 - 3.74 (m, 2H, H_{16}), 3.42 - 3.34 (m, 2H, $H_{1/4}$), 3.26 - 3.24 (m, 1H, H_6), 3.18 - 3.14 (m, 2H, $H_{1/4}$), 2.38 - 2.36 (m, 2H, H_{13}), 2.09 (s, 3H, H_{15}), 1.97 - 1.94 (m, 1H, H_{Alk}), 1.84 - 1.77 (m, 2H, H_{Alk}), 1.76 - 1.73 (m, 2H, H_{Alk}), 1.69 - 1.65 (m, 1H, H_{Alk}), 1.53 - 1.49 (m, 2H, H_{Alk}), 1.27 - 1.22 (m, 8H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.5 (C_{14}), 169.4 (C_5), 138.3 (C_{Ar}), 129.1 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 127.1 (C_{Ar}), 46.2 ($C_{1/4}$), 46.1 ($C_{1/4}$), 45.2 (C_6), 43.9 (C_{13}), 34.0 (C_{16}), 31.9 (C_{Alk}), 30.0 (C_{15}), 29.3 (2C, C_{Alk}), 29.2 (C_{Alk}), 27.6 ($C_{2/3}$), 26.1 ($C_{2/3}$), 24.3 (C_{Alk}), 23.9 (C_{Alk});

HRMS (ESI$^+$): calculated for $C_{22}H_{33}NO_2S$ $[M+Na]^+$ *m/z*: 398.2130, found: 398.2121;

IR (neat) ν_{max}: 2973, 2855, 1713, 1638, 1493, 1427.

6-(Benzylthio)-7-oxo-7-(pyrrolidin-1-yl)heptanenitrile (1.1.201)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:2-20:1) yielded the product as a yellow oil (52.5 mg, 83 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 - 7.25 (m, 4H, H_{Ar}), 7.22 - 7.18 (m, 1H, H_{Ar}), 3.77 - 3.71 (m, 2H, H, H_{12}), 3.41 - 3.34 (m, 1H, $H_{1/4}$), 3.33 - 3.30 (m, 2H, $H_{1/4}$), 3.16 - 3.11 (m, 2H, $H_{1/4/6}$), 2.29 - 2.22 (m, 2H, H_{10}), 1.99 - 1.94 (m, 1H, H_{Alk}), 1.85 - 1.79 (m, 2H, H_7),

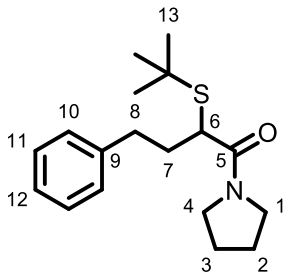
1.77 - 1.72 (m, 2H, H_{Alk}), 1.70 - 1.65 (m, 1H, H_{Alk}), 1.60 - 1.55 (m, 2H, $H_{2/3}$), 1.49 - 1.44 (m, 1H, $H_{2/3}$), 1.40 - 1.35 (m, 1H, $H_{2/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.7 (C_5), 138.2 (C_{Ar}), 129.1 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 127.2 (C_{Ar}), 119.7 (C_{11}), 46.2 ($C_{1/4}$), 46.1 ($C_{1/4}$), 44.9 (C_6), 33.9 (C_{12}), 31.0 (C_7), 26.7 (C_9), 26.1 (C_8), 25.2 ($C_{2/3}$), 24.3 ($C_{2/3}$), 17.1 (C_{10});

HRMS (ESI$^+$): calculated for $C_{18}H_{24}N_2O$ $[M+Na]^+$ *m/z*: 339.1507, found: 339.1419;

IR (neat) ν_{max}: 3061, 3028, 2931, 2872, 1634, 1493, 1429.

2-(*tert*-Butylthio)-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.1.209)



The title compound was prepared according to general procedure **1.2**. Purification by flash column chromatography (EtOAc: heptane = 1:3-4:1) yielded the product as a yellow solid (32.7 mg, 76 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 - 7.25 (m, 2H, H_{Ar}), 7.18 - 7.16 (m, 3H, H_{Ar}), 3.48 - 3.46 (m, 2H, $H_{1/4}$), 3.42 - 3.36 (m, 2H, $H_{1/4}$), 3.26 - 3.23 (m, 1H, H_6), 2.77 - 2.73 (m, 1H, H_8), 2.67 - 2.63 (m, 1H, H_8), 2.39 - 2.33 (m, 1H, H_7), 2.07 - 2.02 (m, 1H, H_7), 1.91 - 1.86 (m, 2H, $H_{2/3}$), 1.83 - 1.77 (m, 2H, $H_{2/3}$), 1.29 (s, 9H, H_{13});

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.7 (C_5), 141.3 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 126.2 (C_{Ar}), 46.5 ($C_{1/4}$), 46.3 ($C_{1/4}$), 44.0 (C_6), 35.8 (C_8), 33.8 (C_7), 31.7 (3C, C_{13}), 26.3 ($C_{2/3}$), 24.2 ($C_{2/3}$);

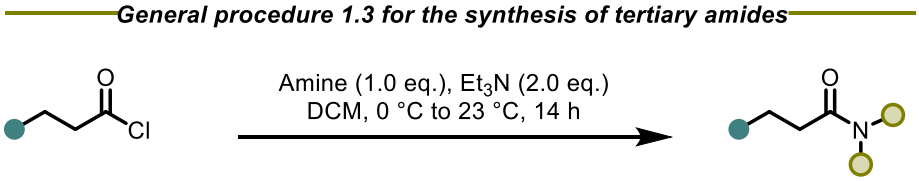
HRMS (ESI$^+$): calculated for $C_{18}H_{27}NOS$ $[M+Na]^+$ *m/z*: 328.1711, found: 328.1708;

IR (neat) ν_{max}: 2943, 1734, 1639, 1424, 1275.

3.3 Experimental Section Chapter 1.2

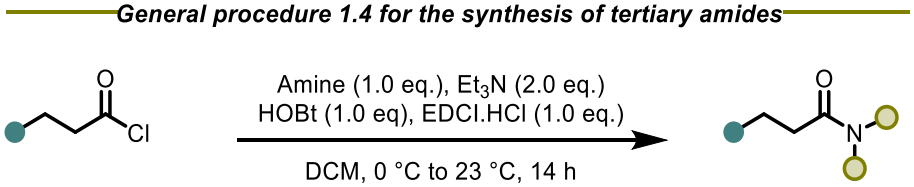
3.3.1 Synthesis of Amides

3.3.1.1 General procedure **1.3** - Procedure for the preparation of amides used in chapter 1.2:



To a solution of the amine (1.0 eq.) and triethylamine (2.0 eq.) in DCM (0.1 M) at 0°C, the corresponding acyl chloride (1.2 eq.) was added dropwise and the resulting reaction mixture was allowed to warm to 23 °C while stirring overnight (14 h). 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 (1×) and the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

3.3.1.2 General procedure **1.4:** General procedure for the preparation of amides used in chapter 1.2:

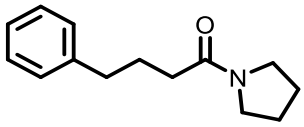


To a solution of the amine (1.0 eq.), triethylamine (1.0 eq.), hydroxybenzotriazole (HOBt, 1.0 eq.) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI.HCl, 1.0 eq.) in DCM (0.1 M), the corresponding acid chloride was added and the resulting solution was stirred at 23 °C overnight (14 h). After this time, the organic solution was washed sequentially with 0.5 M aqueous hydrochloric acid, saturated aqueous sodium

bicarbonate and brine. The washed solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

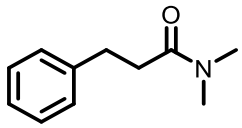
3.3.1.3 Characterisation of the starting materials used in chapter 1.1.

4-Phenyl-1-(pyrrolidin-1-yl)butan-1-one (1.2.91) was used in the synthesis of **(1.2.100)**



General Procedure **1.4** was carried out on 12.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:9 to 3:7) yielded the product as a colourless oil (2.16 g, 83 %) with R_f = 0.4 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[580]

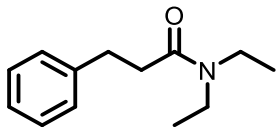
***N*,*N*-Dimethyl-3-phenylpropanamide (1.2.155)** was used in the synthesis of **(1.2.103)**



1.2.155

General Procedure **1.3** was carried out on 3.3 mmol scale (relative to the amine); purification by silica gel flash chromatography (EtOAc/heptanes 1:19 to 3:7) yielded the product as a pale-yellow oil (586 mg, 95 %) with R_f = 0.25 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[581]

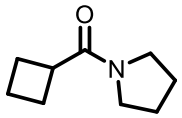
***N*,*N*-Diethyl-3-phenylpropanamide (1.2.156)** was used in the synthesis of **(1.2.116)**



1.2.156

General Procedure **1.3** was carried out on 5.0 mmol scale (relative to the amine); purification by silica gel flash chromatography (EtOAc/heptanes 1:19 to 2:8) yielded the product as a yellow oil (980 mg, 96 %) with R_f = 0.34 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[581]

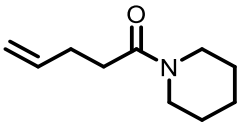
Cyclobutyl(pyrrolidin-1-yl)methanone (1.2.157) was used in the synthesis of **(1.2.112)**



1.2.157

General Procedure **1.4** was carried out on 2.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:19 to 2:8) yielded the product as a colourless oil (220 mg, 74 %) with R_f = 0.36 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[582]

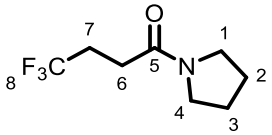
1-(Piperidin-1-yl)pent-4-en-1-one (1.2.158) was used in the synthesis of **(1.2.104)**



1.2.158

General Procedure **1.4** was carried out on 5.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:49 to 1:9) yielded the product as a yellow oil (753 mg, 90 %) with R_f = 0.46 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[583]

4,4,4-Trifluoro-1-(pyrrolidin-1-yl)butan-1-one (1.2.159) was used in the synthesis of **(1.2.106)**



1.2.159

General Procedure **1.4** was carried out on 1.6 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:4 to 1:1) yielded the product as a yellow oil (310 mg, 79 %) with R_f = 0.6 (acetone/heptanes 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (t, *J* = 6.9 Hz, 2H, H_6), 3.41 (t, *J* = 6.8 Hz, 2H, H_7), 2.55 - 2.48 (m, 4H, $H_{1/4}$), 2.02 - 1.93 (m, 2H, $H_{2/3}$), 1.87 (qd, *J* = 6.8, 0.9 Hz, 2H, $H_{2/3}$);

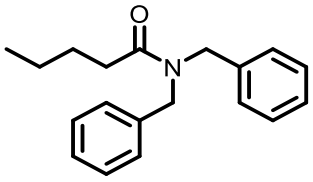
^{13}C NMR (151 MHz, $CDCl_3$): δ 168.3 (C_5), 127.3 (q, *J* = 275 Hz, C_8), 46.7 ($C_{1/4}$), 46.0 ($C_{1/4}$), 29.4 (q, *J* = 29.4 Hz, C_7), 27.4 (q, *J* = 2.8 Hz, C_6), 26.2 ($C_{2/3}$), 24.5 ($C_{2/3}$);

^{19}F NMR (659 MHz, $CDCl_3$): δ -66.7;

HRMS (ESI$^+$): exact mass calculated for $C_8H_{13}NOF_3$ $[M+H]^+$ *m/z*: 196.0944, found: 196.0945;

IR (neat) ν_{max}: 2960, 2878, 1639, 1443, 1380, 1344.

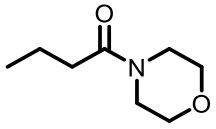
***N*,*N*-Dibenzylpentanamide (1.2.160)** was used in the synthesis of **(1.2.108)**



1.2.160

General Procedure **1.3** was carried out on 5.0 mmol scale (relative to the amine); purification by silica gel flash chromatography (EtOAc/heptanes 1:19 to 2:8) yielded the product as a yellow oil (1.40 g, 95 %) with R_f = 0.50 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[102]

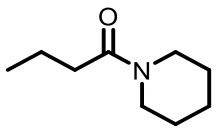
1-Morpholinobutan-1-one (1.2.161) was used in the synthesis of **(1.2.109)**



1.2.161

General Procedure **1.3** was carried out on 3.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:5 to 1:1) yielded the product as a yellow oil (480 mg, 80 %) with R_f = 0.50 (acetone/heptanes 1:2). All analytical data were in good accordance with data reported in the literature.[584]

1-(Piperidin-1-yl)butan-1-one (1.2.162) was used in the synthesis of **(1.2.110)**

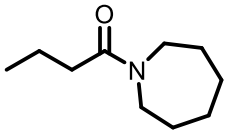


1.2.162

General Procedure **1.3** was carried out on 2 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:19 to 1:4) yielded the product as a colourless oil

(310 mg, 99 %) with R_f = 0.44 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[585]

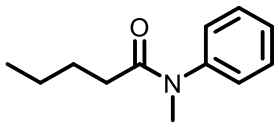
1-(Azepan-1-yl)butan-1-one (1.2.163) was used in the synthesis of **(1.2.111)**



1.2.163

General Procedure **1.3** was carried out on 2.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:5 to 2:3) yielded the product as a yellow oil (330 mg, 95 %) with R_f = 0.65 (acetone/heptanes 1:2). All analytical data were in good accordance with data reported in the literature.[585]

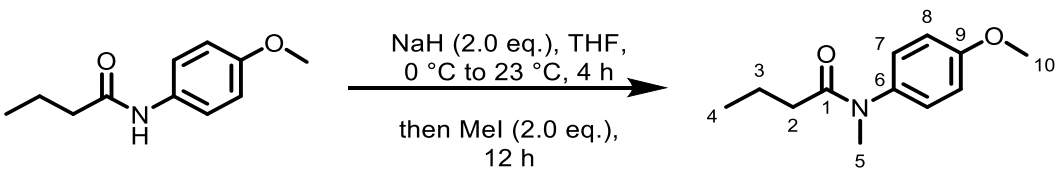
***N*-Methyl-*N*-phenylpentanamide (1.2.164)** was used in the synthesis of **(1.2.113)**



1.2.164

General Procedure **1.3** was carried out on 4.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:9 to 1:4) yielded the product as an orange oil (650 mg, 85 %) with R_f = 0.48 (acetone/heptanes 2:3). All analytical data were in good accordance with data reported in the literature.[586]

***N*-methylation of 1.2.165**



1.2.166

1.2.165, 72 %

***N*-(4-Methoxyphenyl)-*N*-methylbutyramide (1.2.165)** was used in the synthesis of **(1.2.114)**

NaH (2.0 eq., 60% in paraffin oil, 248 mg, 6.2 mmol) was added to a solution of *N*-(4-methoxyphenyl)butyramide (**1.2.166**, 1.0 eq., 600 mg, 3.1 mmol) -prepared in 57 % yield according to general procedure **1.3**- in tetrahydrofuran (15.0 mL, 0.4 M) at 0 °C and stirred for 4 h. Subsequently methyl iodide (2.0 eq., 0.39 ml, 6.2 mmol) was slowly added to the mixture and stirred for 12 h at 23 °C. The mixture was poured into 50.0 mL of water, the aqueous layer extracted with DCM (3 x 25.0 mL) and the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (EtOAc/heptanes 1:9 to 3:7) to yield the product as a yellow oil (**1.2.165**, 462 mg, 72 %) with R_f = 0.40 (acetone/heptanes 2:3);

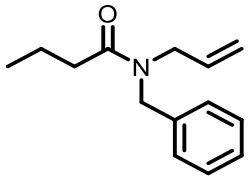
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.08 - 7.05 (m, 2H, H_8), 6.92 - 6.88 (m, 2H, H_7), 3.81 (s, 3H, H_{10}), 3.20 (s, 3H, H_5), 2.03 - 1.99 (m, 2H, H_2), 1.60 - 1.52 (m, 2H, H_3), 0.80 (t, *J* = 7.4 Hz, 3H, H_4);

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.6 (C_1), 158.9 (C_9), 137.2 (C_6), 128.5 (2C, C_7), 114.9 (2C, C_8), 55.6 (C_{10}), 37.5 (C_5), 36.0 (C_2), 19.0 (C_3), 14.0 (C_4);

HRMS (ESI$^+$): exact mass calculated for($C_{12}H_{17}NNaO_2$) $[M+Na]^+$ *m/z*: 230.1151, found: 230.1153;

IR (neat) ν_{max}: 2961, 2934, 2874, 1651, 1510, 1462, 1420, 1385, 1292, 1246, 1171, 1129, 1105, 1036, 839;

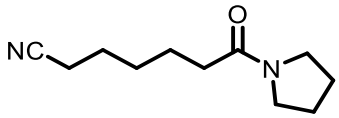
***N*-Allyl-*N*-benzylbutyramide (1.2.166)** was used in the synthesis of **(1.2.115)**



1.2.166

General Procedure **1.3** was carried out on 6.1 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 3:10 to 1:2) gave the product as a yellow oil (1.43 g, 82 %) with an R_f = 0.6 (acetone/heptanes 1:2). All analytical data were in good accordance with data reported in the literature.[102]

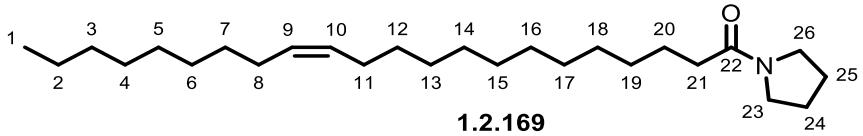
7-Oxo-7-(pyrrolidin-1-yl)heptanenitrile (1.2.168) was used in the synthesis of **(1.2.118)**



1.2.168

General Procedure **1.4** was carried out on 1.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:9 to 1:1) yielded the product as a white crystalline solid (155 mg, 88 %) with R_f = 0.44 (acetone/heptanes 1:2); All analytical data were in good accordance with data reported in the literature.[82]

(*Z*)-1-(Pyrrolidin-1-yl)docos-13-en-1-one (1.2.169) was used in the synthesis of **(1.2.123)**



1.2.169

General Procedure **1.4** was carried out on a 4.0 mmol scale; purification by silica gel flash chromatography (EtOAc/heptanes 1:9 to 1:1) yielded the product as a yellow oil (1.62 g, 82 %) with R_f = 0.35 (acetone/heptanes 1:2);

^{1}H NMR (700 MHz, $CDCl_3$): δ 5.34 (t, *J* = 4.5 Hz, 2H, $H_{9/10}$), 3.46 (t, *J* = 6.9 Hz, 2H, $H_{23/26}$), 3.40 (t, *J* = 6.8 Hz, 2H, $H_{23/26}$), 2.27 - 2.22 (m, 2H, H_{21}), 2.01 (dd, *J* = 12.2, 6.5 Hz, 4H, $H_{8/11}$), 1.97 - 1.91 (m, 2H, H_{Alk}), 1.84 (dd, *J* = 10.7, 4.2 Hz, 2H, H_{Alk}), 1.67 - 1.61 (m, 2H, $H_{Alk/24/25}$), 1.38 - 1.20 (m, 28H, H_{Alk}), 0.88 (t, *J* = 6.9 Hz, 3H, H_1);

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.0 (C_{22}), 130.0 (2C, $C_{9/10}$), 46.7 ($C_{23/26}$), 45.7 ($C_{23/26}$), 35.0 (C_{21}), 32.0 (C_{Alk}), 29.9 (C_{Alk}), 29.7 (4C, C_{Alk}), 29.6 (C_{Alk}), 29.4 (3C, C_{Alk}), 27.3 (C_{Alk}), 26.3 (2C, C_{Alk}), 25.1 (2C, C_{Alk}), 24.5 (2C, C_{Alk}), 22.8 (2C, C_{Alk}), 14.2 (C_1);

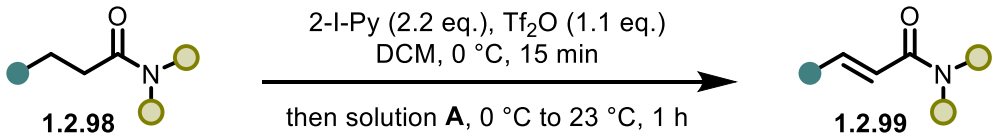
HRMS (ESI$^+$): calculated for $C_{26}H_{50}NO$ $[M+H]^+$ *m/z*: 392.3887, found: 392.3890;

IR (neat) ν_{max}: 2921, 2851, 1646, 1425, 1343.

3.3.2 Products of dehydrogenation of saturated amides

3.3.2.1 General procedure **1.5** – Procedure for the α, β-dehydrogenation of tertiary amides:

General procedure for the desaturation of tertiary amides



Solution **A**: $PhSeO_2H$ (1.0 eq.), Et_3N (3.0 eq.), DMP (2.2 eq.), DCM, rt, 2 h

All reactions were run on a 0.2 mmol scale unless otherwise indicated.

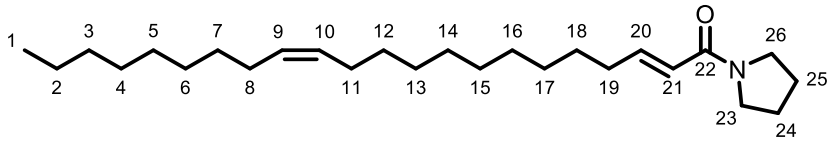
To a solution of amide **1.2.98** (1.0 eq.) and 2-iodopyridine (2.2 eq.) in DCM (2.0 mL, 0.1 M) at 0 °C was added trifluoromethanesulfonic anhydride (1.1 eq.) and the resulting mixture was stirred at 0 °C and colouration of the solution was observed. After 15 min, a previously prepared solution of **A** (1.0 mL, 0.2 M of $PhSeO_2H$) was added and the reaction mixture was stirred at 0 °C for 5 min. The resulting mixture was allowed to warm to ambient temperature (23 °C) over the course of 5 min to 1 h, after which time a saturated aqueous solution of $NaHCO_3$ (5.0 mL) was added. The biphasic mixture was separated and the aqueous phase was extracted with DCM (2 × 5.0 mL). The combined organic phases were dried over anhydrous sodium sulfate, the dried solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, heptanes/ethyl acetate) to afford compounds **1.2.99.** In most cases, the dehydrogenated amide **1.2.99** was isolated with remnants of the corresponding starting material (typically 5 – 10%). A further purification was necessary in most cases and was carried out on preparative TLC, typically using an acetone/heptanes system – to both determine the yield and for full Characterisation of the product – see individual compounds for details.

Preparation of solution **A**: To a suspension of the seleninic acid (1.0 eq.) in DCM (1.0 mL for 0.2 mmol of the seleninic acid) was added the triethylamine (3.0 eq.).

Solubilisation of the suspension was observed and then Dess-Martin periodinane (2.2 eq.) was added at 23 °C and stirred 2 h.

3.3.2.1 Characterisation of the products of α, β-dehydrogenation of amides following general procedure 1.5.

(2*E*,13*Z*)-1-(pyrrolidin-1-yl)docosa-2,13-dien-1-one (1.2.123)



The title compound was prepared according to the General Procedure for the desaturation of tertiary amides on a 0.2 mmol scale. Following purification by silica gel flash chromatography (acetone/heptanes 1:5 to 1:1), the product was isolated as a yellow oil (51.2 mg, 62%) with R_f = 0.6 (acetone/heptanes 1:2);

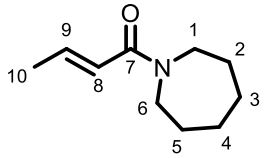
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.95 - 6.87 (m, 1H, H_{20}), 6.94 - 6.88 (m, 1H, H_{21}), 6.08 (d, *J* = 15.2 Hz, 1H, $H_{10/9}$), 5.62 (m, 1H, $H_{10/9}$), 4.03 (m, 1H, $H_{26/23}$), 3.52 (m, 3H, $H_{26/23}$), 2.20 (dt, *J* = 15.2, 7.7 Hz, 2H, H_{19}), 2.02 (m, 2H, H_{11}), 1.96 (dt, *J* = 13.8, 7.0 Hz, 2H, H_8), 1.86 (m, 2H, $H_{25/24}$), 1.47 - 1.42 (m, 2H, $H_{25/24}$), 1.26 (m, 26H, $H_{18\text{-}12/7\text{-}2}$);

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1 (C_{22}), 146.0 (C_{20}), 130.1 ($C_{10/9}$), 130.0 ($C_{10/9}$), 121.7 (C_{21}), 46.6 ($C_{23/26}$), 45.9 ($C_{23/26}$), 32.6 (C_{Alk}), 32.1 (C_{Alk}), 29.9 (C_{Alk}), 29.7 (C_{Alk}), 29.6 (C_{Alk}), 29.5 (C_{Alk}), 29.4 (C_{Alk}), 28.6 (C_{Alk}), 27.4 (C_{Alk}), 26.3 (C_{Alk}), 24.5 (C_{Alk}), 22.8 (C_{Alk}), 14.2 (C1);

HRMS (ESI$^+$): exact mass calculated for $C_{26}H_{47}NO$ $[M+Na]^+$ *m/z*: 412.3555, found: 412.3549;

IR (neat) ν_{max}: 2924, 2853, 1660, 1606, 1439.

(*E*)-1-(Azepan-1-yl)but-2-en-1-one (1.2.111)



The title compound was prepared according to the general procedure **1.5** for the desaturation of tertiary amides on a 0.2 mmol scale. Following purification by silica gel

flash chromatography (acetone/heptanes 1:5 to 1:1), the product was isolated as a yellow oil (16.8 mg, 51 %) with R_f = 0.6 (acetone/heptanes 1:2);

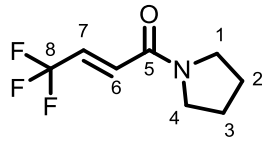
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.90 (dq, *J* = 20.7, 6.9 Hz, 1H, H_9), 6.32 - 6.17 (m, 1H, H_8), 3.59 - 3.54 (m, 2H, $H_{6/1}$), 3.50 - 3.46 (m, 2H, $H_{6/1}$), 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H, H_{10}), 1.76 - 1.68 (m, 4H, $H_{5/2}$), 1.60 - 1.51 (m, 4H, $H_{4/3}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.5 (C_7), 141.1 (C_9), 122.1 (C_8), 47.9 ($C_{1/6}$), 46.3 ($C_{1/6}$), 29.4 ($C_{5/2}$), 27.7 ($C_{5/2}$), 27.1 ($C_{4/3}$), 26.7 ($C_{4/3}$), 18.3 (C_{10});

HRMS (ESI$^+$): exact mass calculated for $C_{10}H_{17}NNaO$ $[M+Na]^+$ *m/z*: 190.1202, found: 190.1200;

IR (neat) ν_{max}: 2925, 2854, 1659, 1607, 1481, 1448, 1425.

(*E*)-4,4,4-Trifluoro-1-(pyrrolidin-1-yl)but-2-en-1-one (1.2.106)



The title compound was prepared according to the general procedure **1.5** for the desaturation of tertiary amides on a 0.2 mmol scale. Following purification by silica gel flash chromatography (acetone/heptanes 1:5 to 1:1) and a further purification on preparative TLC (DCM/methanol 200:3), the product was isolated as a yellow oil (23.0 mg, 60 %) with R_f = 0.6 (acetone/heptanes 1:2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.86 - 6.74 (m, 2H, $H_{7/6}$), 3.59 - 3.56 (m, 4H, $H_{4/1}$), 2.04 - 1.99 (m, 2H, $H_{3/2}$), 1.94 - 1.90 (m, 2H, $H_{3/2}$);

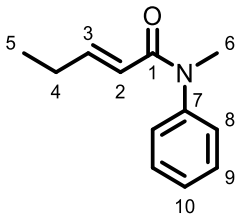
^{13}C NMR (151 MHz, $CDCl_3$): δ 168.3 (C_5), 129.0 (q, *J* = 5.5 Hz, C_6), 129.0 (q, *J* = 35 Hz, C_7), 122.8 (q, *J* = 270 Hz, C_8), 46.9 ($C_{4/1}$), 46.4 ($C_{4/1}$), 26.2 ($C_{2/3}$), 24.4 ($C_{2/3}$);

^{19}F NMR (565 MHz, $CDCl_3$): δ -64.9 (d, *J* = 5.0 Hz);

HRMS (ESI$^+$): exact mass calculated for $C_8H_{11}NOF_3$ $[M+H]^+$ *m/z*: 194.0787, found: 194.0788;

IR (neat) ν_{max}: 2929, 2881, 1723, 1684, 1626, 1447, 1344.

(*E*)-*N*-Methyl-*N*-phenylpent-2-enamide (1.2.113)



The title compound was prepared according to the general procedure **1.5** for the desaturation of tertiary amides on a 0.2 mmol scale. Following purification by silica gel flash chromatography (EtOAc/heptanes 1:9 to 3:7), the product was isolated as a pale-yellow oil (25.2 mg, 67 %) with R_f = 0.38 (acetone/heptanes 2:3);

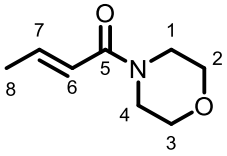
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (t, *J* = 7.7 Hz, 2H, H_9), 7.32 (t, *J* = 7.4 Hz, 1H, H_{10}), 7.17 (d, *J* = 7.3 Hz, 2H, H_8), 6.93 (dt, *J* = 15.1, 6.6 Hz, 1H, H_3), 5.72 (d, *J* = 15.1 Hz, 1H, H_2), 3.33 (s, 3H, H_6), 2.13 - 2.01 (m, 2H, H_4), 0.92 (t, *J* = 7.4 Hz, 3H, H_5);

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.4 (C_1), 147.5 (C_3), 143.9 (C_{Ar}), 129.6 (2C, C_{Ar}), 127.5 (3C, C_{Ar}), 120.6 (C_2), 37.5 (C_6), 25.5 (C_4), 12.7 (C_5);

HRMS (ESI$^+$): exact mass calculated for $C_{12}H_{16}NO$ $[M+H]^+$ *m/z*: 190.1226, found: 190.1224;

IR (neat) ν_{max}: 3061, 3037, 3011, 2964, 2931, 2875, 1726, 1661, 1629, 1291, 1119, 851.

(*E*)-1-Morpholinobut-2-en-1-one (1.2.109)



The title compound was prepared according to the general procedure **1.5** for the desaturation of tertiary amides on a 0.2 mmol scale. Following purification by silica gel flash chromatography (acetone/heptanes 1:4 to 1:1) and a further purification on preparative TLC (acetone/heptanes 2:3), the product was isolated as an orange solid (15.1 mg, 49 %) with R_f = 0.4 (acetone/heptanes 1:2);

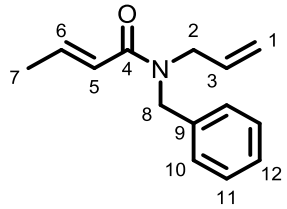
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.94 - 6.87 (m, 1H, H_6), 6.23 (dq, *J* = 15.0, 1.6 Hz, 1H, H_7), 3.62 (d, *J* = 75.2 Hz, 8H, H_{1-4}), 1.89 (dd, *J* = 6.9, 1.7 Hz, 3H, H_8);

^{13}C NMR (151 MHz, $CDCl_3$): δ 165.8 (C_5), 142.3 (C_7), 121.1 (C_6), 66.9 (2C, $C_{2/3}$), 46.2 ($C_{1/4}$), 42.3 ($C_{1/4}$), 18.4 (C_8);

HRMS (ESI$^+$): exact mass calculated for $C_8H_{14}NO_2$ $[M+H]^+$ *m/z*: 156.1019, found: 156.1019;

IR (neat) ν_{max}: 2961, 2851, 1646, 1549, 1530.

(*E*)-*N*-Allyl-*N*-benzylbut-2-enamide (1.2.115)



The title compound was prepared according to the general procedure **1.5** for the desaturation of tertiary amides on a 0.2 mmol scale. Following purification by silica gel flash chromatography (acetone/heptanes 1:5 to 1:2), and a further purification on preparative TLC (acetone/heptanes 1:2), the product was isolated as a yellow oil (17.1 mg, 40 %) with R_f = 0.60 (acetone/heptanes 1:2);

^{1}H NMR (700 MHz, $CDCl_3$): (rotameric effects present) δ 7.36 (t, *J* = 7.2 Hz, 1H, H_{Ar}), 7.32 - 7.28 (m, 1H, H_{Ar}), 7.25 - 7.21 (m, 1H, H_{Ar}), 7.19 (d, *J* = 7.3 Hz, 1H, H_{Ar}), 7.01 (dq, *J* = 13.6, 6.7 Hz, 1H, H_6), 6.23 (d, *J* = 14.9 Hz, 1H, H_5), 5.84 - 5.71 (m, 1H, H_3), 5.23 - 5.10 (m, 2H, H_1), 4.64 - 4.54 (m, 2H, H_8), 4.04 (d, *J* = 5.5 Hz, 1H, H_2), 3.88 (d, *J* = 3.3 Hz, 1H, H_2), 1.87 (dd, *J* = 34.7, 6.7 Hz, 3H, H_7);

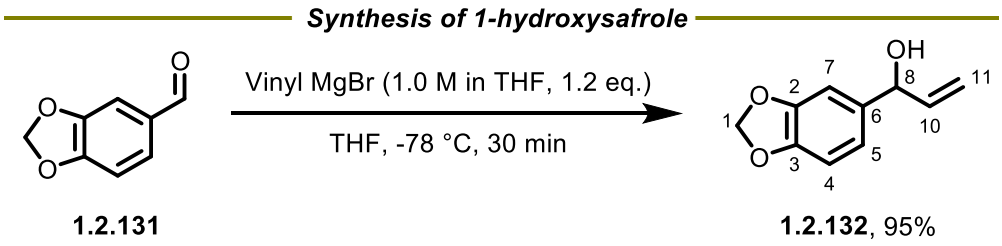
^{13}C NMR (151 MHz, $CDCl_3$): (rotameric effects present) δ 167.2 (C_4), 167.1 (C_4), 142.8 (C_6), 142.5 (C_6), 137.8 (C_9), 137.2 (C_9), 133.2 (C_{Ar}), 133.0 (C_{Ar}), 129.0 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 127.4 (C_3), 126.6 (C_3), 121.8 (2C, C_5), 117.6 (C_1), 117.0 (C_1), 50.1 (C_8), 49.1 (C_8), 48.8 (C_2), 48.3 (C_2), 18.4 (C_7);

HRMS (ESI$^+$): exact mass calculated for $C_{14}H_{18}NO$ $[M+H]^+$ *m/z*: 216.1383, found: 216.1380;

IR (neat) ν_{max}; 2969, 2929, 1661, 1619, 1447, 1416.

3.3.3 Derivatization of the products from α, β-dehydrogenation of amides

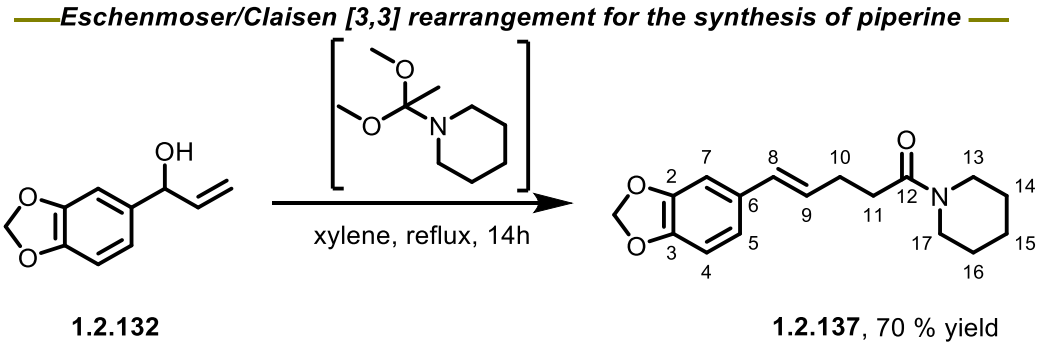
3.3.3.1 General procedure in the synthesis of piperine



1-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (1.2.132)

To a solution of piperonal (2.0 g, 1.3 mmol) in anhydrous THF (50.0 mL) at −78 °C was added, under an atmosphere of argon, vinylmagnesium bromide (1.2 eq., 1.6 mL, 1.0 M solution in THF) and the reaction mixture was allowed to warm up to rt. On re-cooling to 0 °C the reaction was quenched by the addition of saturated aqueous ammonium chloride (20.0 mL), the organic phase was extracted with ether (3 × 30.0 mL), the combined extracts dried with magnesium sulphate and concentrated *in vacuo* to afford 1-hydroxysafrole **1.2.132** in 95 % yield.

Spectral data in accordance with the literature[587]

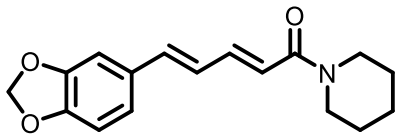


(*E*)-5-(benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)pent-4-en-1-one (1.2.136)

A roundbottomed flask was charged with 3.0 mL piperidine (3.0 eq., 30.0 mmol) and dimethylacetamide dimethyl acetal (1.0 eq., 1.3 mL, 10 mmol) and was slowly heated to 190 °C over 5 hours in a distillation apparatus (to remove all volatile products). After cooling to 23 °C, xylenes (5.0 mL) and the allylic alcohol (**1.2.132**, 1.78 g, 1.0 eq.) were

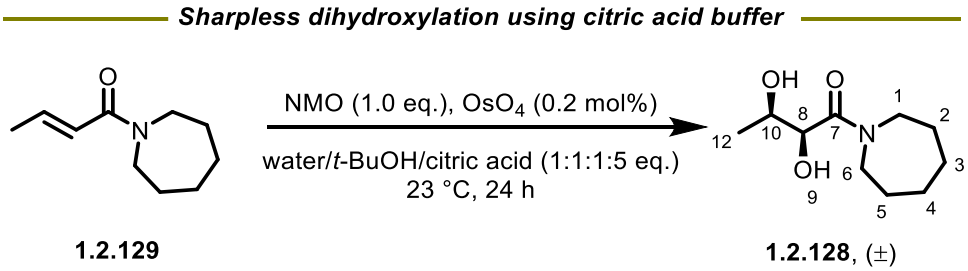
added and the reaction mixture was refluxed until the allylic alcohol was consumed (14 h) as determined by TLC. The title compound was isolated in 70 % yield (**1.2.137**, 2.0 g).[588] Experimental procedure adapted from.[589]

(2*E*,4*E*)-5-(benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one (1.2.137)



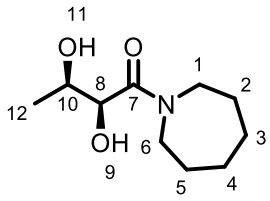
The product was prepared according to general procedure **1.5** on 0.2 mmol scale. The yield of the reaction was determined to be 48 % by NMR using mesitylene as an internal standard (2.0 eq., 24.0 mg). Due to contamination with 2-iodobenzoic acid, a small sample was purified by preparative TLC (run twice in solvent system 3:1:1 heptane/ethyl acetate/DCM) for analytical purposes; All analytical data were in good accordance with data reported in the literature.[590]

3.3.3.1 Procedure for the dihydroxylation of α, β-dehydrogenation of amides



The amide (**1.2.129**, 62.0 mg, 0.4 mmol) was suspended in a solution of citric acid (115 mg, 0.6 mmol) in 10.0 mL of a 1:1 mixture of *tert*–butyl alcohol/water in a 50.0 mL round bottom flask. Potassium osmate (25.0 mg, 0.2 mol%) was then added, followed by NMO (1.1 eq., 51.3 mg in 50 % wt. solution in water, 0.6 mmol). The reaction mixture turned bright green (this color is characteristic for almost all dihydroxylations performed under these acidic conditions) and was stirred at rt for 24 h, after which time it went nearly colorless. The precipitate was then filtered and washed with HCl (1.0 M, 10.0 mL), water, and dried to afford the pure diol product (**1.2.128**, 40.0 mg, 69 %).[591]

1-(Azepan-1-yl)-2,3-dihydroxybutan-1-one (1.2.128) xxx



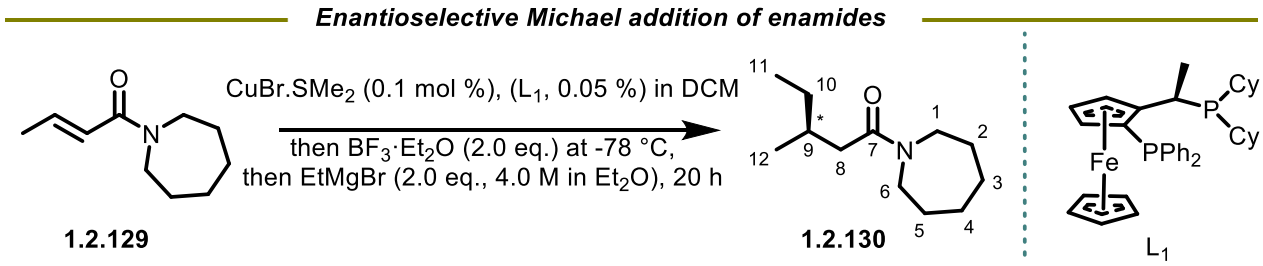
^{1}H NMR (700 MHz, CD_3OD): δ 4.24 (d, *J* = 4.6 Hz, 1H, H_8), 3.94 (qd, *J* = 6.4, 4.7 Hz, 1H, H_{10}), 3.69 – 3.62 (m, 2H, $H_{1/6}$), 3.55 (ddd, *J* = 14.5, 7.0, 5.3 Hz, 1H, $H_{1/6}$), 3.42 (ddd, *J* = 13.7, 8.0, 4.4 Hz, 1H, $H_{1/6}$), 2.91 (d, *J* = 15.7 Hz, 1H, H_9), 2.80 (d, *J* = 15.7 Hz, 1H, H_{11}), 1.80 - 1.70 (m, 4H, $H_{2/5}$), 1.60 (tdd, *J* = 16.6, 12.0, 4.2 Hz, 4H, $H_{3/4}$), 1.18 (d, *J* = 6.4 Hz, 3H, H_{12});

^{13}C NMR (176 MHz, CD_3OD): δ 173.4, 73.7, 69.8, 47.7, 43.8, 30.3, 28.4, 28.1, 27.3, 19.2;

HRMS (ESI^+): exact mass calculated for $C_{10}H_{20}NO_3$ $[M+H]^+$ *m/z*: 202.1438, found: 202.1438;

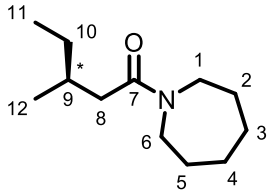
IR (neat) ν_{max}: 3411, 3301, 3260, 2929, 2857, 1723, 1608, 1442, 1440, 1373, 1200.

3.3.3.2 General procedure for the Enantioselective Michael addition to a α, β-dehydrogenation of amides



In a flame-dried Schlenk tube equipped with septum and magnetic stirring bar, $CuBr{\cdot}SMe_2$ and ligand (L_1)- were dissolved in DCM (final concentration of enamide substrate was 0.1 M) and stirred under argon atmosphere for 20 min. The enamide (**1.2.129**) was added at once. After stirring for 5 min. at 23 °C the reaction mixture was cooled down to -78 °C, followed by addition of $BF_3{\cdot}Et_2O$ (2.0 eq.). After 20 min., ethyl magnesium bromine (4.0 M in Et_2O) was added in 1 min. After stirring for 18 h, the reaction was quenched with MeOH followed by addition of saturated aqueous NH_4Cl solution and warming up to 23 °C. The reaction mixture was extracted with DCM (10.0 mL × 3). Combined organic phases were dried over $MgSO_4$, filtered and solvents were evaporated on a rotary evaporator. The crude was purified by flash chromatography on silica gel. Procedure based on Harutyunyan *et al.*[592]

(*S*)-1-(Azepan-1-yl)-3-methylpentan-1-one (1.2.130)



The title compound was purified by silica gel flash chromatography (acetone/heptanes 1:5 to 1:1), the compound was isolated as a yellow oil (36.0 mg, 91 %, 96 % *ee*) with $R_f = 0.6$ (acetone/heptanes 1:2);

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.56 - 3.50 (m, 2H, $H_{1/6}$), 3.47 - 3.41 (m, 2H, $H_{1/6}$), 2.29 (dd, J = 14.7, 5.9 Hz, 1H, H_8), 2.12 (dd, J = 14.7, 8.0 Hz, 1H, H_8), 1.98 (dd, J = 13.4, 6.8 Hz, 1H, H_9), 1.70 (dd, J = 11.3, 5.7 Hz, 4H, $H_{2/5}$), 1.58 - 1.57 (m, 3H, $H_{3/4/5/10}$), 1.43 - 1.37 (m, 1H, $H_{3/4/5/10}$), 1.30 - 1.14 (m, 2H, $H_{3/4/5/10}$), 0.95 - 0.88 (m, 6H, $H_{11/12}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4 (C_7), 48.1 ($C_{1/6}$), 46.1 ($C_{1/6}$), 40.3 (C_9), 32.0 (C_8), 29.8 (C_{10}), 29.4 ($C_{2/5}$), 27.8 ($C_{2/5}$), 27.1 ($C_{3/4}$), 26.9 ($C_{3/4}$), 19.6 (C_{12}), 11.6 (C_{11});

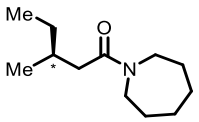
HRMS (ESI$^+$): exact mass calculated for $C_{12}H_{24}NO$ $[M+H]^+$ *m/z*: 198.1852, found: 198.1850;

IR (neat) ν_{max}: 2958, 2927, 2855, 1638, 1453, 1424.

Report

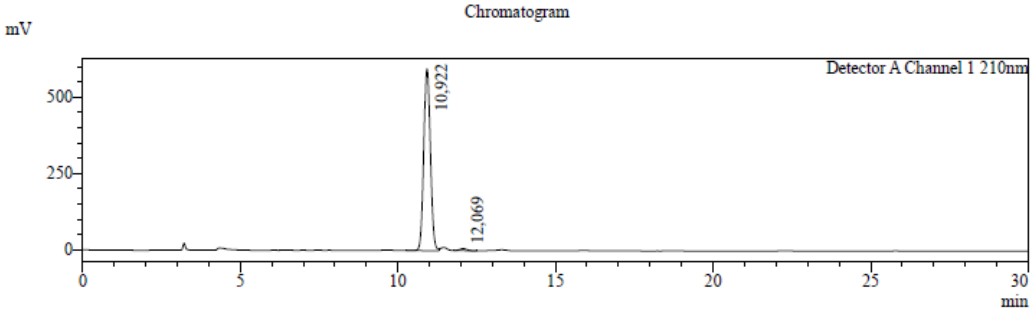
Sample Information

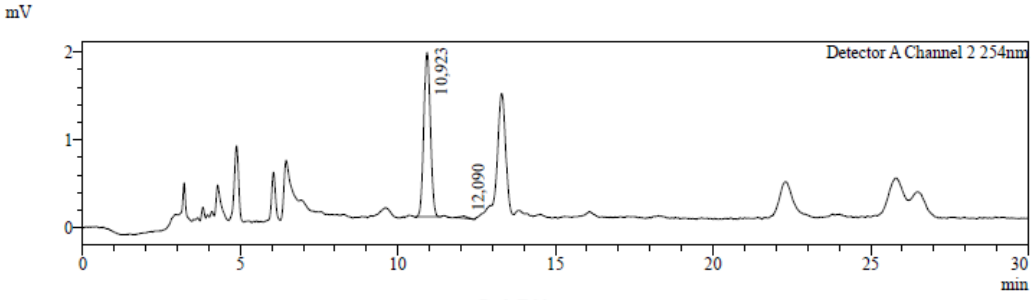
Sample Name	: Carlos_CR813F1_Lux-1
Sample ID	:
Vial#	: 2
Injection Volume	: 6
Data File	: Carlos_CR813F1_Lux-1_18.07.2018_1_002.lcd
Method File	: Run_100DD_F1_Pos4.lcm
Batch File	: 18.07.2018_1.lcb
Report Format File	: Lux-Cellulose-1(OD-H)_98Hep_2IPA_F1.lsr
Date Acquired	: 18.07.2018 11:39:01
Date Processed	: 18.07.2018 12:26:45



Method Description:
Column:Lux-Cellulose1 (Chiralcel OD-H) 250x4,6mm
Solvent System: n-Heptan+0,1%IPA/IPA 98:2
Flow:1 ml/min

Chromatogram





Peak Table

Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	10.922	8667989	98.845
2	12.069	101288	1.155
Total		8769278	100.000

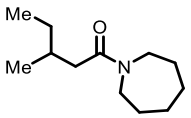
Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	10.923	27011	98.863
2	12.090	311	1.137
Total		27322	100.000

Report

Sample Information

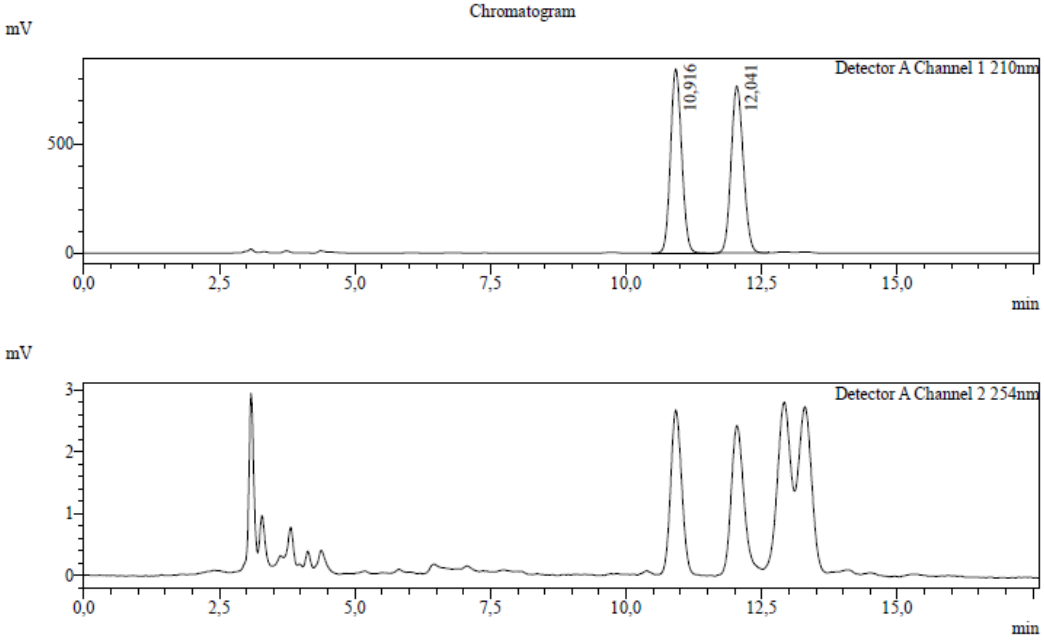
Sample Name	: Carlos_CR810F1_Rac_Lux-1
Sample ID	:
Vial#	: 1
Injection Volume	: 6
Data File	: Carlos_CR810F1_Rac_Lux-1_18.07.2018_1_003.lcd
Method File	: Run_100DD_F1_Pos4.lcm
Batch File	: 18.07.2018_1.lcb
Report Format File	: Lux-Cellulose-1(OD-H)_98Hep_2IPA_F1.lsr
Date Acquired	: 18.07.2018 12:09:26
Date Processed	: 18.07.2018 12:29:00



(±)

Method Description:
Column:Lux-Cellulose1 (Chiralcel OD-H) 250x4,6mm
Solvent System: n-Heptan+0,1%IPA/IPA 98:2
Flow:1 ml/min

Chromatogram



Peak Table

Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	10.916	12019868	50.050
2	12.041	11995984	49.950
Total		24015852	100.000

Detector A Channel 2 254nm

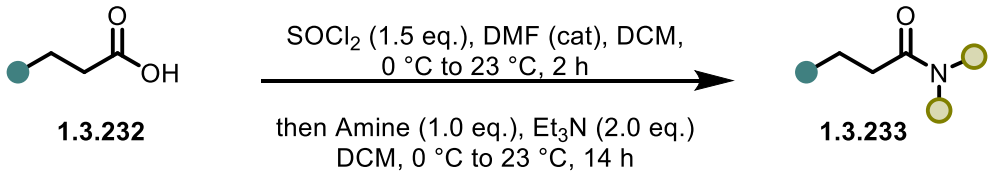
Peak#	Ret. Time	Area	Area%
Total			

3.4 Experimental Section Chapter 1.3

3.4.1 Procedures for the synthesis of starting material used in the chapter 1.3

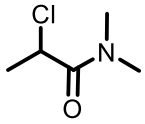
3.4.1.1 General procedure **1.6** – Procedure for the preparation of Amides used in chapter 1.3.

General procedure C for the synthesis of tertiary amides



To a cold solution (0 °C) of carboxylic acid in DCM (**1.3.232**, 1.0 M) was slowly added $SOCl_2$ (1.5 eq.). After adding catalytic amounts of DMF, the mixture was allowed to warm to room temperature and stir for 2 h. After carefully evaporating the solvent and the remaining $SOCl_2$, the crude was resuspended in DCM and put in an ice bath. The amine (1.0 eq.) was then added, followed by triethylamine (2.0 eq.) and the resulting reaction mixture was allowed to warm to room temperature while stirring for 14 h. After this time, a saturated aqueous solution of $NaHCO_3$ was added and the biphasic system was separated. The aqueous phase was extracted with DCM (2×) and then washed with HCl (1.0 M). After extracting with DCM (2x) the organic phases were combined and dried over anhydrous sodium sulfate. The resulting crude material was purified by flash column chromatography on silica gel to afford the desired compound (**1.3.233**, EtOAc/heptane).

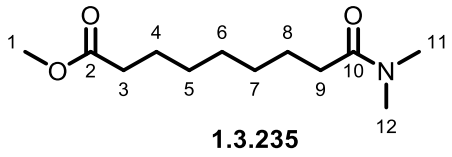
2-chloro-*N*,*N*-dimethylpropanamide (1.3.234) was used in the synthesis of **(1.3.186)**



1.3.234

The title compound was prepared using general procedure **1.6** for the synthesis of amides. After flash chromatography, the compound was isolated in 62 % yield as a yellow oil. All spectral data was found to be in accordance with the literature.[593]

Methyl 9-(dimethylamino)-9-oxononanoat (1.3.235) was used in the synthesis of **(1.3.183)**



1.3.235

The title compound was prepared using general procedure **1.6** for the synthesis of amides. After flash chromatography, the compound was isolated in 72 % yield as a yellow oil.

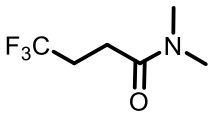
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.66 (s, 3H, H1), 3.00 (s, 3H, H11), 2.94 (s, 3H, H12), 2.29 (t, J = 7.5 Hz, 4H, H3/9), 1.66 - 1.58 (m, 4H, H4/8), 1.36 - 1.30 (m, H5/7);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_2), 173.3 (C_{10}), 51.6 (C_1), 37.4 (C_{11}), 35.5 (C_{12}), 34.2 (C_9), 33.5 (C_3), 29.4 (C_5), 29.2 (C_6), 29.1 (C_7), 25.2 (C_4), 25.0 (C_8);

HRMS(ESI$^+$): calculated for $C_{12}H_{23}NO_3$ $[M+H]^+$ *m/z*: 230.1755 found: 230.1753;

IR (neat) ν_{max}: 2940, 1736, 1646, 1497, 1437, 1398.

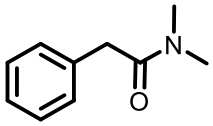
4,4,4-Trifluoro-*N*,*N*-dimethylbutanamide (1.3.236) was used in the synthesis of **(1.3.180** and **1.3.181)**



1.3.236

The title compound was prepared using general procedure **1.6** for the synthesis of amides. After flash chromatography, the compound was isolated in 45 % yield as a colorless oil. All spectral data was found to be in accordance with the literature.[594]

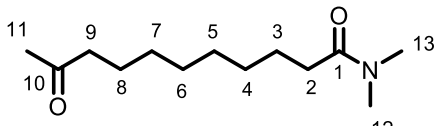
***N*,*N*-Dimethyl-2-phenylacetamide (1.3.237)** was used in the synthesis of **(1.3.185)**



1.3.237

The title compound was prepared using general procedure **1.6** for the synthesis of amides. After flash chromatography, the compound was isolated in 80 % yield as a white solid. All spectral data was found to be in accordance with the literature.[595]

***N,N*-Dimethyl-10-oxoundecanamide (1.3.238)** was used in the synthesis of **(1.3.182)**



1.3.238

The title compound was prepared using general procedure **1.6** for the synthesis of amides. After flash chromatography, the compound was isolated in 34 % yield as a yellow oil.

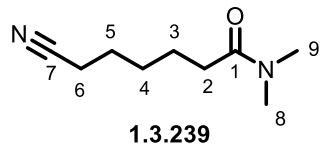
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.99 (s, 3H, $H_{12/13}$), 2.92 (s, 3H, $H_{12/13}$), 2.39 (t, J = 7.5 Hz, 2H, H_9), 2.32 - 2.25 (m, 2H, H_2), 2.11 (s, 3H, H_{11}), 1.64 - 1.50 (m, 4H, $H_{3/8}$), 1.34 - 1.21 (m, 8H, $H_{4\text{-}7}$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.4 (C_{10}), 173.4 (C_1), 43.7 (C_9), 37.3 (C_{Alk}), 35.4 (C_{Alk}), 33.3 (C_{Alk}), 29.8 (C_{Alk}), 29.4 (C_{Alk}), 29.2 (C_{Alk}), 29.0 (C_{Alk}), 25.1 (C_{Alk}), 23.8 (C_{Alk});

HRMS (ESI$^+$): calculated for $C_{13}H_{25}NO_2$ $[M+Na]^+$ *m/z*: 250.1783, found: 250.1689;

IR (neat) ν_{max}: 2928, 2854, 1713, 1664, 1499, 1460, 1398, 1361, 1264, 1164.

6-Cyano-*N,N*-dimethylhexanamide (1.3.239) was used in the synthesis of **(1.3.169** and **1.3.178** and **1.3.179)**



1.3.239

The title compound was prepared using general procedure **1.6** for the synthesis of amides. After flash chromatography, the compound was isolated in 89 % yield as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.71 (s, 3H, $H_{8/9}$), 2.62 (s, 3H, $H_{8/9}$), 2.08 (t, *J* = 7.1 Hz, 2H, H_2), 2.03 (t, *J* = 7.4 Hz, 2H, H_6), 1.42 - 1.32 (m, 4H, $H_{3/5}$), 1.24 - 1.16 (m, 2H, H_4);

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.5 (C_1), 119.0 (C_7), 36.3 (C_{Alk}), 34.4 (C_{Alk}), 31.9 (C_{Alk}), 27.5 (C_{Alk}), 24.4 (C_{Alk}), 23.3 (C_{Alk}), 16.1 (C_6);

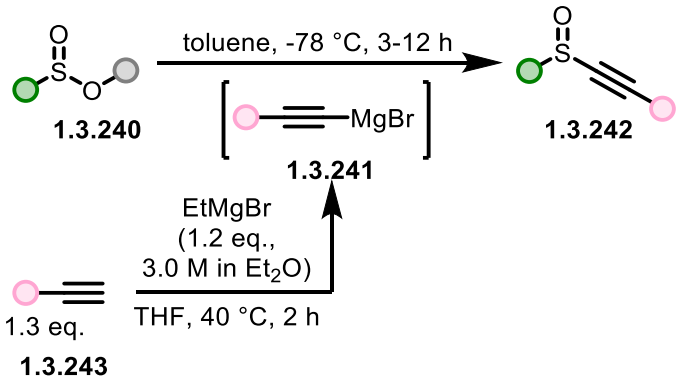
HRMS (ESI$^+$): calculated for $C_9H_{16}N_2O$ $[M+Na]^+$ *m/z*: 191.1160, found: 191.1155;

IR (neat) ν_{max}: 2936, 2865, 1638, 1497, 1461, 1398, 1335, 1265, 1138, 1059.

3.4.2 Synthesis of vinyl sulfoxides used in chapter 1.3

3.4.2.1 General procedure **1.7** – General procedure for the preparation of alkynylsulfoxide (1.3.242)

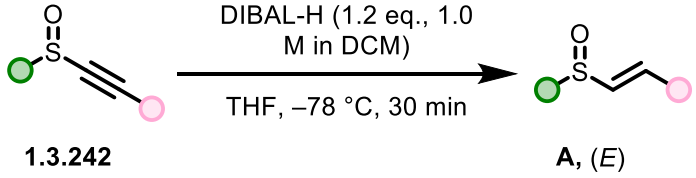
Alkynylsulfoxide synthesis using sulfinates



In a dry Schleck tube, alkyne (**1.3.243**, 1.5-3.0 eq.) was dissolved in THF (0.1 M) and EtMgBr solution (0.9 eq. with respect to the alkyne, 3 M in Et_2O) was added dropwise and the solution was stirred 2 h at 40 °C. After letting the solution cool down to –78 °C, the alkynyl Grignard reagent (**1.3.241**) was added to a second Schlenk tube containing the sulfinate (**1.3.240**, 1.0 eq.) in toluene (0.25 M) at –78 °C. The solution was stirred for 3 – 12 h at –78 °C after being quenched with sat. NH_4Cl solution at this temperature. It was extracted with DCM, dried over $MgSO_4$, filtrated and concentrated. The crude product was purified by column chromatography on silica gel (Heptane: EtOAc 5:1) to afford the alkynyl sulfoxide (**1.3.242**). [596]

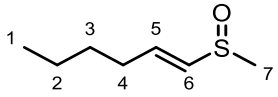
3.4.2.2 General procedure **1.8** – Procedure for the preparation of *E*-vinyl sulfoxides (**A**, (*E*))

Synthesis of E Alkynylsulfoxide



To an acetone bath (–78 °C) containing a solution of alkynyl sulfoxide (**1.3.242**, 1.0 eq.) in THF (0.1 M) was added DIBAL-H (1.2 eq., 1.0 M solution in DCM) dropwise. The resulting suspension was stirred at –78°C for 30 min before a saturated aqueous NH_4Cl solution was added. The mixture was diluted with ether (1:1), a saturated aqueous tartrate solution was added, and mixture was stirred for 1 h at 23 °C. The mixture was extracted with DCM (2x), the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (heptane: EtOAc 5:1 to 1:1) afforded the *E*-alkenyl sulfoxide (A, (*E*)).[596]

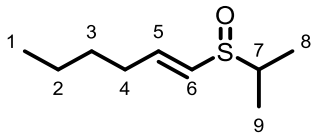
(*E*)-1-(methylsulfinyl)hex-1-ene (1.3.244) was used in the preparation of **(1.3.152, 1.3.153, 1.3.154, 1.3.155, 1.3.156, 1.3.157, 1.3.158, 1.3.174, 1.3.175, 1.3.176, 1.3.177, 1.3.178, 1.3.179, 1.3.180, 1.3.181, 1.3.182, 1.3.183, 1.3.184, 1.3.185, 1.3.186, 1.3.187, 1.3.188, 1.3.192, 1.3.197, 1.3.198, 1.3.212)**



1.3.244

The title compound was prepared according to general procedure **1.8** in 36 % yield as a yellow oil. Spectral data matched literature. [597]

(*E*)-1-(isopropylsulfinyl)hex-1-ene (1.3.245) was used in the preparation of **(1.3.195)**



1.3.245

Title compound was prepared according to general procedure **1.8** in 74 % yield as a yellow oil.

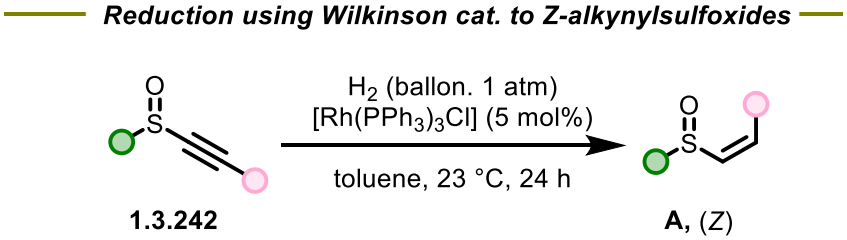
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.45 (dt, *J* = 15.2, 6.9 Hz, 1H, H_5), 6.12 (dt, *J* = 15.2, 1.5 Hz, 1H, H_6), 2.77 (hept, *J* = 6.9 Hz, 1H, H_7), 2.30 - 2.23 (m, 2H, H_4), 1.50 - 1.41 (m, 2H, H_3), 1.40 - 1.31 (m, 2H, H_2), 1.24 (d, *J* = 6.9 Hz, 6H, $H_{8/9}$), 0.91 (t, *J* = 7.2 Hz, 3H, H_1);

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.9 (C_6), 129.6 (C_5), 51.9 (C_7), 32.1 (C_4), 30.5 (C_3), 22.3 (C_2), 15.4 (C_8), 14.8 (C_9), 13.9 (C_1);

HRMS: calculated for $C_9H_{18}OS$ $[M+H]^+$ *m/z*: 175.1156 found: 175.1152**;**

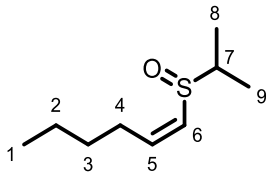
IR (neat) ν_{max}: 2958, 1042.

3.4.2.3 General procedure **1.9** – Procedure for the preparation of *Z*-vinyl sulfoxides.



The alkynylsulfoxide (**1.3.242**, 5.0 mmol, 1.0 eq.) was dissolved in anhydrous toluene (0.1 M) and Wilkinson's catalyst (5 mol%) was added under hydrogen atmosphere. The mixture was stirred under hydrogen atmosphere for 24 h at room temperature under an atmospheric pressure. The mixture was diluted with ether and passed through a short column of Celite. Removal of the solvent under reduced pressure was followed by chromatography of the residue on silica gel (heptane: EtOAc 4:1 to 1:1) to afford the *Z*-alkenyl sulfoxide (**A**, (*Z*)).[596]

(*Z*)-1-(isopropylsulfinyl)hex-1-ene (1.3.246) was used in the preparation of **(1.3.196)**



1.3.246

The title compound was prepared according to general procedure **1.9** in 60 % yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.32 - 6.22 (m, *J* = 9.9, 8.2, 7.1 Hz, 1H, H_5), 6.10 (dt, *J* = 9.9, 1.4 Hz, 1H, H_6), 2.82 (hept, 1H, H_7), 2.50 - 2.41 (m, 1H, H_4), 2.35 - 2.25 (m, *J* = 14.7, 7.2 Hz, 1H, H_4), 1.48 - 1.40 (m, 2H, H_3), 1.39 - 1.34 (m, 2H, H_2), 1.32 (d, *J* = 6.9 Hz, 3H, H_8), 1.21 (d, *J* = 6.9 Hz, 3H, H_9), 0.91 (t, *J* = 7.1 Hz, 3H, H_1);

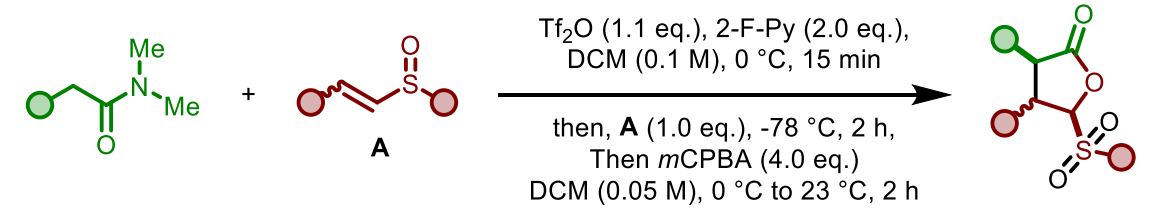
^{13}C NMR (151 MHz, $CDCl_3$): δ 144.5 (C_6), 132.4 (C_5), 52.4 (C_7), 31.2 (C_4), 29.5 (C_3), 22.3 (C_2), 15.5 ($C_{8/9}$), 15.1 ($C_{8/9}$), 13.9 (C_1);

HRMS(ESI$^+$): calculated for $C_9H_{18}OS$ $[M+H]^+$ *m/z*: 175.1156 found: 175.1155;

IR (neat) ν_{max}: 2960, 1669, 1021.

3.4.2.4 General procedure **1.10** – Procedure for the synthesis of sulfonyl lactones.

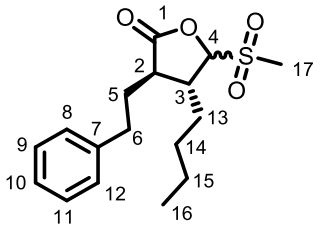
Synthesis of sulfonyl lactones by amide activation



1.3.171 or **1.3.189** (*E*) or (*Z*) **1.3.172, 1.3.173** or **1.3.190, 1.3.191**

To a solution of amide (**1.3.171** or **1.3.189**, 1.2 eq., 23.4 mg, 0.012 mmol) and 2-fluoropyridine (2.0 eq., 11.2 µL, 0.131 mmol) in DCM (1.0 mL, 0.1 M) at 0 °C was added Tf_2O (1.1 eq., 12.1 µL, 0.072 mmol) and the resulting mixture was stirred at 0 °C (by addition of Tf_2O, the mixture turned intense yellow). After 15 min, the solution was kept at -78 °C and a precooled solution of vinyl sulfoxide (**A** (*E*) or (*Z*), 1.0 eq., 15.0 mg, 0.01 mmol) in DCM (1.0 mL, 0.05 M) was quickly added. The color of the solution changed to a pale blue color. After 2 h at this temperature, the reaction was evaporated by reduced pressure and analysed by ^{1}HNMR. Solid *m*CPBA containing water (4.0 eq., 92.0 mg, 0.8 mmol) was added at 0°C. The resulting mixture was allowed to warm to ambient temperature (25 °C) over the course of 2 h, after which time $NaHCO_3$ was added. The biphasic mixture was separated and the aqueous phase was extracted with DCM (3 × 5.0 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, EtOAc in heptanes 5% to 30%) to afford the desired sulfonal lactone products as a mixture of 4 diastereoisomers in different ratios. For simplification, the major diastereosiomer was described when isolated separatelly.

(3,4)-4-Butyl-5-(methylsulfonyl)-3-phenethyldihydrofuran-2(3*H*)-one (1.3.174)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (27.0 mg, 85 %) in 10:1 d.r.

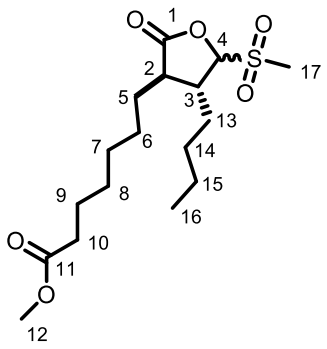
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 - 7.18 (m, 2H, H_{Ar}), 7.13 (dd, *J* = 10.6, 4.4 Hz, 3H, H_{Ar}), 4.73 (d, *J* = 4.2 Hz, 1H, H_4), 2.93 (s, 3H, H_{17}), 2.75 (t, *J* = 7.7 Hz, 2H, H_6), 2.67 (tdd, *J* = 7.3, 5.7, 4.4 Hz, 1H, H_2), 2.34 - 2.26 (m, 1H, H_{Alk}), 2.16 (ddt, *J* = 13.9, 8.0, 6.8 Hz, 1H, H_{Alk}), 2.06 - 1.93 (m, 1H, H_{Alk}), 1.62 - 1.44 (m, 2H, H_{Alk}), 1.33 - 1.13 (m, 4H, H_{Alk}), 0.82 (t, *J* = 7.0 Hz, 3H, H_{16}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.3 (C_1), 140.4 (C_{Ar}), 129.3 (C_{Ar}), 128.5 (3C, C_{Ar}), 126.3 (C_{Ar}), 91.9 (C_4), 43.7 (C_2), 42.9 (C_{17}), 38.5 (C_6), 38.0 (C_{13}), 34.7 (C_2), 32.8 (C_{Alk}), 32.4 (C_{Alk}), 28.4 (C_{Alk}), 22.3 (C_{Alk}), 13.8 (C_{16});

HRMS (ESI$^+$): calculated for $C_{17}H_{24}O_4S$ $[M+Na]^+$ *m/z:* 347.1293, found: 347.1297;

IR (neat) ν_{max}: 3027, 2957, 2930, 1791, 1314, 1131, 958, 744.

Methyl 7-((3,4)-4-butyl-5-(methylsulfonyl)-2-oxotetrahydrofuran-3-yl)heptanoate (1.3.183)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (25.0 mg, 65 %) in 8:1 d.r.

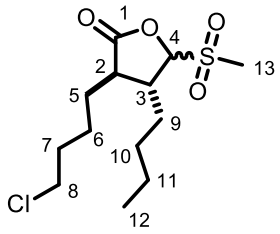
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.80 (d, *J* = 4.3 Hz, 1H, H_4), 3.66 (s, 3H, H_{12}), 3.00 (s, 3H, H_{17}), 2.74 - 2.66 (m, 1H, H_2), 2.35 (dt, *J* = 8.4, 5.7 Hz, 1H, H_{Alk}), 2.30 (t, *J* = 7.5 Hz, 2H, H_{10}), 1.84 (ddt, *J* = 13.8, 11.2, 5.6 Hz, 1H, H_{Alk}), 1.74 (dddd, *J* = 13.8, 10.4, 8.5, 5.3 Hz, 1H, H_{Alk}), 1.69 - 1.58 (m, 4H, H_{Alk}), 1.45 - 1.28 (m, 10H, H_{Alk}), 0.95 - 0.89 (m, 3H, H_{16});

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.4 (C_1), 174.2 (C_{11}), 91.9 (C_4), 51.5 (C_{Alk}), 44.9 (C_{Alk}), 38.3 (C_{Alk}), 38.0 (C_{Alk}), 35.0 (C_{Alk}), 34.0 (C_{Alk}), 30.8 (C_{Alk}), 28.9 (C_{Alk}), 28.8 (C_{Alk}), 28.5 (C_{Alk}), 26.9 (C_{Alk}), 24.8 (C_{Alk}), 22.4 (C_{Alk}), 13.8 (C_{16});

HRMS (ESI$^+$): calculated for $C_{17}H_{30}O_6S$ $[M+Na]^+$ *m/z;* 385.1661, found: 385.1657;

IR (neat) ν_{max}: 2932, 2860, 1794, 1733, 1461, 1437, 1415, 1317, 1247, 1200, 1162, 1135, 1074, 1037, 959, 747, 532.

(3,4)-4-Butyl-3-(4-chlorobutyl)-5-(methylsulfonyl)dihydrofuran-2(3H)-one (1.3.176)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (22.6 mg, 68 %) in 1:6:10:47 d.r.

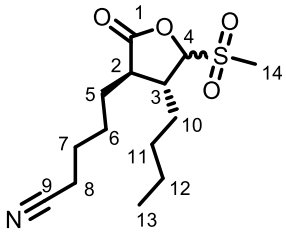
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.82 (d, *J* = 4.1 Hz, 1H, H_4), 3.60 - 3.47 (m, 2H, H_8), 3.00 (s, 3H, H_{13}), 2.75 - 2.67 (m, 1H, H_2), 2.39 - 2.33 (m, 1H, H_{Alk}), 1.93 - 1.74 (m, 4H, H_{Alk}), 1.73 - 1.53 (m, 5H, H_{Alk}), 1.43 - 1.33 (m, 3H, H_{Alk}), 0.97 -0 0.92 (m, 3H, H_{12});

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.2 (C_1), 91.9 (C_4), 44.8 (C_{Alk}), 44.5 (C_{Alk}), 38.3 (C_{Alk}), 38.0 (C_{Alk}), 35.0 (C_{Alk}), 32.1 (C_{Alk}), 30.2 (C_{Alk}), 28.5 (C_{Alk}), 24.4 (C_{Alk}), 22.4 (C_{Alk}), 13.8 (C_{13});

HRMS (ESI$^+$): calculated for $C_{13}H_{23}ClO_4S$ $[M+Na]^+$ *m/z*: 333.0903, found: 333.0897;

IR (neat) ν_{max}: 2955, 2930, 2861, 1795, 1731, 1460, 1377, 1317, 1249, 1163, 1134, 1074, 1037, 958, 745, 651, 532.

5-(4-Butyl-5-(methylsulfonyl)-2-oxotetrahydrofuran-3-yl)pentanenitrile (1.3.178)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (23.1 mg, 77 %) in 2:12:10:60 d.r.

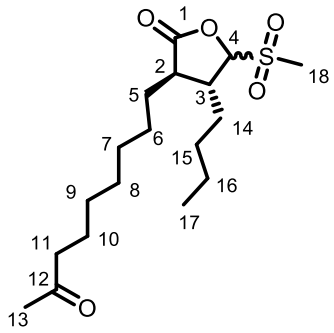
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.83 (d, *J* = 4.1 Hz, 1H, H_4), 3.01 (s, 3H, H_{14}), 2.70 (tdd, *J* = 7.3, 5.5, 4.2 Hz, 1H, H_2), 2.37 (tdd, *J* = 9.7, 6.6, 3.5 Hz, 3H, H_{Alk}), 1.93 - 1.86 (m, 1H, H_{Alk}), 1.83 - 1.54 (m, 7H, H_{Alk}), 1.44 - 1.33 (m, 4H, H_{Alk}), 0.97 - 0.89 (m, 3H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.0 (C_1), 119.3 (C_9), 91.9 (C_4), 44.7 (C_2), 38.3 (C_{Alk}), 38.0 (C_{Alk}), 35.0 (C_{Alk}), 30.1 (C_{Alk}), 28.5 (C_{Alk}), 26.2 (C_{Alk}), 25.2 (C_{Alk}), 22.4 (C_{Alk}), 17.0 (C_{Alk}), 13.8 (C_{13});

HRMS (ESI$^+$): calculated for $C_{14}H_{23}NO_4S$ $[M+Na]^+$ *m/z*: 324.1245, found: 324.1244;

IR (neat) ν_{max}: 2959, 2933, 2864, 1796, 1458, 1424, 1318, 1159, 1135, 1057, 1036, 958, 752, 556, 530.

4-Butyl-5-(methylsulfonyl)-3-(8-oxononyl)dihydrofuran-2(3*H*)-one (1.3.182)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (22.6 mg, 72 %) in 2:15:10:80 d.r.

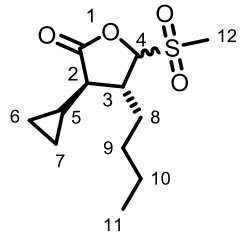
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.80 (d, *J* = 4.3 Hz, 1H, H_4), 3.00 (s, 3H, H_{18}), 2.70 (td, *J* = 11.7, 7.2 Hz, 1H, H_2), 2.41 (t, *J* = 7.5 Hz, 2H, H_{11}), 2.35 (dt, *J* = 8.4, 5.7 Hz, 1H, H_{Alk}), 2.13 (s, 3H_{13}), 1.84 (ddt, *J* = 13.8, 11.2, 5.7 Hz, 1H, H_{Alk}), 1.74 (dddd, *J* = 13.8, 10.4, 8.5, 5.3 Hz, 1H, H_{Alk}), 1.70 - 1.60 (m, 2H, H_{Alk}), 1.60 - 1.52 (m, 3H, H_{Alk}), 1.51 - 1.24 (m, 12H, H_{Alk}), 0.98 - 0.90 (m, 3H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.2 (C_{12}), 176.5 (C_1), 91.9 (C_4), 44.9 (C_{Alk}), 43.7 (C_{Alk}), 38.3 (C_{Alk}), 38.0 (C_{Alk}), 35.0 (C_{Alk}), 30.8 (C_{Alk}), 29.9 (C_{Alk}), 29.1 (C_{Alk}), 29.0 (2C, C_{Alk}), 28.5 (C_{Alk}), 27.0 (C_{Alk}), 23.7 (C_{Alk}), 22.4 (C_{Alk}), 13.8 (C_{17});

HRMS (ESI$^+$): calculated for $C_{18}H_{32}O_5S$ $[M+Na]^+$ *m/z:* 383.1868, found: 383.1864;

IR (neat) ν_{max}: 2930, 2857, 1795, 1712, 1461, 1412, 1358, 1317, 1162, 1134, 1075, 1038, 958, 746, 532.

(3,4)-4-Butyl-3-cyclopropyl-5-(methylsulfonyl)dihydrofuran-2(3*H*)-one (1.3.184)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (27.0 mg, 85 %) in 1:10 d.r.

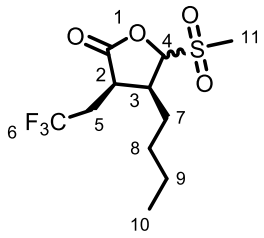
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (d, *J* = 8.5 Hz, 1H, H_4), 3.11 - 3.02 (m, 1H, H_2), 3.02 - 2.93 (m, 3H, H_{12}), 2.14 - 2.07 (m, 1H, H_3), 2.03 - 1.92 (m, 1H, H_5), 1.54 - 1.32 (m, 5H, H_{Alk}), 0.94 - 0.92 (m, 3H, H_{11}), 0.91 - 0.82 (m, 1H, $H_{6/7}$), 0.73 - 0.67 (m, 1H, $H_{6/7}$), 0.65 - 0.58 (m, 1H, $H_{6/7}$), 0.27 - 0.18 (m, 1H, $H_{6/7}$);

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.3 (C_1), 90.9 (C_4), 45.6 (C_2), 42.6 (C_{12}), 39.8 (C_3), 31.2 (C_8), 24.1 (C_9), 22.7 (C_{10}), 13.9 (C_{11}), 8.8 (C_5), 6.1 ($C_{6,7}$), 2.1 ($C_{6,7}$);

HRMS (ESI$^+$): calculated for $C_{12}H_{20}O_4S$ $[M+Na]^+$ *m/z:* 283.0980, found: 283.0972;

IR (neat) ν_{max}: 2958, 2673, 2360, 2342, 1793, 1715, 1637.

(3R,4S)-4-Butyl-5-(methylsulfonyl)-3-(2,2,2-trifluoroethyl)dihydrofuran-2(3*H*)-one (1.3.181)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (20.1 mg, 67 %) in 1:8 d.r.

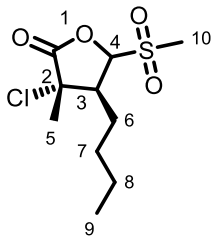
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (d, *J* = 7.7 Hz, 1H, H_4), 3.23 - 3.09 (m, 1H, H_0), 3.01 - 2.97 (m, 3H, H_{11}), 2.76 - 2.65 (m, 1H, H_5), 2.65 - 2.51 (m, 1H, H_5), 2.08 - 1.95 (m, 1H, H_3), 1.79 - 1.67 (m, 1H, H_7), 1.52 - 1.44 (m, 1H, H_7), 1.43 - 1.27 (m, 4H, $H_{8/9}$), 0.93 (t, *J* = 7.1 Hz, 3H, H_{10});

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.3 (C_1), 126.0 (q, *J* = 276.7 Hz, C_6), 90.3 (C_4), 41.4 (C_2), 39.7 (C_7), 34.8 (C_{11}), 31.3 (q, *J* = 30.5 Hz, C_5), 30.0 (C_8), 23.9 (C_3), 22.5 (C_9), 13.7 (C_{10});

^{19}F NMR (565 MHz, $CDCl_3$) δ -64.99;
HRMS (ESI^+): calculated for $C_{11}H_{17}O_4SF_3$ $[M+Na]^+$ *m/z:* 325.0697, found: 325.0693;

IR (neat) ν_{max}: 2961, 2935, 2875, 1805, 1637, 1320, 1280.

(3,4)-4-Butyl-3-chloro-3-methyl-5-(methylsulfonyl)dihydrofuran-2(3H)-one (1.3.186)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:5), the product was isolated as a yellow oil (15.1 mg, 56 %) in 6:1 d.r.

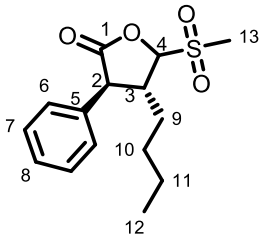
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (d, *J* = 8.6 Hz, 1H, H_4), 3.07 (s, 3H, H_{10}), 2.81 (td, *J* = 8.5, 5.4 Hz, 1H, H_3), 1.97 - 1.92 (m, 2H, H_6), 1.89 (s, 3H, H_5), 1.51 - 1.42 (m, 2H, H_{Alk}), 1.40 - 1.36 (m, 2H, H_{Alk}), 0.94 (t, *J* = 7.3 Hz, 3H, H_9);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9 (C_1), 90.2 (C_4), 66.4 (C_2), 45.4 (C_{10}), 39.2 (C_3), 29.1 (C_7), 28.7 (C_8), 25.8 (C_5), 22.6 (C_6), 13.7 (C_9);

HRMS (ESI$^+$): calculated for $C_{10}H_{17}O_4ClS$ $[M+Na]^+$ *m/z*: 291.0434 found: 291.0434;

IR (neat) ν_{max}: 2959, 2932, 2871, 1800, 1717, 1625, 1320, 1147.

(3,4)-4-Butyl-5-(methylsulfonyl)-3-phenyldihydrofuran-2(3*H*)-one (1.3.185)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:8 to 1:4), the product was isolated as a yellow oil (16.1 mg, 57 %) in 15:1 d.r.

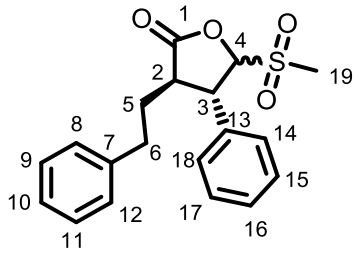
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.3 Hz, 2H, H_{Ar}), 7.35 - 7.31 (m, 3H, H_{Ar}), 4.93 (d, *J* = 6.7 Hz, 1H, H_2), 3.61 (d, *J* = 9.3 Hz, 1H, H_4), 3.23 - 3.15 (m, 1H, H_3), 3.09 (s, 3H, H_{13}), 1.91 - 1.71 (m, 2H, H_{Alk}), 1.37 - 1.20 (m, 4H, H_{Alk}), 0.83 (t, *J* = 7.1 Hz, 3H, H_{12});

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0 (C_1), 135.8 (C_{Ar}), 129.7 (C_{Ar}), 129.2 (C_{Ar}), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 91.0 (C_4), 52.2 (C_2), 41.7 (C_{12}), 38.6 (C_9), 34.1 (C_{10}), 28.5 (C_5), 22.2 (C_{11}), 13.7 (C_{12});

HRMS (ESI$^+$): calculated for $C_{17}H_{30}O_6SNa$ $[M+Na]^+$ *m/z*: 319.0980, found: 319.0979

IR (neat) ν_{max}: 3030, 2956, 2932, 2863, 1802, 1646, 1347, 1156.

5-(Methylsulfonyl)-3-phenethyl-4-phenyldihydrofuran-2(3H)-one (1.3.192)



The title compound was prepared according to the general procedure **1.10** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate/heptanes 1:10 to 1:5), the product was isolated as a yellow oil (15 mg, 46 %) in 1:7 d.r.

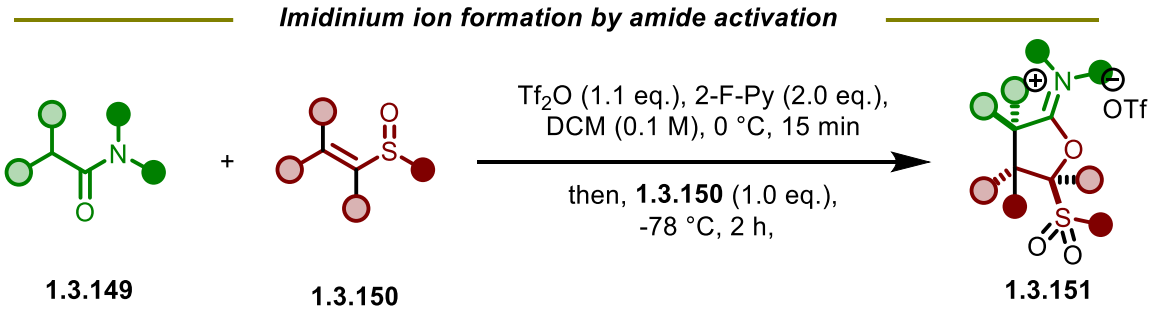
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 - 7.32 (m, 3H, H_{Ar}), 7.25 (d, *J* = 7.0 Hz, 2H, H_{Ar}), 7.21 - 7.12 (m, 3H, H_{Ar}), 6.95 (d, *J* = 6.8 Hz, 2H, H_{Ar}), 5.11 (d, *J* = 5.7 Hz, 1H, H_4), 3.90 (dd, *J* = 7.6, 5.8 Hz, 1H, H_3), 3.00 (s, 3H, H_{19}), 2.87 (td, *J* = 8.4, 5.5 Hz, 1H, H_{Alk}), 2.79 (ddd, *J* = 14.3, 8.6, 5.9 Hz, 1H, H_{Alk}), 2.71 - 2.62 (m, 1H, H_{Alk}), 2.33 - 2.26 (m, 1H, H_{Alk}), 2.20 - 2.10 (m, 1H, H_{Alk});

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5 (C_1), 140.1 (C_7), 139.4 (C_{13}), 129.7 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 127.5 (C_{Ar}), 126.4 (C_{Ar}), 93.0 (C_4), 46.3 (C_2), 45.2 (C_{19}), 38.4 (C_{Alk}), 32.8 (C_{Alk}), 32.41 (C_{Alk});

HRMS (ESI^+): calculated for $C_{19}H_{20}O_4S$ $[M+Na]^+$ *m/z*: 367.0980, found: 367.0963;

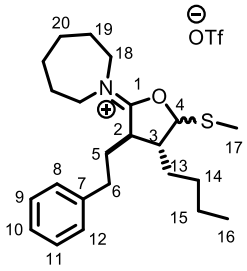
IR (neat) ν_{max}: 3086, 3060, 3028, 2928, 2865, 1794, 1723, 1620, 1409, 1314, 1030, 1003, 960, 920.

3.4.2.5 General Procedure **1.11** – Procedure for the formation and isolation of the imidinium salts.



To a solution of amide (**1.3.149**, 1.2 eq., 23.4 mg, 0.012 mmol) and 2-fluoropyridine (2.0 eq., 11.2 µL, 0.131 mmol) in DCM (1.0 mL, 0.1 M) at 0 °C was added Tf_2O (1.1 eq., 12.1 µL, 0.012 mmol) and the resulting mixture was stirred at 0 °C (by addition of Tf_2O, the mixture turned intense yellow). After 15 min, the solution was kept at -78°C and a precoled solution of vinyl sulfoxide in DCM (**1.3.150**, 1.0 mL) was quickly added. The color of the solution changed to a pale blue color. After 2 h at this temperature, the reaction was evaporated by reduced pressure and analysed by ^{1}H-NMR. The crude residue was purified by flash column chromatography (silica gel, EtOAc in heptanes 30 % to 100 % and then Acetone in Heptane 50 % to 100 %) to afford the desired imidinium salts as a mixture of 4 diastereoisomers. For simplification, the two major diastereosiomer were described when isolated separately.

1-((3,4)-4-Butyl-5-(methylthio)-3-phenethyldihydrofuran-2(3H)-ylidene)azepan-1-ium (1.3.154)



The title compound was prepared according to the general procedure **1.11** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Acetone/heptanes 1:10 to 1:8), the product was isolated as a yellow oil (36 mg, 84 %) in 5:1 d.r.

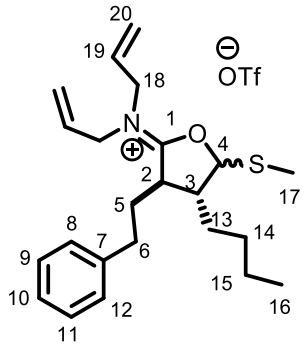
^{1}H NMR (500 MHz, CD_3CN): δ 7.38 - 7.31 (m, 2H, H_{Ar}), 7.31 - 7.20 (m, 3H, H_{Ar}), 6.44 (d, J = 5.2 Hz, 0.2H_2, d1), 6.05 - 5.97 (m, 0.8H_2, d2), 3.82 - 3.72 (m, 1H), 3.70 - 3.54 (m, 3H), 3.30 - 3.23 (m, 0.2H_4, d1), 3.20 - 3.10 (m, 0.8H_4, d2), 2.88 - 2.82 (m, 1H), 2.80 - 2.61 (m, 2H), 2.50 - 2.45 (m, 1H), 2.39 - 2.30 (m, 3H_{17}, d1,2), 2.21 - 2.13 (m, 1H), 1.87 - 1.75 (m, 4H), 1.69 - 1.49 (m, 6H), 1.45 - 1.19 (m, 4H), 0.95 - 0.87 (m, 3H);

^{13}C NMR (126 MHz, CD_3CN): δ 181.4 (d1), 180.7 (d2), 141.3 (d1), 141.1 (2C, d1, d2), 129.7 (2C, d1, d2), 129.50 (2C, d1, d2), 129.3 (d1, d2), 127.6 (2C, d1, d2), 127.5, 104.7, 103.2, 102.7, 53.3, 53.1, 52.8, 52.4, 52.1, 51.7, 48.8, 48.5, 48.4, 46.2, 45.6, 44.4, 34.1, 33.9 (2C, d1,d2), 33.8, 33.4, 31.0, 30.6, 29.5, 29.3, 28,6, 28.5, 28.3, 28.2, 28.1(2C, d1, d2), 27.8, 27.8, 26.6, 26.6, 26.5, 26.5, 26.4, 26.4, 25.2, 23.2, 23.1, 23.1, 16.0, 15.7, 14.1 (3C);

^{19}F NMR (565 MHz, CD_3CN): δ -79.31;
HRMS (ESI$^+$): calculated for $C_{23}H_{36}ONS$ $[M+]^+$ *m/z*: 374.2512, found: 374.2512;

IR (neat) ν_{max}: 3497, 3029, 2834, 2855, 1714, 1652, 1557, 1392, 1321, 1171.

***N*-allyl-*N*-((3R,4R)-4-butyl-5-(methylthio)-3-phenethyldihydrofuran-2(3H)-ylidene)prop-2-en-1-aminium (1.3.155)**



The title compound was prepared according to the general procedure **1.11** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Acetone/heptanes 1:10 to 1:8), the product was isolated as a yellow oil (36 mg, 84 %) in 5:1 d.r.

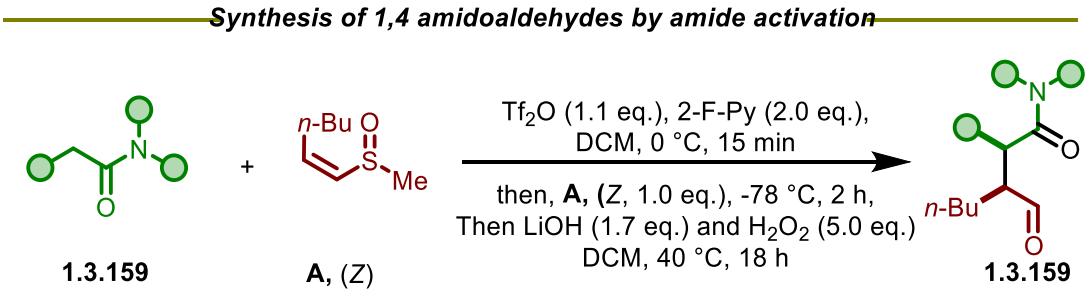
^{1}H NMR (500 MHz, Acetone-d6): δ 7.32 - 7.15 (m, 4H), 6.81 (d, *J* = 5.3 Hz, 0.1H_2, d1), 6.69 – 6.51 (m, 0.7H_2, d2), 6.28 (d, 0.20H_2, d3), 6.00 - 5.75 (m, 2H_{19}), 5.50 - 5.07 (m, 4H_{20}), 4.57 - 4.21 (m, 4H_{18}), 4.09 - 3.98 (m, 0.1H_4, d1), 3.83 - 3.63 (m, 0.20H_4, d2), 3.60 - 3.54 (m, 0.7H_4, d3), 2.78 - 2.67 (m, 2H), 2.56 - 2.48 (m, 1H), 2.02 (s, 3H_{17}), 1.96 - 1.88 (m, 2H), 1.79 - 1.64 (m, 1H), 1.50 - 1.22 (m, 5H), 0.91 - 0.84 (m, 3H).

^{13}C NMR (151 MHz, Acetone-d6): δ 207.1, 143.1, 142.8, 131.4, 130.9, 130.6, 130.4, 130.9, 129.9, 129.9, 129.9, 129.9, 129.8, 129.7, 129.7, 123.6, 123.2, 122.6, 122.4, 122.1, 121.9, 121.5, 106.7, 105.1, 56.4, 55.8, 55.3, 54.3, 54.2, 53.6, 50.2, 49.4, 49.3, 48.5, 36.9, 36.4, 36.3, 34.7, 32.6, 32.3, 31.0, 30.9, 30.9, 30.8, 30.8, 30.6, 30.6, 30.5, 30.4, 30.2, 30.2, 30.1, 30.1, 30.0, 29.7, 23.9, 23.8, 23.7, 16.4, 16.2, 14.8, 14.8, 14.7, 13.1;

^{19}F NMR (565 MHz, Acetone): δ -78.99;
HRMS (ESI^{+}): calculated for $C_{23}H_{34}OSN$ $[M+]^{+}$ *m/z*: 372.2356, found 372.2357;

IR (neat,) ν_{max}: 3481, 2936, 1662, 1421, 1249, 1170, 1032.

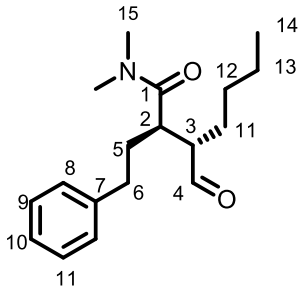
3.4.2.6 General procedure **1.12** – Procedure for the synthesis of 1,4 amidoaldehydes



To a solution of amide (**1.3.159**, 1.2 eq., 23.4 mg, 0.065 mmol) and 2-fluoropyridine (2.0 eq., 11.2 µL, 0.131 mmol) in DCM (1.0 mL) at 0 °C was added trifluoromethanesulfonic anhydride (1.1 eq., 12.1 µL, 0.072 mmol) and the resulting mixture was stirred at 0 °C (by addition of Tf_2O, the mixture turned intense yellow). After 15 min, the solution was kept at -78 °C and a precooled solution of vinyl sulfoxide (**A**, *Z*, 1.0 eq.) in DCM (1.0 mL) was quickly added. The color of the solution changed to a pale blue color. After that time, an aqueous solution of LiOH (5.0 mg, 1.7 eq.) and H_2O_2 (5.0 eq.) was added at 40 °C. The resulting mixture was stirred for 18 h and then allowed to cool down to ambient temperature (25 °C), after which time saturated $NaHCO_3$ and $Na_2S_2O_3$ were added. The biphasic mixture was separated and the aqueous phase was extracted with DCM (3 × 5.0 mL). The combined organic phases were dried over anhydrous magnesium sulfate, the solution was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, EtOAc in heptanes 1 % to 20 %) to afford the desired aldehydes as a mixture of 2 diastereoisomers in different ratios (**1.3.159**). For simplification, the major diastereosiomer was described when isolated separatelly.

3.4.2.1 Characterisation of the 1,4 amidoaldehydes using procedure **1.12**.

(2,3)-3-formyl-*N*,*N*-dimethyl-2-phenethylheptanamide (1.3.162)



The title compound was prepared according to the general procedure **1.12** in 0.1 mmol scale. Following purification by silica gel flash chromatography (ethyl acetate: heptanes 1:10 to 1:8), the product was isolated as a yellow oil (23.1 mg, 77 %) in 20:1 d.r.

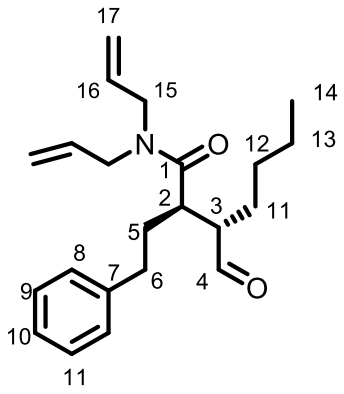
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (d, *J* = 3.3 Hz, 1H, H_4), 7.31 - 7.24 (m, *J* = 9.3, 5.8 Hz, 2H, H_{Ar}), 7.20 - 7.15 (m, 1H, H_{Ar}), 7.14 - 7.10 (m, 2H, H_{Ar}), 3.05 - 3.01 (m, 1H, H_2), 3.00 (s, 3H, H_{15}), 2.94 (s, 3H, H_{15}), 2.68 - 2.58 (m, 2H, H_6), 2.49 - 2.42 (m, 1H, H_3), 2.13 - 2.04 (m, 1H, H_6), 1.83 - 1.74 (m, 1H, H_6), 1.65 - 1.58 (m, 1H, H_{11}), 1.46 - 1.37 (m, 1H, H_{11}), 1.34 - 1.14 (m, 4H, $H_{12/13}$), 0.85 (t, *J* = 7.2 Hz, 3H, H_{14});

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.4 (C_4), 173.4 (C_1), 141.1 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 126.1 (C_{Ar}), 54.3, (C_3), 40.4 (C_{15}), 37.6 (C_{15}), 35.7 (C_2), 33.3 (C_7), 32.0 (C_{Alk}), 29.3 (C_{Alk}), 27.5 (C_{Alk}), 22.7 (C_{Alk}), 13.8 (C_{14});

HRMS (ESI$^+$): calculated for $C_{18}H_{27}O_2N$ $[M+Na]^+$ *m/z*: 312.1939; found: 312.1943;

IR (neat,) ν_{max}: 3027, 2956, 2860, 1780, 1742, 1455, 1319.

(2*R*,3*S*)-*N*,*N*-diallyl-3-formyl-2-phenethylheptanamide (1.3.163)



The title compound was prepared according to the general procedure **1.12** in a 0.1 mmol scale. Following purification by silica gel flash chromatography (ethyl acetate: heptanes 1:10 to 1:8), the product was isolated as a yellow oil (24.2 mg, 67 %) in 10:1 d.r.

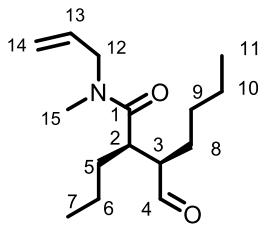
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (d, *J* = 1.7 Hz, 0.1H, d1, H_4), 9.70 (d, *J* = 3.5 Hz, 0.9H, d2, H_4), 7.28 - 7.24 (m, 2H, H_{Ar}), 7.19 - 7.14 (m, 1H, H_{Ar}), 7.14 - 7.10 (m, 2H, H_{Ar}), 5.83 - 5.65 (m, 2H, H_{16}), 5.31 - 5.00 (m, 4H, H_{17}), 4.05 - 3.85 (m, 4H, H_{15}), 2.96 - 2.87 (m, 1H, H_2), 2.63 - 2.49 (m, 3H, $H_{3/6}$), 1.80 - 1.68 (m, 1H, H_5), 1.68 - 1.36 (m, 4H_{Alk}), 1.36 - 1.17 (m, 3$H_{5/Alk}$), 0.89 - 0.79 (m, 3H, H_{14});

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.5 (C_4), 173.6 (C_1), 141.9 (2C, $C_{Ar/16}$), 133.1 (2C, $C_{Ar/16}$), 128.3 (C2, $_{Ar}$), 125.8 (C_{Ar}), 117.7 (C_{17}), 117.5 (C_{17}), 54.2 (C_3), 49.5 (C_{15}), 48.2 (C_{15}), 41.7 (C_3), 36.0 (C_7), 30.6 (C_{Alk}), 29.5 (C_{Alk}), 29.2 (C_{Alk}), 27.8 (C_{Alk}), 22.7 (C_{Alk}), 13.8 (C_{14});

HRMS (ESI$^+$): calculated for $C_{23}H_{34}O_2N$ $[M+Na]^+$ *m/z*: 379.2487, found: 379.2464;

IR (neat) ν_{max}: 3083, 3026, 2930, 2860, 2360, 1720, 1684, 1496.

***N*-allyl-3-formyl-N-methyl-2-propylheptanamide (1.3.166)**



The title compound was prepared according to the general procedure **1.12** in 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate: heptanes 1:10 to 1:8), the product was isolated as a yellow oil (13.5 mg, 44 %) in 1:6 d.r.

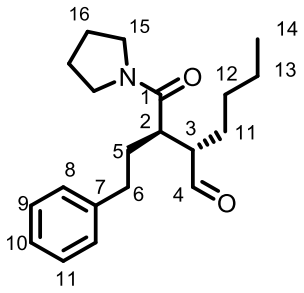
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (dd, *J* = 9.9, 1.7 Hz, 1H, H_4), 5.89 - 5.65 (m, 1H, H_{13}), 5.30 - 5.08 (m, 2H, H_{14}), 4.12 - 3.89 (m, 2H, H_{12}), 3.07 - 2.87 (m, 4H, $H_{5/15}$), 2.68 - 2.45 (m, 1H, H_3), 1.76 - 1.40 (m, 5H, H_{Alk}), 1.40 - 1.15 (m, 5H, H_{Alk}), 0.98 - 0.80 (m, 6H, $H_{7/11}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.7 (C_4), 174.6 (C_1), 133.0 (C_{13}), 117.2 (C_{14}), 52.9 (C_{12}), 50.3 (C_3), 41.8 (C_{12}), 35.3 (C_{Alk}), 32.8 (C_{Alk}), 29.1 (C_{Alk}), 26.6 (C_{Alk}), 22.9 (C_{Alk}), 20.3 (C_{Alk}), 14.3 ($C_{7/11}$), 13.9 ($C_{7/11}$);

HRMS (ESI$^+$): calculated for $C_{15}H_{27}O_2N$ $[M+Na]^+$ *m/z*: 276.1939, found: 276.1934;

IR (neat) ν_{max}: 2958, 2932, 2872, 2560, 1770, 1721, 1636, 1409, 1135, 920;

2-(-1-oxo-4-phenyl-1-(pyrrolidin-1-yl)butan-2-yl)hexanal (1.3.165)



The title compound was prepared according to the general procedure **1.12** in a 0.1 mmol scale. Following purification by silica gel flash chromatography (Ethyl Acetate: heptanes 1:10 to 1:8), the product was isolated as a yellow oil (18.9 mg, 61 %) in 9:1 d.r.

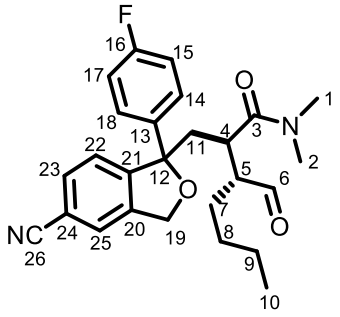
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 3.4 Hz, 1H, H_4), 7.28 (m, 1H, H_{Ar}), 7.26 - 7.25 (m, 1H, H_{Ar}), 7.18 - 7.13 (m, 3H, H_{Ar}), 3.55 - 3.49 (m, 2H, H_{15}), 3.39 - 3.33 (m, 1H, H_{15}), 3.22 - 3.15 (m, 1H, H_{15}), 2.83 – 2.77 (m, *J* = 10.5, 8.5, 3.7 Hz, 1H, H_2), 2.70 - 2.59 (m, 2H, H_6), 2.54 - 2.46 (m, *J* = 14.0, 8.8, 7.7 Hz, 1H, H_3), 2.12 - 2.07 (m, 1H, H_5), 2.00 - 1.78 (m, 5H, $H_{5/Alk}$), 1.68 - 1.52 (m, 2H, H_{Alk}), 1.48 - 1.40 (m, 1H, H_{Alk}), 1.37 – 1.16 (m, 4H, H_{Alk}), 0.85 (t, *J* = 7.2 Hz, 3H, H_{14});

^{13}C NMR (151 MHz, $CDCl_3$): δ 204.7 (C_4), 171.9 (C_1), 141.3 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 126.4 (C_{Ar}), 126.2 (C_{Ar}), 54.5 (C_2), 47.0 (C_3), 45.9 (C_{15}), 43.3 (C_{15}), 33.5 (C_7), 31.9 (C_{Alk}), 29.6 (C_{Alk}), 27.6 (C_{Alk}), 26.2 (C_{Alk}), 24.5 (C_{Alk}), 22.9 (C_{12}), 13.98 (C_{14});

HRMS (ESI$^+$): calculated for $C_{17}H_{30}O_6SNa$ $[M+Na]^+$ *m/z*: 338.2096, found; 338.2024;

IR (neat) ν_{max}: 3026, 2955, 2872, 1721, 1683, 1454, 1341.

(2,3)-2-((5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)methyl)-3-formyl-*N*,*N*-dimethylheptanamide (1.3.170)



The title compound was prepared according to the general procedure **1.12** in 0.1 mmol scale. Following purification by silica gel flash chromatography (ethyl acetate: heptanes 1:10 to 1:8), the product was isolated as a yellow oil (32.7 mg, 75 %) in 4:4:1:1 d.r.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.65 (d, *J* = 3.3 Hz, 0.7H, H_6‘), 9.62 (d, *J* = 3.3 Hz, 1.0H, H_6), 7.60 (d, *J* = 7.8 Hz, 0.7H, H_{23}‘), 7.53 (d, *J* = 7.9 Hz, 1.0H, H_{23}), 7.49 (s, 0.7H, H_{25}‘), 7.47 (s, 1.0H, H_{25}), 7.47 – 7.42 (m, 3.4H, H_{14}+H_{14}‘+H_{18}+H_{18}‘), 7.41 (d, *J* = 8.0 Hz, 0.7H, H_{22}‘), 7.32 (d, *J* = 7.9 Hz, 1.0H, H_{22}), 7.04 (t, *J* = 8.6 Hz, 2.0H, H_{15}+H_{17}), 6.99 (t, *J* = 8.6 Hz, 1.4H, H_{15}‘+H_{17}‘), 5.21 - 5.05 (m, 3.4H, H_{19}+H_{19}‘), 3.15 (t, *J* = 8.9 Hz, 0.7H, H_4‘), 3.11 (t, *J* = 8.9 Hz, 1.0H, H_4), 2.97 (dd, *J* = 14.7, 9.7 Hz, 0.7H, H_{11a}‘), 2.78 - 2.71 (m, 4.0H, H_2+H_{11a}), 2.66 (s, 2.1H, H_2’), 2.64 (s, 3.0H, H_1), 2.57 (s, 2.1H, H_1’), 2.53 – 2.48 (m, 0.7H, H_5’), 2.48 - 2.43 (m, 1.0H, H_5), 2.19 (d, *J* = 14.6 Hz, 1H, H_{11b}), 2.02 (d, *J* = 14.6 Hz, 0.7H, H_{11b}‘), 1.56 - 1.47 (m, 1.7H, H_{7a}+H_{7a}‘), 1.40 - 1.33 (m, 1.7H, H_{7b}+H_{7b}‘), 1.30 - 1.11 (m, 6.8H, H_8+H_8‘+H_9+H_9‘), 0.86 - 0.81 (m, 5.1H, H_{10}+H_{10}‘);

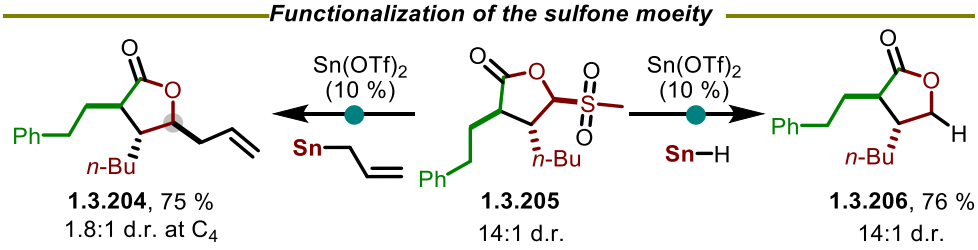
^{13}C NMR (151 MHz, $CDCl_3$): δ 204.3 (C_6‘), 204.2 (C_6), 173.8 (C_3), 173.5 (C_3‘), 162.4 (d, *J* = 247.1 Hz, C_{16}), 162.3 (d, *J* = 247.0 Hz, C_{16}‘), 149.7 (C_{21}‘), 148.8 (C_{21}), 140.2 (C_{20}), 139.7 (C_{20}‘), 138.9 (d, *J* = 3.1 Hz, C_{13}), 137.8 (d, *J* = 3.0 Hz, C_{13}‘), 132.3 (C_{23}‘), 131.6 (C_{23}), 127.3 (d, *J* = 8.1 Hz, 2C, C_{14}‘+C_{18}‘), 126.9 (d, *J* = 8.1 Hz, 2C, C_{14}+C_{18}), 125.4 (C_{25}‘), 125.0 (C_{25}), 123.7 (C_{22}), 122.9 (C_{22}‘), 118.6 (C_{26}), 118.6 (C_{26}‘), 115.7 (d, *J* = 21.4 Hz, 2C, C_{15}+C_{17}), 115.3 (d, *J* = 21.4 Hz, 2C, C_{15}‘+C_{17}‘), 112.2 (C_{24}‘), 111.9 (C_{24}), 90.7 (C_{12}‘), 90.5 (C_{12}), 71.1 (C_{19}‘), 70.8 (C_{19}), 55.1 (C_5‘), 54.8 (C_5), 41.5 (C_{11}‘), 41.0 (C_{11}), 37.4 (C_1), 37.4 (C_1‘), 36.6 (C_4), 36.5 (C_4‘), 35.9 (C_2), 35.6 (C_2‘), 29.3 (C_8+C_8‘), 27.1(C_7‘), 27.1 (C_7), 22.8 (C_9‘), 22.8 (C_9), 13.9 (C_{10}+C_{10}‘);

^{19}F NMR (565 MHz, $CDCl_3$): δ -114.72;

HRMS (ESI^+): calculated for $C_{26}H_{29}O_3N_2F$ $[M+H]^+$ *m/z*: 437.2240, found: 437.2233;

IR (neat) ν_{max}: 2931, 2860, 2229, 1719, 1686, 1507, 1467, 1418, 1299, 1225.

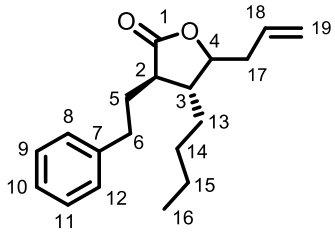
3.4.2.2 General procedure **1.13** - Procedure for the removal of the sulfone moiety in lactones.



To a solution of sulfonal lactone (**1.3.205,** 14:1 d.r., 1.2 eq., 32.4 mg, 0.01 mmol) in toluene (1.0 mL) at 0 °C was added $SnOTf_2$ (0.1 mol %.), and tributylallyltin (2.0 eq., 0.02 mmol) and the resulting mixture was stirred at 110 °C. After that 12 h, the resulting mixture was evaporated and the crude was purified by flash column chromatography (silica gel, EtOAc in heptanes 1 %) to afford the desired lactone in 75 % yield (**1.3.204**, 1.8: 1 d.r.).

3.4.2.3 Characterisation of the products of procedure **1.13**.

(3,4)-5-allyl-4-butyl-3-phenethyldihydrofuran-2(3H)-one (1.3.204)



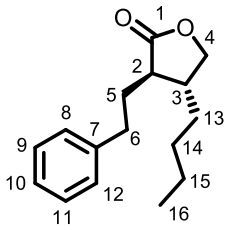
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 - 7.28 (m, 2H, H_{Ar}), 7.23 - 7.17 (m, 3H, H_{Ar}), 5.89 - 5.79 (m, 1H, H_{19}), 5.20 - 5.11 (m, 2H, H_{18}), 4.56 (dd, J = 10.2, 4.2 Hz, 0.5H, H_4, d1), 4.37 (dd, J = 9.7, 4.6 Hz, 0.1H, H_4, d2), 4.24 (d, J = 4.4 Hz, 0.1H, H_4, d3), 4.11 - 4.07 (m, 0.3H, H_4, d4), 2.93 - 2.83 (m, 1H, H_7), 2.78 - 2.71 (m, 1H, H_7), 2.57 - 2.48 (m, 0.5H, d1, H_{13}), 2.41 - 2.29 (m, 2.5H, $H_{5/13}$), 2.28 - 2.22 (m, 1H, H_3), 2.07 - 1.87 (m, 2H, H_{Alk}), 1.50 - 1.34 (m, 2H, H_{Alk}), 1.34 - 1.19 (m, 4H, H_{Alk}), 0.95 - 0.86 (m, 3H, H_{16});

^{13}C NMR (151 MHz, $CDCl_3$): δ major dias described, 178.6 (C_1), 141.2 (C_{18}), 133.3 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.4 (C_{Ar}), 126.1 (2C, C_{Ar}), 118.7 (C_{Ar}), 118.2 (C_{19}), 80.4 (C_4), 44.2 (C_2), 43.7 (C_3), 38.9 (C_{17}), 34.4 (C_{Alk}), 33.0 (C_{Alk}), 31.0 (C_{Alk}), 29.5 (C_{Alk}), 27.7 (C_{Alk}), 22.8 (C_{Alk}), 13.9 (C_{16});

HRMS (ESI$^+$): calculated for $C_{17}H_{30}O_6SNa$ $[M+Na]^+$ *m/z*: 309.1830, found: 309.1822;

IR (neat) ν_{max}: 3027, 2929, 2860, 1769, 1497, 1346.

(3,4)-4-butyl-3-phenethyldihydrofuran-2(3H)-one (1.3.206)



The title compound was isolated following procedure **1.13** and isolated in 14:1 d.r. in 76 % yield**.** Tributyltinydride was used instead of tributylallyltin.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.27 (m, 2H, H_{Ar}), 7.23 - 7.18 (m, 3H, H_{Ar}), 4.44 - 4.33 (m, 1H, H_4), 3.88 - 3.76 (m, 1H, H_4), 2.90 - 2.83 (m, 1H, H_6), 2.83 - 2.71 (m, 1H, H_6), 2.30 - 2.16 (m, 2H, H_5), 2.06 - 1.99 (m, 1H, H_{13}), 1.95 - 1.88 (m, 1H, H_{13}), 1.65 - 1.58 (m, 1H, H_3), 1.41 - 1.19 (m, 5H, H_{Alk}), 0.90 (t, J = 7.2 Hz, 3H, H_{16});

^{13}C NMR (151 MHz, $CDCl_3$): δ 179.2 (C_1), 141.2 (C_{Ar}), 128.5 (3C, C_{Ar}), 126.1 (2C, C_{Ar}), 71.6, (C_4), 44.6 (C_2), 41.2 (C_3), 32.8 (C_7), 32.4 (C_{Alk}), 31.1 (C_{Alk}), 29.2 (C_{Alk}), 22.7 (C_{Alk}), 13.9 (C_{16});

HRMS (ESI$^+$): calculated for $C_{16}H_{22}O_2$ $[M+Na]^+$ *m/z*: 269.1517, found: 269.1355;

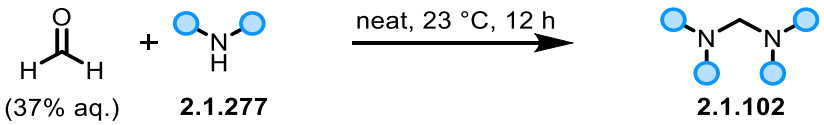
IR (neat) ν_{max}: 2858, 2872, 1750, 1637.

3.5 Experimental Section Chapter 2.1

3.5.1 Procedures for the Synthesis of Starting Materials

3.5.1.1 General Procedure **2.1** – Procedure for the synthesis of aminals

Synthesis of tetraaminomethylene aminals

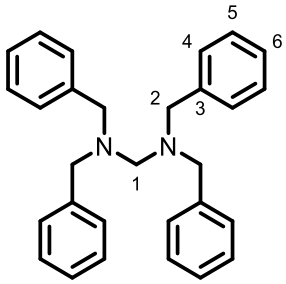


To a round-bottom flask charged with the corresponding free secondary amine[a] (**2.1.227**, 2.0 eq.) and a magnetic stir-bar at 0 °C, an aqueous solution of formaldehyde (1.0 eq., 37 %) was added dropwise and the resulting biphasic mixture was stirred vigorously at ambient temperature (23 °C) for 12 h. The following work-up was dependent on the volatility of the resulting aminal.

Work-up **Z** (for volatile products): Solid KOH was added to the reaction mixture until saturation of the aqueous layer was observed. The phases were subsequently separated, and the aqueous phase was extracted with Et_2O (2 ×). The organic phases were combined, dried over anhydrous potassium carbonate and filtered. The filtrate was then carefully concentrated under reduced pressure with mild heating, affording the title compound in sufficient purity for further use.

Work-up **Y** (for non-volatile products): The biphasic mixture was separated, and the aqueous phase was extracted with EtOAc (3 ×). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure, in most cases affording the title compound in sufficient purity for further use. In the case of incomplete conversion, remaining unreacted amine could be removed by subjection to high vacuum. [a]For amines available only as the corresponding salts, 2.0 eq. of potassium carbonate are added to the reaction mixture.

***N,N,N′,N′*-Tetrabenzyldiaminomethane 2.1.278** was used in the synthesis of **2.1.107**



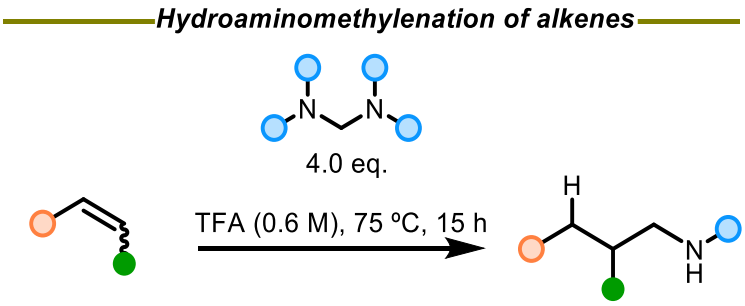
The title compound was prepared according to the general procedure for the synthesis of tetraaminomethylene aminals. Product was isolated after filtration.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.26 (m, 16H, H_{Ar}), 7.26 - 7.22 (m, 4H, H_{Ar}), 3.63 (s, 8H, H_2), 3.11 (s, 2H, H_1);

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9 (4C, C_{Ar}), 129.1 (8C, C_{Ar}), 128.3 (8C, C_{Ar}), 126.9 (4C, C_{Ar}), 72.4 (C_1), 56.3 (4C, C_2);

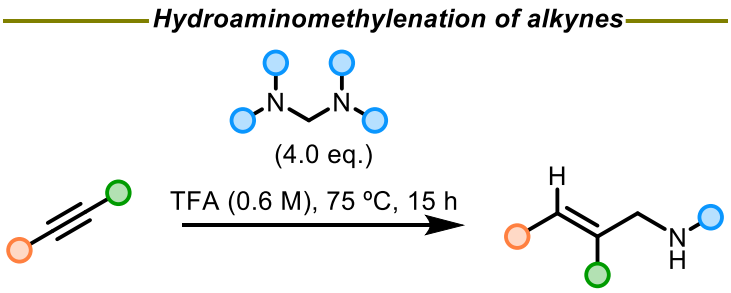
HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{29}H_{31}N_2$) found *m/z:* 407.2482, found: 198.1281 (corresponding to *N,N*-dibenzylamine);
IR (neat) ν_{max}: 3060, 3026, 2927, 2795, 1493, 1451, 1245, 1125, 1072, 1028, 974, 914.

3.5.1.2 General Procedure **2.2.** – Procedure for the Hydroaminomethylenation of Alkenes



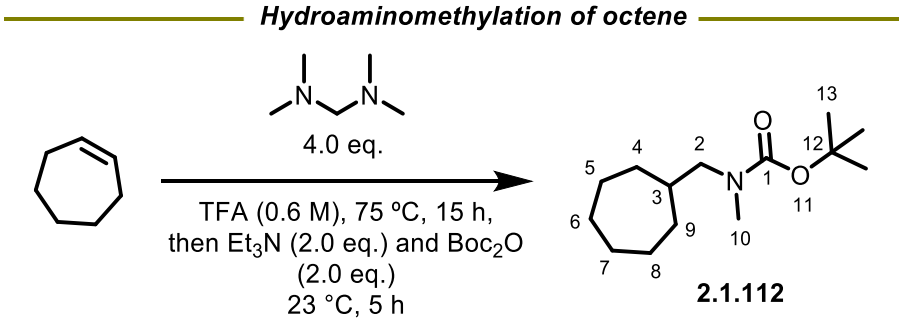
A round-bottom flask charged with *N,N,N',N'*-tetraalkyldiaminomethane (4.0 eq.) and a magnetic stir-bar under argon-atmosphere was cooled to 0 °C. After this, trifluoroacetic acid (TFA, 0.6 M with respect to the alkene) was added slowly, maintaining the low temperature of the contents of the flask. After complete addition of TFA, the alkene was added in one portion, the flask was sealed and placed in an oil bath at 75 °C. The reaction was vigorously stirred at this temperature for 15 h, after which it was allowed to cool to room temperature. Subsequently, volatile components were removed under reduced pressure. The crude mixture was then treated with aqueous NaOH (1.0 M 2.0 mL/1 mmol substrate) and DCM (1.0 mL/1.0 mmol substrate) and stirred vigorously at room temperature for 1 h. After this time, aqueous NaOH (5.0 M) was added until the reaction mixture reaches pH 12. The resulting biphasic mixture was separated, and the aqueous phase was extracted with DCM (3 x 25 mL). The combined organic phases were then dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel (DCM/MeOH/NH_4OH 19:1:0.15) to afford the analytically pure desired product.

3.5.1.3 General Procedure **2.3.** – Procedure for Hydroaminomethylenation of Alkynes



A round-bottom flask charged with *N,N,N',N'*-tetraalkyldiaminomethane (4.0 eq.) and a magnetic stir-bar under argon-atmosphere was cooled to 0 °C and dissolved in DCE (1.2 M with respect to the alkyne). After this, trifluoroacetic acid (11.2 eq. with respect to the alkyne) was added slowly, maintaining the low temperature of the contents of the flask. After completed addition of TFA, the alkene (0.5 mmol) was added in one portion, the flask was sealed and placed in an oil bath at 75 °C. The reaction was vigorously stirred at this temperature for 15 h, after which it was allowed to cool to room temperature. Subsequently, volatile components were removed under reduced pressure. After this time, aqueous NaOH (1.0 M) was added until the reaction mixture reaches pH 12 and the mixture was extracted with DCM (3 x 25.0 mL). The combined organic phases were then dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel (DCM/MeOH/NH_4OH 19:1:0.15) to afford the analytically pure desired product.

3.5.1.4 Characterisation of the products of hydroaminomethylenation of alkenes



***tert*-Butyl (cycloheptylmethyl)(methyl)carbamate (2.1.112)**

After following general Procedure **2.2** for hydroaminomethylation of alkenes, the crude mixture was dissolved in anhydrous chloroform (0.2 M), Et_3N (2.0 eq., 139.0 mL) and di-*tert*-butyldicarbonate (2.0 eq., 218 mg) were added. The solution was stirred for 5 hours at 23 °C, then treated with aqueous NaOH (1.0 M–2 mL/1 mmol substrate) and $CHCl_3$ (1.0 mL/1 mmol substrate). The resulting biphasic mixture was separated, and the aqueous phase was extracted with $CHCl_3$ (3 x 20 mL). The combined organic phases were then dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel (toluene) to afford the analytically pure desired product in 78 % yield.

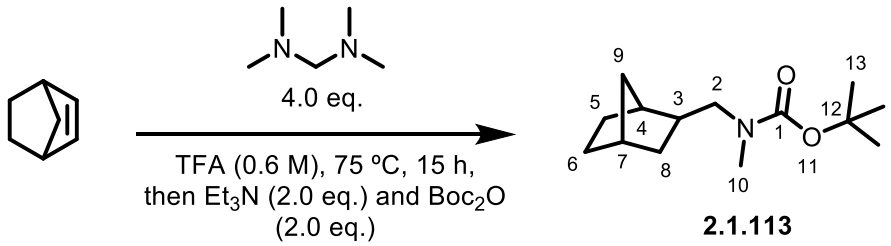
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 - 2.99 (m, 2H, H_2), 2.81 (s, 3H, H_{10}), 1.82 - 1.72 (m, 1H, H_3), 1.70 - 1.46 (m, 8H, H_{Alk}), 1.45 (s, 9H, H_{13}), 1.41 - 1.34 (m, 2H, H_{Alk}), 1.17 - 1.07 (m, 2H, H_{Alk});

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3 (C_1), 79.2 (C_{12}), 55.1 (C_2), 38.0 (C_{10}), 34.5 (C_{Alk}), 31.7 (2C, C_{Alk}), 28.8 (2C, C_{Alk}), 28.6 (3C, C_{13}), 26.3 (2C, C_{Alk});

HRMS (ESI+): exact mass calculated for $[M+Na]^+$ ($C_{14}H_{27}NO_2Na$) requires *m/z* 264.1934, found *m/z* 264.1934;

IR (neat) ν_{max}: 2919, 2853, 1692, 1479, 1457, 1393, 1364, 1276, 1245, 1161, 1132, 881, 769.

Hydroaminomethylation of norbornene



***tert*-Butyl (((1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-yl)methyl)(methyl)carbamate (2.1.113)**

The title compound was purified by flash column chromatography on silica gel (toluene) to afford the analytically pure desired product in 79 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 - 3.09 (m, 1H, H_2), 2.97 - 2.72 (m, 4H, $H_{2/10}$), 2.21 - 2.19 (m, 1H, H_7), 2.02 - 2.00 (m, 1H), 1.75 - 1.68 (m, 1H), 1.53 - 1.46 (m, 2H), 1.45 (s, 9H, H_1), 1.33 - 1.28 (m, 2H), 1.16 - 1.06 (m, 3H), 1.00 (br s, 1H);

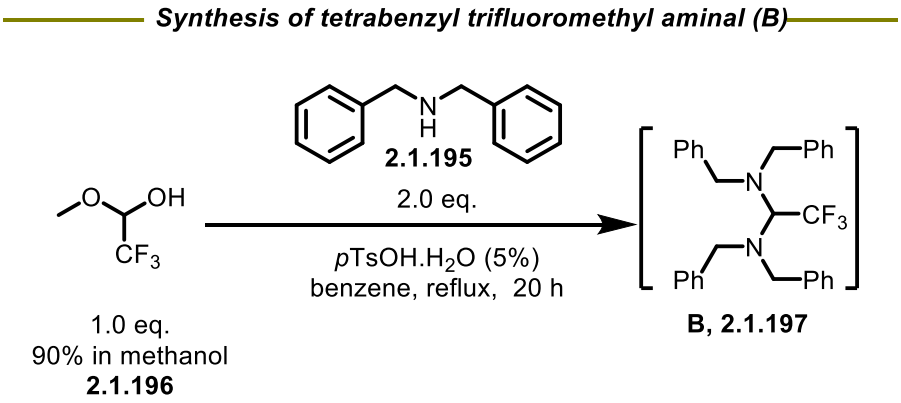
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2 (C_1), 79.2 (C_{12}), 53.3 (C_2), 40.8 (C_4), 38.6, 36.6, 35.2, 34.9, 34.1, 29.9 (C_8), 29.2 (C_6), 28.6 (3C, C_{13});

IR (neat) ν_{max}: 2951, 2870, 1696, 1454, 1396, 1365, 1158, 1128;

HRMS (ESI+): exact mass calculated for $C_{14}H_{25}NO_2$ $[M+Na]^+$ *m/z:* 262.1778, found: 262.1779.

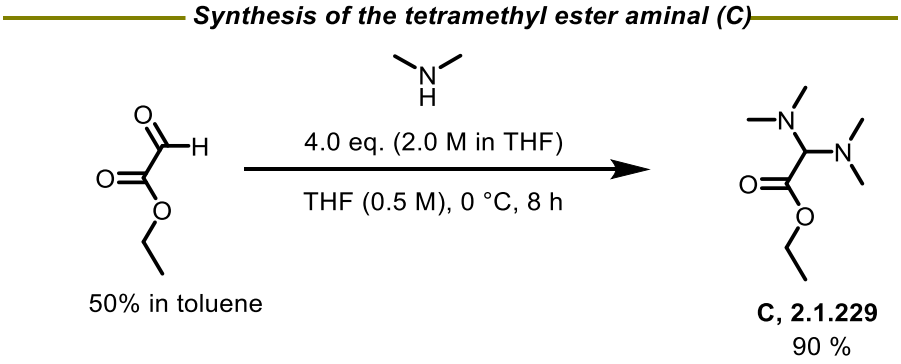
3.5.1.5 Experimental procedures for the Synthesis of Aminals in chapter **2.1**

_N_,_N_,_N_',_N_'-Tetrabenzyl-2,2,2-trifluoroethane-1,1-diamine–hemiaminal B (2.1.197)



To a round bottom flask containing trifluoroacetaldehyde methyl hemiacetal (0.56 mL, 5.25 mmol, 1.0 eq., 90 % in methanol) was added dibenzylamine (1.92 mL, 10 mmol, 2.0 eq.) and benzene (20 mL) at 0 °C. Afterwards *p*TsOH.H_2O (48 mg, 5 %) was added to the solution. A Dean-stark apparatus was then assembled and the reaction heated to reflux for 20 h. After cooling, the solvent was evaporated and used as a mixture in the upcoming reactions.

Ethyl 2,2-bis(dimethylamino)acetate – aminal C (2.1.229)

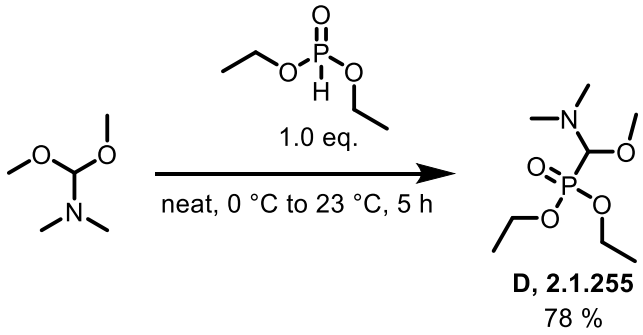


A solution of ethyl glyoxalate (1 eq., 10.0 mmol, 50 % in toluene) was gently heated to 60 °C for 2 h to prevent polimerisation. After that time, the solution was cooled to 0 °C, diluted with THF (3.0 mL) and dimethylamine (4.0 eq., 40 mmol, 2.0 M in THF) was added.

After 8 h, the solution was passed through a short plug of basic alumina and flushed with diethyl ether as an eluent. Evaporation of the solvent afforded the product in 90 % yield as a yellow oil. Spectral data and experimental procedure in accordance with the literature.[598]

Diethyl ((dimethylamino)(methoxy)methyl)phosphonate – hemiaminal D (2.1.255)

Synthesis of tetramethyl phosphonate aminal (D)



D, 2.1.255
78 %

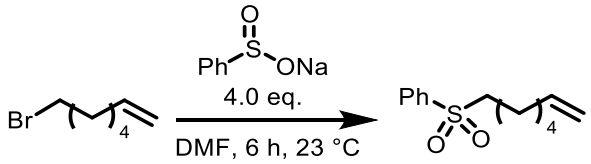
To a round bottom flask containing dimethylformamide dimethyl acetal (1.0 eq., 0.10 mol) was added diethyl phosphonate (1.0 eq., 0.10 mol) at 0 °C. After stirring for 5 h at rt, the crude mixture was distilled using *Kugelrohr* distillation to afford the hemiaminal D, **2.1.255** as a colourless liquid (78 %). Spectral data and experimental procedure are in accordance with the literature. *Hemiaminal C was used as such.*[599]

3.5.1.6 Characterisation and procedures used in the synthesis of starting material in chapter 2.1

Unless otherwise stated, all starting material are commercially available.

(oct-7-en-1-ylsulfonyl)benzene 2.1.279 - used in the synthesis of compound **2.1.245**

Sulfonylation of 8-bromo-octene

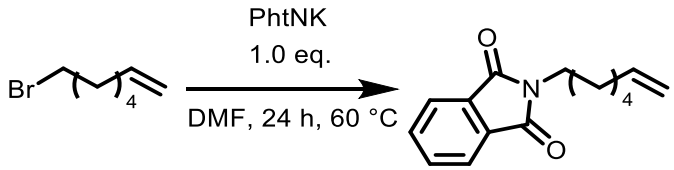


2.1.280 **2.1.279**

To a solution of 8-bromo-hexene (**2.1.280**, 1.0 eq., 5.0 mmol) in DMF (10.0 mL, 0.44 M) was added sodium benzenesulfinate (1.2 eq., 6.0 mmol). After 6 h at 23 °C, diethyl ether (20.0 mL) was added to the reaction mixture and the resulting solution was washed with brine (3 x 20 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-10 % EtOAc / heptane to give the desired sulfone (**2.1.279**, 0.7 g, 67 %) as a colorless oil. Spectral data is in accordance with the literature.[600]

2-(Oct-7-en-1-yl)isoindoline-1,3-dione 2.1.281 - used in the synthesis of compound **2.1.246**

Phthalimidation of 8-bromo-1-octene



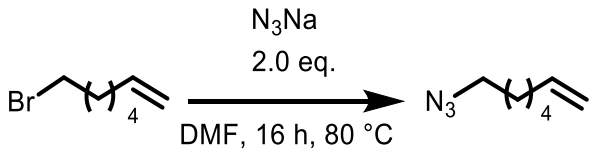
2.1.280 **2.1.281**

A suspension of 8-bromo-1-octene (**2.1.280**, 1.0 eq., 5.96 mmol) and potassium phthalimide (1.0 eq., 6.35 mmol) in dry DMF (0.44 M, 14.0 mL) was heated at 60 °C for 24 h. The resulting cloudy pale-yellow mixture was allowed to cool to room temperature and then solids were filtered off. Brine was added and the mixture was extracted with diethyl ether (3 x 20.0 mL). The combined ether extracts were washed with 20 mL of brine and then dried over K_2CO_3. The ether

solution was filtered and the solvent removed *in vacuo* to give the title compound (**2.1.281**, 1.2 g, 80 %) as a pale-yellow liquid. Spectral data is in accordance with the literature.[600]

8-Azidooct-1-ene 2.1.282 - used in the synthesis of compound **2.1.247**

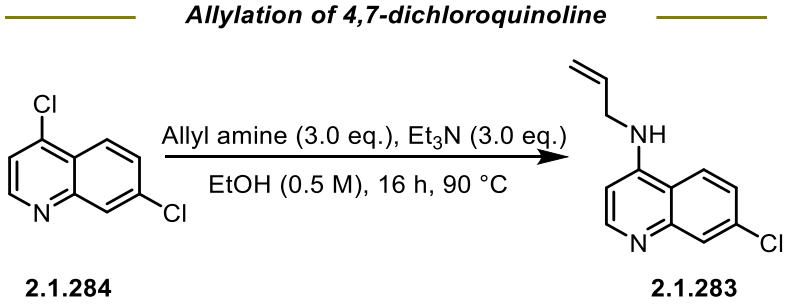
Azidation of 8-bromo-1-octene



2.1.280 **2.1.282**

NaN_3 (0.78 g, 11.9 mmol, 2.00 eq.) was added in one portion to a stirred solution of 8-bromo-1-octene (**2.1.280**, 1.14 g, 5.96 mmol, 1.00 equiv) in dry DMF (0.44 M, 14.0 mL) at 80 °C. After 16 h at 80 °C, the solution was poured into H_2O (50.0 mL). The reaction mixture was extracted with ethyl acetate (3 x 25.0 mL) and the combined organic phases were washed with brine (10.0 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The title compound was isolated (0.80 g, 90 %) as a colorless oil. Spectral data is in accordance with the literature.[600]

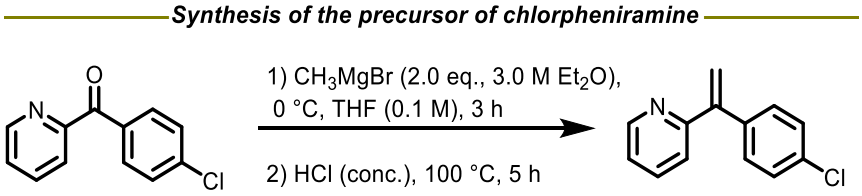
***N*-Allyl-7-chloroquinolin-4-amine 2.1.283** - used in the synthesis of compound **2.1.211**



2.1.284 **2.1.283**

A round-bottom flask containing 10 mL of ethanol was charged with 4,7-dichloroquinoline (**2.1.284**, 1.0 eq., 5.0 mmol), allylamine (3.0 eq., 15.0 mmol) and triethylamine (3.0 eq., 15.0 mmol). The reaction mixture was heated at 90 °C for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and the resulting solid was purified by column chromatography. The title compound was isolated in 63 % as a yellow solid (**2.1.283**). Spectral data is in accordance with the literature. [601]

2-(1-(4-Chlorophenyl)vinyl)pyridine 2.1.285 – used in the synthesis of compound **2.1.212**

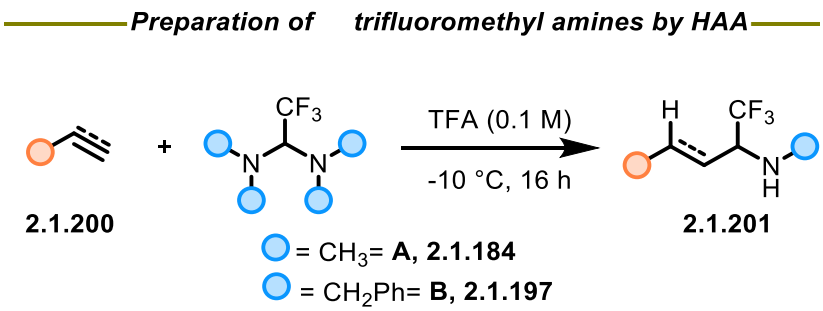


2.1.286 **2.1.285**

To a THF solution of (4-chlorophenyl)(pyridin-2-yl)methanone (**2.1.286**, 1.0 eq., 4.59 mmol) was added, 0 °C dropwise, methyl magnesium bromide (2.0 eq., 3.0 M solution in Et_2O, 9.19 mmol). After immediate color change, the solution was stirred at 23 °C for 3 h. The solution was then diluted with NH_4Cl and extracted with ethyl acetate (3 x 25.0 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting yellow oil was used in the following step without purification. To a round-bottom flask containing the previously obtained tertiary alcohol, were added 10.0 mL of concentrated HCl (36 %). The resulting solution was then heated to 100 °C. After 15 h, the acid was neutralized by addition of a 1.0 M NaOH solution, and subsequently extracted with DCM (3 x 25.0 mL). The combined organic phases were dried over

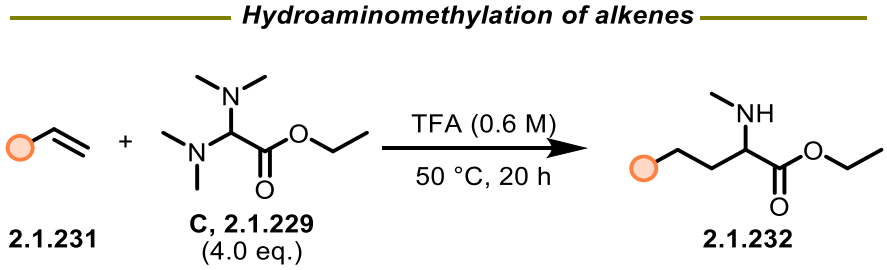
anhydrous $MgSO_4$ and concentrated *in vacuo*. The title compound was obtained in 55 % as a yellow oil after column chromatography (**2.1.285**). https://doi.org/10.1021/acs.orglett.7b02262

3.5.1.7 General procedure **2.4** - Procedure for the preparation of α-trifluromethylamines using aminal A or B



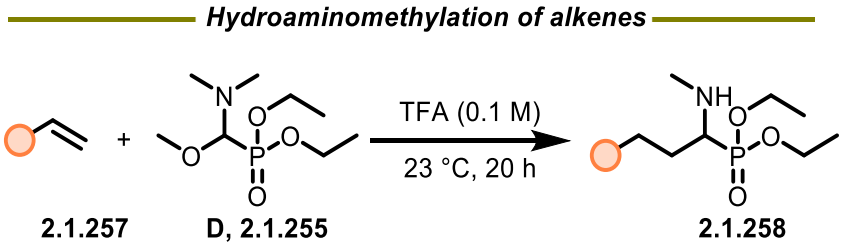
To a flame dried Schlenk flask charged with the aminal (**A, 2.1.184** or **B**, **2.1.197** 4.0 eq., 0.8 mmol) was added, at -10 °C (using a cryostat - isopropanol), TFA (0.1 M). After 5 min, the corresponding alkene/alkyne (1.0 eq., 0.2 mmol) was added to the solution. The reaction was vigorously stirred at this temperature (-10 °C unless otherwise stated) for 16 h, after which it was allowed to warm to 0 °C. Then, aqueous NaOH (1.0 M) was added until a pH > 7 was reached. The resulting biphasic mixture was separated and the aqueous phase was extracted with DCM (3 x 50 mL/mmol). The combined organic phases were then dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel with DCM/DMA system (DMA: 24:1:0.15) to afford the analytically pure desired product.

3.5.1.8 General procedure **2.5** – Procedure for the preparation of α-aminoesters using aminal C



To a flame dried Schlenk flask charged with the aminal (**C, 2.1.229**, 4.0 eq., 0.8 mmol) was added, at -10 °C (using a cryostat - isopropanol), TFA (0.33 mL, 0.6 M). After 5 min, the corresponding alkene (1.0 eq., 0.2 mmol) was added to the solution. The reaction was heated to 50 °C and vigorously stirred (unless otherwise stated) for 20 h, after which it was cooled to 0 °C. Then, aqueous NaOH (1.0 M) was added until a pH > 7 was reached. The resulting biphasic mixture was separated and the aqueous phase extracted with DCM (3 x 50.0 mL/mmol). The combined organic phases were then dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel with DCM/DMA system (DMA = DCM/MeOH/NH_4OH 24:1:0.15) to afford the analytically pure desired product.

3.5.1.9 General procedure **2.6** – Procedure for the preparation of α-aminophosphonates using hemiaminal D



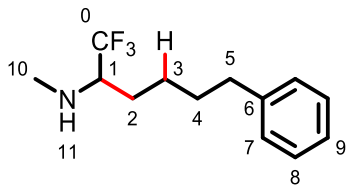
To a flame dried Schlenk flask charged with hemiaminal (**D, 2.1.255**, 4.0 eq., 0.8 mmol) was added, at 0 °C, trifluoroacetic acid (2.0 mL, 0.1 M). After 5 min, the corresponding alkene (1.0 eq., 0.2 mmol) was added to the solution. The reaction was

vigorously stirred at 23 °C (unless otherwise stated) for 20 h, after which it was cooled to 0 °C. Then, aqueous saturated $NaHCO_3$ was added until a pH >7 was reached. The resulting biphasic mixture was separated and the aqueous phase extracted with DCM (3 x 25.0 mL/mmol). The combined organic phases were then dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel with DCM/DMA system (DMA = DCM/MeOH/NH_4OH 24:1:0.15) to afford the analytically pure desired product.

3.5.2 Characterisation of products of hydroaminoalkylation of alkenes

3.5.2.1 Characterisation of α – Trifluoromethylamines following general procedure **2.4** for hydroaminoalkylation using aminal A (**2.1.184**)

1,1,1-Trifluoro-*N*-methyl-6-phenylhexan-2-amine (2.1.188)



The title compound was isolated in 92 % yield (48.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 - 7.28 (m, 2H, H_8), 7.20 - 7.18 (m, 3H, $H_{7/9}$), 2.87 (dqd, *J* = 15.2, 7.6, 3.8 Hz, 1H, H_1), 2.69 - 2.58 (m, 2H, H_5), 2.52 (m, 3H, H_{10}), 1.76 - 1.61 (m, 3H, $H_{2/4}$), 1.57 - 1.55 (m, 1H, $H_{2/4}$), 1.52 - 1.37 (m, 2H, H_3), 1.07 (br s, 1H, H_{11});

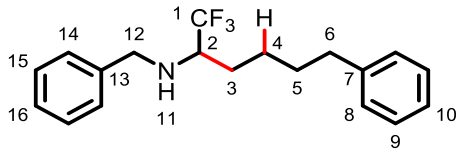
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.4 (C_6), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 127.3 (q, *J* = 288 Hz, C_0), 125.9 (C_{Ar}), 61.0 (q, *J* = 30 Hz, C_1), 35.8 (C_{Ar}), 35.0 (C_5), 31.4 (C_4), 28.5 (C_3), 25.4 (C_2);

^{19}F NMR (565 MHz, $CDCl_3$): δ -74.64 (d, *J* = 8.0 Hz);

HRMS (ESI$^+$): calculated for $C_{13}H_{19}NF_3$ $[M+H]^+$ *m/z*: 246.1464, found: 246.1468.

IR (neat, cm^{-1}): 2925, 2855, 2360, 2341, 1466; 1266.

1,1,1-trifluoro-*N*-methyl-6-phenylhexan-2-amine (2.1.199)



The title compound was isolated in 72 % yield (46.0 mg) as a yellow oil, using Aminal B.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 - 7.34 (m, 1H, H_{Ar}), 7.34 - 7.27 (m, 6H, H_{Ar}), 7.21 - 7.13 (m, 3H, H_{Ar}), 3.99 (d, *J* = 13.2 Hz, 1H, H_{12}), 3.80 (d, *J* = 13.2 Hz, 1H, H_{12}), 3.02 -

2.96 (m, 1H, H_2), 2.64 - 2.53 (m, 2H, H_6), 1.72 - 1.63 (m, 1H, H_3), 1.61 - 1.52 (m, 2H, H_4), 1.51 -1.43 (m, 1H, H_3), 1.39 - 1.24 (m, 2H, H_5);

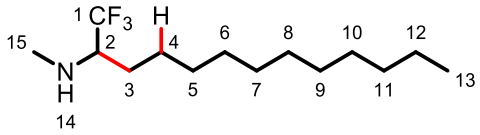
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.2 (C_{Ar}), 139.9 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (3C, C_{Ar}), 128.3 (2C, C_{Ar}), 127.2 (q, J = 285 Hz, C_1), 127.2 (2C, C_{Ar}), 125.8 (C_{Ar}), 58.2 (q, J = 27 Hz, C_2), 51.9 (C_{12}), 35.6 (C_6), 31.1 (C_5), 28.7 (C_4), 25.1 (C_3);

^{19}F NMR (565 MHz, $CDCl_3$): δ -74.65 (d, J = 6.0 Hz);

HRMS (ESI$^+$): calculated for $C_{19}H_{22}NF_3[M+H]^+$ *m/z*: 322.1777, found: 322.1769;

IR (neat, cm^{-1}): 3064, 3028, 2930, 2860, 1494, 1265, 1146.

1,1,1-Trifluoro-*N*-methyldodecan-2-amine (2.1.189)



The title compound was isolated in 91 % yield (53.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.91 - 2.82 (m, 1H, H_2), 2.53 (s, 3H, H_{15}), 1.70 - 1.62 (m, 1H, H_3), 1.54 - 1.42 (m, 2H, H_{Alk}), 1.42 - 1.34 (m, 2H, H_{Alk}), 1.34 - 1.30 (m, 2H, H_{Alk}), 1.30 - 1.29 (m, 2H, H_{Alk}), 1.28 (d, J = 6.2 Hz, 3H, H_{Alk}), 1.27 - 1.25 (m, 9H, H_{Alk}), 1.01 (br s, 1H, H_{14}), 0.88 (t, J = 7.0 Hz, 3H, H_{13});

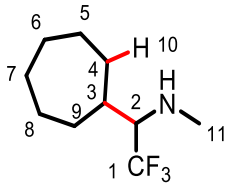
^{13}C NMR (151 MHz, $CDCl_3$): δ 127.2 (q, J = 284.5 Hz, C_1), 61.0 (q, J = 26.7 Hz, C_2), 34.9 (C_{15}), 31.9 (C_{Alk}), 29.6 (2C, C_{Alk}), 29.5 (C_{Alk}), 29.4 (C_{Alk}), 29.3 (C_{Alk}), 28.5 (C_{Alk}), 28.4 (C_{Alk}), 25.7 (C_{Alk}), 22.7 (C_{Alk}), 14.1 (C_{13});

^{19}F NMR (565 MHz, $CDCl_3$): δ -74.69 (d, J = 8.0 Hz);

HRMS (ESI$^+$): calculated for $C_{14}H_{29}NF_3$ $[M+H]^+$ *m/z*: 268.2247, found: 268.2250;

IR (neat, cm^{-1}): 2925, 2855, 2360, 2341, 1466, 1266.

1-cycloheptyl-2,2,2-trifluoro-*N*-methylethan-1-amine (2.1.190)



The title compound was isolated in 73 % yield (31.0 mg) as a yellow oil. Reaction was performed at 23 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.84 - 2.74 (m, 1H, H_2), 2.55 (s, 3H, H_{11}), 1.93 - 1.85 (m, 1H, H_3), 1.77 - 1.64 (m, 4H, H_{Alk}), 1.62 - 1.54 (m, 3H, H_{Alk}), 1.54 - 1.38 (m, 4H, H_{Alk}), 1.36 - 1.28 (m, 1H, H_{Alk}), 1.07 (br s, 1H, H_{10});

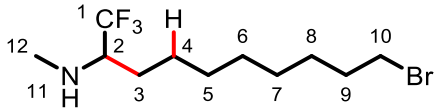
^{13}C NMR (151 MHz, $CDCl_3$): δ 127.4 (q, J = 286.6 Hz, C_1), 67.0 (q, J = 24.5 Hz, C_2), 39.7 (C_{11}), 32.6 (C_{Alk}), 28.3 (C_{Alk}), 28.2 (C_{Alk}), 27.7 (C_{Alk}), 27.4 (C_{Alk}), 27.2 (C_3);

^{19}F NMR (565 MHz, $CDCl_3$): δ -70.20 (d, J = 8.3 Hz);

HRMS (ESI^+): calculated for $C_{10}H_{19}NF_3$ $[M+H]^+$ *m/z*: 210.1464, found: 210.1467;

IR (neat, cm^{-1}): 2924, 2852, 2359, 2341, 1730, 1464, 1274.

10-Bromo-1,1,1-trifluoro-*N*-methyldecan-2-amine (2.1.194)



The title compound was isolated in 82 % yield (37.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.41 (t, J = 6.8 Hz, 2H, H_{10}), 2.86 (ddd, J = 12.0, 7.8, 3.9 Hz, 1H, H_2), 2.53 (s, 3H, H_{12}), 1.88 - 1.83 (m, 2H, H_3), 1.67 - 1.66 (m, 1H, H_{Alk}), 1.45 - 1.32 (m, 11H, H_{Alk}), 1.02 (br s, 1H, H_{11});

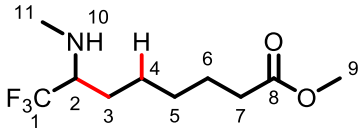
^{13}C NMR (151 MHz, $CDCl_3$): δ 127.3 (q, J = 284.6 Hz, C_1), 61.1 (q, J = 26.8, C_2), 35.0 (C_{12}), 34.1 (C_{10}), 32.9 (C_{Alk}), 29.5 (C_{Alk}), 29.3 (C_{Alk}), 28.8 (C_{Alk}), 28.6 (q, J = 1.7 Hz, C_3), 28.2 (C_{Alk}), 25.8 (C_{Alk});

^{19}F NMR (565 MHz, $CDCl_3$): δ -74.62 (d, J = 7.6 Hz);

HRMS (ESI^+): calculated for $C_{11}H_{22}F_3Br[M+H]^+$ *m/z*: 304.0882, found: 304.0884;

IR (neat, cm^{-1}): 2928, 2857, 1461, 1263, 1146, 1111.

Methyl 8,8,8-trifluoro-7-(methylamino)octanoate (2.1.192)



The title compound was isolated in 74 % yield (35.0 mg) as a yellow oil. Reaction was performed at room temperature.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.67 (s, 3H, H_9), 2.90 - 2.82 (m, 1H, H_2), 2.52 (s, H_{11}), 2.32 (t, J = 7.5 Hz, 2H, H_7), 1.73 - 1.61 (m, 3H, H_{Alk}), 1.56 - 1.47 (m, 1H, H_{Alk}), 1.47 - 1.29 (m, 4H, H_{Alk}), 1.00 (br s, 1H, H_{10});

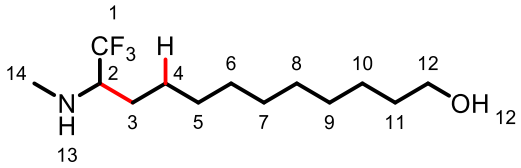
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_8), 127.5 (q, J = 284.6 Hz, C_1), 61.2 (q, J = 26.8 Hz, (C_2), 51.9 (C_9), 35.2 (C_{11}), 34.3 (C_{Alk}), 29.3 (C_{Alk}), 28.7 (C_{Alk}), 25.7 (C_{Alk}), 25.1 (C_{Alk});

^{19}F NMR (565 MHz, $CDCl_3$): δ -74.59 (d, J = 7.6 Hz);

HRMS (ESI$^+$): calculated for $C_{10}H_{19}NO_2F_3$ $[M+H]^+$ *m/z*: 242.1362, found: 242.1367;

IR (neat, cm^{-1}): 2950, 2893, 1736, 1452.

12,12,12-Trifluoro-11-(methylamino)dodecan-1-ol (2.1.193)



The title compound was isolated in 67 % yield (32.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.63 (t, *J* = 6.6 Hz, 2H, H_{12}), 2.91 - 2.87 (m, 1H, H_2), 2.53 (s, 3H, H_{14}), 1.75 (br s, 1H, H_{12}), 1.71 - 1.65 (m, 1H, H_{Alk}), 1.60 - 1.54 (m, 2H, H_{Alk}), 1.51 - 1.44 (m, 2H, H_{Alk}), 1.39 - 1.29 (m, 14H, H_{Alk});

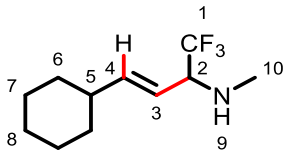
^{13}C NMR (151 MHz, $CDCl_3$): δ 127.2 (q, *J* = 285 Hz, C_1), 63.2 (C_{12}), 61.0 (q, *J* = 27.0 Hz, C_2), 34.9 (C_{14}), 32.9 (C_{11}), 29.7 (C_{Alk}), 29.6 (2C, C_{Alk}), 29.5 (C_{Alk}), 29.5 (C_{Alk}), 28.5 (C_{Alk}), 25.9 (C_{Alk}), 25.8 (C_{Alk});

^{19}F NMR (565 MHz, $CDCl_3$): δ -74.36 (d, *J* = 5.1 Hz);

HRMS (ESI$^+$): calculated for $C_{13}H_{27}NOF_3$ $[M+H]^+$ *m/z*: 270.2039, found: 270.2042;

IR (neat, cm^{-1}): 3338, 2925, 2855, 1676, 1463, 1264, 1148, 1117, 1056.

(*E*)-4-Cyclohexyl-1,1,1-trifluoro-*N*-methylbut-3-en-2-amine (2.1.202)



The title compound was isolated in 82 % yield (36.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.76 (dd, *J* = 15.5, 6.6 Hz, 1H, H_4), 5.24 (ddd, *J* = 15.6, 8.3, 1.4 Hz, 1H, H_3), 3.36 (app p, *J* = 7.5 Hz, 1H, H_2), 2.43 (s, 3H, H_{10}), 2.08 - 1.96 (m, 1H, H_5), 1.77 - 1.70 (m, 3H, H_{Alk}), 1.69 - 1.62 (m, 1H, H_{Alk}), 1.56 (s, 1H, H_9), 1.30 - 1.24 (m, 2H, H_{Alk}), 1.19 - 1.05 (m, 4H, H_{Alk});

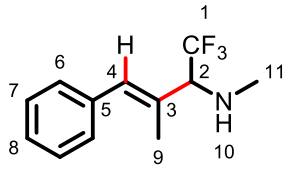
^{13}C NMR (151 MHz, $CDCl_3$): δ 144.5 (C_3), 125.7 (q, *J* = 285 Hz, C_1), 119.8 (C_4), 64.5 (q, *J* = 28 Hz, C_2), 40.6 (C_5), 34.1 (C_{10}), 32.8 (C_{Alk}), 32.7 (C_{Alk}), 32.7 (C_{Alk}), 26.2 (C_{Alk}), 26.0 (C_{Alk});

^{19}F NMR (565 MHz, $CDCl_3$): δ -75.25 (d, *J* = 7.0 Hz);

HRMS (ESI$^+$): calculated for $C_{11}H_{19}F_3N$ $[M+H]^+$ *m/z*: 222.1464, found: 222.1466;

IR (neat, cm^{-1}): 2925, 2852, 2360, 2340, 1735, 1450, 1274.

(*E*)-1,1,1-Trifluoro-*N*,3-dimethyl-4-phenylbut-3-en-2-amine (2.1.203)



The title compound was isolated in 65 % yield (29.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 - 7.34 (m, 2H, H_7), 7.34 - 7.30 (m, 2H, H_6), 7.29 - 7.25 (m, 1H, H_8), 6.61 (s, 1H, H_4), 3.60 (q, *J* = 7.7 Hz, 1H, H_2), 2.47 (s, 3H, H_{11}), 1.92 (s, 3H, H_9);

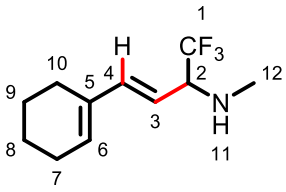
^{13}C NMR (151 MHz, $CDCl_3$): δ 136.6 (C_1), 132.9 (C_4), 130.6 (C_3), 129.1 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 127.1 (C_{Ar}), 125.5 (q, *J* = 283 Hz, C_1), 69.7 (q, *J* = 28 Hz, C_2), 34.0 (C_{11}), 13.6 (C_9);

^{19}F NMR (565 MHz, $CDCl_3$): δ -72.6 (d, *J* = 7.6 Hz);

HRMS (ESI$^+$): calculated for $C_{12}H_{15}F_3N$ $[M+H]^+$ *m/z*: 230.1151, found: 230.1154;

IR (neat, cm^{-1}): 1447, 1350, 1257, 1154, 1134, 1091, 1014, 836, 752, 697.

(*E*)-4-(Cyclohex-1-en-1-yl)-1,1,1-trifluoro-*N*-methylbut-3-en-2-amine (2.1.204)



The title compound was isolated in 37 % yield (14.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.31 (d, *J* = 15.7 Hz, 1H, H_4), 5.83 (s, 1H, H_6), 5.32 (dd, *J* = 15.8, 8.5 Hz, 1H, H_3), 3.46 (app p, *J* = 7.4 Hz, 1H, H_2), 2.45 (s, 3H, H_{12}), 2.17 - 2.11 (m, 4H, $H_{7/10}$), 1.72 - 1.66 (m, 2H, $H_{8/9}$), 1.64 - 1.58 (m, 2H, $H_{8/9}$), 1.40 (br s, 1H, H_{11});

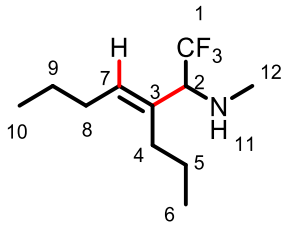
^{13}C NMR (151 MHz, $CDCl_3$): δ 140.3 (C_6), 134.8 (C_5), 132.0 (C_4), 125.8 (q, J = 282 Hz, C_1), 117.3 (C_3), 64.7 (q, J = 29 Hz, C_2), 34.3 (C_{12}), 26.0 ($C_{7/10}$), 24.5 ($C_{7/10}$), 22.5 ($C_{8/9}$), 22.4 ($C_{8/9}$);

^{19}F NMR (565 MHz, $CDCl_3$): δ -75.1 (d, J = 7.2 Hz);

HRMS (ESI$^+$): calculated for $C_{10}H_{12}F_3$ $[M\text{-}NHMe]^+$ *m/z*: 189.0886, found: 189.0889;

IR (neat, cm^{-1}): 2928, 2860, 1650, 1450, 1365, 1261, 1155, 1127, 1101, 966, 792.

(*Z*)-1,1,1-Trifluoro-*N*-methyl-3-propylhept-3-en-2-amine (2.1.205)



The title compound was isolated in 54 % yield (25.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.54 (t, J = 7.2 Hz, 1H, H_7), 3.34 (q, J = 7.7 Hz, 1H, H_2), 2.39 (s, 3H, H_{12}), 2.16 - 2.05 (m, 3H, $H_{4/8}$), 1.94 (ddd, J = 13.9, 10.6, 5.2 Hz, 1H, $H_{4/8}$), 1.47 - 1.36 (m, 4H, $H_{5/9}$), 0.92 (t, J = 7.3 Hz, 6H, $H_{6/10}$);

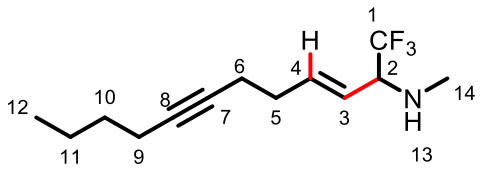
^{13}C NMR (151 MHz, $CDCl_3$): δ 132.9 (C_3), 132.7 (C_7), 125.9 (q, J = 282 Hz, C_1), 67.2 (q, J = 28 Hz, (C_2), 34.5 (C_{12}), 31.3 ($C_{4/8}$), 30.0 ($C_{4/8}$), 22.8 ($C_{5/9}$), 22.1 ($C_{5/9}$), 14.5 ($C_{6/10}$), 13.9 ($C_{6/10}$);

^{19}F NMR (565 MHz, $CDCl_3$): δ -73.2 (d, J = 7.6 Hz);

HRMS (ESI$^+$): calculated for $C_{11}H_{211}F_3N$ $[M+H]^+$ *m/z*: 224.1621, found: 224.1613;

IR (neat, cm^{-1}): 2961, 2873, 1459, 1353, 1261, 1156, 1126, 1094, 708.

(*E*)-1,1,1-Trifluoro-*N*-methyldodec-3-en-7-yn-2-amine (2.1.207)



The title compound was isolated in 43 % yield (21.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.86 (dt, *J* = 15.3, 6.2 Hz, 1H, H_3), 5.36 (dd, *J* = 15.3, 8.3 Hz, 1H, H_4), 3.41 (p, *J* = 7.4 Hz, 1H, H_2), 2.45 (s, 3H, H_{14}), 2.29 - 2.25 (m, 4H, $H_{6/9}$), 2.15 - 2.11 (m, 2H, H_5), 1.47 - 1.42 (m, 2H, H_{10}), 1.41 - 1.36 (m, 2H, H_{11}), 0.90 (t, *J* = 7.2 Hz, 3H, H_{12});

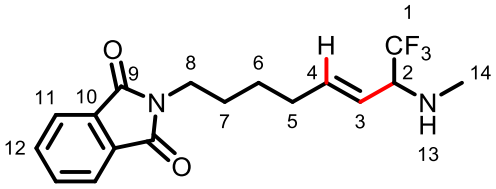
^{13}C NMR (151 MHz, $CDCl_3$): δ 136.9 (C_3), 125.7 (q, *J* = 282 Hz, C_1), 123.6 (C_4), 81.3 (C_7), 78.9 (C_8), 64.3 (q, *J* = 29 Hz, C_2), 34.1 (C_{14}), 32.1 (C_5), 31.3 (C_{10}), 22.2 (C_{11}), 18.8 (C_6), 18.5 (C_9), 13.7 (C_{12});

^{19}F NMR (565 MHz, $CDCl_3$): δ -75.2 (d, *J* = 7.2 Hz);

HRMS (ESI^+): calculated for $C_{13}H_{21}F_3N$ $[M+H]^+$ *m/z*: 248.1621, found: 248.1625;

IR (neat, cm^{-1}): 2932, 2864, 1455, 1365, 1259, 1180, 1156, 1106, 969, 695.

(*E*)-2-(8,8,8-Trifluoro-7-(methylamino)oct-5-en-1-yl)isoindoline-1,3-dione (2.1.208)



The title compound was isolated in 38 % yield (26.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 - 7.81 (m, 2H, $H_{11/12}$), 7.73 - 7.68 (m, 2H, $H_{11/12}$), 5.78 (dt, *J* = 15.4, 6.8 Hz, 1H, H_3), 5.33 - 5.27 (m, 1H, H_4), 3.69 (t, *J* = 7.2 Hz, 2H, H_8), 3.40 - 3.55 (m, 1H, H_2), 2.43 (s, 3H, H_{14}), 2.20 - 2.09 (m, 2H, H_5), 1.76 - 1.63 (m, 2H, H_7), 1.52 - 1.41 (m, 2H, H_6);

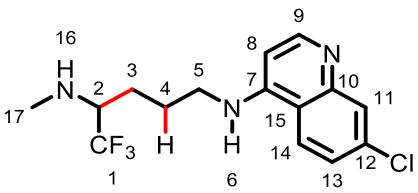
^{13}C NMR (151MHz, $CDCl_3$): δ 168.6 (2C, C_9), 137.9 (C_3), 134.0 (2C, C_{12}), 132.3 (2C, C_{10}), 125.7 (q, *J* = 282 Hz, C_1), 123.3 (2C, C_{11}), 123.1 (C_4), 64.3 (q, *J* = 29 Hz, C_2), 37.8 (C_8), 34.2 (C_{14}), 32.0 (C_6), 28.1 (C_5), 26.2 (C_7);

^{19}F NMR (565 MHz, $CDCl_3$): δ -75.2 (d, *J* = 7.2 Hz);

HRMS (ESI^+): calculated for $C_{17}H_{20}F_3N_2O_2$ $[M+H]^+$ *m/z*: 341.1471, found: 341.1473;

IR (neat, cm^{-1}): 2939, 2861, 1771, 1706, 1396, 1369, 1264, 1154, 1130, 1102, 923, 718.

***N*^{1}-(7-Chloroquinolin-4-yl)-5,5,5-trifluoro-*N*^{4}-methylpentane-1,4-diamine (2.1.211)**



The title compound was isolated in 61 % yield as a yellow oil (40.0 mg, 71 % based on recovery of starting material). Reaction was performed at 75 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 - 8.51 (m, 1H, H_9), 7.98 - 7.97 (m, 1H, H_{14}), 7.69 - 7.68 (m, 1H, H_{11}), 7.38 - 7.37 (m, 1H, H_{11}), 6.41 - 6.40 (m, 1H, H_{13}), 5.68 (br s, 1H, H_6), 3.38 - 3.35 (m, 2H, H_5), 3.02 (dd, $J_{H,H}$ = 9.8 Hz, 3.7 Hz; q, $J_{H,F}$ = 7.4 Hz, 1H, H_2), 2.57 (s, 3H, H_{17}), 2.00 - 1.94 (m, 2H, H_4), 1.90 (dddd, *J* = 14.1 Hz, 9.0 Hz, 6.9 Hz, 3.7 Hz, 1H, H_3), 1.64 (dddd, *J* = 14.0 Hz, 9.8 Hz, 8.4 Hz, 5.6 Hz, 1H, H_3);

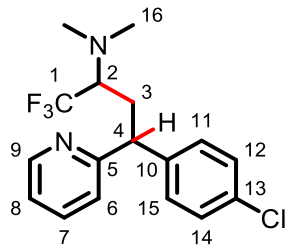
^{13}C NMR (151 MHz, $CDCl_3$): δ 151.5 (C_7), 150.0 (C_9), 148.5 (C_8), 135.2 (C_{12}), 128.4 (C_{11}), 126.9 (*J* = 286 Hz, C_1), 125.5 (C_9), 121.0 (C_{14}), 117.1 (C_{13}), 99.0 (C_{15}), 60.3 (*J* = 26.7 Hz, (C_2), 43.2 (C_5), 34.1 (C_{16}), 26.1 (C_4), 25.0 (C_3);

^{19}F NMR (565 MHz, $CDCl_3$): δ -73.84 (d, *J* = 7.0 Hz);

HRMS (ESI$^+$): calculated for $C_{15}H_{18}ClN_3F_3$ $^+$[M+H]$^+$ *m/z*: 332.1130, found. 332.1132;

IR (neat, cm^{-1}): 3176, 2927, 2885, 2368, 2341, 1621, 1509, 1329, 1227, 1104.

4-(4-Chlorophenyl)-1,1,1-trifluoro-*N*,*N*-dimethyl-4-(pyridin-2-yl)butan-2-amine (2.1.212)



The title compound was isolated in 61 % yield as a yellow oil (41.0 mg, 1:1 d.r.). Reaction was performed at 75 °C.

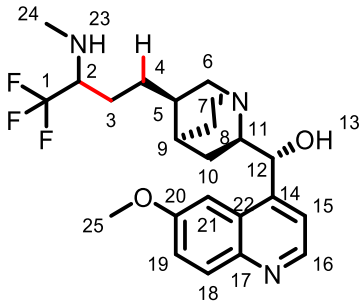
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.60 - 8.57 (m, 1H, H_9), 7.59 - 7.54 (m, 1H, H_7), 7.32 - 7.28 (m, 3H, $H_{6/12/14}$), 7.25 - 7.22 (m, 1H, $H_{8/11/15}$), 7.18 - 7.15 (m, d2, 0.5H, $H_{8/11/15}$), 7.13 - 7.10 (m, 1.5H, $H_{8/11/15}$), 4.32 - 4.30 (m, 2H, H_3), 2.77 (dd, *J* = 10.8 Hz, 4.0 Hz, 0.5H, d2, H_2), 2.70 (dd, 11.1 Hz, 3.7 Hz, 0.5H, d1, H_2), 2.66 - 2.62 (m, 0.5H, d2, H_4), 2.45 - 2.43 (m, 0.5H, d1, H_4), 2.41 (s, 3H, d1, H_{16}), 2.38 (s, 3H, d2, H_{16}), 2.36 - 2.34 (m, 1H, d1, H_2), 2.17 - 2.12 (m, 1H, d2);

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.7 (d1, C_5), 161.7 (d2, C_5), 149.7 (d2, C_9), 149.3 (d1, C_9), 142.2 (d2, C_{10}), 140.9 (d1, C_{10}), 136.5 (d1, d2, C_7), 131.4, 132.6 (d1, C_{13}), 132.4 (d2, C_{13}), 129.8 (d1, C_{11}), 129.3 (d2, C_{11}), 128.8 (d1, C_{12}), 128.6 (d2, C_{12}), 123.6 (d2, C_6), 122.9 (d1, C_6), 121.7 (d2, C_8), 121.6 (d1, C_8), 62.4 (q, *J* = 24.7 Hz, d2, C_2), 62.2 (q, *J* = 24.7 Hz, d1, C_2), 48.4 (d1, C_4), 48.2 (d2, C_4), 40.9 (d2, C_{16}), 40.9 (d1, C_{16}), 31.4 (d2, C_3), 31.1 (d1, C_3);

^{19}F NMR (565 MHz, $CDCl_3$): δ -68.08 (d, *J* = 7.7 Hz, d1), -68.29 (d, *J* = 7.7 Hz, d2);

HRMS (ESI$^+$): calculated for $C_{17}H_{19}ClN_2F_3$ $[M+H]^+$ *m/z*: 343.1183, found: 343.1186.

(1*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-(4,4,4-trifluoro-3-(methylamino)butyl)quinuclidin-2-yl)methanol (2.1.213)



The title compound was isolated in 32 % yield as a yellow solid (28.0 mg, 76 % based on recovery of starting material). Reaction was performed at 75 °C. Diastereoisomers were not clearly visible by **^{1}HNMR** or **^{13}CNMR**. Diasteriomeric ratio was calculated using crude ^{19}F NMR - 1.5 to 1 ratio d1/d2.

^{1}H NMR (600 MHz, MeOD): δ 8.66 (d, *J* = 4.6 Hz, 1H, H_{16}), 7.97 - 7.91 (m, 1H, H_{18}), 7.70 (d, *J* = 4.6 Hz, 1H, H_{15}), 7.42 (dd, *J* = 7.8, 2.4 Hz, 2H, $H_{19/21}$), 5.62 (br s, 1H, H_{13}), 4.72 (s, 1H, H_2), 4.59 (br s, H_{23}), 4.02 - 3.93 (m, 3H, H_{25}), 3.73 (s, 3H, H_{24}), 3.20 - 3.15 (m, 2H), 2.87 (dtd, *J* = 11.6, 7.9, 3.8 Hz, 1H, H_{12}), 2.75 (td, *J* = 12.0, 4.9 Hz, 1H, H_6), 2.51 - 2.41 (m, 1H), 2.34 (s, 3H, H_{24}), 1.98 - 1.97 (m, 2H, H_3), 1.81 - 1.80 (m, 1H), 1.66 (br s, 1H, H_{23}), 1.61 - 1.52 (m, 2H, H_{10}), 1.51 - 1.42 (m, 2H, H_6), 1.41 - 1.27 (m, 2H, H_3);

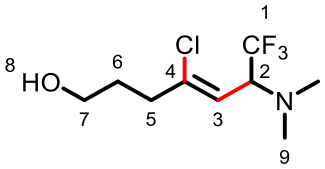
^{13}C NMR (151 MHz, MeOD): δ 159.7 (C_{20}), 150.3 (C_{14}), 148.2 (C_{16}), 144.8 (C_{17}), 131.4 (C_{18}), 128.4 (q, *J* = 282 Hz, (C_1), 128.1 (C_{22}), 120.1 (C_{19}), 102.5 (C_{21}), 74.4 (C_{12}), 71.9 (C_{11}), 61.9 (*J* = 27 Hz, confor, (C_2), 61.0 (d1, C_6), 60.9 (d2, C_{20}), 59.4 (d2, C_{25}), 59.2 (d1, C_{25}), 58.9 (d1), 58.8 (d2), 56.5, 44.3, 36.5 (d2, C_5), 36.4 (d1, C_5), 34.8 (d2, C_{24}), 34.7 (d1, C_{24}), 31.6 (C_4), 31.4 (C_4), 28.4 (d2, C_8) , 28.4 (d1, C_8), 27.3 (d2, (C_9), 27.3 (d1, C_9), 27.2 (C_4), 26.8 (C_{10}), 21.2 (C_3);

^{19}F NMR (565 MHz, $CDCl_3$): δ -75.4 (d, *J* = 7.9 Hz, 1.5H, d1), -74.6 (d, *J* = 7.9 Hz, d2);

HRMS (ESI$^+$): calculated for $C_{23}H_{31}N_3O_2F_3$ $[M+H]^+$ *m/z*: 438.2363, found: 438.2367;

IR (neat, cm^{-1}): 3176, 2927, 2885, 2368, 2341, 1621, 1509, 1329, 1227, 1104.

***(Z)*-4-Chloro-6-(dimethylamino)-7,7,7-trifluorohept-4-en-1-ol (2.1.266)**



The title compound was isolated in 55 % yield (27.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.85 (d, *J* = 9.0 Hz, 1H, H_3), 3.84 (dq, *J* = 8.5, 7.9 Hz, 1H, H_2), 3.71 (br s, 1H H_8), 3.60 (dt, *J* = 11.0, 4.6 Hz, 1H, H_7), 3.52 (ddd, *J* = 11.5, 9.4, 3.9 Hz, 1H, H_7), 2.69 (ddd, *J* = 17.2, 9.4, 6.1 Hz, 1H, H_5), 2.46 (s, 6H, H_9), 2.43 - 2.39 (m, 1H, H_5), 1.91 - 1.80 (m, 2H, H_6);

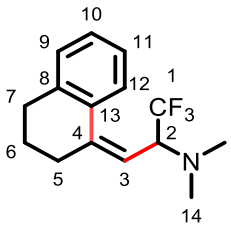
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.8 (C_4), 126.3 (q, *J* = 289 Hz, C_1), 119.9 (C_3), 62.7 (q, *J* = 27 Hz, C_2), 59.4 (C_7), 41.3 (2C, C_9), 30.0 (C_5), 29.2 (C_6);

^{19}F NMR (659 MHz, $CDCl_3$): δ -67.9 (d, *J* = 7.6 Hz);

HRMS (ESI$^+$): calculated for$C_9H_{16}ClF_3NO$ $[M+H]^+$ *m/z*: 246.0867, found: 246.0855,

IR (neat, cm^{-1}): 3386, 2946, 1648, 1459, 1373, 1254, 1157, 1110, 1037, 984, 657.

(*Z*)-3-(3,4-Dihydronaphthalen-1(2H)-ylidene)-1,1,1-trifluoro-*N*,*N*-dimethylpropan-2-amine (2.1.269)



The title compound was isolated in 74 % yield (33.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 - 7.60 (m, 1H, H_{Ar}), 7.25 - 7.18 (m, 2H, H_{Ar}), 7.15 - 7.11 (m, 1H, H_{Ar}), 6.05 (d, *J* = 9.8 Hz, 1H, H_3), 3.95 (dq, *J* = 9.8, 8.1 Hz, 1H, H_2), 2.84 (t, *J* = 6.3 Hz, 2H, H_7), 2.61 - 2.56 (m, 2H, H_5), 2.46 (s, 6H, H_{14}), 1.92 - 1.86 (m, 2H, H_6);

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.0 (C_{13}), 138.1 (C_8), 135.2 (C_4), 129.2 (C_9), 128.1 (C_{10}), 126.4 (d, *J* = 289 Hz, (C_1), 126.3 (C_{11}), 124.5 (C_{12}), 112.6 (C_3), 62.8 (q, *J* = 28 Hz, C_2), 42.4 (2C, C_{14}), 30.3 (C_5), 27.2 (C_7), 23.4 (C_6);

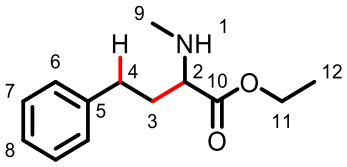
^{19}F NMR (659 MHz, $CDCl_3$): δ -70.5 (d, *J* = 8 Hz);

HRMS (ESI$^+$): calculated for $C_{13}H_{12}F_3$ $[M\text{-}NMe_2]^+$ *m/z*: 225.0886, found: 225.0896;

IR (neat, cm^{-1}): 2939, 2870, 1456, 1260, 1152, 1103, 1033, 754.

3.5.2.2 Characterisation of α – aminoesters following general procedure **2.5.** for hydroaminoalkylation using aminal C (**2.1.229**)

Ethyl 2-(methylamino)-4-phenylbutanoate (2.1.233)



The title compound was isolated in 39 % yield (17.0 mg) as a yellow oil. Reaction was conducted at 23 °C.

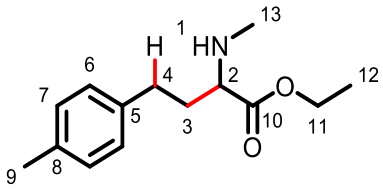
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 - 7.24 (m, 2H, H_7), 7.21 - 7.17 (m, 3H, $H_{6/8}$), 4.20 (q, J = 7.0 Hz, 2H, H_{11}), 3.15 (t, J = 6.8 Hz, 1H, H_2), 2.75 - 2.65 (m, 2H, H_4), 2.38 (s, 3H, H_9), 2.01 - 1.94 (m, 1H, H_3), 1.91 - 1.84 (m, 1H, H_3), 1.29 (t, J = 7.0 Hz, 3H, H_{12});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.2 (C_{10}), 141.4 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 125.9 (C_{Ar}), 62.7 (C_2), 60.6 (C_{11}), 34.9 (C_9), 34.7 (C_3), 32.0 (C_4), 14.4 (C_{12});

HRMS (ESI^+): calculated for $C_{13}H_{20}NO_2$ $[M+H]^+$ *m/z*: 222.1489, found: 222.1487;

IR (neat, cm^{-1}): 2980, 1739, 1663, 1203, 1028, 751, 701.

Ethyl 2-(methylamino)-4-(*p*-tolyl)butanoate (2.1.234)



The title compound was isolated in 41 % yield (19.0 mg) as a yellow oil.

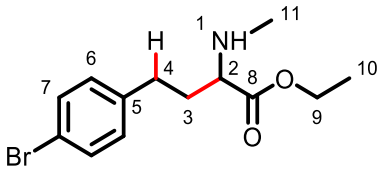
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.10 - 7.07 (m, 4H, ($H_{6/7}$), 4.20 (q, J = 6.5 Hz, 2H, H_{11}), 3.15 (t, J = 6.6 Hz, 1H, H_2), 2.70 - 2.61 (m, 2H, H_4), 2.38 (s, 3H, H_{13}), 2.31 (s, 3H, H_9), 1.98 - 1.91 (m, 1H, H_3), 1.90 - 1.83 (m, 1H, H_3), 1.54 (br s, 1H, H_1), 1.30 - 1.25 (m, 3H, H_{12});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 (C_{10}), 138.5 (C_{Ar}), 135.6 (C_{Ar}), 129.2 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 62.9 (C_2), 60.8 (C_{11}), 35.2 (C_{13}), 34.9 (C_3), 31.7 (C_4), 21.1 (C_9), 14.5 (C_{12});

HRMS (ESI$^+$): calculated for $[M+H]^+$ $C_{14}H_{22}NO_2^+$: 236.1645, found 236.1644;

IR (neat, cm^{-1}): 2980, 2933, 2860, 1731, 1516, 1180, 1037.

Ethyl 4-(4-bromophenyl)-2-(methylamino)butanoate (2.1.235)



The title compound was isolated in 45 % yield (27.0 mg) as a yellow oil.

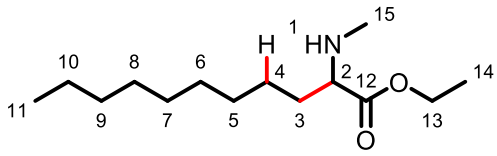
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.7 Hz, 2H, H_7), 7.06 (d, *J* = 8.3 Hz, 2H, H_6), 4.19 (q, *J* =7.2 Hz, 2H, H_9), 3.10 (t, *J* = 6.8 Hz, 1H, H_2), 2.70 - 2.61 (m, 2H, H_4), 2.37 (s, 3H, H_{11}), 1.97 - 1.89 (m, 1H, H_3), 1.88 - 1.80 (m, 1H, H_3), 1.29 (t, *J* = 7.2 Hz, 3H, H_{10});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.2 (C_8), 140.5 (C_5), 131.6 (2C, C_{Ar}), 130.4 (2C, C_{Ar}), 119.9 (C_{12}), 62.6 (C_2), 60.8 (C_9), 34.9 (C_{11}), 34.8 (C_5), 31.6 (C_4), 14.5 (C_{10});

HRMS (ESI$^+$): calculated for $C_{13}H_{19}{}^{79}BrNO_2$ $[M+H]^+$ *m/z*: 300.0594, found: 300.0591;

IR (neat, cm^{-1}): 2978, 2931, 2856, 2799, 1729, 1645, 1487, 1180, 1072, 940, 765.

Ethyl 2-(methylamino)undecanoate (2.1.237)



The title compound was isolated in 59 % yield (28.0 mg) as a yellow oil.

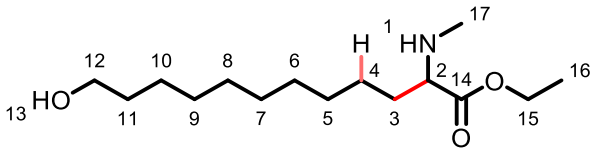
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (q, *J* = 7.2 Hz, 2H, H_{13}), 3.12 (t, *J* = 6.8 Hz, 1H, H_2), 2.37 (s, 3H, H_{15}), 1.66 - 1.53 (m, 2H, H_3), 1.37 - 1.21 (m, 17H, H_{Alk}), 0.87 (t, *J* = 7.0 Hz, 3H, H_{14});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6 (C_{12}), 63.5 (C_2), 60.6 (C_{13}), 34.9 (C_{15}), 33.6 (C_{Alk}), 32.0 (C_{Alk}), 30.0 (C_{Alk}), 29.6 (C_{Alk}), 29.5 (C_{Alk}), 22.8 (C_{Alk}), 14.5 (C_{14}), 14.2 (C_{11});

HRMS (ESI$^+$): calculated for $C_{14}H_{30}NO_2$ $[M+H]^+$ *m/z*: 244.2271, found: 244.2269;

IR (neat, cm^{-1}): 2924, 2855, 1733, 1608, 1370, 1339.

Ethyl 12-hydroxy-2-(methylamino)dodecanoate (2.1.238)



The title compound was isolated in 54 % yield (29.0 mg) as a yellow oil.

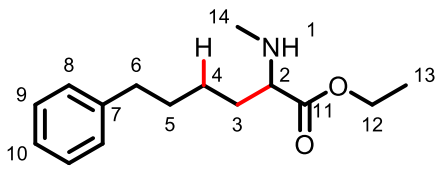
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (q, *J* = 6.9 Hz, 2H, H_{15}), 3.63 (t, *J* = 6.5 Hz, 2H, H_{12}), 3.12 (t, *J* = 6.7 Hz, 1H, H_2), 2.36 (s, 3H, H_{17}), 1.64 - 1.53 (m, 5H, H_{Alk}), 1.39 - 1.23 (m, 18H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6 (C_{14}), 63.5 (C_2), 63.2 (C_{15}), 60.6 (C_{12}), 34.9 (C_{Alk}), 33.6 (C_{Alk}), 32.9 (C_{17}), 29.7 (C_{Alk}), 29.6 (C_{Alk}), 29.5 (C_{Alk}), 29.4 (C_{Alk}), 25.9 (C_{Alk}), 25.8 (C_{Alk}), 14.5 (C_{16});

HRMS (ESI$^+$): calculated for $C_{15}H_{32}NO_3$ $[M+H]^+$ *m/z*: 274.2377, found 274.2375;

IR (neat, cm^{-1}): 2928, 2854, 1731, 1452, 1182, 1110.

Ethyl 2-(methylamino)-6-phenylhexanoate (2.1.236)



The title compound was isolated in 63 % yield (32.0 mg) as a yellow oil. Reaction was conducted at 23 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 - 7.26 (m, 1H, H_{Ar}), 7.25 - 7.24 (m, 2H, H_{Ar}), 7.21 - 7.14 (m, 2H, H_{Ar}), 4.18 (q, *J* = 7.1 Hz, 2H, H_{12}), 3.12 (t, *J* = 6.7 Hz, 1H, H_2), 2.60 (t, *J* =

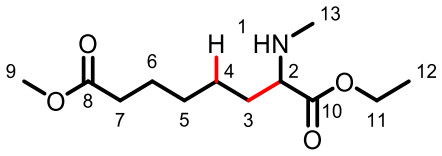
7.9 Hz, 2H, H_6), 2.36 (s, 3H, H_{14}), 1.70 - 1.58 (m, 4H, $H_{3/4}$), 1.46 - 1.34 (m, 2H, H_5), 1.26 (t, J = 7.1 Hz, 3H, H_{13});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 (C_{11}), 142.4 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 125.7 (C_{Ar}), 63.2 (C_2), 60.5 (C_{12}), 35.7 (C_6), 34.8 (C_{14}), 33.3 (C_{Alk}), 31.3 (C_{Alk}), 25.4 (C_{Alk}), 14.3 (C_{13});

HRMS (ESI$^+$): calculated for $[M+H]^+$ $C_{15}H_{24}NO_2$+: 250.1802, found 250.1800;

IR (neat, cm^{-1}): 2978, 1730, 1495, 1179, 1028, 749, 699.

1-Ethyl 8-methyl 2-(methylamino)octanedioate (2.1.241)



The title compound was isolated in 70 % yield (34.0 mg) as a yellow oil.

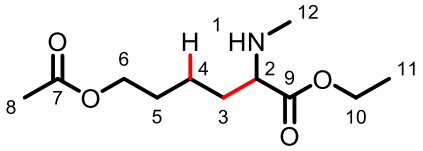
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.19 (q, J = 7.2 Hz, 2H, H_{11}), 3.66 (s, 3H, H_9), 3.11 (t, J = 6.8 Hz, 1H, H_2), 2.36 (s, 3H, H_{13}), 2.30 (t, J = 7.5 Hz, 2H, H_7), 1.67 - 1.54 (m, 4H, $H_{3/6}$), 1.43 - 1.31 (m, 4H, $H_{4/5}$), 1.28 (t, J = 7.2 Hz, 3H, H_{12});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5 (C_8), 174.3 (C_{10}), 63.4 (C_2), 60.7 (C_{11}), 51.6 (C_9), 34.9 (C_7), 34.1 (C_{13}), 33.3 (C_{Alk}), 29.1 (C_{Alk}), 25.6 (C_{Alk}), 24.9 (C_{Alk}), 14.5 (C_{12});

HRMS (ESI$^+$): calculated for $C_{12}H_{24}NO_4$ $[M+H]^+$ *m/z*: 246.1700, found 246.1697;

IR (neat, cm^{-1}): 2938, 2860, 1732, 1440, 1178, 1027.

Ethyl 6-acetoxy-2-(methylamino)hexanoate (2.1.242)



The title compound was isolated in 38 % yield (18.0 mg) as a yellow oil.

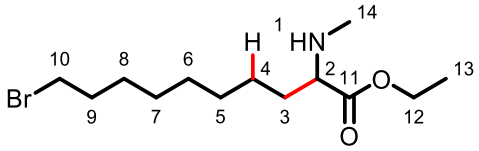
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (q, *J* = 7.2 Hz, 2H, H_{10}), 4.05 (t, *J* = 6.8 Hz, 2H, H_6), 3.12 (t, *J* = 6.6 Hz, 1H, H_2), 2.37 (s, 3H, H_{12}), 2.04 (s, 3H, H_8), 1.71 - 1.61 (m, 4H, $H_{3/5}$), 1.49 - 1.37 (m, 2H, H_4), 1.29 (t, *J* = 7.2 Hz, 3H, H_{11});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 (C_7), 171.3 (C_9), 64.4 (C_2), 63.3 (C_8), 60.7 (C_{10}), 34.9 (C_2), 33.1 (C_{12}), 28.6 (C_{Alk}), 22.5 (C_{Alk}), 21.1 (C_{Alk}), 14.5 (C_{11});

HRMS (ESI$^+$): calculated for $C_{11}H_{22}NO_4$ $[M+H]^+$ *m/z*: 232.1543, found: 232.1540;

IR (neat, cm^{-1}): 3454, 2985, 2945, 2880, 1734, 1275, 1259, 1135, 1102.

Ethyl 10-bromo-2-(methylamino)decanoate (2.1.239)



The title compound was isolated in 62 % yield (38.0 mg) as a yellow oil.

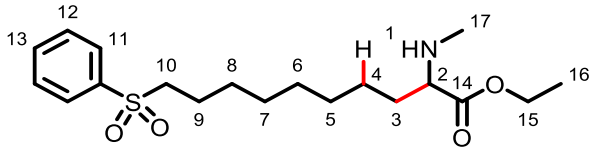
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (q, *J* = 6.7 Hz, 2H, H_{12}), 3.40 (t, *J* = 6.8 Hz, 2H, H_{10}), 3.12 (t, *J* = 6.6 Hz, 1H, H_2), 2.37 (s, 3H, H_{14}), 1.84 (p, *J* = 7.2 Hz, 2H, H_9), 1.66 - 1.56 (m, 2H, H_3), 1.57 - 1.50 (m, 2H, H_{Alk}), 1.41 - 1.28 (m, 12H, $H_{Alk/13}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6 (C_{11}), 63.5 (C_2), 60.6 (C_{12}), 34.9 (C_{10}), 34.1 (C_{14}), 33.5 (C_3), 32.9 (C_{Alk}), 29.5 (C_{Alk}), 29.4 (C_{Alk}), 28.8 (C_{Alk}), 28.3 (C_{Alk}), 25.9 (C_{Alk}), 14.5 (C_{13});

HRMS (ESI$^+$): calculated for $C_{13}H_{27}BrNO_2$ $[M+H]^+$ *m/z*: 308.1220, found: 308.1216;

IR (neat, cm^{-1}): 3419, 2927, 2854, 1737, 1464, 1371, 1213, 1158, 1021.

Ethyl 2-(methylamino)-10-(phenylsulfonyl)decanoate (2.1.245)



The title compound was isolated in 67 % yield (50.0 mg) as a yellow oil.

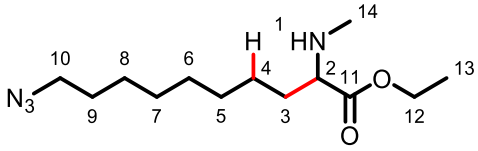
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.65 (d, *J* = 7.2 Hz, 1H, H_{Ar}), 7.61 - 7.49 (m, 2H, H_{Ar}), 4.19 (q, *J* = 6.9 Hz, 2H, H_{15}), 3.13 - 3.01 (m, 3H, $H_{2/10}$), 2.36 (s, 3H, H_{17}), 1.69 (dt, *J* = 7.4, 4.0 Hz, 2H, H_3), 1.63 - 1.48 (m, 4H, $H_{4/9}$), 1.39 - 1.18 (m, 12H, H_{Alk});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5 (C_{14}), 139.4 (C_{Ar}), 133.7 (C_{Ar}), 129.4 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 63.4 (C_2), 60.6 (C_{15}), 56.4 (C_{10}), 34.9 (C_{17}), 33.5 (C_{Alk}), 29.4 (C_{Alk}), 29.2 (C_{Alk}), 29.0 (C_{Alk}), 28.4 (C_{Alk}), 25.8 (C_{Alk}), 22.8 (C_{Alk}), 14.5 (C_{16});

HRMS (ESI+): calculated for $C_{19}H_{32}NO_4S$ $[M+H]^+$ *m/z*: 370.2047, found: 270.2044;

IR (neat, cm^{-1}): 2929, 2855, 1729, 1447, 1304, 1180, 1146, 1025, 749, 690.

Ethyl 10-azido-2-(methylamino)decanoate (2.1.247)



The title compound was isolated in 50 % yield (27.0 mg) as a yellow oil.

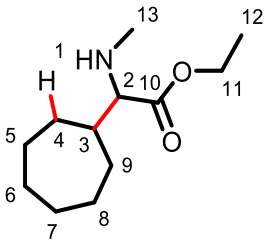
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (q, *J* = 6.9 Hz, 2H, H_{12}), 3.25 (t, *J* = 7.0 Hz, 2H, H_{10}), 3.12 (t, *J* = 6.6 Hz, 1H, H_2), 2.37 (s, 3H, H_{14}), 1.66 - 1.54 (m, 4H, $H_{3/9}$), 1.34 (dd, *J* = 13.2, 6.0 Hz, 4H, H_{Alk}), 1.32 - 1.23 (m, 10H, $H_{Alk/13}$);

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6 (C_{11}), 63.5 (C_2), 60.6 (C_{10}), 51.6 (C_{10}), 34.9 (C_{14}), 33.5 (C_{Alk}), 29.5 (C_{Alk}), 29.4 (C_{Alk}), 29.2 (C_{Alk}), 29.0 (C_{Alk}), 26.8 (C_{Alk}), 25.9 (C_{Alk}), 14.5 (C_{13});

HRMS (ESI$^+$): calculated for $C_{13}H_{27}N_4O_2$ $[M+H]^+$ *m/z*: 271.2129, found: 271.2128;

IR(neat, cm^{-1}): 2931, 2856, 2154, 2095, 1731, 1455, 1180, 1028.

Ethyl 2-cycloheptyl-2-(methylamino)acetate (2.1.244)



The title compound was isolated in 34 % yield (15.0 mg) as a yellow oil.

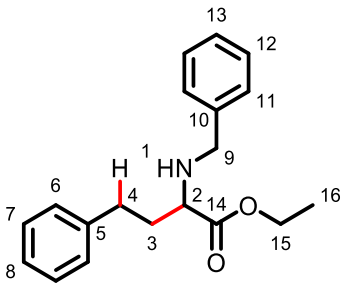
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.20 (m, 2H, H_{11}), 2.93 (d, *J* = 5.6 Hz, 1H, H_2), 2.35 (s, 3H, H_{13}), 1.76 - 1.73 (m, 2H, H_4), 1.68 - 1.65 (m, 3H, $H_{3/9}$), 1.57 - 1.54 (m, 4H, H_{Alk}), 1.48 - 1.44 (m, 2H, H_{Alk}), 1.39 - 1.32 (m, 3H, H_{Alk}), 1.29 (t, *J* = 7.2 Hz, 3H, H_{12});

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.2 (C_{10}), 69.5 (C_2), 60.5 (C_{11}), 43.0 (C_3), 35.5 (C_{13}), 31.5 (C_{Alk}), 30.2 (C_{Alk}), 28.6 (C_{Alk}), 28.1 (C_{Alk}), 27.0 (C_{Alk}), 26.9 (C_{Alk}), 14.6 (C_{12});

HRMS (ESI^+): calculated for $C_{12}H_{24}NO_2$ $[M+H]^+$ *m/z*: 214.1802, found: 214.1800;

IR (neat, cm^{-1}): 2922, 2855, 1729, 1453, 1178, 1105.

Ethyl 2-(benzylamino)-4-phenylbutanoate (2.1.249)



The title compound was isolated in 30 % yield (18.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 - 7.30 (m, 4H, H_{Ar}), 7.28 - 7.27 (m, 2H, H_{Ar}), 7.26 - 7.24 (m, 1H, H_{Ar}), 7.20 - 7.15 (m, 3H, H_{Ar}), 4.19 (qd, *J* = 7.2, 1.7 Hz, 2H, H_{15}), 3.83 (d, *J* = 12.9 Hz, 1H, H_9), 3.63 (d, *J* = 12.9 Hz, 1H, H_9), 3.27 (dd, *J* = 7.5, 5.8 Hz, 1H, H_2), 2.80 - 2.74 (m, 1H, H_4), 2.73 - 2.64 (m, 1H, H_4), 2.02 - 1.95 (m, 1H, H_3), 1.93 - 1.86 (m, 1H, H_3), 1.29 (t, *J* = 7.1 Hz, 3H, H_{16});

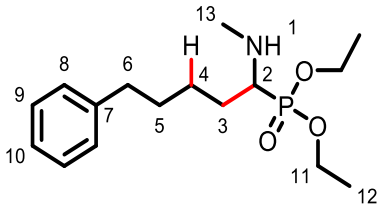
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5 (C_{14}), 141.7 (C_{Ar}), 140.1 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.5 (4C, C_{Ar}), 128.4 (2C, C_{Ar}), 127.2, (C_{Ar}), 126.1, (C_{Ar}), 60.8 (C_2), 60.4 (C_{15}), 52.3 (C_9), 35.3 (C_4), 32.2 (C_3), 14.5 (C_{16});

HRMS (ESI$^+$): calculated for $C_{19}H_{24}NO_2$ $[M+H]^+$ *m/z*: 298.1802, found: 298.1799;

IR (neat, cm^{-1}): 3027, 2932, 2854, 1729, 1454, 1132, 1027, 749, 698.

3.5.2.3 Characterisation of α – Aminophosphonates following general procedure **2.6.** for hydroaminoalkylation using aminal D (**2.1.255**)

Diethyl (1-(methylamino)-3-phenylpropyl)phosphonate (2.1.256)



The title compound was isolated in 52 % yield (32.0 mg) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 - 7.23 (m, 2H, H_9), 7.21 - 7.13 (m, 3H, $H_{8/10}$), 4.18 - 4.08 (m, 4H, H_{11}), 2.75 - 2.68 (m, 1H, H_2), 2.67 - 2.58 (m, 2H, H_6), 2.51 (s, 3H, H_{13}), 1.86 - 1.75 (m, 1H, H_1), 1.69 - 1.54 (m, 4H, $H_{3/5}$), 1.50 - 1.38 (m, 2H, H_4), 1.32 (td, J = 7.2, $^{4}J_{H,P}$ = 1.1 Hz, 6H, H_{12});

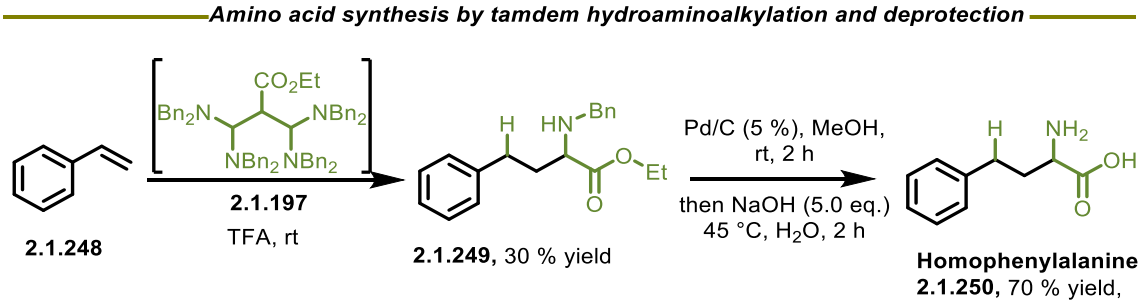
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.5 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 125.7 (C_{Ar}), 61.9 (d, $^{2}J_{C,P}$ = 7.2 Hz, C_{11}), 61.8 (d, $^{2}J_{C,P}$ = 7.1 Hz, C_{11}), 56.8 (d, $^{1}J_{C,P}$ = 148.4 Hz, C_2), 35.8 (C_6), 35.3 (d, $^{3}J_{C,P}$ = 6.9 Hz, (C_{13}), 31.4 (C_5), 29.3 (d, $^{4}J_{C,P}$ = 1.6 Hz, (C_4), 25.9 (d, $^{3}J_{C,P}$ = 10.6 Hz, (C_3), 16.5 (dd, $^{3}J_{C,P}$ = 5.6, 1.5 Hz, 2C, (C_{12});

^{31}P NMR (243 MHz, $CDCl_3$): δ 28.6;

HRMS (ESI^+): calculated for $C_{16}H_{29}NO_3P$ $[M+H]^+$ *m/z*: 314.1880, found: 314.1879;

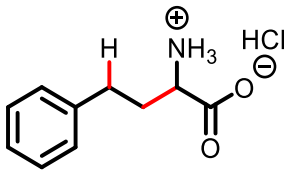
IR (neat, cm^{-1}): 3463, 2983, 2933, 1676, 1602, 1152, 1024, 749.

3.5.2.4 Procedure and characterisation of the direct synthesis of Homophenylalanine (**2.1.250**) from corresponding alkene



Compound ethyl 2-(benzylamino)-4-phenylbutanoate **(2.1.249)** (1.0 eq., 0.07 mmol) was dissolved in absolute MeOH (2.0 mL, 0.035M). After the addition of 5 % Pd/C (2 mg), the flask was evacuated and flushed with hydrogen gas (three times). The hydrogenation was carried out at 25 °C for 2 h. After pooling two identical batches, the catalyst was filtered off and the MeOH was removed at reduced pressure without purification to next step. The crude mixture was dissolved in MeOH (0.7 mL) and aqueous 1.0 M NaOH (5.0 eq., 5.0 mL) was added. The solution was heated at 45 °C for 3 h until complete consumption of starting material (checked by TLC). Then aqueous 2.0 M HCl (~1 mL) was added to this solution until pH was below 7, the resulting mixture was cooled to 0 °C after which a white precipitate formed. The precipitate was collected by vacuum filtration to afford the title compound as a white solid (10.5 mg after drying).

Hydrochloride salt of 2-amino-4-phenylbutanoate

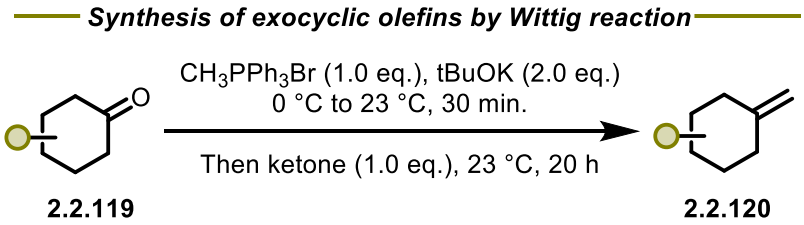


The title compound was isolated in 70 % yield (10.5 mg) as a yellow solid.

3.6 Experimental Section Chapter 2.2

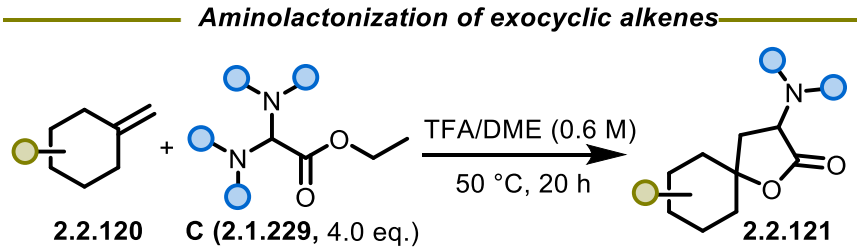
3.6.1 Procedure for the synthesis of starting materials

3.6.1.1 General procedure **2.7** – Procedure for the formation of the exocyclic alkenes



For the preparation of the desired alkenes a standard protocol was used (ref wittig). A solution of methyltriphenylphosphonium bromide (1.0 eq., 5.0 mmol) in Et_2O was cooled to 0° C under argon atmosphere. TBuOK (2.0 eq., 10.0 mmol) was added to the solution at the given temperature and stirred for 30 min, with a noticible color change. After that time a solution of the alkene was added (1.0 eq., 5 mmol) in dry Et_2O at 0 °C and the reaction was left to stir at 23 °C for 14 h. The reaction was followed by TLC, and heated if no conversion was observed. After completion, the mixture was quenched using saturated NH_4Cl and extracted three times with Et_2O (20.0 mL). The pooled organic layers were dried over Mg_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane) to obtain the volatile alkenes.

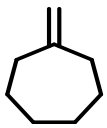
3.6.1.2 General procedure **2.8** for the aminolactonisation of exocyclic alkenes



To a flame dried Schlenk flask charged with the aminal (**C, 2.1.229**, 4.0 eq., 0.8 mmol,) was added, at -10 °C (using a cryostat - isopropanol), TFA (0.33 mL, 0.6 M). After 5 min, the corresponding alkene (**2.2.120**, 1.0 eq., 0.2 mmol) was added in a solution with dry DME (0.33 mL), to the solution. The reaction was heated to 50 °C and vigorously stirred (unless otherwise stated) for 20 h, after which it was cooled to 0 °C. Then, aqueous NaOH (1.0 M) was added until a pH > 7 was reached. The resulting biphasic mixture was separated and the aqueous phase extracted with DCM (3 x 50 mL/mmol). The combined organic phases were then dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography on silica gel with DCM/DMA system to afford the analytically pure desired product (**2.2.121**).

3.6.1.3 Characterisation of the products of aminolactonization of exocyclic alkenes

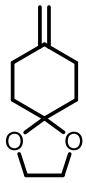
Methylenecycloheptane (2.2.122) used in the synthesis of **(2.2.73)**



2.2.122

The title compound was prepared using general procedure **2.7** for the synthesis of exocyclic alkenes. After flash chromatography, the compound was isolated in 72 % yield as a colorless oil. All spectral data was found to be in accordance with the literature.[602]

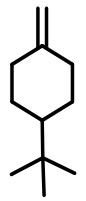
8-Methylene-1,4-dioxaspiro[4.5]decane (2.2.123) used in the synthesis of **(2.2.74)**



2.2.123

The title compound was prepared using general procedure **2.7** for the synthesis of exocyclic alkenes. After flash chromatography, the compound was isolated in 65 % yield as a colorless oil. All spectral data was found to be in accordance with the literature.[603]

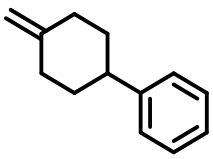
1-(*tert*-Butyl)-4-methylenecyclohexane (2.2.124) used in the synthesis of **(2.2.80)**



2.2.124

The title compound was prepared using general procedure **2.7** for the synthesis of exocyclic alkenes. After flash chromatography, the compound was isolated in 90 % yield as a colorless oil. All spectral data was found to be in accordance with the literature.[604]

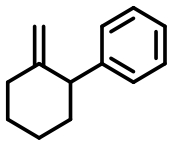
(4-Methylenecyclohexyl)benzene (2.2.125) used in the synthesis of **(2.2.81)**



2.2.125

The title compound was prepared using general procedure **2.7** for the synthesis of exocyclic alkenes. After flash chromatography, the compound was isolated in 75 % yield as a colorless oil. All spectral data was found to be in accordance with the literature.[604]

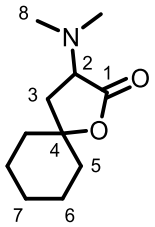
(2-methylenecyclohexyl)benzene (2.2.126) used in the synthesis of **(2.2.82)**



2.2.126

The title compound was prepared using general procedure **2.7** for the synthesis of exocyclic alkenes. After flash chromatography, the compound was isolated in 32 % yield as a colorless oil. All spectral data was found to be in accordance with the literature.

3-(Dimethylamino)-1-oxaspiro[4.5]decan-2-one (2.2.72)



The title compound was prepared using general procedure **2.8** for the aminolactonisation of exocyclic alkenes. After flash chromatography, the compound was isolated in 82 % yield (30.1 mg) as a colorless oil.

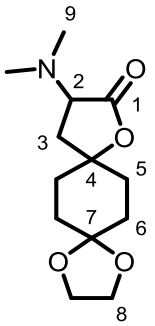
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.70 (t, *J* = 10.1 Hz, 1H, H_2), 2.40 (s, 6H, H_8), 2.23 - 2.16 (m, 1H, H_3), 1.89 (t, *J* = 12.0 Hz, 1H, H_3), 1.77 - 1.63 (m, 4H, H_5), 1.56 - 1.49 (m, 4H, H_6), 1.42 - 1.37 (m, 1H, H_7), 1.30 - 1.25 (m, 1H, H_7);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8 (C_1), 82.9 (C_4), 63.7 (C_2), 41.8 (C2, C_8), 38.5 (C_5), 36.7 (C_5), 34.4 (C_3), 25.1 (C_6), 22.7 (C_6), 22.6 (C_7);

HRMS (ESI+): calculated for $C_{11}H_{19}O_2N_2$ $[M+H]^+$ 198.1494; found 198.1496;

IR (neat, cm^{-1}): 2939, 2870, 1456, 1260, 1152, 1103, 1033, 754.

11-(Dimethylamino)-1,4,9-trioxadispiro[4.2.48.25]tetradecan-10-one (2.2.74)



The title compound was prepared using general procedure **2.8** for the aminolactonization of exocyclic alkenes. After flash chromatography, the compound was isolated in 72 % yield (35.0 mg) as a colorless oil.

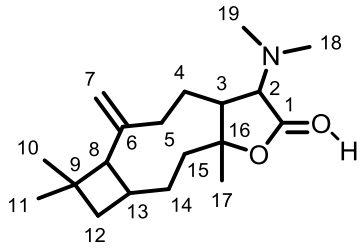
^{1}H NMR: (600 MHz, $CDCl_3$): δ 3.98 - 3.90 (m, 4H, H_8), 3.74 - 3.67 (m, 1H, H_2), 2.41 (s, 6H, H_9), 2.21 - 2.13 (m, 1H, H_3), 2.01 - 1.97 (m, 1H, H_3), 1.97 - 1.92 (m, 1H, H_5), 1.92 - 1.85 (m, 4H, H_6), 1.83 - 1.74 (m, 1H, H_5), 1.68 - 1.63 (m, 2H, H_5);

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.6 (C_1), 107.8 (C_7), 81.4 (C_4), 64.6 (C_2), 64.5 (C_8), 63.7 (C_8), 41.9 (C2, C_9), 36.0 (C_6), 34.4 (C_6), 34.3 (C_3), 31.2 (C_5), 30.9 (C_5).

HRMS (ESI^+): calculated for $C_{13}H_{21}O_4N$ $[M+Na]^+$ *m/z*: 278.1368, found 278.1361

IR (neat, cm^{-1}): 2938, 2876, 2832, 2783, 1763, 1447, 1144.

3-(Dimethylamino)-7,7,10a-trimethyl-6-methylenedodecahydro-2*H* cyclobuta[6,7]cyclonona[1,2-b]furan-2-one (2.2.77)



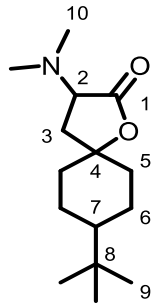
The title compound was prepared using general procedure **2.8** for the aminolactonization of exocyclic alkenes. After flash chromatography, the compound was isolated in 62 % yield (31.9 mg) as a colorless oil.

^{1}H NMR: (600 MHz, $CDCl_3$): δ 5.06 (s, 1H, H_{7a}), 4.96 (s, 1H, H_{7a}), 3.33 (d, *J* = 12.2 Hz, 1H, H_2), 2.50 (s, 6H, $H_{18/19}$), 2.49 - 2.39 (m, 2H), 2.39 - 2.30 (m, 1H), 2.27 - 2.17 (m, 1H, H_3), 2.14 - 2.04 (m, 1H), 1.79 (t+m, *J* = 10.5 Hz, 2H, H_{12a}+H_{Alk}), 1.71 - 1.55 (m, 3H, H_{12b}+2H_{Alk}), 1.38 - 1.29 (m, 1H, H_{Alk}), 1.28 (s, 3H, H_{17}), 1.01 (s, 3H, H_{10}), 0.99 (s, 3H, H_{11}), 2H_{Alk};

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0 (HMBC, C_1), 152.5 (HMBC, C_6), 111.8 (C_7), 85.7 (C_{16}), 70.8 (HSQC, C_2), , 41.9 (C_{13}), 41.60 (2C, C_{18}+C_{19}), 40.8 (C_3), 36.6 (C_{12}), 36.0 (HSQC, C_4/C_5/C_{14}/C_{15}), 34.3 (HMBC, C_9), 30.1 (C_{10}), 28.1 (HSQC, C_4/C_5/C_{14}/C_{15}), 22.7 (HSQC, C_4/C_5/C_{14}/C_{15}), 22.2 (C_{11}), 21.0 (HSQC, C_{17}), C_4,C_5,C_8,C_{14},C_{15} not assignable/observed with certainty;

HRMS (ESI^+): calculated for $C_{19}H_{31}O_2N$ $[M+H]^+$ *m/z*: 306.2433, found: 306.2422

8-(*tert*-Butyl)-3-(dimethylamino)-1-oxaspiro[4.5]decan-2-one (2.2.80)



The title compound was prepared using general procedure **2.8** for the aminolactonisation of exocyclic alkenes. After flash chromatography, the compound was isolated in 70 % yield (31.0 mg), 1:5 d.r. as an off-white solid.

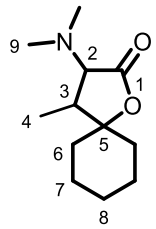
^{1}H NMR: (600 MHz, $CDCl_3$): δ 3.76 - 3.69 (m, 1H, H_2), 2.43 (s, 6H, H_{10}), 2.35 (dt, *J* = 21.0, 10.5 Hz, 1H, H_3), 1.87 - 1.75 (m, 4H, $H_{3/5}$), 1.69 - 1.60 (m, 1H, H_7), 1.19 - 1.03 (m, 4H, H_6), 0.87 (s, 9H, H_9).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.2 (C1), 83.8 (C_4), 63.5 (C_2), 46.7 (C_7), 41.5 (2C, C_{10}), 38.9 (C_5), 35.8 (C_5), 31.5 (C_3), 27.5 (3C, C_9), 24.6 (C_8), 23.6 (C_6), 20.6 (C_6).

HRMS (ESI$^+$): calculated for $C_{15}H_{27}O_2N$ $[M+H]^+$ *m/z*: 254.2120, found 254.2113;

IR (neat, cm^{-1}): 2944, 2865, 2783, 1766, 1457, 1211, 1050.

3-(Dimethylamino)-4-methyl-1-oxaspiro[4.5]decan-2-one (2.2.83)



The title compound was prepared using general procedure **2.8** for the aminolactonisation of exocyclic alkenes. After flash chromatography, the compound was isolated in 65 % yield (24.2 mg) in 1:4 d.r. as a off-white oil.

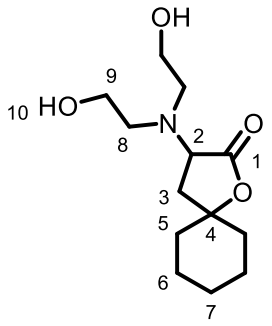
^{1}H NMR: (600 MHz, $CDCl_3$): δ 3.27 (d, *J* = 12.0 Hz, 1H, H_2), 2.50 (s, 6H, H_9), 2.16 - 2.05 (m, 1H, H_1), 1.76 - 1.68 (m, 2H, H_6), 1.67 - 1.54 (m, 6H, $H_{6/7}$), 1.50 - 1.39 (m, 1H, H_3), 1.36 - 1.13 (m, 2H, H_8), 1.13 - 1.06 (m, 3H, H_4).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4 (C_1), 84.9 (C_2), 69.4 (C_5), 42.8 (C_3), 41.6 (2C), 36.4 (C_6), 31.4 (C_6), 25.5 (C_7), 22.3 (C_7), 21.4 (C_8), 13.3 (C_4).

HRMS (ESI$^+$): calculated for $C_{12}H_{21}O_2N$ $[M+H]^+$ *m/z*: 212.1651, found: 212.1645

IR (neat, cm^{-1}): 2964, 2931, 2827, 1736, 1468, 877.

3-(bis(2-hydroxyethyl)amino)-1-oxaspiro[4.5]decan-2-one (2.2.99)



The title compound was prepared using general procedure **2.8** for the aminolactonisation of exocyclic alkenes. After flash chromatography, the compound was isolated in 82 % yield (39.6 mg) as an off-white oil.

^{1}H NMR: (600 MHz, $CDCl_3$): δ 4.06 (dd, *J* = 11.5, 9.2 Hz, 1H, H_2), 3.66 - 3.57 (m, 4H, H_9), 3.52 – 3.29 (m, 2H, H_{10}), 2.92 - 2.84 (m, 2H, H_8), 2.79 - 2.68 (m, 2H, H_8), 2.34 (dd, *J* = 12.8, 9.2 Hz, 1H, H_3), 1.89 (t, *J* = 12.2 Hz, 1H, H_3), 1.82 - 1.60 (m, 4H, H_5), 1.58 - 1.44 (m, 4H, H_6), 1.43 - 1.35 (m, 1H, H_7), 1.33 - 1.19 (m, 1H, H_7);

^{13}C NMR (151 MHz, $CDCl_3$): δ 177.0 (C_1), 83.9 (C_4), 61.7 (C_2), 59.8 (2C, C_9), 53.7 (2C, C_8), 38.6 (C_5), 36.5 (C_5), 35.8 (C_3), 25.0 (C_6), 22.7 (C_6), 22.5 (C_7);

HRMS (ESI$^+$): calculated for $C_{13}H_{23}O_4N$ $[M+H]^+$ *m/z*: 258.1705, found: 258.1701;

IR (neat, cm^{-1}): 3403 (Bs), 2933, 2859, 1750, 1206, 1044

4 References

1. Hoffmann, R. W. H. *Classical Methods in Structure Elucidation of Natural Products*. (Wiley-VCH Verlag GmbH & Co. KGaA, 2018).
2. Sicker, D., Zeller, K.-P., Siehl, H.-U. & Berger, S. *Natural Products Isolation, Structure Elucidation, History*. (Wiley-VCH Verlag GmbH & Co. KGaA, 2018).
3. Book Review: Qualitative Chemical Analysis, A system of Instruction. *J. Educ.* **51**, 139–139 (1990).
4. Pelletier, P. J. and C. J. B. isolation of 'veratrine'. *Ann. Chim. Phys.,* **14**, 69 (1820).
5. Graening, T. & Schmalz, H.-G. Total Syntheses of Colchicine in Comparison: A Journey through 50 Years of Synthetic Organic Chemistry. *Angew. Chem., Int. Ed.* **43**, 3230–3256 (2004).
6. Graening, T., Friedrichsen, W., Lex, J. & Schmalz, H.-G. Facile Construction of the Colchicine Skeleton by a Rhodium-Catalyzed Cyclization/Cycloaddition Cascade. *Angew. Chem., Int. Ed.* **41**, 1524–1526 (2002).
7. Chen, B. *et al.* Enantioselective total synthesis of (−)-colchicine, (+)-demecolcinone and metacolchicine: determination of the absolute configurations of the latter two alkaloids. *Chem. Sci.* **8**, 4961–4966 (2017).
8. B. Woodward. The Harvey Lecture Series. **59**, 31 (1963).
9. S. Zeisel. über Colchicin and Colchicein. *Monatsh. Chem.,* **4**, 162–164 (1883).
10. S. Zeisel. über das Colchicin. *Monatsh. Chem.,* **7**, 557–596 (1886).
11. Johanny, G., Z. S. Zur Kenntniss des Colchicins. *Monatsh. Chem.,* **9**, 865–881 (1888).
12. Zeisel, S. über ein Verfahren zum quantitativen Nachweise von Methoxyl. *Monatsh. Chem.,* **6**, 989–997 (1885).
13. Lange, R. G. Cleavage of Alkyl o-Hydroxyphenyl Ethers. *J. Org. Chem.* **27**, 2037–2039 (1962).
14. Soloway, S. & Wilen, S. H. Improved Ferric Chloride Test for Phenols. *Anal Chem* **24**, 979–983 (1952).
15. Windaus, A. Untersuchungen über die Konstitution des Colchicins. *Justus Liebigs Ann. Chem.* **439**, 59–75 (1924).
16. von Hofmann, Aug. Wilk. Beiträge zur Kenntniss der flüchtigen organischen Basen. *Annalen der Chemie und Pharmacie* **78**, 253–286 (1851).
17. August Wilhelm Von Hofmann. XIV. Researches into the molecular constitution of the organic bases. *Philos. Trans. R. Soc. Lond.* **141**, 357–398 (1851).
18. Mabey, W. & Mill, T. Critical review of hydrolysis of organic compounds in water under environmental conditions. *J. Phys. Chem. Ref. Data* **7**, 383–415 (1978).
19. Jonathan Clayden, Nick Greeves, and S. W. *Organic chemistry*. (Oxford University Press, 2001).
20. T. Saito, T. Yamaji, K. Hayamizu, M. Yanagisawa, O. Yamamoto, S. Matsuyama, S. Kinugasa, K. Tanabe, T. Tamura, ". can be found in https://sdbs.db.aist.go.jp. Preprint at (2022).
21. Wiberg, K. B. The Interaction of Carbonyl Groups with Substituents. *Acc. Chem. Res.* **32**, 922–929 (1999).
22. Glover, S. A. & Rosser, A. A. Reliable Determination of Amidicity in Acyclic Amides and Lactams. *J. Org. Chem.* **77**, 5492–5502 (2012).

23. Wiberg, K. B. & Breneman, C. M. Resonance interactions in acyclic systems. 3. Formamide internal rotation revisited. Charge and energy redistribution along the C-N bond rotational pathway. *J. Am. Chem. Soc.* **114**, 831–840 (1992).

24. Glendening, E. D. & Weinhold, F. Pauling's Conceptions of Hybridization and Resonance in Modern Quantum Chemistry. *Molecules* **26**, 4110 (2021).

25. Pauling, L., Corey, R. B. & Branson, H. R. The structure of proteins: Two hydrogen-bonded helical configurations of the polypeptide chain. *Proc. Natl. Acad. Sci. U.S.A* **37**, 205–211 (1951).

26. Ghose, A. K., Viswanadhan, V. N. & Wendoloski, J. J. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. *J. Comb. Chem.* **1**, 55–68 (1999).

27. Lopes, A. *et al.* Characterization of Amide Bond Conformers for a Novel Heterocyclic Template of N-acylhydrazone Derivatives. *Molecules* **18**, 11683–11704 (2013).

28. Liu, C. & Szostak, M. Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N−C Amide Bond Activation. *Chem. Eur. J.* **23**, 7157–7173 (2017).

29. Wasserman, H. H. Synthesis with a twist. *Nature* **441**, 699–700 (2006).

30. Liu, C. & Szostak, M. Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N−C Amide Bond Activation. *Chem. Eur. J.* **23**, 7157–7173 (2017).

31. Jones, D. S. & Jones, J. H. Sir Edward Penley Abraham CBE. 10 June 1913 — 9 May 1999. *Biogr. mem. Fellows R. Soc.* **60**, 5–22 (2014).

32. Abraham, E. P. Sir Robert Robinson and the early history of penicillin. *Nat. Prod. Rep.* **4**, 41 (1987).

33. Woodward, R. B. & Doering, W. E. The total synthesis of quinine. *J. Am. Chem. Soc.* **66**, 849–849 (1944).

34. Aube, J. & Milligan, G. L. Intramolecular Schmidt reaction of alkyl azides. *J. Am. Chem. Soc.* **113**, 8965–8966 (1991).

35. Wolff, H. The Schmidt Reaction. in *Organic Reactions* 307–336 (John Wiley & Sons, Inc., 2011).

36. Lukeš, R. Sur une nouvelle application de la règle de bredt. *Collect. Czech. Chem. Commun.* **10**, 148–152 (1938).

37. Kirby, A. J., Komarov, I. v., Wothers, P. D. & Feeder, N. The Most Twisted Amide: Structure and Reactions. *Angew. Chem., Int. Ed.* **37**, 785–786 (1998).

38. Woodward, R. B. Penems and related substances. *Philos. Trans. R. Soc. Lond.* **289**, 239–250 (1980).

39. Wang, Q., Su, Y., Li, L. & Huang, H. Transition-metal catalysed C–N bond activation. *Chem. Soc. Rev.* **45**, 1257–1272 (2016).

40. Ghose, A. K., Viswanadhan, V. N. & Wendoloski, J. J. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. *J. Comb. Chem.* **1**, 55–68 (1999).

41. Dander, J. E. & Garg, N. K. Breaking Amides using Nickel Catalysis. *ACS Catal* **7**, 1413–1423 (2017).

42. Wallach, O. Ueber die Einwirkung von Phosphorpentachlorid auf Säureamide. *Justus Liebigs Ann. Chem.* **184**, 1–127 (1877).

43. Fujita, M., Fukuzumi, S. & Otera, J. Lewis acid vs. Brønsted acid as catalysts in solution. The quantitative comparison of reactivities of carbonyl compounds in the triethylsilyl perchlorate- and perchloric acid-catalyzed hydrosilylation in acetonitrile. *J. Mol. Catal.* **85**, 143–148 (1993).

44. Brönsted, J. N. Einige Bemerkungen über den Begriff der Säuren und Basen. *Recl. Trav. Chim. Pays-Bas* **42**, 718–728 (1923).

45. Wallach, O. Zur Kenntniss der Terpene und ätherischen Oele. *Justus Liebigs Ann. Chem.* **238**, 78–89 (1887).

46. Speziale, A. J. & Smith, L. R. The Reaction of Oxalyl Chloride with Amides. II. Oxazolidinediones and Acyl Isocyanates. *J. Org. Chem.* **28**, 1805–1811 (1963).

47. Bischler, Aug. & Napieralski, B. Zur Kenntniss einer neuen Isochinolinsynthese. *Ber. Dtsch. Chem. Ges.* **26**, 1903–1908 (1893).

48. Zerong Wang. Pictet-Gams Synthesis. in *Comprehensive Organic Name Reactions and Reagents* (John Wiley & Sons, Inc., 2010).

49. Mallegol, T., Gmouh, S., Meziane, M. A., Blanchard-Desce, M. & Mongin, O. Practical and Efficient Synthesis of Tris(4-formylphenyl)amine, a Key Building Block in Materials Chemistry. *Synthesis (Stuttg)* **2005**, 1771–1774 (2005).

50. Vilsmeier, A. & Haack, A. Über die Einwirkung von Halogenphosphor auf Alkyl-formanilide. Eine neue Methode zur Darstellung sekundärer und tertiärer p -Alkylamino-benzaldehyde. *Ber. Dtsch. Chem. Ges.* **60**, 119–122 (1927).

51. Ansell, M. F. Preparation of acyl halides. in *Acyl Halides (1972)* 35–68 (John Wiley & Sons, Ltd.).

52. Speziale, A. J. & Smith, L. R. Reaction of Phosphorus Compounds. IV. Haloenamines and Imidoyl Chlorides from Reaction of Phosphines with Haloamides. *J. Am. Chem. Soc.* **84**, 1868–1876 (1962).

53. Buyle, R. & Viehe, H. G. α-Chloro-enamines—III. *Tetrahedron* **25**, 3447–3451 (1969).

54. Staudinger, H. *Die Ketene*. (Ferdinand Enke, Stuttgart, 1912).

55. Ghosez, L., Haveaux, B. & Viehe, H. G. Alkyl and Arylα-Chloro Enamines. *Angew. Chem., Int. Ed.* **8**, 454–455 (1969).

56. Hall, H. K., Smith, C. D. & Plorde, D. E. Cycloaddition of ethylene to acrylonitrile. *J. Org. Chem.* **38**, 2084–2087 (1973).

57. Woodward, R. B. & Hoffmann, R. The Conservation of Orbital Symmetry. *Angew. Chem., Int. Ed. Engl.* **8**, 781–853 (1969).

58. Woodward, R. B. & Hoffmann, R. Stereochemistry of Electrocyclic Reactions. *J. Am. Chem. Soc.* **87**, 395–397 (1965).

59. Seddon, K.R. Ryan, C. *Phosgene: And Related Carbonyl Halides*. (Elsevier Science, 1996).

60. Haveaux, B. Dekoker, A. Rens, A. M. Sidani, R. Toye, J. Ghosez, L. a-chloro enamines, reactive intermediates for synthesis: 1-chloro-n,n,2-trimethylpropenylamine. *Org. Synth.* **59**, 26 (1979).

61. Falmagne, J.-B., Escudero, J., Taleb-Sahraoui, S. & Ghosez, L. Cyclobutanone and Cyclobutenone Derivatives by Reaction of Tertiary Amides with Alkenes or Alkynes. *Angew. Chem., Int. Ed. Engl.* **20**, 879–880 (1981).

62. Charette, A. B. & Grenon, M. Spectroscopic studies of the electrophilic activation of amides with triflic anhydride and pyridine. *Can. J. Chem.* **79**, 1694–1703 (2001).

63. Medley, J. W. & Movassaghi, M. Direct Dehydrative N -Pyridinylation of Amides. *J. Org. Chem.* **74**, 1341–1344 (2009).

64. Charette, A. B., Grenon, M., Lemire, A., Pourashraf, M. & Martel, J. Practical and Highly Regio- and Stereoselective Synthesis of 2-Substituted Dihydropyridines and Piperidines: Application to the Synthesis of (−)-Coniine. *J. Am. Chem. Soc.* **123**, 11829–11830 (2001).

65. Charette, A. B., Mathieu, S. & Martel, J. Electrophilic Activation of Lactams with Tf 2 O and Pyridine: Expedient Synthesis of (±)-Tetraponerine T4. *Org. Lett.* **7**, 5401–5404 (2005).

66. Deng, H.-Q. *et al.* A versatile two-step method for the reductive alkylation and formal [4 + 2] annulation of secondary lactams: step economical syntheses of the ant venom alkaloids (2R,5S)-2-butyl-5-propylpyrrolidine and (+)-monomorine I. *Org. Chem. Front.* **1**, 258 (2014).

67. Xiao, K.-J., Luo, J.-M., Xia, X.-E., Wang, Y. & Huang, P.-Q. General One-Pot Reductive gem -Bis-Alkylation of Tertiary Lactams/Amides: Rapid Construction of 1-Azaspirocycles and Formal Total Synthesis of (±)-Cephalotaxine. *Chem. Eur. J.* **19**, 13075–13086 (2013).

68. Xiao, K.-J., Wang, Y., Ye, K.-Y. & Huang, P.-Q. Versatile One-Pot Reductive Alkylation of Lactams/Amides via Amide Activation: Application to the Concise Syntheses of Bioactive Alkaloids (±)-Bgugaine, (±)-Coniine, (+)-Preussin, and (−)-Cassine. *Chem. Eur. J.* **16**, 12792–12796 (2010).

69. Huo, H.-H., Xia, X.-E., Zhang, H.-K. & Huang, P.-Q. Enantioselective Total Syntheses of (−)-FR901483 and (+)-8- epi -FR901483. *J. Org. Chem.* **78**, 455–465 (2013).

70. Overman, L. E. & Wolfe, J. P. New Cationic Olefin Cyclization−Pinacol Reactions. Ring-Expanding Cyclopentane Annulations That Directly Install Useful Functionality in the Cyclopentane Ring. *J. Org. Chem.* **67**, 6421–6429 (2002).

71. Berson, J. A. What Is a Discovery? Carbon Skeletal Rearrangements as Counter-Examples to the Rule of Minimal Structural Change. *Angew. Chem., Int. Ed.* **41**, 4655–4660 (2002).

72. Madelaine, C., Valerio, V. & Maulide, N. Unexpected Electrophilic Rearrangements of Amides: A Stereoselective Entry to Challenging Substituted Lactones. *Angew. Chem., Int. Ed.* **49**, 1583–1586 (2010).

73. Valerio, V., Madelaine, C. & Maulide, N. Steering Reaction Pathways: From Benzyl Claisen Rearrangements to Powerful Ionic Shifts. *Chem. Eur. J.* **17**, 4742–4745 (2011).

74. Thomas, E. W. The Conversion of Secondary Amides to Tetrazoles with Trifluoromethanesulfonic Anhydride and Sodium Azide. *Synthesis (Stuttg)* **1993**, 767–768 (1993).

75. Tona, V. *et al.* Direct Regioselective Synthesis of Tetrazolium Salts by Activation of Secondary Amides under Mild Conditions. *Org. Lett.* **19**, 2662–2665 (2017).

76. da Costa, R., Gillard, M., Falmagne, J. B. & Ghosez, L. a,b, Dehydrogenation of carboxamides. *J. Am. Chem. Soc.* **101**, 4381–4383 (1979).

77. Tona, V. *et al.* Direct Regioselective Synthesis of Tetrazolium Salts by Activation of Secondary Amides under Mild Conditions. *Org. Lett.* **19**, 2662–2665 (2017).

78. Sandrinelli, F., Perrio, S. & Beslin, P. A New Reaction of 2-(Phenylsulfonyl)-3-phenyloxaziridine (Davis Reagent): Oxidation of Thiolates to Sulfinates. Application to the Synthesis of Sulfones. *Org. Lett.* **1**, 1177–1180 (1999).

79. Davis, F. A., Vishwakarma, L. C., Billmers, J. G. & Finn, J. Synthesis of a-hydroxycarbonyl compounds (acyloins): direct oxidation of enolates using 2-sulfonyloxaziridines. *J. Org. Chem.* **49**, 3241–3243 (1984).

80. Davis, F. A. & Sheppard, A. C. Oxidation of silyl enol ethers using 2-sulfonyloxaziridines. Synthesis of a-siloxy epoxides and a-hydroxy carbonyl compounds. *J. Org. Chem.* **52**, 954–955 (1987).

81. Armstrong, A., Edmonds, I. D., Swarbrick, M. E. & Treweeke, N. R. Electrophilic amination of enolates with oxaziridines: effects of oxaziridine structure and reaction conditions. *Tetrahedron* **61**, 8423–8442 (2005).

82. de la Torre, A., Tona, V. & Maulide, N. Reversing Polarity: Carbonyl α-Aminations with Nitrogen Nucleophiles. *Angew. Chem., Int. Ed.* **56**, 12416–12423 (2017).

83. Pramanik, S., Rej, S., Kando, S., Tsurugi, H. & Mashima, K. Organosilicon Reducing Reagents for Stereoselective Formations of Silyl Enol Ethers from α-Halo Carbonyl Compounds. *J. Org. Chem.* **83**, 2409–2417 (2018).

84. Rubottom, G. M., Vazquez, M. A. & Pelegrina, D. R. Peracid oxidation of trimethylsilyl enol ethers: A facile α-hydroxylation procedure. *Tetrahedron Lett.* **15**, 4319–4322 (1974).

85. Brook, A. G. & Macrae, D. M. 1,4-Silyl rearrangements of siloxyalkenes to siloxyketones during peroxidation. *J. Organomet.Chem.* **77**, C19–C21 (1974).

86. Hassner, A., Reuss, R. H. & Pinnick, H. W. Synthetic methods. VIII. Hydroxylation of carbonyl compounds via silyl enol ethers. *J. Org. Chem.* **40**, 3427–3429 (1975).

87. Sreedhar, B., Surendra Reddy, P. & Madhavi, M. Rapid and Catalyst-Free α-Halogenation of Ketones using N -Halosuccinamides in DMSO. *Synth Commun* **37**, 4149–4156 (2007).

88. N. I. Burakov, A. L. Kanibolotskii, G. Yu. Osichenko, V. A. M. & v. A. Savelova, and V. V. K. Reaction of N,N-Dialkylcarboxamides with Halogens. *Russ. J. Gen. Chem.* **37**, 1210–1219 (2001).

89. Fuson, R. C. & Bull, B. A. The Haloform Reaction. *Chem. Rev.* **15**, 275–309 (1934).

90. France, S., Weatherwax, A. & Lectka, T. Recent Developments in Catalytic, Asymmetric α-Halogenation: A New Frontier in Asymmetric Catalysis. *Chem. Eur. J.* **2005**, 475–479 (2005).

91. Gröbel, B.-T., Seebach, D. Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents. *Synthesis (Stuttg)* **1977**, 357–402 (1977).

92. Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed.* **18**, 239–258 (1979).

93. Belletire, J. L. & Fremont, S. L. Oxidative coupling. *Tetrahedron Lett.* **27**, 127–130 (1986).

94. Smith, A. B. & Xian, M. Anion Relay Chemistry: An Effective Tactic for Diversity Oriented Synthesis. *J. Am. Chem. Soc.* **128**, 66–67 (2006).

95. Dai, X.-J., Li, C.-C. & Li, C.-J. Carbonyl umpolung as an organometallic reagent surrogate. *Chem. Soc. Rev.* **50**, 10733–10742 (2021).

96. Begley, T. P. & Ealick, S. E. Thiamin Biosynthesis. in *Comprehensive Natural Products II* 547–559 (Elsevier, 2010).

97. Washabaugh, M. W. & Jencks, W. P. Thiazolium C(2)-proton exchange: structure-reactivity correlations and the pKa of thiamin C(2)-H revisited. *Biochem.* **27**, 5044–5053 (1988).

98. Myers, M. C., Bharadwaj, A. R., Milgram, B. C. & Scheidt, K. A. Catalytic Conjugate Additions of Carbonyl Anions under Neutral Aqueous Conditions. *J. Am. Chem. Soc.* **127**, 14675–14680 (2005).

99. Breslow, R. On the Mechanism of Thiamine Action. IV. 1 Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **80**, 3719–3726 (1958).

100. Stetter, H. Catalyzed Addition of Aldehydes to Activated Double Bonds? A New Synthetic Approach. *Angew. Chem., Int. Ed. Engl.* **15**, 639–647 (1976).

101. Bauer, A. & Maulide, N. Chemoselective formal β-functionalization of substituted aliphatic amides enabled by a facile stereoselective oxidation event. *Chem. Sci.* **10**, 9836–9840 (2019).

102. de la Torre, A., Kaiser, D. & Maulide, N. Flexible and Chemoselective Oxidation of Amides to α-Keto Amides and α-Hydroxy Amides. *J. Am. Chem. Soc.* **139**, 6578–6581 (2017).

103. G. Godfrey, A. & Ganem, B. Ready oxidation of halides to aldehydes using trimethylamine N-oxide in dimethylsulfoxide. *Tetrahedron Lett.* **31**, 4825–4826 (1990).

104. Kaiser, D., de la Torre, A., Shaaban, S. & Maulide, N. Metal-Free Formal Oxidative C−C Coupling by In Situ Generation of an Enolonium Species. *Angew. Chem., Int. Ed.* **56**, 5921–5925 (2017).

105. Kaiser, D., Teskey, C. J., Adler, P. & Maulide, N. Chemoselective Intermolecular Cross-Enolate-Type Coupling of Amides. *J. Am. Chem. Soc.* **139**, 16040–16043 (2017).

106. Baran, P. S. & DeMartino, M. P. Intermolecular Oxidative Enolate Heterocoupling. *Angew. Chem., Int. Ed.* **45**, 7083–7086 (2006).

107. Decicco, C. P., Nelson, D. J., Corbett, R. L. & Dreabit, J. C. Asymmetric Synthesis of 2,3-Disubstituted Succinates via Chiral Oxazolidinone Controlled Displacement of a-Trifluoromethanesulfonate Substituted Esters. *J. Org. Chem.* **60**, 4782–4785 (1995).

108. Yetra, S., Patra, A. & Biju, A. Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry. *Synthesis (Stuttg)* **47**, 1357–1378 (2015).

109. Robinson, E. E. & Thomson, R. J. A Strategy for the Convergent and Stereoselective Assembly of Polycyclic Molecules. *J. Am. Chem. Soc.* **140**, 1956–1965 (2018).

110. Whittaker, M., Floyd, C. D., Brown, P. & Gearing, A. J. H. Design and Therapeutic Application of Matrix Metalloproteinase Inhibitors. *Chem. Rev.* **101**, 2205–2206 (2001).

111. DeMartino, M. P., Chen, K. & Baran, P. S. Intermolecular Enolate Heterocoupling: Scope, Mechanism, and Application. *J. Am. Chem. Soc.* **130**, 11546–11560 (2008).

112. Gonçalves, C. R. *et al.* Unified Approach to the Chemoselective α-Functionalization of Amides with Heteroatom Nucleophiles. *J. Am. Chem. Soc.* **141**, 18437–18443 (2019).

113. Studte, C. & Breit, B. Zinc-Catalyzed Enantiospecific sp 3 –sp 3 Cross-Coupling of α-Hydroxy Ester Triflates with Grignard Reagents. *Angew. Chem., Int. Ed.* **47**, 5451–5455 (2008).

114. Ohtani, N., Ohta, T., Hosoda, Y. & Yamashita, T. Phase Behavior and Phase-Transfer Catalysis of Tetrabutylammonium Salts. Interface-Mediated Catalysis. *Langmuir* **20**, 409–415 (2004).

115. Fahey, R. C. The Stereochemistry of Electrophilic Additions to Olefins and Acetylenes. in 237–342 (2007).

116. Pincock, J. A. & Yates, K. Kinetics and mechanism of electrophilic bromination of acetylenes. *Can. J. Chem.* **48**, 3332–3348 (1970).

117. Corey, E. J. & Chaykovsky, M. Methylsulfinyl Carbanion (CH3-SO-CH2). Formation and Applications to Organic Synthesis. *J. Am. Chem. Soc.* **87**, 1345–1353 (1965).

118. Pearson, R. G. Hard and Soft Acids and Bases. *J. Am. Chem. Soc.* **85**, 3533–3539 (1963).

119. Pearson, R. G. Hard and soft acids and bases, HSAB, part II: Underlying theories. *J. Chem. Educ.* **45**, 643 (1968).

120. Janssen, M. J. Thiolo, thiono and dithio acids and esters. in *Carboxylic Acids and Esters (1969)* 705–764 (John Wiley & Sons, Ltd.).

121. Jeffrey, J. L. & Sarpong, R. Chichibabin-Type Direct Alkylation of Pyridyl Alcohols with Alkyl Lithium Reagents. *Org. Lett.* **14**, 5400–5403 (2012).

122. Li, J., Berger, M., Zawodny, W., Simaan, M. & Maulide, N. A Chemoselective α-Oxytriflation Enables the Direct Asymmetric Arylation of Amides. *Chem* **5**, 1883–1891 (2019).

123. Byrd, K. M. Diastereoselective and enantioselective conjugate addition reactions utilizing α,β-unsaturated amides and lactams. *Beilstein Journal of Organic Chemistry* **11**, 530–562 (2015).

124. Que, Y. & He, H. Advances in N-Heterocyclic Carbene Catalysis for Natural Product Synthesis. *European J Org Chem* **2020**, 5917–5925 (2020).

125. Yamashita, M., Goto, K. & Kawashima, T. Fixation of Both O 2 and CO 2 from Air by a Crystalline Palladium Complex Bearing N- Heterocyclic Carbene Ligands. *J. Am. Chem. Soc* .**127**, 7294–7295 (2005).

126. Lee, S. & Hartwig, J. F. Improved Catalysts for the Palladium-Catalyzed Synthesis of Oxindoles by Amide α-Arylation. Rate Acceleration, Use of Aryl Chloride Substrates, and a New Carbene Ligand for Asymmetric Transformations. *J. Org. Chem.* **66**, 3402–3415 (2001).

127. Arduengo, A. J., Harlow, R. L. & Kline, M. A stable crystalline carbene. *J. Am. Chem. Soc* .**113**, 361–363 (1991).

128. Burstein, C. & Glorius, F. Organocatalyzed Conjugate Umpolung of a,b-Unsaturated Aldehydes for the Synthesis of y-Butyrolactones. *Angew. Chem., Int. Ed.* **43**, 6205–6208 (2004).

129. Sohn, S. S., Rosen, E. L. & Bode, J. W. N -Heterocyclic Carbene-Catalyzed Generation of Homoenolates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes. *J. Am. Chem. Soc* .**126**, 14370–14371 (2004).

130. Mc.Conathy, J. & Owens, M. J. Stereochemistry in Drug Action. *Prim Care Companion J Clin Psychiatry* **05**, 70–73 (2003).

131. Ouellette, R. J. & Rawn, J. D. Stereochemistry. in *Organic Chemistry* 213–253 (Elsevier, 2018).

132. Ramberg, P. J. *Chemical Structure, Spatial Arrangement*. (Routledge, 2017).

133. Michael, A. Ueber die Einwirkung von Fünffach-Chlorphosphor auf die Aether organischer Säuren. *Ber. Dtsch. Chem. Ges.* **19**, 845–847 (1886).

134. Little, R. D., Masjedizadeh, M. R., Wallquist, O. & Mcloughlin, J. I. The Intramolecular Michael Reaction. in *Organic Reactions* 315–552 (John Wiley & Sons, Inc., 1995).

135. Mather, B. D., Viswanathan, K., Miller, K. M. & Long, T. E. Michael addition reactions in macromolecular design for emerging technologies. *Prog. Polym. Sci.* **31**, 487–531 (2006).

136. Carey, F. & Sundberg, R. Advanced Organic Chemistry. Part B: Reactions and Synthesis. Fourth Edition. *Molecules* **6**, 1015–1016 (2001).

137. Rapson, W. S. & Robinson, R. 307. Experiments on the synthesis of substances related to the sterols. Part II. A new general method for the synthesis of substituted cyclohexenones. *Journal of the Chemical Society (Resumed)* 1285 (1935)

138. Gawley, R. The Robinson Annelation and Related Reactions. *Synthesis (Stuttg)* **1976**, 777–794 (2002).

139. Heathcock, C. H., Ellis, J. E., McMurry, J. E. & Coppolino, A. Acid-catalyzed Robinson Annelations. *Tetrahedron Lett.* **12**, 4995–4996 (1971).

140. Pellissier, H. Asymmetric organocatalysis. *Tetrahedron* **63**, 9267–9331 (2007).

141. Zhang, Y. & Wang, W. Recent advances in organocatalytic asymmetric Michael reactions. *Catal. Sci. Technol.* **2**, 42–53 (2012).

142. Reyes, E., Uria, U., Vicario, J. L. & Carrillo, L. The Catalytic, Enantioselective Michael Reaction. in *Organic Reactions* 1–898 (John Wiley & Sons, Inc., 2016).

143. Kaasik, M. *et al.* Enantioselective Michael addition to vinyl phosphonates via hydrogen bond-enhanced halogen bond catalysis. *Chem Sci* **12**, 7561–7568 (2021).

144. Rozsar, D., Formica, M., Yamazaki, K., Hamlin, T. A. & Dixon, D. J. Bifunctional Iminophosphorane-Catalyzed Enantioselective Sulfa-Michael Addition to Unactivated α,β-Unsaturated Amides. *J. Am. Chem. Soc* .**144**, 1006–1015 (2022).

145. Wadhwa, P., Kharbanda, A. & Sharma, A. Thia-Michael Addition: An Emerging Strategy in Organic Synthesis. *Asian J. Org. Chem.* **7**, 634–661 (2018).

146. Choi, T.-L., Chatterjee, A. K. & Grubbs, R. H. Synthesis of α,β-Unsaturated Amides by Olefin Cross-Metathesis. *Angew. Chem., Int. Ed.* **40**, 1277–1279 (2001).

147. Yu, E. C., Johnson, B. M., Townsend, E. M., Schrock, R. R. & Hoveyda, A. H. Synthesis of Linear (Z)-α,β-Unsaturated Esters by Catalytic Cross-Metathesis. The Influence of Acetonitrile. *Angew. Chem., Int. Ed.* **55**, 13210–13214 (2016).

148. Connon, S. J. & Blechert, S. Recent Developments in Olefin Cross-Metathesis. *Angew. Chem., Int. Ed.* **42**, 1900–1923 (2003).

149. Rosen, T. The Perkin Reaction. in *Comprehensive Organic Synthesis* 395–408 (Elsevier, 1991).

150. Perkin, W. H. On the artificial production of coumarin and formation of its homologues. *J. Chem. Soc.* **21**, 53–63 (1868).

151. Barton, D. H. R., Head, A. J. & Williams, R. J. Stereospecificity in thermal elimination reactions. Part III. The pyrolysis of (–)-menthyl benzoate. *J. Chem. Soc.* 1715–1719 (1953).

152. Tschugaeff, L. Ueber das Thujen, ein neues bicyclisches Terpen. *Ber. Dtsch. Chem. Ges.* **33**, 3118–3126 (1900).

153. Kumar, S., Kumar, V. & Singh, S. P. Group Transfer, Elimination, and Related Reactions. in *Pericyclic Reactions* 283–321 (Elsevier, 2016).

154. Barton, D. H. R., Head, A. J. & Williams, R. J. Stereospecificity in thermal elimination reactions. Part II. The pyrolysis of (—)-menthyl chloride. *J. Chem. Soc.* 453–461 (1952).

155. Cope, A. C., Foster, T. T. & Towle, P. H. Thermal Decomposition of Amine Oxides to Olefins and Dialkylhydroxylamines. *J. Am. Chem. Soc.* **71**, 3929–3934 (1949).

156. Wakamatsu, T., Yamada, S. & Ban, Y. Synthesis of dl-Vermiculine via Control of Olefin Formation. *Heterocycles* **24**, 309 (1986).

157. Nokami, J., Kunieda, N. & Kinoshita, M. Pyrolysis of β-hydroxy sulfoxides to ketones. *Tetrahedron Lett.* **16**, 2841–2844 (1975).

158. Ito, Y., Hirao, T. & Saegusa, T. Synthesis of a,b.-unsaturated carbonyl compounds by palladium(II)-catalyzed dehydrosilylation of silyl enol ethers. *J. Org. Chem.* **43**, 1011–1013 (1978).

159. Nicolaou, K. C., Gray, D. L. F., Montagnon, T. & Harrison, S. T. Oxidation of Silyl Enol Ethers by Using IBX and IBX·N-Oxide Complexes: A Mild and Selective Reaction for the Synthesis of Enones. *Angew. Chem., Int. Ed.* **41**, 996–1000 (2002).

160. Nicolaou, K. C., Montagnon, T., Baran, P. S. & Zhong, Y. L. Iodine(V) reagents in organic synthesis. Part 4. o-Iodoxybenzoic acid as a chemospecific tool for single electron transfer-based oxidation processes. *J. Am. Chem. Soc.* **124**, 2245–2258 (2002).

161. Chen, M. & Dong, G. Copper-Catalyzed Desaturation of Lactones, Lactams, and Ketones under pH-Neutral Conditions. *J. Am. Chem. Soc.* **141**, 14889–14897 (2019).

162. Shang, Y., Jie, X., Jonnada, K., Zafar, S. N. & Su, W. Dehydrogenative desaturation-relay via formation of multicenter-stabilized radical intermediates. *Nat. Commun.* **8**, 2273 (2017).

163. Zhang, X.-W. *et al.* Iron-Catalyzed α,β-Dehydrogenation of Carbonyl Compounds. *Org. Lett.* **23**, 1611–1615 (2021).

164. Nicolaou, K. C. *et al.* Mechanistic Studies of Periodinane-Mediated Reactions of Anilides and Related Systems. *Angew. Chem., Int. Ed.* **40**, 202–206 (2001).

165. Sharpless, K. B., Young, M. W. & Lauer, R. F. Reactions of selenoxides: Thermal -elimination and H218O exchange. *Tetrahedron Lett.* **14**, 1979–1982 (1973).

166. Grieco, P. A., Gilman, S. & Nishizawa, M. Organoselenium chemistry. A facile one-step synthesis of alkyl aryl selenides from alcohols. *J. Org. Chem.* **41**, 1485–1486 (1976).

167. Hughes, D. L. The Mitsunobu Reaction. in *Organic Reactions* 335–656 (John Wiley & Sons, Inc., 1992).

168. Hughes, D. L. Progress in the Mitsunobu reaction. A review: *Org. Prep. Proced. Int.* **28**, 127–164 (1996).

169. Mitsunobu, O. & Yamada, M. Preparation of Esters of Carboxylic and Phosphoric Acid via Quaternary Phosphonium Salts. *Bull. Chem. Soc. Jpn.* **40**, 2380–2382 (1967).

170. Chen, M. & Dong, G. Direct Catalytic Desaturation of Lactams Enabled by Soft Enolization. *J. Am. Chem. Soc.* **139**, 7757–7760 (2017).

171. Szewczyk, S. M., Zhao, Y., Sakai, H. A., Dube, P. & Newhouse, T. R. α,β-Dehydrogenation of esters with free O H and N H functionalities via allyl-palladium catalysis. *Tetrahedron* **74**, 3293–3300 (2018).

172. Tsuji, J., Takahashi, H. & Morikawa, M. Organic syntheses by means of noble metal compounds XVII. Reaction of π-allylpalladium chloride with nucleophiles. *Tetrahedron Lett.* **6**, 4387–4388 (1965).

173. Trost, B. M. & Fullerton, T. J. New synthetic reactions. Allylic alkylation. *J. Am. Chem. Soc.* **95**, 292–294 (1973).

174. Guerrero Rios, I., Rosas-Hernandez, A. & Martin, E. Recent Advances in the Application of Chiral Phosphine Ligands in Pd-Catalysed Asymmetric Allylic Alkylation. *Molecules* **16**, 970–1010 (2011).

175. Tsuji, J., Takahashi, H. & Morikawa, M. Organic syntheses by means of noble metal compounds XVII. Reaction of π-allylpalladium chloride with nucleophiles. *Tetrahedron Lett* **6**, 4387–4388 (1965).

176. Zhao, Y., Chen, Y. & Newhouse, T. R. Allyl-Palladium-Catalyzed α,β-Dehydrogenation of Carboxylic Acids via Enediolates. *Angew. Chem., Int. Ed.* **56**, 13122–13125 (2017).

177. Schuppe, A. W., Huang, D., Chen, Y. & Newhouse, T. R. Total Synthesis of (−)-Xylogranatopyridine B via a Palladium-Catalyzed Oxidative Stannylation of Enones. *J. Am. Chem. Soc.* **140**, 2062–2066 (2018).

178. Chen, Y. *et al.* A Concise Total Synthesis of (−)-Himalensine A. *Angew. Chem., Int. Ed.* **58**, 7390–7394 (2019).

179. Wang, Z., He, Z., Zhang, L. & Huang, Y. Iridium-Catalyzed Aerobic α,β-Dehydrogenation of γ,δ-Unsaturated Amides and Acids: Activation of Both α- and β-C–H bonds through an Allyl–Iridium Intermediate. *J. Am. Chem. Soc* .**140**, 735–740 (2018).

180. Wang, R. *et al.* Iridium/Copper-Catalyzed Oxidative C−H/O−H Annulation of Benzoic Acids with Saturated Ketones for Accessing 3-Substituted Phthalides. *ChemCatChem* **12**, 5907–5911 (2020).

181. Jiang, B. *et al.* Copper-Catalyzed Dehydrogenative Diels–Alder Reaction. *Org Lett* **20**, 3215–3219 (2018).

182. Teskey, C. J., Adler, P., Gonçalves, C. R. & Maulide, N. Chemoselective α,β-Dehydrogenation of Saturated Amides. *Angew. Chem. Int. Ed.* **58**, 447–451 (2019).

183. Majewski, M. Lithium diisopropylamide as a hydride donor. Reduction of aldehydes. *Tetrahedron Lett.* **29**, 4057–4060 (1988).

184. Creary, X. Reactions of pivaloin derivatives with lithium tetramethylpiperidide. *J. Org. Chem.* **45**, 2419–2425 (1980).

185. Jasiński, M., Mlostoń, G., Gebert, A. & Heimgartner, H. Lithium Diisopropylamide (LDA) as an Efficient Reducing Agent for Thioketones—Mechanistic Consideration. *Phosphorus, Sulfur, and Silicon Relat. Elem.* **190**, 1281–1284 (2015).

186. Creary, X. & Rollin, A. J. Reactions of bicyclic a-keto triflates with bases and nucleophiles. *J. Org. Chem.* **44**, 1798–1806 (1979).

187. Fetizon, M., Balogh, V. & Golfier, M. Oxidations with silver carbonate/celite. V. Oxidations of phenols and related compounds. *J. Org. Chem.* **36**, 1339–1341 (1971).

188. Kakis, F. J. *et al.* Mechanistic studies regarding the oxidation of alcohols by silver carbonate on celite. *J. Org. Chem.* **39**, 523–533 (1974).

189. Mitchell, I. S., Pattenden, G. & Stonehouse, J. P. A concise enantioselective total synthesis of rhizoxin D. *Tetrahedron Lett.* **43**, 493–497 (2002).

190. Haag, W. O. & Pines, H. Alumina: Catalyst and Support. III. 1a The Kinetics and Mechanisms of Olefin Isomerization 1b. *J. Am. Chem. Soc.* **82**, 2488–2494 (1960).

191. Lawrence, B. M. The use of silver nitrate impregnated silica gel layers in the separation of monoterpene hydrocarbons. *J. Chromatogr A* **38**, 535–537 (1968).

192. Morita, Makota., Mihashi, Susumu., Itokawa, Hideji. & Hara, Shoji. Silver nitrate impregnation of preparative silica gel columns for liquid chromatography. *Anal. Chem.* **55**, 412–414 (1983).

193. Li, T.-S., Li, J.-T. & Li, H.-Z. Modified and convenient preparation of silica impregnated with silver nitrate and its application to the separation of steroids and triterpenes. *J. Chromatogr A* **715**, 372–375 (1995).

194. Dupau, P., Epple, R., Thomas, A., Fokin, V. & Sharpless, K. Barry. Osmium-Catalyzed Dihydroxylation of Olefins in Acidic Media: Old Process, New Tricks. *Advanced Synthesis & Catalyis* **344**, 421–433 (2002).

195. Rodríguez-Fernández, M., Yan, X., Collados, J. F., White, P. B. & Harutyunyan, S. R. Lewis Acid Enabled Copper-Catalyzed Asymmetric Synthesis of Chiral β-Substituted Amides. *J. Am. Chem. Soc.* **139**, 14224–14231 (2017).

196. McNamara, F. N., Randall, A. & Gunthorpe, M. J. Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1). *Br. J. Pharmacol* **144**, 781–790 (2005).

197. Gradl, S. N., Kennedy-Smith, J. J., Kim, J. & Trauner, D. A Practical Variant of the Claisen-Eschenmoser Rearrangement: Synthesis of Unsaturated Morpholine Amides. *Synlett* **2002**, 0411–0414 (2002).

198. Martín Castro, A. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **104**, 2939–3002 (2004).

199. Wick, A. E., Felix, D., Steen, K. & Eschenmoser, A. Claysein 'sche Umlagerungen bei Allyl- und Benzylalkoholen mit Hilfe von Acetalen des N, N-Dimethylacetamids. Vorläufige Mitteilung. *Helv. Chim. Acta* **47**, 2425–2429 (1964).

200. Frigerio, M., Santagostino, M. & Sputore, S. A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *J. Org. Chem.* **64**, 4537–4538 (1999).

201. Ireland, R. E. & Liu, L. An improved procedure for the preparation of the Dess-Martin periodinane. *J. Org. Chem.* **58**, 2899–2899 (1993).

202. Meyer, S. D. & Schreiber, S. L. Acceleration of the Dess-Martin Oxidation by Water. *J. Org. Chem.* **59**, 7549–7552 (1994).

203. Andar, M., Baruch, Z. & Meyerstein, D. The synthesis of O18-labelled hydrogen peroxide in H2O16. *Int. J. Appl. Radiat Isot* **17**, 256 (1966).

204. Grassi, G., Oldani, M. & Bauder, A. Synthesis of Concentrated18O-Labelled Hydrogen Peroxide and of 2H-,13C- and18O-Labelled Peroxyformic Acid. *Helv. Chim. Acta* **66**, 400–404 (1983).

205. Lamoureux, M. & Milne, J. The disproportionation of diselenium dichloride, Se2Cl2, and diselenium dibromide, Se2Br2. *Can J Chem* **67**, 1936–1941 (1989).

206. Schaefer, J. P. Selenium Dioxide Oxidations. I. Studies on the Mechanism of Oxidation of 1,2-Dibenzoylethane. *J. Am. Chem. Soc* .**84**, 713–716 (1962).

207. Beć, K. B. & Huck, C. W. Breakthrough Potential in Near-Infrared Spectroscopy: Spectra Simulation. A Review of Recent Developments. *Front Chem* **7**, (2019).

208. Kovacs, H., Moskau, D. & Spraul, M. Cryogenically cooled probes—a leap in NMR technology. *Prog Nucl Magn Reson Spectrosc* **46**, 131–155 (2005).

209. Dai, D. *et al.* Room-temperature dynamic nuclear polarization enhanced NMR spectroscopy of small biological molecules in water. *Nat Commun* **12**, 6880 (2021).

210. Meyer, B. Solid Allotropes of Sulfur. *Chem. Rev.* **64**, 429–451 (1964).

211. Karthik, P. S., Himaja, A. L. & Singh, S. P. Carbon-allotropes: synthesis methods, applications and future perspectives. *Carbon lett.* **15**, 219–237 (2014).

212. Allotropes. in *The IUPAC Compendium of Chemical Terminology* (International Union of Pure and Applied Chemistry (IUPAC), 2014).

213. Iijima, S. Helical microtubules of graphitic carbon. *Nature* **354**, 56–58 (1991).

214. Xiao, J. *et al.* The structures of fullerene C40 and its derivatives. *J. Mol. Struct.* **428**, 149–154 (1998).

215. Wainwright, Milton. *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine*. *Perspect. Biol. Med.* vol. 50 (2007).

216. Verheij, T. J. The antibiotic revolution should be more focused. *Br. J. Gen. Pract.* **59**, 716–717 (2009).

217. C., A. The World Sulphur Shortage. *World Today* **7**, 377–383 (1951).

218. Maas, J. & Baunack, F. Chlorosulfuric Acid. in *Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH Verlag GmbH & Co. KGaA, 2000).

219. Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*. (CRC Press, 1991).

220. Rezayati, S. & Ramazani, A. A review on electrophilic thiocyanation of aromatic and heteroaromatic compounds. *Tetrahedron* **76**, 131382 (2020).

221. Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*. (CRC Press, 2018).

222. Tracy, J. S., Kalnmals, C. A. & Toste, F. D. Beyond Allylic Alkylation: Applications of Trost Chemistry in Complex Molecule Synthesis. *Isr. J. Chem.* **61**, 340–366 (2021).

223. Paquette, L. A. *Handbook of Reagents for Organic Synthesis, Sulfur-Containing Reagents.* (2013).

224. Gennari, A., Wedgwood, J., Lallana, E., Francini, N. & Tirelli, N. Thiol-based michael-type addition. A systematic evaluation of its controlling factors. *Tetrahedron* **76**, 1316–37 (2020).

225. Nair, D. P. *et al.* The Thiol-Michael Addition Click Reaction: A Powerful and Widely Used Tool in Materials Chemistry. *Chem. Mater.* **26**, 724–744 (2014).

226. Mondal, M. & Hirsch, A. K. H. Dynamic combinatorial chemistry: a tool to facilitate the identification of inhibitors for protein targets. *Chem. Soc. Rev.* **44**, 2455–2488 (2015).

227. Gröbel, B.-T. & Seebach, D. Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents. *Synthesis (Stuttg)* **1977**, 357–402 (1977).

228. Smith, A. B. & Adams, C. M. Evolution of Dithiane-Based Strategies for the Construction of Architecturally Complex Natural Products. *Acc. Chem. Res.* **37**, 365–377 (2004).

229. Li, A.-H., Dai, L.-X. & Aggarwal, V. K. Asymmetric Ylide Reactions: Epoxidation, Cyclopropanation, Aziridination, Olefination, and Rearrangement. *Chem. Rev.* **97**, 2341–2372 (1997).

230. Gololobov, Yu. G., Nesmeyanov, A. N., Lysenko, V. P. & Boldeskul, I. E. Twenty-five years of dimethylsulfoxonium ethylide (corey's reagent). *Tetrahedron* **43**, 2609–2651 (1987).

231. Lu, L.-Q., Li, T.-R., Wang, Q. & Xiao, W.-J. Beyond sulfide-centric catalysis: recent advances in the catalytic cyclization reactions of sulfur ylides. *Chem. Soc. Rev.* **46**, 4135–4149 (2017).

232. Bisag, G. D., Ruggieri, S., Fochi, M. & Bernardi, L. Sulfoxonium ylides: simple compounds with chameleonic reactivity. *Org. Biomol. Chem.* **18**, 8793–8809 (2020).

233. Tang, Y., Ye, S. & Sun, X.-L. Telluronium and Sulfonium Ylides for Organic Transformation. *Synlett* 2720–2730 (2005).

234. Xiang, Y., Fan, X., Cai, P. & Yu, Z. Understanding Regioselectivities of Corey–Chaykovsky Reactions of Dimethylsulfoxonium Methylide (DMSOM) and Dimethylsulfonium Methylide (DMSM) toward Enones: A DFT Study. *European J. Org. Chem.* **2019**, 582–590 (2019).

235. Trost, B. M. & Kalnmals, C. A. Sulfones as Chemical Chameleons: Versatile Synthetic Equivalents of Small-Molecule Synthons. *Chem. Eur. Joc.* (2019).

236. Šiaučiulis, M., Ahlsten, N., Pulis, A. P. & Procter, D. J. Transition-Metal-Free Cross-Coupling of Benzothiophenes and Styrenes in a Stereoselective Synthesis of Substituted (E,Z)-1,3-Dienes. *Angew. Chem., Int. Ed.* **58**, 8779–8783 (2019).

237. Cao, X.-P. Stereoselective synthesis of substituted all-trans 1,3,5,7-octatetraenes by a modified Ramberg–Bäcklund reaction. *Tetrahedron* **58**, 1301–1307 (2002).

238. Chan, T.-L., Fong, S., Li, Y., Man, T.-O. & Poon, C.-D. A new one-flask Ramberg–Bäcklund reaction. *J. Chem. Soc., Chem. Commun.* 1771–1772 (1994).

239. Paquette, L. A. The Ramberg-Bäcklund Rearrangement. in *Organic Reactions* 1–71 (John Wiley & Sons, Inc., 1977).

240. Aurisicchio, C., Baciocchi, E., Gerini, M. F. & Lanzalunga, O. Thermal and Photochemical Racemization of Chiral Aromatic Sulfoxides via the Intermediacy of Sulfoxide Radical Cations. *Org. Lett.* **9**, 1939–1942 (2007).

241. Amaudrut, J. & Wiest, O. The Thermal Sulfenate−Sulfoxide Rearrangement: A Radical Pair Mechanism. *J. Am. Chem. Soc.* **122**, 3367–3374 (2000).

242. Miller, E. G., Rayner, D. R., Thomas, H. T. & Mislow, K. Thermal racemization of benzyl p-tolyl sulfoxide and thermal rearrangement of benzyl p-toluenesulfenate. *J. Am. Chem. Soc.* **90**, 4861–4868 (1968).

243. Sankaran, G. S., Arumugan, S. & Balasubramaniam, S. Application of chiral sulfoxides in asymmetric synthesis. *Biorg. Org. Chem.* **2**, 93–101 (2018).

244. Han, J., Soloshonok, V. A., Klika, K. D., Drabowicz, J. & Wzorek, A. Chiral sulfoxides: advances in asymmetric synthesis and problems with the accurate determination of the stereochemical outcome. *Chem. Soc. Rev.* **47**, 1307–1350 (2018).

245. Carreño, M. C., des Mazery, R., Urbano, A., Colobert, F. & Solladié, G. Enantioselective Access to 2,7-Cis-Disubstituted Oxepanes: Formal Synthesis of (+)-Isolaurepan. *Org. Lett.* **6**, 297–299 (2004).

246. Smith, L. H. S., Coote, S. C., Sneddon, H. F. & Procter, D. J. Beyond the Pummerer Reaction: Recent Developments in Thionium Ion Chemistry. *Angew. Chem., Int. Ed.* **49**, 5832–5844 (2010).

247. Rojas, C. M. *Molecular Rearrangements in Organic Synthesis*. (John Wiley & Sons, Inc, 2015).

248. Smith, L. H. S., Coote, S. C., Sneddon, H. F. & Procter, D. J. Beyond the Pummerer Reaction: Recent Developments in Thionium Ion Chemistry. *Angew. Chem., Int. Ed.* **49**, 5832–5844 (2010).

249. de Lucchi, O., Miotti, U. & Modena, G. The Pummerer Reaction of Sulfinyl Compounds. in *Organic Reactions* 157–405 (John Wiley & Sons, Inc., 1991).

250. Aukland, M. H., Šiaučiulis, M., West, A., Perry, G. J. P. & Procter, D. J. Metal-free photoredox-catalysed formal C–H/C–H coupling of arenes enabled by interrupted Pummerer activation. *Nat. Catal.* **3**, 163–169 (2020).

251. Minami, H., Otsuka, S., Nogi, K. & Yorimitsu, H. Palladium-Catalyzed Borylation of Aryl Sulfoniums with Diborons. *ACS Catal* **8**, 579–583 (2018).

252. Berger, F. *et al.* Site-selective and versatile aromatic C−H functionalization by thianthrenation. *Nature* **567**, 223–228 (2019).

253. Halder, S. & Satyam, A. Accidental discovery of a 'longer-range' vinylogous Pummerer-type lactonization: formation of sulindac sulfide lactone from sulindac. *Tetrahedron Lett.* **52**, 1179–1182 (2011).

254. Yorimitsu, H. Cascades of Interrupted Pummerer Reaction-Sigmatropic Rearrangement. *Chem. Rec.* **17**, 1156–1167 (2017).

255. Yanagi, T., Nogi, K. & Yorimitsu, H. Recent development of ortho -C–H functionalization of aryl sulfoxides through [3,3] sigmatropic rearrangement. *Tetrahedron Lett.* **59**, 2951–2959 (2018).

256. Kaiser, D., Klose, I., Oost, R., Neuhaus, J. & Maulide, N. Bond-Forming and -Breaking Reactions at Sulfur (IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **119**, 8701–8780 (2019).

257. Alder, R. W. *Advanced organic chemistry. reactions, mechanisms and structure. 3rd edition: Endeavour* vol. 9 (1985).

258. Jursic, B. S. Sigmatropic rearrangement of sulfur and nitrogen allylic ylides studied by ab initio methods. *J. Mol. Struct. Theochem* **339**, 161–168 (1995).

259. Dinda, B. Sigmatropic Rearrangements. in 107–160 (2017).

260. Li, J. J. Morin rearrangement. in *Name Reactions* 272–273 (Springer Berlin Heidelberg, 2003).

261. Kirmse, W. & Kapps, M. Reaktionen des Diazomethans mit Diallylsulfid und Allyläthern unter Kupfersalz-Katalyse. *Chem Ber* **101**, 994–1003 (1968).

262. Prabharasuth, R. & van Vranken, D. L. Iron-Catalyzed Reaction of Propargyl Sulfides and Trimethylsilyldiazomethane. *J. Org. Chem.* **66**, 5256–5258 (2001).

263. Doyle, M. P., Tamblyn, W. H. & Bagheri, V. Highly effective catalytic methods for ylide generation from diazo compounds. Mechanism of the rhodium- and copper-catalyzed reactions with allylic compounds. *J. Org. Chem.* **46**, 5094–5102 (1981).

264. Lin, X., Yang, W., Yang, W., Liu, X. & Feng, X. Asymmetric Catalytic [2,3] Stevens and Sommelet–Hauser Rearrangements of α-Diazo Pyrazoleamides with Sulfides. *Angew. Chem., Int. Ed.* **58**, 13492–13498 (2019).

265. Yamamoto, M., Kakinuma, M., Kohmoto, S. & Yamada, K. Sommelet–Hauser Rearrangement of Oxygen and Sulfur Containing Heteroaromatic Sulfonium Ylides. *Bull. Chem. Soc. Jpn* **62**, 958–960 (1989).

266. Reddy, A. C. S., Ramachandran, K., Reddy, P. M. & Anbarasan, P. Rhodium-catalyzed Sommelet–Hauser type rearrangement of α-diazoimines: synthesis of functionalized enamides. *Chem. Commun.* **56**, 5649–5652 (2020).

267. Thomson, T. & Stevens, T. S. Degradation of quaternary ammonium salts. Part V. Molecular rearrangement in related sulphur compounds. *J. Chem. Soc.* 69–73 (1932).

268. Bhakat, S. The controversial reaction mechanism of the Stevens rearrangement: A review. *J. Chem. Pharm.* **3**, 115–121 (2011).

269. Li, J. J. Mislow-Evans rearrangement. in *Name Reactions* 388–389 (Springer Berlin Heidelberg, 2002).

270. Evans, D. A., Andrews, G. C. & Sims, C. L. Reversible 1,3 transposition of sulfoxide and alcohol functions. Potential synthetic utility. *J. Am. Chem. Soc.* **93**, 4956–4957 (1971).

271. Tang, R. & Mislow, K. Rates and equilibria in the interconversion of allylic sulfoxides and sulfenates. *J. Am. Chem. Soc.* **92**, 2100–2104 (1970).

272. Evans, D. A. & Andrews, G. C. Allylic sulfoxides. Useful intermediates in organic synthesis. *Acc. Chem. Res.* **7**, 147–155 (1974).

273. Sato, T., Shima, H. & Otera, J. A Highly Practical Route for Prostaglandins by Conjugate Addition of a-Lithio-y-methoxyallyl Phenyl Sulfide. *J. Org. Chem.* **60**, 3936–3937 (1995).

274. Shinada, T., Fuji, T., Ohtani, Y., Yoshida, Y. & Ohfune, Y. Syntheses of Gabosine A, B, D, and E from Allyl Sulfide Derived from (-)-Quinic Acid. *Synlett* 1341–1343 (2002).

275. Miller, J. G., Kurz, W., Untch, K. G. & Stork, G. Prostaglandins. 40. Highly stereoselective total syntheses of prostaglandins via stereospecific sulfenate-sulfoxide transformations. 13-cis-15.beta.-Prostaglandins E1 to prostaglandins E1. *J. Am. Chem. Soc.* **96**, 6774–6775 (1974).

276. Yoshida, S., Yorimitsu, H. & Oshima, K. Radical Addition of Alkyl Halides to 2-Methylene-1,3-dithiane Monoxide as a Ketene Equivalent. *Chem Lett* **38**, 248–249 (2009).

277. Murakami, K. *et al.* Copper-Catalyzed Extended Pummerer Reactions of Ketene Dithioacetal Monoxides with Alkynyl Sulfides and Ynamides with an Accompanying Oxygen Rearrangement. *Eur. J. Chem.* **19**, 5625–5630 (2013).

278. Kobatake, T., Yoshida, S., Yorimitsu, H. & Oshima, K. Reaction of 2-(2,2,2-Trifluoroethylidene)-1,3-dithiane 1-Oxide with Ketones under Pummerer Conditions and Its Application to the Synthesis of 3-Trifluoromethyl-Substituted Five-Membered Heteroarenes. *Angew. Chem. Int. Ed.* **49**, 2340–2343 (2010).

279. Schaumann, E. *Sulfur-Mediated Rearrangements II*. vol. 275 (Springer Berlin Heidelberg, 2007).

280. Colomer, I., Velado, M., Fernández de la Pradilla, R. & Viso, A. From Allylic Sulfoxides to Allylic Sulfenates: Fifty Years of a Never-Ending [2,3]-Sigmatropic Rearrangement. *Chem. Rev.* **117**, 14201–14243 (2017).

281. Reggelin, M. *[2,3]-Sigmatropic Rearrangements of Allylic Sulfur Compounds*. *Topics in Current Chemistry 275* (Springer Berlin Heidelberg, 2007).

282. Kaiser, D. & Maulide, N. Making the Least Reactive Electrophile the First in Class: Domino Electrophilic Activation of Amides. *J. Org. Chem.* **81**, 4421–4428 (2016).

283. Yanagi, T., Nogi, K. & Yorimitsu, H. Recent development of ortho -C–H functionalization of aryl sulfoxides through [3,3] sigmatropic rearrangement. *Tetrahedron Lett.* **59**, 2951–2959 (2018).

284. Arjona, O., Fernandez, P., Fernandez de la Pradilla, R., Morente, M. & Plumet, J. Synthesis of endo or exo norbornenic lactones via highly diastereoselective lactonization of bicyclic vinyl sulfoxides. *J Org Chem* **58**, 3172–3175 (1993).

285. Marino, J. P. & Neisser, M. Stereospecific reactions of dichloroketene with vinyl sulfoxides: a new type of polar cycloaddition. *J. Am. Chem. Soc* .**103**, 7687–7689 (1981).

286. Marino, J. P. & Perez, A. D. Enantiospecific lactonizations of chiral 1-(arylsulfinyl)cyclohexenes with chloro ketenes. *J. Am. Chem. Soc* .**106**, 7643–7644 (1984).

287. Marino, J. P., Laborde, Edgardo. & Paley, R. S. Stereospecific replacement of sulfur from chiral y-(arylsulfanyl)butyrolactones. Synthesis of optically pure ring-fused y-butyrolactones. *J. Am. Chem. Soc.* **110**, 966–968 (1988).

288. Posner, G. H., Asirvatham, E. & Ali, S. F. Additive Pummerer rearrangements. Asymmetric synthesis of (–)-methyl jasmonate. *J. Chem. Soc., Chem. Commun.* 542–543 (1985).

289. Marino, J. P., Kim, M. W. & Lawrence, R. Reactions of indole sulfoxides with dichloroketene: a new approach to the physostigmine alkaloids. *J Org Chem* **54**, 1782–1784 (1989).

290. Marino, J. P., Bogdan, S. & Kimura, K. The enantioselective synthesis of (-)-physostigmine via chiral sulfoxides. *J. Am. Chem. Soc* .**114**, 5566–5572 (1992).

291. Kosugi, H., Tagami, K., Takahashi, A., Kanna, H. & Uda, H. Highly enantiospecific synthesis of 4-alkyl and 4,5-dialkyl substituted 4,5-dihydrofuran-2(3H)-ones from optically active (E)- and (Z)-alk-1-enyl p-tolyl sulfoxides: application to the synthesis of lignan lactones. *J. Chem. Soc., Perkin Trans. 1* 935 (1989).

292. Marino, J. P., Bogdan, S. & Kimura, K. The enantioselective synthesis of (-)-physostigmine via chiral sulfoxides. *J. Am. Chem. Soc* .**114**, 5566–5572 (1992).

293. Burke, S. D., Shankaran, K. & Helber, M. J. Synthesis of (+)-fragolide and (−)-pereniporin B via vinylsilane terminated cationic cyclization. *Tetrahedron Lett* **32**, 4655–4658 (1991).

294. Marino, J. P. & Cao, G. Total synthesis of aspidophytine. *Tetrahedron Lett* **47**, 7711–7713 (2006).

295. Arjona, O., Fernandez, P., Fernandez de la Pradilla, R., Morente, M. & Plumet, J. Synthesis of endo or exo norbornenic lactones via highly diastereoselective lactonization of bicyclic vinyl sulfoxides. *J. Org. Chem.* **58**, 3172–3175 (1993).

296. Maryasin, B. *et al.* Unusual mechanisms in Claisen rearrangements: an ionic fragmentation leading to a meta -selective rearrangement. *Chem Sci* **9**, 4124–4131 (2018).

297. Baran, P. S. & DeMartino, M. P. Intermolecular Oxidative Enolate Heterocoupling. *Angew. Chem. Int. Ed.* **45**, 7083–7086 (2006).

298. Richter, J. M. *et al.* Scope and Mechanism of Direct Indole and Pyrrole Couplings Adjacent to Carbonyl Compounds: Total Synthesis of Acremoauxin A and Oxazinin 3. *J. Am. Chem. Soc* .**129**, 12857–12869 (2007).

299. Murarka, S. & Antonchick, A. Metal-Catalyzed Oxidative Coupling of Ketones and Ketone Enolates. *Synthesis (Stuttg)* **50**, 2150–2162 (2018).

300. Decicco, C. P., Nelson, D. J., Corbett, R. L. & Dreabit, J. C. Asymmetric Synthesis of 2,3-Disubstituted Succinates via Chiral Oxazolidinone Controlled Displacement of .alpha.-Trifluoromethanesulfonate Substituted Esters. *J. Org. Chem.* **60**, 4782–4785 (1995).

301. Huang, S., Kötzner, L., De, C. K. & List, B. Catalytic Asymmetric Dearomatizing Redox Cross Coupling of Ketones with Aryl Hydrazines Giving 1,4-Diketones. *J. Am. Chem. Soc.***137**, 3446–3449 (2015).

302. Pratt, L. M. *et al.* Use of the Ireland-Claisen Rearrangement in the Synthesis of 2,3-Disubstituted Succinates. *Synlett* **1998**, 531–533 (1998).

303. Kaldre, D., Klose, I. & Maulide, N. Stereodivergent synthesis of 1,4-dicarbonyls by traceless charge–accelerated sulfonium rearrangement. *Science (1979)* **361**, 664–667 (2018).

304. Seebach, D., Bürstinghaus, R., Gröbel, B.-T. & Kolb, M. Zur Umpolung der Carbonylreaktivität; N2/E1- und N4/E1-Reaktion von 1,1-diheterosubstituierten Olefinen und Dienen. *Justus Liebigs Ann Chem* **1977**, 830–845 (1977).

305. Bauer, A. & Maulide, N. Chemoselective formal β-functionalization of substituted aliphatic amides enabled by a facile stereoselective oxidation event. *Chem Sci* **10**, 9836–9840 (2019).

306. da Costa, R., Gillard, M., Falmagne, J. B. & Ghosez, L. alpha, beta, Dehydrogenation of carboxamides. *J. Am. Chem. Soc.* **101**, 4381–4383 (1979).

307. Kim, E. S., Lee, H. S., Kim, S. H. & Kim, J. N. An efficient InCl3-catalyzed hydration of nitriles to amides: acetaldoxime as an effective water surrogate. *Tetrahedron Lett* **51**, 1589–1591 (2010).

308. Kim, J. N., Lee, H. J. & Gong, J. H. Synthesis of enantiomerically enriched Baylis–Hillman alcohols from their acetates: combination of kinetic resolution during the salt formation with (DHQD)2PHAL and following asymmetric induction during hydrolysis with NaHCO3 as a water surrogate. *Tetrahedron Lett* **43**, 9141–9146 (2002).

309. Kim, S.-H., Park, B.-R. & Kim, J.-N. An Efficient Hydration of Cyanamides to Substituted Ureas with Acetaldoxime as an Effective Water Surrogate. *Bull Korean Chem Soc* **32**, 716–718 (2011).

310. Beutner, G. L. *et al.* Revisiting the Cleavage of Evans Oxazolidinones with LiOH/H2O2. *Org Process Res Dev* **23**, 1378–1385 (2019).

311. Evans, D. A. & Shaw, J. T. Recent Advances in Asymmetric Synthesis with Chiral Imide Auxiliaries. *ChemInform* **34**, (2003).

312. Mickel, S. J. *et al.* Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 1: Synthetic Strategy and Preparation of a Common Precursor. *Org. Process Res. Dev.* **8**, 92–100 (2004).

313. Davison, E. K. & Brimble, M. A. Natural product derived privileged scaffolds in drug discovery. *Curr. Opin. Chem. Biol.* **52**, 1–8 (2019).

314. Newman, D. J. & Cragg, G. M. Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010. *J. Nat. Prod.* **75**, 311–335 (2012).

315. Rodrigues, T., Reker, D., Schneider, P. & Schneider, G. Counting on natural products for drug design. *Nat Chem* **8**, 531–541 (2016).

316. Garnsey, M. R. *et al.* Short Enantioselective Total Syntheses of Cheloviolenes A and B and Dendrillolide C via Convergent Fragment Coupling Using a Tertiary Carbon Radical. *J. Org. Chem.* **83**, 6958–6976 (2018).

317. Cai, X., Liang, W., Liu, M., Li, X. & Dai, M. Catalytic Hydroxycyclopropanol Ring-Opening Carbonylative Lactonization to Fused Bicyclic Lactones. *J. Am. Chem. Soc.* **142**, 13677–13682 (2020).

318. Sakabe, N., Takada, S. & Okabe, K. The structure of ginkgolide A, a novel diterpenoid trilactone. *Chem. Commun.* 259 (1967).

319. Mayol, L., Piccialli, V. & Sica, D. Minor Bisnorditerpenes from the Marine Sponge Spongionella gracilis and Revision of the Δ 6 Configuration of Gracilin B. *J Nat Prod* **49**, 823–828 (1986).

320. Hsu, C. *et al.* Leveraging Electron-Deficient Iminium Intermediates in a General Synthesis of Valuable Amines. *Angew. Chem. Int. Ed.* **61**, (2022).

321. Kaiser, D. *et al.* A General Acid-Mediated Hydroaminomethylation of Unactivated Alkenes and Alkynes. *Angew. Chem., Int. Ed.* **58**, 14639–14643 (2019).

322. Mckie, D. Daniel rutherford and the discovery of nitrogen. *Science Progress (1933)* **29**, 650–660 (1935).

323. Severinghaus, J. W. A World on Fire: A Heretic, an Aristocrat, and the Race to Discover Oxygen A World on Fire. *Phys Today* **59**, 51–51 (2006).

324. West, J. B. Henry Cavendish (1731–1810): hydrogen, carbon dioxide, water, and weighing the world. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **307**, L1–L6 (2014).

325. Weeks, M. E. Daniel Rutherford and the discovery of nitrogen. *J Chem Educ* **11**, 101 (1934).

326. Smith, C., Hill, A. K. & Torrente-Murciano, L. Current and future role of Haber–Bosch ammonia in a carbon-free energy landscape. *Energy Environ Sci* **13**, 331–344 (2020).

327. Cheema, I. I. & Krewer, U. Operating envelope of Haber–Bosch process design for power-to-ammonia. *RSC Adv* **8**, 34926–34936 (2018).

328. Appl, M. The Haber-Bosch Process and the Development of Chemical Engineering. in *A Century of Chemical Engineering* 29–53 (Springer US, 1982).

329. Appl, M. Ammonia. in *Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH Verlag GmbH & Co. KGaA, 2006).

330. Chemistry of Cyanamide. *News Edition, American Chemical Society* **18**, 759–762 (1940).

331. Zilverberg, C., Kreuter, U. & Conner, R. Population Growth and Fertilizer Use: Ecological and Economic Consequences in Santa Cruz del Quiché, Guatemala. *Soc Nat Resour* **23**, 1–13 (2009).

332. Endter, F. Die technische Synthese von Cyanwasserstoff aus Methan und Ammoniak ohne Zusatz von Sauerstoff. *Chemie Ingenieur Technik - CIT* **30**, 305–310 (1958).

333. Ritz, J., Fuchs, H. & Perryman, H. G. Hydroxylamine. in *Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH Verlag GmbH & Co. KGaA, 2000).

334. Meessen, J. H. & Petersen, H. Urea. in *Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH Verlag GmbH & Co. KGaA, 2000).

335. Cohen, P. S. & Cohen, S. M. Wöhler's Synthesis of Urea: How Do the Textbooks Report It? *J Chem Educ* **73**, 883 (1996).

336. Schirmann, J.-P. & Bourdauducq, P. Hydrazine. in *Ullmann's Encyclopedia of Industrial Chemistry* (Wiley-VCH Verlag GmbH & Co. KGaA, 2001).

337. Hayashi, H., Kainoh, A., Katayama, M., Kawasaki, K. & Okazaki, T. Hydrazine Production from Ammonia via Azine. *Product R&D* **15**, 299–303 (1976).

338. Fischer, E. Ueber aromatische Hydrazinverbindungen. *Ber. Dtsch. Chem. Ges.***8**, 589–594 (1875).

339. Wolff, L. Chemischen Institut der Universität Jena: Methode zum Ersatz des Sauerstoffatoms der Ketone und Aldehyde durch Wasserstoff. *Justus Liebigs Ann Chem* **394**, 86–108 (1912).

340. Lewis, D. E. Disability, Despotism, Deoxygenation-From Exile to Academy Member: Nikolai Matveevich Kizhner. *Angew. Chem. Int. Ed.* **52**, 11704–11712 (2013).

341. Hendrickson, J. B., Bergeron, R. & Sternbach, D. D. New "Gabriel" syntheses of amines. *Tetrahedron* **31**, 2517–2521 (1975).

342. Sheehan, J. C. & Bolhofer, W. A. An Improved Procedure for the Condensation of Potassium Phthalimide with Organic Halides. *J. Am. Chem. Soc* .**72**, 2786–2788 (1950).

343. Gibson, M. S. & Bradshaw, R. W. The Gabriel Synthesis of Primary Amines. *Angew. Chem. Int. Ed. in English* **7**, 919–930 (1968).

344. Gabriel, S. Ueber eine Darstellungsweise primärer Amine aus den entsprechenden Halogenverbindungen. *Ber. Dtsch. Chem. Ges.***20**, 2224–2236 (1887).

345. Wallis, E. S. & Lane, J. F. The Hofmann Reaction. in *Organic Reactions* 267–306 (John Wiley & Sons, Inc., 2011).

346. Shioiri, T. Degradation Reactions. in *Comprehensive Organic Synthesis* 795–828 (Elsevier, 1991).

347. Hofmann, A. W. Ueber die Einwirkung des Broms in alkalischer Lösung auf Amide. *Ber. Dtsch. Chem. Ges.***14**, 2725–2736 (1881).

348. Pirrung, M. C. & Ghorai, S. Versatile, Fragrant, Convertible Isonitriles. *J. Am. Chem. Soc* .**128**, 11772–11773 (2006).

349. Patil, P., Ahmadian-Moghaddam, M. & Dömling, A. Isocyanide 2.0. *Green Chemistry* **22**, 6902–6911 (2020).

350. Yale, H. L. The Hydroxamic Acids. *Chem Rev* **33**, 209–256 (1943).

351. Bauer, L. & Exner, O. The Chemistry of Hydroxamic Acids andN-Hydroxyimides. *Angew. Chem. Int. Ed. in English* **13**, 376–384 (1974).

352. Warren, J. D. & Press, J. B. Trimethylsilylazide/KN 3 /18-Crown-6. Formation and Curtius Rearrangement of Acyl Azides from Unreactive Acid Chlorides. *Synth Commun* **10**, 107–110 (1980).

353. Curtius, Th. Ueber Stickstoffwasserstoffsäure (Azoimid) N3H, *Ber. Dtsch. Chem. Ges.* **23**, 3023–3033 (1890).

354. Scriven, E. F. v. & Turnbull, K. Azides: their preparation and synthetic uses. *Chem Rev* **88**, 297–368 (1988).

355. Wolff, H. The Schmidt Reaction. in *Organic Reactions* 307–336 (John Wiley & Sons, Inc., 2011).

356. Schmidt, K. F. Über den Imin-Rest. *Ber. Dtsch. Chem. Ges.***57**, 704–706 (1924).

357. Lang, S. & Murphy, J. A. Azide rearrangements in electron-deficient systems. *Chem. Soc. Rev.* **35**, 146–156 (2006).

358. Gomez, S., Peters, J. A. & Maschmeyer, T. The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control. *Adv. Synth. Catal.* **344**, 1037–1057 (2002).

359. Afanasyev, O. I., Kuchuk, E., Usanov, D. L. & Chusov, D. Reductive Amination in the Synthesis of Pharmaceuticals. *Chem. Rev.* **119**, 11857–11911 (2019).

360. Zhu, G., Xie, C., Li, Z. & Wang, X. Catalytic Processes for Light Olefin Production. in *Handbook of Petroleum Technology* 1063–1079 (2017).

361. Bender, M. An Overview of Industrial Processes for the Production of Olefins - C4 Hydrocarbons. *ChemBioEng Reviews* **1**, 136–147 (2014).

362. Amghizar, I., Vandewalle, L. A., van Geem, K. M. & Marin, G. B. New Trends in Olefin Production. *Engineering* **3**, 171–178 (2017).

363. Coombs, J. R. & Morken, J. P. Catalytic Enantioselective Functionalization of Unactivated Terminal Alkenes. *Angew. Chem., Int. Ed.* **55**, 2636–2649 (2016).

364. Alkyne via solid-liquid phase-transfer catalyzed dehydrohalogenation: acetylene dicarboxaldehyde tetramethyl acetal and acetylene dicarboxaldehyde dimethyl acetal. *Org. Synth.* **82**, 179 (2005).

365. Roberts, I. & Kimball, G. E. The Halogenation of Ethylenes. *J. Am. Chem. Soc.***59**, 947–948 (1937).

366. Slebocka-Tilk, H., Ball, R. G. & Brown, R. S. The question of reversible formation of bromonium ions during the course of electrophilic bromination of olefins. 2. The crystal and molecular structure of the bromonium ion of adamantylideneadamantane. *J. Am. Chem. Soc* .**107**, 4504–4508 (1985).

367. Cristina Silva Costa, D. Additions to non-activated alkenes: Recent advances. *Arabian Journal of Chemistry* **13**, 799–834 (2020).

368. Larock, R. C. & Zhang, L. Halogenation of Alkenes and Dienes. in *Comprehensive Organic Transformations* 1–43 (John Wiley & Sons, Inc., 2018).

369. Markownikoff, W. I. Ueber die Abhängigkeit der verschiedenen Vertretbarkeit des Radicalwasserstoffs in den isomeren Buttersäuren. *Annalen der Chemie und Pharmacie* **153**, 228–259 (1870).

370. Lewis, David. E. *Addition, Elimination and Substitution: Markovnikov, Hofmann, Zaitsev and Walden*. (Elsevier, 2022).

371. Markownikoff Rule and Anti-Markownikoff Rule. in *Comprehensive Organic Name Reactions and Reagents* (John Wiley & Sons, Inc., 2010).

372. Xiong, T. & Zhang, Q. Recent advances in the direct construction of enantioenriched stereocenters through addition of radicals to internal alkenes. *Chem. Soc. Rev.* **50**, 8857–8873 (2021).

373. Lalevée, J., Allonas, X. & Fouassier, J.-P. Addition of Carbon-Centered Radicals to Double Bonds: Influence of the Alkene Structure. *J. Org. Chem.* **70**, 814–819 (2005).

374. Müller, T. E. & Beller, M. Metal-Initiated Amination of Alkenes and Alkynes. *Chem. Rev.* **98**, 675–704 (1998).

375. Müller, T. E., Hultzsch, K. C., Yus, M., Foubelo, F. & Tada, M. Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. *Chem. Rev.* **108**, 3795–3892 (2008).

376. Liu, F., Luo, G., Hou, Z. & Luo, Y. Mechanistic Insights into Scandium-Catalyzed Hydroaminoalkylation of Olefins with Amines: Origin of Regioselectivity and Charge-Based Prediction Model. *Organometallics* **36**, 1557–1565 (2017).

377. Lauzon, J. M., Eisenberger, P., Roşca, S.-C. & Schafer, L. L. Amidate Complexes of Tantalum and Niobium for the Hydroaminoalkylation of Unactivated Alkenes. *ACS Catal* **7**, 5921–5931 (2017).

378. DiPucchio, R. C., Roşca, S.-C. & Schafer, L. L. Catalytic and Atom-Economic Csp3 −Csp3 Bond Formation: Alkyl Tantalum Ureates for Hydroaminoalkylation. *Angew. Chem. Int. Ed.* **57**, 3469–3472 (2018).

379. Bielefeld, J. & Doye, S. Dimethylamine as a Substrate in Hydroaminoalkylation Reactions. *Angew. Chem. Int. Ed.* **56**, 15155–15158 (2017).

380. DiPucchio, R. C., Roşca, S.-C. & Schafer, L. L. Catalytic and Atom-Economic Csp3 −Csp3 Bond Formation: Alkyl Tantalum Ureates for Hydroaminoalkylation. *Angew. Chem.* **130**, 3527–3530 (2018).

381. Reznichenko, A. L. & Hultzsch, K. C. The Mechanism of Hydroaminoalkylation Catalyzed by Group 5 Metal Binaphtholate Complexes. *J. Am. Chem. Soc* .**134**, 3300–3311 (2012).

382. Herzon, S. B. & Hartwig, J. F. Hydroaminoalkylation of Unactivated Olefins with Dialkylamines. *J. Am. Chem. Soc* .**130**, 14940–14941 (2008).

383. Lühning, L. H., Strehl, J., Schmidtmann, M. & Doye, S. Hydroaminoalkylation of Allylsilanes and a One-Pot Procedure for the Synthesis of 1,5-Benzoazasilepines. *Eur. J. Chem.***23**, 4197–4202 (2017).

384. Chong, E., Brandt, J. W. & Schafer, L. L. 2-Pyridonate Tantalum Complexes for the Intermolecular Hydroaminoalkylation of Sterically Demanding Alkenes. *J. Am. Chem. Soc* .**136**, 10898–10901 (2014).

385. Bielefeld, J. & Doye, S. Dimethylamin als Substrat in Hydroaminoalkylierungsreaktionen. *Angew. Chem.* **129**, 15352–15355 (2017).

386. Li, Z. *et al.* Brønsted Acid Catalyzed Addition of Phenols, Carboxylic Acids, and Tosylamides to Simple Olefins. *Org. Lett.* **8**, 4175–4178 (2006).

387. Franke, R., Selent, D. & Börner, A. Applied Hydroformylation. *Chem. Rev.* **112**, 5675–5732 (2012).

388. Ojima, I., Tsai, C.-Y., Tzamarioudaki, M. & Bonafoux, D. The Hydroformylation Reaction. in *Organic Reactions* 1–354 (John Wiley & Sons, Inc., 2000).

389. Kalck, P. & Urrutigoïty, M. Tandem Hydroaminomethylation Reaction to Synthesize Amines from Alkenes. *Chem. Rev.* **118**, 3833–3861 (2018).

390. Vieira, T. O. & Alper, H. Rhodium(I)-catalyzed hydroaminomethylation of 2-isopropenylanilines as a novel route to 1,2,3,4-tetrahydroquinolines. *Chem. Commun* 2710 (2007).

391. Tararov, V. I., Kadyrov, R., Börner, A. & Riermeier, T. H. On the reductive amination of aldehydes and ketones catalyzed by homogeneous Rh(i) complexes. *Chem. Commun* 1867–1868 (2000).

392. Raoufmoghaddam, S. Recent advances in catalytic C–N bond formation: a comparison of cascade hydroaminomethylation and reductive amination reactions with the corresponding hydroamidomethylation and reductive amidation reactions. *Org. Biomol. Chem.* **12**, 7179 (2014).

393. Lewis, D. E. The Logic Behind Markovnikov's Rule: Was It an Inspired Guess? …No! *Angew. Chem. Int. Ed.* **60**, 4412–4421 (2021).

394. Hughes, P. Was Markovnikov's Rule an Inspired Guess? *J. Chem. Educ.* **83**, 1152 (2006).

395. Gual, A., Godard, C., de la Fuente, V. & Castillón, S. Design and Synthesis of Phosphite Ligands for Homogeneous Catalysis. in *Phosphorus (III) Ligands in Homogeneous Catalysis: Design and Synthesis* 81–131 (Wiley, 2012).

396. Chaikin, S. W. & Brown, W. G. Reduction of Aldehydes, Ketones and Acid Chlorides by Sodium Borohydride. *J. Am. Chem. Soc.* **71**, 122–125 (1949).

397. Gribble, G. W. & Ferguson, D. C. Reactions of sodium borohydride in acidic media. Selective reduction of aldehydes with sodium triacetoxyborohydride. *J. Chem. Soc., Chem. Commun.* 535 (1975).

398. Karakhanov, E. *et al.* Methylformate as replacement of syngas in one-pot catalytic synthesis of amines from olefins. *Catal. Sci. Technol.* **4**, 540–547 (2014).

399. Ibrahim, M. Y. S. & Abolhasani, M. Recyclable cooperative catalyst for accelerated hydroaminomethylation of hindered amines in a continuous segmented flow reactor. *Nat. Commun.* **13**, 2441 (2022).

400. Chen, C., Dong, X.-Q. & Zhang, X. Recent progress in rhodium-catalyzed hydroaminomethylation. *Org. Chem. Front.* **3**, 1359–1370 (2016).

401. Koperniku, A., Foth, P. J., Sammis, G. M. & Schafer, L. L. Zirconium Hydroaminoalkylation. An Alternative Disconnection for the Catalytic Synthesis of α-Arylated Primary Amines. *J. Am. Chem. Soc.* **141**, 18944–18948 (2019).

402. Shi, F. & Cui, X. N -Alkyl Amine Synthesis by Hydroaminomethylation. in *Catalytic Amination for N-Alkyl Amine Synthesis* 117–138 (Elsevier, 2018).

403. Bielefeld, J. & Doye, S. Fast Titanium-Catalyzed Hydroaminomethylation of Alkenes and the Formal Conversion of Methylamine. *Angew. Chem., Int. Ed.* **59**, 6138–6143 (2020).

404. Hanna, S., Holder, J. C. & Hartwig, J. F. A Multicatalytic Approach to the Hydroaminomethylation of α-Olefins. *Angew. Chem., Int. Ed.* **58**, 3368–3372 (2019).

405. Thullen, S. M. & Rovis, T. A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System. *J. Am. Chem. Soc.* **139**, 15504–15508 (2017).

406. Elgrishi, N., Kurtz, D. A. & Dempsey, J. L. Reaction Parameters Influencing Cobalt Hydride Formation Kinetics: Implications for Benchmarking H 2 -Evolution Catalysts. *J. Am. Chem. Soc.* **139**, 239–244 (2017).

407. Isidro M. Pastor & Miguel Yus. The Prins Reaction: Advances and Applications. *Curr. Org. Chem.* **11**, 925–957 (2007).

408. Arundale, E. & Mikeska, L. A. The Olefin-Aldehyde Condensation. The Prins Reaction. *Chem Rev* **51**, 505–555 (1952).

409. Hiemstra, H., Fortgens, H. P. & Speckamp, W. N. Intramolecular reactions of acyclic n-acyliminium ions II allyl silanes as nucleophiles. *Tetrahedron Lett* **26**, 3155–3158 (1985).

410. Arundale, E. & Mikeska, L. A. The Olefin-Aldehyde Condensation. The Prins Reaction. *Chem. Rev.* **51**, 505–555 (1952).

411. Hanschke, E. Zur Kenntnis der Prinsschen Reaktion, III. Mitteil. 1) : Über die Reaktion von Allylcarbinol mit Aldehyden und Ketonen. *Chem. Ber.* **88**, 1053–1061 (1955).

412. Miles, R. B., Davis, C. E. & Coates, R. M. Syn- and Anti-Selective Prins Cyclizations of δ,ε-Unsaturated Ketones to 1,3-Halohydrins with Lewis Acids. *J. Org. Chem.* **71**, 1493–1501 (2006).

413. Díaz-Oviedo, C. D., Maji, R. & List, B. The Catalytic Asymmetric Intermolecular Prins Reaction. *J. Am. Chem. Soc.* **143**, 20598–20604 (2021).

414. Subba Reddy, B. v., Nair, P. N., Antony, A., Lalli, C. & Grée, R. The Aza-Prins Reaction in the Synthesis of Natural Products and Analogues. *J. Org. Chem.* **2017**, 1805–1819 (2017).

415. Mittapalli, R. R., Coles, S. J., Klooster, W. T. & Dobbs, A. P. A Stereoselective aza-Prins Reaction: Rapid Access to Enantiopure Piperidines and Pipecolic Acids. *J. Org. Chem.* **86**, 2076–2089 (2021).

416. Subba Reddy, B. v., Nair, P. N., Antony, A., Lalli, C. & Grée, R. The Aza-Prins Reaction in the Synthesis of Natural Products and Analogues. *J. Org. Chem.* **2017**, 1805–1819 (2017).

417. Heathcock, C. H. The Enchanting Alkaloids of Yuzuriha. *Angew. Chem., Int. Ed. Engl.* **31**, 665–681 (1992).

418. Ruggeri, R. B., Hansen, M. M. & Heathcock, C. H. Total synthesis of (.+-.)-methyl homosecodaphniphyllate. A remarkable new tetracyclization reaction. *J. Am. Chem. Soc.* **110**, 8734–8736 (1988).

419. Boger, D. L. Diels-alder reactions of azadienes. *Tetrahedron* **39**, 2869–2939 (1983).

420. Eddaif, A. *et al.* Intramolecular Diels-Alder reactions of 3H-pyrroles resulting from thermal rearrangements of 2H-pyrroles. *J. Org. Chem.* **52**, 5548–5560 (1987).

421. Ofial, A. R. & Mayr, H. Reactions of Allylsilanes with Iminium Salts: Ene Reactions with Inverse Electron Demand. *J. Org. Chem.* **61**, 5823–5830 (1996).

422. Ofial, A. R. & Mayr, H. A Novel Pentaannulation Reaction of Iminium Ions. *Liebigs Annalen* **1997**, 333–335 (1997).

423. Cohen, T. & Onopchenko, A. Competing hydride transfer and ene reactions in the aminoalkylation of 1-alkenes with N,N-dimethylmethyleniminium ions. A literature correction. *J. Org. Chem.* **48**, 4531–4537 (1983).

424. Schmidle, C. J. & Mansfield, R. C. The Aminomethylation of Olefins. I. The Reaction of Secondary Amines, Formaldehyde, and Olefins. *J. Am. Chem. Soc.* **77**, 4636–4638 (1955).

425. Xie, Y., Hu, J., Wang, Y., Xia, C. & Huang, H. Palladium-Catalyzed Vinylation of Aminals with Simple Alkenes: A New Strategy To Construct Allylamines. *J. Am. Chem. Soc.* **134**, 20613–20616 (2012).

426. Kleinman, E. F. Dimethyl(methylene)ammonium Iodide. in *Encyclopedia of Reagents for Organic Synthesis* (John Wiley & Sons, Ltd, 2001).

427. Schreiber, J., Maag, H., Hashimoto, N. & Eschenmoser, A. Dimethyl(methylene)ammonium Iodide. *Angew. Chem., Int. Ed. Engl.* **10**, 330–331 (1971).

428. Haggin, J. Chemists Seek Greater Recognition for Catalysis. *Chemical & Engineering News Archive* **71**, 23–27 (1993).

429. Garro-Helion, F., Merzouk, A. & Guibe, F. Mild and selective palladium(0)-catalyzed deallylation of allylic amines. Allylamine and diallylamine as very convenient ammonia equivalents for the synthesis of primary amines. *J. Org. Chem.* **58**, 6109–6113 (1993).

430. Trowbridge, A., Reich, D. & Gaunt, M. J. Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation. *Nature* **561**, 522–527 (2018).

431. Reich, D., Trowbridge, A. & Gaunt, M. J. Rapid Syntheses of (−)-FR901483 and (+)-TAN1251C Enabled by Complexity-Generating Photocatalytic Olefin Hydroaminoalkylation. *Angew. Chem., Int. Ed.* **59**, 2256–2261 (2020).

432. Müller, K., Faeh, C. & Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science (1979)* **317**, 1881–1886 (2007).

433. Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem* **61**, 5822–5880 (2018).

434. Jin, J. *et al.* Synthesis and comparison of CF3 versus CH3 substituted perfluorocyclobutyl (PFCB) networks for optical applications. *J. Polym. Sci. A Polym Chem* **42**, 5292–5300 (2004).

435. Zanda, M. Trifluoromethyl group: an effective xenobiotic function for peptide backbone modification. *New J. Chem.* **28**, 1401 (2004).

436. Sani, M., Volonterio, A. & Zanda, M. The Trifluoroethylamine Function as Peptide Bond Replacement. *ChemMedChem* **2**, 1693–1700 (2007).

437. Onyeagusi, C. I. & Malcolmson, S. J. Strategies for the Catalytic Enantioselective Synthesis of α-Trifluoromethyl Amines. *ACS Catal.* **10**, 12507–12536 (2020).

438. Alonso, C. *et al.* Synthesis of Fluorinated β-Aminophosphonates and γ-Lactams. *J. Org. Chem.* **78**, 3858–3866 (2013).

439. Supranovich, V. I., Levin, V. v., Struchkova, M. I. & Dilman, A. D. Photocatalytic Reductive Fluoroalkylation of Nitrones. *Org- Lett.* **20**, 840–843 (2018).

440. Fu, W., Guo, W., Zou, G. & Xu, C. Selective trifluoromethylation and alkynylation of tetrahydroisoquinolines using visible light irradiation by Rose Bengal. *J. Fluor Chem.* **140**, 88–94 (2012).

441. Chu, L. & Qing, F.-L. Benzoyl peroxide (BPO)-promoted oxidative trifluoromethylation of tertiary amines with trimethyl(trifluoromethyl)silane. *Chem. Commun.* **46**, 6285 (2010).

442. Mitsudera, H. & Li, C.-J. Copper-catalyzed oxidative trifluoromethylation of benzylic sp3 C–H bond adjacent to nitrogen in amines. *Tetrahedron Lett* **52**, 1898–1900 (2011).

443. Vadagaonkar, K., Kalmode, H., Prakash, S. & Chaskar, A. Iodine-Mediated Domino Protocol for the Synthesis of Benzamides from Ethylarenes via sp3 C–H Functionalization. *Synlett* **26**, 1677–1682 (2015).

444. Prakash, G. K. S. *et al.* Nucleophilic Perfluoroalkylation of Imines and Carbonyls: Perfluoroalkyl Sulfones as Efficient Perfluoroalkyl-Transfer Motifs. *Org. Lett.***12**, 2932–2935 (2010).

445. Gagosz, F. & Zard, S. Z. A Direct Approach to α-Trifluoromethylamines. *Org. Lett.* **5**, 2655–2657 (2003).

446. Neouchy, Z., Gomez Pardo, D. & Cossy, J. Synthesis of Optically Active α-Trifluoromethylamines by Rearrangement of β-Amino-α-trifluoromethyl Alcohols. *Org. Lett.* **20**, 6017–6021 (2018).

447. Eschweiler, W. Ersatz von an Stickstoff gebundenen Wasserstoffatomen durch die Methylgruppe mit Hülfe von Formaldehyd. *Ber. Dtsch. Chem. Ges.***38**, 880–882 (1905).

448. Farkas, E. & Sunman, C. J. Chiral synthesis of doxpicomine. *J. Org. Chem.* **50**, 1110–1112 (1985).

449. Gao, J., Tian, Z. & Yang, X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* **14**, 72–73 (2020).

450. Strecker, A. Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper; *Annalen der Chemie und Pharmacie* **75**, 27–45 (1850).

451. Maruoka, K. & Ooi, T. Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis. *Chem Rev* **103**, 3013–3028 (2003).

452. Miyashita, A. *et al.* Synthesis of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), an atropisomeric chiral bis(triaryl)phosphine, and its use in the rhodium(I)-catalyzed asymmetric hydrogenation of .alpha.-(acylamino)acrylic acids. *J. Am. Chem. Soc.* **102**, 7932–7934 (1980).

453. Bodkin, J. A. & McLeod, M. D. The Sharpless asymmetric aminohydroxylation. *J Chem Soc Perkin 1* 2733–2746 (2002).

454. Heravi, M. M., Lashaki, T. B., Fattahi, B. & Zadsirjan, V. Application of asymmetric Sharpless aminohydroxylation in total synthesis of natural products and some synthetic complex bio-active molecules. *RSC Adv* **8**, 6634–6659 (2018).

455. Liu, D., Rubin, G. M., Dhakal, D., Chen, M. & Ding, Y. Biocatalytic synthesis of peptidic natural products and related analogues. *iScience* **24**, 102512 (2021).

456. Ellis, J. M. *et al.* Biocatalytic synthesis of non-standard amino acids by a decarboxylative aldol reaction. *Nat. Catal.* **5**, 136–143 (2022).

457. Wu, J.-F. *et al.* Regiodivergent and stereoselective hydroxyazidation of alkenes by biocatalytic cascades. *iScience* **24**, 102883 (2021).

458. Piper, S. & Risch, N. Direct Aminoalkylation of α-Branched Aldehydes with in situ Generated Glycine Cation Equivalents. *Synlett* 1489–1496 (2004).

459. Merla, B., Grumbach, H.-J. & Risch, N. ChemInform Abstract: Efficient Synthesis of γ-Oxo- and γ-Hydroxy-α-amino Acids. *ChemInform* **30**, (2010).

460. Hiratake, J. & Oda, J. Aminophosphonic and Aminoboronic Acids as Key Elements of a Transition State Analogue Inhibitor of Enzymes. *Biosci. Biotechnol. Biochem.* **61**, 211–218 (1997).

461. Merino, P., Marqués-López, E. & Herrera, R. P. Catalytic Enantioselective Hydrophosphonylation of Aldehydes and Imines. *Adv Synth Catal* **350**, 1195–1208 (2008).

462. Cherkasov, R. A. & Galkin, V. I. The Kabachnik–Fields reaction: synthetic potential and the problem of the mechanism. *Russ. Chem. Rev.***67**, 857–882 (1998).

463. Risch, N., Piper, S., Winter, A. & Lefarth-Risse, A. An Efficient Synthesis of Novel ?-Aminophosphonates Based on a Mannich-Type Reaction. *European J. Org. Chem.* **2005**, 387–394 (2005).

464. Rehn, S., Ofial, A. R. & Mayr, H. Synthesis of Allylamines from Alkynes and Iminium Ions. *Synthesis (Stuttg)* 1790–1796 (2003).

465. Ofial, A. R. & Mayr, H. Ene Reactions of Alkynes for the Stereoselective Synthesis of Allylamines. *Angew. Chem. Int. Ed. in English* **36**, 143–145 (1997).

466. Ofial, A. R. & Mayr, H. Reactions of Allylsilanes with Iminium Salts: Ene Reactions with Inverse Electron Demand. *J. Org. Chem.* **61**, 5823–5830 (1996).

467. Peterson, P. E. & Duddey, J. E. Possible Vinyl Cation Intermediates, a 1,4-Chlorine Shift, and a Trimerization in the Reaction of Trifluoroacetic Acid with Alkynes. *J. Am. Chem. Soc* .**85**, 2865–2866 (1963).

468. Zafrani, Y. *et al.* CF 2 H, a Functional Group-Dependent Hydrogen-Bond Donor: Is It a More or Less Lipophilic Bioisostere of OH, SH, and CH3? *J. Med. Chem.* **62**, 5628–5637 (2019).

469. Sessler, C. D. *et al.* CF2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **139**, 9325–9332 (2017).

470. Brito, D. A., Yang, Z. & Rieder, C. L. Microtubules do not promote mitotic slippage when the spindle assembly checkpoint cannot be satisfied. *J. Cell Biol.* **182**, 623–629 (2008).

471. Jordan, M. A. & Wilson, L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer* **4**, 253–265 (2004).

472. Ganguly, A., Yang, H. & Cabral, F. Paclitaxel-Dependent Cell Lines Reveal a Novel Drug Activity. *Mol. Cancer Ther* **9**, 2914–2923 (2010).

473. Berveiller, P. & Mir, O. Taxanes during Pregnancy: Probably Safe, but Still to Be Optimized. *Oncology* **83**, 239–240 (2012).

474. Peltier, S., Oger, J.-M., Lagarce, F., Couet, W. & Benoît, J.-P. Enhanced Oral Paclitaxel Bioavailability After Administration of Paclitaxel-Loaded Lipid Nanocapsules. *Pharm. Res.* **23**, 1243–1250 (2006).

475. Sofias, A. M., Dunne, M., Storm, G. & Allen, C. The battle of "nano" paclitaxel. *Adv. Drug. Deliv. Rev.* **122**, 20–30 (2017).

476. Flam, F. Race to Synthesize Taxol Ends in a Tie. *Science (1979)* **263**, 911–911 (1994).

477. Nicolaou, K. C. *et al.* Total synthesis of taxol. *Nature* **367**, 630–634 (1994).

478. Holton, R. A. *et al.* First total synthesis of taxol. 2. Completion of the C and D rings. *J. Am. Chem. Soc.* **116**, 1599–1600 (1994).

479. Holton, R. A. *et al.* First total synthesis of taxol. 1. Functionalization of the B ring. *J. Am. Chem. Soc.* **116**, 1597–1598 (1994).

480. Oshige, M. *et al.* Taxol derivatives are selective inhibitors of DNA polymerase α. *Bioorg. Med. Chem.* **12**, 2597–2601 (2004).

481. Nicolaou, K. C., Chen, J. S. & Dalby, S. M. From nature to the laboratory and into the clinic. *Bioorg. Med. Chem.* **17**, 2290–2303 (2009).

482. Ricciotti, E. & FitzGerald, G. A. Prostaglandins and Inflammation. *Arterioscler Thromb Vasc Biol* **31**, 986–1000 (2011).

483. Kurzrok, R. & Lieb, C. C. Biochemical Studies of Human Semen. II. The Action of Semen on the Human Uterus. *Ex.p Biol. Med.* **28**, 268–272 (1930).

484. Euler, U. S. Über die Spezifische Blutdrucksenkende Substanz des Menschlichen Prostata- und Samenblasensekretes. *Klein. Wochenschr.* **14**, 1182–1183 (1935).

485. Shampo, M. A. & Kyle, R. A. Sune Bergström—Nobel Prize for Prostaglandin Studies. *Mayo. Clin. Proc.* **73**, 462 (1998).

486. Corey, E. J. & Loh, T. P. First application of attractive intramolecular interactions to the design of chiral catalysts for highly enantioselective Diels-Alder reactions. *J. Am. Chem. Soc* .**113**, 8966–8967 (1991).

487. Corey, E. J. *et al.* Stereospecific total synthesis of prostaglandins E3 and F3 a. *J. Am. Chem. Soc* .**93**, 1490–1491 (1971).

489. Corey, E. J., Weinshenker, N. M., Schaaf, T. K. & Huber, W. Stereo-controlled synthesis of dl-prostaglandins F2 a and E2. *J. Am. Chem. Soc* .**91**, 5675–5677 (1969).

490. Corey, E. J., Schaaf, T. K., Huber, Willy., Koelliker, Urs. & Weinshenker, N. M. Total Synthesis of Prostaglandins F 2α and E 2 as the Naturally Occuring Forms. *J. Am. Chem. Soc* .**92**, 397–398 (1970).

491. Zhou, Q. & Snider, B. B. Synthesis of (±)-Vibralactone. *Org. Lett.***10**, 1401–1404 (2008).

492. Baldwin, J. E. Rules for ring closure. *J. Chem. Soc., Chem. Commun.* 734 (1976).

493. Danishefsky, S., Schuda, P. F., Kitahara, T. & Etheredge, S. J. The total synthesis of dl-vernolepin and dl-vernomenin. *J. Am. Chem. Soc* .**99**, 6066–6075 (1977).

494. Dowle, M. D. & Davies, D. I. Synthesis and synthetic utility of halolactones. *Chem. Soc. Rev.* **8**, 171 (1979).

495. Noyori, R. & Suzuki, M. Prostaglandin Syntheses by Three-Component Coupling. New Synthetic Methods(49). *Angew. Chem. Int. Ed.* **23**, 847–876 (1984).

496. Coulthard, G., Erb, W. & Aggarwal, V. K. Stereocontrolled organocatalytic synthesis of prostaglandin PGF2α in seven steps. *Nature* **489**, 278–281 (2012).

497. Prévost, S. *et al.* Synthesis of Prostaglandin Analogues, Latanoprost and Bimatoprost, Using Organocatalysis via a Key Bicyclic Enal Intermediate. *Org. Lett.* **17**, 504–507 (2015).

498. Baars, H., Classen, M. J. & Aggarwal, V. K. Synthesis of Alfaprostol and PGF 2α through 1,4-Addition of an Alkyne to an Enal Intermediate as the Key Step. *Org. Lett.* **19**, 6008–6011 (2017).

499. Pelšs, A. *et al.* Reoptimization of the Organocatalyzed Double Aldol Domino Process to a Key Enal Intermediate and Its Application to the Total Synthesis of Δ12 -Prostaglandin J3. *Eur. J. Chem.***24**, 9542–9545 (2018).

500. Umekubo, N., Suga, Y. & Hayashi, Y. Pot and time economies in the total synthesis of Corey lactone. *Chem Sci* **11**, 1205–1209 (2020).

501. Gil, S., Parra, M., Rodriguez, P. & Segura, J. Recent Developments in γ-Lactone Synthesis. *Mini. Rev. Org. Chem.* **6**, 345–358 (2009).

502. van der Schaft, P. H., ter Burg, N., van den Bosch, S. & Cohen, A. M. Microbial production of natural δ-decalactone and δ-dodecalactone from the corresponding α,β-unsaturated lactones in Massoi bark oil. *Appl Microbiol Biotechnol* **36**, 712–716 (1992).

503. Liu, Q.-A., Zheng, J.-J., Gu, Y.-C., Wang, C.-Y. & Shao, C.-L. The Chemistry and Bioactivity of Macrolides from Marine Microorganisms. 353–401 (2015).

504. Parenty, A., Moreau, X. & Campagne, J.-M. Macrolactonizations in the Total Synthesis of Natural Products. *Chem Rev* **106**, 911–939 (2006).

505. Corey, E. J., Nicolaou, K. C. & Melvin, L. S. Synthesis of novel macrocyclic lactones in the prostaglandin and polyether antibiotic series. *J. Am. Chem. Soc* .**97**, 653–654 (1975).

506. Corey, E. J. & Nicolaou, K. C. Efficient and mild lactonization method for the synthesis of macrolides. *J. Am. Chem. Soc* .**96**, 5614–5616 (1974).

507. Corey, E. J., Brunelle, D. J. & Stork, P. J. Mechanistic studies on the double activation method for the synthesis of macrocyclic lactones. *Tetrahedron Lett* **17**, 3405–3408 (1976).

508. Shiina, I. & Mukaiyama, T. A Novel Method for the Preparation of Macrolides from ω-Hydroxycarboxylic Acids. *Chem Lett* **23**, 677–680 (1994).

509. Shiina, I. An effective method for the synthesis of carboxylic esters and lactones using substituted benzoic anhydrides with Lewis acid catalysts. *Tetrahedron* **60**, 1587–1599 (2004).

510. Shiina, I. An Adventurous Synthetic Journey with MNBA from Its Reaction Chemistry to the Total Synthesis of Natural Products. *Bull. Chem. Soc. Jpn.* **87**, 196–233 (2014).

511. Inanaga, J., Hirata, K., Saeki, H., Katsuki, T. & Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn* **52**, 1989–1993 (1979).

512. Kawanami, Y., Dainobu, Y., Inanaga, J., Katsuki, T. & Yamaguchi, M. Synthesis of Thiol Esters by Carboxylic Trichlorobenzoic Anhydrides. *Bull. Chem. Soc. Jpn* **54**, 943–944 (1981).

513. Krow, G. R. The Baeyer-Villiger Oxidation of Ketones and Aldehydes. in *Organic Reactions* 251–798 (John Wiley & Sons, Inc., 1993).

514. Yamabe, S. & Yamazaki, S. The Role of Hydrogen Bonds in Baeyer−Villiger Reactions. *J. Org. Chem.* **72**, 3031–3041 (2007).

515. Crudden, C. M., Chen, A. C. & Calhoun, L. A. A Demonstration of the Primary Stereoelectronic Effect in the Baeyer–Villiger Oxidation ofα-Fluorocyclohexanones. *Angew. Chem.* **39**, 2851–2855 (2000).

516. Renz, M. & Meunier, B. 100 Years of Baeyer–Villiger Oxidations. *Eur. J. Org. Chem.* **1999**, 737–750 (1999).

517. Turner, R. B. Stereochemistry of the Peracid Oxidation of Ketones 1. *J. Am. Chem. Soc.* **72**, 878–882 (1950).

518. Gallagher, T. F. & Kritchevsky, T. H. Perbenzoic Acid Oxidation of 20-Ketosteroids and the Stereochemistry of C-17 1. *J. Am. Chem. Soc.* **72**, 882–885 (1950).

519. Zhang, Q.-B. *et al.* Preparation of α-Acyloxy Ketones via Visible-Light-Driven Aerobic Oxo-Acyloxylation of Olefins with Carboxylic Acids. *Org. Lett.* **18**, 5256–5259 (2016).

520. Triandafillidi, I., Kokotou, M. G. & Kokotos, C. G. Photocatalytic Synthesis of γ-Lactones from Alkenes: High-Resolution Mass Spectrometry as a Tool to Study Photoredox Reactions. *Org. Lett.* **20**, 36–39 (2018).

521. Duhamel, T., Stein, C. J., Martínez, C., Reiher, M. & Muñiz, K. Engineering Molecular Iodine Catalysis for Alkyl–Nitrogen Bond Formation. *ACS Catal* **8**, 3918–3925 (2018).

522. Nakatsuji, H., Sawamura, Y., Sakakura, A. & Ishihara, K. Cooperative Activation with Chiral Nucleophilic Catalysts and N -Haloimides: Enantioselective Iodolactonization of 4-Arylmethyl-4-pentenoic Acids. *Angew. Chem., Int. Ed.* **53**, 6974–6977 (2014).

523. Beebe, T. R. *et al.* Primary alcohol oxidation with N-iodosuccinimide. *J. Org. Chem.* **48**, 3126–3128 (1983).

524. Im, H., Kang, D., Choi, S., Shin, S. & Hong, S. Visible-Light-Induced C–O Bond Formation for the Construction of Five- and Six-Membered Cyclic Ethers and Lactones. *Org. Lett.* **20**, 7437–7441 (2018).

525. Sathyamoorthi, S. & du Bois, J. Copper-Catalyzed Oxidative Cyclization of Carboxylic Acids. *Org. Lett.* **18**, 6308–6311 (2016).

526. Pandey, G., Pal, S. & Laha, R. Direct Benzylic CH Activation for CO Bond Formation by Photoredox Catalysis. *Angew. Chem., Int. Ed.* **52**, 5146–5149 (2013).

527. Narayanam, J. M. R. & Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **40**, 102–113 (2011).

528. Tucker, J. W. & Stephenson, C. R. J. Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **77**, 1617–1622 (2012).

529. Romero, N. A. & Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **116**, 10075–10166 (2016).

530. Koike, T. & Akita, M. Visible-light radical reaction designed by Ru- and Ir-based photoredox catalysis. *Inorg. Chem. Front.* **1**, 562–576 (2014).

531. Arias-Rotondo, D. M. & McCusker, J. K. The photophysics of photoredox catalysis: a roadmap for catalyst design. *Chem. Soc. Rev.* **45**, 5803–5820 (2016).

532. Shaw, M. H., Twilton, J. & MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **81**, 6898–6926 (2016).

533. Prier, C. K., Rankic, D. A. & MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **113**, 5322–5363 (2013).

534. Skubi, K. L., Blum, T. R. & Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **116**, 10035–10074 (2016).

535. Chatterjee, T., Iqbal, N., You, Y. & Cho, E. J. Controlled Fluoroalkylation Reactions by Visible-Light Photoredox Catalysis. *Acc. Chem. Res.* **49**, 2284–2294 (2016).

536. Huang, L., Jiang, H., Qi, C. & Liu, X. Copper-Catalyzed Intermolecular Oxidative [3 + 2] Cycloaddition between Alkenes and Anhydrides: A New Synthetic Approach to γ-Lactones. *J. Am. Chem. Soc.* **132**, 17652–17654 (2010).

537. Acosta-Quiroga, K., Rojas-Peña, C., Nerio, L. S., Gutiérrez, M. & Polo-Cuadrado, E. Spirocyclic derivatives as antioxidants: a review. *RSC Adv* **11**, 21926–21954 (2021).

538. Luther, J. M. Is there a new dawn for selective mineralocorticoid receptor antagonism? *Curr. Opin. Chem. Biol.* **23**, 456–461 (2014).

539. Sandow, J. Endocrine Pharmacology. in *Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays* 421–520 (Springer Berlin Heidelberg, 2013).

540. Siless, G. E. *et al.* Preparation and antitrypanosomal activity of secochiliolide acid derivatives. *Bioorg. Med. Chem. Lett.* **23**, 4964–4967 (2013).

541. Yeh, M.-C. P. *et al.* Diastereoselective synthesis of vicinal cis-dihydroxyheterospirocycles by one-pot epoxidation/spirocyclization of C(3)-functionalized cyclohex-2-en-1-ols. *Org. Biomol. Chem.* **11**, 3393 (2013).

542. Aparece, M. D. & Vadola, P. A. Gold-Catalyzed Dearomative Spirocyclization of Aryl Alkynoate Esters. *Org. Lett.* **16**, 6008–6011 (2014).

543. Tang, B.-X., Yin, Q., Tang, R.-Y. & Li, J.-H. Electrophilic ipso -Cyclization of N -(p -Methoxyaryl)propiolamides Involving an Electrophile-Exchange Process. *J. Org. Chem.* **73**, 9008–9011 (2008).

545. Zhang, X. & Larock, R. C. Synthesis of Spiro[4.5]trienones by Intramolecular i pso -Halocyclization of 4-(p -Methoxyaryl)-1-alkynes. *J. Am. Chem. Soc.* **127**, 12230–12231 (2005).

546. Low-Beinart, L., Sun, X., Sidman, E. & Kesharwani, T. Synthesis of pyrrolo-[2,1-j]quinolone framework via intramolecular electrophilic ipso-cyclization. *Tetrahedron Lett.* **54**, 1344–1347 (2013).

547. Tang, B.-X. *et al.* Intramolecular ipso -Halocyclization of 4-(p -Unsubstituted-aryl)-1-alkynes Leading to Spiro[4,5]trienones: Scope, Application, and Mechanistic Investigations. *J. Org. Chem.* **77**, 2837–2849 (2012).

548. Palisse, A. & Kirsch, S. F. Metal-free reactions of alkynes via electrophilic iodocarbocyclizations. *Org. Biomol. Chem.* **10**, 8041 (2012).

549. Yu, Q.-F. *et al.* Electrophilic ipso -Iodocyclization of N -(4-Methylphenyl)propiolamides: Selective Synthesis of 8-Methyleneazaspiro[4,5]trienes. *J. Org. Chem.* **73**, 3658–3661 (2008).

550. Dohi, T. *et al.* Discovery of Stabilized Bisiodonium Salts as Intermediates in the Carbon-Carbon Bond Formation of Alkynes. *Angew. Chem., Int. Ed.* **50**, 3784–3787 (2011).

551. Cala, L., Mendoza, A., Fañanás, F. J. & Rodríguez, F. A catalytic multicomponent coupling reaction for the enantioselective synthesis of spiroacetals. *Chem. Commun.* **49**, 2715 (2013).

552. Perron, F. & Albizati, K. F. Chemistry of spiroketals. *Chem. Rev.* **89**, 1617–1661 (1989).

553. Aho, J. E., Pihko, P. M. & Rissa, T. K. Nonanomeric Spiroketals in Natural Products: Structures, Sources, and Synthetic Strategies. *Chem. Rev.* **105**, 4406–4440 (2005).

554. Corvol, P., Michaud, A., Menard, J., Freifeld, M. & Mahoudeau, J. Antiandrogenic Effect of Spirolactones: Mechanism of Action. *Endocrinology* **97**, 52–58 (1975).

555. Terada, M., Soga, K. & Momiyama, N. Enantioselective Activation of Aldehydes by Chiral Phosphoric Acid Catalysts in an Aza-ene-type Reaction between Glyoxylate and Enecarbamate. *Angew. Chem., Int. Ed.* **47**, 4122–4125 (2008).

556. Brückner, R. The β-elimination route to stereodefined γ-alkylidenebutenolides. *Chem. Commun.* 141–152 (2001).

557. Negishi, E. & Kotora, M. Regio- and stereoselective synthesis of γ-alkylidenebutenolides and related compounds. *Tetrahedron* **53**, 6707–6738 (1997).

558. Jusseau, X., Chabaud, L. & Guillou, C. Synthesis of γ-butenolides and α,β-unsaturated γ-butyrolactams by addition of vinylogous nucleophiles to Michael acceptors. *Tetrahedron* **70**, 2595–2615 (2014).

559. Hoffmann, H. M. R. & Rabe, J. Synthesis and Biological Activity of a-Methylene-y-butyrolactones. *Angew. Chem., Int. Ed.* **24**, 94–110 (1985).

560. Rao, Y. S. Chemistry of Butenolides. *Chem. Rev.* **64**, 353–388 (1964).

561. Bandichhor, R., Nosse, B. & Reiser, O. Paraconic Acids: The Natural Products from Lichen Symbiont. *ChemInform* **36**, (2005).

562. Montagnon, T., Tofi, M. & Vassilikogiannakis, G. Using Singlet Oxygen to Synthesize Polyoxygenated Natural Products from Furans. *Acc. Chem. Res.* **41**, 1001–1011 (2008).

563. Mao, B., Fañanás-Mastral, M. & Feringa, B. L. Catalytic Asymmetric Synthesis of Butenolides and Butyrolactones. *Chem. Rev.* **117**, 10502–10566 (2017).

564. Seitz, M. & Reiser, O. Synthetic approaches towards structurally diverse γ-butyrolactone natural-product-like compounds. *Curr. Opin. Chem. Biol.* **9**, 285–292 (2005).

565. Ottow, E. A. *et al.* Populus euphratica Displays Apoplastic Sodium Accumulation, Osmotic Adjustment by Decreases in Calcium and Soluble Carbohydrates, and Develops Leaf Succulence under Salt Stress. *Plant Physiol.* **139**, 1762–1772 (2005).

566. Uchida, M. *et al.* Total synthesis and absolute configuration of avenolide, extracellular factor in Streptomyces avermitilis. *J. Antibiot. (Tokyo)* **64**, 781–787 (2011).

567. Cavallito, C. J., Fruehauf, D. M. & Bailey, J. H. Lactone Aliphatic Acids as Antibacterial Agents. *J. Am. Chem. Soc.* **70**, 3724–3726 (1948).

568. Kitani, S. *et al.* Avenolide, a Streptomyces hormone controlling antibiotic production in Streptomyces avermitilis. *Proc. Natl. Acad. Sci. U.S.A* **108**, 16410–16415 (2011).

569. Yasuda, N., Sugimoto, Y., Kato, M., Inanaga, S. & Yoneyama, K. (+)-Strigol, a witchweed seed germination stimulant, from Menispermum dauricum root culture. *Phytochemistry* **62**, 1115–1119 (2003).

570. Lone, S. H., Bhat, K. A. & Khuroo, M. A. Arglabin: From isolation to antitumor evaluation. *Chem. Biol. interact.* **240**, 180–198 (2015).

571. Mayr, H. & Ofial, A. R. Do general nucleophilicity scales exist? *J. Phys. Org. Chem.* **21**, 584–595 (2008).

572. Phan, T. B., Breugst, M. & Mayr, H. Towards a General Scale of Nucleophilicity? *Angew. Chem., Int. Ed.* **45**, 3869–3874 (2006).

573. Pine, S. H. The Base-Promoted Rearrangements of Quaternary Ammonium Salts. in *Organic Reactions* 403–464 (John Wiley & Sons, Inc., 2011).

574. Fang, H. & Oestreich, M. Reductive Deamination with Hydrosilanes Catalyzed by B(C6F5)3. *Angew. Chem., Int. Ed.* **59**, 11394–11398 (2020).

575. Miller, A. K., Hughes, C. C., Kennedy-Smith, J. J., Gradl, S. N. & Trauner, D. Total Synthesis of (−)-Heptemerone B and (−)-Guanacastepene E. *J. Am. Chem. Soc.* **128**, 17057–17062 (2006).

576. Kleinman, E. F. Dimethyl(methylene)ammonium Iodide. in *Encyclopedia of Reagents for Organic Synthesis* (John Wiley & Sons, Ltd, 2001).

577. Schreiber, J., Maag, H., Hashimoto, N. & Eschenmoser, A. Dimethyl(methylene)ammonium Iodide. *Angew. Chem. Int. Ed. in English* **10**, 330–331 (1971).

578. Kelly, H. C., Yasui, S. C. & Twiss-Brooks, A. B. Hypochlorite chlorination of tertiary amine-boranes. *Inor. Chem.* **23**, 2220–2223 (1984).

579. Su, J., Ma, X., Ou, Z. & Song, Q. Deconstructive Functionalizations of Unstrained Carbon–Nitrogen Cleavage Enabled by Difluorocarbene. *CAS Cent. Sci.* **6**, 1819–1826 (2020).

580. Peng, B., Geerdink, D., Farès, C. & Maulide, N. Chemoselective Intermolecular α-Arylation of Amides. *Angew. Chem. Int. Ed.* **53**, 5462–5466 (2014).

581. Yao, W. *et al.* A highly efficient catalytic α-alkylation of unactivated amides using primary alcohols. *Tetrahedron Lett* **57**, 2919–2921 (2016).

582. D. McConnell, M. Impagnatiello, D. Kessler, O. Kraemer, S. Schneider, L. Van Der Veen, U. W.- & Czernilofsky, T. W. Thiazolyl-Dihydro-Indazoles. (2009).

583. F. Buxton, T. Ehara, P. Ganju, A. Hallett, O. Irie, A. Iwasaki, T. Kanazawa, K. Masuya, K. N. & J. Sakaki, et al. 2-Cyanopyrrolopyrimidines and Pharmaceutical Uses Thereof. (2004). AU2004210422B2

584. Britton, J., Chalker, J. M. & Raston, C. L. Rapid Vortex Fluidics: Continuous Flow Synthesis of Amides and Local Anesthetic Lidocaine. *Eur. J. Chem.***21**, 10660–10665 (2015).

585. Tona, V. *et al.* Chemo- and Stereoselective Transition-Metal-Free Amination of Amides with Azides. *J. Am. Chem. Soc* .**138**, 8348–8351 (2016).

586. Li, J.-S. *et al.* Solvent-, and Catalyst-free Acylation of Anilines with Meldrum's Acids: ANeat Access to Anilides. *ChemistrySelect* **2**, 1770–1773 (2017).

587. Bull, J. A., Hutchings, M. G. & Quayle, P. A Remarkably Simple and Efficient Benzannulation Reaction. *Angew. Chem. Int. Ed.* **46**, 1869–1872 (2007).

588. Das, B., Kashinatham, A. & Madhusudhan, P. Regioselective reduction of the α,β-double bond of some naturally occurring dienamides using NaBH4I2 system. *Tetrahedron Lett* **39**, 677–678 (1998).

589. Gradl, S. N., Kennedy-Smith, J. J., Kim, J. & Trauner, D. A Practical Variant of the Claisen-Eschenmoser Rearrangement: Synthesis of Unsaturated Morpholine Amides. *Synlett* **2002**, 0411–0414 (2002).

590. Leung, P. S.-W., Teng, Y. & Toy, P. H. Chromatography-Free Wittig Reactions Using a Bifunctional Polymeric Reagent. *Org. Lett.* **12**, 4996–4999 (2010).

591. Dupau, P., Epple, R., Thomas, A., Fokin, V. & Sharpless, K. Barry. Osmium-Catalyzed Dihydroxylation of Olefins in Acidic Media: Old Process, New Tricks. *Adv. Synth. Catal.* **344**, 421–433 (2002).

592. Rodríguez-Fernández, M., Yan, X., Collados, J. F., White, P. B. & Harutyunyan, S. R. Lewis Acid Enabled Copper-Catalyzed Asymmetric Synthesis of Chiral β-Substituted Amides. *J. Am. Chem. Soc* .**139**, 14224–14231 (2017).

593. Rademacher, J. T., Baum, M., Pallack, M. E., Brittain, W. J. & Simonsick, W. J. Atom Transfer Radical Polymerization of N,N -Dimethylacrylamide. *Macromolecules* **33**, 284–288 (2000).

594. Bryantsev, V. S. *et al.* Investigation of Fluorinated Amides for Solid–Electrolyte Interphase Stabilization in Li–O2 Batteries Using Amide-Based Electrolytes. *The Journal of Physical Chemistry C* **117**, 11977–11988 (2013).

595. Bonciolini, S., di Filippo, M. & Baumann, M. A scalable continuous photochemical process for the generation of aminopropylsulfones. *Org Biomol Chem* **18**, 9428–9432 (2020).

596. Kosugi, H., Kitaoka, M., Tagami, K., Takahashi, A. & Uda, H. Simple and stereocontrolled preparation of optically pure (E)- and (Z)-1-alkenyl p-tolyl sulfoxides via 1-alkynyl p-tolyl sulfoxides. *J. Org. Chem.* **52**, 1078–1082 (1987).

597. Signore, G., Samaritani, S., Malanga, C. & Menicagli, R. Reinheckel Protocol Revisited: Synthesis of (E)-α,β-Unsaturated Sulfoxides. *Synthesis (Stuttg)* **2006**, 762–764 (2006).

598. Piper, S. & Risch, N. Direct aminoalkylation of α-branched aldehydes with in situ generated glycine cation equivalents. *Synlett* 1489–1496 (2004).

599. Risch, N., Piper, S., Winter, A. & Lefarth-Risse, A. An Efficient Synthesis of Novel ?-Aminophosphonates Based on a Mannich-Type Reaction. *European J. Org. Chem.* **2005**, 387–394 (2005).

600. Zhang, F. *et al.* Cu-Catalyzed Cascades to Carbocycles: Union of Diaryliodonium Salts with Alkenes or Alkynes Exploiting Remote Carbocations. *J. Am. Chem. Soc* .**136**, 8851–8854 (2014).

601. de Souza, M. V. N. *et al.* Synthesis and in vitro antitubercular activity of a series of quinoline derivatives. *Bioorg. Med. Chem.* **17**, 1474–1480 (2009).

602. Gurbanov, R. *et al.* Synthesis of sp3-Enriched β-Fluoro Sulfonyl Chlorides. *Synthesis (Stuttg)* **53**, 1771–1784 (2021).

603. Yin, Y.-N., Ding, R.-Q., Ouyang, D.-C., Zhang, Q. & Zhu, R. Highly chemoselective synthesis of hindered amides via cobalt-catalyzed intermolecular oxidative hydroamidation. *Nat. Commun.* **12**, 2552 (2021).

604. Liu, X., Rong, X., Liu, S., Lan, Y. & Liu, Q. Cobalt-Catalyzed Desymmetric Isomerization of Exocyclic Olefins. *J. Am. Chem. Soc* .**143**, 20633–20639 (2021).