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Development of a stereospecific intramolecular hydroaminoalkylation strategy

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Contents

Abstract

Given the prevalence of amine scaffolds in natural products, pharmaceuticals and process chemicals, the development of efficient and robust synthetic methodologies for their synthesis, particularly in an enantioselective fashion, remains of considerable interest in organic chemistry.

Herein, the development of a novel iminium-ion based intramolecular hydroaminoalkylation strategy is presented. We envisioned that a combination of two of the group's established protocols, particularly for intermolecular hydroaminoalkylation and for the selective intermolecular coupling of aldehydes and alkenes, would provide a new platform for unique transformations. Complementary to previously reported intramolecular hydroaminoalkylation methodologies, which predominantly afford cyclic products, the transformation described in this thesis leads to the formation of acyclic products. In addition to the hydroaminoalkylation reaction, this methodology leads to the simultaneous formation of a carbonyl moiety in a redox-neutral and atom-economical fashion. Notably, this transformation also provides access to enantioenriched amine products in a stereospecific manner, as the proposed mechanism proceeds through a suprafacial 1,5-hydride transfer, thus enabling chirality transfer.

The development of synthetic routes to access the suitable precursor in racemic and enantiopure form will be discussed herein. Despite the successful stereoretention observed for this transformation, extensive optimization studies could not reveal a general set of conditions that enable consistently high levels of product formation and suppress the formation of undesired side products.

Nevertheless, the developed strategy demonstrates considerable synthetic potential, especially for accessing optically pure amine scaffolds. As this methodology is still in its infancy, further investigations, potentially aided by computational studies, are required to establish optimal reaction conditions and therefore broaden the applicability of the transformation.

Kurzfassung

Angesichts der weiten Verbreitung von Aminen in Naturstoffen, Arzneistoffen und industriell relevanten Feinchemikalien bleibt die Entwicklung effizienter und robuster Synthesemethoden für deren Herstellung, insbesondere in enantioselektiver Form, von großem Interesse im Bereich der organischen Chemie.

In der vorliegenden Arbeit wird die Entwicklung einer neuartigen, auf Iminium-Ionen basierenden intramolekularen Hydroaminoalkylierungsstrategie vorgestellt. Es wurde angenommen, dass die Kombination zweier etablierter Methoden der Arbeitsgruppe, nämlich der intermolekularen Hydroaminoalkylierung sowie der selektiven intramolekularen Kupplung von Aldehyden und Alkenen, eine neue Plattform für einzigartige Transformationen schaffen könnte. Im Gegensatz zu den bisher beschriebenen intramolekularen Hydroaminoalkylierungsreaktionen, die überwiegend zur Bildung cyclischer Produkte führen, ermöglicht die in dieser Arbeit entwickelte Methode die Synthese acyclischer Produkte. Neben der Hydroaminoalkylierung erfolgt gleichzeitig die Bildung einer Carbonylfunktion in einer redoxneutralen und atomökonomischen Weise. Bemerkenswert ist zudem, dass diese Transformation einen stereospezifischen Zugang zu enantiomerenangereicherten Aminen ermöglicht. Dies lässt sich durch den vorgeschlagenen Reaktionsmechanismus erklären, der über einen suprafazialen 1,5-Hydridtransfer verläuft und dadurch eine Übertragung der stereochemischen Information ermöglicht.

Im Rahmen dieser Arbeit werden außerdem Syntheserouten zur Herstellung geeigneter Startmaterialen sowohl in racemischer als auch in enantiomerenreiner Form beschrieben. Trotz der erfolgreichen Stereoretention dieser Transformation konnten im Zuge umfangreicher Optimierungsstudien keine allgemein anwendbaren Reaktionsbedingungen identifiziert werden, die gleichzeitig hohe Produktausbeuten ermöglichen und die Bildung unerwünschter Nebenprodukte wirksam unterdrücken.

Dennoch weist die entwickelte Strategie ein erhebliches synthetisches Potenzial auf, insbesondere für den Zugang zu optisch reinen Aminbausteinen. Da sich diese Methodik noch in einem frühen Entwicklungsstadium befindet, sind weitere Untersuchungen, gegebenenfalls unterstützt durch computergestützte Studien, erforderlich, um optimale

Reaktionsbedingungen zu etablieren und die Anwendbarkeit der Transformation auf ein breiteres Substratspektrum auszuweiten.

List of Abbreviations

Å	Ångström
ARA	Asymmetric Reductive Amination
BEHT triflate	BEHT (1,2-bis (ethoxycarbonyl)hydrazineyl) triphenyl-phosium) triflate
BINOL	1,1'-Bi-2-naphthol
Boc	*Tert*-butyloxycarbonyl
CPA	Chiral phosphoric acid
CPME	Cyclopentyl methyl ether
d.r.	Diastereomeric ratio
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
EDG	Electron donating group
ee	Enantiomeric excess
EEA	Solvent mixture of ethyl acetate, ethanol and ammonium hydroxide
eq.	Equivalent
ESI	Electrospray Ionization
EWG	Electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
h	Hour
HFIP	Hexafluoroisopropanol
HPLC	High pressure liquid chromatography
HRMS	High Resolution Mass spectrometry
IPA	Propan-2-ol
IR	Infrared spectroscopy
LA	Lewis Acid
LG	Leaving Group
M	Molarity

min	Minutes
Ms	Mesyl
MW	Molecular weight
n.d.	Not determined
NAD(P)H/NAD(P)$^+$	Nicotinamide adenine dinucleotide (phosphate)
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
Piv	Pivaloyl
pK_a	Negative base 10 logarithm of the acid dissociation constant, K_a
ppm	Parts per million
R&D	Research and Development
r.r	Regioisomeric ratio
T	Temperature
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl

1 Introduction

C–N bonds have central importance in organic chemistry, as demonstrated by the broad range of nitrogen-containing functional groups including amines, imines, enamines, nitriles or amides. Among these, amines are of particular significance as they are prevalent structural scaffolds in natural products, pharmaceuticals and agrochemicals.[1,2]

Ammonia (NH_3) is the simplest amine, possessing three hydrogen atoms attached to a central nitrogen atom with a bond angle of approximately 107°. While its molecular geometry is trigonal pyramidal, ammonia adopts a tetrahedral electron geometry. The H–N–H bond angle of 107° deviates from that of an ideal tetrahedron (109.5°) due to repulsive interactions with the lone electron pair. Replacing the hydrogen atoms with carbon chain substituents gives rise to primary (RNH_2), secondary (R_2NH), or tertiary amines (R_3N) and quaternary ammonium salts (R_4N^+).[3]

The utility of amines in drug design and development stems from two main physicochemical properties: their polarity and basicity.[4] Nitrogen possesses an electronegativity of 3.0 on the Pauling scale and is therefore more electronegative than carbon (2.5) and hydrogen (2.0). This difference in electronegativity leads to the formation of dipoles along the C–N and N–H bonds, in which nitrogen carries a partial negative charge and carbon and hydrogen carry a partial positive charge.[3] As a result, amines can act both as hydrogen-bond acceptors (through the lone pair) and hydrogen-bond donors (hydrogen substituents), which has a substantial influence on solubility. The formation of quaternary ammonium salts can further increase water solubility in drug molecules, consequently influencing binding affinity and selectivity through ionic interactions.[6] Additionally, the basicity of amines, which arises from the lone electron-pair, is another important feature of their properties. Variations in the amine moiety can thus lead to changes in drug properties such as basicity, solubility, membrane permeability, metabolic stability and overall target interaction.[3,5]

Biological systems are inherently chiral, meaning that the interaction with and the subsequent response to a drug molecule is typically dependent on the stereochemistry of the drug molecule itself. In fact, nitrogen atoms of tertiary amines with three different substituents are stereogenic, however, rapid inversion (referred to as umbrella inversion) leads to fast racemization of such species.[7,8] While the inherent chirality of the amine nitrogen is difficult

to regulate, the adjacent (α) stereocenter can be controlled more effectively. Indeed, α-chiral alkylamine scaffolds are ubiquitously found in active pharmaceutical ingredients (APIs). Consequently, the development of selective and efficient methods for the synthesis of α-chiral alkylamines remains a major objective in synthetic chemistry.[9]

1.1 Synthesis of amines

1.1.1 Alkylation

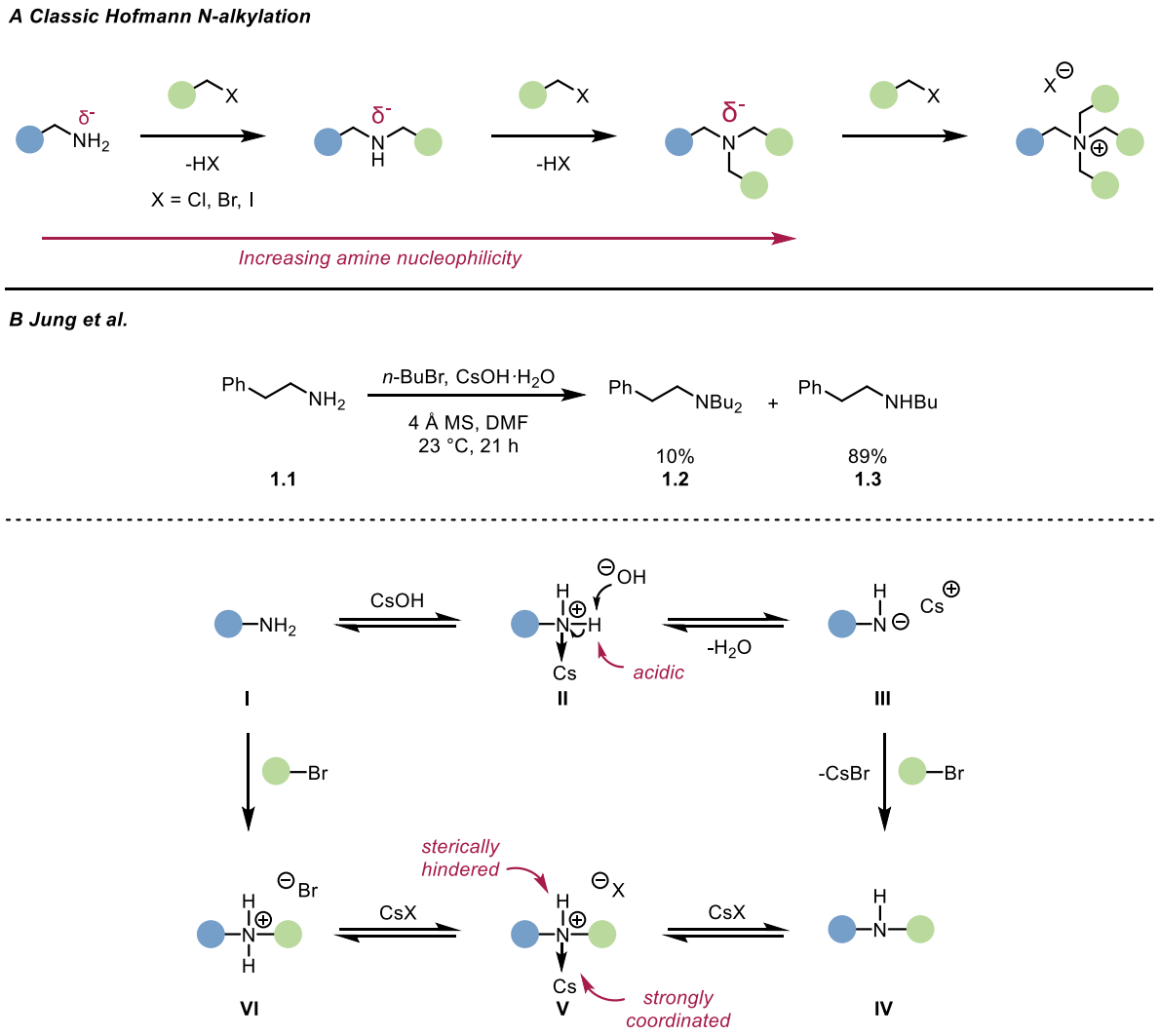
1.1.1.1 Alkylation with alkyl halides

In 1850, August Wilhelm von Hofmann reported the first synthesis of alkylamines through the alkylation of ammonia or primary amines with alkyl halides.[10] To this day, the alkylation of ammonia and amines remains one of the most straightforward approaches for the preparation of alkylamines. In a cross-industry survey conducted in 2006, heteroatom alkylation was identified as the most frequently employed reaction class for the preparation of drug molecules within R&D processes, further highlighting the significance of these transformations in the pharmaceutical industry.[10,14] Yet, standard protocols often suffer from several drawbacks. In particular, overalkylation is a frequently encountered problem: the electron-donating effect of the newly added alkyl groups initially enhances the nucleophilicity of the nitrogen lone pair, driving the reaction to favor products of polyalkylation and leading to mixtures of secondary and tertiary alkylamines, as well as quaternary ammonium salts (***Scheme 1A***).[10,11]

A common strategy to circumvent undesired overalkylation is using an excess of the amine. However, this approach is suboptimal when the amine is valuable and expensive, especially in the case of optically pure amines. In many cases, the fine tuning of reaction conditions is necessary and other factors such as the basicity and steric hindrance of the amine[11] as well as the nature of the alkyl halide[12] must be considered. Employing sterically more demanding amines or alkyl halides suppresses the formation of overalkylated products and usually leads to higher yields for the secondary aliphatic amine.[11,12]

Given the importance of alkylamines, considerable effort has been devoted to improving alkylation protocols. The use of additives such as inorganic bases leads to improved selectivity towards monoalkylated amines, as demonstrated by Jung and co-workers.[15] In particular,

cesium hydroxide proved especially effective in promoting selective monoalkylation of primary amines, affording the monoalkylated product **1.3** in yields of up to 89% (***Scheme 1B***).



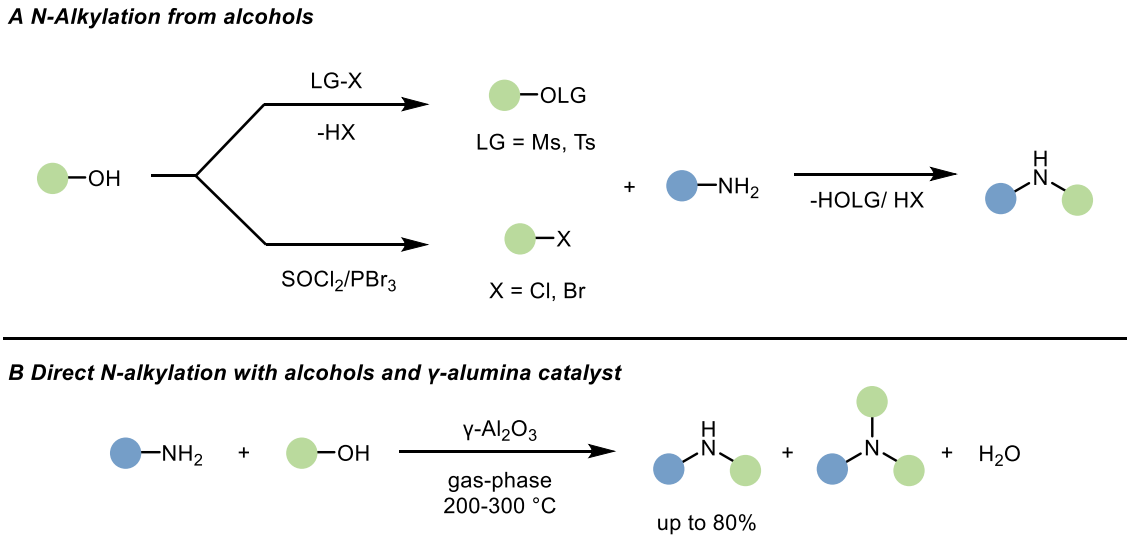
Scheme 1: A: *Hofmann N-alkylation of amines with alkyl halides and the problem of overalkylation.* ***B:*** *Selective N-monoalkylation with cesium hydroxide developed by Jung and co-workers and mechanistic explanation of the "cesium effect".*

This so called "cesium effect" was rationalized by the coordination of cesium to the nitrogen atom, resulting in an increased acidity of the N–H protons **II (*Scheme 1B*)**. As a result, these protons can be more easily abstracted by the hydroxide anion, leading to a more nucleophilic amide species **III** that readily attacks the alkyl halide. The resulting monoalkylated amine **IV** is now able to form a strong coordination complex with cesium **V**. This added steric hindrance results in a less favorable abstraction of a second proton, which ultimately suppresses overalkylation. Importantly, chiral amino acids and their derivatives were also tolerated under these conditions while retaining their stereochemical integrity.[15]

1.1.1.2 Alkylation with alcohols

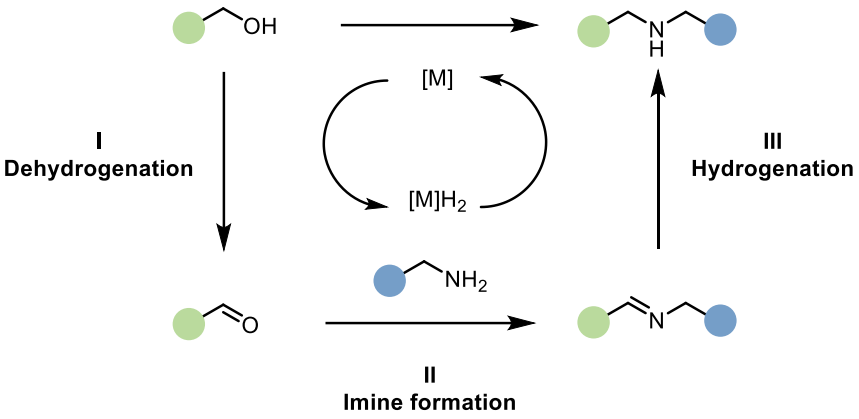
Alkyl halides are not the only precursors that can be employed in N-alkylation reactions. Alcohols that are converted to good leaving groups (such as sulfonates) also serve as suitable electrophiles. Moreover, alcohols can also be transformed into their corresponding alkyl halides using reagents such as thionylchloride ($SOCl_2$) or phosphorus tribromide (PBr_3) (***Scheme 2A***). However, this approach is synthetically less attractive as it requires additional functional group manipulation and exhibits low atom economy due to the generation of stoichiometric amounts of byproducts.[11]

Ideally, directly using alcohols for the N-alkylation would lead to water as the sole byproduct,[11] and there are a few reports demonstrating direct N-alkylation of amines by alcohols.[16,17] One such example utilizes a γ-alumina catalyst in the gas-phase (***Scheme 2B***).[16] While the γ-alumina catalyst is inexpensive, high reaction temperatures (above 200 °C) are required for such transformations.



***Scheme 2**: **A:** Alkylation of amines with alcohols by converting them into good leaving groups (LG) or alkyl halides. **B:** Direct N-alkylation by alcohols with γ-alumina catalyst in the gas-phase.*

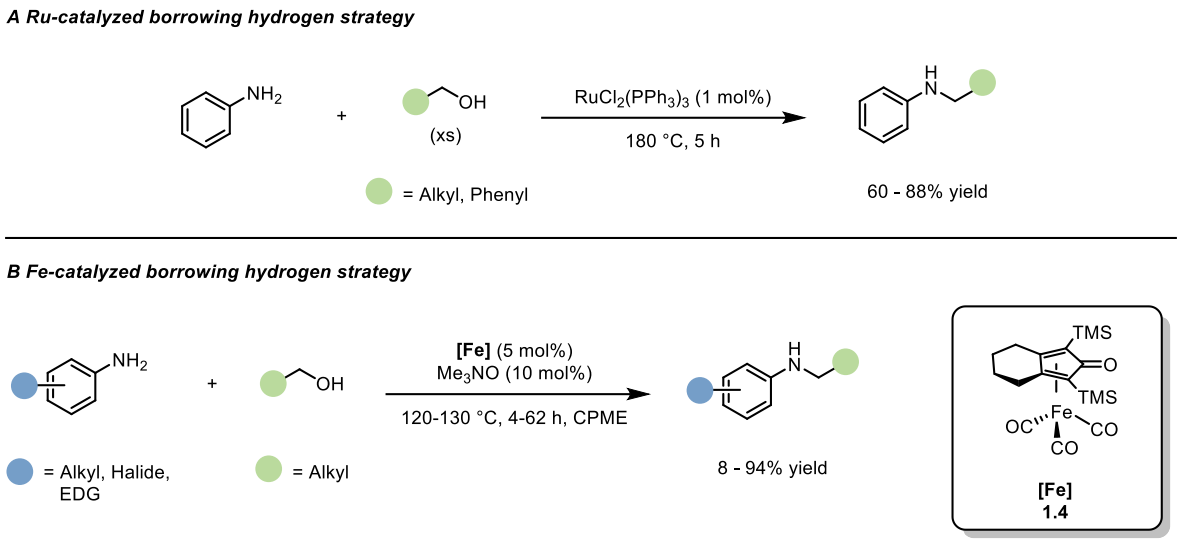
In the pursuit of environmentally friendly alternatives for the N-alkylation of amines with alcohols, transition-metal catalyzed systems were developed. These methods usually follow the principle of "borrowing hydrogen" or "hydrogen autotransfer", which is illustrated in ***Scheme 3***.[18]



Scheme 3: *General concept of the borrowing hydrogen strategy.*

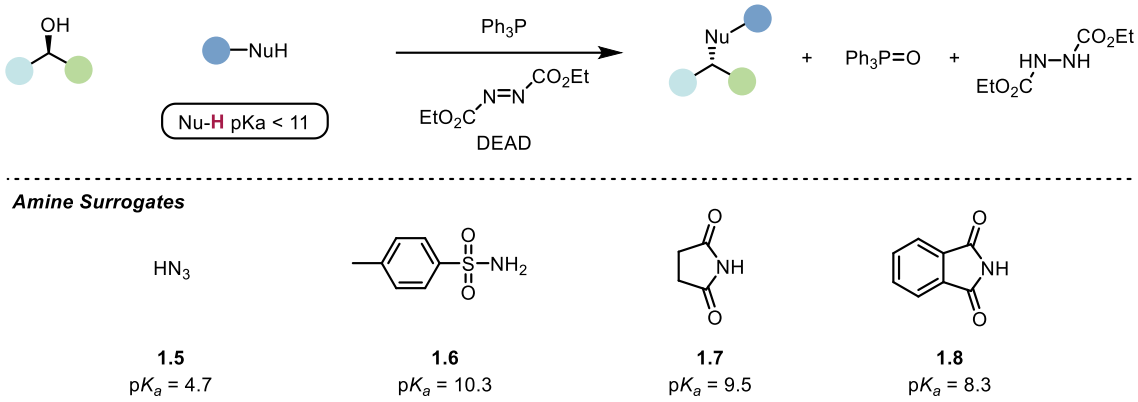
The concept underlying the "borrowing hydrogen" strategy involves the transition-metal catalyzed oxidation of an alcohol to its corresponding carbonyl. In this dehydrogenation step **I**, the hydrogen atoms are temporarily “stored” by the metal. The *in situ* generated carbonyl intermediate subsequently reacts with an amine to form an imine intermediate **II**. The stored hydrogen equivalents are then transferred onto the imine in a hydrogenation step **III**, yielding the desired monoalkylated amine and regenerating the metal catalyst for the next catalytic cycle.[18] Conceptually, the "borrowing hydrogen" methodology involves a reductive amination sequence, another widely applied strategy in alkylamine synthesis, which will be further discussed in Chapter 1.1.2. Since the alcohol serves both as the alkylating agent and the hydrogen donor, the overall synthesis proceeds in a redox-neutral fashion. Numerous synthetic protocols have been developed, all typically employing transition-metals such as nickel (Ni), rhodium (Rh), iridium (Ir) as well as ruthenium (Ru)[18,20]. One such example employing a ruthenium catalyst is shown in ***Scheme 4A***.[19] Enantioselective variants have also been explored and rely on the use of chiral catalysts.[18,20]

A significant drawback of these methodologies is the use of expensive and scarce transition-metal catalysts. To address this limitation, an iron-based **1.4** (***Scheme 4B***) hydrogen borrowing strategy was developed in 2014[21] providing a more cost-effective alternative. While this method demonstrated applicability in the preparation of some pharmaceutically relevant molecules, the substrate scope appears to be largely limited to aryl- and benzylamines, with the substitution pattern influencing the yield.[21]



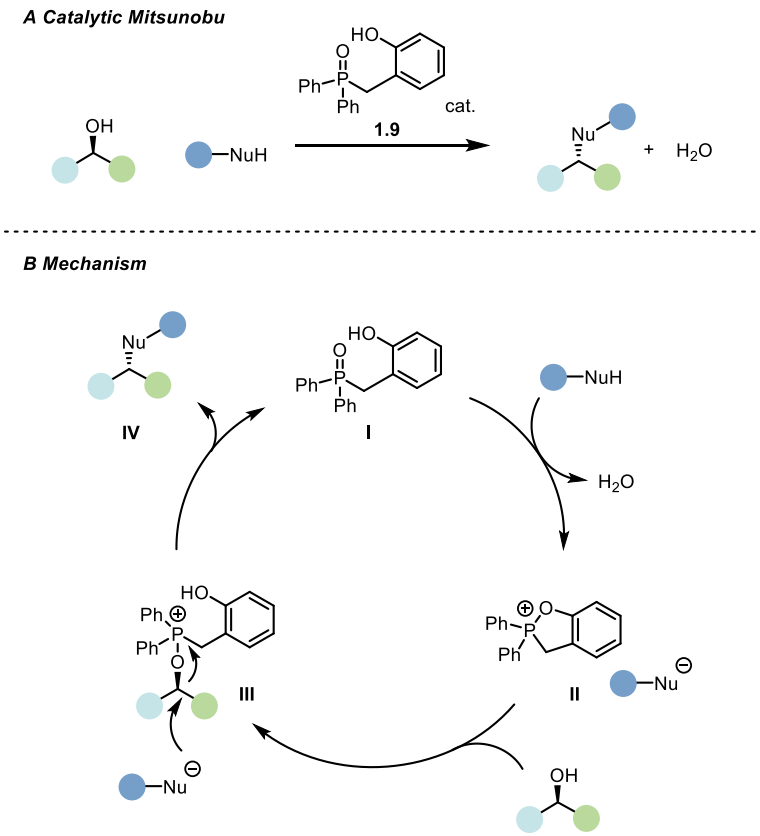
***Scheme 4**: Borrowing hydrogen strategy with Ru (**A**) and Fe (**B**) catalysts.*

Another approach employing alcohols as the starting materials is the Mitsunobu reaction[22], a textbook method for the conversion of alcohols into a diverse range of functional groups. A hallmark of the Mitsunobu reaction is its stereospecificity, as the reaction proceeds with inversion of configuration, rendering it an attractive strategy for the synthesis of optically pure compounds. While being widely recognized as a powerful synthetic tool, the Mitsunobu reaction suffers from substantial drawbacks. First, the use of nucleophiles is confined to those with a pK_a below 11, therefore limiting the use of native primary and secondary amines in that role. Formation of C–N bonds in this setting can usually only be achieved by using more acidic N-containing nucleophiles such as hydrazoic acid **1.5**, sulfonamides **1.6**, succinimides **1.7** and phthalimides **1.8** (***Scheme 5***). These, however, necessitate further downstream steps to obtain the desired chiral amines. Furthermore, the reaction suffers from a poor atom economy since the use of a stoichiometric amount of a crucial azo reagent, such as diethyl azodicarboxylate (DEAD), and reducing agents like triphenylphosphine (PPh_3) are required. In addition to the economic issues associated with generating large quantities of byproducts, they also complicate product purification.[22]



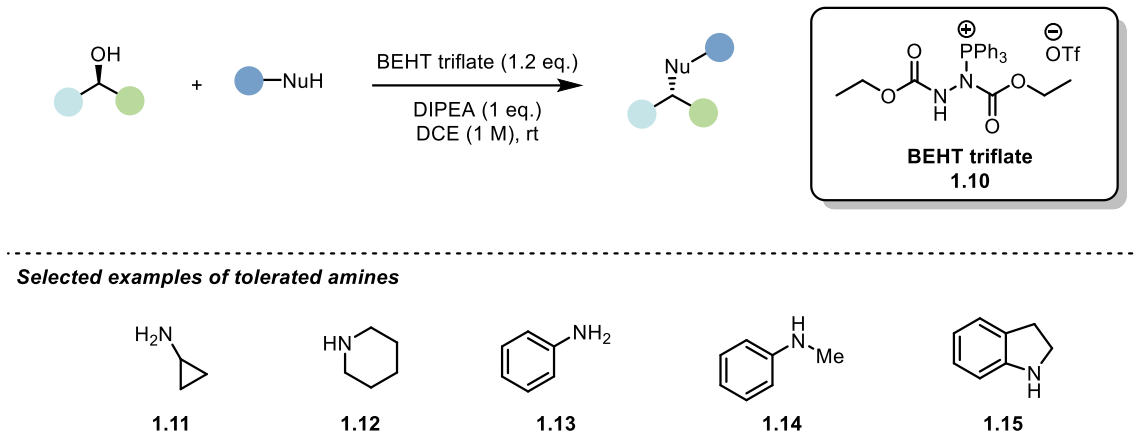
Scheme 5: *The classic Mitsunobu reaction and amine surrogates with their corresponding pK_a values: hydrazoic acid, p-toluenesulfonamide, succinimide and phthalimides (from left to right).*

The development of a truly catalytic version of the Mitsunobu reaction (***Scheme 6A***), utilizing a simple phosphorus organocatalyst **1.9** was achieved by the Denton group in 2019.[23] As shown in ***Scheme 6B***, the proposed catalytic cycle starts with the activation of the catalyst **1.9** by the acidic pronucleophile, which leads to dehydrative cyclization to form the oxophosphonium salt intermediate **II**. Subsequent ring opening by the alcohol substrate **III**, followed by nucleophilic substitution, yields the substituted product **IV** and regenerates the catalyst with water as the only byproduct. Although the catalyst can be easily prepared on multi-gram scale, the scope of compatible pronucleophiles remains limited. The best results were obtained with dinitrobenzoic acid (pK_a = 1.4) and no examples employing unmodified alkylamines were reported. Consequently, this strategy is unsuitable for the direct preparation of optically pure amines from primary or secondary amines.[23]



Scheme 6: A: *General outline of the catalytic Mitsunobu developed by Denton.* ***B:*** *Mechanism.*

Driven by these synthetic gaps, Charette and co-workers[24] reported the development of a novel Mitsunobu reagent, that enables the use of amines as pronucleophiles (***Scheme 7***). The inability to employ amines under classical Mitsunobu conditions arises from the fact that, following nucleophilic attack of PPh_3 on DEAD, the resulting phosphonium intermediate can only be protonated by pronucleophiles with a pK_a lower than 11. BEHT triflate **1.10** circumvents this issue by pre-protonation with trifluoromethanesulfonic acid (TfOH), allowing the isolation of this reactive species – usually formed only as an intermediate – even on multi-gram scale. Since this intermediate is already protonated, the pK_a limitations associated with classic Mitsunobu nucleophiles can be overcome. This methodology expands the synthetic utility of classic Mitsunobu protocols by permitting the direct stereoselective conversion of alcohols into valuable amine scaffolds using primary and secondary amines, of which some examples are shown in ***Scheme 7***.[24]



Scheme 7: *Expanding the scope of applicable nucleophiles with a novel Mitsunobu reagent BEHT (1,2-bis (ethoxycarbonyl)hydrazineyl) triphenyl-phosium) triflate developed by Charette.*

1.1.2 Reductive approaches

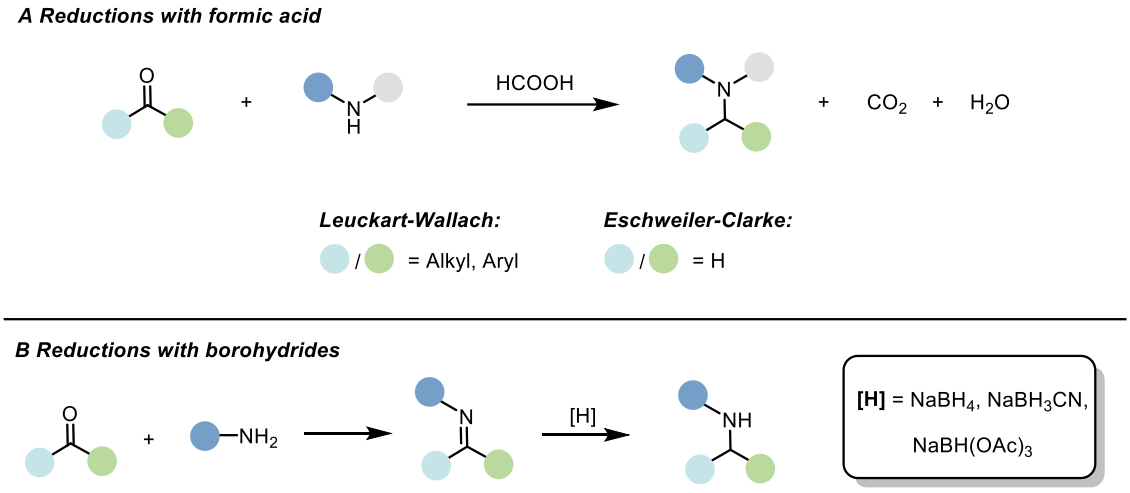
1.1.2.1 Reductive amination

Along with N-alkylation, reductive amination is considered a benchmark reaction for the preparation of amines. Therein, the imines or iminium ions formed through condensation of an amine with a carbonyl are reduced to yield alkylamines. Commonly applied reducing agents are formic acid or borohydrides, along with classic hydrogenation conditions utilizing H_2 with a metal catalyst.[25]

Formic acid is the reductant of choice in the seminal Leuckart-Wallach[26] and Eschweiler-Clarke[27] reactions—the former employs a range of substituted carbonyls, while the latter uses exclusively formaldehyde and thus leads to methylation (***Scheme 8A***). Herein, condensation of the carbonyl and the amine to the corresponding imine is followed by reduction by the formate anion, accompanied by the extrusion of CO_2. A commonly associated problem is the limited control over selective amination, which results in mixtures of primary, secondary and tertiary amines, accompanied by the formation of N-formylated byproducts. Additionally, elevated reaction temperatures are required, which might not be compatible with sensitive functional groups.[28]

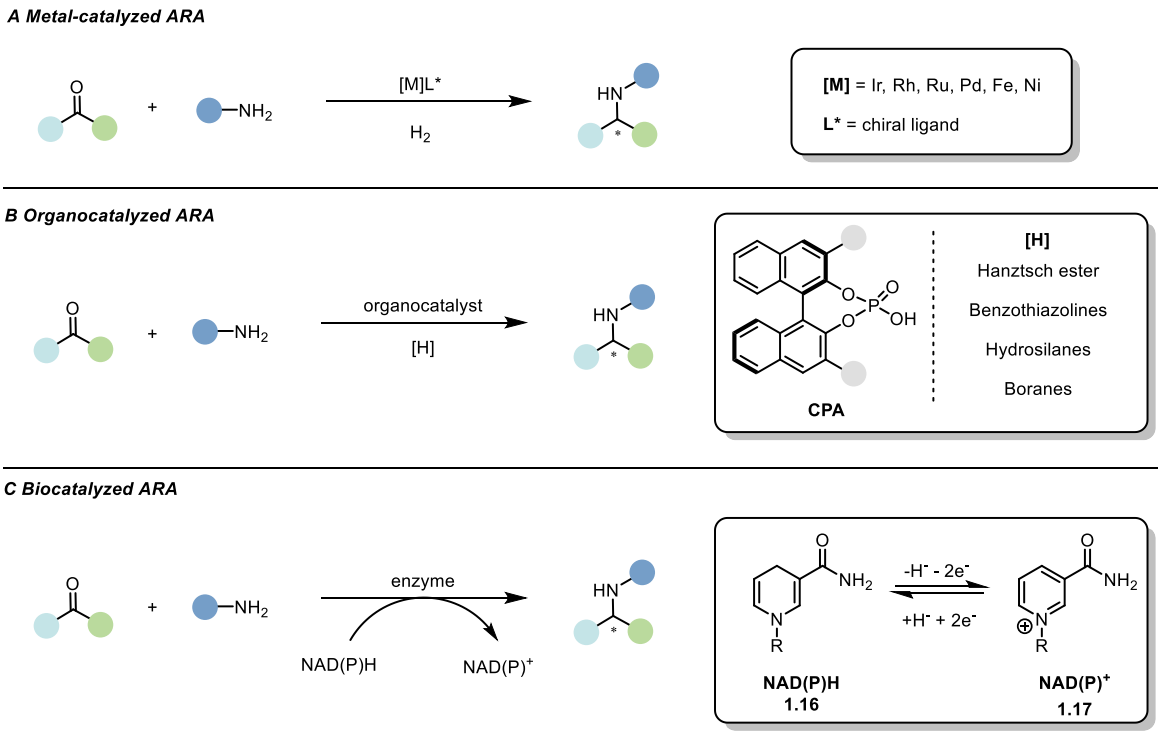
Equally, the deployment of borohydrides is a well-established protocol in the field of reductive aminations (***Scheme 8B***). Among the three most applied borohydrides, $NaBH_4$ is the most reactive and therefore the least selective, as it is also able to reduce other carbonyl groups in the molecule. To prevent undesired reductions, $NaBH_4$ can be replaced by the less reactive

$NaBH_3CN$ or $NaBH(OAc)_3$, which make them more applicable for late-stage functionalization. However, the use of $NaBH_3CN$ produces highly toxic byproducts, such as HCN, which requires proper and careful disposal.[29]



Scheme 8: *Common strategies for reductive ammination.* ***A:*** *Reductions with formic acid (Leuckart-Wallach and Eschweiler-Clarke reaction).* ***B****: Reductive amination using borohydrides as reducing agents*

Asymmetric reductive amination (ARA) is a valuable strategy for the preparation of chiral amine scaffolds. ARA can be divided into three groups based on the catalyst approach: metal catalysis, organocatalysis and biocatalysis. Metal catalyzed ARA (***Scheme 9A***) commonly deploys iridium (Ir), rhodium (Rh), ruthenium (Ru) or palladium (Pd) catalysts in combination with a chiral phosphine ligand.[30] Protocols using more abundant 3d-metals such as nickel (Ni)[31] and iron (Fe)[32] have also been reported, albeit with lower applicability. Hydrogen serves as a suitable reductant due to its abundance and cost-effectiveness. While the field was substantially improved over the last years, the coupling of sterically congested amines and ketones remains challenging. Furthermore, in some cases the reductive power cannot be finely controlled, leading to unwanted concurrent reduction of other functional groups. It is also important to consider that removal of metal residues can be difficult, which could particularly be inconvenient in drug synthesis.[30,33]



Scheme 9: *Common strategies for asymmetric reductive amination (ARA).* ***A:*** *Metal-catalyzed ARA.* ***B:*** *Organocatalyzed ARA.* ***C:*** *Biocatalyzed ARA.*

The field of organocatalyzed ARA (***Scheme 9B***) has expanded due to significant contributions from MacMillan[34,35], List[36] and Rueping[37]. The typically applied hydrogen sources are Hanztsch esters, benzothiazolines, boranes and hydrosilanes in combination with a Lewis base or chiral BINOL-derived phosphoric acid catalyst (CPA). Consequently, the reaction can proceed under milder reaction conditions in comparison to metal-catalyzed approaches as no high pressure systems for hydrogenation are necessary. Nevertheless, organocatalysts exhibit a lower catalytic efficiency and have been only applied to relatively simple systems, with further developments for broad applicability still needed.[30]

Biocatalytic ARA (***Scheme 9C***) is increasingly appealing to the pharmaceutical industry due to its sustainability benefits and high selectivity, owing to enzymes' specifically designed binding pockets.[30,38] The hydride for the reduction stems from the cofactor NAD(P)H **1.16** (nicotinamide adenine dinucleotide (phosphate)), whose redox active core resembles those of Hantzsch esters. While the high substrate specificity is crucial in biological systems, it limits their versatile application in organic chemistry and necessitates enzyme engineering. Furthermore, additional challenges include the reduced stability of enzymes in organic solvents. Although biocatalyzed ARA may not represent a general strategy for the preparation

of optically pure amines, it can be highly valuable for the synthesis of specific pharmaceutical targets.[30,38]

1.1.2.2 Reduction of N-containing functional groups

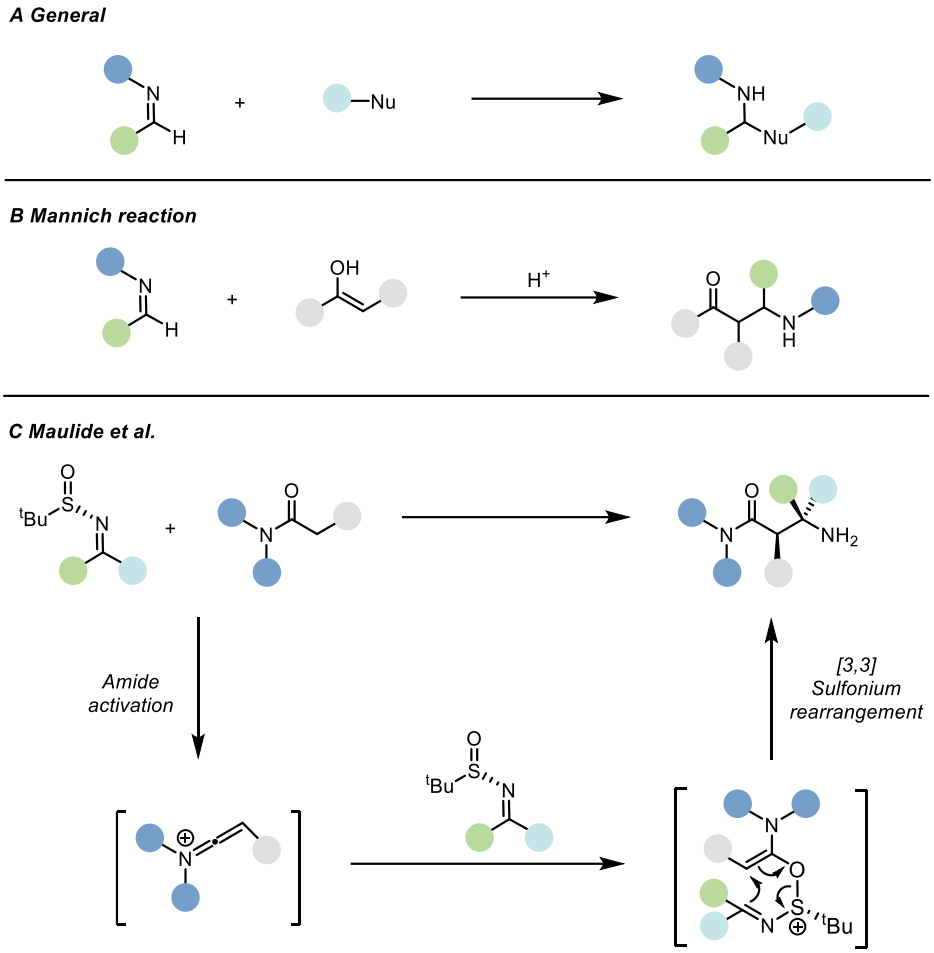
Besides the reduction of imines, the reduction of other nitrogen-containing functional groups is also a widely applied strategy to access aliphatic amines. For instance, amides and nitriles can be converted to the corresponding amines with strongly reducing hydride reagents, such as lithium aluminiumhydride ($LiAlH_4$). Due to its highly reactive nature, $LiAlH_4$ suffers from poor chemoselectivity. The use of milder reducing agents, such as $NaBH_4$ is also possible, however, elevated reaction temperatures and prolonged reaction times are necessary for the desired transformation to proceed.[39]

1.1.3 Nucleophilic addition

While reductive approaches rely on hydride addition to an imine or iminium ion to generate the desired amine, imines can also undergo nucleophilic addition from a broad range of nucleophiles other than hydrides (***Scheme 10A***).[11]

One of the most important named reactions in this sense is the Mannich-reaction (***Scheme 10B***).[40] The classic Mannich-reaction is a three-component reaction using an amine, formaldehyde and an enolizable carbonyl group. The mechanism proceeds with initial formation of an imine or iminium species which is then subsequently attacked by the enol tautomer of the carbonyl compound, yielding β-amino carbonyl compounds. However, several disadvantages are associated with the classic Mannich reaction. For example, using ammonia or primary amines as the nitrogen source can lead to mixtures of overalkylated products. Additionally, regioselectivity issues can occur when employing unsymmetrical ketones with two enolizable positions and unwanted aldol-type side products can be obtained. A way to circumvent these problems is to use preformed enolates generated under kinetic or thermodynamic control.[40] Given their synthetic utility, especially in the sense of accessing chiral Mannich products, considerable efforts were devoted to developing asymmetric approaches to access β-amino carbonyl compounds. Since the reaction proceeds through an enolate intermediate, accessing β-amino amides is challenging due to the higher pK_a of the α protons of amides. To address these current limitations, one notable methodology was developed by the Maulide group (***Scheme 10C***).[41] Preparation of these privileged scaffolds in

a diastereo- and enantioselective fashion was achieved through the combination of electrophilic amide activation and sulfonium rearrangement, thereby circumventing the need for preparation of amide enolates.

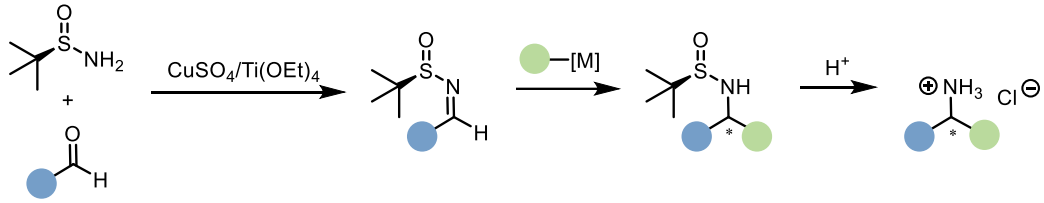


***Scheme 10**: **A:** General approach for the nucleophilic addition to imines. **B:** Mannich reaction. **C:** Asymmetric Mannich reaction surrogate using amides and sulfinimines developed by Maulide.*

One of the most influential strategies for asymmetric nucleophilic addition to imines involves using enantiopure sulfinamides as chiral auxiliaries.[42] These sulfinyl groups are uniquely suited for this role because they simultaneously activate the imine toward nucleophilic attack and serve as a powerful, highly effective stereodirecting group. Furthermore, the auxiliary can be easily cleaved under mild acidic conditions without inducing epimerization at the newly formed stereocenter (***Scheme 11***).[42,43]

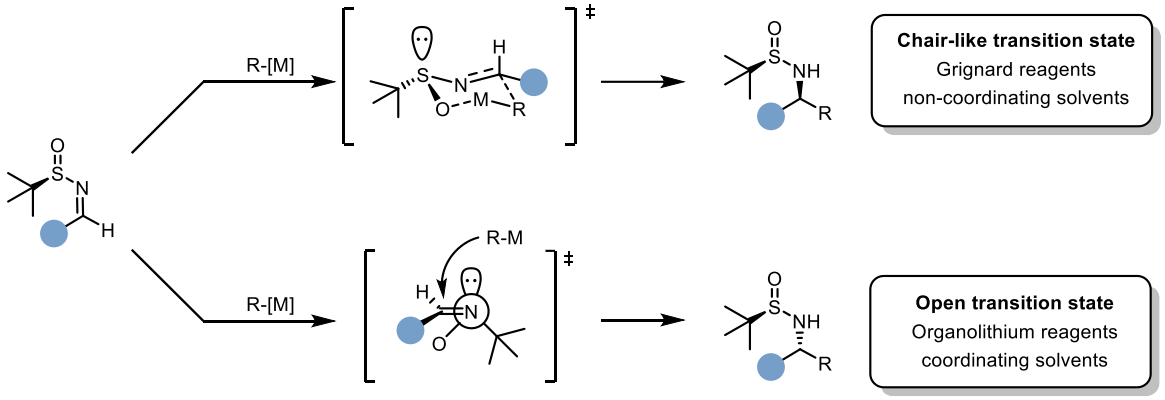
The use of sulfinyl groups for this purpose was pioneered by Davis, who first introduced *p*-toluenesulfinamides for the synthesis of chiral amines.[44] However, a major breakthrough occurred in 1997 when Ellman and coworkers developed *tert*-butanesulfinamides.[42] These

new auxiliaries proved significantly superior to Davis's, offering enhanced diastereofacial selectivity and superior imine activation. Consequently, this scaffold was widely popularized and is now universally referred to as Ellman's chiral auxiliary or Ellman's sulfinamide.[42,43] *tert*-Butanesulfinimines are readily accessible through the condensation of *tert*-butanesulfinamide and aldehydes, requiring the addition of $CuSO_4$ or $Ti(OEt)_4$ in the case of ketones or sterically congested aldehydes.[42]



Scheme 11: *General reaction sequence using Ellman's chiral auxiliary: From sulfinimine preparation to nucleophilic addition and final deprotection.*

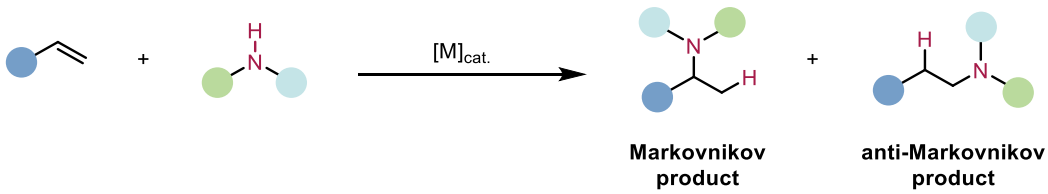
Commonly applied nucleophiles in the 1,2-addition to sulfinimines are organometallic reagents such as Grignard and organolithium reagents. The stereochemical induction is rationalized by the formation of a chair-like transition state resulting from the coordination of the oxygen and the metal center. The stereochemical outcome has been reported to depend on the type of organometallic reagent employed, as depicted in ***Scheme 12***. In the case of Grignard and organolithium reagents, opposite diastereoselectivities have been observed. Additionally, stereocontrol is also influenced by the choice of solvent. Much higher diastereomeric ratios are observed when the reaction is performed in dichloromethane instead of coordinating solvents such as tetrahydrofuran and diethyl ether, as these prevent the efficient formation of the six-membered intermediate through competitive coordination. Despite being widely recognized as a powerful chiral auxiliary, Ellman's sulfinamides do not provide excellent selectivity across all substrate classes, with some systems being less predictable and requiring fine tuning of reaction conditions or additives to achieve satisfactory diastereoselectivity.[42]



Scheme 12: *Different stereochemical outcomes depending on the organometallic reagent and solvent choice.*

1.1.4 Hydroamination

Hydroamination is defined as the direct addition of a N–H bond across an unsaturated C–C bond (***Scheme 13***). The addition of amines to alkenes produces secondary or tertiary amines, while alkynes yield enamines or imines. While they are thermodynamically feasible, kinetically such transformations are not realizable without the presence of a catalyst, as both reactants are electron-rich.[45]



Scheme 13: *Hydroamination of alkenes over a metal catalyst resulting in the formation of two possible regioisomers.*

Hydroamination reactions inherently favor Markovnikov selectivity, making the anti-Markovnikov pathway a primary challenge in catalysis since the early 1990s (***Scheme 13***).[45,47]

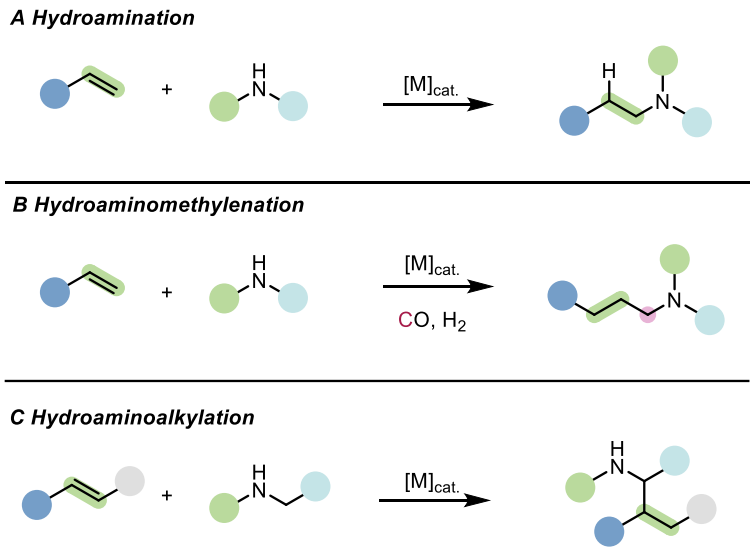
Compared to alkynes, alkenes are inherently less reactive in hydroamination reactions.[85] Although the higher π-electron density of alkynes might suggest increased electrostatic repulsion with the amine nucleophile and consequently lower reactivity, hydroamination is generally more feasible with alkynes. This behavior can be attributed to their interaction with the metal catalyst. Alkynes are weaker π-donors than alkenes and therefore bind less strongly to the metal center. As a result, the alkyne is sufficiently coordinated to activate the C–C triple bond, but not so strongly as to inhibit the reaction, which is often the case for the more strongly π-donating alkenes. Therefore, substantial research effort has been driven by the

need to develop powerful catalytic systems capable of forcing hydroamination of alkenes with amines. The earliest reports for catalytic systems involved the use of rare-earth metals such as lanthanoids that proved to be effective in catalyzing intramolecular hydroaminations but seemed to be inefficient for intermolecular processes.[46] This poor efficiency stems from the competitive coordination to the metal between the strongly binding amine and the weakly binding olefin. Use of an excess of the olefin can be a solution to this problem, however this would oppose the atom-economical aspect of these transformations.[45,46]

Additionally, current asymmetric protocols are largely restricted to intramolecular processes, and intermolecular variants frequently suffer from poor regioselectivity, requiring the use of biased substrates. Nevertheless, developing efficient hydroamination methods remains highly relevant, as it provides direct access to valuable amine architectures with 100% atom economy.[48]

1.2 Hydroaminomethylenation and Hydroaminoalkylation

In contrast to hydroamination (addition of N–H across an unsaturation), hydroaminoalkylation is the addition of the C(NR_2)–H bond across an unsaturated C–C bond, thereby forming a new C–C bond instead of a C–N bond. Hydroaminomethylenation describes the specific addition of an aminomethyl group onto an alkene (***Scheme 14***).



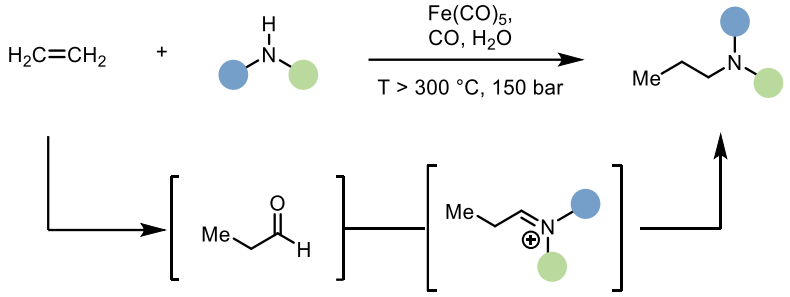
Scheme 14: *The difference between Hydroamination (**A**), Hydroaminomethylenation (**B**) and Hydroaminoalkylation (**C**).*

1.2.1 Hydroaminomethylenation using CO

Classical hydroaminomethylenation is a two-step sequence in which syngas (a mixture of carbon monoxide (CO) and hydrogen (H_2) gas) is initially used for alkene hydroformylation to yield an aldehyde, commonly mediated by ruthenium (Ru) or rhodium (Rh) catalysis. The aldehyde is then condensed with the amine present in the reaction mixture to form an imine or iminium species, which is subsequently hydrogenated under the same conditions (***Scheme 15***).[49]

The broad field of hydroaminomethylation began with the discoveries of Reppe during his time in BASF (*Badische Anilin- und Soda-Fabrik*).[50] He discovered that the reaction of carbon monoxide with alkenes in the presence of amines and water, catalyzed by iron pentacarbonyl ($Fe(CO)_5$), results in the formation of alkylamines (***Scheme 15***). The presence of water is necessary, as it is responsible for the *in situ* generation of hydrogen. The reaction requires harsh reaction conditions (T > 300 °C, 150 bar) and a stoichiometric amount of the iron

promoter. Additionally, the substrate scope is restricted to the use of acetylene and ethylene, with higher alkenes or alkynes only giving low yields.[50]



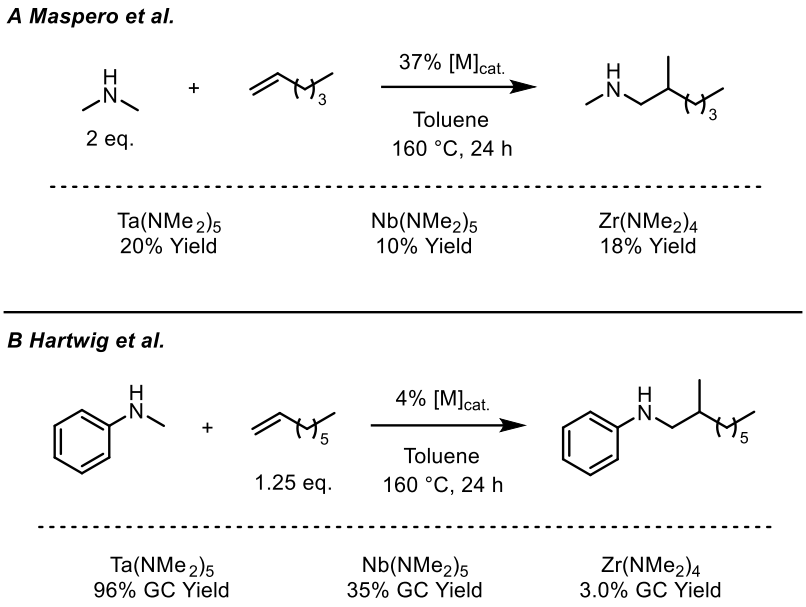
Scheme 15: *Hydroaminomethylation of ethylene over an iron pentacarbonyl catalyst discovered by Reppe.*

1.2.2 Metal-catalyzed Hydroaminoalkylation

Unlike hydroaminomethylation, which relies on a two-step process for the conversion of amines and olefins, hydroaminoalkylation has emerged as a complementary strategy for the direct synthesis of higher substituted amines, often relying on C–H activation processes. In contrast to hydroaminations, hydroaminoalkylations are more favored as the formation of a new C–C σ-bond adds an approximate 10 kcal of energetic driving force compared to C–N σ-bond formation.[51]

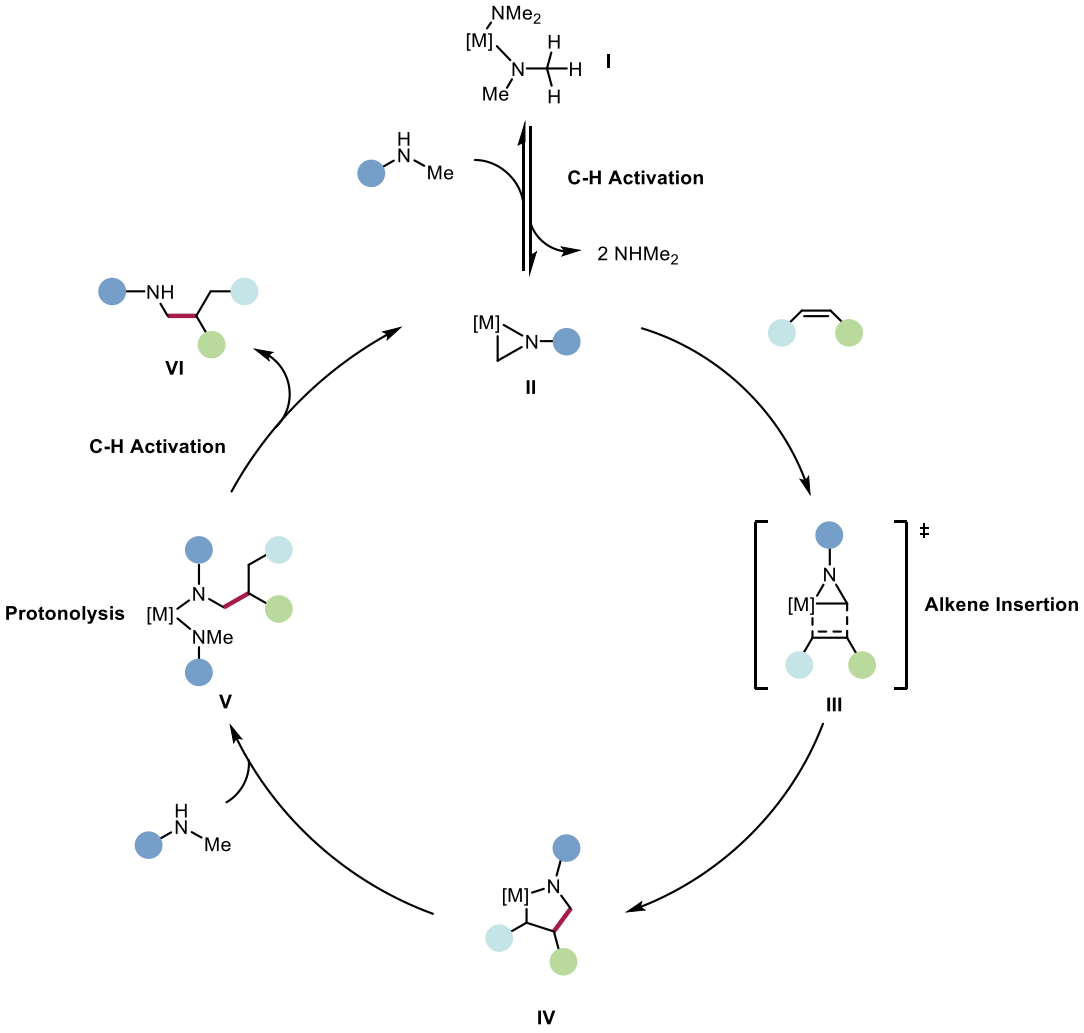
1.2.2.1 Early transition-metal catalysis

The beginnings of hydroaminoalkylation were largely dominated by early transition-metal catalysts. In 1980, the Maspero group reported the hydroaminoalkylation of unactivated olefins such as ethylene, propylene or 1-hexene with dimethylamine gas using group four and five metal amido complexes $M(NMe_2)_x$, based on tantalum (Ta), niobium (Nb) and zirconium (Zr).[52] While these only gave mono-α-alkylated products, despite having two reactive sites, the yield remained in the low range of 10–20% (***Scheme 16A***).[52] Similarly, the Hartwig group developed hydroaminoalkylation with *N*-methyl arylamines and achieved high yields by employing a tantalum catalyst (***Scheme 16B***).[53]



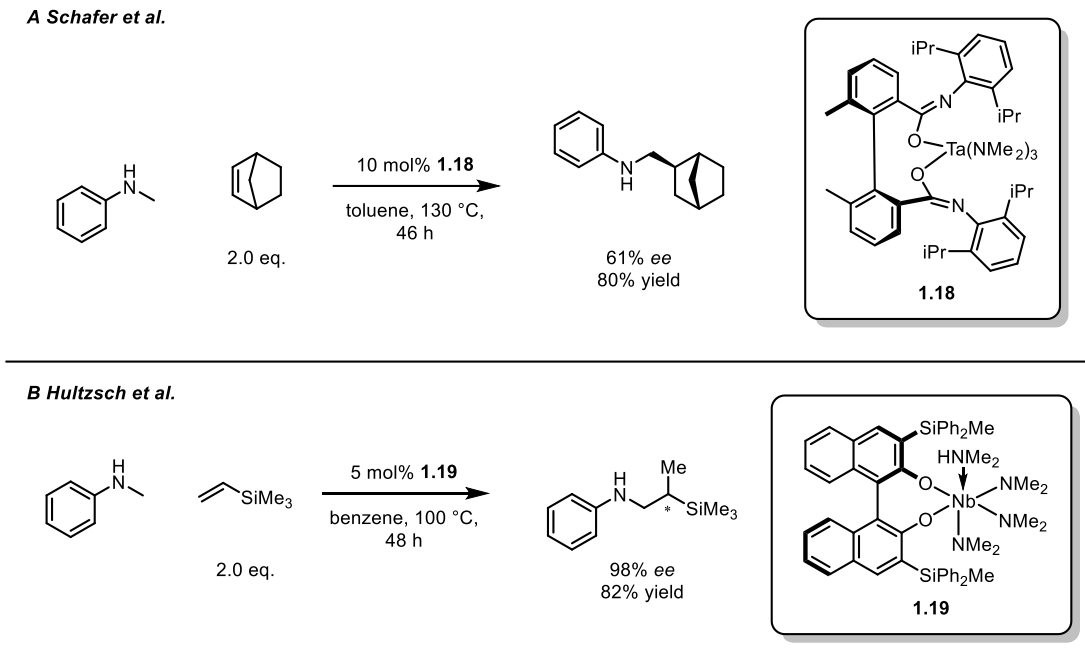
Scheme 16: *Hydroaminoalkylations on the basis of early transition-metal catalysis by Maspero (**A**) and Hartwig (**B**).*

Mechanistic experiments by Nugent and coworkers shed light on the reaction steps involved (***Scheme 17***).[54] Initial C–H activation leads to the formation of catalytically active metallaaziridines **II**, into which the alkene inserts **III**, resulting in the formation of a 5-membered metallacycle **IV**. The metallacycle reacts with the amine substrate, leading to the formation of intermediate **V**, which then undergoes another C–H activation step to generate the hydroaminoalkylation product and release the metallaaziridine.



Scheme 17: *General mechanism for early transition-metal catalyzed hydroaminoalkylation.*

The first enantioselective hydroaminoalkylation was reported with group five metals. The Schafer group demonstrated the use of biphenyl tethered bis(amidate)–tantalum complexes as chiral catalysts, however the reaction only proceeded with a maximum enantiomeric excess (*ee*) of 61% (***Scheme 18A***).[55] Contributions from the Hultzsch group expanded to the use of niobium complexes with chiral BINOL-derived ligands (***Scheme 18B***). Sterically more demanding substrates such as vinyl silanes resulted in high *ee* values of up to 98%, while the enantioselectivity dropped for smaller olefins.[56]



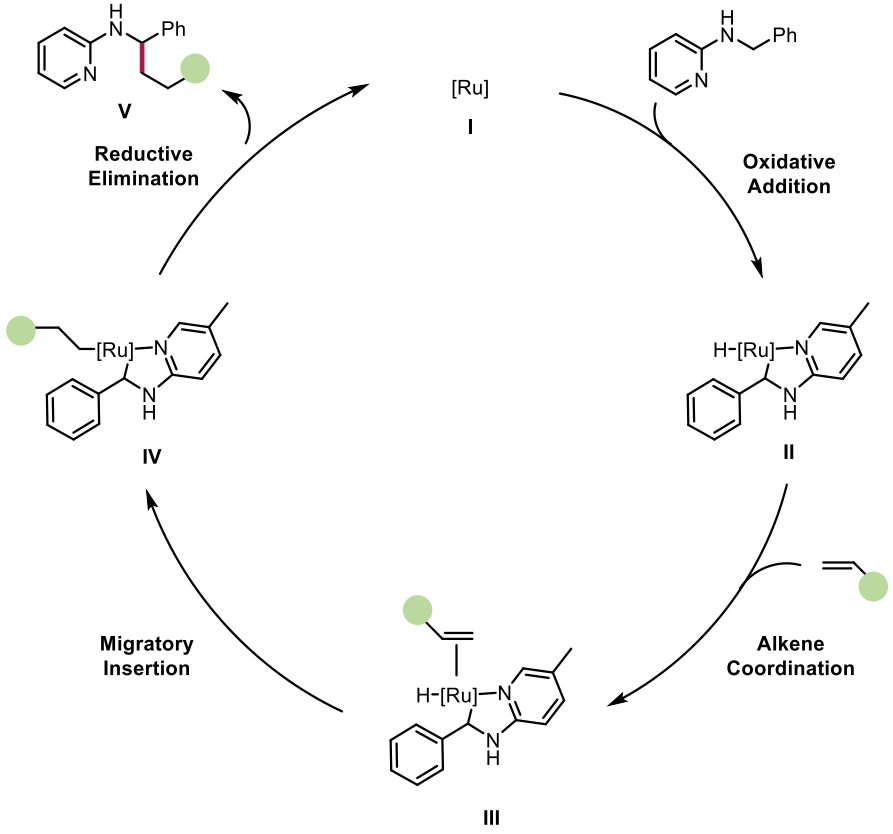
Scheme 18: *Enantioselective hydroaminoalkylations using tantalum (**A**) and niobium (**B**) complexes.*

The development of versatile early transition-metal catalysts, able to cover a broad range of substrate classes, remains an active area of study. A major limitation of these catalytic systems is their poor functional group tolerance. Only a limited number of examples have been reported that are compatible with substrates bearing polar functionalities, such as protected alcohols, ethers, and acetals, owing to the pronounced oxophilicity of early transition-metals. Furthermore, their utility is often constrained due to the need for protecting or directing groups and co-catalysts, which necessitates continued efforts to expand their substrate scope and functional-group compatibility. Despite these challenges, early transition-metals such as scandium (Sc), titanium (Ti), zirconium (Zr) and tantalum (Ta) remain highly attractive due to cost-effectiveness, reduced toxicity and low catalyst loadings in the range of 1–10 mol%.[51]

1.2.2.2 Late transition-metal catalysis

In 1998, Jun and coworkers reported the use of a ruthenium (Ru) catalyst for hydroaminoalkyation (which they referred to as C–H alkylation) with benzylamine derivatives.[57] Hydroaminoalkylations mediated by late transition-metal catalysts require the use of directing groups: the presence of a pyridine substituent as an in-built ligand facilitates oxidative addition of the ruthenium catalyst into the C–H bond due to coordination to metal center **II** (***Scheme 19***). The alkene can then bind to the metal center of the resulting 5-membered metallacycle complex **III**, after which migratory insertion of the metal-hydride

complex onto the alkene **IV** followed by reductive elimination releases the product **V** and regenerates the catalyst **I** for the next catalytic cycle.[57]



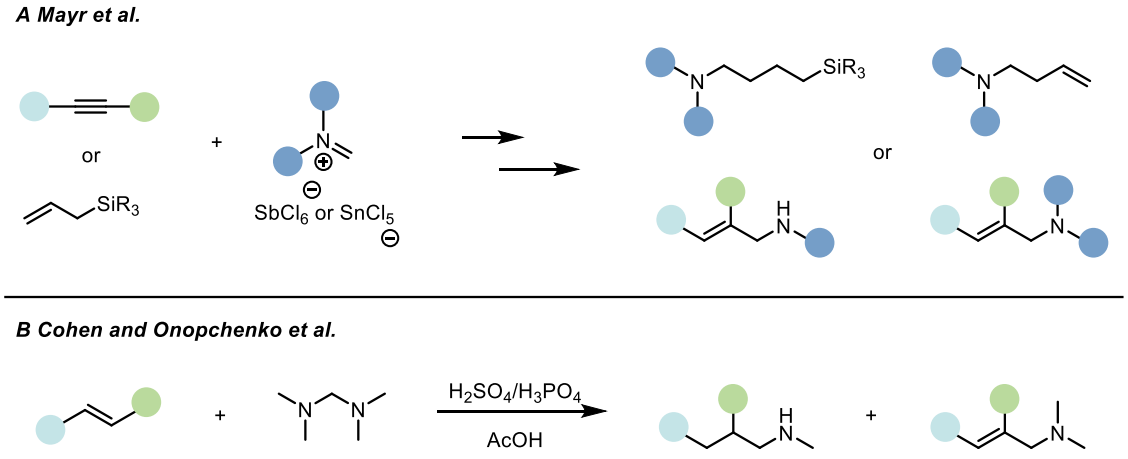
Scheme 19: *General mechanism for late transition-metal catalyzed hydroaminoalkylations with the help of directing groups.*

Besides ruthenium, other metals such as iridium have been reported to efficiently catalyze hydroaminoalkylation processes.[58] In contrast to the previously described early transition-metals, where current research primarily focuses on the design of new ligands, late transition-metal catalysis relies primarily on directing group strategies. In general, hydroaminoalkylations mediated by late transition-metal catalysts showcase their applicability for a broad substrate scope, however some functional groups, such as alcohols, still fall out of range. Moreover, harsh reaction conditions (e.g., elevated reaction temperatures) are required and the use of an excess of the alkene substrate is usually necessary to achieve complete conversion. Asymmetric approaches remain largely unexplored to date.[51]

1.2.3 Metal-free Hydroaminoalkylation

In 1996, Mayr and coworkers reported the use of preformed iminium salts with non-nucleophilic counter ions, such as hexachloroantimonate ($SbCl_6^-$) and pentachlorostannate ($SnCl_5^-$), in a formal hydroaminoalkylation with activated π-systems (***Scheme 20A***).[59] The reaction of *N,N*-dibenzyliminium salts with alkynes afforded *N*-benzyl-*N*-allylalkylidene ammonium salts through an ene-type reaction.[60] These intermediates could then be transformed into either secondary allylamines (upon hydrolytic work up) or tertiary allylamines (reductive work up with sodium borohydride). Moreover, allylsilanes were also found to be amenable to these reaction conditions, and the survival of the silyl group was found to depend on the substituent pattern of the allylsilane.[59,61]

In 1983, Cohen and Onopchenko investigated the reactivity of alkenes with *N,N*-dimethyleneiminium ions, which were generated by the treatment of bis(dimethylamino)methane with strong mineral acids (***Scheme 20B***). The reaction proved to be unselective due to competing reaction pathways, which resulted in mixtures of secondary saturated amines and allylic tertiary amines.[62]



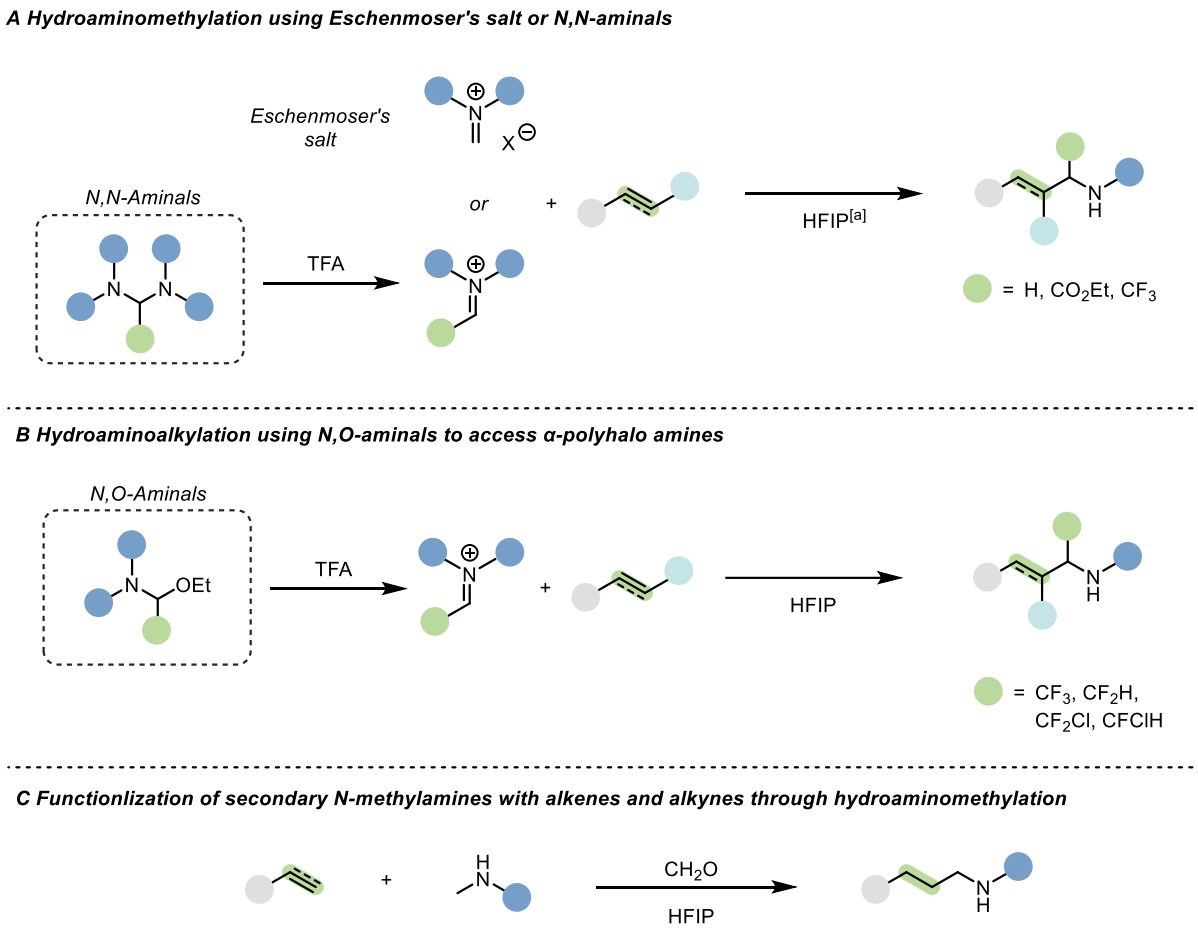
Scheme 20: A: *Metal-free hydroaminoalkylation using iminium hexachloroantimonates or pentachlorostannates developed by Mayr.* ***B:*** *Hydroaminomethylation using N,N-dimethyleniminium ions reported by Cohen and Onopchenko.*

Given that metal-free hydroaminomethylations/-alkylations on the basis of iminium-ions remained largely unexplored and had proven to be comparatively unselective processes, the Maulide group became interested in expanding and generalizing this field (***Scheme 21***). An early protocol involved the use of Eschenmoser's salt (*N,N*-dimethylmethylideneammonium ioidide) in hexafluoroisopropanol (HFIP).[63] While high yields were observed for terminal

alkenes such as styrene, internal alkenes and alkynes were found to be incompatible with these reaction conditions. Thus, the protocol was improved by changing the nature of the iminium ion precursor (moving from Eschenmoser's salt to diaminomethanes—aminals which would form an iminium ion upon exposure to an acid). Under these conditions, the hydroaminomethylation of unactivated alkenes and alkynes was achieved (***Scheme 21A***). Even unprotected alcohols and other amine functionalities were tolerated, thereby overcoming limitations commonly associated with metal-catalyzed hydroaminomethylation. However, complex and highly functionalized substrates remained incompatible with these reaction conditions.[63]

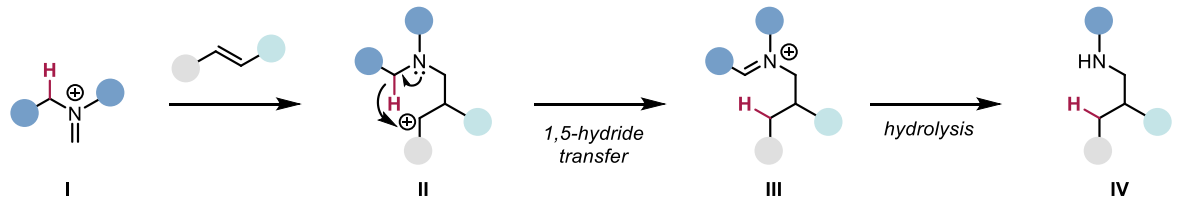
Motivated by these results, electron-deficient iminium ions were also successfully prepared from their corresponding *N,N*-aminals and implemented in a hydroaminoalkylation protocol (***Scheme 21A***).[64] Building on this work, the group subsequently developed a strategy utilizing *N,O*-aminals (hemiaminals) as iminium-ion precursors. This has enabled access to α-polyhalogenated amines, which have gained significant attention in medicinal chemistry (***Scheme 21B***).[65]

The generation of the iminium ion is not limited to the use of *N,N*-aminals or *N,O*-aminals, but can also be realized *in situ* by the condensation of a salt of the amine with paraformaldehyde in HFIP (***Scheme 21C***). In recently published work of the group[66], this approach has allowed the late-stage functionalization of a wide range of complex secondary *N*-methyl amines. A remarkable aspect of this methodology is that marketed drugs can be easily prepared from readily available alkenes and methylamines, hence overcoming the initial limitations.



Scheme 21: *Contributions of the Maulide group.* ***A:*** *Hydroaminomethylation of unactivated alkenes and alkynes with iminium ions generated from Eschenmoser's salt or N,N-aminals and TFA.* [a]*HFIP only when Eschenmoser's salt is used.* ***B:*** *Hydroaminoalkylation with iminium ions generated from N,O-aminals and TFA in HFIP to access α-polyhalo amines.* ***C:*** *Hydroaminomethylation of unactivated alkenes and alkynes with N-methylamines.*

All reactions described above follow a similar mechanism, which starts with the formation of the first iminium intermediate **I** (***Scheme 21***). Nucleophilic, Prins-type, addition of the alkene to the iminium generates the carbocation intermediate **II**, which subsequently undergoes a 1,5-hydride transfer resulting in the formation of the second iminium intermediate **III**. Hydrolysis of this second and less electrophilic iminium ion ultimately yields the desired product.[63]

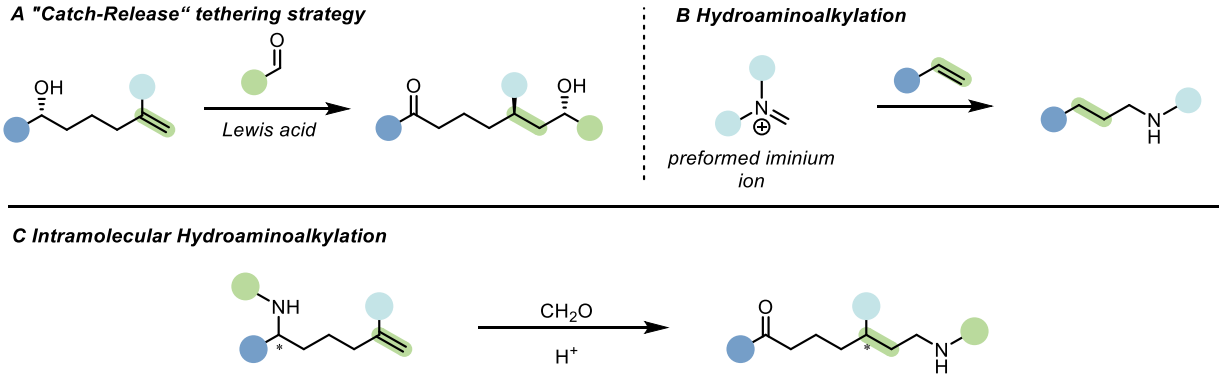


Scheme 22: *General mechanism for hydroaminoalkylation based on iminium ions.*

While this synthetic strategy has proven its applicability for numerous substrates of varying complexity, no enantioselective version of this methodology has been developed. Additionally, intramolecular variants have not yet been investigated.

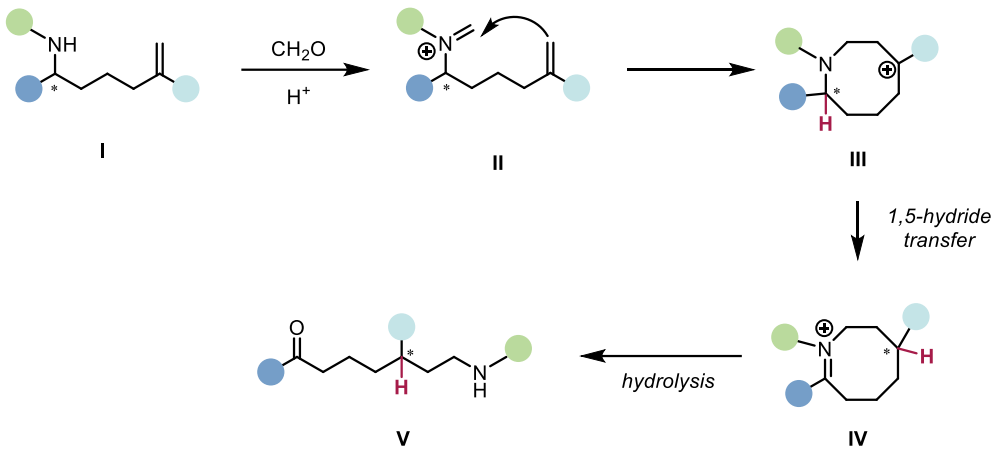
1.3 Aim of this Master's thesis

This master's thesis aimed to develop an intramolecular hydroaminoalkylation strategy on the basis of two concepts previously established by the Maulide group. Conceptually, we envisioned that the group's "catch-release" tethering strategy for the enantioselective coupling of aldehydes and alkenes[67] could be combined with our hydroaminoalkylation chemistry. In contrast to classic intramolecular hydroaminoalkylation reactions, which typically yield cyclic products, this method would provide a unique redox-neutral transformation, affording an acyclic hydroaminoalkylated product bearing an additional carbonyl functionality (***Scheme 23***).



Scheme 23: *A: Intramolecular hydroaminoalkylation (**C**) as a combination of the "catch-release" tethering strategy (**A**) and the established intermolecular hydroaminoalkylation (**B**).*

The proposed reaction was designed to proceed in a similar fashion to the oxygen-based process: as illustrated in ***Scheme 24***, the reaction commences with the formation of an iminium ion **II**, which upon an aza-Prins-type cyclization leads to the formation of an eight-membered ring intermediate **III**. The subsequent 1,5-hydride transfer leads to the formation of the second iminium ion **IV** and upon hydrolysis furnishes the desired product **V**. Due to the suprafacial nature of the hydride transfer event,[67] the oxygen-based variant of this transformation was found to proceed with excellent stereoselectivity, and one of the main goals of this master thesis was to investigate whether this selectivity could be transported to the context of hydroaminoalkylation.

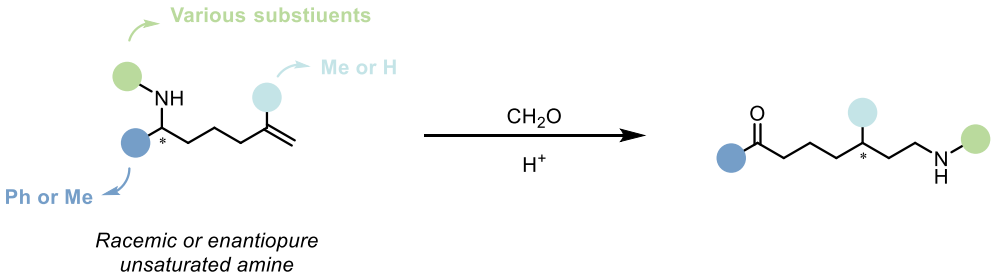


Scheme 24: *Proposed reaction mechanism for the intramolecular hydroaminoalkylation.*

The aims of this master's thesis include the development of a suitable and reliable synthetic route to access both racemic and enantiopure starting materials. The selected strategy should enable the straightforward preparation of a range of differently substituted amines, therefore allowing a systematic investigation of the influence of substituents on the nitrogen atom.

Following the establishment of a robust synthetic protocol for the preparation of the starting materials, the focus will shift towards the optimization of reaction conditions. This will be carried out by screening key parameters such as solvent, temperature, reaction time, and the addition of various Brønsted and Lewis acids. Once suitable conditions have been identified, they will be applied to enantiopure substrates to assess the stereoselectivity of this transformation.

Finally, the substrate scope will be explored by investigating the influence of varying substituents in different positions. These studies aim to provide a deeper understanding of the factors governing the reactivity and selectivity of the transformation.



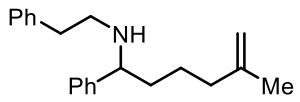
- Preparation of racemic/ enantiopure starting material
- Optimization of reaction conditions
- Chirality transfer from enantiopure starting material
- Changing substituents

Scheme 25: *Aims of this thesis.*

2 Results and Discussion

2.1 Synthesis of starting material

To probe our hypothesis that the translation of the oxygen-centered catch-release strategy developed by the Maulide group could be translated to nitrogen, to enable intramolecular hydroaminoalkylation, first a suitable starting material had to be selected. Compound **2.1a**, as shown in ***Figure 1***, was envisioned as a promising substrate to investigate this transformation.

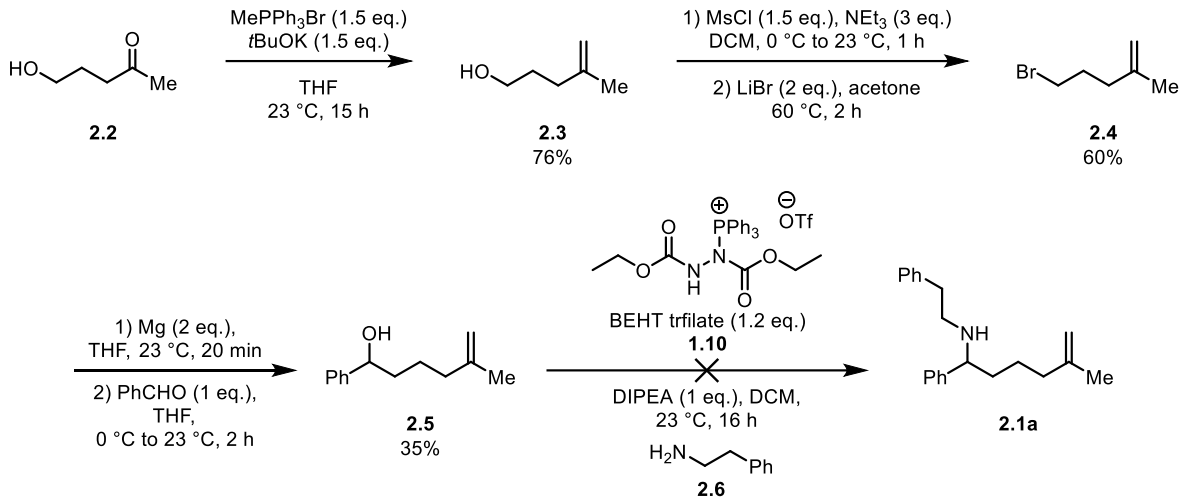


2.1a

Figure 1: *Model substrate* ***2.1a.***

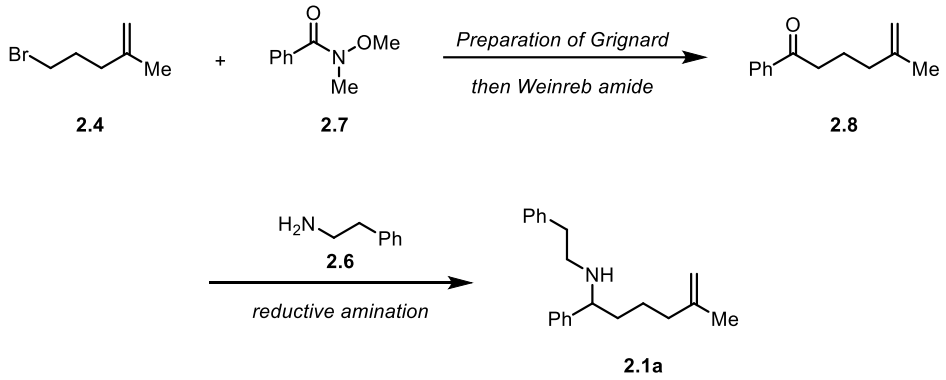
2.1.1 Synthesis of racemic starting material

Initially, the synthesis of **2.1a** was pursued through the reaction sequence shown in ***Scheme 26***, starting from 5-hydroxy-2-pentanone **2.2**, which was subjected to a Wittig olefination[68] to furnish 4-methylpent-4-en-1-ol **2.3** in satisfactory yield. The alcohol functionality was subsequently converted into the corresponding mesylate[69] and, after solvent exchange, subjected to nucleophilic substitution with lithium bromide to yield **2.4**. The alkyl bromide **2.4** was transformed into the corresponding Grignard reagent and added to benzaldehyde, which resulted in the formation of unsaturated alcohol **2.5**. Inspired by the work of Charette and co-workers,[24] who reported the development of a method that allows the use of amines that are typically incompatible under classic Mitsunobu conditions (Chapter 1.1.1), we attempted to use BEHT triflate **1.10** on alcohol **2.5**. This route was selected with the aim of enabling, upon successful conversion, straightforward access to chiral amines from the corresponding enantiopure alcohols. These, in turn, can be readily synthesized from the corresponding enantiopure epoxides, as has been demonstrated for the oxygen analogue of this transformation.[67] However, to our disappointment, no product formation was detected, and alternative synthetic routes had to be explored.



***Scheme 26**: Failed reaction sequence of initial synthetic pathway to access starting material **2.1a**.*

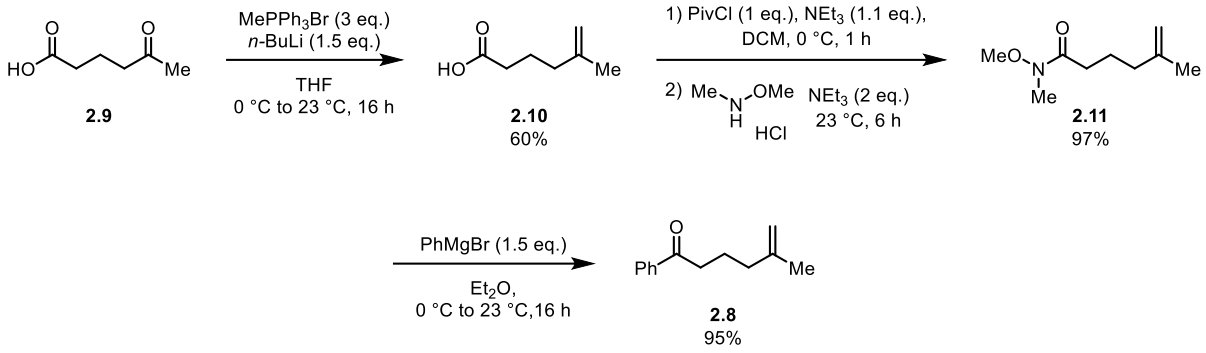
We then turned our attention to more traditional approaches for amine synthesis. As discussed in Chapter 1.1.2 of this thesis, reductive amination represents a widely applied method for the synthesis of amines, for which reason our efforts focused on preparing ketone **2.8** (***Scheme 27***). We initially envisaged the addition of the previously prepared alkyl bromide **2.4** to the Weinreb amide **2.7**. However, after further consideration, we concluded that an alternative synthetic route towards the desired ketone would be more suitable for several reasons: The purification of **2.3** proved challenging due to the presence of triphenylphosphine oxide, which is formed as a byproduct of the Wittig reagent. Additionally, the volatility of **2.3** and **2.4** renders their handling difficult.



***Scheme 27:** Possible synthetic route to access the ketone **2.8**.*

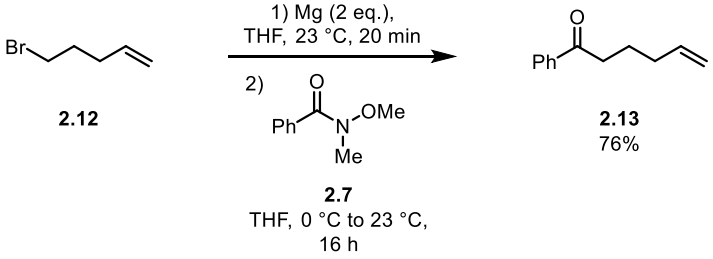
The optimized reaction sequence to ketone **2.8**, as a precursor to the desired amine, is illustrated in ***Scheme 28***. Commercially available 5-methylhex-5-enoic acid **2.9** was first subjected to a Wittig olefination using methyltriphenylphosphonium bromide and *n*-BuLi to

obtain unsaturated carboxylic acid **2.10** in satisfactory yield.[70] Subsequent conversion of **2.10** into the corresponding Weinreb amide **2.11**,[71] via the pivaloyl anhydride, proceeded in near quantitative yield. Finally, phenylmagnesium bromide was added to the Weinreb amide **2.11** to furnish the desired ketone **2.8** in excellent yield.



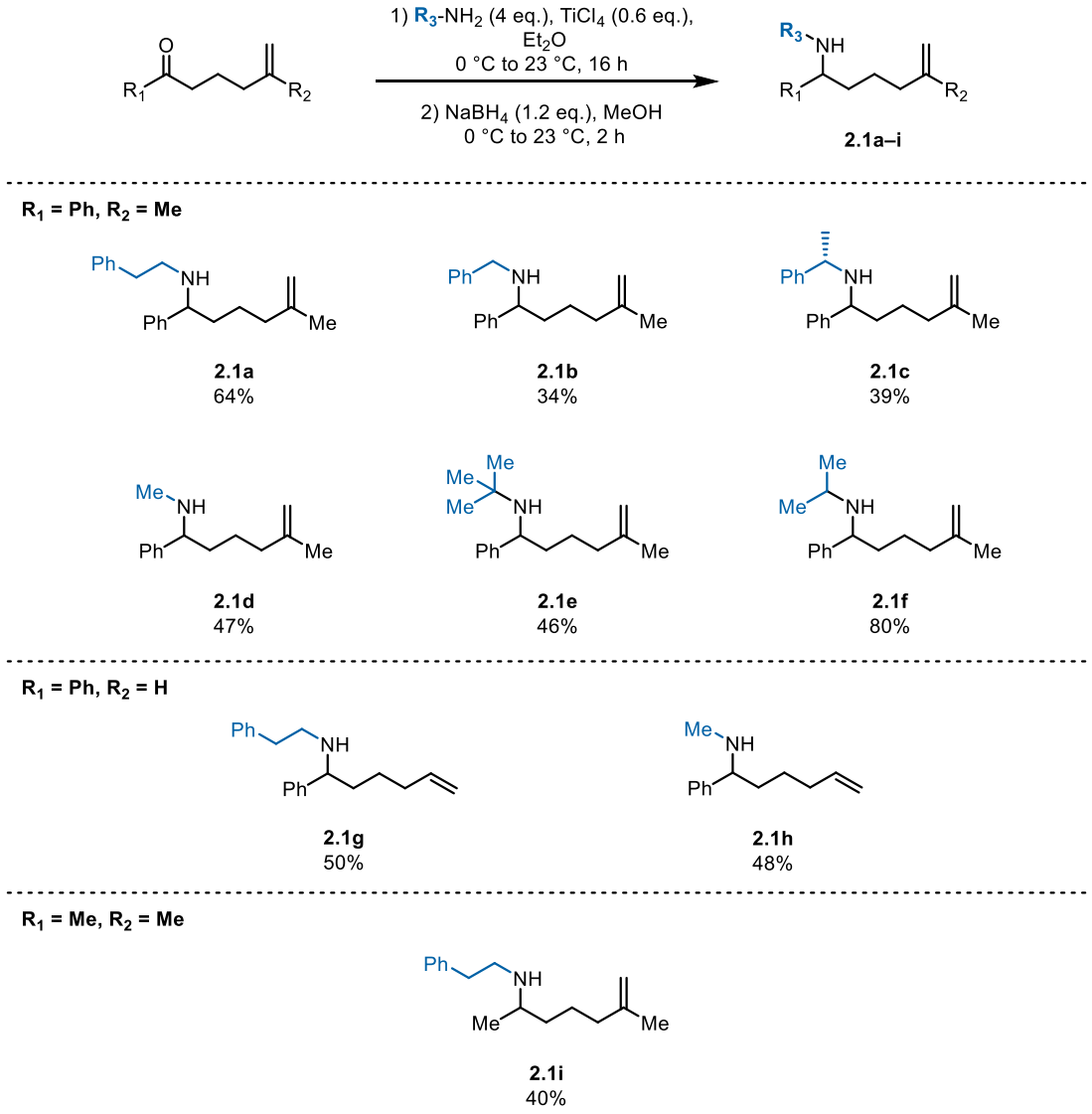
Scheme 28: *Optimized synthetic pathway to the ketone* ***2.8.***

To be able to later compare the envisioned intramolecular hydroaminoalkylation reactions of 1,1-disubstituted alkenes with monosubstituted alkenes, ketone **2.13** (***Scheme 29***) was additionally prepared. In this case, the previously mentioned approach outlined in ***Scheme 27*** was successfully employed, as the required alkyl bromide **2.12** is commercially available. 5-Bromo-1-pentene **2.12** was converted into the corresponding Grignard reagent, followed by addition to the Weinreb amide **2.7**, which resulted in the formation of the desired product **2.13** in 76% yield.



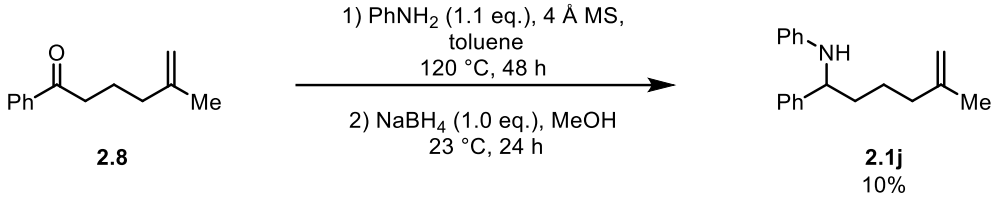
Scheme 29: *Preparation of ketone precursor with monosubstituted alkene* ***2.13****.*

With precursors **2.8** and **2.13** in hand, reductive amination was performed with a variety of amines. Following a literature-known procedure,[72] the reductive aminations were carried out by initial condensation of the corresponding ketone with primary amines in the presence of titanium(IV) chloride. After aqueous work up, reduction of the imines was performed using $NaBH_4$. The results of these transformations are summarized in ***Scheme 30***.



***Scheme 30**: Synthesis of amine starting materials.*

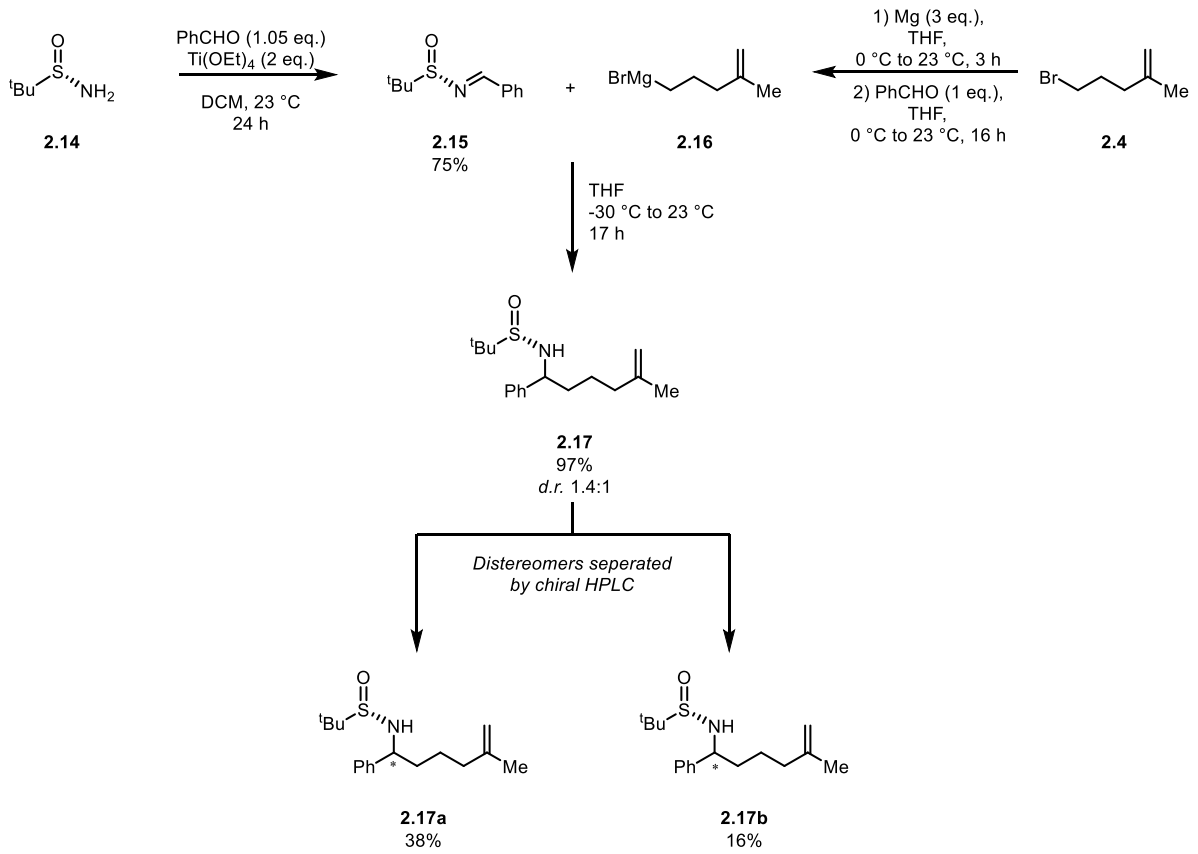
As shown in ***Scheme 31***, the preparation of amine **2.1j**, using aniline, required harsher reaction conditions due to aniline's decreased nucleophilicity.[73] However, even with these more forcing conditions, the condensation step appeared to proceed inefficiently, resulting in a low isolated yield of 10%.



***Scheme 31:** Conditions for reductive amination using aniline.*

2.1.2 Synthesis of enantiopure starting material

For the preparation of enantiopure starting material, we envisioned the synthetic route outlined in ***Scheme 32***, employing Ellman's chiral sulfinamide strategy. Following a reported literature procedure,[75] the preparation of sulfinimine **2.15** proceeded smoothly from enantiopure *(S)*-(–)-*t*-butylsulfinamide **2.14** and benzaldehyde in the presence of titanium(IV) ethoxide. Freshly prepared Grignard reagent **2.16**, formed smoothly from alkyl bromide **2.4**, was slowly added to a cooled solution of sulfinimine **2.15** in anhydrous tetrahydrofuran, resulting in the formation of sulfinamide **2.17** in near quantitative yield. Despite reports of good diastereoinduction,[76] the observed diastereomeric ratio (*d.r.*) of 1.4:1 was unsatisfactory and would not have allowed the assessment of chirality transfer of the intramolecular hydroaminoalkylation reaction. Attempts to separate the diastereomers by conventional silica gel column chromatography were unsuccessful and therefore the separation had to be performed by chiral HPLC to yield the diastereomers **2.17a** and **2.17b**. The absolute configuration of the separated diastereomers remains unknown for now, as none of the commonly employed methods for this purpose, such as single-crystal X-ray crystallography or Mosher's reagent-based derivatization, were used.

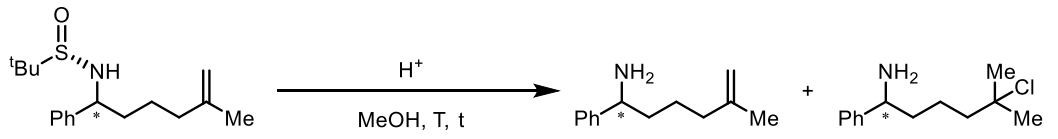


Scheme 32: *Synthetic route for the preparation of the diastereopure precursors for the preparation of enantiopure starting material.*

With the separated diastereomers in hand, we moved on to the cleavage of the sulfinyl group in order to obtain enantiopure amines. In contrast to our expectations, this proved to be a challenging endeavor and required optimization of the reaction conditions (***Table 1***). In our initial attempts, we employed standard deprotection protocols using hydrogen chloride in dioxane (7.0 eq. of a 4 M solution) at 23 °C, monitoring reaction progress by thin layer chromatography (TLC) (***entry 1***).[77] Nevertheless, no successful cleavage was observed. Surprisingly, analysis of the crude NMR spectrum showed no peaks corresponding to the olefin protons, which could possibly be caused by the addition of HCl across the double bond **2.19**. While the product was never isolated, crude mass spectrometric analysis revealed the presence of the mass corresponding to the chlorinated species **2.19**. This claim is further supported by the characteristic chlorine isotope pattern, displaying the expected 3:1 abundance ratio of ^{35}Cl and ^{37}Cl. Considering the unexpected instability of the olefin in the acidic environment, milder reaction conditions were applied by decreasing the equivalents of hydrogen chloride (from 7.0 to 4.0 eq.) and reducing the reaction temperature to 0 °C

(***entry 2***). Analysis of the crude NMR was inconclusive with respect to the extent of deprotection and formation of the proposed chlorinated species. Attempts to isolate either the desired free amine **2.18** or the putative side product **2.19** were unsuccessful as both compounds presumably decomposed during purification. Suspecting that HCl was incompatible with this substrate, we tested an acid with a less nucleophilic counterion: trifluoroacetic acid (TFA, ***entry 3***). However, under these conditions, the desired cleavage was not observed and only starting material was recovered. Finally, successful deprotection was achieved when returning to hydrogen chloride (***entry 4***). Following a reduction of both the stoichiometry (2.0 eq.), the reaction time (10 min, monitored by TLC) and performing the reaction at 23 °C, complete conversion was achieved. Nevertheless, the deprotection proved to be highly sensitive, with isolated yields varying considerably between 53% and 80% over multiple repetitions. While this variability is attributed to the likely formation of the chlorinated species, definitive confirmation of this hypothesis would require the isolation and full characterization of that putative byproduct.

Table 1: *Optimization of the deprotection step.*

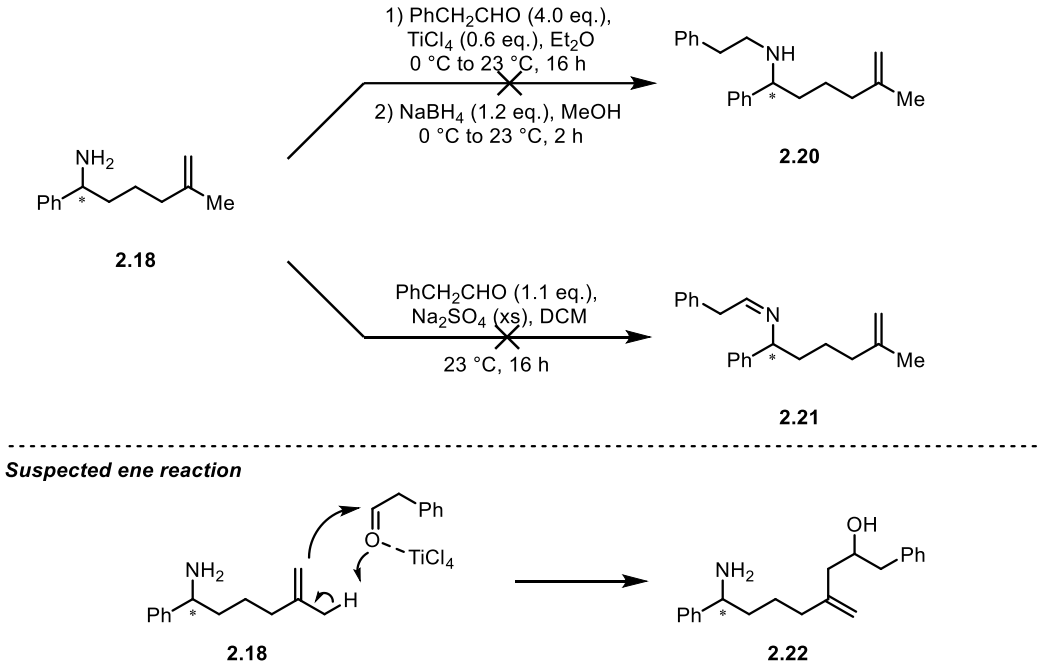


2.17a **2.18** **2.19**
Suspected side product
requires *m/z* 226.13
found *m/z* 226.14

Entry	T (° C)	H^+	Eq.	t	Outcome
1	23 °C	HCl (4 M in dioxane)	7.0	30 min	Decomposition
2	0 °C	HCl (4 M in dioxane)	2.0	1 h	Inconclusive results, Decomposition during isolation
3	0–23 °C	TFA	2.0	1 h	No conversion
4	23 °C	HCl (4 M in dioxane)	2.0	10 min	53 – 80% isolated yield

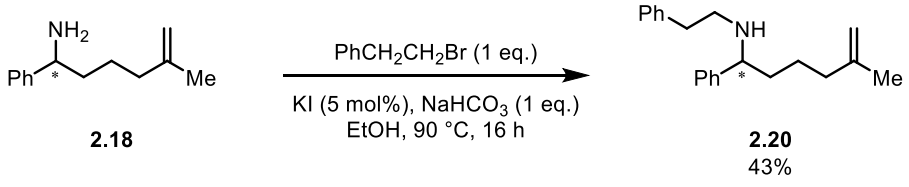
Alkylation of **2.18** by reductive amination proved ineffective for this substrate (***Scheme 33***, top). Instead, analysis of the crude reaction mixture by NMR revealed a complex mixture of unidentified products. We hypothesized that the presence of titanium(IV) tetrachloride ($TiCl_4$) might promote a competing carbonyl ene-type reaction, as this Lewis acid has been reported

to facilitate such transformations (***Scheme 33***, bottom).[78] Nevertheless, the presence of this side product **2.22** was not conclusively proven. We also investigated whether initial imine (**2.21**) formation is feasible in absence of the titanium species, to no avail (***Scheme 33)***.



Scheme 33: *Failed reductive amination and imine formation (top) and suspected $TiCl_4$-promoted ene reaction (bottom).*

We subsequently switched from reductive amination to a literature-known alkylation procedure[79] and successfully obtained the desired enantiopure product **2.20** in 43% yield (***Scheme 34***). The remaining material either did not react or underwent overalkylation, which is a commonly encountered problem in amine alkylation reactions, as discussed in Chapter 1.1.1.

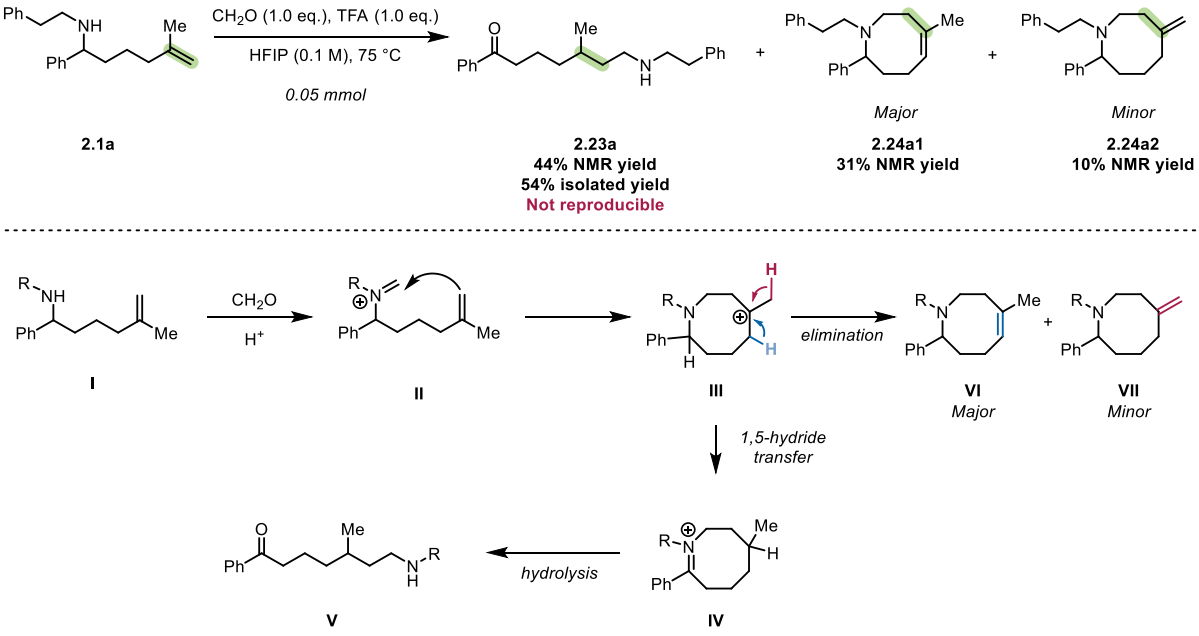


Scheme 34: *Alkylation to yield the final enantiopure product **2.20**.*

2.2 Optimization study

With the starting materials in hand, attention was directed towards identifying suitable reaction conditions for realizing the intramolecular hydroaminoalkylation. The optimization studies presented herein represent selected examples and a comprehensive overview of all investigated sets of reaction conditions can be found in the experimental section. Based on prior work[63-66], we began our optimization studies using paraformaldehyde and trifluroracetic acid (TFA) in hexafluoroisopropanol (HFIP) at 75 °C. Encouragingly, the formation of the desired product was observed under these conditions (***Scheme 35***, top). However, this result could never be reproduced, most likely due to the small scale of the reaction, which increases the likelihood of inaccurate weighing.

From the earliest experiments on, the formation of two side products, identified as the eight-membered ring regioisomers **2.24a1** and **2.24a2** (***Scheme 35***, top), was consistently observed. These side products are likely formed from the putative carbocationic intermediate **III** (***Scheme 35***, bottom) through competing elimination pathways. Similar side products have also been reported for the previously reported reaction of the corresponding oxygen analog.[67] Therefore, the goal of these optimization studies was not only to identify conditions leading to a high conversion but also to suppress the competing elimination pathways.

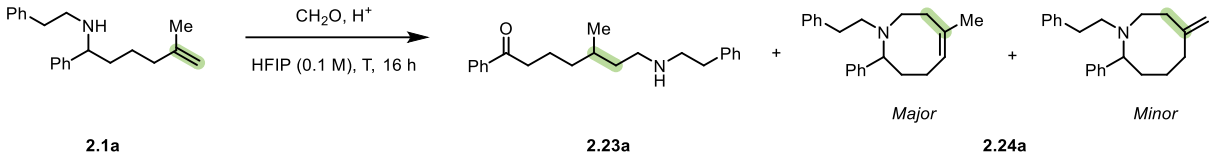


Scheme 35: *Mechanism of the hydroaminoalkylation of model substrate **2.1a** and competing elimination pathway to form eight-membered side products **VI** and **VII**.*

Our initial optimization efforts focused on evaluating the influence of reagent stoichiometry, as summarized in ***Table 2***. First the effect of paraformaldehyde stoichiometry (***entries 2-7***) was investigated. The use of 1.3 eq. of aldehyde provided the highest NMR yield (***entry 4***), while higher amounts only resulted in a decreased yield, accompanied by an increased degree of formation of the elimination side product (***entries 5-7***).

Subsequently, the influence of the stoichiometry of trifluoroacetic acid was examined. Surprisingly, the reaction proceeded even in the absence of additional acid (***entries 8*** and ***9***), albeit to a lesser extent—compare ***entries 4*** and ***9***. While this might suggest that the acidity of HFIP (pK_a = 9.3)[80] is sufficient to promote this transformation, the lower conversion rendered the further exploration of these conditions a low priority. Similarly, increasing the amount of TFA to 2.0 equivalents (***entry 10***) did not improve the reaction outcome, and catalytic quantities of TFA (***entries 11*** and ***12***) likewise diminished the yield. The highest NMR yield was achieved using 1.0 equivalents of TFA in combination with 1.3 equivalents of paraformaldehyde (***entry 4***), however, side products were still formed in significant amounts. We hypothesized that lowering the reaction temperature could favor the desired reaction pathway and reduce the formation of the elimination products. However, ***entries 2*** and ***13*** demonstrate that decreasing the reaction temperature, in addition to leading to a decreased overall yield, had no significant effect on the ratio of product to the side products.

Table 2: *Optimization of the reaction conditions – screening of reagent stoichiometry. All reactions were performed on 0.1 mmol scale, unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^1H NMR analysis of the crude reaction mixtures using mesitylene as internal standard. [a]Reaction performed on 0.05 mmol scale. [b]Isolated yield. [c]Not reproducible results.*



2.1a **2.23a** **2.24a**

Entry	T (° C)	H^+(eq.)	CH_2O (eq.)	NMR yield (2.23a)	NMR yield (2.24a)
1[a]	75	TFA (1.0 eq.)	1.0	44% (54%)[b,c]	41%
2[a]	23	TFA (1.0 eq.)	1.0	25%	26%
3	75	TFA (1.0 eq.)	1.1	24%	29%
4	75	TFA (1.0 eq.)	1.3	50%	41%
5	75	TFA (1.0 eq.)	1.5	41%	42%
6	75	TFA (1.0 eq.)	1.7	39%	50%
7	75	TFA (1.0 eq.)	2.0	32%	40%
8	75	-	1.0	37%	32%
9	75	-	1.3	38%	29%
10	75	TFA (2.0 eq.)	1.0	23%	21%
11	75	TFA (0.2 eq.)	1.0	35%	26%
12	75	TFA (0.2 eq.)	1.3	41%	30%
13	50	TFA (1.0 eq.)	1.3	43%	45%

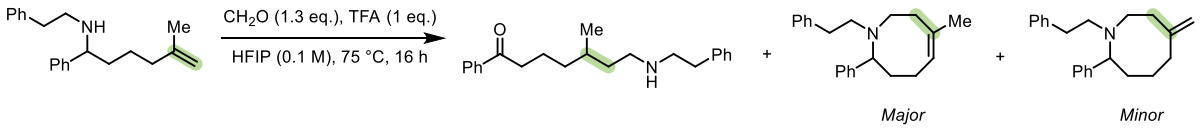
We then turned our attention to screening different solvents and solvent mixtures, as shown in ***Table 3***. When HFIP was replaced with 1,2-dichloroethane (DCE), no product formation was observed, suggesting that HFIP plays a crucial role in this transformation (***entry 1***). This observation can likely be attributed to the ability of HFIP to stabilize various formed carbocationic intermediates.[80] Trifluoroethanol (***entry 2***), another fluorinated alcohol, also promoted the transformation, however, no improvement in product yield was observed compared to HFIP.

Subsequently, we screened for the optimal concentration of the reaction. From ***entries 3*** to ***6***, it is evident that the reaction concentration influences side product formation to a significant

extent. As shown by ***entry 3***, highly concentrated conditions afforded the side product in 56% yield. We hypothesized that by diluting the reaction mixture, we would suppress putative intermolecular elimination caused by the nitrogen's basicity. Indeed, decreasing the concentration to 0.5 M (***entry 4***) lowered the yield of the side products to 42%. Nevertheless, further dilutions to 0.05 M (***entry 5***) and 0.01 M (***entry 6***) had no substantial effect on the side product formation, as the yields remained relatively similar, presumably due to the persisting intramolecular elimination pathway. Despite achieving the highest product yield (57% by NMR analysis) at the lowest concentration (***entry 6***), performing the reaction under such highly diluted conditions is impractical, particularly with regard to future scale up reactions. Moreover, the reaction temperature of 75 °C exceeds the boiling point of HFIP (58 °C)[80], which would necessitate careful pressure control. Consequently, other reaction conditions were explored.

We then proceeded to investigate the effect of co-solvents on the yield and selectivity of this reaction. While a satisfactory yield for ***entry 7*** (employing dichloromethane (DCM)) was observed, significant formation of the side products was still observed. Other solvent mixtures (***entries 8*** and ***9***, using a different amount of DCM and toluene, respectively) appeared to have a deleterious effect on the reaction outcome.

Table 3: *Optimization of the reaction conditions – screening of different solvents and solvent mixtures. All reactions were performed on 0.1 mmol scale, unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^{1}H NMR analysis of the crude reaction products using mesitylene as internal standard. [a]Reaction performed with 1.0 eq. CH_2O.*



2.1a **2.23a** **2.24a**

Entry	Solvent	NMR yield (2.23a)	NMR yield (2.24a)
1[a]	DCE	0%	0%
2	TFE	40%	46%
3	HFIP (1 M)	41%	56%
4	HFIP (0.5 M)	48%	42%
5	HFIP (0.05 M)	53%	42%

6	HFIP (0.01 M)	57%	40%
7	HFIP: DCM (1:1)	50%	47%
8	HFIP: DCM (1:2)	40%	38%
9	HFIP: PhMe (1:1)	43%	39%

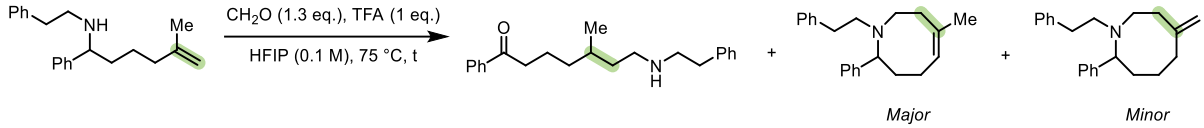
Further optimization studies were conducted by screening a variety of Brønsted and Lewis acids (***Table 4***). The use of the stronger Brønsted acid triflic acid, either in catalytic or stoichiometric amounts (***entries 1*** and ***2***), resulted only in low product yields. Similarly, hydrogen chloride (4 M in dioxane) and acetic acid (***entries 3*** and ***4***) also performed poorly.

In parallel to these screening studies, the reaction progress was monitored by NMR analysis (***Scheme 36***) and revealed complete consumption of the starting material after approximately 30 min. To ensure full conversion under all subsequently investigated reaction conditions, a reaction time of 2 h was chosen starting from ***entry 5*** onwards in ***Table 4***.

During the investigation of various Lewis acids, triflate salts were identified as promising additives, with praseodymium and copper triflate exhibiting particularly favorable results (***entries 5*** and ***6***). Intrigued by these outcomes, we sought to further investigate these systems: We first explored whether a co-solvent effect using a 1:1 mixture of HFIP and DCM (***entries 7*** and ***8***) could improve product yield and selectivity. Interestingly, this led to a decrease in yield which is surprising considering that, as shown before in ***Table 3*** for ***entry 7***, the use of DCM as a co-solvent did not have a significant impact on the yield.

Furthermore, we examined whether a catalytic amount of the respective Lewis acids would be sufficient to promote the transformation. While the yield obtained with a catalytic amount of $Cu(OTf)_2$ (***entry 10***) decreased compared to ***entry 6***, the yield for $Pr(OTf)_3$ (***entry 9***) remained largely unchanged. We further investigated whether a combination of catalytic amounts of $Cu(OTf)_2$ and TFA could lead to a synergistic effect (***entry 11***). Indeed, a higher yield of 58% was achieved in comparison to ***entry 10***, in which only catalytic amount of $Cu(OTf)_2$ was employed. Unfortunately, we cannot comment on the formation of the side product for ***entries 10*** and ***11*** as yield determination was not possible due to overlapping NMR signals.

Table 4: *Optimization of the reaction conditions – screening of different Brønsted or Lewis acids. All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^{1}H NMR analysis of the crude reaction products using mesitylene as internal standard. [a]Isolated yield. [b]Reaction performed with 1.0 eq. CH_2O.*

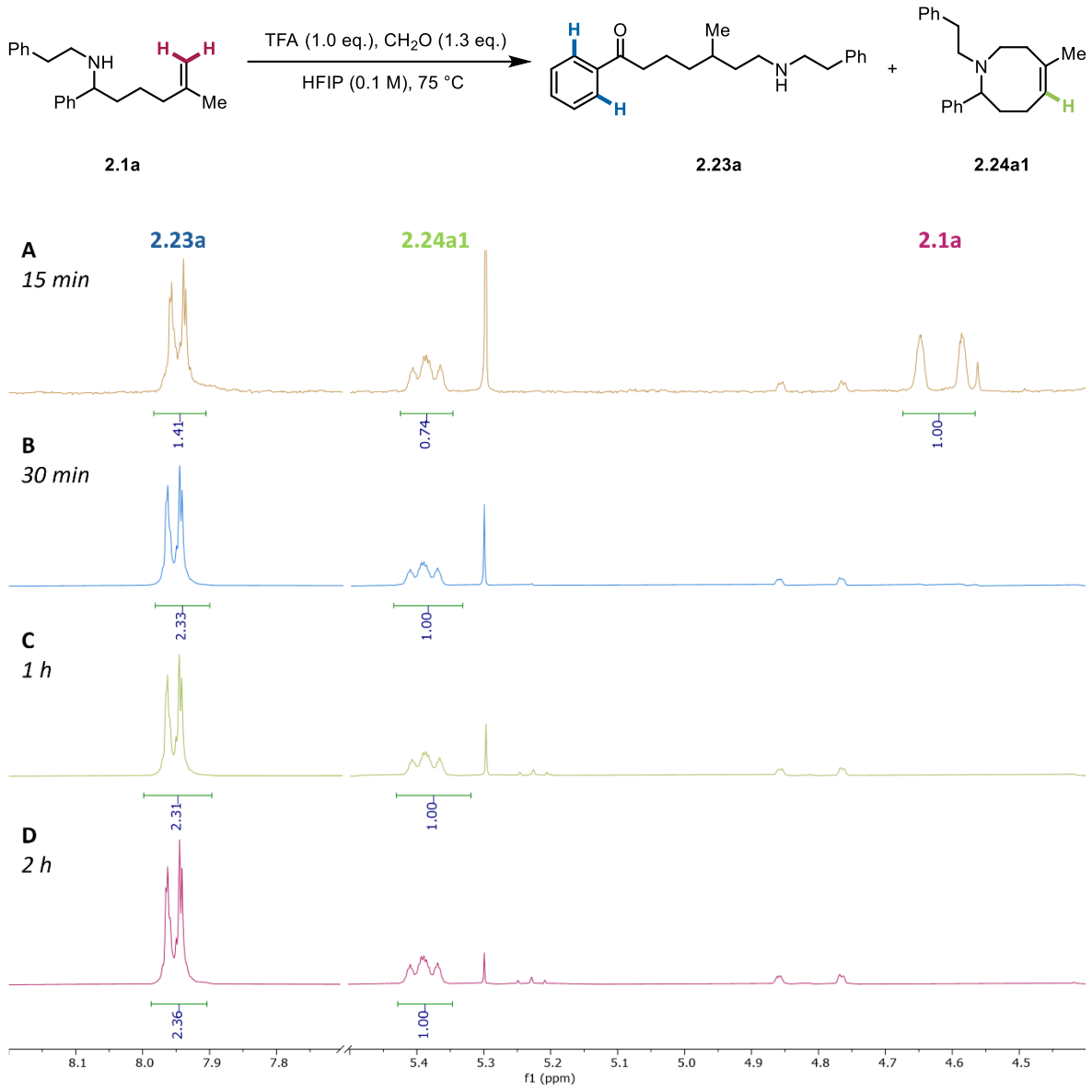


2.1a **2.23a** **2.24a**

Entry	Solvent	H$^+$/LA (eq.)	t	NMR yield (2.23a)	NMR yield (2.24a)
1	HFIP	TfOH (0.2 eq.)	16 h	28%	32%
2	HFIP	TfOH (1.0 eq.)	16 h	5%	14%
3[b]	HFIP	HCl (4M in dioxane) (1.0 eq.)	16 h	16%	15%
4[b]	HFIP	AcOH (1.0 eq.)	16 h	32%	25%
5	HFIP	$Pr(OTf)_3$ (1.0 eq.)	2 h	49%	39%
6	HFIP	$Cu(OTf)_2$ (1.0 eq.)	2 h	59% (51%)[a]	37%
7	HFIP: DCM (1:1)	$Pr(OTf)_3$ (1.0 eq.)	2 h	37%	37%
8	HFIP: DCM (1:1)	$Cu(OTf)_2$ (1.0 eq.)	2 h	32%	42%
9	HFIP	$Pr(OTf)_3$ (0.1 eq.)	2 h	45%	44%
10	HFIP	$Cu(OTf)_2$ (0.1 eq.)	2 h	48%	n.d.
11	HFIP	$Cu(OTf)_2$ (0.1 eq.) + TFA (0.1 eq.)	2 h	58% (46%)[a]	n.d.

Among all the screened reaction conditions, we recognized these four sets of conditions to furnish the best yield: **1:** TFA (1 eq.), **2:** $Cu(OTf)_2$ (1 eq.), **3:** $Cu(OTf)_2$ (0.1 eq.) and **4:** $Cu(OTf)_2$ (0.1 eq.) + TFA (0.1 eq.). However, after these intense optimization studies we were unable to find conditions that would exceed a yield of 60% and suppress the formation of the elimination products, as it appears that the product and side products form at the same rate. Indeed, after monitoring the reaction by NMR, we observed that even after 15 min both the product and side product started to form at the same rate. This is shown in ***Scheme 36A*** by the same integration values for product **2.23a** and side product **2.24a1** (when taking the respective proton counts into consideration). As the reaction progressed (***Scheme 36B-D***), formation of the desired product **2.23a** became slightly favored over that of the eight-membered-ring side product **2.24a1**, affording an approximate product ratio of 1.2:1

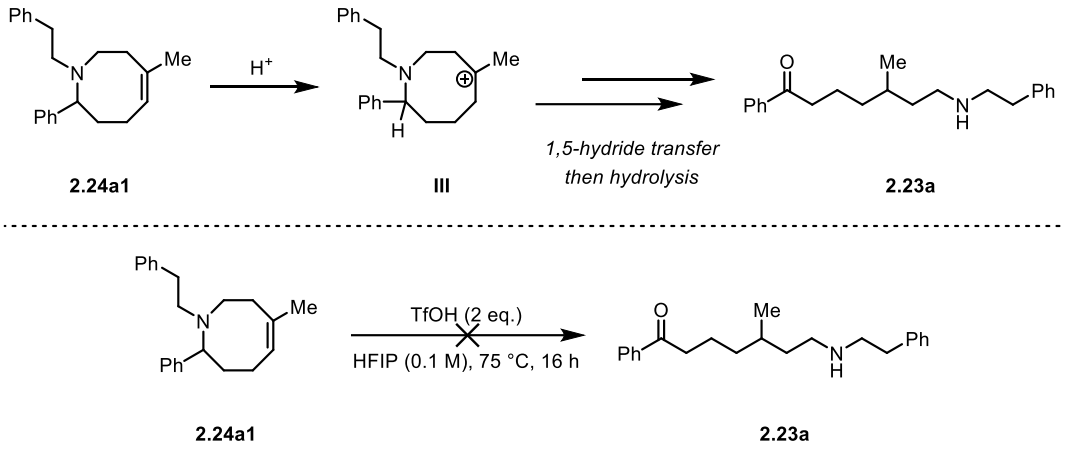
(**2.23a**:**2.24a1**) under these conditions. This ratio is consistent with the NMR yields previously obtained for this reaction (***Table 1***, ***entry 4***).



Scheme 36: *Reaction progress monitored by NMR.* ***A:*** *15 min.* ***B:*** *30 min.* ***C:*** *1 h.* ***D:*** *2 h. The aromatic region was cut for simplification.*

Since the formation of the side product could not be readily suppressed through modifications of the reaction conditions, we investigated whether the elimination product could instead be converted into the desired product (***Scheme 37***). We hypothesized that protonation of the double bond with a strong acid, such as trifluoromethanesulfonic acid, could regenerate the carbocationic intermediate **III** and thereby enable the 1,5-hydride transfer step. Two equivalents of trifluoromethanesulfonic acid were employed, as the first equivalent was

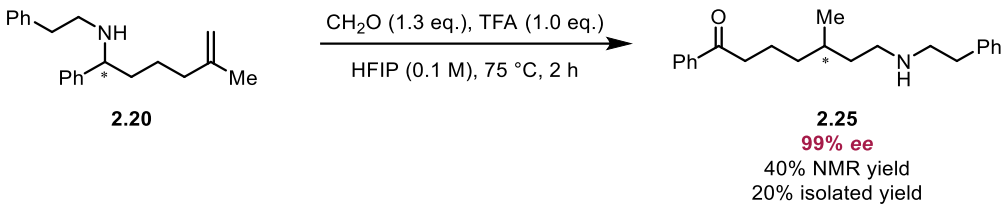
expected to be consumed though protonation of the amine. However, unfortunately, the desired transformation was not observed under these conditions, and therefore this idea was not pursued further.



Scheme 37: *Failed attempt at converting the major side product* ***2.27a1*** *to product* ***2.26a*** *by exposure to trifluoromethanesulfonic acid.*

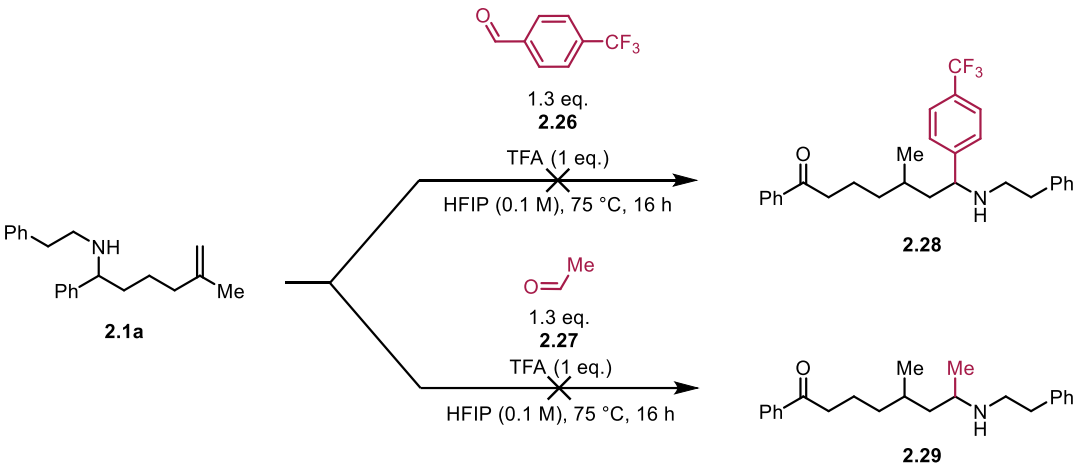
2.3 Stereochemical investigation

Attention was then directed towards applying the optimized reaction conditions to the enantiopure starting material in order to evaluate whether the proposed chirality transfer, as demonstrated for the oxygen version,[67] could be observed in this context. As these experiments were performed prior to obtaining the favorable results of screening triflate salts, the reaction was performed with 1.0 eq. of trifluoroacetic acid (***Scheme 38***). Gratifyingly, the product was obtained with an enantiomeric excess of 99%. This observation strongly supports the proposed stereochemical model, in which the stereocenter adjacent to the nitrogen atom is ablated and the stereochemical information is transferred through a 1,5-hydride transfer. The observed chirality transfer is consistent with the proposed mechanism involving a suprafacial 1,5-hydride transfer, resulting in retention of the stereochemical information throughout the transformation



Scheme 38: *Reaction starting from enantiopure starting material. Yield discrepancy due to difficulties encountered during product isolation.*

It is also worth noting that efforts were made to investigate the use of different aldehydes in order to both expand the substrate scope and gain insights regarding the possibility of diastereocontrol in this the reaction (***Scheme 39***). To date, only 4-(trifluoromethyl)benzaldehyde (**2.26**) and acetaldehyde (**2.27**) have been examined. However, in both cases only starting material was recovered and no product formation was observed. This may suggest that initial imine formation is challenging for these substrates. Additional studies would be required to determine whether this observation reflects a general incompatibility of substituted aldehydes or whether different reaction conditions are necessary. Due to time constraints, these investigations could not be pursued further in the context of this thesis.



Scheme 39: *Failed reactions with other aldehydes.*

2.4 Preliminary survey of amine substitution

As demonstrated in the optimization studies, the product yield consistently remained below 60%. This prompted us to question whether the chosen model substrate was inherently limiting the efficiency of the transformation – a question that we sought to address by investigating the effect of variation of the substrate structure, specifically substitution on

nitrogen. As several sets of reaction conditions had previously resulted in comparable yields (see ***entry 4*** in ***Table 2*** and ***entries 6,10*** and ***11*** in ***Table 4***), different conditions were also applied to a variety of amine substrates. The results of these investigations for amines with geminal disubstituted olefins are shown in ***Scheme 40***.

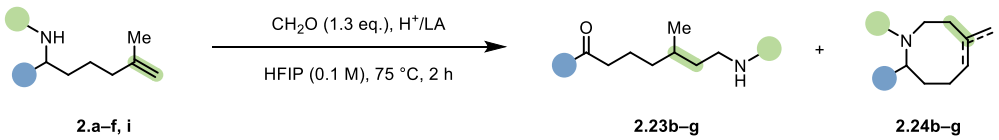
Replacing the phenethyl moiety of the standard substrate by a benzyl group (***Scheme 40A***) did not have a significant influence on the efficiency of the reaction and all employed reaction conditions resulted in similar yields. However, a combination of $Cu(OTf)_2$ and TFA (***conditions d***) afforded the lowest yield of the side product **2.24b**. Notably, this substrate bears a second benzylic position, which we anticipated could lead to a competing alternative 1,5-hydride transfer. The observed absence of the product that was expected to result from this process, however, suggests that the hydride transfer requires a specific spatial arrangement within the eight-membered ring.

Interestingly, the reaction conditions appeared to have the greatest influence on the substrate bearing an isopropylamine substituent on nitrogen (***Scheme 40B***). In this case, only the combination of $Cu(OTf)_2$ and TFA (***conditions d***) lead to higher levels of product formation, while using either of them alone resulted in a significant drop in yield. This observation further supports the hypothesis of a potential synergistic effect of Brønsted and Lewis acid catalysis. However, under all investigated conditions, the elimination product **2.24c** was always preferentially formed over the desired product.

Moreover, sterically more demanding substituents on the amine, such as for the methylbenzyl and *tert*-butyl substrates shown in ***Scheme 40C*** and ***D***, resulted in very low yields or no product formation at all, respectively. This could most likely be attributed to increased steric hindrance, which prevents intermediates from adopting the required conformation for efficient hydride transfer. Interestingly, for both substrates the formation of the elimination pathway was observed, reaching as high as 94% yield (as determined by NMR analysis) for **2.24e** (***conditions b***). However, there is also no generality about which conditions promote the formation of the elimination products. For instance, when applied to α-branched **2.1c**, ***conditions a*** led to the highest yield of side products **2.24d**, whereas for *t*-butyl-substituted **2.1e** the same conditions resulted in the lowest overall yield of **2.24e**.

Suspecting that the basicity of the amine promotes the elimination pathway, we attempted to use an aniline derivative **2.1j** (***Scheme 40E***). Due to the low yield of the starting material synthesis, limited material permitted only two reaction attempts. Using ***conditions d*** at 75 °C and 23 °C neither the desired product **2.23f** nor the side product **2.24f** were detected. Instead, analysis of the crude reaction mixtures by NMR spectroscopy showed complete decomposition of the starting material.

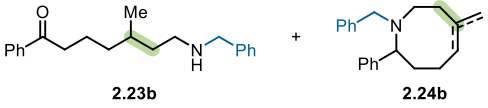
Finally, we investigated the influence of the substituent in α-position to the nitrogen (***Scheme 40F***). When the phenyl group was exchanged with a methyl substituent, as shown for product **2.23g**, lower yields were obtained. This suggests that the benzylic position might be important for promoting the hydride transfer process, presumably through increased stabilization of the corresponding iminium intermediate by conjugation.



2.a–f, i **2.23b–g** **2.24b–g**

Geminal Disubstituted Alkenes

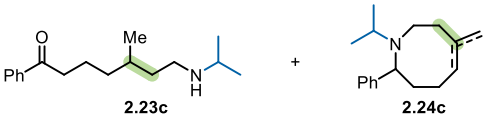
A



2.23b **2.24b**

Entry	Conditions	NMR Yield (2.23b)	NMR Yield (2.24b)
1	a	46% (48%)[a]	29%
2	b	46%	15%
3	d	46%	10%

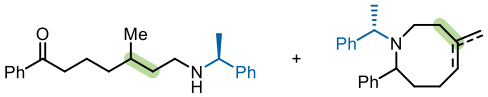
B



2.23c **2.24c**

Entry	Conditions	NMR Yield (2.23c)	NMR Yield (2.24c)
1	a	13%	27%
2	b	12%	45%
3	d	40% (41%)[a]	47%
4	c	39%	43%

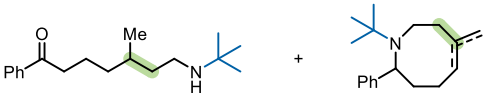
C



2.23d **2.24d**

Entry	Conditions	NMR Yield (2.23d)	NMR Yield (2.24d)
1	a	8%	44%
2	b	10%	42%
3	d	10%	31%

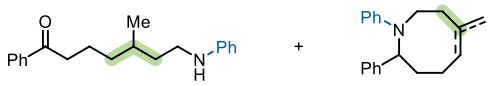
D



2.23e **2.24e**

Entry	Conditions	NMR Yield (2.23e)	NMR Yield (2.24e)
1	a	0%	27%
2	b	0%	94%(59%)[a]
3	d	0%	81%
4	c	0%	35%

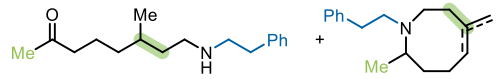
E



2.23f **2.24f**

Entry	Conditions	NMR Yield (2.23f)	NMR Yield (2.24f)
1	d	0%	0%
2[b]	d	0%	0%

F



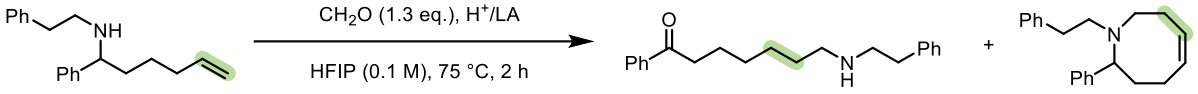
2.23g **2.24g**

Entry	Conditions	NMR Yield (2.23g)	NMR Yield (2.24g)
1	a	23% (18%)[a]	22%
2	e	15%	17%

Scheme 40: *Survey of amines with disubstituted alkenes. All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Conditions used* ***a:*** *TFA (1 eq.),* ***b:*** *$Cu(OTf)_2$ (10 mol%),* ***c:*** *$Cu(OTf)_2$ (10 mol%) + TFA (1 eq.),* ***d:*** *$Cu(OTf)_2$ (10 mol%) + TFA (10 mol%),* ***e:*** *No Brønsted or Lewis acid. Yields were determined by ^1H NMR analysis of the crude reaction products using mesitylene as internal standard. [a]Isolated yield. [b]Performed at 23 °C.*

We then proceeded to investigate substrate **2.1g**, bearing a monosubstituted alkene (***Table 6***). Interestingly, when comparing the results for substrate **2.1g** and the model substrate **2.1a**, we observed different reaction outcomes when the same reaction conditions were applied. For instance, **conditions a** gave relatively good yields for the model substrate **2.1a** (***Table 2***, ***entry 4***), whereas for **2.1g** a diminished yield for **2.23h** was observed (***Table 6***, ***entry 2***). Once again, the combination of both Brønsted and Lewis acids led to a higher product yield and limited formation of the side product **2.24h**, as shown in ***entry 1***.

Table 6: *All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^{1}H NMR analysis of the crude reaction products using mesitylene as internal standard.*

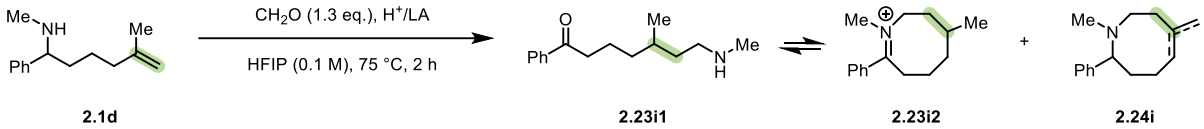


2.1g **2.23h** **2.24h**

Entry	H^+/LA (eq.)	NMR yield (2.23h)	NMR yield (2.24h)
1	$Cu(OTf)_2$ (0.1 eq.) + TFA (0.1 eq.)	50%	15%
2	TFA (1.0 eq.)	20%	16%

We were pleased to observe that a methyl substituent on the amine resulted in improved reaction performance, affording product NMR yields over 60% along with a more favorable product to side product ratio (***Table 7, entries 1–3***). Interestingly, when employing TFA in catalytic amounts (***entry 4***) the yield drops below 60%, whereas the reaction performs better when no acid additive is used at all (***entry 5***). In contrast, the highest isolated NMR yields resulted when stoichiometric amounts of TFA (***entry 1***) were used. Nevertheless, when comparing these results with the other substrates, no general conclusion can be drawn regarding the general, optimal reaction conditions. Instead, the observations suggest that the reaction outcome is, to some extent, substrate dependent.

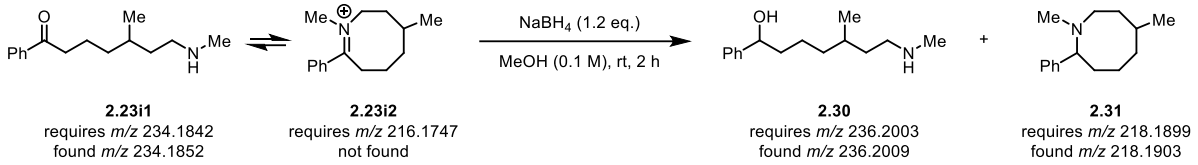
Table 7: *All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^{1}H NMR analysis of the crude reaction products using mesitylene as internal standard.* [a]*Isolated yield.*



2.1d **2.23i1** **2.23i2** **2.24i**

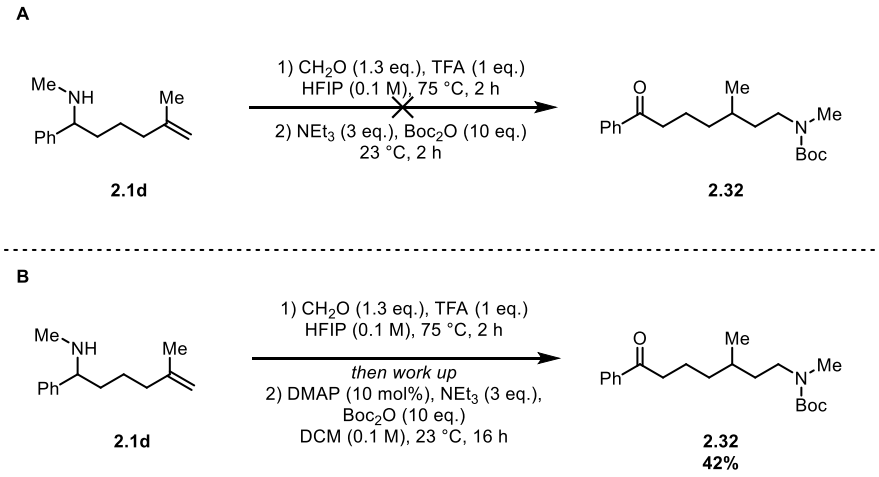
Entry	H^+/LA (eq.)	NMR yield (2.23i)	NMR yield (2.24i)
1	TFA (1.0 eq.)	70% (81%)[a]	30%
2	$Cu(OTf)_2$ (0.1 eq.)	75% (68%)[a]	16%
3	$Cu(OTf)_2$ (0.1 eq.) + TFA (0.1 eq.)	60%	24%
4	TFA (0.1 eq.)	50%	20%
5	-	58%	18%

As shown in ***Table 7*** for ***entries 1*** and ***2*** there is a significant discrepancy between the NMR yield and isolated yield. Furthermore, the NMR spectrum of the isolated product exhibited broadened signals and the integrals did not correspond to the expected proton count in comparison to those typically observed for related compounds. This raised the suspicion that product **2.23i1** exists in equilibrium with its corresponding iminium species **2.23i2 (*Table 7*)**. While the broader and discrepant NMR signals hinted towards this hypothesis, the iminium could not be observed in HRMS (***Scheme 41***), likely attributed to the harsh conditions used for measuring, which hydrolyses the iminium to its open form. To prove our hypothesis, we subjected the isolated product to reduction with sodium borohydride (***Scheme 41***). As anticipated, HRMS analysis of the reaction mixture revealed the formation of both alcohol **2.30** and the eight-membered ring product **2.31**, the latter arising from reduction of the cyclized iminium intermediate **2.23i2**. Consequently, the reported NMR and isolated yields should be interpreted with caution, as the equilibrium between these species complicates their accurate quantification.



Scheme 41: *Reduction of isolated product* ***2.23i1*** *to alcohol* ***2.30*** *and eight-membered ring* ***2.31****.*

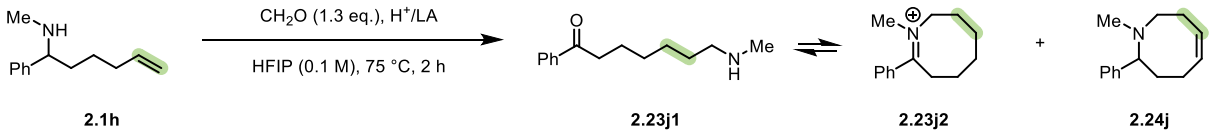
To suppress iminium formation and therefore facilitate product isolation, the amine functionality was protected using a *tert*-butyloxycarbonyl (Boc) group. In a paper published in 2008,[81] the authors reported the beneficial effects of HFIP for *N*-Boc protection, proposing that HFIP acts both as the catalyst and the solvent. Encouraged by these findings, we hypothesized that an *in situ* Boc protection might be feasible. Thus, the reported reaction conditions (which resulted in the highest isolated yield as shown in ***Table 7*** for ***entry 1***), including the addition of base to neutralize the remaining TFA, were carried out. Unfortunately, this initial attempt was unsuccessful, as shown in ***Scheme 42A***. Owing to time limitations, this could not be explored further and therefore remains a subject for future investigations. Successful Boc-protection was then achieved when standard protocols were applied (***Scheme 42B***). While we expected Boc-protection to afford only the linear product and additionally facilitate isolation by attenuating the basicity and nucleophilicity of the amine, a substantial loss in yield was observed. A reason for this might be that only the linear product undergoes Boc-protection, while the iminium species remains untouched, even though we anticipated that removing the free secondary amine would shift the equilibrium and thus push the reaction towards completion.



Scheme 42: A: *Failed attempt at performing in situ Boc protection.* ***B:*** *Successful Boc protection after aqueous work up.*

Moving on to the methylamine substrates bearing a monosubstituted olefin, only two conditions were explored in the remaining time. To compare the results of the previously shown phenylethyl amine substrate **2.1g** (***Table 6***), the same conditions were applied for the methylamine substrate **2.1h**, as shown in ***Table 8***. Surprisingly, the combination of $Cu(OTf)_2$ and TFA in a catalytic amount resulted in a very poor NMR yield of 29% (***entry 1***) in comparison to ***entry 3*** of ***Table 6*** for substrate **2.1g**. TFA (***Table 8***, ***entry 2***) on the other hand performed better and furnished an NMR yield of 80% (isolated with 56% yield as the Boc-protected product), which in contrast resulted in a lower yield for the monosubstituted olefin with the phenylethyl substituent. These results further highlight the substrate dependency of this transformation.

Table 8: *All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^1H NMR analysis of the crude reaction products using mesitylene as internal standard.* [a]*Isolated as the Boc-protected product* ***2.33****.*



2.1h **2.23j1** **2.23j2** **2.24j**

Entry	H^+/LA (eq.)	NMR yield (2.23j)	NMR yield (2.24j)
1	$Cu(OTf)_2$ (0.1 eq.) + TFA (0.1 eq.)	29%	12%
2	TFA (1.0 eq.)	80% (56%)[a]	7%

3 Conclusion and Outlook

This master's thesis aimed to investigate a novel intramolecular hydroaminoalkylation strategy based on the intermolecular hydroaminoalkylation protocol established by the Maulide group. Inspired by the group's earlier work on the enantioselective linear coupling of aldehydes and olefins, we explored the possibility of combining these two concepts in an intramolecular hydroaminoalkylation setting. Such an approach enables simultaneous amine functionalization and carbonyl formation in a redox-neutral and atom-economical manner. In contrast to previously reported intramolecular hydroaminoalkylation reactions, which predominantly afford cyclic products, the transformation investigated herein was designed to furnish linear products. Furthermore, the use of enantiopure starting materials offered the possibility of generating enantiopure products through chirality transfer during the hydride-transfer step.

The synthesis of the starting materials initially proved challenging; however, an efficient synthetic route was ultimately established, providing convenient access to a range of substituted amine substrates. For the preparation of the enantiopure starting material, Ellman's chiral sulfinamide strategy was employed to introduce stereochemical information at the desired stereocenter. This, however, resulted in poor diastereomeric ratios, resulting in the necessity for isomer separation by chiral HPLC. Hence, further investigation is necessary to find a reliable and robust synthetic pathway to access optically pure amine substrates.

Optimization studies were initiated using the group's previously established conditions for hydroaminoalkylation employing paraformaldehyde and trifluoroacetic acid (TFA) in hexafluoroisopropanol (HFIP). While the desired transformation could be achieved, the reaction was consistently accompanied by the formation of side products arising from elimination within the carbocationic intermediate. The reliance of this method on HFIP, as established during solvent screening, is attributed to HFIP's ability to stabilize carbocationic species. Despite extensive further optimization studies, no generally applicable conditions affording high yields could be identified. Nevertheless, TFA, $Cu(OTf)_2$, either in stoichiometric or catalytic amounts, as well as in combination, were found to efficiently promote the transformation.

Suppression of the competing elimination pathway remained challenging throughout the study. Although performing the reaction under more dilute conditions reduced the degree of side product formation, presumably through the suppression of intermolecular elimination, intramolecular elimination still persisted. A more detailed mechanistic understanding, potentially through computational studies, may provide valuable insight into the factors governing selectivity.

One of the most significant findings of this work was the observation of complete transfer of stereochemical information when employing enantiopure starting materials. This outcome can be rationalized by the proposed mechanism, in which, after nucleophilic attack of the olefin to the iminium ion, the resulting cyclic carbocationic intermediate is primed for a 1,5-hydride shift to generate a second iminium ion. Therein, the stereochemical information adjacent to the amine is efficiently transferred onto the carbocation through a suprafacial hydride transfer. While an initial result proved highly promising, further investigations aimed at understanding the diastereoselectivity of this transformation remain necessary, as the aldehydes employed in preliminary studies exhibited limited reactivity.

Application of the reaction conditions to different amine substrates showed that this process cannot yet be considered general, as apparent substrate dependency seemed to dominate. Sterically more demanding substrates generally exhibited poor reactivity for the desired transformation, which can be rationalized by the fact that increased steric hindrance hinders the molecule from adopting the geometrical conformation required for the hydride transfer, therefore leading to the formation of more side products.

Interestingly, *N*-methyl amines exhibited higher reactivity in these transformations. However, the isolated products were found to exist in equilibrium with their corresponding iminium species, currently necessitating an additional protection step to suppress undesired cyclization. While preliminary results are promising, further efforts must be made to develop a one-pot procedure for hydroaminoalkylation and subsequent protection need to be made.

In addition to the optimization of reaction conditions, future research should focus on further exploring the influence of the tether length on the transformation, as only one alternative tether length has been investigated to date. Furthermore, generating the iminium ion from the corresponding hemiaminal represents an attractive strategy to enable the introduction of

additional substituents that were not accessible through the use of different aldehydes thus far. Additionally, extending the methodology to alkynes instead of alkenes could further broaden the scope and synthetic utility of the transformation.

Finally, controlling the reaction outcome to selectively furnish either the linear hydroaminoalkylation product or the corresponding cyclic product would significantly increase the versatility of this approach. While this work focused on the formation of linear amino carbonyl compounds, nitrogen-containing heterocycles are equally valuable structural motifs that are frequently encountered in natural products and pharmaceuticals. The ability to direct the reaction toward either product class through reaction-condition design would therefore greatly enhance the synthetic utility of this methodology.

In conclusion, this study initiated the investigation of a novel intramolecular hydroaminoalkylation strategy using iminium ions. The successful formation of the desired product, combined with the observed stereochemical transfer from enantiopure starting material, highlights the synthetic potential of this methodology.

4 Experimental part

4.1 General information

Unless otherwise stated, all glassware was either oven-dried or flame-dried prior to use. All solvents and reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F254 with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate or ninhydrin. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Neat infrared spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (ν_{max}) are reported in cm^{-1}. Mass spectra were obtained on a Bruker timsTOF flex (ESI/MALDI-Qq-TOF with dual-TIMS analyzer) spectrometer, using electrospray ionization (ESI). Chiral HPLC was performed using AGILENT Infinity 1260 with Chiralpak IC or Lux-Cellulose-1 columns. Details on chromatographic conditions are indicated under each compound. All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300 K. Chemical shifts are given in parts per million (ppm, δ), referenced to the solvent peak of $CDCl_3$, defined at δ = 7.26 ppm (^{1}H NMR) and δ = 77.16 ppm (^{13}C NMR). Coupling constants are quoted in Hz (*J*). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) and septet (sep) as they appeared in the spectrum. If the appearance of a signal differs from the expected splitting pattern, the observed pattern is designated as apparent (app). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br).

4.2 Optimization of reaction conditions

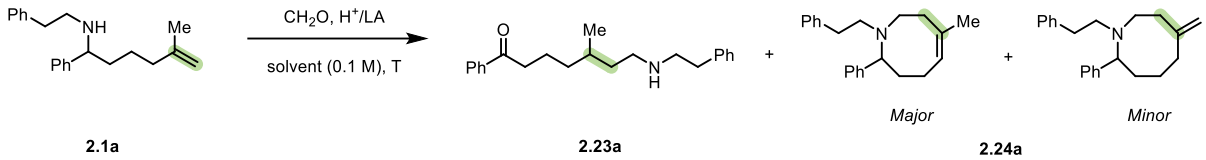


Table 9: *Optimization of the reaction conditions – screening of reagent stoichiometry. All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^1H NMR analysis of the crude reaction mixtures using mesitylene as internal standard. [a]Reaction performed on 0.05 mmol scale. [b]Performed with 4Å molecular sieves. [c]Isolated yield. [d]Not reproducible results.*

Entry	T (° C)	Solvent	H^+/LA (eq.)	CH_2O (eq.)	Time	NMR yield (2.23a)	NMR yield (2.24a)
1[a]	75	HFIP	TFA (1.0 eq.)	1.0	16 h	44% (54%)[c,d]	41%
2	75	HFIP	TFA (1.0 eq.)	1.0	16 h	12%	28%
3[a]	23	HFIP	TFA (1.0 eq.)	1.0	16 h	25%	26%
4	75	HFIP	TFA (1.0 eq.)	1.1	16 h	24%	29%
5	75	HFIP	TFA (1.0 eq.)	1.3	16 h	50%	41%
6	75	HFIP	TFA (1.0 eq.)	1.5	16 h	41%	42%
7	75	HFIP	TFA (1.0 eq.)	1.7	16 h	39%	50%
8	75	HFIP	TFA (1.0 eq.)	2.0	16 h	32%	40%
9	75	HFIP	-	1.0	16 h	37%	32%
10	75	HFIP	-	1.0	3 d	36%	26%
11	75	HFIP	-	1.3	16 h	38%	29%
12	75	HFIP	TFA (2.0 eq.)	1.0	16 h	23%	21%
13	75	HFIP	TFA (0.2 eq.)	1.0	16 h	35%	26%
14	75	HFIP	TFA (0.2 eq.)	1.3	16 h	41%	30%
15[b]	75	HFIP	TFA (0.2 eq.)	1.3	16 h	43%	57%
16	50	HFIP	TFA (1.0 eq.)	1.3	16 h	43%	45%

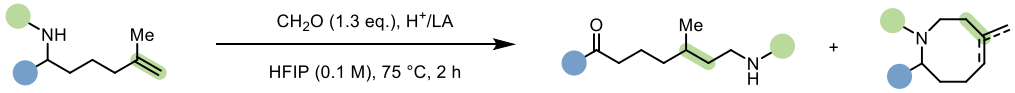
Table 10: *Optimization of the reaction conditions – screening of different solvents and solvent mixtures. All reactions were performed on 0.1 mmol scale, unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^{1}H NMR analysis of the crude reaction products using mesitylene as internal standard.*

Entry	T (° C)	Solvent	H^+/LA (eq.)	CH_2O (eq.)	Time	NMR yield (2.23a)	NMR yield (2.24a)
1	75	DCE	TFA (1.0 eq.)	1.0	16 h	0%	0%
2	75	TFE	TFA (1.0 eq.)	1.3	16 h	40%	46%
3	75	HFIP (1 M)	TFA (1.0 eq.)	1.3	16 h	41%	56%
4	75	HFIP (0.5 M)	TFA (1.0 eq.)	1.3	16 h	48%	42%
5	75	HFIP (0.05 M)	TFA (1.0 eq.)	1.3	16 h	53%	42%
6	75	HFIP (0.01 M)	TFA (1.0 eq.)	1.3	16 h	57%	40%
7	75	HFIP: DCM (1:1)	TFA (1.0 eq.)	1.3	16 h	50%	47%
8	75	HFIP: DCM (1:2)	TFA (1.0 eq.)	1.3	16 h	40%	38%
9	75	HFIP: DCM (1:4)	TFA (1.0 eq.)	1.3	16 h	41%	32%
10	75	HFIP: DCM (1:4), (0.01 M)	TFA (1.0 eq.)	1.3	16 h	41%	44%
11	75	HFIP: PhMe (1:1)	TFA (1.0 eq.)	1.3	16 h	43%	39%
12	75	HFIP: PhMe (1:4)	TFA (1.0 eq.)	1.3	16 h	36%	35%
13	75	HFIP: heptane (4:1)	TFA (1.0 eq.)	1.3	16 h	38%	30%
14	75	HFIP (3.0 eq.) In DCM (0.1 M)	TFA (1.0 eq.)	1.3	16 h	16%	28%

Table 11: *Optimization of the reaction conditions – screening of different Brønsted or Lewis acids. All reactions were performed on 0.1 mmol scale unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by ^{1}H NMR analysis of the crude reaction products using mesitylene as internal standard. [a]Isolated yield.*

Entry	T (° C)	Solvent	H^+/LA (eq.)	CH_2O (eq.)	Time	NMR yield (2.23a)	NMR yield (2.24a)
1	100	DCE	$FeCl_3$ (1.0 eq.)	1.0	16 h	0%	0%
2	100	DCE	$FeCl_3$ (0.1 eq.)	1.0	16 h	0%	0%
3	100	DCE	$SnCl_4$ (1.0 eq.)	1.0	16 h	0%	0%
4	75	HFIP	HCl (1.0 eq.)	1.0	16 h	16%	15%
5	75	HFIP	AcOH (1.0 eq.)	1.0	16 h	32%	25%
6	75	HFIP	TfOH (0.2 eq.)	1.0	16 h	25%	20%
7	75	HFIP	TfOH (0.2 eq.)	1.3	16 h	28%	32%
8	75	HFIP	TfOH (1.0 eq.)	1.3	16 h	5%	14%
9	75	HFIP	$Bi(OTf)_3$ (1.0 eq.)	1.3	2 h	13%	n.d.
10	75	HFIP	$In(OTf)_3$ (1.0 eq.)	1.3	2 h	13%	12%
11	75	HFIP	$Sn(OTf)_2$ (1.0 eq.)	1.3	2 h	9%	n.d.
12	75	HFIP	$Pr(OTf)_3$ (1.0 eq.)	1.3	2 h	49%	39%
13	75	HFIP	$Eu(OTf)_3$ (1.0 eq.)	1.3	2 h	45%	42%
14	75	HFIP	$Gd(OTf)_3$ (1.0 eq.)	1.3	2 h	36%	42%
15	75	HFIP	$Zn(OTf)_2$ (1.0 eq.)	1.3	2 h	40%	41%
16	75	HFIP	$Sc(OTf)_3$ (1.0 eq.)	1.3	2 h	0%	0%
17	75	HFIP	$Mg(OTf)_2$ (1.0 eq.)	1.3	2 h	46%	44%
18	75	HFIP	$Cu(OTf)_2$ (1.0 eq.)	1.3	2 h	59% (51%)[a]	37%
19	75	HFIP: DCM (1:1)	$Pr(OTf)_3$ (1.0 eq.)	1.3	2 h	37%	37%
20	75	HFIP	$Pr(OTf)_3$ (0.1 eq.)	1.3	2 h	45%	44%
21	75	HFIP: DCM (1:1)	$Cu(OTf)_2$ (1.0 eq.)	1.3	2 h	32%	42%
22	75	HFIP	$Cu(OTf)_2$ (0.1 eq.)	1.3	2 h	48%	n.d.
23	50	HFIP	$Cu(OTf)_2$ (0.1 eq.)	1.3	2 h	47%	38%
24	50	HFIP (0.05 M)	$Cu(OTf)_2$ (0.1 eq.)	1.3	2 h	45%	32%
25	75	HFIP	$Mg(NTf)_2$ (0.1 eq.)	1.3	2 h	45%	41%
26	75	HFIP	$Cu(OTf)_2$ (0.1 eq.) + TFA (0.1 eq.)	1.3	2 h	58% (46%)[a]	n.d.

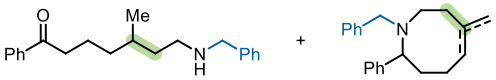
4.3 Preliminary survey of amines



2.a–f, i **2.23b–g** **2.24b–g**

Geminal Disubstituted Alkenes

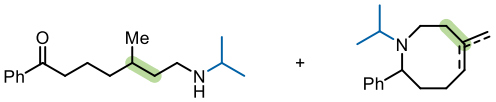
A



2.23b **2.24b**

Entry	Conditions	NMR Yield (2.23b)	NMR Yield (2.24b)
1	a	46% (48%)[a]	29%
2	b	46%	15%
3	d	46%	10%

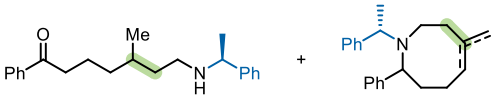
B



2.23c **2.24c**

Entry	Conditions	NMR Yield (2.23c)	NMR Yield (2.24c)
1	a	13%	27%
2	b	12%	45%
3	d	40% (41%)[a]	47%
4	c	39%	43%

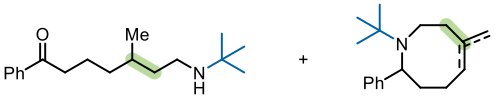
C



2.23d **2.24d**

Entry	Conditions	NMR Yield (2.23d)	NMR Yield (2.24d)
1	a	8%	44%
2	b	10%	42%
3	d	10%	31%

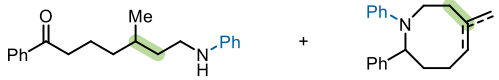
D



2.23e **2.24e**

Entry	Conditions	NMR Yield (2.23e)	NMR Yield (2.24e)
1	a	0%	27%
2	b	0%	94%(59%)[a]
3	d	0%	81%
4	c	0%	35%

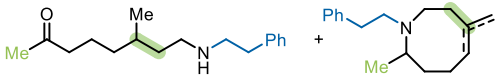
E



2.23f **2.24f**

Entry	Conditions	NMR Yield (2.23f)	NMR Yield (2.24f)
1	d	0%	0%
2[b]	d	0%	0%

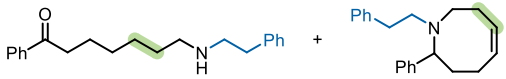
F



2.23g **2.24g**

Entry	Conditions	NMR Yield (2.23g)	NMR Yield (2.24g)
1	a	23% (18%)[a]	22%
2	e	15%	17%

Monosubstituted Alkenes



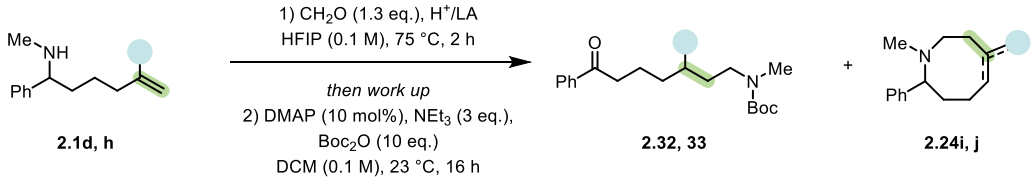
2.23h **2.24h**

Entry	Conditions	NMR Yield (2.23h)	NMR Yield (2.24)
1	d	50%	15%
2	a	20%	30%

Conditions

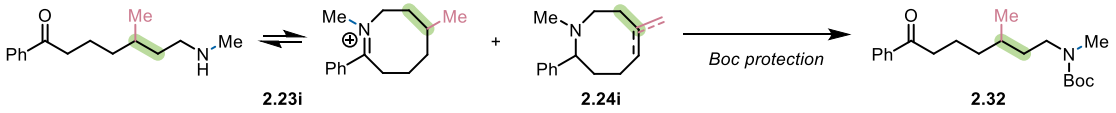
a: TFA (1 eq.)
b: $Cu(OTf)_2$ (10 mol%)
c: $Cu(OTf)_2$ (10 mol%), TFA (1 eq.)
d: $Cu(OTf)_2$ (10 mol%), TFA (10 mol%)
e: No Brønsted or Lewis acid

Scheme 43: *All reactions were performed on 0.1 mmol scale, unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by 1H NMR analysis of the crude reaction products using mesitylene as internal*



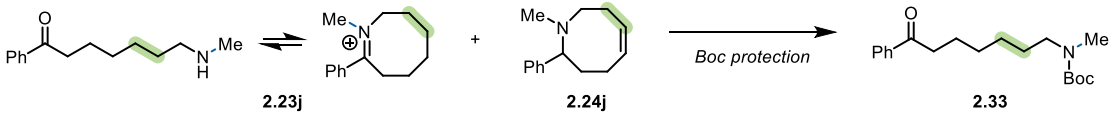
2.1d, h **2.32, 33** **2.24i, j**

Following Boc protection



2.23i **2.24i** **2.32**

Entry	Conditions	NMR Yield (2.23i)	NMR Yield (2.24i)	Isolated Yield (2.32)
1	a	70%	30%	*Not performed*
2	b	75%	16%	*Not performed*
3	d	60%	24%	*Not performed*
4	e	50%	20%	*Not performed*
5	f	58%	18%	*Not performed*
6	a	-	15%	42%



2.23j **2.24j** **2.33**

Entry	Conditions	NMR Yield (2.23j)	NMR Yield (2.24j)	Isolated Yield (2.33)
1	d	29%	12%	*Not performed*
2	a	80%	7%	56%

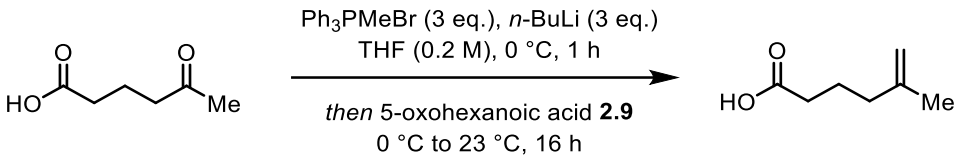
Conditions

a: TFA (1 eq.)
b: $Cu(OTf)_2$ (10 mol%)
c: $Cu(OTf)_2$ (10 mol%), TFA (1 eq.)
d: $Cu(OTf)_2$ (10 mol%), TFA (10 mol%)
e: No Brønsted or Lewis acid
f: TFA (10 mol%)

***Scheme 44**: All reactions were performed on 0.1 mmol scale, unless otherwise stated. The reaction was performed in an oven-dried vial using 1.0 eq. of the amine. Yields were determined by 1H NMR analysis of the crude reaction products using mesitylene as internal*

4.4 Synthesis of racemic starting materials

5-Methylhex-5-enoic acid (2.10)



2.9

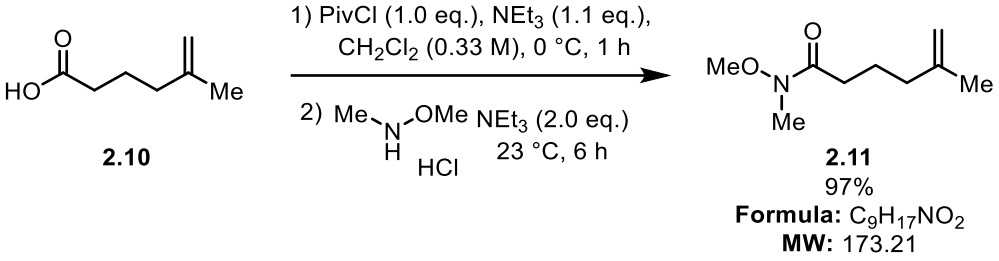
2.10
60%
Formula: $C_7H_{12}O_2$
MW: 128.17

The compound was prepared according to a slightly modified literature procedure.[70] Methyltriphenylphosphonium bromide (32.2 g, 90.0 mmol, 3.00 eq.) was dissolved in anhydrous tetrahydrofuran (150 mL, 0.2 M) under an argon atmosphere and cooled to 0 C. To this solution, *n*-butyllithium (2.5 M in hexanes, 36 mL, 90 mmol, 3.0 eq.) was slowly added and was left stirring for 1 h at the same temperature. Then, 5-oxohexanoic acid **2.9** (3.6 mL, 30 mmol, 1.0 eq.) was added to the reaction mixture and upon completed addition, it was slowly warmed to 23 C and stirred for 16 h. The excess of phosphonium ylide was quenched by addition of an aqueous solution of hydrochloric acid (1 M) and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of pentane/diethyl ether to afford the title compound **2.10** (2.3 g, 18 mmol, 60%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (br s, 1 H), 4.72 (app d, *J* = 19.8 Hz, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 2.07 (t, *J* = 7.5 Hz, 2H), 1.79 (tt, *J* = 7.5 Hz, 7.6 Hz, 2H), 1.72 (s, 3H).

Spectral data is in accordance with that reported in the literature.[70]

***N*-methoxy-*N*,5-dimethylhex-5-enamide (2.11)**

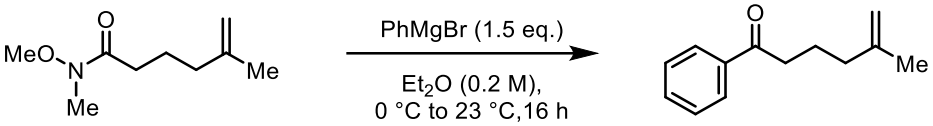


The compound was prepared according to a slightly modified literature procedure.[71] 5-Methylhex-5-enoic acid **2.10** (2.3 g, 18 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (48 mL, 0.38 M) under an argon atmosphere and cooled to 0 C. To this solution, pivaloyl chloride (2.2 mL, 18 mmol, 1.0 eq.) and triethylamine (2.80 mL, 19.8 mmol, 1.10 eq.) were added and the reaction mixture was left to stir for 1 h at 0 C. Then, triethylamine (5.0 mL, 36 mmol, 2.0 eq.) and *N,O*-dimethylhydroxylamine hydrochloride (1.79 g, 18.0 mmol, 1.00 eq.) were added and stirring continued for 6 h at 23 °C. The reaction mixture was diluted with an aqueous solution of hydrochloric acid (1 M) and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of pentane/diethyl ether to afford the title compound **2.11** (3.00 g, 17.5 mmol, 97%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (app d, *J* = 11.6 Hz, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 2.41 (t, *J* = 7.7 Hz, 2H), 2.07 (t, *J* = 7.3 Hz, 2H), 1.78 (tt, *J* = 7.6 Hz, 7.1 Hz 2H), 1.72 (s, 3H).

Spectral data is in accordance with that reported in the literature.[82]

5-Methyl-1-phenylhex-5-en-1-one (2.8)



2.11

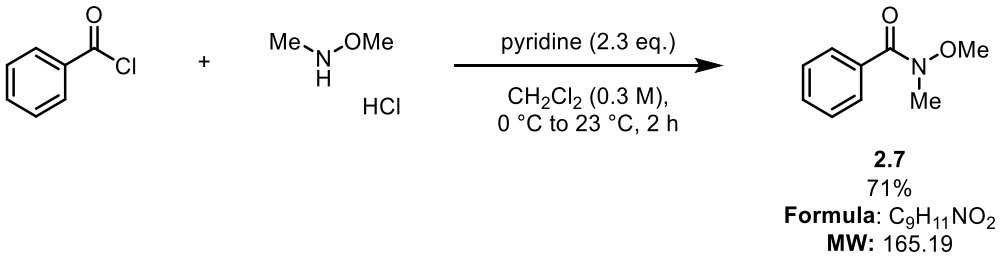
2.8
95%
Formula: $C_{13}H_{16}O$
MW: 188.27

N-Methoxy-*N*,5-dimethylhex-5-enamide **2.11** (3.00 g, 17.5 mmol, 1.00 eq.) was dissolved in anhydrous diethyl ether (65 mL, 0.2 M) under an argon atmosphere and cooled to 0 C. To this solution, phenylmagnesium bromide (3 M solution in diethyl ether, 8.80 mL, 26.3 mmol, 1.50 eq.) was added dropwise and upon completed addition, the reaction mixture was allowed to slowly warm from 0 C to 23 C while stirring for 16 h. The reaction was stopped by addition of a saturated aqueous solution of ammonium chloride (88 mL) and the aqueous phase was extracted with diethyl ether (3 × 88 mL). The combined organic layers were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate to afford the title compound **2.8** (2.30 g, 12.2 mmol, 95%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.44 (m, 5H), 4.73 (app d, *J* = 14.3 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.11 (t, *J* = 7.5 Hz, 2H), 1.90 (tt, *J* = 7.5 Hz, 7.1 Hz, 2H), 1.74 (s, 3H).

Spectral data is in accordance with that reported in the literature.[71]

***N*-Methoxy-*N*-methylbenzamide (2.7)**



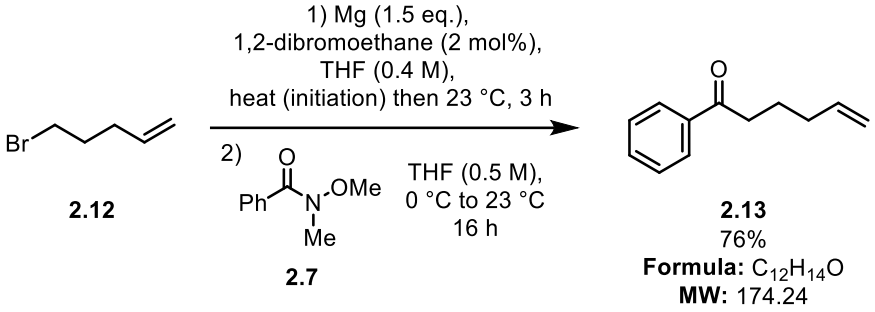
2.7
71%
Formula: $C_9H_{11}NO_2$
MW: 165.19

The compound was prepared according to a slightly modified literature procedure.[83] Benzoyl chloride (2.3 mL, 20 mmol, 1.0 eq.) was dissolved in dichloromethane (66 mL, 0.3 M) under an argon atmosphere, followed by portion-wise addition of *N,O*-dimethyhydroxylamine hydrochloride (2.15 g, 22.0 mmol, 1.10 eq.) at 23 °C. The reaction mixture was left stirring for 15 min before being cooled to 0 °C. After cooling, pyridine (3.7 mL, 46 mmol, 2.3 eq.) was added dropwise, the reaction mixture was allowed to reach ambient temperature (23 °C) and stirring was continued for 2 h at 23 °C. The solution was then diluted with dichloromethane and washed with water. The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (heptane/ethyl acetate 1:1) to afford the title compound **2.7** (2.34 g, 14.2 mmol, 71%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.65 (m, 2H), 7.49 – 7.38 (m, 3H), 3.56 (s, 3H), 3.36 (s, 3H).

Spectral data is in accordance with that reported in the literature.[83]

1-Phenylhex-5-en-1-one (2.13)

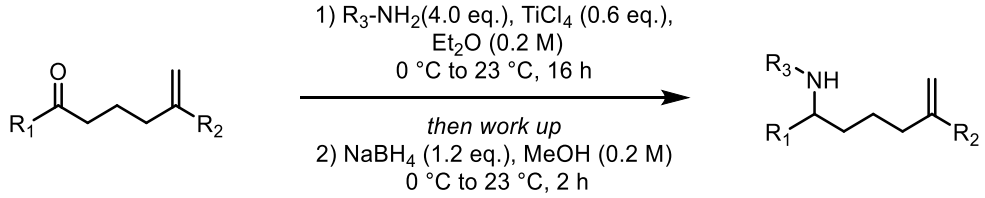


In a flame-dried Schlenk flask, magnesium turnings (365 mg, 15.0 mmol, 1.50 eq.) were suspended in anhydrous tetrahydrofuran (15 mL), followed by the addition of a few drops of 1,2-dibromoethane. The reaction mixture was heated with a blowtorch until continuous ebullition was ensured. Then, a solution of 5-bromo-1-pentene **2.12** (1.2 mL, 10 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (10 mL) was added dropwise to the reaction mixture and left stirring for 3 h at 23 °C. The concentration of the Grignard reagent was determined according to the procedure of Love and Jones,[86] and the supernatant was used directly for the addition to the Weinreb amide. *N*-Methoxy-*N*-methylbenzamide **2.7** (1.2 g, 7.2 mmol, 1.0 eq.) was dissolved in anhydrous tetrahydrofuran (14.4 mL, 0.5 M) under an argon atmosphere and cooled to 0 °C. Subsequently, the freshly prepared solution of the Grignard reagent (0.3 M, 7.2 mmol, 1.0 eq.) was added slowly and the reaction mixture was allowed to slowly warm to 23 °C and left stirring for 16 h. The remaining organomagnesium reagent was quenched by addition of a saturated aqueous solution of ammonium chloride and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate to afford the title compound **2.13** (951 mg, 5.46 mmol, 76%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.74 (m, 5H), 5.83 (ddt, *J* = 16.9, 10.4, 6.7 Hz, 1H), 5.05 (ddd, *J* = 17.1, 5.1, 1.6 Hz, 1H), 5.00 (ddd, *J* = 10.3, 4.9, 1.1 Hz, 1H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.16 (ddd, *J* = 15.0, 6.9, 1.3 Hz, 2H), 1.86 (tt, *J* = 14.7, 7.5 Hz, 2H).

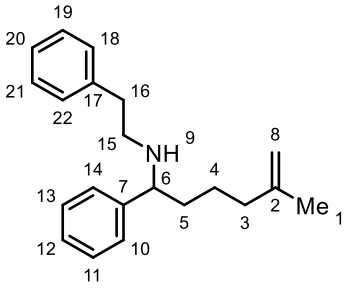
Spectral data is in accordance with that reported in the literature.[84]

General procedure A: Preparation of unsaturated amines through reductive amination



The compounds were prepared according to a slightly modified literature procedure.[72] The ketone (1 eq.) and amine (4 eq.) were dissolved in anhydrous diethyl ether (0.2 M) and cooled to 0 °C, followed by the dropwise addition of titanium(IV) chloride (1 M solution in dichloromethane, 0.6 eq.). The reaction mixture was stirred for 16 h while being allowed to slowly warm to 23 °C. The reaction was stopped by the addition of an aqueous solution of sodium hydroxide (0.5 M). The biphasic mixture was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was then dissolved in methanol (0.2 M) and cooled to 0 °C. Sodium borohydride (1.2 eq.) was added portion-wise and the reaction mixture was left to stir for 1 h at 23 °C. The solvent was removed under reduced pressure and water was added to the crude residue. The aqueous phase was extracted with dichloromethane and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate or heptane/EEA (ethyl acetate/ ethanol/ NH_4OH in a 3:1:0.02 ratio) to obtain the pure products. Compounds that were purified using EEA were, after removing the solvent, dissolved in dichloromethane and extracted with a saturated aqueous solution of sodium bicarbonate to remove the ammonium hydroxide. The biphasic mixture was separated, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to obtain the pure product.

5-Methyl-*N*-phenethyl-1-phenylhex-5-en-1-amine (2.1a)



Formula: $C_{21}H_{27}N$
MW: 293.45

The title compound was prepared following general procedure A using 5-methyl-1-phenylhex-5-en-1-one **2.8** (1.9 g, 10 mmol, 1.0 eq.) and 2-phenylethylamine (5.0 mL, 40 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1a** (1.9 g, 6.4 mmol, 64%) as a yellow oil.

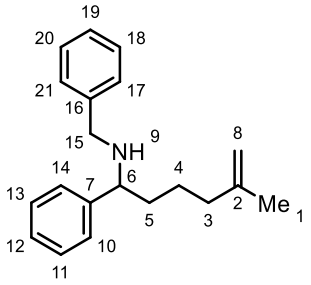
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.32 – 7.13 (m, 10H, H_{Ar}), 4.66 – 4.58 (m, 2H, H8), 3.58 (dd, *J* = 7.9, 6.2 Hz, 1H, H6), 2.80 – 2.67 (m, 4H, H15, H16), 1.98 – 1.90 (m, 2H, H3), 1.68 – 1.56 (m, 5H, H5, H1), 1.35 – 1.18 (m, 2H, H4). *The NH proton was not observed.*

^{13}C NMR (176 MHz, $CDCl_3$): δ 145.8 (C2), 144.4 (C7), 140.3 (C17), 128.8 (2C, C_{Ar}), 128.52 (2C, C_{Ar}), 128.46 (2C, C_{Ar}), 127.4 (2C, C_{Ar}), 127.1 (C_{Ar}), 126.2 (C_{Ar}), 110.1 (C8), 63.5 (C6), 49.0 (C15), 37.83 (C5), 37.78 (C3), 36.5 (C9), 24.3 (C4), 22.4 (C1).

IR (neat) ν_{max}: 3026, 2933, 2855, 1649, 1603, 1494, 1452, 1373, 1119, 1080, 1029, 886, 749, 697, 562, 541, 499, 428, 407 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{21}H_{28}N^+$) requires *m/z* 294.2216 found *m/z* 294.2225.

***N*-Benzyl-5-methyl-1-phenylhex-5-en-1-amine (2.1b)**



Formula: $C_{20}H_{25}N$
MW: 279.43

The title compound was prepared following general procedure A using 5-methyl-1-phenylhex-5-en-1-one **2.8** (377 mg, 2.00 mmol, 1.00 eq.) and benzylamine (87 µL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1b** (188 mg, 0.673 mmol, 34%) as a yellow oil.

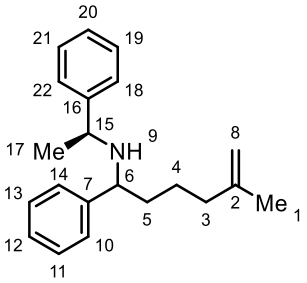
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 10H, H_{Ar}), 4.66 – 4.59 (m, 2H, H8), 3.66 – 3.51 (m, 3H, H6, H15), 1.95 (t, *J* = 7.6 Hz, 2H, H3), 1.72 – 1.68 (m, 1H, $H5_A$), 1.63 (s, 3H, H1), 1.58 – 1.54 (m, 1H, $H5_B$), 1.44 – 1.40 (m, 1H, $H4_A$), 1.31 – 1.27 (m, 1H, $H4_B$). *The NH proton was not observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.8 (C2), 144.5 (C7), 140.9 (C16), 28.52 (2C, C_{Ar}), 128.47 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 127.5 (2C, C_{Ar}), 127.1 (C_{Ar}), 127.0 (C_{Ar}), 110.1 (C8), 62.6 (C6), 51.7 (C15), 38.0 (C5), 37.8 (C3), 24.3 (C4), 22.4 (C1).

IR (neat) ν_{max}: 3025, 2934, 2858, 1650, 1602, 1493, 1452, 1373, 1113, 1028, 886, 734, 697, 616, 555, 465, 437 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}N^+$) requires *m/z* 280.2057 found *m/z* 280.2060.

5-Methyl-1-phenyl-*N*-((*S*)-1-phenylethyl)hex-5-en-1-amine (2.1c)



Formula: $C_{21}H_{27}N$
MW: 293.45

The title compound was prepared following general procedure A using 5-methyl-1-phenylhex-5-en-1-one **2.8** (377 mg, 2.00 mmol, 1.00 eq.) and (*S*)-(–)-1-phenylethylamine (1.0 mL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1c** (227 mg, 0.774 mmol, 39%) as a yellow oil. The *d.r.* was determined by NMR as 1.6:1.

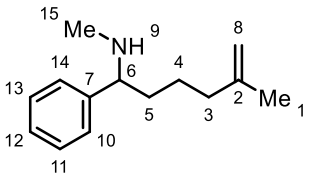
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 – 7.16 (m, 10H, H_{Ar}), 4.66 – 4.55 (m, 2H, H8), 3.69 (q, *J* = 6.5 Hz, 0.4H, $H15_{d2}$), 3.65 (t, *J* = 6.6 Hz, 0.4H, $H6_{d2}$), 3.48 (q, *J* = 6.5 Hz, 0.6H, $H15_{d1}$), 3.29 (t, *J* = 6.8 Hz, 0.6H, $H6_{d1}$), 1.95 (t, *J* = 7.4 Hz, 0.8H, $H3_{d2}$), 1.88 (t, *J* = 7.4 Hz, 1.2H, $H3_{d1}$), 1.79 – 1.72 (m, 0.4H, $H5_{d2A}$), 1.63 (s, 1.2H, $H1_{d2}$), 1.61 (s, 1.8H, $H1_{d1}$), 1.58 – 1.49 (m, 1.6H, $H5_{d1}$, $H5_{d2B}$), 1.44 – 1.35 (m, 1H, $H4_{d1}$), 1.33 (d, *J* = 6.5 Hz, 1.2H, $H17_{d2}$), 1.30 – 1.26 (m, 0.4H, $H4_{d2B}$), 1.25 (d, *J* = 6.6 Hz, 1.8H, $H17_{d1}$), 1.24 – 1.18 (m, 0.6H, $H4_{d2A}$). *The NH proton was not observed.*

^{13}C NMR (151 MHz, $CDCl_3$): δ 146.4 (0.4C, $C16_{d2}$), 146.0 (0.6C, $C16_{d1}$), 145.9 (0.4C, $C2_{d1}$), 145.8 (0.6C, $C2_{d1}$), 144.9 (0.6C, $C7_{d1}$), 144.6 (0.4C, $C7_{d2}$), 128.5 (2C, C_{Ar}), 128.4 (1C, C_{Ar}), 127.32 (1C, C_{Ar}), 127.30 (1C, C_{Ar}), 127.0 (1C, C_{Ar}), 126.92 (1C, C_{Ar}), 126.90 (1C, C_{Ar}), 126.89 (1C, C_{Ar}), 126.7 (1C, C_{Ar}), 110.11 (0.4C, $C8_{d2}$), 110.09 (0.6C, $C8_{d1}$), 60.2 (0.4C, $C6_{d2}$), 59.9 (0.6C, $C6_{d1}$), 55.0 (0.6C, $C15_{d1}$), 54.7 (0.4C, $C15_{d2}$), 38.3 (0.6C, $C5_{d1}$), 37.8 (0.4C, $C3_{d2}$), 37.7 (0.6C, $C3_{d1}$), 37.2 (0.4C, $C5_{d2}$), 25.3 (0.4C, $C17_{d2}$), 24.4 (0.6C, $C4_{d1}$), 24.3 (0.4C, $C4_{d2}$), 22.6 (0.6C, $C17_{d1}$), 22.38 (0.4C, $C1_{d2}$), 22.35 (0.6C, $C1_{d1}$).

IR (neat) ν_{max}: 3025, 2963, 2932, 2861, 1649, 1492, 1451, 1371, 1203, 1114, 1070, 1028, 886, 760, 697, 572, 545, 428 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{21}H_{28}N^+$) requires *m/z* 294.2202 found *m/z* 294.2216.

***N*,5-Dimethyl-1-phenylhex-5-en-1-amine (2.1d)**



Formula: $C_{14}H_{21}N$
MW: 203.33

The title compound was prepared following general procedure A using 5-methyl-1-phenylhex-5-en-1-one **2.8** (377 mg, 2.00 mmol, 1.00 eq.) and methylamine (2 M solution in THF, 4.0 mL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.1d** (190 mg, 0.934 mmol, 47%) as a yellow oil.

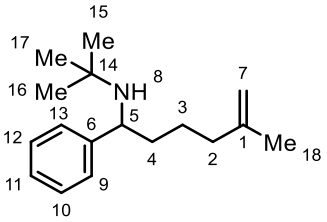
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.22 (m, 5H, H_{Ar}), 4.66 – 4.61 (m, 2H, H8), 3.45 (dd, *J* = 7.9, 5.9 Hz, 1H, H6), 2.27 (s, 3H, H15), 1.97 (t, *J* = 7.4 Hz, 2H, H3), 1.76 – 1.71 (m, 1H, $H5_A$), 1.64 (s, 3H, H1), 1.60 – 1.57 (m, 1H, $H5_B$), 1.43 – 1.38 (m, 1H, $H3_A$), 1.30 – 1.24 (m, 1H, $H3_B$). *The NH proton was not observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.8 (C2), 142.3 (C7), 128.5 (2C, C_{Ar}), 127.4 (2C, C_{Ar}), 127.1 (C_{Ar}), 110.1 (C8), 65.6 (C6), 37.8 (C5), 37.5 (C3), 34.6 (C15), 24.4 (C4), 22.4 (C1).

IR (neat) ν_{max}: 3020, 2934, 2848, 2788, 1649, 1493, 1475, 1452, 1374, 1130, 885, 838, 759, 699, 589, 566, 539, 491, 429 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{14}H_{22}N^+$) requires *m/z* 204.1745 found *m/z* 204.1747.

***N*-(*Tert*-butyl)-5-methyl-1-phenylhex-5-en-1-amine (2.1e)**



Formula: $C_{17}H_{27}N$
MW: 245.41

The title compound was prepared following general procedure A using 5-methyl-1-phenylhex-5-en-1-one **2.8** (377 mg, 2.00 mmol, 1.00 eq.) and *tert*-butylamine (0.8 mL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1d** (225 mg, 0.917 mmol, 46%) as a yellow oil.

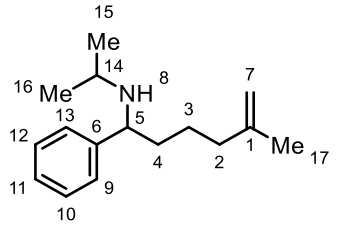
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.16 (m, 5H, H_{Ar}), 4.66 – 4.61 (m, 2H, H7), 3.71 (t, *J* = 7.0 Hz, 1H, H5), 1.97 (t, *J* = 7.6 Hz, 2H, H2), 1.64 (s, 3H, H18), 1.56 (dt, *J* = 8.3, 7.2 Hz, 2H, H4), 1.45 – 1.34 (m, 1H, $H3_A$), 1.29 – 1.20 (m, 1H, $H3_B$), 0.99 (s, 9H, H15, H16, H17). *The NH proton was not observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.2 (C1), 145.9 (C6), 128.3 (2C, C_{Ar}), 127.2 (2C, C_{Ar}), 126.4 (C_{Ar}), 110.1 (C7), 57.6 (C5), 51.4 (C14), 40.4 (C4), 37.8 (C2), 30.4 (3C, C15, C16, C17), 24.8 (C3), 22.4 (C18).

IR (neat) ν_{max}: 3024, 2964, 2934, 2862, 1649, 1481, 1452, 1388, 1363, 1228, 1103, 1027, 886, 760, 700, 571, 545, 450, 408 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{17}H_{28}N^+$) requires *m/z* 246.2214 found *m/z* 246.2216.

***N*-Isopropyl-5-methyl-1-phenylhex-5-en-1-amine (2.1e)**



Formula: $C_{16}H_{25}N$
MW: 231.38

The title compound was prepared following general procedure A using 5-methyl-1-phenylhex-5-en-1-one **2.8** (377 mg, 2.00 mmol, 1.00 eq.) and isopropylamine (0.7 mL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1e** (371 mg, 1.60 mmol, 80%) as a yellow oil.

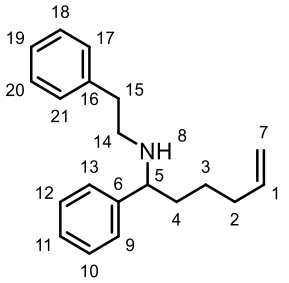
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.21 (m, 5H, H_{Ar}), 4.66 – 4.60 (m, 2H, H7), 3.68 (dd, *J* = 7.9, 5.9 Hz, 1H, H5), 2.58 (sep, *J* = 6.3 Hz, 1H, H14), 1.99 – 1.94 (m, 2H, H2), 1.71 – 1.67 (m, 1H, $H4_A$), 1.63 (s, 3H, H17), 1.58 – 1.53 (m, 1H, $H4_B$), 1.44 – 1.36 (m, 1H, $H3_A$), 1.29 – 1.23 (m, 1H, $H3_B$), 0.98 (dd, *J* = 17.5, 6.3 Hz, 6H, H15, H16). *The NH proton was not observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9 (C1), 145.0 (C6), 128.4 (2C, C_{Ar}), 127.2 (2C, C_{Ar}), 126.9 (C_{Ar}), 110.1 (C7), 60.3 (C5), 45.5 (C14), 38.4 (C4), 37.8 (C2), 24.47 (C3), 24.45 (C15), 22.3 (C17), 22.2 (C16).

IR (neat) ν_{max}: 3020, 2962, 2933, 2863, 1649, 1492, 1452, 1376, 1338, 1171, 1123, 1093, 886, 761, 699, 568, 547, 475, 438 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{16}H_{26}N^+$) requires *m/z* 232.2057 found *m/z* 232.2060.

***N*-Phenethyl-1-phenylhex-5-en-1-amine (2.1g)**



Formula: $C_{20}H_{25}N$
MW: 279.43

The title compound was prepared following general procedure A using 1-phenylhex-5-en-1-one **2.13** (348 mg, 2.00 mmol, 1.00 eq.) and 2-phenylethylamine (1.0 mL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1g** (281 mg, 1.01 mmol, 50%) as a yellow oil.

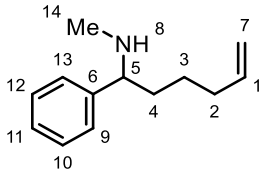
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.14 (m, 10H, H_{Ar}), 5.72 (ddt, *J* = 16.9, 10.3, 6.8 Hz, 1H, H1), 4.93 (ddd, *J* = 16.9, 3.8, 1.7 Hz, 1H, $H7_A$), 4.90 (ddd, *J* = 10.2, 2.2, 1.1 Hz, 1H, $H7_B$), 3.57 (dd, *J* = 7.9, 5.9 Hz, 1H, H5), 2.79 – 2.67 (m, 4H H14, H15), 1.99 – 1.97 (m, 2H, H2), 1.71 – 1.67 (m, 1H, $H4_A$), 1.61 – 1.58 (m, 1H, $H4_B$), 1.33 – 1.28 (m, 1H, $H3_A$), 1.22 – 1.18 (m, 1H, $H3_B$,). *The NH proton was not observed.*

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.4 (C6), 140.3 (C16), 138.8 (C1), 128.8 (2C, C_{Ar}), 128.52 (2C, C_{Ar}), 128.45 (2C, C_{Ar}), 127.4 (2C, C_{Ar}), 127.0 (C_{Ar}), 126.2 (C_{Ar}), 114.7 (C7), 63.5 (C5), 49.0 (C15), 37.8 (C4), 36.6 (C14), 33.8 (C2), 25.7 (C3).

IR (neat) ν_{max}: 3062, 3026, 2930, 2855, 1640, 1603, 1494, 1453, 1361, 1118, 1029, 992, 909, 749, 697, 558, 497 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}N^+$) requires *m/z* 280.2060 found *m/z* 280.2060.

***N*-Methyl-1-phenylhex-5-en-1-amine (2.1h)**



Formula: $C_{13}H_{19}N$
MW: 189.3

The title compound was prepared following general procedure A using 1-phenylhex-5-en-1-one **2.13** (348 mg, 2.00 mmol, 1.00 eq.) and methylamine (2 M solution in THF, 4.0 mL, 8.0 mmol, 4.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.1h** (180 mg, 0.951 mmol, 48%) as a yellow oil.

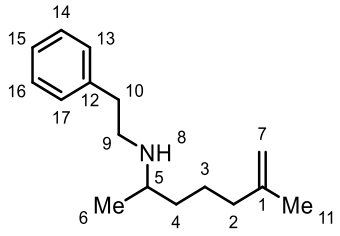
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 5H, H_{Ar}), 5.74 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H1), 4.96 (ddd, *J* = 17.3, 4.1, 1.6 Hz, 1H, $H7_A$), 4.91 (ddd, *J* = 10.3, 4.4, 1.2 Hz, 1H, $H7_B$), 3.22 (dd, *J* = 7.9, 6.0 Hz, 1H, H5), 2.26 (s, 3H, H14), 2.06 – 1.98 (m, 2H, H2), 1.77 – 1.71 (m, 1H, $H4_A$), 1.66 – 1.50 (m, 1H, $H4_B$), 1.39 – 1.32 (m, 1H, $H3_A$), 1.28 – 1.22 (m, 1H, $H3_B$). *The NH proton was not observed.*

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.1 (C6), 138.8 (C1), 128.5 (2C, C_{Ar}), 127.4 (2C, C_{Ar}), 127.1 (C_{Ar}), 114.7 (C7), 65.6 (C5), 37.5 (C4), 34.7 (C14), 33.9 (C2), 25.8 (C3).

IR (neat) ν_{max}: 3021, 2974, 2849, 2788, 1640, 1493, 1453, 1354, 1133, 1028, 992, 910, 759, 699, 638, 589, 565, 505, 427 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{13}H_{20}N^+$) requires *m/z* 190.1590 found *m/z* 190.1590.

6-Methyl-*N*-phenethylhept-6-en-2-amine (2.1j)



Formula: $C_{16}H_{25}N$
MW: 232.38

The title compound was prepared following general procedure A using 6-methylhept-6-en-2-one (313 mg, 2.48 mmol, 1.00 eq.) and 2-phenylethylamine (1.25 mL, 9.92 mmol, 4.00 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.1j** (227 mg, 0.981 mmol, 40%) as a yellow oil.

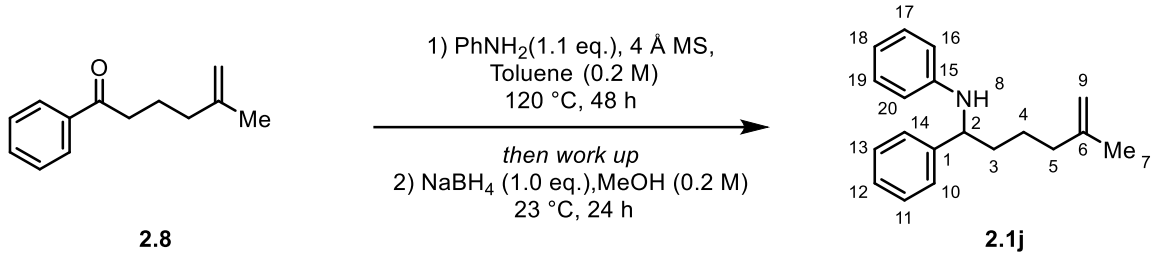
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.19 (m, 5H, H_{Ar}), 4.69 – 4.64 (m, 2H, H7), 2.95 – 2.77 (m, 4H, H9, H10), 2.66 – 2.61 (m, 1H, H5), 1.98 (t, *J* = 6.9 Hz, 2H, H2), 1.69 (s, 3H, H11), 1.44 – 1.25 (m, 4H, H3, H4), 1.03 (d, *J* = 6.3 Hz, 3H, H6). *The NH proton was not observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.0 (C1), 140.3 (C12), 128.8 (2C, C_{Ar}), 128.6 (2C, C_{Ar}), 126.3 (C_{Ar}), 110.0 (C7), 53.1 (C5), 48.8 (C10), 38.0 (C3), 36.84 (C4), 36.79 (C9), 24.1 (C3), 22.5 (C6), 20.5 (C11).

IR (neat) ν_{max}: 3027, 2932, 2868, 1649, 1495, 1453, 1373, 1339, 1181, 1082, 1030, 885, 747, 697, 576, 552, 487, 428, 405 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{16}H_{26}N^+$) requires *m/z* 232.2056 found *m/z* 232.2060.

***N*-(5-Methyl-1-phenylhex-5-en-1-yl)aniline (2.1j)**



2.8

2.1j
10%
Formula: $C_{19}H_{23}N$
MW: 265.4

The compound was prepared according to a slightly modified literature procedure.[73] 5-Methyl-1-phenylhex-5-en-1-one **2.8** (377 mg, 2.00 mmol, 1.00 eq.), aniline (0.20 mL, 2.2 mmol, 1.1 eq.) and 4 Å molecular sieves (MS, 2 g) were suspended in anhydrous toluene (10 mL, 0.2 M) and heated at reflux (120 °C) for 48 h. After the reaction mixture had been allowed to cool to ambient temperature, the suspension was filtered through a pad of celite, washing the pad with additional toluene, and the solvent was removed under reduced pressure. The crude residue was dissolved in anhydrous methanol (10 mL, 0.2 M) and, at 23 °C, sodium borohydride (75.7 mg, 2.00 mmol, 1.00 eq.) was added portion-wise. The resulting suspension was left to stir for 24 h. The solvent was then removed under reduced pressure and water was added to the crude residue. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.1j** (53.4 mg, 0.201 mmol, 10%) as a yellow oil.

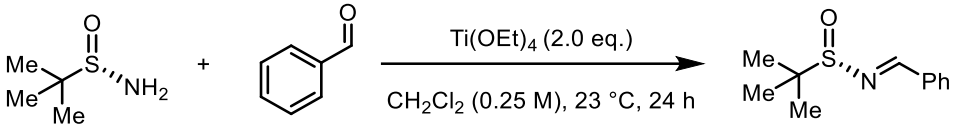
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.05 (m, 7H, H_{Ar}), 6.64 – 6.50 (m, 3H, H_{Ar}), 4.70 – 4.65 (m, 2H, H9), 4.33 – 4.28 (m, 1H, H2), 4.05 (br s, 1H, H8), 2.03 (t, *J* = 7.5 Hz, 2H, H5), 1.82 – 1.74 (m, 2H, H3), 1.67 (s, 3H, H7), 1.62 – 1.55 (m, 1H, $H4_A$), 1.50 – 1.42 (m, 1H, $H4_B$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.4 (C15), 145.4 (C6), 144.2 (C1), 129.1 (2C, C_{Ar}), 128.6 (2C, C_{Ar}), 126.9 (C_{Ar}), 126.4 (2C, C_{Ar}), 117.1 (C_{Ar}), 113.2 (2C, C_{Ar}), 110.3 (C9), 58.1 (C2), 38.4 (C3), 37.5 (C5), 24.2 (C4), 22.3 (C7).

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}N^+$) requires *m/z* 266.1903 found *m/z* 266.1901.

4.5 Synthesis of enantiopure starting material

(*S*,*E*)-*N*-Benzylidene-2-methylpropane-2-sulfinamide (2.15)



2.14 1.05 eq. **2.15**

75%

Formula: $C_{11}H_{15}NOS$

MW: 208.31

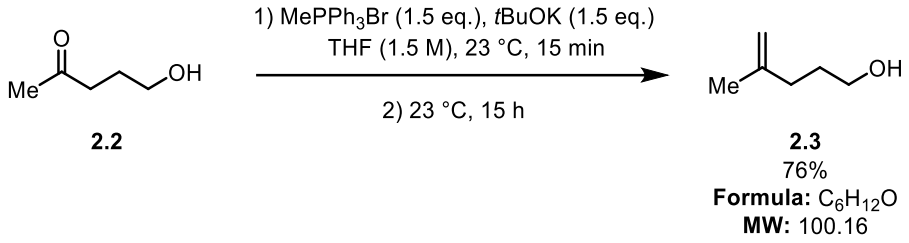
The compound was prepared according to the slightly modified literature procedure.[75]

(S)-(–)-*t*-Butylsulfinamide **2.14** (1.2 g, 10 mmol, 1.0 eq.) was dissolved in anhydrous dichloromethane (40 mL, 0.25 M) under an argon atmosphere. Benzaldehyde (1.10 mL, 10.5 mmol, 1.05 eq.) and titanium(IV) ethoxide (4.2 mL, 20 mmol, 2.0 eq.) were added and the solution was left to stir at 23 °C for 24 h. The reaction mixture was diluted with ethyl acetate (1.5 mL) and brine (0.3 mL) and left stirring for 5 min. The gelatinous solid was filtered through a pad of celite and washed with ethyl acetate and dichloromethane. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with heptane/ethyl acetate (9:1, R_f = 0.12) to afford the title compound **2.15** (1.57 g, 7.50 mmol, 75%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 7.87 – 7.84 (m, 2H), 7.55 – 7.45 (m, 3H), 1.27 (s, 9H).

Spectral data is in accordance with that reported in the literature.[75]

4-Methylpent-4-en-1-ol (2.3)



2.2

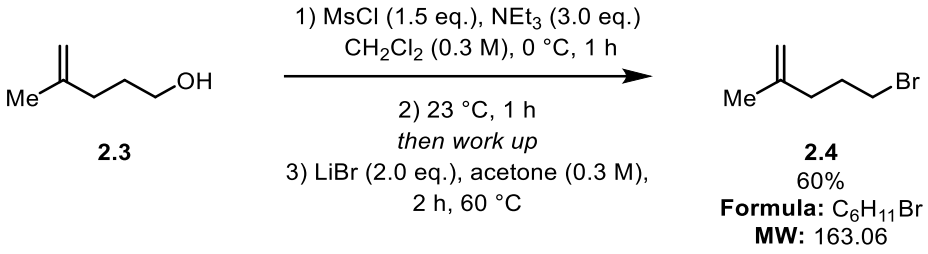
2.3
76%
Formula: $C_6H_{12}O$
MW: 100.16

The compound was prepared according to a slightly modified literature procedure.[68] Methyltriphenylphosphonium bromide (13.4 g, 37.5 mmol, 1.50 eq.) and potassium *tert*-butoxide (97 %, 4.30 g, 37.5 mmol, 1.50 eq.) were dissolved in anhydrous tetrahydrofuran (50 mL, 1.5 M) and stirred at 23 °C for 15 min. Then, a solution of 5-hydroxy-2-pentanone **2.2** (2.5 mL, 25 mmol, 1.0 eq.) in tetrahydrofuran (42.5 mL, 0.6 M) was added dropwise to the yellow suspension and stirring at ambient temperature (23°C) was continued. After 16 h, the reaction was stopped by the addition of a saturated aqueous solution of ammonium chloride (65 mL). The biphasic mixture was separated, and the aqueous phase was extracted with diethyl ether (3 × 65 mL). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of diethyl ether/pentane to afford the title compound **2.3** (1.9 g, 19 mmol, 76%) as a volatile colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 – 4.72 (m, 2H), 3.67 (dt, *J* = 6.2, 5.6 Hz, 2H), 2.10 (t, *J* = 7.6 Hz, 2H), 1.76 – 1.68 (m, 5H), 1.31 (br s, 1H).

Spectral data is in accordance with that reported in the literature.[69]

5-Bromo-2-methylpent-1-ene (2.4)

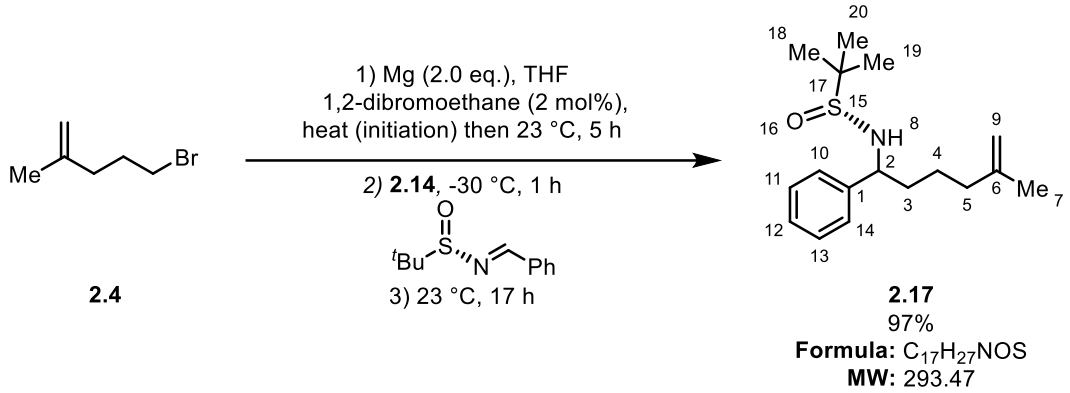


The compound was prepared according to a slightly modified literature procedure.[69] To a solution of 4-methylpent-4-en-1-ol **2.3** (1.9 g, 19 mmol, 1.0 eq.) in dichloromethane (63 mL, 0.3 M) was added triethylamine (7.9 mL, 57 mmol, 3.0 eq.) and methanesulfonyl chloride (2.20 mL, 28.5 mmol, 1.50 eq.) at 0 °C and left to stir for 1 h. The remaining base was carefully quenched with hydrochloric acid (10 mL, 6 M) at 0 °C. The biphasic mixture was separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with a saturated aqueous solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. The suspension was filtered over cotton and the filtrate was concentrated under reduced pressure. The resulting crude material was redissolved in dry acetone (63 mL, 0.3 M) followed by the addition of lithium bromide (3.3 g, 38 mmol, 2.0 eq.). The resulting suspension was heated at reflux (60 °C) for 2 h. The precipitate was filtered, washed with acetone and the solvent was carefully removed under reduced pressure. The crude material was redissolved in diethyl ether and washed with a brine (2 × 40 mL) to remove any remaining salts. The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The resulting crude material was then purified through silica plug with pentane to afford the title compound **2.4** (1.86 g, 11.4 mmol, 60 %) as a volatile colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 - 4.70 (m, 2H), 3.40 (t, *J* = 6.7 Hz, 2H), 2.16 (t, *J* = 7.7 Hz, 2H), 2.03 – 1.96 (m, 2H), 1.72 (s, 3H).

Spectral data is in accordance with that reported in the literature.[69]

(*S*)-2-Methyl-*N*-(5-methyl-1-phenylhex-5-en-1-yl)propane-2-sulfinamide (2.17)



The compound was prepared according to a slightly modified literature procedure.[76] In a flame-dried Schlenk flask, magnesium turnings (333 mg, 13.7 mmol, 1.20 eq.) were suspended in anhydrous tetrahydrofuran (3.8 mL, 3.6 M) under an argon atmosphere. Separately, a solution of 5-bromo-2-methylpent-1-ene **2.4** (1.86 g, 11.4 mmol, 1.00 eq.) in anhydrous tetrahydrofuran (11.4 mL, 1 M) was prepared. To initiate the reaction a few drops of 1,2-dibromoethane were added to the suspension of magnesium, followed by a few drops of the alkyl halide solution. The solution was then cautiously heated with a blowtorch until a color change and an exothermic reaction were observed. Then the remaining alkyl halide solution was then added dropwise. After the addition was complete, the reaction mixture was left to stir for 5 h at 23 °C. The concentration of the Grignard reagent was determined through titration with Love's reagent[86] to be 0.34 M.

A solution of (*S*,*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide **2.14** (1.07 g, 5.12 mmol, 1.00 eq.) in anhydrous tetrahydrofuran (7.3 mL, 0.7 M) was prepared under an argon atmosphere and the solution was then cooled to –30 °C using a mixture of dry ice and acetonitrile. To this solution, the previously prepared solution of Grignard reagent (0.340 M, 15.1 mL, 5.12 mmol, 1.00 eq.) was added dropwise over a period of 20 min and the resulting mixture was stirred for 40 min at this temperature. Then the reaction was warmed to 23 °C and stirred for 17 h. The reaction was stopped by the addition of a saturated aqueous solution of ammonium chloride. The biphasic mixture was separated and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate

to afford the title compound **2.17** (1.46 g, 4.97 mmol, 97 %, *d.r.* 1.4:1) as a white solid. The diastereomers were separated by preparative HPLC using: Chiralpak IC, *n*-heptane + 0.1% IPA/ IPA 8:2, 1 mL/min, 25 °C, detection at 230 nm, retention time (min): 5.0 (major, **2.17a**) and 6.0 (minor, **2.17b**) to afford **2.17a** (575 mg, 1.96 mmol, 38%) as a yellow oil and **2.17b** (247 mg, 0.842 mmol, 16%) as a colourless solid.

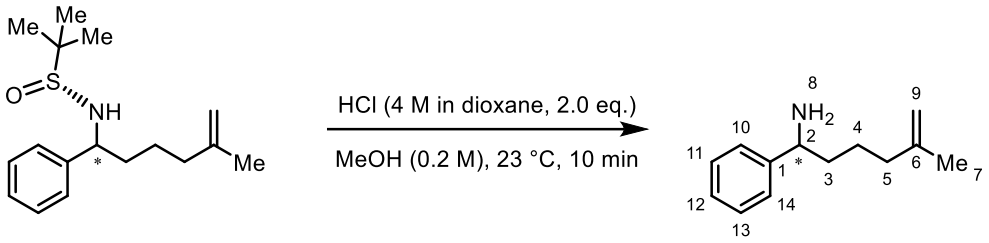
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 5H, H_{Ar}), 4.68 – 4.60 (m, 2H, H9), 4.38 – 4.34 (m, 1H, H2), 3.36 (s, 1H, NH8), 2.00 – 1.97 (m, 2H, H5), 1.82 – 1.69 (m, 2H, H3), 1.63 (s, 2.5H, $H7_{d1}$), 1.55 (s, 0.5 H, $H7_{d2}$), 1.44 – 1.39 (m, 1H, $H4_A$), 1.33 – 1.25 (m, 1H, $H4_B$), 1.23 (s, 4H, $H18_{d2}$, $H19_{d2}$, $H20_{d2}$), 1.17 (s, 5H, $H18_{d2}$, $H19_{d2}$, $H20_{d2}$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.5 (0.4C, $C6_{d2}$), 145.2 (0.6C, $C6_{d1}$), 142.7 (0.4C, $C1_{d2}$), 142.1 (0.6C, $C1_{d1}$), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.3 (C_{Ar}), 110.6 (0.6C, $C9_{d1}$), 110.3 (0.4C, $C9_{d2}$), 59.3 (0.6C, $C2_{d1}$), 59.1 (0.4C, $C2_{d2}$), 55.8 (0.4C, $C17_{d2}$), 55.6 (0.6C, $C17_{d1}$), 38.4 (0.6C, $C3_{d1}$), 37.6 (0.4C, $C3_{d2}$), 37.4 (0.6C, $C5_{d1}$), 36.2 (0.4C, $C5_{d2}$), 23.9 (0.6C, $C4_{d1}$), 23.6 (0.4C, $C4_{d2}$), 22.8 (1.2C, $C18_{d2}$, $C19_{d2}$, $C20_{d2}$), 22.7 (1.8C, $C18_{d1}$, $C19_{d1}$, $C20_{d1}$), 22.4 (0.4C, $C7_{d2}$), 22.3 (0.6C, $C7_{d1}$).

IR (neat) ν_{max}: 3200, 3065, 3026, 2923, 2358, 1648, 1493, 1453, 1364, 1238, 1085, 820, 753, 608 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{27}NOSNa^+$) requires *m/z* 316.1706 found *m/z* 316.1702.

***(R)*- or *(S)*-5-Methyl-1-phenylhex-5-en-1-amine (2.18)**



2.17a
single diastereomer

2.18
53%
Formula: $C_{13}H_{19}N$
MW: 189.3

In an oven-dried vial, sulfinamide **2.17a** (575 mg, 1.96 mmol, 1.00 eq.) was dissolved in anhydrous methanol (1 mL, 0.2 M) under an argon atmosphere. Then, hydrochloric acid (4 M solution in dioxane, 0.1 mL, 0.4 mmol, 2 eq.) was added at 23 °C and the solution was left to stir until the starting material had been consumed, as judged by TLC analysis (heptane/ethyl acetate, 1:1, around 10 min). To the reaction mixture was then added 3 M NaOH until a pH of 11 was reached. The aqueous solution was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were washed with brine (1 x 5 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate to afford the title compound **2.18** (184 mg, 0.974 mmol, 53 %) as a yellow oil. *Note: Absolute configuration was not determined.*

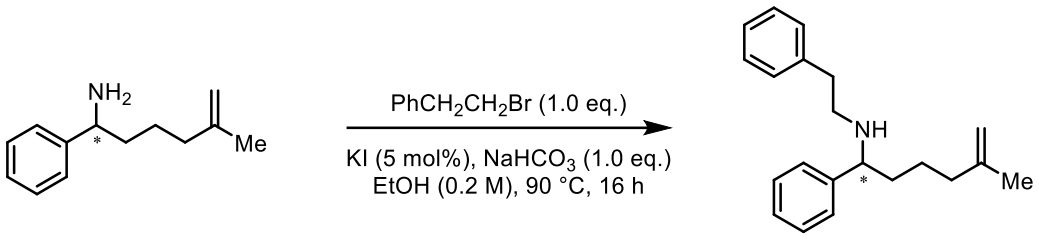
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.21 (m, 5H, H_{Ar}), 4.68 – 4.63 (m, 2H, H9), 3.89 (t, *J* = 6.9 Hz, 1H, H2), 1.99 (t, *J* = 7.4 Hz, 2H, H5), 1.69 – 1.63 (m, 5H, H3, H7), 1.60 (br s, 2H, H8), 1.54 – 1.43 (m, 1H, $H4_A$), 1.40 – 1.31 (m, 1H, $H4_B$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 145.8 (2C, C1, C6), 128.6 (2C, C_{Ar}), 127.1 (C_{Ar}), 126.5 (2C, C_{Ar}), 110.2 (C9), 56.4 (C2), 39.3 (C3), 37.8 (C5), 24.6 (C4), 22.4 (C7).

IR (neat) ν_{max}: 3071, 3027, 2933, 2858, 1648, 1603, 1492, 1452, 1309, 883, 760, 699, 590, 537, 493, 409 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{13}H_{20}N^+$) requires *m/z* 190.1590 found *m/z* 190.1591.

***(R)*- or *(S)*-5-Methyl-N-phenethyl-1-phenylhex-5-en-1-amine (2.20)**



2.18
single enantiomer

2.20
43%
Formula: $C_{21}H_{27}N$
MW: 293.45

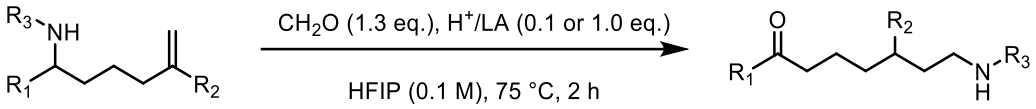
The compound was prepared according to a slightly modified literature procedure.[79] 5-Methyl-1-phenylhex-5-en-1-amine **2.18** ((*R*)- or (*S*)-enantiomer, 75.5 mg, 0.400 mmol, 1.00 eq.) was dissolved in anhydrous ethanol (2 mL, 0.2 M). Then, (2-bromoethyl)benzene (55 µL, 0.40 mmol, 1.0 eq.), potassium iodide (3 mg, 0.02 mmol, 5 mol%) and sodium bicarbonate (34 mg, 0.40 mmol, 1.0 eq.) were added. The reaction mixture was left to stir in a sandbath at 90 °C for 16 h. After 16 h, the reaction mixture was allowed to cool to ambient temperature, followed by the addition of brine (20 mL). The biphasic mixture was separated, and the aqueous phase was extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate to afford the title compound **2.20** (51.0 mg, 0.17 mmol, 43 %) as a yellow oil. *Note: Absolute configuration was not determined.*

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.13 (m, 10H), 4.66 – 4.58 (m, 2H), 3.58 (dd, *J* = 7.9, 6.2 Hz, 1H), 2.80 – 2.67 (m, 4H), 1.98 – 1.90 (m, 2H), 1.68 – 1.56 (m, 5H), 1.35 – 1.18 (m, 2H). *The NH proton was not observed.*

The spectral data is in accordance with previously synthesized racemic material (**2.1a**).

4.6 Product synthesis

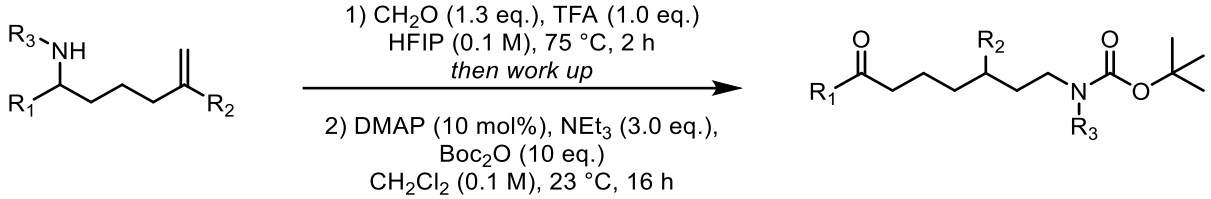
General procedure B: Intramolecular Hydroaminoalkylation



In an oven-dried vial, the amine (1.0 eq.) and paraformaldehyde (1.3 eq.) were dissolved in hexafluoroisopropanol (HFIP, 0.1 M), followed by the addition of trifluoracetic acid (TFA) and/or copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$). The reaction mixture was left to stir at 75 °C in a sand bath for 2 h. The reaction was stopped by the addition of a saturated aqueous solution of sodium bicarbonate and water. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (ethyl acetate/ ethanol/NH_4OH in a 3:1:0.02 ratio) from 0% to 100%. The solvent was removed under reduced pressure and the product was dissolved in dichloromethane. The organic phase was extracted with a saturated aqueous solution of sodium bicarbonate to remove the ammonium hydroxide. The biphasic mixture was separated, dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure to obtain the pure product.

Note: When TFA was used in catalytic amounts, a fresh stock solution in HFIP was prepared prior to use.

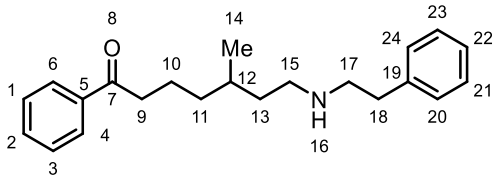
General procedure C: Intramolecular Hydroaminoalkylation with Boc protection



In an oven-dried vial, the amine (1.0 eq.) and paraformaldehyde (1.3 eq.) were dissolved in hexafluoroisopropanol (HFIP, 0.1 M), followed by the addition of trifluoracetic acid (TFA) and/or copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$). The reaction mixture was left to stir at 75 °C in a sand bath for 2 h. The reaction was stopped by the addition of a saturated aqueous solution of sodium bicarbonate and water. The aqueous phase was extracted with dichloromethane and the combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was then dissolved in anhydrous dichloromethane (0.1 M). To this solution, *N,N*-dimethyl-4-pyridinamine (0.10 eq.), triethylamine (3.0 eq.), and di-*tert*-butyl dicarbonate (10 eq.) were added and the resulting mixture was left to stir for 16 h at 23 °C. After this time, a saturated solution of sodium bicarbonate was added and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate from 0% to 50% to obtain the pure product.

Note: When TFA was used in catalytic amounts, a fresh stock solution in HFIP was prepared prior to use.

5-Methyl-7-(phenethylamino)-1-phenylheptan-1-one (2.23a)



Formula: $C_{22}H_{29}NO$
MW: 323.48

The title compound was prepared following general procedure B using *rac*-5-methyl-*N*-phenethyl-1-phenylhex-5-en-1-amine **2.1a** (29.3 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and $Cu(OTf)_2$ (36.2 mg, 0.100 mmol, 1.00 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.23a** (16.5 mg, 0.051 mmol, 51%).

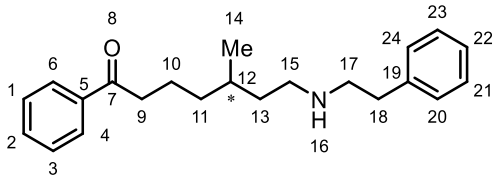
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H, H4, H6), 7.57 – 7.53 (m, 1H, H2), 7.45 (dd, *J* = 8.2, 7.3 Hz, 2H, H1, H3), 7.29 (dd, *J* = 8.0, 7.1 Hz, 2H, H20, H24), 7.24 – 7.18 (m, 3H, H21, H22, H23), 2.99 – 2.88 (m, 6H, H9, H17, H18), 2.73 (ddd, *J* = 23.6, 10.3, 5.7 Hz, 2H, H15), 1.80 – 1.74 (m, 1H, $H10_A$), 1.71 – 1.60 (m, 2H, $H10_B$, $H13_A$), 1.55 – 1.50 (m, 1H, H12), 1.48 – 1.42 (m, 1H, $H13_B$), 1.39 – 1.33 (m, 1H, $H11_A$), 1.24 – 1.19 (m, 1H, $H11_B$), 0.90 (d, *J* = 6.6 Hz, 3H, H14). *The NH proton was not observed.*

^{13}C NMR (176 MHz, $CDCl_3$): δ 200.5 (C7), 139.3 (C5), 137.2 (C19), 133.1 (C2), 128.9 (2C, C_{Ar}), 128.73 (2C, C_{Ar}), 128.71 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 126.6 (C22), 50.8 (C17), 47.5 (C15), 38.8 (C9), 36.6 (C13), 36.1 (C18), 35.4 (C11), 31.1 (C12), 21.8 (C10), 19.6 (C14).

IR (neat) ν_{max}: 2924, 2790, 2357, 1683, 1597, 1492, 1449, 1362, 1232, 1118, 1027, 750, 699, 512 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{22}H_{30}NO^+$) requires *m/z* 324.2322 found *m/z* 324.2319.

***(R)*- or *(S)*-5-Methyl-7-(phenethylamino)-1-phenylheptan-1-one (2.25)**



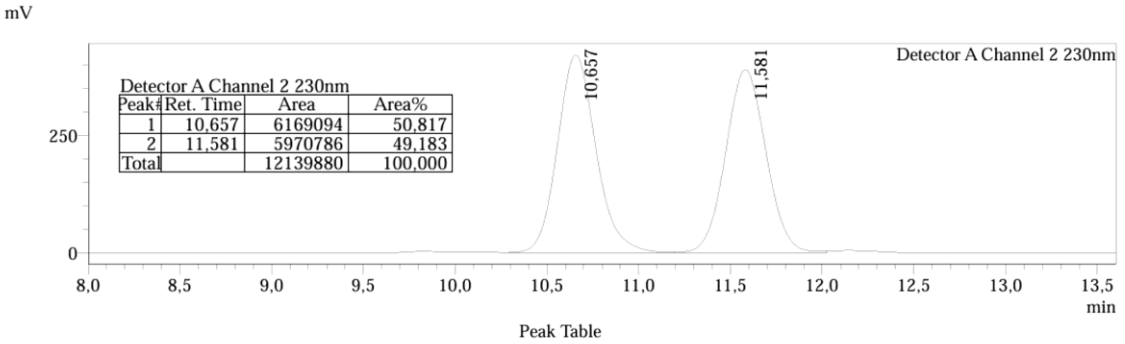
Formula: $C_{22}H_{29}NO$
MW: 323.48

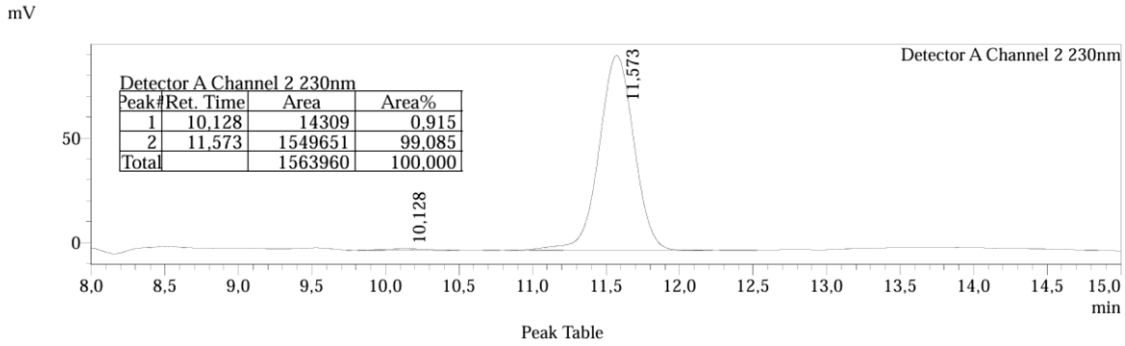
The title compound was prepared following general procedure B using *(R)*- or *(S)*-5-methyl-*N*-phenethyl-1-phenylhex-5-en-1-amine **2.20** (29.3 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and TFA (7.7 μL, 0.10 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane (1% NEt_3)/ethyl acetate (0% to 100%) to afford the title compound **2.25** (6.5 mg, 0.020 mmol, 20%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H, H4, H6), 7.57 – 7.53 (m, 1H, H2), 7.45 (dd, *J* = 8.2, 7.3 Hz, 2H, H1, H3), 7.29 (dd, *J* = 8.0, 7.1 Hz, 2H, H20, H24), 7.24 – 7.18 (m, 3H, H21, H22, H23), 2.99 – 2.88 (m, 6H, H9, H17, H18), 2.73 (ddd, *J* = 23.6, 10.3, 5.7 Hz, 2H, H15), 1.80 – 1.74 (m, 1H, $H10_A$), 1.71 – 1.60 (m, 2H, $H10_B$, $H13_A$), 1.55 – 1.50 (m, 1H, H12), 1.48 – 1.42 (m, 1H, $H13_B$), 1.39 – 1.33 (m, 1H, $H11_A$), 1.24 – 1.19 (m, 1H, $H11_B$), 0.90 (d, *J* = 6.6 Hz, 3H, H14). *The NH proton was not observed.*

The spectral data is in accordance with previously synthesized racemic material (**2.23a**).

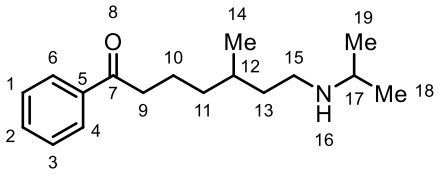
Enantiomeric excess: 99% *ee* was determined by chiral HPLC analysis: Lux-Cellulose1, 90% *n*-heptane + 0.1% IPA + 10% EtOH 9:1, 0.7 mL/min, 25 °C, detection at 230 nm, retention time (min): 11.6 (major) and 10.1 (minor).





Note: Absolute configuration was not determined.

7-(Isopropylamino)-5-methyl-1-phenylheptan-1-one (2.23c)



Formula: $C_{17}H_{27}NO$
MW: 261.41

The title compound was prepared following general procedure B using *N*-isopropyl-5-methyl-1-phenylhex-5-en-1-amine **2.1f** (23.1 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.), $Cu(OTf)_2$ (3.62 mg, 0.010 mmol, 0.100 eq.) and TFA (1 M solution in HFIP, 76.5 μL, 0.010 mmol, 0.100 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.23c** (10.6 mg, 0.0405 mmol, 41%) as a yellow oil.

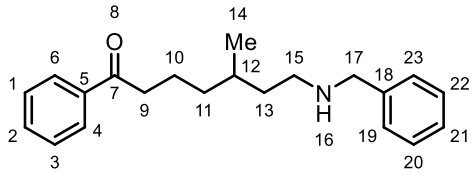
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.94 (m, 2H, H4, H6), 7.56 – 7.53 (m, 1H, H2), 7.47 – 7.44 (m, 2H, H1, H3), 2.95 (ddd, *J* = 8.0, 6.7, 3.0 Hz, 2H, H9), 2.79 (sept, *J* = 6.2 Hz, 1H, H17), 2.60 (ddd, *J* = 11.2, 9.5, 5.6 Hz, 2H, H15), 1.83 – 1.69 (m, 2H, H10), 1.56 – 1.49 (m, 2H, H12, $H13_A$), 1.42 – 1.30 (m, 2H, $H11_A$, $H13_B$), 1.25 – 1.23 (m, 1H, $H11_B$), 1.06 (d, *J* = 6.2 Hz, 6H, H18, H19), 0.91 (d, *J* = 6.5 Hz, 3H, H14). *The NH proton was not observed.*

^{13}C NMR (151 MHz, $CDCl_3$): δ 200.6 (C7), 137.2 (C5), 133.0 (C2), 128.7 (2C, C4, C6), 128.2 (2C, C1, C3), 49.0 (C17), 45.5 (C15), 39.0 (C9), 37.6 (C13), 36.9 (C11), 32.1 (C12), 23.11 (C19), 23.06 (C18), 22.0 (C10), 19.8 (C14).

IR (neat) ν_{max}: 2958, 2924, 2868, 1685, 1597, 1449, 1408, 1377, 1361, 1337, 1203, 1178, 1080, 1002, 973, 752, 732, 691, 570 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{17}H_{28}NO^+$) requires *m/z* 262.2165 found *m/z* 262.2165.

7-(Benzylamino)-5-methyl-1-phenylheptan-1-one (2.23b)



Formula: $C_{21}H_{27}NO$
MW: 309.45

The title compound was prepared following general procedure B using *N*-benzyl-5-methyl-1-phenylhex-5-en-1-amine **2.1b** (27.9 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and TFA (7.7 μL, 0.10 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.23b** (14.8 mg, 0.0478 mmol, 48%) as a yellow oil.

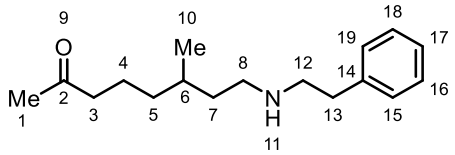
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.94 (m, 2H, H4, H6), 7.56 – 7.54 (m, 1H, H2), 7.47 – 7.45 (m, 2H, H1, H3), 7.33 – 7.30 (m, 4H, H19, H20, H22, H23), 7.25 – 7.23 (m, 1H, H21), 3.79 (s, 2H, H17), 2.94 (ddd, *J* = 8.1, 6.6, 4.5 Hz, 2H, H9), 2.70 – 2.61 (m, 2H, H15), 1.81 – 1.67 (m, 2H, H10), 1.56 – 1.54 (m, 2H, H12, $H13_A$), 1.38 – 1.35 (m, 2H, $H11_A$, $H13_B$), 1.26 – 1.22 (m, 1H, $H11_B$), 0.90 (d, *J* = 6.6 Hz, 3H, H14). *The NH proton was not observed.*

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.6 (C7), 140.6 (C18), 137.2 (C5), 133.0 (C2), 128.7 (2C, C1, C3), 128.5 (2C, C20, C22), 128.3 (2C, C19, C23), 128.2 (2C, C4, C6), 127.0 (C21), 54.3 (C17), 47.5 (C15), 39.0 (C9), 37.3 (C13), 36.9 (C11), 31.1 (C12), 21.9 (C10), 19.8 (C14).

IR (neat) ν_{max}: 2923, 2863, 1683, 1597, 1449, 1358, 1261, 1203, 1180, 1118, 1075, 1027, 1001, 972, 731, 690, 657, 602, 569, 465 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{21}H_{28}NO^+$) requires *m/z* 310.2165 found *m/z* 310.2160.

6-Methyl-8-(phenethylamino)octan-2-one (2.23g)



Formula: $C_{17}H_{27}NO$
MW: 261.41

The title compound was prepared following general procedure B using 6-methyl-*N*-phenethylhept-6-en-2-amine **2.1j** (23.1 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and TFA (7.7 μL, 0.10 mmol, 1.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/EEA (0% to 100%) to afford the title compound **2.23g** (4.8 mg, 0.018 mmol, 18%) as a yellow oil.

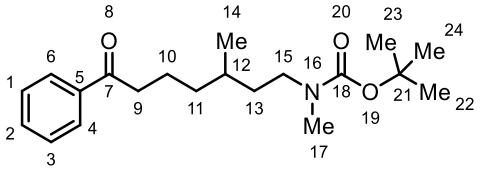
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 – 7.20 (m, 5H, H_{Ar}), 2.90 – 2.87 (m, 2H, H12), 2.83 – 2.80 (m, 2H, H13), 2.67 - 2.58 (m, 2H, H8), 2.43 – 2.35 (m, 2H, H3), 2.12 (s, 3H, H1), 1.63 – 1.41 (m, 5H, H4, H6, H7), 1.32 – 1.29 (m, 1H, $H5_A$,), 1.14 – 1.08 (m, 1H, $H5_B$), 0.87 (d, *J* = 6.5 Hz, 3H, H10). *The NH proton was not observed.*

^{13}C NMR (151 MHz, $CDCl_3$): δ 209.3 (C2), 140.1 (C14), 128.9 (2C, C_{Ar}), 128.6 (2C, C_{Ar}), 126.3 (C17), 51.3 (C12), 47.8 (C8), 44.1 (C3), 37.1 (C7), 36.7 (C5), 36.4 (C13), 31.0 (C6), 30.0 (C1), 21.4 (C4), 19.7 (C10).

IR (neat) ν_{max}: 2924, 2853, 1715, 1603, 1496, 1455, 1408, 1363, 1228, 1163, 1123, 1082, 1030, 749, 700, 525 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{17}H_{28}NO^+$) requires *m/z* 262.2162 found *m/z* 262.2165.

***tert*-Butyl methyl(3-methyl-7-oxo-7-phenylheptyl)carbamate (2.32)**



Formula: $C_{20}H_{31}NO_3$
MW: 333.47

The title compound was prepared following general procedure C using *N*,5-dimethyl-1-phenylhex-5-en-1-amine **2.1d** (20.3 mg, 0.10 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and TFA (7.7 μL, 0.10 mmol, 1.0 eq.). Boc-protection was carried out using *N,N*-dimethyl-4-pyridinamine (1 mg, 0.01 mmol, 0.1 eq.), triethylamine (41.8 μL, 0.300 mmol, 3.00 eq.), and di-*tert*-butyl dicarbonate (218 mg, 1.00 mmol, 10.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate (0% to 50%) to afford the title compound **2.32** (14.1 mg, 0.0423 mmol, 42%) as a yellow oil.

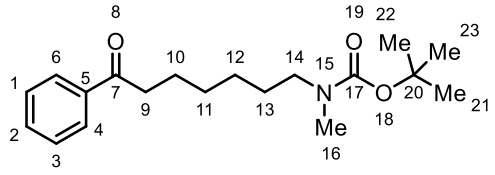
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.98 – 7.94 (m, 2H, H4, H6), 7.55 (t, *J* = 7.4 Hz, 1H, H2), 7.46 (t, *J* = 7.5 Hz, 2H, H1, H3), 3.25 – 3.16 (m, 2H, H15), 3.00 – 2.91 (m, 2H, H9), 2.82 (s, 3H, H17), 1.82 – 1.75 (m, 1H, $H10_A$), 1.74 – 1.67 (m, 1H, $H10_B$), 1.59 – 1.52 (m, 1H, $H11_A$), 1.45 (s, 9H, H22, H23, H24), 1.38 – 1.29 (m, 2H, $H11_B$, $H13_A$), 1.26 – 1.22 (m, 2H, H12, $H13_B$), 0.93 (d, *J* = 6.6 Hz, 3H, H14).

^{13}C NMR (176 MHz, $CDCl_3$): δ 200.3 (C7), 155.9 (C18), 137.2 (C5), 133.1 (C2), 128.7 (2C, C1, C3), 128.2 (2C, C4, C6), 79.3 (C21), 47.1 (C15), 38.9 (C9), 36.8 (C13), 34.9 (C11), 34.1 (C17), 30.6 (C12), 28.6 (3C, C22, C23, C24), 21.9 (C10), 19.6 (C14).

IR (neat) ν_{max}: 2953, 2928, 2871, 1687, 1481, 1449, 1423, 1394, 1365, 1306, 1222, 1203, 1156, 1098, 1051, 883, 769, 753, 733, 691 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{20}H_{31}NO_3Na^+$) requires *m/z* 356.2196 found *m/z* 356.2197.

***tert*-Butyl methyl(7-oxo-7-phenylheptyl)carbamate (2.33)**



Formula: $C_{19}H_{29}NO_3$
MW: 319.44

The title compound was prepared following general procedure C using *N*-methyl-1-phenylhex-5-en-1-amine **2.1h** (18.9 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and TFA (7.7 μL, 0.10 mmol, 1.0 eq.). Boc-protection was carried out using *N,N*-dimethyl-4-pyridinamine (1 mg, 0.01 mmol, 0.1 eq.), triethylamine (41.8 μL, 0.300 mmol, 3.00 eq.), and di-*tert*-butyl dicarbonate (218 mg, 1.00 mmol, 10.0 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate (0% to 50%) to afford the title compound **2.33** (18 mg, 0.056 mmol, 56%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 – 7.94 (m, 2H, H4, H6), 7.55 (t, *J* = 7.3 Hz, 1H, H2), 7.46 (dd, *J* = 8.2, 7.2 Hz, 2H, H1, H3), 3.19 (app s, 2H, H14), 2.96 (t, *J* = 7.4 Hz, 2H, H9), 2.82 (s, 3H, H16), 1.77 – 1.71 (m, 2H, H10), 1.56 – 1.48 (m, 2H, H13), 1.45 (s, 9H, H21, H22, H23), 1.42 – 1.38 (m, 2H, H11), 1.35 – 1.29 (m, 2H, H12).

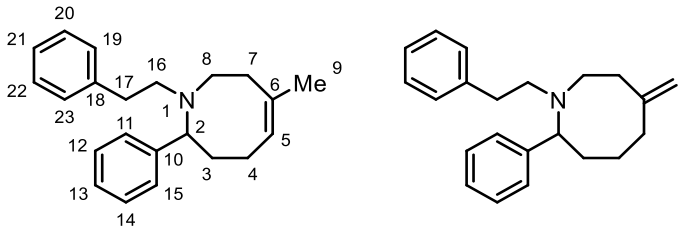
^{13}C NMR (151 MHz, $CDCl_3$): δ 200.5 (C7), 156.0 (C17), 137.2 (C5), 133.1 (C2), 128.7 (2C, C1, C3), 128.2 (2C, C4, C6), 79.2 (C20), 49.0 (C14), 38.6 (C9), 34.2 (C16), 29.2 (C11), 27.6 (C13), 28.6 (3C, C21, C22, C23), 26.7 (C12), 24.4 (C10).

IR (neat) ν_{max}: 2972, 2930, 2858, 1687, 1598, 1481, 1449, 1423, 1393, 1365, 1306, 1219, 1160, 1093, 1051, 1002, 880, 754, 691 cm^{-1}.

HRMS (ESI$^+$): exact mass calculated for $[M+H]^+$ ($C_{19}H_{29}NO_3Na^+$) requires *m/z* 342.2040 found *m/z* 342.2040.

4.7 Isolation of side products

(*Z*)-6-Methyl-1-phenethyl-2-phenyl-1,2,3,4,7,8-hexahydroazocin and 6-methylene-1-phenethyl-2-phenylazocane (2.24a)



Major *Minor*

Formula: $C_{22}H_{27}N$
MW: 305.46

The title compounds were isolated following general procedure B using 5-methyl-*N*-phenethyl-1-phenylhex-5-en-1-amine **2.1a** (29.3 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and $Cu(OTf)_2$ (36.2 mg, 0.100 mmol, 1.00 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate (0% to 50%) to afford the title compounds **2.24a** (11.9 mg, 0.0390 mmol, 39%, 7:1 *r.r.*) as a yellow oil. *Note: NMR characterization only on major isomer.*

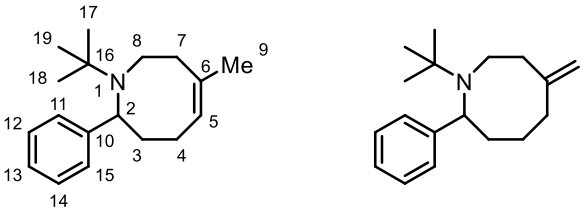
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.37 – 7.02 (m, 10H, H_{Ar}), 5.41 – 5.37 (m, 1H, H5), 4.01 (dd, *J* = 12.0, 4.4 Hz, 1H, H2), 3.41 (ddd, *J* = 14.7, 5.1, 2.3 Hz, 1H, $H8_A$), 2.97 – 2.91 (m, 2H, $H17_A$, $H8_B$), 2.82 – 2.68 (m, 3H, $H7_A$, $H16_A$, $H17_B$), 2.41 (ddd, *J* = 13.1, 10.2, 5.5 Hz, 1H, $H16_B$), 2.28 – 2.22 (m, 1H, $H4_A$), 2.20 – 2.15 (m, 1H, $H3_A$), 2.05 – 2.00 (m, 1H, $H4_B$), 1.95 – 1.90 (m, 1H, $H3_B$), 1.81 (s, 3H, H9), 1.67 (ddd, *J* = 13.8, 5.1, 1.6 Hz, 1H, $H7_B$).

^{13}C NMR (176 MHz, $CDCl_3$): δ 145.7 (C10), 141.0 (C18), 138.4 (C6), 128.9 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 128.0 (2C, C_{Ar}), 127.4 (2C, C_{Ar}), 126.2 (C_{Ar}), 125.9 (C_{Ar}), 123.6 (C5), 62.0 (C2), 52.1 (C8), 48.0 (C17), 36.2 (C16), 33.9 (C3), 31.3 (C7), 25.3 (C4), 25.0 (C9).

IR (neat) ν_{max}: 2920, 2851, 1494, 1447, 1374, 1186, 1132, 1109, 1081, 1053, 1031, 1003, 938, 897, 746, 696, 602, 509 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{22}H_{28}N^+$) requires *m/z* 306.2216 found *m/z* 306.2215.

(*Z*)-1-(*tert*-Butyl)-6-methyl-2-phenyl-1,2,3,4,7,8-hexahydroazocine and 1-*tert*-butyl-6-methylene-2-phenylazocane (2.24e)



Major *Minor*

Formula: $C_{18}H_{27}N$
MW: 257.42

The title compound was prepared following general procedure B using *N*-(*tert*-butyl)-5-methyl-1-phenylhex-5-en-1-amine **2.1e** (24.5 mg, 0.100 mmol, 1.00 eq.), paraformaldehyde (3.9 mg, 0.13 mmol, 1.3 eq.) and $Cu(OTf)_2$ (3.6 mg, 0.010 mmol, 0.10 eq.). The crude residue was purified by flash column chromatography on silica gel with a gradient of heptane/ethyl acetate (0% to 50%) to afford the title compound **2.24e** (15.2 mg, 0.0590 mmol, 59%, 6:1 *r.r*) as a yellow oil. *Note: NMR characterization only on major isomer.*

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.7 Hz, 2H, H11, H15), 7.28 – 7.25 (m, 2H, H12, H14), 7.18 – 7.15 (m, 1H, H13), 5.48 – 5.43 (m, 1H, H5), 4.24 – 4.19 (m, 1H, H2), 3.25 (app s, 1H, $H8_A$), 2.95 – 2.89 (m, 1H, $H8_B$), 2.48 – 2.41 (m, 2H, H4A, $H7_A$), 2.22 – 2.14 (m, 2H, $H3_A$, $H4_B$), 1.91 (dd, *J* = 13.7, 2.9 Hz, 1H, $H7_B$), 1.84 – 1.78 (m, 1H, $H3_B$), 1.74 (s, 3H, H9), 1.03 (s, 9H, H17, H18, H19).

^{13}C NMR (176 MHz, $CDCl_3$): δ 146.3 (C10), 137.9 (C6), 128.3 (2C, C11, C15), 127.7 (2C, C12, C14), 126.0 (C13), 125.1 (C5), 62.1 (C2), 55.7 (C16), 43.5 (C8), 37.9 (C7), 35.7 (C3), 30.1 (3C, C17, C18, C19), 26.2 (C9), 25.7 (C4).

IR (neat) ν_{max}: 2956, 2919, 2851, 1492, 1448, 1389, 1360, 1293, 1241, 1153, 1089, 1029, 916, 823, 752, 700, 591 cm^{-1}.

HRMS (ESI^+): exact mass calculated for $[M+H]^+$ ($C_{18}H_{28}N^+$) requires *m/z* 258.2216 found *m/z* 258.2215.

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