Synthesis and Reactivity of Allylic Amines in Palladium Catalysis

by

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Abstract

Reaction of unsymmetrical allylic electrophiles with amines gives rise to regioisomeric allylamines. It was found that linear products result from the thermodynamically controlled isomerization of the corresponding branched products, which form initially. The isomerization was found to be promoted by the presence of acid and active palladium catalyst. The use of base shut down the isomerization pathway and allowed for the preparation and isolation of branched allylamines.\(^1\) This methodology provides a powerful control element, which allows for the installation of quaternary and chiral centres next to nitrogen. Later, the isomerization was combined with ring-closing metathesis to afford the synthesis of exocyclic allylamines from their thermodynamically less-stable endocyclic precursors. This rearrangement became feasible as a result of the electrophilic nature of a C – N bond in allylamines.\(^2\) When compared to the conventional intramolecular allylic amination, such approach escapes chemoselectivity issues, which makes it attractive attractive for late-stage synthetic modifications.


Acknowledgments

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<th>Meaning</th>
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<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-<em>bis</em>(diphenylphosphino)-1,1’- binaphthalene</td>
</tr>
<tr>
<td>Biphep</td>
<td>(<em>R</em>)-(++)-(6,6’-Dimethoxybiphenyl-2,2’-diyl)bis(diphenylphosphine)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>di-tert-butyl dicarbonate</td>
</tr>
<tr>
<td>'Bu</td>
<td><em>tert</em>-butyl</td>
</tr>
<tr>
<td>⁰C</td>
<td>degrees Celcius</td>
</tr>
<tr>
<td>cat</td>
<td>catalytic</td>
</tr>
<tr>
<td>COD</td>
<td>cyclooctadiene</td>
</tr>
<tr>
<td>conv</td>
<td>conversion</td>
</tr>
<tr>
<td>CPME</td>
<td>cyclopentyl methyl ether</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet (multiplicity in NMR)</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets (multiplicity in NMR)</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets (multiplicity in NMR)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
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<tr>
<td>DABCO</td>
<td>1,4-diazobicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazobicyclo[5.4.0]undecene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N’-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
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<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
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<td>DIOP</td>
<td>(+)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4 bis(diphenylphosphino)butane</td>
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<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>dpff</td>
<td>1,1’-Bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electron spray ionization (mass spectrometry)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HG II</td>
<td>Hoveyda Grubbs catalyst, 2\textsuperscript{nd} generation</td>
</tr>
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HPLC  high performance liquid chromatography

Hz  hertz

HRMS  high resonance mass spectrometry

$J$  coupling constant in NMR

L  liter(s)

LDA  lithium diisopropylamide

m  mili

µ  micro

M  molar (moles/liter)

M  mega

$M^+$  Parent molecular ion

Me  methyl

mL  milliliter

mmol  millimole

MS  mass spectrometry

m/z  mass-to-charge ratio

NBS  $N$-bromosuccinamide

NMM  $N$-methy1morpholine
<table>
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<th>Full Form</th>
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<tbody>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>o</td>
<td>ortho (position on the benzene ring)</td>
</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
</tr>
<tr>
<td>p</td>
<td>para (position on benzene ring)</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Phth</td>
<td>phthalyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>Pr</td>
<td>normal propyl</td>
</tr>
<tr>
<td>ppm</td>
<td>part(s) per million</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR multiplicity)</td>
</tr>
<tr>
<td>R</td>
<td>generic group</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR multiplicity)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR multiplicity)</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>Tol</td>
<td>tolyl</td>
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</table>
1 Introduction

1.1 Importance of allylamines

Allylamines are structural motifs that have received a lot of attention from the synthetic community. In addition to their abundance in nature, the value of allylamines stems from their use as synthetic intermediates. The independent reactivity of the alkene and the amine portions of allylamines allows for the stepwise functionalization of these motifs. Scheme 1.1 illustrates this point on two examples where allylamines were used to synthesize biologically-active compounds. In the first example, an allylamine prepared by rhodium-catalyzed allylic amination was subjected to ozonolysis, after which a primary amine was released through a series of deprotection steps to give and unnatural α- amino acid.\(^1\) In the second example, an allylamine prepared by iridium-catalyzed allylic amination was subjected to Wacker oxidation, which upon additional oxidation and deprotection yielded a β-amino acid.\(^2\)

Scheme 1.1 Use of allylamines as synthetic intermediates

\(^1\) Evans, 1999

\(^2\) Feringa, 2009
1.2 Preparation of allylamines

Approaches toward the synthesis of allylamines can be divided into two main categories, the first one where the nitrogen comes from a nucleophile that attacks an alkene-containing electrophile, and the second one, where the alkene is part of a nucleophile that is attacking an N-containing electrophile (Scheme 1.2).

Scheme 1.2  Retrosynthetic analysis applied to allylamines

\[
\begin{align*}
\text{R}^* & \xrightleftharpoons{a} \text{R}^*\text{R}^\prime \xrightarrow{b} \text{R}^* & \xrightarrow{a} \text{R}^*\text{R}^\prime \xrightarrow{b} \text{R}^*\text{R}^\prime
\end{align*}
\]

1.2.1 Uncatalyzed amination of activated allylic electrophiles

Among the arsenal of transforms that can be represented by disconnection \(a\) (Scheme 1.2) the simplest reaction for the construction of allylamines would be an \(S_N2\) reaction of an allylic halide or a sulfonate with ammonia or a primary amine. Such combination, however, would lead to the formation of overallylated products, since the product of the first allylation is more reactive in the iterative allylation.\(^3\) One solution to this issue is to use more electron-poor N-containing ammonia surrogates such as di-tert-butyl iminocarbonate or tert-butyl diethoxyphosphorylcarbamate (Scheme 1.3).\(^4\) Finkelstein conditions are often applied to increase the reaction yield.\(^5\) The required primary allylamine can later be obtained by a deprotection under acidic conditions. Recently, however, a more-direct solution to the overallylation problem was found by the Alcantara group, where the authors discovered that the nucleophilicity of anilines could be attenuated by using KF-Celite.\(^6\)
Scheme 1.3 Uncatalyzed preparation of allylamines

\[
\text{(Boc)}_2 \text{NH} + \text{nPrOMs} \xrightarrow{\text{5 mol\% LiI, K}_2\text{CO}_3, \text{butanone, } 16\text{h, } 80^\circ\text{C}} \text{nPrNHBoc}
\]

Overall, this approach has a number of advantages over the more modern metal-catalyzed transformations. First of all, the reaction set-up is simple, and does not require special reaction conditions such as inert atmosphere. Secondly, since this reaction proceeds by an S\text{N}2 mechanism, the stereochemistry of the alkene is fully retained. The disadvantages of this approach include limited substrate scope, as only primary halides and sulfonates give good yields.

1.2.2 Mitsunobu reaction

The Mitsunobu reaction is a more direct approach that is still very popular today.\(^7\) Its advantage over the standard S\text{N}2 reaction is that the hydroxyl group of the reacting alcohol does not need to be transformed into a better leaving group prior to the reaction. Rather, the alcohol is activated \textit{in situ}, giving rise to the nitrogen-containing motifs via a formal bimolecular substitution reaction. The selective substitution at the sp\(^3\)-centre not only insures that the reaction proceeds with high stereocontrol at that centre, but also that the geometry of the alkene does not change.\(^7\) The allylic rearrangement pathway is suppressed under the reaction conditions. Another attractive feature of the Mitsunobu reactions is that it allows for the synthesis of primary allylamines (Scheme 1.4).
Scheme 1.4 Synthesis of allylamines via the Mitsunobu reaction

Unfortunately, due to the specifics of the reaction, amines cannot be used as nucleophiles, as they are too basic. Instead, less basic amine synthons such as phthalimide or hydrazoic acid are often employed. These amine-surrogates are later converted to primary amines by trans-amidation with hydrazine or Staudinger reduction with triphenylphosphine, respectively. The main limitation of this reaction is that it works best with primary, as well as cyclic secondary allylic alcohols, whereas the reaction is slow with secondary acyclic alcohols, and does not proceed at all with tertiary alcohols.

1.2.3 Overman rearrangement

A less-straight forward, but a much more elegant and powerful method to prepare allylamines is through the Overman rearrangement. This approach requires the conversion of an allylic alcohol to the corresponding trichloroacetamidate, which, in turn, undergoes the aza-Claisen rearrangement (Scheme 1.5). The formation of a new carbonyl group is the driving force for the reaction. Unlike the substitution reactions outlined above, the intramolecular nature of the Overman rearrangement makes it possible to form allylamines with substituents next to the nitrogen. The trichloroacetamide group can later be removed by basic hydrolysis.
Scheme 1.5 Synthesis of allylamines using the thermal Overman rearrangement

In addition to thermal reaction conditions, the Overman rearrangement can also be catalyzed by metals such as mercury,\textsuperscript{11} palladium,\textsuperscript{12} and gold.\textsuperscript{13} Not only does this variation make the reaction conditions milder, but it also renders the reaction asymmetric with an appropriate choice of a chiral ligand. Unlike the thermal variation, the catalyzed reaction does not proceed through a concerted pathway, but rather contains stable intermediates (Scheme 1.6).

Scheme 1.6 Synthesis of allylamines using the metal-catalyzed Overman rearrangement

The palladium-catalyzed Overman rearrangement is an example of a finely-balanced transformation. Because palladium acts as a Lewis acid without changing its oxidation state throughout the reaction, phosphine ligands cannot be used, as they reduce palladium (II) to palladium (0), thereby switching off its reactivity as a Lewis acid. On the other hand, cationic palladium catalysts are considered to be too Lewis-acidic and therefore coordinate to imidate nitrogen promoting the undesired elimination,\textsuperscript{14} which is why neutral palladium catalysts with oxazoline ligands seem to be ideal for these transformations. Another feature of the palladium-
catalyzed Overman rearrangement is that, in addition to the nature of the chiral ligand, the enantiomeric excess in the reaction is also a function of the stereochemistry of the starting alkene. Thus, in the example shown on Scheme 1.6, the starting E-allylic alcohol gives a 95% ee of the S enantiomer, whereas the starting Z-allylic alcohol gives the R enantiomer, albeit in 71% ee and lower yield. The major limitation of the Overman rearrangement is that it fails with aromatic or bulky aliphatic substituents on the alkene.

1.2.4 Hydroamination

Metal-catalyzed hydroamination of dienes and allenenes is also an attractive method for the synthesis of allylamines. In contrast to the metal-catalyzed allylic amination, vide infra, hydroamination is a more direct and a more atom-economical method, since all the atoms from reactants end up in the product. This transformation has been shown to work with palladium, nickel, bismuth and gold-based catalysts, each of which possesses its characteristic features. A palladium-catalyzed system was shown to be the only system that allowed for the synthesis of allylamines with high enantioselectivities. The main limitations of this reaction are long reaction times and a narrow reaction scope that is limited to anilines. Shorter reaction times were obtained by the addition of a substoichiometric amount of acid, which accelerated the formation of palladium π-allyl intermediate, albeit at the cost of enantioselectivity. Later, it was found that Xantphos ligand accelerated the reaction in the absence of acid. This modification led to the system where hydrazines could be used as nucleophiles. This observation is significant as allylhydrazines can be easily transformed to primary allylamines using reductive cleavage with zinc in acetic acid. The nickel-catalyzed system similarly requires the addition of acid, and, as a result, the reaction is also not enantioselective. In contrast to palladium, the nickel-containing system works with a broad range of aliphatic amines as well as anilines (Scheme 1.7).
Complementary to hydroamination of alkenes, oxidative amination is also a very direct approach to the synthesis of allylamines. In contrast to hydroamination, where dienes are used because one of the alkenes is consumed, monoalkenes are used during the oxidative amination because the alkene is regenerated. Oxidative amination can proceed by a number of mechanisms, such as C – H amination and Wacker-type processes depending on the conditions used. White and coworkers argued that in the presence of benzoquinone and a sulfoxide ligand the reacting alkene coordinates to palladium catalyst, which forms a palladium π-allyl complex via allylic-proton abstraction. The resulting intermediate is attacked by a nucleophile, which forms the allylamine.
product and palladium (0) catalyst, which in turn gets reoxidized to palladium (II) species by benzoquinone (Scheme 1.8).

**Scheme 1.8** Synthesis of allylamines by oxidative amination

![Scheme 1.8](image_url)

Oxidative amination that proceeds by this pathway affords linear allylamines in high yield with high linear selectivity and high selectivity for the $E$-alkene.$^{21}$ This approach, however, is limited to terminal alkenes, and cannot be used if the $Z$-alkene geometry is required. Terminal allylamines with substituents at the $\alpha$-position to the nitrogen can be prepared by the intramolecular variant of this reaction, where the length of the nucleophile tether regulates selectivity.$^{22}$

The alternative pathway proceeds via aminopalladation of the reacting alkene, which is then followed by $\beta$-hydride elimination. Active palladium (II) catalyst is then regenerated by an oxidant such as molecular oxygen. While the intramolecular variant of this transformation has become an attractive tool in the synthesis of cyclic allylamines in high yields and high enantioselectivities,$^{23}$ the success of the intermolecular reaction is often very alkene-dependent, and in most cases is complicated by the competing $\beta$-hydride elimination that leads to the corresponding enamine (Scheme 1.9).$^{24}$
**Scheme 1.9** Synthesis of allylamines by the Wacker-type amination.

Presumably, this side reaction is very slow with cyclic substrates, as the amino-palladation leads to the cis-arrangement of palladium and phthalimide.\(^{25}\) As a result, the only $\beta$-hydride elimination that can occur leads to the formation of the allylic phthalimide. The minor enamide product forms as a result of the reinsertion of palladium hydride species from the opposite face, followed by a $\beta$-hydride elimination (Scheme 1.9).

### 1.2.6 Metal-catalyzed allylic amination

Metal-catalyzed allylic amination is one of the most popular methods to synthesize allylamines. The reaction typically occurs between a primary or a secondary amine and an allylic electrophile in the presence of a metal catalyst. The role of a catalyst in allylic amination is to act as a control element by favouring the attack on one particular terminus or face of the allylic fragment, which forms the basis for regio- or stereoselectivity, respectively. Although activated electrophiles such as allyl chlorides have been employed in the past, they quite often react via a competing uncatalyzed pathway, which would lower the selectivity of the reaction. The uncatalyzed pathway can be suppressed if less activated electrophiles, such as allylic carbonates or acetates are used instead. The reaction generally starts by coordination of the alkene to the electron-rich
metal complex, followed by an ionization step, during which a metal-allyl intermediate is formed. Finally, an amine attacks the allyl ligand liberating the catalytically active metal species.

Different catalysts exercise different regio- and stereocontrol depending on the innate electronic properties of reactive intermediates that are being formed. Rhodium-catalyzed reactions were found to be very regio- and stereospecific owing to rhodium’s chelation-controlled preference to form non-interconverting $\sigma^+\pi$-allyl intermediates.\(^{26}\) This results in a double inversion, or overall retention of both regio- and stereochemistry, \textit{Scheme 1.10}. The presence of such memory effect makes rhodium-based systems quite competitive in the synthesis of optically-pure allylamines. In addition, in the presence of chiral ligands, such systems can be used for kinetic resolution of allylic carbonates.\(^{27}\)

\textit{Scheme 1.10} Synthesis of allylamines by allylic amination using rhodium-based catalysts

Palladium is another metal that has been used effectively in allylic amination. Unlike rhodium, however, palladium-based catalysts are known to undergo fast $\sigma\pi$ equilibration, which makes the position of the leaving group, as well as the stereochemistry of the terminus the leaving group resides on, completely irrelevant.\(^{28}\) Nonetheless, stereocontrol can still be exercised on such systems during the nucleophilic addition step by taking advantage of the fact that the two faces of the $\pi$-allyl intermediate are enantiotopic by virtue of having chiral ligands on palladium. Such reactivity feature of palladium-based systems allows for the use of achiral allylic electrophiles, which are arguable easier to prepare. High enantioselectivities have been observed with ferrocene-\(^{29}\), binaphthyl-\(^{30}\), and diamine-based\(^{31}\) phosphine ligands. In addition, in contrast to rhodium catalysts, palladium-based catalysts are compatible with a wider range of amines, such as aromatic heterocycles and ammonia. The main challenge with palladium-based systems
is that they are typically limited to electrophiles that form symmetric palladium \( \pi \)-allyl intermediates. Such limitation indicates that there is still no general way to establish control over linear vs branched regioselectivity with palladium catalysts.\(^{32}\)

Finally, iridium-based systems are superior in terms of functional group tolerance, substrate scope, and most importantly control over both regio- and enantioselectivity. Such success resulted from detailed mechanistic studies that were conducted by the Hartwig group.\(^{33}\) It was observed that iridium-based catalysts were very sensitive to electronic effects, when compared to other catalysts. Indeed originally, iridium-based catalysts were found to work well only with aliphatic amines.\(^{34}\) Careful mechanistic investigations supported by X-ray diffraction methods helped reveal that the active catalytic species in the reaction is a cyclometalated iridium complex that forms from \([(\text{COD})\text{IrCl}]_2\) and a phosphoramidite ligand via iridium insertion into one of the ligand’s C – H bonds.\(^{33}\) The cyclometalation process that leads to the catalytically active species was found to be promoted by a base, which explains why the reactions with less nucleophilic anilines experience long induction periods. Addition of DABCO has resolved this issue and broadened the scope of nucleophiles that can react under such conditions.\(^{35}\) In addition, the identification of the cyclometallated intermediate helped explain the high branched regioselectivity. Hartwig and coworkers suggested that high selectivity was a consequence of the more-substituted terminus being in the \(\text{trans}\)-relation to the phosphine ligand, whereas the less substituted terminus being placed \(\text{trans}\) to the alkene (Scheme 1.11). Since phosphine ligands have higher \(\text{trans}\)-influence than alkenes, the branched product forms faster.\(^{36}\) In contrast, both termini are \(\text{trans}\) to phosphine ligands in palladium-based systems, therefore, there is less control over regioselectivity.\(^{37}\)

In addition to activating the iridium catalyst and playing the key role in providing regioselectivity, phosphoramidites are powerful chiral ligands that are composed of two chiral subunits, the binol subunit and a distal phenethyl group that work complementarily to enhance the overall enantioselectivity.\(^{38}\)

The substrate scope of iridium-containing systems is quite broad. Because the problem of catalyst activation is solved by the addition of exogenous base, even weak nucleophiles such as
Indoles, imidazoles, benzimidizoles, purines, carbamates, amides and aqueous ammonia give branched products in high yield and enantioselectivity. Importantly, ammonia undergoes only one allylation, which is quite unusual, as most systems give rise to overallylated products. Also, due to the minimal participation of iridium catalysts in cross-coupling reactions, sensitive functionalities such as aryl iodides can be tolerated under the reaction conditions. As for electrophiles, allylic alcohols can be used directly in addition to allylic acetates and carbonates. This is successfully achieved by employing either stoichiometric or catalytic amounts of Lewis acids, both of which activate alcohols in situ.

Scheme 1.11 Synthesis of allylamines by allylic amination using iridium-based catalysts.

In addition to rhodium, palladium, and iridium-based systems, other metals such as platinum and gold have recently started finding use in amination of allylic carbonates and alcohols.
1.2.7 Morita – Baylis – Hillman reaction

Complementary to the approaches described above, another group of methods represented by disconnection \( b \), shown on Scheme 1.2, can be used to prepare allylamines. The Morita – Baylis – Hillman reaction allows for the selective preparation of allylamines that contain an electron-withdrawing group on the alkene. The Krische group showed that the corresponding allylic acetates can react with phthalimides in the presence of triphenylphosphine to yield such allyl phthalimides, which can later be transformed into primary allylamines. Enantioselective systems have been developed, where enones react with imines in the presence of a bifunctional catalyst to give the corresponding allylamine. Such catalysts are composed of two units, which include the nucleophilic portion, such as pyridine, as well as a hydrogen-bond donor, which activates the ketone. Biphenols create a chiral environment for the facially-selective attack on the imine. Such catalysts can be composed of two separate units, or the two units can be tethered to one another (Scheme 1.12).

Scheme 1.12 Synthesis of allylamines using the Morita-Baylis-Hillman approach
The Morita-Baylis-Hillman approach is limited to a very narrow subclass of allylamines that contain an electron-withdrawing group on the alkene. The other drawback is long reaction times (sometimes several days) that result from conducting reactions at low temperatures to achieve high levels of stereocontrol.

1.2.8 Synthesis of allylamines by Ene Reactions

Sulfur and selenium diimides, which are analogues of selenium dioxide, have found use in the synthesis of allylamines through a two-step procedure, an intermolecular ene-reaction followed by a [2,3]-sigmatropic rearrangement (Scheme 1.13). The resulting sulfur or selenium-containing allylamine can later be transformed into a secondary allylamine under a number of deprotection conditions. Optically–pure products have been prepared by either employing chiral auxiliaries, or copper catalysts in combination with chiral oxazoline ligands.

Scheme 1.13 Synthesis of allylamines using ene / [2,3] reaction sequence

Alternatively, a more direct variant of the process shown above has been developed with azo- and nitroso-compounds, where an allylamine is the ene product. Both types of enophiles give the corresponding allylamine products, however, the products derived from nitroso compounds are not stable and typically react further to give mixtures of products under the reaction conditions. One solution to this problem is to use nitroso compounds with a chloro-substituent at the $\alpha$-position, which insures that the resulting ene-product is transformed into a stable nitrone salt.
This elegant solution has made this approach an attractive candidate for the development of an asymmetric version of this reaction. Thus, $\alpha$-chloro nitroso derivatives of sugars were used to achieve the synthesis of allylamines in high yields (Scheme 1.14).$^{57}$

**Scheme 1.14** Synthesis of allylamines from nitroso-compounds

![Scheme 1.14](image)

Despite the numerous protocols developed for the ene-reaction, its utility in the synthesis of allylamines is still limited. First of all, alkenes in acyclic systems suffer from erosion of stereochemistry because the reaction mechanism involves a transposition of the $\pi$-system. In addition, the reaction regioselectivity is very difficult to control for unsymmetrical internal alkenes.

### 1.2.9 Reductive coupling

Addition of an organoalkenyl reagent to an imine seems to be the most direct way of making allylamines using disconnection b shown on Scheme 1.2. Such process, however, would require the corresponding organometallic reagent to be prepared separately. In addition, controlling enantioselectivity of such stoichiometric reaction is often problematic.$^{58}$ Alternatively, such addition may take place by reductive coupling of an alkyne and an imine. Krische and coworkers showed that in the presence of a rhodium or iridium catalyst a new C – C bond is formed between the imine and the former sp-carbon of the alkyne. The resulting organometallic intermediate gives rise to the desired allylamine and regenerates the active catalyst in the
presence of hydrogen gas (*Scheme 1.15*). Alternatively, tetrasubstituted allylamines can be formed if hydrogen is replaced with trialkylborane, which in the presence of a nickel-based catalyst can transfer one of the alkyl groups to nickel via transmetallation.

*Schemes 1.15* Synthesis of allylamines by reductive coupling

This method is quite powerful not only because it allows for the high-yielding synthesis of allylamines with high enantioselectivity, but also because it provides excellent control over the regiochemistry of attack, as well as stereochemistry of the resulting alkene due to the chelation-controlled *syn*-addition. So far, the only limitation of this method has been the low reactivity of aryl alkynes, which lead to the competing hydrogenation of the starting imines.

### 1.2.10 Petasis reaction

Allylamines can also be prepared by the Petasis reaction, which is a multicomponent reaction that employs an amine, an alkenyl boronic acid, and an aldehyde. Formation of a new boron-oxygen bond is the driving force of this transformation. This reaction is particularly useful if a
divergent approach is required to make a large library of allylamines with different properties (Scheme 1.16).

**Scheme 1.16** Synthesis of allylamines using the Petasis reaction

![Scheme 1.16](image)

The reaction offers a number of advantages over metal-catalyzed approaches. Indeed the absence of a transition-metal catalyst renders the reaction very tolerant towards a wide range of functional groups such as hydroxyl, carboxylic acid, and carbinolamine, which would not be compatible with transition-metal catalysts outlined above.\(^6\)\(^1\),\(^6\)\(^2\),\(^6\)\(^3\) In addition, chiral centres in the \(\alpha\)-position to the aldehyde do not undergo racemization. The Petasis reaction can allow for the formation of enantiomerically pure allylamines with a high degree of stereospecificity by using either optically pure aldehydes\(^6\)\(^4\) or amines.\(^6\)\(^2\),\(^6\)\(^5\) The reaction also provides high levels of stereoselectivity with catalysts containing chiral thioureas\(^6\)\(^6\) and chiral biphenols.\(^6\)\(^7\),\(^6\)\(^8\) Finally, the Petasis reaction is stereoretentive with respect to the stereochemistry of alkene, which is the result of a concerted alkenyl transfer in the “ate”-complex.\(^6\)\(^1\) The only limitations of the Petasis reaction are long reaction times, as well as the need to prepare the corresponding vinyl boronic acid.
1.2.11 Synthesis of allylamines by other means

In addition to the approaches described above, other methods have proposed solutions, that are yet to gain broad support by the scientific community. Such methods include allylic C – H amination by nitrene precursors,\(^\text{69}\) ring-opening reactions of epoxides\(^\text{70}\), azetidines\(^\text{71}\) and aziridines\(^\text{72}\) followed by elimination, olefination of \(N\)-protected \(\alpha\)-aminoaldehydes,\(^\text{73}\) as well as reductions of conjugated imines and amides.

1.3 Conclusions

Allylamines are important motifs in synthesis, and a lot of different methods have been developed for their preparation. These methods are constantly improving on the substrate scope, as well as the degree of rigio- and stereoselectivity, and each method summarized or mentioned here has its own advantages and limitations when compared to other approaches. Transition metal catalysis can be regarded as a superior category of allylic amination methods mostly because they offer the most variability by virtue of having additional parameters to control the fate of reaction intermediates. Unfortunately, even though such systems can be very selective for one particular isomer, it’s difficult, however, to force the catalysts to act as a “switch”, which would selectively favour any of the possible products upon a slight change in reaction conditions. This additional flexibility with such commonly used metals as palladium can enable the development of cascade reactions that would allow reaching high degrees of structural product complexity in an efficient manner.
1.4 References

For a more-detailed discussion of branched regioselectivity control with palladium-based systems refer to Chapter 2.


2 Regioselective Palladium-catalyzed Allylation of Primary and Secondary Amines

2.1 Introduction

Controlling regioselectivity in transition metal-catalyzed allylic substitution\(^1\)\(^-\)\(^2\) has been an important goal. Branched allyl amines have attracted particular interest due to the frequent occurrence of these structural fragments among natural products and pharmaceuticals. In addition, branched allyl amines are valuable building blocks in chemical synthesis.\(^3\) The use of palladium catalysts in the amination of allyl acetates and carbonates typically leads to the formation of the more thermodynamically stable linear products.\(^1\) The synthesis of branched allyl amines using this approach has been of little preparative value.

Nonetheless, branched product formation with palladium has been observed and reported in the literature since 1981. Åkermark and co-workers were the first to describe amination of crotyl and prenyl palladium chloride complexes to be reversible, suggesting that the linear product was formed as a result of isomerization of the kinetic branched product (Scheme 2.1).\(^4\) The original explanation suggested σ-complexes as reactive species, but subsequent studies provided no evidence supporting this claim.\(^5\) It should be noted here that this isomerization is not an issue with iridium-based catalysts, as the initial formation of an allylamine was shown to be irreversible.\(^6\) Hou,\(^7\)\(^a\) Hayashi,\(^7\)\(^b\) and Faller\(^7\)\(^c\) argued that certain bidentate ligands direct amines to the more substituted site on the palladium π-allyl complex, which ultimately results in the irreversible formation of branched products (Scheme 2.2). In addition to catalyst modifications, there were also instances when the reactants themselves were biased to give high branched selectivities. Trost and coworkers have shown that ring size could be used to control selectivities in intramolecular allylic amination.\(^8\) Indeed, 2-vinyl pyrrolidines form kinetically faster via a favourable 5-exo-trig transition state, and are more thermodynamically stable than the corresponding allylic tetrahydroazepines (Scheme 2.2). Certain substituents on the allyl substrates such as trifluoromethyl group may
**Scheme 2.1** Branched-linear isomerization

![Schema image](image.png)

Also favor the formation of branched isomers. Another factor that can control regioselectivity is transient intermolecular interactions. Cook showed that the presence of homoallylic secondary amide directs the approaching phthalimide to the vicinal terminus via a hydrogen bond between the amide proton and the oxygen of the phthalimide (Scheme 2.2).

Our own investigations in allylic amination started with a finding that, unlike typical branched allyl amines, branched allyl aziridines are stable against branched-to-linear (b/l) isomerization. Despite the fact that the origins of this stability are still not well understood, it became clear that the regioselectivity can be controlled by the selection of an appropriate amine nucleophile. Subsequently, Hartwig and co-workers found that hydrazine and hydroxylamine derivatives can also be used to form the corresponding branched products, which are also stable to isomerization (Scheme 2.2).

**Scheme 2.2** Palladium-based systems reported to give branched selectivity in allylic amination

_Faller 1999. Special ligand control_
**Trost 1996. Ring-size control**

\[
\text{PMBNH} + \text{OAc} \xrightarrow{\text{[allylPdCl}_2\text{Ligand}}} \text{PMB} + \text{PMBNH} \]

**Cook 2002. H-bond-directed control**

\[
\text{Ph.CO.O} + \text{NPh.H.O} \xrightarrow{\text{[allylPdCl}_2\text{(R)-BINAP}}} \text{Ph.NH.CO.N} \]


\[
\text{NH} + \text{OAc} \xrightarrow{\text{[allylPdCl}_2\text{BINAP}}} \text{NH} + \text{OAc} \]

\[
\text{XNH}_2 + \text{XOCO}_2\text{Et} \xrightarrow{\text{[allylPdCl}_2\text{Xantphos}}} \text{XNH} + \text{XOCO}_2\text{Et} \]

\(X=\text{Ph}_2\text{CN, BnO, Ph}_3\text{CO}\)
2.2 Synthesis of branched allylamines

Our group earlier found that trisubstituted allyl acetates undergo palladium-catalyzed amination with primary and secondary amines to form linear products. In cases where allylic acetates were present in excess, primary amines underwent double allylation. Later we showed that linear amines formed as a result of palladium-catalyzed acid-promoted isomerization of their kinetically-favoured branched counterparts. Together, these results inspired us to find conditions, which would allow the reaction to proceed under kinetic control, thus giving rise to branched products. Branched products are arguably more interesting since they may give rise to chiral centres next to nitrogen. We began our studies by screening for an appropriate base that would scavenge acetic acid that is being formed as a by-product (Table 2.1).

Table 2.1 Optimization of base additives in palladium-catalyzed allylic amination

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equiv</th>
<th>Time, h</th>
<th>GC Conv %</th>
<th>(b/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N</td>
<td>10</td>
<td>96</td>
<td>50</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N</td>
<td>5</td>
<td>96</td>
<td>50</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃</td>
<td>2</td>
<td>24</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DABCO</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>2:1</td>
</tr>
<tr>
<td>7</td>
<td>N-Methylmorpholine</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>1:3</td>
</tr>
<tr>
<td>8</td>
<td>TMEDA</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>2:1</td>
</tr>
<tr>
<td>9</td>
<td>Amberlyst</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>1:1</td>
</tr>
<tr>
<td>10</td>
<td>¹BuOK</td>
<td>1</td>
<td>24</td>
<td>15</td>
<td>2:1</td>
</tr>
<tr>
<td>11</td>
<td>DBU</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>19:1</td>
</tr>
<tr>
<td>12</td>
<td>DBN</td>
<td>1</td>
<td>24</td>
<td>91</td>
<td>19:1</td>
</tr>
<tr>
<td>13</td>
<td>Phosphazene base P₅⁻²Bu-tris- (tetramethylene)</td>
<td>1</td>
<td>24</td>
<td>100</td>
<td>19:1</td>
</tr>
</tbody>
</table>
At the outset, we noted that during allylation of piperidine one equivalent of the amine acted as a base, giving piperidinium acetate salt precipitate and the corresponding branched allylated product with a 4:1 selectivity. Starting with an equimolar mixture of 1,2,3,4-tetrahydroisoquinoline (1a) and prenyl acetate gave full conversion to the corresponding linear allylamine as the only product (Table 2.1, entry 1), which indicates that the presence of base in solution is critical to achieving high branched selectivity. 7b With 2 equivalents of 1a, the corresponding linear product was formed exclusively (Table 2.1, entry 18), whereas 2,6-di-‘butylpyridine, a commonly used proton scavenger,13 gave a very low conversion (Table 2.1, entry 19). We carried out an extensive search for base additives that could lead to high branched selectivity with amine nucleophiles without concomitant base allylation. Pyridine and Hünig’s base (Table 2.1, entries 14 and 15) had almost no effect on the reaction giving the linear product, whereas other bases such as triethylamine, DABCO, and TMEDA (Table 2.1, entries 2-4, 6, 8) gave the branched product with a low 2:1 selectivity even when a tenfold excess of base was used. The reactions with stronger bases such as potassium t-butoxide and NaH (Table 2.1, entries 10 and 16) produced very little allyl amine product because these bases reacted with the acetate. Finally, DBU (Table 2.1, entry 11) was found to give the branched product with a 19:1 selectivity. DBU has a $pK_{dH}$ of 16.6 in THF, which is substantially higher than that of other organic bases 14 such as triethylamine ($pK_{dH}$ 12.5). DBN and P$_{1}$-‘Bu-tris-(tetramethylene)phosphazine (Table 2.1, entries 12 and 13) showed the same selectivity for the branched product as did DBU, although with DBN the reaction took longer to reach completion, whereas with P$_{1}$-‘Bu-tris-(tetramethylene)phosphazine the reaction was not as clean, probably due to the decomposition of this base. Optimal conditions were developed using 1a (1 equiv) and
prenyl acetate (1 equiv). Full conversion was reached after 17 hours using 1 mol % of \([\eta^3\text{-allyl}]\text{PdCl}_2\) as the source of palladium, 4 mol % of P(OEt)_3 as the ligand, and 1 equiv. DBU as the base (Table 2.1 entry 18). Interestingly, when the branched product 3aa, prepared by an alternative approach, was subjected to the reaction conditions shown on Scheme 2.3, full isomerization to the corresponding linear product occurred. This suggests that DBU suppresses the isomerization, rather than changes the selectivity of the reaction.

**Scheme 2.3** Palladium-catalyzed acid promoted isomerization

We then proceeded with the optimization of solvents. Interestingly, our system was found to exhibit a strong solvent effect.\(^{15}\) Table 2.2 shows that the branched products are favoured in THF, whereas the selectivity drops substantially in less polar solvents such as dichloromethane. While 2-methyl THF (Table 2.2, entry 3) was found to provide identical selectivity to the reaction in THF, 2,5-dimethyl THF (Table 2.2, entry 4) showed a decrease in the b/l selectivity. The reaction in less polar THP displayed a preference for the branched product,\(^{16}\) albeit with lower selectivity (Table 2.2, entry 5).

**Table 2.2** Solvent optimization in palladium-catalyzed allylic amination

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>b/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)Cl(_2)</td>
<td>1:1</td>
</tr>
<tr>
<td>3</td>
<td>2-methyl THF</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>2,5-dimethyl THF</td>
<td>78:22</td>
</tr>
</tbody>
</table>
Table 2.3 shows the scope of reactivity of secondary as well as primary amines with prenyl acetate. Interestingly, primary amines exhibited no overallylation in the presence of DBU. This is contrary to what happens in the absence of DBU. For example, with no DBU added, the allylation of benzylamine in the presence of 2 equiv. of prenyl acetate gave the linear bis-allylated product, whereas, with DBU present, only the monoallylated branched product 3ad (Table 2.3, entry 4) was observed even when a twofold excess of prenyl acetate was used (Scheme 2.2). Most other amines showed high regioselectivity in the presence of DBU, except for aniline (Table 2.3, entry 6). It should also be noted that the reaction was found to tolerate the presence of such reactive functional groups as aryl bromide (Table 2.3, entry 15) and sulfur-containing heterocycles (Table 2.3, entry 10).

**Table 2.3** Allylic amination substrate scope with prenyl acetate

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>product</th>
<th>%yield (b/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="1a" /></td>
<td><img src="image" alt="3aa" /></td>
<td>92 (19:1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="1b" /></td>
<td><img src="image" alt="3ab" /></td>
<td>80 (99:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="1c" /></td>
<td><img src="image" alt="3ac" /></td>
<td>81b (19:1)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="1d" /></td>
<td>3ad</td>
<td>90 (9:1)</td>
</tr>
</tbody>
</table>
The reaction was carried out at 50°C.

Scheme 2.4 Pd-catalyzed allylic amination outcomes with and without DBU

We opted to examine the reasons for the lack of overallylation. It transpired that substituents next to the nitrogen center had a profound effect on the reaction outcome. Thus, sterically congested cis-2,6-dimethyl piperidine 11 (Table 2.3, entry 12) showed no conversion even at elevated temperatures. Neither was any conversion observed when the branched allyl amine 3ae (Table 2.3, entry 16) was re-subjected to the reaction conditions in the presence of DBU. The fact that without DBU primary amines can produce bis-allylated linear products such as 3ad', while amines with substituents next to nitrogen are completely unreactive, suggests that the kinetic branched product has to undergo isomerization before another allylation can occur (Scheme 2.4). When the monoallylated branched product cannot isomerize, it is too hindered to react with another molecule of prenyl acetate leading to the monosubstituted branched product (Scheme 2.5).

Scheme 2.5 Rationale for the lack of overallylation of primary amines

aisolated yields, b/l obtained by GC. bThe reaction was carried out at 50°C.
Switching to more electron-poor amines such as the ones shown in Scheme 2.6 resulted in full recovery of prenyl acetate even at 50°C. Surprisingly, amine 1q gave no conversion. It is possible that the close proximity of the amino and hydroxyl group may have resulted in chelation to palladium, thus diminishing its reactivity.

**Scheme 2.6** Nucleophiles that did not react with prenyl acetate

![Scheme 2.6 Nucleophiles](image)

We later decided to explore the reactivity of allyl carbonates. Allyl enol carbonates were previously explored by Stoltz\(^{17}\) and Trost\(^{18}\) towards allylation of ketone enolates. The formation of stable palladium enolates took place upon extrusion of CO\(_2\) from the carbonate (Scheme 2.7). The formation of CO\(_2\) and palladium enolate is the driving force for the decarboxylation step. When we replaced prenyl acetate with the corresponding carbonate 2a\(^*\) there was no change in selectivity for the branched product. Similarly, when no DBU was used, only the linear product was observed. This result suggests that ethyl carbonic acid that forms as an intermediate does not decompose into ethanol and carbon dioxide, but rather remains in solution long enough to promote product ionization and the b/l isomerization in the absence of DBU (Scheme 2.8). If ethyl carbonic acid did form ethanol in situ, such isomerization would have been unlikely, due to the fact that the \(pK_a\) value for ethanol is 12 units higher than that of ethyl carbonic acid.
**Scheme 2.7** Decarboxylative allylic alkylation

```
\begin{align*}
\text{O} \quad \text{O} \\
\text{LnPd}^2 \quad \text{CO}_2
\end{align*}
```

**Scheme 2.8** Rationale behind the reaction outcome with allyl carbonate

```
\begin{align*}
\text{O} \quad \text{O} \\
\text{PdL}_2 \\
\text{EtO}^- + \text{CO}_2
\end{align*}
```

We then decided to broaden the scope of the reaction by varying the nature of allylic acetate. While we were able to control regioselectivity with prenyl acetate, achieving high levels of selectivity with disubstituted substrates was not as straightforward. The reaction outcome strongly depended on the nature of the ligand and the acetate. When hex-2-enylacetate 2d was reacted with amine 1a in the presence of P(OEt)₃, a 1:4 b/l ratio was detected. In contrast, with prenyl acetate 2a, P(OEt)₃ afforded 19:1 branched selectivity. In order to test whether the inferior selectivity with the disubstituted substrate was kinetic in origin, we monitored the reaction progress using GC. The b/l ratio of 1:4 remained constant throughout the experiment, which rules out any possibility of isomerization. This finding suggests that the presence of DBU is necessary to prevent isomerization, whereas a ligand provides additional control over the initial amine attack on the allyl unit derived from a disubstituted allylic acetate.
Replacing triethyl phosphite with other ligands showed a strong variation in selectivity (Table 2.4). The bidentate ligands such as (±)BINAP, dpff, and (S,S)-DIOP (Table 2.4, entries 4,8,9) gave the linear product almost exclusively. The highest selectivity for the branched product was obtained with (o-biphenyl)dicyclohexyl phosphine and tri-tert-butylphosphine (Table 2.4, entries 5,12). The former one was chosen since it resulted in a faster reaction and was easier to handle. Buchwald and co-workers pioneered the utility of this ligand in borylation, silylation, amination, Suzuki cross-coupling of aryl halides, as well as indole and ketone arylation.

Table 2.4 Ligand optimization in allylic amination of disubstituted acetates

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>% conversion</th>
<th>b/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(OEt)_3</td>
<td>100</td>
<td>1:4</td>
</tr>
<tr>
<td>2</td>
<td>P(OEt)_3</td>
<td>100</td>
<td>0:1^a</td>
</tr>
<tr>
<td>3</td>
<td>(t-Bu)_2 P(o-Biphenyl)</td>
<td>100</td>
<td>1:6</td>
</tr>
<tr>
<td>4</td>
<td>(rac-BINAP)</td>
<td>100</td>
<td>1:32</td>
</tr>
<tr>
<td>5</td>
<td>Cy2P(o-biphenyl)</td>
<td>80 (2 days)</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>CyPPh_2</td>
<td>100</td>
<td>1:3</td>
</tr>
<tr>
<td>7</td>
<td>Ph_3P(Ph-oxazoline)</td>
<td>100</td>
<td>1:19</td>
</tr>
<tr>
<td>8</td>
<td>dpff</td>
<td>100</td>
<td>1:19</td>
</tr>
<tr>
<td>9</td>
<td>(S,S)-DIOP</td>
<td>100</td>
<td>4:96</td>
</tr>
<tr>
<td>10</td>
<td>Xantphos</td>
<td>100</td>
<td>4:96</td>
</tr>
<tr>
<td>11</td>
<td>dppp</td>
<td>100</td>
<td>1:24</td>
</tr>
<tr>
<td>12</td>
<td>P(t-Bu)_3</td>
<td>40 (2 days)</td>
<td>2:1</td>
</tr>
<tr>
<td>13</td>
<td>P(OPh)_3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>PPh_3</td>
<td>100</td>
<td>1:3</td>
</tr>
<tr>
<td>15</td>
<td>Pd(PPh_3)_4</td>
<td>100</td>
<td>1:4</td>
</tr>
<tr>
<td>16</td>
<td>PCy_3</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
The reactions with *trans*-hex-2-enylacetate 2d were very slow, and therefore crotyl acetate 2b was used instead. (*o*-Biphenyl)dicyclohexyl phosphine significantly improved the selectivity, giving greater than 13:1 b/l ratio for this challenging allyl acetate (Table 2.5 entry 1). Triethylphosphite, the ligand of choice for the trisubstituted substrates, gave inferior 6:1 b/l selectivity with 2c. Table 2.5 shows the substrate scope with *trans*-disubstituted allyl acetates.

When the methyl group on the crotyl substituent was replaced with ethyl group, the selectivity dropped to 6:1 (Table 2.5, entry 2). Finally, when the phenyl substituent was introduced, the linear product predominated with a 2.6:1 selectivity (Table 2.5, entry 4). These results follow a trend, where a more electron-rich terminus of the allyl unit is attacked when R₃ is a methyl group. However, as R₃ becomes larger the approach to that terminus becomes progressively more hindered, until a critical point is reached with R₃ being phenyl, when steric effects override electronic ones, and the nucleophile attacks the less-substituted terminus. In the case of cinnamyl acetate 2e, approach at the more substituted terminus also costs more energy due to the disruption of the conjugated system.

**Table 2.5** Substrate scope with trans-disubstituted allyl acetates

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>acetate</th>
<th>product</th>
<th>%yield (b/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="1a" /></td>
<td><img src="image2" alt="2b" /></td>
<td><img src="image3" alt="3ba" /></td>
<td>82 (13:1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1" alt="1a" /></td>
<td><img src="image4" alt="2c" /></td>
<td><img src="image5" alt="3ca" /></td>
<td>83 (6:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1" alt="1a" /></td>
<td><img src="image6" alt="2d" /></td>
<td><img src="image7" alt="3da" /></td>
<td>80 (2:1)</td>
</tr>
</tbody>
</table>

34
Finally, the reactivity of benzylic acetates as well as their heterocyclic analogues has been investigated. Hartwig and coworkers reported that the attack of aniline on the palladium-π-allyl complex derived from benzylic acetate (Scheme 2.9) occurs faster than the attack on the unsubstituted allylic complex. They suggested that the reason for such difference is a larger positive charge on the benzylic terminus comparing to the allylic one.

**Scheme 2.9** Hartwig’s stoichiometric study of aniline attack on benzylic π-allyl Pd complex

![Scheme 2.9](image)

We were interested in whether it would be possible to attain branched selectivity using our reaction conditions. To test this we have prepared different acetates and subjected them to the reaction conditions (Scheme 2.10).
**Scheme 2.10** Attempted allylic amination using benzylic acetates and their analogues.

Scheme 2.10

\[
\begin{align*}
\text{Scheme 2.10} & \quad \text{Attempted allylic amination using benzylic acetates and their analogues.} \\
& \quad \text{Catalyst: } [(\text{allyl})\text{PdCl}]_2 \text{CpPd(allyl)} \\
& \quad \text{Ligand: } \text{P(OEt)}_3 \text{BINAP} \\
& \quad \text{Solvent: } \text{THF, CH}_2\text{Cl}_2 \\
& \quad \text{Ar} = \begin{array}{c}
\text{2f} \\
\text{2g} \\
\text{2h} \\
\text{2i} \\
\text{2j}
\end{array}
\end{align*}
\]

Unfortunately, none of the acetates shown above gave an allylation product with any permutation of catalysts, ligands, or solvents. The only products that were obtained in addition to the recovered starting amine and acetate, were the acetyl 1,2,3,4-tetrahydroisoquinoline, that formed through a background trans-amidation reaction with the acetate, as well as a small amount of N-allyl-1,2,3,4-tetrahydroisoquinoline that resulted from the corresponding N-H amine reacting with the catalyst. The reaction proceeded to full conversion to give the acylated starting amine as the only product when benzyl acetate was replaced with benzyl trifluoroacetate. Upon taking a closer look at acetates in **Scheme 2.10**, we began to suspect that the reaction was failing possibly due to the inability of these acetates to coordinate to palladium(0) species. Such coordination is beneficial as it lowers the activation barrier for the ionization step. To test if this hypothesis were true, we have designed a substrate that carried a vinyl group in the position ortho to the acetoxyethyl 2k (**Scheme 2.11**).
Subjecting acetate 2k to the same reaction also did not result in the formation of the allylic amination product. This finding suggests that even though benzylic palladium π-allyl complex reacts much faster with nucleophiles compared to the unsubstituted π-allyl palladium complex, the activation barrier to the formation of the former is still higher. The presence of an olefin handle in the 2k is not sufficient to allow palladium to interact well with the σ*-orbital of the C – O bond.

2.3 Mechanistic investigations

We have achieved control over regioselectivity in palladium-catalyzed allylic amination by suppressing the proton-assisted b/l isomerization. Optimization of the reaction conditions has led to the formation of branched allyl amines with high selectivities, and gave some insight into the reaction mechanism. Solvent is an important parameter that influences the regioselectivity of this process. As can be seen from Table 2.2, the formation of the branched product is kinetically favoured in THF, whereas in other solvents lower or no selectivity was observed. To explain the formation of both branched and linear products, the involvement of two different intermediates would be necessary. π-Complexes are known to be in equilibrium with the σ-isomers,\(^{21}\) and the extent of this equilibrium depends on the nature of the metal, ligand, solvent, and counteranion (Scheme 2.13).\(^{22}\) Earlier, we showed that σ-complexes were the only species observed by NMR in THF-\(d_8\) (Scheme 2.12).\(^{11a}\) This observation combined with the fact that high branched selectivity is only observed in THF led us to suspect that the absence of palladium π-allyl
intermediate in THF was the only reason behind the high branched selectivity. Later, however, we observed σ-complex formation in other solvents, such as dichloromethane, in which there is no kinetic branched selectivity at all. This finding suggests that even though the σ-complex is the more abundant of the two allyl-palladium intermediates in solution, its reactivity strongly depends on the nature of the solvent. The 1:1 selectivity in dichloromethane is the result of equal reactivity of σ- and π-complexes.

Scheme 2.12 Reaction of [(prenyl)PdCl]₂ with PPh₃

![Scheme 2.12](image)

It is not clear whether THF can activate the catalytically relevant σ-complex by coordinating to it, and thus acting as a ligand. Such behavior would certainly explain the selectivity trend in other ethereal solvents. When THF was replaced by 2,5-dimethylmethyl-THF, the THF oxygen becomes less nucleophilic (Table 2.2, entry 4), and the kinetic selectivity for the branched product dropped. Similar result was observed with the less-coordinating THP. To test this hypothesis we monitored branched selectivity in THF/CH₂Cl₂ mixtures of different composition. We have found that in the presence of triethyl phosphite, it takes as little as 10% THF in solution to maintain branched selectivity of 9:1. On the other hand, with BINAP, almost 90% THF is required in order to favour the branched product. With a ligand acting as a switch, the reaction could have a different sensitivity towards THF (Fig 2.1).
This result supports the notion that THF is able to compete with triethylphosphite favouring the formation of the $\sigma$-complex and giving rise to branched selectivity. On the other hand, it is much more difficult for THF to compete with bidentate ligands such as BINAP. The fact that THF cannot be used in substoichiometric quantities to dictate the selectivity does not necessarily revoke the coordination of THF to palladium. Such large amounts of THF may be needed due to the fact that compared to phosphines, acetate, or chloride, THF is a very weak ligand, and high concentrations of it are required to make it competitive in terms of binding. However, at this point it becomes difficult to define whether the effect of THF is molecular or that of the solvent bulk.

The next aspect that interested us was the origin of branched selectivity. Amine attack on intermediate A should yield the linear product because the less substituted terminus is more favoured for the attack based on steric considerations. On the other hand, intermediate B is susceptible to a nucleophilic attack proceeding in an $S_N2'$ fashion at the more substituted terminus, which would lead to the branched allyl amine (Scheme 2.13).
This hypothesis is in accordance with the observation that the branched product forms first followed by the amine dissociation giving rise to the \(\pi\)-complex A, attack on which results in the formation of the linear product. If the \(\pi\)-complex A was the only active species in solution, then in order for the branched product to be kinetic, this intermediate would have to be attacked at the more substituted position. Once the branched product forms, it would ionize and reform the \(\pi\)-complex A in the presence of an acid, which now, in order to form the linear product, would have to be attacked at the less substituted terminus.\(^4\) However, if the attack at the less substituted terminus is proceeding faster, then the more substituted terminus cannot be attacked first. The observed selectivity is consistent with intermediate B which, unlike the \(\pi\)-complex A, is attacked at the more substituted terminus and therefore gives rise to the branched product.\(^23\)

Testing our system for the presence of the memory effect has revealed some unexpected results. When acetate 2a was replaced with its isomer 2l, no change in selectivity took place. When the reaction was monitored by GC, the formation of the acetate 2a was observed (Scheme 2.14). More significantly, when no amine was added, acetate 2l was found to isomerize into prenyl acetate 2a, which again suggests that the initial attack on an allyl acetate proceeded through the palladium \(\pi\)-allyl complex, which later isomerized into the \(\sigma\)-intermediate. It is interesting to note that acetate isomerization proceeds only in the presence of DBU. We therefore hypothesized that DBU may have initiated elimination, after which the resulting isoprene would undergo palladium-catalyzed hydroamination (Scheme 2.15). However, when prenyl acetate was replaced with isoprene and subjected to the reaction conditions in the presence or absence of DBU, no
allyl amine product was formed, which is not consistent with hydroamination happening under these conditions. A potential involvement of DBU in an uncatalyzed reaction with allyl acetate has also been ruled out.

**Scheme 2.14** Identical reactivity of branched and linear allyl acetates.

In addition, when the deuterated allyl acetate was used, our system showed deuterium scrambling in the product (Scheme 2.16).\(^{24}\) This observation is indicative of the absence of a memory effect that is known to occur with carbon-based nucleophiles.\(^ {25} \) The absence of the memory effect always suggests that there is a common intermediate, which is consistent with the presence of a symmetrical \( \pi \)-complex. This result again supports the hypothesis that the \( \pi \)-complex forms first, and then later may isomerize to form the corresponding \( \sigma \)-complex.

**Scheme 2.15** A test for the hydroamination mechanism.

In addition, when the deuterated allyl acetate was used, our system showed deuterium scrambling in the product (Scheme 2.16).\(^ {24} \) This observation is indicative of the absence of a memory effect that is known to occur with carbon-based nucleophiles.\(^ {25} \) The absence of the memory effect always suggests that there is a common intermediate, which is consistent with the presence of a symmetrical \( \pi \)-complex. This result again supports the hypothesis that the \( \pi \)-complex forms first, and then later may isomerize to form the corresponding \( \sigma \)-complex.

**Scheme 2.16** Test for memory effects.
2.4 Conclusions and Outlook

Controlling regioselectivity in palladium-catalyzed allylic amination is a long-standing problem that has not found a general solution, despite the years of study. Based on the finding that linear selectivity is thermodynamically preferred in nature and results from acid-promoted, palladium-catalyzed isomerization, we have discovered that DBU is sufficiently strong base to suppress the effective build-up of acid, therefore keeping the reaction under the kinetic control, allowing the branched regioisomer to be the only product in the reaction. The reaction is very regioselective for allylic acetates carrying methyl groups, however, is much less efficient with larger substituents. In addition, this reaction is not enantioselective at this stage, as all the chiral bidentate ligands kinetically favour the linear isomer.

2.5 Experimental details

2.5.1 General aspects

**General.** Anhydrous acetonitrile, dichloromethane, diethyl ether, and toluene were obtained using the method described by Grubbs. Tetrahydrofuran (THF) was distilled from sodium benzophenone under argon. Acetone was stored over 4Å molecular sieves.

**Chromatography.** Column chromatography was carried out using Silicycle 230-400 mesh silica gel or aluminum oxide, neutral, Brockman type 1. Analytical thin layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass-backed TLC plates (SIL G/UV254, 0.25 mm) and visualized by UV lamp (254 nm), iodine and potassium permanganate stains. Gas-phase chromatography (GC) was performed on a Hewlett Packard HP-6890 series instrument using an HP-5 column (crosslinked 5% phenyl methyl siloxane, 30 m x 0.32 mm x 0.25 µm film thickness). Oven was heated at 50°C for 5 min followed by a temperature gradient of 10°C/min.
to 250°C followed by being held at 250°C for 10 min. Inlet temperature and pressure were 200°C and 4.88 psi respectively, with a split ratio of 50:1. Hydrogen was the carrier gas. Internal standard was biphenyl (T = 15.6 min).

**Nuclear magnetic resonance spectra.** $^1$H and $^{13}$C spectra were recorded on a Varian Mercury 300, VRX-S (Unity) 400 or Unity 500 spectrometer. $^1$H NMR spectra were referenced to TMS (0 ppm) and $^{13}$C NMR spectra were referenced to CDCl$_3$ (77.23 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; td, triplet of doublets; br, broad; and $J$, coupling constant in Hz.

### 2.5.2 Preparation of Allylic Acetates and Carbonates

In a flame-dried, 250 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed allylic alcohol (98.4 mmol), triethylamine (35 mL, 250 mmol), and dry dichloromethane (75 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.60 g, 4.92 mmol) was added. The flask was cooled in an ice bath and acetic anhydride (23.5 mL, 250 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight, when GC analysis showed no remaining starting material. The reaction mixture was washed with saturated NaHCO$_3$ (2 x 100 mL). The combined organic fractions were then washed with brine (100 mL) and dried over Na$_2$SO$_4$. Solvent was removed in vacuo and crude product was obtained as slightly yellow oil, which was subjected to Kugelrohr distillation to yield the corresponding allylic acetate as a clear oil.
**Prenyl acetate (2a)**

GC retention time of 2a: T = 6.7 min. Yield = 88%. $^1$H NMR (CDCl$_3$, 300 MHz): δ 5.35 (t, $J = 6.3$ Hz, 1H), 4.57 (d, $J = 6.3$ Hz, 2H), 2.05 (s, 3H), 1.76 (s, 3H), 1.71 (s, 3H).

![2b]

**Crotyl acetate (a mixture of trans and cis) (2b)**

GC retention time of 2b: T = 3.65 min. Yield = 63%. $^1$H NMR (CDCl$_3$, 300 MHz): δ 5.86-5.72 (m, 1H), 5.65-5.54 (m, 1H), 4.50 (d, $J = 6.3$ Hz, 2H), 2.06 (s, 3H), 1.72 (d, $J = 7.9$ Hz, 3H).

![2d]

**(E)-hex-2-enyl acetate (2d)**

GC retention time of 2d: T = 8.8 min. Yield = 88%. $^1$H NMR (CDCl$_3$, 400 MHz): δ 5.81-5.72 (m, 1H), δ 5.61-5.53 (m, 1H), 4.51 (d, $J = 6.5$ Hz, 2H), 2.06 (s, 3H), 2.04 (q, $J = 6.4$ Hz, 2H), 1.46-1.37 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H).

![2c]

**(E)-pent-2-enyl acetate (2c)**

GC retention time of 2c: T = 6.5 min. Yield = 51%. $^1$H NMR (CDCl$_3$, 300 MHz): δ 5.89-5.78 (m, 1H), 5.56 (dt, $J = 15.3$, 6.5 Hz, 1H), 4.5 (d, 6.5 Hz, 2H), 2.11-2.04 (m, 2H), 2.06 (s, 3H), 1.01 (t, $J = 7.5$ Hz, 3H).
2-methylbut-3-en-2-yl acetate (2l)\(^{31}\)

GC retention time of 2l: T =3.2 min. Yield = 23%. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 6.06 (dd, \(J =17.5, 10.9\) Hz, 1H), 5.17 (d, \(J =17.5\) Hz, 1H), 5.07 (d, \(J =10.9\) Hz, 1H), 1.99 (s, 3H), 1.52 (s, 6H).

eethyl 3-methylbut-2-enyl carbonate (2a\(\prime\))\(^{32}\)

GC retention time of 2a\(\prime\): T =10.6 min. Yield = 55%. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.38 (t, \(J =7.3\) Hz, 1H), 4.62 (d, \(J =7.3\) Hz, 2H), 4.19 (q, \(J =7.1\) Hz, 2H), 1.76 (s, 3H), 1.73 (s, 3H), 1.30 (q, \(J =7.1\) Hz, 3H).

cinnamyl acetate (2e)\(^{33}\)

In a flame-dried, 250 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed cinnamyl alcohol (6.3 mL, 49.2 mmol), triethylamine (16.5 mL, 125 mmol) and dry dichloromethane (84 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.30 g, 2.46 mmol) was added. The flask was cooled in an ice bath and acetic anhydride (11.8 mL, 125 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO\(_3\) (2 x 200 mL). The combined organic fractions were then washed with brine (100 mL) and dried (Na\(_2\)SO\(_4\)). Solvent was removed in
vacuo and the residue was purified by flash chromatography (Rf = 0.57, SiO₂, 9:1 hexanes/ethyl acetate) to yield 2e (8.67 g, 37.4 mmol, 76%) as a clear liquid.

\(^1\)H NMR (CDCl₃, 300 MHz): δ 7.41-7.26 (m, 5H), 6.60 (d, J = 15.9 Hz, 1H), 6.29 (dt, J = 15.9, 6.4 Hz, 1H), 4.73 (d, J = 6.4 Hz, 2H), 2.10 (s, 3H).

\[
\text{benzyl acetate (2f)}^{34}
\]

GC retention time of 2f: T = 11.9 min. Yield = 88%. \(^1\)H NMR (CDCl₃, 400 MHz): δ 7.45 – 7.14 (m, 5H), 5.10 (s, 2H), 2.10 (s, 3H).

\[
\text{furan-2-ylmethyl acetate (2g)}^{35}
\]

In a flame-dried, 250 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed furan-2-ylmethanol (4.3 mL, 49.2 mmol), triethylamine (23 mL, 175 mmol) and dry dichloromethane (50 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.30 g, 2.46 mmol) was added. The flask was cooled in an ice bath and acetic anhydride (17 mL, 175 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO₃ (2 x 200 mL). The combined organic fractions were then washed with brine (100 mL) and dried (Na₂SO₄). Solvent was removed \textit{in vacuo} and the residue was purified by flash chromatography (Rf = 0.56, SiO₂, 4:1 hexanes/ethyl acetate) to yield 2g (5.29 g 77%) as a clear liquid.
$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.42 (dd, $J = 1.8$, 0.8 Hz, 1H), 6.40 (s, 1H), 6.37 (d, $J = 1.8$ Hz, 1H), 5.06 (s, 2H), 2.08 (s, 3H). $^{13}$C-NMR ($CDCl_3$, 100 MHz): $\delta$ 170.8, 149.6, 143.4, 110.7, 58.2, 21.0.

![thiophen-2-ylmethyl acetate (2h)](image)

**thiophen-2-ylmethyl acetate (2h).**$^{36}$

In a flame-dried, 100 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed thiophen-2-ylmethanol (24.6 mmol, 2.3mL), triethylamine (11.7 mL, 88 mmol), and dry dichloromethane (25 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.60 g, 4.92 mmol) was added. The flask was cooled in an ice bath and acetic anhydride (8.3 mL, 88 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO$_3$ (2 x 100 mL). The combined organic fractions were then washed with brine (100 mL) and dried over Na$_2$SO$_4$. Solvent was removed *in vacuo* and crude product was obtained as slightly yellow oil, which was subjected to Kugelrohr distillation to yield the corresponding acetate $2h$ as clear oil in 90% yield.

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.31 (dd, $J = 5.1$, 1.2 Hz, 1H), 7.12 – 7.04 (m, 1H), 6.98 (dd, $J = 5.1$, 3.5 Hz, 1H), 5.25 (s, 2H), 2.08 (s, 3H).

![thiophen-3-ylmethyl acetate (2i)](image)

**thiophen-3-ylmethyl acetate (2i).**$^{37}$

In a flame-dried, 100 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed thiophen-2-ylmethanol (24.6 mmol, 2.3mL), triethylamine (11.7 mL, 88 mmol), and dry dichloromethane (25 mL) via syringe. The resulting solution was stirred under nitrogen at room
temperature for 30 min, after which DMAP (0.60 g, 4.92 mmol) was added. The flask was cooled in an ice bath and acetic anhydride (8.3 mL, 88 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO$_3$ (2 x 100 mL). The combined organic fractions were then washed with brine (100 mL) and dried over Na$_2$SO$_4$. Solvent was removed in vacuo and crude product was obtained as slightly yellow oil, which was subjected to Kugelrohr distillation to yield the corresponding acetate 2h as clear oil in 85% yield.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41 – 7.22 (m, 2H), 7.09 (dd, $J$ = 4.7, 1.6 Hz, 1H), 5.11 (s, 2H), 2.08 (s, 3H).

\[
\text{pyridin-3-ylmethyl pivalate (2j).} \quad 38
\]

In a flame-dried, 50 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed pyridin-3-ylmethanol (19.6 mmol, 1.9 mL), triethylamine (6.6 mL, 50 mmol), and dry diethyl ether (15 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which the flask was cooled in an ice bath and pivalyl chloride (6.1 mL, 50 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO$_3$ (2 x 100 mL). The combined organic fractions were then washed with brine (100 mL) and dried over Na$_2$SO$_4$. Solvent was removed in vacuo and crude product was obtained as slightly yellow oil in 13% yield.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.83 – 8.62 (m, 2H), 8.29 (d, $J$ = 7.8 Hz, 1H), 7.97 – 7.77 (m, 1H), 5.26 (s, 2H), 1.25 (s, 9H).
1,1-dideuteroallyl alcohol (2n).\textsuperscript{39}

In a flame-dried, 100 mL one-neck round bottom flask, equipped with septum and magnetic stir bar was placed LiAlH\textsubscript{4} (1.0 g, 23.8 mmol) and 50 mL of anhydrous ether. The solution was cooled down to -8\textdegree{}C and acryloyl chloride was added dropwise, and the reaction was allowed to stir for 4 hours. After that the reaction was quenched with 1.3 mL of water, NaOH (1.3 mL, 4 N), and 1.3 mL of water, extracted with ether, and dried over sodium sulfate. The crude solution was concentrated and distilled on Kugehlrohr at room temperature at 0.9 mm Hg to yield 1,1-dideuteroallyl alcohol 2n (1.14 g, 19 mmol, 80\%) as a clear liquid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \textdelta{}5.99 (dd, \textit{J} =17.2, 10.4 Hz, 1H), 5.28 (dd, \textit{J} =17.2, 1.4 Hz, 1H), 5.15 (dd, \textit{J} =10.4, 1.5 Hz, 1H), 2.26 (s, 1H).

1,1 -dideuteroallyl acetate (2m).\textsuperscript{40}

In a flame-dried, 50 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed 2,2-dideuteroallyl alcohol 2n (1.21 g, 20.13 mmol), triethylamine (6.68 mL, 50.32 mmol) and dry dichloromethane (20 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.125 g, 1.02 mmol) was added. The flask was cooled in an ice bath and acetic anhydride (4.7 mL, 50.32 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO\textsubscript{3} (2 x 100 mL). The combined organic fractions were then washed with brine (50 mL) and dried (Na\textsubscript{2}SO\textsubscript{4}). Solution was concentrated and distilled on Kugehlrohr at room temperature at 0.9 mm Hg to yield 1,1-dideuteroallyl acetate 2m (0.551 g, 5.4 mmol, 27\%) as a clear liquid.
1H NMR (CDCl₃, 300 MHz): δ5.92 (dd, J = 17.2, 10.4 Hz, 1H),  5.32 (dd, J = 17.2, 1.5 Hz, 1H),  5.24 (dd, J = 10.4, 1.5 Hz, 1H),  2.08 (s, 1H).

(2-iodophenyl)methanol⁴¹

To a flame-dried round-bottom flask equipped with a stir bar, 2.0 g (8.06 mmol) of 2-iodobenzoic acid was added under nitrogen. The acid was dissolved in 8.0 mL of anhydrous THF. Once the reaction mixture was cooled down to -10°C, N-methylmorpholine (8.06 mmol, 0.89 mL) and isobutylchloroformate (8.06 mmol, 1.05 mL) were added to the reaction solution. White precipitate formed within 5 minutes, and was filtered out. The filtrate was cooled down to -10°C and sodium borohydride (12.1 mmol, 0.45 g) was added as a solution in 4 mL of water to the reaction solution. The reaction mixture was washed with water, and extracted with ethyl acetate. The organic layer was washed with saturated solution of sodium bicarbonate to remove the unreacted acid. The organic layer was later washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude solid was washed with hexanes and ether to give the resulting product in 82% yield.

1H NMR (CDCl₃, 400 MHz): δ 7.83 (dd, J = 7.9, 0.9 Hz, 1H),  7.45 (dd, J = 7.6, 1.5 Hz, 1H),  7.37 (td, J = 7.5, 0.9 Hz, 1H),  7.00 (td, J = 7.6, 1.8 Hz, 1H),  4.68 (s, 2H),  2.01 (s, 1H).

2-iodobenzyl acetate⁴²

In a flame-dried, 100 mL one-neck round bottom flask, equipped with a magnetic stir bar, were placed (2-iodophenyl)methanol (7.63 g, 32.6 mmol), triethylamine (8.7 g, 65.2 mmol), and dry dichloromethane (35 mL) via syringe. The resulting solution was stirred under nitrogen at room temperature for 30 min, after which DMAP (0.268 g, 2.2 mmol) was added. The flask was
cooled in an ice bath and acetic anhydride (6.2 mL, 65.2 mmol) was added dropwise via syringe. The resulting solution was stirred under a stream of nitrogen at room temperature overnight. The reaction mixture was washed with saturated NaHCO₃. The combined organic fractions were then washed with brine and dried over Na₂SO₄. Solvent was removed \textit{in vacuo} and crude product was purified on silica (hex/EtOAc = 4:1, Rₐ = 0.70) to yield 2-iodobenzyl acetate in 93% yield as a clear liquid.

\begin{align*}
1^H \text{NMR (CDCl}_3, 400 \text{ MHz)}: & \quad \delta 7.95 – 7.75 (m, 1H), 7.36 (dd, J = 8.2, 1.6 Hz, 2H), 7.09 – 6.93 (m, 1H), 5.13 (s, 3H), 2.14 (s, 3H).
\end{align*}

\begin{center}
\includegraphics[width=0.2\textwidth]{2-iodobenzyl-acetate.png}
\end{center}

\textbf{2-vinylbenzyl acetate (2k)}

To a vial equipped with a stir bar palladium tetrakis(triphenylphosphine) (0.18 mmol, 208 mg) added under nitrogen. The complex was dissolved in anhydrous DME (36 mL), and to the resulting solution 2-iodobenzyl acetate (3.6 mmol, 1.0 g) was added. The solution was allowed to stir at room temperature under nitrogen for 20 min. After that unground potassium carbonate (3.6 mmol, 0.500 g), vinyl boroxane-pyridine complex (3.6 mmol, 0.886 g) were added to the reaction solution under nitrogen, followed by the addition of water (11 mL). The reaction mixture was subjected to reflux for 40 hours. The reaction was then washed with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified on silica (hex/EtOAc = 4:1, Rₐ = 0.55) to give a light-yellow liquid \textbf{2k} in 87% yield.

\begin{align*}
1^H \text{NMR (CDCl}_3, 400 \text{ MHz)}: & \quad \delta 7.54 (d, J = 7.8 Hz, 1H), 7.43 – 7.20 (m, 3H), 6.97 (dd, J = 17.4, 11.0 Hz, 1H), 5.69 (dd, J = 17.4, 1.0 Hz, 1H), 5.36 (dd, J = 11.0, 1.0 Hz, 1H), 5.18 (s, 2H), 2.09 (s, 3H).
\end{align*}
2.5.3 Preparation of N-Allyl Amines.

2-(2-methylbut-3-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (3aa)\(^{44}\)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(\(\eta^3\)-C\(_3\)H\(_5\))Cl\(_2\)] (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt\(_3\)) (9\(\mu\)L, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.17 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3aa: \(T = 18.2\) min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo} and the residue was purified by flash chromatography (R\(f = 0.28\), SiO\(_2\), 4:1 hexanes/ethyl acetate) to yield 3aa (253 mg, 1.26 mmol, 92%) as a yellow liquid.

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 7.08-7.06\) (m, 3H), 7.02-7.00 (m, 1H), 5.95 (dd, \(J = 17.9, 10.8\) Hz, 1H), 5.11 (dd, \(J = 17.9, 1.5\) Hz, 1H), 5.08 (dd, \(J = 10.8, 1.5\) Hz, 1H), 3.76 (s, 2H), 2.84 (t, \(J = 5.6\) Hz, 2H), 2.76 (t, \(J = 5.6\) Hz, 2H), 1.23 (s, 6H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta 146.0, 135.8, 134.7, 128.6, 126.8, 125.7, 125.3, 112.4, 58.3, 49.0, 44.4, 30.4, 22.4\).

1-(2-methylbutyl-3-en-2-yl)piperidine (3ab)\(^{45}\)

In a 50 mL round bottom flask, equipped with septum and magnetic stir bar, were placed [Pd(\(\eta^3\)-C\(_3\)H\(_5\))Cl\(_2\)] (25 mg, 0.0685 mmol) and dry THF (5 mL). P(OEt\(_3\)) (61\(\mu\)L, 0.235 mmol), DBU (1.07 mL, 7.00 mmol), prenyl acetate (2a) (0.95 mL, 6.85 mmol) and piperidine (0.67 mL, 6.85
mmol) were added via syringe and the solution was stirred under argon at room temperature for 20h; when GC analysis showed no remaining prenyl acetate (2a). (GC retention time of 3ab: T = 10.0 min). Water (20 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was distilled under reduced pressure to yield 3ab (838 mg, 5.48 mmol, 80%) as a clear oil.

$$\text{H NMR (CDCl}_3, 300 \text{ MHz}: \delta 5.95 (dd, J = 17.9, 10.8 \text{ Hz}, 1H), 5.11 (dd, J = 17.9, 1.5 \text{ Hz}, 1H), 5.08 (dd, J = 10.8, 1.5 \text{ Hz}, 1H), 2.48 (t, J = 5.0 \text{ Hz} 4H), 1.61-1.51 (m, 4H), 1.43 (q, J = 5.3 \text{ Hz} 2H), 1.12 (s, 6H).}$$

$$\text{C NMR (CDCl}_3, 75 \text{ MHz}: \delta 146.8, 111.8, 58.5, 47.2, 26.8, 24.9, 22.5.}$$

$N$-(cyclopropylmethyl)-2-methylbut-3-en-2-amine (3ac)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η⁢³-C₃H₅)Cl]₂ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)₃ (9µL, 0.0547mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and cyclopropylmethaneamine (0.100 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3ac: T = 7.8 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was distilled under reduced pressure to yield 3ac (152 mg, 1.1 mmol, 81%) as a clear oil contaminated with 10 % of P(OEt)₃ that co-distills at 85 °C at 0.9 mm Hg.

$$\text{H NMR (CDCl}_3, 300 \text{ MHz}: \delta 5.75 (dd, J = 17.9, 10.8 \text{ Hz}, 1H), 5.02 (dd, J = 17.9, 1.5 \text{ Hz}, 1H), 4.97 (dd, J = 10.8, 1.5 \text{ Hz}, 1H), 2.32 (d, J = 6.7 \text{ Hz} 2H), 1.64 (s, 1H), 1.16 (s, 6H), 0.85-1.0 (m, 1H), 0.46 (ddd J = 10.0, 5.9, 4.4 \text{ Hz} 2H), 0.42-0.50 (m, 2H).}$$

$$\text{C NMR (CDCl}_3, 75 \text{ MHz}: \delta}$$
146.6, 112.2, 54.3, 48.6, 27.3, 12.2, 3.8. HRMS (ESI) [M+H]+ calcd. for C9H17N 140.1433, found 140.1441.

\[
\text{3ae}
\]

\textit{N-\textit{benzyl-2-methylbut-3-en-2-amine (3ae)}}\textsuperscript{46}

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed \([\text{Pd(\eta^3-C_3H_5)Cl]}_2\) (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)\textsubscript{3} (9\textmu L, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate \textit{2a} (0.19 mL, 1.37 mmol) and benzylamine (0.150 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 20h; when GC analysis showed no remaining prenyl acetate \textit{2a}. (GC retention time of \textit{3ae}: T = 14.4 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo} and the residue was purified by flash chromatography (R\textsubscript{f} = 0.56, SiO\textsubscript{2}, 1:1 CH\textsubscript{2}Cl\textsubscript{2}/methanol) to yield \textit{3ae} (216 mg, 1.23 mmol, 90%) as a clear oil.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 7.35-7.22 (m, 5H), 5.84 (dd, \(J = 17.9, 10.8\) Hz, 1H), 5.14 (dd, \(J = 17.9, 1.5\) Hz, 1H), 5.08 (dd, \(J = 10.8, 1.5\) Hz, 1H), 3.65 (s, 2H), 1.25 (s, 6H).

\[
\text{3af}
\]

\textit{N-(2-methylbut-3-en-2-yl)benzenamine (3af)}\textsuperscript{46}

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed \([\text{Pd(\eta^3-C_3H_5)Cl]}_2\) (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)\textsubscript{3} (9\textmu L, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate \textit{2a} (0.19 mL, 1.37 mmol) and aniline (0.130 mL,
1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3af: T = 13.7 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.41, SiO₂, 9:1 hexanes/ethyl acetate) to yield 3af (156 mg, 0.97 mmol, 71%) as a yellow oil.

\[ \text{1H NMR (CDCl₃, 400 MHz):} \delta \text{ 7.10 (dd, } J = 8.8, 7.0 \text{ Hz, 2H), 6.70-6.69 (m, 1H), 6.68 (d, } J = 7.0 \text{ Hz 2H), 6.00 (dd, } J = 17.4, 10.6 \text{ Hz, 1H), 5.20 (dd, } J = 17.4, 1.2 \text{ Hz, 1H), 5.08 (dd, } J = 10.6, 1.2 \text{ Hz, 1H), 1.38 (s, 6H).} \]

2-(but-3-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (3ba)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η³-C₃H₅)Cl]₂ (5 mg, 0.0137 mmol), (2-biphenyl)dicyclohexylphosphine (19 mg, 0.0547 mmol) and dry THF (1.3 mL). DBU (0.21 mL, 1.40 mmol), crotyl acetate 2b (0.156 g, 1.37 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.17 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 20h; when GC analysis showed no remaining crotyl acetate 2b. (GC retention time of 3ba: T = 17.1 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.41, SiO₂, 9:1 hexanes/ethyl acetate) to yield 3ba (210 mg, 1.12 mmol, 82%) as a yellow oil.

\[ \text{1H NMR (CDCl₃, 400 MHz):} \delta \text{ 7.10-7.05 (m, 3H), 7.01-6.99 (m, 1H), 5.88 (ddd, } J = 17.6, 10.4, 7.6 \text{ Hz, 1H), 5.16 (d, } J = 17.6 \text{ Hz, 1H), 5.14 (d, } J = 10.4 \text{ Hz 1H), 3.74 (d, } J = 14.8 \text{ Hz 1H), 3.68 (d, } J = 14.8 \text{ Hz 1H), 3.19-3.15 (m, 1H), 2.90-2.81 (m, 3H), 2.74-2.62 (m, 1H), 1.26 (d, } J = 6.6 \text{ Hz,} \]
$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 140.8, 134.8, 127.9, 127.1, 126.3, 125.9, 116.1, 62.8, 58.1, 47.4, 29.8, 17.6.

$^{1}H$ NMR (CDCl$_3$, 300 MHz): $\delta$ 7.32-7.30 (m, 5H), 5.73 (ddd, $J$ = 17.6, 10.3, 7.9 Hz 1H), 5.14 (d, $J$ = 17.6 Hz 1H) 5.09 (d, $J$ = 10.3 Hz 1H), 3.81 (d, $J$ = 13.0 Hz 1H), 3.69 (d, $J$ = 12.9 Hz 1H), 3.28-3.18 (m, 1H), 1.18 (d, $J$ = 6.5 Hz, 3H)

$N$-benzylbut-3-en-2-amine (3bd)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (5 mg, 0.0137 mmol), (2-biphenyl)dicyclohexylphosphine (19 mg, 0.0547 mmol) and dry THF (1.3 mL). DBU (0.21 mL, 1.40 mmol), crotyl acetate 2b (0.156 g, 1.37 mmol) and benzylamine (0.150 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 20h; when $^{1}H$ NMR showed no remaining crotyl acetate 2b. Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.41, SiO$_2$, 9:1 hexanes/ethyl acetate) to yield 3bd (184 mg, 1.15 mmol, 84%) as a yellow oil.

$^{1}H$ NMR (CDCl$_3$, 300 MHz): $\delta$ 7.32-7.30(m, 5H), 5.73 (ddd, $J$ = 17.6, 10.3, 7.9 Hz 1H), 5.14 (d, $J$ = 17.6 Hz 1H) 5.09 (d, $J$ = 10.3 Hz 1H), 3.81 (d, $J$ = 13.0 Hz 1H), 3.69 (d, $J$ = 12.9 Hz 1H), 3.28-3.18 (m, 1H), 1.18 (d, $J$ = 6.5 Hz, 3H)

$O$N

$N$-(4-methoxybenzyl)-2-methylbut-3-en-2-amine (3ae)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)$_3$ (9µL, 0.0547mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 4-
methoxybenzylamine (0.180 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50\(^\circ\)C for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3ae: T = 17.9 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo and the residue was purified by flash chromatography (R\(_f\) = 0.31, SiO\(_2\), 19:1 CH\(_2\)Cl\(_2\)/MeOH) to yield 3ae (238 mg, 1.16 mmol, 85%) as a clear oil.

\[\begin{align*}
&\text{H NMR (CDCl}_3, 300 MHz): \delta 7.25 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 5.84 (dd, J = 17.9, 10.6 Hz, 1H), 5.11 (dd, J = 5.6, 1.2 Hz, 1H), 5.08-5.06 (m, 1H), 3.78 (s, 3H), 3.57 (s, 2H), 1.23 (s, 6H). \\
&C NMR (CDCl}_3, 75 MHz): \delta 158.5, 146.1, 138.2, 129.4, 113.8, 112.2, 55.3, 54.7, 46.9, 27.0. \\
&HRMS (ESI) [M+H]^+ \text{calcd. for C}_{13}\text{H}_{19}\text{NO} 206.1539, \text{found 206.1541.}
\end{align*}\]

\[\text{O} \]

\[\text{H} \]

\[\text{N} \]

\[\text{3be} \]

\[\text{N-(4-methoxybenzyl) but-3-en-2-amine (3be)}^{49} \]

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η\(^3\)-C\(_3\)H\(_5\))Cl\(_2\) (5 mg, 0.0137 mmol), (2-biphenyl)dicyclohexylphosphine (19 mg, 0.0547 mmol) and dry THF (1.3 mL). DBU (0.21 mL, 1.40 mmol), crotyl acetate 2b (0.156 g, 1.37 mmol) and 4-methoxybenzylamine (0.150 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature at 50\(^\circ\)C for 20h; when GC analysis showed no remaining crotyl acetate 2b. (GC retention time of 3be: T = 17.0 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo and the residue was purified by flash chromatography (R\(_f\) = 0.40, SiO\(_2\), 19:1 CH\(_2\)Cl\(_2\)/MeOH) to yield 3be (217 mg, 1.12 mmol, 82%) as a clear oil.

\[\begin{align*}
&\text{H NMR (CDCl}_3, 300 MHz): \delta 7.22 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 5.71 (ddd, J = 17.6, 10.0, 7.6 Hz, 1H), 5.11 (dd, J = 17.6, 1.2 Hz, 1H), 5.07 (dd, J = 10.0, 1.2 Hz, 1H), 3.79 (s, 3H),
\end{align*}\]
3.77 (d, J = 12.9 Hz 1H), 3.61 (d, 12.9 Hz, 1H), 3.26-3.15 (m, 1H), 1.34 (s, 1H), 1.16 (d, J = 6.4 Hz 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 158.4, 142.5, 132.6, 129.2, 114.5, 113.6, 55.8, 55.1, 50.6, 21.6.

$\text{N}$-isopentyl-$2$-methylbut-$3$-en-$2$-amine (3ag)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed $[\text{Pd}(\eta^3$-$\text{C}_3\text{H}_5)\text{Cl}]_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)$_3$ (9µL, 0.0547mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and isoamylamine (0.160 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°С for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3ag: T = 8.5 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.21, SiO$_2$, 19:1 CH$_2$Cl$_2$/MeOH) to yield 3ag (170 mg, 1.10 mmol, 80%) as a clear oil.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 5.77 (dd, J = 17.9, 10.3 Hz, 1H), 5.05-5.03 (m, 1H), 4.99 (dd, J =5.7, 1.2 1H), 2.48 (t, J = 7.6 Hz, 2H), 1.68-1.52 (m, 1H), 1.34 (q, J = 7.3 Hz, 2H), 1.17 (s, 6H), 0.88 (d, J = 6.5 Hz, 6H) $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 145.8, 111.3, 53.8, 40.5, 39.5, 26.5, 25.8, 22.2. HRMS (ESI) [M+H]$^+$ calcd. for C$_{10}$H$_{21}$N 156.1746, found 156.1754.

$\text{N}$-(2-methylbutyl)but-$3$-en-$2$-amine (3ah)

2-methyl-$N$-(2-methylbutyl)but-$3$-en-$2$-amine (3ah)
In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η³-C₃H₅)Cl]₂ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)₃ (9 µL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 2-methylbutylamine (0.160 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20 h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3ah: T = 8.4 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.18, SiO₂, 19:1 CH₂Cl₂/MeOH) to yield 3ah (185 mg, 1.19 mmol, 87%) as a clear oil.

1H NMR (CDCl₃, 300 MHz): δ 5.77 (dd, J = 17.9, 10.3 Hz, 1H), 5.03 (dd, J = 17.9, 1.1 Hz, 1H), 4.99 (dd, J = 10.3, 1.1 Hz, 1H), 2.40 (dd, J = 11.2, 5.6 Hz, 1H), 2.24 (dd, J = 10.9, 6.8 Hz, 1H), 1.48-1.34 (m, 3H), 1.17 (s, 6H), 0.91-0.86 (m, 6H) ¹³C NMR (CDCl₃, 75 MHz): δ 146.9, 112.2, 54.6, 49.4, 36.0, 28.0, 27.4, 18.2, 11.7. HRMS (ESI) [M+H]⁺ calcd. for C₁₀H₂₁N 156.1746, found 156.1751.

N-(2-methylbutyl)but-3-en-2-amine, a mix of diastereomers (3bh)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η³-C₃H₅)Cl]₂ (5 mg, 0.0137 mmol), (2-biphenyl)dicyclohexylphospine (19 mg, 0.0547 mmol) and dry THF (1.3 mL). DBU (0.21 mL, 1.40 mmol), crotyl acetate 2b (0.156 g, 1.37 mmol) and 2-methylbutylamine (0.160 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20 h; when GC analysis showed no remaining crotyl acetate 2b. (GC retention time of 3bh: T = 8.5 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.18, SiO₂, 19:1 CH₂Cl₂/MeOH) to yield 3bh (157 mg, 1.1 mmol, 81%) as a clear oil.
$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 5.69 (ddd, $J = 17.6$, 10.3, 2.6 Hz, 1H), 5.09 (dm, $J = 17.3$, 1H), 5.03 (dm, $J = 10.3$ Hz, 1H), 3.19-3.10 (m, 1H), 2.50 (ddd, $J = 17.6$, 11.4, 6.2 Hz, 1H), 2.33 (ddd, $J = 17.6$, 11.4, 6.2 Hz, 1H), 1.57-1.35 (m, 3H), 1.16 (d, $J = 6.5$ Hz, 3H), 0.92-0.85 (m, 6H) $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 142.4, 113.8, 56.4, 56.3, 53.1, 34.5, 34.4, 27.2, 27.0, 21.3, 21.2, 17.3, 10.9, 10.8. HRMS (ESI) [M+H]$^+$ calcd. for C$_9$H$_{19}$N 142.1590, found 142.1593.

![Image of 3ai](image_url)

$N$-(2,2-dimethoxyethyl)-2-methylbut-3-en-2-amine (3ai).

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)$_3$ (9µL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 2,2-dimethoxyethanamine (0.150 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20h; when GC analysis showed no remaining prenyl acetate 2a (GC retention time of 3ai: T = 10.7 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.21, SiO$_2$, 19:1 CH$_2$Cl$_2$/MeOH) to yield 3ai (185 mg, 1.19 mmol, 87%) as a clear oil.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 5.76 (dd, $J = 17.9$, 10.6 Hz, 1H), 5.06 (dd, $J = 16.4$, 1.1 Hz, 1H), 5.00 (dd, $J = 10.6$, 1.1 Hz, 1H), 4.40 (t, $J = 5.6$ Hz, 1H), 3.37 (s, 6H), 2.61 (d, $J = 5.6$ Hz, 2H), 1.35 (s, 1H), 1.17 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 145.6, 112.2, 104.5, 53.7, 44.5, 26.7. HRMS (ESI) [M+H]$^+$ calcd. for C$_9$H$_{19}$NO$_2$ 174.1488, found 174.1494.
N-((3,4-dimethylthieno[2,3-b]thiophen-2-yl)methyl)-N,2-dimethylbut-3-en-2-amine. (3aj)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η^3-C_3H_5)Cl]_2 (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)_3 (9µL, 0.0547mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and (3,4-dimethylthieno[2,3-b]thiophen-2-yl)-N-methylmethanamine (0.290 g, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3aj: T = 29.0 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and the residue was purified by flash chromatography (R_f = 0.21, SiO_2, 98:2 pentane/ether) to yield 3aj (233 mg, 0.84 mmol, 61%) as a clear oil.

^1H NMR (CDCl_3, 300 MHz): δ 6.80 (s, 1H), 5.98 (dd, J = 17.6, 10.5 Hz, 1H), 5.11 (dd, J = 17.6, 1.3 Hz, 1H), 5.07 (dd, J = 10.6, 1.3 Hz, 1H), 3.65 (s, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 2.24 (s, 3H), 1.21 (s, 6H). ^13C NMR (CDCl_3, 75 MHz): δ 146.1, 142.7, 135.2, 130.3, 125.4, 121.6, 111.8, 58.3, 49.0, 34.7, 22.4, 15.2, 12.5. HRMS (EI) calcd. for C_{15}H_{21}NS_2 279.1115, found 279.1117.

(1,1-Dimethyl-allyl)-(4,5-dimethyl-naphthalen-1-ylmethyl)-methyl-amine. (3ak)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η^3-C_3H_5)Cl]_2 (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)_3 (9µL, 0.0547mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and (4,5-dimethylnaphthalen-1-ylmethyl)methylamine (0.273 g, 1.37 mmol) were added via syringe and
the solution was stirred under argon at 50°C for 20 h; when \textsuperscript{1}H NMR analysis showed no remaining prenyl acetate 2a. Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo} and the residue was purified by flash chromatography (Rf = 0.59 in hexanes, SiO\textsubscript{2}, graduate elution from hexanes to 98:2 hexanes/ethyl acetate) to yield 3ak (291 mg, 1.04 mmol, 76%) as a clear oil.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 8.13 (d, \(J = 8.5\) Hz, 1H), 7.42 (d, \(J = 7.3\) Hz, 1H), 7.35-7.15 (m, 3H), 6.08 (dd, \(J = 17.6, 10.9\) Hz, 1H), 5.13 (dd, \(J = 17.6, 1.3\) Hz, 1H), 5.08 (dd, \(J = 10.9, 1.3\) Hz, 1H), 3.91 (s, 2H), 2.91 (s, 3H), 2.89 (s, 3H), 2.10 (s, 3H), 1.28 (s, 6H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 146.9, 136.1, 135.1, 134.6, 134.4, 133.7, 129.4, 129.2, 126.4, 125.0, 123.5, 112.4, 59.3, 54.2, 35.3, 26.6, 26.5, 23.0. HRMS (EI) calcd. for C\textsubscript{19}H\textsubscript{25}N\textsubscript{2} 267.1987, found 267.1989.

4-methoxy-N-(2-methylbut-3-en-2-yl)aniline (3am).

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(\eta\textsuperscript{3}-C\textsubscript{3}H\textsubscript{5})Cl]\textsubscript{2} (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)\textsubscript{3} (9\(\mu\)L, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and p-anisidine (0.169 g, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 16 h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3am: T =17.0 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo} and the residue was purified by flash chromatography (Rf = 0.63 in SiO\textsubscript{2}, 4:1 hexanes/ethyl acetate) to yield 3am (190 mg, 1.0 mmol, 73%) as a yellow oil.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 6.70 (s, 4 H), 5.99 (dd, \(J = 17.5, 10.7\) Hz, 1H), 5.12 (d, \(J = 17.5\) Hz, 1H), 5.05 (dd, \(J =10.7, 1.1\) Hz, 1H), 3.69 (s, 3H), 3.28 (s, NH), 1.30 (s, 6H). \textsuperscript{13}C NMR
(CDCl$_3$, 75 MHz): $\delta$ 152.8, 146.5, 140.1, 118.9, 114.0, 112.2, 55.4, 54.9, 28.0. HRMS (ESI) [M+H]$^+$ calcd. for C$_{12}$H$_{18}$NO 192.1382, found 192.1382.

$\text{N-(2,3-dimethoxybenzyl)-2-methylbut-3-en-2-amine (3an).}$

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)$_3$ (9$\mu$L, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 2,3-dimethoxybenzylamine (0.20 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 37$^0$C for 40 h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3an: $T = 19.1$ min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo and the residue was purified by flash chromatography ($R_f = 0.28$ in SiO$_2$, 3:97 MeOH/ether) to yield 3an (173 mg, 0.73 mmol, 54%) as a clear oil.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.00 (dd, $J = 7.9, 7.7$ Hz, 1H), 6.92 (dd, $J = 7.7, 1.6$ Hz, 1H), 6.81 (dd, $J = 7.9, 1.6$ Hz, 1H), 5.87 (dd, $J = 17.5, 10.7$ Hz, 1H), 5.11 (dd, $J = 17.6, 1.3$ Hz, 1H), 5.08 (dd, $J = 10.7, 1.3$ Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.63 (s, 2H), 1.24 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$152.7, 147.4, 146.4, 135.1, 124.2, 122.1, 112.2, 111.3, 60.9, 55.8, 54.7, 42.7, 27.1. HRMS (ESI) [M+H]$^+$ calcd. for C$_{14}$H$_{22}$NO$_2$ 236.1645, found 236.1656.

$\text{N-(2-bromobenzyl)-2-methylbut-3-en-2-amine (3ao).}$
In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η^3-C_3H_5)Cl]_2 (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)_3 (9µL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 2-bromobenzylamine (0.255 g, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20 h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3ao: T = 17.8 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and the residue was purified by flash chromatography (R_f = 0.27 in SiO_2, 19:1 CH_2Cl_2/MeOH) to yield 3ao (281 mg, 1.1 mmol, 81%) as a clear oil.

^1H NMR (CDCl_3, 300 MHz): δ 7.50 (dd, J = 7.9, 1.1 Hz, 1H), 7.45 (dd, J = 7.6, 1.4 Hz, 1H), 7.26 (dt, J = 7.4, 1.1 Hz, 1H), 7.08 (dt, J = 7.8, 1.4 Hz, 1H), 5.88 (dd, J = 17.6, 10.7 Hz, 1H), 5.13 (dd, J = 17.6, 1.2 Hz, 1H), 5.10 (dd, J = 10.7, 1.2 Hz, 1H), 3.70 (s, 2H), 1.26 (s, 6H).

^13C NMR (CDCl_3, 75 MHz): δ 146.1, 140.4, 132.7, 130.6, 128.5, 127.7, 124.0, 112.5, 54.9, 47.7, 27.1. HRMS (EI) calcd. for C_{12}H_{17}BrN 253.0466, found 253.0470.

1,2,3,4-tetrahydro-2-(pent-1-en-3-yl)isoquinoline (3ca)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η^3-C_3H_5)Cl]_2 (5 mg, 0.0137 mmol) and (2-biphenyl)dicyclohexylphosphine (19 mg, 0.0547 mmol), and dry THF (1.3 mL). DBU (0.21 mL, 1.40 mmol), (E)-pent-2-enyl acetate 2c (0.176 g, 1.37 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.17 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 20 h; when ^1H NMR analysis showed no remaining (E)-pent-2-enyl acetate 2c. Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and the residue was purified by flash chromatography (R_f = 0.32 in SiO_2, 4:1 hexanes/ethyl acetate) to yield 3ca (228 mg, 1.44 mmol, 83%) as a clear oil.
$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.11-7.07 (m, 3H), 7.02-6.99 (m, 1H), 5.75 (ddd, $J = 17.1, 10.3, 8.2$ Hz, 1H), 5.22 (dd, $J = 10.3, 2.0$ Hz, 1H), 5.14 (dd, $J = 17.1, 2.0$ Hz, 1H), 3.76 (d, $J = 14.9$ Hz 1H), 5.22 (dd, $J = 10.3, 2.0$ Hz, 1H), 5.14 (dd, $J = 17.1, 2.0$ Hz, 1H), 3.68 (d, $J = 14.9$ Hz 1H), 2.94-2.80 (m, 4H), 2.70-2.64 (m, 1H), 1.86-1.72 (m, 1H), 1.61-1.47 (m, 1H), 0.91 (t, $J = 7.4$ Hz 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 137.5, 135.4, 134.6, 128.6, 126.6, 125.8, 125.4, 117.6, 69.6, 52.8, 46.8, 29.5, 24.7, 10.8. HRMS (EI) calcd. for C$_{14}$H$_{19}$N 201.1517, found 201.1512.

$\begin{array}{c}
\text{3ea} \\
\text{3ea'}
\end{array}$

1,2,3,4-tetrahydro-2-(1-phenylallyl)isoquinoline (3ea) and 2-cinnamyl-1,2,3,4-tetrahydroisoquinoline (3ea').

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)$_3$ (9 $\mu$L, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), cinnamyl acetate 2e (0.214 g, 1.37 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.182 g, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 6 h; when NMR analysis showed no remaining cinnamyl acetate 2e. Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.69 and 0.24 in SiO$_2$, respectively, 19:1 hexanes/EtOAc) to yield 3ea and 3ea' (453 mg, 0.9 mmol, 66 %) as a clear oil and an orange solid, respectively.

3ea $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.40-7.28 (m, 5H), 7.11-7.08 (m, 3H), 6.98-6.96 (m, 1H), 6.02 (ddd, $J = 17.6, 10.7, 8.8$ Hz, 1H), 5.29 (dd, $J = 17.1, 1.5$ Hz, 1H), 5.15 (dd, $J = 10.1, 1.6$ Hz, 1H), 3.86 (d, $J = 8.8$ Hz, 1H), 3.75 (d, $J = 15.2$ Hz, 1H), 3.54 (d, $J = 15.7$ Hz, 1H), 2.88-2.84 (m, 2H), 2.74-2.70 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 141.7, 139.7, 134.7, 134.2, 128.2, 127.4, 126.8, 126.4, 125.6, 125.1, 115.9, 74.0, 54.1, 47.9, 28.7. HRMS (EI) calcd. for C$_{18}$H$_{19}$N 249.1517, found 249.1511.
3ea' 1H NMR (CDCl₃, 300 MHz): δ 7.43-7.30 (m, 5H), 7.12-7.11 (m, 3H), 7.03-7.01 (m, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.37 (dt, J = 15.9, 6.6 Hz, 1H), 3.68 (s, 2H), 3.34 (d, J = 6.31 Hz, 2H), 2.94 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H). 13C NMR (CDCl₃, 100 MHz): δ 136.5, 134.3, 133.8, 132.4, 128.2, 127.1, 126.5, 126.2, 125.9, 125.7, 125.2, 60.4, 55.7, 50.4, 28.7. HRMS (EI) calcd. for C₁₈H₁₉N 249.1517, found 249.1513.

2-(1,1-dideuteroallyl)-1,2,3,4-tetrahydroisoquinoline (3ma) and 2-(3,3-dideuteroallyl)-1,2,3,4-tetrahydroisoquinoline (3ma’)

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η³-C₅H₅)Cl]₂ (2.5 mg, 0.0069 mmol) and dry THF (0.6 mL). P(OEt)₃ (5µL, 0.0274 mmol), DBU (0.080 mL, 0.53 mmol), 1,1-dideuteroallyl acetate 2m (51 mg, 0.50 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.062 g, 0.50 mmol) were added via syringe and the solution was stirred under argon at room temperature for 17 h; when NMR analysis showed no remaining 1,1-dideuteroallyl acetate 2m. Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo and the residue was purified by flash chromatography (Rf = 0.41 in SiO₂, 4:1 hexanes/EtOAc) to yield a 1:1 mixture of 3ma and 3ma’.

3ma and 3ma’ 1H NMR (CDCl₃, 300 MHz): δ 7.11 -7.09 (m, 3), 7.01-6.99 (m, 1H), 5.95 (m, 1H), 5.25 (dd, J =17.2, 1.9 Hz, 1H), 5.19 (dd, J =10.2, 2.0 Hz, 1H), 3.62 (s, 2H), 3.17 (d, J = 6.5 Hz, 2H), 2.90 (t, J = 5.9 Hz, 2H), 2.74 (td, J = 5.9, 1.9 Hz, 2H).
Prenyl palladium chloride dimer\textsuperscript{50}

Palladium chloride (0.933 g, 5.3 mmol) and lithium chloride (0.45 g, 13.4 mmol) were weighed into a 50 mL round-bottom flask equipped with a stir bar. The mixture was diluted with water (1.5 mL) and methanol (13 mL). The reaction flask was purged with nitrogen gas, and prenyl chloride (18.1 mmol, 1.6 mL) was added to the reaction solution. CO gas was bubbled through the solution for 2 hours when the yellow precipitate appeared. The solution was poured in water, extracted with chloroform, dried over sodium sulphate, and concentrated. The product was recrystallized out of chloroform and methanol to give 567 mg (1.3 mmol) of yellow solid in 48% yield.

\[ {^1}H \text{ NMR (CDCl}_3, 400 \text{ MHz): } \delta 5.08 \text{ (dd, } J = 12.6, 7.3 \text{ Hz, 2H), 3.85 (dd, } J = 7.3, 1.3 \text{ Hz, 2H), 3.09 (dd, } J = 12.6, 1.3 \text{ Hz, 2H), 1.44 (s, 6H), 1.24 (s, 6H).} \]

\[ \text{Pd Ph}_3 \text{Cl PPh}_3 \text{Cl} \]

\( \sigma \)-Palladium prenyl Complex in THF.

In the glove-box prenyl palladium chloride dimer (1 equiv) and triphenyl phosphine (4 equiv) were added to the 8 inch NMR tube. The contents were dissolved in deuterated THF and the solution was submitted to NMR. \[ {^1}H \text{ NMR (THF-}d_8, 400 \text{ MHz): } \delta 5.16 \text{ (t, } J =10.0 \text{ Hz, 1H), 2.75 (d, } J =10.0 \text{ Hz, 2H), 1.86 (s, 3H), 1.40 (s, 3H).} \]

\[ \text{Pd Ph}_3 \text{Cl PPh}_3 \text{Cl} \]

\( \sigma \)-Palladium prenyl Complex in CH\textsubscript{2}Cl\textsubscript{2}. 

In the glove-box prenyl palladium chloride dimer (1 equiv) and triphenyl phosphine (4 equiv) were added to the 8 inch NMR tube. The contents were dissolved in deuterated dichloromethane and the solution was submitted to NMR. $^1$H NMR (CD$_2$Cl$_2$, 300 MHz): $\delta$ 5.11 (t, $J = 9.9$ Hz, 1H), 2.74 (d, $J = 9.9$ Hz, 2H), 1.79 (s, 3H), 1.35 (s, 3H).

![PdCl$_2$](image)

**Crotyl palladium chloride dimer**

Palladium chloride (88 mg, 0.5 mmol) and sodium chloride (58 g, 1.0 mmol) were weight into a 17 x 60 mm screw cap vial equipped with a stir bar. The mixture was diluted with water (0.20 mL) and methanol (1.2 mL). The reaction flask was purged with nitrogen gas, and crotyl chloride (1.34 mmols, 0.13 mL) was added to the reaction solution. CO gas was bubbled through the solution for 1.2 hours when the yellow precipitate appeared. The solution was poured in water, extracted with chloroform, dried over sodium sulfate, and concentrated. The product was recrystallized out of chloroform and methanol to give 66 mg (0.17 mmol) of yellow solid in 67% yield.

$^1$H NMR (THF-$d_8$, 300 MHz): $\delta$ 5.31 (ddd, $J = 22.8$, 11.4, 6.7 Hz, 2H), 3.87-3.77 (m, 2H), 3.73 (d, $J = 6.7$ Hz, 2H), 2.72 (d, $J = 11.8$ Hz, 2H), 1.27 (d, $J = 6.3$ Hz, 6H).

![PdPh$_3$Cl](image)

**$\sigma$-Palladium Crotyl Complex in THF.**

In the glove-box crotyl palladium chloride dimer and triphenyl phosphine were added to the 8 inch NMR tube. The contents were dissolved in deuterated THF and the solution was submitted to NMR. $^1$H NMR (THF-$d_8$, 300 MHz): $\delta$ 5.37 (dt, $J = 12.7$, 9.3 Hz, 1H), 4.39-4.28 (m, 1H), 2.71 (d, $J = 9.3$ Hz, 2H), 1.74 (d, $J = 6.3$ Hz, 3H).
2.5.4 Solvent Studies

In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η3-C₃H₅)Cl]₂ (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)₃ (9 µL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate (0.19 mL, 1.37 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.17 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at room temperature for 17 h. Biphenyl (0.685 mmol, 105 mg) was added to the reaction mixture, after which the reaction was allowed to stir for additional 5 minutes to allow biphenyl to dissolve. Saturated solution of sodium bisulfite (4 mL) was added and the resulting mixture was extracted with dichloromethane (3 x 2 mL). A sample from organic layer was passed through a small celite and silica plug with 3 mL of HPLC grade acetonitrile, and 0.2 mL of the resulting solution was analyzed by GC using the method described above. (GC retention time of branched product: T = 18.2 min, linear: T = 18.2 min). The procedure was repeated using 0.035 mL, 0.065 mL, 0.100 mL, 0.130 mL, 0.350 mL, 0.650 mL, 1.00 mL, and 1.3 mL of anhydrous dichloromethane in THF keeping the reaction volume at 1.3 mL.

The reaction was then repeated using BINAP (0.274 mmol, 17 mg) ligand in 0 mL, 0.130 mL, 0.350 mL, 0.650 mL, 1.00 mL, 1.1 mL, 1.2 mL, and 1.3 mL of anhydrous dichloromethane in THF keeping the reaction volume at 1.3 mL.

2.6 References

Due to the presence of DBU in the reaction it is safe to assume that it proceeded under kinetic control, and that the product ratios were not altered by the allylic isomerization.

In a personal communication, Prof. Buchwald (MIT) suggested an unsymmetrical α-allyl as the reactive intermediate that could account for the formation of the branched product. This hypothesis is supported by the fact that such an intermediate would have a partial positive charge on the more substituted terminus, which would then be readily attacked by the amine. However, the proposed system cannot account for the formation of the linear product that results from amine attack on the less substituted terminus.

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3 Palladium-catalyzed rearrangements of cyclic allylamines

3.1 Introduction

Intramolecular allylic amination is an elegant transformation that is used for the synthesis of cyclic amines. In addition to its highly-valued applications in total synthesis, this transformation caught our attention because it has provided a solution to the problem of regioselectivity in allylic amination with palladium-based catalysts. Indeed, the reaction gives rise to branched cyclic allylamines having alkenes with a different degree of substitution, including monosubstituted isomers. Such control of regioselectivity is achieved by virtue of kinetically as well as thermodynamically-favourable formation of a five- as opposed to the seven-membered ring (Scheme 3.1).

Scheme 3.1 Preparation of branched cyclic allylamines by intramolecular Pd-catalyzed allylic amination

Despite the utility of this reaction we have realized that it suffers from a particular drawback; the starting material contains both a secondary amine and an acetate, which suggests that the electrophile had to be installed in the presence of a strong nucleophile. Not only does this assume the use of protecting groups to avoid chemoselectivity issues, but such limitation makes it difficult to use this reaction for late-stage modifications.

To find a way around this problem we have envisioned a new system in which the leaving group would be replaced by a latent functionality or a bond that would become activated under a very
specific set of conditions. In addition, the system would also have to contain a “handle” that would differentiate between the bond of interest and the rest of the bonds in the molecule.

In the literature, there are many examples of metal-catalyzed or metal-promoted scission reactions of “unactivated” C – N bonds (Scheme 3.2). Such transformations became useful because they store hidden reactivity until it can be revealed. For example, hydrogenolysis turns an unreactive tertiary amine into a more nucleophilic secondary amine in the presence of palladium on carbon, and hydrogen gas. In this reaction, the benzyl group acts as a handle by specifically binding to the surface of palladium, thus providing complete chemoselectivity over other C – N bonds. Alloc-group is another important protecting group that is used in synthesis. It is selectively cleaved by a palladium (0) catalyst that binds to the alkene, triggering ionization to form a palladium π-allyl intermediate, a primary or a secondary amine, as well as carbon dioxide, which is the driving force for the reaction. Active palladium (0) catalyst is regenerated as a result of an external nucleophile capturing the π-allyl intermediate. Recently, Lipshutz and coworkers reported a homoallyl protecting group for amines. It is removed by a tandem process, in which homoallylic amines undergo cross-metathesis followed by a retro-Michael reaction, which produces a secondary amine and a polyconjugated ketone. Amines can also be dealkylated upon their conversion to enamines followed by hydrolysis. Such processes typically employ rhodium-based hydrides, and the formation of a carbonyl-containing product drives the reaction forward. Alternatively, amines can become activated by quaternarization. For instance, MacMillan and coworkers have reported a cross-coupling reaction, where trialkylanilinium salts underwent oxidative addition with nickel to form an aryl-nickel intermediate, that later underwent a transmetallation with a boronic acid. High chemoselectivity was provided by the favourable formation of a more stable aryl-nickel species, as opposed to alkyl-nickel intermediate. In addition to aryl groups, allyl group in particular can be used in such transformations due to its ability to form stable complexes with palladium. Thus, Hirao and Yamamoto independently discovered that allyl triethylammonium salts were able to undergo ionization with palladium to form a palladium-π-allyl complex as well as triethylamine. Such C – N scission process in quaternary amine salts started finding applications in C – C bond-formation reactions. Murahashi and coworkers designed a system for a formal aza-Claisen
reaction, which contained both an enamine and an allylamine. In the presence of mild acid, palladium (0) catalyst reacts with the allylammonium salt, leading to the formation of a palladium-\(\pi\)-allyl complex, and releases the enamine, that subsequently attacks it to form a new C – C bond. Similarly, List and coworkers developed an intermolecular variation in which an allylamine was activated in the presence of TRIP-acid, and the resulting palladium-\(\pi\)-allyl complex was coupled to an enol, which led to the formation of a new C – C bond. This approach is quite useful because, in addition to being general, as a wide range of aldehydes can be employed, it is also highly stereoselective. Trost and coworkers showed that 2-vinyl aziridines can undergo ring-opening reactions in the presence of a palladium (0) catalyst. This reaction, driven by strain release, forms a palladium-\(\pi\)-allyl intermediate, which is then trapped with an external nucleophile to form a new C – N bond. Our group has earlier investigated the loss of branched selectivity in allylic amination and showed that a branched allylamine in the presence of acid can re-ionize to form the corresponding palladium-\(\pi\)-allyl intermediate, which is subsequently attacked by the free amine. Finally, strained allylamines can undergo C – N bond scission without the additional activation. Scheme 3.2 shows deamination reactions described above.
Scheme 3.2 Examples of C – N bond scission reactions

Lipshutz

\[
\text{RHN} + \text{HgII} \rightarrow \text{RHN} \rightarrow \text{RHN} + \text{NaH} \rightarrow \text{RHN}_2 + \text{R}
\]

Retro-Michael

Allylamine-to-enamine isomerization

\[
\text{RHN} \rightarrow \text{RHN} \rightarrow \text{RHN} \rightarrow \text{RHN} \rightarrow \text{RNH}_2
\]

Acid hydrolysis

MacMillan

\[
\text{RMe}_3 \rightarrow \text{N} \rightarrow \text{N} \rightarrow \text{B(OH)}_2
\]

Hirao, Yamamoto

\[
\text{Pd}^{2+} \rightarrow \text{Pd}^{4+} \rightarrow \text{Pd}^{4+} \rightarrow \text{Pd}^{4+}
\]

Murahashi

\[
\text{Ts} \rightarrow \text{Ts} \rightarrow \text{Ts} \rightarrow \text{Ts} \rightarrow \text{Ts}
\]

mild acid
3.2 Preparation of cyclic allylamines

Previously, we have developed a system where the thermodynamically-driven branched-to-linear isomerization was prevented by avoiding the build-up of acid in solution. Later, however, we decided to reexamine this process, and design a system where such isomerization would lead
to a useful transformation. We reasoned that this system would contain a ring as a control element, and the stability of this ring would determine the outcome of the reaction. Out of the two possible types of ring-rearrangements, ring-contraction was envisioned to be the most attractive as it would result in the formation of a new chiral centre.

*Scheme 3.3* Aza-allylic rearrangement

*Scheme 3.3* shows the desired transformation. As substrates for this reaction are not commercially available, approaches to their preparation had to be developed. Such approaches needed to be scalable, reliable, concise, and divergent to allow for the preparation of multiple substrates.

Our first goal was to design a synthesis of azepine 3.74, that was viewed to be the most biased type of substrates for the ring-contraction reaction due to its expected ability to form the more stable ring, as well as the more stable alkene. We envisioned the ring-closing metathesis reaction to be the key transformation in the preparation of this substrate. To set the stage for it, one of the terminal olefins was proposed to come from a reaction with a carboxylic acid, whereas the other one, from the regioselective amination of an allylic acetate, developed by our group (*Scheme 3.4*).

*Scheme 3.4* Retrosynthetic analysis of 3.74
The synthesis began with a DCC-type coupling of \( p \)-methoxybenzylamine with hex-5-enoic acid to give amide 3.2 in a 64% yield, Scheme 3.5. The subsequent reduction with alane gave the corresponding amine 3.3 in 66% yield, which upon the palladium-catalyzed prenylation protocol developed by our group, gave mostly unreacted starting material together with the linear product that was formed in 15% yield. Such outcome was not surprising with hindered acyclic secondary amines,\(^\text{11}\) since the linear product does not experience the severe steric repulsions between the methyl group and the aliphatic chain. The low yield for this product indicates that the amination at the less-substituted terminus of the prenyl fragment is very slow. Amine 3.3 also failed to react with the hindered \( \alpha \)-bromoester in a substitution reaction. At this point it became clear that the prenyl group had to be installed first.

**Scheme 3.5 Attempted preparation of a metathesis precursor**

Prenylation of \( p \)-methoxybenzylamine gave the expected branched product 3.5 in 85% yield.\(^\text{12}\) Likewise, allylation of \( p \)-methoxybenzylamine with crotyl acetate gave the corresponding product 3.6 in high yield (Table 3.1). This step is quite important in the overall synthetic sequence as it allows us to apply our methodology, and it is also the first point where diversity can be introduced. The next step affords the other olefin, required for the ring-closing metathesis step, via acylation with an acid chloride to give the corresponding tertiary amide (Table 3.2). In this reaction, the acid acts as a second diversity-introducing element. The yields are moderate
due to the steric repulsions between the approaching electrophile and the methyl groups on the amine’s α-carbon.

**Table 3.1** Palladium-catalyzed allylic amination in substrate preparation

<table>
<thead>
<tr>
<th>entry</th>
<th>allylic acetate</th>
<th>allylamine</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>allylic acetate</td>
<td>PMBH ( \text{H} )</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>allylic acetate</td>
<td>PMBH 3.5</td>
<td>82</td>
</tr>
</tbody>
</table>

**Table 3.2** Acylation reaction of allylamines

<table>
<thead>
<tr>
<th>entry</th>
<th>allylamine</th>
<th>acid chloride</th>
<th>amide</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>allylamine 3.5</td>
<td>acid chloride</td>
<td>PMBH 3.7</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>allylamine 3.6</td>
<td>acid chloride</td>
<td>PMBH 3.8</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>allylamine 3.6</td>
<td>acid chloride</td>
<td>PMBH 3.9</td>
<td>65</td>
</tr>
</tbody>
</table>
In addition to the allyl group, substituents can also be placed on the other aliphatic fragment. Thus, $\beta$-substituted esters were prepared from the corresponding allylic alcohols by Johnson-Claisen rearrangement (Table 3.3).\textsuperscript{13} The lowest yield was observed with 2-hex-en-1-ol, where the reaction transition state is likely most destabilized due to the steric interactions between the $n$-propyl group and the olefin that resulted from trimethyl orthoacetate.

\textbf{Table 3.3} Johnson-Claisen rearrangement in substrate preparation

<table>
<thead>
<tr>
<th>entry</th>
<th>allylic alcohol</th>
<th>ester</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph\textsubscript{-} \textsuperscript{3.10}OH</td>
<td>\textsuperscript{3.10} PHO \textsuperscript{3.10}</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>\textsuperscript{3.11}OH</td>
<td>\textsuperscript{3.11} OMe</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>\textsuperscript{3.12}OH</td>
<td>\textsuperscript{3.12} OMe</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Pr\textsuperscript{3.13}OH</td>
<td>\textsuperscript{3.13} OMe</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>\textsuperscript{3.14}OH</td>
<td>\textsuperscript{3.14} OMe</td>
<td>60</td>
</tr>
</tbody>
</table>

The newly-formed $\beta$-substituted esters were transformed to the corresponding amides in the presence of DIBAL-H reagent. DIBAL-H is thought to deprotonate $p$-methoxybenzylamine to make it more reactive.\textsuperscript{14} In addition, aluminium salts may have activated the carbonyl group of the ester towards the addition-elimination reaction (Table 3.4).
Table 3.4 Trans-amidation of substituted esters

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>amide</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3.10" alt="ester" /></td>
<td><img src="3.15" alt="amide" /></td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td><img src="3.11" alt="ester" /></td>
<td><img src="3.16" alt="amide" /></td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td><img src="3.12" alt="ester" /></td>
<td><img src="3.17" alt="amide" /></td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td><img src="3.13" alt="ester" /></td>
<td><img src="3.18" alt="amide" /></td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td><img src="3.14" alt="ester" /></td>
<td><img src="3.19" alt="amide" /></td>
<td>58</td>
</tr>
</tbody>
</table>

The amides were later transformed to the corresponding amines in good-to-excellent yields by reduction with alane (Table 3.5).

Table 3.5 Secondary amide reductions with alane

<table>
<thead>
<tr>
<th>entry</th>
<th>amide</th>
<th>amine</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3.15" alt="amide" /></td>
<td><img src="3.20" alt="amine" /></td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td><img src="3.16" alt="amide" /></td>
<td><img src="3.21" alt="amine" /></td>
<td>71</td>
</tr>
</tbody>
</table>
Finally, the second alkene was added by another acylation reaction with acryloyl chloride. The same reaction was also applied to the already-prepared amine 3.3 (Scheme 3.5) and its shorter homologue 3.3’ (Table 3.6).

Table 3.6 Acylation of secondary amines with acryloyl chloride

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>amide</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3.20" alt="image" /></td>
<td><img src="3.25" alt="image" /></td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td><img src="3.21" alt="image" /></td>
<td><img src="3.26" alt="image" /></td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td><img src="3.22" alt="image" /></td>
<td><img src="3.27" alt="image" /></td>
<td>57</td>
</tr>
</tbody>
</table>
In addition to adding substituents to the \( \beta \)-carbon, diversity could also be introduced by alkylation of the \( \alpha \)-carbon. This was accomplished by first placing an allyl group on the secondary amide, followed by lithium enolate formation, and subsequent addition of an alkyl halide (Table 3.7).

**Table 3.7 Preparation of 3.34 and 3.35**

<table>
<thead>
<tr>
<th>entry</th>
<th>amide</th>
<th>electrophile</th>
<th>product</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="amide 3.32" /></td>
<td>Mel</td>
<td><img src="image" alt="product 3.34" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="amide 3.32" /></td>
<td>BnBr</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
As can be seen from Table 3.7, even though the installation of the allyl group proceeds with high yield, the subsequent α-alkylation is problematic. The sterically hindered lithium enolates of 3.32 and 3.33 were able to react with very small and strong electrophiles such as methyl- and ethyl iodosides. As the substituents on the electrophile became larger, the enolate could no longer approach it leading to the recovery of unreacted starting material. The use of 1,3-dibromopropane led to the formation of a complex mixture of products (Table 3.7, entry 3). The reaction scope was broadened later, when enolates of cyclic amides were used instead (Table 3.10).

**Scheme 3.6** Attempted prenylation of 2-aminophenol
In addition to the preparation of metathesis precursors shown above, we also decided to broaden the reaction scope by introducing additional heteroatoms. Such change may simplify the synthesis since most heteroatoms can serve as tethering points for terminal olefins. Thus, 2-aminophenol was subjected to the palladium-catalyzed prenylation conditions, Scheme 3.6. Unfortunately, only the linear product 3.36 was formed. Such selectivity is probably the result of the isomerization, which is occurring because of phenol’s high acidity. To overcome this problem, the aminophenol was subjected to acylation conditions with acryloyl chloride, which gave the corresponding amide 3.37. The amide was then reacted with allyl bromide to give the dialkene 3.38. Thus both heteroatoms were conveniently used as tethering points for alkenes. The same strategy was applied to (2-aminophenyl)methanol (Scheme 3.7). Finally, the resulting alcohol-protected amides were subjected to N-alkylation with benzyl bromide, giving tertiary amides 3.39 and 3.42. Similarly, diamines were subjected to diacylation and dibenzylation to give tertiary amides 3.44 and 3.46. It should be noted that the yields for the dibenzylation of diamides were extremely poor. The isolation of the monobenzylated intermediates indicates that the reaction cannot proceed further due to the sterically-unfavourable formation of the reactive rotamer. In addition to steric factors, the presence of intramolecular hydrogen bonding between N-H of the secondary amide and the carbonyl group of the tertiary amide may further retard the formation of the rotamer that would lead to the dibenzylated product (Scheme 3.7).

The diolefin precursors were subjected to ring closing metathesis, and the results are summarized in Table 3.8.

**Table 3.8** Synthesis of lactams by ring-closing metathesis

<table>
<thead>
<tr>
<th>entry</th>
<th>diolefin</th>
<th>product</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="3.47" /></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Several conclusions can be drawn from Table 3.8. Amine 3.47, which was prepared by the reduction of 3.7 (Table 3.11, entry 20), did not react, most likely because it is too basic (Table 3.8, entry 1). In general, amines are known to deactivate ruthenium-based metathesis catalysts. In general, 7-membered rings are formed faster than 8-membered rings (Table 3.8 entries 3, 4, 11,
12), which are in turn formed faster than 9-membered rings (Table 3.8, entries 17, 18). This trend correlates well with the order of rates of formation of cycloalkanes, which is $7>8>9$.\textsuperscript{16} In addition, the reaction was more high-yielding when one of the alkenes was conjugated to a carbonyl group (Table 3.8, entries 5, 11). Such a deactivated system is less likely to participate in intermolecular cross-metathesis side reactions or alkene isomerization reactions, when compared to a system where both alkenes are electron-rich. However, when both alkenes are electron-poor, the reaction does not occur at all (Table 3.8, entries 19-22). Substituents along the chain have a mixed effect on reactivity. Substituents that are not placed directly on the alkenes do not seem to have any effect on the rate of ring-closing metathesis, even though one might expect that the Thorpe-Ingold effect would enhance the rate of reaction. One reasoning for the lack of enhanced reactivity is the fact that alkenes do need to bind to ruthenium prior to the cyclization. This process is unlikely to be rate-determining since alkenes are such strong ligands to ruthenium, and because when one of the alkene reacts with the catalyst, the reaction becomes intramolecular. On the other hand, when the substituents are placed on the alkene, the steric repulsion inhibits the alkene coordination to ruthenium. Finally, it appears that secondary amides can be completely unreactive towards the ring-closing metathesis, unlike their tertiary counterparts (Table 3.8, entries 15-18). We reasoned that such difference can be attributed to the reactive conformations of specific amides (Scheme 3.8). For example, in conformation I\textsubscript{1}, the R group is positioned in between the alkene and ruthenium carbenoid making it impossible for them to encounter one another. On the other in conformation I\textsubscript{2}, the R group is on the outside, forcing the alkene and carbenoid to come in close proximity, thus increasing the likelihood of the reaction. The size of the R-group determines which conformation is predominant. When the R group is benzyl, I\textsubscript{2} would be the major conformation, since in I\textsubscript{1} the benzyl group would be experiencing strong steric repulsion with the ruthenium carbenoid tether. On the other hand, when R=H, achieving I\textsubscript{2} would be very difficult, whereas in I\textsubscript{1}, hydrogen due to its small size would be able to fit in between the ruthenium carbenoid and the alkene tether.
Later, we have developed a different approach to the synthesis of conjugated lactams, the one that did not involve the use of any transition metals. The first attempt started with the bromination of ε-caprolactam, followed by elimination (Table 3.9). Surprisingly, the elimination step was problematic as it gave mixtures of 3.64 (conjugated) and 3.65 (skipped). Upon prolonged reaction times the skipped product became the only product. In addition, mixtures of products would undergo full isomerization to the skipped product if resubjected to the reaction conditions. The “skipped” product 3.65 forms as a result of subsequent removal of the γ-proton from product 3.64. Such counterintuitive observation can only be rationalized by invoking arguments of strain. In a conjugated lactam 3.64, all four atoms prefer to lie in one plane, placing severe torsional strain on the ring. On the other hand, the “skipped” lactam 3.65 contains a methylene group in between the two π-systems, which acts as a spacer to release this strain.

**Table 3.9** Attempted preparation of lactam 3.64 by elimination

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,6-lutidine, reflux</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>LDA, THF, -78°C</td>
<td>skipped</td>
</tr>
<tr>
<td>3</td>
<td>'BuOK, DMF, 0°C</td>
<td>c/s = 2:1</td>
</tr>
</tbody>
</table>
Even though 'BuOK in DMF was found to favour the conjugated product, the separation of the two products proved to be challenging. Therefore, an alternative method had to be developed that would not employ base. We envisioned the Beckman rearrangement as an alternative to the previous approach, especially, since it does not require the use of base. The starting cyclohex-2-en-1-one was converted to the corresponding oxime \(3.66\), which in turn was subjected to phosphorus pentoxide in refluxing methanesulfonic acid to give conjugated product \(3.64\) in 43% yield \(\text{(Scheme 3.9)}\). The resulting secondary lactam could then be subjected to alkylation conditions with an alkyl halide of choice. This approach is quite straightforward and employs cheap reagents and very simple reactions despite the modest yield. It is also general, since substituted cyclohex-2-en-1-ones can be readily prepared in one pot from \(\beta\)-ketoesters using a Robinson annulation / hydrolysis / decarboxylation sequence.

\begin{align*}
\text{Scheme 3.9 Metathesis-free synthesis of conjugated lactams}
\end{align*}

Once lactams became available, some issues described earlier could now be readdressed. For example, due to the lower steric hindrance associated with lactams, certain \(\alpha\)-alkylations that failed with acyclic amides became possible with lactams, \textit{Table 3.10}. Even though the yields were low, the reaction did proceed with activated non-hindered electrophiles. This is in contrast to the alkylation of acyclic amides shown in \textit{Table 3.7}.
Table 3.10. Functionalization of lactams by α-alkylation

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;I</td>
<td><img src="3.67" alt="Product Image" /></td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;I</td>
<td><img src="3.68" alt="Product Image" /></td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>PhBr</td>
<td><img src="3.69" alt="Product Image" /></td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td><img src="3.70" alt="Product Image" /></td>
<td>19</td>
</tr>
</tbody>
</table>

Even though ring-closing metathesis is a powerful technique, and was used as the key step in the synthesis of many of our substrates, it could not be used to prepare cyclic allylic bis-amides due to the deactivated nature of both alkenes in the metathesis precursor (Table 3.8, entries 21, 22).
An alternative synthetic route was developed for a representative of this family of substrates (*Scheme 3.10*).

*Scheme 3.10* Metathesis-free preparation of a 3.73

The synthesis began with a double condensation between phenylenediamine and dimethyl succinate. Low yield associated with this reaction is most likely a consequence of competing polymerization reaction, as well as poor electrophilicity of the unactivated diester. The newly-formed dilactam 3.71 was subjected to the double alkylation with benzyl bromide. The synthesis of the lactam 3.73 was achieved via a bromination/dehalogenation sequence.17

The substrates for the rearrangement were obtained by reducing the resulting lactams to the corresponding cyclic allylamines (*Table 3.11*). One trend that these results seem to follow is that the reduction of conjugated lactams is very low-yielding comparing to the isolated lactams (*Table 3.11*, entries 4-10, 13-15). The reason for this is the competing reduction of the conjugated alkene, which is then followed by the reduction of the resulting saturated lactam. Isolated lactams with α-substituents (*Table 3.11*, entries 11-12, 16-19) led to somewhat lower yields, as a consequence of these substituents blocking the approach of the hydride (Refer to 3.52, *Table 3.11* for the substituent designation). The same logic, however, cannot explain why substituents in the γ-position on conjugated lactams also lead to lower yields (*Table 3.11*, entries 4-7). Such substituents would be expected to inhibit the hydride approach to the alkene. One explanation for this could be that the γ-substituents are being placed in the equatorial position on the ring. This leads to A1,2 strain due to the steric interaction of olefinic hydrogen with the carbon atom of the substituent. Reduction of the alkene alleviates this strain, which explains why 3.57 (*Table 3.11*, entry 9) gives higher yield. When two substituents are placed in the γ-position, one
of them has no choice but to occupy the axial position on the ring, which would then hinder the attack of the approaching hydride, thus disfavouring the 1,4-reduction (Table 3.11, entry 6).

Table 3.11 Reduction of lactams and amides with alane

<table>
<thead>
<tr>
<th>entry</th>
<th>lactam</th>
<th>cyclic amine</th>
<th>%yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Lactam 3.48" /></td>
<td><img src="image" alt="Cyclic Amine 3.74" /></td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Lactam 3.49" /></td>
<td><img src="image" alt="Cyclic Amine 3.75" /></td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Lactam 3.50" /></td>
<td><img src="image" alt="Cyclic Amine 3.76" /></td>
<td>90&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Lactam 3.52" /></td>
<td><img src="image" alt="Cyclic Amine 3.77" /></td>
<td>30&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Lactam 3.53" /></td>
<td><img src="image" alt="Cyclic Amine 3.78" /></td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Lactam 3.54" /></td>
<td><img src="image" alt="Cyclic Amine 3.79" /></td>
<td>79</td>
</tr>
</tbody>
</table>
In addition to the substrates shown above, more substrates were prepared using approaches that did not involve the use of ring-closing metathesis. For example, an allylic tetrahydropyridine 3.93 was constructed by first alkylating 2-phenylpyridine, followed by reduction, *Scheme 3.11*. Interestingly, only one regioisomer 3.93 formed with the alkene in the 4,5-position, which can be rationalized by invoking resonance effects (*Scheme 3.11*). This particular isomer is preferred.

\[ ^{a}\text{The reaction was allowed to warm up to rt instead of 50} ^{\circ}\text{C} \]
because it comes from a more stabilized conjugated intermediate, whereas the isomer with a 3,4-olefin would come from a less stabilized cross-conjugated precursor.

*Scheme 3.11* Regioselective reduction of benzyl 2-phenylpyridinium chloride

Another substrate containing a 6-membered ring, 3.96, was prepared by a two-step oxidation of a tetrahydroisoquinoline to a dihydroisoquinoline, followed by alkylation at the nitrogen, and addition of a Grignard reagent, *Scheme 3.12*. Interestingly, addition of the Grignard reagent to the imine 3.94 directly gave only the reduction-product. Such a side-reaction occurs because both reagents are bulky, and the imine is very much deactivated, compared to the iminium ion. Because of these factors, the isopropenylmagnesium bromide reacts via a cyclic transition state by transferring the hydride to the imine.
The next family of substrates was designed to have a built-in element of strain. Cyclic allylamines containing azetidines were prepared from the corresponding β-lactams by benzylation, followed by reduction, Table 3.12. Such benzylation of bicyclic β-lactams is obstructed by the presence of another ring (Table 3.12, entries 2-3) giving lower yields compared to the simple β-lactam. Reduction of N-benzyl-β-lactams, on the other hand, does follow the opposite trend. One explanation for the very high yields of the fused N-benzyl-β-lactams could be that the energy benefit from changing the carbon hybridization from sp² to sp³ could be much higher in those systems comparing to the simple N-benzyl-β-lactam.

Table 3.12 Preparation of allylic azetidines

<table>
<thead>
<tr>
<th>entry</th>
<th>β-lactam</th>
<th>N-benzyl-β-lactam</th>
<th>azetidine</th>
<th>yield 1</th>
<th>yield 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="3.97" /></td>
<td><img src="image" alt="3.98" /></td>
<td></td>
<td>60</td>
<td>33</td>
</tr>
</tbody>
</table>
Finally, the last family of substrates was prepared from amino alcohols and conjugated aldehydes (Table 3.13). Acrolein gave a mixture of products including imine and dimerized products. Myrtenal, on the other hand, gave the corresponding oxazoline (3.103) and thiazolidine (3.104) in high yield.

Table 3.13 Preparation of oxazoline 3.103 and thiazolidine 3.104

<table>
<thead>
<tr>
<th>entry</th>
<th>aminoalcohol</th>
<th>aldehyde</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂NCHR₂OH</td>
<td>R⁴R⁵</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H₂NCHR₂OH</td>
<td>R⁴R⁵</td>
<td>R⁴R⁵</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>H₂NR²SH</td>
<td>R⁴R⁵</td>
<td>R⁴R⁵</td>
<td>81</td>
</tr>
</tbody>
</table>
3.3 Rearrangement of cyclic allylamines

Inspired by our observations that branched allylamines undergo palladium-catalyzed acid-promoted isomerization, we envisioned a straightforward access to complex amines by skeletal rearrangements of allylamine scaffolds. This methodology can be strategically applied to late-stage modifications of complex amines by using amine-containing fragments as both nucleophiles and leaving group precursors, especially since amines that do not bear electron-withdrawing substituents have long been recognized for their reluctance to undergo palladium-catalyzed C-N bond scission.  

Table 3.14 shows the condition optimization for the isomerization-driven ring construction. We were encouraged that in dichloromethane tetrahydroazepine 3.74 gave the corresponding 2-prenyl pyrrolidine 3.107 in 50% yield after 8 hours (Table 3.14 Entry 2). 1 equiv. TFA was employed to activate the amine. Interestingly, the addition of morpholine (10 mol%) gave further boost and pushed the reaction to completion (Table 3.14 Entry 3). With no ligand present, the rearrangement of 3.74 provided no conversion (Table 3.14 Entry 4). Likewise, no conversion was observed when the reaction was performed with triethyl phosphite, but without any source of palladium. In addition, uncatalyzed alkene isomerization of 3.74 was not observed. Switching the solvent to THF with or without the addition of morpholine gave no conversion (Table 3.14 Entries 1,5). Reaction with only 5 mol % TFA gave no conversion with or without morpholine added (Table 3.14 Entries 6 and 7).

Table 3.14 Condition optimization for Palladium-catalyzed aza-allylic rearrangement

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Additive</th>
<th>% Conv (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(OEt)₃</td>
<td>THF</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>P(OEt)₃</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Entry</td>
<td>Ligand/Reagent</td>
<td>Solvent</td>
<td>Additive</td>
<td>Conversion (%)</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>---------</td>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>3</td>
<td>P(OEt)$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>morpholine</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>CH$_2$Cl$_2$</td>
<td>morpholine</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>P(OEt)$_3$</td>
<td>THF</td>
<td>morpholine</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>P(OEt)$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>-</td>
<td>0$^b$</td>
</tr>
<tr>
<td>7</td>
<td>P(OEt)$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>morpholine</td>
<td>0$^b$</td>
</tr>
<tr>
<td>8</td>
<td>P(OEt)$_3$</td>
<td>CH$_2$Cl$_2$</td>
<td>N-methylmorpholine</td>
<td>100</td>
</tr>
</tbody>
</table>

$^a$Conversion was monitored by $^1$H-NMR. $^b$5mol% acid was used.

Originally, morpholine was added with the intention to help activate the catalyst. However, the reaction did achieve 50% conversion in the absence of morpholine, which suggests that the catalyst is being activated via a different pathway. Another possibility is that morpholine acts as a nucleophilic catalyst in the reaction. To test if this was the case, morpholine was replaced with N-methylmorpholine. This modification gave full conversion (Table 3.14, entry 8), which suggests that morpholine does not act as a catalyst. In addition, morpholine-containing products have never been isolated or observed spectroscopically during our studies. The only other possibility is that morpholine acts as a buffer by generating morpholinium trifluoroacetate in situ, which acts as an active acid to allow for the controlled protonation of the starting tetrahydroazepine. Such careful protonation is necessary to avoid the undesirable protonation of palladium catalyst or the ligand. Indeed, even in the presence of morpholine the reaction fails when a phosphite ligand is replaced by a phosphine (Table 3.14, entry 9).

The reaction substrate scope is shown in Tables 3.15 – 3.19. **3.74** was chosen to be the test substrate for the condition optimization because it is the most biased one in the sense that upon rearrangement it would give the more-stable alkene, as well as the more stable ring. The corresponding amide **3.48** (Table 3.15, entry 2) did not undergo the rearrangement reaction, most likely because on one hand amides are poor leaving groups, while on the other hand, they are not basic enough to be activated by acid. In contrast heterocycles **3.103** and **3.104** (Table 3.15, entries 3,4) underwent full hydrolysis after being subjected to the reaction conditions. At this
point it became clear that the window of reactivity for this reaction is very narrow, and a suitable substrate has to be basic enough to be activated by acid, and yet it cannot be sensitive to acid hydrolysis.

We have turned back to our test substrate trying to figure out which element was tipping the balance in favour of the product. Subjecting tetrahydroazepines 3.75 and 3.82 to the reaction conditions yielded the corresponding 2-vinylic pyrrolidines with di- and monosubstituted alkenes, respectively, in high yield (Table 3.15, entries 5 and 7). Similar yields were observed when analogous hexahydroazocines 3.76 and 3.83 were used in place of tetrahydroazepines (Table 3.15 entries 6 and 8). In cases where disubstituted olefins were observed, trans-isomers formed preferentially. The fact that products containing the less-substituted alkenes formed in high yields suggests that the rearrangement is primarily driven by the stability of the ring, which is why it is not surprising that tetrahydropyridine 3.93 (Table 3.15, entries 9) failed to form the corresponding vinylazetidine. On the contrary, the reverse of this reaction is strongly favoured and proceeds in high yield (Table 3.19, entry 6). The formation of the more stable ring also overrides the formation of a conjugated alkene, as can be seen from the attempted ring-expansion of a tetrahydroisoquinoline 3.94 that would lead to an eight-membered ring with the alkene conjugated to the aromatic ring, if this reaction were favourable (Table 3.15, entry 10).

**Table 3.15** Substrate scope for the aza-allylic rearrangement

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>product</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3.74" alt="NPMB" /></td>
<td><img src="3.107" alt="PMB" /></td>
<td>CH$_2$Cl$_2$</td>
<td>97</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Compound</td>
<td>Solvent</td>
<td>Yield</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------</td>
<td>-----------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>S.M.</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>Ph₂NH₂</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>Et₂O₂</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>CH₂Cl₂</td>
<td>94</td>
<td>(E/Z=3.6:1)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>DCE</td>
<td>92</td>
<td>(E/Z=4.6:1)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>CH₂Cl₂</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td>CH₂Cl₂</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
<td>S.M.</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td><img src="image9.png" alt="Chemical Structure" /></td>
<td>S.M.</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 3.16 Substrate scope for the rearrangement of α-substituted cyclic amines

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>product</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Reactant 1]</td>
<td>decomposition</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>![Reactant 2]</td>
<td>decomposition</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>![Reactant 3]</td>
<td>![Product 3]</td>
<td>DCE</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>![Reactant 4]</td>
<td>![Product 4]</td>
<td>CH₂Cl₂</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>![Reactant 5]</td>
<td>![Product 5]</td>
<td>DCE</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>![Reactant 6]</td>
<td>![Product 6]</td>
<td>DCE</td>
<td>68</td>
</tr>
</tbody>
</table>

So far, all the ring-contraction examples that were shown led to the formation of products containing a single chiral centre. We were interested in whether it would be possible to control the diastereoselectivity of this reaction. To test this we have subjected seven- and eight-membered precursors (Table 3.16, entries 1-6) to the reaction conditions. None of the subjected allylamines gave the rearranged products except for 3.85, which rearranged to the
Table 3.17 Substrate scope for the rearrangement of γ-substituted cyclic amines

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>product</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Reactant 1" /></td>
<td>S.M. 3.77</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Reactant 2" /></td>
<td>S.M. 3.80</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Reactant 3" /></td>
<td>S.M. 3.78</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Reactant 4" /></td>
<td>S.M. 3.79</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Reactant 5" /></td>
<td>S.M. 3.81</td>
<td>DCE</td>
<td>-</td>
</tr>
</tbody>
</table>

corresponding piperidine 3.113 in good yield with a 3:1 selectivity for the trans-isomer. When dichloromethane was replaced with dichloroethane, tetrahydroazepines 3.84 and 3.91 (Table 3.16, entries 1, 2) fully decomposed, whereas tetrahydroazepines 3.89, 3.90, and 3.119 (Table 3.16, entries 3-6) gave the corresponding ring-contracted products in modest yields with very low selectivity for the trans-product. Such poor selectivities are probably thermodynamic in nature, and reflect the difference in relative stability between the trans- and the cis- isomers. Moreover, the resulting chiral centres are not contiguous, and are less likely to affect each other.
Tetrahydroazepines 3.77, 3.80, and 3.78 with substituents in the 4-positions (Table 3.17, entries 1-3) were designed such that in case the rearrangement did occur, the products would contain two contiguous chiral centres, therefore, the diastereoselectivity would likely be higher. Unfortunately, none of these substrates underwent the rearrangement, probably due to the excessive steric interactions between the substituents that are placed in close proximity during cyclization (Scheme 3.13). Likewise, 3.79 and 3.81 gave no rearranged product, most likely for the same reason.

Scheme 3.13 Rationale for the absence in reactivity of 3.77 – 3.80.

One possible solution to this problem was to remove the PMB protecting group, which was expected to alleviate the interactions between the remaining vicinal substituents. Ironically, at this point we realized how difficult it would be to remove this protecting group (Table 3.18). None of the oxidative cleavage protocols led to any conversion even at elevated temperatures. An attempt to form an amide using chloroethyl chloroformate also did not give any conversion, whereas hydrogenolysis seemed to reduce the alkene. Despite the current difficulties, substrates of this class have the highest probability of showing high diastereoselectivity, which is why their preparation is worth pursuing.

Table 3.18 Condition screen for the attempted PMB deprotection

<table>
<thead>
<tr>
<th>entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ, CH₂Cl₂/H₂O reflux</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>DDQ, DCE/H₂O reflux</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>CAN, MeCN/H₂O reflux</td>
<td>S.M.</td>
</tr>
<tr>
<td>4</td>
<td>1. C₂Cl₂, THF, -78°C-&gt;rt</td>
<td>S.M.</td>
</tr>
</tbody>
</table>
Another class of substrates that was subjected to the rearrangement reaction contained an extra heteroatom (Table 3.19, entries 1-3). Unlike oxazolidine and thiazolidine (Table 3.15, entries 3,4), these heterocycles did not contain the carbanolamine elements and thus were expected to be stable to acid hydrolysis. When subjected to the reaction conditions, tetrahydrodiazocine 3.88 gave the corresponding tetrahydroquinoxaline 3.116 in good yield (Table 3.19, entry 1). Similarly, dihydrooxazocine 3.86 gave the expected dihydrobenzooxazine 3.117 along with its isomer 3.117’, which was formed from the ionization of the phenol ether (Table 3.19, entry 2). Indeed, phenoxide is a good leaving group, and has been utilized as a leaving group in allylic alkylation. Unfortunately, at this point, there is no control over chemoselectivity of this system as both products form in an equimolar ratio. Interestingly, the homologated version of this substrate, 3.87, showed no conversion to the expected tetrahydrobenzooxazepine (Table 3.19, entry 3). This is unusual because 9-membered rings are less stable than the 7-membered once, therefore the equilibrium should favour the product. In addition, the ring-closing step is not likely to be problematic because the preparation of the desired product of this reaction has been achieved using the classical intramolecular allylic amination. This result indicates that the reaction must be failing due to the ionization step. While attaining the reactive conformation is a necessary requirement for any intramolecular reaction, it is unlikely to be an issue, since nine-membered rings are even more flexible than eight-membered rings, which means that 3.87 should be even more reactive than 3.86. The only other key difference between these two substrates is electronics. Both substrates are anilines, however, 3.86 is also a phenol ether, which makes the aniline much more basic when compared to 3.87, where oxygen cannot contribute to resonance, and can only make the aniline less basic via σ-induction. As a result, effective protonation of the weaker aniline in the already-buffered system is quite low. Substrate 3.88 is even more electron rich, which explains why product 3.116 is also formed in a high yield. In order to delineate the basicity from reactive conformation factors, the ideal substrate that would
support or disprove this hypothesis would be an isomer of 3.87, where oxygen would be bonded directly to the aromatic ring.

Table 3.19 Substrate scope for the rearrangement of bicyclic amines

<table>
<thead>
<tr>
<th>entry</th>
<th>reactant</th>
<th>product</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3.88" alt="Image" /></td>
<td><img src="3.116" alt="Image" /></td>
<td>CH₂Cl₂</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td><img src="3.86" alt="Image" /></td>
<td><img src="3.117" alt="Image" /></td>
<td>CH₂Cl₂</td>
<td>83 (1:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="3.87" alt="Image" /></td>
<td>S.M.</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td><img src="3.102" alt="Image" /></td>
<td>S.M.</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td><img src="3.100" alt="Image" /></td>
<td>S.M.</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td><img src="3.98" alt="Image" /></td>
<td><img src="3.118" alt="Image" /></td>
<td>CH₂Cl₂</td>
<td>96</td>
</tr>
</tbody>
</table>
For the ring-expansion chemistry, once the simple vinyl azetidine 3.98 rearranged to give the expected tetrahydropyridine 3.118 (Table 3.19, entry 6), we became interested in whether we could use strain to drive the rearrangement of two rings simultaneously in a fused bicyclic system. To test this out we have prepared bicycles 3.100 and 3.102 (Table 3.19, entries 4,5) and subjected them to the reaction conditions. Surprisingly, none of them showed any conversion even in DCE at reflux. Such difference in behavior between the simple vinyl azetidine 3.98 and its bicyclic analogues 3.100 and 3.102, must be embedded in the ability to reach the reactive conformation. For the simple vinyl azetidine the vinyl group has rotational freedom, and therefore can easily reach a conformation where it would be orthogonal to the C – N bond (Scheme 3.14). Such condition is necessary to ensure the favourable overlap between the π-orbital of the alkene and the σ* orbital of the C – N bond. On the other hand, in a bicyclic system, the vinyl group is part of another ring. For the bicyclic system 3.100, the reactive conformation can be reached either at the cost of bending one of the C – C – N angles, or forcing the 6-membered ring to adopt the boat conformation (Scheme 3.15).
Scheme 3.14 Rationale for the observed reactivity of 3.98

In addition to the ring-opening step, the ring-closing step may also be problematic. In contrast to the simple vinyl azetidine, in the bicyclic system 3.100 the carbocyclic 6-membered ring of the flat π-allyl intermediate has to adopt another boat conformation in order for the N-benzylaminomethylene tether to be able to reach over to the other terminus of the allyl fragment, thus forming the corresponding [2.2.2] product. Such changes in conformation lead to the build-up of torsional as well as transannular strain.

Scheme 3.15 Rationale behind the inertness of 3.100 and 3.102

Finally, bicyclic systems containing aziridines (Table 3.19, entries 5,6) also failed to undergo the rearrangement, leading to the full recovery of the starting material. In addition to the arguments
that were used to describe the challenges with azetidine-containing systems, which in case of aziridines become even more significant due to the fact that the bridging fragment is even shorter, basicity factors should also be taken into consideration. Both aziridine and hydrazine elements are present in these systems, and coincidentally, the presence of either of these elements is required in order for an allyl amine to resist the necessary protonation by acid.\textsuperscript{20}

By looking at Tables 3.15 – 3.19, it can be concluded that similarly to the branched-to-linear isomerization, thermodynamics governs the feasibility of the aza-allylic rearrangement. There are, however, important differences between the two processes. First of all, in the branched-to-linear isomerization, the stability of the alkene governs the direction of the process, whereas for the rearrangement, the product with the most-stable ring, irrespective of the substitution on the alkene, will always be preferred. Secondly, the aza-allylic rearrangement is an intramolecular process, and therefore the achievement of the reactive conformation can further limit the types of substrates that are likely to react based on the differences in ground-state energy between them and their corresponding products alone.

Analogous to the branched-to-linear isomerization, the solvent plays a crucial role in aza-allylic rearrangement. As can be seen from Tables 3.15 – 3.19, the reaction proceeds in CH\textsubscript{2}Cl\textsubscript{2} and not at all in THF. The rational involving reactivity of certain palladium-containing intermediates in allylic amination is not reliable, as it would only explain the behavior of certain substrates, such as entry 3.74 (Scheme 3.16).
Scheme 3.16 Pd σ-allylic intermediates fail to explain the outcome of aza-allylic rearrangement

Assuming that σ-complex is the reactive species in THF, entry 1 would not be expected to react because in order for it to form the expected product, the amine would have to attack sigma I in S_N2 fashion, which is unlikely given the size of palladium-based leaving group. Alternatively, the attack could proceed on sigma II via S_N2’ pathway, however, concentration and the rate of formation of sigma II are expected to be very low due to the steric repulsions between palladium centre and the two methyl groups.

On the other hand, the same argument predicts the unobserved reactivity of 3.82. The attack on the unhindered sigma IV is expected to proceed via the favourable S_N2’ mechanism, which is why, it is surprising that no reaction is observed.

It appears that the only thermodynamic effect that could explain both isomerization and the aza-allylic rearrangement, is the difference in acidity of morpholinium trifluoroacetate in THF and DCM. In THF this salt may exist as an ion pair shielded by the solvent cage, which prevents it from achieving the proton transfer to the cyclic allylamine. On the other hand, in dichloromethane, ion-pair dissociation and the proton transfer occur to a much greater extent. This explanation would also be consistent with our observations that in allylic amination in
CH\textsubscript{2}Cl\textsubscript{2} even in the presence of DBU, the full isomerization occurs after four days, whereas in THF, also in the presence of DBU, only 30\% of the linear product is seen after one week.

3.4 Conclusions and Outlook

Aza-allylic rearrangement is a special case of the previously-observed palladium-catalyzed acid promoted isomerization, that is applied to the synthesis of heterocycles. Even though challenges still remain, such as the synthesis of bridged heterocycles, fused systems containing 7-membered rings, as well as the synthesis of certain highly-substituted 5-membered heterocycles, this reaction serves as a stepping stone towards understanding the mechanistic underpinnings and the role of conformational effects in metal catalysis. In addition, owing to the masked reactivity of our system, such as the presence of a tertiary amine and the absence of any apparent electrophiles, the aza-allylic rearrangement has potential in finding applications in synthesis, perhaps, serving as a late-stage modification tool. For example, we can see the emergence of new non-trivial disconnection approaches in the synthesis of polysubstituted saturated heterocycles such as dehydrogenation to form an allylamine, preceded by ring rearrangement.

3.5 Experimental Details

3.5.1 General aspects

General. Anhydrous acetonitrile, dichloromethane, diethyl ether, and toluene were obtained using the method described by Grubbs.\textsuperscript{22} Tetrahydrofuran (THF) was distilled from sodium benzophenone under argon. Acetone was stored over 4Å molecular sieves.
**Chromatography.** Column chromatography was carried out using Silicycle 230-400 mesh silica gel or aluminum oxide, neutral, Brockman type 1. Analytical thin layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass-backed TLC plates (SIL G/UV254, 0.25 mm) and visualized by UV lamp (254 nm), iodine and potassium permanganate stains. Gas-phase chromatography (GC) was performed on a Hewlett Packard HP-6890 series instrument using an HP-5 column (crosslinked 5% phenyl methyl siloxane, 30 m x 0.32 mm x 0.25 µm film thickness). Oven was heated at 50°C for 5 min followed by a temperature gradient of 10°C/min to 250°C followed by being held at 250°C for 10 min. Inlet temperature and pressure were 200°C and 4.88 psi respectively, with a split ratio of 50:1. Hydrogen was the carrier gas. Internal standard was biphenyl (T = 15.6 min).

**Nuclear magnetic resonance spectra.** $^1$H and $^{13}$C spectra were recorded on a Varian Mercury 300, VRX-S (Unity) 400 or Unity 500 spectrometer. $^1$H NMR spectra were referenced to TMS (0 ppm) and $^{13}$C NMR spectra were referenced to CDCl$_3$ (77.23 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; td, triplet of doublets; br, broad; and $J$, coupling constant in Hz.

### 3.5.2 Synthesis of acyclic dialkenes

![N-(4-methoxybenzyl)hex-5-enamide (3.2)](image)

**N-(4-methoxybenzyl)hex-5-enamide (3.2)**

In a round bottom flask equipped with a stir bar dicyclohexylidiamide (42 mmoles, 8.67 g) was dissolved in anhydrous dichloromethane (120 mL). To the resulting solution 5-hexenoic acid (42 mmol, 4.81 g), DMAP (2.1 mmol, 0.256 g) and $p$-methoxybenzylamine (42 mmol, 5.76 g) were added. The reaction was allowed to stir at room temperature overnight. White precipitate was
filtered off, and filtrate was washed with 5% sulfuric acid, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified using flash chromatography (Hex/EtOAc = 4:1, Rf = 0.41 in a corresponding 1:1 mixture) to yield 3.2 (29.4 mmol, 6.90 g, 70%) as a white amorphous solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.20 (d, \(J = 8.4\) Hz, 2H), 6.86 (d, \(J = 8.4\) Hz, 2H), 5.77 (ddt, \(J = 16.9, 10.0, 6.7\) Hz, 1H), 5.68 (br, NH), 5.07-4.95 (m, 2H), 4.37 (d, \(J = 5.5\) Hz, 2H), 3.80 (s, 3H), 2.20 (t, \(J = 7.5\) Hz, 2H), 2.09 (dd, \(J = 14.0, 6.9\) Hz, 2H), 1.82 – 1.71 (m, 1H). \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 172.6, 159.2, 138.0, 130.6, 129.3, 115.5, 114.2, 55.4, 43.2, 36.1, 33.3, 24.9. ESI [M+1]^+ = 234.1(100%), [M+2]^+ = 235.1(15%)

\[\text{N-(4-methoxybenzyl)pent-4-enamide (3.2')}\]

Yield = 76%, amorphous solid. Rf = 0.41 (hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.20 (d, \(J = 8.7\) Hz, 2H), 6.86 (d, \(J = 8.7\) Hz, 2H), 5.83 (ddt, \(J = 17.0, 10.2, 6.4\) Hz, 1H), 5.65 (s, 1H), 5.07 (dd, \(J = 17.0, 1.6\) Hz, 1H), 5.01 (dd, \(J = 10.2, 1.6\) Hz, 1H), 4.37 (d, \(J = 5.6\) Hz, 2H), 3.80 (s, 3H), 2.49 – 2.35 (m, 2H), 2.33 – 2.25 (m, 2H).

\[\text{N-(4-methoxybenzyl)hex-5-en-1-amine (3.3')}\]

In a flame-dried round bottom flask equipped with a stir bar lithium aluminum hydride (42.8 mmol, 1.62 g) was weighed in. The powder was mixed with 150 mL of anhydrous THF, and the reaction mixture was allowed to cool down to 0°C. After that anhydrous aluminum chloride (13.6 mmol, 1.82 g) was transferred in small portions to the reaction vial under the flow of nitrogen. The reaction mixture was allowed to stir at 0°C for additional 15 minutes after which 3.2 (21.4
mmol, 5.0 g) was transferred to the reaction mixture. The reaction flask was equipped with a condenser and the reaction was allowed to stir at 50°C overnight. After that the reaction mixture was cooled down to 0°C followed by the addition of 1.6 mL of distilled water, 1.6 mL of 10% NaOH(aq), and 4.8 mL of distilled water. The resulting mixture was filtered through celite and the filtrate was diluted with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated. The crude product was not purified any further to yield 3.3 (10.7 mmol, 2.32 g, 50%) as a yellow honey-like semisolid.

\[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz): } \delta 7.23 (d, J = 8.7 \text{ Hz}, 2H), 6.86 (d, J = 8.7 \text{ Hz}, 2H), 5.80 (ddt, J = 17.0, 10.2, 6.7 \text{ Hz}, 1H), 4.99 (dq, J = 17.0, 2.1 \text{ Hz}, 1H), 4.94 (dm, J = 10.2, 2.1 \text{ Hz}, 1H), 3.79 (s, 3H), 3.72 (s, 2H), 2.62 (t, J = 7.3 \text{ Hz}, 2H), 2.05 (qt, J = 7.1, 1.4 \text{ Hz}, 2H), 1.59 – 1.47 (m, 2H), 1.46 – 1.37 (m, 2H). \]

\[ N-(4\text{-methoxybenzyl})\text{pent-4-en-1-amine (3.3')} \]

Yield = 64%, honey-like semisolid. \[ ^1H \text{ NMR (CDCl}_3, 300 \text{ MHz): } \delta 7.26 (d, J = 8.5 \text{ Hz}, 2H), 6.86 (d, J = 8.5 \text{ Hz}, 2H), 5.80 (ddt, J = 17.0, 10.2, 6.7 \text{ Hz}, 1H), 5.01 (dd, J = 17.0, 1.5 \text{ Hz}, 1H), 4.95 (dd, J = 10.2, 1.0 \text{ Hz}, 1H), 3.79 (s, 3H), 3.74 (s, 2H), 2.64 (t, J = 7.2 \text{ Hz}, 2H), 2.13-2.06 (m, 2H), 1.71 – 1.57 (m, 2H). \]

\[ N-(4\text{-methoxybenzyl})\text{-2-methylbut-3-en-2-amine (3.5)} \]
In a 17 x 60 mm screw cap vial, equipped with septum and magnetic stir bar, were placed [Pd(η^3-C_3H_5)Cl]_2 (5 mg, 0.0137 mmol) and dry THF (1.3 mL). P(OEt)_3 (9µL, 0.0547 mmol), DBU (0.21 mL, 1.40 mmol), prenyl acetate 2a (0.19 mL, 1.37 mmol) and 4-methoxybenzylamine (0.180 mL, 1.37 mmol) were added via syringe and the solution was stirred under argon at 50°C for 20h; when GC analysis showed no remaining prenyl acetate 2a. (GC retention time of 3.5: T = 17.9 min). Water (4 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and the residue was purified by flash chromatography (R_f = 0.31, SiO_2, 19:1 CH_2Cl_2/MeOH) to yield 3.5 (238 mg, 1.16 mmol, 85%) as a clear oil.

1H NMR (CDCl_3, 300 MHz): δ 7.25 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 5.84 (dd, J = 17.9, 10.6 Hz, 1H), 5.11 (dd, J = 5.6, 1.2 Hz, 1H), 5.08-5.06 (m, 1H), 3.78 (s, 3H), 3.57 (s, 2H), 1.23 (s, 6H). 13C NMR (CDCl_3, 75 MHz): δ 158.5, 146.1, 138.2, 129.4, 113.8, 112.2, 55.3, 54.7, 46.9, 27.0. HRMS (ESI) [M+H]^+ calcd. for C_{13}H_{19}NO 206.1539, found 206.1541.

N-(4-methoxybenzyl)but-3-en-2-amine (3.6).

Yield = 82%, clear oil. R_f = 0.40 (SiO_2, 19:1 CH_2Cl_2/MeOH). 1H NMR (CDCl_3, 300 MHz): δ 7.22 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 5.71 (ddd, J = 17.6, 10.0, 7.6 Hz, 1H), 5.11 (dd, J = 17.6, 1.2 Hz, 1H), 5.07 (dd, J = 10.0, 1.2 Hz, 1H), 3.79 (s, 3H), 3.77 (d, J = 12.9 Hz 1H), 3.61 (d, 12.9 Hz, 1H), 3.26-3.15 (m, 1H), 1.34 (s, 1H), 1.16 (d, J = 6.4 Hz 3H). 13C NMR (CDCl_3, 75 MHz): δ 158.4, 142.5, 132.6, 129.2, 114.5, 113.6, 55.8, 55.1, 50.6, 21.6.
N-(4-methoxybenzyl)-N-(3-methylbut-2-en-1-yl)hex-5-en-1-amine (3.4)

Yield = 15%, yellow oil. Rf = 0.52 (CH₂Cl₂/MeOH = 19:1). ^1H NMR (300 MHz, CDCl₃) δ 7.22 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.87 – 5.65 (m, 1H), 5.27 (t, J = 6.7 Hz, 1H), 4.96 (dd, J = 22.8, 5.8 Hz, 2H), 3.79 (s, 3H), 3.48 (s, 2H), 2.99 (d, J = 6.6 Hz, 2H), 2.47 – 2.30 (m, 2H), 2.02 (dd, J = 14.1, 7.0 Hz, 2H), 1.72 (s, 3H), 1.59 (s, 3H), 1.48 (dd, J = 14.8, 7.6 Hz, 2H), 1.35 (dd, J = 13.6, 6.9 Hz, 2H). ESI [M+1]^+ = 288.2(100%), [M+2]^+ = 289.2(15%).

N-(4-methoxybenzyl)-N-(2-methylbut-3-en-2-yl)pent-4-enamide (3.7)

In a flame-dried flask equipped with a stir bar 4-pentenoic acid (40.2 mmol, 4.02 g) was mixed with thionyl chloride (48.2 mmol, 5.73 g) at 0 °C. The resulting mixture was allowed to stir at reflux for 5 hours, after which it was concentrated and added drop wise to a stirring mixture of 3.5 (12 mmol, 2.47 g) and triethylamine (35 mmol, 3.50 g) dissolved in 17 mL of anhydrous THF at 0 °C. The final mixture was allowed to warm up room temperature and was stirred overnight. The reaction mixture was concentrated, diluted with dichloromethane, washed with sodium bicarbonate, extracted 3 times with dichloromethane, dried over anhydrous sodium sulfate, and concentrated. The crude mixture was purified by flash chromatography (Hex/EtOAc = 9:1, Rf = 0.097) to yield 3.7 (8.04 mmol, 2.31 g, 67% yield) as a yellow oil.

^1H NMR (CDCl₃, 300 MHz): δ 7.13 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.08 (dd, J = 17.5, 10.8 Hz, 1H), 5.87 – 5.73 (m, 1H), 5.08 – 4.89 (m, 4H), 4.55 (s, 2H), 3.81 (s, 3H), 2.38-2.37 (m, 4H), 1.48 (s, 6H). ^13C NMR (CDCl₃, 75 MHz): δ 173.8, 158.7, 145.9, 137.8, 131.4,
126.9, 115.2, 114.3, 110.6, 61.0, 55.4, 48.4, 35.1, 29.7, 26.5. ESI [M+1]$^+$ = 288.2(100%), [M+2]$^+$ = 289.2(15%).

\[ \text{N-(but-3-en-2-yl)-N-(4-methoxybenzyl)pent-4-enamide (3.8)} \]

Yield = 70%, yellow oil. $R_f$ = 0.097 (SiO$_2$, Hex/EtOAc = 9:1). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$

**Major Rotomer**

7.10 (d, $J$ = 8.5 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 5.96 – 5.71 (m, 2H), 5.20 – 4.88 (m, 4H), 4.59 – 4.50 (m, 1H), 4.43 (d, $J$ = 17.6 Hz, 1H), 4.33 (d, $J$ = 17.6 Hz, 1H), 3.78 (s, 3H), 2.42 – 2.27 (m, 4H), 1.18 (d, $J$ = 6.9 Hz, 2H).

**Minor Rotomer**

7.16 (d, $J$ = 8.4 Hz, 2H), 6.80 (d, $J$ = 8.4 Hz, 2H), 5.96 – 5.71 (m, 2H), 5.20 – 4.88 (m, 4H), 4.72 (d, $J$ = 15.2 Hz, 1H), 4.19 (d, $J$ = 15.3 Hz, 1H), 3.76 (s, 3H), 2.59 – 2.42 (m, 4H), 1.23 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): Mixture of rotomers $\delta$ 173.1, 172.7, 138.3, 137.5, 137.4, 131.6, 130.2, 128.5, 127.0, 115.8, 115.6, 115.1, 114.0, 113.6, 55.2, 54.6, 51.3, 46.5, 44.9, 33.2, 29.5, 18.5, 16.7. ESI [M+1]$^+$ = 274.2 (100%), [M+2]$^+$ = 275.2(15%).

\[ \text{N-(but-3-en-2-yl)-N-(4-methoxybenzyl)hex-5-enamide (3.9)} \]

Yield = 65%, yellow oil. $R_f$ = 0.097 (SiO$_2$, Hex/EtOAc = 9:1). $^1$H NMR (CDCl$_3$, 400 MHz):

**Major rotamer:** $\delta$ 7.06 (d, $J$ = 8.5 Hz, 2H), 6.88 – 6.80 (m, 2H), 5.80 – 5.70 (m, 2H), 5.15 – 5.00 (m, 2H), 4.94 – 4.86 (m, 2H), 4.38 (d, $J$ = 17.5 Hz, 1H), 4.29 (d, $J$ = 17.6 Hz, 1H), 3.81 – 3.65 (m, 3H), 2.24 – 2.15 (m, 2H), 1.98 (dd, $J$ = 13.4, 6.3 Hz, 2H), 1.70 (dd, $J$ = 9.8, 4.9 Hz, 2H),
1.15 (d, $J = 6.9$ Hz, 3H). **Minor rotamer:** δ 7.12 (d, $J = 8.3$ Hz, 2H), 6.77 (t, $J = 7.1$ Hz, 2H), 5.80 – 5.70 (m, 2H), 4.94 – 4.86 (m, 2H), 4.68 (d, $J = 15.3$ Hz, 1H), 4.15 (d, $J = 15.3$ Hz, 1H), 3.81 – 3.65 (m, 3H), 2.39 (dd, $J = 10.3$, 4.1 Hz, 2H), 2.11 (d, $J = 6.9$ Hz, 2H), 1.70 (dd, $J = 9.8$, 4.9 Hz, 2H), 1.19 (d, $J = 6.9$ Hz, 1H).

**$^{13}$C NMR (CDCl$_3$, 100 MHz)** Both rotamers: δ 173.7, 173.3, 138.4, 138.1, 130.4, 128.6, 127.5, 127.0, 115.8, 115.6, 115.2, 115.1, 114.9, 114.3, 114.2, 114.0, 113.6, 55.2, 54.6, 51.3, 46.6, 44.8, 33.3, 33.2, 33.1, 32.8, 24.6, 24.5, 18.5, 16.7. ESI [M+1]$^+$ = 288.2 (100%), [M+2]$^+$ = 289.2 (15%).

methyl 3-phenylpent-4-enoate (3.10)$^{26}$

To a flame-dried vial equipped with a stir bar, trimethylorthoacetate (69.5 mmol, 8.8 mL) was mixed with cinnamyl alcohol (13.9 mmol, 1.8 mL) and propionic acid (0.84 mmol, 0.07 mL). The reaction was allowed to stir for 24 hours at 120°C. The reaction mixture was poured into ether, washed with 1.0 N sulfuric acid. The organic layer was washed with water, sodium bicarbonate and brine. The organic layer was dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified on SiO$_2$ (hex/EtOAc = 9:1, $R_f$ = 0.63) to give 3.10 in 66% yield.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.37 – 7.12 (m, 5H), 5.98 (ddd, $J = 17.3$, 10.0, 7.0 Hz, 1H), 5.10 (d, $J = 1.2$ Hz, 1H), 5.05 (dd, $J = 4.6$, 1.0 Hz, 1H), 3.87 (q, $J = 7.4$ Hz, 1H), 3.62 (s, 3H), 2.87 – 2.61 (m, 2H).

methyl 3-methylpent-4-enoate (3.11)$^{27}$
Yield = 54%. R<sub>f</sub> = 0.63 (SiO<sub>2</sub>, Hex/EtOAc = 9:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.37 – 7.12 (m, 5H), 5.98 (ddd, <i>J</i> = 17.3, 10.0, 7.0 Hz, 1H), 5.10 (d, <i>J</i> = 1.2 Hz, 1H), 5.05 (dd, <i>J</i> = 4.6, 1.0 Hz, 1H), 3.87 (q, <i>J</i> = 7.4 Hz, 1H), 3.62 (s, 3H), 2.87 – 2.61 (m, 2H).

![methyl 3,3-dimethylpent-4-enoate (3.12)]

methyl 3,3-dimethylpent-4-enoate (3.12)<sup>28</sup>

Yield = 75%. R<sub>f</sub> = 0.63 (SiO<sub>2</sub>, Hex/EtOAc = 9:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 5.90 (dd, <i>J</i> = 17.4, 10.7 Hz, 1H), 5 – 4.93 (m, 2H), 3.64 (s, 3H), 2.31 (s, 2H), 1.76 (s, 1H), 1.71 (s, 1H), 1.13 (s, 6H).

![methyl 3-vinylhexanoate (3.13)]

methyl 3-vinylhexanoate (3.13)<sup>29</sup>

Yield = 38%. R<sub>f</sub> = 0.63 (SiO<sub>2</sub>, Hex/EtOAc = 9:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 5.62 (ddd, <i>J</i> = 17.3, 10.2, 8.4 Hz, 1H), 5.13 – 4.76 (m, 2H), 3.65 (s, 3H), 2.54 – 2.52 (m, 1H), 2.41 – 2.25 (m, 2H), 1.44 – 1.19 (m, 4H), 0.99 – 0.79 (m, 3H).

![methyl 4-methylpent-4-enoate (3.14)]

methyl 4-methylpent-4-enoate (3.14)<sup>30</sup>

Yield = 60%. R<sub>f</sub> = 0.63 (SiO<sub>2</sub>, Hex/EtOAc = 9:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 4.75 (s, 1H), 4.69 (s, 1H), 3.68 (s, 3H), 2.53 – 2.42 (m, 2H), 2.39 – 2.26 (m, 2H), 1.74 (s, 3H).
**N-(4-methoxybenzyl)-3-phenylpent-4-enamide (3.15)**

In a flame-dried round-bottom flask p-methoxybenzylamine (42.50 mmol, 5.5 mL) was dissolved in 25 mL of anhydrous THF. The reaction was cooled down to 0°C and DIBAL-H solution in toluene (40.75 mmol, 27 mL) was added slowly. The reaction mixture was then allowed to warm up to room temperature, and was stirred for 2 hours. This solution was transferred via canula under nitrogen into a flask containing 3.10 (8.67 mmol, 1.65 g) dissolved in 45 mL of anhydrous THF and cooled to 0°C. The resulting solution was allowed to stir overnight. The reaction was quenched with aqueous solution of sodium hydroxide (10% w/v), extracted with ethyl acetate, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified on SiO₂ (hex/EtOAc = 9:1, Rf = 0.13) to give 3.15 in 76% yield as a clear oil. ¹H NMR (399 MHz, cdcl₃) δ 7.32 – 7.20 (m, 8H), 6.96 (d, J = 8.5 Hz, 2H), 6.81 – 6.73 (m, 1H), 6.09 – 5.94 (m, 1H), 5.10 (d, J = 1.3 Hz, 1H), 5.07 (dt, J = 7.5, 1.2 Hz, 1H), 4.37 – 4.27 (m, 1H), 4.22 (dd, J = 14.6, 5.3 Hz, 1H), 3.92 (dd, J = 14.9, 7.0 Hz, 1H), 3.79 (s, 4H), 2.66 (dd, J = 14.0, 7.1 Hz, 1H), 2.52 (dd, J = 14.0, 8.2 Hz, 1H). ¹³C NMR (100 MHz, cdcl₃) δ 170.9, 159.1, 142.8, 140.6, 130.3, 129.1, 128.9, 127.8, 126.9, 115.1, 114.1, 55.4, 46.2, 43.2. ESI [M+1]^+ = 296.2(100%), [M+2]^+ = 297.2

**N-(4-methoxybenzyl)-3-methylpent-4-enamide (3.16)**

Yield = 76%, clear oil. Rf = 0.10 (SiO₂, Hex/EtOAc = 9:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.18 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.76 (ddd, J = 17.2, 10.2, 7.1 Hz, 1H), 5.02 (d, J = 17.2 Hz, 1H), 4.95 (d, J = 10.3 Hz, 1H), 4.34 (d, J = 5.5 Hz, 2H), 3.78 (s, 3H), 2.80 – 2.50 (m,
1H), 2.22 (dd, J = 14.0, 7.3 Hz, 1H), 2.12 (dd, J = 14.0, 7.2 Hz, 1H), 1.04 (d, J = 6.7 Hz, 3H). 

$^{13}$C NMR (CDCl$_3$, 75 MHz): δ 171.6, 159.1, 142.9, 130.6, 129.3, 114.1, 113.6, 55.4, 43.9, 43.1, 34.9, 19.8. ESI [M+1]$^+$ = 234.1(100%), [M+2]$^+$ = 235.1(15%).

\[\begin{align*}
\text{N-(4-methoxybenzyl)-3,3-dimethylpent-4-enamide (3.17)}
\end{align*}\]

Yield = 31%, clear oil. R$_f$ = 0.10 (SiO$_2$, Hex/EtOAc = 9:1). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.19 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.90 (dd, J = 17.4, 10.8 Hz, 1H), 5.01 (dd, J = 7.6, 1.0 Hz, 1H), 4.96 (s, 1H), 4.34 (d, J = 5.6 Hz, 2H), 3.80 (s, 3H), 2.20 (s, 2H), 1.13 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 170.9, 159.1, 147.4, 130.6, 129.4, 114.2, 111.8, 55.4, 49.7, 43.2, 36.5, 27.1. ESI [M+1]$^+$ = 248.2(100%), [M+2]$^+$ = 249.2(15%).

\[\begin{align*}
\text{N-(4-methoxybenzyl)-3-vinylhexanamide (3.18)}
\end{align*}\]

Yield = 53%, clear oil. R$_f$ = 0.10 (SiO$_2$, Hex/EtOAc = 9:1). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.17 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.94 (s, 1H), 5.59 (ddd, J = 17.2, 10.2, 8.5 Hz, 1H), 5.14 – 4.85 (m, 2H), 4.41 – 4.23 (m, 2H), 3.79 (d, J = 5.5 Hz, 3H), 2.62 – 2.45 (m, 1H), 2.25 (dd, J = 14.1, 5.9 Hz, 1H), 2.13 (ddd, J = 14.1, 8.5 Hz, 1H), 1.42 – 1.18 (m, 4H), 0.93 – 0.80 (m, 3H). $^1$H NMR (CDCl$_3$, 75 MHz): δ 171.7, 159.1, 141.5, 130.6, 129.2, 115.3, 114.1, 55.4, 43.1, 42.7, 40.8, 36.9, 20.2, 14.1. ESI [M+1]$^+$ = 262.2(100%), [M+2]$^+$ = 263.2(15%).
**N-(4-methoxybenzyl)-4-methylpent-4-enamide (3.19)**

Yield = 53%, clear oil. \( R_f = 0.10 \) (SiO₂, Hex/EtOAc = 9:1). \(^1\)H NMR (CDCl₃, 300 MHz): \( \delta \) 7.20 (d, \( J = 8.8 \) Hz, 2H), 6.86 (d, \( J = 8.7 \) Hz, 2H), 4.75 (s, 1H), 4.70 (s, 1H), 4.38 (d, \( J = 5.6 \) Hz, 2H), 3.80 (s, 3H), 2.36 (s, 4H), 1.74 (s, 3H).

**N-(3-phenylpent-4-en-1-yl)-N-(4-methoxybenzyl)acrylamide (3.25)**

Yield = 86%, clear oil. \( R_f = 0.71 \) (SiO₂, Hex/EtOAc = 4:1). \(^1\)H NMR (CDCl₃, 300 MHz): \( \delta \) 7.34 – 7.02 (m, 7H), 6.86 – 6.79 (m, 2H), 6.44 (dd, \( J = 34.2, 8.2 \) Hz, 2H), 5.99 – 5.84 (m, 1H), 5.70 – 5.60 (m, 1H), 5.03 (dd, \( J = 20.2, 4.3 \) Hz, 2H), 4.54 (s, 1H), 4.45 (s, 1H), 3.78 (s, 3H), 3.31 – 3.04 (m, 3H), 2.08 – 1.90 (m, 2H). \(^{13}\)C NMR (CDCl₃, 100 MHz) both rotamers: \( \delta \) 166.6, 166.3, 159.2, 159.1, 143.5, 142.9, 141.6, 141.1, 129.8, 128.9, 127.9, 127.6, 115.0, 114.6, 114.3, 114.0, 55.4, 53.5, 51.0, 48.4, 47.8, 47.4, 45.5, 45.2, 34.4, 32.6. ESI [M+1]^+ = 336.2(100%), [M+2]^+ = 337.2(23%).

**N-(3,3-dimethylpent-4-en-1-yl)-N-(4-methoxybenzyl)acrylamide (3.27)**

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Yield = 53%, clear oil. $R_f = 0.71$ (SiO$_2$, Hex/EtOAc = 4:1). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.24 – 6.76 (m, 4H), 6.64 – 6.31 (m, 2H), 5.87 – 5.55 (m, 2H), 5.11 – 4.80 (m, 2H), 4.51 (d, $J = 17.4$ Hz, 2H), 4.51 (d, $J = 17.4$ Hz, 3H), 3.42 – 3.25 (m, 1H), 3.25 – 3.04 (m, 1H), 1.64 – 1.39 (m, 2H), 0.98 (s, 6H).

N-(4-methoxybenzyl)-N-(3-vinylhexyl)acrylamide (3.28)

Yield = 37%, clear oil. $R_f = 0.71$ (SiO$_2$, Hex/EtOAc = 4:1). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.20 (d, $J = 8.5$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 1H), 6.86 (t, $J = 9.0$ Hz, 2H), 6.55 (dt, $J = 19.3$, 9.7 Hz, 1H), 6.49 – 6.30 (m, 1H), 5.78 – 5.60 (m, 1H), 5.49 (dt, $J = 19.0$, 9.6 Hz, 1H), 5.10 – 4.86 (m, 2H), 4.58 (dd, $J = 29.3$, 12.7 Hz, 2H), 3.79 (s, 3H), 3.46 – 3.00 (m, 2H), 2.08 – 1.79 (m, 1H), 1.75 – 1.55 (m, 1H), 1.55 – 1.11 (m, 5H), 0.85 (d, $J = 6.4$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 165.9, 158.7, 142.1, 129.3, 127.5, 114.5, 114.0, 113.7, 55.0, 53.3, 50.6, 48.2, 45.1, 44.9, 41.6, 37.0, 33.8, 32.0, 19.8, 13.8. ESI [M+1]$^+$ = 302.2(100%), [M+2]$^+$ = 303.2(20%).

N-(4-methoxybenzyl)-N-(4-methylpent-4-en-1-yl)acrylamide (3.29)

Yield = 62%, clear oil. $R_f = 0.71$ (SiO$_2$, Hex/EtOAc = 4:1). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.21 (d, $J = 8.4$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 6.86 (t, $J = 9.2$ Hz, 2H), 6.58 (dt, $J = 16.6$, 11.0 Hz, 1H), 6.49 – 6.31 (m, 1H), 5.85 – 5.55 (m, 1H), 4.88 – 4.30 (m, 4H), 3.79 (s, 3H), 3.53 – 3.31 (m, 1H), 3.31 – 3.16 (m, 1H), 1.99 (dt, $J = 15.5$, 7.8 Hz, 2H), 1.81 – 1.50 (m, 5H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 166.7, 166.4, 159.2, 159.0, 145.1, 144.3, 129.9, 129.6, 129.0, 128.4, 128.3, 128.0,
127.7, 114.3, 114.0, 110.8, 110.2, 55.4, 53.5, 50.8, 48.5, 46.7, 46.4, 35.2, 34.8, 26.8, 25.4, 22.4.  
ESI \([M+1]^+ = 274.2(100\%), \ [M+2]^+ = 275.2(20\%).

\[
\text{N-}(4\text{-methoxybenzyl})\text{-N-}(\text{pent-4-en-1-yl})\text{acrylamide (3.30)}
\]

Yield = 47\%, clear oil. R\(_f\) = 0.71 (SiO\(_2\), Hex/EtOAc = 4:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.20 (d, \(J = 8.5\) Hz, 1H), 7.09 (d, \(J = 8.4\) Hz, 1H), 6.86 (t, \(J = 9.3\) Hz, 2H), 6.64 – 6.49 (m, 1H), 6.46 – 6.33 (m, 1H), 5.90 – 5.61 (m, 2H), 5.04 – 4.93 (m, 2H), 4.59 – 4.53 (m, 2H), 3.78 (s, 3H), 3.47 – 3.32 (m, 1H), 3.31 – 3.19 (m, 1H), 2.12 – 1.92 (m, 2H), 1.77 – 1.49 (m, 2H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 166.4, 159.0, 137.8, 137.1, 129.5, 128.9, 128.3, 128.0, 127.6, 115.7, 114.9, 114.1, 55.2, 50.67, 48.4, 46.4, 46.1, 31.2, 30.7, 28.1, 26.6. ESI \([M+1]^+ = 260.2(100\%), \ [M+2]^+ = 261.2(15\%).

\[
\text{N-}(\text{hex-5-en-1-yl})\text{-N-}(4\text{-methoxybenzyl})\text{acrylamide (3.31)}
\]

Yield = 20\%, clear oil. R\(_f\) = 0.75 (SiO\(_2\), Hex/EtOAc = 4:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.20 (d, \(J = 8.5\) Hz, 1H), 7.09 (d, \(J = 8.5\) Hz, 1H), 6.86 (dd, \(J = 13.4, 8.6\) Hz, 2H), 6.67 – 6.49 (m, 1H), 6.47 – 6.29 (m, 1H), 5.87 – 5.57 (m, 2H), 5.07 – 4.87 (m, 2H), 4.59 (s, 1H), 4.53 (s, 1H), 3.79 (s, 3H), 3.43 – 3.35 (m, 1H), 3.29 – 3.17 (m, 1H), 2.06 – 2.01 (m, 2H), 1.66 – 1.48 (m, 2H), 1.42 – 1.32 (m, 2H). Mix of rotamers \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 166.7, 166.4, 159.2, 159.1, 138.7, 138.2, 129.6, 128.4, 127.8, 115.2, 114.8, 114.4, 114.0, 55.4, 50.7, 48.4, 46.9, 46.3, 33.6, 33.3, 28.5, 27.1, 26.4, 26.1. ESI \([M+1]^+ = 274.2(100\%), \ [M+2]^+ = 275.2(15\%).

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**N-allyl-N-(4-methoxybenzyl)pent-4-enamide (3.32)**

Yield = 83%, clear oil. R\(_f\) = 0.30 (SiO\(_2\), CH\(_2\)Cl\(_2\)/MeOH= 49:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz):  
**Major rotamer:** δ 7.18 (d, \(J = 8.6\) Hz, 2H), 6.86 – 6.75 (m, 2H), 5.96 – 5.65 (m, 2H), 5.26 – 4.91 (m, 4H), 4.53 (s, 2H), 3.99 (d, \(J = 5.9\) Hz, 4H), 3.87 – 3.71 (m, 4H), 2.54 – 2.35 (m, 4H).  
**Minor rotamer:** δ 7.08 (d, \(J = 8.6\) Hz, 2H), 6.88 (d, \(J = 8.7\) Hz, 2H), 5.96 – 5.65 (m, 2H), 5.26 – 4.91 (m, 4H), 4.45 (s, 2H), 3.99 (d, \(J = 5.9\) Hz, 1H), 3.87 – 3.71 (m, 4H), 2.54 – 2.35 (m, 4H).

**N-allyl-N-(4-methoxybenzyl)hex-5-enamide**

Yield = 83%, clear oil. R\(_f\) = 0.30 (SiO\(_2\), CH\(_2\)Cl\(_2\)/MeOH= 49:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz):  
**Major rotamer:** δ 7.16 (d, \(J = 8.7\) Hz, 2H), 6.85 – 6.78 (m, 2H), 5.86 – 5.63 (m, 2H), 5.21 – 5.07 (m, 2H), 5.07 – 4.89 (m, 2H), 4.51 (s, 2H), 3.98 (d, \(J = 5.9\) Hz, 2H), 3.77 (s, 3H), 2.43 – 2.28 (m, 2H), 2.16 – 2.02 (m, 2H), 1.86 – 1.69 (m, 2H).  
**Minor rotamer:** δ 7.06 (d, \(J = 8.7\) Hz, 2H), 6.87 (d, \(J = 8.7\) Hz, 2H), 4.42 (s, 2H), 3.98 (d, \(J = 5.9\) Hz, 2H), 3.79 (s, 3H), 2.43 – 2.28 (m, 2H), 2.16 – 2.02 (m, 2H), 1.86 – 1.69 (m, 2H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz)  
**Both rotamers:** δ 173.1, 159.0, 138.2, 133.3, 132.9, 130.0, 129.6, 127.7, 117.3, 116.7, 115.2, 114.3, 114.0, 55.4, 55.3, 49.6, 48.9, 47.7, 47.6, 33.4, 33.3, 32.5, 32.3, 24.5. ESI [M+1]+ = 274.2(100%), [M+2]+ = 275.2(15%).
N-allyl-N-(4-methoxybenzyl)pent-4-enamide (3.34)

Yield = 80%, clear oil. Rf = 0.26 (SiO2, CH2Cl2/MeOH = 99:1). 1H NMR (CDCl3, 300 MHz): δ 7.21 – 6.97 (m, 2H), 6.83 (dd, J = 13.9, 8.7 Hz, 2H), 5.88 – 5.58 (m, 2H), 5.30 – 4.90 (m, 4H), 4.68 – 4.29 (m, 2H), 3.76 (s, 3H), 2.82 – 2.60 (m, 1H), 2.44 (dd, J = 11.4, 5.0 Hz, 2H), 2.25 – 2.03 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H). 13C NMR (CDCl3, 100 MHz): δ 176.4, 176.2, 172.5, 159.1, 158.9, 136.1, 133.2, 132.8, 130.0, 129.6, 127.6, 117.4, 117.2, 116.8, 115.3, 115.2, 114.2, 113.7, 55.3, 49.5, 49.4, 48.7, 47.8, 47.6, 38.6, 36.0, 35.7, 32.6, 29.4. ESI [M+1]+ = 274.2(100%), [M+2]+ = 275.2(15%).

N-allyl-2-ethyl-N-(4-methoxybenzyl)hex-5-enamide (3.35)

In a flame-dried flask equipped with a stir bar 3.33 (0.50 mmol, 0.137 g) was dissolved in anhydrous THF (60 mL). The mixture was cooled down to -78°C. A solution of LDA (1.00 mmol, 2.0 M in THF) was added drop wise, and the reaction was allowed to stir for 5 minutes, followed by a drop-wise addition of ethyl iodide (0.60 mmol, 0.0936g). The reaction was slowly allowed to warm-up to room temperature and was left to stir overnight. Upon completion, the reaction flask was placed in an ice bath and was quenched with saturated ammonium chloride, extracted with ether, washed twice with saturated sodium bicarbonate, brine, and was dried over sodium sulfate and concentrated. The crude product was purified on silica (CH2Cl2/MeOH = 100:1, Rf = 0.26) to give 3.35 (95.3 mg, 0.31 mmol, 63%) as a yellow oil.
\[ \text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ 7.19 (d, } J = 8.7 \text{ Hz, 2H) (Maj. Rot.), 7.10 (d, } J = 8.8 \text{ Hz, 2H) (Min. Rot.), 6.89 (d, } J = 8.7 \text{ Hz, 2H) (Min. Rot.), 6.84 (d, } J = 8.7 \text{ Hz, 2H) (Maj. Rot.), 5.87 – 5.64 \text{ (m, 4H), 5.25 – 5.12 (m, 2H) (Maj. Rot.), 5.18 – 5.05 (m, 2H) (Min. Rot.), 5.02 – 4.89 (m, 3H), 4.55 (d, } J = 1.0 \text{ Hz, 2H) (Maj. Rot.), 4.48 (s, 2H) (Min. Rot.), 4.05 – 3.99 \text{ (m, 2H) (Min. Rot.), 3.84 (dd, } J = 4.7, 2.4 \text{ Hz, 2H) (Maj. Rot.), 3.84 (dd, } J = 4.7, 2.4 \text{ Hz, 3H) (Min. Rot.), 3.79 (s, 3H) (Maj. Rot.), 2.66 – 2.47 \text{ (m, 4H), 2.16 – 1.87 (m, 5H), 1.87 – 1.62 (m, 4H), 1.61 – 1.42 \text{ (m, 4H), 0.89 (t, } J = 7.4 \text{ Hz, 3H) (Maj. Rot.), 0.85 (t, } J = 7.4 \text{ Hz, 3H) (Min. Rot.).} \]

\[ \text{13C NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ 176.2, 159.1, 158.9, 138.5, 138.4, 133.4, 130.1, 129.7, 129.1, 127.8, 117.4, 117.0, 114.9, 114.2, 113.9, 55.4, 55.3, 49.4, 48.8, 48.1, 47.6, 42.3, 42.1, 31.9, 31.8, 31.7, 31.6, 26.0, 25.8, 12.2, 12.1.} \]

\[ \text{ESI [M+1]}^+ = 302.2(100\%), [M+2]^+ = 303.2(15\%).} \]

\[ \text{2-((3-methylbut-2-en-1-yl)amino)phenol (3.36)} \]

Yield = 60\%, yellow oil. \( R_f = 0.35 \) (SiO\(_2\), CH\(_2\)Cl\(_2\)). \[ \text{H NMR (CDCl}_3, 300 \text{ MHz): } \delta \text{ 6.87 – 6.82 (m, 1H), 6.74 – 6.58 (m, 3H), 5.35 (d, } J = 6.7 \text{ Hz, 1H), 3.69 (d, } J = 6.7 \text{ Hz, 2H), 1.75 (s, 3H), 1.71 (s, 3H). ESI [M+1]}^+ = 178.1(100\%), [M+2]^+ = 179.1(15\%).} \]

\[ \text{N-(2-hydroxyphenyl)acrylamide (3.37)}^{34} \]

In a flame-dried vial equipped with a magnetic stir bar, were placed 2-aminophenol (3.0 mmol, 0.33 g), triethylamine (3.0 mmol, 0.45 g), and dry THF (4 mL) via syringe. The resulting
solution was stirred under nitrogen at room temperature for 30 min, after the flask was cooled in an ice bath and acryloyl chloride (1.5 mmol, 0.14 g) was added dropwise via syringe. The resulting solution was warmed up to room temperature and was allowed to stir overnight. The reaction mixture was washed with saturated NaHCO$_3$, brine, and the organic layer was dried over Na$_2$SO$_4$ and concentrated. The crude product was purified on flash chromatography (Hex/EtOAc = 1:1, Rf = 0.63) to yield 3.37 (0.145 g, 0.9 mmol, 60%) as an orange solid.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.84 (s, 1H), 7.51 (s, broad, 1H), 7.21 – 7.10 (m, 1H), 7.05 (dt, $J = 8.0$, 1.8 Hz, 2H), 6.93 – 6.82 (m, 1H), 6.53 (dd, $J = 16.7$, 1.0 Hz, 1H), 6.33 (dd, $J = 16.7$, 10.2 Hz, 1H), 5.88 (dd, $J = 10.2$, 1.0 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 163.6, 138.0, 133.8, 132.1, 129.4, 127.0, 126.1, 124.0, 121.9, 118.2, 71.7, 70.9.

$N$-(2-(allyloxy)phenyl)acrylamide (3.38)$^{35}$

In a vial equipped with a stir bar well-ground potassium carbonate (4.0 mmol, 0.55 g) was combined with 3.37 (1.0 mmol, 0.163 g) in 3 mL of acetone, and the mixture was allowed to stir for 1 hour under reflux. The mixture was then cooled down to 0°C and allyl bromide (1.2 mmol, 0.145 g) was added dropwise. The resulting mixture was then allowed to stir under reflux overnight. The reaction mixture was then filtered off through celite, and the filtrate was diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified using flash chromatography (Hex/EtOAc = 4:1, Rf = 0.33) to yield 3.38 (0.152 g, 0.75 mmol, 75%) as yellow solid.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.47 (d, $J = 7.3$ Hz, 1H), 7.94 (s, broad, 1H), 7.07 – 6.95 (m, 2H), 6.88 (dd, $J = 7.9$, 1.6 Hz, 1H), 6.40 (dd, $J = 16.9$, 1.5 Hz, 1H), 6.28 (dd, $J = 16.9$, 10.1 Hz,
1H), 6.13 – 5.98 (m, 1H), 5.74 (dd, J = 10.0, 1.5 Hz, 1H), 5.42 – 5.31 (m, 2H), 4.61 (dt, J = 5.4, 1.4 Hz, 2H).

\[
\text{N-(2-(allyloxy)phenyl)-N-benzylacrylamide (3.39)}
\]

To a flame dried flask equipped with a stir bar 60% dispersion of sodium hydride in mineral oil (1.0 mmol, 40 mg) was weighed out. It was mixed with 0.75 mL of anhydrous THF, and the resulting suspension was placed in ice. 3.38 (0.49 mmol, 0.100 g) was dissolved in 0.75 mL of anhydrous THF and was added drop wise to the reaction mixture. The resulting solution was allowed to stir for 5 minutes at 0°C, after which benzyl bromide (1.0 mmol, 0.171 g) was added drop wise to the reaction mixture. The reaction was heated up to 50°C and was stirred overnight, after which the reaction solution was cooled down and quenched with distilled water, extracted with ethyl acetate, dried with saturated sodium sulfate and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc = 4:1, Rf = 0.28) to yield 3.39 (0.094 g, 0.32 mmol, 65%) as a yellow oil.

\[^{1}\text{H NMR (CDCl}_3, 400 MHz): \delta 7.37 – 7.12 (m, 5H), 6.90 – 6.82 (m, 4H), 6.39 (dd, J = 16.8, 2.1 Hz, 1H), 6.01 (dd, J = 16.8, 10.3 Hz, 1H), 5.96 – 5.81 (m, 1H), 5.48 (dd, J = 10.3, 2.1 Hz, 1H), 5.33 (d, J = 14.2 Hz, 1H), 5.30 – 5.19 (m, 2H), 4.50 (d, J = 14.3 Hz, 1H), 4.52 – 4.34 (m, 2H).
\]^{}

\[^{13}\text{C NMR (CDCl}_3, 100 MHz): \delta 166.3, 154.4, 137.7, 132.7, 130.6, 130.4, 129.4, 129.2, 128.7, 128.2, 127.5, 127.3, 120.9, 117.5, 113.2, 69.0, 52.0. ESI [M+1]^+ = 294.1(100%), [M+2]^+ = 295.1(20%).\]
**N-(2-(hydroxymethyl)phenyl)acrylamide (3.40)**

Yield = 81%, yellow solid. R_f = 0.28 (SiO_2, hex/EtOAc = 4:1). \(^1\)HNMR (CDCl_3, 300 MHz): \(\delta\) 8.80 (s, 1H), 8.17 (d, \(J = 7.7\) Hz, 1H), 7.47 – 7.30 (m, 1H), 7.19 (d, \(J = 6.3\) Hz, 1H), 7.09 (t, \(J = 7.5\) Hz, 1H), 6.41 (dd, \(J = 17.0, 1.4\) Hz, 1H), 6.27 (dd, \(J = 17.0, 10.0\) Hz, 1H), 5.77 (dd, \(J = 10.0, 1.4\) Hz, 1H), 4.73 (d, \(J = 4.5\) Hz, 2H).

**N-(2-((allyloxy)methyl)phenyl)acrylamide (3.41)**

Yield = 43%, yellow oil. R_f = 0.40 (SiO_2, hex/EtOAc = 9:1). \(^1\)HNMR (CDCl_3, 300 MHz): \(\delta\) 8.93 (s, 1H), 8.30 (d, \(J = 7.8\) Hz, 1H), 7.41 – 7.30 (m, 1H), 7.15 (d, \(J = 7.4\) Hz, 1H), 7.06 (td, \(J = 7.5, 1.0\) Hz, 1H), 6.38 (dd, \(J = 17.0, 1.2\) Hz, 1H), 6.22 (dd, \(J = 17.0, 10.2\) Hz, 1H), 5.99 – 5.84 (m, 1H), 5.74 (dd, \(J = 10.2, 1.3\) Hz, 1H), 5.32 (ddd, \(J = 17.2, 3.1, 1.6\) Hz, 1H), 5.26 (ddd, \(J = 10.4, 2.7, 1.2\) Hz, 1H), 4.62 (s, 2H), 4.06 – 3.95 (m, 2H). \(^{13}\)HNMR (CDCl_3): \(\delta\) 163.6, 138.0, 133.8, 132.1, 129.4, 127.0, 126.1, 124.0, 121.9, 118.2, 71.7, 70.9. ESI [M+1]^+ = 218.1(100%), [M+2]^+ = 219.1(15%).
N-(2-((allyloxy)methyl)phenyl)-N-benzylacrylamide (3.42)

Yield = 65%, yellow oil. R$_f$ = 0.31 (SiO$_2$, hex/EtOAc = 4:1). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.54 (d, $J$ = 6.8 Hz, 1H), 7.38 (d, $J$ = 1.0 Hz, 1H), 7.24 (dd, $J$ = 6.5, 4.2 Hz, 5H), 6.92 – 6.68 (m, 1H), 6.43 (dd, $J$ = 16.7, 2.0 Hz, 1H), 6.01 – 5.77 (m, 2H), 5.51 (dd, $J$ = 10.3, 2.0 Hz, 1H), 5.34 – 4.94 (m, 3H), 4.55 (d, $J$ = 13.9 Hz, 1H), 4.24 (d, $J$ = 12.3 Hz, 1H), 4.12 (d, $J$ = 12.3 Hz, 1H), 3.89 (d, $J$ = 5.6 Hz, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 165.6, 139.6, 137.2, 136.8, 134.4, 129.7, 128.8, 128.5, 128.2, 127.7, 117.5, 72.0, 68.0, 52.9. ESI [M+1]$^+$ = 308.2(100%), [M+2]$^+$ = 309.2(20%).

N,N'-(1,2-phenylene)diacrylamide (3.43)

Yield = 78%, white amorphous solid. R$_f$ = 0.20 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.68 (d, $J$ = 3.8 Hz, 2H), 7.27 – 7.10 (m, 2H), 6.45 (dd, $J$ = 17.0, 9.7 Hz, 2H), 6.35 (t, $J$ = 8.5 Hz, 2H), 5.76 (dd, $J$ = 9.7, 2.3 Hz, 2H). $^{13}$C NMR (d$^6$-DMSO, 75 MHz): δ 163.6, 131.9, 130.4, 126.8, 125.0, 124.85. ESI [M+1]$^+$ = 217.1(100%), [M+2]$^+$ = 218.1(20%).
**N,N’-(1,2-phenylene)bis(N-benzylacrylamide) (3.44)**

Yield = 14%, yellow oil. R<sub>f</sub> = 0.62 (SiO<sub>2</sub>, hex/EtOAc = 1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.45 – 7.02 (m, 14H), 6.81 (dd, J = 5.8, 3.6 Hz, 2H), 6.59 (dd, J = 16.7, 1.7 Hz, 2H), 6.05 (dd, J = 16.6, 10.2 Hz, 2H), 5.84 (d, J = 14.6 Hz, 2H), 5.71 (dd, J = 10.2, 1.7 Hz, 2H), 3.92 (d, J = 14.6 Hz, 2H). ESI [M+1]<sup>+</sup> = 397.2(100%), [M+2]<sup>+</sup> = 398.2(15%).

**N,N’-((1R,2R)-cyclohexane-1,2-diyl)diacrylamide (3.45)**

Yield = 83%, white amorphous solid. R<sub>f</sub> = 0.35 (SiO<sub>2</sub>, hex/EtOAc = 1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.39 (s, 2H), 6.22 (dd, J = 17.0, 1.5 Hz, 2H), 6.07 (ddd, J = 17.0, 10.2, 0.9 Hz, 2H), 5.61 (dd, J = 10.2, 1.5 Hz, 2H), 3.74 (t, J = 8.0 Hz, 2H), 2.09 (d, J = 11.4 Hz, 2H), 1.88 – 1.68 (m, 2H), 1.45 – 0.91 (m, 4H). <sup>13</sup>C NMR (d<sub>6</sub>-DMSO, 100 MHz): δ 164.3, 132.1, 124.7, 60.2, 32.0, 24.4. ESI [M+1]<sup>+</sup> = 223.1(100%), [M+2]<sup>+</sup> = 224.1(15%).
**N,N’-((1R,2R)-cyclohexane-1,2-diyl)bis(N-benzylacrylamide) (3.46)**

Yield = 83%, yellow oil. R₇ = 0.30 (SiO₂, hex/EtOAc = 2:1). ¹H NMR (CDCl₃, 300 MHz): δ 7.62 – 6.90 (m, 10H), 6.38 – 6.09 (m, 4H), 5.53 (dd, J = 7.8, 4.6 Hz, 2H), 5.01 – 4.82 (m, 2H), 4.66 (s, 4H), 1.79 – 1.73 (m, 2H), 1.71 – 1.54 (m, 2H), 1.31 – 1.20 (m, 4H). ¹H NMR (CDCl₃, 75 MHz): δ 168.0, 139.2, 128.9, 128.7, 128.3, 127.0, 126.0, 53.5, 47.8, 30.3, 25.1. ESI [M+1]⁺ = 403.2(100%), [M+2]⁺ = 404.2(15%).

**N-(4-methoxybenzyl)-N-(2-methylbut-3-en-2-yl)pent-4-en-1-amine (3.47)**

In a flame-dried scintillation vial equipped with a stir bar lithium aluminium hydride (8.63 mmol, 0.318 g) was weighed in. The powder was mixed with 25 mL of anhydrous THF, and the reaction mixture was allowed to cool down to 0°C. After that anhydrous aluminum chloride (2.50 mmol, 333 mg) was transferred in small portions to the reaction vial under a flow of nitrogen. The reaction mixture was allowed to stir at 0°C for additional 15 minutes after which a solution of 3.7 (3.93 mmol, 0.113 g) in 5 mL of anhydrous THF was added drop wise to the reaction mixture. The reaction vial was sealed with a cap and was allowed to stir at 50°C overnight. After that the reaction mixture was cooled down to 0°C followed by the addition of 0.32 mL of distilled water, 0.32mL of 10% NaOH(aq), and 1.26 mL of distilled water. The resulting mixture
was filtered through celite and the filtrate was diluted with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc = 9:1, Rf = 0.32) to yield **3.47** (78%) as a yellow oil.

$^1$H NMR (300 MHz, cdcl$_3$) $\delta$ 7.29 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.00 (dd, $J = 17.7$, 10.8 Hz, 1H), 5.68 (ddt, $J = 16.9$, 10.2, 6.7 Hz, 1H), 5.14 – 4.82 (m, 4H), 3.81 (s, 3H), 3.62 (s, 2H), 2.61 – 2.47 (m, 2H), 2.03 (t, $J = 7.6$ Hz, 2H), 1.91 (dd, $J = 14.4$, 7.1 Hz, 2H), 1.39 – 1.23 (m, 2H), 1.18 (s, 6H). ESI [M+1]$^+$ = 274.2(100%), [M+2]$^+$ = 275.2(20%).

### 3.5.3 Synthesis of lactams by ring-closing metathesis

![3.48](1-(4-methoxybenzyl)-7,7-dimethyl-3,4-dihydro-1H-azepin-2(7H)-one (3.48)]

**1-(4-methoxybenzyl)-7,7-dimethyl-3,4-dihydro-1H-azepin-2(7H)-one (3.48)**

In the glove-box Hoveyda-Grubbs II catalyst (0.007 mmol, 4.5 mg) was weighed out in a flame-dried scintillation vial equipped with a stir bar. The vial was removed from the glove-box and the complex was dissolved in 15 mL of anhydrous dichloromethane. **3.7** (0.35 mmol, 0.100g) was then added drop wise to the reaction solution, and the reaction mixture was allowed to stir under reflux for 2 days. The reaction mixture was then washed with brine, extracted with dichloromethane, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc = 1:1, Rf = 0.59) to yield **3.48** (0.23 mmol, 58 mg, 65%) as a yellow oil.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.11 (d, $J = 8.8$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 5.73 (dt, $J = 12.0$, 4.5 Hz, 1H), 5.40 (dt, $J = 11.9$, 2.0 Hz, 1H), 4.76 (s, 2H), 3.78 (s, 3H), 2.97 – 2.81 (m, 2H),
2.47 – 2.35 (m, 2H), 1.45 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 174.2, 158.9, 130.4, 130.2, 129.3, 129.0, 114.0, 55.4, 53.6, 50.1, 36.1, 24.8, 20.8. ESI [M+1]$^+$ = 260.2(100%), [M+2]$^+$ = 261.2(15%).

1-(4-methoxybenzyl)-7-methyl-3,4-dihydro-1$H$-azepin-2(7$H$)-one (3.49)

Yield = 64%, yellow oil. $R_f$ = 0.32 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.15 (d, $J$ = 8.7 Hz, 2H), 6.83 (d, $J$ = 8.6 Hz, 2H), 5.73 (dd, $J$ = 11.6, 5.0 Hz, 1H), 5.55 – 5.46 (m, 1H), 4.96 (d, $J$ = 15.0 Hz, 1H), 4.16 (d, $J$ = 15.0 Hz, 1H), 3.93-3.86 (m, 1H), 3.78 (s, 3H), 2.85 (td, $J$ = 12.9, 3.4 Hz, 1H), 2.68 (ddd, $J$ = 13.3, 5.9, 2.5 Hz, 1H), 2.50 – 2.37 (m, 1H), 2.34-2.25 (m, 1H), 1.33 (d, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 172.2, 158.9, 130.3, 130.2, 130.1, 129.3, 128.9, 114.0, 55.3, 53.5, 50.1, 36.0, 24.7, 20.7. ESI [M+1]$^+$ = 246.1(100%), [M+2]$^+$ = 247.1(15%).

(Z)-1-(4-methoxybenzyl)-8-methyl-1,4,5,8-tetrahydroazocin-2(3$H$)-one (3.50)

Yield = 20%, yellow oil. $R_f$ = 0.32 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.23 (d, $J$ = 8.7 Hz, 2H), 6.83 (d, $J$ = 8.7 Hz, 2H), 5.56 (dddd, $J$ = 10.8, 8.9, 7.3, 2.0 Hz, 1H), 5.38 (d, $J$ = 10.8 Hz, 1H), 2.81 (s, 3H).
(ddd, $J = 11.5, 5.4, 1.9$ Hz, 1H), 4.76 (d, $J = 14.7$ Hz, 1H), 4.37 (d, $J = 14.7$ Hz, 1H), 4.34 – 4.26 (m, 1H), 3.78 (s, 3H), 2.71 (ddd, $J = 12.3, 10.8, 4.5$ Hz, 1H), 2.54 (ddd, $J = 12.4, 5.7, 4.0$ Hz, 1H), 2.36 – 2.23 (m, 1H), 2.12 – 2.00 (m, 1H), 1.95 (tt, $J = 14.8, 4.0$ Hz, 1H), 1.57 – 1.44 (m, 1H), 1.26 (d, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 174.8, 158.8, 134.3, 130.9, 129.6, 127.1, 113.9, 55.3, 54.4, 48.0, 34.3, 24.6, 24.0, 20.7. ESI [M+1]$^+$ = 260.2 (100%), [M+2]$^+$ = 261.2 (15%).

1-(4-methoxybenzyl)-3,4-dihydro-1H-azepin-2(7H)-one (3.51)

Yield = 60%. R$_f$ = 0.32 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.16 (d, $J = 8.7$ Hz, 2H), 6.93 – 6.74 (m, 2H), 5.72 (dt, $J = 11.2, 3.7$ Hz, 1H), 5.67 – 5.47 (m, 1H), 4.56 (s, 2H), 3.91 – 3.65 (m, 5H), 2.90 – 2.68 (m, 2H), 2.43 (ddd, $J = 7.8, 4.0, 1.9$ Hz, 2H).

1-(4-methoxybenzyl)-6,7-dihydro-1H-azepin-2(3H)-one (3.51’)

Yield = 20%. R$_f$ = 0.63 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.21 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.61 (d, $J = 2.8$ Hz, 2H), 4.56 (s, 2H), 3.79 (s, 3H), 3.55 – 3.42 (m, 2H), 3.30 (d, $J = 4.0$ Hz, 2H), 2.13 – 2.01 (m, 2H).

1-(4-methoxybenzyl)-5-phenyl-6,7-dihydro-1H-azepin-2(5H)-one (3.52)
Yield = 58%, yellow oil. \( R_f = 0.33 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.34 – 7.20 (m, 5H), 7.14 (dd, \( J = 8.0, 1.1 \) Hz, 1H), 6.85 (d, \( J = 8.7 \) Hz, 2H), 6.23 (ddd, \( J = 12.2, 4.1, 0.5 \) Hz, 1H), 6.15 (dd, \( J = 12.3, 2.1 \) Hz, 1H), 4.71 (d, \( J = 14.4 \) Hz, 1H), 4.56 (d, \( J = 14.4 \) Hz, 1H), 3.77 (s, 3H), 3.65 (tdd, \( J = 6.4, 4.0, 2.1 \) Hz, 1H), 3.45 – 3.27 (m, 1H), 2.20 – 2.07 (m, 1H), 1.80 (dddd, \( J = 14.3, 10.1, 6.1, 2.8 \) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 168.0, 159.1, 143.0, 141.1, 129.7, 129.6, 128.8, 127.7, 126.9, 126.4, 114.1, 55.3, 50.6, 46.3, 45.5, 37.7. ESI [M+1]\(^+\) = 308.2(100%), [M+2]\(^+\) = 309.2(20%).

1-(4-methoxybenzyl)-5-methyl-6,7-dihydro-1H-azepin-2(5H)-one (3.53)

Yield = 83%, yellow oil. \( R_f = 0.33 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.35 – 7.00 (m, 2H), 6.94 – 6.78 (m, 2H), 6.05 – 5.93 (m, 2H), 4.64 (d, \( J = 14.4 \) Hz, 1H), 4.54 (d, \( J = 14.4 \) Hz, 1H), 3.79 (s, 3H), 3.39 – 3.13 (m, 2H), 2.53 – 2.45 (m, 1H), 1.97 – 1.86 (m, 1H), 1.48 – 1.47 (m, 1H), 1.04 (d, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 168.3, 160.0, 144.0, 129.8, 129.5, 124.8, 113.9, 55.2, 50.4, 45.5, 36.4, 34.2, 20.6. ESI [M+1]\(^+\) = 246.1(100%), [M+2]\(^+\) = 247.1(15%).

1-(4-methoxybenzyl)-5,5-dimethyl-6,7-dihydro-1H-azepin-2(5H)-one (3.54)
Yield = 27%, yellow oil. R<sub>f</sub> = 0.33 (SiO<sub>2</sub>, hex/EtOAc = 1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.21 (d, <i>J</i> = 8.7 Hz, 2H), 6.85 (d, <i>J</i> = 8.7 Hz, 2H), 5.85 (s, 2H), 4.60 (s, 2H), 3.80 (s, 3H), 3.31 – 3.16 (m, 2H), 1.73 – 1.55 (m, 2H), 1.03 (s, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 167.3, 159.1, 148.5, 129.7, 122.4, 114.1, 55.4, 51.0, 44.0, 41.6, 38.5, 29.8. ESI [M+1]<sup>+</sup> = 260.2(100%), [M+2]<sup>+</sup> = 261.2(15%).

1-(4-methoxybenzyl)-5-propyl-6,7-dihydro-1H-azepin-2(5H)-one (3.55)

Yield = 22%, yellow oil. R<sub>f</sub> = 0.33 (SiO<sub>2</sub>, hex/EtOAc = 1:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.23 (d, <i>J</i> = 8.7 Hz, 2H), 6.85 (d, <i>J</i> = 8.7 Hz, 2H), 6.06 (dd, <i>J</i> = 12.0, 4.2 Hz, 1H), 5.99 (dd, <i>J</i> = 12.0, 1.9 Hz, 1H), 4.67 (d, <i>J</i> = 14.4 Hz, 1H), 4.52 (d, <i>J</i> = 14.4 Hz, 1H), 3.80 (s, 3H), 3.39 – 3.26 (m, 1H), 3.20 (ddd, <i>J</i> = 14.6, 5.3, 3.6 Hz, 1H), 2.41 – 2.29 (m, 1H), 1.97 – 1.83 (m, 1H), 1.48 – 1.19 (m, 5H), 0.87 (t, <i>J</i> = 7.0 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 168.8, 159.1, 143.0, 130.1, 129.7, 125.6, 114.1, 55.4, 50.3, 45.8, 38.5, 37.4, 34.8, 20.4, 14.1. ESI [M+1]<sup>+</sup> = 274.2(100%), [M+2]<sup>+</sup> = 275.2(15%).

1-(4-methoxybenzyl)-4-methyl-6,7-dihydro-1H-azepin-2(5H)-one (3.56)
Yield = 37%, yellow oil. R_f = 0.33 (SiO_2, hex/EtOAc = 1:1). ^1^H NMR (CDCl_3, 400 MHz): δ 7.23 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.88 (s, 1H), 4.59 (s, 2H), 3.79 (s, 3H), 3.36 – 3.07 (m, 2H), 2.20 (t, J = 7.1 Hz, 2H), 1.89 (s, 3H), 1.75 (dd, J = 12.1, 6.5 Hz, 2H). ^1^C NMR (CDCl_3, 100 MHz): δ 169.3, 159.1, 147.6, 130.3, 129.7, 122.6, 114.0, 55.38, 50.2, 46.4, 32.4, 28.0, 26.0. ESI [M+1]^+ = 246.1(100%), [M+2]^+ = 247.1(15%).

![Diagram](image1)

1-(4-methoxybenzyl)-6,7-dihydro-1H-azepin-2(5H)-one (3.57)

Yield = 94%, yellow oil. R_f = 0.52 (SiO_2, EtOAc). ^1^H NMR (CDCl_3, 400 MHz): δ 7.23 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.20 (dt, J = 11.9, 5.1 Hz, 1H), 6.04 (d, J = 12.1 Hz, 1H), 4.60 (s, 2H), 3.79 (s, 3H), 3.36 – 3.21 (m, 2H), 2.27 (qd, J = 6.8, 1.2 Hz, 2H), 1.86 – 1.67 (m, 2H).

![Diagram](image2)

(Z)-1-(4-methoxybenzyl)-5,6,7,8-tetrahydroazocin-2(1H)-one (3.58)

Yield = 78%, yellow oil. R_f = 0.59 (SiO_2, EtOAc). ^1^H NMR (CDCl_3, 300 MHz): δ 7.23 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.97 (dt, J = 12.5, 5.2 Hz, 1H), 5.81 (dt, J = 12.6, 1.6 Hz, 1H), 4.58 (s, broad, 2H), 3.76 (s, 3H), 3.44 (s, broad, 2H), 2.24 (s, broad, 2H), 1.58 (s, broad, 4H). ^1^C NMR (CDCl_3, 100 MHz): δ 168.9, 158.7, 136.9, 129.4, 129.3, 122.0, 113.6, 54.9, 46.8, 45.5, 30.1, 26.4, 20.0. ESI [M+1]^+ = 246.1(100%), [M+2]^+ = 247.1(15%).
1-(4-methoxybenzyl)-3-methyl-3,4-dihydro-1H-azepin-2(7H)-one (3.59)

Yield = 90%, yellow oil. R$_f$ = 0.50 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.14 (d, $J$ = 8.8 Hz, 2H), 6.81 (d, $J$ = 8.7 Hz, 2H), 5.74 – 5.63 (m, 1H), 5.63 – 5.52 (m, 1H), 4.59 (d, $J$ = 14.7 Hz, 1H), 4.53 (d, $J$ = 14.7 Hz, 1H), 4.34 – 4.18 (m, 1H), 3.76 (s, 3H), 3.29 (dd, $J$ = 14.7 Hz, 1H), 4.34 – 4.18 (m, 1H), 3.76 (s, 3H), 3.29 (dd, $J$ = 17.5, 7.7 Hz, 1H), 3.25 – 3.13 (m, 1H), 2.20 (ddd, $J$ = 6.0, 4.6, 2.9 Hz, 2H), 1.18 (d, $J$ = 6.6 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.5, 158.9, 131.5, 129.9, 129.3, 124.5, 113.9, 55.3, 50.7, 44.9, 35.2, 34.2, 17.4. ESI [M+1]$^+$ = 246.1(100%), [M+2]$^+$ = 247.1(15%).

(Z)-3-ethyl-1-(4-methoxybenzyl)-1,4,5,8-tetrahydroazocin-2(3H)-one (3.60)

Yield = 34%, yellow oil. R$_f$ = 0.25 (SiO$_2$, hex/EtOAc = 9:1). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.21 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.7 Hz, 2H), 5.82 – 5.71 (m, 1H), 5.36 (dt, $J$ = 12.0, 4.5, 2.3 Hz, 1H), 5.04 (d, $J$ = 14.5 Hz, 1H), 4.25 – 4.15 (m, 1H), 4.15 (d, $J$ = 14.4 Hz, 1H), 3.79 (s, 3H), 3.66 (dd, $J$ = 19.6, 4.5 Hz, 1H), 2.81 – 2.73 (m, 1H), 2.32 – 2.18 (m, 1H), 1.97 – 1.75 (m, 4H), 1.65 – 1.54 (m, 1H), 1.47 – 1.34 (m, 1H), 0.91 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.9, 159.0, 129.9, 129.8, 129.6, 127.3, 114.0, 55.4, 50.4, 49.7, 42.6, 35.4, 25.0, 23.3, 13.0. ESI [M+1]$^+$ = 274.2(100%), [M+2]$^+$ = 275.2(15%).
(Z)-6-benzyl-2H-benzo[b][1,4]oxazocin-5(6H)-one (3.61)

Yield = 64%, yellow oil. R_f = 0.51 (SiO_2, hex/EtOAc = 1:1). {^1}H NMR (CDCl_3, 300 MHz): δ 7.41 – 6.97 (m, 9H), 6.03 (d, J = 13.6 Hz, 1H), 5.52 (ddd, J = 12.7, 3.5, 1.9 Hz, 1H), 5.23 (dd, J = 15.0, 2.3 Hz, 1H), 4.98 (dd, J = 16.8, 1.9 Hz, 1H), 4.82 (d, J = 14.9 Hz, 1H), 4.48 – 4.25 (m, 1H). {^{13}}C NMR (CDCl_3, 100 MHz): δ 168.7, 152.5, 137.4, 137.1, 128.6, 128.4, 128.1, 127.8, 127.4, 125.2, 125.0, 122.2, 73.3, 52.4. ESI [M+1]^+ = 296.1(100%), [M+2]^+ = 297.1(20%).

(Z)-1-(4-methoxybenzyl)-5,7-dihydrobenzo[c][1,5]oxazin-2(1H)-one (3.62)

Yield = 46%, yellow oil. R_f = 0.38 (SiO_2, hex/EtOAc = 1:1). {^1}H NMR (CDCl_3, 300 MHz): δ 7.46 – 7.18 (m, 7H), 7.18 – 7.06 (m, 1H), 6.92 (dd, J = 7.2, 1.7 Hz, 1H), 5.64 (dt, J = 12.2, 2.0 Hz, 1H), 5.34 (dt, J = 12.2, 3.0 Hz, 1H), 5.02 (d, J = 14.0 Hz, 1H), 4.92 (d, J = 14.0 Hz, 1H), 4.45 – 4.33 (m, 1H), 4.26 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 13.1 Hz, 1H), 3.88 – 3.69 (m, 1H). {^{13}}C NMR (CDCl_3, 100 MHz): δ 169.9, 143.0, 137.3, 136.2, 131.4, 131.2, 129.7, 129.6, 129.2, 128.6, 128.1, 127.8, 123.8, 73.3, 69.2, 52.2. ESI [M+1]^+ = 310.1(100%), [M+2]^+ = 311.1(20%).
**3-bromoazepan-2-one (3.63)**

A solution of caprolactam (0.15 mol, 16.97 g) in 150 mL of benzene was added to a solution of bromine (0.3 mol, 15 mL) and phosphorus tribromide (0.3 mol, 28 mL) at 10°C. The reaction was allowed to warm-up to 50°C and was stirred overnight. Out of the two layers formed lower layer was quenched with ice, extracted with chloroform, washed with saturated solution of sodium thiosulfate, dried over anhydrous sodium sulfate and concentrated. The crude product was purified on SiO₂.

Yield = 40%, white solid. Rf = 0.51 (SiO₂, EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 6.18 (s, 1H), 4.76 – 4.58 (m, 1H), 3.60 (ddd, J = 15.0, 10.9, 4.2 Hz, 1H), 3.28 – 3.01 (m, 1H), 2.19 – 1.96 (m, 2H), 1.96 – 1.77 (m, 2H), 1.67 – 1.43 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): δ 173.3, 51.7, 42.3, 31.3, 29.6, 26.0.

**6,7-dihydro-1H-azepin-2(5H)-one (3.64)⁴⁰**

Phosphorus pentoxide (57.1 mmol, 8.11 g) was dissolved in 54 mL of methanesulfonic acid. Once homogeneous solution formed (4 hours), 3.66 (48.6 mmol, 5.4 g) was added, and the reaction was allowed to heat up to 110°C until TLC showed the disappearance of the starting material. The reaction was cooled down to room temperature, and carefully quenched with
anhydrous sodium bicarbonate. The resulting solution was extracted with chloroform, dried over anhydrous magnesium sulfate, and concentrated. The product was purified on basic alumina.

Yield = 43%, brown semisolid. R<sub>f</sub> = 0.13 (SiO<sub>2</sub>, EtOAc). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.13 – 6.87 (m, 1H), 6.29 (dt, <i>J</i> = 12.4, 4.7 Hz, 1H), 5.90 (dd, <i>J</i> = 12.4, 1.9 Hz, 1H), 3.35 – 3.20 (m, 2H), 2.53 – 2.36 (m, 2H), 1.98 (ddd, <i>J</i> = 5.9, 5.2, 4.3 Hz, 2H).

6,7-dihydro-1H-azepin-2(3H)-one (3.65)<sup>41</sup>

In a flame-dried vial equipped with a stir bar diisopropyl amine (1.52 mmol, 0.21 mL) was dissolved in anhydrous THF (1 mL). The reaction solution was cooled down to -78<sup>0</sup>C and butyllithium solution in hexanes (1.52 mmol, 0.70 mL) was added. The resulting solution was slowly warmed up to 0<sup>0</sup>C and was allowed to stir for 15 minutes. The solution was then cooled down to -78<sup>0</sup>C, and was added drop wise to a solution of 3.63 (0.52 mmol, 100 mg) in 2 mL of anhydrous THF. The reaction was allowed to warm up to room temperature and quenched with saturated aqueous ammonium chloride solution, extracted with ethyl acetate, dried with anhydrous sodium sulfate and concentrated.

Yield = 73%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 6.36 (s, 1H), 5.60 (dtd, <i>J</i> = 6.8, 3.7, 1.8 Hz, 1H), 5.50 (dddd, <i>J</i> = 13.6, 5.6, 3.8, 2.1 Hz, 1H), 3.37 (dd, <i>J</i> = 11.5, 6.5 Hz, 2H), 3.16 – 3.03 (m, 2H), 2.29 – 2.13 (m, 2H).
cyclohex-2-enone oxime (3.66)\textsuperscript{42}

In a 250 mL round-bottom flask equipped with a stir bar cyclohex-2-ene (208 mmol, 20 mL), hydroxylamine hydrochloride (208 mmol, 14.45 g) and sodium acetate (416 mmol, 34.13 g) were dissolved in 100 mL of water and were allowed to stir at 60\thinspace^\circ\mathrm{C} for 2 hours. The reaction was then cooled down to room temperature, extracted with chloroform, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified on SiO\textsubscript{2}.

Yield = 26\%, white amorphous solid. R\textsubscript{f} = 0.47 (SiO\textsubscript{2}, chloroform/MeOH = 9:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): Major isomer: $\delta$ 6.23 (dd, $J = 9.2$, 5.0 Hz, 1H), 6.14 (dd, $J = 10.0$, 1.6 Hz, 1H), 2.69 – 2.59 (m, 2H), 2.19 (ddd, $J = 8.5$, 5.8, 2.8 Hz, 2H), 1.76 (dt, $J = 12.6$, 6.3 Hz, 2H).

3-ethyl-1-(4-methoxybenzyl)-3,4-dihydro-1H-azepin-2(7H)-one (3.67)

In a flame-dried vial equipped with a stir bar 3.51 (2.16 mmol, 0.500 g) was dissolved in anhydrous THF (2.5 mL). The mixture was cooled down to -78\thinspace^\circ\mathrm{C}. A solution of LDA (3.24 mmol, 0.65 M in THF) was added drop wise, and the reaction was allowed to stir for 5 minutes, followed by a drop-wise addition of ethyl iodide (6.48 mmol, 1.01 g). The reaction was slowly allowed to warm-up to room temperature and was left to stir overnight. Upon completion, the reaction flask was placed in an ice bath and was quenched with saturated ammonium chloride, extracted with ether, washed twice with saturated sodium bicarbonate, brine, and was dried over
sodium sulfate and concentrated. The crude product was purified on silica (hex/EtOAc = 9:1, Rf = 0.31) to give 3.67 (55.5 mg, 0.216 mmol, 10%) as a yellow oil.

\[ ^1 \text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ 7.15 (d, } J = 8.6 \text{ Hz, 2H), 6.83 (d, } J = 8.6 \text{ Hz, 2H), 5.74 – 5.64 (m, 1H), 5.62 – 5.55 (m, 1H), 4.61 (d, } J = 14.7 \text{ Hz, 1H), 4.55 (d, } J = 14.8 \text{ Hz, 1H), 3.78 (s, 3H), 3.30 (dd, } J = 17.5, 7.6 \text{ Hz, 1H), 3.02 – 2.88 (m, 1H), 2.39 – 2.07 (m, 2H), 1.96 (tt, } J = 15.2, 7.6 \text{ Hz, 1H), 1.45 – 1.29 (m, 1H), 0.98 (t, } J = 7.4 \text{ Hz, 3H).} \]

\[ ^{13} \text{C NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ 175.9, 158.9, 131.5, 130.1, 129.3, 124.6, 114.0, 55.3, 50.6, 44.9, 42.7, 32.2, 24.9, 12.5. ESI [M+1]^+ = 260.2(100%), [M+2]^+ = 261.2(15%).} \]

3-isopentyl-1-(4-methoxybenzyl)-3,4-dihydro-1H-azepin-2(7H)-one (3.68)

Yield = 32%, yellow oil. Rf = 0.48 (SiO2, hex/EtOAc = 4:1). \[ ^1 \text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ 7.16 (d, } J = 8.5 \text{ Hz, 2H), 6.83 (d, } J = 8.5 \text{ Hz, 2H), 5.75 – 5.64 (m, 1H), 5.64 – 5.50 (m, 1H), 4.61 (d, } J = 14.7 \text{ Hz, 1H), 4.54 (d, } J = 14.7 \text{ Hz, 1H), 4.38 – 4.22 (m, 1H), 3.78 (s, 3H), 3.30 (dd, } J = 17.5, 7.6 \text{ Hz, 1H), 3.05 – 2.91 (m, 1H), 2.37 – 2.08 (m, 2H), 2.02 – 1.86 (m, 1H), 1.57 (dt, } J = 13.1, 6.5 \text{ Hz, 1H), 1.40 – 1.25 (m, 2H), 1.23 – 1.11 (m, 1H), 0.91 (dd, } J = 6.5, 4.7 \text{ Hz, 6H).} \]

\[ ^{13} \text{C NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ 176.0, 158.9, 131.5, 130.0, 129.3, 124.6, 113.9, 55.3, 50.6, 44.9, 41.2, 37.2, 32.5, 29.8, 28.4, 22.7. ESI [M+1]^+ = 302.2(100%), [M+2]^+ = 303.2(20%).} \]
3-benzyl-1-(4-methoxybenzyl)-3,4-dihydro-1H-azepin-2(7H)-one (3.69)

Yield = 25%, yellow oil. R_f = 0.48 (SiO_2, pentane/acetone = 9:1). ^1H NMR (CDCl_3, 300 MHz): δ 7.29 – 7.12 (m, 7H), 6.82 (d, J = 8.7 Hz, 2H), 5.73 – 5.38 (m, 2H), 4.62 (d, J = 14.7 Hz, 1H), 4.54 (d, J = 14.7 Hz, 1H), 4.28 (dd, J = 20.0, 2.5 Hz, 1H), 3.78 (s, 3H), 3.56 – 3.12 (m, 3H), 2.65 (td, J = 9.6, 2.5 Hz, 1H), 2.36 – 2.10 (m, 2H). ^13C NMR (CDCl_3, 100 MHz): δ 177.5, 153.9, 148.5, 140.5, 131.0, 129.9, 129.4, 128.4, 126.2, 124.6, 114.0, 55.4, 50.8, 45.0, 42.7, 37.7, 31.4. ESI [M+1]^+ = 322.2(100%), [M+2]^+ = 323.2(20%).

1-(4-methoxybenzyl)-3-((tetrahydro-2H-pyran-2-yl)methyl)-3,4-dihydro-1H-azepin-2(7H)-one (3.70)

Yield = 19%, yellow oil. R_f = 0.63 (SiO_2, hex/EtOAc = 2:1). ^1H NMR (CDCl_3, 400 MHz): δ 7.15 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.71 – 5.62 (m, 1H), 5.64 – 5.53 (m, 1H), 4.62 (d, J = 14.8 Hz, 1H), 4.57 (d, J = 14.8 Hz, 1H), 4.44 – 4.31 (m, 1H), 4.00 – 3.90 (m, 1H), 3.79 (s, 3H), 3.54 – 3.34 (m, 3H), 3.27 (dd, J = 17.5, 7.6 Hz, 1H), 2.25 – 2.17 (m, 2H), 2.17 – 2.09 (m, 1H), 1.82 – 1.75 (m, 1H), 1.69 (d, J = 12.7 Hz, 1H), 1.59 – 1.45 (m, 3H), 1.36 – 1.23 (m, 2H). ^13C NMR (CDCl_3, 100 MHz): δ 175.6, 158.9, 131.4, 130.0, 129.2, 124.5, 114.0, 76.3, 68.6, 55.3, 50.7, 44.9, 39.4, 36.6, 33.4, 32.8, 26.4, 23.6. ESI [M+1]^+ = 330.1(100%), [M+2]^+ = 331.1(15%).
3,4-dihydrobenzo[b][1,4]diazocine-2,5(1H,6H)-dione (3.71)

To a flame dried flask equipped with a stir bar 60% dispersion of sodium hydride in mineral oil (100 mmol, 4.0 g) was weighed out. In was mixed with 15 mL of anhydrous THF, and the resulting suspension was placed in ice. 1,2-phenylenediamine (50 mmol, 5.4 g) was dissolved in 10 mL of anhydrous THF and was added drop wise to the reaction mixture. The resulting solution was allowed to stir for 5 minutes at 0°C, after which diethyl succinate (50 mmol, 8.7 g) was added drop wise to the reaction mixture. The reaction was allowed to stir for additional 2 hours at 0°C, after which it was allowed to warm up to room temperature and was stirred overnight. Upon completion the reaction solution was cooled down and quenched with distilled water, extracted with ethyl acetate, dried with saturated sodium sulfate and concentrated. The crude product not purified any further to yield 3.71 (2.44 g, 13 mmol, 26%) as a white solid. 1H NMR (DMSO, 300 MHz): δ 9.55 (s, 2H), 7.30 (dd, J = 5.8, 3.6 Hz, 2H), 7.18 (dd, J = 5.8, 3.7 Hz, 2H), 2.33 (s, 4H). 13C NMR (DMSO, 75 MHz): δ 172.3, 134.8, 127.5, 127.0, 30.6.

1,6-dibenzyl-3,4-dihydrobenzo[b][1,4]diazocine-2,5(1H,6H)-dione (3.72)

To a flame dried flask equipped with a stir bar 60% dispersion of sodium hydride in mineral oil (41.6 mmol, 1.7 g) was weighed out. In was mixed with 35 mL of anhydrous THF, and the resulting suspension was placed in ice. 3.71 (10.4 mmol, 1.98 g) was dissolved in 15 mL of anhydrous THF and was added drop wise to the reaction mixture. The resulting solution was
allowed to stir for 5 minutes at 0°C, after which benzyl bromide (41.6 mmol, 7.12 g) was added drop wise to the reaction mixture. The reaction was heated up to 50°C and was stirred overnight, after which the reaction solution was cooled down and quenched with distilled water, extracted with ethyl acetate, dried with saturated sodium sulfate and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc = 1:1, Rf = 0.35) to yield 3.72 (1.3 g, 3.5 mmol, 34%) as a white solid.

1H NMR (CDCl$_3$, 300 MHz): δ 7.35 – 7.17 (m, 8H), 7.10 (dd, $J = 7.4$, 2.0 Hz, 3H), 7.04 (dd, $J = 6.0$, 3.6 Hz, 2H), 4.56 (d, $J = 14.5$ Hz, 2H), 3.82 (d, $J = 14.5$ Hz, 2H), 2.69 (dd, $J = 13.7$, 5.0 Hz, 2H), 2.26 (dd, $J = 13.6$, 5.0 Hz, 2H). 13C NMR (CDCl$_3$, 75 MHz): δ 170.8, 140.1, 137.8, 129.3, 129.1, 128.8, 128.2, 127.8, 52.1, 31.9. ESI [M+1]$^+$ = 371.2(100%), [M+2]$^+$ = 372.2(20%).

(Z)-1,6-dibenzylbenzo[b][1,4]diazocine-2,5(1H,6H)-dione (3.73)

In a flame-dried round bottom flask equipped with a stir bar 3.72 was transferred under nitrogen and dissolved in 5 mL of anhydrous THF. The reaction mixture was cooled down to -78°C and a solution of sodium hexamethyldisilyzide in THF (1.0 M, 10mL) was added dropwise. The reaction was left stirring for an hour at -78°C, after which N-bromosuccinamide (0.80 g, 4.5 mmol) was added to the reaction mixture as a solution in 5 mL of THF. The reaction was slowly allowed to warm up to room temperature, and was allowed to stir overnight. Upon reaching completion the reaction was cooled down to 0°C and was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated solution of sodium thiosulfate, then brine, dried over anhydrous sodium sulfate and concentrated. The crude product was
purified using flash chromatography (Hex/EtOAc = 1:1, Rf = 0.63) to yield 3.73 (0.57 g, 1.52 mmol, 58%) as a white solid.

\[ ^1H \text{NMR (CDCl}_3, 300 MHz): \delta 7.34 – 7.09 (m, 12H), 6.96 (dd, J = 6.0, 3.6 Hz, 1H), 6.04 (s, 2H), 4.61 (d, J = 14.4 Hz, 2H), 4.04 (d, J = 14.5 Hz, 2H). \]

\[ ^{13}C \text{NMR (CDCl}_3, 75 MHz): \delta 166.4, 140.3, 137.3, 129.2, 128.9, 128.6, 128.0, 127.3, 51.5. \]

ESI [M+H]+ = 369.2(100%), [M+2]+ = 370.2(25%).

3.5.4 Preparation of cyclic allylamines by reduction of lactams

\[ \text{NPMB} \]

3.74

1-(4-methoxybenzyl)-7,7-dimethyl-2,3,4,7-tetrahydro-1H-azepine (3.74)

In a flame-dried scintillation vial equipped with a stir bar lithium aluminium hydride (1.00 mmol, 38 mg) was weighed in. The powder was mixed with 2 mL of anhydrous THF, and the reaction mixture was allowed to cool down to 0°C. After that anhydrous aluminum chloride (0.28 mmol, 37 mg) was transferred in small portions to the reaction vial under a flow of nitrogen. The reaction mixture was allowed to stir at 0°C for additional 15 minutes after which a solution of 3.48 (0.45 mmol, 0.117 g) in 1 mL of anhydrous THF was added drop wise to the reaction mixture. The reaction vial was sealed with a cap and was allowed to stir at 50°C overnight. After that the reaction mixture was cooled down to 0°C followed by the addition of 0.040 mL of distilled water, 0.040 mL of 10% NaOH(aq), and 0.160 mL of distilled water. The resulting mixture was filtered through celite and the filtrate was diluted with water, extracted with ethyl acetate, dried over anhydrous sodium sulfate and concentrated. The crude product was purified
by flash chromatography (Hex/EtOAc = 1:1, Rf = 0.32) to yield 3.74 (0.36 mmol, 87.2 mg, 79%) as a yellow oil.

1H NMR (CDCl$_3$, 300 MHz): δ 7.29 (d, J = 8.6 Hz, 2H), 6.85 (dt, J = 8.6, 2.4 Hz, 2H), 5.57 (dt, J = 11.4, 6.4 Hz, 1H), 5.33 (dt, J = 11.4, 1.1 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 2H), 2.79 (t, J = 6.1 Hz, 2H), 2.29 (ddd, J = 13.3, 6.6, 1.1 Hz, 2H), 1.49 – 1.40 (m, 2H), 1.28 (s, 6H).

13C NMR (CDCl$_3$, 100 MHz): δ 158.7, 136.0, 132.9, 131.4, 130.0, 113.8, 55.6, 55.5, 52.6, 52.1, 28.3, 21.9, 19.1. ESI [M+1]$^+$ = 246.2(100%), [M+2]$^+$ = 247.2(25%).

1-(4-methoxybenzyl)-7-methyl-2,3,4,7-tetrahydro-1H-azepine (3.75)

Yield = 80%, yellow oil. Rf = 0.32 (SiO$_2$, hex/EtOAc = 1:1). 1H NMR (CDCl$_3$, 300 MHz): δ 7.24 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.88 – 5.81 (m, 1H), 5.50 (ddd, J = 10.9, 5.4, 1.9 Hz, 1H), 3.78 (s, 3H), 3.61 (d, J = 14.0 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.04 (ddd, J = 14.1, 5.0, 3.9 Hz, 1H), 2.83 (ddd, J = 13.9, 10.1, 3.5 Hz, 1H), 2.37-2.28 (m, 1H), 2.22 (ddt, J = 10.1, 7.1, 3.0 Hz, 1H), 1.75-1.61 (m, 1H), 1.45-1.37 (m, 1H), 1.25 (d, J = 7.1 Hz, 3H). 13C NMR (CDCl$_3$, 100 MHz): δ 158.5, 135.9, 132.8, 131.3, 129.8, 113.6, 56.5, 56.3, 52.5, 52.0, 28.2, 21.8, 18.9. HRMS (ESI) [M+H]$^+$ calcd. for C$_{15}$H$_{21}$NO 232.1685, found 232.1695.

(Z)-1-(4-methoxybenzyl)-8-methyl-1,2,3,4,5,8-hexahydroazocine (3.76)

153
Yield = 90%, yellow oil. R$_f$ = 0.32 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.15 (d, $J$ = 8.6 Hz, 2H), 6.76 (d, $J$ = 8.6 Hz, 2H), 5.60 (dtd, $J$ = 9.6, 8.0, 1.6 Hz, 1H), 5.26 (ddd, $J$ = 10.9, 7.1, 1.6 Hz, 1H), 3.70 (s, 3H), 3.62 (d, $J$ = 13.2 Hz, 1H), 3.34 (d, $J$ = 13.2 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.62 – 2.46 (m, 2H), 1.95 (ddd, $J$ = 12.7, 8.1, 4.1 Hz, 1H), 1.72 – 1.56 (m, 2H), 1.42 – 1.20 (m, 2H), 1.14 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.5, 133.6, 132.6, 130.1, 129.6, 113.7, 55.3, 54.2, 53.2, 50.7, 27.8, 26.3, 23.6, 17.4. ESI [M+1]$^+$ = 246.2(100%), [M+2]$^+$ = 247.2(20%).

![3.77](image)

### 1-(4-methoxybenzyl)-4-phenyl-2,3,4,7-tetrahydro-1H-azepine (3.77)

Yield = 30%, yellow oil. R$_f$ = 0.44 (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.35 – 7.23 (m, 6H), 7.21 (dd, $J$ = 6.8, 1.7 Hz, 1H), 6.85 (d, $J$ = 8.7 Hz, 2H), 5.95 – 5.82 (m, 1H), 5.70 (dtd, $J$ = 11.1, 5.4, 2.5 Hz, 1H), 3.79 (s, 3H), 3.71 (d, $J$ = 11.5 Hz, 1H), 3.62 (s, 2H), 3.24 (d, $J$ = 5.2 Hz, 2H), 3.01 – 2.87 (m, 1H), 2.82 – 2.73 (m, 1H), 2.07 (dtd, $J$ = 14.2, 10.3, 3.9 Hz, 1H), 1.81 (ddddd, $J$ = 11.1, 5.5, 3.9, 2.9 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.7, 147.0, 137.8, 131.3, 130.2, 128.8, 128.6, 127.5, 126.2, 113.7, 60.7, 56.2, 55.4, 53.4, 46.1, 35.3. ESI [M+1]$^+$ = 294.2(100%), [M+2]$^+$ = 295.2(20%).

![3.78](image)

### 1-(4-methoxybenzyl)-4-methyl-2,3,4,7-tetrahydro-1H-azepine (3.78)
Yield = 14%, yellow oil. R\textsubscript{f} = 0.44 (SiO\textsubscript{2}, hex/EtOAc = 1:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 7.24 (d, \(J = 8.7\) Hz, 2H), 6.87 – 6.83 (m, 2H), 5.69 – 5.60 (m, 1H), 5.57 (ddd, \(J = 11.1, 5.4, 2.2\) Hz, 1H), 3.80 (s, 3H), 3.57 (d, \(J = 2.2\) Hz, 2H), 3.14 (d, \(J = 5.3\) Hz, 2H), 3.01 – 2.93 (m, 1H), 2.74 – 2.67 (m, 1H), 2.55 – 2.51 (m, 1H), 1.69 – 1.60 (m, 1H), 1.55 – 1.50 (m, 1H), 1.07 (d, \(J = 7.2\) Hz, 3H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 158.7, 140.4, 130.3, 127.6, 113.6, 60.2, 56.6, 55.4, 53.4, 34.4, 33.9, 22.6. ESI [M+1]\textsuperscript{+} = 232.2(100%), [M+2]\textsuperscript{+} = 233.2(20%).

1-(4-methoxybenzyl)-4,4-dimethyl-2,3,4,7-tetrahydro-1H-azepine (3.79)

Yield = 79%, yellow oil. R\textsubscript{f} = 0.44 (SiO\textsubscript{2}, hex/EtOAc = 1:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.25 (d, \(J = 9.2\) Hz, 2H), 6.99 – 6.71 (m, 2H), 5.51 (d, \(J = 11.6\) Hz, 1H), 5.42 (dt, \(J = 11.6, 5.2\) Hz, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.11 (d, \(J = 4.5\) Hz, 2H), 2.86 – 2.60 (m, 2H), 1.71 – 1.49 (m, 2H), 1.08 (s, 6H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 158.7, 142.7, 131.6, 130.2, 125.3, 113.7, 61.2, 55.4, 52.9, 52.7, 39.5, 36.6, 29.8. ESI [M+1]\textsuperscript{+} = 246.2(100%), [M+2]\textsuperscript{+} = 247.2(20%).

1-(4-methoxybenzyl)-4-propyl-2,3,4,7-tetrahydro-1H-azepine (3.80)

Yield = 21%, yellow oil. R\textsubscript{f} = 0.44 (SiO\textsubscript{2}, hex/EtOAc = 1:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.24 (d, \(J = 9.6\) Hz, 2H), 6.85 (d, \(J = 8.6\) Hz, 2H), 5.70 (dd, \(J = 11.3, 3.4\) Hz, 1H), 5.64 – 5.56 (m, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.13 (d, \(J = 5.3\) Hz, 2H), 2.99 (dt, \(J = 12.9, 4.4\) Hz, 1H), 2.77 –
2.60 (m, 1H), 2.40 – 2.36 (m, 1H), 1.61 – 1.47 (m, 2H), 1.47 – 1.24 (m, 4H), 0.90 (t, \( J = 6.9 \) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 158.7, 139.4, 131.5, 130.3, 127.9, 113.7, 60.2, 56.8, 55.4, 53.3, 38.9, 38.8, 32.0, 20.5, 14.4. ESI [M+1]\(^+\) = 260.2(100%), [M+2]\(^+\) = 261.2(20%).

1-(4-methoxybenzyl)-5-methyl-2,3,4,7-tetrahydro-1H-azepine (3.81)

Yield = 41%. \( R_f = 0.44 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.33 – 7.09 (m, 2H), 6.84 (d, \( J = 8.7 \) Hz, 2H), 5.54 – 5.25 (m, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.07 (d, \( J = 5.9 \) Hz, 2H), 2.90 – 2.72 (m, 2H), 2.24 – 2.10 (m, 2H), 1.76 (s, 3H), 1.71 – 1.60 (m, 2H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 158.7, 143.2, 131.3, 130.4, 122.8, 113.7, 60.4, 58.8, 55.4, 52.8, 33.7, 26.2, 25.2. ESI [M+1]\(^+\) = 232.2(100%), [M+2]\(^+\) = 233.2(15%).

1-(4-methoxybenzyl)-2,3,4,7-tetrahydro-1H-azepine (3.82)

Yield = 54%, yellow oil. \( R_f = 0.37 \) (SiO\(_2\), EtOAc). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.24 (d, \( J = 8.6 \) Hz, 2H), 6.84 (d, \( J = 8.7 \) Hz, 2H), 5.98 – 5.80 (m, 1H), 5.63 (dtt, \( J = 10.9, 5.4, 1.2 \) Hz, 1H), 3.78 (s, 3H), 3.58 (s, 2H), 3.15 (d, \( J = 5.4 \) Hz, 2H), 2.88 – 2.78 (m, 2H), 2.23 (ddd, \( J = 11.5, 5.8, 1.2 \) Hz, 2H), 1.66 (dt, \( J = 11.5, 5.7 \) Hz, 2H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 158.7, 133.5, 130.1, 129.4, 113.5, 59.9, 58.0, 55.3, 53.4, 28.3, 25.9. HRMS (ESI) [M+H]\(^+\) 218.1534, found 218.1539.
(Z)-1-(4-methoxybenzyl)-5,6,7,8-tetrahydroazocin-2(1H)-one (3.83)

Yield = 48%, yellow oil. Rf = 0.59 (SiO2, EtOAc). 1H NMR (CDCl3, 300 MHz): δ 7.23 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.97 (dt, J = 12.5, 5.2 Hz, 1H), 5.81 (dt, J = 12.6, 1.6 Hz, 1H), 4.58 (s, broad, 2H), 3.76 (s, 3H), 3.44 (s, broad, 2H), 2.24 (s, broad, 4H). 13C NMR (CDCl3, 100 MHz): δ 168.9, 158.7, 136.9, 129.4, 129.3, 122.0, 113.6, 54.9, 46.8, 45.5, 30.1, 26.4, 20.0. ESI [M+1]+ = 232.2(100%), [M+2]+ = 233.2(20%).

1-(4-methoxybenzyl)-3-methyl-2,3,4,7-tetrahydro-1H-azepine (3.84)

Yield = 41%, yellow oil. Rf = 0.45 (SiO2, hex/EtOAc = 7:3). 1H NMR (CDCl3, 300 MHz): δ 7.38 – 7.10 (m, 2H), 6.94 – 6.68 (m, 2H), 5.95 – 5.74 (m, 1H), 5.63 (dt, J = 7.7, 5.4, 2.3 Hz, 1H), 3.80 (s, 3H), 3.61 (d, J = 13.1 Hz, 1H), 3.57 (d, J = 13.1 Hz, 1H), 3.14 (d, J = 5.4 Hz, 2H), 2.89 (dd, J = 12.9, 3.7 Hz, 1H), 2.43 (dd, J = 12.9, 9.9 Hz, 1H), 2.23 – 2.01 (m, 2H), 1.95 (ddd, J = 13.1, 6.6, 3.3 Hz, 1H), 0.83 (d, J = 6.7 Hz, 3H). 13C NMR (CDCl3, 100 MHz): δ 158.7, 132.0, 131.5, 130.2, 129.6, 113.7, 65.6, 60.2, 55.4, 53.2, 36.2, 30.6, 21.0. ESI [M+1]+ = 232.2(100%), [M+2]+ = 233.2(20%).
(Z)-3-ethyl-1-(4-methoxybenzyl)-1,2,3,4,5,8-hexahydroazocine (3.85)

Yield = 37%, yellow oil. R_f = 0.20 (SiO_2, hex/EtOAc = 4:1). ^1H NMR (CDCl_3, 400 MHz): δ 7.26 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.74 (ddd, J = 10.9, 9.3, 8.0 Hz, 1H), 5.49 (dt, J = 11.1, 5.5 Hz, 1H), 3.80 (s, 3H), 3.57 (d, J = 13.1 Hz, 1H), 3.46 (d, J = 13.1 Hz, 1H), 3.18 (dd, J = 15.9, 5.0 Hz, 1H), 3.06 (dd, J = 15.6, 5.9 Hz, 1H), 2.99 – 2.85 (m, 1H), 2.58 (dd, J = 12.6, 9.0 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.23 – 2.11 (m, 1H), 1.80 – 1.58 (m, 2H), 1.19 (dq, J = 14.3, 7.3 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^13C NMR (CDCl_3, 100 MHz): δ 158.6, 131.1, 130.0, 127.9, 113.7, 61.4, 61.2, 55.4, 52.7, 36.3, 33.7, 29.2, 25.1, 12.0. ESI [M+1]^+ = 260.2(100%), [M+2]^+ = 261.2(20%).

![Diagram](image-url)

(Z)-6-benzyl-5,6-dihydro-2H-benzo[b][1,4]oxazocine (3.86)

(Z)-6-benzyl-3,4,5,6-tetrahydro-2H-benzo[b][1,4]oxazocine (3.86')

Yield = 46%, clear oil. R_f = 0.83 (SiO_2, dichloromethane). (3.86) ^1H NMR (CDCl_3, 400 MHz): δ 7.40 – 7.18 (m, 5H), 7.02 – 6.89 (m, 2H), 6.80 – 6.67 (m, 2H), 5.87 – 5.66 (m, 2H), 4.79 – 4.72 (m, 2H), 4.51 (s, 2H), 4.17 (s, 2H). ESI [M+1]^+ = 282.2(100%), [M+2]^+ = 283.2(20%). (3.86') 7.40 – 7.18 (m, 5H), 6.88 – 6.82 (m, 2H), 6.62 (dd, J = 11.8, 4.6 Hz, 2H), 4.47 (s, 2H), 4.21 – 4.15 (m, 2H), 3.79 – 3.70 (m, 2H), 1.87 (dt, J = 11.8, 5.7 Hz, 2H), 1.76 (ddd, J = 8.0, 6.7, 3.0 Hz, 2H). ESI [M+1]^+ = 284.2(100%), [M+2]^+ = 285.2(20%).

^13C NMR (CDCl_3, 100 MHz): δ (3.86) + (3.86') 148.6, 146.3, 144.3, 142.7, 139.5, 130.7, 128.7, 127.4, 127.08, 126.9, 126.7, 125.1, 124.7, 124.1, 123.7, 119.3, 118.5, 117.9, 115.7, 75.4, 74.6, 58.8, 55.8, 50.0, 49.5, 27.0, 24.7.
(Z)-1-(4-methoxybenzyl)-1,2,5,7-tetrahydrobenzo[c][1,5]oxazinone (3.87)

Yield = 68%, clear oil. R<sub>f</sub> = 0.90 (SiO<sub>2</sub>, dichloromethane). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.51 – 7.17 (m, 7H), 7.10 (d, <i>J</i> = 7.9 Hz, 1H), 6.97 (t, <i>J</i> = 7.3 Hz, 1H), 5.48 – 5.18 (m, 2H), 4.66 (s, 2H), 4.32 (d, <i>J</i> = 2.9 Hz, 2H), 3.79 (d, <i>J</i> = 7.2 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 154.6, 139.6, 132.5, 132.2, 129.5, 129.1, 128.4, 127.2, 122.4, 119.8, 69.5, 68.7, 58.8, 54.0. ESI [M+1]<sup>+</sup> = 296.2(100%), [M+2]<sup>+</sup> = 297.2(20%).

(Z)-1,6-dibenzyl-1,2,5,6-tetrahydrobenzo[b][1,4]diazocine (3.88)

Yield = 32%, yellow oil. R<sub>f</sub> = 0.83 (SiO<sub>2</sub>, dichloromethane). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.38 – 7.12 (m, 10H), 6.98 (dd, <i>J</i> = 5.9, 3.6 Hz, 2H), 6.82 (dd, <i>J</i> = 5.9, 3.6 Hz, 2H), 4.34 (s, 4H), 3.85 (d, <i>J</i> = 3.1 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 144.8, 139.6, 129.6, 128.4, 128.3, 126.9, 121.8, 120.8, 58.7, 51.5. ESI [M+1]<sup>+</sup> = 341.2(100%), [M+2]<sup>+</sup> = 342.2(25%).

3-ethyl-1-(4-methoxybenzyl)-2,3,4,7-tetrahydro-1<i>H</i>-azepine (3.89)
Yield = 62%, yellow oil. \( R_f = 0.34 \) (SiO\(_2\), hex/EtOAc = 1:1). \( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta 7.24 \) (d, \( J = 8.5 \) Hz, 2H), 6.84 (d, \( J = 8.6 \) Hz, 2H), 5.90 – 5.77 (m, 1H), 5.61 (dtd, \( J = 7.4, 5.2, 2.2 \) Hz, 1H), 3.79 (s, 3H), 3.58 (s, 2H), 3.13 (d, \( J = 5.0 \) Hz, 2H), 2.87 (dd, \( J = 12.7, 3.9 \) Hz, 1H), 2.47 (dd, \( J = 12.7, 9.6 \) Hz, 1H), 2.20 (dd, \( J = 15.2, 7.3, 2.3 \) Hz, 1H), 2.07 (tdd, \( J = 15.5, 4.0, 1.9 \) Hz, 1H), 1.68 (dt, \( J = 12.8, 6.2, 3.1 \) Hz, 1H), 1.25 – 1.14 (m, 2H), 0.83 (t, \( J = 7.4 \) Hz, 3H). \( ^13C \) NMR (CDCl\(_3\), 100 MHz): \( \delta 158.7, 131.7, 130.2, 129.4, 113.7, 63.4, 60.7, 55.4, 53.9, 37.8, 33.4, 27.8, 11.9. \) ESI [M+1]\(^+\) = 246.2(100%), [M+2]\(^+\) = 247.2(20%).

3-isopentyl-1-(4-methoxybenzyl)-2,3,4,7-tetrahydro-1H-azepine (3.90)

Yield = 64%, yellow oil. \( R_f = 0.45 \) (SiO\(_2\), hex/EtOAc = 7:3). \( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta 7.24 \) (d, \( J = 8.7 \) Hz, 2H), 6.85 (d, \( J = 8.7 \) Hz, 2H), 5.83 (ddd, \( J = 11.6, 7.5, 4.3 \) Hz, 1H), 5.61 (dtd, \( J = 7.4, 5.2, 2.2 \) Hz, 1H), 3.79 (s, 3H), 3.57 (s, 2H), 3.13 (d, \( J = 5.1 \) Hz, 2H), 2.85 (dd, \( J = 12.7, 3.8 \) Hz, 1H), 2.47 (dd, \( J = 12.7, 9.5 \) Hz, 1H), 2.19 (ddd, \( J = 15.3, 7.3, 2.0 \) Hz, 1H), 2.11 – 2.03 (m, 1H), 1.79 – 1.63 (m, 1H), 1.52 – 1.37 (m, 1H), 1.20 – 1.02 (m, 4H), 0.84 (dd, \( J = 6.6, 1.8 \) Hz, 6H). \( ^13C \) NMR (CDCl\(_3\), 100 MHz): \( \delta 158.7, 131.7, 130.2, 129.4, 113.7, 63.7, 60.7, 55.4, 53.9, 36.7, 36.4, 33.8, 32.8, 28.4, 22.8, 22.7. \) ESI [M+1]\(^+\) = 288.2(100%), [M+2]\(^+\) = 289.2(20%).

3-benzyl-1-(4-methoxybenzyl)-2,3,4,7-tetrahydro-1H-azepine (3.91)

Yield = 73%, clear oil. \( R_f = 0.44 \) (SiO\(_2\), hex/EtOAc = 7:3). \( ^1H \) NMR (CDCl\(_3\), 300 MHz): \( \delta 7.29 – 7.12 \) (m, 7H), 6.82 (d, \( J = 8.7 \) Hz, 2H), 5.73 – 5.38 (m, 2H), 4.62 (d, \( J = 14.7 \) Hz, 1H), 4.54 (d, \( J
= 14.7 Hz, 1H), 4.28 (dd, J = 20.0, 2.5 Hz, 1H), 3.78 (s, 3H), 3.56 – 3.12 (m, 3H), 2.65 (td, J = 9.6, 2.5 Hz, 1H), 2.36 – 2.10 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 175.5, 159.0, 140.5, 131.3, 129.9, 129.4, 128.4, 126.2, 124.6, 114.0, 55.4, 50.8, 45.0, 42.7, 37.7, 31.4. ESI [M+1]$^+$ = 308.2(100%), [M+2]$^+$ = 309.2(20%).

1-(4-methoxybenzyl)-3-((tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,7-tetrahydro-1H-azepine (3.119)

Yield = 60%, clear oil. R$_f$ = 0.23 (SiO$_2$, hex/EtOAc = 7:3). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.25 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.87 – 5.77 (m, 1H), 5.62 (dtd, J = 6.8, 5.3, 1.6 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.80 (s, 3H), 3.58 (d, J = 13.0 Hz, 1H), 3.54 (d, J = 13.0 Hz, 1H), 3.27 (td, J = 11.4, 2.7 Hz, 1H), 3.23 – 3.17 (m, 1H), 3.13 (dd, J = 15.6, 5.2 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.82 (dd, J = 12.9, 3.4 Hz, 1H), 2.53 (dd, J = 12.9, 8.5 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.15 – 1.95 (m, 2H), 1.76 (dd, J = 12.7, 2.1 Hz, 1H), 1.59 – 1.08 (m, 9H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.7, 131.7, 131.6, 130.4, 129.3, 113.7, 75.7, 68.5, 62.3, 60.5, 55.4, 54.6, 41.6, 34.7, 32.6, 31.7, 26.3, 23.7. ESI [M+1]$^+$ = 316.2(100%), [M+2]$^+$ = 317.2(20%).

3.5.5 Preparation of cyclic allylamines by other means
1-benzyl-2-phenyl-1,2,3,6-tetrahydropyridine (3.93)

**3.92** (0.31 mmol, 100 mg) was dissolved in 8 mL of absolute ethanol. The solution was cooled down in ice, and sodium borohydride (0.62 mmol, 24 mg) was added to the reaction flask in small portions. The reaction was allowed to run in ice until TLC showed full conversion of the starting material. The reaction was quenched with water, extracted with ethyl acetate, dried over sodium sulfate and concentrated. The crude product was purified on SiO\(_2\) (hex/EtOAc = 9:1, \(R_f = 0.52\)) to give 3.93 in 75% yield. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 7.57 – 6.93 \text{ (m, 10H)}, 5.99 – 5.76 \text{ (m, 1H)}, 5.69 \text{ (dd, } J = 9.9, 2.1 \text{ Hz, 1H)}, 3.78 \text{ (d, } J = 13.1 \text{ Hz, 1H}), 3.65 – 3.47 \text{ (m, 1H)}, 3.21 \text{ (dd, } J = 17.2, 1.7 \text{ Hz, 1H)}, 2.96 \text{ (d, } J = 13.2 \text{ Hz, 1H)}, 2.83 \text{ (d, } J = 17.1 \text{ Hz, 1H}), 2.54 – 2.21 \text{ (m, 2H)}, 1.56 \text{ (s, 3H)}. \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta 143.8, 139.5, 128.9, 128.7, 128.3, 128.0, 127.3, 126.9, 125.4, 124.9, 63.9, 59.4, 51.9, 35.1\). ESI [M+1]\(^+\) = 250.2(100%), [M+2]\(^+\) = 251.2(20%).

![](3.94.png)

3,4-dihydroisoquinoline (3.94)

NBS (41.3 mmol, 7.34 g) was added in small portions at room temperature to a stirring solution of 1,2,3,4-tetrahydroisoquinoline (37.5 mmol, 4.7 mL) in 100 mL of dichloromethane. After TLC showed the disappearance of the starting material, 25 mL of aqueous solution of potassium hydroxide (30% w/v) was added, and the stirring was continued overnight. The organic layer was extracted with dilute sulfuric acid. The combined aqueous layers were neutralized with aqueous ammonium hydroxide until the solution reached pH = 9.0. The resulting solution was extracted with dichloromethane, and dried over anhydrous sodium sulfate. The crude product was subjected to vacuum distillation to yield 3.94 in 76% yield.
1H NMR (CDCl₃, 300 MHz): δ 8.34 (t, J = 2.1 Hz, 1H), 7.44 – 7.21 (m, 3H), 7.16 (d, J = 7.3 Hz, 1H), 3.95 – 3.53 (m, 2H), 2.88 – 2.50 (m, 2H). 13C NMR (CDCl₃, 100 MHz): δ 160.5, 136.5, 131.2, 128.7, 127.6, 127.3, 127.2, 47.6, 25.2.

2-methyl-1-(prop-1-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (3.96)

3.94 (15.2 mmol, 2.0g) was dissolved in acetone (60 mL), after which methyl iodide (45.6 mmol, 2.85 mL) was added. The reaction was allowed to stir for 10 min, after which the newly-formed precipitate was filtered and dried. The resulting iminium salt was suspended in 125 mL of anhydrous THF. The solution was cooled down to -78°C and isopropenyl magnesium bromide was added in one portion. The reaction was allowed to warm up to room temperature and was left to stir overnight. The reaction was then carefully quenched with aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated to give 3.96 in 98% without further purification.

1H NMR (CDCl₃, 300 MHz): δ 7.14 – 7.09 (m, 4H), 5.09 (s, 2H), 3.68 (s, 1H), 3.19 – 3.10 (m, 1H), 3.10 – 2.98 (m, 1H), 2.69 (d, J = 15.1 Hz, 1H), 2.49 (ddd, J = 15.2, 9.9, 3.1 Hz, 1H), 2.33 (s, 3H), 1.49 (d, J = 1.0 Hz, 3H). 13C NMR (CDCl₃, 100 MHz): δ 146.2, 136.1, 135.2, 128.6, 126.8, 126.2, 125.9, 116.0, 74.1, 52.5, 44.2, 29.8, 17.2. ESI [M+1]+ = 188.2(100%), [M+2]+ = 189.2(20%).
1-benzyl-4-methyl-4-vinylazetidin-2-one (3.97)\textsuperscript{44}

Yield = 60%, yellow oil. \(R_f = 0.50\) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.37 – 7.20 (m, 5H), 5.83 (dd, \(J = 17.5, 10.6\) Hz, 1H), 5.25 – 5.06 (m, 2H), 4.45 (d, \(J = 15.3\) Hz, 1H), 4.10 (d, \(J = 15.3\) Hz, 1H), 2.90 (d, \(J = 14.5\) Hz, 1H), 2.84 (d, \(J = 14.4\) Hz, 1H), 1.30 (s, 3H).

\[\text{N} \text{Bn} \]

1-benzyl-4-methyl-4-vinylazetidine (3.98)\textsuperscript{45}

Yield = 33%, yellow oil. \(R_f = 0.69\) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.37 – 7.12 (m, 5H), 6.05 (dd, \(J = 17.4, 10.7\) Hz, 1H), 5.19 (d, \(J = 17.4\) Hz, 1H), 5.07 (d, \(J = 10.6\) Hz, 1H), 3.58 (d, \(J = 13.1\) Hz, 1H), 3.48 (d, \(J = 13.1\) Hz, 1H), 3.22 – 3.08 (m, 2H), 2.22 – 2.07 (m, 1H), 1.91 (ddd, \(J = 10.3, 8.0, 4.9\) Hz, 1H), 1.33 (s, 3H).

\[\text{O} \text{Bn} \]

7-benzyl-7-azabicyclo[4.2.0]oct-4-en-8-one (3.99)

Yield = 35%, clear oil. \(R_f = 0.50\) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 7.44 – 7.05 (m, 5H), 6.24 – 6.03 (m, 1H), 5.82 – 5.63 (m, 1H), 4.61 (d, \(J = 15.1\) Hz, 1H), 4.02 (d, \(J = 15.1\) Hz, 1H), 3.86 (t, \(J = 4.8\) Hz, 1H), 3.45 (dd, \(J = 8.4, 3.5\) Hz, 1H), 2.26 – 1.98 (m, 3H), 1.66 – 1.47 (m, 1H). \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 170.6, 136.2, 135.9, 128.8, 128.4, 127.27, 124.4, 48.9, 47.8, 44.7, 22.2, 21.7. ESI [M+1]\(^+\) = 214.1(100%), [M+2]\(^+\) = 215.1(15%).

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7-benzyl-7-azabicyclo[4.2.0]oct-4-ene (3.100)

Yield = 83%, clear oil. \( R_f = 0.72 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 7.44 – 6.93 (m, 5H), 6.09 – 5.90 (m, 1H), 5.54 (dd, \( J = 10.1, 1.8 \) Hz, 1H), 3.82 – 3.53 (m, 2H), 3.16 (t, \( J = 7.2 \) Hz, 1H), 3.07 (dd, \( J = 6.8, 4.6 \) Hz, 1H), 2.59 (ddd, \( J = 13.8, 11.2, 7.0 \) Hz, 1H), 2.19 – 2.03 (m, 1H), 2.03 – 1.87 (m, 1H), 1.87 – 1.67 (m, 2H). ESI [M+1]^+ = 200.1(100%), [M+2]^+ = 201.1(15%).

(Z)-9-benzyl-9-azabicyclo[6.2.0]dec-6-en-10-one (3.101)

Yield = 14%, clear oil. \( R_f = 0.50 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 7.68 – 7.00 (m, 5H), 5.73 (tdd, \( J = 10.0, 7.6, 2.5 \) Hz, 1H), 5.54 – 5.34 (m, 1H), 5.54 – 5.34 (m, 1H), 4.34 (dd, \( J = 3.1, 1.8 \) Hz, 1H), 4.11 (d, \( J = 15.2 \) Hz, 1H), 3.27 (ddd, \( J = 12.2, 5.3, 1.8 \) Hz, 1H), 2.15 – 1.51 (m, 6H), 1.38 (t, \( J = 9.2 \) Hz, 2H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 117.0, 136.0, 134.0, 128.9, 128.4, 127.8, 122.4, 58.1, 54.3, 44.1, 31.5, 29.2, 25.9, 22.6. ESI [M+1]^+ = 242.2(100%), [M+2]^+ = 243.2(20%).
(Z)-9-benzyl-9-azabicyclo[6.2.0]dec-6-ene (3.102)

Yield = 82%, yellow oil. \( R_f = 0.70 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 7.52 – 6.98 (m, 5H), 5.67 – 5.35 (m, 1H), 5.24 (d, \( J = 11.2 \) Hz, 1H), 4.05 (d, \( J = 7.9 \) Hz, 1H), 3.72 (d, \( J = 12.8 \) Hz, 1H), 3.57 (d, \( J = 12.8 \) Hz, 1H), 3.21 (dd, \( J = 10.0, 5.9 \) Hz, 1H), 3.21 (dd, \( J = 10.0, 5.9 \) Hz, 1H), 3.02 (dd, \( J = 7.1, 4.0 \) Hz, 1H), 2.70 – 2.44 (m, 1H), 2.25 – 1.12 (m, 8H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 138.4, 129.9, 129.6, 129.0, 128.9, 128.3, 128.2, 127.0, 65.8, 62.0, 59.3, 39.3, 32.3, 29.5, 28.2, 27.0. ESI \([M+1]^+ = 228.2(100\%), [M+2]^+ = 229.2(20\%).

(3.103)

(S)-2-((E)-(((1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methylene)amino)-2-phenylethanol (3.103)

Yield = 84%. \( R_f = 0.40 \) (SiO\(_2\), hex/EtOAc = 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 7.85 (s, 1H), 7.36 – 7.08 (m, 5H), 6.04 – 5.89 (m, 1H), 4.24 (dd, \( J = 7.8, 5.0 \) Hz, 1H), 3.87 – 3.60 (m, 2H), 3.08 – 2.94 (m, 1H), 2.49 – 2.30 (m, 3H), 1.29 (s, 3H), 1.02 (d, \( J = 9.0 \) Hz, 1H), 0.74 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \( \delta \): 163.7, 148.4, 141.2, 135.7, 128.6, 127.6, 127.4, 75.5, 67.9, 41.1, 40.2, 37.8, 32.6, 31.4, 26.1, 21.1.

(3.104)

(4R)-ethyl 2-((1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)thiazolidine-4-carboxylate

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(R)-Myrtenal (2.6 mmol, 0.45 mL) was mixed with cysteine ethyl ester (2.6 mmol, 0.385 g) in dichloromethane in the presence of 4Å molecular sieves overnight. The reaction was filtered, and the filtrate was concentrated and purified on SiO₂.

Yield = 81%. Rᵥ = 0.30 (SiO₂, hex/EtOAc = 9:1). ¹H NMR (CDCl₃, 300 MHz): Major diastereomer δ: 5.70 (s, 1H), 5.05 (s, 1H), 4.30 – 4.23 (m, 2H), 3.87 – 3.75 (m, 1H), 3.32 (dd, J = 10.2, 6.8 Hz, 1H), 2.87 – 2.77 (m, 1H), 2.51 – 2.15 (m, 6H), 2.15 – 2.04 (m, 1H), 1.39 – 1.22 (m, 6H), 0.84 (d, J = 5.8 Hz, 3H). Minor diastereomer: δ 5.59 (dd, J = 2.9, 1.4 Hz, 1H), 5.21 (d, J = 1.0 Hz, 1H), 4.30 – 4.23 (m, 2H), 4.16 (dd, J = 7.1, 5.3 Hz, 1H), 3.21 (dd, J = 10.6, 7.2 Hz, 1H), 3.10 (dd, J = 10.6, 5.1 Hz, 1H), 2.51 – 2.15 (m, 6H), 2.15 – 2.04 (m, 1H), 1.39 – 1.22 (m, 6H), 0.84 (d, J = 5.8 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz) both diastereomers: δ 172.0, 171.2, 146.0, 143.5, 121.7, 118.6, 73.5, 71.9, 65.3, 64.5, 61.6, 61.5, 42.2, 40.9, 38.3, 37.3, 31.5, 31.1, 26.1, 26.0, 21.3, 21.0, 14.2.

3.5.6 Preparation of cyclic allylamines by Pd-catalyzed rearrangement

1-(4-methoxybenzyl)-2-(2-methylprop-1-en-1-yl)pyrrolidine (3.107)

In the glove-box to a flame-dried vial equipped with a stir bar allyl palladium chloride dimer (0.01 mmol, 3.6 mg) was weighed out. Outside of the glove-box the complex was dissolved in 1.0 mL of anhydrous dichloromethane. To the reaction mixture triethyl phosphite (0.04mmol, 6.6 mg) and morpholine (0.05 mmol, 4.36 mg) were added, and the mixture was allowed to stir for 5 minutes. 3.74 (0.40mmol, 98 mg) was dissolved in 1.0 mL of anhydrous dichloromethane and was added to the reaction mixture, followed by the addition of trifluoroacetic acid (0.40 mmol, 45.6 mg). The reaction vial was sealed and allowed to stir under reflux for 10 hours. The reaction
mixture was cooled down to room temperature, washed with saturated solution of sodium bicarbonate, extracted with dichloromethane, dried with sodium sulfate and concentrated. The crude material was purified on flash chromatography (Hex/EtOAc = 9:1, Rf = 0.36) to give 3.107 (0.39 mmol, 96 mg, 97%) as an orange solid.

1H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.23 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.26 (d, $J = 9.1$ Hz, 1H), 4.00 (d, $J = 12.9$ Hz, 2H), 3.79 (s, 3H), 3.26 (d, $J = 12.6$ Hz, 2H), 3.28 – 3.24 (m, 1H), 3.11 – 3.00 (m, 1H), 2.40 – 2.19 (m, 1H), 2.02 – 1.81 (m, 2H), 1.78 (s, 3H), 1.68 (s, 3H), 1.80 – 1.58 (m, 2H). 13C NMR (CDCl$_3$, 75 MHz): $\delta$ 159.2, 136.5, 130.9, 128.7, 124.7, 113.8, 63.1, 56.5, 55.4, 52.3, 30.9, 29.8, 26.1, 21.7, 18.5. HRMS (ESI) [M+H]$^+$ calcd. for C$_{16}$H$_{23}$NO 246.1856, found 246.1852.

(E)-1-(4-methoxybenzyl)-2-(prop-1-en-1-yl)pyrrolidine (3.108)

Yield = 94%, yellow oil. R$_f$ = 0.36 (SiO$_2$, hex/EtOAc = 9:1). 1H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.20 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 5.63 (dq, $J = 15.1, 6.4$ Hz, 1H), 5.41 (ddd, $J = 15.2, 8.4, 1.4$ Hz, 1H), 5.41 (ddd, $J = 15.2, 8.4, 1.4$ Hz, 1H), 3.97 (d, $J = 12.8$ Hz, 1H), 3.79 (s, 3H), 3.01 (d, $J = 12.9$ Hz, 1H), 2.94 – 2.86 (m, 1H), 2.70 (dd, $J = 16.1, 8.2$ Hz, 1H), 2.06 (dd, $J = 16.1, 8.2$ Hz, 1H), 1.96 – 1.84 (m, 1H), 1.72 (dd, $J = 6.4, 1.6$ Hz, 3H), 1.80 – 1.55 (m, 3H). 13C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.6, 133.8, 130.4, 130.3, 67.7, 57.4, 55.4, 53.2, 31.7, 22.0, 18.0.

(E)-1-(4-methoxybenzyl)-2-(prop-1-en-1-yl)piperidine (3.109)

168
Yield = 92%, yellow oil. R\textsubscript{f} = 0.39 (SiO\textsubscript{2}, hex/EtOAc = 4:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 7.21 (d, \(J = 8.6\) Hz, 2H), 6.83 (d, \(J = 8.7\) Hz, 2H), 5.60 (dq, \(J = 12.7, 6.2\) Hz, 1H), 5.50 – 5.44 (m, 1H), 3.99 (d, \(J = 13.4\) Hz, 1H), 3.79 (s, 3H), 2.99 (d, \(J = 13.5\) Hz, 1H), 2.77 (dd, \(J = 11.6, 3.1\) Hz, 1H), 2.66 – 2.51 (m, 1H), 1.91 – 1.77 (m, 1H), 1.70 (d, \(J = 6.0\) Hz, 3H), 1.67 – 1.23 (m, 6H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 158.6, 135.2, 130.6, 130.5, 126.7, 113.5, 65.8, 59.1, 55.4, 52.2, 34.0, 25.9, 24.2, 18.0. HRMS (ESI) [M+H]\textsuperscript{+} calcd. for C\textsubscript{16}H\textsubscript{24}NO 246.1852, found 246.1848.

1-(4-methoxybenzyl)-2-vinylpyrrolidine (3.110)\textsuperscript{46}

Yield = 93%, yellow oil. R\textsubscript{f} = 0.51 (SiO\textsubscript{2}, hex/EtOAc = 9:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.27 (d, \(J = 8.7\) Hz, 2H), 6.88 (d, \(J = 8.6\) Hz, 2H), 6.08 – 5.83 (m, 1H), 5.39 – 5.34 (m, 2), 4.14 (d, \(J = 13.1\) Hz, 1H), 3.79 (s, 3H), 3.59 (d, \(J = 13.1\) Hz, 1H), 3.37 – 3.30 (m, 1H), 3.28 – 3.18 (m, 1H), 2.71 – 2.56 (m, 1H), 2.17 – 1.75 (m, 4H).

1-(4-methoxybenzyl)-2-vinylpiperidine (3.111)\textsuperscript{47}

Yield = 97%, yellow oil. R\textsubscript{f} = 0.51 (SiO\textsubscript{2}, hex/EtOAc = 9:1). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 7.21 (d, \(J = 8.6\) Hz, 2H), 6.83 (d, \(J = 8.7\) Hz, 2H), 5.89 (ddd, \(J = 17.4, 10.2, 8.6\) Hz, 1H), 5.35 – 5.15 (m, 1H), 5.10 (dd, \(J = 10.2, 1.7\) Hz, 1H), 3.97 (d, \(J = 13.4\) Hz, 1H), 3.79 (s, 3H), 3.03 (d, \(J = 13.4\) Hz, 1H), 2.80 (dt, \(J = 11.4, 3.0\) Hz, 1H), 1.87 (td, \(J = 11.2, 2.5\) Hz, 1H), 1.74 – 1.58 (m, 2H), 1.58 – 1.39 (m, 3H), 1.34 – 1.22 (m, 1H).
4-ethyl-1-(4-methoxybenzyl)-2-vinylpyrrolidine (3.112)

Yield = 53%, yellow oil. R_f = 0.31 (SiO_2, hex/EtOAc = 9:1). ^1^H NMR (CDCl_3, 300 MHz): δ 7.21 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.87 – 5.70 (m, 1H), 5.18 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 3.93 (d, J = 12.8 Hz, 1H), 3.80 (s, 3H), 3.06 – 2.98 (m, 2H), 2.88 – 2.77 (m, 1H), 2.09 – 1.97 (m, 1H), 1.87 – 1.79 (m, 1H), 1.73 (t, J = 9.1 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.31 (dtd, J = 14.5, 7.3, 1.8 Hz, 2H), 0.83 (t, J = 7.4 Hz, 3H). ^1^C NMR (CDCl_3, 100 MHz): δ 158.7, 141.3, 130.3, 116.2, 113.7, 67.8, 60.2, 57.6, 55.4, 38.3, 37.9, 28.4, 12.8. HRMS (ESI) [M+H]^+ calcd. for C_{16}H_{24}NO 246.1852, found 246.1843.

syn-5-ethyl-1-(4-methoxybenzyl)-2-vinylpiperidine (3.113)

Yield = 71%, yellow oil. R_f = 0.66 (SiO_2, hex/EtOAc = 1:1). ^1^H NMR (CDCl_3, 400 MHz): δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.85 (ddd, J = 17.5, 10.1, 8.6 Hz, 1H), 5.20 (dd, J = 17.3, 1.7 Hz, 1H), 5.10 (dd, J = 10.2, 1.7 Hz, 1H), 4.00 (d, J = 13.5 Hz, 1H), 3.80 (s, 3H), 3.01 (d, J = 13.5 Hz, 1H), 2.81 (ddd, J = 11.1, 3.2, 2.0 Hz, 1H), 2.56 (dd, J = 8.6, 3.2 Hz, 1H), 1.86 – 1.71 (m, 1H), 1.66 – 1.61 (m, 2H), 1.50 – 1.44 (m, 2H), 1.19 – 1.03 (m, 2H), 0.87 (dd, J = 12.8, 3.9), 0.80 (t, J = 7.5 Hz, 3H). ^1^C NMR (CDCl_3, 100 MHz): δ 159.0, 143.4, 130.5, 115.8, 113.6, 67.0, 59.2, 58.5, 55.4, 38.0, 34.0, 30.7, 27.5, 11.5. HRMS (ESI) [M+H]^+ calcd. for C_{17}H_{26}NO 260.2008, found 260.2001.
4-isopentyl-1-(4-methoxybenzyl)-2-vinylpyrrolidine (3.114)

Yield = 50%, yellow oil. Rf = 0.24 (SiO2, hex/EtOAc = 9:1). 1H NMR (CDCl3, 400 MHz): δ 7.21 (dd, J = 8.6, 2.9 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.86 – 5.68 (m, 1H), 5.18 (dddd, J = 17.1, 5.7, 1.9, 0.6 Hz, 1H), 5.10 (dd, J = 10.1, 1.9 Hz, 1H), 3.92 (dd, J = 13.0, 3.5 Hz, 1H), 3.80 (s, 3H), 3.18 – 3.02 (m, 1H), 2.99 (d, J = 13.0 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.60 – 1.53 (m, 1H), 1.52 – 1.40 (m, 1H), 1.38 – 1.23 (m, 4H), 1.13 – 1.05 (m, 2H), 0.85 – 0.83 (m, 3H), 0.83 – 0.81 (m, 3H). 13C NMR (CDCl3, 100 MHz): δ 141.4, 130.3, 116.4, 113.6, 67.8, 60.5, 57.7, 55.4, 38.6, 37.7, 36.3, 33.4, 29.9, 28.3, 22.8. HRMS (ESI) [M+H]+ calcd. for C19H30NO 288.2321, found 288.2325.

1-(4-methoxybenzyl)-4-((tetrahydro-2H-pyran-2-yl)methyl)-2-vinylpyrrrolidine (3.115)

Yield = 68%, yellow oil. Rf = 0.42 (SiO2, hex/EtOAc = 9:1). 1H NMR (CDCl3, 400 MHz): δ 7.21 (dd, J = 8.7, 2.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.88 – 5.67 (m, 1H), 5.18 (dddd, J = 17.1, 8.0, 1.9 Hz, 1H), 3.92 (d, J = 12.8 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.80 (d, J = 1.0 Hz, 1H), 3.34 (td, J = 11.4, 2.7 Hz, 1H), 3.18 – 2.99 (m, 2H), 2.94 – 2.81 (m, 1H), 2.63 (dd, J = 9.6, 4.2 Hz, 1H)(minor), 2.38 (t, J = 9.1 Hz, 1H), 2.34 – 2.21 (m, 1H)(minor), 2.09 (ddd, J = 12.3, 8.1, 6.2 Hz, 1H)(minor), 1.90 – 1.72 (m, 4H), 1.68 – 1.13 (m, 13H), 0.93 – 0.82 (m, 1H). 13C NMR (CDCl3, 100 MHz): δ 158.6, 141.2, 130.3, 116.3, 113.6, 77.4, 68.6, 67.7, 60.4, 57.5, 55.4, 42.4, 38.5, 32.4, 32.3, 32.0, 31.1, 29.9, 26.3, 23.7. HRMS (ESI) [M+H]+ calcd. for C20H30NO2 316.2271, found 316.2273.
1,4-dibenzyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (3.116)

Yield = 78%, yellow oil. Rf = 0.27 (SiO2, hex/EtOAc = 4:1). 1H NMR (CDCl3, 300 MHz): δ 7.34 – 7.28 (m, 10H), 6.62 – 6.46 (m, 4H), 5.98 (ddd, J = 16.6, 10.6, 7.8 Hz, 1H), 5.19 – 5.08 (m, 2H), 4.65 – 4.26 (m, 4H), 3.92 (dt, J = 11.2, 3.4 Hz, 1H), 3.52 (dd, J = 7.1, 3.4 Hz, 1H), 3.5 (s, 2H). 13C NMR (CDCl3, 100 MHz): δ 139.0, 138.8, 137.3, 135.6, 135.1, 128.7, 127.4, 118.8, 117.6, 117.0, 111.6, 111.4, 60.1, 55.9, 53.1, 52.6. HRMS (ESI) [M+H]+ calcd. for C24H24N2 341.2006, found 341.2012.

4-benzyl-3-vinyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (3.117)

4-benzyl-2-vinyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (3.117')

Yield = 83%, yellow oil. Rf = 0.37 (SiO2, hex/EtOAc = 19:1). (3.117) 1H NMR (CDCl3, 300 MHz): δ 7.39 – 7.20 (m, 5H), 6.98 – 6.72 (m, 2H), 6.71 – 6.46 (m, 2H), 6.03 – 5.80 (m, 1H), 5.57 – 5.13 (m, 2H), 4.62 (d, J = 16.9 Hz, 1H), 4.29 (d, J = 16.8 Hz, 1H), 4.22 (dd, J = 7.9, 3.4 Hz, 2H), 3.94 – 3.82 (m, 1H). (3.117') 1H NMR (CDCl3, 300 MHz): δ 7.39 – 7.20 (m, 5H), 6.98 – 6.72 (m, 2H), 6.71 – 6.46 (m, 2H), 6.03 – 5.80 (m, 1H), 5.57 – 5.13 (m, 2H), 4.67 – 4.63 (m, 1H), 4.45 (s, 2H), 3.32 (dd, J = 11.8, 2.7 Hz, 1H), 3.20 (dd, J = 11.8, 7.8 Hz, 1H). HRMS (ESI) [M+H]+ calcd. for C17H17NO 252.1361, found 252.1358.
1-benzyl-4-methyl-4-vinylazetidin-2-one (3.118)

Yield = 97%, yellow oil. $R_f = 0.23$ (SiO$_2$, hex/EtOAc = 1:1). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.26 – 7.25 (m, 5H), 5.27 – 5.19 (m, 1H), 3.52 – 3.46 (m, 2H), 3.02 – 2.92 (m, 2H), 2.50 – 2.41 (m, 2H), 2.19 -2.13 (m, 2H), 1.50 (s, 3H).

3.6 References

12. If the reaction is scaled up from 1 mmol to 1 g scale, the reaction yield drops to 56%. However, scaling out allowed for the preparation of the required product in 85% yield.
17. Originally, the reaction was quenched with DBU; however, later it was discovered that diisopropyl amine, that is generated as a side-product, can react to achieve the required dehalogenation.


[27] Zhang, M.; Hanson, P. R. *Science of Synthesis* **2006**, *20b*, 863


