Pd$^0$-CATALYZED FORMAL 1,3-DIAZA-CLAISEN REARRANGEMENT.
DESIGN AND DEVELOPMENT OF CATIONIC 1,3-DIAZA-CLAISEN REARRANGEMENT.

A Dissertation Presented

by

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ABSTRACT

The dissertation describes Pd⁰-catalyzed formal 1,3-diaza-Claisen rearrangement and the design and development of cationic 1,3-diaza-Claisen rearrangement.

Our previous work has shown that isocyanates react with azanorbornenes and azabicyclo[2.2.2]octenes under thermal conditions to afford zwitterionic intermediates that undergo a thermal 1,3-diaza-Claisen rearrangement to give both ureas and isoureas. However, some azanorbornenes and azabicyclooctenes failed to rearrange or proceeded in low yields. To address these challenging substrates for the thermal 1,3-diaza-Claisen rearrangement, we have developed a Pd⁰-catalyzed formal 1,3-diaza-Claisen rearrangement. Interestingly, under Pd⁰-catalyzed condition, both isocyanates with electron-withdrawing groups and isocyanates without electron-withdrawing groups react with azanorbornenes and azabicyclo[2.2.2]octenes to provide ureas as the only products in high yields. More importantly, the reactions that failed under thermal conditions were all successful under Pd⁰-catalysis. In addition to azanorbornenes and azabicyclo[2.2.2]octenes, other ring systems were also investigated. Pd⁰ catalysis has broadened the scope of tertiary allylic amines that react with isocyanates to afford 1,3-diaza-Claisen rearrangement products.

In the presence of p-TsCl and NEt₃, allylaminopropyl benzyl ureas were initially dehydrated to form protonated carbodiimides whose presence was confirmed by the infrared absorption frequency at 2100 cm⁻¹ which is the characteristic band of –N=C=N--; then the in situ generated protonated carbodiimides were poised for further cationic 1,3-diaza-Claisen rearrangement to afford synthetically challenging guanidines. The effect of acid on the rearrangement was ascertained by the fact that no rearrangement product was observed by simply heating free base carbodiimide 3.10 in benzene at reflux. Other dehydration reagents, such as Tf₂O, Ts₂O, MsCl were also investigated, and none of them provide satisfactory results. A selection of allylamine benzyl ureas with different tether length, substituents, or in varied ring systems, were synthesized to explore the scope of this methodology. This methodology works best at allylaminopropyl benzyl ureas, and the substituents on the benzyl group does not seem to affect the reaction rate in a significant way.
This thesis is dedicated to

My mom

My husband

All the people who never stop believing in me
ACKNOWLEDGEMENTS

Six-year graduate study in University of Vermont has been such a wonderful journey for me, and I am very grateful for all the help and encouragement I have received along the way. I want to give my most sincere thanks to my graduate advisor, Prof. José S. Madalengoitia for his unfailing support and encouragement throughout my graduate career, especially during some challenging times. He has been a great teacher to me, of everything from bench chemistry, to the principles of organic chemistry, to scientific writing and presentation. Most importantly, he has taught me through example that dedication to details and passion for science are paramount. José is absolutely the best teacher I’ve ever had in my whole academic career. There is no doubt that any success I may find in my future career will be a result, direct or indirect, of the training and opportunities that José has given me.

None of this could have happened without the tremendous support and unconditional love from my mother, and to her I dedicate this thesis. Although my mother never went to college, she placed the highest emphasis on education. As a single parent, she worked three jobs to put me through college. When I told her about my plan of pursing graduate study abroad in USA, she was fully supportive, even though she was well aware of the fact that she might not be able to see her only child for a long time. She sacrificed everything for me, and to me, she is the greatest mom in the world, it is because of her that I am where I am today. I have made it my life goal to be the daughter she will always be proud of. Mom, I love you, and you mean the whole world to me.
Finally, I want to give my deepest thanks to the person who has made all of this worthwhile, my husband Yue Jiang. His love and support for me have been limitless and essential. Whether it was giving up everything to accompany me in US or staying up until 11 pm to drive me to the lab to check up on a reaction, he has always devoted himself to help me follow my dreams. I consider myself the luckiest woman in the world. Yue, for all your love, friendship and sacrifice, thank you!
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CHAPTER 1: CLAISEN REARRANGEMENT

1.1 Claisen Rearrangement and Claisen Variants

The Claisen rearrangement was first reported in 1912 by L. Claisen, describing the thermal [3,3]-sigmatropic rearrangement of allyl vinyl ethers to the corresponding γ, δ-unsaturated carbonyl compounds,\(^1\) and ever since then it has held the interest of chemists, due to its efficient utility and stereochemical reliability in constructing complex molecules from simple starting materials. The rearrangement can be defined by thermal isomerization, from 1,5-dienes 1 to 2, with X = nitrogen for the aza-Claisen, X = sulfur for the thio-Claisen (Figure 1).

![Figure 1. Claisen rearrangement.]

The Claisen rearrangement is a suprafacial, concerted process in which the substrate adopts a chairlike transition state. In acyclic systems, the observed stereoselectivity can usually be rationalized by assuming that the unfavorable 1,3-diaxial interactions are minimized in the chairlike transition state with the large groups adopting an equatorial position (Figure 2). When the geometry of the ring or other steric effects preclude or
disfavor a chairlike transition state, the reaction can proceed through a boatlike transition state (Figure 3).^2

![Diagram of favored and disfavored transition states](image)

**Figure 2.** Chairlike transition state for acyclic systems.

![Diagram of reaction and products](image)

**Figure 3.** Boatlike transition state in cyclic systems.
The interest generated by Claisen rearrangement since its initial discovery has prompted the developments of a considerable number of different versions of the [3,3]-sigmatropic rearrangement.

The Carroll reaction, first reported in 1940, is a thermal rearrangement of allylic β-ketoesters 3 followed by decarboxylation to yield γ, δ-unsaturated ketones 6 (Figure 4). This reaction has found limited use in synthetic organic chemistry, since harsh conditions (temperatures of 130-220 °C) are required to perform the [3,3]-sigmatropic rearrangement.

![Figure 4. Carroll rearrangement.](image)

In 1964, another example of the [3,3]-sigmatropic rearrangement was published by Eschenmoser, based on the observations reported by Meerwein in 1961 regarding the exchange between allylic alcohols and amide acetals, illustrated the [3,3] rearrangement of N,O-ketene acetals 9, affording γ, δ-unsaturated amides 10 (Figure 5). However, elevated temperatures which are required for the preparation of more elaborated N,O-ketene acetals, in some cases, result in decomposition of the rearrangement products.
An improvement on the Eschenmoser rearrangement was reported several years later by reaction of lithium allyl alkoxides 12 with acyclic\(^7\) and cyclic salts\(^8\) of \(N,N\)-dialkylalkoxymethylene-iminium 11, and the rearrangements proceeded in excellent yields. (Figure 6). The mild reaction conditions employed for the preparation of \(N,O\)-ketene acetals depicted in Figure 6 increased the synthetic interest of the method.

Figure 5. Eschenmoser-Claisen rearrangement.

Figure 6. Eschenmoser-Claisen rearrangement of lithium alkoxides with iminium salts.
In related work, Johnson\textsuperscript{9} found that treatment of allylic alcohols \textbf{14} with ethyl orthoacetate and trace amounts of weak acids (typically propionic acid) results in the formation of ketene acetal \textbf{16} (Figure 7), which undergoes facile [3,3]-sigmatropic rearrangement leading to γ, δ-unsaturated ester \textbf{17}. The reaction is highly stereoselective and well-suited for synthesis of trans-disubstituted olefinic bonds.

![Figure 7. Johnson-Claisen rearrangement.](image)

In 1972 Ireland reported the rearrangement of allyl trimethylsilyl ketene acetals \textbf{20},\textsuperscript{10} prepared by reaction of allylic ester enolates \textbf{19} with trimethylsilyl chloride, to yield γ, δ-unsaturated carboxylic acids \textbf{21} (Figure 8). The Ireland-Claisen rearrangement takes place under much milder conditions (room temperature and above) than the regular Claisen rearrangement. The ease of the rearrangement is attributed to the highly nucleophilic enolate that generally accelerates sigmatropic processes.
Figure 8. Ireland-Claisen rearrangement.

The high product stereoselectivities can be realized by efficient control of the ketene acetal geometry (Figure 9); deprotonation with LDA/THF leads to the kinetically favored (Z)-ester enolates 23, whereas the (E)-ester enolates 26 are formed in the presence of HMPA/THF. The rearrangement of the (Z)-ester enolates 23 affords anti-products 25, whereas syn-products 28 are obtained by the rearrangement of the (E)-ester enolates 26. The stereochemical control, together with very mild reaction conditions, has led to the extraordinarily broad application of the Ireland-Claisen rearrangement. The first asymmetric enantioselective version of the Ireland-Claisen rearrangement using a chiral boron reagent was reported by E. J. Corey et al.\textsuperscript{11} It is also possible to achieve high levels of enantioselectivity by using chiral auxillaries or chiral catalysts.\textsuperscript{12,13}
Shortly after the discovery of Ireland–Claisen rearrangement, Baldwin and co-workers reported the [3,3]-sigmatropic rearrangement of zinc enolates, known as the Reformatsky-Claisen rearrangement. These zinc enolates, generated by Reformatsky reaction of α-haloesters with zinc dust, lead to the corresponding γ, δ-unsaturated zinc carboxylates in good yields under neutral conditions (Figure 10).

Figure 9. Ketene acetal geometry controls the stereoselectivity of the product.

Figure 10. Reformatsky-Claisen rearrangement.
The [3,3]-sigmatropic rearrangement of N-allyl-enamines, known as the aza-Claisen rearrangement (Figure 11), usually requires more drastic conditions (temperatures of 200-350 °C) than those required for classic Claisen rearrangement of oxygenated substrates. In a number of cases the reaction only evolves under Lewis-acid catalysts.

![Figure 11. Aza-Claisen rearrangement.](image)

### 1.2 Zwitterionic Claisen Rearrangement

In 1978, Bellus and Malherbes first reported the zwitterionic ketene-Claisen rearrangement (Figure 12). In an attempt to perform [2 + 2] cycloaddition, the authors discovered that treatment of an allyl ether 32 with dichloroketene resulted instead in the formation of a 1,3-dipolar allyl vinyl ether 34, which subsequently underwent [3,3]-sigmatropic rearrangement. Although the scope of this reaction was determined to be limited to highly electrophilic ketenes, this study first demonstrated the capacity of zwitterionic 1,5-dienes to readily participate in charge-accelerated sigmatropic rearrangement.
In spite of great values of Claisen rearrangement, this transformation requires temperatures too high for the survival of sensitive functional groups. One solution to this problem has been to change the rate of Claisen rearrangement through appropriate substituents. Thus, with π-donor substituents at position C-2 (Figure 13), the temperature for Claisen rearrangement can range from 200 °C to ambient temperature. The rates follow the usual order of donor strength: sodium or lithium enolates (R = ONa⁺, OLi⁺) > zinc enolate (R = OZnBr⁺) > amide acetal (R = NMe₂) > ortho ester (R = OMe) >> vinyl ether (R = H, Me).

A positively charged heteroatom at position 3 would be the other solution to lower the activation energy of the [3,3]-sigmatropic rearrangement (Figure 14).

Figure 12. Zwitterionic ketene-Claisen rearrangement.

Figure 13. Effect of substituents at C-2 on Claisen rearrangement.
Figure 14. Charged heteroatom at position 3 lowers the activation energy.

The importance of the zwitterionic Claisen rearrangement reported by Bellus and Malherbes lies in that it has the advantage of combining the two solutions together, thus greatly lowering the activation energy for Claisen rearrangement. Subsequently, the utility of tertiary allylic amines in analogous zwitterionic [3,3]-sigmatropic rearrangements has been demonstrated by several research groups.

In 1983, Mariano reported a general hydroisoquinoline synthetic methodology based on the zwitterionic aza-Claisen rearrangement (Figure 15).\textsuperscript{18a} The zwitterionic intermediate 38, generated by reversible addition of tertiary isoquinuclidenes 36 to acetylenic esters 37, undergoes [3,3]-sigmatropic rearrangement to afford corresponding cis-fused hydroisoquinolines 39.

Figure 15. Zwitterionic aza-Claisen rearrangement: Mariano, et al.
Several years later, Edstrom adopted the zwitterionic aza-Claisen rearrangement to synthesize unsaturated lactam precursors to indolizidine and quinolizidine ring systems which are important scaffolds in alkaloids natural products. Edstrom’s methodology involves the reaction of 2-vinylazacycles with the appropriate ketene, which generated zwitterionic intermediates that proceeded through facile [3,3] ring expansions to give macrocyclic lactams (Figure 16).

Figure 16. Zwitterionic aza-Claisen rearrangement: Edstrom.

A breakthrough in zwitterionic aza-Claisen rearrangement was made in 1995 by the Nubbemeyer research group. Before his synthetic methodology, most of the rearrangement was restricted to activated ketenes like dichloroketene. Allyl amines had been rarely used in the ketene-Claisen rearrangement. The reported cases focused on conformationally fixed bicyclic systems or amines bearing an unhindered terminal olefinic unit. Nubbemeyer and co-workers successfully synthesized optically active hexahydroazoninones by a zwitterionic aza-Claisen reaction with complete 1,3-chirality
transfer from chiral allyl amines. For the mechanism, it was assumed that the acyl ammonium salt 45 forms initially after the addition of chiral tertiary allyl amine 44 to acetyl chloride in the presence of a base. This intermediate 45 could be attacked by a base (e.g. the chloride ion) which could deprotonated the α-position of the activated carbonyl group. The resulting zwitterionic intermediate 46 could then undergo [3,3]-sigmatropic rearrangement resulting in the azoninones 47 (Figure 17).

Figure 17. Zwitterionic aza-Claisen rearrangement: Nubbemeyer, et al.
1.3 Zwitterionic 1,3-Diaza-Claisen Rearrangement

In 2004, zwitterionic 1,3-diaza-Claisen rearrangement was first reported by the Madalengoitia group. This methodology was inspired by the group’s initial attempt to synthesize guanidines 49, 52a-c from thiourea 48 and 51a-c, respectively, in a reaction mediated by EDCI (Figure 18). In all instances, an intramolecular cyclization pathway was preferred, affording the cyclic guanidines 50 and 53a-c. In particular, the cyclization of 51b and 51c in which the nitrogens are highly deactivated through protection with methyltrityl (Mtt) and trifluromethylacyl groups, respectively, indicating that the activation of the thiourea affords a highly electrophilic intermediate.

The interesting observation has led to the development of a novel 1,3-diaza-Claisen rearrangement. A mechanistic overview of the reaction of allylic amines with heterocumulenes is showed in Figure 19. Tertiary allylic amines 54 added to heterocumulenes 55 (isocyanates, isothiocyanates, carbodiimides) to afford the corresponding zwitterionic intermediates 56. In turn, the zwitterionic intermediates 56 would then be poised for a 1,3-diaza-Claisen rearrangement, affording ureas, thioureas, or guanidines A, or alternatively, the isoureas, isothioureas, or regioisomeric guanidines B.
The reaction of thiourea with a primary amine or secondary amine in the presence of an activating agent such as EDCI, I₂, N-methyl-2-chloropyridinium iodide, Hg(II) salts is one of the most common strategies used for the construction of the guanidine functionality. The most commonly accepted mechanism for this transformation is the conversion of the thiourea (through reaction with an activating agent) to a carbodiimide.

Figure 18. A remarkable reactivity discovered by the Madalengoitia group.
followed by addition of the amine to the carbodiimide to afford the guanidine. Accordingly, we reasoned that in situ-generated N-alkyl-N'-EWG-carbodiimide would be sufficiently electrophilic to react with tertiary amines azanorbornene 2.1 and isoquinuclidene 2.4 affording a 1,3-diaza-Claisen rearrangement. As can be seen from Table 1, azanorbornene 2.1 was smoothly transformed to highly substituted, bicyclic guanidines in moderate to good yields. 23, 26

**Figure 19.** Mechanistic overview of 1,3-diaza-Claisen rearrangement.
The reactions of isocyanates and isothiocyanates with azanorbornene 2.1 and isoquinuclidine 2.4 are summarized in Table 2.24,26 From the table, we can see that the more electron-deficient isocyanates TsNCO and BzNCO are more reactive than the less electron-deficient BnNCO. The reactivity of isoquinuclidine 2.4 is decreased compared with azanorbornene 2.1, probably due to the lower ring straining in isoquinuclidine 2.4 and the fact that C-N bond breakage would be coupled to release of ring strain. TsNCS is the most reactive, since it can smoothly react with isoquinuclidines 2.4 at room temperature, but afforded exclusively the isothiourea in 81% yield.

**Table 1.** Reaction of thiourea with azanorbornene 2.1 and isoquinuclidine 2.4.

<table>
<thead>
<tr>
<th>allylic amine</th>
<th>thiourea</th>
<th>conditions</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="2.1" /></td>
<td><img src="image" alt="63" /></td>
<td>EDCI, EtNi-Pr&lt;sub&gt;2&lt;/sub&gt; CHCl&lt;sub&gt;3&lt;/sub&gt;, r.t.</td>
<td><img src="image" alt="64" /></td>
</tr>
<tr>
<td><img src="image" alt="2.1" /></td>
<td><img src="image" alt="65" /></td>
<td>Mukayama salt, EtNi-Pr&lt;sub&gt;2&lt;/sub&gt; CHCl&lt;sub&gt;3&lt;/sub&gt;, 60 °C</td>
<td><img src="image" alt="66" /></td>
</tr>
<tr>
<td><img src="image" alt="2.1" /></td>
<td><img src="image" alt="67" /></td>
<td>EDCI, EtNi-Pr&lt;sub&gt;2&lt;/sub&gt; CHCl&lt;sub&gt;3&lt;/sub&gt;, r.t.</td>
<td><img src="image" alt="68" /></td>
</tr>
</tbody>
</table>

16
### Table 2.

Table 2. Reaction of isocyanates and isothiocyanates with azanorbornene 2.1 and isoquinuclidene 2.4.

<table>
<thead>
<tr>
<th>allylic amine</th>
<th>R-NCX</th>
<th>conditions</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 BnNCO</td>
<td>TsNCO</td>
<td>benzene, r.t.</td>
<td>2.14 53%</td>
</tr>
<tr>
<td>2.1 BnNCO</td>
<td>benzene, reflux</td>
<td></td>
<td>2.13 71%</td>
</tr>
<tr>
<td>2.1 BnNCO</td>
<td>benzene, r.t.</td>
<td>EDCI, EtNi-Pr₂, CHCl₃, r.t.</td>
<td>70 62%</td>
</tr>
<tr>
<td>2.1 BnNCO</td>
<td>benzene, r.t.</td>
<td>Mukayama salt, EtNi-Pr₂, CHCl₃, r.t.</td>
<td>71 62%</td>
</tr>
<tr>
<td>2.1 BnNCO</td>
<td>benzene, r.t.</td>
<td>Mukayama salt, EtNi-Pr₂, CHCl₃, 60 °C</td>
<td>72 57%</td>
</tr>
<tr>
<td>2.1 BnNCO</td>
<td>benzene, r.t.</td>
<td>(X-ray) 42%</td>
<td></td>
</tr>
<tr>
<td>allylic amine</td>
<td>R-NCX</td>
<td>conditions</td>
<td>product</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>2.1</td>
<td>TsNCS</td>
<td>benzene, r.t.</td>
<td>![Product 75] 52%</td>
</tr>
<tr>
<td>![Bicyclic Allylic Amine 2.1]</td>
<td>![TsNCS]</td>
<td>![Benzene, r.t.]</td>
<td>![Product 76] 39%</td>
</tr>
<tr>
<td>2.4</td>
<td>TsNCO</td>
<td>benzene, reflux</td>
<td>![Product 2.20] 48%</td>
</tr>
<tr>
<td>![Bicyclic Allylic Amine 2.4]</td>
<td>![TsNCO]</td>
<td>![Benzene, reflux]</td>
<td>![Product 77] 46%</td>
</tr>
<tr>
<td>2.4</td>
<td>BzNCO</td>
<td>neat, 120 °C</td>
<td>Isocyanate decomposition</td>
</tr>
<tr>
<td>2.4</td>
<td>TsNCS</td>
<td>benzene, r.t.</td>
<td>![Product 78] 46%</td>
</tr>
</tbody>
</table>

Further, the group broadens the reaction scope from conformationally fixed bicyclic allylic amines (ananorbornene 2.1 and isoquinuclidene 2.4) to tertiary allylic amines bearing an electron-deficient alkene 79.\(^{25}\)

**Table 3.** 1,3-diaza-Claisen rearrangement of allyl pyrrolidines with isocyanates and isothiocyanates.
<table>
<thead>
<tr>
<th>entry</th>
<th>tertiary allylic amine</th>
<th>$R_2\text{-N}=C=X$</th>
<th>conditions</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO$_2$Me</td>
<td>TsNCO</td>
<td>benzene, reflux</td>
<td><img src="image1.png" alt="Image" /> 93%</td>
</tr>
<tr>
<td>2</td>
<td>CO$_2$Et</td>
<td>TsNCS</td>
<td>CHCl$_3$, r.t.</td>
<td><img src="image2.png" alt="Image" /> 67%</td>
</tr>
<tr>
<td>3</td>
<td>CO$_2$Me</td>
<td>$p$-NO$_2$-PhNCS</td>
<td>benzene, reflux</td>
<td><img src="image3.png" alt="Image" /> 76%</td>
</tr>
<tr>
<td>4</td>
<td>SO$_2$Ph</td>
<td>TsNCO</td>
<td>benzene, reflux</td>
<td><img src="image4.png" alt="Image" /> 83%</td>
</tr>
<tr>
<td>5</td>
<td>CO$_2$Me</td>
<td>PhNCS</td>
<td>benzene, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>SO$_2$Ph</td>
<td>TsNCS</td>
<td>benzene, reflux</td>
<td><img src="image5.png" alt="Image" /> 57%</td>
</tr>
<tr>
<td>7</td>
<td>SO$_2$Ph</td>
<td>BzNCO</td>
<td>benzene, reflux</td>
<td><img src="image6.png" alt="Image" /> 48%</td>
</tr>
<tr>
<td>8</td>
<td>SO$_2$Ph</td>
<td>PhSO$_2$NCO</td>
<td>benzene, reflux</td>
<td><img src="image7.png" alt="Image" /> 97%</td>
</tr>
</tbody>
</table>
From the results obtained above, we can see that electron-deficient isocyanates and isothiocyanates are more reactive than their unactivated counterparts, thus emphasizing the importance of an electron withdrawing substituent on the heterocumulenes in the 1,3-diaza-Claisen rearrangement.

In summary, The 1,3-diaza-Claisen rearrangement developed by the Madalengoitia group represents a novel synthetic methodology in constructing complex molecules from simple starting materials. However, this methodology still has its limitation of working well on conformationally fixed bicycle allylic amines, such as azanorbornene 2.1 and isoquinuclidene 2.4, while simple tertiary allylic amines show lower or no reactivity to this methodology. In order to fully explore the scope of the methodology, we will focus on employing some catalysts which could potentially lower the activation energy, or change the reaction pathway, thus speeding up the reactions or even realizing the transformations of substrates which are thermodynamically challenging for 1,3-diaza-Claisen rearrangement. The work will be described in chapter 2: Pd\(^0\)-catalyzed formal 1,3-diaza-Claisen rearrangement.

Meanwhile, the study of cationic charge-accelerated 1,3-diaza-Claisen rearrangement will be demonstrated in chapter 3, which may overcome the shortcomings of requisite of highly electron-deficient heterocumulenes in zwitterionic 1,3-diaza-Claisen rearrangement reported by our group.\(^{23, 24, 25, 26}\)
CHAPTER 2: Pd⁰-CATALYZED FORMAL 1,3-DIAZA-CLAISEN REARRANGEMENT

2.1 Introduction

In 1987, Trost reported Pd⁰-catalyzed reactions of vinyloxiranes with isocyanates to synthesize Oxazolidin-2-one (Figure 20). When vinyloxiranes 82 were treated with Pd⁰, zwitterionic intermediate 83 were formed via π-allyl palladium intermediates. The intermediate 83 were intercepted by isocyanates to form zwitterionic intermediate 84, which proceeded by intramolecular N-alkylation to afford oxazolidin-2-one 85. Pd⁰ catalysts greatly facilitate the reactions by lowering the reaction temperature significantly (room temperature in THF), compared with ca. 150 °C or higher under thermal conditions.

![Scheme](image)

Figure 20. Pd⁰-catalyzed oxazolidin-2-one synthesis.

Later, Howard Alper found that in the presence of chiral ligands such as BINAP and p-TolBINAP, highly enantioselective vinyloxazolidine derivatives can be obtained through cycloaddition of vinyloxirane with heterocumulenes under Pd⁰ catalysis conditions.
Oxidative addition of a phosphine-palladium complex to racemic vinyl oxirane 86, followed by heterocumulene interception affords the diastereomeric zwitterionic \( \pi \)-allyl palladium intermediates 88 and 89. Intramolecular attack of the nitrogen nucleophile at the C-3 of 88 and 89 can give the corresponding enantiomers 90 and 91. The interconversion between \( \pi \)-allyl palladium complexes 88 and 89 via a \( \eta^3 \)-\( \eta^1 \)-\( \eta^3 \) mechanism is faster than the attack of the nitrogen nucleophile. Thus, one of the two intermediate complexes (88 and 89) reacts faster than the other and consequently gives the major enantiomer. The usage of a chiral ligand can make one of the two intermediate complexes (88 and 89) react at a greater rate affording the corresponding enantiomer as the major stereoisomer.

![Figure 21](image-url)  
**Figure 21.** Pd\(^{0}\)-catalyzed enantioselective reactions of vinyloxirane with heterocumulenes.

Subsequently, the utility of vinyl exocyclic amines in this cycloaddition methodology was also demonstrated by Alper group.\(^{30}\) Catalyzed by [Pd(OAc)\(_2\)]/PPh\(_3\), 2-vinyl aziridines 92 react with isocyanates, isothiocyanates, and carbodiimides to afford
imidazolidinones, imidazolidinethiones and imidazolidineimines \[94\], respectively (Figure 22). The regioselectivity of these reactions is excellent, with cycloaddition occurring between the \(N\)-1 and \(C\)-2 (vinyl-substituted) bond of the aziridine, giving a single regioisomer. However, at reduced catalyst loading, an inseparable mixture of structural isomers \[96\] and \[97\] was obtained as products. It was assumed that during the cycloaddition reactions, both isomers \[96\] and \[97\] were formed, but the presence of sufficient catalyst would facilitate the isomerization from \[97\] to \[96\]. The internal cyclization \[99\] would be in equilibrium with ring opening of \[97\] and would eventually yield only the more thermodynamically favorable product \[96\] (Figure 23).

**Figure 22.** Reactions of vinyl aziridines with heterocumulenes.

**Figure 23.** \(\text{Pd}^0\) facilitates the isomerization form \[97\] to \[96\].
In 2002, Alper applied his methodology to 2-vinylpyrrolidines, which are not strained ring compounds in contrast to aziridines and azetidines.\textsuperscript{31} As anticipated, with higher catalyst loading, elevated reaction temperature, and longer reaction time, 2-vinylpyrrolidines \textbf{100} react with heterocumulenes (aryl isocyanates or carbodiimides) \textbf{101} to afford desired seven-membered ring \textbf{102} and a ring-opened by products \textbf{103} under Pd\textsuperscript{0} catalysis conditions (Figure 24).\textsuperscript{32} It is noteworthy that heterocumulenes with an electron-withdrawing group on the phenyl ring afford good to excellent conversion; and more basic bidentate phosphine ligand Dpppentane gives the cyclized product \textbf{102} in high selectivity and in good yield.\textit{Figure 24.} Pd\textsuperscript{0}-catalyzed reaction of 2-vinylpyrrolidines with heterocumulenes.

Especially, during the reaction of 2-vinylpyrrolidines with carbodiimides, the choice of ligands plays a very important role in achieving higher regioselectivity. When PPh\textsubscript{3} was used as the ligand, the reaction conversion was only 10% at 130 °C. The alkyl phosphine ligands, such as dppf, dppp and dppb gave high yields of ring-opened products \textbf{103}. The high regioselectivity of favoring the seven-membered rings \textbf{102} was finally
achieved by the choice of more basic bidentate phosphine ligand: Dpppentane (Figure 25), indicating that phosphine ligand with higher basicity favors the formation of ring-cyclized products.

![Dpppentane](Figure 25)

**Figure 25.** Dpppentane.

In summary, Trost and Alper’s pioneering work have shown that exocyclic allylic amines 104 (Figure 26), such as vinyl aziridines and vinyl pyrrolidines undergo formal 1,3-rearrangements with isocyanates, isothiocyanates and carbodiimides to give the ring expanded product 107. The 1,3-rearrangement occurs because after C-N bond breakage and formation of the π-allyl palladium intermediate 106, the preferred cyclization favors the formation of the smaller-sized ring. However, in our work, we envision that under Pd⁰ catalysis conditions, the zwitterionic intermediate 109 generated by nucleophilic addition of endocyclic tertiary allylic amines 108 to heterocumulenes, will fragment to zwitterionic π-allyl palladium intermediates 110 which undergo [3,3]-formal rearrangement to form the smaller ring 111.
2.2 Results and Discussion

2.2.1 Syntheses of Tertiary Allylic Amines

An array of azanorbornenes and azabicycle [2.2.2] octenes was synthesized via [4 + 2] Diels-Alder reaction (Figure 27). The bridged-bicyclic amines 2.2, 2.3, 2.5, 2.6 were synthesized in order to determine what effects steric crowding adjacent to the nucleophilic nitrogen of the tertiary allylic amine would have on reactivity.
Figure 27. Syntheses of azanorbornenes and azabicyclo[2.2.2]octenes
In order to investigate the scope of the rearrangement, several cyclic nonbridged tertiary allylic amines were also synthesized. Benzyl tetrahydropyridine 2.7 was obtained through a solvent free benzylation of pyridine and subsequent treatment of the benzylpyridinium chloride with sodium borohydride (Figure 28).\textsuperscript{35}

\[
\begin{array}{c}
\text{N} \\
\text{Bn} \\
\text{Cl}, 140 \degree \text{C} \\
\text{EtOH, NaBH}_4, \text{rt.} \\
78\% \\
\end{array}
\]

\textbf{Figure 28.} Synthesis of tetrahydropyridine 2.7.

Benzyl azepine 2.8 was prepared in four steps (Figure 29).\textsuperscript{36} The secondary amine 2.9 was prepared in 71\% yield by alkylation of allylamine with 5-bromopent-1-ene using sodium iodine as a catalyst. The coupling between 2.9 and acid chloride afford amide 2.10 in almost quantitative yield. Ring closing metathesis (RCM) of amide 2.10 and subsequent reduction with LAH gave azepine 2.8 in good yield.
Figure 29. 1-Benzyl-2,3,4,7-tetrahydro-1H-azepine 2.8.

Fused-bicyclic tertiary allylic amines were also synthesized to further explore the reaction scope. As shown in Figure 30, after aminolysis of glutaric anhydride with allylamine and formation of imide 2.27, a partial reduction of the imide 2.27 to the corresponding ethoxyamide 2.28 was effected using sodium borohydride and acid following the procedure of Speckamp. The pH of the mixture was monitored by bromocresol green indicator, avoiding over acidification which could lead to ring-opening of the imide 2.27. BF₃ OEt₂ mediated formation and allylation of the iminium ion resulted in suitable bis-alkene 2.29, which was subjected to ring closing metathesis to afford bicyclic amide 2.30. After reduction of the amide, the desired product quinolizine 2.31 was obtained.
Figure 30. Synthesis of 4,6,7,8,9,9a-hexahydro-1H-quinolizine 2.31.

For the synthesis of hexahydroindolizine 2.37 (Figure 31), succinimide was first N-alkylated by Mitsunobu reaction, and the following steps were similar to those of quinolizine 2.31 above. However, during the last reduction step, for some unknown reasons, we cannot observe any bicyclic tertiary amine 2.37. So the synthetic strategy was adjusted, placing the reduction step before ring closing of bis-alkeneyl γ-membered lactam 2.34. Upon obtaining the reduction product 2.36, it was subjected to ring-closing metathesis to give the target molecule 2.37.
2.2.2 Reaction of Azanorbornene 2.1 and Isoquinuclidene 2.4 with Isocyanates

The Pd⁰-catalyzed 1,3-diaza-Claisen rearrangement and thermal 1,3-diaza-Claisen rearrangement of azanorbornene 2.1 with isocyanates are summarized and compared in Figure 33. Under both conditions, azanorbornene 2.1 reacts with TsNCO at room temperature, while the thermal reactions of azanorbornene 2.1 with PhNCO and BnNCO require in benzene at reflux. Thus, the more electron-deficient isocyanates TsNCO are more reactive than the less electron-deficient isocyanates PhNCO and BnNCO. Under
thermal conditions, the reaction of azanorbornene 2.1 with TsNCO afforded urea 2.14 and isourea 74 in 53% and 41% yields, respectively. However, under Pd\(^0\) catalysis conditions, only urea 2.14 was observed. It is likely that both urea 2.14 and isourea 74 were formed in the reaction, however, upon exposure to palladium, isourea 74 was isomerized to more thermodynamically favorable urea 2.14. The isomerization occurred so efficiently that it masked the formation of 74. Indeed, when azanorbornene 2.1 and TsNCO were allowed to react at room for 30 minutes, and a mixture of urea 2.14 and isourea 74 with 1:1 ratio was obtained (analyzing from crude \(^1\)H NMR). However, isourea 74 disappeared immediately after palladium catalyst was added into the reaction system, and urea 2.14 was the only observed product (Figure 32).

\[ \text{Figure 32. Pd}^0 \text{ facilitates the isomerization from isourea to urea.} \]
Under thermal conditions:

\[
\text{2.1} \quad \text{Benzene, reflux} \quad \text{75%}
\]

\[
\text{2.1} \quad \text{PhNCO} \quad \text{Benzene, reflux} \quad \text{71%}
\]

\[
\text{2.1} \quad \text{TsNCO} \quad \text{Benzene, rt} \quad \frac{53\%}{74\%}
\]

Pd\textsuperscript{0} Catalysis:

\[
\text{2.1} \quad \text{10 mol\% Pd(OAc)}_2 \quad \text{20 mol\% Dppp} \quad \text{THF, rt, 15 mins} \quad \text{86%}
\]

\[
\text{2.1} \quad \text{10 mol\% Pd(OAc)}_2 \quad \text{20 mol\% Dppp} \quad \text{THF, rt, 45 h} \quad \text{85%}
\]

\[
\text{2.1} \quad \text{10 mol\% Pd(OAc)}_2 \quad \text{20 mol\% Dppp} \quad \text{THF, rt, 5 mins} \quad \text{80%}
\]
**Figure 33.** Reactions of azanorbornene 2.1 with isocyanates under Pd⁰ catalysis and thermal conditions.

The possible explanation for the isomerization from isourea to urea is shown in Figure 34. When isourea 2.38 is exposed to Pd⁰, a ring opening zwitterionic π-allyl palladium intermediate 2.39 is formed, 2.39 will equilibrate with zwitterionic intermediate 2.40, which will close the ring to give the thermodynamically stable urea 2.41 and regenerate Pd⁰.

**Figure 34.** Possible mechanism of isomerization from isourea to urea.

Under thermal conditions, isoquinuclidene 2.4 failed to afford rearrangement products with less reactive isocyanates BnNCO and PhNCO (not shown), and even electron-deficient BzNCO under forcing conditions (neat, 120 °C). The lower reactivity of isoquinuclidene 2.4, compared with azanorbornene 2.1, may be explained by the lower ring
straining in isoquinuclidene 2.4. However, after employing Pd$^0$ catalyst, the reaction of isoquinuclidene 2.4 with BzNCO afforded the rearrangement product 2.21 in 70% yield, which demonstrates the requirement of palladium catalyst. It is worth noting that due to the instability of BzNCO, a syringe pump was utilized in the reaction to add BzNCO solution in THF over 12 hours; adding all BzNCO in portion resulted in low yields (not shown). With Pd$^0$ catalyst, the less reactive isocyanate PhNCO also reacted with isoquinuclidene 2.4 in THF for 72 hours, affording the rearrangement 2.22 in 38% yield; the reaction was also attempted in higher boiling point solvent toluene, and 39% yield was obtained after heating at reflux for 7 hours. As for the highly reactive TsNCO, the role of Pd$^0$ was not significantly demonstrated, since the reaction even went pretty smoothly in the absence of palladium catalyst (Figure 35).

We also investigated the effect of reduced catalyst loading on the reaction of isoquinuclidene 2.4 with BzNCO, and 14% yield was obtained when 5 mol% palladium catalyst was used (Figure 36), which illustrates the necessity of sufficient catalyst loading for the rearrangement to occur.

**Under thermal conditions:**

\[
\begin{align*}
\text{TsNCO} & \quad \text{THF, reflux 2 h} \quad \text{2.20 67\%} \\
\text{BzNCO} & \quad \text{neat, 120 °C} \quad \text{Isocyanate decomposition}
\end{align*}
\]
**Figure 35.** Reactions of isoquinuclidene 2.4 with isocyanates under Pd\(^0\) catalysis and thermal conditions.

**Figure 36.** Reaction of isoquinuclidene 2.4 with BzNCO at reduced catalyst loading.
2.2.3 Reaction of Azanorbornenes 2.2, 2.3 and Isoquinuclidenes 2.5, 2.6 with Isocyanates

From Figure 37, we can see that with highly reactive TsNCO, both diastereomeric aza-norbornenes 2.2 (exo-ethoxycarbonyl group) and 2.3 (endo-ethoxycarbonyl group) underwent rearrangement smoothly at room temperature to afford both ureas 2.15, 2.17 and isoureas 2.42, 2.43 under thermal conditions. Endo-azanorbornene 2.3 reacted with BzNCO to give urea 2.18 and isourea 2.19 in 32% yield and 20% yield, respectively; while the reaction between exo-azanorbornene 2.2 and BzNCO proved to be very sluggish, affording urea 2.16 in 12% yield after heating at reflux in THF for 21 hours. Previous research from our group\textsuperscript{26} has shown that for BnNCO to react with endo-aza-norbornene 2.3, heating at 120 °C under neat conditions was required to afford the expected urea 112 in 38% yield and the hydantoin 2.45 in 39% yield. The exo-aza-norbornene 2.2 proved even less reactive toward rearrangement with BnNCO affording none of the expected urea, but affording as the sole isolable product the hydantoin 2.45 in 67% yield under forcing conditions (120 °C, neat). Thus, both diastereomeric azanorbornenes 2.2 and 2.3 exhibit diminished reactivity toward rearrangement with BnNCO as compared with azanorbornene 2.1. For the formation of hydantoin 2.45 (Figure 38), it is assumed that azanorbornenes 2.2 and 2.3 are added to BnNCO to form zwitterionic intermediates 2.46 and 2.47, which undergo retro-Diels-Alder reaction to afford cyclopentadiene and isomeric 1,4-dipoles 2.48a and 2.48b. Isomerization from 2.48b to 2.48a is required for the next nucleophilic attack of nitrogen anion on the ester carbonyl to form intermediate 2.49. Finally, [1,2]-migration of the ethoxy group will give the hydantoin 2.45. If the retro-Diels-Alder theory is right, we believe that 1,4-dipoles 2.48a and 2.48b should be eliminated to afford isomeric
imines and BnNCO, and the process should be reversible such that addition of imine to 
BnNCO would result in 1,4-dipoles 2.48a and 2.48b (Figure 38). The reaction we designed 
in Figure 39 proved the theory, when glyoxylate imine 2.50 and BnNCO were subjected to 
the rearrangement reaction condition (120 °C, neat), hydantoin 2.45 was formed in 66% 
yield. In Palladium catalyzed reaction systems, both exo-azanorbornene 2.2 and endo-
azanorbornene 2.3 react excellently with TsNCO to give ureas 2.15 and 2.17, and no 
isoureas were observed. Exo-azanorbornene 2.2 exhibited good reactivity toward BzNCO 
to afford urea 2.16 in 77% yield as compared with the sluggish reaction under thermal 
conditions. In the case of the less reactive BnNCO, a complex mixture was obtained for 
both 2.2 and 2.3, no rearrangement products were isolated.
Under thermal conditions:

\[
\text{2.2} \quad \text{CO}_2\text{Et} + \text{TsNCO} \quad \xrightarrow{\text{CHCl}_3, \text{rt}} \quad \begin{array}{c}
\text{2.15} \quad 47% \\
\text{2.42} \quad 44%
\end{array}
\]

\[
\text{2.2} \quad \text{CO}_2\text{Et} + \text{BzNCO} \quad \xrightarrow{\text{THF, reflux}} \quad \begin{array}{c}
\text{2.16} \quad 12% \\
\text{2.17} \quad 24% \\
\text{2.18} \quad 32% \\
\text{2.19} \quad 20%
\end{array}
\]

\[
\text{2.3} \quad \text{NCO}_2\text{Et} + \text{TsNCO} \quad \xrightarrow{\text{CHCl}_3, \text{rt}} \quad \begin{array}{c}
\text{2.17} \quad 24% \\
\text{2.43} \quad 64%
\end{array}
\]

\[
\text{2.3} \quad \text{NCO}_2\text{Et} + \text{BzNCO} \quad \xrightarrow{\text{THF, reflux}} \quad \begin{array}{c}
\text{2.18} \quad 32% \\
\text{2.19} \quad 20%
\end{array}
\]

\[
\text{2.2} \quad \text{CO}_2\text{Et} + \text{BnNCO} \quad \xrightarrow{\text{neat, 120 °C}} \quad \begin{array}{c}
\text{2.45} \quad 67%
\end{array}
\]

\[
\text{2.3} \quad \text{NCO}_2\text{Et} + \text{BnNCO} \quad \xrightarrow{\text{neat, 120 °C}} \quad \begin{array}{c}
\text{112} \quad 38% \\
\text{2.45} \quad 39%
\end{array}
\]
Figure 37. Reactions of azanorbornene 2.2 and 2.3 with isocyanates under Pd\(^0\) catalysis and thermal conditions.
Figure 38. Mechanism of formation of hydantoin 2.45.

Figure 39. Reaction designed to support the proposed mechanism of elimination of 2.48a/b.
In the case of isomeric isoquinuclidenes 2.5 and 2.6, the *endo*-isoquinuclidene 2.6 underwent rearrangement with TsNCO under forcing condition (120 °C, neat), while reaction between *exo*-isoquinuclidene 2.5 and TsNCO resulted in decomposition of isocyanates. For Pd⁰-catalyzed reactions, initially all the reactions were performed in THF. After no satisfactory results were obtained, toluene was used instead as a higher boiling point solvent. *Exo*-isoquinuclidene 2.5 reacted with TsNCO to afford desired urea 2.23 in 87% yield after heating at reflux in toluene for 23 hours. *Endo*-isoquinuclidene 2.6 underwent rearrangement with TsNCO smoothly to give urea 2.24 in 95% yield after refluxing in toluene for 9 hours (Figure 40).

**Pd⁰ catalysis:**

![Diagram of reactions](image)

42
2.2.4 Reaction of Cyclic Nonbridged Tertiary Allylic Amines with Isocyanates

We have additionally investigated the rearrangement of cyclic nonbridged tertiary allylic amines \textit{N}-benzyl pyrroline 2.51, \textit{N}-benzyl tetrahydropyridine 2.7 and \textit{N}-benzyltetrahydroazepine 2.8 with highly reactive TsNCO. Under all thermal conditions investigated, none of the tertiary allylic amines underwent rearrangement with TsNCO (Figure 41). When these reactions were performed under Pd$^0$ catalysis, \textit{N}-benzyl pyrroline 2.51 was oxidized to \textit{N}-benzylpyrrole 2.52, and no rearrangement was observed. The reaction of \textit{N}-benzyltetrahydropyridine 2.7 with TsNCO failed to give rearrangement product with 10 mol\% Pd$^0$ catalyst, however, after increasing the catalyst loading to 20 mol\% , the rearrangement product 2.26 was obtained in 19\% yield. \textit{N}-benzyltetrahydroazepine 2.8 underwent rearrangement smoothly with TsNCO to afford urea 2.25 in good yield. The reaction of \textit{N}-benzyltetrahydroazepine 2.8 with less reactive PhNCO was also performed, and as anticipated, only trace amount of rearrangement product 2.53 was observed (Figure 41).
**Under thermal conditions:**

\[
\begin{align*}
\text{N} & + \text{TsNCO} \quad \text{many conditions} \quad \text{No rearrangement} \\
\text{2.51} & \\
\text{N} & + \text{TsNCO} \quad \text{many conditions} \quad \text{No rearrangement} \\
\text{2.7} & \\
\text{N} & + \text{TsNCO} \quad \text{Toluene, reflux 3 h} \quad \text{No rearrangement} \\
\text{2.8} & 
\end{align*}
\]

**Under Pd\textsuperscript{0} catalysis:**

\[
\begin{align*}
\text{N} & + \text{TsNCO} \quad \text{10 mol% Pd(OAc)}_2 \\
& \quad \text{20 mol% Dpppentane} \\
& \quad \text{Toluene, reflux 40 mins} \\
& \quad \text{Not Observed} \\
\text{2.51} & \\
& \quad \text{2.52} \\
\text{N} & + \text{TsNCO} \quad \text{10 mol% Pd(OAc)}_2 \\
& \quad \text{20 mol% Dpppentane} \\
& \quad \text{1,4-Dioxane, reflux 22 h} \\
\text{2.7} & \\
& \quad \text{No rearrangement} \\
\text{N} & + \text{TsNCO} \quad \text{20 mol% Pd(OAc)}_2 \\
& \quad \text{40 mol% Dpppentane} \\
& \quad \text{1,4-Dioxane, reflux 28 h} \\
& \quad \text{2.26} \\
\text{2.7} & \\
& \quad \text{19%} \\
\text{N} & + \text{PhNCO} \quad \text{10 mol% Pd(OAc)}_2 \\
& \quad \text{20 mol% DPPpentane} \\
& \quad \text{Toluene, reflux 23 h} \\
\text{2.8} & \\
& \quad \text{2.53} \quad \text{trace amount}
\end{align*}
\]
Figure 41. Reactions of cyclic nonbridged tertiary allylic amines with isocyanates under Pd\(^0\) catalysis and thermal conditions.

Based on the results obtained, we propose that the unreactivity and lower reactivity of amines 2.51 and 2.7 may be explained by stereoelectronic effect (Figure 42). The concerted reaction would require an approximate coplanar alignment of the breaking bond with the \(\pi\)-bond of the alkene in the transition state. To accommodate this geometry the transition state arising from the pyrroline 2.51 would require severely puckering the pyrroline nitrogen out of the plane of the other four carbons as in transition state 2.54 (Figure 42). In addition, for proper orbital alignment, the transition state arising from the tetrahydropyridine 2.7 would require a boat geometry such as 2.55. We thus believe that these are higher energy transition states that make the rearrangement less favorable than those arising from the aza-norbornene 2.1 and isoquinuclidene 2.4, which would proceed through a better orbital alignment. In the case of \(N\)-benzyltetrahydroazepine 2.8, the seven-membered ring is more flexible, thus the orbital alignment is better accommodated in transitions state 2.56 (Figure 42).
2.2.5 Reaction of Fused Bicyclic Tertiary Allylic Amines with Isocyanates

Encouraged by the results from benzyl tetrahydroazepine 2.8, we proceed to probe even more challenging fused bicyclic tertiary allylic amines 2.31 and 2.37. Unfortunately, under Pd\(^0\) catalysis conditions, hexahydroquinolizine 2.31 did not undergo the rearrangement with TsNCO; as for hexahydroindolizine 2.37, only trace amount of urea was observed in the crude \(^1\)H NMR (Figure 43).
2.3 Conclusions

We have explored the scope and limitations of Pd\(^0\)-catalyzed 1,3-diaza-Claisen rearrangement. Adding an electron-deficient group to isocyanates is an effective strategy to accomplish 1,3-diaza-Claisen rearrangement with less reactive tertiary allylic amines. For the reactions of azanorbornenes 2.1, 2.2, 2.3 and isoquinuclidenes 2.4, 2.5, 2.6 with isocyanates, palladium catalyst proves to be very effective in lowering the activation energy, by increasing the reaction rate, decreasing reaction temperature, as well as realizing the rearrangement of challenging substrates which were unreactive under thermal conditions. In case of some stereoelectronically disfavored substrates such as N-benzyl pyrrolidine 2.51, N-benzyl tetrahydropyridine 2.7, hexahydroquinolizine 2.31, palladium catalyst apparently has its limitations, thus requiring further improvements on this methodology.
2.4 Experimental Section

General Experimental Details

All reactions were performed under a nitrogen atmosphere in oven–dried glassware. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. THF and 1,4-dioxane were distilled under nitrogen from potassium immediately before use. Dichloromethane and toluene were distilled under nitrogen from CaH₂ prior to use. THF is generally employed as the solvent for reactions. However, when reactions were sluggish in THF, solvents with higher boiling points such as toluene and 1,4-dioxane, will be applied, and better solubility of isocyanates and higher yields of products were observed in 1,4-dioxane than in toluene. Where required, solvents were degassed by bubbling of nitrogen through a needle for at least 15 minutes. Analytical thin layer chromatography (TLC) was performed using EMD TLC silica gel 60 F₂₅₄ pre-coated plate. Visualization was achieved by UV light (254 nm), I₂, or Phosphomolybdic acid. The products were purified by flash chromatography on silica gel (60 Å). Mixtures of ethyl acetate, hexane and triethylamine were generally used as eluents. ¹H NMR spectra were recorded on a Bruker ARX 500 (500 MHz) or a Varian Unity Inova 500 (500 MHz) spectrometer. ¹³C NMR spectra were recorded on a Bruker ARX 500 (125 MHz) or a Varian Unity Inova 500 (125 MHz) spectrometer. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH and coupling constants are reported as a J value in Hz. ¹³C NMR spectra are reported in terms
of chemical shift (δ, ppm) relative to the triplet at 77.00 ppm for CDCl₃. IR spectra were obtained neat at room temperature using an ATF probe.

Experimental Procedures

Syntheses of Rearrangement Precursors

6-Benzyl-6-aza-bicyclo[2.2.1]hept-2-ene (2.1). To a solution of 37% w/w aqueous formaldehyde (8.12 g, 7.45 ml, 0.1 mol, 1.3 eq.) in water (35 ml) was added benzylamine hydrochloride (14.36 g, 0.1 mol, 1.3 eq.) and the resulting solution was stirred under N₂ for 10 minutes. Freshly distilled cyclopentadiene (5.08 g, 6.5 ml, 0.077 mol) was added and the resulting mixture was allowed to stir for 4 hours. The resulting mixture was diluted with water (35 ml) and washed with Et₂O (35 ml × 2). The aqueous layer was adjusted to basic with KOH pellets (5.6 g), and extracted with EtOAc (50 ml × 3). The organic layers (in EtOAc) were combined, dried over Na₂SO₄, filtered and concentrated. The crude oil was chromatographically purified over silica gel (30% ethyl acetate in hexane with 0.5% NEt₃) to afford 2.1 as yellow oil (14.2 g, 100% yield). ¹H NMR data matched the reported data.³³
6-benzyl-6-aza-bicyclo[2.2.2]oct-2-ene (2.4). To a solution of 37% w/w aqueous formaldehyde (8.12 g, 7.45 ml, 0.1 mol, 1.3 eq.) in water (35 ml) was added benzylamine hydrochloride (14.36 g, 0.1 mol, 1.3 eq.), and cyclohexadiene (6.42 g, 7.6 ml, 0.077 mol). The mixture was stirred at 55 °C for 48 hours. The resulting mixture was diluted with water (35 ml) and washed with Et₂O (35 ml × 2). The aqueous layer was adjusted to basic with KOH pellets (5.6 g), and extracted with EtOAc (50 ml × 3). The organic layers (in EtOAc) were combined, dried over Na₂SO₄, filtered and concentrated. The crude oil was chromatographically purified over silica gel (30% ethyl acetate in hexane with 0.5% NEt₃) to afford 2.4 as yellow oil (6.5 g, 41% yield). ¹H NMR data matched the reported data.³³a

Ethyl 2-benzyl-2-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylate (exo 2.5 and endo 2.6).

Benzylamine hydrochloride (5 g, 34.8 mmol) was dissolved in DMF (60 ml), to which ethyl glyoxylate (ca. 50% in toluene, 10 g, 9.9 ml, 48.7 mmol, 1.4 eq.) and cyclohexadiene (5.75 g, 7 ml, 69.6 mmol, 2 eq.) were added. The reaction mixture was stirred at room
temperature for 2 weeks. Solvent was removed in vacuo, 5% NaHCO₃ (150 ml) was added to the residue, and the mixture was extracted with chloroform (50 ml × 3). The combined organic layers were washed with saturated brine, dried over Na₂SO₄, filtered and concentrated. The crude product was chromatographically purified over silica gel (10% ethyl acetate in hexane with 0.2% NEt₃) to afford exo isoquinuclidene 2.5 as a yellow oil (420 mg, 4.5% yield), and endo isoquinuclidene 2.6 (300 mg, 3.2% yield). ¹H NMR data matched the reported data.¹³

1-Benzyl-1,2,3,6-tetrahydropyridine (2.7). A mixture of pyridine (21 g, 266 mmol, 1 eq.) and benzyl chloride (40.32 g, 318.5 mmol, 1.2 eq.) was stirred at 140 °C for 1 hour. After cooling to ambient temperature, the yellow resin was dissolved in absolute ethanol (700 ml). Since the resin was barely soluble in ethanol, this dissolution was best performed by repeated addition of portions of ethanol (30 ml) to the resin, equilibrating the mixture with ultrasonication and decanting the liquid phase. NaBH₄ (22.54 g, 584.08 mmol, 2.2 eq.) was added portion-wise to the stirred solution between 0 °C and negative 5 °C. After 15 minutes, the solution was warmed to room temperature and stirred further for 18 hours. Addition of water (350 ml) gave a suspension of colorless solid in a yellow liquid, which was filtered. The filtrate was extracted with dichloromethane (250 ml×4). The combined organic layers were washed with saturated brine (500 ml), dried over Na₂SO₄, filtered, and concentrated
under reduced pressure to afford yellow oil, which was subjected to vacuum distillation (bp 100 °C/6mm Hg) to give 2.7 as colorless oil (36 g, 78% yield). $^1$H NMR data matched the reported data.$^{35}$

*N-allylpent-4-en-1-amine (2.9).* 5-bromopent-1-ene (2.5 g, 16 mmol, 1 eq.) was slowly added to a vigorously stirred suspension of sodium iodide (480 mg, 3.2 mmol, 0.2 eq.) in allylamine (4.64 g, 80 mmol, 5 eq.). The mixture was stirred between 55 °C and 60 °C for 22 hours. After cooling to ambient temperature, K$_2$CO$_3$ (12.5 g) was added, and water was added to dissolve K$_2$CO$_3$. The mixture was extracted with dichloromethane (25 ml × 4), and the combined organic layers were collected, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give crude product, which was subjected to vacuum distillation (b.p. 55 °C/20mm Hg) to afford 2.9 as colorless oil (1.5 g, 71% yield). $^1$H NMR data matched the reported data.$^{36}$

*N-allyl-N-(pent-4-en-1-yl)benzamide (2.10).* N-allylpent-4-en-1-amine (2.9) (190 mg, 1.52 mmol, 1.1 eq.), triethylamine (212 mg, 2.07 mmol, 1.5 eq.) and DMAP (17 mg, 0.14
mmol, 0.1 eq.) were dissolved in 6 ml of diethyl ether/dichloromethane (1:1) and brought to 0 °C under N₂ atmosphere. Benzoyl chloride (200 mg, 1.38 mmol, 1 eq.) dissolved in dichloromethane (0.5 ml) was added dropwise at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred overnight. Solvent was removed under reduced pressure. 10 ml 5% NaHCO₃ solution and 10 ml dichloromethane were added. The aqueous layer was extracted with dichloromethane (10 ml×3), and the combined organic layers were washed with saturated brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude product, which was chromatographically purified over silica gel (20% ethyl acetate in hexane with 0.1% NEt₃) to afford 2.10 as colorless oil (320 mg, 98% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.39 (s, 5H), 6.07-5.44 (m, 2H), 5.37-4.81 (m, 4H), 3.67 (q, J = 159.0 Hz, 4H), 2.24-1.48 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 26.15, 27.35, 30.33, 30.93, 44.32, 46.95, 47.82, 51.48, 114.80, 115.03, 117.15, 126.22, 128.11, 129.11, 133.29, 136.51, 136.82, 137.64, 171.47 ppm; FT-IR (neat) 1628, 1416, 698 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₀NO 230.1539, found 230.1541 [M+H]^+.

((Z)-3,4-dihydro-2H-azepin-1(7H)-yl)(phenyl)methanone (2.11). Under N₂ atmosphere, N-allyl-N-(pent-4-en-1-yl)benzamide (2.10) (160 mg, 0.70 mmol, 1 eq.) was dissolved in dry degassed dichloromethane (20 ml), then Grubbs’ 2nd catalyst (6 mg, 0.007 mmol, 1
mol%) dissolved in dry degassed dichloromethane (5 ml) was added. The reaction mixture was heated at reflux for 2 hours. After removal of the solvent, the crude product was chromatographically purified over silica gel (30% ethyl acetate in hexane with 0.2% NEt₃) to afford **2.11** as colorless oil (100 mg, 71% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.55-7.32 (m, 5H), 6.01-5.72 (m, 1.5H), 5.62-5.45 (m, 0.5H), 4.19 (s, 1H), 3.95-3.71 (m, 2H), 3.54 (t, J = 6.0 Hz, 1H), 2.40-1.65 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 25.64, 26.24, 26.56, 26.90, 43.43, 46.31, 48.05, 51.00, 126.30, 126.49, 127.04, 127.75, 127.83, 127.97, 128.96, 129.05, 131.42, 132.64, 136.12, 136.30, 170.58, 171.04 ppm; FT-IR (neat) 1625, 1419, 701 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₆NO 202.1226, found 202.1227 [M+H]⁺.

**Benzyl-2,3,4,7-tetrahydro-1H-azepine (2.8).** A solution of phenyl(2,3,4,7-tetrahydro-1H-azepin-1-yl)methanone **2.11** (90 mg, 0.45 mmol, 1 eq.) in dry THF (2 ml) was added dropwise to a suspension of lithium aluminum hydride (36 mg, 0.90 mmol, 2 eq.) in dry THF (1 ml) at 0 °C under N₂ atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 hours. At 0 °C, 0.04 ml H₂O, 0.04 ml 15% NaOH solution, and 0.12 ml H₂O were added successively, and the reaction mixture was stirred at room temperature for 30 minutes, and then filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up by 5 ml dichloromethane and 5 ml H₂O, and
then the mixture was extracted with dichloromethane (5 ml×3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give crude product, which was chromatographically purified over silica gel (10% ethyl acetate in hexane with 0.2% NEt₃) to afford 2.8 as colorless oil (80 mg, 95% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.19 (m, 5H), 5.97-5.89 (m, 1H), 5.70-5.61 (m, 1H), 3.67 (s, 2H), 3.19 (d, J = 5.0 Hz, 2H), 2.88 (t, J = 5.5 Hz, 2H), 2.29-2.23 (m, 2H), 1.75-1.64 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 25.83, 28.18, 53.47, 58.05, 60.51, 126.81, 128.15, 128.91, 129.28, 133.41, 139.41 ppm; FT-IR (neat) 1494, 1348, 1116, 741, 696 cm⁻¹; HRMS (ESI) calcd for C₁₃H₁₈N 188.1434, found 188.1435 [M+H]+.

1- Allylpiperidine-2,6-dione (2.27). Step One: Allylamine (1.42 ml, 18.56 mmol, 1.06 eq.) was added to a stirred solution of glutaric anhydride (17.5 mmol, 1eq.) in THF (30 ml) at room temperature. The reaction mixture was stirred for one hour at room temperature. After the solvent was removed in vacuo, the resulting mixture was treated with aqueous HCl solution (1M, 10 ml) and extracted with EtOAc (20 ml×4), dried over Na₂SO₄ and concentrated to afford 2.44 as red oil (2.45 g), which was put into subsequent step without further purification.
Step two: Under N₂ protection, NEt₃ (3.6 ml, 25.57 mmol, 1.46 eq.) was added to a stirred solution of 2.44 obtained in step one in Ac₂O (5 ml, 52.37 mmol, 3 eq.). The reaction mixture was heated at 80 °C for one hour to completion. After removal of the solvent, the residue was taken up by EtOAc 50 ml, and the solution was washed with 5% NaHCO₃ solution (70 ml), saturated brine, then dried over Na₂SO₄ and concentrated under reduced pressure to afford 2.27 as brown oil (1.55 g, 56% yield), which was pure enough for immediate spectrographic characterization. The spectroscopic data for 2.27 matched that reported in the literature.³⁷

1-Allyl-6-ethoxypiperidin-2-one (2.28). Under N₂ protection, at -10 °C, NaBH₄ (1.70 g, 44 mmol, 4 eq.) was added to 1-allylpiperidine-2,6-dione 2.27 (1.69 g, 11 mmol, 1 eq.) solution in absolute EtOH (47 ml), then 6 drops of bromocresol green solution (0.04 wt% in H₂O) was added. At a regular interval (ca. 15 minutes), 6 drops of 2M HCl aqueous solution was added to the mixture until the reaction was complete, which was 3.5 hours. After the reaction was complete, at -10 °C, HCl aqueous solution (6M) was added to the reaction mixture over one hour to adjust the pH to 4, then the mixture was stirred at 0 °C for an hour before 20 ml water was added, followed by 40 ml CH₂Cl₂. The mixture was extracted with CH₂Cl₂ (40 ml × 2). The combined organic layers were washed with
saturated NaHCO₃ aqueous solution (40 ml), then dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 2.28 as yellow oil (1.70 g, 84%). Due to the instability of the compound, chromatography is not advised, and 2.28 should be carried on to next step without further purification. The spectroscopic data for 2.28 matched that reported in the literature.₃⁷

1,6-Diallylpiperidin-2-one (2.29). Under N₂ protection, to a solution of 1-allyl-6-ethoxypiperidin-2-one 2.28 (1.61 g, 8.79 mmol, 1 eq.) in CH₂Cl₂ (25 ml) was added allyltrimethylsilane (3 g, 4.2 ml, 26.36 mmol, 3 eq.) and boron trifluoride diethyl etherate (2.49 g, 2.16 ml, 17.57 mmol, 2 eq.) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. After the reaction was complete, 20 ml CH₂Cl₂ was added, and the reaction mixture was washed with H₂O (25 ml × 2). The organic layer was collected and dried over Na₂SO₄, then filtered, concentrated in vacuo to afford yellow oil which was chromatographically purified over silica gel (10% Et₂O in CH₂Cl₂ with 0.2% NEt₃, Rᵣ = 0.16, I₂ stain) to afford 2.29 as colorless oil (970 mg, 62% yield). The spectroscopic data for 2.29 matched that reported in the literature.₃⁷
2,3,9,9a-Tetrahydro-1H-quinolizin-4(6H)-one (2.30). Under N₂ protection, 1,6-diallylpiperidin-2-one 2.29 (560 mg, 3.12 mmol, 1 eq.) was dissolved in degassed CH₂Cl₂ (128 ml), to which Grubbs’ 2nd generation catalyst (26 mg, 0.031 mmol, 1 mol%) dissolved in degassed CH₂Cl₂ (8 ml) was added. The reaction mixture was heated at reflux for 2 hours. After the reaction was complete, the solvent was removed in vacuo, and the resulting brown oil was chromatographically purified over silica gel (10% Et₂O in CH₂Cl₂ with 0.2% NEt₃, Rᵣ = 0.16, phosphomolybdic acid stain) to afford 2.30 as yellow oil (400 mg, 85% yield). The spectroscopic data for 2.30 matched that reported in the literature.³⁷

4,6,7,8,9,9a-Hexahydro-1H-quinolizine (2.31). Under N₂ protection, a solution of 2,3,9,9a-tetrahydro-1H-quinolizin-4(6H)-one 2.30 (1.1 g, 7.27 mmol, 1 eq.) in THF (20 ml) was added dropwise into a LAH (0.58 g, 14.55 mmol, 2 eq.) suspension in THF (10 ml) at 0 °C. After the addition, the mixture was allowed to warm up to room temperature, and the reaction mixture was stirred at room temperature overnight. After the reaction was complete, cooling the mixture to 0 °C, then 0.6 ml H₂O, 0.6 ml 15%NaOH solution, and
1.8 ml H₂O were added successively, and the resulting mixture was stirred at room temperature for 2 hours to afford milky suspension, which was filtered, and the white solid on the top of the filter was washed several times with THF. The filtrate was concentrated in vacuo at room temperature (< 30 °C) to give crude product which was further chromatographically purified over silica gel (10% Et₂O in CH₂Cl₂ with 0.5% NEt₃) to afford 2.31 as yellow oil (600 mg, 60% yield). ¹H NMR (500 MHz, CDCl₃) δ 5.72-5.62 (m, 2H), 3.27-3.17 (m, 1H), 2.99-2.92 (m, 1H), 2.75-2.66 (m, 1H), 2.15-1.18 (m, 10H); ¹³C NMR (125 MHz, CDCl₃) δ 24.39, 25.86, 33.50, 33.56, 54.65, 55.99, 57.28, 124.47 ppm; FT-IR (neat) 2925, 1289, 1123 cm⁻¹.

1-Allylpyrrolidine-2,5-dione (2.32). Under N₂ protection, to a solution of succinimide (22.0 g, 217.8 mmol, 1 eq.), triphenylphosphine (74.8 g, 282.7 mmol, 1.3 eq.) and allyl alcohol (15.29 g, 17.93 ml, 260.7 mmol, 1.2 eq.) in THF (330 ml) at 0 °C was added dropwise diethyl azodicarboxylate (50.82 g, 45.76 ml, 282.7 mmol, 1.3 eq.). The mixture was warmed up to room temperature and stirred for 24 hours. After the reaction was complete, and solvent was removed in vacuo and diethyl ether (100 ml) was added, and the mixture was kept in refrigerator overnight. On the second day, there was precipitate in the container, and the mixture was filtered, and the precipitate was washed with ether.
several times. The filtrate was concentrated in vacuo and purified by flash column chromatography over silica gel (30% ethyl acetate in hexane with 0.2% NEt₃, Rf = 0.12, UV light) to afford 2.32 as colorless oil (30 g, 97% yield). The spectroscopic data for 2.32 matched that reported in the literature.³⁷

1-Allen-5-ethoxypyrroolidin-2-one (2.33). The procedure of synthesizing 2.28 was followed on a 21.56 mmol scale to synthesize 2.33 except that 1-allylprrrolidine-2,5-dione 2.32 was used instead of 1-allylpiperidine-2,6-dione 2.27. After workup, 2.33 was obtained as white solid (2.62 g, 72% yield). Due to the instability of the compound, chromatography is not advised, and 2.33 should be carried on to next step without further purification. The spectroscopic data for 2.33 matched that reported in the literature.³⁷
1,5-Diallylpyrrolidin-2-one (2.34). The procedure of synthesizing 2.29 was followed on a 5.9 mmol scale to synthesize 2.34 except that 1-allyl-5-ethoxypyrrolidin-2-one 2.33 was used instead of 1-allyl-6-ethoxypiperidin-2-one 2.28. The crude product was chromatographically purified over silica gel (10% Et₂O in CH₂Cl₂ with 0.2% NEt₃, Rₜ = 0.3) to afford 2.34 as white solid (700 mg, 72% yield). The spectroscopic data for 2.34 matched that reported in the literature.³⁷

![2.35](image)

1,2,8,8a-Tetrahydroindolizin-3(5H)-one (2.35). The procedure of synthesizing 2.30 was followed on a 3.15 mmol scale to synthesize 2.35 except that 1,5-diallylpyrrolidin-2-one 2.34 was used instead of 1,6-diallylpiperidin-2-one 2.29. The crude product was chromatographically purified over silica gel (10% Et₂O in CH₂Cl₂ with 0.2% NEt₃, Rₜ = 0.22) to afford 2.35 as yellow oil (300 mg, 70% yield). The spectroscopic data for 2.35 matched that reported in the literature.³⁷

![2.36](image)
**1,2-Diallylpyrrolidine (2.36).** Under N\textsubscript{2} protection, a solution of 1,5-diallylpyrrolidin-2-one 2.34 (1.6 g, 9.68 mmol, 1 eq.) in THF (30 ml) was added dropwise to a LAH (780 mg, 19.37 mmol, 2 eq.) suspension in THF (10 ml) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 2 hours. After the reaction was complete, 0.8 ml H\textsubscript{2}O, 0.8 ml 15% NaOH solution, and 2.4 ml H\textsubscript{2}O were added successively at 0 °C. The mixture was stirred at room temperature for 2 hours to afford milky suspension which was filtered, and the white residue on top of the filter was washed several times with THF. The filtrate was concentrated in vacuo at room temperature, making sure the temperature never exceeded 30 °C, since the product is very volatile. The concentrated crude product was vacuum distillated (62 °C, 10 mmHg) to afford 2.36 as colorless oil (530 mg, 36% yield). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 5.97-5.88 (m, 1H), 5.84-5.75 (m, 1H), 5.21-5.00 (m, 4H), 3.49 (dd, \textit{J} = 15.3 Hz, 5.5 Hz, 1H), 3.09 (td, \textit{J} = 8.3 Hz, 2.5 Hz, 1H), 2.77 (q, \textit{J} = 7.8 Hz, 1H), 2.45-2.40 (m, 1H), 2.36-2.30 (m, 1H), 2.15 (q, \textit{J} = 9 Hz, 1H), 2.07-2.01 (m, 1H), 1.91-1.84 (m, 1H), 1.78-1.62 (m, 2H), 1.56-1.48 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 21.52, 29.70, 38.14, 53.69, 56.85, 63.05, 115.76, 116.15, 135.43, 135.79 ppm; FT-IR (neat) 3077, 1641, 994, 911 cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{10}H\textsubscript{18}N 152.1434, found 152.1433 [M+H]\textsuperscript{+}. 

![Diagram of 1,2-Diallylpyrrolidine (2.36)](image-url)
**1,2,3,5,8,8a-Hexahydroindolizine (2.37).** Under N\textsubscript{2} protection, 1,2-diallylpyrrolidine 2.36 (800 mg, 5.29 mmol) and p-TsOH (911 mg, 5.29 mmol) were dissolved in CH\textsubscript{2}Cl\textsubscript{2} (160 ml), and the solution was degassed for 1 hour before Grubbs’ 2\textsuperscript{nd} generation catalyst (90 mg, 0.11 mmol, 2 mol\%) in degassed CH\textsubscript{2}Cl\textsubscript{2} (25 ml) was transferred to the flask via a syringe. The mixture was heated at reflux for 20 hours. After the reaction was complete, 200 ml 1M NaOH aqueous solution was added. The resulting mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (150 ml ×3). The combined organic layers were washed with 1M NaOH solution, saturated brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated at room temperature (< 30 °C) to give crude product, which was subjected to vacuum distillation (70 °C, 80 mmHg) to give 2.37 as colorless oil (600 mg, 38% yield). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 5.78-5.67 (m, 2H), 3.49 (d, J = 16 Hz, 1H), 3.21 (t, J = 9 Hz, 1H), 2.78 (d, J = 16 Hz, 1H), 2.33-1.37 (m, 8H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 20.88, 30.63, 32.50, 52.59, 54.33, 59.40, 125.19, 125.25 ppm; FT-IR (neat) 2909, 1157, 999, 660 cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{8}H\textsubscript{14}N\textsubscript{124.1121}, found 124.1120 [M+H]\textsuperscript{+}.

![E-ethyl 2-(benzylimino)acetate structure](image)

\textbf{(E)-ethyl 2-(benzylimino)acetate (2.50).} Under N\textsubscript{2} protection, ethyl glyoxylate (ca. 50% in toluene solution) (926 mg, 0.92 ml, 4.54 mmol, 1 eq.) and benzylamine (491 mg, 0.5 ml, 4.54 mmol, 1 eq.) were dissolved in CH\textsubscript{2}Cl\textsubscript{2} (dry, 14 ml), and then MgSO\textsubscript{4} (2.82 g, 22.7 mmol, 5 eq.) was added into the solution. The resulting mixture was heated at reflux for 3
hours. After cooling to room temperature, the mixture was filtered through celite and concentrated in vacuo to give glyoxylate imine 2.50 as yellow oil (830 mg, 96% yield), which was carried on into next step without further purification. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.72 (t, \(J = 1.5\) Hz, 1H), 7.37-7.26 (m, 5H), 4.86 (d, \(J = 1.5\) Hz, 2H), 4.34 (q, \(J = 7.3\) Hz, 2H), 1.36 (t, \(J = 7.3\) Hz, 3H).

1,3-Dibenzyl-5-ethoxyimidazolidine-2,4-dione (2.45). Benzyl isocyanate (535 mg, 0.5 ml, 3.97 mmol) was added to glyoxylate imine 2.50 (760 mg, 3.97 mmol), and the mixture was stirred at 120 °C for 12 hours. The resulting mixture was chromatographically purified over silica gel (10% ethyl acetate in hexane with 0.1% NEt\(_3\), R\(_f\) = 0.18, UV light) to afford 2.45 as yellow oil (850 mg, 66% yield). The spectroscopic data for 2.45 matched that reported in the literature.\(^26\)

**General Experimental Procedures for Pd\(^0\)-Catalyzed 1,3-Diaza-Claisen Rearrangement**

General Procedure A:
(4aS,7aS)-3-benzyl-1-phenyl-3,4,4a,5-tetrahydro-1H-cyclopenta[d]pyrimidin-2(7aH)-one (2.12). Pd(OAc)$_2$ (53 mg, 0.24 mmol, 10 mol%) was weighed into a flask under a stream of nitrogen, and then Dpppentane (215 mg, 0.48 mmol, 20 mol%) dissolved in dry degassed THF (2 ml) was added via syringe. The mixture was stirred at room temperature for 30 minutes before azanorbornene 2.1 (440 mg, 2.38 mmol, 1 eq.) and phenyl isocyanate (340 mg, 2.85 mmol, 1.2 eq.) were added successively. The reaction mixture was stirred for 15 minutes at room temperature to completion. After removal of the solvent, the crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% of triethylamine to afford 2.12 (620 mg, 86% yield) as yellow oil. The spectroscopic data for 2.12 matched that reported in the literature.$^{24}$

General Procedure B:

(4S,4aR,7aS)-ethyl-1-benzoyl-3-benzyl-2-oxo-2,3,4,4a,5,7a-hexahydro-1H-cyclopenta[d]pyrimidine-4-carboxylate (2.16). Pd(OAc)$_2$ (34 mg, 0.15 mmol, 10 mol%)
was weighed into a flask under a stream of nitrogen, and then Dpppentane (140 mg, 0.30 mmol, 20 mol%) dissolved in dry degassed THF (1.5 ml) was added via syringe. The mixture was stirred at room temperature for 30 minutes before precursor 2.2 (390 mg, 1.52 mmol, 1 eq.) was added. Benzoyl isocyanate (370 mg, 2.30 mmol, 1.5 eq.) dissolved in dry degassed THF (1 ml) was added via syringe pump over 12 hours, due to instability of benzoyl isocyanate. The reaction mixture was stirred at 55 °C for 16 hours, including the 12 hours of addition of benzoyl isocyanate. After removal of the solvent, the crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% of triethylamine to afford 2.16 (470 mg, 77% yield) as white solid. mp 146-149 °C; 

\[
\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 7.89 (d, J = 8.5 \text{ Hz, 2H}), 7.51-7.26 (m, 8H), 5.76 (s, 2H), 5.42 (d, J = 6.0 \text{ Hz, 1H}), 4.88 (d, J = 15.0 \text{ Hz, 1H}), 4.25 (d, J = 15.0 \text{ Hz, 1H}), 4.12-4.01 (m, 2H), 3.85 (d, J = 6.5 \text{ Hz, 1H}), 2.92 (q, J = 7.0 \text{ Hz, 1H}), 2.73 (d, J = 16.5 \text{ Hz, 1H}), 2.60 (dd, J = 17.0 \text{ Hz, 7.0 Hz, 1H}); 1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta 13.97, 33.58, 39.81, 50.86, 58.42, 61.72, 62.28, 127.81, 127.85, 128.48, 128.59, 130.90, 131.04, 136.12, 137.12, 154.91, 169.24, 173.73 ppm; FT-IR (neat) 1720, 1655, 700 cm\textsuperscript{-1}; HRMS (ESI) calcd for C\textsubscript{24}H\textsubscript{25}N\textsubscript{2}O\textsubscript{4} 405.1809, found 405.1806 [M+H]\textsuperscript{+}. 
\]

(4aS,7aS)-1,3-dibenzyl-3,4,4a,5-tetrahydro-1H-cyclopenta[d]pyrimidin-2(7aH)-one (2.13). The general procedure A was followed on a 1.3 mmol scale to synthesize 2.13
except that benzyl isocyanate was used instead of phenyl isocyanate. The reaction mixture was stirred at room temperature for 45 hours to completion. The crude product was purified by flash chromatography on silica gel using 25% ethyl acetate in hexane with 0.5% triethylamine to afford 2.13 as yellow oil (350 mg, 85% yield). The spectroscopic data for 2.13 matched that reported in the literature.\(^{24}\)

![Chemical Structure](image)

(4aS,7aS)-3-benzyl-1-tosyl-3,4,4a,5-tetrahydro-1H-cyclopenta[d]pyrimidin-2(7aH)-one (2.14). The general procedure A was followed on a 1.78 mmol scale to synthesize 2.14 except that \(p\)-toluenesulfonyl isocyanate was used instead of phenyl isocyanate. The reaction mixture was stirred at room temperature for 5 minutes to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.14 as white solid (545 mg, 80% yield). m.p. 167–168 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.02 (d, \(J = 8.5\) Hz, 2H), 7.40-7.12 (m, 7H), 5.80-5.76 (m, 1H), 5.66-5.61 (m, 1H), 5.43 (d, \(J = 9.0\) Hz, 1H), 4.46 (q, \(J = 15.0\) Hz, 2H), 3.31 (dd, \(J = 12.3\) Hz, 4.3 Hz, 1H), 2.96-2.85 (m, 2H), 2.44 (s, 3H), 1.82 (d, \(J = 17.0\) Hz, 1H), 1.53 (d, \(J = 15.5\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 21.55, 36.32, 36.61, 47.52, 50.98, 65.12, 127.66, 128.26, 128.49, 128.58, 129.20, 129.97, 134.35, 136.37, 137.32, 143.92, 153.96; FT-IR (neat) 1682, 1342, 1157 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{21}\)H\(_{23}\)N\(_2\)O\(_3\)S 383.1424 ; found 383.1425 [M+H]\(^+\).
(4S,4aS,7aS)-ethyl-3-benzyl-2-oxo-1-tosyl-2,3,4,4a,5,7a-hexahydro-1H-cyclopenta[d]pyrimidine-4-carboxylate (2.15). The general procedure A was followed on a 0.85 mmol scale to synthesize 2.15 except that precursor 2.2 was used instead of precursor 2.1 and p-toluenesulfonyl isocyanate was used instead of phenyl isocyanate. The reaction mixture was stirred at room temperature overnight to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.15 as white solid (350 mg, 90% yield). The spectroscopic data for 2.15 matched that reported in the literature.26

(4R,4aS,7aS)-ethyl-3-benzyl-2-oxo-1-tosyl-2,3,4,4a,5,7a-hexahydro-1H-cyclopenta[d]pyrimidine-4-carboxylate (2.17). The general procedure A was followed on a 0.85 mmol scale to synthesize 2.17 except that precursor 2.3 was used instead of precursor 2.1 and p-toluenesulfonyl isocyanate was used instead of phenyl isocyanate. The
reaction mixture was stirred at room temperature for 3 hours to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.17 as yellow oil (300 mg, 77% yield). The spectroscopic data for 2.17 matched that reported in the literature.²⁶

(4R,4aR,7aS)-ethyl-1-benzoyl-3-benzyl-2-oxo-2,3,4,4a,5,7a-hexahydro-1H-cyclopenta[d]pyrimidine-4-carboxylate (2.18). The general procedure B was followed on a 1.17 mmol scale to synthesize 2.18 except that precursor 2.3 was used instead of precursor 2.2. The reaction mixture was stirred at 55 °C for 18 hours to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.18 as yellow oil (250 mg, 53% yield).¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 7.0 Hz, 2H), 7.52-7.23 (m, 8H), 5.91-5.85 (m, 1H), 5.78-5.72 (m, 1H), 5.35 (d, J = 10.0 Hz, 1H), 5.18 (d, J = 14.5 Hz, 1H), 4.39-4.20 (m, 2H), 4.03 (d, J = 14.5 Hz, 1H), 3.81 (s, 1H), 3.58-3.47 (m, 1H), 2.51 (dd, J = 17.3 Hz, 9.5 Hz, 1H), 1.69-1.48 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H);¹³C NMR (125 MHz, CDCl₃) δ 14.05, 37.73, 37.87, 51.08, 60.94, 62.09, 127.71, 128.02, 128.13, 128.52, 129.22, 130.01, 130.98, 133.77, 135.97, 136.08, 155.52, 170.37, 172.16; FT-IR (neat) 1736, 1686, 1670, 698 cm⁻¹; HRMS (ESI) calcd for C₂₄H₂₅N₂O₄ 405.1809, found 405.1807 [M+H]⁺.
(4R,4aS,7aS)-ethyl-2-(benzoylimino)-3-benzyl-2,3,4,4a,5,7a-hexahydrocyclopenta[e][1,3]oxazine-4-carboxylate (2.19). Under a stream of nitrogen gas, benzoyl isocyanate (250 mg, 1.5 mmol) dissolved in dry THF (1 ml) was added via syringe pump over 12 hours into precursor 2.3 (260 mg, 1 mmol) dissolved in dry THF (1 ml). The reaction mixture was stirred at 60 °C for 96 hours. After removal of the solvent in vacuo, the resulting brown oil was chromatographically purified over silica gel (20% ethyl acetate in hexane with 0.5% triethylamine to give 2.18 as yellow oil (130 mg, 32% yield), 2.19 as yellow oil (80 mg, 20% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.15-8.12 (m, 2H), 7.50-7.36 (m, 8H), 6.03-6.01 (m, 1H), 5.86-5.83 (m, 1H), 5.45 (d, $J = 14.5$ Hz, 1H), 5.37 (d, $J = 9.0$ Hz, 1H), 4.32-4.23 (m, 2H), 4.17 (d, $J = 14.5$ Hz, 1H), 3.71 (s, 1H), 3.46-3.39 (m, 1H), 2.49 (dd, $J = 17.5$ Hz, 9.0 Hz, 1H), 1.85-1.78 (m, 1H), 1.33 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.08, 37.18, 38.25, 53.03, 59.13, 62.08, 85.07, 127.79, 128.22, 128.66, 129.16, 129.32, 129.56, 131.59, 135.58, 136.64, 137.62, 154.80, 170.07, 176.03; FT-IR (neat) 1736, 1636, 1574, 710 cm$^{-1}$; HRMS (ESI) calcd for C$_{24}$H$_{25}$N$_2$O$_4$ 405.1809, found 405.1809 [M+H]$^+$.
(4aS,8aS)-3-benzyl-1-tosyl-1,4,4a,5,6,8a-hexahydroquinazolin-2(3H)-one (2.20). The general procedure A was followed on a 2.41 mmol scale to synthesize 2.20 except that precursor 2.4 was used instead of precursor 2.1 and p-toluenesulfonyl isocyanate was used instead of phenyl isocyanate. The reaction mixture was refluxed for 2 hours to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.20 as white solid (750 mg, 79% yield). The spectroscopic data for 2.20 matched that reported in the literature.26

(4aS,8aS)-1-benzoyl-3-benzyl-1,4,4a,5,6,8a-hexahydroquinazolin-2(3H)-one (2.21). The general procedure B was followed on a 2.16 mmol scale to synthesize 2.21 except that precursor 2.4 was used instead of precursor 2.2, and 2 equivalents of benzoyl isocyanate was used. The reaction mixture was refluxed for 24 hours to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.21 as white solid (520 mg, 70% yield). mp 90-100 °C; 1H NMR (500 MHz, CDCl3) δ 7.67-7.20 (m, 10H), 5.83-5.74 (m, 2H), 5.08 (s, 1H), 4.65 (d, J
= 15.0 Hz, 1H), 4.41 (d, J = 15.0 Hz, 1H), 3.32 (t, J = 11.0 Hz, 1H), 3.20 (dd, J = 12.0 Hz, 6.0 Hz, 1H), 2.60-2.47 (m, 1H), 2.14-1.86 (m, 3H), 1.80-1.67 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 20.54, 23.41, 30.00, 45.71, 51.42, 52.30, 126.49, 127.33, 127.55, 127.84, 128.00, 128.56, 128.79, 130.77, 136.93, 137.57, 153.47, 173.30; FT-IR (neat) 1653, 1223, 693 cm⁻¹; HRMS (ESI) calcd for C22H23N2O2 347.1754, found 347.1756 [M+H]⁺.

(4aS,8aS)-3-benzyl-1-phenyl-1,4,4a,5,6,8a-hexahydroquinazolin-2(3H)-one (2.22).

The general procedure A was followed on a 2.0 mmol scale to synthesize 2.22 except that precursor 2.4 was used instead of precursor 2.1, and dry toluene was used as the solvent instead of THF. The reaction mixture was refluxed for 7 hours when there was no progress can be monitored. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.22 as yellow oil (250 mg, 39% yield). ¹H NMR (500 MHz, CDCl3) δ 7.40-7.22 (m, 10H), 5.70 (d, J = 10.0 Hz, 1H), 5.61 (d, J = 12.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.42 (s, 1H), 3.35 (t, J = 10.0 Hz, 1H), 3.15 (dd, J = 11.8 Hz, 4.8 Hz, 1H), 2.53-2.46 (m, 1H), 2.08-2.01 (m, 2H), 1.87-1.72 (m, 2H); ¹³C NMR (125 MHz, CDCl3) δ 21.77, 23.26, 30.47, 45.85, 51.50, 57.18, 126.02, 126.45, 127.18, 127.80, 128.01, 128.12, 128.53, 128.91, 138.46, 142.88, 155.17; FT-IR (neat) 1633, 1485, 1275, 696 cm⁻¹; HRMS (ESI) calcd for C21H23N2O 319.1805, found 319.1808 [M+H]⁺.
(4S,4aS,8aS)-ethyl-3-benzyl-2-oxo-1-tosyl-1,2,3,4,4a,5,6,8a-octahydroquinazoline-4-carboxylate (2.23). The general procedure A was followed on a 0.41 mmol scale to synthesize 2.23 except that precursor 2.5 was used instead of precursor 2.1, p-toluenesulfonyl isocyanate was used instead of phenyl isocyanate, and dry toluene was used as the solvent instead of THF. The reaction mixture was refluxed for 22 hours to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.23 as colorless oil (165 mg, 87% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.94 (d, $J$ = 8.0 Hz, 2H), 7.33 (d, $J$ = 8.0 Hz, 2H), 7.29-7.23 (m, 3H), 7.12-7.09 (m, 2H), 5.93 (d, $J$ = 10.5 Hz, 1H), 5.69-5.66 (m, 1H), 5.08 (s, 2H), 4.06-3.91 (m, 2H), 3.75 (td, $J$ = 15.5 Hz, 5.5 Hz, 2H), 2.63 (s, 1H), 2.44 (s, 3H), 2.23-1.89 (m, 4H), 1.18 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 13.69, 20.10, 21.63, 21.78, 34.17, 50.07, 54.07, 59.81, 61.66, 127.70, 127.83, 128.11, 128.46, 128.65, 128.84, 129.27, 135.78, 137.97, 143.89, 151.69, 170.58; FT-IR (neat) 1732, 1670, 1427, 1342, 1165 cm$^{-1}$; HRMS (ESI) calcd for C$_{25}$H$_{29}$N$_2$O$_5$S 469.1792, found 469.1791 [M+H]$^+$. 
(4R,4aS,8aS)-ethyl-3-benzyl-2-oxo-1-tosyl-1,2,3,4,4a,5,6,8a-octahydroquinazoline-4-carboxylate (2.24). The general procedure A was followed on a 0.44 mmol scale to synthesize 2.24 except that precursor 2.6 was used instead of precursor 2.1, p-toluenesulfonyl isocyanate was used instead of phenyl isocyanate, and dry toluene was used as the solvent instead of THF. The reaction mixture was refluxed for 9 hours to completion. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.24 as colorless oil (197 mg, 95% yield). The spectroscopic data for 2.24 matched that reported in the literature.26

1-Benzyl-3-tosyl-4-vinyl-1,3-diazepan-2-one (2.25). The general procedure A was followed on a 0.91 mmol scale to synthesize 2.25 except that precursor 2.8 was used instead of precursor 2.1, 2 equivalents of p-toluenesulfonyl isocyanate was used instead of 1.2 equivalents of phenyl isocyanate, and dry 1,4-dioxane was used as the solvent instead of THF. The reaction mixture was refluxed for 20 minutes to completion. The crude product
was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.25 as colorless oil (276 mg, 79% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 (d, $J$ = 8.5 Hz, 2H), 7.40-7.22 (m, 7H), 5.57-5.50 (m, 1H), 5.01 (d, $J$ = 11.0 Hz, 1H), 4.89 (d, $J$ = 17.5 Hz, 1H), 4.76 (s, 1H), 4.50 (q, $J$ = 15.0 Hz, 2H), 3.66 (t, $J$ = 14.0 Hz, 1H), 3.13 (d, $J$ = 12.5 Hz, 1H), 2.43 (s, 3H), 2.07-1.93 (m, 2H), 1.61-1.40 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 21.55, 31.97, 48.40, 52.40, 58.15, 118.23, 127.66, 128.31, 128.59, 128.69, 129.18, 133.97, 136.32, 136.69, 143.78, 156.23; FT-IR (neat) 1681, 1419, 1342, 1219, 1157 cm$^{-1}$; HRMS (ESI) calcd for C$_{21}$H$_{25}$N$_2$O$_3$S 385.1580, found 385.1579 [M+H]$^+$. 

**1-Benzyl-3-tosyl-4-vinyltetrahydropyrimidin-2(1H)-one (2.26).** The general procedure B was followed on a 1.44 mmol scale to synthesize 2.26 except that precursor 2.7 was used instead of precursor 2.2, 2 equivalents of $p$-toluenesulfonyl isocyanate was used instead of 1.5 equivalents of benzoyl isocyanate, dry 1,4-dioxane was used as the solvent instead of THF, and catalyst loading of Pd(OAc)$_2$ and Dpppentane were increased to 20 mol% and 40 mol%, respectively. The reaction mixture was refluxed for 28 hours. The crude product was purified by flash chromatography on silica gel using 20% ethyl acetate in hexane with 0.5% triethylamine to afford 2.26 as yellow oil (100 mg, 19% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.94 (d, $J$ = 8.0 Hz, 2H), 7.47-7.08 (m, 7H), 5.84-5.72 (m, 1H), 5.37-5.23 (m,
2H), 4.48 (s, 2H), 3.15 (td, J = 12.5 Hz, 4.5 Hz, 1H), 3.02 (dd, J = 12.0 Hz, 5.0 Hz, 1H),
2.43 (s, 3H), 2.20-2.08 (m, 2H), 1.97-1.90 (m, 1H); 13C NMR (125 MHz, CDCl3) 21.60,
26.77, 41.58, 50.98, 56.23, 117.89, 127.52, 127.86, 128.54, 128.72, 129.02, 135.06, 136.45,
137.49, 143.89, 151.19 cm⁻¹; δ FT-IR (neat) 1667, 1342, 1165 cm⁻¹; HRMS (ESI) calcd for
C₂₀H₂₃N₂O₃S 371.1424, found 371.1424 [M+H]+.
CHAPTER 3: DESIGN AND DEVELOPMENT OF CATIONIC 1,3-
DIAZA-CLAISEN REARRANGEMENT

3.1 Introduction

As noted in chapter 1, the aza-Claisen rearrangement normally requires harsh conditions. Thermal aliphatic aza-Claisen rearrangement would occur at 170-250 °C, while the reactions of aromatic aza-Claisen rearrangement have been observed at 200-350 °C, excluding the presence of a variety of functional groups upon running the reactions. Among the methods of promoting aza-Claisen rearrangements at lower temperature, it is well established that the rearrangement benefits from acceleration by the cationic charge at nitrogen (Figure 44).\textsuperscript{39, 40, 41}

\[ \begin{align*}
\text{NH} & \quad \text{cationic charge} \\
\text{H-X} & \quad \text{protonation} \\
150 \degree \text{C} & \quad \text{temperature}
\end{align*} \]

\[ \begin{align*}
\text{MeCN, 80 \degree C} & \quad \text{activation}
\end{align*} \]

\[ \begin{align*}
\text{Br} & \quad \text{functional group}
\end{align*} \]

\[ \begin{align*}
\text{H}_2\text{O} & \quad \text{water}
\end{align*} \]

Figure 44. Cationic charge-accelerated aza-Claisen rearrangement.

A significant contribution in cationic aza-Claisen rearrangement was provided by the Vedejs group who found that protic acids could catalyze the zwitterionic aza-Claisen rearrangement through protonation of Michael adduct 116 which was formed by addition.
of tertiary allylic amines 115 to dimethyl acetylenedicarboxylate. The quaternary nitrogen cation 117 subsequently underwent facile cationic aza-Claisen rearrangement to afford vinylogous urethanes 119 (Figure 45). Both Brønsted–Lowry acids and Lewis acids were found to accelerate the aza-Claisen rearrangement, and the reaction temperature was substantially lowered to 23-0 °C by acid catalysis in most of the experiments.

![Diagram showing the cationic aza-Claisen rearrangement](image)

**Figure 45.** Cationic aza-Claisen rearrangement from Vedejs group.

Similar trends are also observed for the ketene-based aza-Claisen rearrangement. Both Nubbemeyer and MacMillan have shown that Lewis acids catalyze the rearrangement (Figure 46). Lewis acid coordination complex of the enolates (121, 124) results in a “cationic” intermediate that more readily undergoes rearrangement.
Inspired by these observations, we became interested in the cationic 1,3-diaza-Claisen rearrangement. We envisioned that quaternary ammonium salt 127 generated by protonation of zwitterionic intermediate 126, would undergo facile 1,3-diaza-Claisen rearrangement to afford guanidine derivatives 128, which are very important natural products scaffolds (Figure 47).

However, in order to explore the cationic 1,3-diaza-Claisen rearrangement, contrary to our previous research, we need to move away from highly electron-deficient carbodiimides (R = EWG for 126, Figure 47) as this diminishes the Brønsted–Lowry
basicity of the zwitterionic intermediate 126, thus impeding the protonation of 126 to form the cationic intermediate 127, which would readily rearrange to afford 128.

3.2 Results and Discussion

3.2.1 Reaction Design

In 1960, Gregory Boshart and coworkers found that hydrochloride salts of carbodiimides 129 are capable of existence in two structural isomeric forms. An infrared absorption spectrum in chloroform solution has the 2130 cm$^{-1}$, which is the characteristic band of the -N=C=N- chromophore. The infrared absorption of the crystalline solid, however, has $\nu_{\max}$ at 3230 cm$^{-1}$ and 1700 cm$^{-1}$, characteristic of –NH- and C=N-, respectively. They therefore suggested a ring-chain tautomerism 129 $\rightleftharpoons$ 130 (Figure 48).

![Figure 48. Ring-chain tautomerism of hydrochloride salts of carbodiimides.](image)

Based on this observation, we envisioned that the carbodiimide salt 3.1 would equilibrate with the quaternary nitrogen cations 3.2 and 3.3, which would be poised for cationic 1,3-diaza-Claisen rearrangement to afford guanidines 3.4 and 3.5 (Figure 49). However, the acquisition of guanidines 3.4 and 3.5 would proceed through transition states C and D, respectively. In transition state C, the rehybridizing lone pair of the nitrogen is
properly aligned with the adjacent C-N π system; while in transition state D, the rehybridizing lone pair of the nitrogen is orthogonal to the adjacent C-N π system, and so guanidine 3.4 should be formed in preference to 3.5 (Figure 49).

![chemical structures](image_url)

**Figure 49.** Cationic 1,3-diaza-Claisen rearrangement.

Our study began with synthesis of 1-(3-(diallylamino)propyl)-3-benzylurea 3.6 (Figure 50). Diallylamine reacted with acrylamide to give amide 3.7 in quantitative yield, which was reduced by lithium aluminum hydride to afford primary amine 3.8. Due to the instability of amine 3.8, it was allowed to react with BnNCO without chromatography purification, affording urea 3.6 in 50% yield.
Upon acquisition of urea 3.6, we envisioned that carbodiimide salt 3.1 could be obtained by dehydration of 3.6 effected with p-toluenesulfonyl chloride and triethylamine, and then 3.1 would equilibrate with ring tautomer cation 3.2, which would proceed to cationic 1,3-diaza-Claisen rearrangement to afford guanidine 3.4 (Figure 51). Initially, the reaction was performed in CH$_2$Cl$_2$, and carbodiimide salt 3.1 was formed after 3 hours of heating at reflux in CH$_2$Cl$_2$. The presence of carbodiimide 3.1 was confirmed by infrared absorption of 2124 cm$^{-1}$ which is the characteristic band of −N=C=N−. However, after the reaction was continued for 48 hours, only trace amount of expected rearrangement product 3.4 was observed from analyzing crude $^1$H NMR, so higher boiling point solvent chloroform was used instead of methylene chloride which apparently could not provide enough activation energy for the rearrangement to occur smoothly. To our delight, the expected rearrangement product 3.4 was formed in 63% yield after the reaction was heated at reflux for 40 hours in chloroform (Figure 51).

\[
\text{Figure 50. Synthesis of 1-}(3-\text{(diallylamino)propyl})-3\text{-benzylurea 3.6.}
\]
Upon acquisition of the rearrangement product, we needed to verify its structure as guanidine 3.4 or 3.5. If it were 3.4, it would undergo a ring metathesis to afford guanidine 3.9; otherwise, there should be no reaction. Indeed, when the rearrangement product we obtained was subjected to ring closing metathesis, the bicyclic guanidine 3.9 was formed in 95% yield (Figure 52), which proved that our prediction of 3.4 as the stereoelectronically favorable (Figure 49) product is correct.
Figure 52. Ring closing metathesis of 3.4.

We recognized the possibility that proton transfer from chloroform could confuse the proton source, therefore the reaction in aprotic solvent benzene was investigated. We were pleased to find that the reaction proceeded successfully to afford 3.4 in 65% yield in even shorter reaction time (Figure 53).

Figure 53. Cationic 1,3-diaza-Claisen rearrangement in benzene.

3.2.2 Mechanism Investigation

In order to ascertain the effect of acid on the rearrangement, basic carbodiimide 3.10 was synthesized by dehydration of urea 3.6 effected with p-toluenesulfonyl chloride and potassium carbonate in the presence of phase transfer catalyst triethyl benzyl ammonium chloride (Figure 54).46 The basic carbodiimide 3.10 was subjected to a number
of rearrangement conditions (Table 4). Simply heating the free base 3.10 in benzene at reflux did not afford any of the rearrangement product 3.4, thus providing evidence for the cationic 1,3-diaza-Claisen rearrangement. However, heating the free base 3.10 in benzene at reflux with excess anhydrous p-TsOH (2 eq.) did not afford any rearrangement product, but substoichiometric p-TsOH (0.5 eq.) did afford the guanidine 3.4 in 42% yield. We hypothesize that the reaction does not proceed to completion because of product inhibition. Besides of p-TsOH, 0.5 eq. HCl (generated in situ from benzoyl chloride and methanol) was also added to the free base 3.10, however, no rearrangement product 3.4 was formed. Initially, we conjecture that it is probably due to the counterion effect, and tosylate anion may aid better than chloride anion in the rearrangement. However, when we added 1 eq. tetrabutylammonium tosylate into the reaction system, the rearrangement was significantly inhibited, and only trace amount of rearrangement product 3.4 was observed. At this point, the effect of counterion on the rearrangement is poorly understood (Figure 55).

![Figure 54. Synthesis of basic carbodiimide 3.10.](image)

**Table 4.** Effect of acid on rearrangement of 3.10 to 3.4.
Conditions 3.10 → 3.4  
<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzene, reflux, 24 h</td>
<td>0</td>
</tr>
<tr>
<td>2 eq. $p$-TsOH, benzene, reflux, 24 h</td>
<td>0</td>
</tr>
<tr>
<td>0.5 eq. $p$-TsOH, benzene, reflux, 48 h</td>
<td>42%</td>
</tr>
<tr>
<td>0.5 eq. HCl, benzene, reflux, 48 h</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 55. Tetrabutylammonium tosylate inhibits the rearrangement.

3.2.3 Optimization of Reaction Conditions

The optimum reaction conditions for cationic 1,3-diaza-Claisen rearrangement from ureas 3.6 to 3.4 were investigated, and the results are summarized in Table 5. From the table, we can see that, excess $p$-TsCl could speed up the reaction at the sacrifice of relatively lower yields (entries 3, 4, 5). Higher boiling point solvent like benzene proved to shorten the reaction time. However, when toluene was used as the solvent, surprisingly, the solubility in toluene became a big issue, and gum-like precipitates were formed during the reaction, which might account for the low yield (entry 5). Most surprisingly, the rearrangement was completely shut down in oxygen-containing solvents, such as tetrahydrofuran, 1,4-dioxane and isopropyl alcohol (entries 14, 15, 16). We suspected that the oxygen in these solvents might react with $p$-TsCl, interfering with the dehydration of
urea 3.6, thus halting the rearrangement. Higher temperature such as 120 °C does increase the reaction rate, while the yield was decreased to 68% (entry 18). Microwave irradiation also proved beneficial (entry 19), since the reaction was complete in only 4 hours at 120 °C in 76% yield. Finally, we chose the reaction with 1.2 eq. p-TsCl, 1 eq. NEt₃ in benzene at 80 °C as the optimum reaction condition (entry 12).

**Table 5.** Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>3.6 (eq.)</th>
<th>p-TsCl (eq.)</th>
<th>NEt₃ (eq.)</th>
<th>solvent</th>
<th>reaction time</th>
<th>isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>CHCl₃, reflux</td>
<td>120 h</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
<td>CHCl₃, reflux</td>
<td>91 h</td>
<td>53%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>CHCl₃, reflux</td>
<td>40 h</td>
<td>63%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>benzene, 80 °C</td>
<td>23 h</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>toluene, reflux</td>
<td>6 h</td>
<td>40%</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>benzene, 80 °C</td>
<td>48 h</td>
<td>41%</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>benzene, 80 °C</td>
<td>96 h</td>
<td>64%</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>benzene, 80 °C</td>
<td>48 h</td>
<td>75%</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>benzene, 80 °C</td>
<td>120 h</td>
<td>64%</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>benzene, 80 °C</td>
<td>96 h</td>
<td>43%</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
<td>benzene, 80 °C</td>
<td>48 h</td>
<td>75%</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>benzene, 80 °C</td>
<td>48 h</td>
<td>79%</td>
</tr>
</tbody>
</table>
3.2.4 Reaction with Other Dehydration Reagents

Encouraged by our initial effort with \( p\text{-TsCl} \) as the dehydration reagent which gave us satisfactory results, we investigated other dehydration reagents: \( \text{T}s_2\text{O}, \text{T}f_2\text{O} \) and \( \text{MsCl} \). It is disappointing to find that all the other dehydration reagents we tried are not as effective as \( p\text{-TsCl} \). As demonstrated in Table 6, the reactions with \( \text{MsCl} \) in different conditions always give urea 3.60 as the only product, and no rearrangement product 3.4 was obtained at all. However, when it comes to \( \text{T}s_2\text{O} \) and \( \text{T}f_2\text{O} \), the amount of \( \text{NEt}_3 \) makes all the difference. When excess activating reagents (\( \text{T}s_2\text{O}, \text{T}f_2\text{O} \)) were used, urea 3.61 and 3.62 were the major products; when 2 equivalents \( \text{NEt}_3 \) were used, the yield of rearrangement product 3.4 increased, and neither urea 3.61 or 3.62 was observed (Table 7, Table 8). It is worth noting that urea 3.60 is not stable when it was subjected to basic workup or chromatography purification. As for urea 3.61 and 3.62, the evidence for their existence is
from mass spectrometry, which shows the protonated molecular weight of ESI-MS: M+1=442.4, and 420.3 for urea \textbf{3.61} and \textbf{3.62}, respectively.

\textbf{Table 6.} Reaction with MsCl.

\[
\begin{array}{cccc}
\text{entry} & \textbf{3.6} \text{ (eq.)} & \text{MsCl} \text{ (eq.)} & \text{NEt}_3 \text{ (eq.)} & \text{product} \\
1 & 1 & 2 & 1 & \textbf{3.60} \\
2 & 1 & 1 & 1 & \textbf{3.60} \\
3 & 1 & 1 & 2 & \textbf{3.60} \\
\end{array}
\]

\textbf{Table 7.} Reaction with Ts\textsubscript{2}O.

\[
\begin{array}{cccc}
\text{entry} & \textbf{3.6} \text{ (eq.)} & \text{Ts}_2\text{O} \text{ (eq.)} & \text{NEt}_3 \text{ (eq.)} & \text{product} \\
1 & 1 & 2 & 1 & \textbf{3.61} + \text{trace} \textbf{3.4} + \text{S.M.}^a \\
2 & 1 & 1.2 & 1 & \textbf{3.61} + \textbf{3.4} (27\% \text{ yield})^* + \text{S.M.} \\
3 & 1 & 1 & 2 & \textbf{3.4} (30\% \text{ yield})^* + \text{S.M.} \\
\end{array}
\]
* Isolated yield.

*a S.M. = Starting Material

Table 8. Reaction with Tf₂O.

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>3.6 (eq.)</th>
<th>Tf₂O (eq.)</th>
<th>NEt₃ (eq.)</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3.62 + trace 3.4 + S.M.(^a)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3.62 + 3.4 (20% yield)* + S.M.</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3.4 (33% yield)* + S.M.</td>
</tr>
</tbody>
</table>

* Isolated yield.

\(^a\) S.M. = Starting Material

### 3.2.5 Syntheses of rearrangement precursors

In order to further investigate the scope and functional group tolerance of this methodology, a wide variety of ureas were synthesized. The substrates in Table 9 were synthesized to examine the effect of different R groups on the rearrangement.
Table 9. Syntheses of ureas with different R groups.

\[
\text{N} \text{H} + \text{N} \text{H} \text{N} \text{O} \rightarrow \text{N} \text{H} \text{N} \text{O} \text{R} \rightarrow \text{N} \text{H} \text{N} \text{O} \text{R}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>two-step yield from 3.7 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c-cyclo</td>
<td>3.11</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>phenyl</td>
<td>3.12</td>
<td>49%</td>
</tr>
<tr>
<td>3</td>
<td>isopropyl</td>
<td>3.13</td>
<td>48%</td>
</tr>
<tr>
<td>4</td>
<td>c-carboxy</td>
<td>3.14</td>
<td>42%</td>
</tr>
<tr>
<td>entry</td>
<td>R</td>
<td>product</td>
<td>two-step yield from 3.7 *</td>
</tr>
<tr>
<td>-------</td>
<td>----</td>
<td>---------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td><img src="image" alt="3.15" /></td>
<td>47%</td>
</tr>
<tr>
<td>6</td>
<td>O</td>
<td><img src="image" alt="3.16" /></td>
<td>40%</td>
</tr>
<tr>
<td>7</td>
<td>O</td>
<td><img src="image" alt="3.64" /></td>
<td>59%</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td><img src="image" alt="3.65" /></td>
<td>55%</td>
</tr>
</tbody>
</table>

* Isolated yield.

Besides of urea 3.6 which undergoes rearrangement to afford six-membered guanidine 3.4, urea 3.17 and 3.20 were synthesized, investigating the length of the tether. (Figure 56). Lewis acid AlCl₃ was employed to promote aminolysis of succinimide to afford bis-amides 3.21, which were reduced by LAH to generate 3.22, and further coupling between 3.22 and BnNCO afforded 3.20 in good yield.
Figure 56. Syntheses of urea 3.17 and 3.20.
Urea 3.26 and 3.30 were also synthesized to examine the steric effects on the allyl moiety (Figure 57).

![Synthesis of ureas 3.26 and 3.30.

Additional ureas representing different ring systems were also synthesized. Urea 3.36 possessing bridged endo cyclic tertiary allylic amine was synthesized in 6 steps. Diels-Alder reaction between cyclohexadiene and chlorosulfonyl isocyanate afforded N-chlorosulphonyl lactam 3.31 in good yield,\(^{49}\) which was hydrolyzed to give lactam 3.32.
The reduction product isoquinuclidene **3.33** was coupled with acrylamide to afford amide **3.34**, which was further reduced by LAH, and subsequent coupling with BnNCO to afford **3.36** in moderate yield.

![Chemical structure](image)

**Figure 58.** Synthesis of urea **3.36**.

Ureas **3.41** and **3.51** both contain non-bridged *endo* cyclic tertiary allylic amine were prepared similarly in 7 steps (Figure 59). Both *endo* cyclic tertiary amines **3.38** and **3.48** were generated by hydrolysis in the presence of hydrazine and potassium hydroxide. Upon obtaining **3.38** and **3.48**, they were transformed to amide **3.39** and **3.49**, which were further reduced by LAH, and subsequently coupled with BnNCO to afford urea **3.41** and **3.51**, respectively.
Figure 59. Syntheses of ureas 3.41 and 3.51.

The steric effect on the tether was also be investigated by synthesizing urea 3.54. Cyclohexanecarbonitrile 3.52 was prepared by coupling of cyclohexanone, KCN and diallylamine under acidic condition, and then 3.52 was reduced by LAH and further coupled with BnNCO, to afford urea 3.54 in moderate yield (Figure 60).

```
Figure 60. Synthesis of 3.54.
```

In order to facilitate preliminary investigation of our methodology in the application of natural product synthesis, 3.47 was synthesized (Figure 61), since it would undergo rearrangement to afford 3.63 which possesses the tricyclic framework of the left-hand unit of Batzelladine F (Figure 62).
Figure 61. Synthesis of 3.47.
However, during the preparation of urea 3.47, we realized that the rearrangement of this urea might be troublesome. The in situ-generated carbodiimide 3.78 can cyclize to form two diastereomeric cationic intermediates 3.79 and 3.80 that differ in the stereochemistry of the ammonium nitrogen. However, in intermediate 3.79, the breaking bond will be properly aligned with the \( \pi \)-orbital on the alkene to allow a thermal rearrangement. It is also worth noting that the conformation of the tetrahydropyridine ring should be a boat. In contrast, intermediate 3.80 should not undergo a thermal rearrangement since the breaking bond is not properly aligned with the \( \pi \)-orbital on the alkene. However, there is a repulsion between the \( H_1 \) and C-C bond of the tetrahydropyridine in intermediate 3.79, which might make the transition state unstable (Figure 63). We believe urea 3.76 on the other side, with the C-C bond of tetrahydropyridine \textit{anti} to \( H_1 \), thus avoiding the repulsion in the intermediate 3.79, should be more facile to undergo rearrangement. The initial synthetic route of urea 3.76 is shown in Figure 64. However, upon ring cyclization of 3.57, the major product we obtained is still the \textit{cis} ester 3.44, while the desired \textit{trans}
ester 3.58 was obtained in only 9% yield, therefore a new synthetic strategy is required for the preparation of urea 3.76, which is not accomplished in this thesis.

![Chemical structures and reaction scheme](image)

**Figure 63.** Transition states of 3.78.
Figure 64. Synthetic route of urea 3.76.

3.2.6 Results and Discussion

From Table 10, we can see that the length of tether is critical for the rearrangement, when the tether length is shortened (entry 10) or elongated (entry 11), the rearrangement did not proceed as expected. R group also plays an important role in the cationic 1,3-diaza-Claisen rearrangement. It is not surprising that entry 2 and entry 5 do not afford
rearrangement products, since the phenyl group and the electron-withdrawing group (the ester group) diminish the Brønsted–Lowry basicity of the zwitterionic intermediate 126 (Figure 47), thus impeding its further protonation and following rearrangement. Aliphatic groups (entries 3, 4, 6) greatly inhibit the rearrangements. This methodology works best at allylaminopropyl benzyl ureas (entries 1, 7, 8, 9), and the electronic properties of the benzyl group do not affect the rearrangement in a significant way. However, the rearrangement was affected dramatically by the steric effects on the allyl moiety (entries 12, 13). Introduction of two methyl groups on the terminal allyl moiety resulted in decomposition, which might be caused by the 1,3-diaxial interaction (Figure 65).

Figure 65. Rearrangement of urea 3.30 with disubstituted terminal allyl moiety.

Substrates containing non-bridged endo cyclic tertiary allylic amine (entries 14, 15) do not afford satisfactory results, and no rearrangement products can be observed from crude $^1$H NMR, and the only evidence for their existence is from mass spectrometry, which
shows the protonated molecular weight of desired rearrangement products. Urea 3.36 which possesses bridged *endo* cyclic tertiary allylic amine underwent rearrangement to afford guanidine 3.72 in 43% yield (entry 16). The reaction of urea 3.54 which has a bulky Cy group on the tether proceeded much better than urea 3.17 (entry 10), affording the rearrangement product 3.73 in 64% yield (entry 18). As anticipated, the rearrangement of urea 3.47 was troublesome, and no rearrangement product was observed (entry 17).

**Table 10.** Scope of the cationic 1,3-diaza-Claisen rearrangement.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = ( \text{Ph} ) (3.6)</td>
<td>( \text{N} )</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>R = ( \text{C}<em>{6} \text{H}</em>{4} ) (3.12)</td>
<td>Trace of rearrangement product</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R = ( \text{Cy} ) (3.11)</td>
<td>Trace of rearrangement product</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R = ( \text{Me} ) (3.13)</td>
<td>Trace of rearrangement product</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R = ( \text{O} ) (3.14)</td>
<td>No rearrangement</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R = ( \text{CH}<em>{2} \text{CH}</em>{2} ) (3.65)</td>
<td>( \text{N} )</td>
<td>33%</td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Product</td>
<td>Yield *</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>7</td>
<td>R = ( \text{phenyl} ) (3.15)</td>
<td>3.67</td>
<td>66%</td>
</tr>
<tr>
<td>8</td>
<td>R = ( \text{phenyl} ) (3.16)</td>
<td>3.66</td>
<td>68%</td>
</tr>
<tr>
<td>9</td>
<td>R = ( \text{phenyl} ) (3.64)</td>
<td>3.68</td>
<td>62%</td>
</tr>
<tr>
<td>10</td>
<td>( \text{N-H-N} ) (3.17)</td>
<td>( \text{N-H-N} ) (3.71)</td>
<td>21%</td>
</tr>
<tr>
<td>11</td>
<td>( \text{N-H-N} ) (3.20)</td>
<td>Trace of rearrangement product</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>( \text{N-H-N} ) (3.26)</td>
<td>( \text{N-H-N} ) (3.70)</td>
<td>59%</td>
</tr>
<tr>
<td>13</td>
<td>( \text{N-H-N} ) (3.30)</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Product</td>
<td>Yield *</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Substrate 3.41" /></td>
<td>Trace of rearrangement product</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Substrate 3.51" /></td>
<td>Trace of rearrangement product</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Substrate 3.36" /></td>
<td><img src="image" alt="Product 3.72" /></td>
<td>43%</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Substrate 3.47" /></td>
<td>No rearrangement</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Substrate 3.54" /></td>
<td><img src="image" alt="Product 3.73" /></td>
<td>64%</td>
</tr>
</tbody>
</table>

*: isolated yield.

### 3.2.7 Effect of Lewis acid on the Rearrangement

The effect of Lewis acid on the rearrangement was also evaluated. In order to avoid over acidification of the reaction system, 2 equivalents of base (triethylamine) were
introduced into the reaction. Table 11 shows that BF₃.OEt₂ does not affect the rearrangement in a noticeable way, while Sc(OTf)₃ actually inhibits the rearrangement significantly, resulting in only 8% yield of the rearrangement product 3.4.

**Table 11.** Effect of Lewis acid on the rearrangement.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield *</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Lewis acid</td>
<td>40%</td>
</tr>
<tr>
<td>10 mol% BF₃.OEt₂</td>
<td>37%</td>
</tr>
<tr>
<td>0.9 eq. BF₃.OEt₂</td>
<td>44%</td>
</tr>
<tr>
<td>10 mol% Sc(OTf)₃</td>
<td>8%</td>
</tr>
</tbody>
</table>

*: isolated yield.

### 3.3 Conclusions

We have designed and developed a novel cationic 1,3-diaza-Claisen rearrangement, which provides entry into synthetically challenging guanidines. In the presence of p-TsCl and NEt₃, ureas were initially dehydrated to form protonated carbodiimides whose presence was confirmed by the infrared absorption frequency at 2100 cm⁻¹ which is the characteristic band of –N=C=N–; then the in situ generated protonated carbodiimides were poised for further cationic 1,3-diaza-Claisen rearrangement to afford guanidines. The effect of protic acid on the rearrangement was ascertained by the fact that no rearrangement
product was observed by simply heating free base carbodiimide 3.10 in benzene at reflux. However, this methodology works best at allylaminopropyl benzyl ureas, while has limited application on ureas of different length of tether, or ring systems.

3.4 Experimental Section

General Experimental Details

All reactions were performed under a nitrogen atmosphere in oven–dried glassware. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. THF was distilled under nitrogen from potassium immediately before use. Dichloromethane was distilled under nitrogen from CaH₂ prior to use. Where required, solvents were degassed by bubbling of nitrogen through a needle for at least 15 minutes. Analytical thin layer chromatography (TLC) was performed using EMD TLC silica gel 60 F₂₅₄ pre-coated plate. Visualization was achieved by UV light (254 nm), I₂, or Phosphomolybdic acid. The products were purified by flash chromatography on silica gel (60 Å). Mixtures of methanol, dichloromethane and triethylamine or ethyl acetate, hexane and triethylamine were generally used as eluents. ¹H NMR spectra were recorded on a Bruker ARX 500 (500 MHz) or a Varian Unity Inova 500 (500 MHz) spectrometer. ¹³C NMR spectra were recorded on a Bruker ARX 500 (125 MHz) or a Varian Unity Inova 500 (125 MHz) spectrometer. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH and coupling constants are
reported as a J value in Hz. $^{13}$C NMR spectra are reported in terms of chemical shift (δ, ppm) relative to the triplet at 77.00 ppm for CDCl$_3$. IR spectra were obtained neat at room temperature using an ATF probe.

Experimental Procedures

Syntheses of rearrangement precursors

![Chemical structure of 3.7](image)

3-(Diallylamino)propanamide (3.7). Diallylamine (19.43 g, 24.6 ml, 0.2 mol) and acrylamide (14.21 g, 0.2 mol) in methanol (25 ml) were heated at reflux for 3 hours. After removal of the solvent, 3.7 was obtained as yellow oil (32.45 g, 100%), and the product was pure enough for immediate spectroscopic characterization. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.87-5.78 (m, 2H), 5.22-5.17 (m, 4H), 3.13 (d, $J = 6.5$ Hz, 4H), 2.72 (t, $J = 6$ Hz, 2H), 2.39 (t, $J = 6.3$ Hz, 2H).

![Chemical structure of 3.8](image)
$N^1,N^1$-diallylpropane-1,3-diamine (3.8). Under N$_2$ protection, a solution of amide 3.7 (2 g, 11.89 mmol, 1 eq.) in THF (40 ml) was added dropwise into LAH suspension (950 mg, 23.78 mmol, 2 eq.) in THF (20 ml) at 0°C, and then the mixture was allowed to warm up to room temperature, and then heated to reflux. The mixture was heated at reflux for 20 hours. After the reaction was complete, the mixture was cooled to 0 °C, then 1 ml H$_2$O, 1 ml 15% NaOH aqueous solution, and 3 ml H$_2$O were added successively at 0 °C, and the mixture was stirred at room temperature for 2 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.8 as yellow oil (1.44 g, 78%). Due to the instability of the primary amine 3.8, it was carried on to next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.89-5.81 (m, 2H), 5.19-5.12 (m, 4H), 3.08 (d, $J$ = 6.5 Hz, 4H), 2.75 (t, $J$ = 6.8 Hz, 2H), 2.49 (t, $J$ = 7.0 Hz, 2H), 1.63 (quintet, 2H).

1-(3-(Diallylamino)propyl)-3-benzylurea (3.6). Under N$_2$ protection, BnNCO (4.99 g, 4.66 ml, 37.11 mmol, 1.2 eq.) was added dropwise to a solution of amine 3.8 (4.77 g, 30.92 mmol, 1 eq.) in CH$_2$Cl$_2$ (80 ml). The mixture was stirred at room temperature for 30 minutes to completion. After removal of the solvent, the crude product was
chromatographically purified over silica gel (5% MeOH in CH\(_2\)Cl\(_2\) with 0.5% NEt\(_3\), R\(_f\) = 0.20, Phosphomolybdic acid as the stain) to afford 1-(3-(diallylamino)propyl)-3-benzylurea 3.6 as yellow oil (4.55 g, two-step yield 51% starting from 3.7 to 3.6). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.21 (m, 5H), 5.85-5.67 (m, 2H), 5.36 (br s, 1H), 5.20-5.09 (m, 4H), 4.97 (br s, 1H), 4.37 (d, \(J = 6\) Hz, 2H), 3.26 (t, \(J = 6.0\) Hz, 2H), 3.03 (d, \(J = 6.5\) Hz, 4H), 2.50 (t, \(J = 6.0\) Hz, 2H), 1.67-1.61 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 26.87, 39.79, 44.52, 51.39, 56.54, 117.79, 121.19, 127.42, 128.57, 135.12, 139.50, 158.64 ppm; FT-IR (neat) 1626, 1567 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{17}\)H\(_{26}\)N\(_3\)O 288.20704, found 288.20746 [M+H]\(^+\).

1-(3-(Diallylamino)propyl)-3-cyclohexylurea (3.11). The procedure of synthesizing 3.6 was followed on a 2.6 mmol scale to synthesize 3.11, except CyNCO was used instead of BnNCO. The crude product was chromatographically purified over silica gel (5% MeOH in CH\(_2\)Cl\(_2\) with 0.5% NEt\(_3\), Phosphomolybdic acid as the stain) to afford 1-(3-(diallylamino)propyl)-3-cyclohexylurea 3.11 as yellow oil (380 mg, two-step yield 52% starting from 3.7 to 3.11). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.88-5.80 (m, 2H), 5.29 (br s, 1H), 5.21-5.14 (m, 4H), 4.23 (br s, 1H), 3.50-3.39 (m, 1H), 3.23 (t, \(J = 6.5\) Hz, 2H), 3.08 (d, \(J = 6.5\) Hz, 4H), 2.51 (t, \(J = 6.5\) Hz, 2H), 1.99-1.88 (m, 2H), 1.75-1.58 (m, 4H), 1.38-
1.28 (m, 2H), 1.21-1.04 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 24.96, 25.57, 26.61, 33.97, 39.89, 49.12, 51.71, 56.67, 117.82, 135.17, 157.79 ppm; FT-IR (neat) 1626, 1567 cm$^{-1}$; HRMS (ESI) calcd for C$_{16}$H$_{24}$N$_3$O 274.19139, found 274.19195 [M+H]$^+$. 

1-(3-(Diallylamino)propyl)-3-phenylurea (3.12). The procedure of synthesizing 3.6 was followed on a 2.6 mmol scale to synthesize 3.12, except PhNCO was used instead of BnNCO. The crude product was chromatographically purified over silica gel (5% MeOH in CH$_2$Cl$_2$ with 0.5% NEt$_3$, $R_f = 0.20$, UV light) to afford 1-(3-(diallylamino)propyl)-3-phenylurea 3.12 as yellow oil (350 mg, two-step yield 49% starting from 3.7 to 3.12). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30-7.26 (m, 4H), 7.08-7.03 (m, 1H), 6.89 (br s, 1H), 6.0 (br s, 1H), 5.80-5.65 (m, 2H), 5.20-5.06 (m, 4H), 3.36-3.26 (m, 2H), 3.01 (d, $J = 6.5$ Hz, 4H), 2.50 (t, $J = 6.5$ Hz, 2H), 1.67-1.62 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 26.58, 39.55, 51.24, 56.61, 117.83, 120.78, 123.29, 129.06, 135.04, 138.96, 156.40 ppm; FT-IR (neat) 1650, 1556 cm$^{-1}$; HRMS (ESI) calcd for C$_{16}$H$_{24}$N$_3$O 274.19139, found 274.19195 [M+H]$^+$. 

![Image of 3.12](image_url)
1-(3-(diallylamino)propyl)-3-isopropylurea (3.13). The procedure of synthesizing 3.6 was followed on a 4.86 mmol scale to synthesize 3.13, except isopropyl isocyanate was used instead of BnNCO. The crude product was chromatographically purified over silica gel (5% MeOH in CH2Cl2 with 0.5% NEt3, Rf = 0.20, Phosphomolybdic acid as the stain) to afford 1-(3-(diallylamino)propyl)-3-isopropylurea 3.13 as yellow oil (800 mg, two-step yield 48% starting from 3.7 to 3.13). 1H NMR (500 MHz, CDCl3) δ 5.90-5.78 (m, 2H), 5.27 (br s, 1H), 5.20-5.14 (m, 4H), 4.21 (br s, 1H), 3.87-3.76 (m, 1H), 3.28-3.18 (m, 2H), 3.08 (d, J = 6.5 Hz, 4H), 2.51 (t, J = 6.5 Hz, 2H), 1.67-1.61 (m, 2H), 1.14 (d, J = 6.5 Hz, 6H); 13C NMR (125 MHz, CDCl3) δ 23.50, 26.77, 39.77, 42.12, 51.67, 56.67, 117.71, 135.24, 157.91 ppm; FT-IR (neat) 1626, 1566 cm⁻¹; HRMS (ESI) calcd for C13H26N3O 240.20704, found 240.20744 [M+H]⁺.

The procedure of synthesizing 3.6 was followed on a 6.94 mmol scale to synthesize 3.14, except ethyl isocyanatoacetate was used instead of BnNCO. The crude product was
chromatographically purified over silica gel (6% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.29, Phosphomolybdic acid as the stain) to afford 3.14 as yellow oil (1.43 g, two-step yield 42% starting from 3.7 to 3.14). ¹H NMR (500 MHz, CDCl₃) δ 5.89-5.81 (m, 2H), 5.52 (br s, 1H), 5.25-5.15 (m, 4H), 5.09 (br s, 1H), 4.20 (q, J = 7.3 Hz, 2H), 3.97 (d, J = 5.0 Hz, 2H), 3.29-3.25 (m, 2H), 3.11 (d, J = 6.5 Hz, 4H), 2.55 (t, J = 6.3 Hz, 2H), 1.69-1.64 (m, 2H), 1.28 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 13.96, 26.94, 38.90, 42.01, 50.85, 56.16, 60.84, 117.77, 134.70, 158.58, 171.25 ppm; FT-IR (neat) 1748, 1643, 1566 cm⁻¹; HRMS (ESI) calcd for C₁₄H₂₆N₃O₃ 284.19687, found 284.19736 [M+H]⁺.

![Image of 3.15](image_url)

1-(3-(Diallylamino)propyl)-3-(4-fluorobenzyl)urea (3.15). The procedure of synthesizing 3.6 was followed on a 5.2 mmol scale to synthesize 3.15, except 4-fluorobenzyl isocyanate was used instead of BnNCO. The crude product was chromatographically purified over silica gel (6% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.32, UV light) to afford 1-(3-(diallylamino)propyl)-3-(4-fluorobenzyl)urea 3.15 as yellow oil (850 mg, two-step yield 47% starting from 3.7 to 3.15). ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.24 (m, 2H), 7.02-6.98 (m, 2H), 5.81-5.72 (m, 2H), 5.40 (br s, 1H), 5.20-5.11 (m, 4H), 5.02 (br s, 1H), 4.33 (d, J = 5.5 Hz, 2H), 3.28-3.24 (m, 2H), 3.05 (d, J = 6.5 Hz, 4H), 2.52 (t, J = 6.3 Hz, 2H), 1.68-1.62 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 26.93, 39.28,
1-(3-(Diallylamino)propyl)-3-(4-methoxybenzyl)urea (3.16). The procedure of synthesizing 3.6 was followed on a 9.34 mmol scale to synthesize 3.16, except 4-methoxybenzyl isocyanate was used instead of BnNCO. The crude product was chromatographically purified over silica gel (5% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.20, UV light) to afford 1-(3-(diallylamino)propyl)-3-(4-methoxybenzyl)urea 3.16 as yellow oil (1.52 g, two-step yield 40% starting from 3.7 to 3.16). ¹H NMR (500 MHz, CDCl₃) δ 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.81-5.72 (m, 2H), 5.31 (br s, 1H), 5.18-5.12 (m, 4H), 4.84 (br s, 1H), 4.29 (d, J = 5.5 Hz, 2H), 3.79 (s, 3H), 3.28-3.24 (m , 2H), 3.04 (d, J = 6.5 Hz, 4H), 2.50 (t, J = 6.3 Hz, 2H), 1.67-1.62 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 26.88, 39.42, 43.82, 51.21, 55.18, 56.41, 113.85, 117.82, 128.62, 131.56, 134.90, 158.67, 158.70 ppm; FT-IR (neat) 1620, 1574, 1242 cm⁻¹; HRMS (ESI) calcd for C₁₈H₂₈N₃O₂ 318.21760, found 318.21804 [M+H]⁺.
1-(3-(diallylamino)propyl)-3-(3,4,5-trimethoxybenzyl)urea (3.64). The procedure of synthesizing 3.6 was followed on a 3.62 mmol scale to synthesize 3.64, except 3,4,5-trimethoxybenzyl isocyanate was used instead of BnNCO. The crude product was chromatographically purified over silica gel (5% MeOH in CH$_2$Cl$_2$ with 0.5% NEt$_3$, R$_f$ = 0.14, phosphomolybdic acid as the stain) to afford 1-(3-(diallylamino)propyl)-3-(3,4,5-trimethoxybenzyl)urea 3.64 as yellow oil (1.04 g, two-step yield 59% starting from 3.7 to 3.64). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.54 (s, 2H), 5.81-5.72 (m, 2H), 5.42 (br s, 1H), 5.18-5.13 (m, 4H), 4.98 (br s, 1H), 4.30 (d, J = 5.5 Hz, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 3.27 (t, J = 5.8 Hz, 2H), 3.07 (d, J = 16.5 Hz, 4H), 2.53 (t, J = 6.3 Hz, 2H), 1.67 (quintet, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 26.87, 39.21, 44.47, 51.05, 55.92, 56.29, 60.66, 104.20, 118.06, 134.51, 135.39, 136.74, 153.12, 158.69 ppm; FT-IR (neat) 1633, 1591, 1233, 1125 cm$^{-1}$; HRMS (ESI) calcd for C$_{20}$H$_{32}$N$_3$O$_4$ 378.23873, found 378.23878 [M+H]$^+$. 
1-(3-(diallylamino)propyl)-3-propylurea (3.65). The procedure of synthesizing 3.6 was followed on a 4.41 mmol scale to synthesize 3.65, except propyl isocyanate was used instead of BnNCO. The crude product was chromatographically purified over silica gel (5% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.27, phosphomolybdic acid as the stain) to afford 1-(3-(diallylamino)propyl)-3-propylurea 3.65 as yellow oil (760 mg, two-step yield 55% starting from 3.7 to 3.65). ¹H NMR (500 MHz, CDCl₃) δ 5.88-5.80 (m, 2H), 5.33 (br s, 1H), 5.22-5.15 (m, 4H), 4.51 (br s, 1H), 3.24 (t, J = 6 Hz, 2H), 3.12-3.08 (m, 6H), 2.53 (t, J = 6.3 Hz, 2H), 1.66 (quintet, 2H), 1.55-1.48 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 11.29, 23.42, 26.91, 39.38, 42.17, 51.37, 56.50, 117.82, 134.94, 158.90 ppm; FT-IR (neat) 1636, 1566 cm⁻¹; HRMS (ESI) calcd for C₁₃H₂₆N₃O 240.20704, found 240.20712 [M+H]⁺.

![3.18](image)

2-(Diallylamino)acetamide (3.18). Under N₂ protection, to a solution of diallylamine (0.2 ml, 158 mg, 1.58 mmol, 1 eq.) in CH₃CN (6.5 ml) at 0 °C, was added K₂CO₃ (437 mg, 3.16 mmol, 2 eq.) in small portions, then 2-bromoacetamide (327 mg, 2.37 mmol, 1.5 eq.) was added. The reaction mixture was stirred at room temperature overnight. After the reaction was complete, the suspension was filtered, and the filtrate was evaporated in vacuo. The residue was taken up by 10 ml 2M NaOH aqueous solution, and the mixture was extracted with CHCl₃ (10 ml × 3). The combined organic layers were washed with 10 ml 2M NaOH
solution, 10 ml saturated NaCl solution, dried over Na₂SO₄, filtered, concentrated to yield 2-(diallylamino)acetamide 3.18 as white solid (220 mg, 88% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.08 (br s, 1H), 5.86-5.78 (m, 2H), 5.43 (br s, 1H), 5.23-5.19 (m, 4H), 3.13 (d, J = 6.5 Hz, 4H), 3.08 (s, 2H).

N¹,N¹-diallylethane-1,2-diamine (3.19). The procedure of synthesizing 3.8 was followed on a scale of 1.37 mmol to synthesize 3.19, except 2-(diallylamino)acetamide 3.18 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.1 ml H₂O, 0.1 ml 15% NaOH aqueous solution, and 0.3 ml H₂O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.19 as yellow oil (180 mg). Due to the instability of the primary amine 3.19, it was carried on to next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.90-5.81 (m, 2H), 5.23-5.10 (m, 4H), 3.11 (d, J = 6 Hz, 4H), 2.75 (t, J = 6 Hz, 2H), 2.51 (t, J = 6 Hz, 2H).
1-(2-(Diallylamino)ethyl)-3-benzylurea (3.17). The procedure of synthesizing 3.6 was followed on a 1.28 mmol scale to synthesize 3.17, except 3.19 was used instead of 3.8. The crude product was chromatographically purified over silica gel (5% MeOH in CH$_2$Cl$_2$ with 0.5% NEt$_3$, R$_f$ = 0.23, Phosphomolybdic acid as the stain) to afford 1-(2-(diallylamino)ethyl)-3-benzylurea 3.17 as colorless oil (100 mg, two-step yield 27% starting from 3.18 to 3.17). $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.42-7.21 (m, 5H), 5.77-5.65 (m, 2H), 5.34 (br s, 1H), 5.20-5.08 (m, 4H), 4.91 (br s, 1H), 4.36 (d, $J$ = 6 Hz, 2H), 3.28-3.20 (m, 2H), 3.05 (d, $J$ = 6.5 Hz, 4H), 2.56 (t, $J$ = 5.5 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 38.97, 45.14, 53.66, 57.41, 118.79, 127.82, 128.18, 129.21, 135.55, 140.23, 159.71 ppm; FT-IR (neat) 1627, 1566, 698 cm$^{-1}$; HRMS (ESI) calcd for C$_{16}$H$_{24}$N$_3$O 274.19139, found 274.19209 [M+H]$^+$. 

$N'$,$N'$-diallylsuccinamide (3.21). Under N$_2$ protection, diallylamine (24.7 ml, 19.46 g, 194.29 mmol, 2.5 eq.) was added dropwise to a suspension of aluminum chloride (13.7 g,
101 mmol, 1.3 eq.) in 1,2-dichloroethane (300 ml) at 0 °C. Upon the reaction mixture was warmed up to room temperature, succinimide (7.7 g, 77.7 mmol, 1 eq.) was added to the above mixture, and then resulting mixture was stirred at room temperature for 16 hours. After the reaction was complete, 200 ml ice-water was added to the reaction mixture, and the organic layer was collected. 500 ml 2M NaOH solution was added to the aqueous layer, and the resulting solution was extracted with dichloromethane (300 ml × 3), and all the organic layers were combined (both the dichloromethane and 1,2-dichloroethane layers), washed with saturated brine solution (400 ml), dried over Na₂SO₄, filtered, concentrated in vacuo to give red oil which was chromatographically purified over silica gel (5% MeOH in CH₂Cl₂ with 0.5% NEt₃) to afford \( \text{N}^\text{1},\text{N}^\text{1}-\text{diallylsuccinamide} \) \( 3.21 \) as yellow oil (6 g, 40% yield). \(^1\text{H} \text{NMR} \) (500 MHz, CDCl₃) \( \delta \) 6.19 (br s, 1H), 5.83-5.70 (m, 2H), 5.46 (br s, 1H), 5.27-5.09 (m, 4H), 3.99 (d, \( J = 5.5 \text{ Hz} \), 2H), 3.91 (d, \( J = 4.5 \text{ Hz} \), 2H), 2.67 (t, \( J = 7.0 \text{ Hz} \), 2H), 2.58 (t, \( J = 7.0 \text{ Hz} \), 2H); \(^13\text{C} \text{NMR} \) (125 MHz, CDCl₃) \( \delta \) 27.85, 30.17, 47.62, 48.80, 116.31, 116.72, 132.31, 132.74, 171.71, 174.94 ppm; FT-IR (neat) 1680, 1632, 1405 cm⁻¹; HRMS (ESI) calcd for C₁₀H₁₇N₂O₂ 197.12845, found 197.12858 [M+H]⁺.

\[ \text{N}^\text{1},\text{N}^\text{1}-\text{diallylbutane-1,4-diamine} \, 3.22 \]. Under N₂ protection, \( \text{N}^\text{1},\text{N}^\text{1}-\text{diallylsuccinamide} \) \( 3.21 \) (1.44 g, 7.34 mmol, 1 eq.) in THF (40 ml) was added dropwise to a stirred suspension
of LAH (0.88 g, 22.02 mmol, 3 eq.) in THF (15 ml) at 0 °C. After the addition, the mixture was warmed up to room temperature and stirred overnight (16 hours), and after that the mixture was heated at reflux for another 24 hours. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.9 ml H2O, 0.9 ml 15% NaOH aqueous solution, and 2.7 ml H2O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.22 as yellow oil (720 mg). Due to the instability of the primary amine 3.22, it was carried on to next step without further purification. 1H NMR (500 MHz, CDCl3) δ 5.89-5.81 (m, 2H), 5.18-5.10 (m, 4H), 3.08 (d, J = 6.5 Hz, 4H), 2.69 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H), 1.54-1.38 (m, 4H).

1-Benzyl-3-(4-(diallylamino)butyl)urea (3.20). The procedure of synthesizing 3.6 was followed on a 4.28 mmol scale to synthesize 3.20, except 3.22 was used instead of 3.8. The crude product was chromatographically purified over silica gel (5% MeOH in CH2Cl2 with 0.5% NEt3, Rf = 0.22, Phosphomolybdic acid as the stain) to afford 1-benzyl-3-(4-(diallylamino)butyl)urea 3.20 as colorless oil (1.05 g, two-step yield 48% starting from
3.21 to 3.20. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.36-7.22 (m, 5H), 5.91-5.81 (m, 2H), 5.25-5.16 (m, 4H), 4.95 (br s, 1H), 4.77 (br s, 1H), 4.38 (d, $J$ = 5.5 Hz, 2H), 3.19 (t, $J$ = 6.0 Hz, 2H), 3.14 (d, $J$ = 6.5 Hz, 4H), 2.50 (t, $J$ = 7.0 Hz, 2H), 1.60-1.49 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 23.68, 27.87, 39.86, 44.10, 52.60, 56.27, 118.94, 126.95, 127.22, 128.41, 133.77, 139.68, 158.68 ppm; FT-IR (neat) 1634, 1563 cm$^{-1}$; HRMS (ESI) calcd for C$_{18}$H$_{28}$N$_3$O 302.22269, found 302.22325 [M+H]$^+$.  

(E)-N-methylbut-2-en-1-amine (3.23). Crotyl bromide (0.48 ml, 4 mmol) was added dropwise at 0 °C to methylamine (2M, 10 ml, 20 mmol, 5 eq.). The reaction mixture was stirred at room temperature overnight. After removal of the solvent, the white solid was taken up by 10 ml 1M NaOH aqueous solution, and the resulting mixture was extracted with diethyl ether (10 ml × 3). The combined organic layers were washed with saturated brine, and distilled at ambient pressure to afford a mixture of 3.23 and Et$_2$O (310 mg mixture, which has 2 mmol 3.23 after $^1$H NMR analysis). The mixture was carried on to next step directly without further purification. The spectroscopic data for 3.23 matched that reported in the literature.$^{47}$
3-(N-((E)-but-2-ENYL)-N-methylamino)propanamide (3.24). The above mixture of 3.23 and Et₂O (310 mg, 2 mmol 3.23) was dissolved in methanol (6 ml), and acrylamide (142 mg, 2 mmol) was added. The resulting mixture was heated at reflux for 3 hours. After removal of the solvent, the mixture was chromatographically purified over silica gel (10% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.27, Phosphomolybdic acid as the stain) to afford 3.24 as yellow oil (140 mg, 45% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.92 (br s, 1H), 5.77-5.66 (m, 1H), 5.55-5.48 (m, 1H), 5.43 (br s, 1H), 3.17 (d, J = 7 Hz, 0.5H), 3.11 (d, J = 7 Hz, 1H), 3.10 (d, J = 7 Hz, 0.5H), 3.08 (d, J = 6.5 Hz, 2H), 2.77 (t, J = 6.5 Hz, 2H), 2.52 (t, J = 6.5 Hz, 2H), 2.34 (s, 3H), 1.73 (d, J = 6.5 Hz, 2.3H), 1.67 (d, J = 6.5 Hz, 0.7H); ¹³C NMR (125 MHz, CDCl₃) δ 17.73, 32.55, 40.89, 52.56, 59.31, 126.03, 130.55, 174.95 ppm; FT-IR (neat) 1663 cm⁻¹; HRMS (ESI) calcd for C₈H₁₇N₂O 157.13354, found 157.13369 [M+H]⁺.

N¹-((E)-but-2-ENYL)-N¹-methylpropane-1,3-diamine (3.25). The procedure of synthesizing 3.8 was followed on a scale of 9.28 mmol to synthesize 3.25, except 3.24 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.75 ml H₂O, 0.75 ml 15% NaOH aqueous solution, and 2.25 ml H₂O were added
successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.25 as yellow oil (840 mg). Due to the instability of the primary amine 3.25, it was carried on to next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.62-5.55 (m, 1H), 5.52-5.46 (m, 1H), 3.00 (d, $J = 6.5$ Hz, 0.3H), 2.91 (d, $J = 6.0$ Hz, 1.7H), 2.73 (t, $J = 6.8$ Hz, 2H), 2.37 (t, $J = 7.3$ Hz, 2H), 2.19 (s, 3H), 1.69 (d, $J = 6$ Hz, 3H), 1.65-1.59 (m, 2H).

The procedure of synthesizing 3.6 was followed on a 5.91 mmol scale to synthesize 3.26, except 3.25 was used instead of 3.8. The crude product was chromatographically purified over silica gel (10% MeOH in CH$_2$Cl$_2$ with 0.5% NEt$_3$, R$_f = 0.25$, Phosphomolybdic acid as the stain) to afford 3.26 as yellow oil (1.3 g, two-step yield 51% starting from 3.24 to 3.26). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35-7.22 (m, 5H), 5.59-5.51 (m, 1H), 5.36-5.32 (m, 1H), 4.36 (d, $J = 5.5$ Hz, 2H), 3.29-3.24 (m, 2H), 2.84 (d, $J = 6.5$ Hz, 2H), 2.40 (t, $J = 6.5$ Hz, 2H), 2.09 (s, 3H), 1.70-1.60 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 17.67, 27.20, 39.28, 41.44, 44.26, 54.62, 59.48, 126.91, 127.23, 127.49, 128.35, 128.84, 139.60, 159.10 ppm; FT-IR (neat) 1632, 1568, 696 cm$^{-1}$; HRMS (ESI) calcd for C$_{16}$H$_{26}$N$_3$O 276.20704, found 276.20764 [M+H]$^+$. 

123
*N,3-dimethylbut-2-en-1-amine (3.27).* 3,3-Dimethylallyl bromide (621 mg, 0.49 ml, 4 mmol) was added dropwise at 0 °C to methylamine (2M, 10 ml, 20 mmol, 5 eq.). The reaction mixture was stirred at room temperature overnight. After removal of the solvent, the white solid was taken up by 10 ml 1M NaOH aqueous solution, and the resulting mixture was extracted with diethyl ether (10 ml × 3). The combined organic layers were washed with saturated brine, and distilled at ambient pressure to afford a mixture of 3.27 and Et₂O (430 mg mixture, which has 3.16 mmol 3.27 after ¹H NMR analysis). The mixture was carried on to next step directly without further purification. The spectroscopic data for 3.27 matched that reported in the literature.⁴₈

*3-(N-methyl-N-(3-methylbut-2-enyl)amino)propanamide (3.28).* The above mixture of 3.27 and Et₂O (430 mg, 3.16 mmol 3.27) was dissolved in methanol (9 ml), and acrylamide (224 mg, 3.16 mmol) was added. The resulting mixture was heated at reflux for 3 hours. After removal of the solvent, the mixture was chromatographically purified over silica gel (10% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.27, Phosphomolybdic acid as the stain) to
afford 3.28 as yellow oil (260 mg, 48% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.24 (br s, 1H), 5.24-5.20 (m, 1H), 5.32 (br s, 1H), 3.03 (d, $J = 7$ Hz, 2H), 2.64 (t, $J = 6.5$ Hz, 2H), 2.42 (t, $J = 6.5$ Hz, 2H), 2.25 (s, 3H), 1.75 (s, 3H), 1.65 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 17.85, 25.72, 32.59, 40.81, 52.51, 54.68, 120.05, 136.17, 175.27 ppm; FT-IR (neat) 1667 cm$^{-1}$; HRMS (ESI) calcd for C$_9$H$_{19}$N$_2$O 171.14919, found 171.14934 [M+H]$^+$. 

3.29

$N^1$-methyl-$N^1$-(3-methylbut-2-enyl)propane-1,3-diamine (3.29). The procedure of synthesizing 3.8 was followed on a scale of 5.29 mmol to synthesize 3.29, except 3.28 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.4 ml H$_2$O, 0.4 ml 15% NaOH aqueous solution, and 1.2 ml H$_2$O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.29 as yellow oil (500 mg). Due to the instability of the primary amine 3.29, it was carried on to next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.26-5.22 (m, 1H), 2.93 (d, $J = 7.0$ Hz, 2H), 2.74 (t, $J = 7.0$ Hz, 2H), 2.37 (t, $J = 7.5$ Hz, 2H), 2.19 (s, 3H), 1.73 (s, 3H), 1.65-1.59 (m, 5H).
The procedure of synthesizing 3.6 was followed on a 3.20 mmol scale to synthesize 3.30, except 3.29 was used instead of 3.8. The crude product was chromatographically purified over silica gel (10% MeOH in CH₂Cl₂ with 0.5% NEt₃, R_f = 0.21, Phosphomolybdic acid as the stain) to afford 3.30 as yellow oil (600 mg, two-step yield 39% starting from 3.28 to 3.30). ¹H NMR (500 MHz, CDCl₃) δ 7.41-7.20 (m, 5H), 5.47 (br s, 2H), 5.12-5.04 (m, 1H), 4.35 (d, J = 6.0 Hz, 2H), 3.33-3.18 (m, 2H), 2.85 (d, J = 7.0 Hz, 2H), 2.40 (t, J = 6.0 Hz, 2H), 2.08 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 17.76, 25.64, 27.35, 38.94, 41.42, 43.98, 54.75, 120.91, 126.71, 127.03, 128.19, 134.86, 139.61, 159.16 ppm; FT-IR (neat) 1632, 1568, 697 cm⁻¹; HRMS (ESI) calcd for C₁₇H₂₈N₃O₂ 290.22269, found 290.22328 [M+H]+.

3-oxo-2-aza-bicyclo[2.2.2]oct-5-ene-2-sulfonyl chloride (3.31). Under N₂ protection, a solution of cyclohexa-1,3-diene (3.49 ml, 35.48 mmol, 1.05 eq.) in chloroform (5 ml) was added to a solution of chlorosulfonyl isocyanate (3 ml, 33.78 mmol, 1 eq.) in chloroform (50 ml) at room temperature over 10 minutes, then the mixture was stirred at room
temperature for 3.5 hours. After that, the mixture was heated at reflux for 17 hours. The resulting red solution was filtered to remove a small amount of polymeric material and the filtrate was evaporated yielding $3.31$ as red oil (5.28 g, yield 70%) which was carried on to next step without further purification. The spectroscopic data for $3.31$ matched that reported in the literature.  

![3.32](image)

**2-azabicyclo[2.2.2]oct- 5-en-3-one (3.32).** A solution of $N$-chlorosulfonyl lactam $3.31$ (1.99 g, 8.98 mmol) in acetone (5 ml), and 2M NaOH aqueous solution were added simultaneously drop by drop to a stirred 1:1 mixture of acetone and saturated NaCl solution (20 ml), maintaining the reaction mixture at pH 6-7. After the addition, the mixture was stirred at room temperature overnight. The mixture was extracted with CH$_2$Cl$_2$ (25 ml × 4). The combined organic layers were washed with saturated brine, dried over Na$_2$SO$_4$, filtered, concentrated. The crude product was chromatographically purified over silica gel (Et$_2$O: MeOH = 20: 1 with 0.1% NEt$_3$, $R_f = 0.29$, Phosphomolybdic acid as the stain) to afford $3.32$ as white solid (400 mg, 36% yield). The spectroscopic data for $3.32$ matched that reported in the literature.
6-aza-bicyclo[2.2.2]oct-2-ene (3.33). The procedure of synthesizing 3.8 was followed on a scale of 2.84 mmol to synthesize 3.33, except 3.32 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.2 ml H₂O, 0.2 ml 15% NaOH aqueous solution, and 0.6 ml H₂O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.33 as yellow oil (210 mg), and it was carried on to next step without further purification. The spectroscopic data for 3.33 matched that reported in the literature.⁴⁹

3-(2-aza-bicyclo[2.2.2]oct-5-en-2-yl)propanamide (3.34). The mixture of 3.33 (800 mg, 7.33 mmol, 1 eq.) and acrylamide (469 mg, 6.60 mmol, 0.9 eq.) in methanol (20 ml) was heated at reflux for 3 hours. After removal of the solvent, the crude product was chromatographically purified over silica gel (20% MeOH in CH₂Cl₂ with 0.2% NEt₃, Rₜ =
0.21, Phosphomolybdic acid as the stain) to afford 3.34 as white solid (1.02 g, yield 86%, m.p. 70-73 °C). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.56 (br s, 1H), 6.49-6.43 (m, 1H), 6.31-6.26 (m, 1H), 5.28 (br s, 1H), 3.47 (br s, 1H), 3.07 (d, $J = 9$ Hz, 1H), 2.85-2.80 (m, 1H), 2.60 (br s, 1H), 2.53-2.48 (m, 1H), 2.40-2.33 (m, 2H), 2.06-1.93 (m, 2H), 1.61-1.55 (m, 1H), 1.42-1.34 (m, 1H), 1.32-1.26 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 21.55, 26.51, 30.28, 32.77, 52.07, 53.53, 54.07, 130.85, 133.55, 175.92 ppm; FT-IR (neat) 1671, 1637, 704 cm$^{-1}$; HRMS (ESI) calcd for C$_{10}$H$_{17}$N$_2$O 181.13354, found 181.13380 [M+H]$^+$. 

![3.35](image)

3-(2-aza-bicyclo[2.2.2]oct-5-en-2-yl)propan-1-amine (3.35). The procedure of synthesizing 3.8 was followed on a scale of 4.22 mmol to synthesize 3.35, except 3.34 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.3 ml H$_2$O, 0.3 ml 15% NaOH aqueous solution, and 0.9 ml H$_2$O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.35 as yellow oil (500 mg). Due to the instability of the primary amine 3.35, it was carried on to next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.38-6.35 (m, 1H), 6.25-6.22 (m, 1H), 3.37 (br s, 1H), 2.98 (dd, $J = 9.5$ Hz, 2 Hz, 1H), 2.71 (t, $J = 6.8$ Hz, 2H), 2.56-2.45 (m, 2H), 2.27-
2.21 (m, 1H), 1.97 (t, J = 2.7 Hz, 1H), 1.96 (t, J = 2.5 Hz, 1H), 1.65-1.51 (m, 2H), 1.34-1.18 (m, 3H).

1-(3-(2-aza-bicyclo[2.2.2]oct-5-en-2-yl)propyl)-3-benzy lurea (3.36). The procedure of synthesizing 3.6 was followed on a 3.0 mmol scale to synthesize 3.36, except 3.35 was used instead of 3.8. The crude product was chromatographically purified over silica gel (30% MeOH in CH₂Cl₂ with 0.2% NEt₃, Rₑ = 0.14, Phosphomolybdic acid as the stain) to afford 3.36 as yellow oil (750 mg, two-step yield 59% starting from 3.34 to 3.36). ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.24 (m, 5H), 6.37-6.35 (m, 1H), 6.21-6.18 (m, 1H), 4.40 (q, J = 6 Hz, 2H), 3.32-3.21 (m, 3H), 2.84 (dd, J = 10 Hz, 2 Hz, 1H), 2.54 (quintet, 1H), 2.47 (s, br, 1H), 2.32 (quintet, 1H), 1.94 (dt, J = 9.5 Hz, 2.5 Hz, 1H), 1.85-1.75 (m, 1H), 1.64-1.54 (m, 2H), 1.44-1.33 (m, 1H), 1.30-1.13 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 21.97, 26.25, 27.61, 30.46, 39.61, 44.41, 51.81, 54.67, 126.99, 127.27, 128.42, 131.32, 133.45, 139.79, 159.28 ppm; FT-IR (neat) 1638, 1564, 696 cm⁻¹; HRMS (ESI) calcd for C₁₈H₂₆N₃O 300.20704, found 300.20759 [M+H]⁺.
Ethyl 5,6-dihydropyridine-1(2H)-carboxylate (3.37). Under N₂ protection, benzyl tetrahydropyridine 2.7 (5.1 g, 5 ml, 30 mmol, 1 eq.) and ethyl chloroformate (3.56 g, 3.2 ml, 32.5 mmol, 1.1 eq.) in benzene (75 ml) were heated at reflux for 1 hour. After the reaction was complete, 70 ml H₂O was added, and the mixture was stirred at room temperature for 1 hour. The mixture was extracted with EtOAc (100 ml × 3). The combined organic layers were washed with saturated NaCl solution (100 ml), dried over Na₂SO₄, filtered, and concentrated to crude product, which was further chromatographically purified over silica gel (10% ethyl acetate in hexane with 0.5% NEt₃, Rₕ = 0.33, Phosphomolybdic acid as the stain) to afford 3.37 as colorless oil (3.60 g, 79%). The spectroscopic data for 3.37 matched that reported in the literature.⁵⁰

1,2,3,6-tetrahydropyridine (3.38). A solution of 3.37 (3 g, 19.33 mmol, 1 eq.), KOH (28 g, 502.61 mmol, 26 eq.) and 35% NH₂NH₂ ∙xH₂O (8.85 g, 8.67 ml, 96.66 mmol, 5 eq.) in ethylene glycol (140 ml) was refluxed for 1.5 hours. After cooling to room temperature, the mixture was poured into water (140 ml), and the mixture was extracted with ether (200
ml × 3). The combined organic layers were dried over Na₂SO₄, filtered, concentrated under atmospheric pressure to afford 3.38 as yellow oil (1.45 g), which was carried on to next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.83-5.77 (m, 1H), 5.74-5.69 (m, 1H), 3.33-3.31 (m, 2H), 2.96 (t, J = 5.8 Hz, 2H), 2.10-2.05 (m, 2H).

![3.39](image)

3-(5,6-dihydropyridin-1(2H)-yl)propanamide (3.39). A solution of 3.38 (1.45 g, 17.40 mmol, 1 eq.) and acrylamide (1.11 g, 15.66 mmol, 0.9 eq.) in methanol (50 ml) was refluxed for 3 hours. After removal of the solvent, the crude product was chromatographically purified over silica gel (10% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.28, Phosphomolybdic acid as the stain) to afford 3.39 as colorless oil (3.16 g, 100%). ¹H NMR (500 MHz, CDCl₃) δ 8.21 (br s, 1H), 5.80-5.74 (m, 1H), 5.69-5.64 (m, 1H), 5.37 (br s, 1H), 3.02 (quintet, 2H), 2.70 (t, J = 6 Hz, 2H), 2.63 (t, J = 5.8 Hz, 2H), 2.44 (t, J = 6 Hz, 2H), 2.23-2.17 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 25.91, 32.17, 49.19, 52.07, 53.68, 124.63, 125.20, 175.20 ppm; FT-IR (neat) 1662, 1622 cm⁻¹; HRMS (ESI) calcd for C₈H₁₅N₂O 155.11789, found 155.11775 [M+H]⁺.
3-(5,6-dihydropyridin-1(2H)-yl)propan-1-amine (3.40). The procedure of synthesizing 3.8 was followed on a scale of 7.1 mmol to synthesize 3.40, except 3.39 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.6 ml H₂O, 0.6 ml 15% NaOH aqueous solution, and 1.8 ml H₂O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.40 as yellow oil (520 mg). Due to the instability of the primary amine 3.40, it was carried on to next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.80-5.72 (m, 1H), 5.71-5.64 (m, 1H), 2.97-2.94 (m, 2H), 2.76 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 5.8 Hz, 2H), 2.46 (t, J = 7.5 Hz, 2H), 2.20-2.15 (m, 2H), 1.69 (quintet, 2H).

1-benzyl-3-(3-(5,6-dihydropyridin-1(2H)-yl)propyl)urea (3.41). The procedure of synthesizing 3.6 was followed on a 3.71 mmol scale to synthesize 3.41, except 3.40 was used instead of 3.8. The crude product was chromatographically purified over silica gel
(10% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rᵣ = 0.29, Phosphomolybdic acid as the stain) to afford 3.41 as yellow oil (550 mg, two-step yield 28% starting from 3.39 to 3.41). ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.21 (m, 5H), 6.24 (br s, 1H), 6.11 (br s, 1H), 5.82-5.76 (m, 1H), 5.62-5.57 (m, 1H), 4.33 (d, J = 6 Hz, 2H), 3.36-3.27 (m, 2H), 3.19-3.11 (m, 2H), 2.79-2.67 (m, 4H), 2.29-2.18 (m, 2H), 1.89-1.75 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 23.96, 25.93, 37.55, 43.72, 48.98, 51.00, 54.31, 122.26, 125.16, 126.65, 126.95, 128.20, 139.89, 159.63 ppm; FT-IR (neat) 1639, 1558, 1254 cm⁻¹; HRMS (ESI) calcd for C₁₆H₂₄N₃O 274.19139, found 274.19194 [M+H]⁺.

1,2,8,8a-tetrahydroindolizine-3(5H)-thione (3.42). Under N₂ protection, a solution of 1,2,8,8a-tetrahydroindolizin-3(5H)-one 2.35 (0.13 g, 0.95 mmol, 1 eq.) and Lawesson’s reagent (198 mg, 0.47 mmol, 0.5 eq.) in CH₂Cl₂ (2 ml) was stirred at room temperature for 2 hours. After removal of the solvent, the crude product was chromatographically purified over silica gel (first washing the column with CH₂Cl₂, then with 20% ethyl acetate in hexane with 0.1% NEt₃, Rᵣ = 0.25, UV light) to afford thioamide 3.42 as yellow oil (140 mg, 97% yield). ¹H NMR (500 MHz, CDCl₃) δ 5.93-5.76 (m, 2H), 4.78 (d, J = 20 Hz, 1H), 3.99-3.89 (m, 1H), 3.77 (d, J = 20 Hz, 1H), 3.21-2.91 (m, 2H), 2.60-2.33 (m, 2H), 2.18-2.06 (m, 1H), 1.81-1.72 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 26.79, 32.05, 42.51, 45.20,
(2E)-ethyl 2-(1,2,8a-tetrahydroindolizin-3(5H)-ylidene)acetate (3.43). Under \( \text{N}_2 \) protection, a solution of thioamide 3.42 (1.1 g, 7.2 mmol, 1 eq.), NaI (1.18 g, 7.9 mmol, 1.1 eq.) and ethyl bromoacetate (2.08 g, 1.4 ml, 12.2 mmol, 1.7 eq.) in \( \text{CH}_3\text{CN} \) (21 ml) were stirred at room temperature for 18 hours. After that, PPh\(_3\) (3.8 g, 14.36 mmol, 2 eq.) and NEt\(_3\) (1.47 g, 2.02 ml, 14.26 mmol, 2 eq.) were added in this order, and the resulting mixture was stirred at room temperature for another 24 hours. After removal of the solvent, the residue was chromatographically purified over silica gel (first washing the column with 10% ethyl acetate in hexane, then 20% ethyl acetate in hexane) to afford 3.43 as yellow oil (900 mg, 60% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.89-5.82 (m, 1H), 5.76-5.70 (m, 1H), 4.52 (s, 1H), 4.10 (q, \( J = 7.5 \) Hz, 2H), 3.82-3.73 (m, 1H), 3.55-3.35 (m, 3H), 2.91-2.79 (m, 1H), 2.44-2.34 (m, 1H), 2.29-2.20 (m, 1H), 2.05-1.95 (m, 1H), 1.57-1.47 (m, 1H), 1.26 (t, \( J = 7.5 \) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 14.51, 28.47, 30.63, 31.97, 43.52, 56.96, 58.03, 78.85, 122.47, 124.25, 164.54, 168.98 ppm; FT-IR (neat) 1674, 1597, 1134 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{12}\)H\(_{18}\)NO\(_2\) 208.13321, found 208.13344 [M+H]^+.
Ethyl 2-((3S,8aR)-1,2,3,5,8,8a-hexahydroindolizin-3-yl)acetate (3.44). Under N₂ protection, to a solution of 3.43 (530 mg, 2.55 mmol, 1 eq.), NaBH₃CN (1M in THF, 3.83 ml, 3.83 mmol, 1.5 eq.) and bromocresol green (5.3 mg, 1wt%) in CH₃CN (24 ml) was added dropwise a methanolic solution of HCl (1M). The addition was stopped when the solution turned yellow. The reaction was stirred at room temperature for 30 minutes. After that, 50 ml CH₂Cl₂, 10 ml saturated Na₂CO₃, and 50 ml H₂O were added successively into the reaction mixture, and the organic layer was collected. The aqueous layer was extracted with CH₂Cl₂ (50 ml × 2). All the organic layers were combined, washed with saturated brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was chromatographically purified over silica gel (20% ethyl acetate in hexane with 0.1% NEt₃, Rₚ = 0.19, I₂ as the stain) to afford 3.44 as yellow oil (380 mg, 71% yield). ¹H NMR (500 MHz, CDCl₃) δ 5.79-5.69 (m, 2H), 4.14 (q, J = 7 Hz , 2H), 3.48-3.40 (m, 1H), 2.80-2.60 (m, 3H), 2.41-2.20 (m, 3H), 2.10-1.90 (m, 3H), 1.57-1.37 (m, 2H), 1.26 (t, J = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 14.07, 28.66, 29.25, 32.69, 39.16, 51.12, 59.95, 60.11, 61.93, 124.92, 125.15, 172.08 ppm; FT-IR (neat) 1732, 1128, 660 cm⁻¹; HRMS (ESI) calcd for C₁₂H₂₀NO₂ 210.14886, found 210.14926 [M+H]⁺.
2-((3S,8aR)-1,2,3,5,8,8a-hexahydroindolizin-3-yl)acetamide (3.45). A solution of 3.44 (110 mg, 0.52 mmol, 1 eq.) and concentrated NH₃ H₂O (0.65 ml, 16.82 mmol, 32 eq.) in methanol (2 ml) was stirred at room temperature for 3 days to completion. After the solvent was removed, 2M NaOH solution (2 ml), H₂O (2 ml) were added to the residue. The mixture was extracted with CH₂Cl₂ (3 ml × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford 3.45 as white solid (90 mg, 96% yield, m.p. 119-120 °C). The white solid was pure enough for immediate spectroscopic characterization. ¹H NMR (500 MHz, CDCl₃) δ 8.15 (br s, 1H), 5.79-5.69 (m, 2H), 5.32 (br s, 1H), 3.56-3.46 (m, 1H), 2.75-2.67 (m, 1H), 2.66-2.60 (m, 2H), 2.42-2.34 (m, 2H), 2.32-2.26 (m, 1H), 2.05-1.92 (m, 3H), 1.71-1.64 (m, 1H), 1.49-1.38 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 26.95, 29.48, 32.51, 36.95, 50.37, 59.92, 61.61, 124.56, 124.96, 174.26 ppm; FT-IR (neat) 1678, 1408, 1123 cm⁻¹; HRMS (ESI) calcd for C₁₀H₁₇N₂O 181.13354, found 181.13371 [M+H]⁺.
2-((3S,8aR)-1,2,3,5,8,8a-hexahydroindolizin-3-yl)ethanamine (3.46). The procedure of synthesizing 3.8 was followed on a scale of 2.89 mmol to synthesize 3.46, except 3.45 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.23 ml H₂O, 0.23 ml 15% NaOH aqueous solution, and 0.7 ml H₂O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.46 as yellow oil (450 mg). Due to the instability of the primary amine 3.46, it was carried on to next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.77-5.68 (m, 2H), 3.53 (dt, J = 16 Hz, 3 Hz, 1H), 2.84-2.77 (m, 1H), 2.73-2.62 (m, 2H), 2.30-2.20 (m, 3H), 2.07-1.83 (m, 4H), 1.52-1.37 (m, 3H).

1-benzyl-3-((3S,8aR)-1,2,3,5,8,8a-hexahydroindolizin-3-yl)ethyl)urea (3.47). The procedure of synthesizing 3.6 was followed on a 2.71 mmol scale to synthesize 3.47, except 3.46 was used instead of 3.8. The crude product was chromatographically purified over silica gel (10% MeOH in CHCl₃ with 0.5% NEt₃, Rf = 0.24, Phosphomolybdic acid as the stain) to afford 3.47 as yellow solid (600 mg, 74% yield, m.p. 110-112 °C). ¹H NMR (500
(Z)-2,3,4,7-tetrahydro-1H-azepine (3.48). A solution of 2.11 (1.4 g, 7.0 mmol, 1 eq.), KOH (10.13 g, 180.87 mmol, 26 eq.) and 35% NH₂NH₂ xH₂O (3.18 g, 3.1 ml, 34.79 mmol, 5 eq.) in ethylene glycol (50 ml) was refluxed for 1.5 hours. After cooling to room temperature, the mixture was poured into water (140 ml), and the mixture was extracted with ether (180 ml × 3). The combined organic layers were dried over Na₂SO₄, filtered, concentrated under atmospheric pressure to afford 3.48 as yellow oil (1.13 g mixture of 3.48 and Et₂O), which was carried on to next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.85-5.75 (m, 2H), 3.35-3.33 (m, 2H), 3.01 (t, J = 5.8 Hz, 2H), 2.28-2.22 (m, 2H), 1.73-1.68 (m, 2H).
3-((Z)-3,4-dihydro-2H-azepin-1(7H)-yl)propanamide (3.49). A solution of above 3.48 mixture (1.13 g mixture of 3.48 and Et₂O), acrylamide (410 mg, 5.78 mmol) in methanol (18 ml) was heated at reflux for 3 hours. After removal of the solvent, the mixture was chromatographically purified over silica gel (10% MeOH in CH₂Cl₂ with 0.5% NEt₃) to afford 3.49 as yellow oil (800 mg).

3-((Z)-3,4-dihydro-2H-azepin-1(7H)-yl)propan-1-amine (3.50). The procedure of synthesizing 3.8 was followed on a scale of 4.76 mmol to synthesize 3.50, except 3.49 was used instead of 3.7. After the reaction was complete, the reaction mixture was cooled to 0 °C, and 0.4 ml H₂O, 0.4 ml 15% NaOH aqueous solution, and 1.2 ml H₂O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with THF. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.50 as yellow oil (440 mg). Due to the
instability of the primary amine 3.50, it was carried on to next step without further purification.

1-benzyl-3-((Z)-3,4-dihydro-2H-azepin-1(7H)-yl)propylurea (3.51). The procedure of synthesizing 3.6 was followed on a 2.85 mmol scale to synthesize 3.51, except 3.50 was used instead of 3.8. The crude product was chromatographically purified over silica gel (10% MeOH in CH₂Cl₂ with 0.5% NEt₃, Rₚ=, Phosphomolybdic acid as the stain) to afford 3.51 as yellow oil (530 mg, four-step yield 27% starting from 2.11 to 3.51).

1-(diallylamino)cyclohexanecarbonitrile (3.52). To a mixture solution of EtOH/H₂O (1:1, 14 ml) was added diallylamine (0.95 ml, 7.47 mmol, 1.1 eq.), 2M HCl aqueous solution (3.8 ml, 1.1 eq.), cyclohexanone (0.7 ml, 6.79 mmol, 1 eq.) and KCN (484 mg, 7.47 mmol, 1.1 eq.) in that order. The resulting mixture was stirred at room temperature overnight. The mixture was extracted with Et₂O (20 ml × 3). The combined organic layers were dried over
Na₂SO₄, filtered, and concentrated to give 3.52 as yellow oil (870 mg). Due to the instability of 3.52, it was carried on to next step without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.94-5.86 (m, 2H), 5.22-5.12 (m, 4H), 3.35 (d, J = 6 Hz, 4H), 2.25-2.07 (m, 2H), 1.84-1.47 (m, 6H), 1.32-1.17 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.51, 24.87, 35.41, 51.70, 60.85, 117.15, 121.31, 135.50 ppm; FT-IR (neat) 2937, 2218, 1642, 918 cm⁻¹.

![Image of 3.53](image)

N,N-diallyl-1-(aminomethyl)cyclohexanamine (3.53). Under N₂ protection, 3.52 (870 mg, 4.26 mmol, 1 eq.) in Et₂O (15 ml) was added dropwise to LAH (558 mg, 14.26 mmol, 3.35 eq.) suspension in Et₂O (5 ml) at 0 °C. After the addition, the mixture was warmed up to room temperature first, then was refluxed overnight. After the mixture was cooled to 0 °C, 0.56 ml H₂O, 0.56 ml 15% NaOH aqueous solution, and 1.68 ml H₂O were added successively, and the mixture was stirred at room temperature for 3 hours to form milky suspension. The suspension was filtered, and white solid left on the top of the filter was washed with Et₂O. The yellow filtrate was concentrated in vacuo at room temperature (keeping the temperature below 30 °C) to afford 3.53 as colorless oil (800 mg). Due to the instability of the primary amine 3.53, it was carried on to next step without further
puriﬁcation. $^1$H NMR (500 MHz, CDCl₃) δ 5.88-5.80 (m, 2H), 5.12-5.00 (m, 4H), 3.25 (d, $J$ = 6.5 Hz, 4H), 2.70 (s, 2H), 1.93-1.23 (m, 10H).

![Image](image_url)

**1-((1-(Diallylamino)cyclohexyl)methyl)urea (3.54).** The procedure of synthesizing 3.6 was followed on a 3.70 mmol scale to synthesize 3.54, except 3.53 was used instead of 3.8. The crude product was chromatographically puriﬁed over silica gel (30% ethyl acetate in hexane with 0.2% NEt₃, Rf = 0.11, UV light or I₂) to afford 3.54 as colorless oil (410 mg, two-step yield 18% starting from cyclohexanone to 3.54). $^1$H NMR (500 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 5.75-5.66 (m, 2H), 5.09 (br s, 1H), 5.07-4.98 (m, 4H), 4.90 (br s, 1H), 4.34 (d, $J$ = 6.0 Hz, 2H), 3.28 (d, $J$ = 4.5 Hz, 2H), 3.16 (d, $J$ = 6.0 Hz, 4H), 1.61-1.53 (m, 3H), 1.47-1.43 (m, 4H), 1.41-1.31 (m, 2H), 1.20-1.07 (m, 1H); $^{13}$C NMR (125 MHz, CDCl₃) δ 22.46, 25.79, 30.78, 42.05, 44.80, 49.62, 59.51, 115.55, 127.27, 127.32, 128.60, 138.10, 139.17, 158.39 ppm; FT-IR (neat) 1628, 1558 cm⁻¹; HRMS (ESI) calcd for C₂₁H₃₂N₃O 342.25399, found 342.25446 [M+H]⁺.
1,5-diallylpyrrolidine-2-thione (3.55). Under N₂ protection, a solution of 1,5-diallylpyrrolidin-2-one 2.34 (1.44 g, 8.7 mmol, 1 eq.) and Lawesson’s reagent (1.82 g, 4.4 mmol, 0.5 eq.) in CH₂Cl₂ (25 ml) was stirred at room temperature for 4 hours. After removal of the solvent, the crude product was chromatographically purified over silica gel (10% ethyl acetate in hexane with 0.2% NEt₃, Rᵣ = 0.26, UV light) to afford 3.55 as colorless oil (1 g, yield 63%). ¹H NMR (500 MHz, CDCl₃) δ 5.88-5.78 (m, 1H), 5.73-5.62 (m, 1H), 5.30-5.24 (m, 2H), 5.21-5.14 (m, 2H), 5.03-4.97 (m, 1H), 4.00 (septet, 1H), 3.91 (dd, J = 15 Hz, 6.5 Hz, 1H), 3.10-2.93 (m, 2H), 2.51-2.45 (m, 1H), 2.32-2.24 (m, 1H), 2.20-2.11 (m, 1H), 1.89-1.80 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 24.75, 36.67, 43.22, 48.18, 64.51, 118.82, 119.15, 130.57, 132.04, 201.66 ppm; FT-IR (neat) 2916, 1643, 481 cm⁻¹; HRMS (ESI) calcd for C₁₀H₁₆NS 182.09980, found 182.10000 [M+H]⁺.

(E)-ethyl 2-(1,5-diallylpyrrolidin-2-ylidene)acetate (3.56). Under N₂ protection, a solution of thioamide 3.55 (180 mg, 1 mmol, 1 eq.), NaI (164 mg, 1.1 mmol, 1.1 eq.) and
ethyl bromoacetate (288 mg, 0.19 ml, 1.69 mmol, 1.7 eq.) in CH₃CN (4 ml) were stirred at room temperature for 24 hours. Then solvent was removed, and fresh CH₃CN (4 ml) was added, PPh₃ (526 mg, 2.0 mmol, 2 eq.) and NEt₃ (203 mg, 0.28 ml, 2.0 mmol, 2 eq.) were added in this order, and the resulting mixture was stirred at room temperature for another 24 hours. After removal of the solvent, the residue was chromatographically purified over silica gel (10% ethyl acetate in hexane with 0.2% NEt₃, Rₐ = 0.21, UV light) to afford **3.56** as yellow oil (230 mg, 98% yield). ¹H NMR (500 MHz, CDCl₃) δ 5.84-5.63 (m, 2H), 5.22-5.03 (m, 4H), 4.53 (s, 1H), 4.08 (q, J = 7.9 Hz, 2H), 3.89-3.81 (m, 1H), 3.78-3.69 (m, 1H), 3.65-3.60 (m, 1H), 3.20-3.06 (m, 2H), 2.43-2.35 (m, 1H), 2.20-2.02 (m, 2H), 1.78-1.69 (m, 1H), 1.24 (t, J = 7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 14.65, 26.28, 30.78, 37.60, 46.94, 58.19, 62.74, 117.10, 118.15, 131.43, 133.39, 165.00, 169.32 ppm; FT-IR (neat) 1681, 1585, 1129 cm⁻¹; HRMS (ESI) calcd for C₁₄H₂₂NO₂ 236.16451, found 236.16506 [M+H]⁺.

**Ethyl 2-(1,5-diallylpyrrolidin-2-yl)acetate (3.57).** Under N₂ protection, to a solution of **3.56** (2.73 g, 11.60 mmol, 1 eq.), NaBH₃CN (1M in THF, 17.4 ml, 17.4 mmol, 1.5 eq.) and bromocresol green (27 mg, 1wt%) in CH₃CN (116 ml) was added dropwise a methanolic solution of HCl (1M). The addition was stopped (ca. 20 ml) when the solution became
yellow. The reaction was stirred at room temperature for 30 minutes. After that, 250 ml CH₂Cl₂, 100 ml saturated Na₂CO₃, and 250 ml H₂O were added successively into the reaction mixture, and the organic layer was collected. The aqueous layer was extracted with CH₂Cl₂ (250 ml × 2). All the organic layers were combined, washed with saturated brine, dried over Na₂SO₄, filtered, and concentrated afford crude 3.57 as yellow oil (2.87 g). The crude product has two isomers, and it was carried onto next step without separation of the two isomers. But the spectroscopic data for the major isomer (>90%) is as followed: ¹H NMR (500 MHz, CDCl₃) δ 5.95-5.85 (m, 1H), 5.82-5.74 (m, 1H), 5.20-4.98 (m, 4H), 4.11 (q, J = 7.5 Hz, 2H), 3.29-3.25 (m, 2H), 3.11-3.06 (m, 1H), 2.74-2.69 (m, 1H), 2.60 (dd, J = 15 Hz, 4.5 Hz, 1H), 2.35-2.31 (m, 1H), 2.23 (q, J = 9 Hz, 1H), 2.02-1.97 (m, 1H), 1.93-1.87 (m, 1H), 1.81-1.76 (m, 1H), 1.54-1.43 (m, 2H), 1.25 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 14.20, 28.84, 29.68, 39.81, 41.06, 54.84, 60.06, 60.44, 63.16, 116.03, 116.83, 135.60, 136.07, 172.31 ppm; FT-IR (neat) 1734, 913 cm⁻¹; HRMS (ESI) calcd for C₁₄H₂₄NO₂ 238.18016, found 238.18065 [M+H]⁺.

**Ethyl 2-((3R,8aR)-1,2,3,5,8,8a-hexahydroindolizin-3-yl)acetate (3.58).** Under N₂ protection, Grubbs’ 2nd generation catalyst (178 mg, 0.21 mmol, 0.02 eq.) in degassed CH₂Cl₂ (40 ml) was added to a degassed solution of 3.57 (2.49 g, 10.49 mmol, 1 eq.) and
$p$-TsOH (1.81 g, 10.49 mmol, 1 eq.) in CH$_2$Cl$_2$ (270 ml). The mixture was heated at reflux for 20 hours. After removal of the solvent, 220 ml saturated NaHCO$_3$ aqueous solution was added, and the resulting mixture was extracted with EtOAc (180 ml × 3). The combined organic layers were washed with saturated brine, dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was chromatographically purified over silica gel (20% ethyl acetate in hexane with 0.2% NEt$_3$) to afford the major isomer 3.44 as yellow oil (1.38 g, $R_f = 0.21$, yield 63%) and 3.58 (200 mg, $R_f = 0.15$, yield 9%). The spectroscopic data for 3.58 is as followed: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.78-5.67 (m, 2H), 4.14 (q, $J = 7$ Hz, 2H), 3.70-3.60 (m, 1H), 3.30-3.23 (m, 2H), 2.86-2.77 (m, 1H), 2.60 (dd, $J = 14.5$ Hz, 5 Hz, 1H), 2.21-1.92 (m, 5H), 1.63-1.54 (m, 1H), 1.51-1.42 (m, 1H), 1.26 (t, $J = 7$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.21, 28.33, 29.60, 31.48, 35.31, 45.93, 54.62, 57.51, 60.35, 124.97, 125.17, 172.78 ppm; FT-IR (neat) 1732, 1180, 660 cm$^{-1}$; HRMS (ESI) calcd for C$_{12}$H$_{20}$NO$_2$ 210.14886, found 210.14919 [M+H]$^+$.

**Experimental Procedure for Cationic 1,3-Diaza-Claisen Rearrangement**

**General procedure:** Under N$_2$ protection, to a solution of urea in benzene (1.0 eq, 0.3 M in benzene), was added NEt$_3$ (1.0 eq), and followed by $p$-TsCl (1.2 eq). The resulting mixture was heated at reflux for 48 hours. After the reaction mixture was cooled down to room temperature, the solvent was removed under reduced pressure. The residue was taken up by CH$_2$Cl$_2$ and 1M NaOH solution. The aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated. The crude
product was chromatographically purified over silica gel to afford guanidine compounds.

![Diagram](image)

**N,N,N-1-diallyl-N-benzyl-1,4,5,6-tetrahydropyrimidin-2-amine (3.4).** The general procedure for the cationic rearrangement was adapted using 1-(3-(diallylamino)propyl)-3-benzylurea 3.6 (270 mg, 0.94 mmol, 1.0 eq.), 3.6 (270 mg, 0.94 mmol, 1.0 eq.), p-TsCl (218 mg, 1.13 mmol, 1.2 eq.), NEt₃ (96 mg, 0.94 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (first using 5% MeOH in CH₂Cl₂ with 0.5% NEt₃, then 20% MeOH in CH₂Cl₂ with 2% NH₃·H₂O, Rᶠ = 0.15 in the latter solvent system, UV light) to give guanidine 3.4 as yellow oil (200 mg, 79% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.30-7.20 (m, 5H), 5.86-5.75 (m, 2H), 5.25-5.04 (m, 4H), 4.19 (s, 2H), 3.82 (dt, J = 5.5 Hz, 1.5 Hz, 2H), 3.50 (d, J = 6.5 Hz, 2H), 3.39 (t, J = 6 Hz, 2H), 3.08 (t, J = 5.5 Hz, 2H), 1.72-1.68 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 21.76, 44.66, 45.47, 51.09, 51.52, 53.69, 116.36, 117.01, 126.42, 127.93, 128.03, 134.18, 134.49, 138.81, 157.10 ppm; FT-IR (neat) 1615 cm⁻¹; HRMS (ESI) calcd for C₁₇H₂₄N₃ 270.19647, found 270.19717 [M+H]⁺.
(7Z)-10-benzyl-2,3,4,6,9,10-hexahydropyrimido[1,2-a][1,3]diazepine (3.9). Under N₂ protection, to a stirred solution of guanidine 3.4 (130 mg, 0.48 mmol, 1 eq.) in CH₂Cl₂ (dry, 16 ml) at room temperature was added p-TsOH (249 mg, 1.45 mmol, 3 eq.). The resulting mixture was heated at reflux for 30 minutes, then Grubbs’ 2nd generation catalyst (20 mg, 0.024 mmol, 5 mol%) in CH₂Cl₂ (dry, 8 ml) was transferred to the reaction mixture, and the resulting mixture was continued to heat at reflux for further 7 hours. After the mixture was cooled down to room temperature, 50 ml 1M NaOH aqueous solution was added, and the mixture was extracted with CH₂Cl₂ (25 ml × 3). The combined organic layers were washed with 20 ml 1M NaOH, brine (60 ml), dried over Na₂SO₄, and concentrated. The residue was chromatographically purified over silica gel (20% MeOH in CH₂Cl₂ with 2% NH₃ H₂O, Rᵣ = 0.14, UV light) to afford 3.9 as brown oil (110 mg, 95% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.20 (m, 5H), 5.80-5.74 (m, 1H), 5.55-5.50 (m, 1H), 4.29 (s, 2H), 3.85-3.82 (m, 2H), 3.48-3.45 (m, 2H), 3.39 (t, J = 5.5 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H), 1.85-1.80 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 23.19, 44.00, 49.47, 50.77, 51.15, 54.47, 125.94, 126.68, 127.86, 128.26, 128.74, 139.38, 160.11 ppm; FT-IR (neat) 1614 cm⁻¹; HRMS (ESI) calcd for C₁₅H₂₀N₃ 242.16517, found 242.16571 [M+H]+.
N-(4-methoxybenzyl)-N,1-diallyl-1,4,5,6-tetrahydropyrimidin-2-amine (3.66). The general procedure for the cationic rearrangement was adapted using 1-(3-(diallylamino)propyl)-3-(4-methoxybenzyl)urea 3.16 (140 mg, 0.44 mmol, 1.0 eq.), p-TsCl (102 mg, 0.53 mmol, 1.2 eq.), NEt₃ (45 mg, 0.44 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (first using 5% MeOH in CH₂Cl₂ with 0.5% NEt₃, then 20% MeOH in CH₂Cl₂ with 2% NH₃ H₂O, Rₚ = 0.14 in the latter solvent system, UV light) to give guanidine 3.66 as yellow oil (90 mg, 68% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.18-7.15 (m, 2H), 6.84-6.81 (m, 2H), 5.85-5.75 (m, 2H), 5.22-5.05 (m, 4H), 4.11 (s, 2H), 3.81 (dt, J = 5.5 Hz, 1.5 Hz, 2H), 3.79 (s, 3H), 3.48 (d, J = 6.0 Hz, 2H), 3.39 (t, J = 6.3 Hz, 2H), 3.08 (t, J = 5.8 Hz, 2H), 1.70 (quintet, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 22.02, 44.98, 45.68, 51.02, 51.13, 53.94, 55.19, 113.56, 116.51, 117.07, 129.48, 130.99, 134.59, 134.86, 157.31, 158.42 ppm; FT-IR (neat) 1612 cm⁻¹; HRMS (ESI) calcd for C₁₈H₂₆N₃O 300.20704, found 300.20703 [M+H]⁺.

N-(4-fluorobenzyl)-N,1-diallyl-1,4,5,6-tetrahydropyrimidin-2-amine (3.67). The general procedure for the cationic rearrangement was adapted using 1-(3-(diallylamino)propyl)-3-(4-fluorobenzyl)urea 3.15 (360 mg, 1.18 mmol, 1.0 eq.), p-TsCl (272 mg, 1.41 mmol, 1.2 eq.), NEt₃ (120 mg, 1.18 mmol, 1.0 eq.). The crude product was
chromatographically purified over silica gel (first using 5% MeOH in CH$_2$Cl$_2$ with 0.5% NEt$_3$, then 20% MeOH in CH$_2$Cl$_2$ with 2% NH$_3$ H$_2$O, $R_f$ = 0.15 in the latter solvent system, UV light) to give guanidine 3.67 as yellow oil (220 mg, 66% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.23-7.19 (m, 2H), 6.99-6.94 (m, 2H), 5.86-5.73 (m, 2H), 5.22-5.05 (m, 4H), 4.14 (s, 2H), 3.80 (dt, $J$ = 5.5 Hz, 1.5 Hz, 2H), 3.48 (d, $J$ = 6.0 Hz, 2H), 3.38 (t, $J$ = 5.8 Hz, 2H), 3.07 (t, $J$ = 5.8 Hz, 2H), 1.69 (quintet, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 21.97, 44.95, 45.69, 50.92, 51.48, 53.86, 114.80, 114.97, 116.57, 117.31, 129.79, 129.85, 134.37, 134.71, 157.09, 160.78, 162.72 ppm; FT-IR (neat) 1619 cm$^{-1}$; HRMS (ESI) calcd for C$_{17}$H$_{23}$FN$_3$ 288.18705, found 288.18708 [M+H]$^+$. 

![Image](image_url)

N-(3,4,5-trimethoxybenzyl)-N,1-diallyl-1,4,5,6-tetrahydropyrimidin-2-amine (3.68).

The general procedure for the cationic rearrangement was adapted using 1-(3-(diallylamino)propyl)-3-(3,4,5-trimethoxybenzyl)urea 3.64 (220 mg, 0.58 mmol, 1.0 eq.), p-TsCl (135 mg, 0.70 mmol, 1.2 eq.), NEt$_3$ (60 mg, 0.58 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (first using 5% MeOH in CH$_2$Cl$_2$ with 0.5% NEt$_3$, then 20% MeOH in CH$_2$Cl$_2$ with 2% NH$_3$ H$_2$O, $R_f$ = 0.15 in the latter solvent system, UV light) to give guanidine 3.68 as yellow oil (130 mg, 62% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.50 (s, 2H), 5.88-5.75 (m, 2H), 5.23-5.10 (m, 4H), 4.11 (s, 2H), 3.83-3.80 (m,
1H), 3.53 (d, J = 6.0 Hz, 2H), 3.40 (t, J = 5.8 Hz, 2H), 3.09 (t, J = 5.8 Hz, 2H), 1.71 (quintet, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 22.04, 45.04, 45.78, 51.39, 51.96, 53.86, 55.97, 60.77, 105.10, 116.54, 117.07, 134.68, 134.71, 134.73, 136.62, 152.98, 157.08 ppm; FT-IR (neat) 1620 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{20}\)H\(_{30}\)N\(_3\)O\(_3\) 360.22817, found 360.22810 [M+H]\(^+\).

![Image](image.png)

\(N,1\)-diallyl-1,4,5,6-tetrahydro-N-propylpyrimidin-2-amine (3.69). The general procedure for the cationic rearrangement was adapted using 1-(3-(diallylamino)propyl)-3-propylurea 3.65 (230 mg, 0.96 mmol, 1.0 eq.), \(p\)-TsCl (222 mg, 1.15 mmol, 1.2 eq.), NEt\(_3\) (98 mg, 0.96 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (first using 5% MeOH in CH\(_2\)Cl\(_2\) with 0.5% NEt\(_3\), then 20% MeOH in CH\(_2\)Cl\(_2\) with 2% NH\(_3\)\(\cdot\)H\(_2\)O, \(R_f\) = 0.08 in the latter solvent system, UV light) to give guanidine 3.69 as yellow oil (70 mg, 33% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 5.85-5.74 (m, 2H), 5.24-5.10 (m, 4H), 3.76 (dt, J = 5.5 Hz, 1.5 Hz, 2H), 3.65 (d, J = 5.0 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H), 3.07 (t, J = 5.5 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 1.72 (quintet, 2H), 1.53-1.45 (m, 2H), 0.84 (t, J = 7.0 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 11.54, 20.12, 21.95, 44.34, 45.66, 50.19, 52.25, 54.03, 116.57, 116.65, 134.53, 135.32, 157.82 ppm; FT-IR (neat) 1620 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{13}\)H\(_{24}\)N\(_3\) 222.19647, found 222.19649 [M+H]\(^+\).
N-benzyl-N-(but-3-en-2-yl)-1,4,5,6-tetrahydro-1-methylpyrimidin-2-amine  (3.70).

The general procedure for the cationic rearrangement was adapted using urea 3.26 (180 mg, 0.65 mmol, 1.0 eq.), p-TsCl (161 mg, 0.79 mmol, 1.2 eq.), NEt₃ (67 mg, 0.65 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (first using 5% MeOH in CH₂Cl₂ with 0.5% NEt₃, then 20% MeOH in CH₂Cl₂ with 2% NH₃·H₂O, Rₜ = 0.08 in the latter solvent system, UV light) to give guanidine 3.70 as yellow oil (100 mg, 59% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.29-7.14 (m, 5H), 6.07-6.00 (m, 1H), 5.19-5.14 (m, 2H), 4.17 (d, J = 11 Hz, 1H), 4.03 (d, J = 13.5 Hz, 1H), 3.98-3.93 (m, 1H), 3.30-3.17 (m, 2H), 3.07-3.02 (m, 2H), 2.89 (s, 3H), 1.66 (quintet, 2H), 1.26 (d, J = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 15.82, 22.35, 38.58, 44.26, 46.83, 48.80, 56.85, 115.32, 126.01, 127.76, 127.94, 139.86, 141.00, 156.49 ppm; FT-IR (neat) 1616 cm⁻¹; HRMS (ESI) calcd for C₁₆H₂₄N₃ 258.19647, found 258.19645 [M+H]+.
**N,1-diallyl-N-benzyl-4,5-dihydro-1H-imidazol-2-amine (3.71).** The general procedure for the cationic rearrangement was adapted using urea 3.17 (200 mg, 0.73 mmol, 1.0 eq.), p-TsCl (169 mg, 0.88 mmol, 1.2 eq.), NEt₃ (75 mg, 0.73 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (5% MeOH in CH₂Cl₂ with 0.5% NH₃·H₂O, Rₐ = 0.11, UV light) to give guanidine 3.71 as yellow oil (40 mg, 21% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.23 (m, 5H), 5.87-5.77 (m, 2H), 5.27-5.09 (m, 4H), 4.37 (s, 2H), 3.74-3.68 (m, 6H), 3.41 (t, J = 9 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 50.07, 51.44, 51.84, 52.12, 53.57, 116.51, 118.05, 127.14, 127.79, 128.45, 133.31, 134.09, 137.51, 166.09 ppm; FT-IR (neat) 1605 cm⁻¹; HRMS (ESI) calcd for C₁₆H₂₂N₃ 256.18082, found 256.18092 [M+H]⁺.

![Image](image.png)

**N-Bn (6aS,10aS)-11-benzyl-3,4,6,6a,7,8,10a,11-octahydro-2H-pyrimido[2,1-b]quinazoline (3.72).** The general procedure for the cationic rearrangement was adapted using urea 3.36 (100 mg, 0.33 mmol, 1.0 eq.), p-TsCl (77 mg, 0.40 mmol, 1.2 eq.), NEt₃ (34 mg, 0.33 mmol, 1.0 eq.), except that the mixture was stirred in a sealed tube at the external temperature of 80 °C in a sand bath for 48 hours. The crude product was chromatographically purified over silica gel (first using 5% MeOH in CH₂Cl₂ with 0.5% NEt₃, then 20% MeOH in CH₂Cl₂ with 2% NH₃·H₂O, Rₐ = 0.05 in the latter solvent system, UV light) to give
guanidine 3.72 as yellow oil (40 mg, 43% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.23 (m, 5H), 5.80-5.75 (m, 1H), 5.68-5.62 (m, 1H), 5.58 (d, $J = 16.5$ Hz, 1H), 4.24 (d, $J = 16.5$ Hz, 1H), 3.81 (s, 1H), 3.65-3.56 (m, 1H), 3.35-3.30 (m, 1H), 3.27-3.18 (m, 3H), 3.07 (dd, $J = 6$ Hz, 5.5 Hz, 1H), 2.35-2.28 (m, 1H), 2.08-2.00 (m, 2H), 1.98-1.85 (m, 2H), 1.80-1.69 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 20.77, 21.00, 22.71, 28.89, 47.93, 48.43, 51.26, 53.48, 124.56, 127.71, 127.76, 128.76, 129.26, 150.25 ppm; FT-IR (neat) 1597 cm$^{-1}$; HRMS (ESI) calcd for C$_{18}$H$_{24}$N$_3$ 282.19647, found 282.19649 [M+H]$^+$. 

The general procedure for the cationic rearrangement was adapted using urea 3.54 (426 mg, 1.25 mmol, 1.0 eq.), p-TsCl (288 mg, 1.50 mmol, 1.2 eq.), NEt$_3$ (128 mg, 1.25 mmol, 1.0 eq.). The crude product was chromatographically purified over silica gel (first using 30% EtOAc in Hexane with 0.5% NEt$_3$, then 5% MeOH in CH$_2$Cl$_2$ with 0.5% NH$_3$ H$_2$O, $R_f = 0.19$ in the latter solvent system, UV light) to give guanidine 3.73 as yellow oil (260 mg, 64% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.22 (m, 5H), 5.86-5.77 (m, 2H), 5.22-5.11 (m, 4H), 4.36 (s, 2H), 3.83 (dt, $J = 5.5$ Hz, 1.8 Hz, 2H), 3.68 (d, $J = 6.0$ Hz, 2H), 3.50 (s, 2H), 1.68 (d, $J = 11$ Hz, 4H), 1.61 (d, $J = 13$ Hz, 1H), 1.54-1.48 (m, 2H), 1.38-1.27 (m, 2H), 1.11-1.02 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 22.99, 25.21, 35.37, 45.56, 51.55, 52.49, 61.36, 64.74, 115.36, 117.52, 126.82, 127.99, 128.23, 133.81, 137.42, 138.30,
164.79 ppm; FT-IR (neat) 1605 cm$^{-1}$; HRMS (ESI) calcd for C$_{21}$H$_{30}$N$_{3}$ 324.24342, found 324.24341 [M+H]$^+$. 
REFERENCES

(1) Claisen, B. *Chem. Ber.* 1912, 45, 3157.


## APPENDIX

### List of Abbreviations

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<thead>
<tr>
<th>Entry</th>
<th>Abbreviation</th>
<th>Chemical Name</th>
<th>Chemical Structure</th>
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