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Generation Of Electron Deficient Carbodiimides And Their Application In The Guanidine Forming, Zwitterionic 1,3-Diaza-Claisen Rearrangement

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GENERATION OF ELECTRON DEFICIENT CARBODIIMIDES AND THEIR APPLICATION IN THE GUANIDINE FORMING, ZWITTERIONIC 1,3-DIAZA-CLAISEN REARRANGEMENT

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ABSTRACT

The 1,3-diaza Claisen rearrangement was initially discovered by the Madalengoitia group in the early 2000s. Tertiary, allylic, amines nucleophilically add to the carbon of a heterocumulene (isocyanate, isothiocyanate, or carbodiimide) to generate a zwitterion which then undergoes [3,3]-sigmatropic rearrangement. The rearrangements conducted with a carbodiimide generate guanidine-containing skeletons. The guanidine functional group is found in many biologically active products, making it a worthwhile chemical target.

To this end, strained, tertiary, allylic, amine 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene reacts with *in-situ* generated carbodiimides in the 1,3-diaza-Claisen rearrangement to afford structurally interesting bicyclic guanidines. Use of more electron deficient carbodiimides makes these rearrangements more facile; however, there are not sufficient methods for the synthesis of highly electron deficient carbodiimides. The synthesis of such carbodiimides was explored through new synthetic methodologies for the dehydration of ureas and desulfurization of isothioureas and the carbodiimides were used in a series of intermolecular rearrangements with the strained, tertiary, allylic, amine.

The new methodologies for the synthesis of electron deficient carbodiimides were then applied to a series of intramolecular substrates, further expanding the 1,3-diaza Claisen rearrangement methodologies. To date series of bicyclic, tricyclic, and monocyclic guanidines of varying structures have been synthesized. The synthetic efforts towards these products are herein described.

CITATIONS

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Secondly, I need to thank the life-long friends I made while making my way through the maze that is graduate-level chemistry. As a young student I developed strong friendships with several older students who not only are significant to me for their friendship outside of chemistry but also because they were a constant source of help as I tried to figure out my path. As a senior graduate student I have developed friendships with students in several of the subsequent years. I hope (and intend) to continue these

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Finally, I want to thank my parents. From a young age, they helped to instill a strong work ethic in both my brother and I and it's only through that ethic and attitude of perseverance that I was able to complete this Ph.D. They have remained unwaveringly supportive as I worked through my undergraduate degree, told them that I'd be doing graduate work, then further postdoctoral training, and then not knowing exactly where I'd go from there. They have certainly bent backwards through some hoops to help me out when I truly needed it and several of my accomplishments may not have succeeded otherwise, so for that I give my utmost thanks. Whether it's helping through a difficult move, giving big or small life advice, or anything simpler, they were always available. Future parents should hold them up as models and I certainly hope to be half as good of a parent in the future. Thanks mom and dad!

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1 THE CLAISEN REARRANGEMENT: BACKGROUND

1.1 Rearrangement Discovery and Modifications

The Claisen rearrangement is one of the most well-known sigmatropic rearrangements and as such has been the focus of constant research and modification since it was originally reported in 1912 by Ludwig Claisen.[1] The Claisen rearrangement can be defined as the thermal [3,3]-sigmatropic rearrangement of an allyl, vinyl ether to a γ,δ-unsaturated carbonyl compound (Figure 1.1). The rearrangement and modifications thereof are well regarded by chemists due to the ability of the rearrangement to prepare complex molecules in a single step and the reliably predictable stereochemical outcomes.[2]

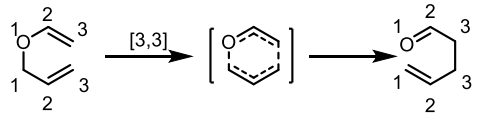


Figure 1.1. The generic Claisen rearrangement.

Many of the modifications have become famous named reactions in their own right, including the Carroll Rearrangement (rearrangement of allylic β-ketoesters followed by decarboxylation),[3] the Ireland-Claisen Rearrangement (rearrangement of allyl

trimethylsilyl ketene acetals),[4] and the Reformatsky-Claisen Rearrangement (rearrangement of zinc enolates),[5] among thousands of other investigations.

1.1.1 Rearrangement Mechanistic Aspects

The classical Claisen rearrangement is a suprafacial, concerted, non-synchronous [3,3]-sigmatropic rearrangement. Typically the chair-like transition state 1.1.1 is favored, particularly for acyclic systems, and the stereochemistry of the allyl vinyl ether (1.1) is transferred to the resultant product (Figure 1.2).[6] In many cases the product in acyclic rearrangements that is derived from the chair-like transition state dominates by over 90 %.[7]

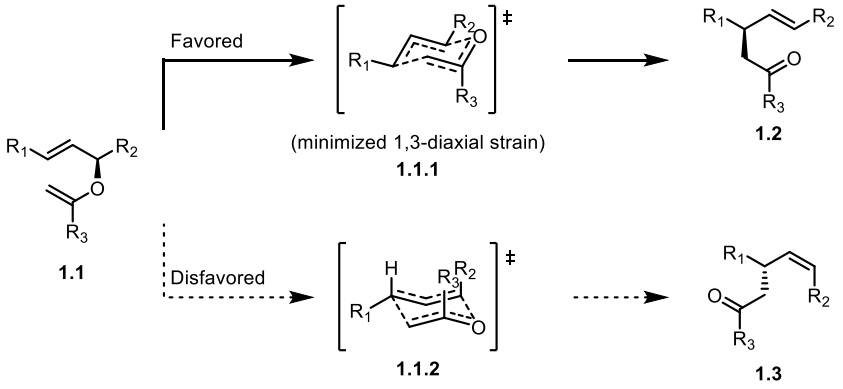


Figure 1.2. Acyclic Claisen rearrangement: chair-like transition states.

A boat-like transition state can be rationalized if steric hindrance or the geometry of the ring precludes the chair-like state. For example, the major product (1.5) in Figure

1.3 is derived from the boat-like transition state 1.4.1, due to the unfavorable steric interaction of the silyl ether substituent and the atoms of the dihydro-pyran in the chair-like transition state 1.4.2.[7]

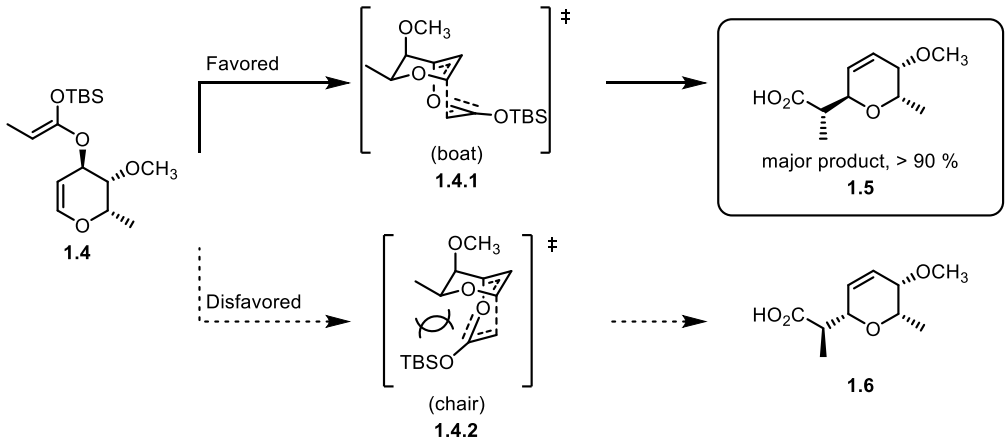


Figure 1.3. Boat-like transition state favorability.

1.2 Zwitterionic aza-Claisen Rearrangements

In the late 1970s Mariano began exploring the use of the nitrogen analog of the Claisen rearrangement: the aza-Claisen rearrangement.[8-9] The few previous attempts at the aza-Claisen rearrangement had shown that this variant often required harsher conditions than the standard oxo-Claisen rearrangement, often at temperatures of 200 – 300 °C.[10-11] His work began on the rearrangement of N-vinylammonium salts (Figure 1.4,

1.7.1). These salts underwent sigmatropic rearrangement at 25 °C to afford the hexahydroisoquinoline products 1.8 in yields of 30 – 60 %.

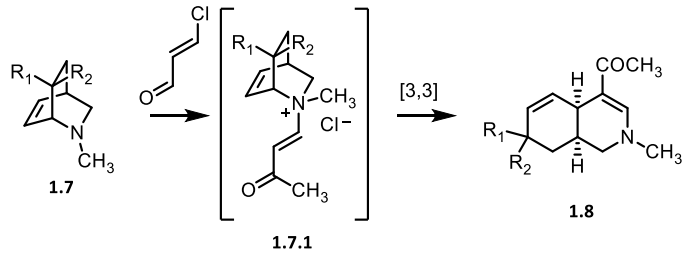
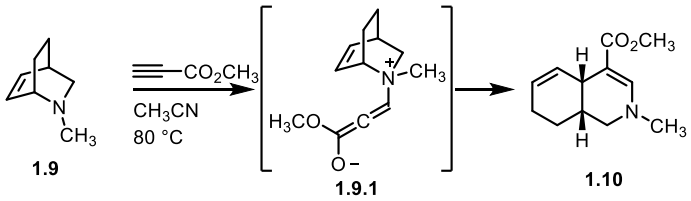


Figure 1.4. Mariano's rearrangement of N-vinylammoniums.

Eventually this rearrangement work was developed into the rearrangement of *in-situ* generated zwitterions to afford hexahydroisoquinolines. The tertiary allylic amine 1.9 adds 1,4 to a propargyl ester to generate the allyl, vinyl ammonium zwitterion 1.9.1. The zwitterion undergoes a [3,3]-sigmatropic rearrangement to provide the desired product 1.10 at only 80 °C, significantly lower than the typical neutral aza-Claisen requirements of 200 – 300 °C.[11]



Scheme 1.1. Mariano's zwitterionic 3-aza Claisen rearrangement.

1.3 Discovery of the 1,3-diaza Claisen Rearrangement

Discovered in 2003,[12] the 1,3-diaza Claisen rearrangement is the extension of Mariano's 3-aza Claisen rearrangement. The 1,3-diaza Claisen rearrangement replaces both the oxygen and terminal vinyl carbon of the standard Claisen rearrangement with nitrogen atoms (Figure 1.5). Nucleophilic addition of tertiary allylic amine 1.11 to the electrophilic carbon of a heterocumulene (1.12) and subsequent [3,3]-sigmatropic rearrangement of intermediate 1.11.1 will afford the final product 1.13, a urea, thiourea, or guanidine respectively, depending on the heterocumulene (isocyanate, isothiocyanate, or carbodiimide) used. The rearrangement can be conducted in several ways: catalyzed by palladium (0),[13] protonation of the zwitterionic intermediate for a cationic pathway,[13] or a zwitterionic pathway.[12, 14] The work presented in this dissertation is a study of the zwitterionic 1,3-diaza Claisen rearrangement.

1.3.1 The Zwitterionic 1,3-diaza Claisen Rearrangement

The zwitterionic 1,3-diaza Claisen rearrangement follows the standard pathway outlined in Figure 1.5. The addition of a tertiary allylic amine to the electrophilic carbon of a heterocumulene generates the key zwitterionic intermediate 1.11.1. [3,3]-sigmatropic rearrangement affords the final product 1.13; a urea, thiourea, or guanidine depending on

X. The limitation of the zwitterionic variant has been in the scope of tertiary allylic amines that will undergo rearrangement with carbodiimides.

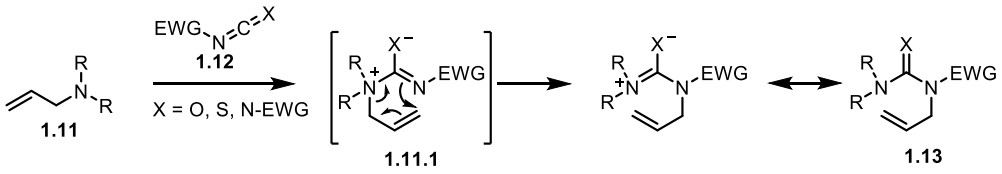
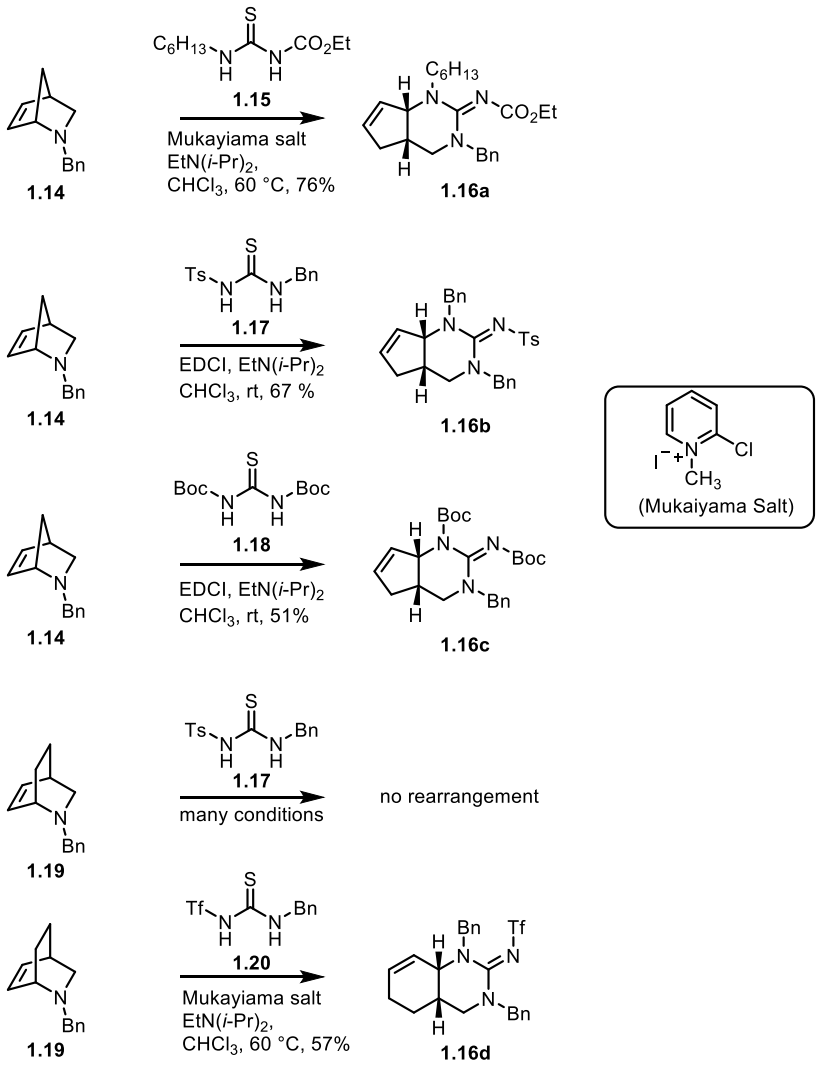


Figure 1.5. The general zwitterionic 1,3-diaza Claisen rearrangement.

Previously in the Madalengoitia group the carbodiimides used for the rearrangement were obtained via the desulfurization of thioureas.[12, 14]

In the original work and discovery of the zwitterionic variant the rearrangement would only proceed when conducted with ring-strained bicyclic tertiary allylic amines, typically N-benzyl 2-aza-[2.2.1]bicyclo-3-heptene or N-benzyl 2-aza-[2.2.2]bicyclo-3-octene. Over a host of rearrangements, a trend became clear for the intermolecular versions of the rearrangement: the rearrangement becomes more facile as the electron deficiency of the heterocumulene increases. This trend is most evident in Scheme 1.2.

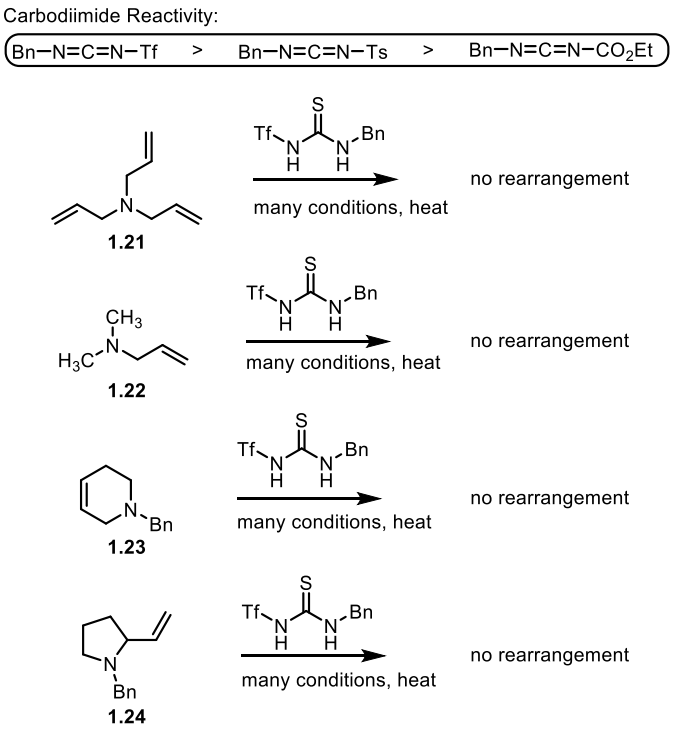


Scheme 1.2. Trend: more electron deficient carbodiimide – faster overall reaction.

The reaction of N-benzyl azanorbornene 1.14 with the alkyl, carbamoyl carbodiimide generated from the desulfurization of 1.15 affords the bicyclic guanidine rearrangement product 1.16a in moderate yield at 60 °C. As the electron withdrawing nature of the carbodiimide is increased from a single carbamoyl group to either the para-toluene sulfonyl (tosyl, Ts, 1.17) or two *tert*-butyloxycarbonyl (Boc, 1.18) groups, the reaction with the same N-benzyl azanorbornene 1.14 occurs at room temperature to

provide rearrangement products 1.16b and 1.16c, respectively. The trend becomes more evident when the rearrangement was attempted with the less ring-strained bicyclic amine N-benzyl isoquinuclidene 1.19. The rearrangement of this tertiary allylic amine does not proceed under any thermal conditions when the N-tosyl, N'-benzyl carbodiimide (from 1.17) is used as the heterocumulene, the same reaction that worked with the more ring-strained azanorbornene at room temperature (1.16b). However, when the tosyl group is replaced with the more electron withdrawing group trifluoromethane sulfonyl (Triflate, Tf, 1.20) the rearrangement occurs at just 60 °C to provide bicyclic guanidine 1.16d in a 57 % isolated yield.

This most reactive carbodiimide, the N-triflate, N'-benzyl variant, was subjected to rearrangement conditions with multiple different tertiary allylic amines that do not have high amounts of bridging ring strain (Scheme 1.3).



Scheme 1.3. Reaction of the N-Tf, N'-Bn carbodiimide with simple tertiary allylic amines.

Despite forcing reaction conditions, the rearrangements of the above tertiary allylic amines (lacking ring-strain) did not occur. It was inferred that there is a threshold of electron deficiency of the carbodiimide for the rearrangement to be generalized for the tertiary allylic amine, ring-strained or otherwise.

1.4 Guanidines

1.4.1 Guanidine-Containing Natural Products

When a carbodiimide is used as the heterocumulene in the 1,3-diaza Claisen rearrangement process the product will contain a protected guanidine moiety (Figure 1.6). The guanidine functional group is found in many natural products and bioactive compounds and therefore the development of efficient methods of complex guanidine synthesis is necessary.

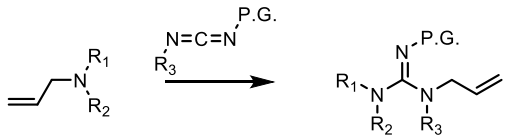


Figure 1.6. The 1,3-diaza Claisen generates guanidines.

The conditionally essential amino acid arginine, which is a precursor for creatine,[15] contains a guanidine in its side chain (1.25). Guanidine subunits are found in the sodium channel blocker saxitoxin (1.26), the highly potent puffer fish toxin tetrodotoxin (1.27), and guanine (1.28), one of the main nucleobases in DNA and RNA.[16]

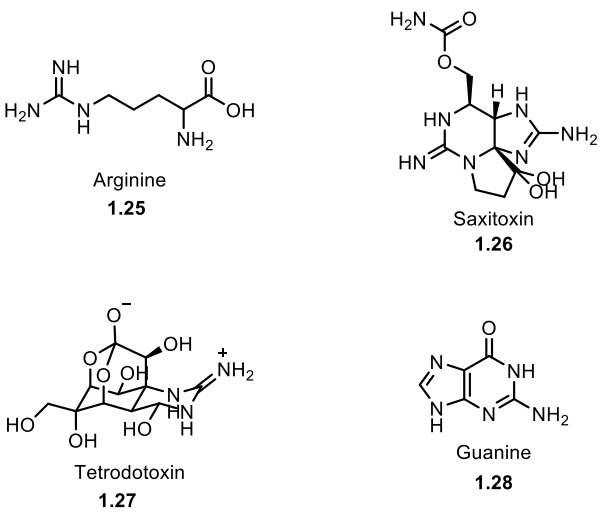


Figure 1.7. Biologically active guanidines.

Guandines are found in many other natural products, from sources such as marine microorganisms, terrestrial microorganisms, plants, and various invertebrates.[17-18] Members of guanidine alkaloid families, such as the crambescidin and batzelladine families, among others (polycyclic as well as acyclic), have shown promising biological activity including: anticancer activity,[19-20] antiviral activity,[21-22] inhibition of protein-protein interactions,[23-24] inhibition of HIV-1 envelope-mediated fusion,[25] and the inhibition of several other biological processes.[16, 26-27] In 2009 seven new guanidine alkaloids were isolated and tested for biological activity. It was found that of these new alkaloids norbatzelladine L (1.29) which contains two of the distinctive tricyclic guanidine cores, was the most active compound, particularly against the breast cancer cell line MDA-MB-231.[28] Merobatzelladines A and B (1.30, 1.31) (isolated as the triflouroacetate salts) (Figure 1.8) exhibit antimicrobial activity in IC_{50} values lower than 0.5 μg/mL.[29] Alkaloids of the *crambe* family (1.32) were tested and found to inhibit HIV-1 envelope-mediated fusion with IC_{50}'s of 1-3 μM.[30]

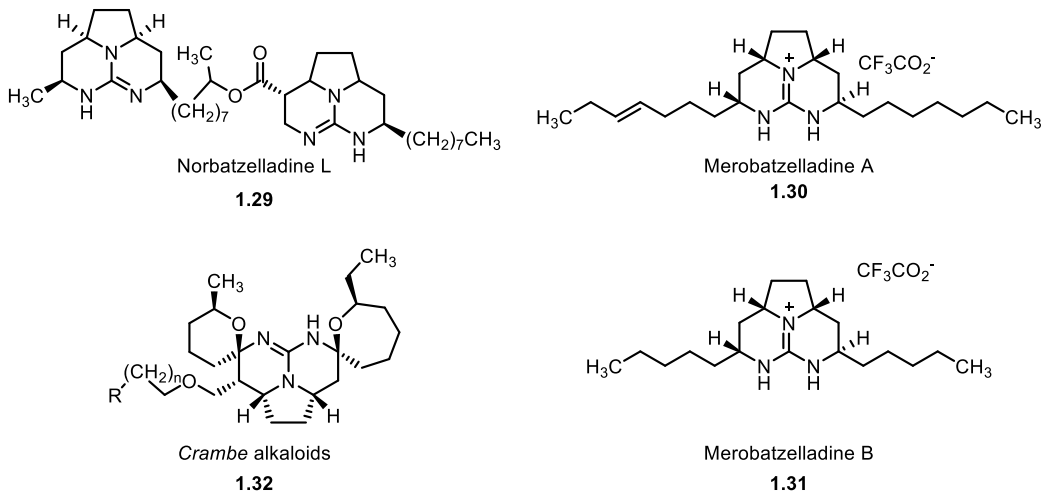


Figure 1.8. Bioactive guanidine-containing natural products.

Despite the promising biological activity of several of these natural products, many have not been studied due to low natural availability combined with the difficulty of complex guanidine synthesis. Methods do exist for the synthesis of some of these compounds, but the addition of new tools to the synthetic toolbox will be highly beneficial for medicinal screening of a new guanidine containing compounds.

1.4.2 Current Methods of Guanidine Synthesis

The Overman group has used tethered Biginelli reactions to great success for the synthesis of several of the batzelladine alkaloids (Figure 1.9).[16, 25, 31-34]

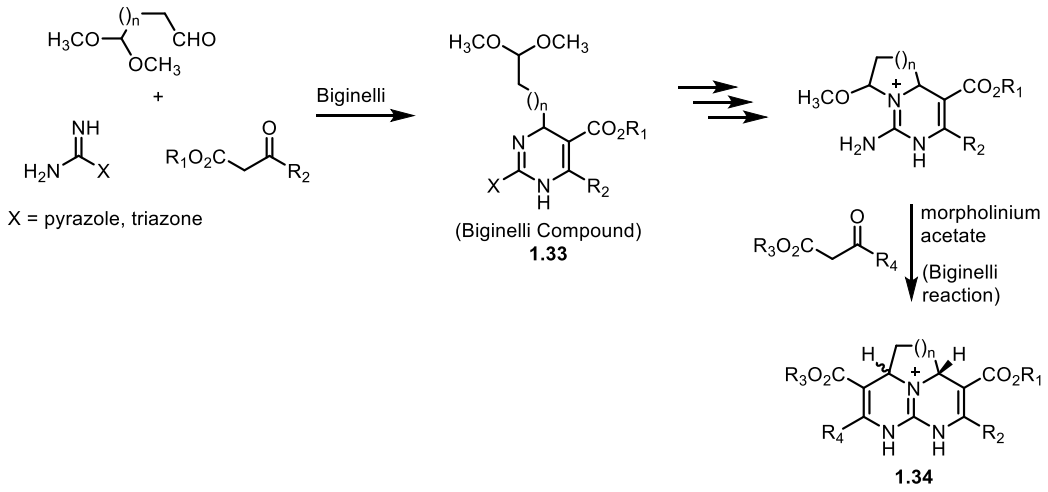


Figure 1.9. Synthetic overview of Overman batzelladine core synthesis.

The Biginelli reaction is a three component reaction traditionally consisting of an aldehyde, urea, and 1,3-dicarbonyl which come together to form so-called 'Biginelli Compounds' 1.33. Overman's modification replaces the urea component with the structurally similar guanidine (X = nitrogen) and the second Biginelli reaction in the synthesis tethers the guanidine aldehyde to the β-ketoester to produce the tricyclic guanidine core of the batzelladine alkaloids 1.34.

The Gin group has developed a [4+2] annulation to generate the tricyclic guanidine core of the batzelladines (Figure 1.10).[35]

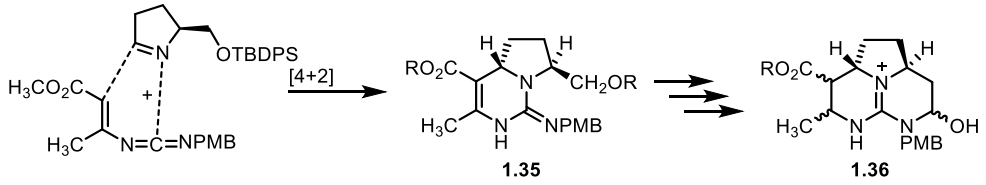


Figure 1.10. Gin's annulation strategy.

Chiral *N*-alkyl imines and vinyl carbodiimides can be diastereoselectively annulated to form the bicyclic guanidine skeleton 1.35. This architecture can be further elaborated into the tricyclic guanidinium core 1.36. The strategy has been applied to the total synthesis of (+)-batzelladine A and (-)-batzelladine D.[36]

Due to the abundance of biological activity of guanidine containing compounds studies are underway by many groups to achieve the development of complex guanadines such as the tricyclic core of the batzelladine family.[37-39] Varying the tertiary allylic amine or the carbodiimide component of the Madalengoitia group's 1,3-diaza Claisen rearrangement strategy allows for significant modification of the resultant guanidine. Expanding the rearrangement methodology to the point of generalization would provide a powerful tool for the synthesis of a diverse number of biologically active guanidines. The work presented in the dissertation details the further development of the zwitterionic variant of the guanidine-forming 1,3-diaza Claisen rearrangement via the synthesis of highly electron deficient carbodiimides and further elaboration of the intramolecular 1,3-diaza Claisen rearrangement.

2 INTERMOLECULAR ZWITTERIONIC 1,3-DIAZA CLAISEN REARRANGEMENTS

2.1 A Novel Smiles Rearrangement

2.1.1 Reactivity Trends

As previously mentioned, a trend in the rearrangement activity had been noticed; as the electron-withdrawing nature of the carbodiimide constituents was increased the rearrangement became more facile. At the onset of this research project, the benzyl, triflate carbodiimide was not electron withdrawing enough to meet the threshold for general reactivity. The unsuccessful reactions of Scheme 1.3 also show that the rearrangement is the rate determining step of the reaction process because the isoquinuclidine reaction proves that the N-benzyl, N'-trifyl thiourea can be desulfurized and tertiary allylic amines nucleophilically add to the carbodiimide, however the rearrangement did not work with simpler tertiary allylic amines.

Further evidence of the rearrangement being rate determining can be seen in Figure 2.1. The third reaction, with a full equivalent of the isocyanate, shows formation of a new product (2.1.1) due to the downfield shift of the methyl (**B**) and methylene (**A**)

protons but the desired rearrangement product was not acquired from this rearrangement. This prompted the study of the reaction with half an equivalent of the isocyanate (the middle reaction). The methyl and allylic protons again shifted downfield, but only half the shift that was observed when the full equivalent is used. Also, half peaks for both the starting amine and the product are not seen, indicating that the peaks in the middle NMR are an average signal of the two. The conclusion drawn from these experiments is that the formation of the zwitterion is a fast and reversible process and the rearrangement is rate-limiting.

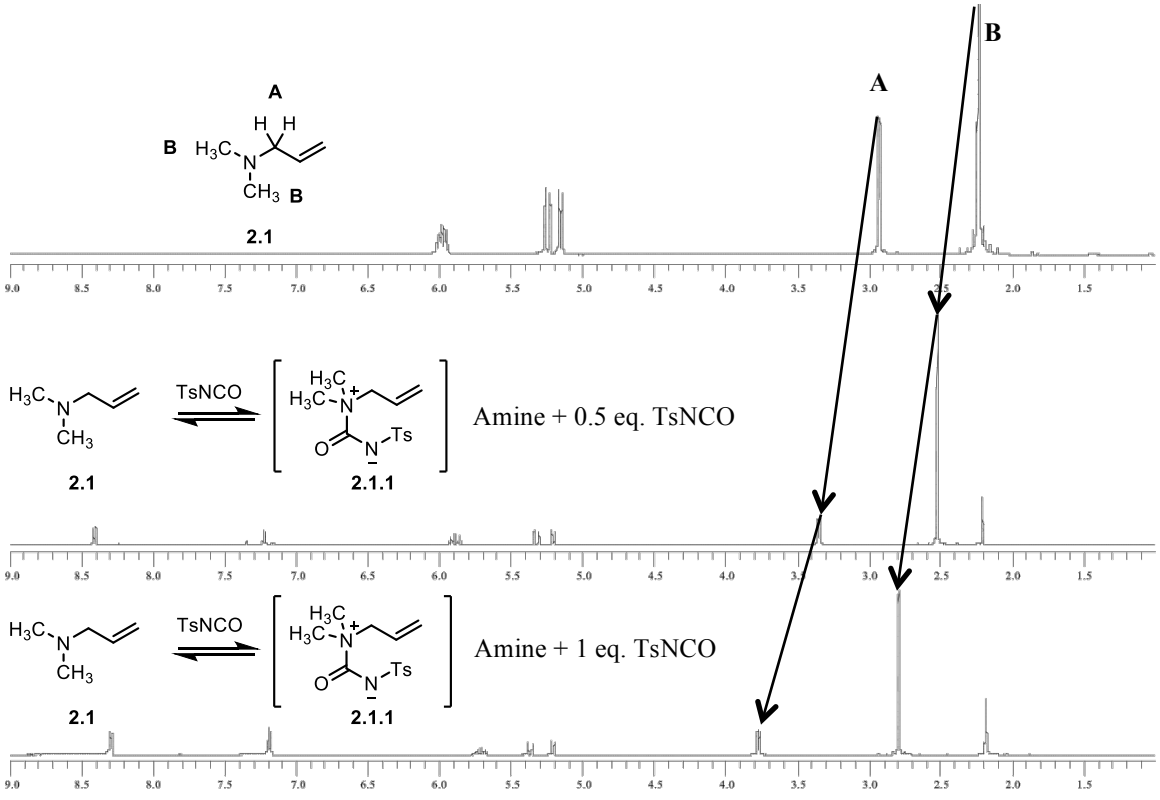


Figure 2.1. Evidence of fast and reversible zwitterion formation.

From this set of results, the general rearrangement process can be viewed as depicted in Figure 2.2: zwitterion formation is fast and reversible, while 1,3-diaza Claisen rearrangement is rate-limiting.

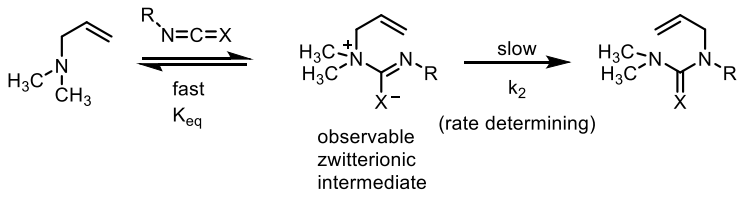


Figure 2.2. Rearrangement is rate-determining.

The simple fix for furthering the rearrangement would be to synthesize thioureas that are more electron deficient than the N-benzyl, N'-trifyl and desulfurize them to generate the related carbodiimide. However, the more electron deficient thioureas are unknown, unreported compounds (Figure 2.3).

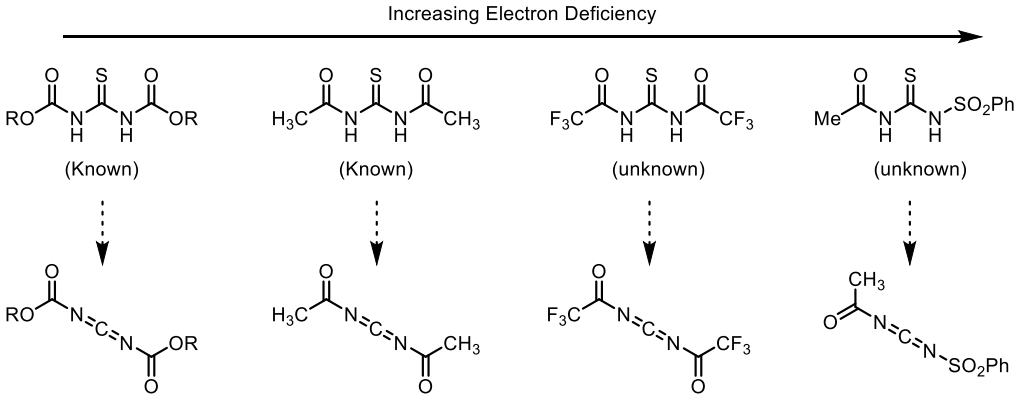
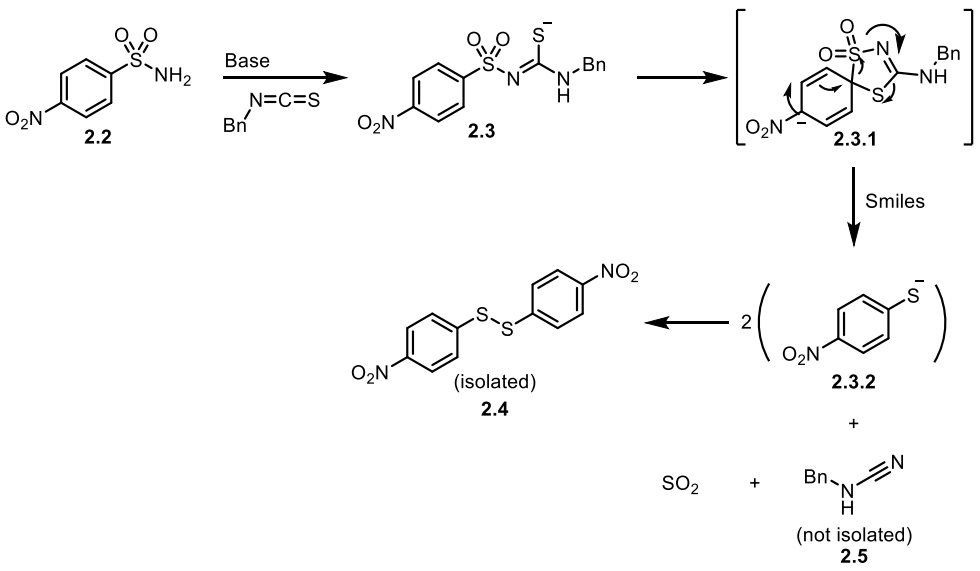


Figure 2.3. Highly electron deficient thioureas are unknown.

Lack of literature support suggests that these highly-electron deficient thioureas are unstable, difficult to synthesize compounds and therefore the subsequent carbodiimides needed to be generated using a different method.

2.1.2 Genesis of the Smiles Rearrangement

The genesis for the first attempted route to highly electron deficient carbodiimides grew from an attempt to synthesize 1-(4-nitrobenzene sulfonyl), 3-benzyl thiourea by Amy Bowser Ph.D. (a former student from the Madalengoitia group) from the reaction of 4-nitrobenzene sulfonamide with benzyl isothiocyanate. Instead of providing the desired thiourea, only the disulfide 2.4 was isolated from the reaction mixture. This product was most likely generated from the outlined Smiles rearrangement (Scheme 2.1). Addition of nosyl sulfonamide 2.2 to benzyl isothiocyanate generated the thioanion 2.3, which would then undergo a Smiles rearrangement (2.3.1) on the aromatic ring due to the electrophilic activation by the *para*-nitro group. Upon collapse of the rearrangement intermediate, sulfur dioxide would be released (entropically favored) as well as *p*-nitrobenzene thiolate (2.3.2) and benzyl cyanamide. Two equivalents of *p*-nitrobenzene thiolate would oxidatively dimerize to the isolated disulfide 2.4.



Scheme 2.1. Unexpected Smiles rearrangement.

This interesting result became the basis for the first attempted method of carbodiimide generation. A general scheme of the plan is shown in Figure 2.4. A secondary sulfonamide would be deprotonated with strong base to generate a nitrogen anion. This anion would be added to an isothiocyanate to generate a thioanion 2.6.1 (much like thiolate 2.3.2 from Scheme 2.1) which would then undergo a Smiles rearrangement. Upon collapse of the spirocyclic intermediate 2.6.2 the aromatic ring would be regenerated, SO_2 would be lost (an entropically favored outcome) and a carbodiimide (2.7) would be generated. Addition of tertiary allylic amine 1.14 to the system would trap the carbodiimide and then undergo the 1,3-diaza Claisen rearrangement to provide guanidine-containing products.

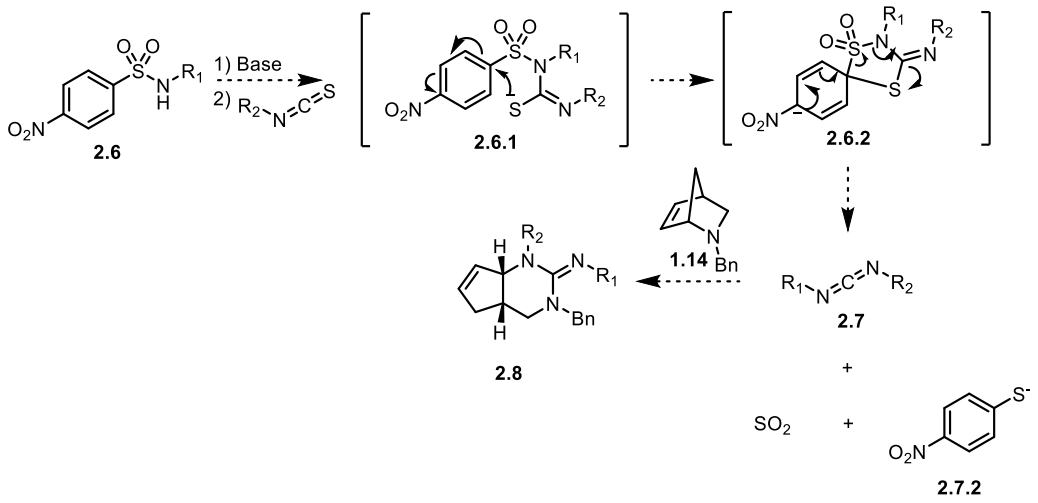
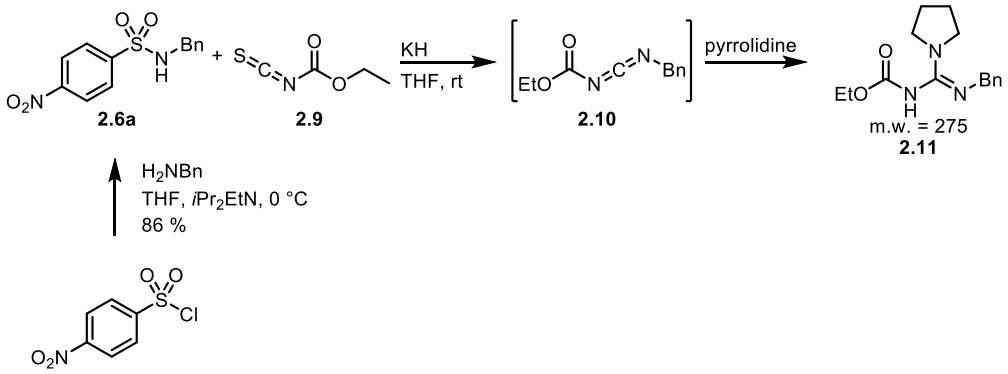


Figure 2.4. Proposal for a carbodiimide generating Smiles rearrangement.

2.2 Initial Target and Attempts



Scheme 2.2. Initial target of Smiles rearrangement.

The initial target was the 3-benzyl, 1-ethoxycarbonyl carbodiimide 2.10 as it was a carbodiimide that had been generated in the group before and it contained an

electron withdrawing group. N-benzyl-4-nitrobenzene sulfonamide 2.6a was synthesized as shown in Scheme 2.2. The sulfonamide was exposed to potassium hydride followed by ethoxycarbonyl isothiocyanate. As carbodiimides are unstable toward silica gel purification and typically too reactive to isolate, attempts were made to trap the *in-situ* generated carbodiimide 2.10 as a guanidine by addition of pyrollidine (Scheme 2.2, 2.11). Despite the fact that mass spectrometry of the crude reaction mixture indicated formation of the guanidine product, it could never be isolated and characterized. Reactions conducted with sodium hydride and *t*-butyl lithium as the base gave inseparable product mixtures. Crude NMR analysis of the product mixture indicated that the nitrogen anion added to both the isothiocyanate carbon as well as the carbonyl carbon of the ethoxycarbonyl isothiocyanate. Because of this side pathway, a switch was made to attempt the rearrangement with isopropyl isothiocyanate (1 eq) as it removed the second electrophilic site.

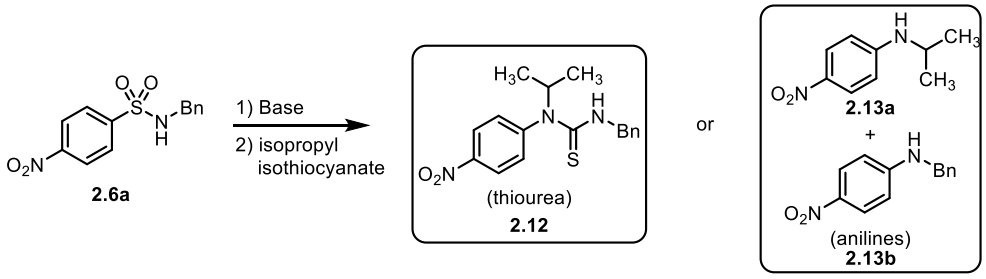
Rather than attempt to isolate the reactive carbodiimide, the reaction was monitored by IR spectroscopy. Carbodiimides give a diagnostic IR peak around 2100-2200 cm^{-1}.[40] Despite multiple rearrangement attempts this IR peak was never observed. Due to the inability to track carbodiimide formation by IR spectroscopy, it was decided to monitor the four protons of the 4-nitrobenzene ring via NMR spectroscopy, as they would give a distinct pair of doublets upon conversion to 4-nitrothiophenol.

A reaction was conducted between sulfonamide 2.6a (Table 2.1) and isopropyl isothiocyanate using *n*-butyl lithium as the base. An NMR of the crude reaction mixture showed that there was still unconsumed starting material, but that there was also another compound with the characteristic two doublets of the 4-nitrophenyl group. This meant

that a change had occurred in the 4-nitrobenzene ring. The two compounds were isolated by column chromatography with 30% EtOAc in hexanes. As expected one was the starting sulfonamide 2.6a, but the other product was not the desired 4-nitrothiophenol 2.7.2 or the disulfide dimer of the 4-nitrothiophenol. The isolated product was eventually determined to be thiourea 2.12 as shown in Table 2.1. The identity of this product is supported by mass spectrometry as well. Unexpectedly, this thiourea would occur based on a Smiles rearrangement on the nitrogen atom of the isothiocyanate rather than the sulfur as expected.

As the reaction was not providing the desired product, as well as not going to completion with *n*-BuLi as the base, a switch was made to trying sodium hydride and potassium hydride. In this case, the reaction went to completion (complete consumption of starting material), but rather than the thiourea product a pair of anilines was obtained (Table 2.1, 2.13a, 2.13b).

Table 2.1. Undesired Smiles rearrangement.

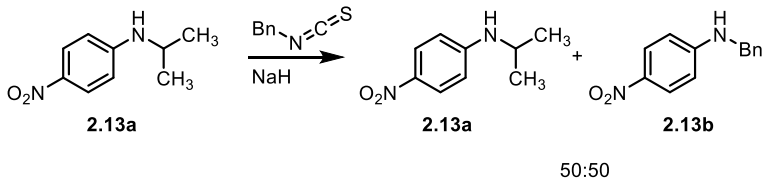


Entry	Base	Product	Isothiocyanate	Isothiocyanate eq.	Base eq.	Time	Temperature	Completion*
1	NaH	Anilines	*i*-Pr	1	1.1	Overnight	0 °C to rt	100%
2	KH	Anilines	*i*-Pr	1	1.2	Overnight	0 °C to rt	100%
3	*n*-BuLi	Thiourea	*i*-Pr	1	1	24 hrs	-78 °C to rt	50%
4	LiH	Thiourea	*i*-Pr	2	2	48 hrs	rt	50%
5	LiH	Thiourea	*i*-Pr	2	1.1	2 hrs	Reflux	50%
6	LiH	Thiourea	*i*-Pr	2	2	48 hrs	rt	60%
7	LiH	Complex Mix	Bn	2	2	5 days	rt	-
8	LiH	Complex Mix	Bn	2	2	5 days	rt to reflux (2 days)	-

*by NMR

To determine the process of formation for the anilines a control experiment was conducted (Scheme 2.3.) N-isopropyl-4-nitroaniline 2.13a was synthesized and then allowed to react with benzyl isothiocyanate in the presence of sodium hydride. What was obtained from this experiment was a 50:50 mixture of the two anilines 2.13 (by NMR). Another control was conducted by the simple reaction of N-isopropyl-4-nitroaniline and sodium hydride. Upon workup, only starting aniline was isolated. This makes it likely that the anilines similarly come from the nitrogen based Smiles arrangement, but upon formation of the thiourea the benzyl isothiocyanate would be expelled when sodium and potassium act as the counterion. The resultant aniline then would nucleophilically add to the carbon of the isothiocyanate and go through another nitrogenous Smiles

rearrangement to provide the N-benzyl aniline and isopropyl isothiocyanate. The anilines then equilibrate.



Scheme 2.3. Equilibration of the anilines.

Due to the ability of the hydride bases to drive the reaction to completion and the interesting nitrogenous rearrangement activity to generate the thiourea when lithium was the counterion, the rearrangement was attempted using lithium hydride as the base (Table 2.1, entries 4-8). Despite multiple attempts at this rearrangement the reaction never went above 60 % completion. Due to minimal returns, this attempted novel pathway to carbodiimides was abandoned (along with undiscussed attempts at an aza-Wittig reaction and the desulfurization of bis-acyl thioureas).

2.3 Dehydration of Ureas

2.3.1 Methods of Carbodiimide Formation

Previously in the Madalengoitia group electron deficient carbodiimides had been generated by the desulfurization of thioureas by the Mukaiyama salt or the thiourea transfer agent EDCI•HCl.[12] Aliphatic carbodiimides had also been generated by the dehydration of ureas via reaction with *p*-toluenesulfonyl chloride in the presence of a base. Finally, it was being shown among co-workers in the Madalengoitia group that isothioureas could be desulfurized using mercury (II) chloride to afford carbodiimides. As stated above, the generation of thioureas for highly electron deficient carbodiimides was unlikely as the higher order electron deficient thioureas are unreported compounds and potentially unstable. Both the urea and isothiourea pathways have an advantage over the original thiourea desulfurization pathway, there are literature examples of highly electron deficient members of both the urea species[41-44] (Figure 2.5) and the isothiourea species[43] (Figure 2.6).

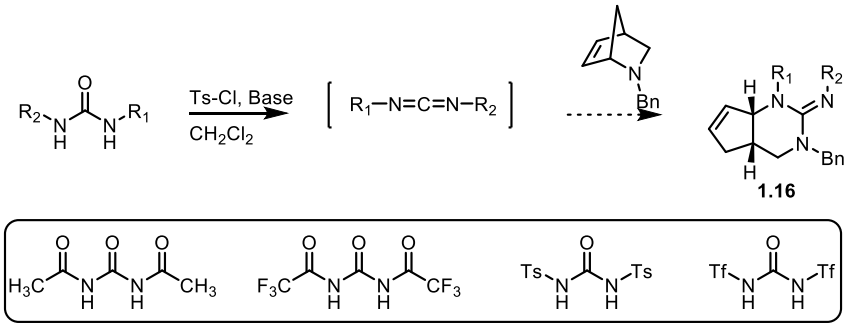


Figure 2.5. Potential dehydration of ureas route and known ureas.

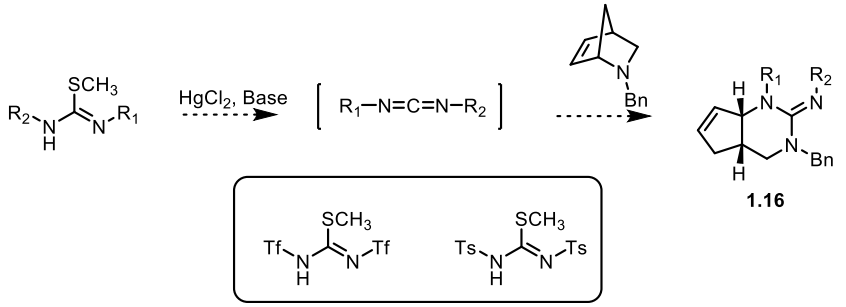
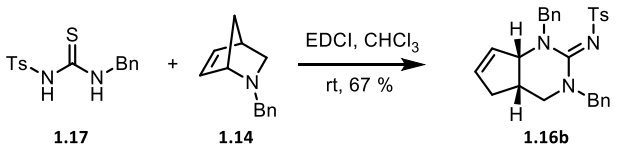


Figure 2.6. Potential desulfurization of isothioureas and known isothioureas.

There is a preponderance of methods of urea dehydration: via the Burgess reagent,[45] *p*-toluenesulfonyl chloride,[46] triphenyl phosphine with carbon tetrabromide,[47] and others, the decision was made to explore the dehydration of electron deficient ureas rather than the desulfurization of isothioureas.

2.3.2 Synthesis

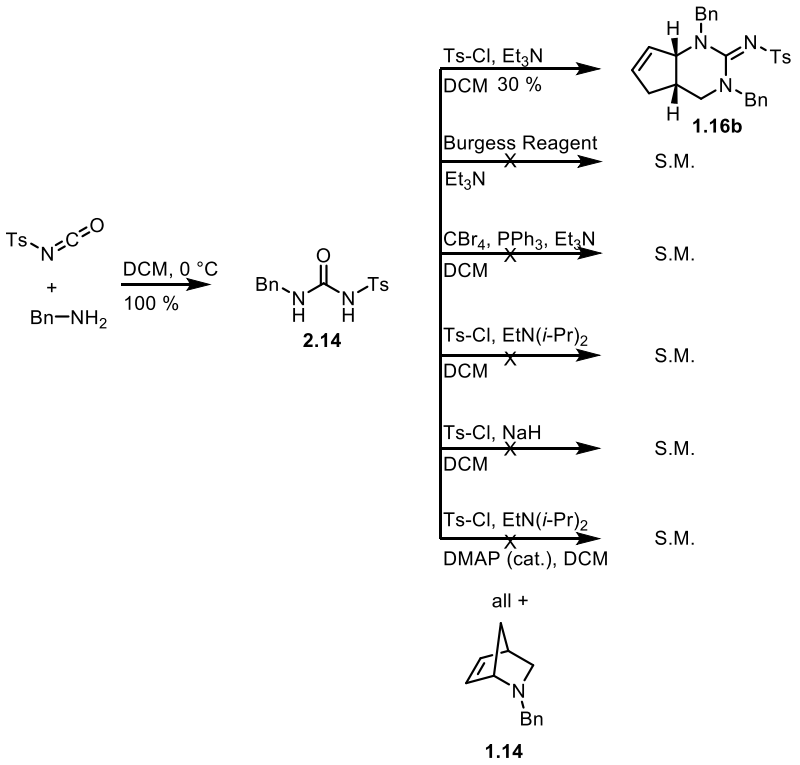
Initially a known carbodiimide was targeted: 3-benzyl-1-tosyl carbodiimide, generated in the past from the parent thiourea (Scheme 2.4).[12] The 3-benzyl-1-tosyl carbodiimide is modestly electron withdrawing and since the Madalengoitia group had synthesized the corresponding bicyclic guanidine in the past the characterization of the product could be confirmed.



Scheme 2.4. Initial target and previous synthesis.

3-benzyl-1-tosyl urea was easily generated by the reaction of tosyl isocyanate with benzylamine in dichloromethane (Scheme 2.5). This urea was then used in several dehydration reactions utilizing known methods of urea dehydration and subsequent 1,3-diaza Claisen rearrangement with N-benzyl 2-azanorbornene (1.14). The known urea dehydration methods were generally reported for reaction with aliphatic ureas and none reported for ureas with electron withdrawing groups as strong as the tosyl group. As shown, many of the methods did not produce any desired product and returned simply starting urea. While disappointing, this was not overly surprising due to the lack of

reports dealing with electron deficient ureas. The reaction with tosyl chloride and triethylamine did produce the desired product 1.18, but only in a 30 % yield.

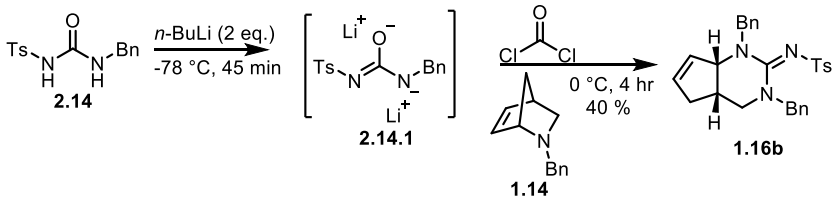


Scheme 2.5. Initial dehydration and rearrangement attempts.

Despite the low yield of the tosyl chloride reaction, it was an encouraging result as it proved that electron deficient ureas could be dehydrated and it was just a matter of optimizing reaction conditions. Despite attempts to increase the yield of the tosyl chloride dehydration the 30 % yield could not be improved upon. At this point it became clear that a stronger dehydration method would need to be explored.

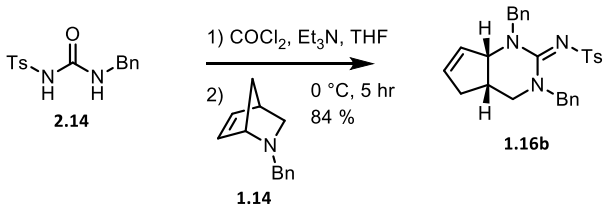
The objective was to generate the oxyanion of the urea, thereby making it a hard nucleophile. Addition of a hard, oxophilic electrophile would affect a hard/hard

interaction and dehydrate the urea. Two equivalents of *n*-BuLi, a strong base, were introduced to urea 2.14 to deprotonate both of the protons on the nitrogens of the urea, providing the oxyanion (Scheme 2.6, 2.14.1). Phosgene, a hard electrophile, was added as the dehydrating agent followed by the N-benzyl 2-azanorbornene (2.14) to form the zwitterionic intermediate and thus incite the 1,3-diaza Claisen rearrangement.



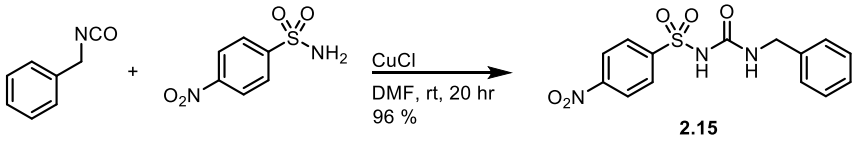
Scheme 2.6. Phosgene dehydration, initial attempts.

While the crude reaction mixture appeared to be quite clean via NMR the bicyclic guanidine could only be isolated in 40 % yield at most. This was an improvement over the tosyl chloride reaction, albeit only by 10 %, but progress had been made. In an effort to decrease the harshness of the reaction, and because some success had been seen with it in the tosyl chloride reaction, the *n*-BuLi was replaced with triethylamine (Scheme 2.7). Gratifyingly these reaction conditions led to the isolation of the desired product in an 84 % yield. Not only was this exciting as a new urea dehydration/carbodiimide generation chemistry, but the same bicyclic guanidine had only ever been generated in a 67 % yield from the thiourea, meaning the rearrangement yield had been increased by 17 %.



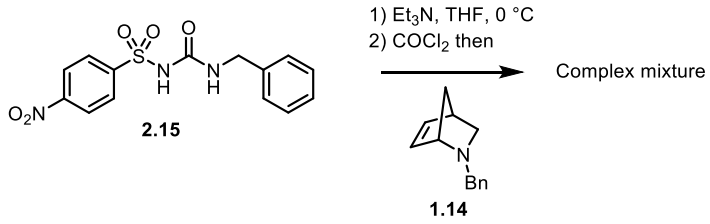
Scheme 2.7. Success with a simple base switch.

As had been proven before, the 3-benzyl-1-tosyl carbodiimide did not reach the desired electron deficiency threshold. With this in mind, and the successful phosgene dehydration conditions, higher order electron deficient carbodiimides were targeted. The first target was the 3-benzyl-1-(4-nitrobenzensulfonyl) urea (2.15). Not only was this a more electron deficient carbodiimide than the tosyl variant, but it was a product previously unavailable by the thiourea route due to the unexpected Smiles chemistry previously described.



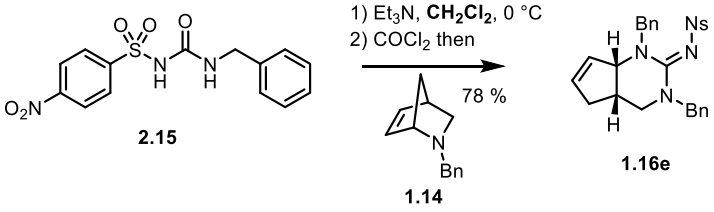
Scheme 2.8. Synthesis of the nosyl, benzyl urea.

A method of sulfonylurea synthesis developed by Cervello and Sastre, which uses CuCl as a catalyst, was utilized to generate the desired urea in 96 % yield (Scheme 2.8).[48]



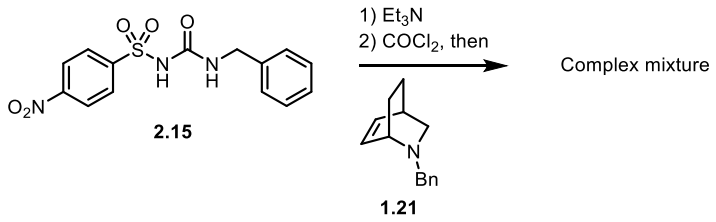
Scheme 2.9. Initial rearrangement attempt of the nosyl, benzyl carbodiimide.

However, upon exposure to the newly developed reaction conditions, only a complex, inseparable crude mixture was obtained (Scheme 2.9). Thankfully, simply switching the solvent of the rearrangement from tetrahydrofuran to dichloromethane provided the desired rearrangement product with an isolated yield of 78 % (Scheme 2.10). Clearly the solvent choice in the rearrangement can have dramatic effects, although that is still not fully understood.



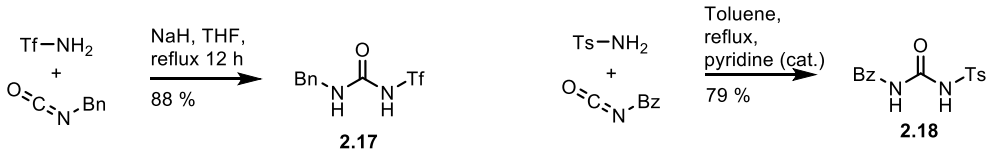
Scheme 2.10. Dramatic solvent effects.

The nosyl, benzyl urea was exposed to the new rearrangement conditions with N-benzyl 2-azaisoquinuclidine, the less ring-strained tertiary allylic amine (Scheme 2.11).



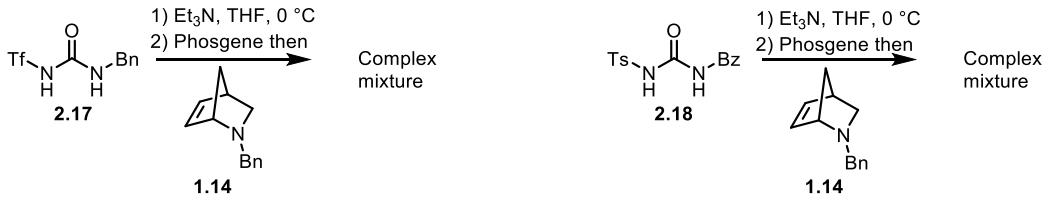
Scheme 2.11. Failed reaction with isoquinuclidine.

The rearrangement was attempted in both tetrahydrofuran and dichloromethane. Both solvents gave complex mixtures with no detectable desired product. Since it was known that the nosyl, benzyl urea wouldn't reach the desired electron deficiency threshold, ureas that were more electron deficient were synthesized (Scheme 2.12).



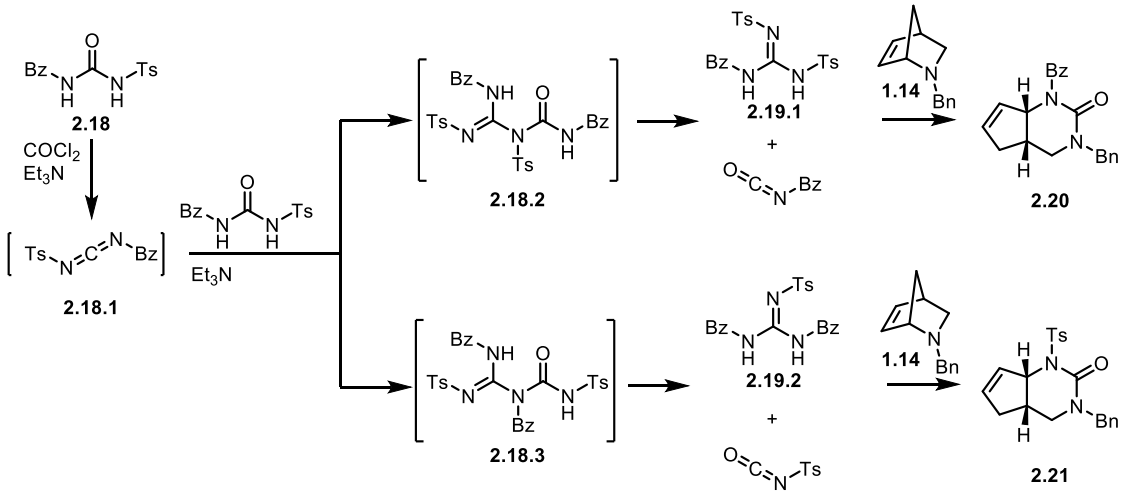
Scheme 2.12. Synthesis of more electron deficient ureas.

Trifluoromethanesulfonamide was deprotonated with sodium hydride in THF and benzyl isocyanate was added to make the N-benzyl, N'-trifluoromethanesulfonyl urea 2.17. Tosyl sulfonamide and benzoyl isocyanate were allowed to react in toluene at reflux with pyridine as a catalyst to generate the N-benzoyl, N'-tosyl urea 2.18, the most electron deficient carbodiimide precursor to date. Both of these more electron deficient ureas were exposed to the general reaction conditions for the rearrangement (Scheme 2.13).



Scheme 2.13. Rearrangements of highly electron deficient ureas.

While the triflate urea 2.17 rearrangement gave an inseparable, complex mixture, the tosyl, benzoyl urea 2.18 proved more intriguing and produced an interesting mixture of isolable products. The two major products isolated were bicyclic ureas 2.20 and 2.21. The proposed method of their formation is shown in Figure 2.7.

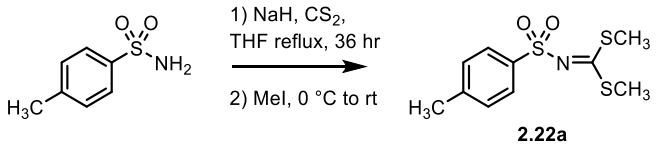


Scheme 2.7. Proposed formation of product mixture.

Upon formation of the highly reactive 3-benzoyl-1-tosyl carbodiimide (2.18.1) another equivalent of the deprotonated urea would add nucleophilically to the carbon of the carbodiimide. The nucleophilicity of the two distinct nitrogens of the urea generates either 2.18.2 or 2.18.3. These intermediates would decompose to give a guanidine

(2.19.1, 2.19.2) and the corresponding isocyanate. The corresponding isocyanate, being a reactive heterocumulene, would undergo the 1,3-diaza Claisen rearrangement with the N-benzyl 2-azanorbornene to give one of the two bicyclic ureas 2.20 or 2.21. While this was an interesting result, it was not the desired outcome. Due to the inability of the urea dehydration methodology to work with these highly electron deficient starting materials, attention was switched to developing the methodology of isothiourea desulfurization that was seeing some success within the group.

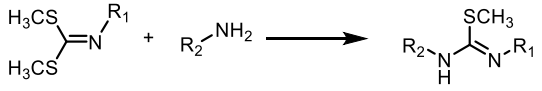
The isothiourea desulfurization method was less explored than the thiourea and urea methodologies, so the decision was made to compare and contrast the three current carbodiimide generation methods: the original thiourea desulfurization, the newly developed urea dehydration, and the desulfurization of isothioureas. A series of moderately electron deficient ureas and isothioureas were synthesized for this comparison study. The isothioureas were synthesized by the reaction of a primary amine with an S,S-dimethyldithiocarboimidate (2.22). Dimethyl toluenesulfonylcarbonimidodithioate (2.22a, R_1 = tosyl) was synthesized by the reaction of *p*-toluenesulfonamide with carbon disulfide in the presence of sodium hydride. The dithio-anion was methylated with methyl iodide to provide the carbodithioimidate (Scheme 2.14).



Scheme 2.14. Synthesis of tosyl carbodithioimidate.

The other carbondithimoimidates were developed in a similar fashion. The generation of the isothiourea series of carbodiimide precursors is summarized in Table 2.1.

Table 2.1. Synthesis of the isothiourea series.



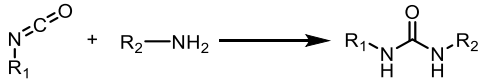
2.22 a & b **2.23 a-e**

Isothiourea	Conditions	Product	Yield (%)
R_1 = Ts (2.22a), R_2 = Bn	MeOH, reflux, 3 h	2.23a	97
R_1 = Ts (2.22a), R_2 = *i*-Pr	MeOH, Et_3N, reflux, 3 h*	2.23b	70
R_1 = Ts (2.22a), R_2 = *n*-hexyl	MeOH, reflux, 3 h	2.23c	89
R_1 = Ts (2.22a), R_2 = Bz	NaH, THF, rt	2.23d	51
R_1 = Tf (2.22b), R_2 = Bn	MeOH, 0 °C, 30 min	2.23e	75

**i*-Pr•HCl used instead of the free base

Similarly, a series of ureas was synthesized as well (Table 2.2.) A primary amine or amide was allowed to react with the corresponding isocyanate to generate the desired urea.

Table 2.2. Synthesis of the urea series.

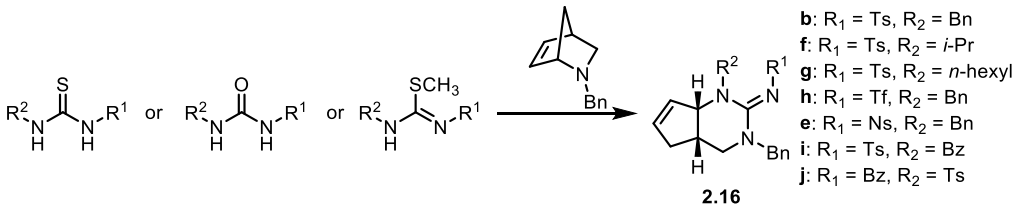


Urea	Conditions	Product	Yield (%)
R_1 = Bn, R_2 = Ns	10 mol% CuCl, DMF, rt, 20 h	2.15	96
R_1 = *i*-Pr, R_2 = Ts	NaH, THF, 0 °C	2.24a	95
R_1 = Ts, R_2 = *n*-hexyl	CH_2Cl_2, 0 °C	2.24b	91
R_1 = Ts, R_2 = Bn	CH_2Cl_2, 0 °C	2.14	84
R_1 = Bz, R_2 = Ts	toluene, reflux 4 h, pyridine	2.17	79
R_1 = Bn, R_2 = Tf	NaH, THF, 0 °C to rt	2.18	88

The two series of carbodiimide precursors were subjected to the standard reaction methodology for the 1,3-diaza Claisen rearrangement. They were compared to

the original work done on the desulfurization of thioreas; the results of the comparison can be seen in Table 2.3.

Table 2.3. Comparison of the methods for carbodiimide generation and subsequent 1,3-diaza Claisen rearrangement.



2.16

Thiourea	Conditions	Yield (%)	Urea	Conditions	Yield (%)	Isothiourea	Conditions	Yield (%)
R_1 = Ts R_2 = Bn	EDCI, EtN(*i*-Pr)$_2$, $CHCl_3$, rt	67 (b)	R_1 = Ts R_2 = Bn	$COCl_2$, THF, 0 °C to rt, 6 h	84 (b)	R_1 = Ts R_2 = Bn	$HgCl_2$, Et_3N, THF, rt	69 (b)
R_1 = Ts R_2 = *i*-Pr	EDCI, EtN(*i*-Pr)$_2$, $CHCl_3$, rt	72 (f)	R_1 = Ts R_2 = *i*-Pr	$COCl_2$, THF, 0 °C to rt, 6 h	61 (f)	R_1 = Ts R_2 = *i*-Pr	$HgCl_2$, Et_3N, THF, rt	56 (f)
R_1 = Ts R_2 = *n*-hex	EDCI, EtN(*i*-Pr)$_2$, $CHCl_3$, rt	77 (g)	R_1 = Ts R_2 = *n*-hex	$COCl_2$, THF, 0 °C to rt, 6 h	67 (g)	R_1 = Ts R_2 = *n*-hex	$HgCl_2$, Et_3N, DMF, rt	67 (g)
R_1 = Tf R_2 = Bn	Muk. Salt EtN(*i*-Pr)$_2$, $CHCl_3$, rt	62 (h)	R_1 = Tf R_2 = Bn	$COCl_2$, THF, 0 °C to rt, 6 h	Complex Mix	R_1 = Tf R_2 = Bn	$HgCl_2$, Et_3N, DMF, rt	Complex Mix
-	-	-	R_1 = Ns R_2 = Bn	$COCl_2$, DCM, 0 °C to rt, 6 h	78 (e)	-	-	-
-	-	-	R_1 = Ts R_2 = Bz	$COCl_2$, THF, 0 °C to rt, 6 h	Complex Mix	R_1 = Ts R_2 = Bz	$HgCl_2$, Et_3N, CH_2Cl_2*, rt	54 (i) 36 (j)

It should be noted that the final entry for the isothiourea series, the 3-benzoyl-1-tosyl carbodiimide, was conducted in dichloromethane because the standard conditions with dimethylformamide (DMF) as the solvent were leading to a side product where the oxygen of DMF was nucleophilically adding to the highly reactive carbodiimide intermediate to generate an amidine side product.

In the first three rows of the table, the comparison of the three methods was conducted with tosyl, alkyl carbodiimides. Each methodology afforded the bicyclic guanidine rearrangement product in comparable moderate yields. The final three rows

showcase the different electron deficient products that can be generated depending on the methodology chosen. The new urea dehydration pathway expands the overall 1,3-diaza Claisen rearrangement methodology as the nosyl, benzyl carbodiimide was available through that pathway, something that couldn't be achieved with either the thiourea or isothiourea due to the potential Smiles rearrangement chemistry previously discussed. The isothiourea chemistry also expanded the overall rearrangement methodology as it allowed for the synthesis of the mixed tosyl, benzoyl products in a very high combined yield (90 %, 2.16i and 2.16j). This is the most electron deficient carbodiimide generated in the group to date.

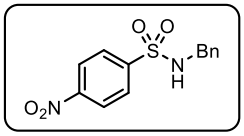
Following the expansion of the intermolecular rearrangement methodology, attention was turned to the further development of the intramolecular 1,3-diaza Claisen rearrangement. Simultaneously to the intermolecular work discussed above other members of the Madalengoitia group were seeing significant progress with the intramolecular rearrangement. The work on the intramolecular rearrangement was beginning to show a trend that indicated the carbodiimide did not need to be as electron deficient as with the intermolecular rearrangement, meaning complex skeletons would be accessible without the challenge of dealing with the highly reactive intermolecular substrates.

2.4 Conclusions

Following attempts at the synthesis of highly electron deficient carbodiimides via a Novel Smiles rearrangement as well as attempts through an aza-Wittig pathway and bis-acyl thioureas, new conditions were developed to dehydrate electron deficient ureas. Ureas as electron deficient as N-benzoyl, N'-tosyl urea are dehydrated by phosgene in the presence of Et_3N to form carbodiimides. The *in-situ* generated carbodiimides were then exposed to tertiary allylic amine N-benzyl 2-azanorbornene for 1,3-diaza Claisen rearrangement to afford complex bicyclic guanidine structures. Concurrently conditions were developed for the desulfurization of highly electron deficient isothioureas. Isothioureas were desulfurized to generate carbodiimides using mercury (II) chloride and Et_3N which were also exposed to N-benzyl 2-azanorbornene. The two methodologies were compared with the original carbodiimide generation method of thiourea desulfurization for a series of rearrangements. Both of the new conditions have strengths with rearrangement products available only through that singular method.

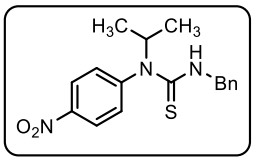
2.5 Experimental

General: Reagents and solvents were of high analytical grade and purchased from Sigma-Aldrich, Fisher Science, and Acros Organics. Anhydrous DMF was prepared by drying of 3 Å molecular sieves. Anhydrous THF was prepared by distillation over potassium metal. Anhydrous CH_2Cl_2 was prepared by distillation over calcium chloride. Anhydrous Et_3N was prepared by distillation over calcium hydride. ^1H NMR spectra were acquired on a Bruker 500 MHz spectrometer or a Varian 500 MHz spectrometer. 1H chemical shifts are reported in reference to residual solvent signals; $CDCl_3$ at d 7.26 ppm, DMSO-d_6 at 2.50 ppm. ^{13}C NMR spectra were acquired on a Bruker 500 MHz spectrometer at 125 MHz. High resolution mass spectrometry data was collected on a Waters Xevo G2-XS QTOF spectrometer. Column chromatography was conducted on Sorbtech silica gel, standard grade, 60A, 40-63 μm.

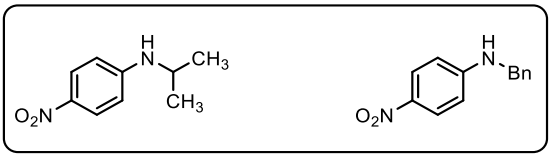


N-benzyl-4-nitrobenzenesulfonamide (2.6a). To a stirred solution of 4-nitrobenzenesulfonyl chloride (1.00 g, 4.50 mmol) in anydrous THF (5 mL) at 0 °C was added benzyl amine (0.50 mL, 4.50 mmol) dropwise. Diisopropyl ethyl amine (0.86 mL, 4.90 mmol) was then added and the reaction was stirred for five minutes at 0 °C. The ice bath was removed and the reaction was allowed to warm to rt and to stir for 3 hr.

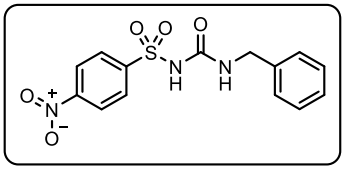
Distilled H_2O (10 mL) was then added and the reaction mixture was stirred for 1 hr. Five drops of concentrated HCl were added and extracted with EtOAc (3 x 10 mL). The combined organic layers were combined, dried ($MgSO_4$), and concentrated to afford sulfonamide 2.6a (1.29 g, 86 % yield). Spectral data matched literature reported values.



3-benzyl-1-isopropyl-1-(4-nitrophenyl)thiourea (2.12). To a reaction flask was charged lithium hydride (0.012 g, 1.51 mmol). To the reaction flask was added a solution of sulfonamide **25** (0.40 g, 1.37 mmol) in anhydrous THF (10 mL) at 0 °C. The deprotonation was allowed to stir for five minutes, and then isopropyl isothiocyanate (0.29 mL, 2.74 mmol) was added slowly. The reaction was allowed to stir at rt for 24 hr and then 2 hr at reflux. The reaction mixture was worked up with 2 mL of 10 % HCl and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by column chromatography (30% EtOAc in hexanes) to afford thiourea 2.12 as a yellow crystalline solid. R_f = 0.63 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.25 (d, 2H), 7.18 – 7.06 (m, 5H), 5.80 (dtd, *J* = 14.2, 7.4, 7.0, 5.9 Hz, 1H), 5.27 (s, 1H), 4.72 (d, *J* = 5.4 Hz, 2H), 1.04 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.0, 147.8, 144.0, 138.0, 131.7, 128.8, 127.6, 127.5, 125.5, 52.6, 49.7, 21.4.

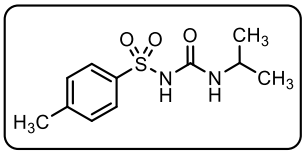


N-isopropyl-4-nitroaniline (31), **N-benzyl-4-nitroaniline (2.13 a&b)**. Potassium hydride (0.033 g, 0.82 mmol, 30% in mineral oil) was charged to a reaction flask. Excess mineral oil was washed out with hexanes (3 x 2 mL). To the reaction flask was added a solution of sulfonamide **25** (0.200 g, 0.685 mmol) in anhydrous THF (5 mL). After five minutes of stirring, N-isopropyl isothiocyanate (0.146 mL, 1.40 mmol) was charged to the reaction mixture drop-wise and allowed to stir overnight at room temperature. 1 mL of 10% HCl was added to the reaction mixture in a seperatory funnel, diluted with 3 mL distilled H_2O, and extracted with EtOAc. The organic layers were collected, dried ($MgSO_4$), and concentrated to afford a mixture of anilines 2.13a and 2.13b. The compounds were separated via column chromatography (30% EtOAc in hexanes). Spectral data matched literature reported values.



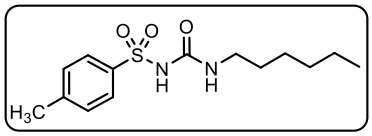
N-(benzylcarbamoyl)-4-nitrobenzenesulfonamide (2.15). Procedure adapted from Cervello.[48] Benzyl isocyanate (3.81 mL, 30.9 mmol) was added to a solution of 4-nitrobenzenesulfonamide (5.00 g, 24.7 mmol) and copper (I) chloride (0.29 g, 2.97 mmol) in dimethyl formamide (20 mL) at ambient temperature. The mixture was stirred

under nitrogen at ambient temperature for 20 hr. The mixture was then poured into an ice/water bath (200 mL) and the resultant mixture was acidified with conc. aqueous HCl to pH 2. Toluene was added until a precipitate formed. The precipitate was isolated by vacuum filtration and washed with water to give 2.15 (7.93 g, 96 %). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35 (d, *J* = 8.05 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 2H) 7.28-7.15 (m, 5H), 4.16 (d, *J* = 4.95 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) 144.7, 140.2, 128.99, 128.97, 128.7, 128.6, 127.5, 127.1, 124.4, 43.3 ppm; IR (solid), 3314, 3109, 1662, 1520, 1346 cm^{-1}; HRMS (*pos.* ESI (2Na-H)+ adduct) *m/*z 380.0285 (380.0300 calcd. for $C_{14}H_{12}N_3O_5SNa_2$); R_f = 0.19, eluent: 75 % EtOAc in hexanes; m.p. 195 – 223 °C.



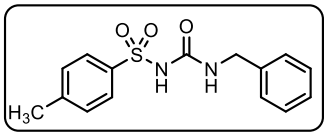
N-(isopropylcarbamoyl)-4-methylbenzenesulfonamide (2.24a). Sodium hydride (0.13 g, 60 % in mineral oil, 3.21 mmol) was charged to a flame dried flask with a stir bar, capped under nitrogen, and cooled to 0 °C. A solution of p-$TsNH_2$ (0.50 g, 2.92 mmol) in freshly distilled THF (5 mL) was added slowly to the sodium hydride and the mixture was stirred for five minutes at 0 °C. Isopropyl isocyanate (0.29 mL, 2.92 mmol) was added to the flask and the reaction mixture was stirred for 4 hr. The THF was removed under reduced pressure and the remaining material was transferred to a seperatory funnel with EtOAc (6 mL) and distilled H_2O (6 mL). Concentrated aqueous HCl was added until the aqueous layer was acidic (pH 2). The layers were separated and the aqueous layer was

extracted with EtOAc (3 x 6 mL). The four combined organic layers were dried ($MgSO_4$) and concentrated to give colorless solid 2.24a (0.71 g, 95 %). ^{1}H NMR data matches literature reported values[49], herein reported is further spectral characterization. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14 (broad singlet, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 6.40 (d, *J* = 6.8 Hz, 1H), 3.96-3.85 (m, 1H), 2.44 (s, 3H), 1.15 (d, *J* = 6.55, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 151.1, 144.7, 136.8, 129.8, 127.0, 42.6, 22.7, 21.6 ppm; IR (solid) 3294, 3240, 1667 cm^{-1}; MS (*pos*. ESI) *m/z* 257.0955 (257.1000 calcd. for $C_{11}H_{17}N_2O_3S$, MH; R_f = 0.39, eluent: 40 % EtOAc in hexanes; m.p. 137 – 140 °C.

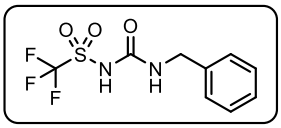


N-(hexylcarbamoyl)-4-methylbenzenesulfonamide (2.24b). TsNCO (0.39 mL, 2.5 mmol) was dissolved in dichloromethane (5 mL) in a flame dried flask, capped under nitrogen, and cooled to 0 °C. Hexyl amine (0.23 mL, 2.50 mmol) was added to the isocyanate and the reaction mixture was stirred for 4 hr while the ice bath was allowed to warm to room temperature. The dichloromethane was removed under reduced pressure to give colorless solid 2.24b (0.69 g, 91 %). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.29-8.63 (broad s, 1H), 7.77 (d, *J* = 8.35 Hz, 2H), 7.30 (d, *J* = 8.05 Hz, 2H), 6.54 (broad t, 1H), 3.20 (q, *J* = 6.9, 6.0, 7.0 Hz, 2H), 2.43 (s, 3H), 1.45 (m, 2H), 1.32-1.20 (m, 6H), 0.87 (t, *J* = 6.85, 7.00 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 152.0, 144.7, 136.8, 129.86, 127.0, 40.3, 31.4, 29.5, 26.4, 22.5, 21.6, 14.0 ppm; IR (film) 3333, 3109, 1659 cm^{-1}; MS (*pos*. ESI)

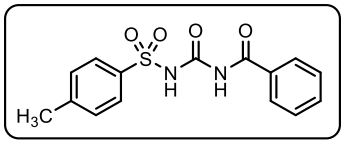
m/z 299.14 (299.14 calcd. for $C_{14}H_{22}N_2O_3S$, MH); R_f = 0.53, eluent: 40 % EtOAc in hexanes; m.p. 113 – 115 °C, lit 120-121 °C.[50]



N-(benzylcarbamoyl)-4-methylbenzenesulfonamide (2.14). TsNCO (8.56 mL, 56.00 mmol) and dichloromethane (100 mL) were added to a flame dried 250 mL round bottom flask equipped with a stir bar. The mixture was cooled to 0 °C and capped under nitrogen. Benzyl amine (6.41 mL, 56.00 mmol) was added to the reaction flask. A colorless precipitate formed immediately. The reaction was stirred at 0 °C for 2 hr. The dichloromethane was removed under reduced pressure to afford 2.14 (14.22 g, 84%) as a white powder that was used without further purification. ^{1}H NMR data matches literature reported values,[51] herein reported is further spectral characterization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.31-7.27 (m, 5H), 7.17 (d, *J* = 5.7 Hz, 2H), 6.91 (broad s, NH), 4.41 (d, *J* = 5.8 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 151.6, 144.9, 137.5, 136.5, 130.0, 128.7, 127.7, 127.5, 127.0, 44.2, 21.7 ppm; IR (solid) 3318, 3109, 1659, 1551; HRMS (*pos*. ESI) *m/z* 305.10 (305.37 calcd. for $C_{15}H_{16}N_2O_3S$, MH); R_f = 0.38, eluent: 30 % EtOAc in hexanes, m.p. 175 – 179 °C, lit 176-179 °C.[52]

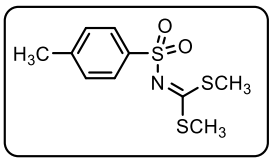


N-(benzylcarbamoyl)-1,1,1-trifluoromethanesulfonamide (2.17). The procedure used to synthesize 2.24a was used, with an overnight reflux. The reaction provided a white solid. The crude product was purified on a silica gel column to give pure 2.17 (1.67 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 9H), 7.30 (d, *J* = 1.7 Hz, 1H), 6.81 (s, 1H), 4.51 (d, *J* = 5.7 Hz, 2H), ^{13}C NMR (THF, 126 MHz): δ 138.5, 128.2, 127.1, 127.0, 121.0, 118.5, 44.1 ppm; HRMS (*pos*. ESI) *m/z* 326.9998 (2Na-H)+ adduct (327.0000 calcd. for $C_9H_8F_3N_2O_3SNa_2$, M2Na-H).



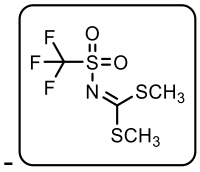
N-(tosylcarbamoyl)benzamide (2.18). To a mixture of *p*-tosyl sulfonamide (0.51 g, 2.90 mmol) in anhydrous toluene (15 mL) was added benzoyl isocyanate (0.51 g, 3.50 mmol). The reaction mixture was heated at reflux for 4 hr, five drops of pyridine (0.038 g, 0.48 mmol) were added and the reaction was heated at reflux further for 2 hr. The toluene was removed *in-vacuo* to give crude 2.18 as a white solid. The crude reaction mixture was purified on a silica gel column with 50 % EtOAc in hexanes to give pure 2.18 (0.73 g, 79 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.49 (s, 1H), 9.00 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 7.1 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.62 – 7.56 (m, 3H), 7.31 (d, *J* = 8.0 Hz,

2H), 2.44 (s, 3H), ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.0, 149.4, 145.16, 135.7, 134.2, 130.8, 129.5, 129.3, 128.6, 127.9, 21.7 ppm.

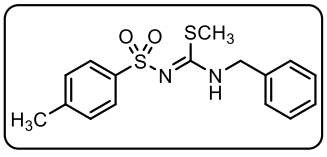


Dimethyl toluenesulfonylcarbonimidodithioate (2.22a). Potassium hydride (12.1 g, 35 % in mineral oil, 105 mmol) was added to a flame dried 1000 mL round bottom flask equipped with a stir bar. The excess mineral oil was removed by rinsing with hexanes (3 x 10 mL). The flask was capped under nitrogen and cooled to 0 °C. A solution of *p*-$TsNH_2$ (6.00 g, 35.0 mmol) in anhydrous THF (200 mL) was added slowly to the potassium hydride. The mixture was stirred for 30 minutes at 0 °C. 300 additional milliliters of anhydrous THF were added to the reaction flask and the flask was connected to a condenser. Carbon disulfide (29.7 mL, 490 mmol) was added to the reaction flask. The mixture was stirred at reflux for 36 hr. The reaction flask was allowed to cool to room temperature and then cooled to 0 °C. Methyl iodide (4.36 mL, 70.9 mmol) was added and the reaction mixture was stirred overnight while warming to room temperature. A short-path distillation apparatus was connected to the reaction flask. Excess carbon disulfide was removed via distillation; half of the liquid in the flask was removed by distillation, then 100 mL anhydrous THF was added to the reaction flask and the liquid was distilled again. This process was repeated a third time. The remaining THF was removed under reduced pressure to afford a yellow solid. This solid was purified on

a silica gel column using a gradient of solvent from 10, 30, and 50 % EtOAc in hexanes and a final flush with pure EtOAc to afford 2.22a as a yellow solid (9.08, 94 %). Proton NMR data matches literature reported values[53], herein reported is further spectral characterization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (d, J = 7.3 Hz, 2H), 7.21 (d, J = 7.3 Hz, 2H), 2.44 (s, 6H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 184.7, 143.6, 137.8, 129.4, 127.2, 21.6, 16.4 ppm; IR (solid) 2924, 1597, 1458; HRMS (*pos.* ESI) *m/z* 276.0182 (276.0200 calcd. for $C_{10}H_{13}NO_2S_3$, MH); R_f = 0.19, eluent: 30 % EtOAc in hexanes; m.p. = 117 – 118 °C.

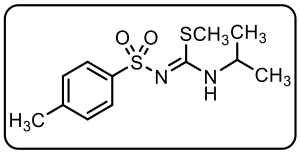


Dimethyl ((trifluoromethyl)sulfonyl)carbonimidodithioate (2.22b). The reported literature procedure was followed to afford 2.22b. Spectral data and identification match reported literature values.[43]



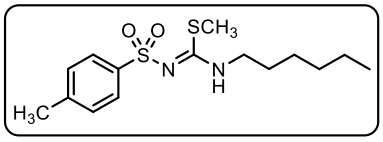
Methyl-N-benzyl-N'- toluenesulfonylcarbonimidodithioate (2.23a). Dimethyl toluenesulfonylcarbonimidodithioate (2.22a) (0.50 g, 1.81 mmol) was added to a flame

dried 100 mL pear shaped flask equipped with a stir bar and the flask was then connected to a condenser. Five milliliters of methanol were added to the reaction flask followed by benzyl amine (0.24 mL, 2.17 mmol). The reaction mixture was heated at reflux for 3 hr. The methanol was removed under reduced pressure to afford crude 2.23a. The crude reaction material was purified on a silica gel column with 30 % EtOAc in hexanes as an eluent to afford pure 2.23a (0.59 g, 97 %). This compound has been previously reported,[54] herein reported is further spectral characterization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.5 (broad s, 1H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.37-7.26 (m, 5H), 7.23 (d, *J* = 6.45 Hz, 2H), 4.48 (d, *J* = 5.9 Hz, 2H), 2.42 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 169.5, 142.8, 139.6, 135.6, 129.4, 129.0, 128.2, 127.3, 126.3, 48.6, 21.5, 14.3 ppm; IR (solid) 3302[54], 2924, 1573 cm^{-1}; HRMS (*pos*. ESI) *m/z* 335.0882 (335.0900 calcd. for $C_{16}H_{18}N_2O_2S_2$, MH); R_f = 0.36, eluent: 30 % EtOAc in hexanes; m.p. = 131 – 133 °C, lit 138 °C.[54]



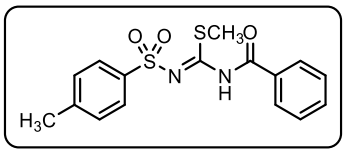
Methyl-N-isopropyl-N'- toluenesulfonylcarbonimidodithioate (2.23b). Dimethyl toluenesulfonylcarbonimidodithioate (0.50 g, 1.63 mmol) was added to a flame dried 100 mL pear shaped flask equipped with a stir bar and the flask was then connected to a condenser. Five milliliters of methanol were added to the reaction flask followed by isopropylamine hydrochloride (0.19 g, 1.95 mmol). Triethyl amine (0.27 mL, 1.95 mmol)

was added to the reaction flask and the mixture was stirred at reflux for 3 hr. The methanol was removed under reduced pressure to afford crude product. The crude product was purified on a silica gel column using 30 % EtOAc in hexanes to give 2.23b as a colorless solid (0.33 g, 70 %). This compound has been previously reported,[54] herein reported is further spectral characterization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.1 (broad s, NH) 7.78 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.86-2.78 (m, 1H), 2.41 (s, 3H), 2.36 (s, 3H), 1.25 (2, *J* = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 168.1, 142.6, 139.9, 129.3, 126.1, 46.8, 22.9, 21.5, 14.1 ppm; IR (solid) 3279, 2970, 1558 cm^{-1}; MS (*pos*. ESI) *m/z* 287.0884 (287.09 calcd. for $C_{12}H_{18}N_2O_2S_2$, MH); R_f = 0.8, eluent: 30 % EtOAc in hexanes; m.p. = 114 – 115 °C, lit 119 °C.[54]

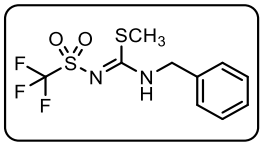


Methyl-N-hexyl-N'- toluenesulfonylcarbonimidodithioate (2.23c). 9c was synthesized by the same method as 2.23a above to afford 2.23c (0.529 g, 89 %) as a pale yellow oil after purification on a silica gel column with 30 % EtOAc in hexanes as the eluent. This compound has been previously reported,[54] herein reported is further spectral characterization. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19-8.13 (broad s, NH) 7.79 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 2H), 3.26 (dt, *J* = 7.0, 5.9, 6.9 Hz, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.63-1.56 (m, 2H), 1.36-1.26 (m, 6H), 0.89 (t, *J* = 6.8, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 169.4, 142.6, 139.9, 129.3, 126.2, 44.2, 31.3, 29.1, 26.3, 22.5, 21.5,

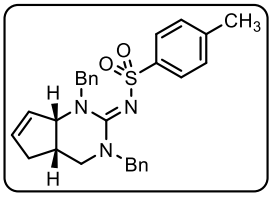
14.1, 14.0 ppm; IR (solid), 3294, 2931, 1573; MS (*pos*. ESI) *m/z* 329.14 (329.14 calcd. for $C_{15}H_{24}N_2O_2S_2$, MH); R_f = 0.48, eluent: 30 % EtOAc in hexanes.



Methyl N-benzoyl-N'-tosylcarbonimidithioate (2.23d). Sodium hydride (1.32 g, 60 % in mineral oil, 33.0 mmol) was added to a flame dried 100 mL round bottom flask equipped with a stir bar. The flask was sealed under N_2 pressure and cooled to 0 °C. Benzamide (2.00 g, 16.5 mmol), dissolved in freshly distilled THF (20 mL) was added slowly to the reaction flask. The mixture was stirred at 0 °C for 10 minutes. Dimethyl toluenesulfonylcarbonimidodithioate (4.54 g, 16.5 mmol) was added to the reaction flask along with freshly distilled THF (30 mL). The mixture was stirred at 0 °C for 40 minutes then the ice bath was removed and the reaction was stirred at rt for 5 days. The yellow precipitate was removed via filtration. The filtrate was concentrated to give a gummy yellow solid (5.46 g). The solid was dissolved in dichloromethane, after which a solid crashed out of solution. The solid was isolated by filtration to give crude desired product (2.94 g, 51 % crude). Samples of the product were purified on silica gel with 30 % EtOAc in hexanes individually for use in future reactions. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.19 (s, 1H), 8.03 – 7.97 (m, 2H), 7.90 – 7.84 (m, 2H), 7.71 – 7.64 (m, 1H), 7.61 – 7.54 (m, 2H), 7.37 – 7.31 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H).



Methyl N-benzyl-N'-((trifluoromethyl)sulfonyl)carbamimidothioate (2.23e). 2.22b (0.50 g, 1.98 mmol) was added to a flame-dried 50 mL pear-shaped flask equipped with a stir bar. The flask was capped under N_2 and cooled to 0 °C. Methanol (5 mL) was added. Benzyl amine (0.25 mL, 2.4 mmol) was added to the reaction flask dropwise. The reaction was stirred at 0 °C for 30 minutes. The methanol was removed *in-vacuo*. The crude material was purified on a silica gel column with a gradient of eluent from 10 % EtOAc in hexanes to 30 % to afford pure 2.23e (0.47 g, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (t, *J* = 5.9 Hz, 1H), 7.39 (ddd, *J* = 13.5, 7.8, 6.0 Hz, 3H), 7.32 – 7.28 (m, 2H), 4.57 (d, *J* = 5.8 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.2, 134.4, 129.2, 128.6, 127.4, 123.8, 121.2, 120.7, 118.6, 118.2, 116.1, 48.6, 14.6 ppm.



N-(1,3-dibenzyl-1,3,4,4a,5,7a-hexahydro-2H-cyclopenta[d]pyrimidin-2-ylidene)-4-methylbenzenesulfonamide (1.16b).

General procedure for the dehydration and rearrangement of ureas

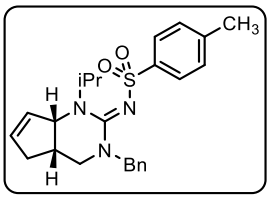
N-(benzylcarbamoyl)-4-methylbenzenesulfonamide 2.14 (0.24 g, 0.80 mmol) was added to a flame dried 100 mL pear shaped flask and was then capped under nitrogen and

cooled to 0 °C. Freshly distilled THF (2.4 mL) was added to the reaction flask followed by triethyl amine (0.22 mL, 1.6 mmol). The reaction mixture was stirred at 0 °C for 25 minutes. Phosgene (0.42 mL, 20 % w/w in toluene, 0.80 mmol) was added to the reaction mixture followed immediately by 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene 1.14 (0.15 g, 0.80 mmol). The reaction mixture was stirred for 6 hr while allowing the ice bath to warm to room temperature. The mixture was then transferred to a seperatory funnel with EtOAc (6 mL) and distilled water (6 mL). The layers were separated and the water layer was extracted with EtOAc (3 x 6 mL). The four organic layers were collected, dried ($MgSO_4$), and concentrated to give 0.353 g of crude product mixture. The product was purified on a silica gel column with 40 % EtOAc in hexanes to afford 1.16b (0.287 g, 71 %). Spectral data and identification match reported literature values.[12]

General procedure for the desulfurization and rearrangement of carbonimidithioate

Methyl-N-benzyl-N'- toluenesulfonylcarbonimidodithioate 2.23a (0.080 g, 0.24 mmol) was added to a flame dried 50 mL pear shaped flask equipped with a stir bar. Freshly distilled THF (1 mL) and triethyl amine (0.07 mL, 0.5 mmol) were added and the reaction flask was capped under nitrogen and stirred for 5 minutes. Mercury (II) chloride (0.072 g, 0.26 mmol) was added followed immediately by 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene 1.14. The reaction flask was stirred under nitrogen at room temperature overnight. Reaction flask contents were transferred to two test tubes using chloroform and the precipitate that had formed was centrifuged out of the reaction mixture. The supernatant was collected and the solvent was removed under reduced pressure to afford crude product mixture. The crude mixture was purified on a silica gel

column using 40 % EtOAc in hexanes to give colorless solid 1.16b (0.078 g, 69 %). Spectral data and identification match reported literature values.[12]



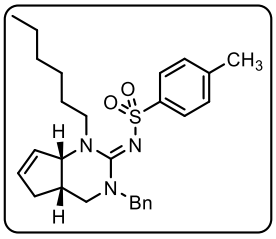
N-(3-benzyl-1-isopropyl-1,3,4,4a,5,7a-hexahydro-2H-cyclopenta[d]pyrimidin-2-ylidene)-4-methylbenzenesulfonamide (1.16f).

From the corresponding urea:

The general procedure used for 1.16b was conduct to afford 1.16f as a colorless solid (0.200 g, 61 %). Spectral data and identification match reported literature values.[12]

From the corresponding carbonimidithioate:

The general procedure used for 1.16b was conduct to afford 1.16f as a colorless solid (0.083 g, 56 %). Spectral data and identification match reported literature values.[12]



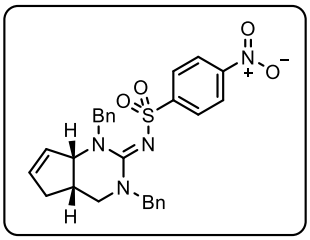
N-(3-benzyl-1-hexyl-1,3,4,4a,5,7a-hexahydro-2H-cyclopenta[d]pyrimidin-2-ylidene)-4-methylbenzenesulfonamide (1.16g).

From the corresponding urea:

The general procedure used for 1.16b was conduct to afford 1.16g as an off-white solid (0.210 g, 67 %). Spectral data and identification match reported literature values.[12]

From the corresponding carbonimidithioate:

The general procedure used for 1.16b was conduct to afford 1.16g as an off-white solid (0.197 g, 63 %). Spectral data and identification match reported literature values.[12]

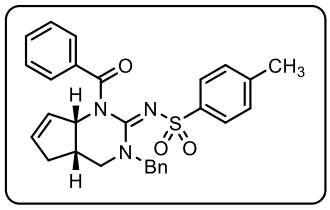


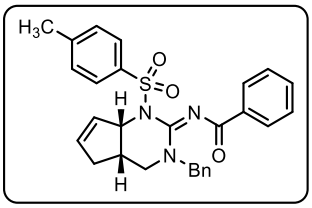
N-(1,3-dibenzyl-1,3,4,4a,5,7a-hexahydro-2H-cyclopenta[d]pyrimidin-2-ylidene)-4-nitrobenzenesulfonamide (1.16e).

From the corresponding urea:

The general urea dehydration and rearrangement procedure for 1.16b was used to afford 1.16e as a colorless solid (0.116 g, 78 %) when conducted in dichloromethane. ^{1}H NMR

($CDCl_3$, 500 MHz) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.39-7.17 (m, 10H), 5.85-5.81 (m, 1H), 5.77-5.73 (m, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.93 (d, *J* = 14.9 Hz, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.53 (d, *J* = 14.9 Hz, 1H), 4.36 (d, *J* = 8.5 Hz, 1H), 3.26 (dd, *J* = 4.9, 4.9 Hz, 1H), 3.07 (dd, *J* = 6.7, 6.7 Hz, 1H), 2.60-2.52 (m, 1H), 2.45-2.37 (m, 1H), 1.86-1.8 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 157.7, 151.4, 148.5, 136.7, 135.8, 133.5, 128.8, 128.8, 128.6, 128.3, 127.8, 127.3, 126.6, 123.7, 65.2, 55.5, 53.7, 47.9, 36.9, 36.6 ppm; IR (solid) 3061, 3026, 1522, 1503, 1346 cm^{-1}; HRMS (*pos*. ESI) *m/z* 503.1747 (503.1800 calcd. for $C_{27}H_{26}N_4O_4S$, MH); R_f = 0.48, eluent: 50 % EtOAc in hexanes; m.p. 140 – 146 °C.



and


1.16i **1.16j**

N-((4aS,7aS,E)-1-benzoyl-3-benzyl-1,3,4,4a,5,7a-hexahydro-2H-cyclopenta[d]pyrimidin-2-ylidene)-4-methylbenzenesulfonamide (1.16i), N-((4aS,7aS,E)-3-benzyl-1-tosyl-1,3,4,4a,5,7a-hexahydro-2H-cyclopenta[d]pyrimidin-2-ylidene)benzamide (1.16j).

From the corresponding carbonimidithioate: The general procedure used for the desulfurization of carbonimidithioates was used with 2.23d. The reaction was conducted in dichloromethane instead of dimethylformamide. An aliquot of crude reaction mixture

was purified via HPLC with a gradient eluent of water:acetonitrile to give both 1.16i (54 %) and 1.16j (36 %).

1.16i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.5 Hz, 4H), 7.49 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.31 (s, 1H), 7.28 – 7.22 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 5.97 (s, 1H), 5.75 (s, 2H), 4.59 (s, 2H), 3.66 (dd, *J* = 13.0, 3.7 Hz, 1H), 3.22 (d, *J* = 13.1 Hz, 1H), 3.14 (s, 1H), 2.54 – 2.42 (m, 1H), 2.36 (s, 3H), 2.03 (d, *J* = 30.2 Hz, 3H), 1.62 (d, *J* = 17.6 Hz, 1H). IR (solid) 3062, 2924, 2252, 1681, 1558, 1473; MS (*pos*. ESI) *m/z* 486.3 (486.6 calcd. for $C_{28}H_{27}N_3O_3S$, MH); R_f = 0.16, eluent: 50 % EtOAc in hexanes.

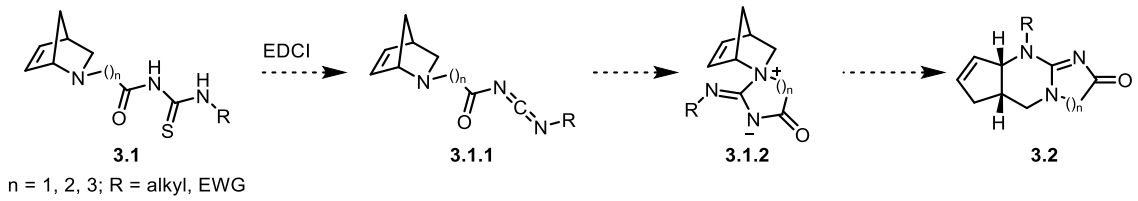
1.16j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.96 (m, 2H), 7.73 – 7.68 (m, 2H), 7.48 – 7.43 (m, 1H), 7.39 – 7.30 (m, 8H), 7.16 – 7.11 (m, 2H), 5.87 – 5.79 (m, 2H), 5.56 – 5.50 (m, 1H), 4.72 – 4.54 (m, 2H), 3.56 (dd, *J* = 13.0, 4.6 Hz, 1H), 3.09 (ddddd, *J* = 9.5, 8.1, 4.8, 3.6, 1.5 Hz, 1H), 2.97 (dd, *J* = 12.9, 1.6 Hz, 1H), 2.57 – 2.41 (m, 2H), 2.38 (s, 3H), 1.79 – 1.72 (m, 1H), 1.28 (s, 2H), 0.89 (dt, *J* = 18.2, 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.3, 152.5, 144.0, 136.6, 136.5, 135.7, 135.2, 131.3, 129.7, 129.4, 129.2, 128.8, 128.6, 128.1, 127.6, 65.6, 54.3, 50.0, 38.8, 37.6, 29.7, 21.6 ppm; IR (solid) 3062.96, 2245, 1589, 1573, 1450, 1296 cm^{-1}; MS (*pos*. ESI) *m/z* 486.4 (486.6 calcd. for $C_{28}H_{27}N_3O_3S$, MH); R_f = 0.26, eluent: 50 % EtOAc in hexanes.

3 INTRAMOLECULAR 1,3-DIAZA CLAISEN REARRANGEMENTS

3.1 Intramolecular Rearrangement of Bridged, Bicyclic Precursors

3.1.1 Original Design

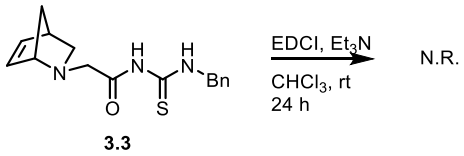
The original design of the bridged, bicyclic, intramolecular project can be seen in Scheme 3.1. For the project, the carbodiimide precursor, thiourea 3.1, would be tethered to the tertiary allylic amine by a variable length alkyl chain.



Scheme 3.1. Potential intramolecular rearrangement pathway.

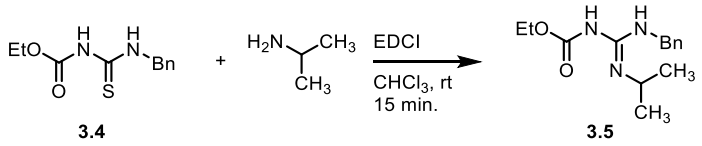
Generation of the carbodiimide *in-situ* (3.1.1) would allow the tethered tertiary allylic amine to attack the carbon of the carbodiimide. This would generate the spirocyclic

zwitterion 3.1.2. The 1,3-diaza Claisen rearrangement would then occur, providing the tricyclic guanidine product 3.2.



Scheme 3.2. Initial attempt.

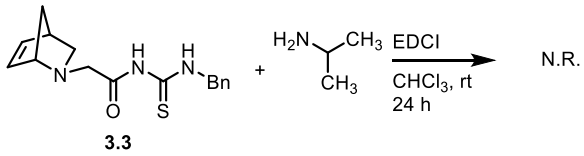
Initially this project was explored by Amy Bowser, her first attempt at the rearrangement was conducted on acyl, benzyl thiourea 3.2, a moderately electron withdrawing carbodiimide precursor. However, upon exposure to EDCI in the typical rearrangement conditions the reaction produced no desired product. It's known that EDCI will desulfurize acyl, benzyl thioureas quickly, as seen in the control experiment of Scheme 3.3.



Scheme 3.3. Desulfurization of acyl thiourea control.

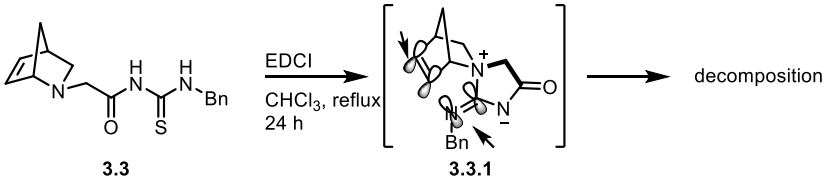
Since it was unknown whether the problem with the rearrangement of thiourea 3.3 was the carbodiimide generation or the rearrangement itself, a control reaction was conducted with an equivalent of isopropyl amine added. If the carbodiimide were formed,

isopropyl amine would trap the carbodiimide as the guandine, similarly to Scheme 3.4, if the carbodiimide was being generated.



Scheme 3.4. Carbodiimide trapping attempts.

Strangely, these reaction conditions provided no trapped guanidine with the isopropyl amine. It's one of several examples in the group that show that the nearby nitrogen of the azanorbornene somehow inhibits the carbodiimide formation, although the reason behind this is unclear. The reaction was attempted in forcing conditions (heating in chloroform at reflux), but this only caused decomposition rather than rearrangement (Scheme 3.5).



Scheme 3.5. Forcing conditions cause decomposition.

The potential issue for this rearrangement is that the spirocyclic zwitterionic intermediate 3.3.1 contains a very rigid five membered ring. This could be a problem because for a true suprafacial/suprafacial rearrangement the lobe on the imine nitrogen

needs to be overlapped with the lobe of the alkene (3.3.1, pointed to by arrows). The rigidity of the spirocycle forces these two lobes to be nearly perpendicular to each other, potentially preventing rearrangement.

The plan for the intramolecular rearrangement was then changed; the acyl group would be removed so the electron withdrawing group would be on the terminal nitrogen and the tether length would be made longer. These two changes would allow for more flexibility in the zwitterionic intermediate, hopefully allowing for better orbital overlap. The switch of the internal acyl group to the terminal electron withdrawing group allows for tunability of the electron withdrawing nature of the carbodiimide.

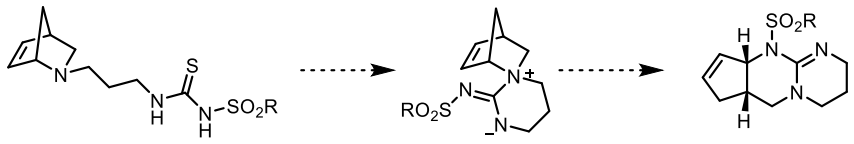


Figure 3.1. New intramolecular rearrangement plans.

The change to having the electron withdrawing group on the terminal nitrogen would have an interesting effect though; it would force the rearrangement to produce the typically disfavored product. In the previous intermolecular rearrangements, the sulfonyl group was always observed on the exocylic imine nitrogen of the guanidine in the final product (Figure **3.2**).

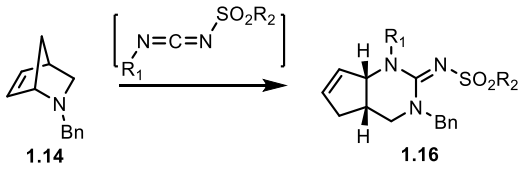
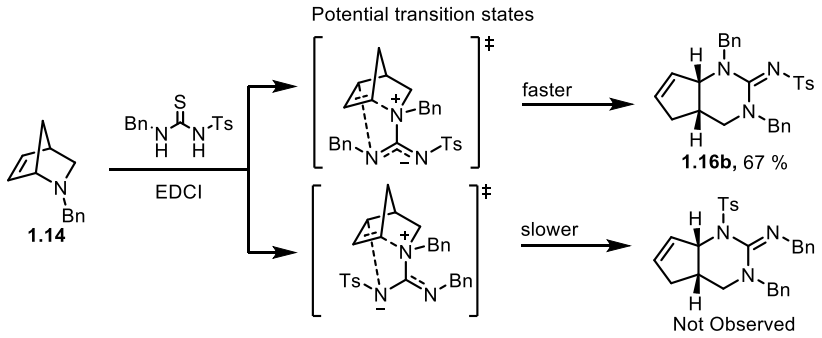


Figure 3.2. General regioselectivity trends.

Scheme 3.6 is an example from the previous work by Amy Bowser showing this trend. In the typical rearrangement with the N-benzyl azanorbornene and the tosyl, benzyl carbodiimide the only rearrangement product observed is the one in which the tosyl group is on the imine nitrogen. This result shows that the transition state where the rearrangement occurs with the tosyl nitrogen is higher in energy (and therefore slower) than the rearrangement with the alkyl nitrogen, which is the only product observed, meaning it is the lower energy pathway.



Scheme 3.6. Potential transition states.

Geometric constraints due to the tether in the intramolecular rearrangement will force the intramolecular variant to occur with the sulfonyl-substituted nitrogen (Figure

3.3). This rearrangement occurring via the higher energy transition state would provide an interesting development.

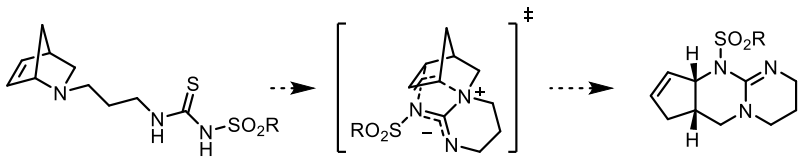
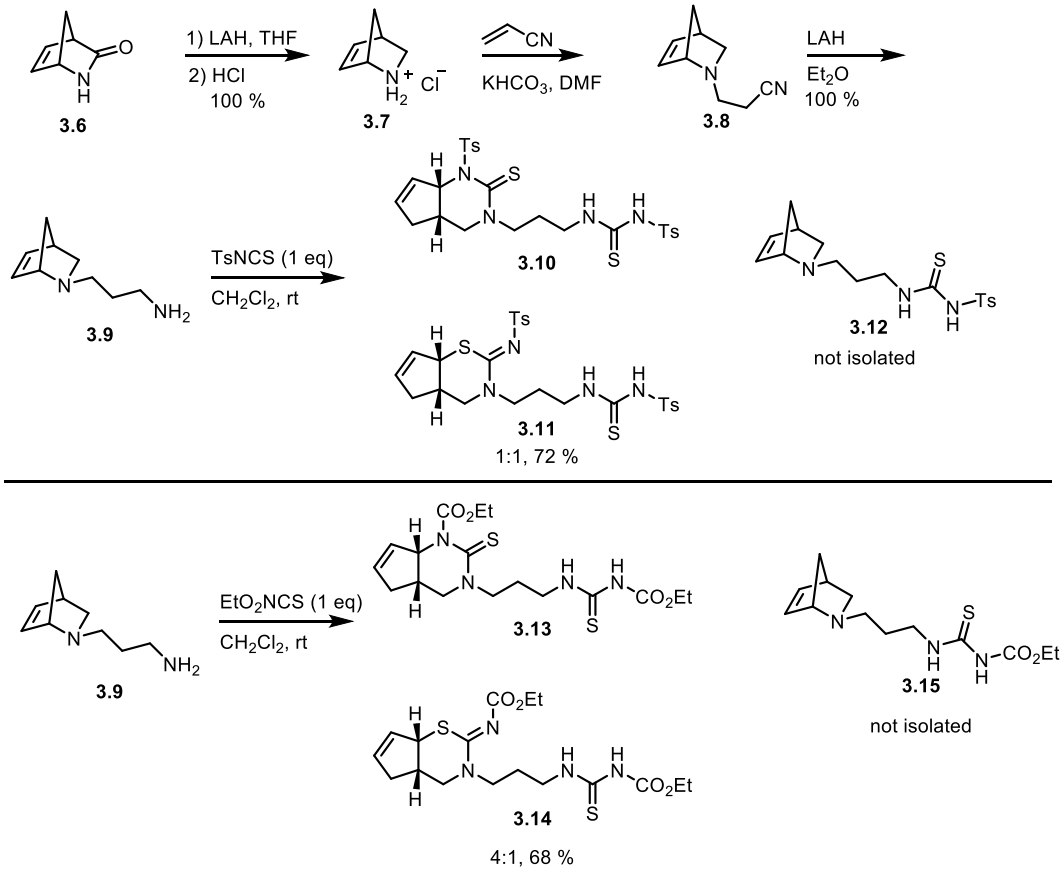


Figure 3.3. Intramolecular rearrangement forced through higher energy transition state.

3.1.2 Initial Intramolecular Rearrangement

The first rearrangement precursor targeted was an N-tosyl thiourea tethered to the N-benzyl azanorbornene via a three-carbon chain. The initial work was conducted by Stevenson Flemer Jr., Ph.D. The starting bridged bicyclic lactam 3.6 was easily reduced with lithium aluminum hydride (LAH) and acidified to give the hydrochloride salt 3.7. Simple 1,4-addition to acrylonitrile provided the tethered nitrile which was also easily reduced with LAH to provide the three-carbon tethered primary amine. However, when this amine was exposed to the standard thiourea synthesis conditions to desired thiourea products were not generated. Rather, for both the reaction with tosyl isothiocyanate and the less-reactive ethoxycarbonyl isothiocyanate two rearrangement products were generated (Scheme 3.7).



Scheme 3.7. Initial intramolecular thiourea synthesis attempts.

The formation of these rearrangement products indicates that the reaction/rearrangement between the tertiary allylic amine of 3.12 and the isothiocyanate is faster than the addition of the primary amine of 3.9 to the isothiocyanates. This is potentially explained by the likely stabilization of the zwitterion's negative charge due to hydrogen bonding from the thiourea; this possible stabilization can be seen in Figure 3.4.

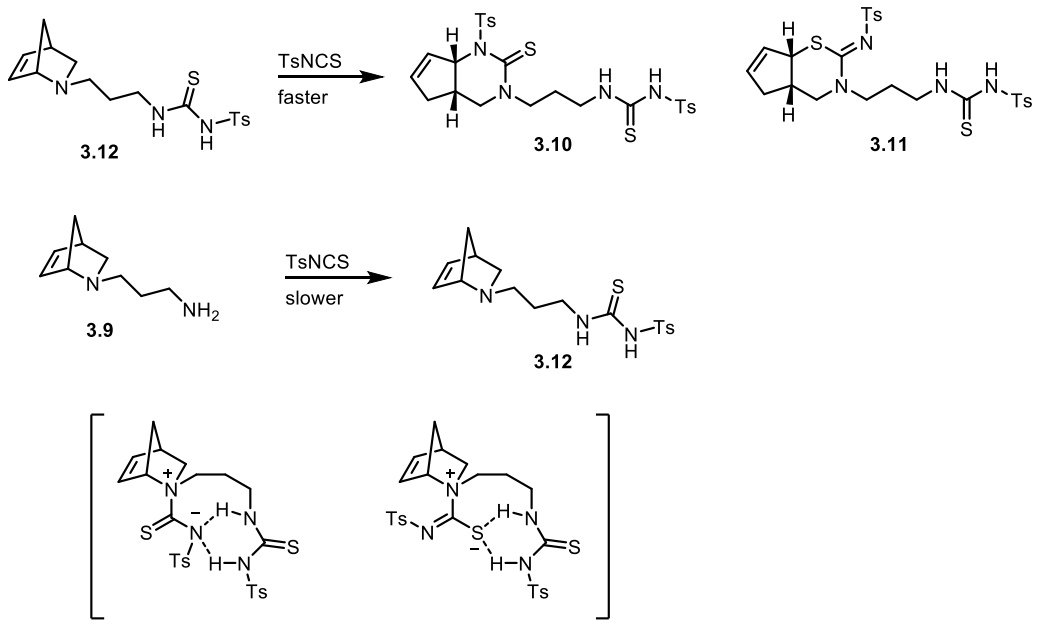
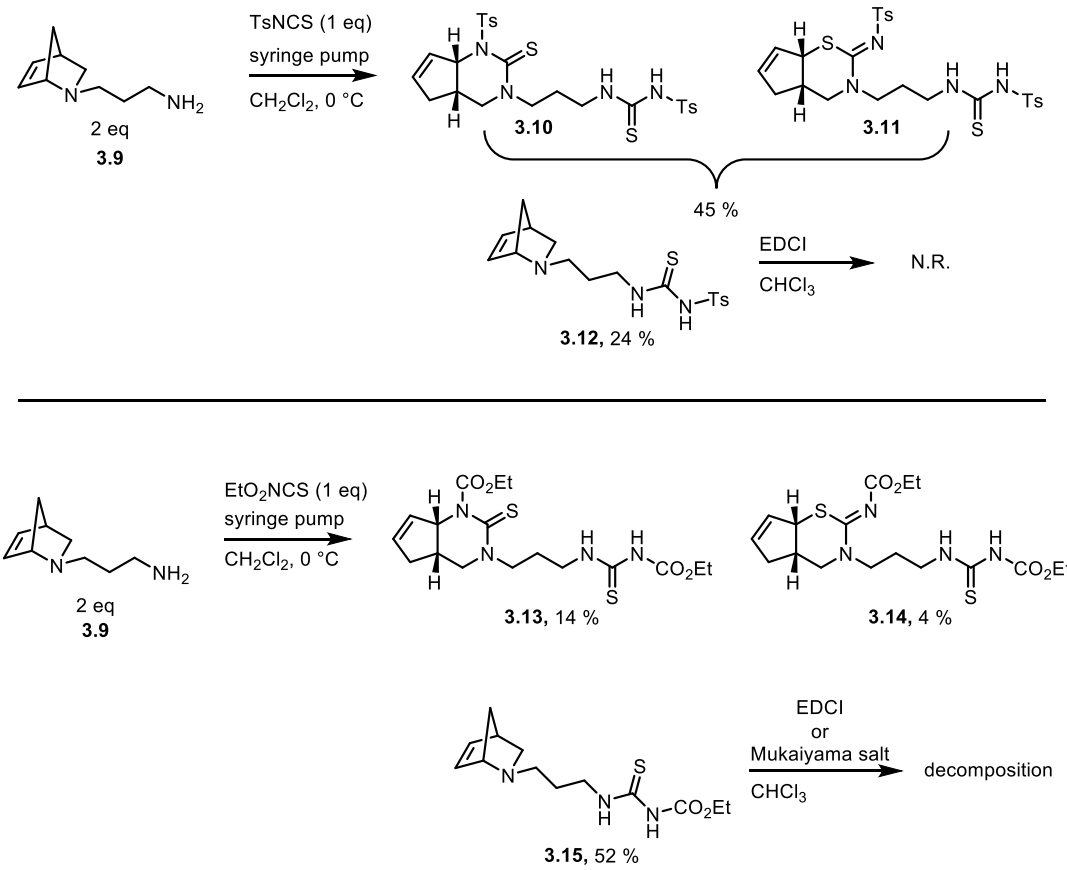


Figure 3.4. Rearrangement is faster than isothiourea formation.

Other projects in the group have shown that stabilization of the negative charge of the zwitterion leads to an increased reaction rate.[13] As this is a problem when the concentration of the isothiocyanate is equal to the concentration of amine, an attempt was made to synthesize the thiourea by adding the isothiocyanate to the reaction mixture via syringe pump, thereby increasing the relative concentration of primary amine (Scheme 3.8). While this process worked, the thiourea was still the minor product, produced in nearly half the amount of the undesired rearrangement products.



Scheme 3.8. Syringe pump synthesis of isothioureas.

While minimal amounts of both the desired thioureas were generated, there was enough for isolation and attempts at rearrangement. However, neither the tosyl variant or the ethoxycarbonyl underwent 1,3-diaza Claisen rearrangement when exposed to the standard conditions. The intramolecular project was shelved until the isothiourea desulfurization method was developed and applied.

3.2 Intramolecular Developments

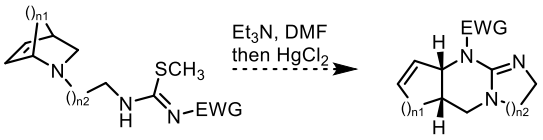
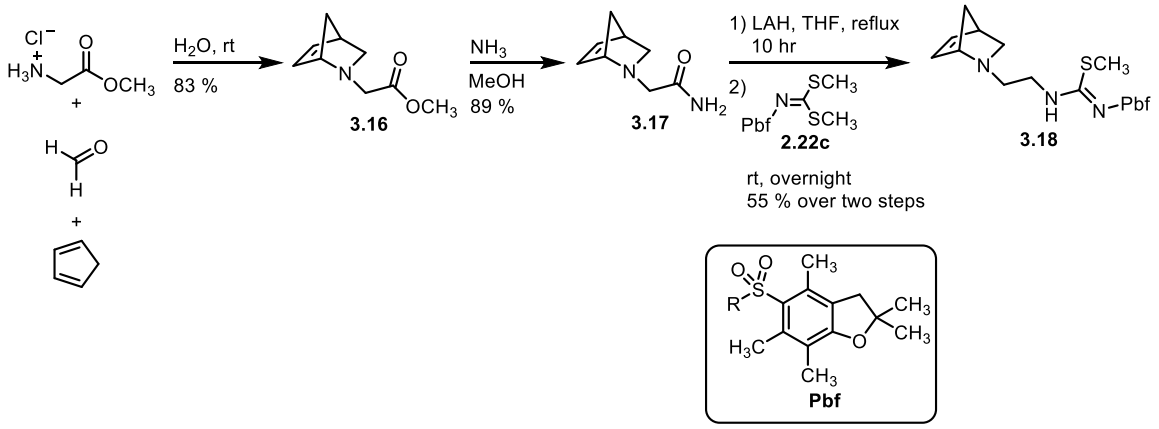


Figure 3.5. Intramolecular rearrangement with isothioureas.

The previous results in the intramolecular work suggested the need for a carbon source that could react with an amine and then be converted to a carbodiimide while not undergoing side rearrangements. As such, the isothiourea work is a good basis as it provides carbodiimide precursors but the carbodithioimidates would not react with the tertiary allylic amine. A series of isothioureas, tethered to the tertiary allylic amine, could be synthesized by the reaction of a primary amine with the appropriate S,S-dimethyldithiocarbonimidate in the fashion that the isothioureas were developed for the intermolecular rearrangement project. Exposure to the developed desulfurization conditions and rearrangement would provide a series of complex tricyclic guanidines (Figure 3.5).

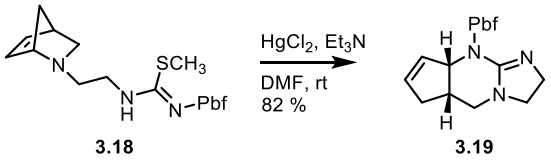
For the intramolecular rearrangements, the decision was made to develop ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl) (Pbf) isothioureas because the Pbf group has a similar electron withdrawing nature to the tosyl group, but the extra methyl groups help with solubility in organic solvents and it can be deprotected with trifluoroacectic acid. The synthesis of the Pbf carbodithioimidate was conducted in the same fashion as the tosyl, starting from the relevant sulfonamide.

Synthesis of the analog with a two-carbon chain began with the Grieco iminum Diels-Alder reaction between glycine methyl ester hydrochloride, formaldehyde, and cyclopentadiene.[55-56] The glycine methyl ester hydrochloride and formaldehyde form an iminium ion which undergoes Diels-Alder [4+2] cycloaddition with freshly cracked cyclopentadiene to provide methyl ester 3.16 in an 83 % yield. Conversion of the ester to amide 3.17 was achieved via stirring the ester in an ammonia-saturated solution of methanol over five days to provide the primary amide. Conversion of the primary amide to the isothiourea 3.18 took place over a two-step process. The amide was first reduced to the volatile primary amine using LAH. This was a surprisingly long process, because, not only was isolating the primary amine difficult due to its volatility, but azanorbornenes are known to undergo retro-Diels-Alder reactions in the presence of acid,[57] so forming the hydrochloride salt for isolation was not an option. Because the primary amine could never be isolated, following the work-up for the reduction the addition of the Pbf-carbodithioimidate 2.22c was conducted immediately. The isothiourea was isolated in a 55 % yield over the two-step process.



Scheme 3.9. Synthesis of the two-carbon analog.

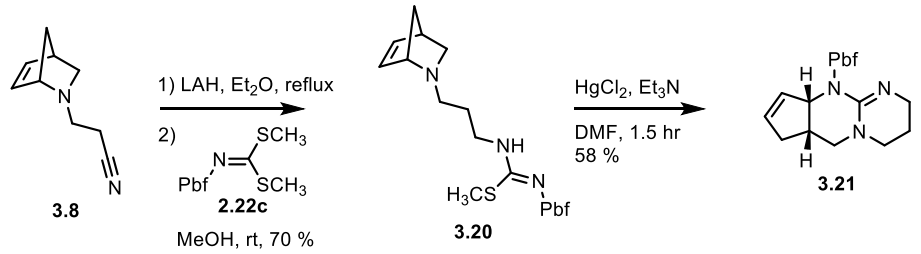
Carrying out rearrangement with this analog under the standard reaction conditions of triethylamine and mercury (II) chloride in DMF produced the desired tricyclic guanidine 3.19 in an 82 % yield (Scheme 3.10).



Scheme 3.10. Rearrangement of the two-carbon analog.

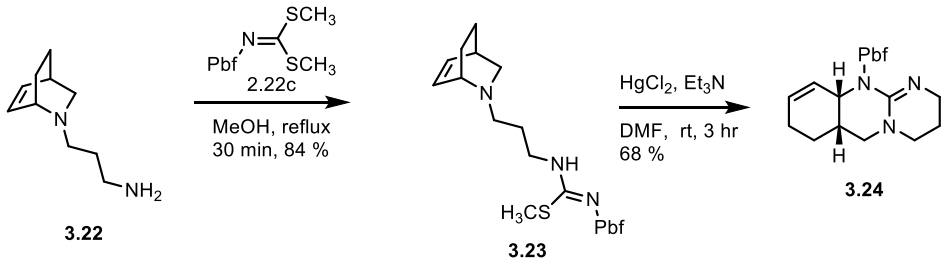
The next target for the intramolecular rearrangement study is the azanorbornene analog with a three-carbon tether. The strategy discussed earlier (Scheme 3.7) for the synthesis of the nitrile (3.8) with the three-carbon chain was utilized. In a one-pot process, the nitrile was reduced using LAH and the Pbf-carbodithioimidate (2.22c) was added to generate the desired isothiourea 3.20 in an isolated yield of 70 % (Scheme 3.11).

The isothiourea was exposed to the standard rearrangement conditions and provided the desired tricyclic guanidine 3.21 in a 58 % yield (Scheme 3.11).



Scheme 3.11. Synthesis and isolation of three-carbon analog.

The isoquinuclidine analog of this compound was synthesized in a similar fashion. Primary amine 3.22 (received from Dr. Stevenson Flemer) was allowed to react with the Pbf-carbondithiomimidate to give isothiourea 3.23. Exposure of this isothiourea to the standard rearrangement conditions provided the desired tricyclic guanidine 3.24 in a 68 % yield (Scheme 3.12).

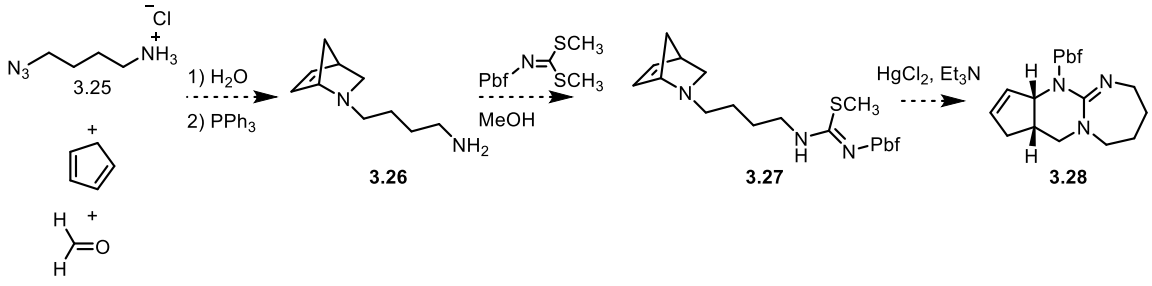


Scheme 3.12. Synthesis of isoquinuclidine three-carbon analog.

This rearrangement was particularly exciting, as the related intermolecular rearrangement could not be effected. Attempts were previously made at conducting the

rearrangement with N-benzyl isoquinuclidine and N-benzyl, N'-tosyl carbodiimide (Scheme 1.2, fourth entry) but the rearrangement did not occur under any conditions. The intramolecular rearrangement proceeding in the moderate yield of 68 %, with an electron withdrawing group similar to tosyl, indicates that the intramolecular variant of the rearrangement does not require carbodiimides that are extremely electron withdrawing.

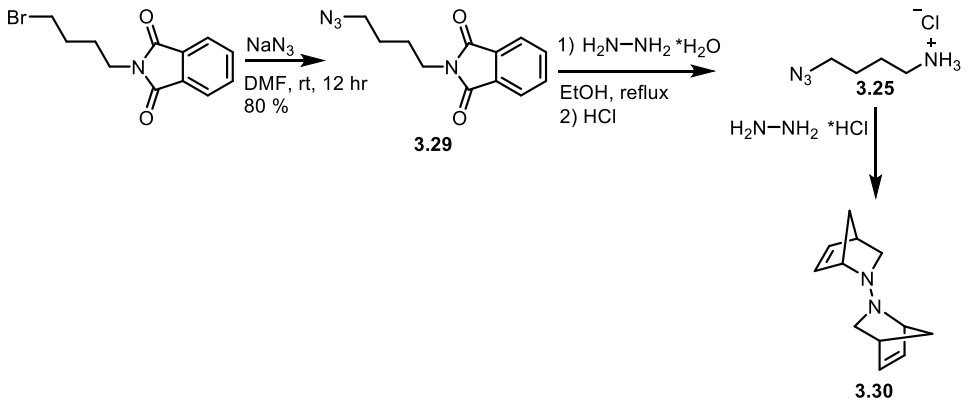
The next rearrangement precursor desired for this project was the four-carbon tether azanorbornene analog, which was the major sticking point of the project. The conjugate addition strategy used for the synthesis of the three-carbon analog's nitrile wouldn't provide a carbon tether long enough, leaving the iminium Diels-Alder as the most-likely pathway. However, previous experience in the Madalengoitia group had shown that the iminium Diels-Alder was fairly sensitive to having functionality on the iminium component. A previous graduate student had attempted the Diels-Alder with 3-aminopropanoate hydrochloride with limited success, the same pathway used for the two-carbon analog. Because of this, the initial synthetic route utilized 1-azido-4-aminobutane hydrochloride (Scheme 3.14).



Scheme 3.13. Initial proposed pathway to four-carbon analog.

The ammonium hydrochloride salt 3.25 would be exposed to the previously discussed Grieco iminium Diels-Alder conditions with cyclopentadiene. The resultant azide could be reduced to primary amine 3.26 using the Staudinger reduction, which would then be allowed to react with the Pbf-carbodithioimidate to provide the desired isothiourea rearrangement precursor 3.27. The rearrangement product 3.28 would then be generated using the standard conditions of $HgCl_2$ and Et_3N in DMF.

In the first attempt at this pathway, sodium azide was allowed to react with the commercially available N-(4-bromobutyl)phthalimide to provide protected amine 3.29. The phthalimide protecting group was removed by hydrazine hydrate in ethanol at reflux and the resultant product was acidified to generate the desired ammonium hydrochloride 3.25. However, exposure of the apparently clean crude reaction mixture to the Diels-Alder conditions provided (nearly exclusively) the double Diels-Alder product of acidified hydrazine hydrate with cyclopentadiene (3.30).



Scheme 3.14. Initial cyclization attempts.

Despite steps that were taken to remove the excess hydrazine from the crude reaction mixture, the Diels-Alder never gave the desired rearrangement product. There is the potential for a 1,3-dipolar cycloaddition occurring between the primary azide and the alkene of the azanorbornene (Figure 3.6), if the initial Diels-Alder product worked. If this is the case, the dipolar cycloaddition is a fast reaction, occurring before the primary azide could be isolated. The 1,3-dipolar cycloaddition product was never isolated, but the NMR of the crude material from the reaction showed no alkene peaks, which would be consistent with this product.

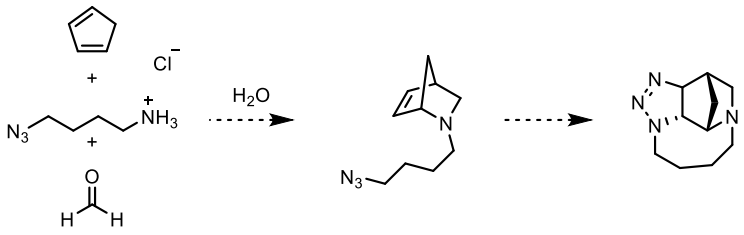
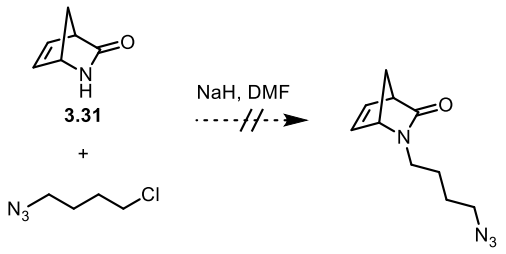


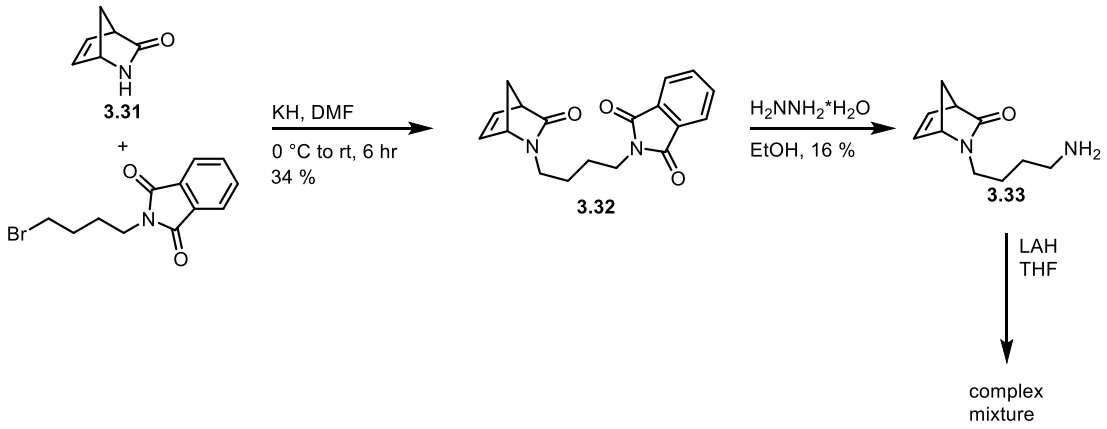
Figure 3.6. Potential 1,3-dipolar cycloaddtion.

Rather than continue to attempt the Diels-Alder, the next iteration of the synthesis involved alkylation of the bicyclic lactam 3.31. The lactam was deprotonated with sodium hydride and alkylation attempts were made with 4-azido-1-chlorobutane, but no desired product was ever isolated. The same problematic 1,3-dipolar cycloaddition may have been occurring with the azide as the crude reaction material also appeared to show no alkene.



Scheme 3.15. Lactam alkylation failure.

Due to the potential azide cyclization, alternate pathways were investigated to achieve the primary amine. The decision was made to alkylate the lactam with N-(4-bromobutyl)phthalimide and subsequently remove the phthalimide protecting group to afford the primary amine (Scheme 3.16).



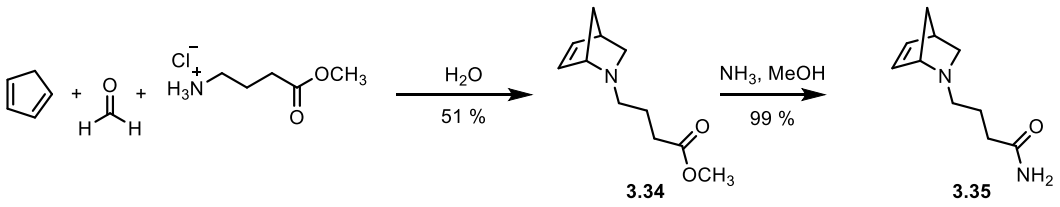
Scheme 3.16. Initial phthalimide lactam alkylation route.

Alkylation of the lactam was achieved, however, the protected amine 3.32 was only isolated in a 34 % yield. Despite this, the phthalimide was deprotected using standard hydrazine hydrate conditions, but the primary amine was only provided in a 16 % yield (3.33). Attempts at LAH reduction of the lactam 3.33 only produced complex product

mixtures. Attempts were made to reduce the lactam with LAH before the phthalimide deprotection (3.32), however these conditions also reduce the imide of the phthalimde, making it considerably harder to remove this protecting group. It also should be noted that following production of the primary amine 3.33, the isothiourea could not be synthesized as the following reduction of the lactam would also reduce the isothiourea.

Low yields among all the attempts at the synthesis of the four-carbon analog precursors via the S_N2 reactions and lactam reductions halted this pathway towards the final bridge-bicyclic analog. Instead, attention was returned to the Diels-Alder pathway that, due to previous experience in the group, was originally discounted.

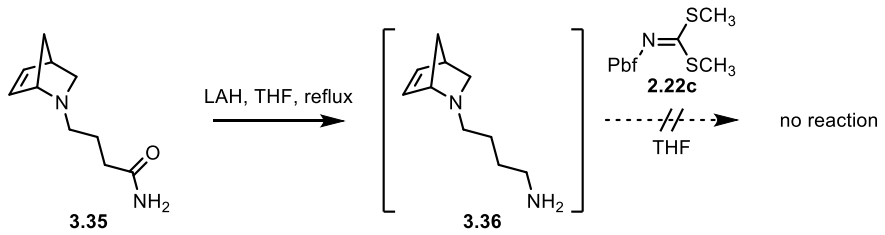
Gratifyingly, the Diels-Alder reaction between cyclopentadiene and methyl 4-aminobutyrate hydrochloride provides the bicyclic ester Diels-Alder adduct 3.34 in a 51 % yield (Scheme 3.17).



Scheme 3.17. Synthesis of four-carbon substrate amine precursor.

The ester was converted to primary amide 3.35 by dissolving the ester in methanol and saturating the solution with ammonia gas and stirring at room temperature for four days, bubbling more ammonia into the solution, and stirring for 3 more days. The clean product was obtained in a 99 % yield, finally providing an amine precursor in a short synthetic pathway that was scalable (up to 15 grams of ester 3.34).

However, solving this problem led to another; the primary amine 3.36 (generated from LAH reduction) would not add to the Pbf-carbodithioimidate 2.22c. Due to the success of the one-pot reaction pathway conducted on the two-carbon analog the same process was attempted for this substrate, with no success.



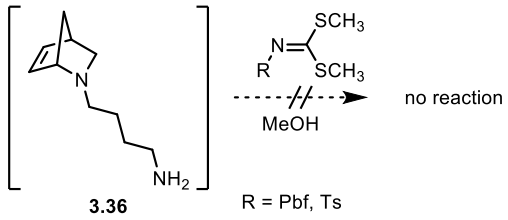
Scheme 3.18. Initial four-carbon isothiourea synthesis attempt.

Initially the choice of solvent for the carbodithioimidate addition reaction seemed the most likely culprit. In the past this reaction had been conducted in polar, protic methanol. While THF had worked for the two-carbon analog, that was not a guarantee for the four-carbon analog to work.

For the reaction to be conducted in methanol, the primary amine would need to be concentrated from the THF solution. This was done by blowing N_2 over the THF overnight to gently remove the solvent and to avoid losing product under vacuum. Unfortunately, despite forcing conditions (methanol, reflux, 3 days) the primary amine would not add to the Pbf carbodithioimidate.

Originally used because the extra methyl groups would help with solubility, the Pbf group may have simply been causing too much steric hindrance with the azanorbornene moiety. The simple switch was made to using the tosyl

carbodithioimidate, as it's of similar electron withdrawing nature, but much smaller. The amine also does not add to the tosyl carbodithioimidate, despite heating in methanol at reflux (Scheme 3.19).

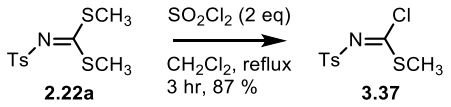


Scheme 3.19. Isothiourea synthesis failures.

For some reason, it seemed that the carbodithioimidates were not reactive enough to add to the primary amine when tethered to the tertiary allylic amine with a longer chain length. The electrophilicity can be increased by replacing one of the S-methyls with a chlorine, while still providing the desired isothiourea products. Justin du Bois (and others) have shown that this chlorination can be conducted simply by reacting the carbodithioimidate with sulfuryl chloride.[58-61]

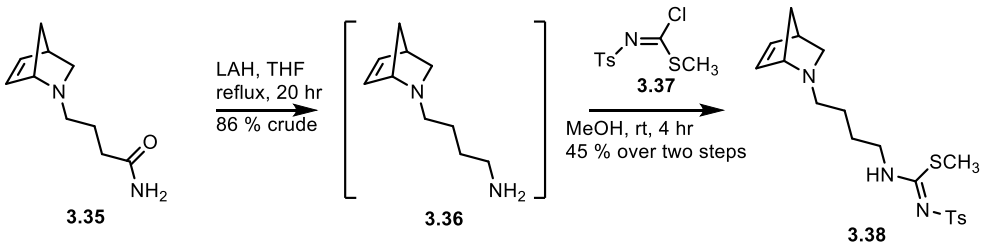
Originally this reaction was attempted with the Pbf carbodithioimidate to keep the rearrangement chemistry consistent with the other species in this series. The carbodithioimidate was dissolved in dichloromethane and sulfuryl chloride was added dropwise. The reaction was heated at reflux for 3 hr, until the carbodithioimidate was no longer detected by TLC. The desired product, however, was not obtained. ^{1}H NMR and mass spec of the crude reaction mixture appear to show that rather than replacing the S-methyl with a chlorine, the sulfuryl chloride somehow radically chlorinated the Pbf group at one of its many benzylic sites. Thankfully, the tosyl carbodithioimidate 2.22A easily

underwent the cholorination with sulfuryl chloride to provide methyl tosylcarbonochloridoimidothioate 3.37 in an 87 % isolated yield (Scheme 3.20).[61]



Scheme 3.20. Synthesis of methyl tosylcarbonochloridoimidothioate.

The two-step reduction and isothiourea synthesis was then conducted on the four-carbon primary amide using the methyl tosylcarbonochloridoimidothioate as the electrophilic agent.

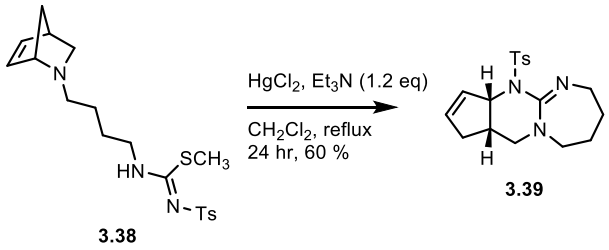


Scheme 3.21. Final synthesis of the four-carbon isothiourea analog.

LAH reduction converted the primary amide 3.35 to the primary amine in an 86 % crude yield following gentle blowing of N_2 to remove the ethereal solvent. The primary amine 3.36 was immediately dissolved in methanol and the methyl tosylcarbonochloroimidothioate was added, providing the isolated isothiourea 3.38 in a moderate 45 % yield over the two steps (Scheme 3.21). It should be noted that not only does this isothiourea decompose, even when stored in a freezer, but later experiments

showed that methanol was nucleophilic enough to add to the carbonochloroimidate 3.37, an unproductive side pathway, which explains a depressed yield. Future isothiourea syntheses with reactant 3.37 were conducted using dichloromethane as the solvent.

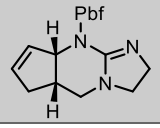
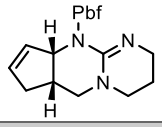
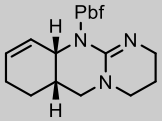
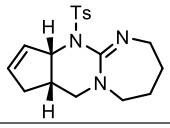
Isothiourea 3.38 was then exposed to the 1,3-diaza Claisen rearrangement conditions. Rearrangement of the isothiourea proceeded smoothly to afford isolated tricyclic guanidine 3.39 in a 60 % yield (Scheme 3.22).



Scheme 3.22. Rearrangement of four-carbon bridged-bicyclic analog.

The rearrangement of the four-carbon analog completed the desired series of bridged-bicyclic 1,3-diaza Claisen substrate rearrangements. While synthesis of the isothioureas was occasionally challenging the rearrangement was generally completed in moderate to high yields of complex tricyclic-guanidine skeletons (Table 3.1).

Table 3.1. Summary of bridged-bicyclic rearrangements.

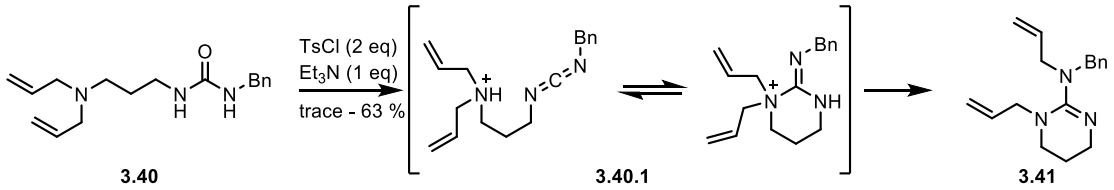
Entry	Tricyclic Guanidine	Yield (%)
1		82
2		58
3		68
4		60

The 1,3-diaza Claisen rearrangement has already been shown to work on intermolecular substrates for the formation of bicyclic guanidine skeletons. The ability to conduct the rearrangement on these bridged-bicyclic intramolecular rearrangement substrates allows for further variation in the complex guanidine products available from the reaction. Another significant benefit from this work comes from entry 3 of Table 3.1. As mentioned earlier this rearrangement implies that for intramolecular variants of the 1,3-diaza Claisen process the carbodiimide does not need to be as strong electron withdrawing as in the intermolecular rearrangements. This revelation builds the basis for the acyclic and monocyclic rearrangement work being conducted now and discussed next.

3.3 Acyclic and Monocyclic Intramolecular 1,3-diaza Claisen Substrates

Work done by Dr. Yanbo Yang, an earlier Ph.D. student in the Madalengoitia group, had originally conducted rearrangement attempts on a series of substrates that were either monocyclic (intermolecular) and acyclic (intramolecular).[13]

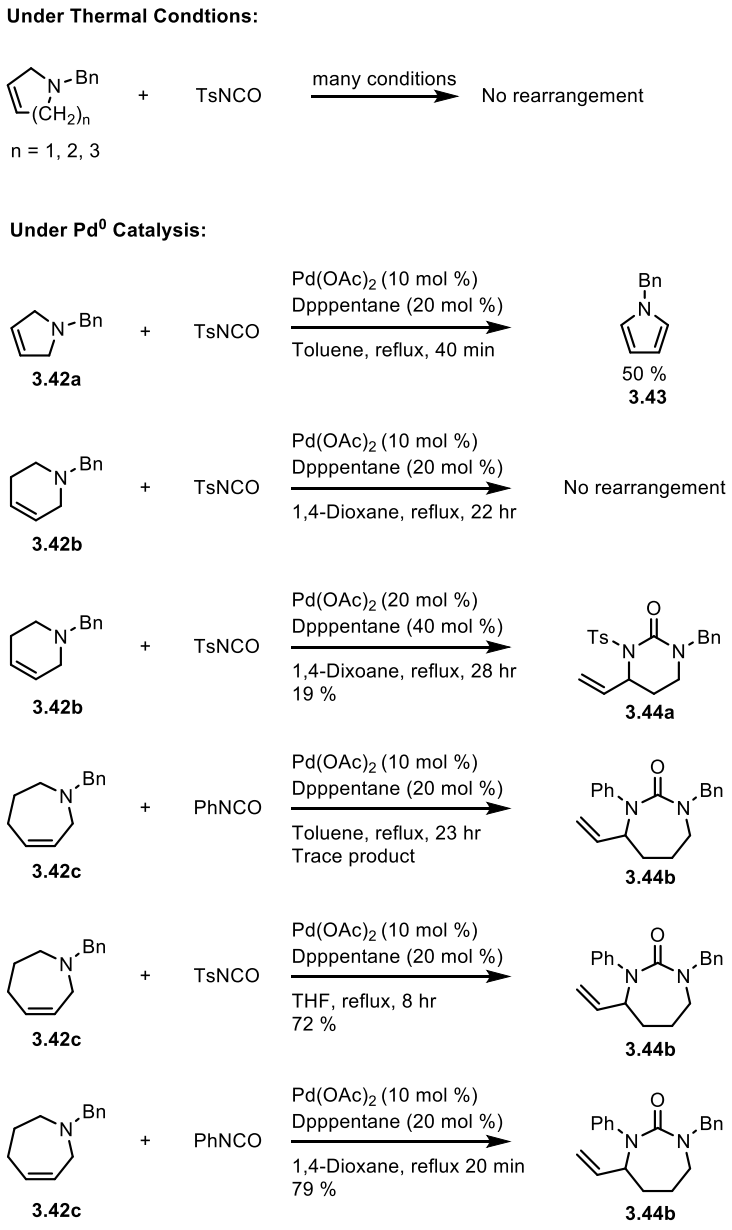
Her work on cyclic species was conducted on a series of substrates in the cationic 1,3-diaza Claisen research she completed. In this work a urea was tethered to diallyl amine (3.40). The ureas were dehydrated using tosyl chloride with only one equivalent of base, which causes the anion of the zwitterion to be protonated, thereby making the rearrangement intermediate cationic (3.40.1). This process was shown to increase rearrangement rate (Scheme 3.23).



Scheme 3.23. Cationic 1,3-diaza Claisen rearrangement.

In the intermolecular work, she found that the substrates would not rearrange under thermal conditions, but once a Pd^0 catalyst was introduced some of the rearrangements would proceed, albeit in low yield unless the electron deficient tosyl isocyanate was used as the heterocumulene (Scheme 3.24).

While it was concluded that the inability of the pyrroline 3.42a and tetrahydropyridine 3.42c to rearrange may be attributed to a stereoelectronic effect, it was encouraging that the N-benzyltetrahydroazepine 3.42b rearranged when that substrate would not rearrange thermally.

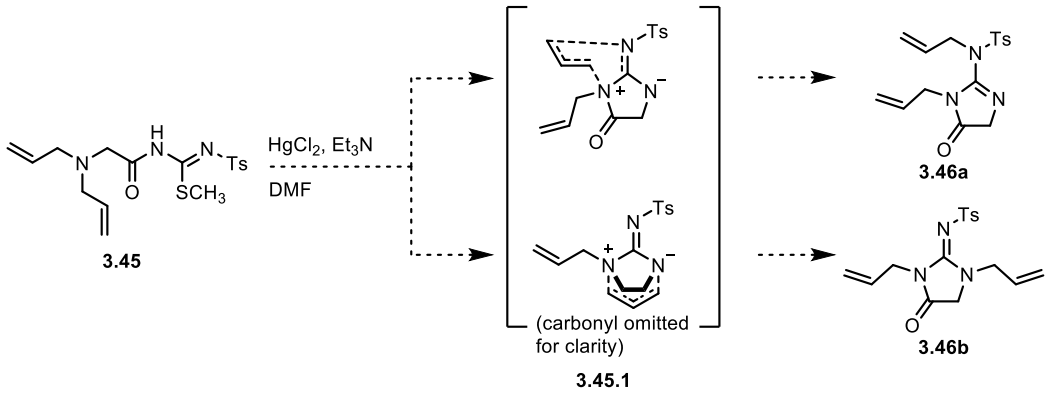


Scheme 3.24. Dr. Yanbo Yang Pd^0 cat. rearrangements.

Both of these sets of reaction conditions produced product, but it can be seen that these rearrangements of the non-ring strained products did not proceed under zwitterionic conditions and needed to be coaxed either by being conducted cationically or with palladium catalysis. The advent of the new reactions to develop electron deficient carbodiimides allows for the study of the zwitterionic 1,3-diaza Claisen rearrangement on the simpler substrates.

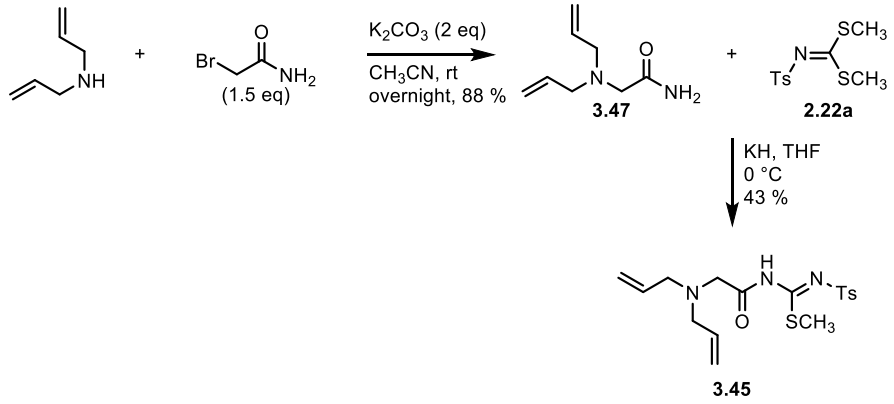
3.3.1 Diallylamino tethered 1,3-diaza Claisen Rearrangements

Initially the exploration of the rearrangement of simpler intramolecular substrates began when it was still unsure whether the carbodiimide needed to be significantly electron withdrawing. The initial target, isothiourea 3.45, consists of an acyl group on interior of the molecule as well as the electron withdrawing tosyl group at the terminus of the isothiourea, making the carbodiimide that would be generated from it highly electron deficient.



Scheme 3.25. Initial target of diallylamino series.

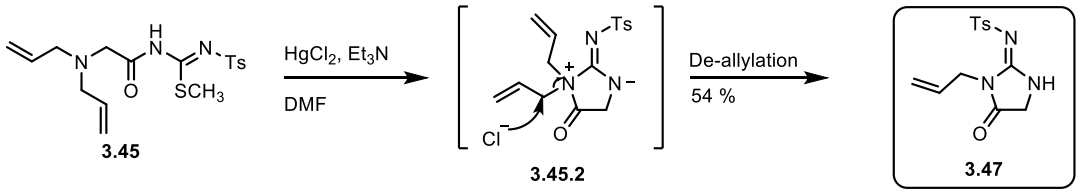
Exposure of the isothiourea 3.45 to the standard rearrangement conditions would provide one of the two rearrangement products 3.46a or 3.46b depending on which nitrogen undergoes rearrangement.



Scheme 3.26. Synthesis of highly electron deficient diallylamino precursor: two-carbon tether.

The diallylamino acetamide 3.45 was easily prepared by the reaction of α-bromoacetamide with diallylamine following Yanbo Yang's procedure.[13] Deprotonation of the amide with sodium hydride and reaction with the tosyl carbodithioimidate provided

isothiourea 3.45 swiftly (Scheme 3.26). The isothiourea was then exposed to the standard isothiourea desulfurization and rearrangement conditions with mercury (II) chloride and trimethylamine in DMF (Scheme 3.27).



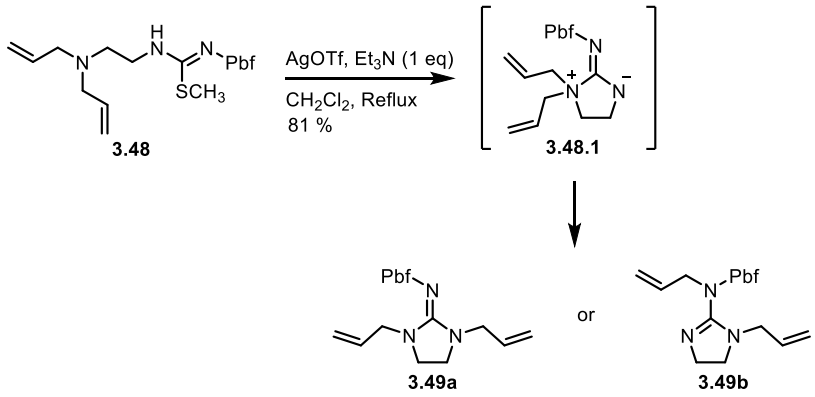
Scheme 3.27. Deallylation of the zwitterion.

Neither desired rearrangement product (3.46a or 3.46b) was isolated from the reaction. Instead, deallylation product 3.47 was isolated, indicated by the proton NMR spectrum containing only one allyl group. Initially the chloride anion was suspected of inducing the dealkylation as shown in 3.45.2. Upon formation of the carbodiimide followed by cyclization to the zwitterion, S_N2 attack of the nucleophilic chloride anion on one of the allyl groups of the cation would provide the deallylation product obtained via a von Braun-type[62-63] ammonium dealkylation.

Since the chloride anion was suspected as the main culprit of deallylation, a different desulfurization agent was needed with a less nucleophilic counterion. The initial idea was to continue using mercury (II) and have the triflate ion, but $HgOTf_2$ is extremely toxic so other agents were investigated. Silver has been shown to be a thiophile[64-65] so desulfurization was attempted with silver (I) triflate as it was readily available.

Scheme 3.28. Deallylation with silver triflate.

Silver triflate was thankfully able to desulfurize the isothiourea, but the only product in the reaction was again the deallylated product. The other potential deallylating culprit was the nucleophilic oxygen of DMF. Also, at this point it had been discovered (via the bridged-bicyclic project) that the intramolecular rearrangement did not need to be as electron deficient as the intermolecular variant. Considering these two factors, the same rearrangement was conducted without the acyl group and in dichloromethane (Scheme 3.29). Desulfurization of isothiourea 3.45 with silver (I) triflate provided a new product that had not been deallylated.



Scheme 3.29. Intramolecular diallylamino rearrangement without acyl group.

Initially however, it was unclear which of the potential rearrangement products was formed, as the proton NMR did not perfectly coordinate with either 3.49a or 3.49b. In the proton NMR for this rearrangement (Figure 3.7) the allyl groups (peaks at 5.6 – 5.8 ppm) were shown to be symmetrical, which fits with the 3.49a but the methylene peaks were not symmetrical (peaks at 3.5 – 3.75), fitting with 3.49b.

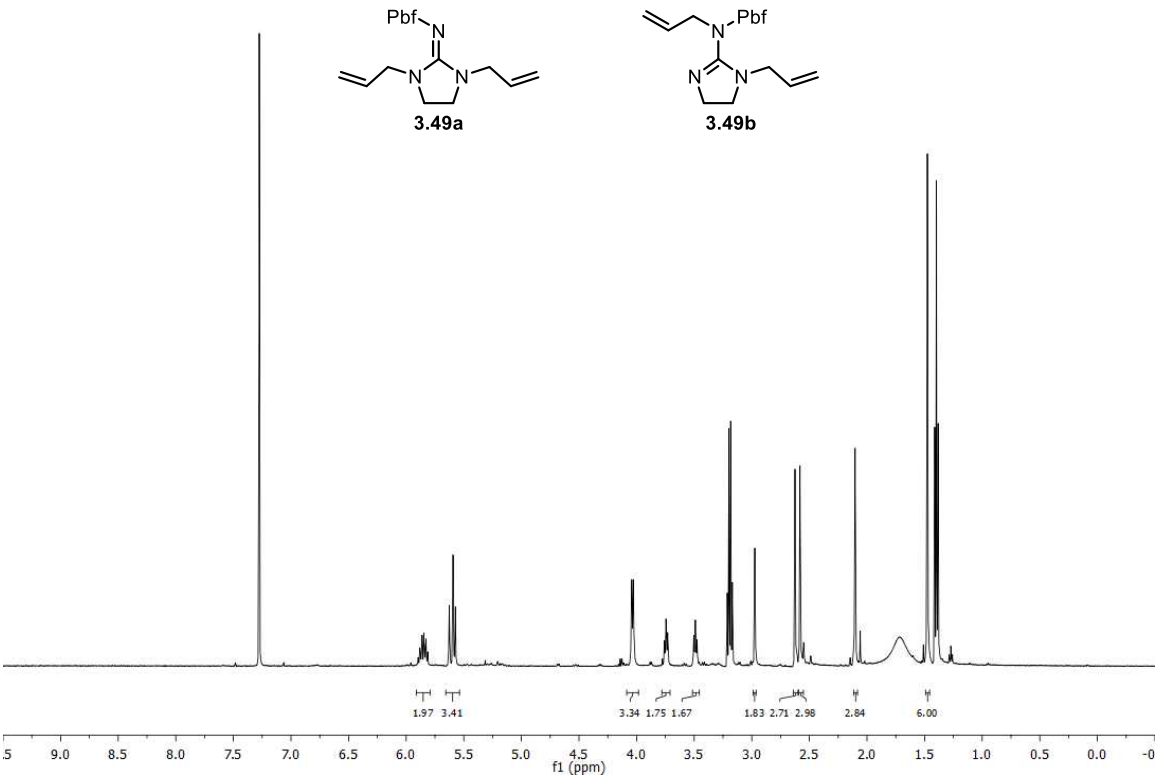
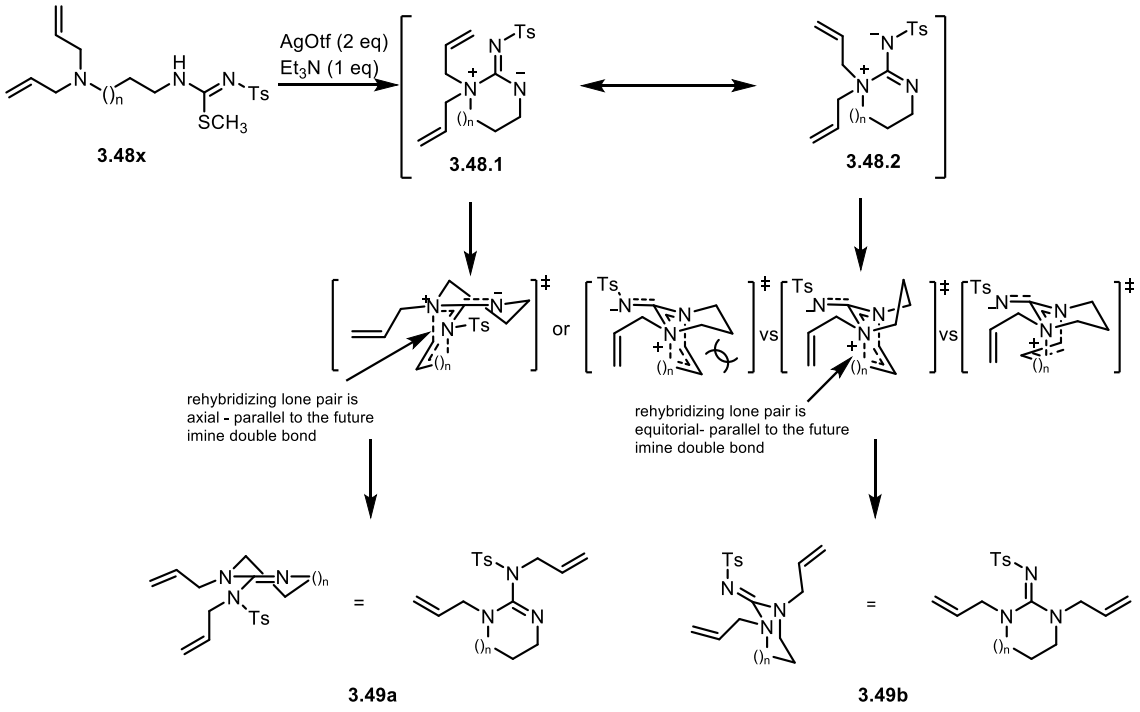


Figure 3.7. Curious NMR for two-carbon diallylamino rearrangement.

Prior to running the rearrangement experiment, it was unclear which regioisomer (3.49a or 3.49b) would predominate as the major product considering there are several competing effects that play a role in determining the product. There are two potential resonance structures of the zwitterionic intermediate (3.48.1 or 3.48.2), leading

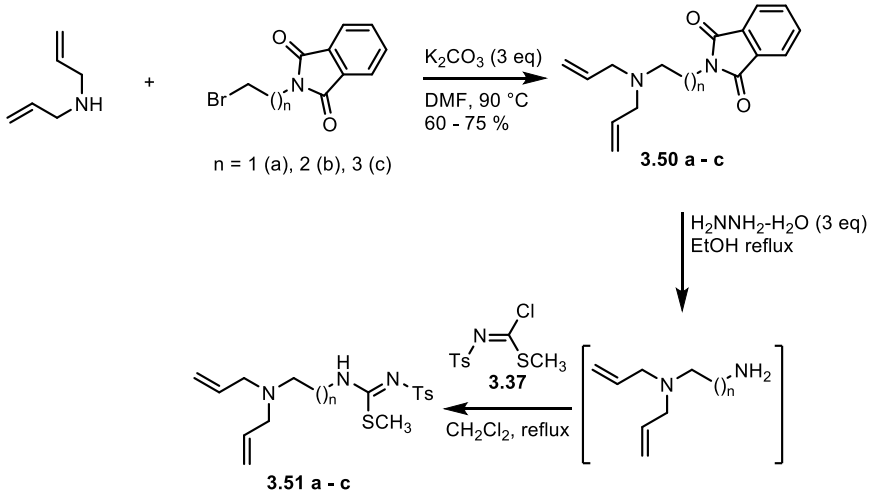
to two different transition states and products (Scheme 3.30). Zwitterionic intermediate 3.48x.1 is formed and the half-chair transition state is obtained. What is seen is that the bond on the quaternary nitrogen that is breaking to re-form the lone pair will be parallel to the future imine double bond to have the best orbital overlap for resonance, which leads to product 3.49a – this product predominates in the cationic variant of the rearrangement where the nitrogen anion is protonated. However, in the zwitterionic variant it appears that the rearrangement predominantly occurs via the second transition state (3.48.2). Upon formation of intermediate 3.48.2 and desired half-chair transition state, with again, the overlap between the rehybridizing lone pair and the future double bond, a significant steric interaction will likely occur between the two flagpole carbons likely forcing the one or the other of the rings into the sterically unfavored boat conformation, making this the likely higher energy transition state. However, the results showed that this is the preferred transition state as the imine of the guanidine in the final product has the tosyl group (3.49b), which fits the electronic control mentioned earlier.



Scheme 3.30. Diallylamino intramolecular rearrangement regioselectivity.

Prior to investigating the rearrangement, the focus was on improving the synthetic pathways towards all the isothioureas. Yields of the LAH reductions were unreliable, and the addition of the primary amines to the carbodithioimidates 2.22 also gave very poor yields. New methods of primary amine synthesis would be explored and the new, more reactive, methyl tosylcarbonochloroimidothioate 3.37 was discovered around this time so it was implemented in the synthetic pathway. The new synthetic pathway for a series of three diallylamino isothioureas is shown in Table 3.2.

Table 3.2. Synthesis of diallylamino rearrangement isothioureas.

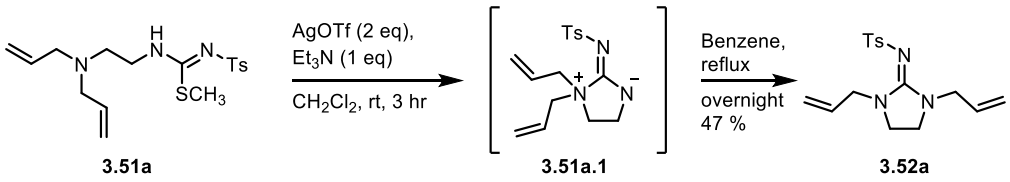


n	Isothiourea Yield (%)
1 (3.51a)	66
2 (3.51b)	65
3 (3.51c)	30

Following experimentation, the optimized synthesis of the diallyamino-substrates is depicted in Table 3.2. Reaction of diallylamine with the commercially available primary bromides of differing chain lengths (ethyl, propyl, butyl) with potassium carbonate in DMF at 90 °C provides the protected primary amine 3.50. The phthalimide group is removed by hydrazine hydrate in absolute ethanol at reflux to give an *in-situ* generated primary amine. This produces a white precipitate (the hydrazine/phthalimide adduct) which is removed by filtration. The amine and excess hydrazine hydrate are separated as follows: the majority of the ethanol is removed by rotary evaporation at room temperature then the remaining concentrated solution of ethanol and primary amine is mixed with dichloromethane and saturated sodium bicarbonate, to assure a basic environment. The hydrazine hydrate is highly water soluble while not at all soluble in the dichloromethane and the desired primary amines are soluble

in dichloromethane and partially soluble in the water, so the two layers are added to a heavier-than-water continuous extractor and the amine is extracted with dichloromethane overnight. The majority of the dichloromethane is removed under vacuum and one equivalent of both the methyl tosylcarbonochloroimidothioate 3.37 and Hunig's Base, which is there to soak up the equivalent of HCl generated are added. The reaction is then refluxed for 3 – 12 hr to form the isothiourea 3.51. The isothiourea then washed with saturated sodium bicarbonate again to remove any acidic protons and extracted with dichloromethane, concentrated, and purified by silica gel column.

The initial result (Scheme 3.29), when it was unclear which rearrangement product was obtained was to be tested again. However, that strange result, along with others in the group, implied that the product being isolated was not a rearrangement product, but the zwitterionic intermediate. The two-carbon analog (3.51a) was subjected to the rearrangement conditions at room temperature in dichloromethane and was worked up (to remove excess silver) when the starting material had disappeared by TLC. The zwitterionic intermediate 3.51a.1 was then dissolved in benzene and heated at reflux to induce rearrangement. Gratifyingly, the increased heat induced the 1,3-diaza Claisen rearrangement (Scheme 3.31), to the apparently opposite regioisomer as is found in the cationic rearrangement, 3.52a in a 47 % isolated yield. This followed the electronic trend of the zwitterionic rearrangement providing the product with the sulfonyl group on the imine nitrogen.



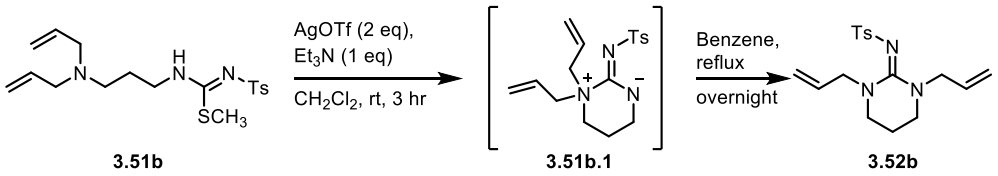
Scheme 3.31. Rearrangement with increased heat.

The isolation of this rearrangement product was a very exciting development after the inconclusive results of the many previous attempts, despite the low yield. While it was unable to be fully isolated, there was NMR evidence that the deallylated product was still present following this rearrangement. In an effort to suppress this pathway, the crude zwitterion, which contained a significant amount of triethylammonium triflate, was washed with sodium bicarbonate to remove this salt. Because it wasn't clear if the zwitterion was soluble, the product was washed only once and while this didn't completely remove the salt, a significant portion was removed. Upon heating the cleaned zwitterion at reflux in benzene, the rearrangement product was isolated in a 60 % yield, a 13 % increase from the initial rearrangement. This suggest that the triethylammonium salts are at least partially responsible for the deallylation of the zwitterion. This information will allow for further exploration of the intramolecular rearrangements and hopefully full suppression of the deallylation pathway.

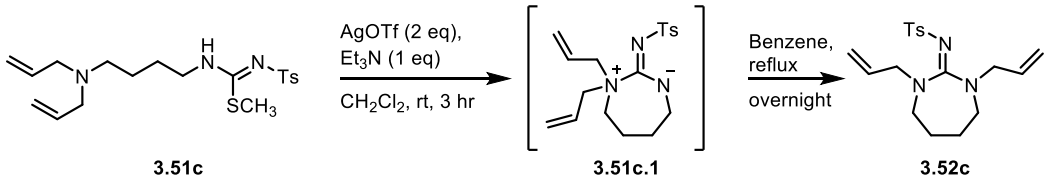
At this point preliminary studies have been completed on the rearrangement of the three-carbon tether isothiourea 3.51b. It is currently unclear if the zwitterion 3.51b.1 of this rearrangement is isolable as it is in the two-carbon variant or if the system requires less energy and rearranges at room temperature in dichloromethane.

3.4 Future Work

The intramolecular rearrangements of the diallylamino substrates will continue to be explored. The initial results discovered with the two-carbon analog further showcase that the rearrangement is the rate-determining step of the 1,3-diaza Claisen process, while the formation of the zwitterion is fast and reversible. The two-carbon analog will initially be studied in hopes of improving the product yield and decreasing the deallylation pathway. Following the optimization of the rearrangement process, the three and four-carbon tether-length analogs will be tested for rearrangement (Schemes 3.33 and 3.34)

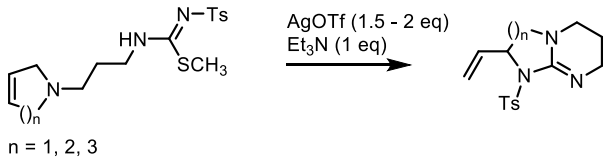


Scheme 3.32. Rearrangement of three-carbon diallylamino substrate.



Scheme 3.33. Rearrangement of four-carbon diallylamino substrate.

In addition to the acyclic diallyamino rearrangement substrates a series of monocyclic rearrangement substrates will be synthesized and rearranged for further exploration of the intramolecular zwitterionic 1,3-diaza Claisen rearrangement (Scheme 3.35).



Scheme 3.34. Monocyclic 1,3-diaza Claisen rearrangements.

3.5 Conclusions

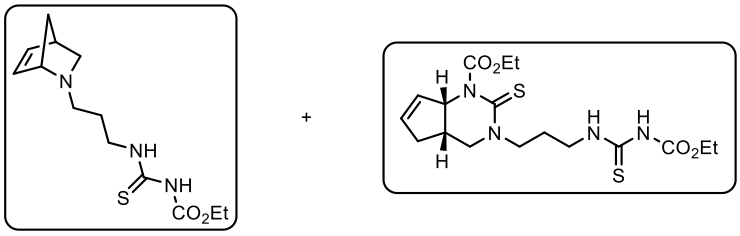
The intramolecular, zwitterionic, 1,3-diaza Claisen rearrangement has been studied extensively. Initially the rearrangement was conducted on substrates containing the highly ring-strained tertiary, allylic amines azanorbornene and isoquinuclidine. The rearrangement was conducted on several substrates and it was shown that in the intramolecular rearrangement the carbodiimide does not need to be as electron deficient as in the intermolecular rearrangement.

This revelation has led to the development of intramolecular rearrangements on substrates in which the tertiary allylic amine does not have any ring-strain to encourage rearrangement. This result is especially exciting as many of these tertiary allylic amines would not have undergone 1,3-diaza Claisen rearrangement in intermolecular rearrangements.

Despite the obstacles for the synthesis of the rearrangement precursors, the 1,3-diaza Claisen methodology has been significantly expanded via the intramolecular pathway. There is a myriad of ways to apply the 1,3-diaza Claisen rearrangement to various inter- and intramolecular substrates, leading to a host of guanidine containing structures. These are simply some of the potential products available from the zwitterionic 1,3-diaza Claisen.

3.6 Experimental

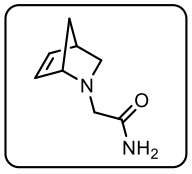
General: Reagents and solvents were of high analytical grade and purchased from Sigma-Aldrich, Fisher Science, and Acros Organics. Anhydrous DMF was prepared by drying of 3 Å molecular sieves. Anhydrous THF was prepared by distillation over potassium metal. Anhydrous CH_2Cl_2 was prepared by distillation over calcium chloride. Anhydrous Et_3N was prepared by distillation over calcium hydride. ^1H NMR spectra were acquired on a Bruker 500 MHz spectrometer or a Varian 500 MHz spectrometer. 1H chemical shifts are reported in reference to residual solvent signals; $CDCl_3$ at d 7.26 ppm, DMSO-d_6 at 2.50 ppm. ^{13}C NMR spectra were acquired on a Bruker 500 MHz spectrometer at 125 MHz. High resolution mass spectrometry data was collected on a Waters Xevo G2-XS QTOF spectrometer. Column chromatography was conducted on Sorbtech silica gel, standard grade, 60A, 40-63 μm.



(3.15 and **3.13)**. 3-(2-azabicyclo[2.2.1]hept-5-en-2-yl)propan-1-amine (0.29 g, 1.91 mmol) was dissolved in dichloromethane (5 mL) and cooled to 0 °C under N_2 protection. Ethoxycarbonyl isothiocyanate (0.11 mL, 0.80 mmol, 0.5 eq) was added to the solution by syringe pump over 2 hr. The crude reaction mixture was concentrated and purified on a silica gel column with a gradient eluent of 50 % EtOAc/Hexanes to 100 % EtOAc to 10

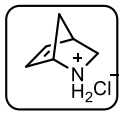
% MeOH/CH_2Cl_2 to provide the two products. ^{1}H NMR of 3.15 (thiourea) (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.01 (s, 1H), 6.40 (ddd, *J* = 5.7, 3.0, 1.2 Hz, 1H), 6.04 (dd, *J* = 5.7, 2.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.04 (d, *J* = 1.7 Hz, 1H), 3.76 (dt, *J* = 13.1, 6.4 Hz, 1H), 3.63 (dt, *J* = 13.7, 6.9 Hz, 1H), 3.32 (dd, *J* = 8.8, 3.1 Hz, 1H), 2.97 (s, 1H), 2.59 (dt, *J* = 12.0, 7.5 Hz, 1H), 2.35 (dt, *J* = 12.1, 6.7 Hz, 1H), 1.86 (p, *J* = 6.8 Hz, 2H), 1.75 (dd, *J* = 8.6, 1.7 Hz, 1H), 1.56 (dd, *J* = 8.8, 1.9 Hz, 1H), 1.46 – 1.40 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{1}H NMR of 3.13 (rearrangement) (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.98 (s, 1H), 5.93 – 5.90 (m, 1H), 5.78 – 5.73 (m, 1H), 5.35 (ddt, *J* = 9.8, 3.2, 1.6 Hz, 1H), 4.38 – 4.27 (m, 5H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.85 – 3.69 (m, 3H), 3.64 (dt, *J* = 13.6, 6.8 Hz, 1H), 3.57 (dd, *J* = 12.8, 4.4 Hz, 1H), 3.23 (dd, *J* = 12.7, 2.8 Hz, 1H), 3.15 (td, *J* = 9.6, 9.2, 4.6 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.30 – 2.21 (m, 1H), 2.10 (p, *J* = 6.9 Hz, 2H), 1.33 (dt, *J* = 21.0, 7.1 Hz, 8H), 0.99 – 0.80 (m, 3H).



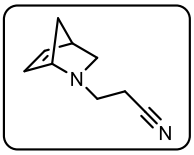
2-azabicyclo[2.2.1]hept-5-en-2-yl)acetamide (3.17). The literature procedure reported by Grieco[66] was followed using glycine ethyl ester hydrochloride (6.00 g, 43.1 mmol) to afford the bicyclic ester Diels-Alder product (6.5 g, 83 %). The ester was used without further purification. The ester was dissolved in a solution of 7N ammonia in methanol (40 mL) and stirred capped at r.t. for five days. The solvent was removed to give a crude

yellow solid. This solid was dissolved in methanol, absorbed onto silica gel, and the methanol was removed. The product was purified on a silica gel column with 90:9:1 CH_2Cl_2:MeOH:NH_4OH as the eluent to give pure 3.17 (4.86 g, 89 % from the ester) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.33 (ddd, *J* = 5.7, 3.1, 1.2 Hz, 2H), 6.05 (dd, *J* = 5.7, 2.1 Hz, 1H), 3.82 (d, *J* = 1.6 Hz, 1H), 3.20 (d, *J* = 16.9 Hz, 2H), 3.01 – 2.90 (m, 1H), 2.65 (d, *J* = 16.8 Hz, 1H), 1.63 – 1.53 (m, 1H), 1.50 (dd, *J* = 8.5, 1.7 Hz, 1H), 1.42 (dd, *J* = 8.1, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.8, 136.9, 130.9, 65.7, 58.78, 54.2, 48.8, 44.3 ppm; IR (solid) 3371.57, 3194.12, 2985.81, 2854.65, 1651.07 cm^{-1}; HRMS (*pos*. ESI) *m/z* 153.1021 (Theoretical mass: 153.1028); R_f = 0.5, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH; m.p. = 89-91 °C



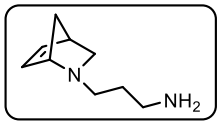
2-azabicyclo[2.2.1]hept-5-en hydrochloride (3.7). To a slurry of LAH (1.39 g, 36.7 mmol) in freshly distilled THF (50 mL) cooled to 0 °C and under N_2 protection was added a solution of 2-azabicyclo[2.2.1]hept-5-en-3-one (2.00 g, 18.4 mmol) in freshly distilled THF (20 mL) slowly. The reaction mixture was stirred at 0 °C for 30 minutes, then allowed to warm to r.t. The mixture was then heated at reflux for 20 hr. The reaction mixture was cooled to 0 °C and diluted with 20 mL Et_2O. The Fieser workup for LAH reactions was conducted: 1.39 mL of distilled water were added slowly, and then 1.39 mL of 0.1 M NaOH was slowly added, followed by 4.2 mL of distilled water. This mixture was warmed to r.t. and stirred for 15 minutes. $MgSO_4$ was added to absorb the water and the mixture was stirred for another 15 minutes. The solids were removed by

filtration through Celite. The filtrate was acidified using anhydrous 15 m L, 2M HCl (made from MeOH and AcCl). This solution was concentrated with a rotovap and dried on a Welch vacuum pump overnight to give 3.7 (1.81 g, 75 %) as an off-white solid. This material was used without any further purification. Characterization data matches reported values.[66]



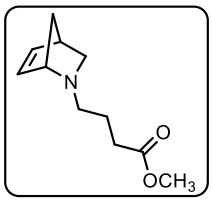
3-(2-azabicyclo[2.2.1]hept-5-en-2-yl)propanenitrile (3.8). To a mixture of 2-azabicyclo[2.2.1]hept-5-en hydrochloride (3.7) (1.50 g, 11.4 mmol) in DMF (15 mL) in a flame dried flask was added $KHCO_3$ (2.28 g, 22.8 mmol) and the mixture was cooled to 0 °C. Acrylonitrile (0.90 mL, 13.7 mmol) was added slowly to the solution and the reaction was stirred under N_2 for 3 hr at r.t. The reaction mixture was transferred to a seperatory funnel with 100 mL H_2O and 150 mL EtOAc. The aqueous layer was removed and the organic layer was washed with 60 mL H_2O. The combined aqueous layers were washed with 50 mL EtOAc. The organic layers were combined and dried ($MgSO_4$). The $MgSO_4$ was removed via filtration and some of the EtOAc was removed on the rotovap. The nitrile product is volatile on the pump, so it was isolated by blowing N_2 over the solution for 24 hr to remove the rest of the EtOAc to give 3.8 (1.24 g, 72 %) as an amber oil that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$ δ 6.34 (ddd, J = 5.8, 3.1, 1.2 Hz, 1H), 6.02 (dd, J = 5.8, 2.0 Hz, 1H), 3.88 (h, J = 1.5 Hz, 1H), 3.21 (dd, J =

8.4, 3.1 Hz, 1H), 2.95 (dt, *J* = 3.9, 1.9 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.48 – 2.42 (m, 2H), 2.35 (ddd, *J* = 11.7, 7.6, 6.1 Hz, 1H), 1.57 (dt, *J* = 8.2, 1.7 Hz, 1H), 1.46 (dd, *J* = 8.4, 1.7 Hz, 1H), 1.41 (dq, *J* = 8.2, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.8, 130.8, 130.3, 119.0, 65.1, 52.8, 50.7, 48.4, 43.9, 18.2 ppm; HRMS (*pos.* ESI) *m/z* 149.1070 (Theoretical mass: 149.1079); R_f = 0.56, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH.

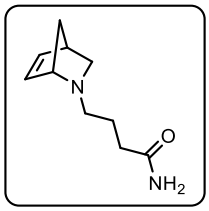


3-(2-azabicyclo[2.2.1]hept-5-en-2-yl)propan-1-amine (3.9). To a slurry of LAH (0.256 g, 6.76 mmol) in Et_2O (8 mL) cooled to 0 °C under N_2 protection was added a solution of 3-(2-azabicyclo[2.2.1]hept-5-en-2-yl)propanenitrile (3.8) (0.50 g, 3.38 mmol) in Et_2O (2 mL) slowly. The reaction was heated at reflux overnight. The reaction mixture was cooled to 0 °C and diluted with 10 mL Et_2O. The Fieser workup for LAH reactions was conducted: 0.256 mL of distilled water were added slowly, and then 0.26 mL of 0.1 M NaOH was slowly added, followed by 0.75 mL of distilled water. This mixture was warmed to r.t. and stirred for 15 minutes. $MgSO_4$ was added to absorb the water and the mixture was stirred for another 15 minutes. The solids were removed by filtration through Celite. The filtrate was concentrated by blowing N_2 over it to remove the Et_2O for 5 hr to give 3.9 (0.27 g, 52 %) as a pale amber oil that was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (dt, *J* = 8.0, 3.8 Hz, 1H), 6.00 (dt, *J* = 7.0, 3.4 Hz, 1H), 3.87 (d, *J* = 4.8 Hz, 1H), 3.16 (dq, *J* = 9.2, 5.2, 4.2 Hz, 1H), 2.90 (s, 1H), 2.72 (q, *J* = 6.4

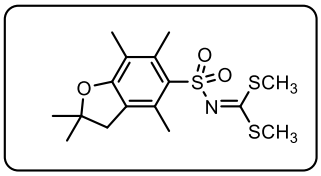
Hz, 2H), 2.46 (dddd, J = 13.6, 10.8, 7.0, 4.0 Hz, 1H), 2.17 (ddd, J = 12.0, 9.0, 5.9 Hz, 1H), 1.64 – 1.53 (m, 3H), 1.47 – 1.34 (m, 2H), 1.25 (s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 136.1, 130.6, 64.5, 53.1, 52.6, 48.2, 43.7, 40.9, 33.2 ppm.



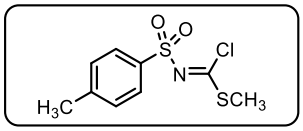
Methyl 4-(2-azabicyclo[2.2.1]hept-5-en-2-yl)butanoate (3.34). The literature procedure reported by Grieco[66] was followed using methyl 4-aminobutyrate hydrochloride (15.0 g, 97.6 mmol) to afford the bicyclic ester Diels-Alder product (9.71 g, 51 %) as an amber oil. The ester was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 – 6.27 (m, 1H), 5.99 (dd, J = 5.8, 2.0 Hz, 1H), 3.84 (q, J = 1.8 Hz, 1H), 3.65 (s, 3H), 3.15 (dd, J = 8.5, 3.1 Hz, 1H), 2.90 (s, 1H), 2.42 (ddd, J = 11.6, 8.9, 6.6 Hz, 1H), 2.33 (t, J = 7.4 Hz, 2H), 2.10 (ddd, J = 11.6, 8.5, 5.9 Hz, 1H), 1.78 (qt, J = 8.9, 7.0 Hz, 2H), 1.56 (dt, J = 8.1, 1.7 Hz, 1H), 1.45 – 1.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.0, 136.0, 130.5, 64.5, 54.4, 52.5, 51.4, 48.1, 43.7, 32.1, 24.5 ppm; HRMS (*pos.* ESI) 196.1341 (Theoretical mass: 196.1338); R_f = 0.26, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH, iodine stain.



4-(2-azabicyclo[2.2.1]hept-5-en-2-yl)butanamide (3.35). Methyl 4-(2-azabicyclo[2.2.1]hept-5-en-2-yl)butanoate 3.34 (9.71 g, 49.8 mmol) was charged to a flame-dried 100 mL round bottom flask equipped with a stir bar and dissolved in methanol (50 mL). The flask was sealed with a septum and $NH_{3\ (g)}$ was bubbled through the solution for 30 mins. The reaction was stirred for 7 days sealed at room temp (on the fourth day $NH_{3\ (g)}$ was bubbled through the solution again for 30 mins). The solution was rotovapped and placed on a vacuum pump overnight to afford the product (8.93 g, 99 %) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.33 (ddd, *J* = 5.7, 3.2, 1.1 Hz, 1H), 6.01 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.33 (s, 1H), 3.85 (q, *J* = 1.7 Hz, 1H), 3.14 (dd, *J* = 8.6, 3.1 Hz, 1H), 2.93 (s, 1H), 2.50 (dt, *J* = 12.0, 7.0 Hz, 1H), 2.33 (td, *J* = 7.0, 1.8 Hz, 2H), 2.20 (dt, *J* = 12.3, 6.4 Hz, 1H), 1.76 (pd, *J* = 6.9, 2.6 Hz, 2H), 1.53 (dt, *J* = 8.2, 1.7 Hz, 1H), 1.47 (dd, *J* = 8.5, 1.7 Hz, 1H), 1.42 (dq, *J* = 8.2, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.8, 136.5, 130.6, 64.6, 54.6, 52.5, 48.2, 43.7, 34.9, 24.4 ppm; HRMS (*pos.* ESI) *m/z* 181.1341 (Theoretical mass: 181.1341); R_f = 0.06, eluent: 85:14:1 CH_2Cl_2:MeOH:NH_4OH, ninhydrin stain.

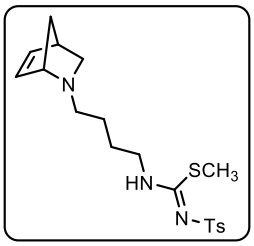


Dimethyl ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl) carbonimidodithioate (2.22c). Using our previously published method for the synthesis of dimethyl tosylcarbonimidodithioate 2.22a,[67] dimethyl ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbonimidodithioate was synthesized on a 14.9 mmol scale to provide the product as a pale yellow solid (3.5 g, 63 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.98 (s, 2H), 2.56 (s, 3H), 2.53 (s, 3H), 2.53 (s, 6H), 2.11 (s, 3H), 1.48 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 181.7, 159.8, 139.6, 133.8, 129.8, 124.9, 117.8, 86.8, 43.1, 28.6, 19.2, 18.1, 16.4, 12.4 ppm; HRMS (*pos.* ESI) 374.0915 (Theoretical mass: 374.0918); R_f = 0.30, eluent: 20 % EtOAc in hexanes.



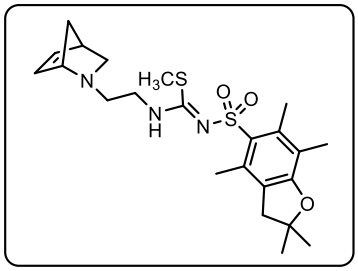
Methyl tosylcarbonochloridoimidothioate (3.37).[61] Dimethyl tosylcarbonimidodithioate 2.22a (4.00 g, 14.5 mmol) was dissolved in freshly distilled dichloromethane (40 mL) in a flame-dried 100 mL round bottom flask equipped with a stir bar and the flask was connected to a reflux condenser sealed under N_2 atmosphere. Sulfuryl chloride (2.36 mL, 29.1 mmol) was added to the flask and the flask was stirred at reflux for 3 hr. The solution was concentrated by rotovap to give the crude product. The crude material was purified on a silica gel column with 20 % EtOAc in hexanes as

the eluent to give the pure product (3.34 g, 87 %) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, 2H), 7.34 (d, 2H), 2.45 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 161.1, 144.9, 137.3, 130.0, 128.0, 22.0, 18.4; HRMS (*pos*. ESI) *m/z* 263.9930 (Theoretical mass: 263.9920); R_f = 0.13, eluent: 20 % EtOAc in hexanes.



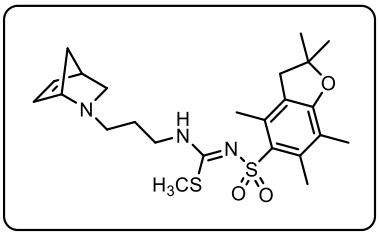
Methyl N-(4-(2-azabicyclo[2.2.1]hept-5-en-2-yl)butyl)-N'-tosylcarbamimidothioate (3.38). Lithium aluminum hydride (0.264 g, 6.94 mmol) was added to a flame-dried 50 mL round bottom flask. The flask was sealed under N_2 and cooled to 0 °C. Freshly distilled THF (1.5 mL) was added to the LAH to make a slurry. A solution of 4-(2-azabicyclo[2.2.1]hept-5-en-2-yl)butanamide (0.500 g, 2.78 mmol) in freshly distilled THF (8 mL) was added to the LAH dropwise. The reaction mixture was then allowed to warm to rt and then was heated at reflux for 20 hr. The Feiser workup for LAH reductions was conducted and the solids were removed by filtration. The filtrate was added to a round bottom flask and the solvent was removed by gently blowing N_2 over it to provide the amine (with some THF left) as a pale amber oil (0.40 g, 86 % crude). The amine is very volatile and unstable so it was used without further purification.

The primary amine was dissolved in methanol (10 mL) and methyl tosylcarbonochloridoimidothioate (0.619 g, 2.35 mmol) was added followed by freshly distilled triethylamine (0.33 mL, 2.4 mmol). The flask was sealed under N_2 and the reaction was stirred at r.t. for 4 hr. The solvent was removed by rotovap and overnight vacuum pump to produce a crude orange-yellow solid. The crude material was purified on a silica gel column with a gradient of eluent (70 % EtOAc in hexanes to 90:9:1 CH_2Cl_2:MeOH:NH_4OH) to give the product (0.42 g, 45 % over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.33 (dd, *J* = 6.1, 3.1 Hz, 1H), 6.01 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.31 (s, 1H), 3.85 (d, *J* = 2.4 Hz, 1H), 3.14 (dd, *J* = 8.6, 3.1 Hz, 1H), 2.93 (s, 1H), 2.50 (dt, *J* = 12.0, 7.0 Hz, 1H), 2.33 (td, *J* = 7.0, 1.8 Hz, 2H), 2.20 (dt, *J* = 12.3, 6.4 Hz, 1H), 1.76 (pd, *J* = 6.9, 2.6 Hz, 2H), 1.54 (dd, *J* = 8.2, 2.0 Hz, 1H), 1.47 (dd, *J* = 8.6, 1.6 Hz, 1H), 1.45 – 1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.8, 136.5, 130.6, 64.6, 54.6, 52.5, 48.2, 43.7, 34.9, 24.4 ppm; HRMS (*pos.* ESI) *m/z* 394.1617 (Theoretical mass: 394.1623); R_f = 0.21, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH.

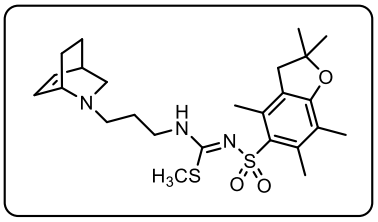


Methyl-N-(2-(2-azabicyclo[2.2.1]hept-5-en-2-yl)ethyl)-N'-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbamimidothioate (3.18). In a flame-dried 100 mL pear-shaped flask equipped with a stir bar a stirred, N_2 protected suspension of

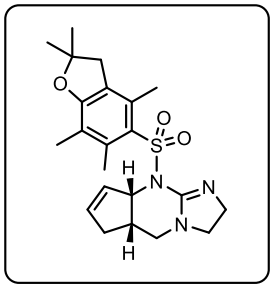
$LiAlH_4$ (0.299 g, 7.88 mmol) in freshly distilled tetrahydrofuran (8 mL) was created and cooled to 0 °C. 2-azabicyclo[2.2.1]hept-5-en-2-yl)acetamide 3.17 (0.600 g, 3.94 mmol) was added and the mixture was stirred at 0 °C under N_2 atmosphere for 45 minutes then warmed to reflux to stir for 12 hr. The reaction mixture was allowed to cool to room temperature and the Feiser $LiAlH_4$ work-up was conducted: 0.3 mL distilled water was added to the stirring mixture, followed by 0.3 mL of 10% sodium hydroxide in water, then 0.9 mL distilled water. The mixture was stirred for 15 minutes then dried (Na_2SO_4) and filtered. The solid was rinsed with distilled THF (2 x 5 mL). The THF filtrate was added to a flame-dried reaction flask equipped with a stir bar. Then dimethyl ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbonimidodithioate 2.22c (1.47 g, 3.94 mmol) was added. The solution was stirred overnight at room temperature under N_2 atmosphere. After 14 hr the solvent was removed *in-vacuo* to give the crude product. The crude material was purified on a silica gel column with 90:9:1 CH_2CH_2:MeOH:NH_4OH as the eluent to give pure 3.18 (1.00 g, 55 % over two steps). Note: The amine afforded following $LiAlH_4$ reduction of the amide is volatile and therefore is not isolated due to difficulties therein. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 6.35 (s, 1H), 6.04 (s, 1H), 3.82 (s, 1H), 3.31 (s, 1H), 3.20 (s, 2H), 2.99 (s, 3H), 2.69 (d, *J* = 9.7 Hz, 1H), 2.64 (s, 3H), 2.58 (s, 3H), 2.39 (s, 3H), 2.26 (s, 1H), 2.13 (s, 3H), 1.65 (d, *J* = 7.8 Hz, 1H), 1.49 (s, 6H), 1.43 (d, *J* = 8.3 Hz, 2H); 13C NMR (CDCl3, 126 MHz): δ 167.4, 159.0, 138.9, 136.6, 132.9, 132.1, 130.4, 124.6, 117.5, 86.5, 65.0, 52.8, 52.1, 48.4, 43.9, 43.2, 42.9, 28.6, 19.2, 18.1, 14.2, 12.5 ppm; HRMS (*pos*. ESI) *m/z* 464.2051 (Theoretical mass: 464.2042); IR (solid) 3294.42, 2970.38, 1674.00, 1558.48 cm^{-1}; R_f = 0.64, eluent: 90:9:1 CH_2CH_2:MeOH:NH_4OH; m.p. = 58-62 °C.



Methyl-N-(3-(2-azabicyclo[2.2.1]hept-5-en-2-yl)propyl)-N'-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbamimidothioate (3.20). 3-(-2-azabicyclo[2.2.1]hept-5-en-2-yl)propan-1-amine 3.9 (0.200 g, 1.31 mmol) and dimethyl ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbonimidodithioate 2.22c (0.54 g, 1.5 mmol) were dissolved in methanol (5 mL) and heated at reflux under N_2 for 30 minutes. The solvent was removed *in-vacuo* and the crude reaction material was purified on a silica gel column with 10 % MeOH in EtOAc to give pure 3.20 (0.44 g, 70 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 6.37 (s, 1H), 6.22 (t, *J* = 6.7 Hz, 1H), 3.37 (d, *J* = 23.9 Hz, 3H), 3.06 (d, *J* = 9.6 Hz, 1H), 2.95 (s, 2H), 2.58 (s, 4H), 2.52 (s, 4H), 2.28 (d, *J* = 16.9 Hz, 3H), 2.09 (s, 4H), 1.89 (d, *J* = 9.4 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.45 (s, 6H), 1.28 – 1.21 (m, 2H), 1.17 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.3, 159.0, 138.8, 133.6, 132.7, 132.2, 131.3, 124.6, 117.5, 86.5, 55.8, 54.9, 53.1, 43.2, 43.1, 30.7, 28.6, 27.0, 26.4, 21.7, 19.2, 18.0, 14.1, 12.4 ppm; HRMS (*pos*. ESI) *m/z* 478.2199 (Theoretical mass: 478.2198); IR (film) 3302.13, 2978.09, 1681.93, 1573.91 cm^{-1}; R_f = 0.4, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH.

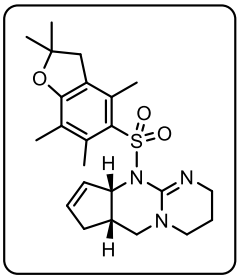


Methyl-N-(3-(2-azabicyclo[2.2.2]oct-5-en-2-yl)propyl)-N'-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbamimidothioate (3.23). 3-(2-azabicyclo[2.2.2]oct-5-en-2-yl)propan-1-amine 3.9 (0.145 g, 0.873 mmol) and dimethyl ((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbonimidodithioate 2.22c (0.326 g, 0.873 mmol) were dissolved in methanol (3 mL) and were heated at reflux under N_2 for 30 minutes. The solvent was removed *in-vacuo* and the crude reaction material was purified on a silica gel column with 90:9:1 $CHCl_3$:MeOH:NH_4OH to afford pure 3.23 (0.288 g, 84 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 6.37 (s, 1H), 6.22 (t, J = 6.7 Hz, 1H), 3.37 (d, J = 23.9 Hz, 3H), 3.06 (d, J = 9.6 Hz, 1H), 2.95 (s, 2H), 2.58 (s, 4H), 2.52 (s, 4H), 2.28 (d, J = 16.9 Hz, 3H), 2.09 (s, 4H), 1.89 (d, J = 9.4 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.45 (s, 6H), 1.28 – 1.21 (m, 2H), 1.17 (d, J = 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.3, 159.0, 138.8, 133.6, 132.7, 132.2, 131.3, 124.6, 117.5, 86.5, 55.8, 54.9, 53.1, 43.2, 43.1, 30.7, 28.6, 27.0, 26.4, 21.7, 19.2, 18.01, 14.1, 12.4 ppm; HRMS (*pos*. ESI) *m/z* 494.2348 (Theoretical mass: 492.2355); IR (solid) 3278.99, 2931.80, 1712.79, 1566.20 cm^{-1}; R_f = 0.6, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH; m.p. = 51 – 54 °C.



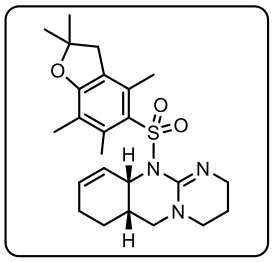
9-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-2,5,5a,6,8a,9-hexahydro-3H-cyclopenta[d]imidazo[1,2-a]pyrimidine (3.19). To a flame-dried 50 mL pear-shaped flask equipped with a stir bar was added Methyl-N-2-azabicyclo[2.2.1]hept-5-en-2-yl)ethyl)-N'-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)carbamimidothioate 3.18 (0.250 g, 0.540 mmol) and anhydrous dimethyl formamide (3 mL) at room temperature. To this solution was added $HgCl_2$ (0.161 g, 0.594 mmol) followed by Et_3N (0.15 mL, 1.08 mmol). The reaction mixture was stirred under N_2 at room temperature for 1.5 hr. 10 mL Et_2O was added to each of two test tubes. The reaction mixture was dripped slowly into the Et_2O, split between the two test tubes. The white precipitate was removed by centrifugation and decanting of the ether layer. The solid remaining in the test tubes was washed with Et_2O (10 mL for each test tube) and centrifuged again. The four Et_2O/DMF layers were combined and washed with 0.1M NaOH (2 x 15 mL). The remaining Et_2O layer was collected, dried ($MgSO_4$) and concentrated to give crude product. The crude material was purified on a silica gel column with 90:9:1 CH_2CH_2:MeOH:NH_4OH as the eluent to give pure 3.19 (0.184 g, 82 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 – 5.85 (m, 2H), 5.32 (ddd, *J* = 10.2, 5.1, 3.1 Hz, 1H), 3.63 (ddd, *J* = 12.6, 9.3, 7.8 Hz, 1H), 3.37 (ddd, *J* = 12.6, 9.8, 7.2 Hz, 1H), 3.27 – 3.11 (m, 2H), 3.04 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.00 (d, *J* = 5.7 Hz, 2H), 2.96 (dq, *J* = 5.9, 2.7 Hz, 1H), 2.78 (dd, *J* = 10.9, 5.9 Hz, 1H), 2.67 (ddt, *J* = 16.5, 7.6, 2.1 Hz, 1H), 2.56 (s,

3H), 2.51 (s, 3H), 2.31 – 2.22 (m, 1H), 2.12 (s, 3H), 1.48 (d, J = 4.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.3, 155.8, 140.3, 136.4, 132.6, 131.5, 127.6, 125.0, 117.6, 87.0, 62.6, 51.6, 49.8, 48.6, 43.1, 37.2, 34.8, 28.6, 28.5, 19.2, 17.3, 12.5 ppm; HRMS (*pos*. ESI) *m/z* 416.2012 (Theoretical mass: 416.2008); IR (solid): 1627.92, 1573.91, 1327.03, 1165.00, 1141.86, 1087.85 cm^{-1}; R_f = 0.2, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH; m.p. = 72 – 75 °C.

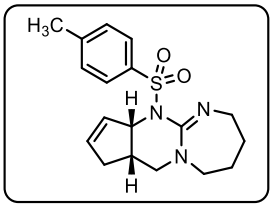


10-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-2,3,4,6,6a,7,9a,10-octahydrocyclopenta[d]pyrimido[1,2-a]pyrimidine (3.21).The general rearrangement procedure outlined for 3.19 above was conducted with 3.20 to give 3.21 (0.051 g, 57 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dq, J = 6.2, 2.2 Hz, 1H), 5.71 (dq, J = 4.6, 2.2 Hz, 1H), 5.47 (ddq, J = 9.9, 3.3, 1.5 Hz, 1H), 3.57 (dd, J = 12.6, 3.8 Hz, 1H), 3.28 (dtd, J = 14.8, 4.5, 2.4 Hz, 1H), 3.23 – 3.16 (m, 1H), 3.13 (dtd, J = 11.5, 4.9, 1.6 Hz, 1H), 3.00 (dddd, J = 26.7, 14.3, 9.2, 4.1 Hz, 2H), 2.90 (s, 2H), 2.64 – 2.56 (m, 2H), 2.46 (s, 3H), 2.45 (s, 3H), 2.27 – 2.16 (m, 1H), 2.03 (s, 3H), 1.74 (dtt, J = 13.5, 9.0, 4.7 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.8, 146.7, 138.8, 134.5, 133.5, 129.2, 128.0, 123.8, 116.6, 85.7, 61.7, 50.5, 48.1, 42.5, 42.2, 36.9, 36.7, 27.6, 27.6, 20.9, 28.3, 16.8, 11.5 ppm; HRMS (*pos*. ESI) *m/z* 430.2164 (Theoretical mass:

430.2164); IR (solid) 2962.66, 2846.93, 1712.79, 1643.35 cm^{-1}; R_f = 0.2, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH; m.p. = 54 – 59 °C.

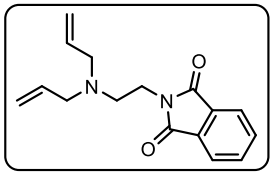


11-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-3,4,6,6a,7,8,10a,11-octahydro-2H-pyrimido[2,1-b]quinazoline (3.24). The general rearrangement procedure outlined for 3.18 above was conducted on 3.23 to give 3.24 (0.061 g, 68 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 – 5.70 (m, 2H), 3.34 (ddd, *J* = 14.8, 8.0, 4.8 Hz, 1H), 3.18 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.16 – 3.08 (m, 2H), 3.05 (dt, *J* = 14.8, 5.3 Hz, 1H), 3.01 – 2.93 (m, 3H), 2.60 – 2.52 (m, 1H), 2.50 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 2.06 (d, *J* = 5.0 Hz, 2H), 1.88 (dddd, *J* = 13.2, 9.3, 7.0, 3.6 Hz, 1H), 1.80 – 1.70 (m, 2H), 1.66 (qt, *J* = 7.9, 3.9 Hz, 1H), 1.47 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.6, 144.4, 138.7, 134.4, 128.5, 128.2, 126.4, 123.7, 116.4, 85.7, 50.8, 48.2, 47.3, 42.1, 42.1, 29.6, 27.5, 27.5, 23.1, 20.8, 19.9, 18.0, 16.3, 11.5 ppm; HRMS (*pos*. ESI) *m/z* 444.2327 (Theoretical mass: 444.2321); IR (neat): 2931.80, 1643.35, 1577.77, 1303.88, 1138.00 cm^{-1}; R_f = 0.13, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH



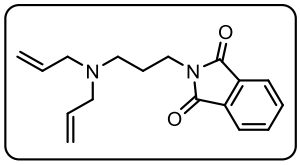
11-tosyl-2,4,5,7,7a,8,10a,11-octahydro-3H-cyclopenta[4,5]pyrimido[1,2-a][1,3]diazepine (3.39). methyl N-(4-(2-azabicyclo[2.2.1]hept-5-en-2-yl)butyl)-N'-tosylcarbamimidothioate 3.38 (0.320 g, 0.813 mmol) was dissolved in freshly distilled dichloromethane in a flame-dried 50 mL pear shaped flask equipped with a stir bar. The flask was sealed and placed under $N_{2\ (g)}$ atmosphere. Freshly distilled triethylamine (0.14 mL, 0.98 mmol) was added followed by $HgCl_2$ (0.243 g, 0.895 mmol). The rearrangement was stirred at rt for three days then was heated at reflux for 24 hr until ninhydrin stain proved the disappearance of starting material 3.38 (the starting material and product have similar R_f values but stain differently, the rearrangement can be conducted at reflux without the r.t. stirring). The reaction mixture was separated between two test tubes with 8 mL dichloromethane apiece. The test tubes were centrifuged and the mother liquor was removed and combined. The remaining solids were washed twice more with dichloromethane (6 mL each). The dichloromethane washes were all combined and concentrated via rotary evaporation and vacuum pump (overnight) to give a crude white solid. The crude material was purified on a silica gel column with a gradient of 50 % EtOAc/Hexanes to 90:9:1 CH_2Cl_2:MeOH:NH_4OH to give the product (0.168 g, 60 %). An analytical sample was removed and recrystallized via slow evaporative recrystallization from acetonitrile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H), 7.26 (s, 3H), 5.86 (dq, *J* = 6.2, 2.2 Hz, 1H), 5.61 – 5.56 (m, 1H), 5.50 (dq, *J* = 4.8, 2.3 Hz, 1H), 3.67 (dd, *J* = 13.8, 4.3 Hz, 1H), 3.56 (dddd, *J* = 13.3, 5.0, 2.7, 1.3 Hz, 1H), 3.27

– 3.20 (m, 1H), 3.09 – 3.02 (m, 2H), 2.95 (ddd, *J* = 13.3, 11.2, 2.2 Hz, 1H), 2.81 (d, *J* = 13.8 Hz, 1H), 2.68 (ddq, *J* = 17.5, 9.5, 2.2 Hz, 1H), 2.40 (s, 3H), 2.36 (ddt, *J* = 16.9, 4.8, 2.3 Hz, 1H), 1.74 – 1.64 (m, 3H), 1.50 – 1.40 (m, 1H), 1.33 – 1.22 (m, 1H); ^{13}C NMR ($CDCl_3$), 126 MHz): δ 149.8, 143.1, 138.6, 134.2, 130.5, 129.0, 128.5, 63.8, 55.5, 54.8, 48.2, 39.7, 37.9, 28.4, 26.5, 21.6 ppm; HRMS (*pos*. ESI) *m/z* 346.1596 (Theoretical mass: 346.1589); R_f = 0.14, eluent: 90:9:1 CH_2Cl_2:MeOH:NH_4OH.



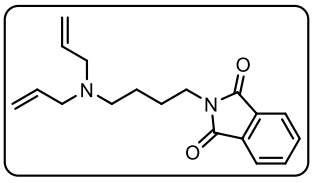
2-(2-(diallylamino)ethyl)isoindoline-1,3-dione (3.50a). N-(2-bromoethyl)phthalimide (4.00 g, 15.8 mmol) was added to a flame-dried 100 mL round bottom flask equipped with a stir bar and dissolved in anhydrous DMF (40 mL). Diallylamine (1.94 mL, 15.8 mmol) was added followed immediately by potassium carbonate (5.44 g, 39.4 mmol). The flask was fitted with a reflux condenser and stirred at 90 °C overnight. The reaction mixture was allowed to cool to rt and was diluted with EtOAc (30 mL). The white solid was removed by filtration and the filtrate was added to a seperatory funnel with water (100 mL). The aqueous layer was extracted with EtOAc (4 x 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated (rotary evaporation, overnight on vacuum pump) to give a dark yellow oil (3.55 g, 84 % crude). The crude product was purified on a silica gel column with 20 % EtOAc in hexanes to give a pale yellow oil (2.12 g, 50 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J*

= 5.4, 3.0 Hz, 2H), 5.74 (ddt, *J* = 16.7, 10.2, 6.4 Hz, 2H), 5.17 – 5.05 (m, 4H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.13 (dt, *J* = 6.5, 1.3 Hz, 4H), 2.72 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.3, 135.5, 133.8, 132.2, 123.1, 117.6, 56.8, 50.5, 36.0 ppm; HRMS (*pos*. ESI) *m/z* 271.1447 (Theoretical mass: 271.1447); R_f = 0.5, eluent: 20 % EtOAc in hexanes.



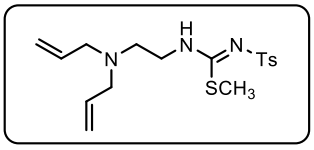
2-(3-(diallylamino)propyl)isoindoline-1,3-dione (3.50b). N-(3-bromopropyl)phthalimide (6.62 g, 24.7 mmol) was added to a flame-dried 100 mL round bottom flask equipped with a stir bar and dissolved in anhydrous DMF (40 mL). Diallylamine (2.53 mL, 20.6 mmol) was added followed immediately by sodium carbonate (6.55 g, 61.8 mmol). The flask was fitted with a reflux condenser and stirred at 90 °C until the alkyl halide had disappeared from TLC (9 hr). The reaction mixture was allowed to cool to rt and was diluted with EtOAc (30 mL). The white solid was removed by filtration and the filtrate was added to a seperatory funnel with water (100 mL). The aqueous layer was extracted with EtOAc (4 x 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated (rotary evaporation, overnight on vacuum pump) to give a dark yellow oil, containing excess DMF. The crude material was diluted with water (60 mL) and extracted with EtOAc (5 x 50). The organic layers were combined, dried ($MgSO_4$), and concentrated to give a dark yellow oil (6.22 g). The crude material

contained some starting material, so the product was acidified (pH ~ 2) with HCl and extracted with CH_2Cl_2 (2 x 10 mL). The aqueous layer was made basic with saturated sodium bicarbonate and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated (rotary evaporation, overnight on vacuum pump) to give a yellow oil. The crude oil was purified on a silica gel column with 30 % EtOAc in hexanes to give a pale yellow oil (3.81 g, 65 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.79 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 2H), 5.17 – 5.04 (m, 4H), 3.73 – 3.67 (m, 2H), 3.06 (dt, *J* = 6.5, 1.3 Hz, 4H), 2.53 – 2.47 (m, 2H), 1.83 (tt, *J* = 8.4, 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.4, 135.6, 133.8, 132.2, 123.1, 117.4, 56.7, 50.5, 36.4, 25.8 ppm; HRMS (*pos*. ESI) *m/z* 285.1604 (Theoretical mass: 285.1603); R_f = 0.56, eluent: 30 % EtOAc in hexanes.



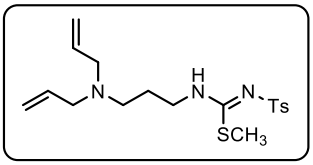
2-(3-(diallylamino)butyl)isoindoline-1,3-dione (3.50c). N-(4-bromobutyl)phthalimide (2.33 g, 9.24 mmol) was added to a flame-dried 100 mL round bottom flask and was dissolved in anhydrous DMF (50 mL). Potassium carbonate (3.42 g, 24.7 mmol) was added and the flask was attached to a reflux condenser. Diallylamine (1.14 mL, 9.24 mmol) was added and the reaction mixture was stirred at 90 °C for 20 hr. The flask was allowed to cool to rt and the solids were removed by filtration and were rinsed with EtOAc (20 mL). The filtrate was added to a seperatory funnel with 30 mL EtOAc and 50

mL DI water. The aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layers were combined and extracted with brine (3 x 15 mL). The organic layer was dried, ($MgSO_4$) and concentrated to give crude amber oil (2.54 g). The crude oil was purified on a silica gel column with 30 % EtOAc in hexanes to give the product (0.636 g, 23 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.85 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 2H), 5.20 – 5.07 (m, 4H), 3.71 (t, *J* = 7.3 Hz, 2H), 3.08 (dt, *J* = 6.5, 1.3 Hz, 4H), 2.51 – 2.39 (m, 2H), 1.74 – 1.66 (m, 2H), 1.55 – 1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.4, 135.8, 133.9, 132.1, 123.1, 117.3, 56.9, 52.7, 38.0, 26.5, 24.4 ppm; HRMS (*pos*. ESI) *m/z* 299.1764 (Theoretical mass: 299.1760); R_f = 0.49, eluent: 30 % EtOAc in hexanes.



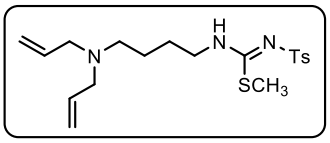
methyl N-(2-(diallylamino)ethyl)-N'-tosylcarbamimidothioate (3.51a). 2-(2-(diallylamino)ethyl)isoindoline-1,3-dione 3.50a (1.00 g, 3.70 mmol) was dissolved in absolute ethanol (15) a flame-dried, 50 mL round bottom flask equipped with a stir bar. Hydrazine hydrate (35-55 % hydration, 0.55 mL, 11.1 mmol) was added and the flask was connected to a reflux condenser. The reaction was stirred at reflux for 3 hr, when 3.50a was no longer visible by TLC. The reaction was allowed to cool to room temperature and the while precipitate was removed by filtration and the solid was rinsed with ethanol (2 x 10 mL). The filtrate was concentrated down to 5 mL by rotary

evaporation at rt. The solution was transferred to a continuous extractor with saturated sodium bicarbonate (30 mL) and dichloromethane (70 mL). The mixture was continuously extracted with dichloromethane overnight. The organic layer (containing the primary amine) was concentrated to 10 mL solvent by rotary evaporation. Hunig's base (0.65 mL, 3.70 mmol) was added followed by methyl tosylcarbonochloroimidothioate (0.98 g, 3.70 mmol). The reaction was stirred at reflux for 12 hr. The reaction mixture was allowed to cool to rt then concentrated by rotovap and overnight on a vacuum pump to give a crude amorphous solid. The crude product was purified on a silica gel column with 30 % EtOAc in hexanes to give pure product (0.90 g, 66 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.20 (d, 2H), 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 2H), 5.18 – 5.06 (m, 4H), 3.22 (q, *J* = 5.6 Hz, 2H), 3.07 (dd, *J* = 6.5, 1.4 Hz, 4H), 2.59 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.7, 142.4, 139.8, 135.1, 129.1, 126.3, 118.0, 56.7, 50.3, 41.3, 21.4, 14.2 ppm; HRMS (*pos*. ESI) *m/z* 368.1471 (Theoretical mass: 368.1466); R_f = 0.31, eluent: 30 % EtOAc in hexanes.

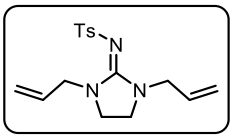


methyl N-(3-(diallylamino)propyl)-N'-tosylcarbamimidothioate (3.51b). The procedure for 3.50a was conducted with 3.50b (1.00 g, 3.52 mmol) as the starting protected amine. Following purification on a silica gel column with 50 % EtOAc in

hexanes with 0.5 % Et_3N the desired isothiourea 3.51b was isolated as a viscous pale yellow oil (0.87 g, 65 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.26 (d, 2H), 5.89 (ddt, *J* = 16.8, 10.1, 6.5 Hz, 2H), 5.20 – 5.11 (m, 4H), 3.34 (q, *J* = 6.2 Hz, 2H), 3.10 (d, *J* = 6.6 Hz, 4H), 2.51 (t, *J* = 6.4 Hz, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 1.73 (p, *J* = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.8, 142.5, 140.1, 135.3, 129.2, 126.2, 117.8, 57.1, 50.4, 43.4, 26.2, 21.5, 14.2 ppm; HRMS (*pos*. ESI) *m/z* 382.1631 (Theoretical mass: 382.1623); R_f = 0.29, eluent: 50 % EtOAc in hexanes with 0.5 % Et_3N.



methyl N-(4-(diallylamino)butyl)-N'-tosylcarbamimidothioate (3.51c). The procedure for 3.50a was conducted with 3.50c (0.250 g, 0.838 mmol) as the starting protected amine. Following purification on a silica gel column with 50 % EtOAc in hexanes with 0.5 % Et_3N the desired isothiourea 3.51c was isolated as a viscous pale yellow oil (0.104 g, 30 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.26 (d, 2H), 5.83 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 2H), 5.22 – 5.07 (m, 4H), 3.28 (q, *J* = 6.7 Hz, 2H), 3.06 (d, *J* = 6.5, 1.3 Hz, 4H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 3H), 1.62 (p, *J* = 7.2 Hz, 2H), 1.48 (p, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 142.6, 139.8, 135.7, 129.3, 126.2, 117.5, 56.9, 52.3, 44.1, 27.1, 24.1, 21.5, 14.2 ppm; HRMS (*pos*. ESI) *m/z* 396.1790 (Theoretical mass: 396.1779); R_f = 0.18, eluent: 50 % EtOAc in hexanes with 0.5 % Et_3N.



N-(1,3-diallylimidazolidin-2-ylidene)-4-methylbenzenesulfonamide (3.52a). Methyl N-(2-(diallylamino)ethyl)-N'-tosylcarbamimidothioate (3.50a) (0.200 g, 0.545 mmol) was charged to a flame-dried 25 mL pear-shaped flask equipped with a stir bar and was sealed under N_2. The isothiourea was dissolved in freshly distilled CH_2Cl_2 (4 mL). Freshly distilled Et_3N (0.076 mL, 0.545 mmol) was added by micropipette followed by silver trifluormethanesulfonate (0.28 g, 1.09 mmol). The reaction was stirred overnight when the starting isothiourea disappeared from TLC analysis. The crude material was partitioned between two 13x100mm test tubes with CH_2Cl_2 (6 mL each). The solids were removed by centrifuging and decanting the mother liquor by pipette. The solids were washed with CH_2Cl_2 (2 x 6 mL each). The combined organic layers were concentrated to give zwitterionic intermediate 3.51a.1 (0.314 g, > 100 %). The zwitterion was dissolved in CH_2Cl_2 and was washed with saturated sodium bicarbonate (1 x 8 mL) to remove excess triethylammonium triflate. The aqueous layer was back-extracted with CH_2Cl_2 (1 x 8 mL) and the organics were concentrated. The crude zwitterionic material was then dissolved in benzene (8 mL) and heated at reflux for 6 hr. The solvent was removed under vacuum and the crude material was purified on a silica gel column with a gradient eluent of 30 % EtOAc in hexanes – 50 % EtOAc in hexanes – 90:9:1 CH_2Cl_2:MeOH:NH_4OH to afford the rearrangement product as a viscous, clear, colorless oil (0.105 g, 61 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, 2H), 7.22 (d, 2H), 5.79 (ddt, *J* = 16.9, 10.7, 6.4 Hz, 2H), 5.23 – 5.17 (m, 4H), 4.05 (dt, *J* = 6.3, 1.3 Hz, 4H), 3.47 (s, 4H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.3, 142.8, 141.2, 132.3, 129.0,

125.7, 119.0, 50.1, 44.6, 21.4 ppm; HRMS (*pos*. ESI) *m/z* 320.1425 (Theoretical mass: 320.1433); R_f = 0.14, eluent: 30 % EtOAc in hexanes.

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5 CONCLUDING REMARKS

The 1,3-diaza Claisen rearrangement has the potential to be an extremely powerful tool for the synthesis of complex guanidine-containing skeletons. The guanidine functionality is present in many biologically active molecules and the various potential interactions of the functional group is likely the reason why. In light of this, the extensive development of a reaction that is capable of generating complex guanidines in short order is a worthy pursuit.

Initially two new methodologies were described for the generation of the carbodiimide component of the intermolecular, zwitterionic 1,3-diaza Claisen rearrangement. The first was a new urea dehydration, developed for use with electron deficient ureas. The second was the desulfurization of S-methyl isothioureas, initially conducted with mercury (II) chloride and recently found to work with the less toxic silver triflate. Both of these reaction methodologies were used to generate a series of complex bicyclic guanidines.

The isothiourea desulfurization methodology has since been applied to a series of intramolecular rearrangements. The electron deficiency requirement to the intermolecular rearrangement has been discovered to be much lower for the intramolecular variant. Currently, this new methodology is being applied to simpler intramolecular rearrangement substrates that don't contain strained bicyclic, tertiary allylic amines.

Overall, the work described in this dissertation has expanded the toolbox of the 1,3-diaza Claisen methodology. The intermolecular work allowed for the synthesis of bicyclic guanidines that were previously unavailable using the original technique. The intramolecular work has shown that complex guanidine structures can be generated without the need to generate extremely electron deficient carbodiimides, making the syntheses of these compounds simpler.

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