University of Nevada, Reno

Exploring New Methods of Aza-Oxyallyl Cation Generation

A thesis submitted in partial fulfillment of the
requirements for the degree of
Bachelor of Science in Chemistry and the Honors Program

By

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Abstract

Considering that carbon-nitrogen bond formation is frequently required at various stages in the synthesis of pharmaceuticals and materials, developing efficient new methods of C-N bond formation is a worthwhile endeavor. The (4+3)-cycloaddition through a new reaction intermediate, known as the aza-oxyallyl cation, has recently been established as a premiere method of synthesizing seven-membered heterocycles containing nitrogen. The goal of this study was to expand the scope of this novel reactivity by exploring the possibility of Lewis acid-catalyzed aza-oxyallyl cation generation from hydroxamate chalcone epoxides and imidates in the presence of electron-rich arenes. Hydroxamate chalcone epoxides were found to undergo electrophilic aromatic substitution at the β-position, indicating that an aza-oxyallyl cation is not in fact generated under these conditions. Imidates were found to undergo two electrophilic aromatic substitution reactions to yield doubly substituted furan products. These initial results are a promising indication that aza-oxallyl cations can indeed be generated under Lewis-acid mediated conditions.

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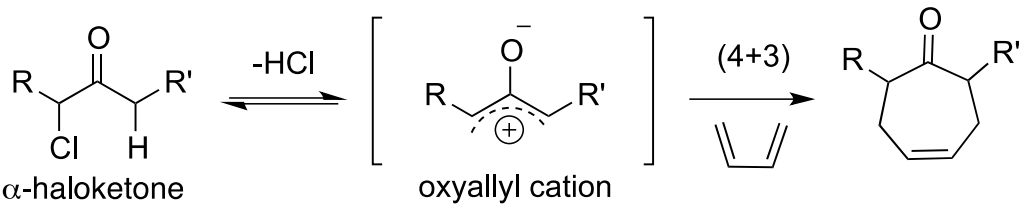
Chapter 1: Introduction to the history of the aza-oxyallyl cation

In old Irish folklore, the leprechaun is depicted as an elusive and mischievous dwarf, never seen, always avoiding capture, and hoarding a pot of gold at the end of a rainbow. Such was the case with the aza-oxyallyl cation, an elusive reaction intermediate that had mischievously teased chemists for decades and that quickly piqued the curiosity of our young research lab. The existence of the aza-oxyallyl cation had long been suspected, but previous attempts at trapping the species had all been unsuccessful. The Jeffrey lab's proposal to intercept the aza-oxyallyl cation was largely inspired by the work of Harmata, Lohse, and others on oxyallyl cations and their use in (4+3)-cycloaddition reactions with dienes to form seven-membered rings.[1, 2] With the larger goal of developing new C-N bond-forming reaction methodology, we envisioned that the aza-oxyallyl cation could be similarly employed to create seven-membered heterocycles containing nitrogen.

One of the primary methods of generating oxyallyl cations for (4+3)-cycloaddition is through the dehydrohalogenation of α-haloketones (Scheme 1). It is worth mentioning that (4+3) refers to the number of atoms coming together to generate

Scheme 1: General (4+3) cycloaddition through an oxyallyl cation.



the seven-membered ring, as opposed to the bracketed [4+2] notation, which instead indicates the number of electrons involved in the process.[1] The first example of such a (4+3)-cycloaddition reaction was reported by Fort in 1962.[3] In this experiment, Fort

reacted α-chlorodibenzylketone with furan in the presence of a base to produce a seven-membered carbocycle with a bridging oxygen atom. H. M. R. Hoffmann continued work in this area, pioneering much of the chemistry surrounding the synthesis of seven-membered rings though reaction of allyl cations with dienes. In 1965, Woodward and Hoffmann published a paper proposing that a concerted cycloaddition reaction of a diene and allyl cation was allowed by orbital symmetry.[4] To support his theory, Hoffmann published the first example of such a reaction in 1968.[5]

In subsequent studies, Hoffmann noted the difficulties of handling unstable allylic cation intermediates for cycloaddition reactions, as well as the problems that arise with open-chain dienes that are more stable in the *trans*- conformation than the *cis*-conformation.[6] Citing the example by Fort, Hoffmann observed an increase in the stability of the allylic cation when its termini were substituted by aromatic phenyl groups. Additionally, Hoffmann acknowledged the advantage of using cyclic dienes, such as furan, for cycloaddition, since they are fixed in the s-*cis*-conformation required for correct orbital alignment with the allyl cation. In a 1984 paper, Hoffmann made yet another important observation. Like Fort, he used α-haloketones to generate oxyallyl cations in the presence of furan and a base, but instead of methanol or DMF, he used trifluroethanol (TFE) as the solvent.[7] He noticed that TFE was effective at stabilizing the cation intermediate but was less nucleophilic than methanol, resulting in less competition from solvolysis.[7] Hoffmann's observations about substituent and solvent effects turned out to be critical in the success of our generation of the aza-oxyallyl cation.

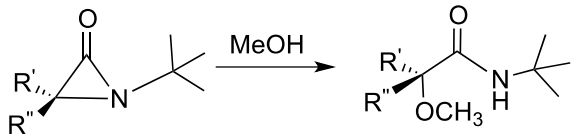
Following Hoffman's work, numerous examples of (4+3)-cycloaddition reactions through oxyallyl cations have been reported.[8] As initially hypothesized by Fort,[3] the

(4+3)-cycloaddition of an allylic cation with a diene indeed follows a concerted mechanism analogous to the Diels-Alder reaction.[1] Strategic placement of electron-donating groups, such as nitrogen, oxygen, or sulfur, on the dienophile has been shown to facilitate the (4+3)-cycloaddition reactions through the extra stability afforded to the oxyallyl cation intermediate.[9] It was this simple observation that led to the capture of the aza-oxyallyl cation and the pot of gold at the end of our rainbow. The difference between the aza-oxyallyl cation and the oxyallyl cation is, of course, the replacement of a carbon atom with a more electronegative nitrogen atom. This makes the aza-oxyallyl cation a much more reactive species than the oxyallyl cation. Placement of a positive charge on an electronegative nitrogen atom is unfavorable and creates a nitrenium ion. Nitrenium ions are analogous to carbenes and consist of a positively-charged nitrogen atom with two substituents and a lone pair of electrons. Like carbenes, they can exist in either the singlet or triplet state and are highly reactive. In the singlet state, the nitrenium ion has a filled *p* orbital and an empty σ orbital, giving it the interesting property of being ambident.[10] As a result of the higher energy barrier to their formation,[11] aza-oxyallyl cations are much more difficult to generate than oxyallyl cations and require much more specialized reaction conditions. The key difference in our reaction conditions, compared to those of our predecessors, was the realization that an intermediate such as the aza-oxyallyl cation could potentially be stabilized by an electron-donating group attached to the positively-charged nitrogen atom, giving the intermediate a long enough lifetime to react with a nucleophile in the same way as its all-carbon analogue.

The idea of the aza-oxyallyl cation was not new when our lab began experimenting with the intermediate in 2010. The aza-oxyallyl cation was first suggested

by Sheehan in the 1960s during his foray into the chemistry of α-lactams.[12] The first α-lactam to be isolated and characterized was synthesized in 1962 by Baumgarten and colleaugues.[13] Prior to this synthesis, α-lactams were thought to be intermediates in a variety of reactions, but it was unknown if the three-membered ring structure would create too much ring strain to permit isolation. Building on the work of Baumgarten, Sheehan and Lengyel were able to isolate a variety of α-lactams,[12] yet the chemical

Scheme 2: Nucleophilic attack at the C-2 carbon of an α-lactam, resulting in the retention of stereochemistry.



α-lactam

behavior of the species remained poorly understood. Sheehan and Lengyel noticed that the stability of the α-lactams seemed to be enhanced by the presence of a *tert*-butyl group or other bulky substituent on the nitrogen atom.[12] Despite this general trend, their attempted syntheses of α-lactams with bulky phenyl substituents on the nitrogen atom were surprisingly unsuccessful.

Sheehan hypothesized that charge delocalization through the phenyl rings made possible a highly reactive acyclic intermediate (an aza-oxyallyl cation) that was more stable than the corresponding α-lactam he was trying to synthesize.[12] Sheehan also suggested that this dipolar intermediate was involved in the thermal decomposition of some α-lactams, as well as the nucleophilic ring-opening of the species.[12, 14] Like the dipolar oxyallyl cation in the Favorskii rearrangement previously described by House and Gilmore,[15] Sheehan did not rule out the possibility of an analogous dipolar aza-oxyallyl cation intermediate in the nucleophilic substitution reaction of α-lactams at the C-3

position.[16] In the case of the α-lactams that were stable enough to be isolated, this theory was later disproven. While it remained difficult to predict whether nucleophilic attack would be favored at the C-2 or C-3 position according to the type of nucleophile, it was shown that attack at the C-2 position consistently produced a retention in stereochemistry while attack at the C-3 position produced an inversion in stereochemistry (Scheme 2).[16] Such stereospecificity was inconsistent with the formation of a planar aza-oxyallyl cation intermediate, which would instead result in product racemization.

Suspicions of the existence of the aza-oxyallyl cation continued through the end of the twentieth century. In 1993, Kikugawa and co-workers in Japan, proposed that their observed alkoxy-substitution of *N*-alkoxy-*N*-chloroarylacetamides at the α-position in the presence of a base and ethanol could proceed through an aza-oxyallyl cation intermediate.[17] Further evidence for the aza-oxyallyl cation came from Stang and Anderson. In 1995, Stang and Anderson published a reaction suggesting that an aza-oxyallyl cation intermediate was responsible for the transformation of alkylidene oxazirine to an α-lactam.[18] Following up on this hypothesis, Tuscano and co-workers performed isomerization studies on the interconversion of alkylidene oxazirines to α-lactams in 2004.[19] Computational analysis of their system indicated that an aza-oxallyl cation transition state was involved in the process. More encouraging evidence for the existence of the aza-oxyallyl cation was later provided by Kikugawa and co-workers. As previously described, Kikugawa treated the *N*-alkoxy-*N*-chloroarylacetamide substrate with base and ethanol and again observed that the sovolysis product was the major product.[20] Kikugawa then replaced the alkoxy group on his substrate with a simple alkyl group and observed that no solvolysis product was observed. In fact, no reaction was

observed at all.[20] This result strongly suggested that the presence of an electron-donating group was critical for the stabilization of an aza-oxyallyl cation. As a whole, this body of evidence led us to believe that the aza-oxyallyl cation indeed existed and could potentially be trapped for cycloaddition given the presence of a stabilizing electron-donating group. The only remaining step was to experimentally test our hypothesis in the lab.

Chapter 2: Trapping the aza-oxyallyl cation for (4+3)-cycloaddition

In an effort to provide the first example of (4+3)-cycloaddtion, our research group began by computationally modeling our hypothesis (Figure 1). As substrates, we chose two α-lactams, one *N*-substituted with an ethyl group and one *N*-substituted with a methoxy group. The energy profiles for the isomerization of each α-lactam to an aza-oxyallyl cation in methanol were predicted using the B3LYP/6-31G* level of theory on a relaxed potential energy surface.[21] As expected, the ethyl-substituted α-lactam did not

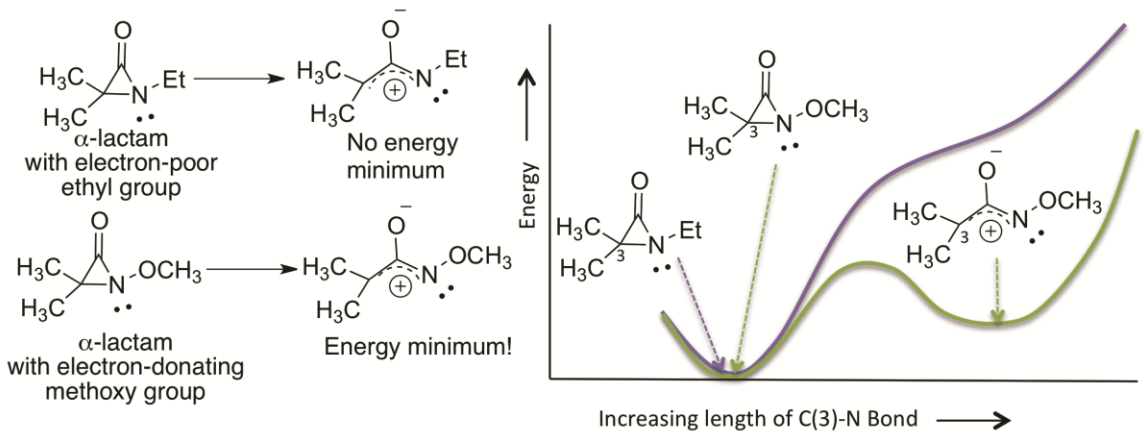
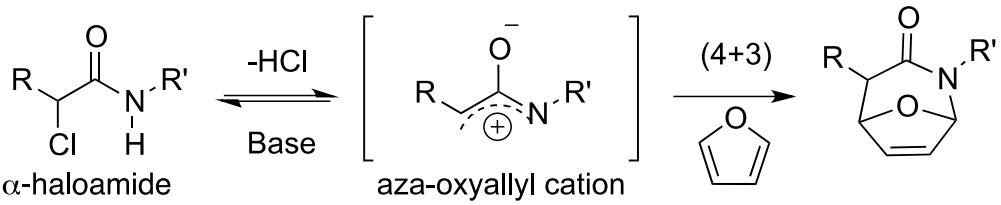


Figure 1: Qualitative potential energy surface of an electron-rich verses an electron-poor α-lactam opening to an aza-oxyallyl cation intermediate. The computational model predicts that the presence of an electron-donating group to stabilize the aza-oxyallyl cation will allow for an energetically favorable formation of the desired intermediate.

display an energy well that would be suggestive of an aza-oxyallyl cation intermediate. On the other hand, the α-lactam with a strongly electron-donating methoxy substituent showed a clear energy minimum indicative of aza-oxyallyl cation formation. Furthermore, a comparison of isomerization in the gas phase and in methanol for the methoxy α-lactam indicated that the well depth at the stationary point was directly related to solvent effects. According to these calculations, the aza-oxyallyl cation intermediate

was more stable in a polar protic solvent than in the gas phase, which was consistent with the proposed zwitterionic structure of an aza-oxyallyl cation intermediate.

Scheme 3: General (4+3)-cycloaddition through an aza-oxyallyl cation generated by dehydrohalogenation of an α-haloamide.

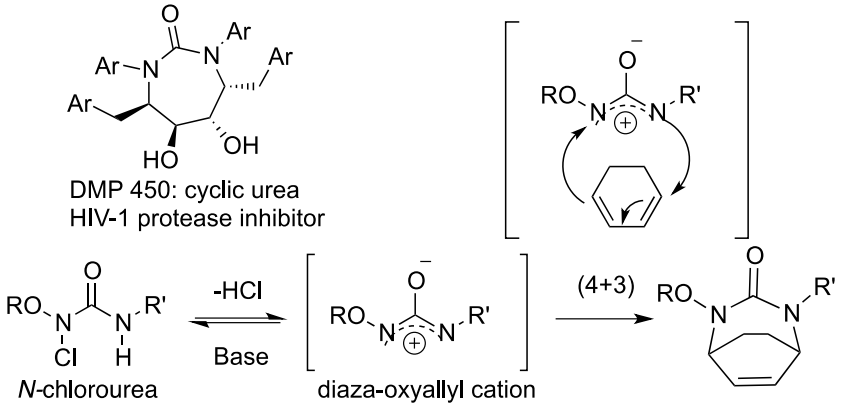


After our initial computational calculations, we proceeded to synthesize 2-bromo-*N*-benzylbutyramide from an acid bromide and benzylamine.[11] In accordance with our hypothesis, treatment of 2-bromo-*N*-benzylbutyramide with base in the presence of furan did not result in a reaction. The presence of the benzyl group was clearly not enough to stabilize the aza-oxyallyl cation intermediate for a long enough interval to allow for a reaction. To test the necessity of a strong electron-donating group adjacent to the nitrogen atom, we then synthesized the same substrate but with an O-benzyl group instead of simply a benzyl group. As expected, subjecting this substrate to trifluoroethanol and triethylamine in the presence of furan result in the formation of the desired cycloadduct in 38% yield, thus providing the first example of a (4+3)-cycloaddition through an aza-oxyallyl cation intermediate (Scheme 3).[11] Yields of the cycloadduct were improved to 78% by using a hexafluoroisopropanol solvent, which was too bulky to act as a nucleophile. Changing the solvent to hexfluoroisopropanol completely eliminated the competing solvolysis reaction pathway and produced the desired cycloadduct as the major product.

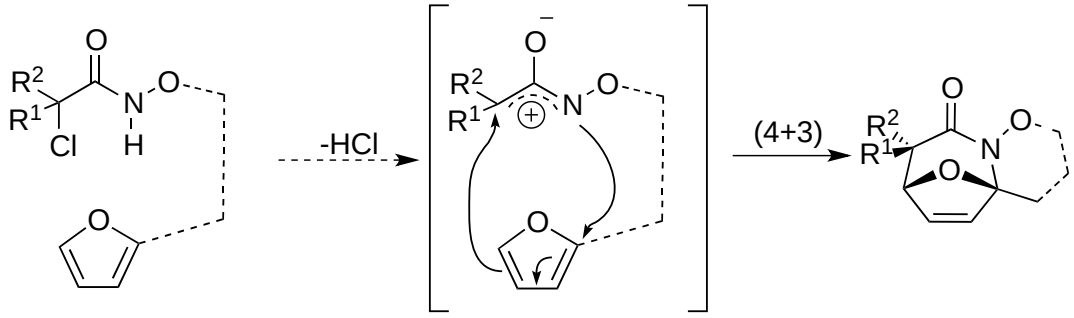
The (4+3)-cycloaddition reaction was found was found to work with a variety of substrates and generated the cycloadduct in good yield. On the whole, substitution of the substrate α-carbon proved nearly as important as O-benzyl substitution at the nitrogen atom for stabilization of the aza-oxyallyl cation. When only a proton was present at the α-position, no product was observed. Monoalkyl species produced the cycloadduct in moderate yields. The most dramatic differences, however, occurred with aryl or dialkyl substituted α-haloamides. These substrates produced similar yields to the monoalkyl substrates but also appeared to greatly enhance the reaction rate of the cycloaddition. Increased inductive stabilization of the aza-oxyallyl cation at the α-carbon decreased reaction times from 16 hours to 30 minutes! The identity of the halogen in the α-haloamide substrates also appears to play a role in rate of cycloaddition. In cases where direct comparison was feasible, chloroamides reacted much more slowly than bromoamides (48 hours vs. 16 hours, respectively), possibly because bromine is a slightly better leaving group than chlorine due to its increased ionic radius and polarizability.

Recently, the Jeffrey lab has expanded the scope of reactivity for the aza-oxallyl cation to include (4+3)-cycloaddition through diaza-oxyallyl cation intermediates (Scheme 4),[22] as well as intramolecular cycloaddition through a tethered, cyclic diene (Scheme 5).[23] In the diaza-oxayllyl cation case, the reactions proceed through an *N*-chlorourea substrate in the presence of a base and a cyclic diene.[22]

Scheme 4: General (4+3) cycloaddition through a diaza-oxyallyl cation generated from dehydrohalogenation of an *N*-chlorourea. Also shown is an example of an HIV-I protease inhibitor that may be accessible by this synthetic route.



Scheme 5: General (4+3)-cycloaddition through an aza-oxyallyl cation tethered to a cyclic diene for the synthesis of polyheterocyclic molecules.



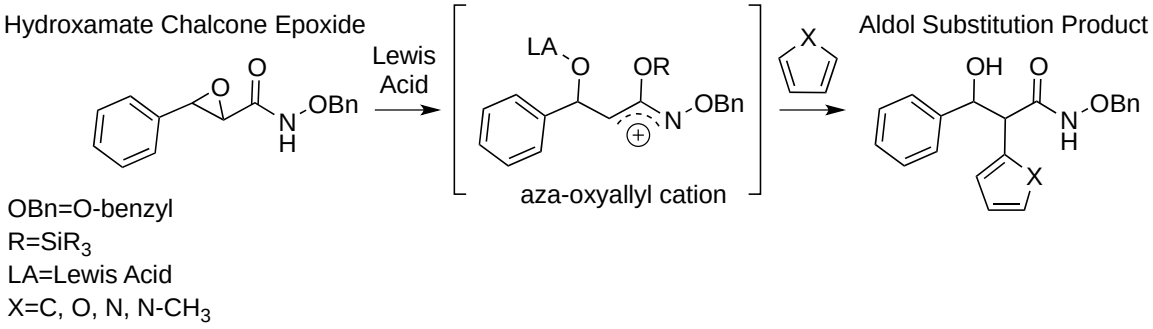
This is a significant advance, as the products of these reactions have the potential to increase the synthesis efficiency of such molecules as DMP 450, which is an important HIV-1 protease inhibitor (Scheme 4). [22] Efficient synthetic routes to polyheterocyclic molecules, such as the general molecule shown in Scheme 5, also have important implications, particularly in the realm of drug discovery and peptidomimetics.

Chapter 3: Aza-oxyallyl cations from hydroxamate chalcone epoxides

3.1 Synthesis of aldol products through Lewis-acid catalyzed ring opening of hydroxamate chalcone epoxides

Because of the poor atom economy involved in synthesizing and using α-haloamides as starting materials, the Jeffrey lab wondered if there was a way to generate aza-oxyallyl cations under Lewis acid-catalyzed conditions instead of base-mediated conditions. This would minimize waste by eliminating the need to synthesize pre-functionalized, halogenated starting materials. In addition, we were excited by the prospect of developing a method to induce stereoselectivity into a reaction that was dependent on a planar cationic intermediate. Because some Lewis acids are chiral, it is possible to control the stereochemical outcome of a reaction that proceeds through a planar cation, which can have important biological implications in pharmaceuticals. We

Scheme 6: General proposal for the synthesis of aldol products from hydroxamate chalcone epoxides.



began thinking about various substrates that could be used to generate aza-oxyallyl cations in the presence of catalytic amounts of Lewis acids. Lewis acids are well-known to catalyze epoxide ring-opening; thus, installing an epoxide functional group α to an O-benzyl-substituted amide, seemed to be a viable method of triggering the desired aza-oxyallyl cation intermediate.

To effect ring-opening of an epoxide, Lewis acids coordinate to the electron-rich oxygen atom and draw electron density away from the strained ring system, leading to breakage of one of the carbon-oxygen single bonds. A variety of Lewis acids have been known to effect this transformation. Depending on the way the Lewis acid coordinates to the substrate and also the substitution pattern of the epoxide, the stereospecificity of such reactions can be controlled. We hypothesized that generation of aza-oxyallyl cations by this method could provide a novel stereospecific route to pharmaceutical precursors containing the aldol moiety, not only achieving our goal of finding a novel method of aza-oxyallyl cation generation but also synthesizing useful pharmaceutical precursors in the process.

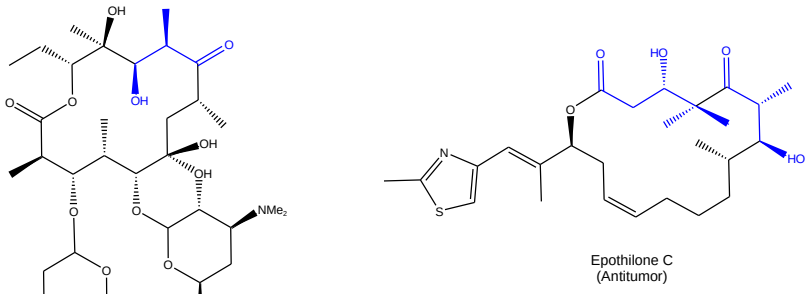


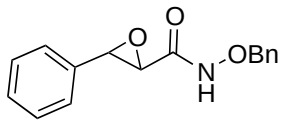
Figure 2: Examples of polyketide natural products with medicinal properties. Aldol moieties, which are defined by the β-hydroxy group, are highlighted in blue.

A common attribute of many biologically active molecules is the presence of the aldol moiety, which is generally characterized by a β-hydroxy, β-keto, or β-unsaturated carbonyl group. Aldol products are precursors to an important class of biologically active natural products called polyketides (Figure 2), which are secondary metabolites in a variety of fungi, plants, and bacteria. Synthesis of polyketides is a key interest in the pharmaceutical industry because these molecules demonstrate a wide variety of medicinal

properties, including antibiotic, antitumor, immunosuppressant, and antifungal properties. However, a difficult problem in designing any drug lies in controlling the product stereochemistry, since stereochemistry can have profound effects on biological activity.

While the aldol reaction is a well-established and important chemical transformation for synthesis of polyketide precursors, the reaction may produce a mixture of syn- and anti- products. Stereochemistry can be controlled through careful selection of substituents, but designing a reaction in this manner may limit the variety of products that can be synthesized. A more desirable method would allow for synthesis of aldol products with a wider variety of substituents, as well as provide precise control over which diastereoisomer is formed. Furthermore, it would provide a means for synthesis of either pure diastereoisomer through minor adjustments to reactions conditions.

The Jeffrey lab proposed that hydroxamate chalcone epoxides would be ideal substrates for exploring new mechanisms of Lewis-acid mediated aza-oxyallyl cation generation (Figure 3), as well as developing a new method for synthesizing aldol



1

A "Hydroxamate Chalcone Epoxide"
(*N*-O-benzyl-3-phenyloxirane-2-carboxamide)
OBn=O-benzyl

Figure 3: Hydroxamate chalcone epoxide starting material that was used to determine if aza-oxyallyl cations can be triggered through Lewis acid catalysis to generate aldol products.

products. We hypothesized that the Lewis-acid catalyzed ring-opening of the epoxide would trigger the formation of an aza-oxyallyl cation (Scheme 6). Synthesis of an aldol product would then proceed through an electrophilic aromatic substitution mechanism in

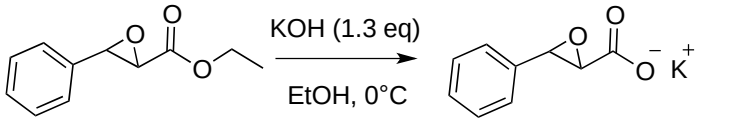
the presence of a nucleophile, thus providing a novel method of nitrogen incorporation into biologically relevant organic molecules for the synthesis of a variety of pharmaceuticals.

3.2 Experimental

The hydroxamate chalcone epoxide *N*-O-benzyl-3-phenyloxirane-2-carboxamide (**1**) was synthesized in two steps from commercially available ethyl-3-phenylglycidate (Sigma-Aldrich). The hydroxamate chalcone epoxide starting material was treated with a variety of Lewis acids in the presence of several different electron-rich arenes to determine if electrophilic aromatic substitution does in fact occur under these conditions (Scheme 6). A diverse assortment of Lewis acids known to effect epoxide ring-opening were tested, including $BF_3{\cdot}OEt_2$, $TiCl_4$, $Sm(OTf)_3$, TMS-OTf, and TIPS-OTf. Furan and *N*-methylpyrrole were employed as nucleophiles under a variety of temperature and solvent conditions. The carbonyl group was capped with a silyl protecting group prior to subjecting the starting material to a Lewis acid in order to create the appropriate conditions for generating an aza-oxyallyl cation. All NMR spectra were obtained using a Varian 500 MHz NMR spectrometer. Crystal structures were obtained on a Bruker SMART APEX single-crystal diffractometer.

3.2.1 Synthesis of potassium 3-phenylglycidate

Scheme 7: Synthesis of potassium 3-phenylglycidate.

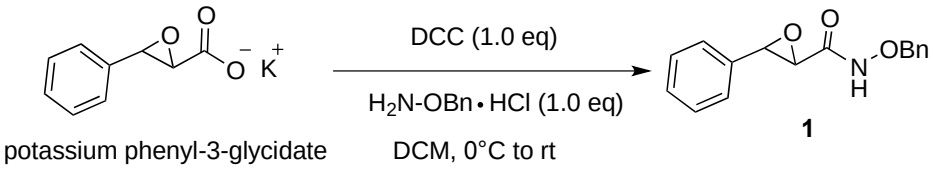


ethyl-3-phenylglycidate potassium phenyl-3-glycidate

Ethyl-3-phenylglycidate (EPG, 1.0 eq, 10 ml) was dissolved in ethanol (146 ml) and cooled to 0˚C in an ice bath, according to the procedures of Yudin, *et al*.[24] A solution of potassium hydroxide (1.3 eq, 4.18 g) in ethanol (56 ml) was added dropwise to the cooled EPG solution to form potassium 3-phenylglycidate. After 20 minutes, this white precipitate was vacuum-filtered, washed with diethyl ether, and dried under vacuum for 15 hours (60% yield). No further purification was required.

3.2.2 Synthesis of N-O-benzyl-3-phenyloxirane-2-carboxamide

Scheme 8: Synthesis of N-O-benzyl-3-phenyloxirane-2-carboxamide (**1**).



potassium phenyl-3-glycidate

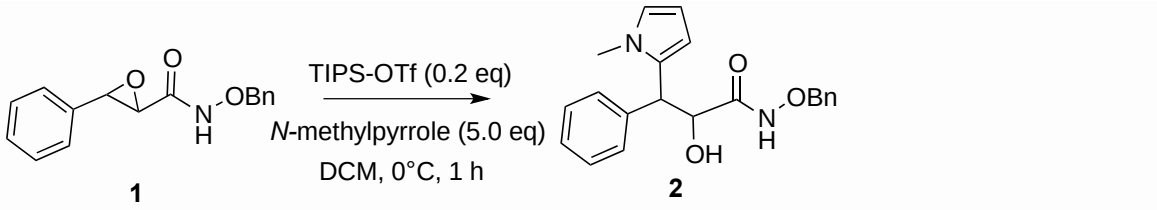
N-O-benzyl-3-phenyloxirane-2-carboxamide was synthesized according to the procedures of Yudin, *et al.* with minor modifications.[24] *N*,*N*'-dicyclohexylcarbodiimide (DCC, 1.0 eq, 5.1 g) was added to a solution of potassium 3-phenyl glycidate (1.0 eq, 5.0 g) in DCM (25 ml) under a nitrogen atmosphere at 0˚C. O-benzylhydroxylamine hydrochloride (1.0 eq, 3.95 g) was then added to the solution, and the mixture was slowly warmed to room temperature. The reaction mixture was stirred overnight (20 h) at room temperature. At the end of this period, the solid present in the reaction mixture was removed by vacuum filtration, and the filtrate was dried under vacuum to provide a viscous yellow residue. The crude product was purified by column chromatography (1:5, ethyl acetate: hexane) to give a white crystalline product in 30% yield.

3.2.3 Silylation of N-O-benzyl-3-phenyloxirane-2-carboxamide

Compound **1** (1.0 eq, 50 mg) was added to 1.5 ml acetonitrile. Commercially available *N*-(tert-butyldimethylsilyl)-*N*-methyltrifluoroacetamide (1.2 eq, 52 µl) from Sigma-Aldrich was subsequently added to the reaction vessel, which was then loosely capped with a clean septum. The reaction mixture was heated to 65˚C and stirred for 50-60 minutes until completion, as indicated by complete disappearance of the starting material by TLC and appearance of a product with a much higher Rf value near the solvent front (50:50 hexane: ethyl acetate). Excess solvent was immediately evaporated off under vacuum, and the product was immediately used for subsequent reactions without further purification.

3.2.4 Synthesis of Compound 2 and Compound 3 with trifluoromethanesulfonate (TIPS-OTf) or trimethylsilyl trifluoromethanesulfonate (TMS-OTf)

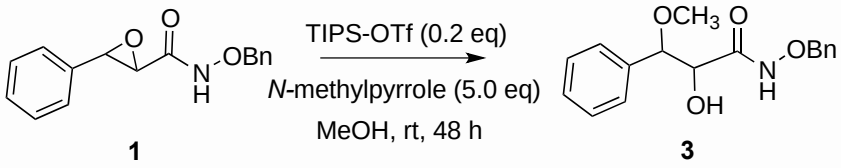
Scheme 9: Synthesis of Compound **2**.



Compound **1** (1.0 eq, 50 mg) was dissolved in 0.75 ml dichloromethane (0.25 M) followed by addition of an excess of *N*-methylpyrrole or furan (5.0 eq, ~83 µl). The reaction flask was placed in a 0˚C ice bath. Triisopropylsilyl trifluoromethanesulfonate (TIP-OTf) or trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 0.2 eq, 10 µl) was added last, and the reaction mixture was stirred for 1 hour. The reaction mixture was diluted with a few milliliters of brine and diethyl ether, and the aqueous layer was extracted with diethyl ether (3 x 2 ml). The ether layer was dried over $MgSO_4$ and was

evaporated down to give a yellow residue. Similar results are obtained regardless of whether or not the extraction step is performed. The major product (Compound **2**) was purified by column chromatography in a mixture of 1:1 v/v ethyl acetate: hexane (Rf = 0.5). Compound **2** was obtained in an overall yield of 74% with a mixture of the (*R,S*)- and (*S,R*)-diastereomers present in an approximate ratio of 2:3. Epoxide starting materials were not enantiomerically pure, so this ratio is not reflective of a preference for one diastereomer over the other in the reaction.

Scheme 10: Synthesis of compound **3**.

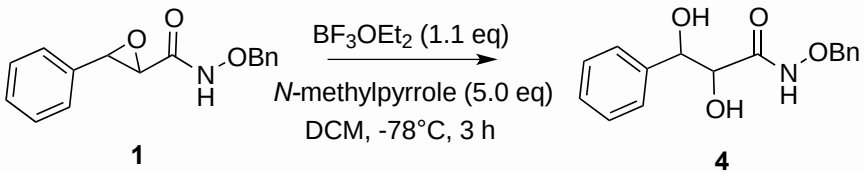


1 **3**

Synthesis of Compound **3** was achieved by followed the same procedure described above but with use of 0.75 ml methanol (0.25 M) in place of dichloromethane. The reaction mixture was stirred for 6 hours to overnight and warmed from 0˚C to room temperature until completion substrate conversion was observed by TLC. A single major product (compound **3**) was isolated in 57% yield.

3.2.5 Synthesis of Compound 4 through boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$)

Scheme 11: Synthesis of compound **4**.



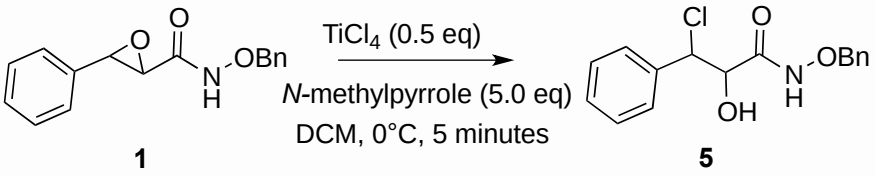
1 **4**

Compound **1** (1.0 eq, 50 mg), 0.75 ml dichloromethane (0.25 M), and *N*-methylpyrrole (1.2 eq, 20 µl) were added to a 5 ml round-bottom flask and stirred to dissolve the starting material. The flask was then placed in a -78˚C dry ice/acetone bath.

The Lewis acid $BF_3{\cdot}OEt_2$ (1.1 eq, 25µl) was then added quickly in one portion through a septum on top of the flask. The reaction mixture was stirred at -78˚C for 2 hours and 45 minutes with no changes observed by TLC. The reaction was then slowly warmed to 0˚C and stirred for another 45 minutes. At this point, complete disappearance of the starting material was observed by TLC. Note: if addition of $BF_3{\cdot}OEt_2$ is performed at 0˚C, rapid polymerization occurs, and no substitution products are observed. No work-up was performed. Excess solvent was removed under vacuum, and the product (**4**) was purified by column chromatography in a mixture of 1:1 v/v ethyl acetate: hexane.

3.2.6 Synthesis of Compound 5 with titanium tetrachloride

Scheme 12: Synthesis of compound **5**.

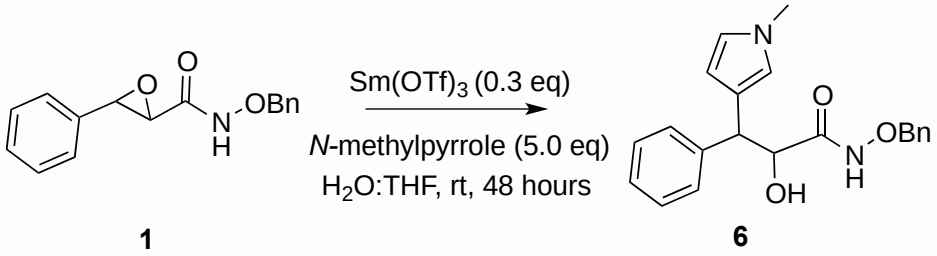


1 **5**

Compound **1** (1.0 eq, 50 mg), 0.75 ml dichloromethane (0.25 M), and *N*-methylpyrrole (5.0 eq, 83 µl) were added to a 5 ml round-bottom flask and stirred to dissolve the starting material. The flask was then placed in a –10˚C dry ice/acetone bath. Due to its high volatility, $TiCl_4$ (0.5 eq, 100 µl) was added rapidly through a septum atop the flask. An orange solid formed immediately upon addition of $TiCl_4$, and the reaction was complete within 5 minutes. The reaction was extracted with water and diethyl ether. The orange solid remained in the aqueous layer. The organic layer was evaporated down under vacuum, and the major product (Compound **5**) was isolated by column chromatography in a mixture of 1:1 v/v ethyl acetate: hexane.

3.2.7 Synthesis of Compound 6 with samarium (III) triflate

Scheme 13: Synthesis of compound **6**.



1 **6**

Compound **1** (1.0 eq, 50 mg), 0.60 ml THF: 0.15 ml water (4:1), and *N*-methylpyrrole (5.0 eq, 83 µl) were added to a vial with samarium triflate (0.3 eq, 0.33 mg) and stirred at room temperature for 48 hours. The crude reaction mixture was allowed to air dry and was further dried under high vacuum. The major product (Compound **6**) was isolated by column chromatography in a mixture of 1:1 v/v ethyl acetate: hexane.

3.2 Results and Discussion

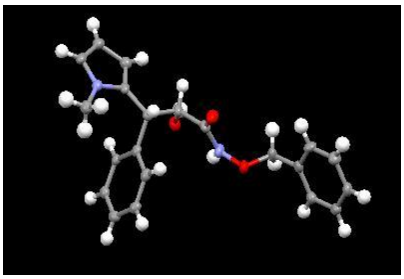
At the outset of this study, there were several questions we sought to address. First, if a Lewis acid does effect the desired transformation, how does the choice of Lewis acid affect yield and diastereoselectivity? Second, how do temperature and choice of solvent affect yield, reaction rate, and diastereoselectivity? Third, what is the substrate scope for the parent epoxide? Finally, what aromatic nucleophiles will participate in the electrophilic aromatic substitution reaction with the Lewis-acid generated cation?

Initial trials were carried out in dichloromethane at 0˚C, using TMS-triflate as the Lewis acid in the presence of a furan nucleophile (Scheme 9). The reaction was extremely fast and showed complete disappearance of starting material in only 30 minutes. Interestingly, the outcome of the reaction did not seem to be affected by the

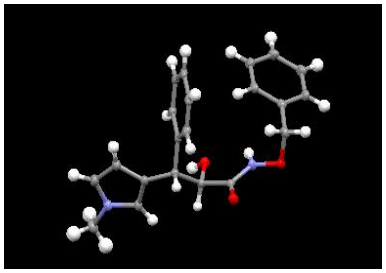
prior silylation of the epoxide starting material (Section 3.2.3). Although ^{1}H NMR spectra clearly indicated incorporation of furan into the product, we began to suspect that perhaps the reaction was not proceeding through an aza-oxyallyl cation as we initially anticipated. Because rapid polymerization of furan appeared to compete with the desired substitution reaction, we instead turned to *N*-methylpyrrole as the standard nucleophile in all subsequent reactions. This made product isolation and characterization much easier and allowed us to pinpoint what was actually happening in our reaction. Use of 2-methoxyfuran as a nucleophile was attempted, but upon addition of TIPS-OTf, a crystalline solid immediately began to form in the reaction flask, possibly due Lewis acid-catalyzed polymerization of the arene. A similar problem was observed with cyclopentadiene. Stirring the reaction mixture for several hours resulted in a series of brilliant color changes in the reaction mixture from teal green to purple to orange to brown, possibly indicating the presence of an extensive pi-system. The reaction mixture could not be purified due to the re-dimerization of cyclopentadiene. On the other end of the spectrum, reactions employing unsubstituted benzene as the nucleophile returned only starting material, indicating that the arene must be relatively electron-rich in order to act as a nucleophile under these conditions.

The reason that silylation of the starting material prior to addition of the Lewis acid catalyst did not appear to affect the reaction became immediately clear once crystal structures of the substitution products were obtained (Figures 3 & 4). We found in all

cases that substitution occurs at the β-position instead of the α-position of the



Compound **2**



Compound **6**

Figure 4: X-ray crystal structure of substitution product (**2**) of reaction shown in Scheme 9. Substitution is at the 2-position of *N*-methylpyrrole. Conversely, the X-ray crystal structure of substitution product (**6**) of the reaction shown in Scheme 13 illustrates substitution at the 3-position of *N*-methylpyrrole.

hydroxamate chalcone epoxide, implying that the reaction is not in fact proceeding through an aza-oxyallylcation intermediate as hypothesized. Instead, Lewis acid-catalyzed epoxide ring-opening appears to generate a traditional carbocation at the β-position, which is inductively stabilized by the phenyl group. While these reactions are regioselective, they are not stereoselective when hydroxamate chalcone epoxide substrates are used. Both the *(R,S)*- and *(S,R)*-diastereoisomers were isolated from the reaction.

Nonetheless, we determined that electrophilic aromatic substitution reactions at the β-position of hydroxamate chalcone epoxides proceed most quickly and cleanly in polar aprotic solvents, such as DCM and chloroform, with TIPS-triflate or TMS-triflate catalysts (Scheme 9). Acetonitrile and THF may also be used, but the reaction rate is much slower. The efficiency of substrate conversion to product also appears to be directly related to the concentration of the aromatic nucleophile. When the concentration of *N*-methylpyrrole was varied from a 0.25 M excess to 5.0 equivalents to 1.1 equivalents for the reaction shown in Scheme 9, the yield of the substitution product (**2**) was found to

steadily decrease from 84% to 61% to 52%, respectively. In the interest of maximizing yield and minimizing the amount of *N*-methylpyrrole required for the reaction, 5.0 eq of *N*-methylpyrrole were used in all subsequent reactions.

While polar aprotic solvent conditions are favored, the reaction will also proceed slowly in semi-aqueous media with a samarium(III) triflate catalyst. Strangely, this reaction resulted in *N*-methylpyrrole substituted at the 3-position (**6**) instead of the 2-position, as might be expected (Figure 4). Because the reaction took much longer to go to completion than the reactions employing other Lewis-acid catalysts, it is possible that this is the thermodynamically favored product, while the product with substitution at the 2-position is the kinetically favored product. The electrophilic aromatic substitution reaction either did not proceed in polar protic solvents or resulted in solvolysis products (**3**), regardless of the catalyst used (Scheme 10).

The optimum reaction temperature was found to vary according to choice of Lewis acid. Substitution of compound **1** with *N*-methylpyrrole occurred within one hour at 0˚C when the reaction was conducted in a halogenated polar aprotic solvent, such as chloroform or dichloromethane, in the presence of TMS-OTf or TIPS-OTf (Scheme 9). However, when the reaction was conducted in a polar protic solvent, such as methanol, the reaction temperature needed to be increased to 20˚C in order to observe conversion of substrate to product. In addition, the reaction time increased to approximately 12 hours, and the solvolysis product was the major observed product (Scheme 10, Figure 5). Instead of stabilizing the carbocation, excess of methanol clearly acts as a competing nucleophile, which results in greater substitution by the solvent than *N*-methylpyrrole. We proposed that perhaps this problem could be corrected through use of a more bulky

protic solvent that would enhance the rate of substitution without acting as a nucleophile, itself; however, no reaction was observed when the reaction was performed in ethanol or isopropanol.

Reactions with the Lewis acids boron trifluoride diethyl etherate and titanium tetrachloride both produced unexpected results. Reactions employing $BF_3{\cdot}OEt_2$ in DCM were conducted at -78˚C (Scheme 11). Within 3 hours, complete conversion of starting

Compound **3** Compound **4**

Figure 5: X-ray crystal structure of substitution product (**3**) of the reaction shown in Scheme 10, a solvolysis product, and the X-ray crystal structure of substitution product (**4**) of the reaction shown in Scheme 11 , a diol product.

material to products was observed, however, the resulting product was a diol (Figure 5). The source of the second hydroxyl group is not known, as an aqueous work-up was not performed. Because $BF_3{\cdot}OEt_2$ reacts violently with water, aqueous conditions were also strictly avoided during the course of the reaction. Reactions with $TiCl_4$ in DCM were first performed at -78˚C, but no reaction was observed. When the temperature was increased to 0˚C, the reaction was complete within 5 minutes but produced a halohydrin as the major product (**5**) instead of a product substituted with *N*-methylpyrrole (Scheme 12). Apparently, substitution by a chlorine atom proceeds much more quickly than substitution by *N*-methylpyrrole under these conditions.

While the Lewis acid-catalyzed generation of β-substituted products was interesting, it did not achieve our primary aim of finding a new Lewis acid-catalyzed method of generating an aza-oxallyl cation and, thus, did not provide a novel method of synthesizing aldol products. We initially chose to synthesize hydroxamate chalcone epoxides as starting materials because they are generated from commercially available ethyl-3-phenylglycidate, which already contains an epoxide group. A better choice of substrate would have been a terminal epoxide that opens the epoxide ring to favor cation formation at the more substituted, and thus more stable, α-position. This would provide a way to generate aldol products through an aza-oxyallyl cation, as we initially envisioned. Because of the ring-strain present in an epoxide, however, they are often difficult to synthesize. Compared to other chemical transformations, there are relatively few general methods of epoxidation that generate epoxides in good yield, and terminal unsubstituted epoxides from electron-poor alkenes can pose a particularly difficult synthesis challenge.[25] Nonetheless, in a final effort to test our hypothesis, we attempted synthesis of several unsubstituted epoxides from commercially available crotonic acid and methacrylic acid starting materials. We tested a variety of oxidation methods, including high-temperature *m*-CPBA epoxidation with a radical inhibitor,[26] nickel(II) actetate catalyzed epoxidation with sodium hypochlorite,[27] and epoxidation with DMDO.[28] These epoxidations were either followed or preceded by coupling of the carboxylic acid and O-benzylhydroxylamine hydrochloride with either DCC or EDCI. None of these reactions resulted in a sufficient amount of starting material to enabling testing of our hypothesis.

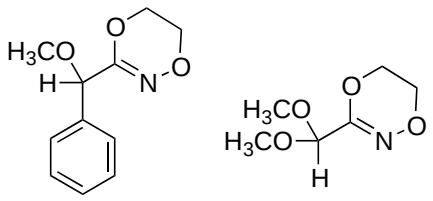
Chapter 4: Aza-oxyallyl cations from imidates

4.1 Electrophilic aromatic substitution of imidates through Lewis acid-catalyzed generation of aza-oxyallyl cations

Given the difficulties experienced working with epoxides, we proceeded to think about alternative methods of generating aza-oxyallyl cations by way of Lewis acid catalysis. As such, we began to research methods of synthesizing a class of imidates derived from hydroxamic acids. Imidates are the nitrogen analogues of esters and may be generally defined by the formula R-C(=NR')OR". The imidates we sought to synthesize were additionally characterized by a methoxy leaving group α to the carbon-nitrogen double bond. We hypothesized that the addition of a Lewis acid would induce removal of the methoxy group and subsequently generate an aza-oxyallyl cation. This cation could then be trapped by furan for (4+3)-cycloaddition or electrophilic aromatic substitution. If successful, this would provide the first known example of Lewis acid-catalyzed generation of an aza-oxyallyl cation.

4.2 Experimental

Imidates **9** and **11** were synthesized in two to three steps from commercially available mandelic acid and methyl dimethoxyacetate (Sigma-Aldrich). Hydroxamic



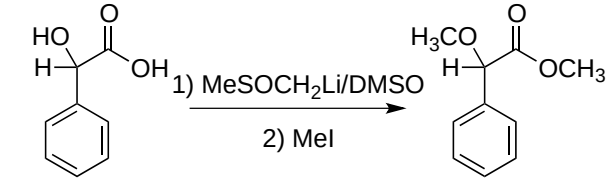
9 **11**

Figure 6: Examples of imidates that were synthesized from hydroxamic acids to determine if aza-oxyallyl cations may be generated through Lewis acid catalysis for electrophilic aromatic substitution or (4+3)-cycloaddition.

acids were generally synthesized from the appropriate methoxy ester in the presence of a strong sodium methoxide base and hydroxylamine hydrochloride. The hydroxamic acids were used without further purification to synthesize capped imidates (**9** and **11**) from dibromoethane in the presence of a weak potassium carbonate base (Scheme 16 and 18). Compounds **9** and **11** were then treated with a variety of Lewis acids in the presence of furan to determine if cycloaddition or electrophilic aromatic substitution does in fact occur through an aza-oxyallyl cation under these conditions. Several different Lewis acids were used to test our hypothesis, including $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, and TIPS-OTf, in the presence of furan. All NMR spectra were obtained using a Varian 500 MHz NMR spectrometer, and mass spectra were obtained on an Agilent GC-MS.

4.2.1 Synthesis of the alkoxy-ester derivative of mandelic acid (7)

Scheme 14: Synthesis of compound **7**.



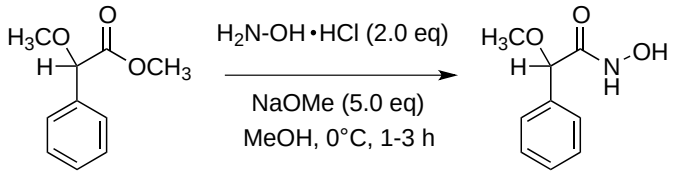
mandelic acid **7**

Compound **7** was synthesized from commercially available mandelic acid (Sigma-Aldrich) according to the procedures of Heaney, *et al*.[29] A 1.6 M solution of *n*-butyllituium in hexane (2.1 eq, 17.25 ml) was added dropwise to 20.0 ml of dry DMSO in an oven- and vacuum-dried round-bottom flask at room temperature under a nitrogen atmosphere. An ice water bath was kept beneath the flask to prevent overheating. Mandelic acid (1.0 eq, 2.0 g) was added and the solution was stirred under nitrogen for 2 hours. Upon addition of the mandelic acid, the reaction vessel heated up slightly, and the

solution became bright yellow. At the end of 2 hours, methyl iodide (2.3 eq, 1.88 ml) was added, and the reaction mixture was stirred overnight. To quench the reaction, the reaction mixture was carefully poured into water and then extracted with diethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. Excess solvent was removed under vacuum, and the product was purified by column chromatography (1:5 ethyl acetate: hexane). The product was a yellow oil and was isolated in 45% yield.

4.2.2 Synthesis of the hydroxamic acid derivative of mandelic acid (8)

Scheme 15: Synthesis of compound **8.**



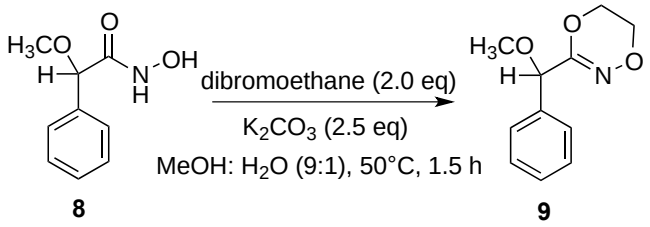
7 **8**

Hydroxylamine hydrochloride (2.0 eq, 0.36 g) and a stir bar were added to a flask containing 11 ml of methanol. The flask was placed in a 0˚C ice bath. Sodium methoxide (5.0 eq, 0.75 g) was added, and the mixture was stirred for approximately 10 minutes to free the base. Compound **7** (1.0 eq, 0.5 g) was added to the flask, and the reaction mixture was stirred until disappearance of the starting material was observed by TLC (approximately 1 hour). To ensure complete protonation of the hydroxamic acid product, concentrated hydrochloric acid was added dropwise until the pH was between 0 and 2. Remaining solid in the reaction mixture was quickly filtered through a plug of silica and flushed with pure ethyl acetate. Excess solvent was removed under vacuum to yield a pale orange solid product in crude yield of 94.4%. Aqueous extraction was not performed prior to evaporation of the solvent, as the product is very polar and becomes trapped in

the aqueous layer. The product was used immediately without further purification. ^{1}HNMR (500 MHz, DMSO) δ: 3.26 (s, 3H), 4.59 (s, 1H), 7.3-7.4 (m, 5H), 8.9 (s, broad), 10.9 (s, 1H).

4.2.3 Synthesis of hydroxamic acid capped with dibromoethane (9)

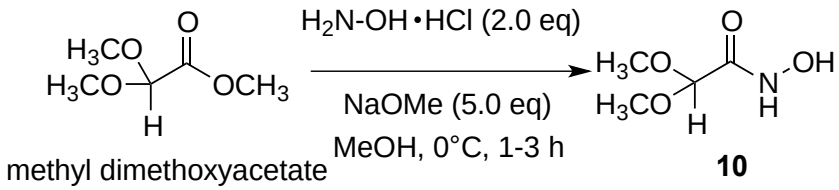
Scheme 16: Synthesis of compound **9.**



Compound **8** (1.0 eq, 95 mg) was dissolved in a 9:1 solution of methanol:water (~1.8 ml methanol: 0.2 ml water) at room temperature in a round-bottom flask equipped with a reflux condenser. Potassium carbonate (2.5 eq, 0.217 g) was added, followed by (2.0 eq, 0.10 ml) dibromoethane. The reaction mixture was gradually heated to 50˚C and was stirred until completion (~1.5 h). Excess potassium carbonate was filtered through a plug of cotton and rinsed with methanol. Solvent was removed under vacuum to yield a yellow residue (>100% crude yield). The product was used without further purification, due to evidence of decomposition on a silica column.

4.2.4 Synthesis of the hydroxamic acid derivative of methyl dimethoxyacetate (10)

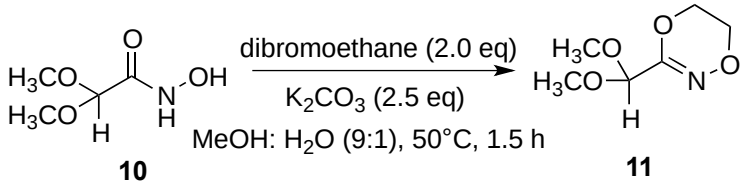
Scheme 17: Synthesis of compound **10.**



Hydroxylamine hydrochloride (2.0 eq, 0.518 g) and a stir bar were added to a flask containing 15 ml of methanol. The flask was placed in a 0˚C ice bath. Sodium methoxide (5.0 eq, 0.97 g) was added, and the mixture was stirred for approximately 10 minutes to free the base. Methyl dimethoxyacetate (1.0 eq, 0.5 g) was added to the flask, and the reaction mixture was stirred for 2 hours and 15 minutes. To ensure complete protonation of the hydroxamic acid product, concentrated hydrochloric acid was added dropwise until the pH was between 0 and 2. Remaining solid in the reaction mixture was quickly filtered through a plug of silica and flushed with pure ethyl acetate. Excess solvent was removed under vacuum. Aqueous extraction was not performed prior to evaporation of the solvent, as the product is very polar and becomes trapped in the aqueous layer. The product was used without further purification.

4.2.5 Synthesis of hydroxamic acid derivative capped with dibromoethane (11)

Scheme 18: Synthesis of compound **11**.

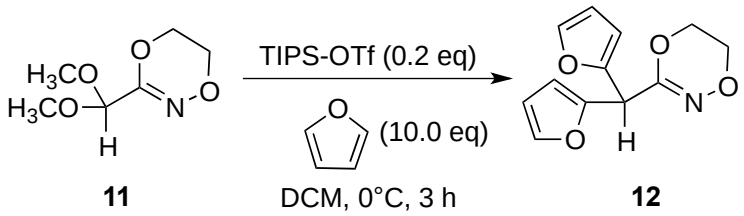


Compound **10** (1.0 eq, 0.544 g) was dissolved in a 9:1 solution of methanol:water (~12 ml methanol: 1.3 ml water) at room temperature in a round-bottom flask equipped with a reflux condenser. Potassium carbonate (2.5 eq, 0.217 g) was added, followed by (2.0 eq, 0.10 ml) dibromoethane. The reaction mixture was gradually heated to 50˚C and was stirred until completion (~1.5 h). Excess potassium carbonate was filtered through a plug of cotton and rinsed with methanol. Solvent was removed under vacuum to yield a solid and yellow liquid. The reaction mixture was then diluted with approximately 30 ml

water and was extracted with ethyl acetate (3 x 30 ml). The organic layer was dried over $MgSO_4$, and the solvent was removed under vacuum to give clear, viscous oil as the product (19% yield).

4.2.6 Synthesis of compound 12 through triisopropylsilyl trifluoromethanesulfonate

Scheme 19: Synthesis of compound **12.**



11 **12**

Compound **11** (1.0 eq, 28 mg) was dissolved in 0.75 ml dichloromethane (0.25 M) with furan (10.0 eq, 0.136 ml) at 0˚C. TIPS-OTf (0.2 eq, 10 µl) was added, and the reaction mixture was stirred for about 3 hours. The reaction mixture was diluted with water and then was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and the excess solvent was evaporated under vacuum. The products were isolated by column chromatography. The substitution product (compound **12**) has an Rf value of approximately 0.3 in a mixture of 40% ethyl acetate: hexane. ^{1}HNMR (500 MHz, $CDCl_3$) δ: 4.096 (t, 2H), 4.368 (t, 2H), 5.05 (s, 1H), 6.261 (m, 2H), 6.356 (m, 2H), 7.397 (m, 2H). ^{13}CNMR (500 MHz, $CDCl_3$) δ: 30.93, 42.86, 63.48, 64.98, 108.23, 110.51, 142.36, 149.20. GC-MS m/z: 233.

4.3 Results and Discussion

Synthesis of the desired imidate starting materials proved to be difficult, primarily because hydroxamic acids are quite reactive and difficult to purify. These highly polar molecules are easily deprotonated in the basic conditions under which their syntheses are

performed (Schemes 15 & 17). Great care must be taken to ensure that the reaction mixture is thoroughly acidic before synthesis of the imidate is attempted. In addition, the reaction mixture cannot be extracted under aqueous conditions because hydroxamic acids are highly soluble in water and become stuck in the aqueous layer. The hydroxamic acids synthesized in these experiments (Compounds **8** and **10**) were crystalline solids that seemed to oxidize upon prolonged exposure to air. Because the subsequent capping step to make the imidate is performed under semi-aqueous conditions, it was found that the best method to synthesize imidates (**9** and **11**) was to evaporate the majority of the methanol solvent off under vacuum and then immediately cap the crude substrate with dibromoethane (Scheme 16 & 18). This resulted in synthesis of imidates that were quite pure, even in crude form, and avoided oxidation and decomposition of the hydroxamic acid starting materials that seemed to occur every time their purification was attempted. The same procedure appears to be applicable to a variety of different methoxy ester substrates.

Following synthesis, the imidate derived from mandelic acid (compound **9**) was subjected to treatment by three different Lewis acids in the presence of furan. Treatment of the substrate with boron trifluoride diethyl etherate in dichloromethane at -30˚C with slow warming to room temperature resulted in a variety of products, none of which displayed characteristic furan peaks by NMR analysis. Treatment of the substrate with scandium(III) triflate in acetonitrile, hexafluoroisopropanol, or THF:water (4:1) also did not show any evidence of furan incorporation. The most promising results were achieved through the use of the Lewis acid TIPS-OTf. Treatment of compound **11** with TIPS-OTf in dichloromethane in the presence of 10.0 equivalents of furan at 0˚C resulted in double

furan substitution (Scheme 19, Compound **12**). As expected, TIPS-OTf appeared to catalyze removal of the methoxy groups α to the carbonyl to generate aza-oxyallyl cations, not once, but twice. Again, the concentration of furan seems to play a role in the efficiency of the reaction. When the experiment was repeated with only 1.0 equivalent of furan, no substitution products were observed.

The results for treatment of compound **9** with TIPS-OTf in dichloromethane in the presence of 10.0 equivalents of furan at 0˚C were more ambiguous. One would expect the reaction to proceed in similar fashion to the dimethoxy substrate with loss of the single methoxy group α to the carbonyl and generation of a monosubstituted furan product. On the contrary, this reaction resulted in recovery of the starting material and three diastereomers of a furan-substituted product. Strangely, the proton and carbon NMR spectra of these closely related products indicate the incorporation of furan into a material bearing the characteristic peaks of the dibromoethane cap but no phenyl group. Removal of the phenyl substituent from the starting material seems to defy the rules of organic chemistry. Studies are underway to scale-up and reproduce this result in an effort to elucidate the structure of these products. GC-MS studies also indicated presence of three products, but determination of the product masses was inconclusive.

Studies of the methyl dimethoxyacetate starting material in the presence of TIPS-OTf and furan are also currently underway to determine what products are formed in the all-carbon case of this reaction. So far, we have confirmed by NMR and GC-MS that double furan substitution also occurs in this case, but the reaction does not happen as cleanly, and many side-products are also present in the crude reaction mixture. We are

hopeful that analysis of these results will help to determine the mechanism by which this reaction proceeds.

Chapter 5: Conclusions, Future Work, and Potential Impacts

Because of the nature of our research, work in the Jeffrey Lab has the potential to have a broad practical impact on improving the sustainability of organic reactions through more efficient methods of C-N bond construction. Given the prevalence of nitrogen in biologically active natural products, novel approaches to carbon-nitrogen bond formation warrant exploration. Current synthesis methods for nitrogen incorporation often employ hazardous reagents, such as hydrazine and azides. In response to this problem, the ACS Green Chemistry Institute Pharmaceutical Roundtable recently named the development of new 'green' methods of C-N bond formation through electrophilic nitrogen sources as one of the top goals for the pharmaceutical industry.[30]

The work we have undertaken in the Jeffrey lab with aza-oxyallyl cation intermediates directly addresses this challenge. In addition to the inherent benefits of shorter, more atom economical routes to interesting natural product targets through aza-oxyallyl cations, we have also discovered a highly efficient way to synthesize seven-membered heterocycles. Such structures are common in biologically active natural products; however, such structures have historically presented a great challenge to synthetic chemists. Our work with the (4+3)-cycloaddition reaction has already shown great potential for target-directed synthesis of a variety of natural products, including balanol, bannisternoside A, and various amino glycosides.

While we have made great progress with developing methods of aza-oxyallyl cation generation, there is always more work to be done to expand the reaction scope and improve efficiency. The studies presented in this thesis aimed to explore new methods of generating aza-oxyallyl cations through Lewis acid catalysis. Our goal was to eliminate

the need for pre-functionalization starting materials and go directly to the desired intermediate. In the first half of this study, we aimed to synthesize aldol products through electrophilic aromatic substitution of hydroxamate chalcone epoxide substrates in the presence of an electron-rich arene and a Lewis acid catalyst. This reaction was thought to proceed through an aza-oxyallyl cation. Instead, we found that the generation of an aza-oxyallyl cation is not favored for this reaction substrate, as substitution occurs at the β-position instead of the α-position.

Nonetheless, we have discovered a variety of novel reactions to synthesize potentially useful pharmaceutical building blocks. We have recently been invited to submit the β-substituted compounds presented in this study for biological activity screening through the NIMH Psychoactive Drug Screening Program (PDSP) at UNC-Chapel Hill and the Eli Lilly Openinnovation Program. Because of the similarity of our compounds to the stimulant ephedrine, they are likely to have similar activity on certain receptors within the brain. The Eli Lilly Program will screen these compounds for potential applications for the treatment of heart disease, diabetes, cancer, and tuberculosis.

In the second half of this study, we aimed to provide the first example of an aza-oxyallyl cation generated through Lewis acid catalysis. Treatment of compound **11** with the Lewis acid triisopropylsilyl trifluoromethanesulfonate in the presence of furan generated a product with double furan substitution at the carbon α to the carbonyl (**12**). These results provide strong evidence that an aza-oxyallyl cation is indeed being generated. Future studies will be directed toward understanding the reaction mechanism and optimizing reaction conditions to induce Lewis acid-catalyzed (4+3)-cycloaddition.

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