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Development of a Microwave-Assisted Epoxide Aminolysis and Investigation of the aza-Cope Rearrangement--Mannich Cyclization for Alkaloid Synthesis

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DEVELOPMENT OF A MICROWAVE-ASSISTED EPOXIDE AMINOLYSIS AND INVESTIGATION OF THE AZA-COPE REARRANGEMENT—MANNICH CYCLIZATION FOR ALKALOID SYNTHESIS

by

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ABSTRACT

β-Amino alcohols are important organic compounds with numerous applications. Commonly β-amino alcohols are prepared by ring opening of epoxides using an amine nucleophile and a catalyst or promoter. Ring opening can take place by the S_N1 pathway or the S_N2 pathway, but no single catalyst or promoter consistently gives S_N2 selectivity. Additionally, long reaction times are often required to obtain adequate yields. We have demonstrated that microwave heating reduces reaction times for the aminolysis of both reactive and unreactive, sterically hindered epoxides. These reactions were accomplished with various amines. In all cases, only one equivalent of amine and epoxide were needed to give good yields and modest to excellent regioselectivity for the S_N2 product.

Amino alcohols made by aminolysis and other methods were used to investigate the aza-Cope rearrangement—Mannich cyclization. We proposed that this procedure could be used to produce compounds we could modify and transform into several alkaloids.

TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

LIST OF TABLES

LIST OF TABLES (CONTINUED)

LIST OF FIGURES

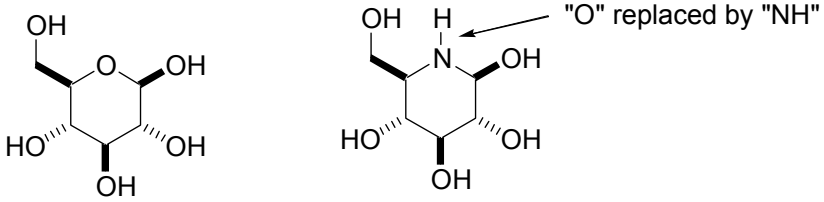
Chapter 1: Introduction

I. Pyrrolizidine alkaloids

Great potential has been seen in compounds that mimic the functions of sugars. These compounds are of use especially as pharmaceuticals. Sugar mimics function by preferentially binding to sugar-metabolizing enzymes (glycosidases), thus modifying the activity of those enzymes [1]. Glycosidases play a primary role in a number of biological functions such as digestion of carbohydrates and processing of glycoproteins on cell surfaces. Consequently, compounds that inhibit these enzymes could ultimately be used as treatments for diabetes, cancer, and viral infections such as HIV [1a].

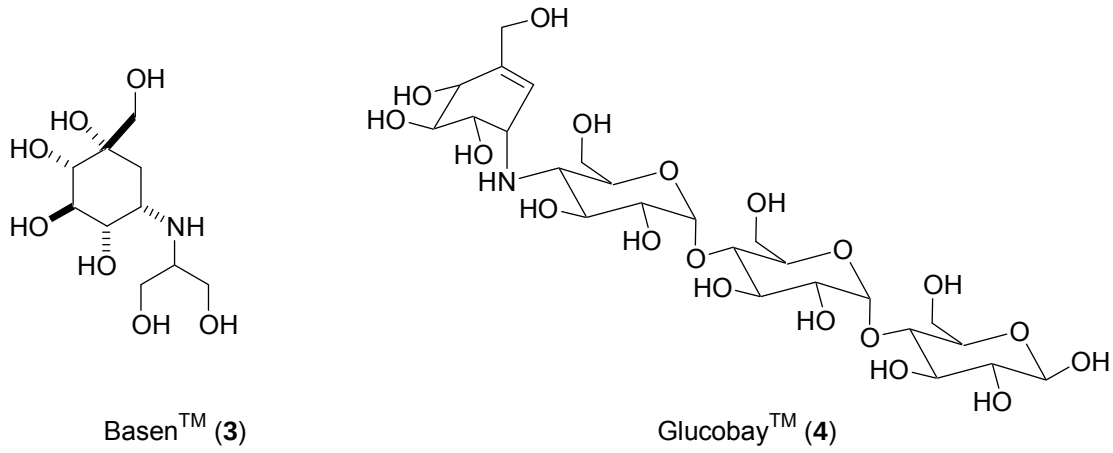
One class of sugar mimics consists of compounds that replace the oxygen of the natural sugar with nitrogen. A comparison of glucose (**1**) with the sugar mimic nojirimycin (**2**) (**Figure 1**) reveals that the structures of the two molecules are identical except that the ring oxygen of the sugar has been replaced by nitrogen and hydrogen in the mimic. This close structural resemblance between

Figure 1. Structural comparison of a sugar with a sugar mimic.



natural sugars and nitrogen-containing mimics allows a number of them to be good inhibitors of sugar-metabolizing enzymes, and makes them excellent candidates for pharmaceuticals. Indeed, two nitrogen-containing sugar mimics are currently on the market for the treatment of diabetes: Basen™(**3**) in Japan and Glucobay™ (**4**) in Germany (**Figure 2**)[1a].

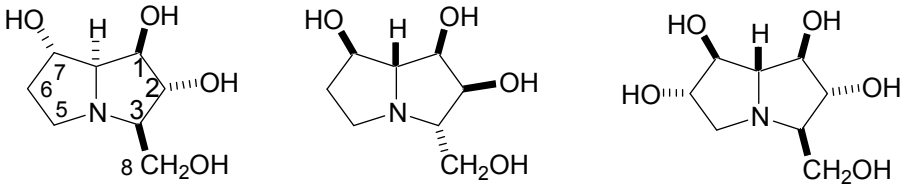
Figure 2. Nitrogen containing sugar mimics used as pharmaceuticals.



Basen™ (**3**) Glucobay™ (**4**)

Pyrrolizidine alkaloids are a class of bicyclic alkaloid sugar mimics that contain two 5-membered rings. A number of these compounds have also demonstrated glycosidase inhibition (**Figure 3**) [1]. Due to this activity, the demand for such compounds has increased. (+)-Alexine (**5**) is a natural product isolated from the pods of the legume *Alexa leiopetala* [2a]. Because it contains five contiguous stereocenters, Alexine has 32 natural and unnatural stereoisomers. It has been shown that glycosidase inhibition ability of pyrrolizidine alkaloids is dependent on the number and stereochemistry of the hydroxyl groups [2,3], so versatile synthetic routes that can lead to many of these isomers are needed.

Figure 3. Biologically active pyrrolizidine alkaloids.



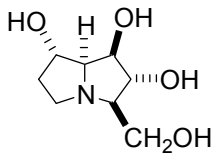
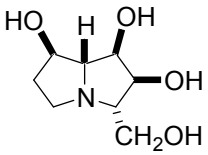
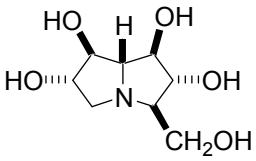
(+)-alexine (**5**)

2,3,7-triepi-australine (**6**)

casuarine (**7**)

(+)-Alexine (**5**), 2,3,7-triepi-australine (**6**) and casuarine (**7**) [2b] have similar structures but differ in the number and stereochemistry of hydroxyl groups. This changes the glycosidase inhibitory activity of these compounds. The data in **Table 1** suggest that the stereochemistry and/or the number of hydroxyl groups is important. For example, casuarine (**7**), which has the best inhibition ability against all three enzymes, contains a C6 hydroxyl but also has different relative stereochemistry than alexine (**5**) and 2,3,7-triepi-australine (**6**) [2c]. Alexine's (**5**) inhibition is better than that of 2,3,7-triepi-australine (**6**) for rice α-glycosidase and for β-glycosidase. Alexine (**5**) has different stereochemistry than 2,3,7-triepi-australine (**6**), indicating the importance of relative stereochemistry. Since the stereochemistry and/or the number of hydroxyl groups play an important role in determining the glycosidase inhibitory activity, our goal is to synthesize a number of alexine stereoisomers to aid in exploring the structure-activity relationship of these glycosidases. Hence, an appropriate synthetic route is needed to give flexibility in the installation of the stereocenters of these compounds.

Table 1. Glycosidase inhibitory activity for three pyrrolizidine alkaloids [2c].

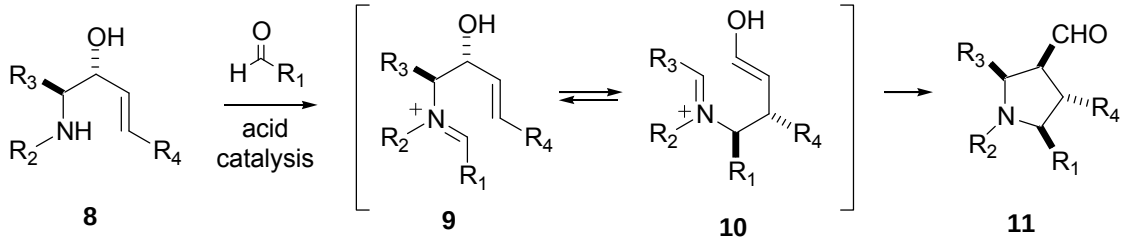
	 alexine (**5**)	 2,3,7-triepi-australine (**6**)	 casuarine (**7**)
Enzyme		IC_{50} (μM)	
α–Glucosidase			
rice	250	420	1.2
rat intestinal maltase	540	130	0.7
β–Glucosidase			
porcine kidney	55	310	12

Synthesis of (+)-alexine derivatives with up to 4 stereocenters have been published [5,6]. However, these methods use sugars as the starting material, so the stereochemistry is set at the start of the synthesis. Thus, most of the published research in this area does not allow the *de novo* generation of stereocenters. By contrast, installing stereocenters in the course of the synthesis is a more flexible strategy for the synthesis of alexine stereoisomers, so new methods that utilize this approach need to be developed. Our synthetic plan employs a sequence called the tandem aza-Cope rearrangement Mannich cyclization (ACM). We believe this to be a flexible route that should give us the ability to control the C_1, C_2, and C_3 relative stereochemistry (*vide infra*).

II. Aza-Cope rearrangement—Mannich cyclization

The ACM reaction was first introduced in 1979 by Overman [7,8]. It is a cationic reaction that results in the formation of a 3-acylpyrrolizidine **11** (**Scheme 1**). The reaction begins by the formation of an iminium cation **9** from amino alcohol **8**. The iminium cation undergoes a [3,3]-sigmatropic rearrangement to give enol **10**, followed by intramolecular Mannich cyclization of the enol to give the acylpyrrolidine **11** [7d].

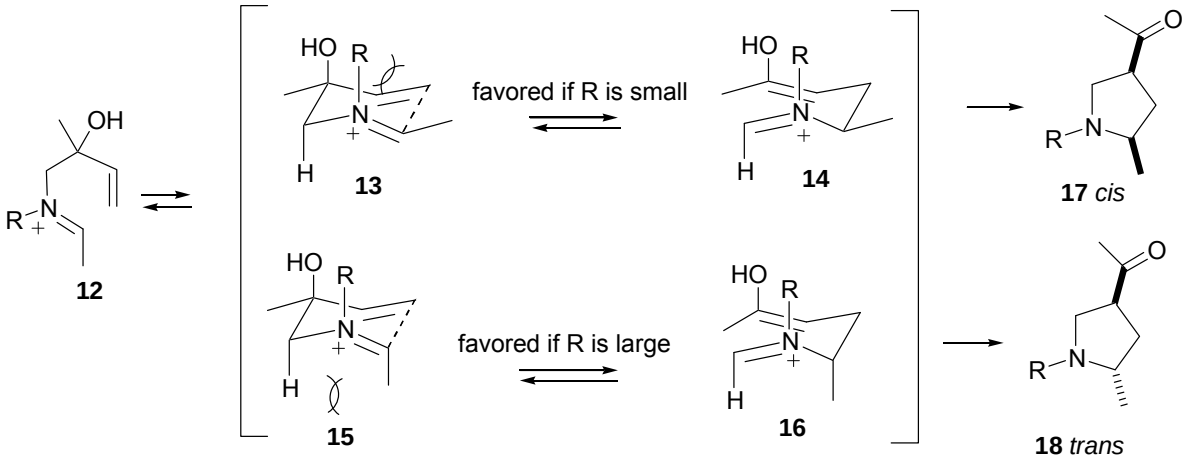
Scheme 1



8 **9** **10** **11**

Carbons bearing the R_1 and R_4 substituents (**Scheme 1**) become two new stereocenters in the product [7c]. Thus a pyrrolidine with up to four contiguous stereocenters can be formed via this sequence. The pyrrolidine relative stereochemistry will depend on the geometry of the carbon-carbon double bond, the iminium cation geometry, and the extent to which the reaction proceeds through an ordered chair-like transition state (**Scheme 2**) [7f].

Scheme 2

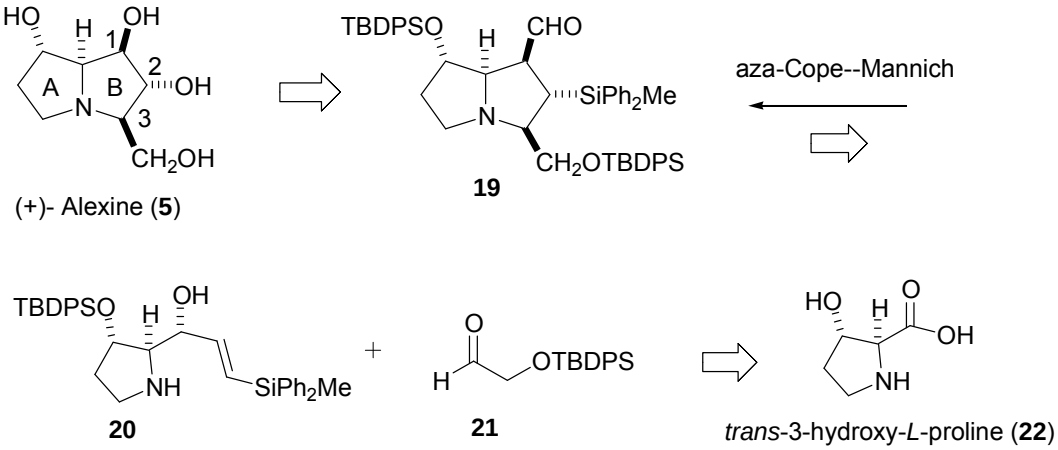


In the transition state, allylic strain [8] and pseudo-1,3-diaxial interactions should control the stereochemical outcome [7f]. Specifically, the size of the R group on the nitrogen should dictate the relative stereochemistry in the product. If R is small, the allylic strain in cation **13** is less significant than the pseudo-1,3-diaxial interaction in cation **15**. ACM reaction of **13** should lead to *cis*-pyrrolidine **17.** By contrast, if the R group is large, allylic strain between the R group and methyl group is significant. The methyl group would likely prefer to occupy the pseudo axial position as in cation **15** [7f,8]. ACM reaction of **15** should lead to *trans*-pyrrolidine **18**. We anticipate using this stereocontrol in the synthesis of (+)-alexine and its stereoisomers. This work represents the first attempt to synthesize (+)-alexine and its stereoisomers using the aza-Cope—Mannich cyclization.

III. Retrosynthetic analysis for alexine total synthesis

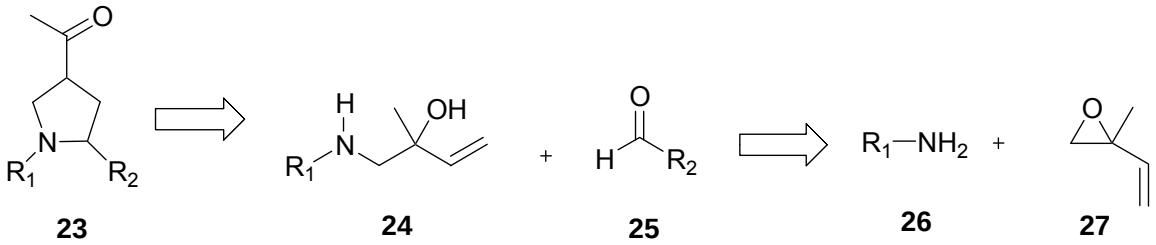
Our plan for the synthesis of (+)-alexine (**5**) is shown in **Scheme 3**. An ACM reaction would establish the relative stereochemistry at C_1, C_2, and C_3. The natural product would be available from the aldehyde **19** after oxidation, hydrolysis, and deprotection. Aldehyde **19** would be the product of the aza-Cope-Mannich cyclization of amino alcohol **20** and aldehyde **21.** Amino alcohol **20** can be prepared by reduction and vinyl addition to commercially available *trans*-3-hydroxy-L-proline (**22**).

Scheme 3



Because of the dense functionality of alexine, we elected to use a simplified model system to test the viability of our stereocontrol hypothesis in the ACM reaction (**Scheme 4**). Pyrrolidine **23** would be available via condensation of amino alcohol **24** with the aldehyde **25** and the subsequent ACM reaction. Amino alcohol **24** should be produced from the regioselective aminolysis of epoxide **27** with amine **26**.

Scheme 4



23 **24** **25** **26** **27**

We report herein the results of regioselective aminolysis reactions, which appear to be general for several epoxides. In addition, we have used the resulting amino alcohols as starting material for ACM reactions to form pyrrolidines. Finally, we report the results of the ACM reactions of these amino alcohols as well as other amino alcohols synthesized from L-proline. Ultimately, we plan to use similar L-proline derived amino alcohols and the resulting ACM products as intermediates in the synthesis of pyrrolizidine alkaloids such as alexine (**5**).

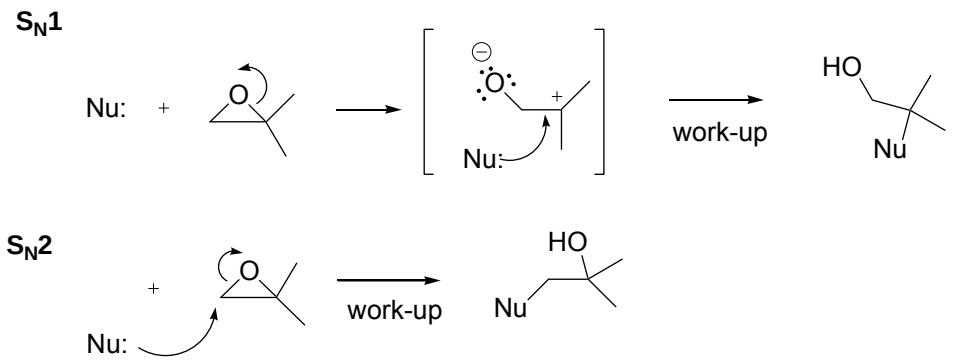
Chapter 2: Literature Review

I. Introduction

Unimolecular nucleophilic substitution (S_N1) reactions involve the substitution of a leaving group with a nucleophile. The reaction is characterized by the formation of a carbocation intermediate in the rate determining step. In the second step, the incoming nucleophile can attack the carbocation from the same side as the leaving group to give retention of configuration in the product, or the nucleophile can attack from the side opposite to the leaving group to give a product with the opposite configuration as the starting material. Bimolecular nucleophilic substitution (S_N2) involves the substitution of a leaving group with a nucleophile. In a single step the incoming nucleophile attacks the carbon atom from the side opposite the leaving group. The product is formed with inversion of configuration.

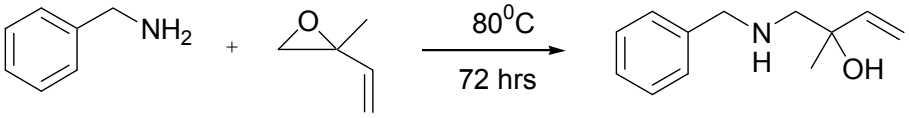
In the ring opening of epoxides, S_N2 and S_N1 may be competing reaction pathways under certain reaction conditions. Depending on the substitution of the epoxide, the two pathways may lead to two regioisomers (**Scheme 5**). When an amine is used as a nucleophile in a substitution reaction (aminolysis) of an epoxide, the reaction conditions often dictate the regioselectivity.

Scheme 5



Three issues with these reactions are that they are often low-yielding, require large excesses of amine, and/or require long reaction times [9]. For example, Cooke required amino alcohol **29** for use in a novel aza-Cope rearrangement—Mannich cyclization [9] (**Scheme 6**). Accordingly, the authors used benzylamine (**28**) in the aminolysis of 2-methyl-2-vinyloxirane (**27**). Five equivalents of benzylamine were stirred with the epoxide at 80°C for 72 hours. Alcohol **29**, which arises from attack at the least hindered carbon atom, was the only product isolated. The yield for the reaction was 89%.

Scheme 6



28 **27** **29**

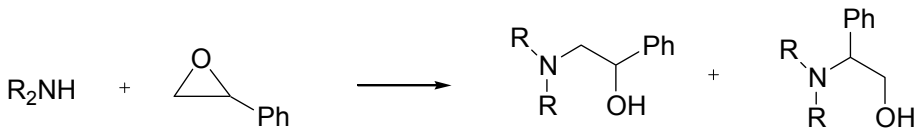
89%

In an effort to reduce reaction times and/or amount of amine required, researchers have used a variety of Lewis acids [10-23], solvents [24], and alternative heating methods [27-36] for the aminolysis of epoxides.

II. Lewis acid catalyzed or assisted epoxide aminolyses

De has used scandium triflate as a catalyst for epoxide aminolysis under solvent-free conditions [10]. The amine, epoxide, and 5 mole percent of the catalyst were stirred at room temperature for 2-5 hours. The reaction of a 1:1 molar ratio of styrene oxide (**30**) and aniline gave a regioisomeric ratio of 5:95 favoring alcohol **32** (**Scheme 7**), the result of favored attack on the more hindered carbon. The overall yield was 95% (**Table 2**, entry 1). When benzylamine was used, the attack at the less hindered carbon atom was favored with a ratio of 85:15 and an overall yield of 89% (**Table 3**, entry 1). Piperidine gave poorer regioselectivity, favoring the attack at the less hindered carbon atom with a 75:25 regioisomeric ratio and an overall yield of 91% (**Table 4**, entry 1). The regioisomeric ratios were determined by ^{1}H NMR.

Scheme 7



styrene oxide (**30**) **31** **32**

Cepanic used calcium trifluoromethanesulfonate with acetonitrile as the solvent for epoxide aminolysis [11]. Between 10 and 25 mole percent of catalyst was used for the reactions, which were stirred at room temperature for 20 minutes to 72 hours depending on the amine structure. Various aliphatic and aromatic amines were used for the reaction. The reaction of 10 mmol styrene oxide (**30**) and 10 mmol benzylamine (**28**) gave a regioisomeric ratio of 85:15 (**Table 3**, entry 2) favoring alcohol **31**, presumably the result of S_N2 attack

(**Scheme 7**). The regioisomeric ratio was determined by HPLC. The overall yield for the reaction was 99%.

Cossy [12] has described a method for epoxide aminolysis using lithium bistrifluoromethanesulfonimide. The reaction of 1.2 equivalents of benzylamine and 1 equivalent of styrene oxide with 0.1 eq of $LiNTf_2$ in CH_2Cl_2 was stirred for 20 hours at room temperature and gave a regioisomeric ratio of 80:20, favoring alcohol **31** formed by the attack at the less hindered carbon (**Scheme 7**). The overall yield of the reaction was 77% (**Table 3**, entry 3)**.**

Mirkhani has used an ammonium decatungstocerate (IV) catalyst [13]. Many catalysts reported in the literature are expensive, hazardous, moisture sensitive, and ineffective when deactivated amines are used as nucleophiles. Ammonium decatungstocerate (IV) was used as a heterogeneous catalyst that could be recycled after the reaction. The aminolysis was carried out in refluxing acetone with reaction times varying from 15 minutes to 180 minutes. Once the reaction was completed, the product was simply isolated by filtration and evaporation of the solvent, and the crude product was purified by column chromatography. In the example of styrene oxide (1 mmol) aniline (1.2 mmol) and catalyst (0.04 mmol), alcohol **31** (**Scheme 7**) was formed with a yield of 92% as a single regioisomer according to ^{1}H NMR (**Table 2**, entry 2). The attack was reported to be at the more hindered carbon of styrene oxide. One disadvantage of this method is that tungsten can be hazardous if released into the environment and that the catalyst is not commercially available.

Rafiee used potassium dodecatungstocobaltate trihydrate as the catalyst for the ring opening of epoxides using a variety of amines [14]. The amine (2.0 mmol), epoxide (1.0 mmol), and the catalyst (0.02 mmol) were refluxed in acetonitrile for a period of 1-7 hours. It was noteworthy that the yields reported were determined by GLC analysis of the crude product rather than by product isolation. The reaction of styrene oxide and aniline gave a yield of 98% (**Table 2**, entry 3) with a single regioisomer **35**, formed by attack at the more hindered carbon of styrene oxide.

Akamanchi has used diisopropoxyaluminium trifluoroacetate (DIPAT) for the ring opening of epoxides [15]. DIPAT had previously been used as a Lewis acid catalyst for accelerating the Meerwein-Ponndorf-Verley reduction and the Oppenauer oxidation [16]. The aminolysis reaction was carried out by reacting the epoxide (1 eq), amine (1 eq), and DIPAT (1 eq) in acetonitrile at room temperature for 1-12 hours, depending upon the amine and epoxide. The reaction of styrene oxide with aniline or benzylamine gave exclusively alcohols **35** (**Scheme 8**), and **37** (**Scheme 9**) in 90% yield (**Table 2**, entry 4) and 86% yield (**Table 3**, entry 4), respectively. These products were formed by the attack at the more hindered carbon atom. Piperidine and styrene oxide gave the regioisomeric ratio of 47:53, slightly favoring alcohol **40** from attack at the more hindered carbon (**Scheme 10**), with an overall yield of 90% (**Table 4**, entry 2). The regioisomeric ratio in each reaction was determined by ^{1}H NMR.

Collin has used samarium iodide as a catalyst for the ring opening of epoxides [17]. The catalyst was used as a $SmI_2(THF)_2$ suspension in

dichloromethane. All reactions were carried out at room temperature. When styrene oxide (**30**) (2 mmol) was reacted with benzylamine (**28**) (2 mmol) and catalyst (0.10 mmol) in dichloromethane, alcohol **37**, arising from attack at the more hindered carbon, was favored by a ratio of 35:65 with an overall yield of 70% (**Table 3**, entry 5). The reaction of styrene oxide (**30**) and piperidine gave a regioisomeric ratio of 53:47, slightly favoring the attack at the less hindered carbon and a very modest 56% overall yield (**Table 4**, entry 3). The regioisomeric ratios were determined by GLC and ^{1}H NMR.

Chakraborti used a new catalyst, zirconium (IV) chloride, for epoxide aminolysis [18]. The reasons for the choice of zirconium chloride were low cost, the environmentally benign nature of the catalyst, and low toxicity. The authors examined a number of reactions of epoxides and amines with the intention of studying the mechanistic pathway of the product formation using this catalyst. The reactions were carried out at room temperature. The reaction of styrene oxide (2.5 mmol), aniline (2.5 mmol), and catalyst (5 mole%) at room temperature gave a regioisomeric ratio of 8:92 favoring alcohol **35** (**Scheme 8**), the isomer formed by the attack at the more hindered carbon. The overall yield of the reaction was 98% (**Table 2**, entry 5). The reaction of styrene oxide and benzylamine gave alcohol **36**, arising from the attack at the less hindered carbon, as the preferred regioisomer with a ratio of 78:22 and an overall yield of 96% (**Table 3**, entry 6). The reaction of styrene oxide and piperidine gave a regioisomeric ratio of 60:40, with the attack at the less hindered carbon atom

favored. The overall yield of the reaction was 98% (**Table 4**, entry 4). The regioisomeric ratios for all reactions were determined by GC-MS.

Reedijk has discussed a novel method for the synthesis of β-amino alcohols via epoxide aminolysis using a zinc (II) catalyst [19]. The authors have used zinc chloride because it is inexpensive and effective for epoxide ring opening reactions. In the reactions, a 1:1 molar ratio of amine to epoxide and 5 mole percent catalyst were heated in acetonitrile at 82^{o} C for 12 hours to 3 days. The reaction with styrene oxide and aniline gave a regioisomeric ratio of 7:93, favoring the attack at the more hindered carbon to give alcohol **35** (**Scheme 8**) with an overall yield of 100% (**Table 2**, entry 6). The reaction of styrene oxide and benzylamine (**Table 3**, entry 7) gave a yield of 40%, with a regioisomeric ratio of 41:59 narrowly favoring alcohol **37** (**Scheme 9**) via attack at the more hindered carbon. The use of zinc as a catalyst may be effective, but the time required for the reaction is quite substantial.

Sundararajan has described a method for the regioselective ring opening of epoxides using catalytic cobalt (II) chloride catalyst in acetonitrile [20]. All the reactions were carried out at room temperature using a 1:1 molar ratio of amine to epoxide and 10 mole percent $CoCl_2$. Reaction between styrene oxide and the bulky amine 2,6-diisopropylaniline gave a 12:88 mixture of isomers favoring alcohol **32** (**Scheme 7**), which was characterized by single crystal x-ray analysis. The overall yield of the reaction was 76%. The regioisomeric ratio from the reaction of styrene oxide and aniline was 5:95, favoring alcohol **35** (**Scheme 8**). The overall yield was 98% (**Table 2**, entry 8). Lower reactivity and poorer

regioselectivity was seen with electron withdrawing groups, such as chlorine, on the aromatic ring of the epoxide. Some of the reactions were very slow, requiring 4-24 hours. All regioisomeric ratios were determined by ^{1}H NMR.

Chakraborti has also described a method for the ring opening of epoxides using montmorillonite K-10 [21], a type of clay that is often used as a Lewis acid catalyst in organic reactions. The authors have discussed the drawbacks of the other reported methods for epoxide aminolysis which include long reaction time, elevated temperatures, high pressures, and use of moisture sensitive catalysts. In addition, they noted that methods for the ring opening of epoxides are limited to more nucleophilic amines. By contrast, they have used an environmentally friendly method for epoxide aminolysis and have used this method to study less nucleophilic amines. Various unsymmetrical epoxides were subjected to aminolysis and the ratio of regioisomers was determined by GCMS. The reaction of styrene oxide and aniline using a 1:1 molar ratio and 10 percent by weight of catalyst gave a ratio of 7:93 with alcohol **35** (**Scheme 8**) as the major isomer arising from the attack at the more hindered carbon of the epoxide with an overall yield of 93% (**Table 2**, entry 7). The reaction of styrene oxide and benzylamine gave a regioisomeric ratio of 82:18, with the attack at the less hindered carbon favored and an overall yield of 89% (**Table 3**, entry 8). The reaction of piperidine and styrene oxide gave a single regioisomer with the attack at the less hindered carbon atom with an overall yield of 75% (**Table 4**, entry 5).

Chakraborti [22] has also outlined a method for the ring opening of epoxides using silica gel as a Lewis acid catalyst. The purpose of using silica gel

was to use a cost effective and non-toxic Lewis acid and also to use solvent-free conditions to open the epoxide ring. The reaction was carried out by stirring the amine (2.5 mmol), epoxide (2.5 mmol), and 10 percent by weight of silica gel at room temperature under nitrogen for 3 hours. The regioisomeric ratio was determined by the ^{1}H NMR analysis. The ratio for the reaction of styrene oxide and aniline was 5:95 favoring alcohol **35** (**Scheme 8**), arising from attack at the more hindered carbon of styrene oxide with an overall yield of 93% (**Table 2**, entry 9). In the reaction of styrene oxide and benzylamine, the regioselectivity was opposite to that observed for aniline. The overall yield was 100%, with a regioisomeric ratio of 78:22 favoring attack at the less hindered carbon (**Table 3**, entry 9). The silica gel was reused after washing with diethyl ether and activation at 100°C.

Kotsuki [23] also investigated epoxide aminolyses using silica gel as the Lewis acid. In these reactions, imidazole (1.5 mmol), styrene oxide (1.5 mmol), and silica gel (500 mg) were kept at room temperature for 7 days to get a yield of 47%. This is significantly lower than yields reported by Chakraborti using benzylamine and aniline as nucleophiles [22]. Alcohol **31** (**Scheme 7**) was formed as the single isomer, arising by the attack at the less hindered carbon of styrene oxide.

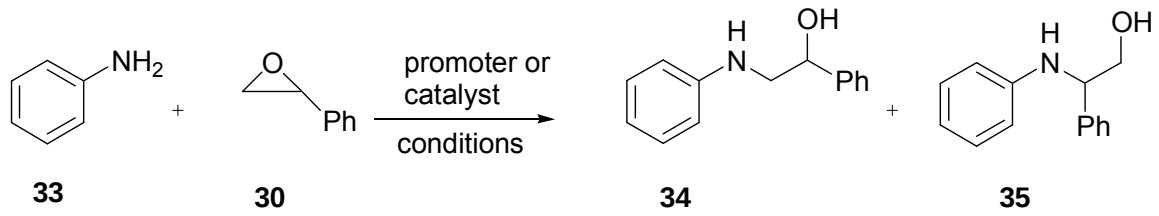
III. Uncatalyzed aminolysis reactions

Kotsuki also carried out aminolysis under high pressure to reduce the reaction time and improve yields. The overall yield for the reaction of imidazole and styrene oxide was 59%, giving alcohol **31** as a single regioisomer via attack at the less hindered carbon (**Scheme 7**). The reaction was carried out under solvent-free conditions in a teflon reaction vessel with a pressure of 10 kbar. This procedure had two distinct drawbacks: the reaction required three days for completion, and the pressure had to be maintained at 10 kbar for the duration of the reaction.

Saidi has described a new method for the preparation of amino alcohols from epoxides and amines using water as the solvent [24]. Water had not been previously used as a solvent for ring opening of epoxides, as most reactions involving catalysts require moisture-free conditions. Typically the reaction is carried out by stirring the epoxide (5 mmol) and the amine (6 mmol) in water at room temperature for 5-24 hours. The reaction of styrene oxide and aniline gave a regioisomeric ratio of 4:96 favoring alcohol **35** (**Scheme 8**), arising from the attack at the more hindered carbon of styrene oxide. The overall yield was 97% (**Table 2**, entry 10). The reaction of styrene oxide and benzylamine also favored the attack at the more hindered carbon with a regioisomeric ratio of 30:70 and an overall yield of 88% (**Table 3**, entry 10). When styrene oxide and piperidine were reacted, alcohol **39** (**Scheme 10**), which arose from attack at the less hindered carbon, was favored. The regioisomeric ratio was 65:35 with an overall yield of

96% (**Table 4**, entry 6). In all cases, the regioisomeric ratios were determined by ^{1}H NMR.

Scheme 8

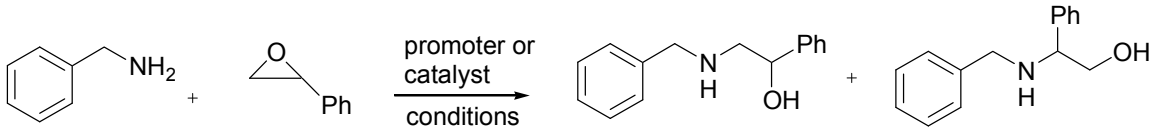


33 **30** **34** **35**

Table 2. Aminolysis of styrene oxide (**30**) using aniline (**33**).

entry	promoter/catalyst	conditions (ratio of amine to epoxide, temp., solvent, time)	ratio (**34**:**35**)	(%) yield	reference
1	scandium triflate	1:1, room temp., neat, 4 hr	5:95	95	[10]
2	ammonium decatungstocerate	1.2:1, 60°C, $(CH_3)_2CO$, 3 hr	0:100	92	[13]
3	potassium dodecatungsto-cobaltate	2:1, 80°C, CH_3CN, 3.5 hr	0:100	98	[14]
4	diisopropoxy-aluminium trifluoroacetate	1:1, room temp., CH_3CN, 2.5 hr	0:100	90	[15]
5	zirconium(IV) chloride	1:1, room temp., neat, 15 min	8:92	98	[18]
6	zinc chloride	1:1, 82°C, CH_3CN, 12 hr	7:93	100	[19]
7	montmorillonite K-10	1:1, room temp., neat, 1.5 hr	7:93	93	[21]
8	cobaltous chloride	1:1, room temp., CH_3CN, 3 hr	5:95	98	[20]
9	silica gel	1:1, room temp., neat, 3 hr	5:95	93	[22]
10	None	1:1.2, room temp., H_2O, 14 hr	4:96	93	[24]

Scheme 9

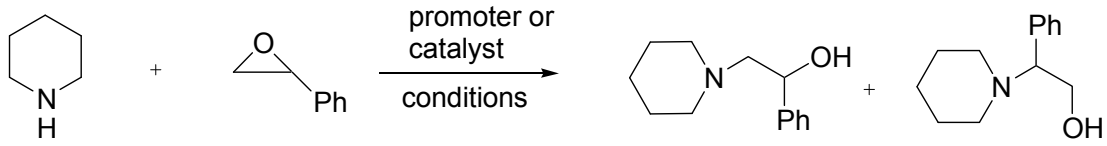


28 **30** **36** **37**

Table 3. Aminolysis of styrene oxide (**30**) using benzylamine (**28**).

entry	promoter/catalyst (amount)	conditions (ratio of amine to epoxide, temp., solvent, time)	ratio (**36**:**37**)	(%) yield	reference
1	scandium triflate	1:1, room temp., neat, 2 hr	85:15	89	[10]
2	calcium triflate	1:1, room temp., CH_3CN, 22 hr,	85:15	99	[11]
3	lithium bistrifluoromethane-sulfonimide	1:1.2, room temp., CH_2Cl_2, 20 hr	80:20	77	[12]
4	diisopropoxy-aluminium trifluoroacetate	1:1, room temp., CH_3CN, 1.5 hr	0:100	86	[15]
5	samarium iodide	1:1.2, room temp., CH_2Cl_2, 24 hr	35:65	70	[17]
6	zirconium (IV) chloride	1:1, room temp., neat, 15 min	78:22	96	[18]
7	zinc chloride	1:1, 80^{o}C, CH_3CN, 12 hr	41:59	40	[19]
8	montmorillonite K-10	1:1, room temp., neat, 1.5 hr	82:18	89	[21]
9	silica gel	1:1, room temp., neat, 3 hr	78:22	100	[22]
10	none	1:1.2, room temp., H_2O, 13 hr	30:70	88	[24]

Scheme 10



38 **30** **39** **40**

Table 4. Aminolysis of styrene oxide (**30**) using piperidine (**38**).

entry	promoter/catalyst	conditions (ratio of amine to epoxide, temp., solvent, time)	ratio (**39**:**40**)	(%) yield	reference
1	scandium triflate	1:1, room temp., neat, 2 hr	75:25	91	[10]
2	diisopropxyaluminium trifluoroacetate	1:1, room temp., CH_3CN, 1.3 hr	47:53	90	[15]
3	samarium iodide	1:1.2, room temp., CH_2Cl_2, 8 hr	53:47	56	[17]
4	zirconium (IV) chloride	1:1, room temp., neat, 15 min	60:40	98	[18]
5	montmorillonite K-10	1:1, room temp., neat, 3 hr	100:0	75	[21]
6	None	1:1, room temp., H_2O, 14 hr	65:35	96	[24]

Table 2 summarizes the various catalysts and promoters used for the ring opening reaction of styrene oxide and aniline. All of the catalysts and promoters favor the S_N1 product over the S_N2 product with 92-100% regioselectivity. The strong S_N1 selectivity is probably a result of the fact that aniline is a poor nucleophile.

By contrast, the regioselectivity of the ring opening of styrene oxide by the more nucleophilic benzylamine is less consistent, as shown in **Table 3**. Scandium triflate, calcium triflate, lithium bistrifluoromethanesulfonimide, zirconium chloride, montmorillonite K-10, and silica gel all resulted in S_N2 selective aminolyses with regioselectivities from 78 to 85%. However, the zinc chloride showed very modest S_N1 selectivity, while samarium iodide and the aqueous aminolysis performed without catalyst gave better S_N1 selectivity. Finally, the aminolysis using diisopropoxyaluminium trifluoroacetate was completely selective for the S_N1 product. It is likely that the stronger Lewis acids favor S_N1 selectivity, although this does not explain the fact that the aqueous aminolysis run in the absence of Lewis acid was modestly S_N1 selective. Perhaps the use of a polar protic solvent (water) in that case increased S_N1 selectivity by reducing the nucleophilicity of benzylamine and/or increasing the reactivity of the more hindered carbon of the epoxide.

Table 4 summarizes the results of various catalysts/promoters used in the ring opening of styrene oxide with piperidine. Regioselectivities were inconsistent with those of reactions using aniline and benzylamine as nucleophiles (cf. **Tables 2** and **3**). In four of the six entries, the S_N2 selectivity was increased substantially over that observed when benzylamine was used as a nucleophile (entries 2, 3, 5, and 6, **Table 4**). These results are consistent with the facts that piperidine is a more sterically demanding nucleophile than benzylamine and a stronger nucleophile than aniline. However, for reactions using scandium triflate and zirconium (IV) chloride, the S_N2 selectivity was

slightly decreased compared to analogous reactions using benzylamine. There is no clear explanation for these results.

Almost all of the above reactions in **Table 2** through **Table 4** require only one equivalent of the amine. In this regard, all these methods improve on Cooke's procedure [9], which required 5 equivalents of the amine.

In all the above examples, not one catalyst/promoter consistently gave S_N2 regioselectivity. Additionally, many of the reported reactions required hours to days to go to completion. One possible method for addressing these issues is the use of microwaves as an energy source for the reactions.

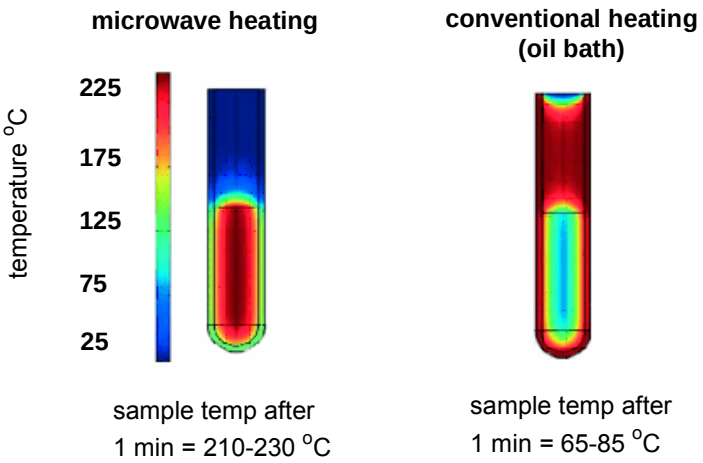
IV. Microwave-assisted aminolysis of epoxides

Microwaves are a kind of electromagnetic radiation [25]. In electromagnetic radiation, the electric and magnetic fields are perpendicular to each other. The electric field transfers energy to heat a substance. In a chemical reaction, microwaves couple with the molecules of the reaction mixture, which causes a rapid rise in temperature. This rise in temperature can occur by dipole rotation or ionic rotation, both of which could affect the rate of the reaction.

The solvent's ability to absorb microwaves and transfer that energy to the reaction affects the overall rate of the reaction. A solvent has two main factors that influence its ability for microwave absorbance: dielectric constant and dielectric loss. The tangent delta (δ) is called the dissipation factor, which expresses the efficiency of the solvent for converting microwave energy to thermal energy. This factor is expressed as the ratio of the dielectric loss to the

dielectric constant. It is generally the dielectric loss, however, that is used to rate microwave absorption (and energy transfer) for a particular solvent. For example, methanol is considered a high microwave absorber (dielectric loss = 21.5), acetonitrile a medium absorber (dielectric loss = 2.3), and toluene a weak absorber (dielectric loss = 0.096) [25]. **Figure 4** shows the difference between microwave heating versus conventional oil bath heating for water in a sealed tube over one minute. The figure illustrates that while conventional heating requires that the vessel must be heated and the energy then transferred to the liquid, microwave heating allows the liquid to be heated directly. This allows for much quicker and more efficient heating.

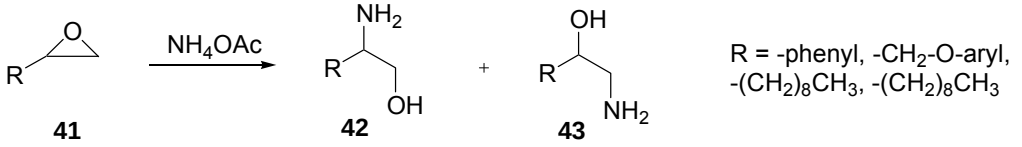
Figure 4. Comparison of microwave and oil bath heating [26].



Although no one has performed a comprehensive examination of microwave-assisted epoxide aminolysis, several examples appear in the literature. Sabitha has described a new method for the epoxide aminolysis using microwave irradiation as a source of heat [27]. A household microwave operating at 600 Watts with an open reaction vessel was used for the reaction. For the amine nucleophile, ammonium acetate was used as a source of

ammonia. The neat epoxide (10 mmol) and ammonium acetate (15 mmol) were reacted in the microwave for 40-120 seconds. In the reaction of styrene oxide with ammonium acetate, only alcohol **43** (**Scheme 11**) was formed by the attack at the less hindered carbon atom of styrene oxide. The regioisomeric ratio for all the compounds was determined by ^{1}H NMR, and varied from 75-100% in favor of alcohol **43**, depending on the nature of the R group, and yields ranged from 65-85%. Ammonium acetate was the only nucleophile used in this investigation.

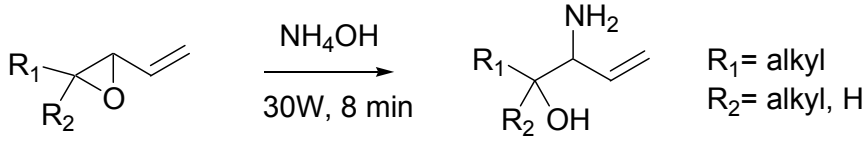
Scheme 11



41 **42** **43**

Lindstrom has reported the ring opening of vinyl epoxides using microwave irradiation [28]. The authors used di- and trisubstituted vinyl epoxides with ammonium hydroxide at 30 W for 8-30 minutes. In all cases, the major regioisomer arose from with the attack of the amine at the allylic position, although selectivity varied from 67-100% according to the nature of the R_2 substituent (**Scheme 12**). All the regioisomeric ratios were determined by ^{1}H NMR. Because the reaction was reported to be diastereoselective, it likely proceeded by the S_N2 pathway.

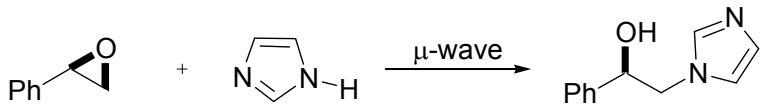
Scheme 12



44 **45**

Thiel [29] used microwave irradiation to improve the yields reported by Kotsuki, who carried out aminolysis of epoxides using high pressure reactions or silica gel promotion at room temperature, but reported only modest yields [23]. Thiel's reactions were carried out in a microwave oven using a sealed tube. Imidazole (**46**) and 1 equivalent of styrene oxide (**34**) were reacted in a pressure tube by irradiating at 360 Watts for 3 minutes. The overall yield was 90%. Alcohol **47** (**Scheme 13**), arising by attack at the less hindered carbon, was the only isomer detected by GC-MS. In the communication, the authors reported amino alcohol **47** as a single enantiomer but offered no data to confirm the enantiomeric excess of the product.

Scheme 13

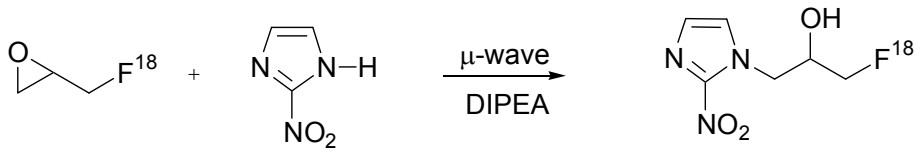


30 **46** **47**

Welch has described a method for the preparation of [^{18}F]-fluoromisonidazole ([^{18}F]-FMISO) [30] that requires a microwave-assisted aminolysis. ^{18}F-FMISO is used as a hypoxic marker to identify ischemic tissue for patients with suspected myocardial infarction. Emergency situations demand that the compound be prepared quickly and at very short notice. Thus, the authors decided to reduce the reaction time of the critical epoxide aminolysis step by using microwave heating for the preparation of ^{18}F-FMISO. A solution of 3.3 μmol epi-[^{18}F]fluorohydrin in 50 μL DMSO was added to a 2 ml vial containing 4 molar equivalents (1.5 mg) of 2-nitroimidazole **49** and 15 μL of *N,N*-diisopropylethylamine (**Scheme 14**). Following this, the vial was tightly capped

and irradiated with microwaves (500 W) for 12 minutes. A single regioisomer was produced via attack of the nucleophile at the less hindered carbon of the epoxide. Amino alcohol **50** was produced in 69% yield.

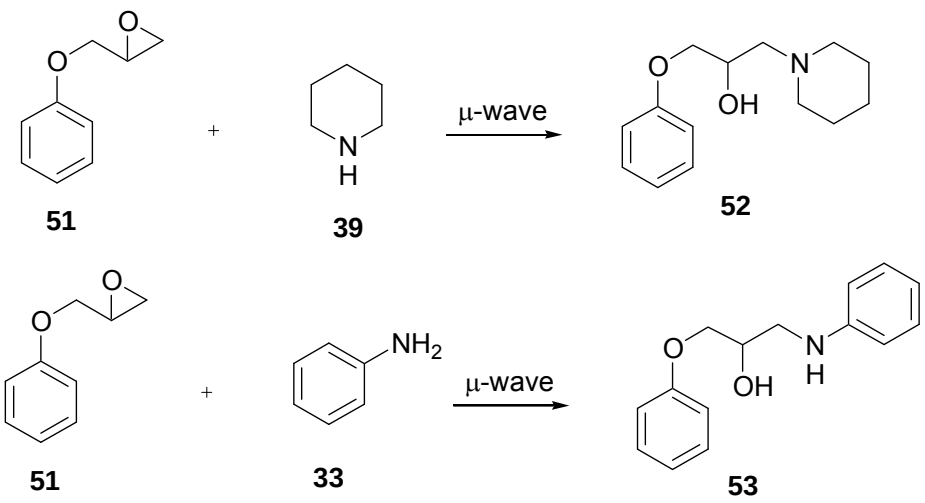
Scheme 14



48 **49** **50**

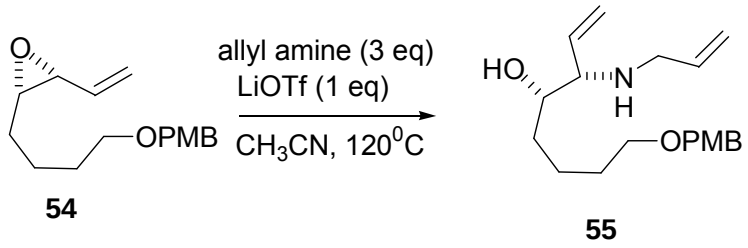
Gupta [31] has used microwave irradiation for the aminolysis of 1,2-epoxy-3-phenoxypropane **52** (**Scheme 15**). The authors used a household microwave with an open vessel for the reaction. The epoxide (0.01 mole), amine (0.015 mole), and ethanol were subjected to microwave irradiation (210 W). When piperidine (**39**) was reacted with epoxide **51** for 3.5 minutes, the yield of amino alcohol **52** was 87%. When aniline (**33**) was used as the nucleophile, amino alcohol **53** was produced as the single regioisomer in 89% yield after four minutes of microwave irradiation. Both amino alcohols **52** and **53** arise from the attack at the less hindered carbon. The reported yields represent isolations of pure amino alcohols, but the authors do not comment on regioisomeric ratios of the crude reaction mixtures.

Scheme 15



Pyne [32] used microwaves for the ring opening of a vinyl epoxide in the total synthesis of a bicyclic alkaloid. In the reaction, the (-)-vinyl epoxide **54** (1 eq), allyl amine (3 eq), and the promoter lithium triflate (1 eq) in acetonitrile were irradiated for 1 hour in a teflon tube with a 100 bar pressure cap at 120°C to give the corresponding amino alcohol **55** as a single regioisomer in 97% yield (**Scheme 16**). Because only a single stereoisomer was isolated, it was presumed that the reaction proceeded via an S_N2 pathway.

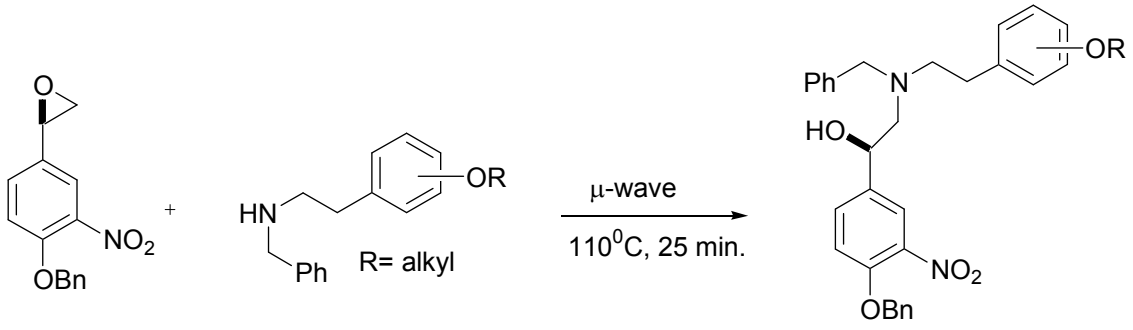
Scheme 16



Fairhurst has studied the effect of increase of amino-substituent chain length on the β-adrenoceptor activity [33]. The activities of the various analogues to the two available agonists, formoterol and salmeterol, were compared. A key

step in the analogue synthesis was a microwave-assisted aminolysis of chiral epoxide **56** using various substituted phenyl ethyl amines **57** (**Scheme 17**). The reaction was carried out at 110°C with an irradiation time of 25 minutes. The microwave power was not reported. Alcohols **58** were obtained in 63-92% yield. The attack at the epoxide was at the less hindered carbon, giving the S_N2 regioisomer as the only product.

Scheme 17

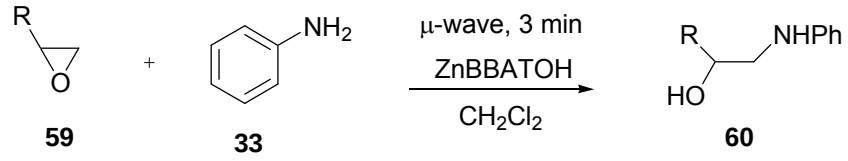


56 **57** **58**

Eshghi has described a method for synthesizing β-amino alcohols by using microwave energy [34]. The reaction is carried out using 1,7-bis(2-benzoic acid)-1,4,7-trioxaheptane—zinc complex (ZnBBATOH) as catalyst. When the reaction was carried out with aniline (**33**) (2 mmol), styrene oxide (**30**) (2 mmol) (cf. **Scheme 8**) and ZnBBATOH (0.2 mmol) in dichloromethane at room temperature, amino alcohols **34** and **35** were formed in a 40:60 regioisomeric ratio with a yield of 83%. When the reaction was performed without solvent using microwave radiation, the regioisomeric ratio was 10:90, also favoring the attack at the more hindered carbon with a purified yield of 85%. When an unsymmetrical epoxide **59** was reacted with aniline (**33**) (**Scheme 18**), amino alcohol **60** was the only product formed due to attack at the less hindered

carbon. The purified yields of alcohol **60** were 76% to 88%. Details of the experimental procedures, including microwave conditions, were not provided.

Scheme 18

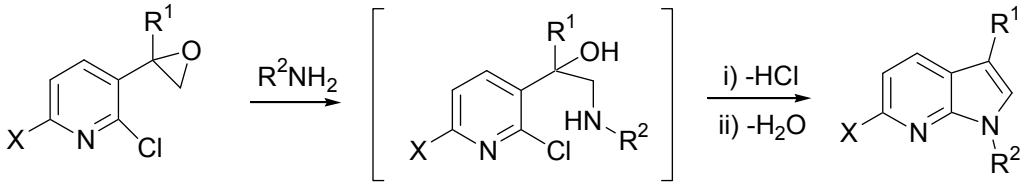


59 **33** **60**

R= $-CH_2OR_1$
R_1= alkyl

Schirok has described a novel method for the synthesis of 7-azaindoles [35]. 7-Azaindoles are used as bioisosteres of indoles or purines. The synthesis of 7-azaindoles **63** follows a pathway that involves the formation of amino alcohols **62** by the ring opening of epoxides, which then cyclize to give 7-azaindoles **63** as the products (**Scheme 19**). The reaction is carried out using 4 equivalents of epoxide **61** and 1 equivalent of amine in 1-butanol with microwave conditions of 200°C and 30 minute reaction times. Yields of azaindoles **63** ranged from 60-90%. The amino alcohol was not isolated in the reaction, but for azaindole **63** formation to occur, epoxide aminolysis must have occurred at the less hindered carbon.

Scheme 19

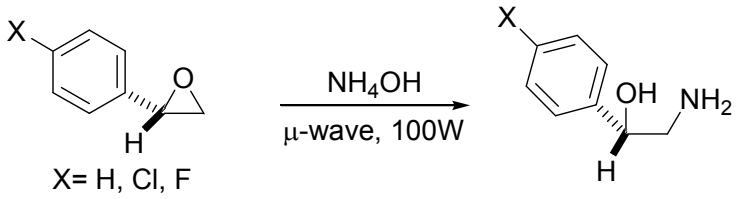


61 **62** **63**

Sello has described a method for the preparation of enantiopure 2-amino alcohols using a household microwave [36]. Styrene oxide and several

derivatives **64** were reacted with ammonium hydroxide to give alcohol **65**, arising from the attack at the less hindered carbon as the only regioisomer (**Scheme 20**). The overall yields for the reactions were 75% to 100%. One disadvantage of this reaction is that the reactions were performed on milligram quantities of epoxides. The authors did not comment on the feasibility of scale-up.

Scheme 20



64 **65**

Based on the data presented in these reports, microwave radiation can significantly reduce reaction times for epoxide aminolysis. However, regioselectivity in these reactions varied according to the epoxide and/or amine used and whether a catalyst/promoter was employed in the reaction.

A goal of this study is to develop a general method for microwave-assisted aminolysis that would consistently give S_N2 selectivity. Ideally, this method would proceed in the absence of a catalyst or promoter but would still reduce reaction times when compared with previously reported aminolysis reactions.

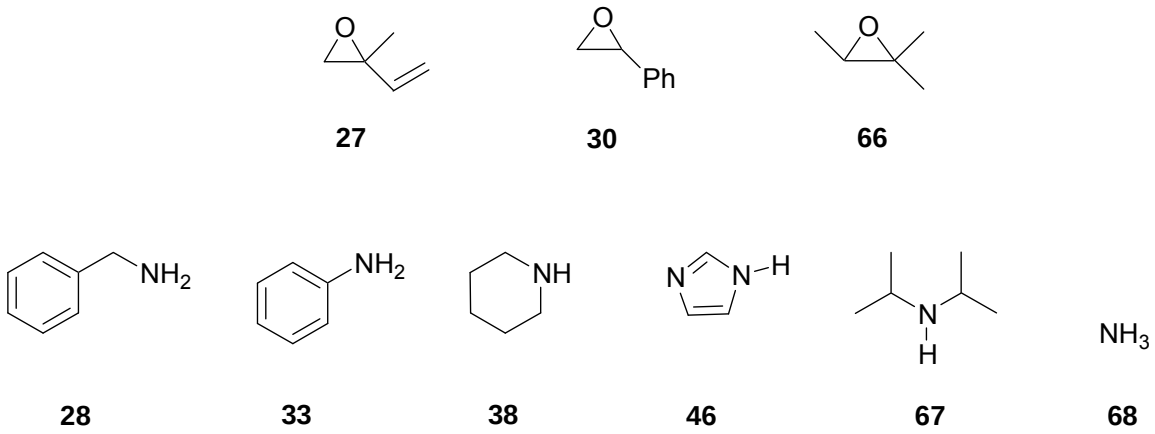
Chapter 3: Results and Discussion

I. Microwave-assisted aminolysis of epoxides

A. Introduction

β-Amino alcohols are an important class of organic compounds with various applications. For example, they are used as chiral auxiliaries [37a,b] and as building blocks in the synthesis of biologically active natural and synthetic products [37c,d]. β-Amino alcohols are commonly prepared by the ring opening of epoxides using a nitrogen nucleophile with various catalysts or promoters [10-23]. Depending on the site of attack on an unsymmetrical epoxide, ring opening can take place by the S_N1 pathway or the S_N2 pathway (cf. **Scheme 5**). One problem with these methods is that no single catalyst consistently gives S_N2 selectivity. Additionally, long reaction times are often required to obtain adequate yields. One potential solution to these issues is the use of microwave energy in the reaction. Scattered examples of microwave-assisted aminolysis of epoxides appear in the literature [27-36], but no one has conducted a comprehensive examination of the scope and limitations of this method for synthesizing β-amino alcohols. Accordingly, three epoxides were chosen for this study: styrene oxide (**30**), 2,3-epoxy-2-methylbutane (**66**), and 2-methylvinyl oxirane (**27**). The amines used in the study were benzylamine (**28**), aniline (**33**), piperidine (**38**), imidazole (**46**), diisopropylamine (**67**), and ammonia (**68**) (**Figure 5**).

Figure 5. Epoxides and amines used in the investigation.



27 **30** **66**

28 **33** **38** **46** **67** **68**

B. Aminolysis of styrene oxide

In the reaction of styrene oxide (**30**) with 1 molar equivalent of piperidine (**38**), two regioisomeric alcohols **39** and **40** could be formed. Alcohol **39** would arise from attack at the less hindered carbon, and alcohol **40** would be formed by the attack at the more hindered carbon of the epoxide (**Scheme 21**). With a run time of 10 minutes in the presence of triethylamine (TEA) (1 eq), the yield was 80% with alcohol **39** being favored over alcohol **40** by a ratio of 4:1 (**Table 5**, entry 1). When the run time was reduced to 5 minutes, the ^{1}H NMR showed unreacted styrene oxide (**Table 5**, entries 2 and 3). In these reactions, a continuous air stream was delivered to the outside of the reaction vessel in an attempt to better control the temperature. This process is simply called “cooling.” Aminolysis in methanol without TEA gave a quantitative yield with 4:1 regioselectivity favoring alcohol **39** (**Table 5**, entry 4) as determined by ^{1}H NMR analysis.

Scheme 21

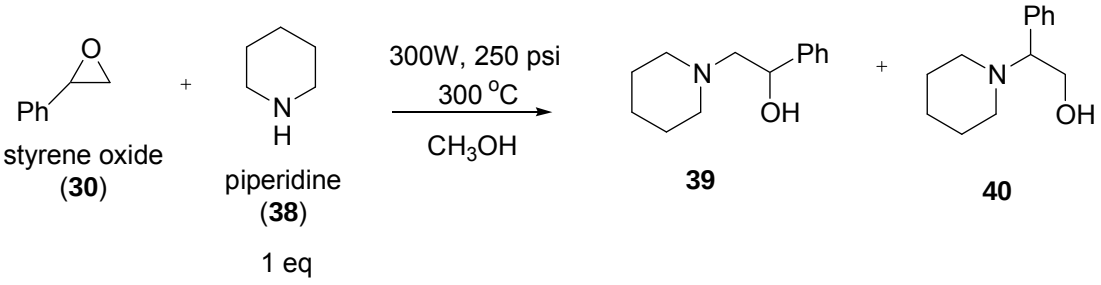


Table 5. Microwave-assisted aminolysis of styrene oxide (**30**) with piperidine (**38**).

entry	expt. no.	eq TEA	run time	max temp., max pressure	yield (%)	ratio **39:40***
1	BD-2-129	1	10 min	160°C, (cooling off) 200 psi	80	4:1
2	BD-2-139	1	5 min	160°C, (cooling on) 175 psi	incomplete conversion	4:1
3	BD-2-140	1	5 min	175°C, (cooling on) 275 psi	incomplete conversion	4:1
4	BD-2-136	----	10 min	175°C, (cooling off) 240 psi	100	4:1

*Determined by integration of ^{1}H NMR.

Alcohols **69** and **70** were prepared by reacting a 1:1 molar ratio of styrene oxide (**30**) and imidazole (**46**) (**Scheme 22**, **Table 6**). The major regioisomer was alcohol **69**, which was formed by the attack at the less hindered carbon atom of styrene oxide (**30**). The yield of the reaction was quantitative, and the regioisomer ratio was 75:25 favoring alcohol **70** as determined by ^{1}H NMR

(**Table 6**, entry 1). To study the influence of solvent on the regioselectivity, acetonitrile was used instead of methanol (entry 4). The ^{1}H NMR was complex. Further experiments need to be carried out to draw any kind of conclusion of the solvent effect on the regioisomeric ratio. In this reaction, neither cooling nor the addition of TEA had a measurable effect on the reaction outcome.

Scheme 22

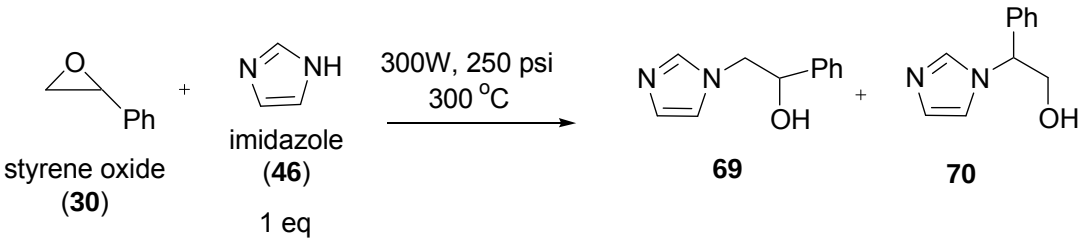


Table 6. Microwave-assisted aminolysis of styrene oxide (**30**) with imidazole (**46**)

entry	expt. no.	eq TEA, solvent	run time	max. temp., max. pressure	yield (%)	ratio **69:70***
1	BD-2-137	1 eq, CH_3OH	10 min	160°C, (cooling on) 250 psi	100	3:1
2	BD-2-141	1 eq, CH_3OH	5 min	160°C, (cooling on) 250 psi	100	3:1
3	BD-3-007	--, CH_3OH	5 min	160°C, (cooling off) 220 psi	100	3:1
4	BD-3-23	--, CH_3CN	10 min	225°C, (cooling on) 250 psi	---	complex mixture

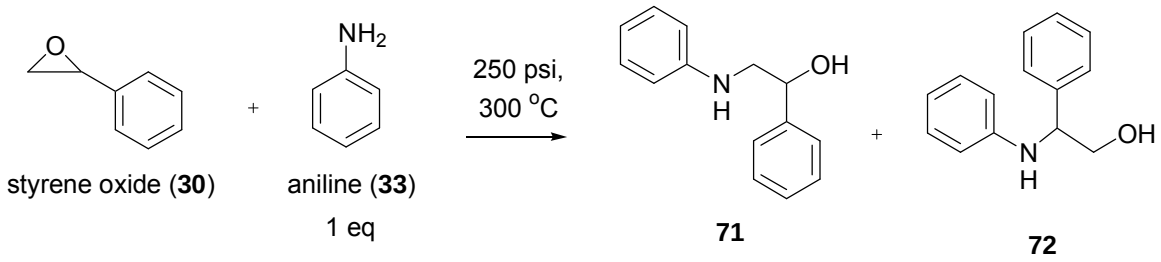
* Determined by integration of ^{1}H NMR.

Aniline (**33**) was reacted with styrene oxide (**30**) (**Scheme 23**) and the regioisomeric ratio was studied (**Table 7**). When the reaction was run for 5 minutes (entry 1), ^{1}H NMR indicated unreacted styrene oxide and a 1:1.5 regioisomeric ratio of alcohols **71** and **72**. The yields for the entries 1-3 were not

calculated due to the presence of significant amounts of starting material at the end of the reaction. The microwave settings were changed to 300W and run time to 10 minutes, but this did not change the overall yield or the regioisomer ratio by significantly (entry 2). The run time was then increased to 15 minutes (entry 3), again with no increase in conversion. Finally, by using 25 W in combination with cooling, a good yield was obtained (entry 4), but the modest regioselectivity for alcohol **72** did not improve.

Bis-alkylation was a common problem when the aminolysis of styrene oxide was performed using aniline. Bis-alkylation occurs when the initial product of the aminolysis reacts with another equivalent of epoxide **74** to give amino diol **76** (**Scheme 24**). Bis-alkylation can be suppressed by the use of excess of amine in the reaction mixture (**Table 7**, entry 5). By increasing the equivalents of the amine from one to two, the ratio of mono to bis-alkylation increased from 5.5:1 to 24:1.

Scheme 23



styrene oxide (**30**) + aniline (**33**) 1 eq → **71** + **72**

Table 7. Microwave-assisted aminolysis of styrene oxide (**30**) with aniline (**33**)

entry	expt. no.	microwave power, rxn time, solvent	max. temp., max. pressure.	yield (%)	**71**:**72*** comment
1	BD-2-150	25 W, 5 min, CH_3OH	--- (cooling off)	----	1:1.5 Unreacted styrene oxide and bis-alkylation were present, 5.5:1 mono:bis-alkylation
2	BD-2-152	300W, 10 min, CH_3OH	160°C, (cooling off) 150 psi	----	1:1.5 styrene oxide plus bis-alkylation present
3	BD-2-144	300W, 15 min, CH_3OH	170°C, (cooling off) 140 psi	----	1:1.5 styrene oxide and bis-alkylation present
4	BD-3-1	25W, 30 min., CH_3OH	70°C, (cooling on) 10 psi	70	1:1.5 bis-alkylation present
5	BD-3-30	300W, 30 min, CH_3OH	not available (cooling on)	75	1:1.5 2 eq aniline, 24:1 mono:bis-alkylation

* Determined by integration of ^{1}H NMR.

Scheme 24

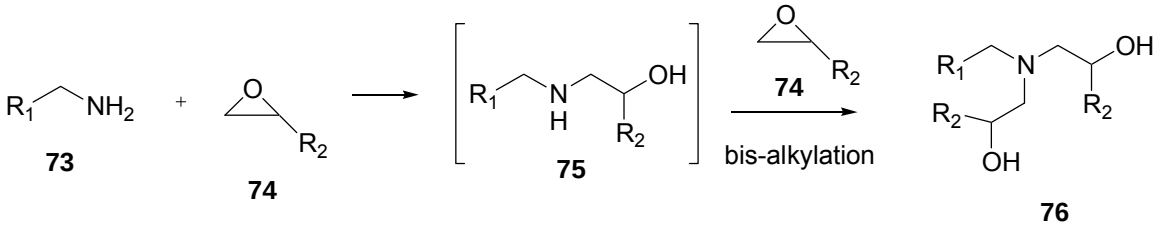


Table 8 gives the summary of the various nucleophiles used for the ring opening of styrene oxide (**30**). Imidazole gave a moderate 3:1 regioselectivity favoring the S_N2 product with a 100% yield (entry 1). Piperidine gave 4:1 regioselectivity favoring the S_N2 product (entry 2). However, aniline gave a regioisomeric ratio of 1:1.5, narrowly favoring the S_N1 pathway with an 5.5:1 monoalkylation to bis-alkylation when a 1:1 molar equivalence of amine to epoxide was used (entry 3). When two equivalents of aniline were used, bis-alkylation was somewhat suppressed and the yield was excellent, but the regioselectivity remained poor (entry 4). It was concluded from the regioselectivities that piperidine was the best nucleophile for the S_N2 reaction whereas aniline was a poorest nucleophile, thus allowing more S_N1 reaction to occur.

Scheme 25

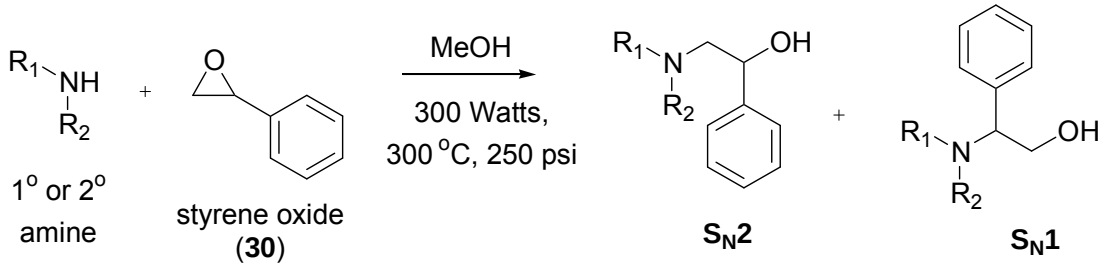
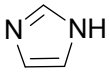
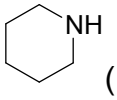
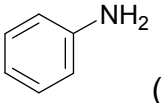
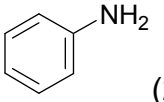


Table 8. Aminolysis of styrene oxide (**30**)

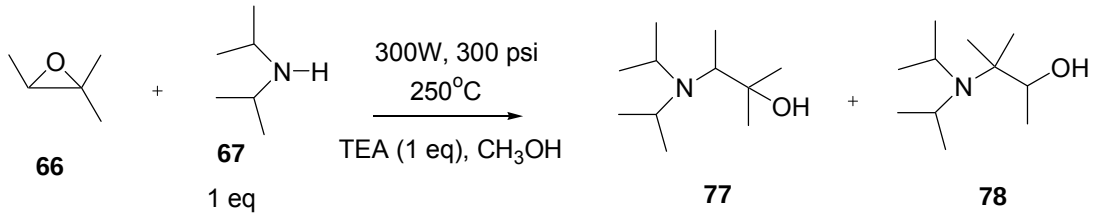
entry	amine (eq)	run time	yield (%)	S_N2:S_N1	mono:bis-alkylation
1	 (1)	5 min	98	3:1	---
2	 (1)	5 min	100	4:1	---
3	 (1)	10 min	70	1:1.5	5.5:1
4	 (2)	10 min	75	1:1.5	24:1

C. Aminolysis of 2,3-epoxy-2-methylbutane

The second epoxide to be used for the ring opening reaction was 2,3-epoxy-2-methylbutane (**66**). By contrast to styrene oxide (**30**), this epoxide was expected to be less reactive because of the absence of the aromatic ring and because it is more sterically hindered. Several amines of varying nucleophilicities and steric hindrances were used for the aminolysis reactions. **Table 9** gives the details of the attempts to synthesize amino alcohols **77** and **78** from trimethylepoxide (**66)** and diisopropylamine (**27**) (**Scheme 26**), a hindered, 2° amine. Initially a 30-minute reaction time was used, but the isolated yield was

only 2.8% (entry 1, **Table 9**). It was thought that 30 minutes may have been too long, and perhaps the product was decomposing, so the reaction time was reduced to 15 minutes (entry 2), but this did not improve the yield. It was also thought that the product was simply not forming, and the starting materials were being evaporated during the isolation procedure. To test this hypothesis, 45- and 60-minute reaction times (entries 3 and 4) were used, but the yield remained poor. One possible explanation for the low yield is that the boiling points of alcohols **77** and **78** were such that they were being removed *in vacuo* with the starting materials and solvent. Further investigations suggest that little conversion was occurring, given the relatively short reaction times that were used (*vide infra*).

Scheme 26



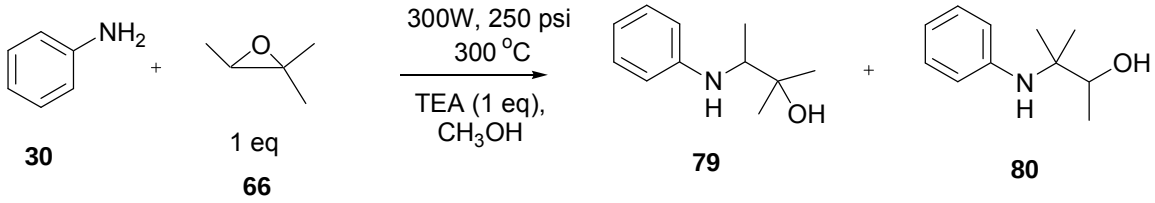
66 + **67** (1 eq) → **77** + **78**

Table 9. Microwave-assisted aminolysis of epoxide **66** with diisopropylamine (**67**)

entry	expt. no.	rxn time	max.temp., max. pressure	yield (%)	comment
1	BD-2-53	30 min	---	2.8	trace amounts of product precluded regioisomer integration
2	BD-2-59	15 min	---	1.3	same as entry 1
3	BD-2-60	45 min	145°C, 145 psi	0.6	same as entry 1 (2 eq diisopropylamine)
4	BD-2-79	60 min	---	<0.5	same as entry 1

Next, the aminolysis of epoxide (**66**) with aniline (**30**) was attempted (**Scheme 7**, **Table 10**). After 30 minutes reaction time, the yield was 39% (entry 1). This was improved to 60% when the reaction time was increased to 180 minutes (entry 2). In both cases, a 3:1 regioisomeric ratio of alcohols **79:80** resulted as determined by the integration of the ^{1}H NMR of the crude reaction mixture**.**

Scheme 27



30 1 eq **66** **79** **80**

Table 10. Microwave-assisted aminolysis of epoxide **66** with aniline (**30**)

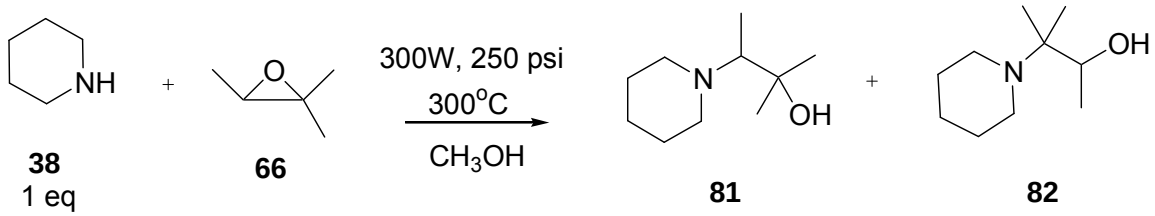
entry	expt. no	rxn time	max. temp., max. pressure	yield (%)	ratio **79**:**80***
1	BD-2-67	30 min	140°C, 135 psi	39	3:1
2	BD-2-68	80 mins	---	60	3:1

*Determined by integration of ^{1}H NMR

We then attempted the aminolysis of epoxide **66** with piperidine (**38**) (**Scheme 28**, **Table 11**). Initially the reaction was tried with TEA in methanol with a run time of 45 minutes (entry 1). The yield was low and the ^{1}H NMR showed unreacted piperidine (**38**), so the reaction time was changed to 60 minutes. In addition, TEA was not used. However, the yield was not significantly improved

(entry 2). When the reaction was run for 120 minutes (entry 3), the yield improved to 48%. Each reaction gave a 7:1 ratio of alcohols **81**:**82** as determined by integration of the ^{1}H NMR of the crude reaction mixture. Again, it is possible that the low boiling point of the product caused it to be evaporated along with the solvent during isolation.

Scheme 28



38
1 eq

66

81

82

Table 11. Microwave-assisted aminolysis of epoxide **66** with piperidine (**38**)

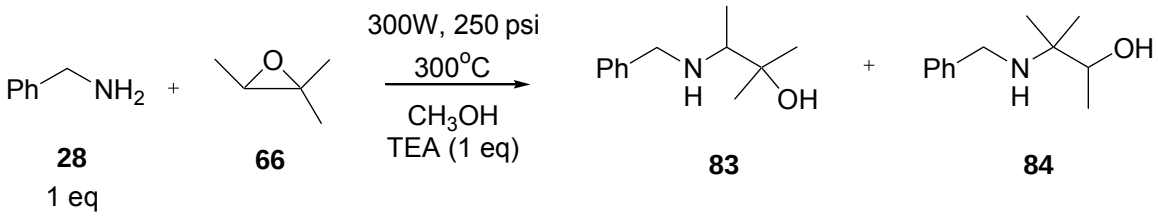
entry	expt. no.	rxn time	max.temp., max. pressure	yield (%)	ratio **81**:**82***
1	BD-2-123	45 min	125°C, 180 psi	17	7:1 (1 eq TEA used)
2	BD-3-15	60 min	130°C,180 psi	20	7:1
3	BD-3-20	120 min	130°C, 200 psi	48	7:1

* Determined by integration of ^{1}H NMR.

Next we turned our attention to an unhindered 1° amine, benzylamine (**36**), as a nucleophile for the aminolysis reaction**.** Benzylamine (**36**) was reacted with epoxide **66** and one equivalent of TEA to give two regioisomers **83** and **84** (**Scheme 29, Table 12**). When the reaction was run for 30 minutes, alcohols **83** and **84** were produced in a 5:1 ratio and a combined yield of 54% (entry 1).

When the reaction time was increased to 45 minutes, the yield improved to 80% (entry 2). This yield could also be obtained when no TEA was added (entry 3). We initially believed that the TEA is needed to act as a proton shuttle, but apparently that is not the case. Omitting TEA allowed the temperature and pressure in the microwave reaction tube to increase from 160°C to 190°C and from 200 psi to 210 psi. However, these changes did not affect the yield or the selectivity.

Scheme 29



28
1 eq

66

83

84

Table 12. Microwave-assisted aminolysis of epoxide **66** with benzylamine (**28**)

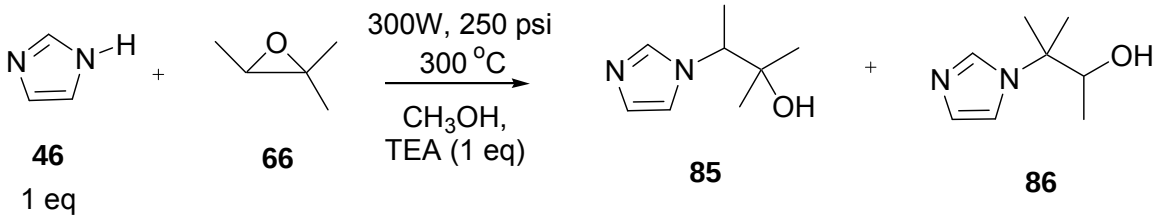
entry	expt. no.	rxn time	max.temp., max. pressure	yield (%)	ratio **83**: **84***
1	BD-2-55	30 min	145°C, 200 psi	54	5:1
2	BD-2-77	45 min	160°C,160 psi	80	5:1
3	BD-3-14	45 min	190°C, 210 psi	80	5:1 (no TEA used)

* Determined by integration of ^{1}H NMR.

Last we examined imidazole as the nucleophile for the aminolysis of epoxide **66**. Thus, epoxide **66** was reacted with imidazole (**46**) to give regioisomers **85** and **86** (**Scheme 30**, **Table 13**). When the reaction was carried out in the presence of TEA, alcohols **85** and **86** were produced in 95% yield and

a 6:1 regioisomeric ratio (entry 1). Very similar results were observed when no TEA was added (entry 2).

Scheme 30



46 1 eq + **66** → **85** + **86**

Table 13. Microwave-assisted aminolysis of epoxide **66** with imidazole (**46**)

entry	expt. no.	rxn time	yield (%)	max.temp., max.pressure	ratio **85 : 86***
1	BD-2-73	30 min	95	160°C, 260 psi	6:1
2	BD-3-21	30 min	97	200°C, 275 psi	6:1 (no TEA added)

* Determined by integration of ^{1}H NMR.

Table 14 gives the summary of the aminolysis of 2,3-epoxy-2-methylbutane with various nucleophiles. No bis-alkylation was observed in any of these reactions. Benzylamine (**28**) gave a regioisomeric ratio of 5:1 favoring the S_N2 product with a yield of 80% (entry 1). Imidazole (**46**) gave a regioisomeric ratio of 6:1, favoring the S_N2 product with a crude yield of 97% (entry 2). Piperidine (**38**) gave a regioisomeric ratio of 7:1, favoring the S_N2 product with an overall yield of 44%. Aniline gave a regioisomeric ratio of 3:1, favoring the S_N2 product with a 60% yield (entry 4). Thus it was concluded that with an approximate 5-7:1 regioisomeric ratio, piperidine, benzylamine, and

imidazole were the best nucleophiles for S_N2 reaction. Alternatively, because aniline is a weak nucleophile, the S_N1 pathway may become more favorable, resulting in the less selective 3:1 ratio.

Scheme 31

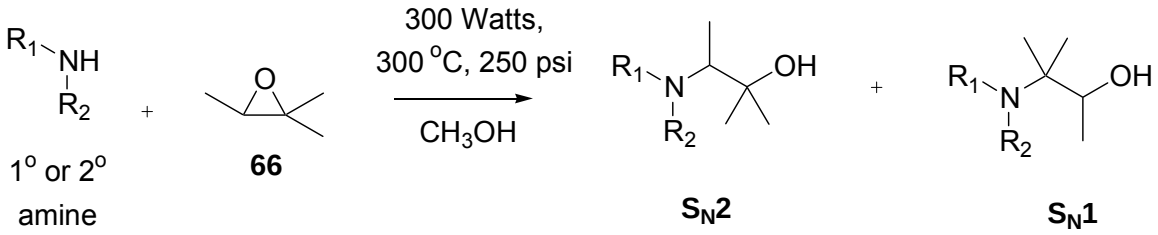
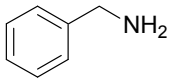
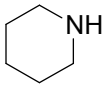
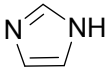
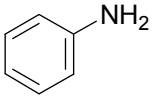


Table 14. Aminolysis of 2,3-epoxy-2-methylbutane (**66**)

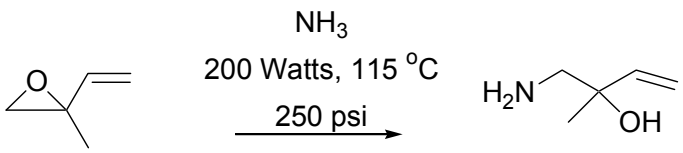
entry	amine (1 eq)	run time	yield (%)	S_N2:S_N1
1		45 min	80	5:1
2		30 min	97	7:1
3		120 min	48	6:1
4		180 min	60	3:1

D. Aminolysis of methylvinyl oxirane

In the course of our efforts to synthesize pyrrolidine alkaloids (*vide infra*), we required amino alcohol **87** (**Scheme 32**), which we anticipated could be synthesized by the aminolysis of methylvinyl oxirane **27** using ammonia. Initially, we exposed epoxide **27** to 2 equivalents of ammonia in methanol (entry 1, **Table 15**). The reaction was run without cooling for 8 minutes using the conditions as

given in **Table 15** to give a mass return of 79%. Unfortunately there was much difficulty in preparing the amino alcohol **87** without overalkylation. The reaction was again run with cooling (entry 2), but there was very little difference in the yield or in the amount of overalkylation. The amount of the amine was increased in the attempt to improve selectivity and yield (entry 3). However ^{1}H NMR again indicated significant overalkylation with a mass return of only 30%. The reaction was tried with ammonium acetate, but only trace amounts of product were recovered (entry 4) [27]. The reaction was also attempted using triethylamine as an additive. However, when the run time was changed to 30 minutes, there was no decrease in the amount of overalkylation (entry 5). To increase the ratio of the monoalkylation to dialkylation, 8 equivalents of the amine were used, which gave a crude mass return of 74% (entry 7). However, the ratio of the mono to dialkylation was the same. The monoalkylated compound was separated successfully by distillation although the yield of pure alcohol **87** was low (entry 6). The ratio of mono to dialkylation was determined by chemical ionization mass spectrometry in some cases (entries 6-8).

Scheme 32



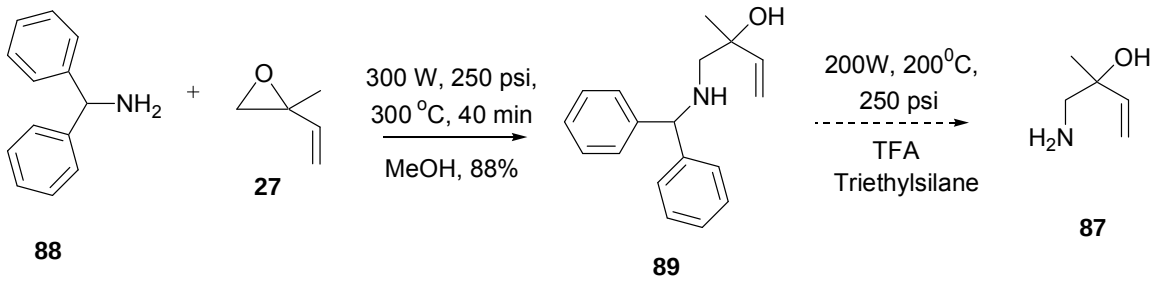
27 **87**

Table 15. Aminolysis of methylvinyl oxirane **27** with ammonia

entry	expt. no.	mmol epoxide	NH_3 source (eq)	crude mass return (%)	max temp., max.pressure	comment
1	BD-1-263	1.2	NH_4OH (2.0)	79	100°C, (cooling off) 160psi	ratio of mono: dialkylation 1:1
2	BD-1-269	1.2	NH_4OH (2.0)	77	90°C, (cooling on) 110 psi	same as entry 1
3	BD-1-289	1.2	7N NH_3 in MeOH (4.0)	30	100°C, (cooling on) 140 psi	same as entry 1
4	BD-1-293	2.4	NH_4OAc (1.5)	--	120°C, (cooling on) 135 psi	too little product to determine ratio of products or mass return
5	BD-1-301	2.4	7N NH_3 in MeOH (2.0)	not measured	120°C, (cooling on) 200 psi	1:1, (30 min rxn time, 2 eq TEA added)
6	BD-2-002	2.4	7N NH_3 in MeOH (4.0)	100	120°C, (cooling on) 160 psi	same as entry 1
7	BD-2-45	1.8	7N NH_3 in MeOH (8.0)	74	120°C (cooling on) 200 psi	same as entry 1
8	BD-2-44	3.6	7N NH_3 in MeOH (4.0)	--	120°C, (cooling off) 200 psi	19% yield of pure alcohol **87** after distillation

The difficulty in synthesizing amino alcohol **87** directly from aminolysis prompted us to try a two-step aminolysis-deprotection sequence. To that end, amino alcohol **89** was obtained by the aminolysis of methylvinyl oxirane **27** using diphenylmethylamine **88** (**Scheme 33**)[38]. An attempt at deprotecting amino alcohol **89** was made using trifluoroacetic acid (TFA) and triethylsilane [39] (5.0 eq) as in **Scheme 33**. The microwave settings for the reaction were 200W, 250 psi, and 200^{0}C, with a reaction time of 15 minutes. The ^{1}H NMR showed only starting material and unknown side reaction products were present. Since we could obtain amino alcohol **87** via direct aminolysis (cf. **Scheme 32**, **Table 15**), this two-step method was abandoned.

Scheme 33



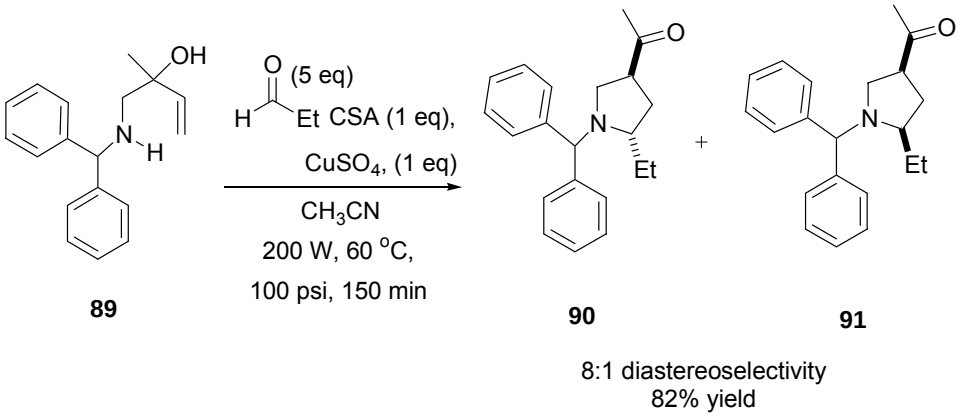
88 **27** **89** **87**

II. Aza-Cope—Mannich approach to the synthesis of pyrrolizidine alkaloids

We then set out to use amino alcohol **87** in the synthesis of pyrrolidines using the aza-Cope rearrangement—Mannich cyclization (ACM). The ACM reaction is carried out by condensation of a β-amino alcohol and an aldehyde, resulting in an iminium cation formation. This iminium cation undergoes a [3,3] sigmatropic rearrangement to give the corresponding enol. Finally, the enol undergoes Mannich cyclization to give the corresponding pyrrolidine (cf. **Scheme**

1). Beginning with amino alcohol **87**, we imagined that we could access pyrrolidines containing a secondary amine using this reaction. This was prompted by the successful ACM reaction carried on amino alcohol **89** [40] (**Scheme 34**) using microwave irradiation.

Scheme 34



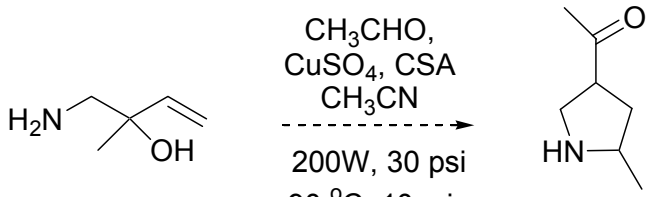
89 **90** **91**

8:1 diastereoselectivity
82% yield

The ACM reaction was thus attempted with primary amino alcohol **87** (**Scheme 35**, **Table 16**). Amino alcohol **87** (0.3-0.6 mmol) was reacted with camphorsulfonic acid (CSA) (1.1 eq), $CuSO_4$ (8.0 eq), and acetaldehyde (10 eq) in acetonitrile. The mass recovery was 69% after 10 minutes run time with microwave settings of 200W, 30 psi, 90°C, and cooling off (entry 1). However, the ^{1}H NMR spectrum of the crude reaction mixture showed that the product had not formed and that the starting material and unidentified byproducts were present. The absence of a methyl ketone resonance in the ^{1}H NMR ca. 2.1 ppm confirmed that no product was formed. For the next reaction, the molar ratio of CSA was increased to 2.3 eq (entry 2), acetaldehyde was increased to 50 eq, and the drying agent, copper sulfate, was decreased to 4.3 eq. The same

microwave settings were used. Unfortunately, starting material and unidentified byproducts were observed again.

Scheme 35



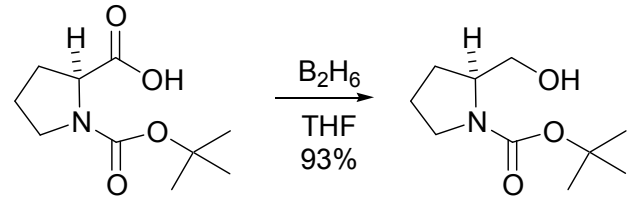
87 **92**

Table 16. Attempts at aza-Cope—Mannich reaction with amino alcohol **87**

entry	expt no.	eq CH_3CHO	eq CSA	eq $CuSO_4$	comment
1	BD-2-7	10	1.1	8.0	recovered unreacted starting material (69%)
2	BD-2-28	50	2.3	4.3	same as entry 1

Even though the aza-Cope—Mannich reaction of primary amine **87** was not successful, we were still confident that our proposed synthesis of pyrrolizidine alkaloids could be accomplished with this reaction (cf. **Scheme 3**) because of the successful result from the reaction with the secondary amine **89** (**Scheme 34**). We began our pyrrolizidine synthesis using Boc-L-proline (**94**) as a model for the more expensive 3-hydroxy-L-proline (**25**). Alcohol **95** was prepared by reduction of N-Boc-L-proline (**94**) with 1 M borane in THF (**Scheme 36**) [41]. The product yield was 93%. The ^{1}H NMR confirmed the structure of the product. The product was taken for the next step without purification.

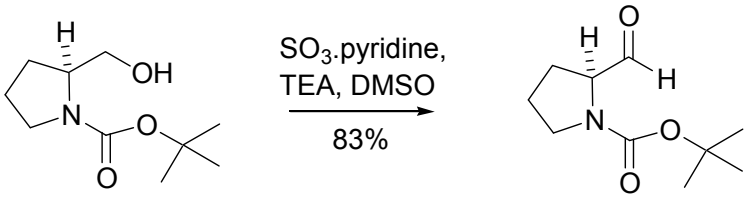
Scheme 36



Boc-L-proline (**94**) **95**

Aldehyde **96** was prepared from alcohol **95** by Swern-type oxidation [41, 42] using sulfur trioxide-pyridine in dimethylsulfoxide in the presence of triethylamine (**Scheme 37**). The aldehyde **96** was isolated with 83% yield. The ^{1}H NMR confirmed the structure of the product.

Scheme 37



95 **96**

The aldehyde **96** was subjected to carbonyl addition without purification (**Scheme 39**). Alcohols **97** and **98** were prepared using vinyl magnesium bromide in 75% yield (entry 1, **Table 17**) [42, 43]. The ^{1}H NMR of the alcohols confirmed the structures of the products. The yields of alcohols **97** and **98** produced from this method were not reproducible, so another reagent was used to improve the yield. Vinyl lithium was freshly prepared from the transmetallation of tetravinyl tin with n-butyl lithium and was allowed to react with aldehyde **96** (entry 2). The products were isolated in the same 2:1 diastereoselectivity and the ^{1}H NMR confirmed the structure with a yield of 80% after purification. Stereochemistry of addition was assigned based on the assumption that the

addition followed the Felkin-Anh model [43, 44], so the major isomer was assigned as alcohol **97** [43] (**Scheme 39, 40**). A more rigorous stereochemical determination was not performed because this route was ultimately abandoned (*vide infra*). Allylic alcohols **97** and **98** were purified by column chromatography and taken for the next step as an inseparable mixture of diastereomers.

Scheme 39

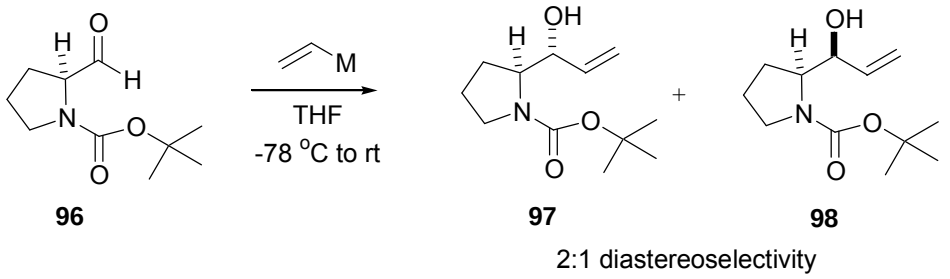
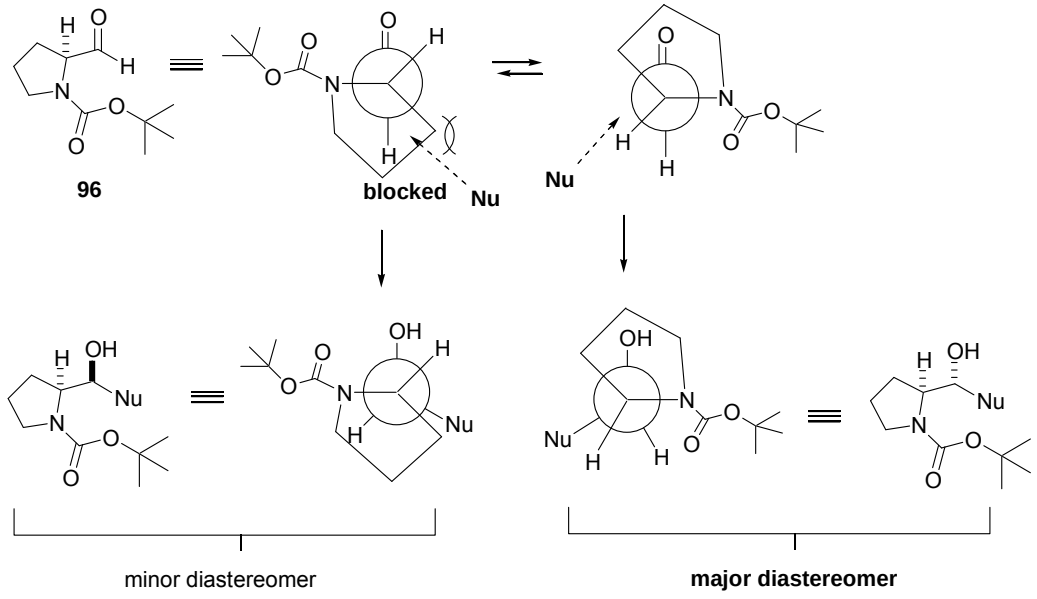


Table 17. Preparation of allylic alcohols **97** and **98** from aldehyde **96**

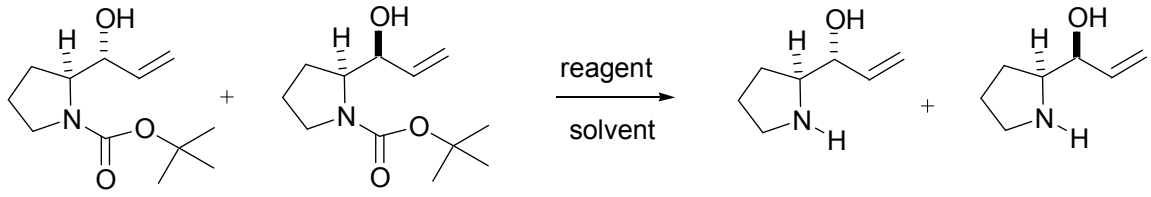
entry	expt. no.	metal counterion (M)	yield (%)
1	BD-1-59	MgBr	75
2	BD-1-111	Li	80

Scheme 40



The Boc-deprotection of allylic alcohols **97** and **98** was a challenging task (**Scheme 41**). Typically, removing a Boc group requires acidic conditions. However, to avoid allylic rearrangement, mildly basic conditions were initially attempted. Unfortunately, potassium carbonate (K_2CO_3) (entry 1) (**Table 18**) did not show any change in the reaction mixture by TLC. A stronger base, potassium hydroxide, (KOH) was also used without much success (entry 2). Finally, trifluoroacetic acid (TFA) was successful in the deprotection of the Boc group without significant side reactions [45]. The yield for the reaction was a modest 49% (entry 3), probably due in part to the water solubility of the product. Purification of the deprotected allylic alcohols **99** and **100** was attempted but was unsuccessful because the products adhered to the silica gel no matter what solvent system was used. Thus, alcohols **99** and **100** were used in the next step without purification.

Scheme 41



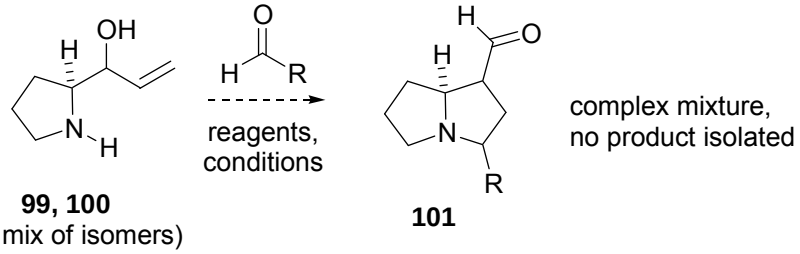
97 **98** **99** **100**

Table 18. Boc deprotection of alcohols **97**and **98**

entry	expt. no.	reagent	solvent	yield
1	BD-1-25	K_2CO_3	MeOH	product not isolated
2	BD-1-27	KOH	MeOH	product not isolated
3	BD-1-101	TFA	none	53%

The ACM reaction was tried on the deprotected allylic alcohols **99** and **100** (**Scheme 42, Table 19**)**.** Allylic alcohols **99** and **100**, butyraldehyde, copper sulfate, and CSA were refluxed in benzene for 24 hrs. After work up, the ^{1}H NMR showed unreacted starting material and no desired product formation (**Table 19**, entry 1). Then a microwave reaction was carried out with the deprotected allylic alcohols **99** and **100**, acetaldehyde, copper sulfate, and CSA in acetonitrile. After a 15-minute run time, the ^{1}H NMR showed a complex mixture with no desired product formation (**Table 19**, entry 2). Next, the reaction was carried out using a Dean-Stark apparatus. The deprotected allylic alcohols **99** and **100**, propionaldehyde, and CSA (**Table 19**, entry 3) were refluxed in toluene. No copper sulfate was used since the apparatus would remove the water formed in the reaction. The reaction was allowed to run for 96 hours. The ^{1}H NMR showed a complex mixture with no desired product formation or starting material. Another reaction was carried out using propionaldehyde, N-deprotected allylic alcohol, copper sulfate, and CSA (**Table 19**, entry 4). This reaction was performed without solvent, using microwave heating. After the work-up, ^{1}H NMR again showed a complex mixture with no desired product formation.

Scheme 42



99, 100
(2:1 mix of isomers)

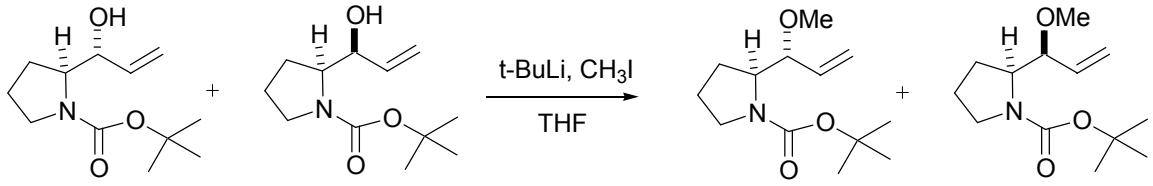
101

Table 19. Attempts at preparation of pyrrolizidine **101**

entry	expt. no.	R (eq)	mmol **99**, **100**	reagents	solvent (mL)	reaction conditions
1	BD-1-95	nPr (50)	0.40	$CuSO_4$, CSA	C_6H_6 (5)	reflux in sealed tube, 16 hr
2	BD-1-115	Et (100)	0.54	$CuSO_4$, CSA	CH_3CN (2)	microwave reaction (settings: 200 W, 100 psi, 90 ^oC, 30 min)
3	BD-1-117	Et (2)	1.60	CSA	CH_3Ph (5)	refluxed for 16 hr using Dean Stark condenser
4	BD-1-119	Et (63)	0.42	Na_2SO_4	none	reflux in sealed tube, 16 hr

In order to make the deprotected amine less water soluble and also easier to purify, we attempted O-methylation of alcohols **97** and **98** prior to amine deprotection. Thus, ethers **102** and **103** were prepared from **97** and **98** by the O-methylation of the alcohol group using t-butyllithium and methyl iodide in THF with a yield of 87% (**Scheme 43**) (Expt. No. BD-1-137).

Scheme 43

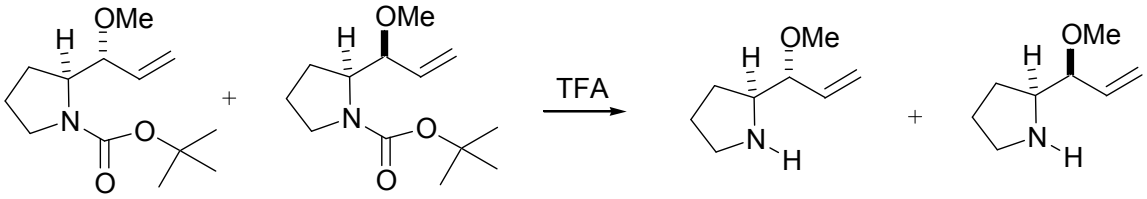


97 **98** **102** **103**

Boc-protected methyl ethers **102** and **103** were deprotected to give free amines **104** and **105**, using trifluoroacetic acid as before (**Scheme 44**). The yield was 57% (Expt. No. BD-1-139). Various solvents were tested using amines **104** and **105** with hopes of finding a suitable solvent system for purification by flash

chromatography. However, hexane, hexane: ethyl acetate (9:1, 8:2), acetonitrile: methanol (1:1), acetonitrile, and methanol did not give any separation. Hence, the crude 2:1 diastereomeric mixture of amines **104** and **105** was used for the ACM reaction.

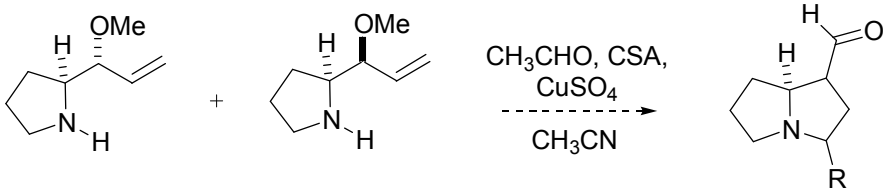
Scheme 44



102 **103** **104** **105**

We anticipated that the amino ethers **104** and **105** would undergo the ACM cyclization to give pyrrolizidine **101** (**Scheme 45**)**.** Thus, they were treated with copper sulfate, acetaldehyde, and CSA in acetonitrile and heated in a microwave with the following settings: 200W, 115°C, 250 psi, and cooling on (Expt. No BD-1-145). The ^{1}H NMR showed a complex mixture.

Scheme 45

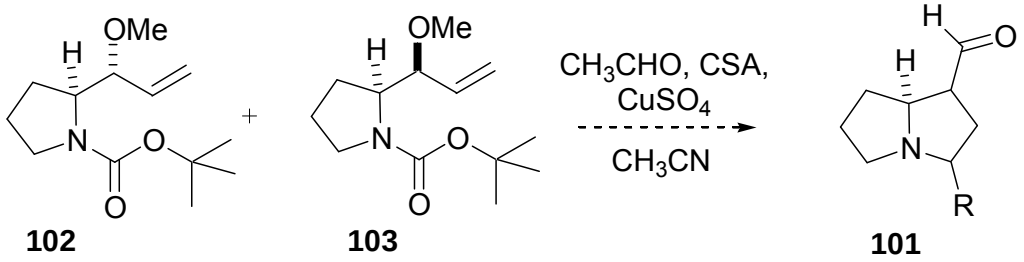


104 **105** **101**

We attempted a one-pot amine deprotection—ACM sequence (**Scheme 46**). Protected amino ethers **102** and **103** (0.2 mmol) were treated with CSA (1 eq) (entry 1, **Table 20**) or TFA (1 eq) (entry 2, **Table 20**), acetaldehyde (100 eq), and copper sulfate (1 eq) in acetonitrile (1 mL) with the following microwave

parameters: 200W, 90°C, 115 psi, run time = 15 minutes, and cooling off. The reaction resulted in a mass recovery of 48%, but the ^{1}H NMR showed that pyrrolizidine **101** was not formed and the reaction mixture contained unreacted acetaldehyde and ethers **104** and **105**, among other unknown products (entry 1). Similar results were observed when TFA was used as the acid (entry 2).

Scheme 46



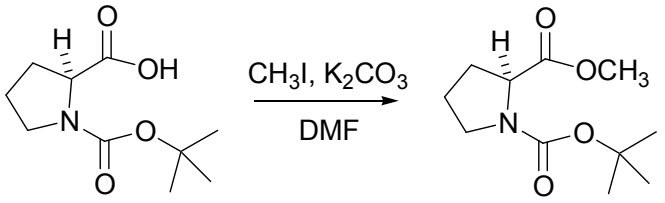
102 **103** **101**

Table 20. Preparation attempts of pyrrolizidine **101** from ethers **102** and **103.**

entry	expt no.	reagent	microwave settings	comment
1	BD-1-145	CSA	200W, 115°C, 250 psi, 15 min, cooling on	unreacted starting material
2	BD-1-147	TFA	same as 1	same as 1

We then tried an alternative approach by synthesizing methyl ester **106** from *N*-Boc proline **94** using potassium carbonate (K_2CO_3) and methyl iodide in dimethyl formamide (DMF) (**Scheme 47**) [46]. The yield of the reaction was 66%, somewhat lower than the 91% reported in the literature (Expt. No. BD-1-161).

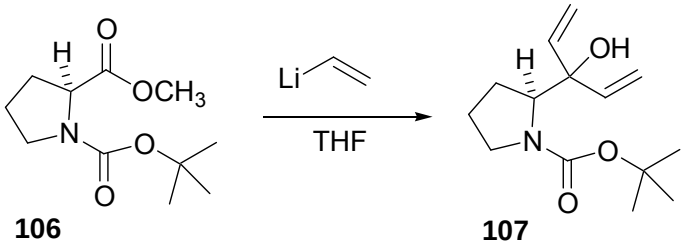
Scheme 47



Boc-L-proline (**94**) **106**

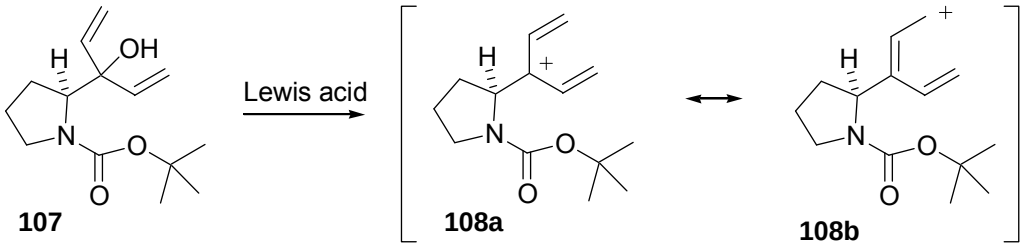
N-Boc bisallylic alcohol **104** was then prepared from methyl ester **106** using excess vinyl lithium (**Scheme 48**) (Expt No. BD-1-175). The crude product was purified by flash chromatography with a yield of only 39%. Side products were present but were not rigorously identified. It was assumed that conjugate addition products could be formed as the side products. In addition, in the presence of a Lewis acid such as silica gel, ionization of the OH group could occur, which would form resonance-stabilized tertiary bisallylic carbocation **108a,b** (**Scheme 49**). This cation could undergo several side reactions.

Scheme 48



106 **107**

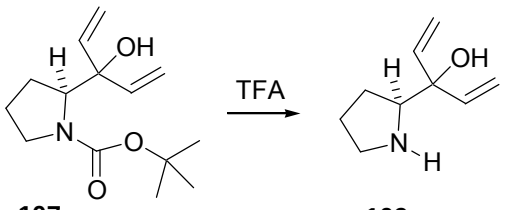
Scheme 49



107 **108a** **108b**

Deprotected bisallylic alcohol **109** was prepared from N-Boc bisallylic alcohol **107** using TFA in 43% yield (**Scheme 50**) (Expt. No. BD-1-179). The deprotected bisallylic alcohol **109** was used without purification for the ACM cyclization reaction.

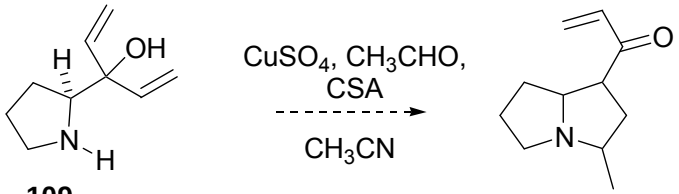
Scheme 50



107 **109**

Free amine **109** (0.27 mmol) was then subjected to ACM conditions using copper sulfate (1.2 eq), acetaldehyde (20 eq), CSA (1.2 eq), and acetonitrile (2 mL) as solvent (Expt. No. BD-1-181). The microwave conditions for the reaction were 200 W, 90 ^{o}C, 150 psi, with a 15-minute hold time and cooling on. The ^{1}H NMR showed complete decomposition except for the product of homo aldol reaction of acetaldehyde under acidic conditions.

Scheme 51

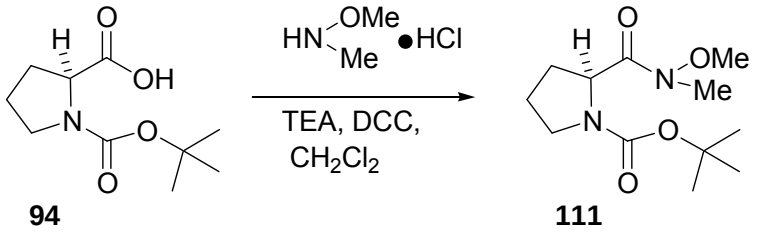


109 **110**

Because of the difficulties associated with the ACM reaction using 2° alcohols **99** and **100** and bisallylic alcohol **109**, we hypothesized that a 3° allylic alcohol might be better behaved. The formation of such a 3° alcohol required the

synthesis of Weinreb amide **111** [42, 47], which was made in 90% yield from N-Boc-proline (**94**) (**Scheme 52**).

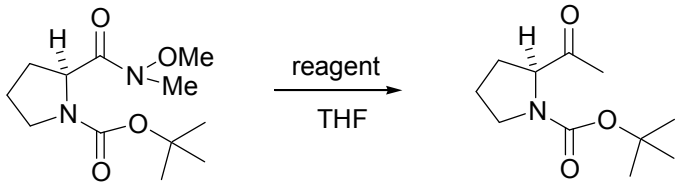
Scheme 52



94 **111**

Next, methyl ketone **112** was prepared from amide **111** using methyllithium in 58% yield (**Scheme 53**, entry 1, **Table 21**). However, the yield improved to 95% when methylmagnesium bromide was used (entry 2).

Scheme 53



111 **112**

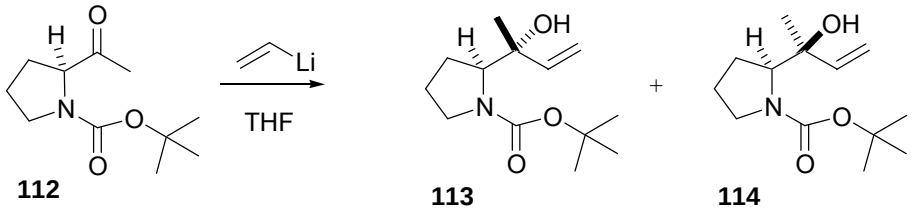
Table 21. Preparation of methyl ketone **112** from Weinreb amide **111**

entry	expt. no.	reagent	yield (%)
1	BD-1-209	MeLi	58%
2	BD-1-257	MeMgBr	95%

A 2:1 mixture of alcohol diastereomers **113** and **114** were prepared in 70% combined yield from methyl ketone **112** using vinyl lithium (**Scheme 55**) (Expt no. BD-1-277). The major isomer was likely formed from Felkin-Anh addition (cf. **Scheme 40**) of the nucleophile, and the stereochemistry was assigned based on

this assumption [43, 44]. A rigorous stereochemical assignment is part of future investigations.

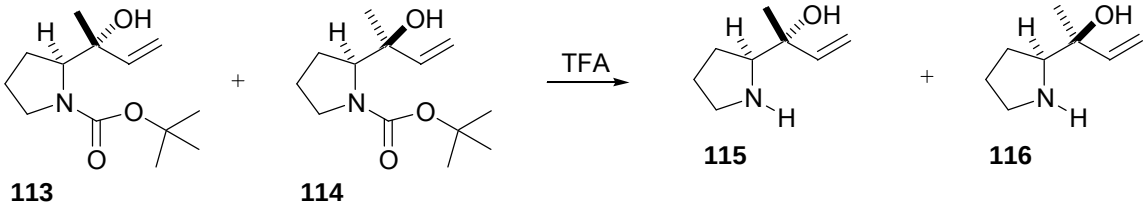
Scheme 55



2:1 diastereoselectivity

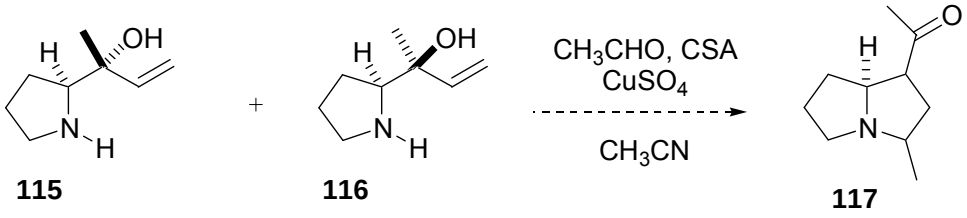
Free amines **115** and **116** were prepared by deprotection of Boc-protected amino alcohols **113** and **114** using neat trifluoroacetic acid (TFA) in 58% yield (**Scheme 56**) (Expt. No. BD-1-273).

Scheme 56



The ACM reaction was attempted using the 2:1 mixture of amino alcohol diastereomers **115** and **116** with no success (**Scheme 57**) (Expt. No. BD-1-271). The amino alcohols **115** and **116** (0.61 mmol) were reacted with acetaldehyde (50 eq), $CuSO_4$ (2 eq), and CSA (4 eq) in acetonitrile (1 mL) using the following microwave settings: 200W, 90°C, 150 psi, 15 min, and cooling off. No desired product formation was shown by ^1H NMR analysis of the crude reaction mixtures.

Scheme 57



III. Conclusion

We have demonstrated that microwave-assisted aminolysis can be accomplished for a somewhat reactive epoxide such as styrene oxide and an unreactive, sterically hindered epoxide like 2,3-epoxy-2-methyl butane to yield the corresponding β-amino alcohols. These reactions were accomplished with a variety of amine nucleophiles. In both cases only one equivalent of the amine and the epoxide were needed to give good yields and modest to excellent regioselectivity for the S_N2 product. The aminolysis of methylvinyl oxirane was also attempted with ammonia, but overalkylation was a significant side product. The microwave-assisted aza-Cope—Mannich reaction of the primary amino alcohol synthesized from this aminolysis reaction was attempted, but to date has not been successful. In addition, secondary and tertiary amino alcohols derived from L-proline were prepared by a four-step synthesis. The aza-Cope—Mannich reaction of these amino alcohols was also attempted, but has not been successful. This type of aza-Cope—Mannich reaction is currently the subject of further investigation in our laboratory.

Chapter 4: Experimental

I. General methods

All commercially available compounds were purchased from Aldrich Chemical Co., or Acros, and used as received, unless otherwise specified. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Purification of the compounds by flash chromatography was performed by using silica gel (32-63 μm particle size, 60 Å pore size). TLC analyses were performed on silica gel 60 F_{254} plates (250 μm thickness). Microwave-assisted reactions were performed using a CEM Discover^{TM} reactor. Pressure was monitored using an IntelliVentTM external pressure monitor. Temperature was monitored using an on-board infrared temperature sensor. Microwave reactor vials and caps were purchased from CEM Corporation. All ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz JEOL ECX instrument, and chemical shifts (δ) reported relative to residual solvent peak $CHCl_3$. All NMR spectra were obtained at room temperature. In some cases, mixtures of diastereomers were obtained and were not separated for characterization purposes. Consequently, some spectroscopic data have been reported on a mixture of diastereomers. Where possible, the diastereomeric ratios were measured by integration of ^{1}H NMR spectra. All reported regio- and stereoselectivity ratios represent averages of at least two duplicate reactions. ^{1}H and ^{13}C NMR chemical shifts were in agreement with those for previously reported compounds **39** [48], **69** [23], **71** [49], **111** [47], **112** [50].

II. Procedures for microwave-assisted aminolyses

General procedure for microwave-assisted epoxide aminolysis: To a 10 mL microwave reactor vial equipped with a magnetic stirring bar was added solvent (0.5 mL), amine (2.0 mmol), and epoxide (2.0 mmol). The vial was sealed with a reusable cap and then placed into the microwave reactor. The reaction was carried out with the following input parameters: temperature: 250 ^{o}C; max. pressure: 250 psi; power: 300 W. After a specified reaction time and brief cooling period, the solution was concentrated *in vacuo* and purified using silica gel column chromatography.

Amino alcohols **39, 40** [48]. According to the general procedure, methanol (0.5 mL), piperidine (0.17 g, 2.0 mmol), and styrene oxide (0.24 g, 2.0 mmol) were reacted using a 30-second ramp time and a 10-minute hold time. Chromatography using CH_2Cl_2-hexanes-MeOH (65:30:5, v/v/v) afforded the title compounds as a pale yellow semi-solid (0.416 g, 100%, mixture of regioisomers). For compound **39**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.71 (dd, *J* = 10.5 Hz, 3.7 Hz, 1H), 2.70 (br s, 2H), 2.49 (dd, *J* = 12.8 Hz, 3.7 Hz, 1H), 2.38 (m, 3H), 1.63 (m, 4H), 1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 128.4, 127.5, 125.9, 68.7, 67.0, 54.5, 26.3, 24.4.

Amino alcohols **69, 70** [23]. According to the general procedure, methanol (0.5 mL), imidazole (0.14 g, 2.0 mmol), and styrene oxide (6) (0.24 g, 2.0 mmol) were reacted using a 30-second ramp time and a 5-minute hold time. Chromatography using CH_2Cl_2-MeOH (95:5, v/v) afforded the title compound as a pale yellow semi-solid (0.377 g, 100%, mixture of regioisomers). For

compound **69**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 6H), 6.89 (br s, 2H), 4.91 (dd, *J* = 7.8 Hz, 4.1 Hz, 1H), 4.11 (dd, *J* = 14.2 Hz, 4.1 Hz, 1H), 4.07 (dd, *J* = 14.2 Hz, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 141.7, 137.7, 128.1, 127.6, 127.0, 125.8, 120.2, 72.9, 54.1.

Amino alcohols **71, 72** [49]. According to the general procedure, methanol (0.5 mL), aniline (0.37 g, 4.0 mmol), and styrene oxide (0.24 g, 2.0 mmol) were reacted using a 30-second ramp time and a 30-minute hold time. Chromatography using hexanes-EtOAc (95:5, v/v) afforded the title compound as a pale yellow oil (0.320 g, 75%, mixture of regioisomers). For compound **71**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 3H), 7.35 (m, 4 H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 4.88 (dd, *J* = 8.7 Hz, 4.1, 1H) 3.40 (dd, *J* = 13.3 Hz, 4.1 Hz, 1H) 3.26 (dd, *J* = 13.3 Hz, 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 142.1, 129.5, 128.8, 128.1, 126.0, 118.2, 113.6, 72.5, 51.9

Amino alcohols **79, 80**. According to the general procedure, methanol (0.5 mL), aniline (0.19 g, 2.0 mmol), and 2,3-epoxy-2-methylbutane (0.17 g, 2.0 mmol) were reacted using a 30-second ramp time and a 180-minute hold time. Chromatography using hexanes-EtOAc (70:30, v/v) afforded the title compound as a pale yellow liquid (0.214 g, 60%, mixture of regioisomers). For compound **79**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.2 Hz, 2H), 6.71 (m, 3H), 3.41 (br s, NH), 3.40 (q, *J* = 6.4 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 129.4, 118.2, 114.4, 72.7, 58.8, 27.0, 24.7, 16.3. IR (thin film) υ 3851, 3439, 1602 cm^{-1}. EI-HRMS calcd for $C_{11}H_{17}NO$ [M^{+}] 179.1310; found 179.1312.

Amino alcohols **81, 82**. According to the general procedure, methanol (0.5 mL), piperidine (0.17 g, 2.0 mmol), and 2,3-epoxy-2-methylbutane (0.17 g, 2.0 mmol) were reacted using a 30-second ramp time and a 120-minute hold time. Chromatography using EtOAc-MeOH (80:20, v/v) afforded the title compound as a pale yellow liquid (0.165 g, 48%, mixture of regioisomers). For compound **81:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (m, 2H), 2.38 (m, 2H), 2.36 (q, *J* = 6.9 Hz, 1H), 1.57 (m, 4H), (1.41, m, 2H), 1.13 (s, 3H), 1.08 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.3, 70.9, 69.2, 52.8, 28.5, 26.9, 24.6, 8.3. IR (thin film) υ 2971, 2932, 1386 cm^{-1}. Electrospray HRMS calcd for $C_{10}H_{21}NO$ [M^+H^+] 172.1701; found 172.1708.

Amino alcohols **83, 84**: According to the general procedure, methanol (0.5 mL), benzylamine (0.21 g, 2.0 mmol), and 2,3-epoxy-2-methylbutane (0.17 g, 2.0 mmol) were reacted using a 30-second ramp time and a 45-minute hold time. Chromatography using EtOAc-MeOH (50:50, v/v) afforded the title compound as a pale yellow liquid (0.309 g, 80%, mixture of regioisomers). For compound **83**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 Hz), 3.94 (d, *J* = 12.8 Hz, 1H), 3.68 (d, *J* = 12.8 Hz, 1H), 2.51 (q, *J* = 6.9 Hz, 1H), 1.19 (s, 3H),1.09 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl^3$) δ 140.4, 128.6, 128.3, 127.3, 71.6, 61.9, 52.6, 27.0, 23.0, 15.4. IR (thin film) υ 3027, 2970, 1454 cm^{-1}. Electrospray HRMS calcd for $C_{12}H_{19}NO$ [M^+Na^+] 216.1357; found 216.1364.

Amino alcohols **85, 86**: According to the general procedure, methanol (0.5 mL), imidazole (0.14 g, 2.0 mmol), and 2,3-epoxy-2-methylbutane (0.17 g, 2.0 mmol) were reacted using a 30-second ramp time and a 30-minute hold time.

Chromatography using EtOAc-MeOH (80:20, v/v) afforded the title compound as a pale yellow liquid (0.299 g, 97%, mixture of regioisomers). For compound **85**: ^{1}H NMR (400 MHz, $CDCl^{3}$) δ 7.52 (s, 1H), 6.99 (s, 2H), 4.02 (q, *J* = 7.3 Hz, 1H), 1.86 (br s, OH), 1.52 (d, *J* = 7.3 Hz, 3H), 1.22 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 128.5, 118.7, 72.2, 62.1, 27.3, 26.0, 15.9. IR (thin film) υ 3439, 2978, 1645 cm^{-1}. EI-HRMS calcd for $C_8H_{14}N_{2O}$ [M^+] 154.1109; found 154.1106.

III. Procedures for L-proline-derived amino alcohol synthesis

Weinreb amide **111**. [47] To a round-bottom flask under nitrogen atmosphere was added *N*-Boc proline (1.0 g, 4.65 mmol) and dichloromethane (50 ml). *N,O*-dimethylhydroxylamine hydrochloride (0.68 g, 6.97 mmol), dicyclohexylcarbodiimide (0.880 g, 6.97 mmol), and triethylamine (2.6 ml, 18.6 mmol) were then added. The reaction mixture was stirred at room temperature for 12 hr, after which the dichloromethane was evaporated *in vacuo*. The resulting slurry was stirred with 50 ml of acetone and filtered through a fritted funnel. The filtrate was evaporated under vacuum to afford the title compound as a yellow oil (1.02 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.5 (m, 1H), 3.65 (s, 3H, OMe), 3.4 (m 2H), 3.1 (s, 3H, N-Me), 2.1 (m, 1 H), 1.8 (m, 3H), 1.3 (s, 9H, *t*-Bu).

Methyl ketone **112.** [50] To a round-bottom flask under nitrogen atmosphere was added Weinreb amide **111** (1.3 g, 5.4 mmol) and THF (25 ml). The solution was cooled to between -70°C and -75°C, and methylmagnesium bromide (1.4 M in THF, 29 mL, 32 mmol) was then added. The reaction was

stirred at -70°C to -75°C for 20 min. and then warmed to room temperature and stirred for 12 hr. The reaction mixture was then poured into a stirring ice and saturated $NaHCO_3$ solution (100 ml). After stirring for 15 minutes, the reaction mixture was extracted with diethyl ether (3 x 25 ml), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography using hexanes-EtOAc (50:50, v/v) afforded the title compound as a yellow oil (1.24 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.1- 4.25 (m, 1H), 3.3 -3.4 (m, 2H), 2.1 (s, 3H), 1.8-1.9 (m, 2H), 1.5-1.6 (m, 2H), 1.4 (s, 9H).

Allylic alcohols **113, 114**. To a round-bottom flask under nitrogen atmosphere was added tetravinyl tin (0.58 g, 3.2 mmol) and THF (15 ml). The resulting solution was cooled to -70°C to -75°C. To this was added n-BuLi (1.6 M in hexanes, 8.0 mL, 12.8 mmol). The reaction was stirred for 15 min. and then warmed to room temperature and stirred for 1 hr. After 1 hour the reaction mixture was again cooled to between -70°C and -75°C. Methyl ketone **112** (1.1 g, 5.8 mmol) in THF (15 ml) and added via cannula to the cooled reaction mixture. After the addition was completed, the reaction was allowed to stir at -70°C to -75°C for 15 minutes and then was warmed to room temperature and stirred for 3 hr. The reaction was quenched by pouring into saturated $NaHCO_3$ solution (100 ml). The product was extracted using diethyl ether (3 x 25 ml), dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography using hexanes-EtOAc (90:10, v/v) afforded the title compound as a yellow oil (0.98 g, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.7-5.8 (dd, 1H), 5.3-5.4 (dd, 1H), 4.8-4.9 (dd, 1H), 3.4-3.6 (m, 3H), 2.4 (br s, 1H,), 1.5-1.65 (m, 4H), 1.45 (s, 3H), 1.4 (s, 9H).

Amino alcohols **115, 116**. To a round-bottom flask were added allylic alcohols **113, 114** (0.157 g, 0.65 mmol) and trifluoroacetic acid (TFA) (1 ml). The reaction was stirred at room temperature for 1 hr. The reaction mixture was then concentrated in vacuo. Water (1 mL) was added, and the solution was made allkaline by addition of NH_4OH. The product was extracted using dichloromethane (3 x 5 ml), dried over $MgSO_4$, and concentrated *in vacuo* to give the title compound as a brown oil. (0.053 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.3-5.8 (dd, 1H), 5.1-5.3 (dd, 2H), 3.4-3.6 (m, 3H), 2.4 (br s, 1H), 1.5-1.65 (m, 4H), 1.45 (s, 3H).

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