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Microwave-assisted synthesis of ß-amino alcohols

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Microwave-assisted Synthesis of β-Amino Alcohols

by

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ABSTRACT

β-amino alcohols are common substructures in many biologically active compounds and can also be used as catalysts for asymmetric reactions. One common method for forming these moieties is by ring opening of unsymmetrical epoxides using amines via a substitution reaction. However, the majority of these methods requires excess of reagents, inorganic initiators, and/or extended reaction times. We have developed an efficient, regioselective route to synthesize amino alcohols via microwave-assisted aminolysis of several hindered and unhindered epoxides using amine nucleophiles of varying strengths. Microwave reactions can be done without Lewis acids or promoters, even for the most hindered trisubstituted epoxides. In most of these cases, the reaction requires only a 1:1 ratio of amine to epoxide. Regioselectivity for the S_N2 pathway can be increased in some reactions by decreasing the polarity of the solvent.

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Chapter 1: Introduction

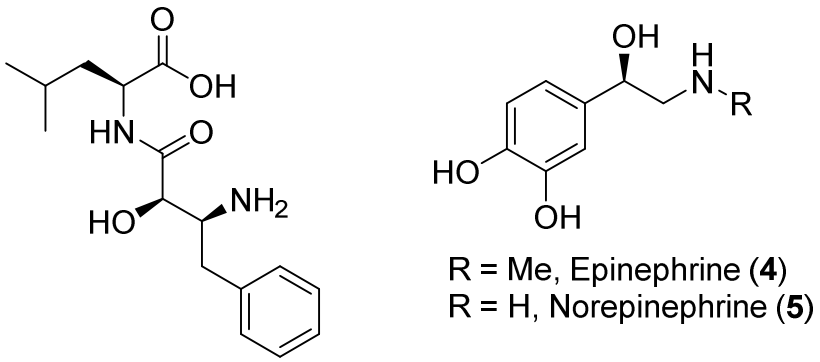
β-amino alcohols, also known as vicinal amino alcohols or 1,2-amino alcohols, can be found in naturally occurring and synthetic molecules [1]. The existence of the β-amino alcohol moiety and its stereochemistry tend to play an important role in the biological activity of the molecule [1]. The literature has described both naturally occurring and synthetic β-amino alcohols.

Naturally occurring hydroxy amino acids are the most common examples of β-amino alcohols [1]. Amino acids are biologically important organic molecules that contain amine and carboxylic acid functional groups. Amino acids are the second largest constituent in the human body after water [2]. These acids exist as proteins and are essential for an enormous variety of biological functions [2]. The two amino acids that contain amino alcohol moieties are shown in **Figure 1**. In addition to their role as components of proteins, each has more specific functions. L-Serine (**1**) (**Figure 1**) is an important neurotrophic factor and a precursor for phosphatidyl-L-serine, L-cysteine, nucleotides, sphingolipids, and neurotransmitters such as D-serine and glycine [3]. It plays a critical role in neuronal development and the function of the central nervous system [3]. L-threonine (**2**) (**Figure 1**) is another amino acid that contains an amino alcohol. The heart, skeletal muscles, and central nervous system contain high concentration of L-threonine [4,5]. Threonine is also important in maintaining appropriate protein balance in the body as well as supporting the development of collagen and elastin in the skin [6,7].

L-serine (**1**) L-threonine (**2**)

Figure 1. Amino acids containing a β-amino alcohol.

Another well-known example of a naturally occurring amino alcohol is bestatin (**3**) (**Figure 2**) which was initially isolated from culture filtrates of *Streptomyces olivoreticuli* [8]. Bestatin is used as an adjuvant in chemotherapy for acute myelocytic leukemia [9] as it works as an aminopeptidase inhibitor due to its immunomodulatory characteristics [1,10-13]. Epinephrine (β-3,4-trihydroxy-*N*-methylphenethylamine) (**4**) (**Figure 2**), also known as adrenaline, is a less-complex amino alcohol and is a hormone and neurotransmitter [14]. It is useful in treatment of cardiac arrest [15] and anaphylaxis [16]. Norepinephrine (4,5-β-trihydroxy phenethylamine) (**5**) (**Figure 2**) is a hormone and neurotransmitter and is also known as noradrenaline [14]. Norepinephrine is utilized as a vasopressor medication for critical hypotension [17].



Bestatin (**3**)

Figure 2. Naturally occurring molecules containing a β-amino alcohol.

Lipid molecules are another set of naturally occurring molecules that may contain β-amino alcohols. Sphingosine and myriocin are the two common examples of such lipids. Sphingosine (**6**) (**Figure 3**) is useful in cell signaling [1, 18, 19]. Further, the sphingosine derivative sulfobacin B acts as an antithrombotic agent [1,20]. Myriocin (**7**) is an amino alcohol-containing lipid (**Figure 3**) that acts as an immunostimulatory agent [1, 21, 22].

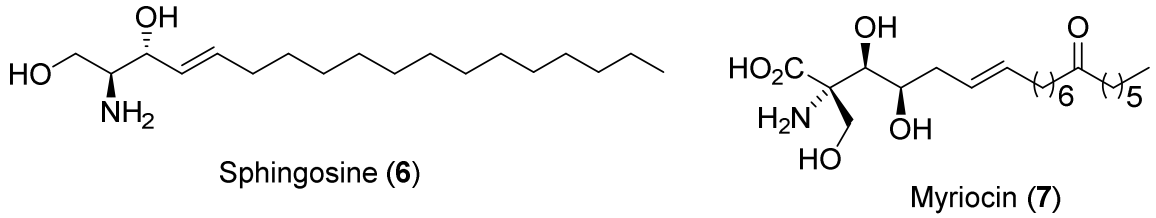


Figure 3. Lipid molecules containing β-amino alcohols.

Febrifugine (**8**) is an example of a β-amino alcohol in which the amine is contained within a ring (**Figure 4**). Febrifugine was originally isolated from *Dichroa febrifuga*, a chinese herb [23]. Febrifugine acts as an antimalarial agent [1, 24].

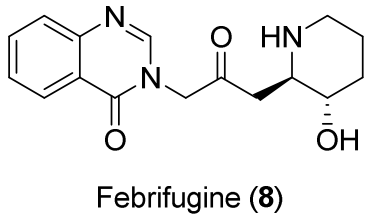


Figure 4. Example of a cyclic amino alcohol.

A number of non-naturally occurring β-amino alcohols have demonstrated pharmacological activity. One example is amino alcohol **9**, which is known to interact with RNA and also functions as an anti-HIV agent (**Figure 5**) [1, 25]. Another example is amidine-containing amine diol **10**, (**Figure 5**) which can inhibit nitric oxide synthetase and has potential as a therapeutic agent in the treatment of conditions such as arthritis [1,

26, 27]. Metoprolol (**11**) (**Figure 5**) is a B1 receptor blocker. It is used in medical conditions such as heart failure [28], vasovagal syncope [29], and as an adjunct treatment of hyperthyroidism [30]. Finally, ranolazine (**12**) (**Figure 5**) is used in treatment of chronic angina [31].

Because of the biological significance of these and related molecules, many methods have been described for their synthesis [1]. One straightforward method is epoxide aminolysis, which is reviewed in detail in the next chapter.

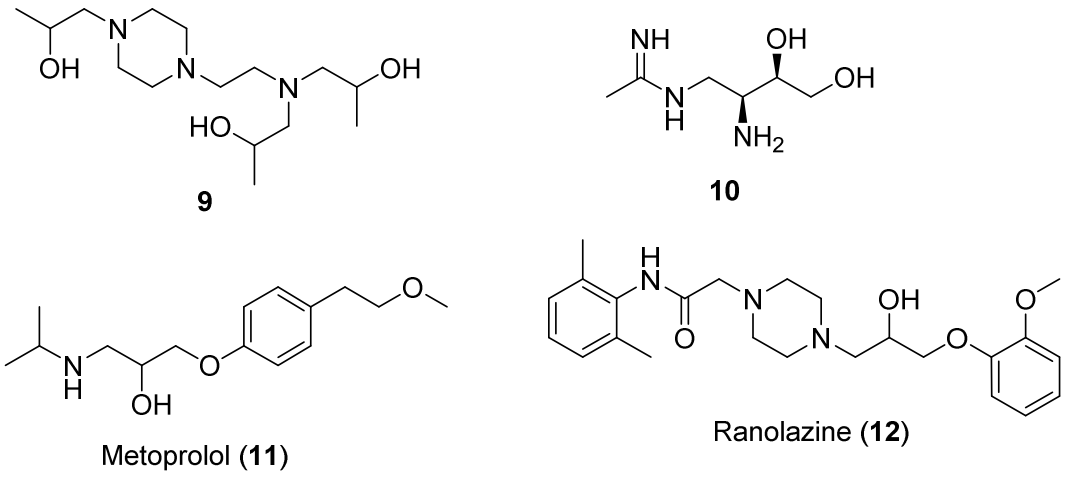


Figure 5. Synthetic β-amino alcohols

Chapter 2: Literature Review

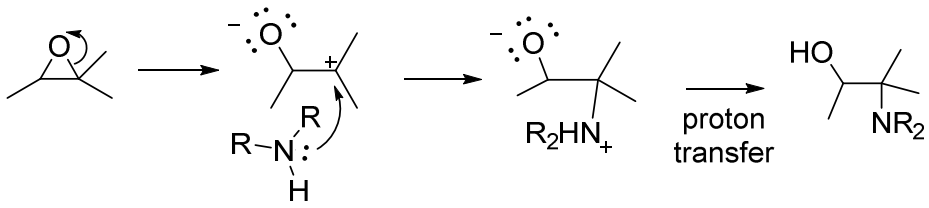
I. Introduction

β-amino alcohols are important substructures in natural and synthetic molecules [1]. Biologically active compounds such as antibiotics, alkaloids, and enzyme inhibitors contain β-amino alcohol substructures [32]. Furthermore, the presence of the β-amino alcohol moiety and its stereochemistry play an important role in the biological activity of the molecule [1].

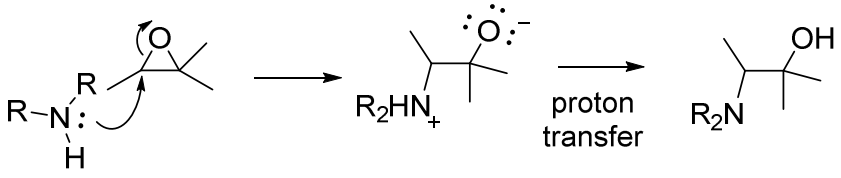
Aminolysis of epoxides is a common method used to synthesize β-amino alcohols. Aminolysis of epoxides can be performed using a catalyst/promoter either in substoichiometric or superstoichiometric amounts or by using microwave irradiation. Epoxide aminolysis is a nucleophilic substitution reaction that may follow two different mechanisms that lead to two different regioisomeric amino alcohols (**Scheme 1**) [33,34].

Scheme 1

S_N1 mechanism



S_N2 mechanism

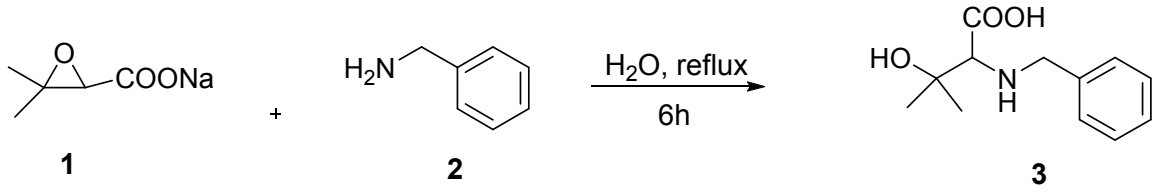


The S_N1 (unimolecular nucleophilic substitution) mechanism is a two-step mechanism in which a carbon-heteroatom bond breaks to form a more stable carbocation. In a second step, a nucleophile adds to the carbocation (equation 1, **Scheme 1**). β-amino alcohols are likely to be formed via an S_N1 reaction when a weaker nucleophile and/or an epoxide that can form a stable carbocation is used. By contrast, S_N2 (bimolecular nucleophilic substitution) is a single-step mechanism in which the nucleophile attacks with simultaneous displacement of the leaving group. This mechanism is likely to occur when stronger nucleophiles and/or sterically unhindered nucleophiles and epoxides are used (equation 2, **Scheme 1**). In some situations, the two pathways may compete, forming two regioisomers. This literature review will examine methods that have been developed to synthesize β-amino alcohols via epoxide aminolysis.

II. Uncatalyzed aminolysis reactions

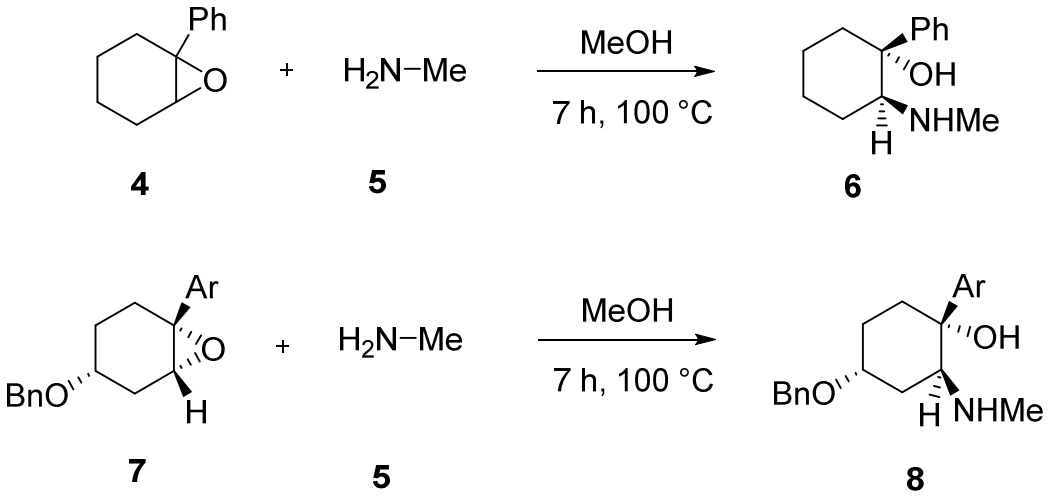
Harada has described a method to synthesize DL-β-hydroxyvaline using an epoxide aminolysis [35]. Epoxide **1** (50 mmol) was treated with benzylamine (**2**) (70 mmol, 1.4 eq) in 7 mL water and then refluxed for 6 hours. Amino alcohol **3** was obtained as the only isomer in 62% yield. In this case, the relative ease of the reaction could have been due to the electron deficient nature of the epoxide.

Scheme 2



Ikeda has used an epoxide aminolysis in the syntheses of the sceletium alkaloid (±)-mesembranol and the amaryllidaceae alkaloid (±)-elwesine [36]. A mixture of 1-phenylcyclohexane oxide (**4**) (12.6 mmol) was dissolved in 40% methylamine (**5**) in methanol (126 mmol, 10 eq) and heated in a sealed tube for 7 hours at 100 °C (**Scheme 3**). Amino alcohol **6** was obtained in 62% yield as a single regioisomer after purification. Also, epoxide **7** was subjected to identical reaction conditions, producing amino alcohol **8** in 78% yield (**Scheme 3**).

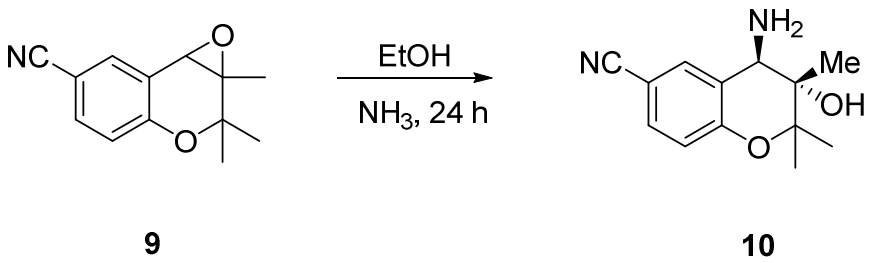
Scheme 3



Gericke has described a method to synthesize 3-methyl-2*H*-1-benzopyran potassium channel activators that requires the formation of β-amino alcohols [37]. Epoxide **9** (20 mmol) in ethanol (50 mL) was treated with a continuous stream of

ammonia gas for 24 hours (**Scheme 4**). Amino alcohol **10** was obtained as only product in 71% yield.

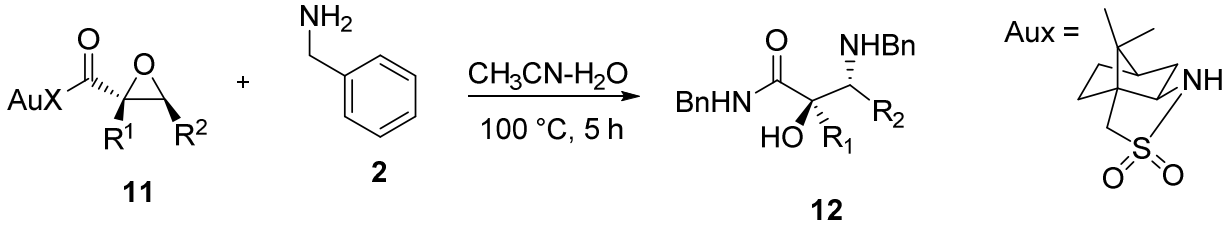
Scheme 4



9 **10**

Zhang described a method for diastereoselective epoxidation of N-enoylsultams with different chiral sultams [38]. Benzylamine was used as nucleophile for the ring opening of these epoxides. The aminolysis reaction was carried out by treating the epoxide **11** (0.15 mmol) with benzylamine (**2**) (3.08 mmol, 20 eq) in CH_3CN/H_2O (9:1, 6 mL) and heated at 100 °C for 5 hours (**Scheme 5**). Amino alcohol **12** was obtained as a single isomer in 82% yield.

Scheme 5

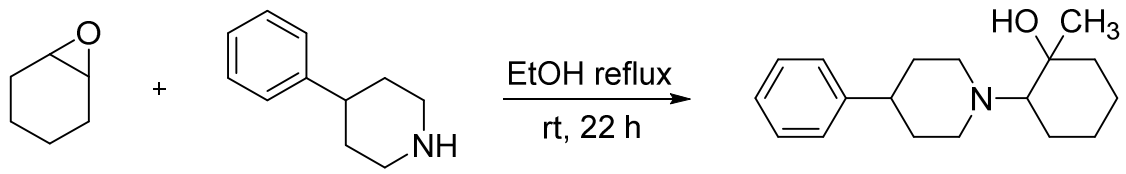


11 **2** **12**

Parsons has described an epoxide aminolysis to generate several acetylcholine-storage-blocking drug analogues [39]. A mixture of 1-methylcyclohexane oxide (**13**) (198 mmol, 2 eq) and 4-phenylpiperidine (**14**) (93.0 mmol) was dissolved in 50 mL of ethanol and the solution was refluxed for 22 hours. However, amino alcohol **15** was obtained in

only 23% yield (**Scheme 6**). This example is unusual in that an excess of epoxide rather than amine is employed.

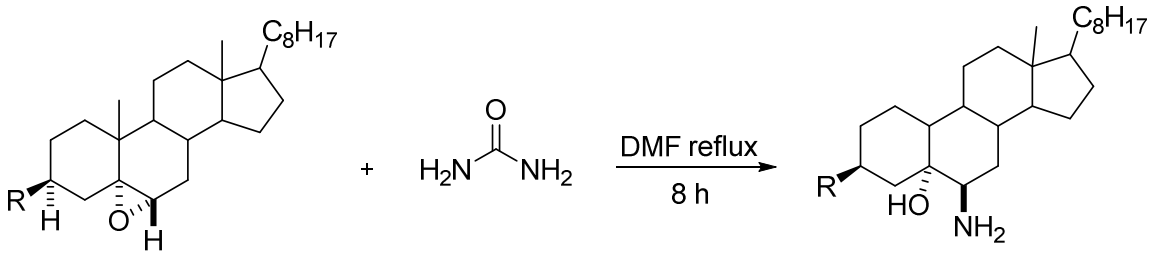
Scheme 6



13 **14** **15**

Shafiullah has introduced a method to synthesize amino sterols and their derivatives using amino alcohols as intermediates [40]. A mixture of 5,6 α-epoxy-5α-cholestane (**16**) (6.5 mmol) and urea (**17**) (32.5 mmol, 5 eq) was refluxed in dimethylformamide (DMF) (100 mL) for 8 hours (**Scheme 7**). Amino alcohol **18** was obtained in a modest 14.5% yield.

Scheme 7

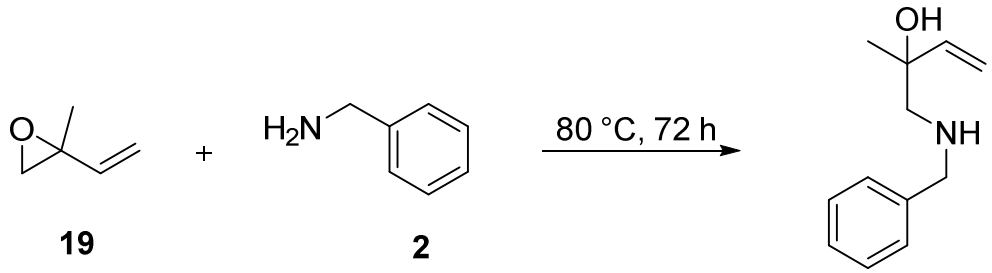


16 **17** **18**

R = H, Cl, OAc

Cooke has described the synthesis of *N*-benzyl-4-acetylproline via a tandem cationic aza-Cope rearrangement—Mannich cyclization [41]. The synthesis of the required *N*-benzyl amino alcohol **20** was done via aminolysis of isoprene monoxide **19** using benzylamine **2**. A mixture of benzyl amine **2** (375 mmol, 5 eq) and 2-methyl-2-vinyloxirane **19** (75 mmol) was treated for 72 hours at 80 °C (**Scheme 8**). Only one isomer **20** was obtained with 89% yield.

Scheme 8

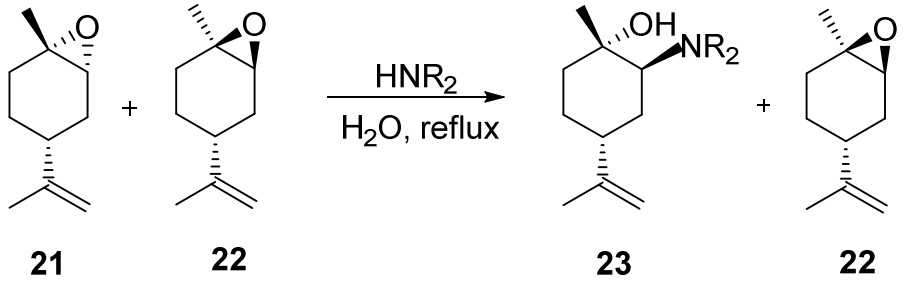


19 **2** **20**

Singaram has described a method for the synthesis of β-amino alcohols that were then used as chiral ligands in the alkynylation of aldehydes [42]. Secondary amines were used for a selective ring opening of diastereomeric epoxides. Epoxides **21** and **22** (0.5 mmol) were added to deionized water (18 mL) and a secondary amine (5 mmol, 5 eq).

The solution was refluxed for 24 hours (**Scheme 9**). Amino alcohol **23** was obtained in 70-94% yield via an S_N2 pathway, while epoxide **22** was unreactive.

Scheme 9

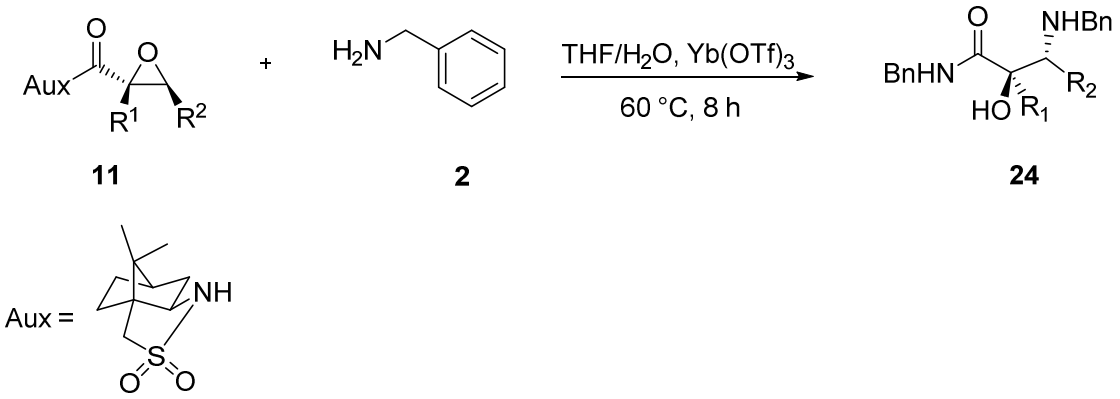


HNR_2= Piperdine, Pyrrolidine, Isoquinoline

III. Lewis acid catalyzed or promoted epoxide aminolyses

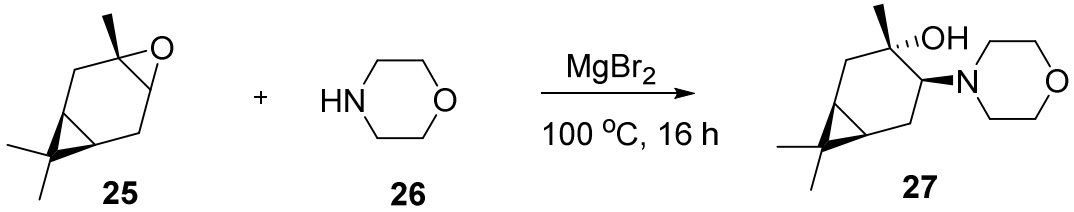
Zhang also reported using $Yb(OTf)_3$ catalysis for the aminolysis of his chiral epoxides [38]. Epoxide **11** (0.23 mmol) in THF-H_2O (8:2, 5 mL) was stirred with benzylamine (**2**) (0.69 mmol, 3eq) and $Yb(OTf)_3$ (0.023 mmol, 0.1 eq) at 60°C for 8 hours, giving amino alcohol **24** in 84% yield (**Scheme 10**). Interestingly, little improvement in yield or reaction time was realized through this approach.

Scheme 10



Nugent has described a method to prepare a NNRTI (HIV-1 non-nucleoside reverse transcriptase inhibitor) drug candidate DPC 963. The synthesis required the formation of amino alcohol **27** [43]. Magnesium bromide was used as a Lewis acid promoter for the epoxide aminolysis. A mixture of 2,3-epoxypinane (**25**) (32.8 mmol) and morpholine (**26**) (333 mmol, 10.2 eq) were treated with $MgBr_2$ (2 eq) for 16 hours at 100°C (**Scheme 11**). Amino alcohol **27** was obtained as the major isomer in 60% yield. The major product arose by attack at the less hindered carbon via an S_N2 pathway.

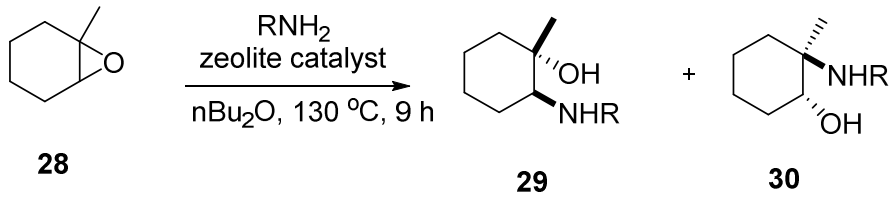
Scheme 11



Onaka has examined the aminolysis of 1,2-epoxy-1-methylcyclohexane using several zeolites as catalysts. The author compared the zeolites' catalytic activities to determine which enhanced the regioselectivity of reactions [44]. In the reaction, a 1:1 molar ratio of 1,2-epoxy-1-methylcyclohexane (**28**) and aniline was treated with catalyst (1.2 g) in 6 mL n-butyl ether (**Scheme 12**). The mixture was heated for 9 hours at 130 °C.

As described in (**Table 1**) below, amino alcohols **29** and **30** were obtained in a range of 22% to 90% yield (entries 1-8). Isomeric ratios varied depending upon the catalyst used. In general, nucleophilic attack occurred at the less hindered carbon of the epoxide when neutral or basic zeolite catalysts such as HY, CaY, NaY were used. In contrast, when more Lewis acidic zeolite catalysts were used for the ring opening, nucleophilic attack occurred at the more hindered carbon. Because the NaY zeolite produced the best yield and selectivity for the initial reaction, the aminolysis of epoxide **28** was carried out using 1-octylamine in the presence of NaY catalyst (entry 9). Amino alcohol **29** was formed in 86% yield as a single isomer by attack at the less hindered carbon. The greater regioselectivity was likely due to the use of a stronger nucleophile.

Scheme 12



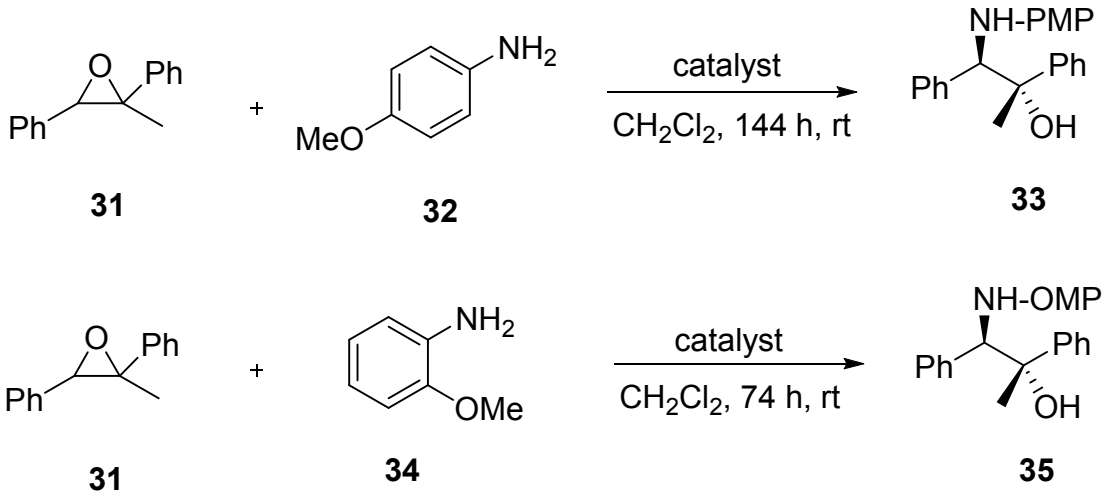
28 **29** **30**

Table 1. Aminolysis of 1,2-epoxy-1-methylcyclohexane using aniline.

Entry	R	Catalyst	29+30 yield %	Ratio 29:30
1	Ph	HY	22	1:1
2	Ph	CaY	74	2:5
3	Ph	NaY	90	6:1
4	Ph	KY	70	4:1
5	Ph	CsY	68	4:3
6	Ph	SiO_2	75	1:0
7	Ph	Al_2O_3	69	1:1
8	Ph	Al_2O_3	74	2:3
9	n-C_8H_{17}	NaY	86	29 only

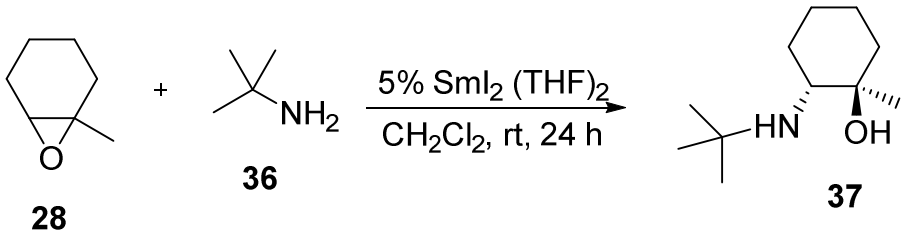
Bartoli has described a novel method used to prepare β-amino alcohols by aminolysis of a 1,2,2'-trisubstituted epoxide using commercially available (Cr(salen)-Cl) (0.1 eq) as a catalyst [45]. When epoxide **31** (2.5 mmol, 2.5 eq) was treated with p-anisidine (**32**) (1 mmol) in CH_2Cl_2 at room temperature for 144 hours, amino alcohol **33** was formed as the only isomer by attack at the less hindered carbon. The yield for the reaction was only 44%. However, when the aminolysis of epoxide **31** was performed with o-anisidine (**34**) at room temperature for 74 hours, amino alcohol **35** was formed in 94% yield. It is noteworthy that in these reactions, as well as that described by Parsons [39] (cf. **Scheme 6**), the amine was the limiting reagent.

Scheme 13



Collin has examined a method for epoxide aminolysis using a catalytic amount of $SmI_2(THF)_2$ [46]. A mixture of epoxide **28** (2 mmol) and tert-butylamine (**36**) (2.4 mmol, 1.2 eq) was added to $SmI_2(THF)_2$ (0.10 mmol) in CH_2Cl_2 (5 mL) and stirred at room temperature for 24 hours (**Scheme 14**). Amino alcohol **37** was obtained as the only isomer in 67% yield by attack at the less hindered carbon.

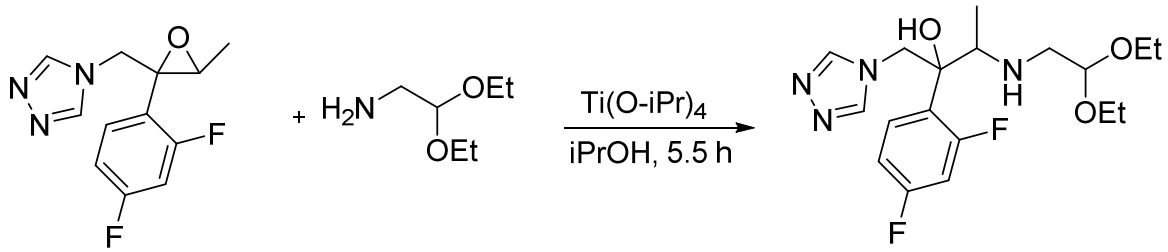
Scheme 14



Ichikawa described a method for the synthesis of several amino alcohols to be tested for antifungal activity [47]. The formation of a β-amino alcohol was an intermediate step in these syntheses. A mixture of epoxide **38** (16.6 mmol) and 2,2-diethoxyethanamine (**39**) (330 mmol, 20.0 eq) was stirred in $Ti(OiPr)_4$ (7.35 mL, 1.5 eq)

with iPrOH (50 mL) for 5.5 hours (**Scheme 15**). The yield of the reaction was 71%; alcohol **40** was obtained as the only regioisomer.

Scheme 15



38 **39** **40**

IV. Microwave-assisted epoxide aminolyses

Microwave irradiation of reaction mixtures has been demonstrated as effective for accelerating both organic and inorganic reactions [48]. Microwave radiation frequency ranges from 0.3 to 300 GHz, a range too low for breaking any chemical bonds [48]. During a chemical reaction, microwave energy is absorbed by a solvent or reagent and gets converted into heat from the friction of the irradiated molecule as it oscillates with the microwave field [48]. This heat affects the rate of reaction. In microwave-assisted reactions, a higher temperature can be obtained when polar materials are irradiated by the microwave field. The most useful measure of this effect is called dielectric loss. This value is an expression of the amount of energy a sample absorbs or the amount of microwave energy that is "lost" to the sample as heat. [48]. This is beneficial in determining the relative absorption ability for different solvents. For example, the dielectric loss value for ethanol is 22.9 while the value for hexane is 0.038, which illustrates that ethanol is a much better absorber of microwave energy than hexane.

Overall, polar substances have a higher dielectric loss values than non-polar substances. **Figure 6** shows a comparison between microwave heating and conventional heating [48]. Conventional heating requires longer reaction time since it is completely dependent upon the thermal conductivity of the vessel material to transfer heat into a reaction medium. On the other hand, microwave energy requires less time as it only depends upon the polarity of the reaction mixture. No vessel heating is required [48].

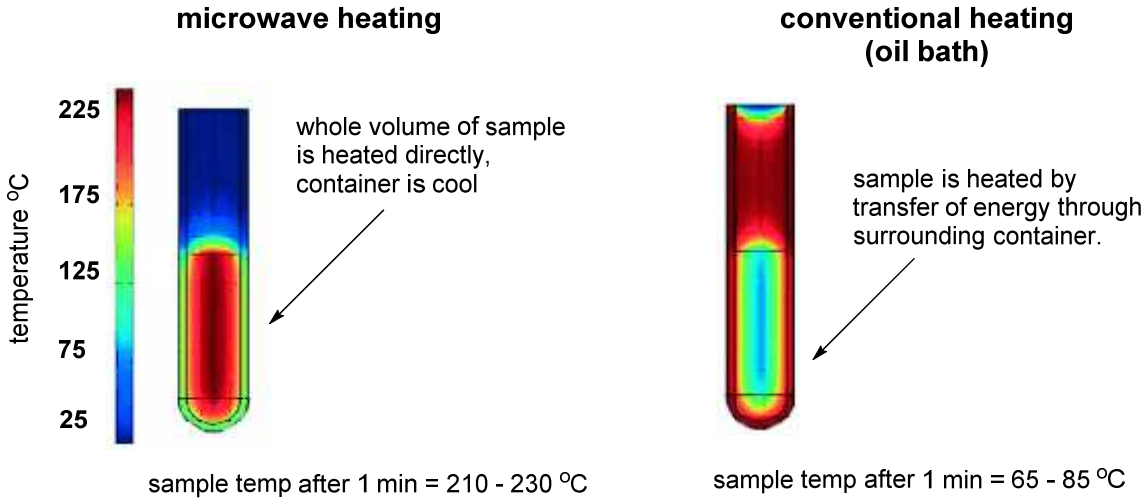
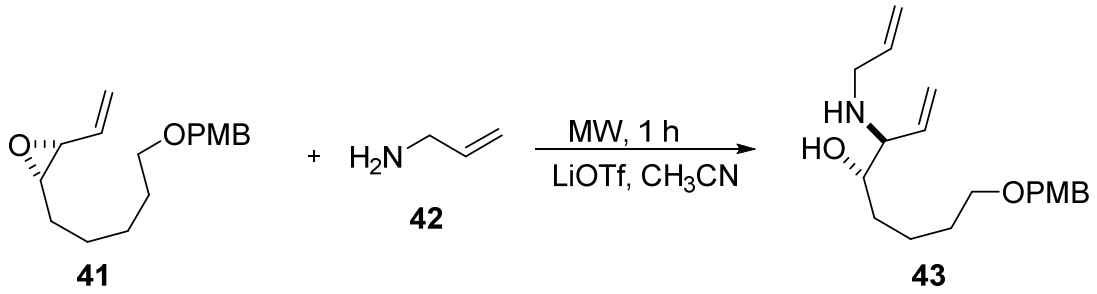


Figure 6. Comparison of microwave and oil bath heating [48]**.**

As described below, microwave heating was used in a number of epoxide aminolyses. While some reactions still use Lewis acid promoters, many of these reactions do not require the addition of those reagents.

Pyne has described the synthesis of a novel azepine triol that acts as a potential glycosidase inhibitor [49]. Microwave irradiation was used for the aminolysis of an epoxide to obtain synthetic intermediate **43**. Vinyl epoxide **41** (1.90 mmol), allyl amine **42** (5.72 mmol, 3 eq), and lithium triflate as a promoter (1 eq) in acetonitrile were run for 1 hour in a closed Teflon vessel with a pressure of 100 bar at 120 °C. Amino alcohol **43** was obtained as a single isomer in 97% yield via an S_N2 pathway (**Scheme 16**).

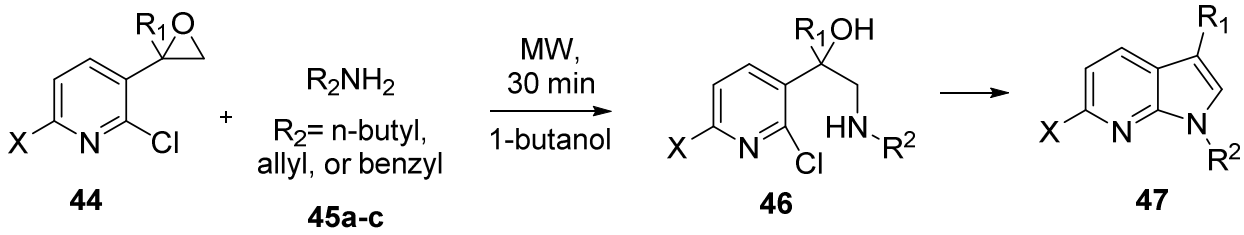
Scheme 16



41 **42** **43**

Schirok has developed a short and flexible method to synthesize azaindoles [50]. Microwave heating was used for the ring opening of the epoxide. The resulting amino alcohol would then immediately undergo cyclization to form the azaindole. The reactions were performed using a 1:2 molar ratio of epoxide **44** to amine **45a**, **b**, or **c** in 1-butanol, presumably forming amino alcohols **46** (**Scheme 17**). The reaction time was varied according to the amine used. The reactions were run in sealed pressure tubes at 100 - 120 °C. The yields of azaindole **47** ranged from 60% - 90%. The formation of 7-azaindoles shows that the aminolysis of epoxide must be proceeding through an S_N2 pathway.

Scheme 17

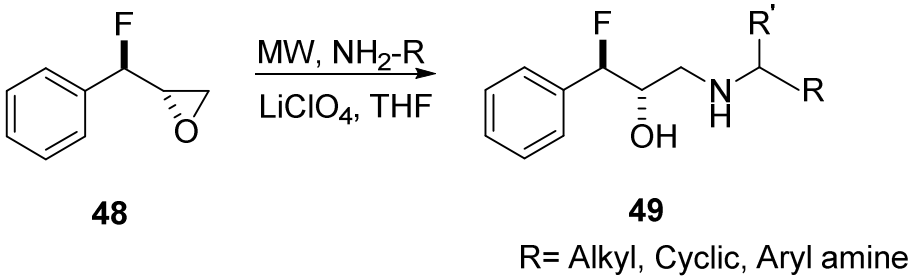


44 **45a-c** **46** **47**

Pericas has used α-chiral primary amines for ring openings of enantiopure fluoroepoxides [51]. In these reactions, $LiClO_4$ was used as a promoter. The mixture of primary amines (0.371 mmol), enantiopure terminal epoxide **48** (0.530 mmol, 1.4 eq), and 10 eq of $LiClO_4$ (5.20 mmol) in THF solution was irradiated for 90 minutes at 75 °C.

The reaction pathway favored attack at the less hindered carbon (**Scheme 18**). The overall yields of amino alcohols **49** ranged from 50% - 92%. Lower yields were observed when an amine with a long hydrocarbon chain was used. No obvious reason for this decrease in yield was evident.

Scheme 18

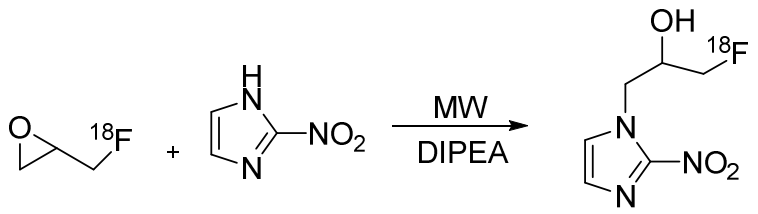


48 **49**

R= Alkyl, Cyclic, Aryl amine

Patients with suspected myocardial infarction can be identified by determining the amount of ischemic tissue present. To quantify these tissues, (^{18}F) fluoromisonidazole is used with positron emission tomography. Welch has described a flexible and fast synthesis of (^{18}F) fluoromisonidazole using microwave irradiation [52]. A solution of epi-(^{18}F) fluorohydrin (**50**) in DMSO was treated with 2-nitroimidazole (**51**) (0.0130 mmol) and 15 µL of *N*,*N*-diisopropylethylamine. The reaction was run for 12 minutes at 500 watts. Amino alcohol **52** (**Scheme 19**) was obtained as a single regioisomer in 65% yield via the S_N2 pathway.

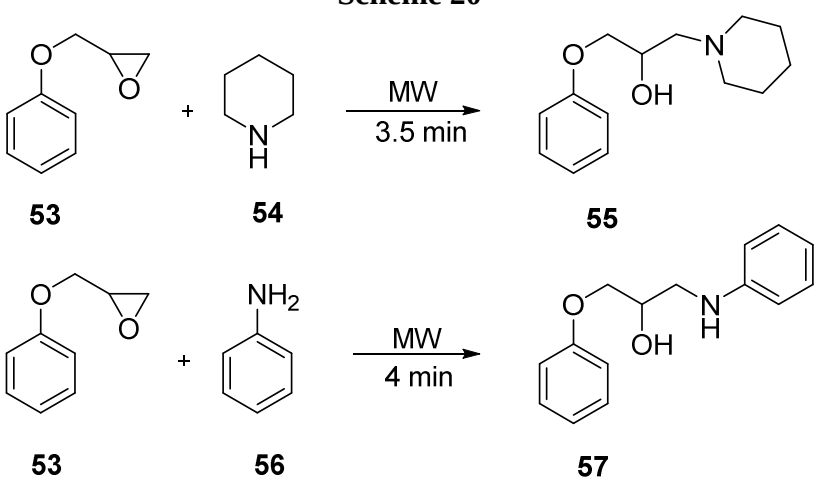
Scheme 19



50 **51** **52**

Gupta has reported microwave-assisted aminolyses of epoxides and compared these results with those from conventional heating methods [53]. The microwave reactions were run in open vessels at 210 watts. A mixture of 1,2-epoxy-3-phenoxypropane (**53**) (10 mmol) and piperidine (**54**) (15 mmol, 1.5 eq) in ethanol was irradiated for 3.5 minutes. Alcohol **55** (**Scheme 20**) was formed with an 87% yield. However, using the conventional heating for the same reaction required 5 hours to produce the same yield. When epoxide **53** was treated with MW for 4 minutes aniline (**56**), amino alcohol **57** was formed as the single isomer in 89% yield, indicating that a less nucleophilic amine could still produce a high yield of amino alcohol.

Scheme 20

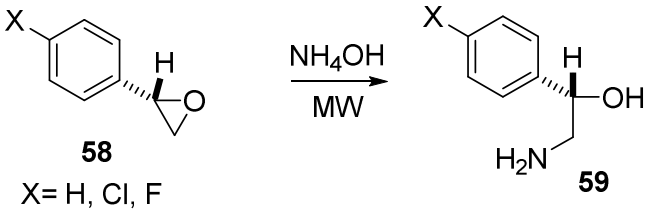


53 **54** **55**

53 **56** **57**

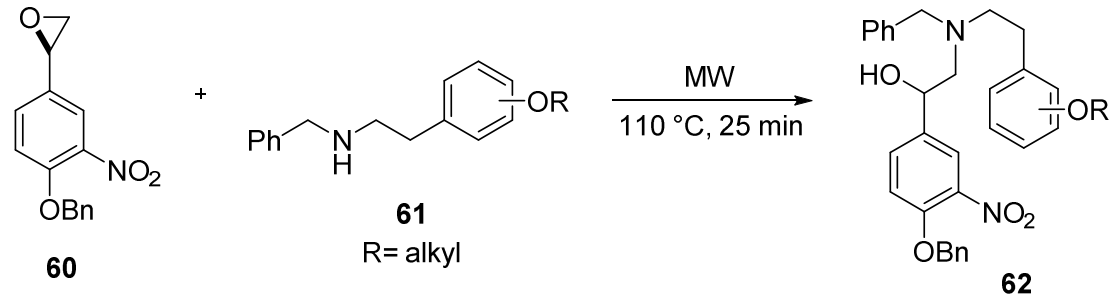
Sello has described an epoxide aminolysis to prepare enantiopure 2-aminoalcohols by using a household microwave [54]. Ammonium hydroxide was used as the nucleophile for aminolysis of substituted styrene oxides. A mixture of epoxide (0.15 mmol - 0.25 mmol) **57** and ammonium hydroxide (**58**) (90 mmol, 360 - 600 eq) was irradiated in a closed container from 6 to 20 minutes at 100 - 200 watts. The desired regioisomer **59** was obtained as the only product along with some unreacted starting material. The overall yields were 75% to 90%.

Scheme 21



Fairhurst has investigated the effect of increasing amino-substituted chain length on the β_2-adrenoceptor activity [55]. The author has compared the specific activity of different analogous on two agonists, formoterol and salmeterol. These two agonists play an important role as bronchodilators in the treatment of asthma and COPD. In this article, the analogue synthesis was done using microwave irradiation. Chiral epoxide **60** was irradiated with various substituted phenyl ethyl amines **61** at 110 °C for 25 minutes. Alcohols **62** were obtained with 63% to 92% yield, favoring the attack on the less hindered carbon (**Scheme 22**). Absolute or relative amounts of reactants were not given.

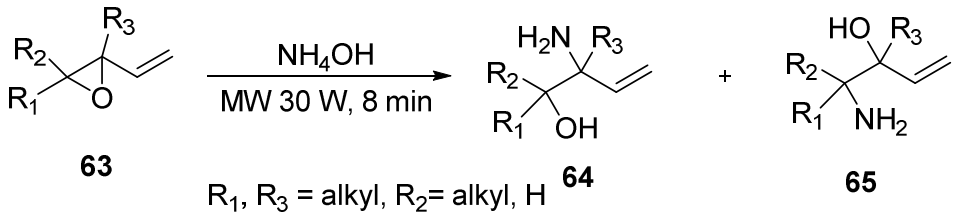
Scheme 22



Lindstrom has also described the aminolysis of vinyl epoxides using microwave irradiation [56]. The reaction was carried out by stirring di- and trisubstituted vinyl epoxides **63** (0.086 mmol) in NH_4OH (45 mmol, 523 eq) at 30 W for 8 - 16 minutes. The overall yields for alcohols **64** and **65** were 76% to 100% (**Scheme 23**). In all cases except when R_3 = alkyl, attack of ammonia occurred predominately at the allylic position to

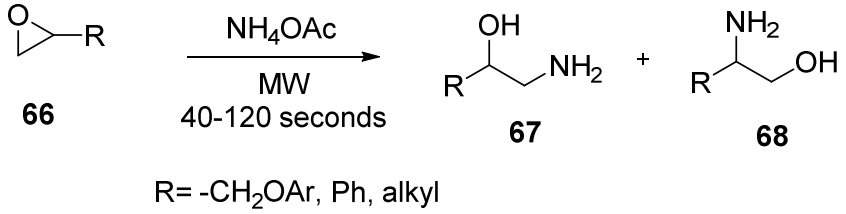
produce either exclusively or predominately amino alcohol **64**. The only exception to this selectivity was when R3 = alkyl, a 1:1 mixture of **64**:**65** was formed. For the reaction of (2S, 3S)-2,3-epoxy-1-heptene (R_1 and R_3 = H, R_2 = n-propyl) decreasing the microwave power increased the regioselectivity from 6:1 to 9:1 favoring amino alcohol **64**.

Scheme 23



Sabitha has used ammonium acetate in a neat aminolysis reaction for the formation of amino alcohols [57]. The reaction of epoxides **66** and ammonium acetate gave β-amino alcohols **67** as a major product, and, in some cases, a small to significant amount (2% to 25%) of regioisomeric amino alcohols **68** (**Scheme 24**). All reactions were run by irradiating a mixture of epoxide (10 mmol) and NH_4OAc (15 mmol, 1.5 eq) in a household microwave oven at 600 watts, with yields ranging from 65% to 83%.

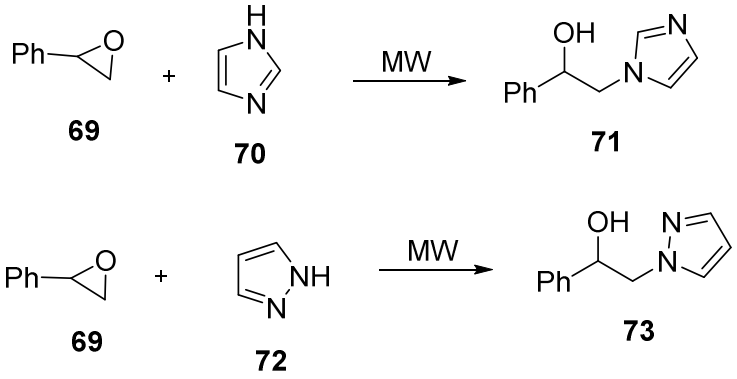
Scheme 24



Thiel has described the aminolysis of styrene oxide (**69**) with imidazole (**70**) or pyrazole (**72**) using microwave irradiation (**Scheme 25**) [58]. The microwave reactions were performed without solvent using a 1:1 molar ratio of amine to epoxide. The reaction using imidazole was stirred for 3 minutes in a pressure tube at 360 watts. Amino alcohol

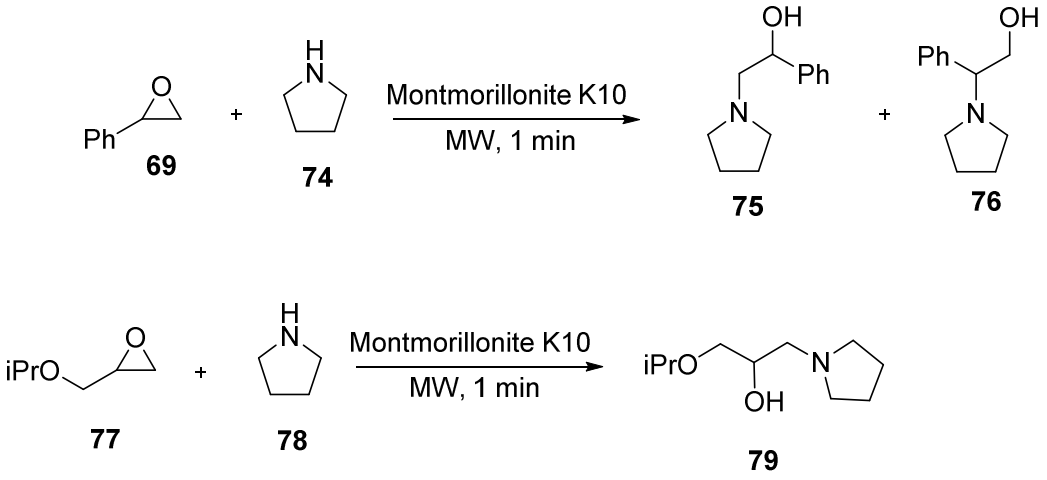
71 was obtained in 90% yield with only a trace amount of the regioisomeric amino alcohol according to GC-MS analysis of the reaction mixture. The aminolysis using pyrazole **72** required 6 minutes of irradiation time for complete conversion, giving amino alcohol **73** in 88% yield.

Scheme 25



Epoxide aminolysis has also been performed using Montmorillonite K10 clay as a promoter in a solvent-free, microwave-assisted reaction [59]. Reactions were carried out in a conventional microwave oven. For each reaction, a 1:1 molar ratio of epoxide to amine was mixed with 0.2 g K10 clay and then irradiated at 900 watts in an open vessel. The range of the amino alcohols yields was from 25% to 91%. In the case of the reaction of pyrrolidine (**74**) with styrene oxide (**69**), a 69% yield was obtained, but with only 2.9:1 selectivity favoring amino alcohol **75**, arising from attack at the less hindered position rather than the benzylic position (**Scheme 26**). By contrast, treatment of epoxide **77** with pyrrolidine (**74**) resulted in complete selectivity for amino alcohol **79** in 79% yield.

Scheme 26



V. Summary

The preceding review of epoxide aminolysis examined uncatalyzed reactions, reactions that required Lewis acid catalysts or promoters, and microwave-assisted reactions (with and without catalysts or promoters). Aminolyses generally required large to very large excesses of amines or promoter and long reaction times. Some of the examples in the previous review required less than a 100% excess of amine, but several of these were performed with unhindered, mono-substituted epoxides and were microwave assisted [53, 57-59] or used an electron deficient epoxide [35]. Only two examples used the more hindered methylcyclohexene monoxide **28**, but both also required the addition of a promoter [43, 45]. Furthermore, the use of promoters has the potential to reduce selectivity via attack at the more hindered carbon, particularly when that carbon is activated [59] or when a poor nucleophile is used [43].

The research described in this thesis attempts to address these issues by reporting a microwave-assisted method that minimizes the use of excess amine whenever possible.

In addition, the use of promoters is avoided in an effort to maximize selectivity for reaction at the less hindered carbon of the epoxide.

Chapter 3: Results and Discussion

I. Introduction

β-amino alcohols are an important structural unit in a variety of biologically active natural products and synthetic molecules and have been used as chiral building blocks in a variety of asymmetric synthesis [1]. One common method to synthesize β-amino alcohols is aminolysis of epoxides. The ring opening of the epoxides can be done via the S_N1 or the S_N2 pathway depending upon the nucleophilic attack at the less/more hindered carbon. Common problems with epoxide aminolysis are that the reaction requires an extended reaction time, an excess of amine, and can result in the formation of regioisomeric amino alcohols. We describe here our efforts to address these issues by developing a microwave assisted aminolysis for both hindered and unhindered epoxides that minimizes the use of excess amine whenever possible. The epoxides used in the investigation were 2,3-epoxy-2-methylbutane (**1**), methylvinyl oxirane (**2**), styrene oxide (**3**), and 2,3-epoxypropyl benzene (**4**) (**Figure 7**). We have used primary and secondary amines for aminolysis including benzylamine (**5**), aniline (**6**), piperidine (**7**), imadazole (**8**), and diphenylmethylamine (**9**) (**Figure 7**).

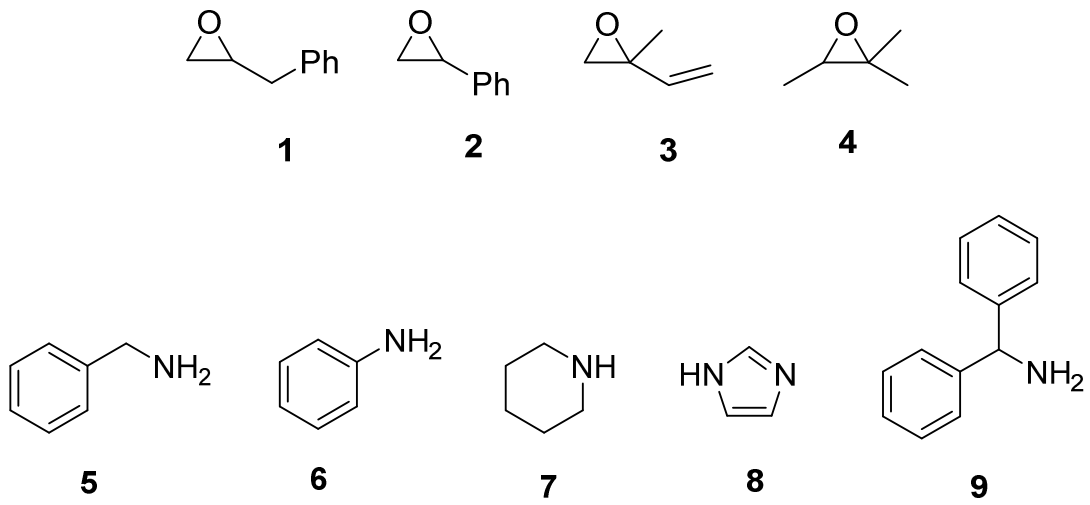


Figure 7. Epoxides and amines examined in the aminolysis.

II. Aminolysis of 2,3-epoxypropyl benzene

To test the efficacy of microwave-assisted epoxide aminolysis, we began by examining the aminolysis of (2,3-epoxypropyl) benzene (**1**) using several amines that were chosen according to their varied nucleophilicity (reactions performed by H. Lindsay [60], **Scheme 1**).

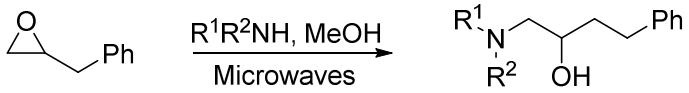
A mixture of epoxide **1**, piperidine (1 eq), and MeOH was irradiated using a 30 second ramp time and a 10 minute hold time. Amino alcohol **10a** was formed with excellent regioselectivity and in 95% yield (entry 1, **Table 2**). Only a trace of minor regioisomer was detectable by ^{1}H NMR analysis of the crude reaction mixture. Likewise amino alcohol **10b** was formed in 96% yield with complete regioselectivity (entry 2, **Table 2**).

However, when primary amines were used, significant bis-alkylation resulted (entries 3 and 5), which could not be mitigated by using milder microwave conditions.

Not surprisingly, doubling the molar equivalence of amine significantly reduced bis-alkylation (entries 4 and 6) and produced good yields of amino alcohols **10c** and **10d**.

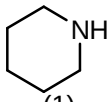
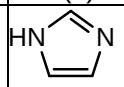
In summary, all four amines rapidly reacted to produce the corresponding secondary amino alcohols **10a**–**d** with excellent regioselectivity and good yields. Bis-alkylation that was observed in the reaction of primary amines could be eliminated by using an excess of amine. Purified yields for major isomers were between 82% and 96%. Only trace amounts of minor regioisomers were detectable by ^{1}H NMR analysis.

Scheme 1



1 **10**

Table 2. Microwave-assisted aminolysis of 2,3-epoxypropyl benzene .

Entry	*Amine (equiv)*	*Time (min)*	*Product, yield (%)*	*Temp (˚C) ave, range*	*Pressure (psi) ave, range*
1	 (1)	10	**10a** (95)	169, 145-182	234,148-245
2	 (1)	10	**10b** (96)	179, 175-180	246, 154-251
3	$BnNH_2$ (1)	20	**10c** (69)	148, 116-172	183, 81-196
4	$BnNH_2$ (2)	20	**10c** (82)	148, 116-172	98, 16-107
5	$PhNH_2$ (1)	60	**10d** (67)	157, 110-184	193, 118-201
6	$PhNH_2$ (2)	60	**10d** (86)	167, 108-207	126,29-151

III. Aminolysis of styrene oxide

Next we investigated the aminolysis of styrene epoxide **16** (**Scheme 2**, **Table 3**, reactions performed by H. Lindsay [60]), which has been used frequently as a substrate in

the development of Lewis acid-mediated aminolysis reactions [61]. Compared to our previous series of aminolyses, analogous reactions with styrene oxide (**2**) were less regioselective. However, some notable regioselectivity increases were observed when solvents were varied.

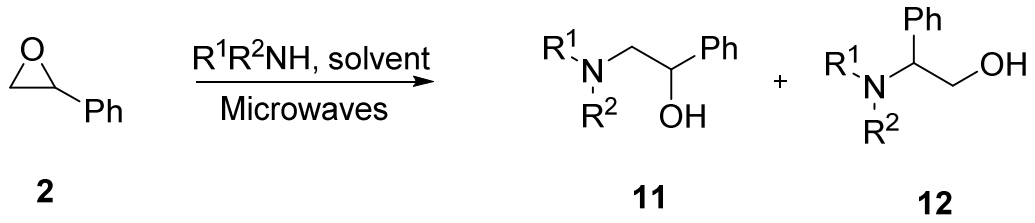
When methanol was used as a solvent, the selectivities for aminolysis using piperidine (entry 1), imidazole (entry 4) and benzylamine (entry 7) were modest, ranging from 3:1 to 3.5:1 in favor of alcohols **11a - c**. Changing the solvent to acetonitrile increased regioselectivity for the reaction of piperidine (entry 2), and slightly increased regioselectivity for imidazole (entry 5) and benzylamine (entry 8). Further decreasing the polarity of the solvent to that of toluene increased the selectivity for the piperidine reaction to 12:1 (entry 3), but did not improve epoxide aminolyses for reactions using imidazole and benzylamine (entries 6 and 9).

When aniline was used as a nucleophile for epoxide aminolysis in methanol, the reaction was unselective (entry 10). Changing the solvent to acetonitrile improved the selectivity to 2:1 favoring amino alcohol **11d** (entry 11), but no further improvement occurred when toluene was used as a solvent (entry 12).

Apart from the differences in solvent polarities that likely affect the rates and selectivities of the reactions, it is noteworthy that selectivities apparently varied in some cases due to the temperature and pressure of the reaction. For example, comparing the reaction conditions for the piperidine aminolysis in methanol, acetonitrile, and toluene reveals that the selectivity for alcohol **11a** increases with increasing temperature and decreasing pressure (entries 1 - 3). Whether this observation is coincidental is not obvious from the data. The increase in selectivity could simply be a result of change in solvent

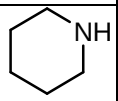
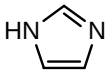
polarity. At any rate, this phenomenon is clearly nucleophile dependent as no increase in selectivity was observed when toluene was used as the solvent in the reaction of aniline with styrene oxide (**2**), in spite of the observed temperature increase and pressure decrease relative to these conditions when acetonitrile was used (entries 11 and 12).

Scheme 2



2 **11** **12**

Table 3. Microwave-assisted aminolysis of styrene oxide.

Entry	*Amine*	*Time (min)*	*Solvent*	*Product*	*Regioisomer ratio (yield, %)*	*Temp (˚C) ave, range*	*Pressure (psi) ave, range*
1		10	MeOH	**11a, 12a**	3.2:1 (87)	148, 136-154	158, 135-164
2		15	MeCN	**11a, 12a**	8.0:1 (84)	136, 89-149	54, 20-59
3		60	PhMe	**11a, 12a**	12:1 (83)	180, 73-207	45, 11-51
4		2	MeOH	**11b, 12b**	3.6:1 (81)	185, 178-190	248, 245-260
5		2	MeCN	**11b, 12b**	4.6:1 (83)	237, 207-247	231, 202-236
6		10	PhMe	**11b, 12b**	4.5:1 (84)	247, 217-251	120, 105-124
7	$BnNH_2$	10	MeOH	**11c, 12c**	3.2:1 (85)	152, 137-157	139, 110-142
8		15	MeCN	**11c, 12c**	4.5:1 (84)	138, 81-152	60, 22-68
9		25	PhMe	**11c, 12c**	4.6:1 (82)	157, 77-183	27, 3-37
10	$PhNH_2$	15	MeOH	**11d, 12d**	1:1.2 (79)	152, 121-165	108, 72-121
11		60	MeCN	**11d, 12d**	2.1:1 (82)	172, 87-200	75, 3-95
12		120	PhMe	**11d, 12d**	2.1:1 (81)	213, 91-234	55, 12-64

IV. Aminolysis of methylvinyl oxirane

To probe the regioselectivity in a more sterically biased system, we investigated the aminolysis of isoprene monoxide **3** (**Scheme 3**, **Table 4**). Microwave-assisted aminolysis of vinyl epoxides has been reported to be regioselective for substitution at the allylic carbon in sterically unbiased epoxides [49] and unselective in epoxides where a steric bias exists [56].

The investigation was again carried out using amines of varying nucleophile strengths of amine and in solvents of varying polarities. In all cases, a 1:1 molar ratio of amine to epoxide was used.

When the aminolysis was carried out in MeOH with strong nucleophiles, very good regioselectivity for alcohols **13a-d** was observed (entries 1, 3, 5, and 7). For the aminolysis using diphenylmethylamine in methanol, only a trace amount of the minor regioisomer **14d** was observed, presumably due to the bulk of the nucleophile (entry 7).

Switching to the aprotic solvent acetonitrile resulted in almost complete regioselectivity for alcohol **13a-c** (entries 2, 4, and 6). However, each of these reactions required significantly longer reaction times to obtain comparable yields to the reactions performed in methanol. These slower reactions could be due to the lower dielectric loss of acetonitrile (2.3) versus that of methanol (21.5), the differences in solvent boiling points which led to significantly lower reaction pressures in the acetonitrile reactions, or some combination of the two factors.

The aminolysis using the poorer nucleophile aniline again resulted in the poorest selectivity (entry 8). Changing the solvent to acetonitrile improved the selectivity to

4.2:1 favoring regioisomer **13e** but at the expense of conversion. Only 51% purified yield was obtained after a reaction time of six hours (entry 9).

Scheme 3

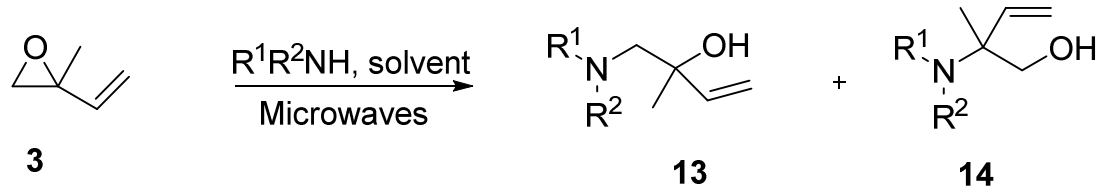
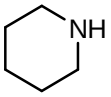
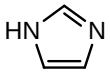


Table 4. Microwave-assisted aminolysis of methylvinyl oxirane.

Entry	*Amine (equiv)*	*Time (min)*	*Solvent*	*Products*	*Regioisomer ratio (yield, %)*	*Temp (˚C) ave, range*	*Pressure (psi) ave, range*
1		30	MeOH	**13a,14a**	16:1 (99)	145, 118-161	126,91-144
2		90	MeCN	**13a, 14a**	>50:1 (99)	163, 75-190	89, 26-106
3		20	MeOH	**13b, 14b**	18:1 (97)	193, 199-205	189, 172-237
4		**30**	MeCN	**13b, 14b**	>50:1 (96)	183, 131-198	118, 70-131
5	$BnNH_2$	10	MeOH	**13c, 14c**	13:1 (83)	146, 111-164	130, 81-154
6		150	MeCN	**13c, 14c**	30:1 (85)	191, 111-194	57, 23-67
7	PH_2CHNH_2	40	MeOH	**13d, 14d**	>50:1 (88)	169, 125-194	151, 96-182
8	$PhNH_2$	60	MeOH	**13e, 14e**	2.1:1 (87)	165, 116-187	146,81-179
9		360	MeCN	**13e, 14e**	4.2:1 (51)	207, 105-228	121, 29-136

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

Very few Lewis acid-promoted aminolyses have been performed using trisubstituted epoxides, and in most cases the yields were modest, the reactions required at least 24 hours reaction time, and/or required significant excesses of amine [43, 44, 62 - 64]. With regard to microwave-assisted aminolyses of trisubstituted epoxides, those reported procedures are limited to reactions using excess NH_4OH [30, 32].

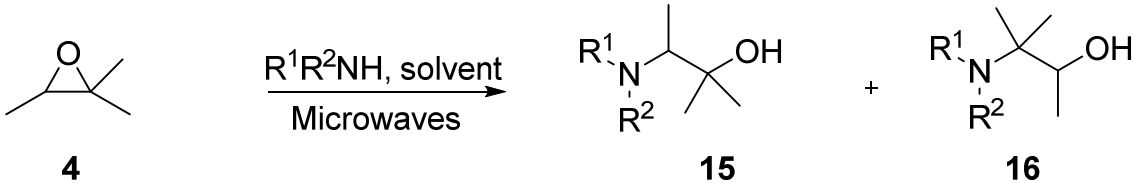
In contrast to those results, we have synthesized amino alcohols **15a - d** from epoxymethylbutane **4** by using a 1:1 molar ratio of epoxide to amine (**Scheme 4**). Once

again, reactions were performed using amine nucleophiles of varying strengths and in solvents with varying boiling points and microwave absorbing properties.

Using methanol as a solvent, the aminolysis of epoxide **4** with piperidine, imidazole, and benzylamine produced amino alcohols **14a - c**, respectively with good regioselectivity and in good yields (entries 1, 3, and 5, **Table 5**). Unfortunately, our attempts to increase the regioselectivity by using acetonitrile as solvent either resulted in no change in selectivity (entry 4) or in low conversions after somewhat lengthy microwave irradiations (entries 2 and 6).

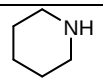
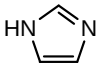
As in previously described aminolyses using aniline as a nucleophile, selectivity was significantly lower than when stronger nucleophiles were used (entry 7). Attempts at using acetonitrile to improve the regioselectivity resulted in no reaction (entry 8).

Scheme 4



4 **15** **16**

Table 5. Microwave-assisted aminolysis of 2,3-epoxy-2-methylbutane .

Entry	*Amine*	*Time (min)*	*Solvent*	*Products*	*Regioisomer ratio (yield, %)*	*Temp (°C) ave, range*	*Pressure (psi) ave, range*
1		60	MeOH	**15a, 16a**	9.8:1 (70)	200, 153-214	234,148-245
2		360	MeCN	**15a, 16a**	14:1 (29)	177, 77-190	99, 24-106
3		30	MeOH	**15b, 16b**	6.5:1 (84)	175, 137-182	246, 154-251
4		120	MeCN	**15b, 16b**	6.5:1 (84)	256, 162-269	211, 97-230
5	$BnNH_2$	240	MeOH	**15c, 16c**	7.5:1 (82)	183, 114-193	183, 81-196
6		300	MeCN	**15c, 16c**	9.2:1 (19)	186, 64-195	98, 16-107
7	$PhNH_2$	300	MeOH	**15d, 16d**	3.1:1 (64)	182, 142-189	193, 118-201
8		300	MeCN	**15d, 16d**	no reaction	213, 105-234	126,29-151

VI. Conclusions

Based on the results obtained in our lab, we conclude that it is feasible to use microwave-assisted epoxide aminolysis as a method for the regioselective formation of β-amino alcohols. In addition, this procedure serves as a viable alternative to Lewis acid-mediated aminolysis procedures. The results described above show that this procedure has several advantages over those previously reported in the literature such as shorter reaction times, little to no required excess amine, predictable regioselectivity resulting from nucleophilic attack at the less hindered carbon of the epoxide, and reliably good

yields. In some cases, regioselectivity could be improved by decreasing the polarity of the solvent. In addition, the procedure works for even the most hindered, trisubstituted epoxides. Very few procedures for reactions of these hindered epoxides have been reported, and those involved Lewis acid promotion or used large excesses of ammonia as a nucleophile. One important question is whether microwave energy is required for these reactions or if the reactions can be carried out in a sealed tube in an oil bath. Preliminary results from our lab suggest that oil bath reactions could be as successful [60], but further investigation is needed to make a conclusion as to whether the source of heat is important.

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 [60]. Piperidine, aniline, and benzylamine were distilled from KOH prior to use. Purification of the compounds by flash chromatography was performed using silica gel (40 - 75 mm particle size, 60 Å pore size). TLC analyses were performed on silica gel 60 F254 plates (250 mm thickness). All ^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz instrument and chemical shifts (δ) reported relative to residual solvent peak $CDCl_3$. All NMR spectra were obtained at room temperature. IR spectra were obtained using a Nicolet Impact 410 FT-IR spectrometer. EI and electrospray mass spectrometry were performed using a Micromass AutoSpec mass spectrometer. Microwave-assisted reactions were performed using a CEM Discover™ reactor. Pressure was monitored using an IntelliVent™ external pressure monitor. Temperature was monitored using an on-board infrared temperature sensor unless otherwise noted. Microwave reactor vials and caps were purchased from CEM Corporation. ^{1}H NMR and ^{13}C NMR chemical shifts were in agreement with those published for known compounds **13c** [41] and **13e** [67].

II. General procedure for microwave-assisted epoxide aminolyses

To a 10 mL microwave reactor vial equipped with a magnetic stir bar were 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 °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.

2-Methyl-1-piperidin-1-yl-3-buten-2-ol (13a). According to the general procedure, acetonitrile (0.5 mL), piperidine (0.17 g, 2.0 mmol), and isoprene monoxide (**9**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 90 minute hold time. Chromatography using diethyl ether-hexanes (50:50, v/v) afforded the title compound as a pale yellow liquid (0.335 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.4 Hz, 10.5, Hz, 1H), 5.30 (d, *J* = 17.4 Hz, 1H), 4.99 (d, *J* = 10.5 Hz, 1H), 2.62, (m, 2H), 2.42 (d, *J* = 13.3 Hz, 1H), 2.41 (m, 2H), 2.29 (d, *J* = 13.3 Hz, 1H), 1.52 (m, 4H), 1.39 (m, 2H), 1.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 111.7, 70.8, 68.3, 56.6, 26.9, 26.4, 24.0.

IR (thin film) υ 3117, 2932 cm^{-1}.

Electrospray HRMS calcd for $C_{10}H_{19}NO$ [$M+H^+$] 170.1545; found 170.1545.

1-Imidazol-1-yl-2-methyl-3-buten-2-ol (13b). According to the general procedure, acetonitrile (0.5 mL), imidazole (0.14 g, 2.0 mmol), and isoprene monoxide (**9**) (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 (0.292 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 6.91 (s, 2H), 5.89 (dd, *J* = 17.4 Hz, 11.0 Hz, 1H), 5.30, (d, *J* = 17.4 Hz, 1H), 5.15 (d, *J* = 11.0 Hz, 1H), 3.89 (s, 2H), 1.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 138.4, 128.6, 120.7, 114.9, 72.7, 56.9, 25.4.

IR (thin film) υ 3269, 1642, 1511 cm^{-1}.

EI-HRMS calcd for $C_8H_{12}N_2O$ [M^+] 152.0949; found 152.0951.

1-Benzylamino-2-methyl-3-buten-2-ol (13c) [41]. According to the general procedure, acetonitrile (0.5 mL), benzylamine (0.21 g, 2.0 mmol), and isoprene monoxide (**9**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 150 minute hold time. Chromatography using EtOAc-MeOH (50:50, v/v) afforded the title compound as a pale yellow liquid (0.325 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5 H), 5.80 (dd, *J* = 17.0 Hz, 10.5 Hz, 1H), 5.31 (d, *J* = 17.0 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 2H), 2.71 (d, *J* = 11.5 Hz, 1H), 2.51 (d, *J* = 11.5 Hz, 1H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.2, 128.6, 128.1, 127.2, 113.3, 71.8, 58.1, 54.1, 25.9.

1-(Benzhydryl-amino)-2-methyl-3-buten-2-ol (13d). According to the general procedure, MeOH (0.5 mL), diphenylmethylamine (0.37 g, 2.0 mmol), and isoprene monoxide (**9**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 40 minute hold time. Chromatography using hexanes-EtOAc (85:15, v/v) afforded the title compound as a pale yellow liquid (0.471 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 10H), 5.81 (dd, *J* = 17.4 Hz, 10.5 Hz, 1H), 5.34 (d, *J* = 17.4 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 4.82 (s, 1H), 3.43 (br s, NH), 2.64 (d, *J* = 11.4 Hz, 1H), 2.50 (d, *J* = 11.4 Hz, 1H), 1.72 (br s, OH), 1.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.8, 143.4, 128.7, 128.6, 127.4, 127.3, 127.2 (2C), 113.5, 72.1, 67.1, 57.0, 25.9. IR (thin film) υ 3453, 1646, 1495 cm^{-1}.

Electrospray HRMS calcd for $C_{18}H_{21}NO$ [M+Na^+] 290.1521; found 290.1510.

2-Methyl-1-phenylamino-3-buten-2-ol (13e) [67]. According to the general procedure, acetonitrile (0.5 mL), aniline (0.19 g, 2.0 mmol), and isoprene monoxide (**9**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 360 minute hold time. Chromatography using hexanes-EtOAc (70:30, v/v) afforded the title compound as a pale yellow liquid (0.181 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 2 H), 5.94 (dd, *J* = 17.4 Hz, 10.5 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 3.77 (br s, NH), 3.22 (d, *J* = 12.4 Hz, 1H), 3.12 (d, *J* = 12.4 Hz, 1H), 2.19 (br s, OH) 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 143.0, 129.4, 118.2, 114.0, 113.6, 73.0, 53.8, 26.0.

2-Methyl-3-piperidin-1-yl-2-butanol (15a). According to the general procedure, methanol (0.5 mL), piperidine (0.17 g, 2.0 mmol), and epoxymethylbutane (**12**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 60 minute hold time. Chromatography using EtOAc-MeOH (80:20, v/v) afforded the title compound as a pale yellow liquid (0.240 g, 70%, mixture of regioisomers). ^{1}H NMR for **13a** (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.

3-Imidazol-1-yl-2-methyl-2-butanol (15b). According to the general procedure, methanol (0.5 mL), imidazole (0.14 g, 2.0 mmol), and epoxymethylbutane (**12**) (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 (0.259 g, 84%). ^{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.

3-Benzylamino-2-methyl-2-butanol (15c). According to the general procedure, methanol (0.5 mL), benzylamine (0.21 g, 2.0 mmol), and epoxymethylbutane (**12**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 240 minute hold time. Chromatography using EtOAc-MeOH (50:50, v/v) afforded the title compound as a pale yellow liquid (0.317 g, 82%). ^{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.

2-Methyl-3-phenylamino-2-butanol (15d). According to the general procedure, methanol (0.5 mL), aniline (0.19 g, 2.0 mmol), and epoxymethylbutane (**12**) (0.17 g, 2.0 mmol) were reacted using a 30 second ramp time and a 360 minute hold time. Chromatography using hexanes-EtOAc (70:30, v/v) afforded the title compound as a pale yellow liquid (0.229 g, 64%). ^{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.

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