CHAPTER I

INTRODUCTION

1.1 Vicinal amino alcohols

Vicinal amino alcohols are one of the most interesting classes of bifunctional compounds. They have been playing many important roles in synthetic pharmacologically active molecules, in biologically active natural products, and as chiral auxiliaries or ligands in asymmetric syntheses.[1] They are building blocks of many pharmaceutical active compounds. For example, the amino alcohol **(1)** obtained from the epoxide **(2)** is an important intermediate for a synthesis of an important HIV-protease inhibitor, Saquinavir **(3)** (Figure 1.1).[2]

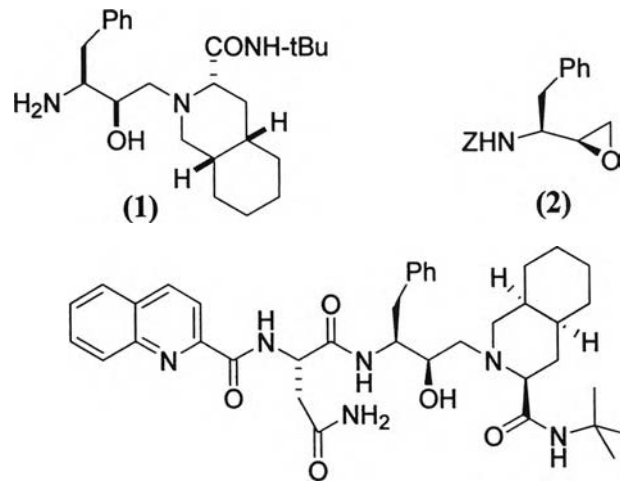


Figure 1.1. Synthetic molecules containing vicinal amino alcohols

Recently, the amino alcohol **(4a)** (Figure 1.2) has been reported to selectively interact with RNA. This molecule as a mixture of diastereomers was discovered during a random screening of commercially available amino alcohols as an anti HIV agent.[1,2] Another important amino alcohol derivative is amprenavir **(4b)**, a second generation HIV protease inhibitor with a number of clinical advantages (Figure 1.2).[3]

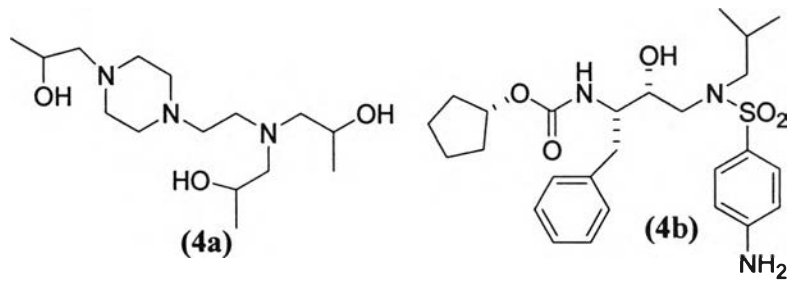
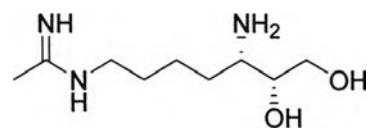


Figure 1.2. Aminol: selectively interact with RNA

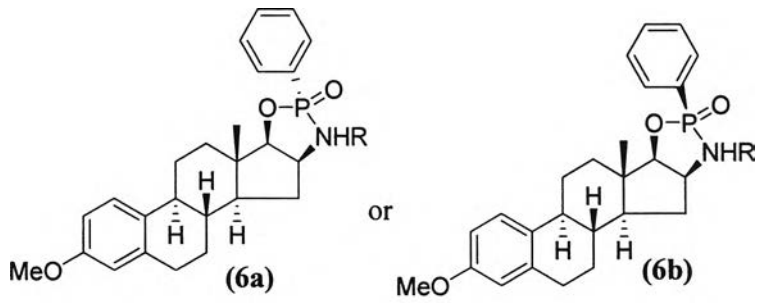
An acetamidine lysine derivative **(5)** shown in Figure 1.3 was reported to be an selective inhibitor of nitric oxide synthetase (iNOS) that has been shown to suppress the increase in plasma nitrites and joint inflammation associated with adjuvant arthritis.[1,4]



(5)

Figure 1.3. *N*-(5(*S*)-amino-6,7-dihydroxyheptyl)ethanimidamide dihydrochloride: nitric oxide synthetase inhibitor

Oxazaphosphorinanes **(6a, 6b)** are of special interest, since cyclophosphamide, one of the most potent drugs in the treatment of human cancers, contains this type of heterocyclic ring. These two diastereomers were synthesized from their precursors, benzyl or *n*-propyl-substituted aminoalcohols.[5]



(6a, 6b) R = Bn or *n*-Pr

Figure 1.4. Diastereomers of oxazaphosphorinanes (**6a** and **6b**)

Another well-known example for biologically active natural product is bestatin **(7a)** which is a *syn*-α-hydroxy-β-amino acid.[6] This is an aminopeptidase inhibitor that exhibits immunomodulatory activity and is used clinically as an adjuvant in cancer chemotherapy.[1] Many of the lipids or lipid-like molecules are made up of the vicinal amino alcohol moiety such as myriocin **(7b)**, isolated from the thermophilic ascomycete *M. albomyces* and used as potent immunostimulatory agents.[7] Another group of the amino alcohols is the cyclic amino alcohols in which the amino group of the vicinal amino alcohol is contained within a ring like anisomycin **(7c)**. It is the pyrrolidine amino alcohol that was obtained from extracts of a *streptomyces sp.* This cyclic amino alcohol is a potent inhibitor of protein biosynthesis useful as an anticancer agent.[8] The structure of these compounds are shown in Figure 1.5.[1]

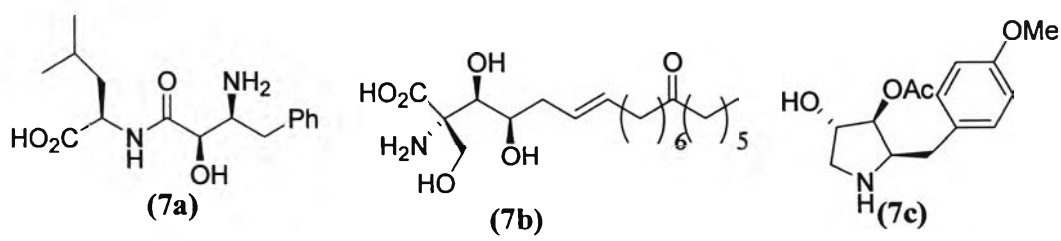
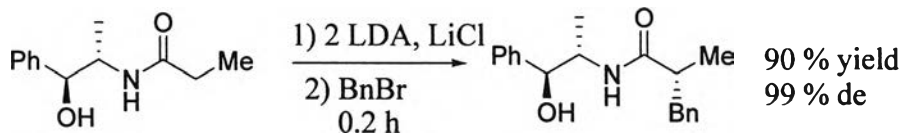


Figure 1.5. bestatin (**7a**), myriocin (**7b**), and anisomycin (**7c**)

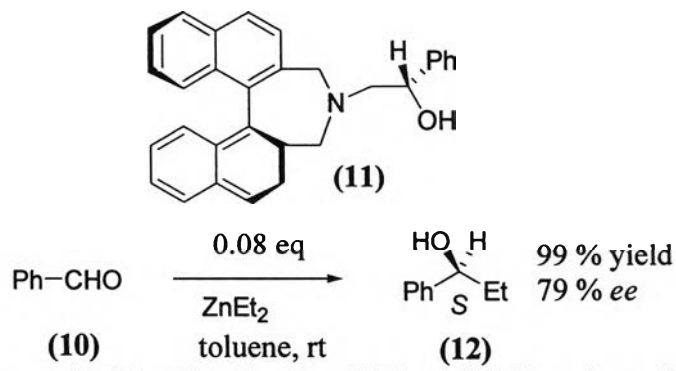
As a chiral auxiliary, pseudoephedrine is highly effective and very practical for the asymmetric alkylation of carboxamides. Treatment of either enantiomer of pseudoephedrine with carboxylic acid chlorides and anhydrides leads to efficient and selective *N*-acylation to form the corresponding tertiary amide derivatives. Diastereoselective alkylation of pseudoephedrine amides is accomplished by dianion formation with lithium diisopropylamide in tetrahydrofuran (THF) in the presence of lithium chloride, followed by the addition of an alkylating agent as shown in Figure 1.6.[9]



(8) **(9)**

Figure 1.6. Asymmetric alkylation of carboxamides

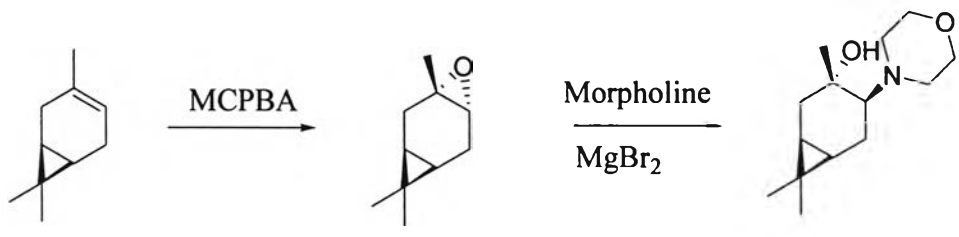
A number of asymmetric syntheses utilize enantiomerically pure amino alcohols as chiral ligands or chiral auxiliaries. For example, an enantiopure 1,2-aminoalcohol **(11)** having 1,1'-binaphthylazepine skeleton was tested as a chiral catalyst in an enantioselective addition of $ZnEt_2$ to benzaldehyde in Figure 1.7.[10]



(10) **(12)**

Figure 1.7. Enantioselective addition of $ZnEt_2$ to benzaldehyde

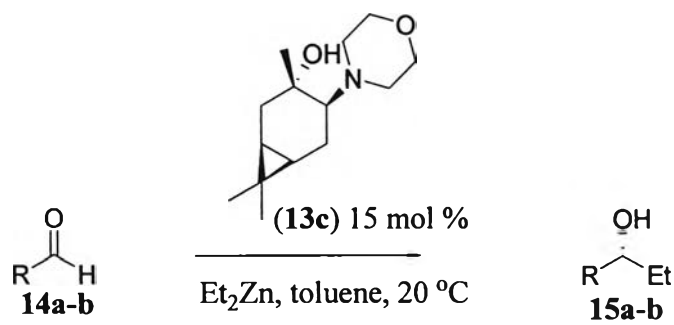
A (+)-3-carene derived aminoalcohol was successfully used as a chiral ligand in the catalytic enantioselective diethylzinc addition to various aldehydes. Figure 1.8 shows the synthesis of this vicinal aminoalcohol in two steps, and Figure 1.9 also illustrates the use of (1*S*,3*S*,4*S*,6*R*)-4-amino-3-caranol **(13c)** as chiral catalyst in the enantioselective addition of diethylzinc to aldehydes to achieve 98 % *ee* of 1-(2-methoxyphenyl)-1-propanol **(15b)**.[11]



(+)-3-Carene (**13a**) 80 % yield (**13b**) 60 % yield (**13c**)

Figure 1.8. Preparation of (1*S*,3*S*,4*S*,6*R*)-4-amino-3-caranol **(13c)**

Table 1.1. Enantioselective addition of diethylzinc to aldehydes catalyzed by β-amino alcohol **(13c)**



entry	aldehydes	products	% yield[a]	% *ee*	Config.[b]
1	Benzaldehyde (**14a**)	**15a**	68	81	(*R*)-(+)
2	*o*-Methoxybenzaldehyde (**14b**)	**15b**	76	98	(*R*)-(+)

[a] Isolated yield; [b] determined by comparison of specific rotation with literature value

Another novel example to use vicinal amino alcohol derivative in a direct catalytic asymmetric Mannich-type reaction is shown in Figure 1.9. The reaction of hydroxyacetophenone **(16)** and glyoxalate imine **(17)** with dinuclear zinc catalyst **(18)** provided a derivative of amino alcohol, *syn*-amino alcohol **(19)**, with excellent enantioselectivity and diastereoselectivity (Figure 1.9).[12]

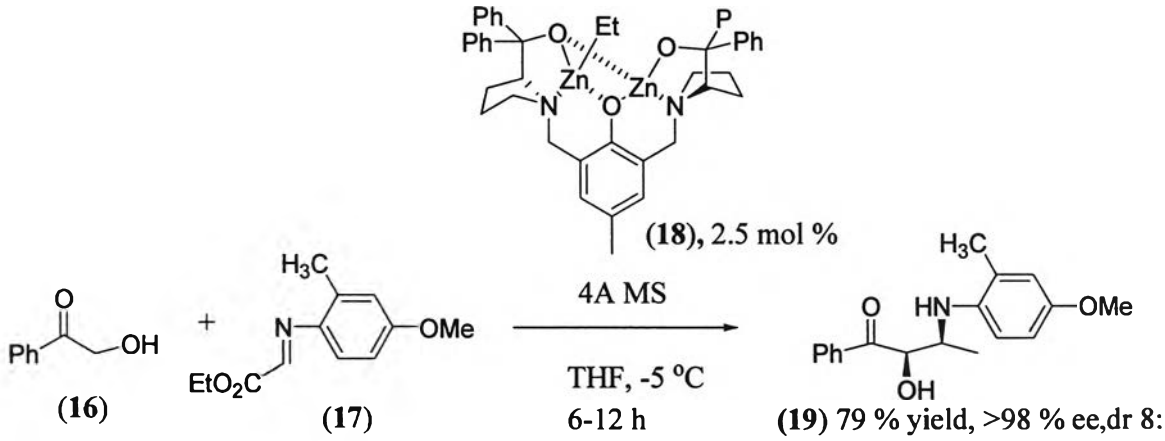


Figure 1.9. Catalytic asymmetric Mannich-type reaction to *syn*-amino alcohol with dinuclear zinc catalyst

In addition, many highly enantioselective diethylzinc addition to imines employ chiral amino alcohol ligand as well. For example, diethylzinc addition to *N*-diphenylphosphinoyl benzaldimine **(20)** in the presence of the chiral amino alcohol **(21)** at stoichiometric amount afforded the product **(22)** with excellent yield and *ee* (Figure 1.10).[13]

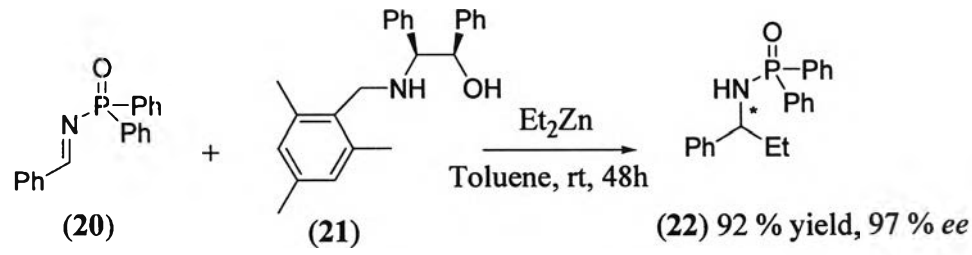


Figure 1.10. Asymmetric diethylzinc addition to imine **(20)** in the presence of a chiral amino alcohol **(21)**

1.2 Synthetic routes to vicinal amino alcohols

Conceptually one can divide vicinal amino alcohols into four different classes as shown in Figure 1.11: (1) addition of one heteroatom to a molecule which already contains one heteroatom; (2) addition of both heteroatoms to a molecule which has neither *eg.* by aminohydroxylations; (3) coupling of two molecules, each of which has one heteroatom; (4) functional group manipulation of a molecule containing both heteroatoms.[1]

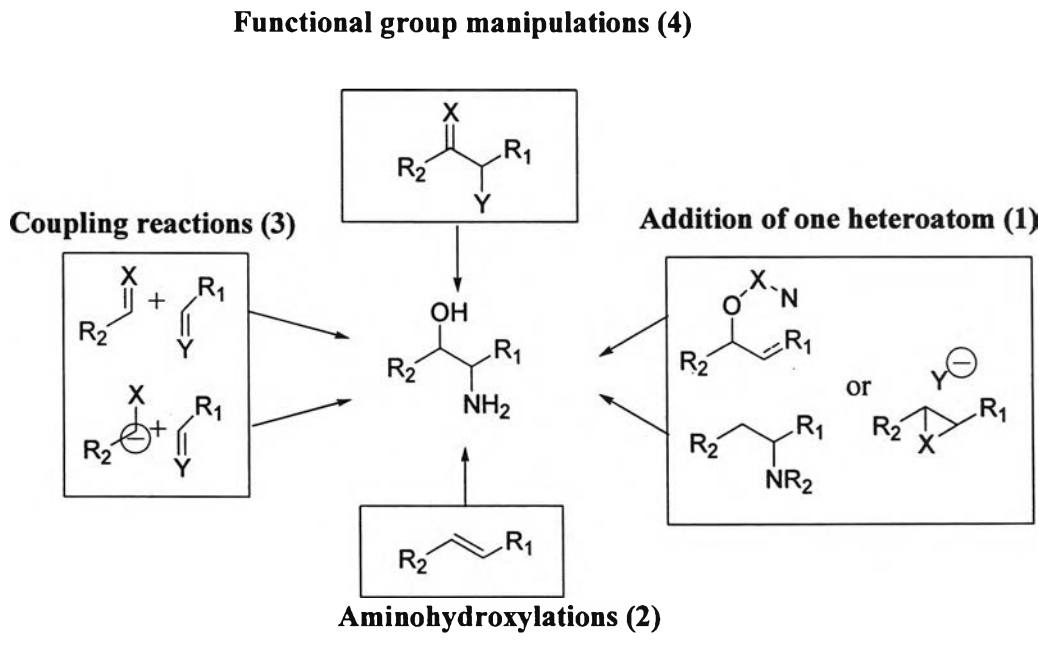
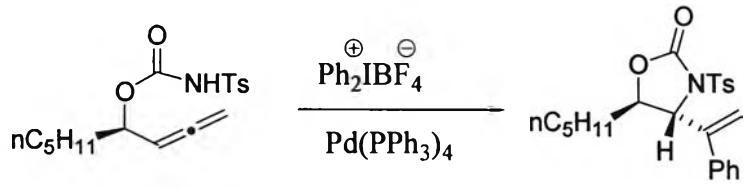


Figure 1.11. General disconnections for the synthesis of vicinal amino alcohols

1.2.1 Addition of one heteroatom

There are a number of methods by which one heteroatom can be added to a molecule already containing a heteroatom. These routes rely on the stereochemistry of the resident heteroatom to control or direct the stereochemistry of the incoming heteroatom. (a) Addition of nitrogen is a method that employs the intramolecular addition of nitrogen to an electrophilic carbon, typically olefin activated by an electrophilic agent.

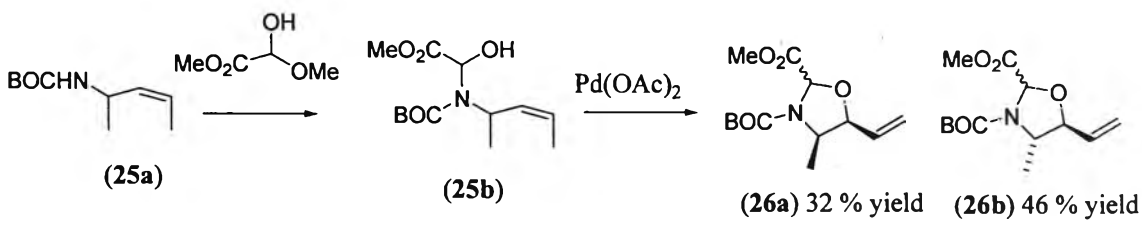
For example, the intramolecular cyclization of the allenyl carbamate **(23)** with an aryliodonium salt and a palladium catalyst provides oxalidinone **(24)** (Figure 1.12).[14]



(23) **(24)**, 71 % yield

Figure 1.12. Intramolecular cyclization of the allenyl carbamate **(23)**

(b) Addition of oxygen is the method that adds the oxygen to a molecule already containing nitrogen. For example, the intramolecular reaction of a hemiaminal **(25b)** treated with $Pd(OAc)_2$ can provide a mixture of oxazolidines **(26a)** and **(26b)** *via* addition of its nitrogen counterpart to an olefin side chain of the molecule in fair yield (Figure 1.13). The diastereoselectivity of the reaction was not good.[15]



(25a) **(25b)** **(26a)** 32 % yield **(26b)** 46 % yield

Figure 1.13. Intramolecular reaction of a hemiaminal **(25b)** to oxazolidines **(26a, b)**

(c) Another possibility is to carry out an aziridine ring opening with a heteroatom nucleophile to provide the amino alcohol. The reactions of aziridines with oxygen nucleophiles have been widely applied by making use of a somewhat strained bicyclic aziridines. The aziridine ring can be opened with water, alcohols, and carboxylic acids.[16-20] A major limitation of this route to vicinal amino alcohols is the relative dearth of methods to prepare aziridines. In fact, aziridines are usually obtained from amino alcohols. There has been the work reported for the diastereoselective or enantioselective

synthesis of aziridines.[6,21,22] As with the upcoming epoxide opening reactions, the regioselectivity of the ring opening can sometimes be problematic when non-terminal aziridines are used.

d) For ring opening reactions of epoxides the synthesis of amino alcohols by epoxide ring opening has been exploited extensively in recent years.[23] This is no doubt due to the many available methods for the synthesis of optically pure epoxides from olefins.[24] The chemical characteristics of the epoxides, particularly the ring strain due to their triangular structure, which has to be 60° instead of the ideal tetrahedral angle of 109° at the sp^3 carbon and the high polarization of the C-O bonds contribute to their reactivity towards many kinds of reagents such as electrophiles,[25] nucleophiles,[26] acids,[27] bases,[27] reducing agents, and oxidizing agents.[28] This method has a potential to provide a variety of derivatives of vicinal amino alcohols depending on types of epoxides and nucleophiles used. Furthermore, by choosing a condition to control the regioselectivity of the ring opening, two products may be obtained from only one set of starting materials. Ring opening of optically active epoxides is usually stereospecific. Notwithstandingly, a viable problem with this route to vicinal amino alcohols has been the issue of regioselectivity; that is, either carbon of the epoxide can react with the nucleophile to produce regioisomeric amino alcohols, *eg.* in azidolysis[29] or aminolysis.[30] In particular, the regioselectivity in azidolysis and aminolysis of styrene oxide has been known to be notoriously low.[29,31] As a consequence, this incentive brings about the potential improvement of developing conditions on controlling the regioselectivity and stereoselectivity of epoxides, especially styrene oxide with nitrogen nucleophiles. The

study of the development on the ring opening of the epoxides with the nitrogen nucleophiles will be reviewed in details in the next section.

1.2.2 Aminohydroxylation reactions

The hydroxyamination reaction of an olefin is a way in which both nitrogen and oxygen are added in a single reaction. Two general methods exist for such a transformation. The first is the sequential addition of nitrogen followed by oxygen addition. For example, the addition of a chiral amide anion **(28a)** to an α,β-unsaturated ester **(27)** is followed by trapping of the resulting enolate with an oxygen electrophile **(28b)** to produce the amino alcohol **(29)** (Figure 1.14).[1] Even if an excellent diastereoselectivity has been obtained, its limitation is that only one out of the two possible regioisomers has been obtained.

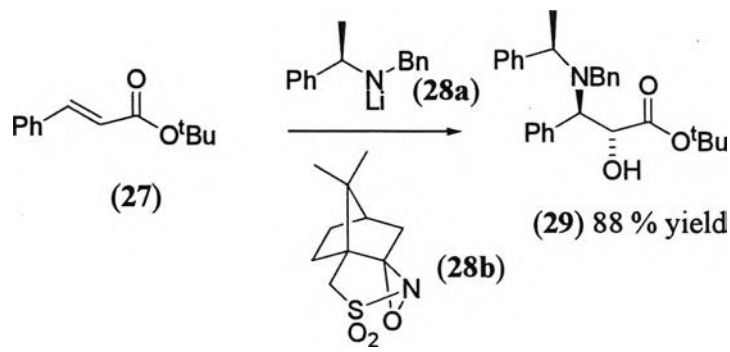


Figure 1.14. Preparation of the amino alcohol **(29)** by two sequential steps

The second method to carry out hydroxyamination is the metal catalyzed aminohydroxylation reaction studied by Sharpless.[32] The reaction used a chiral amine ligand to generate asymmetric addition of an amide and OH across a double bond. For example, in asymmetric aminohydroxylation isopropyl cinnamate **(30)** reacts with $K_2OsO_2(OH)_4$ 1.5 mol% and *N*-bromoacetamide **(31a)** with a chiral ligand **(31b)** to generate amino alcohol **(32)** of 99 % *ee* in 71 % yield (Figure 1.15).[1] However, control of

regioselectivity and stereoselectivity of the method is still not yet perfect for many types of unsymmetrical alkene.[33]

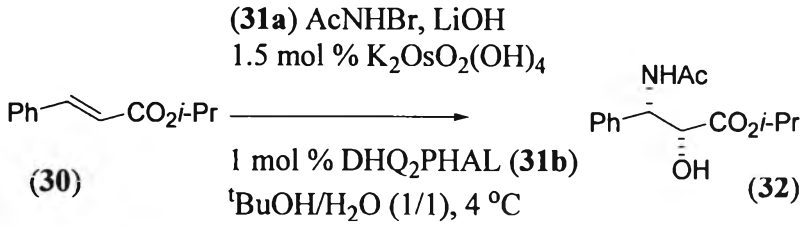


Figure 1.15. One step for asymmetric aminohydroxylation by Sharpless

1.2.3 Coupling reactions

There are two general types of these reactions: (a) the reaction of an α-metalloheteroatom with aldehyde or imine (Aldol-type reactions), and (b) a pinacol-type coupling between an aldehyde and imine. In class (a) the reactions employ generation of an anion α to a heteroatom (N or O) and can be further divided into two groups, stabilized anions and non-stabilized anions. The most common are those in which the anion is generated adjacent to an anion stabilizing group. For example, in Henry reaction the nitro compound **(34)** reacts with aldehyde **(33)** in the presence of a chiral Lewis acid. This produces the *syn*-amino alcohol **(35a)** in good yield and enantioselectivity (Figure 1.16).[34] The nitro group can then be reduced to the desired amino functionality.

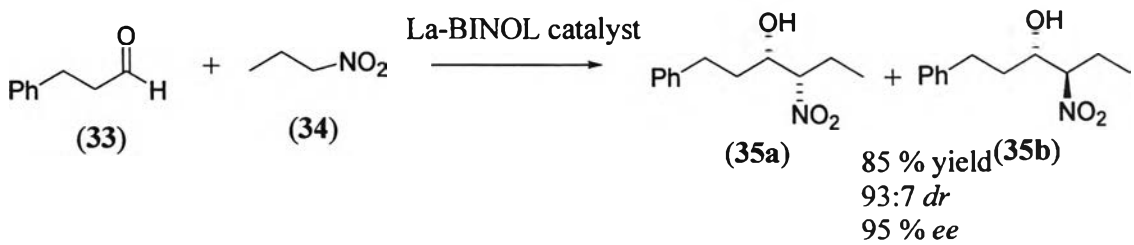
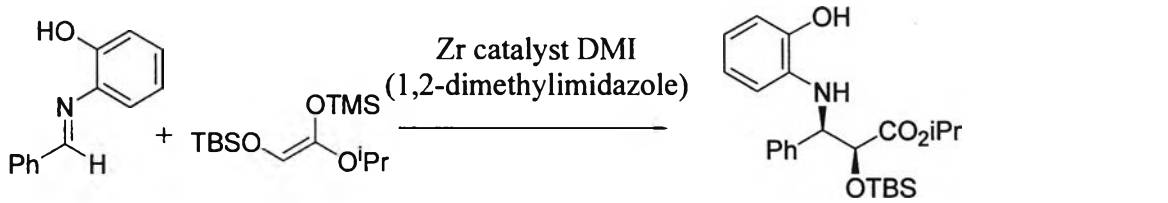


Figure 1.16. Diastereoselective and enantioselective nitroaldol reaction to a precursor of amino alcohol

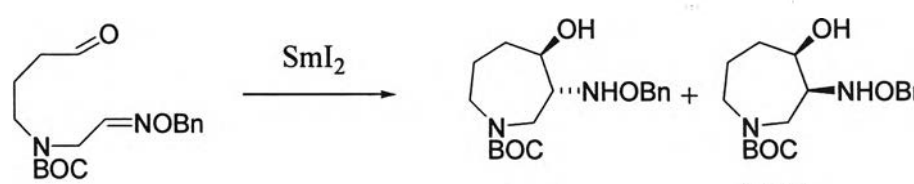
Non-stabilized anions α to an oxygen functionality can react with electrophiles such as imines as well. An example of the usage of the anion is the reaction of the silyl enol ether **(37)** with imine **(36)** (Figure 1.17). Most of the stable imines have been made used of arylaldehydes. Also diastereoselectivity of the reaction is still problematic.[35]



(36) **(37)** **(38)** 65 % yield, 96 % *ee*, > 99:1 *syn*:*anti*

Figure 1.17. Catalytic asymmetric synthesis of *syn*-amino alcohol **(38)**

(b) The use of pinacol type coupling reaction can be shown by (Figure 1.18) the coupling of the oximino aldehyde **(39)** for its intramolecular. It proceeds in good yield (53 %) but a 7:1 mixture of the *trans*:*cis* amino alcohols **(40a:40b)** is obtained.[36]



(39) **(40a)** **(40b)**

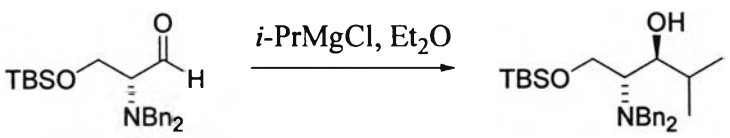
Figure 1.18. Radical cyclization of oxime ether **(39)**

1.2.4 Functional group manipulation

It is one of the most commonly used methods for the synthesis of vicinal amino alcohols that contains two heteroatoms on vicinal carbons. This version utilizes the functional group modification of an imine or carbonyl group, through reduction or nucleophilic addition. The popularity of this route stems from a plenty of work on stereospecific addition of nucleophiles to carbonyl compounds.

a) Addition of a nucleophile to an α-amino carbonyl

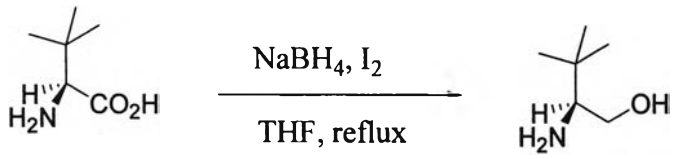
Nucleophilic addition to α-aminocarbonyl compounds provides a convenient means to vicinal amino alcohol. Generation of high levels of diastereoselectivity and the stability of the α-amino carbonyl compound has sometimes been problems with this method. In a recent example, the addition of a Grignard reagent to the aldehyde **(41)** provides the *anti* product **(42)** in 88-95 % yield (Figure 1.19).[37] The diastereoselectivity of this addition reaction follows the Felkin-Anh model.[38] It is noteworthy that the aldehyde **(41)** is not particularly stable and is either used as a crude or prepared *in situ*. By a careful selection of protecting groups either of the products resulting from Felkin-Anh or Chelation controls should be possible. However, as mentioned earlier, the diastereoselectivity is not usually perfect and requirement for stereospecificity of most addition to α-amino aldehydes is that there are no acidic hydrogens on the nitrogen atom.



(41) **(42)**, 88-95 % yield

Figure 1.19. Addition of a Grignard reagent to aldehyde

The reduction of chiral α-amino acid derivatives is a common route to vicinal amino alcohols. For example, L-*tert*-leucine was reduced by $NaBH_4$-iodine to obtain a high yield (84 %) of L-*tert*-leucinol with complete integrity of its original configuration (Figure 1.20).[39]

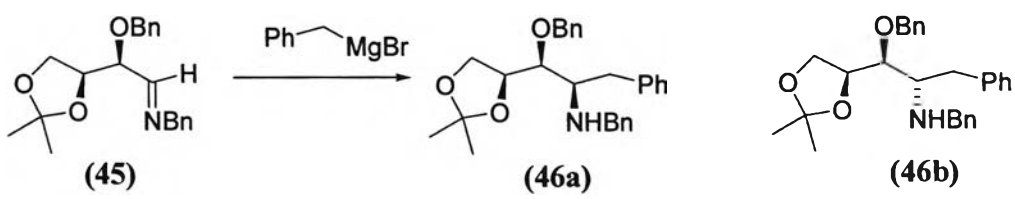


L-(+)-**43** (+)-**44**

Figure 1.20. Reduction of an α-Amino Acid with $NaBH_4$-Iodine

b) Addition of a nucleophile to an α-hydroxy imine

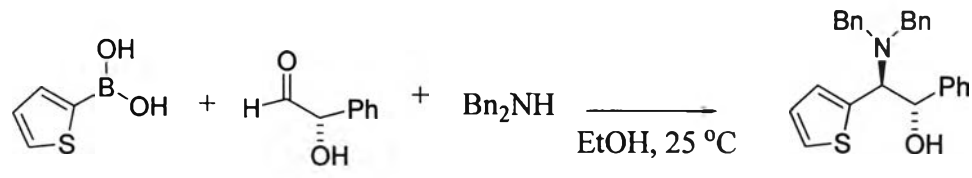
The corresponding reactions between a protected α-hydroxy imine and a nucleophile are not as well represented due to the relative instability of the imines. However, a different approach to solve the case is the *in situ* generation of the imine followed by a nucleophilic addition. One example in which a protected α-hydroxy imine **(45)** is used directly is shown in Figure 1.21.[40] The imine **(45)** was treated with an organometallic reagent to provide the *syn*-isomer **(46a)** as the major product. Yields for such a reaction were generally good (37-78 %) and up to 95:5 *dr* was obtained.



(45) **(46a)** **(46b)**

Figure 1.21. Addition of an organometallic reagent to an α-hydroxy imine

To avoid isolation of unstable imines, one can make use of stereocontrolled one-step synthesis of *anti*-β-amino alcohols from organoboronic acids, amines, and α-hydroxy aldehydes: the so-called Boronic Mannich reactions. An example is to use α-hydroxy aldehyde **(47b)** condensed *in situ* with an amine **(47c)** and followed by boronic acid derivative **(47a)**. The reaction provided the product **(48)** in 86 % yield and 99 % *ee* (Figure 1.22).[41]

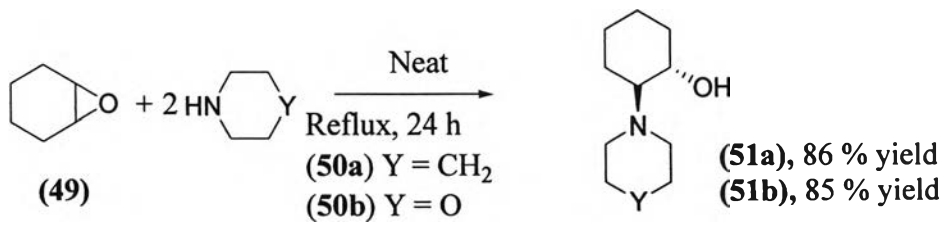


(47a) **(47b)** **(47c)** **(48)**

Figure 1.22. Synthesis of *anti*-α-amino alcohols **(48)** by the reaction of organoboronic acids **(47a)** with amines **(47c)** and α-hydroxy aldehydes **(47b)**

1.3 Regioselectivity and stereoselectivity in ring opening of epoxides by nitrogen nucleophiles

The most commom approach to obtain the vicinal amino alcohols is to react the epoxides directly with the nitrogen nucleophiles, such as azides and amines, the so-called first generation approach.[42] The conversion of epoxides to amino alcohols has been known since 1952.[43] Refluxing a neat mixture of the epoxide **(49)** and the appropriate primary or secondary amines result in fair to excellent yields of the desired amino alcohols as shown in Figure 1.23.



(49)

Figure 1.23. Ring opening of cyclohexene oxide with secondary amines

However, this methodology is limited by highly variable yields, long reaction times, and often the rigorous reaction conditions not only detrimental to certain functional groups, but also to the control of regioselectivity.[44] Further, the need to use a large excess of amine in order to achieve a reasonable yield makes this route less

desirable if the amine is poorly nucleophilic, highly hindered, or valuable. Direct alkylations of primary amine with styrene oxide or arylethylene oxide **(52)** in stoichiometric ratio in polar solvents give low yields (ca. 20-50 %) of the desired 1-phenylethanolamine (**53b**, "β-product") admixed with significant amounts of the 2-phenylethanolamine (**53a**, "α-product") and all possible corresponding products of bis-alkylation (**53c**, **53d**, and **53e**) as shown in Figure 1.24.[45] Although the strain of their three-membered ring together with the polarization of the C-O bonds makes epoxides susceptible to reaction with a variety of nitrogen nucleophiles, there are a number of the limitations of such routes. According to Lutz's work,[46] when the ring opening of *cis* and *trans* stilbene oxides with primary and secondary amines was carried out with an excess of the nucleophiles in ether at a very high temperature (>150 °C), the reaction provides poor reactivity and poor yield, especially with sterically hindered nucleophiles.

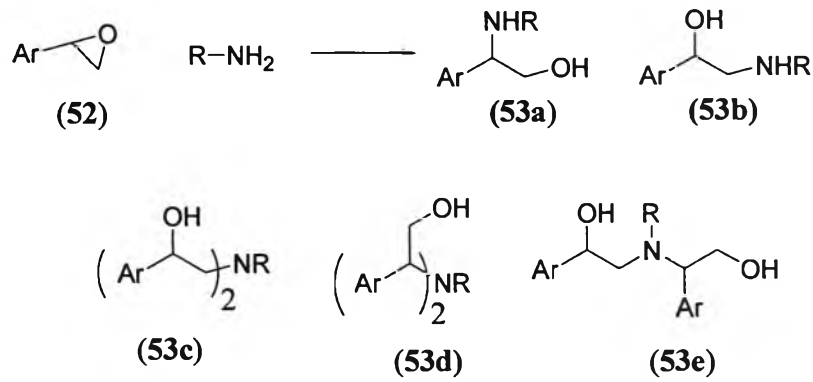


Figure 1.24. Direct alkylation of primary amine with arylethylene oxide in protic solvents

To overcome the problems of reactivity, the more nucleophilic metal amides have been used instead of free amines. Several metal amides such as Al, Mg, Li, Pb, Sn, Si,

and Cu each have particular regioselectivity on unsymmetrical epoxides as exemplified in Figure 1.25 whereby they can be generally divided into two regioselectively attacked positions: type A for beta-attacked position and type B for alpha-attacked position.[47,48] Basic metal amides (type A), for instance, lithium, magnesium, lead, and copper amides attack the less hindered carbon with moderate regioselectivity. A major drawback associated with lithium amides is that the acidic hydrogen alpha to epoxide ring is also abstracted by the amide base and thus the corresponding allylic alcohol is frequently obtained as the major side product.

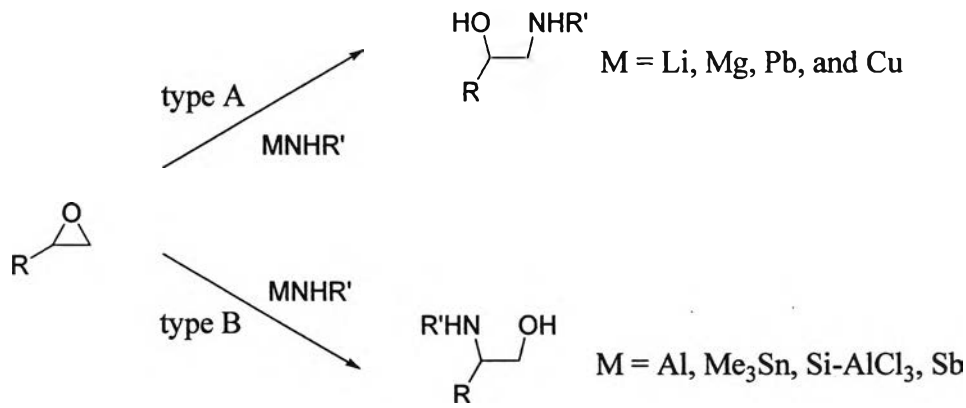
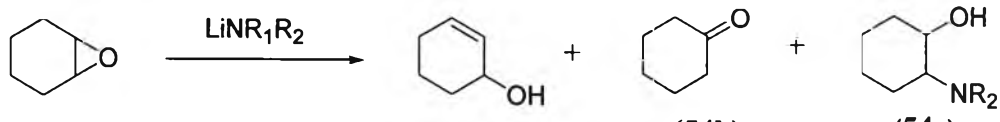


Figure 1.25. Regioselectivity of metal amides

An example in Figure 1.26 shows reactions of cyclohexene oxide with lithium amides. When the primary alkylamide such as (R_1, R_2 = *n*-C_3H_7, H) was used, the reaction gave the desired amino alcohol in poor yield. With bulkier bases (R_1, R_2 = 2 *iso*-C_3H_7 or 2 C_2H_5), the allylic alcohol and its rearrangement to a carbonyl compete successfully *via* the proton abstraction.[49]



(49) (54a) (54b) (54c)

R_1,R_2 = *n*-C_3H_7,H	17h	15 %	0.5 %	77 %
R_1,R_2 = 2 C_2H_5	2h	86 %	3 %	10 %
R_1,R_2 = 2 *iso*-C_3H_7 (ether)	3h	38 %	33 %	28 %

Figure 1.26. Reaction of cyclohexene oxide with lithium alkylamides

Ring opening of epoxides with three different metal amides of type A can be comparatively represented by Table 1.2.[47, 48, 50]

Table 1.2. Regioselectivity of epoxide ring opening by metal amides for type A

(55a-b) α-56a-b β-57a-b

epoxides

(55a) R_1 = Ph, R_2 = CH_3, R_3 = H

(55b) R_1 = Ph, R_2 = H, R_3 = H

entry	epoxides→ products	metal amides	temp °C, solvents (rxn time, h)	product ratio[a]	% yield[b]
1	**55a→57a**[c]	R_5R_4NMgBr (R_4 = *tert*-Bu, R_5 = H)	35,THF (3.75)	-	65
2	**55b→56b,57b**	*n*-$Bu_3PbNR_4R_5$	rt,ether	6:94	82

		(R_4 = ethyl, R_5 = H)	(0.5)		
3	**55b→56b,57b**	*n*-$Bu_3PbNR_4R_5$ (R_4 = benzyl, R_5 = H)	rt,ether (2)	19:81	77
4	**55b→56b,57b**	$(R_5R_4N)_2Cu(CN)Li_2$ (R_4, R_5 = benzyl)	-78 to rt, THF (O/N)	11:89	91
5	**55b→56b,57b**	$(R_5R_4N)_2Cu(CN)Li_2$ (R_4 = benzyl, R_5 = H)	-78 to rt, THF (O/N)	12:88	93

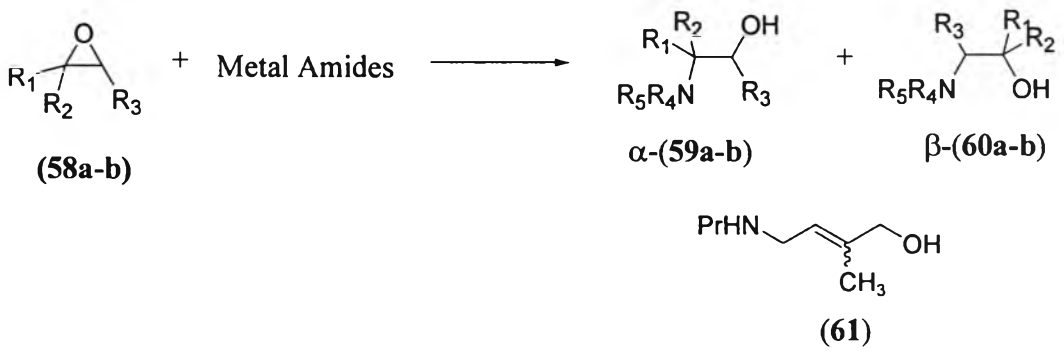
[a] ratio α:β as determined by ^{1}H NMR; [b] isolated yield; [c] beta product only; All data were taken from refs 47, 48, and 50.

Indeed amino-magnesium derivatives are generally considered as strong bases. However, the somewhat covalent character of the nitrogen-magnesium bond could be sufficient to confer magnesium amides with efficient nucleophilic reactivity towards epoxides. However, if a large excess of $MgBr_2$ is also present in the reaction medium, large quantities of bromohydrins are formed. Under the usual conditions, this by-product is formed in yields varying from 8 to 20 %. According to the study, it was apparent that such a method did not show the ring opening regioselectivity of unsymmetrical aromatic epoxide with amines explicably enough for all substrates. For alpha-substituted epoxides the nucleophilicity of the magnesium amide contributes to high regioselectivity of beta-substituted product because of electronic effect and steric effect from the epoxide ring. Even though the use of aminolead compounds and amide cuprates was accomplished in high yield and good regioselectivity without the significant trace of the abstracted proton of epoxides, the lack of adequate representative amines used in the studies creates doubts

on the generality of the reaction. Moreover, isolation of the lead-mediated product from the procedure may be difficult, since it requires for transamination reaction for some types of aminoleads such as benzylaminolead.[47]

For metal amides of type B (Table 1.3), the regioselectivity of Ph_4SbOTf-derived epoxide cleavage ranged fair to good regioselective for many unsymmetrical epoxides. However, the results with styrene oxide have been poor so far.[51, 52]

Table 1.3. Regioselectivity of epoxides by metal amides for type B



(58a-b) α-(**59a-b**) β-(**60a-b**)

(61)

epoxides

(58a) R_1 = Ph, R_2 = H, R_3 = H

(58b) R_1 = vinyl, R_2 = CH_3, R_3 = H

entry	epoxides→ products	metal amides	temp °C, solvents (rxn time,h)	product ratio[a]	% yield[b]
1	**(58a)→(59a,60a)**	$R_5R_4NSbPh_4$ (R_4, R_5 = ethyl)	40,CH_2Cl_2 (3)	35:65	82
2	**(58b)→(59b,60b,61)**	$R_5R_4NAlEt_2$ (R_4 = *n*-Pr, R_5 = H)	25, CH_2Cl_2 (O/N)	72:17:11	50

[a] ratio α:β as determined by ^{1}H NMR; [b] isolated yield; All data were taken from refs: 51 and 52.

As with diethylaluminum *n*-propylamide, the reaction of isoprene oxide gave a mixture of products in which the tertiary carbonyl amine predominated in a fair yield, attributed to the Lewis-acidic property of the aluminum. The problematic reaction was obviously derived from its chemoselectivity with the attack of the nucleophile at alkenyl terminal carbon.[52]

A new reagent system in which ring opening takes place with amines in the presence of a catalytic or stoichiometric amount of metal salts such as $LiClO_4$,[25,53] $MgClO_4$,[25,53] $CoCl_2$,[54] LiOTf,[55] $Ti(O^iPr)_4$,[56] $LiNTf_2$,[57] $ZrCl_4$,[58] and LiBr[59] has been brought up as the third generation. It was reported that cobalt (II) chloride mediates a redox-type of epoxide aminolysis reaction with relatively nonnucleophilic anilines; however, the method is apparently ineffective with benzylic or aliphatic amines.[25,53] Chini *et al.*'s studies[25,53] comparing with Auge's[55] have brought about how to direct the regioalternating selectivity in the metal salt catalysts such as $LiClO_4$, $MgClO_4$, LiOTf, and $LiNTf_2$ on aminolysis of oxiranes[25] and, more importantly, styrene oxide[60] in Table 1.4. With respect to the latter with $LiClO_4$, the stereoselectivity also observed in the reactions are complete inversion of configuration, allowing one to confer about their mechanism as shown in Figure 1.27.

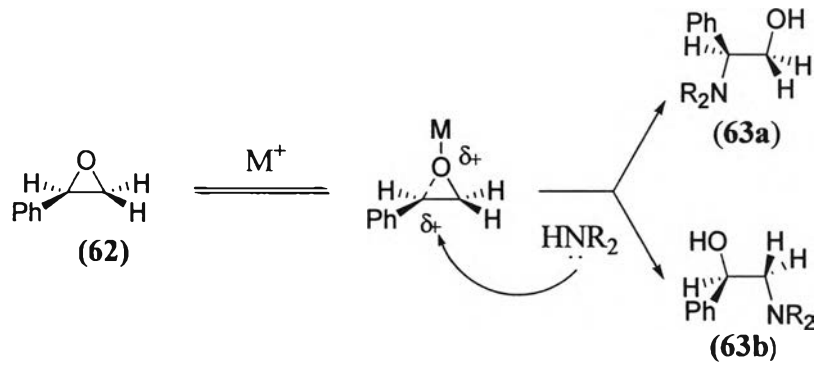
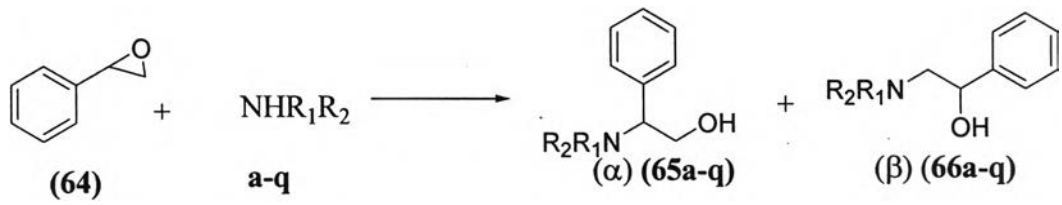


Figure 1.27. Regioselective aminolysis of optically active styrene oxide in the presence of metal salts

Table 1.4. Regioselectivity of the aminolysis of styrene oxide in the presence of metal salts



entry	amines[a]	Salts (solvent)[b]	Rxn time (h)[c]	% yield[d]	ratio α:β	products
1	*p*-$NO_2C_6H_4NH_2$ (a)	$LiClO_4$ (A)	20 (65°C)	66	95:5	**65a:66a**
2	$PhNH_2$ (b)	$LiClO_4$ (A)	3.5	95	92:8	**65b:66b**
3	PhNHMe (c)	$LiClO_4$ (A)	4	94	90:10	**65c:66c**
4	*p*-$OMePhNH_2$ (d)	$LiClO_4$ (A)	2.5	94	87:13	**65d:66d**

5	$BnNH_2$ (e)	$LiClO_4$ (A)	1.5	98	58:42	**65e:66e**
6	Piperidine (f)	$LiClO_4$ (A)	0.5	98	58:42	**65f:66f**
7	$BuNH_2$ (g)	$LiClO_4$ (A)	1	96	53:47	**65g:66g**
8	*tert*-$BuNH_2$ (h)	$LiClO_4$ (A)	1	94	47:53	**65h:66h**
9	(*iso*-Pr)$_2$NH (i)	$LiClO_4$ (A)	24	93	<1:>99	**65i:66i**
10	$(Cy)_2NH$ (j)	$LiClO_4$ (A)	72	88	<1:>99	**65j:66j**
11	Et_2NH (k)	$LiClO_4$ (A)	0.5	96	43:57	**65k:66k**
12	Et_2NH (k)	$LiClO_4$ (A)[c]	2.5	92	53:47	**65k:66k**
13	Et_2NH (k)	$Zn(Tf)_2$ (A)	0.5	92	55:45	**65k:66k**
14	Et_2NH (k)	$Mg(ClO_4)_2$ (A)	0.5	94	30:70	**65k:66k**
15	Et_2NH(k)	$CaCl_2$ (A)	4	93	20:80	**65k:66k**
16	Et_2NH (k)	$NaClO_4$ (A)	6	92	12:88	**65k:66k**
17	Et_2NH (k)	(B)	96 (80°C)	90	5:95	**65k:66k**
18	Et_2NH (k)	$LiClO_4$ (B)	2.5	92	20:80	**65k:66k**
19	Et_2NH (k)	$LiClO_4$ (C)	2.5	90	52:48	**65k:66k**
20	Et_2NH (k)	$LiClO_4$ (D)	2.5	94	43:57	**65k:66k**

21	morpholine (l)	LiOTf (E)	24	79	26:74	**65l:66l**
22	morpholine (l)	LiOTf (F)	12	80	45:55	**65l:66l**
23	morpholine (l)	LiOTf (G)	1	88	42:58	**65l:66l**
24	morpholine (l)	LiOTf (H)	1	85	45:55	**65l:66l**
25	morpholine (l)	LiOTf (I)	1	89	38:62	**65l:66l**
26	Et_2NH (k)	LiOTf (G)	11.5	87	26:74	**65k:66k**
27	Et_2NH (k)	LiOTf (J)	0.33	98	26:74	**65k:66k**
28	Et_2NH (k)	$Zn(OTf)_2$ (G)	0.5	92	56:44	**65k:66k**
29	Et_2NH (k)	$SmI_2(THF)_2$ (K)	18	63	100[f]	**65k:66k**
30	$BnNH_2$ (e)	LiOTf (G)	3.5	83	40:60	**65e:66e**
31	*tert*-$BuNH_2$ (h)	LiOTf (G)	1.5 (81°C)	80	28:72	**65h:66h**
32	$H_2N(CH_2)_2Ph$ (m)	$LiNTf_2$ (L)	20	77	20:80	**65m:66m**
33	$PhNH_2$ (b)	LiBr (M)	5 (rt)	98	92:8	**65b:66b**
34	*p*-$MePhNH_2$ (o)	LiBr (M)	5 (rt)	98	100:0	**65o:66o**
35	*p*-$ClPhNH_2$ (p)	LiBr (M)	5 (rt)	100	100:0	**65p:66p**
36	Pyrrolidine (q)	LiBr (M)	5 (rt)	92	45:55	**65q:66q**

37	Piperidine (f)	LiBr (M)	5 (rt)	98	42:58	**65f:66f**
38	Morpholine (l)	LiBr (M)	5 (rt)	94	48:52	**65l:66l**

Entries 1-20 use 2 equiv of salts and amines, entries 21-31 use 1.1 equiv of amines with the amount of salts as specified in their entries and entries 33-38 use 1 equiv of amines. [a] Cy = cyclohexyl. [b] Entry 17 was carried out without any metal salt being added: Tf = triflate; A, CH_3CN; B, EtOH; C, Et_2O; D, acetone; E, $PhCH_3$ and 0.05 equiv LiOTf; F, CH_2Cl_2 and 0.1 equiv LiOTf; G, CH_3CN and 0.5 equiv LiOTf or $Zn(OTf)_2$; H, THF and 0.5 equiv LiOTf; I, $(CH_3)_2CO$ and 0.5 equiv LiOTf; J, CH_3CN and 2 equiv LiOTf; K, CH_2Cl_2 and 0.5 equiv $SmI_2(THF)_2$; L, CH_2Cl_2 and 0.1 equiv $LiNTf_2$; M, No solvent and 5 mol % catalyst used. [c] With the only exception of entries 1 and 17 all the reactions were carried out at 25 °C. [d] Yields based on GC analysis and weight of the crude isolated reaction product. [e] A double amount of salt was employed.; [f] beta product only. Data were taken from refs: 25, 53, 55, 57, and 59.

The results indicated that it was possible to obtain a reversal of the regiochemistry in the opening process on passing from the reaction with poorly nucleophilic *p*-nitroaniline (entry 1) (prefer alpha) to the highly nucleophilic and sterically hindered diisopropyl- and dicyclohexylamine (entries 9 and 10, respectively), even with the same catalyst ($LiClO_4$). On the basis of the regiochemistry observed in each case, the amines can be divided into three main classes: (i) aromatic amines of low nucleophilicity that give almost exclusively the benzylic attacked amino alcohols in entries 1-4. (ii) benzylamine and other aliphatic unhindered amines that afford almost equimolar amounts of the two regioisomers in entries 5-8 and 11, and (iii) sterically hindered amines in entries 9 and 10 that afford the terminal attacked amino alcohols. The metal ions of the salt are also able to modulate the regiochemistry of the reactions markedly as shown in entries 11-16. Weaker Lewis acid cations like Na^+ promote more S_N2-type nucleophilic attack on the less substituted carbon in entry 16. Better Lewis acids, for instance, Zn^{2+}, Li^+, and Mg^{2+} in entries 11-14, are more effective in directing the attack of the amine to

the benzylic carbon. As for secondary amines of low nucleophilicity like morpholine (entries 21 to 25) their regioselectivity ranges from fair to moderate. It is worthnoting that the regioselectivity of the ring opening with 2-phenylethylamine is higher in the presence of $LiNTf_2$ (entry 32) than that in $LiClO_4$ or LiOTf (entry 5, 30, and 31) if the comparison of the selectivity is based on the primary amines. LiBr was also used in the ring opening in entries 33-38 with aromatic amines and secondary alphatic amines. Like other aromatic amines (entries 1-4) the higher alpha- to beta-attacked aromatic amine products were predominant (entries 33-35). Also similar to other secondary aliphatic amines (entries 23-24) the preferred beta-to alpha-attacked secondary aliphatic amine products were found (entries 36-38).

Chini *et al.*[60] also found that lanthanide(III) trifluoromethanesulfonates [$Ln(OTf)_3$] such as $Yb(OTf)_3$, $Nd(OTf)_3$, and $Gd(OTf)_3$, at catalytic amounts were able to promote in a more effective way the aminolysis of styrene oxide with (*iso*-Pr)$_2$NH and $(Cy)_2NH$ in terms of their rate of reactions, within 1-2 hours, than $LiClO_4$ or LiOTf. The use of a new and efficient catalyst, $ZrCl_4$,[58] for the ring opening styrene oxide by secondary aliphatic amines, in particular, pyrrolidine, piperidine, and morpholine, has allowed a moderate selectivity at the regioisomeric ratio of 40-45 to 60-55 for the attack of benzylic to terminal positions. More recently, copper (II) tetrafluoroborate [$Cu(BF_4)_2.xH_2O$] [61] and scandium triflate [$Sc(OTf)_3$] [62] have been used in the catalytic aminolysis of styrene oxide ring opening with aromatic amines and secondary aliphatic amines in the absence of solvents at room temperature. As expected, the regioselectivity of both catalysts was of preference to alpha-attacked products for aromatic amines and to

beta-attacked products for secondary aliphatic amines. The reaction time was ranged from minutes to a few hours.

The effect of unsymmetrical epoxides substituted with electron-withdrawing or electron-donating groups on the mechanism of their ring opening was studied by kinetic studies.[63] This study explained regioselective ring opening of epoxides with the only benzylamine used as the nucleophile. A series of *m*- and *p*-substituted styrene oxides were allowed to react with benzylamine in ethanol as shown in Figure 1.28.

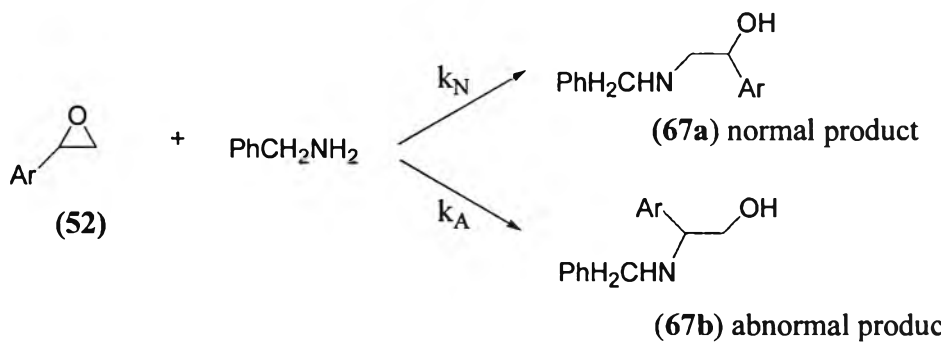


Figure 1.28. Regioselectivity of *m*- and *p*-substituted styrene oxide ring opening with benzylamine in ethanol

The overall rate constants, which are measured by following the decrease in the concentration of benzylamine and the ratios of products, are divided in the ratio of the products to give the rate constants for β or normal (k_N) and for α or abnormal (k_A) attack. Afterwards, the plots of log k_N and k_A against σ for each isomeric product reveal the ρ values. According to this study, a positive value of the Hammett reaction constant ρ of +0.87 was obtained for the normal reaction, since the rate of the normal reaction is increased by electron-withdrawing substituents and decreased by electron-releasing substituents. Conversely, the rate of the abnormal reaction is decreased by electron-

withdrawing substituents and increased by electron-releasing substituents; hence, this reaction has a negative ρ at -1.15. According to this kinetics study, it was therefore concluded that in Figure 1.29 the two partial bonds in each transition state would be together less than a full single bond and that the attacked carbon atom carries more positive charge than in the initial state. The negative value of ρ for the abnormal reaction reflects the mechanism, since one of the charges on carbon is nearer than the other two to the substituent group of the aromatic ring. Only the interaction between this charge and the substituent group needs to be considered for the value of ρ. Therefore, electron withdrawing group destabilizes the alpha attack. On the other hand the positive value of ρ for the normal reaction also reflects the mechanism, because two of the three charges on the transition state for the normal reactions (those on oxygen and carbon) are almost equidistant from the substituent group and are nearer than the charge on nitrogen. Only the interaction between the substituent group and these two charges affect the value of ρ. Hence, electron withdrawing group stabilizes the beta attack by reducing or stabilizing the negative charge on oxygen.

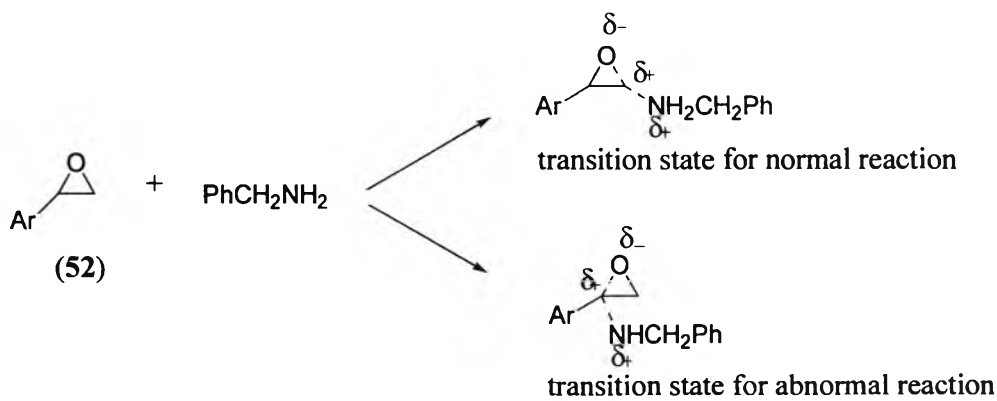
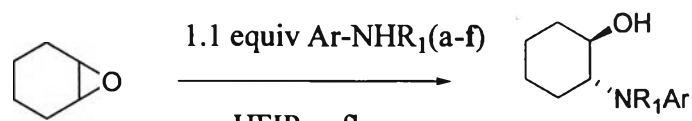


Figure 1.29. Transition states with charge distribution of the aromatic oxide ring opening with benzylamine

Several useful modifications of the classical procedures have been illustrated as earlier said, for example, metal amides. However, many functional groups are potentially incompatible with their use. In order to avoid drawbacks due to basic medium, a variety of activators such as metal salts or Lewis acid catalysts have been introduced to affect the epoxide ring opening at room temperature. Yet the interest to use fluorous medium such as TFE and HFIP in the epoxide ring opening with amines was possible to be another alternative *via* activating the ring opening,[64] because there were some other syntheses in the fluoroalcohols such as a selective conversion of sulfide to sulfoxide in HFIP.[65] The study of the effect of the fluoroalcohol as a solvent was rather limited. Only the reactivity of cyclohexene oxide ring opening with aromatic amines in HFIP (Table 1.5) and a few examples of styrene oxide ring opening (Table 1.6) were studied.

Table 1.5. Ring opening of cyclohexene oxide with aromatic amines in HFIP



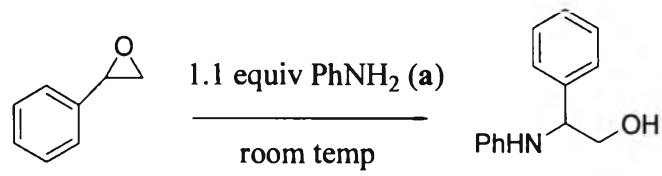
(49) **(68a-f)**

entry	amines	rxn time (h)	% yield[a]	products
1	**(a)** R_1 = H, Ar = Ph	4	84	**68a**
2	**(b)** R_1 = Me, Ar = C_6H_5-	4	86	**68b**
3	**(c)** R_1 = H, Ar = *o*-Me-C_6H_4-	2.5	92	**68c**
4	**(d)** R_1 = H, Ar = α-naphthyl	3	87	**68d**
5	**(e)** R_1 = H, Ar = *p*-MeO-C_6H_4-	2.5	88	**68e**

6	(**f**) R_1 = H, Ar = *p*-NO_2-C_6H_4-	-	No rxn	**68f**

[a] Isolated yield; All data were taken from ref (64).

Table 1.6. Styrene oxide ring opening with aniline (**a**) in HFIP and TFE at room temp



(64) **(65a)**

entry	solvents	rxn time (h)	% yield[a]	products
1	HFIP	3	50	**65a**
2	TFE	6	80	**65a**

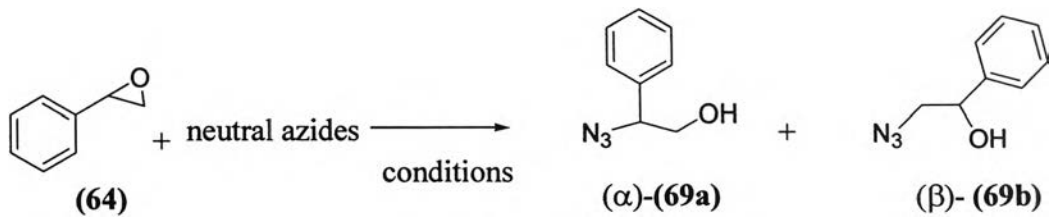
[a] Isolated yield; All data were taken from ref (64).

The reactivity of cyclohexene oxide ring opening with aromatic amines in HFIP was quite successful with high yields except with *p*-nitroaniline (Table 1.5). The conditions in Table 1.6 showed a high reactivity and regioselectivity similar to metal salts and Lewis acid catalysts. Nevertheless, the study also reported that the aliphatic amines such as diethylamine, *n*-butylamine, benzylamine, and pyrrolidine failed to effect the ring opening under the similar reaction conditions even after 4 days at reflux. Moreover, when the cyclohexene oxide ring opening was carried out in isopropanol without any promotor, no conversion was observed with aniline, but piperidine underwent the reaction at 82 % yield. The study concluded that there are competitive effects of HFIP depending on the nucleophilicity of the amines by activation of the oxirane through hydrogen bonding and deactivation of amines. Due to a still lack of regioselective study for the epoxide ring

opening we aimed at proposing further whether the general acid catalysis by using alcohols as reaction media can eliminate the requirement of the Lewis acid catalysts and may further improve the regioselectivity towards alpha attack in aminolysis of styrene oxide and also other oxiranes.

Azide has also been used as the nucleophilic species to form a vicinal azidohydrin. Subsequent reduction with, *eg*. $LiAlH_4$, produces the β-amino alcohol.[29] The classical protocol uses NaN_3 as a reagent in the presence of a weak acid such as NH_4Cl or HOAc in alcohol-water at 65-80 °C. Under these conditions, the azidolysis is generally completed within 12-48 h, and the azidohydrin is often accompanied by isomerization, epimerization, and rearrangement products.[29,66] There are two recent improved azidolysis of styrene oxide by neutral azide and anionic azide ion. These have been used with either stoichiometric or catalytic amount of organometallic or organoimido complex reagents. The application of Me_3SiN_3, Bu_3SnN_3,[67] and $Bu_2Sn(N_3)_2$,[68] as neutral azides, with catalytic organometallic reagents such as $Yb(O\textit{i}\text{-}Pr)_3$,[69] $Ti(O\textit{i}\text{-}Pr)_4$ and $Al(O\textit{i}\text{-}Pr)_3$,[70] $SmI_2(THF)_2$[71] or with catalytic organoimido complexes[72] such as $Cr(NBu^t)Cl_3(dme)$ (dme = 1,2-dimethoxyethane) was shown in Table 1.7. The regioselective results of azidolysis of styrene oxide with azide both in neutral and anionic forms were of very high preference to alpha-attacked products with high yields.

Table 1.7. Azidolysis of styrene oxide with neutral azides in the presence of catalytic organometallic reagents



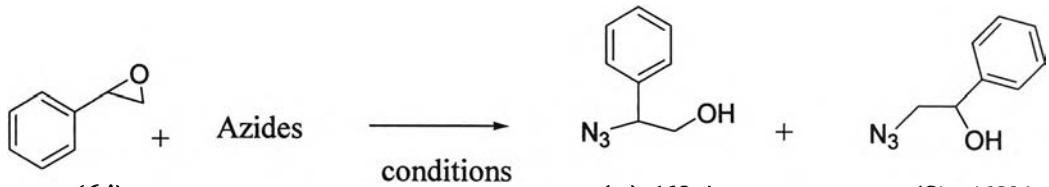
(64) **(α)-(69a)** **(β)- (69b)**

entry	azides	catalysts	solvent	Temp,rxn time (h)	ratio α:β[a]	% yield[b]	products
1	Bu_3SnN_3	-	-	60 °C (1)	93:7	86	**69a,69b**
2	$Bu_2Sn(N_3)_2$	-	DMF	60 °C (0.2)	93:7	94	**69a,69b**
3	Me_3SiN_3	$SmI_2(THF)_2$	CH_2Cl_2	rt (4.5)	90:10	55	**69a,69b**
4	Me_3SiN_3	$Cr(NBu^t)Cl_3(dme)$	CH_2Cl_2	rt (3)	67:33	95	**69a,69b**
5	Me_3SiN_3	Yb(O*i*-Pr)$_3$	THF	rt (13)	86:14	83	**69a,69b**
6	Me_3SiN_3	Ti(O*i*-Pr)$_4$	THF	rt (6d)	99:1	74	**69a,69b**
7	Me_3SiN_3	Al(O*i*-Pr)$_3$	CH_2Cl_2	rt (1d)	93:7	73	**69a,69b**

[a] determined by gas chromatography and ^{1}H NMR; [b] isolated yield; entries 1, 2, 3, and 4 use 1.5, 2, 1.2, and 3, respectively, equiv of azides but entries 5-7 use 1.5 equiv of azides; entries 3 and 4 use 5 mmol % of catalysts, and entries 5-7 use 10, 1.5, and 1, respectively, mmol % of catalysts All data were taken from refs: 67, 68, 69, 70 and 71.

Another useful method for direct azidolysis of epoxides is to use anionic azide under various conditions. Chini *et al.*[73,74] found a useful direct azidolysis of styrene oxide with anionic azides catalyzed by metals or transition metals in polar aprotic solvents. The results were compared with the same reaction differently carried out in protic solvents (an 8:1 mixture of MeOH:H_2O) in the presence of NH_4Cl, according to Sharpless.[75] Furthermore, Fringuelli *et al.*[27] performed a regioselective pH-controlled reaction of the ring opening of styrene oxide with sodium azide shown in Table 1.8.

Table 1.8. Azidolysis of styrene oxide with anionic azides in the presence of metal salts and under some other representative reaction conditions



(64) (α)-**(69a)** (β)- **(69b)**

entry	azides	reagent (conditions)[a]	rxn time (h)	ratio α:β[b]	% yield[c]	products
1	NaN_3	$LiClO_4$ (A)	5	82:18	92	**69a,69b**
2	NaN_3	$Mg(ClO_4)_2$ (A)	2	83:17	78	**69a,69b**
3	LiN_3	(B)	5	81:19	90	**69a,69b**
4	NaN_3	NH_4Cl (C)	20	79:21	94	**69a,69b**
5	TMGA	$Zr(OTf)_4$ (D)	42	74:26	67	**69a,69b**
6	TMGA	$Hf(OTf)_4$ (D)	42	78:22	65	**69a,69b**
7	TMGA	$Yb(OTf)_4$ (D)	42	72:28	82	**69a,69b**
8	NaN_3	(E)	13	97:3	90	**69a,69b**
9	NaN_3	(F)	0.3	97:3	92	**69a,69b**
10	LiN_3	β-CD (G)	6	41:59	32[d]	**69a,69b**

[a] A: NaN_3 (1.5 equiv), metal salt (1.5 equiv), and CH_3CN with room temp; B: LiN_3 used instead of NaN_3 in MeCN; C: NaN_3 (5 equiv), NH_4Cl (2.2 equiv), MeOH/H_2O (8/1), reflux; D: TMGA (1.8 equiv), transition metal salt (2-20 % mol), and CH_3CN with room temp; E: at pH 9.5, NaN_3 (5 equiv) in water; F: at pH 4.2 by using HOAc, NaN_3 (5 equiv) in water; G: LiN_3 (1 equiv), β-CD (2 equiv) in water with room temp; [b]

determined by gas chromatography and ^{1}HNMR; [c] isolated yield; [d] 68 % yield of unreacted styrene oxide; All data were taken from refs: 27, 73, and 74.

According to Table 1.8, like regioselective results of azidolysis of styrene oxide with neutral azide the regioselectivity of all conditions with anionic azide were not yet to be satisfactory due to only high preference to alpha-attacked products obtained with high yields. However, according to Chini's study,[73] for example, in entry 1-2, the observed catalytic effect appears to be linked to the effect of the Lewis acid metal ion which, in aprotic solvent as acetonitrile, can coordinate the oxirane oxygen. The fact that lithium azide can achieve the azidolysis reaction practically as efficiently as the combination of sodium azide-lithium perchlorate in entry 1 and 3, but differently from sodium azide itself or from the NaN_3-$NaClO_4$ or NaN_3-$KClO_4$ couples is in accordance with the mechanistic suggestion about the role of the metal ions in these reactions. With the TMGA as the reagent, azido alcohols are obtained in moderate to good yield (60-80 %). The lack of regioselectivity still remains. Even though the attack of azide ion at pH 9.5 occurred preferentially on the less substituted β-carbon of many types of epoxides in Fringuelli's study,[27] the reversal of the regioselective ring-opening styrene oxide under both acidic or basic pHs have not been successful. In all cases the alpha product was preferentially formed. As molecular reaction vessels, cyclodextrins (entry 10) are expected to exert microenvironmental effects leading to selective reactions.[76] The result clearly showed that there was an increase in the regioselectivity of the β-ring opening when the reaction was performed in the presence of β-CD in entry 10. Meanwhile, the kinetic resolution of racemic styrene oxide also observed during the course of this reaction indicated that the selectivity comes from the combination step between styrene oxide and β-CD. The unreacted styrene oxide recovered is enriched (20 % *ee*) in *S*-(-),

whereas 1-phenyl-2-azidoethanol shows an enantiomeric excess of 78 % while the 2-phenyl-2-azidoethanol was obtained as a racemic compound. Nevertheless, in no cases the reversal of selectivity was observed (*i.e.* $\beta > \alpha$) for azidolysis of styrene oxide.

Another interesting anionic nucleophile used in regioselective ring opening of styrene oxide derivative is phthalimide anion. For example, in the asymmetric synthesis of chelonin B its synthetic pathway contains regioseletive ring opening of optically active styrene oxide derivative **(70)** with phthalimide on preference of the β-attacked product. However, the use of potassium phthalimide alone was inefficient and resulted in poor yield of the product. Presumably the alkoxide **(71a)**, generated from the ring opening process, is sufficiently nucleophilic to also react with the oxirane itself. The benzylic position of **(71)** is somewhat sensitive to racemization, so the use of Lewis acids to catalyze the reaction should be avoided. The condition involving the use of catalytic potassium phthalimide (5 mol %) and phthalimide (1.1 equiv) for regioselective ring opening of **(70)** in DMF (90 °C) provided good yield (70 %) and high stereospecificity (99 % *ee*) within 18 h.[77]

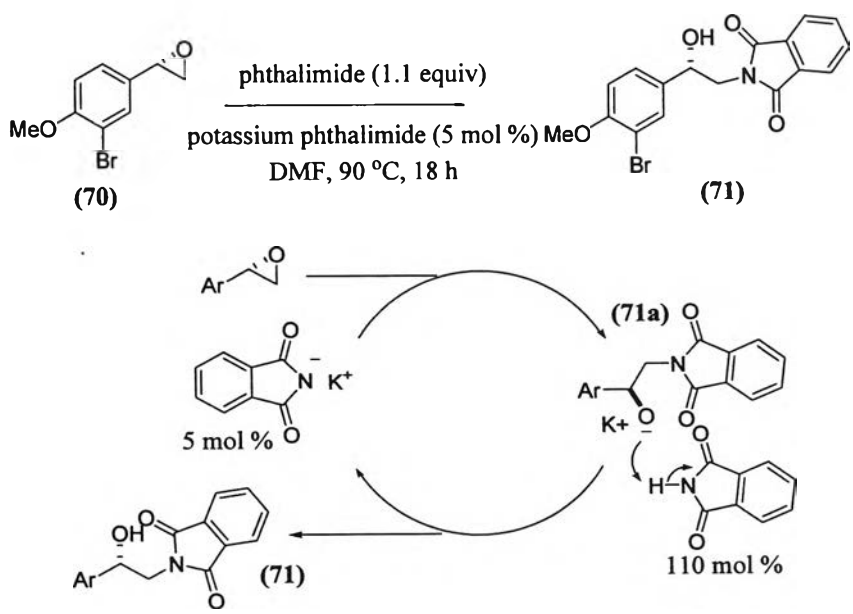
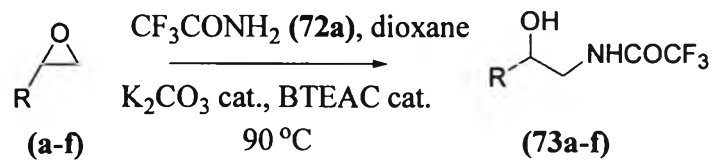


Figure 1.30. Oxirane ring opening with phthalimide in the presence of a catalytic amount of potassium phthalimide

The ring opening of epoxides with trifluoroacetamide **(72a)** or *p*-toluenesulfonamide **(72b)** under solid-liquid phase transfer catalysis along with catalytic amount of potassium carbonate has also been important intermediates to synthesize vicinal amino alcohols due to the easy removal of the trifluoracetamide or *p*-toluenesulfonamide group by mild alkaline hydrolysis.[78,79]

Table 1.9. The reaction of trifluoroacetamide with a series of epoxides under SL-PTC condition and catalytic amount of K_2CO_3



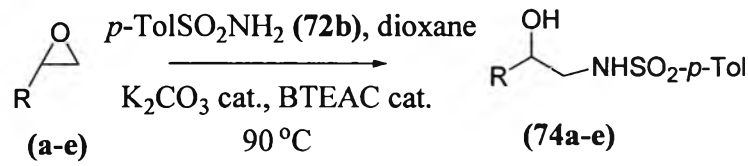
(a-f) **(73a-f)**

entry	epoxides	rxn time (h)	% yield	products
1	R = -CH_2OPh **(a)**	7.5 18[a]	75 30[a]	**73a**
2	R = -CH_2OBOM **(b)**	27	76	**73b**
3	R = -$CH_2OAllyl$ **(c)**	9	55	**73c**
4	R = -(*S*)-(+)-CH_2OBn **(d)**	29	58	(*R*)-(-)-**73d**
5	R = *n*-C_6H_{13} **(e)**	24	75	**73e**
6	R = Ph **(f)**	48	58	**73f**

Use 2 equiv of CF_3CONH_2 **(72a)** for all entries; [a] Without BTEAC

All the reactions were completely regioselective affording in only the beta products. However, the reactivity of ring opening of each epoxide with **(72a)** was still low even with the phase transfer catalyst (BTEAC).

Table 1.10. The reaction of *p*-toluenesulfonamide with a series of epoxides under SL-PTC condition and catalytic amount of K_2CO_3



(a-e) **(74a-e)**

entry	epoxides	rxn time (h)	% yield	products
1	R = -CH_2OPh **(a)**	2.5 11[a]	75 54[a]	**74a**
2	R = -$(CH_2)_4$ **(b)**	12	93	**74b**
3	R = -CH_2OBn **(c)**	2	85	**74c**
4	R = *n*-C_6H_{13} **(d)**	6	91	**74d**
5	R = Ph **(e)**	6	93	**74e**

2 equiv of *p*-toluenesulfonamide **(72b)** were used for all entries; [a] Without BTEAC

Under these conditions similar to Table 1.9, only β-amido alcohols were obtained. Likewise, the reactions also took place in a complete regioselectivity with high yields. Epoxide ring opening with both amines resulted in excellent regioselectivity and introduced a phase transfer catalyst to be used in the synthesis of vicinal amino alcohols.

1.4 Objective of the research

The objective of the research is to develop and delineate optimal conditions of the oxirane ring opening, particularly styrene oxide with nitrogen nucleophiles. It is aimed to be able to direct the regiochemistry and stereochemistry of the reactions reliably in order to synthesize optically active vicinal amino alcohols from styrene oxide.

We divided the nitrogen nucleophiles into two types: anionic and neutral nucleophiles. The anionic nucleophiles are composed of azide and phthalimide anions, and the neutral nucleophiles are also further diversified into three main groups: primary aliphatic amines, aromatic amines, and secondary aliphatic amines. For the anionic nucleophiles, we investigated many factors that affect regioselectivity and reactivity of the styrene oxide ring opening under a variety of conditions. Particularly for the azide anion, many factors such as aprotic and protic solvents, reaction temperature, metal counterion of azide, and a phase transfer catalyst were studied for the regioselectivity and reactivity of the styrene oxide ring opening. For phthalimide anion, we investigated the effect of aprotic and protic solvents on the regioselective styrene oxide ring opening and its reactivity as well. Like anionic nucleophiles, the effect of a variety of factors on the regioselectivity and reactivity of styrene oxide with three different groups of amine nucleophiles was investigated.

In order to confirm the stereochemical integrity of the reaction and to verify the mechanism of the reaction, ring opening of the optically active (*R*)-styrene oxide with morpholine under the optimized conditions was investigated. This investigation can contribute to many future applications, for example, in synthesis of natural products, pharmaceutical intermediates and chiral ligands.