CHAPTER III

RESULTS AND DISCUSSION

3.1 Analytical method for the determination of regioselectivity of either azidolysis or aminolysis of oxiranes under conditions

3.1.1 NMR spectroscopy

Regioisomers can usually be distinguished by NMR spectroscopy in such a way their certain resonances must be chemical shift nonequivalent, saying, anisochronous. By integration of one or more pairs of suitable proton signals, the ratio of each regioisomer may be obtained, provided that the magnitude of the observed chemical shifts of nonequivalent protons between these two regioisomers are sufficient to give good baseline resolution. In order to do this, identifying which appropriate chemical shifts belongs to which regioisomers must be achieved. The relative comparison of integration between these two isomeric protons is then calculated by any NMR spectroscopy software such as mestrec23, which is used in this study. The data of the outcome are most reliable just when there are no intervening processes after stopping the reaction. For example, purification process such as extraction or chromatography may cause a significant change of the ratios. It is therefore very important to analyze the crude product before any other purification to be attempted.

3.1.1.1 Direct determination of regioselectivity of the regioisomeric products

For obtaining the crude ^{1}H NMR spectra for integration, the crude sample was prepared by adding 5-6 drops of the reaction mixture into a test tube, and the solvent was

removed by gentle stream of nitrogen for a few minutes. It is important to ascertain that there was no solvent or styrene oxide left because their presence would obscure interesting peaks for integration. However, it must be careful that the drying process should not be too long, since the products may eventually evaporate completely or, otherwise, evaporate at different rates. In such cases the ratio could be misinterpreted. The direct determination requires no additional agent to comparatively integrate the interesting chemical shifts of both regioisomers. An example of NMR spectrum of the crude product from ring opening of styrene oxide by morpholine in TFE is illustrated in Figure 3.1.

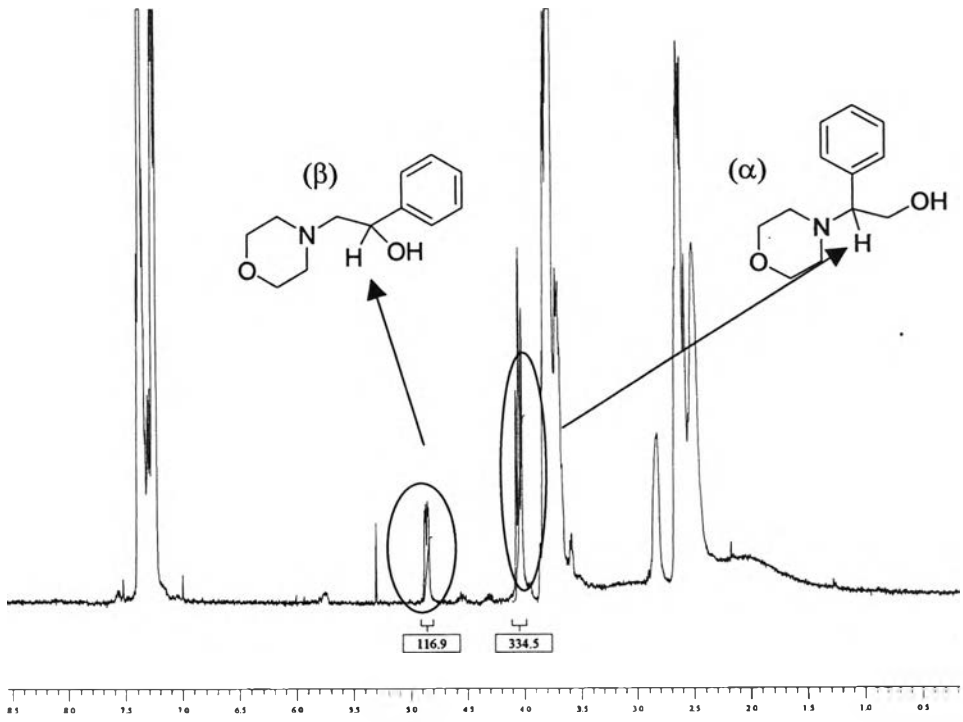


Figure 3.1. The crude ^{1}H NMR spectrum of morpholine ring opening of styrene oxide in TFE at 60 °C for 1.30h

From Figure 3.1, the steps of direct determination are delineated as earlier said. First, the proton chemical shifts of both regioisomers must be identified. Second, the

relative height integration of the same pair of protons for each isomer can be calculated. Then, each alpha and beta regioisomer is calculated in percent of sum of both integration values: that is, the sum of alpha and beta products is one hundred percent of total. In this particular example, the fraction of alpha product = 334.5/(116.9+334.5) or 74 %. The fraction of beta product is then 116.9/(116.9+334.5) or 26 %.

3.1.1.2 Indirect determination of regioselectivity of the regioisomeric products: Internal standard

In contrast with the direct method, there is one more step required for the internal standard method, *i.e.* the addition of an internal standard. It helps not only determine the ratio of the alpha to beta regioisomers similar to the direct method, but, more importantly, also calculate the chemical yield of each isomer even when the products contain other impurity. If possible to apply for our study, it should cut down the process of isolating the regioisomers *via* column chromatography in order to determine the yield of each isomer. The internal standard can be added during the reaction process or after complete reaction. The principal criteria to select an internal standard suitable for determining regioselectivity of the ratio of regioisomers are a) high boiling point, so that it will not evaporate during flowing N_2 (g) to dry solvent off the crude product, b) inert, so that no reaction will occur with other reagents in the reaction, c) its chemical shifts in ^{1}H NMR should not overlap with the chemical shifts of the peaks to be integrated, and d) solubility in the reaction media. If not, a few drops of dichloromethane are added to help solubilize the internal standard into the system. Therefore, it should be enclosed as well whether the method can benefit for our study or not in terms of comparing the ratio of alpha to beta by this indirect method with that of the direct. There were some trial internal standards

used, for example, 1,4-dimethoxy benzene, 4,4'-di-*tert*-butyl biphenyl but hexadecane ($C_{16}H_{34}$) was found to be the most suitable internal standard. The only problem with this standard is the low solubility in alcohols. However, after the reaction was completed, a few drop of dichloromethane may be added to keep the solution homogenous. Analysis of employing this internal standard addition is illustrated in Figure 3.2 which is the same reaction as in Figure 3.1.

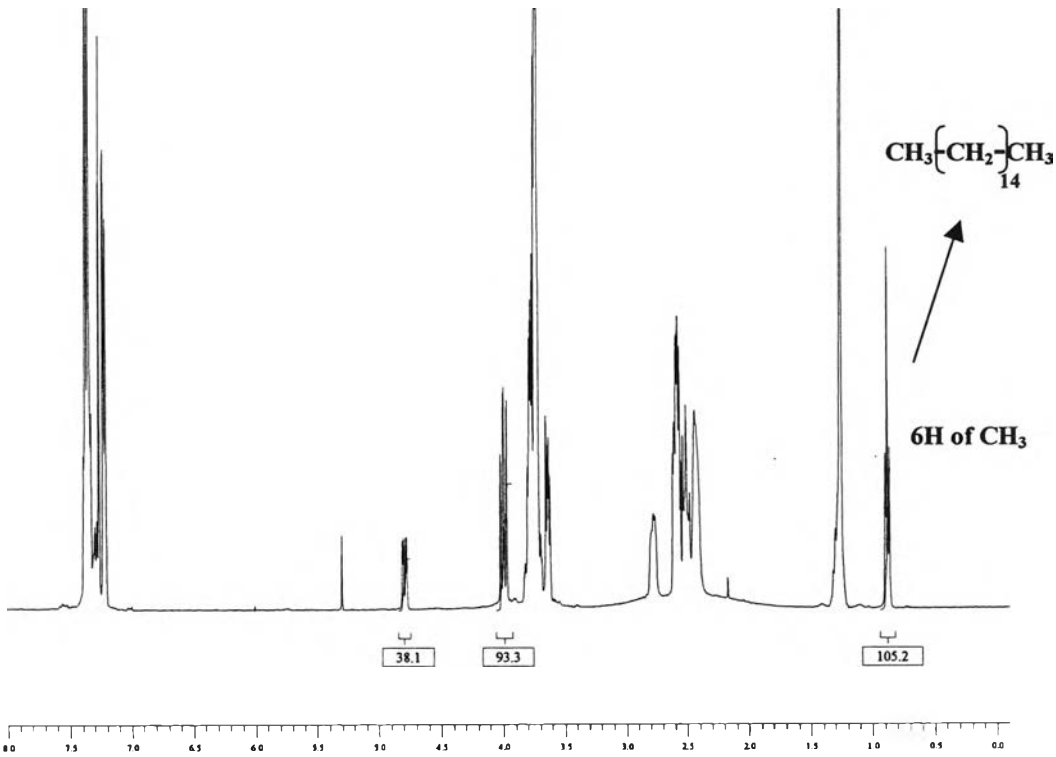


Figure 3.2. The crude ^{1}H NMR spectrum of morpholine ring opening of styrene oxide with an internal standard ($C_{16}H_{34}$) in TFE at 60 °C for 3h, identified for the 6H of CH_3 of $C_{16}H_{34}$

The ratio of alpha to beta regioisomer can be calculated as in Figure 3.1. To calculate the chemical yield for each isomer, the original mole of internal standard must be known. Since the methyl peak of the internal standard contains 6 protons, and then the value is multiplied by the peak height integration per 1 proton of each regioisomer. In this

example, 0.083 mmol of the internal standard was added to the reaction at the beginning. The amount of the alpha product formed in mmol is then (0.083 mmol of $C_{16}H_{34}$/(105.2/6H)) x 93.3/1H = 0.442 mmol or 88 % yield. The amount of the beta product can then be calculated similarly, (0.083 mmol/105.2/6H)) x 38.1/1H = 0.180 mmol or 36 % yield. However, the sum of calculated yield of both regioisomers is more than the amount of starting materials added. Therefore, the method was, unfortunately, yet to fit for the determination of isomeric yield or total yield of the reaction.

3.1.2 Chromatography[83]

Normal column chromatography or flash chromatography is also one of the commonly preparative and affirmative choices for separating and purifying nonvolatile mixtures of organic compounds. Both uses a column packed with a solid stationary phase, the former using silica gel at the size of 70-230 mesh or 0.06-0.2 mm and the latter using silica gel with a smaller particle size at 230-400 mesh or 0.04-0.06 mm. A liquid mobile phase flows through the column by gravity or applied pressure. The techniques use polarity differences to separate materials by two opposing forces: first, the solubility of the sample in the elution solvent system and, second, the adsorption of the sample to the solid phase. These interactions comprise equilibrium, allowing the isomers to be separated. The regioisomeric ratios of the separated alpha to beta products including the isolated yield of the reaction was then determined gravimetrically.

3.2 Analytical methods for the determination of enantiomeric purity of β-amino alcohols by chiral HPLC[84]

The principle of enantiomeric separation by chromatographic method involves short term diastereomeric interactions of the two enantiomers with a chiral stationary phase. The diastereoisomeric complexes formed will have non-identical stabilities and hence elute at different times. The separability factor, $\Delta\delta$, for two components in HPLC chromatogram depends upon the peak shape and is related directly to the several parameters of column, *i.e.* flow rate, particle size, sample size, and quality of packing. Efficient HPLC systems produce good separations for two components having $\alpha \geq 1.05$. In HPLC technique, pre-column derivatization in the absence of racemization with a chiral derivatizing agent may be required to give chromatographically separable diastereomers. An alternative is to use an achiral support and to elute with a chiral eluant. However, the use of chrial stationary phase appears to be the most convenient method. In our work, chromatographic analysis for the optically purity of 2-morpholino-2-phenyl-1-ethanol (alpha-product) and 2-morpholino-1-phenyl-1-ethanol (beta-product) were carried out using the last method on Daicel ChiralCel OD® and ChiralPak AD®. The ChiralCel OD contains *tris*(3,5-dimethylphenyl carbamate) derivative of cellulose, and the ChiralPak AD contains *tris*(3,5-dimethylphenyl carbamate) derivative of amylase as chiral stationary phases. Both have been known for successfully resolving alcohols or aromatic compounds.

3.3 Synthesis of vicinal azido alcohols and phthalimido alcohol

Vicinal azidohydrins are compounds of interest in organic synthesis, and have been largely utilized in synthesis as precursors of 1,2-aminoalcohols or in carbohydrate

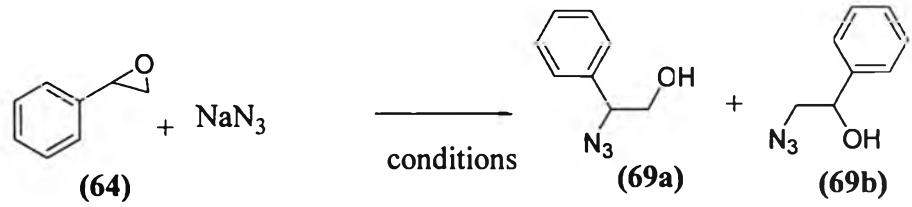
and nucleoside chemistry.[27] Even though there have been a number of methodologies for the azidation of epoxides,[71,73] which seemed to be effective for high yield, most of the study that used styrene oxide was yet to succeed in obtaining high regioselectivity of the beta product in preference to the alpha product. To the best of our knowledge the highest beta to alpha product of azidation of styrene oxide was carried out by using LiN_3 and β-CD in water at room temperature. The condition resulted in the ratio of α:β, 41:59, respectively, with only 32 % yield for 6 h.[85] Therefore, it brought our interest to achieve high ratio of beta to alpha regioisomers at high yield. A simple methodology for the direct azidation of styrene oxide in a variety of protic and aprotic solvents or with a phase transfer catalyst is still lacking.

3.3.1 Regioselective ring opening of styrene oxide with azide as a nucleophile

According to several studies,[27,73,74] the regioselective ring cleavage of styrene oxide to yield beta azido alcohol (beta product) resulting from terminal carbon attack has been low so far. The preference for the formation of the azidoalcohol derived from the attack at the benzylic carbon (α-product) may be explained by the effect of Lewis acidic metal ion or low pH required to activate the oxirane ring. This allows the transition state constituting a partial positive charge at the benzylic carbon stabilized by delocalization energy of benzene ring. In this work we attempted to improve the beta selectivity by optimizing the ring opening reaction of the styrene oxide. Many parameters are known to influence nucleophilicity of the nucleophile. Those considered to be most significant are, first, the solvation energy of the nucleophile, second, the strength of the bond being formed, third, the size of nucleophile, fourth, the electronegativity of the attacking atom, finally, the polarizability of the attacking atom.[86] According to Chini's study,[73] there was

no ring opening reaction of phenyl glycidyl ether with 5 equiv of the sodium azide in acetonitrile at reflux. We first investigate simple azidolysis of styrene oxide by sodium azide without any additive. The effect of solvents and temperatures is shown in Table 3.1.

Table 3.1. Azidolysis of styrene oxide under different conditions



(64) **(69a)** **(69b)**

entry	solvents[a]	reaction time(h)	temp (°C)	ratio α:β[b]	% yield[c]
1	DMF	48	60	40:60	41
2	MeCN	48	60	-	-
3	DMSO	48	100	-	-
4	THF	48	60	-	-
5	EtOH	48	60	-	-
6	2-propanol	48	67	-	-
7	2-propanol:H_2O (1:1)	48	67	-	-
8	EtOH:H_2O (1:1)	48	67	-	-
9[d]	DMF	48	60	26:74	53

10[d]	DMF	7	90	30:70	48
11	DMF (125 μL)	24	90	-	-
12	DMF	8	90	57:43	38
13[e]	DMF	3	90	56:44	22

All entries were done under 0.5 mmol of styrene oxide and 1 equiv of NaN_3 except entries 9 and 10; [a] all entries use 1 mL of a solvent except entry 11; [b] ratio α:β **(69a:69b)** determined by ^{1}H NMR of a crude product which had been extracted by CH_2Cl_2/H_2O; [c] isolated yield of both isomers; [d] use 3 equiv of NaN_3; [e] use 1 equiv of KN_3

From entries 1 to 4, the reaction in DMF appeared to be more efficient than those in DMSO, MeCN, and THF. The reaction time in entry 1 was set up by, at first, follow the reaction by TLC until the styrene oxide was used up. The reaction temperature was arbitrarily assigned to suit for the boiling point of the solvent. The regioselectivity of the products from entry 1 had the beta product in preference to the alpha at 60:40, respectively. The reactions carried out in protic solvents such as ethanol, 2-propanol, and their mixture with water (entries 5-8) gave poor results. In these cases, crude ^{1}H NMR spectra revealed some products resulting from ring opening of styrene oxide by the solvent. The poor yield should not be related to the basicity of the azide anion, since the pK_a of HN_3 is at 4.7 (H_2O)[87], a weak base compared to pK_a of EtOH at 15.9, and therefore this can be explained by solvent effect on the reaction mechanism. Even though the reaction seemed to be favored by polar solvent, these polar protic solvents used did not provide good yield in contrast to polar aprotic solvent particularly for DMF. Stabilization of charge separation of the epoxide is probably favored by polar solvent but at the same time the nucleophilicity of the azide anion may adversely be reduced by

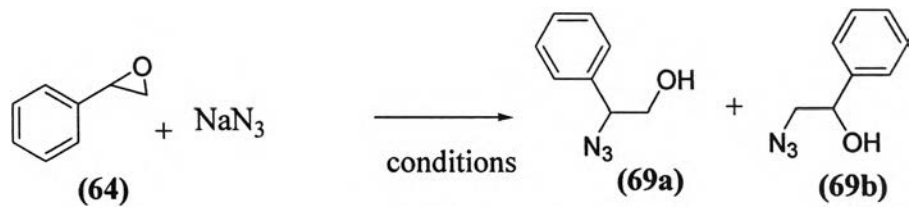
forming hydrogen bonds to the protic solvent which is present in high concentration. Hydrogen bonding decreases the availability of the electrons of the anion to participate in the reaction. Stated another way, the energy required to disrupt hydrogen bonding adds to the activation energy of the reaction.[86] DMF was therefore chosen for further optimization. When the amount of sodium azide increased to 3 equiv at the same temperature, 60 °C (entry 9) it seemed the yield and beta selectivity seemed to be improved. The reaction temperature was increased to 90 °C (entry 10), yet about the same regioselectivity and yield were obtained. Nevertheless, the increased reaction temperature could accelerate the reaction rate significantly and about the same yield was obtained in only 7h. The reason behind applying high excess of sodium azide in entry 9 and ascend of reaction temperature in entry 10, is because a dissolved ionic reactant, sodium azide, is likely to present as ion pairs or larger aggregates in which the reactivity of the anion is diminished by the counter ion attraction with the cation, sodium ion. In polar, aprotic solvents, no hydrogen bonding exists. Not only is the lone pair electron of anion, therefore, more easily available for nucleophilic attack in such solvents, but also has higher energy level because of the absence of solvent stabilization by hydrogen bonding. Dissociation energy must be compensated against this electrostatic attraction to permit the anion to react as a nucleophile by applying polar, aprotic solvents or reaction temperature. Metal cations such as Na^+ or K^+ are strongly solvated by the solvents, particularly dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF). The oxygen atoms of these molecules act as electron donors toward the cations. Hence the results in entry 1 and 9-10 whereby the reactions were conducted in DMF appeared to be the most fruitful, whereas those carried out in other protic solvents did not. However, the most

difficult problem to be solved in working up of these reactions is how to get rid of DMF from the crude products. This was achieved by partitioning the reaction in CH_2Cl_2/H_2O and extracted several times with H_2O. As a consequence, the isolated yields of these reactions must be impaired. In entry 11 an attempt was made to reduce the amount of DMF used as reaction media from 1 mL to 125 μL. Unfortunately, no desired reaction took place. It should be enclosed that when comparing entry 1 with entry 12 or 13, of which the increased reaction temperature or metal salt ion, respectively, were used with a fixed 1 equiv of sodium azide, their regioselective yields changed to be more alpha than beta ratios. It may be because of the effect of higher activation of styrene oxide ring opening generated by increasing reaction temperature or better coordinating with the size of potassium ion.

Phase transfer catalysts (PTC) are salts in which one of the ions has large nonpolar substituent groups that confer good solubility in organic solvents. Solid-liquid phase transfer catalysts have been used in assisting the ring opening of epoxides by anionic nucleophiles. As an example, epoxide ring opening with anion of trifluoroacetamide as a nucleophile in the presence of benzyltriethylammonium chloride (BTEAC) as a PTC has been successfully achieved in dioxane.[78] This kind of the reaction can be analogous to our study; hence, it is worth investigating this condition. In previous experiment sodium azide and styrene oxide are in separated phases due to the insolubility of NaN_3 in the reaction medium. In the presence of a phase transfer catalyst, its cation should trap the azide anion and extract the anion into organic phase in which styrene oxide is solubilized, and as a result such anion is induced into the organic phase. Apart from tetralkylammonium salts, crown ethers[85] such as 15-crown-5 or 18-crown-6 can also

be used as another type of PTC. In the absence of the crown ether, sodium or potassium azides may be poorly reactive toward styrene oxide. The solubility and reactivity enhancement result in when the ionic compound is dissociated to a tightly complexed cation and a "naked" anion. The complexed cation, surrounded by the nonpolar crown ether, has high solubility in the nonpolar media. Hence, the anion should be free to attack the oxirane.

Table 3.2. Effects of PTC on yield and regioselectivity in azidolysis of styrene oxide



(64) (69a) (69b)

entry	azide / PTC	reaction time (h) and temp (°C)	solvents	ratio α:β[a]	% yield[b]
1	NaN_3/BTEAC	3 (90)	DMF	37:63	47
2	NaN_3/TBAH	7 (90)	DMF	39:61	51
3	NaN_3/TAHS	7 (90)	DMF	47:53	38
4	NaN_3/BTEAC	24 (90)	Dioxane	-	-
5	NaN_3/15-crown-5	3 (90)	DMF	52:48	41
6	KN_3/18-crown-6	24 (90)	DMF	61:39	30
7	NaN_3/15-crown-5	24 (rt)	DMF	25:75	53

8	NaN_3/15-crown-5[c]	24 (rt)	DMF	18:82	59
9	KN_3	3 (90)	DMF	56:44	22
10	NaN_3	8 (90)	DMF	57:43	38

All entries were done under 0.5 mmol of styrene oxide, 1 equiv of NaN_3 or 1 equiv of KN_3 and 10 mol % of a phase transfer catalyst; [a] ratio α:β or **(69a:69b)** determined by ^1H NMR of a crude product which had been extracted by CH_2Cl_2/H_2O; [b] isolated yield % of both isomers; [c] 30 mol % used

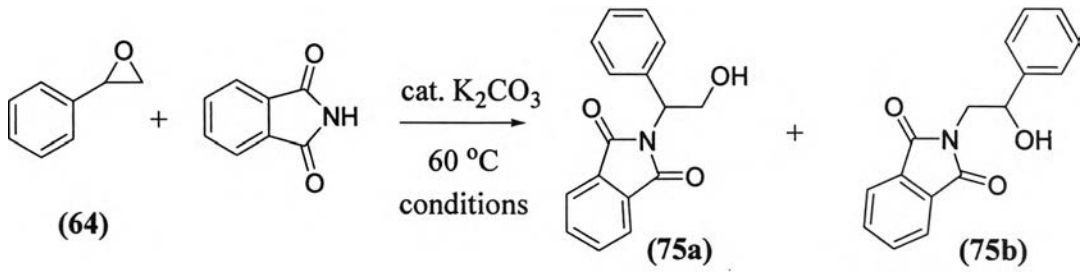
It is the BTEAC, TBAH, and TAHS that are a group of phase transfer catalysts commonly used in the heterogeneous reaction. In the presence of these catalysts, approximately similar reactivity and regioselectivity (entry 1-3) to the reaction in DMF alone were obtained. In all cases a moderate regioselectivity for beta isomer was observed. 1,4-dioxane was also used as an example of a lower polar, aprotic solvent to investigate whether the two phases may come into contact better. However, the result is very mediocre due to very low conversion of styrene oxide even after a prolonged reaction time (entry 4). When the reactions in entry 5 and 6 were performed in the presence of 15-crown-5 or 18-crown-6, the beta-regioselectivity was deteriorated. The reaction in the presence of 18-crown-6 required longer reaction time to provide complete conversion. It was proposed that by reducing the activation energy of the reaction, *eg.* by descending its reaction temperature the regioselectivity might be improved. This assumption was likely to be true, since when the reaction was changed to run under room temperature within longer reaction time, a much better beta was achieved at about 4:1 (β:α). The effect of a phase transfer catalyst (entry 1-3) becomes more obvious to provide higher beta than alpha products, but contrarily when there was no phase transfer catalyst used (entry 9-10), lower beta to alpha products ratios were obtained. To the best of our

knowledge, this is the best achievement to obtain the beta isomer of azido alcohols derived from styrene oxide.

3.3.2 Regioselective ring opening of styrene oxide with phthalimide as a nucleophile

Another anionic nitrogen nucleophile that has captivated our attention was a phthalimide anion. Ring opening of 3-bromo-4-methoxy styrene oxide by phthalimide in the presence of potassium phthalimide (5 mol %) in DMF at 90 °C for 18 h can provide 70 % yield of β-attack product to be used as an intermediate for synthesis of chelonin B in Lawrence's study.[77] Compared to the previous study using a polar, aprotic solvent introduction of the neutral nucleophile with catalytic amount of a strong base to cause the ring opening of epoxide in protic or aprotic solvents was indeed interesting if the conditions for the phthalimide ring opening of styrene oxide can improve its reactivity, or visualize any desired results such as reverse regioselectivity of the product ratio as in Table 3.3.

Table 3.3. Phthalimide ring opening of styrene oxide in protic and aprotic solvents under conditions



		solvents				
entry		EtOH	TFE	DMF	MeCN	Dioxane
1	reaction time(h)	12	48	12	48	48
2	ratio α:β[a]	>99 %[c]	No rxn	5:95	No rxn	No rxn
3	% yield α,β[b]	22 %[c]	No rxn	49 %[c]	No rxn	No rxn

The reactions done under 0.5 mmol of styrene oxide with 1.1 equiv of phthalimide and 5 mol % K_2CO_3; [a] ratio α:β or **(75a:75b)** determined by ^{1}H NMR of a crude product; [b] isolated yields of alpha and beta products from column chromatography; [c] only the β product has been isolated

The result in Table 3.3 showed that the solvent type of the reaction had strong effect on the reaction efficiency as compared with protic, ethanol and trifluoroethanol, and aprotic, dimethyl formamide, acetonitrile, and 1,4-dioxane. There were only beta isomers obtained in the reactions in ethanol and DMF. Moreover, the yield of the reaction performed in DMF appeared to be significantly better than in ethanol. According to Lawrence's proposed mechanism in his study,[77] once the catalytic phthalimide anion formed, the attack of ring opening of an epoxide occurred. Then, the ring opening

intermediate can protonate excess of free neutral phthalimide, which was regenerated to be phathalimide anion. In this case, the potassium carbonate should behave similarly to the potassium phthalimide as shown in Figure 3.3.

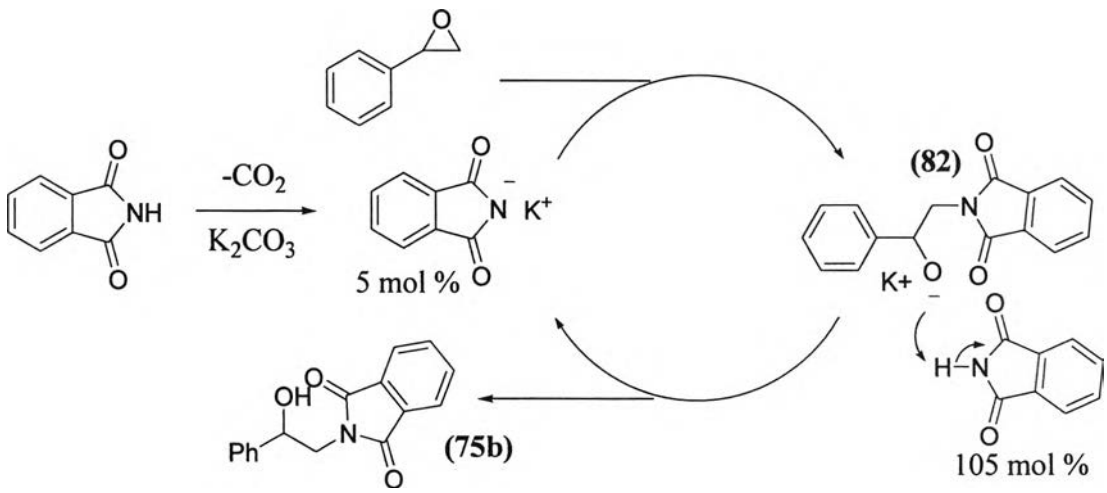
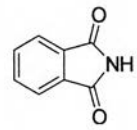


Figure 3.3. The proposed mechanism of phthalimide ring opening with catalytic amount of K_2CO_3 in DMF

However, the catalytic cycle may not be appropriately applied for protic solvents, especially for TFE which is quite acidic. The basicity of catalytic carbonate anion, with pK_{a2} at 10.32 in Table 3.4 can be strong enough to be interfered by such acidic solvent, as TFE (pK_a = 12.5). Although the pK_a is high relative to that of neutral phathalimide (8.3), the concentration of TFE is much higher in the reaction medium. This interference can deter the formation of the phathalimide anion. In addition, if the intermediate **(82)** is basic enough to deprotonate the neutral phathalimide at this pH, it will be possible to deprotonate the TFE in some certain extent too. This hypothesis was quite substantiated, because no reaction was observed in TFE. As anticipated, the effect of basicity of catalytic carbonate anion on efficiency of the reaction became subsided in ethanol. This may be attributed to a higher pK_a of ethanol at 15.9. Solvation of metal ion by ethanol is

less efficient than that by DMF, a high polar aprotic solvent. This factor can also be used to explain for poor efficiency of the reactions when they were experimented in acetonitrile or dioxane. As earlier, we have discussed that with anionic nucleophile, azide anion, the effect of polar aprotic solvent is more likely to provide good yield. Also we provided the reason with that the solvent polarity on stabilizing charge separation of the epoxide is probably favored by the polar solvent. Once anionic nucleophile form, they must consequently come closely to the partial positive carbon electrophile to produce the products. Therefore, we can conclude again that both for azide and phthalimide anions, their nucleophilicity may adversely be reduced by forming hydrogen bond to protic solvent, so that the reaction of styrene oxide ring opening with anionic nucleophiles should work well in polar aprotic solvent, particularly DMF. The effect of solvent polarity on charge separation at the transition state of this reaction mechanism can also infer why the nonpolar aprotic solvents such as dioxane and THF used in phthalimide and azide anions in Table 3.3 and 3.1, respectively, did not provide good yield, because on top of providing low solubility for ionic compounds the solvents have small dipole moments, and hence are much less effective at stabilizing the development of charge separation.[86] Moreover, specific structural effect may cause either the reactants or the transition states to be differently strongly solvated by other polar aprotic solvents such as acetonitrile and DMSO (Table 3.1 and 3.3) used for study in azide or phthalimide anionic nucleophiles, so that their yields were very different.

Table 3.4. Lists of pK_a of conjugate acids[87,88]

entry		pK_a in H_2O
1		8.3
2	HCO_3^-	10.32 (pK_{a2})

The regioselective ring opening of styrene oxide with either azide or phthalimide as a nucleophile in our study can be differentiated from each other. Phthalimide provided the higher regioselectivity of α:β products (5:95, respectively) than azide. This is because in addition to the earlier discussion of the effects phthalimide is a more sterically demanding nucleophile; therefore, it can enhance this high regioselectivity in preference for the beta product.

3.4 Synthesis of vicinal amino alcohols by epoxide ring opening with amines

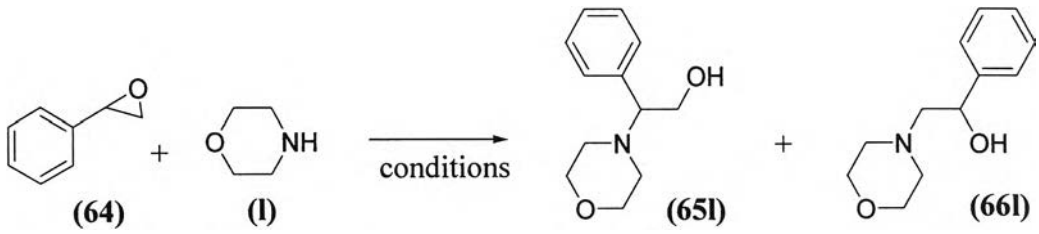
A regioselectivity in ring opening of styrene oxide with amines was also investigated. Aminolysis of epoxide is often carried out in an aprotic solvent in the presence of a Bronsted acid or Lewis acid catalyst[25,60] or reagent.[61] Aminolysis of epoxides has ever been performed in protic solvents such as alcohols or fluoroalcohols.[64] However, only one example of aminolysis of styrene oxide has been studied so far and no regioselectivity and stereochemistry have been illustrated. Like anionic nucleophiles, the poor regioselectivity of aminolysis of styrene oxide may generally deem due to the opposing steric and electronic effect of the phenyl substituent. In this study we have attempted at performing the ring-opening reactions of styrene oxide by a variety of

representative amines in alcoholic media. The amines used can be classified in 3 types: (i) aliphatic primary amines, (ii) aromatic amines, (iii) aliphatic secondary amines. The principle is to employ acidity of the alcohols, forming hydrogen bonds with the oxirane oxygen atom due to the electron-withdrawing character of fluoroalkyl groups, to enhance the rate as well as to control the regioselectivity. We also demonstrated the effect of the solvents on the streospecificity of the product by virtue of optically active styrene oxide.

3.4.1 Kinetics of aminolysis of styrene oxide with morpholine in protic and aprotic solvents

At first, to define the conditions for aminolysis of styrene oxide with amines, there must be investigation of the kinetics of the reactions in protic and aprotic solvents. A reaction between styrene oxide and morpholine was chosen as a model. This can be followed by monitoring the limiting agent every 30 minutes-1 h by thin layer chromatography (TLC). Morpholine was chosen as the limiting agent, because its existence can be proven by staining with $KMnO_4$, which oxidizes the amine to become a brown spot. The reaction times were recorded when the expected spot of the morpholine had disappeared to confirm completing the reactions. The reactions were experimented using an excess of styrene oxide (1.5 equiv) in five representative solvents at room temperature and 60 °C. The regioselectivity was also measured by NMR and by gravimetry after column chromatography as mentioned earlier. The yield of the products was determined gravimetrically (Table 3.5).

Table 3.5. Ring opening styrene oxide with morpholine under protic and aprotic solvents at 29 and 60 °C



(64) (l) (65l) (66l)

temperatures		solvents				
		EtOH	TFE	HFIP	MeCN	CH_2Cl_2
29 °C	reaction time(h)	O/N	3.5	2	O/N	O/N
	ratio α:β[a]	40:60	76:24	78:22	-[d]	39:61
	% yield α,β (total yield)[c]	34,56 (90)	66,25 (91)	48,6 (54)	4,15 (19)	20,31 (51)
	ratio α:β[b]	38:62	73:27	89:11	21:79	39:61
60 °C	reaction time(h)	4	1.5	1.5	O/N	-
	ratio α:β[a]	37:63	74:26	73:27	13:87	-
	% yield α,β (total yield)[c]	35,56 (91)	68,28 (96)	55,8 (63)	8,35 (43)	-
	ratio α:β[b]	38:62	71:29	87:13	19:81	-

The reactions done under 0.5 mmol of morpholine with 1.5 equiv of styrene oxide in 1 mL of solvent; O/N overnight; [a] ratio α:β or **(65l:66l)** as determined by ^{1}H NMR of a crude product; [b] ratio α:β or **(65l:66l)** as determined from isolated yields after column chromatography; [c] isolated yields of alpha and beta products, and total of both isomers in bracket after column chromatography; [d] the α:β could not be determined due to a poor quality of its crude ^{1}H NMR

In other studies,[25,53] particularly when metal salts were used for aminolysis of ring opening epoxides, the ratio of α:β products usually determined by ^{1}H NMR of crude products after extraction with water and petroleum ether. Determining the ratio of α:β in these studies, therefore, contains some error. The absence of metal salt in this work allows simple evaporation to obtain the crude product. In this way calculating the ratio of their regioisomers from ^{1}H NMR spectra from their crudes can be attained without any interfering purification, which may contribute to altering the ratios. The different rate of reactions between these two kinds of the solvents, protic and aprotic was remarkable. Even at room temperature the reactions in protic solvents are faster than in aprotic solvents, especially in the fluoroalcohols, TFE and HFIP. Not only did the reactivity of styrene oxide ring opening with morpholine increase both at 60 °C and room temperature to become comparable to that of the Lewis acid-catalyzed styrene oxide ring opening with morpholine,[62] but also their yields seemed to be quite high.

The reactivity and regioselectivity of styrene oxide ring opening with the amine is highly dependent on the solvent. The solvent effect is caused by (a) effect of solvent polarity and (b) specific structural effect (explained in the next table). The effect of solvent polarity (a) on charge separation can stabilize the relative energies of the ground state of the reactants (amine and epoxide) and their transition states. The relationship between reactivity as well as regioselectivity and solvent type of styrene oxide ring opening with amines is probably favored by polar protic solvent (Table 3.5). Morpholine

nucleophile should approach closely at the partial positive carbon electrophile. Therefore the reactivity of the reaction depends on the acidity of the protic solvents (determined by pK_a of the solvents) relative to basicity of morpholine to deactivate the amines or to activate the epoxide ring opening for increasing reactivity of the reaction. The activation is from H-bonding of protic solvents with the epoxide ring opening, and the solvation of the protic solvents can stabilize the reaction by neutral-neutral molecule interaction which contains charge at the transition state as shown in Figure 3.4. Therefore, the polar solvents such as alcohols may better help stabilize charge at this transition state than the aprotic solvents. Solvents that fall in the aprotic class, namely acetonitrile and dichloromethane, are much less effective at stabilizing the development of charge separation.[86] These molecules do not have hydrogen capable of forming hydrogen bonds and dichloromethane has very small dipole moments; therefore, the reactions used by these aprotic solvents usually proceed much more slowly to provide only at 19 % (29 °C) and 43 % (60 °C) in MeCN and 51 % (29 °C) in CH_2Cl_2. Because the reactivity of the reactions using aprotic solvents was much relied on nucleophile itself, their regioselectivity is of more beta than alpha products.

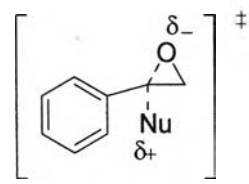


Figure 3.4. Transition state of the aminolysis of styrene oxide ring opening

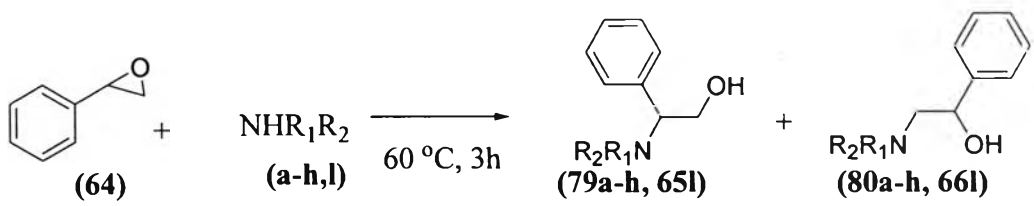
It can be concluded now that for the regioselective ring opening of styrene oxide with morpholine the higher acidicidity of the protic solvents HFIP > TFE > EtOH, the more predominant alpha regioisomer and the faster their reactivity obtained at both temperatures with high yields. It is interesting that this selectivity was inverse to the

regioselectivity of the same reaction catalyzed by metal triflates, which contributed to slightly higher ratios of β to α.[55]

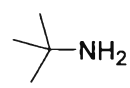
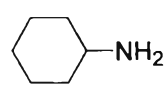
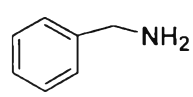
3.4.2 Study of other nucleophilic ring opening of styrene oxide in alcoholic solvents

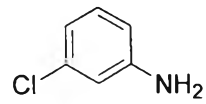
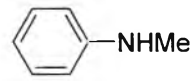
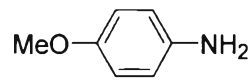
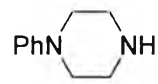
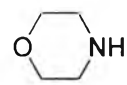
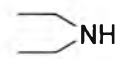
Here the alcoholic solvents have provided us with regioselective development on aminolysis of styrene oxide ring opening. Further investigation included three representative kinds of amines, for the first type: primary aliphatic amines, the second one: aromatic amines, and the last: secondary aliphatic amines. The objective of the study is to compare these three groups of the amines for the ring opening reactions of racemic styrene oxide in protic solvents.

Table 3.6. Regioselective ring opening of styrene oxide with amines in the protic solvents at 60 °C for 3 h.



(64) **(79a-h, 65l)** **(80a-h, 66l)**

code	structure	equiv	R_1	R_2
a		5	H	*tert*-butyl
b		2.5	H	cyclohexyl
c		2.5	H	benzyl

d		1.1	H	*m*-Cl-C_6H_4-
e		1.1	CH_3	C_6H_5-
f		1.1	H	*p*-OCH_3-C_6H_4-
g		1.1	-$(C_2H_4)_2$-N-C_6H_5	-$(C_2H_4)_2$-N-C_6H_5
l		1.1	-$(C_2H_4)_2$-O	-$(C_2H_4)_2$-O
h		5	-$(C_2H_5)_2$	-$(C_2H_5)_2$

		solvents					
		EtOH		TFE		HFIP	
entry	amine→ products	α:β[a]	% yield α,β[b]	α:β[a]	% yield α,β[b]	α:β[a]	% yield α,β[b]
1	**a→79a,80a**	11:89 (24:76)	4,13 (17)	44:56 (44:56)	40,51 (91)	No rxn	No rxn
		13:87 (22:78)	12,43 (55)[c]				
2	**b→79b,80b**	21:79	12,57	54:46	47,24	No rxn	No rxn

		(17:83)	(69)	(66:34)	(71)		
3	**c→79c,80c**	34:66 (27:73)	20,53 (73)	68:32 (63:37)	50,29 (79)	87:13 (79:21)	38,10 (48)
4	**d→79d,80d**	76:24 (75:25)	15,5 (20)	>99 %[d] (97:3)	90,3 (93)	>99 %[d] (>99 %)[d]	57,<1 (57)
		74:26 (73:27)	30,11 (41)[c]				
5	**e→79e,80e**	76:24 (78:22)	40,11 (51)	94:6 (96:4)	89,4 (93)	99:1 (98:2)	88,2 (90)
6	**f→79f,80f**	68:32 (71:29)	41,17 (58)	>99 %[d] (>99 %)[d]	63[d]	-	-
7	**g→79g,80g**	35:65 (35:65)	32,60 (92)	69:31 (68:32)	63,29 (92)	86:14 (74:26)	26,9 (35)[e]
						85:15 (88:12)	51,7 (58)[f]
8	**l→65l,66l**	37:63 (37:63)	30:51 (81)	71:29 (69:31)	68,30 (98)	78:22 (88:12)	74,10 (84)[f]
9	**h→79h,80h**	16:84 (20:80)	14,57 (71)	49:51 (49:51)	44,46 (90)	No rxn	No rxn

The reactions done under 0.5 mmol of styrene oxide usually with 1.1 equiv of amines, except those indicated in the table, in 1 mL of solvent; [a] ratio α:β as determined by ^{1}H NMR of a crude product and ratio α:β as determined by an isolated yield after column chromatography in the parenthesis; [b] isolated yields of alpha and beta products, and total of both isomers in bracket from column chromatography; [c] reaction time prolonged to be overnight; [d] α product only identified; [e] use 1.1 equiv of the amine; [f] use 2.5

equiv of the amine; Entries 1-3 are primary aliphatic amines; Entries 4-6 are primary and secondary aromatic amines; Entries 7-9 are secondary aliphatic amines

For reactivity of styrene oxide ring opening with the amines, secondary aliphatic amines (entries 7-9) used in the reactions were more effective nucleophiles in all the solvents than primary aliphatic and aromatic amines (entries 1-6). However, in TFE all types of amines reacted efficiently to produce very high yields of the expected products. For regioselectivity, It becomes more evidenced that stronger acidic protic solvents can induce the higher ratio of the alpha regioisomers. Much consistent with our preceding hypothesis, the alpha:beta ratios increased with the order: EtOH < TFE < HFIP for all kinds of amines tested under this condition. Primary and secondary aliphatic amines (entries 1-3 and 7-9) gave more of the beta regioisomers in ethanol and the proportion of the alpha-regioisomer increases when TFE and HFIP were used. Primary and secondary aromatic amines (entries 4-6) provide the alpha regioisomers as the major product, especially in TFE and HFIP whereby the alpha-regioisomers formed almost exclusively. The regioselectivity of these amines along with their reactivity of the reactions depend on a number of effects that are important to explicate as followings.

Concerning the reactivity, first, the quantity of the amines used is important, since it can be observed that as when stoichiometric amount of benzylamine was allowed to react with styrene oxide in ethanol (not reported in the table), very poor yield was obtained even after 2 days at 60 °C. A significant improvement was achieved upon applying an excess of benzylamine (2.5 equiv), whereby a good isolated yield of 73 percent was obtained. It can be explained by the formation of *N,N*-disubstituted product resulted from the attack of the styrene oxide by the mono-substituted product initially

formed, which resulted in a lower amount of the desired product. The same improvement in yield upon increasing the amounts of the amines used was also applicable for other amines as well. For example in entry 7 the isolated yields were increased from 35 to 58 percent when the *N*-phenyl piperazine was changed from 1.1 equiv to 2.5 equiv. This is in agreement with Das,[64] who reported that the method using, HFIP, failed to promote cyclohexene oxide ring opening with both diethylamine and benzylamine at 1.1 equiv under reflux for 4 days. In our case, however, a fair yield of benzylamine ring opening product was obtained in HFIP under a milder condition. It can be, therefore, concluded at this beginning by the fact that the kinetic mechanism of S_N2 holds the answer for such factor, because the second order reaction is based on both of the concentration of styrene oxide and nucleophile to enhance their reaction rate.

Second, another important factor is the relationship between nucleophilicity and basicity of amines, which contributes to their reactivity and regioselectivity of products. When comparing three different kinds of the representative amines for each solvent, we observed that the primary aliphatic amines (entries 1-3) showed more tendency to form more beta isomer than aromatic and secondary aliphatic amines (entries 4-8) except entry 9. This was more evidenced in ethanol than in TFE or HFIP. For their reactivity, secondary aliphatic amines are the most efficient in all alcohols used. The nucleophilicity of the amines is determined by a delicate balance of steric, electronic, and solvation effects as well as others. The rather sterically hindered and highly nucleophilic *tert*-butylamine (entry 1), diethylamine (entry 9), and cyclohexylamine (entry 2) provide a rather high ratio of beta products especially in ethanol solvent. Both steric effect and high nucleophicity contribute to the preference of beta attack. The steric effect may also result

in poor yield. For example, in entry 1 the styrene oxide ring opening with *tert*-butylamine in ethanol gave the products (α and β) in only 17 % yield. However, its higher yield was obtained when the reaction time was increased. Electronic effect which is imparted by the inductive effect of each amine can influence their nucleophilicity on reactivity and regioselectivity of the styrene oxide ring opening with these three groups of amines in the alcohols. The effect can be caused by electronegativity of the heteroatom or functional group that is attached to the amine. For aromatic nucleophiles, partially or fully delocalization of lone pair electron nitrogen into π-electron of aromatic ring is also able to withdraw electron density. The HOMO of the nucleophile is decreased due to the aromatic ring, so the reactivity of *m*-chloroaniline (entry 4), which is also attached to a withdrawing group able to stabilize the electron delocalized within the ring, is very low in ethanol. The nucleophilicity also relies on the solvation energy of the amines or the solvent effect which is related to the acidity of the solvents: EtOH < TFE < HFIP relative to the basicity of the amines. The solvent effect is caused by (a) effect of solvent polarity and (b) specific structural effect. The effect of solvent polarity or electrostatic solvent effect (a) on the reaction mechanism can be explained by the fact that it affects the relative energies of the ground state of the reactants (amines and epoxide) and their transition states by stabilizing charge separation. The relationship between reactivity as well as regioselectivity and solvent type of styrene oxide ring opening with amines is probably favored by polar protic solvent according to the result shown in Table 3.5. The reactivity of the reaction depends on the acidity of the protic solvents determined by pK_a of the solvents relative to basicity of the amines to protonate or deactivate the amines, or to activate the epoxide ring opening for increasing reactivity of the reaction. As a result,

the acidity of the protic solvents for aminolysis of styrene oxide ring opening must not be too high relative to the basicity of amines. Due to the electron-withdrawing character of fluoroalkyl groups, TFE and HFIP have high acidity and ability to form hydrogen bonds, not only to epoxide but to the amines. Thus it seems that there are two competitive impacts of TFE and HFIP on ring opening of styrene oxide dependent on basicity of the three groups of amines which contributes to their nucleophilicity. First is an activation of the oxirane through hydrogen bonding, and second is a deactivation of the amines by salt or hydrogen bond formation with the solvent. In ethanol which is not particularly acidic, the solvation energy to stabilize the reactants and their transition states (hydrogen bonding) may be low compared with the other two protic solvents. HFIP interacts more strongly on the primary aliphatic amines than either aromatic or secondary amines as observed from heat evolution upon mixing the amine with the alcohol. The results showed no reaction in entries 1, 2, and 9 (Table 3.6) when the primary aliphatic amines and diethylamine were used in HFIP. It proposed that the amines were deactivated by salt formation oı HFIP. This can be verified by interrelation between the pK_a value of HFIP and the pK_a values of the amines. Considering the three amines that failed to provide the ring opening product in HFIP, which are *tert*-butylamine, cyclohexylamine, and diethylamine, of which pK_{aH} values are 10.45, 10.67, and 10.99, respectively (Table 3.8) comparing with the pK_a of HFIP at 9.3 (Table 3.7). There must be strong acid-base interaction of these highly basic amines with HFIP. As a result their nucleophilicity was decreased even at excess of the amines used. From Table 3.8, benzylamine has the lowest basicity of all primary aliphatic amines used in the study; hence, providing better yield than the others. On the other hand the interaction between the amines and the solvents,

especially for TFE and HFIP, becomes less affected when they are either aromatic or contain an electron withdrawing group used (entries 4-8). The low basicity of other secondary aliphatic amines, for example, *N*-phenyl piperazine and morpholine, is similarly attributed to electronic effect. As with this effect on their nucleophilicity, the reactivity of styrene oxide ring opening with secondary aliphatic or aromatic amines (entries 5, 7 and 8) was high in ethanol and even higher in TFE. Therefore, there is low electron density of nitrogen accessible to deprotonate an acidic solvent. In aromatic amines, the electron on the nitrogen is of course delocalized by the presence of the aromatic ring. The low basicity of *m*-chloroaniline is not only because of effect of aromatic ring but also chlorine atom on less electron density to abstract proton. In these cases the beneficial effect of higher acidic protic solvents is more readily observed, since the activation of epoxide by the acidic solvents, HFIP at most, is accounted for on higher alpha regioisomer. For example, it contributed to excellent yields for *N*-methylaniline at the ratio of 99:1 (α:β) and 90 % yield in entry 5 as well as in entry 8 for morpholine at the ratio of 78:22 (α:β) and 84 % yield. In addition, reactions in ethanol generally resulted in poorer yield, especially for *tert*-butylamine and *m*-chloroaniline (entries 1 and 4) presumably because ethanol is poor at activating epoxide ring opening towards sterically hindered or weakly nucleophilic amines. However, the reactivity can be increased by a more acidic alcohol such as TFE. Therefore, the reactivity and regioselectivity of styrene ring opening with amines largely depend on the relationship between nucleophilicity and basicity of amines by the acid-base interaction determined by pK_a of the solvents and pK_{aH} of the amines. The lower the pK_a of the solvents is, the higher the reactivity of the reaction and the higher the ratios of alpha to beta products

become, with the exception that such amines must not be too strongly basic relative to the protic solvent. In contrast, when there is low acid-base interaction like in EtOH, the more nucleophilic the amines, the higher the reactivity of the reactions became and the higher the ratios of beta to alpha product obtained.

Another kind of the effect that contributes to reactivity and regioselectivity of styrene oxide ring opening with amines is specific structural effect on reactivity (b). This is because such solvation can also affect the relative energies of the ground state and transition state and cause rate variations from solvent to solvent. For example, when the reactions of morpholine were carried out similarly to entry 8, except change of a solvent to be phenol (pK_a 9.95) or pentafluorophenol (pK_a 5.3),[89] their crude ^{1}H NMR results showed phenol or pentafluorophenol ring opening products of styrene oxide predominantly. Even though the pK_a of HFIP (9.3) is about the same as that of phenol, the reactions between two solvents were not the same. The effect can be related to its chemical nature such as its polarizability or solubility.[86]

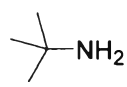
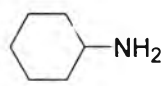
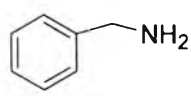
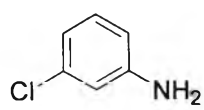
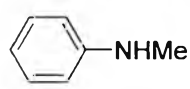
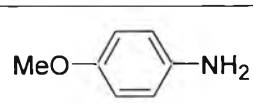
Interestingly, as far as morpholine ring opening of styrene oxide concerned, there has never been any study that showed high regioselectivity and yield on alpha to beta products.[43,55,61,62] Another example that was obvious to show the efficiency of using the fluoroalcohols to enhance high regioselectivity was entry 3, which increased the α-benzylamine-substituted regioisomer at the ratio of 68:32 (α:β) in TFE or 87:13 in HFIP, but there was only 60:40 (α:β) ratio of similarly benzylamine-substituted regioisomer found in the use of $LiClO_4$ as a catalyst in MeCN.[25] Therefore our methodology may be able to use for reversing regioselectivity of styrene oxide ring opening with primary and secondary aliphatic amines in preference of the alpha substituted product, because

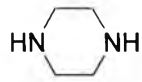
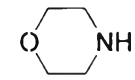
primary and secondary aliphatic amines usually considered as good nucleophiles often prefer attack of styrene oxide at the beta position.[58,62]

Table 3.7. Lists of K_a and pK_a of protic solvents in H_2O[90]

solvents	K_a	pK_a
EtOH	1.25×10^{-16}	15.9
TFE	3.98×10^{-13}	12.4
HFIP	5.01×10^{-10}	9.3

Table 3.8. Lists of K_{aH}, pK_{aH} of their conjugate acids in H_2O

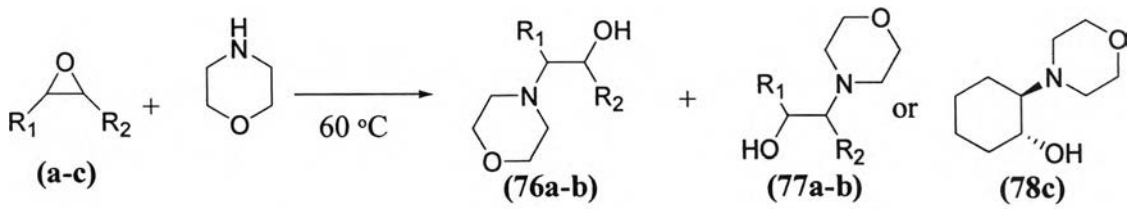
amines	K_{aH}	pK_{aH}
	3.55×10^{-11}	10.45[91]
	2.14×10^{-11}	10.67[92]
	4.68×10^{-10}	9.33[92]
	3.31×10^{-4}	3.48[93]
	1.62×10^{-5}	4.79[92]
	5.01×10^{-6}	5.3[92]

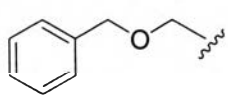
	1.48×10^{-10} and 2.75×10^{-6}	9.83 and 5.56[94]
	4.37×10^{-9}	8.36[87]
	1.02×10^{-11}	10.99[92]

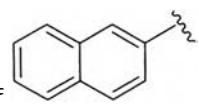
3.4.3 Kinetics of aminolysis of other oxiranes with morpholine in protic and aprotic solvents

As previously seen that the protic solvents especially fluoroalcohols can promote the ring opening of styrene oxide with a variety of amines, it is interesting to see whether they still impart the same contribution to different oxiranes. Three other oxiranes, namely benzyl glycidyl ether, β-naphthalene oxide, and cyclohexene oxide were selected for kinetics study with morpholine in different solvents as shown in Table 3.9.

Table 3.9. Regioselective ring opening of unsymmetrical and symmetrical oxiranes with morpholine in protic and aprotic solvents at 60 °C



(a) R_1 =  R_2 = H

(b) R_1 =  R_2 = H

(c) R_1, R_2 = $-CH_2CH_2CH_2CH_2-$

			solvents			
entry	substrate→ products		EtOH	TFE	MeCN	Toluene
1	**(a)→76a,77a**	reaction time(h)	3	2	O/N	O/N
		% yield[a]	89	86	78	44
		ratio α:β[b]	← β-only →			
2	**(b)→76b,77b**	reaction time(h)	3	1.5	O/N	O/N
		% yield (α,β) (total yield)[a]	37,56 (93)	69,24 (93)	27,57 (84)	16,32 (48)
		ratio α:β[b]	39:61	74:26	29:71	41:59
3	**(c)→78c**	reaction time(h)	O/N	4.5	O/N	O/N
		% yield[a]	70 (trans)[c]	89 (trans)[c]	No rxn	No rxn

The reactions done under 0.5 mmol of morpholine with 1.5 equiv of three oxiranes in 1 mL of solvent; O/N overnight; [a] isolated yields of alpha and beta products, and total of both isomers in bracket from column chromatography; [b] ratio α:β as determined by ^{1}H NMR of a crude product; [c] stereoisomer of the isolated products determined to be *trans* by ^{1}H NMR (J = 3.2, 10.4, 10.8 Hz of C*H*N and J = 3.6, 10, and 10.4 Hz of C*H*OH)

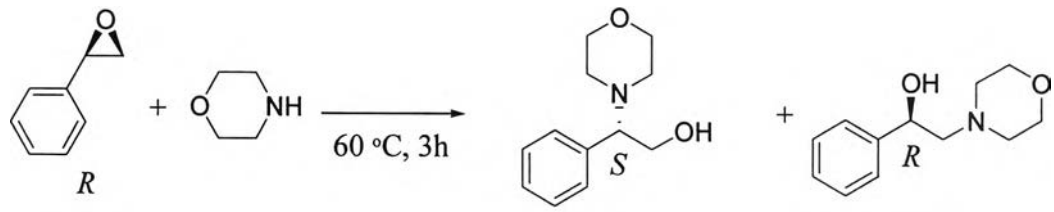
Like in previous experiments (Table 3.5) morpholine was used as the limiting agent and the progress of the reaction was monitored by thin layer chromatography. The reaction times were recorded when the TLC spot of the morpholine had disappeared. The reactions were performed in the presence of excess of epoxides in four representative solvents at 60 °C. In entry 1 using benzyl glycidyl ether as a substrate, only the beta regioisomer was obtained as indicated by its chemical shift at 3.93 ppm with dddd's coupling constants and its integration for 1H, C*H*OH. This was confirmed by comparison of NMR with the same regioisomer in a reference.[53] This single product was obtained, probably because benzyl glycidyl ether has no stabilization due to delocalization of π electron from aromatic ring as observed in styrene oxide. In entry 2, β-naphthyloxirane showed similar tendency as styrene oxide in Table 3.5 for all aspects such as reaction rate, regioselectivity, and yield of the reactions. Specifically, the reactivity and the ratio of alpha to beta isomers became increased in TFE relative to EtOH. Intriguingly, not only was our method for aminolysis of cyclohexene oxide in entry 3 with morpholine considerably reactive and able to compare its reactivity with Lewis acid catalyst in other study,[61] but the undesired side-product, the allylic alcohol, which may form by deprotonation of the alpha proton of cyclohexene oxide was observed very little at δ 5.35 and 6.0 ppm in cyclohexene oxide ring opening.[49] Only *trans*-stereoisomers were obtained both in ethanol and TFE. The configuration of which was identified by ^{1}H NMR ($J_{a,a}$ = 10.4 Hz of C*H*N and $J_{a,a}$ = 10.4 Hz of C*H*OH), which suggests a *trans*-diaxial relationships. Moreover, no reaction was observed in aprotic solvents. In conclusion for this table, comparing these two solvent types, protic and aprotic, on aminolysis of each epoxide, there were distinct rates of reactions found in this study in the way the

fluoroalcohol represented by TFE had highest reactivity and ethanol came after, and the slowest are in aprotic solvents. Therefore, the effect of acidity of the protic solvents, particularly for fluoroalcohol, on accelerating the rate of aminolysis of epoxides is general, although a different degree of acceleration was observed for different kind of epoxides.

3.4.4 Stereospecificity study of the protic solvents on morpholine ring opening of optically active styrene oxide under the specified condition

For application of the developed aminolysis of epoxides in production of optically active vicinal amino alcohols, the reaction must take place stereospecifically. In order to test this, ring opening of optically active (*R*)-styrene oxide with morpholine was carried out in these three protic solvents at 60 °C. Such a stereospecificity was reported in the form of enantiomeric excess or *ee* of the ring opening products in Table 3.10.

Table 3.10. Regioselectivity and stereospecificity of (*R*)-styrene oxide ring opening with morpholine at 60 °C for 3h



(62) **(81a)** **(81b)**

entry	products	solvents	ratio α:β[a]	% yield α,β (total yield)[c]	ratio α:β[b]	% *ee* of α[d]	% *ee* of β[e]
1	**81a,81b**	EtOH[f]	35:65	24,51 (75)	32:68	96	94
2	**81a,81b**	TFE[f]	72:28	66,28 (94)	70:30	91	94
3	**81a,81b**	HFIP[g]	96:4	78,10 (88)	89:11	87	90

The reactions done under 0.5 mmol of styrene oxide in 1 mL of solvent; [a] ratio α:β as determined by ^{1}H NMR of a crude product; [b] ratio α:β as determined by an isolated yield after column chromatography; [c] isolated yields of alpha and beta products, and total of both isomers in bracket from column chromatography; [d] The *ee* of all the α isolated products determined by chiral HPLC on a Chiralcel OD-H; [e] The *ee* of all the β isolated products determined by chiral HPLC on a Chiralpak AD-H; [f] use 1.1 equiv of morpholine; [g] use 2.5 equiv of morpholine

The yield and regioselectivity of morpholine ring opening of (*R*)-styrene oxide for all three protic solvents are similar to that of racemic styrene oxide (Table 3.6). In addition, the enantiomeric excess of all the alpha and beta regioisomeric products in every kind of solvents were at high *ee*, enabling us to explain the pathway of formation of the α-product in Figure 3.5.

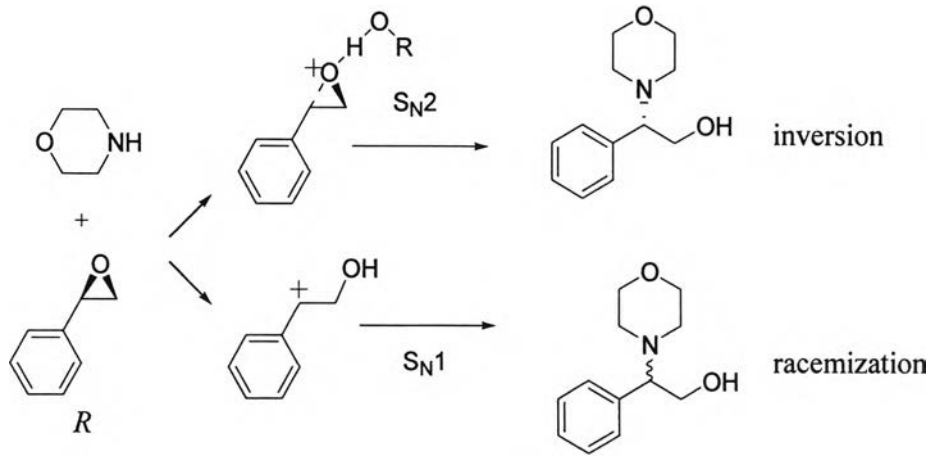


Figure 3.5. Proposed stereospecificity mechanisms between S_N2 or S_N1 processes for α regioisomeric product

The alpha regioisomer is drawn for our more attention to its stereospecific result, because the phenyl group can stabilize the benzylic position under an acidic environment. It is possible to generate alpha morpholine-substituted racemic product through a free carbocation intermediate. On the contrary, the beta product is more likely to be S_N2 by all means, since its electrophilic position at the terminal carbon contains no stericity, kinetically allowing to be attacked through S_N2 mechanism. The high *ee* of all the beta products confirms our hypothesis. In Figure 3.5 there are two hypothetical mechanisms for the alpha regioisomer pathways, S_N2 or S_N1. If the ring opening of styrene oxide in alcohols by morpholine attack at the alpha position does not involve a free carbocation intermediate, the configuration of the obtained product should predominantly inverted. However if the benzylic cation intermediate is instead formed, the product should be racemic. From the stereospecificity study (Table 3.10), the stereochemical integrity of all the alpha products is largely preserved as shown by the high *ee* values obtained ($\geq$ 90 %); therefore, the ring opening should take place *via* an S_N2 rather than S_N1 process.

Moreover, the degree of racemization for both isomeric products increases from EtOH < TFE < HFIP, indicating that the higher the acidity of the protic solvents, the more racemization pathway develops. The *ee* in the best case appears to be modest (β 94 % and α 91 %). However, this might be attributed to the low % *ee* (94 %) of the (*R*)-styrene oxide used. This was investigated by using a chiral shift reagent, $Pr(hfc)_3$ or Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]praseodymium (III) as shown in Figure 3.6. Figure 3.6 showed that Line 1 is the equal ratio of (*R*) and (*S*)-enantiomer separation of the racemic styrene oxide spiked with $Pr(hfc)_3$ and Line 2 is the approximate 9:1 ratio of the (*R*) to (*S*)-enantiomer separation of the (*R*)-styrene oxide with $Pr(hfc)_3$. Therefore, by comparing the chemical shifts of the racemic styrene oxide in Line 1 with those of the known (*R*)-styrene oxide in Line 2, the peak assignments for each enantiomer can be assigned for (*R*) δ 2.91 (C*H*Ph) and 1.94, 2.10 (OCH_2), and for (*S*) δ 2.85 (C*H*Ph) and 1.98, 2.26 (OCH_2). Furthermore, the *ee* of alpha product in entry 1, which was 100 % *ee* should be treated as suspicious. Nevertheless the study clearly showed a utility of the alcohol-mediated aminolysis of epoxides in synthesis of optically active vicinal amino alcohols.

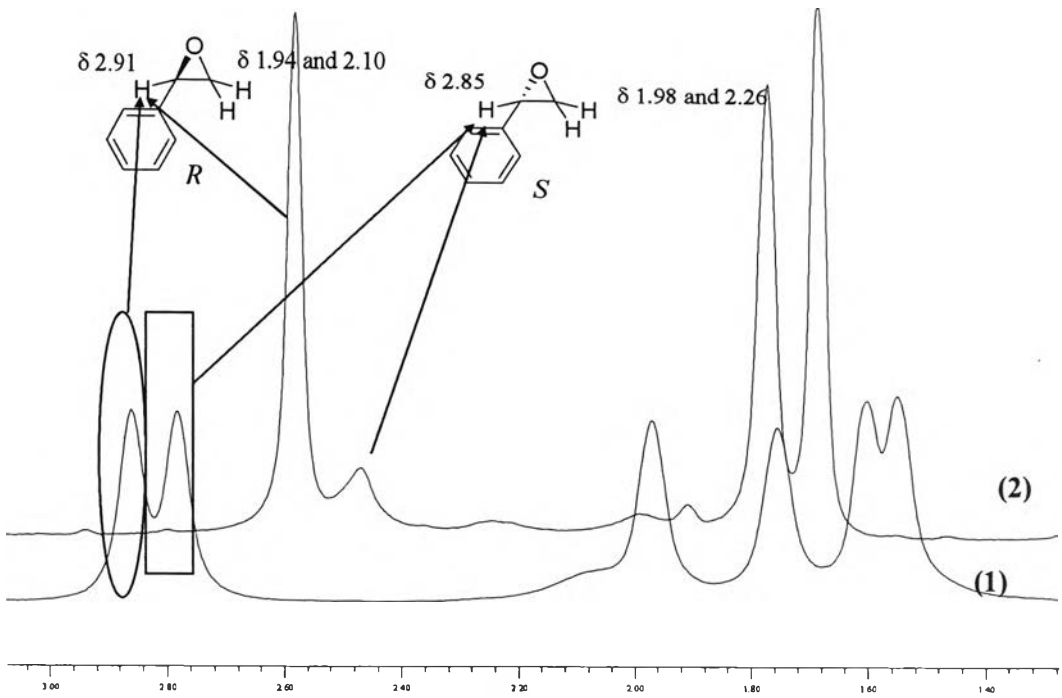


Figure 3.6. ^{1}H NMR of racemic styrene oxide spiked with (+)-Pr(hfc)$_3$ (Line 1) and optically active (*R*)-styrene oxide after addition of (+)-Pr(hfc)$_3$ (Line 2)