CHAPTER III

RESULTS AND DISCUSSION

Enantiopure naphthyl β-amino alcohols, both 1-naphthyl and 2-naphthyl, could be synthesized by several methods. For example, a ring opening of an enantiopure epoxide with an azide followed by a hydride reduction would yield the desired amino alcohol. An alternative method includes a Sharpless aminohydroxylation[*33*] of an appropriate alkene. The other method involves kinetic resolution of racemic epoxide followed by an *in-situ* epoxide ring-opening with a suitable protected amine which can be conveniently deprotected to free amine later by a proper method. Figure 3.1 shows retrosynthetic analysis of naphthyl β-amino alcohols.

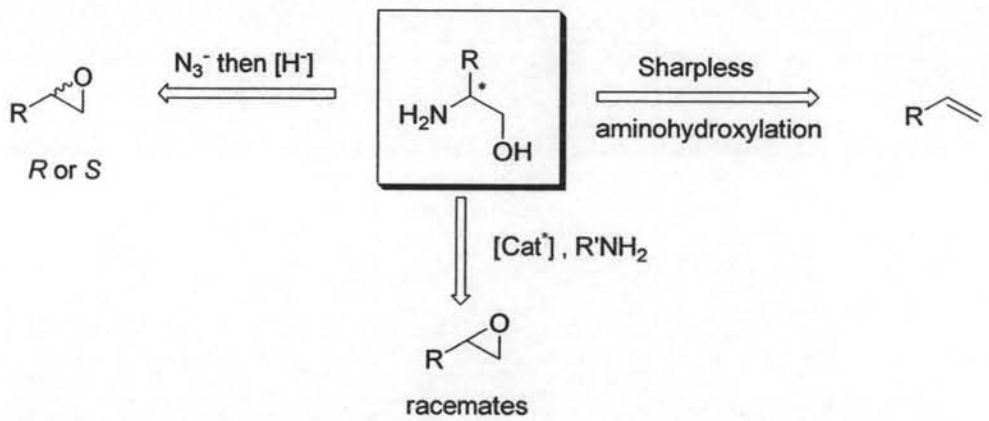


Figure 3.1 The retrosynthetic analysis of naphthyl β-amino alcohol (R = 1- or 2-naphthyl)

Sharpless aminohydroxylation is one of the methods having been reported as a successful synthetic route to enantiopure naphthyl β-amino alcohols. [*33*] However, the cost of the starting 1-vinyl, 2-vinylnaphthalene reactants and aminohydroxylation reagents are quite high. Moreover, an important disadvantage of this method which has not been overcome is the lack of regioselectivity of the reaction. The alternative aminolytic kinetic resolution pathway could be a successful method with racemic styrene oxide.[*34*] Suitable amines in this method are mostly aromatic amines which are rather difficult to be deprotected to give pure free amino alcohol. Therefore, we chose to synthesize chiral naphthyl β-amino alcohols from the corresponding chiral

naphthyl oxiranes. One of the ultimate goals is to synthesize enantiomerically pure naphthyl oxiranes. Figure 3.2 shows a retrosynthetic analysis of chiral naphthyl oxiranes.

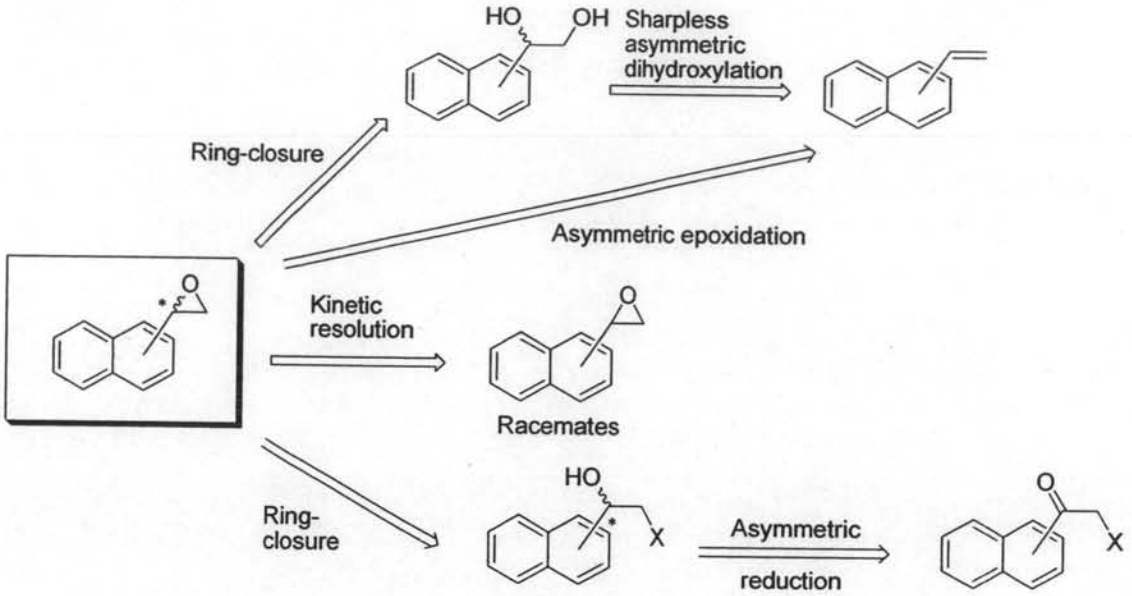


Figure 3.2 The retrosynthetic analysis of chiral naphthyl oxiranes

A hydrolytic kinetic resolution of racemic oxirane to optically pure oxirane by Jacobsen's catalyst is precedented.[*44*] Attemps to carry out a resolution of a racemic naphthyl oxirane by water as a nucleophile failed to yield the enantiomerically pure materials. As laid out in the reviews in Chapter I, the efficiencies in asymmetric epoxidation for the synthesis of enantiopure 1- and 2-naphthyloxiranes were quite low. Furthermore, Sharpless asymmetric dihydroxylation pathway requires the use of 1- and 2-vinylnaphthalene which proves too costly for large-scale synthesis. We had, therefore, turned our attention to focus on the synthesis of the desired compounds from an enantioselective reduction pathway.

After the desired chiral β-naphthylaminoalcohols were obtained, they were further converted to *N*-salicyl-β-naphthylaminoalcohols which were subsequently evaluated for their use as ligands in various metal-catalyzed asymmetric reactions.

3.1 Synthesis of the ligand

The first step of the synthesis involved an acid-catalyzed alpha-bromination of acetonaphthone (**52**). The reaction mechanism was proposed in Figure 3.3.

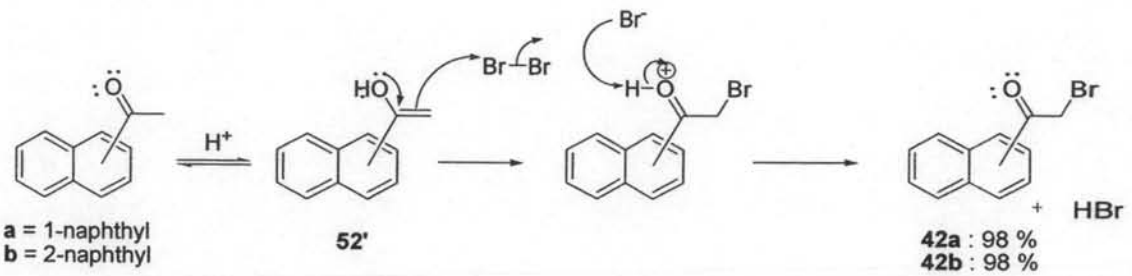


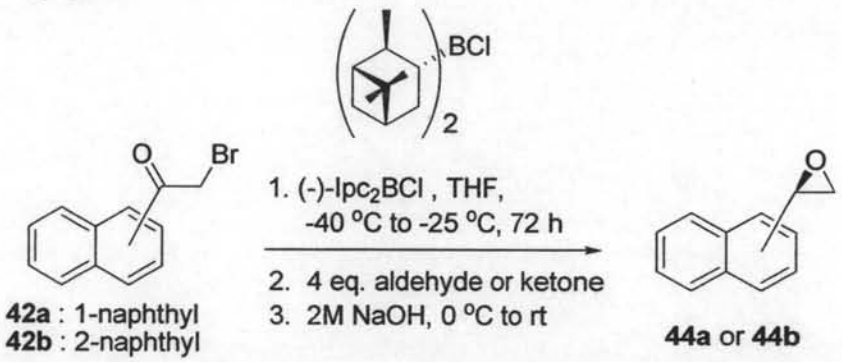
Figure 3.3 Reaction mechanism of alpha-bromination reaction

This reaction occurred in a weakly acidic condition in methanol as protic solvent. This is known to occur *via* enol intermediate **52′**. It was found that as the bromine solution was added, the rate of disappearance of bromine increased until excess amount of bromine was added. This result indicated that the reaction was autocatalytic. We hypothesized that the by-product, hydrobromic acid, could be partly dissolved in methanol and could come back to accelerate the rate of enol formation, which was hypothesized as the rate-determining step, in an acid-catalyzed fashion. Conventionally, alpha-bromination of acetonaphthone must be done in the presence of an acid, such as acetic acid. This usually results in the desired product with some impurities that are difficult to be purified by column chromatography or crystallization. This is due to the fact that the polarities of the brominated product and the reactant were nearly equal. This new procedure, in turn, has brought about quite a pure product in high yield (98 % in both 1-naphthyl and 2-naphthyl cases). Any purifications were not necessary after a routine workup.

The second step was reduction of bromoketone (**42a** and **42b**) to bromohydrin, followed by a cyclization resulting in the desired naphthyl oxiranes. In order to carry out a reduction of the bromoketone in an asymmetric fashion, various choices are available. Many expensive organometallic reagents or catalysts were effectively used in asymmetric reduction of α-haloketone or α-tosylketone, such as chiral rhodium or chiral ruthenium catalyst,[*50-53*] and borane reagents,[*45-49*] *etc*.. *B*-chlorodiisopinocampheyl borane (Ipc_2BCl or DIP-Cl®) has been a borane reagent widely used in asymmetric reduction of ketones or aldehydes to corresponding alcohols for many years. [*58-59*] The reagent is commercially available, inexpensive, and easier to handle than other moisture-sensitive organometallic reagents. Therefore, (-)-Ipc_2BCl was employed in an asymmetric reduction of α-bromoacetonaphthone,

followed by a treatment with 2 M NaOH at 0 °C to facilitate a cyclization to the corresponding oxiranes. This condition was similar to a previous report in 2001 by Cho and coworker.[*45*] The optimization of reaction conditions are shown in Table 3.1.

Table 3.1 Optimization of asymmetric bromoacetonaphthone reduction by (-)-Ipc_2BCl



entry	bromo acetonaphthone	(-)-Ipc_2BCl (equiv.)	quencher	yield (%)	*ee* (%)
1	**42a**	1.1	acetaldehyde	28	92.7
2	**42b**	1.1	acetaldehyde	45	96.5
3	**42b**	1.1	acetone	31	93.5
4	**42a**	2	acetone	41	>99
5	**42b**	2	acetone	67	>99

The reaction time required for the reaction to go to completion (72 h) was longer than what was previously reported (48 h) presumably because the reaction was set at low temperature (-25 °C) without stirring. The reduction completeness was monitored by ^{1}H-NMR spectroscopy from sampled crude solution. The disappearance of the COCH_2Br signal at δ4.58 ppm after 72 hours of reaction time indicated that the reduction was complete. (Figure 3.4)

After quenching, evaporation, and a basic work up, naphthyl oxiranes were obtained. Cyclization was later accomplished by the treatment of excess NaOH, the mechanism of which will be discussed (*vide infra*). The results in entries 1 and 2 were obtained from using the same condition as that in Cho's report. The leaving group illustrated in the literature was a tosyl group, whereas, in our case bromine was the leaving group.

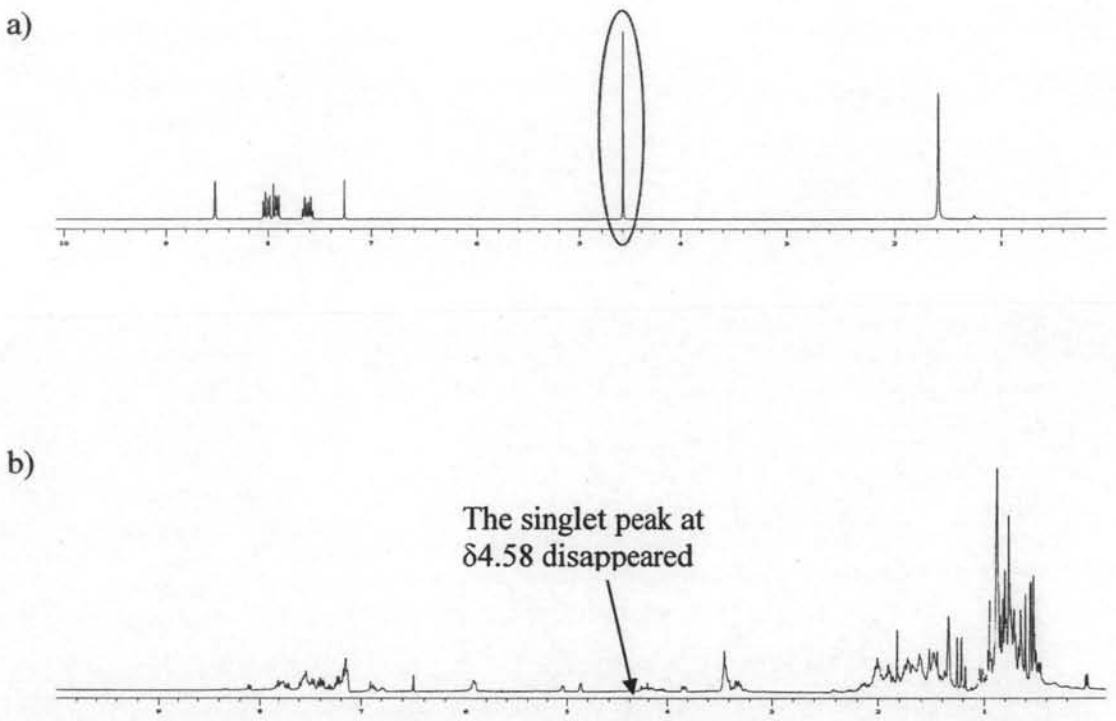


Figure 3.4 ^{1}H-NMR ($CDCl_3$, 400 MHz) of a) 2-bromo-1-(naphthalen-2-yl)ethanone (**42b**) b) Sampled crude solution from reduction step of **42b** to **44b** after being quenched by acetone and dried over N_2 gas. We could observe the disapperance of a singlet peak at δ4.58 ppm.

It was found that the observed enantioselectivity (up to 92.7 and 96.5 %*ee* for 1-naphthyl and 2-naphthyl oxiranes, respectively) were higher than those reported earlier (65 and 72 %*ee*).[*58*] In a typical procedure in the reduction ceasing step, acetaldehyde is used as a quencher when (-)-Ipc_2BCl is employed.[*58*] However, in our case, using excess acetaldehyde, in an amount typically used, was rather problematic. The desired epoxides were difficult to be isolated from the remaining acetaldehyde by simply washing with extremely cold hexanes (in the case of 2-naphthyl) or column chromatography (in the case of 1-naphthyl). Acetaldehyde is easily polymerized to give a viscous yellow liquid. Hence, acetone, which is easier to be removed from the crude solution, was chosen as an alternative quencher (entry 3).

The only drawbacks observed were slightly lower %*ee* and %yield than when acetaldehyde was used. This was, however, reasoned as an effect of using an inadequate amount of (-)-Ipc_2BCl, not an effect of the type of quencher. Indeed, when the amount of (-)-Ipc_2BCl was increased from 1.1 to 2 equivalents, enantioselectivity toward both oxiranes **44a** and **44b** increased up to 99% (entries 4-5). In all cases, the degree of enantioselectivity of the reaction was determined by ^{1}H-NMR technique

with an employment of *tris*-[3-(heptafluoropropylhydroxy-methylene)-*d*-camphorato]praseodym(III) ((*d*)-Pr(hfc)$_3$) as a chiral solvating agent (Figure 3.5).

The absolute configuration of the major isomeric epoxide in both the 1-naphthyl and 2-naphthyl cases were (*R*). This was determined by the measurment of specific rotations ($[\alpha]_D$) of the products followed by a comparison with literature data.[*45*] The specific rotation of **44a** and **44b** were -81.3 (c=1.01, $CHCl_3$) and -9.27 (c=1.00, $CHCl_3$) respectively. This is consistent with the (*R*)-isomer assigned in the previous report [-63.51 (c=1.2, $CHCl_3$) and -7.2 (c=1.1, $CHCl_3$) for 65 %*ee* of **44a** and 72 %*ee* of **44b**, respectively][*45*]. It is well known that the mechanism of asymmetric reduction by chiral borane reagents is a concerted process. We proposed a possible transition state, based on the model reported previously,[*58-59*] which led to (*R*)-isomer products in Figure 3.6.

We hypothesized that the lower %*ee* observed in the epoxides when only 1.1 equivalents of (-)-Ipc$_2$BCl were used could be due to moisture contamination of the borane reagent, causing a non-stoichiometric ratio of reactants. Moreover, reducing power of an intermediate from asymmetric reduction step, which still contained a pinene moiety bonded with boron atom, was still remained. Therefore, this intermediate could also reduce α-bromoacetonaphthone substrate when non-stoichiometric ratios of the borane reagent were employed. Perhaps, the lower enantioselectivity observed in the oxirane product arose from this pathway. Nevertheless, when an excess of (-)-Ipc$_2$BCl, 2 equivalents, was used, all of α-bromoacetonaphthone substrate was assurely reduced by (-)-Ipc$_2$BCl because the reducing power of (-)-Ipc$_2$BCl was certainly stronger than the intermediate as mentioned above. The higher enantioselectivities of products were obtained from this reason.

When 2 equivalents of (-)-Ipc$_2$BCl were used in the reduction of **42b** (entry 5), the obtained epoxide **44b** spontaneously precipitated upon an addition of 2M NaOH at 0 °C. It could be purified easily by washings with extremely cold hexane. In contrast, **44a** and the other intermediate products in the synthesis of **44b** could not. Purification by flash-column chromatography under basic condition of 1% triethylamine was necessary. In the absence of triethylamine, the epoxide could rearrange to naphthylacetaldehyde by an acid-catalyzed process caused by the acidic SiO_2 groups of the stationary phase (Figure 3.7).

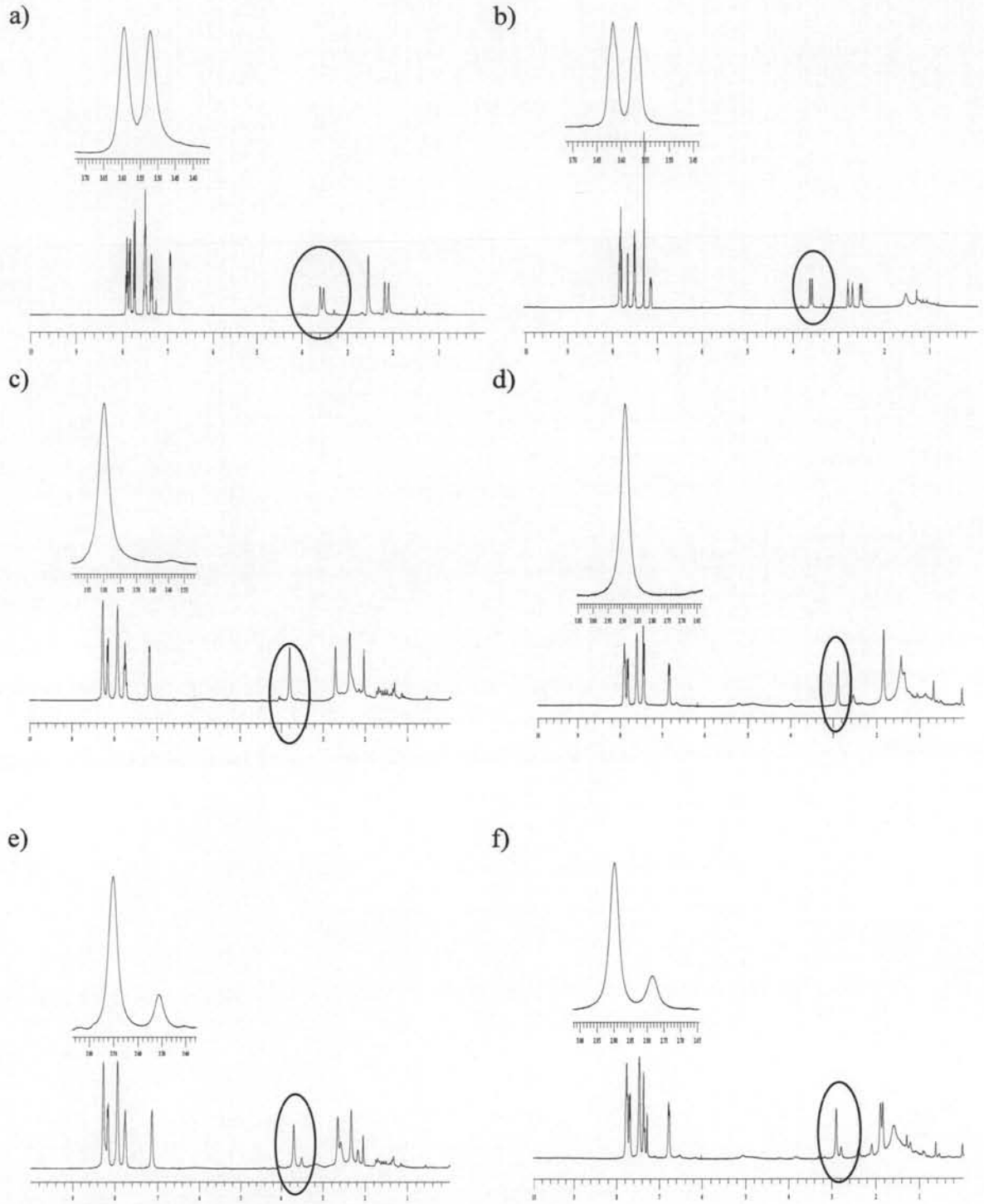


Figure 3.5 ^{1}H-NMR spectra ($CDCl_3$, 400 MHz) of
a) (±)-2-(naphthalen-1-yl)oxirane (**43a**) + (*d*)-Pr(hfc)$_3$
b) (±)-2-(naphthalen-2-yl)oxirane (**43b**) + (*d*)-Pr(hfc)$_3$
c) (*R*)-2-(naphthalen-1-yl)oxirane (**44a**) + (*d*)-Pr(hfc)$_3$ (> 99 %*ee*)
d) (*R*)-2-(naphthalen-2-yl)oxirane (**44b**) + (*d*)-Pr(hfc)$_3$ (> 99 %*ee*)
e) (*R*)-2-(naphthalen-1-yl)oxirane (**44a**) + (*d*)-Pr(hfc)$_3$ + spiked with racemic(**43a**)
f) (*R*)-2-(naphthalen-2-yl)oxirane(**44b**) + (*d*)-Pr(hfc)$_3$ + spiked with racemic(**43b**)

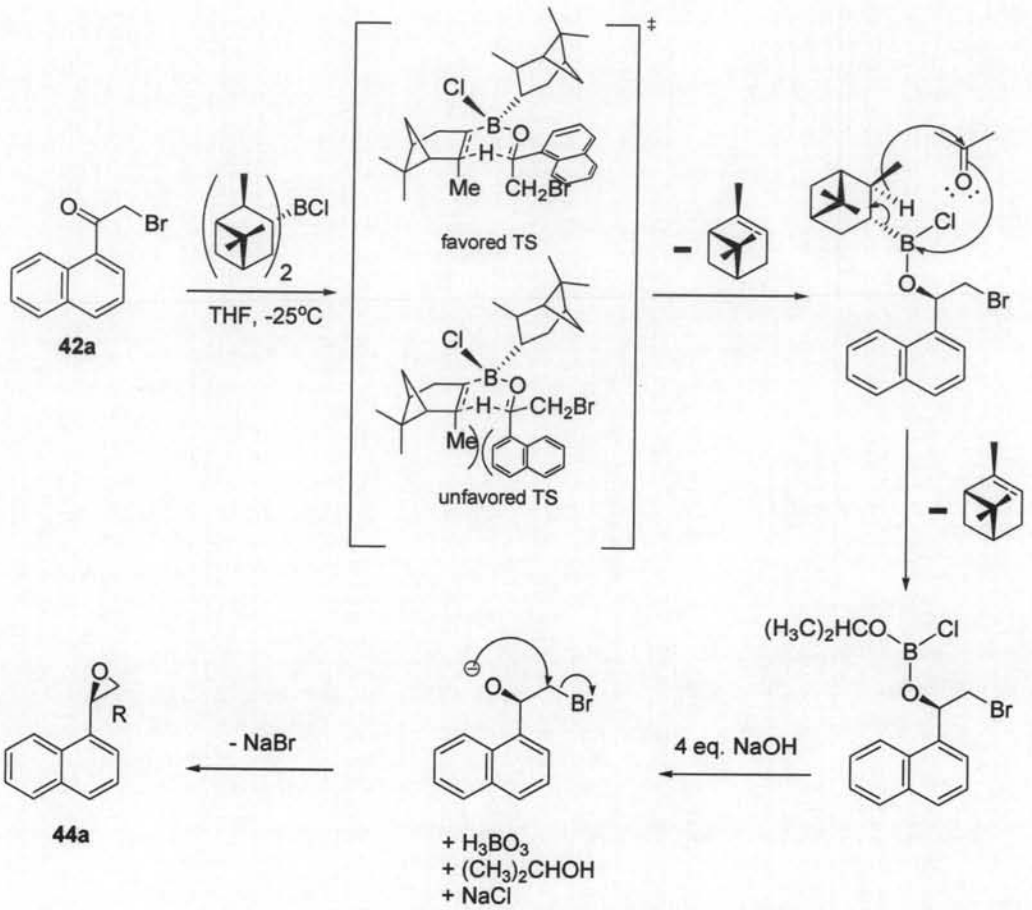


Figure 3.6 A plausible mechanism and transition state of asymmetric reduction of 2-bromo-1-(naphthalen-1-yl)ethanone (**42a**) which led to (*R*)-isomer of the corresponding bromohydrin and oxirane (**44a**)

The following step of the synthesis is an epoxide ring opening to give naphthyl amino alcohols. Two pathways may be envisaged. The first method is racemic epoxide ring-opening by chiral amine auxilliary. The other is enantiopure epoxide a ring-opening by an azide ion, followed by hydrogenation to amino alcohol. (Figure 3.8)

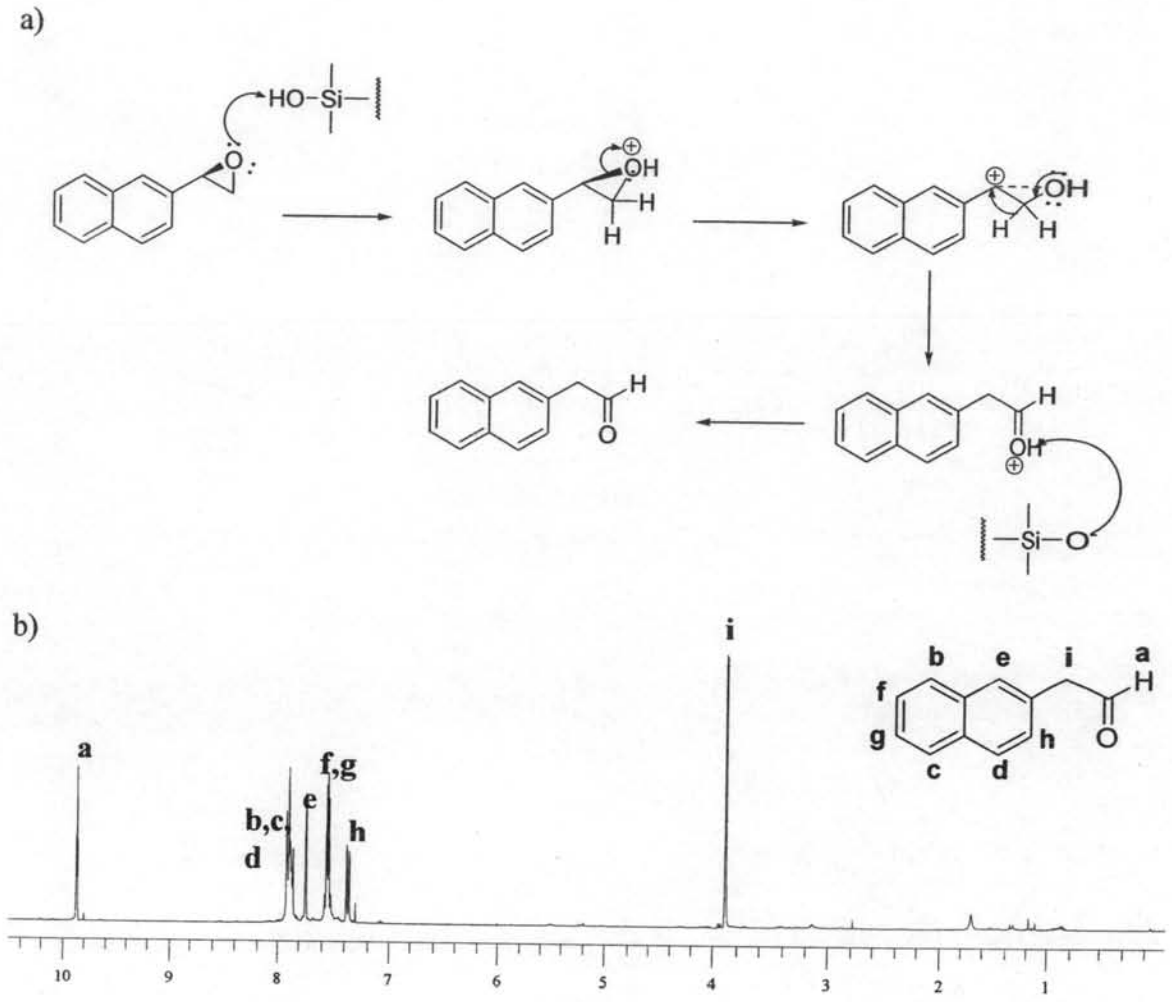


Figure 3.7 a) A possible mechanism of the rearrangement from **44b** to naphthylacetaldehyde on the SiO_2 stationary phase.
b) ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of naphthyl acetaldehyde as an impurity.

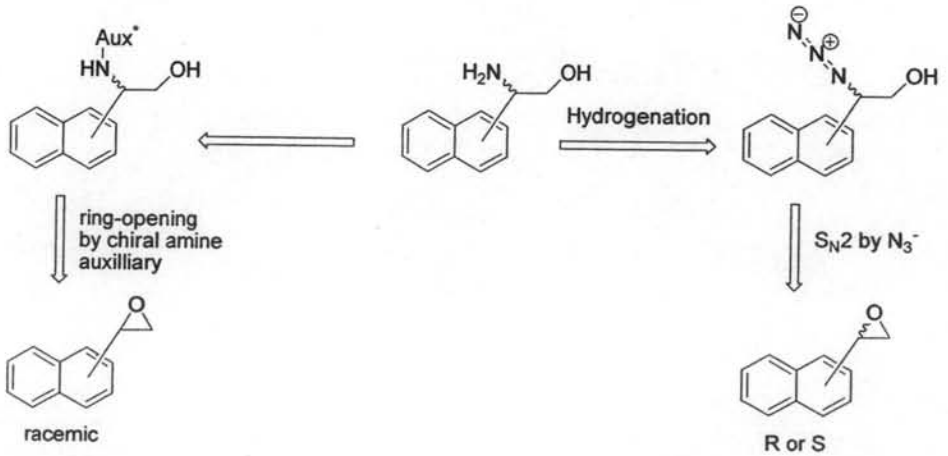


Figure 3.8 The retrosynthetic pathways of naphthyl amino alcohols

The ring-opening of oxiranes by sodium azide in water has been reported in 1999 by Fringuelli.[*60*] Starting from racemic styrene oxide, the ring-opening was accomplished in both the acidic (pH = 5 by acetic acid) and weakly basic conditions (pH = 9 without any basic additives). The ratio of α/β attack products was 97/3. Firstly, the acidic condition was carried out in our experiment with (*R*)-2-(naphthalen-2-yl)oxirane (**44b**) which was initially at 96 %*ee*. Only 21% of the desired optically active azidoalcohol (*S*)-**45b** with the loss of enantioselectivity to 33 %*ee* was obtained. Subsequently, the acidic condition led to the formation of 2 by-products as shown in Figure 3.9.

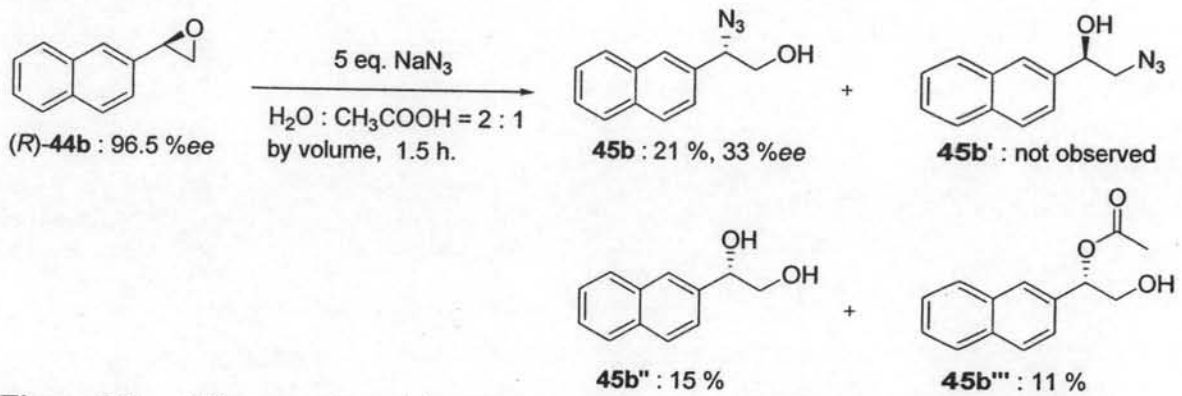
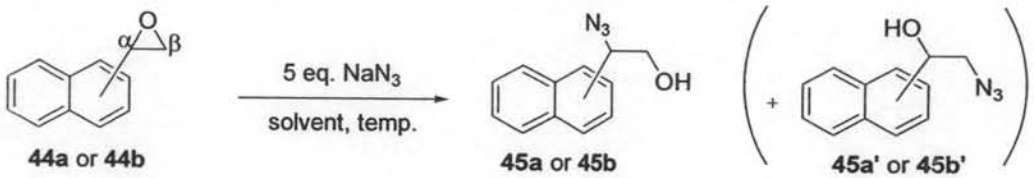


Figure 3.9 Ring-opening of the (*R*)-2-(naphthalen-2-yl)oxirane (**44b**) in acidic condition

It is noteworthy to point out 2 observations which were different from the previous report. Firstly, a product resulting from the β attack (**45b′**) was not observed. Moreover, the diol (**45b′′**) and the acetylated diol (**45b′′′**) were formed in nearly equal quantities with the desired product. These evidences are strongly indicative of an explicit α-attack of nucleophiles, azide ion and water molecule. A basic explanation was that the reaction might occur *via* an acid-catalyzed unimolecular nucleophilic substitution pathway (an "S_N1-like" mechanism). Acetic acid led to the formation of a stabilized partial carbocation at the benzylic position. Consequently, the α-position of the epoxide is much more electrophilic towards the two nucleophiles than the β-position. Therefore, only the α-attack products were only observed.

The reaction was performed again in a weakly basic condition (no protic additives at approximately pH 9.2 [*60*]). The results are shown in Table 3.2

Table 3.2 The ring opening of epoxide by sodium azide in a weakly basic condition.[a]



44a or **44b** → **45a** or **45b** + **45a'** or **45b'**

entry	epoxide	solvent	temp. (°C)	yield of 45a or 45b (%)
1	**44b**	H_2O	r.t.	37
2	**44b**	MeOH : H_2O = 2 : 1	r.t.	66
3[b]	**44b**	MeOH : H_2O = 2 : 1	70	69
4	**44a**	MeOH : H_2O = 2 : 1	r.t.	60

[a] All reactions were performed on a 1 mmol scale and were followed by TLC until the remaining epoxide spot intensity appeared to be constant (about 48 hours).
[b] The epoxide approximately decreased more than 50 % when the reaction time was only 1 hour (visualized by TLC)

From the results, solvent has a significant role on the %yield of the major product (**45a** or **45b**). Because of the insolubility of the epoxide in water, the reaction mixture was heterogeneous and the %yield may be limited by solubility of epoxides (entry 1). Methanol was chosen to be a cosolvent because it was miscible with water. The epoxides could be simultaneously dissolved. The %yield of the reactions had increased to approximately two folds of that obtained when only water was used as a solvent (entries 1 and 2). Furthermore, when the temperature was increased to 70 °C (entry 3), the reaction seemed to be faster than when carried out at room temperature. Over 50% of the epoxide was consumed after 1 hour only as easily visualized by TLC. Unfortunately, the isolated yield of the major product after 48 hours of the reaction increased only slightly from that at room temperature condition.

Under this weakly basic condition, only a trace amounts of by-products, arising from β-attacks of an azide ion and a water molecule, were detected even in the presence of unreacted starting epoxide. However, when the reaction was scaled up to 3.6 mmol, only 1-2% each of the diol and azide from β-attack (**45a´** or **45b´**) were observed. We can discriminate among the products from the α-attack, β-attack of an azide and a diol by ^{1}H-NMR and determination from polarity in separation. We choose products from epoxide **43b** to explain as shown in Figure 3.10.

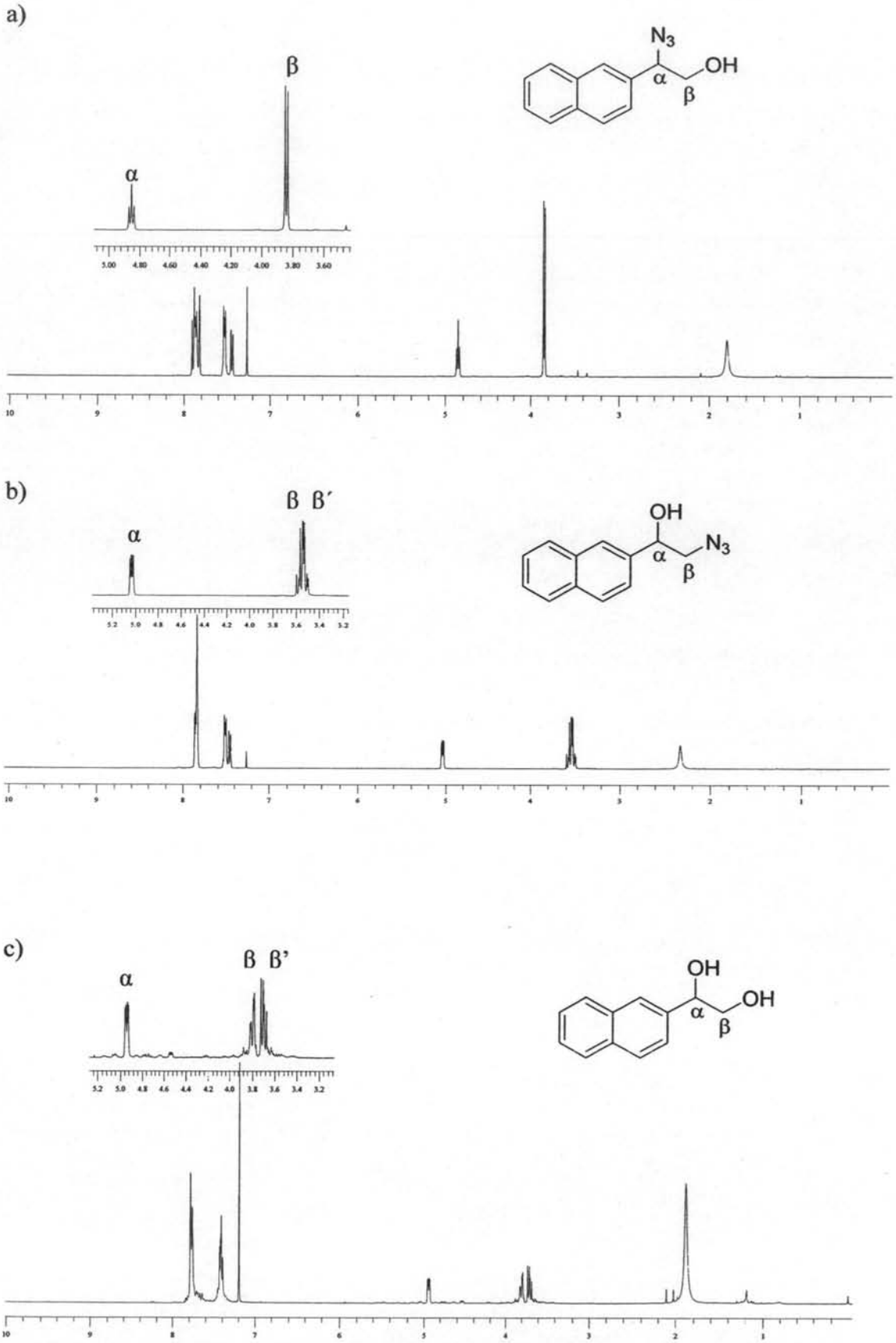


Figure 3.10 ^{1}H-NMR (400 MHz, $CDCl_3$) of a) 2-azido-2-(naphthalen-2-yl)ethanol (**45b**) b) 2-azido-1-(naphthalen-2-yl)ethanol (**45b´**) c) 1-(naphthalen-2-yl)ethane-1,2-diol (**45b´´**)

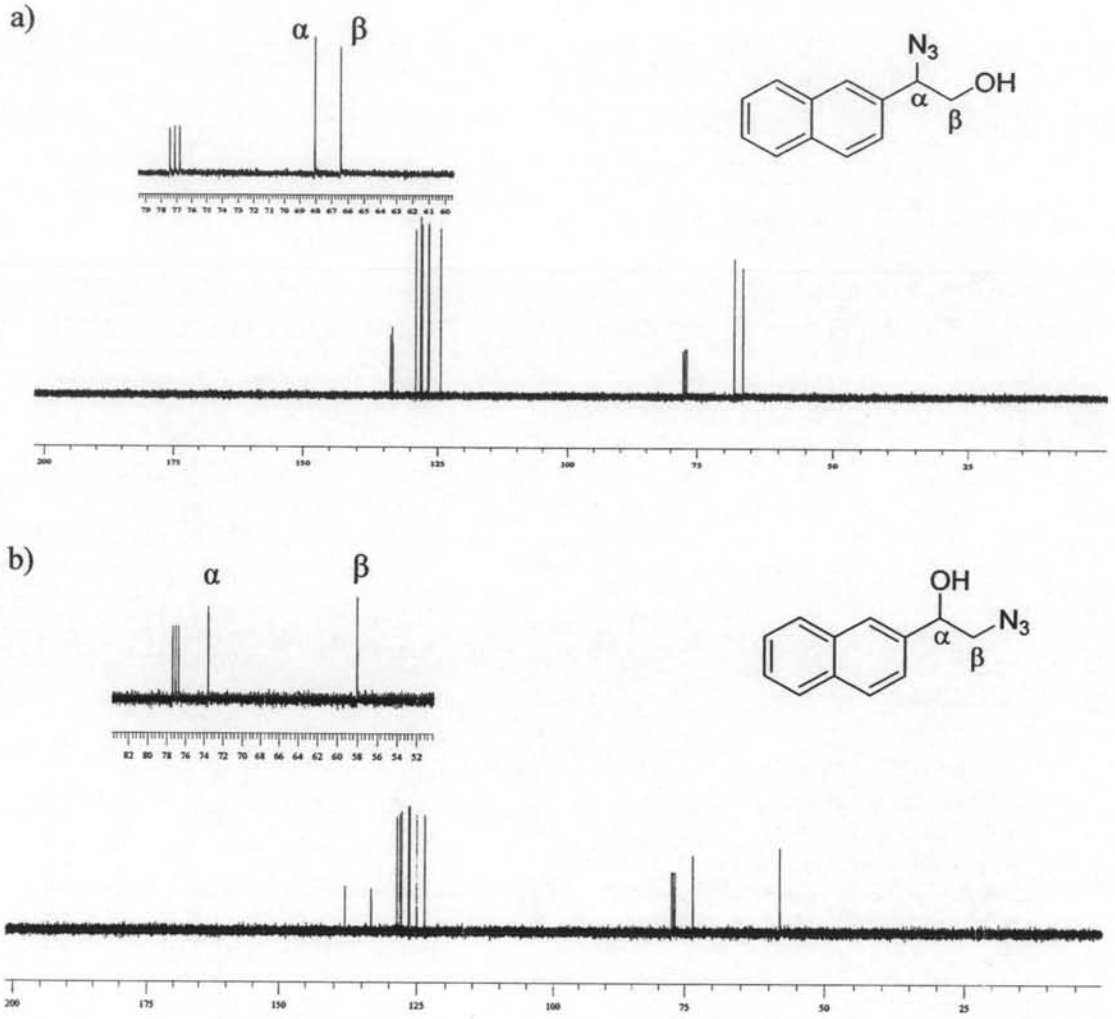


Figure 3.11 ^{13}C-NMR (100 MHz, $CDCl_3$) of a) 2-azido-2-(naphthalen-2-yl)ethanol (**45b**) b) 2-azido-1-(naphthalen-2-yl)ethanol (**45b´**)

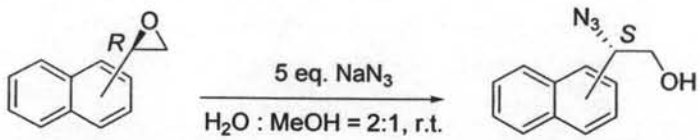
The product which was the first to be eluted from column chromatography was assigned to 1-(naphthalen-2-yl)ethane-1,2-diol (**45b´´**) based on NMR characterization. As shown in Figure 3.10c, the chemical shift of 3 important peaks are 3.75 [1H, dd ABX system, $^2J_{AB}$ = 11.3 Hz and $^3J_{AX}$ = 8.1 Hz, H_β], 3.85 [1H, dd ABX system, $^2J_{BA}$ = 11.3 Hz and $^3J_{BX}$ = 3.3 Hz, $H_{\beta'}$] and 5.00 [1H, dd ABX system, $^3J_{XA}$ = 8.1 Hz and $^3J_{XB}$ = 3.4 Hz, H_α] ppm. These chemical shifts match precisely with the literature data.[*61*]

To preliminarily distinguish compound **45b** from **45b´**, the order of which they were eluted from the column were taken into consideration. The polarity of **45b´** is slightly lower than **45b** and would be eluted first. Further discrimination was based on the chemical shift of the benzylic proton (H_α) of **45b´** which should be further

downfield than the benzylic proton of **45b** because oxygen atom is more electronegative than the nitrogen atom. As illustrated in Figures 3.10a and 3.10b, chemical shifts of H_α are 4.85 and 5.03 ppm for **45b** and **45b′** respectively. Therefore, the ^{1}H-NMR spectrum of the major product as shown in Figure 3.10a is of **45b** which came from an α-attack of epoxide **43b** with azide ion while Figure 3.10b represents **45b'** which was a result of β-attack. This implication was reaffirmed by comparing the H_β chemical shifts of of **45b** and **45b′**. The chemical shift of H_β in case of **45b** (3.84 ppm) is also further downfield than that of **45b′** (3.49-3.59 ppm) due to a difference in electronegativity as described above. Moreover, the chemical shift of benzylic carbon C_α in the ^{13}C-NMR spectrum, as demonstrated in Figures 3.11a and 3.11b, of **45b** is more obviously downfield than that of **45b′** (68.0 and 73.5 ppm for **45b** and **45b′**, respectively). This is in excellent agreement with ^{1}H-NMR results. These ^{13}C-NMR spectra could strongly assure the validity of the prior implication.

The optimized conditions were applied to chiral naphthyloxiranes **44a** and **44b** as shown in Table 3.3.

Table 3.3 Chiral naphthyl oxirane ring-opening by azide ion to give chiral azido alcohols



44a or **44b** → **45a** or **45b**

entry	epoxide	*ee* of **45a** or **45b** (%)[a]	yield of **45a** or **45b** (%)	*ee* of **45a** or **45b** (%)[b]
1	**44b**	96.5	61	96.3
2	**44a**	> 99	64	99.1
3	**44b**	> 99	65	99.5

[a] %*ee* were determined by ^{1}H-NMR technique with (*d*)-Pr(hfc)$_3$

[b] %*ee* were determined by HPLC (Chiralpak AD-H, 20 : 80 2-propanol : hexane, flow rate = 0.5 mL/min, 260.0 nm)

The results from Table 3.3 demonstrated that the mechanism of ring-opening by the azide ion in the weakly basic condition is absolutely bimolecular nucleophilic

substitution (S_N2) as the enantiomeric composition of the obtained chiral naphthyl azido alcohols did not change significantly from the started chiral epoxides. The negative sign of optical rotation value, compared with references, were suggestive that the absolute configuration of the obtained chiral naphthyl azido alcohols was an *S* configuration. In terms of relative configuration, these reactions are 100% inversion of configuration. Fortunately, the *%ee* of both **45a** and **45b** could be precisely determined by chiral HPLC technique. The enantiomeric pairs of **45a** and **45b** were successfully separated on the Chiralpak AD-H analytical column, packed with amylose tris(3,5-diphenylmethylcarbamate), with a baseline resolution. Even though the observed optical rotation values of the obtained azido alcohols were lower than what were reported in the references, the degree of enantioselectivity reported here is based on chiral HPLC analysis due to the fact that HPLC technique is more reliable.

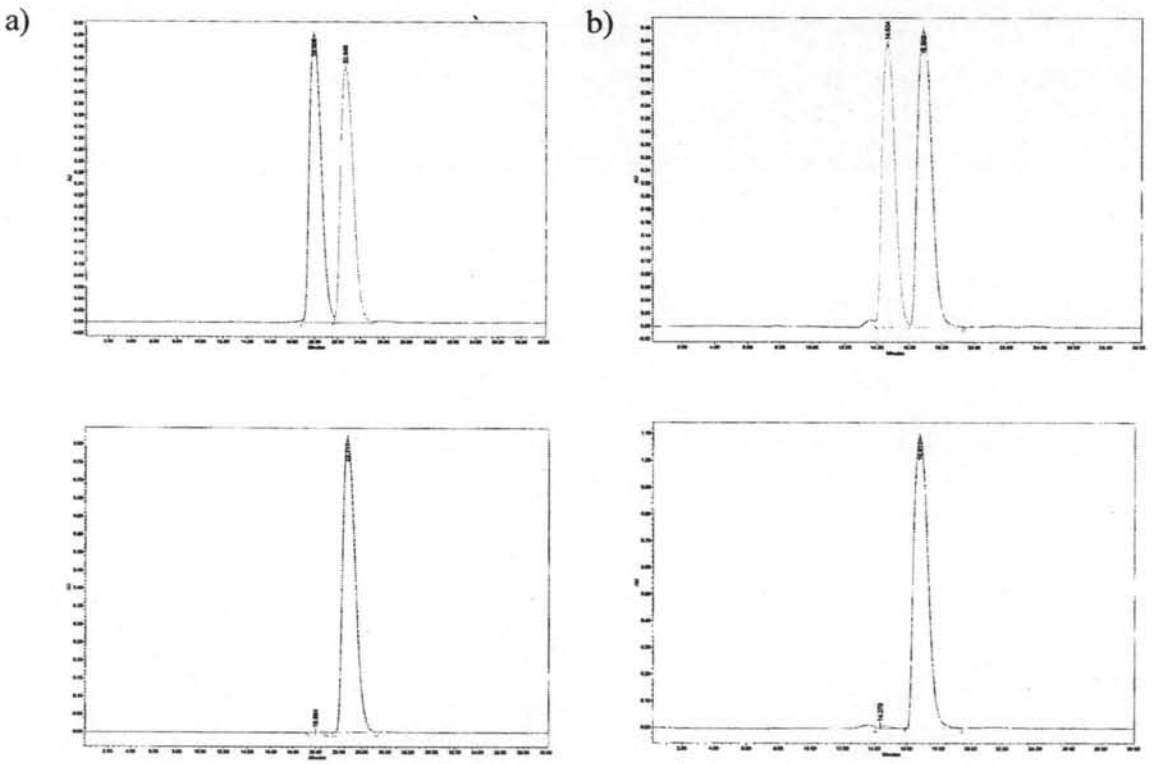


Figure 3.12 HPLC chromatograms of a) (*S*)-**45a** and, b) that of (*S*)-**45b**

The last synthetic step is the azide reduction to the corresponding amino alcohol. Using A catalytic hydrogenation on 10% Pd/C is a method which has been reported recently.[*62*] Normally, this condition has also been used in the benzyl group

cleavage *via* a radical mechanism. Therefore, one of the side reactions which might be anticipated was the cleavage of the C-C bond at the benzylic position of the desired naphthyl amino alcohol. Fortunately, no evidence of such a cleavage was observed in our system. After an overnight hydrogenation and a basic workup, the ^{1}H-NMR spectra revealed that the obtained amino alcohols were quite pure, suggesting no participation of any side reaction. The enantiomeric purity of the obtained chiral aminoalcohols was performed using an HPLC technique, by derivertizing to Boc-*N*-protected alcohol prior to the analysis. Representative results are shown in figure 3.13.

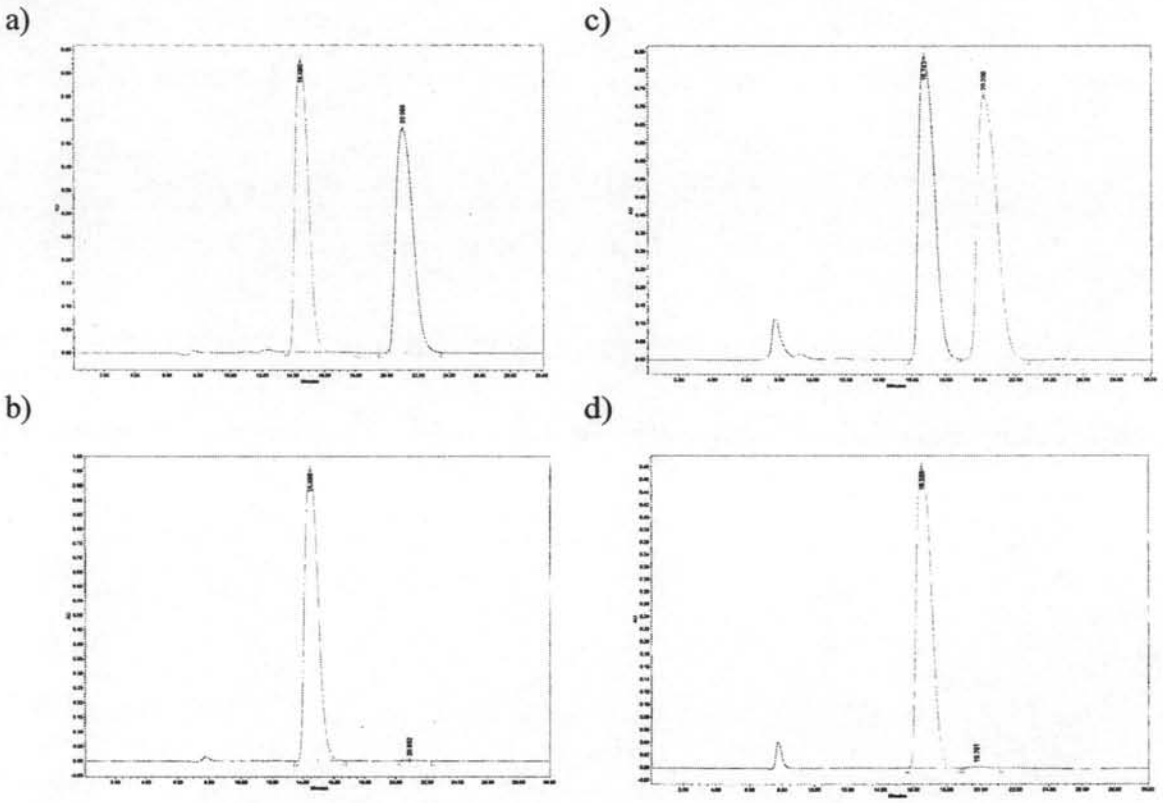
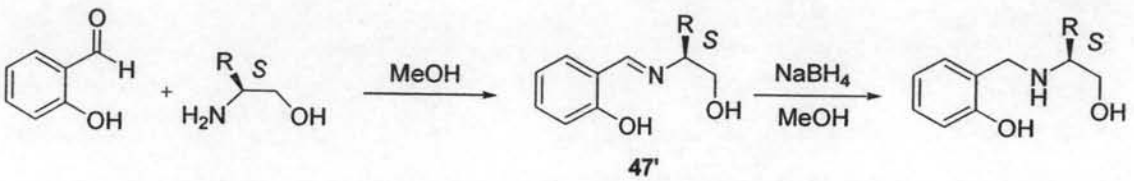


Figure 3.13 HPLC chromatograms (Chiralpak AD-H, 20 % i-PrOH in hexane, flow rate = 0.5 mL/min, 229 nm.) of
a) *rac*-tert-butyl 2-hydroxy-1-(naphthalen-1-yl)ethylcarbamate (**46a**)
b) (*S*)-tert-butyl 2-hydroxy-1-(naphthalen-1-yl)ethylcarbamate (**46a**)
c) *rac*-tert-butyl 2-hydroxy-1-(naphthalen-1-yl)ethylcarbamate (**46b**)
d) (*S*)-tert-butyl 2-hydroxy-1-(naphthalen-1-yl)ethylcarbamate (**46b**)

HPLC chromatograms indicated no racemization during hydrogenation process as the *%ee* of amino alcohols remained unchanged from that of the azido alcohol at >99 %.

N-salicyl β-aminoalcohols were prepared using the same conditions reported in our earlier work.[*28*] The initial step involved imine formation between salicylaldehyde and an chiral aminoalcohol using methanol as a solvent under neutral condition. A subsequent imine reduction with 1.1 equivalents of $NaBH_4$ resulted in the desired products. Table 3.4 shows the yields of various ligands prepared *via* this method. A mechanism of imine formation was depicted in Figure 3.14. Although, pKa value of methanol is only approximately 15, it could act as a protic solvent to preactivate a carbonyl group of aldehyde by protonation. Besides, imine formation could occur easily because all of amino alcohols used in this work are primary amines which were very good nucleophiles.

Table 3.4 Percentage of yield of *N*-salicyl β-aminoalcohols which were prepared



entry	ligand	R	yield (%)
1	**47a**	1-naphthyl	57
2	**47b**	2-naphthyl	57
3	**47c**	phenyl	90
4	**26**	benzyl	77
5	**25**	*t*-butyl	81

Ligands **47c**, **25,** and **26** were prepared from commercially available enantiopure β-amino alcohols whereas **47a** and **47b** were prepared from our synthesized β-naphthyl amino alcohols. Both of the naphthyl ligands were purified by crystallization. A mechanism for the formation of the products is illustrated below.

Ligand **48** was synthesized by the method of Narasimhan's [*25*] for comparison of catalytic effeciencies in Michael addition reaction. Moreover, asymmetric induction results between *N*-salicyl-*t*-butyl ligands in the forms of leucine methylester and leucinol could be compared.

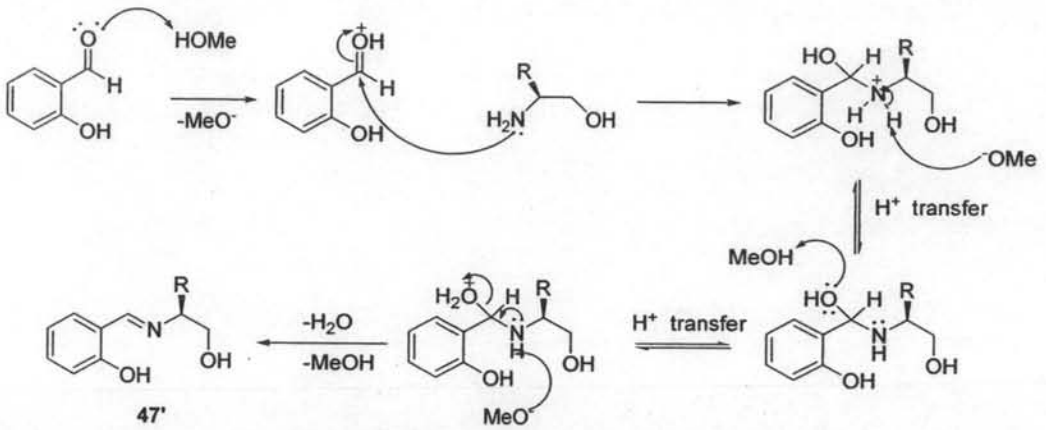
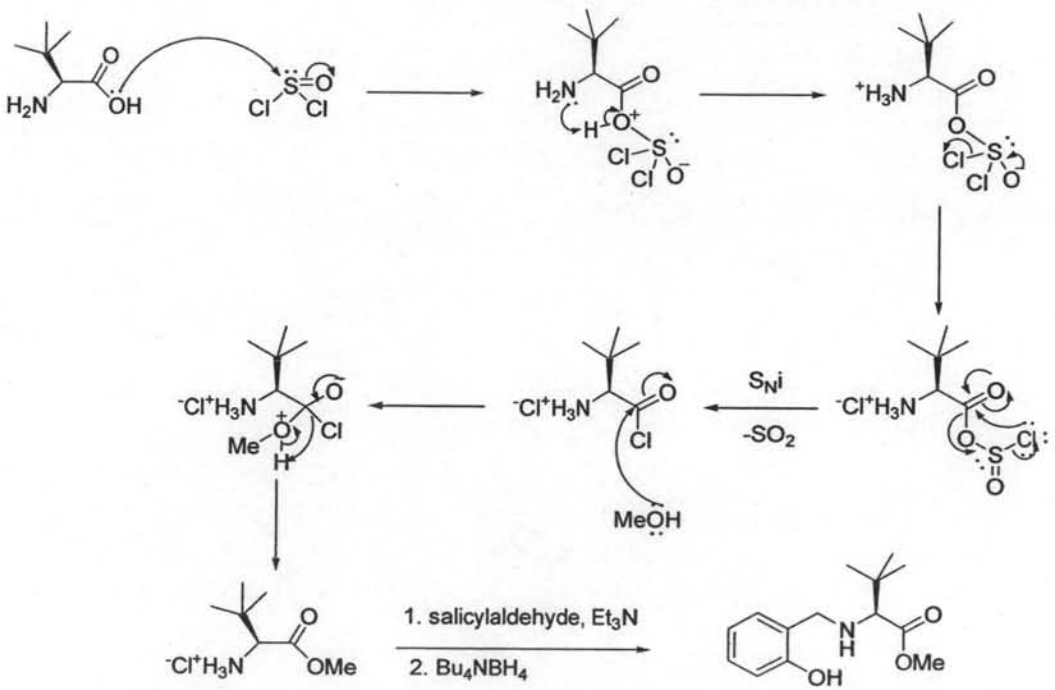


Figure 3.14 A general mechanism of imine **47′** formation between salicylaldehyde and an aminoalcohol under neutral condition

The first step involved a conversion of (*S*)-*t*-butylleucine to the corresponding acid chloride by thionyl chloride. The mechanism of this step consists of the formation of anhydride sulfonyl chloride, followed by intramolecular nucleophilic substitution (S_Ni) to carboxyl group. Acid chloride of (*S*)-*t*-butylleucine was formed. Amine hydrochloride salt was also available in the presence of hydrochloric acid generated as one of the by-products from the substitution. Methanol which is a solvent of the reaction, could act as a nucleophile to react with the acid chloride by nucleophilic acyl substitution to give the corresponding methyl ester hydrochloride salt of (*S*)-*t*-butylleucine. The mechanistic detail is depicted as figure 3.15.



48

Figure 3.15 Mechanism of methylester amine hydrochloride formation from (*S*)-t-butylleucine

The next step is a connection of the salicyl moiety to the amino ester *via* an imine formation between salicylaldehyde and the amino methylester in basic condition. A mechanism of this step is similar to that in figure 3.14. The final important step is the reduction of imine to amino group. The difficulty of this step is to find a suitable reducing agent and reaction conditions under which the reduction is orthogonal that the C=N is reduced whereas the ester group remains unchanged. A procedure by Narasimhan using tetrabutylammonium borohydride (Bu_4NBH_4) in THF which reportedly reduced only the C=N was followed.[*25*] However, only a low yield of the desired ligand was obtained. When the reaction was monitored by TLC, 2 spots were found visualized in blue by a $Co(SCN)_2$ dipping agent which is selective for primary and secondary amino groups. Unfortunately, the blue spot of the desired product looked much less intensed than the other which was also of higher polarity. Therefore, the undesired reduction of an ester might have occurred in a higher extent.

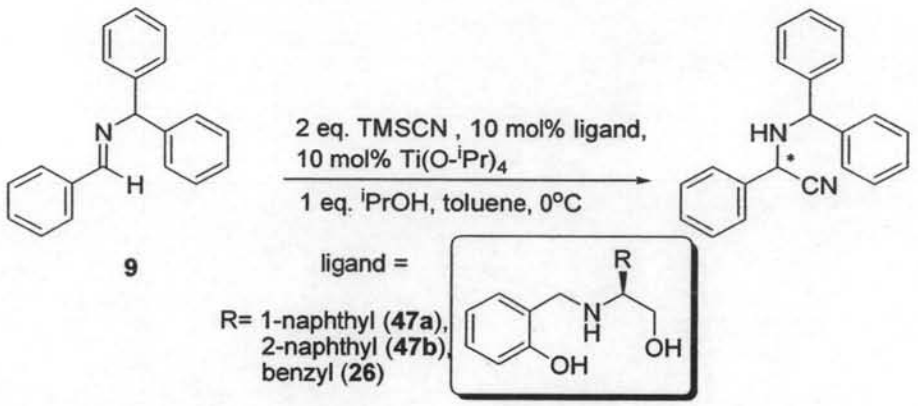
3.2 Evaluation of catalytic activities of 47a and 47b as novel potential ligands in catalytic asymmetric addition reactions

3.2.1 Asymmetric Strecker reaction

A versatile method for an asymmetric strecker reaction catalyzed by optically active *N*-salicyl-β-aminoalcohols-Ti(O^iPr)$_4$ has been reported by Mansawat, *et al.* [*28*] An improved protocols of the conditions was later reported by Banphavichit. [*56*] The reaction between *N*-benzylidenebenzhydrylamine **49** and 2 equivalents of trimethylsilyl cyanide (TMSCN) was carried out in the presence of 10 mol % of ligand, 10 mol% of Ti(O^iPr)$_4$, 1 equivalent of isopropanol as a protic additive and toluene as a solvent at -5 to 0 °C. *N*-salicyl-β-aminoalcohols derived from (*S*)-phenylalaninol (**26**) which was the best ligand in the previous reports was used in this work for comparison of enantioselective activity with our new ligands. The results are shown in Table 3.5.

Percent of enantioselectivity could be determined by ^{1}H NMR spectroscopy using (+)-10-camphorsulfonic acid ((+)-CSA) as a chiral solvating agent. In the presence of CSA, proton signals of C*H*Ph$_2$ of each enantiomer which, upon a solvation effect of (+)-CSA, exhibited diastereomeric relationships and were clearly separated. The C*H*CN proton signals were also well resolved under the same chiral solvating effect. Percent enantioselectivity could be accurately determined from integration difference of H_a proton of each enantiomer (Figure 3.16).

Table 3.5 Asymmetric Strecker reaction of *N*-benzylidenebenzhydrylamine **49** catalyzed by *N*-salicyl-β-aminoalcohols



entry	ligand	R	conversion (%)	*ee* (%)
1	**47a**	1-naphthyl	> 99	97
2	**47b**	2-naphthyl	> 99	82
3	**26**	benzyl	> 99	97

From the splitting pattern of H_a and H_b, the absolute configuration of the optically active products were assigned to the (*S*)-configuration based on literature values. This is in good agreement with a prediction based on (*S*)-configuration of our new ligands.(Figure 3.16)[*56*] The degree of enantiomeric induction catalyzed by complexation between $Ti(O^iPr)_4$ and our new naphthyl ligand **47a** was similar to ligand **26** (97 %*ee*), the best ligand in the previous report.(entries 1 and 3) When ligand **47b** was used, percent enantioselectivity dropped to 82 %*ee*. (entry 2). The asymmetric model of addition can be used for explanation of the results (Figure 3.17).

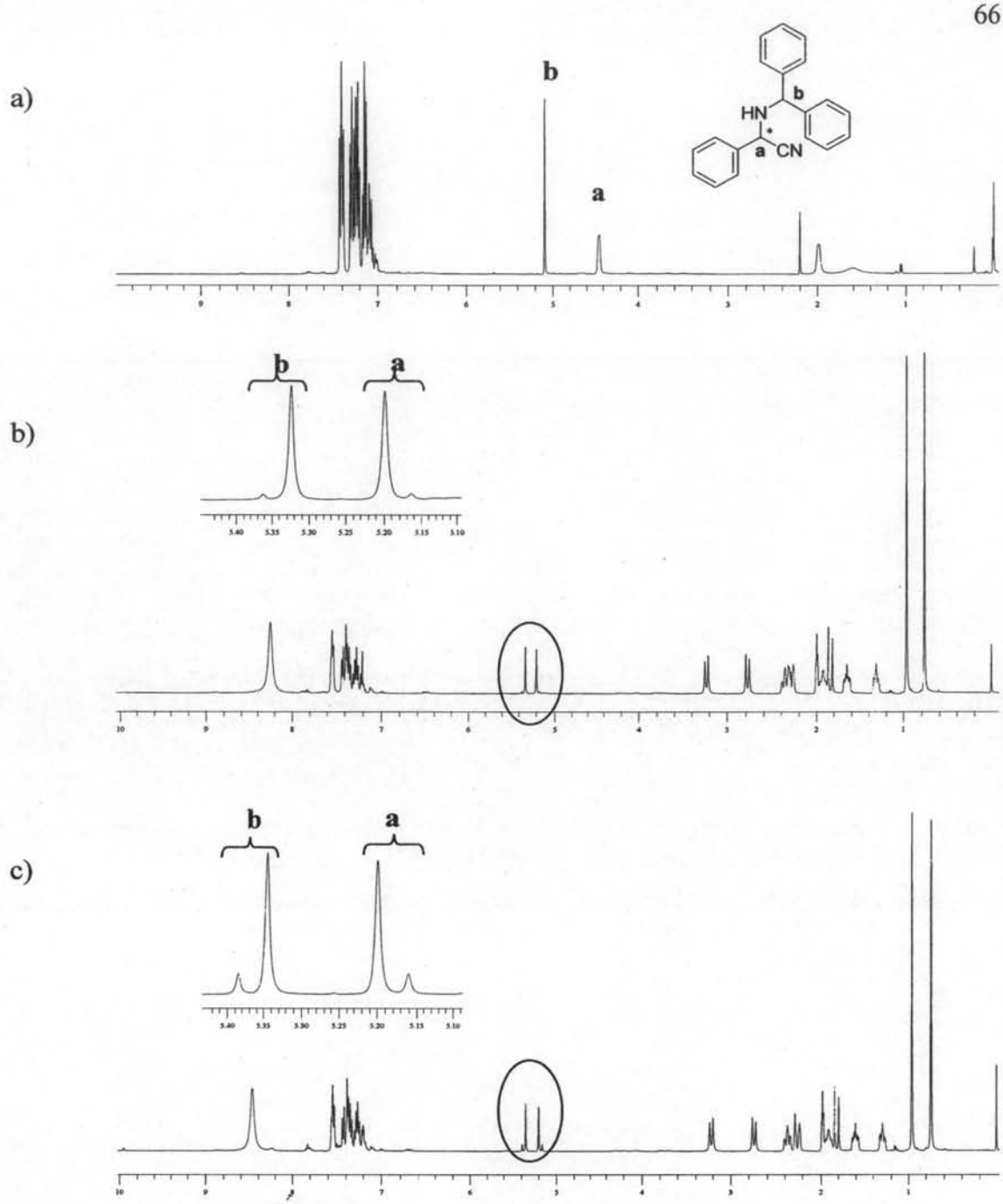


Figure 3.16 Crude ^{1}H-NMR spectra of Strecker reaction from imine **49**
a) without CSA b) from using of ligand **47a** + CSA (97 %*ee*)
c) from using of ligand **47b** + CSA (82 %*ee*)

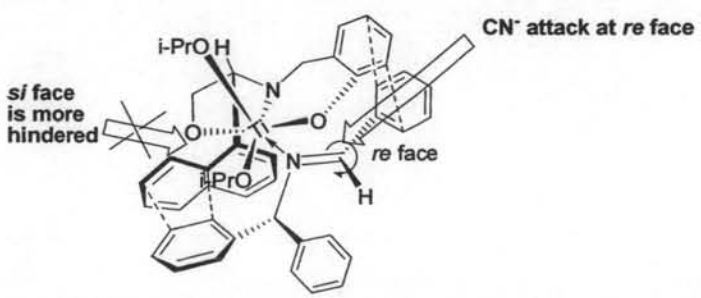


Figure 3.17 Transition state model of Strecker reaction catalyzed by Ti- **47a**

The proposed transition state model can explain why (*S*)-**47a**-Ti complex preferably induced the formation of the product with (*S*)-configuration. It is proposed here that the (*E*)-imine, representing the most stable geometry, coordinated to Ti below the plane of the coordinating catalyst. Possible two of the π-π stacking interactions, which were indicated on the model by dashed line, were established. The first interaction is between phenyl group of the salicyl moiety and the imine. The other is between the 1-naphthyl group and a phenyl of the diphenylmethyl group. These important interactions cause the stability and rigidity of the transition-state resulting in an excellent enantioselectivity. The model suggests that the *si* face of the imine is more hindered than the *re-face* due to the blocking by the naphthyl group. The decrease in the degree of enantioselectivity upon changing to the (*S*)-**47b** Ti complex might be a consequence of a less efficient π-π stacking interaction between aromatic rings of the 2-naphthyl group and a phenyl of the diphenylmethyl group than in the case of 1-naphthyl. The data suggests that the stacking of the 1-naphthyl and the phenyl groups are comparable to the benzyl-phenyl interaction in the (*S*)-**26**-Ti complex. As a result, the enantioselectivities in both cases are essentially the same.

3.2.2 Asymmetric Michael reaction

An asymmetric Michael reaction between an α,β-unsaturated cyclic enone and a malonate using heterobimetallic catalysts generated from *N*-salicyl-β-aminoalcohol ligand and lithium aluminium hydride was developed recently.[*25-27*] It has been reported the best enantioselectivity is 87% from using (*S*)-2-((1-hydroxy-3,3-dimethylbutan-2-ylamino)methyl)phenol (**25**) as a ligand 15 hours. We envisaged that the reaction time could be optimized. As a consequence, the kinetic of this reaction were studied.

3.2.2.1 The study of the reaction time parameter

^{1}H-NMR was applied to determine an optimum reaction time. The reaction was set following the previously optimized condition[*27*] using **25** as a ligand. An aliquot of the crude reaction mixture (0.25 mL) was withdrawn every 1 hour and a spectrum of each sample was acquired without removal of THF because both reactants, di-*t*-butylmalonate and 2-cyclohexen-1-one, have quite low boiling points. The integration ratios between the malonate and the product formed indicate the reaction time required for the reaction to complete as shown in figure 3.18.

a)

b)

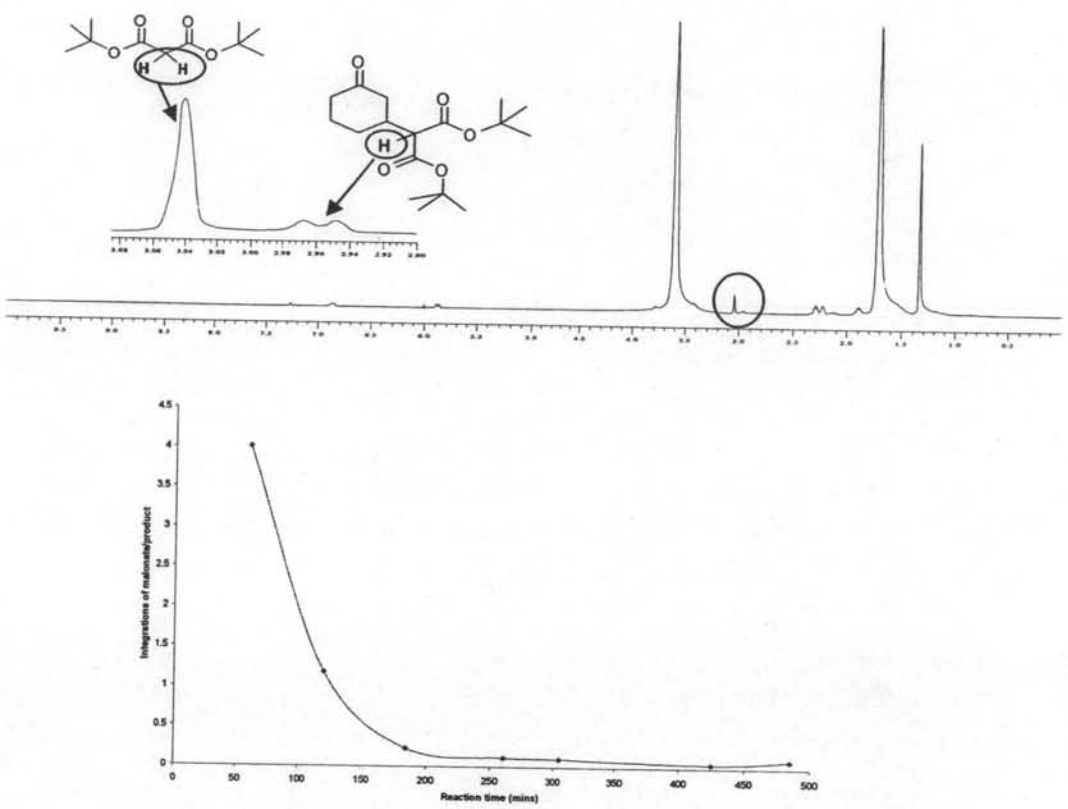
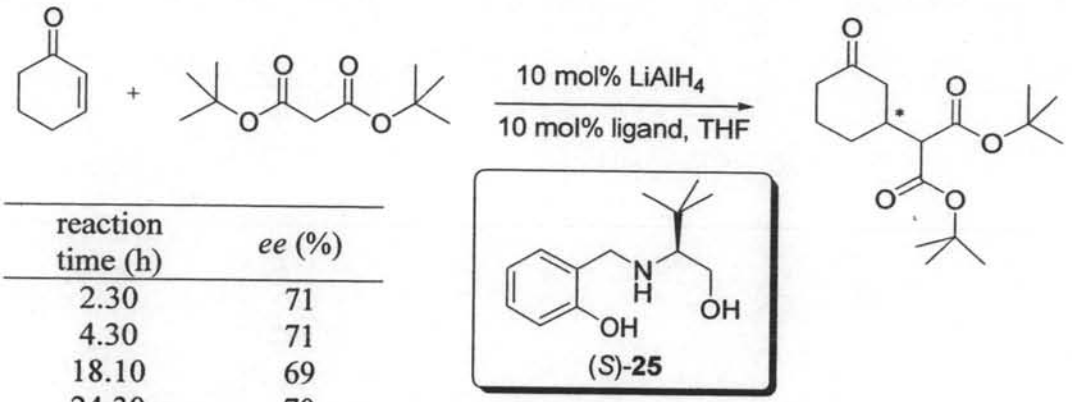


Figure 3.18 a) ^{1}H-NMR of crude reaction mixture after 1 hour of reaction
b) Plot between integration ratios of malonate/product and reaction time (minutes)

The doublet signal at δ2.96 ppm belongs to the methylene proton of the malonate and the singlet signal at δ3.04 ppm is of the proton of the Michael adduct from the malonate moiety. An exponential-like plot between the malonate to the product integration ratio versus the reaction time indicated that over 90 % of the malonate was consumed when the reaction time was 5 hours. Beyond that point the amount of the malonate remained relatively constant. Therefore, the most suitable reaction time was determined to be only 5 hours, not 15 hours. Furthermore, a relationship between the reaction time and the degree of enantioselectivity was investigated. A reaction on a larger scale (2 mmol) was carried out. The crude solution was withdrawn at intervals of time, dried by purging with N_2, and purified by column chromatography. Percentage of enantioselectivity could be determined by gas chromatographic analysis using 10% BSiMe as a chiral capillary column. The results are shown in Table 3.6.

Table 3.6 The relationship between reaction time and percent of enantioselectivity



reaction time (h)	*ee* (%)
2.30	71
4.30	71
18.10	69
24.30	70

Clearly, the results show that the enantioselectity of the formed product is independent of the reaction time. This could also be interpreted that the enantioselectivity in the product is regularly high and remains constant throughout the course of the reaction. This is indicative of no interference from other reaction pathways which could affect the degree of enantioselectivity of product after extension of the time over 5 hours. The values of percent enantioselectivity observed in this series of study, all of which were not significantly different (69-71%), were lower than our highest result (80 %*ee*). A rationale may be based on the freshness of the $LiAlH_4$ used in the reactions at difference period of time. We have sometimes experienced the less effectiveness of the catalyst as reflected by lower percent enantiomeric excess in the product when a relatively old bottle of $LiAlH_4$ was used.

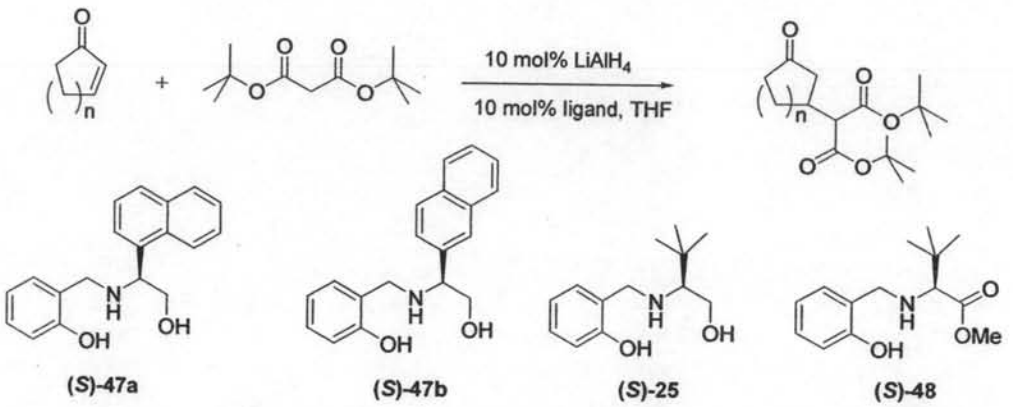
3.2.2.2 The comparative study of the enantioselectivity induced by the naphthyl ligand and *t*-butyl ligands

Asymmetric Michael reactions were achieved using the optimized condition [*27*] employing various ligands . The results are shown in Table 3.7

2-Cyclohexen-1-one was used as a substrate in the Micheal addition with di-*t*-butyl malonate in the presence of catalysts derived from different ligands with various substituents on the amino alcohol moeity (entries 1-3). The new ligand **47a**, bearing a 1-naphthyl group on the amino alcohol moeity, led to 91 %*ee* of the product. This is so far the best enantioselectivity obtained from the Li-Al-*N*-salicyl-β-amino alcohol catalyst systems.[*25-27*] In the cases of catalysts **47b** and **25** with the 2-naphthyl and *t*-butyl group respectively, the %*ee* were lower than that of **47a** (entry 2 and 3). In addition, our new ligand **47a** also led to higher enantioselective outcome than when

ligand **25** was used in the case of the reactions between 2-cyclopenten-1-one and di-*t*-butylmalonate (entries 5 and 6).

Table 3.7 Asymmetric Michael reaction using various of ligands



entry	n	ligand	yield (%)	*ee* (%)
1	2	**25**	91	80
2	2	**47a**	91	91
3	2	**47b**	90	87
4	2	**48**	87	-55
5	1	**47a**	88	66
6	1	**25**	93	48

From the previous report, the absolute configuration of the products were (*R*) when ligands with an (*S*)-configuration were used.[*26*] In addition, the literature claimed an enantiomer switching effect in the product which was described to be related to the functional group of the catalysts. When the methoxy ligand (such as **48**) with an (*S*)-configuration was used, the (*S*)-product was obtained. This hypothesis was put to test by using ligand **48**. Enantiomer switching could be found in moderate enantioselection (55 %*ee*, major enantiomer was (*S*)) which is not better than an isopropyl was present as a bulky substituent in the ester ligand (65 %*ee*, major enantiomer was (*S*)) of the previous report. (entry 4) However, the rationale from Narasimhan's work[*25-26*] that methoxy ligand **48** led to the formation of a complex with a metal to ligand ratio of 1:1, whereas the amino alcohol such as **25** led to the complex with a 1:2 ratio is still ambiguous. In addition, there were no strong and

obvious evidences, such as crystal structure of the complex or a mass spectrum, to confirm the differences in the ligand to metal ratios. Actually, when 20 mol% of ligand **25** and 10 mol% of $LiAlH_4$ were employed, the %*ee* dropped from 80 to 57 %. These results raised a question that if the ratio between ligand **25** and the metal was actually 2:1, this condition of 20 mol% of ligand should achieve a higher enantioselectivity than when a 10 mol% ligand was used. A plausible transition state in case of using the best ligand **47a** is proposed in figure 3.19. This transition state is based on our hypothesis that the ratio of ligand/metal is equal to 1:1.

It is noteworthy that the results obtained in this work using 20 mol% ligand are consistent with what was previously reported.[*27*]

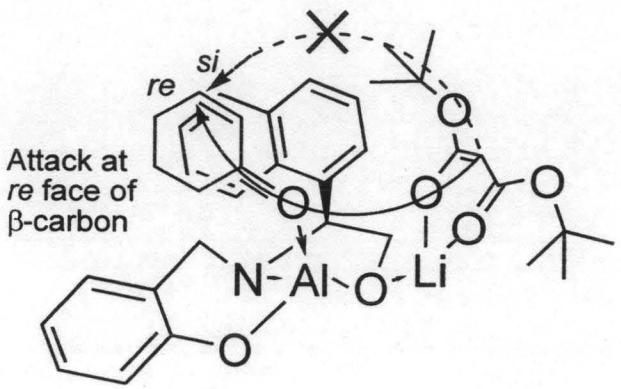


Figure 3.19 A plausible transition state of asymmetric Michael reaction using **47a** as a ligand

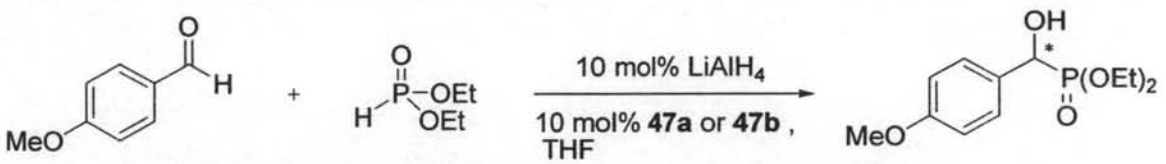
This metal complex is proposed to be heterobimetallic in nature. A lithium ion acts as a Lewis base which deprotonates di-*t*-butylmalonate and is coordinated by a negative oxygen atom of the malonate. Hence, the malonate can bind to catalyst structure at the transition state by this coordinated bond. In contrast, an aluminium ion, serves as a Lewis acid to activate a carbonyl group on 2-cyclohexen-1-one. In case of using **47a** or **47b** as a ligand, it is possible that an aromatic system of the naphthyl group can partially stack with π-conjugated system of 2-cyclohexen-1-one by a π-π stacking interaction. More rigid transition state than that obtained using of **25** was formed. In addition, this stacking assists the blocking of *si*-face of the ketone at the β-position from malonate attack. This proposed transition state corresponds with the (*S*)-configuration of the products from *re*-face attack by the malonate.

However, this model cannot explain the enantiomer switching phenomenon addressed by Narasimhan from the use of ligand **48**. In principle, ligand **48** which consists of methoxycarbonyl group, the ester functional group, might be reduced by $LiAlH_4$ to the corresponding aminoalcohol. Only one difference from prior cases is the availability of methoxy anion in the solution. At this stage, strong evidences of an involvement in the transition state have not been achieved.

3.2.3 Asymmetric Pudovik reaction

An asymmetric Pudovik reaction between an aldehyde and dialkylphosphite using heterobimetallic catalysts generated from *N*-salicyl-β-aminoalcohol ligand and lithium aluminium hydride was developed recently.[*29*] It has been reported that the best enantioselectivity is 72% from a reaction between 4-methoxybenzaldehyde and diethylphosphite using (*S*)-2,4-di-*t*-butyl-6-((1-hydroxy-3-methylbutan-2-ylamino)methyl)phenol (**27**) as a ligand. The previously optimized condition, 10 mol% of the ligand and $LiAlH_4$, was employed with our two new naphthyl ligands (**47a** and **47b**) to evaluate the capability in asymmetric induction. (Table 3.8)

Table 3.8 Asymmetric Pudovik reaction



entry	ligand	yield (%)	*ee* (%)
1	**47a**	68	0
2	**47b**	67	0

From the results, our new naphthyl ligands could catalyze the Pudovik reaction to proceed in moderate yields. However, no enantioselectivity was detected in the product. An explanation for the lack of asymmetric induction by our new naphthyl ligands may be based on the fact that Ligand **47a** and **47b** do not possess similar substituents on the salicyl moiety which was present in ligand **27**. This rationale reaffirms the previous conclusion which mentioned the necessity to have a salicyl group present in the molecule as well as the relationship between substituents of the salicyl moiety and the induction of enantioselectivities. [*29*] *N*-salicyl β-naphthyl aminoalcohol ligands which contain various substituents on salicyl moiety should be further developed for this reaction in the future.