CHAPTER III

RESULTS AND DISCUSSION

## 3.1 Synthesis of racemic Michael adducts
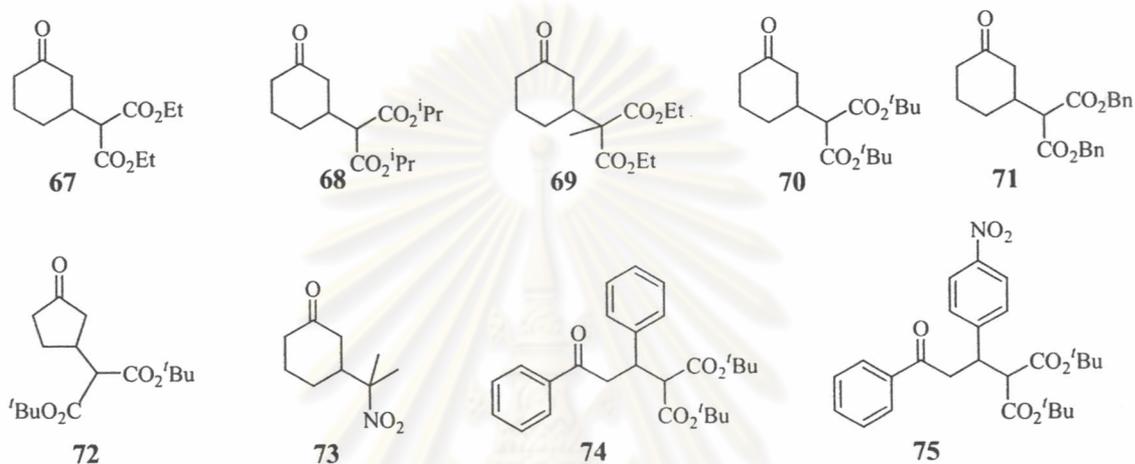
Figure 46. Structure of racemic Michael adducts.

In order to obtain racemic Michael adducts for development of *ee* analysis techniques, a variety of Michael adducts were synthesized. The results were shown in **Table 1**. Among Michael adducts **67-72**, it was found that only **67** could be synthesized by using DBU as a base in stoichiometric amount but no reaction was observed with other adducts. The remaining compounds required the use of $LiAlH_4$ as base. For method A, the Michael reactions carried out by using only $LiAlH_4$ gave racemic Michael adducts in moderate to high yields except for **69** and **73** where there were no reactions. Interestingly, when the racemic ligand (*R/S*)-**87d** complexed with $LiAlH_4$ (10 mol %) was used as catalyst, the Michael adducts were obtained in high yields (**Table 1**, entries 1-9). The results showed that the addition of the racemic achiral ligand (*R/S*)-**87d** greatly increased the reactivity of the reaction compared with using $LiAlH_4$ alone. ^{1}H NMR of all Michael adducts (**67-72**) showed the similar doublet signals around 3.0 ppm that belonged to $C\underline{H}(CO_2R)_2$ which cyclohexyl protons of cyclohexenone around 1.47-2.49 ppm. Characteristic signals of ethyl, isopropyl, *tert*-butyl and benzyl esters were also observed for compounds **67**, **68**, **69**, **70** and **71**, respectively. Moreover, the singlet signal at 1.39 ppm due to the methyl group of compound **69** was evidenced. For

compound **73** a characteristic singlet of two CH$_3$ group on quaternary carbon was observed at 1.82 ppm. ^{1}H NMR of the Michael adduct **72** showed special signal of di-*tert*-butyl moiety, cyclopentyl of cyclopentenone, and a doublet of C$\underline{H}$(CO$_2$^{t}Bu)$_2$. ^{1}H NMR of the acyclic Michael adducts **74** and **75** revealed important signal due to the di-*tert*-butyl malonate moiety and aromatic group.

Table 1. Synthesis of racemic Michael adducts

entry	substrate	nucleophile	product	method A (yield[a] (%))	method B (yield[a] (%))
1	cyclohex-2-enone	CH$_2$(CO$_2$Et)$_2$	**67**	85	87
2	cyclohex-2-enone	CH$_2$(CO$_2$^{i}Pr)$_2$	**68**	80	80
3	cyclohex-2-enone	CH$_3$CH(CO$_2$Et)$_2$	**69**	-[b]	83
4	cyclohex-2-enone	CH$_2$(CO$_2$^{t}Bu)$_2$	**70**	80	82
5	cyclohex-2-enone	CH$_2$(CO$_2$Bn)$_2$	**71**	88	90
6	cyclopent-2-enone	CH$_2$(CO$_2$ ^{t}Bu)$_2$	**72**	82	87
7	cyclohex-2-enone	(CH$_3$)$_2$CHNO$_2$	**73**	-[b]	30
8		CH$_2$(CO$_2$ ^{t}Bu)$_2$	**74**	60	65
9		CH$_2$(CO$_2$ ^{t}Bu)$_2$	**75**	48	57
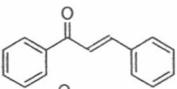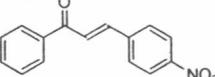
Method A: LiAlH$_4$ 10 mol % was used as catalyst. Method B: LiAlH$_4$:racemic ligand (*R/S*)-**87d** (1:1) complexes 10 mol %. [a]Isolated yield. [b]no reaction.

3.2 Determination of enantiomeric excess

Based upon availability and accessibility of the equipment, three techniques were selected as candidates for determination of the enantioselectivity of Michael adducts. These included nuclear magnetic resonance (NMR) spectroscopy, high performance liquid chromatography (HPLC), and gas chromatography (GC).

3.2.1 NMR spectroscopy

Enantiomers cannot be distinguishably separated in an achiral medium by NMR technique because their resonances are chemical shift equivalent (isochronous). In contrast, diastereomeric signals are separable because they are chemical shift non-equivalent (anisochronous). Determination of enantiomeric purity using NMR requires the intervention of a chiral auxiliary to convert an enantiomeric mixture into a diastereomeric mixture. If the magnitude of the chemical shift non-equivalence was

sufficient to give baseline resolution, integration of the appropriate singnals give a measure of the diastereomeric composition. The enantiomeric composition of the original mixture can then be calculated.

Three types of chiral auxiliary were widely used. Chiral derivatizing agents (CDAs) form diastereomers while chiral solvating agents (CSAs) and chiral lanthanide shift reagents (CLSRs) form diastereomeric complexes *in situ* with the substrate enantiomers.

An effective chiral auxiliary should induce significant NMR chemical shift anisochronicity in as large a range of substrates as possible. Furthermore, if the sense of non-equivalence was consistent in a series of compounds, then once a standard of known stereochemistry has been studied, the absolute configuration of the unknown can be deduced from the NMR spectra.

According to previous reports [24,30], (2R,3R)-2,3-butanediol (76) was used as chiral derivatizing agent for enantioselective determination of Michael adduct. Unfortunately, the derivatization of Michael adduct with diol was inconvenient. It requires separated synthetic and purification steps before characterization by NMR. We have used, (1R,2R)-diphenyl-ethane-1,2-diamine (77) in place of 76. Unfortunately, no baseline resolution could be observed for Michael adduct 71.

(2R,3R)-76   (1R,2R)-77

Figure 47. (2R,3R)-2,3-butanediol (76) and (1R,2R)-diphenyl-ethane-1,2-diamine (77).

The enantiomeric excess of Michael adducts were also examined by chiral lanthanide shift reagents (CLSRs) because carbonyl group on Michael adduct could form diastereomeric complexes with chiral lanthanide shift reagents (CLSRs). However, after several attempts, the enantioselectivities of Michael adducts 67 could not be determined by this method. Therefore, an alternative method employing chiral high performance liquid chromatographic analysis has been investigated.

3.2.2 High Performance Liquid Chromatography (HPLC)

Liquid chromatography which are rapid and simple for determination of enantiomeric purity have perhaps been continuously developed in the analysis of chiral compounds since the 1990s. Most of the works employed chiral HPLC columns such as Daicel Chiralpak AD, AS, and Chiralcel OD to determine the optical purity of Michael adducts.

For example, Shibasaki and co-workers reported the determination of enantiomeric excess of Michael adducts, **71**, **79**, and **80** by HPLC analysis on chiral stationary phase column (Chiralpak AS, isopropanol:hexane (10:90)).[*31*]
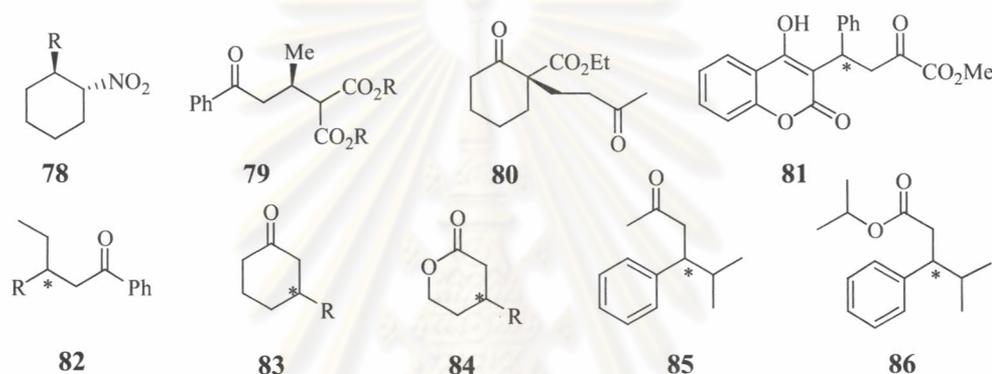

Figure 48. Several structures of Michael adducts form previous reports.

Hayashi's reported the determination of enantiomeric excess of Michael adduct **78** by HPLC analysis on chiral stationary phase (Daicel Chiralcel OJ, OD-H, or Chiralpak AD).[*13*]

Recently, Jørgensen reported that % *ee* of **81** was measured by chiral HPLC technique using Chiralpak AD column and hexane:2-propanol (70:30) containing 0.15 % of TFA as an eluent.[*17*]

In addition, Zhou reported the use of Chiralcel OJ column to determine the enantiomeric purity of the Michael adduct **82** using 99:1, hexane:2-propanol as eluent. [*12*] The enantiomeric excess of the Michael adducts **83-86** could be determined by HPLC analysis with chiral stationary phase columns (Chiralpak AD column).[*11*]

For this experiment, the enantioselectivity of Michael adducts (**70**, **71** and **74**) were tested by chiral HPLC (AD and OD columns) which were available in our laboratory. The results showed that enantiomers of Michael adducts could not be separated by chiral HPLC when both Chiralpak AD and Chiralcel OD columns were

used. Only the enantiomeric composition of Michael adduct **74** could be determined by using Chiralpak AD column (90:10 hexane:2-propanol, 1mL/min).

3.2.3 Gas chromatographic methods

Another well-known method for determination of enantiomeric excess is chiral gas chromatography (GC). The premise upon which the method was based was that molecular association may lead to sufficient chiral recognition that enantiomer resolution results. Since Michael adducts are small molecules, easily volatile, and thermally stable, they should be ideal for chiral GC analysis.

It is precedent that determination of several volatile chiral compounds by chiral GC on chiral column containing modified β-cyclodextrins which is heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose was successful.[49] The enantiomeric pair of Michael adduct **67** containing both carbonyl and ester groups might be separated on a chiral column. Gratifyingly, separation of a racemic mixture of the Michael adduct **67** on a chiral gas chromatographic column coated with 10 % β-cyclodextrin derivative was achieved in good to excellent baseline separation under both isothermal and temperature program conditions. The results are shown in **Figure 49**. Assignment of absolute configuration of the major enantiomer has not yet been carried out at this stage.
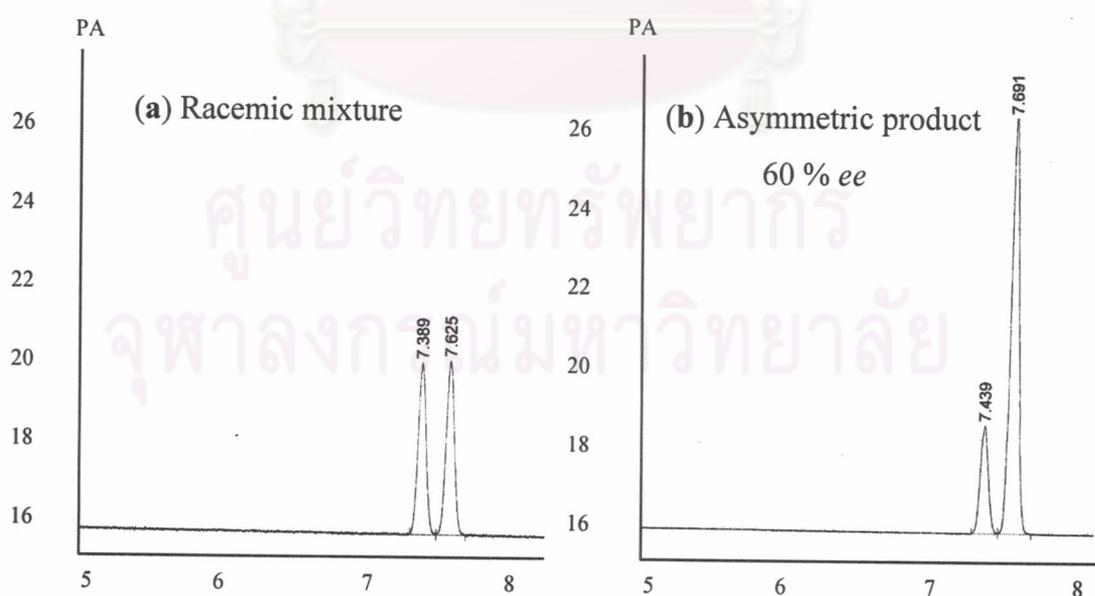
Figure 49. Representative chiral GC chromatograms of **(a)** a racemic mixture of Michael adduct **67**. and **(b)** an enantiomerically enriched Michael adduct **67** (60 % *ee*).

Apart from **67**, excellent baseline separations were observed for all of the Michael adducts **68-70** and **72**. Apparently, chiral GC using the specified stationary phase offers itself as a reliable and speedy method for determination of *ee* of the Michael adduct with high accuracy.

### 3.3 Synthesis of ligands

3.3.1 Structure of ligands for asymmetric Michael reaction

To examine the influence of substituents on various positions of the ligand on the degree of enantioselectivity of the Michael addition, many *N*-salicyl-β-amino alcohol ligands containing substituents at various positions of the salicyl and aminoalcohol parts were selected. Moreover, non-salicyl ligands such as binol and other amino alcohol ligands were also included for comparison in the same asymmetric Michael reaction. The *N*-salicyl-β-amino alcohol and related ligands used in this study can be categorized into the following groups.

**Group 1: *N*-salicyl-β-amino alcohol ligands bearing bulky side chain at the α-position**
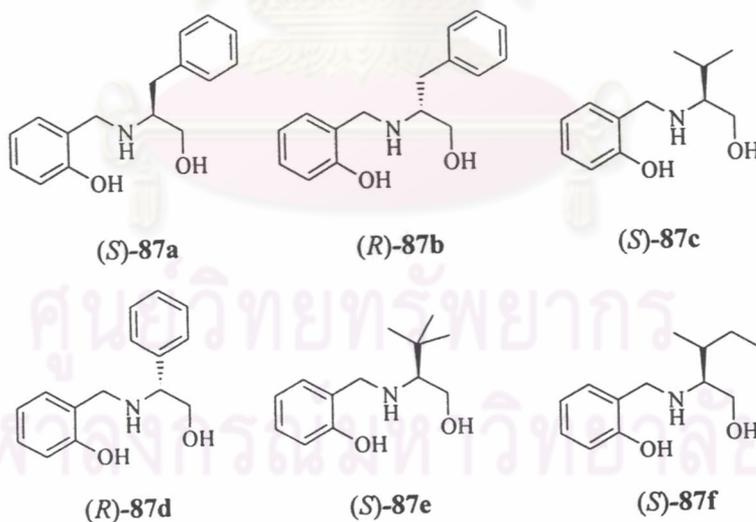
(*S*)-**87a**   (*R*)-**87b**   (*S*)-**87c**

(*R*)-**87d**   (*S*)-**87e**   (*S*)-**87f**

Group 2: *N*-salicyl-β-amino alcohol ligands bearing substitutents at both α-, and β-positions.

87g   (1*R*,2*S*)-87h   (*S*)-87i

(1*S*,2*R*)-87j   87k   87l
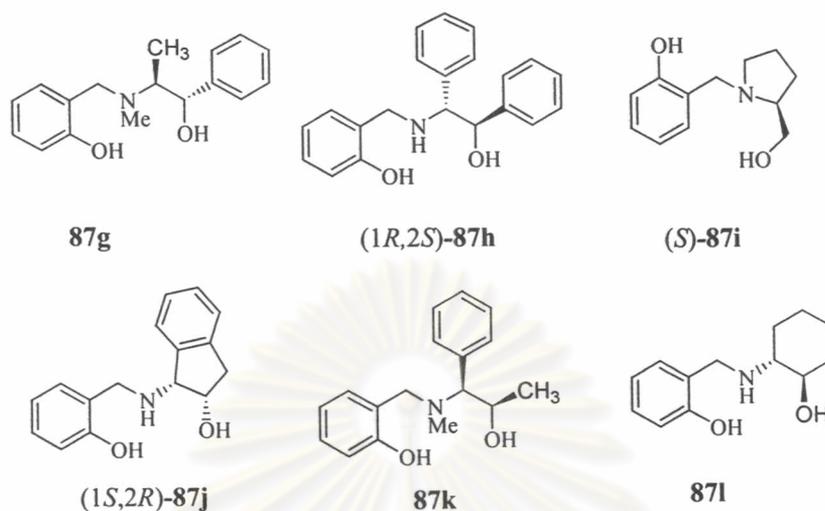
**Group 3:** *N*-salicyl-β-amino alcohol ligands bearing substituents with different steric bulkiness on the salicyl moiety.


(*S*)-87m   (*S*)-87n   (*S*)-87o

(*S*)-87p   (*S*)-87q
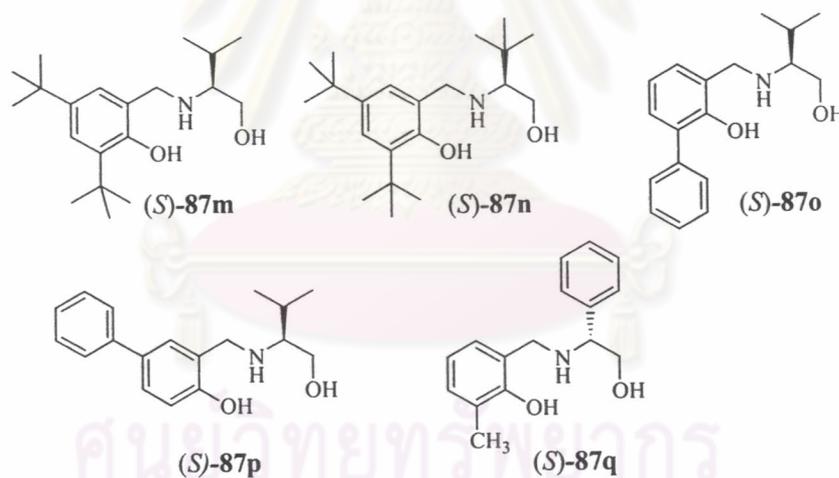
Group 4: *N*-salicyl-β-amino alcohol ligands bearing substituents with different electronic effect on the salicyl moiety.


(*R*)-87r   (*R*)-87s   (*R*)-87t   (*R*)-87u
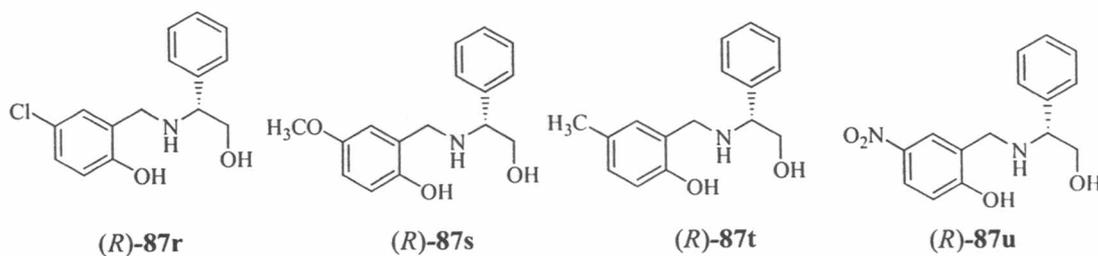
Group 5: Bidentate amino alcohol ligands
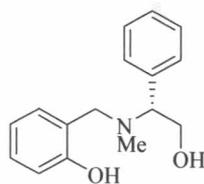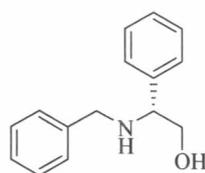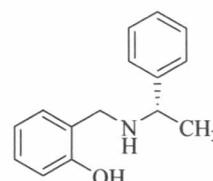
(*R*)-**87v**   (*R*)-**87w**   (*R*)-**87x**

Group 6: non-salicyl ligands
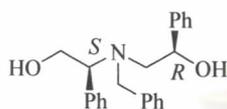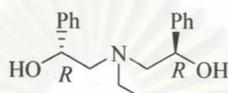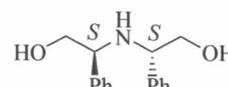
88a   **88b**   **88c**
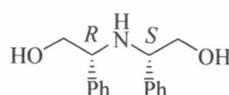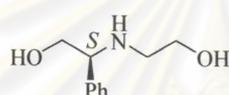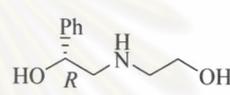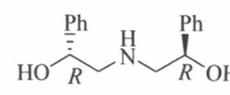
88d   **88e**   **88f**   **88g**

3.3.2 Synthesis of *N*-salicyl-β-amino alcohol ligands by NaBH₄ reduction and hydrogenation

Table 2. Comparison of *N*-salicyl-β-amino alcohol ligands by using NaBH₄ and hydrogenation.

entry	ligands	method A (yield[a] (%))	method B (yield[a] (%))
1	**87h**	-[b]	84
2	**87i**	60	-[b]
3	**87j**	33	67
4	**87k**	60	-[b]
5	**87l**	20	-[b]
6	**87q**	60	-[b]
7	**87r**	82	-[b]
8	**87s**	50	-[b]
9	**87t**	45	-[b]
10	**87u**	41	-[b]

Method A: NaBH₄. Method B: hydrogenation. [a]isolated yield. [b]ligands were not synthesized by this method.

The *N*-salicyl-β-amino alcohol ligands (**87**) were synthesized by condensation reaction between salicylaldehyde and the appropriate aminoalcohol in methanol or ethanol followed by *in situ* NaBH$_4$ reduction.[*42-43*] After purification by flash column chromatography, ligands **87** were obtained in 20-82 % yield (**Table 2**). Ligands **87h** and **87j** were synthesized by using hydrogenation over palladium/carbon (method B) which provided the products in excellent yield (67 and 84 %, **Table 2**, entries 1 and 3). However, over-reduction may accompany the hydrogenation. Therefore, it was not practical for general use in ligand synthesis.

The ligand **87v** was synthesized from phenol, formaldehyde and D-phenylglycinol using LiCl as a catalyst under 80 °C for 18h.[*51*] After purification by flash column chromatography, the oxazolidine **89** was obtained. In the next step the oxazolidine underwent ring-opening reaction with NaBH$_4$/TFA to give ligand **87v** in 22 % yield. The chiral ligands **87j-l** and **87q-v** were new compounds.
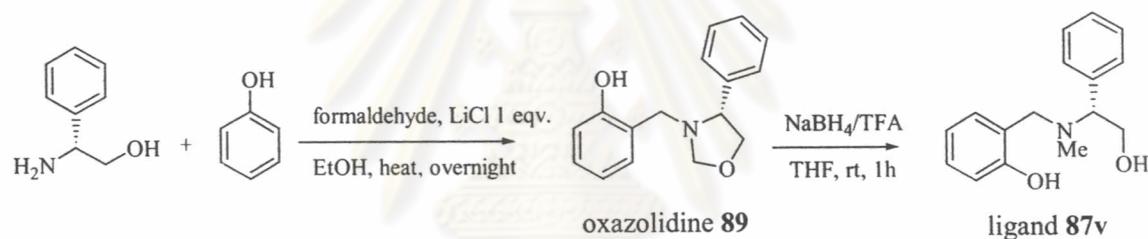

Figure 50. The synthesis of ligand **87v**

3.3.3 Synthesis of other ligands

The chiral *N*-salicyl-β-amino alcohol ligands **87a-87e**, **87g**, **87m-87p**, **87i** and **91** were synthesized by Mr. Vorawit Banphavichit. Ligands **87w** and **87x** were synthesized by Miss Woraluk Mansawat and the non-salicyl ligands **88a-f** were synthesized by Miss Roejarek Kanjanawarut. Ligand **88b** had previously been reported by Sundararajan to be effective in asymmetric Michael addition reactions of malonates and thiophenols to cyclic and acylclic enones.[*38-39*]

3.4 Asymmetric Michael reactions catalyzed by metal-chiral amino alcohol ligand complexes.

3.4.1   Optimization of the reaction conditions
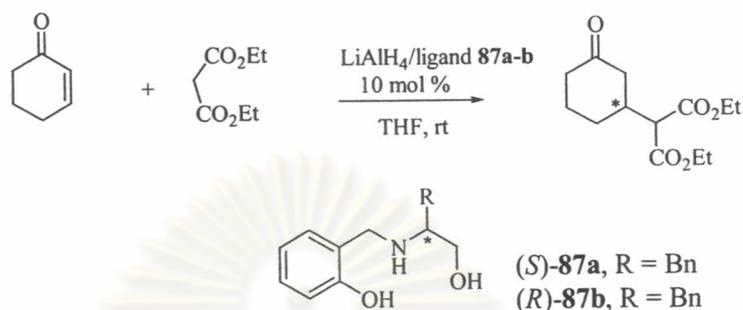
Table 3. Asymmetric Michael reactions of diethyl malonate and cyclohex-2-enone catalyzed by LiAlH$_4$:**87** complexes.

| entry	cat (10 mol %)	solvent	time[a]	temp	yield[b] (%)	ee[c](%)
1	LiAlH$_4$: **87a** (1:1)	THF	3d	rt	62	20
2	LiAlH$_4$: **87a** (1:2)	THF	3d	rt	44	8
3	LiAlH$_4$:**87a** (1:1)	THF	1 week	0	56	9
4	LiAlH$_4$:**87a** (1:2)	toluene	3d	rt	64	5
5	LiAlH$_4$:**87a** (1:2)	DCM	3d	rt	52	13
6	LiAlH$_4$:**87b** (1:2)	THF	1 week	0	37	-2
7	LiAlH$_4$:**87b** (1:2)	THF	1 week	-6	26	-11
9	LiAlH$_4$:**87b** (1:1)	THF	1 week	0	40	-16
10	LiAlH$_4$:**87b** (1:1)	THF	3d	rt	88	-6

[a]The progress of the reaction was monitored by TLC until complete consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC.

Asymmetric Michael reactions were screened using 10 mol % of lithium aluminium hydride (LiAlH$_4$):ligand **87a** in 1:1 and 1:2 ratios prepared *in situ* from the ligand and LiAlH$_4$ (1 M in THF) in dry THF at room temperature for 1h. Then diethyl malonate and cyclohex-2-enone were added. The ratio of chiral amino ligand to metal, polarity of solvent, and temperature have also been investigated and the results were shown in **Table 3**. The results showed that the complexes of LiAlH$_4$:ligand **87a** in 1:1 and 1:2 ratios catalyzed the asymmetric Michael reaction with moderate yield (**Table 3**, entries 1 and 2; 62 % and 44 %) and low % *ee* (20 % and 8 %). The different ratio of

complexes of LiAlH$_4$: ligand **87a** afforded the same sense of asymmetric induction, which is in sharp contrast to the previous reports.[40-41] It was noted that the rate of reaction at room temperature was faster than the lower temperature (0°). Reactions at room temperature (**Table 3**, entries 1 and 10) and lower temperatures (0 and -6° C, **Table 3**, entry 3, 6, 7, and 9) showed similar results in terms of enantioselectivity, therefore, subsequent reactions were set up at room temperature. For solvent effects, toluene, THF, and DCM gave comparable % *ee* but THF was chosen as the solvent of choice of convenience in catalyst preparation. It can be concluded from **Table 3** that the best condition for asymmetric Michael reaction was to use 10 mol % of the catalyst in 1:1 ratio of LiAlH$_4$:ligand **87** at room temperature for 72h in THF. The product with opposite configuration was obtained in yield and enantioselectivity (entries 6-10) when the LiAlH$_4$:**87b** complex with opposite configuration of the ligand from **87a** was used.

3.4.2 Screening of the ligands

The ligands **87a-p** were screened under the best condition obtained above (**Table 4**, entries 1-11). A significant improvement in the enantioselectivity was achieved by using chiral ligands **87c**, **87d**, **87e**, and **87j** (**Table 4**, entries 2, 3, 4, and 9). Chiral ligand **87e** with a *tert*-butyl substituent on the amino alcohol moiety gave the highest % *ee*. The results showed that steric bulky groups at the α-position play a significant role to improve enantioselectivity of the Michael adduct.

(*S*)-**87a**, R = H, R$_1$ = Bn, R$_2$ = H, R$_3$ = H, R$_4$ = H
(*S*)-**87c**, R = H, R$_1$ = ^{i}Pr, R$_2$ = H, R$_3$ = H, R$_4$ = H
(*R*)-**87d**, R = H, R$_1$ = Ph, R$_2$ = H, R$_3$ = H, R$_4$ = H
(*S*)-**87e**, R = H, R$_1$ = ^{t}Bu, R$_2$ = H, R$_3$ = H, R$_4$ = H
(1*S*,2*R*)-**87g**, R = Me, R$_1$ = Me, R$_2$ = Ph, R$_3$ = H, R$_4$ = H
(1*R*,2*S*)-**87h**, R = H, R$_1$ = Ph, R$_2$ = Ph, R$_3$ = H, R$_4$ = H
(*S*)-**87i**, R = R$_1$ = -(CH$_2$)$_3$-, R$_3$ = H, R$_4$ = H
(1*S*,2*R*)-**87j**, R = H, R$_1$ = R$_2$ = -C$_6$H$_4$CH$_2$-, R$_3$ = H, R$_4$ = H
(*S*)-**87m**, R = H, R$_1$ = ^{i}Pr, R$_2$ = H, R$_3$ = ^{t}Bu, R$_4$ = ^{t}Bu
(*S*)-**87n**, R = H, R$_1$ = ^{t}Bu, R$_2$ = H, R$_3$ = ^{t}Bu, R$_4$ = ^{t}Bu
(*S*)-**87p**, R = H, R$_1$ = ^{i}Pr, R$_2$ = H, R$_3$ = Ph, R$_4$ = H
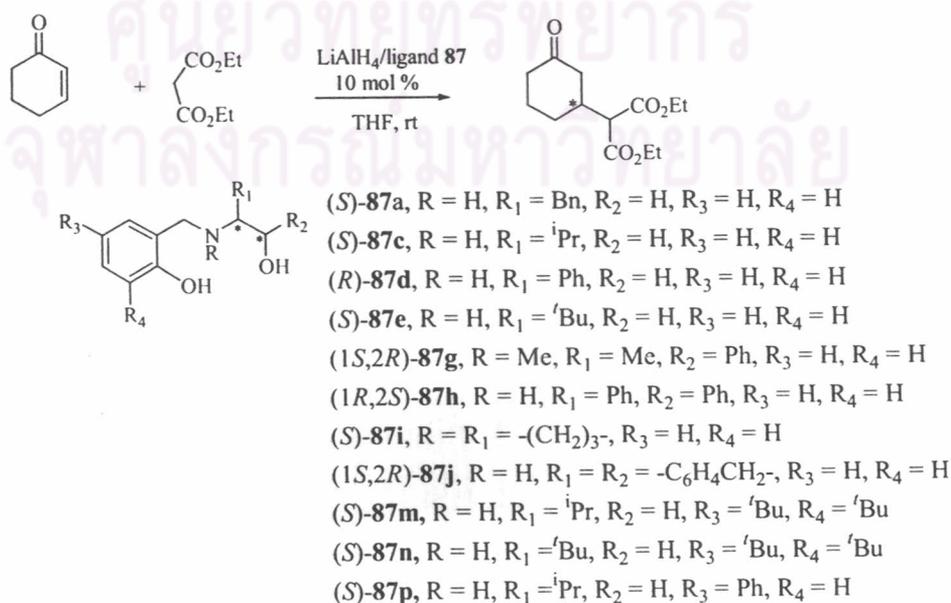
Table 4. Asymmetric Michael reactions of diethyl malonate and cyclohex-2-enone catalyzed by several LiAlH$_4$:**87** complexes.

entry	cat (10 mol %)	time^d(h)	yield^a (%)	ee^{b,c} (%)
1	LiAlH$_4$:**87a** (1:1)	72	62	20 (S)
2	LiAlH$_4$:**87c** (1:1)	72	50	49 (S)
3	LiAlH$_4$:**87d**(1:1)	72	87	39 (R)
4	LiAlH$_4$:**87e** (1:1)	72	78	67 (S)
5	LiAlH$_4$:**87g** (1:1)	72	80	1 (S)
6	LiAlH$_4$:**87h** (1:1)	72	15	5 (S)
7	LiAlH$_4$:**87i** (1:1)	40	56	4 (S)
8	LiAlH$_4$:**87j** (1:1)	40	87	42 (R)
9	LiAlH$_4$:**87m** (1:1)	40	69	3 (S)
10	LiAlH$_4$:**87n** (1:1)	40	48	0
11	LiAlH$_4$:**87p** (1:1)	72	87	7 (S)

^{a}Isolated yield. ^{b}Enantiomeric excess was determined by chiral GC. ^{c}Absolute configuration was determined by comparing the specific rotation with literature data. ^{d}The progress of the reaction was monitored by TLC until complete consumption of cyclohex-2-enone.

3.4.3 Effects of substrate structure

From the results shown in **Table 4**, the best ligand for asymmetric Michael addition of diethyl malonate to cyclohex-2-enone was found to be **87e**. In order to investigate the effect of substrate structure, the R and R' substituents on the malonate were varied. The results are shown in **Table 5**. The reaction of cyclohex-2-enone with diisopropyl malonate, di-*tert*-butyl malonate and diethyl methylmalonate catalyzed by 10 mol % of LiAlH$_4$:**87e** (1:1) in THF at room temperature gave the products in high yield and enantioselectivity (entries 2, 4, and 5). It is interesting to observe that α-methylsubstituted malonate (entry 5) also gave a good result. However, when the substituent was large, no reaction was observed (entries 6 and 7). The *ee* of the Michael adduct of dibenzyl malonate (entry 3) could not be determined by chiral GC (cyclodextrin) or chiral HPLC (AD, OD). When optical activity of this Michael adduct of dibenzyl malonate was measured, the racemic compound was obtained ([α]$_D$ = 0). The result suggested that bulkier nucleophile gave improved enantioselectivity of asymmetric Michael reaction. However, the exception of dibenzyl malonate may imply a different transition state of the reaction caused by the large and planar benzyl group.
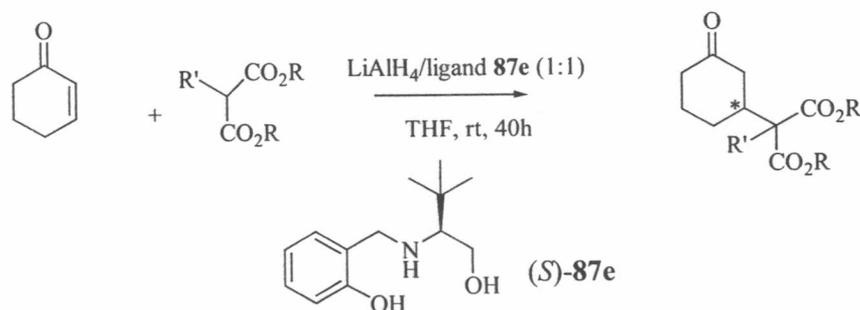
Table 5. Asymmetric Michael reactions of diethyl malonate and cyclohex-2-enone catalyzed by $LiAlH_4$:**87e** complex.

entry	R	R'	yield[a,b] (%)	ee[c,d] (%)
1	Et	H	88	67 (*S*)
2	^{i}Pr	H	90	70 (*S*)
3	Bn	H	92	-[e]
4	^{t}Bu	H	90	88 (*S*)
5	Et	Me	83	80 (*S*)
6	Et	^{n}Bu	-[f]	-
7	Et	^{t}Bu	-[f]	-

[a]Isolated yield. [b]The progress of the reaction was monitored by TLC until complete consumption of cyclohex-2-enone. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data. [e]ee can not be determined by chiral GC or HPLC (AD and OD column). [f]No reaction.

3.4.4 Effects of ligand structure

3.4.4.1 Side chain

Since di-*tert*-butyl malonate was established as the best nucleophile for asymmetric Michael addition to cyclohex-2-enone, screening of the ligands was repeated under the optimal conditions. In general, better enantioselectivities were observed (up to 88 %) with di-*tert*-butyl malonate comparing to diethyl malonate. Again, ligand **87e** bearing a bulky *tert*-butyl group at the α-position was still the best. As observed for diethylmalonate substrates, the enantioselectivity depended on the size of the side chain α-substituent on the ligand as shown for ligands **87a**, **87c**, **87d**, and **87e** (**Table 6**, entries 1-5). Substitution at both α- and β-positions of the ligand resulted in racemic mixtures when they were *trans* to each other (**Table 6**, entries 6, and 11). However, when the substituents at the α- and β-positions were *cis*, the Michael adduct

was obtained with high % *ee* (**Table 6**, entries 8 and 9). The LiAlH$_4$:ligand ratios of 1:1 and 1:2, gave the product with the same configurations (**Table 6**, entries 4, 5, 8, and 9) which again confirmed our previous results and was in sharp contrast to Narasimhan's work.[38-39] *N*-alkylated ligands gave racemic products (**Table 6**, entries 7 and 10), therefore, the free N-H appears to be essential for the enantioselectivity.


(*S*)-**87a**, R = H, R$_1$ = Bn, R$_2$ = H
(*S*)-**87c**, R = H, R$_1$ = ^{i}Pr, R$_2$ = H
(*R*)-**87d**, R = H, R$_1$ = Ph, R$_2$ = H
(*S*)-**87e**, R = H, R$_1$ = ^{t}Bu, R$_2$ = H
(1*R*,2*S*)-**87h**, R = H, R$_1$ = Ph, R$_2$ = Ph
(*S*)-**87i**, R = R$_1$ = -(CH$_2$)$_3$-, R = H
(1*S*,2*R*)-**87j**, R$_1$ = R$_2$ = -C$_6$H$_4$CH$_2$-
(1*S*,2*R*)-**87k**, R = Me, R$_1$ = Ph, R$_2$ = Me
(1*S*,2*R*)-**87l**, R = H, R$_1$ = R$_2$ = -(CH$_2$)$_4$-
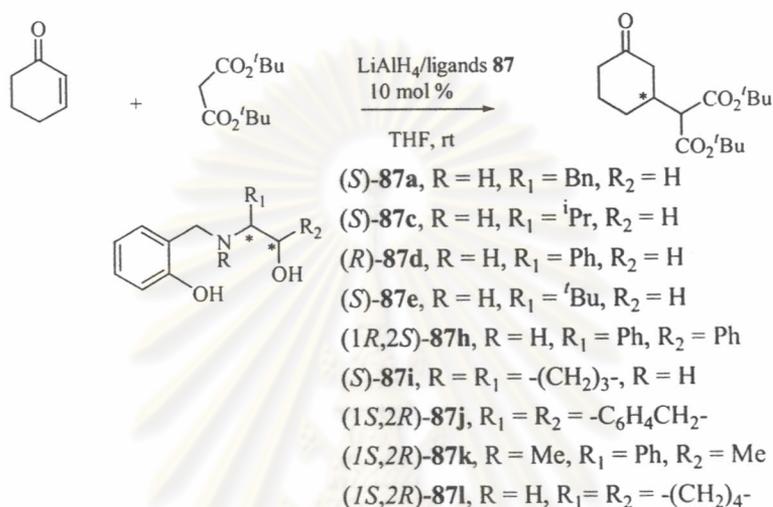
Table 6. Asymmetric Michael reaction of di-*tert*-butyl malonate to cyclohex-2-enone catalyzed by LiAlH$_4$:**87** complexes.

entry	cat	time[a] (h)	yield[b] (%)	ee[c,d](%)
1	LiAlH$_4$:**87a** (1:1)	40	47	34 (*S*)
2	LiAlH$_4$:**87c** (1:1)	15	86	77 (*S*)
3	LiAlH$_4$:**87d** (1:1)	15	61	86 (*R*)
4	LiAlH$_4$:**87e** (1:1)	15	90	88 (*S*)
5	LiAlH$_4$:**87e** (1:2)	15	56	87 (*S*)
6	LiAlH$_4$:**87h** (1:1)	15	86	6 (*S*)
7	LiAlH$_4$:**87i** (1:1)	15	88	5 (*S*)
8	LiAlH$_4$:**87j** (1:1)	15	92	77 (*R*)
9	LiAlH$_4$:**87j** (1:2)	72	90	83 (*R*)
10	LiAlH$_4$:**87k** (1:1)	72	70	0
11	LiAlH$_4$:**87l** (1:1)	15	95	16 (*S*)

[a]The progress of the reaction was monitored by TLC until complete consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data.

3.4.4.2 Electronic effect on the salicyl moiety of the ligands

To study electronic effect of the substituent on the salicyl moiety of the ligands, several ligands containing various electron donating and withdrawing substituents at the *para*-position of the OH group were prepared (**Table 2**). Screening results revealed that the electronic effect on the salicyl group did not have singnificant effect on enantioselectivity. The reaction catalyzed by ligands with a variety of electronically different substituents at the *para*-position such as Cl, CH_3O, and CH_3 gave the products in 76, 83, and 82 % *ee*, respectively (**Table 7**, entries 2-4). However, ligand **87u** with a strong electron withdrawing substituent (NO_2) provided the product in low yield and enantioselectivity (**Table 7**, entries 5, 34 % *ee*). It is assumed that the complex between the metal and the ligand was not stable because of the electron withdrawing effect of the NO_2.

**Table 7.** The effect of electronic on salicyl group was investigated in asymmetric Michael reaction of dialkyl malonate to 2-cyclohexenone.

entry	cat	yield[a,b] (%)	ee[c,d] (%)
1	$LiAlH_4$:**87d**	75	86 (*R*)
2	$LiAlH_4$:**87r**	72	76 (*R*)
3	$LiAlH_4$:**87s**	73	83 (*R*)
4	$LiAlH_4$:**87t**	80	83 (*R*)
5	$LiAlH_4$:**87u**	26	34 (*R*)

[a]The progress of the reaction was monitored by TLC until complete consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data.

3.4.4.3 The effect of bulky group on the salicyl moiety.

As sterically bulky groups such as *tert*-butyl were often introduced to ligands in order to improve the enantioselectivity.[17,18,21] It is interesting to study the effect of bulky group on the salicyl moiety of the ligands. Several ligands with bulky substituents at *ortho* and/or *para* position to the OH group of the salicyl moiety were synthesized and screened under the best condition obtained as before. The result showed that the presence of a sterically bulky group on the salicyl moiety, such as 'Bu and Ph at the *ortho* position gave racemic products (**Table 8**, entries 2, 3, and 4). A smaller substituent such as a methyl group at the *ortho* position still provided a low *ee* (**Table 8**, entry 6). Interestingly, a ligand with a phenyl group (**87p**) at the *para*-position appeared to produce sufficient steric effect so that very poor *ee* was obtained (**Table 8**, entry 5).

(*S*)-**87c**, R = ^{i}Pr, R_1 = H, R_2 = H
(*S*)-**87m**, R = ^{t}Bu, R_1 = ^{t}Bu, R_2 = ^{t}Bu
(*S*)-**87n**, R = ^{i}Pr, R_1 = ^{t}Bu, R_2 = ^{t}Bu
(*S*)-**87o**, R = ^{i}Pr, R_1 = H, R_2 = Ph
(*S*)-**87p**, R = ^{i}Pr, R_1 = Ph, R_2 = H
(*R*)-**87q**, R = Ph, R_1 = H, R_2 = CH_3
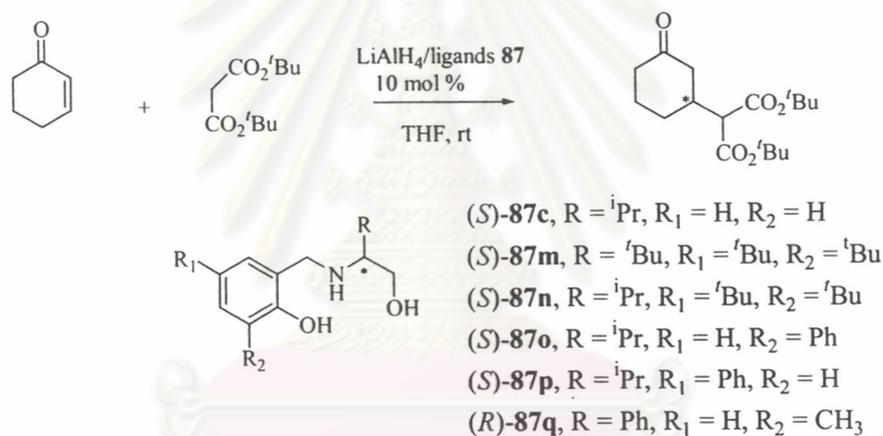
Table 8. The effect of bulky groups on salicyl moiety explored by using 10 % mol of LiAlH$_4$:ligands **87** catalyzed asymmetric Michael addition of di-*tert*-butyl malonate to cyclohex-2-enone.

entry	cat	yield[a,b] (%)	ee[c,d] (%)
1	LiAlH$_4$:**87c**	86	77 (*S*)
2	LiAlH$_4$:**87m**	61	0
3	LiAlH$_4$:**87n**	48	0
4	LiAlH$_4$:**87o**	72	0
5	LiAlH$_4$:**87p**	70	0
6	LiAlH$_4$:**87q**	94	55 (*R*)

[a]The progress of the reaction was monitored by TLC until complete consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data.

3.4.4.4 Comparison between salicyl and non-salicyl ligands

1) Bidentate and tridentate salicyl ligands

To study the minimum number of chelating groups on the ligand required for the asymmetric induction, ligands **87d**, and **87v-x** were investigated. The results clearly showed that the two OH and the NH groups are essential for the asymmetric reactions since all the deoxy- and *N*-methylated ligands provide racemic products. Nevertheless, the presence of a CH_3 group on nitrogen as well as the absence of OH group on the alkyl side chain and the salicyl group gave racemic adducts in 43, 65 and 75 % yield, respectively (entries 2-4). The results showed that the *N*-salicyl amino alcohols are indeed a minimum requirement for behaving as a ligand for asymmetric Michael reaction. It can be further speculated that in the active catalyst, the ligand must bind to the metal in a tridentate fashion.


(*R*)-**87d**, R = OH, R_1 = H, R_2 = OH
(*R*)-**87v**, R = OH, R_1 = Me, R_2 = OH
(*R*)-**87w**, R = H, R_1 = H, R_2 = OH
(*R*)-**87x**, R = OH, R_1 = H, R_2 = H
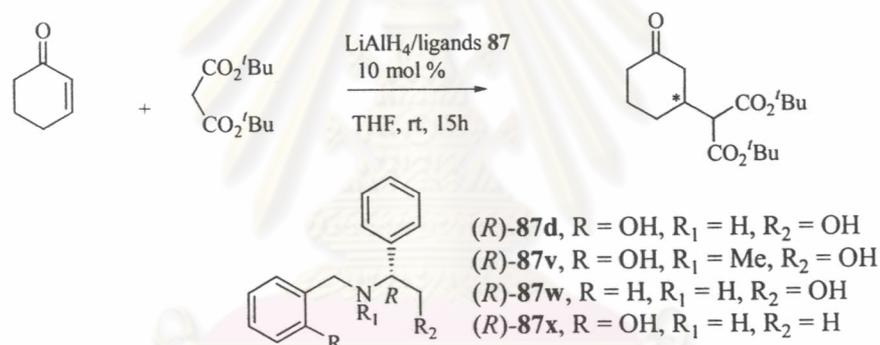
Table 9. Effect of number of chelating group tested by 10 mol % of $LiAlH_4$:ligand **87** catalyzed asymmetric Michael reaction of di-*tert*-butyl malonate to cyclohex-2-enone.

entry	cat	yield[a, b]	ee[c,d] (%)
1	$LiAlH_4$:**87d** (1:1)	75	86 (*R*)
2	$LiAlH_4$:**87v** (1:1)	43	0
3	$LiAlH_4$:**87w** (1:1)	65	0
4	$LiAlH_4$:**87x** (1:1)	75	0

[a]The progress reaction was monitored by TLC until the consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data.

2) Non-salicyl ligands

Vilaivan and Kanjanawarut found an easy method for the synthesis of several chiral non-salicyl amino alcohol ligands effectively through epoxide ring opening.[50]

It is interesting to investigate these ligands as catalyst for asymmetric Michael reaction. The results from these investigations are shown in **Table 10**. The chiral ligands (**88a, 88c-f**) could catalyze Michael addition with high yields (77-83 %) although no significant enantioselectivity was observed. Disappointingly, only poor % *ee* and yield were observed when ligand **88b** was used as catalyst. In the report by Sundararajun,[*37*] this ligand could catalyze asymmetric Michael reaction of diethyl malonate to cyclohex-2-enone with high enantiomeric excess (80 %).[*37*] However, the authors have determined the *ee* based on optical rotation data which may not be accurate. With the use of chiral ligand **88g** as catalyst, the Michael adduct was not formed at all.
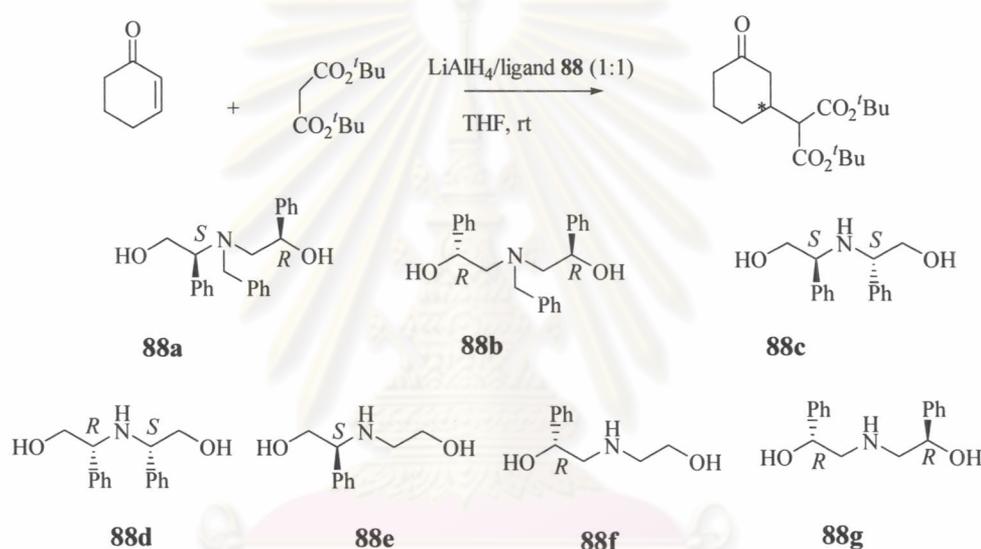
Table 10. Asymmetric Michael reaction of di-*tert*-butyl malonate to cyclohex-2-enone catalyzed by $LiAlH_4$:non-salicyl ligands **88a-g** complexes.

entry	cat	yield[a,b] (%)	ee[c,d] (%)
1	$LiAlH_4$:**88a**	75	0
2	$LiAlH_4$:**88b**	26	30 (*R*)
3	$LiAlH_4$:**88c**	80	0
4	$LiAlH_4$:**88d**	83	0
5	$LiAlH_4$:**88e**	80	0
6	$LiAlH_4$:**88f**	77	0
7	$LiAlH_4$:**88g**	-[e]	0

[a]The progress of the reaction was monitored by TLC until the consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data. [e]No reaction.

3.4.4 Effect of metals

The effect of both metals, the Lewis acid and the Lewis base, were studied using other metal-**87e** complexes as catalysts for asymmetric Michael addition of di-*tert*-butyl malonate to cyclohex-2-enone. The original Li-Al catalyst prepared from $LiAlH_4$ was the only one that gave high yield (86 %) and high *ee* (88 %). The Li-B catalyst prepared from lithium borohydride ($LiBH_4$) afforded no reaction. The use of titanium instead of aluminium Lewis acid gave low chemical yield (38 %) and no enantioselectivity (entry 3). Replacing the Li with Na resulted in poor yield (26 %) which could be improved to 72 % by replacing with K. Nevertheless, in both cases no enantioselectivity was observed (**Table 11**, entries 4 and 5).
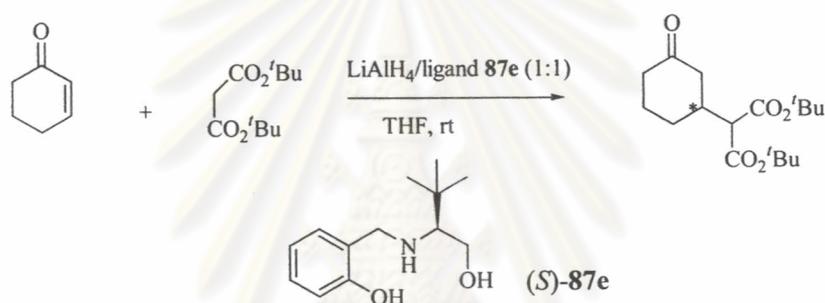

Table 11. Asymmetric Michael reaction of di-*tert*-butyl malonate to cyclohex-2-enone catalyzed by several metal:**87e** (1:1) complexes.

entry	metal	time[a]	yield[b] (%)	*ee*[c,d] (%)
1	$LiAlH_4$	15 h	86	88 (*S*)
2	$LiBH_4$	-	-[e]	0
3	$LiH + Ti(O^iPr)_4$	3 d	38	0
4	$NaOH + Al(O^iPr)_3$	3 d	26	0
5	$KOH + Al(O^iPr)_3$	40 h	72	0

[a]The progress of the reaction was monitored by TLC until the consumption of cyclohex-2-enone. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral GC. [d]Absolute configuration was determined by comparing the specific rotation with that of literature data. [e]No reaction.

3.5 Application of the catalyst to other Michael-type additions

To extend the range of substrates and to investigate the scope and limitation of the catalyst, the catalytic asymmetric Michael reaction of several nucleophiles such as di-*tert*-butyl malonate, nitroalkane, or other active methylene compounds and cyclic and acyclic enones had been studied (**Table 12**). Although the addition of di-*tert*-butyl malonate to 2-cyclopentene gave the desired product (**72**) in high yield, the enantioselectivity was only moderate (**Table 12**, entry 1). The analogous asymmetric Michael additions of di-*tert*-butyl malonate to acyclic enones provide the expected product in 75 and 35 % yield (**Table 12**, entries 2 and 3) but no enantioselectivity was observed. When using nitroalkanes such as nitromethane, nitroethane, and 2-nitropropane as nucleophile for addition to cyclohex-2-enone, the Michael adducts were obtained in low yields (**Table 12**, entries 4-6) and the reaction was not clean due to the formation of disubstituted Michael adducts such as **89** and **90**. Furthermore, other nucleophiles such as acetyl acetone, ethyl cyanoacetate, and 1,3-diketone were not able to act as nucleophiles for these reactions (**Table 12**, entries 7-9). The greater acidity of these compounds make them harder nucleophiles and therefore are not quite as good in adding to the soft enones according to hard-soft acid base theory. In most cases no enantioselectivities were observed although in some reactions, the enantioselectivity could not be determined.
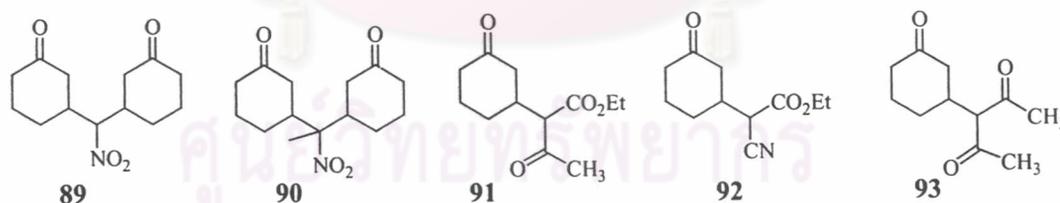

Figure 51. Several structures of Michael adduct.

Table 12. Asymmetric Michael reaction of several nucleophiles such as di-*tert*-butyl malonate, nitroalkane, and carbonyl derivatives to cyclic and acyclic enones catalyzed by 10 mol % of LiAlH$_4$:**87e** (1:1) complexes.

Y:-CH$_2$NO$_2$, malonate and other methylene compound
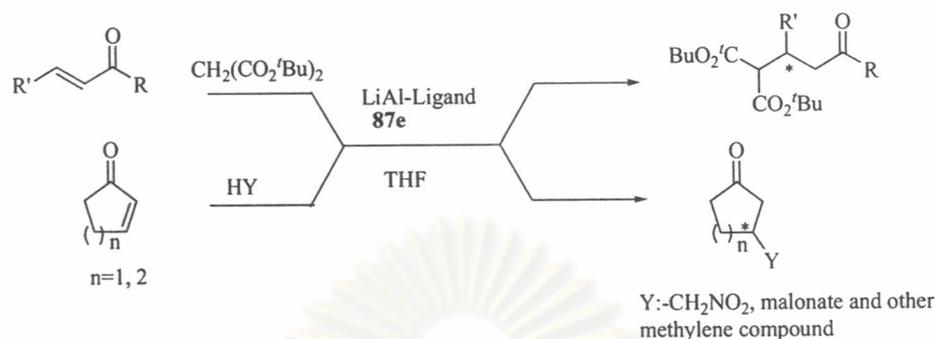
entry	ketone	nucleophile	product	yield^a (%)	$ee^{b,c}$ (%)
1	2-cyclopentenone	di-*tert*-butyl malonate	72	83	50 (*S*)
2	R = R' = Ph	di-*tert*-butyl malonate	74	75	0^d
	R = Ph, R' = 2-NO$_2$Ph	di-*tert*-butyl malonate	75	35	-^{e}
3	cyclohex-2-enone	H$_3$C–NO$_2$	89	60^f	-^{e}
4	cyclohex-2-enone	H$_3$C⌃NO$_2$	90	54^f	-^{e}
5	cyclohex-2-enone	(H$_3$C)$_2$CH–NO$_2$	73	45	-^{e}
6	cyclohex-2-enone	H$_3$C(CO)(CO)OEt	91	-^{g}	-
7	cyclohex-2-enone	NC(CO)OEt	92	-^{g}	-
8	cyclohex-2-enone	H$_3$C(CO)(CO)CH$_3$	93	-^{g}	-

^{a}Isolated yield. ^{b}Enantiomeric excess was determined by chiral GC. ^{c}Absolute configuration was determined by comparing the specific rotation with that of literature data. ^{d}determined by chiral HPLC (OD column). ^{e}not determined. ^{f}Not pure. ^{g}No reaction

3.6 Absolute configuration and Mechanistic study

The absolute configuration of Michael adduct **70** were first reported by Yamaguchi and co-workers.[24] It was determined by decarboxylation of the Michael adduct in 6 M HCl followed by esterification with diazomethane to give the known ester **95**, from which comparison of the optical rotation can be less ambiguous.
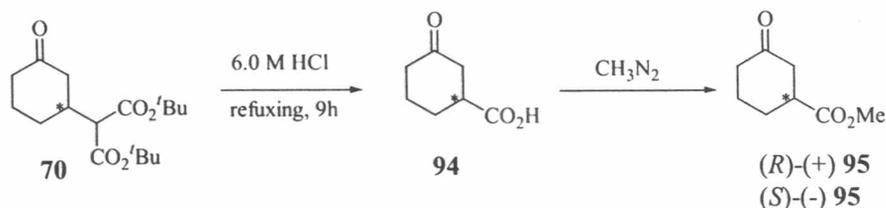

Figure 52. Decarboxylation and esterification with diazomethane of the Michael adduct **70**.

In this work, the absolute configuration of Michael adduct **70** were determined by measurement of the optical rotation of the ester **95** prepared by Yamaguchi. The value obtained was $[\alpha]_D^{26} = +4.26$ (from ligand **87d** as catalyst, 86 % *ee* according to chiral GC). The optical rotation of the methyl ester **95** ($[\alpha]_D^{26} = +4.26$ (CHCl$_3$, *c* 1.7)) was lower than that of the reference ($[\alpha]_D^{22} = +12.0$ (CHCl$_3$, *c* 2.9)) but these clearly confirmed absolute configuration of the product as "*R*". The possible reason for this large difference may be due to partial racemization during the transformation.

The possibility of the reaction pathway was shown in **Figure 53**. The reaction of a lithium enolate (**II**) derived from a malonate and an enone should lead to an aluminium enolate (**III**) intermediate. Then, the lithium enolate reacts with aluminium enolate to give the enantiomeric aluminium enolate (**IV**). Furthermore, this enolate (**IV**) would abstract a hydrogen atom from acidic α-proton of malonate to give the desired Michael adduct.
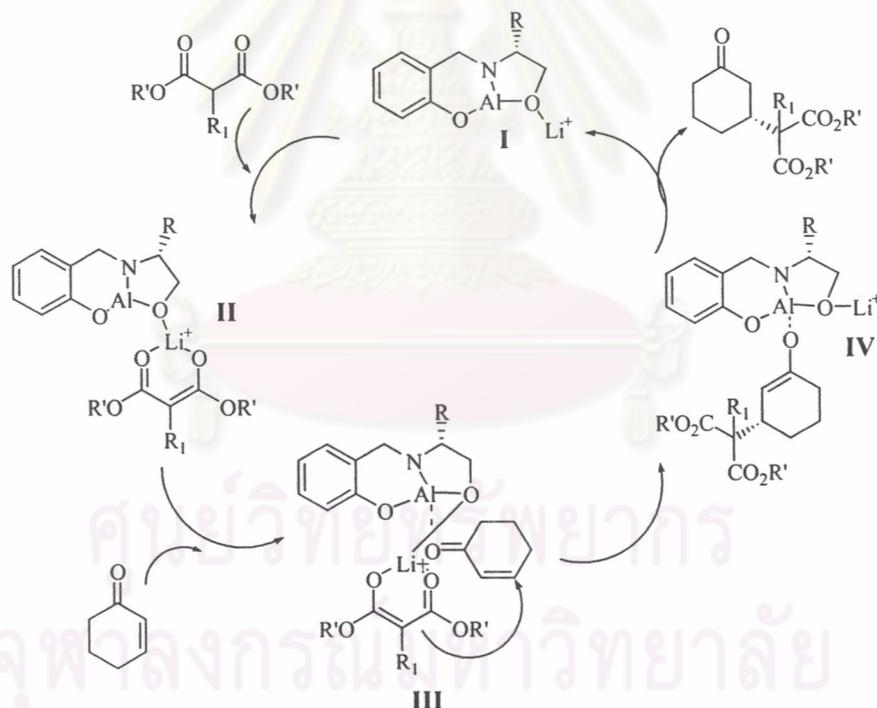
Figure. 53. Proposed mechanistic pathway of Michael addition.

The observed stereochemistry could be rationalized from the proposed transition state model illustrated in **Figure 54**. In the transition state model, the *Si*-face of the alkene double bond is shielded by the (*R*) ligands, leaving the *Re*-face open for the attracted to afford an (*R*)-configuration at the chiral center formed in the reaction.

Likewise this model can explain the formation of the (R)-product when (R)-ligands were used.
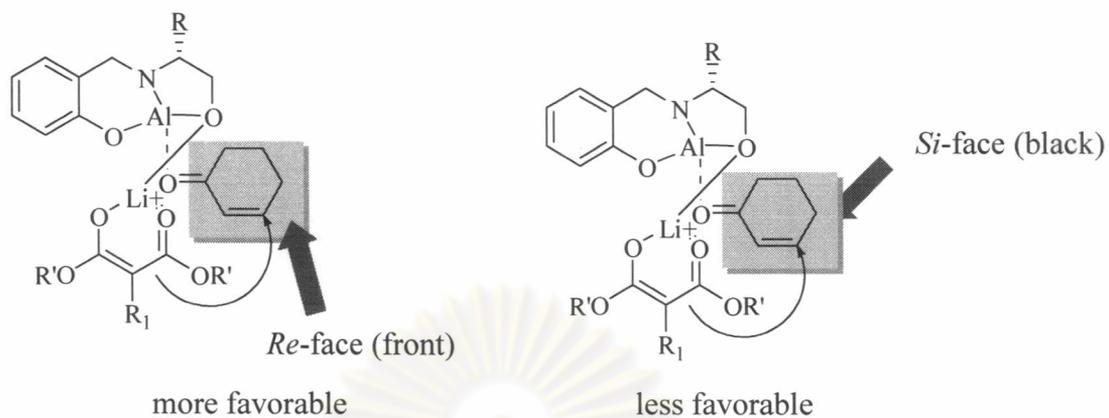

Figure 54. The proposed transition state model of asymmetric Michael addition.