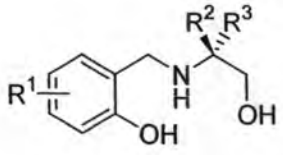
CHAPTER III
RESULTS AND DISSCUSSION

3.1 Design of the chiral ligand

At the present days, a large number of privileged chiral ligands and catalysts for a wide range of enantioselective reactions are available.[17] Often, such ligands or catalysts are large and complex molecules containing multiple stereogenic centers. They are difficult to obtain on a large scale, especially when both enantiomers are desired. Recently, simple tridentate chiral amino-alcohol (**64**) were discovered as effective ligands for titanium-catalyzed asymmetric Strecker reactions, [126,127] related asymmetric cyanosilylation of aldehydes, [128] and enantioselective borane reduction of ketones.[129] The enantioselectivities obtained with such simple ligands in many cases are comparable or even superior to those obtained from catalysts with a more complex design. Inspired by these ligands, it was proposed that substitution of one or more of the hard oxygen atoms of **64** with a soft donor atom such as sulfur would lead to ligands such as **69** and **70** having affinities for soft metal ions such as copper. These ligands should be applicable as an alternative for synthetically useful copper-catalyzed asymmetric reactions, whose ligands are largely dominated by chiral bis(oxazolines) [102] and diamines.[130]



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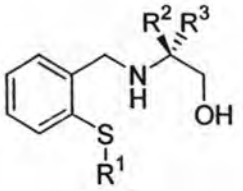
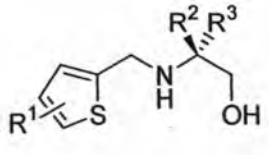


69



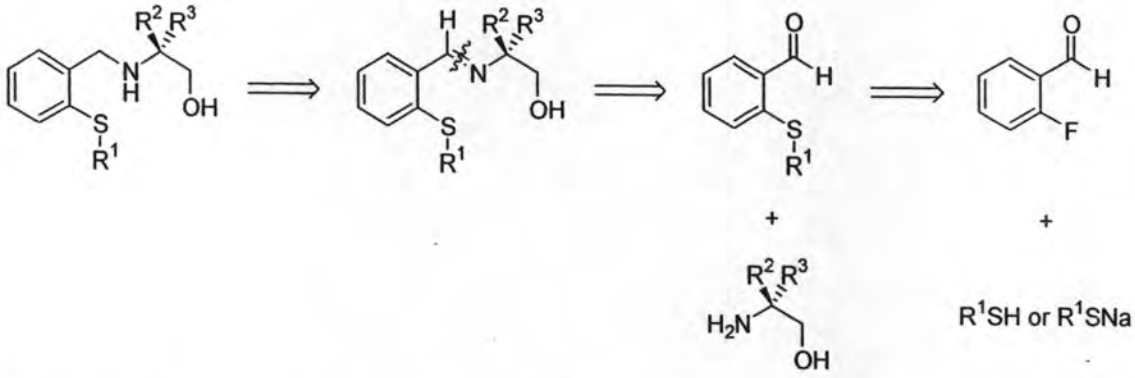
70

3.2 Synthesis of new chiral ligands

3.2.1 Synthesis of thiolated chiral amino-alcohol ligands

Ligand **69**, derived from replacement of the phenolic group in ligand **64** with thiol or thioether, was viewed as a logical starting point for the development. Due to the high reactivities of free thiol group which could complicate the synthesis, it was

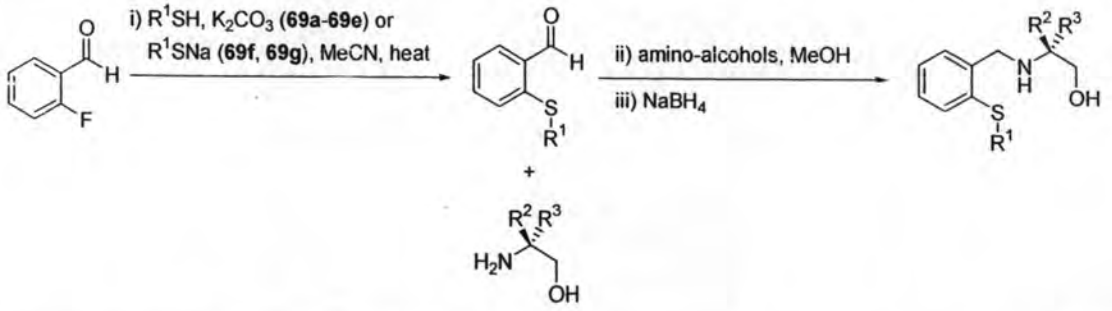
considered more appropriate to use thioethers as substituents. In principle, thiolated amino-alcohol ligand (*S*)-**69a** (R^1 = 4-ClC_6H_4; R^2 = Bn; R^3 = H) could be synthesized in three steps from commercially available, or easily prepared, starting materials as outlined in Scheme 3.1.



Scheme 3.1 Retrosynthesis of the thiolated chiral amino-alcohol ligands (**69**) by disconnection approach

2-Phenylthiobenzaldehyde was not commercially available but could easily be prepared by a nucleophilic aromatic substitution (S_NAr) type reaction. When 2-fluorobenzaldehyde reacted with 4-chlorothiophenol in the presence of potassium carbonate, the thiolated aldehyde (**71a**) was obtained in 61% yield. Condensation of this thiolated aldehyde with (*S*)-phenylalaninol in methanol at room temperature afforded the imine or Schiff's base. The Schiff's base was not isolated but further reduced *in situ* with sodium borohydride to give ligand (*S*)-**69a** in 85% yield. Other thiolated aldehydes (**71b-71d**) were successfully prepared in a similar manner. Ligands (*S*)-**69b**-(*R*)-**69g** with different sulfur substituents (R^1) and amino-alcohol substituents (R^2 and R^3) were similarly prepared from appropriate thiolated aldehydes and chiral amino-alcohols in good yields as shown in Table 3.1. All ligands were obtained as odorless, stable crystalline solids.

Table 3.1 Structure and yield of the thiolated chiral amino-alcohol ligands (**69**)



entry	ligand	amino alcohol	R^1	R^2	R^3	yield (%)
1	(*S*)-**69a**	(*S*)-phenylalaninol	4-ClC_6H_4	CH_2Ph	H	85
2	(*S*)-**69b**	(*S*)-phenylalaninol	C_6H_5	CH_2Ph	H	86
3	(*R*)-**69c**	(*R*)-phenylglycinol	C_6H_5	H	Ph	73
4	(*S*)-**69d**	(*S*)-*tert*-leucinol	C_6H_5	^{t}Bu	H	80
5	(*S*)-**69e**	(*S*)-naphth-1-yl glycinol	C_6H_5	1-naphthyl	H	89
6	(*R*)-**69f**	(*R*)-phenylglycinol	Et	H	Ph	87
7	(*R*)-**69g**	(*R*)-phenylglycinol	Me	H	Ph	83

3.2.2 Synthesis of thiophene-substituted chiral amino-alcohol ligands

3.2.2.1 Substituted thiophene-based chiral amino-alcohol ligands

Thiophene-substituted amino-alcohols (**70**) were also prepared from the corresponding aldehydes and amino-alcohols in an analogous manner to the thiolated ligand **69**. Commercially available thiophenecarboxaldehydes with a variety of substitution on the thiophene ring reacted with a wide range of chiral amino-alcohols or chiral amines to form the imines analogous to the Schiff's base as described for ligand **69**. Sodium borohydride reduction of the imines *in situ* afforded the desired ligands in moderate to excellent yields (49-95%) after usual work up and chromatographic purification (Table 3.2). In general, NMR spectra of these substituted thiophene-based amino-alcohol chiral ligands show a pair of ABX and AB system as a common dominant feature. In the ABX system, for example chiral ligand (*R*)-**70b**, proton correlation between H_a, H_b protons of -CH_2OH and H_x proton of –NHCH_xPh were observed. The ligand (*R*)-**70b** also showed proton NMR pattern of –NHCH_2thienyl in the AB system. Other ligands generally give similar spectrum patterns. The proton NMR spectrum of (*R*)-**70b** was as shown in Figure 3.1.

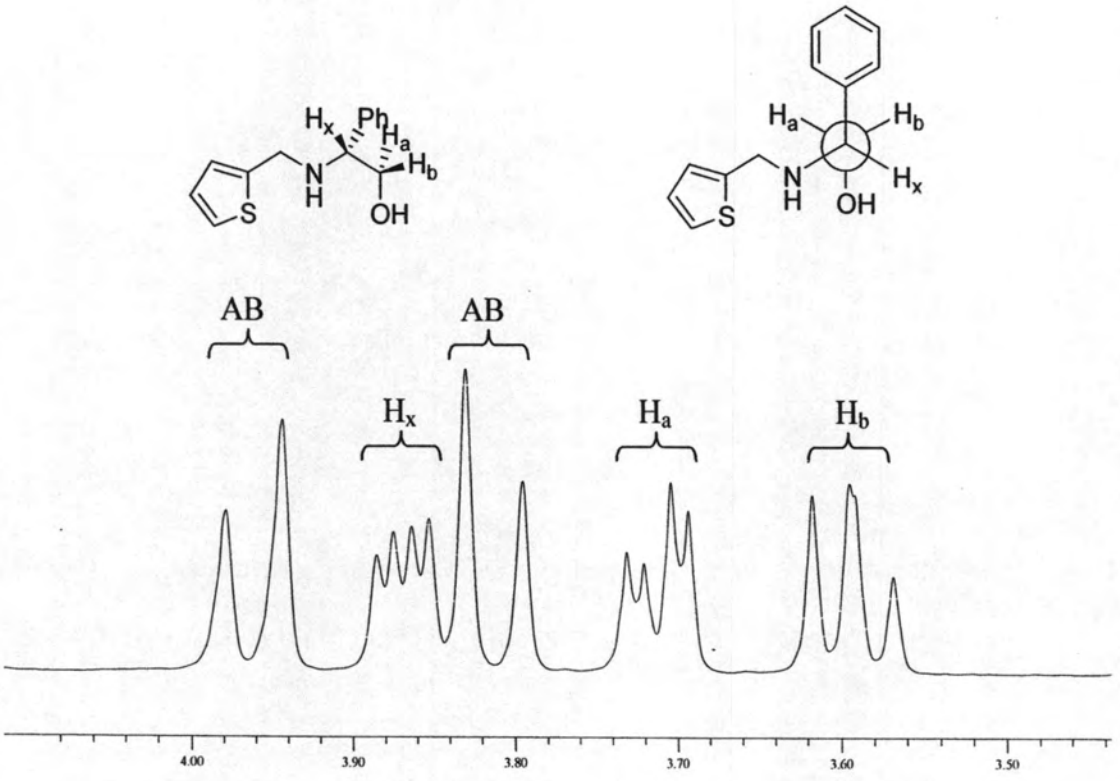
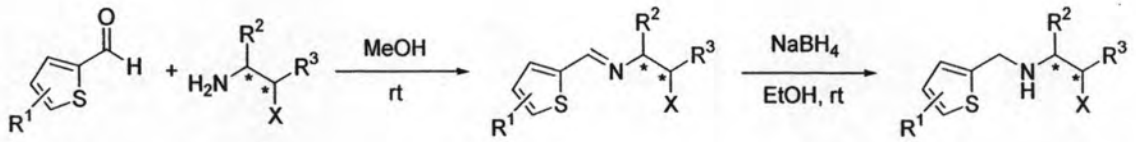
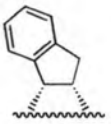
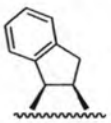


Figure 3.1 The proton NMR spectrum of chiral ligand (*R*)-**70b** at 3.50-4.00 ppm showed proton NMR pattern of ABX and AB systems

Proton, carbon NMR data and spectroscopic information of substituted thiophene-based chiral amino-alcohol ligands revealed that all proposed ligands had been successfully prepared. The data are in good agreement with those expected from the structures.

Table 3.2 Structure and yield of substituted thiophene-based chiral amino-alcohol ligands (**70**)

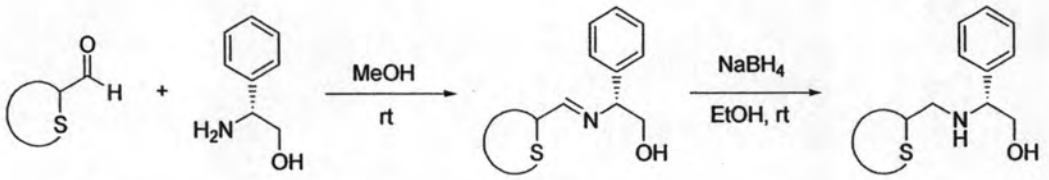


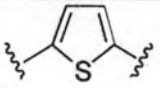
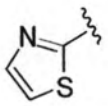
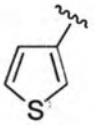
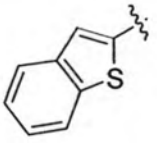
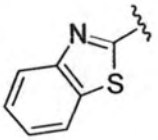
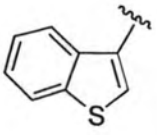
entry	ligand	amino alcohols (X = OH) or chiral amines (X = H)	R^1	R^2 (β)	R^3 (α)	yield (%)
1	(*R*)-**70a**	(*R*)-phenylalaninol	H	CH_2Ph	H	92
2	(*S*)-**70a**	(*S*)-phenylalaninol	H	CH_2Ph	H	84
3	(*R*)-**70b**	(*R*)-phenylglycinol	H	Ph	H	93
4	(*S*)-**70b**	(*S*)-phenylglycinol	H	Ph	H	89
5	(*S*)-**70c**	(*S*)-methylbenzylamine	H	Ph	H	92
6	(*R*)-**70c**	(*R*)-methylbenzylamine	H	Ph	H	94
7	(*S*)-**70d**	(*S*)-alaninol	H	CH_3	H	90
8	(*R*)-**70e**	(*R*)-1-amino-propan-2-ol	H	H	CH_3	85
9	(1*S*,2*R*)-**70f**	(1*S*,2*R*)-2-amino-1,2-diphenylethanol	H	Ph	Ph	91
10	(1*R*,2*S*)-**70g**	(1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol	H			86
11	(1*S*,2*R*)-**70h**	(1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol	H			94
12	(*S*)-**70i**	(*S*)-valinol	H	^{i}Pr	H	95
13	(*S*)-**70j**	(*S*)-*tert*-leucinol	H	^{t}Bu	H	94
14	(*S,S*)-**70k**	(*S,S*)-isoleucinol	H	^{sec}Bu	H	91
15	(*R*)-**70m**	(*R*)-phenylglycinol	5-CH_3	Ph	H	91
16	(*R*)-**70n**	(*R*)-phenylglycinol	5-Ph	Ph	H	95
17	(*R*)-**70o**	(*R*)-phenylglycinol	5-Br	Ph	H	49
18	(*R*)-**70p**	(*R*)-phenylglycinol	4-Br	Ph	H	95
19	(*R*)-**70q**	(*R*)-phenylglycinol	3-CH_3	Ph	H	90

3.2.2.2 Other thiophene-related chiral amino-alcohol ligands

Employing the same synthetic protocol of chiral substituted thiophene-based amino-alcohols **70a-70q** as described before, other thiophene-related amino-alcohol ligands were also prepared. In order to examine the effect of the size and the position of substitution on the thiophene moiety, the chiral amino-alcohol part was fixed as (*R*)-phenylglycinol. Two thiazole-based ligands and one C_2-symmetrical disubstituted thiophene ligands were also successfully prepared. The desired ligands were obtained in moderate to excellent yields as shown in Table 3.3.

Table 3.3 Structure and yield of other thiophene-related chiral amino-alcohol ligands (**70l, 70r-70v**)

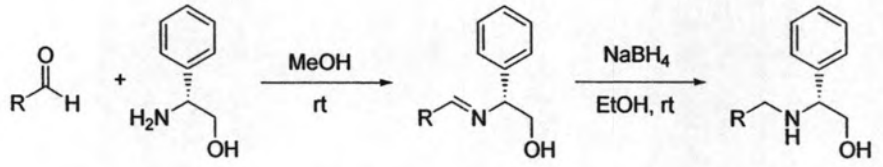


entry	ligand	aldehyde	yield (%)
1	(*R*)-**70l**		84
2	(*R*)-**70r**		88
3	(*R*)-**70s**		92
4	(*R*)-**70t**		64
5	(*R*)-**70u**		58
6	(*R*)-**70v**		89

3.2.3 Synthesis of non-thiolated amino-alcohol ligands for structure-activity relationship study

Chiral non-thiolated amino-alcohols **72a-72c** and **73a-73g** were also prepared for comparison purposes. These ligands could be synthesized by similar sodium borohydride reduction of imines derived from the condensation between a variety of aldehydes and chiral amino-alcohols. The structure and yield of the desired compounds were as shown in Tables 3.4 and 3.5.

Table 3.4 Structure and yield of heteroatom-substituted chiral amino-alcohol ligands (**72**)



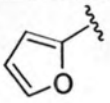
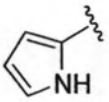
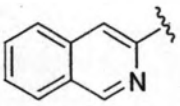
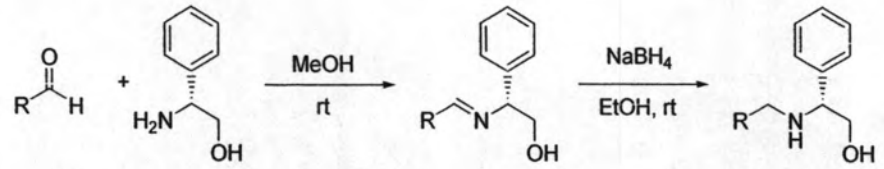
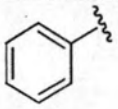
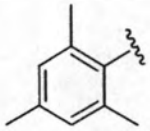
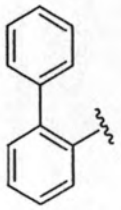
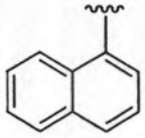
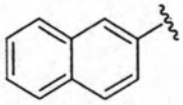
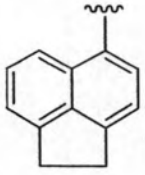
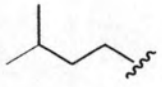
entry	ligand	aldehyde (R)	yield (%)
1	(*R*)-**72a**		94
2	(*R*)-**72b**		85
3	(*R*)-**72c**		36

Table 3.5 Structure and yield of bidentate chiral amino-alcohol ligands (**73**)

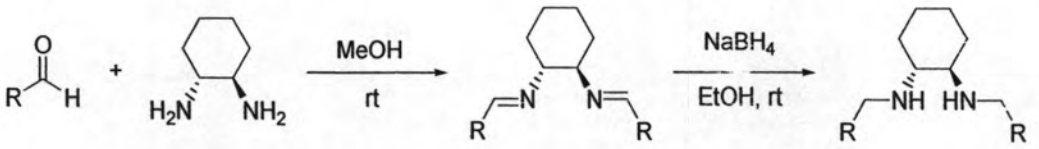


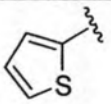
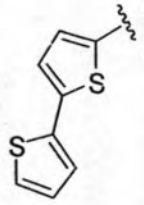
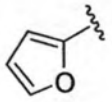
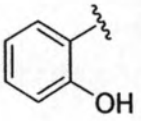
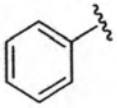
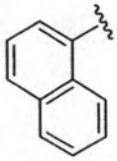
entry	ligand	aldehyde (R)	yield (%)
1	(*R*)-**73a**		94
2	(*R*)-**73b**		88
3	(*R*)-**73c**		85
4	(*R*)-**73d**		97
5	(*R*)-**73e**		98
6	(*R*)-**73f**		95
7	(*R*)-**73g**		72

3.2.4 Synthesis of C_2-symmetrical diamino ligands

C_2-symmetrical diamino ligands (**49a-49f**) were also prepared for asymmetric synthesis. These ligands were synthesized by similar sodium borohydride reduction of imines derived from the condensation between various aldehydes and (1*R*,2*R*)-*trans*-diaminocyclohexane. The structure and yield of the desired compounds were as shown in Table 3.6.

Table 3.6 Structure and yield of C_2-symmetrical bis-amino ligands (**49**)



entry	ligand	aldehyde (R)	yield (%)
1	**49a**		66
2	**49b**		63
3	**49c**		87
4	**49d**		59
5	**49e**		87
6	**49f**		93

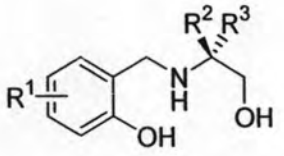
3.3 Asymmetric nitro-aldol (Henry) reaction

The objectives of this research were to develop a synthetic method for optically active β-nitroalkanols by addition of nitronate ion to aldehydes (nitro-aldol or Henry reaction) in the presence of chiral catalysts. Two of the most important parameters to be considered whether the reaction is successful or not were percent yield and optical purity of the products. Optical purity could be expressed in term of % ee which is defined as

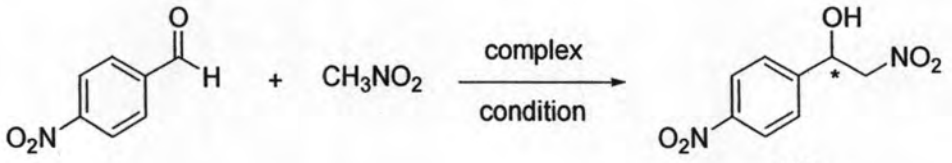
$$\%\ \text{ee} = \frac{|\%R - \%S|}{|\%R + \%S|} \qquad (1)$$

In general, % ee may be determined by a variety of ways such as the use of chromatographic or spectroscopic techniques.

Since *N*-salicyl-β-amino alcohols (**64**) had been shown to be powerful ligands for many asymmetric nucleophilic addition reactions, [126-129] this type of such ligand was put to a test for other asymmetric synthesis. Initially, the well-studied nitro-aldol reaction between nitromethane and 4-nitrobenzaldehyde [106] was explored in order to search for optimal conditions, as shown in Scheme 3.2.

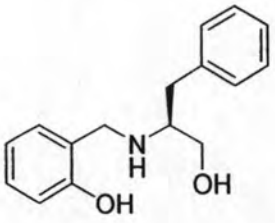


64

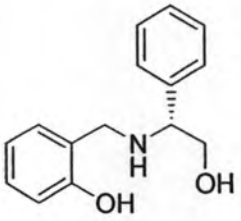


74a

Scheme 3.2 The nitro-aldol reaction of nitromethane with 4-nitrobenzaldehyde in order to search for the optimal conditions



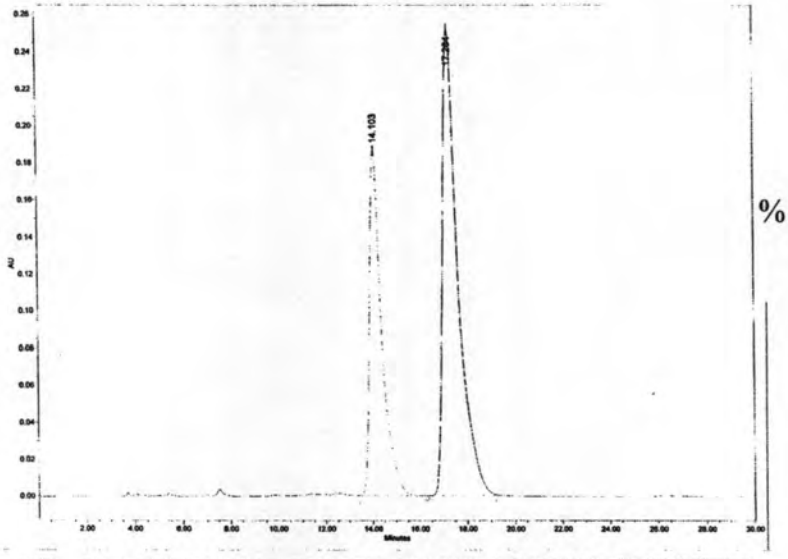
(*S*)-**64a**



(*R*)-**64d**

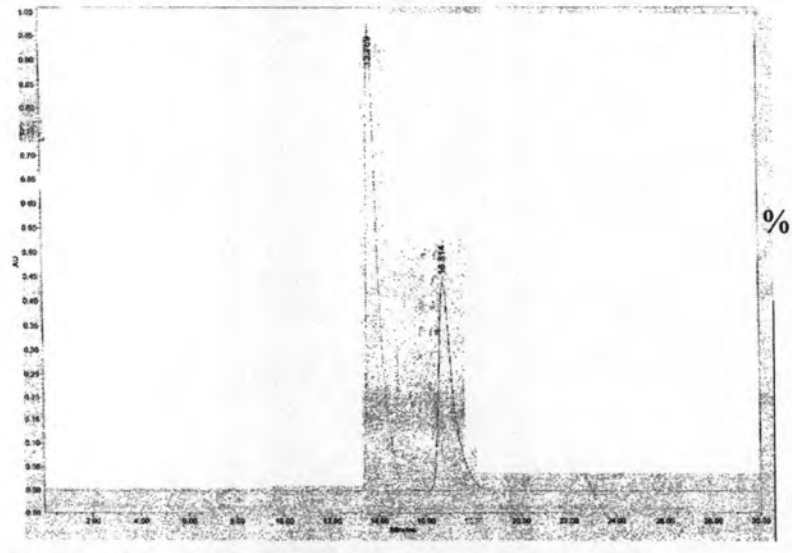
When the chiral ligand (*S*)-**64a** (R^1 = H; R^2 = Bn; R^3 = H) was mixed with $Cu(OAc)_2{\cdot}H_2O$ in 2-propanol at a 1.1:1 ratio, a soluble green complex was formed immediately. This complex was employed as a catalyst for asymmetric nitro-aldol reaction using 4-nitrobenzaldehyde and nitromethane as starting materials under the similar conditions described by Evans *et al.*.[106] Pleasingly, this complex could catalyze the reaction between 4-nitrobenzaldehyde and nitromethane (10 equiv) at room temperature (30 °C) to provide the expected nitro-aldol product (**74a**) in 97% yield and 25% ee (Figure 3.2 (up)) after 48 h at 15 mol% ligand and 13.5 mol% Cu.

The configuration of the major nitro-aldol product was determined by chiral HPLC and comparison of the chiral HPLC pattern with literature data.[106] Percent ee was observed from calculation of percent area of HPLC chromatogram according to equation (1). When the copper(II) acetate complex of chiral ligand (*R*)-**64d** (R^1 = H; R^2 = H; R^3 = Ph) was used as a catalyst under the same reaction condition, it was found that the same product was obtained in 95% yield. Chiral HPLC analysis revealed the enantiomeric excess of 29%, but the major enantiomer obtained was opposite to that obtained from ligand **64a** (Figure 3.2 (below)). It was later revealed that ligand **64a** with *S*-configuration at the stereogenic center yielded the (*S*)-nitro-aldol product while ligand **64d** (*R*-configuration) provided the (*R*)-nitro-aldol product as the major enantiomer, respectively.



$$\% \text{ ee} = \frac{(62.61-37.39)}{(62.61+37.39)} \times 100$$

$$= 25\% \text{ (}S\text{-isomer)}$$



$$\% \text{ ee} = \frac{(64.46-35.54)}{(64.46+35.54)} \times 100$$

$$= 29\% \text{ (}R\text{-isomer)}$$

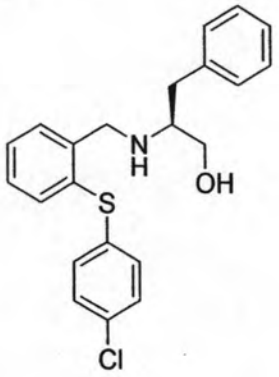
Figure 3.2 The determination of enantiomeric purity of the nitro-aldol product **74a** using chiral HPLC analysis in the presence of (*S*)-**64a** (up) and (*R*)-**64d** (below) as chiral ligands

Although these non-thiolated ligands could catalyze the reaction, the enantioselectivity was not satisfactory. It was proposed that substitution of the hard phenolic oxygen atom in **64** with a sulfur atom would lead to new ligands having higher affinities for copper and should be more efficient as ligands for copper-catalyzed asymmetric nitro-aldol reactions. Based on this proposal, a number of thiolated and non-thiolated ligands were further prepared and evaluated as catalysts for asymmetric nitro-aldol reactions.

3.3.1 Optimization of reaction parameters

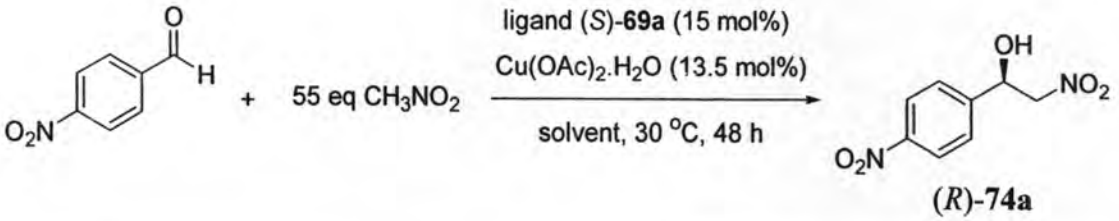
3.3.1.1 Thiolated amino-alcohol ligands

The easily synthesized thiolated amino-alcohol compound, (*S*)-**69a** was the first ligand used for initial optimization of the reaction conditions. When the ligand was mixed with copper(II) acetate at a 1.1:1 ratio, a blue color was observed in the solution. The color change was observed even in toluene where $Cu(OAc)_2$ was completely insoluble, indicating that a complex has formed. The same asymmetric nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane as reported by Evans *et al.*.[106] was again used for condition optimization in various solvents. The results are summarized in Table 3.7.



(*S*)-**69a**

Table 3.7 Optimization of reaction conditions for the enantioselective nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane promoted by copper(II)-(*S*)-**69a** catalyst in various solvents



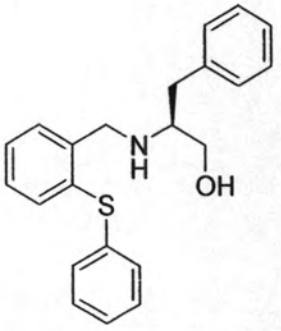
(*R*)-**74a**

entry	solvent	yield (%)	ee (%)
1	^{i}PrOH	90	30
2	MeOH	90	22
3	CH_2Cl_2	76	22
4	toluene	69	26
5	THF (dry)	92	21

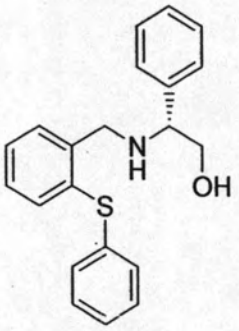
From Table 3.7, it was found that reactions carried out in polar protic solvent such as 2-propanol and methanol as well as polar solvent such as tetrahydrofuran provided better yields than those performed in nonpolar solvents (dichloromethane and toluene). In terms of enantioselectivity, the best result was obtained when 2-propanol was used as the solvent (30% ee, entry 1). In all cases the configuration of the major β-nitroalcohol was *R* as determined by chiral HPLC and comparison of the $[\alpha]_D$ with literature data (*R* as a major isomer; 78% ee; $[\alpha]_D^{21}$ -31.6 (*c* 1.05, CH_2Cl_2)).[106] Interestingly, the sense of asymmetric induction was opposite to that provided by the *N*-salicyl ligand possessing the same absolute configuration, which suggests that the complexes might have different structures. When copper(II) acetate was used alone to catalyze the reaction, the nitro-aldol product was obtained in only 32% yield after 24 h and 30 °C. This finding suggested that copper(II) acetate was a poor catalyst for this reaction in the absence of a ligand. In addition, the alkylthiobenzyl substituent on the ligand must play an active role in both accelerating and governing the stereochemical outcome of the nitro-aldol reaction.

From the results as described above, 2-propanol provided the best enantioselectivity and yield, it was therefore selected as the solvent for further optimization. To improve enantioselectivity of the reaction, chiral ligands (**69b-69g**) with different sulfur substituents (R^1) and amino-alcohol substituents (R^2 and R^3)

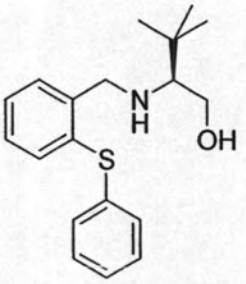
were prepared and screened in the similar manner as described for ligand (*S*)-**69a**. Furthermore, other reaction parameters including the equivalent of nitromethane, temperature, and mole ratio of ligand/$Cu(OAc)_2 \cdot H_2O$ were also optimized. The results are shown in Table 3.8.



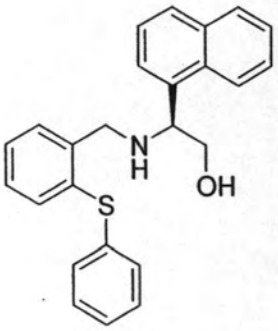
(*S*)-**69b**



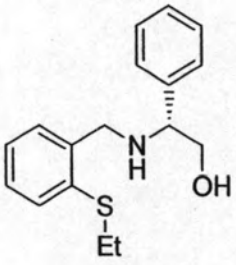
(*R*)-**69c**



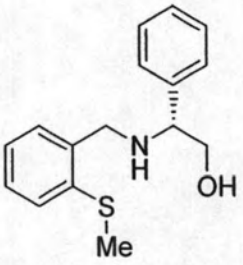
(*S*)-**69d**



(*S*)-**69e**

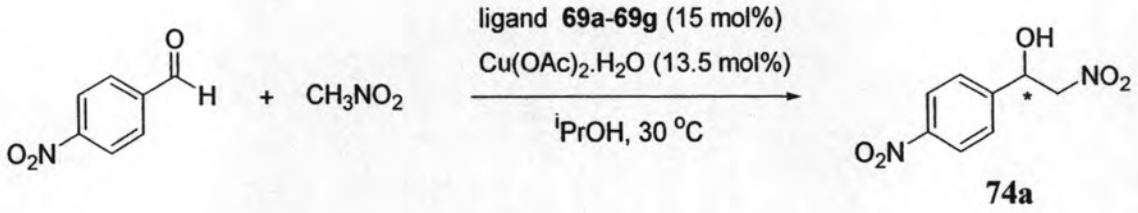


(*R*)-**69f**



(*R*)-**69g**

Table 3.8 Optimization of reaction conditions for the enantioselective nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane promoted by various copper(II)-thiolated chiral ligands



74a

entry	ligand	$MeNO_2$ (equiv)	reaction time (h)	yield (%)	ee (%)
1	(*S*)-**69a**	55	48	90	30 (*R*)
2	(*R*)-**69c**	55	48	92	35 (*S*)
3	(*R*)-**69c**	10	24	92	35 (*S*)
4	(*R*)-**69c**	5	24	91	3 (*S*)
5	(*R*)-**69c**	2	48	67	16 (*S*)
6[a]	(*R*)-**69c**	10	24	93	28 (*S*)
7[b]	(*R*)-**69c**	10	8 days	89	46 (*S*)
8	Schiff's base-**69a**	10	48	40	0
9[c]	(*S*)-**69a**	10	24	86	28 (*R*)
10[d]	(*S*)-**69a**	10	1	72	0
11	(*S*)-**69b**	10	24	79	33 (*R*)
12	(*S*)-**69d**	10	24	90	0
13	(*S*)-**69e**	10	24	94	22 (*R*)
14	(*R*)-**69f**	10	24	88	29 (*S*)
15	(*R*)-**69g**	10	24	87	24 (*S*)

[a] The reaction was carried out without any solvent.

[b] The temperature for the reaction was 0 °C.

[c] The ligand/metal ratio = 2:1.

[d] Et_3N was used as an additive (1 equiv).

Results from Table 3.8 revealed that a decrease in the amount of nitromethane from 55 to 10 equivalents did not affect the yield and enantioselectivity of the product (entries 1-3). However, when the amount of nitromethane was decreased further to 5 and 2 equivalents, the yield and the selectivity of the product significantly decreased

(entries 4 and 5). When the reaction was performed without any solvent, the enantioselectivity slightly decreased (entry 3 *vs* entry 6). The possible beneficial effect of temperature was investigated by setting up the reaction at 0 °C. Although the enantioselectivity was increased from 35% to 46% ee, a significantly longer reaction time was required (entry 3 *vs* entry 7). When the reaction was carried out using the parent Schiff's base of ligand (*S*)-**69a**, both low yield and low enantioselectivity were obtained (entry 8). When the mole ratio of ligand/$Cu(OAc)_2 \cdot H_2O$ was changed from 1/1 to 2/1, no improvement in enantioselectivity was observed (entry 9). In general, the nitro-aldol reaction could be catalyzed or promoted by addition of organic bases.[62] Addition of a base promoter such as triethylamine significantly increased the rate of this reaction. Unfortunately, addition of the base completely deminished the enantioselectivity (entry 10). Changing the steric nature of the sulfur substituent (R^1) resulted in no significant improvement in terms of yield and enantioselectivity (entries 3, 14, and 15). A slightly improved enantioselectivity was observed on replacing the benzyl group in (*S*)-**69a** with a phenyl group in (*R*)-**69c** (entries 1 and 2). Attempts to increase the bulkiness further by substitution with the more sterically hindered ^{t}Bu group resulted in a negligible enantioselectivity (entry 12). In all cases no significant amount of the 2-nitroalkene dehydration product, which often accompanies as competing reaction to the desired nitro-aldol reaction, was observed.

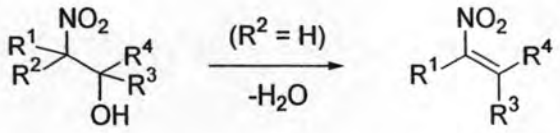
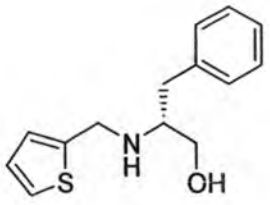


Figure 3.3 The 2-nitroalkene dehydration product obtained from the nitro-aldol product

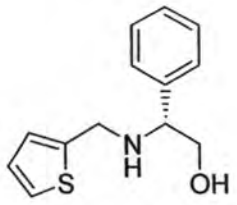
It can be seen that optimization of the reaction parameters including solvent and temperature suggested that 2-propanol was the solvent of choice and room temperature (30 °C) provided a balance between good reactivity and high enantioselectivity. Steric bulkiness of the R^1 substituent has some effects on the enantioselectivity but the trend is not clear. On the other hand, the nature of the S-substituent has virtually no effect on the enantioselectivity.

3.3.1.2 Thiophene-substituted amino-alcohol ligands

In addition to the new chiral thiolated amino-alcohol ligands, a series of thiophene-derived ligands were synthesized. These ligands were also prepared by the same procedure as described for the synthesis of thiolated amino-alcohol ligands (**69**), by sodium borohydride reduction of the imine formed *in situ* from thiophene-2-carbaldehyde and the appropriate amino-alcohols. Unlike thiolated amino-alcohol ligand (*S*)-**69a**, the sulfur in thiophene-substituted amino-alcohol ligand (*R*)-**70a** had a part of soft donor atom, sulfur, derived from thiophene-2-carbaldehyde. The different thing resulted in the difference in the degree of selectivity. Surprisingly, a considerable improvement was achieved when copper(II) complexes of thiophene-substituted amino-alcohols **70** were used as catalyst for asymmetric nitro-aldol reaction. Under the optimized conditions described above, ligand (*R*)-**70a** provided the nitro-aldol product in 87% yield and 53% ee. The configuration of the major nitro-aldol product was *S* as determined by chiral HPLC and comparison of the chiral HPLC pattern and the $[\alpha]_D$ with literature data.[106] By changing substituent R^3 from benzyl in (*R*)-**70a** to the more bulky phenyl group in (*R*)-**70b**, a considerably improved yield (97%) and enantioselectivity (75% ee) of the nitro-aldol product was realized. A comprehensive optimization of the reaction condition (solvent, temperature, metal, and source of copper) was then repeated on ligand (*R*)-**70b**. The results are shown in Tables 3.9 and 3.10.

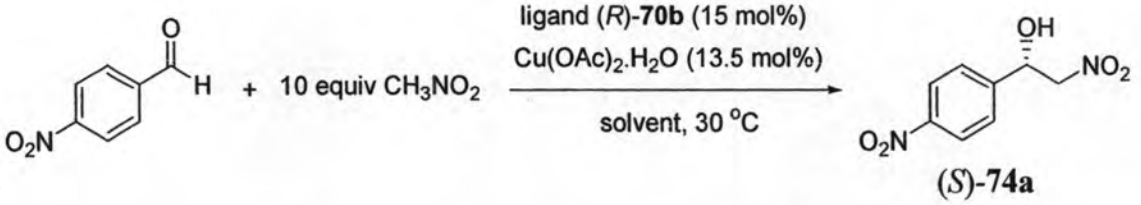


(*R*)-**70a**



(*R*)-**70b**

Table 3.9 Optimization of reaction conditions for the enantioselective nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane promoted by copper(II)-(*R*)-**70b** catalyst in various solvents



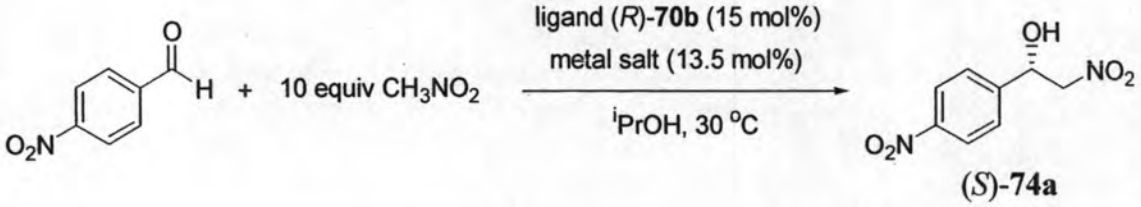
(*S*)-**74a**

entry	solvent	reaction time (h)	yield (%)	ee (%)
1	^{i}PrOH	24	97	75
2	EtOH	24	95	61
3	^{t}BuOH	24	93	70
4	toluene	48	71	55

The effect of solvents on the enantioselectivity and yield of the nitro-aldol product was studied. The results from Table 3.9 revealed that in all alcoholic solvents the reaction consistently performed better than in toluene. Comparable yields and enantioselectivities were observed in *tert*-butyl alcohol and 2-propanol. However, the use of 2-propanol was preferred to avoid solubility problem of catalysts in *tert*-butyl alcohol.

Attempts had been made to further improve the enantioselectivity by varying metal ions as well as the source of metal ions (at 13.5 mol%) in the presence of 15 mol% of chiral ligand (*R*)-**70b**. The reactions of 4-nitrobenzaldehyde and 10 equiv of nitromethane in the presence of metal complexes of (*R*)-**70b** generated *in situ* were carried out in 2-propanol at room temperature (Table 3.10).

Table 3.10 Optimization of reaction conditions for the enantioselective nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane promoted by different metal salts complexed with (*R*)-**70b**



(*S*)-**74a**

entry	metal salt	reaction time (h)	yield (%)	ee (%)
1	none	48	35	3
2	$Cu(OAc)_2 \cdot H_2O$	24	97	75
3	$Zn(OAc)_2 \cdot 2H_2O$	48	74	0
4	$Cu(OTf)_2$	48	55	6
5	$Zn(OTf)_2$	48	81	0
6	CuTC	24	87	65
7	CuOAc	24	86	47
8	$Cu(acac)_2$	24	83	0
9	Cu(2-ethyl hexanoate)$_2$	24	95	64
10	Cu(4-O_2N benzoate)$_2$	24	79	72
11	Cu(II)(4-PhO benzoate)$_2$	24	91	42
12	$Cu(OH)_2$	48	34	9

Copper(II) was found to be a more effective metal ion than copper(I) and zinc(II) for this nitro-aldol reaction. Interestingly, when the counterions were triflates, both yield and enantioselectivity were poor, even with copper(II) (entry 2 *vs* entry 4). Apparently Lewis acidic copper(II) metal bearing moderately basic acetate anions facilitate deprotonation of nitromethane as a prelude to the aldol addition process as originally noted by Evans *et al.*.[106] Copper(II) salts of other weakly basic counterions (entries 9 and 11) were also effective in terms of enantioselectivity. However, none of these provide better results than the original copper(II) acetate. Interestingly, the also weakly basic acetoacetate counter ion in $Cu(acac)_2$ provided no

selectivity, although the yield were relatively good (entry 8). It is possible that the acac ligand bind to the cooper tightly in a chelate fashion so that the chiral ligand cannot bind to the copper.

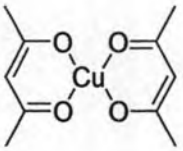
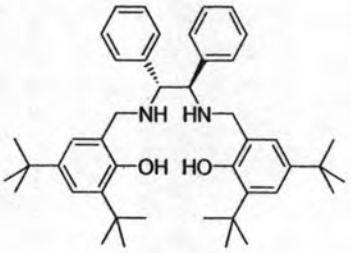


Figure 3.4 Structure of copper(II) acetylacetonate

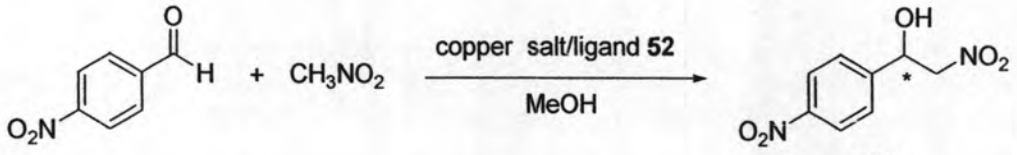
When chiral ligand (*R*)-**70b** was present alone (*i.e.* no metal salt), both percent yield and enantioselectivity of reaction were very low after 48 h (35% yield and 3% ee, entry 1). This suggests that the ligand alone might also act as organocatalyst, albeit a poor one. Possible reasons for this may be explained as follows: In general, the classical nitro-aldol reaction needs a slightly basic condition to initiate the reaction. The base would abstract proton from nitromethane to generate a nucleophile that would add to the carbonyl carbon. The chiral ligand (*R*)-**70b**, bearing a weakly basic secondary amino group, may act as a base but may not be strong enough to drive the reaction to completion.

In a recently reported studies by Feng *et. al.*, [114] a tetrahydrosalen ligand (**52**) complexed with copper metal possessing various counter ions including $Cu(OAc)_2$, $Cu(OTf)_2$, and $(CuOTf)_2{\cdot}C_7H_8$ were used to catalyze the same reaction. Under similar conditions is was found that $Cu(OAc)_2$ gave better results in terms of yield and selectivity compared to $Cu(OTf)_2$ (entry 1 *vs* entry 2, Table 3.11) but Cu(I), $(CuOTf)_2{\cdot}C_7H_8$ gave the best results.

Table 3.11 Asymmetric nitro-aldol reaction of 4-nitrobenzaldehyde with nitromethane promoted by tetrahydrosalen (**52**) complexed with different copper salts reported by Feng *et al.* [114]



52



74a

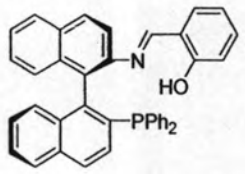
entry[a]	catalyst (mol%)	copper salt	t (°C)	reaction time (h)	yield (%)	ee (%)
1	20	$Cu(OAc)_2$	13	9	40	67
2	20	$Cu(OTf)_2$	13	9	trace	not detected
3	10	$(CuOTf)_2 \cdot C_7H_8$	13	9	21	83
4[b]	10	$(CuOTf)_2 \cdot C_7H_8$	13	9	33	93
5[b]	5	$(CuOTf)_2 \cdot C_7H_8$	45	30	95	91

[a] All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde in the mixture of 0.8 mL of methanol and 0.6 mL of nitromethane.

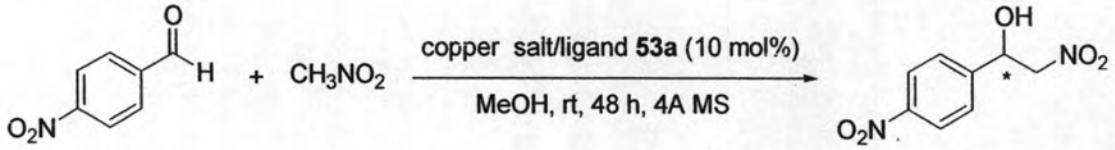
[b] In the presence of 10 mg of 4Å MS.

An additional example includes Shi's report on the use of copper complexes of chiral phosphine-salen type ligand (**53a**) to catalyze the same reaction under similar condition.[115] In this case $Cu(OTf)_2$ showed better result in terms of selectivity, even at 45 °C compared to the case of $Cu(OAc)_2 \cdot H_2O$ (entry 3 *vs* entry 4, Table 3.12). The achievement in selectivity was observed when $(CuOTf)_2 \cdot C_6H_6$ was employed as a metal catalyst (entry 5).

Table 3.12 Optimization of the reaction conditions in the asymmetric nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane catalyzed by chiral phosphine-salen type ligand (**53a**) complexed with different copper salts reported by Shi *et al.* [115]



53a



74a

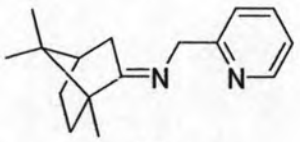
entry[a]	copper salt	yield (%)	ee (%)
1	CuI	68	0
2	CuCl	78	13
3[b]	$Cu(OTf)_2$	49	37
4	$Cu(OAc)_2 \cdot H_2O$	75	24
5	$(CuOTf)_2 \cdot C_6H_6$	99	68
6	$Cu(CH_3CN)_4ClO_4$	71	39

[a] All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde in 0.8 mL of methanol and 0.6 mL of nitromethane in the presence of 10 mg of 4Å MS.

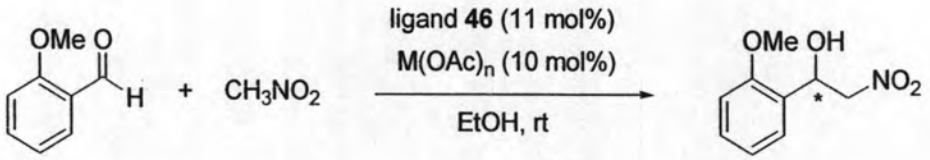
[b] The reaction was performed at 45 °C for 4 days.

Furthermore, Pedro *et al.* reported using chiral ligand **46** complexed with various Lewis acids to find a suitable metal salt for catalytic asymmetric nitro-aldol reaction.[108] The results are shown in Table 3.13.

Table 3.13 Lewis acids screening for the asymmetric nitro-aldol reaction between nitromethane and *o*-anisole in the presence of **46** as a chiral ligand reported by Pedro *et al.* [108]



46



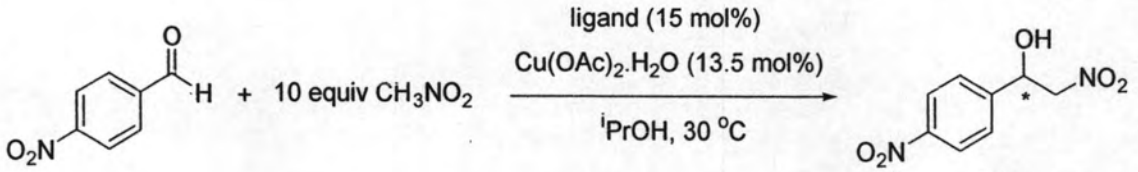
entry	copper salt	time (h)	yield (%)	ee (%)
1	$Co(OAc)_2 \cdot 4H_2O$	24	94	0
2	$Ni(OAc)_2 \cdot 4H_2O$	24	94	0
3	$Zn(OAc)_2 \cdot 2H_2O$	93	77	10
4	$Pd(OAc)_2$	70	40	37
5	$Cu(OAc)_2 \cdot H_2O$	24	93	61

The results from Table 3.13 showed the reactions were carried out at room temperature in ethanol and in the presence of 11 mol % of ligand **46** and 10 mol% of copper acetate as the source for the metal ion. A screening of some late transition metal acetates showed copper acetate to be the best promoter for this reaction (entry 5) which is consistent to the results obtained in this study.

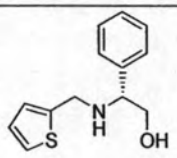
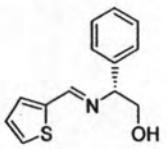
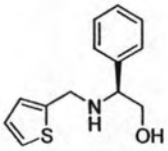
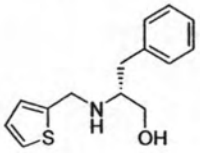
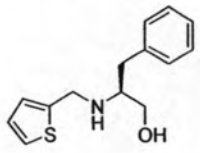
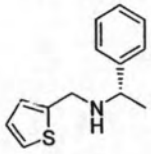
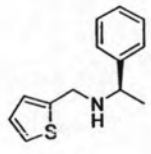
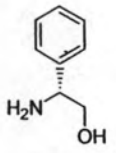
3.3.1.3 Evaluation of the ligands for asymmetric nitro-aldol reaction

The effect of ligand structure on the enantioselectivity of the reaction was also investigated. The reactions of 4-nitrobenzaldehyde with nitromethane in the presence of **70**-$Cu(OAc)_2 \cdot H_2O$ complexes were repeated using different thiophene-based ligands under the optimized condition obtained for (*R*)-**70b** outlined above. The results are summarized in Table 3.14.

Table 3.14 Effect of the structure of the thiophene-based amino-alcohol ligands on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions



74a

entry	ligand		reaction time (h)	yield (%)	ee (%)
	code	structure			
1	(*R*)-**70b**		24	97	75 (*S*)
2	Schiff's base (*R*)-**70b**		48	72	6 (*R*)
3	(*S*)-**70b**		24	90	72 (*R*)
4	(*R*)-**70a**		24	87	53 (*S*)
5	(*S*)-**70a**		24	84	53 (*R*)
6	(*S*)-**70c**		48	79	0
7	(*R*)-**70c**		48	82	0
8	(*R*)-phenylglycinol		24	72	3 (*R*)

From Table 3.14, ligand (*R*)-**70a** with a smaller benzyl substituent in place of the phenyl substituent in (*R*)-**70b** provided the nitro-aldol product in 87% yield and 53% ee (entry 4). As expected, ligands (*S*)-**70b** and (*S*)-**70a** bearing the same configurations at the stereogenic center afforded the products with the same configuration (entries 3 and 5). In both cases, the configuration of the major enantiomer of the nitro-aldol product was determined to be *R*. Similar to the benzylthioether ligand series (**69**), enantioselectivity in the product using Schiff's base of (*R*)-**70b** as a chiral ligand yielded poor (6% ee, entry 2). The importance of the hydroxyl group in the amino-alcohol part was also demonstrated. Chiral compounds (*S*)-**70c** and its opposite enantiomer, (*R*)-**70c**, were proper examples to justify their actions. Apparently, no enantioselectivity was observed in the absence of the OH group. The results from entries 6 and 7 revealed that the hydroxyl group of the chiral ligand was essential for coordination with copper to initiate the enantioselectivity. To test for the necessity of having the thiophene moiety, (*R*)-phenylglycinol was used as a ligand. In the absence of the thiophene moiety, very poor enantioselectivity was obtained (3% ee, entry 8). In conclusion, both the thiophene part and the amino-alcohol hydroxyl group are crucial for the enantioselective induction. Comparison of results shown in entries 2 and 3 reveal another piece of information. Apparently, the parent Schiff's base is a poor ligand compared to its reduced form, giving only 6% ee of *R* product in lower yield and with longer reaction time. The above results have been rationalized by proposed transition state models shown in Figure 3.5.

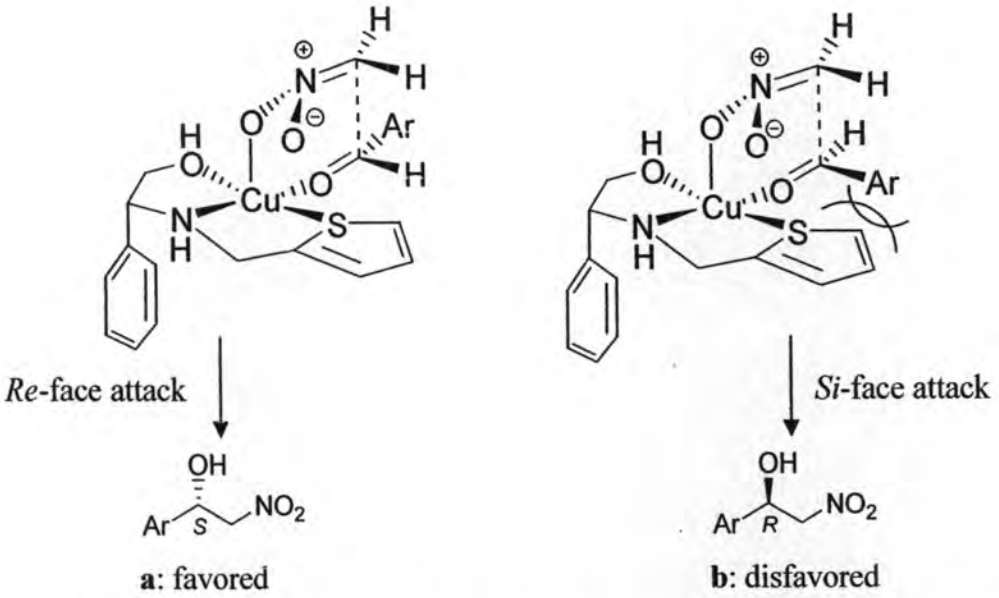


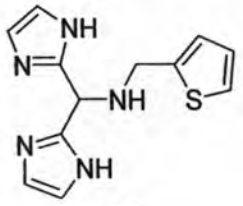
Figure 3.5 Proposed transition state models for the enantioselective nitro-aldol reaction when (*R*)-**70b** used as a chiral ligand

All transition state models were proposed on the basis that the *S*-configuration of nitro-aldol products were obtained from an attack of nitronate ion to the *re*-face of the aldehydes. There are two major possibilities of coordination in a tridentate fashion between SNO atoms of the chiral ligand and copper ion. The models shown in Figures 3.5 (**a**) and (**b**) were proposed in accordance with prior literature reports.[103,106] In these models, copper, as the metal center, was coordinated by all 3 donor atoms of the ligand in equatorial positions. Hence, the oxygen atom of the aldehyde approaches the metal-ligand complex in the other equatorial position, while an oxygen atom of nitromethane coordinates with Cu at the more accessible axial position. These directions were perceived that the lowest energy of transition state was accomplished.[106] Figure 3.5 (**a**) depicts an orientation with a lower energy in which the aldehyde orients its molecule by pointing the aryl ring away from the thienyl ring of the ligand to avoid steric interaction. The nitronate would attack directly to the *re*-face of the aldehyde giving rise to the *S* product. With an orientation in Figure 3.5 (**b**), on the other hand, the aldehyde is ready for the *si*-face attack by the nitronate yielding the *R* product. This, however, would be a higher energy transition state due to steric hindrance between the aryl group of the aldehyde and the thiophene moiety.

Even though these models could explain the stereochemistry observed in the products obtain, they still lack a clear reasoning to support some results. As outlined earlier in the ligand screening experiments, a phenyl substituent in the ligand

appeared to be the most effective substituent to induce enantioselectivity in the reaction (entries 1 and 3, Table 3.14). This is strongly indicative of the influence of the type of substituent on the amino alcohol moiety of the ligand on the stereochemical outcome of the reaction. Our proposed transition state model depicted in Figure 3.5 (**a**) and (**b**) seem to have placed the substituent on the amino alcohol so much further away from the aldehyde and the nitronate that the effect of this substituent in terms of both steric and electronic on face selectivity of the carbonyl group would be too weak.

An example of ligand-Cu(II) complex involving Cu(II)-sulfur atom coordinate was described by Reedijk *et al.*. They reported a structure of trinuclear copper(II) complex prepared from 1,1-bis(imidazol-2-yl)-3-(thiophen-2-yl)-2-azapropane (himthio) ligand (**77**) and $Cu(NO_3)_2 \cdot 3H_2O$ in MeOH.[139]



77

Figure 3.6 Molecular structure of the Himthio ligand

Surprisingly, the reaction of Himthio with $Cu(NO_3)_2$ in methanol results in a trinuclear copper(II) complex in which three copper ions are linearly bridged by two ligands. The crystal structure shows that the thiophene sulfur atoms are semicoordinated to the central Cu(II) atom, and such S-Cu(II) interactions are quite rare. No other examples of trinuclear copper(II) complex in which the central Cu(II) atom is coordinated by sulfur atoms have been found in the literature, it therefore represents the first example of a trinuclear linear copper(II) complex with semicoordination of thiophene moieties (Figure 3.7).[139]

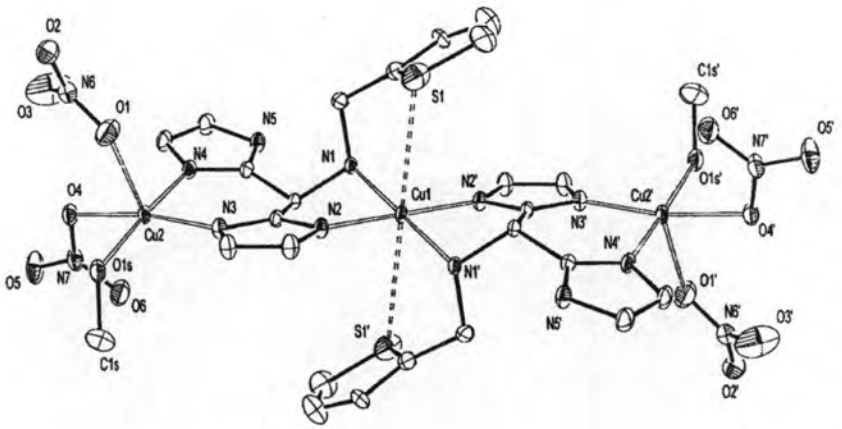


Figure 3.7 Thermal ellipsoid plot (20% probability level) of the trinuclear copper complex $[Cu_3(imthio)_2(NO_3)_4(MeOH)_2]$; hydrogen atoms have been omitted for clarity [139]

Based on the information as described by Reedijk, more feasible models were proposed as depicted in Figure 3.8 (**a**) and (**b**). This transition state model outlined another coordinating behavior with a supposition that the S atom of the ligand could coordinate to copper in an axial position and the others (O and N) bind in equatorial positions.

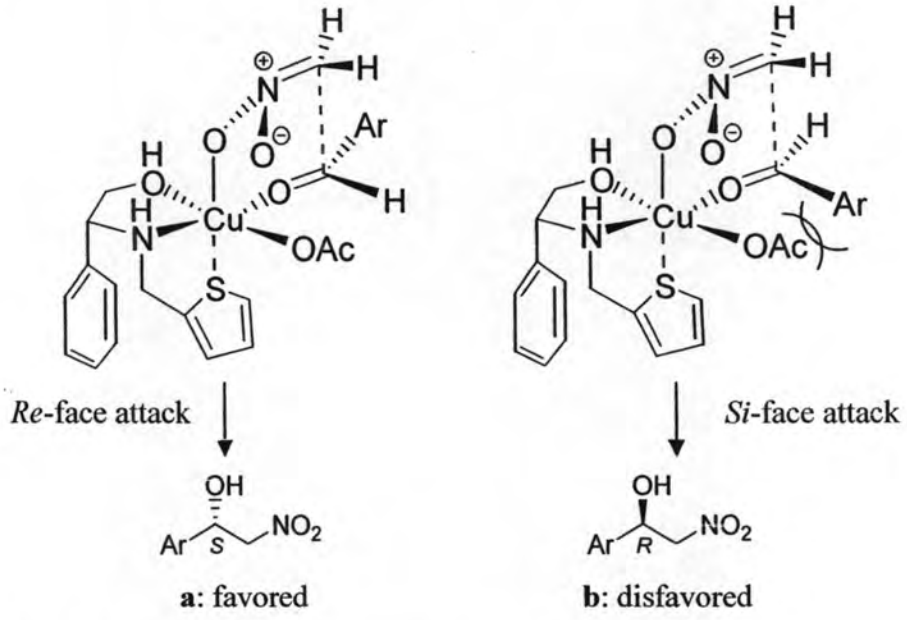


Figure 3.8 Proposed feasible transition state models for the enantioselective nitro-aldol reaction when (*R*)-**70b** used as a chiral ligand

In this orientation, the thiophene and the phenyl substituent of ligand (*R*)-**70b** would line in such a way that they are parallel to each other. This, therefore, enables a

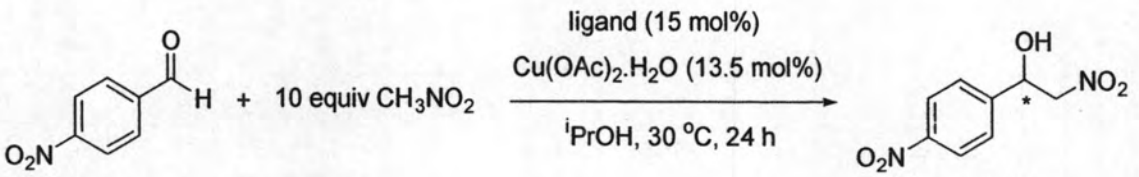
π-π stacking interaction to take place. As a result, this transition state becomes more rigid. An aldehyde and nitromethane coordinated to the copper center in such a fashion that there is a maximum activation for the reactive partners. Thus, the oxygen atom of the nitromethane approaches the metal center from the axial side and the carbonyl oxygen atom comes from the equatorial side. This is a good accordance with what was proposed by Evans [106] and Jørgensen.[103] One of the most plausible arrangements of aldehyde was to direct the aryl group to the farest position from the acetate anion for minimization of steric hindrance. Consequently, nitronate ion could attack directly to the *re*-face of the aldehyde through a chair-like transtion state to yield (*S*)-configuration nitro-aldol product (Figure 3.8 (**a**)). In contrast, in the less favorable transition state (Figure 3.8 (**b**)), aldehyde was rotated to the opposite direction and was attacked at the *si*-face. Since a steric hindrance between aldehyde and acetate ion could develop, this orientation is of higher energy. As a result, the (*R*)-isomer of the aldol product was the minor one.

Attempts have been made to obtain a strong evidence to support the model, unfortunately, the suitable crystals of the copper complexes with thiophene-based chiral ligands have not been obtained for X-ray analysis. However, based on our experimental observations and the previously reported steric and electronic considerations,[106] the transition state models, illustrated in Figure 3.8 (**a**) and (**b**) can be used to account for the absolute configuration of the products obtained with ligands (*R*)-**70b**. The active species simultaneously binds the two reaction partners with the nucleophile positioned perpendicular to the ligand plane, while the electrophile, for maximum activation, should be positioned in one of the more Lewis acidic equatorial sites in the ligand plane. The fourth equatorial position should be occupied by the aldehyde and transfer of the nitronate from the less hindered apical position to the *re* face of the carbonyl group would lead to the (*S*)-nitro-aldol product. From all information as described above including the X-ray analysis of trinuclear copper complex $[Cu_3(imthio)_2(NO_3)_4(MeOH)_2]$ from Figure 3.7, the suitable transition state model was proposed to be Figure 3.8 (**a**).

In order to investigate the effect of the position and the type of substituents on amino-alcohol moiety on the selectivity of the reaction, the corresponding thiophene-substituted amino-alcohol ligands (*S*)-**70d**-(*R*)-**70l** were also screened under the best conditions obtained for (*R*)-**70b**. Screening of the Cu(II)-(*S*)-**70d**-(*R*)-**70l** complexes

were compared with those for the Cu(II)-(*R*)-**70b** complex, and the results are as shown in Table 3.15.

Table 3.15 Effect of the position and the type of substituents on amino-alcohol moiety on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions



74a

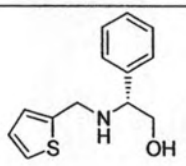
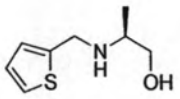
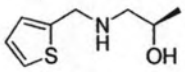
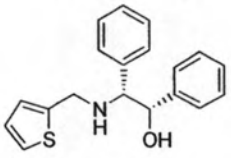
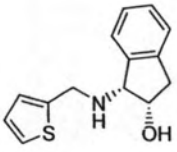
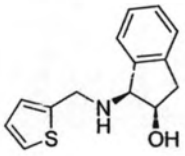
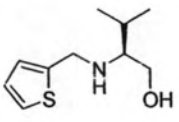
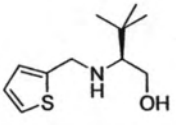
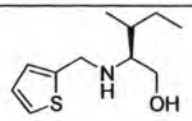
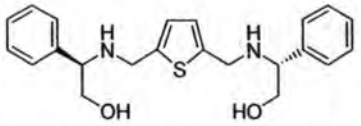
entry	ligand		yield (%)	ee (%)
	code	structure		
1	(*R*)-**70b**		97	75 (*S*)
2	(*S*)-**70d**		79	49 (*R*)
3	(*R*)-**70e**		70	12 (*R*)
4	(1*S*,2*R*)-**70f**		80	0
5	(1*R*,2*S*)-**70g**		89	42 (*S*)
6	(1*S*,2*R*)-**70h**		82	54 (*R*)
7	(*S*)-**70i**		83	44 (*R*)
8	(*S*)-**70j**		87	43 (*R*)

Table 3.15 (cont.)

entry	ligand		yield (%)	ee (%)
	code	structure		
9	(*S*,*S*)-**70k**		85	61 (*R*)
10	(*R*)-**70l**		72	60 (*S*)

The results from Table 3.15 revealed that ligand (*S*)-**70d**, possessing a small methyl substituent at the β-position of the amino-alcohol, could induce the enantioselectivity of the nitro-aldol product in 79% yield and 49% ee (*R*-isomer) after 24 h (entry 2). In contrast, when ligand (*R*)-**70e** carrying the same methyl substituent, however, at the α-position of the amino-alcohol was used, the *R*-product was also obtained as the major enantiomer (entry 3), however, low enantioselectivity was obtained. The result from entry 2 are suggestive of the influence of the absolute configuration of substituent at the β-position of the amino-alcohol moiety in controlling the absolute configuration of the nitro-aldol product. It was proposed that the ligand with *R* configuration would yield the product with opposite *S* configuration and vice versa. The result from entry 3, on the other hand, suggested that the absolute configuration of substituent at the α-position would yield product with the same configuration as that in the ligand (R->R or S->S). If this assumption is true, chiral amino-alcohol having substituents with opposite absolute configuration at both the alpha and beta positions (*R* and *S* or *S* and *R*) would be attractive. To test for this hypothesis, ligand (1*S*,2*R*)-**70f** prepared from (1*S*,2*R*)-2-amino-1,2-diphenylethanol, was employed as a ligand complexed with copper(II) acetate to catalyze asymmetric nitro-aldol reaction. Unfortunately, no enantioselectivity of the product was observed (entry 4).

Ligands derived from other bulky amino-alcohols, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol and (1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol were also synthesized and screened similarly. When copper(II) complexes of (1*R*,2*S*)-**70g** and (1*S*,2*R*)-**70h** were used as the catalysts for the nitro-aldol reaction under the same screening condition. It was found that ligand (1*R*,2*S*)-**70g** complexed with Cu(II) acetate could induce the enantioselectivity of the product in 89% yield and 42% ee (*S*-isomer) after 24 h (entry

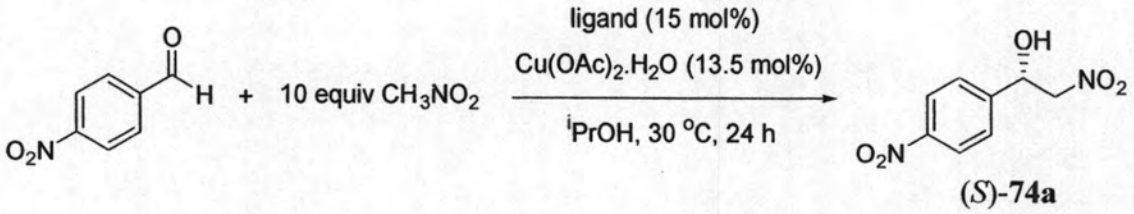
5). As expected, the configuration of the major enantiomer of the nitro-aldol product obtained from the use of Cu(II) acetate complex of the enantiomeric chiral ligand (1*S*,2*R*)-**70h** was *R* (82% yield and 54% ee, entry 6). Because of a limitation on the number of chiral amino-alcohols we could use, it was evident that the use of chiral ligand bearing substituents on both alpha and beta positions did not improve the enantioselectivity. This, together with the cost of these disubstituted amino-alcohol starting materials, led us to focus on varying substituent only at the beta position of amino-alcohols instead.

The ligands (*S*)-**70i**, (*S*)-**70j**, and (*S*)-**70k** bearing the bulky ^{i}Pr, ^{t}Bu, and ^{sec}Bu groups were attractive choices. Such highly branched substituents have been reported to increase the selectivity of the Ti-catalyzed Strecker reactions.[126] The results from Table 3.15 showed that copper-thiophene-substituted amino-alcohol complexes of (*S*)-**70i** and (*S*)-**70j** could similarly produce the nitro-aldol product in terms of yield and selectivity (entries 7 and 8, respectively). Nevertheless, the leucinol-derived (*S,S*)-**70k** ligand performed much better than (*S*)-**70i** and (*S*)-**70j** in terms of enantioselectivity (entry 9). This selectivity, however, was still lower than the original phenyl-substituted ligand (*R*)-**70b**.

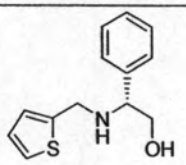
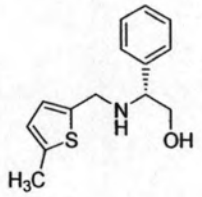
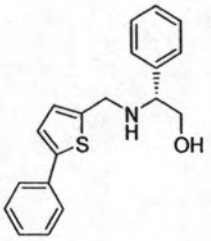
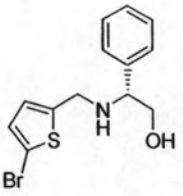
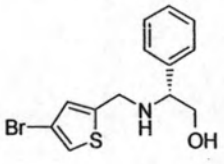
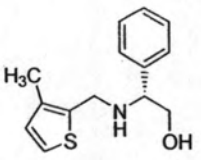
In addition, C_2 symmetric thiophene-based ligand, (*R*)-**70l** was also investigated since it is believed that 'auxiliaries with C_2 symmetry elements perform as stereochemical directors to provide higher levels of absolute stereochemical control, as compared to those totally lacking symmetry'.[140] Disappointingly, when the (*R*)-**70l** ligand complexed with Cu(II) acetate was employed as a catalyst, the enantioselectivity of the product was only 60% ee (entry 10), which is lower than the original (*R*)-**70b** ligand.

In conclusion, the use of the thiophene-substituted amino-alcohol ligand possessing several different types of substituents on chiral amino-alcohol could not improve the enantioselectivity of the product compared to the original ligand (*R*)-**70b** bearing phenyl group substituent at the β position of amino-alcohol. The phenyl side-chain is therefore chosen for further optimization of the ligand by varying the thiophene (and related) moiety. Ligands (*R*)-**70m**, **70n**, **70o**, **70p**, and **70q** bearing substituents on various positions of the thiophene ring were synthesized. There were then employed in the reaction and the results are summarized in Table 3.16.

Table 3.16 Effect of the position and the type of substituents on thiophene (and related) moiety on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions



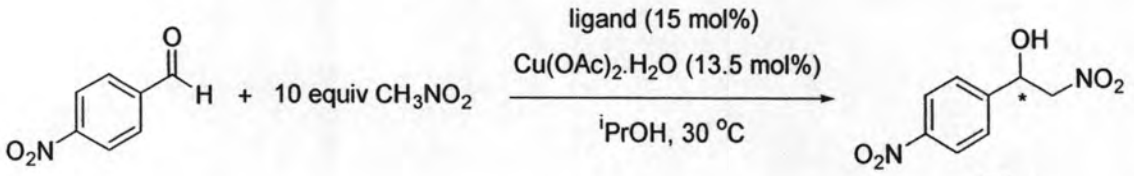
(*S*)-**74a**

entry	ligand		yield (%)	ee (%)
	code	structure		
1	(*R*)-**70b**		97	75
2	(*R*)-**70m**		92	63
3	(*R*)-**70n**		95	65
4	(*R*)-**70o**		97	66
5	(*R*)-**70p**		98	71
6	(*R*)-**70q**		95	65

The results from Table 3.16 revealed that attempts to improve the enantioselectivity of the product by using Cu-complexes of (*R*)-**70m**, (*R*)-**70n**, (*R*)-**70o**, (*R*)-**70p**, and (*R*)-**70q** bearing various substituents at different positions on thiophene moiety resulted in slightly decreased enatioselectivities (63-71% ee, entries 2-6) compared to what was observed in the case of the original ligand "lead" (*R*)-**70b** (75% ee, entry 1). Nevertheless, this shows that a variety of thiophene-substituted amino-alcohol ligands can be used in the reaction and can consistently provide good enantioselectivity.

In order to investigate the effect of the size and other coordinating atom of the thiophene ring on the selectivity of the reaction, the related thiophene-substituted amino-alcohol ligands (*R*)-**70r**-(*R*)-**70v** were also synthesized and screened under the best conditions obtained for (*R*)-**70b**. The results are given in Table 3.17.

Table 3.17 Effect of the size and other coordinating atom of the thiophene ring on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions



74a

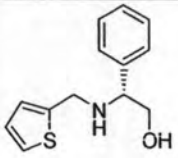
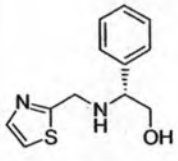
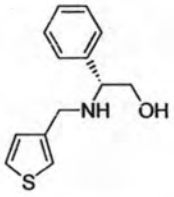
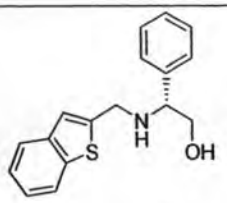
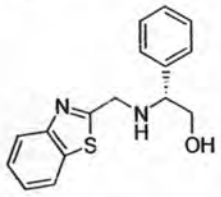
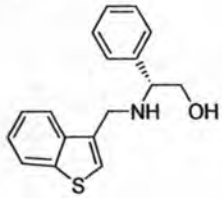
entry	ligand		reaction time (h)	yield (%)	ee (%)
	code	structure			
1	(*R*)-**70b**		24	97	75 (*S*)
2	(*R*)-**70r**		7	94	8 (*R*)
3	(*R*)-**70s**		24	92	59 (*S*)

Table 3.17 (cont.)

entry	ligand		reaction time (h)	yield (%)	ee (%)
	code	structure			
4	(*R*)-**70t**		24	91	70 (*S*)
5	(*R*)-**70u**		7	86	0
6	(*R*)-**70v**		24	88	38 (*S*)

Interestingly, when the position of the sulfur atom on the thiophene moiety was changed from 2- position in ligand (*R*)-**70b** to 3- position in ligand (*R*)-**70s**, it was found that the Cu(II)-(*R*)-**70s** complex could still induce a reaction with moderate enantioselectivity (entry 3). Although the enantioselectivity was lower than the observed enantioselectivity when using (*R*)-**70b** as a ligand, the enantioselectivity was reasonably good. This is somewhat surprising because the sulfur atom in (*R*)-**70s** is different from (*R*)-**70b** and one would predict that this position would not be suitable to form a stable chelate with copper metal. This raised some uncertainties about the transition state model proposed since the data suggested that chelation by the sulfur atom might not be a pre-requisite for obtaining good enantioselectivities. Ligands with benzothiophene [(*R*)-**70t**, (*R*)-**70v**)] or benzothiazole [(*R*)-**70u**)] instead of thiophene were also synthesized to investigate the effect of the size of thiophene unit. The copper(II) complexes of (*R*)-**70t**, and (*R*)-**70v** ligands could induce the enantioselectivity of the nitro-aldol product with 70% and 38% ee, respectively (entries 4 and 6). The enantioselectivity of the product observed from the use of (*R*)-**70v** as a ligand was lower than the enantioselectivity of the product observed from the use of (*R*)-**70t** as a ligand. This is in accordance with the results obtained from the thiophene ligands (*R*)-**70b** and (*R*)-**70s**.

When a nitrogen atom was incorporated into the thiophene ring, forming a thiazole ring as in (*R*)-**70r** and (*R*)-**70u**, a markedly different behavior was observed. The copper(II) complex of ligand (*R*)-**70r** was apparently more active catalyst as shown by the short reaction time (7 h) compared to the original thiophene ligand (*R*)-**70b** (24 h). However, the enantioselectivity was poor when this complex was used as a catalyst (entry 2). Moreover, this ligand provided a reversed enantioselectivity compared to ligand (*R*)-**70b**, *i.e.* the *R*-nitro-aldol product was obtained instead of the expected *S*. Similar to the copper complexes of (*R*)-**70r** chiral ligand, (*R*)-**70u** complexed with Cu(II) acetate could not induce the enantioselectivity, although it was catalytically more active than the corresponding benzothiophene ligand (*R*)-**70t** as shown by a shorter reaction time (entry 5). From the results described here it was found that increasing the size of the thiophene unit did not improve the enantioselectivity.

A possible explanation for the observation that the incorporation of a nitrogen atom into the thiophene ring resulted in a reaction with lower enantioselectivity than when N is absent is as follows. Since the thiazole ring of (*R*)-**70r** ligand consisted of nitrogen and sulfur atoms, so there could be two possible ways in coordination between the ligand and copper atom. One was by S-N-O chelation and the other by N-N-O chelation to the copper(II). Alternatively, the thiophene sulfur atom might not actually participate in the chelation as originally proposed, leading to the ligand acting in bidentate mode.

In contrast to thiophene, nitrogen heterocycle are known to be good ligands for copper.[102] The presence of additional nitrogen atom would change this to a tridentate binding mode. Apparently the two chelation modes (S-N-O *vs* N-N-O or N-O *vs* N-N-O) provide opposite enantioselectivity. The coordination between N-N-O and copper metal should be a strong coordination and a stable catalyst which could accelerate the reaction faster. This is not necessarily related to the enantioselectivity because the geometry of the complex might not be optimal to provide good enantioselectivity. It would be interesting to study further on how to improve the enantioselectivity of copper(II) complexes of N-N-O chelating ligands. However, this is considered beyond the scope of the present work and the focus was directed to improving the thiophene-based ligands. The fact that position of the sulfur atom on the thiophene ring has little effect on the enantioselectivity, together with the fact that thiazole derivatives are much more catalytically active but less enantioselective

suggest that the role of thiophene unit could be more on steric rather than coordination with the copper atom as previously proposed (Figure 3.5).

There were not many chiral thiophene-based ligands reported in asymmetric synthesis.[111,141] Indeed, only a few thiophene-based ligands had previously been employed in asymmetric nitro-aldol reactions.[100,112] Apart from the data reported by Reedijk (Figure 3.7), [139] in other few crystallographic information available regarding the structure of copper-thiophene containing ligand complexes, no explicit coordination between copper and thiophene has been observed (Figure 3.9).[112] In one of such structure, the expected distorted square planar geometry of the copper center was observed with the non-bounded oxygen of the acetate groups occupying vacant apical coordination sites. The two bithiophene arms are parallel to each other and oriented in opposite directions.[112] Attempts to crystallize copper(II) complexes of ligand (*R*)-**70b** and (*R*)-**70o** in the presence of a variety of counter ions (ClO_4^- and OAc^-) failed in our hands therefore no crystal structures could be obtained.

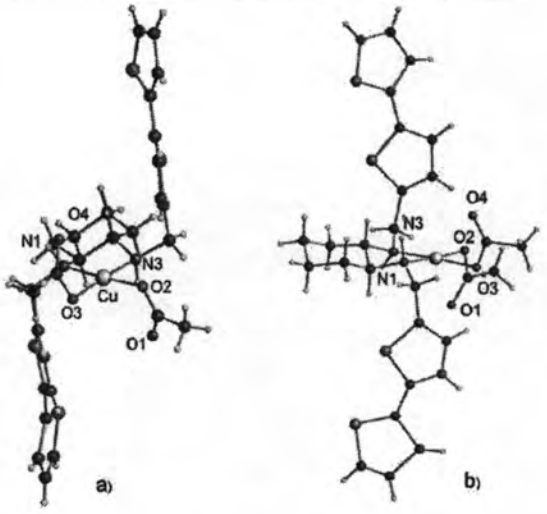


Figure 3.9 Molecular structure of (±)-**49b**/$Cu(OAc)_2$. The (*S*,*S*)-enantiomer is shown; (**a**) front view; (**b**) side view [112]

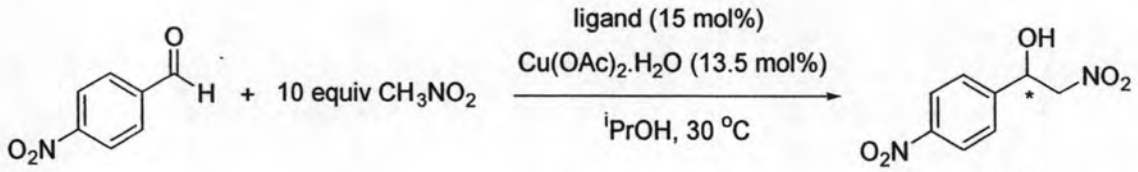
Because of the ambiguity in the role of the thiophene part in chiral thiophene-based amino-alcohol ligand system on the reaction, other non-thiophene amino-alcohol ligands were synthesized and examined for asymmetric nitro-aldol reactions.

3.3.1.4 Heteroatom-based amino-alcohol ligands

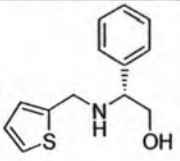
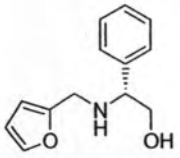
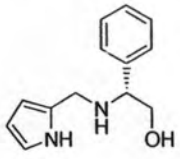
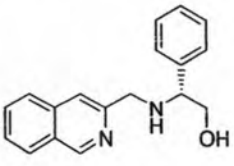
In order to access the necessity of having the sulfur atom in the ligand, other five-membered heteroaromatic rings, including some benzo-fused analogues, were

used in place of the thiophene. Ligands such (*R*)-**72a** with a furfuryl moiety, (*R*)-**72b** with a pyrrole gruop, and (*R*)-**72c** with were isoquinoline prepared. These ligands all possess bearing amino-alcohol moiety derived from (*R*)-phenylglycinol. Catalyst testing results for the Cu(II)-(*R*)-**72a**, (*R*)-**72b**, and (*R*)-**72c** complexes were compared with those of the Cu(II)-(*R*)-**70b** complex for the asymmetric nitro-aldol reaction, and the results are summarized in Table 3.18.

Table 3.18 Effect of the structure of the heteroatom-based amino-alcohol ligands on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions

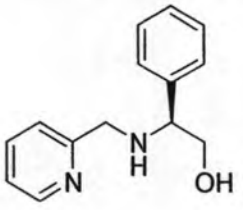


74a

entry	ligand		reaction time (h)	yield (%)	ee (%)
	code	structure			
1	(*R*)-**70b**		24	97	75 (*S*)
2	(*R*)-**72a**		24	92	60 (*S*)
3	(*R*)-**72b**		24	72	39 (*S*)
4	(*R*)-**72c**		5	90	6 (*R*)

The furfuryl-based ligand (*R*)-**72a** complexed with copper(II) acetate could catalyze the reaction and induce the enantioselectivity of the nitro-aldol product in 92% yield and 60% ee (entry 1). A decrease of enantioselectivity to 39% was

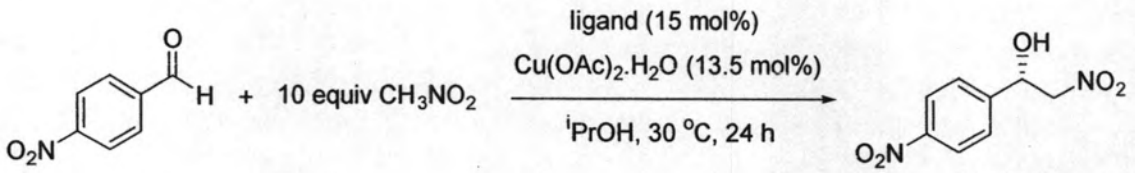
observed with a pyrrole group in (*R*)-**72b**. The results showed that both furfuryl and pyrrole-based ligand performed almost as good as the original thiophene-based ligand. As both furfuryl and pyrrolyl groups are not expected to be a good ligands for copper(II), the reasonable enantioselectivity obtained in both cases strengthen the proposal that the role of thiophene unit could be more on steric rather than coordination with the copper atom. The rate and enantioselectivity of the nitro-aldol reaction catalyzed by the isoquinoline ligand, (*R*)-**72c** was in good agreement with the results obtained with thiazole ligands described above. The fast reaction rate and reversed but poor enantioselectivity (6% ee, entry 3) must be due to the high chelating ability of the nitrogen atom in the quinoline moiety. A related ligand with the study shown below was also tested as a ligand for nitro-aldol reaction. The yield of 91% and 4% ee (*S* isomer) of the nitro-aldol product was obtained after 24 h.



3.3.1.5 Bidentate amino-alcohol ligands

Realizing that the coordinating atom may not be required as sulfur substituents, other types of chiral amino-alcohol based ligands which should only be capable of forming bidentate complexed with copper(II) were prepared from various aldehydes and (*R*)-phenylgylcinol. Screening results of the Cu(II)-(*R*)-**73a**-(*R*)-**73g** complexes are shown in Table 3.19.

Table 3.19 Effect of the structure of the bidentate amino-alcohol ligands on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions



(*S*)-**74a**

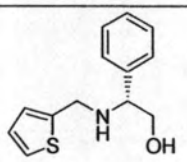
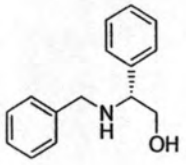
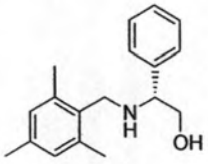
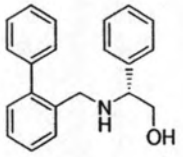
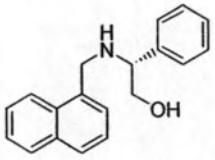
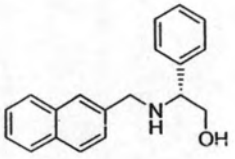
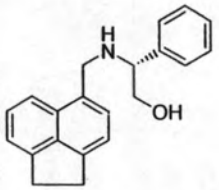
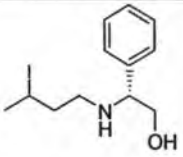
entry	ligand		yield (%)	ee (%)
	code	structure		
1	(*R*)-**70b**		97	75
2	(*R*)-**73a**		90	52
3	(*R*)-**73b**		89	6
4	(*R*)-**73c**		95	34
5	(*R*)-**73d**		95	12
6	(*R*)-**73e**		88	42
7	(*R*)-**73f**		88	37

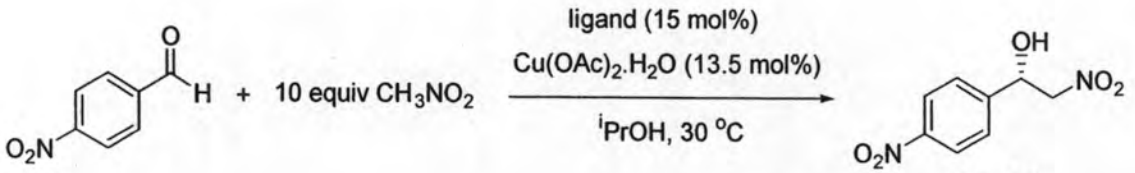
Table 3.19 (cont.)

entry	ligand		yield (%)	ee (%)
	code	structure		
8	(*R*)-**73g**		77	4

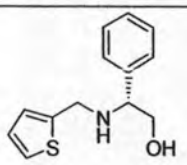
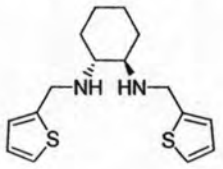
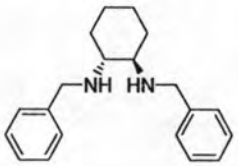
As shown in Table 3.19, copper(II) complexes of most bidentate chiral amino-alcohol ligands could catalyze the addition of 4-nitrobenzaldehyde with nitromethane to afford the nitro-aldol product with good to excellent yields (77-95%) and with poor to moderate enantioselectivities. With the chiral bidentate ligand, (*R*)-**73a**, having a phenyl ring in place of thiophene ring in (*R*)-**70b**, a moderate degree of selectivity was obtained (entry 2). The more bulky ligand (*R*)-**73b**, bearing three methyl groups substituent at 2-, 4-, and 6- position on phenyl ring caused a drastic decrease in enantioselectivity of the product (entry 3). Ligand (*R*)-**73c** bearing only one phenyl substituent at 2- position on phenyl ring complexed with copper(II) acetate could also induce the enantioselectivity of the product with moderate enantioselectivity. The results confirmed that an extra coordinating atom other than the N and O of the amino-alcohol moiety is not required to get the enantioselectivity. It is most likely that steric effect caused by the pendant N-substituent plays a role in determining the selectivity. Apparently the size of the N-substituent cannot be too large. Five membered aromatic rings are probably optimal.

There were some previous reports on the use of C_2-symmetrical diamine ligand **49a** in some asymmetric reactions including asymmetric transfer hydrogenation of aromatic ketones, [141] or asymmetric allylic alkylation.[111] At the time this work was being carried out, the ligand had not yet been used for asymmetric nitro-aldol reactions, therefore it was interesting to use this ligand for this reaction under the best conditions obtained for ligand (*R*)-**70b**. The structurally related C_2-symmetrical bis-amino ligand **49e** possessing a phenyl ring in place of thiophene ring in **49a** was also tested in the same reaction to investigate the role of thiophene ring. The results are as shown in Table 3.20.

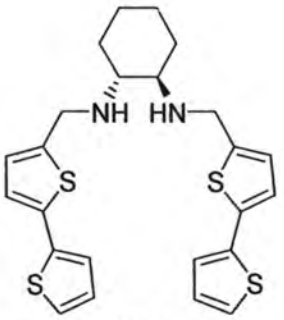
Table 3.20 Effect of the structure of the C_2-symmetrical bis-amino ligands on the efficiency of the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane under the optimized conditions



(*S*)-**74a**

entry	ligand		reaction time (h)	yield (%)	ee (%)
	code	structure			
1	(*R*)-**70b**		24	97	75
2	**49a**		1	90	67
3	**49e**		1	93	67

The results from Table 3.20 revealed that although only moderate selectivities were obtained (67% ee, entries 2 and 3), the reaction rate of the nitro-aldol reaction catalyzed by chiral bis-amino ligands **49a** and **49e** was very fast. The fast reaction rate must be due to the high chelating ability of the nitrogen atom in the cyclodiamine moiety making these better ligands than aminoalcohols. The enantioselectivity observed when **49e** used as a ligand was the same as the use of **49a** under the same conditions, confirming that the presence of sulfur atom was not a pre-requisite for the high enantioselectivity nor high reaction rate. During the course of this project, a highly enantioselective (81-99% ee, 17 examples) copper-catalyzed nitro-aldol reaction in the presence of C_2-symmetrical ligands (**49b**) derived from *trans*-1,2-diaminocyclohexane and 2,2′-bithiophene-5-carbaldehydes has been reported by Bandini.[112]



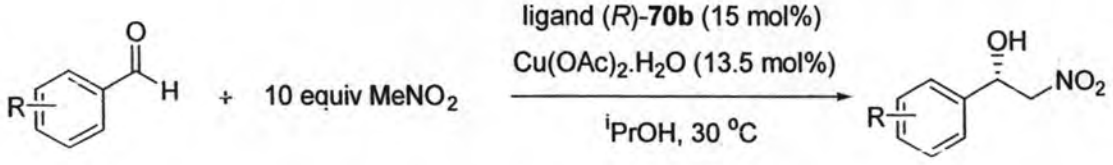
49b

Moreover, Bandini *et al.* also reported using **49a** complexed with $Cu(OAc)_2$ for catalytic asymmetric nitro-aldol reaction of benzaldehyde with nitromethane in the presence of ethanol as a solvent at room temperature. This catalyst could afford the corresponding nitro-aldol product with 70% conversion and 89% ee after 1.2 h (*S* isomer). In our project, (*R*)-**70b** was the suitable chiral ligand and 2-propanol was the proper solvent obtained from screening to search the optimized reaction conditions. When Cu(II)-(*R*)-**70b** complex was used to catalyze the nitro-aldol reaction of benzaldehyde under the optimized condition, the product was obtained in 77% yield and 69% ee after 48 h (Table 3.21).

3.3.1.6 Cu-catalyzed addition of nitromethane to various aldehydes

With the optimized conditions in hand, the scope of the reaction in terms of substrate generality was explored. Other aromatic aldehydes were investigated using Cu(II) complexed with the best chiral ligand, (*R*)-**70b**. The results are as shown in Table 3.21.

Table 3.21 Scope of the aldehydes for the nitro-aldol reaction with nitromethane catalyzed by Cu(II)-(*R*)-**70b** complexes under the optimized conditions



entry	R	reaction time (h)	yield (%)	ee (%)
1	H	48	77	69
2	2-NO_2	24	98	85
3	4-NO_2	24	97	75

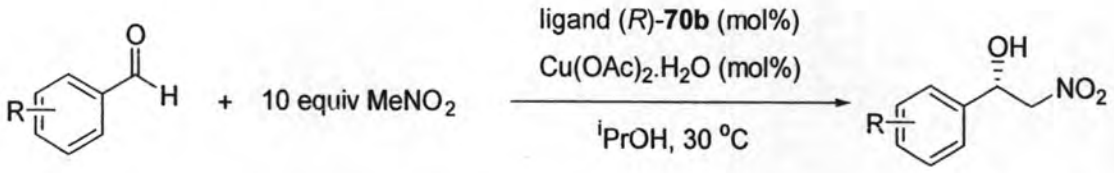
Table 3.21 (cont.)

entry	R	reaction time (h)	yield (%)	ee (%)
4	2-CF_3	24	91	88
5	4-CF_3	24	93	78
6	4-CN	24	98	76
7	2-F	24	92	83
8	4-F	24	65	77
9	2-CH_3	48	66	66
10	2-OMe	48	85	75
11	4-OMe	48	39	61

From Table 3.21, the reactions proceeded smoothly at room temperature, affording the desired nitro-aldol products in all cases. For more reactive electron-deficient aromatic aldehyde substrates in entries 2-8, the nitro-aldol products were obtained in higher ee's (75-88%) under short reaction times (24 h). The aldehydes containing electron-withdrawing groups at *ortho* position gave the optical products in higher enantiomeric excess compared with the aldehydes bearing electron-withdrawing groups at *para* position (entry 2 *vs* 3, entry 4 *vs* 5, and entry 7 *vs* 8). For those less reactive electron-rich aromatic aldehydes (entries 1, 9-11), the reactions afforded the products in lower ee's (61-75%) and required longer reaction time (48 h).

As the catalyst loading of 15% was still somewhat too high for practical purposes, the effect of reducing catalytic loading was also investigated for addition to nitromethane in various aldehydes. The results are shown in Table 3.22.

Table 3.22 Effect of the reducing catalytic loading on the efficiency of the nitro-aldol reaction between various aldehydes and nitromethane[a]



entry	R	catalyst loading (mol%)	reaction time (h)	yield (%)	ee (%)
1	4-NO_2	ligand (15 mol%) $Cu(OAc)_2 \cdot H_2O$ (13.5 mol%) (mole ratio = 1.1:1)	24	97	75
2	4-NO_2	5	24	96	69
3	4-NO_2	10	24	94	70
4	4-NO_2	20	24	93	69
5	2-CF_3	5	24	85	88
6	4-CF_3	5	24	91	77
7	4-NO_2	1	10 days	88	56
8	2-CF_3	1	12 days	10	59

[a] Mole ratio of ligand:$Cu(OAc)_2 \cdot H_2O$ = 1:1

The results from Table 3.22 showed that within the same reaction period of 24 h, the optically active Cu(II) complex of the ligand (*R*)-**70b** at 5, 10 and 20 mol% afforded the same nitro-aldol product in 96, 94, and 93% yield, respectively (entries 2, 3, and 4). Furthermore, similar enantiomeric excesses were obtained in all cases. However, under the previous condition, ligand (15 mol%) and $Cu(OAc)_2 \cdot H_2O$ (13.5 mol%), the nitro-aldol product was obtained in better result (97% yield and 75% ee, entry 1). Two other substrates were also tested at 5 mol% catalyst loading, namely 2- and 4-trifluoromethylbenzaldehydes. These were also acceptable substrates as shown by the very good enantioselectivities of 88 and 77%, respectively at 5 mol% catalyst (entries 5 and 6). Attempt to further reduce the amount of the catalyst was unsuccessful. When the catalyst loading was reduced to 1 mol%, the reaction time was very long (>10 days) and both yield and enantioselectivity decreased (entries 7 and 8).

The data in Table 3.23 below exhibit some of chiral ligands successfully used for catalytic asymmetric nitro-aldol reaction compared to our ligand.

Table 3.23 Comparison results of the nitro-aldol reaction between nitroalkane and a series of aldehydes catalyzed by various catalysts

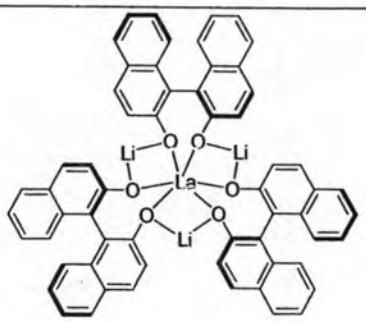
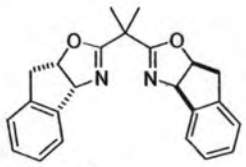
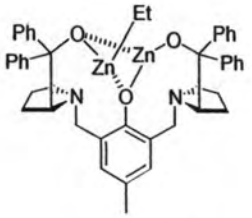
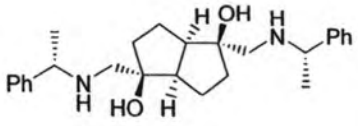
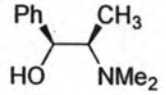
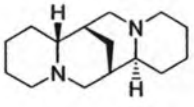
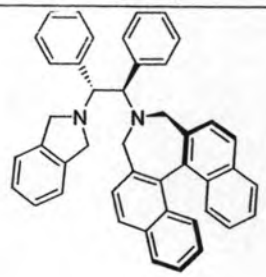
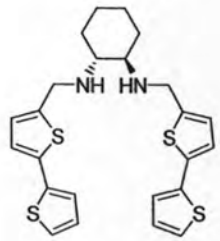
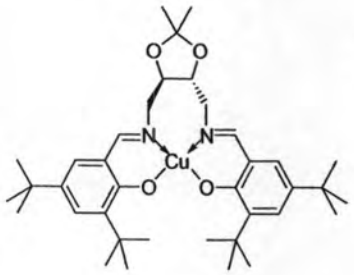
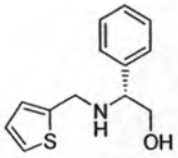
entry	ligand/ catalyst structure	conditions	substrates (RCHO)	yield (%) and ee (%)	year [ref]
1		catalyst (3.3 mol%) THF, -42 °C, 18 h	R = alkyl	79-91% yield 73-90% ee	Shibasaki, 1992 [92]
2		ligand (5.5 mol%) $Cu(OAc)_2 \cdot H_2O$ (5 mol%) EtOH, rt, 4-96 h	R = aryl, alkyl	66-95% yield 87-94% ee	Evans, 2003 [106]
3		catalyst (5 mol%) THF, -35 °C, 24 h	R = aryl, alkyl	56-90% yield 78-93% ee	Trost, 2002 [96,97]
4		ligand/Et_2Zn = 1/2 (5 mol%), THF -25 °C, 8-42 h	R = aryl, alkyl	40-90% yield 21-74% ee	Lin, 2004 [98]
5		ligand/$Zn(OTf)_2$/$^{i}Pr_2EtN$ = 1.5/1/1 (30 mol%) -40/-60 °C, 16-60 h	R = aryl, alkyl	71-92% yield 84-98% ee	Palomo, 2005 [101]
6		ligand/$CuCl_2$ = 1/1 (20 mol%), Et_3N (3 mol%) MeOH, 0 °C, 7-24 h	R = aryl, alkyl	60->95% yield 73-97% ee	Mahes-waran, 2006 [109]

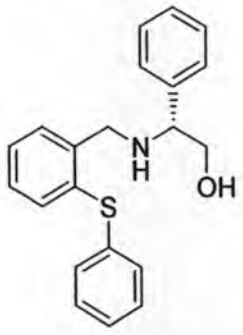
Table 3.23 (cont.)

entry	ligand/ catalyst structure	conditions	substrates (RCHO)	yield (%) and ee (%)	year [ref]
7		ligand/$Cu(OAc)_2$ = 1/1 (5 mol%), *n*-PrOH, rt 24-72 h	R = aryl, alkyl	92->99% yield 91->99.5% ee	Arai, 2007 [110]
8		ligand/$Cu(OAc)_2$ = 1.2/1 (5 mol%), EtOH, 0 °C/rt 16-40 h	R = aryl, alkyl	42-93% yield 81-99% ee	Bandini, 2007 [112]
9		catalyst 10 mol% toluene, rt, 72-84 h	R = aryl, alkyl	40-79% yield 45-84% ee	Gan, 2008 [113]
10		ligand (13.5 mol%) $Cu(OAc)_2 \cdot H_2O$ (15 mol%) ^{i}PrOH, rt, 24-48 h	R = aryl	39-98% yield 61-88% ee	Vilaivan, 2007 [142]

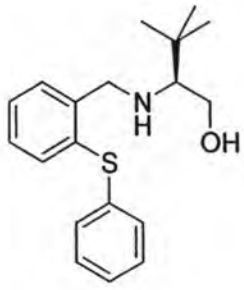
Examples of various ligands for catalytic asymmetric nitro-aldol reaction as shown in the Table 3.23 revealed that the effective ligands or catalysts such as heterobimetallic complex in entry 1, bis(oxazoline) in entry 2, or dinuclearzinc catalyst in entry 3 are suitable catalysts for asymmetric nitro-aldol reaction but some of the ligands or catalysts are large and complex molecules containing multiple stereogenic centers compare to the simple thiophene-based amino alcohol ligand in entry 10.

Furthermore, the use nitroethane for asymmetric nitro-aldol reaction was also investigated. Attempts to analyze racemic product obtained from reaction between 4-nitrobenzaldehyde and nitroethane by using a Daicel Chiralcel OD® column were not successful because the lack of baseline separation. In addition, when a Chiralpak AD-H® column was used to analyze the racemic sample, only one pair of enantiomers was

separated. Nevertheless, nitro-aldol reaction between 4-nitrobenzaldehyde with nitroethane in the presence of thiolated amino-alcohols (*R*)-**69c** and (*S*)-**69d** as ligands, were carried out.



(*R*)-**69c**



(*S*)-**69d**

Chiral ligand (*R*)-**69c** in the presence of copper(II) acetate in 2-propanol as a solvent could smoothly accelerate the reaction between 4-nitrobenzaldehyde and 55 or 10 equiv of nitroethane to obtain the corresponding nitro-aldol product in 98% and 82% yield after 24 h, respectively. Consistent with the reaction performed without any solvent, 98% yield was obtained after 24 h when 10 equiv of nitroethane was used. In an attempt to analyze the product obtained from the use of 55 equiv of nitroethane using a Chiralpak AD-H® column, only one pair of enantiomers was separated with 34% ee.

In the case of chiral ligand (*S*)-**69d**, the $Cu(OAc)_2$-(*S*)-**69d** complex could also accelerate the same reaction when 10 equiv of nitroethane was used both with and without any solvent to obtain the nitro-aldol product in 92% and 94% yield, respectively. Attempts to analyze these products using a Daicel Chiralcel OD® column, HPLC chromatograms showed that there was no difference between the racemic chromatogram and chromatograms processed from the products.

2-Nitropropane was also used in the nitro-aldol reaction. Racemic product obtained from the reaction between 4-nitrobenzaldehyde and 2-nitropropane could be easily analyzed using a Daicel Chiralcel OD® column. The chiral ligand (*R*)-**69c** complexed with copper(II) acetate in 2-propanol as a solvent could give the nitro-aldol product from the reaction between 4-nitrobenzaldehyde and 55 equiv of 2-nitropropane in 30% yield after 6 days. The HPLC chromatogram of this product showed 20% ee of the optical yield.

3.4 Asymmetric borohydride reduction

Schiff's base ligands complexed with $CoCl_2$ to catalyze borohydride reduction of a set of ketone employing the modification of $NaBH_4$ with tetrahydrofurfuryl alcohol (THFA) had been reported by Yamada *et al.*.[143] To expand the utilizing of our chiral amino-alcohol ligands in other asymmetric reactions, the ligands were also tested for enantioselective borohydride reduction. Such reduction of prochiral ketones is one of the most reliable and efficient methods to obtain the corresponding optically active secondary alcohols. Some of the chiral ligands with the structures shown in Figure 3.10 were tested using the conditions shown below.

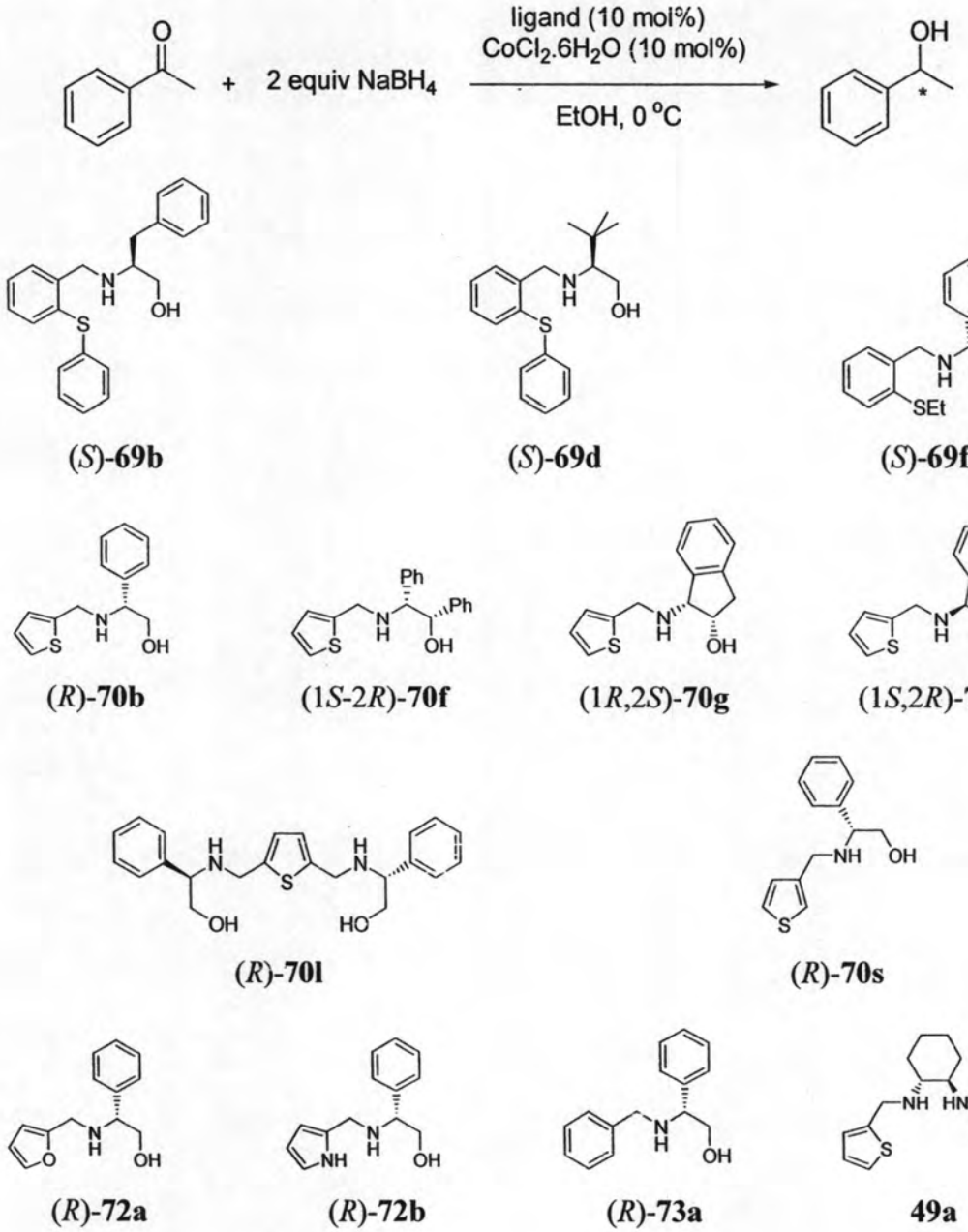
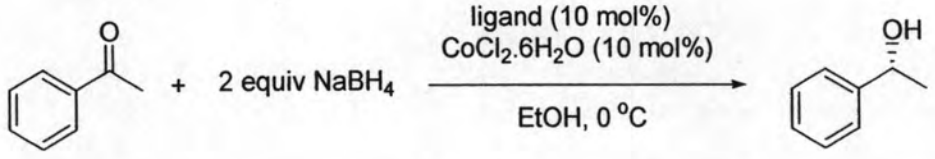
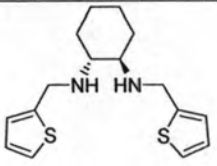
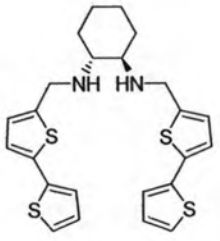
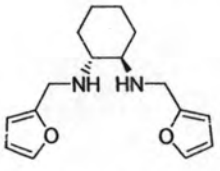
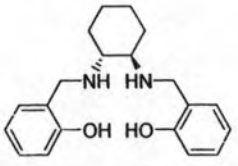


Figure 3.10 The ligands of interest used in asymmetric borohydride reduction

The background reaction of $NaBH_4$ reduction of acetophenone was quite substantial. The reduction could be finished rapidly (0.5 h) when 2 equiv of $NaBH_4$ was used at 0 °C. Under the same screening condition, most of the cobalt(II) complexes of the ligands shown in Figure 3.9 could not induce any enantioselectivity except that of ligand **49a** (96% yield, 64% ee (*R*)-isomer). From this encouraging preliminary study, other chiral diamine ligands were synthesized and evaluated for asymmetric $NaBH_4$ reduction using acetophenone as a substrate model (Table 3.24).

Table 3.24 Effect of the structure of the C_2-symmetrical bis-amino ligands on the efficiency of the borohydride reduction between acetophenone and $NaBH_4$

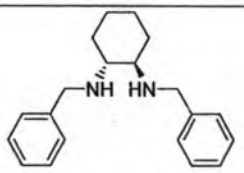
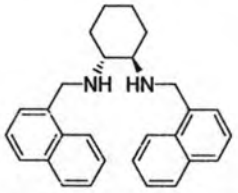


entry	ligands		yield (%)	ee (%)[a]
	code	structure		
1	**49a**		96	64
2[b]	**49b**		>99	61
3	**49c**		94	52
4	**49d**		94	0

[a] Enantiomeric excess was determined by chiral GC analysis.

[b] The precipitate of complex was happened when complex was preformed *in situ* for 5 min at room temperature.

Table 3.24 (cont.)

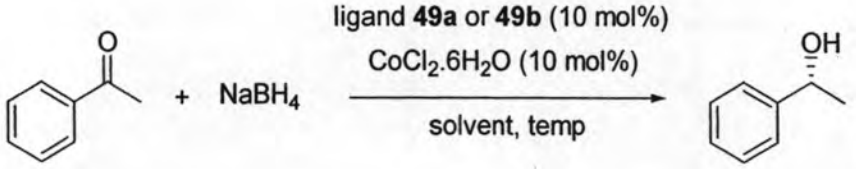
entry	ligands		yield (%)	ee (%)[a]
	code	structure		
5	**49e**		93	45
6[b]	**49f**		85	40

[a] Enantiomeric excess was determined by chiral GC analysis.

[b] The precipitate of complex was happened when complex was preformed *in situ* for 5 min at room temperature.

The results from Table 3.24 revealed that chiral bis-amino ligands bearing mono- and oligothiophene ring, **49a** and **49b**, respectively could induce the enantioselectivity of the reduction in moderately good enantiomeric excess (entries 1 and 2). The chiral ligands **49c** and **49e** possessing furan and phenyl in place of the thiophene rings afforded the reduction product with decreased enantioselectivity (entries 3 and 5). Disappointingly, no selectivity was observed when reduced salen ligand (**49d**) was employed (entry 4). When the bulkiness of the aromatic ring in the chiral ligand increased, the enantioselectivity decreased (entry 5 *vs* entry 6). From the results shown above, the chiral ligands **49a** and **49b** were selected to optimize the reaction conditions to improve the enantioselectivity of the reduction.

Table 3.25 Effect of the reaction parameters on the efficiency of the borohydride reduction between acetophenone and $NaBH_4$ catalyzed by Co(II) complexes of chiral ligand **49a** or **49b**



entry	reaction conditions			ligand			
				49a		49b	
	$NaBH_4$ (equiv)	solvent	temp (°C)	yield (%)	ee (%)	yield (%)	ee (%)
1	2	EtOH	0	96	64	>99	61
2	1.2	EtOH	0	98	64	97	59
3	2	MeOH	0	95	29	97	29
4	2	^{i}PrOH	0 to rt	87	36	90	8
5[a]	2	EtOH	-20	97	65	93	62
6[b]	2	EtOH	-50	96	69	-	-
7[c]	2	EtOH	-75	87	68	-	-
8[d]	1.2	EtOH	0	93	0	-	-

[a] The reaction was finished within 0.5 h.

[b] The reaction was finished within 1 h.

[c] The reaction was finished over 4 h.

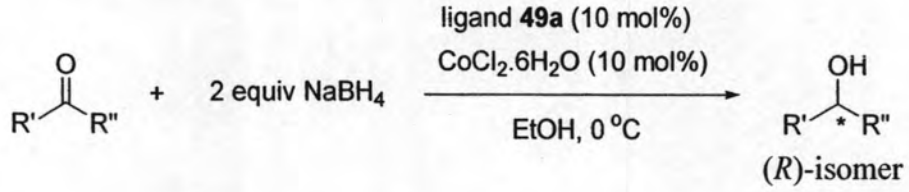
[d] The reaction was performed without $CoCl_2 \cdot 6H_2O$. Ligand and 1.2 equiv of $NaBH_4$ were dissolved in EtOH and stirred for 1 h at room temperature before cool down to 0 °C.

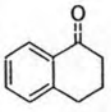
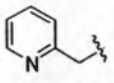
Table 3.25 showed the yield and selectivity of the secondary alcohol obtained from various conditions by varying the amount of $NaBH_4$, solvent, and temperature. From the results, the selectivities were not different when quantity of $NaBH_4$ was reduced from 2 to 1.2 equivalent (entry 1 *vs* entry 2). The enantioselectivities decreased in methanol and 2-propanol therefore ethanol was the solvent of choice to improve the enantioselectivity (entry 1 *vs* entries 3 and 4). The enantioselectivity could not be further improved by lowering the temperature (entries 5-7) and no enantioselectivity was observed when chiral ligand was used alone in the reaction (*i.e.*, without $CoCl_2$ added) (entry 8). In summary, after optimization, the best reaction

conditions for the asymmetric borohydride reduction were: cobalt(II) complex of chiral ligand **49a** as catalyst, ethanol as a solvent, reaction temperature 0 °C.

The Co(II)-**49a** complex was used to catalyze asymmetric borohydride reduction of other ketone substrates under the optimized conditions. A variety of aromatic ketones and derivatives were tested to expand the scope of the reaction. The results are summarized in Table 3.26.

Table 3.26 Reduction of various ketones with $NaBH_4$ catalyzed by Co(II)-**49a** complex under the optimized conditions



entry	ketone		yield (%)	ee (%)[a]
	R′	R″		
1	Ph	Me	96	64
2[b]	2-OH-Ph	Me	27	31
3	2-Br-Ph	Me	>99	49
4	2-OMe-Ph	Me	>99	69
5	2-thienyl	Me	68	47
6	Ph	Et	97	70
7	Ph	CH_2Cl	23	30
8	1-naphthyl	Me	85	76
9	2-naphthyl	Me	>99	75
10[c]			83	27[d]
11[c]	Ph	CH_2CO_2Et	23	0[d]
12[c]		Ph	56	5[d]

[a] Enantiomeric excess was determined by chiral GC analysis.

[b] Starting material was already consumed.

[c] The reaction was performed at 0 °C to room temperature overnight.

[d] Enantiomeric excess was determined by chiral HPLC.

As shown in Table 3.26, Co(II)-**49a** complex could induce the reduction of the secondary alcohols with low to good selectivities (*R* as a major isomer). Disappointingly, in the case of β-keto ester and 2-phenacylpyridine were used as substrates; no selectivity was observed (entries 11 and 12). It is possible that these substrates, carrying additional chelating groups, could interfere with the normal ligand coordination site and cause decreased enantioselectivity.

Yamada *et al.* [143] have proposed a possible mechanism to explain the observed enantioselectivity in asymmetric reduction with (*S*,*S*)-cobalt complex. The observed enantiofacial selection of the corresponding (*S*)-alcohols to the (*S*,*S*)-cobalt complexes (*re* attack) can be explained by considering the favorable transition state illustrated in Figure 3.11.

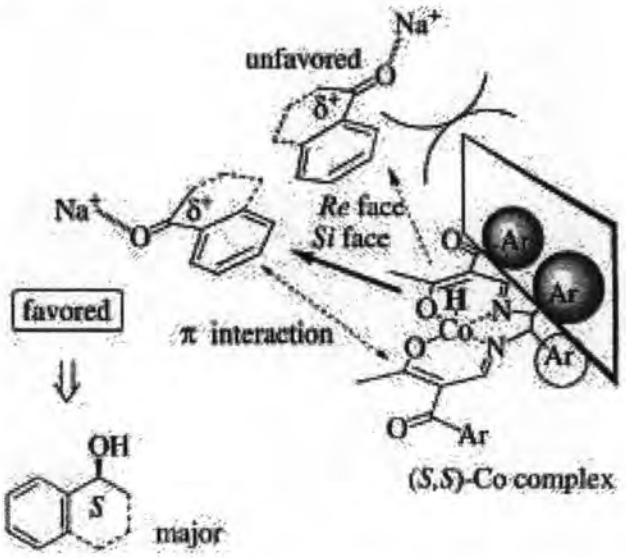
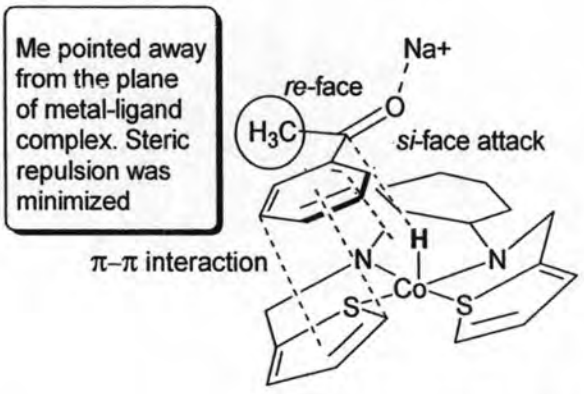


Figure 3.11 Possible mechanistic explanation for the observed enantioface selection in asymmetric reduction with (*S*,*S*)-cobalt complex [143]

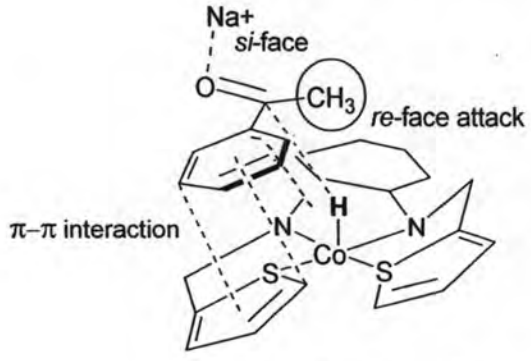
As illustrated in Figure 3.11, the substrates aryl ketones would approach the postulated cobalt-hydride through the open site (*re* attack) to obtain *S* isomer. The aromatic ring of the aryl ketones was placed parallel to the square delocalized π system plane of the cobalt complex by π interaction. Because π-π interaction occurred efficiently between the catalyst and aromatic ketone, the reduction of the aryl ketone proceeded faster than the alkyl ketone in the catalytic system.[143] The approaching carbonyl group of the substrates was oriented away from the cobalt complex to avoid any steric hindrance by the bulky aryl groups. The alternative transition state (*si*

attack) is not rationalized because of the steric repulsion of the bulky aryl groups of the complex with the carbonyl group from the incoming ketones.

In our system, cobalt(II) complexes of chiral ligands possessing (*R*,*R*)-cyclodiamine were used as catalysts for asymmetric borohydride reduction of acetophenone to give the *R* secondary alcohol as a major isomer. Based on the experimental observations previously reported, proposed transition state models, which account for the absolute configuration of the products obtained with ligands C_2-symmetrical diamine ligand are as shown in Figure 3.12.



Favorable transition state



Unfavorable transition state

Figure 3.12 Proposed transition state models for the cobalt-catalyzed enantioselective borohydride reduction with ligand **49a**

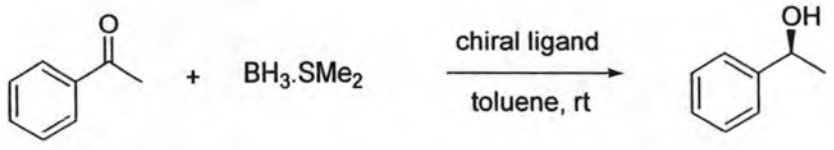
Ligand **49a** possessing (*R*,*R*)-cyclohexanediamine moiety complexed with cobalt(II) chloride led to the opposite enantiomer of the optical product compared to similar (*S*,*S*)-cobalt complex reported by Yamada. The transition state models involved π-π interactions between thiophene unit and phenyl group of acetophenone. Thus, there were two major possibility of coordination between acetophenone and Co(II) complex. These two orientations resulted in the different selectivity. A sensible

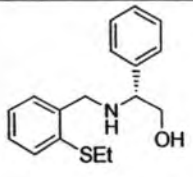
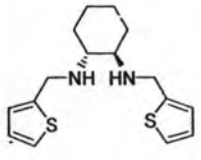
reason to explain these results was that in the favorable transition state model, the methyl group of acetophenone would point away from the plane of metal-ligand complex in order to avoid steric repulsion. Therefore, transfer of the hydride ion would occur at the *si* face of the carbonyl group and lead to the (*R*)-secondary alcohol. On the other hand, in the unfavorable transition state, the *S* isomer would be observed if methyl group should be positioned in such a way. Due to steric interaction between the methyl group and the plane of complex developed in such orientation, the disfavored isomer (*S* isomer) was formed as the minor product.

3.5 Asymmetric borane reduction

Lee *et al.* have recently shown that chiral aminoalcohol ligands are effective in enantioselective reduction of ketones when used in combination with borane-dimethyl sulfide complex without any metal catalysts. This reaction is analogous to the famous Corey's oxazoborolidine catalysts [144] and a similar mechanism has been proposed. Following the protocol described by Lee *et al.* [129], the enantioselective reduction of acetophenone using selected chiral ligands synthesized in this work with $BH_3 \cdot SMe_2$ as a hydride source was attempted. The results are as shown in Table 3.27.

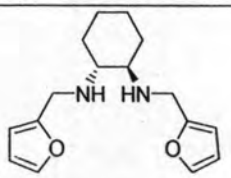
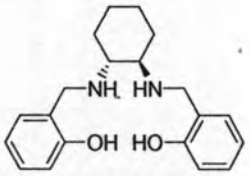
Table 3.27 Metal-free asymmetric reduction of acetophenone with $BH_3 \cdot SMe_2$ using selected chiral ligands[a]



entry	ligand (10 mol%) code	ligand (10 mol%) structure	yield (%)	ee (%)
1	(*R*)-**69f**		85	5
2	**49a**		72	8

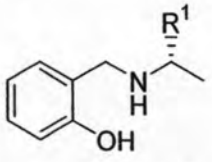
[a] The stoichiomeric ratio of ketone:chiral ligand:$BH_3 \cdot SMe_2$ was 1.0:0.1:1.1 in the reaction above. The reactions were allowed to stir overnight.

Table 3.27 (cont.)

entry	ligand (10 mol%) code	ligand (10 mol%) structure	yield (%)	ee (%)
3	**49c**		51	15
4	**49d**		74	0

[a] The stoichiomeric ratio of ketone:chiral ligand:$BH_3 \cdot SMe_2$ was 1.0:0.1:1.1 in the reaction above. The reactions were allowed to stir overnight.

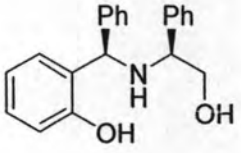
From Table 3.27 it was found that all ligand tested gave disappointingly poor enantioselectivities. Compared to the results obtained by Lee [129] this may not be surprising since bidentate ligands were generally found to give low enantioselectivities. Under the same reaction condition, Lee revealed that chiral ligands **78a-78c** with two donor atoms generated product, 1-phenylethanol with only low enantioselectivity (<20% ee). The ligand **64c** with three donor atoms gave significantly improved enantioselectivity (68% ee). Since the initial results obtained were disappointing compared to the Co-catalyzed reduction, this reaction has not been investigated further.



78a: R^1 = Ph

78b: R^1 = ^{i}Pr

78c: R^1 = ^{t}Bu

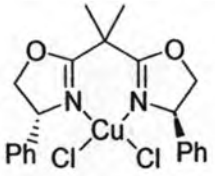


64c

3.6 Asymmetric benzoylation

Enantiospecific acylation of alcohols is a very synthetically useful reaction. Enantiotopic hydroxyl groups of racemic secondary alcohols should in principle be acylated in different rate under an influence of a chiral catalyst. Traditionally this transformaion is carried out using nucleophilic catalysts such as chiral DMAP

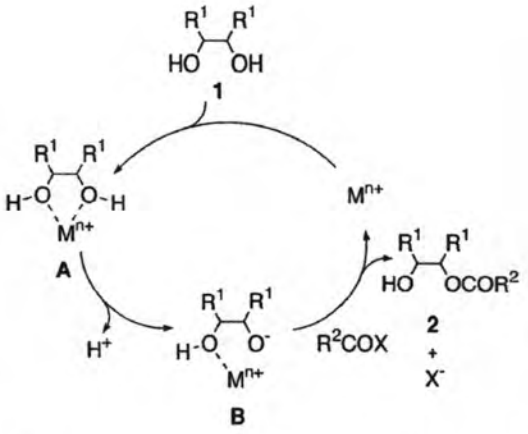
derivatives [145] or other chiral bases.[146] Recently, metal-catalyzed variants have been developed especially by Cu(II). Kinetic resolution of *trans*-(±)-1,2-diol by Cu(II)-bis(oxazoline) catalyzed selective benzoylation was reported by Matsumura *et al.*[136] and Reiser *et al.*[137]. Reiser had reported the use of novel bisbenzyl-substituted aza(bisoxazoline) ligand immobilized on $MeOPEG_{5000}$ to catalyze the same reaction, allowing facile recovery of the catalyst.



79

80

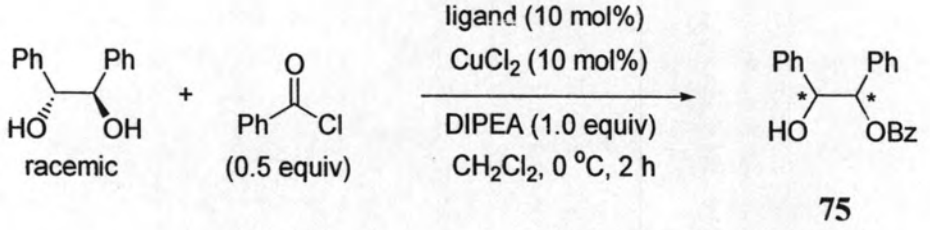
A mechanism for this reaction has been proposed.[136] It was suggested that the enantiodiscrimination mainly takes place during the acylation step (**2** from **B** in Scheme 3.3).



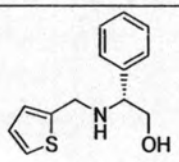
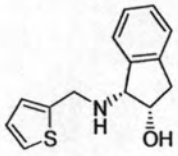
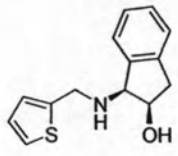
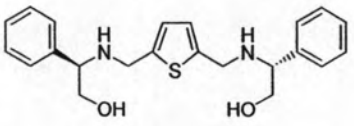
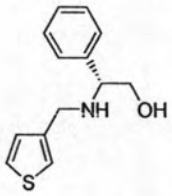
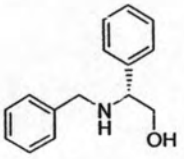
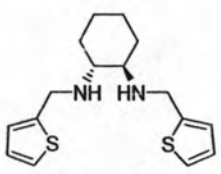
Scheme 3.3 The reaction mechanism of kinetic resolution of (±)-diols proposed by Matsumura *et al.*[136]

Under the same screening conditions described by Reiser, [137] selected chiral ligands were tested to search whether they are suitable ligands for kinetic resolution of 1,2-diols. Racemic hydrobenzoin was chosen as the model compound. Benzoylation using 0.5 equivalents of benzoyl chloride in the presence of catalyst should produce monobenzoylation product (**75**) with some enantiomer preference (Table 3.28).

Table 3.28 Cu(II)-catalyzed asymmetric benzoylation of (±)-hydrobenzoin in the presence of the various ligands of interest



75

entry	ligand		monobenzoylated product (75)		
	code	structure	yield (%)[a]	$[\alpha]_D^{20}$ (*c* 1.00, MeOH)[b]	config
1	(*R*)-**70b**		47	+29.5	*S,S*
2	(1*R*,2*S*)-**70g**		38	+11.2	*S,S*
3	(1*S*,2*R*)-**70h**		38	-5.9	*R,R*
4	(*R*)-**70l**		42	+73.8	*S,S*
5	(*R*)-**70s**		43	+21.7	*S,S*
6	(*R*)-**73a**		32	+24.2	*S,S*
7	**49a**		31	+60.5	*S,S*

[a] Isolated yield based on diol.

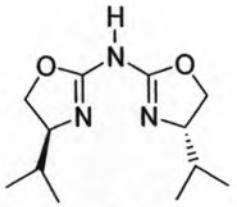
[b] lit. $[\alpha]_D^{20}$ -85.6 (*c* 1.37, MeOH), (*R,R*)-isomer, >99% ee.[137]

The results from Table 3.28 revealed that successful kinetic resolution of (±)-hydrobenzoin was achieved by benzoylation in the presence of copper(II) chloride and the chiral ligands (10 mol%) as catalysts generated *in situ*. These catalysts gave the monobenzoylated product (**75**) in 31-47% yield based on diol. Ligands which showed the best enantioselectivity in this asymmetric benzoylation were the C_2 symmetrical ligands, (*R*)-**70l** and **49a** (entries 4 and 7). In favorable cases, the results are comparable to those reported in the literature.[137]

Reiser reported the use of PEG-bound aza(bisoxazoline) catalyst **80** (0.7 mol%) to catalyze benzoylation of (±)-hydrobenzoin gave the **75** in 41% yield and >99% ee (cycle 1). The specific rotation of this product (>99% ee) was -85.6 (c = 1.37, CH_3OH) (*R* as a major isomer). The product **75** obtained from using chiral ligands (*R*)-**70l** and **49a** showed the specific rotation values of +73.8 (86% ee) and +60.5 (71% ee), respectively (c = 1.00, CH_3OH) (*S,S* as a major isomer). From preliminary results, it seems that the enantioselectivity of the product were quite good. However, since the suitable condition for chiral HPLC or chiral GC sepearation of the monobenzoylated benzoin has not yet been found, the enantioselectivities were determined by optical rotation. Attempts are still being made to find a more reliable method to determine the enantioselectivity

3.7 Michael additions of indole to benzylidene malonate

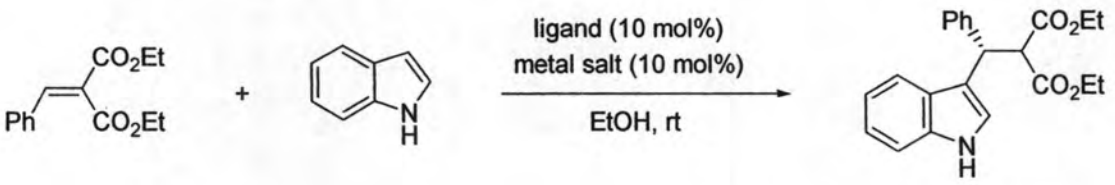
Since indole derivatives are considered as privileged structures in pharmaceutical drugs, asymmetric Friedel-Crafts alkylations of indoles are of considerable interest. Reiser *et al.* reported asymmetric Michael additions of indole to benzylidene malonate using simple azabis(oxazoline) ligands (**81**) complexed with copper(II) triflate. Under the optimized condition, the catalyst obtained from chiral ligand **81** (5 mol%) complexed with $Cu(OTf)_2$ (4.8 mol%) could induce the enantioselectivity of Michael product (**76**) with 97% yield and >99% ee within 8 h (*S* isomer). They found that excess of chiral ligand is detrimental for this reactions and should be avoided.[138]



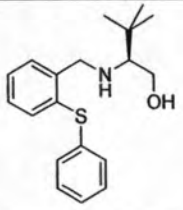
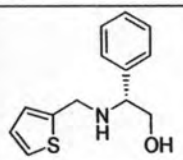
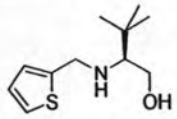
81

The initially study involved selected ligands which were tested to search for suitable ligands for this reaction. Tests included various metal salts to optimize the conditions. The reaction between indole and benzylidene diethylmalonate was chosen. The results are shown in Table 3.29.

Table 3.29 Asymmetric conjugate addition between indole and benzylidene diethyl malonate



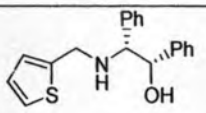
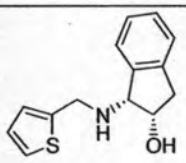
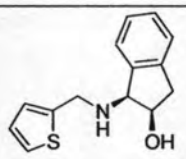
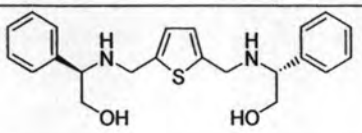
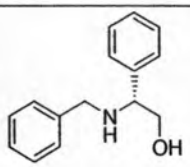
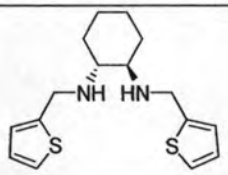
76

entry	ligand code	ligand structure	metal salt	yield (%)[a]	ee (%)[b]
1	(*S*)-**69d**		$Cu(OTf)_2$	78	0
2	(*S*)-**69d**		$Fe(OAc)_2$	no reaction	-
3	(*R*)-**70b**		$Cu(OTf)_2$	70	13
4	(*R*)-**70b**		$Cu(ClO_4)_2 \cdot 6H_2O$	75	12
5	(*R*)-**70b**		$Cu(OAc)_2 \cdot H_2O$	9	7
6	(*S*)-**70j**		$Cu(OTf)_2$	83	0
7	(*S*)-**70j**		$Fe(ClO_4)_2 \cdot 6H_2O$	62	3
8	(*S*)-**70j**		$Fe(OAc)_2$	no reaction	-

[a] The reactions were performed at room temperature for 168 h (entries 1-8) or 48 h for entries 9-15.

[b] Enantiomeric excess was determined by chiral HPLC.

Table 3.29 (cont.)

entry	ligand		metal salt	yield (%)[a]	ee (%)[b]
	code	structure			
9	(1*S*,2*R*)-**70f**		$Cu(OTf)_2$	62	3
10	(1*R*,2*S*)-**70g**		$Cu(OTf)_2$	67	14
11	(1*S*,2*R*)-**70h**		$Cu(OTf)_2$	70	13[c]
12	(*R*)-**70l**		$Cu(OTf)_2$	69	31
13	(*R*)-**70l**		$Cu(OTf)_2$	88	13[d]
14	(*R*)-**73a**		$Cu(OTf)_2$	71	9
15	**49a**		$Cu(OTf)_2$	89	46

[a] The reactions were performed at room temperature for 168 h (entries 1-8) or 48 h for entries 9-15.

[b] Enantiomeric excess was determined by chiral HPLC.

[c] *R* is major isomer.

[d] The ligand/metal ratio = 1:2.

Preliminary investigation started with the use of chiral ligands, (*S*)-**69d** and (*R*)-**70b**. Ligand (*R*)-**70b** complexed with $Cu(OTf)_2$ could render the asymmetric reaction giving rise to 13% ee in the product while ligand (*S*)-**69d** failed to give significant enantioselectivity (entry 1 *vs* entry 3). When the counter ion ClO_4^- was used, no change in selectivity was observed (entry 3 *vs* entry 4). When $Cu(OAc)_2 \cdot H_2O$-(*R*)-**70b** complex was employed, poor yield and decreased selectivity were obtained (entry 5). Ligand (*S*)-**70j** possessing ^{t}Bu group complexed with $Cu(OTf)_2$ could not induce the enantioselectivity of the product although good yield was obtained compared to ligand (*R*)-**70b** (entry 3 *vs* entry 6). When metal salt was

changed from $Cu(OTf)_2$ to $Fe(OAc)_2$ no reaction was observed (entry 1 *vs* entry 2) and (entry 6 *vs* entry 8). The results from metal survey showed that $Cu(OTf)_2$ was the suitable metal, which is in good agreement with that reported by Reiser.[138] The results from chiral ligand survey of the asymmetric 1,4-addition of indole to benzylidene diethylmalonate from Table 3.29 revealed that C_2 symmetrical ligands, (*R*)-**70l**, when complexed with $Cu(OTf)_2$ in 1:1 ratio could induce enantioselectivity in the products with significant selectivity (31% ee, entry 12) but when the ligand/metal ratio was decreased to 1:2 the selectivity was decreased substantially (13% ee, entry 13). The C_2-symmetrical ligand **49a** showed the best result in selectivity (46% ee, entry 15). The results described above showed that the selectivity of chiral ligands used here for the asymmetric 1,4-addition to benzylidene malonate with indole could not compete with the C_2-symmetrical bis(oxazoline) ligands.