Catalytic, Enantioselective Michael Addition Reaction

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

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DIVISION OF ORGANIC SYNTHESIS

NATIONAL CHEMICAL LABORATORY

PUNE 411 008

AUGUST 2002

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "Catalytic, Enantioselective Michael Addition Reaction" submitted by Mr. Sushil C. Jha was carried out by him under my supervision at National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged.

Date: 21st Aug, 2002

National Chemical Laboratory, (Dr. N. N. Joshi)

Pune – 411 008 Research Guide

Acknowledgements

I want to take this opportunity to thank my guide Dr. N. N. Joshi, for introducing me to the wonderful and exciting world of asymmetric synthesis. His encouraging presence and constant emphasis at the minutest details immensely helped me into presenting this piece of work.

I would like to thank Dr. Ganesh Pandey and Prof. D. Basavaiah who generously provided their HPLC facility. I am also thankful to Dr. K. N. Ganesh (Head, Division of Organic Synthesis) for his valuable suggestions during my research work.

My thanks are also to my lab-mate and my senior Dr. Kavirayani R. Prasad, who taught me the practical nitty-gritty's of experimentation during our short association.

My sister Rani Jha has been a nice companion throughout graduation and post-graduation.

I am thankful to Dr. Trusar D. Bagul for his help in getting the HRMS data for my compounds.

Mr. A. G. Samuel (Retd.) helped me by teaching the operation of NMR machine. I must thank Mrs. V. Kale for providing me IR spectra and Mrs. Shantakumari for Mass spectra.

My lab-mate Anamitra Chatterjee assisted me throughout the thesis-writing period. I thank him for all his efforts.

I am thankful to Dr. R. P. Jain, Iliyas, Anand, Sureshan, Dhananjoy, Sidhtharth, Madhuri, Rodney, Aditya and Kartick who have been good friends and have generously helped in many ways whenever needed.

I thank Council for Scientific and Industrial Research (CSIR), New Delhi for the financial assistance and Director, NCL for allowing me to work in this laboratory.

Sushil Chandra Jha

General Remarks

All the melting points are uncorrected and determined in centigrade scale on Yamaco micro melting point apparatus.

Infrared spectra were recorded on FTIR-8400 Shimadzu spectrophotometer.

^{1}H-NMR spectra were recorded at 200 MHz using tetramethylsilane as an internal standard in $CDCl_3$ on a Bruker-AC-200 machine.

^{13}C-NMR spectra were recorded at 50 MHz with $CDCl_3$ ($\delta = 77$ ppm) as the reference.

Chemical shifts are reported in parts per million (ppm) on δ scale. The abbreviations s, d, t, q, m, refer to the singlet, doublet, triplet, quartet and multiplet respectively. Coupling constants wherever mentioned, have been given in Hz.

Mass spectra were recorded on Fenningan-MAT-1020B instrument at an ionization voltage of 70 eV. FAB-Mass was recorded on VG-ZAB mass-spectrometer.

TLC was performed on Merck precoated silicagel $60F_{254}$ plates.

Column chromatography was performed on silica gel (200-400 mesh) supplied by Merck.

Optical rotations were measured on a JASCO DIP-181 digital polarimeter.

HPLC analysis was performed on a Shimadzu LC-10AD equipped with SPD-10A UV-VIS detector using special grade solvents.

Abbreviations

BINOL	: 2,2'-dihydroxy-1,1'-binaphthyl
NOBINOL	: 2-amino-2'-hydroxy-1,1'-binaphthyl
HMDS	: 1,1,1,3,3,3-hexamethyldisilazane
HMTS	: hexamethylenetetramine
PPTS	: pyridinium para-toluene sulphonate
TMEDA	: *N,N,N',N'*-tetramethylethylenediamine
TMSCl	: chlorotrimethylsilane
$LiAlH_4$	: lithium aluminium hydride
Red-Al®	: sodium bis(2-methoxyethoxy)aluminium hydride
THF	: tetrahydrofuran
CH_2Cl_2	: dicholoromethane
$CHCl_3$	: choloroform
$CDCl_3$	: deuterated chloroform
MeOH	: methanol
EtOH	: ethanol
DMSO	: methyl sulfoxide
AcOH	: acetic acid
ee	: enantiomeric excess
m.p.	: melting point
rt.	: room temperature

ABSTRACT

Catalytic, Enantioselective Michael Addition Reaction

Amongst asymmetric reactions stereoselective formation of C-C bond is of paramount interest. In recent years asymmetric metal catalysis has been intensively studied and several efficient methods for the synthesis of enantiomerically pure compounds have been developed.

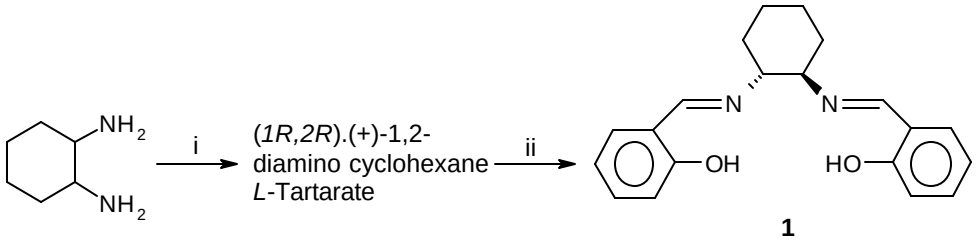
Our work which is based on catalytic enantioselective Michael addition reactions is divided into three chapters:

Chapter-I : This chapter provides background to the present work by reviewing the literature on catalytic enantioselective Michael addition of soft nucleophiles to *a,ß*-unsaturated systems.

Chapter- II : Heterobimetallic catalyst for Michael addition

The concept of heterobimetallic catalyst in organic transformation was introduced by Noyor*i* et. al. for the addition of diethylzinc to aldehydes, and perfected by Shibasaki et. al. for stereoselective Michael addition reactions. We planned to design new heterobimetallic catalysts for asymmetric Michael reactions. At the onset, heterobimetallic complexes based on chiral diols and Red-Al [sodium bis(2-methoxyethoxy)aluminium hydride] were made. Although these new complexes catalyzed the Michael reaction the product was obtained with low enantioselectivity.

Recently heterobimetallic complexes based on SALEN ligands has received wide attention, however their use in Michael reaction remained unexplored. This prompted us to examine aluminium-SALEN complex. The chiral SALEN we chose was (*1R,2R*)-bis(salicylaldehyde)-*trans* cyclohexyl diamine (Scheme 1).

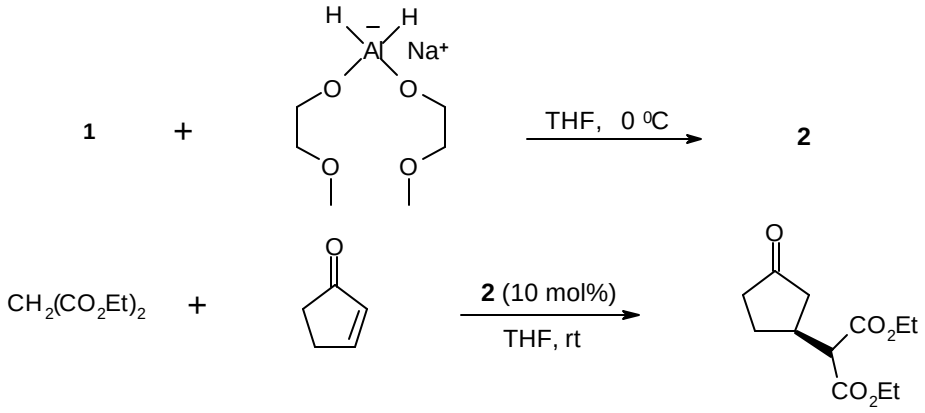


1

(i). *L*-Tartaric acid; (ii). salicylaldehyde, K_2CO_3

Scheme 1

SALEN **1** was reacted with Red-Al® and the resulting complex was used as a catalyst (Scheme 2).

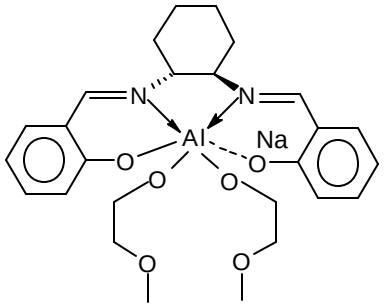


Scheme 2

3 (78% *ee*)

To our surprise, $[a]_D$ value of the Michael adduct obtained was found to be much higher than the one reported in literature. These compounds were not well resolved by chiral HPLC-column. We could eventually estimate the enantiomeric excess of the product through the ^{1}H NMR of their diastereomeric ketals.

Following tentative structure was proposed for the catalyst.

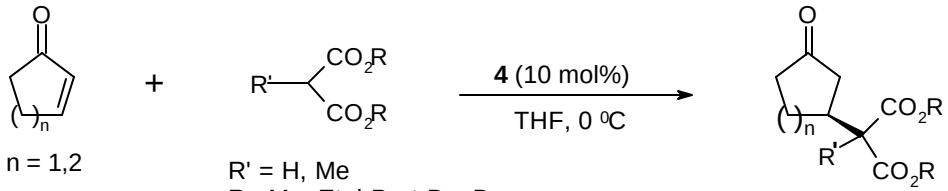


4

A catalytic cycle based on the concept of Bronsted base-Lewis acid was proposed for the reaction. We rationalized that the aluminium alkoxide (or phenoxide) moiety would act as a Lewis acid and the sodium alkoxide (or phenoxide) as a Bronsted base.

We also studied the Michael addition using sterically different malonate esters.

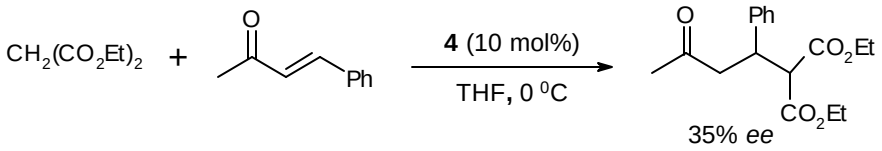
Addition of malonate esters to cycloalkenones in the presence of complex **4**



R' = H, Me
R= Me, Et, i-Pr, t-Bu, Bn

33-58% ee

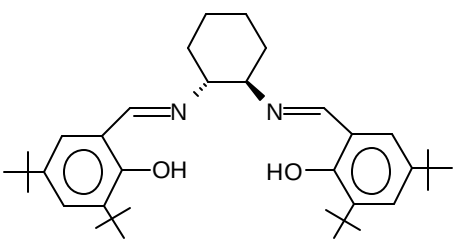
Complex **4** also catalyzed the addition of diethylmalonate to benzylidene acetone (eqn. 1).



35% *ee*

(1)

To study the steric and electronic factors, modified SALEN ligands **5** and **6** were made as shown in Scheme 3.



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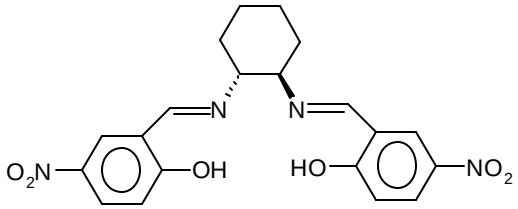

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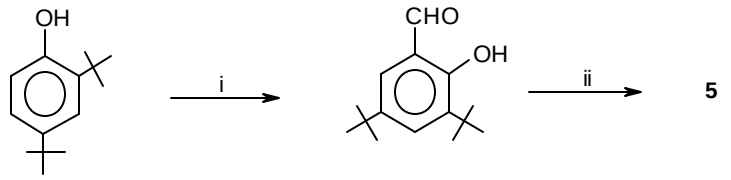
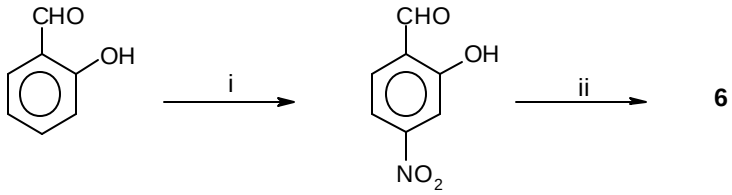


(i). a: HMTA, AcOH, 130 ^{o}C ; b: H_2SO_4(30%), 110 ^{o}C
ii. (*1R,2R*).(+)-1,2-diaminocyclohexane *L*-tartarate

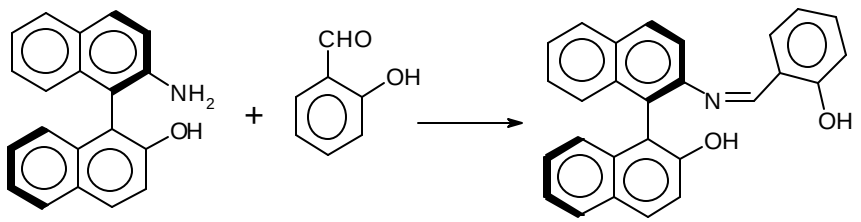


i. a: AcOH / HNO_3 ; b: crystallisation
ii. (*1R,2R*).(+)-1,2-diamino cyclohexane *L*-tartarate

Scheme 3

These ligands were reacted with Red-Al® to obtain the corresponding heterobimetallic complexes. However neither of the two proved to be superior to the parent catalyst **4**.

In yet another attempt, a new ligand **7** based on NOBINOL was made (eqn. 2).



(2)

7

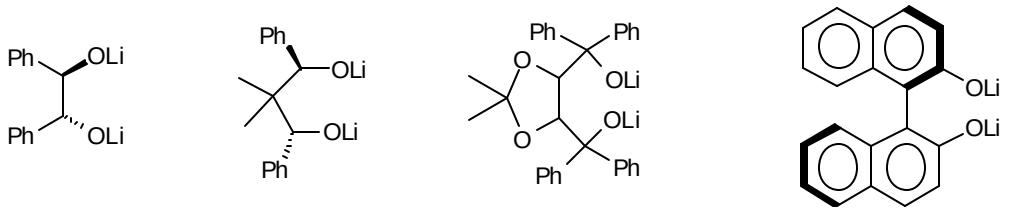
Heterobimetallic complex prepared from **7** and Red-Al® though catalyzed the addition of thiophenol to cyclohexenone, the product was of low enantiomeric excess (< 6%).

We have thus examined a variety of sodium aluminium–SALEN complexes as heterobimetallic catalyst for Michael reaction. Although enantioselectivities are modest, this is conceptually a new catalyst system.

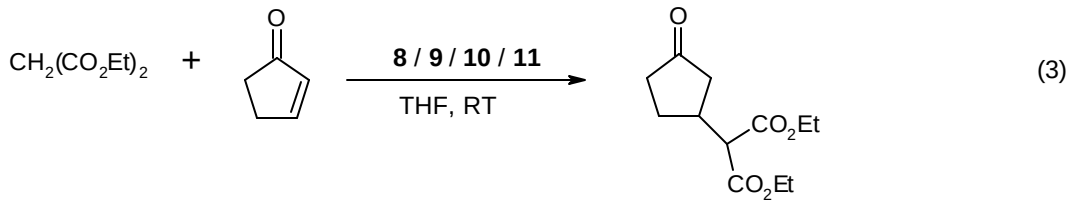
Chapter-III: Homobimetallic catalyst for Michael addition

Our interest in homobimetallic catalyst stems from two recent reports; one by Trost et. al. where zinc based homobimetallic complex was used for a direct catalytic enantioselective aldol reaction and the other by Nevalainen et. al. where aluminium based homobimetallic catalyst was used for generating aldol adducts of aldehydes from aldol adducts of ketones.

In the present work, various chiral diols were selected and their dilthio salts were examined as possible catalyst (eqn. 3).



8 **9** **10** **11**

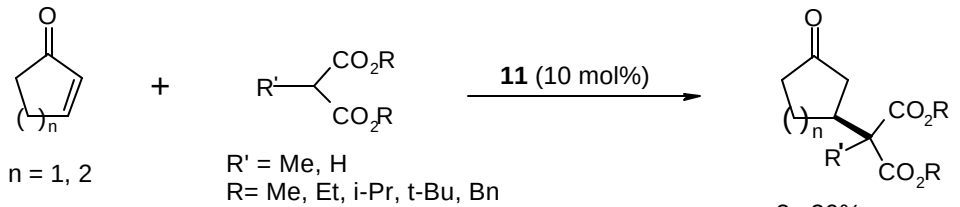


(3)

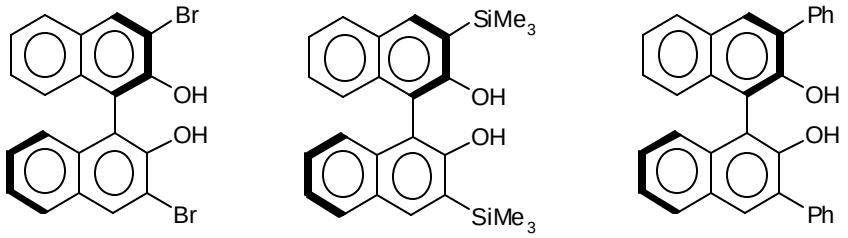
Amongst these salts, **11** proved to be an efficient promoter to give product in 12% *ee.* To account for the product formation and resulting optical induction, a catalytic cycle based on the concept of Bronsted base - Lewis acid was postulated. To justify the proposed cycle lithium salt of mono-O-methoxy BINOL was made which failed to catalyze the reaction. A maximum *ee* of 18%

was obtained with 10 mol% of the catalyst. Also studied was the effect of external additives. Both polar protic as well as chelating amine additives proved counter productive for the reaction. We next studied the Michael reaction using sterically varying malonate esters.

Addition of malonate esters to cycloalkenones in the presence of complex **11**

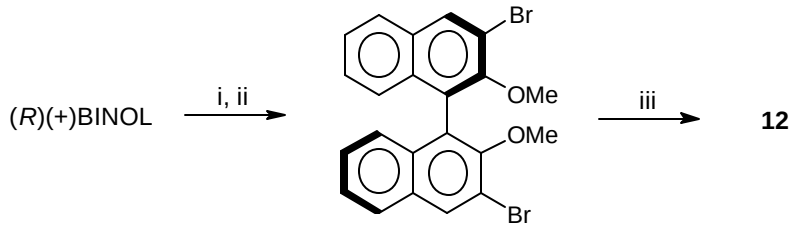


Molecular weight of the active dilithio BINOLate was found to be around 800 which corresponds to the dimeric nature of the catalyst in solution. We reasoned that substituents at 3,3'-positions will result into a well defined monomeric catalytic structure. BINOL derivatives (**12**–**14**) were therefore synthesized.



12 **13** **14**

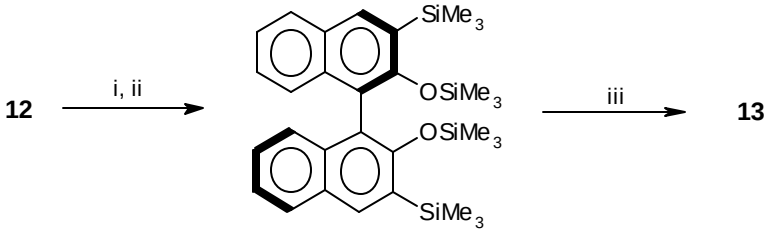
Derivative **12** was made using the following strategy (Scheme 4).



(i). K_2CO_3 , MeI / acetone ; (ii).a: TMEDA / Et_2O , BuLi ; b: Br_2 / hexane , -78 ^{0}C ;
(iii). BBr_3/ CH_2Cl_2

Scheme 4

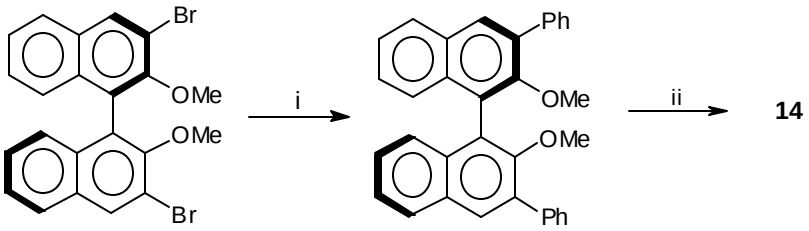
Compound-**12** thus obtained was used for making derivative-**13** (Scheme 5).



(i). HMDS, H_2SO_4 ;(ii). Na, toluene ;(iii). K_2CO_3 / acetone

Scheme 5

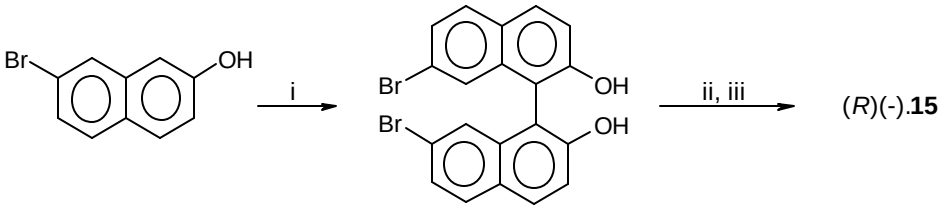
3,3'-Diphenyl derivative was made *via* Suzuki coupling reaction (Scheme 6).



(i). $Pd(PPh_3)_4$, $PhB(OH)_2$, $Na_2CO_3(aq)$, EtOH / DME ; (ii). BBr_3 / CH_2Cl_2

Scheme 6

We also made 7,7'-dibromo BINOL derivative as this results in increase in the bite angle at the reaction center (scheme 7).

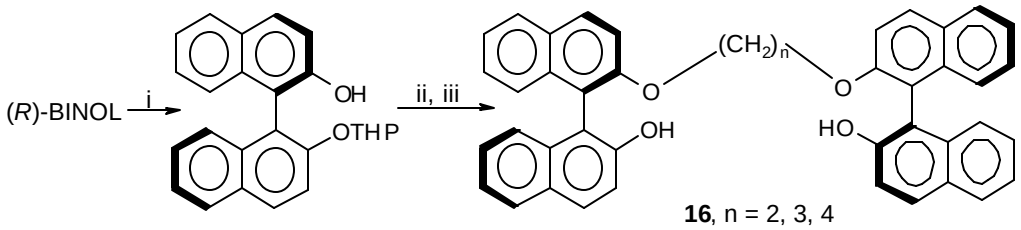


(±)-**15**

(i). $CuCl_2$ / t-$BuNH_2$, MeOH ; (ii). menthyl chloroformate, NEt_3 ; (iii). KOH / MeOH

Scheme 7

A new series of bis-BINOL derivatives(**16**) where the two BINOL moieties grooved together *via* hydroxyl functionality was also synthesized (scheme 8).



16, n = 2, 3, 4

(i). DHP, PPTS(cat) / CH_2Cl_2 ; (ii). TsO-$(CH_2)_n$-OTs , K_2CO_3 , DMF ; (iii). PPTS / EtOH

Scheme 8

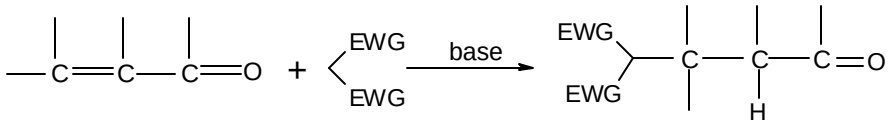
The above-described derivatives(**12**–**16**) though efficiently catalyzed the standard Michael addition, product obtained showed low enantioselectivity. It is thus evident that the parent dimeric dilithio BINOLate is a superior catalyst than any other monomeric derivatives. A complex three-dimensional structure of the catalyst in solution is perhaps responsible for the enantioselectivity.

Research Guide
(Dr. N. N. Joshi)

Research Student
(Sushil C. Jha)

CHAPTER – 1
Catalytic, Enantioselective Michael Addition Reaction

Michael addition reaction refers to the addition of carbanion to unsaturated systems in conjugation with an activating group. As enormous amount of work has been documented in this area[1], we will survey only the work involving catalytic enantioselective addition of stabilized soft nucleophiles (eqn. 1).

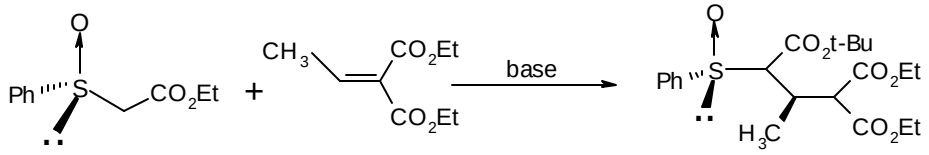


(1)

EWG = CO_2R, CO_2NR_2, CN, NO_2 etc.

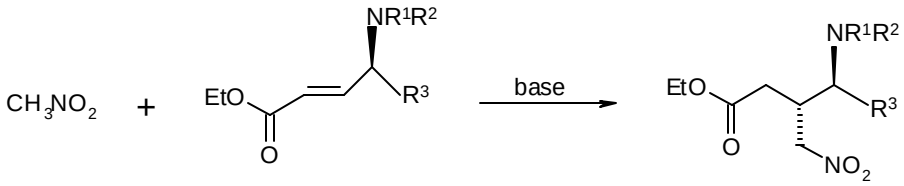
Essentially there are three ways to generate chiral adducts using Michael reaction namely,

(a). Addition of chiral Michael donor to achiral Michael acceptor – here the source of chirality is present in the Michael donor which controls the new stereogenic center formed in the product. (eqn. 2).



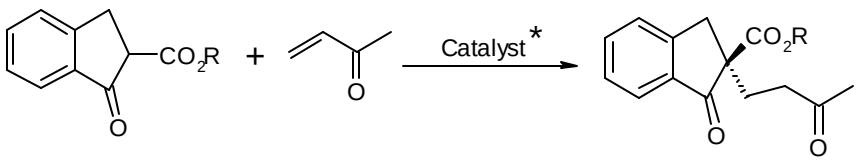
(2)

(b). Addition of achiral Michael donor to chiral Michael acceptor – here the source of chirality is present in the Michael acceptor which controls the new stereogenic center formed in the product (eqn. 3).



(3)

(c). Both the reactants *i.e.* Michael donor and Michael acceptor are achiral however the catalyst used for the reaction is chiral (eqn. 4).

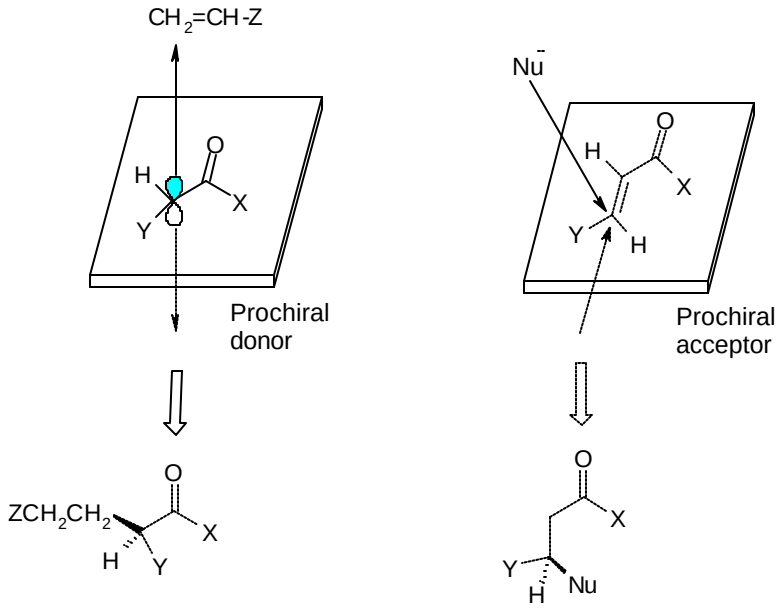


(4)

It is the last type of reaction which has received much attention in recent times mainly because of the easy availability of the starting reactants (as they are racemic) and also because of the fact that reaction could be promoted by the use of chiral additive in catalytic amount. The asymmetric Michael reaction could be categorized in two groups:

(i). Enantioselective addition of prochiral enolates *i.e.* Michael donor to acceptor.

(ii). Enantioselective addition of enolates to prochiral Michael acceptor (Fig. 1).



Reaction of Prochiral Donor Reaction of Prochiral Acceptor

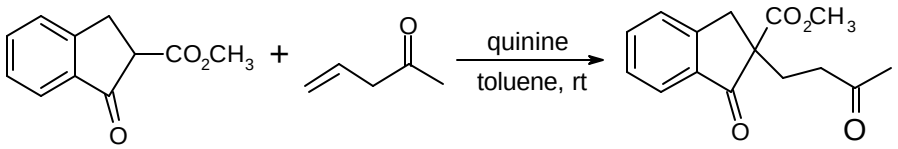
Figure 1

In the former reaction, there is discrimination of the enantioface of the prochiral Michael donor and the asymmetric centers are formed on the donor. In

the latter reaction, there is discrimination of the enantioface of the prochiral Michael acceptor and the resulting asymmetric centers are formed on the Micahel acceptor. Since the first reported[2] example of catalytic enantioselective Michael addition reaction by Wynberg in 1975, there has been plethora of publications in this area and the reaction has become one of the important methods for the enantioselective C-C bond formation. Several chiral additives have been used for promoting the reaction including chiral alkaloids, chiral diamines, chiral alkoxides, chiral amino acids, chiral lanthanoide complexes etc. Due to the wide variations in the nature of catalyst used for the reaction, it becomes important to classify Michael reaction according to the kind of catalyst used. Broadly they can be categorized in two groups *viz.* organo catalysts and organometallic catalysts.

ORGANO CATALYSTS

Optically active alkaloids: Various alkaloids based on cinchona and ephedra have been used for the enantioselective Michael addition. Indeed the catalytic enantioselective Michael reaction first reported[1] by Wynberg utilized optically active quinine as catalyst for the addition of 1-oxo-2-indane-carboxylate (**1**) to methyl vinyl ketone giving Michael adduct (**2**) in 68 % *ee* (eqn. 5).



1 **2** (68% *ee*) (5)

Various chiral cinchona alkaloids, which have been used for Michael addition reaction, are shown in Fig. 2.

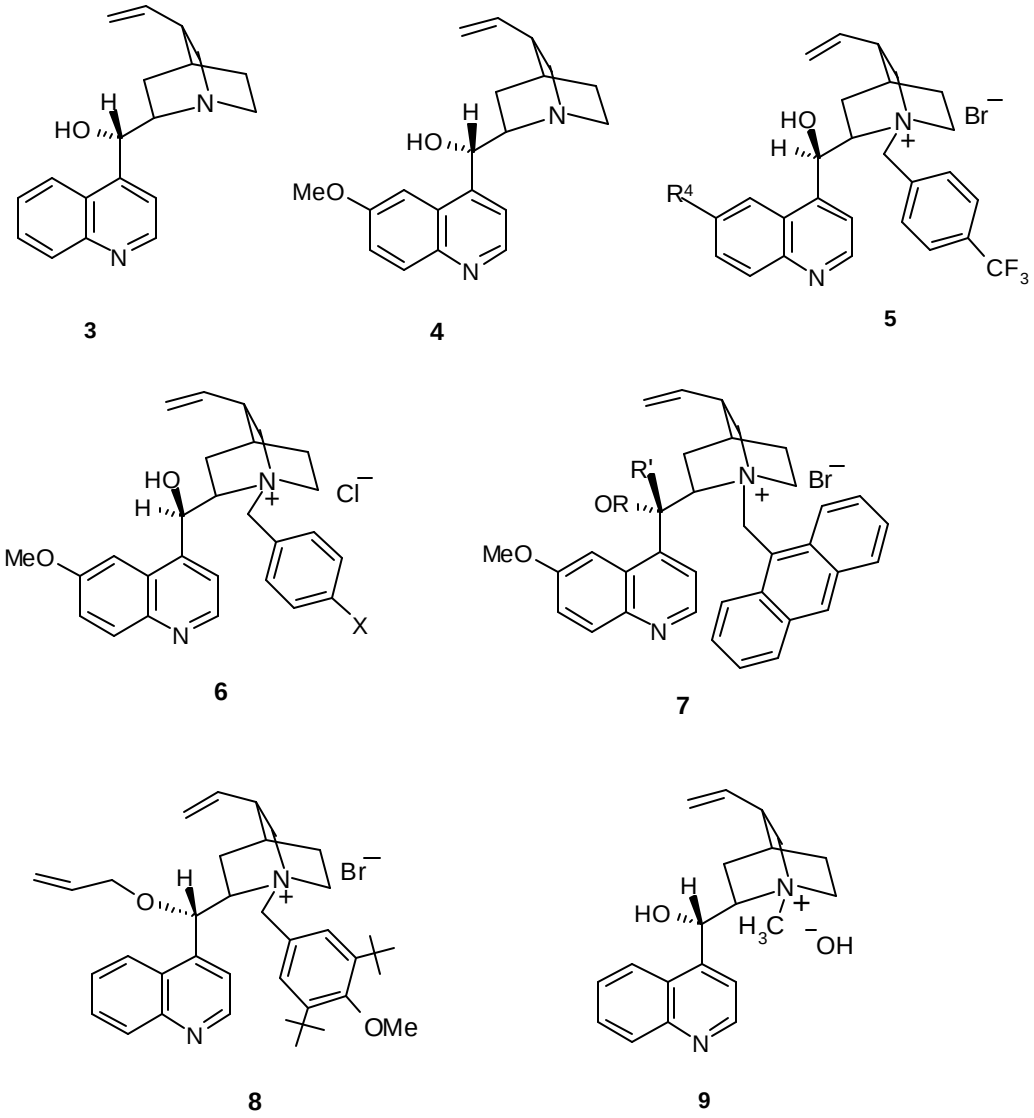
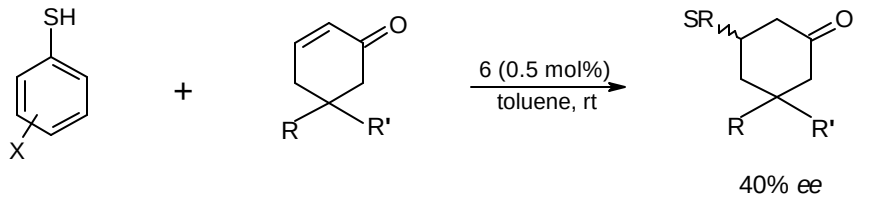


Figure 2

Addition of aromatic thiols to conjugated cycloalkenones was also reported. Quinine or *N*-(*p*-nitrobenzyl) quininium chloride (**6**) showed comparable catalytic activity (eqn. 6).[3, 4]



(6)

Catalysts containing the ß-hydroxy amine moiety (cinchona and ephedra) gave higher reaction rates and higher *ee* than the catalyst without a hydroxyl functionality. Polar solvents and concentrated reaction solutions were counterproductive for the enantioselectivity. It was proposed[5] that *erythro* cinchona and ephedra alkaloids catalyze the reaction *via* tight transistion state complex comprising all the three species *viz*. thiol, enone and the catalyst (Fig. 3).

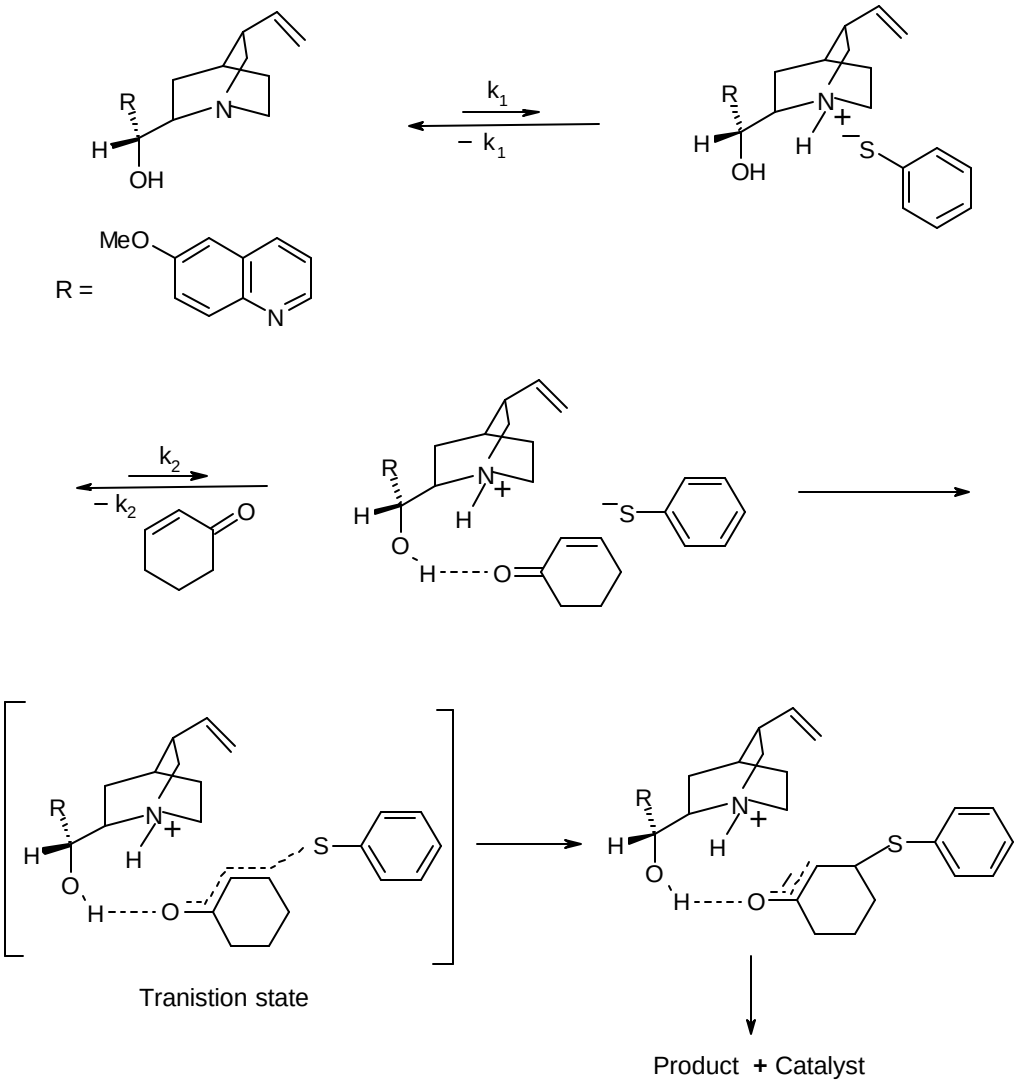
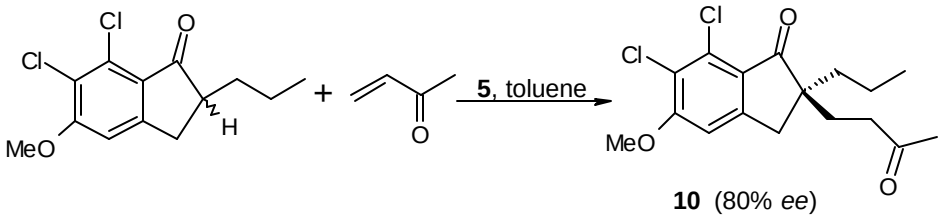


Figure 3

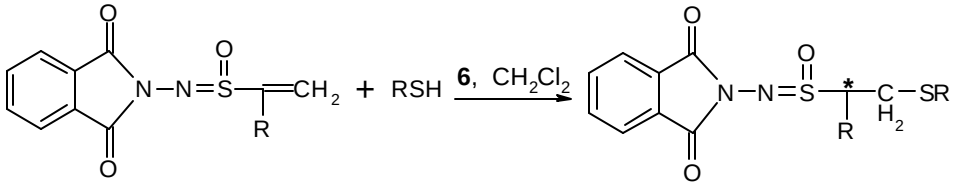
An electrostatic interaction between the thiol anion and the ammonium cation and a hydrogen bond between the catalyst hydroxyl group and the enone carbonyl group stabilizes the geometry of these complexes whereas steric factors imposes a free energy difference between the two possible orientations of the enone which results in the formation of unequal amounts of *R* and *S* products. *Threo* cinchona alkaloids and the catalyst without a hydroxyl group lack at least one of the stabilizing interactions leading to less stabilized transistion states and consequently lower enantioselectivity.

Conn et. al. reported[6] enantioselective addition of 2-alkylindanones to methyl vinyl ketone. Using [*p*-(trifluoromethyl)benzyl] cinchoninium bromide (**5**) the Michael adduct (**10**) was obtained in upto 80% *ee* and in 95% overall yield (eqn. 7).



10 (80% *ee*) (7)

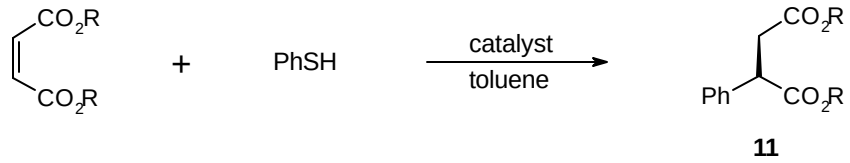
Colonna et. al. reported[7] the addition of thiols to *a*,*ß*-unsaturated sulphoximides to obtain the product, albeit in low enantiomeric excess. Several catalysts like quinine, *N*-benzyl quininium chloride (**6**), *N*-dodecyl-*N*-methyl ephedrinium bromide were examined (eqn. 8).



13% *ee* (8)

Mukaiyama et. al. reported[8] asymmetric addition of thiophenol to dialkyl maleate using catalysts like cinchonine, cinchonidine, quinine, quinidine. Although product with *ee* as high as 86% was obtained the overall yield was

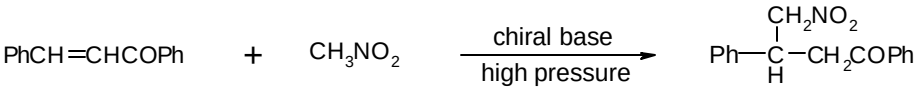
only 7% that to after several days of stirring at 0°C. However reaction at 20°C gave product (**11**) in 92% yield and in 55% *ee* (eqn. 9).



(9)

11

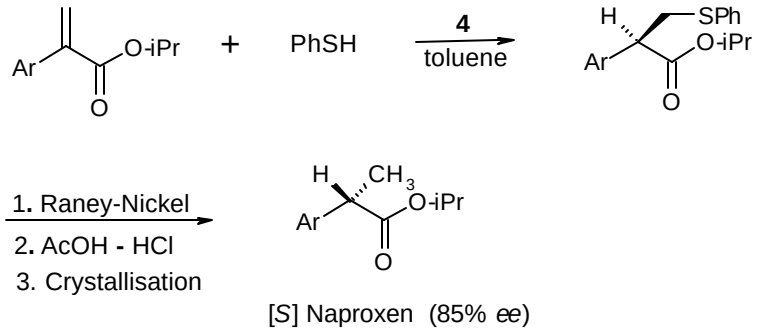
Matsumoto et. al. carried out addition of nitromethane to chalcone under high pressure. Various cinchona based alkaloids were used for the reaction, quinidine giving the best result[9] with up to 26% enantioselectivity (eqn. 10).



(10)

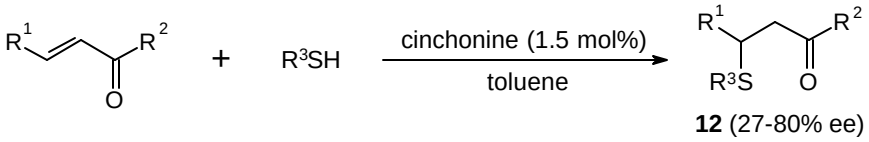
26% *ee*

A novel synthesis of optically active 2-phenylpropionic acid or esters which can be used for the synthesis of [S]-naproxen, a non steroidal anti-inflammatory agent, was reported by Dike et. al.[10] The key step in the reaction was the enantioselective protonation of the prochiral carbanion generated in the addition of benzene thiol to *a*-aryl acrylates catalysed by cinchona alkaloids. Amongst various alkaloids used, quinidine gave the best result. An interesting feature of this addition was the formation of a new chiral center one atom away from the incoming sulphur atom. The benzene thiol group can be removed easily by standard Raney-nickel desulphurization to give the corresponding a-aryl propionates (Scheme 1).



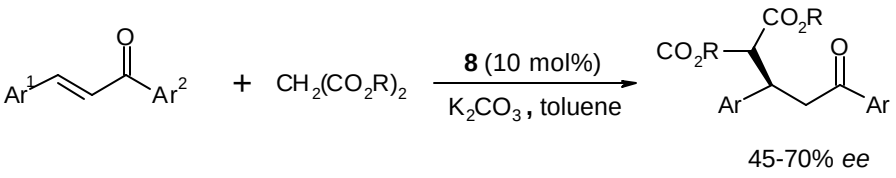
Scheme 1

Recently Skarzewski et. al. reported[11] enantioselective addition of thiophenols to chalcones in the presence of cinchonine to give Michael adduct (**12**) in up to 80% *ee* (eqn. 11).

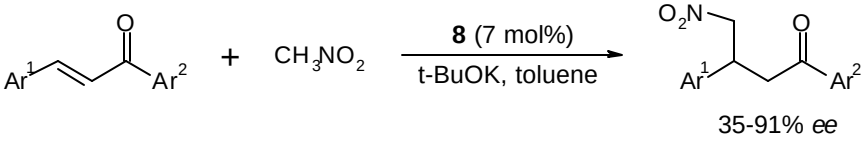


(11)

Kim et. al. reported[12] the addition of malonates and nitromethane to chalcone using chiral quaternary ammonium salts derived from cinchona. Cinchona derived alkaloids (e.g. **8**) were used giving product in up to 70% *ee* (eqn. 12 & 13).

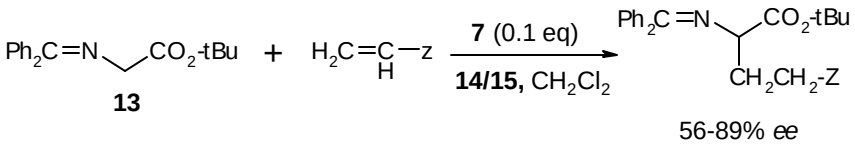


(12)

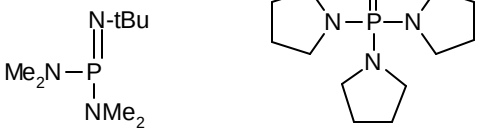


(13)

O'Donell et. al. reported[13] the preparation of optically active unsaturated *a*-amino derivatives by the conjugate addition of schiff base ester derivatives (**13**) to Michael acceptor using cinchona derivatized (**7**) along with non ionic phosphazene bases(Schwesinger bases) BEMP(**14**) or BTPP (**15**) (eqn. 14).



(14)



In addition to cinchona based alkaloids, ephedra based alkaloids have also been used (Fig. 4).

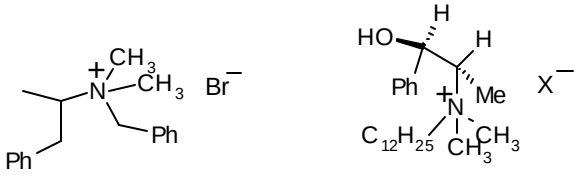
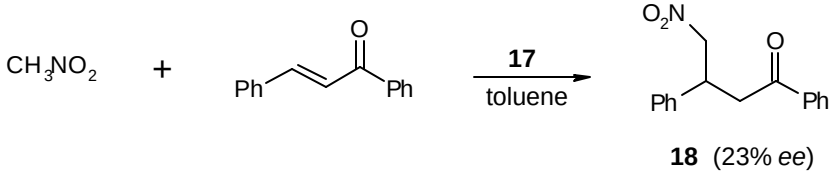


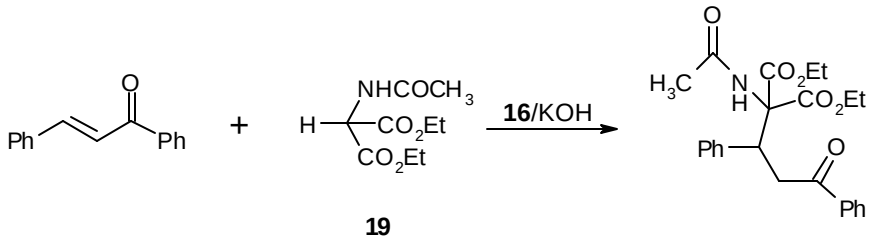
Figure 4

Wynberg et. al. reported[14] the addition of nitromethane to chalcone using *N*-dodecyl fluoride of *N*-methyl ephedrine (**17**) to obtain product (**18**) in 23% *ee* (eqn. 15).



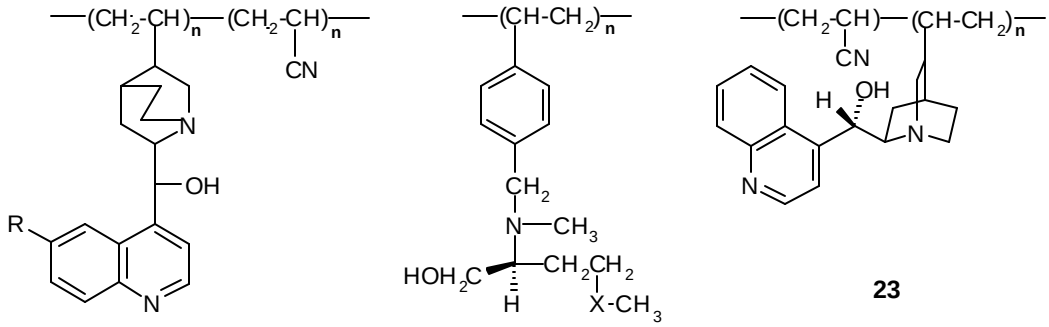
(15)

Loupy *et. al.* reported[15] the addition of diethylacetylamine malonate (**19**) to chalcone using *N*-methyl-*N*-benzyl ephedrinium bromide (**16**) to give product (**20**) in 66% *ee* (eqn. 16).



19 **20** (66% ee) (16)

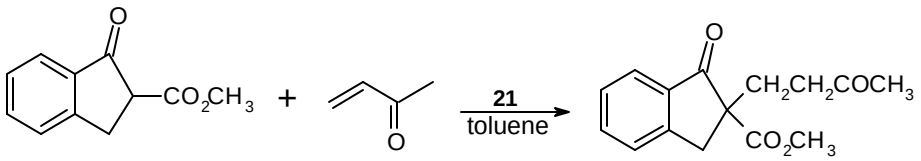
Polymer supported catalysts: The principal drawback in the use of alkaloid catalysts is the relative difficulty of separating the product from the catalyst. One way to overcome this drawback would be to fix the alkaloid on a solid support in a way that retains the stereochemistry of the alkaloid. To serve this purpose, various polmer supported alkaloids were prepared (Fig. 5).



21 **22** **23**

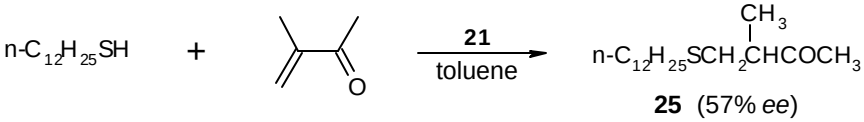
Figure 5

Burri et. al. carried out[16] addition of 1-oxo-2-indane carboxylate to methyl vinyl ketone using **21** to obtain **24** in 42% *ee*. The same group reported the addition of dodecanethiol to iso-propentyl methyl ketone to get the **25** in 57% *ee* (eqn. 17 & 18).



24 (42% *ee*)

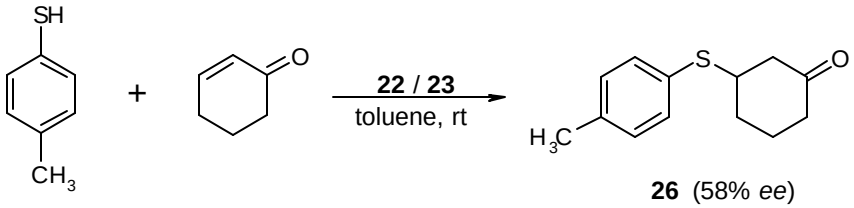
(17)



25 (57% *ee*)

(18)

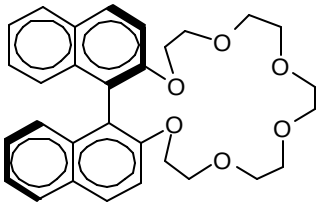
Hodge et. al. carried[17] out the addition of *p*-methyl thiophenol to cyclohexenone using **22** and **23** to give product (**26**) in almost quantitative yield (eqn. 19).



26 (58% *ee*)

(19)

Crown Ethers: Crown ethers of wide structural variations have been used for the asymmetric Michael addition reactions. Since the first report[18] by Cram et. al. using chiral crown complexes based on optically active *R/S* – BINOL, much progress has been made in this area. Some of the chiral crown ethers which have been used for this purpose are shown in Fig. 6.



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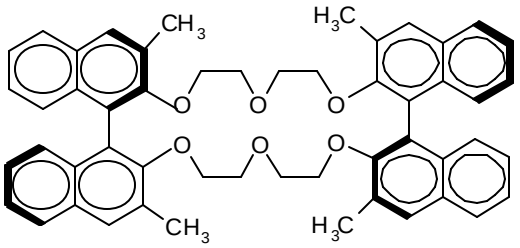

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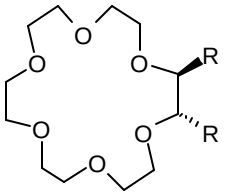

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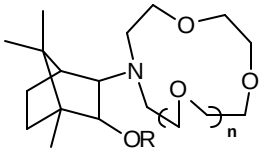

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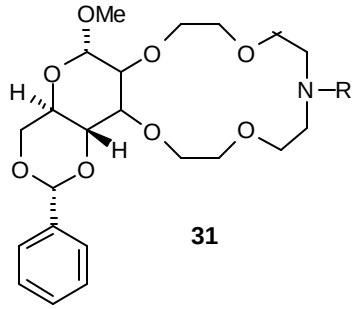

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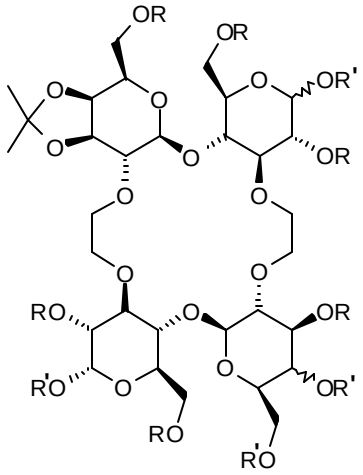

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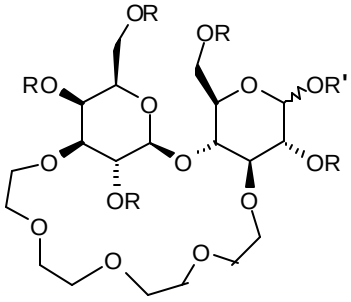

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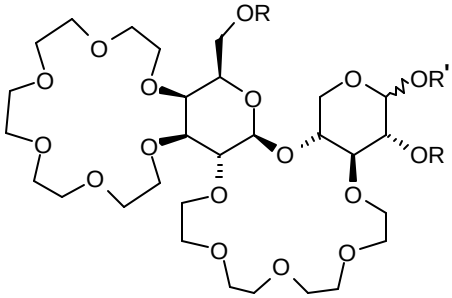
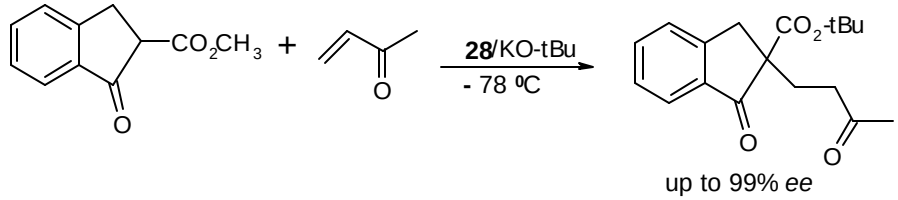


34

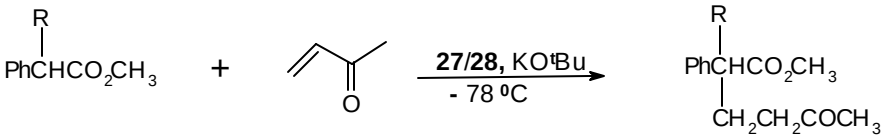
Figure 6

Cram et. al. carried out the addition of methyl-1-oxo-2-indane carboxylate to methyl vinyl ketone using 20 mol% of crown ether **27**/**28** (eqn. 20). They also reported[18] the addition of substituted methylphenyl acetate to methyl vinyl ketone (eqn. 21).



up to 99% *ee*

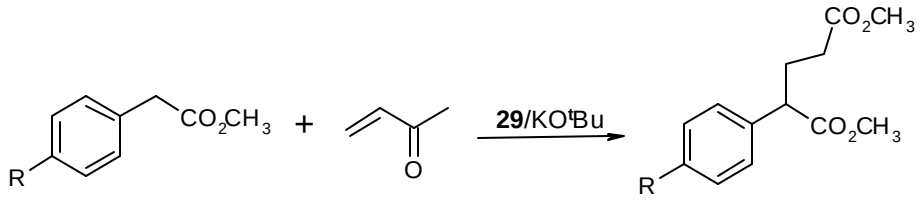
(20)



65 - 83% *ee*

(21)

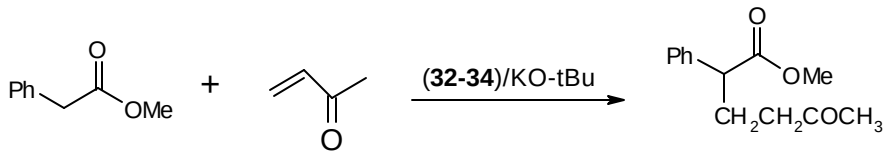
Koga et al. reported[19] the addition of methylphenyl acetate to acrylates using the crown ether **29** (eqn. 22).



up to 88% *ee*

(22)

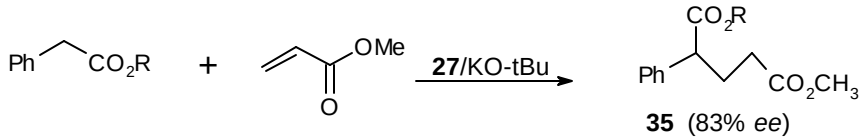
Penandes et. al. prepared[20] several *bis* lacto-18-crown-6 ethers (**32-34**) and examined their efficiency for the enantioselective addition of methyl phenyl acetate to methyl vinyl ketone (eqn. 23).



7-44% *ee*

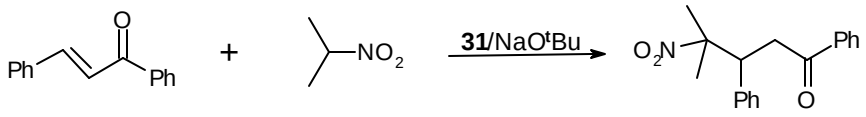
(23)

Camphor derived crown ether **30** was used by Brunet et. al.[21] for the addition of alkyl phenyl acetate to methyl acrylate to obtain the product **35** up to 85% yield (eqn. 24).



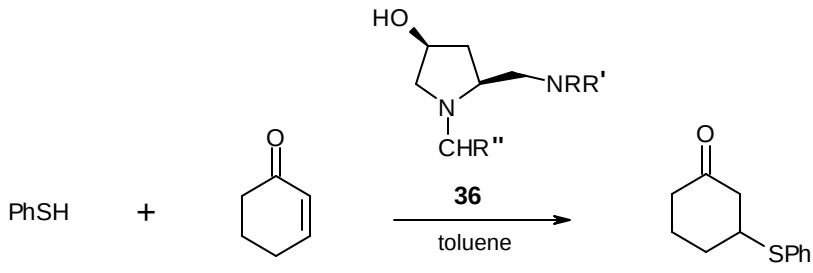
35 (83% *ee*) (24)

Toke *et. al.* reported[22] the addition of nitroalkanes to chalcone using crown **31** (eqn. 25).



60% *ee* (25)

Chiral diamines: Mukaiyama et. al reported[23] the enantioselective addition of thiols to cyclohexenone using chiral diamines. The best results were obtained using (*2S,4S*)-2-anilinomethyl-1-ethyl-4-hydroxy pyrrolidine (**36**) as the catalyst to realize the product in up to 67% optical purity and in 24-90% yield (eqn. 26).



up to 67% *ee* (26)

It was proposed that the product formation takes place *via* formation of an ammonium thiolate complex where the ammonium counterpart has a 5,5-fused ring structure (Fig. 7).

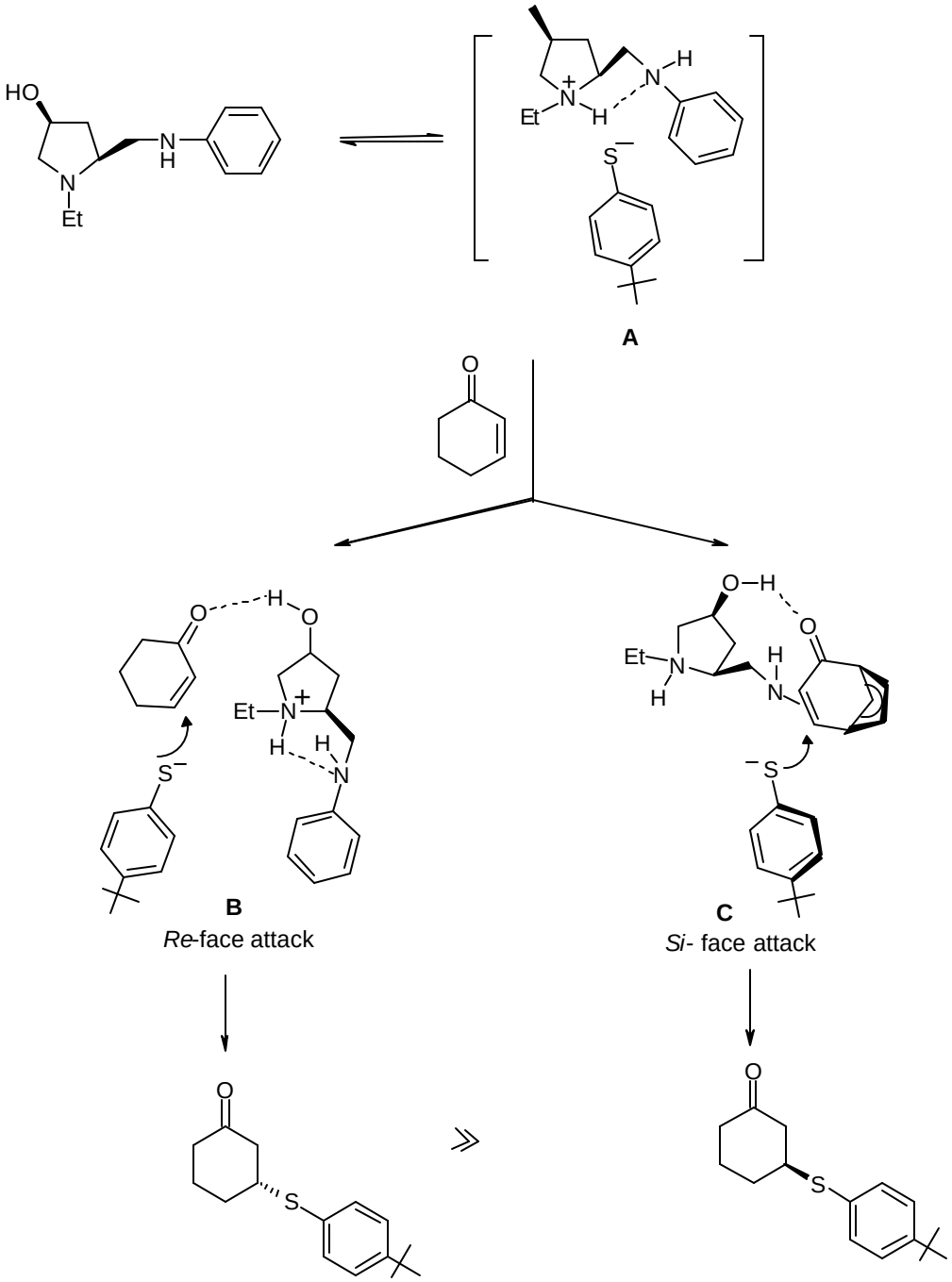
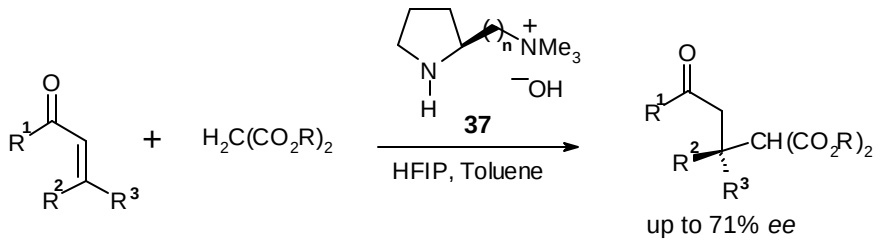


Figure 7

Such rigid structure was supposed to be a crucial factor in the enantioselection because the enantioselectivity decreased when the substituent of the amine was replaced by bulkier groups and therefore this structure no longer remained a preferred one. Also in a solvent like toluene, the thiolate

anion is stabilized by the *p-p* interaction and the freedom of its location is further limited by the interaction with the aromatic ring of the catalyst. Approach of cyclohexenone to complex-A takes place with a hydrogen-bond interaction between the carbonyl group and the hydroxyl group of the catalyst. In a protic solvent like ethanol this interaction is reduced resulting in no enantioselection. It was also postulated that the attack of thiolate anion to the enone occurs where two pathways B and C are possible (Fig. 7). In case of the pathway C, the steric congestion of the aniline group and the cyclohexenone ring prevents the complex-A and the enone from reaching a favourable transistion state leading to a preferential attack on the *Re* face of the cyclohexenone through pathway B resulting in the predominant formation of the [*R*]-enantiomer.

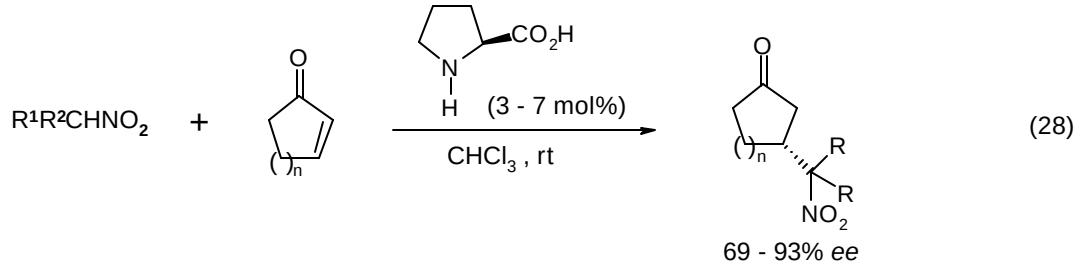
Amino acid and their derivatives: Taguchi et. al. [24] used [*S*]-*N*-(2-pyrrolidylmethyl)-*N*,*N*,*N*-trimethylammonium hydroxide (**37**) for the addition of soft nucleophiles to enones giving product with moderate to high optical purity (eqn. 27).



(27)

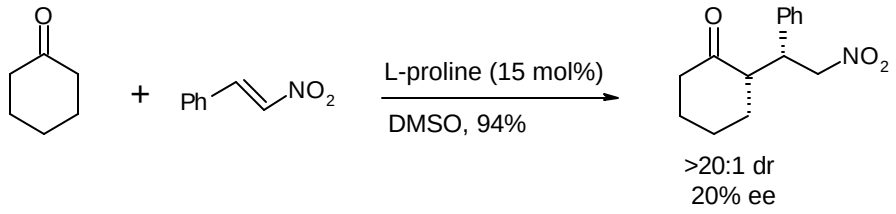
A test reaction done between dibenzyl malonate and cyclohexenone using the catalyst **37** gave the product in 88% yield with 3.5% *ee*. Taguchi et al. concluded that due to the strong basicity of the catalyst direct attack of malonate to the enone causes lowering of the enantioselectivity. HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) was therefore added to reduce bascity and to control the imminium intermediate formation which resulted in product with up to 70% *ee*. These results suggested that the face selective attack on enone was controlled through the reversible imminium intermediate.

Hanessian et al reported[25] the conjugate addition of nitroalkanes to cycloalkenones using L-proline as the catalyst (eqn. 28).



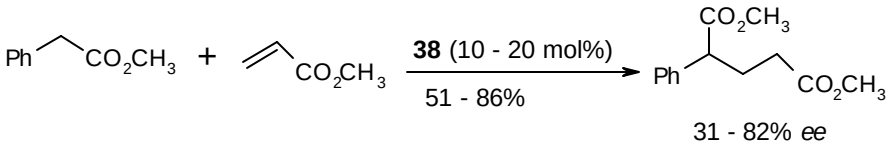
(28)

List et. al reported[26] the addition of cyclohexanone to 2-phenyl-1-nitroethane also using L-proline (eqn. 29).

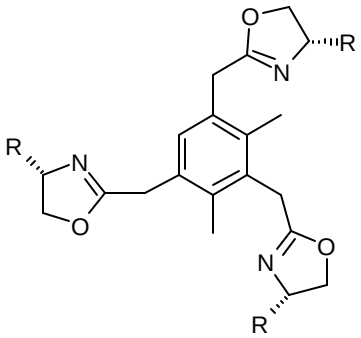


(29)

Chiral oxazoline: Ahn et. al. reported[27] the Michael addition catalyzed by chiral tripodal oxazoline (38) in conjuction with KO^{t}Bu (eqn. 30).



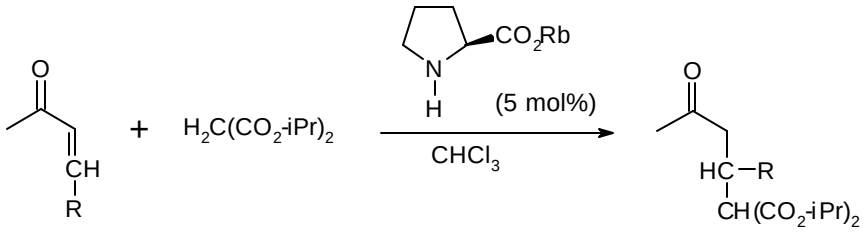
(30)



38 - (*S*,*S*,*S*)- BTO

ORGANOMETALLIC CATALYSTS

Metal salts of amino acids: Yamaguchi et. al. reported[28] the first catalytic asymmetric Michael addition of a simple maolnate ion to prochiral enones and enals employing readily available rubidium salt of L-proline (eqn. 31).



(31)

The catalyst was found to be associated with water of hydration and the reaction rate was considerably lowered in the presence of molecular sieves 4A. In fact, small amount of water was found to promote the reaction. Rubidium salts of *N*-methyl-proline, pyrrolidine or trimethyl amine were found to be ineffective for the reaction showing that the secondary amine and the metal carboxylate moieties of the catalyst are essential for high catalytic activity. It was proposed that the asymmetric induction takes place through enantioface differentiation of the Michael acceptor (Fig. 8).

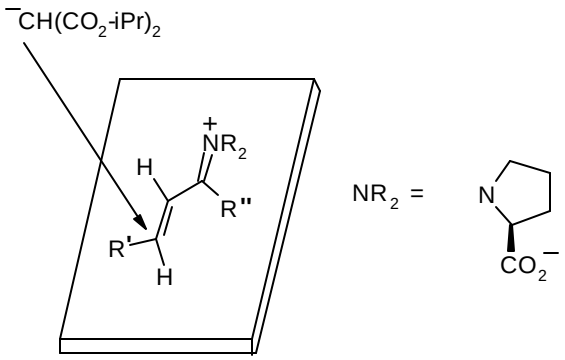
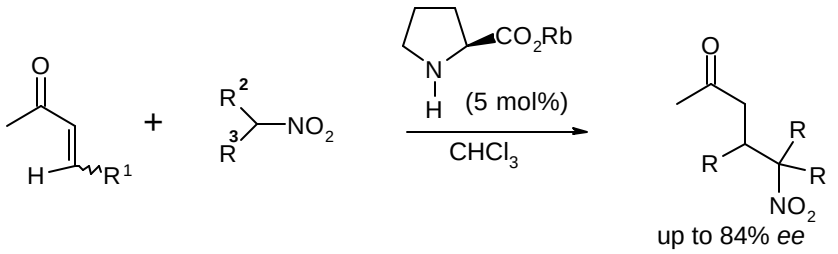


Figure 8

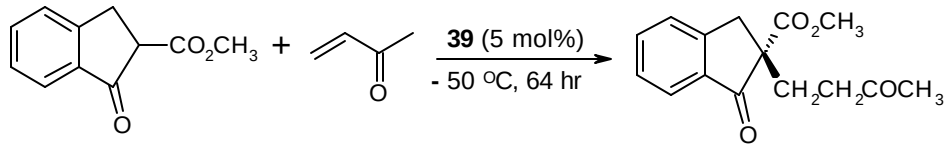
The same group later reported[29] the addition of nitroalkanes to enones and enals by using rubidium salt of L-proline to obtain the product in up to 84%

ee (eqn. 32). [*R*]-adducts were obtained from cyclic [*Z*]-enones and [*S*]-adducts from acyclic [*E*]-enones.



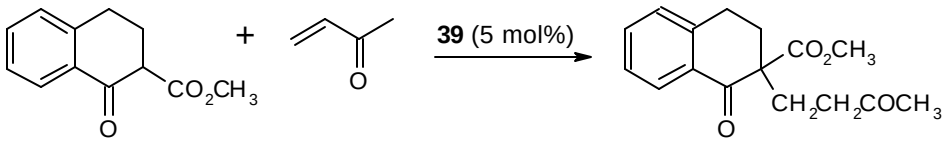
(32)

Metal-Diamine complexes: Michael reaction catalyzed by inorganic salts is widely reported.[30-37] Along with these reports, the use of metal-diamine complexes[38] is also known. Brunner et. al. reported[39] the first transistion metal catalyzed Michael addition using cobalt(II)-diamine complex. It was postulated that an octahedral complex involving Co(II), diamine and 2-indane carboxylates first formed, which then undergoes stereoselective Michael addition to methyl vinyl ketone (eqn. 33 & 34).



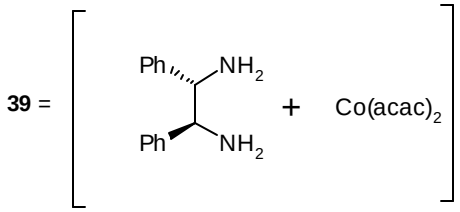
66% *ee*

(33)



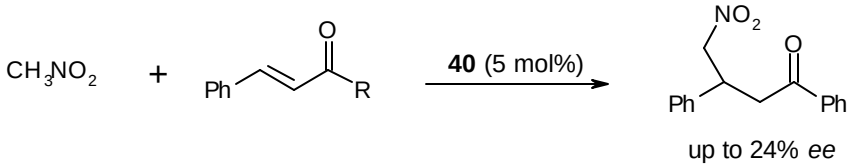
39% *ee*

(34)

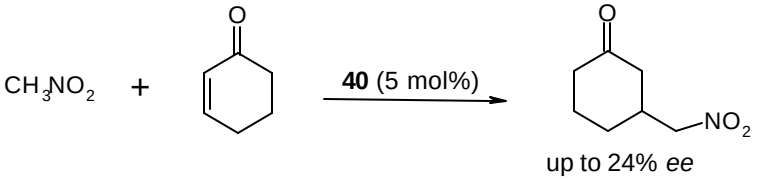


Botteghi et. al. prepared[40] Ni(II) complexes with chiral chelating nitrogen ligands such as 2,2'-bipyridines, 1,10-phenanthroline and 1,2-diamines for the

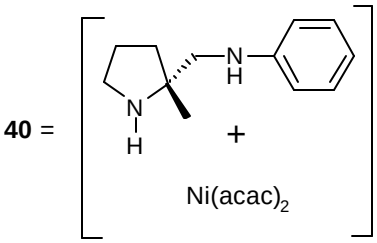
addition of nitromethane to benzalacetone, chalcone and 2-cyclohexenone. Catalyst derived from $Ni(acac)_2$ and (+)-(*S*)-2-(anilinomethyl)-pyrrolidine (**40**) showed good catalytic activity providing up to 24% *ee* (eqn. 35 & 36).



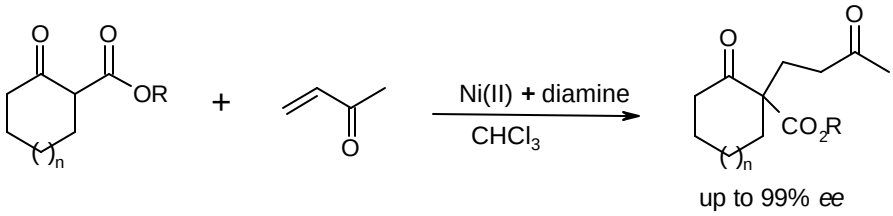
(35)



(36)



Recently Christoffers et. al.[41] created quaternary chiral centers using catalyst derived from $Ni(OAc)_2.2H_2O$ and (*R,R*)-1,2-cyclohexane diamine (eqn. 37).



(37)

It was proposed that the Michael donor forms a dinato complex with the metal whereas Michael acceptor co-ordinates at the vacant co-ordination site of the metal of the dinato complex and this leads to alkylation by the enone but only if the enone is in *s-cis* conformation.

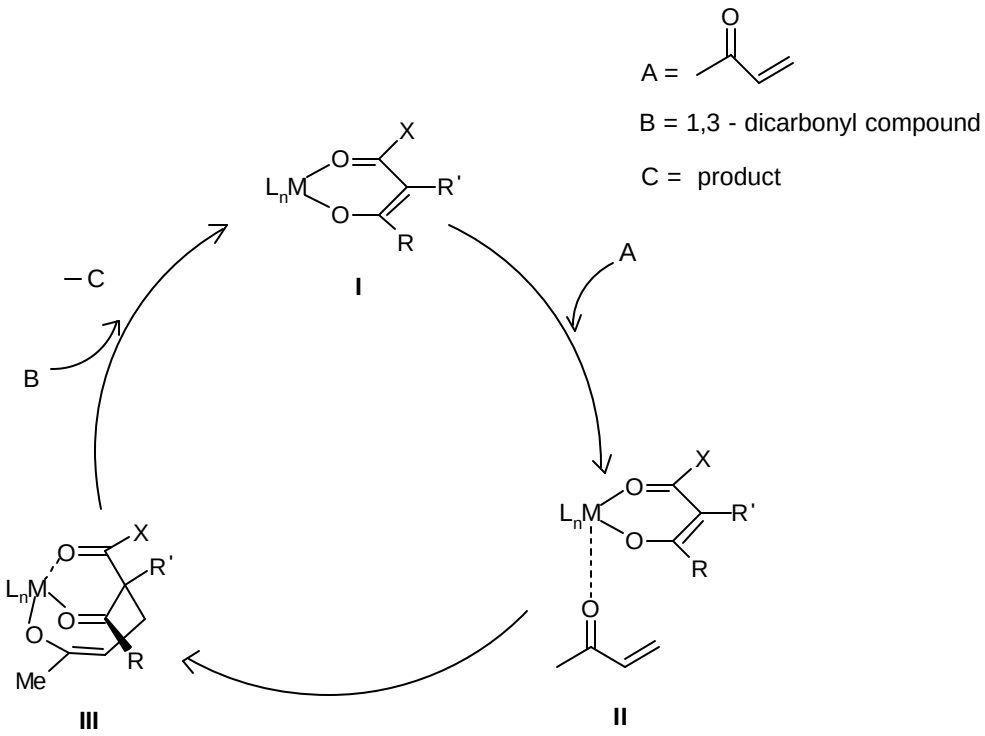
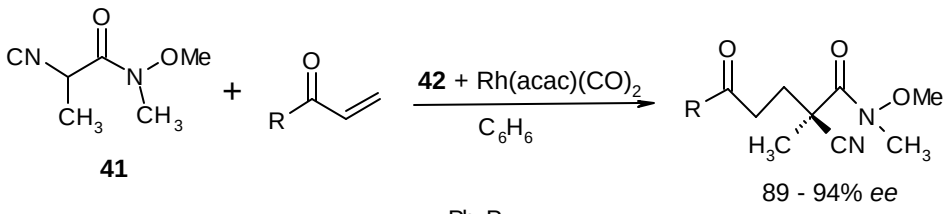
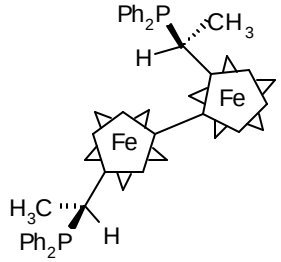


figure 9

Transistion Metal Complexes: Ito et. al. reported[42] the addition of *N*-methoxy-*N*-methyl-2-cyanopropionamide (**41**) to vinyl ketones or acrolein using 0.1-1 mol% of rhodium catalyst prepared in situ from $Rh(acac)(CO)_2$ and diphosphine ligand (*S,S*)-(*R,R*)-PhTRAP (**42**) (eqn. 38).

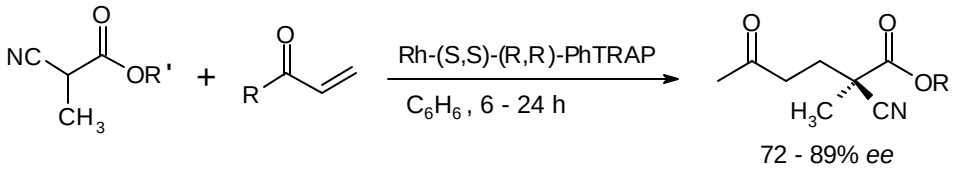


(38)



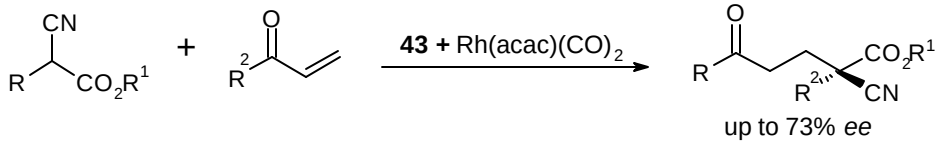
42 (*S,S*)-(*R,R*)-PhTRAP

They also reported[43] the addition of alkyl-2-cyano carboxylate to vinyl ketones using Rh-(*S,S*)-(*R,R*)-PhTRAP complex giving the product in more than 90% yield and up to 89% *ee* (eqn. 39).

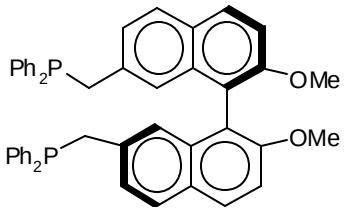


(39)

Nozaki et. al. used[44] chiral bisphosphine ligand (**43**) and prepared a chiral Rh(I) complex which was used for the addition of a-cyano esters to vinyl ketones (eqn. 40).

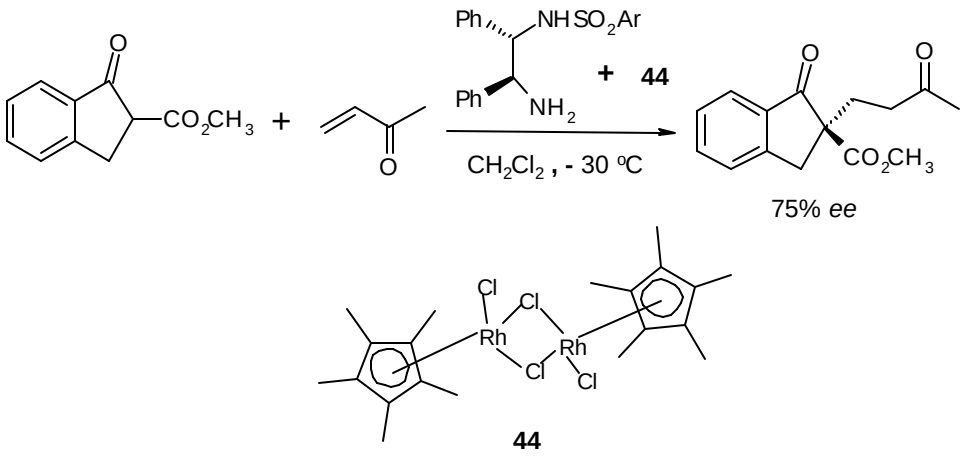


(40)



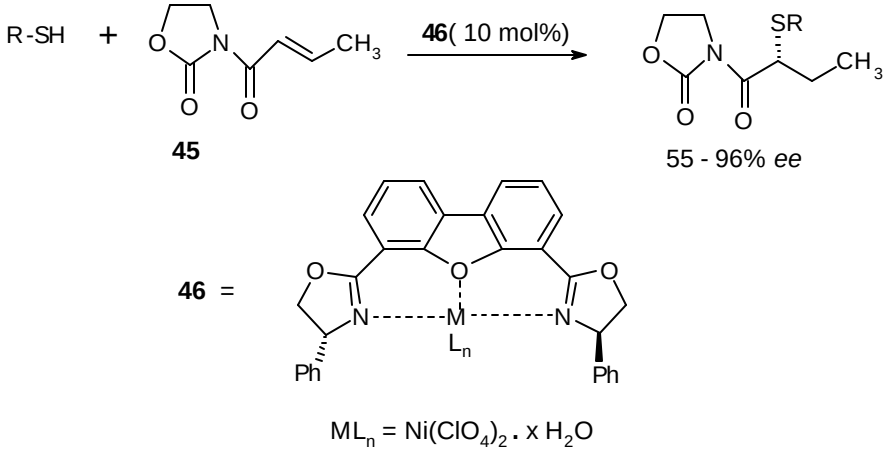
43

Suzuki et. al. prepared rhodium complex[45] for the addition of methyl-1-oxo-2-indane carboxylate to methyl vinyl ketone (eqn. 41).



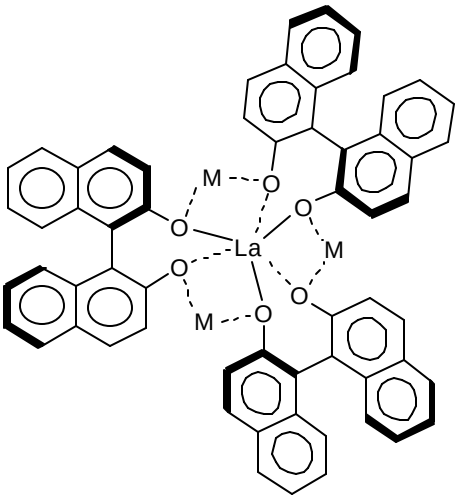
(41)

Kanemasa et. al. reported[46] the asymmetric conjugate addition of thiols to 3-(2-alkenoyl)-2-oxazolidinone (**45**) catalysed by chiral cationic Ni(II) complex (**46**) (eqn. 42).

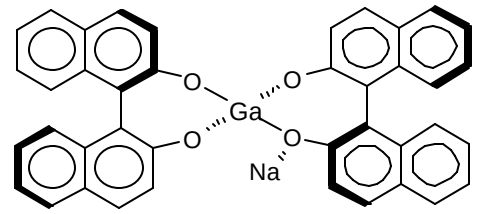


(42)

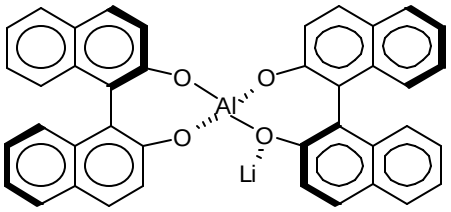
Heterobimetallic complexes: Heterobimetallic complex in which each metal plays a different role in the enantiodifferentiation represents another class of potent catalyst for enantioselective Michael reaction. The development of the multifunctional alkalimetal lanthanide-BINOL catalyst by Shibasaki *et al.*[47,48]marked the milestone in this area enabling efficient catalytic conjugate additions of malonates to acyclic as well as cyclic substrates with high enantioselectivities. These complexes are depicted in Fig. 10.



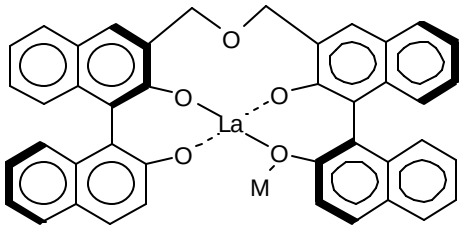
47 a (M = Na)
b (M = K)



48



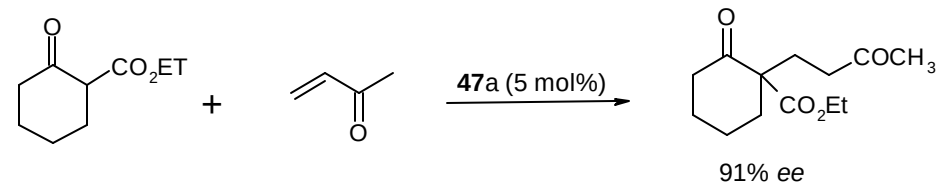
49



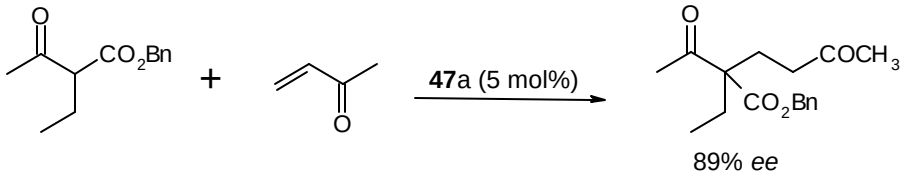
50 a (M = K)
b (M = H)

Figure 10

Extensive studies showed[49-51] that the lanthanum-sodium-BINOL complex (LSB) (**47**a) is very selective in the addition of prochiral *ß*-keto esters to methyl vinyl ketone (eqn. 43 & 44). Mechanism for the mode of action with this class of catalyst is discussed in CHAPTER-2.

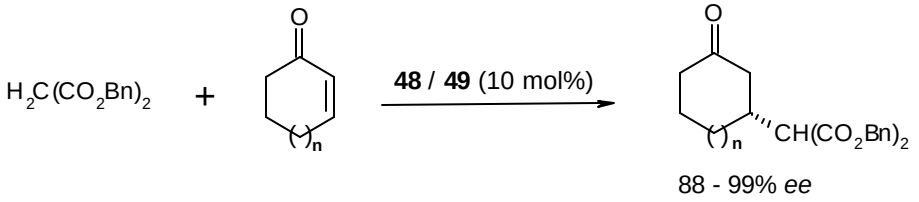


(43)



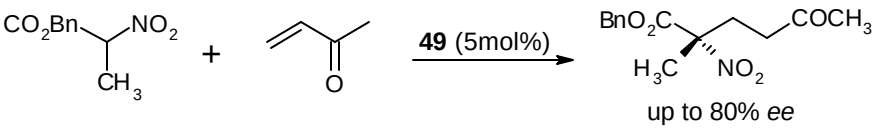
(44)

However for cyclic enones of different ring-size, the gallium-sodium complex (GSB) (**48**) and the aluminium lithium complex (**49**) proved[52] to be the catalyst of choice (eqn. 45).



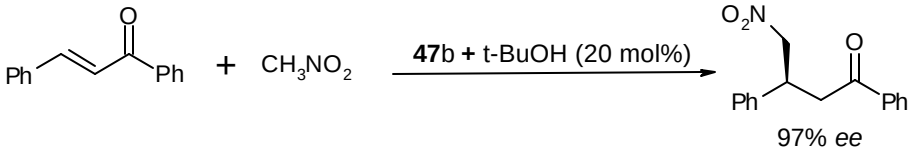
(45)

Feringa et. al. demonstrated[53] that the conjugate addition reactions catalysed by (**49**) can be extended to *a*-nitro esters as nucleophiles to get the product in up to 80% *ee* (eqn. 46).



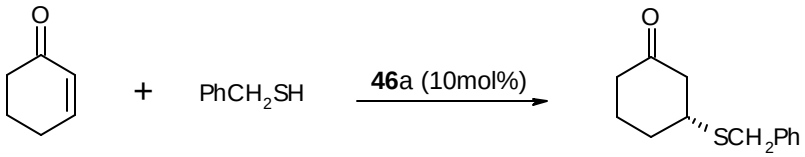
(46)

By the use of 20 mol% of **47**b as catalyst, Shibasaki et al.[54] were able to obtain the addition product of nitromethane to chalcone in 97% *ee* (eqn. 47).



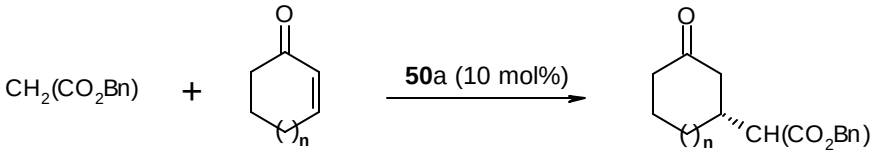
(47)

Besides carbon nucleophiles, thiols were also subjected to 1,4-addition to cyclic enones furnishing the corresponding Michael adducts with good yields and high enantioselectivities. Amongst various heterobimetallic complexes, the lanthanum catalyst **47**a showed the highest level of stereoselectivity. Thus the reaction of benzylmercaptan and cyclohexenone in the presence of 10 mol% of **47**a afforded the Michael adduct[55] in 90% *ee* (eqn. 48).

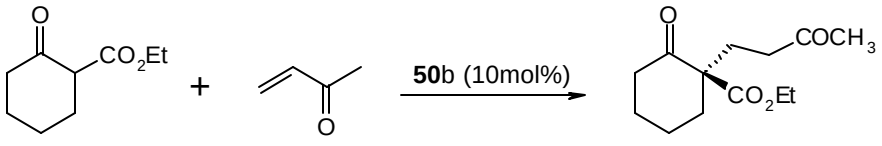


56 - 90% *ee* (48)

The same group later reported[56,57] the structurally modified catalyst **50** in which two BINOL-moieties were linked by an ether group. This heterobimetallic complex (**50**a) gave only moderate selectivities in the conjugate addition of dibenzyl malonate to cyclic enones whereas alkali metal free lanthanum catalyst (**50**b) displayed perfect enantioselection in the addition of malonates to cyclic enones (eqn. 49 & 50).

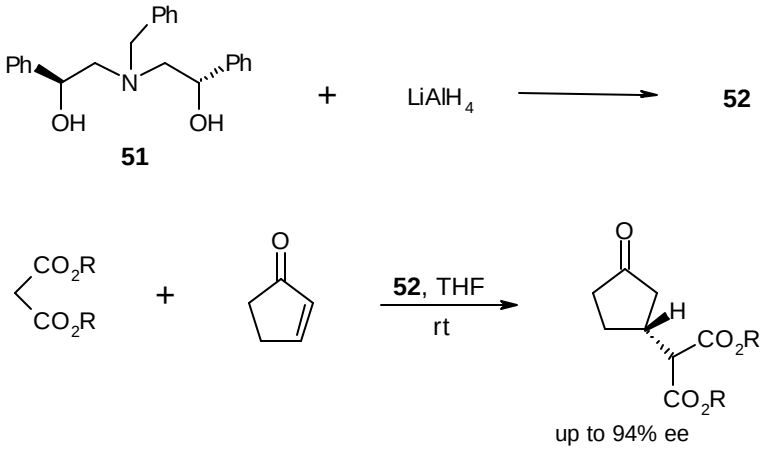


>99% *ee* (49)



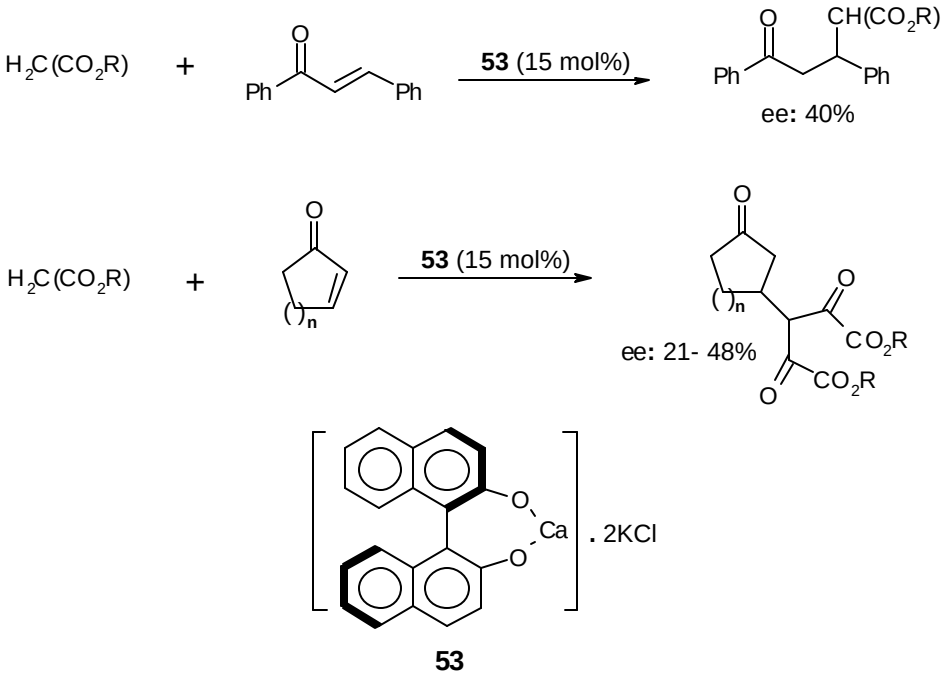
75% *ee* (50)

Sundarajan et. al.[58] used chiral amino diol (**51**) for preparing the heterobimetallic complex with lithium aluminium hydride (Scheme 2).



Scheme 2

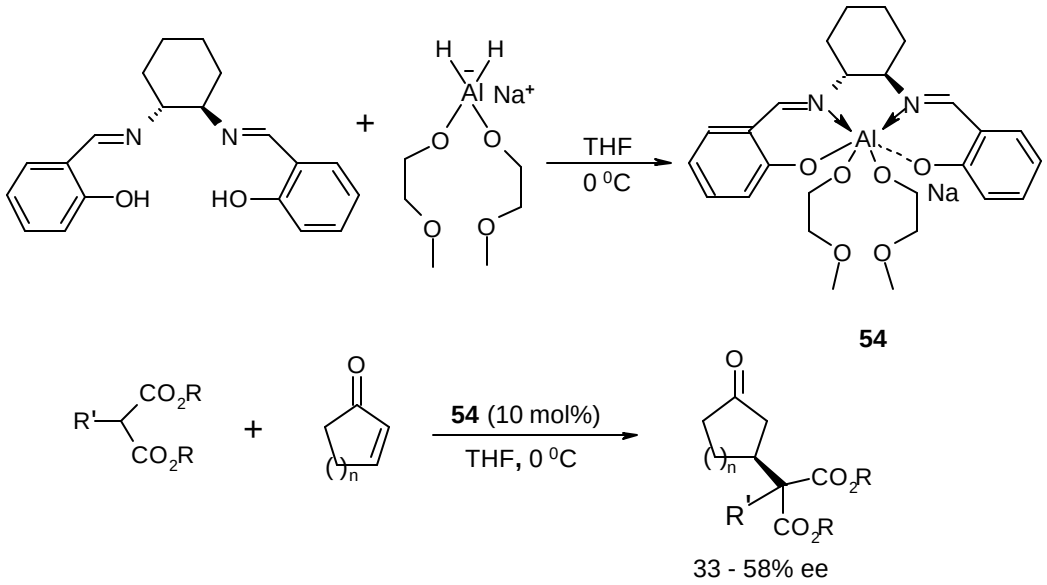
Kumaraswamy et. al. reported[59] a new calcium-BINOL (**53**) catalyst for asymmetric addition of malonates to chalcone and cycloalkenones (Scheme 3).



53

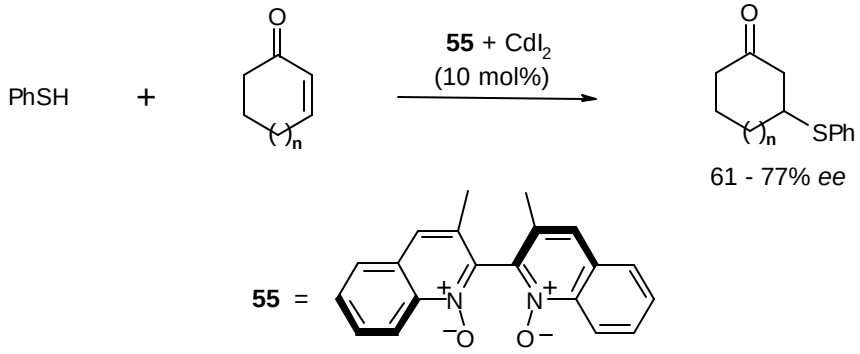
Scheme 3

We have recently reported[60] a new aluminium-salen complex for the enantioselective addition of various alkylmalonates to cycloalkenones (Scheme 4). The details of this work is presented in CHAPTER-2.



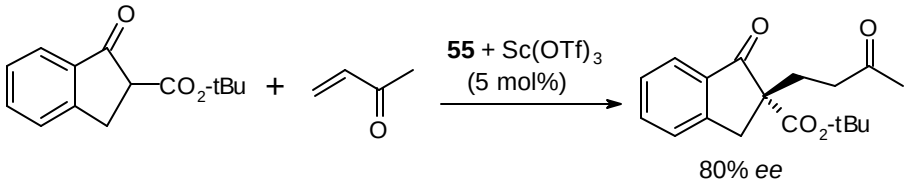
Scheme 4

Chiral *N*,*N*-Dioxides: The *N*-oxide functional group is known to form complexes with a variety of metals[61] due to its strong electron donating ability. However only a limited number of attempts to employ *N*-oxides as chiral catalysts have been reported.[62-69] Nakajima et. al. developed[70] a cadmium catalyst containing (*S*)-3,3'-dimethyl-2,2'-bisquinoline-*N*,*N*'-dioxide (**55**) as a chiral ligand. With this system, the conjugate addition of thiophenol to enones was carried out to obtain the desired products in 61-81% *ee* (eqn. 51).



(51)

The same group also reported[71] the enantioselective Michael addition of ß-ketoesters to methyl vinyl ketone employing **55** along with scandium triflate. The Michael adduct was obtained in 90% yield with up to 80% *ee* (eqn. 52).



(52)

The predominant formation of (*R*) adduct was explained by the transistion state model (Fig. 11). The bulky *tert*-butyl ester moiety should be located on the *si*-face of the keto ester plane in order to avoid steric repulsion with the quinoline moiety which leads the attack of MVK at the *re*-face preferentially.

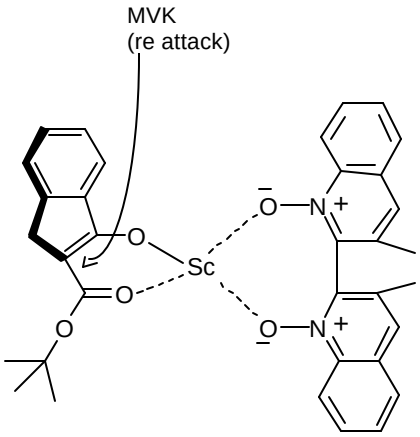
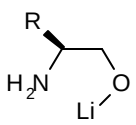


Figure 11

Miscellaneous catalysts: Koga et. al. examined[72] various chiral lithium-2-amino alkoxides (**56-58**) for catalyzing enantioselective Michael addition of methyl phenyl acetate and methyl acrylates. Product with as high as 84% *ee* was obtained. However the chiral alkoxides were effective only in stoichiometric amount (eqn. 53).



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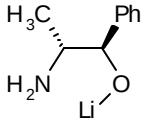

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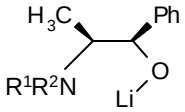

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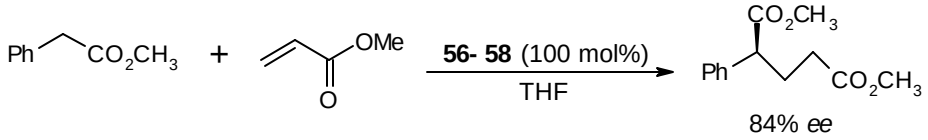
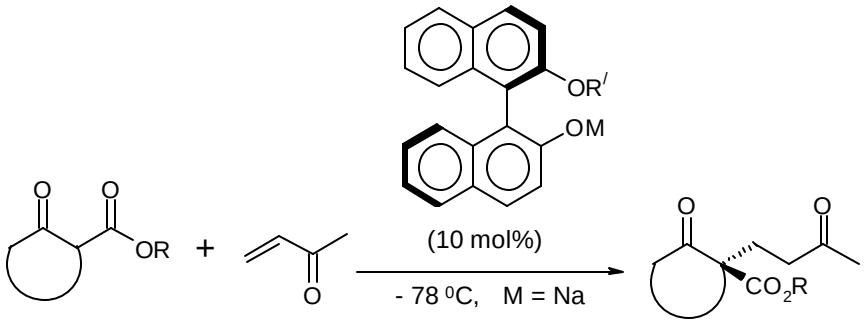


84% *ee*

(53)

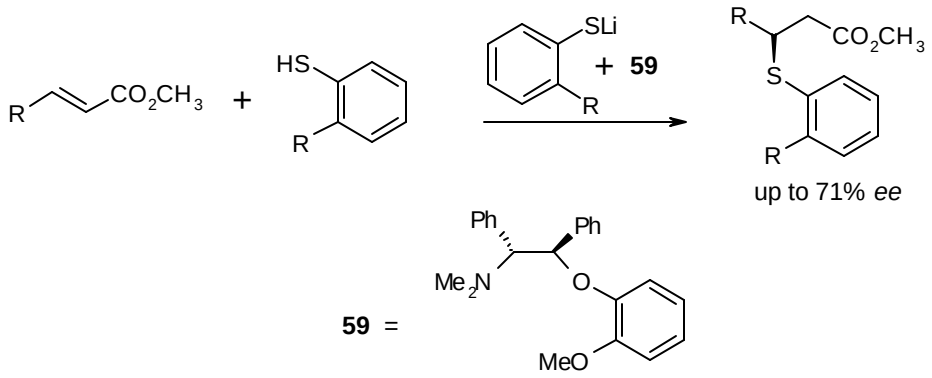
Miyano et. al. reported[73] the use of mono-sodium salt of 2'-substituted-1,1'-binaphthalene-2-oxides as a catalyst for promoting stereoselective reaction between 1,3-diketones and vinyl ketones (eqn. 54).



upto 66% *ee*

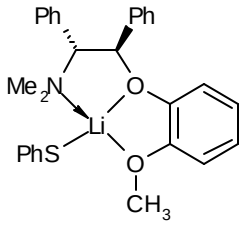
(54)

Tomioka et. al. reported[74] the addition of thiols to acrylate derivatives in the presence of chiral ligand (**59)** and lithium phenolate (eqn. 55).



(55)

The existence of bicyclo[3.3.0] complex (**60**) as active species in the reaction was postulated.



60

Conclusion: Catalysts with wide structural variations have been used for asymmetric Michael addition reactions. Organocatalyst include chiral diamines, chiral crown ethers, chiral alkaloids, chiral aminoacids and chiral oxazolines. Organometallic catalysts include salts of amino acids, metal-diamine complexes, schiff base-metal complexes, transistion metal complexes, heterobimetallic complexes and metal-*N*,*N*-dioxide complexes. There is no single catalyst discovered so far, that is good for the entire range of Michael reaction. However some recent developments have made it possible to select an efficient catalyst for a particular series of transformation.

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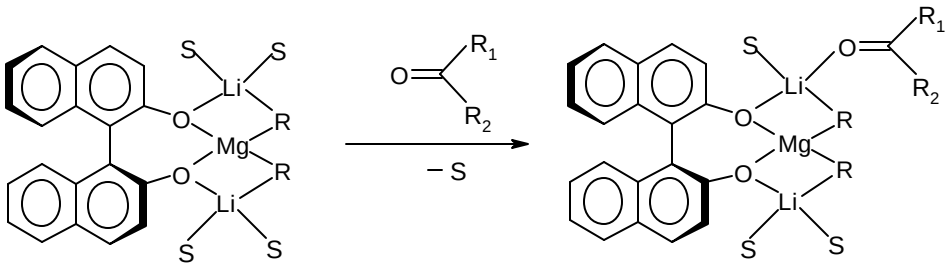
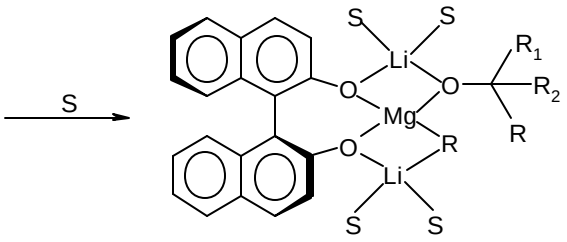
CHAPTER – 2

Heterobimetallic Catalyst for Michael Addition

Introduction: The concept of heterobimetallic catalyst was first introduced by Noyori et. al.[1] in 1988 for the enantioselective addition of diethyl magnesium to aldehydes. They prepared lithium–magnesium binary organometallic system having chiral 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) as a ligand. The multinuclear organometallic species play a significant role in alkylation of carbonyl compounds. The two kinds of metal play specific roles as the alkyl donor and carbonyl activator (Scheme 1).



S = Solvent molecule



Scheme 1

Noyori et. al. stated that such well defined, co-ordinatively saturated reagents consisting of tetrahedral lithium and magnesium metal centers could avoid the formation of complicated polymers or aggregates in ethereal solvents.

A Heterobimetallic complex in which each metal plays a different role in the enantiodifferentiation represents another class of potent catalyst. The concept of heterobimetallic catalyst for use in catalytic asymmetric Michael addition reaction was introduced by Shibasaki et. al.[2] which marked the climax in this area enabling catalytic addition of malonates to acyclic as well as cyclic substrates with high enantioselectivities (Fig. 1).

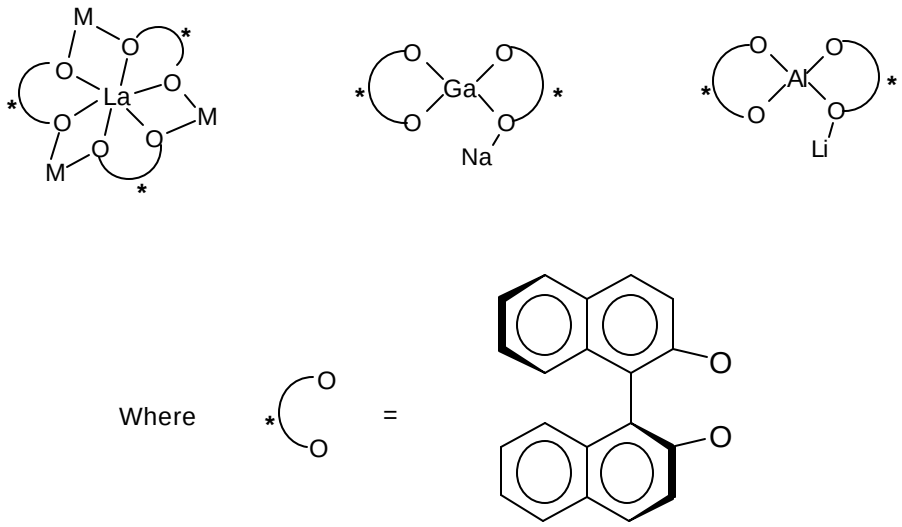


Figure 1

Extensive studies by the group of Shibasaki showed that lanthanum-sodium–BINOL complex[3] (LSB) is very selective in the addition of prochiral *ß*-ketoesters to methyl vinyl ketones whereas gallium–sodium complex[4] (GSB) and the aluminium–lithium complex[5] proved to be the catalyst of choice furnishing the Michael adducts of dibenzyl malonate in excellent yields and optical purity.

To clarify the nature of interaction between enone and the asymmetric catalyst, the complexation was studied by ^{1}H NMR spectroscopy. The chemical shift of the *a*-proton of cyclohexenone was observed upon mixing with the asymmetric bimetallic complex, where a small downfield shift of the *a*-proton was observed. This NMR study clearly indicated that the carbonyl group of the enone is coordinated to the La atom in the LSB complex. Following catalytic cycle was proposed for the addition of dimethyl malonate to cyclohexenone (Fig. 2).

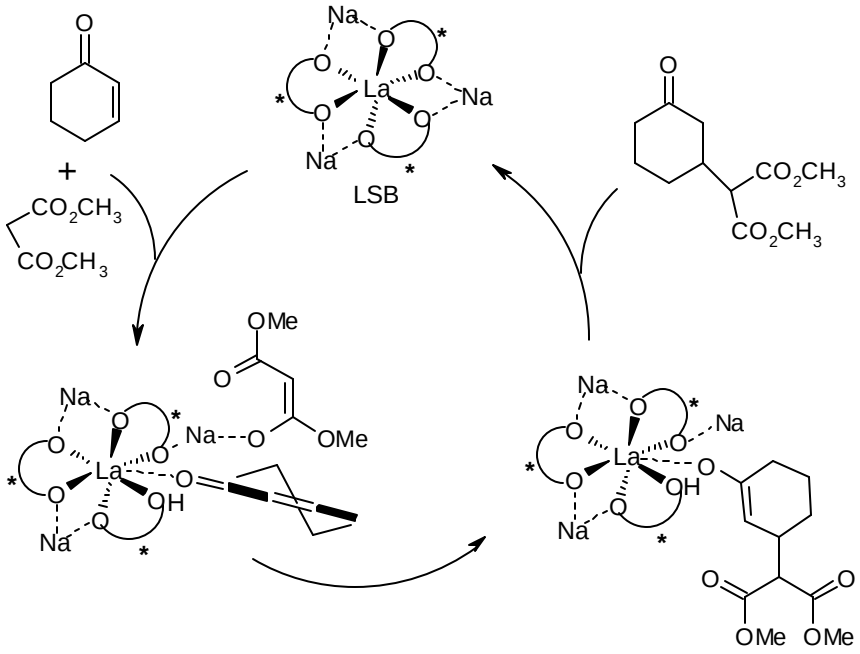


Figure 2

With cyclohexenone coordinated to the La metal cation, the plane of the cyclohexenone ring should be almost parallel to the closest naphthyl ring system. This facilitates attack of the coordinated sodium enolate of dimethyl malonate. The resulting sodium enolate of the optically active Michael adduct abstract a proton from an acidic-OH group to regenerate the LSB. Therefore the basic LSB complex also acts as a Lewis acid and controls the orientation of the carbonyl function to activate the enone to attack. The multifunctional nature of the LSB catalyst makes possible the formation of Michael adduct with high enantiomeric purity even at room temperature.

LSB was also applied to a catalytic asymmetric Michael reaction in which the asymmetric center is induced on the side of the adduct originating from the Michael donor.[6] The reaction of 2-ethyl cyclohexanone carboxylate to methyl vinyl ketone gave product in 23 %*ee* in THF whereas the reaction in toluene afforded product in 75 %*ee*. It was found that the slow addition of *ß*-ketoester using syringe pump method gave product with high enantiomeric excess. On the other hand, malonates give adducts with high enantiomeric purity regardless of the solvent used. These results can be rationalized by comparing the pK_a of *ß*-ketoester with that of a malonate, the former being significantly more acidic.

Therefore the concentration of the resulting Na-enolate can be expected to be greater in the case of the *ß*-ketoester. Furthermore this Na-enolate will react with an enone more slowly than than the Na-enolate derived from a malonate. It was suggested that this combination of more rapid formation and longer lifetime increases the likelihood of dissociation of the Na-enolate from the chelated ensemble to give a product of lower enantiomeric purity. In less polar CH_2Cl_2 the Na-enolate would remain part of the ensemble to afford the product with high enantiomeric excess (Fig. 3).

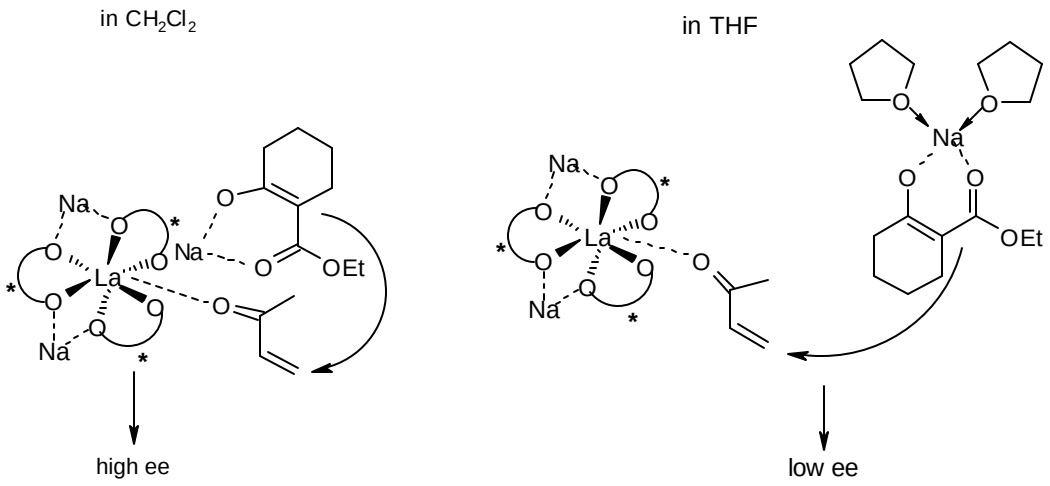


Figure 3

Proposed mechanism for the *ß*-ketoester also acts to limit undesired ligand exchange between BINOL moieties and the Michael donor.

The use of aluminium-lithium-BINOL complex was extended to *a*-nitro esters by Feringa et. al.[7] to get the desired product in up to 80 % optical purity. The 1,4-addition reaction is proposed to proceed *via* double coordination of the Michael acceptor to the heterobimetallic catalyst in accordance with the mechanism proposed by Shibasaki and co-workers. The lithium napthoxide moiety can function as a Bronsted base and the aluminium alkoxide function as a Lewis acid (Fig. 4).

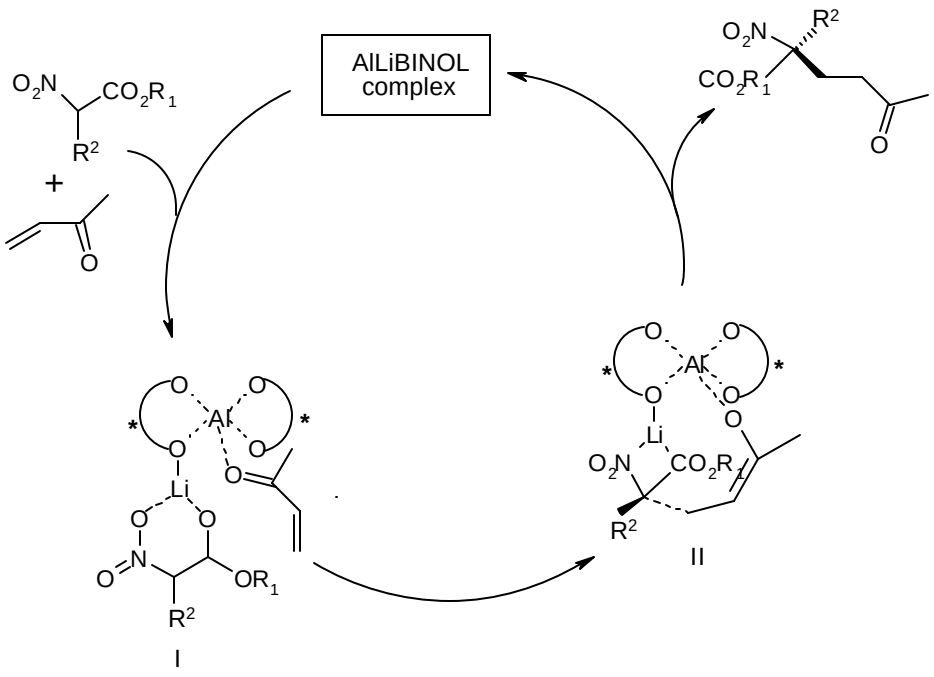


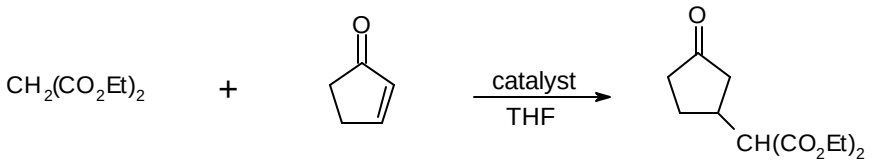
Figure 4

The reaction of *a*-nitro ester with the 'AlLiBINOL' complex gives the corresponding lithium enolate (I). This enolate then reacts with the enone, which is pre-coordinated to the aluminium Lewis acid center to give the aluminium enolate (II) after 1,4-addition. The resulting alkoxide then reacts with an acidic hydrogen of a Michael donor to form the desired Michael adduct and the 'Al Li BINOL' complex is regenerated.

Besides carbon nucleophiles, thiols were also subjected to 1,4-addition to cyclic enones furnishing the corresponding Michael adducts[8] with good yields and high enantioselectivities using LSB.

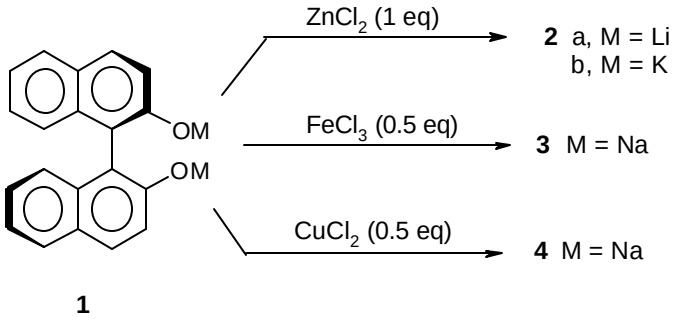
As heterobimetallic complexes proved to be excellent promoter for the Michael reaction, we set out to make a new class of heterobimetallic complex capable of catalyzing steroselective Michael addition reactions.

Results and discussion: At the onset, we chose diethyl malonate as Michael donor and cyclopentenone as Michael acceptor. Both these reactants are easily available and the resulting Michael adduct was reported[9] to have high specific rotation value of +28.35 (82% *ee*). We prepared several heterobimetallic complexes and checked their efficiency in promoting stereoselective Michael reaction of diethyl malonate to cyclopentenone (eqn. 1).



(1)

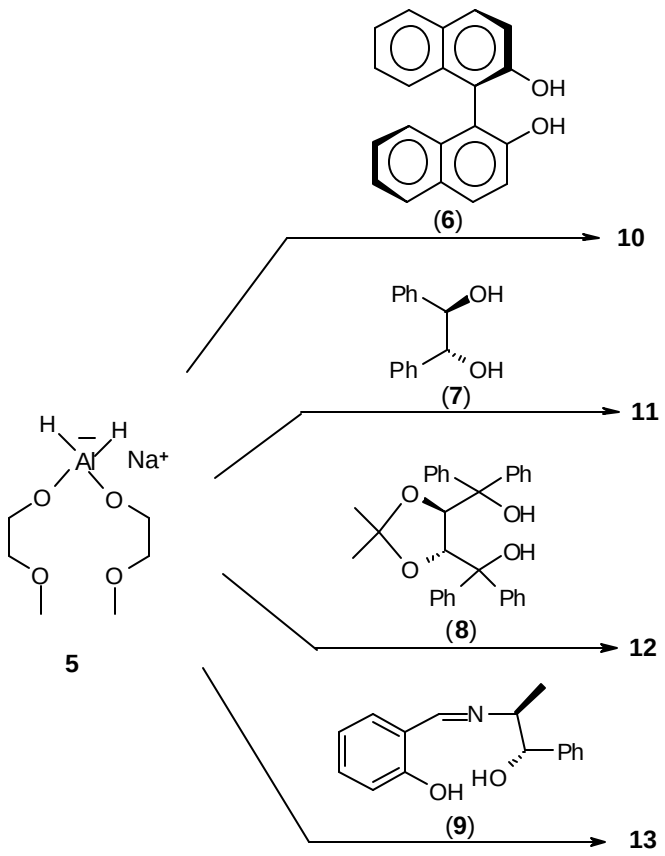
Initial attempts were made using dinaphthoxy salts of optically active BINOL in conjunction with various metal salts (Scheme 2).



Scheme 2

Except with the catalyst **2a** no product formation was observed with catalysts **2b**, **3** and **4** (eqn. 1). Though catalyst **2a** was found to be a good promoter of the reaction, the resulting product showed low optical purity (< 5%).

We next prepared a new series of heterobimetallic complexes using Red-Al® [sodium bis(2-methoxy ethoxy) aluminium hydride]. Red-Al® (**5**) is a cheap source for aluminium and sodium metals and these metals are known to act as an efficient promoter of the Michael reaction. The desired heterobimetallic complexes were prepared by the dropwise addition of Red-Al® solution (in toluene) to the solution of diol (1 equivalent) in THF at 0^{o}C as shown in Scheme 3.



Scheme 3

Catalyst **10** gave the Michael adduct in low optical purity (< 5%) after 6 hours stirring at room temperature. The catalyst **11** gave the product after 3 hours stirring at 0^{o}C in 8 % optical purity, whereas the catalyst **12** and **13** gave the Michael adduct in racemic form.

Recently a new class of ligand based on chiral SALEN has been made and their metal complexes have found application in various organic transformations.[10-17]

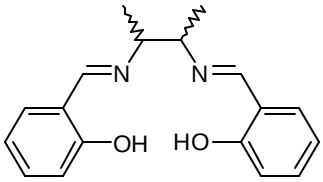


Figure-5

These tetra dentate ligands (Fig. 5) have been shown by several X-ray investigations[18] to coordinate with its donor atoms in a plane around the metal. This configuration is imposed by the shortness of the $-(CH_2)-$ bridge and the conjugated system of the ligand. Some of the applications for the metal-SALEN complexes are shown in Fig. 6.

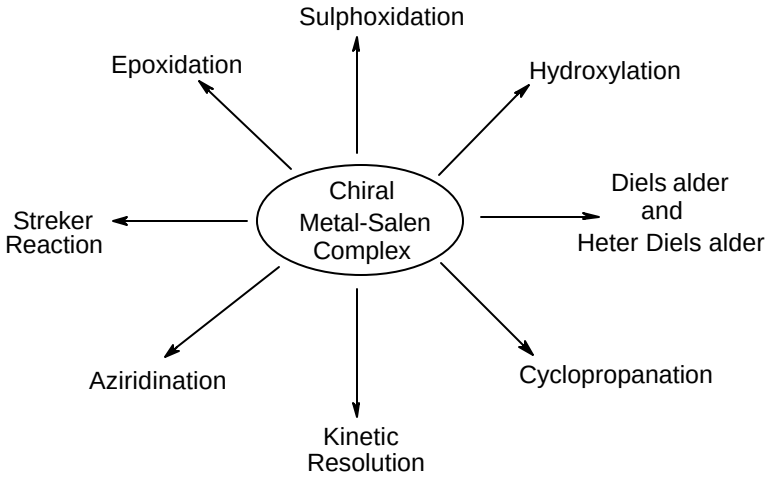
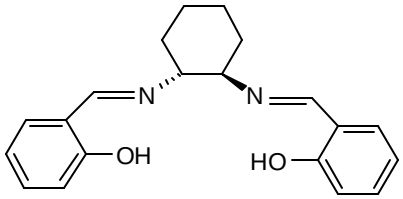


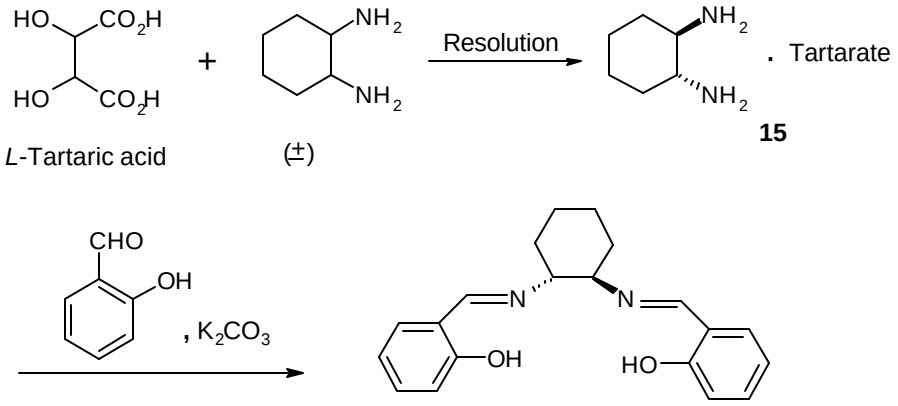
Figure 6

Although the SALEN-metal complexes have received wide applicability, their use in stereoselective Michael addition reaction is not reported. The chiral SALEN ligand we chose for our study was (*1R*,*2R*)-bis(salicylaldehyde)-*trans* cyclohexyl diamine (**14**).



14

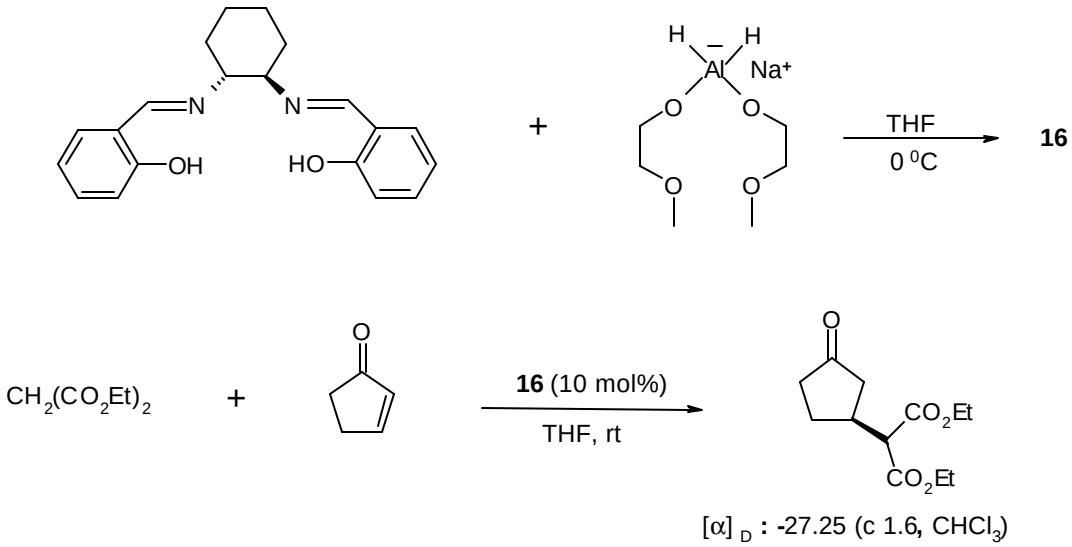
This SALEN ligand was prepared using the following strategy (Scheme 4).



Scheme 4

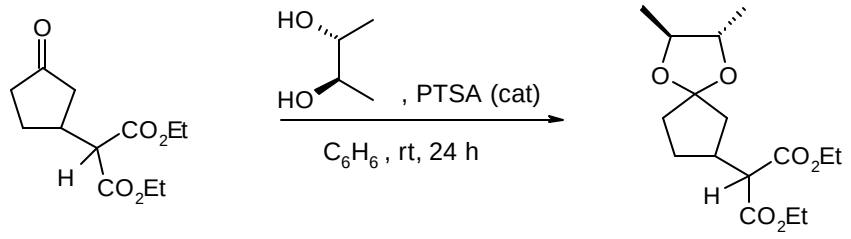
Cyclohexyl diamine was first resolved using *L*-tartaric acid. The optically active (*1R*,*2R*)-(+)-1,2-diamino cyclohexyl-*L*-tartarate thus obtained was treated with salicylaldehyde in the presence of potassium carbonate to get the desired SALEN ligand (**14**).

We next prepared a heterobimetallic complex using Red-Al® and the ligand **14**. This was achieved by the dropwise addition of Red-Al® solution (in toluene) to the SALEN ligand (**14**) in THF at 0^{o}C followed by the addition of diethyl malonate and cyclopentenone (in THF) at room temperature (Scheme 5).



Scheme 5

The reaction got over in 10 minutes to give the Michael adduct in 85% yield. The Michael adduct showed an $[a]_D$ value of –27.25 which corresponds to enantioselectivity of 78% based on the known literature value $[a]_D^{25}$ = +29.9 for 86 %*ee*. Same reaction when performed at 0^oC gave the adduct in 92% yield within 15 minutes. However much to our surprise, this product showed an $[a]_D^{25}$ value of –45.72 corresponding to more than 100% optical purity, which was not possible. Initial attempts to resolve the problem by HPLC analysis (Chiralpak OD® and Chiralpak AS® columns) failed. We resorted to another method reported[19] in the literature by making the diastereomeric ketal of the racemic Michael adduct using (*2R*,*3R*)-2,3-butanediol (eqn. 2).



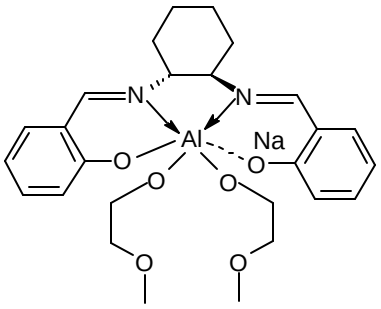
(2)

17

The methyne proton(H) comes as a doublet in the Michael adduct whereas in the ketalized product due to the diastereomeric nature of the compound **17**, methyne proton splits to give two sets of doublets with equal

integral areas in the racemic Michael adduct. However in the optically active product, these two doublets shows variations in their integral areas and thus the amount of optical induction in the product can be studied. Based on this method we found that the Michael adduct with $[a]_D$ value of –45.72 is of 33% enantiomeric excess.

We proposed the following tentative structure for our catalyst (**18**).



18

Although we have shown (**18**) as a hexa-coordinated aluminium center, we believe the coordinatively unsaturated aluminium is generated by the cleavage of phenoxy-aluminium bond. The complex was found to be moisture sensitive. Initial attempts to obtain the NMR of the complex failed due to line broadening. Also the heterobimetallic complex could not be crystallized for XRD-study.

We proposed the following catalytic cycle for the Michael addition reaction promoted by the heterobimetallic complex **18** (Fig. 7).

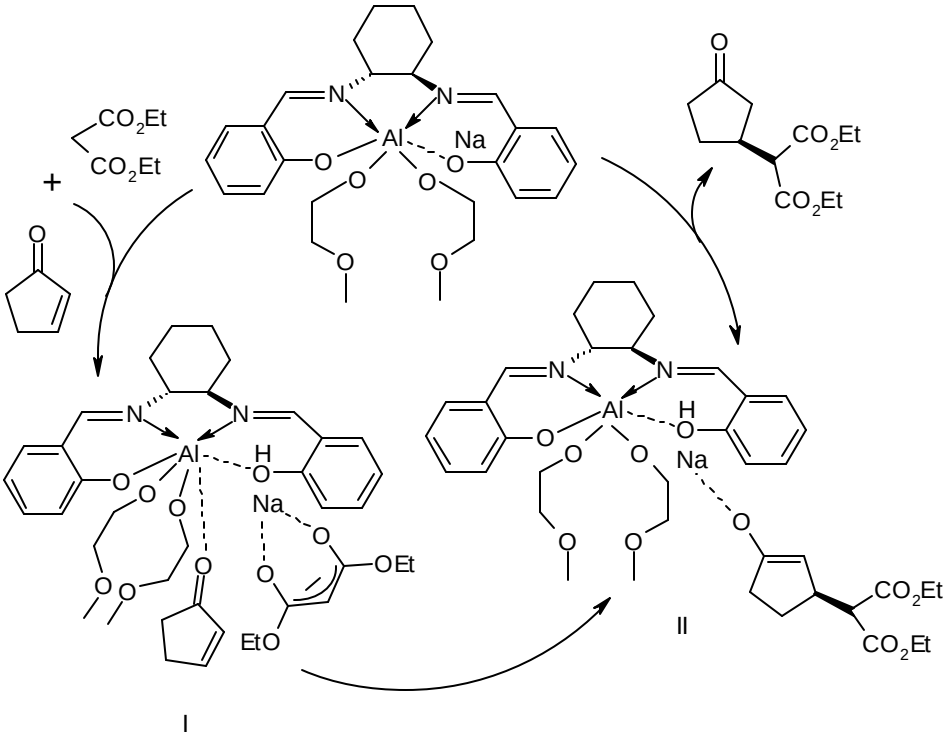
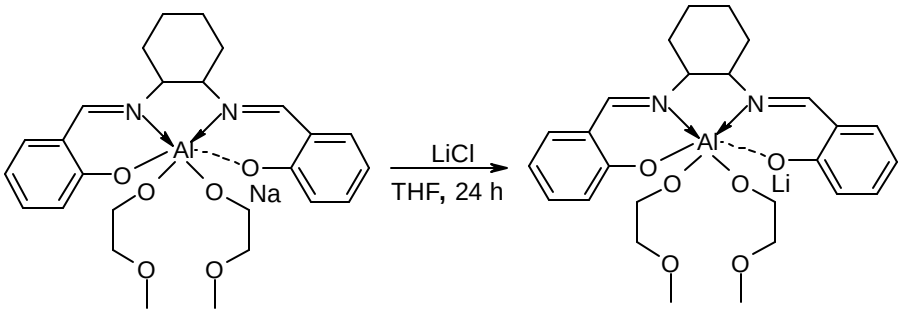


Figure 7

Due to the presence of Lewis acid as well as Bronsted base sites in the heterobimetallic complex **18**, Michael donor and acceptor co-ordinates with complex **18** to form species I. Sodium phenoxide which behaves as a Bronsted base, abstracts the proton from the Michael donor to form the corresponding sodium enolate whereas due to the Lewis acidic nature of the aluminium, the Michael acceptor coordinates to it *via* its lone pair of electrons present on the oxygen of the carbonyl functionality. This in turn brings the two reacting species in close proximity of each other in a well-defined stereoselective fashion. This leads to the attack of sodium enolate of Michael donor to the Michael acceptor to form species II. With the formation of the desired Michael product, the active catalyst is released back to the catalytic cycle.

To see the effect of other alkali metal on catalytic cycle, Na was replaced with Li by stirring complex **18** with 2 equivalents of LiCl over a period of 24 hours (eqn. 3).



(3)

19

When complex **19** was used (eqn. 1), the reaction was found to be extremely sluggish thus clearly highlighting the superiority of complex **18** over complex **19**. To study the solvent effect on enantioselection, the reaction (eqn. 1) was performed in various solvents, the results of which is summarized in Table 1.

Table 1. Solvent effect on the asymmetric Michael addition reaction.

Entry	Solvent	Temp (^{o}C)	*ee* (%)
1	THF	25	20
2	THF	0	33
3	Toluene	0	18
4	Ether	0	16
5	CH_2Cl_2	0	21

At room temperature, reaction in THF and dichloromethane gave the product in comparable optical purity, however at 0^{o}C reaction in THF showed considerable increase in optical purity of the Michael adduct compared to the reaction in dichloromethane. Reaction in toluene and ether gave the Michael adduct with 18% and 16% enantioselectivity. These reactions clearly showed the advantage of THF over other solvents.

In order to optimize the catalyst concentration, reaction was carried out using varying amount of the heterobimetallic complex **18**, the results of which is summarized in Table 2.

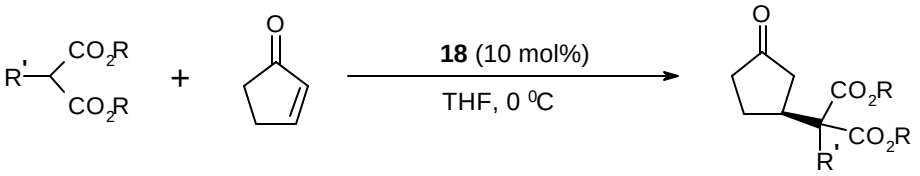
Table 2 . Catalyst concentration for the asymmetric Michael addition reaction.

Entry	**18** (in mol%)	Time (min.)	*ee* (%)
1	5	60	15
2	10	15	33
3	20	10	36

As shown in Table 2, reaction performed with 5 mol% of the catalyst **18** gave the desired Michael product in 15% optical purity after 60 minutes. As already mentioned, with 10 mol% of the catalyst Michael adduct obtained showed 33% enantioselectivity whereas reaction using 20 mol% of the complex **18** gave the Michael adduct in 36% optical purity. Thus doubling the catalyst concentration resulted in an increase of only 3% enantiomeric excess. These reactions clearly showed that the optimum catalyst concentration for the reaction (eqn. 1) using heterobimetallic complex **18** is 10 mol%.

After standardizing the reaction conditions, we next studied[20] Michael addition reaction using various sterically different Malonate esters with cycloalkenones the results of which are summarized in Table 3.

Table 3. Addition of malonate esters to cycloalkenones using catalyst **18**.

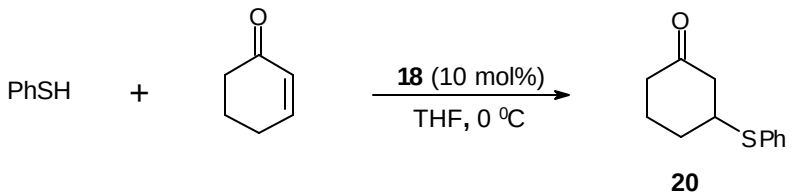


Entry	Enone	R	R'	Time (min.)	Yield[a] (%)	$[a]_D$ in $CHCl_3$	*ee* (%)
1	1	Me	H	10	86	- 46.2(c 1.60)	58[b]
2	1	Et	H	15	92	- 45.7(c 1.60)	33[c]
3	1	i-Pr	H	15	89	- 37.2(c 1.63)	36[c]
4	1	t-Bu	H	45	83	- 39.6(c 1.66)	40[c]
5	1	CH_2Ph	H	240	75	- 25.2(c 1.36)	41[c]
6	2	Me	H	15	85	- 1.5(c 2.10)	37[b]
7	2	Et	H	20	88	- 1.2(c 2.56)	34[b]
8	1	Et	Me	15	88	- 37.0(c 1.63)	56[b]

a: isolated yield.; b: by HPLC analysis.; c: by NMR study.

A maximum of 58% enantiomeric excess was observed for the Michael addition of dimethyl malonate to cyclopentenone as found by chiral HPLC column (Diacel Chiralpak-AS® column).[21] All the products obtained were *(S)*-configured as confirmed by the sign of optical rotation for two compounds of known configuration (entry 6 and 7 in Table 3). Also in all the cases the *(S)*-isomer was second to elute from the chiral HPLC column.

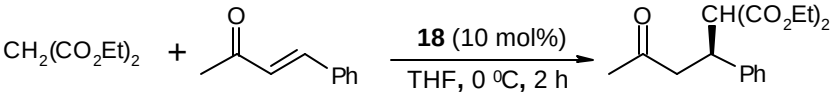
The heterobimetallic complex **18** was also checked for its efficiency involving other class of Michael reactants. It was found to be an excellent promoter for the addition of thiophenol to cyclohexenone to give the desired adduct (**20**) within 5 minutes at 0^0C in more than 90% yield. However resulting product showed no optical activity (eqn. 4).



(4)

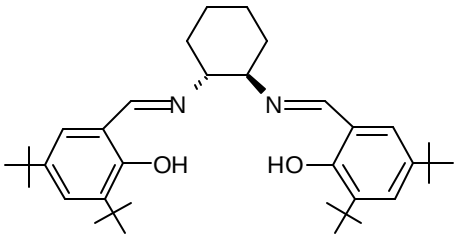
20

Complex **18** was found to catalyze the addition of diethyl malonate to benzylidene acetone to give the desired Michael adduct[22] (**21**) in 35% enantioselectivity. Further decrease in the reaction temperature resulted in sharp fall of the reaction rate (eqn. 5).

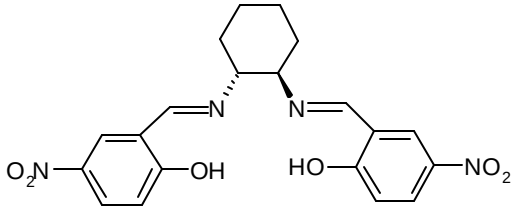


21 35% *ee* (5)

To study the steric and electronic factors which influences the catalyst activity, modified SALEN ligands **22** and **23** were made.

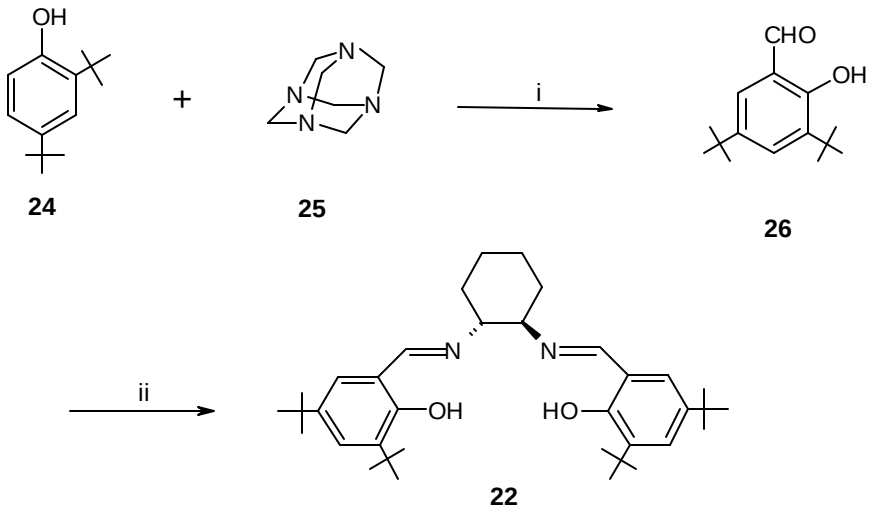


22



23

The SALEN **22** was made using 2,4-di-tert butyl phenol (**24**) as shown in Scheme 6.



24 **25** **26** **22**

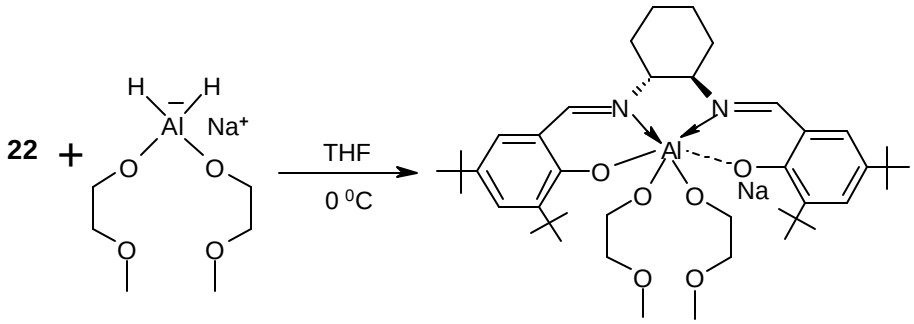
(i)**.** a : AcOH, 130 ^{0}C, 2 h ; b : H_2SO_4 (30%), 110 ^{0}C, 1 h

(ii)**.** (*1R*,*2R*)-(+)-1,2-diamino cyclohexane-*L*-tartarate, K_2CO_3, EtOH

Scheme 6

Using Duff formylation,[23] 2,4-di-tert butyl phenol was reacted with hexamethylene tetraamine (**25**) and glacial acetic acid at 130^{o}C followed by the addition of sulphuric acid (30%) to get the desired formyl derivative (**26**) in 50% yield. Compound **26** on treatment with (1R,2R)-(+)-1,2-diaminocyclohexane-L-tartarate gave the required 2,4-di-tert butyl substituted SALEN ligand[24] (**22**).

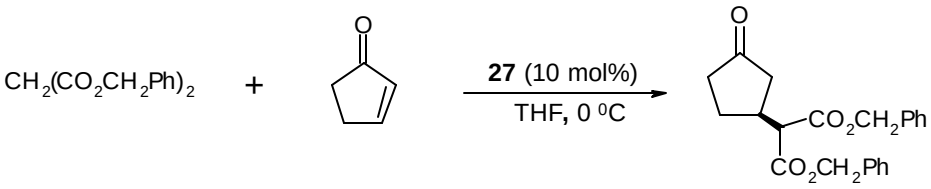
The SALEN ligand **22** was reacted with Red-Al® to get the desired heterobimetallic complex **27** (eqn. 6).



(6)

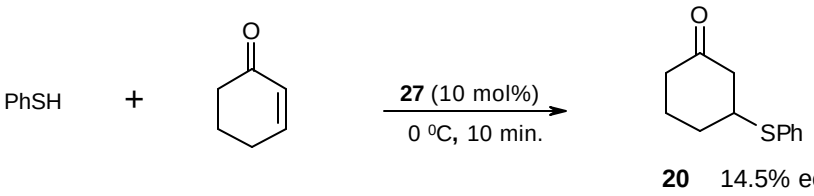
27

In the complex **27** due to the presence of bulky tert-butyl groups at the reaction center, we predicted that this would lead to a more well defined catalytic pocket at the reaction site. The heterobimetallic complex **27** was checked for its efficiency in promoting stereoselective Michael addition of dibenzyl malonate to cyclopentenone. Complex **27** was found to be a good promoter of the reaction giving the product in 85% yield. However the Michael adduct obtained was near racemic (eqn. 7).



(7)

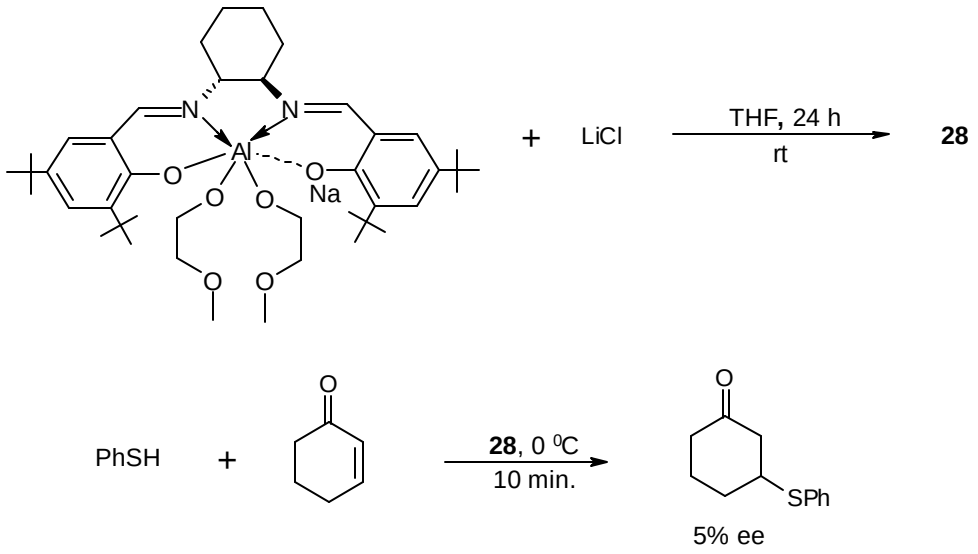
Heterobimetallic complex **27** was also checked for the stereoselective addition of thiphenol to cyclohexenone. The Michael adduct[25] (**20**) was obtained in more than 85% yield and in 14.5% enantiomeric excess (eqn. 8).



20 14.5% ee

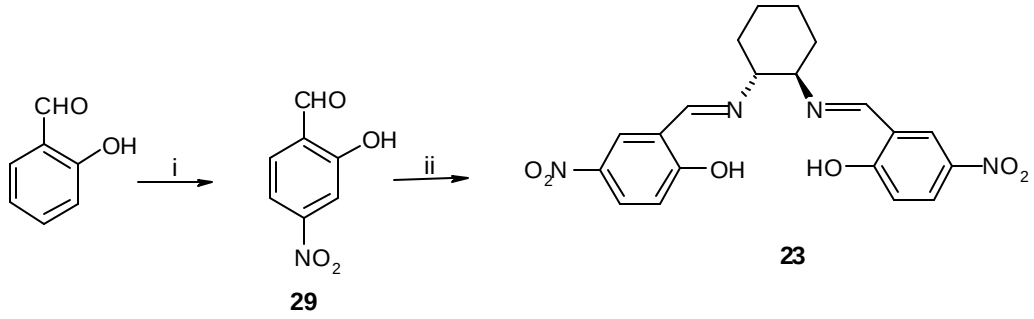
(8)

Change of solvent did not improve the enantioselectivity. Similar to the reaction in eqn. 3, replacement of sodium by lithium in the complex **27** results in decrease of the enantioselectivity (Scheme 7).



Scheme 7

To study electronic factors affecting the heterobimetallic complex **18**, nitro substituted SALEN ligand **23** was made as shown in the Scheme 8.



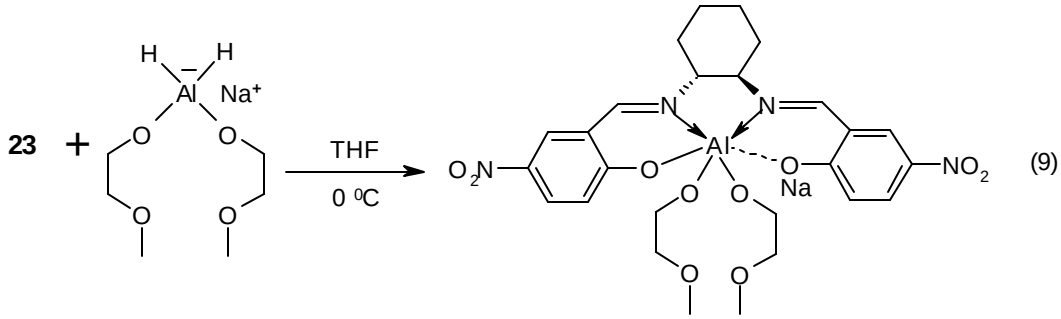
29 **23**

i. a: AcOH / HNO_3 ; b: crystallisation
ii. (*1R*,*2R*)-(+)-1,2-diamino cyclohexane-*L*-tartarate

Scheme 8

A solution of salicylaldehyde in glacial acetic acid was nitrated using nitric acid to give 5-nitro and 3-nitro derivative of salicylaldehyde. The required 5-nitro derivative[26] was separated from the 3-nitro derivative by crystallization from sodium hydroxide solution followed by acidification to get pure 5-nitro salicylaldehyde (**29**). Compound **29** was used for the SALEN ligand preparation[27] by reacting it with (1R,2R)-(+)-1,2-diamino cyclohexane-L-

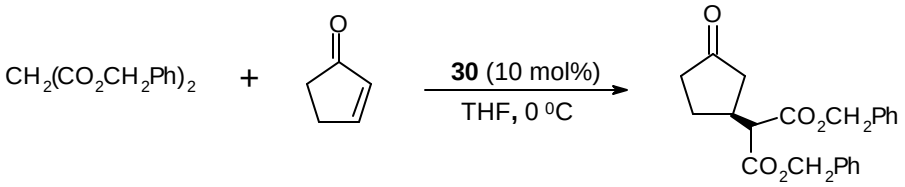
tartarate. The desired SALEN ligand (**23**) was then utilized for the preparation of heterobimetallic complex **30** (eqn. 9).



(9)

30

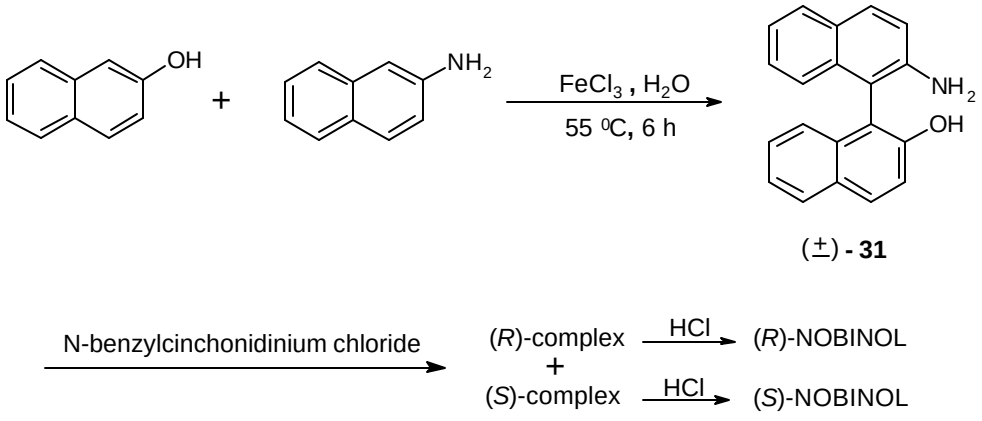
In the complex **30**, due to the presence of electron withdrawing nitro group the acidity of the phenolic group increases, which enhances the Lewis acidity of the central aluminium metal. This should make aluminium to coordinate strongly with the Michael acceptor. Based on this idea we checked the heterobimetallic complex **30** for the Michael reaction of dibenzyl malonate to cyclopentenone (eqn. 10).



(10)

Complex **30** was found to be an efficient catalyst to give the Michael adduct in more than 80% yield with up to 17% optical purity of the adduct. Complex **30** was also used for the addition of thiophenol to cyclohexenone. Though the catalyst was an efficient promoter, the resulting product was racemic.

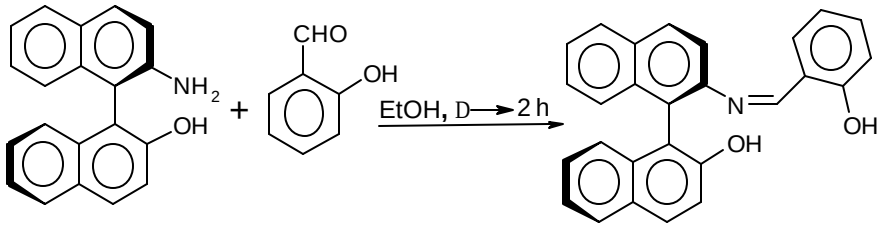
Another heterobimetallic complex based on NOBINOL (**31**) was also used (Scheme 9).



Scheme 9

ß-Naphthol and ß-naphthylamine were coupled using ferric chloride. The racemic NOBINOL was resolved[29] using N-benzylcinchonidinium chloride. (R)-NOBINOL cinchonidinium complex remained in the mother liquor. Treatment with aqueous hydrochloric acid gave the two isomers in optically pure form.

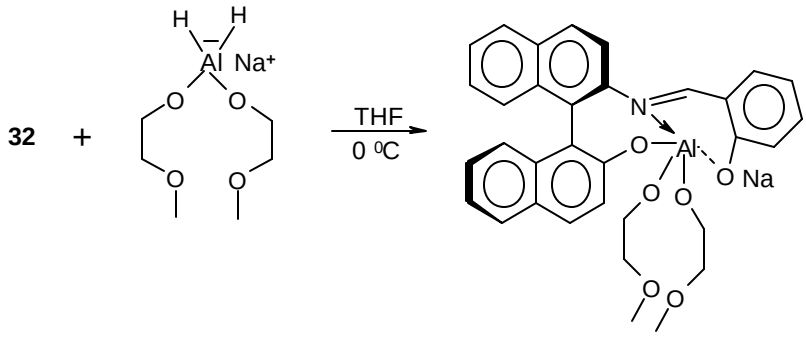
The Schiff base of optically active NOBINOL was made using salicylaldehyde (eqn. 11).



(11)

32

(R)-(+)-NOBINOL and salicylaldehyde were refluxed in ethanol for 2 hours to give the desired Schiff base (**32**). Compound **32** was then used for preparing the heterobimetallic complex with Red-Al® (eqn. 12).

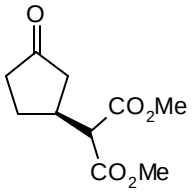


(12)

33

This new heterobimetallic complex (**33**) was found to be an excellent promoter for the Michael addition of thiophenol to cyclohexenone, however it failed to induce chirality in the resulting Michael adduct.

Chiral Michael adducts synthesized during the study



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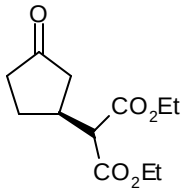

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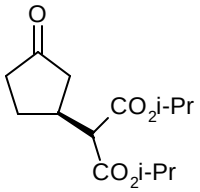

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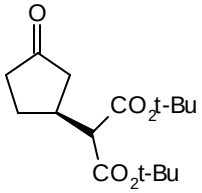

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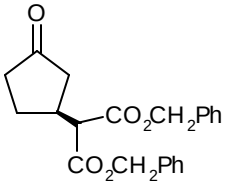

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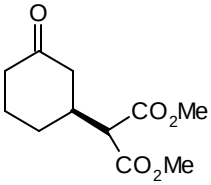

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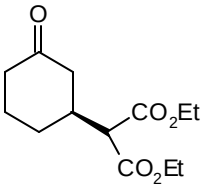

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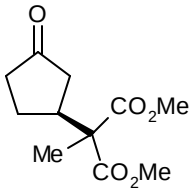

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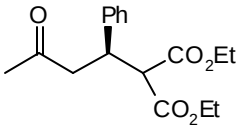

21

Scheme 10

Conclusion

1. The catalysts prepared from Red-Al® and various chiral diols, though catalyzed the Michael addition of diethyl malonate to cyclopentenone, the resulting product showed low enantioselectivity.
2. A new heterobimetallic complex prepared form Red-Al® and (1R,2R)-bis (salicylaldehyde)-trans cyclohexyl diamine efficiently catalyzed the Michael addition of diethyl malonate to cyclopentenone to give product in 33% optical purity.
3. The optcal purity was determined either by using ^{1}H NMR method or by using chiral HPLC column.
4. The heterobimetallic complex also catalyzed the Michael addition of diethyl malonate to benzylidene acetone to give product in 35% ee.
5. The heterobimetallic complex obtained from 2,4-di-tert butyl SALEN and Red-Al® catalyzed the Michael addition of thiophenol to cyclohexenone to give product in up to 10% enantioselectivity.
6. Heterobimetallic complex prepared from 4-nitro substituted SALEN and Red-Al® catalyzed the addition of dibenzyl malonate to cyclopentenone to give product in up to 17% optical purity.
7. Heterobimetallic complex based on optically active NOBINOL and Red-Al® though efficiently catalyzed the addition of thiophenol to cyclohexenone, it failed to induce chirality in the product.
8. In conclusion we have examined a variety of sodium-aluminium-SALEN complexes as heterobimetallic catalyst for the Michael addition. Although enantioselectivities are only modest, this is a conceptually new catalytic system.

Experimental Section

Resolution of cis/trans-1,2-diamino cyclohexane **:** To a solution of L-tartaric acid (30 g, 200 mmol) in distilled water (80 mL) cis/trans-1,2-diamino cyclohexane was added at such a rate that temperature does not exceed 70°C followed by the addition of glacial acetic acid at such a rate that temperature does not exceed 90°C. The reaction mixture was stirred at room temperature for 2 hours, then cooled to 5°C and kept at this temperature for further 2 hours. The reaction mixture was filtered, the solid residue washed with cold distilled water (1 x 20 mL) followed by methanol (5 x 20 mL) and then dried under reduced pressure to get the desired (1R,2R)-(+)-1,2-diamino cyclohexane-L-tartarate (**15**) as a white solid.

Yield.	25.6 g (80%)
$[a]_D^{25}$	+15.0 (c 4, H_2O)
	lit.[30] +12.5 (c 4, H_2O)

Preparation of (1R,2R)-bis(salicylaldehyde)-trans-cyclohexyl diamine (**14**) **:**

To the solution of **15** (2.65 g, 10 mmol) and anhydrous K_2CO_3 (4.15 g, 30 mmol) in distilled water (30 mL), a solution of salicylaldehyde (2.10 mL, 20 mmol) in ethanol (10 mL) was added. The reaction mixture was stirred at 60°C for 1 hour, then cooled to room temperature, diluted with water (20 mL) and extracted with ether (3 x 10 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The viscous residue was dissolved in hexane and cooled to −10°C to obtain (1R,2R)-bis (salicylaldehyde)-trans-cyclohexyl diamine **14** as yellow crystals.

Yield.	5.15 g (80%)
m.p.	64-66°C
^{1}H NMR	δ 1.18-2.05 (m, 8H), 3.12-3.48 (m, 2H), 6.04-6.95 (m, 4H), 7.05-7.35 (m, 4H), 8.25 (s, 2H), 13.33 (br.s, OH, 2H)
^{13}C NMR	δ 24.00, 32.89, 72.37, 116.66, 118.39, 118.61, 131.33, 131.99, 160.92, 164.63
MS: m/z	322 [M^+], 201, 184, 122 (base peak)
$[a]_D^{25}$	-650 (c 1, MeOH)
	lit.[31] - 644 (c 1, MeOH)

Preparation of Al-SALEN complex (**18**) **:** To a stirred solution of SALEN ligand **14** (0.064 g, 0.2 mmol) in THF (1 mL) at 0°C, Red-Al® (0.2 mmol, 1M solution in toluene) was added dropwise and stirred for additional 15 minutes. The resulting solution of the complex **18** was used directly.

General procedure[20] *for Michael reaction involving addition of dialkyl malonates to cycloalkenones* **:** The catalyst solution **18** was cooled to 0°C and to this a solution of malonate ester (2 mmol) and cycloalkenone (2 mmol) in THF (4 mL) was added dropwise. The reaction was monitored by TLC. After completion of the reaction, it was quenched by 1N HCl (1 mL) and brought to room temperature. The reaction mixture was diluted with ether (10 mL), washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to "flash chromatography" on silica gel (200-400 mesh) using ethyl acetate-petroleum ether as the eluent to obtain pure product.

(S)-3-[Bis(methoxy carbonyl)methyl] cyclopentanone (**34**)

Colourless oil

Yield.	86%
^{1}H NMR	δ 1.45-1.76 (m, 1H), 1.96 (dd, J = 11.7 and 19.5 Hz, 1H), 2.06-2.35 (m, 3H), 2.46 (dd, J = 6.8 and 18.1, 1H), 2.65-2.95 (m, 1H), 3.34 (d, J = 9.3 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H)
^{13}C NMR	δ 26.7, 35.8, 37.4, 42.1, 51.9, 55.4, 167.9, 168.0, 216.2
MS: m/z	214 [M^+], 132 (base peak)
$[a]_D^{25}$	-46.2 (c 1.60, $CHCl_3$)
ee.	58% (estimated by Diacel Chiralpak-AS® column (0.46 x 25 cm), 220 nm detector, i-PrOH in Hexane (40%), 2 mL / min flow rate, t_R = 8.5 minutes and t_S = 9.5 minutes).

(S)-3-[Bis(ethoxy carbonyl)methyl] cyclopentanone (**35**)

Colourless oil

Yield	92%
^{1}H NMR	δ?1.18-1.39 (m, 6H), 1.52-1.82 (m, 1H), 2.10 (dd, J = 11.7 and 18.6 Hz, 1H), 2.12-2.41 (m, 3H), 2.52 (dd, J = 7.8 and 18.6 Hz,

	1H), 2.72-3.00 (m, 1H), 3.34 (d, J = 9.3 Hz, 1H), 4.10-4.30 (m, 4H)
^{13}C NMR	δ 13.4, 26.8, 35.7, 37.4, 42.1, 55.6, 60.6, 167.6, 216.2
MS: m/z	242 [M^+], 160 (base peak)
$[a]_D^{25}$	-45.7 (c 1.60, $CHCl_3$)
ee.	33% (estimated by ^{1}H NMR of the diasteromeric ketal)

(S)-3-[Bis(iso-propoxy carbonyl)methyl] cyclopentanone (**36**)

Colourless oil

Yield	89%
^{1}H NMR	δ 1.09-1.41 (m, 12H), 1.50-1.81 (m, 1H), 2.02 (dd, J = 11.2 and 18.1 Hz, 1H), 2.13-2.40 (m, 3H); 2.51 (dd, J = 7.3 and 18.1 Hz, 1H), 2.69-3.00 (m, 1H), 3.27 (d, J = 9.3 Hz, 1H), 4.90-5.25 (m, 2H)
^{13}C NMR	δ 21.1,26.9, 35.7, 37.6, 42.3, 56.4, 68.5, 68.6, 167.2, 216.5
MS: m/z	270 [M^+], 104 (base peak)
$[a]_D^{25}$	-37.17 (c 1.63, $CHCl_3$)
ee.	36% (estimated by ^{1}H NMR)

(S)-3-[Bis(tert-butoxy carbonyl)methyl] cyclopentanone (**37**)

White solid

Yield	83%
m.p.	72^{o}C
^{1}H NMR	δ 1.46 (s, 9H), 1.48 (s, 9H), 1.67-1.87 (m, 1H), 2.01 (dd, J = 11.3 and 18.5 Hz), 2.12-2.39 (m, 1H), 3.13 (d, J = 9.8 Hz, 1H)
^{13}C NMR	δ 27.2, 27.7, 36.0, 37.9, 42.6, 58.4, 81.6, 167.2, 217.0
MS: m/z	298 [M^+], 186 (base peak)
$[a]_D^{25}$	-39.6 (c 1.66, $CHCl_3$)
ee.	40% (estimated by ^{1}H NMR)

(S)-3-[Bis(benzyloxy carbonyl)methyl] cyclopentanone (**38**)

Colourless oil

Yield	75%

^{1}H NMR	δ 1.44-1.75 (m, 1H), 1.98 (dd, J = 11.2 and 18.6 Hz, 1H), 2.08-2.33 (m, 3H), 2.45 (dd, J = 6.8 and 18.6 Hz, 1H), 2.72-3.10 (m, 1H), 3.44 (d, J = 9.3 Hz, 1H), 5.14 (s, 2H), 5.16 (s, 2H), 7.11-7.47 (m, 10H)
^{13}C NMR	δ 27.0, 35.9, 37.7, 42.3, 56.0, 66.9, 127.9, 128.2, 134.9, 167.4, 216.5
MS: m/z	366 [M^{+}], 90 (base peak)
$[a]_D^{25}$	-25.15 (c 1.60, $CHCl_3$)
ee.	41% (estimated by ^{1}H NMR)

(S)-3-[Bis(methoxy carbonyl)methyl] cyclohexanone (**39**)

Colourless oil

Yield	85%
^{1}H NMR	δ 1.32-1.83 (m, 2H), 1.93-2.17 (m, 2H), 2.18-2.66 (m, 5H), 3.37 (d, J = 7.8 Hz, 1H), 3.76 (s, 6H)
^{13}C NMR	δ 23.9, 28.0, 37.5, 40.2, 44.3, 51.7, 55.7, 167.6, 208.6
MS: m/z	228 [M^{+}], 97 (base peak)
$[a]_D^{25}$	-1.5 (c 2.10, $CHCl_3$)
	lit.[32] +3.33 (c 2.10, $CHCl_3$) for (R)-isomer with 83% ee.
ee.	37% (estimated by HPLC)

(S)-3-[Bis(ethoxy carbonyl)methyl] cyclohexanone (**40**)

Colourless oil

Yield	88%
^{1}H NMR	δ 1.28 (t, 6H), 1.36-1.84 (m, 2H), 1.94-2.16 (m, 2H), 2.26-2.66 (m, 5H), 3.34 (d, J = 7.8 Hz, 1H), 4.15-4.25 (m, 4H)
^{13}C NMR	δ 13.4, 23.9, 28.0, 37.4, 40.2, 44.3, 56.1, 60.7, 167.1, 167.2, 208.6
MS: m/z	256 [M^{+}], 160 (base peak)
$[a]_D^{25}$	-1.2 (c 2.56, $CHCl_3$)
	lit.[32] +2.89 (c 2.56, $CHCl_3$) for (R)-isomer with 81% ee.
ee	34%

(S)-3-[1,1-Bis(ethoxy carbonyl)ethyl] cyclopentanone (**41**)

Colourless oil

Yield	88%
^{1}H NMR	δ 1.27 (t, J = 7.3 Hz, 6H), 1.45 (s, 3H), 1.56-1.93 (m, 1H), 2.00-2.57 (m, 5H), 2.74-3.00 (m, 1H), 4.05-4.34 (m, 4H)
^{13}C NMR	δ 13.7, 17.4, 24.2, 38.0, 40.3, 41.1, 55.2, 61.0, 170.9, 216.9
MS: m/z	256 [M^+], 174 (base peak)
$[a]_D^{25}$	-37.0 (c 1.60, $CHCl_3$)
ee	56% (estimated by HPLC)

General procedure for making the diasteromeric ketal for ^{1}H NMR analysis[19] **:** A solution of ketone (0.1 mmol), (2R,3R)-butane diol (0.1 mmol) and PTSA (10 mg) in toluene (1 mL) was stirred at room temperature for 24 hours. The reaction mixture was diluted with petroleum ether, passed through a short pad of alumina and concentrated under reduced pressure to provide the ketal.

Procedure for the Michael addition of diethyl malonate to benzylidiene acetone **:** The catalyst solution **18** was cooled to 0^{o}C and to this, a solution of diethyl malonte (0.32 g, 2 mmol) and benzylidene acetone (0.29 g, 2 mmol) in THF (2 mL) was added and the reaction was monitored by TLC. After the completion of reaction (2 hours), reaction was quenched by 1N HCl (1 mL) and brought to room temperature. The reaction mixture was then diluted with ether (10 mL), washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to "flash chromatography" using ethyl acetate–petroleum ether as eluent to obtain the pure product **21**.

Yield	87%
^{1}H NMR	δ 1.02 (t, 6.82 Hz, 3H), 1.27 (t, 6.83 Hz, 3H), 2.03 (s, 3H), 2.84-3.02 (m, 2H), 3.71 (d, J = 10.24 Hz, 1H), 3.96-4.02 (m, 3H), 4.18 (q, J = 7.32 Hz, 2H), 7.20-7.28 (m, 5H)
^{13}C NMR	δ 13.34, 13.59, 29.77, 4017, 47.01, 57.04, 60.79, 61.12, 126.77, 127.84, 128.02, 140.26, 167.24, 167.76, 205.43
MS: m/z	306 [M^+], 146 (base peak)
$[a]_D^{25}$	+7.1 (c 1.02, CCl_4)

	lit.[22] $[a]_D^{25}$ +10.8 (c 1.04, CCl_4) for (R) isomer with 53% ee
ee.	35.4%

Procedure for the formylation of 2,4-di-tert butyl phenol: A mixture of the phenol **24** (8.4 g, 41 mmol), HMTA (11.4 g, 82 mmol) and glacial acetic acid (20 mL) was heated at 130°C for 2 hours. It was the cooled to 75°C and H_2SO_4 (20 mL, 30%) was added and the reaction mixture was kept at 105-110°C for 60 minutes. The reaction mixture was then transferred to a preheated separating funnel (at 75°C) so as to separate the lower aqueous phase. The top organic phase was separated and MeOH (5 mL) was added to it and then kept at 10°C for 12 hours. The desired product (**26**) was filtered and dried under vacuum.

Yield	4.8 g (50%)
mp.	57-59°C
	lit.[23] 58-60°C

Preparation of (R,R)-N,N'-bis(3,5-di-tert-butyl-salicylidene)-1,2-cyclohexane diamine (**22**) : To the solution of **15** (2.65 g, 10 mmol) and anhydrous K_2CO_3 (4.15 g, 30 mmol) in distilled water (14 mL), EtOH (53 mL) was added and the reaction mixture refluxed. To this refluxing solution, **26** (4.68 g, 20 mmol) dissolved in EtOH (22 mL) was added dropwise over a period of 10 minutes and the reaction mixture was further refluxed for 2 hours. Water (50 mL) was added and the reaction mixture was cooled to 5°C and kept at this temperature for 2 hours, then filtered. The solid residue was redissolved in CH_2Cl_2, given a brine wash and the organic phase was kept over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a yellow solid which on recrystallization from toluene gave the pure product **22**.

Yield	5.20 g, 95%
mp.	208-210°C
	lit.[24] mp. 200-203°C
^{1}H NMR	δ 1.23 (s, 18H), 1.41 (s, 18H), 1.82-2.10 (m, 8H), 3.25-3.39 (m, 2H), 6.99 (s, 2H), 7.31 (s, 2H), 8.30 (s, 2H), 13.77 (br.s, OH, 2H)
^{13}C NMR	δ 24.40, 29.58, 31.46, 33.26, 34.07, 35.02, 72.44, 118.02, 126.07, 126.81, 136.55, 140.00, 158.12, 165.99
MS: m/z	546 (M^++1, base peak), 313, 258, 218
$[a]_D^{25}$	-301.7 (c 1, CH_2Cl_2)

lit.[24] $[\alpha]_D^{20}$ -315 (c 1.00, CH_2Cl_2)

*Preparation of the heterobimetallic complex **27** and its use in the Michael addition of thiophenol to cyclohexenone* **:** To a stirred solution of SALEN ligand **22** (0.11 g, 0.2 mmol) in THF (1 mL) at 0°C, Red-Al® (0.2 mmol, 1M solution in toluene) was added dropwise and stirred for 15 minutes. To this, a solution of thiophenol (0.21 mL, 2 mmol) and cyclohexenone (0.20 mL, 2 mmol) in THF (2 mL) was added at 0°C. The progress of the reaction was monitored by TLC. After the completion of reaction (10 minutes), 1N HCl (1 mL) was added and the reaction was brought to room temperature. The reaction mixture was diluted with ether (10 mL), washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to "flash chromatography" to obtain the desired Michael adduct **20**.

Yield	0.38 g (90%)
^{1}H NMR	δ 1.55-1.87 (m, 2H), 1.87-2.55 (m, 5H), 3.27-3.62 (m, 1H), 7.18-7.67 (m, 5H)
^{13}C NMR	δ 23.48, 30.72, 40.39, 45.61, 47.26, 127.28, 128.68, 132.65, 208.04
MS: m/z	206 [M^+](base peak), 110, 77
$[\alpha]_D^{25}$	-10.43 (c 1, C_6H_6)
	lit.[25] $[\alpha]_D^{25}$ -16.4 (c 1, C_6H_6) for (S) isomer with 22.5% ee.
ee.	14.5%

Procedure for the nitration of salicylaldehyde[26] **:** A solution of glacial acetic acid (80 mL) and salicylaldehyde (77.5 mL, 164 mmol) was cooled to 10°C and HNO_3 (16 mL, 69-72 %) was slowly added over a period of 2 hours. After the addition, temperature was allowed to increase up to 45°C. Ice cooled water (400 mL) was poured and the reaction mixture was allowed to stand overnight. It was then filtered and the solid residue was dissolved in 1N NaOH solution (120 mL) and again left overnight and filtered. The solid residue thus obtained was stirred with in 1N aqueous HCl solution and extracted with ethyl acetate (3 x 25 mL), followed by brine wash and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the solid residue was crystallized from ethyl acetate-petroleum ether. The resulting 5-nitro-salicylaldehyde derivative **29** was directly used for the next step without further purification.

Preparation of (R,R)-N,N'-bis(5-nitro-salicylidene)-1,2-cyclohexane diamine (**23**)[27]**:** To the solution of **15** (2.65 g, 10 mmol) and anhydrous K_2CO_3 (4.14 g, 30 mmol) in distilled water (20 mL), derivative **29** (3.30 g, 20 mmol) dissolved in EtOH (10 mL) was added. TLC after an hour showed completion of the reaction. To the reaction mixture, water (50 mL) was added and extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid residue was crystallized in toluene to obtain the desired SALEN ligand (**23**).

Yield	3.80 g, (92%)
mp.	216-217°C
^{1}H NMR	δ 1.50-2.25 (m, 8H), 3.28-3.62 (m, 2H), 6.94 (d, J = 8 Hz, 2H), 7.78-8.50 (m, 6H), 14.34 (br.s, OH, 2H)
^{13}C NMR	δ 23.77, 32.49, 71.45, 116.85, 118.35, 127.95, 139.12, 163.71, 167.68
MS: m/z	412 (M^+), 246, 229, 167 (base peak), 130
$[a]_D^{25}$	-32.58 (c 1, $CHCl_3$)

*Preparation of the heterobimetallic complex **30** and its use in the Michael addition of dibenzyl malonate to cyclopentenone* **:** To a stirred solution of the SALEN ligand **23** (0.082 g, 0.2 mmol) in THF (1 mL) at 0°C, Red-Al® (0.2 mmol, 1M solution in toluene) was added dropwise and stirred for 15 minutes. To this, a solution of dibenzyl malonate (0.57 g, 2 mmol) and cyclopentenone (0.17 mL, 2 mmol) dissolved in THF (2 mL) was added at 0°C and the progress of the reaction was monitored by TLC. After completion of the reaction (1.5 hours), 1N HCl (1 mL) was added and reaction was brought to room temperature. The reaction mixture was diluted with ether, washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by "flash chromatographed" to obtain the desired Michael adduct **38**.

Yield	0.61 g (80%)
$[a]_D^{25}$	-11.04 (c 1.35, $CHCl_3$)
ee.	18% (estimated by ^{1}H NMR)

Preparation[28] *of 2-hydroxy-2'-amino-1,1'-binaphthalene* (**31**) **:** To a solution of ß-naphthol (7.21 g, 50 mmol) and ß-naphthylamine (7.16 g, 50 mmol) in water (200 mL), $FeCl_3$ (32.44 g, 200 mmol) dissolved in water (50 mL) was added and the reaction mixture was stirred at 55°C for 6 hours, cooled to room temperature and filtered. The solid residue was crystallized from toluene.

Yield 13.50 g (95%)

mp. 234-237°C

lit.[33] mp. 239-241°C

Resolution of **31:** To the suspension of 2-amino-2'-hydroxy-1,1'-binaphthalene (7.12 g, 25 mmol) in acetone (120 mL), N-benzyl cinchonidinium chloride (5.26 g, 12.50 mmol) was added and the reaction mixture was refluxed for 4 hours, cooled to room temperature and filtered. The solid residue was a 1:1 complex of (R)-(+)-**31** and N-benzyl cinchonidinium chloride. This solid residue was suspended in 1N HCl (50 mL), ethyl acetate (100 mL) was added and stirred. The upper organic layer was separated, given a brine wash and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave (R)-(+)-2-amino-2'-hydroxy-1,1'-binaphthalene (**31**).

$[a]_D^{25}$ +115.19 (c 1.00, THF)

lit.[29] $[a]_D^{25}$ +117 (c 1, THF)

The mother liquor was evaporated to dryness, 1N HCl (20 mL) and ethyl acetate (100 mL) was added and stirred for 30 minutes. The upper organic layer was removed, washed with brine wash and stored over anhydrous Na_2SO_4. The solvent was evaporated to obtain (S)-(-)-2-amino-2'-hydroxy-1,1'-binaphthalene (**31**).

$[a]_D^{25}$ -110 (c 1, THF)

lit.[29] $[a]_D^{25}$ = -117 (c 1, THF)

To the solution of **31** (2.85 g, 10 mmol) in EtOH (10 mL), salicylaldehyde (1.05 mL, 10 mmol) dissolved in EtOH (5 mL) was added and the reaction mixture was refluxed for 2 hours. It was then cooled to room temperature. EtOH was removed under reduced pressure, water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL), organic phase given a brine wash, dried over anhydrous Na_2SO_4 and solvent was removed to obtain schiff **32**.

Yield 3.51 g (90%)

mp. 226-228°C

^{1}H NMR	δ 5.01 (br.s, OH, 1H), 6.55-8.20 (m, 16H), 8.66 (s, 1H), 12.05 (br.s, OH, 1H)
^{13}C NMR	δ 116.12, 116.67, 117.59, 118.66, 118.91, 119.46, 122.70, 124.13, 125.97, 126.45, 126.85, 128.21, 128.36, 129.46, 129.65, 132.62, 132.84, 133.10, 133.40, 133.87, 143.61, 153.02, 160.45, 162.51
MS: m/z	389(M^{+}), 372, 268(base peak), 239
$[a]_D^{25}$	+145.28 (c 0.50, MeOH)
Analysis for	$C_{27}H_{19}NO_2$
Calculated	C : 83.54 H : 4.81 N : 3.46
Found	C : 83.48 H : 4.80 N : 3.49

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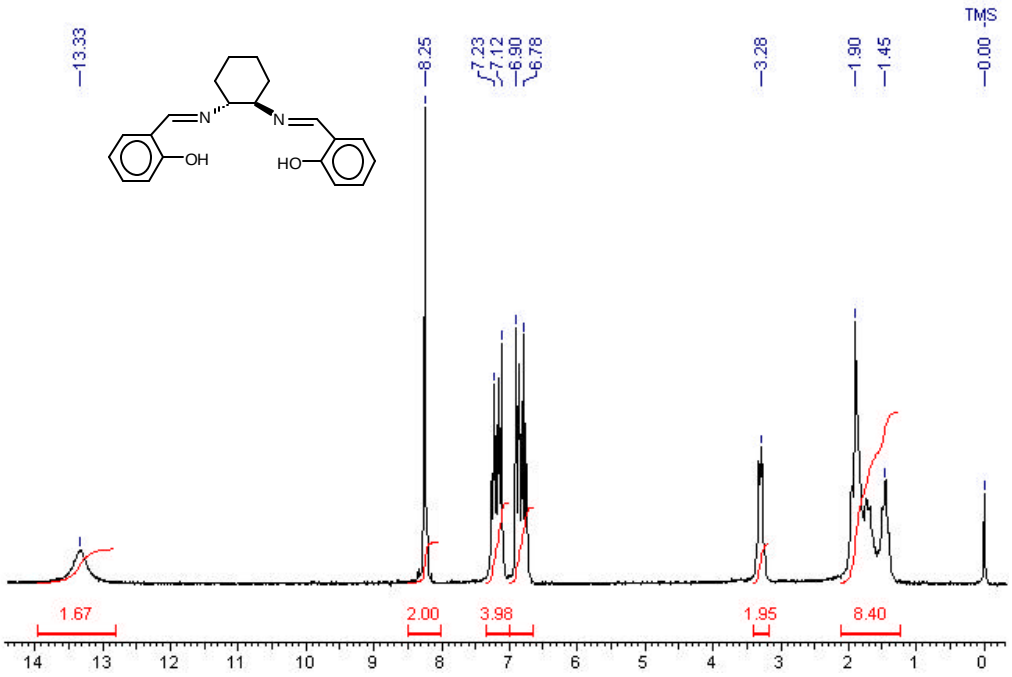
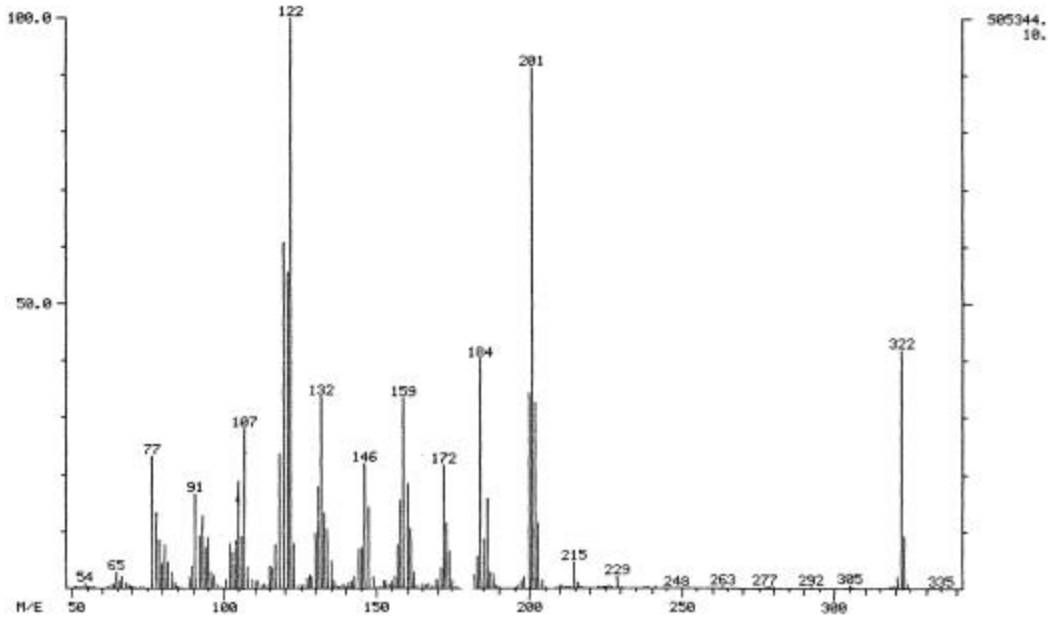
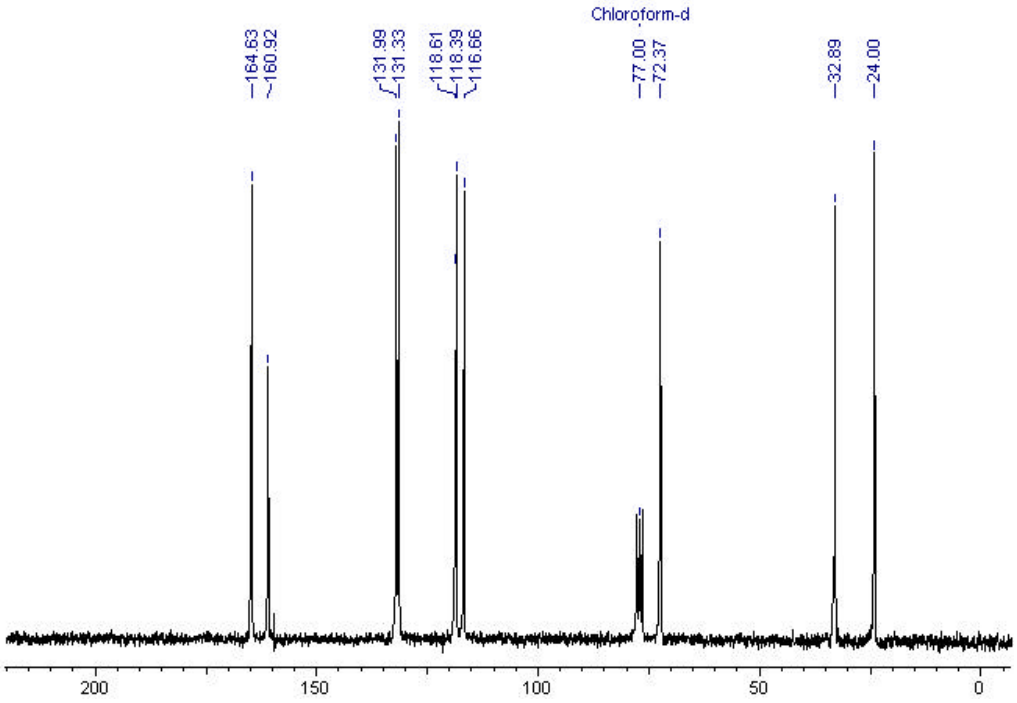
➢ ^{1}H NMR(in $CDCl_3$) of **14**



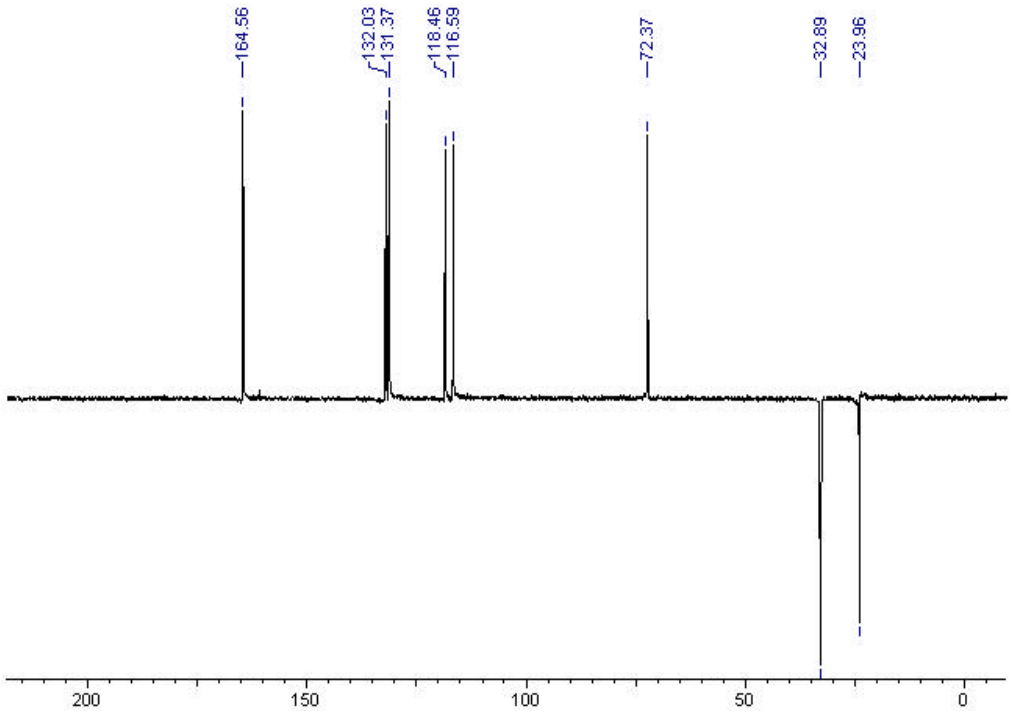
➢ Mass spectrum of **14**



- ^{13}C NMR (in $CDCl_3$) of **14**



- DEPT (in $CDCl_3$) of **14**



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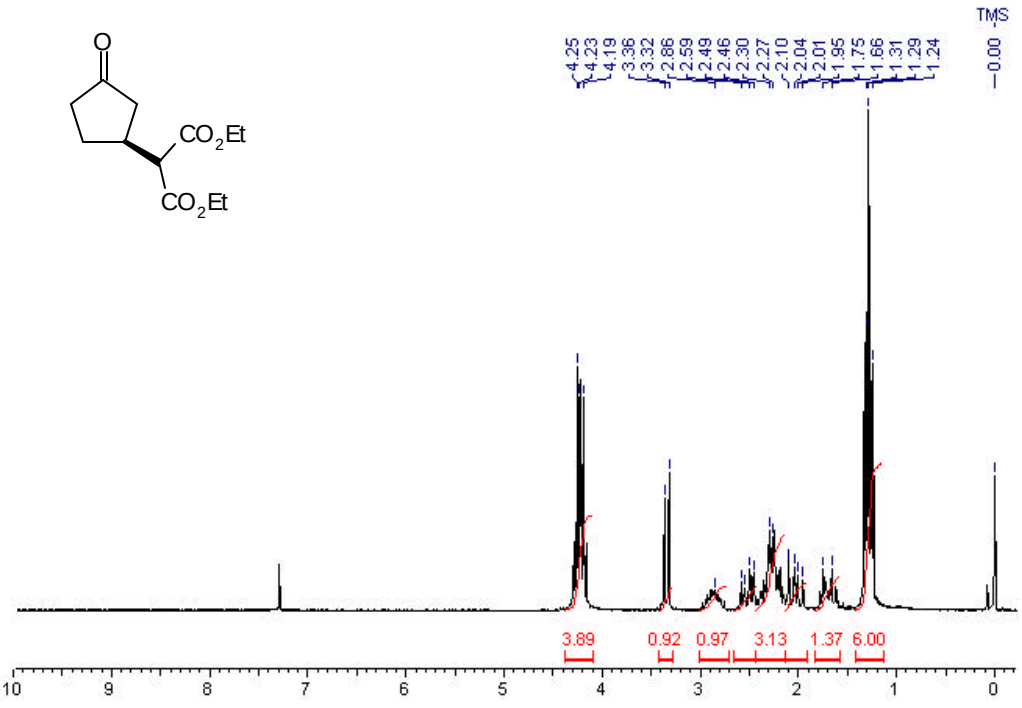

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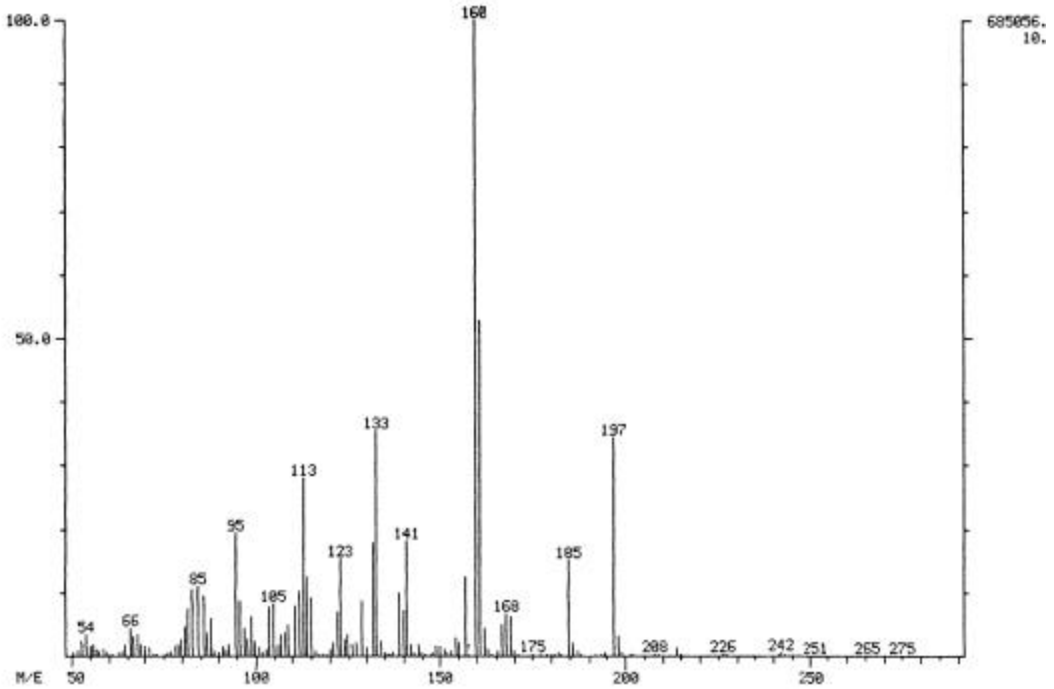

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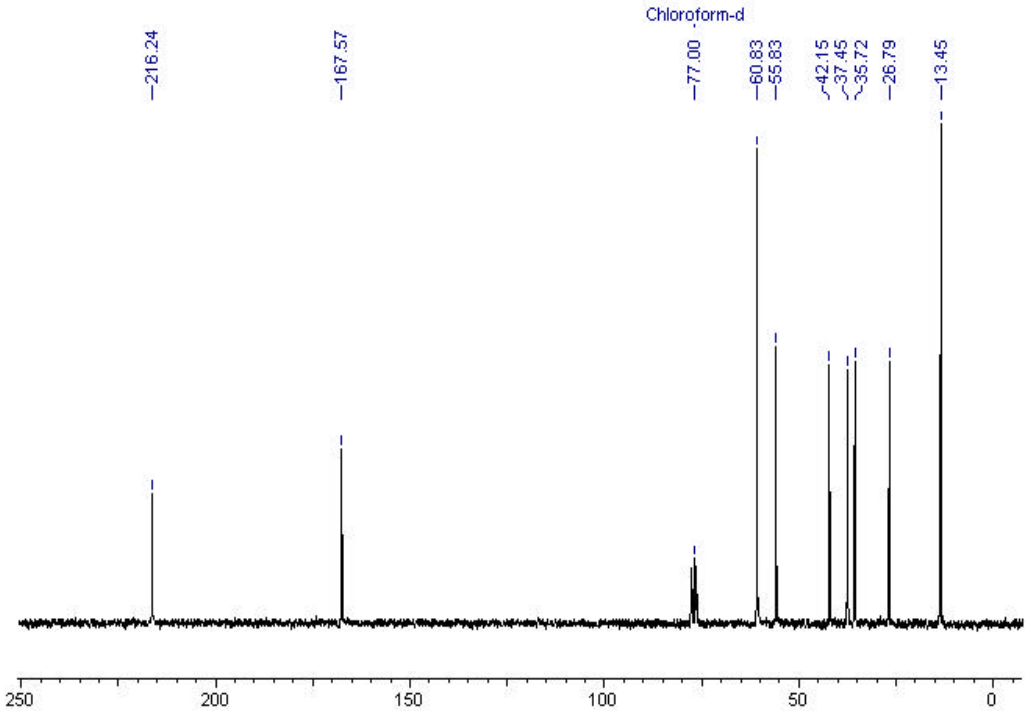

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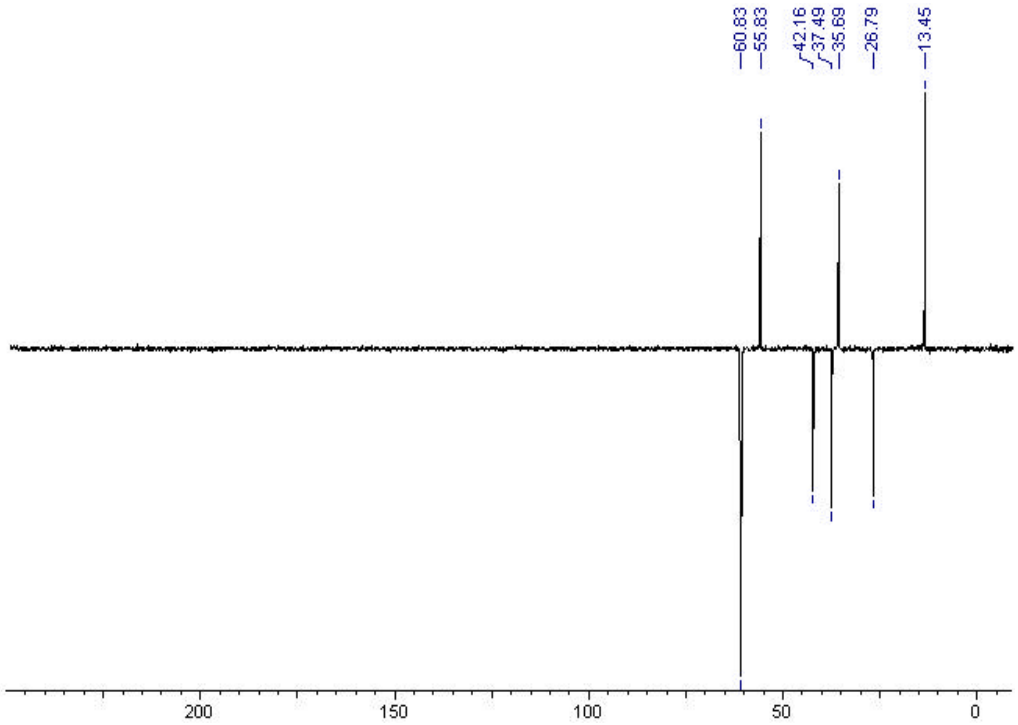
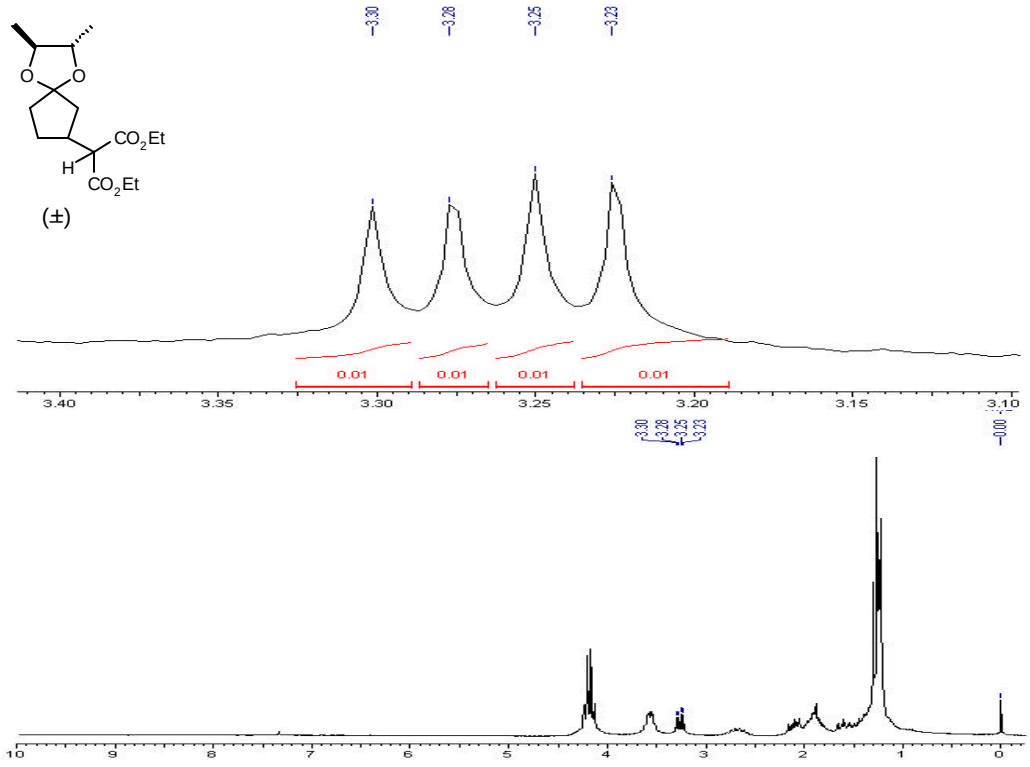


➢ ^{1}H NMR (in $CDCl_3$) of (±)-**17** for ee determination.



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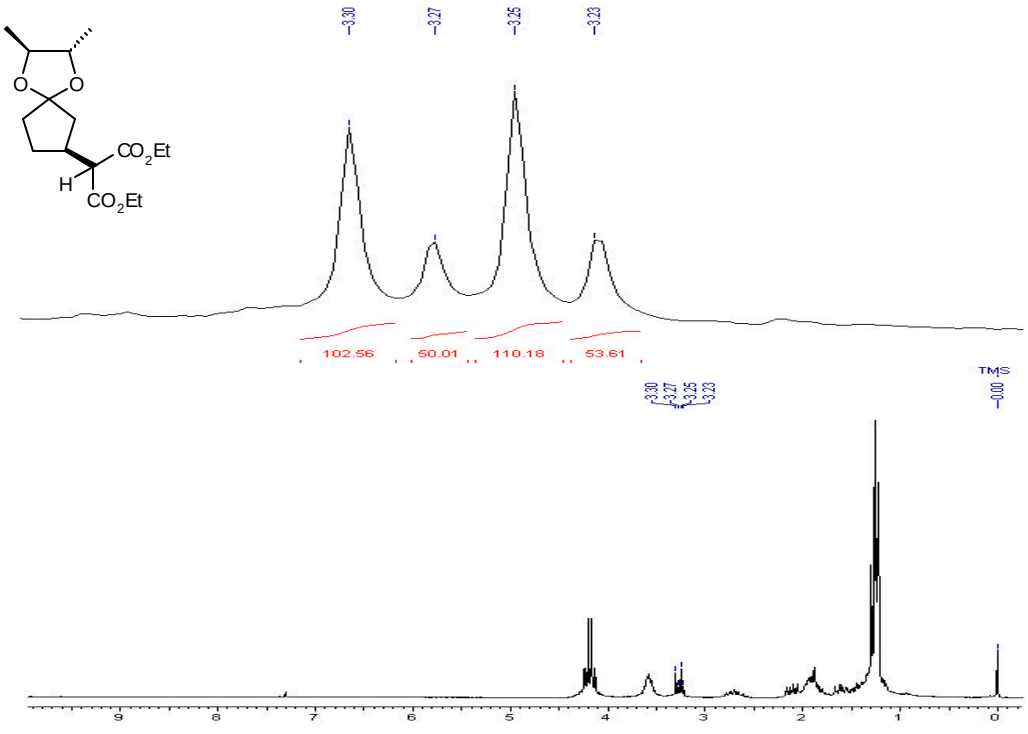
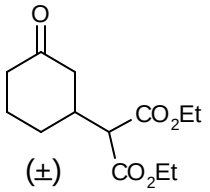
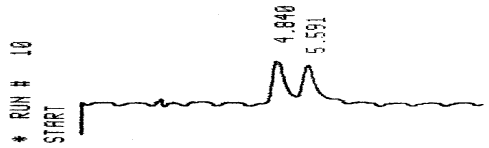
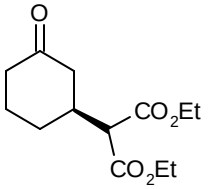


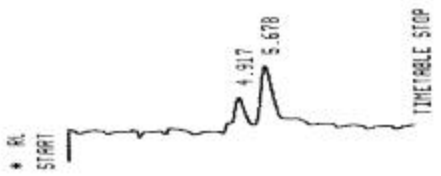
- HPLC of (±)-**40** on Diacel Chiralpak-AS® column.



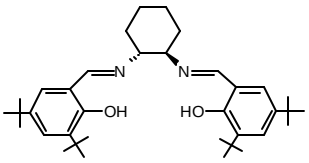


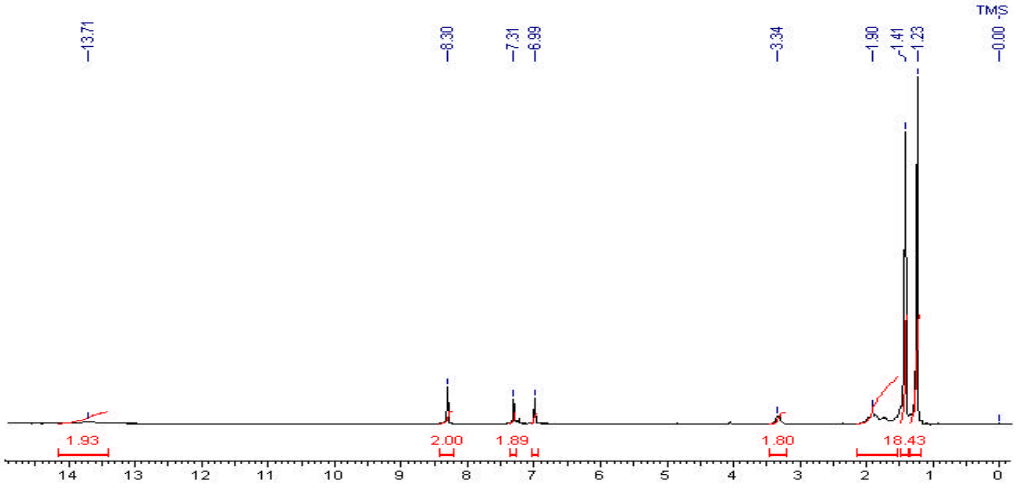
- HPLC of (S)-**40** on Diacel Chiralpak-AS® column



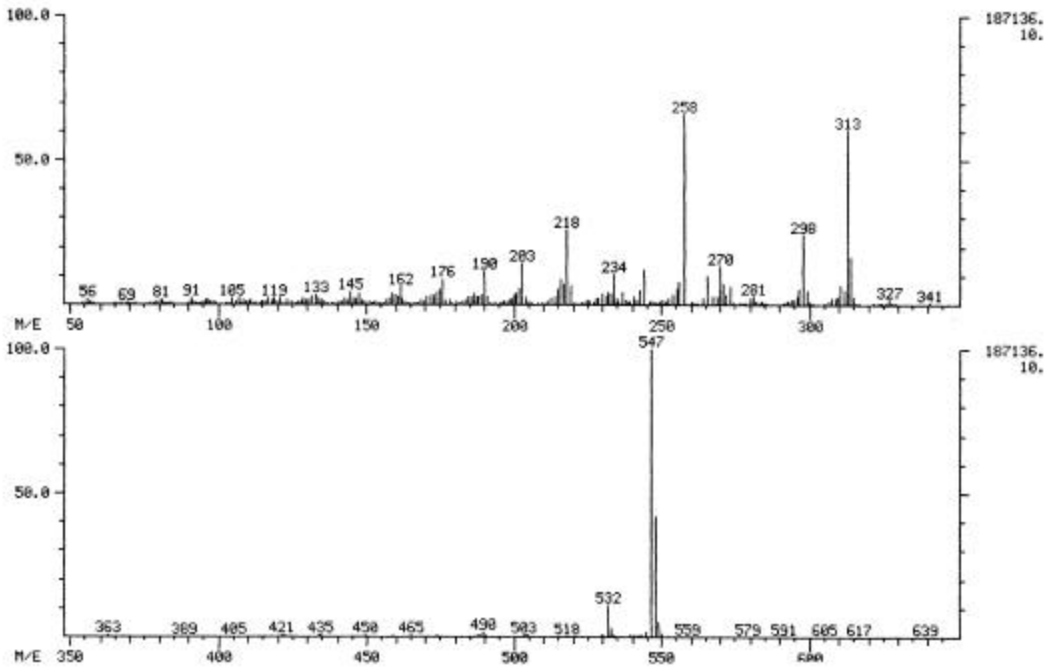


- ^{1}H NMR(in $CDCl_3$) of **22**

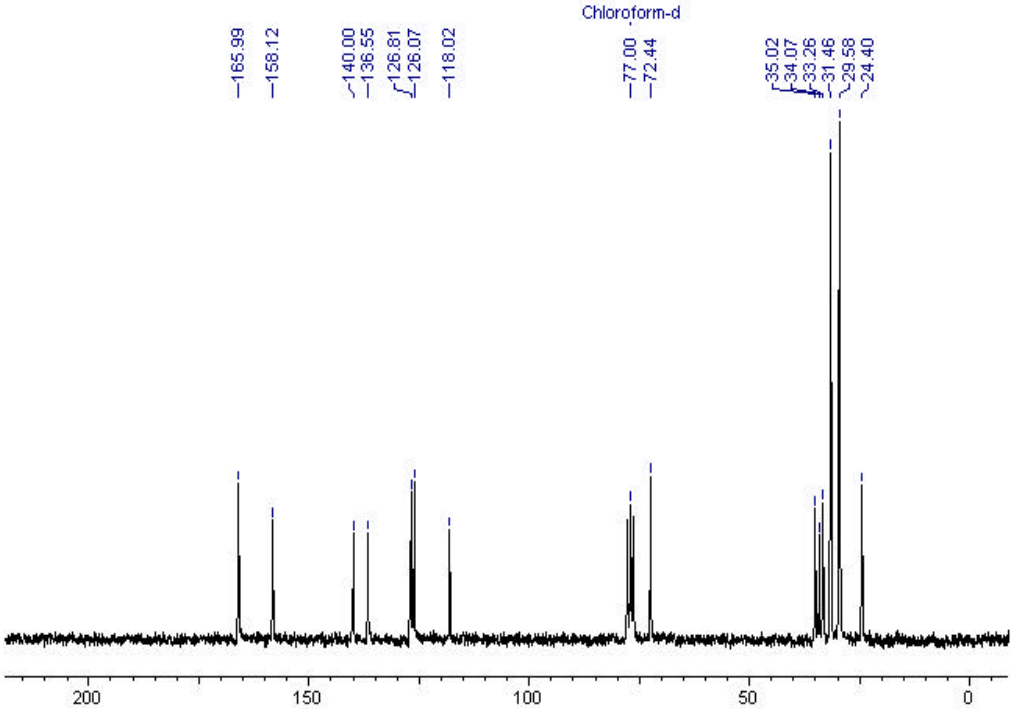




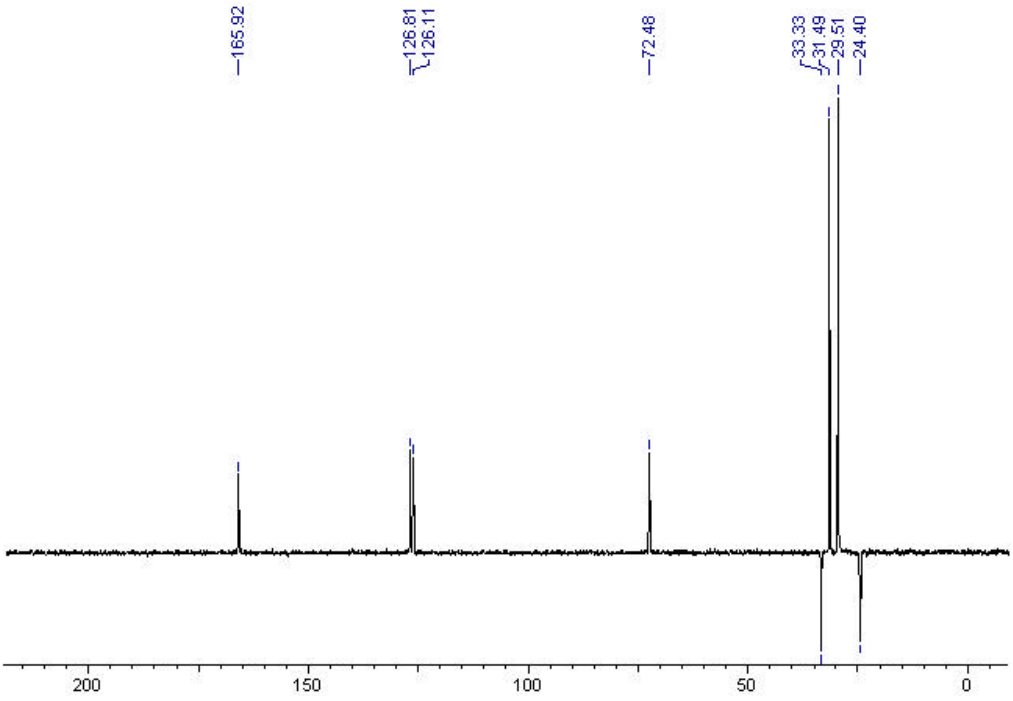
- Mass spectrum of **22**



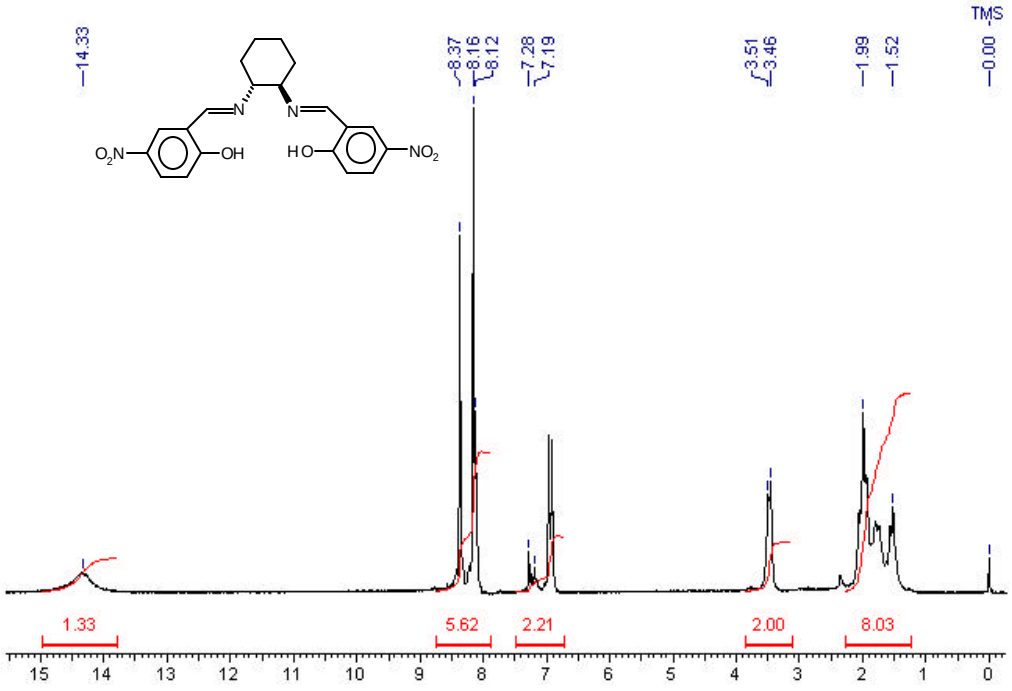
➢ ^{13}C NMR (in $CDCl_3$) of **22**



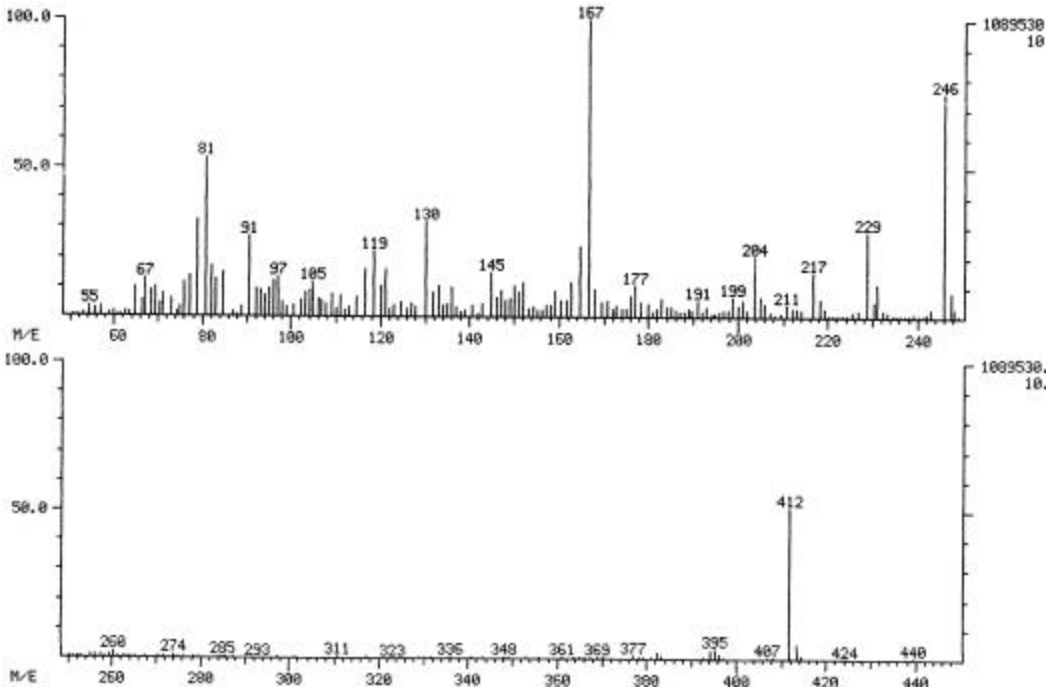
➢ DEPT (in $CDCl_3$) of **22**



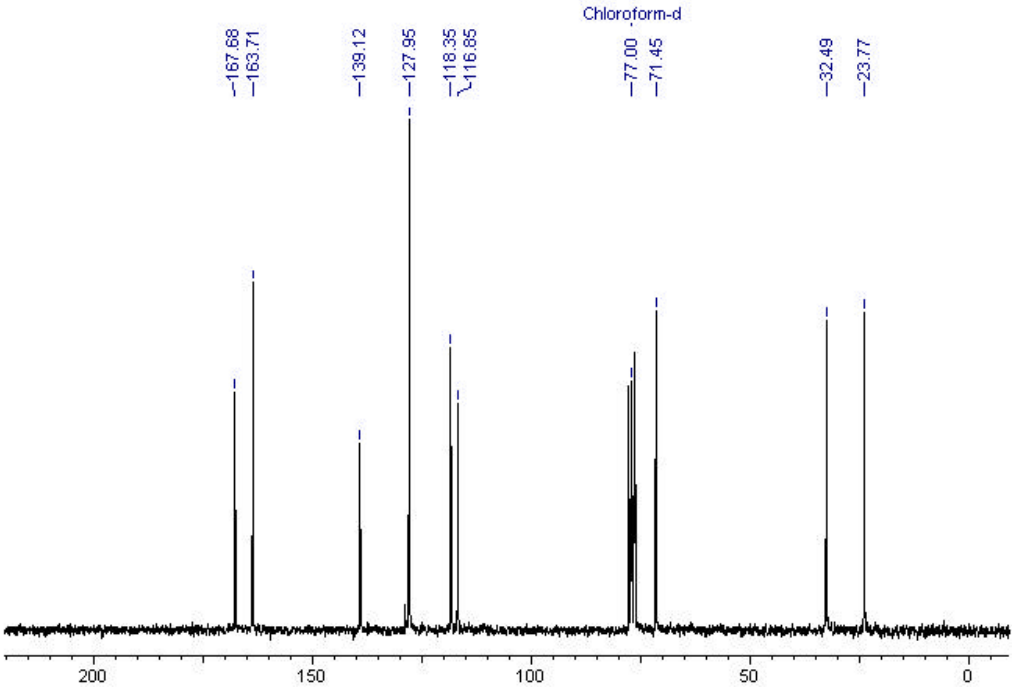
➢ ^{1}H NMR(in $CDCl_3$) of **23**



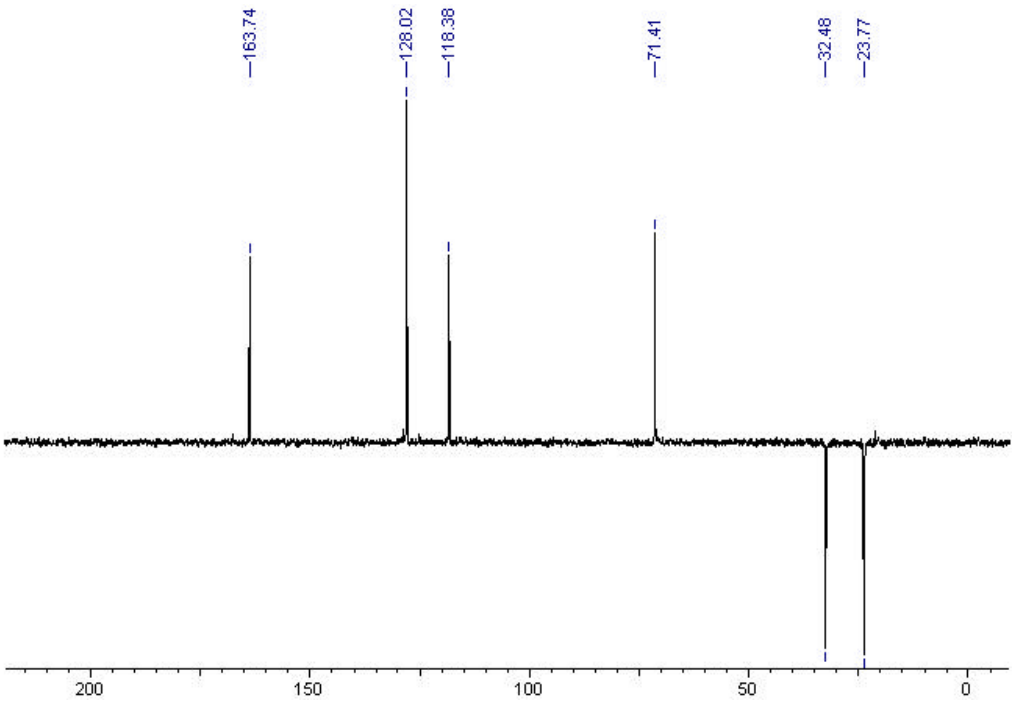
➢ Mass spectrum of **23**



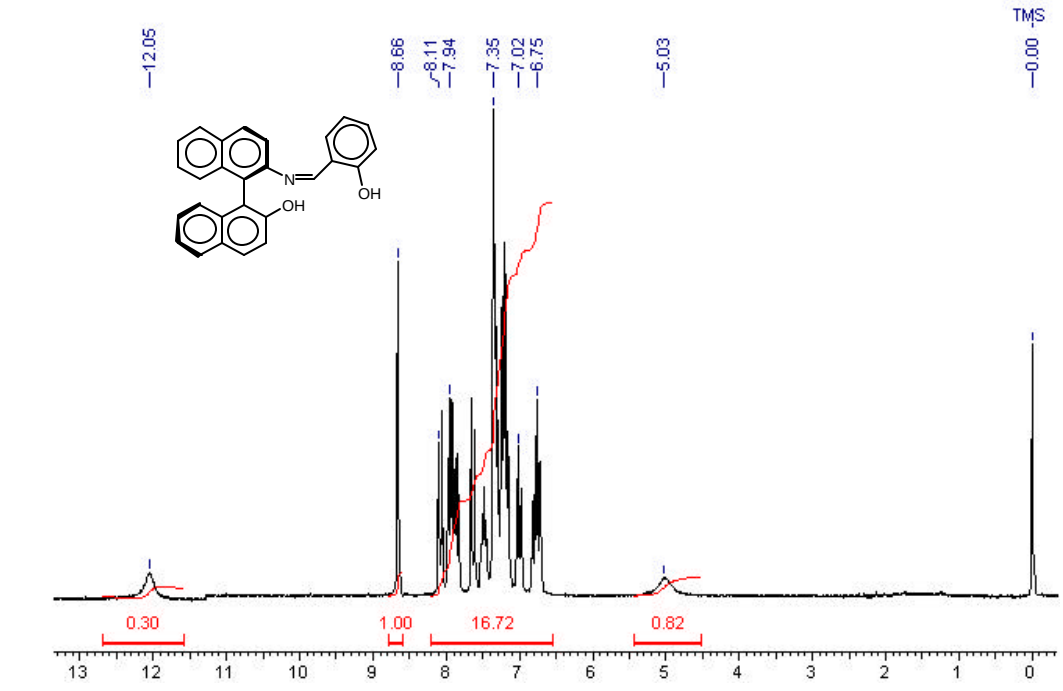
➢ ^{13}C NMR (in $CDCl_3$) of **23**



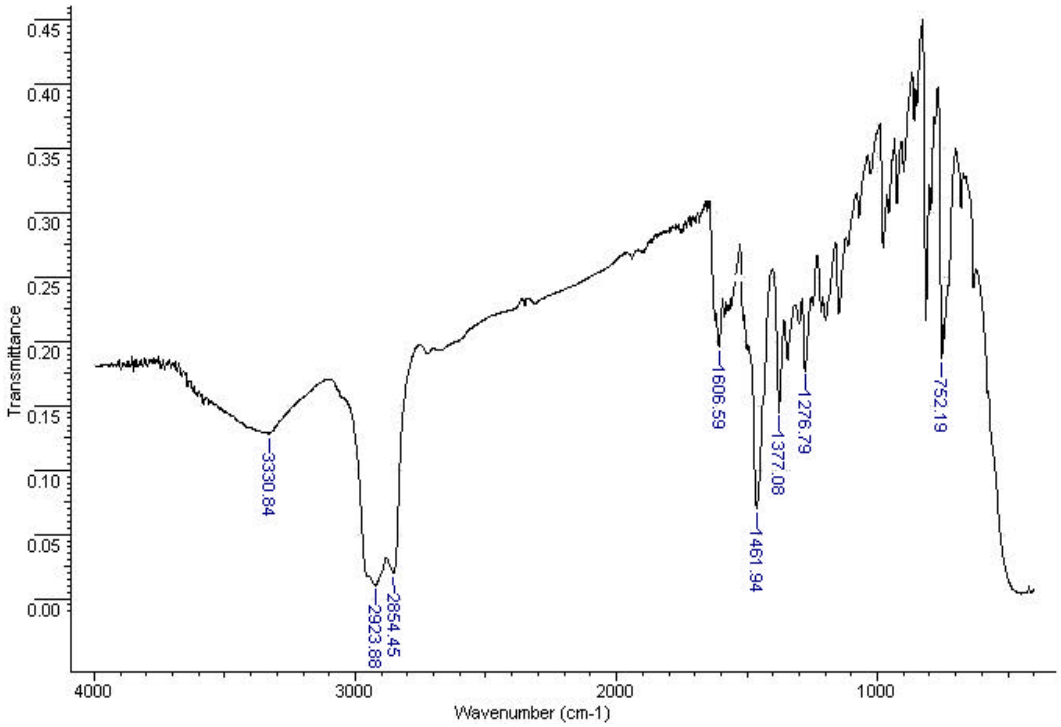
➢ DEPT (in $CDCl_3$) of **23**



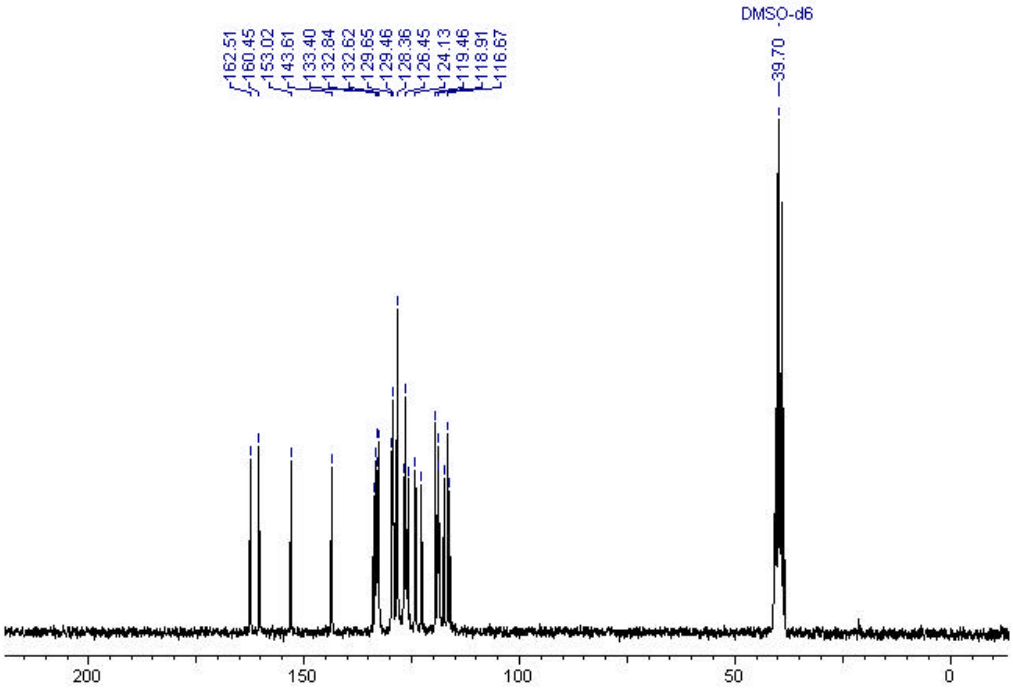
➢ ^{1}H NMR(in $CDCl_3$) of **32**



➢ IR(cm^{-1})(in Nujol) of **32**



^{13}C NMR(in DMSO-d_6) of **32**

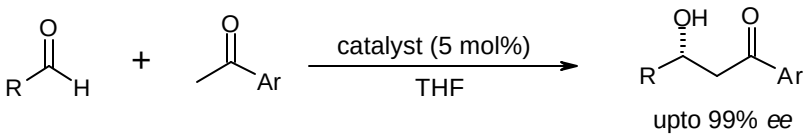


CHAPTER – 3
Homobimetallic Catalyst for Michael Addition

Introduction : The area of heterobimetallic catalyst witnessed tremendous growth after the initial report by Noyori et. al.[1] for the enantioselective addition of dialkyl zinc to prochiral ketones. However much to our surprise the area of homobimeatallic catalyst has remained unexplored.

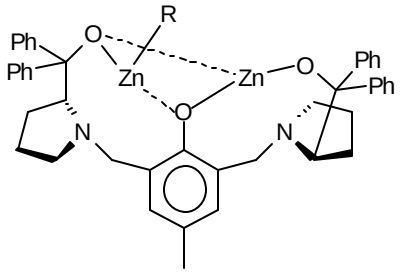
Two very recent publications one by Trost et. al.[2] who described a direct catalytic enantioselective aldol reaction using zinc based homobimetallic complex and the other by Nevalainen et. al.[3] who reported the first catalytic aldol transfer reaction using aluminium based homobimetallic catalyst drew our attention in the area.

Trost et. al. reported[2] a direct catalytic enantioselective aldol reaction by making use of zinc based homobimetallic catalyst (eqn. 1).

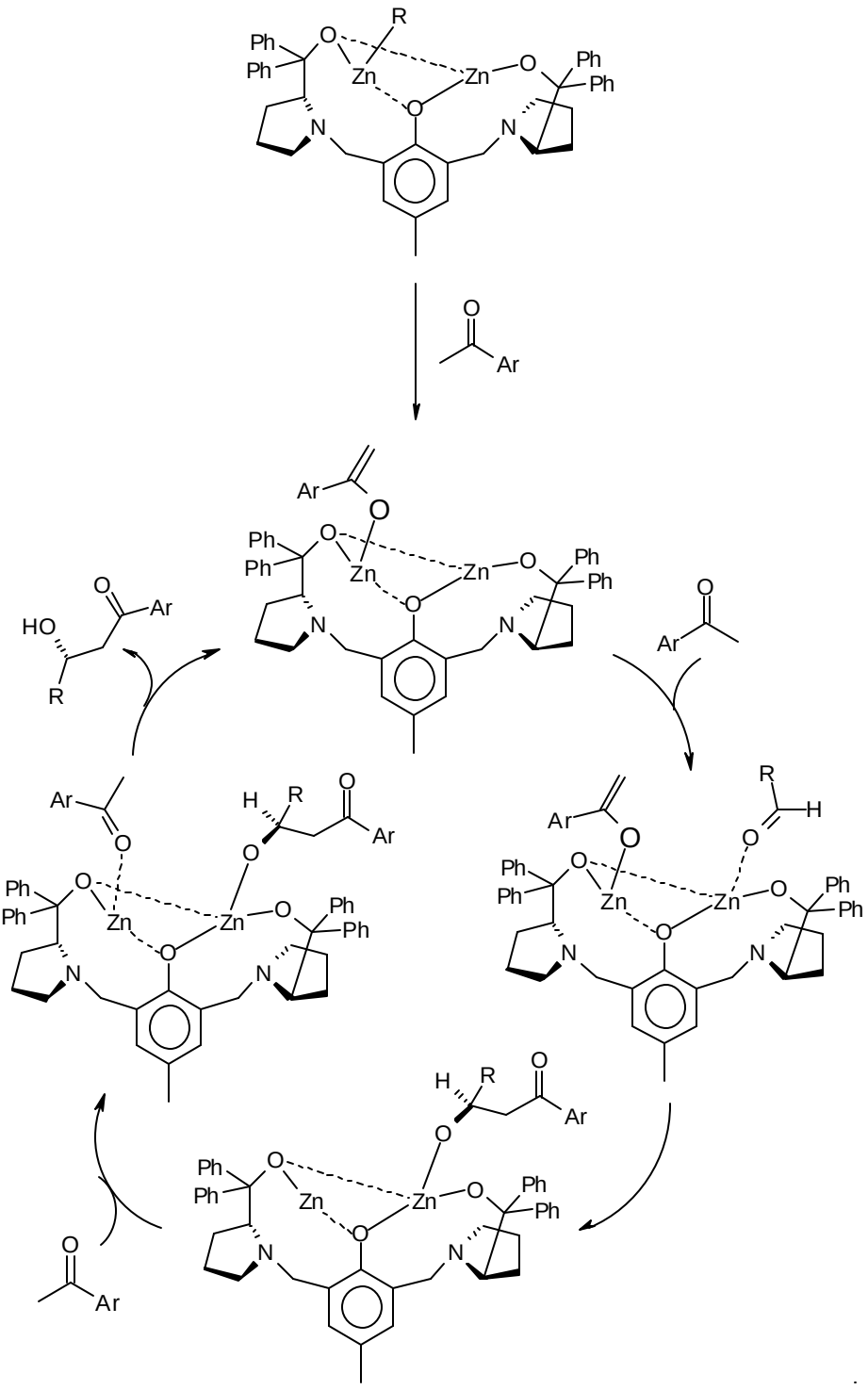


(1)

Catalyst =



The role of two proximal zinc species is to provide both a zinc to form the requisite enolate and a second zinc to function as a Lewis acid to coordinate to the aldehyde. Following catalytic cycle was proposed to account for the product formation (Fig. 1).


R
Ph
Ph
O
Zn
Zn
O
Ph
Ph
N
N
O
Ar
Ar
O
HO
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Ar
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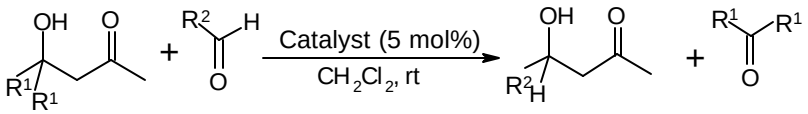
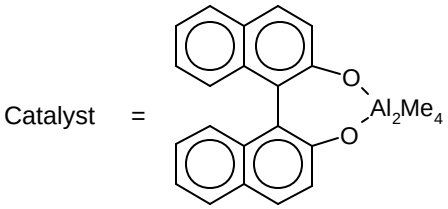
Ar
O
H
R
O
Ar
Ar
O
R
H
O
Ar
H
R
O
Ar

Figure 1

Nevalainen et. al. reported[3] a new way for generating aldol adducts of aldehydes by utilizing aldol adducts of ketones (eqn. 2).





The active catalyst was made by adding two equivalents of trimethylaluminium to BINOL in dichloromethane. The following possible mechanism was proposed to rationalize the aldol transfer reaction (Fig. 2).

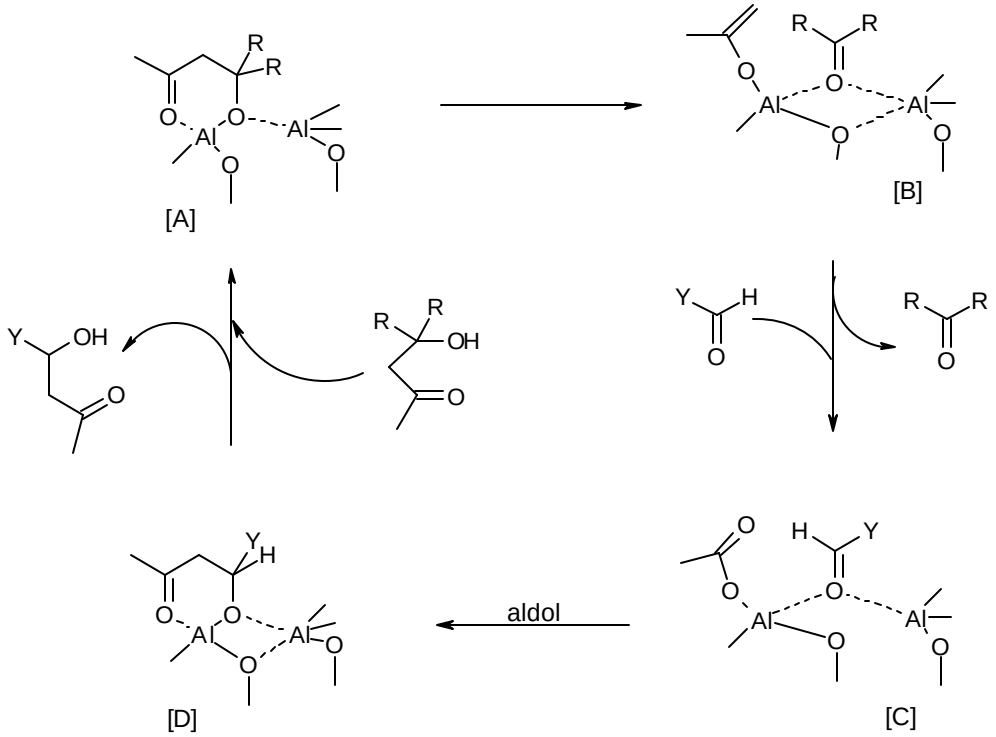
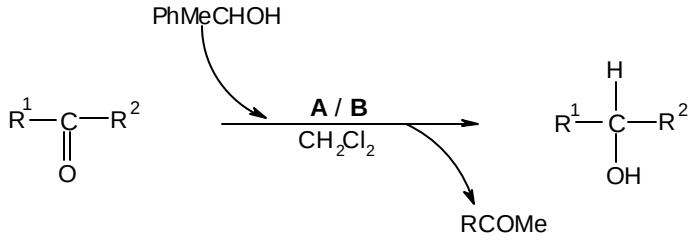


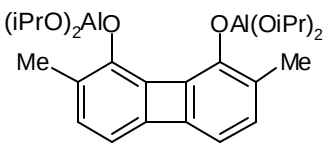
Figure 2

The aluminium chelate [A] went through retro aldol reaction to give species [B], which in turn undergoes ketone aldehyde exchange to give species [C]. This species undergoes aldol reaction to give the desired aldol adduct. One of the aluminium metal facilitates the retro aldol step and the other chelates with the carbonyl group of the aldehyde making it more reactive. The combined effect of these two metal atoms leads to the formation of desired aldol product.

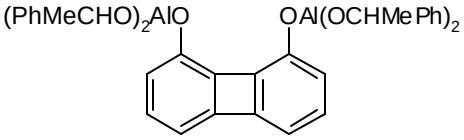
Maruoka et. al.[4] carried out highly efficient, catalytic Meerwein-Ponndorf-Verley reduction using novel bidentate aluminium catalyst (eqn. 3).



(3)



A

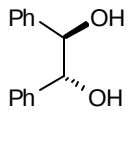


B

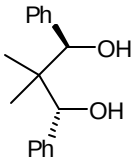
Using bidentate aluminium catalyst **A** / **B**, benzaldehyde was reduced to benzyl alcohol instantaneously in almost quantitative yield within 1h. This remarkable efficiency can be ascribed to the double electrophilic activation of carbonyl group by the bidentate aluminium catalyst.

Except for these reports, the application of homobimetallic catalysts to the area of organic synthesis remained vastly unexplored. This prompted us to look for its application in the field of stereoselective Michael addition reactions.

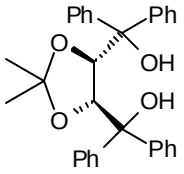
Results and Discussions : The above reports prompted us to look for various chiral diols to check their utility as a catalyst in the stereoselective Michael addition reaction. This we thought could be achieved by making their dialkoxy or phenoxy metal salts. We predicted that one of the metal alkoxy / phenoxy moiety will behave as a Bronsted base while the other metal alkoxy / phenoxy moiety will acts as a Lewis acid and this cumulative effect will make it an efficient catalyst for Michael reaction. Based on this logic we examined various diols[5-8] (**1**/**2**/**3**/**4**).



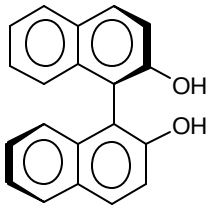
1



2

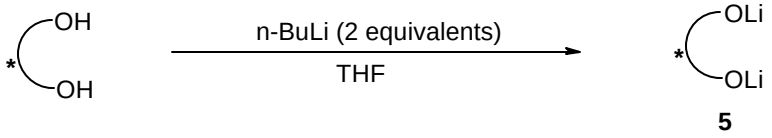


3



4

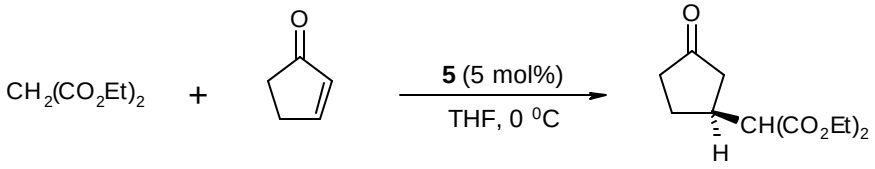
These diols were converted to the corresponding dilithiosalts using n-BuLi (eqn. 4).



5

(4)

These dilithio derivatives were evaluated as catalysts for stereoselective Michael addition reaction. Diethyl malonate and cyclopentenone were chosen as model reactants (eqn. 5).



(5)

These dilithio salts were found to be excellent promoter of the Michael reaction to give the desired product in high yield within 60-90 minutes. However the reaction catalyzed by the bimetallic salts made from aliphatic diols gave racemic product whereas those from BINOL (**5**) gave product in 12% ee.[9] To account for the product formation and resulting optical induction, a catalytic cycle based on the concept of Bronsted base–Lewis acid pathway was proposed (Fig. 3).

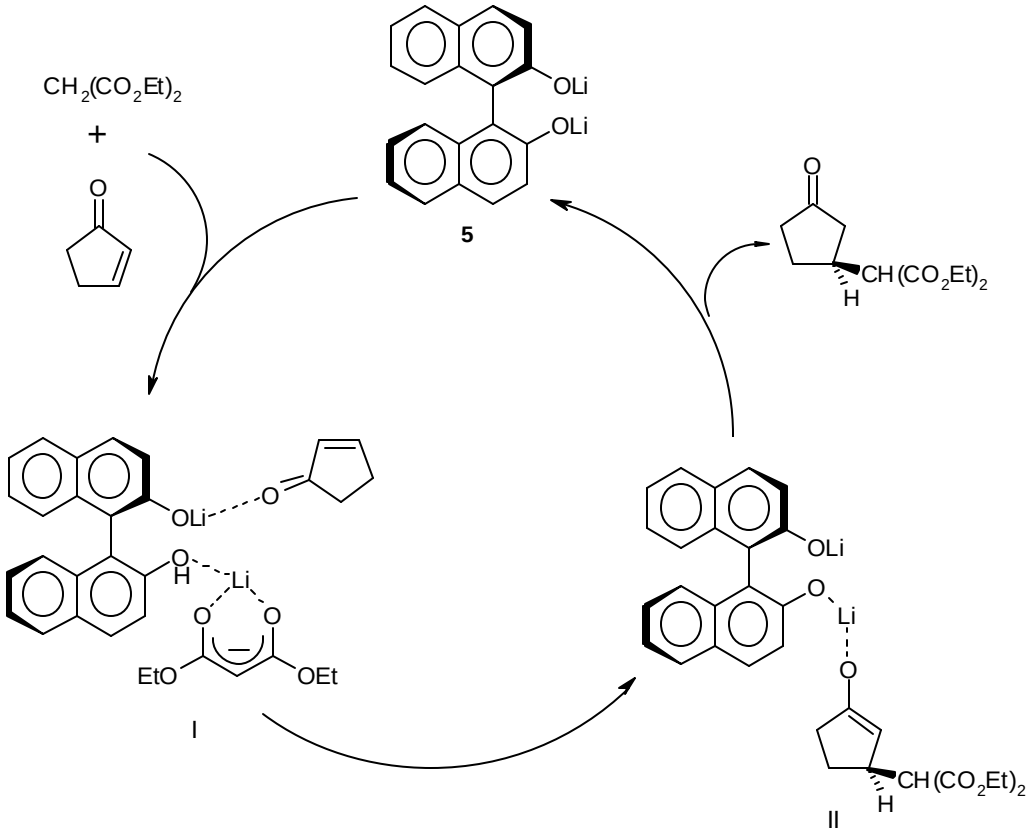
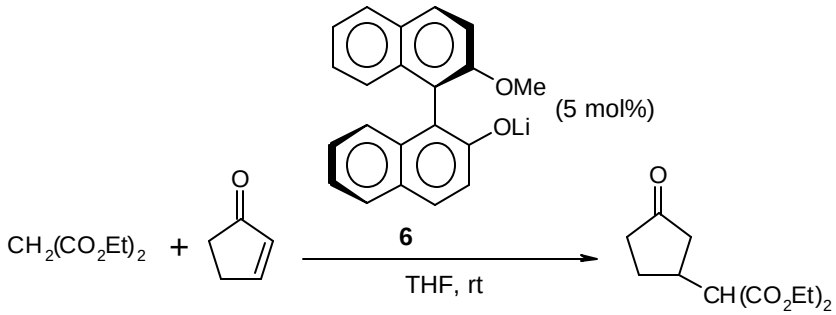


Figure 3

As shown in Fig. 3, diethyl malonate and cyclopentenone reacts with the active catalyst (**5**) to give species I. One of the lithio naphthoxide moiety abstracts the proton from diethyl malonate forming lithium enolate whereas the other lithio naphthoxide moiety complexes with the carbonyl group of the cyclopentenone. This brings the two reactants in close proximity to each other in a well-defined stereoselective fashion leading to the attack of lithium enolate

of diethyl malonate to cyclopentenone (II). With the formation of the product, the active catalyst (**5**) is released back to the catalytic cycle.

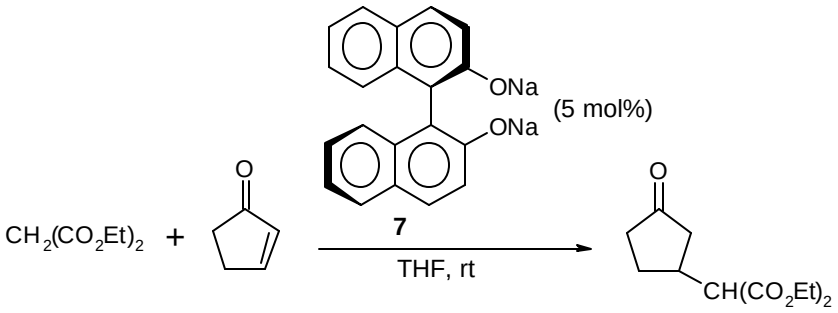
To prove the proposed catalytic cycle and the synergistic involvement of Bronsted base–Lewis acid reactive centers, mono lithio salt of mono-O-methoxy BINOL (**6**) was made by adding 1 equivalents of n-BuLi to the solution of mono-O-methoxy BINOL in THF and examined for catalytic activity (eqn. 6).



(6)

With 5 mol% catalyst, the reaction took 12 hours for completion to give product in 1.7% optical purity. This reaction (eqn. 6) clearly showed the importance for both the lithio naphthoxide moiety as blocking one of the active site resulted into decrease in the rate and optical purity of the Michael adduct. This substantiates our hypothesis regarding the involvement of Bronsted base–Lewis acid synergised catalytic pathway.

To compare the efficiency of lithium cation with other alkali metal c ations, lithium was replaced by sodium. This was achieved by preparing di-sodio salt of (R)-BINOL by adding sodium tert-butoxide (2 equivalents) to the solution of BINOL in THF and the resulting disodium phenoxide was used for the Michael reaction (eqn. 7).



(7)

7 turned out to be a poor catalyst completing the reaction in 5 hours and providing the product in 86% yield with 1.5% ee. This experiment proved that lithium which also acts as a Lewis acid, is most desirable amongst alkali metal cations.

We next studied the effect of temperature on the selectivity of the present reaction. Reactions were carried out at different temperatures, the results of which are summarized in Table 1.

Table 1. Temperature effect on the asymmetric Michael addition reaction

Entry	Temp (^{o}C)	Time (min.)	Yield (%)	ee (%)
1	-25	600	70	10.6
2	0	90	85	12.3
3	25	30	85	14.2
4	50	10	60	6.1

As seen from Table 1, room temperature was found to be the optimum. To study the effect of catalyst concentration on optical induction, reactions were carried out using 5%, 10% and 20 mol% of dilithio BINOLate (**5**). Enantiomeric excess of 12%, 18% and 19% were observed with 5%, 10% and 20 mol% of the dilithio BINOLate used for the reaction. Based on these experiments, the optimum reaction conditions for the Michael addition of diethyl malonate to cyclopentenone was found to be room temperature using 10 mol% of the dilithio BINOLate as catalyst.

After standardization of temperature and catalyst concentration, we then studied the effect of solvent which is tabulated in Table 2.

Table 2. Solvent effect on the asymmetric Michael addition reaction.

Entry	Solvent	Yield (%)	ee (%)
1	THF	91	17.8
2	Et_2O	83	3.0
3	MeOH	72	1.1
4	CH_3CN	88	4.2
5	DME	88	11.3
6	Toluene	72	8.1

As seen from Table 2, reaction in methanol gave almost racemic product (1.1% ee) showing that polar protic solvents are counter productive. Amongst all the solvents studied, THF proved to be the solvent of choice giving product in up to 18% ee.

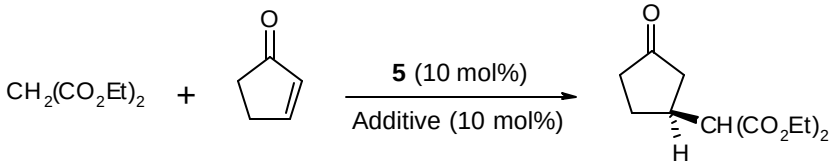
In recent years additives have been used[10] to increase the selectivity of the catalyst, which in turn leads to increase in yield and optical purity of the products. Indeed additives not only help to optimize a reaction by increasing good ee values to excellent ee values but can also efficiently improve reactions with low enantioselectivity to modest enantioselectivity. Generally it is difficult to predict how additive takes part in the reaction. Although a confusing variety of reasons and several mechanistic effects which influences the catalysis are likely to exist. Due to the complexity of the resulting catalytic system, even reproducibility of the result becomes difficult. Several explanations have been put forth suggesting the role of additives. Some of them are as follows:

1. Additives might de-oligomerize non-reactive or less reactive catalyst structure resulting in the formation of the desired active monomeric species.
2. Sometimes additives help to homogenize a heterogeneous catalytic system resulting in an increase in the number of active monomeric species.
3. Active catalyst can be generated more rapidly by additives, which helps in dissociation of the formed catalyst-product complex by ligand exchange reactions.

4. Sometimes basic additives coordinate to the metal center thereby changing the chiral geometry around the active center, which accelerates the desired reaction by tuning the catalyst into a more active species.
5. Additives sometimes serve as a buffer, for example to maintain the water concentration at a defined level (use of molecular sieves).

We also studied the effect of additives the result of which is summarized in Table 3.

Table 3. Additive effect on the asymmetric Michael addition reaction.



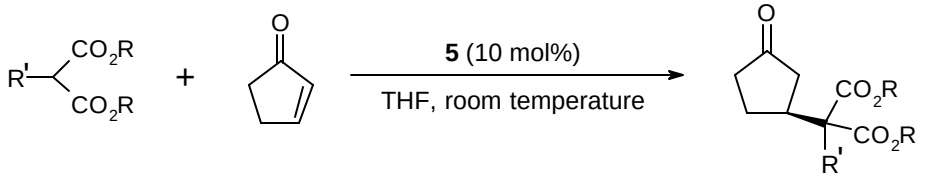
Entry	Additive	Yield (%)	e.e.(%)
1	H_2O	58	8
2	MeOH	75	10
3	EtOH	75	13
4	i-PrOH	63	12
5	t-BuOH	71	13
6	Pyridine	67	12
7	Collidine	75	9
8	Net_3	75	11
9	TMEDA	75	16
10	LiCl	42	2
11	$ZnCl_2$	83	4

As seen from the Table 3, presence of external additives affected the yield as well as ee of the resulting Michael adduct. These additives were found to be detrimental for the overall ee of the product. Polar protic solvents like methanol, ethanol, iso-propanol and tert-butanol behaved in a similar fashion and tend to reduce the yield and ee of the Michael adduct. Amines too were found to reduce the ee of the product. The most dramatic effects were observed

with inorganic salt additives like lithium chloride and zinc chloride, which sharply reduced the ee of the product.

Examination of the steric effect : Michael addition using sterically different malonate esters to cycloalkenones was studied, the results of which are summarized in Table 4.

Table 4. Addition of malonate esters to cycloalkenones using catalyst **5**.



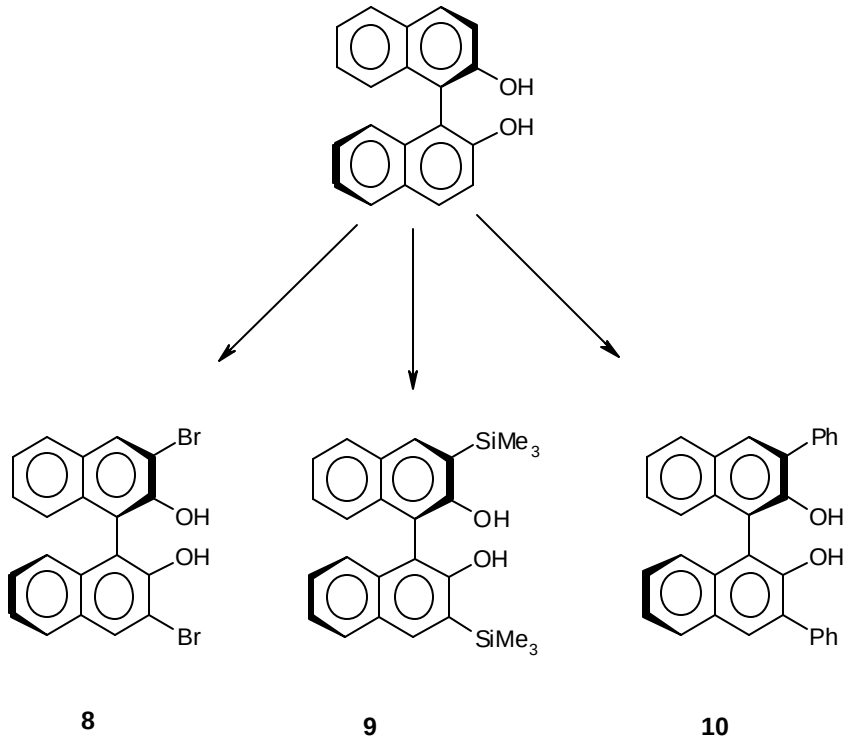
Entry	R	R'	n	Time (min.)	Yield[a] (%)	ee (%)
1	Me	H	1	10	83	29.6[b]
2	Et	H	1	10	91	18.0[c]
3	i-Pr	H	1	15	76	14.1[c]
4	t-Bu	H	1	25	77	16.5[c]
5	CH_2Ph	H	1	45	83	8.6[c]
6	Me	H	2	20	79	4.8[b]
7	Et	H	2	20	84	3.2[b]
8	Et	Me	1	10	77	6.7[b]

a: isolated yield; b: determined by chiral HPLC; c: determined by NMR

From the data in Table 4, we can conclude that with increase in the size of alkyl group of the ester functionality, there is a decrease in the ee of the Michael adduct. The highest ee obtained was with the dimethyl malonate to cyclopentenone. In case of the reaction of dibenzyl malonate with cyclopentenone, the reaction took around 45 minutes for completion to give the product in 9% ee. Also for the addition of alkyl malonates (Me and Et) to cyclohexenone, products with very low enantiomeric excess were obtained.

Molecular weight determination**:** To determine the actual species catalyzing the reaction involving dilithio BINOLate, experiment based on the principles of “colligative properties” was carried out using Landsberger’s method. The experiment involved measuring the elevation in boiling point of the

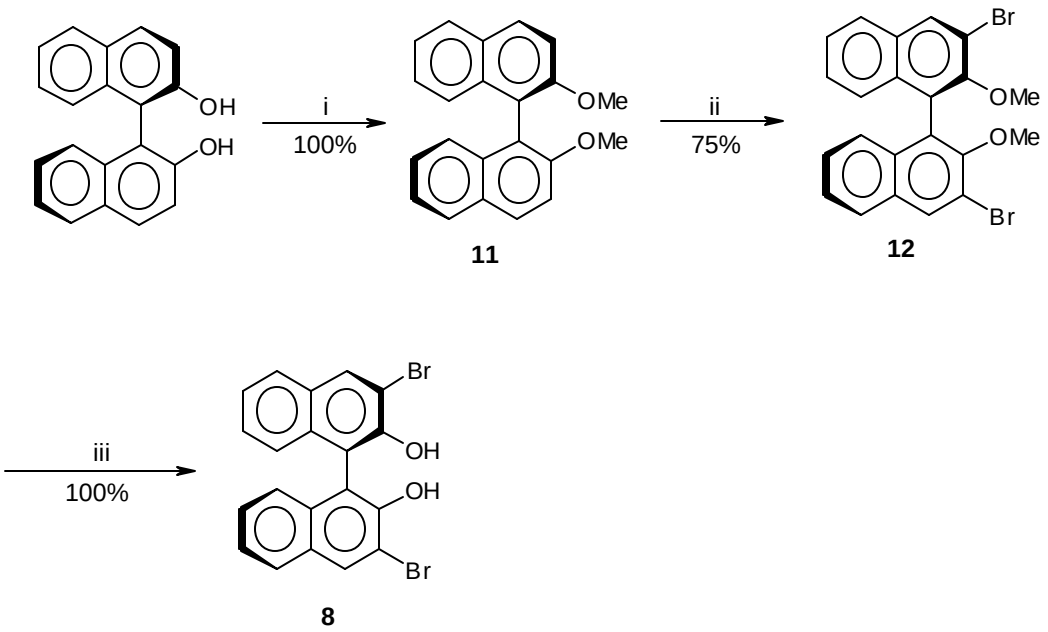
solvent due to the presence of external additives (here dilithio BINOLate). Based on this method, we found the molecular weight of the dilithio BINOLate to be around 800, approximately corresponding to a dimeric nature of the dilithio BINOLate species with three molecules of THF coordinating to it. Since dilithio BINOLate exists as a dimmer in THF solution, we reasoned that bulky substituents at 3 and 3' positions of the BINOL ring would provide a more defined monomeric structure. As we are now creating a pocket at the reaction site, better stereo differentiation should be possible. We therefore decided to prepare various 3,3'-disubstituted BINOL derivatives (**8**, **9, 10**).



8 **9** **10**

To begin with, we protected the hydroxyl groups of the BINOL. This was done by refluxing BINOL, potassium carbonate and iodomethane in acetone for 6 hours, workup involving simple filtration to give methoxy protected BINOL (**11**) in quantitative yield. The 3,3'-dibromo substituted derivative was made[11] by the addition of **11** to the solution of n-BuLi and TMEDA in ether at room temperature. The reaction mixture was allowed to stir for 3 hours followed by the addition of bromine at –78^{o}C. After 4 hours stirring at room temperature, the

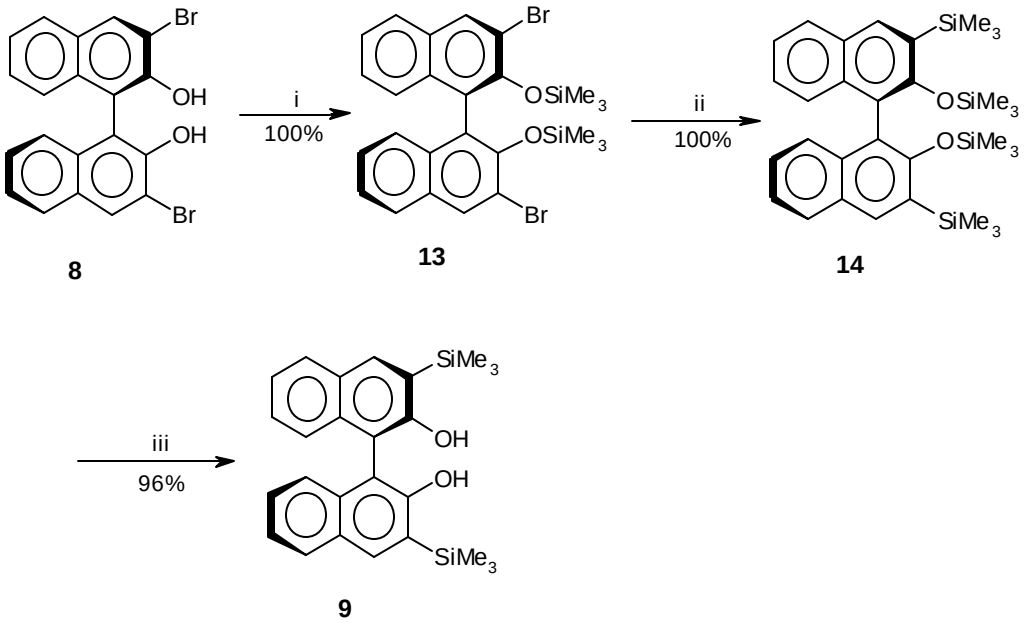
reaction was quenched with sodium sulfite to obtain 3,3'-dibromo derivative (**12**) in 75% yield. The methoxy group was removed using BBr_3 (Scheme 1).



(i). K_2CO_3 , MeI / acetone, reflux ; (ii).a: TMEDA / Et_2O , BuLi ;
b: Br_2 / hexane , -78 ^{0}C ; (iii). BBr_3 / CH_2Cl_2

Scheme 1

We next prepared the 3,3'-disilyl derivative (**9**) using the following strategy (Scheme 2).



8 **13** **14** **9**

(i). HMDS, H_2SO_4(cat), 140 ^{0}C; (ii).a: Na, toluene, reflux.; b: TMSCl; (iii). K_2CO_3 / acetone, reflux

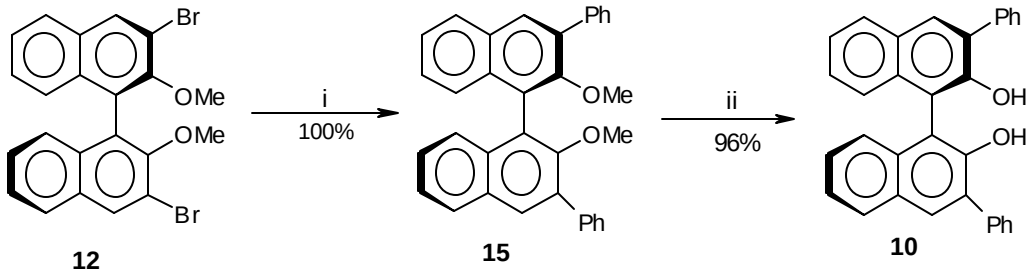
Scheme 2

Derivative **8** was heated with hexamethyldisilazane (HMDS) using conc. sulphuric acid as a catalyst to obtain compound **13** in quantitative yield.[12] It was treated[13] with sodium in refluxing toluene followed by trimethylsilyl chloride to obtain compound **14** again in quantitative yield. The O-silyl group was de protected using potassium carbonate in acetone to obtain the final 3,3'-disilyl derivative (**9**)[14] in 98% overall yield.

After making 3,3'-dibromo (**8**) and 3,3'-disilyl (**9**) derivatives, we then made 3,3'-diphenyl derivative by coupling of compound **12** with phenyl magnesium bromide using bis (triphenyl phosphine) Nickel(II) chloride[15] as a catalyst to obtain the desired compound in 40% yield. Due to low yield of the reaction, we prepared derivative **10** using another route via Suzuki coupling reaction.

Starting with compound **12** and using tetrakis(triphenyl phosphine) palladium(0) as a catalyst[16] in dimethoxy ethane, an ethanolic solution of aryl boronic acid and sodium carbonate (aq) was added and the reaction mix was refluxed for 15 hours to obtain compound **15** in 96% yield (after column). The

methoxy groups were then deprotected to obtain the final 3,3'-diphenyl compound (**10**)[17] in 95% overall yield (Scheme 3).

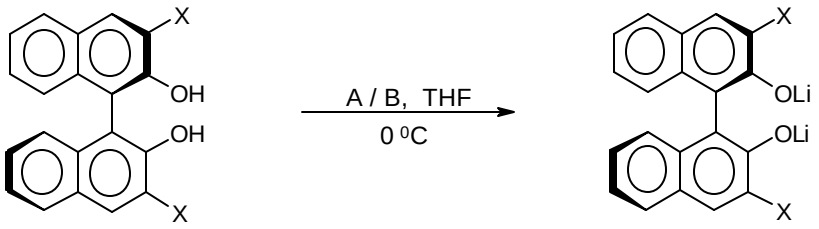


12 **15** **10**

(i). $Pd(PPh_3)_4$, $PhB(OH)_2$, Na_2CO_3(aq) , EtOH / DME, reflux ; (ii). BBr_3 / CH_2Cl_2

Scheme 3

The next step was to obtain dilithio salts of **8**–**10** as possible catalysts (eqn. 8).

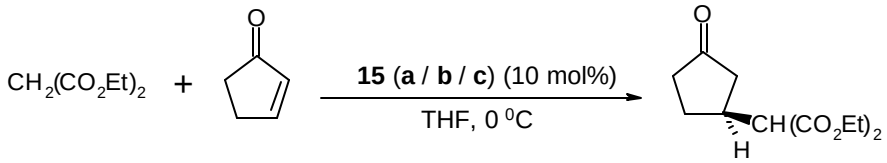


(8)

A = t-BuOLi for **15 a**
B = n-BuLi for **15 b**/**c**

15 a, X = Br
15 b, X = $SiMe_3$
c, X = Ph

n-BuLi was used to prepare the salts **15b** and **15c**, while t-BuOLi was used to obtain **15a**. These catalysts were examined for asymmetric Michael addition of dimethyl malonate to cyclopentenone (eqn. 9).



(9)

Though these catalysts were found to be good promoter for the Michael reaction, they failed to provide good enantioselectivity. Michael adduct obtained using catalyst **15a** showed 8% ee whereas those obtained using cat-**15b** and **15c** were nearly racemic products. These results indicated that substituents at 3,3'-posistions resulted in dissociation of the dimeric structure of the catalyst leading to distortion of the overall stereo differentiating environment around the reactive center and therefore decrease in the optical purity of the Michael adduct.

In yet another attempt to improve the catalytic efficiency of the BINOL based ligand, we envisioned that substituents at 7,7' positions of the BINOL ring will increase the overall bite angle between two naphthyl rings which will lead to a better stereo differentiating environment at the minor groove of the BINOL system (Fig. 4).

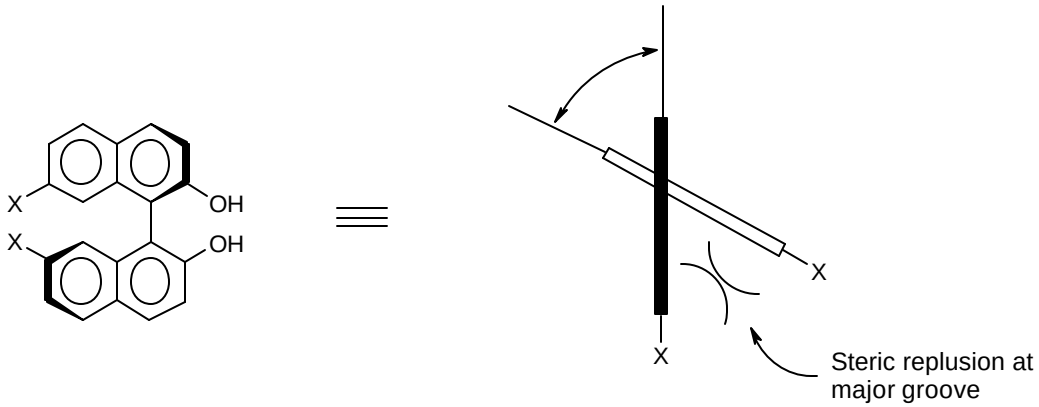
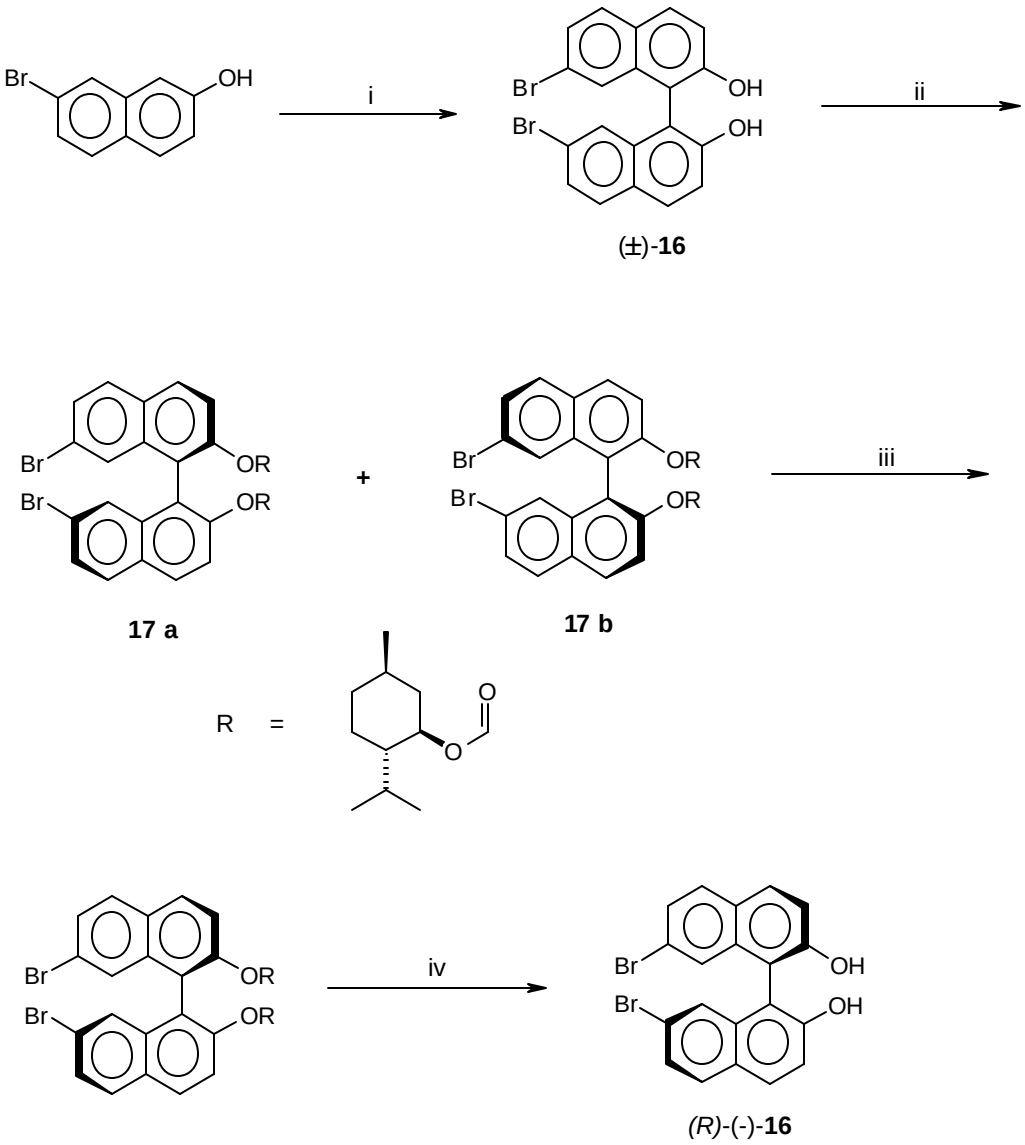


Figure 4

Based on this idea, we made 7,7'-dibromo BINOL derivative. 7-Bromo-2-naphthol was coupled[18] using cupric chloride and tert-butyl amine in methanol to obtain racemic 7,7'-dibromo BINOL (**18**) in 85% yield. Racemic-**18** was then resolved[19] using (-)-menthyl chloroformate as shown in the following Scheme 4.



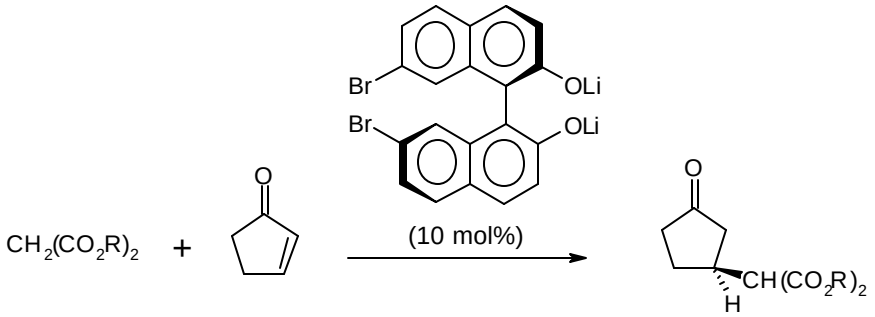
(i). $CuCl_2$ / t-$BuNH_2$, MeOH ; (ii).(-)-menthyl chloroformate, NEt_3 ; (iii). crystallization

(iv). KOH / MeOH

Scheme 4

(-)-Menthyl chloroformate was reacted with racemic 7,7'-dibromo BINOL derivative (**16**) to obtain diastereomeric diesters **17a** and **17b** respectively. The diastereomeric diesters on crystallization (from hexane) gave one of the diastereomeric diester which on saponification gave enantiomerically pure (R)-(-)-7,7'-dibromo BINOL derivative[20] in 35% overall yield.

Chiral ligand **16** was then examined as a ligand for enantioselective Michael addition reaction after making its dilithio salt (eqn. 10).



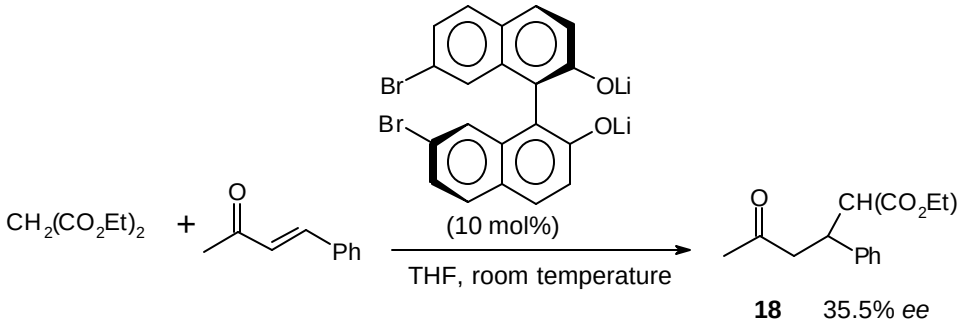
(10)

R = Et, 12.2% *ee*

R = Bn 18.5% *ee*

With diethyl malonate as a Michael donor, the resulting Michael adduct showed an enantiomeric excess of 12% whereas with dibenzyl malonate, product with up to 19% ee was obtained. As mentioned earlier, under similar reaction conditions, the use of dilithio BINOLate gave the Michael adduct from dibenzyl malonate in 9% optical purity. This shows that substituents at 7,7'-posistions resulted in a better stereo differentiating environment at the active reaction site which favours the reaction involving sterically bulkier Michael donors.

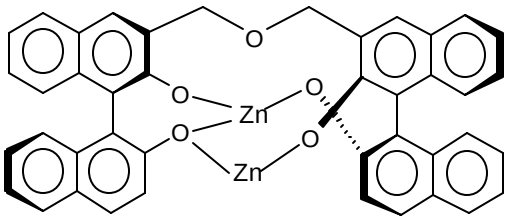
The dilithio salt of (R).(-)-**16** was also examined for promoting Michael addition of diethyl malonate to benzylidiene acetone which gave the desired product[21] (**18**) in up to 35.5% ee (eqn. 11).



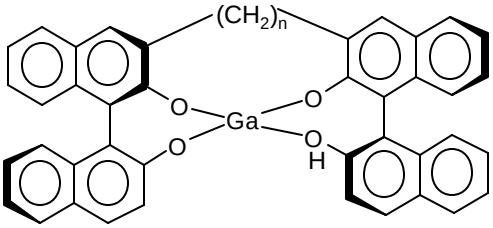
(11)

18 35.5% *ee*

Recently several bis-BINOL derivatives have been prepared (Fig. 5) and used for various reactions like aldol[22], Michael[23] and epoxide[24] opening reactions etc.



19



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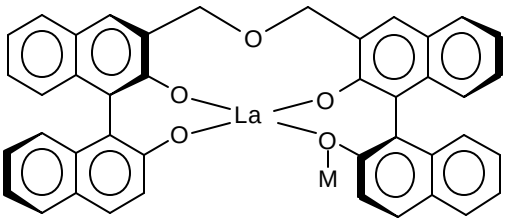
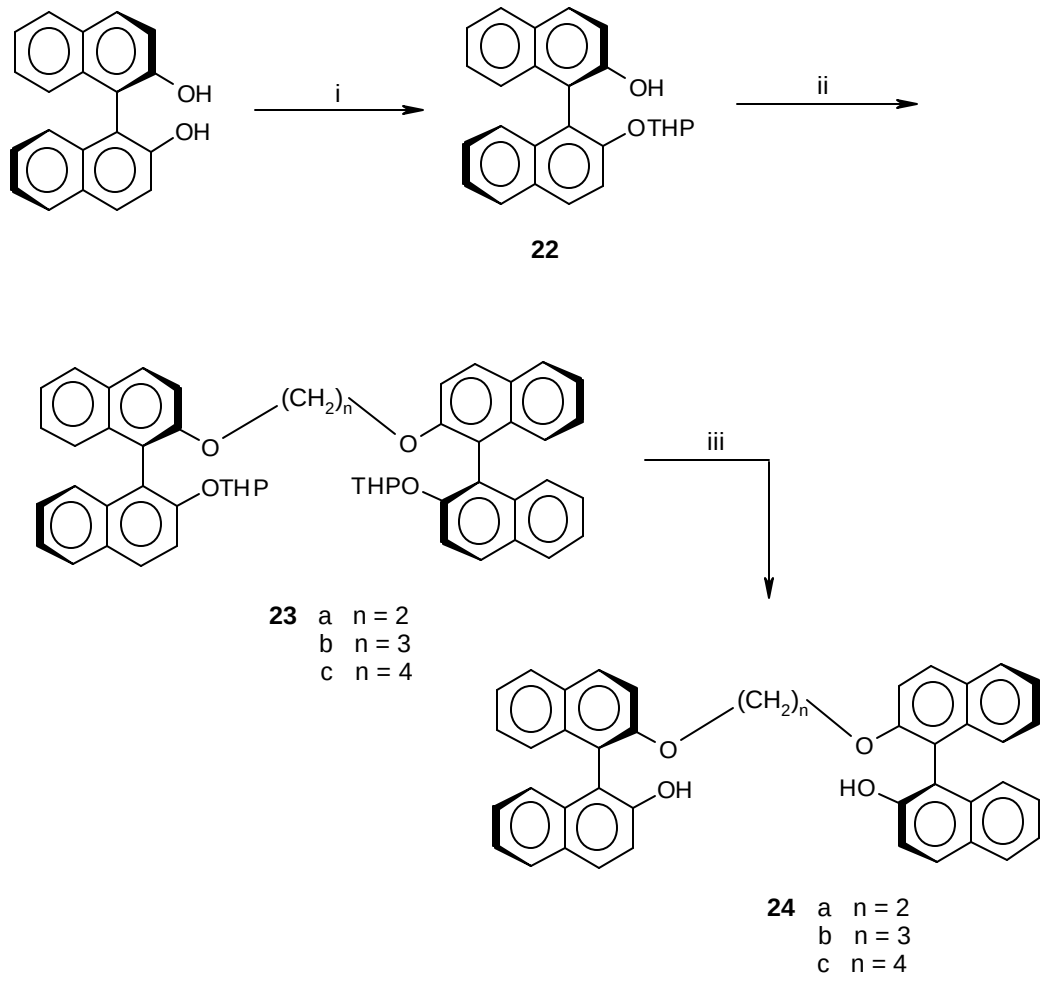


21

Figure 5

Encouraged by these successful reports, we made a few bis-BINOL derivatives. The free hydroxy groups of the optically active (R)-BINOL was mono-protected using dihydropyran. The use of dihydropyran as a protecting reagent was due to the ease with which both protection and deprotection could be achieved. Pyridinium-para-toluene sulfonate (PPTS)[25] was used as a catalyst. BINOL was protected to obtain the required mono-OTHP derivative

(**22**) in 55% yield which was then used for making bis-BINOL ethers as shown in Scheme 5.

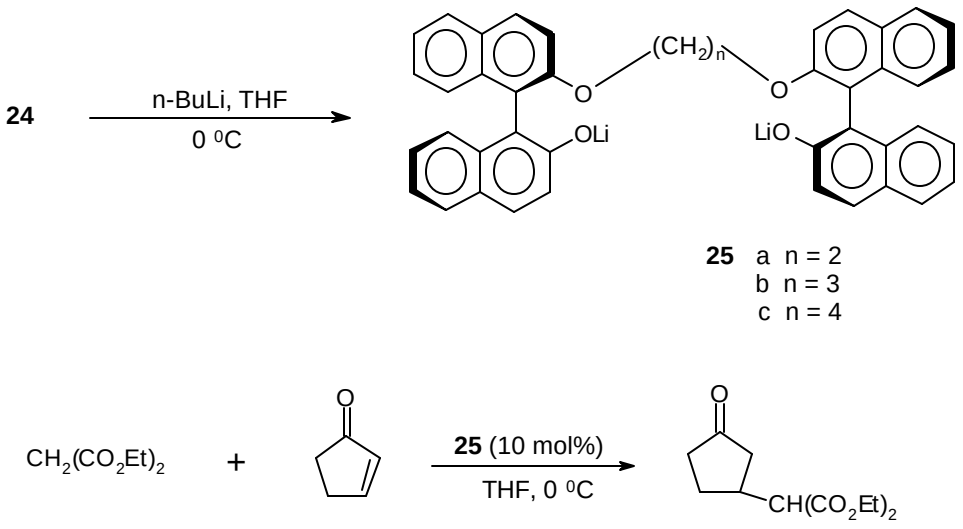


(i). DHP, PPTS(cat) / CH_2Cl_2 ; (ii). TsO-$(CH_2)_n$-OTs , K_2CO_3 , DMF ; (iii). PPTS / EtOH

Scheme 5

As shown in the Scheme 5, a mix of **22**, potassium carbonate and ditosyl alkane in DMF was heated at 100^{0}C for 2-4 hours to obtain the bis-BINOL derivative **23** which on treatment with PPTS in refluxing ethanol gave the desired bis-BINOL ether **24** in 54-65% overall yield.[26]

The dilithio salts of these bis-BINOL ethers were then made using n-BuLi and were examined as catalyst for stereoselective Michael addition reaction (Scheme 6).



Scheme 6

Though these new bis-BINOL derived catalysts were found to be an excellent promoter for Michael reaction, the resulting Michael adduct showed very low optical purity (<5%).

Conclusion :

1. Dilithio BINOLate acts as a catalyst due to the synergistic effect of Bronsted base-Lewis acid reactive centers, as blocking one of the centers leads to drastic decrease in the enantiomeric excess as well as in the reaction rate.
2. Lithium cation was found to be superior to other alkali metal cations and use of external additives proved to be counter productive.
3. Various 3,3'-disubstituted BINOL derivatives with substituents like Br, $SiMe_3$ and Ph were prepared. The dilithio salts of these derivatives were found to be good promoter of the Micahel reaction although the resulting adduct showed low optical purity compared to the parent dilitho-BINOLate.
4. 7,7'-Di-bromo BINOL derivative was also made and its dilithio salt when used for the Michael reaction, gave product with higher optical purity from the addition of dibenzyl malonate to cyclopentenone compared to the parent dilithio BINOLate.
5. Several new bis-BINOL ethers were prepared and their dilithio salts were examined as catalyst. Though they were found to be good promoter for the Michael reaction, they failed to provide good enantioselectivity.
6. Finally it can be concluded from these experiments that designing an enantioselective catalyst is a complex task. The catalyst structure in solid state is invariably different than in solution, which is the active species.

Experimental Section :

Preparation and resolution of 2,2'-dihydroxy-1,1'-binaphtahlene[27] **:** To a solution of ß-naphthol (14.40 g, 50 mmol) in CH_2Cl_2 (500 mL), catalyst [CuCl(OH)TMEDA] (0.3 g) was added and stirred at 0^oC under 0_2-atmosphere over a period of 18 hours. The reaction mixture was washed with water, organic phase was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude product was crystallized from toluene.

Yield 12.50 g (86%)

Resolution[8] **:** Racemic BINOL and N-benzylcinchonidinium chloride were suspended in CH_3CN, refluxed for 4 hours and then left overnight stirring at room temperature. The suspension was further stirred for 2 hours at $0–5^oC$. The reaction mixture was filtered, filtrate was evaporated and the solid was redissolved in ethyl acetate. The solution was washed with 1N HCl (3 x 25 mL), followed by brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give (S)-(-)-BINOL.

$[a]_D^{25}$ -33.2 (c 1.00, THF)

lit.[8] $[a]_D^{25}$ -34.0 (c 1.00, THF)

The solid residue in turn was refluxed with dry MeOH (25 mL) for 24 hours, cooled to room temperature and filtered. It was suspended in ethyl acetate (70 mL) and 1N HCl (35 mL) was added and then stirred. The organic phase was separated, washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to give (R)-(+)-BINOL.

$[a]_D^{25}$ +34.6 (c 1.02, THF)

lit.[8] $[a]_D^{25}$ +34.3 (c 1.00, THF)

Preparation of di-lithio BINOLate and its use as a catalyst for Michael addition of dialkyl malonates to cycloalkenones **:** To the solution of (R)-(+)-BINOL (0.057 g, 0.2 mmol) in THF (1 mL), n-BuLi (0.4 mmol, 1.5M solution in cyclohexane) was added dropwise at 0^oC and then stirred for 10 minutes at room temperature. A solution of dialkyl malonate (2 mmol) and cycloalkenone (2 mmol) in THF (2 mL) was added at room temperature. The progress of the

reaction was monitored by TLC. The reaction was quenched with 1N HCl (1 mL), diluted with ether (5 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the product purified by "flash chromatography" (for enantiomeric excess and yield see Table 4, and for spectral data's see CHAPTER II).

Preparation of 3,3'-di-bromo-2,2'-di-hydroxy-1,1'-binaphthalene (**8**) **:** To a solution of (R)-(+)-BINOL (2.86 g, 10 mmol) in acetone (20 mL), anhydrous K_2CO_3 (7.0 g, 50 mmol) and Iodomethane (1.8 mL, 30 mmol) were added and the reaction mixture was refluxed for 12 hours. It was then cooled to room temperature and filtered. Filtrate on evaporation gave the desired dimethoxy BINOL derivative (**11**) which was directly used for the next step.

Yield	3.14 g (100%)
$[a]_D^{25}$	+79.75 (c 1.00, THF)
	lit.[11] $[a]_D^{25}$ +72.80 (c 1.00, THF)

Compound **11** (3.14 g, 10 mmol) was added to a solution of TMEDA (3.22 mL, 21.3 mmol) and n-BuLi (25 mmol, 1.5M solution in cyclohexane) in ether (85 mL) and stirred at room temperature for 3 hours. The reaction mixture was cooled to -78^oC and a solution of bromine (5.0 mL, 97 mmol) in hexane (10 mL) was added dropwise. After the addition was over, reaction mixture was allowed to warm to room temperature and then stirred for 4 hours. A saturated solution of Na_2SO_3 was slowly added to the reaction mixture and stirred for 2 hours. The upper organic phase was separated and the aqueous phase was extracted with ether. The combined organic phase was given a brine wash, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The desired compound **12** was purified by "flash chromatography" using ethyl acetate-petroleum ether as eluent.

Yield	3.30 g (70%)
mp.	166-167^oC
	lit.[11] mp. 174-175^oC
^1H NMR	δ 3.05 (s, 6H), 7.30 (m, 6H), 7.82 (m, 2H), 8.27 (s, 2H)
$[a]_D^{25}$	+12.85 (c 1.20, $CHCl_3$)

lit.[11] $[a]_D^{25}$ +13.20 (c 1.20, $CHCl_3$)

To the solution of compound **12** (2.37 g, 5.0 mmol) in CH_2Cl_2 (15 mL) at 0°C, BBr_3 (1.13 mL, 12 mmol) was added and stirred for an hour at room temperature (progress of the reaction was monitored by TLC). Water was slowly added and the reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL), washed with brine and dried over anhydrous Na_2SO_4, solvent removed under reduced pressure to gave the desired product **8**.

Yield	2.22 g (100%)
mp.	282°C
^{1}H NMR	δ 5.62 (br.s, OH, 2H), 7.18-7.45 (m, 6H), 7.63-7.82 (m, 2H), 8.20 (s, 2H)
^{13}C NMR	δ 112.11, 114.75, 121.77, 124.67, 124.86, 127.39, 127.58, 128.31, 129.82, 132.76, 132.87, 148.13, 159.74
MS: m/z	444 [M^+](base peak), 284, 255, 226, 142
$[a]_D^{25}$	+113.21 (c 1.00, THF)

Preparation of (R)-(+)-3,3'-bis(trimethylsilyl)-2,2'-dihydroxy-1,1'-binaphthalene (**9**) **:** A mixture of **8** (2.23 g, 5 mmol), HMDS (3.13 mL, 15 mmol) and a drop of conc.H_2SO_4 (catalytic) was heated[14] at 140°C for 2 hours, cooled to 100°C and then kept under vacuum to remove traces of HMDS and NH_3. The solid thus obtained was crystallized from petroleum ether to obtain compound **13** in quantitative yield.

Compound **13** (2.94 g, 5 mmol) dissolved in toluene (5 mL) was added to a suspension of Na (0.46 g, 20 mmol) in refluxing toluene (5 mL) followed by the addition of TMSCl (2.53 mL, 20 mmol).[13] TLC after one hour showed completion of the reaction. The reaction mixture was cooled to room temperature, treated with MeOH (5 mL) and extracted with petroleum ether. The organic phase was dried over anhydrous Na_2SO_4, solvent removed under reduce pressure to obtain compound **14** in quantitative yield, which was directly used for the next step without further purification. The O-silyl group of compound **14** was deprotected by refluxing it in acetone for 30 minutes in the presence of anhydrous K_2CO_3 (2.1 g, 15 mmol) to obtain the desired product **9**.

Yield 2.17 g (98%)

m.p.	81-85^{o}C
	lit.[13] mp. 68-71^{o}C
1H NMR	δ 0.41 (s, 18H), 5.26 (s, OH, 2H), 6.95-7.47 (m, 7H), 7.75-8.21 (m, 3H)
^{13}C NMR	δ -0.85, 109.53, 123.65, 123.98, 127.58, 128.50, 129.01, 129.27, 134.27, 137.83, 156.95
MS: m/z	430 [M^{+}], 398, 309, 192 (base peak), 183, 147
$[a]_D^{25}$	+162.70 (c 1.00, THF)
	lit.[14] $[a]_D^{25}$ +143 (c 1.00, THF)

Preparation of (R)-(+)-3,3'-di-phenyl-2,2'-dihydroxy-1,1'-binaphthalene[17] (**10**) **:** To a solution of **12** (2.36 g, 5 mmol) and $Pd(PPh_3)_4$ (0.35 g, 0.3 mmol)[16] in 1,2-dimethoxy ethane (25 mL), a solution of $PhB(OH)_2$ (1.46 g, 12 mmol) in EtOH (15 mL) was added followed by the addition of Na_2CO_3 solution (10 mL, 2 M aq) and the reaction mixture was refluxed for 18 hours. It was then cooled to room temperature, water (20 mL) was added and the product extracted with CH_2Cl_2 (3 x 10 mL). The crude product **14** thus obtained was dissolved in CH_2Cl_2 (15 mL) and treated with BBr_3 (1.13 mL, 12 mmol) at 0^{o}C and then stirred at room temperature for an hour. Reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was washed with brine wash and drie over anhydrous Na_2SO_4, solvent removal provied **10**.

Yield	2.15 (98%)
mp.	205-206^{o}C
	lit.[17] mp. 197-198^{o}C
^{1}H NMR	δ 5.36 (s, OH, 2H), 7.08-8.15 (m, 20H)
^{13}C NMR	δ 112.47, 124.27, 127.28, 127.69, 128.42, 129.56, 130.67, 131.33, 132.95, 137.47, 150.11
MS: m/z	438 [M^{+}](base peak), 210, 191, 157
$[a]_D^{25}$	+110 (c 0.98, THF)
	lit.[17] $[a]_D^{25}$ +106.5 (c 1.00, THF)

Preparation and resolution of 7,7'-di-bromo-2,2'-dihydroxy-1,1'-binapthalene (**16**) **:** A solution of 7-bromo-2-hydroxynaphthalene (10 g, 45 mmol) and $CuCl_2$ (12.80 g, 95 mmol) in degassed MeOH (250 mL) was stirred for 15 minutes. To

this a solution of tert-butyl amine (40.5 mL, 385 mmol) in MeOH (320 mL) was added over a period of 2 hours. The resulting solution was stirred at room temperature for 24 hours, cooled to 0^{o}C and a 6 N HCl solution was carefully added. MeOH was removed under reduced pressure and the residue was diluted with ethyl acetate (100 mL), organic phase washed with brine solution, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting solid residue was crystallized from cyclohexane.

Yield	9.0 g (90%)
mp.	194-196^{o}C
	lit.[17] mp. 195-197^{o}C
^{1}H NMR	δ 5.11 (br.s, OH, 2H), 7.23-7.48 (m, 6H), 7.74 (d, J = 10 Hz, 2H), 7.92 (d, J = 10 Hz, 2H)
^{13}C NMR	δ 110.03, 118.27, 122.24, 125.98, 127.49, 127.79, 129.99, 131.34, 134.74, 153.52
MS: m/z	444 [M^{+}](base peak), 442, 256, 142

Preparation of (-)-menthylchloroformate[28] **:** To a solution of triphosgene (2.5 g, 8.3 mmol) in anhydrous THF (20 mL), (1R,2S,5R)-(-)-menthol (3.91 g, 25 mmmol) and triethylamine (8.4 mL, 60 mmol) dissolved in dry THF (50 mL) was added over a period of 2 hours and then stirred overnight. The resulting solution of (-)-menthylchloroformate was directly used for the next stage without further purification.

Resolution[19] **:** To the above prepared solution of (-)-menthylchloroformate, a solution of racemic **16** (5.0 g, 12 mmol) in THF (20 mL) was added followed by the addition of NEt_3 (7.4 mL, 53 mmol) dissolved in THF (15 mL) to it. The resulting solution was stirred at room temperature for 4 hours, THF was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (15 mL). The solution was washed with 2 N HCl (5 mL) followed by brine and then dried over anhydrous Na_2SO_4. The solvent was removed and the solid residue was crystallized from hexane to get pure **17a** from which optical purity was confirmed by comparing with the known literature value. Compound **17a** was refluxed in 1 M methanolic solution of KOH for 3.5 hours and then solvent removed under reduced pressure. The solid residue was suspended in 2 N HCl solution and extracted with $CHCl_3$. The organic phase was given a brine wash,

dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. Compound (R)-**16** was further purified by crystallization from ethyl acetate-petroleum ether.

Yield	1.4 g (52%)
$[a]_D^{25}$	-212 (c 1.00, $CHCl_3$)
	lit.[20] $[a]_D^{20}$ -215.9 (c 1.00, $CHCl_3$)

Mono-OTHP derivative of (R)-BINOL (**22**) **:** To a solution of (R)-BINOL (2.86 g, 10 mmol) and PPTS (0.25 g, 1 mmol)[24] in dichloromethane (20 mL), dihydropyran (1.0 ml, 11 mmol) was added and the mixture was stirred at ambient temperature for 6 hours. The reaction mixture was then washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by "flash chromatography" on silica gel using hexane-acetone as the eluent to obtain pure **22**.

Yield	2.20 g (60%)
mp.	134-136^oC
^1H NMR	δ 0.80-1.95 (m, 7 H), 3.08-4.05 (m, 2 H), 5.34 (br.s, 1 H, OH), 6.95-8.10 (m, 12 H)
^{13}C NMR	δ 19.5, 25.23, 30.5, 61.3, 62.6, 111.3, 117.2, 123.7, 124.2, 125.0, 126.9, 127.9, 128.9, 129.4, 130.9, 152.6
MS: m/z	370 [M^+], 286 (base peak), 268, 257, 226, 115
$[a]_D^{25}$	+40.55 (c = 1.00, THF)

Preparation of ditosylalkanes[29] **:** Sodium hydroxide (8.4 g, 212 mmol) dissolved in water (40 mL) and the diol (60 mmol) in THF (40 mL) were mixed. To this stirring solution, p-toluenesulfonyl chloride (25.2 g, 132 mmol) dissolved in THF (60 mL) was added at 0^oC over a period of 2 hours and stirring was continued for an additional 2 hours at that temperature. The mixture was then poured into 10% aqueous hydrochloric acid at 0^oC. The precipitated ditosylate was filtered, washed with water and 5% aqueous sodium hydrogen carbonate and then dried under reduced pressure. Recrystallization from methanol gave the ditosylate in 80-85% yield.

General procedure for the preparation of bis-BINOL ethers (**23a-23c**) **:** A mixture containing **22** (0.74 g, 2 mmol), anhydrous K_2CO_3 (0.35 g, 2.5 mmol) and ditosylalkane (1 mmol) in anhydrous DMF (4 mL) were stirred at 100^oC till TLC indicated complete disappearance of the starting material (2-4 hours). Water (10 mL) was added and the product was extracted with ether. Usual work-up provided the bis-BINOL derivatives (**23a-23c**), which were used as such for the next step.

Bis-BINOL derivatives **(24a-24c)**[26] **:** The crude product (**23**) was dissolved in ethanol (5 mL), PPTS (0.05 g, 0.2 mmol) was added and the mixture refluxed for 1 hours. Water (10 mL) was added and the reaction mixture was extracted with ether. The product obtained after the usual work-up was purified by "flash chromatography" on silica gel using hexane-acetone as the eluent to obtain pure **24** characterized as follows.

(R,R)-1,2-Bis{2'(2-hydroxy-1,1'-binahthyl)oxy}ethane (**24a**)**:**

Yield	65%
mp.	113-115^oC
IR (cm^{-1})	3487
^1H NMR	δ 3.80-4.08 (m, 4 H), 5.05 (br.s, 2 H, OH), 6.88-7.48 (m, 16 H), 7.48-7.98 (m, 8 H)
^{13}C NMR	δ 68.77, 115.2, 115.78, 116.7, 117.6, 124.2, 124.8, 125.0, 126.3, 127.0, 128.0, 129.1, 129.6, 133.8, 151.2, 155.2, 159.5
MS: m/z	598 [M^+], 286, 268 (base peak), 239, 228
HRMS M^+	598.2144 (found).
	598.2144 (calculated for $C_{24}H_{30}O_4$)
$[a]_D^{25}$	+98.30 (c 1.00, THF)

(R,R)-1,3-Bis{2'(2-hydroxy-1,1'-binahthyl)oxy}propane (**24b**)**:**

Yield	56%
mp.	112-114^oC
IR (cm^{-1})	3498

^{1}H NMR	δ 1.63 (m, 2 H), 3.70 (m, 4 H), 5.35 (br.s, 2 H, OH), 6.95-7.60 (m, 16 H), 7.70-8.22 (m, 8H)
^{13}C NMR	δ 29.0, 64.9, 114.9, 115.3, 115.8, 124.0, 124.9, 126.3, 127.1, 128.1, 129.1, 129.5, 130.7, 151.2, 155.1, 159.7
MS: m/z	612 [M^+], 326, 286, 268 (base peak), 239, 184
HRMS M^+	612.2323 (found)
	612.2301 (calculated for $C_{43}H_{32}O_4$)
$[a]_D^{25}$	+123.80 (c 1.00, THF)

(R,R)-1,4-Bis{2'(2-hydroxy-1,1'-binahthyl)oxy}butane (**24c**)**:**

Yield	50%
mp.	103-105°C
IR (cm^{-1})	3500
^{1}H NMR	δ 0.88-1.20 (m, 4 H), 3.30-3.84 (m, 4 H), 4.94 (br.s, 2 H, OH), 6.85-7.50 (m, 16 H), 7.70-8.08 (m, 8 H)
^{13}C NMR	δ 25.1, 68.7, 115.3, 115.6, 116.5, 117.5, 151.3, 155.3, 159.6
MS: m/z	626 [M^+], 341, 299, 286 (base peak), 268, 239, 197
HRMS M^+	626.2462 (found)
	626.2457 (calculated for $C_{44}H_{34}O_4$)
$[a]_D^{25}$	+68.80 (c 1.00, THF)

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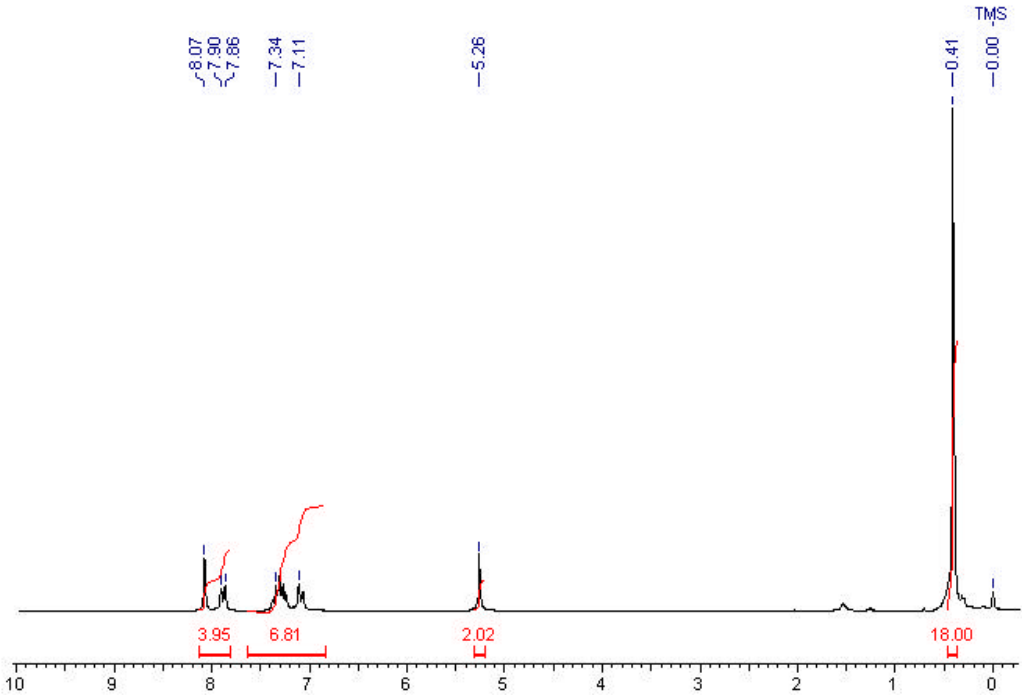
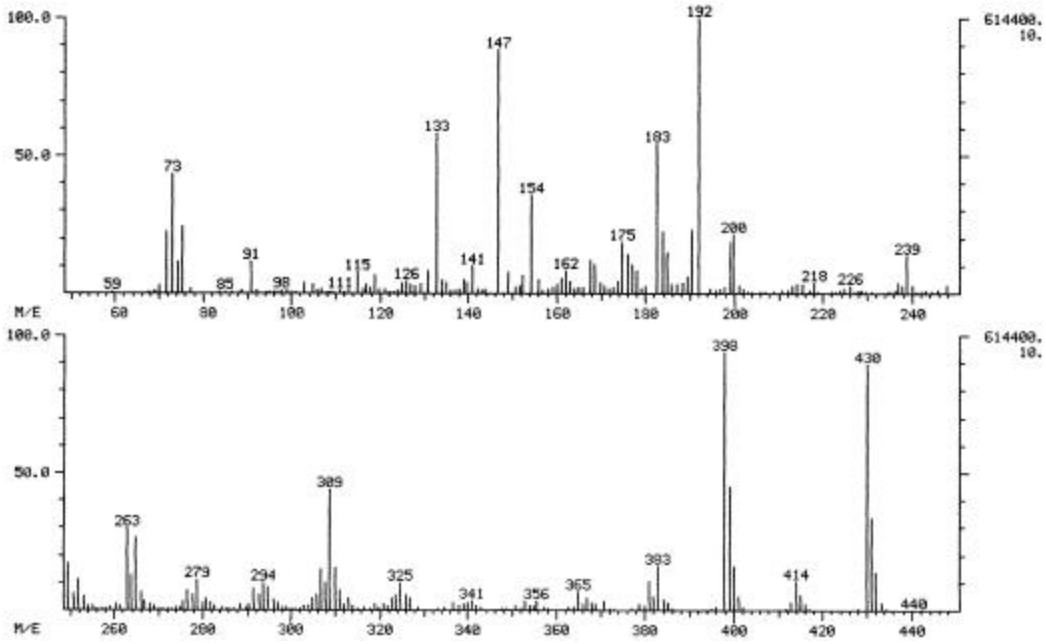
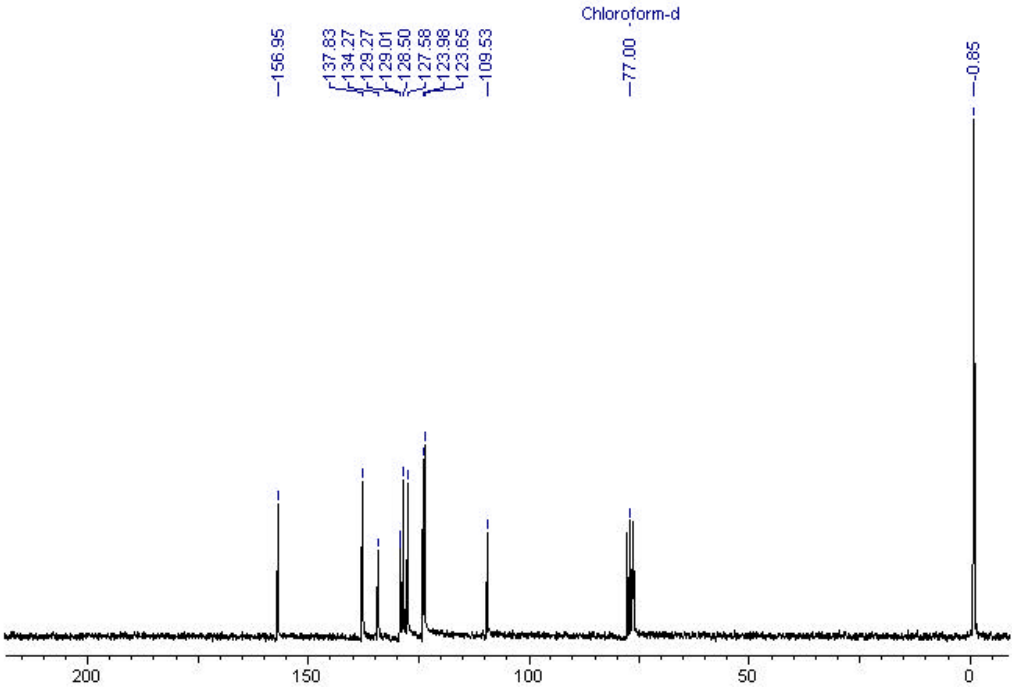
- ^{1}H NMR(in $CDCl_3$) of **9**



- Mass spectrum of **9**



➢ ^{13}C NMR(in $CDCl_3$) of **9**



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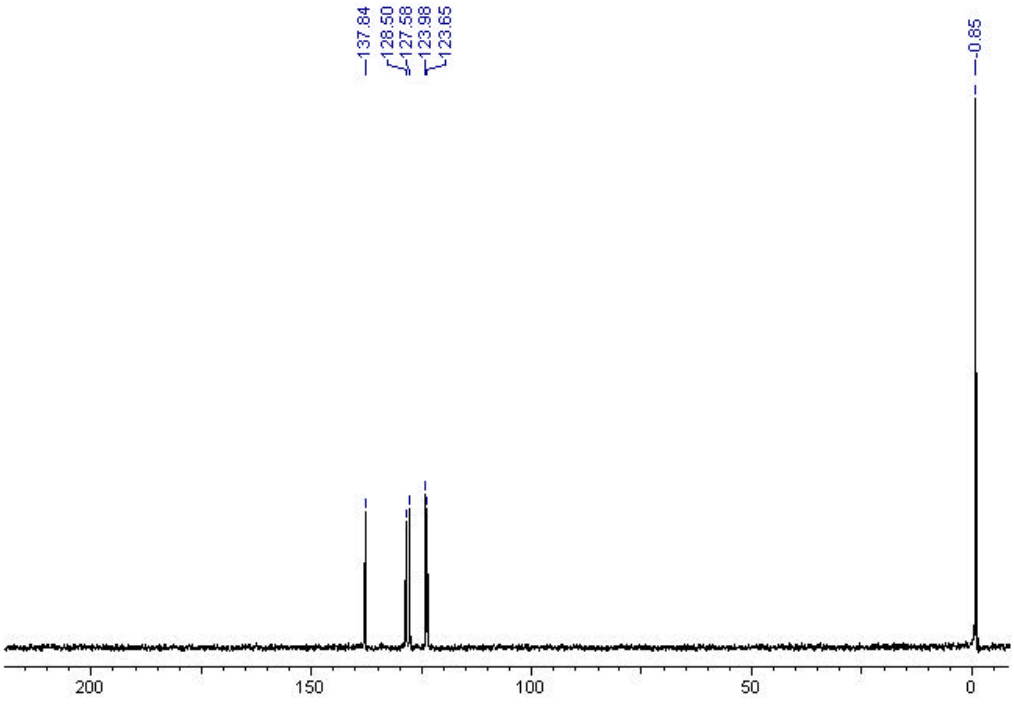
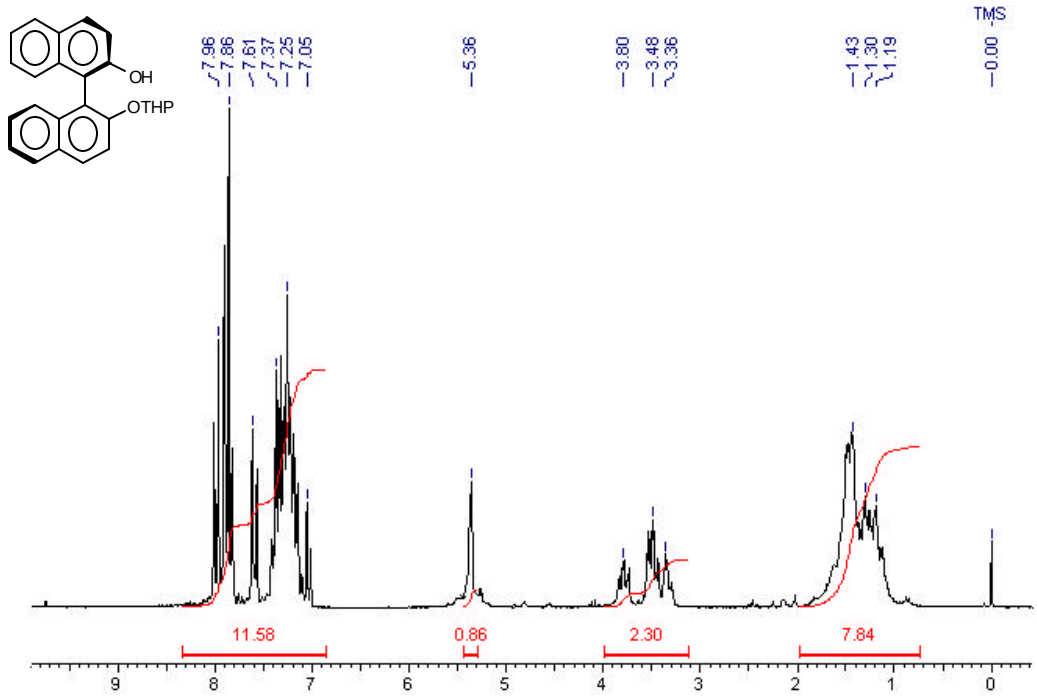
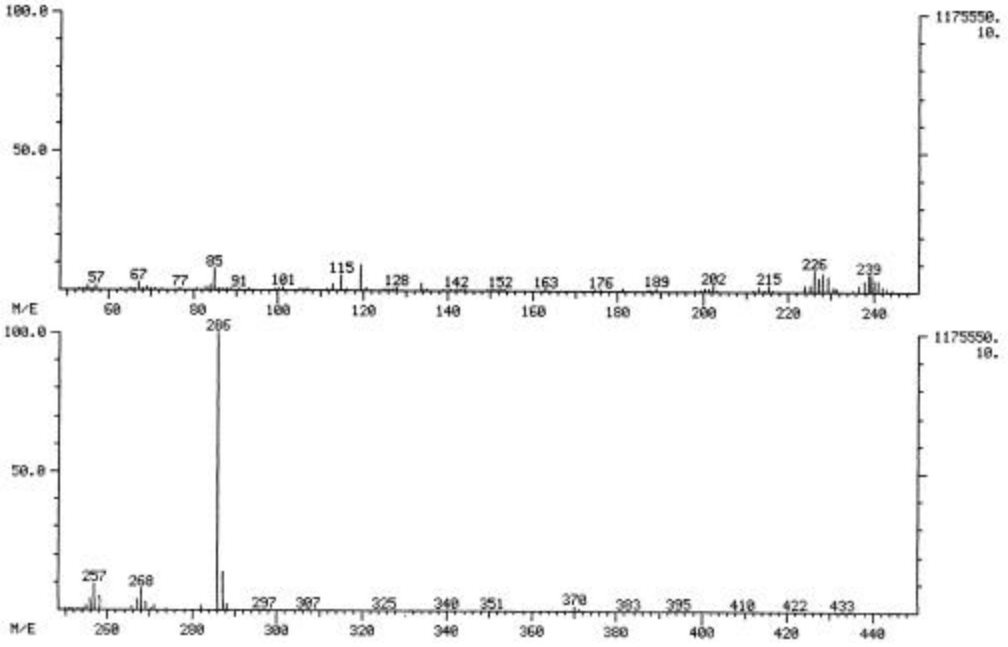


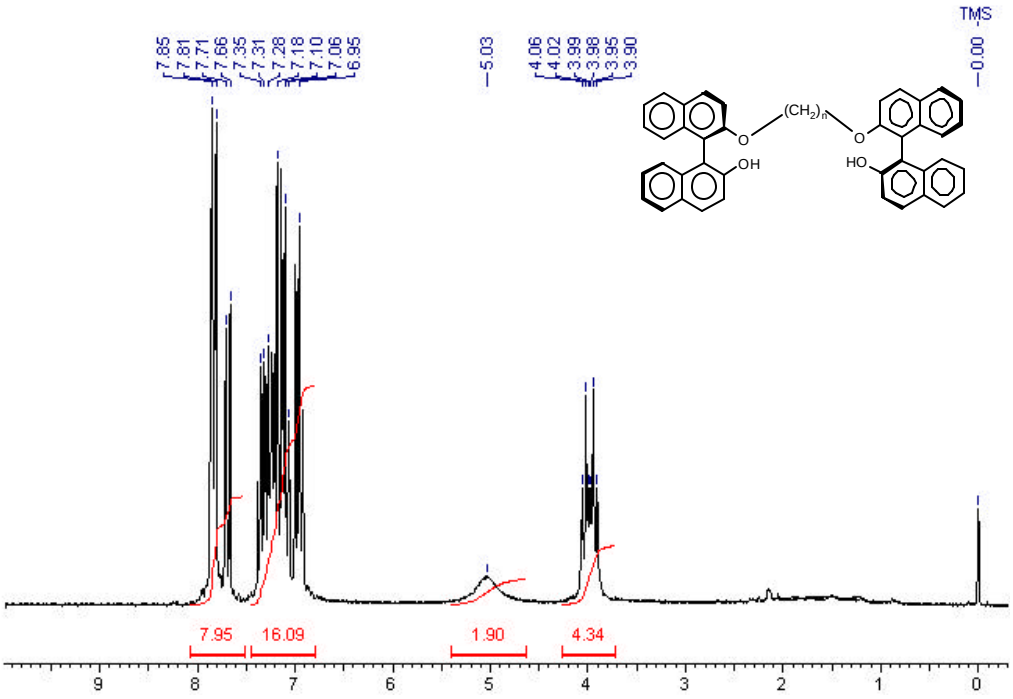
- ^{1}H NMR(in $CDCl_3$) of **22**



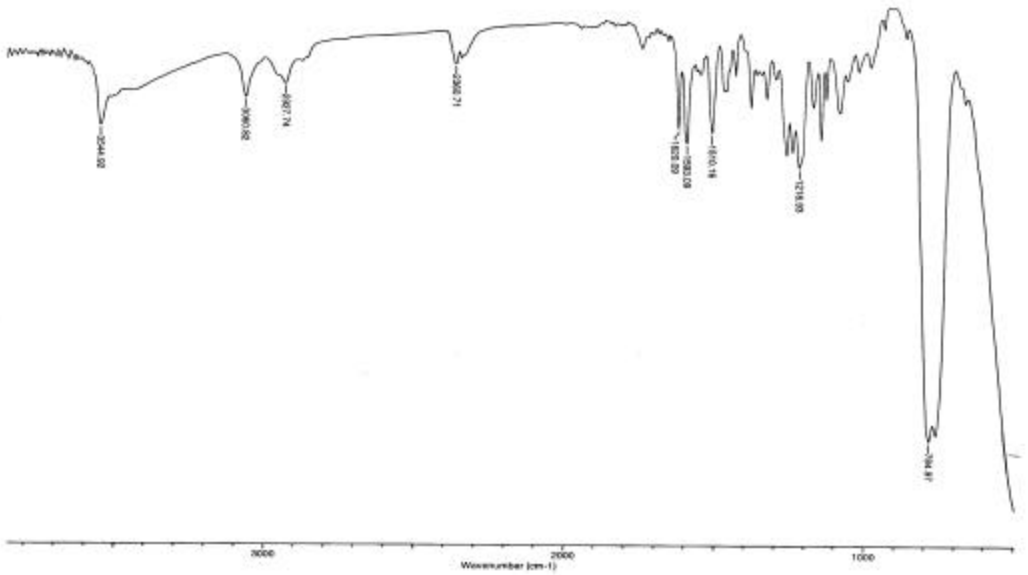
- Mass spectrum of **22**



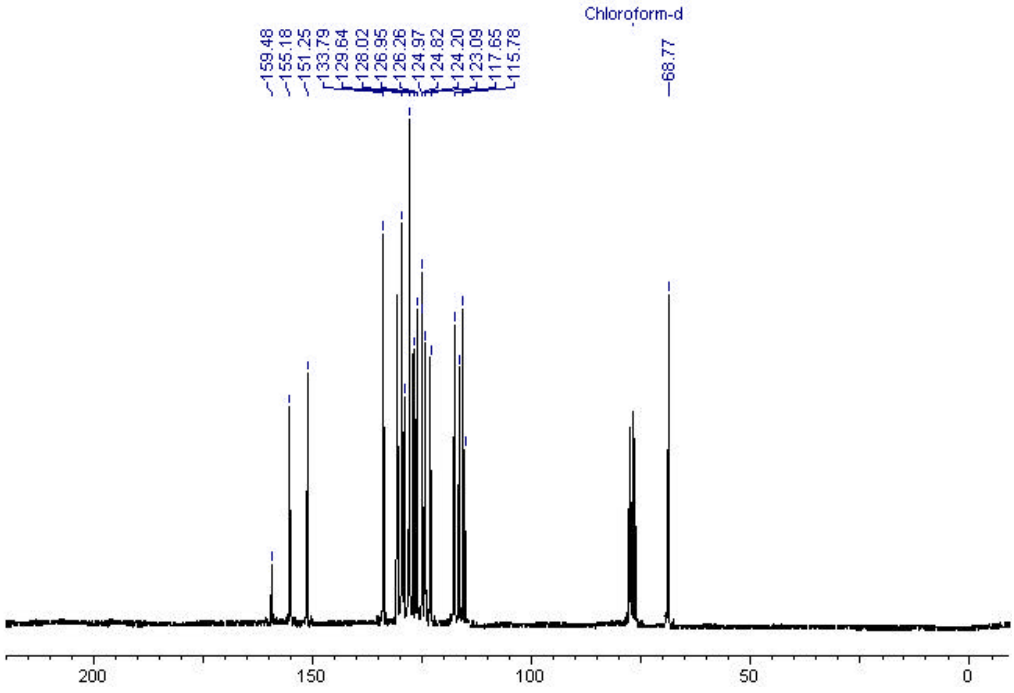
➢ ^{1}H NMR(in $CDCl_3$) of **24a**



➢ IR(cm^{-1})(in Nujol) of **24a**



➢ ^{13}C NMR(in $CDCl_3$) of **24a**



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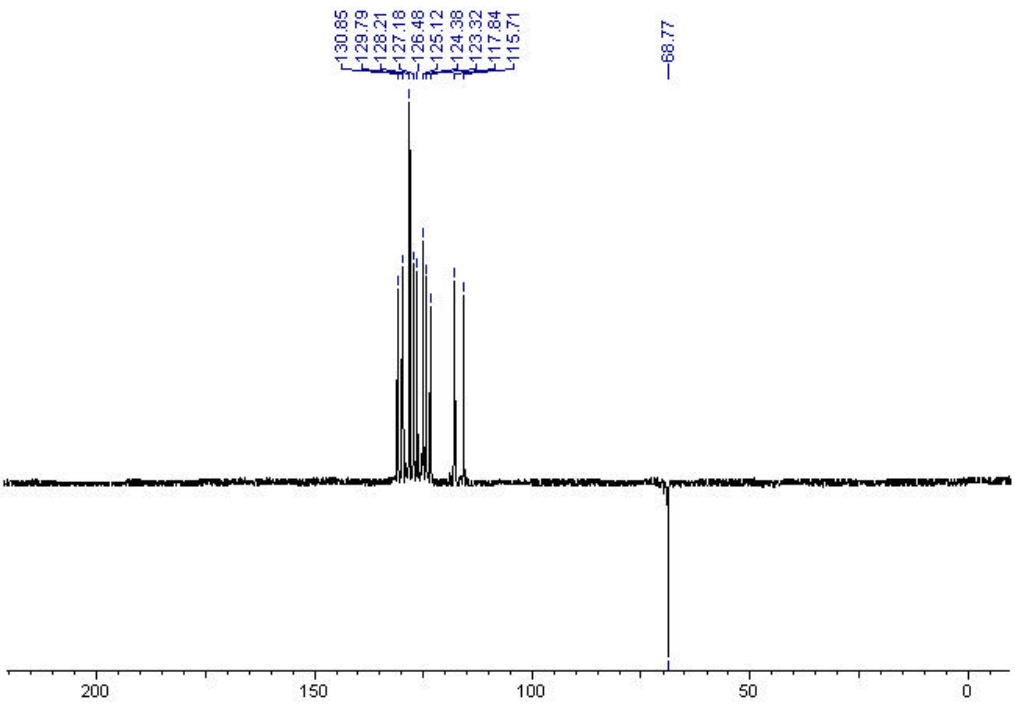

- Mass spectrum of **24a**