Study of Asymmetric Cyanohydrin and Sulfoxidation Reactions, and Fluorometric Recognition of Zn^{2+} and Optically Active 2-Substituted Pyridines

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

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February 2012

Dedicated

To

My Lord Vaikuntar

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati S. Sakthivel

February 2012

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. S. Sakthivel has been working under my supervision since January 2008. I am forwarding his thesis entitled "*Study of Asymmetric Cyanohydrin and Sulfoxidation Reactions, and Fluorometric Recognition of* Zn^{2+} *and Optically Active 2-Substituted Pyridines*" for being submitted for the award of Ph.D. degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute, and regarding the investigations embodied in his thesis, this work has not been submitted elsewhere for a degree.

Guwahati

February 2012

Prof. Tharmalingam Punniyamurthy

Supervisor

ACKNOWLEDGEMENT

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Finally, no words would suffice to express my feelings to my parents and sisters for their sustained help, patience and encouragement in all my academic endeavors. I feel deeply indebted to them for whatever I have achieved so far.

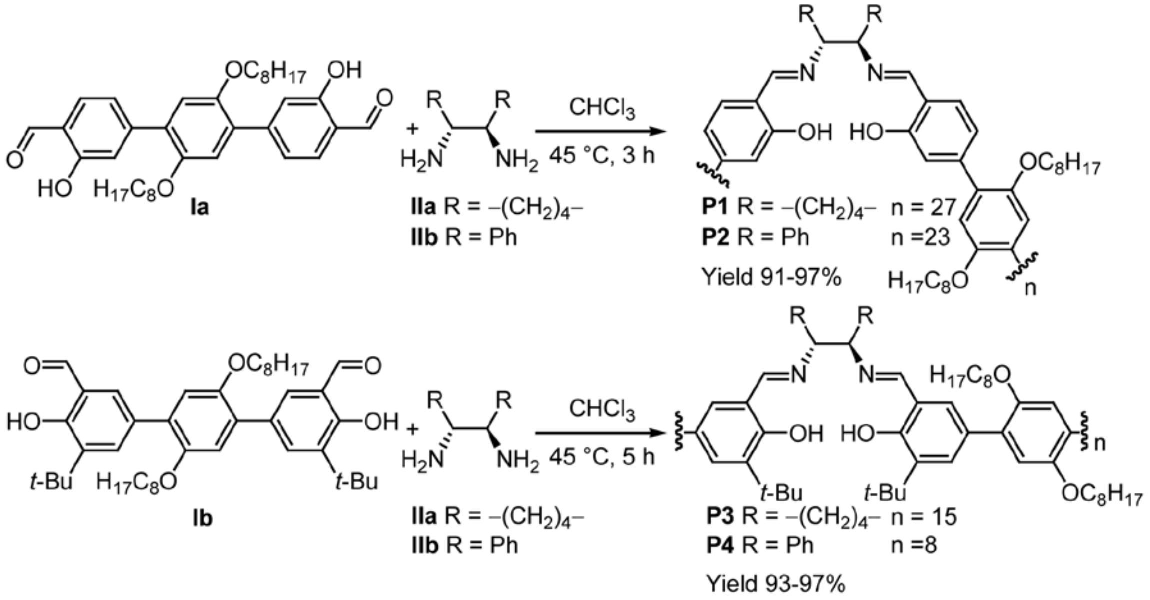
Sakthivel

Abstract

The thesis contains five chapters. The first chapter describes the synthesis of chiral main-chain polymers bonded with (*R*,*R*)-salen and 1,4-dioctyloxybenzene as alternate segments. The chapter two deals with the titanium polymer complex formation and its application for 1,2-addition of trimethylsilyl cyanide (TMSCN) to aldehydes. The third chapter focuses on chiral titanium-catalyzed asymmetric sulfoxidation with aqueous hydrogen peroxide. The fourth and fifth chapters deal with the use of the polymers as chemosensor for cascade Zn^{2+} detection and chiral recognition toward optically active 2-substituted pyridines.

1 Synthesis of Chiral Main Chain Polymers Bonded with (*R*,*R*)-Salen and 1,4-Dioctyloxybenzene as Alternate Segments

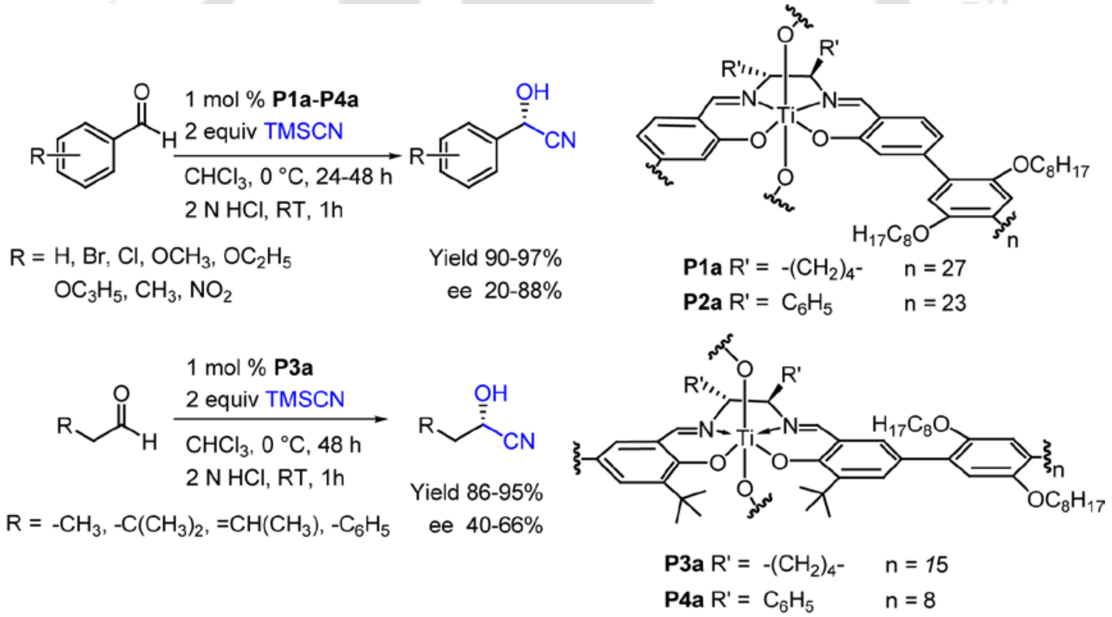
Asymmetric catalysis is an ideal method for making most of the chiral molecules using metal complexes chelated with chiral ligands. Thousands of chiral ligands are known for chiral induction. Still, the synthesis of recyclable chiral ligands is quite challenging for researchers. This chapter describes the synthesis of new class of chiral main chain polymers **P1-P4** using Suzuki C-C cross-coupling and Schiff base formation as key steps (Scheme 1).



Scheme 1

2 Chiral Titanium(IV)-Catalyzed Asymmetric 1,2-Addition of TMSCN to Aldehydes

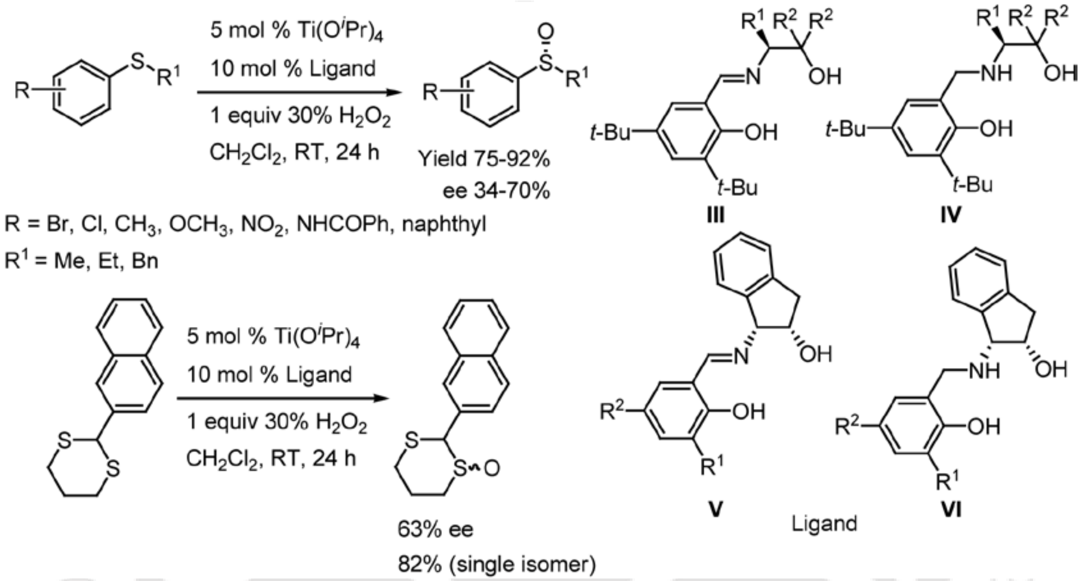
The addition of cyanide to a carbonyl compound to form a cyanohydrin is one of the fundamental carbon-carbon bond forming reactions in organic chemistry and has frequently been at the forefront of advances in chemical transformations. In this chapter, we have successfully applied the titanium(IV) polymer catalysts **P1a-P4a** for asymmetric synthesis of cyanohydrins. The aldehydes readily proceeded the reactions with TMSCN to give the corresponding cyanohydrins with up to 88% ee (Scheme 2). The reactivity and selectivity of polymer catalyst **P3a** was similar to that of the monomer catalyst. The system provides the advantages of simplified product isolation and easy recovery and recyclability of the catalyst **P3a** without loss of activity and selectivity.



Scheme 2

3 Chiral Titanium(IV)-Catalyzed Asymmetric Sulfoxidation with Aqueous Hydrogen Peroxide

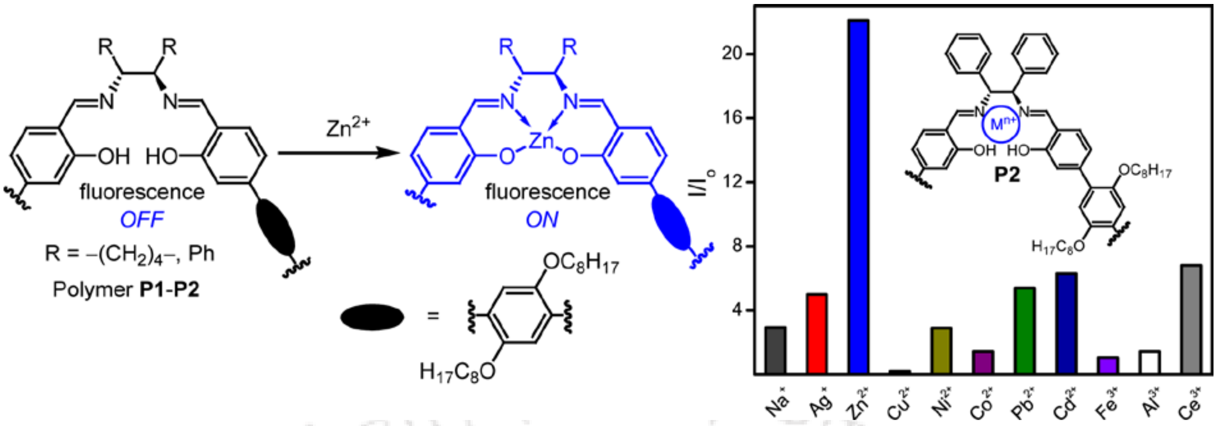
Optically active sulfoxides are structural constituents of many biologically active compounds and they also serve as versatile chiral auxiliaries in asymmetric synthesis. From an environmental and economic stand point, the use of aqueous H_2O_2 as a terminal oxidant is attractive because it is readily available, cheap and generates only water as by-product. Metal complexes bearing chiral bidentate, tridentate and tetradentate ligands have been found to be effective with aqueous hydrogen peroxide for the oxidation of sulfides. In this chapter, the synthesis and application of a series chiral tridentate ligands **III-VI** derived from optically active α-amino alcohols were studied with $Ti(O^iPr)_4$ for the oxidation of sulfides to sulfoxides in the presence of 30% H_2O_2 at ambient conditions (Scheme 3).



Scheme 3

4 Chiral Polymers as *OFF-ON* Chemosensor for the Fluorometric Detection of Zn^{2+}

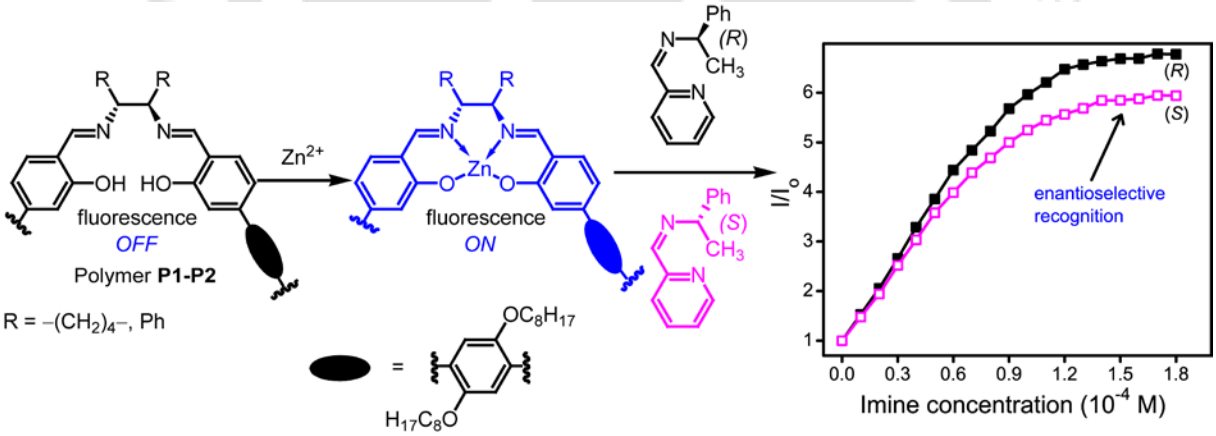
The sensors based on ion-induced changes in fluorescence appear to be particularly attractive due to their simplicity, sensitivity and selectivity. Therefore, numerous studies are focused on the design of fluorescent chemosensors for the detection of transition metal ions found in biological systems as well as in the environment. This chapter deals with the study of the chiral non-linear polymers **P1-P2** as chemosensor for the detection of Zn^{2+}metal ion. The polymer **P2** containing (*R*,*R*)-1,2-diphenyethylenediamine was found to be superior to **P1** bearing (*R*,*R*)-cyclohexyldiamine in exhibiting the best sensitivity to Zn^{2+}.



Scheme 4

5 Chiral Polymers for Fluorometric Recognition of Optically Active 1-Phenyl-*N*-[(pyridin-2-yl)methylene/methyl]ethanamines

Fluorescent sensors that are capable of differentiating the two enantiomers of a chiral compound should provide a real time technique in the rapid chiral assays with many unique advantages. This chapter presents the study of chiral main chain polymers **P1/P2** for cascade Zn(II) and chiral recognition of (*R*)-1-phenyl-*N*-[(pyridin-2-yl)methylene/methyl]ethanamine and (*S*)-1-phenyl-*N*-[(pyridin-2-yl)methylene/methyl]ethanamine (Scheme 5).



Scheme 5

Contents

5 Chiral Polymers for the Fluorometric Recognition of Optically Active 1-Phenyl-*N*-[(pyridin-2-yl)methylene/methyl]ethanamines 141

Chapter I

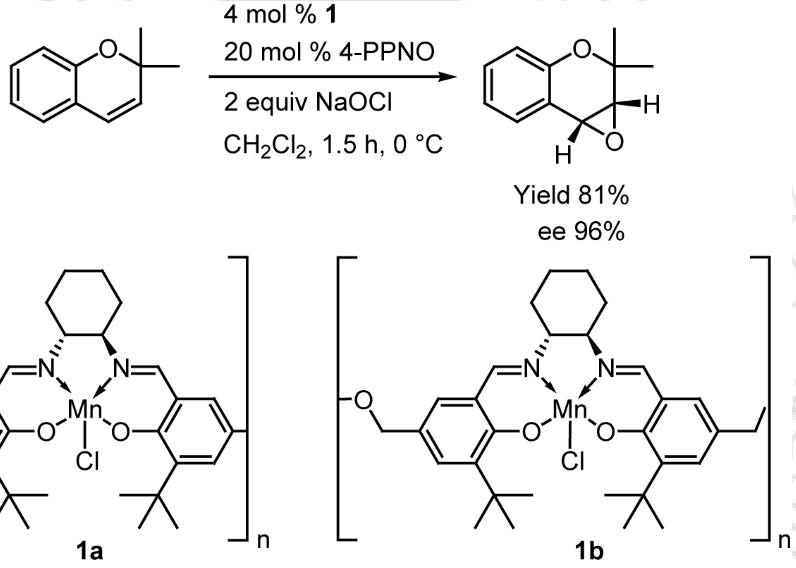
Synthesis of Chiral Main Chain Polymers Bonded with (*R*,*R*)-Salen and 1,4-Dioctyloxybenzene as Alternate Segments

1.1 Introduction

Asymmetric catalysis is an ideal method for making most of the chiral molecules using metal complexes chelated with chiral ligands. Thousands of chiral ligands and their transition metal complexes have been reported,[1] and many of them are known to be highly effective in the asymmetric formation of C-H, C-C, C-O and C-N bonds. But still, the application of such methodologies in chemical industry is rather limited due to the high cost of the chiral ligands and use of noble metals in such transformations, which have to be separated from the reaction mixture after use. Along with this unsolved problem, one more critical problem for the pharmaceutical and food industry is the high levels of metal contaminant in the final products derived from catalyst decomplexation or degradation phenomena. The potent goal of the world wide synthetic organic chemists is to overcome the above drawbacks and to transfer the asymmetric catalysis methodology to large scale synthesis technology. To facilitate the separation of the chiral catalysts from the reaction mixture, the first concept born in scientific mind is immobilizing the homogeneous catalysts on insoluble inorganic supports[2a] such as silica, zeolite, alumina, zirconia, ZnO, clay etc., and highly cross linked organic polymers.[2b] The heterogenization facilitates the separation of the catalyst from reagents and products, simplifies the efficient recovery of the often expensive or toxic catalysts, and potentially allows the adaptation of the immobilized catalysts to continuous flow type processes. Unfortunately, the immobilization of chiral catalysts often results in lower activities and enantioselectivities as compared to those observed for their homogeneous counterparts. The slightly improved thinking of scientific mind proposed the idea of soluble polymers as catalyst support.[3] Soluble macromolecules like oligomeric or soluble polymers having low cross link and PEG are the standard supports for the synthesis of soluble macromolecular stereoselective catalysts. By using such catalysts, organic reactions can be carried out in a homogeneous manner and thus may have similar catalytic activity and stereoselectivity as the homogeneous parent system. When the reaction is completed, the catalyst can be separated either by solvent or heat precipitation, membrane filtration, or size-exclusion chromatography. The drawback of these methodologies are the determination exact molecular weight and structures of polymer supported catalyst which cause problem in loading of metal and hence if there is any free metallic species bound with polymer support can cause severe drop in enantioselectivity. To find a solution for that problem, scientists discovered the way of making stereoregular chiral polymer[4] and dendrimer[5] type macromolecules having precisely defined molecular structures and mass. Complexes containing these ligands are also soluble in many common organic solvents and can be separated from the products by precipitation, membrane or nanofiltration techniques. These chiral main chain polymers and dendrimers find their applications not only in catalytic organic synthesis but also act as sensor for metal detection and chiral recognition of optically active compounds.

1.2 Chiral Main Chain Polymers with (*R*,*R*)-Salen

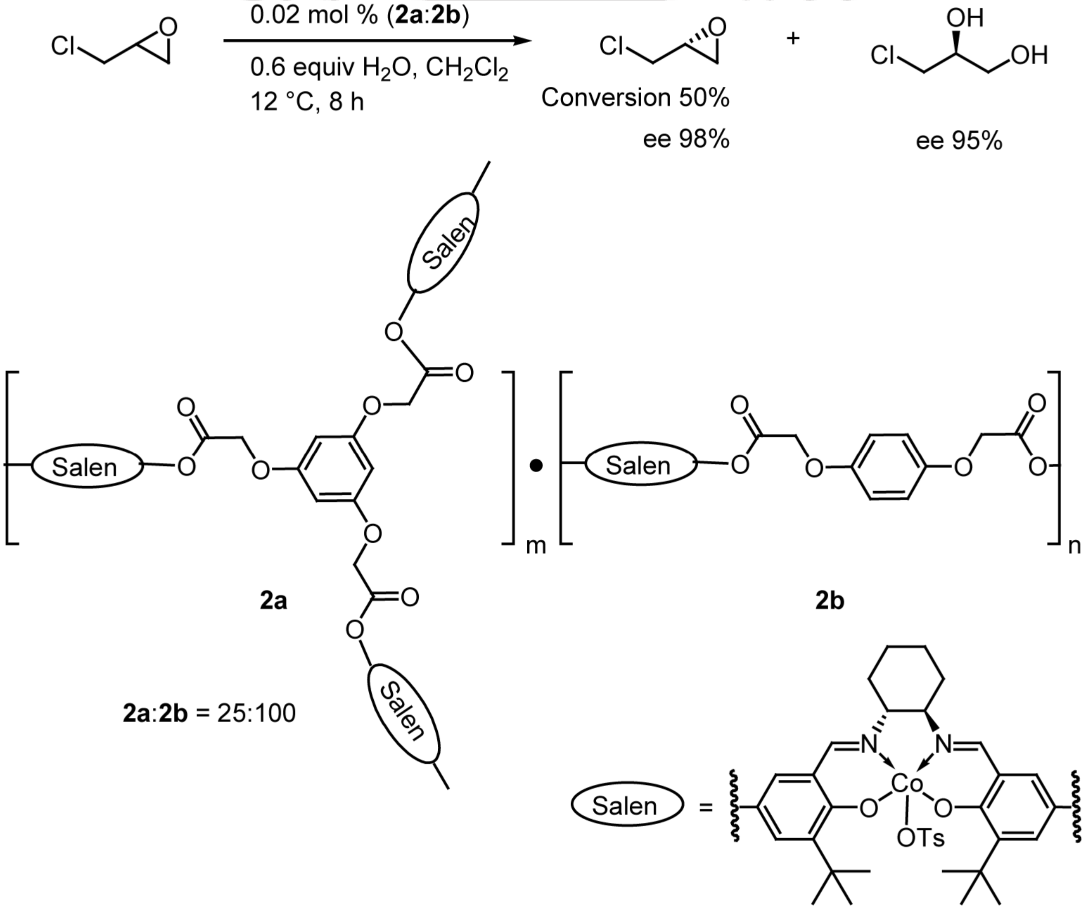
Achiral and chiral salen ligands have been studied by chemists for over 60 years for catalysis.[6] Metal complexes derived from chiral salen ligands are among the most powerful enantioselective catalysts.[7] The importance of chiral salen ligands in enantioselective catalysis was attributed to their high chiral induction and general applicability to a wide range of reactions. The discrimination between the two diastereomeric transitions states could be achieved with chiral salen ligands having bulky substituents, which can create a strongly stereogenic environment at the active metal center. As a result effective transmission of chirality from the catalysts to the reaction product will occur. Therefore, the use of chiral salen was an attractive process when it can be recovered and recycled. Because, they provide the advantages of simplified product isolation, easy recovery and recyclability of the generally quite expensive chiral catalysts and potential use for continuous production. In general, in the recyclable homogeneous catalysis, chiral ligands have typically been attached as pendent or terminal groups on a polymeric support.[8] Anchoring the chiral salen ligands in the main chain of the polymer and preserving its microenvironment were quite challenging to the researchers. Zheng *et al*. reported the first synthesis of a soluble chiral main chain polymers with Mn(III)-salen repeating units **1a-b** for the catalysis of asymmetric alkene epoxidation using NaOCl and 4-phenylpyridine-*N*-oxide (4-PPNO) as the terminal oxidants with up to 81% yield and 96% ee (Scheme 1).[9] The catalysts **1a-b** could be recovered from the reaction mixture by precipitation and recycled without loss of activity and selectivity.



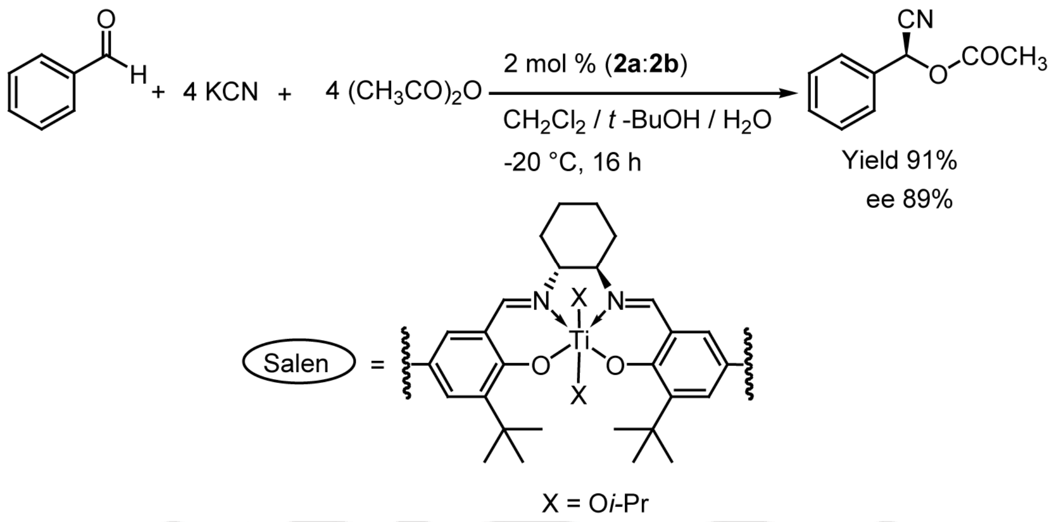
Scheme 1

The same group has subsequently employed polymeric Co-salen catalysts **2a-b** for the kinetic resolution of epoxides with water (Scheme 2).[10] Oligomeric catalysts **2b** were less reactive than highly cross-linked materials **2a**:**2b** = 25:100. Fully cross-linked catalyst **2a** was found to be less reactive due to inaccessible catalytic sites. These results reflect that the effect of cooperativity between two nearby cobalt atoms is dependent on cobalt concentration and polymer rigidity.

Following the success of the cross-linked chiral main chain polymer catalysts, Zheng *et al*. prepared a polymeric Ti(IV)-salen catalyst for the synthesis of *O*-acetylcyanohydrins from KCN, Ac_2O and aldehydes (Scheme 3).[11] The polymeric catalysts were prepared by copolymerization of di- or tribenzaldehydes with a chiral diamine to obtain supported catalysts with several degrees of cross-linking. The optimal cross-linking degree was placed between 0.5/ 100 and 2/100 (tri/di), where 91% conversion with 89% ee was obtained. With increase of the cross-linking degree, it became more difficult for the catalyst to form oxo bridges between two near metal centers, which resulted in lower levels of enantioselectivity. However, the respective catalysts became more stable and therefore more reusable. The polymeric ligand with a cross-linking ratio of 25/100 has been reused up to six times.

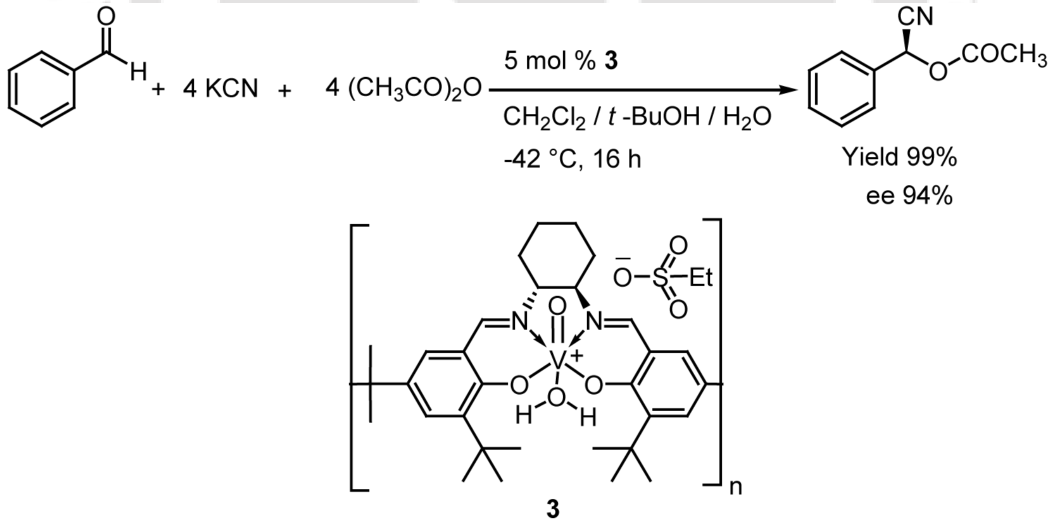


Scheme 2

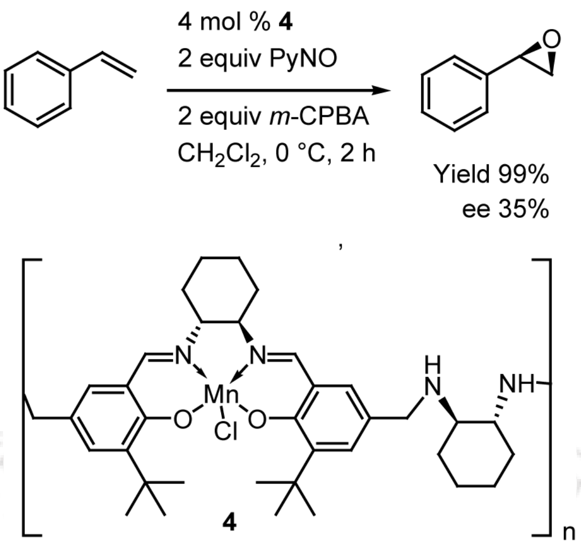


Scheme 3

On continuation to the Ti-catalysed cyanohydrins synthesis, Zheng *et al*. prepared the polymeric linear V(V)-salen catalyst **3** and tested it for the same transformation. It was quite interesting that catalyst **3** have been found to be superior to the linear polymeric Ti(IV)salen (Scheme 4).[12] Unfortunately, it was not possible to reuse it.



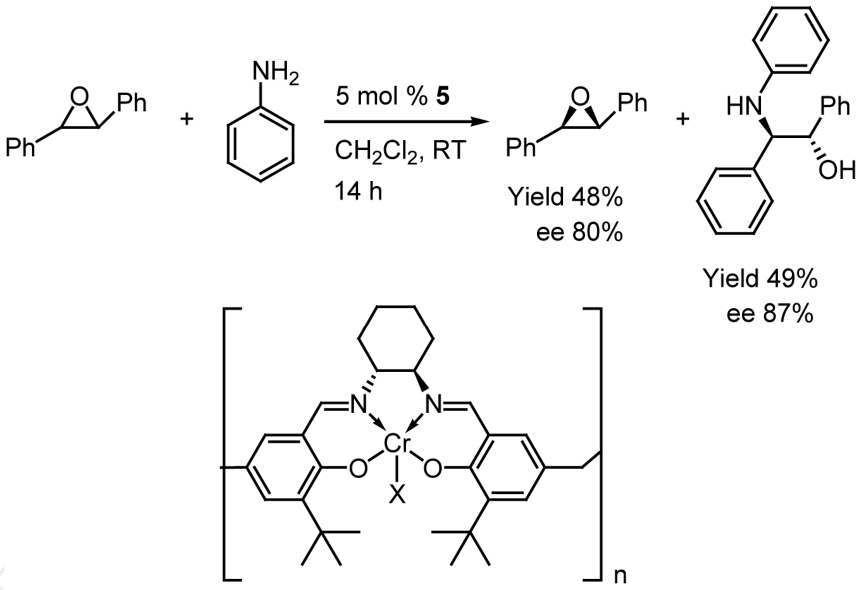
Scheme 4



Scheme 5

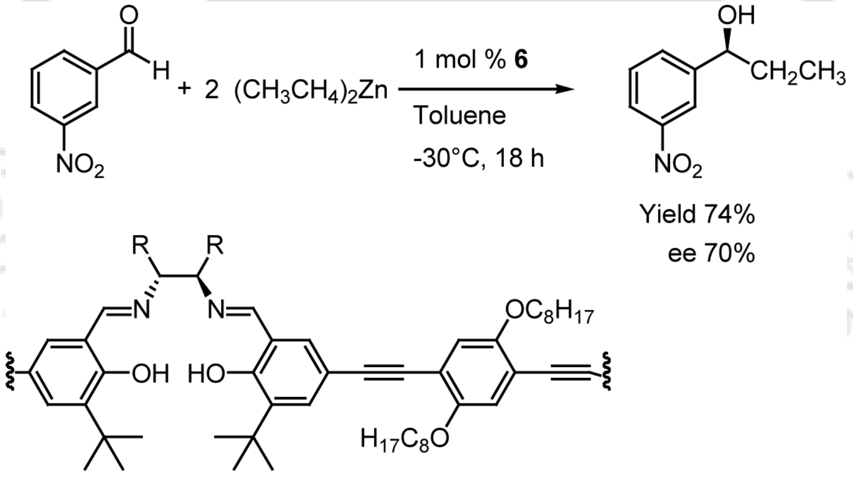
Tan *et al*. prepared a polymer containing a Mn(III)-salen complex and tested it in unfunctionalized olefin asymmetric epoxidations in the presence of *m*-CPBA/NMO (Scheme 5).[13] The enantioselectivity and reactivity observed with catalyst **4** was in the range of those obtained with the homogeneous Mn(III)-salen complex for styrene epoxidation, reaching 98% yield and 47% ee. The polymeric catalyst was recovered by solvent precipitation and was reused efficiently twice.

Kureshy *et al*. used chiral polymeric Cr(III)-salen complexes for enantioselective aminolytic kinetic resolution (AKR) of epoxides (Scheme 6).[14a-b] This work showed that a recyclable polymeric Cr(III) salen complex **5** containing Cl, NO_3 or ClO_4 counter ion had different activities (Scheme 6). The 80% ee of the recovered epoxide and 87% ee of the product amino alcohol at 49% conversion changed slightly to 71% ee and 86% ee at 45% conversion in the fifth cycle with a slight increase in reaction times (14 to 20 h). The authors also studied the AKR chemistry using microwave reactor in a 9:1 mixture of CH_2Cl_2/MeOH solvent.[15b] Under these conditions, the reaction times decreased from 14 h to 2 min. Recycling was as efficient as in the thermal process, but the % ee for both the recovered epoxide and the amino alcohol advantageously increased in the microwave process to *ca*. 90%



5a X = Cl **5b** X = NO_3 **5c** X = ClO_4

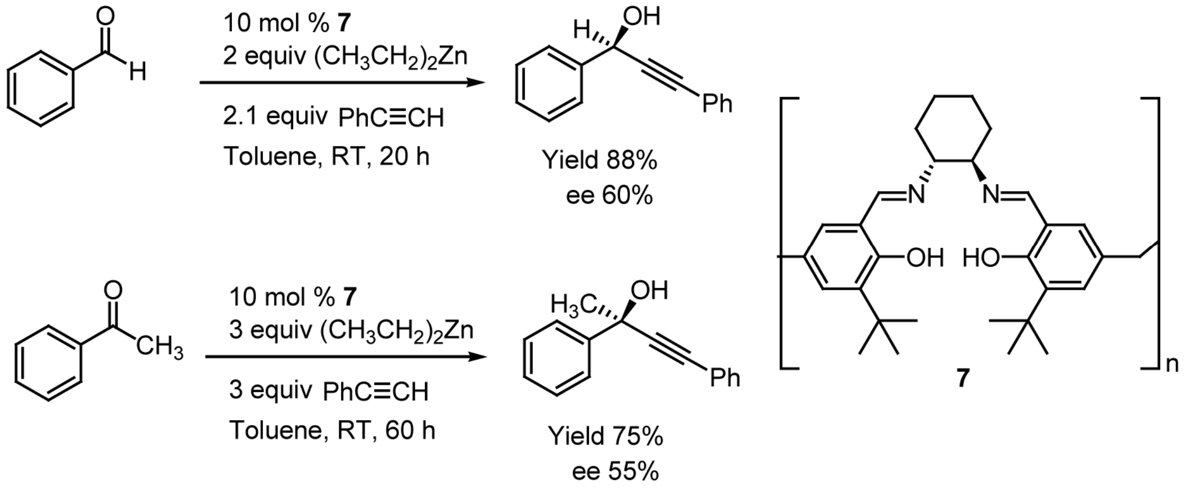
Scheme 6



6a R = $-(CH_2)_4-$ **6b** R = Ph

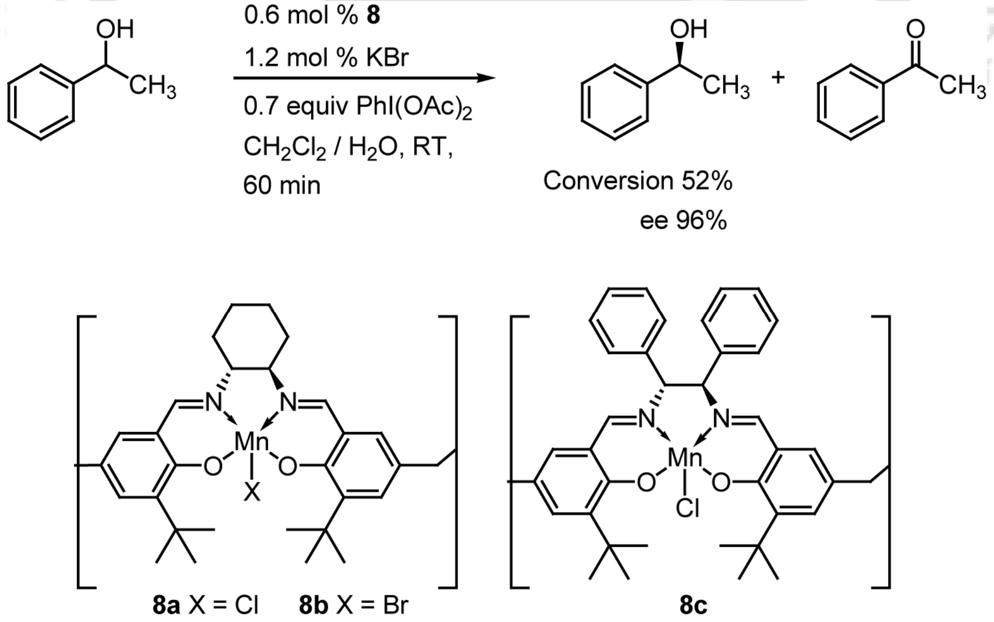
Scheme 7

Our group prepared a new class of π-conjugated chiral main chain polymers **6** bonded alternatively with (*R*,*R*)-salen and 1,4-diethynyl-2,5-dioctyloxybenzene (Scheme 7).[15] These polymers were studied for direct diethylzinc addition to aldehydes as recyclable ligands. The respective secondary alcohol was obtained in good yields (74%) and good enantioselectivities (70% ee).



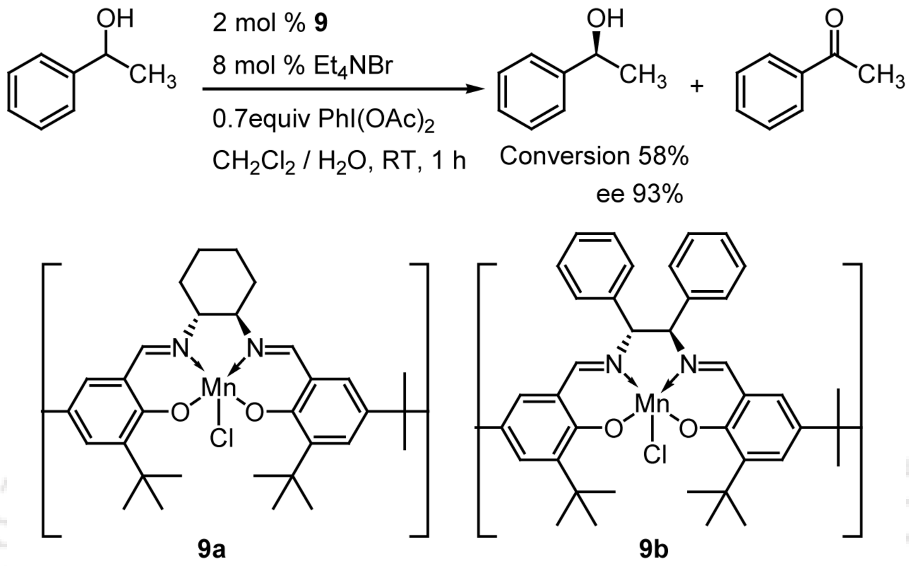
Scheme 8

Pathak *et al*. employed chiral Zn(II)-salen polymer formed *in situ* from Et_2Zn and **7** for the enantioselective addition of phenylacetylene to aryl aldehydes and aryl methyl ketones with *ca*. 60% ee (Scheme 8).[16] The catalyst was reused up to four runs without affecting the yield and selectivity.



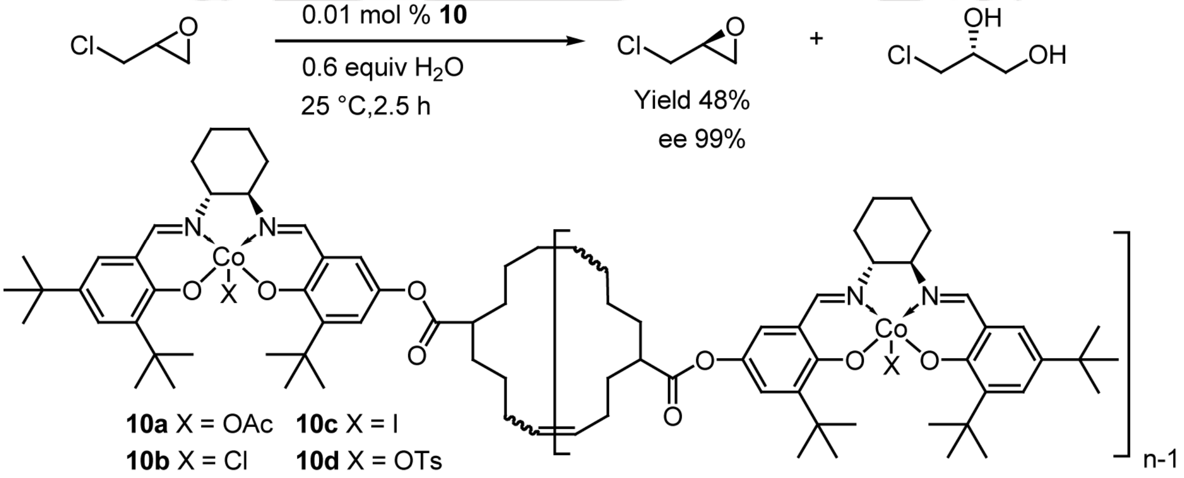
Scheme 9

Kureshy *et al.*[17a] and Sun *et al.*[17b] reported the use of chiral Mn(III)-salen polymer for the oxidative kinetic resolutions of secondary alcohols with up to >90% ee (Scheme 9-10). The catalysts could be precipitated from the reaction mixture using hexane for recyclabilty without loss of activity and selectivity.



Scheme 10

Zheng *et al.* investigated chiral cobalt(III)-salen **10** for kinetic resolution of terminal epoxides with 99% ee (Scheme 11). The catalyst is also recyclable without loss of activity and selectivity.[18]



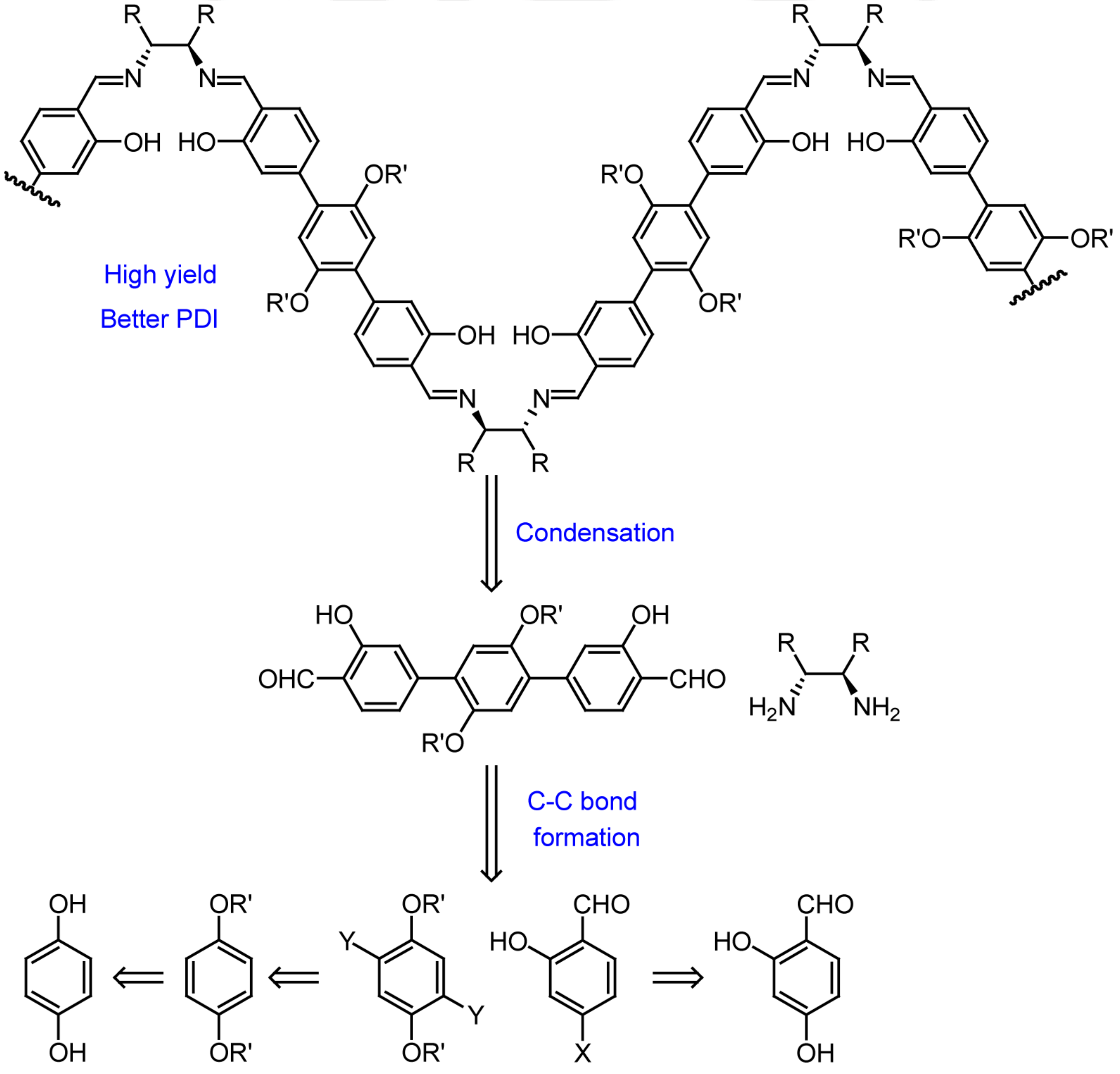
Scheme 11

1.3 Present Study

In continuation to our studies on stereoregular chiral polymers,[15] we here describe the synthesis of stereoregular chiral main chain polymers **P1-P4** bonded with chiral (*R*,*R*)-salen and 1,4-dioctyloxybenzene as alternate segments.

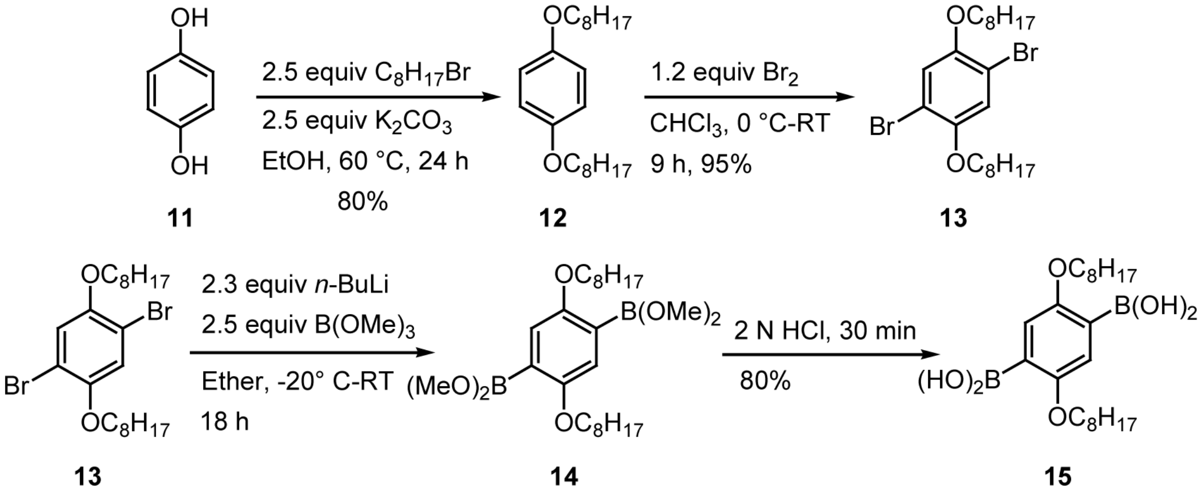
1.3.1 Synthesis of Non-linear Polymers P1-P2

The reterosynthetic pathway for the synthesis of the non-linear polymers **P1-P2** is shown in Scheme 12.



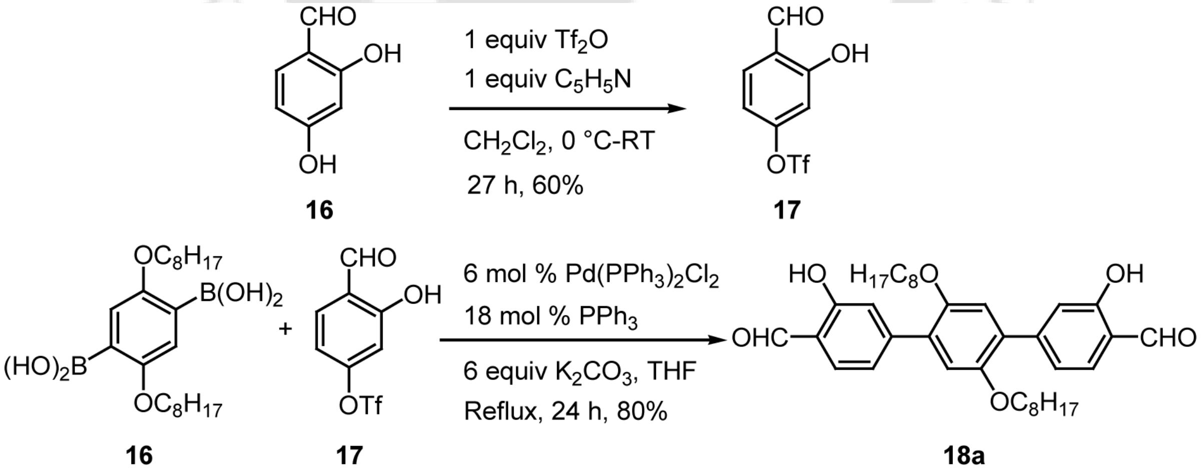
Scheme 12

The reaction of 1,4-hydroquinone **11** with 1-bromooctane in the presence of K_2CO_3 gave 1,4-dioctyloxybenzene **12** that could be brominated using Br_2 to afford 1,4-dibromo-2,5-dioctyloxybenzene **13** in 85% yield.[15] The latter **13** was reacted with trimethoxyborane in the presence of *n*-BuLi followed by acid hydrolysis to give 2,5-dioctyloxyphenyldiboronate **15** in 80% yield (Scheme 13).[19]

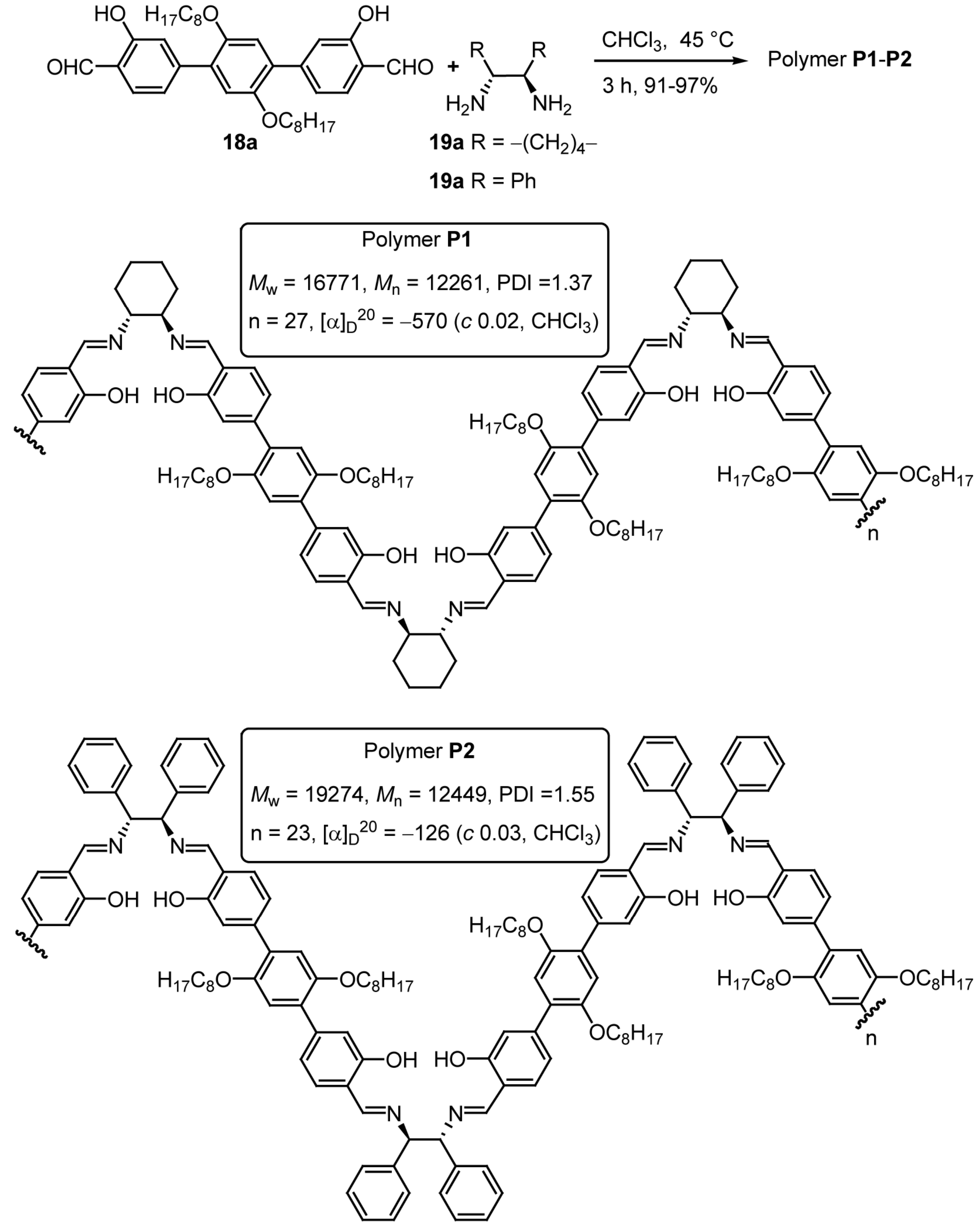


Scheme 13

The selective reaction of 2,4-dihydroxybenzaldehyde **16** with trifluoromethanesulfonic anhydride in the presence of pyridine gave 4-formyl-3-hydroxyphenyl trifluoromethanesulfonate[20] **17** in 60% yield, which could be C-C cross-coupled with **15** using $Pd(PPh_3)_2Cl_2$ to afford the desired dialdehyde **18a** in 80% yield (Scheme 14).[21]



Scheme 14


HO
H17C8O
OH
OHC
CHO
OC8H17
18a
+
R
R
H2N
NH2
19a R = –(CH2)4–
19a R = Ph
CHCl3, 45 °C
3 h, 91-97%
Polymer P1-P2
Polymer P1
Mw = 16771, Mn = 12261, PDI =1.37
n = 27, [α]D20 = –570 (c 0.02, CHCl3)
N
N
OH
HO
H17C8O
OC8H17
n
Polymer P2
Mw = 19274, Mn = 12449, PDI =1.55
n = 23, [α]D20 = –126 (c 0.03, CHCl3)

Scheme 15

Schiff base formation of the dialdehyde **18a** with (*R*,*R*)-1,2-diaminocyclohexane **19a** and (*R*,*R*)-1,2-diphenylethylenediamine **19b** on heating in $CHCl_3$ gave the polymers **P1-P2** as yellow powder (Scheme 15).[15,22] The octyloxy substituent of the polymers backbone assists the polymers to be soluble in common organic solvents such as THF, $CHCl_3$ and CH_2Cl_2. The average molecular weights of the polymers was determined using GPC analysis with polystyrene as an internal standard and THF as an eluent, which correspond to *ca.* 27 repeating units for **P1** (M_w = 16771, M_n =12261 and PDI = 1.37) and *ca.* 23 repeating units for **P2** (M_w = 19274, M_n = 12449 and PDI = 1.55). The ^{1}H NMR spectra recorded at 400 MHz and FT-IR spectra are consistent with their structures. The disappearance of aldehyde proton -C*H*O peak at δ 9.78 and the appearance of imine proton -C*H*=N- at δ 8.33(4) confirms the formation of polymers.

Figure 1-3 illustrates the UV-vis, fluorescence and TGA of the polymers **P1-P2**. The UV-vis spectra showed absorption maxima at *ca.*289 ($\varepsilon = 2.70 \times 10^4\ M^{-1}cm^{-1}$) and 349 nm ($\varepsilon = 2.98 \times 10^4\ M^{-1}cm^{-1}$) for **P1**, and 290 ($\varepsilon = 2.77 \times 10^4\ M^{-1}cm^{-1}$) and 352 nm ($\varepsilon = 3.2 \times 10^4\ M^{-1}cm^{-1}$) for **P2**, respectively, due to π-π* transition.

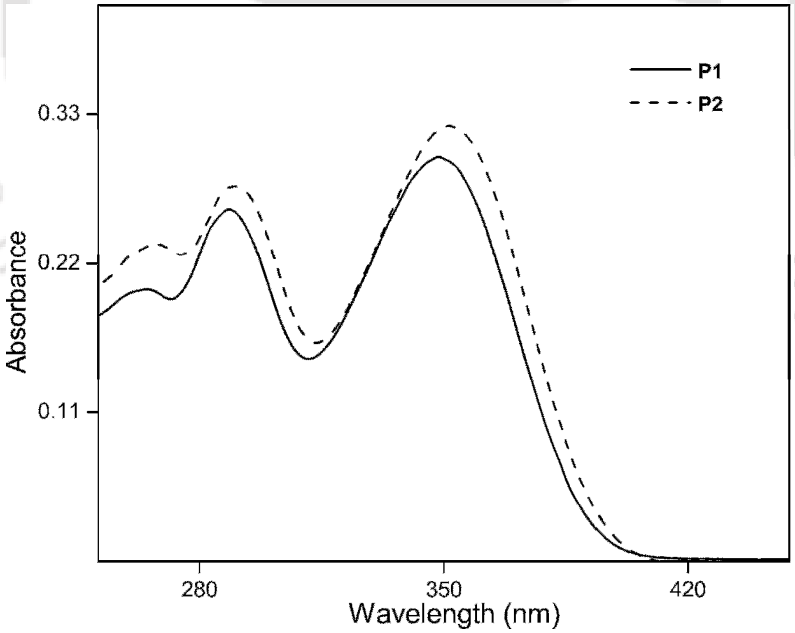


Figure 1. UV-visible Spectra of Polymers **P1-P2** in THF (1×10^{-5} M).

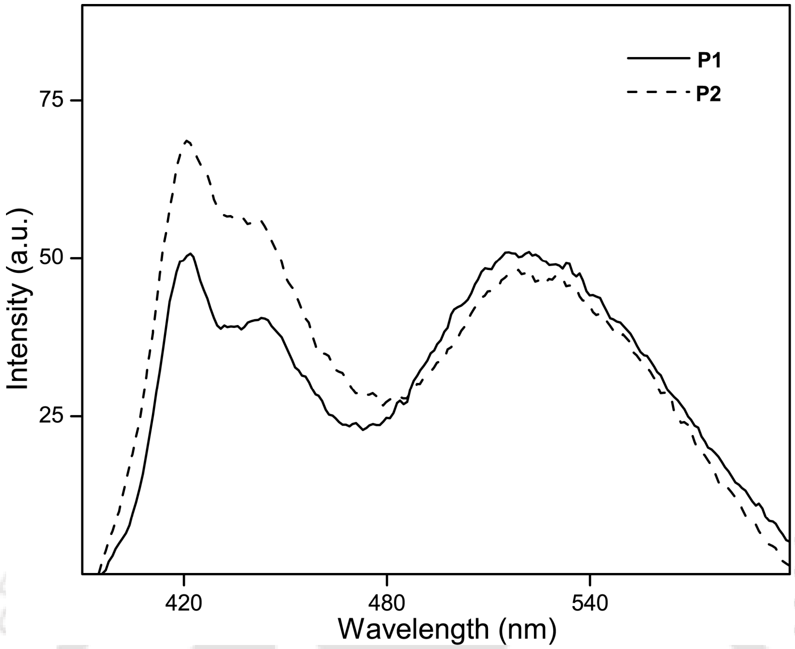


Figure 2. Fluorescence Spectra of Polymers **P1-P2** in THF (1 x 10^{-5} M, λ_{ex} = 360 nm).

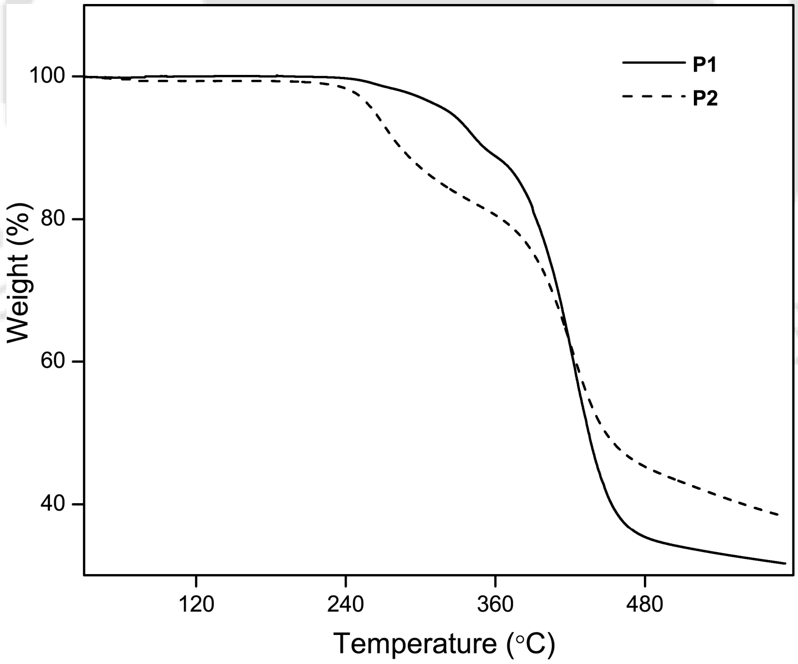
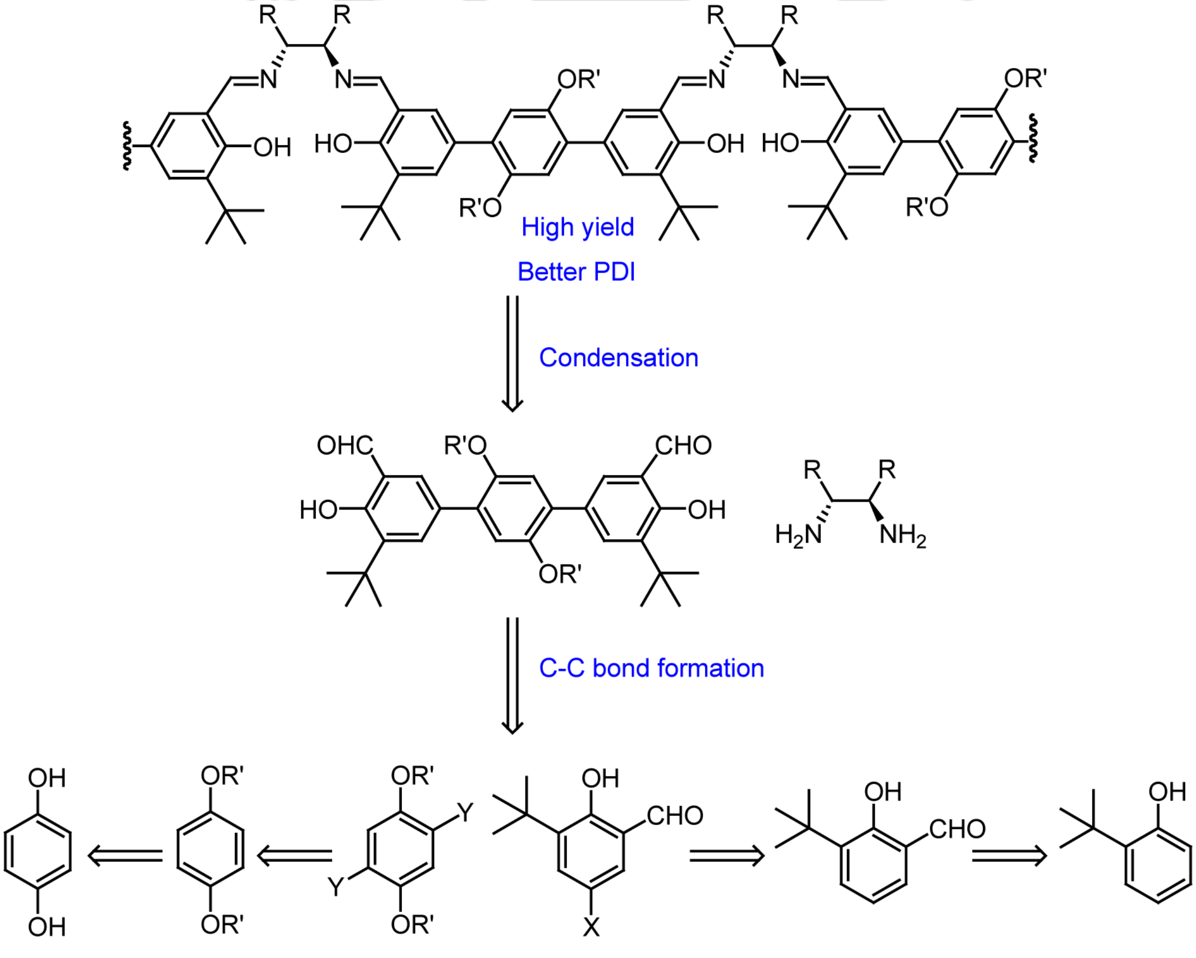


Figure 3. TGA of Polymers **P1-P2**.

Regarding fluorescence, **P1** emitted a weak blue light at 423 and 521 nm (λ_{ex} = 360 nm), and **P2** at 421 and 519 nm (λ_{ex} = 360 nm). The thermal analysis showed that the polymers **P1-P2** are quite stable up to *ca.* 270 °C and a total weight loss of 58-68% was observed when the temperature was increased to 600 °C.

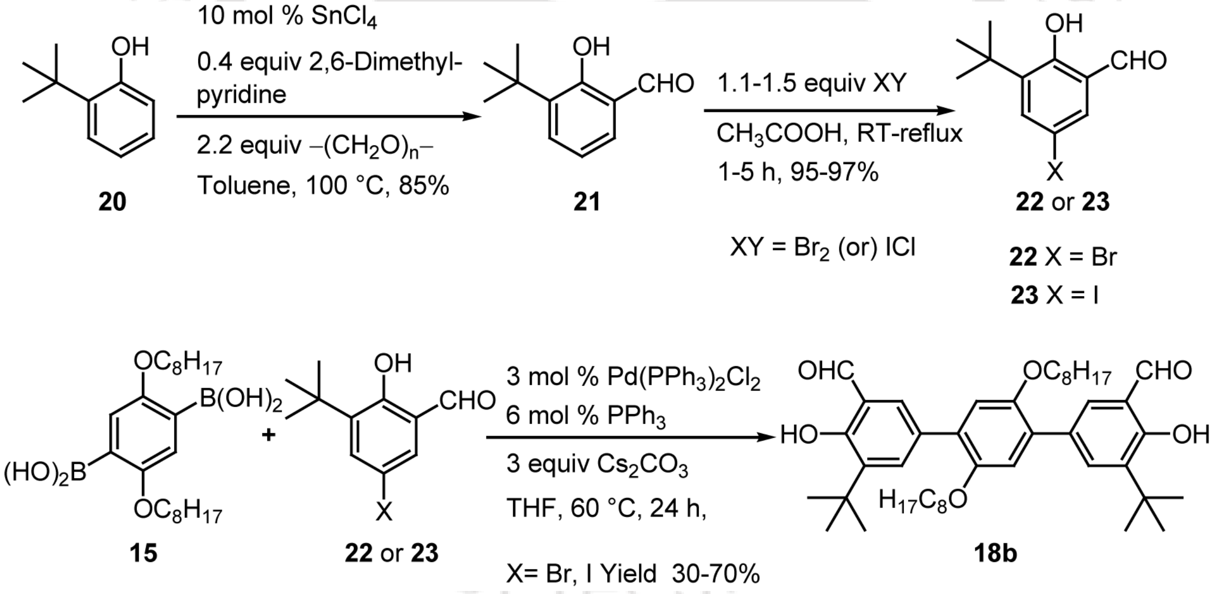
1.3.2 Synthesis of Linear Polymers P3-P4

The linear polymers **P3-P4** have also been synthesized in a similar fashion to that of non-linear **P1-P2** and Scheme 16 presents the reterosynthetic analysis.



Scheme 16

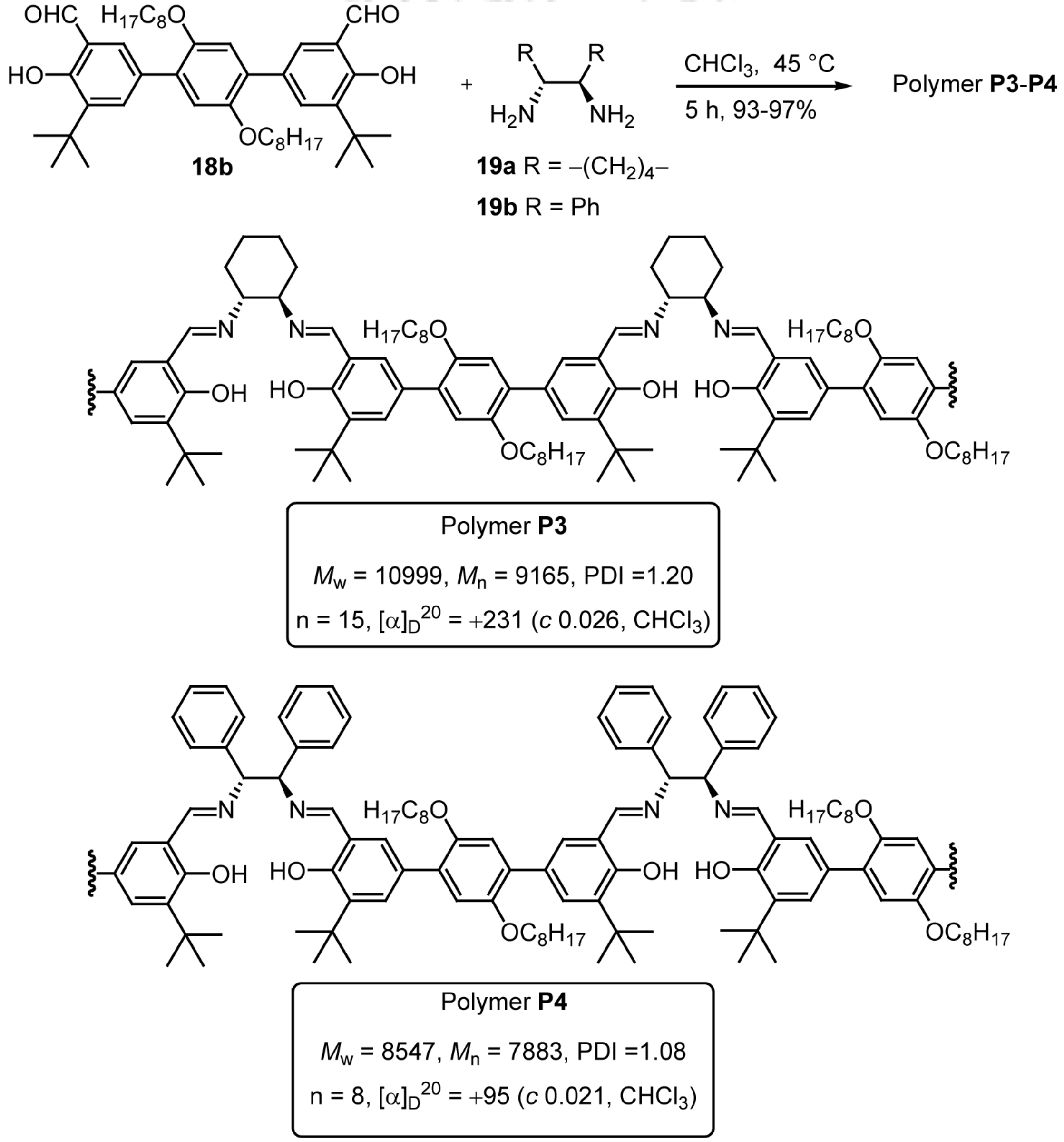
The synthesis of 2,5-dioctyloxyphenyldiboronic acid **15** was accomplished as shown in Scheme 13. Next, the synthesis of the 3-*tert*-butyl-2-hydroxybenzaldehyde **21** was carried out by the selective introduction of formyl group to the *ortho* position of phenolic functionality of 2-*tert*-butylphenol **20**. Bromination of aldehyde **21** with bromine in CH_3COOH provided 3-*tert*-butyl-2-hydroxy-5-bromobenzaldehyde[15] **22** in 95% yield that could be C-C cross-coupled with **15** using $Pd(PPh_3)_2Cl_2$ to give the target molecule **18b** in 30% yield (Scheme 17).[23] The yield of the dialdehyde **18b** was not quite satisfactory, hence, the improvement in the yield was done through cross-coupling of **15** with the iodo derivavtive of the aldehyde **21.** Iodination of the aldehyde **21** was performed with iodine monochloride in CH_3COOH to provide 3-*tert*-butyl-2-hydroxy-5-bromobenzaldehyde[23] **23** in 95% yield. Finally, the iodoaldehyde **23** was C-C cross-coupled with boronic acid **15** to give the dialdehyde **18b** in 70% yield.



Scheme 17

The synthesis of the polymers **P3**-**P4** was then pursued by condensation of **18b** with chiral (1*R*,2*R*)-diaminocyclohexane **19a** and (1*R*,2*R*)-diphenylethylenediamine **19b** in $CHCl_3$ (Scheme 18). [15,22] The reactions proceeded smoothly to afford the polymers **P3**-**P4** in 93-97% yield. The polymers **P3**-**P4** were soluble in common organic solvents such as THF,

$CHCl_3$, CH_2Cl_2 and toluene. GPC analysis, with polystyrene as an internal standard and THF as eluent, exhibited their average molecular weights that correspond to *ca.* 15 repeating units for **P3** (M_w = 10999, M_n = 9165 and PDI = 1.20) and *ca.* 8 repeating units for **P4** (M_w = 8547, M_n = 7883 and PDI = 1.08). The ^{1}H NMR spectra recorded at 400 MHz and FT-IR spectra were consistent with their structure. The appearance of imine proton -C*H*=N- at δ 8.40(1) and the absence of aldehyde proton -C*H*O peak at δ 9.91 confirms the complete formation of polymers.



Scheme 18

Figures 4-6 presents the UV-vis, fluorescence and TGA of the polymers **P3-P4**. The UV-vis spectra showed absorption maxima at *ca.*258 ($\varepsilon = 3.97 \times 10^4\ M^{-1}cm^{-1}$) and 321 nm ($\varepsilon = 1.95 \times 10^4\ M^{-1}cm^{-1}$) for **P3,** and 265 ($\varepsilon = 4.65 \times 10^4\ M^{-1}cm^{-1}$) and 321 nm ($\varepsilon = 2.10 \times 10^4\ M^{-1}cm^{-1}$) for **P4**, respectively, due to π-π* transition. Regarding fluorescence, THF solution of polymer **P3** emitted a very weak blue light at 371 and 543 nm (λ_{ex} = 330 nm), and **P4** at 367 and 544 nm (λ_{ex} = 330 nm). The thermal analysis under nitrogen atmosphere showed that the polymers **P3-P4** are quite stable up to *ca.* 270 °C and a total weight loss of >80% was observed when the temperature was gradually increased to 600 °C.

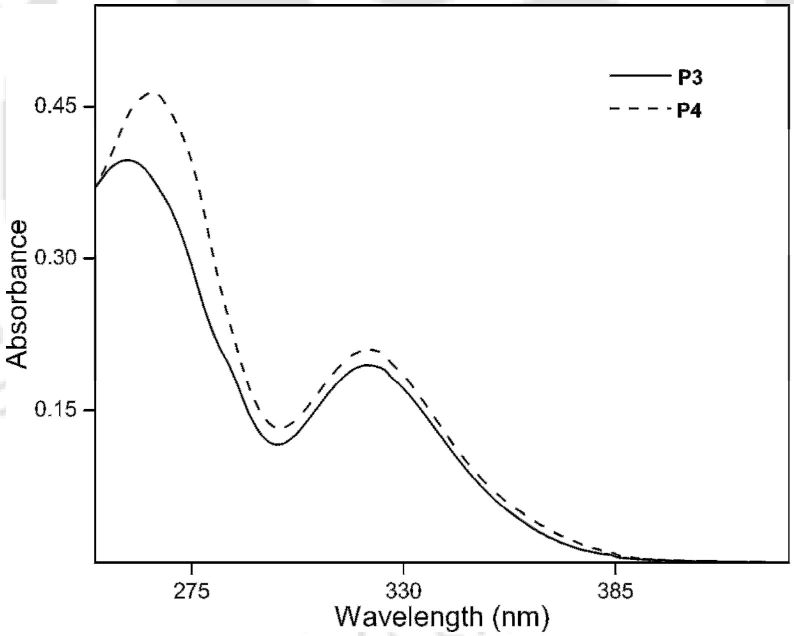


Figure 4. UV-visible Spectra of Polymers **P3-P4** in THF (1 x 10^{-5} M).

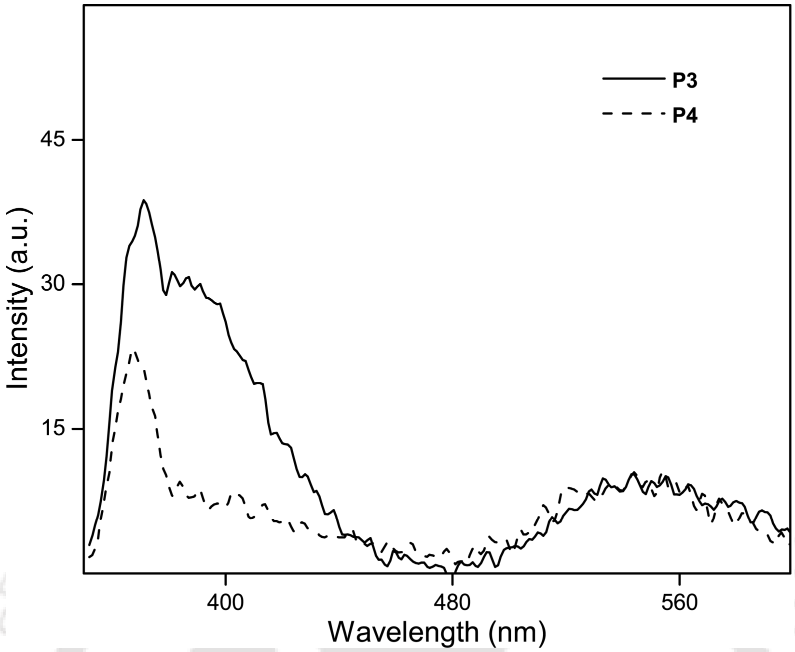


Figure 5. Fluorescence Spectra of Polymers **P3-P4** in THF (1 x 10^{-5} M, λ_{ex} = 330 nm).

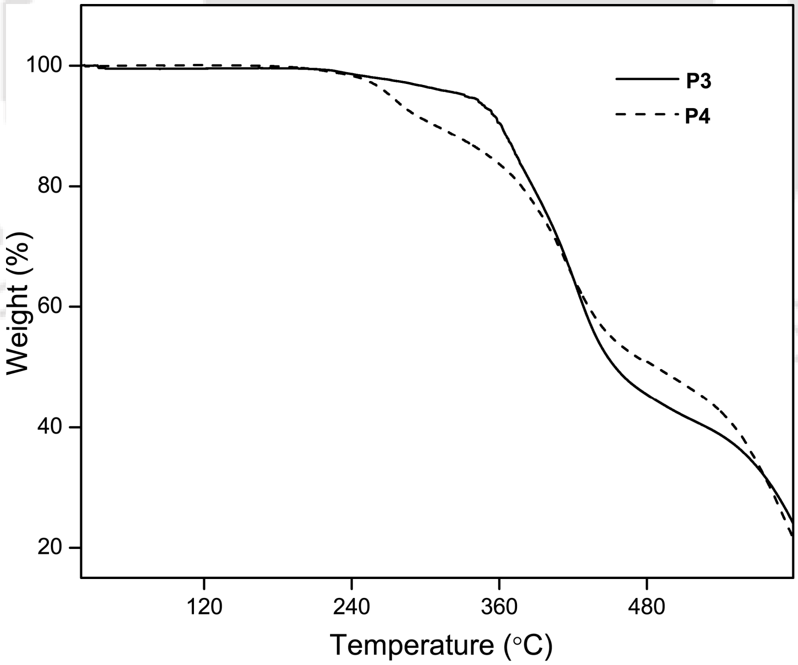
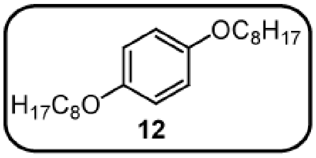


Figure 6. TGA of Polymers **P3-P4**.

In summary, the design and synthesis of the stereoregular chiral main chain polymers **P1-P4** having (*R*,*R*)-salen and 1,4-dioctyloxybenzene moieties have been accomplished through Suzuki cross-coupling reaction and Schiff base formation as key steps. These materials are soluble in common organic solvents and exhibit high thermal stability.

Experimental section

General. 2,4-Dihydroxybenzaldehyde (98%), trifluoromethanesulfonic anhydride (≥99%), hydroquinone (≥99%), octyl bromide (99%), trimethyl borate (≥98%), *n*-BuLi (2.0 M in cyclohexane), $Pd(PPh_3)_2Cl_2$ (98%), PPh_3 (99%) were purchased from Aldrich. Bromine and iodine monochloride were purchased from Merck. Et_2O and THF were freshly distilled from sodium and benzophenone under nitrogen prior to use. Column chromatography was carried out with Rankem 60-120 mesh silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra (400 MHz for ^1H and 100 MHz ^{13}C) were recorded on DRX-400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvent and Me_4Si as an internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Melting points were determined using Buchi B-540 and are uncorrected. IR spectra were recorded using PerkinElmer spectrum one spectrometer. UV-vis spectra were recorded on PerkinElmer Lambda 25 UV/vis spectrometer. Fluorescence spectra were recorded on Varian Carey Eclipse fluorescence spectrophotometer. GPC analysis was performed with stationary phase column Styragel® WAT044221 using polystyrene as an internal standard and THF as eluent. The optical rotation was measured on PerkinElmer model-343. Thermal gravimetric analysis was performed on SDT Q600 under nitrogen atmosphere. Elemental analysis was carried out using PerkinElmer 2400 CHNS analyzer.



12

1,4-Dioctyloxybenzene 12. A mixture of 1-bromooctane (24.1 g, 125 mmol), 1,4-hydroquinone **11** (5.5 g, 50 mmol) and K_2CO_3 (17.3 g, 125 mmol) were stirred in ethanol (50 mL) for 24 h at 70 °C. The solvent was then evaporated and the residue was dissolved in ethyl acetate (100 mL). The solution was washed with water (2 x 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue which was crystallized in ethanol to provide **12** as a colorless solid in 80% (13.4 g) yield.

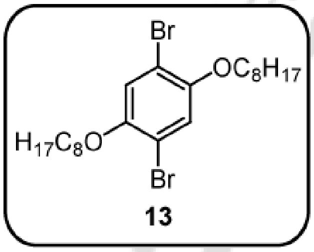
Mp: 54-55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 4H), 3.89 (t, *J* = 3.1 Hz, 4H), 1.70-1.79 (m, 4H), 1.20-1.57 (m, 20H), 0.88 (t, *J* = 3.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 140.3, 131.3, 112.4, 53.0, 24.1, 11.0.

FT-IR (KBr): 2955, 2934, 2921, 2872, 2856, 1511, 147, 1395, 1290, 1245, 1114, 1030, 1009, 827, 772, 535 cm^{-1}.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 79.07; H, 11.43.



13

1,4-Dibromo-2,5-dioctyloxybenzene 13. To a stirred solution of 1,4-dioctyloxybenzene **12** (21 g, 63 mmol) in $CHCl_3$ (200 mL) at 0 °C, Br_2 (10.5 mL, 134 mmol) in $CHCl_3$ (100 mL) was added. After allowing the reaction mixture at ambient temperature for 8 h, it was cooled to 0 °C and aqueous KOH (1 N) was added until the excess Br_2 completely consumed. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic solution was washed with water (2 x 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to provide a residue which was crystallized in ethanol to afford **13** as a colorless solid in 95% (29.5 g) yield.

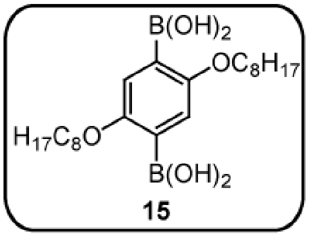
Mp: 64-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 2H), 3.95 (t, *J* = 3.1 Hz, 4H), 1.70-1.79 (m, 4H), 1.20-1.57 (m, 20H), 0.88 (t, *J* = 3.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 118.5, 111.1, 70.3, 31.8, 29.3, 29.1, 26.0, 22.7, 14.1.

FT-IR (KBr): 2955, 2920, 2849, 1495, 1459, 1395, 1361, 1272, 1211, 1126, 1066, 1028, 998, 806, 724 cm^{-1}.

Anal. Calcd for $C_{22}H_{36}Br_2O_2$: C, 53.67; H, 7.37. Found: C, 53.74; H, 7.41.



15

2,5-Dioctyloxyphenyldiboronic acid 15.[24] *n*-BuLi (11.5 mL, 2.0 M in cyclohexane) was added to a stirred solution of 1,4-dibromo-2,5-dioctyloxybenzene **13** (4.92 g, 10 mmol) in dry Et_2O (40 mL) at -20 °C under nitrogen atmosphere. After 1 h, trimethylborate (2.8 mL, 25 mmol) was added and the mixture was allowed to warm up to room temperature and the stirring continued for additional 12 h. The reaction mixture was then treated with 2 N HCl (25 mL) and the precipitate was collected by filtration and washed successively with water (10 mL) and Et_2O (20 mL) to give **15** as colorless solid in 80% (3.38 g) yield.

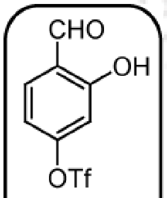
Mp: 139-140 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (s, 4H), 7.16 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 4H), 1.70 (t, *J* = 7.4 Hz, 4H), 1.38-1.24 (m, 20H), 0.84 (t, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 156.9, 124.5, 118.0, 68.4, 31.1, 28.7, 28.65, 28.59, 25.4, 22.1, 13.9.

FT-IR (KBr): 3498, 3362, 2941, 2921, 2870, 2852, 1495, 1470, 1417, 1389, 1299, 1272, 1205, 1127, 1083, 1049, 1002, 887, 804, 722, 652, 566 cm^{-1}.

Anal. Calcd for $C_{22}H_{40}B_2O_6$: C, 62.59; H, 9.55. Found: C, 62.55; H, 9.59.

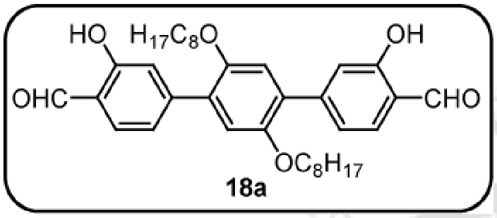


17

Preparation of 4-Trifluoromethanesulfonyl-2-hydroxybenzaldehyde 17.[25] To a stirred solution of 2,4-dihydroxybenzaldehyde **16** (2.0 g, 14.5 mmol) and pyridine (1.2 mL, 14.5 mmol) in CH_2Cl_2 (15 mL) at 0 ^{o}C was added trifluoromethanesulfonic anhydride (2.5 mL, 14.5 mmol). After 0.5 h, the reaction mixture was allowed to warm to ambient temperature and the stirring was continued for an additional 27 h. The organic layer was separated and the residue was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic solution was then washed with water (2 x 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a residue which was purified by silica gel flash column chromatography using ethyl acetate and hexane to afford **17** as colorless liquid in 60% (2.35 g) yield.

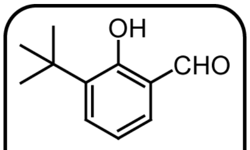
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.27 (s, 1H), 9.90 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 6.94-6.89 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 163.2, 154.7, 135.9, 120.46, 120.39, 113.2, 111.0.
FT-IR (neat): 3406, 3109, 2873, 1706, 1688, 1602, 1432, 1216, 1133, 969, 879, 608 cm^{-1}.
Analysis calcd for $C_8H_5F_3O_5S$: C, 35.56; H, 1.87; S, 11.87. Found. C, 35.62; H, 1.89; S, 11.88.



18a

Preparation of the Dialdehyde 18a. 4-Formyl-3-hydroxyphenyl trifluoromethanesulfonate **17** (1.94 g, 7.2 mmol), 2,5-di(octyloxy)phenyldiboronate **15** (1.44 g 3.4 mmol), $Pd(PPh_3)_2Cl_2$ (6 mol %), PPh_3 (18 mol %) and K_2CO_3 (2.8 g, 20.4 mmol) were stirred under reflux for 24 h in THF (30 mL) under nitrogen atmosphere. The solvent was then evaporated on rotary evaporator to give a residue that was dissolved in EtOAc (30 mL) and washed with brine (5 mL) and water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a solid that was purified by silica gel column chromatography using EtOAc and hexane as eluent to give **18a** as yellow solid in 80% (1.55 g) yield.
Mp: 115-116 °C.
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.07 (s, 2H), 9.92 (s, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 7.19 (s, 2H), 6.96 (s, 2H), 3.93 (t, J = 6 Hz, 4H), 1.69 (t, J = 6.8 Hz, 4H), 1.35-1.23 (m, 20H) 0.85 (t, J = 6.2 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 161.5, 150.5, 147.4, 133.2, 130.3, 121.8, 119.6, 118.5, 115.8, 69.7, 32.0, 29.4, 26.2, 22.8, 14.3.
FT-IR (KBr): 3055, 2923, 2853, 1645, 1621, 1557, 1520, 1493, 1467, 1434, 1392, 1371, 1317, 1266, 1211, 1198, 1134, 1055, 1030, 971, 939, 904, 883, 818, 741, 717, 587 cm^{-1}.
Anal. Calcd for $C_{36}H_{46}O_6$: C, 75.23; H, 8.07. Found: C, 75.19; H 8.11.



21

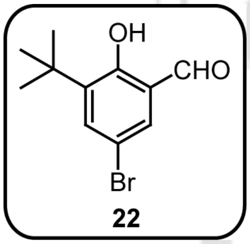
3-*tert*-Butylsalicylaldehyde 21. To a stirred solution of 2-*tert*-butylphenol **20** (5 g, 33.3 mmol) and 2,6-dimethylpyridine (2.5 g, 13.33 mmol) in toluene (30 mL) at ambient temperature, $SnCl_4$ (0.4 mL, 3.33 mmol) was added. After 0.2 h, the reaction mixture was treated with paraformaldehyde (2.2 g, 33.3 mmol) and the resultant yellow solution was heated at 100 ^{o}C for 10 h. The reaction mixture was then cooled to ambient temperature and transferred into a 250 mL flask having 100 mL water. The pH of the solution was adjusted to 2 using 2 M HCL and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic solution was washed with brine (1 x 30 mL) and water (1 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent provided a residue which was purified on column chromatography using hexane as eluent to afford **21** as yellow liquid in 85% (5.1 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.75 (s, 1H), 9.83 (s, 1H), 7.50 (dd, J = 7.6, 1.6 Hz, 1H), 7.35 (dd, J = 7.6, 1.6 Hz, 1H), 6.91 (m, 1 H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 161.2, 138.3, 134.1, 132.0, 120.8, 119.3, 35.1, 29.5.

FT-IR (neat): 3412, 2960, 2873, 2736, 1652, 1613, 1481, 1432, 1385, 1314, 1264, 1190 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.21; H, 7.96.



22

5-Bromo-3-*tert*-butylsalicylaldehyde 22. To a stirred solution of 3-*tert*-butyl-2-hydroxybenzaldehyde **21** (5.21 g, 29.3 mmol) in CH_3COOH (15 mL), Br_2 (2.3 mL, 30.7 mmol) in CH_3COOH (2 mL) was added at ambient temperature. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed successively with saturated $Na_2S_2O_5$ (1 x 10 mL), saturated $NaHCO_3$ (1 x 10 mL), brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent afforded yellow solid which was crystallized in methanol to give **22** in 95% (6.77g) yield.

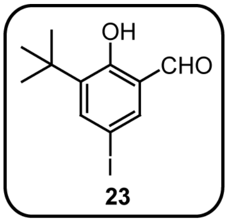
Mp: 62-63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.68 (s, 1H), 9.77 (s, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 2 Hz, 1H),1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 160.2, 141.2, 137.1, 133.6, 121.8, 111.2, 35.4, 29.2.

FT-IR (KBr): 3087, 2956, 2868, 2719, 1654, 1603, 1430, 1303, 1272, 1197, 1166, 931, 867, 738, 713 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.88; H, 5.10. Found: C, 51.94; H, 5.14.



3-*tert*-Butyl-2-hydroxy-5-iodobenzaldehyde 23[7] To a stirred solution of 3-*tert*-butyl-2-hydroxybenzaldehyde **21** (1.78 g, 10 mmol) in glacial CH_3COOH (15 mL) at room temperature, iodinemonochloride (2.43 g, 15 mmol) in glacial CH_3COOH (7 mL) was added drop wise. After refluxing the mixture for 5 h, cooled to room temperature and treated with CH_2Cl_2 (25 mL) and water (15 mL). The organic layer was separated and washed with brine (10 mL) and water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give **23** as pale yellow solid in 97% (2.95 g) yield.

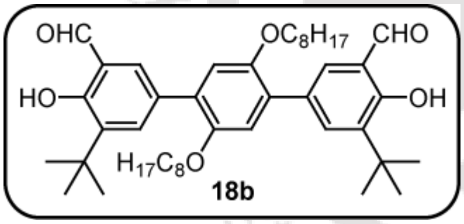
Mp: 54-55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.72 (s, 1H), 9.78 (s, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.68 (t, *J* = 2 Hz, 2H), 1.37(s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 160.9, 142.6, 141.4, 140.1, 122.6, 80.8, 35.1, 29.2.

FT-IR (KBr): 3435, 3088, 2963, 2871, 2728, 1651, 1599, 1475, 1434, 1413, 1350, 1303,1269, 1196, 1163, 1024, 930, 769, 756, 704, 559, 512 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}IO_2$: C, 43.44; H, 4.31. Found: C, 43.47; H, 4.32.



Preparation of Dialdehyde 18b. To a stirred solution of aldehyde **23** (1.6 g, 5.25 mmol), 2,5-dioctyloxyphenyldiboronic acid **15** (2.5 mmol, 1.05 g) and Cs_2CO_3 (2.4 g, 7.5 mmol) in THF (30 mL) under nitrogen atmosphere was added $Pd(PPh_3)_2Cl_2$ (3 mol %) and PPh_3(9 mol %), and the mixture was stirred at 60 °C for 24 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (25 mL) and washed with brine (5 mL) and water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a solid that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give **18b** as pale yellow solid in 70% (1.21 g) yield.

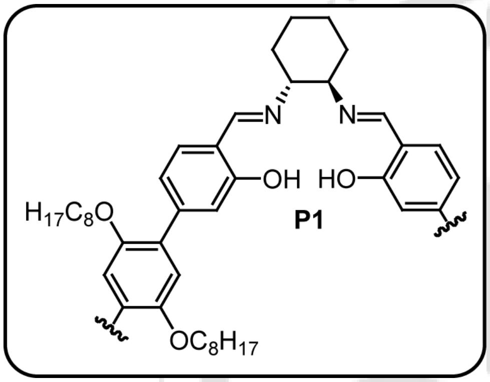
Mp: 193-194 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 11.80 (s, 2H), 9.91 (s, 2H), 7.81 (d, *J* = 2 Hz, 2H), 7.59 (d, *J* = 2 Hz, 2H), 6.94 (s, 2H), 3.94 (t, *J* = 6.4 Hz, 4H), 1.70-1.66 (m, 4H), 1.45 (s, 18H), 1.34-1.21 (m, 20H) 0.85 (t, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 197.5, 160.6, 150.4, 137.8, 136.1, 132.6, 129.7, 129.5, 120.6, 115.7, 69.7, 35.2, 31.9, 29.7, 29.53, 29.48, 29.43, 26.4, 22.8, 14.3.

FT-IR (KBr): 3433, 2930, 2857, 1643, 1514, 1441, 1388, 1366, 1322, 1266, 1234, 1221, 1210, 1168, 1087, 1023, 960, 876, 783, 736, 709, 521 cm^{-1}.

Anal. Calcd for $C_{44}H_{62}O_6$: C, 76.93; H, 9.10. Found: C, 76.97; H, 9.07.



Polymer P1. To a stirred solution of the dialdehyde **18a** (1.04 g, 1.8 mmol) in CHCl$_3$ (5 mL) was added (1*R*,2*R*)-diaminocyclohexane **19a** (0.205 g, 1.8 mmol) and the resultant mixture was stirred at 45 °C for 3 h. The reaction mixture was then concentrated (*ca.* 2 mL) and treated with MeOH (3 mL). The resultant precipitate **P1** was collected by filtration as yellow powder in 91% (1.06 g) yield.

GPC: $M_w = 16771$, $M_n = 12261$ (PDI 1.37).

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.33 (s, 2H), 7.21-7.07 (m, 6H), 6.91 (s, 2H), 3.84 (t, *J* = 8.6 Hz, 4H), 3.35 (s, 2H), 1.92-1.20 (m, 32 H), 0.83 (t, *J* = 7 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 164.5, 160.8, 150.4, 142.6, 131.0, 130.4, 120.4, 117.8, 117.6, 116.1, 72.8, 69.6, 33.4, 31.9, 29.3, 26.1, 24.4, 22.8, 14.3.

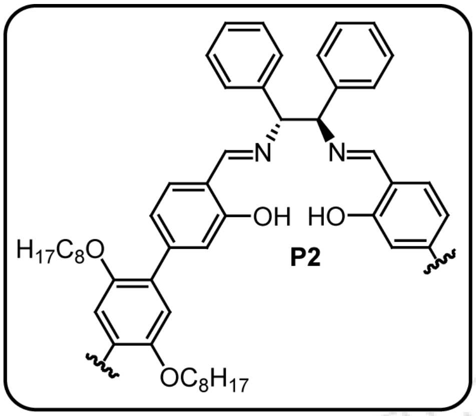
FT-IR (KBr): 3440, 2926, 2855, 1622, 1563, 1491, 1468, 1367, 1205, 1142, 1037, 936, 863, 813 cm^{-1}.

UV-vis (CHCl$_3$): λ_{max} (ε) = 289 (2.60 x 10^4), 349 (2.98 x 10^4) nm (M^{-1}cm^{-1}).

Fluorescence (THF): λ_{ex} = 360 nm; λ_{em} = 423, 521 nm.

$[\alpha]_D^{20}$ = -570 (*c* 0.02, CHCl$_3$).

Anal. Calcd for $(C_{42}H_{56}N_2O_4)_n$: C 77.26, H 8.65, N 4.29. Found: C 77.19, H 8.67, N 4.23.



Polymer P2. To a stirred solution of the dialdehyde **18a** (1.04 g, 1.8 mmol) in $CHCl_3$ (5 mL) was added (1*R*,2*R*)-diphenylethylenediamine **19b** (0.382 g, 1.8 mmol) and the resultant mixture was stirred at 45 °C for 3 h. The reaction mixture was then concentrated (*ca.* 2 mL) and treated with MeOH (3 mL). The resultant precipitate **P2** was collected by filtration as yellow powder in 97% (1.26 g) yield.

GPC: M_w = 19274, M_n = 12449 (PDI 1.55).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 2H), 7.19-7.08 (m, 16H), 6.92 (s, 2H), 4.77 (s, 2H), 3.84 (t, *J* = 6.4 Hz, 4H), 1.62-1.19 (m, 24H), 0.80 (t, *J* = 6.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 160.8, 150.4, 143.1, 139.8, 131.2, 130.4, 128.5, 128.1, 127.8, 120.7, 117.9, 117.6, 116.1, 80.4, 69.7, 31.9, 29.4, 26.2, 22.8, 14.3.

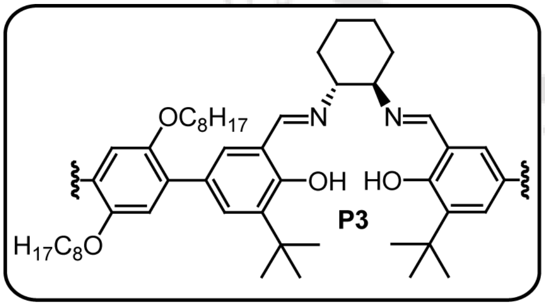
FT-IR (KBr): 3435, 3029, 2924, 2853, 1622, 1561, 1490, 1467, 1454, 1367, 1260, 1207, 1137, 1027, 935, 865, 812, 766, 698, 603 cm^{-1}.

UV-vis ($CHCl_3$): λ_{max} (ε) = 290 (2.77 x 10^4), 352 (3.21 x 10^4) nm ($M^{-1}cm^{-1}$).

Fluorescence (THF): λ_{ex} = 360 nm; λ_{em} = 421, 519 nm.

$[\alpha]_D^{20}$ = -126 (*c* 0.03, $CHCl_3$);

Anal. Calcd for $(C_{50}H_{58}N_2O_4)_n$: C, 79.96; H, 7.78; N, 3.73. Found: C, 79.91; H, 7.81; N, 3.76.



Polymer P3. To a stirred solution of the dialdehyde **18b** (158 mg, 0.23 mmol) in $CHCl_3$ (5 mL) was added (1*R*,2*R*)-diaminocylcohexane **19a** (27 mg, 0.23 mmol) and the resultant mixture was stirred at 45 °C for 5 h. The reaction mixture was then concentrated (*ca.* 0.5 mL) and treated with MeOH (1 mL). The resultant precipitate **P3** was collected by filtration as yellow powder in 97% (171 mg) yield.

GPC: M_w = 10999, M_n = 9165 (PDI 1.20).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 2H), 7.56 (s, 2H), 7.24 (s, 2H), 6.85 (s, 2H), 3.87-3.81 (m, 4H), 1.94-1.21 (m, 52H), 0.86 (t, J = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 159.8, 150.4, 136.5, 131.4, 130.6, 130.2, 128.2, 118.6, 116.1, 72.8, 69.7, 35.1, 33.6, 32.0, 29.7, 29.6, 29.5, 26.5, 24.5, 22.8, 14.2.

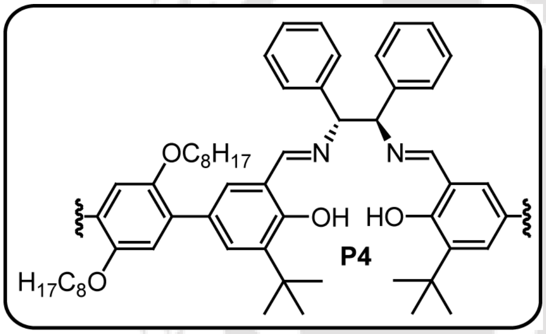
FT-IR (KBr): 3465, 2928, 2857, 1629, 1507, 1465, 1440, 1389, 1264, 1203, 1083, 1035, 973, 862, 802, 707 cm^{-1}.

UV-vis ($CHCl_3$): λ_{max} (ε) = 258 (3.97×10^4), 321 (1.95×10^4) nm ($M^{-1}cm^{-1}$).

Fluorescence (THF): λ_{ex} = 330 nm; λ_{em} = 371, 543 nm.

$[\alpha]_D^{20}$ = +231 (c 0.026, $CHCl_3$).

Anal. Calcd for $(C_{50}H_{72}N_2O_4)_n$: C, 78.49; H, 9.49; N, 3.66. Found: C, 78.51; H, 9.45; N, 3.69.



Polymer P4. To a stirred solution of the dialdehyde **18b** (158 mg, 0.23 mmol) in $CHCl_3$ (5 mL) was added (1*R*,2*R*)-diphenylethylenediamine **19b** (49 mg, 0.23 mmol) and the resultant mixture was stirred at 45 °C for 5 h. The reaction mixture was then concentrated (*ca.* 0.5 mL) and treated with MeOH (1 mL). The resultant precipitate **P4** was collected by filtration as yellow powder in 93% (185 mg) yield.

GPC: M_w = 8547, M_n = 7883 (PDI 1.08).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.59 (s, 2H), 7.25-7.21 (m, 12H), 6.84 (s, 2H), 4.81 (s, 2H), 3.82-3.79 (m, 4H), 1.63-1.19 (m, 42H), 0.83 (t, J = 6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167, 159.8, 150.4, 139.9, 136.6, 131.7, 130.8, 130.2, 128.5, 128.2, 127.7, 118.5, 116.1, 80.1, 69.7, 35.1, 31.9, 29.6, 29.5, 26.3, 22.8, 14.2.

FT-IR (KBr): 3445, 3062, 3031, 2954, 2926, 2856, 1626, 1507, 1453, 1439, 1390, 1376, 1264, 1202, 1087, 1028, 864, 801, 774, 698, 555 cm^{-1}.

UV-vis ($CHCl_3$): λ_{max} (ε) = 265 (4.65×10^4), 321(2.10×10^4) nm ($M^{-1}cm^{-1}$).

Fluorescence (THF): λ_{ex} = 330 nm; λ_{em} = 367, 544 nm.

$[\alpha]_D^{20}$ = +95 (c 0.021, $CHCl_3$).

Anal. Calcd for $(C_{58}H_{74}N_2O_4)_n$: C, 80.70; H, 8.64; N, 3.25. Found: C, 80.68; H, 8.60; N, 3.27.

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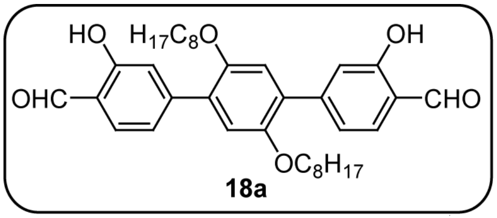
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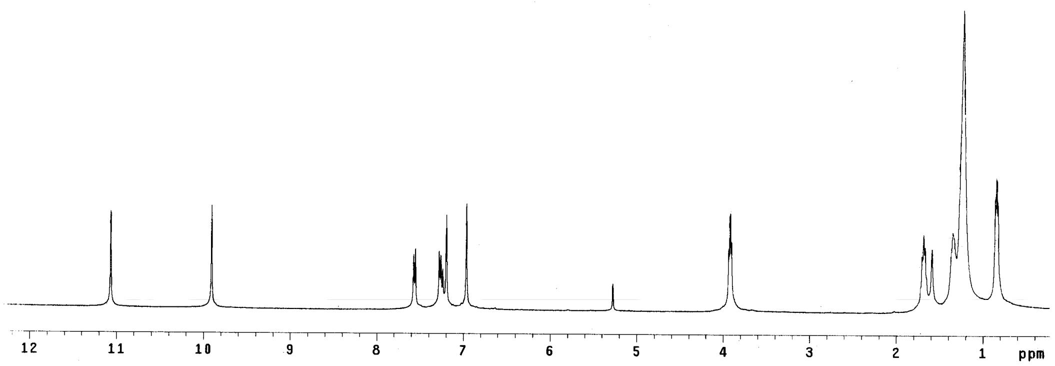
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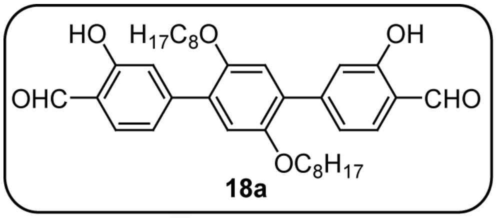
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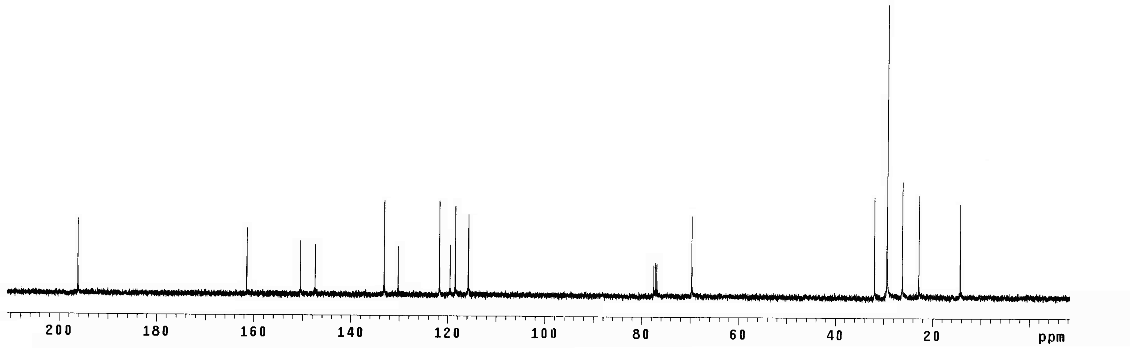
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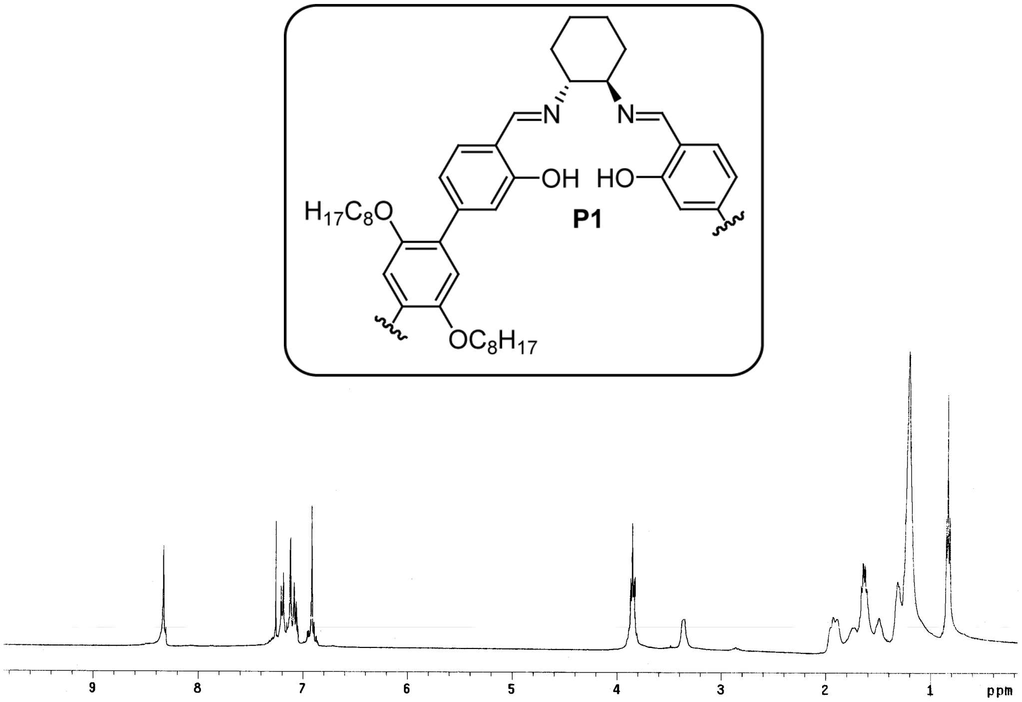
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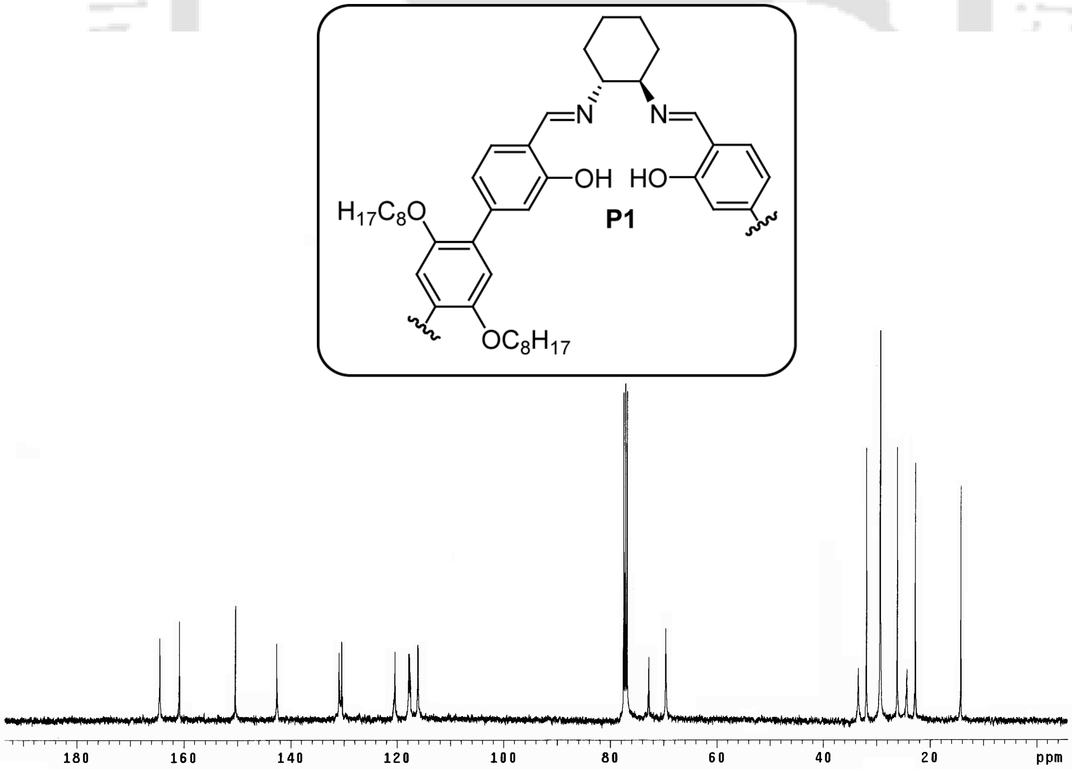
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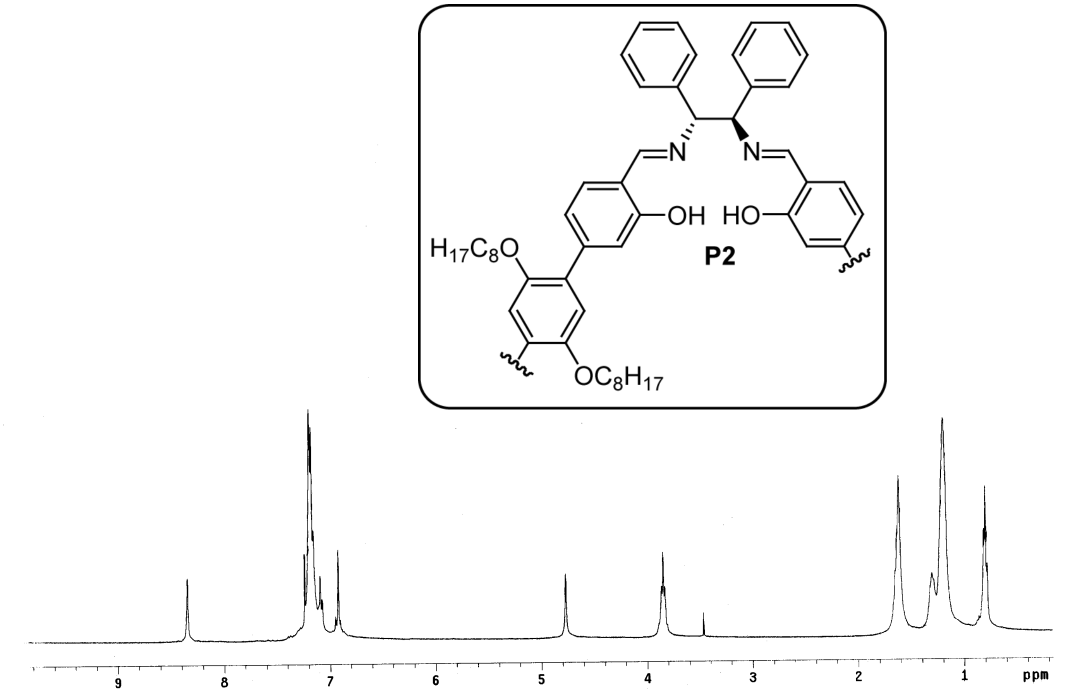
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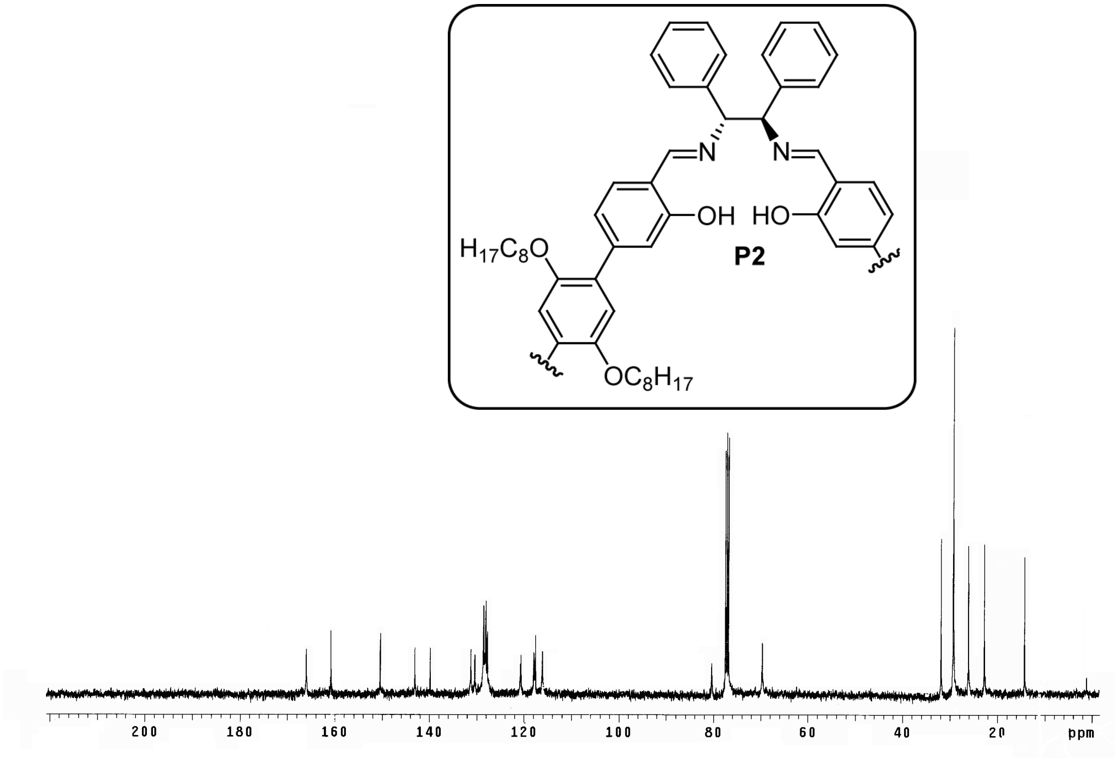
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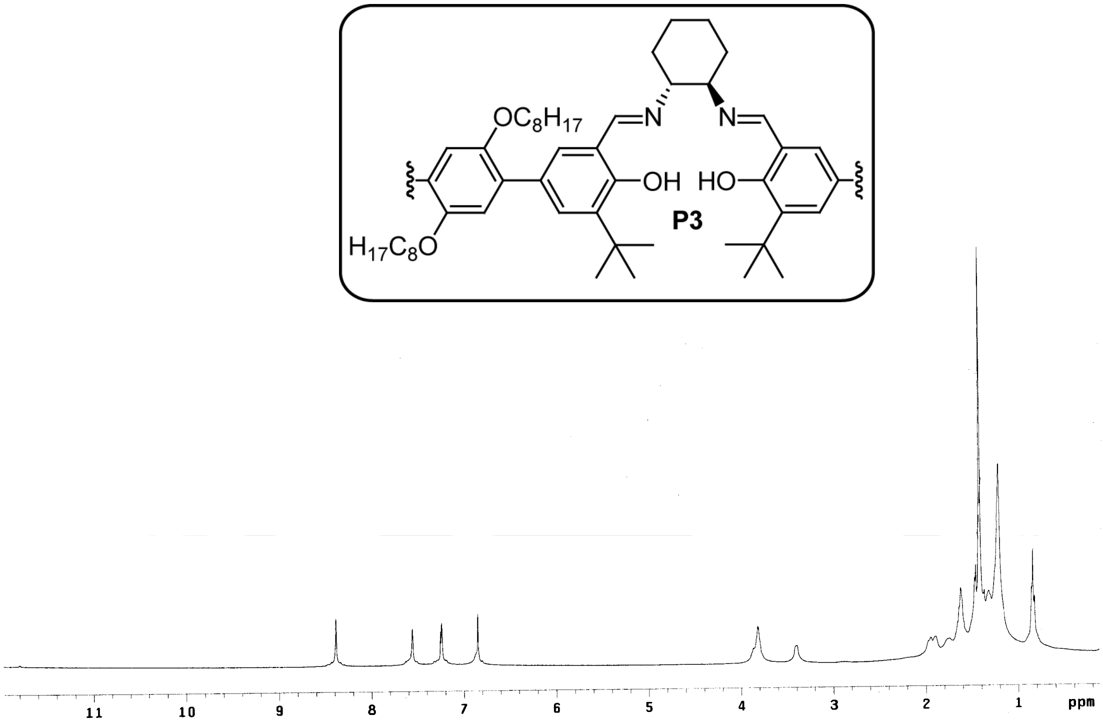
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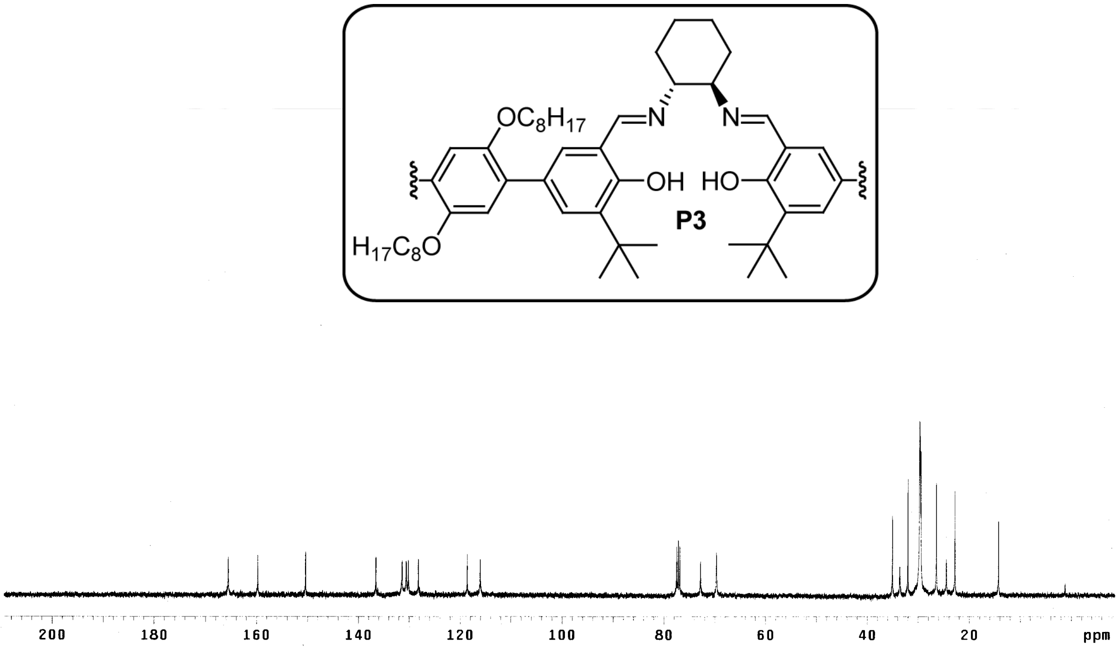
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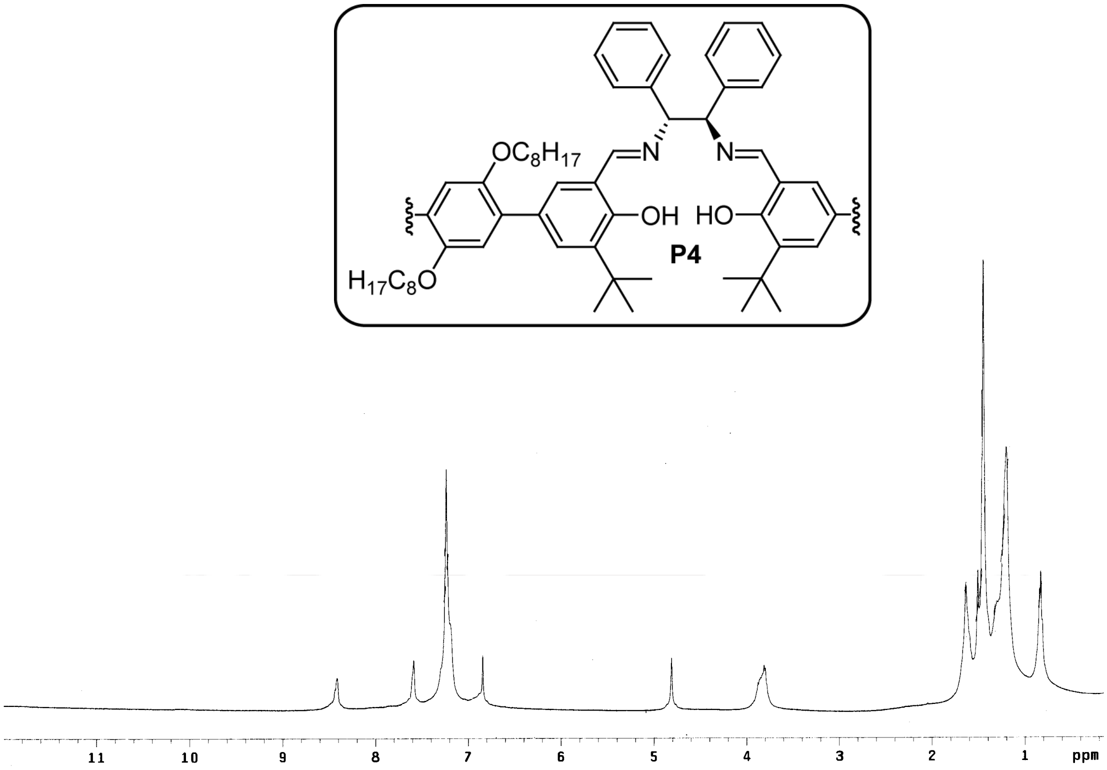
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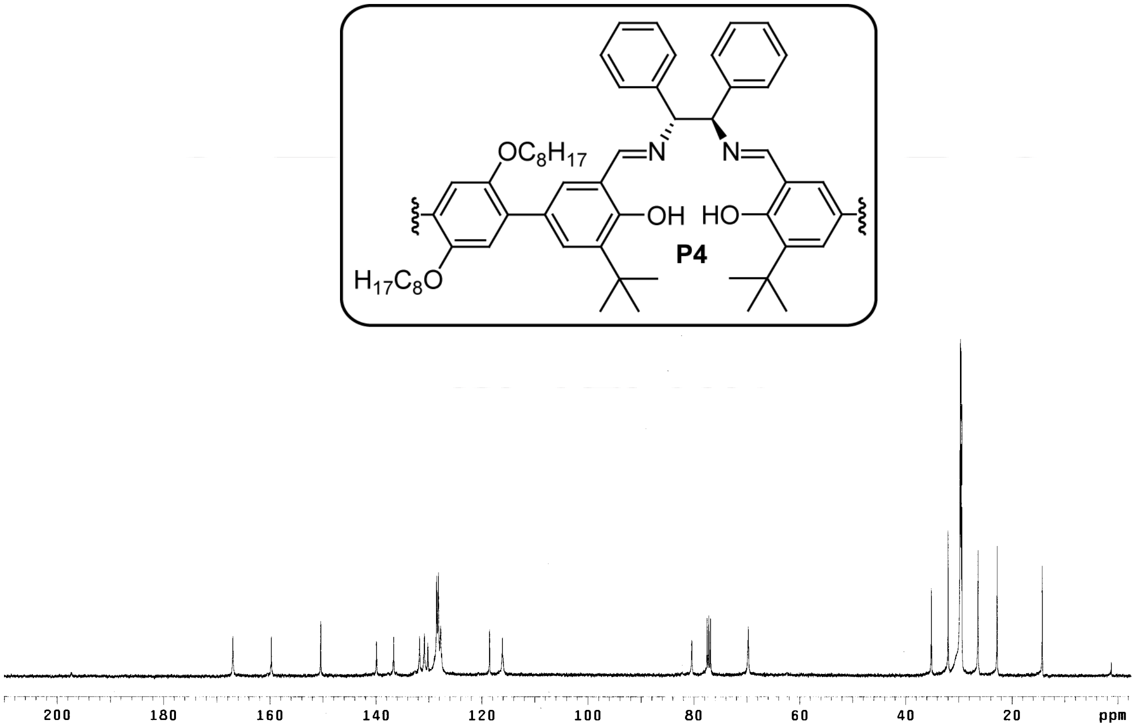
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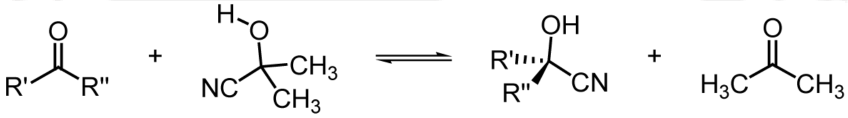
Chapter II

Chiral Titanium(IV)-Catalyzed Asymmetric 1,2-Addition of TMSCN to Aldehydes

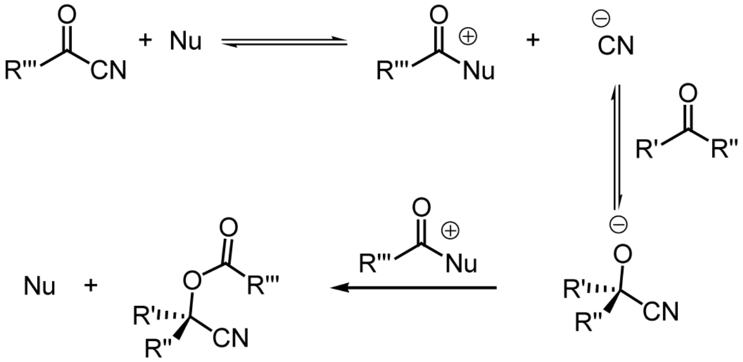
2.1 Introduction

The heart of organic synthesis is the carbon-carbon bond formation. Among them, the addition of cyanide to a carbonyl compound to form a cyanohydrin is one of the fundamental reactions.[1] The cyanide addition to a carbonyl compound can be achieved by using different cyanide precursors. Early work on cyanohydrin synthesis was all carried out with hydrogen cyanide as the cyanide source.[2] The volatility and extreme toxicity of this reagent caused obvious difficulties, and numerous alternative cyanide-based reagents have since been developed. Acetone cyanohydrin is one of the well known cyanide sources. It may function as an *in situ* source of hydrogen cyanide, since cyanide addition will go through a Meerwein-Ponndorf-Verley type transition state, the position of the equilibrium is more favorable for addition to aldehydes than to ketones (Scheme 1).[3]



Scheme 1

Acyl cyanides,[4] cyanoformates[5] and cyanophosphonates[6] can also be used as cyanating reagents and produces *O*-protected cyanohydrins which do not revert to carbonyl compounds (Scheme 2). Thus, the cyanohydrin formation becomes irreversible and the addition reactions are 100% atom economical.[7] However, they are not the true cyanating agents, because the addition of these reagents to a carbonyl compound has to be performed in the presence of a nucleophilic catalyst or solvent.

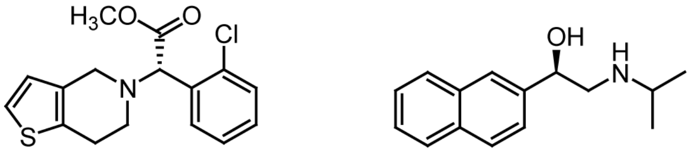


Scheme 2

The most commonly used alternative cyanide source is trimethylsilyl cyanide (TMSCN = $(CH_3)_3SiCN$).[8] Reaction can be induced thermally or by a range of catalysts including Lewis acids, bases and nucleophiles. Since trimethylsilyl cyanide is also a good silylating agent,[9] it would silylate the initially formed cyanohydrin, leading to the formation of the cyanohydrin trimethylsilyl ether and regenerating the hydrogen cyanide. Trimethylsilyl cyanide is only the simplest example of a family of silyl cyanides, and there are reports of the addition of other silyl cyanides to carbonyl compounds.[10] In general, the other silyl cyanides are less reactive than trimethylsilyl cyanide but have the advantage of producing cyanohydrins silyl ethers which are more stable with respect to hydrolysis.

2.2 Synthetic Applications of Chiral Cyanohydrins

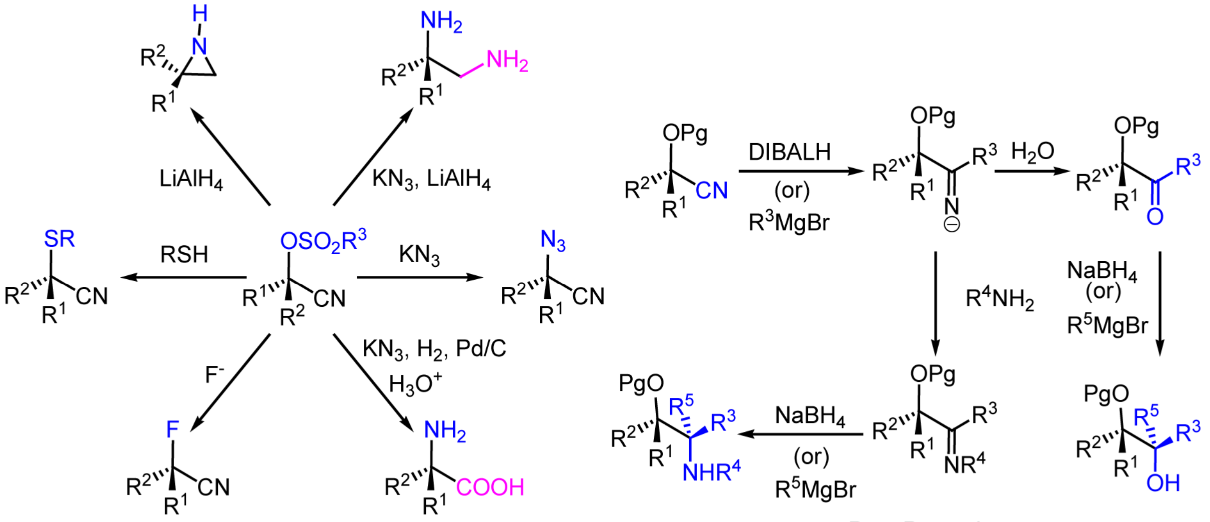
Cyanohydrins contain two functional groups, a nitrile and an alcohol. These two functional groups can be readily transformed to other functional moiety that are pharmaceutically important intermediates (Scheme 3-4).[11] The most important transformation of cyanohydrins is their conversion into α-hydroxy acids. This reaction can be achieved simply by treating a cyanohydrin or any of the protected cyanohydrins with aqueous acid at ambient or elevated temperature.[11b-c] Not only does this process not cause racemization, but recrystallization during the purification of the α-hydroxy acid can be used to raise the enantiomeric excess of the product above that of the cyanohydrin. This process has been used industrially for the synthesis of 2-chloromandelic acid, which is a key component of Clopidogrel **1**.[11a,11c] Clopidogrel is used as an antidepressant and a platelet-aggregation inhibitor in the treatment of coronary artery disease as well as peripheral vascular and cerebrovascular diseases.



1 **2**

Scheme 3

Another reaction of commercial importance is the reduction of the nitrile group to provide *β*-amino alcohols.[11c] This reduction can be achieved by treatment of either a free cyanohydrin or an *O*-protected derivative with lithiumaluminumhydride.[11b,11e-g] An example of this approach is the synthesis of the *β*-blocker pronethalol **2** from 2-napthaldehyde.[11e] Cyanohydrin esters can also be hydrogenated over nickel supported on alumina, and under these conditions the intermediate amino esters undergo spontaneous *O*- to *N*-acyl migration, leading to pharmaceutically relevant *N*-acyl *β*-amino alcohols.[11h]



R^3 = Me, C_6H_4Me, CF_3

Pg = Protecting group

Scheme 4

With less reactive nucleophiles (DIBALH and Grignard reagents), suitably protected cyanohydrins undergo a single addition reaction, leading initially to iminates, as shown in Scheme 7.[11e-f] Subsequent hydrolysis of the iminates gives α-hydroxy aldehydes and ketones, whilst transimination yields imines. The second nucleophilic addition (with sodium borohydride or a Grignard reagent), leads to a diverse range of 1,2-diols and β-amino alcohols with two consecutive stereocenters. The second nucleophilic addition occurs in a stereoselective manner due to the formation of a chelated intermediate and has been used to prepare a range of ephedrine analogues.

Another class of transformation which cyanohydrins undergo is S_N2 type reactions on the alcohol group. Cyanohydrins can be converted into sulfonate esters, and the latter undergo S_N2 reactions with a range of nucleophiles and with inversion of configuration, as shown in Scheme 8.[11i] This approach has been used to prepare chiral α-azido nitriles,[11j] α-amino nitriles,[11j-k] aziridines,[11l] α-thionitriles[11m] and α-fluoronitriles[11n] and to invert the stereochemistry of cyanohydrins.[11i] The α-azido nitriles are particularly versatile intermediates for the synthesis of both α-amino acids and 1,2-diamines.[11j]

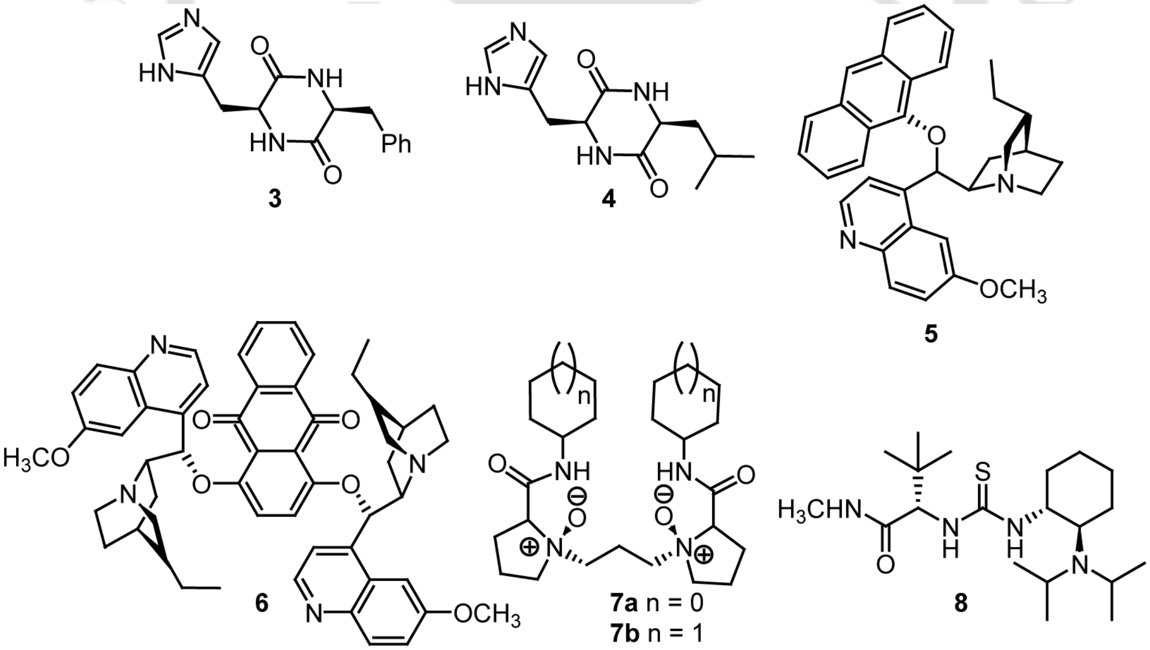
2.3 Enzyme Catalysis

The first oxynitrilase catalyzed asymmetric cyanohydrin synthesis was reported in 1908.[2c,12] It has been shown that oxynitrilases can control the diastereoselective and enantioselective addition of hydrogen cyanide to suitable substrates.[13a-c] The oxynitrilase enzyme obtained from *Hevea brasiliensis* can be used in combination with TEMPO/$PhI(OAc)_2$ to carry out a one pot transformation of alcohols into cyanohydrins.[13d] Even oxynitrilases will catalyze the transcyanation reactions to aldehydes using acetone cyanohydrins[13e] or a racemic ketone derived cyanohydrins [13f-g] as the cyanide source. The latter process is particularly interesting, as both the aldehyde and ketone derived cyanohydrins can be obtained enantiomerically enriched from a single enzyme catalyzed reaction. Ethyl cyanoformate has also been employed as the cyanide source in oxynitrilase catalyzed reactions carried out under organic aqueous biphasic conditions leading to (*R*)-cyanohydrin ethyl carbonates. It was shown that ethyl cyanoformate is hydrolyzed to hydrogen cyanide that is the true cyanating agent.[13h]

2.4 Organocatalysis

The first report of organocatalysed cyanohydrin synthesis was reported by Bredig and Fiske in 1912 using alkaloids to catalyze the asymmetric addition of hydrogen cyanide to aldehydes.[14a-c] The real breakthrough in this area happened in 1979, when Inoue discovered that cyclic dipeptide (diketopiperazine) **3** could catalyze the asymmetric addition of hydrogen cyanide to benzaldehyde with 97% enantioselectivity (Scheme 5).[14d-f] Catalyst **3** was found to be a general catalyst for the asymmetric addition of hydrogen cyanide to aromatic aldehydes.[14g-j] Subsequently, Inoue group reported diketopiperazine **4** as suitable catalyst for the hydrogen cyanide addition with aliphatic aldehydes.[14k]

In 2001, Tian *et al*. reported that monomeric and dimeric *O*-arylated cinchona alkaloids **5** and **6** were excellent catalysts for the asymmetric addition of ethyl cyanoformate to aliphatic ketones with up to 97% enantioselectivity (Scheme 5). [14l-m] This is an example of a reaction where the asymmetric induction is thought to be due to a dynamic kinetic resolution of the cyanohydrins alkoxide rather than enantioselective cyanide addition.



Scheme 5

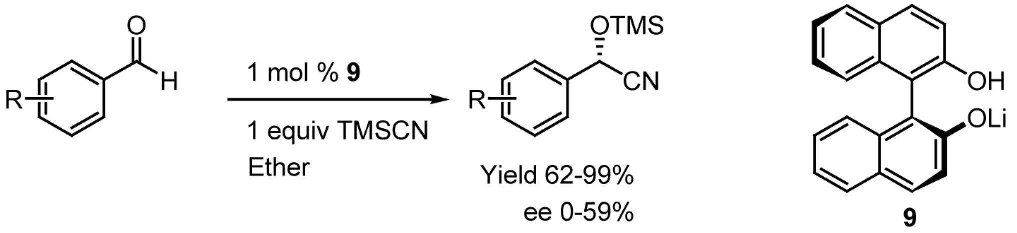
Feng group reported the use of chiral and achiral *N*-oxides as catalysts for both racemic and asymmetric cyanohydrin synthesis.[14n-o] Bis-*N*-oxides **7a**,**b** were found to function as effective organocatalysts for the asymmetric addition of trimethylsilyl cyanide to aromatic aldehydes[14p] and the monoacetals of 1,2-diketones (Scheme 5).[14q] Interestingly, much higher enantioselectivities (85-93% using catalyst **7a**) were obtained with the ketone substrates than that of the aldehydes (53-73% using catalyst **7b**). Thioureas have been considerably used as organocatalysts for a number of reactions.[14r] Fuerst *et al*. developed bifunctional thiourea **8** as a catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones (Scheme 5).[14s] Under the optimized conditions, very high enantioselectivities (86-97%) and chemical yields (>80%) were obtained from a range of aromatic *α*,*β*-unsaturated ketones.

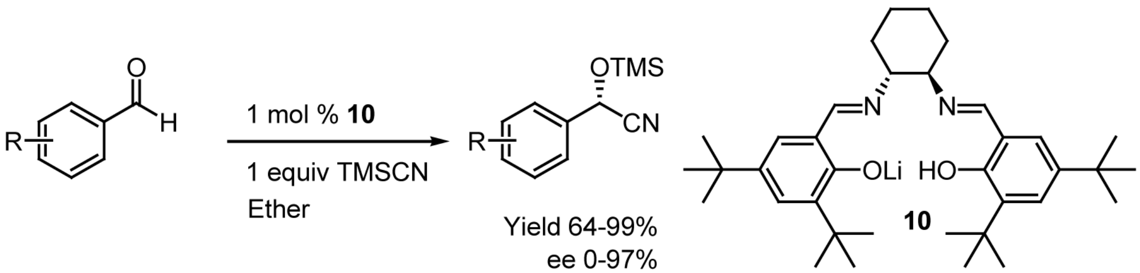
2.5 Chiral Metal Catalysts

Methods belong to the chiral metal complexes catalyzed reactions can be broadly divided into the group to which the metal belongs.

2.5.1 Chiral Alkali Metal Catalysts

Holmes *et al*. reported examples of catalysis by lithium salts of chiral phenols derived from BINOL and salen.[15] The use of 1 mol % of the BINOL monolithium salt **9** resulted in cyanosilylation of a range of aromatic aldehydes with 62-99% yield and 0-59% ee (Scheme 6). For aliphatic substrates, the enantioselectivity of the process did not exceed 30% (62-95% chemical yield).[15a] The monolithium salt of salen **10** gave greater ee than those seen for BINOL salt **9**. A wide range of aromatic aldehydes was screened in the cyanosilylation reaction, which was conducted in diethyl ether at ambient temperature with 1 mol % catalyst loading (Scheme 6).[15b]

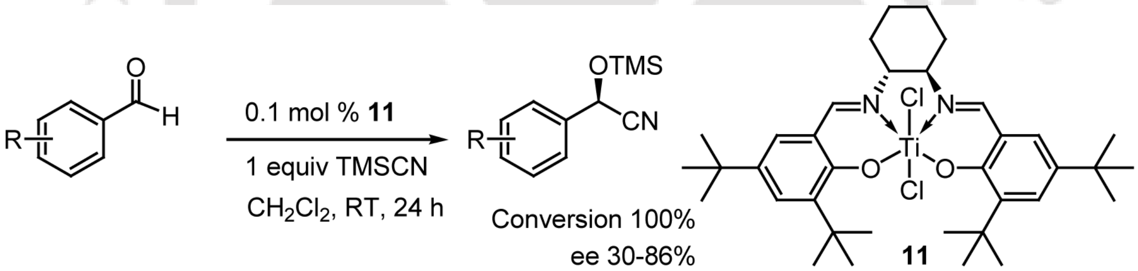




Scheme 6

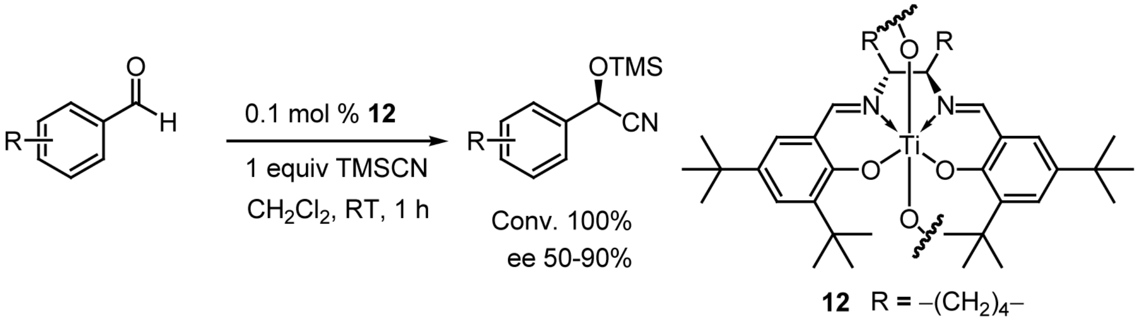
2.5.2. Chiral Transition Metal Catalysts

Belokon *et al*. reported the use of chiral Ti(IV)-salen **11** for the asymmetric synthesis of cyanohydrins (Scheme 7).[16a] In the cyanosilylation of benzaldehyde, the complex **9** gave *ee* in the range of 18-86% with complete conversion. These reactions required only 0.1 mol % of the catalyst in dichloromethane at ambient temperature. Decrease in the reaction temperature did not result in a significant enhancement of the enantioselectivity (90% enantiomeric excess at -80 °C as opposed to 86% ee at ambient temperature).



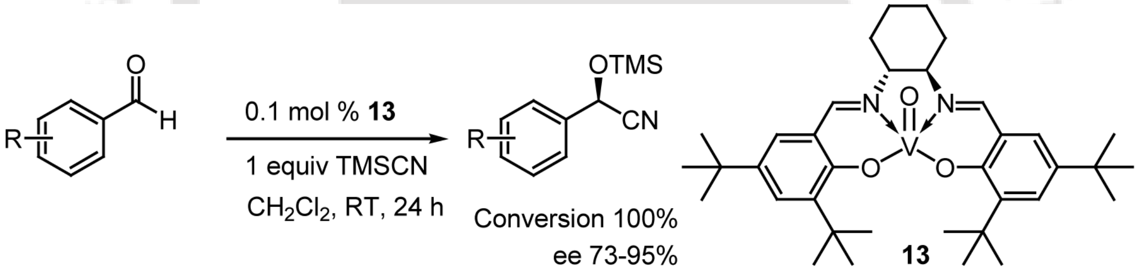
Scheme 7

The authors subsequently reported the use of chiral dimeric Ti(IV)-salen complex **12** for the asymmetric cyanohydrins synthesis (Scheme 8).[16b-f] Complex **12** was exceptionally active in the asymmetric cyanosilylation of aldehydes, giving full conversion in most cases after just 1 h when only 0.1 mol % of catalyst was employed.



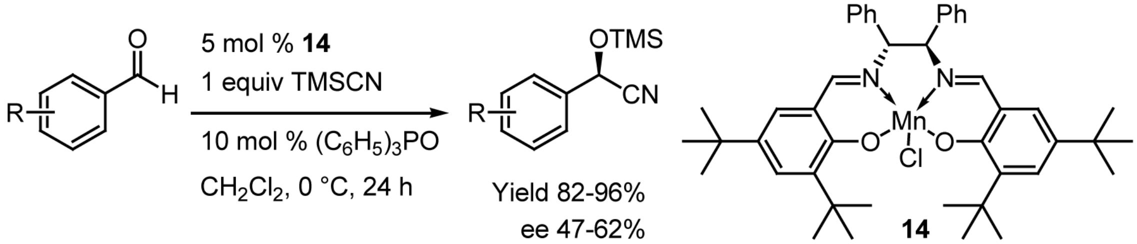
Scheme 8

The above authors further described a catalytic system based on a chiral V(IV)-salen complex **13**.[16g-h] This system was able to convert aromatic aldehydes into cyanohydrin silyl ethers with 90-95% ee (Scheme 9). The reaction could be carried out with 0.1 mol % catalyst in dichloromethane at ambient temperature.



Scheme 9

Kim and Lee used chiral Mn(III)-salen **14** for the catalysis of the trimethylsilyl cyanide addition to aromatic and aliphatic aldehydes with 82-96% yield and 44-62% ee (Scheme 10).[16i] A triphenylphosphine oxide co-catalyst was used to increase the rate of reaction. A number of different aldehydes were used as substrates and the best result of 62% ee was obtained with *p*-chlorobenzaldehyde.

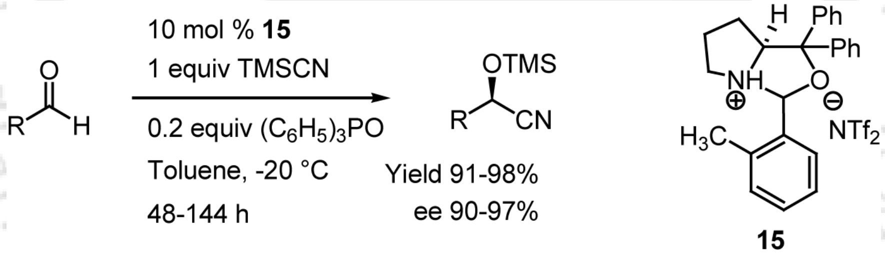


14

Scheme 10

2.5.3 Chiral Group(III) Metal Catalysts

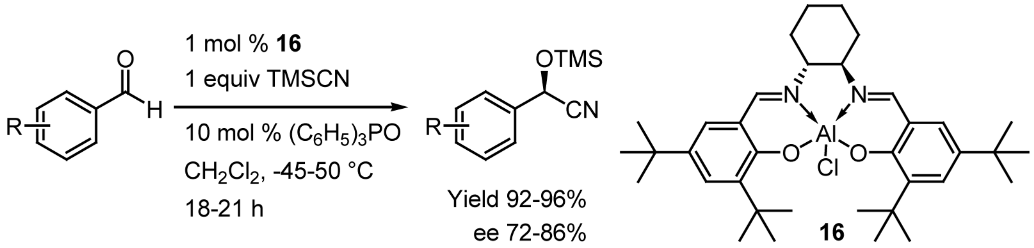
In 2004, Ryu *et al*. described boron based chiral catalyst **15** for the cyanide addition in the presence of 20 mol % of triphenylphosphine oxide (Scheme 11).[16j] Using 10 mol % of **15** in toluene at 0 °C for 40-144 h, a series of silylated cyanohydrins were obtained in 91-98% yield and 90-97% ee. A similar asymmetric induction could be obtained for both aromatic (electron rich and electron deficient) and aliphatic substrates.



15

Scheme 11

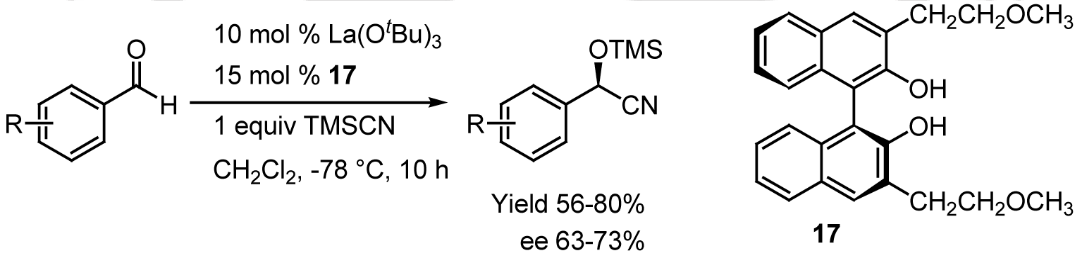
Kim and Song used chiral Al(III)-salen **16** with triphenylphosphine oxide as an additive for the cyanosilylation of aldehydes (Scheme 12).[16k-l] A range of aliphatic and aromatic aldehydes were studied with up to 86% ee.



Scheme 12

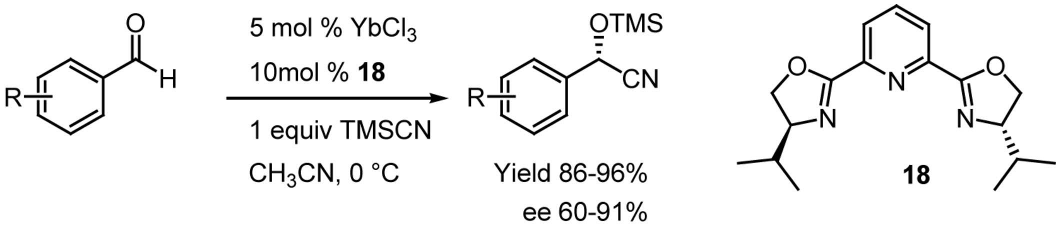
2.5.4 Chiral Rare Earth Metal Catalysts

Qian *et al*. found that the complexes of BINOL based ligand **17** with La(O^{t}Bu)$_3$ could carry out the asymmetric addition of trimethylsilyl cyanide to aromatic and aliphatic aldehydes with up to 73% ee (Scheme 13).[16m]



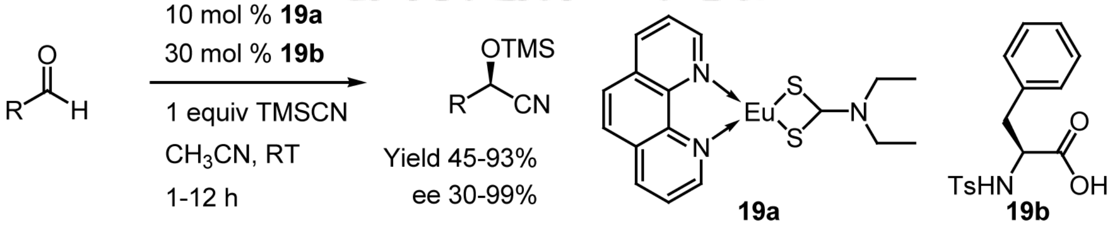
Scheme 13

Greeves *et al*. investigated ytterbium(III) complex derivied from PyBOX **18** and YbCl$_3$ for the asymmetric cyanosilylation of aldehydes with up to 91% ee (Scheme 14).[16n-p] The substrates having electron rich substituents exhibited the highest selectivity.



Scheme 14

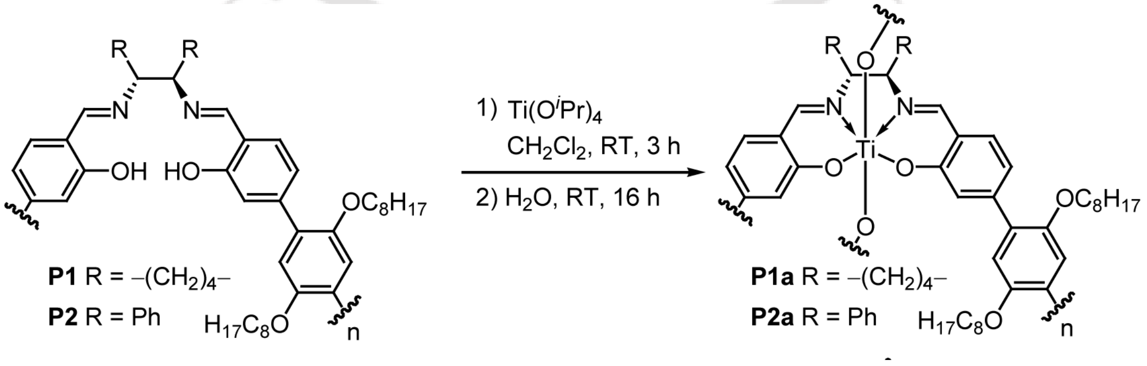
Vale *et al*. elaborated a catalytic system for the asymmetric cyanosilylation of aldehydes using chiral europium complex derived from a 1:3 mixture of **19a** and **19b** (Scheme 15).[16q] A series of aromatic and aliphatic aldehydes were converted into the corresponding silylated cyanohydrins in 45-93% yield and 30-99% ee. Remarkably, the best results were observed for electron deficient substrates, in particular the nitrobenzaldehydes gave products with the highest ee.

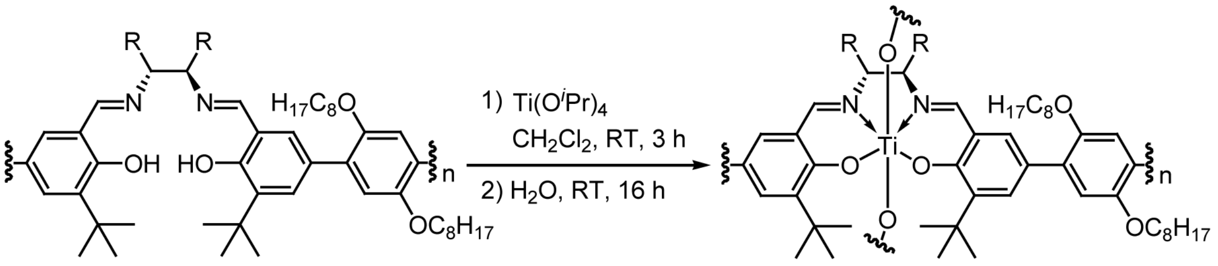


Scheme 15

2.6 Present Study

Polymers **P1**-**P4** were studied as chiral ligands for the titanium catalysed enantioselective 1,2-addition of TMSCN to aldehydes. First the Ti-polymer complexes **P1a**-**P4a** were prepared by reaction of the polymers **P1**-**P4** with Ti(O^{i}Pr)$_4$ (Scheme 16).[16b] The 1,2-addition of TMSCN to 4-methoxybenzaldehyde was carried out under inert condition in different solvents at varied temperatures (Table 1).



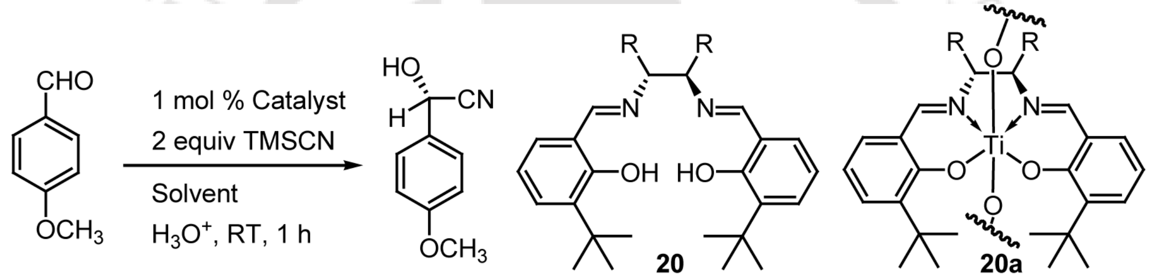


P3 R = –(CH$_2$)$_4$–
P4 R = Ph

P3a R = –(CH$_2$)$_4$–
P4a R = Ph

Scheme 16

Table 1. Optimization of the Reaction Conditions



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)^{a,b}	ee (%)^{c}	Config.^{d}
1	**P1a**	CHCl$_3$	0	98	50	(*S*)
2	**P2a**	CHCl$_3$	0	95	36	(*S*)
3	**P3a**	CHCl$_3$	0	95	78	(*S*)
4	**P4a**	CHCl$_3$	0	90	43	(*S*)
5	**P3a**	CH$_2$Cl$_2$	0	90	43	(*S*)
6	**P3a**	THF	0	Trace	---	(*S*)
7	**P3a**	Toluene	0	70	16	(*S*)
8	**P3a**	CHCl$_3$	-5	90	72	(*S*)
9	**P3a**	CHCl$_3$	25	95	43	(*S*)

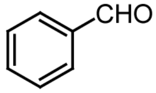
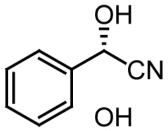
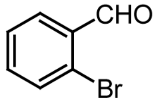
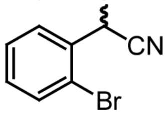
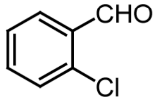
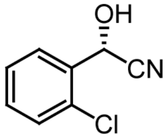
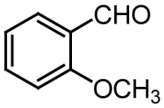
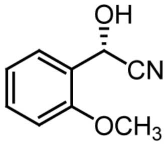
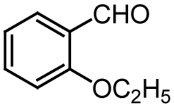
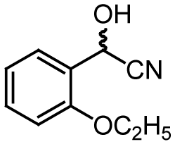
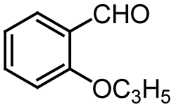
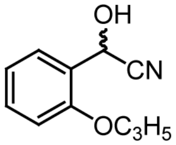
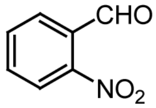
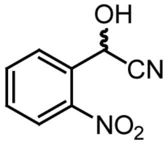
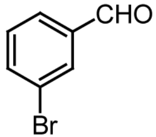
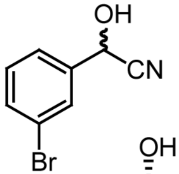
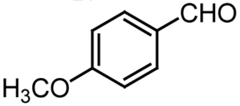
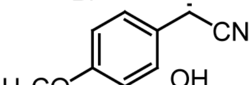
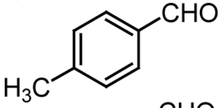
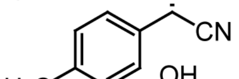
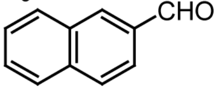
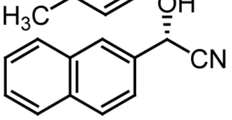
10	**20a**	$CHCl_3$	0	97	76	(*S*)
11	**P3**	$CHCl_3$	0	n.r.	---	(*S*)

[a] *p*-Methoxybenzaldehyde (1 mmol), catalyst (1 mol % with respect to monomeric unit), TMSCN (2 mmol) and solvent (3 mL) were stirred for 48 h under N_2 atmosphere. [b] Isolated yield. [c] Determined by HPLC analysis of the acetyl derivative with chiralcel OD-H column using 99:1 *n*-hexane : 2-propanol. [d] Assigned from sign optical rotation. n.r. - no reaction.

The reaction occurred to afford the corresponding cyanohydrin with *S*-configuration in 16-78 % ee when the reaction was stirred in the presence of 1 mol % of **P1a-P4a** (with respect to monomeric unit) and 2 equiv of TMSCN in $CHCl_3$ at 0 °C.[15] Among the catalysts **P1a-P4a**, **P3a** was found to be best providing the cyanohydrin in 95% yield and 78% ee. The effect of temperature was then studied and 0 °C afforded the best results. $CHCl_3$ was found to be the solvent of choice, whereas CH_2Cl_2, THF and toluene gave inferior results. Control experiment confirmed that without Ti no reaction occurred. A similar result has been observed with the monomeric salen ligand for TMSCN addition to 4-methoxybenzaldehyde (Table 1, entry 10). These reactions did not involve any additive.

Using the optimized conditions, the scope of the procedure was further explored (Table 2). The reactions of the aryl aldehydes having 2-Br, 2-Cl, 2-OCH_3, 2-OC_2H_5, 2-OC_3H_5, 3-Br and 4-CH_3 substituents were studied. The substrates readily proceeded the reactions with TMSCN to give the corresponding cyanohydrins with up to 88% ee. Likewise, 2-naphthaldehyde underwent reaction with TMSCN to give the respective cyanohydrin in 90% yield and 74% ee. Aliphatic aldehydes (propanal, isobutanal, crotonal and 2-phenylacetaldehyde) proceeded reactions with TMSCN to afford corresponding cyanohydrins in 86-95% yield with 40-66% ee (Table 3).

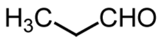
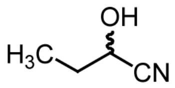
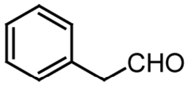
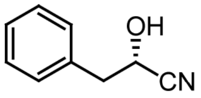
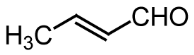
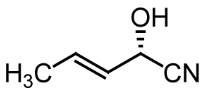
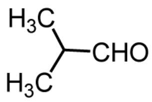
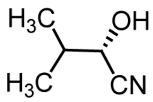
Table 2. The Complex **P3a** Catalyzed TMSCN Addition to Aromatic Aldehydes

Entry	Aldehyde	Product	Yield (%)[a,b]	ee (%)[c]	Config.[d]
1			97	77 (54)	(*S*)
2			95	50 (20)	n.d.
3			97	60 (30)	(*S*)
4			95	88 (64)	(*S*)
5			91	78 (34)	n.d.
6			90	75 (48)	n.d.
7			70	20 (20)	n.d.
8			90	75 (42)	n.d.
9			97	78 (50)	(*S*)
10			97	68 (46)	(*S*)
11			90	74 (42)	(*S*)

[a] Aldehyde (0.5 mmol), TMSCN (1 mmol) and catalyst **P3a** (1 mol % with respect to monomeric unit) were stirred at 0 °C in $CHCl_3$ (1.5 mL) under N_2 atmosphere. [b] Isolated yield. [c] Determined by HPLC analysis of the

acetyl derivative. [d] Determined by sign of optical rotation. ee in parenthesis were obtained with catalyst **P1a**. n.d. - not determined.

Table 3. Chiral Poly-Ti **P3a** Catalyzed TMSCN Addition to Aliphatic Aldehydes

Entry	Aldehyde	Product	Yield (%)[a,b]	ee (%)[c]	Config.[e]
1			95	40	n.d.
2			86	57 (20)[d]	(*S*)
3			93	55	(*S*)
4			90	66	(*S*)

[a] Aldehyde (0.5 mmol), TMSCN (1 mmol) and catalyst **P3a** (1 mol % with respect to monomeric unit) were stirred at 0 °C in $CHCl_3$ (1.5 mL) under N_2 atmosphere. [b] Isolated yield. [c] Determined by HPLC analysis of the benzoyl derivative. [d] Determined by HPLC analysis of the acetyl derivative. [e] Determined by sign of optical rotation. ee in parenthesis was obtained with catalyst **P1a**.

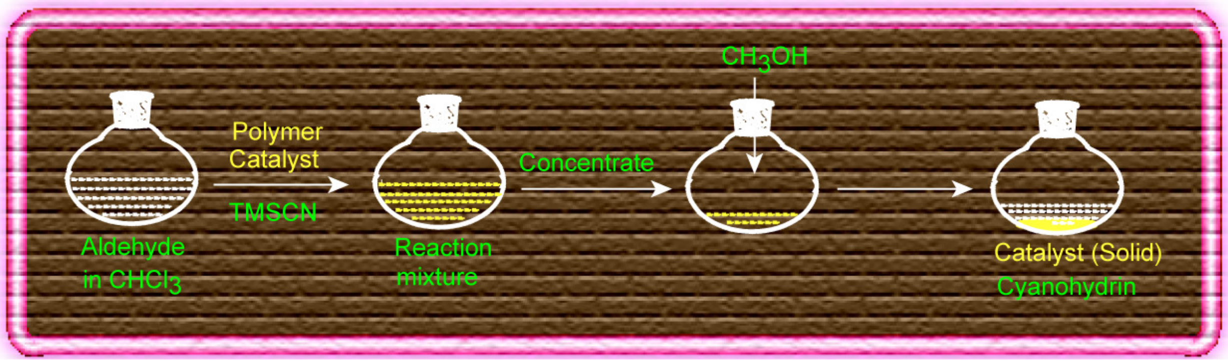
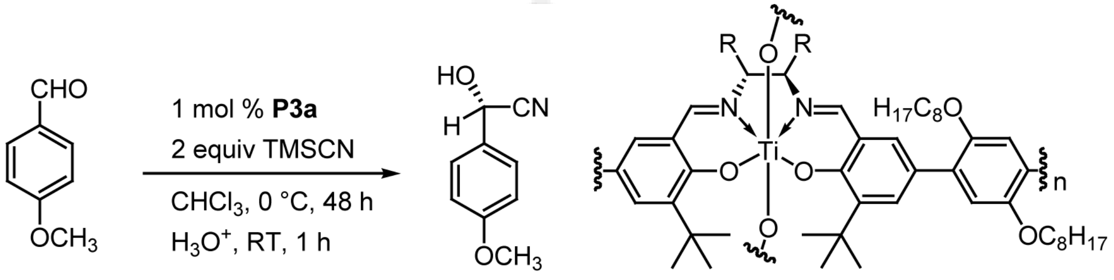


Figure 1. Pictorial Illustration of Recovering and Recycling the Catalyst.

The advantage of this system is that the catalyst **P3a** can be recovered and recycled (Figure 1 and table 4). After completion, the reaction mixture was concentrated (*ca.* 0.5 mL) and the resultant solution was treated with MeOH (*ca.* 0.5 mL). The precipitated out Ti-polymer catalyst **P3a** was filtered, dried and reused for the fresh reaction of *p*-methoxybenzaldehyde with TMSCN. This process was repeated for three runs and the reactions occured to afford the target cyanohydrin with 93-95% yield and 78% ee. These results clearly suggest that the catalyst **P3a** can be recycled without loss of activity and selectivity.

Table 4. Recyclability of the Catalyst **P3a**



P3a R = $-(CH_2)_4-$

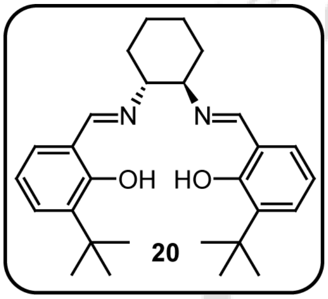
Run	Catalyst recoverability (%)	Product yield (%)	ee (%)[c]
1[a]	99	95	78
2[b]	99	93	78
3 [b]	99	93	78

[a] *p*-Methoxybenzaldehyde (1 mmol), catalyst **P3a** (1 mol % with respect to monomeric unit) and TMSCN (2 mmol) were stirred at 0 °C for 48 h in $CHCl_3$ (3 mL) under N_2 atmosphere. [b] Recovered **P3a** was used. [c] Determined by HPLC analysis of the acetyl derivative.

In summary, the chiral poly-Ti catalysts **P1a**-**P4a** were synthesized from the polymers **P1**-**P4** and $Ti(O^iPr)_4$. These catalysts were used to study the asymmetric cyanohydrins synthesis and it has been found that catalyst **P3a** derived from linear polymer **P3** was superior providing cyanohydrins upto 88% ee. The system provides the advantages simplified product isolation and easy recovery and recyclability of the polymer catalyst **P3a**.

Experimetal Section

General. TMSCN (98%) and aldehydes were purchased from Aldrich. $Ti(O^iPr)_4$ (98%) was procured from Acros Organics. Solvents were purchased from Rankem and purified prior to use by standard procedure. Column chromatography was carried out with Rankem 60-120 mesh silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained using PerkinElmer spectrum one spectrometer. HPLC analysis was carried out for acetylated cyanohydrin using Waters-2489 with Daicel chiralcel OD-H column and for benzoylated cyanohydrin using Waters-2489 with Daicel chiralcel OJ column. Elemental analysis was carried out using PerkinElmer-2400 CHNS analyzer.



20

Preparation of Monomer 20.[17] To a stirred solution of (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate salt (520 mg, 1.97 mmol) and K_2CO_3 (543 mg, 3.94 mmol) in distilled water (3 mL) was added EtOH (15 mL). The cloudy mixture was heated to 80 °C and EtOH (5 mL) solution of the 3-*tert*-butyl-2-hydroxybenzaldehyde (702 mg, 3.94 mmol) was added. The resultant yellow colored slurry was stirred for 2 h at the same temperature and water (3 mL) was added. The mixture was then cooled to <5 °C over 2 h and maintained at that temperature for an additional hour. The product was collected by vacuum filtration and washed with EtOH (2 mL)**.** The crude solid was redissolved in CH_2Cl_2 (10 mL) and washed with water (2 x 5 mL) and brine (3 mL). Drying (Na_2SO_4) and evaporation of the solvent gave **10** as yellow powder in 97% (831 mg) yield.

Mp: 75-76 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 2H), 7.18 (dd, *J* = 1.2, 8 Hz, 2H), 6.92 (dd, *J* = 1.2, 7.2 Hz, 2H), 6.63 (t, *J* = 7.2 Hz, 2H), 3.26 (m, 2H), 1.91-1.41 (m, 8H), 1.33 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 160.5, 137.2, 129.9, 129.4, 118.8, 117.9, 72.4, 34.9, 33.3, 29.5, 24.4.

FT-IR (KBr): 3454, 2959, 2934, 2860, 1629, 1436, 1390, 359, 1306, 1264, 1199, 1144, 1083, 1037, 848, 800, 750, 691 cm^{-1}.

$[\alpha]_D^{20} = -433$ (*c* 0.25, $CHCl_3$).

Anal. Calcd for $C_{28}H_{38}N_2O_2$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.35; H, 8.76; N, 6.51.

Preparation of the Chiral Poly-Ti Catalysts[16a]

Catalyst P1a. To a solution of **P1** (201 mg, 12.1 µmol) in dry CH_2Cl_2 (60 mL) was added CH_2Cl_2 (2 mL) solution of $Ti(O^iPr)_4$ (90 mg, 320 µmol) at room temperature. After 3 h, water (0.1 mL) was added and the stirring continued for an additional 16 h. The resultant solution was concentrated in vacuo, and the residue was washed with MeOH (5 mL) to afford **P1a** as yellow solid (221 mg).

Catalyst P2a. To a solution of **P2** (201 mg, 11.9 µmol) in dry CH_2Cl_2 (6 mL) was added CH_2Cl_2 (2 mL) solution of $Ti(O^iPr)_4$ (77 mg, 273 µmol) at room temperature. After 3 h, water (0.1 mL) was added and the stirring continued for an additional 16 h. The resultant solution was concentrated in vacuo, and the residue was washed with MeOH (5 mL) to afford **P2a** as yellow solid (217 mg).

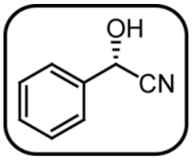
Catalyst P3a. To a stirred solution of **P3** (100 mg, 8.3 µmol) in CH_2Cl_2 (3 mL) was added CH_2Cl_2 (1 mL) solution of $Ti(O^iPr)_4$ (35 mg, 125 µmol) at room temperature. After 3 h, water (0.1 mL) was added and the stirring continued for an additional 16 h. The resultant solution was concentrated in vacuo, and the residue was washed with MeOH (5 mL) to afford **P3a** as yellow solid (106 mg).

Catalyst P4a. To a stirred solution of **P4** (100 mg, 14.6 µmol) in CH_2Cl_2 (3 mL) was added CH_2Cl_2 (1mL) solution of $Ti(O^iPr)_4$ (33 mg, 117 µmol) at room temperature. After 3 h, water (0.1 mL) was added and the stirring continued for an additional 16 h. The resultant solution was concentrated in vacuo, and the residue was washed with MeOH (5 mL) to afford 9a as yellow solid (108 mg).

Preparation of 20a. To a stirred solution of **20** (55 mg, 125 µmol) in CH_2Cl_2 (3 mL) was added CH_2Cl_2 (4 mL) solution of $Ti(O^iPr)_4$ (35 mg, 125 µmol) at room temperature. After 3 h, water (0.1 mL) was added and the stirring continued for an additional 16 h. The resultant solution was concentrated in vacuo, and the residue was washed with MeOH (5 mL) to afford **20a** as yellow solid (63 mg).

General Procedure for TMSCN Addition to Aldehydes. To a stirred solution of aldehyde (0.5 mmol) and **P1a-P4a/20a** (1 mol % with respect to monomeric unit) in dry $CHCl_3$ (1.5 mL) was added TMSCN (1 mmol) and the reaction mixture was stirred for 48 h under nitrogen atmosphere (Table 2-3). Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then concentrated (*ca.* 0.5 mL) and MeOH (0.5 mL) was added drop wise. The precipitated out **P1a-P4a/20a** was collected and the filtrate was evaporated to give a residue that was stirred with 2 N HCl (2 mL) in ethyl acetate (5 mL) for 1 h. The resultant solution was extracted with ethyl acetate (2 x 5 mL) and washed with brine (3 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford analytically pure cyanohydrins.

General Procedure for Cyanohydrins Acylation.[18] To a stirred solution of cyanohydrin (0.5 mmol) and pyridine (0.6 mmol) in $CHCl_3$ (1 mL) at 0 °C was added Ac_2O (1.5 mmol) or benzoyl chloride (1 mmol). The mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was passed through a short pad of silica gel using ethyl acetate and hexane to give the acetyl derivative whose ee was determined by HPLC analysis.



(S)-(-)-2-Hydroxy-2-phenylacetonitrile (Table 2, entry 1)[19a] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and benzaldehyde (53 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as color less oil in 97% (64 mg) yield.

$[\alpha]_D^{20}$ = -18.0 (*c* 0.50, $CHCl_3$).[19b]

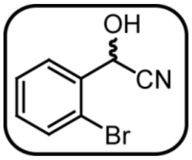
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (m, 2H), 7.46-7.39 (m, 3H), 5.52 (s, 1H), 3.12 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 129.8, 129.2, 126.8, 119.1, 63.3.

FT-IR (neat): 3412, 2926, 2857, 1690, 1627, 1495, 1455, 1405, 1244, 1193, 1085, 1040, 1026, 932, 820, 761, 739, 697, 647, 595 cm^{-1}.

Anal. Calcd for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.36; N, 10.49.

HPLC of the acetylated product: Chiralcel OD-H column, 99:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 1 mL/min, retention time: 10.42 min, 11.27 min; 77% ee.



(+)-2-Hydroxy-2-(2’-bromophenyl)acetonitrile (Table 2, entry 2).[19c] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-bromobenzaldehyde (93 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless solid in 95% (101 mg) yield.

Mp: 57-58 °C.

$[\alpha]_D^{20} = +6.3$ (*c* 1.09, $CHCl_3$).

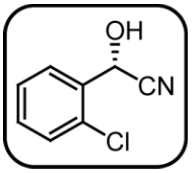
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 5.84 (d, *J* = 5.6 Hz, 1H), 3.53(d, *J* = 5.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.3, 133.3, 131.3, 128.5, 128.3, 122.3, 118.3, 62.9.

FT-IR (KBr): 3390, 3088, 2913, 1592, 1571, 1475, 1440, 1416, 1277, 1193, 1125, 1050, 1030, 940, 813, 750, 721, 682, 636, 607, 590 cm^{-1}.

Anal. Calcd for C_8H_6BrNO: C, 45.31; H, 2.85; N, 6.61. Found: C, 45.27; H, 2.89; N, 6.57.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength: 254 nm, flow rate: 1 mL/min, retention time: 10.49 min, 13.42 min, 50% ee.



(*S*)-(+)-2-Hydroxy-2-(2’-chlorophenyl)acetonitrile (Table 2, entry 3).[19a] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-chlorobenzaldehyde (71 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless oil in 97% (82 mg) yield.

$[\alpha]_D^{20} = +1.6$ (*c* 0.43, $CHCl_3$).[19d]

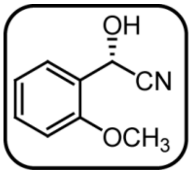
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7 (s, 1H), 7.43-7.34 (m, 3H), 5.84 (s, 1H), 3.70(s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 132.5, 131.0, 130.0, 128.3, 127.7, 118.2, 60.5.

FT-IR (neat): 3417, 3071, 2923, 2851, 1712, 1624, 1594, 1577, 1475, 1444, 1280, 1192, 1133, 1058, 1034, 943, 919, 869, 817, 756, 727, 707, 635, 470 cm^{-1}.

Anal. Calcd for C_8H_6ClNO: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.23; H, 3.65; N, 8.31.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 9.26 min, 11.10 min, 60% ee.



(*S*)-(-)-2-Hydroxy-2-(2'-methoxyphenyl)acetonitrile (Table 2, entry 4).[19b] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-methoxybenzaldehyde (68 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless solid in 95% (77 mg) yield.

Mp: 72-73 °C.

$[\alpha]_D^{20}$ = -23.9 (*c* 0.37, $CHCl_3$).[19b]

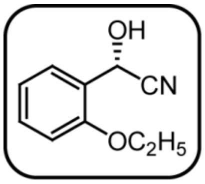
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4-7.36 (m, 2H), 6.99-6.93 (m, 2H), 5.57 (s, 1H), 3.9(s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 131.2, 128, 123.8, 121.1, 119.1, 111.2, 59.9, 55.8.

FT-IR (KBr): 3430, 3010, 2941, 2842, 1602, 1493, 1465, 1439, 1289, 1252, 1191, 1163, 1115, 1050, 1025, 926, 819, 784, 755, 643, 573 cm^{-1}.

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.60; N, 8.60.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 12.53 min, 14.22 min, 88% ee.



(-)-2-Hydroxy-2-(2'-ethoxyphenyl)acetonitrile (Table 2, entry 5). Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-ethoxybenzaldehyde (75 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless solid in 91% (81 mg) yield.

Mp: 88-89 °C.

$[\alpha]_D^{20}$ = -38 (*c* 0.61, $CHCl_3$).

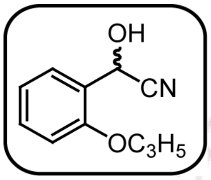
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 7.0-6.93 (m, 2H), 5.52 (d, *J* = 10.4 Hz, 1H), 4.2-4.14 (m, 2H), 3.63 (d, *J* = 9.2 Hz, 1H), 1.49 (t, *J* = 7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 131.2, 128.1, 123.9, 121.1, 119.1, 112.1, 64.4, 60.6, 14.8.

FT-IR (KBr): 3368, 2982, 2936, 2887, 2251, 1601, 1590, 1494, 1473, 1457, 1391, 1307, 1285, 1258, 1237, 1182, 1160, 1125, 1112, 1060, 1043, 927, 910, 796, 758, 616, 591 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.32; N, 7.87.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 8.78 min, 10.76 min,78% ee.



(+)-2-Hydroxy-2-(2'-allyloxyphenyl)acetonitrile (Table 2, entry 6). Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-allyloxybenzaldehyde (74 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as oil in 90% (79 mg) yield.

$[\alpha]_D^{20} = +22.5$ (*c* 0.75, $CHCl_3$).

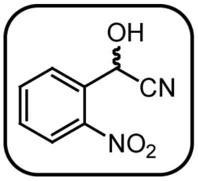
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.34 (m, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.10-6.02 (m, 1H), 5.57 (d, *J* = 6.8 Hz, 1H), 5.47-5.42 (td, *J* = 1.6, 9.2 Hz, 1H), 5.35-5.31 (m, 1H), 4.67-4.65 (m, 2H), 3.66 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 132.4, 131, 128, 124, 121.3, 119, 118.3, 112.3, 69.3, 60.0.

FT-IR (neat): 3463, 2923, 2855, 2253, 2071, 1650, 1491, 1458, 1287, 1252, 1185, 1162, 1120, 1030, 927, 812, 753, 699 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.79; H, 5.92; N, 7.36.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 10.55 min, 13.94 min, 75% ee.



(-)-2-Hydroxy-2-(2'-nitrophenyl)acetonitrile (Table 2, entry 7). Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-nitrobenzaldehyde (76 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless solid in 70% (62 mg) yield.

Mp: 92-93 °C.

$[\alpha]_D^{20}$ = -24 (*c* 0.3, $CHCl_3$).

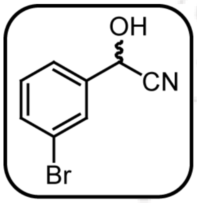
^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 6.18 (s, 1H), 4.11(s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.5, 134.4, 132.1, 130, 128.4, 125.1, 118.6, 59.3.

FT-IR (KBr): 3493, 3371, 3110, 2924, 2853, 1727, 1609, 1578, 1523, 1339, 1306, 1178, 1093, 1061, 1043, 925, 857, 811, 791, 798, 733, 704, 678, 633, 604 cm^{-1}.

HPLC of the acetylated product: Chiralcel OD-H column, 99:1 *n*-hexane/2-propanol, wavelength: 254 nm, flow rate: 1 mL/min, retention time: 27.08 min, 35.07 min; 20% ee.

Anal. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 53.90; H, 3.43; N, 15.69.



(-)-2-Hydroxy-2-(3'-bromophenyl)acetonitrile (Table 2, entry 8).[19a] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 3-bromobenzaldehyde (93 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless oil in 90% (95 mg) yield.

$[\alpha]_D^{20}$ = -19.5 (*c* 1.34, $CHCl_3$).

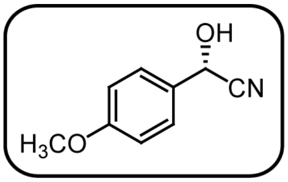
^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (s, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 5.53 (d, *J* = 6.8 Hz, 1H), 3.17(s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 132.9, 130.8, 129.7, 125.3, 123.1, 118.7, 62.6.

FT-IR (neat): 3414, 3065, 2917, 2823, 2725, 1693, 1591, 1573, 1474, 1429, 1385, 1303, 1275, 1192, 1091, 1064, 1042, 936, 882, 853, 828, 784, 706, 673, 642 cm^{-1}.

Anal. Calcd for C_8H_6BrNO: C, 45.31; H, 2.85; N, 6.61. Found: C, 45.35; H, 2.87; N, 6.58.

HPLC of the actyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time:15.12 min, 16.36 min, 75% ee.



(*S*)-(-)-2-Hydroxy-2-(4'-methoxyphenyl)acetonitrile (Table 2, entry 9).[19b] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 4-methoxybenzaldehyde (68 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless soild in 97% (79 mg) yield.

Mp: 67-68 °C.

$[\alpha]_D^{20}$ = -32.4 (*c* 0.55, $CHCl_3$).[19b]

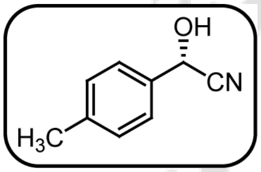
^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.42 (s, 1H), 3.8 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 128.4, 127.6, 119.3, 114.5, 63.0, 55.5.

FT-IR (KBr): 3419, 3009, 2962, 2936, 2841, 1673, 1610, 1600, 1576, 1514, 1463, 1306, 1257, 1178, 1162, 1113, 1028, 925, 833, 768, 608, 540 cm^{-1}.

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.19; H, 5.58; N, 8.62.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 17.37 min, 19.08 min, 78% ee.



(*S*)-(-)-2-Hydroxy-2-(4'-methylphenyl)acetonitrile (Table 2, entry 10).[19b] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 4-methylbenzaldehyde (60 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless soild in 97% (71 mg) yield.

$[\alpha]_D^{20}$ = -31.5 (*c* 0.51, $CHCl_3$).[19b]

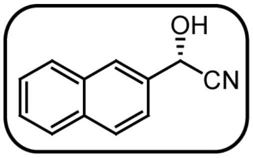
^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 5.48 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 132.5, 129.8, 126.7, 119.3, 63.2, 21.2.

FT-IR (neat): 3419, 3031, 2924, 2857, 1912, 1679, 1615, 1514, 1445, 1416, 1244, 1196, 1182, 1114, 1037, 1019, 928, 836, 815, 765, 719, 607, 528 cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.41; H, 6.21; N, 9.48.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 10.10 min, 12.27 min, 68% ee.



(*S*)-(-)-2-Hydroxy-2-(2'-naphthyl)acetonitrile (Table 2, entry 11).[19e] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 4-naphthaldehyde (78 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless soild in 90% (82 mg) yield.

Mp: 119-120 °C.

$[\alpha]_D^{20}$= -24.6 (*c* 1.16, $CHCl_3$).[19e]

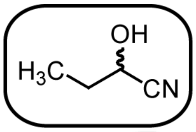
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.91-7.84 (m, 3H), 7.57-7.53 (m, 3H), 6.69 (d, *J* = 6.8 Hz, 1H), 3.09 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 133.2, 132.8, 128.8, 128.1, 127.6, 126.7, 126.5, 125.6, 123.9, 119.8, 62.9.

FT-IR (KBr): 3470, 3055, 2927, 2890, 1602, 1503, 1399, 1361, 1255, 1236, 1121, 1064, 859, 823, 753, 487 cm^{-1}.

Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.63; H, 5.01; N, 7.59.

HPLC of the acetyl derivative: Chiralcel OD-H column, *n*-hexane/2-propanol (99:1), wavelength 254 nm, flow rate: 1 mL/min, retention time: 26.67 min, 29.65 min, 74% ee.



(-)-2-Hydroxybutanenitrile (Table 3, entry 1).[19a] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and propionaldehyde (29 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless liquid in 95% (40 mg) yield.

$[\alpha]_D^{20}$= -10.3 (*c* 0.89, $CHCl_3$).

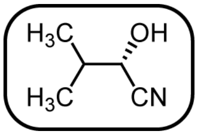
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.39 (t, *J* = 6.8 Hz, 1H), 2.06 (d, *J* = 13.6 Hz, 1H), 1.84 (p, *J* = 7.2 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 120.1, 62.4, 28.5, 14.1, 9.0.

FT-IR (neat): 3437, 2976, 2942, 2884, 2247, 1633, 1463, 1385, 1334, 1281, 1105, 1062, 1026, 983, 924, 851 cm^{-1}.

Anal. Calcd for C_4H_7NO: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.49; H, 8.27; N, 16.49.

HPLC of the benzoyl derivative: Chiralcel OJ column, *n*-hexane/2-propanol (90:10), wavelength 254 nm, flow rate: 0.5 mL/min, retention time: 16.57 min, 18.14 min, 40% ee.



(*S*)-(-)-2-Hydroxy-3-methylbutanenitrile (Table 3, entry 2).[19e] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 2-butanaldehyde (36 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless liquid in 90% (45 mg) yield.

$[\alpha]_D^{20}$= -10.5 (*c* 1.19, $CHCl_3$).[19e]

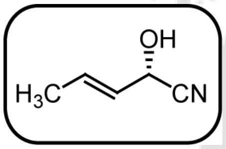
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (d, *J* = 6 Hz, 1H), 1.98-2.06 (m, 1H), 1.02-1.07 (dd, *J* = 11.6, 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 119.5, 67.0, 33.1, 17.8, 17.3.

FT-IR (neat): 3436, 2970, 2937, 2879, 2247, 1633, 1469, 1391, 1348, 1254, 1180, 1063, 1017, 972, 953, 880 cm^{-1}.

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.64; H, 9.17; N, 14.09.

HPLC of the benzoyl derivative: Chiralcel OJ column, *n*-hexane/2-propanol (90:10), wavelength 254 nm, flow rate: 0.5 mL/min, retention time: 12.04 min, 13.11 min, 66% ee.



(E)-(*S*)-(+)-2-Hydroxypent-3-enenitrile (Table 3, entry 3).[19e] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and crotonaldehyde (35 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless liquid in 93% (45 mg) yield.

$[\alpha]_D^{20}$= +10.5 (*c* 0.50, $CHCl_3$).[19f]

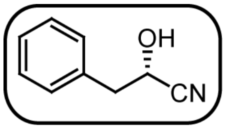
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08-6.02 (m, 1H), 5.63-5.57 (dd, *J* = 15.2, 6 Hz, 1H), 4.90 (d, *J* = 6 Hz, 1H), 1.77 (d, *J* = 5.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.5, 125.1, 118.8, 61.5, 17.5.

FT-IR (neat): 3406, 2972, 2922, 2857, 2247, 1670, 1447, 1380, 1259, 1124, 1087, 1023, 964, 933, 909, 791 cm^{-1}.

Anal. Calcd for C_5H_7NO: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.89; H, 7.29; N, 14.37.

HPLC of the benzoyl derivative: Chiralcel OJ column, *n*-hexane/2-propanol (90:10), wavelength 254 nm, flow rate: 0.8 mL/min, retention time: 9.83 min, 10.36 min, 55% ee.



(*S*)-(-)- 2-Hydroxy-3-phenylpropanenitrile (Table 3, entry 4).[19e] Catalyst **P3a** (5 mg, 1 mol %), TMSCN (99 mg, 1 mmol), and 4-methoxybenzaldehyde (60 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as colorless liquid in 86% (63 mg) yield.

$[\alpha]_D^{20}$ = -3.2 (*c* 0.43, $CHCl_3$).[19e]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 4.59 (t, *J* = 6.4 Hz, 1H), 3.23 (s, 1H), 3.09 (d, *J* = 6.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2, 129.7, 128.9, 127.7, 119.7, 62.2, 41.2.

FT-IR (neat): 3431, 2929, 2857, 1633, 1604, 1496, 1455, 1432, 1335, 1266, 1205, 1081, 1064, 1031, 935, 911, 862, 746, 701, 621, 480 cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.19; N, 9.48.

HPLC of the acetylated product: Chiralcel OB-H column, 97:3 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 1 mL/min, retention time: 21.07 min, 23.07 min; 57% ee.

Recyclability Experiment. To a stirred solution of 4-methoxybenzaldehyde (136 mg, 1 mmol) and **P3a** (10 mg, 1 mol % with respect to monomeric unit) in dry $CHCl_3$ (3 mL) was added TMSCN (198 mg, 2 mmol) and the reaction mixture was stirred for 48 h under nitrogen atmosphere (Table 4). The reaction mixture was then concentrated (*ca.* 0.5 mL) and MeOH (0.5 mL) was added. The precipitated out **P3a** was collected and reused for the fresh reaction.

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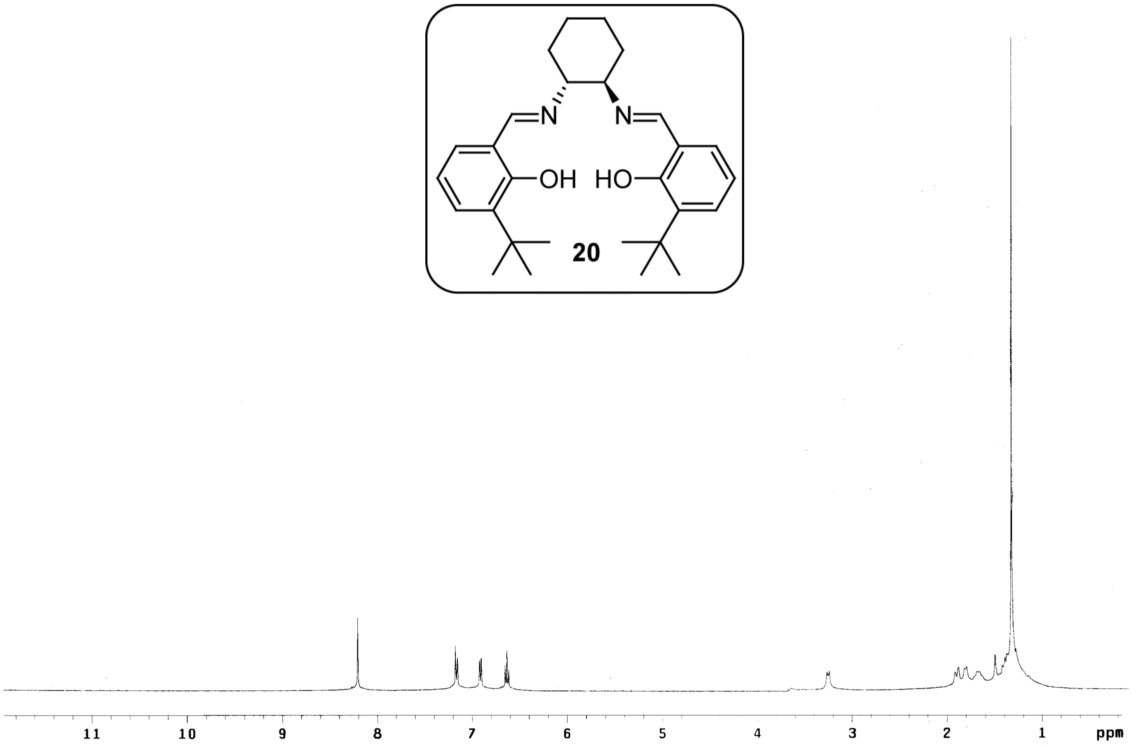
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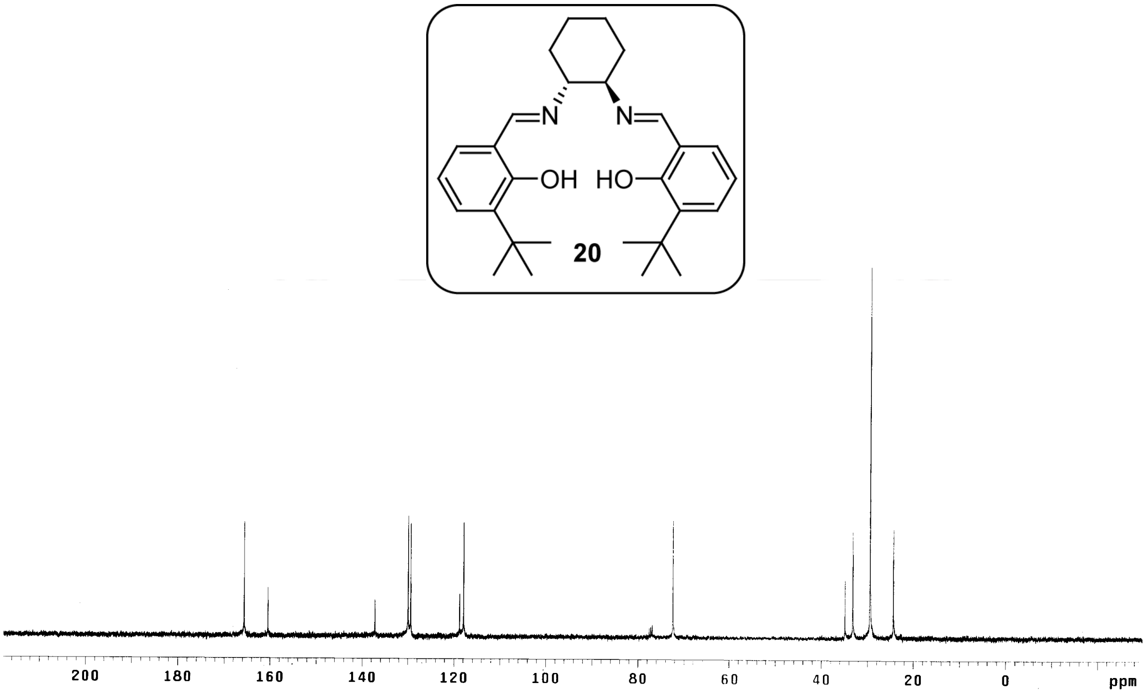
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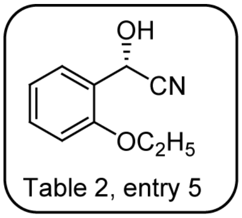

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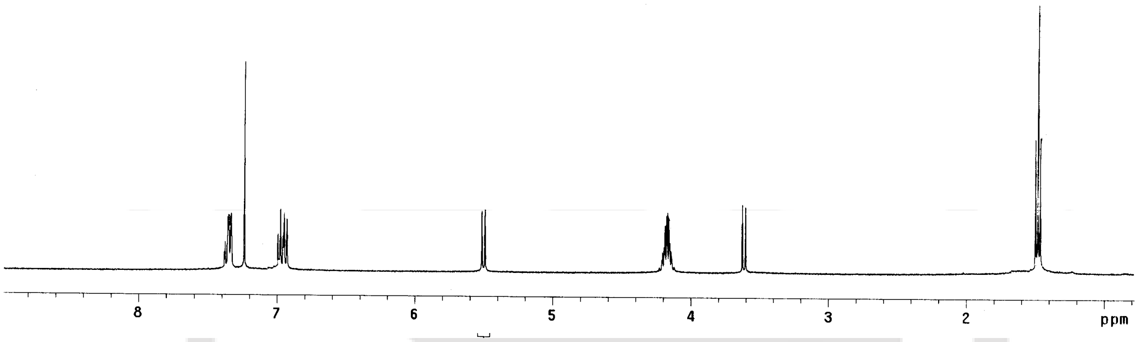

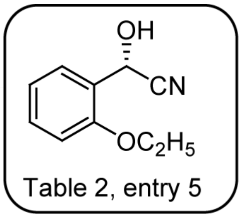

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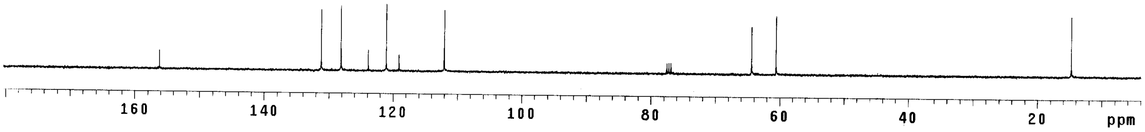

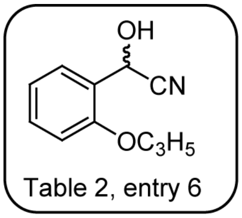

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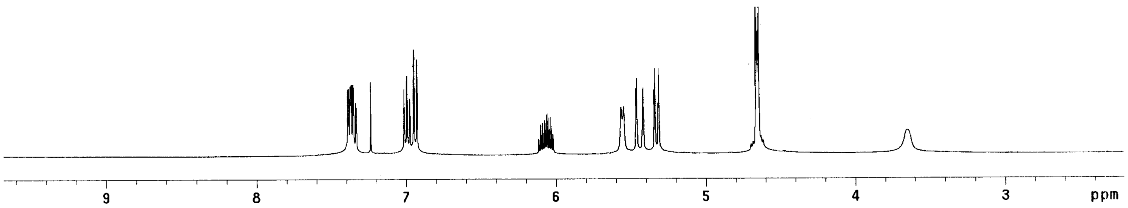

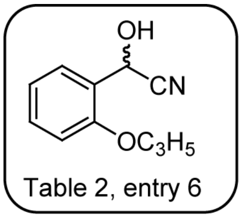

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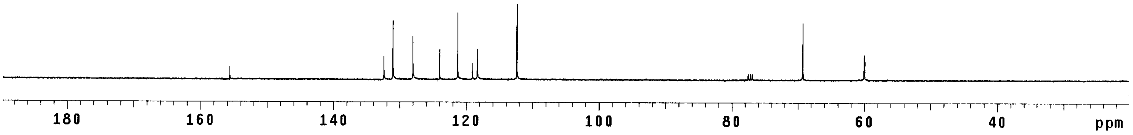

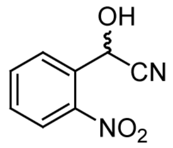

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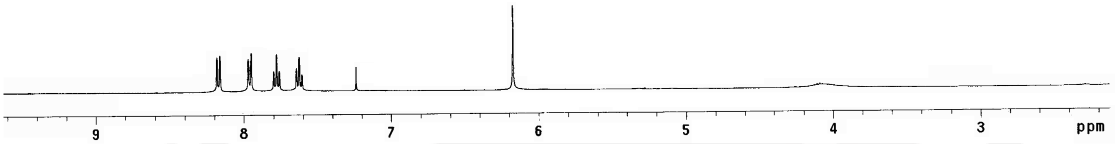

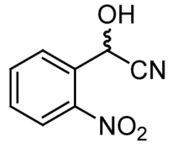

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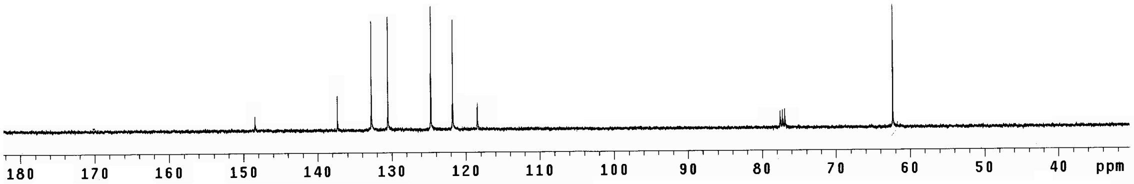


Chapter III

Chiral Titanium(IV)-Catalyzed Asymmetric Sulfoxidation with Aqueous Hydrogen Peroxide

3.1 Introduction

Optically active sulfoxides serve as intermediates in the synthesis of bioactive ingredients as well as chiral auxiliaries for C-C[1a-b] and C-O[1c] bonds formation, cycloaddition,[1d-e] radical addition[1g-h] and asymmetric transformations.[1i-n] The success of the sulfinyl group as a chiral auxiliary is due to its configurational stability (generally stable up to 200 °C), accessibility in both enantiomeric forms, and an excellent carrier of chiral information.[2] Chiral sulfoxides have also been found to be used in the pharmaceutical industry due to their potent biological activity (Figure 1).[3]

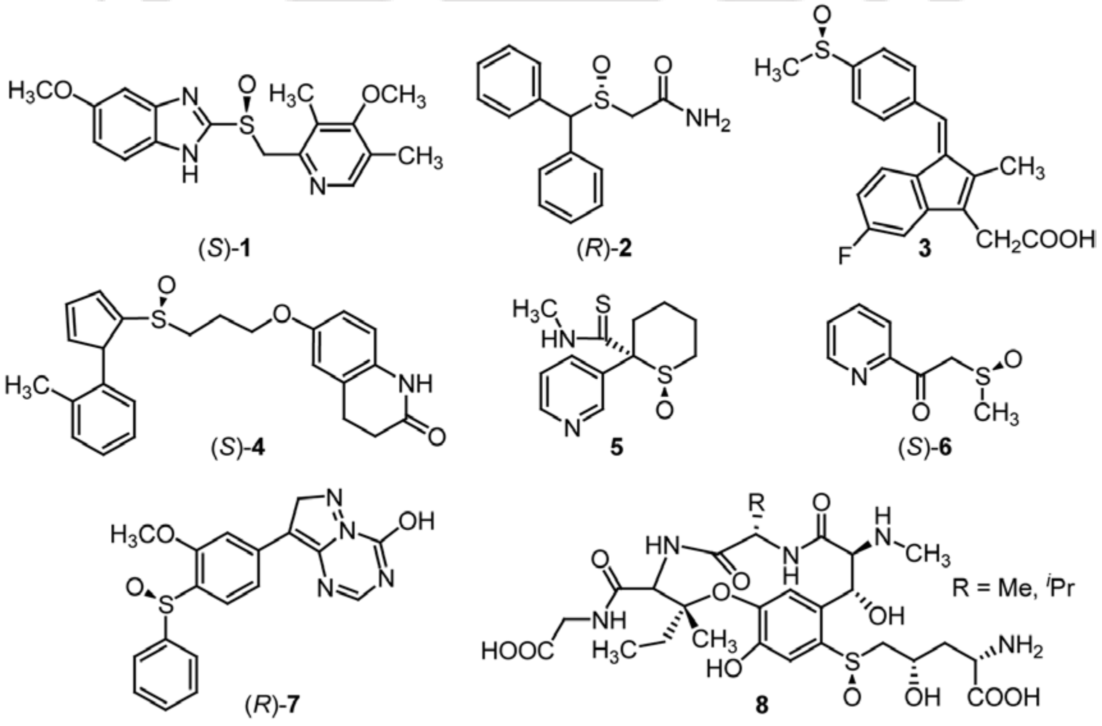


Figure 1

Esomeprazole **1**, the (*S*)-form of omeprazole, which is used to heal and relieve symptoms of gastric or duodenal ulcers, is counted among the world's highest selling drug in 1997 ($5 billion U.S.).[3b-d] The manifold activity of chiral sulfoxide based drugs can be illustrated by armodafinil (the (*R*)-enantiomer of modafinil **2**), a stimulant drug approved for treatment of sleep disorders;[3e-g] sulindac **3**, for inflammation treatment;[3h] OPC- 29030 **4**, a platelet adhesion inhibitor;[3i-j] aprikalim **5**, an activator of the potassium channel;[3k] oxisurane **6**, an immunosuppressor;[3l] pyrazolotriazine derivative **7**, effective in hyperuricemia;[3m] or ustiloxins **8**, active against human breast and lung cancer lines.[3n]

There are two principal routes to the preparation of optically active sulfoxides[2,4]

- ❖ Oxidation (metal catalyzed and metal free reactions, electrochemical and biological methods, and kinetic resolution of sulfoxides).
- ❖ Nucleophilic substitution.

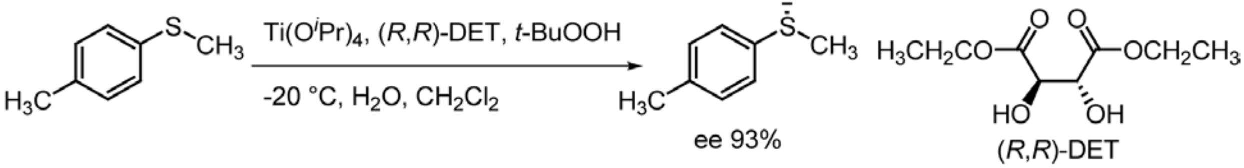
3.2 Oxidation Reactions

The most attractive method for the preparation of enantiopure sulfoxides is asymmetric sulfoxidation.

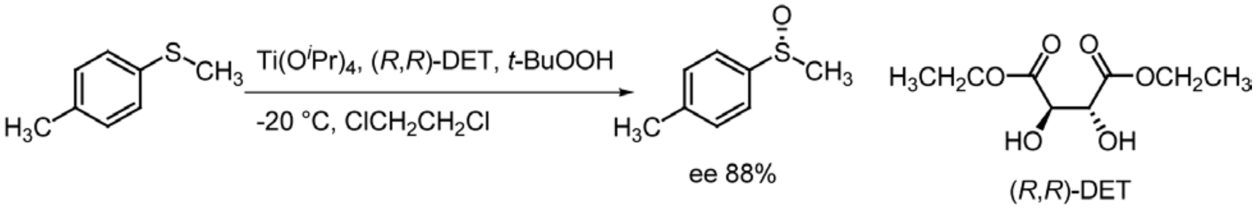
3.2.1 Metal Catalyzed Reactions

3.2.1.1 Reactions with Organic Peroxides

The first practical and efficient oxidation method for the metal catalyzed asymmetric oxidation of sulfides was reported by Kagan and Modena independently in 1984 (Scheme 1-2).[5-7]

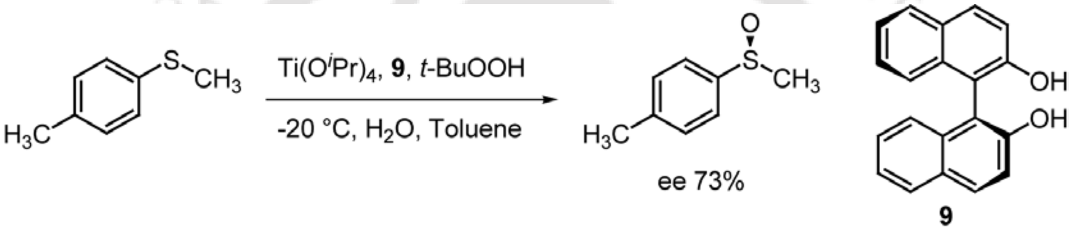


Scheme 1



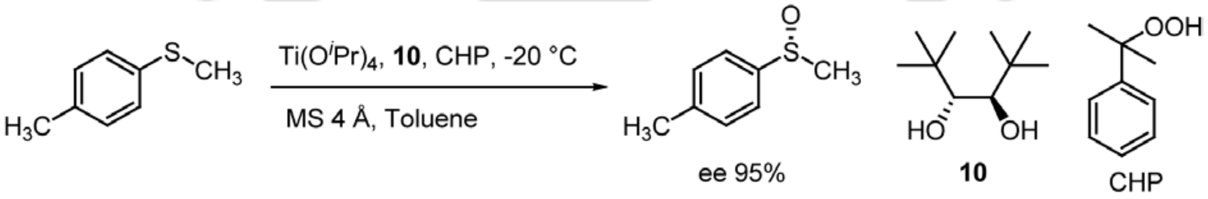
Scheme 2

Komatsu *et al*. used BIONL **9** in the place of (*R*,*R*)-DET and showed the product with 73% ee (Scheme 3).[8]



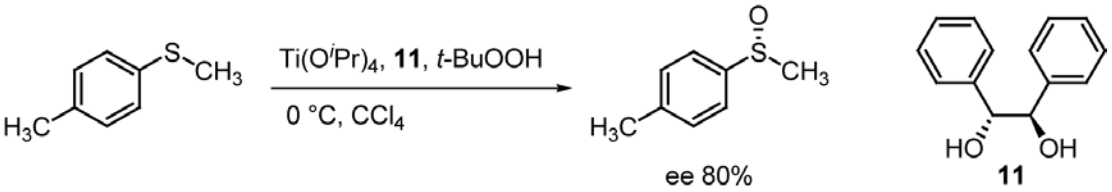
Scheme 3

Yamanoi *et al*. used chiral titanium complex derived from Ti(O^{i}Pr)$_4$ and chiral ligand **10** in the presence of cumyl hydroperoxide to afford the sulfoxide in 95% ee (Scheme 4).[9]

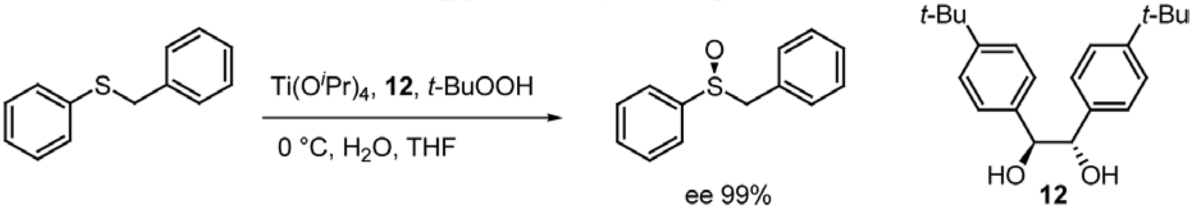


Scheme 4

Superchi *et al*. used diols **11-12** as chiral ligands to give the sulfoxides with up to 99% ee (Scheme 5-6).[10]

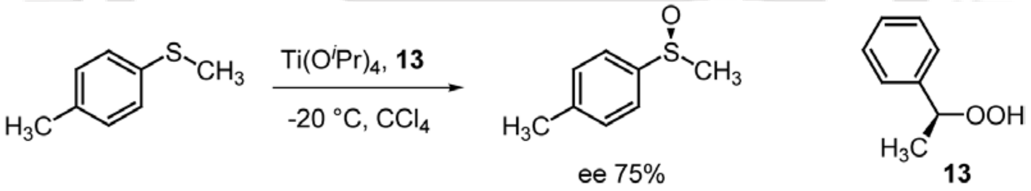


Scheme 5



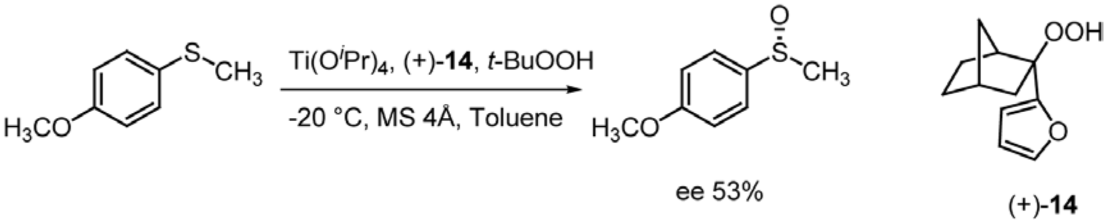
Scheme 6

Adam *et al.* investigated chiral hydroperoxide **13** to afford the sulfoxide in 73% ee (Scheme 7).[11] Under these conditions, considerable amount of sulfone formation observed.



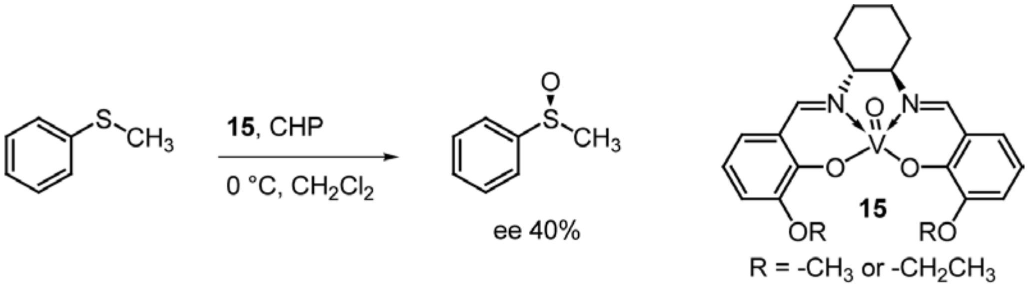
Scheme 7

Lattanzi *et al.* used camphor derived furyl hydroperoxides **14** to provide the sulfoxide in moderate enantioselectivity (Scheme 8).[12] Sulfone formation was a significant feature for all the camphor derived furyl hydroperoxides.



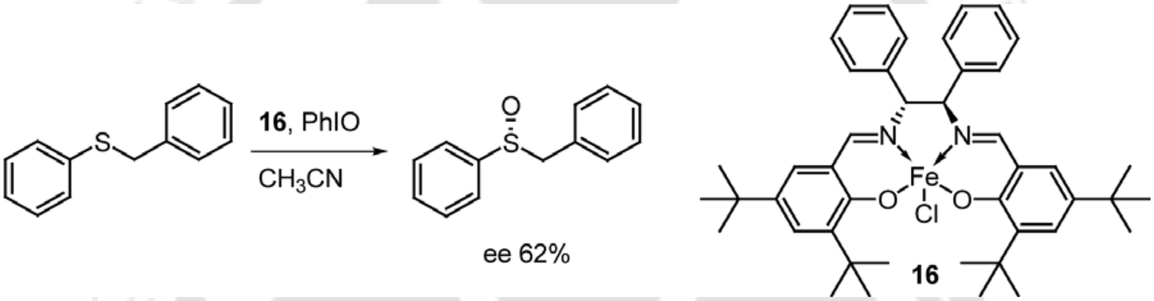
Scheme 8

Nakajima *et al*. used chiral V(IV)-salen in the presence of CHP to provide the sulfoxide in 43% ee (Scheme 9).[13]



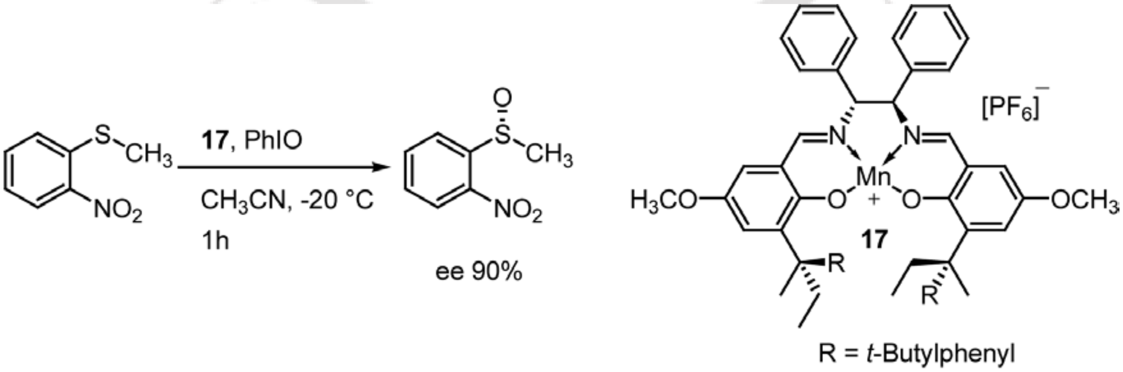
Scheme 9

Bryliakov *et al*. employed chiral iron(III)-salen **16** in the presence of PhIO to give the sulfoxide in 62% ee (Scheme 10).[14]



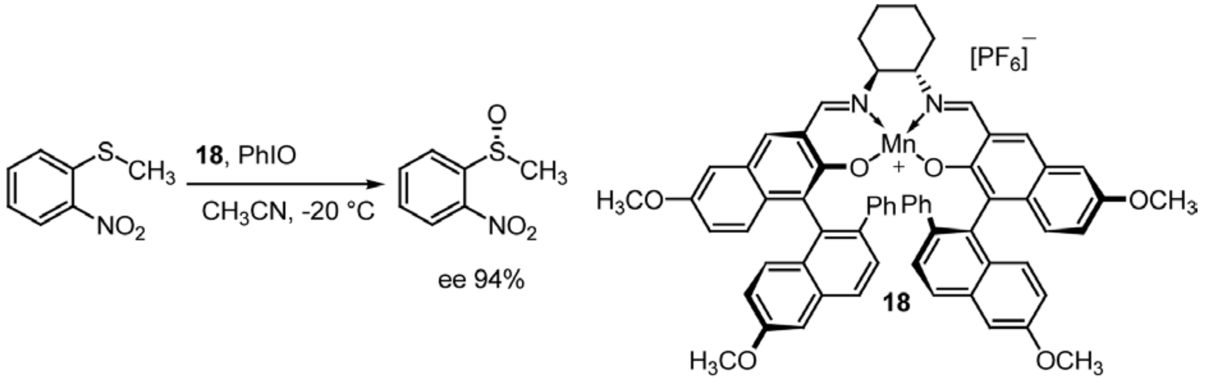
Scheme 10

Palucki *et al*. and Noda *et al*. used chiral Mn(III)-salen complexes in the presence of PhIO to afford the sulfoxide in 90% ee (Scheme 11).[15a-c]



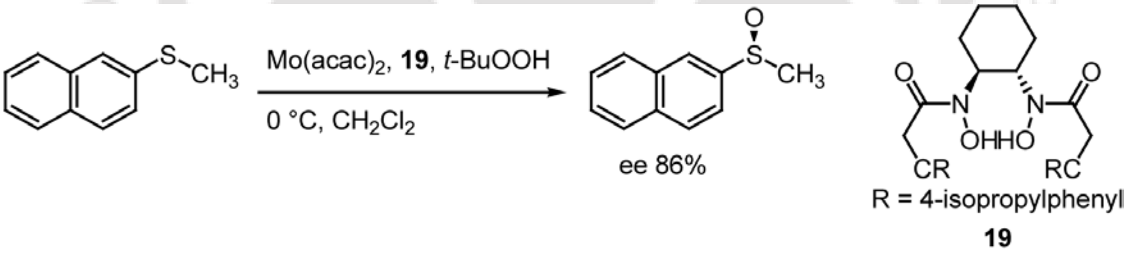
Scheme 11

Kokubo *et al*. used chiral Mn(III)-salen **18** in the presence of PhIO as terminal oxidant and 4-phenylpyridine-*N*-oxide (4-PPNO) as an additive to afford the sulfoxide in 94% ee (Scheme 12).[15d]



Scheme 12

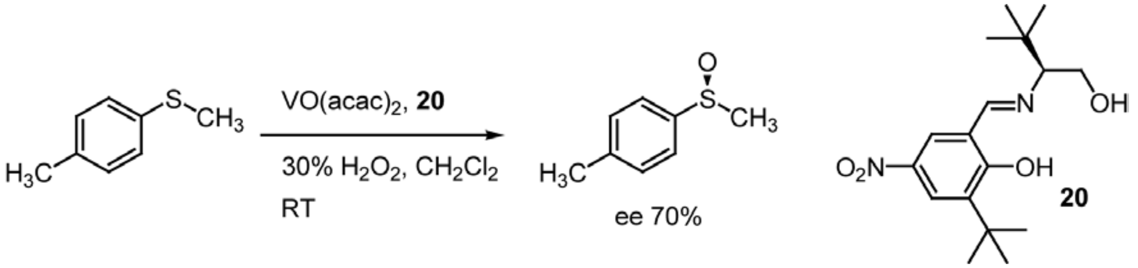
Basak *et al*. showed the use of chiral molybdenum complex derived from Mo(acac)$_2$ and chiral ligand **19** in the presence of TBHP to give the sulfoxide in 86% ee (Scheme 13).[16]



Scheme 13

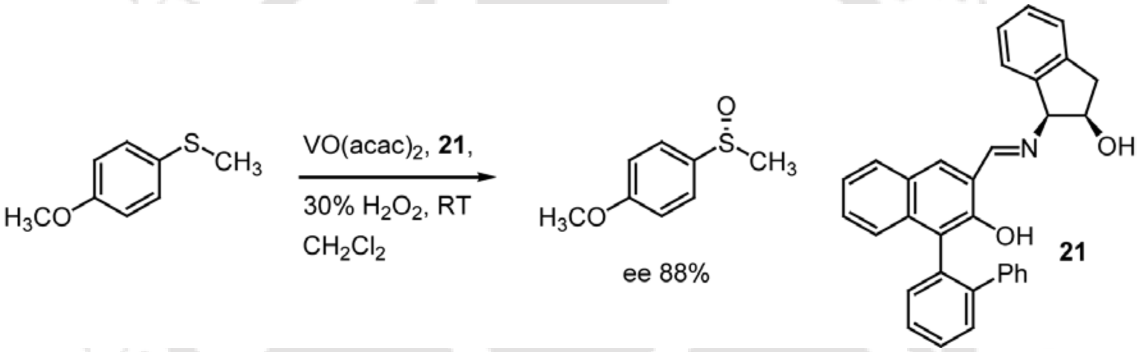
3.2.1.2 Reactions with Hydrogen Peroxide

Bolm *et al*. studied sulfoxidation with 70% ee using chiral vanadium Schiff base complex derived from VO(acac)$_2$ and chiral ligand **20** in the presence of hydrogen peroxide (Scheme 14).[17]



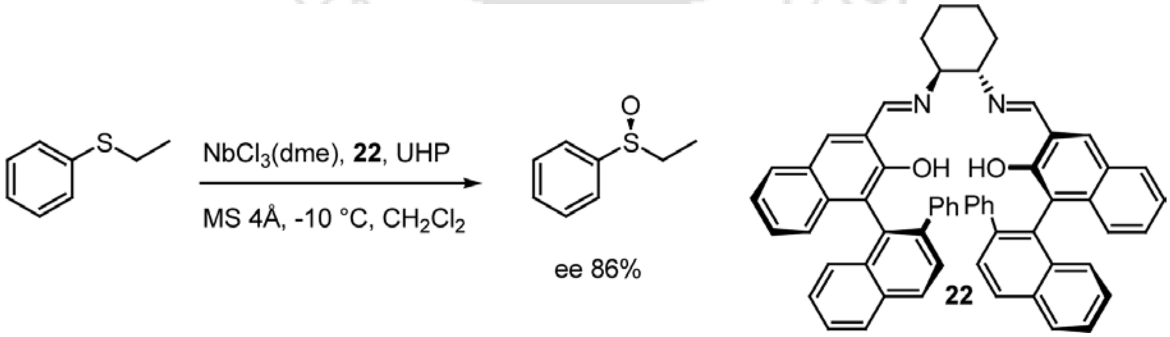
Scheme 14

Ohta *et al*. investigated sterically hindered chiral ligand **21** with VO(acac)$_2$ to afford the sulfoxide in 88% ee (Scheme 15).[18]



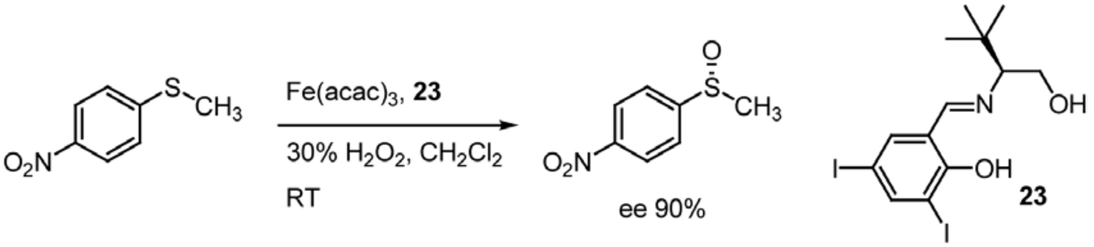
Scheme 15

Chiral Nb(III)-salen derived from niobium chloride dimethoxyethane [NbCl$_3$(dme)] and salen **22** studied with urea hydrogen peroxide (UHP) to give the sulfoxide in 86% ee (Scheme 16).[19]



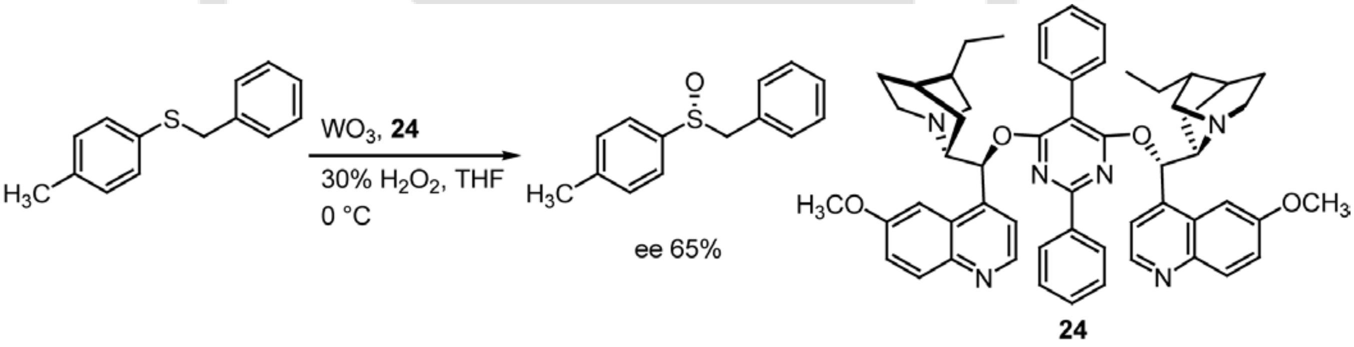
Scheme 16

Chiral iron(III) complexes derived from Fe(acac)$_3$ and chiral Schiff base **23** investigated in the presence of aqueous hydrogen peroxide to give the sulfoxide in 90% ee (Scheme 15).[20]



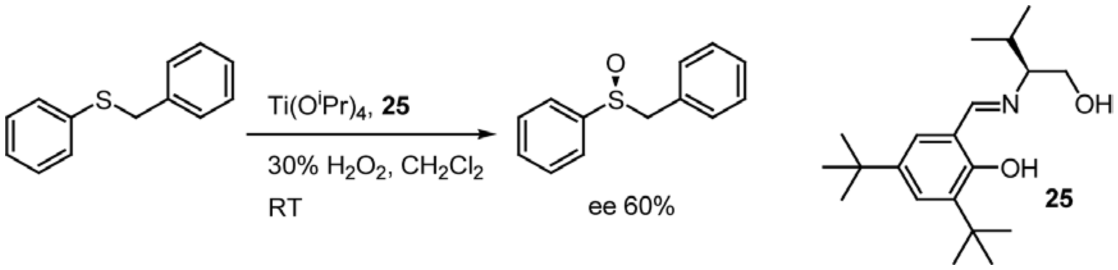
Scheme 17

Thakur *et al*. studied the sulfoxidation using chiral tungsten complex derived from WO$_3$ and ligand **24** in the presence of aqueous hydrogen peroxide with moderate enantioselectivity (Scheme 18).[21]



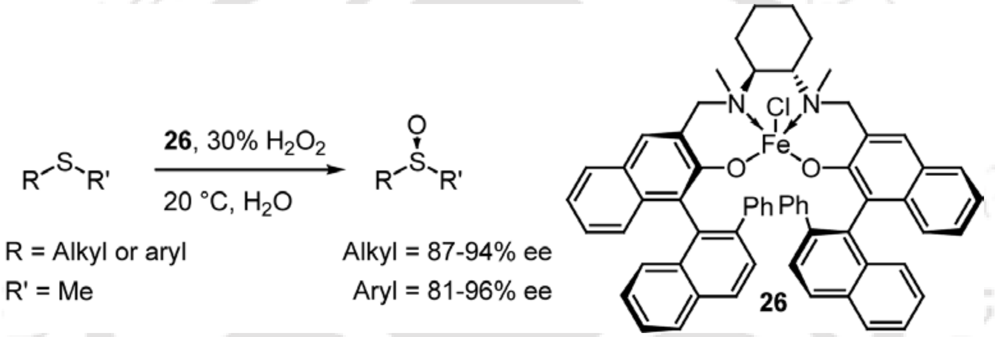
Scheme 18

Bryliakov *et al*. employed chiral titanium complex derived from Ti(O^{i}Pr)$_4$ and Schiff base ligand **25** in the presence of aqueous hydrogen peroxide to provide the sulfoxide in 60% ee (Scheme 19).[22]



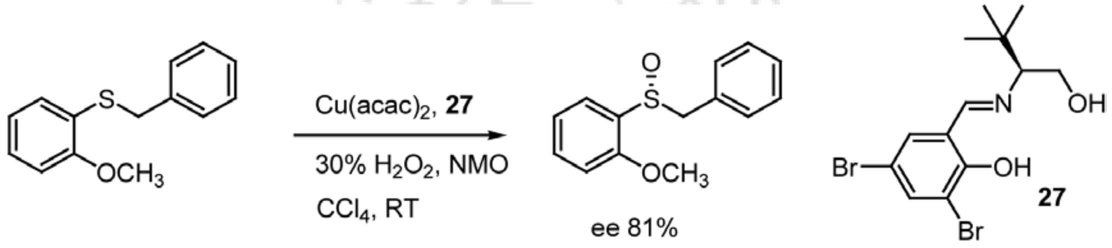
Scheme 19

Chiral Fe(III)-salen **26** used for the oxidation of sulfides in aqueous condition with hydrogen peroxide with high enantioselectivity (Scheme 20).[23]



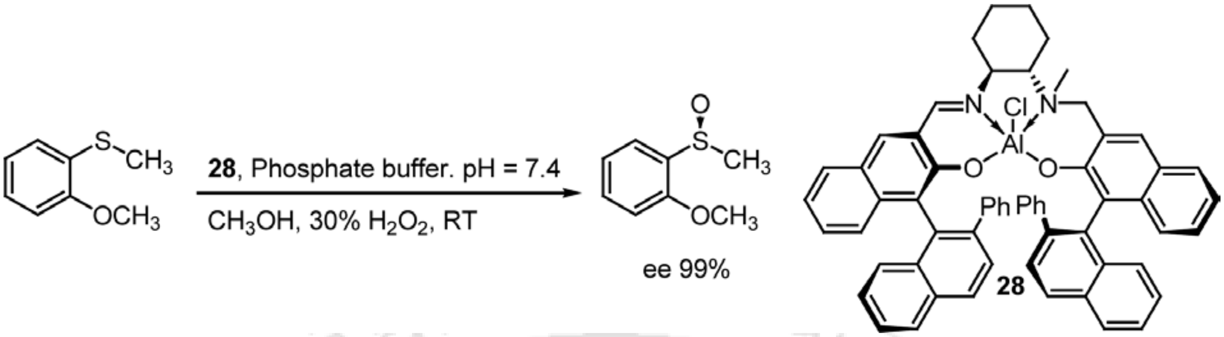
Scheme 20

Kelly *et al*. showed use of chiral copper complex derived from Cu(acac)$_2$ and ligand **27** for the oxidation of sulfides in the presence of aqueous hydrogen peroxide with 81% ee (Scheme 21).[24] The direction of the stereoselectivity observed is opposite to that obtained for the iron/vanadium-catalyzed processes.



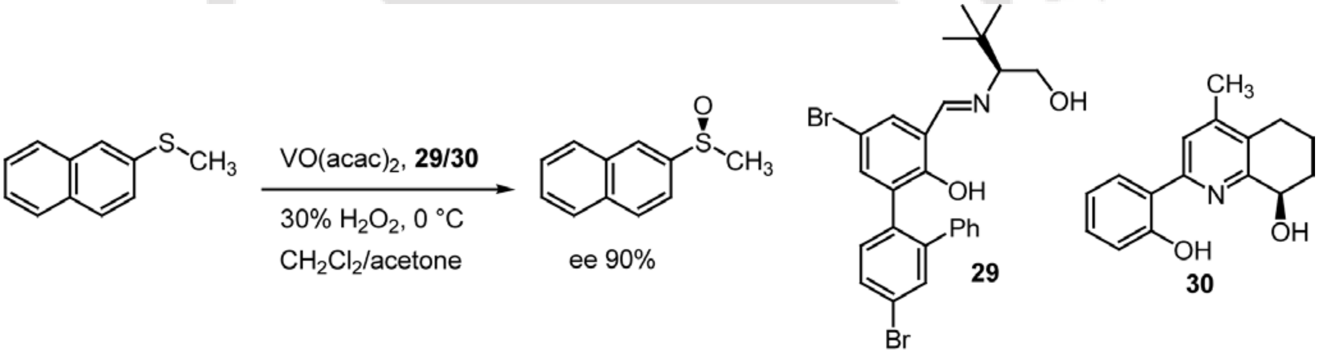
Scheme 21

Chiral aluminum(III)-salen **28** studied for the oxidation of sulfides in the presence of aqueous hydrogen peroxide with 99% ee (Scheme 22).[25]



Scheme 22

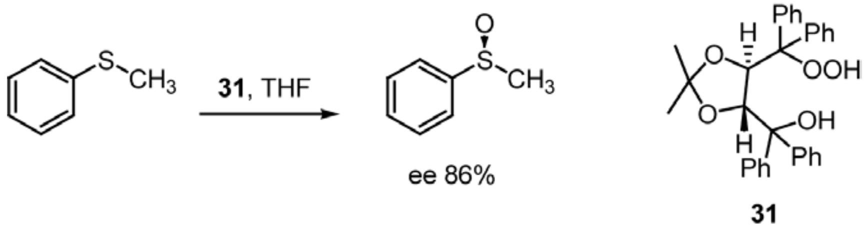
Chiral vanadium complex derived from $VO(acac)_2$ and ligands **29-30** investigated for the oxidation of sulfides in the presence of aqueous hydrogen peroxide with 90% ee (Scheme 23).[26,27]



Scheme 23

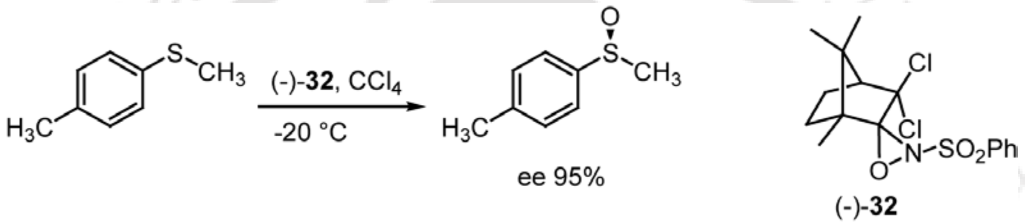
3.2.2 Metal-Free Reactions

(4*R*,5*R*)-5-[(Hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl-diphenylmethanol **31** (TADOOH) derived from hydrogen peroxide and tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) studied for the oxidation of sulfides with 86% ee (Scheme 24).[28]



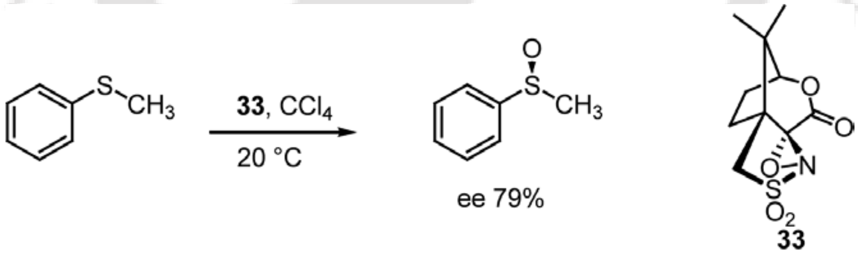
Scheme 24

Davis *et al*. used dichlorocamphorylsulfonyloxaziridine **32** for the oxidation of sulfides with 95% ee (Scheme 25).[29]



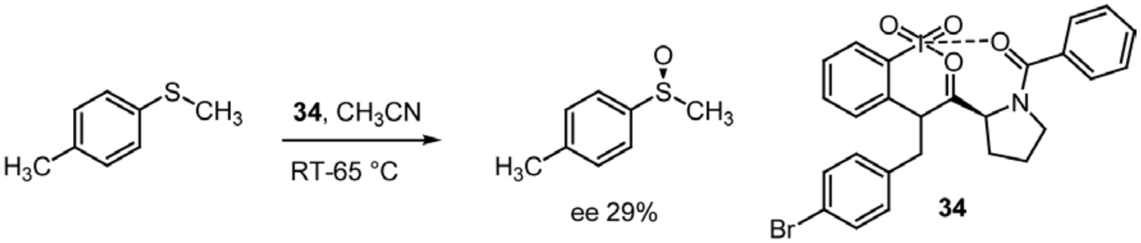
Scheme 25

Meladinis *et al.* investigated camphorylsulfonyloxaziridine **33** for oxidation of sulfides with 79% ee (Scheme 26).[30]



Scheme 26

Ladziata *et al.* studied chiral benziodoxazine derivative **34** to yield the sulfoxide in 29% ee (Scheme 27).[31]



Scheme 27

3.2.3 Electrochemical Methods

In 1976 Firth and Miller reported the electrochemical oxidation of sulfides with limited enantioselectivity.[32a] While the results obtained were poor (3% ee), it was the first report of electrochemical asymmetric sulfide oxidation.

A few years later, Komori and Nonaka reported a variety of poly(amino acid) coated platinum/graphite electrodes to give the sulfoxide with up to 93% ee (Figure 2).[32b-c]

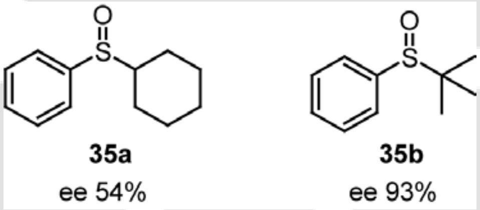
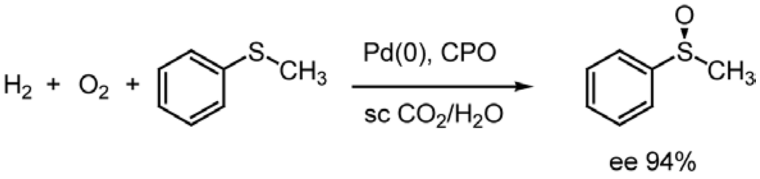

35a ee 54%
35b ee 93%

Figure 2

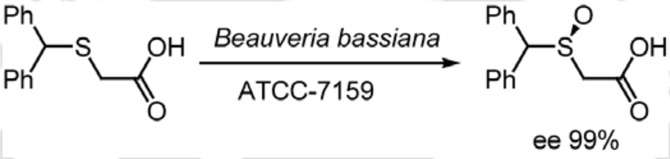
3.2.4 Biological Methods

Biological asymmetric sulfide oxidation is a less popular than chemical method. Generally, the biological reaction is carried out using whole cell cultures or isolated enzymes.[33] Leitner and Greiner carried out an enantioselective sulfoxidation by cascade reaction of Pd-catalyzed formation of hydrogen peroxide and enzymatic oxidation using chloroperoxidase (CPO). Supercritical carbon dioxide (sc CO_2) was used as medium for *in situ* generation of hydrogen peroxide from hydrogen and oxygen. The system afforded phenyl methyl sulfoxide in 34% yield and 94% ee (Scheme 28).[34]



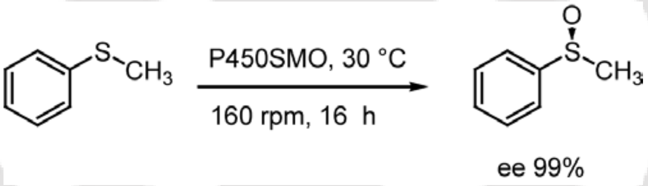
Scheme 28

Olivo *et al.* reported a highly enantioselective oxidation of benzhydrylsulfanyl acetic acid using the fungus *Beauveria bassiana* (Scheme 29).[3g]



Scheme 29

Cytochrome P450 monooxygenase was cloned from *Rhodococcus species ECU0066* used for the oxidation of sulfides with 99% ee (Scheme 30).[35]



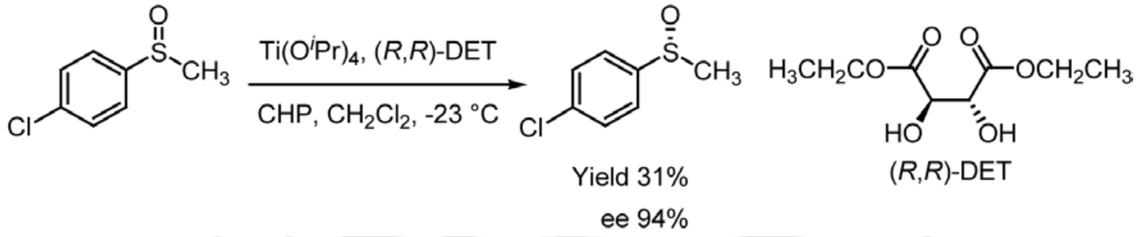
Scheme 30

3.2.5 Kinetic Resolution of Sulfoxides

While asymmetric sulfoxidation is attractive for the preparation of optically active sulfoxides, kinetic resolution of sulfoxides has also been considerably explored as alternative method. Kinetic resolution strategies can be divided into oxidative and non-oxidative methods.

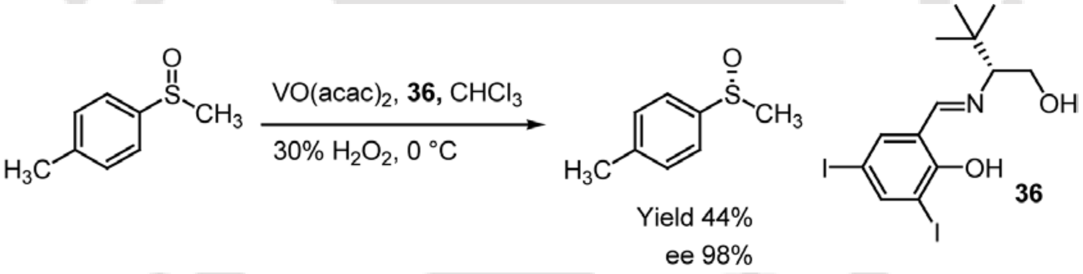
3.2.5.1 Oxidative Methods

Most of the kinetic resolutions involve the preferential oxidation of one enantiomer compared to other. Scettri and co-workers resolved *p*-chlorophenyl methyl sulfoxide using chiral titanium(IV)-complex derived from $Ti(O^iPr)_4$ and (*R*,*R*)-diethyl tartrate (DET) (Scheme 31).[36]



Scheme 31

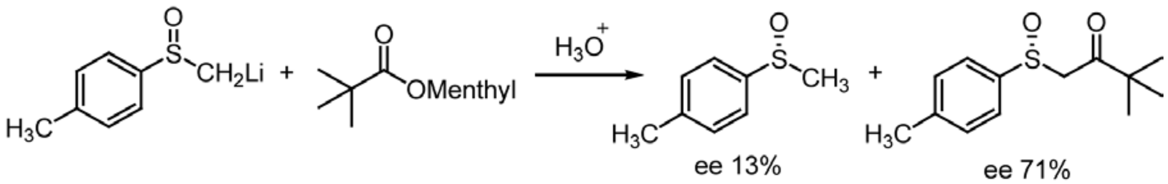
Drago *et al*. reported the kinetic resolution of sulfoxides using chiral vanadium complex derived from $VO(acac)_2$ and Schiff base ligand **36** in the presence of aqueous hydrogen peroxide with 98% ee (Scheme 32).[37]



Scheme 32

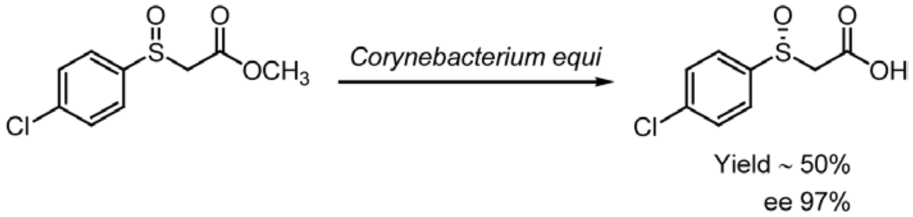
3.2.5.2 Non-Oxidative Methods

The reaction of *α*-sulfinyl carbanion derived from methyl *p*-tolyl sulfoxide with an optically active menthyl carboxylate afforded *β*-ketosulfoxide with up to 71% ee (Scheme 33).[38]



Scheme 33

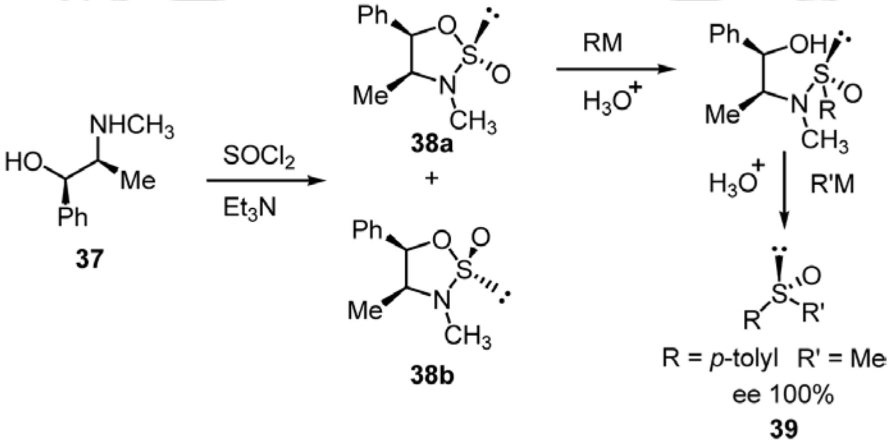
Ohta *et al*. reported the hydrolysis of methyl benzenesulfinylacetate in the presence of *Corynebacterium equi* with 97% ee (Scheme 34).[39]



Scheme 34

3.3 Nucleophilic Substitution

Wudl and Lee were the first to develop a synthesis where the starting reagent possessed two groups of different leaving ability which underwent successive nucleophilic attack from two different nucleophiles.[40] For an example, ephedrine **37** was reacted with thionyl chloride to form two separable diastereomers **38a** and **38b** (Scheme 35). The latter was reacted with an organometallic reagent to yield a chiral hydroxysulfinamide **39**, which underwent subsequent reaction with another organometallic reagent to yield ephedrine and the sulfoxide. High selectivity with yields was observed when Grignard reagents were used for the final nucleophilic displacement. Organolithium reagents as nucleophiles provide the sulfoxide in high yields with lower selectivity, due to racemization occurring during the *S-N* bond breaking step.

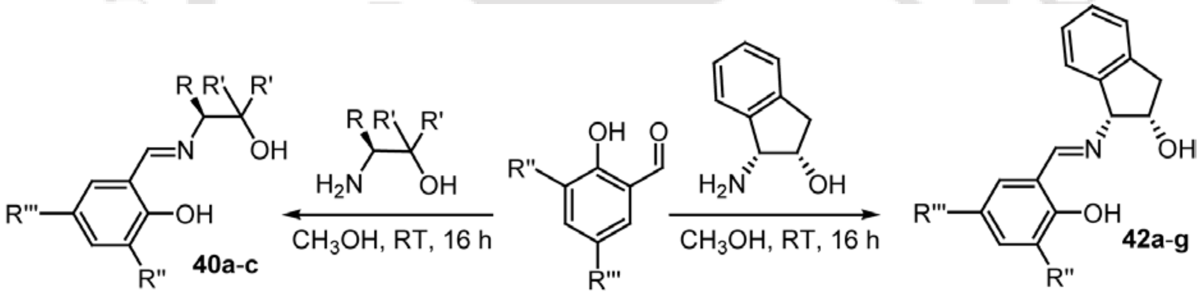


Scheme 35

3.4 Present Study

Titanium is well known for its oxidation chemistry of olefins and sulfur compounds in the presence of peroxides. The asymmetric oxidation of prochiral sulfides employing chiral titanium complexes provides a convenient route to sulfoxides because of its simplicity and atom-economy. From an environmental and economic stand point, the use of aqueous H_2O_2 as a terminal oxidant is attractive because it is readily available, cheap and generates only water as by-product.[41] Here we describe the application of chiral tridentate ligands **40-43** derived from optically active amino alcohols and salicylaldehydes with $Ti(O^iPr)_4$ for the oxidation of sulfides in the presence of 30% H_2O_2 at ambient conditions.

The preparation of the Schiff base ligands **40** and **42** was accomplished from chiral amino alcohols and substituted benzaldehydes in MeOH at ambient conditions (Scheme 36). They were reduced *in situ* with $NaBH_4$ to give the ligands **41** and **43** as colorless solids (Scheme 37).

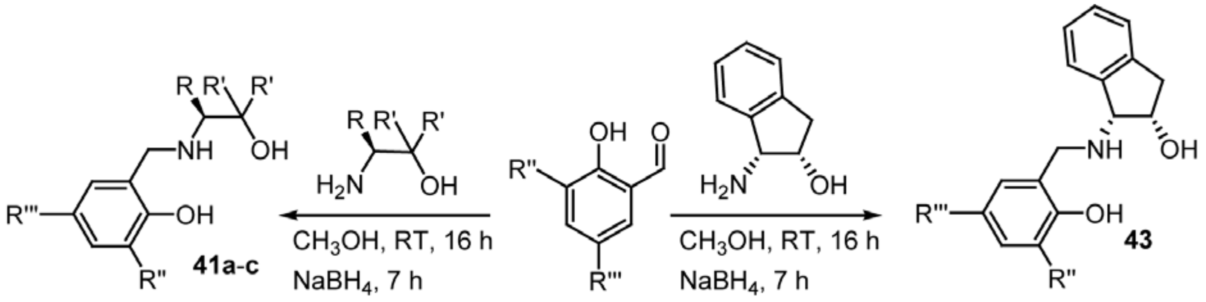


40a R = *i*-Pr, R' = H, R'' = R''' = *t*-Bu
40b R = *t*-Bu, R' = H, R'' = R''' = *t*-Bu
40c R = *i*-Pr, R' = Ph, R'' = R''' = *t*-Bu

42a R'' = *t*-Bu, R''' = H
42b R'' = *t*-Bu, R''' = Br
42c R'' = *t*-Bu, R''' = I
42d R'' = *t*-Bu, R''' = NO_2

42e R'' = *t*-Bu, R''' = *t*-Bu
42f R'' =I, R''' = I
42g R'' = H, R''' = H

Scheme 36



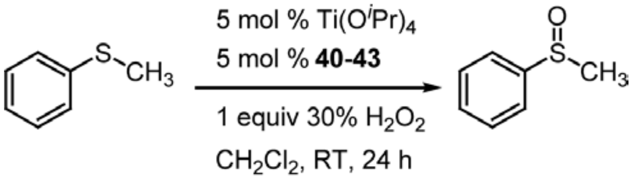
41a R = *i*-Pr, R' = H, R'' = R''' = *t*-Bu
41b R = *t*-Bu, R' = H, R'' = R''' = *t*-Bu
41c R = *i*-Pr, R' = Ph, R'' = R''' = *t*-Bu

43 R'' = *t*-Bu, R''' = *t*-Bu

Scheme 37

Titanium(IV) complexes were prepared *in situ* from Ti(O^{i}Pr)$_4$ and the ligands **40-43** in toluene by treating with water at ambient conditions.[42] Their catalytic activities were compared choosing methyl phenyl sulfide as a model substrate in the presence of 30% H_2O_2 (Table 1). The complex with **42b** was found to be superior to others affording the desried sulfoxide in 64% ee and 84% yield. In general all the solvents were effective to provide the sulfoxide in quantitative yield and CH_2Cl_2 gave the best results in terms of yield and enantioselectivity (Table 2). Lowering (0 °C) or increasing (30 °C) of the reaction temperature led the sulfoxide in <51% ee. A similar result was obtained with the addition of carboxylic acid as an additive, but the yield of the sulfoxide was improved to 99%. In the presence of the strong oxidant, *tert*-butyl hydroperoxide and phenyl iodosoacetate, no enantioselectivity was observed for sulfoxidation, despite the greater steric bulk of the *t*-butyl and phenyl moiety. In summary, the optimal conditions for this protocol consist of Ti(O^{i}Pr)$_4$ (5 mol %), **42b** (5 mol %) and 30% H_2O_2 (1 equiv) in CH_2Cl_2 at room temperature for 24 h.

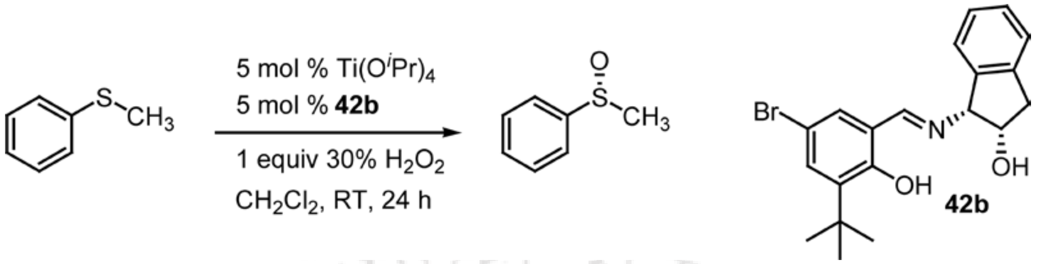
Table 1. Chiral Titanium-Catalyzed Oxidation of Methyl Phenyl Sulfide: Effect of Ligands



Entry	Ligand	Yield (%)[a,b]	ee (%)[c]	Config.[d]
1	**40a**	69	43	(*S*)
2	**40b**	70	24	(*S*)
3	**40c**	65	0	---
4	**41a**	67	23	(*S*)
5	**41b**	63	21	(*S*)
6	**41c**	61	0	---
7	**42a**	57	61	(*R*)
8	**42b**	84	64	(*R*)
9	**42c**	77	58	(*R*)
10	**42d**	75	41	(*R*)
11	**42e**	52	64	(*R*)
12	**42f**	75	27	(*R*)
13	**42g**	61	29	(*R*)
14	**43**	82	33	(*R*)

[a] To a stirred solution of methyl phenyl sulfide (0.5 mmol) in CH_2Cl_2 were added the catalyst solution, prepared from Ti(O^{i}Pr)$_4$ (5 mol %) and ligand **40-43** (5 mol %), and 30% H_2O_2 (0.5 mmol). The resultant mixture was stirred at ambient conditions for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiralcel OB-H using 4:1 *n*-hexane-*i*-PrOH. [d] Assigned by comparing the HPLC elution orders.[23a]

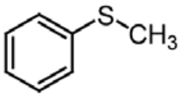
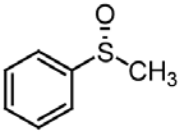
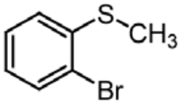
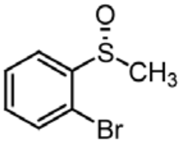
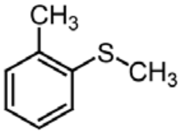
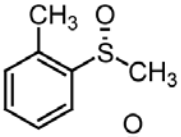
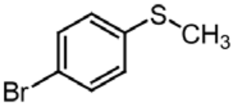
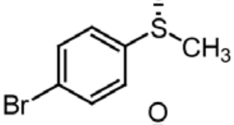
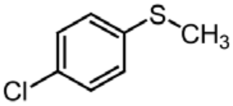
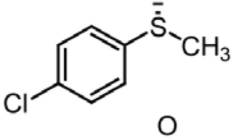
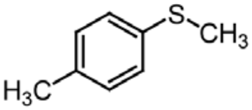
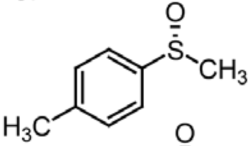
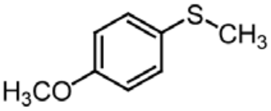
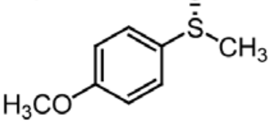
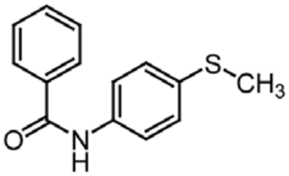
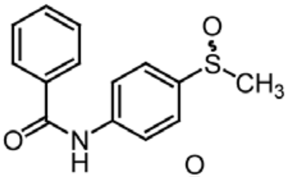
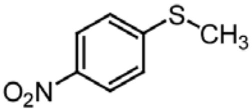
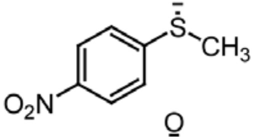
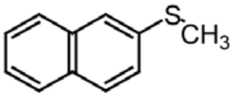
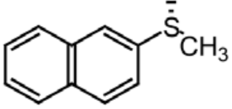
Table 2. Chiral Titanium-Catalyzed Oxidation of Methyl Phenyl Sulfide: Effect of Solvents and Temperature

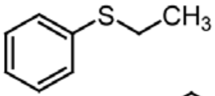
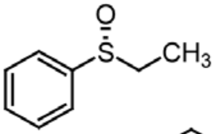
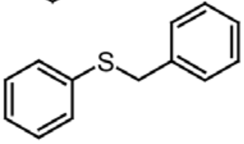
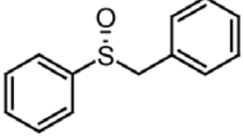


Entry	Solvent	Temp. (°C)	Additive	Yield (%)^{a,b}	ee (%)^e
1	CH_2Cl_2	RT	---	84	64
2	$CHCl_3$	RT	---	81	60
3	THF	RT	---	84	46
4	1,4-Dioxane	RT	---	79	44
5	CH_3CN	RT	---	87	53
6	Toluene	RT	---	73	63
7	CH_2Cl_2	0	---	84	51
8	CH_2Cl_2	10	---	84	51
9	CH_2Cl_2	15	---	83	57
10	CH_2Cl_2	35	---	82	60
11	CH_2Cl_2	RT	Benzoic acid	84	62
12	CH_2Cl_2	RT	4-Methylbenzoic acid	84	52
13	CH_2Cl_2	RT	Salicylic acid	99	58
14	CH_2Cl_2	RT	Pyridine-2-carboxylic acid	99	57
15	CH_2Cl_2	RT	---	93^c	3
16	CH_2Cl_2	RT	---	90^d	2

[a] To a stirred solution of methyl phenyl sulfide (0.5 mmol) in solvent (1 mL) were added the catalyst solution, prepared from Ti(O^{i}Pr)$_4$ (5 mol %) and ligand **42b** (5 mol %), and 30% H_2O_2 (0.5 mmol). The resultant mixture was stirred at ambient conditions for 24 h. [b] Isolated yield. [c] PhIO and [d] *t*-BuOOH as oxidizing agent. [e] Determined by HPLC analysis with Daicel Chiralcel OB-H using 4:1 *n*-hexane-*i*-PrOH.

Table 3. Chiral Titanium-Catalyzed Asymmetric Oxidation of Sulfides with 30% H_2O_2

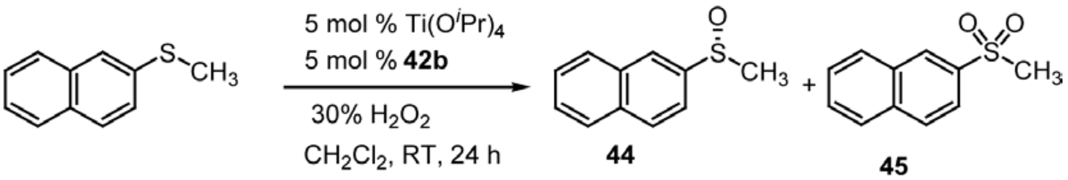
Entry	Substrate	Product	Yield (%)^{a,b}	ee (%)^{c}	config.^{j}
1			84	64	(*R*)
2			90	37	(*R*)
3			89	34^{d}	(*R*)
4			91	53	(*R*)
5			90	54^{e}	(*R*)
6			87	66^{e}	(*R*)
7			86	60	(*R*)
8			79	54^{f}	n.d.
9			75	50^{g}	(*R*)
10			92	70	(*R*)

11			91	54[h]	(*R*)
12			87	61[i]	(*R*)

[a] To a stirred solution of the substrate (0.5 mmol) in CH_2Cl_2 were added catalyst solution, prepared from $Ti(O^iPr)_4$ (5 mol %) and **42b** (5 mol %), and 30% H_2O_2 (0.5 mmol), and the resultant mixture was stirred at ambient conditions for 24 h. [b] Isolated yield. Determined by HPLC analyses: Daicel Chiralcel OB-H using [c] 4:1 *n*-hexane-*i*-PrOH, [d] 3:2 *n*-hexane-*i*-PrOH, [e] 7:3 *n*-hexane-*i*-PrOH and [f] 1:1 *n*-hexane-*i*-PrOH; [g] Daicel Chiralcel OJ using 7:3 *n*-hexane-*i*-PrOH and Daicel Chiralcel OD using [h] 9:1 *n*-hexane-*i*-PrOH and [i] 19:1 *n*-hexane-*i*-PrOH. [j] See experimental. n.d. - not determined .

With the optimized conditions in hand, the scope of the protocol for other sulfides was explored (Table 3). Methyl phenyl sulfides having 2-Br, 2-CH_3, 4-Br, 4-Cl, 4-CH_3, 4-OCH_3, 4-$NHCOC_6H_5$ and 4-NO_2 substituents proceeded oxidation to afford the corresponding sulfoxides with 66% ee and 91% yield. The substituent present in *ortho* position provided the sulfoxide with poor enantioselectivity (Table 3, entry 2-3) than the substituent at *para* position (Table 3, entry 4 and 6). Methyl 2-naphthyl sulfide underwent oxidation in 70% ee and 92% yield, where as ethyl phenyl sulfide and benzyl phenyl sulfide proceeded oxidation to give the respective sulfoxide with up to 61% ee and 91% yield. The reactions were selective and no sulfone formation was observed.

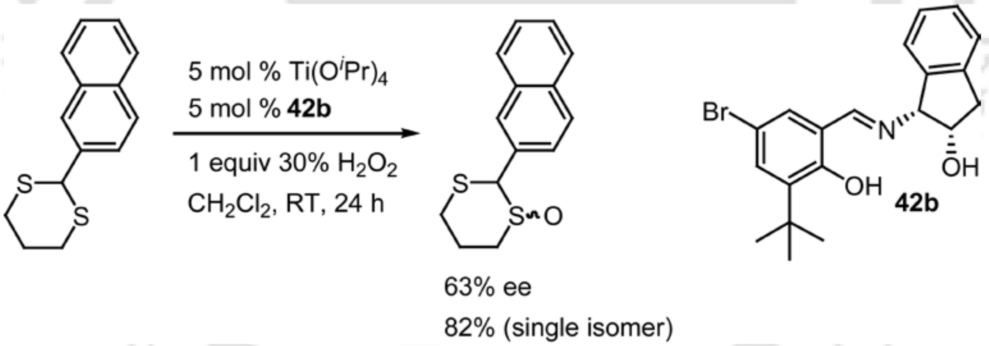
Usually, the kinetic resolution of sulfoxide is a complementary reaction occurring in case of sulfide oxidation, therefore, the oxidation of methyl 2-naphthyl sulfide was further studied with excess of 30% H_2O_2 (1.2, 1.5 and 2 equiv). The reactions afforded the sulfoxide along with sulfone as by-product. However, the ee of the sulfoxide was remain same as 70% with irrespective of the quantity of the sulfone formed (Scheme 38). These results clearly suggest that under these conditions no kinetic resolution occurred.



H$_2$O$_2$ equiv	**44** Yield (%)	**45** Yield (%)	ee %
1	92	0	70
1.2	82	17	70
1.5	53	46	70
1.7	34	65	70

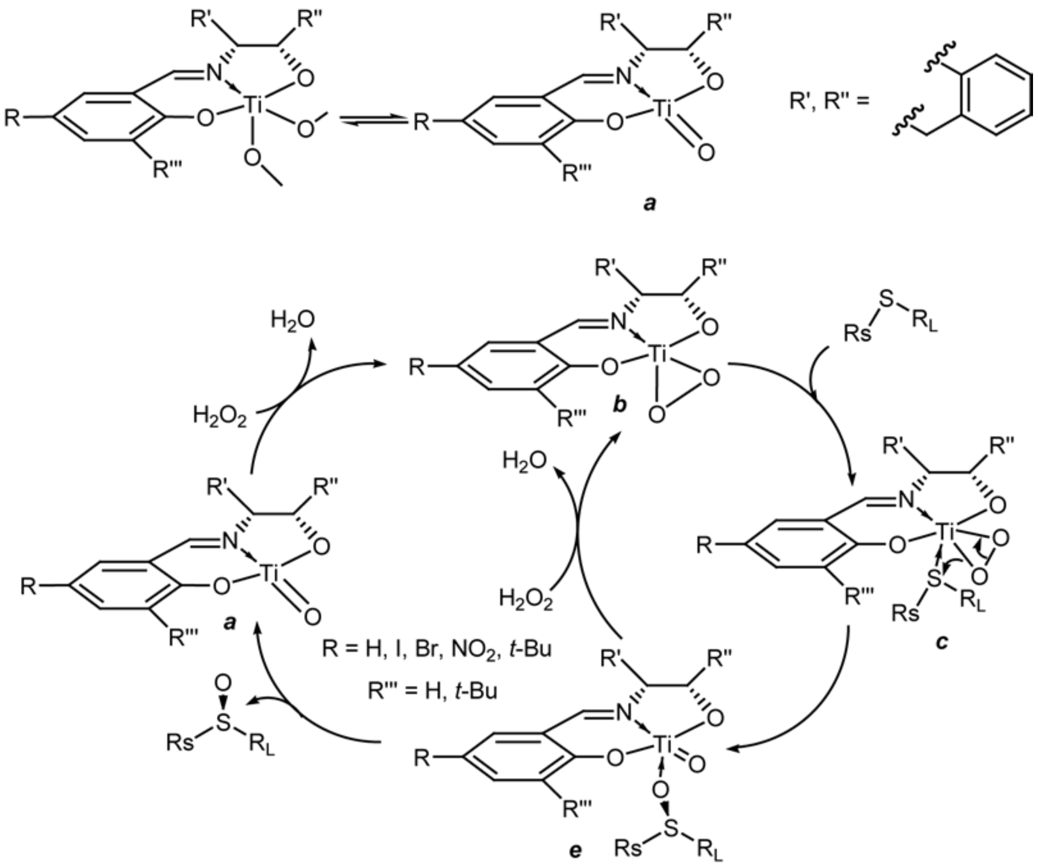
Scheme 38

Finally, the oxidation of cyclic thioacetal, 2-(naphthalene-3-yl)-1,3-dithiane was performed (Scheme 39). The reaction occurred diastereoselectively to afford a single isomer with 63% ee and 82% yield. These results suggest that the protocol is general and selective for the oxidation of sulfides.

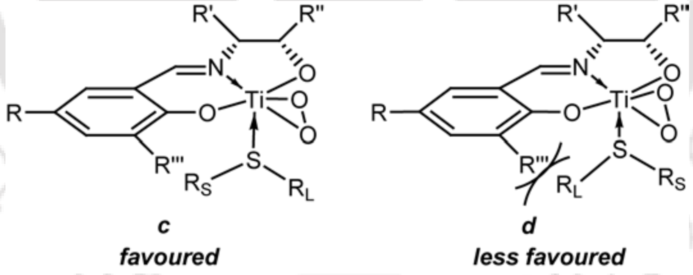


Scheme 39

The proposed catalytic cycle is shown in Scheme 40. Titanium(IV) complex ***a*** may undergo reaction with 30% H_2O_2 to give the peroxo complex ***b***. The latter with substrate may give intermediate ***c***. The formation of the intermediate ***c*** could be favored compared to ***d*** to minimize the steric repulsion (Scheme 41). The oxidation of the coordinated sulfide in ***c*** by oxygen transfer can give the intermediate ***e*** that could complete the catalytic cycle.



Scheme 40



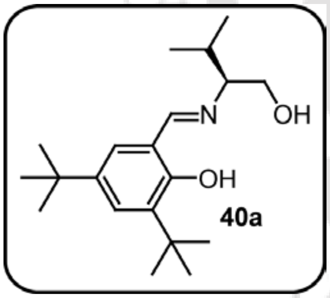
Scheme 41

In summary, the synthesis and application of a series chiral tridentate ligands **40-43** derived from optically active α-amino alcohols studied with $Ti(O^iPr)_4$ for the oxidation of sulfides to sulfoxides in the presence of 30% H_2O_2 at ambient conditions. The Schiff bases are found to be superior to the reduced amines affording the sulfoxides in high ee.

Experimental section

General. All sulfides were prepared by alkylation of corresponding thiols according to the literature.[43] Ti(O^{i}Pr)$_4$ (98%) was procured from Acros Organics. Solvents were purchased from Rankem and purified prior to use by standard procedure. Column chromatography was carried out with 60-120 mesh silicagel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using CDCl$_3$ and DMSO-d$_6$ as solvent and Me$_4$Si as internal standard. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained from PerkinElmer spectrum one spectrometer. HPLC analysis was carried out using Waters-2489 instrument. Elemental analysis was carried out using PerkinElmer-2400 CHNS analyzer.

General procedure for preparation of ligands 40a-c and 42a-g. Aldehyde (0.25 mmol) and chiral amino alcohol (0.25 mmol) were stirred for 16 h in MeOH (1 mL) at ambient temperature. The solvent was evaporated and the residue was purified on silica gel column chromatography using hexane and EtOAc as eluent.



40a

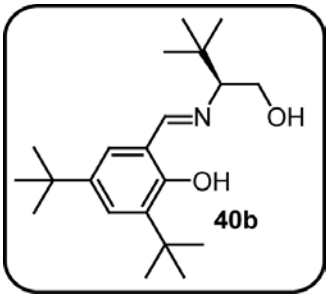
2-(((*S*)-1-Hydroxy-3-methylbutan-2-ylimino)-methyl)-4,6-di-*tert*-butylphenol 40a.[44a] 3,5-Di-*tert*-butylsalicylaldehyde (59 mg, 0.25 mmol) and (*S*)-2-amino-3-methylbutanol (26 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 97% (77 mg) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.35 (s, 1H), 7.39 (d, *J* = 3.6 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 3.84-3.72 (m, 2H), 3.03-2.99 (m, 1H), 1.95-1.90 (m, 1H), 1.43 (s, 9H), 1.29 (s, 9H), 0.94 (t, *J* = 6 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.1, 158.4, 140.3, 136.9, 127.3, 126.3, 117.9, 77.9, 64.8, 35.2, 34.3, 31.7, 30.2, 29.6, 20, 18.9.

FT-IR (neat): 3302, 2962, 2871, 1629, 1467, 1439, 1391, 1361, 1347, 1276, 1251, 1233, 1202, 1150, 1131, 1080, 1028, 976, 901, 877, 851, 825, 774, 696, 526 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.21; H, 10.43; N, 4.35.



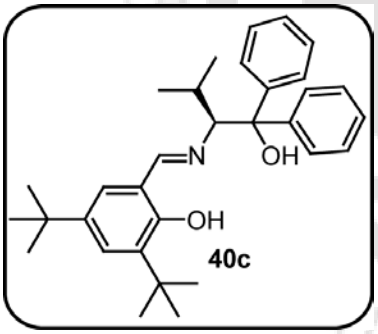
2-(((*S*)-1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl)-4,6-di-*tert*-butylphenol 40b.[44a] 3,5-Di-*tert*-butylsalicylaldehyde (59 mg, 0.25 mmol) and (*S*)-2-amino-3,3-dimethylbutanol (29 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 97% (81 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.39 (d, *J* = 2 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 3.93-3.89 (dd, *J* = 2.8, 11.2 Hz, 1H), 3.73 (t, *J* = 9.2 Hz, 1H) 2.93-2.89 (dd, *J* = 3.2, 9.6 Hz, 1H), 1.43 (s, 9H), 1.29 (s, 9H), 0.96 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 158.4, 140.3, 136.9, 127.2, 126.3, 117.9, 81.5, 62.6, 35.2, 34.3, 33.3, 31.7, 29.7, 27.3.

FT-IR (neat): 3409, 2958, 2870, 1631, 1469, 1441, 1393, 1362, 1327, 1273, 1251, 1203, 1172, 1132, 1100, 1046, 1020, 1001, 919, 896, 826, 771, 731, 700, 645 cm^{-1}.

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.60; H, 10.60; N, 4.33.



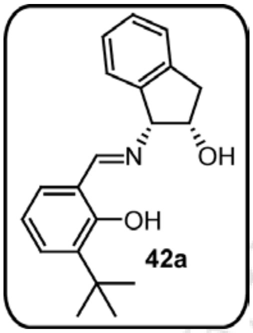
2-(((*S*)-1-Hydroxy-3-methyl-1, 1-diphenylbutan-2-ylimino)-methyl)-4, 6-di-*tert*-butylphenol 40c: 3,5-Di-*tert*-butyl salicylaldehyde (59 mg, 0.25 mmol) and (*S*)-2-amino-3-methyl-1,1-diphenylbutanol (64 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow gummy liquid in 95% (112 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.53 (dd, *J* = 1.2, 8 Hz, 2H), 7.18-7.12 (m, 3H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 4.02 (d, *J* = 1.6 Hz, 1H), 2.9 (br s, 1H), 1.34 (s, 9H), 1.21 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 158.1, 146.8, 144.7, 140.3, 136.9, 128.43, 128.41, 127.6, 126.8, 126.5, 126.2, 125.9, 117.9, 80.6, 80.3, 35.2, 34.3, 31.7, 29.6, 29.2, 29.7, 18.0.

FT-IR (neat): 3585, 3059, 2959, 2871, 1727, 1626, 1598, 1469, 448, 1391, 1361, 1325, 1272, 1249, 1203, 1172, 1137, 1064, 1015, 906, 878, 754, 702, 667, 636 cm^{-1}.

Anal. Calcd for $C_{32}H_{41}NO_2$: C 81.48, H 8.76, N 2.97, O 6.78. Found: C 81.45, H 8.78, N 2.96, O 6.81.



42a

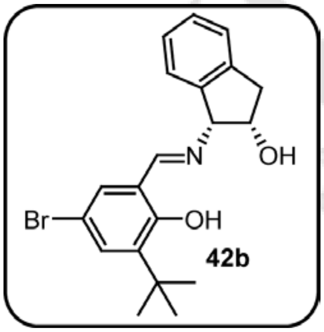
(1*R*,2*S*)-1-(3-*tert*-Butyl-2-hydroxybenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42a. 3-*tert*-Butylsalicylaldehyde (45 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 97% (75 mg) yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.53 (s, 1H), 7.29-7.10 (m, 6H), 6.78, (dt, *J* = 1.2, 7.6 Hz, 1H), 4.73 (d, *J* = 5.2 Hz, 1H), 4.64-4.60 (q, *J* = 5.2, 10.8 Hz, 1H), 3.21-3.15 (dd, *J* = 6, 15.6 Hz, 1H), 3.08-3.03 (dd, *J* = 4.8, 15.6 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.5, 160.7, 140.94, 140.87, 137.6, 130.4, 130.0, 128.5, 127.0, 125.5, 124.9, 118.7, 118.2, 75.4, 75.2, 39.5, 34.9, 29.4.

FT-IR (neat): 3419, 2955, 2917, 2873, 1626, 1458, 1434, 1389, 1307, 1265, 1199, 1144, 1088, 1053, 1017, 797, 750 cm^{-1}.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.65; H, 7.51; N, 4.52.



42b

(1*R*,2*S*)-1-(3-*tert*-Butyl-5-bromo-2-hydroxybenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42b. 3,5-Di-*tert*-butyl-5-bromosalicylaldehyde (64 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 93% (90 mg) yield.

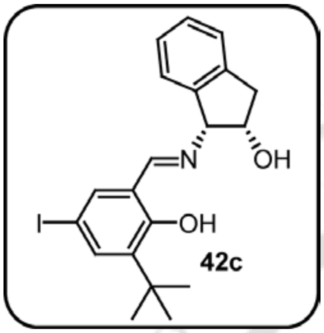
Mp: 96-97 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.50 (s, 1H), 7.41 (d, *J* = 2 Hz, 1H), 7.32-7.16 (m, 5H), 4.82 (d, *J* = 5.2 Hz, 1H), 4.72-4.68 (q, *J* = 4.8, 10.4 Hz, 1H), 3.28-3.23 (dd, *J* = 6, 16.4 Hz, 1H), 3.14-3.09 (dd, *J* = 5.2, 16 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 159.8 140.9, 140.5, 140.4, 133.0, 132.2, 128.8, 127.2, 125.7, 125.1, 120.0, 110.1, 75.4, 75.3, 39.7, 35.2, 29.2.

FT-IR (KBr): 3414, 2955, 2917, 2868, 1628, 1459, 1429, 1392, 1301, 1270, 1200, 1173, 1089, 1054, 1021, 977, 952, 869, 771, 754, 737, 706, 632, 572 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}NO_2Br$: C, 61.86; H, 5.71; N, 3.61. Found: C, 61.87; H, 5.70; N, 3.57.



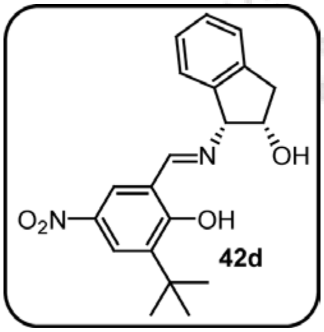
(1*R*,2*S*)-1-(3-*tert*-Butyl-2-hydroxy-5-iodobenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42c. 3-*tert*-Butyl-5-iodosalicylaldehyde (76 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 95% (103 mg) yield.

^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.54 (s, 1H), 7.49 (s, 1H), 7.32-7.17(m, 4H), 4.82 (d, J = 4.8 Hz, 1H), 4.72-4.69 (m, 1H), 3.29-3.24 (dd, *J* = 5.6, 16.4 Hz, 1H), 3.14-3.09 (dd, *J* = 4.8, 16 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 160.7, 140.8, 140.7, 140.4, 138.4, 138.3, 128.7, 127.1, 125.6, 124.9, 120.7, 79.6, 75.1, 75.0, 39.5, 35.0, 29.2.

FT-IR (neat): 3429, 2955, 2923, 2857, 1717, 1626, 1459, 1431, 1297, 1270, 1172, 1080, 1050, 1019, 869 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}INO_2$: C, 55.18; H, 5.09; N, 3.22. Found: C, 55.16; H, 5.11; N, 3.25.



(1*R*,2*S*)-1-(3-*tert*-Butyl-2-hydroxy-5-nitrobenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42d. 3-*tert*-Butyl-5-nitrosalicylaldehyde (56 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 91% (81 mg) yield.

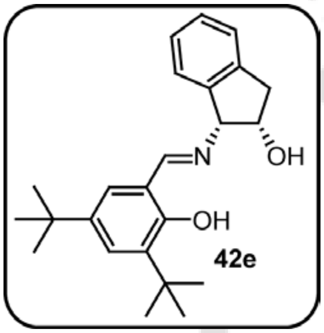
Mp: 146-147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.19 (d, *J* = 2.8 Hz, 1H), 8.14 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 4 Hz, 2H), 7.27-7.19 (m, 2H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.76-4.71 (q, *J* = 5.2, 10.8 Hz, 1H), 3.29-3.24 (dd, *J* = 6, 16 Hz, 1H), 3.12-3.07 (dd, *J* = 4.8, 16 Hz, 1H), 1.4 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 141.2, 141.0, 138.8, 137.2, 129.4, 128.4, 128.2, 127.5, 125.9, 125.6, 125.1, 115.9, 74.6, 72.1, 39.4, 35.4, 29.0.

FT-IR (KBr): 3418, 2955, 2912, 2868, 1641, 1601, 1556, 1483, 1434, 1387, 1320, 1266, 1221, 1175, 1107, 1021, 922, 748, 719, 533 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.75; H, 6.23; N, 7.92.



42e

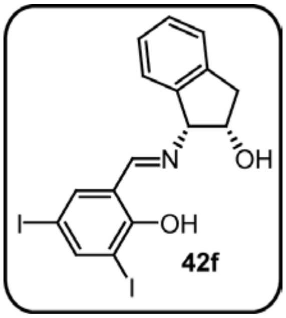
(1*R*,2*S*)-1-(3,5-Di-*tert*-butyl-2-hydroxybenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42e.[44b] 3,5-Di-*tert*-butylsalicylaldehyde (59 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 97% (89 mg) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.41 (d, *J* = 2 Hz, 1H), 7.31-7.16 (m, 5H), 4.79 (d, *J* = 5.2 Hz, 1H), 4.69-4.65 (q, *J* = 5.6, 10.8 Hz, 1H), 3.26-3.21 (dd, *J* = 5.6, 16 Hz, 1H), 3.14-3.09 (dd, *J* = 5.2, 16 Hz, 1H), 1.4 (s, 9H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 158.2, 141.1, 141.0, 140.7, 137.1, 128.7, 127.9, 127.2, 126.7, 125.7, 125.1, 118.0, 75.9, 75.4, 39.9, 35.2, 34.4, 31.7, 29.6.

FT-IR (neat): 3417, 2957, 2923, 2862, 1726, 1625, 1596, 1463, 1439, 1392, 1361, 1272, 1250, 1202, 1173, 1082, 1017, 879, 755, 739 cm^{-1}.

Anal. Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.85; N, 3.83. Found: C, 78.82; H, 8.83; N 3.87.



42f

(1*R*,2*S*)-1-(2-Hydroxy- 3,5-diiodobenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42f. 3,5-Di-iodosalicylaldehyde (94 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 95% (120 mg) yield.

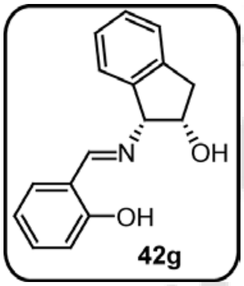
Mp: 209-210 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.20 (s, 1H), 8.01 (d, *J* = 2 Hz, 1H), 7.49 (d, *J* = 2 Hz, 1H) 7.29-7.14 (m, 4H), 4.87 (d, *J* = 5.6 Hz, 1H), 4.74-4.70 (q, *J* = 6, 12 Hz, 1H), 3.29-3.20 (dd, *J* = 6, 16 Hz, 1H), 3.09-3.04 (dd, *J* = 6, 16.4 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.3, 163.5, 149.07, 140.9, 140.6, 138.6, 128.6, 126.7, 125.1, 124.6, 117.4, 92.8, 74.7, 73.4, 70.2 38.5.

FT-IR (KBr): 3383, 3038, 2942, 2846, 1638, 1577, 1500, 1481, 1401, 114, 1220, 1129, 1100, 1050, 1016, 867, 751 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}I_2NO_2$: C, 38.05; H, 2.59; N, 2.77. Found: C, 38.02; H, 2.60; N, 2.79.



42g

(1*R*,2*S*)-1-(2-Hydroxybenzylideneamino)-2,3-dihydro-1*H*-inden-2-ol 42g. Salicylaldehyde (31 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 90% (57 mg) yield.

Mp: 114-115 °C.

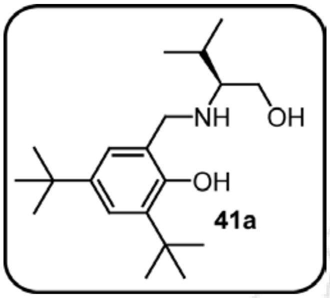
^{1}H NMR (400 MHz, CDCl$_3$): δ 8.61 (s, 1H), 7.36-7.15 (m, 6H), 6.97-6.90 (m, 2H), 4.81 (d, *J* = 5.6 Hz, 1H), 4.71-4.68 (q, *J* = 5.2, 10.8 Hz, 1H), 3.28-3.23 (dd, *J* = 6, 15.6 Hz, 1H), 3.13-3.08 (dd, *J* = 5.2, 16 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.9, 161.4, 140.88, 140.84, 133.0, 132.0, 128.8, 127.2, 125.6, 125.0, 118.9, 118.8, 117.3, 75.6, 75.4, 39.7.

FT-IR (KBr): 3417, 3146, 3017, 2955, 2851, 1638, 1514, 1492, 1383, 1336, 1219, 1196, 1151, 1092, 1050, 1016, 989, 856, 761, 744, 731, 567, 507, 480 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.89; H, 5.96; N, 5.55.

General procedure for preparation of ligands 41a-c and 43. To a stirred solution of aldehyde (0.25 mmol) and chiral amino alcohol (0.25 mmol) in MeOH (1mL) for 16 h at ambient temperature was added $NaBH_4$ (0.5 mmol). The reaction mixture was further stirred for 7 h at ambient conditions and quenched with 1N HCl. The solvent was evaporated and the residue was extracted with ethyl acetate (2 x 10 mL). The combined organic solution was washed with saturated $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was further purified on silica gel column chromatography using hexane and EtOAc as eluent.



41a

2-(((*S*)-1-Hydroxy-3-methylbutan-2-yl-amino)methyl)-4,6-di-*tert*-butylphenol 41a.[44c] 3,5-Di-*tert*-butyl salicylaldehyde (59 mg, 0.25 mmol) and (*S*)-2-amino-3-methylbutanol (26 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 93% (75 mg) yield.

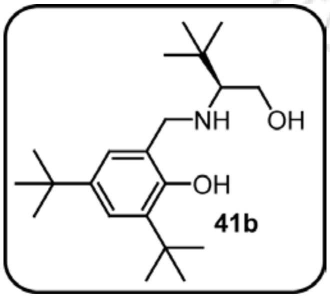
Mp: 75-76 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 2.4 Hz, 1H), 6.86 (d, *J* = 2 Hz, 1H), 3.97 (d, *J* = 1.2 Hz, 1H), 3.82-3.78 (dd, *J* = 3.6, 11.2 Hz, 1H), 3.66-3.62 (dd, *J* = 6, 10.8 Hz, 1H), 2.5-2.46 (m, 2H), 1.96-1.91 (m, 1H), 1.41 (s, 9H), 1.27 (s, 9H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 140.8, 136.2, 123.3, 123.2, 122.8, 64.2, 61.5, 51.9, 35.0, 34.3, 31.9, 29.8, 28.9, 19.3, 19.1.

FT-IR (KBr): 3365, 3434, 3302, 2962, 2909, 2873, 1602, 1479, 1440, 1402, 1359, 1296, 1256, 1233, 1116, 1124, 1089, 1073, 1052, 1019, 996, 971, 928, 886, 824, 798, 774, 757, 723, 679, 645 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.70; H, 10.99; N, 4.35.



41b

2-(((*S*)-1-Hydroxy-3-dimethylbutan-2-yl-amino)methyl)-4,6-di-*tert*-butylphenol 41b.[44c] 3,5-Di-*tert*-butyl salicylaldehyde (59 mg, 0.25 mmol) and (*S*)-2-amino-3,3-dimethylbutanol (29 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 95% (80 mg) yield.

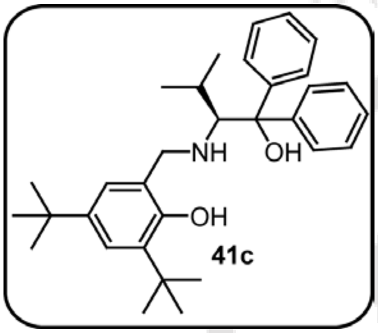
Mp: 90-91 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.23 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 4.11-3.93 (m, 3H), 3.73-3.70 (m, 1H), 2.37-2.33 (m, 1H), 1.42 (s, 9H), 1.28 (s, 9H), 0.99 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.7, 140.7, 136.2, 123.4, 123.2, 123.1, 67.6, 61.6, 53.9, 35.1, 34.4, 34.3, 31.9, 29.9, 27.7.

FT-IR (KBr): 3308, 2962, 2870, 1606, 1480, 1445, 1392, 1361, 1302, 1252, 1236, 1202, 1164, 1115, 1078, 1023, 932, 874, 801, 759, 723, 465 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.17. Found: C, 75.14; H, 11.13; N, 4.20.



41c

2-(((*S*)-1-Hydroxy-3-methyl-1, 1-diphenylbutan-2-ylamino)-methyl)-4, 6-di-*tert*-butylphenol 41c. 3,5-Di-*tert*-butylsalicylaldehyde (59 mg, 0.25 mmol) and (*S*)-2-amino-3-methyl-1,1-diphenylbutanol (64 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 94% (111 mg) yield.

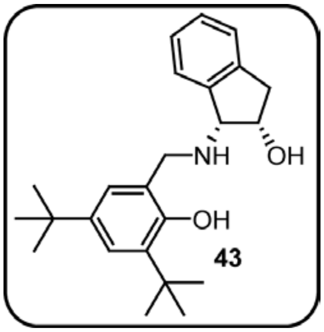
Mp: 156-157 °C

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57-7.51 (m, 4H), 7.35-7.29 (m, 4H), 7.24-7.21 (m, 2H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.54 (d, *J* = 2.8 Hz), 3.67 (d, *J* = 12 Hz, 1H), 3.51 (d, *J* = 1.8 Hz, 1H), 3.21 (d, *J* = 12.8 Hz, 1H), 2.47 (br s, 1H), 2.10-2.04 (m, 1H), 1.34 (s, 9H), 1.23(s, 9H), 1.12(d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 154.4, 146.1, 145.6, 140.6, 135.9, 128.7, 128.6, 127.2, 125.9, 123.6, 123.3, 123.3, 123.2, 82.3, 68.4, 55.3, 35.1, 34.2, 31.8, 29.7, 29.2, 24.2, 17.3.

FT-IR (KBr): 3589, 3436, 3313, 3061, 2961, 2869, 1602, 1477, 1446, 1390, 1362, 1256, 1235, 1203, 1165, 1125, 1077, 1065, 1033, 970, 606, 881, 767, 736, 705, 636 cm^{-1}.

Anal. Calcd for $C_{32}H_{43}NO_2$: C 81.14, H 9.15, N 2.96, O 6.76. Found: C 81.10, H 9.17, N 2.96, O 6.77.



43

(1*R*,2*S*)-1-(3,5-Di-*tert*-butyl-2-hydroxybenzylamino)-2,3-dihydro-1*H*-inden-2-ol 43. 3,5-Di-*tert*-butylsalicylaldehyde (59 mg, 0.25 mmol) and (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (37 mg, 0.25 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 93% (85 mg) yield.

Mp: 122-123 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 5.6 Hz, 1H), 7.25-7.23 (m, 4H), 6.92 (d, *J* = 2.4 Hz, 1H), 4.71 (q, *J* = 3.2, 4.4 Hz, 1H), 4.28 (d, *J* = 13.6 Hz, 1H), 4.15 (d, *J* = 4.8 Hz, 1H), 4.08 (d, *J* = 13.6 Hz, 1H), 3.14-3.08 (dd, *J* = 4.4, 16.4 Hz, 1H), 2.95 (d, *J* = 16.8 Hz, 1H), 1.43 (s, 9H), 1.28 (s, 9H).

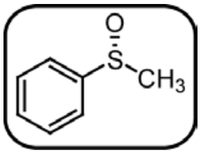
^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 141.9, 140.8, 139.8, 136.2, 128.2, 127.3, 125.6, 124.9, 123.7, 123.3, 122.2, 71.9, 64.9, 51.9, 40.3, 35.1, 34.4, 31.9, 29.9.

FT-IR (KBr): 3405, 2956, 2868, 1631, 1479, 1459, 1390, 1361, 1235, 1202, 1163, 1116, 1019, 878, 798, 742, 667, 590 cm^{-1}.

Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.41; H, 9.04; N, 3.82.

General procedure for prepartion of titanium(IV) complexes. To a stirred solution of $Ti(O^iPr)_4$ (0.25 mmol) and ligand **1-4** (0.25 mmol) in toluene (1 mL) for 3 h at ambient conditions was added water (0.25 mmol). The resultant mixture, after stirring for 3 h, was used for the catalysis of the oxidation reaction.

General procedure for asymmetric sulfoxidation. To a stirred solution of the sulfide (0.5 mmol) in CH_2Cl_2 (1 mL), the above prepared solution of the titanium(IV) complex (5 mol %, 100 μL) and 30% H_2O_2 (0.5 mmol) were added. The resultant mixture was stirred for 24 h at ambient conditions and treated with Na_2SO_3. After 0.5 h, the mixture was extracted with ethyl acetate (2 x 5 mL) and the combined organic solution was washed with brine (3 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and EtOAc as eluent.



(*R*)-Methyl phenyl sulfoxide (Table 3, entry 1).[23a] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and methyl phenyl sulfide (62 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 84% (59 mg) yield.

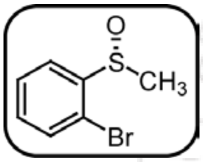
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (m, 2H), 7.53-7.48 (m, 3H), 2.71 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 131.1, 129.4, 123.5, 43.9.

FT-IR (neat): 3058, 2999, 2961, 2924, 1721, 1477, 1444, 1413, 1304, 1261, 1150, 1089, 1071, 1035, 958, 798, 748, 691, 539, 502 cm^{-1}.

Anal. Calcd for C_7H_8OS: C, 59.97; H, 5.75; S, 22.87. Found: C, 59.92; H, 5.79; S, 22.82.

HPLC: Chiralcel OB-H column, 4:1 n-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.8 mL/min, retention time: 15.08 min, 24.82 min; 64% ee.[23a]



(*R*)-2-Bromophenyl methyl sulfoxide (Table 3, entry 2).[45a] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and 2-bromophenyl methyl sulfide (102 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 90% (99 mg) yield.

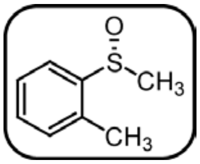
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.58-7.53 (m, 2H), 7.38-7.33 (dt, *J* = 8, 1.6 Hz, 1H), 2.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 132.9, 132.3, 128.7, 125.6, 118.3, 41.8.

FT-IR (neat): 3059, 2997, 2961, 2915, 1722, 1566, 1541, 1447, 1415, 1293, 1260, 1244, 1125, 1093, 1057, 1014, 958, 757, 713, 672, 517, 482 cm^{-1}.

Anal. Calcd for C_7H_7BrOS: C, 38.37; H, 3.22; S, 14.63. Found: C, 38.33; H, 3.24; S, 14.61.

HPLC: Chiralcel OB-H column, 4:1 n-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 17.75 min, 28.94 min; 37% ee.[45b]



(*R*)-Methyl 2-methylphenyl sulfoxide (Table 3, entry 3). Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and methyl 2-methylphenyl sulfide (69 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 89% (69 mg) yield.

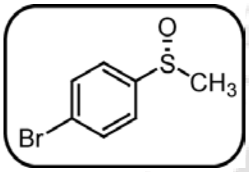
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.93 (d, *J* = 8 Hz, 1H), 7.44-7.39 (t, *J* = 7.2 Hz, 1H), 7.38-7.34 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 2.65 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 143.7, 134, 130.8, 130.7, 127.5, 123, 42, 18.1.

FT-IR (neat) 3052, 2958, 2926, 2860, 1724, 1541, 1471, 1456, 1412, 1384, 1290, 1196, 1134, 1067, 1032, 958, 757, 78, 685, 554, 459 cm^{-1}.

Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54; S, 20.79. Found: C, 62.27; H, 6.53; S, 20.80.

HPLC: Chiralcel OB-H column, 3:2 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 11.18 min, 26.02 min; 34% ee.[45c]



(*R*)-4-Bromophenyl methyl sulfoxide (Table 3, entry 4).[45d] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and 4-bromophenyl methyl sulfide (102 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 91% (100 mg) yield.

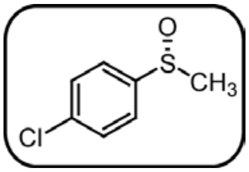
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 2.70 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 144.8, 132.6, 129, 125.2, 43.9.

FT-IR (neat): 3079, 3004, 2960, 2915, 1721, 1573, 1471, 1416, 1386, 1311, 1152, 1085, 1066, 1047, 1007, 958, 817, 773, 723, 511 cm^{-1}.

Anal. Calcd for C_7H_7BrOS: C, 38.37; H, 3.22; S, 14.63. Found: C, 38.35; H, 3.25; S, 14.59.

HPLC: Chiralcel OB-H column, 4:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 18.81 min, 29.07 min; 53% ee.[20]



(*R*)-4-Chlorophenyl Methyl Sulfoxide (Table 3, entry 5).[45d] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and 4-chlorophenyl methyl sulfide (79 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 90% (79 mg) yield.

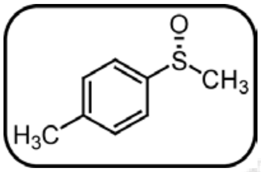
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.8 Hz 2H), 2.69 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 144.1, 137.3, 129.7, 125.1, 43.9.

FT-IR (neat): 3082, 2959, 2927, 2858, 1723, 1575, 1476, 1415, 1391, 1291, 1275, 1123, 1090, 1040, 1011, 958, 823, 741, 681, 533, 502 cm^{-1}.

Anal. Calcd for C_7H_7ClOS: C, 48.14; H, 4.04; S, 18.36. Found: C, 48.10; H, 4.06; S, 18.39.

HPLC: Chiralcel OB-H column, 7:3 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 17.07 min, 28.18 min; 54% ee.[23a]



(*R*)-Methyl 4-Methylphenyl Sulfoxide (Table 3, entry 6).[45d] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and methyl 4-methylphenyl sulfide (69 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 87% (67 mg) yield.

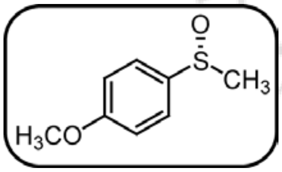
^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 2.68 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 141.6, 130.1, 123.6, 43.9, 21.5.

FT-IR (neat): 3054, 2959, 2926, 2872, 1725, 1598, 1494, 1458, 1411, 1289, 1148, 1122, 1088, 1073, 1039, 1015, 957, 811, 759, 746, 683, 534, 506, 465 cm^{-1}.

Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54; S, 20.79. Found: C, 62.34; H, 6.55; S, 20.78.

HPLC: Chiralcel OB-H column, 7:3 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 12.24 min, 27.61 min; 66% ee.[23a]



(*R*)-4-Methoxyphenyl methyl sulfoxide (Table 3, entry 7).[45d] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and 4-methoxyphenyl methyl sulfide (77 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 86% (73 mg) yield.

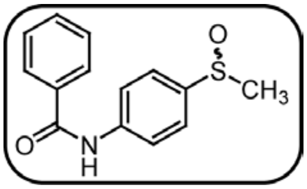
^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz 2H), 3.83 (s, 3H), 2.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 136.4, 125.6, 114.9, 55.6, 43.9.

FT-IR (neat): 3005, 2963, 2928, 2840, 1595, 1497, 1463, 1409, 1303, 1257, 1175, 1144, 1090, 1025, 957, 831, 797, 529 cm^{-1}.

Anal. Calcd for $C_8H_{10}O_2S$): C, 56.44; H, 5.92; S, 18.84. Found: C, 56.48; H, 5.90; S, 18.80.

HPLC: Chiralcel OB-H column, 4:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 12.56 min, 23.46 min; 60% ee.[23a]



4-Benzamidophenyl methyl sulfoxide (Table 3, entry 8). Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and 4-benzamidophenyl methyl sulfide (122 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 75% (98 mg) yield.

Mp: 177-178 °C.

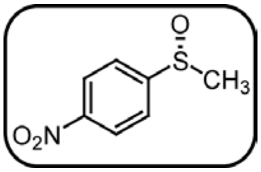
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.78 (s, 1H), 7.82-7.76 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.36-7.34 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 2.53 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 164.8, 140.5, 138.5, 133.5, 130.3, 126.9, 126.5, 122.8, 119.4, 42.3.

FT-IR (KBr): 3326, 3291, 3057, 2959, 2928, 2859, 1729, 1652, 1590, 1578, 1517, 1465, 1396, 1313, 1292, 1265, 1121, 1074, 1038, 1014, 973, 954, 824, 795, 721, 690, 636, 524, 466 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.88; H, 5.02; N ,5.42; S, 12.35.

HPLC: Chiralcel OB-H column, 1:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 13.17 min, 17.73 min; 54% ee.



(*R*)-Methyl 4-nitrophenyl sulfoxide (Table 3, entry 9).[45e] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and methyl 4-nitrophenyl sulfide (85 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as pale yellow oil in 79% (73 mg) yield.

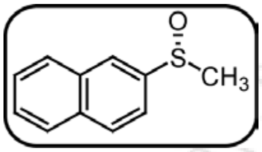
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 9.2 Hz 2H), 2.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 149.5, 124.8, 124.5, 43.9.

FT-IR (neat): 3354, 3329, 3026, 3005, 2960, 2929, 2859, 1729, 1686, 1539, 1533, 1505, 1464, 1399, 1369, 1312, 1283, 1261, 1144, 1089, 1073, 1041, 1017, 971, 824, 779, 670, 590, 538, 522 cm^{-1}.

Anal. Calcd for $C_7H_7NO_3S$: C, 45.40; H, 3.81; N, 7.56; S, 17.31. Found: C, 45.45; H, 3.78; N, 7.58; S, 17.29.

HPLC: Chiralcel OJ column, 7:3 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 30.71 min, 38.09 min; 50% ee.[20]



(*R*)-Methyl 2-naphthyl sulfoxide (Table 3, entry 10).[45d] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and methyl 2-naphthyl sulfide (87 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow solid in 92% (87 mg) yield.

Mp: 102-103 °C.

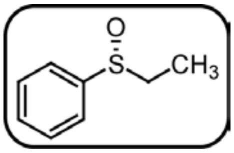
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.99-7.88 (m, 4H), 7.62-7.55 (m, 2H), 2.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 134.5, 133.0, 129.7, 128.6, 128.2, 127.9, 127.5, 124.1, 119.5, 43.9.

FT-IR (KBr): 3054, 2978, 2925, 2851, 1722, 1613, 1587, 1409, 1343, 1293, 1130, 1069, 1045, 1034, 967, 953, 906, 865, 822, 754, 741, 678, 634, 519, 485 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85. Found: C, 69.40; H, 5.29; S, 16.87.

HPLC: Chiralcel OB-H column, 4:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 22.37 min, 35.50 min; 70% ee.[45f]



(*R*)-Ethyl phenyl sulfoxide (Table 3, entry 11).[45d] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and ethyl phenyl sulfide (69 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as yellow liquid in 91% (70 mg) yield.

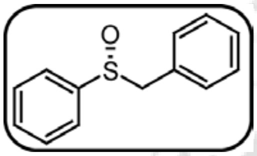
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (m, 2H), 7.52-7.46 (m, 3H), 2.90-2.84 (m, 1H), 2.78-2.71 (m, 1H), 1.19-1.15 (dt, J = 3.6, 2.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 131.0, 129.2, 124.2, 50.3, 6.0.

FT-IR (neat): 3060, 2960, 2930, 2859, 1727, 1617, 1458, 1444, 1380, 1275, 1123, 1086, 1072, 1045, 1021, 746, 692, 538 cm^{-1}.

Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54; S, 20.79. Found: C, 62.28; H, 6.57; S, 20.77.

HPLC: Chiralcel OD column, 9:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 15.66 min, 19.02 min; 70% ee.[20]



(*R*)-Benzyl phenyl sulfoxide (Table 3, entry 12).[45c] Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and benzyl phenyl sulfide (100 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 87% (94 mg) yield.

Mp: 123-124 °C.

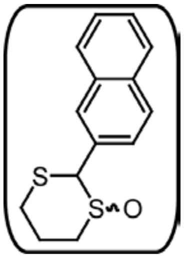
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.36 (m, 5H), 7.28-7.25 (m, 3H), 6.99 (d, J = 6.8 Hz, 2H), 4.11 (d, J =12.8 Hz, 1H), 4.01 (d, J =12.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 131.2, 130.4, 129.2, 128.9, 128.5, 128.3, 124.5, 63.6.

FT-IR (KBr): 3059, 2960, 2910, 1493, 1454, 1442, 1414, 1305, 1261, 1149, 1085, 1036, 1021, 998, 913, 892, 803, 765, 744, 690, 494, 479 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82. Found: C, 72.15; H, 5.57; S, 14.79.

HPLC: Chiralcel OD column, 19:1 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 28.32 min, 34.87 min; 61% ee.[20]



2-Naphthyl-1,3-dithiane-1-oxide. Titanium(IV) complex (5 mol %, 100 μL in toluene), 30% H_2O_2 (17 mg, 0.5 mmol) and 2-naphthyl-1,3-dithiane (123 mg, 0.5 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as white solid in 82% (108 mg) yield.

Mp: 162-163 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.91-7.80 (m, 4H), 7.51-7.47 (m, 3H), 4.71 (s, 1H), 3.59 (d, *J* = 8.8 Hz, 1H), 2.94-2.711 (m, 3H), 2.68-2.37 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 133.6, 133.2, 130.8, 129.0, 128.6, 128.1, 127.7, 126.8, 126.6, 125.6, 69.8, 54.7, 31.3, 29.5.

FT-IR (KBr): 3054, 2957, 2923, 2906, 1597, 1433, 1412, 1369, 1289, 1272, 1036, 903, 826, 789, 759, 480 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}OS_2$: C, 64.08; H, 5.38; S, 24.44. Found: C, 64.112; H, 5.36; S, 24.48.

HPLC: Chiralcel OJ column, 7:3 *n*-hexane:2-propanol, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 23.66 min, 39.09 min; 63% ee.

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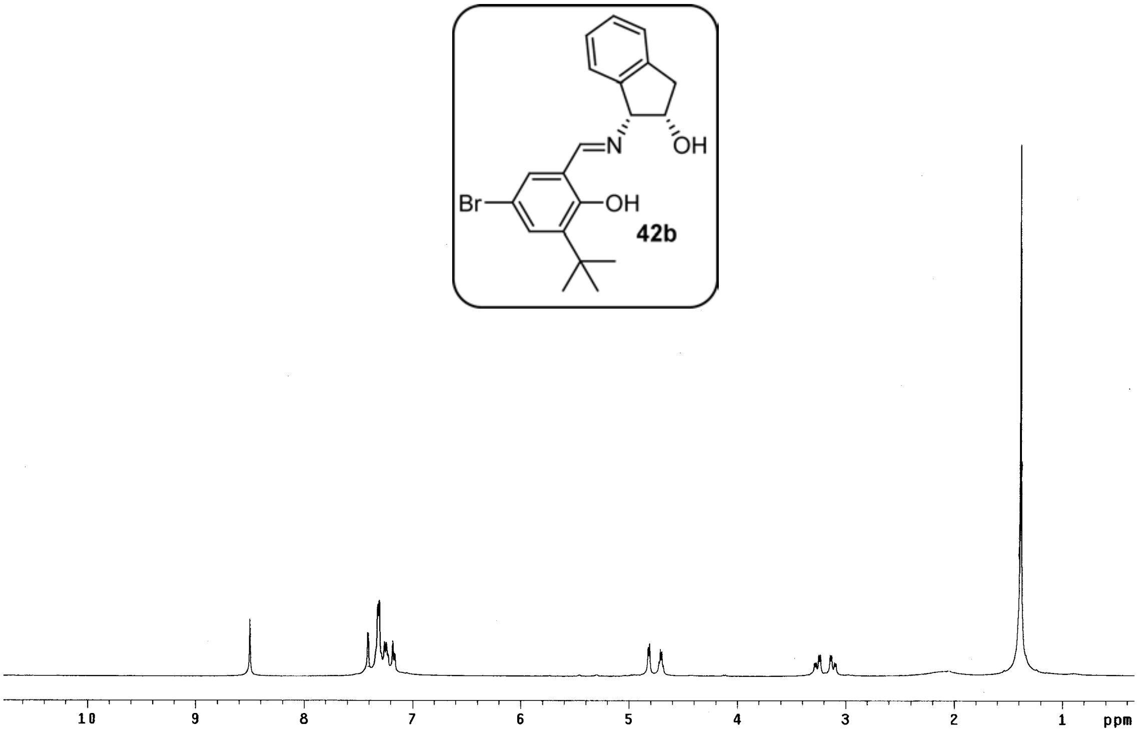
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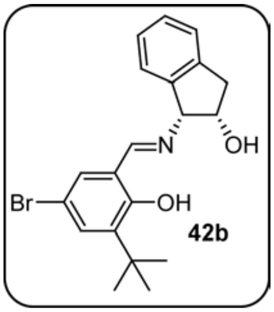
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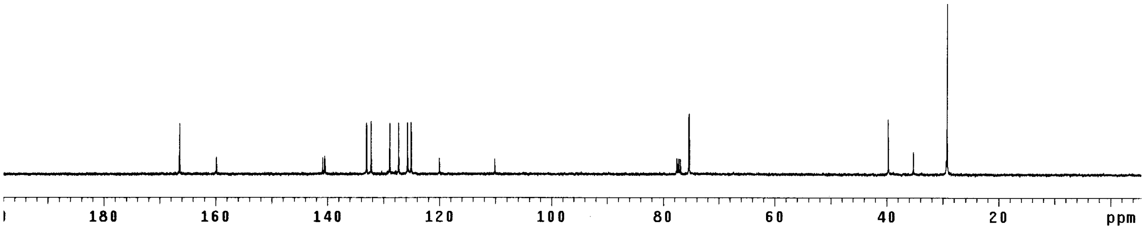
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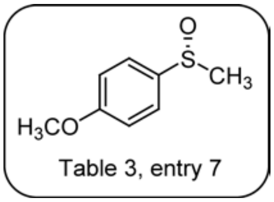

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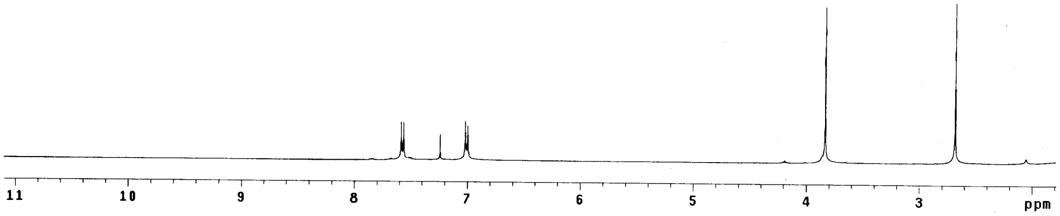


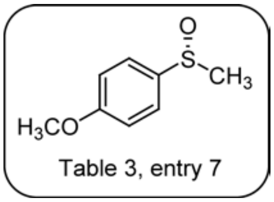
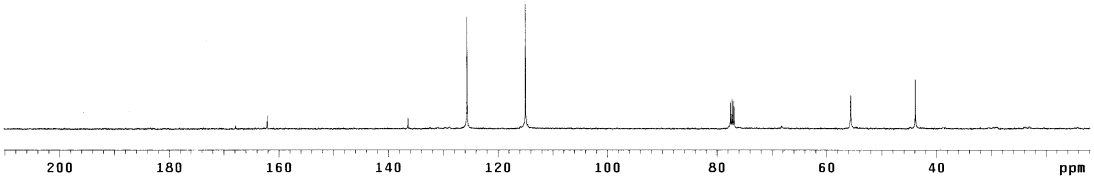


Table 3, entry 7



Chapter IV

Chiral Main Chain Polymers as *OFF-ON* Chemosensor for the Fluorometric Detection of Zn^{2+}

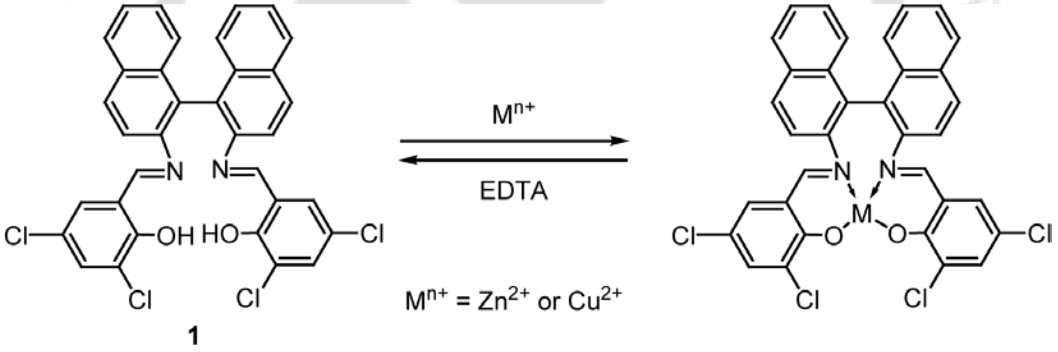
4.1 Introduction

Selective recognition and sensing of transition metal ions found in chemical, biological systems and in the environment has received considerable attention in recent years, as these ions are either quite beneficial or toxic to human health.[1]. Among them, detection of the zinc ion has drawn considerable attention in the chemistry community due to its biological importance. Zn^{2+} is the second most essential transition metal ion for the human especially it is in highest concentrations in the brain, and plays an indispensable role in various biological processes such as gene transcription, cell apoptosis, regulation of metalloenzymes, neural signal transmission and insulin secretion.[2] The deviation of Zn^{2+} concentration from the normal level causes diabetes and many severe neurological diseases including epilepsy and Alzheimer's disease.[3] Thus, the selective detection of Zn^{2+} in various samples is a vital toxicological and environmental importance. However, unlike other transition metal ions such as Cu^{2+}, Co^{2+} and Ni^{2+}, Zn^{2+} does not give any spectroscopic or magnetic signal due to its complete valence shell electronic configuration. In this context, the fluorometric detection of Zn^{2+} has been quite appealing since it is easy to perform with high sensitivity.[4] Numerous scientific endeavours have thus been made in the development of fluorescent Zn^{2+} probes based on small molecules (such as quinolines,[5] rhodamine,[6] bis(benzoxazole),[7] bipyridine,[8] spirobenzopyravarien,[9] anthracene,[10] naphthalimide[11] and tricarbocyanine[12]), peptides[13] and nanoparticles.[14] Furthermore in case of fluorometric sensing, fluorescence enhancement of the probe is more desirable than fluorescence quenching. Additionally, the probing molecule would be able to form stable complexes with transition metal ions with defined optical properties have advantages over the simple coordinating probe molecule. This is possible by the use of highly coordinating Schiff's base which could provide the stable complexes of most of the metal ions. Among various Schiff base derivatives, diamine based Schiff's bases are attractive, because it can be easily synthesized through simple condensation of diamine and aldehyde derivatives and it can be readily used as chemosensor.

4.2 Diamine Based Schiff's Bases as Chemosensor for Zn^{2+} Detection

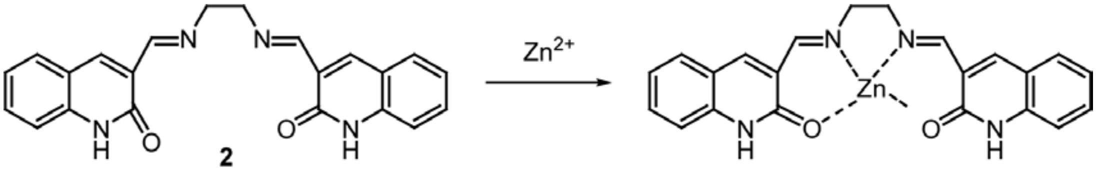
4.2.1 Small Molecules as Probe for Zn^{2+} Detection

Wang *et al*. reported the binaphthylamine based salen-type Schiff base **1**, for the detection of Zn^{2+} and Cu^{2+} in the presence of other metal ions.[15] Addition of Zn^{2+} (or) Cu^{2+} ion to the ligand **1** gave metal-**1** complex that exhibit different fluorescent properties (Scheme 1).



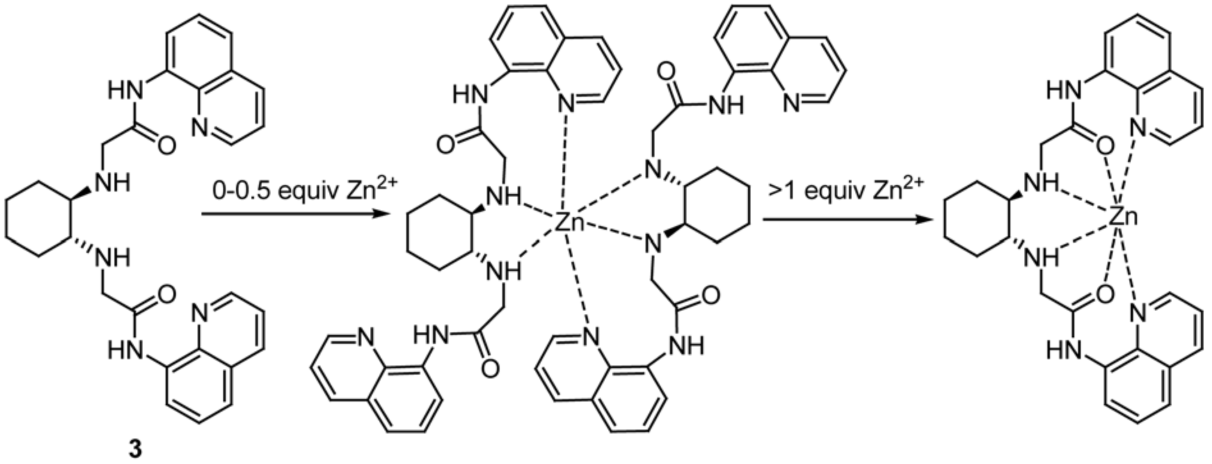
Scheme 1

Liu *et al* synthesized Schiff-base ligand **2** derived from 2-oxoquinoline-3-carbaldehyde and ethylene diamine and used as chemosensor for detection of Zn^{2+}.[16] It exhibits high selectivity and sensitivity for Zn(II) in acetonitrile solution with 1:1 binding and the complex showed 20 fold increase in fluorescence intensity when compared to ligand **2**.



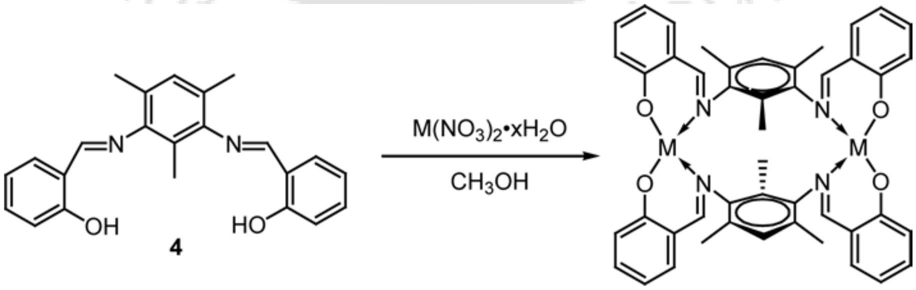
Scheme 2

Zhou *et al* developed a selective fluorescent Zn^{2+} based chemosensor **3** by incorporating two 8-aminoquinoline moieties onto *trans*-1,2-diaminocyclohexene backbone with suitable spacers.[17] Using the fluorescent probe **3** under physiological pH conditions, the detection of Zn^{2+} at subnanomolar concentration was achieved in aqueous methanol solution. After binding with 1 equiv of Zn^{2+}, ligand **3** exhibited a 12-fold fluorescence enhancement. In addition, they showed that the interference caused by Cu^{2+} and Cd^{2+} in the determination of Zn^{2+}can be completely eliminated by the use of diethyldithiocarbamate as the screening agent.



Scheme 3

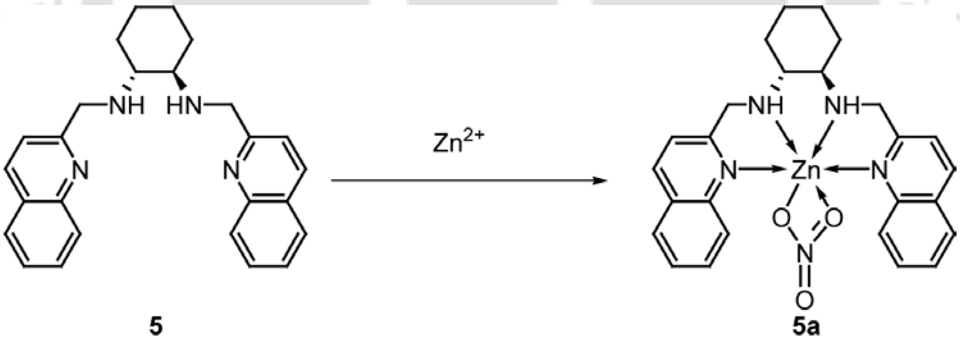
Pandey *et al* described the synthesis of salen type ligand **4** and its zinc complex displays strong fluorescence measurable at nanomolar concentrations.[18] It exhibits turn-“*OFF*” and turn-“*ON*” in the presence of Cu^{2+} and Ag^{+} ions in aqueous environment at neutral pH. The “*OFF-ON*” processes are reversible, and it has been established that they arises from weak interaction between Cu^{2+}/Ag^{+} and -CH=N- unit.



Scheme 4

The observed fluorescence quenching of **4** in the presence of paramagnetic Cu^{2+} has been attributed to interaction of Cu^{2+} with the -CH=N unit, subsequently metal to ligand charge transfer (MLCT) to the chromophore of **4**. On the other hand, fluorescence enhancement in the presence of Ag^+ possibly arises from ligand to metal charge transfer (LMCT) between **4** and Ag^+. Moreover, **4** can be applied as a molecular keypad lock system which follows correct chemical input order CZA ($Cu^{2+} \longrightarrow Zn^{2+} \longrightarrow Ag^+$) because of reversible switch-“*OFF*” and switch-“*ON*” signaling in the presence of Cu^{2+} and Ag^+ ions, respectively.

Ravikumar *et al*. reported a quinoline-based receptor **5** as a selective fluorescent chemosensor for Zn^{2+} compared to other competing cations *via* fluorescence turn-“*ON*”.[4h] This turn-“*ON*” species **5a** shows selectivity toward pyrophosphate in the presence of other competing anions like phosphate, adenosine 5'-monophosphate and adenosine triphosphate *via* fluorescence turn-“*OFF*” in a 100% aqueous HEPES ((4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)) buffer (pH 7.4). Since, quinoline derivative **5** can acts as an “*OFF-ON-OFF*” molecular switch by Zn^{2+} and pyrophosphate inputs, respectively, it could be used in biological application for the selective sensing of Zn^{2+} and pyrophosphate simultaneously.



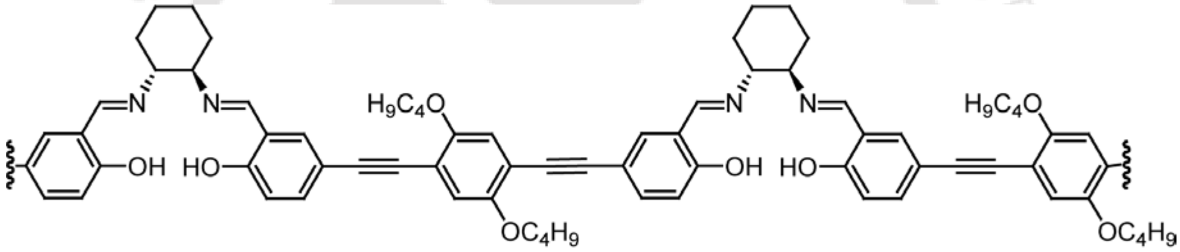
5 **5a**

Scheme 5

4.2.2 Polymers as Probe for Zn^{2+} Detection

A few studies have focused on the use of stereoregular organic polymers for detection of metal ions,[4a,19] because the selective coordination and binding of certain metal ions to the chromophoric site of the polymers can greatly influence the optical properties of the materials, making them as promising candidates for sensors.[20] In conjugated polymers, a small change in the chromophoric site can generate a signal which can be amplified through the delocalized π-electron cloud of the polymer backbone to produce an effective optical response in comparison to small molecules as chemosensor.[19f,g]

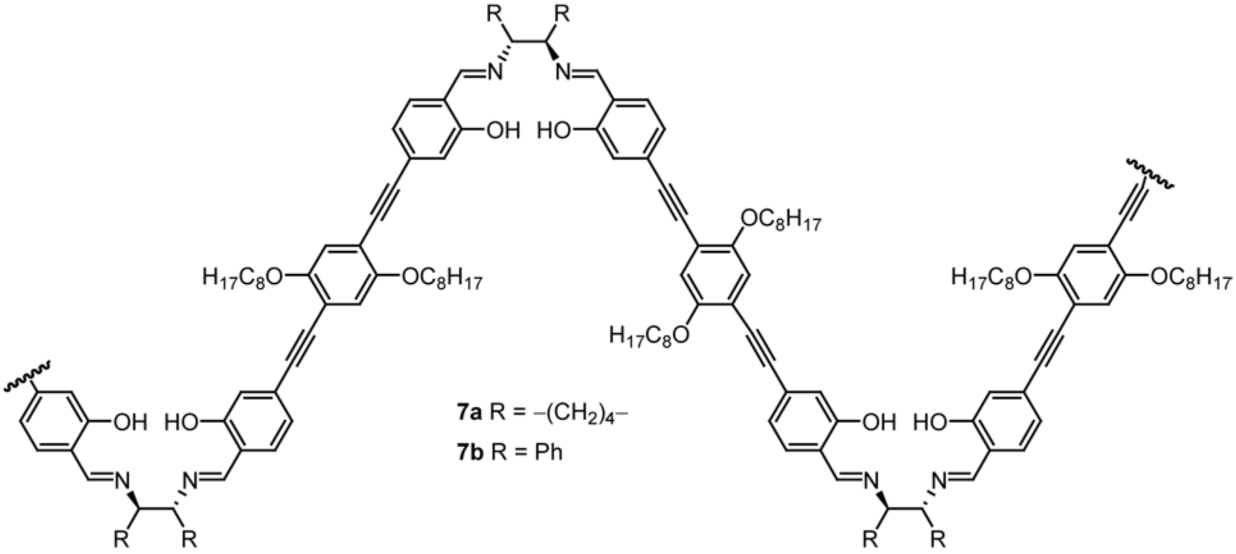
Xu *et al* synthesised a chiral polymer **6** incorporating an (*R*,*R*)-salen moiety through our condensation methodology and showed that the polymer **6** exhibits excellent fluorescent sensor properties for the detection of Zn^{2+} (Scheme 6).[19k,21] Compared with other cations (Na^+, K^+, Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ag^+, Cd^{2+}, Hg^{2+} and Pb^{2+}), Zn^{2+} can produce a pronounced fluorescence enhancement as well as a large blue shift of the polymer fluorescence. This polymer **6** can be applied to the detection of Zn^{2+} by a simple, rapid, sensitive and selective method.



6

Scheme 6

Recently, we have developed a new class of chiral main chain polymers **7a-b** using the Pd-catalyzed C-C cross-coupling reaction as a key step (Scheme 7).[4a] They can be used as effective chemosensor for the recognition of Zn^{2+} ion at ambient conditions. The polymer **7b** having (*R*,*R*)-1,2-diphenylethylenediamine with Zn^{2+} has exhibited the best fluorescence enhancement. The fluorescence enhancement of the polymer was saturated with 3 equivalent of Zn^{2+}.



Scheme 7

4.3 Present Study

Here we describe the use of stereoregular non-linear polymers **P1**-**P2** as chemosensor for the detection of Zn^{2+}. An addition of 1 equiv (with respect to the monomeric unit of the polymer) of an aqueous solution of the nitrate salts of Na^{+}, Ag^{+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Al^{3+} and Ce^{3+} to the THF solution of **P1**-**P2** led to change in the fluorescence intensity and the best selectivity was observed toward Zn^{2+} (Figure 1). The polymer **P2**, derived from (*R*,*R*)-1,2-diphenylethylenediamine, exhibited the best fluorescence enhancement with Zn^{2+} compared to **P1** that was obtained from (*R*,*R*)-1,2-diaminocyclohexane. Figure 2 illustrates the images of fluorescence of **P2** without (a) and with (b) Zn^{2+}, and (c) shows the graphical presentation of the selectivity of **P2** with different metal ions. To reveal the effectiveness of **P2** compared to (*R*,*R*)-salen **7**, the fluorescences of **7** and **P2** were measured with and without Zn^{2+}. The Zn(II)-polymer complex derived from **P2** exhibited 2.5 times enhanced fluorescence compared to Zn(II)-salen **7** complex (Figure 3). This result clearly suggests that the polymer **P2** based chemosensor is more effective compared to (*R*,*R*)-salen **7**.

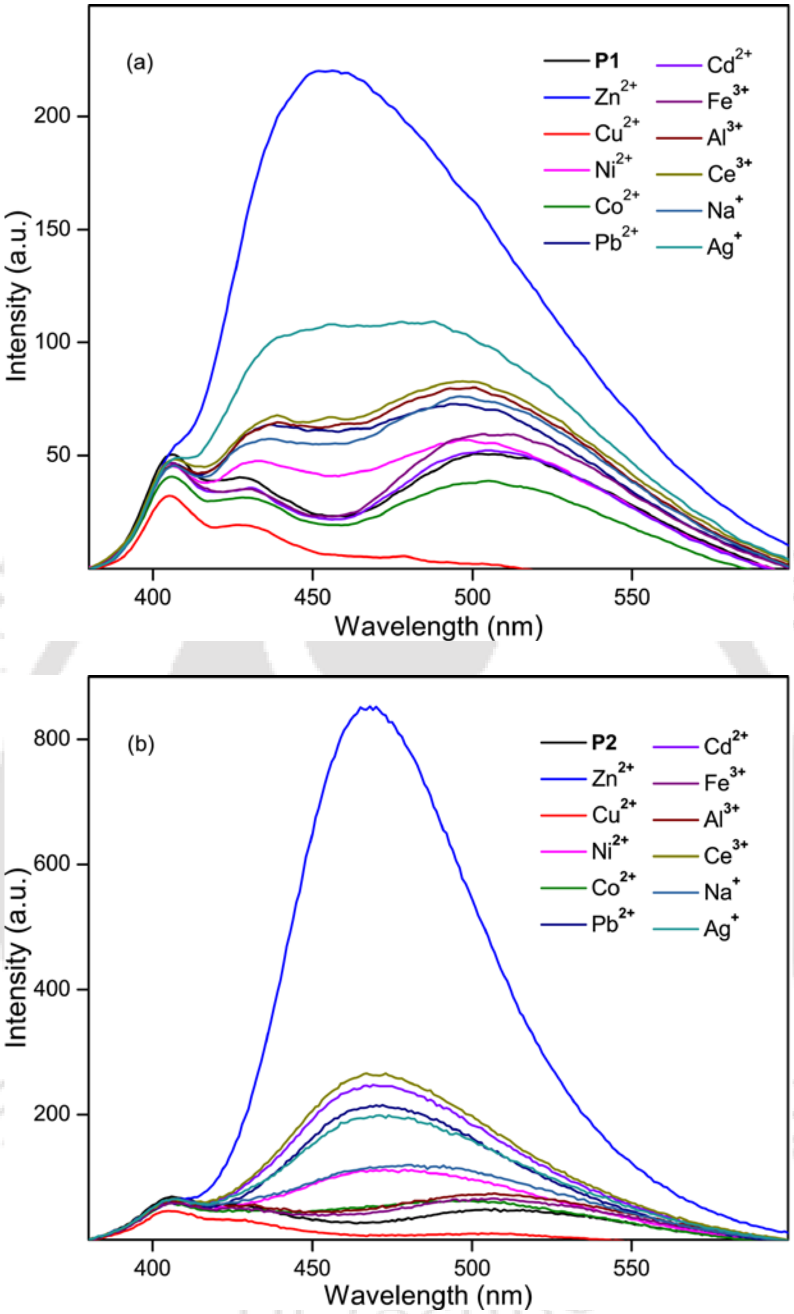


Figure 1. Fluorometric titration: (a) **P1** (λ_{ex} = 360 nm) and (b) **P2** (λ_{ex} = 360 nm) (1 x 10^{-5} M in THF) with different metal nitrate salts (3 x 10^{-4} M in water, 1 equiv with respect to the monomeric unit).

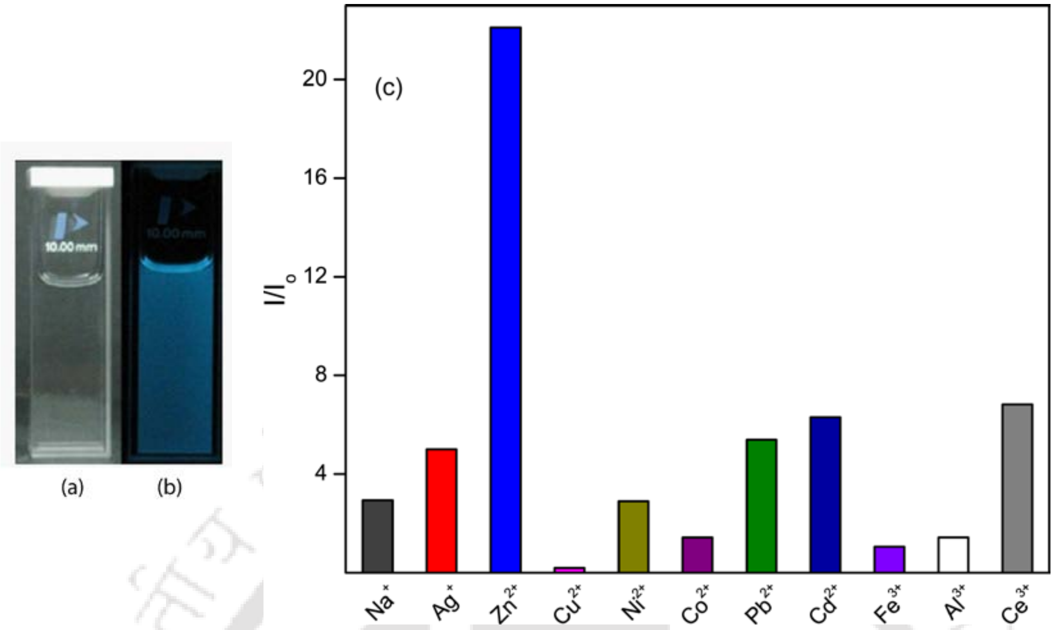


Figure 2. The polymer **P2** (1 x 10^{-5} M in THF): (a) fluorescence image without Zn^{2+} and (b) fluorescence image with 1 equiv Zn^{2+} (3 x10^{-4} M in water) (both are excited using a commercially available UV lamp (λ = 360 nm). (c) The selectivity of **P2** (1 x 10^{-5}M in THF) with metal ions (3 x10^{-4} M in water).

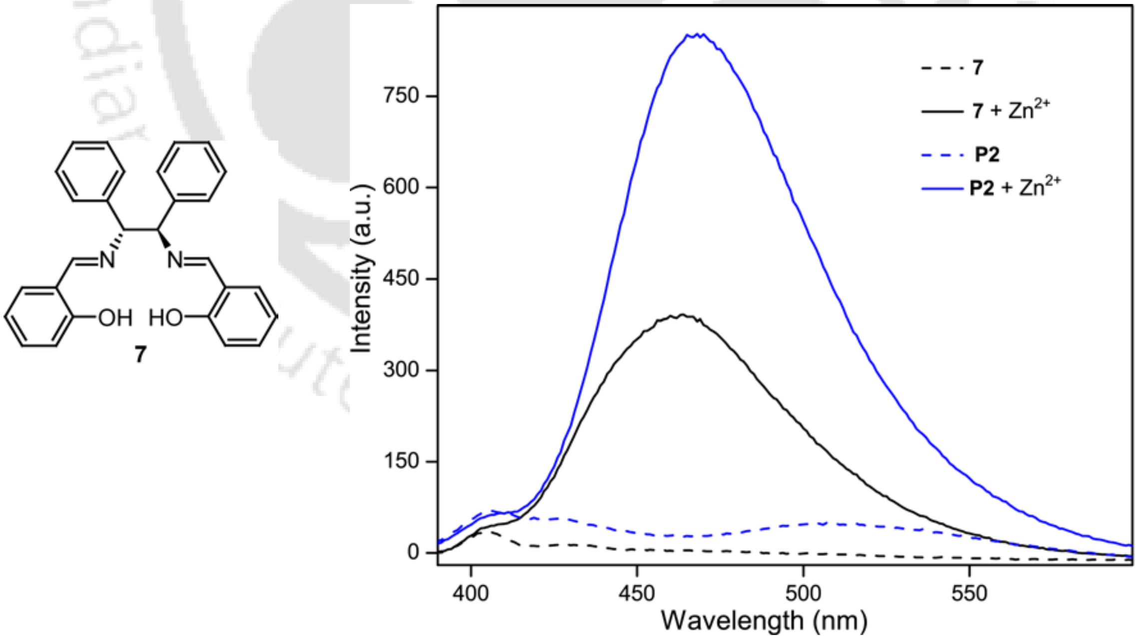


Figure 3. Fluorescence spectra of **7** and **P2** (1 x 10^{-5} M in THF) Without/With 1 equiv of Zn^{2+} (3 x 10^{-4} M in water, λ_{ex} = 360 nm).

The polymer **P2** with Zn^{2+}emits a strong blue fluorescence, due to the formation of Zn(II)-polymer complex that can reduce the non-radiative decay of the excited state of the Zn(II)-polymer complex as well as the quenching contributed from the photoinduced-electron-transfer (PET) of the lone pair of the electrons of nitrogen.[22] Furthermore, a blue shift (~50 nm) in the emitted light was observed that could be caused by reduction in the HOMO energy level of the polymer upon the formation of the Zn(II)-polymer complex.[23] The polymer **P2** that gave the best fluorescence enhancement was further studied with varied Zn^{2+} concentrations (Figure 4). The absorption band at 290 nm slightly shifted to 293 nm with a gradual decrease of intensity. The isosbestic points at 296 and 366 nm indicate the formation of Zn(II)-polymer complex.

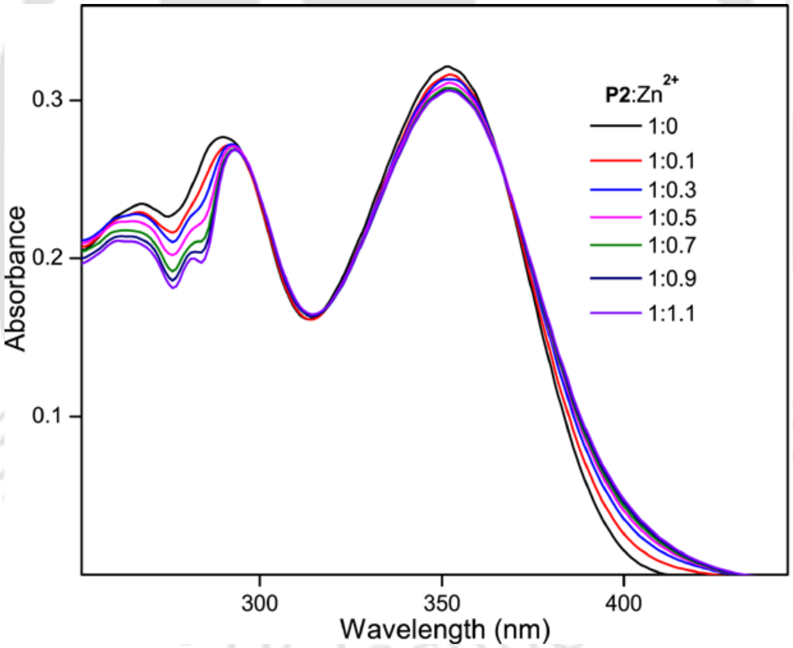


Figure 4. UV-vis titration of **P2** (1×10^{-5} M in THF) with 0.1-1.1 equiv of Zn^{2+} ion (3×10^{-4} M in water with respect to the monomeric unit of **P2**).

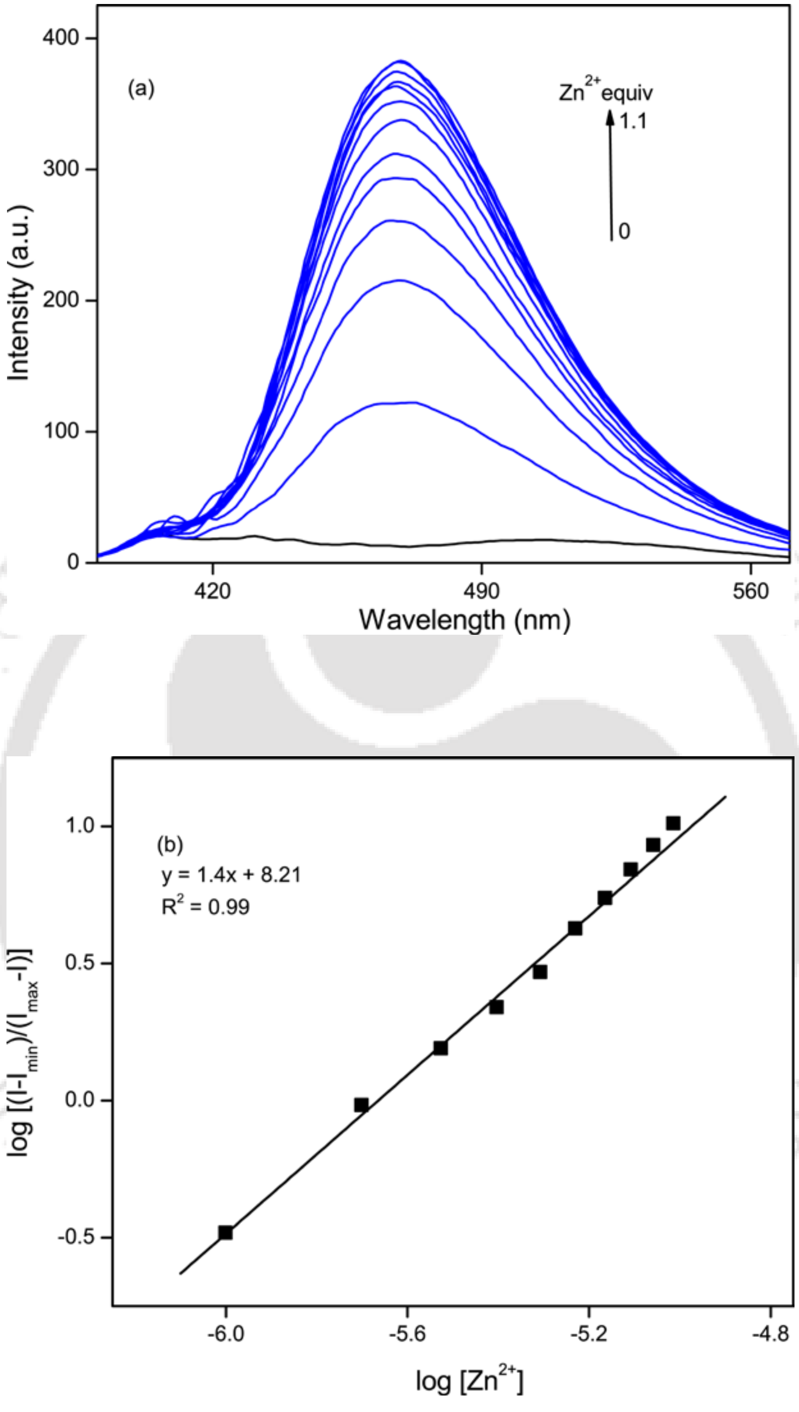


Figure 5. (a) Fluorometric titration of **P2** (1 x 10^{-5} M in THF, λ_{ex} = 360 nm) with 0.1-1.1 equiv of Zn^{2+} ion (3 x 10^{-4} M in water, with respect to the monomeric unit of **P2**). (b) Hill plot of polymer **P2** (1 x 10^{-5} M in THF) with 0.1-1 equiv of Zn^{2+} (I = fluorescence intensity of Zn(II)-polymer complex at a given concentration of Zn^{2+}, I$_{min}$ = fluorescence intensity of polymer, I$_{max}$ = saturated fluorescence intensity of Zn(II)-polymer complex).

Next, the sensing selectivity of the polymer **P2** with different Zn^{2+}concentrations was pursued (Figure 5a). The weakly emissive **P2** (THF, 1.0 x 10^{-5} M) at *ca.* 519 nm, upon addition of Zn^{2+} (3 x 10^{-4} M), exhibited a blue-shifted emission at 471 nm. The enhancement in the intensity of the emission band was proportional to the Zn^{2+} concentration. When the Zn^{2+}concentration was reached to 1.1 equiv with respect to the monomer unit of the polymer **P2**, the fluorescence intensity increased to maximum with a 22-fold enhancement. Further enhancement in the addition of Zn^{2+} concentration led to no change in the fluorescence intensity. By applying a Hill plot to this titration data (Figure 5b), the stability constant of Zn(II)- polymer **P2** complex was calculated as 1.62 x 10^8 M^{-1}.[24]

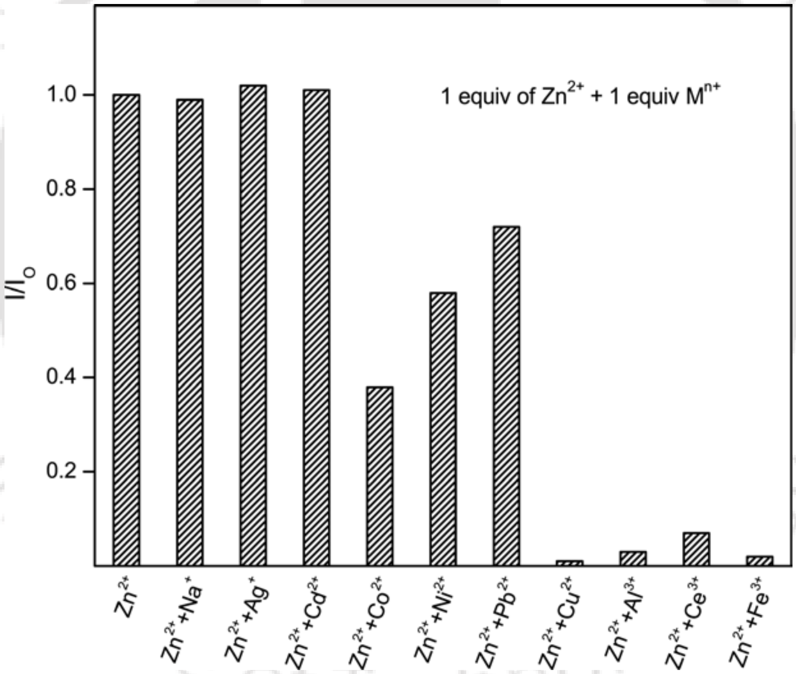


Figure 6. Metal ion interference with Zn(II)-polymer complex: I = fluorescence intensity of the Zn(II)-polymer complex, derived from **P2** and Zn^{2+}, in the presence of other metal salts (3 x 10^{-4} M, 1 equiv) and I_o = fluorescence intensity of the Zn(II)-polymer complex, derived from **P2** and Zn^{2+} (1 x10^{-5} M in THF).

The interference effect of other metal ions to the fluorescence of Zn(II)-**P2** complex was also investigated. The addition of metal ions such as Na^+, Ag^+ and Cd^{2+} did not affect the fluorescence intensity of the Zn(II)-polymer complex (Figure 6). In contrast, the addition of metal ions such as Ni^{2+}, Co^{2+} and Pb^{2+}, and Cu^{2+}, Al^{3+}, Ce^{3+} and Fe^{3+} ions to the solutions of the Zn(II)-polymer complexes led to quenching of the fluorescence of the Zn(II) complex.

Next, the metal ions (Na^+, Ag^+ and Cd^{2+}) and their mixture (1:1:1) concentrations were increased from 1 to 25 equiv with respect to the Zn(II)-polymer complex whose fluorescence was measured (Figure 7). However, no change in the fluorescence intensity of the Zn(II)-polymer complex was observed.

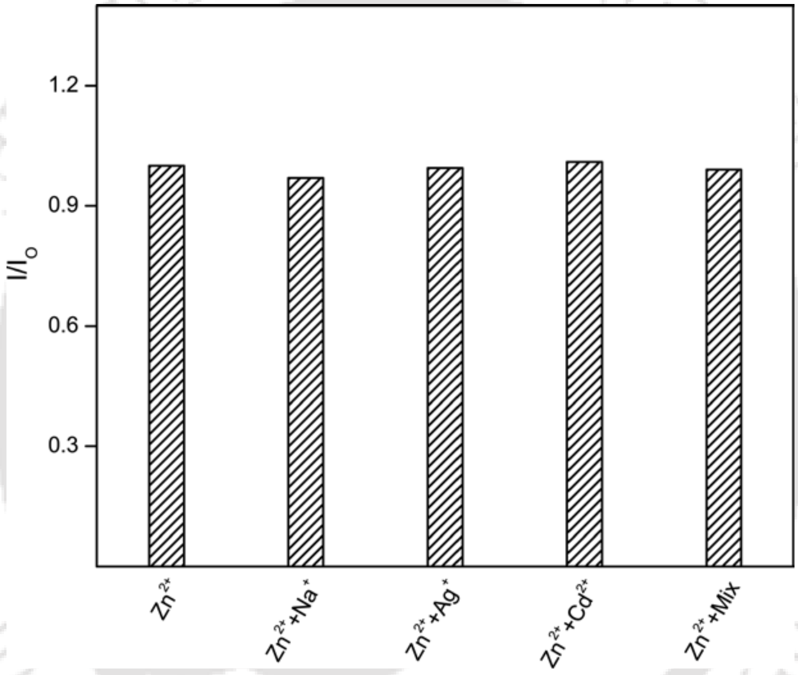
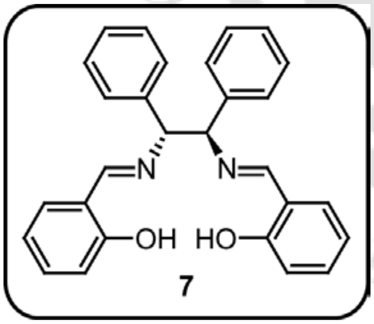


Figure 7. Metal ion interference with Zn(II)-polymer complex: I = fluorescence intensity of the Zn(II)-polymer complex, derived from **P2** and Zn^{2+}, in the presence of Na^+, Ag^+, Cd^{2+} (3 x 10^{-2} M, 25 equiv) and I_o = fluorescence intensity of the Zn(II)-polymer complex, derived from **P2** and Zn^{2+} (1 x10^{-5} M in THF).

In conclusion, the non-linear polymers **P1**-**P2** could serve as highly selective fluorescent chemosensor toward Zn^{2+}. The polymer **P2** having (*R*,*R*)-1,2-diphenylethylenediamine with Zn^{2+} has exhibited the best fluorescence enhancement as an *OFF-ON* chemosensor. The association constant of polymer **P2** with Zn^{2+} was found to be 1.62 x 10^8 M^{-1}.

Experimental Section

General. $Ce(NO_3)_3{\cdot}6H_2O$ (≥98%), $Cd(NO_3)_2{\cdot}4H_2O$ (≥99%) and $Zn(NO_3)_2{\cdot}6H_2O$ (98%) were purchased from Aldrich. $Co(NO_3)_2{\cdot}6H_2O$ (97%), $Cu(NO_3)_2{\cdot}3H_2O$ (≥99%), $Ni(NO_3)_2{\cdot}6H_2O$ (98%), $Al(NO_3)_3{\cdot}9H_2O$ (≥95%) and $NaNO_3$(≥99%) were purchased from Merck. $Fe(NO_3)_3{\cdot}9H_2O$(98%), $Pb(NO_3)_2$(98%) and $AgNO_3$(99%) were purchased from Rankem and used as received without further purification. Column chromatography was carried out with Rankem 60-120 mesh silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra (400 MHz for ^1H and 100 MHz ^{13}C) were recorded on DRX-400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvent and Me_4Si as an internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Melting points were determined using Buchi B-540 and are uncorrected. IR spectra were recorded using PerkinElmer spectrum one spectrometer. UV-vis spectra were recorded on PerkinElmer Lambda 25 UV/vis spectrometer. Fluorescence spectra were recorded on Varian Carey Eclipse fluorescence spectrophotometer. Elemental analysis was carried out using PerkinElmer 2400 CHNS analyzer.



7

Preparation of (*R*,*R*)-Salen 7. Salicylaldehyde (61 mg, 0.50 mmol) and (1*R*,2*R*)-diphenylethylenediamine (53 mg, 0.25 mmol) were stirred for 16 h in MeOH (1 mL) at ambient temperature. The solvent was evaporated and the residue was purified on basic silica gel column chromatography using hexane and EtOAc as eluent to provide compound **7** as yellow solid.

Mp: 154-155 °C

^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 2H), 7.26-7.12 (m, 14H), 6.96 (d, J = 8 Hz, 2H), 6.79 (t, J = 7.2 Hz, 2H), 4.73 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 161.0, 139.5, 132.7, 131.8, 128.5, 128.0, 127.8, 118.9, 118.7, 117.0, 80.3.

FT-IR (KBr): 3446, 3061, 3027, 2923, 2879, 1630, 1582, 1496, 1450, 1410, 1276, 1208, 1058, 1028, 982, 901, 869, 755, 718 cm^{-1}.
Anal. Calcd for $C_{28}H_{24}N_2O_2$: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.95; H, 5.73; N, 6.69.

Metal Ion Titration. The solutions of the polymers **P1-P2** (3 mL, 1 x 10^{-5} M in THF with respect to the monomeric unit) and metal nitrate salts (100 μL, 3 x 10^{-4} M in water, 1 equiv) were thoroughly mixed at ambient temperature to produce the corresponding metal-polymer complexes (Figure 1). After 5 min, the fluorescent properties of the solution having the *in situ* generated metal-polymer complexes were measured.

UV-vis and Fluorescence Titration of Zn^{2+} with Polymer P2. The solution of the polymer **P2** (3 mL, 1 x 10^{-5} M in THF with respect to the monomeric unit) and $Zn(NO_3)_2$ (10-120 μL, 3 x 10^{-4} M in water, 0.1-1.2 equiv) were thoroughly mixed at ambient temperature to produce the corresponding metal-polymer complexes (Figure 4 and 5a). The UV-vis and fluorescence of the respective solutions were measured.

Fluorescence Titration of Zn(II)-P2 with Other Metal Ions. To the solutions of the Zn(II)-polymer complex (1 x 10^{-5} M in THF with respect to the monomeric unit), derived from $Zn(NO_3)_2$ (3 x 10^{-4} M in water, 1 equiv) and **P2** (1 x 10^{-5} M in THF with respect to the monomeric unit) for 1 h, was added the solutions of various metal salts (3 x 10^{-4} M in water, 1-25 equiv). The resultant solutions were thoroughly mixed. After 5 min, fluorescence of the respective solutions was measured (Figure 6-7).

4.4 References

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Chapter V

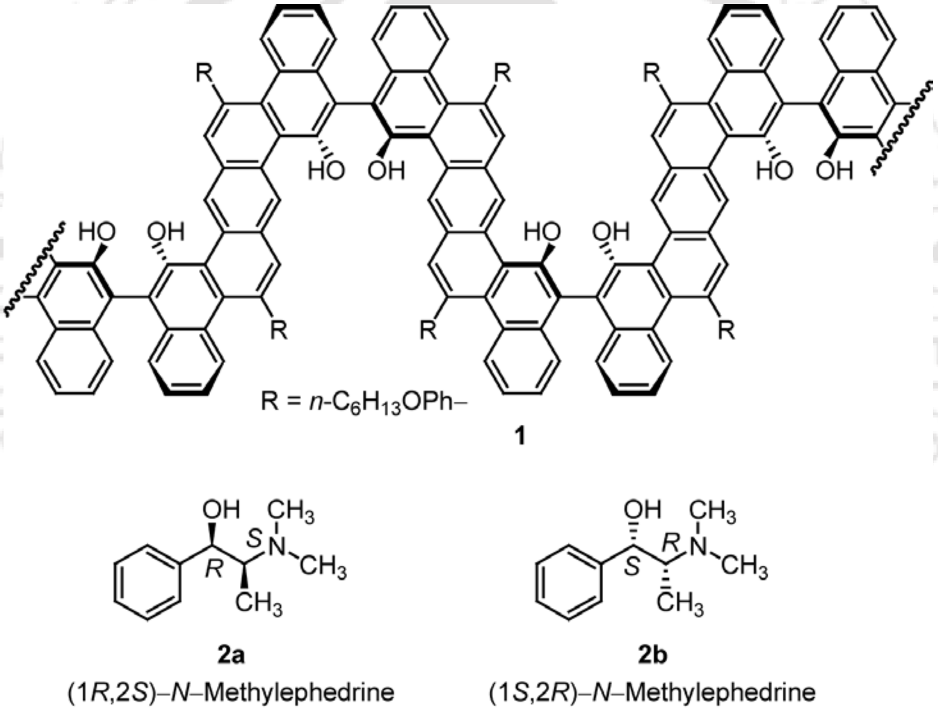
Chiral Recognition of Optically Active 1-Phenyl-*N*-[(pyridin-2-yl) methylene/methyl]ethanamines

5.1 Introduction

Molecule-based fluorescent sensors are generally composed of a binding site and a fluorophore which responds to the event at the binding sites. Depending on the fluorophore nature, a number of fluorescent signaling modes can be used (quenching, enhancement, excimers, exciplexes, lifetimes and anisotropy). Fluorescence efficiency can be correlated with many structural features of chemicals including π-π* and n-π* transitions, structural rigidity, non-covalent interactions (e.g., hydrogen bonds, π-π* interactions, and hydrophilic and hydrophobic interactions), intra or intermolecular energy transfers, and photoinduced electron transfers. These allow the development of well defined fluorescent sensors with very diverse structures as well as specific responses for substrate detection. Since, the fluorescence technique is highly sensitive, it requires the use of only very narrow amounts of sensor molecules and/or analytes. A wide variety of fluorescent sensors have been constructed to detect protons, metal ions, anions and neutral molecules.[1-3] Fluorescent sensors or labels have also been extensively applied in biological studies.[4] Chiral recognition in fluorescence has been studied in the past two decades. The introduction of chirality on the binding site would be able to enantioselectively recognize the chiral organic molecules and thus, it can act as fluorescent sensor for chiral discrimination. Rapid determination of the enantiomeric composition of optically active organic molecules is of great significance in drug discovery and catalyst screening in asymmetric synthesis. Several analytical tools such as electron spray mass spectroscopy, NMR and electrophoresis are under investigation for this purpose.[5-9] Fluorescent sensors that are capable of differentiating the two enantiomers of a chiral compound should provide a real time technique in the rapid chiral assays with many unique advantages. Significant progress has been made in the development of enantioselective sensors.

5.2 Chiral Main Chain Polymers for Chiral Recognition

Zhang *et al*. investigated the fluorescence property of the chiral helical polybinaphthyl **1** for chiral recognition of amino alcohol.[10] Polymer **1** was found to be a much more efficient fluorescent sensor than chiral BINOL when interacting with an optically active amino alcohol quencher.



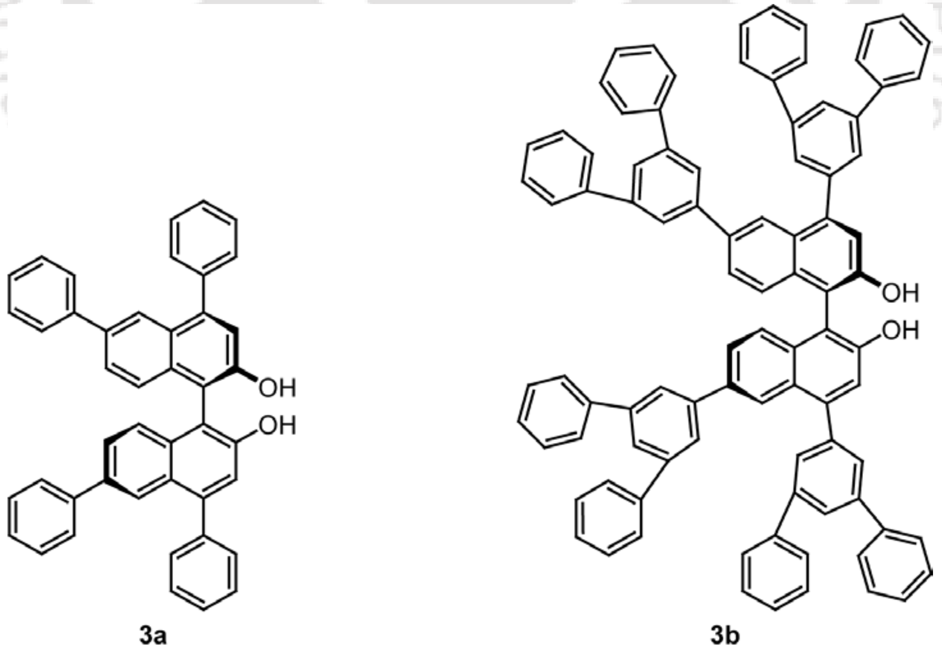
Enantiomeric fluorescence = $(I_O\text{-}I_{RS})/(I_O\text{-}I_{SR})$ =1.12

Figure 1

The fluorescence spectra of (*R*)-BINOL and **1** were recorded at 1 × 10^{-5} M in CH_2Cl_2/hexane (1:1) with (1*R*,2*S*)-(-)-*N*-methylephedrine (**2**, 3 × 10^{-2} M) was compared with that of **7** under similar condition. The fluorescence intensity ratio I_o/I (I_o = without the amino alcohol and I = with the amino alcohol) was 1.3 for BINOL, but 3.4 for **1**. This significantly increased fluorescence sensitivity of the polymer over BINOL toward the amino alcohol might be due to an energy migration along the helical conjugated polymer chain. It could also be attributed to the lower π-π^* band-gap of the polymer which may facilitate the photoinduced electron transfer quenching by the amino alcohol. The fluorescence quenching of **1** by the two enantiomers of **2** was also found to be different with an ef (enantiomeric fluorescence difference ratio (ef) = $(I_o-I_{RS})/(I_o-I_{SR})$) value of 1.12 ± 0.01. Although this enantioselectivity was small, it was larger than using (*R*)-BINOL which showed no difference at all in the fluorescence quenching when treated with the two enantiomers of the amino alcohol **2**.

5.3 Chiral Dendrimers for Chiral Recognition

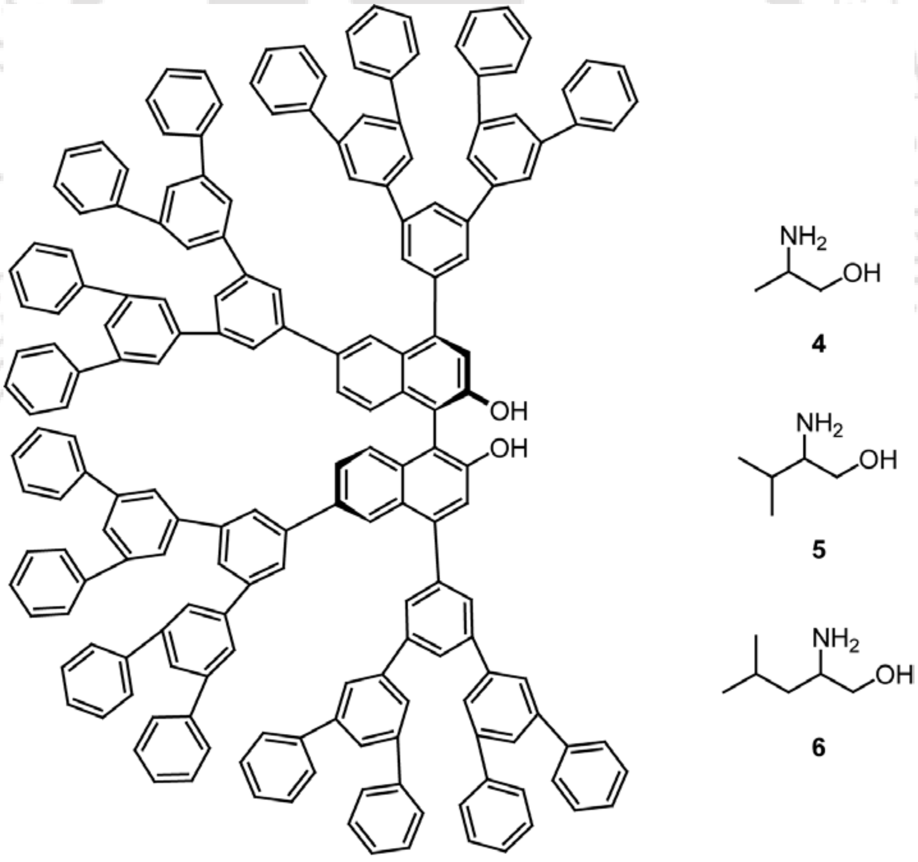
Gong *et al*. also investigated phenylene-based chiral binaphthyl dendrimers **3a-c** for chiral recogniation of 2-amino-1-propanol **4** in dichloromethane and hexane as the co-solvent, the amino alcohol efficiently quenched the fluorescence of the dendrimer (Figure 2-3).[11]



3a **3b**

Figure 2

The fluorescence quenching of (*R*)-**3c** (1×10^{-7} M) by the optically pure amino alcohol (*R*)- and (*S*)-**4** (2×10^{-3} to 6×10^{-3} M) obeyed the Stern-Volmer equation with $K_{SV}(R) = 243.5$ M^{-1} and $K_{SV}(S) = 216.0$ M^{-1}. Therefore, the fluorescence quenching of **3c** by the amino alcohol was enantioselective with $K_{SV}(R)/ K_{SV}(S) = 1.13$. The (*R*)-enantiomer of the amino alcohol quenched the fluorescence of the (*R*)-dendrimer more efficiently than the (*S*)-enantiomer. The fluorescence quenching of the G0 dendrimer and the G1 dendrimer by (*R*)- and (*S*)-**4** gave $K_{SV}(R) = 75.5$ M^{-1} and $K_{SV}(S) = 63.5$ M^{-1} for **3a**, and $K_{SV}(R) = 99.9$ M^{-1} and $K_{SV}(S) = 88.4$ M^{-1} for **3b**. It was quite interesting that the higher generation dendrimers displayed greater fluorescence intensity change and were much more sensitive sensors toward the chiral quenchers. The fluorescence quenching of dendrimer **3c** in the presence of other amino alcohols such as leucinol **5** and 2-amino-3-methylbutanol **6** was also enantioselective with $K_{SV}(R)/K_{SV}(S)$ in the range of 1.09-1.18.



3c

Figure 3

5.4. Chiral Macrocyclic System for Chiral Recognition

Pu *et al*. found that the bisbinaphthyl macrocycles **7a-b** were useful in the enantioselective fluorescent recognition of α-hydroxycarboxylic acid **8** (Figure 4).[12] Treatment of **7a** with (*S*)-mandelic acid **8a** led to greatly enhanced fluorescence especially at λ_{long} (424 nm). However, very little fluorescence enhancement at λ_{long} was observed when **7a** was interacted with (*R*)-mandelic acid **8b** under the same conditions.

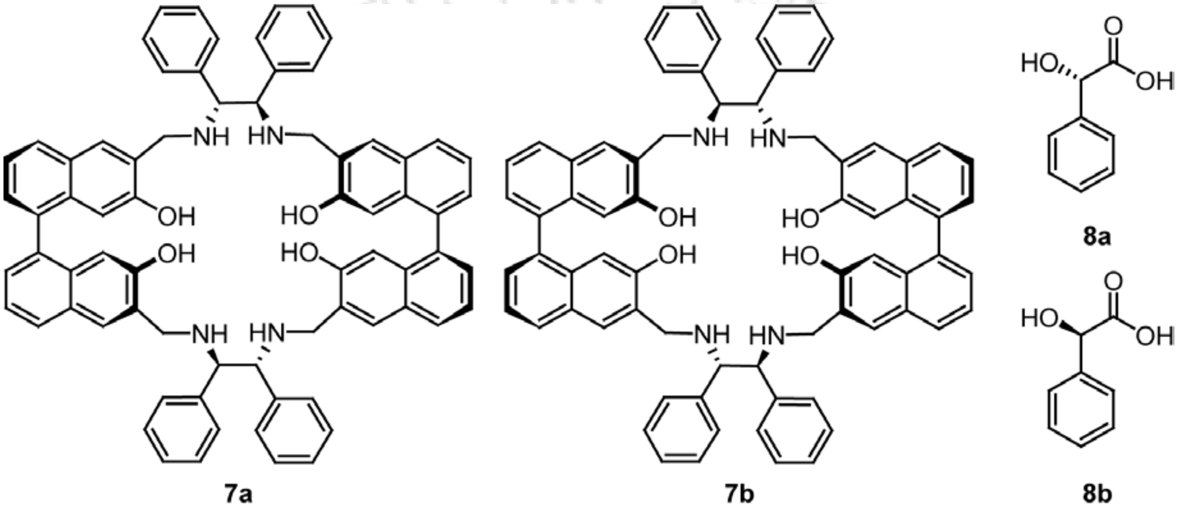
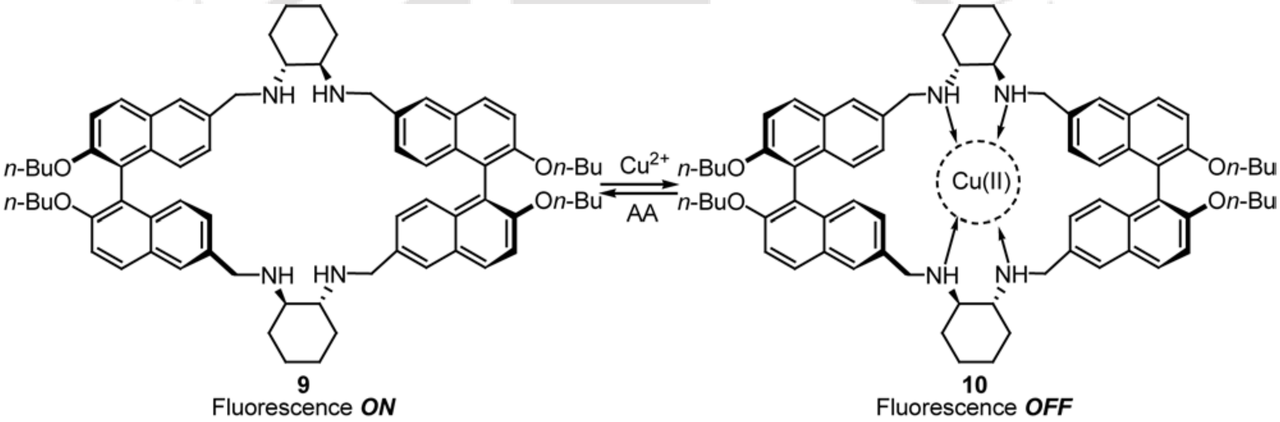


Figure 4

Thus, **7a** had exhibited an extremely high enantioselective fluorescent response toward the chiral acid. In a concentration range of 5×10^{-3} to 2×10^{-2} M of (*R*)- and (*S*)-mandelic acid in benzene containing 2% DME, the fluorescence enhancement of **7a** (1×10^{-4} M) at λ_{long} was studied. An ef $[(I_S\text{-}I_o)/(I_R\text{-}I_o)]$ of over 12 was observed. The chiral recognition was confirmed by using the enantiomeric macrocycle (+)-**7b** to interact with (*R*)- and (*S*)-mandelic acid. The Job plot of ^{1}H NMR measurements indicated the formation of 1:4 complex between the macrocycle and the acid. This enantioselective recognition was attributed from the binding of the nitrogen atoms of the macrocycle with the acidic proton of the acid. This interaction inhibited the PET fluorescence quenching of the macrocycle by lone pair of electrons on nitrogen atoms, leading to the enhanced fluorescence. The fluorescence measurements suggested that (*R*)-mandelic acid should bind **7b** more strongly than (*S*)-mandelic acid and (*S*)-mandelic acid should bind **7a** more strongly than (*R*)-mandelic acid. The relationship between the fluorescence intensity of **7a** at λ_{long} and the enantiomeric composition of mandelic acid was found to be close to linear. Thus, the chiral bisbinaphthyl macrocycle could be used as a fluorescent sensor to readily determine the enantiomeric composition of mandelic acid.

Yang *et al*. synthesized chiral perazamacrocycle **9** which serves as a fluorescent turn-off sensor for Cu(II) and the *in situ* generated Cu(II)-**9** can exhibit remarkable fluorescent enhancement responses and considerable enantioselectivity recognition toward unmodified *R*-amino acids in protic solutions *via* a ligand displacement mechanism.[13] An excess of Cu^{2+} ions could lead to the enhancement of enantioselectivity. A possible explanation might be that the excess Cu(II) (2 equiv) could drive the balance to move to the left in Scheme 1.



Scheme 1

The enantiomers of amino acids **11-15** were used for the chiral recognition of Cu(II)-**9** complex (Figures 5). Based on the $(\Delta I/I_o)_{max}$ values, the authors concluded that the increase of bulkiness of the group in the α-position of amino acid could enhances the enantioselectivity.

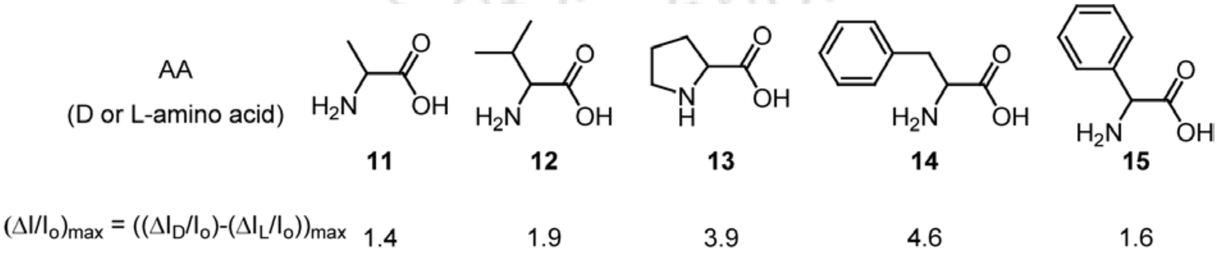
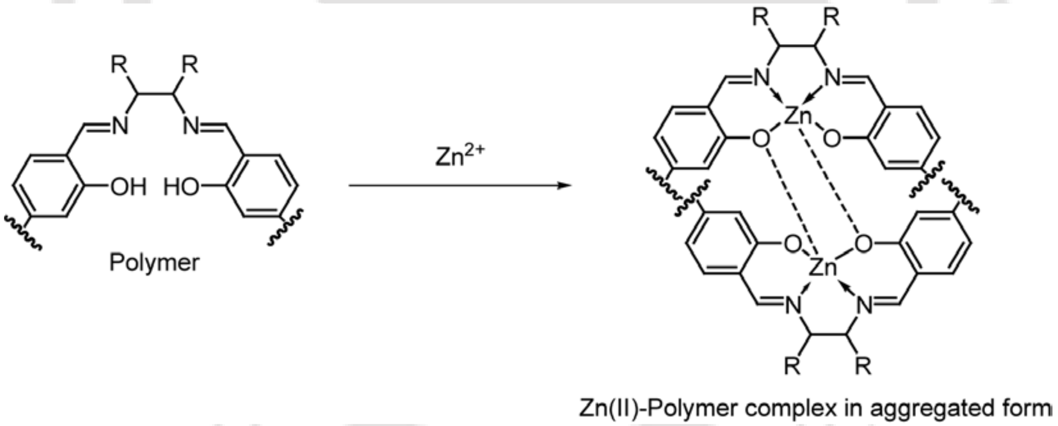


Figure 5

5.5 Present Study

Herein we present the inter-strand interaction of Zn(II)-polymer **P1/P2** complex by titrating with Lewis base (pyridine) and their application for chiral recognition towards (*R*)- and (S)-1-phenyl-*N*-[(pyridin-2-yl)methylene/methyl]ethanamines using fluorometric titration. It is well known that the four coordinated Zn^{2+} can extend its coordination number with the help of coordinating ligands such as pyridine.[14] Since the coordinating ligand reduces the inter-strand interaction, the degree of iner-strand interactions could be studied with the fluorescence titration of Lewis base against Zn(II)-polymer **P2** complex. The Zn(II)-polymer **P2** can exist in aggregated form through Zn---O interactions shown in Scheme 2.[15] Due to this excimer like inter-strand interactions, the fluorescence intensity was reduced by quenching. The addition of pyridine enhances the deaggregation of Zn(II)-polymer **P2** and thereby increases the fluorescence emission (Figure 6). The slight increase in fluorescence emission observed could be attributed to the helical or coil nature of the polymer inhibiting the self aggregation of Zn(II)-polymer **P2** (Figure 7).[14a,15c]



Scheme 2

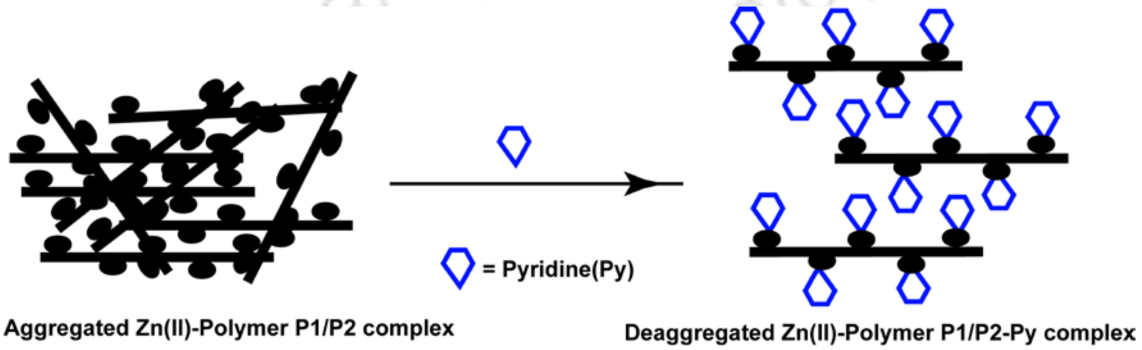


Figure 6. Pictorial Representation of Inter-strand Interaction of Zn(II)-**P1/P2** Complex.

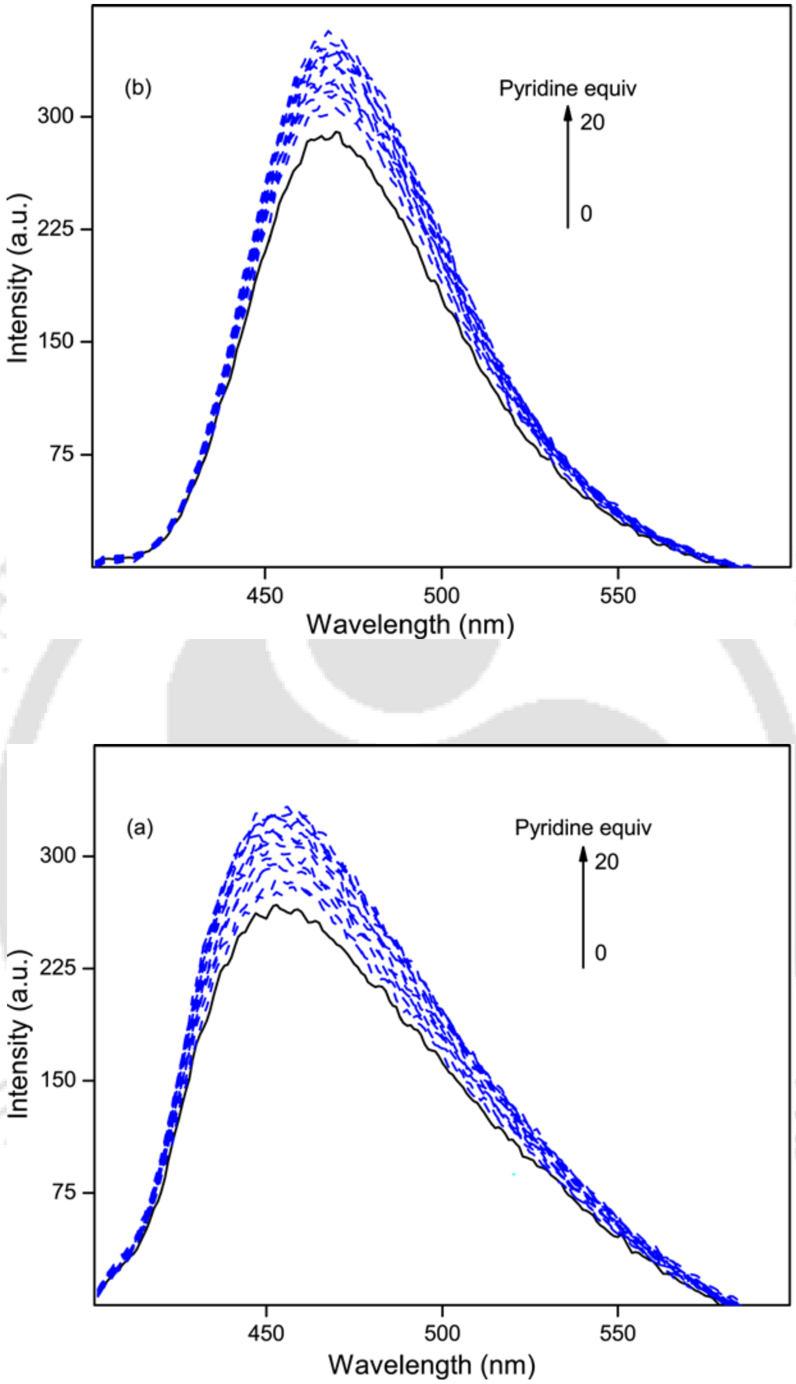


Figure 7. Fluorescence spectra of Zn(II)-polymer **P1-P2** (1.0 x 10^{-5} M in THF, λ_{ex} = 360 nm) with 0-20 equiv of pyridine (6 x 10^{-3} M in THF, with respect to the monomeric unit of **P1-P2**).

The axial coordination ability of substituted pyridines with Zn-salphen **16** as a representative family of *N*-heterocycles was well established by Kleij *et al*. (Figure 8).[14g] The extend of coordination of substituted pyridines **17-21** depends on the *ortho* groups present next to the heteroatom (Figure 8). In the case of 2,6-dimethylpyridine, the *N*-heterocycle is unable to coordinate directly to the Zn(II) ion due to strong steric infringement of the salphen geometry around the metal centre upon formation of the 1:1 complex. Therefore, the strength of the Zn–N*pyr* in salphen derivatives is a function of the substitution pattern on the *N*-heterocycle and particularly sensitive to *ortho* substitution. However, the strength of the supramolecular coordination motif is also dependent on the ability of the salen bridging group to facilitate geometrical changes upon enforcing the Zn–N*pyr* interaction. Clearly, for salphen complexes there is little degree of freedom to accommodate coordinating pyridine ligands with bulky (*ortho*) substituents. Therefore, a successful use and fine-tuning of the Zn(salen)–N coordination pattern in the build up of more complicated non-covalent architectures will depend on a delicate balance between the steric requirements of the guest molecule (e.g., *N*-heterocycles) and the flexibility of the host system (Zn-salen).

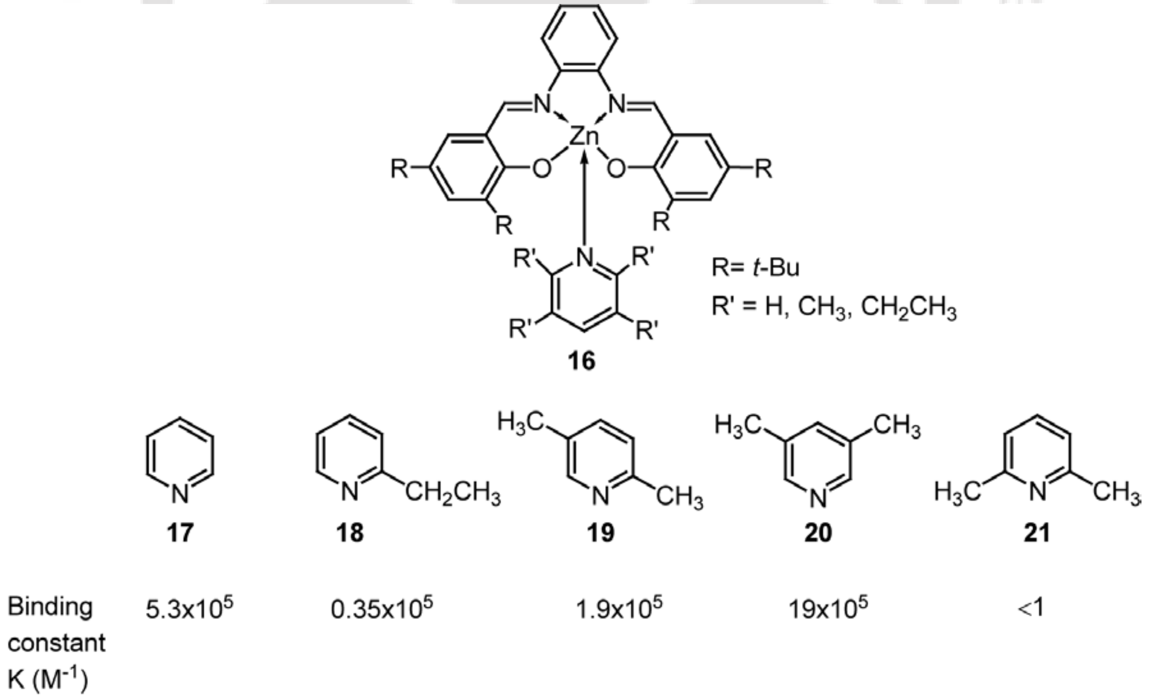
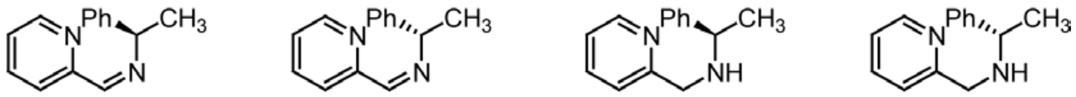


Figure 8

Thus, we investigated the chiral recognition of chiral 2-substituted pyridines (Figure 9). Since the Zn(II)-polymer **P1-P2** complexes are optically active, the *in situ* generated Zn(II)-polymer **P1-P2** complexes were used to study the selective recognition of chiral imines *R- or S*-**22** and amines *R- or S*-**23** having pyridine moiety (Figure 10-11 and Table 1). Interestingly, the Zn(II)-polymer **P1-P2** complexes exhibited considerable enantioselective discrimination toward (*R*)-1-phenyl-*N*-[(pyridin-2-yl)methylene]ethanamine *R*-**22** and (*S*)-1-phenyl-*N*-[(pyridin-2-yl)methylene]ethanamine *S*-**22**. In the context, an excess of *R*-**22** and *S*-**22** (1-18 equiv) is required with respect to the Zn(II)-polymer **P1-P2** complexes, which may be due to involvement of an equilibrium process (Figure 12). Thus, the fluorescent "*OFF*" polymers **P1-P2** may form complex with Zn^{2+} to give fluorescent "*ON*" Zn(II)-polymer **P1-P2** complexes that could enantioselectively discriminate *R*-**22** from *S*-**22** to afford an enhanced fluorescent Zn(II)-polymer **P1/P2-*R*-22** or **P1/P2-*S*-22** complexes. Experiments with *R*-**22** $((I_R/I_o)_{max}$ = 6.78 and 3.19, respectively, for **P1** and **P2**) showed higher fluorescence intensity compared to that with *S*-**23** $((I_S/I_o)_{max}$ = 5.94 and 2.58, respectively, for **P1** and **P2**), which suggests that *R*-**22** was discriminated more strongly with the Zn(II)-polymer complex compared to *S*-**22**. To reveal the effect of the chelation of the imine, *R*-**22** and *S*-**22** were reduced with $NaBH_4$ to give (*R*)-1-phenyl-*N*-[(pyridin-2-yl)methyl]ethanamine *R*-**23** and (*S*)-1-phenyl-*N*-[(pyridin-2-yl)methyl]ethanamine *S*-**23**, whose interaction with Zn(II)-polymer **P1-P2** complexes was investigated (Figure 11). Amines *R*-**23** and *S*-**23** $(\Delta(I/I_o)_{max} = ((I_R/I_o)–(I_S/I_o))_{max}$ = 0.07 and 0.47, respectively, for **P1** and **P2**) exhibited lesser extent of enantioselective discrimination toward Zn(II)-polymer **P1-P2** complexes compared to imines *R*-**22** and *S*-**22** $(\Delta(I/I_o)_{max}$ = 0.91 and 0.61, respectively, for **P1** and **P2**). These results suggest that the chelation of chiral imines *R*-**22** and *S*-**22** are more selective compared to amines *R*-**23** and *S*-**23** toward the Zn(II)-polymer **P1-P2** complexes.



R-**22** **S-22** *R*-**23** *S*-**23**

Figure 9

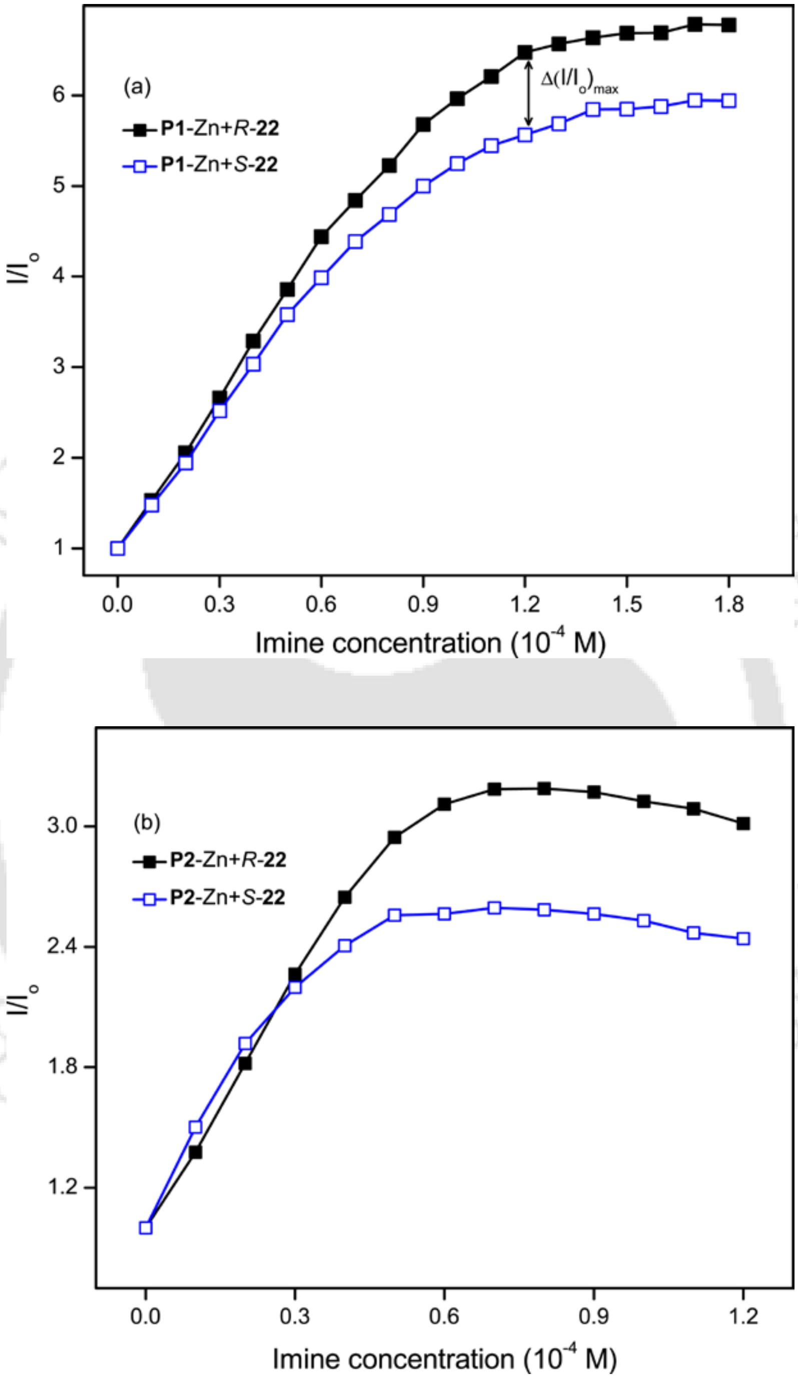


Figure 10. Chiral recognition of the Zn(II)-polymer **P1-P2** complexes (generated *in situ* from 1 x 10^{-5} M of **P1-P2** in THF and 12 x 10^{-4} M of Zn^{2+}in water (1:1.1)) with 1-18 equiv of *R*-**22** and *S*-**22** (6 x 10^{-3} M in THF). $\Delta(I/I_o)_{max}$ corresponds to 0.91 and 0.61 respectively, for (a) and (b).

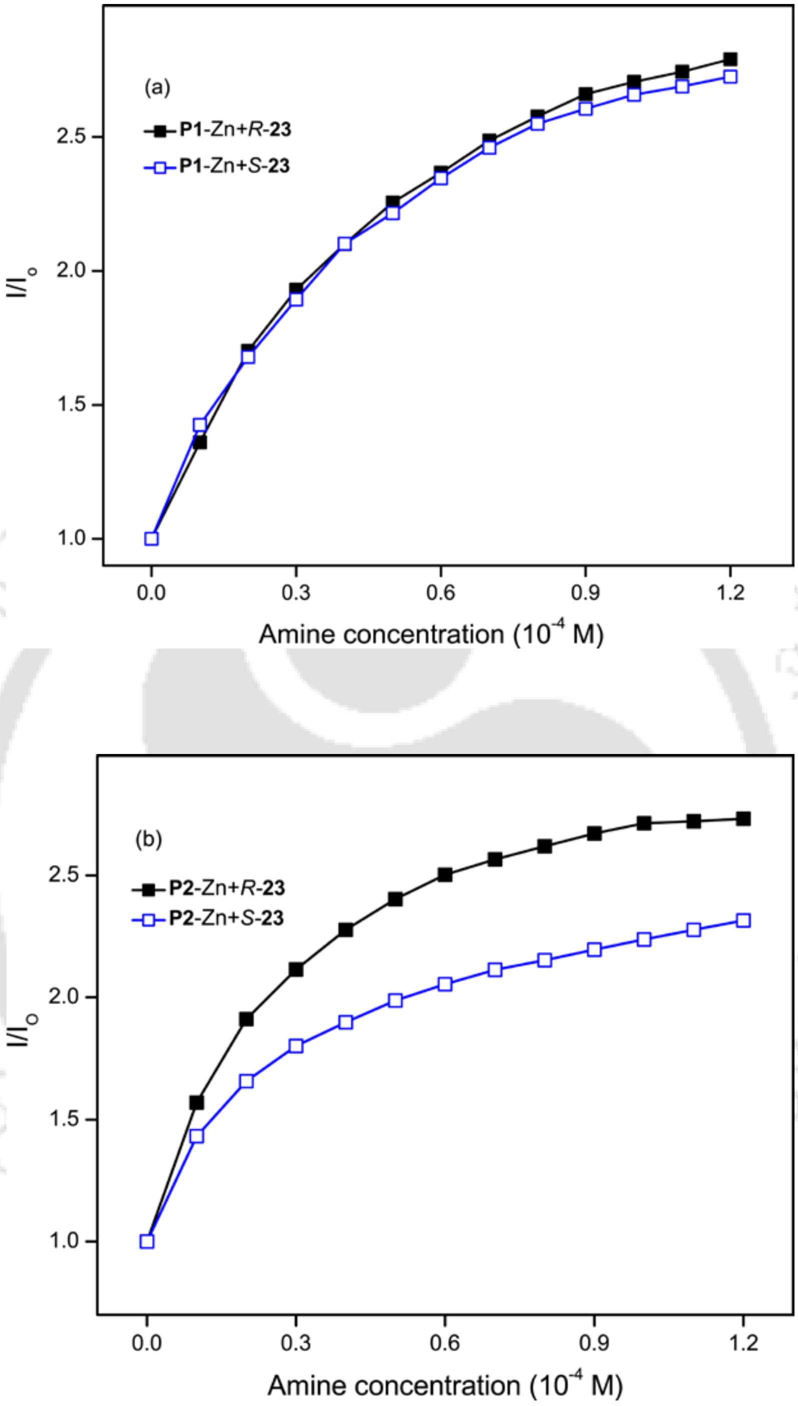


Figure 11. Chiral recognition of the Zn(II)-polymer **P1-P2** complexes (generated *in situ* from 1 x 10^{-5} M of **P1-P2** in THF and 12 x 10^{-4} M of Zn^{2+}in water (1:1.1)) with 1-18 equiv of *R*-**23** and *S*-**23** (6 x 10^{-3} M in THF). $\Delta(I/I_o)_{max}$ corresponds to 0.07 and 0.47 respectively, for (a) and (b).

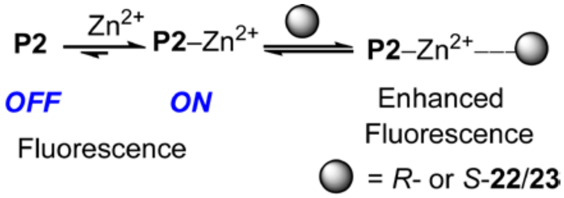


Figure 12

Table 1. Chiral Recognition of *R*-**22**, *S*-**22**, *R*-**23** and *S*-**23** with Zn^{2+}-Polymer Complexes

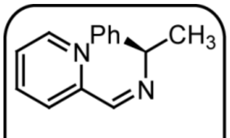
Zn^{2+}-Polymer	Enantiomer	I_{max}/I_o	$\Delta(I/I_o)_{max}$
Zn^{2+}-**P1**	*R*-**22**	6.78	0.91
Zn^{2+}-**P1**	*R*-**23**	2.79	0.07
Zn^{2+}-**P2**	*R*-**22**	3.19	0.61
Zn^{2+}-**P2**	*R*-**23**	2.73	0.47

$[C_1]$ = 1 x 10^{-5} M in THF.

In conclusion, inter-strand interaction of *in situ* generated Zn(II)-polymer **P1-P2** complex has been studied through fluorometric titration with pyridine. Chiral recognition of optically acive 2-substituted pyridines with Zn(II)-polymer complex was observed with enhanced fluorescence. Zn(II)-polymer **P1** complex having (*R*,*R*)-diaminocyclohexane moiety could able to discriminate chiral imines but not amines. Zn(II)-polymer **P2** complex with (*R*,*R*)-diphenylethylenediamine moiety can discriminate chiral imines as well as amines.

Experimetal Section

General. (*R*)- and (*S*)-Phenylethanamine were procured from Sigma-Aldrich. Solvents were purchased from Rankem and purified prior to use by standard procedure. Column chromatography was carried out with 60-120 mesh basic silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. FT-IR spectra were obtained from PerkinElmer spectrum one spectrometer. UV-vis spectra were recorded on Perkin-Elmer Lambda 25 UV/vis spectrometer. Fluorescence spectra were recorded on Varian Carey Eclipse fluorescence spectrophotometer. The optical rotation was measured on PerkinElmer model-343. Elemental analysis was carried out using Perkin Elmer-2400 CHNS analyzer.



R-**22**

Preparation of (*R*)-1-Phenyl-*N*((pyridin-2-yl)methylene)ethanamines *R*-22.[16a] To a stirred solution of pyridine-2-carboxaldehyde (1 mmol, 107 mg) in CH_3OH (1 mL), (*R*)- or (*S*)-1-phenylethanamine (1 mmol, 121 mg) was added and the resulting solution was stirred at room temperature for 3 h. The solvent was evaporated on rotary evaporator to give a residue that was dissolved in EtOAc (10 mL) and washed with brine (5 mL) and water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on basic silica gel column chromatography using EtOAc and hexane as eluent to give *R*-**22** as yellow liquid in 97% (203 mg) yield.

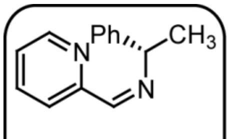
$[\alpha]_D^{20}$ = -34.1 (*c* 1.05, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.8 Hz, 1H), 8.47 (s, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.71 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.39-7.23 (m, 4H), 4.65 (q, *J* = 13.2, 6.8 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 154.8, 149.4, 144.6, 136.6, 128.6, 127.1, 126.8, 124.8, 121.5, 69.6, 24.6.

FT-IR (neat): 3060, 2972, 2926, 2861, 1587, 1567, 1467, 1436, 1371, 1080, 993, 908, 762, 699, 549 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.90; H, 6.73; N, 13.37.



S-**22**

Preparation of (*S*)-1-Phenyl-*N*((pyridin-2-yl)methylene)ethanamines *S*-22.[16b] To a stirred solution of pyridine-2-carboxaldehyde (1 mmol, 107 mg) in CH_3OH (1 mL), (*R*)- or (*S*)-1-phenylethanamine (1 mmol, 121 mg) was added and the resulting solution was stirred at room temperature for 3 h. The solvent was evaporated on rotary evaporator to give a residue that was dissolved in

EtOAc (10 mL) and washed with brine (5 mL) and water (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on basic silica gel column chromatography using EtOAc and hexane as eluent to give *S*-**22** as yellow liquid in 97% (203 mg) yield.

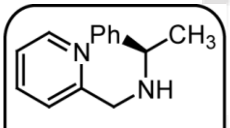
$[\alpha]_D^{20}$ = +34.8 (*c* 1.04, $CHCl_3$)

^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.8 Hz, 1H), 8.47 (s, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.71 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.39-7.23 (m, 4H), 4.65 (q, *J* = 13.2, 6.8 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 154.8, 149.4, 144.6, 136.6, 128.6, 127.1, 126.8, 124.8, 121.5, 69.6, 24.6.

FT-IR (neat): 3060, 2972, 2926, 2861, 1587, 1567, 1467, 1436, 1371, 1080, 993, 908, 762, 699, 549 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.92; H, 6.73; N, 13.35.



R-**23**

Preparation of (*R*)-1-Phenyl-*N*-((pyridin-2-yl)methyl)ethanamines *R*-23.[16c] To a stirred solution of pyridine-2-carboxaldehyde (1 mmol, 107 mg) in CH_3OH (1 mL), (*R*)-1-phenylethanamine (1 mmol, 121 mg) was added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was then treated with $NaBH_4$ (2 mmol, 76 mg) and the stirring was continued for an additional 3 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (10 mL). The organic solution was washed with brine (5 mL) and water (2 x 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using EtOAc and hexane as eluent to give *R*-**23** as colorless liquid in 95% (201 mg) yield.

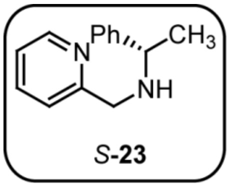
$[\alpha]_D^{20}$ = +39.3 (*c* 0.98, $CHCl_3$).[16c]

^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 4.8 Hz, 1H), 7.60 (dt, *J* = 7.6 Hz, 1H), 7.38-7.31 (m, 4H), 7.27-7.24 (m, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.16-7.13 (m, 1H), 3.83 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 2H), 2.11 (s, 1H), 1.42 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 149.2, 145.3, 136.4, 128.5, 127.0, 126.8, 122.5, 121.9, 58.0, 53.0, 24.4.

FT-IR (neat): 3438, 3062, 2966, 1593, 1570, 1451, 1433, 1370, 1127, 994, 760, 701, 545 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 79.18; H, 7.58; N, 13.25.



S-**23**

Preparation of (*S*)1-Phenyl-*N*-((pyridin-2-yl)methyl)ethanamines *S*-23.[16d] To a stirred solution of pyridine-2-carboxaldehyde (1 mmol, 107 mg) in CH_3OH (1 mL), (*S*)-1-phenylethanamine (1 mmol, 121 mg) was added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was then treated with $NaBH_4$ (2 mmol, 76 mg) and the stirring was continued for an additional 3 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (10 mL). The organic solution was washed with brine (5 mL) and water (2 x 10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using EtOAc and hexane as eluent to give *S*-**23** as colorless liquid in 95% (201 mg) yield.

$[\alpha]_D^{20} = -38.7$ (*c* 0.99, $CHCl_3$).[16d]

^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 4.8 Hz, 1H), 7.60 (dt, *J* = 7.6 Hz, 1H), 7.38-7.31 (m, 4H), 7.27-7.24 (m, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.16-7.13 (m, 1H), 3.83 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 2H), 2.11 (s, 1H), 1.42 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 149.2, 145.3, 136.4, 128.5, 127.0, 126.8, 122.5, 121.9, 58.0, 53.0, 24.4.

FT-IR (neat): 3438, 3062, 2966, 1593, 1570, 1451, 1433, 1370, 1127, 994, 760, 701, 545 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 79.22; H, 7.61; N, 13.17.

Pyridine Titration. To the solutions of the Zn(II)-polymer complex (3 mL, 1 x 10^{-5} M in THF with respect to the monomeric unit, Zn^{2+} and polymer ratio was 1.1:1), derived from $Zn(NO_3)_2$ (9 x 10^{-4} M in water, 1 equiv) and **P2** (3 mL, 1 x 10^{-5} M in THF with respect to the monomeric unit) for 1 h, was added the solutions of pyridine in THF (6 x 10^{-3} M in THF, 1-20 equiv). The resultant solutions were thoroughly mixed. After 5 min, fluorescence of the respective solutions was measured using λ_{ex} = 360 nm (Figure 7).

Enantioselective Fluorocent Recognition. The solution of the polymers **P1-P2** (3 mL, 1 x 10^{-5} M in THF with respect to monomeric unit) and $Zn(NO_3)_2{\cdot}6H_2O$ (25 μL, 12 x 10^{-4} M in H_2O, 1 equiv) were thoroughly mixed at ambient temperature to produce the respective Zn(II)-polymer **P1-P2** complexes. After 5 min, they were treated with *R*-**22**, *S*-**22**, *R*-**23** or *S*-**23** (5-90 μL (1-18 equiv), 6 x 10^{-3} M in THF). The solutions were mixed and left for 5 min at ambient temperature to generate the corresponding Zn(II)-polymer-*R*-**22**/*S*-**22**/*R*-**23** or *S*-**23** complexes. The fluorescence spectrum of the respective solutions was monitored using λ_{ex} = 360 nm.

5.6 References

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List of Publications

1. Chiral Titanium Catalysts Derived From (1*R*,2*S*)-1-Amino-2,3-dihydro-1*H*-inden-2-ol Based Tridentate Ligands for Asymmetric Oxidation of Sulfides with Aqueous Hydrogen Peroxide.
   Sakthivel, S.; Punniyamurthy, T. *Manuscript submitted*.

2. Fluorescent *OFF-ON* Polymer Chemosensor Bonded Alternatively with 1,4-Dioctyloxybenzene and (*R*,*R*)-Salen for Cascade Zn^{2+} and Chiral Recognition.
   Sakthivel, S.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2012**, *23*, 570.

3. Fluorescent Non-linear Chiral Polymer Chemosensor Bonded Alternatively with 1,4-Diethynyl-2,5-dioctyloxybenzene and (*R*,*R*)-Salen for Zn^{2+} Recognition.
   Sakthivel, S.; Jammi, S.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2012**, *23*, 101.

4. Chiral Linear Polymers Bonded Alternatively with Salen and 1,4-Dialkoxybenzene: Synthesis and Application for Ti-catalyzed Asymmetric TMSCN addition to Aldehydes.
   Sakthivel, S.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2010**, *21*, 2834.

5. Cu_2O Nanoparticles Catalyzed *N*-Arylation of Amides and Imidazoles and *S*-Arylation of Thiols with Aryl Iodides.
   Jammi, S.; Krishnamurthy, S.; Saha, P.; Kundu, D. S.; Sakthivel, S.; Ali, Md. A.; Paul, R.; Punniyamurthy, T. *Synlett* **2009**, 3323.

6. Synthesis, Structure, and Application of Self-Assembled Copper(II) Aqua Complex by H-Bonding for Acceleration of the Nitroaldol Reaction onWater.
   Jammi, S.; Ali, Md. A.; Sakthivel, S.; Rout, L.; Punniyamurthy, T. *Chem. Asian. J.* **2009**, *4*, 314.

7. CuO Nanoparticles Catalyzed *C-N*, *C-O*, and *C-S* Cross-Coupling Reactions: Scope and Mechanism.
   Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971.

8. Chiral Binuclear Copper(II) Catalyzed Nitroaldol Reaction: Scope and Mechanism.
   Jammi, S.; Saha, P.; Sanyashi, S.; Sakthivel, S.; Punniyamurthy, T. *Tetrahedron* **2008**, 11724.

Conferences

1. Fluorescent *OFF-ON* Polymer Chemosensor Bonded Alternatively 1,4-Dioctyloxybenzene and (*R*,*R*)-Salen for Cascade Zn^{2+} and Chiral Recognition. Sakthivel, S.; Punniyamurthy, T. *7th Junior National Organic Symposium Trust*, Indian Institute for Science and Educational Research Mohali, Mohali, December 15-18 , **2011**.

2. Synthesis and Application of Chiral Poly(Ti-salen) for Asymmetric TMSCN Addition to Aldehydes.
   Sakthivel, S.; Punniyamurthy, T. *6th Junior National Organic Symposium Trust*, University of Hyderabad, Hyderabad, January 28-31, **2011**.

3. Synthesis and Application of Chiral Poly(Ti-salen) for asymmetric TMSCN Addition to Aldehydes.
   Sakthivel, S.; Punniyamurthy, T. *Frontier in Chemical Sciences 2010*, Indian Institute of Technology Guwahati, Guwahati, December 3-4, **2010.**