Studies Toward Copper-Catalyzed Asymmetric Nitroaldol and Iron-Catalyzed Thia-Michael/Aldol Cascade Reactions

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated To

My Family Members and

Teachers

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 M. Kannan

December 2016

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

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CERTIFICATE

This is to certify that Mr. M. Kannan has been working under my supervision since July 2010. I am forwarding his thesis entitled "*Studies Toward Copper-Catalyzed Asymmetric Nitroaldol and Iron-Catalyzed Thia-Michael/Aldol Cascade Reactions*" being submitted for the 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 and this work has not been submitted elsewhere for a degree.

Guwahati — Prof. Tharmalingam Punniyamurthy

December 2016 — Supervisor

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M. Kannan

List of Abbreviations

Ac	acetyl
Bz	benzoyl
Bn	benzyl
BQ	benzoquinone
Bu	butyl
BaO	barium oxide
$CHCl_3$	chloroform
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	diisopropylamine
dr	diastereomeric ratio
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
ee	enantiomeric excess
EWG	electron wthdrawing group
EDG	electron donating group
FT-IR	Fourier transform infrared spectroscopy
HCHO	formaldehyde
HRMS	high-resolution mass spectrometry
^{i}Pr	isopropyl
HPLC	high performance liquid chromatography
ICl	Iodine monochloride
m/z	mass to charge ratio
mp	melting point
Me	methyl
$N_2H_4 \cdot H_2O$	hydrazine hydrate
NMR	nuclear magnetic resonance

Ph	phenyl
KF	potassium fluoride
4-PPNO	4-phenylpyridine n-oxide
$KICl_2$	Potassium dichloroiodide
Ts	*p*-toluenesulfonyl
rt	room temperature
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
NEt_3	triethylamine
TMS	trimethylsilyl
TMSCN	trimethlsilyl cyanide
NaOCl	sodium hypochlorite
$NaCNBH_3$	sodium cyanoborohydride
$NaBH_4$	sodium borohydride
$SnCl_4$	Tin(IV) chloride
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
DIPEA	*N*,*N*-diisopropylethylamine
PyBOX	pyridine bis(oxazoline)

Abstract

The thesis contains four chapters. The first chapter describes a brief literature survey of asymmetric catalytic synthetic methodologies based on chiral salen, salan, salalen ligands and tridentates aminoalcohol derived ligands. The second chapter focuses on the synthesis of chiral copper(II) complexes based on salen, salan and salalen ligands and their application for enantioselective nitroaldol reaction. The third chapter deals with chiral iron-catalyzed enantioselective synthesis of tetrahydrothiophenes. The fourth chapter discusses about the synthesis of chiral dendrimers and their application for enantioselective synthesis of tetrahydrothiophenes with chiral iron-dendrimer catalyst.

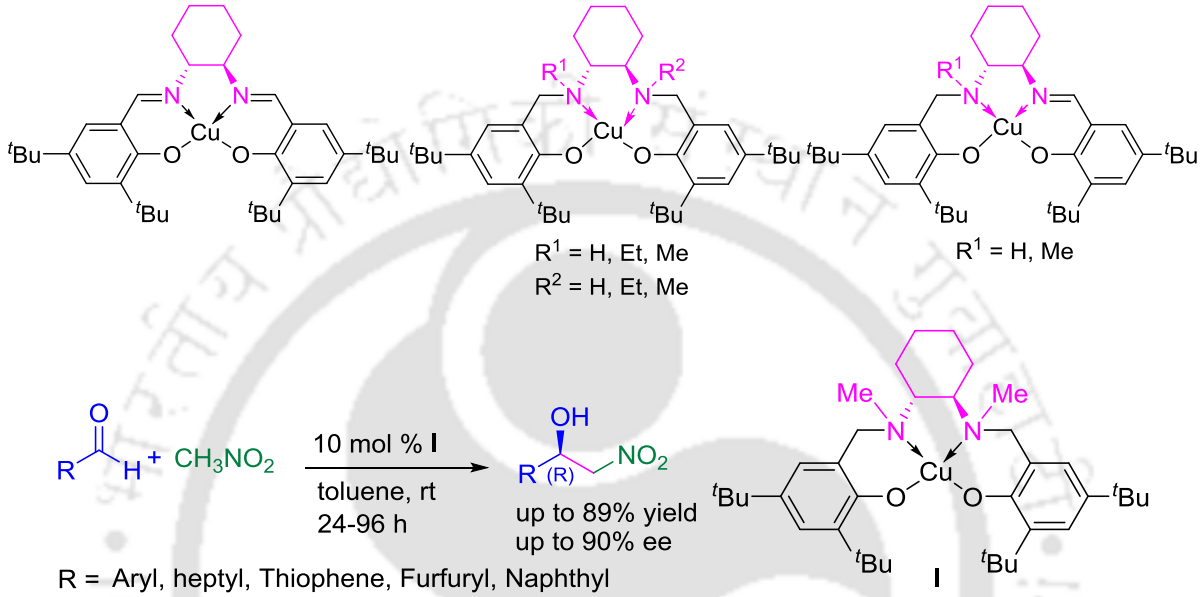
Chapter I. Chiral Salen, Salan, Salalen and Tridendate *β*-Aminoalcohol Ligands in Asymmetric Metal Catalysis

Asymmetric metal catalysis affords an ideal method for making the chiral molecules. Thousands of chiral ligands and their transition metal complexes have been reported 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. Among them, salen type Schiff base ligand has received much attention because of its easy preparation and allows modification at different sites to attain a specific geometry such as chiral diamine backbone, 3,3’ and 5,5’ position of the ligand. Thus, one can control steric and electronic requirement of the catalyst easily. This chapter discusses about selected enantioselective synthetic methodology based on chiral tetradendate salen, salan and salalen ligands and tridendate *β*-aminoalcohol derived ligands.

Chapter II. Chiral Copper(II)-Catalyzed Enantioselective Nitroaldol Reaction

Chiral *β*-nitroalcohols serve as versatile synthetic intermediates for the asymmetric synthesis of numerous pharmaceutically important compounds. A variety of chiral metal catalysts as well as organocatalysts have been developed for nitroaldol reaction in recent decades because of the wide spread applications of *β*-nitroalcohol derivatives. In this chapter, first the synthesis of symmetrical as well as unsymmetrical chiral copper(II)-complexes bearing salen, salan, salalen and salalan ligands have been described. Further, the effect of ligand *N*,*N*-

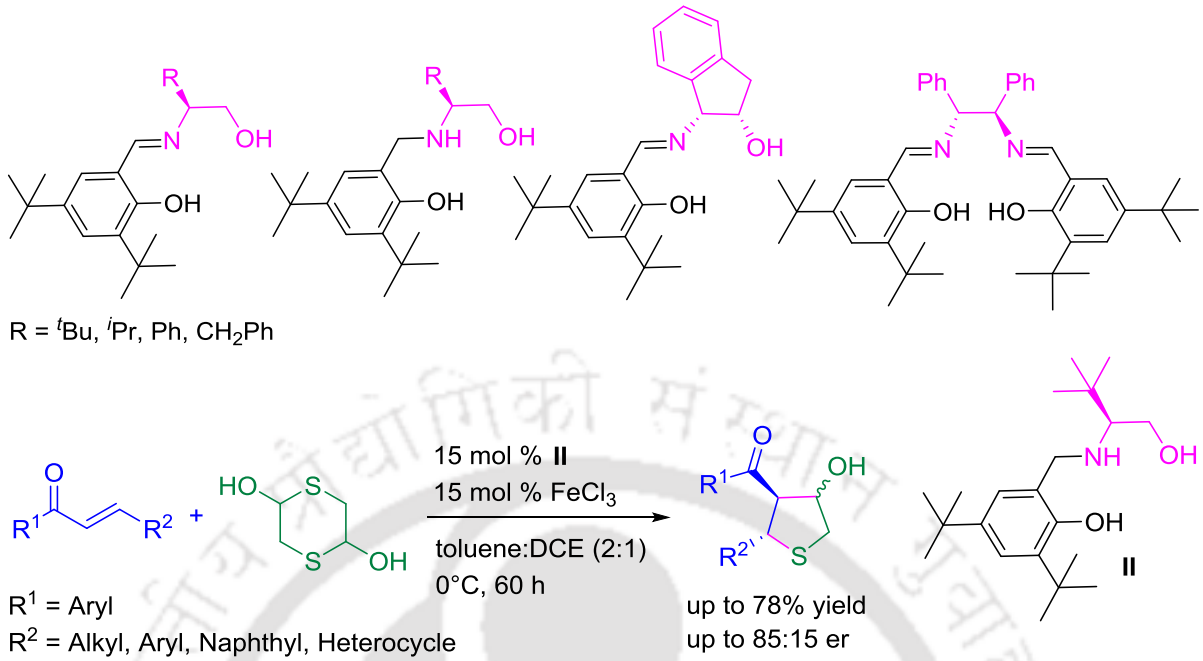
substituents on reactivity of chiral copper(II) salalen, salalan and salan complexes towards nitroaldol reaction has been studied (Scheme 1). The reaction of aliphatic and aromatic aldehydes with nitromethane in the presence of chiral copper(II)-complex have been accomplished with high enantioselectivities at room temperature under additive free conditions.



Scheme 1. Chiral Copper(II)-Complex Catalyzed Enantioselective Nitroaldol Reaction

Chapter III. Chiral Iron-Catalyzed Enantioselective Synthesis of Tetrahydrothiophenes

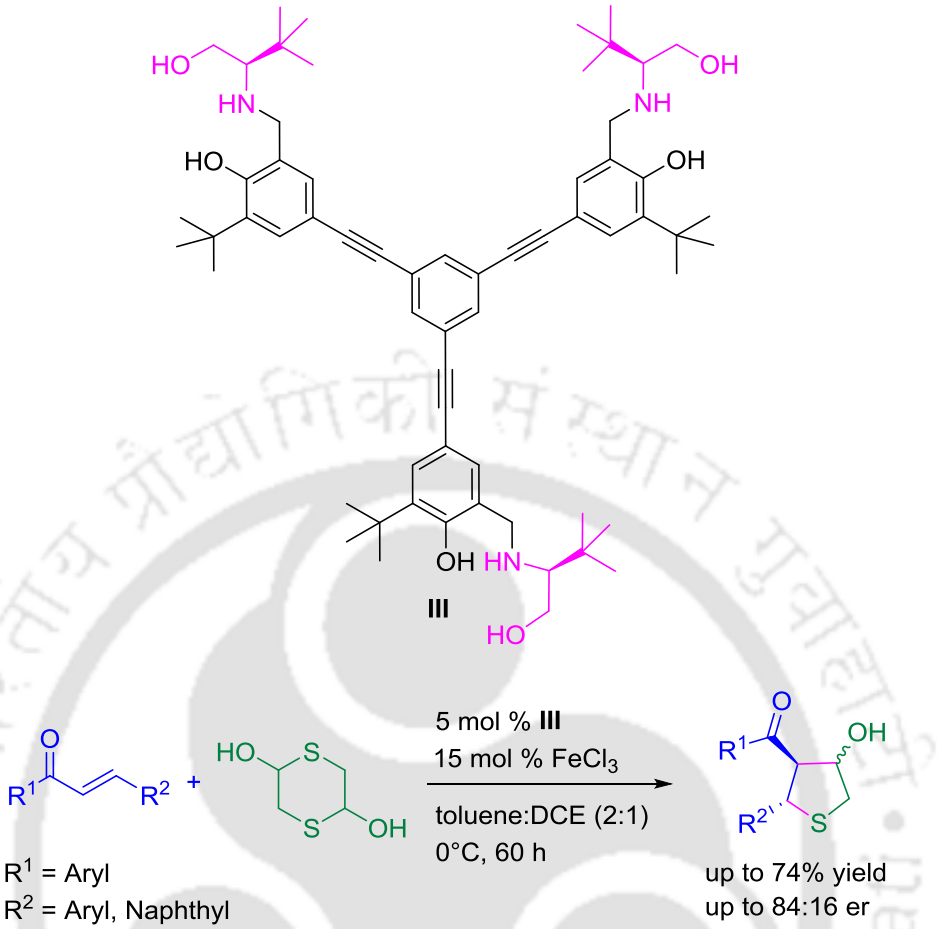
Optically active polysubstituted tetrahydrothiophenes are important structural motif present in many biologically active compounds and also they serve as versatile chiral auxiliaries in asymmetric synthesis. Traditionally, chiral trisubstituted tetrahydrothiophenes were synthesized by organocatalyst mediated asymmetric domino reactions. In this chapter, we describe a general route for chiral metal catalyzed tetrahydrothiophenes synthesis *via* asymmetric domino reaction (Scheme 2). A series of tridentate ligands derived from *β*-aminoalcohols were synthesized and its catalytic application was examined with $FeCl_3$ for enantioselective synthesis of tetrahydrothiophenes using substituted chalcones and 1,4-dithiane-2,5-diol at 0 °C.



Scheme 2. Fe(III)-Catalyzed Enantioselective Synthesis of Tetrahydrothiophenes

Chapter IV. Chiral Iron-Dendrimer Catalyzed Enantioselective Synthesis of Tetrahydrothiophenes

Asymmetric methodologies in chemical industry are rather limited due to the high cost of chiral ligands and use of noble metals, which have to be separated from the reaction mixture after use. The common strategies used in homogeneous catalysis to make costly chiral ligands as recoverable and recyclable catalyst are dendrimer catalysis, stereo-regular polymers and soluble polymer anchored catalyst. Dendrimers are regular highly branched and well-defined macromolecular structure with three dimensional networks, which preserves the microenvironment around the catalytic site similar to that of monomeric unit and thus retains the activity similar to that one of the monomer unit. This chapter first discusses about the synthesis of chiral tridentate *tert*-lucinol derived dendrimer. Further, its application as recyclable catalyst for enantioselective synthesis of trisubstituted tetrahydrothiophenes with $FeCl_3$ has been demonstrated (Scheme 3). This catalytic-system provides the advantages of simplified product isolation, easy recovery and recyclability of the dendrimer Fe(III)-catalyst.



Scheme 3. Iron-Dendrimer Catalyzed Enantioselective Synthesis of Tetrahydrothiophenes

Contents

Chapter I

1.1 Importance of Asymmetric Metal Catalysis

Asymmetric synthesis is a key process for making optically active molecules in organic synthesis. Indeed many natural products, sugar moieties, proteins, pharmaceuticals and enzymes exist as single isomer in nature.[1] More interestingly, enantiomers of a single molecule show different biological activities for example (*R*)-thalidomide is an effective sedative, where as the (*S*)-thalidomide is highly teratogenic and cause fetal abnormalities;[2] L-DOPA a drug for treating Parkinson's disease but D-DOPA is biologically inactive; L-penicillamine is toxic but D-penicillamine is used for the treatment of rheumatoid arthritis. As a result of superior performance of pure enantiomers, the increasing demand for the asymmetric synthesis of enantiopure single isomer has received much attention in the field of medicinal chemistry, pharmaceuticals, agrochemicals, flavors and fragrances etc. Generally three fundamental strategies are adopted in asymmetric synthesis; chiral pool synthesis, racemate resolution and asymmetric catalysis. However, the first two approaches suffer from severe drawbacks such as requiring stoichiometric amounts of a suitable precursor and yielding only up to 50% of the desired enantiomer. Indeed, asymmetric catalysis provides the potential advantages of minimum use of costly chiral catalyst, mild reaction condition, short synthetic route for a given target (atom economy), wide substrate scope, less by-products and ease purification.[3] Asymmetric catalysis can further be classified into metal catalysis, enzyme catalysis and organocatlaysis. However, the present study is focused on asymmetric metal catalysis.

A major breakthrough has been achieved in the field of asymmetric metal catalysis by Knowles in early 1970's for the enantioselective synthesis of L-DOPA using chiral rhodium complex.[4] Justifiably, he shared the 2001 Nobel Prize in chemistry with Noyori and Sharpless for their outstanding work on metal catalyzed enantioselective hydrogenation and allylic epoxidation reactions. Many chiral ligands have been reported in literature for asymmetric metal catalysis. Some of the most popular ligands include chiral BINAP, BINOL, tartaric acid derivatives, Schiff base derivatives (salen, salan, salalen and aminoalcohol derived ligands) and bisoxazoline ligands (figure 1). Among them, chiral tetradentate Schiff base

ligands particularly salen derivatives have been widely studied for asymmetric catalysis in recent decades.[5] The strong coordinating ability of these ligands with transition metals and main group elements including Mn, Co, Cu, Cr, Fe, Al, Ti, V, Zn, Ru and Ir allows the synthesis of a wide range of metal Schiff base complexes and display its catalytic applications into a large number of useful transformations such as alkene epoxidation, sulfide oxidation, cyclopropanation, cyclopropenation, aziridination, cyanide addition, diethylzinc addition, dimethylphosphite addition, carbonyl-ene reaction, hetero-ene reaction, Nazarov cyclization, pinacol coupling, Passerini reaction, aziridine ring opening reaction, oxidative coupling reaction of 2-naphthol and kinetic resolution of secondary alcohols.

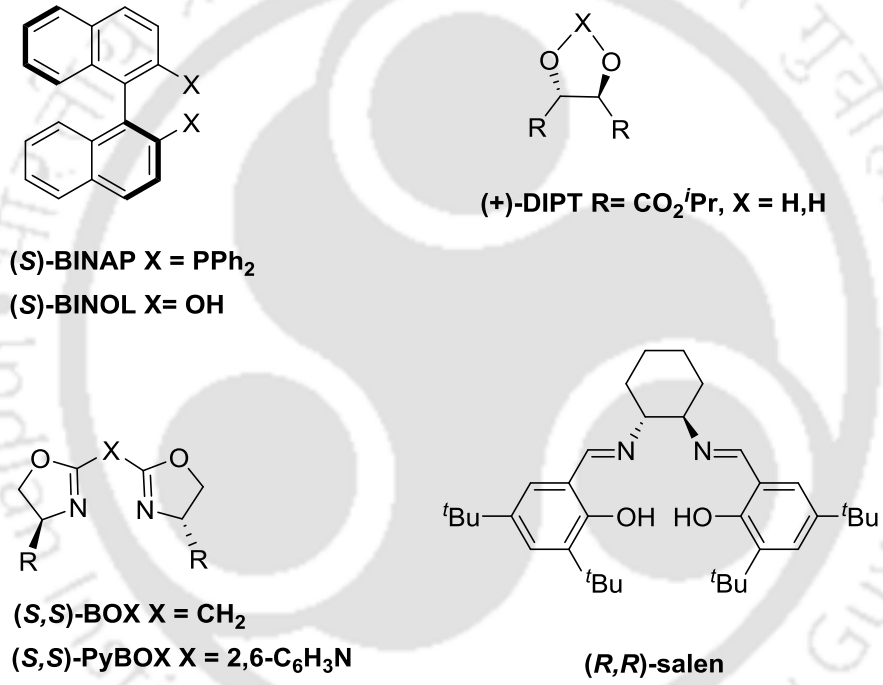


Figure 1. Family of Privilege Chiral Ligands

Generally, tetradentate Schiff base ligand is termed as salen (sal = salicylaldehyde + en = ethylelne diamine). The basic salen structure is shown in figure 2 which shows the following impressive key features 1. The modification at the 3,3' and 5,5' position of the salicyladehyde unit with suitable substituent alters the steric and electronic nature of the salen. 2. The choice of different chiral diamine alters the dihedral angle of the ligand. 3. In addition the use of different metals allows salen complex to attain required conformation or geometry. Having modified the above three features one could easily control the structure,

geometry, steric and electronic nature of a complex required for a particular reaction. Due to the diverse applications of salen ligands in asymmetric reactions, we have focused attention on the development of tetradentate and tridentate Schiff base ligands in asymmetric metal catalysis.

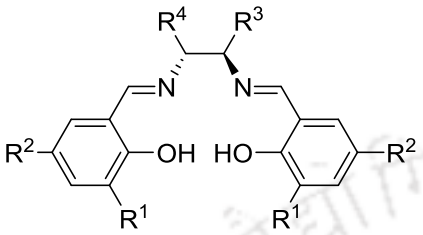
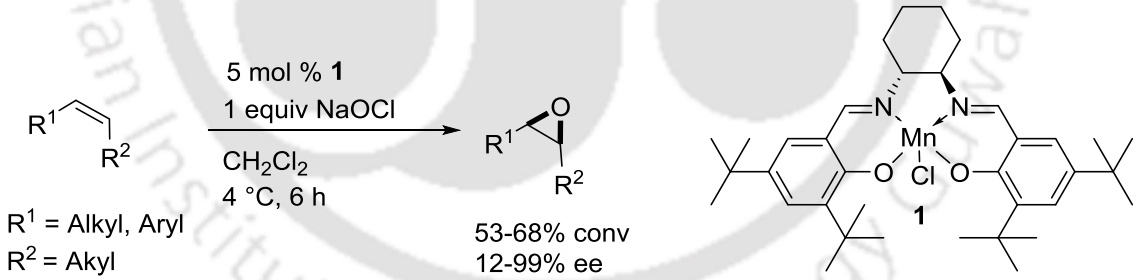


Figure 2. The Basic Salen Structure

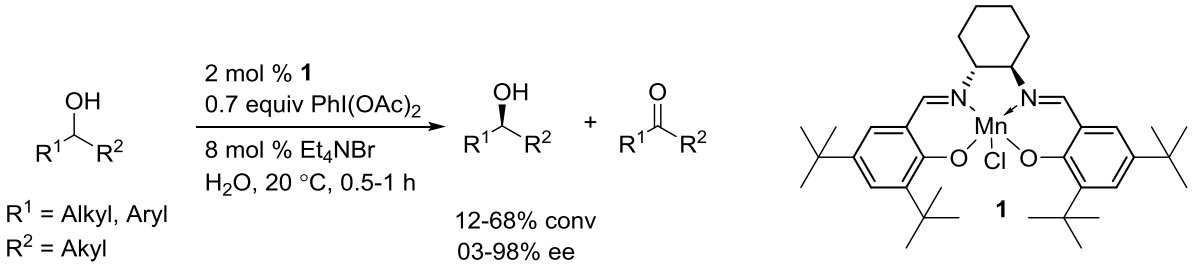
1.2 Selected Synthetic Methodologies Based on Salen Ligands

Jacobsen and co-workers have developed chiral Mn(III)-salen complex for enantioselective epoxidation of simple *cis*-olefins (Scheme 1).[6] They have observed greater enantioselectivity >90% ee for majority of substrates. This was attributed to the presence of bulky *tert*-butyl group on 3,3' and 5,5'-position of the catalyst allowing the substrate molecules to approach the catalyst along axial orientation.



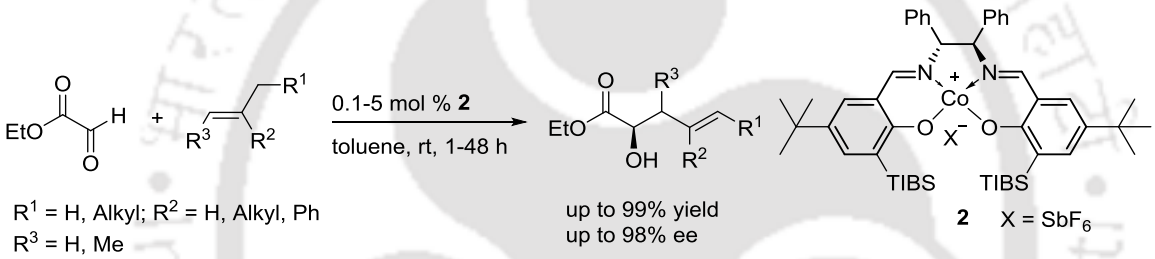
Scheme 1. Mn(III)-Salen Catalyzed Enantioselective Epoxidation of Simple Olefins

Xia and co-workers have reported an effective protocol utilizing chiral Mn(III)-salen complex for oxidative kinetic resolution of secondary alcohols with the cooxidant diacetoxyiodobenzene (Scheme 2).[7a] This protocol is mild and requires short reaction time in water medium to afford secondary alcohols in high enantioselectivity. Later, they proved the formation of oxomanganese intermediate by ESI-MS experimental studies.[7b] Further, a detailed mechanistic study was reported by Corey and co-workers.[7c]



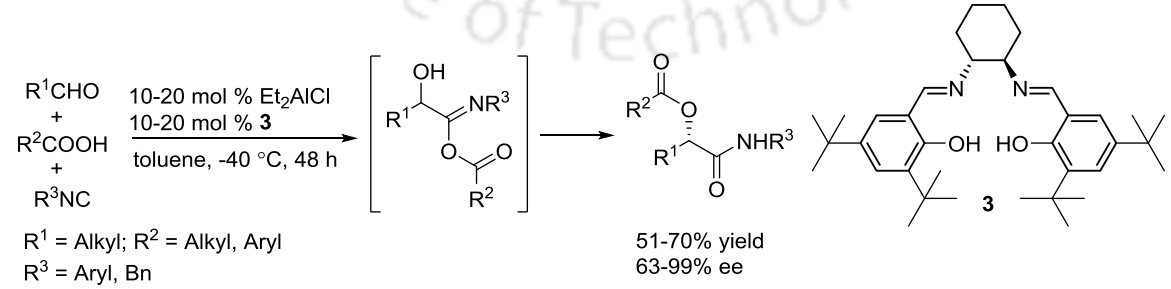
Scheme 2. Mn(III)-Salen Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols

Rawal and co-workers have demonstrated the use of diphenyl Co-salen complex for enantioselective carbonyl-ene reaction of disubstituted and trisubstituted alkenes with ethyl glyoxalate (Scheme 3).[8] The presence of bulky triisobutylsilyl substituents on the catalyst provided the corresponding chiral homoallylic alcohols in high enantioselectivities.



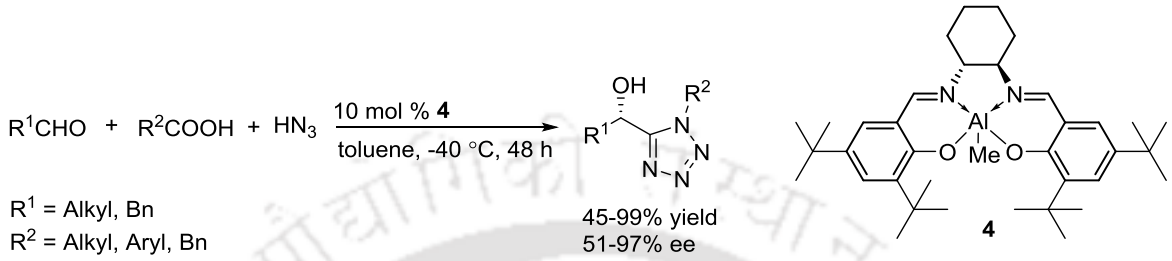
Scheme 3. Co(III)-Salen Catalyzed Enantioselective Carbonyl-Ene Reaction

Wang and co-workers have described an efficient chiral Al(III)-salen catalyzed three component enantioselective Passerini reaction involving condensation of aldehyde, carboxylic acid and isocyanide (Scheme 4).[9] The reaction readily proceeded with aliphatic aldehydes using 10 mol % catalyst and afforded the corresponding α-acyloxyamides in high enantioselectivity.



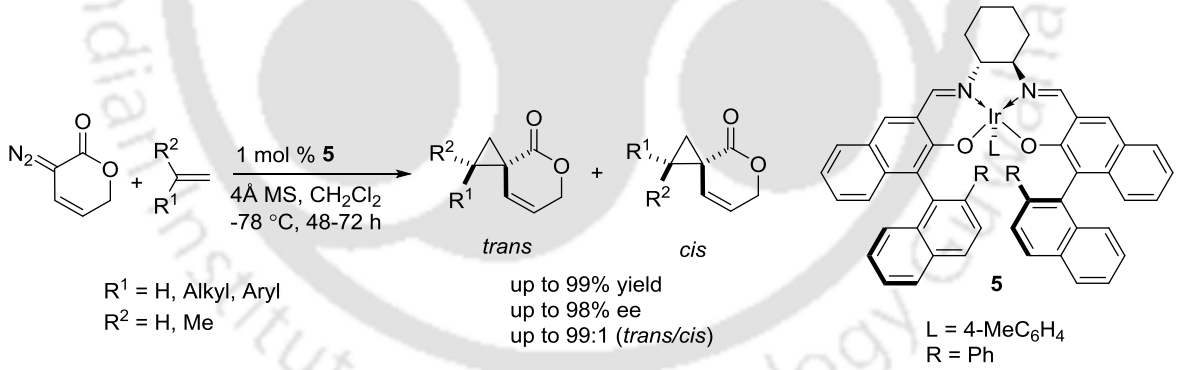
Scheme 4. Al(III)-Salen Catalyzed Enantioselective Passerini Reaction

The same group has subsequently developed hydrazoic acid modified enantioselective three component Passerine type reaction with chiral Al(III)-salen complex (Scheme 5).[10] The reaction is accomplished with a variety of aliphatic aldehydes and aromatic carboxylic acids in high yield and enantioselectivity.



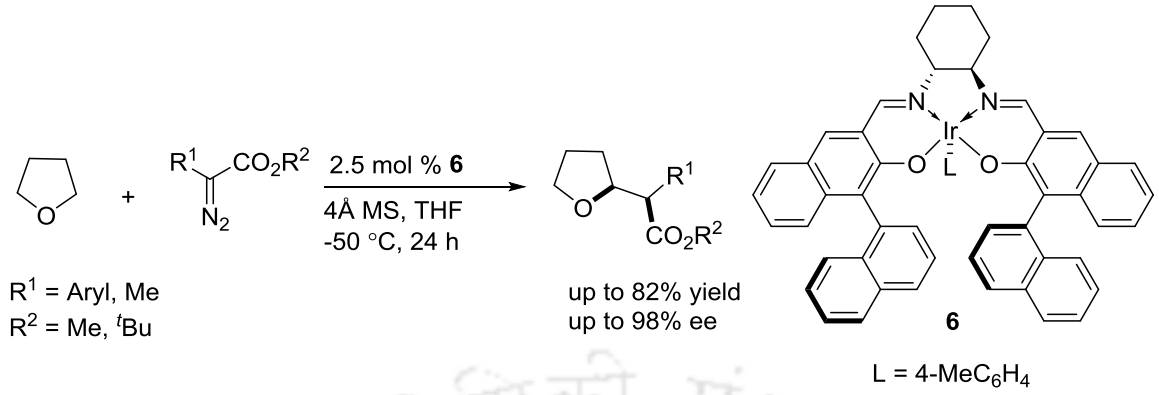
Scheme 5. Al(III)-Salen Catalyzed Enantioselective Tetrazole Synthesis

Katsuki and co-workers have found chiral Ir(III)-salen complex bearing axially chiral salicylaldehyde derivatives for enantioselective cyclopropanation reaction of aryl and alkenyl substituted olefins with vinyl diazolactone (Scheme 6).[11] This process proceeded with low catalyst loading and provided the corresponding 5-oxaspiro[2.5]oct-7-en-4-ones in high enantioselectivity (≥97% ee) and *trans* selectivity (≥94:6).



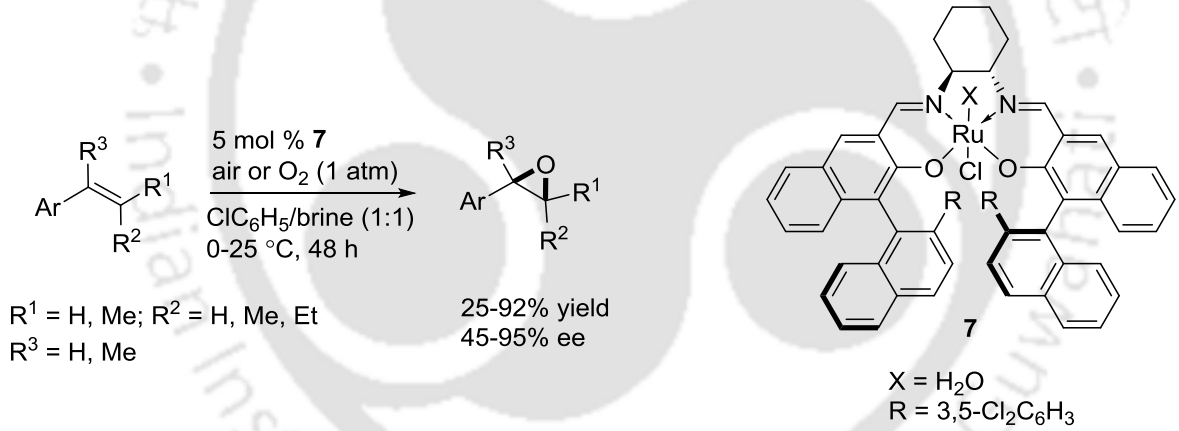
Scheme 6. Ir(III)-Salen Catalyzed Enantioselective Cyclopropanation Reaction

Later, the same group has reported Ir(III)-salen catalyzed asymmetric carbenoid insertion into the C-H bond at the α-position of tetrahydrofuran using α-aryl-α-diazoacetate and α-diazopropionate (Scheme 7).[12] This study revealed enantioselective intermolecular C-H carbene insertion with chiral salen complex in high enantio and diastereoselectivities.



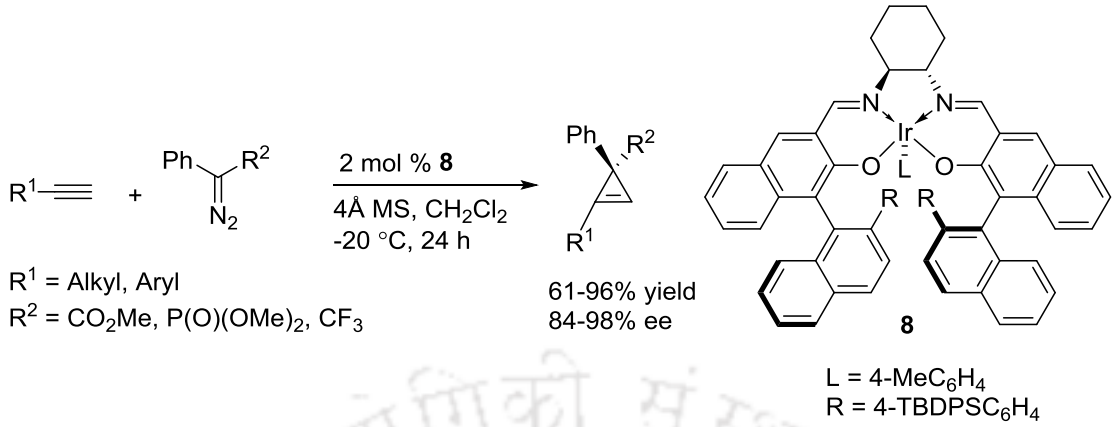
Scheme 7. Ir(III)-Salen Catalyzed Enantioselective C-H Bond Functionalization

A highly robust aqua Ru(III)-salen complex has been reported for enantioselective epoxidation of conjugated olefins (Scheme 8).[13] This process is mild and consumes atmospheric oxygen as oxidant at 25 °C or oxygen gas at 0 °C. Further, this catalyst provided corresponding epoxides in high enantioselectivity.



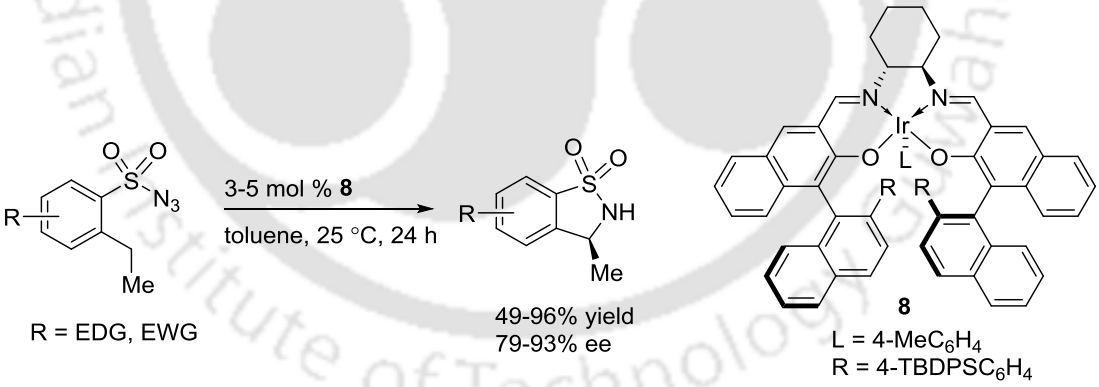
Scheme 8. Ru(III)-Salen Catalyzed Aerobic Enantioselective Epoxidation

Ir(III)-salen complex has been demonstrated for enantioselective cyclopropenation of aryl acetylenes with donor/acceptor or acceptor/acceptor substituted diazo compounds such as *α*-aryl-*α*-diazoacetates, *α*-phenyl-*α*-diazophosphonate, 2,2,2-trifuloro-1-phenyl-1-diazoethane and *α*-cyano-*α*-diazoacetamide (Scheme 9).[14] These diazocompounds serves as carbenoid precursors and provide highly enantioselective cyclopropenes containing quaternary carbon with cyano, phosphonate and trifuloromethy groups.



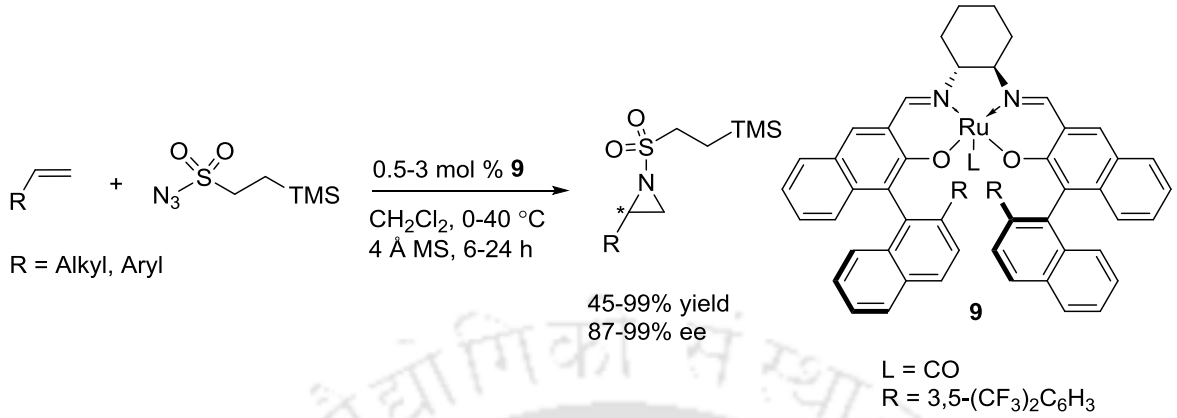
Scheme 9. Ir(III)-Salen Catalyzed Enantioselective Cyclopropenation Reaction

In continuation of enantioselective Ir(III)-salen catalysed reactions, an intramolecular enantioselective C-H bond amination reaction has been demonstrated with sulfonyl azide (Scheme 10).[15] The cyclization of 2-ethylbenzenesulfonyl azides at the benzylic position produces five-membered sultams, where as substrates having a homobenzylic methylene carbon atom produces six-membered sultams with excellent enantioselectivity. Here the sulfonyl azide serves as convenient metal-carbenoid precursors in the presence of a Ir(III)-salen with loss of molecular nitrogen.



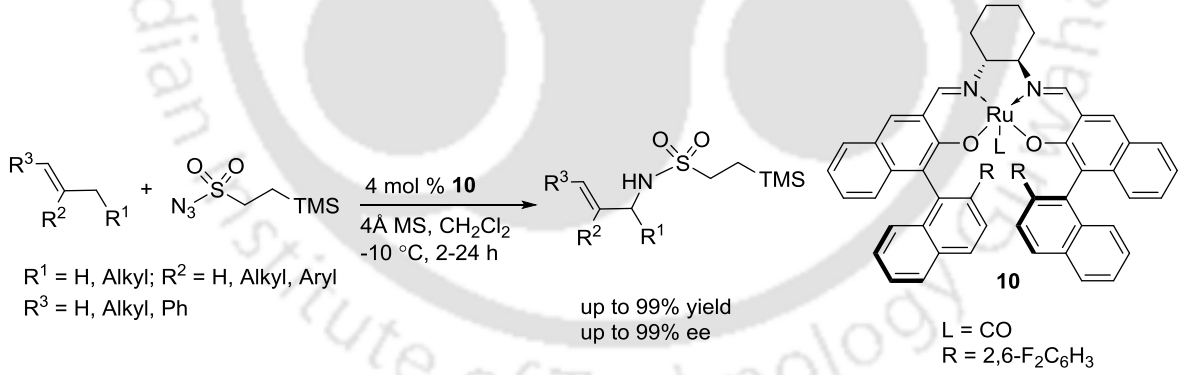
Scheme 10. Ir(III)-Salen Catalyzed Intramolecular Enantioselective C-H Amination

A newly designed Ru(CO)-salen complex bearing 3,5-ditrifluoromethylphenyl group has been developed for enantioselective aziridination of conjugated and non-conjugated olefins (Scheme 11).[16] This reaction proceeds under very low catalyst loading and affords the desired aliphatic as well as aromatic aziridines in high yield and high enantioselectivity. Further, the presence of sulfonyl oxygen atom enhances the reactivity of the nitrenoid intermediate.



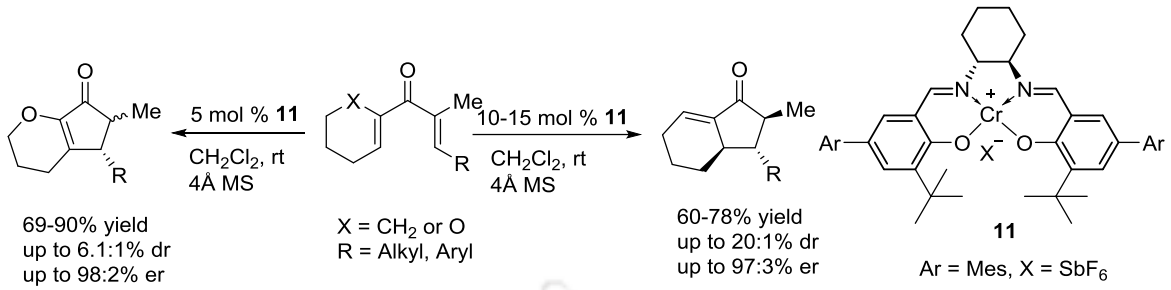
Scheme 11. Ir(III)-Salen Catalyzed Enantioselective Cyclopropenation Reaction

Ru(CO)-salen complex bearing 2,6-difluorophenyl group has been described for enantio- and regioselective intermolecular benzylic and allylic C-H bond amination reaction (Scheme 12).[17] Generally, intermolecular reaction takes longer time than intramolecular reaction and this complex efficiently catalyses intermolcular C-H amination in short reaction time with substrates bearing methyl, ethyl and cyclic methelene groups present in the allylic and benzylic position in high yield and high enantioselectivity.



Scheme 12. Ru(CO)-Salen Catalyzed Enantioselective allylic C-H Amination

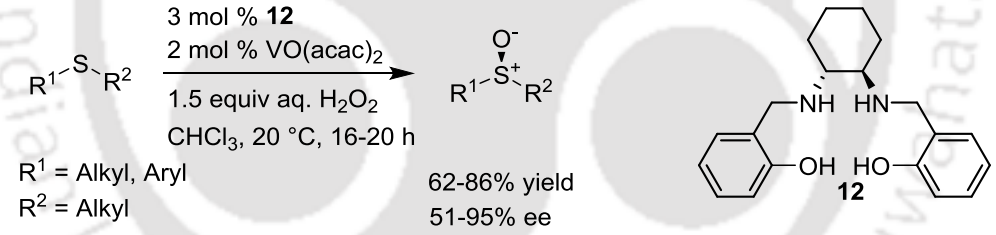
Rawal and co-workers have discovered Cr(III)-salen catalysed enantioselective Nazarov cyclization of activated and unactivated dienones (Scheme 13).[18] Gratifyingly, the salen complexes bearing 5,5'-diaryl substituents yielded Nazarov cyclization under mild reaction condition without any additive giving cyclopentenoids with three contiguous chiral centers in high enantio- and diastereoselectivities.



Scheme 13. Cr(III)-Salen Catalyzed Enantioselective Nazarov Cyclization

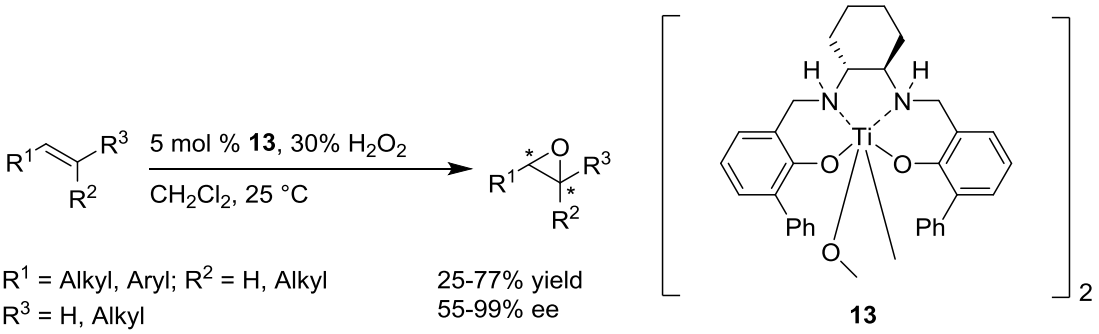
1.3 Selected Synthetic Methodologies based on Chiral Salan Ligands

Zhu and co-workers have studied enantioselective oxidation of sulphides as well as kinetic resolution of sulfoxides with hydrogen peroxide under air in the presence of chiral V(V)-salan catalyst (Scheme 14).[19] Interestingly, this catalytic system oxidises various dialkyl and arylalkyl sulphides to afford the corresponding chiral sulfoxides in higher enantioselectivity with opposite configuration as compared with that of the salen catalyst.



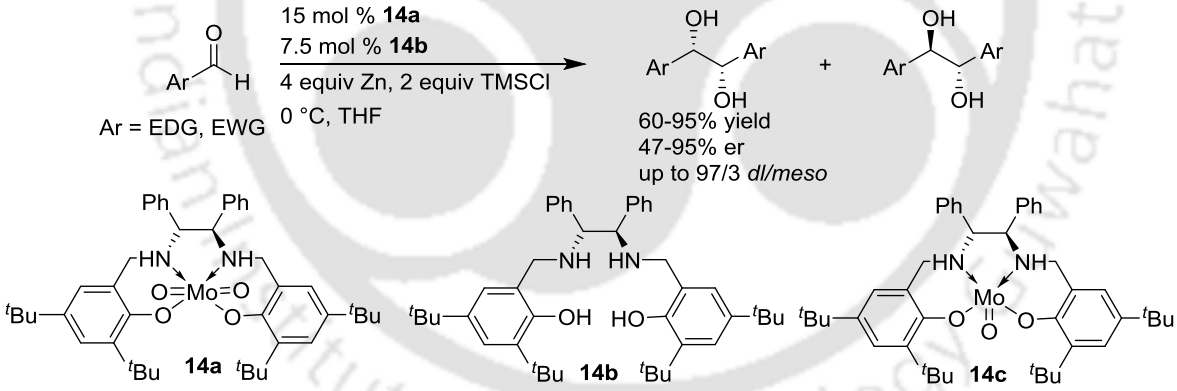
Scheme 14. V(V)-Salan Catalyzed Enantioselective Sulfoxidation

Katsuki and co-workers have developed chiral Ti(IV)-salan catalyst for enantioselective epoxidation of unfunctionalized olefins using 30% aqueous hydrogen peroxide as oxidant (Scheme 15).[20] This method efficiently oxidizes various olefins to provide the corresponding epoxides in high enantioselectivity at room temperature.



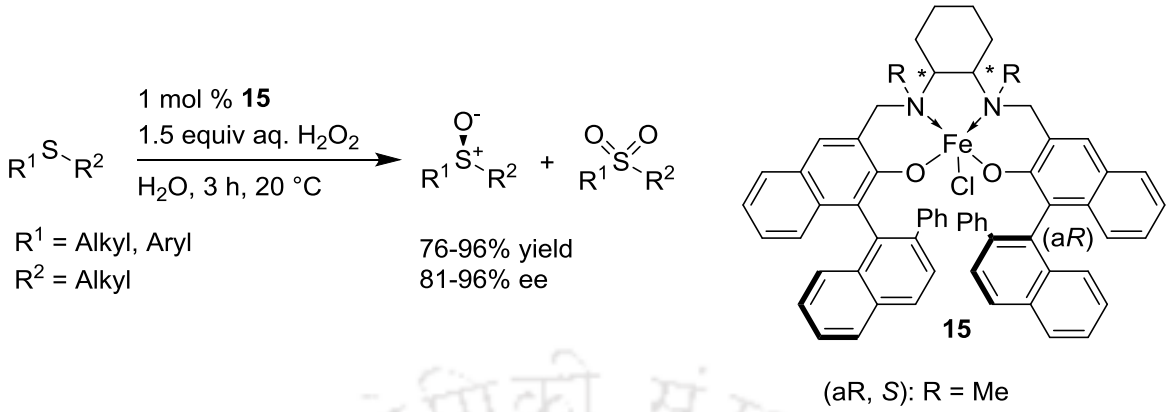
Scheme 15. Ti(IV)-Salan Catalyzed Enantioselective Epoxidation

Zhu and co-workers have reported chiral Mo(VI)-salan complex for asymmetric pinacol coupling of aromatic aldehydes (Scheme 16).[21] This transformation was successfully applied to various aromatic aldehydes bearing electron donating and electron withdrawing groups to furnish *cis*-diols as major isomer in high enantiomeric excess. Here trimethylsilyl chloride acts as a mediator and Zn powder serves as co-reductant. In addition, X-ray photoelectron spectroscopy studies revealed that the active catalytic species involved in the reaction is Mo(IV) **14c**.



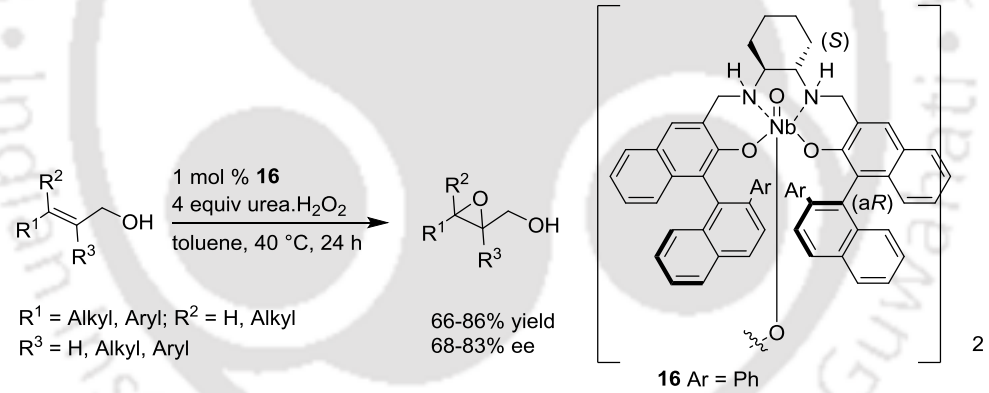
Scheme 16. Mo(VI)-Salan Catalyzed Asymmetric Pinacol Coupling Reaction

Katsuki and co-workers have developed Fe(III)-Salan Complex for asymmetric oxidation of sulfides with hydrogen peroxide (Scheme 17).[21] This transformation has been successfully accomplished for various dialkyl and arylalkyl sulphides to provide sulfoxides with high enantioselectivity under water medium in remarkably high catalytic turn over number.



Scheme 17. Fe(III)-Salan Catalyzed Enantioselective Sulfoxidation Reaction

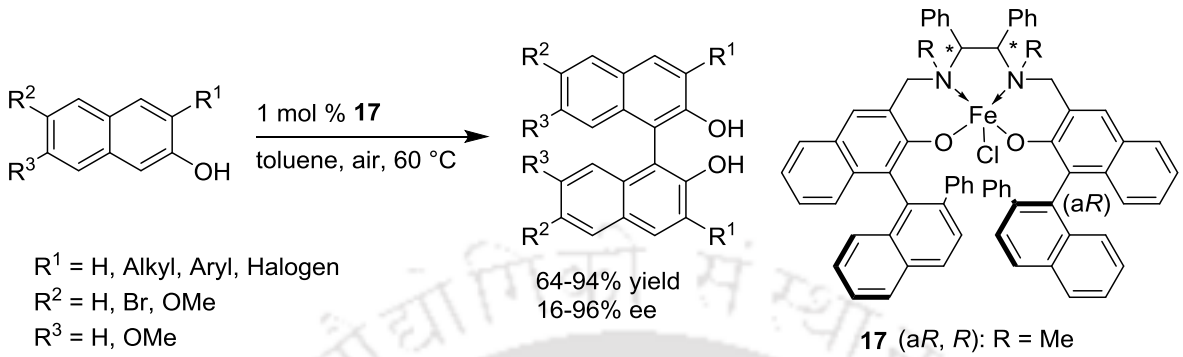
Dimeric oxo-bridged Nb(V)-salen complex has been discussed for asymmetric oxidation of allylic alcohols (Scheme 18).[23] The epoxidation of various allylic alcohols has been carried out with urea-hydrogenperoxide in toluene to provide the corresponding epoxides in high enantioselectivity.



Scheme 18. Nb(V)-Salan Catalyzed Enantioselective Epoxidation of Allylic Alcohols

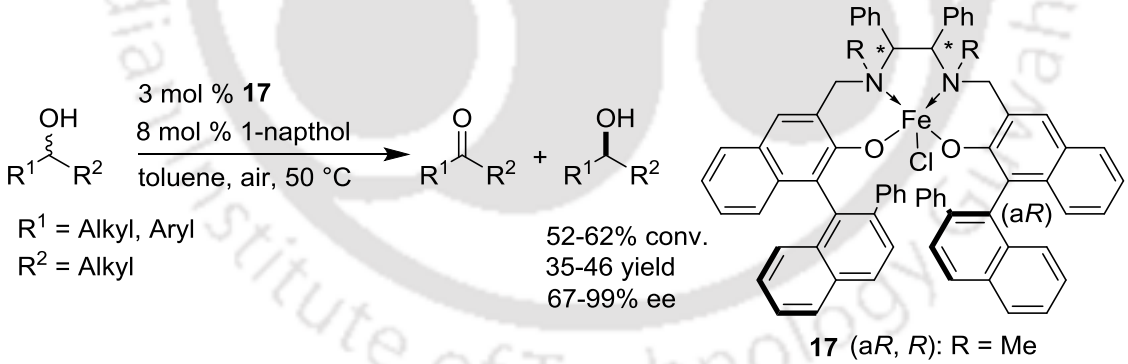
Chiral diphenylethylene diamine based dimeric oxo-bridged Fe(III)-Salan complex has reported for enantioselective aerobic oxidative coupling of substituted 2-naphthols (Scheme 19).[24a] This method provides a mild and eco-friendly process for the synthesis of 3,3'-disubstituted binaphthols without any additives. Further, extending the application of the same catalyst, enantioselective aerobic oxidative cross coupling of 2-naphthols has been studied with Fe(III)-salan complex.[24b] The reaction readily proceeds to afford both homo-

coupled and cross-coupled BINOL in high enantioselectivity. Gratifyingly, the cross-coupled products have been observed as major isomer.



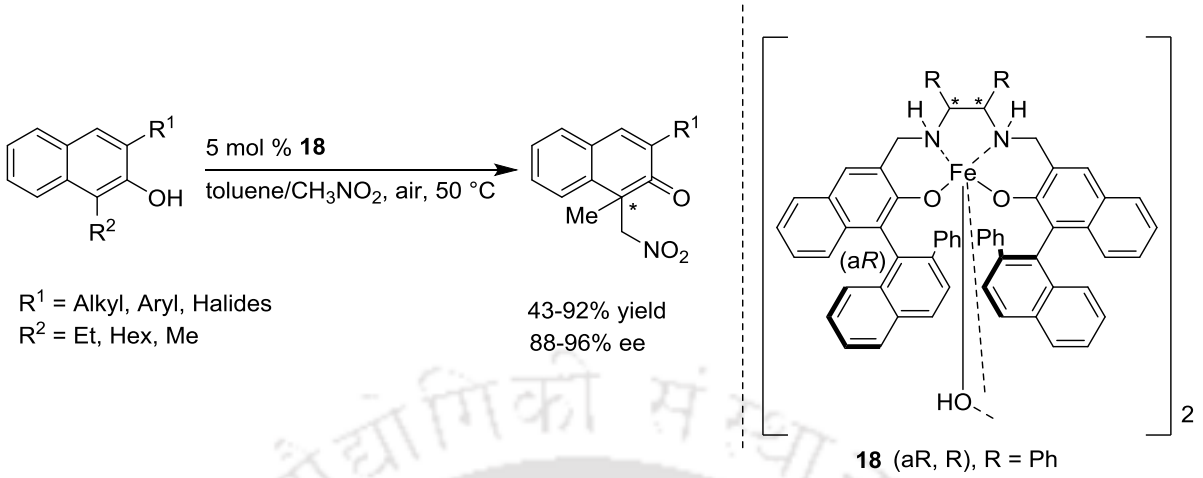
Scheme 19. Fe(III)-Salan Catalyzed Oxidative Coupling of 2-Naphthols

Chiral Fe(III)-salan complex has been shown for aerobic oxidative kinetic resolution of secondary alcohols (Scheme 20).[25] Interestingly, the enhancement of the catalytic activity was observed by the addition of 1-napthol additive. This transformation has been successfully accomplished for various secondary alcohols containing aliphatic and aromatic substituents to give the corresponding secondary alcohols in high enantioselectivity.



Scheme 20. Fe(III)-Salan Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols

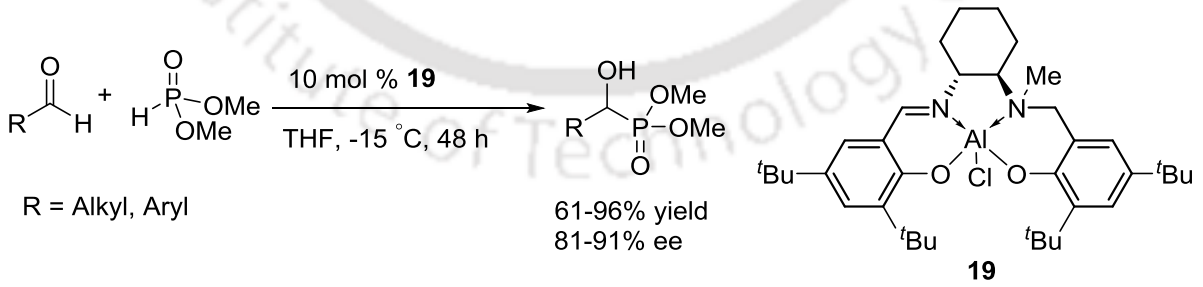
Fe(III)-salan complex has been reported for aerobic oxidative dearomatization of 1-substituted 2-naphthols with nitromethane (Scheme 21).[26] This reaction is shown to driven by oxygen reduction followed by nucleophilic addition of nitromethane leads to the formation of cyclic enones with quaternary stereocenter in high enantiomeric excess.



Scheme 21. Fe(III)-Salan Catalyzed Asymmetric Oxidative Dearomatization of 2-naphthols

1.4 Selected Synthetic Methodologies Based on Salalen Ligands

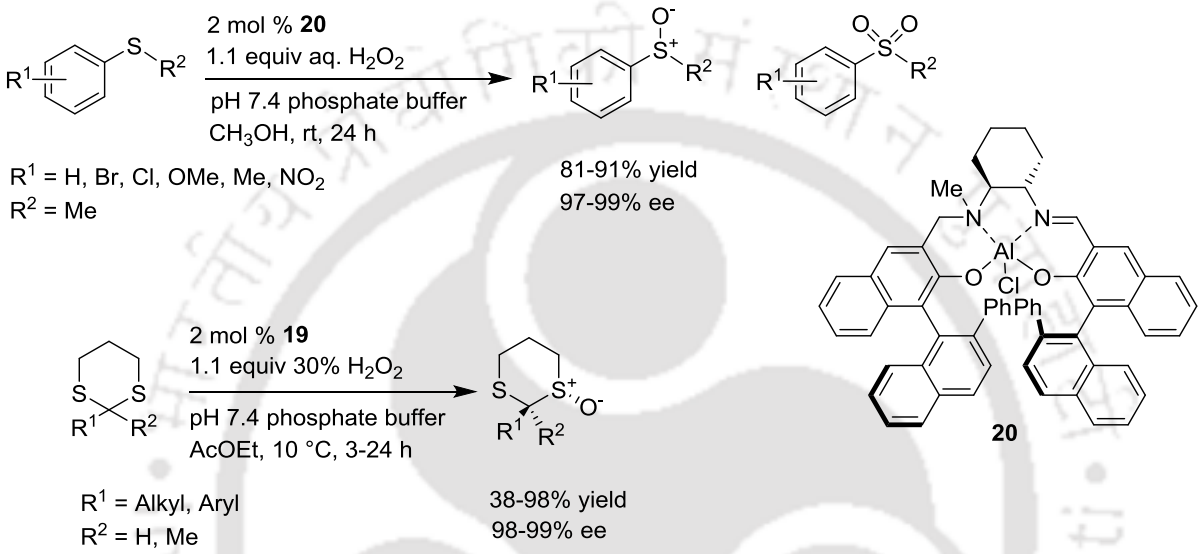
Katsuki and co-workers have investigated chiral Al(III)-salalen complex for enantioselective dimethyl phosphite addition to aldehydes (Scheme 22).[27a] The geometry of this complex was found to be distorted trigonal-bipyramidal by X-ray analysis. This process has been applied to various aliphatic and aromatic aldehydes without additive to afford the corresponding α-hydroxyphosphonates in high enantioselectivities. Besides, they extended the scope of the process for asymmetric hydrophosphonylation of aldimines with dimethyl phosphate.[27b] Later, they found that the addition of inorganic base such as potassium carbonate enhanced the reaction rate of asymmetric Al(III)-salalen catalyzed hydrophosphonylation of aldehydes with dimethyl phosphite.[27c]



Scheme 22. Al(III)-Salalen Catalyzed Asymmetric Hydrophosphonylation of Aldehydes

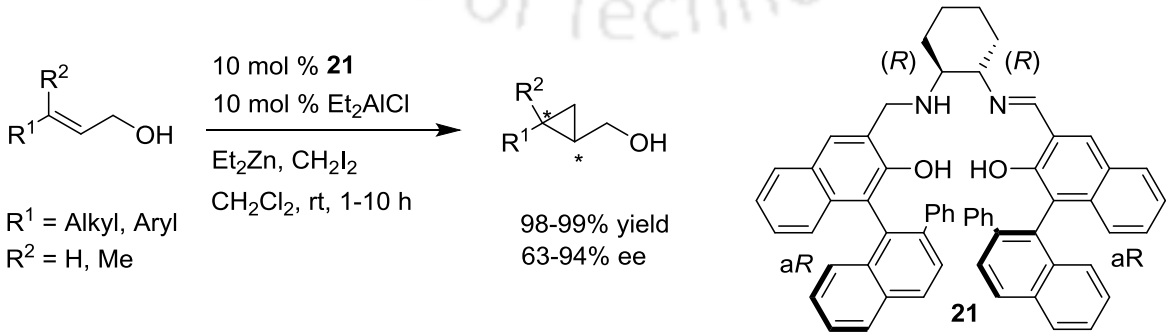
Chiral Al(III)-Salalen complex has been demonstrated for asymmetric oxidation of sulfides with aqueous hydrogen peroxide (Scheme 23).[28] This process has been accomplished

successfully to a variety of aryl methyl sulfides consists of electron-donating and electron-withdrawing substituents in high enantioselectivity. Later, they found under solvent free condition only 0.002-0.01 mol % catalyst is sufficient to perform this enantioselective oxidation. Further, the same catalyst has been examined for asymmetric oxidation of cyclic dithioacetals.[28c] This catalyst converted a series of 2-substituted-1,3-dithianes bearing alkyl, alkenyl, alkynyl and aryl substituents into *trans*-monoxides with high enantioselectivity.



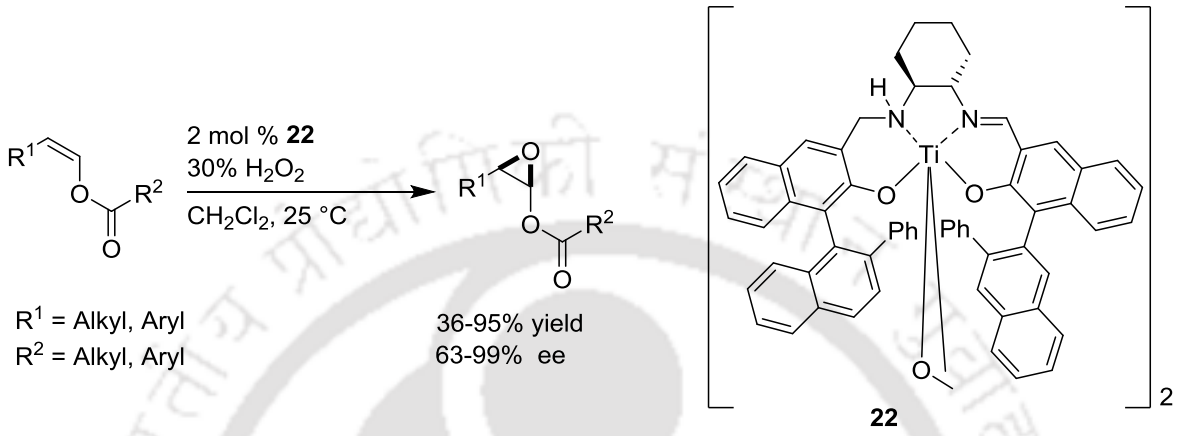
Scheme 23. Al(III)-Salalen Catalyzed Asymmetric Oxidation of Sulfides

Asymmetric Simmons-Smith reaction of allylic alcohols has been studied with chiral Al(III)-salalen catalyst (Scheme 24).[29] This reacation has been applied successfully to various *trans*-allylic alcohols with diiodomethane and diethylzinc in the presence of Al(III)-salalen catalyst at room temperature. This reaction readily proceeded to give the corresponding *β*-hydroxyl cyclopropanes with high enantioselectivities in short reaction time.



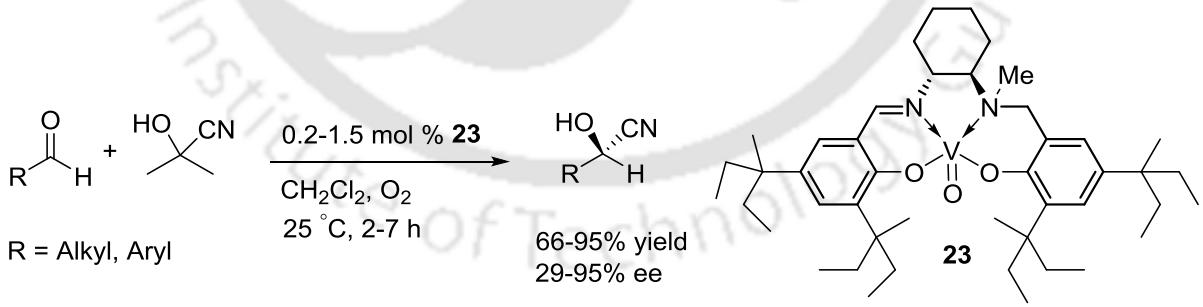
Scheme 24. Al(III)-Salalen Catalyzed Asymmetric Simmins-Smith Reaction

Chiral Ti(IV)-salalen complex has been developed for enantioselective epoxidation of (*Z*)-enol esters (Scheme 25).[30a] A series of aliphatic and aromatic (*Z*)-enol esters have been transformed into the corresponding epoxides with high enantioselectivities in the presence of aqueous hydrogen peroxide.



Scheme 25. Ti(IV)-Salalen Catalyzed Enantioselective Epoxidation of (*Z*)-Enol Esters

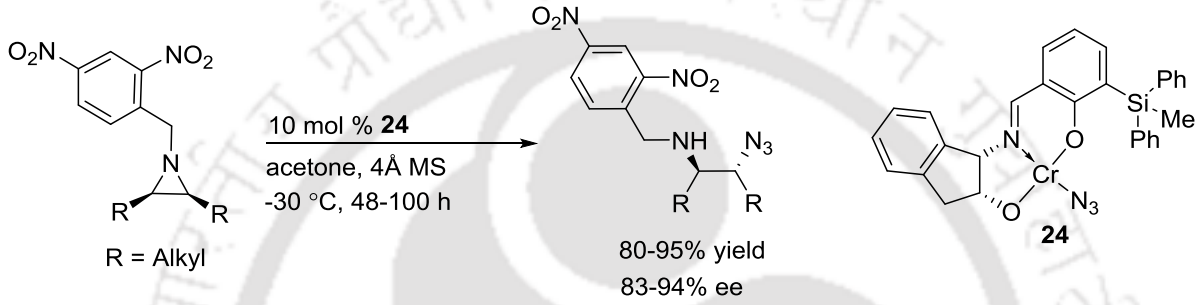
Chiral V(V)-salalen complex has been reported for enantioselective cyanohydrin synthesis (Scheme 26).[31] This reaction has been carried out successfully between various aliphatic aldehydes and acetone cyanohydrin at room temperature. The formed aliphatic cyanohydrins were observed with high enantioselectivities where as aromatic aldehydes showed poor enantioselectivity.



Scheme 26. V(V)-Salalen Catalyzed Enantioselective Cyanohydrin Synthesis

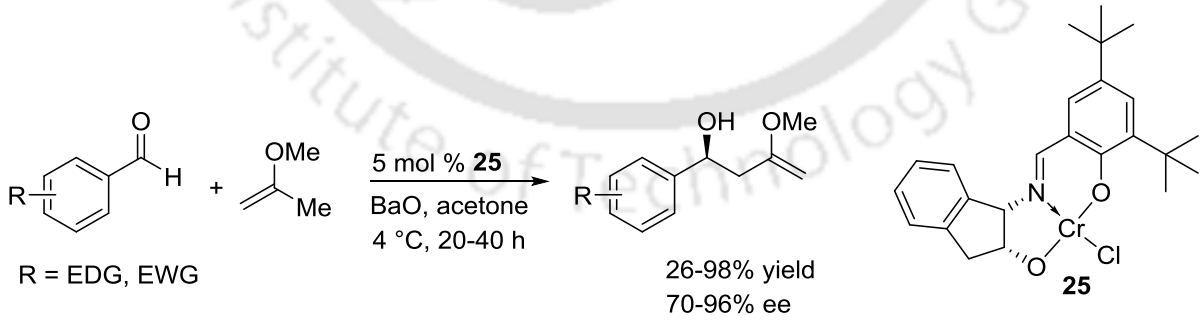
1.5 Selected Synthetic Methodologies Based on Tridentate Schiff Base Ligands

Jacobsen and co-workers have developed chiral Cr(III)-tridentate Schiff base complex for enantioselective ring opening of *meso*-aziridines (Scheme 27).[32] This reaction has been accomplished with various cyclic and acyclic aliphatic *meso* aziridines and trimethylsilyl azide using 10 mol % catalyst and the corresponding ring opening products were observed in high enantioselectivity.



Scheme 27. Enantioselective Ring Opening of Aziridines

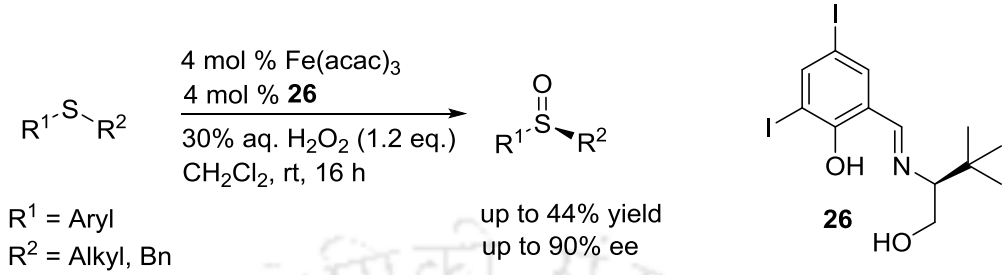
The same group has extended the application of chiral Cr(III)-tridentate Schiff base complex for enantioselective hetero-ene reaction (Scheme 28).[33] A wide range of aromatic aldehydes bearing electron-donating and electron-withdrawing groups underwent reaction with 2-methoxypropene in the presence of 5 mol % catalyst and provided the corresponding *β*-hydroxyenol ethers in high enantioselectivities.



Scheme 28. Enantioselective Hetero-Ene Reaction

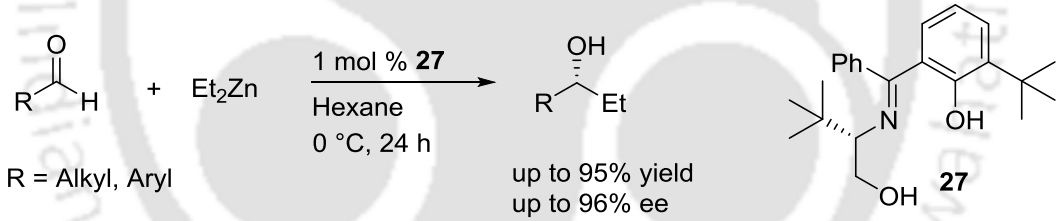
Bolm and co-worker have reported chiral *tert*-leucinol derived Fe(III) -tridentate Schiff base catalyst for asymmetric sulfide oxidation reaction with aqueous hydrogen peroxide

(Scheme 29).[34] The process efficiently oxidizes various aryl methyl sulfides in high enantioselectivities at room temperature.



Scheme 29. Enantioselective Sulfoxidation Reaction

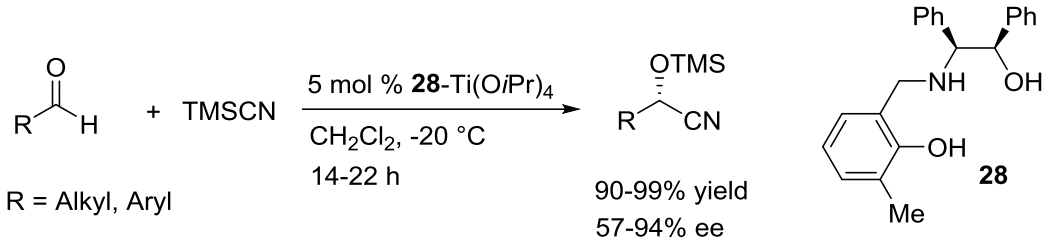
Hayashi and co-workers have investigated *tert*-leucinol derived Zn(II)-tridentate Schiff base catalyst for enantioselective diethylzinc addition reaction to aldehydes (Scheme 30).[35] This transformation has been successfully accomplished in high enantioselectivities for various aliphatic, aromatic and heteroaromatic aldehydes. In addition, non-linear effect of Zinc-Schiff base system has been observed in the reaction.



Scheme 30. Enantioselective Diethylzinc Addition Reaction to Aldehydes

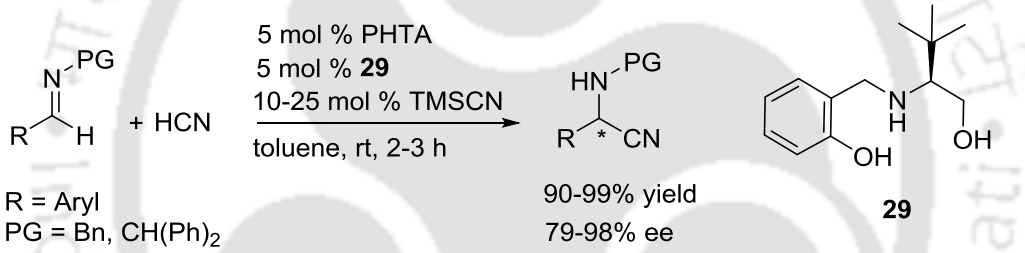
1.6 Selected Synthetic Methodologies Based on *β*-Amino Alcohol Ligands

Feng and co-workers have developed chiral *β*-amino alcohol derived Ti(IV)-catalyst for enantioselective trimethylsilyl cyanide addition reaction to aldehydes (Scheme 31).[36] The reaction of a series of aldehydes such as aliphatic, aromatic, conjugated and heteroaromatic aldehydes with trimethylsilyl cyanide is reported to give the corresponding trimethylsilyl ethers in 90-99% yields with up to 94% ee.



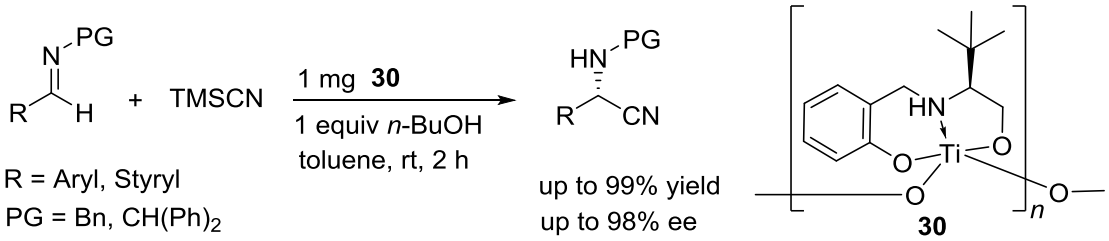
Scheme 31. Enantioselective Trimethylsilyl Cyanide Addition Reaction to Aldehydes

Seayad and co-workers have reported chiral Ti(IV)-*β*-amino alcohol catalytic system prepared from partially hydrolyzed titanium alkoxide and chiral *β*-amino alcohol ligand for asymmetric Strecker reaction (Scheme 32).[37] This catalyst efficiently catalyzes Strecker reaction of various aromatic and heteroaromatic imines in high enantioselectivities using economically cheap hydrogen cyanide as cyanide source at room temperature. Further, this methodology has been described for gram scale synthesis of *α*-amino acids.



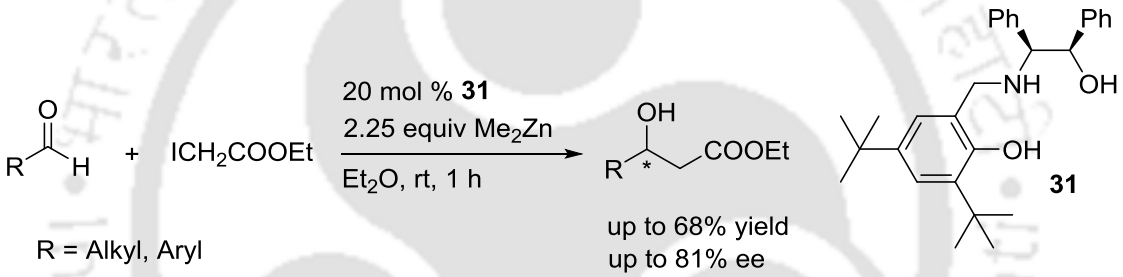
Scheme 32. Partially Hydrolysed Ti(IV) Catalyzed Enantioselective Strecker Reaction

The same group has developed self-supported chiral titanium clusters as a robust heterogeneous catalyst for enantioselective Strecker reaction of imines with trimethylsilyl cyanide (Scheme 33).[38] This catalyst has been prepared by controlled hydrolysis of preformed chiral *β*-amino alcohol derived Ti(IV)-alkoxide complex. Further, this catalyst was shown to recyclable up to 10 times without any loss in activity and enantioselectivity. In addition, this catalyst has been applied successfully for a three component continuous flow Strecker reaction at room temperature to afford the corresponding aminonitriles in high enantioselectivities



Scheme 33. Self-Supported Ti(IV)-Cluster Catalyzed Enantioselective Strecker Reaction

He and co-workers have investigated chiral *β*-amino alcohol derived tridentate ligands for enantioselective Reformatsky reaction of aldehydes with ethyl iodoacetate in the presence of dimethylzinc (Scheme 34).[39] This process has been accomplished successfully between various aldehydes bearing aliphatic, aromatic, conjugated and heteroaromatic substituents and ethyl iodoacetate with good enantioselectivities at room temperature.



Scheme 34. Enantioselective Reformatsky Reaction

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Chapter II

Chiral Copper(II) Catalyzed Enantioselective Nitroaldol Reaction

Enantioselective nitroaldol (Henry) reaction, an aldol type reaction, represents one of the fundamental *C-C* bond-forming processes. This reaction involves, the nucleophilic addition of *in situ* generated nitronate species (nucleophile) with a carbonyl electrophile by a range of catalysts including Lewis acids. The formed enantioenriched nitroaldol product serve as versatile synthetic intermediates for the asymmetric synthesis of numerous pharmaceutically important compounds (Figure 1).[1,2] Furthermore, optically active *β*-nitro alcohols can be readily transformed into valuable chiral *β*-amino alcohols by reduction and α-hydroxy acids by Nef reaction.[3,4] Development of effective methods for their asymmetric synthesis have thus received much attention.[5]

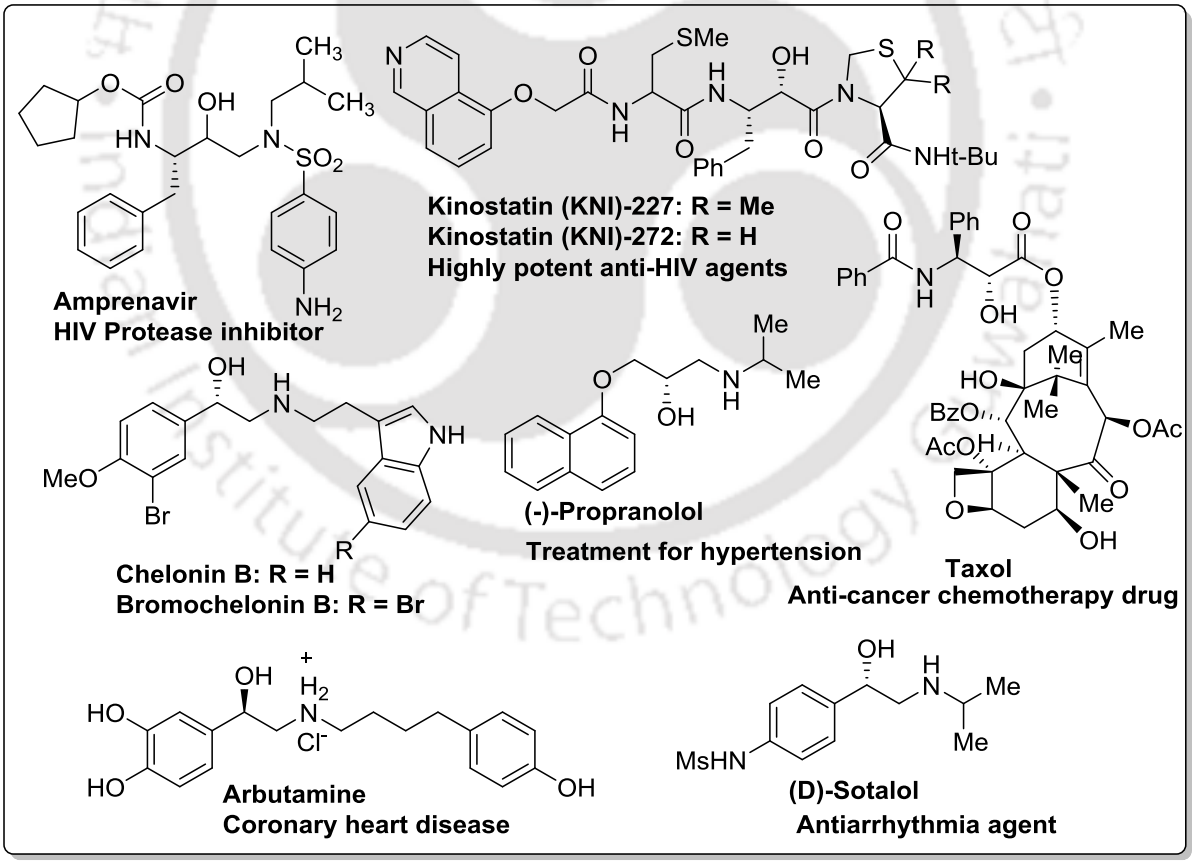


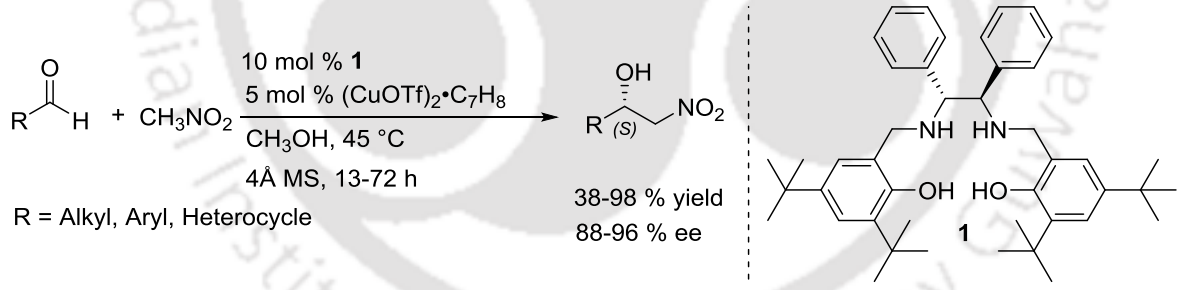
Figure 1. Examples of Pharmaceutical Compounds Containing Nitroaldol Core Structure

2.1 Enantioselective Nitroaldol Reaction Using Salen Based Ligands

Chiral salalen and salan have attracted significant recent interests as effective ligands for the metal catalyzed asymmetric synthesis because they are more flexible and can be readily modified compared to a salen ligand.[6] In addition, metal salalen and salan complexes have a greater tendency to adopt the *cis*-*β*-configuration that might produce strong asymmetric induction in some reactions.[7] Many methods have been developed for the synthesis of enantioselective nitroaldol products because of their widespread application. Some recent examples on enantioselective nitroaldol reactions with salen ligands have been discussed below and the reactions have been categorized based on the metal involved.

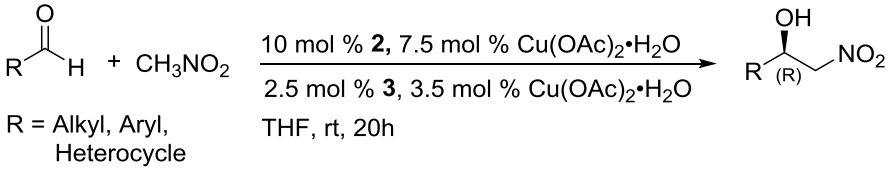
2.1.1 Chiral Cu-Catalysts

Feng and co-workers have reported (1*R*,2*R*)-(+)-1,2-diphenylethelene-diamine based chiral Cu(I)-tetrahydrosalen **1** for enantioselective nitroaldol reaction with aldehydes in the absence of base (Scheme 1).[2a] This process is simple, air tolerant and provides moderate to high yield (up to 98%) with excellent enantioselectivities (up to 96%) for aliphatic as well as aromatic substrates.

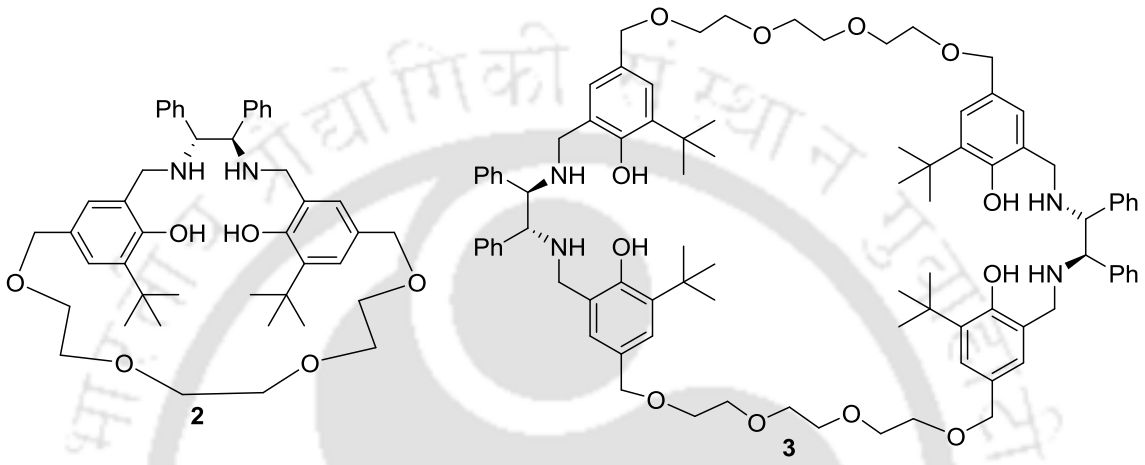


Scheme 1. Cu(I)-Catalyzed Enantioselective Nitroaldol Reaction

Kureshy and co-workers have explored Cu(II)-macrocyclic salan catalysts **2** and **3** for nitroaldol reaction (Scheme 2).[5h] This process is accomplished at room temperature without any base. Moreover, they observed high yield (up to 95%) as well as high enantioselectivity (up to 99%). In general, the dinuclear catalyst is more active and recyclable up to eight cycles with no significant loss in enantioselectivity.

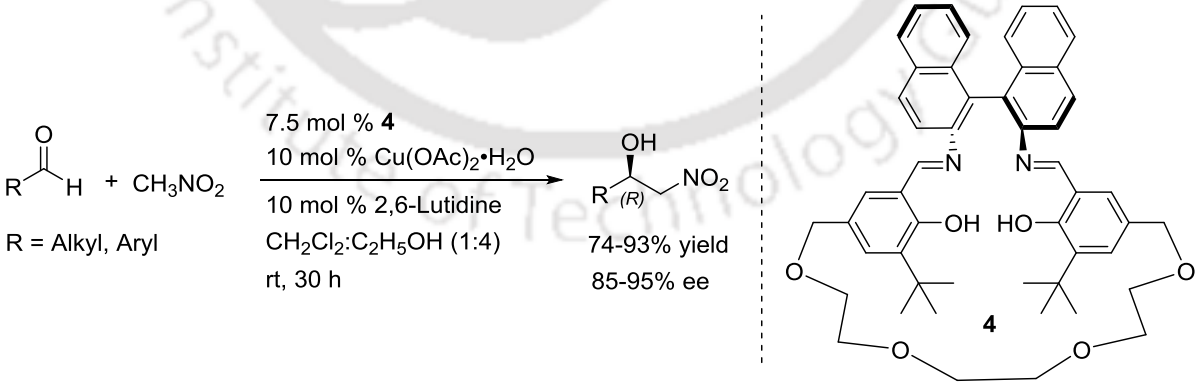


entry	catalyst	time(h)	yield (%)	ee (%)
1	**2**	20	45-95	15-99
2	**3**	15	47-98	3-98



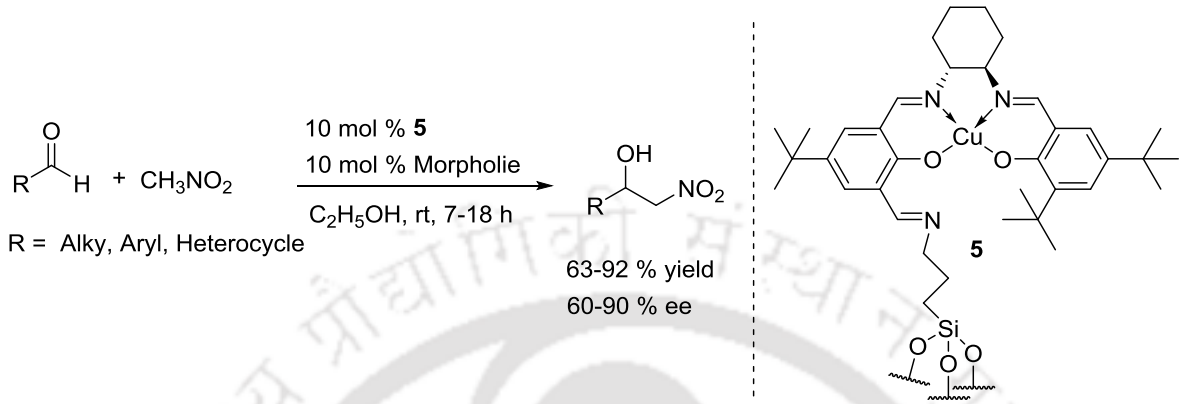
Scheme 2. Macrocyclic Cu(II)-Salen Catalyzed Reaction

Later, the same group have developed (*R*)-(+)-1,1'-binapthyl-2,2'-diamine based Cu(II)-macrocyclic salen complex **4** for nitroaldol reaction. This catalyst is also recyclable up to eight cycles with high efficiency even at room temperature but requires 0.5 equivalent of 2,6-lutidine as a base in a mixture of DCM and EtOH (Scheme 3).[2c]



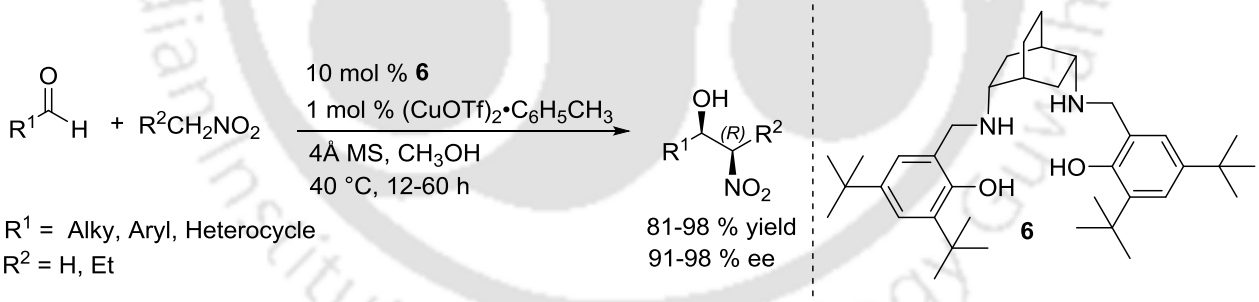
Scheme 3. Binaphthyl Macrocyclic Cu(II)-Salen Catalyzed Reaction

Rajagopal and co-workers have synthesized chiral modified MCM-41 supported Cu(II)-salen complex **5** for nitroaldol reaction. This method employs 10 mol % morpholine as a base in absolute EtOH at room temperature (Scheme 4).[5k]



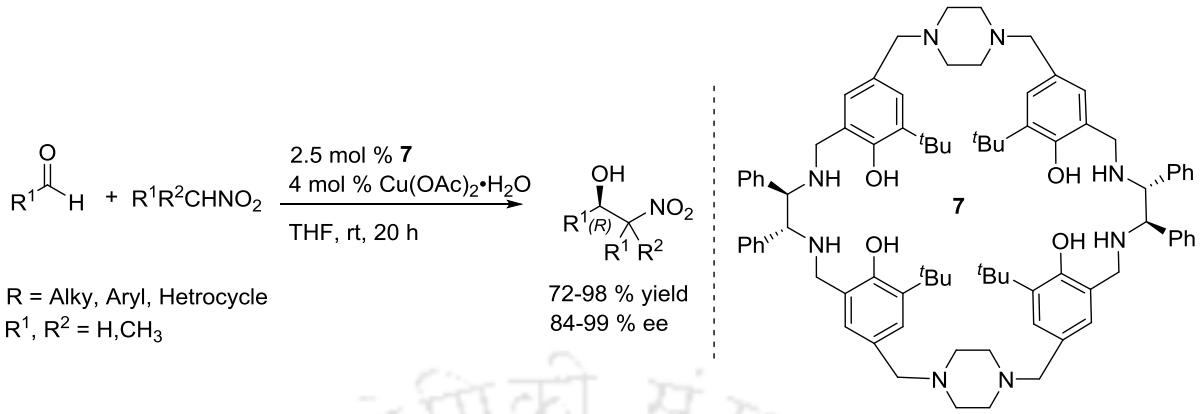
Scheme 4. MCM-41 Supported Cu(II)-Salen Catalyzed Reaction

White and co-workers have reported tetrahydrosalen **6** based *cis*-2,5-diaminobicyclo[2.2.2]-octane scaffold for enantioselective nitroaldol reaction (Scheme 5).[2f] The reaction proceeds through *in situ* formation of Cu(I)-complex that subsequently activates the nucleophilic attack of the nitromethane under mild reaction condition in the absence of base at room temperature.



Scheme 5. *Cis*-2,5-Diaminobicyclo[2.2.2]-octane Scaffolded Cu(I)-Tetrahydrosalen Catalyzed Reaction

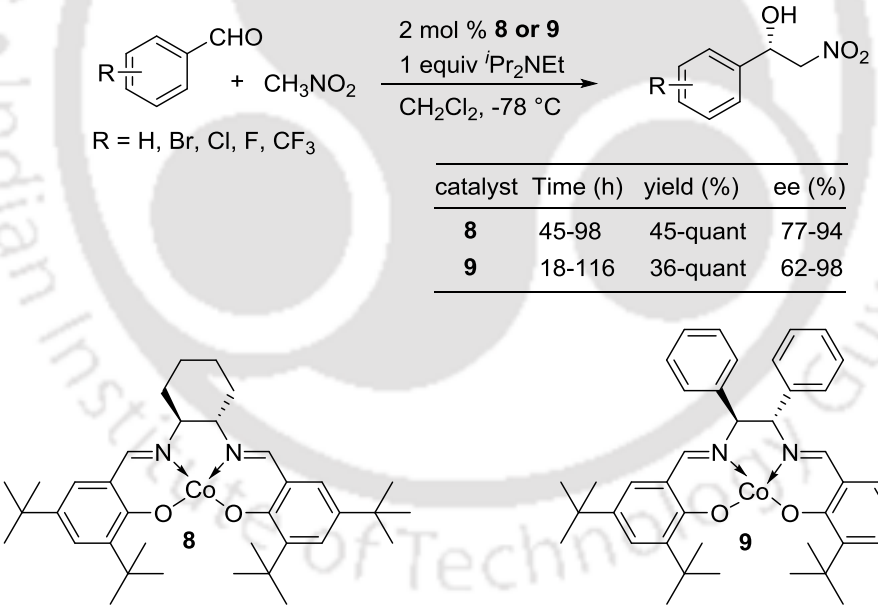
Kureshy and co-workers synthesized chiral Cu(II)-dimeric macrocyclic salen **7** for enantioselective nitroaldol reaction (Scheme 6).[8] They observed high enantioselectivity using THF as a solvent at room temperature without any base.



Scheme 6. Macrocyclic Cu(II)-Tetrahydrosalen Catalyzed Reaction

2.1.2 Chiral Co-Catalysts

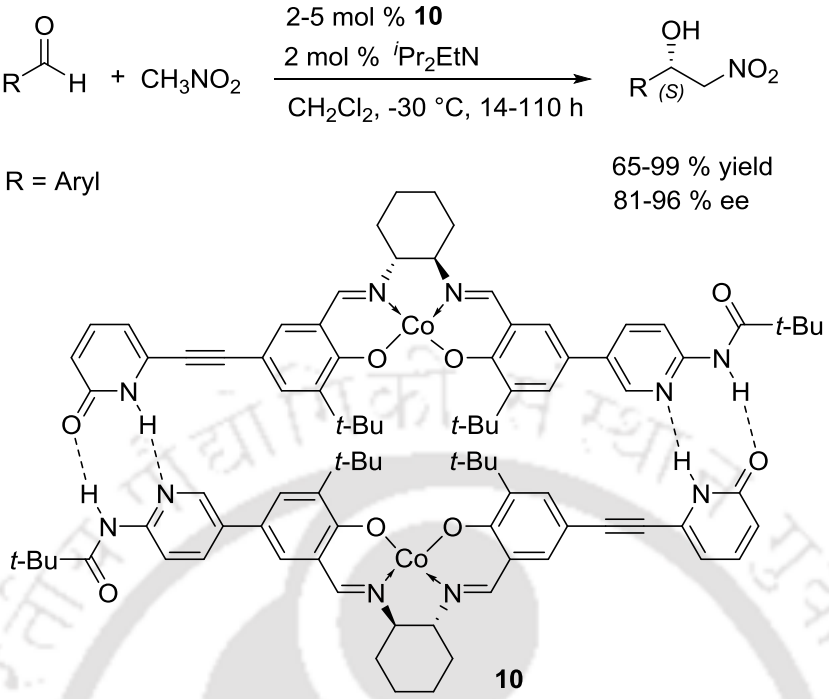
Yamada and co-workers have reported the synthesis of chiral *β*-nitroalcohols derived from aromatic aldehydes using Co(II)-salen complexes **8** and **9**. This reaction proceeds in good to high yields with high enantioselectivity (Scheme 7).[9]



catalyst	Time (h)	yield (%)	ee (%)
8	45-98	45-quant	77-94
9	18-116	36-quant	62-98

Scheme 7. Chiral Co(II)-Salen Catalyzed Reaction

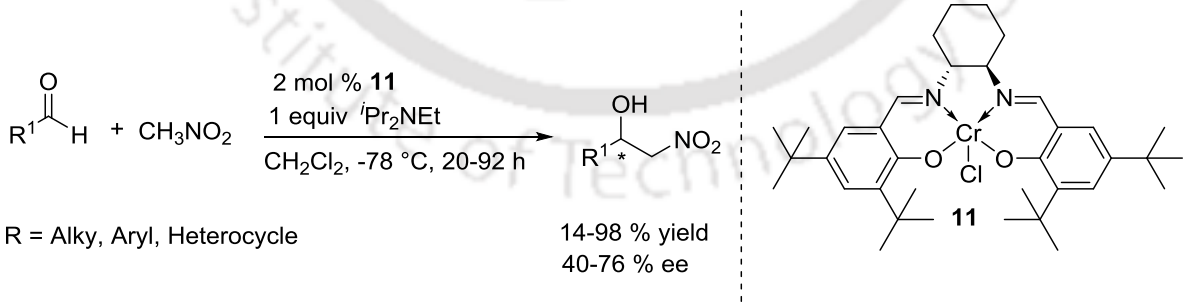
Chiral self-assembled dinuclear Co(II)-salen **10** was developed by Hong and co-workers for nitroaldol reaction. The self-assembly of **10** through hydrogen bonding enhances the rate and enantioselectivity of the reaction in the presence of diisopropylethylamine base (Scheme 8).[5f]



Scheme 8. Self Assembled Dinuclear Co(II)-Salen Catalyzed Reaction

2.1.3 Chiral Cr-Catalysts

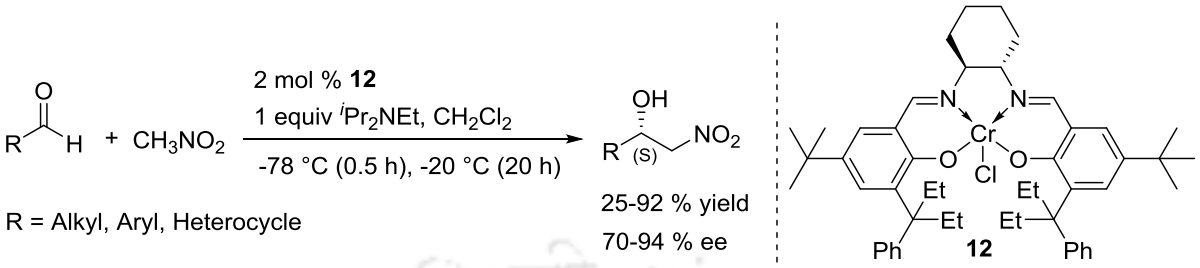
Skarżewski and co-workers have reported chiral Cr(III)-salen **11** for enantioselective nitroaldol reaction. This process catalyzes aryl, aliphatic and heteroaryl aldehydes with nitromethane in the presence of $^{i}Pr_2NEt$ and subsequently provides the respective nitroaldol products in moderate to good enantiomeric excess (Scheme 9).[10]



Scheme 9. Chiral Cr(III)-Salen Catalyzed Reaction

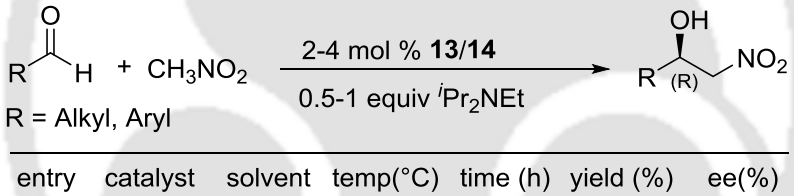
The same group studied modified Cr(III)-salen **12** for enantioselective nitroaldol reaction. The complexes with bulky benzylic groups in the 3,3′-position of the salicylidene moiety

have increased the enantioselectivity. This reaction proceeds under mild reaction condition with short reaction time and low catalyst loading (Scheme10).[11]

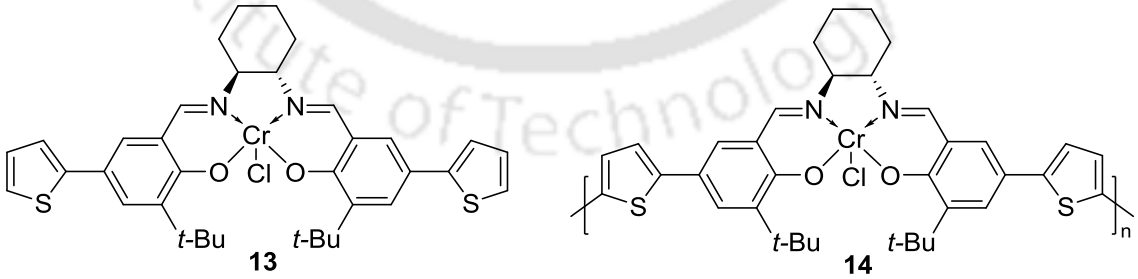


Scheme 10. Sterically Modified Cr(III)-Salen Catalyzed Reaction

Schulz and co-workers have synthesized chiral heterogeneous polymeric Cr(III)-complex **14** by anodic polymerization of chiral monomeric complex **13**. This heterogeneous polymeric complex catalyses the nitroaldol reaction up to 77% ee. The catalyst **14** is recyclable up to four times with a slight loss in efficiency (Scheme 11).[5h]



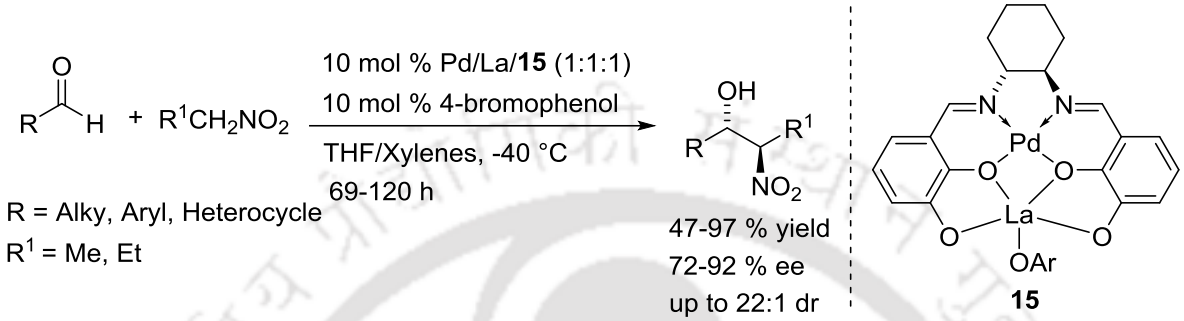
entry	catalyst	solvent	temp(°C)	time (h)	yield (%)	ee(%)
1	**13**	CH_2Cl_2	20	24	13-92	<5-64
2	**13**	CH_2Cl_2	-40	48	29-81	40-83
3	**13**	MTBE	20	24	33-79	34-69
4	**14**	MTBE	20	24	11-100	27-65



Scheme 11. Thiophene Cr(III)- Salen Catalyzed Reaction

2.1.4 Chiral Heterobimetallic Catalysts

Shibasaki and co-workers have developed a heterobimetallic Pd/La/salen **15** to catalyze enantioselective nitroaldol reaction. The co-operative function of the two metals with 4-bromophenol as an additive results the product with high enantioselectiity (Scheme 11).[12]

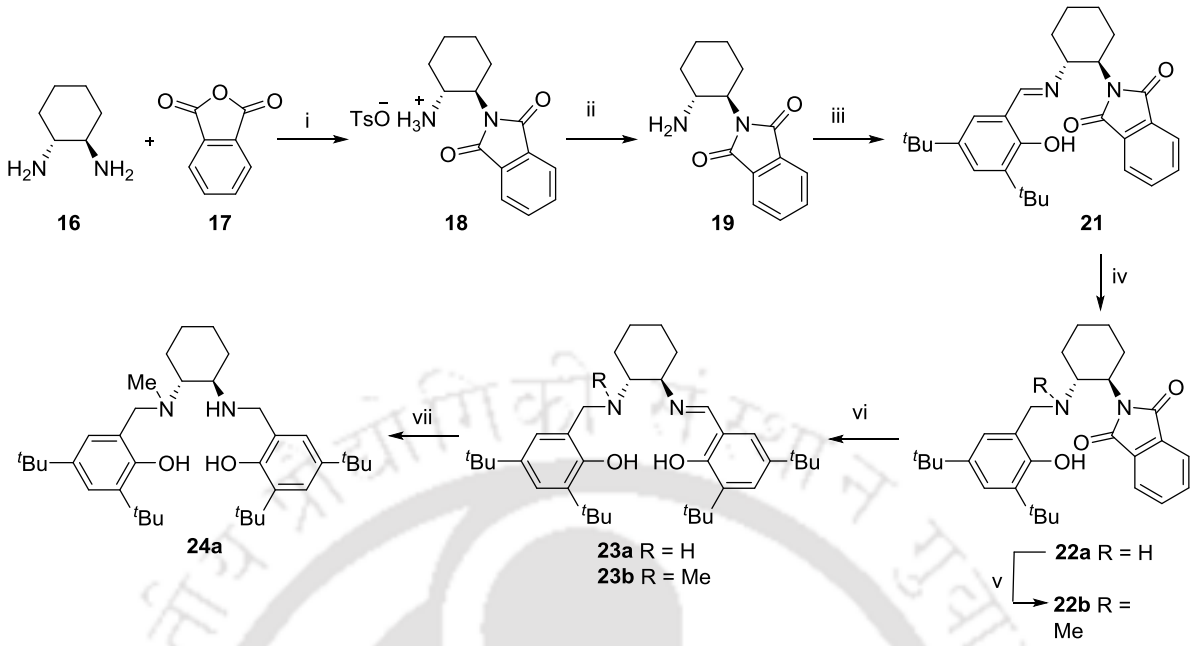


Scheme 11. Heterobimetallic Pd(II)/La(III) Salen Catalyzed Reaction

2.2 Present Study

Herein we describe the effect of ligand *N,N*-substituents on the reactivity of chiral Cu(II)-salalen **26a-b,** salan **27a-c** and salalan **28** towards nitroaldol reaction of nitromethane with aldehydes at room temperature. The chiral salan complexes **27a-c** have exhibited superior results compared to the salalen and salalan complexes, and the nature of the *N,N*-substituents plays a crucial role on the enantioselectivity of the nitroaldol products.

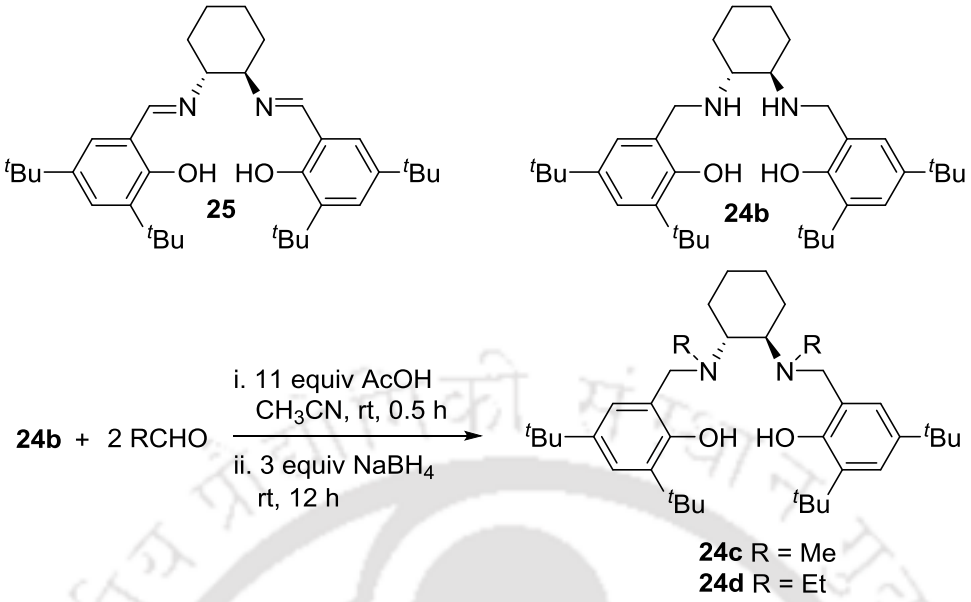
The syntheses of the chiral salalen **23a-b** and salan **24a** ligands are shown in Scheme 12. The reaction of (*R,R*)-1,2-diaminocyclohexane **16** with phthalic anhydride **17** using hydrated *p*-toluenesulphonic acid gave the imide **18** in 95% yield that could be reacted with triethylamine (Et_3N) to afford **19** in 87% yield.[13] The condensation of **19** with 3,5-di-*tert*-butyl-2-hdyroxybenzaldehyde **20** gave the Schiff base **21** in 85% yield that could be readily reduced utilizing $NaBH_4$ to furnish the amine **22a** in high yield. The latter proceeded reaction with formaldehyde followed by $NaCNBH_3$ to provide the *N*-methylated amine **22b** in 88% yield. Treatment of **22a** and **22b** with hydrazine hydrate provided the respective amines that could be reacted with **20** to give the salalen **23a** and **23b** in 60 and 64% yield, respectively. The reduction of the salalen **23b** using $NaBH_4$ afforded the salalan **24a** in high yield.



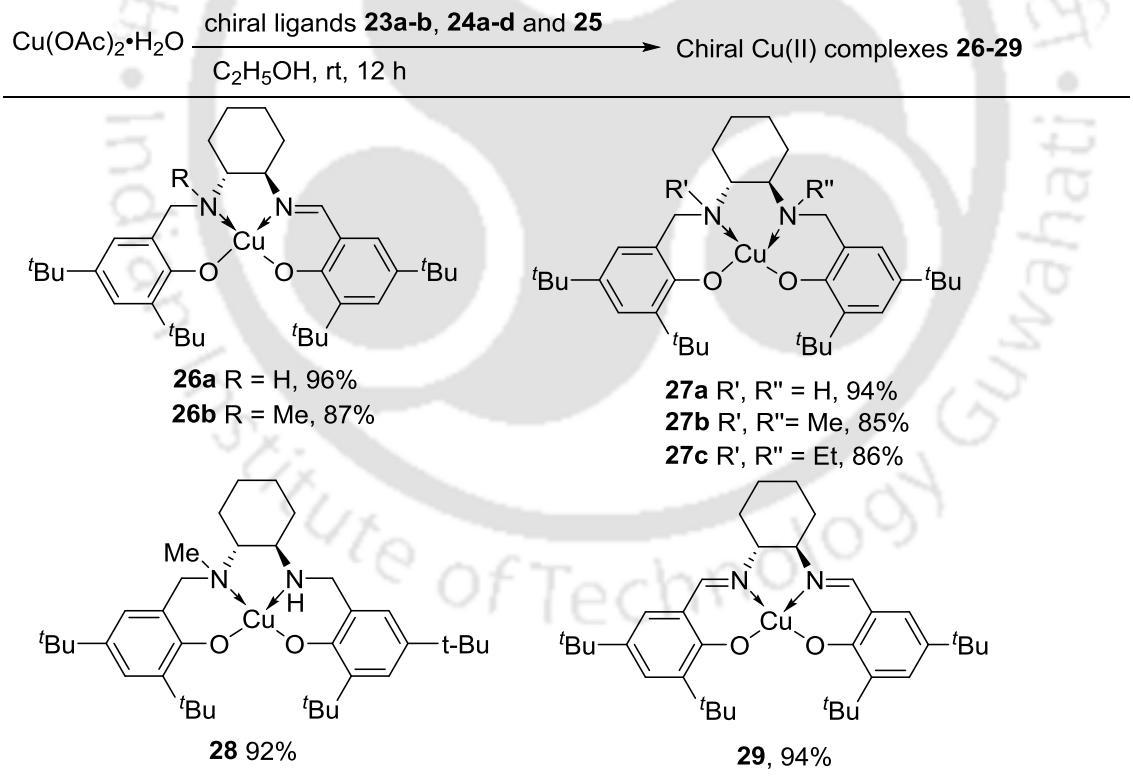
Scheme 12. *Reagents and conditions*: (i) *p*-TsOH·H_2O (1 equiv), xylene, reflux, 5 h, 95%; (ii) Et_3N (1.2 equiv), CH_2Cl_2/MeOH (1:1), rt, 3 h, 87%; (iii) 3,5-di-*tert*-butyl-2-hydroxyben-zaldehyde **20** (1 equiv), MeOH, 50 ^oC, 8 h, 85%; (iv) $NaCNBH_3$ (2.1 equiv), MeOH/CH_3CN (1:4), rt, 3 h, 97%; (v) HCHO solution (37-41% w/v) (5 equiv), AcOH (11 equiv), MeOH, rt, 0.5 h, then $NaCNBH_3$ (3 equiv), rt, 12 h, 88%; (vi) a. N_2H_4·H_2O (10 equiv), THF, reflux, 4 h, b. **5** (1 equiv), MeOH, 50 ^oC, 8 h, 60% (R = H), 64% (R = Me); (vii) $NaBH_4$ (1.2 equiv), MeOH/THF (3:1), rt, 3 h, 95%.

Chiral salen **25** was prepared by condensation of the diamine **16** with the aldehyde **20** in high yield.[14] Treatment of **25** with $NaBH_4$ in MeOH furnished the salan **24b** in 96% yield. The latter readily proceeded reaction with formaldehyde and acetaldehyde to afford the corresponding imines that could be reduced using $NaBH_4$ to produce *N*,*N*-dialkylated salan **24c-d** in high yields (Scheme 13).[15]

Reaction of the chiral ligands **23-25** with $Cu(OAc)_2$·H_2O in EtOH gave the corresponding chiral Cu(II)-complexes **26-29** in high yields (scheme 14).[16] Since the Cu(II)-complexes are to be the effective Lewis acids for the 1,2-addition reactions,[17] the catalytic activity of the complexes **26-27** was studied towards the nitroaldol reaction.

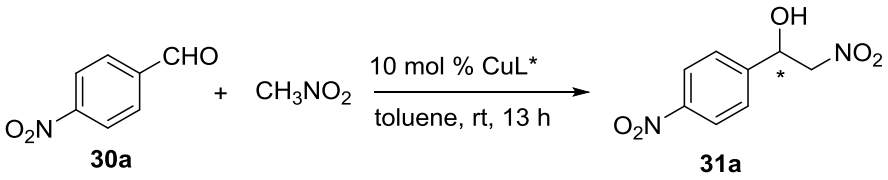


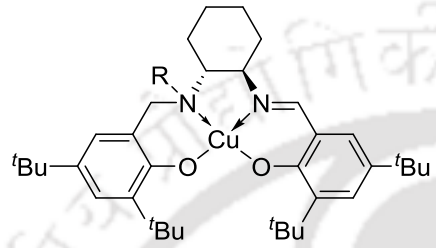
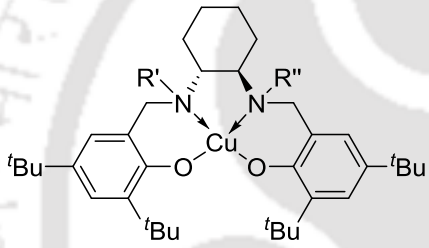
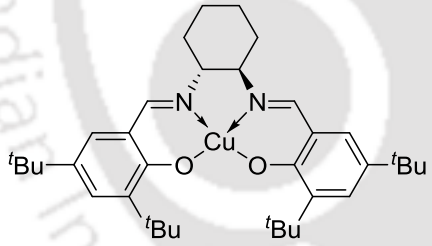
Scheme 13. *Reagents and conditions*: (i) RCHO (HCHO solution 37-41% w/v for **24c**, 5 equiv), AcOH (11 equiv), CH_3CN, rt, 0.5 h; (ii) $NaBH_4$ (3 equiv), rt, 12 h, 84% (R = Me), 86% (R = Et)



Scheme 14. Synthesis of Chiral Cu(II)-Salalen **26a-b**, Salan **27a-c,** Salalan **28** and Salen **29** Complexes

Table 1. Screening of the Chiral Cu(II)-Complexes **26-29**[a]



Entry	CuL*		Yield (%)[b]	ee (%)[c]
1		**26a** R = H	95	21
2		**26b** R = Me	99	21
3		**27a** R', R'' = H	86	41
4		**27b** R', R'' = Me	95	69
5		**27c** R', R''= Et	90	54
6		**28** R '= Me, R'' = H	99	38
7		**29**	58	19

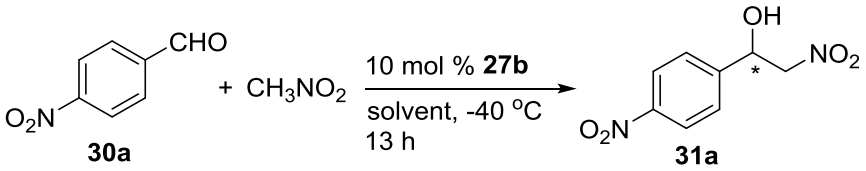
[a] Reaction conditions: 4-nitrobenzaldehyde **30a** (0.25 mmol), nitromethane (2.5 mmol), catalyst (10 mol %), toluene (0.75 mL), 13 h, rt, N_2.

[b] Isolated yield.

[c] Determined by HPLC analysis with chiralcel OJ column using 80:20 n-hexane/2-propanol.

First, the optimization of the reaction was performed using 4-nitrobenzaldehyde **30a** as a model substrate with nitromethane (Table 1). To our delight the reaction readily occurred to give the nitroaldol product with 21% ee when the substrates were stirred with 10 mol % of the salalen complex **26a** in toluene at room temperature (entry 1). Similar results were obtained using the *N*-methylated salalen complex **26b** as catalyst.

Table 2. Screening of Solvents, Temperature and Base[a]



Entry	Solvent	Base[b]	Yield (%)[c]	ee (%)[d]
1	**Toluene**	-	**56,** 85[e], 72[f]	**76,** 70[e], 73[f]
2	CH_2Cl_2	-	43	35
3	EtOAc	-	46	60
4	CH_3CN	-	15	32
5	EtOH	-	69	12
6	Et_2O	-	34	67
7	THF	-	52	55
8	Xylene	-	72	53
9	Chlorobenzene	-	75	35
10	Toluene	Et_3N	87	47
11	Toluene	DIPEA	85	39
12	Toluene	Morpholine	91	09
13	Toluene	*N*-Methylmorpholine	79	21
14	Toluene	*N*-Methylimidazole	81	17
15	Toluene	DMAP	84	15
16	Toluene	2,6-Lutidine	14	64

[a] 4-Nitrobenzaldehyde **30a** (0.25 mmol), nitromethane (2.5 mmol), **27b** (10 mol %), solvent (0.75 mL), 13 h, -40 °C, N_2.

[b] Base (0.5 equiv) used.

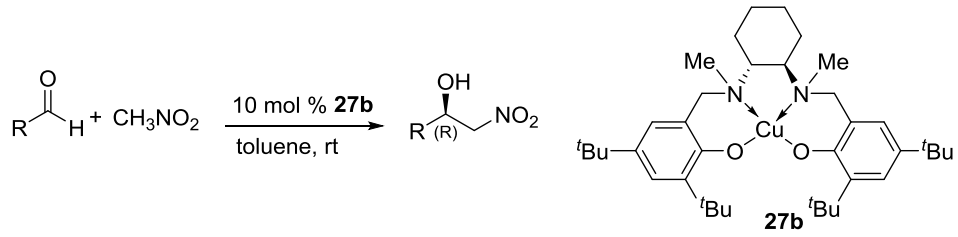
[c] Isolated yield.

[d] Determined by HPLC analysis with Chiralcel OJ column using 80:20 n-hexane/2-propanol.

[e] Reaction performed at 0 °C.

[f] Rreaction Temp. -20 °C.

Table 3. Chiral Cu(II)-Salan **27b** Catalyzed Asymmetric Nitroaldol Reaction[a]



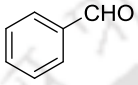
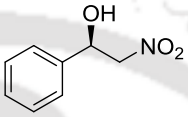
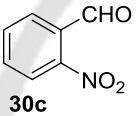
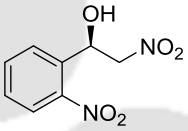
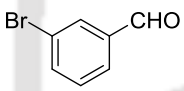
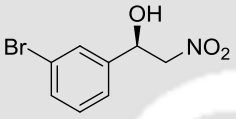
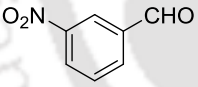
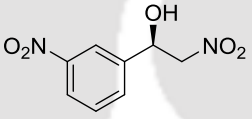
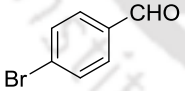
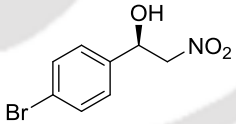
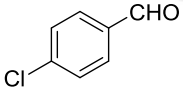
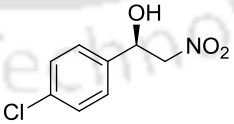
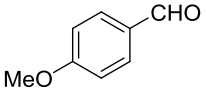
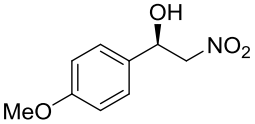
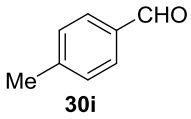
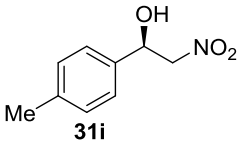
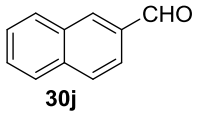
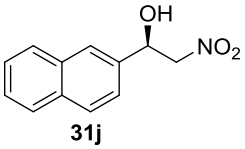
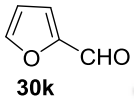
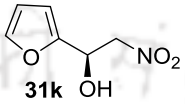
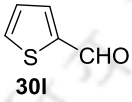
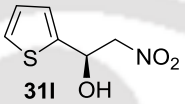
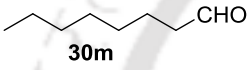
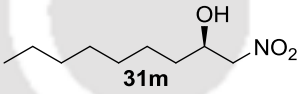
Entry	Substrate	Time (h)	Product	Yield (%)[b]	ee (%)[c]	Configuration[d]
1	 **30b**	48	 **31b**	64	78	*R*
2[e]	 **30c**	96	 **31c**	86	90	*R*
3	 **30d**	48	 **31d**	61	80	*R*
4[e]	 **30e**	96	 **31e**	76	81	*R*
5	 **30f**	24	 **31f**	65	82	*R*
6	 **30g**	48	 **31g**	89	65	*R*
7	 **30h**	96	 **31h**	54	70	*R*

Table 3 Continues……..

8	 **30i**	72	 **31i**	68	79	*R*
9	 **30j**	48	 **31j**	43	77	*R*
10	 **30k**	48	 **31k**	71	76	*R*
11	 **30l**	48	 **31l**	34	71	*R*
12	 **30m**	72	 **31m**	67	90	R

[a] Reaction conditions: aldehyde **30** (0.25 mmol), nitromethane (2.5 mmol) and catalyst **27b** (10 mol %) were stirred in toluene (0.75 mL) for appropriate time at room temperature (28 ^{o}C) under N_2 atmosphere.

[b] Isolated yield.

[c] Determined by HPLC analysis with Chiralcel OD-H (**31d**, **31f**, **31g** and **31m**), Chiralpak AD-H (**31c** and **31e**), Chiralcel OJ (**31a** and **31j-l**) and Chiralcel OJ-H (**31b** and **31h-i**) using n-hexane/2-propanol.

[d] Determined from sign of optical rotation.

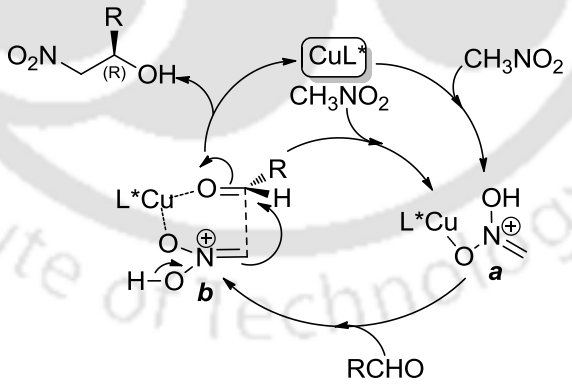
[e] reaction performed at -40 ^{o}C

However, the use of the chiral salan complexes **27a-c** led to an improvement in the enantioselectivity of **31a**, and the best result was observed using the *N*,*N*-dimethylated **27b** with 69% ee, whereas **27a** afforded 41% ee. In contrast, the complexes **27c** having bulkier *N*,*N*-diethyl substituents yielded 54% ee. Furthermore, the *N*-methyl salalan complex **28** gave the product with 38% ee. In addition, the catalytic activity of the chiral salen complex **29** was examined; however, it was less effective affording inferior results.

The effect of reaction temperature, solvent and base was next examined (Table 2). Decrease of the reaction temperature to -40 ^{o}C led to an increase in the enantioselectivity to 76% (entry 1). Toluene was found to be the solvent of choice affording the best results. In contrast, CH_2Cl_2, EtOAc, CH_3CN, EtOH, Et_2O, THF, xylene and chlorobenzene were less

effective giving **31a** in 12-67% ee (entries 2-9). The use of base such as Et_3N, diisopropylethylamine (DIPEA), morpholine, *N*-methylmorpholine, *N*-methylimidazole, *N*,*N*-dimethylamino-pyriridine (DMAP) and 2,6-lutidine led to an acceleration of the reaction but the *ee* was dropped, which may be due to the base catalyzed reactions (entries 10-16).

Having the optimal conditions, the substrate scope was examined for the reaction of various aldehydes (Table 3). The substrates having electron withdrawing groups exhibited a greater reactivity compared to that bearing electron donating groups. For examples, benzaldehyde **30b** underwent reaction with 78% ee at room temperature, while the more reactive 2-nitrobenzaldehyde **30c** readily proceeded reaction at -40 ^oC to give the product with 90% ee. Likewise, 3-bromobenzaldehyde **30d** proceeded reaction with 61% yield and 80% ee at room temperature, whereas the highly reactive 3-nitrobenzaldehyde **30e** underwent reaction at -40 ^oC with 76% yield and 81% ee. Furthermore, 4-bromo-, 4-chloro-, 4-methoxy- and 4-methylbenzaldehdyes **30f-i** underwent reaction with 54-89% yields and 65-82% ee. In addition, 2-furyl **30j**, 2-naphthyl **30k** and 2-thiophene **30m** aldehydes proceeded reaction with 34-71% yields and 71-77% ee, whereas n-heptyl aldehyde **30l** underwent reaction with 67% yield and 90% ee. These results suggest that the reaction of aryl, heteroaryl and alkyl aldehydes can be accomplished with good to high enantioselectitivies at room temperature.



Scheme 15. Proposed Catalytic Cycle

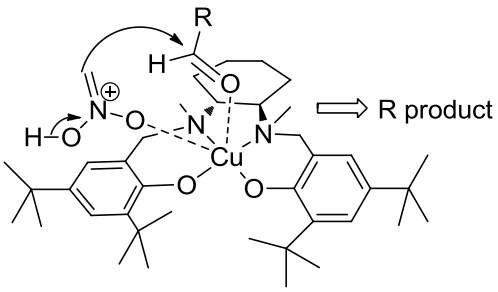


Figure 2. Proposed Transition State

Proposed catalytic cycle is shown in Scheme 15. Coordination of nitromethane with Cu(II)-salan complex may lead to the formation of the nitronate intermediate ***a*** that could undergo reaction with aldehyde to give intermediate ***b***. An intramolecular reaction of the nitronate to the chelated aldehyde can give the nitroaldol product and the catalyst to complete the catalytic cycle. Figure 2 shows the proposed transition state for the formation of the nitroaldol with *R* configuration.

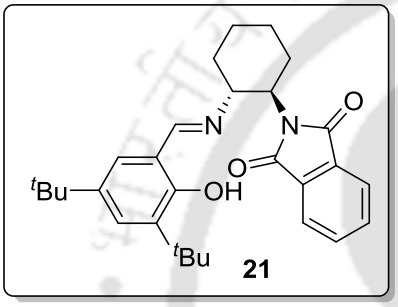
In summary, the effect of ligand *N*,*N*-substituents on reactivity of chiral Cu(II)-salalen, salalan and salan complexes towards nitroaldol reaction has been described. The reaction of aryl, heteroaryl, naphthyl and alkyl aldehydes can be accomplished with nitromethane in high enantioselectivities at room temperature under additive free conditions. The salan complexes exhibit superior results, and the *N*,*N*-substituents play a crucial role on the enantioselectivity of the nitroaldol products.

2.3. Experimental Section

General Information. The reactions were carried out in oven-dried glassware under nitrogen atmosphere. CH_3NO_2 (96%), aldehydes, and 2,4-di-*tert*-butyl phenol (99%) purchased from Aldrich, $NaBH_4$ (95%), HCHO solution (37-41% W/V), phthalic anhydride (98%), $N_2H_4{\cdot}H_2O$ (99%) and $Cu(OAc)_2{\cdot}H_2O$ (>98%) purchased from Merck, and $NaCNBH_3$ (>96%) purchased from Spectrochem were used as received. Solvents were purchased from Rankem and purified prior to use by standard procedure.[18a] The compounds **18**, **19**,[13] **24b**[15] and **25**[18b] were prepared according to the reported 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 were recorded using DRX-400 Varian spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) and Bruker Avance III 600 MHz spectrometer

(600 MHz for ^{1}H and 150 MHz for ^{13}C) using $CDCl_3$ as solvent and Me_4Si as an internal standard. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained using Perkin–Elmer spectrum one spectrometer. Optical rotations were measured with a Rudolph Autpol II automatic polarimeter in the solvent indicated. HRMS mass was analyzed with Agilent Q-TOF 6500. UV–vis spectra were recorded using Perkin–Elmer Lambda 25 UV/vis spectrometer. EPR spectra were measured on X-Band Microwave unit, JESFA200 ESR spectrometer. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD-H, OJ-H, AD-H and OJ columns.

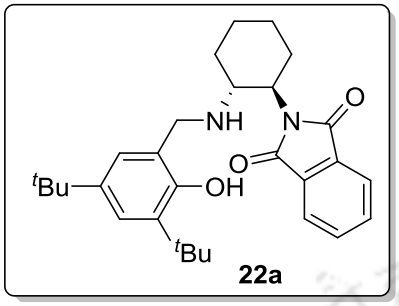
Synthesis of Ligands



21

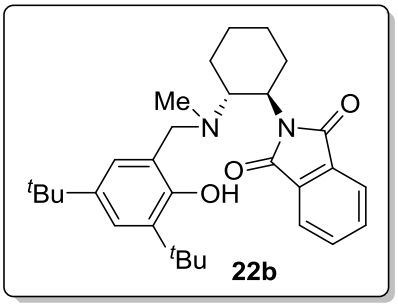
2-((1*R*,2*R*)-2-((*E*)-(3,5-Di-*tert*-butyl-2-ydroxybenzylidene)-amino)cyclohexyl)isoindoline-1,3-dione 21. 2-((1*R*, 2R)-2-Aminocyclohexyl)isoindoline-1,3-dione **4** (4 mmol, 976 mg) and 3,5-di-*tert*-butylsalicyladehyde **20** (4 mmol, 937 mg) were stirred in MeOH (15 mL) for 8 h at 50 ^{o}C. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the solvent was evaporated under reduced pressure and the residue was treated with water (10 mL), and extracted with CH_2Cl_2 (3x10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator gave a residue that was purified on a silica gel column chromatography using ethyl acetate and hexane (3:17) as eluent to give **21** as a pale yellow solid; yield (1.566 g, 85%); Mp: 141-143 °C; $[\alpha]_D^{29}$ = -130.6 (c = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.27 (s, 1H), 8.30 (s, 1H), 7.75-7.73 (m, 2H), 7.65 (dd, *J = 12.4, 4.0* Hz, 2H), 7.30 (s, 1H), 6.95 (s, 2H), 4.42-4.37 (m, 1H), 4.16-4.11 (m, 1H), 2.23-2.18 (m, 1H), 1.94-1.83 (m, 3 H), 1.75-1.66 (m, 1H), 1.61-1.45 (m, 2H), 1.34 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 165.9, 158.0, 139.7, 136.6, 133.8, 131.7, 126.8, 125.9, 123.1, 117.6, 67.8, 55.6, 34.9, 34.8, 34.0, 31.4, 29.3, 29.0, 25.4, 24.2; FT-IR (KBr): 3464, 2952, 2864, 1769, 1713, 1627, 1595, 1468, 1440, 1390, 1362, 1330, 1273, 1255, 1244, 1202, 1173, 1156, 1133, 1099, 1066, 1052, 1016,

1000, 981, 948, 932, 906, 869, 860, 843, 868, 804, 773, 719, 698, 639, 531, 474 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{37}N_2O_3$ 461.2799, found 461.2812.



22a

2-((1*R*,2*R*)-2-((3,5-Di-*tert*-butyl-2-hydroxybenzyl)amino)-cyclohexyl)isoindoline-1,3-dione 22a. To a stirred solution of 2-((1*R*, 2R)-2-((*E*)-(3,5-di-*tert*-butyl-2-hydroxy benzylidene)amino)cyclohexyl)isoindoline-1,3-dione **21** (3.5 mmol, 1.612 g) in a 1:4 mixture of MeOH and CH_3CN (25 mL) was added $NaCNBH_3$ (7.35 mmol, 461 mg) at ice-cooled temperature. After complete consumption of the starting material, the solvents were evaporated under reduced pressure, and the residue was dissolved in water (10 mL), and extracted with CH_2Cl_2 (3x10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator afforded a residue that was purified on a silica gel column chromatography using ethyl acetate and hexane (3:17) as eluent to give **22a** as white solid; yield (1.570 g, 97%); Mp: 172-174 °C; $[\alpha]_D^{29}$ = -7.62 (*c* =0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.10 (d, *J* = 1.6 Hz, 1H), 6.78 (d, *J* = 1.2 Hz, 1H), 4.04-3.96 (m, 2H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.51 (td, *J* = 11.1, 3.6 Hz, 1H), 2.42-2.28 (m, 2H), 1.86 (bs, 3H), 1.22 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 154.9, 140.3, 135.9, 133.9, 132.1, 123.3, 122.9, 122.9, 121.9, 56.8, 50.6, 34.7, 34.2, 31.8, 29.6, 29.5, 25.6, 24.8; FT-IR (KBr): 3462, 3305, 2954, 1947, 1767, 1717, 1699, 1683, 1612, 1546, 1480, 1393 1331, 1330, 1236, 1155, 1116, 1084, 1047, 1017, 1002, 978, 955, 926, 903, 871, 859, 843, 823, 798, 719, 700, 677, 667, 648, 639, 530, 509, 454 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{29}H_{39}N_2O_3$ 463.2955, found 463.2951.

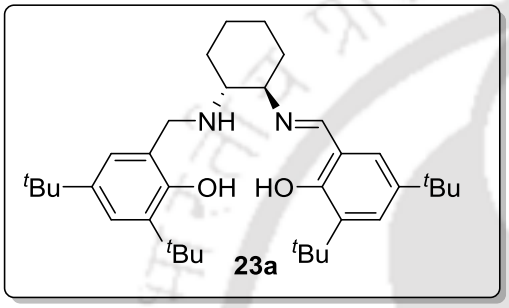


22b

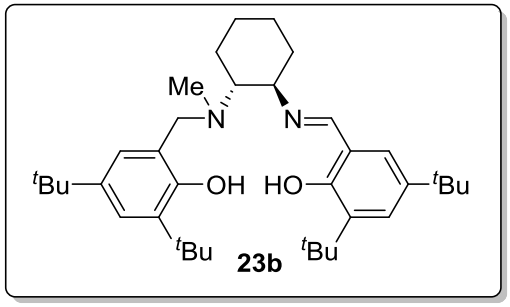
2-((1*R*,2R)-2-((3,5-Di-*tert*-butyl-2-hydroxybenzyl)(methyl)amino)cyclohexyl)isoindo-line-1,3-dione 22b. To a stirred solution of 2-((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)amino)cyclohexyl)--isoindoline-1,3-dione **22a** (1.5 mmol, 693.9 mg) in a 3:1 mixture of CH_3CN and MeOH (15 mL) was added drop wise CH_3COOH (3.5 mL) and then HCHO solution (650 µL) at room temperature. The reaction mixture was stirred for 0.5 h, and then, $NaCNBH_3$ (4.5 mmol, 282 mg) was added portion wise at 0 ^oC. The reaction mixture was then stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the solvent was evaporated under reduced pressure, and the residue was treated with saturated $NaHCO_3$ solution followed by water (5 mL). The mixture was then extracted with CH_2Cl_2 (3x10 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to give a residue that was purified on a silica gel column chromatography using ethyl acetate and hexane (3:17) as eluent to give **22b** as colorless solid; yield (714 mg, 88%); Mp: 183-185 °C; $[\alpha]_D^{29}$ = -24.80 (*c* = 0.76, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 11.32 (s, 1H), 7.82 (dd, *J* = 4.5, 2.4 Hz, 2H), 7.70 (dd, *J* = 5.0, 2.8 Hz, 2H), 7.02 (d, *J* = 1.4 Hz, 1H), 6.71 (d, *J* = 2.2 Hz, 1H), 4.32 (td, *J* = 11.6, 3.4 Hz, 1H), 3.76-3.66 (m, 3H), 2.36-2.28 (m, 1H), 2.15 (s, 3H), 2.06 (d, *J* = 9.1, 1H), 1.92-1.84 (m, 3H), 1.49-1.31 (m, 3H), 1.21 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 154.8, 139.9, 135.0, 133.7, 123.2, 123.0, 122.5, 120.2, 110.1, 63.2, 51.7, 34.5, 34.2, 31.8, 30.1, 29.2, 25.7, 24.9, 23.5; FT-IR (KBr): 3372, 2955, 2867, 1766, 1703, 1659, 1606, 1482, 1468, 1390, 1361, 1302, 1233, 1202, 1163, 1125, 1027, 1012, 937, 905, 876, 822, 797, 763, 720, 668, 648, 530, 510 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{30}H_{41}N_2O_3$ 477.3112, found 477.3118.

General Procedure for the Synthesis of the Compounds 23a-b. To a stirred solution of **7** (1.5 mmol) in dry THF (10 mL), $N_2H_4{\cdot}H_2O$ (2.25 mL) was added. After refluxing for 4 h, the reaction mixture was cooled to room temperature and diluted with Et_2O (20 mL) to

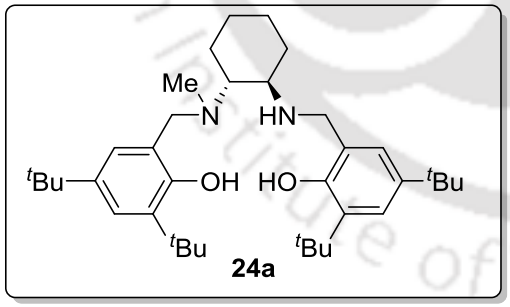
precipitate out phthaloyl hydrazide. After filtering the solid, the filtrate was concentrated under reduced pressure to give a residue that was dissolved in EtOAc (5 mL) and extracted with dilute HCl (2 x 5 mL). The solution was then neutralized using saturated $NaHCO_3$ and extracted using dichloromethane (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator furnished colorless solid that was reacted with **5** in MeOH (15 mL) at 50 ^oC for 8 h to give a pale yellow solid, which was filtered and washed with cold MeOH to yield analytic pure compounds **23a-b**.



2,4-Di-*tert*-butyl-6-((*E*)-((1*R*,2*R*)-2-(3,5-di-*tert*-butyl-2-hydroxybenzylamino)cyclohexyl imino)methyl)phenol 23a. Pale yellow solid; yield (494 mg, 60%); Mp: 146-148 ^oC; $[\alpha]_D^{29}$ = -103.73 (*c* = 1.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 13.47 (s, 1H), 11.63 (s, 1H), 8.40 (s, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 2H), 6.8 (d, *J* = 2.0 Hz, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.81 (d, *J* = 13.44 Hz, 1H), 3.06 (td, *J* = 10.8, 2.8 Hz, 1H), 2..83 (td, *J* = 10.8, 3.2 Hz, 1H), 2.25 (d, *J* = 12.8 Hz, 1H), 1.82-1.81 (m, 3H), 1.43 (s, 9H), 1.33 (s, 9H), 1.27 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 158.1, 154.7, 140.5, 140.3, 136.7, 136.0, 127.3, 126.3, 123.2, 123.0, 122.9, 117.9, 74.1, 61.2, 50.9, 35.2, 35.0, 34.2, 34.1, 31.8, 31.6, 29.8, 29.7, 24.7, 24.6; FT-IR (KBr): 3490, 2955, 2863, 1734, 1648, 1627, 1479, 1467, 1440, 1391, 1361, 1301, 1273, 1251, 1202, 1172, 1125, 1080, 1025, 981, 931, 877, 827, 801, 772, 738, 713, 645, 535, 510 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{36}H_{57}N_2O_2$ 549.4415, found 549.4426.



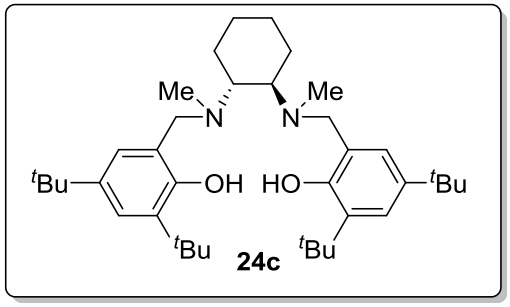
2,4-Di-*tert*-butyl-6-((*E*)-(((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)(methyl)amino) cyclohexyl)imino)methyl)phenol 23b. Pale yellow solid; yield (540 mg, 64%); Mp: 114-116 °C; $[\alpha]_D^{29}$ = -97.03 (*c* = 0.88, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 13.57 (s, 1H), 10.59 (s, 1H), 8.37 (s, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 3.83-3.70 (m, 2H), 3.27-3.25 (m, 1H), 2.98-2.91 (m, 1H), 2.22 (s, 3H), 1.99-1.63 (m, 6H), 1.47 (s, 9H), 1.44-1.32 (m, 2H), 1.28 (s, 9H), 1.24 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 158.3, 154.9, 139.9, 139.9, 136.7, 135.5, 127.0, 125.9, 123.4, 122.6, 121.1, 118.3, 70.4, 66.8, 58.5, 35.4, 35.2, 34.8, 34.2, 31.9, 31.7, 31.5, 29.8, 29.6, 25.3, 24.8, 23.92; FT-IR (KBr): 3472, 2954, 2863, 1678, 1630, 1479, 1467, 1455, 1441, 1390, 1361, 1302, 1273, 1245, 1234, 1203, 1173, 1113, 1073, 1025, 982, 948, 938, 878, 825, 801, 772, 763, 738, 714, 695, 645, 566, 538, 509 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{37}H_{59}N_2O_2$ 563.4571, found 563.4579.



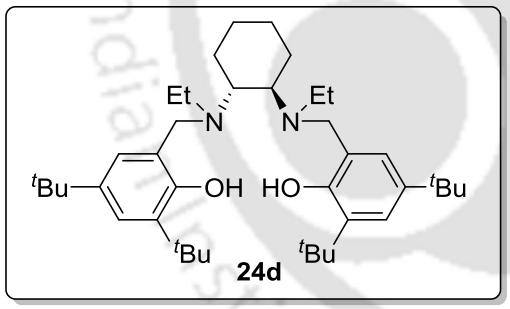
2,4-Di-*tert*-butyl-6-((((1*R*,2*R*)-2-((3,5-di-tert-butyl-2-hydroxybenzyl)(methyl)amino)-cyclo hexyl) amino)methyl)phenol 24a. To a stirred solution of 2,4-di-*tert*-butyl-6-((*E*)-(((1*R*,2*R*)-2-((3,5-di-*tert*-butyl-2-hydroxy-benzyl) (methyl)amino)cyclohexyl)imino)methyl)phenol **23b** (0.75 mmol, 422 mg) in a 1:3 a mixture of THF:MeOH at 0 °C, $NaBH_4$ (0.9 mmol, 30.2 mg) was added, and the resultant mixture was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC using EtOAc and hexane. After completion, the solvent was evaporated under reduced

pressure and the residue was neutralized with saturated $NaHCO_3$ solution. The mixture was then treated with water (5 mL) and extracted with CH_2Cl_2 (3x10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator provided a residue that was purified on a silica gel column chromatography using EtOAc and hexane (3:17) as eluent to give 24**a** as colorless viscous liquid; yield (382 mg, 95%); $[\alpha]_D^{29}$ = -5.04 (*c* = 1.38, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (d, *J* = 2.4 Hz, 2H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 4.08 (d, *J* = *13.2* Hz, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.77 (d, *J* = 13.2 Hz, 1H), 2.67 (td, *J* = 10.8, 4.2 Hz, 1H), 2.52 (td, *J* = 10.8, 3 Hz), 2.28 (s, 3H), 1.98 (d, *J* = 13.2 Hz, 1H), 1.82-1.81 (m, 1H), 1.73-1.72 (m, 1H), 1.42 (s, 9H), 1.37 (s, 9H), 1.29 (s, 19H), 1.20-1.13 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.7, 154.3, 140.8, 140.5, 135.9, 135.8, 123.6, 123.3, 123.1, 123.0, 122.6, 121.2, 65.3, 58.7, 56.8, 50.4, 35.7, 35.0, 34.3, 32.2, 31.9, 29.9, 29.9, 29.8, 25.2, 25.0, 22.5, 14.4; FT-IR (neat): 3503, 2954, 2860, 2071, 1634, 1480, 1390, 1361, 1302, 1235, 1202, 1165, 1124, 1096, 1018, 977, 878, 822, 799, 758, 724, 695, 667, 648, 509 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{37}H_{61}N_2O_2$ 565.4728, found 565.4732.

General Procedure for the Synthesis of the Compounds 24c-d. To a solution of 6,6'-(1*R*,2*R*)-cyclohexane-1,2-diylbis(azanediyl)bis(methylene)bis(2,4-di-*tert*-butylphenol) **24b** (2 mmol, 1.101 g) in CH_3CN (25 mL) was added dropwise CH_3COOH (5 mL) and HCHO solution (2 mL) at room temperature. The resultant mixture was stirred for 0.5 h, and then treated with $NaBH_4$ (10 mmol, 378 mg) at 0 ^oC. After stirring at room temperature for 12 h, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL) and neutralized with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2x 10mL), and the combined organic layer was washed with water, dried (Na_2SO_4), and evaporated on a rotary evaporator to give a residue that was purified on silica gel column chromatography using EtOAc and hexane as eluent to give the compounds **24c-d**.

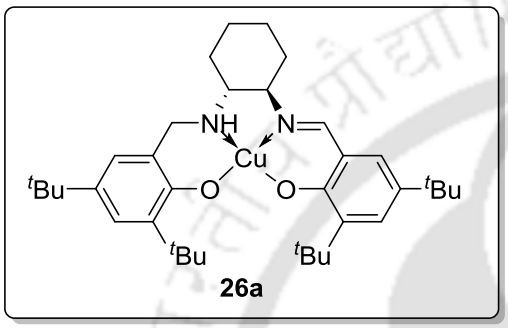


6,6'-(((1*R*,2*R*)-Cyclohexane-1,2-diylbis(methyl-azanediyl))bis(methylene))bis(2,4-di-*tert*-butylphenol) 24c.[15]Colorless viscous liquid; yield (995 mg, 84%); $[\alpha]_D^{29}$ = +37.3 (*c* = 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 2.0 Hz, 2H), 6.80 (d, *J* = 2.0 Hz, 2H), 7.73 (dd, *J* = 5.6, 2.8 Hz, 2H), 3.82-3.72 (m, 4H), 2.67 (m,2H), 2.19 (s, 6H), 2.00-1.97 (m, 2H), 1.78-1.76 (m, 2H), 1.35 (s, 18H), 1.26 (s, 18H), 1.12-1.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 140.3, 135.7, 123.7, 122.9, 121.5, 61.5, 58.8, 35.0, 34.3, 31.9, 29.8, 27.1, 25.5, 22.7; FT-IR (neat): 3451, 2950, 2899, 2866, 1603, 1559, 1469, 1437, 1412, 1389, 1381, 1362, 1349, 1293, 1279, 1264, 1238, 1204, 1166, 1134, 1102, 1012, 994, 968, 879, 873, 831, 812, 777, 739, 668, 639, 538 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{38}H_{63}N_2O_2$ 579.4884, found 579.4906.



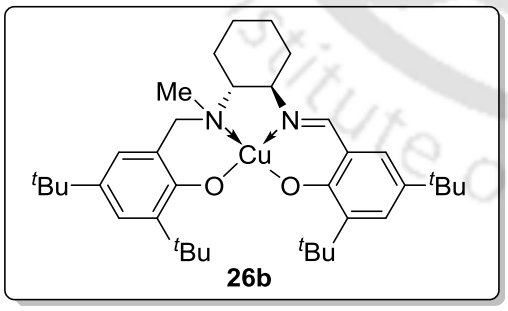
6,6'-(((1*R*,2*R*)-Cyclohexane-1,2-diylbis(ethylaz-anediyl))bis(methylene))bis(2,4-di-*tert*-butyl phenol) 24d. Colorless solid; yield (1.068 g, 86%); Mp: 170-173 °C; $[\alpha]_D^{29}$ = +10.96 (*c* = 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 2.4Hz, 4H), 6.77 (s, 4H), 3.96 (s, 2H), 3.50 (q, *J* = 7.2Hz, 4H), 3.29 (s, 2H), 2.43-2.35 (m, 4H), 2.04 (s, 4H), 1.76 (d, = 7.2Hz, 4H), 1.25 (s, 36H), 1.22 (t, *J* =7.2Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 153.8, 140.4, 135.9, 124.2, 122.6, 122.2, 58.6, 52.7, 42.6, 34.9, 34.2, 31.9, 29.7, 25.9, 23.4, 13.0; FT-IR (KBr): 3387, 2952, 2863, 1739, 1605, 1481, 1470, 1390, 1361, 1285, 1262, 1240, 1216, 1201, 1164, 1123, 1109, 1069, 1055, 1033, 993, 971, 946, 928, 877, 865, 820, 800, 772, 759, 740, 726, 695, 672, 649, 605, 566, 540 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{40}H_{67}N_2O_2$ 607.5197, found 607.5205.

General Procedure for Synthesis of Cu(II) Complexes. To a stirred solution of ligand **(**0.5 mmol) in EtOH (5 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol) in EtOH (2 mL). After stirring at room temperature under air for 12 h, the solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (3x5 mL) and washed with water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator gave a residue that was purified on a silica gel column chromatography using hexane and EtOAc (2:3) as eluent to give the respective complex as a green solid.



26a

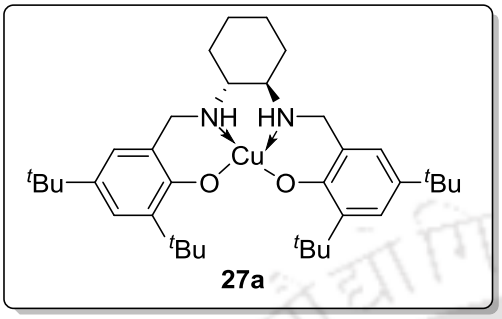
Complex 26a. Green solid; yield (292 mg, 96%); $[\alpha]_D^{29}$ = -1471.4 (c = 0.028, $CHCl_3$); FT-IR (KBr): 3505, 3226, 2950, 2865, 1728, 1658, 1622, 1526, 1467, 1435, 1409, 1383, 1360, 1349, 1301, 1286, 1254, 1236, 1201, 1167, 1134, 1092, 1025, 970, 927, 877, 858, 830, 807, 789, 741, 639, 624, 535, 503, 467 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 586 (4655), 382 (37355), 275 (124897), 246 nm (186347 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; $g_{\parallel}$ = 2.333, $g_{\perp}$ = 2.019, $A_{\parallel}$ = 21.19 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{36}H_{55}N_2O_2Cu$ 610.3554, found: 610.3561.



26b

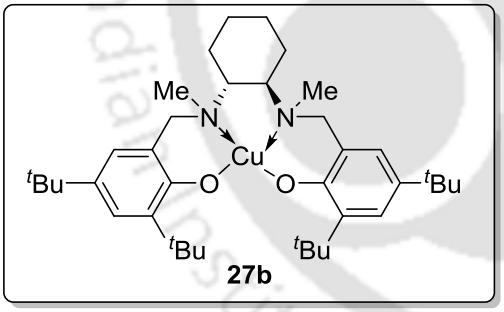
Complex 26b. Green solid; yield (271 mg, 87%); $[\alpha]_D^{29}$ = -1828.6 (c = 0.028, $CHCl_3$); FT-IR (KBr): 2950, 2905, 2866, 1726, 1674, 1617, 1527, 1474, 1433, 1412, 1386, 1360, 1333, 1303, 1254, 1235, 1202, 1167, 1133, 1090, 1004, 973, 931, 874, 831, 809, 790, 778, 742, 658, 639, 534, 480 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 594 (5024), 402 (37346), 276 (133740), 251 nm (191144 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid

N_2 temp; $g_{\parallel}$ = 2.333, $g_{\perp}$ = 2.009, $A_{\parallel}$ = 21.71 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{37}H_{57}N_2O_2Cu$ 624.3711, found 624.3715.



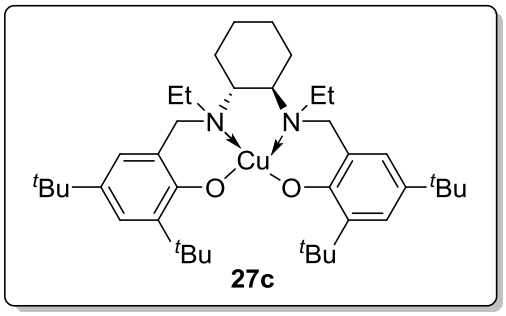
27a

Complex 27a. Green solid; yield (287 mg, 94%); $[\alpha]_D^{29}$ = -558.8 (c = 0.068, $CHCl_3$); FT-IR (KBr): 3428, 3188, 2950, 2865, 1773, 1665, 1623, 1527, 1469, 1439, 1411, 1388, 13611, 1299, 1254, 1235, 1201, 1166, 1094, 1059, 876, 827, 805, 783, 738, 668, 536, 460 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 623 (894), 423 (2406), 290 (13752), 246 nm (21776 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; $g_{\parallel}$ = 2.356, $g_{\perp}$ = 2.027, $A_{\parallel}$ = 21.29 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{36}H_{57}N_2O_2Cu$ 612.3711, found 612.3715.

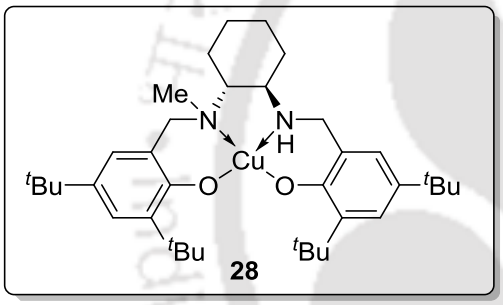


27b

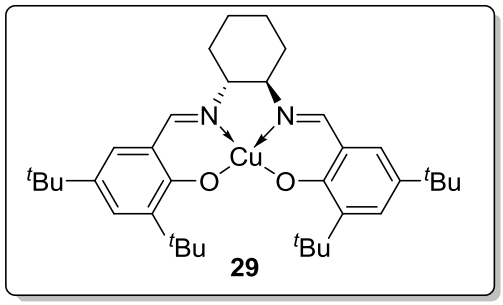
Complex 27b. Green solid; yield (272 mg, 85%); $[\alpha]_D^{29}$ = -1981.4 (c = 0.022, $CHCl_3$); FT-IR (KBr): 3418, 2948, 2899, 2866, 1761, 1604, 1539 1469, 1437, 1412, 1380, 1360, 1349, 1326, 1295, 1238, 1203, 1166, 1134, 1102, 1012, 994, 969, 876, 831, 812, 776, 739, 640,538, 488 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 641 (5396), 445 (8110), 299 (62478), 254 nm (80632 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; $g_{\parallel}$ = 2.341, $g_{\perp}$ = 2.016, $A_{\parallel}$ = 20.52 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{38}H_{61}N_2O_2Cu$ 640.4024, found 640. 4020.



Complex 27c. Green solid; yield (287 mg, 86%); $[\alpha]_D^{29}$ = -33.33 (c = 0.024, $CHCl_3$); FT-IR (KBr): 3414, 2951, 2901, 2867, 1731, 1674, 1469, 1438, 1412, 1388, 1360, 1300, 1242, 1203, 1167, 1132, 1094, 969, 874, 831, 770, 741, 685, 669, 650, 538, 492 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 669 (5968), 457 (8888), 300 (82100), 253 nm (104388 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; $g_{\|}$ = 2.345, $g_{\perp}$ = 2.026, $A_{\|=}$ 20.57 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{40}H_{65}N_2O_2Cu$ 668.4337, found 668.4346.



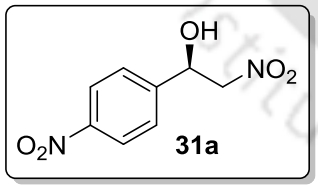
Complex 28. Green solid; yield (288 mg, 92%); $[\alpha]_D^{29}$ = -3422.2 (c = 0.090, $CHCl_3$); FT-IR (KBr): 2949, 2864, 1726, 1661, 1619, 1602, 1467, 1439, 1412, 1389, 1361, 1299, 1287, 1253, 1237, 1203, 1166, 1132, 998, 877, 828, 807, 778, 661, 642, 535 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 622 (4933), 436 (8425), 298 (53208), 250 nm (71646 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; $g_{\|}$ = 2.329, $g_{\perp}$ = 2.010, $A_{\|=}$ 21.87 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{37}H_{59}N_2O_2Cu$ 626.3867, found 626.3872.



29

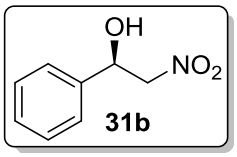
Complex 29. Green solid; yield (285 mg, 94%); $[\alpha]_D^{29}$ = -331.2 (c = 0.046, $CHCl_3$); FT-IR (KBr): 3313, 2954, 2905, 2867, 1726, 1621, 1527, 1463, 1431 1383, 1362, 1348, 1323, 1254, 1200, 1167, 1132, 1097, 968, 877, 832, 788, 743, 556, 537, 476 cm^{-1}; UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ = 569 (940), 378 (14452), 281 (40276), 256 nm (43531 mol^{-1} dm^3 cm^{-1}); EPR (THF): liquid N_2 temp; $g_{\parallel}$ = 2.333, $g_{\perp}$ = 2.008, $A_{\parallel}$ = 22.24 mT; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{36}H_{53}N_2O_2Cu$ 608.3398, found 608.3394.

General Procedure for Enantioselective Nitroaldol Reaction. To a stirred solution of the catalyst **27b** (16 mg, 0.025 mmol) and aldehyde (0.25 mmol) in dry toluene (0.75 mL), nitromethane (2.5 mmol) was added at appropriate temperature. After the indicated time, the reaction mixture was treated with saturated NH_4Cl solution (1 mL) followed by water (3 mL). The mixture of was then extracted using EtOAc (3x5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and EtOAc (4:1) as eluent to afford the analytically pure nitroaldol product.

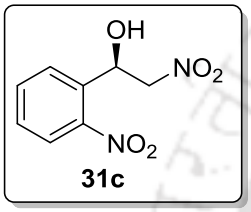


31a

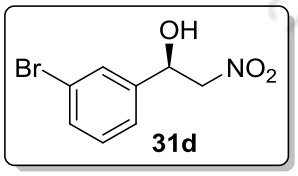
(*R*)-(-)-2-Nitro-1-(4-nitrophenyl)ethanol 31a.[19] Yellow oil, yield (30 mg, 56%); $[\alpha]_D^{29}$ = -29.6 (*c* 0.52, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, *J* = 6.4, 1.2 Hz, 2H), 7.63 (d, *J* = 9.2 Hz, 2H), 5.62-5.58 (m, 1H), 4.63–4.55 (m, 2H), 3.21 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 145.3, 127.1, 124.3, 80.8, 70.1; FT-IR (neat): 3528, 1557, 1520, 1350 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (85:20), λ_{max}: 215 nm, flow rate: 1 mL/min, retention time: 11.5 min, 14.9 min; 76% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_8N_2O_5$ 213.0506, found 213.0509.



(*R*)-(-)-2-Nitro-1-phenylethanol 31b.[20] Yellow oil, yield (27 mg, 64%); $[\alpha]_D^{29}$ = -33.1 (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H), 5.49-5.45 (m, 1H), 4.64-4.49 (m, 2H), 2.84 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 129.0, 129.0, 126.0, 81.3, 71.0; FT-IR (neat): 3548, 1553, 1379 cm^{-1}; HPLC: Chiralcel OJ-H, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.8 mL/min, retention time: 21.6 min, 26.1 min; 78% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_9NO_3$ 168.0655, found 168.0658.

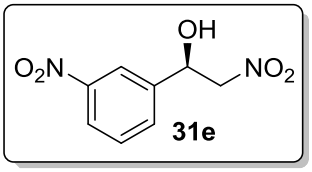


(*R*)-(+)-2-Nitro-1-(2-nitrophenyl)ethanol 31c.[2a] Yellow oil, yield (46 mg, 86%); $[\alpha]_D^{20}$ = +185 (*c* 0.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, *J* = 8, 1.2 Hz, 1H), 7.96 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.76 (td, *J* = 7.6, 0.8 Hz, 1H), 7.57 (td, *J* = 8.4, 0.8 Hz, 1H), 6.05-6.02 (m, 1H), 4.88-4.84 (m, 1H), 4.58-4.52 (m, 1H), 3.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 134.5, 134.3, 129.7, 128.8, 125.0, 80.2, 66.9. FT-IR (neat): 3529, 1555, 1525, 1346 cm^{-1}; HPLC: Chiralcel AD-H, n-hexane/isopropanol (90:10), λ_{max}: 215 nm, flow rate: 1 mL/min, retention time: 14.3 min, 15.7 min; 90% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_8N_2O_5$ 213.0509, found 213.0507.

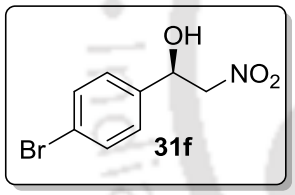


(*R*)-(-)-1-(3-Bromophenyl)-2-nitroethanol 31d.[20] Yellow oil, yield (38 mg, 61%); $[\alpha]_D^{20}$ = -23.2 (*c* 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.50 (d, *J*=7.6 Hz, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.30 (d, *J*=7.6 Hz, 1H), 5.47-5.43 (m, 1H), 4.61-4.49 (m, 2H), 2.91 (d, *J*=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 132.0, 130.7, 129.2, 124.7, 123.1, 81.0, 70.2; FT-IR (neat): 3542, 1556, 1377 cm^{-1}; HPLC: Chiralcel OD-H, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.8 mL/min,

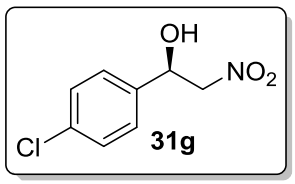
retention time: 11.7 min, 14.5 min; 80% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_8BrNO_3$ 245.9760, found 245.9766.



(*R*)-(-)-2-Nitro-1-(3-nitrophenyl)ethanol 31e.[20] Yellow oil, yield (41 mg, 76%); $[\alpha]_D^{29}$ = -28.8 (*c* 0.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 5.63-5.59 (m, 1H), 4.66–4.56 (m, 2H), 3.23 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 140.4, 132.2, 130.3, 123.9, 121.3, 80.8. 70.0; FT-IR (neat): 3546, 1557, 1538, 1347 cm^{-1}; HPLC: Chiralcel AD-H, n-hexane/isopropanol (90:10), λ_{max}: 215 nm, flow rate: 1 mL/min, retention time: 16.1 min, 18.5 min; 81% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_8N_2O_5$ 213.0509, found 213.0501.

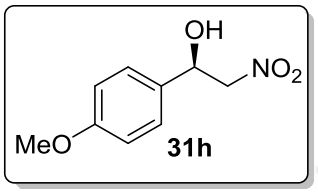


(*R*)-(-)-1-(4-Bromophenyl)-2-nitroethanol 31f.[20] Yellow oil, yield (40 mg, 65%); $[\alpha]_D^{29}$ = -22.1 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 9.0, 4.2 Hz, 2H), 7.28 (d, *J* = 10.2 Hz, 2H), 5.43-5.40 (m, 1H), 4.57-4.46 (m, 2H), 2.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2, 132.3, 127.8, 123.0, 81.0, 70.4; FT-IR (neat): 3404, 1553, 1381 cm^{-1}; HPLC: Chiralcel OD-H, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.9 mL/min, retention time: 12.5 min, 15.9 min; 82% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_8BrNO_3$ 245.9760, found 245.9764.

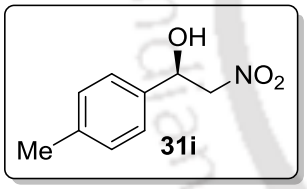


(*R*)-(-)-1-(4-Chlorophenyl)-2-nitroethanol 31g.[20] Yellow oil, yield (45 mg, 89%); $[\alpha]_D^{29}$ = -27.0 (*c* 0.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.40-7.34 (m, 4H), 5.48-5.44 (m, 1H), 4.60–4.47 (m, 2H), 2.89 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz,

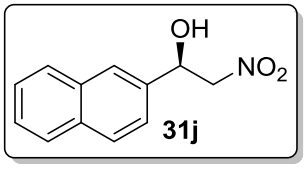
$CDCl_3$): δ 136.7, 134.7, 129.2, 127.4, 81.0, 70.3; FT-IR (neat): 3528, 1553, 1380 cm^{-1}; HPLC: Chiralcel OD-H, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.9 mL/min, retention time: 11.3 min, 12.5 min; 65% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_8H_8ClNO_3$ 202.0265, found 202.0260.



(*R*)-(-)-1-(4-Methoxyphenyl)-2-nitroethanol 31h.[20] Yellow oil, yield (27 mg, 54%); $[\alpha]_D^{29}$ = -18 (*c* 1.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.44-5.39 (m, 1H), 4.63–4.46 (m, 2H), 3.81 (s, 3H), 2.72 (t, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 130.0, 127.4, 126.1, 121.4, 110.7, 80.0, 68.0, 55.6; FT-IR (neat): 3472, 1553, 1379 cm^{-1}; HPLC: Chiralcel OJ-H, n-hexane/isopropanol (90:10), λ_{max}: 215 nm, flow rate: 0.6 mL/min, retention time: 42.4 min, 50.1 min; 70% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_9H_{11}NO_4$ 198.0761, found 198.0768.

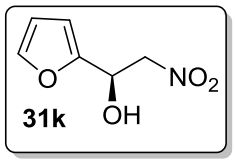


(*R*)-(-)-2-Nitro-1-(p-tolyl)ethanol 31i.[20] Yellow oil, yield (31 mg, 68%); $[\alpha]_D^{29}$ = -24.3 (*c* 1.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 5.45-5.41 (m, 1H), 4.63–4.47 (m, 2H), 2.75 (d, *J* = 4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 138.9, 135.3, 129.7, 126.0, 81.3, 70.9, 21.2; FT-IR (neat): 3551, 1554, 1378 cm^{-1}; HPLC: Chiralcel OJ-H, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.8 mL/min, retention time: 18.7 min, 21.7 min; 79% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_9H_{11}NO_3$ 182.0812, found 182.0807.



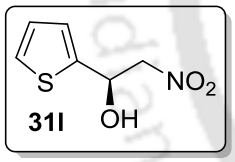
(*R*)-(-)-1-(Naphthalen-2-yl)-2-nitroethanol 31j.[20] Colorless solid, mp 80-81 °C; yield (24 mg, 43%); $[\alpha]_D^{29}$ = -35.6 (*c* 0.38, $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$): δ 7.90-7.84 (m, 4H), 7.54-7.46 (m, 3H), 5.66-5.62 (m, 1H), 4.72-4.58 (m, 2H), 2.94 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 135.3, 129.7, 126.0, 81.3, 70.9. FT-IR (KBr): 3547, 1553, 1377 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (80:20), λ_{max}: 215 nm, flow rate: 1 mL/min, retention time: 18.2 min, 25.9 min; 77% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{11}NO_3$ 218.0812, found 218.0819.



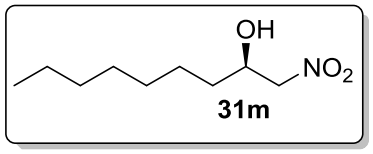
31k

(*R*)-(-)-1-(Furan-2-yl)-2-nitroethanol 31k.[19] Yellow oil, yield (28 mg, 71%); $[\alpha]_D^{29}$ = -32.8 (*c* 0.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 1H), 6.38 (d, *J* = 3.6 Hz, 1H), 6.36 (dd, *J* = 3.0, 1.8 Hz, 1H), 5.46-5.45 (m, 1H), 4.78–4.74 (m, 1H), 4.67-4.64 (m, 1H), 2.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 143.3, 110.8, 108.4, 78.5, 65.0; FT-IR (neat): 3418, 1555, 1380 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.9 mL/min, retention time: 15.9 min, 18.6 min; 76% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_6H_7NO_4$ 158.0448, found 158.0440.



31l

(*R*)-(-)-2-Nitro-1-(thiophen-2-yl)ethanol 31l.[21a] Yellow oil, yield (15 mg, 34%); $[\alpha]_D^{29}$ = -16 (*c* 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 1H), 7.06–7.04 (m, 1H), 7.01-6.99 (m, 1H), 5.72-5.70 (m, 1H), 4.73–4.57 (m, 2H), 3.00 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 127.3, 126.2, 125.1, 81.0, 67.2; FT-IR (neat):3416, 1618, 1557, 1380 cm^{-1}; HPLC: Chiralcel OD-H, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.9 mL/min, retention time: 10.1 min, 11.5 min; 71% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_6H_7NO_3S$ 174.0219, found 174.0211.



31m

(*R*)-(-)-1-Nitrononan-2-ol 31m.[21b] Yellow oil, yield (32 mg, 67%); $[\alpha]_D^{29}$ = -15.1 (*c* 1.0, $CHCl_3$); ^1H 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 80.8, 68.8, 33.9, 31.8, 29.4, 29.2, 25.3, 22.7. FT-IR (neat): 3418, 1555, 1382 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (85:15), λ_{max}: 215 nm, flow rate: 0.8 mL/min, retention time: 12.2 min, 16.0 min; 90% ee; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_9H_{19}NO_3$ 190.1438, found 190.1433.

2.4 References

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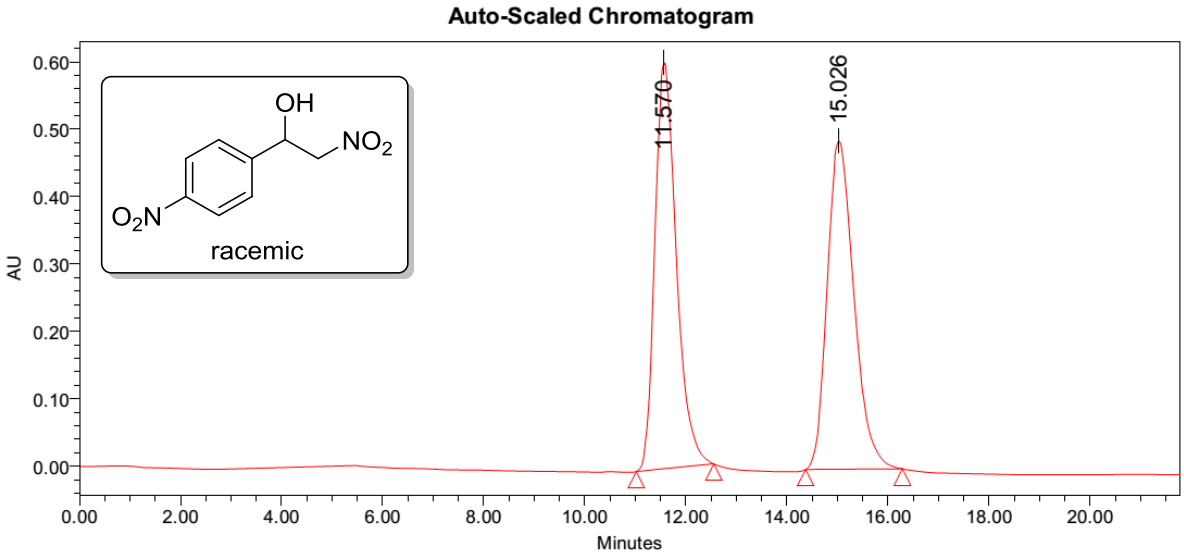
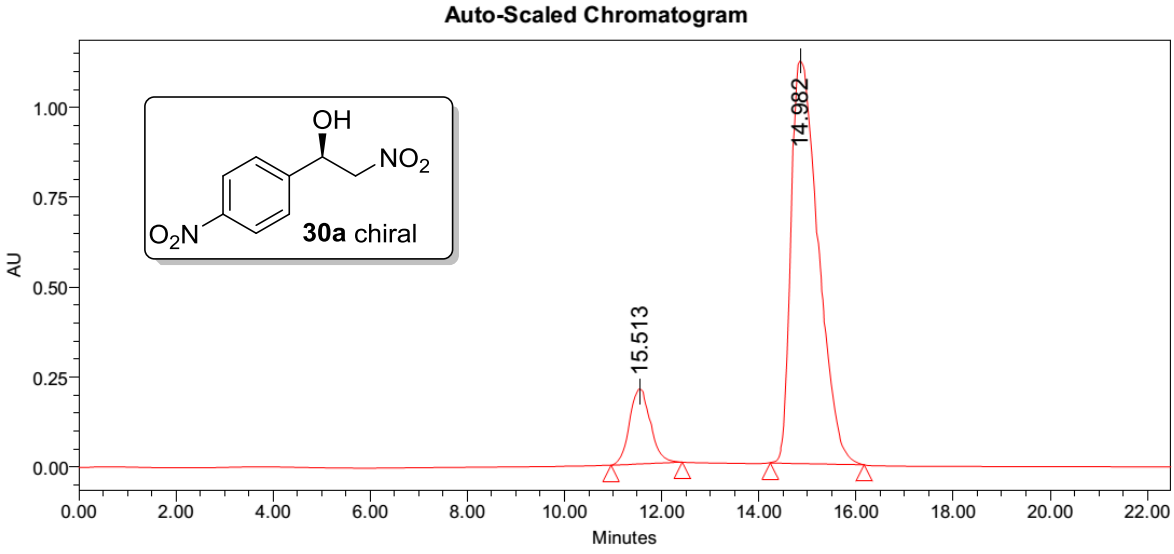
2.5 Selected HPLC Chromatograms



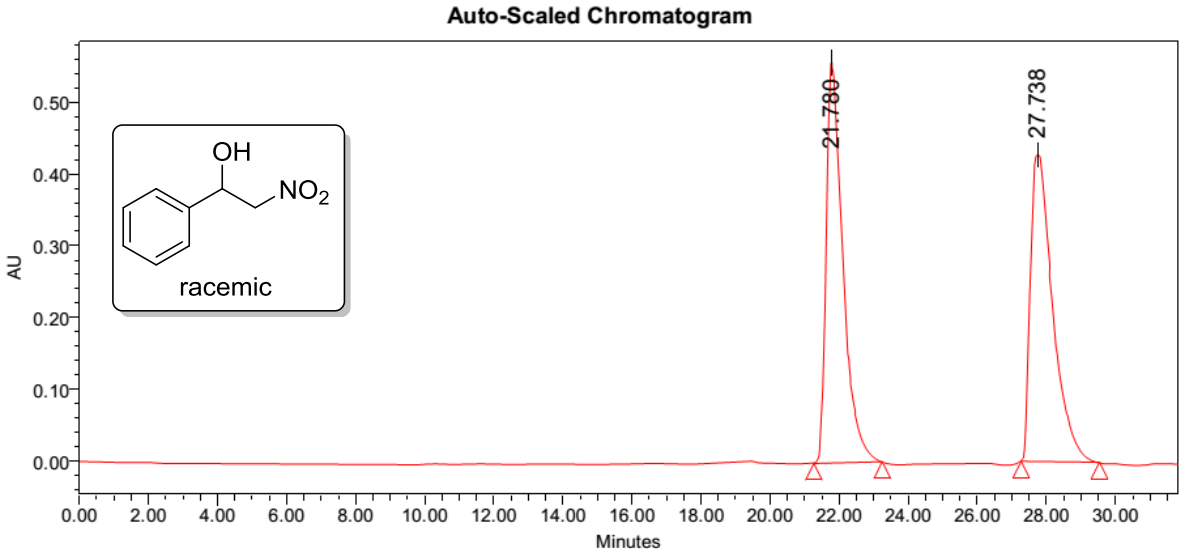
Peak Results

	RT	Height (μV)	% Area
1	11.570	602986	49.96
2	15.026	487556	50.04



Peak Results

	RT	Height (μV)	% Area
1	15.513	207905	11.92
2	14.982	1014082	88.08



Peak Results

	RT	Height (μV)	% Area
1	21.780	557773	50.26
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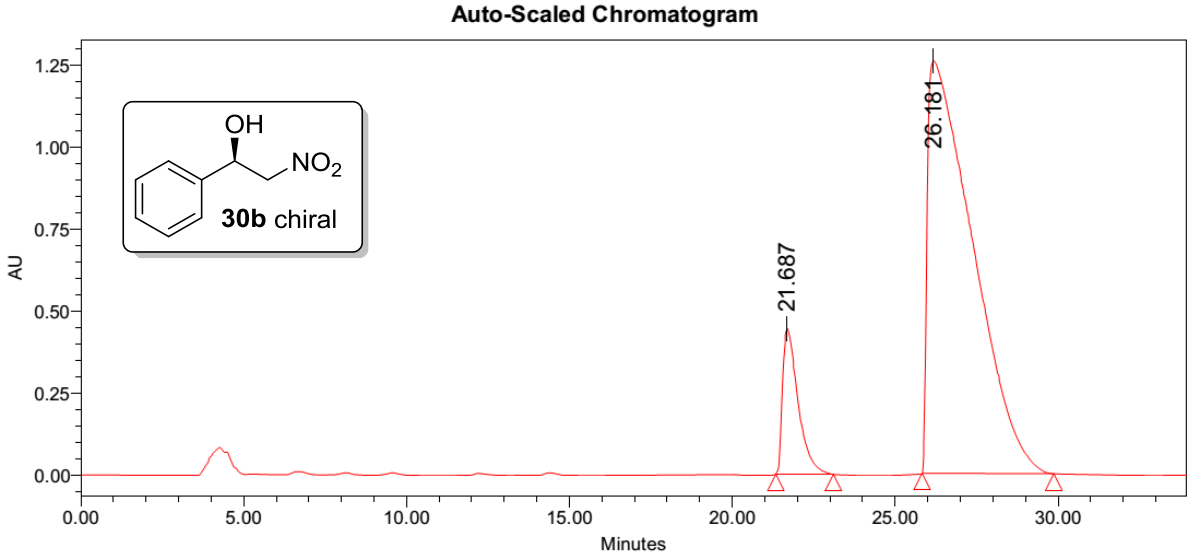

Peak Results

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1	21.687	443047	10.74
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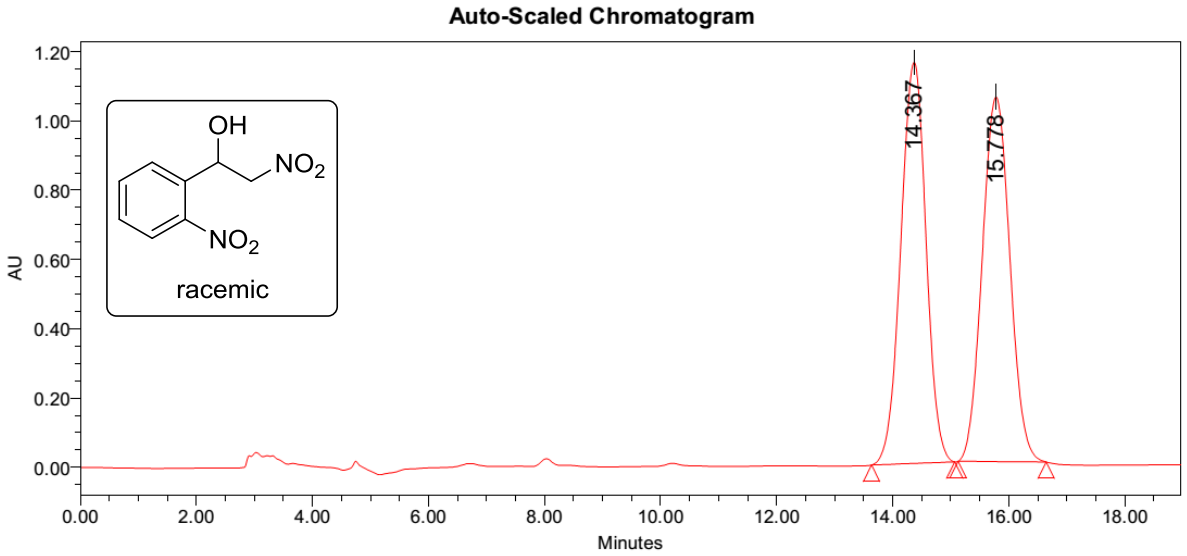

Peak Results

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1	14.367	1157981	50.06
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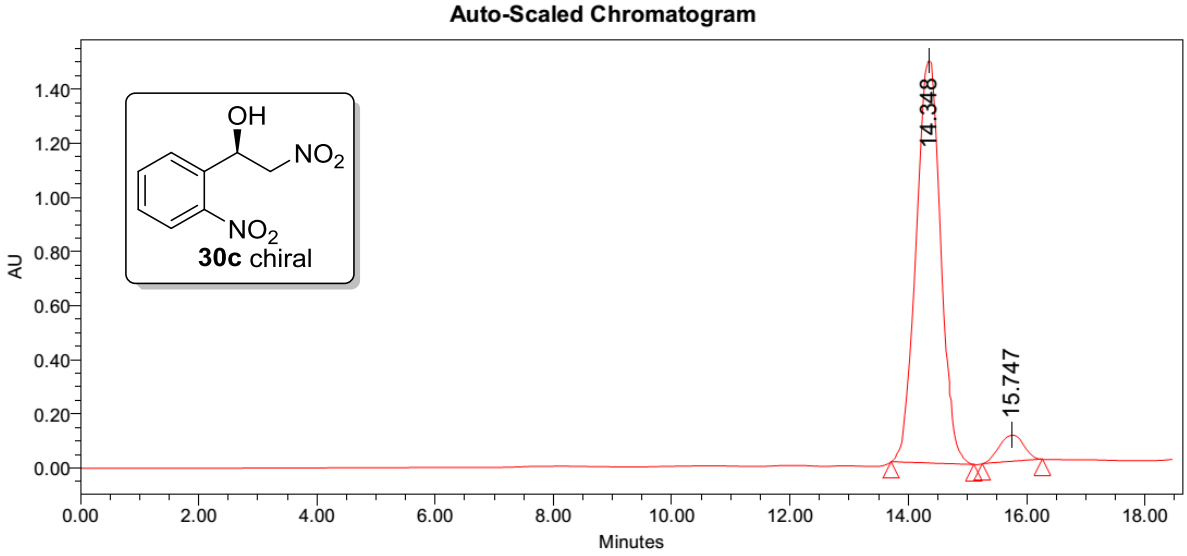
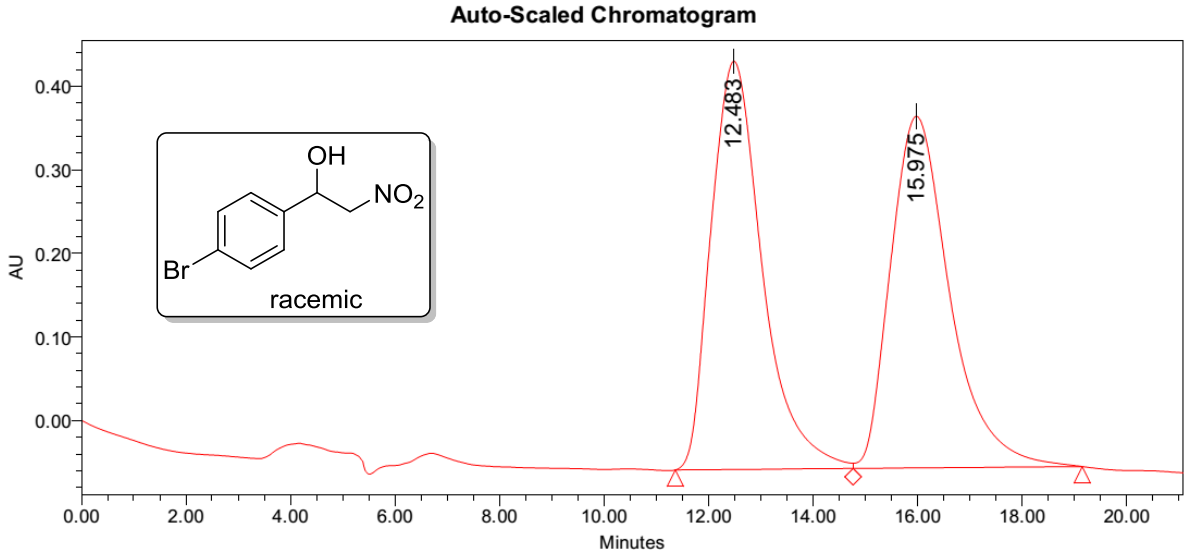


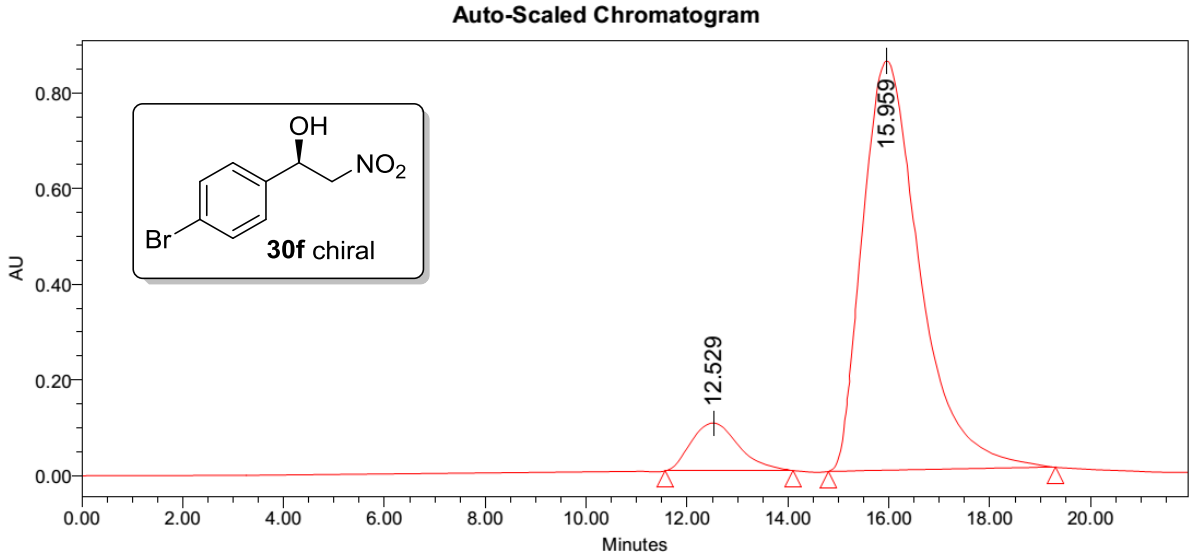
Peak Results

	RT	Height (μV)	% Area
1	14.348	1487313	95.08
2	15.747	97211	4.92



Peak Results

	RT	Height (μV)	% Area
1	12.483	488545	50.15
2	15.975	420921	49.85



Peak Results

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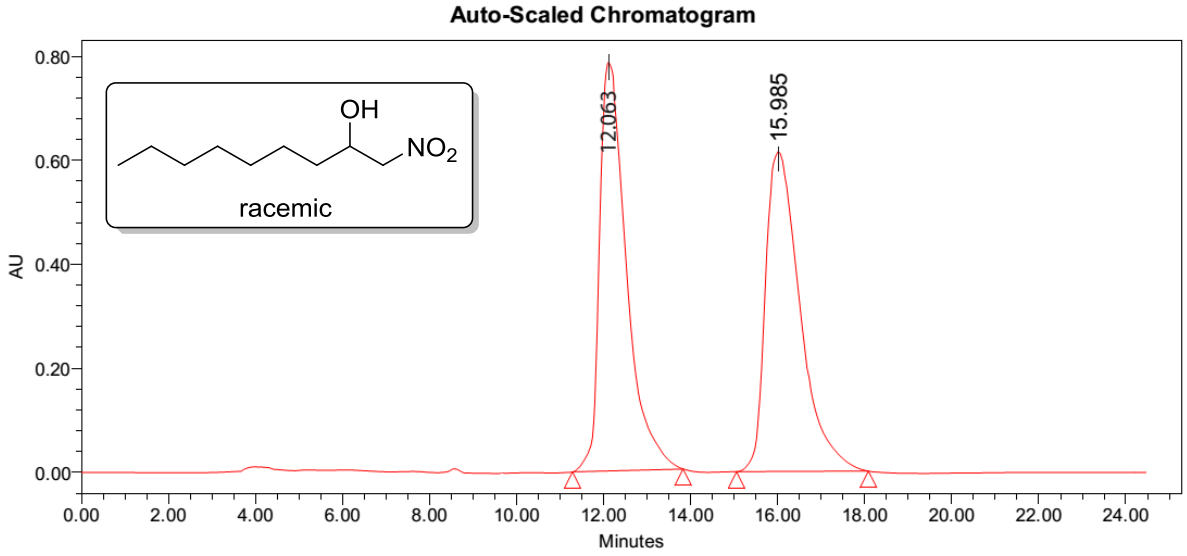
2	15.959	854720	91.23



Peak Results

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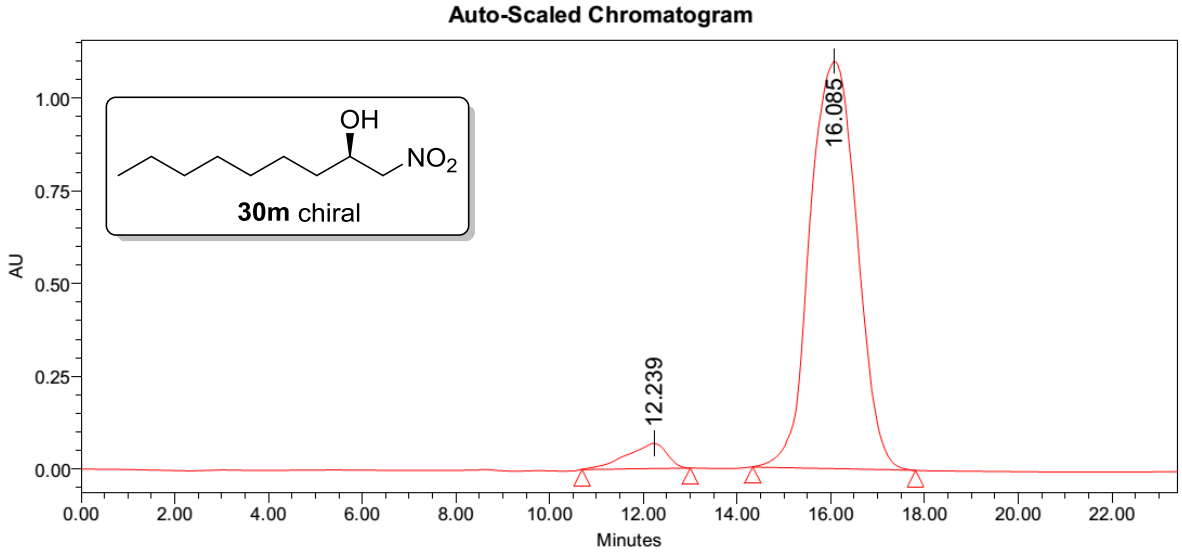

Peak Results

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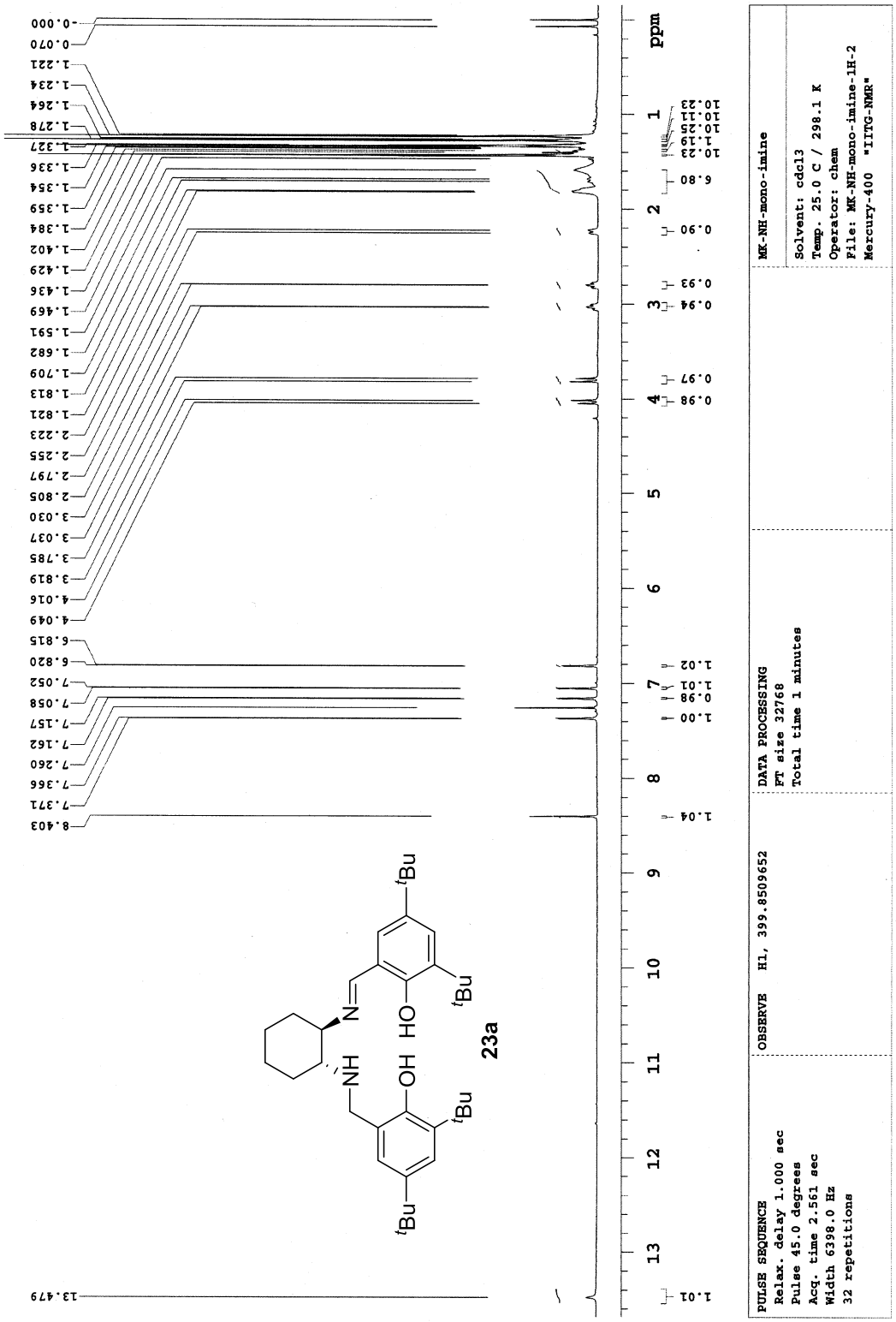
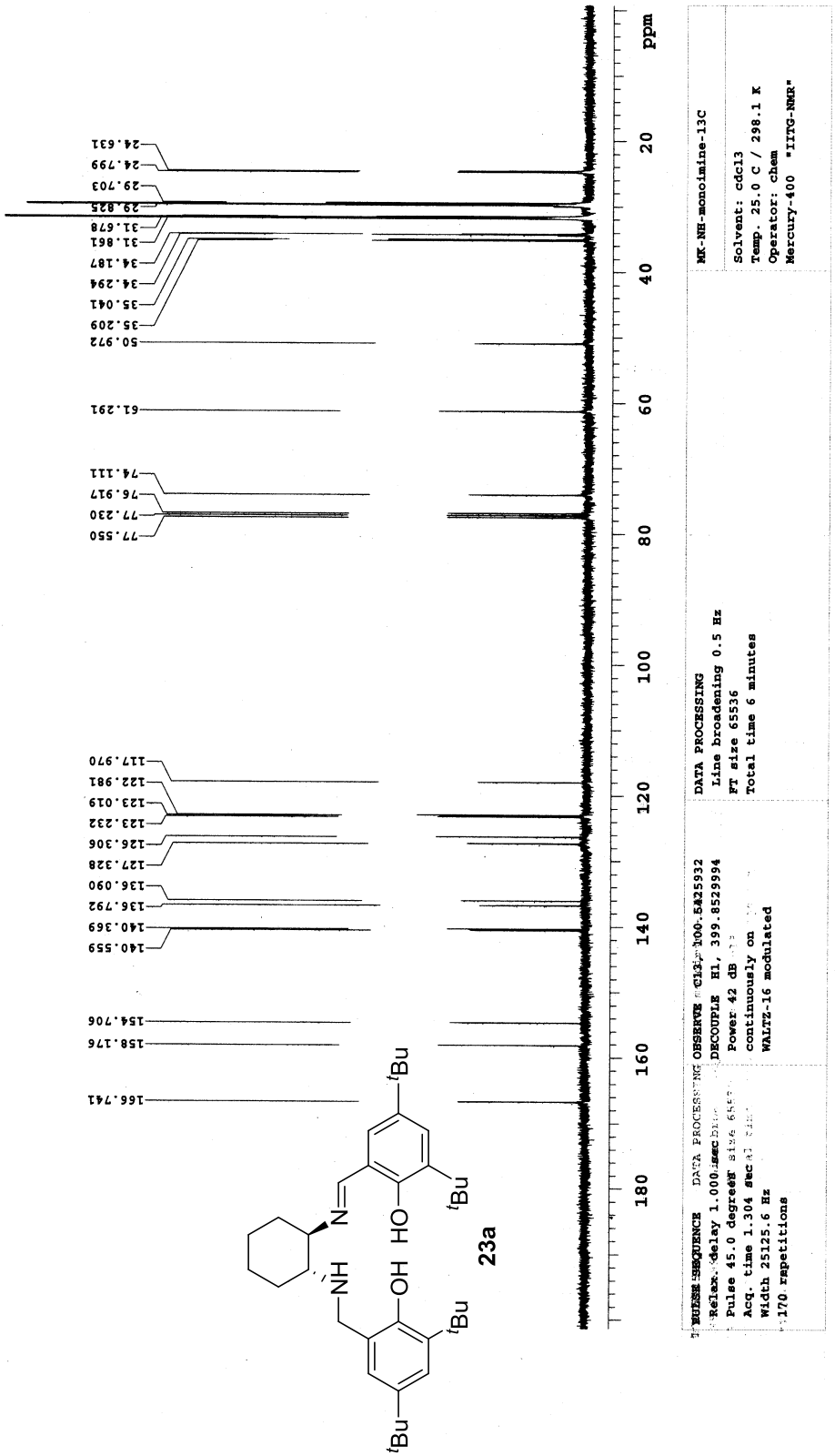
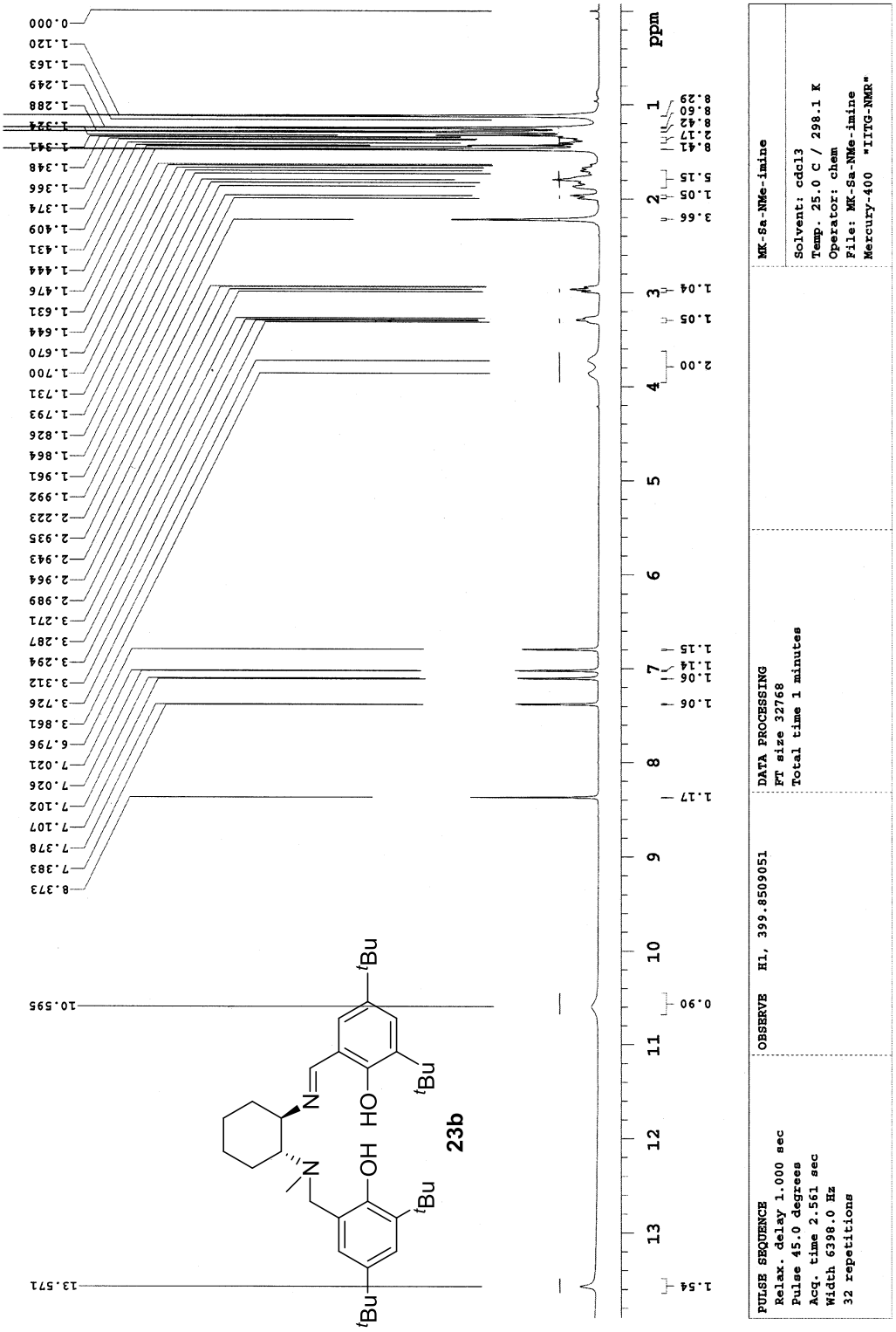
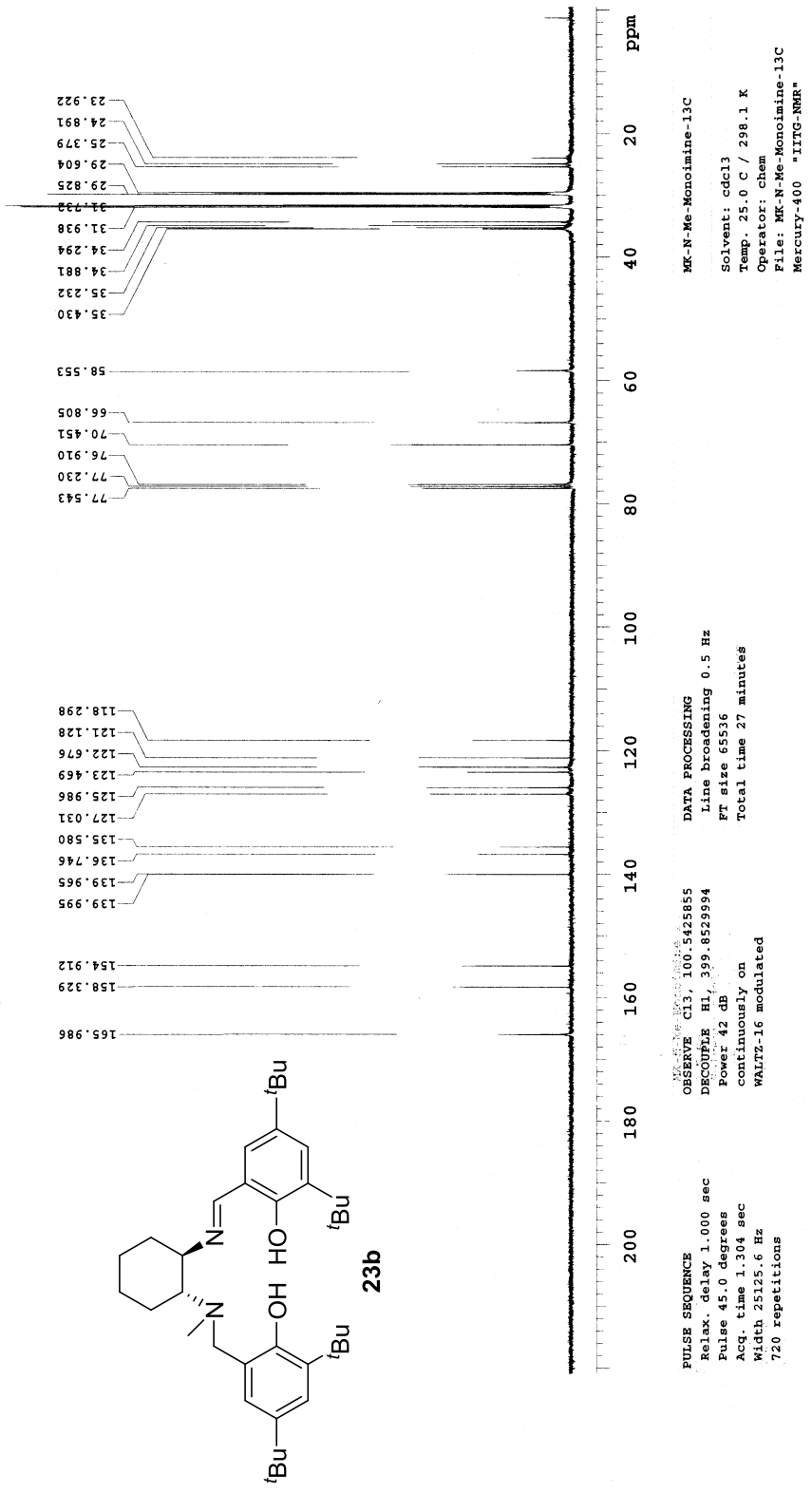
1	12.239	75928	5.06
2	16.085	1999293	94.94

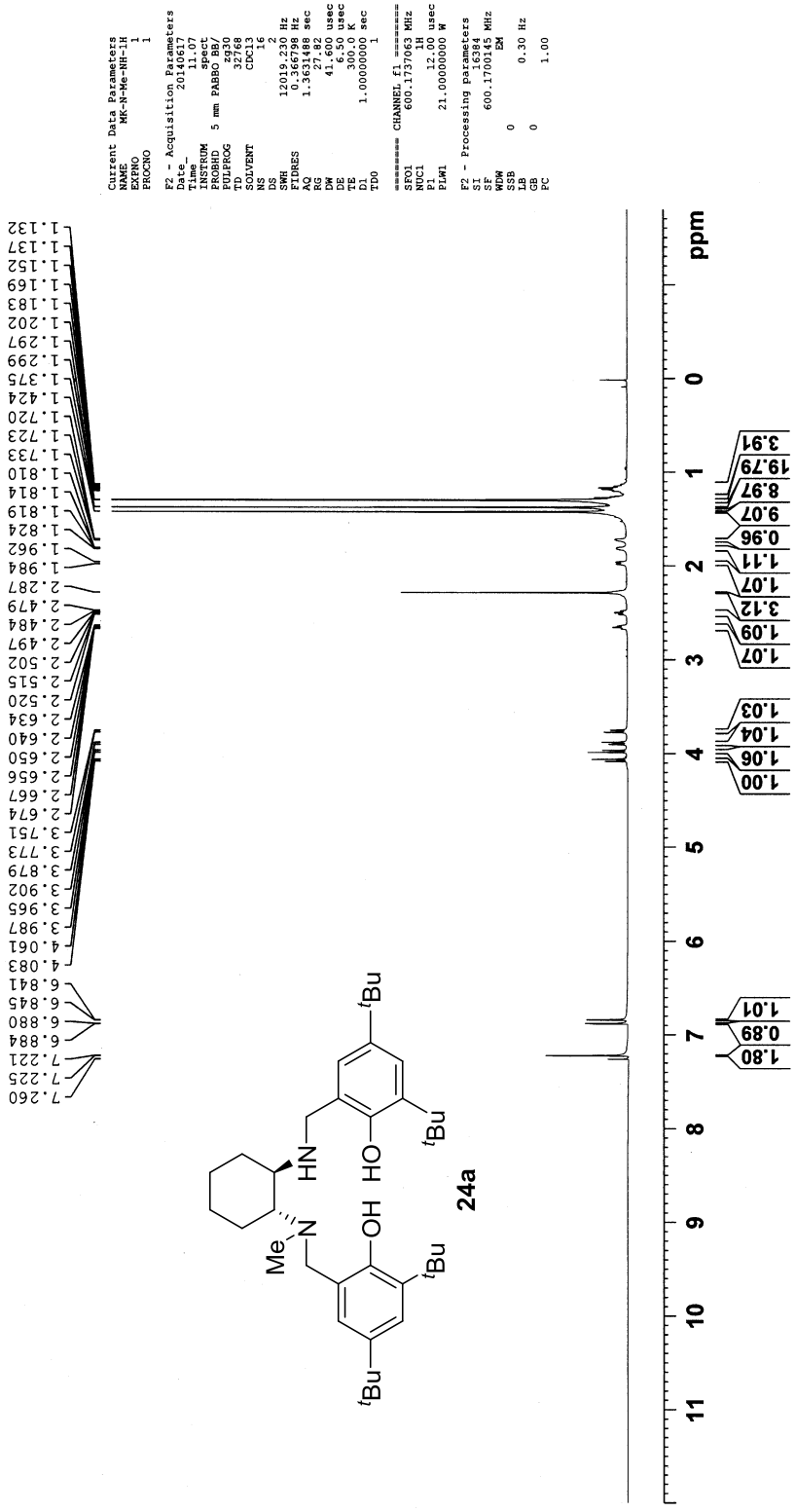
2.6 Selected NMR (^{1}H and ^{13}C) Spectra

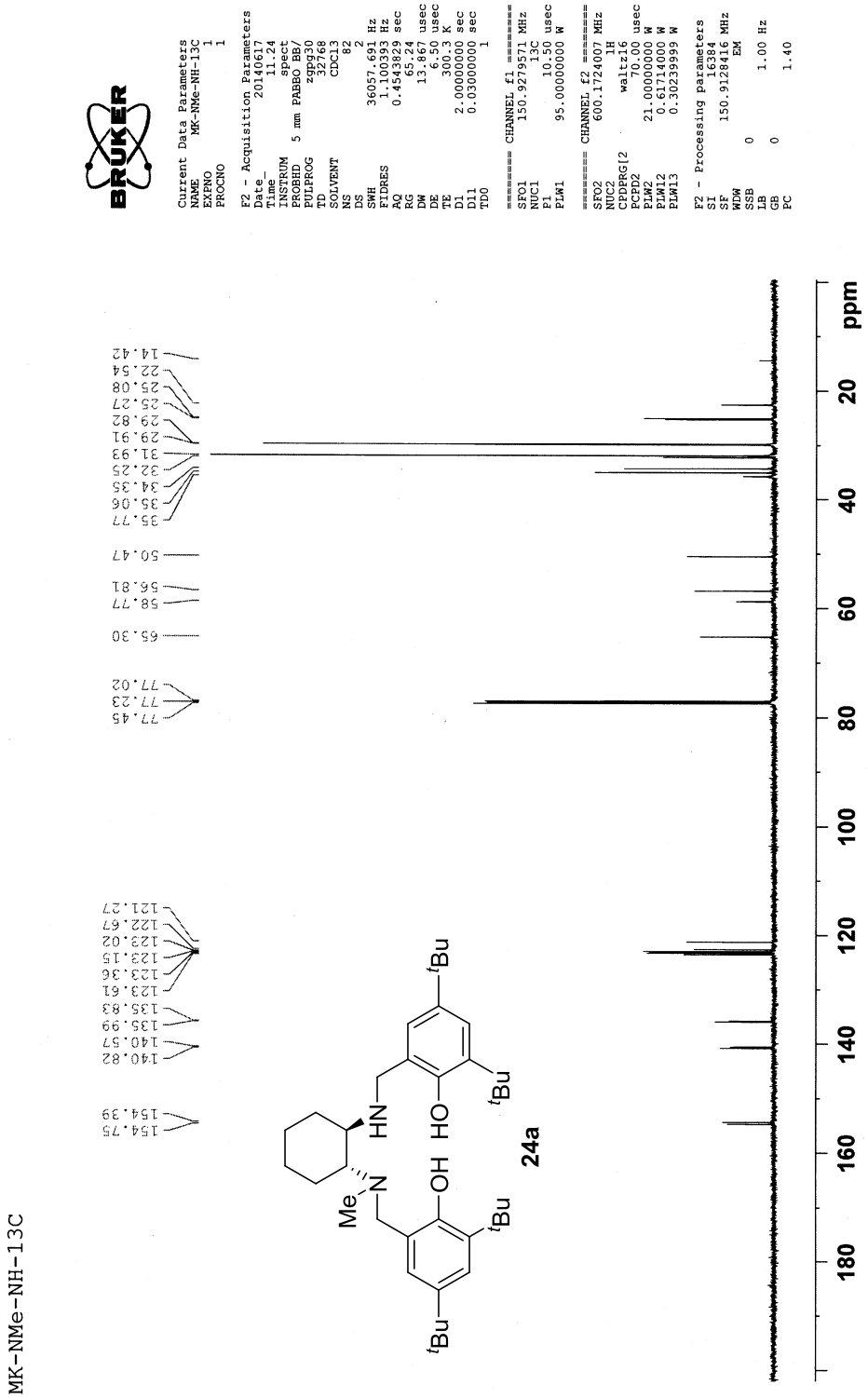


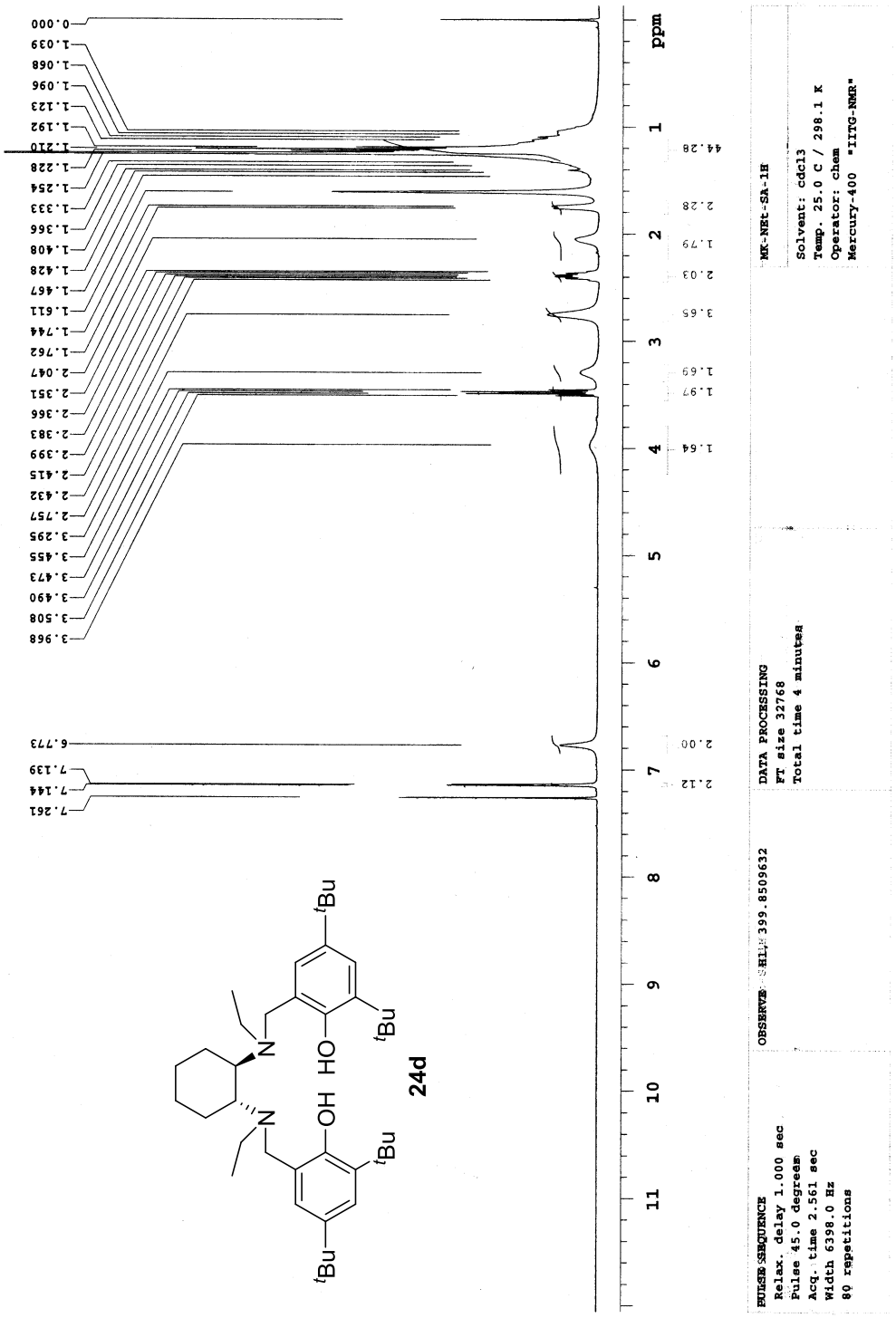


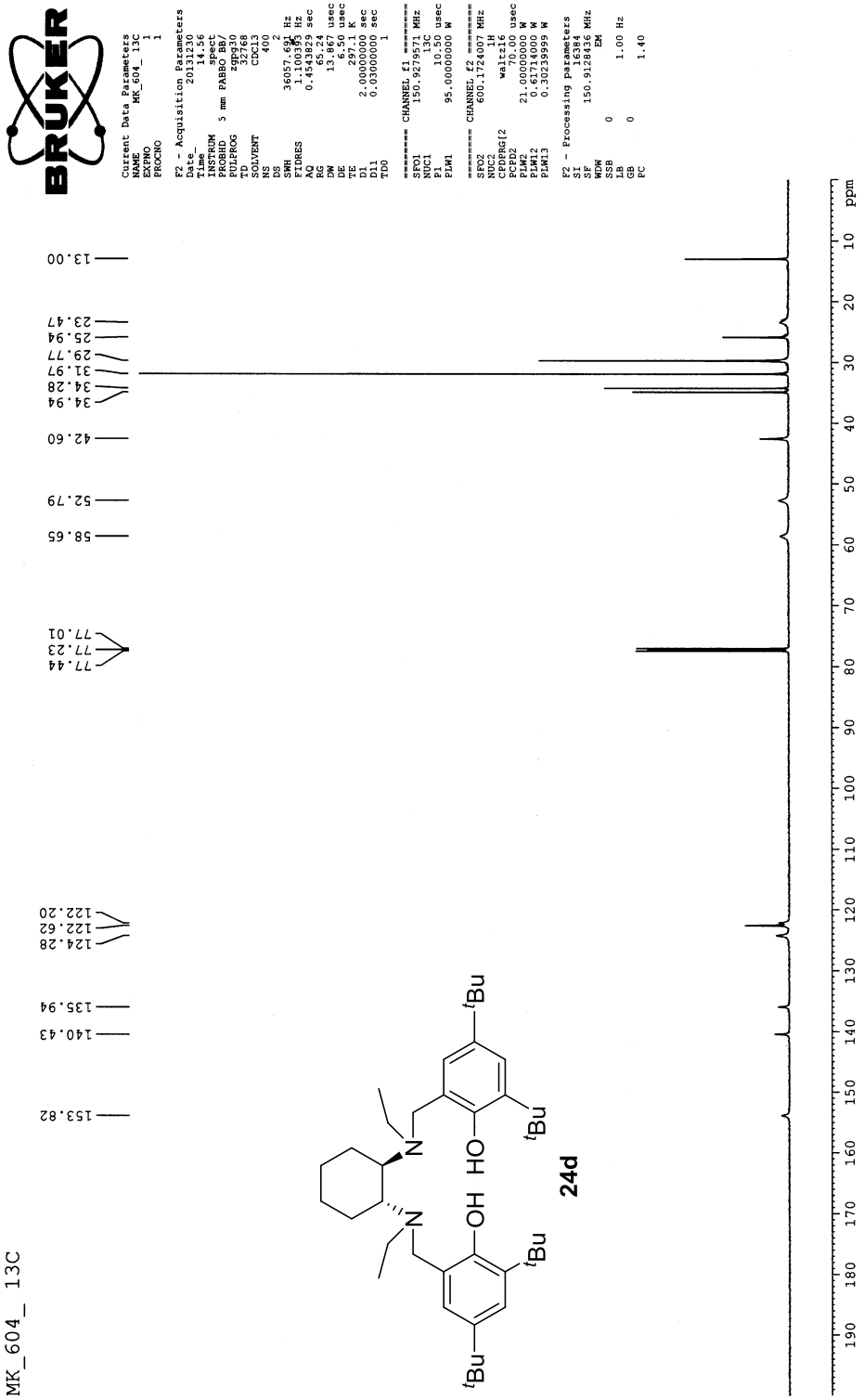


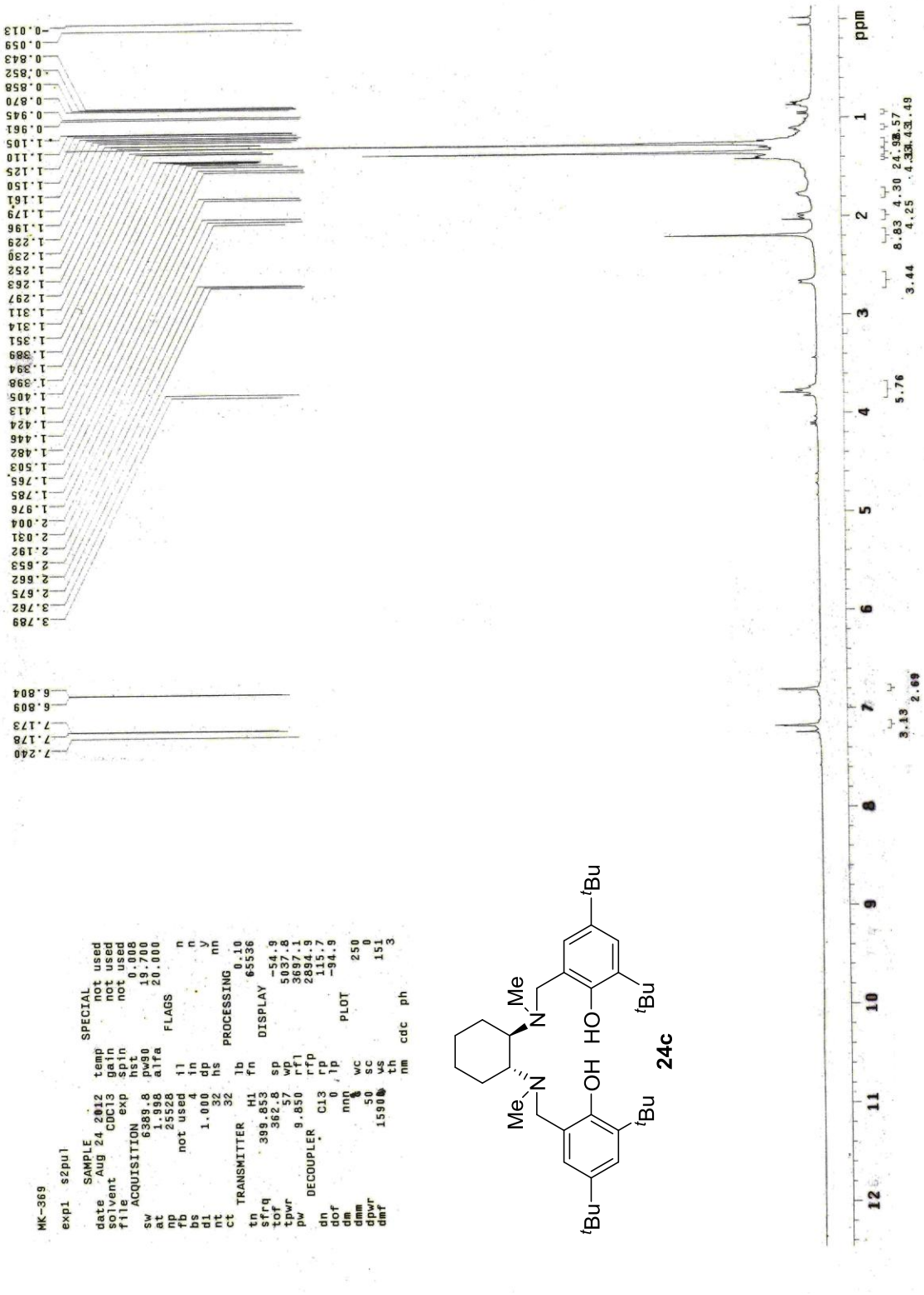


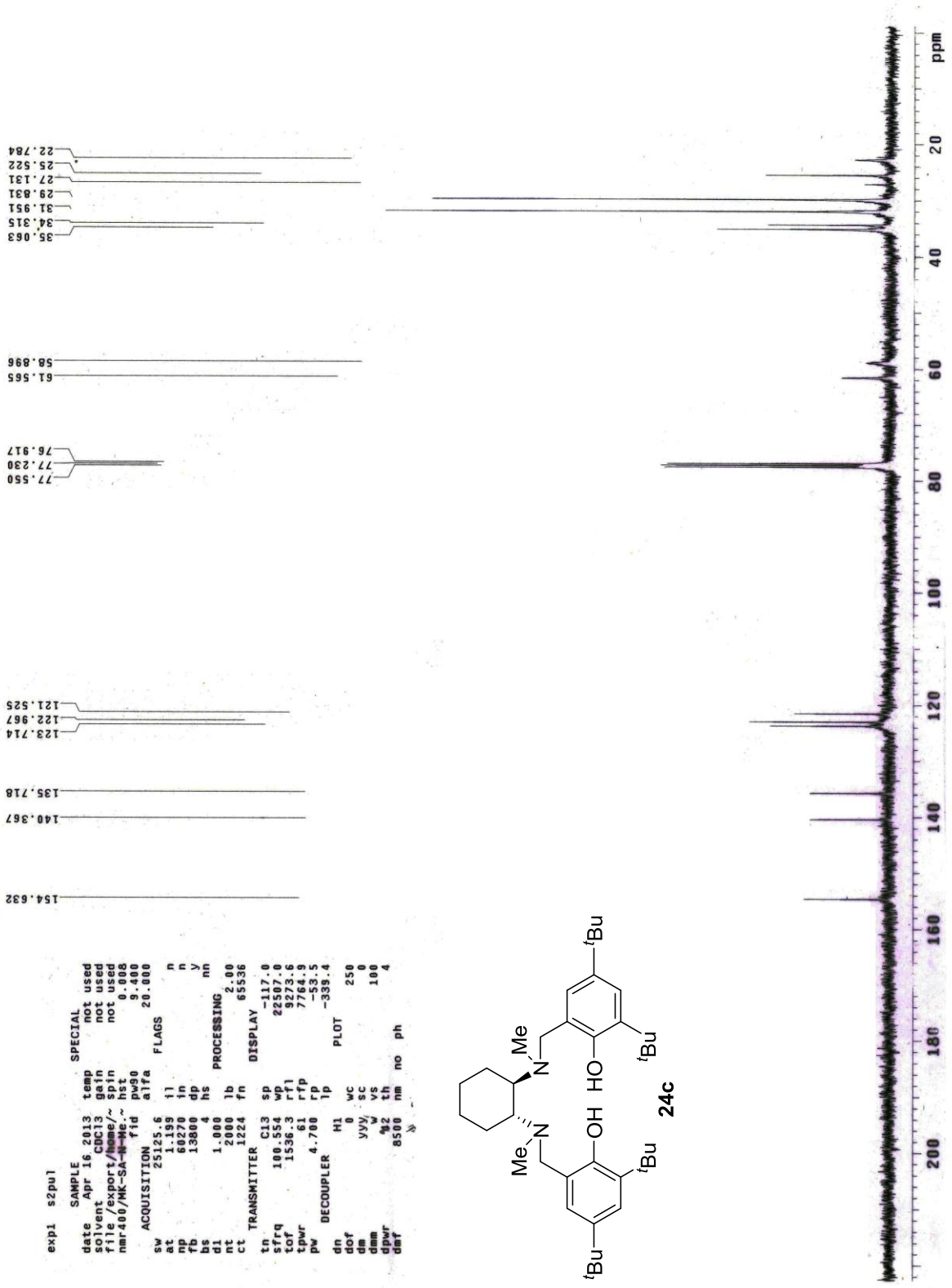


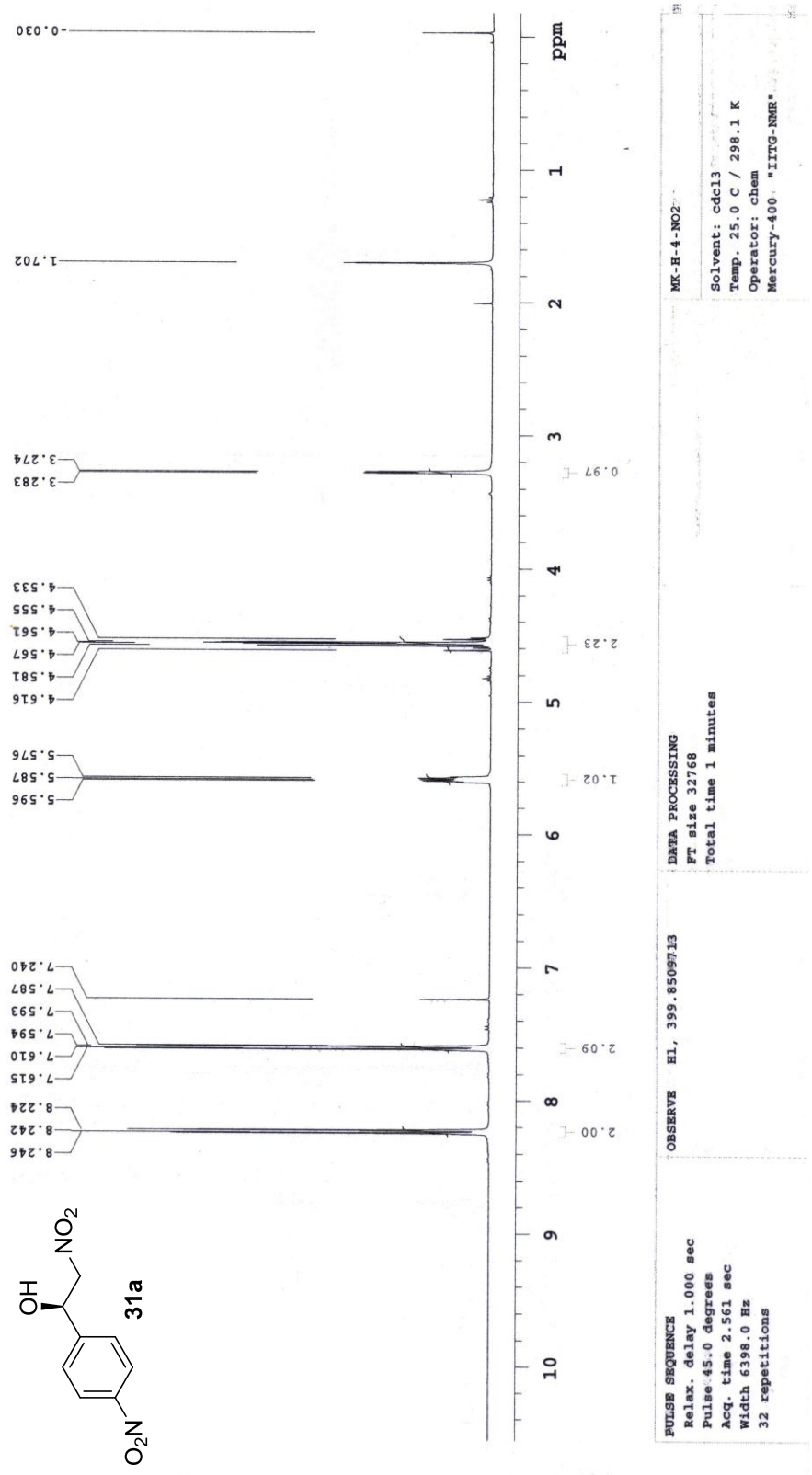


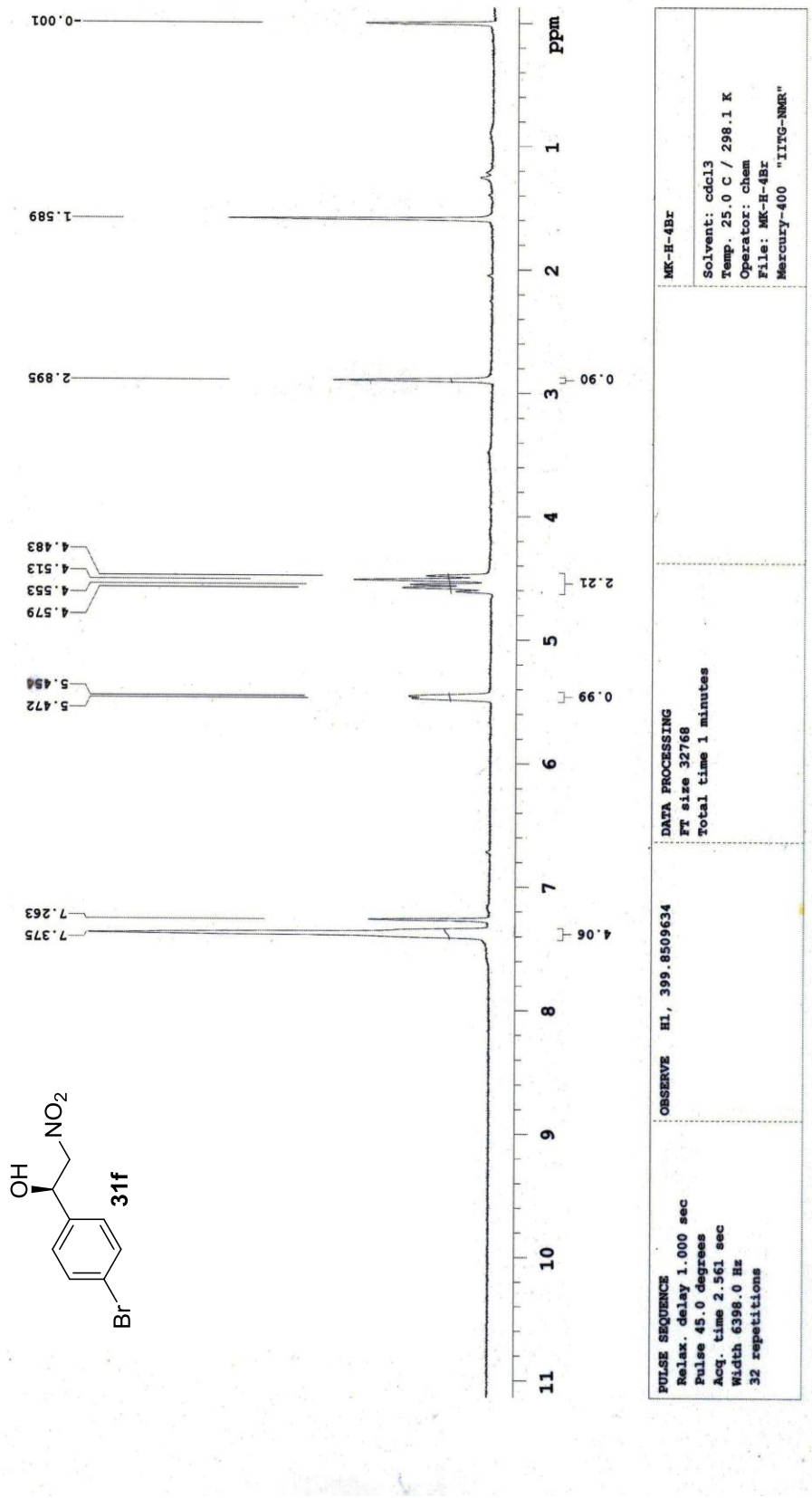












Chapter III

Chiral Iron(III)-Catalyzed Enantioselective Tetrahydrothiophene Synthesis

Polysubstituted thiophenes are potential structural constituents of many biologically active compounds including essential coenzyme biotin,[1] cholecystokinin type-B receptor antagonist tetronothiodin,[2] nucleoside analogues active against HSV-1 and HSV-2,[3] human A3 adenosine receptor,[4] hypocholesterolemic active[5] agent and peniciline analogue.[6] In addition, chiral tetrahydrothiophenes serve as versatile chiral auxiliaries in asymmetric metal catalyzed reactions,[7b] chiral organocatalysis as well as in natural product synthesis.[7] Because of the high benefits of chiral thiophenes in numerous applications, the development of the new methodologies for the synthesis of dihydrothiophenes and tetrahydrothiophenes has become highly desirable in contemporary organic synthesis.

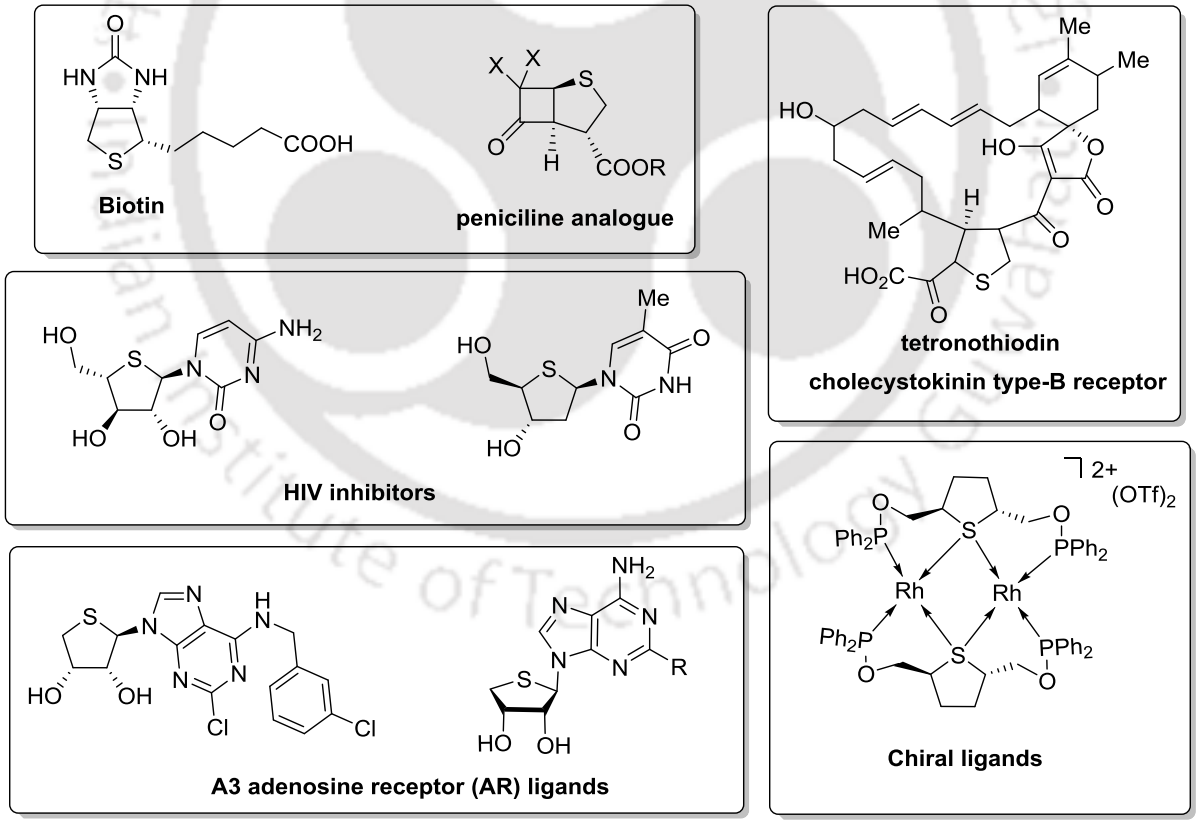
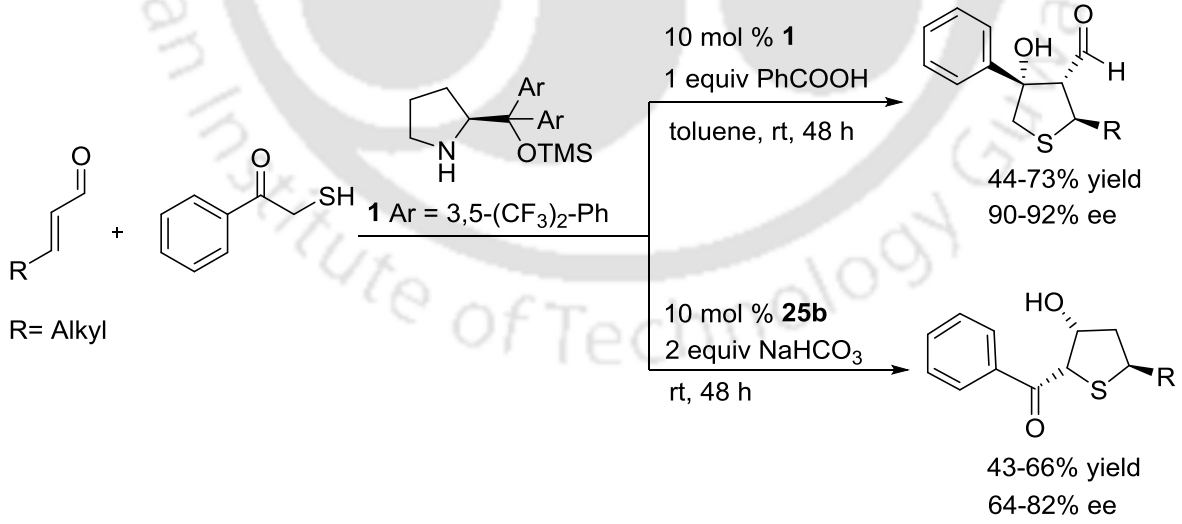


Figure 1. Some of the Biologically Important Tetrahydrothiophene Moieties

Asymmetric domino reaction is one of the most powerful synthetic tools to form multiple stereogenic centers by a single manipulation in modern organic synthesis.[8] They are atom economical, operationaly simple and minimize generation of chemical waste and the use of energy. The most efficient synthetic approaches for stereoselective cascade reactions are the metalcatalysis,[9] organocatalysis, hydrogen bonding catalysis[10] and aminocatalysis.[11] Although the later has been more extensively applied in contemporary studies, the traditional methods for the synthesis of chiral polysubstituted tertrahydrothiophenes employ asymmetric domino reactions *via* hetero-Michael/Michael, hetero-Michael/aldol mediated by organo as well as metal catalyses.[12] However, few synthetic routes have been reported for asymmetric domino Michael-Michael (also called double Michael) reactions with various organocatlysts such as chiral squaramide, chiral diphenyl prolinol, chiral thiourea and cinchona catalysts etc,. Still, metal catalyzed enantioselective domino reactions are sparse.

3.1 Selected Literature Reports on Tetrahydrothiophenes Synthesis

Jørgensen and co-workers have reported the synthesis of trisubstituted tetrahydrothiophenes *via* thia-Michael-aldol domino reaction at room temperature using bis(3,5-ditrifuoromethyl-diphenyl)prolinol TMS ether (Scheme 1).[13] The regioselectivity has been controlled by the



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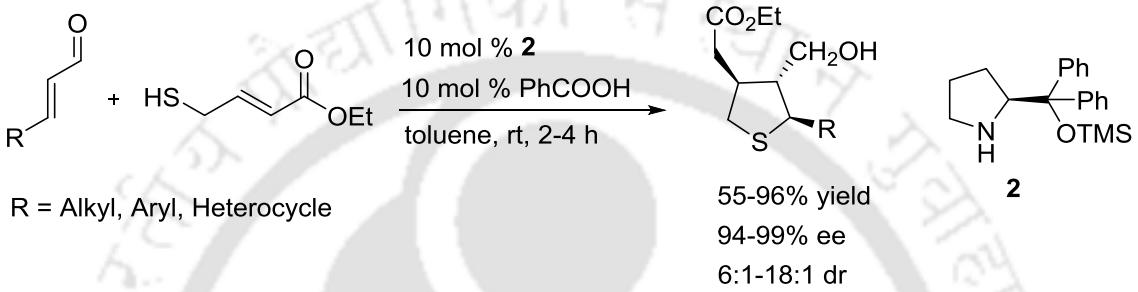
Scheme 1. Effect of Additives in Tetrahydrothiophene Synthesis

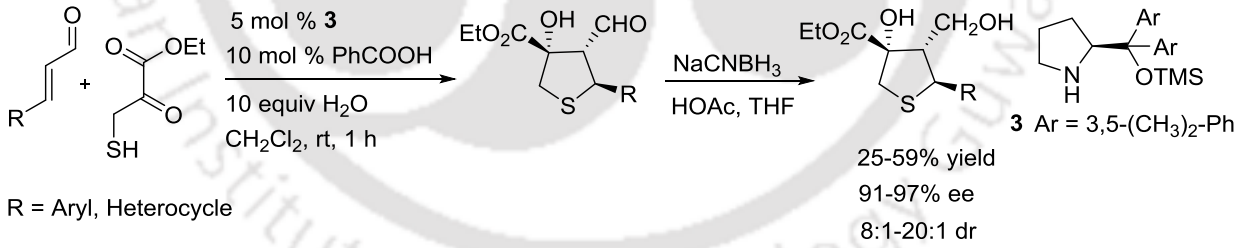
choice of the additive. The addition of benzoic acid gave tetrahydrothiophene carbaldehydes, while the use of sodium bicarbonate led to the formation of (tetrahydrothiophen-2-yl)phenyl methanones with excellent enantioselectivities.

Wang and co-workers have developed enantioselective domino double Michael addition reaction using a variety of *α,β*-unsaturated aldehydes and ethyl 4-mercapto-2-butenoate (Scheme 2).[14] The reaction conditions are mild and utilize the easely available (*S*)-diphenylprolinol TMS ether.



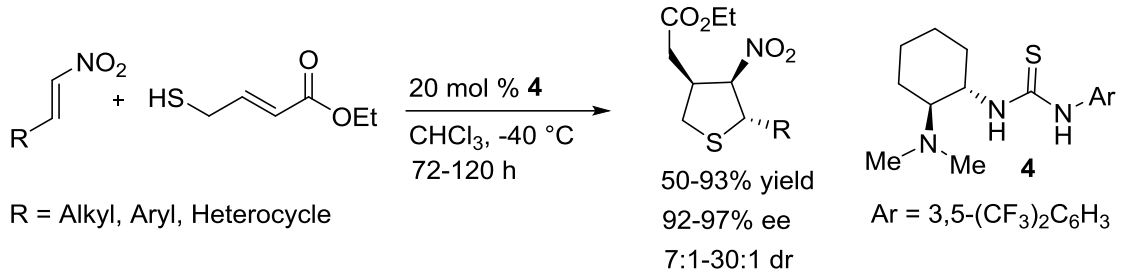
Scheme 2. Synthesis of Tetrahydrothiophenes from Ethyl (*E*)-4-Mercaptobut-2-Enoate

The same group subsequently explored the synthesis of structurally diverse trisubstituted tetrahydrothiophenes from 3-mercapto-2-oxopropanoate with a variety of cinnamic aldehydes (Scheme 3).[15]



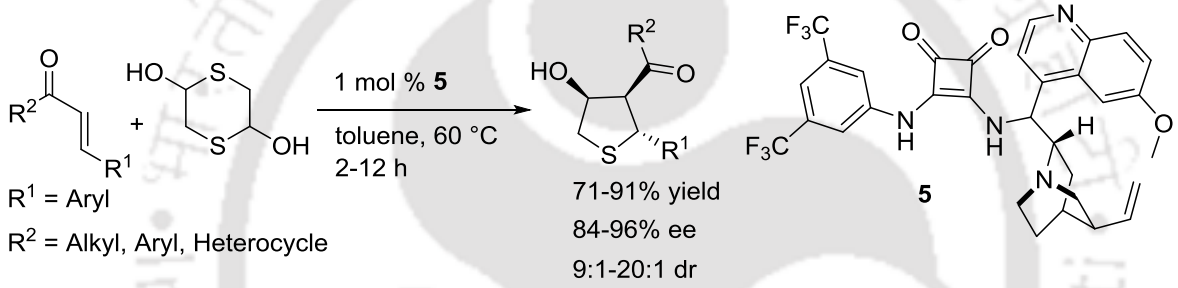
Scheme 3. Synthesis of Tetrahydrothiophenes from Ethyl 3-Mercapto-2-oxopropanoate

Bifunctional thiourea catalyzed diastereoselective synthesis of tetrahydrothiophenes has been reported from *trans*-ethyl-4-mercapto-2-butenoate with *trans-β*-nitrostyrene (Scheme 4).[16] The activation of this domino thia-Michael-Michael reaction proceeds through co-operative direct stereocontrolled non-covalent bond mediated asymmetric cascade reaction.



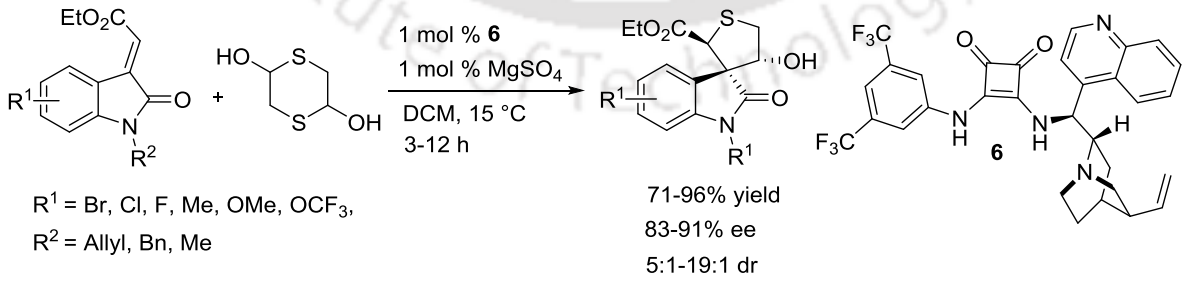
Scheme 4. Chiral Thiourea Catalyzed Tetrahydrothiophene Synthesis

Xu and co-workers have developed a bifunctional squaramide catalyst for stereospecific thia-Michael/aldol cascade reaction (Scheme 5).[17] The synthetic protocol requires relatively very low catalyst loading and they observed a remarkable temperature effect upon reaction efficiency.



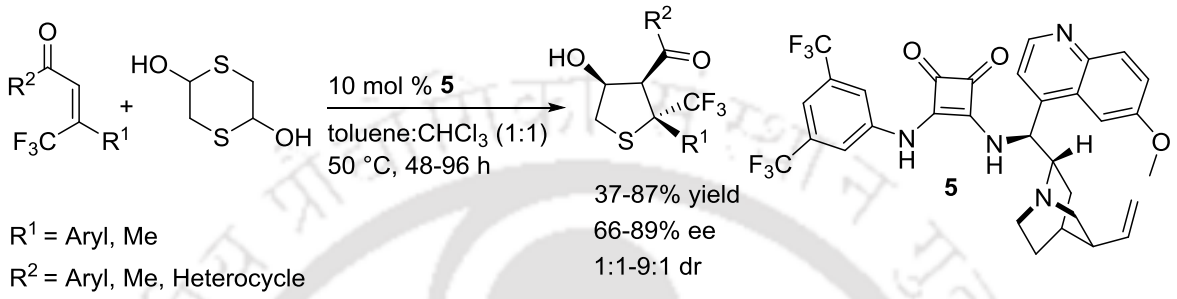
Scheme 5. Chiral Squaramide Catalyzed Tetrahydrothiophene Synthesis from Chalcone

Xiao and co-workers have reported chiral squaramide catalyzed Michael-aldol cascade reaction for stereoselective synthesis of siprocyclic oxindole fused with tetrahydro thiophenes (Scheme 6).[18] This method provides the stereoselective synthesis of three stereogenic center bearing spiroxindole derivative through H-bond mediated cascade reaction.



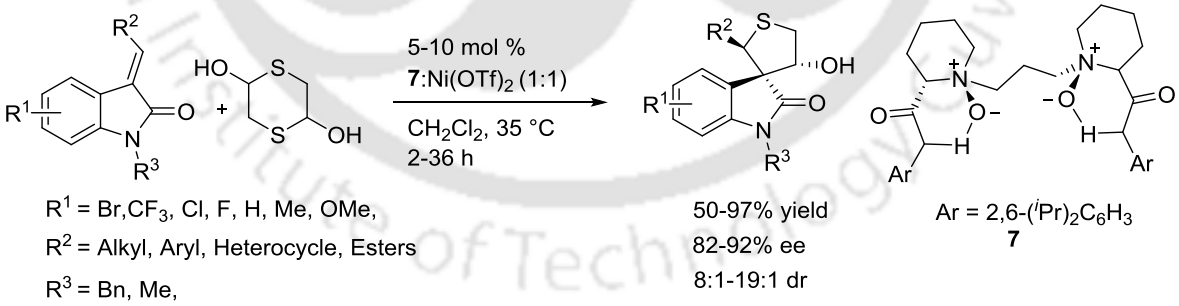
Scheme 6. Chiral Squaramide Catalyzed Tetrahydrothiophene Synthesis from Oxindole

Xu and co-workers have developed a synthetic method for the stereoselective synthesis of trifluoromethylated quarternary centered tetrahydrothiophenes by domino thia-Michael-Michael addition of mercaptoacetaldehyde to *β*-aryl-*β*-trifluoromethylated enones (Scheme 7).[19] This reaction provides a general method for the stereoselective construction of trifluoromethylated tetrahydrothiophenes under mild reaction conditions.



Scheme 7. Chiral Tetrahydrothiophene Synthesis from trifluoromethyl Chalcones

Feng and co-workers have reported chiral *N*,*N*′-dioxide-nickel(II) catalytic system for the stereoselective synthesis of spirocyclic oxindole fused tetrahydrothiophenes by domino thia-Michael-aldol reaction of 1,4-dithiane-2,5-diol with 3-alkenyloxindoles (Scheme 8).[20] A series of alkyl, aryl heterocycle and ester *N*-substituted 3-alkenyloxindoles underwent reaction to afford the desired products with excellent enantio- and diastereoselectivities (up to 97% yield, 98% ee, >19:1 dr).

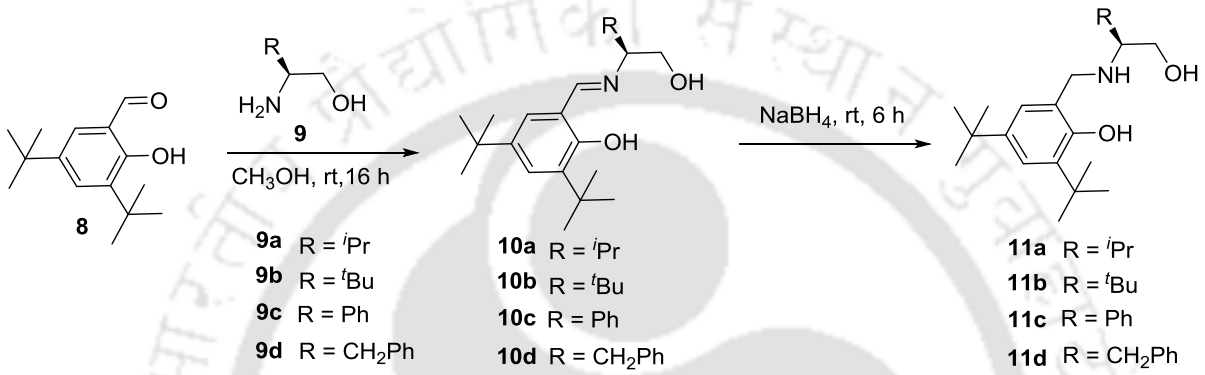


Scheme 8. Chiral Nickel(II)-Catalyzed Tetrahydrothiophene Synthesis from Chalcone

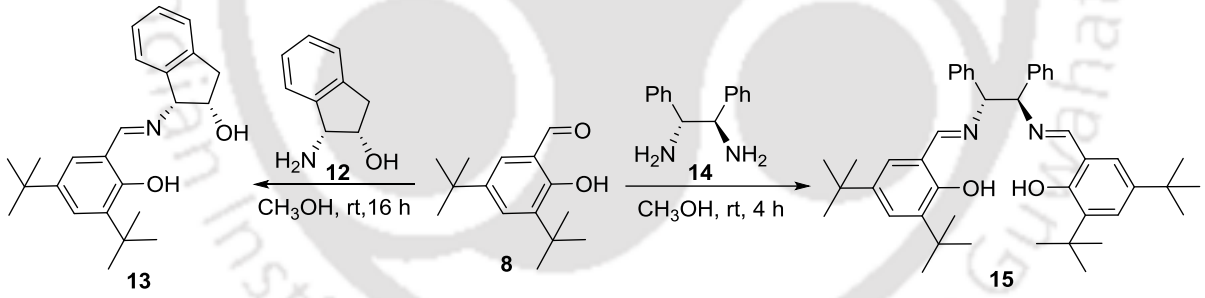
3.2 Present Study

Herein we describe the construction of trisubstituted tetrahydrothiophenes from 1,4-dithiane-2,5-diol with chalcones via thia-Michael-aldol cascade reaction using iron complexes bearing chiral tridentate **10a-d**, **11a-d** and tetradentate **15** based ligands with good enantioselectivities

(Scheme 6 and 7). The condensation of 3,5-di-tert-butylsalicylaldehyde **8** with (*S*)-amino alcohols **9a-d** and **12** in methanol at room temperature gave the corresponding tridendate Schiff base ligands **10a-d** and **13** in 86-92% yields. Treatment of **10a-d** with $NaBH_4$ in methanol furnished corresponding reduced ligands **11a-d** in 90-96% yields. Similarly chiral salen **15** was prepared by condensation of the (*R*,*R*)-1,2-diphenylethylenediamine **14** with the aldehyde **8** in 96% yield.



Scheme 6. Synthesis of Chiral Tridentate Ligands **10a-d** and **11a-d**.

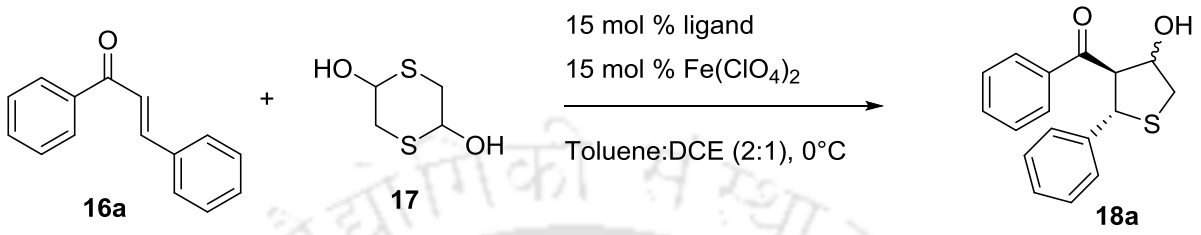


Scheme 7. Synthesis of the Chiral Salen **15.**

First, the optimization of the ligands was performed with the *in-situ* generated Fe-catalyst by reacting 15 mol % $(FeClO_4)_2$ and 15 mol % of chiral tridentate imine **10a** with chalcone **16a** and 1,4-dithiane-2,5-diol **17** as the model substrates (Table 1). The reaction readily occurred to provide thia-Michael-aldol cascade product **18a** in 65% with 3% ee in a 2:1 mixture of toluene and 1,2-dichlorehane at 0 °C (entry 1). Similar results were observed with the chiral tridentate imines **10b-d** and **13**, amines **11a** and **11c-d**, and salen **15** (entry 2-10).

However, the reaction using the chiral amine **11b** bearing *tert*-butyl substituents in the aryl ring produced 43% ee (entry 2).

Table 1. Screening of the Chiral Ligands **10a-d** and **11a-d**[a]



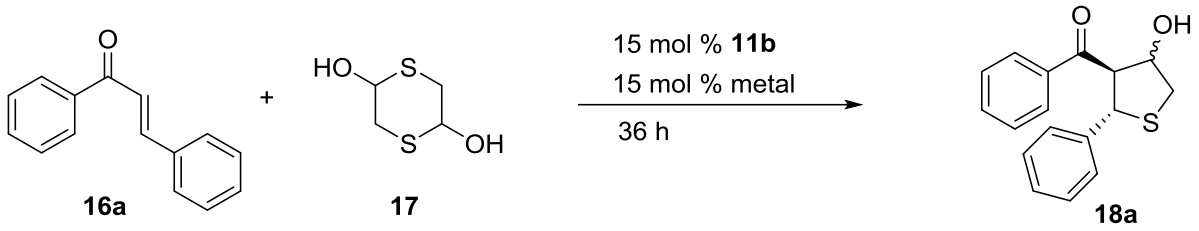
Entry	Ligand	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	**10a**	36	65	3
2	**10b**	36	45	2
3	**10c**	36	48	2
4	**10d**	36	54	3
5	**11a**	36	62	2
6	**11b**	**36**	**56**	**43**
7	**11c**	36	52	4
8	**11d**	36	60	2
9	**13**	36	70	7
10	**15**	36	78	3

[a] Reaction conditions: chalcone **16a** (0.2 mmol), 1,4-dithiane-2,5-diol (0.2 mmol), $Fe(ClO_4)_2$ (15 mol %), ligand (15 mol %), toluene : DCE (2:1, 2 mL), 36 h, 0 °C.

[b] Isolated yield.

[c] Determined by HPLC analysis with Chiralcel OJ using n-hexane/2-propanol.

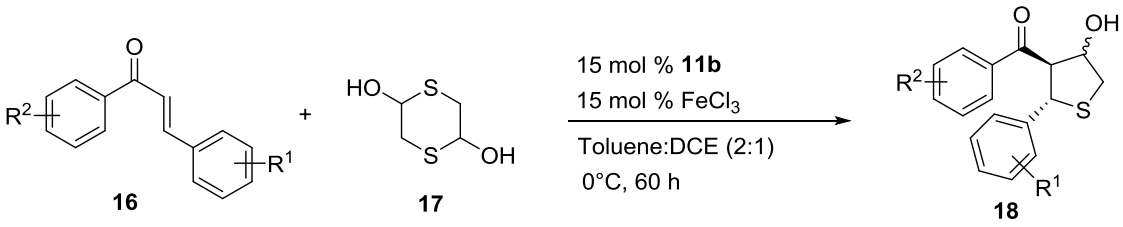
Table 2. Screening of Metal Source, Solvents, Temperature and Base[a]



Entry	Metal	Solvent	Base[b]	Temp (°C)	Yield (%)[c]	*ee* (%)[d]
1	$Fe(ClO_4)_2$	Toluene:DCE (2:1)	-	0	56	43
2	$Fe(acac)_3$	Toluene:DCE (2:1)	-	0	45	1
3	**$FeCl_3$**	**Toluene:DCE (2:1)**	**-**	**0**	**52**	**55**
4	”	THF	-	0	43	23
5	”	DCM	-	0	38	2
6	”	$CHCl_3$	-	0	32	2
7	”	DCE	-	0	34	2
8	”	Toluene	-	0	42	34
9	”	CH_3CN	-	0	56	17
10	”	^{i}PrOH	-	0	68	0
11	”	Toluene:DCM(2:1)	-	0	55	21
12	”	Toluene:$CHCl_3$(2:1)	-	0	58	45
13	”	Xylene:DCE(2:1)	-	0	63	32
14	”	Hexane:DCE(2:1)	-	0	38	42
15	”	Toluene:DCE(2:1)	Et_3N	0	72	2
16	”	Toluen:DCE(2:1)	2,6-lutidine	0	54	5
17	”	Toluen:DCE(2:1)	DIPEA	0	78	0
18	”	Toluen:DCE(2:1)	-	-40	32	42
19	”	Toluen:DCE(2:1)	-	rt	56	26

[a] Reaction conditions: chalcone **16a** (0.2 mmol), 1,4-dithiane-2,5-diol (0.2 mmol), $FeCl_3$ (15 mol %), ligand **11b** (15 mol %), solvent (2 mL), 36 h, 0°C.
[b] Base 15 mol %.
[c] Isolated yield.
[d] Determined by HPLC analysis with Chiralcel OJ using n-hexane/2-propanol.

Table 6: Chiral Iron (III)-**11b** Catalyzed Asymmetric Tetrahydrothiophenes Synthesis[a]



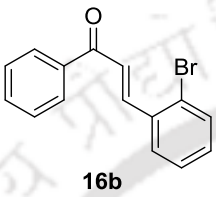
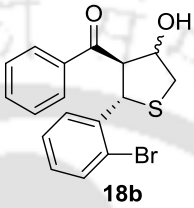
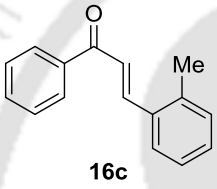
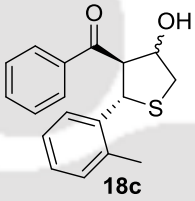
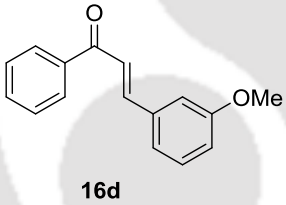
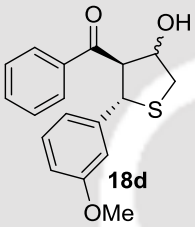
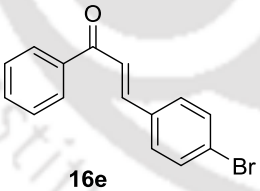
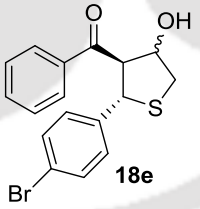
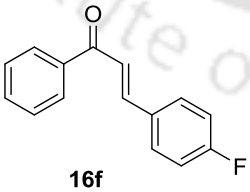
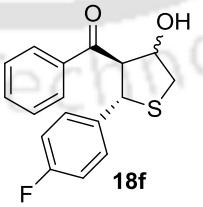
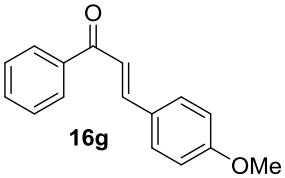
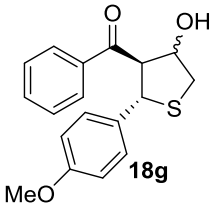
Entry	Substrate	Product	Yield (%)[b]	*er*[c]
1	 **16b**	 **18b**	67	46:54
2	 **16c**	 **18c**	40	58:42
3	 **16d**	 **18d**	53	74:26
4	 **16e**	 **18e**	68	77:23
5	 **16f**	 **18f**	54	81:19
6	 **16g**	 **18g**	48	82:18

Table 3 continued.....

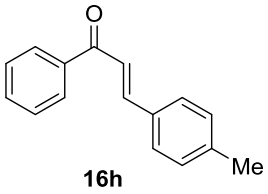
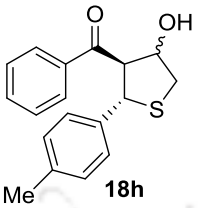
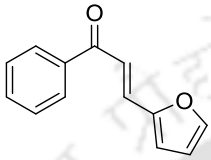
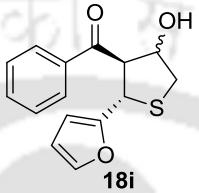
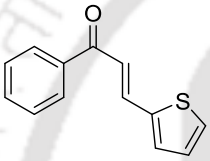
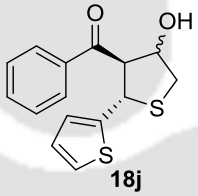
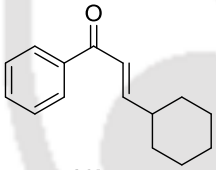
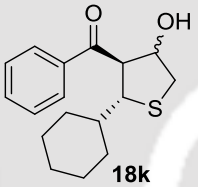
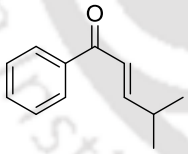
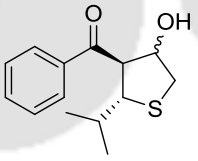
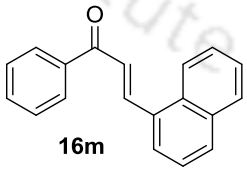
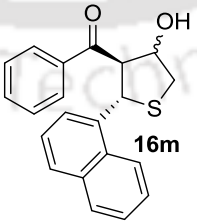
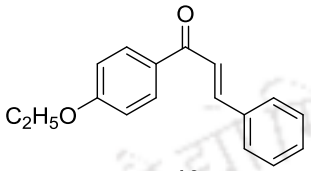
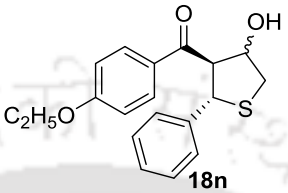
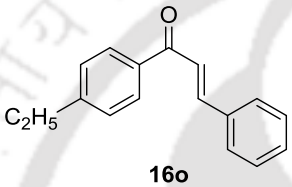
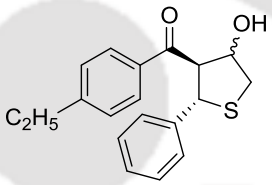
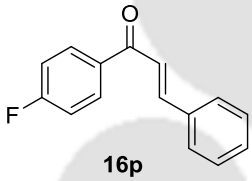
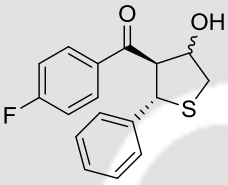
Entry	Substrate	Product	Yield (%)[b]	*er*[c]
7	 **16h**	 **18h**	56	81:19
8	 **16i**	 **18i**	69	65:35
9	 **16j**	 **18j**	52	70:30
10	 **16k**	 **18k**	45	60:40
11	 **16l**	 **18l**	75	62:38
12	 **16m**	 **16m**	78	83:17

Table 3 continued.....

Entry	Substrate	Product	Yield (%)[b]	*er*[c]
13	 **16n**	 **18n**	63	85:15
14	 **16o**	 **18o**	74	80:20
15	 **16p**	 **18p**	65	24:76

[a] Reaction conditions: chalcone **16** (0.20 mmol), 1,4-dithiane-2,5-diol (0.20 mmol), $FeCl_3$ (15 mol %), ligand **11b** (15 mol %), toluene:DCE (2:1) (2 mL), 60 h at 0°C.

[b] Isolated yield.

[c] Determined by HPLC analysis with Chiralcel OJ and AD-H using n-hexane/2-propanol.

After screening the ligands, we next studied the effect of Fe source, solvent, base and temperature using **11b** as the ligand (Table 2). The use of $FeCl_3$ as the Fe source led to improve the *ee* to 55%, while $Fe(acac)_3$ and $FeClO_4$ produced inferior results (entries 1-3). A 2:1 mixture of toluene and 1,2-dichloroethane was found to be the solvent of choice, whereas THF, dichloromethane, chloroform, 1,2-dichloromehtane, toluene, acetonitrile and isopropanol afforded the product in 34% ee (entries 4-10). Similar results were observed with a mixture of toluene:dicholoromethane (2:1), toluene:chloroform (2:1), xylene:1,2-dichloroethane(2:1) and hexane:1,2-dichloroethane(2:1) (entries 11-14). The use of additives

such as Et_3N, 2,6-leutidine and DIPEA accelerated product formation but ee was dropped to <2% (entries 15-17). Decrease in the reaction temperature into -40 °C or room temperature (28 °C) led to the formation of target heterocycle in <46% ee(entries 18, 19).

Having the optimized reaction conditions, we examined the generality of this domino thia-Michael-aldol reaction (Table 3). In general the electronic nature of the substituents on the phenyl ring had little effect on enantioinduction but its position on the phenyl ring has a remarkable effect. For examples, more sterically hindered substrates (*ortho*-substituents of the phenyl ring) 2-bromophenylchalcone **16b** and 2-methylpheylchalcone **16c** proceeded reaction with 46:54 er (67%) and 58:42 er (40%), respectively (Table 3 entries 1-2). 3-Methoxyphenylchalcone**16d** improved the product enantioselectivity with 74:26 er and 53% yield (entry 3). Interestingly, *para*-substituents on the phenyl ring of the chalcone afforded the corresponding products with high enantioselectivities (entries 4-7). For example, both electron-withdrawing and electron-donating groups, 4-bromo, 4-fluoro, 4-methoxy and 4-methyl, substituted phenylchalcones **16e-h** gave 77:23-82:18 er and 48-68% yields. In addition, heteroaryl substrates, 2-furyl and 2-thienylchalcones **16i-j**, and alkyl substrates cyclohexyl and isoproplyl-chalcones **16k-l** underwent reaction 60:40-70:30 er and 45-75% yields (entries 8-11). Furthermore, 1-naphthylchalcone **16m** afforded the desired product in 60:40 er and 45% yield (entry 12). Likewise, 4'-ethoxy, 4'-ethyl and 4'-fluoro substituted phenylchalcones **16n-p** provided the reaction with 24:76-80:20 er and 63-74% yields (entries 13-15). These results suggest that Fe-based catalysts can be utilized for the domino thia-Michael-aldol reaction of aryl, heteroaryl and alkyl chalcones **16** and 1,4-dithiane-2,5-diol **17** with good enantioselectivities.

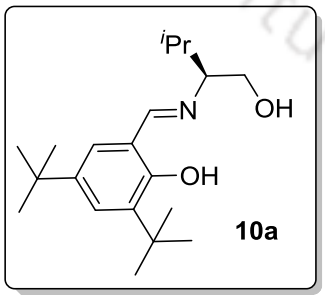
In summary, the syntheses of chiral tridendate **10a-d**, **11a-d**, **13** and tetradendate **15** and their application for Fe-catalyzed thia-Michael-aldol cascade reaction has been demonstrated. The reaction of aryl, heteroaryl and alkyl chalcones with 1,4-dithiane-2,5-diol to afford the corresponding trisubstituted tetrahydrothiophene has been accomplished with good enantioselectivies.

3.3 Experimental Section

General Information. The reactions were carried out in oven-dried glassware under nitrogen atmosphere. Aldehydes, acetophenones, 1,4-dithiane-2,5-diol (97%) and 2,4-di-*tert*-butyl

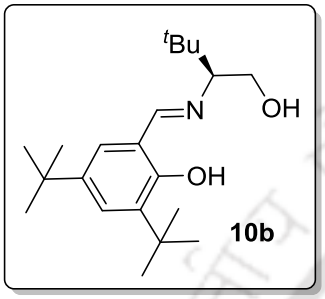
phenol (99%) purchased from Aldrich, aminoacids purchased from SRL and $NaBH_4$ (95%) purchased from Merck were used as received. Solvents were purchased from Rankem and purified prior to use by standard procedure.[21] The compounds **9**[22] and **16**[23] were prepared according to the reported procedure. 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 were recorded using DRX-400 Varian spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) and Bruker Avance III 600 MHz spectrometer (600 MHz for ^1H and 150 MHz for ^{13}C) using $CDCl_3$ as solvent and Me_4Si as an internal standard and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. Chemical shifts (δ) are reported relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR). Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained using Perkin–Elmer spectrum one spectrometer. Optical rotations were measured with a Rudolph Autpol II automatic polarimeter. HRMS mass was analyzed with Agilent Q-TOF 6500. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OJ and AD-H columns.

General Procedure for Preparation of Ligands 10a-d and 13. Aldehyde (0.5 mmol) and amino alcohol (0.5 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.

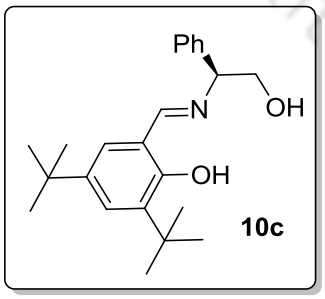


(*S*,*E*)-2,4-Di-*tert*-butyl-6-(((1-hydroxy-3-methylbutan-2-yl)-imino)methyl)phenol 10a. Yellow solid; yield (140 mg, 88%); Mp: 102-105 °C; $[\alpha]_D^{29}$ = -23.4 (c = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.13 (d, J = 2.8 Hz, 1H), 3.83-3.75 (m, 2H), 3.05-3.00 (m, 1H), 1.97-1.92 (m, 1H), 1.44 (s,

9H), 1.31 (s, 9H), 0.96 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 158.3, 140.3, 136.9, 127.2, 126.3, 117.8, 78.0, 64.8, 35.2, 34.3, 31.6, 30.2, 29.6, 20.0, 19.0; FT-IR (KBr): 3382, 3238, 3043, 2942, 1639, 1579, 1500, 1481, 1406, 1369, 1314, 1220, 1195, 1131, 1100, 1050, 1015, 952, 912, 897, 867, 817, 751, 731, 679, 668, 658, 623, 601, 589, 541, 520 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{33}NO_2$ 320.2584 , found 320.2584.

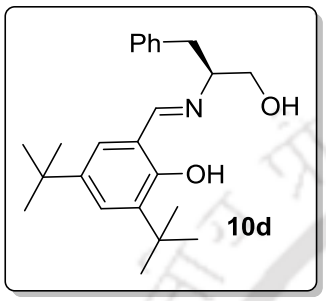


(*S*,*E*)-2,4-Di-*tert*-butyl-6-(((1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)phenol 10b. Yellow solid; yield (154 mg, 92%); Mp: 82-84 °C; $[\alpha]_D^{29}$ = -37.1 (c =1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 3.92-3.73 (m, 2H), 2.93 (dd, *J* = 9.6, 3.2 Hz, 1H), 1.45 (s, 9H), 1.31 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 158.3, 140.3, 136.9, 127.3, 126.3, 117.8, 81.5, 62.7, 35.2, 34.3, 33.4, 31.6, 29.6, 27.3; FT-IR (KBr): 3298, 3216, 2962, 2870, 1629, 1595, 1466, 1439, 1391, 1361 1347, 1276, 1250, 1233, 1202, 1171, 1150, 1131, 1119, 1080, 1028, 1019, 990, 975, 953, 918, 901, 877, 851, 825, 801, 774, 731, 696, 668, 646, 619, 526, 510 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{35}NO_2$ 334.2741, found 334.2742.

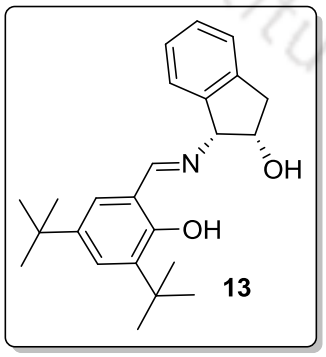


(*S*,*E*)-2,4-Di-*tert*-butyl-6-(((2-hydroxy-1-phenylethyl)imino)-methyl)phenol 10c. Yellow liquid; yield (152 mg, 86%); $[\alpha]_D^{29}$ = -24.3 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.42-7.36 (m, 5H), 7.30 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 2 Hz, 1H), 4.47-4.54 (m, 1H), 3.95-3.92 (m, 2H), 1.46 (s, 9H), 1.30 (s, 9H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 167.4, 158.0, 140.4, 139.6, 136.7, 128.8, 127.8, 127.3, 127.2, 126.5, 118.0, 75.8, 67.6, 35.1, 34.2, 31.6, 29.6; FT-IR (neat): 3439, 2956, 2907, 2868, 1626, 1475, 1439, 1392, 1361, 1318, 1272, 1250, 1202, 1173, 1132, 1084, 1056, 1020, 982, 954, 879, 826, 800, 773, 755, 739, 701, 666, 645, 535 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{31}NO_2$ 354.2428, found 354.2424.

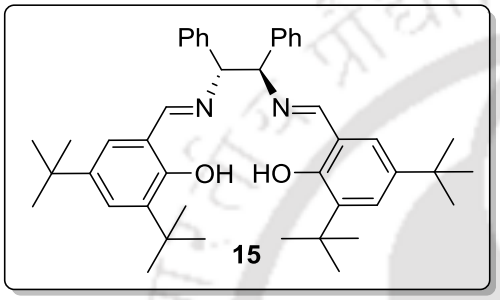


(*S*,*E*)-2,4-Di-*tert*-butyl-6-(((1-hydroxy-3-phenylpropan-2-yl)imino)methyl)phenol 10d. Yellow liquid; yield (163 mg, 89%); $[\alpha]_D^{29}$ = -19.3 (c = 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.38 (d, *J* = 2.8 Hz, 1H), 7.28–7.24 (m, 2H), 7.20–7.16 (m, 3H), 7.00 (d, *J* = 2.4 Hz, 1H), 3.80–3.76 (m, 2H), 3.53–3.50 (m, 1H), 2.97–2.90 (m, 2H), 1.45 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 158.2, 140.1, 138.1, 136.7, 129.5, 128.5, 127.2, 126.4, 126.2, 117.8, 73.1, 65.7, 39.2, 35.1, 34.2, 31.6, 29.6; FT-IR (neat): 3381, 3057, 3026, 2921, 2849, 1628, 1601, 1527, 1459, 1436, 1386, 1337, 1285, 1265, 1216, 1180, 1155, 1120, 1094, 1053, 1029, 957, 885, 795, 781, 755, 698, 671, 656, 633, 594, 526, 502 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{33}NO_2$ 368.2584, found 368.2584.



(1*R*,2*S*)-1-(((*E*)-3,5-Di-*tert*-butyl-2-hydroxybenzylidene)amino)-2,3-dihydro-1H-inden-2-ol 13. Yellow solid; yield (168 mg, 92%); Mp: 65-68 °C; $[\alpha]_D^{29}$ = -36.2 (c = 0.71, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): *δ 13.15 (s, 1H),* 8.63 (s, 1H), 7.43 (s,

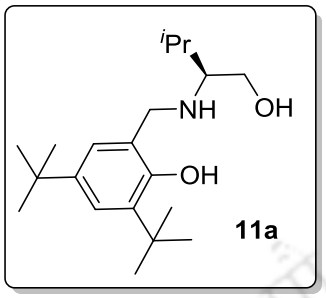
1H), 7.33-7.19 (m, 5H), 4.81 (d, J = 5.2 Hz, 1H), 4.71-4.67 (m, 1H), 3.24 (dd, J = 15.6, 5.6 Hz, 1H), 3.12 (dd, J = 16.0, 5.2 Hz, 1H), 1.43 (s, 9H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 158.2, 141.0, 140.9, 140.4, 137.0, 128.6, 127.7, 127.1, 126.6, 125.5, 125.0, 117.9, 75.6, 75.2, 39.6, 35.1, 34.3, 31.6, 29.5; FT-IR (KBr): 3439, 2956, 2904, 2871, 1767, 1605, 1560, 1480, 1389, 1361, 1301, 1255, 1236, 1202, 1165, 1125, 1079, 1040, 877, 820, 799, 760, 739, 723, 671, 648, 508 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{31}NO_2$ 366.2428, found 366.2428.



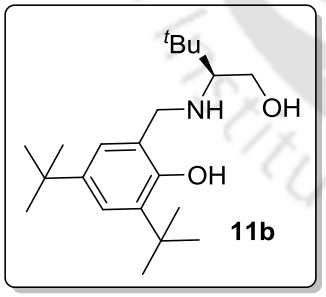
6,6'-((1*E*,1'*E*)-(((1*R*,2*R*)-1,2-Diphenylethane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-di-*tert*-butylphenol) 15. Aldehyde (0.5 mmol) and (1*R*,2*R*)-(+)-1,2-Diphenylethylenediamine (0.25 mmol) were stirred for 12 h in MeOH (1 mL) at ambient temperature. Then it was cooled to 5 °C and the formed precipitate was filtered to afford **15**. Yellow solid; yield (154 mg, 96%); Mp: 194-195 °C; $[\alpha]_D^{29}$ = -98.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.59 (s, 2H), 8.40 (s, 2H), 7.30 (s, 2H), 7.19-7.15 (m, 10H), 6.97(s, 2H), 4.72 (s, 2H), 1.41 (s, 18H), 1.21 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 158.1, 140.2, 140.0, 136.5, 128.4, 128.2, 127.6, 127.3, 126.5, 118.0, 80.3, 35.1, 34.2, 31.6, 29.6; FT-IR (KBr): 3395, 3085, 3063, 3028, 2957, 2868, 1629, 1495, 1469, 1454, 1440, 1390, 1361, 1273, 1251, 1201, 1172, 1132, 1087, 1032, 972, 901, 878, 826, 802, 773, 749, 730, 701, 645, 608, 502 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{44}H_{56}N_2O_2$ 645.4415, found 645.4415.

General Procedure for the Preparation of Ligands 11a-d. To a stirred solution of imines **10a-d** (0.5 mmol) in MeOH (2mL) at 0 °C, $NaBH_4$ (1 mmol) was added, then 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.

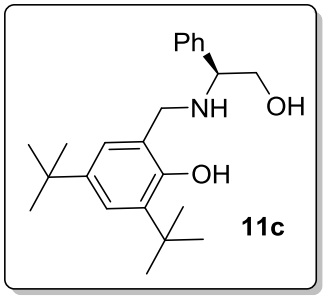


(*S*)-2,4-Di-*tert*-butyl-6-(((1-hydroxy-3-methylbutan-2-yl)amino)methyl)phenol 11a. Colourless solid; yield (151 mg, 94%); Mp: 75-76 °C; $[\alpha]_D^{29}$ = +26.3 (c =1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 3.98 (s, 2H), 3.82-3.64 (m, 2H), 2.49- 2.48 (m, 1H), 1.96-1.91 (m, 1H), 1.42 (s, 9H), 1.28 (s, 9H), 0.99 (dd, J = 11.6, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 140.7, 136.2, 123.3, 123.1, 122.8, 64.1, 61.4, 51.9, 35.0, 34.3, 31.8, 29.8, 28.8, 19.3, 19.1; FT-IR (KBr): 3418, 2960, 2870, 1802, 1781, 1751, 1633, 1535, 1471, 1454, 1441, 1390, 1379, 1361, 1305, 1273, 1250, 1202, 1173, 1149, 1132, 1065, 1026, 972, 956, 930, 897, 878, 824, 801, 773, 731, 700, 668, 645, 617, 597, 542, 524, 509, 452, 420, 410 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{20}H_{35}NO_2$ 322.2741 , found 322.2741.

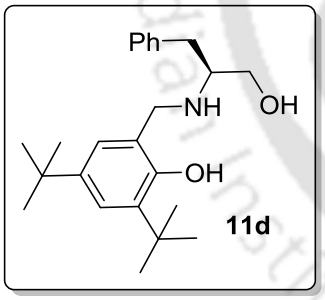


(*S*)-2,4-Di-*tert*-butyl-6-(((1-hydroxy-3,3-dimethylbutan-2-yl)-amino)methyl)phenol 11b. Colourless solid; yield (151 mg, 90%); Mp: 90-91 °C; $[\alpha]_D^{29}$ = +9.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 4.14-4.11(d, J = 12.8 Hz, 1H), 3.98-3.94 (m, 2H), 3.74-3.70 (m, 1H), 2.36-2.33 (m, 1H), 1.42 (s, 9H), 1.28 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 140.7, 136.2, 123.4, 123.2, 123.1, 67.6, 61.7, 53.8, 35.1, 34.4, 34.3, 31.8, 29.8, 27.7; FT-IR (KBr): 3415, 2955, 2918, 2864, 1641, 1601, 1557, 1482, 1433, 1386, 1317, 1266, 1222,

1108, 1052, 1019, 910, 800, 748, 718, 667, 531 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{37}NO_2$ 336.2897, found 336.2896.



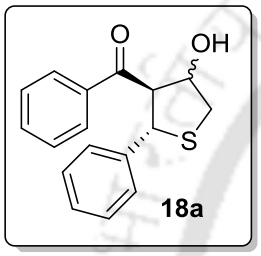
(*S*)-2,4-Di-*tert*-butyl-6-(((2-hydroxy-1-phenylethyl)amino)-methyl)phenol 11c. Colourless viscous liquid; yield (167 mg, 94%); $[\alpha]_D^{29}$ = +64.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7.31 (m, 6H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.86-3.82 (m, 2H), 3.80 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.74 (d, *J* = 13.2 Hz, 1H), 1.46 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.4, 140.8, 139.1, 136.1, 129.1, 128.2, 127.6, 123.6, 123.2, 122.4, 66.8, 64.2, 51.4, 35.1, 34.3, 31.8, 29.8; FT-IR (neat): 3440, 3031, 2955, 2900, 2868, 1628, 1604, 1479, 1455, 1391, 1360, 1301, 1235, 1203, 1165, 1123, 1106, 1049, 1026, 909, 878, 820, 798, 759, 736, 701, 668, 648 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{33}NO_2$ 356.2584, found 356.2584.



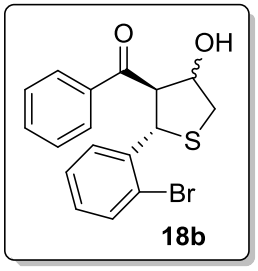
(*S*)-2,4-Di-*tert*-butyl-6-(((1-hydroxy-3-phenylpropan-2-yl)-amino)methyl)phenol 11d. Colourless viscous liquid; yield (183 mg, 96%); $[\alpha]_D^{29}$ = -16.3 (c = 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (t, J = 7.2 Hz, 2H), 7.24–7.16 (m, 4H), 6.84 (d, J = 2.4 Hz, 1H), 3.98 (q, J = 13.2 Hz, 2H), 3.70 (dd, J = 11.4, 4.2 Hz, 1H), 3.52 (dd, J = 10.8, 4.8 Hz, 1H), 2.97–2.92 (m, 1H), 2.90 (dd, J = 13.2, 6.0 Hz, 1H), 2.82-2.78 (m, 1H), 1.41 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): 154.5, 140.8, 138.3, 136.2, 129.4, 128.8, 126.7, 123.3, 123.2, 122.4, 62.9, 60.0, 51.3, 37.6, 35.0, 34.3, 31.8, 29.8; FT-IR (neat): 3449, 2953, 2907, 2864, 1630, 1604, 1479, 1391, 1360, 1300, 1235, 1203, 1164, 1122, 1035,

982, 909, 877, 820, 798, 738, 701, 669, 648, 590, 505 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{35}NO_2$ 382.2741, found 382.2742.

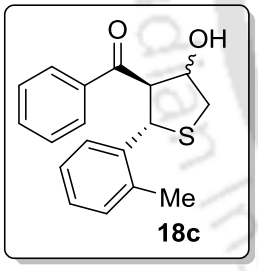
General Procedure for the Synthesis of Tetrahydrothiophenes. Ligand **11b** (0.03 mmol) and $FeCl_3$ (0.03 mmol) were stirred in toluene:1,2-dichloroethane (2 mL) at room temperature for 10 minutes, then it was cooled to 0 °C, and treated with chalcone (0.2 mmol) and 1,4-dithian-2,5-diol (0.2 mmol). The reaction mixture was stirred at 0 °C for 60 h, and the progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was then evaporated on a rotary evaporator to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as eluent.



((2*S*,3*R*)-4-Hydroxy-2-phenyltetrahydrothiophen-3-yl)(phenyl)-methanone 18a. Colourless solid, yield (30 mg, 52%); Mp: 106-108 °C; $[\alpha]_D^{29}$ = +56.3 (c = 0.25, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.68-7.67 (d, *J* = 7.8 Hz, 2H), 7.51-7.48 (m, 1H), 7.45-7.44 (m, 2H), 7.35-7.32 (m, 2H), 7.23-7.21 (m, 2H), 7.17-7.14 (m, 1H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.92 (d, *J*= 3.0 Hz, 1H), 4.08 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.60-3.57(m, 2H), 3.18-3.16 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 139.8, 136.8, 133.9, 128.8, 128.5, 128.2, 127.9, 127.6, 77.6, 62.9, 52.1, 41.3; FT-IR (KBr): 3452, 3055, 3024, 2922, 1680, 1596, 1579, 1512, 1447, 1364, 1327, 1299, 1271, 1221, 1180, 1150, 1110, 1035, 1009, 973, 876, 815, 798, 770, 748, 731, 694, 650, 633, 546, 509 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.9 min, 20.9 min; 78:23 er; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}O_2S$ 285.0944, found 285.0944.

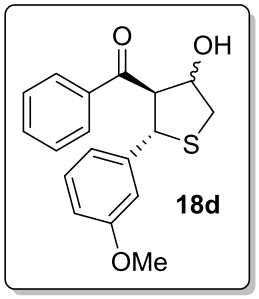


((2*S*,3*R*)-2-(2-Bromophenyl)-4-hydroxytetrahydrothiophen-3-yl)(phenyl)methanone 18b. Colourless solid, yield (48 mg, 67%); Mp: 124-126 °C; $[\alpha]_D^{29}$ = -7.2 (c = 1.02, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.33-7.26 (m, 4H), 7.01-6.99 (m, 1H), 5.60 (d, *J* = 10.2 Hz, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 4.17 (d, *J* = 10.2 Hz, 1H), 4.00 (s, 1H), 3.58 (d, *J* = 11.4 Hz, 1H), 3.19 (dd, *J* = 11.4, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.1, 161.0, 142.7, 141.5, 140.2, 122.6, 80.8, 35.2, 29.2; FT-IR (KBr): 3443, 3061, 3028, 2980, 2931, 1670, 1599, 1573, 1510, 1475, 1453, 1421, 1394, 1331, 1261, 1226, 1172, 1118, 1040, 971, 921, 878, 839, 737, 698, 632, 517 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 13.6 min, 25.2 min; 46:54 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}BrO_2S$ 363.0049, found 363.0049.

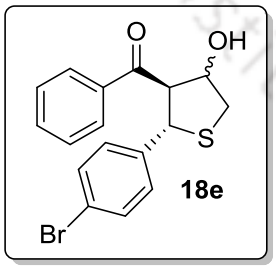


((2*S*,3*R*)-4-Hydroxy-2-(o-tolyl)tetrahydrothiophen-3-yl)(phenyl)-methanone 18c. Colourless oil, yield (24 mg, 40%); $[\alpha]_D^{29}$ = +14.2 (c = 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.72–7.70 (m, 3H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.48 (d, *J* = 10.2 Hz, 1H), 4.95 (s, 1H), 4.20 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.74 (s, 1H), 3.60 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.18 (d, *J* = 11.4 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.6, 137.8, 136.8, 136.6, 133.9, 130.6, 128.7, 128.4, 127.5, 127.3, 126.6, 61.8, 47.2, 41.1, 19.7; FT-IR (neat): 3449, 3062, 3022, 2930, 1681, 1596, 1578, 1490, 1463, 1447, 1382, 1324, 1273, 1217, 1181, 1149, 1033, 1010, 973, 931, 877, 798, 775, 734, 694, 651, 600, 558 cm^{-1};

HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 7.2 min, 14.2 min; 58:42 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}O_2S$ 299.1100, found 299.1101.

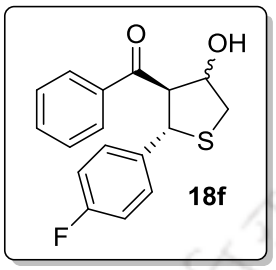


((2*S*,3*R*)-4-Hydroxy-2-(3-methoxyphenyl)tetrahydrothiophen-3-yl)(phenyl)methanone 18d. Colourless solid, yield (33 mg, 53%); Mp: 111-112 °C; $[\alpha]_D^{29}$ = +70.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.03-7.00 (m, 2H), 6.70 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 4.91 (s, 1H), 4.08 (dd, *J* = 10.8, 3.0 Hz, 3H), 3.72 (s, 3H), 3.57 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.15 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.8, 159.7, 141.5, 136.8, 133.8, 129.7, 128.7, 128.4, 120.4, 113.8, 113.2, 77.5, 62.8, 55.3, 51.8, 41.2; FT-IR (KBr): 2961, 2913, 2869, 2742, 2212, 1656, 1608, 1577, 1444, 1409, 1393, 1382, 1363, 1327, 1269, 1212, 1166, 1142, 1126, 1098, 1032, 1008, 953, 883, 799, 771, 759, 718, 680, 613, 583, 540, 510 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.7 min, 18.3 min; 74:26 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}O_3S$ 315.1049, found 315.1048.

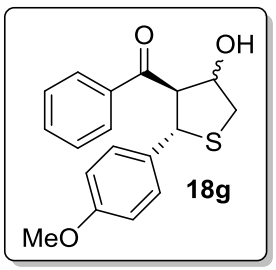


((2*S*,3*R*)-2-(4-Bromophenyl)-4-hydroxytetrahydrothiophen-3-yl)(phenyl)methanone 18e. Colourless solid, yield (49 mg, 68%); Mp: 125-127 °C; $[\alpha]_D^{29}$ = +57.2 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.69 (m, 2H), 7.54-7.52 (m, 1H), 7.40-7.32 (m, 6H), 5.16 (d, *J* = 10.8 Hz, 1H), 4.93 (s, 1H), 4.03 (d, *J* = 10.4 Hz, 1H), 3.60 (d, *J* = 11.6 Hz, 1H), 3.96 (s, 1H), 3.18 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 139.0, 136.6, 134.0, 131.8, 129.9, 128.9, 128.4, 121.5, 77.5, 63.2, 51.1,

41.2. FT-IR (KBr): 3439, 3051, 2933, 2900, 1924, 1681, 1596, 1578, 1510, 1447, 1396, 1346, 1299, 1263, 1216, 1180, 1150, 1075, 1030, 1017, 972, 932, 874, 800, 778, 735, 695, 651, 629, 599, 541, 521 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.3 min, 26.5 min; 77:23 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}BrO_2S$ 363.0049, found 363.0048.

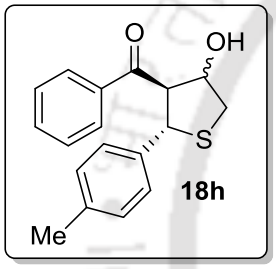


((2*S*,3*R*)-2-(4-Fluorophenyl)-4-hydroxytetrahydrothiophen-3-yl)(phenyl)methanone 18f. Colourless solid, yield (33 mg, 54%); Mp: 107-109 °C; $[\alpha]_D^{29}$ = +94.6 (c = 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): 7.69 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.43-7.41 (m, 2H), 7.37-7.35 (m, 2H), 6.90 (t, *J* = 8.4 Hz, 2H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.92 (d, *J* = 2.4 Hz, 1H), 4.02 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.58 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.51 (d, *J* = 3.6 Hz, 1H), 3.16 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.7, 163.0 (d, J_{C-F} = 244.5 Hz), 136.7, 135.4, 134.0, 129.8 (d, J_{C-F} = 6.0 Hz), 128.8, 128.4, 115.6 (d, J_{C-F} = 21.0 Hz), 77.4, 63.2, 51.2, 41.1; FT-IR (KBr): 3470, 2949, 2928, 2881, 2859, 1774, 1709, 1586, 1495, 1465, 1385, 1371, 1334, 1188, 1127, 1100, 1040, 1012, 915, 871, 817, 724, 691, 640, 570, 531 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.1 min, 24.7 min; 81:19 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}FO_2S$ 303.0850, found 303.0850.

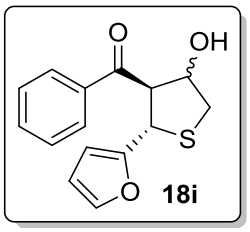


((2*S*,3*R*)-4-Hydroxy-2-(4-methoxyphenyl)tetrahydrothiophen-3-yl)(phenyl)methanone 18g. Colourless solid, yield (30 mg, 48%); Mp: 115-117 °C; $[\alpha]_D^{29}$ = +77.5 (c = 0.88, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.51 (t, *J* =

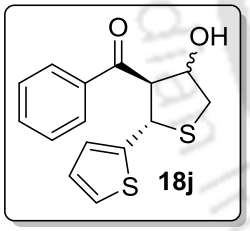
7.8 Hz, 1H), 7.37-7.33 (m, 4H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 4.90 (s, 1H), 4.06 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.71 (s, 3H), 3.60 (s, 1H), 3.57 (dd, *J* = 11.4, 3.6 Hz, 2H), 3.14 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 159.1, 136.8, 133.8, 131.4, 129.2, 128.7, 128.4, 114.1, 77.4, 62.9, 55.3, 51.6, 41.1; FT-IR (KBr): 3429, 3080, 3033, 2984, 2945, 1911, 1676, 1593, 1503, 1491, 1453, 1428, 1392, 1337, 1296, 1269, 1222, 1206, 1197, 1180, 1161, 1146, 1100, 1079, 1065, 1025, 1006, 966, 918, 889, 876, 862, 835, 817, 808, 759, 766, 739, 713, 696, 672, 644, 602, 577 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.7 min, 17.0 min; 81:19 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}O_3S$ 315.1049, found 315.1048.



((2*S*,3*R*)-4-Hydroxy-2-(p-tolyl)tetrahydrothiophen-3-yl)(phenyl)-methanone 18h. Colourless solid, yield (33 mg, 56%); Mp: 100-103 °C; $[\alpha]_D^{29}$ = +84 (c = 0.82, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.2 Hz, 2H), 7.50-7.49 (m, 1H), 7.36-7.32 (m, 4H), 7.03 (d, *J* = 7.8 Hz, 2H), 5.16 (d, *J* = 10.8 Hz, 1H), 4.90 (s, J = 7.2 Hz, 1H), 4.08 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.58 (dd, *J* = 11.4, 3.00 Hz, 1H), 3.52 (d, *J* = 4.2 Hz, 1H), 3.16 (dd, *J* = 12, 1.2 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.1, 137.5, 136.9, 136.6, 133.8, 129.4, 128.8, 128.5, 128.0, 77.6, 62.9, 51.7, 41.2, 21.1; FT-IR (KBr): 3471, 3058, 3002, 2937, 2835, 2249, 1681, 1597, 1582, 1490, 1465, 1448, 1436, 1362, 1319, 1263, 1217, 1149, 1039, 1010, 974, 931, 908, 876, 782, 768, 749, 731, 694, 652, 563 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 7.3 min, 12.5 min; 81:19 er. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}O_2S$ 299.1100, found 299.1100.

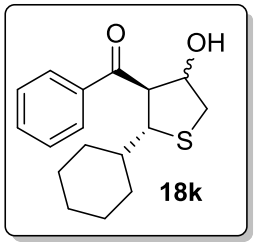


((2*S*,3*R*)-2-(Furan-2-yl)-4-hydroxytetrahydrothiophen-3-yl)(phenyl)-methanone 18i. Dark red solid, yield (38 mg, 69%); Mp: 115-117 °C; $[\alpha]_D^{29}$ = +39.4 (c = 0.93, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.29 (m, 1H), 6.18–6.15 (m, 2H), 5.20 (d, *J* = 10.2 Hz, 1H), 4.92 (s, 1H), 4.35 (dd, J = 10.2, 3.0 Hz, 1H), 3.69 (s, 1H), 3.53 (dd, J = 11.4, 3.6 Hz, 1H), 3.13 (dd, *J* = 11.4, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.9, 151.8, 142.5, 136.6, 134.0, 128.9, 128.5, 110.6, 108.1, 77.1, 58.7, 44.5, 44.5, 40.8; FT-IR (KBr): 3448, 3103, 3085, 3065, 2931, 2853, 1680, 1596, 1579, 1447, 1350, 1287, 1216, 1150, 1035, 1009, 971, 932, 873, 857, 830, 765, 740, 693, 651, 668, 631, 597, 531 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 12.9 min, 21.2 min; 65:35 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}O_3S$ 275.0736, found 275.0734.

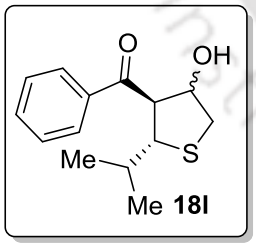


((2*S*,3*R*)-4-Hydroxy-2-(thiophen-2-yl)tetrahydrothiophen-3-yl)-(phenyl)methanone 18j. Yellow oil, yield (30 mg, 52%); $[\alpha]_D^{29}$ = +69.2 (c = 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.54-7.53 (m, 1H), 7.40-7.38 (m, 2H), 7.14 (d, *J* = 4.8 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.76 (dd, *J* = 4.8, 3.6 Hz, 1H), 5.48 (d, *J* = 10.2 Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 4.12 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.60 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.53 (d, *J* = 3.6 Hz, 1H), 3.16 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.0, 144.4, 136.8, 134.1, 128.9, 128.5, 127.0, 126.2, 125.0, 77.4, 63.6, 47.4, 41.0; FT-IR (neat): 3358, 3087, 3061, 3028, 2955, 2869, 1674, 1598, 1581, 1463, 1448, 1413, 1385, 1366, 1335, 1312, 1283, 1231, 1215, 1183, 1158, 1122, 1075, 1035, 1014, 956, 935, 896, 869, 843, 782, 753, 722, 696, 641, 530 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol

(90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 12.5 min, 26.2 min; 70:30 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}O_2S_2$ 291.0508, Found 291.0501.

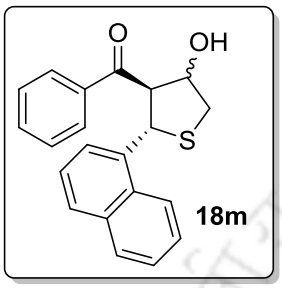


((2*R*,3*R*)-2-Cyclohexyl-4-hydroxytetrahydrothiophen-3-yl)(phenyl)-methanone 18k. Yellow oil, yield (26 mg, 45%); $[\alpha]_D^{29}$ = +29.6 (c = 0.94, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 4.75 (t, *J* = 3.0 Hz, 1H), 4.04-4.01 (m, 1H), 3.88 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.21 (dd, *J* = 11.4, 3.0 Hz, 1H), 2.97-2.95 (m, 1H), 2.82 (d, *J* = 7.2 Hz, 1H), 1.83 (d, *J* = 10.8 Hz, 1H), 1.73-1.71(m, 1H), 1.64-1.41 (m, 4H), 1.19-1.07 (m, 4H), 0.98-0.94 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 198.5, 136.7, 133.6, 128.9, 128.7, 128.2, 77.5, 58.0, 53.4, 43.3, 40.0, 32.5, 31.1, 26.2, 26.1, 26.0; FT-IR (neat): 3451, 3061, 3029, 2962, 2903, 2872, 1677, 1605, 1568, 1480, 1454, 1414, 1389, 1360, 1332, 1302, 1236, 1203, 1182, 1152, 1124, 1029, 1009, 972, 920, 878, 829, 723, 698, 648, 583 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 6.8 min, 13.5 min; 60:40 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}O_2S$ 291.1413, found 291.1413.

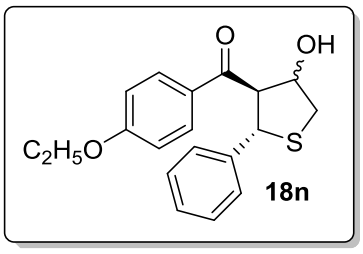


((2*R*,3*R*)-4-Hydroxy-2-isopropyltetrahydrothiophen-3-yl)(phenyl)-methanone 18l. Colourless oil, yield (38 mg, 75%); $[\alpha]_D^{29}$ = +33.4 (c = 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 4.75-4.74 (m, 1H), 4.07 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.85 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.21 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.98-2.94 (m, 2H), 1.82 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.0, 136.9, 133.7, 128.9, 128.2, 77.6, 58.1, 54.7, 40.2, 33.0, 22.0, 19.7; FT-IR (neat): 3095, 2999, 2957, 2868,

1650, 1611, 1445, 1410, 1338, 1362, 1270, 1192, 1159, 1034, 995, 942, 929, 901, 891, 880, 814, 771, 762, 743, 715, 617, 583, 548, 535, 497 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 7.1 min, 14.2 min; 62:38 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}O_2S$ 251.1100, found 251.1101.

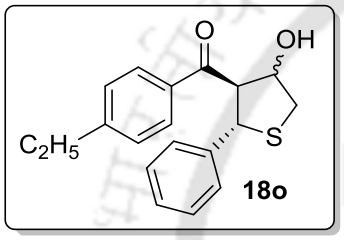


((2*S*,3*R*)-4-Hydroxy-2-(naphthalen-1-yl)tetrahydrothiophen-3-yl)(phenyl)methanone 18m. Colourless solid, yield (55 mg, 78%); Mp: 124-126 °C. $[\alpha]_D^{29}$ = +87.0 (c = 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.76–7.74 (m, 2H), 7.68–7.66 (m, 3H), 7.48–7.35 (m, 4H), 7.27 (d, *J* = 4.8 Hz, 2H), 6.04–6.02 (m, 1H), 5.02 (s, 1H), 4.47 (dd, *J* = 7.2, 3.0 Hz, 1H), 3.62 (t, *J* = 11.4 Hz, 2H), 3.25 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 136.7, 135.7, 134.0, 133.9, 132.0, 128.9, 128.7, 128.5, 128.3, 126.5, 126.0, 125.5, 124.6, 123.6, 77.3, 60.8, 47.2, 41.21; FT-IR (KBr): 3476, 3061, 3001, 2934, 2835, 1680, 1596, 1579, 1511, 1463, 1447, 1328, 1303 1250, 1220, 1176, 1150, 1109, 1030, 1010, 973, 933, 876, 828, 798, 752, 732, 695, 651 cm^{-1}; HPLC: Chiralcel OJ column, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.6 min, 18.0 min; 83:16 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{18}O_2S$ 355.1100, found 355.1103.

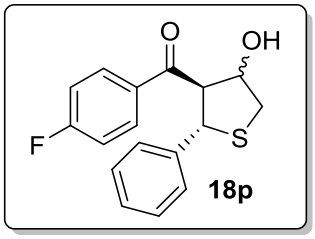


(4-Ethoxyphenyl)((2*S*,3*R*)-4-hydroxy-2-phenyltetrahydro-thiophen-3-yl)methanone 18n. Colourless solid, yield (41 mg, 63%); Mp: 131-133 °C; $[\alpha]_D^{29}$ = +36.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.43

(d, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.16-7.14 (m, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 1.8 Hz, 1H), 4.06-3.98 (m, 4H), 3.55 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.18 (d, *J* = 11.4 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 198.8, 163.6, 139.6, 130.9, 129.4, 128.6, 128.1, 127.7, 114.2, 77.5, 63.9, 61.7, 52.5, 41.1, 14.6; FT-IR (KBr): 3448, 2977, 2932, 1665, 1598, 1573, 1510, 1496, 1476, 1453, 1421, 1395, 1331, 1306, 1262, 1227, 1171, 1119, 1040, 972, 919, 874, 837, 828, 804, 738, 699, 680, 668, 646, 631, 624, 617 cm^{-1}; HPLC: Chiralcel AD-H, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 13.0 min, 20.4 min; 84:16 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}O_3S$ 329.1206, found 329.1205.



(4-Ethylphenyl)((2*S*,3*R*)-4-hydroxy-2-phenyltetrahydro-thiophen-3-yl)methanone 18o. Colourless solid, yield (46 mg, 74%); Mp: 125-126 °C; $[\alpha]_D^{29}$ = +53.4 (c =1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.16-7.14 (m, 3H), 5.16 (d, *J* = 10.8 Hz, 1H), 4.90 (s, 1H), 4.06 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.66 (s, 1H), 3.57 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.18-3.16 (m, 1H), 2.65-2.62 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.5, 151.0, 139.7, 134.4, 128.6, 128.6, 128.2, 128.1, 127.7, 77.5, 62.6, 52.0, 41.1, 28.9, 15.1; FT-IR (KBr): 3448, 3082, 3060, 3029, 2966, 2932, 2873, 1676, 1605, 1568, 1494, 1453, 1414, 1375, 1331, 1274, 1224, 1182, 1152, 1028, 1009, 972, 879, 830, 736, 698, 605, 582, 545 cm^{-1}; HPLC: Chiralcel AD-H, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 10.1 min, 18.9 min; 80:20 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}O_2S$ 313.1257, found 313.1258.



(4-Fluorophenyl)((2*S*,3*R*)-4-hydroxy-2-phenyltetrahydro-thiophen-3-yl)methanone 18p. Colourless solid, yield (39 mg, 65%); Mp: 118-120 °C; $[\alpha]_D^{29}$ = -62.6 (c = 0.7, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69-7.67 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 2H), 7.18-7.17 (m, 1H), 6.99 (t, *J* = 8.4 Hz, 2H), 5.13 (d, *J* = 10.2 Hz, 1H), 4.91 (d, *J* = 3.0 Hz, 1H), 4.00 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.69 (d, *J* = 3.6 Hz, 1H), 3.58 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.18 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 198.8, 167.1 (d, J_{C-F} = 256.5 Hz), 139.7, 133.3, 131.2 (d, J_{C-F} = 9.0 Hz), 128.8, 128.1 (d, J_{C-F} = 16.5 Hz), 116.0, 115.9, 77.5, 62.7, 52.3, 41.2; FT-IR (KBr): 3462, 3060, 2924, 2851, 2662, 1681, 1596, 1580, 1447, 1365, 1326, 1216, 1149, 1029, 1006, 894, 755, 698 cm^{-1}; HPLC: Chiralcel AD-H, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 13.9 min, 23.0 min; 24:76 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}FO_2S$ 303.0850, found 303.0849.

3.4 References

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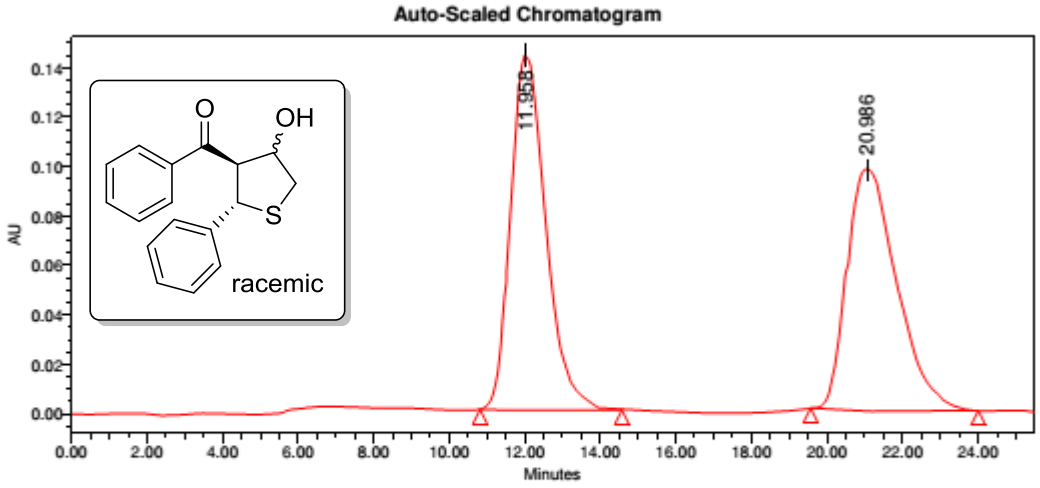
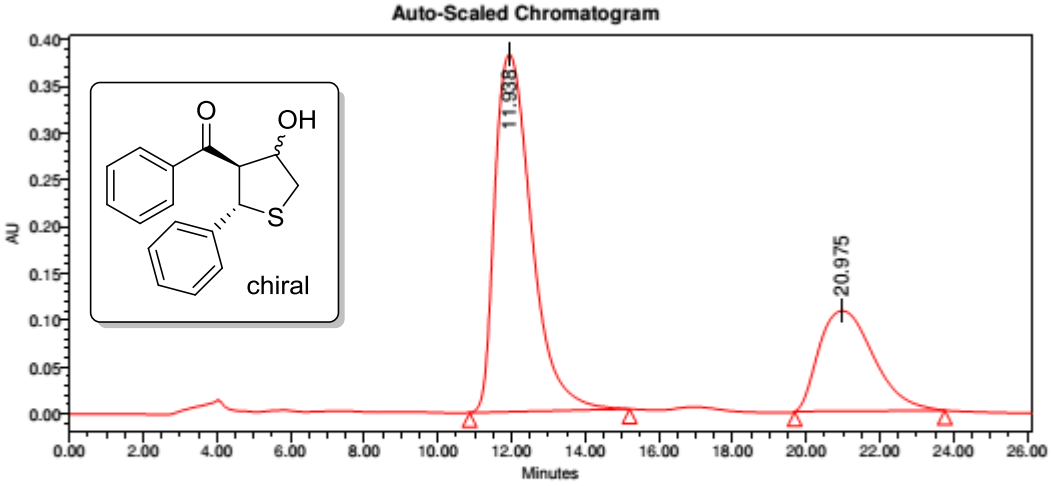
3.5 Selected HPLC Chromatograms



Peak Results

	RT	Height (μV)	% Area
1	11.958	143372	50.38
2	20.986	97692	49.62



Peak Results

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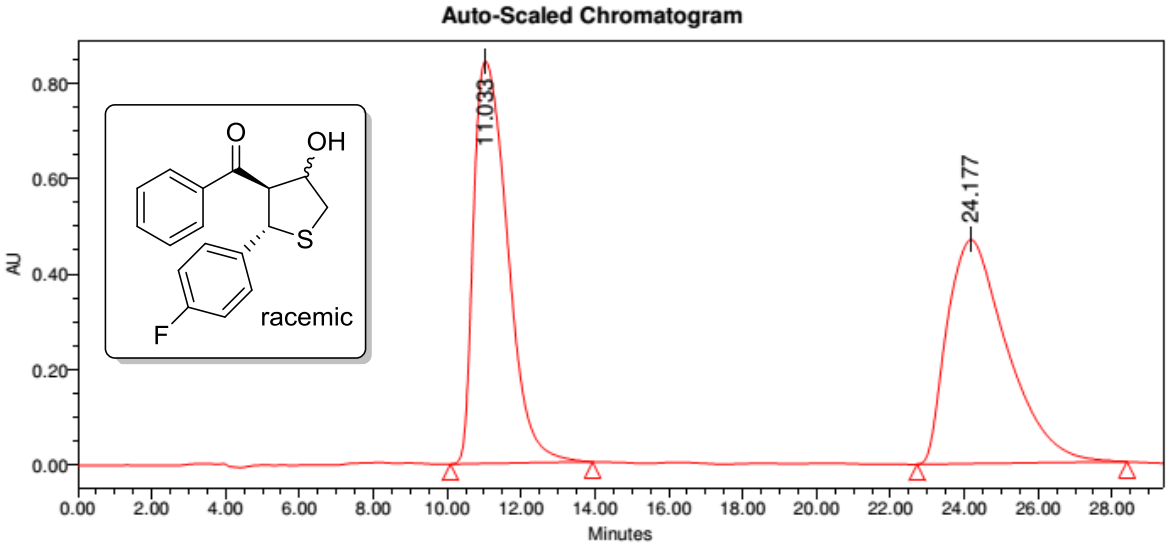
1	11.938	381769	77.58
2	20.975	107004	22.42



Peak Results

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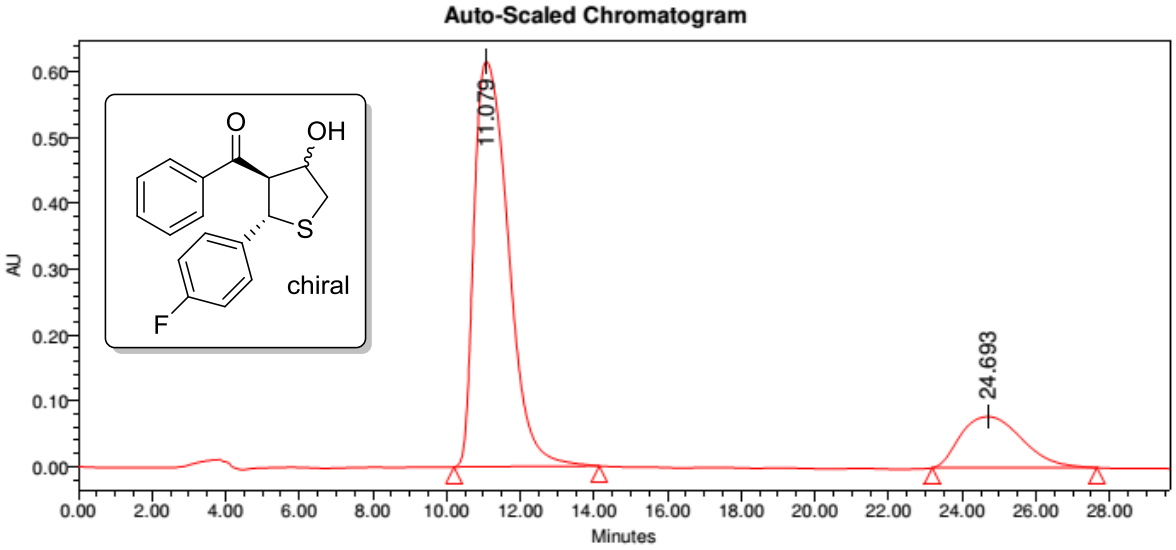
1	11.033	841510	50.45
2	24.177	468527	49.55



Peak Results

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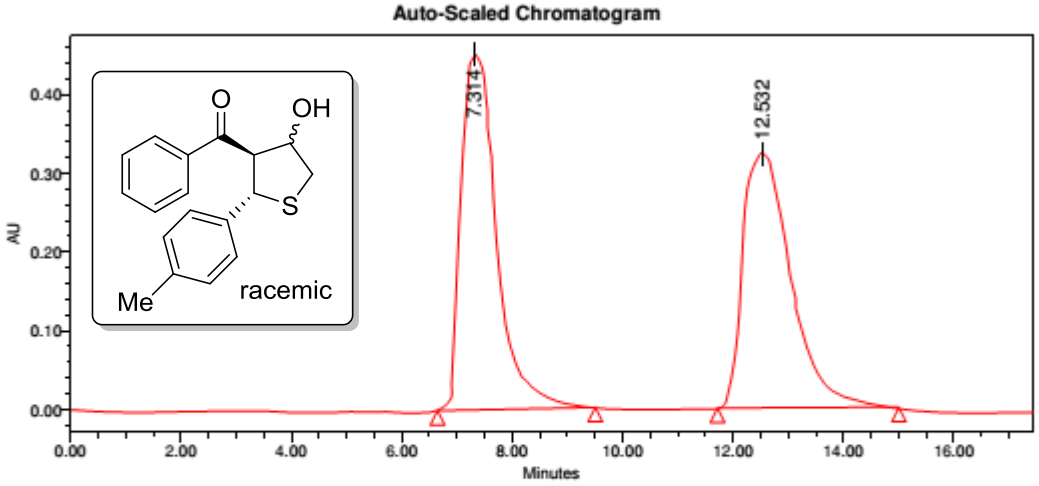
1	11.079	616201	81.42
2	24.693	77694	18.58



Peak Results

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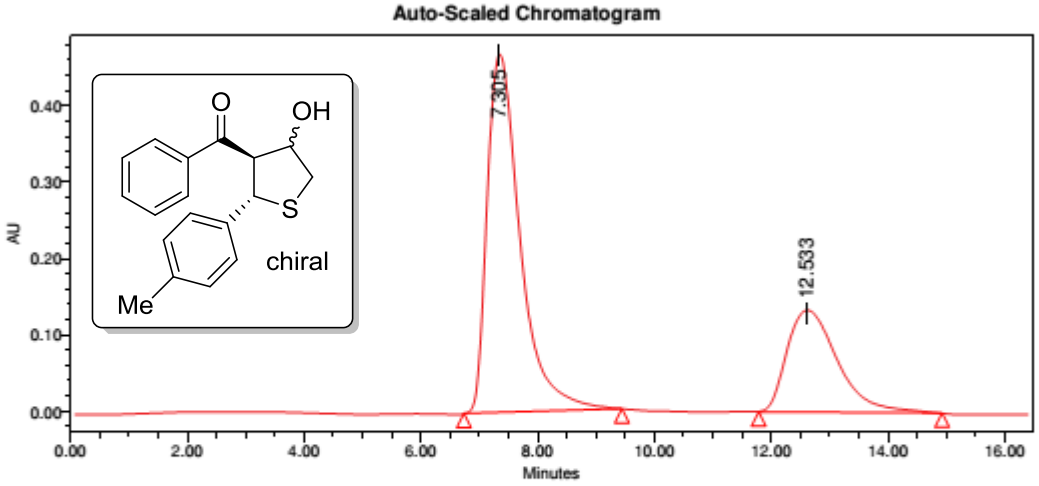
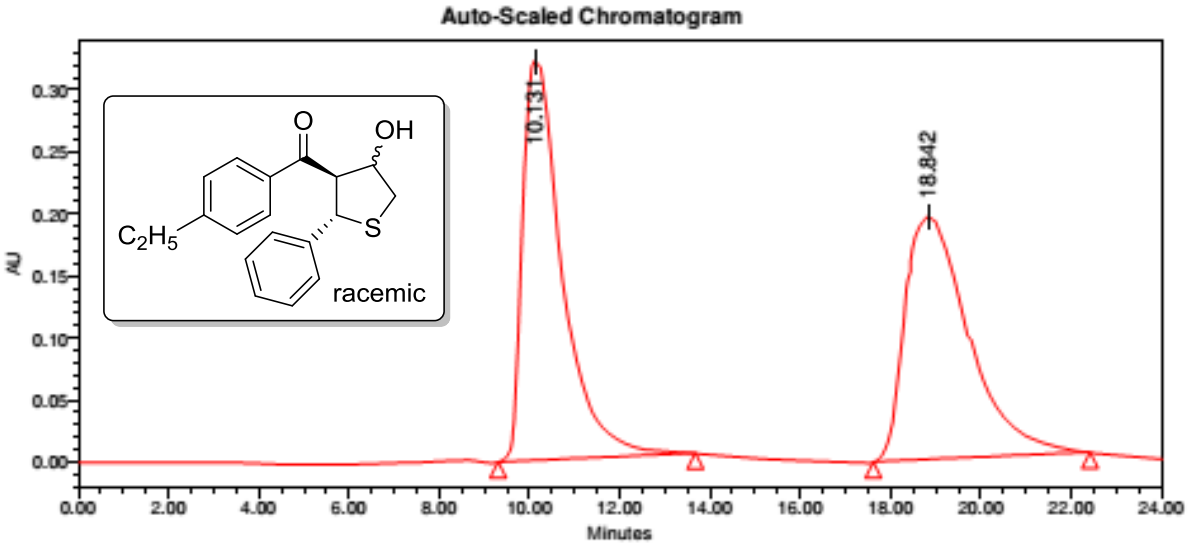
1	7.314	450965	50.85
2	12.532	320988	49.15



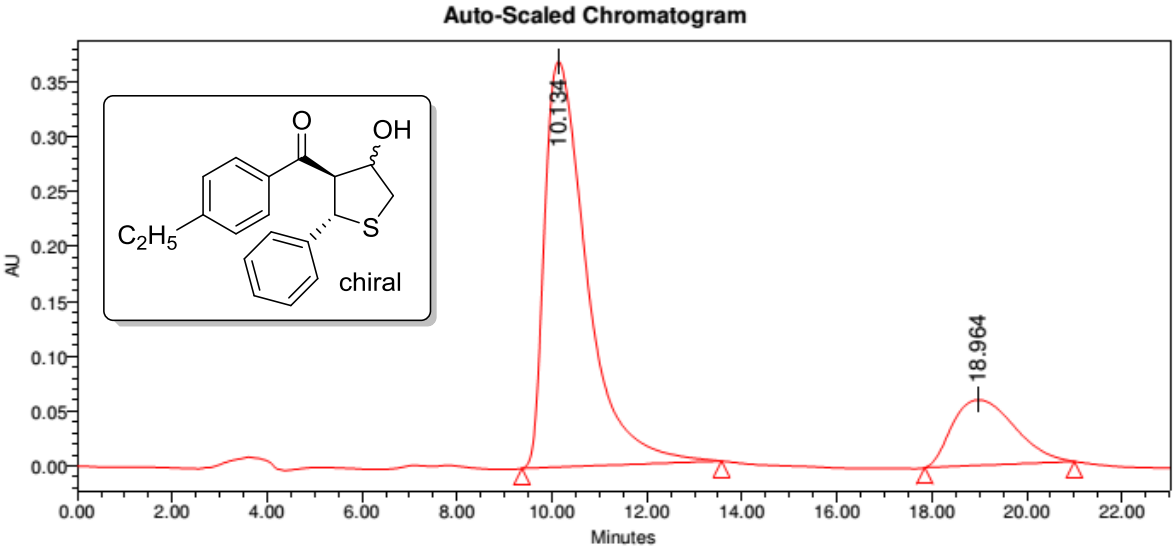
Peak Results

	RT	Height (μV)	% Area
1	7.305	472639	81.29
2	12.533	141013	18.71



Peak Results

	RT	Height (μV)	% Area
1	10.131	321409	50.68
2	18.842	195180	49.32



Peak Results

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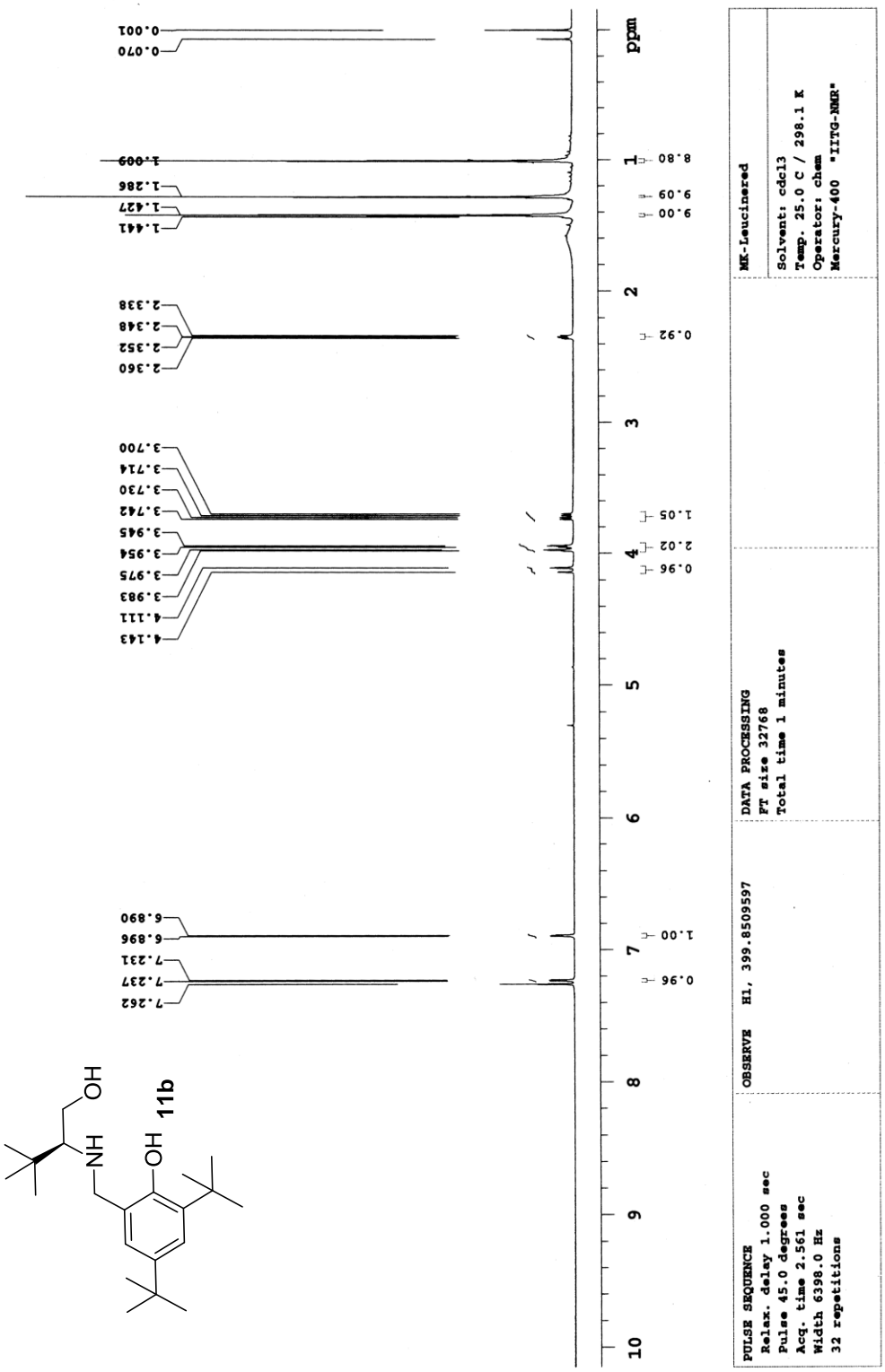
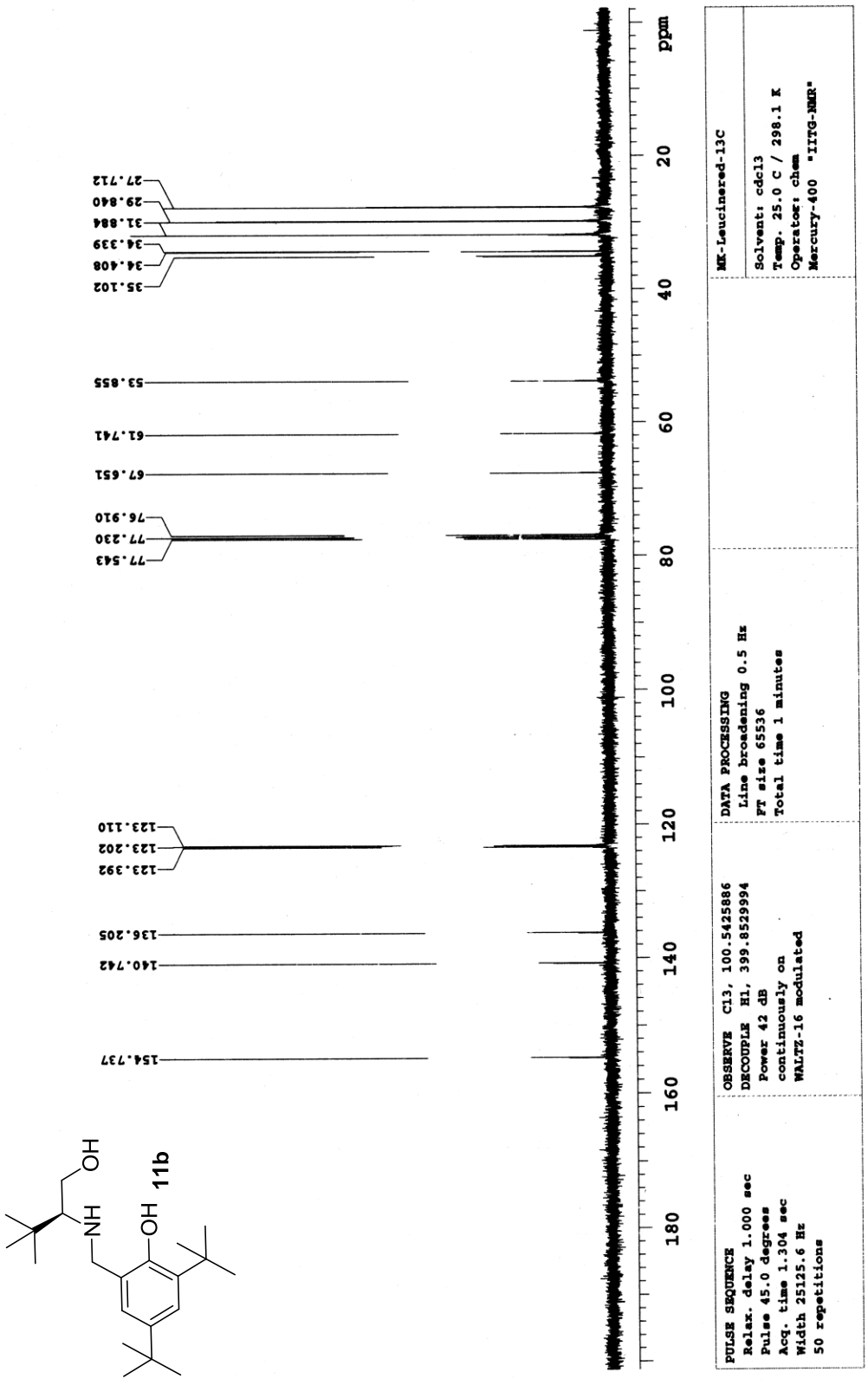
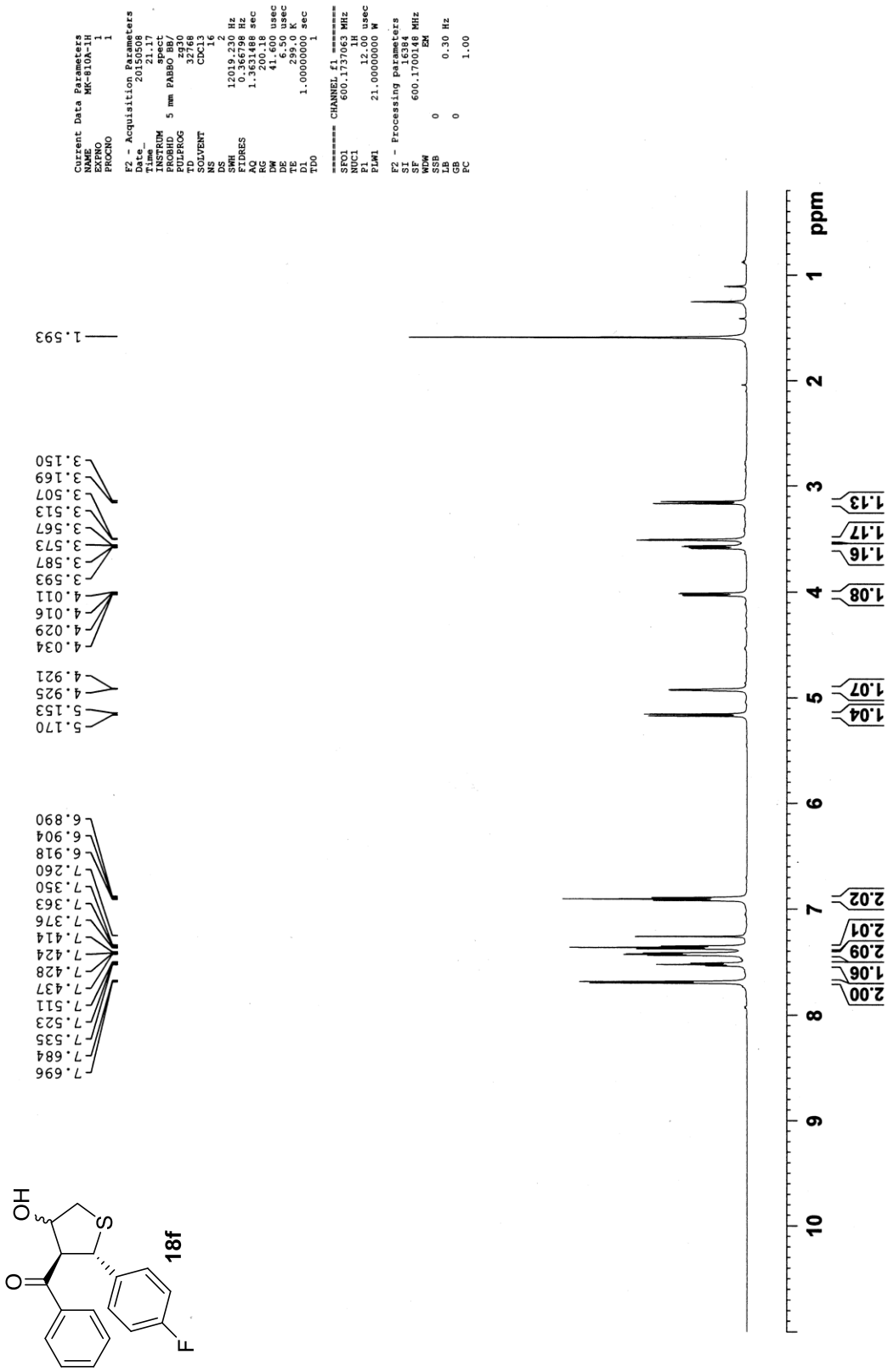
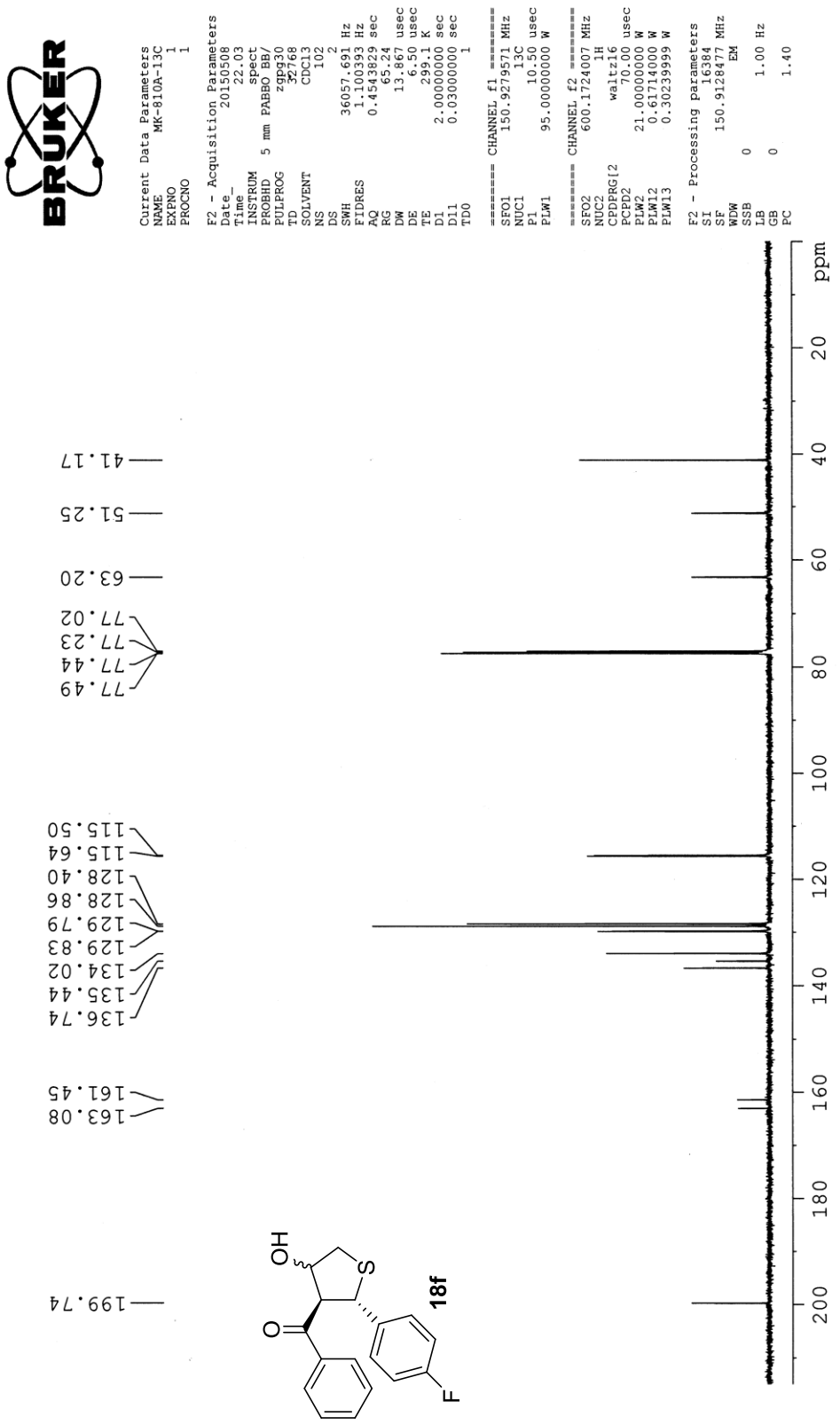
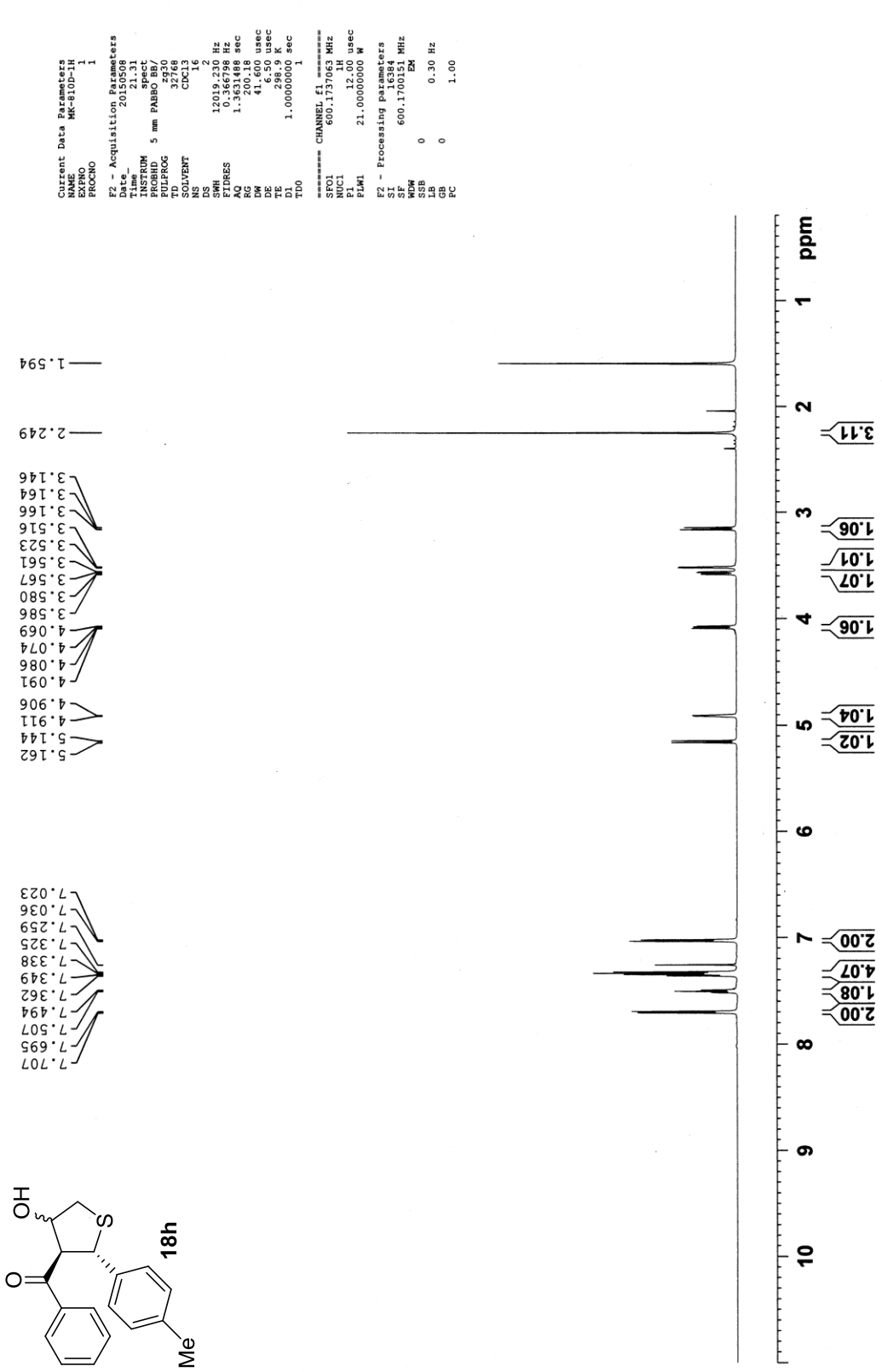
3.6 Selected NMR (^{1}H and ^{13}C) Spectra

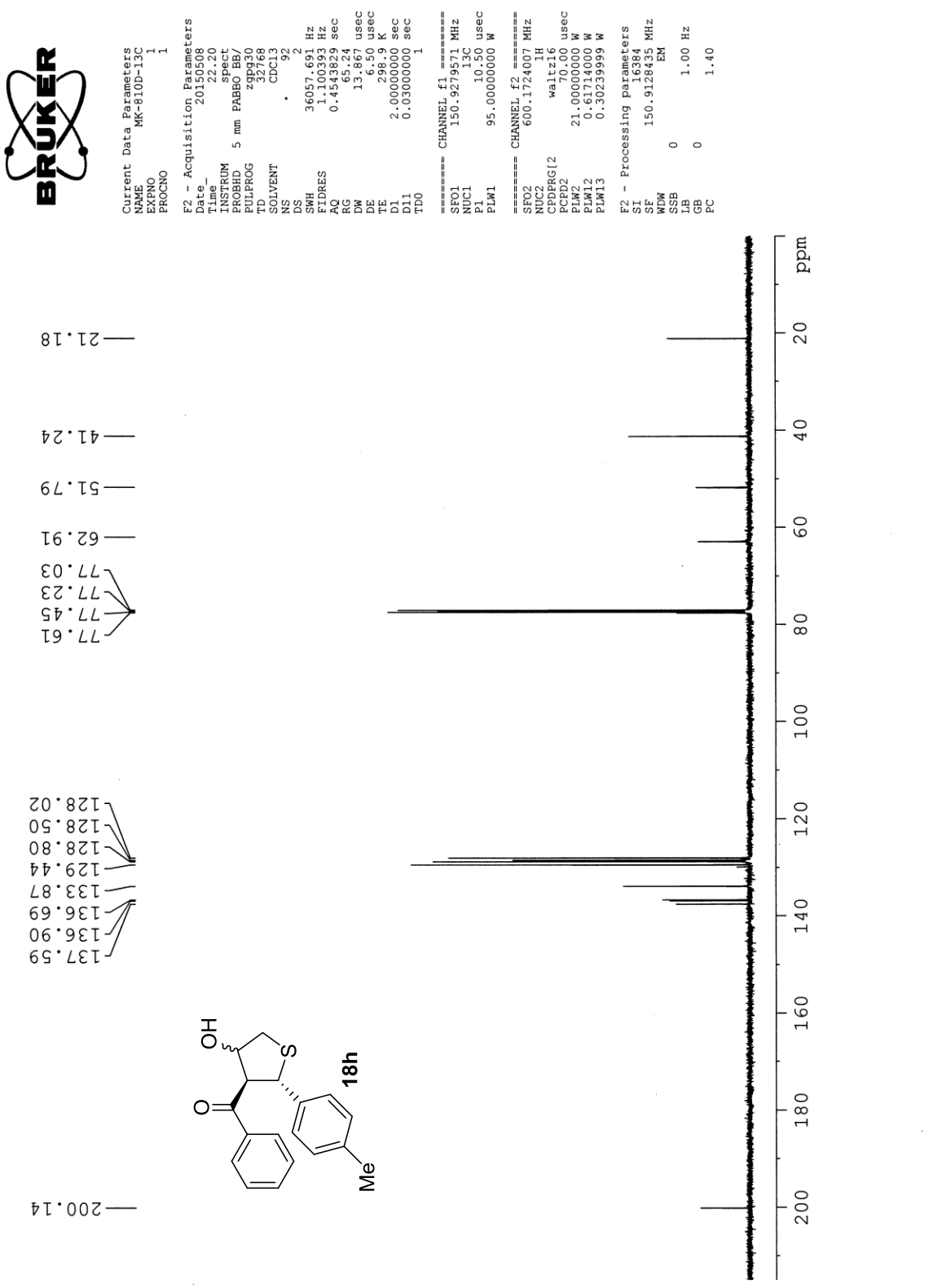


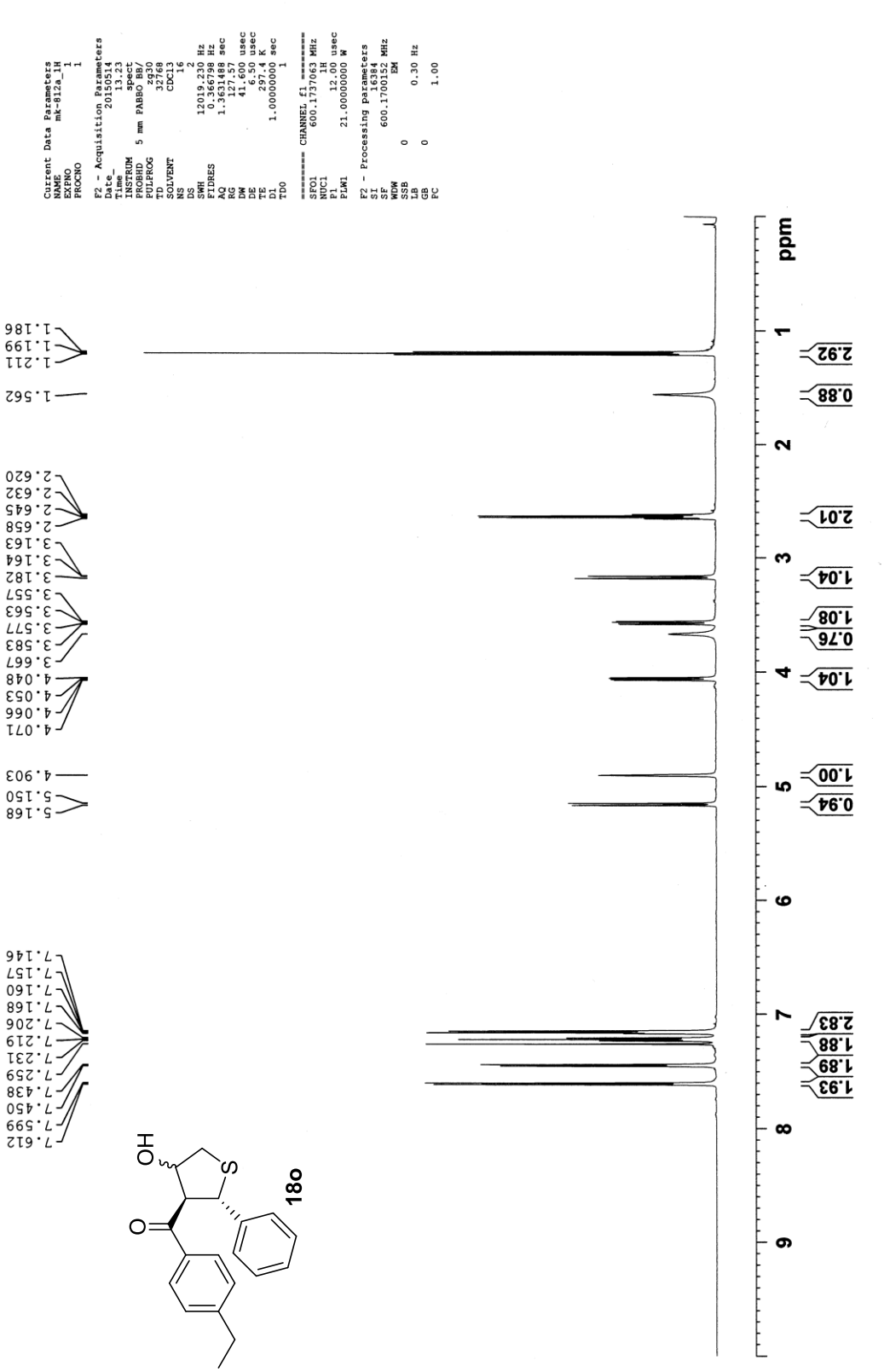


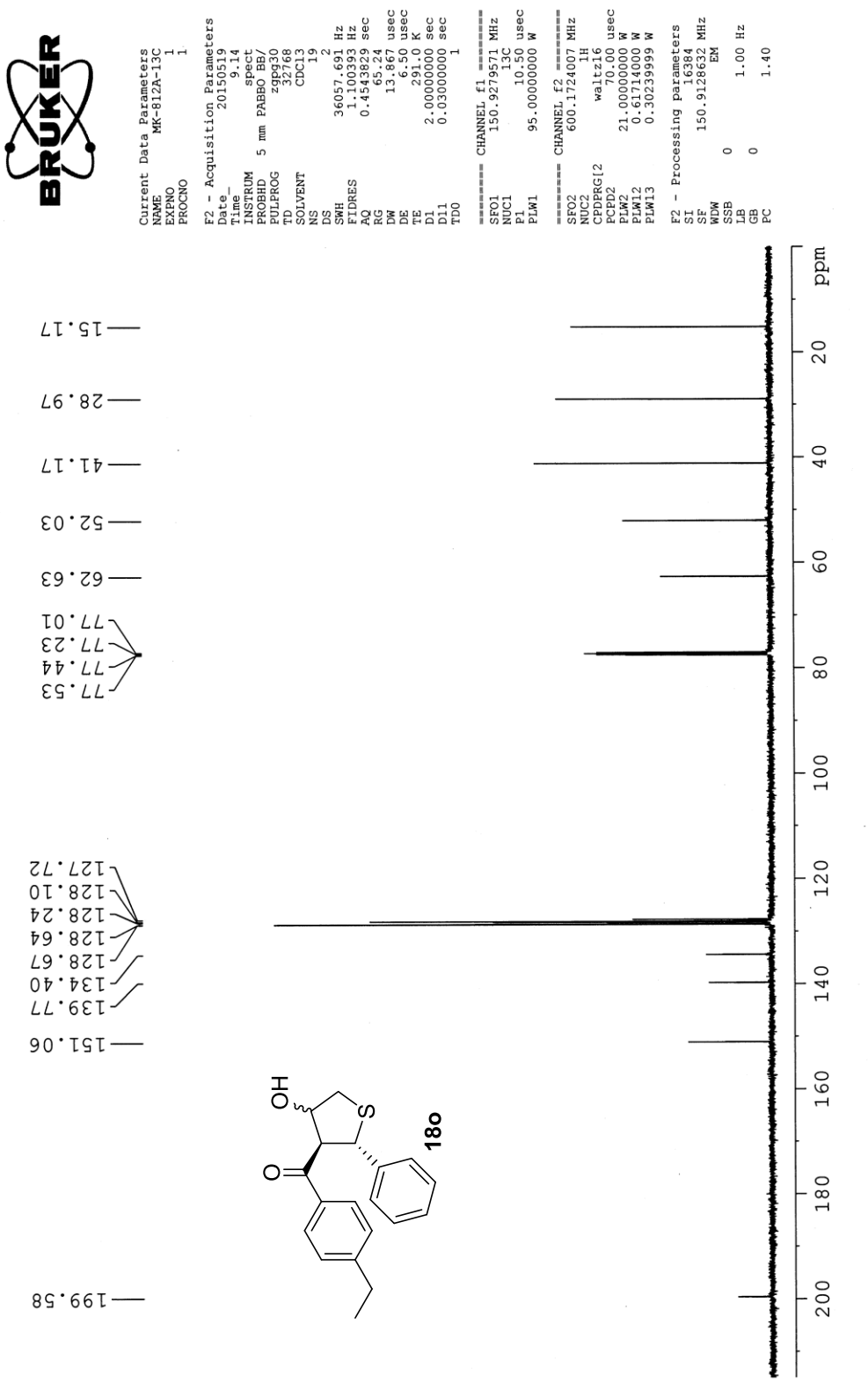












Chapter IV

Chiral Iron-Dendrimer Catalyzed Enantioselective Synthesis of Tetrahydrothiophenes

Asymmetric catalysis is an ideal method for making chiral molecules in organic synthesis. Many chiral ligands have been reported in literature for enantioselective C-C, C-H, C-N, and C-O bond formation reactions.[1] However, asymmetric methodologies in chemical industry are rather limited due to the high cost of chiral ligands and use of noble metals in such transformations, which have to be separated from the reaction mixture after use. Along with these unsolved problems, one more critical problem for the pharmaceutical and food industry is the high levels of metal contaminants 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.

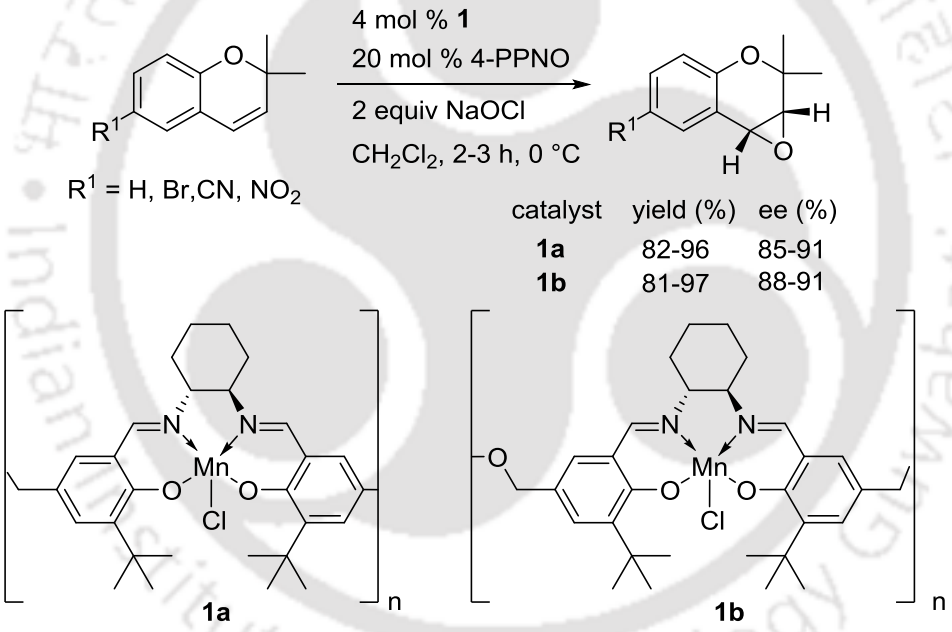
The most successful way of making chiral ligands into recoverable and reusable catalyst is immobilization of chiral ligands on solid heterogeneous support.[2] However, they allow ease separation of catalyst, but they often results in lower activities and enantioselectivities. In general, efficiency of a chiral catalyst mainly depends on the placement of the reaction site and its ease access by the reaction partners. To avoid the above said problems chiral ligands are converted into soluble macromolecular catalysts such as stereoregular soluble polymer,[3] dendrimer[4] or soluble polymer anchored chiral catalyst.[5] Dendrimers are regular highly branched and well-defined macromolecular with three dimensional network which preserves the microenvironment around the catalytic site similar to that of monomeric unit. Thus, it is possible to fine-tune the catalytic properties of dendrimer catalysts through the adjustment of their structure, size, shape, and solubility. Similarly, stereoregular soluble polymer catalyst behaves like a homogeneous catalyst during the reaction and can be easily separated via selective precipitation upon completion of the reaction. This class of catalysts combines the advantages of homogeneous and heterogeneous catalysis; high catalytic activity, stereoselectivity with easy recyclability and convenient separation through extraction, precipitation or nanofiltration, thus allowing recovery and reuse of the catalysts.[6] As a result

the development of new methodology for the synthesis of stereoregular polymer or chiral dendrimer is highly desirable.

4.1 Synthetic Methodologies Based on Recoverable Schiff Base Catalysts

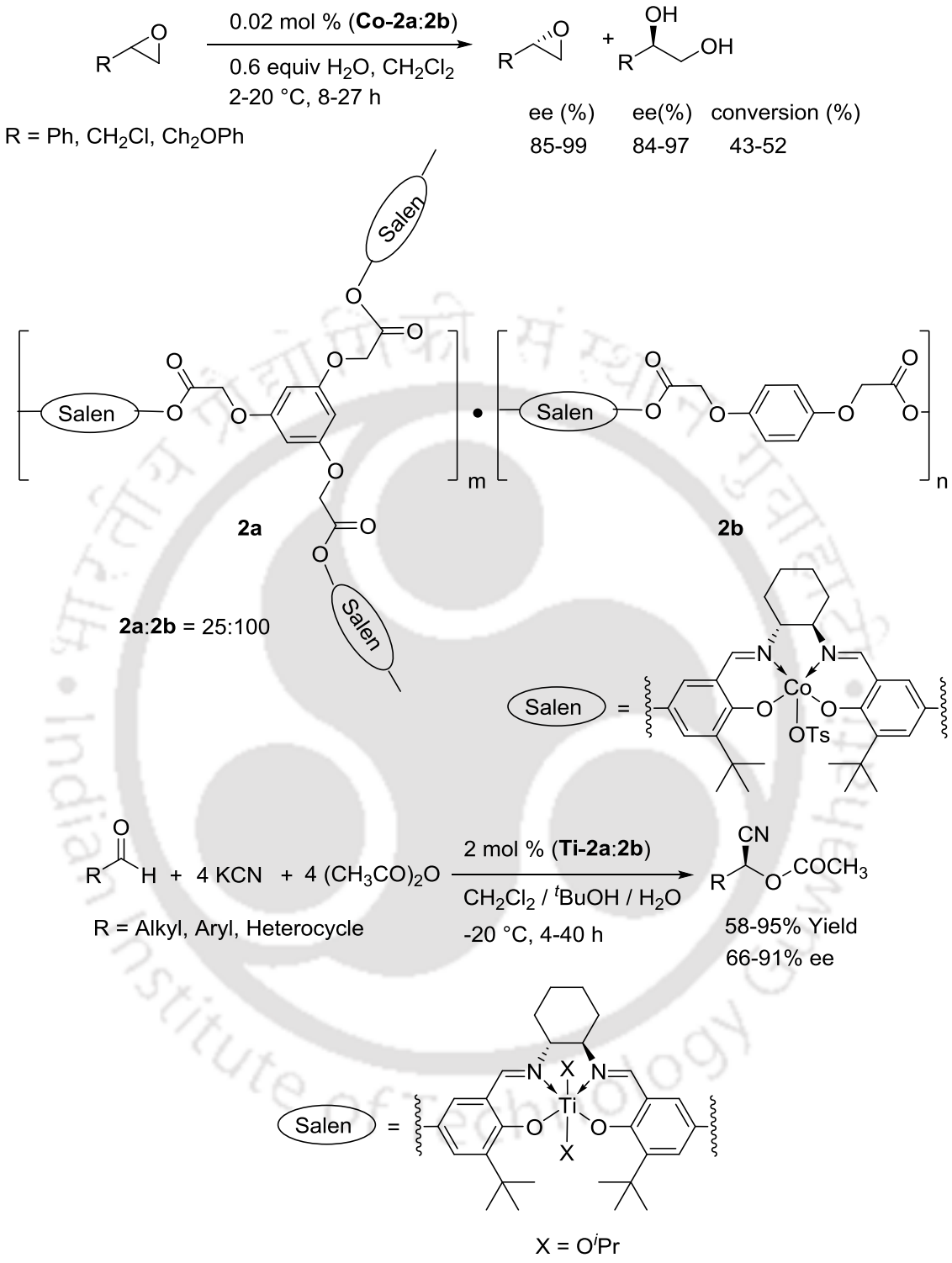
The traditional methods for utilizing tridendate and tetradendate Schiff base chiral ligands as recoverable catalyst includes stereoregular polymer or polymer anchored catalyst. However, very few methods have been reported using tridendate Schiff base derived chiral catalysts.

Zheng and co-workers have reported chiral Mn-salen polymers **1** for the enantioselective epoxidation of 2,2-dimethychromenes with NaOCl and 4-phenylpyridine-*N*-oxide (4-PPNO) (Scheme 1).[7] This protocol provides high yield as well as enantioselectivity and the catalysts have been recycled up to five cycles without loss of activity and selectivity.



Scheme 1. Mn(III)-Salen Polymer Catalyzed Enantioselective Epoxidation

They have subsequently developed cross linked polymeric Co(III)-salen catalysts for the kinetic resolution of epoxides with water (Scheme 2).[8a] The cross linked polymeric ligand was prepared by mixing different proportions of di- and tribenzaldehydes with chiral diamine. Similar to Jacobsen's oligomeric catalyst[8b-c] here also they observed cooperative effect of the catalytic units with increased activity and high enantioselectivity.

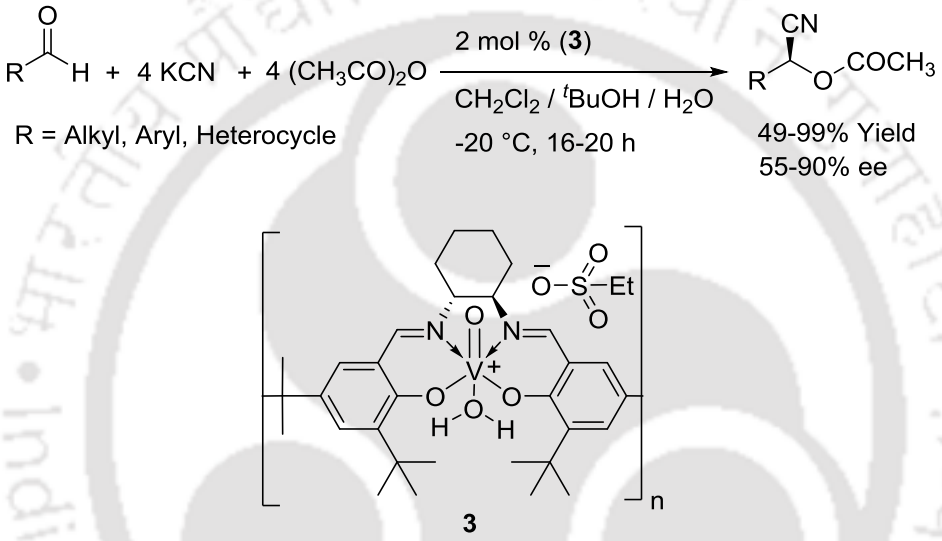


Scheme 2. Cross Linked Polymeric Salen Catalyzed Enantioselective Reaction

Later, Zheng and co-workers synthesized similar type of cross linked polymeric Ti(IV) salen complexes for enantioselective KCN and Ac_2O addition reaction to aldehydes (Scheme

2).[9] The polymeric catalyst with degree of cross linking tri/di aldehyde in the ratio 0.5/100 afforded *O*-acetyl cyanohydrins with high yield and high enantioselectivities up to 94% yield and 91% ee. The polymeric catalyst was recovered and reused up to six cycles without loss of activity and enantioselectivity.

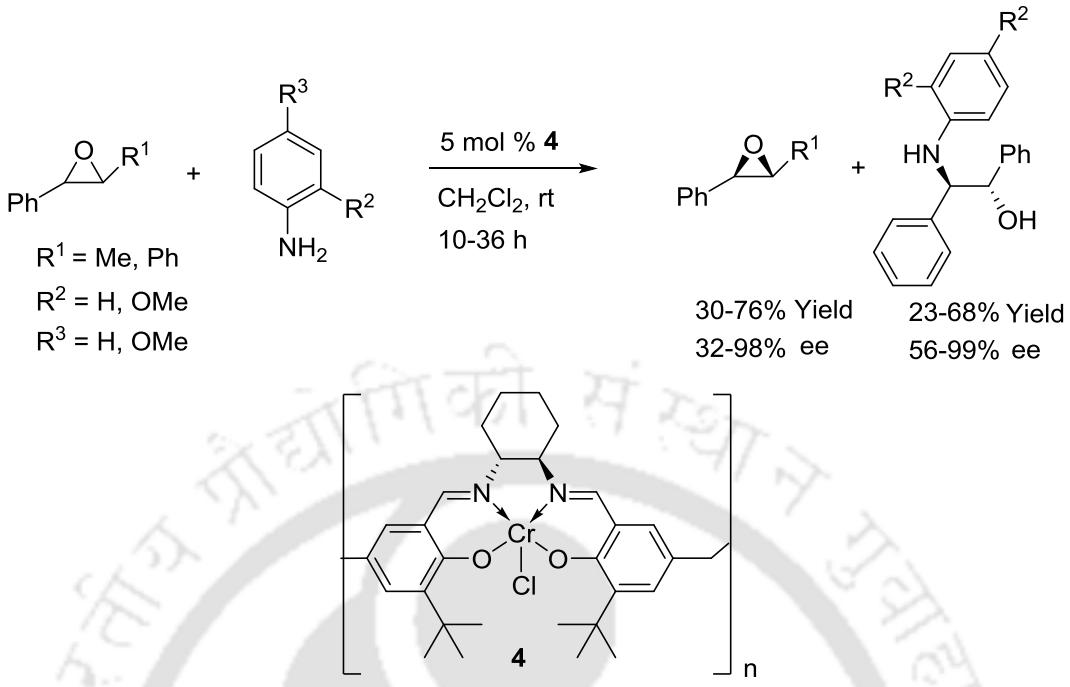
They have also prepared polymeric linear V(V) salen **3** for enantioselective KCN and Ac_2O addition reaction to aldehydes (Scheme 3).[10] The activities and enantioselectivities were similar to that of the earlier Ti(IV) catalyst. However, the recyclability experiments were not successful.



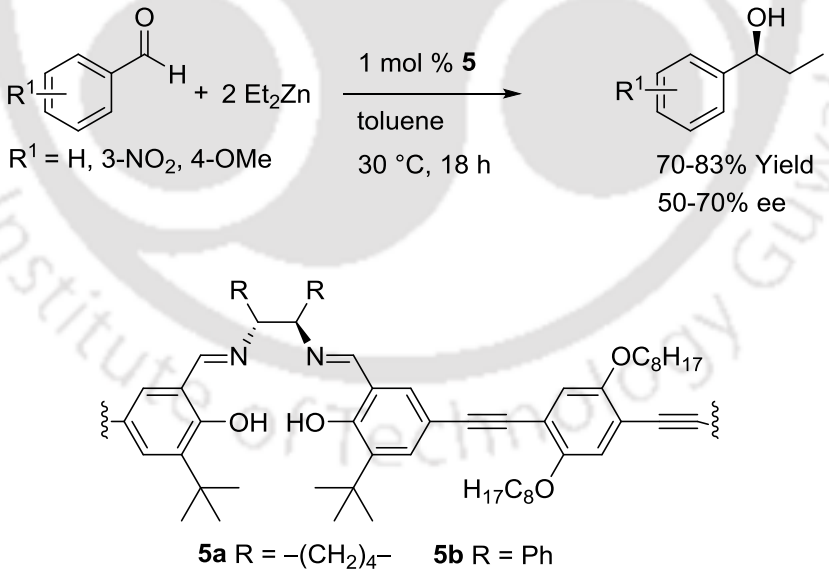
Scheme 3. V(V)-Salen Polymer Catalyzed Enantioselective *O*-Acetylcyanohydrin Synthesis

Kureshy and co-workers have reported polymeric chiral Cr(III)-salen complexe **4** for enantioselective aminolytic kinetic resolution of *trans*-epoxides (Scheme 4).[11] The *β*-aminoalcohols are obtained in high yield and enantioselectivity. This catalyst has been recycled up to four cycles without loss in activity and selectivity.

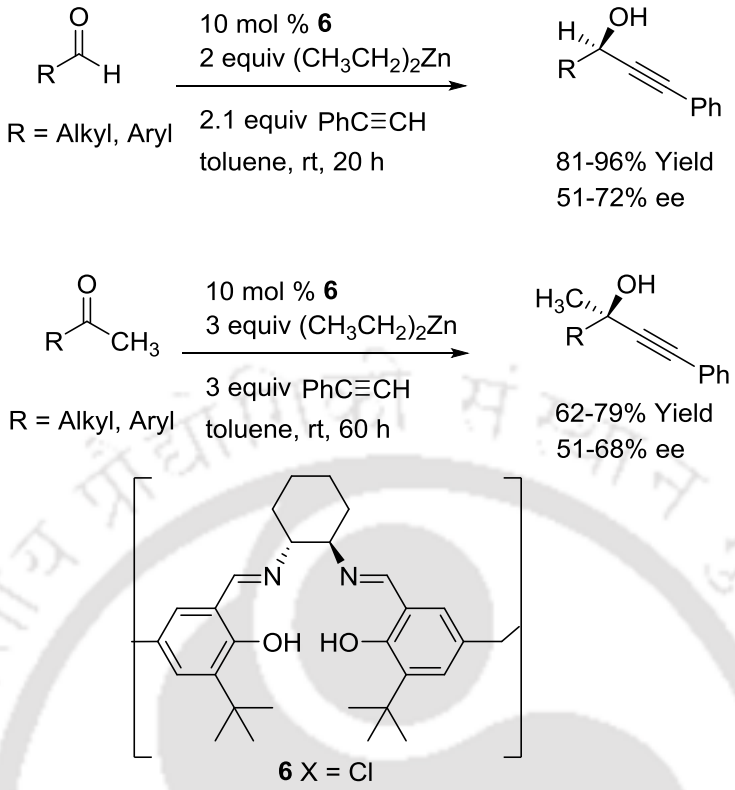
Our group has prepared chiral linear polymer **5** containing chiral salen catalytic sites with 1,4-dialkoxy-2,6-diethynylbenzene linker for enantioselective diethylzinc addition to aldehydes (Scheme 5).[12] This method provided the corresponding secondary alcohols in good yield and high enantioselectivity at 30 °C. Further this polymer is also recyclable without any loss in activity and selectivity.



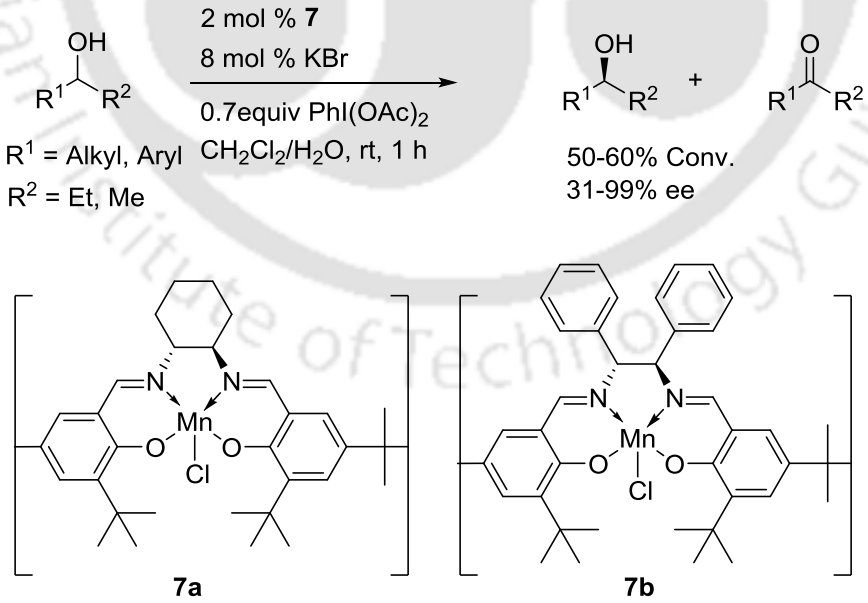
Scheme 4. Cr(III)-Salen Catalyzed Aminolytic Kinetic Resolution of Epoxides



Scheme 5. Zn(II)-Salen Catalyzed Enantioselective Secondary Alcohol Synthesis



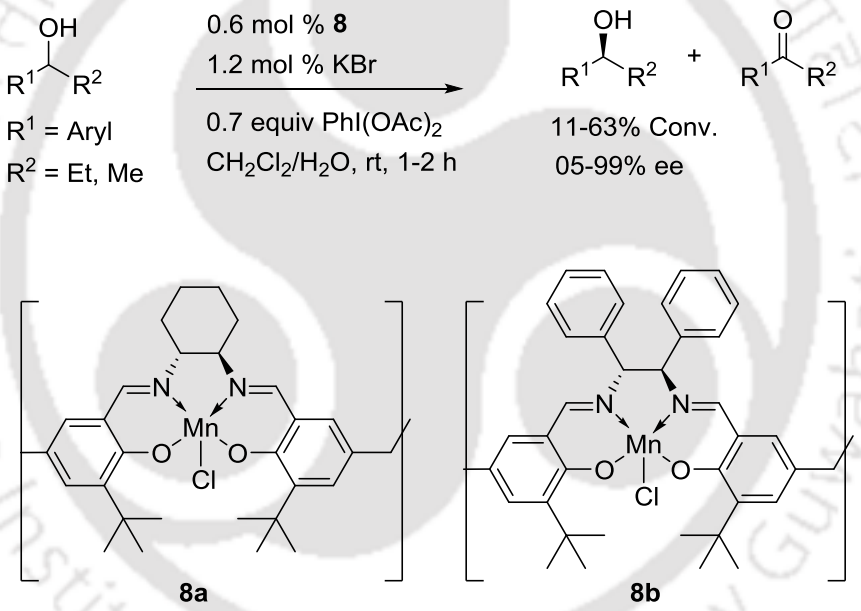
Scheme 6. Zn(II)-Salen Catalyzed Enantioselective Phenylacetylene Addition Reaction



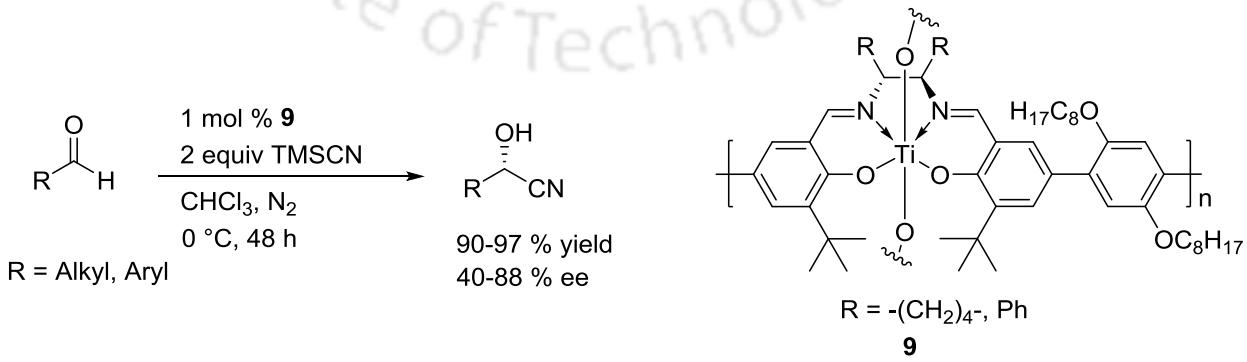
Scheme 7. Mn(III)-Salen Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols

Abdi and co-workers have developed chiral polymeric Zn(II)-Salen for enantioselective phenylacetylene addition to aldehydes and ketones (Scheme 6).[13] The protocol proceeded reaction at room temperature and provided the corresponding secondary propargylic and tertiary propargylic alcohols in good yield and enantioselectivities. This polymer complex has been reused for four times with no loss in enantioselectivity.

Sun and Kureshy groups have demonstrated the use of chiral Mn(III)-salen polymers **7**-**8** for oxidative kinetic resolution of secondary alcohols (Scheme 7,8).[14] The reaction readily takes place in biphasic solvent system at room temperature and successfully applied to a broad range of substrates including various aromatic and aliphatic secondary alcohols. This polymer catalyst has been reused for five times without loss in activity and enantioselectivity.



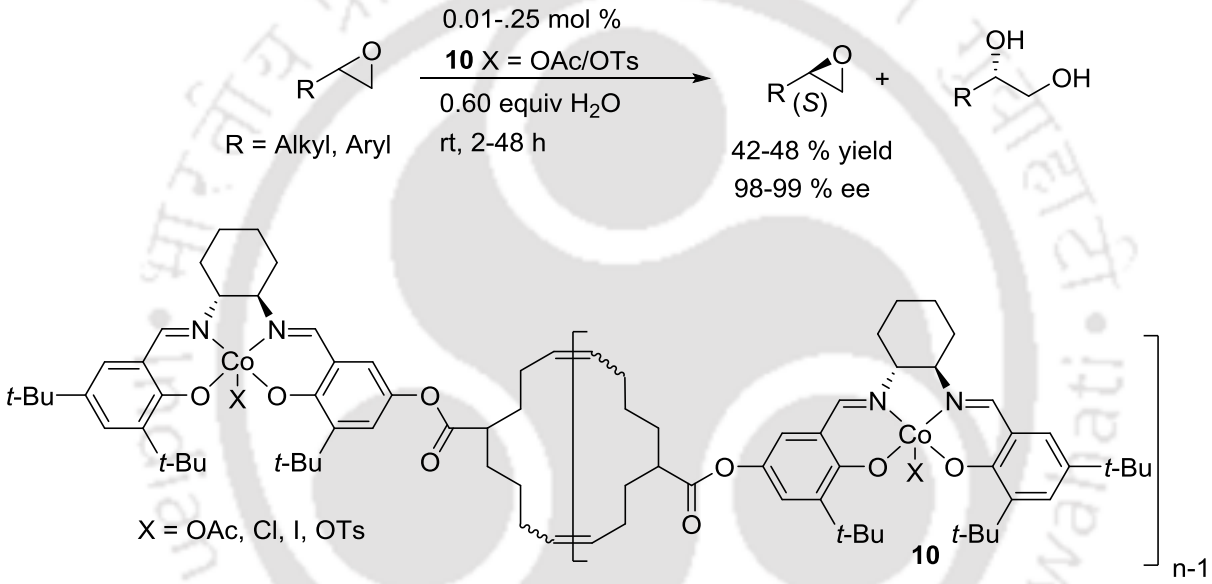
Scheme 8. Mn(III)-Salen Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols



Scheme 9. Ti(IV)-Salen Catalyzed Enantioselective Cyanohydrins Synthesis

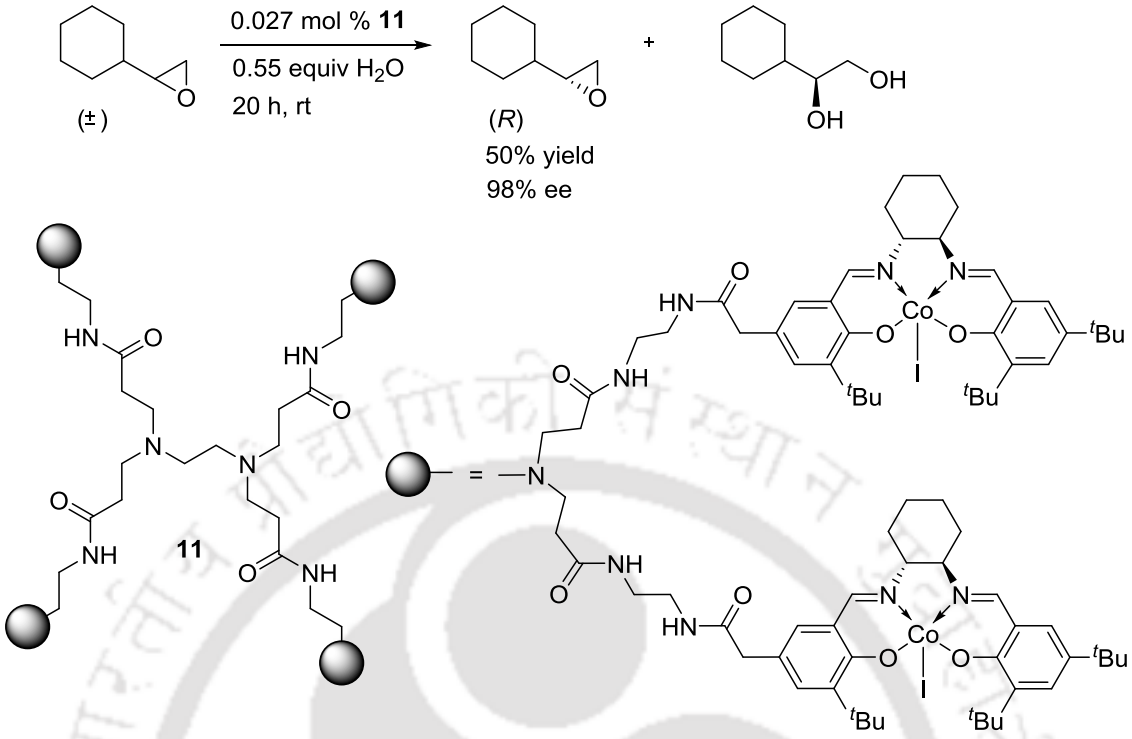
Our group has developed chiral linear polymer **9** containing Ti(IV)-salen units and 1,4-dialkoxybenzene for enantioselective TMSCN addition to aldehydes (Scheme 9).[15] This polymer retained the same selectivity as that of the monomer catalyst. This method provides simplified product isolation and easy recovery and recyclability of the catalyst without any loss in activity and selectivity.

Weck and co-workers have synthesized chiral oligomeric Co(III)-salen complex **10** for hydrolytic kinetic resolution of terminal epoxides (Scheme 10).[16] The high reactivity and enantioselectivity of this catalyst was explained by the extreme flexibility of the oligomeric backbone. The catalyst is also recyclable without loss of activity and selectivity.



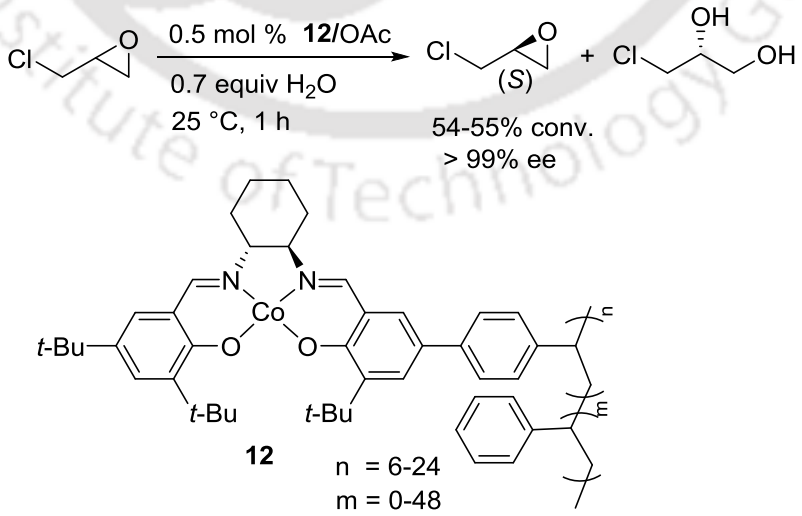
Scheme 10. Oligomeric Co(III)-Salen Catalyzed Kinetic Resolution of Epoxides

Jacobsen and co-workers have reported highly active dendrimer bound chiral Co(III)-salen complex **11** for hydrolytic kinetic resolution of terminal epoxides (Scheme 11).[17] They observed high activity and enantioselectivity for dendrimer supported salen complex whereas the monomer complex showed no activity. This positive dendrimer effect arises from the restricted rotation of the dendrimer structure and also by co-operative interaction between Co(III)-salen units.



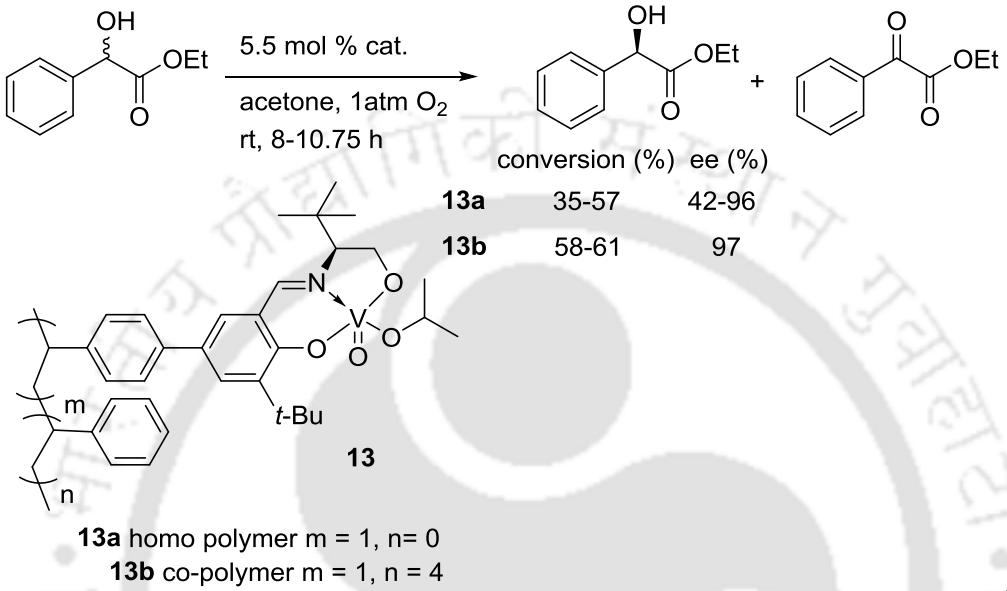
Scheme 11. Co(III)-Salen Dendrimer Catalyzed Kinetic Resolution of Epoxides

Weck and co-workers have reported polystyrene supported Co(II)-salen complex **12** for enantioselective hydrolytic kinetic resolution of epichlorohydrin (Scheme 12).[18] This polymer supported catalyst can be prepared by free radical homo and co-polymerization of unsymmetrical monostyryl substituted salen monomers. This polymer showed increased reactivity and selectivity while diluting the homopolymer unit with unfunctionalized styryl monomers.



Scheme 12. Polystyrene Supported Co(II)-Salen Catalyzed Kinetic Resolution of Epoxides

Jones and co-workers reported polystyrene supported chiral tridentate Schiff base vanadium catalyst for oxidative kinetic resolution of ethyl mandelate (Scheme 13).[19] Here the co-polymer catalyst showed better catalytic activity and selectivity than the homopolymer catalyst.



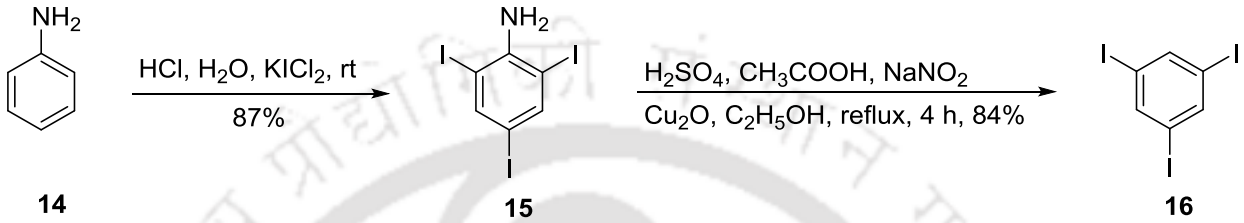
Scheme 13. Kinetic Resolution of Ethyl Mandelate by Polystyrene Supported V(V)-Catalyst

4.2 Present Study

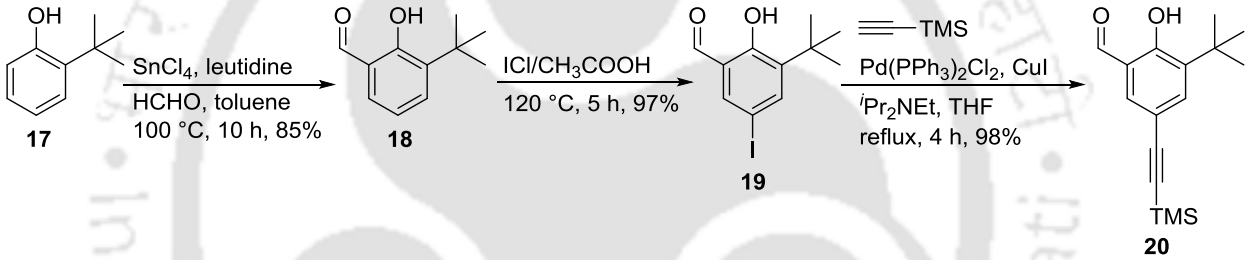
This chapter describes the synthesis of tridendate L-*tert*-leucinol derived chiral dendrimer **24** *via* palladium catalyzed Sonogashira cross-coupling and Schiff's base formation from optically active L-*tert*-leucinol followed by reduction with $NaBH_4$. Further its application as recyclable catalyst for enantioselective synthesis of trisubstituted tetrahydrothiophenes is reported *via* domino sulfa-Michael/aldol reaction.

The synthesis of L-*tert*-leucinol derived chiral dendrimer **24** is shown in Scheme 14-17. Iodination of aniline **14** with $KICl_2$ gave 2,4,6-triiodoaniline **15** in 87% yield that could be transformed into 1,3,5-triiodobenzene **16** by deamination using $NaNO_2$ and Cu_2O in 84% yield (Scheme 14). Formylation of 2-*tert*-butylphenol **17** with $SnCl_4$ furnished 3-*tert*-butyl-2-hydroxybenzaldehyde **18** in 85% yield that could be iodinated to give **19** in 97% yield. The Pd-catalyzed C-C cross-coupling of **19** with trimethylsilylacetylene provided **20** in 98% yield

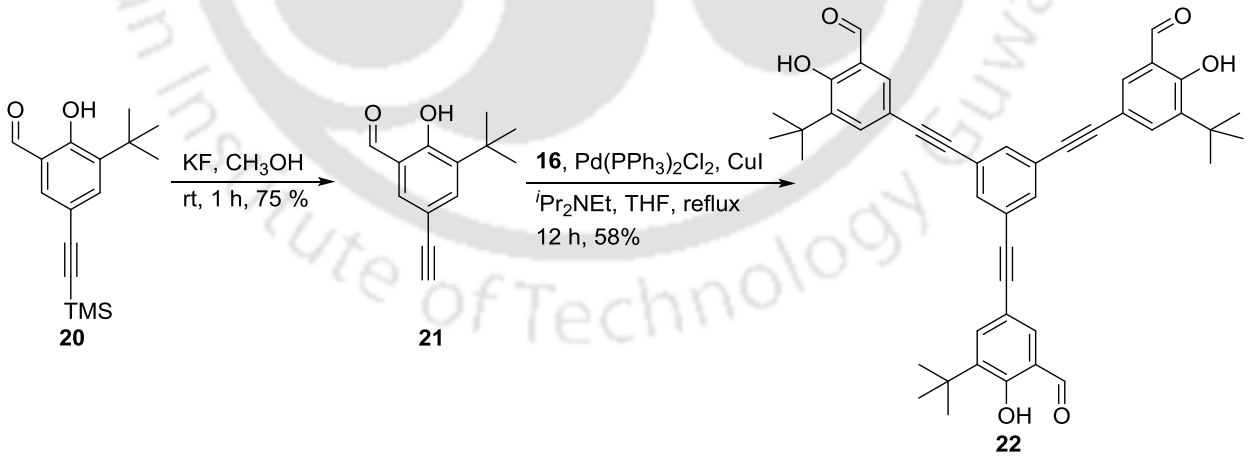
(Scheme 15). Desilylation of **20** with KF followed by C-C cross coupling with triiodobenzene by palladium catalyst afforded the trialdehyde **22** in 58% yield (Scheme 16). Further condensation of the trialdehyde with *tert*-leucinol in $CHCl_3$ at 50 °C for 6 h provided the corresponding triimine **23** in 88% yield. Subsequently, the triimine was reduced with $NaBH_4$ in MeOH at room temperature for 3 h to provide the desired dendrimer **24** in 92% yield.



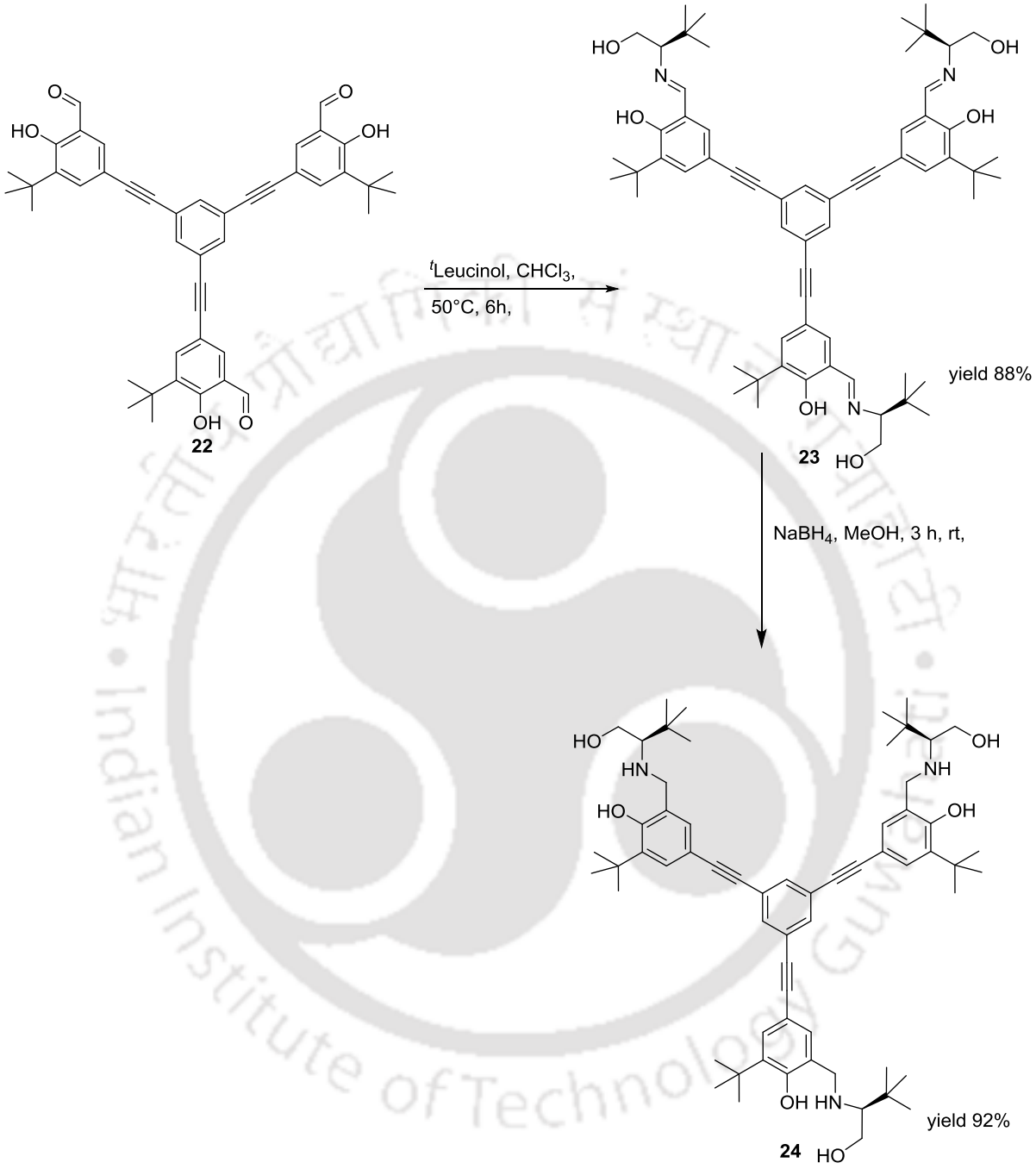
Scheme 14. Synthesis of Triiodobenzene **16**



Scheme 15. Syntheis of Aldehyde **20**



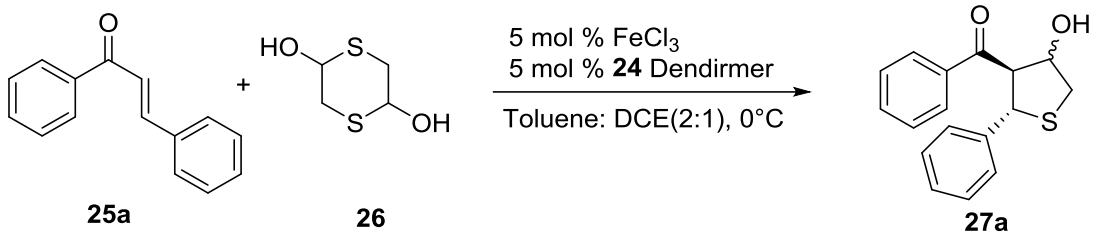
Scheme 16. Synthesis of Trialdehyde **22**



Scheme 17. Synthesis of Dendirmer **24**

The utility of the synthesized chiral dendrimer has been demonstrated in enantioselective trisubstituted tetrahydrothiophenes synthesis *via* domino thia-Michael/aldol reaction.

Table 1. Effect of Solvent on Dendrimer Catalyst[a]



Entry	Solvent	Yield (%)[b]	er[c]
1	toluen:DCM	68	64:36
2	toluene:CH_3Cl	65	72:28
3	toluene:DCE	62	74:26

[a] Reaction conditions: chalcone **25a** (0.2 mmol), 1,4-dithiane-2,5-diol **26** (0.2 mmol), dendrimer **24** (5 mol %), $FeCl_3$ (15 mol %), toluene:DCE (2:1), 2 mL, 60 h at 0 °C.

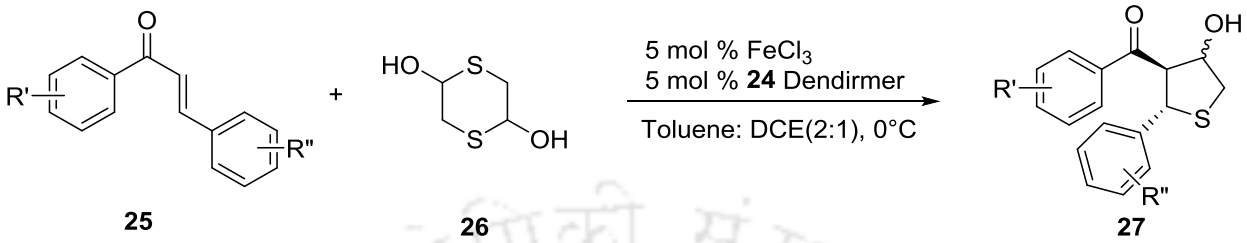
[b] Isolated yield.

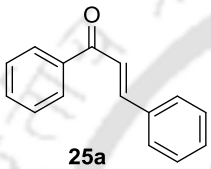
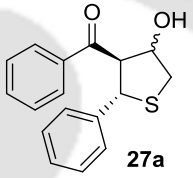
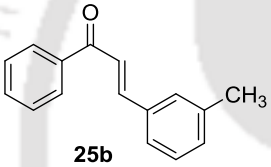
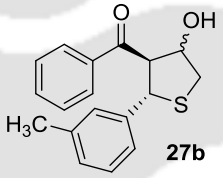
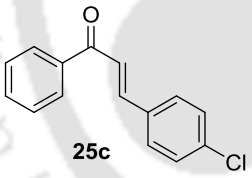
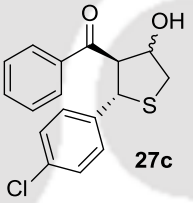
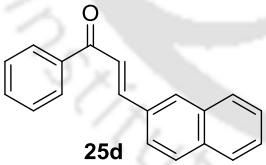
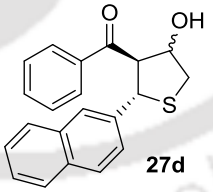
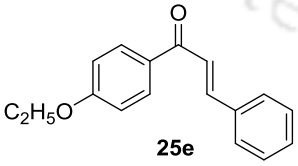
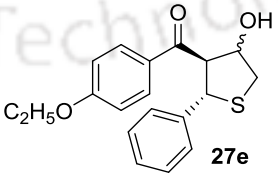
[c] Determined by HPLC analysis with Chiralcel OJ using *n*-hexane/2-propanol.

In chapter 3, we have described the synthesis of trisubstituted tetrahydrothiophenes with monomer catalyst. Having the standard condition for monomer catalyst in hand, we further studied the effect of solvent for dendrimer catalyst with mixture of solvents such as toluene : DCM, toluene : $CHCl_3$ and toluene : DCE (Table 1). As anticipated, the best result was obtained with toluene : DCE and the reaction readily occurred with 5 mol % of the *in-situ* prepared Fe(III)-dendrimer catalyst to afford the desired trisubstituted tetrahydrothiophene at 0 °C. The selectivity was similar to that of the monomer catalyst. Using the optimized conditions, the reactivity of the dendrimer catalyst was further explored with various chalcones (Table 2). The reaction of phenylchalcone **25a** with 1,4-dithiane-2,5-diol **26** proceeded readily with 5 mol % dendrimer catalyst at 0 °C to afford trisubstituted tetrahydrothiophenes **27a** in 62% yield and 74:26 er. In addition, 3-methylphenylchalcone **25b** was observed slightly less reactive and provided the desired trisubstituted tetrahydrothiophene **27b** in 58% yield and 77:23 er. Interestingly, *para*-substituted phenyl and 2-naphthyl chalcones proceeded the reaction in good yield and enantioselectivity. For

examples, 4-chlorophenyl, 4‘-ethoxyphenyl and 2-naphthylchalcones **25c-d** gave the corresponding trisubstituted tetrahydrothiophenes in 55-74% yield and 82:18-84:16 er.

Table 2. Chiral Dendrimer Catalyzed Asymmetric Tetrahydrothiophenes Synthesis[a]



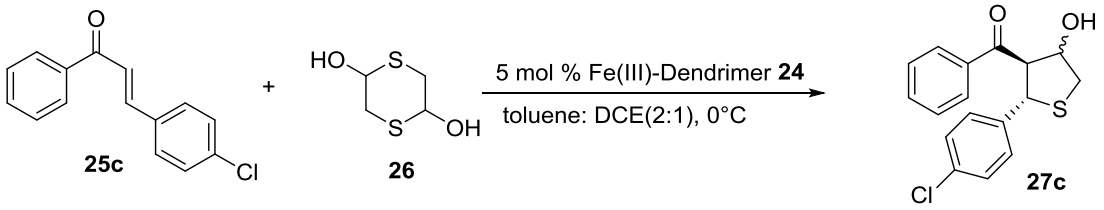
entry[a]	substrate	time (h)	product	yield (%)[b]	er[c]
1	 **25a**	60	 **27a**	65	74:26
2	 **25b**	60	 **27b**	58	77:23
3	 **25c**	60	 **27c**	74	82:18
4	 **25d**	60	 **27d**	72	83:17
5	 **25e**	60	 **27e**	55	84:16

[a] Reaction conditions: chalcone **25** (0.20 mmol), 1,4-dithiane-2,5-diol **26** (0.20 mmol), dendrimer **24** (5 mol %), $FeCl_3$ (15 mol %), toluene:DCE (2:1) (2 mL), 60 h at 0°C.

[b] Isolated yield.

[c] Determined by HPLC analysis with Chiralcel OJ and AD-H using *n*-hexane/2-propanol.

Table 3: Recyclability of the Dendrimer Catalyst[a]



Entry	Catalyst recoverability	Yield (%)[b]	er[c]
1	95	74	82:18
2	95	72	82:18
3	94	72	82:18

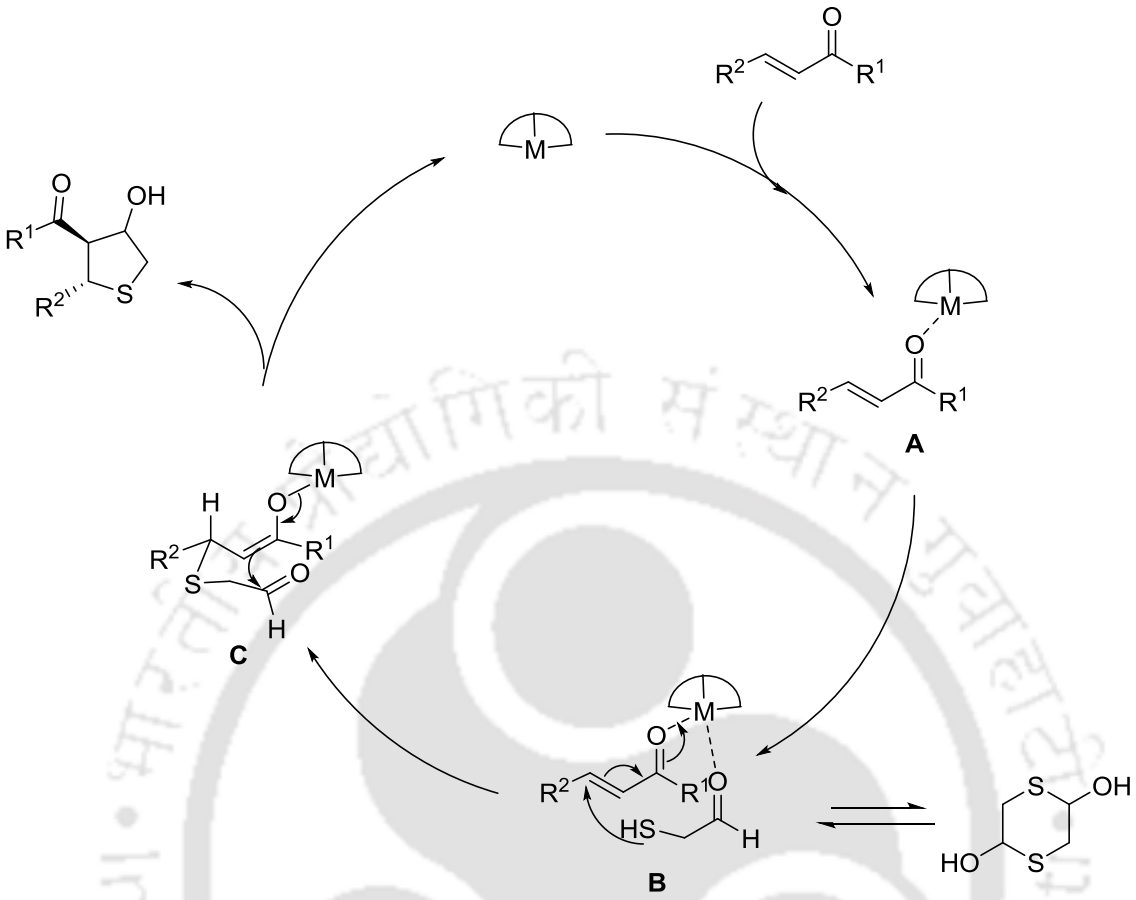
[a] Reaction conditions: chalcone **25c** (0.20 mmol), 1,4-dithiane-2,5-diol **26** (0.20 mmol), Fe(III)-dendrimer **24** (5 mol %), toluene:DCE (2:1) (2 mL), 60 h at 0°C.

[b] Isolated yield.

[c] Determined by HPLC analysis with Chiralcel OJ and AD-H using *n*-hexane/2-propanol.

The advantage of this dendrimer catalyst is that the catalyst can be recovered and recycled (Table 3). After completion, the reaction mixture was concentrated (ca. 0.5 mL) and the resultant solution was treated with a 1:1 mixture of hexane : diethylether (ca. 2 mL). The precipitated out Fe(III) dendrimer catalyst was filtered, dried and reused for the fresh reaction of chalcone **25c** with 1,4-dithiane-2,5-diol **26**. This process was repeated for three runs and the reaction afforded the target trisubstituted tetrahydrothiophenes **27c** in 72-74% yields and 82:18 er. These results clearly suggest that the catalyst can be recovered and reused without loss of activity and selectivity.

The proposed catalytic cycle is shown in Scheme 18. Co-ordination of chalcone with catalyst may give the intermediate **A** that may chelate with 2-mercaptoacetaldehyde to give the intermediate **B**. Intermolcular Michael addition can give the intermediate **C** that can undergo aldol condensation to yield the target trisubstituted tetrahydrothiophene to complete the catalytic cycle.



Scheme 18. Proposed Catalytic Cycle

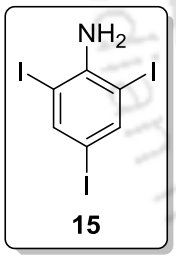
In conclusion, the synthesis and application of chiral iron dendrimeric catalyst derived derived from tridentate *tert*-leucinol is demonstrated for enantioselective domino synthesis of trisubstituted tertahydrothiophenes. The reactivity and selectivity of dendrimer Fe(III)-catalyst was similar to that of the monomer catalyst. The system provides the advantages of simplified product isolation, easy recovery and recyclability of the dendrimer Fe(III)-catalyst.

4.3 Experimental Section

General Information. All reactions were carried out in oven-dried glassware under nitrogen atmosphere. Aldehyde, acetophenone, aniline, 2-*tert*-butylphenol, trimethylsilylacetylene, CuI (99.99 %), $Pd(PPh_3)_2Cl_2$ (99.99 %), PPh_3 and 1,4-Dithiane-2,5-diol (97%) purchased from Aldrich, *tert*-leucinol purchased from SRL, and $NaBH_4$ (95%) and $NaNO_2$ purchased

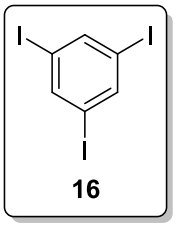
from Merck were used as received. Solvents were purchased from Rankem and purified prior to use by standard procedure.[20] Column chromatography was carried out with Rankem 60–120 mesh silica gel. Analytical TLC was performed with Rankem silica gel G and GF 254 plates. NMR spectra were recorded using DRX-400 Varian spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) and Bruker Avance III 600 MHz spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C) using $CDCl_3$ as solvent and Me_4Si as an internal standard and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. Chemical shifts (δ) are reported relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR). Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were obtained using Perkin–Elmer spectrum one spectrometer. Optical rotations were measured with a Rudolph Autpol II automatic polarimeter in the solvent indicated. HRMS mass was analyzed with Agilent Q-TOF 6500. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OJ and AD-H columns.

Synthesis of Dendrimer 24.



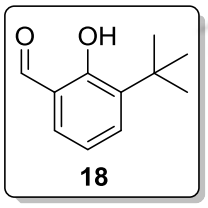
15

2,4,6-Triiodoaniline 15.[21] Freshly distilled aniline (1 mL, 11 mmol) was dissolved in con. HCl (50 mL) and the solution is diluted with water (700 mL). To this solution $KICl_2$ (7.8 g, 33 mmol) was added portion wise with vigorous stirring at 20 °C. After completion of the reaction (3 h), the product was filtered out and recrystallized from hexane. Brown solid; yield (4.361 g, 87%); Mp: 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 2H), 4.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 143.6, 87.5, 87.1; FT-IR (KBr): 3454, 3058, 3022, 2930, 2865, 1682, 1596, 1579, 1488, 1447, 1361, 1321, 1271, 1215, 1149, 1094, 1035, 1010, 973, 933, 914, 875, 846, 787, 768, 745, 696, 653, 593 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_6H_4I_3N$ 471.7551, found 471.7552.



16

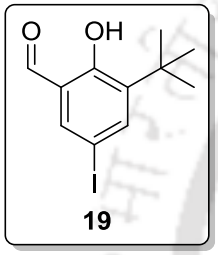
1,3,5-Triiodobenzene 16.[22] Finely powdered $NaNO_2$ (2.2 g, 32 mmol) was slowly added to sulfuric acid (4 mL) with stirring. Then it was cooled in an ice bath and a solution of 2,4,6-triiodoaniline (3.3 g, 7 mmol) in glacial acetic acid (135 mL) was added drop wise. After stirring for 30 minutes, the resulting solution was added drop wise to a suspension of copper(I)oxide (2.9 g) in dry ethanol (70 mL) with vigorous stirring for 15 minutes. This reaction mixture was brought to boiling and stirred for 4 h until evolution of N_2 completely ceases. Then, the reaction mixture was cooled to room temperature and poured into ice water 300 mL, extracted with benzene (3x50 mL), dried with Na_2SO_4 and the solvent was evaporated in rotary evaporator. The crude product was recrystallized from benzene. Colourless solid; yield (2.67 g, 84%); Mp: 182-183°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 144.6, 95.4; FT-IR (KBr): 3392, 3085, 3055, 3026, 2032, 2852, 1962, 1908, 1814, 1678, 1631, 1597, 1579, 1508, 1447, 1412, 1374, 1349, 1305, 1280, 1214, 1157, 1124, 1072, 1039, 1015, 978, 933, 908, 883, 870, 859, 819, 759, 737, 692, 651, 633, 617, 539 cm^{-1}; HRMS (APCI) m/z: $[M]^+$ calcd for $C_6H_3I_3$ 455.7369, found 455.7369.



18

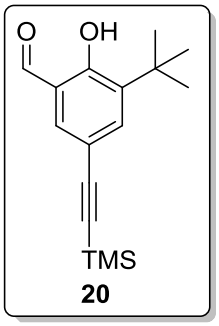
3-(*Tert*-butyl)-2-hydroxybenzaldehyde 18.[23] To a stirred solution of 2-*tert*-butylphenol **17** (5 g, 33.3 mmol) and 2,6-dimethylpyridine (2.5 g, 13.33 mmol) in toluene (30 mL) at ambient temperature, $SnCl_4$ (0.4 mL, 3.33 mmol) was added. After 0.2 h, the reaction mixture was treated with paraformaldehyde (2.2 g, 33.3 mmol) and the resultant yellow solution was heated at 100 ^oC for 10 h. The reaction mixture was then cooled to ambient temperature and transferred into a 250 mL flask having 100 mL water. The *p*H 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 **18** as yellow liquid in 85 % (5.1 g) yield. Pale yellow oil; yield (5.06 g, 85%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.80 (s, 1H), 9.87 (s, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 1.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.3, 161.3, 138.3, 134.3, 132.1, 120.8, 119.4, 35.0, 29.36; FT-IR (neat): 3449, 3059, 2933, 2848, 1681, 1596, 1579, 1567, 1469, 1447, 1395, 1368, 1323, 1268, 1218, 1181, 1149, 1070, 1024, 974, 932, 878, 783, 739, 694, 669, 649, 590, 552, 515 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{14}O_2$ 179.1067, found 179.1068.

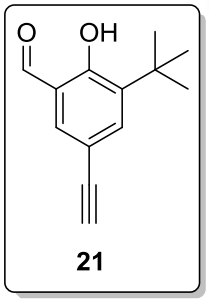


19

3-(*Tert*-butyl)-2-hydroxy-5-iodobenzaldehyde 19.[15] To a stirred solution of 3-*tert*-butyl-2-hydroxybenzaldehyde **18** (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 at ambient temperature. After refluxing for 5 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (30 mL), 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 **19**. Pale yellow solid; yield (2.95 g, 97%); Mp: 43-44 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.73 (s, 1H), 9.79 (s, 1H), 7.71(d, J = 1.8 Hz, 1H), 7.69 (s, 1H), 1.38 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.0, 160.9, 142.6, 141.3, 140.1, 122.5, 80.8, 35.1, 29.1; FT-IR (KBr): 2999, 2960, 2912, 2870, 2734, 1656, 1600, 1482, 1463, 1431, 1393, 1364, 1304, 1272, 1216, 1197, 1166, 1121, 1024, 952, 931, 905, 870, 859, 797, 769, 750, 706, 689, 575, 561, 535, 513 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{13}IO_2$ 305.0033, found 305.0034.

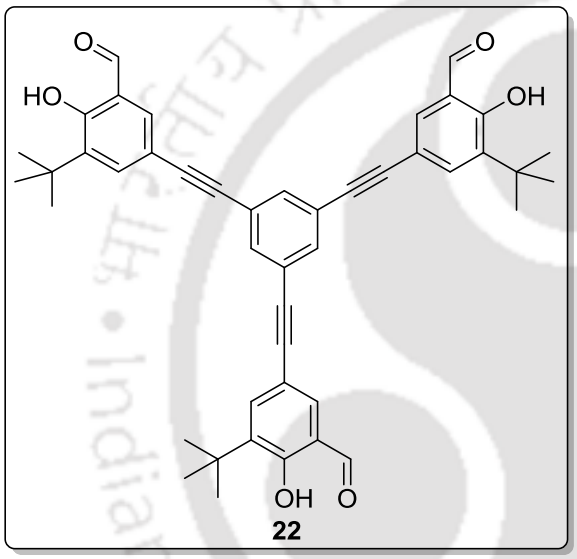


3-(*Tert*-butyl)-2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde 20.[12] To a stirred solution of the aldehyde **19** (1.66 g, 5.45 mmol), Pd $(PPh_3)_2Cl_2$ (115 mg, 3 mol %) and PPh_3 (21 mg, 2 mol %) in dry THF (20 mL) at ambient temperature, $^{i}Pr_2NEt$ (1.9 mL, 10.9 mmol) and trimethylsilylacetylene (0.85 mL, 6 mmol) were added. After 0.2 h, the reaction mixture was treated with CuI (40 mg, 4 mol %) and the resultant dark brown solution was refluxed for 4 h. Then the solvent was evaporated and the residue was dissolved in Et_2O. The solution was passed through a short pad of celite and the filtrate was evaporated under reduced pressure to give yellow oil which was purified on silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent to give **20**. Yellow oil; yield (1.47 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.92 (s, 1H), 9.83 (s, 1H), 7.58 (dd, J = 12.8, 2.4 Hz, 2H), 1.40 (s, 9H), 0.26(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 161.4, 138.8, 135.7, 137.4, 120.3, 114.2, 104.0, 93.1, 34.9, 29.1; FT-IR (neat): 3007, 2965, 2151, 1653, 1605, 1442, 1414, 1320, 1268, 1153, 1030, 981, 930, 888, 857 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{22}O_2Si$ 275.1462, found 275.1462.



3-(*Tert*-butyl)-5-ethynyl-2-hydroxybenzaldehyde 21.[12] To a stirred solution of the aldehyde **20** (1 g, 5.65 mmol) in dry MeOH (15 mL) at ambient temperature, KF (0.410 g, 7 mmol) was added. After 1 h, the salt was filtered and the filtrate was evaporated under reduced pressure to afford a residue which was treated with water (8 mL) and CH_2Cl_2 (25 mL). The organic layer was separated and the aqueous solution was further extracted with CH_2Cl_2 (3 x 8 mL). The combined organic solution was dried (Na_2SO_4) and

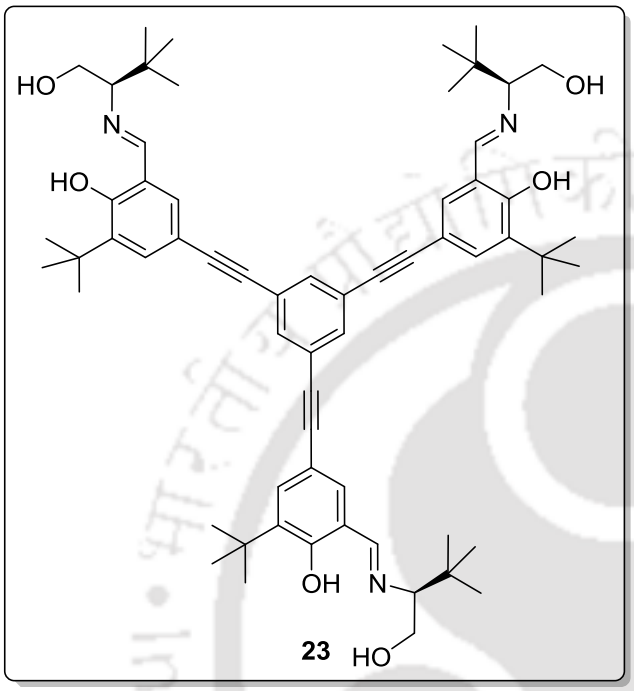
evaporated to give a residue which was purified on silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent to provide **21**. Orange oil; Mp: 57-58 °C; yield (858 mg, 75%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.93 (s, 1H), 9.83 (s, 1H), 7.61 (s, 1H), 7.57 (d, J = 1.2 Hz 1H), 3.02 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.8, 161.7, 139.1, 137.6, 135.9, 120.5, 113.2, 82.8, 76.4, 35.1, 29.2; FT-IR (neat): 3338, 3056, 2938, 1673, 1595, 1580, 1503, 1447, 1411, 1357, 1330, 1300, 1282, 1222, 1214, 1148, 1070, 1036, 1012, 974, 944, 927, 882, 869, 842, 815, 768, 752, 736, 689, 616, 595, 541 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{14}O_2$ 203.1067, found 203.1068.



22

5,5',5''-(Benzene-1,3,5-triyltris(ethyne-2,1-diyl))tris(3-(*tert*-butyl)-2-hydroxybenzaldehyde) 22.[24] To a stirred solution of the aldehyde **21** (815 g, 4.03 mmol), 1,3,5-triiodobenzene **16** (593 mg, 1.3 mmol), $Pd(PPh_3)_2Cl_2$ (85 mg, 3 mol %) and PPh_3 (21 mg, 2 mol %) in dry THF (20 mL) at ambient temperature, $^{i}Pr_2NEt$ (2.8 mL, 16 mmol) was added. After 0.2 h, the reaction mixture was treated with CuI (40 mg, 4 mol %) and the resultant dark brown solution was refluxed for 12 h. The solvent was then evaporated and the residue was dissolved in Et_2O. The solution was passed through a short pad of celite and the filtrate was evaporated under reduced pressure to give yellow solid which was purified on silica gel column chromatography using hexane and ethyl acetate (19:1) as eluent to give **22**. Pale yellow solid; Mp: 136-138 °C; yield (512 mg, 58%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 11.96 (s, 3H), 9.88 (s, 3H), 7.66-7.64 (m, 6H), 7.61 (d, J = 2.4 Hz, 3H), 1.44 (s, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 161.8, 139.2, 137.1, 135.5, 134.0, 124.2, 120.7, 114.0, 89.0, 87.0, 35.2, 29.3; FT-IR (KBr): 3454, 3059, 2933, 1680,

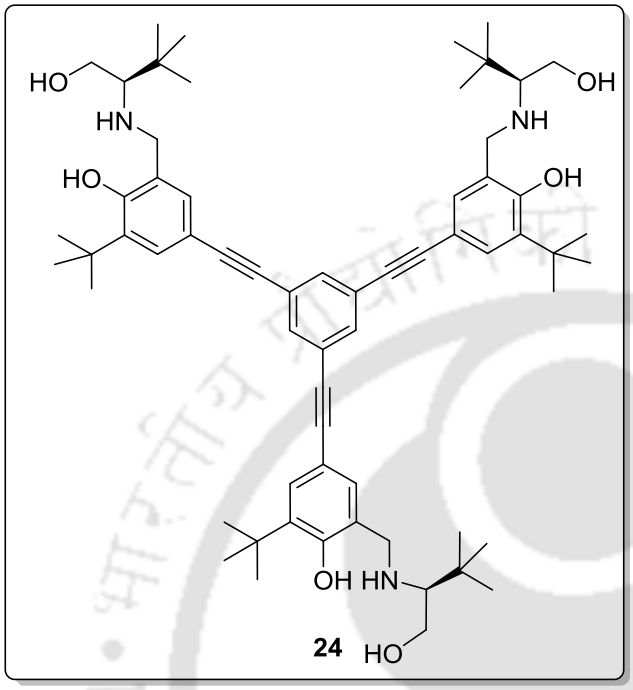
1595, 1579, 1486, 1447, 1405, 1364, 1323, 1289, 1268, 1219, 1180, 1149, 1101, 1072, 1033, 1009, 972, 931, 897, 876, 820, 782, 743, 695, 687, 647, 608, 542 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{45}H_{42}O_6$ 679.3054, found 679.3058.



23

4,4'-((5-((3-(*tert*-Butyl)-4-hydroxy-5-((*E*)-(((*R*)-1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)phenyl)ethynyl)-1,3-phenylene)bis(ethyne-2,1-diyl))bis(2-(*tert*-butyl)-6-((*E*)-(((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)phenol) 23. To a stirred solution of aldehyde (238 mg, 0.35 mmol) in chloroform (4 mL) (*S*)-*tert*-leucinol (135 mg, 1.16 mmol) in chloroform (2mL) was added slowly at room temperature and the reaction mixture was stirred at 50 °C for 4 h. After completion the solvents were removed using rotary evaporator and the residue was purified on silica gel column chromatography using hexane and ethyl acetate (9:1) to give **23**. Yellow solid; yield (300 mg, 88%); Mp: 114-116 °C; $[\alpha]_D^{29}$ = -130.2 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.26 (s, 3H), 8.34 (s, 3H), 7.59 (s, 3H), 7.50 (d, *J* = 1.2 Hz, 3H), 7.37 (d, *J* = 1.8 Hz, 3H), 3.98-3.96 (m, 3H), 3.79-3.74 (m, 3H), 2.98-2.96 (m, 3H), 1.45 (s, 27H), 0.99 (s, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 158.5, 140.8, 138.5, 133.8, 125.0, 124.9, 118.5, 112.1, 90.6, 86.4, 81.9, 62.7, 34.9, 33.4, 29.3, 27.3; FT-IR (KBr): 3472, 2962, 2903, 2871, 1630, 1468, 1438, 1390, 1361, 1270, 1252, 1240, 1203, 1173, 1134, 1085, 1062,

1037, 982, 878, 862, 829, 803, 772, 731, 712, 644 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{63}H81N_3O_6$ 976.6198, found 976.6201.

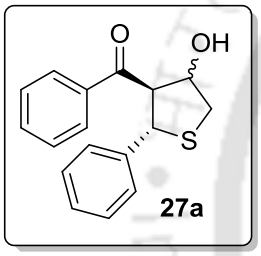


24

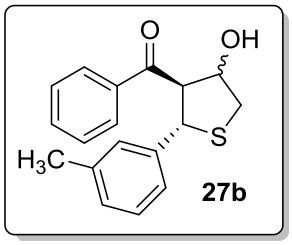
4,4'-((5-((3-(*tert*-Butyl)-4-hydroxy-5-((((*R*)-1-hydroxy-3,3-dimethylbutan-2-yl)amino)methyl)phenyl)ethynyl)-1,3-phenylene)bis(ethyne-2,1-diyl))bis(2-(*tert*-butyl)-6-((((*S*)-1-hydroxy-3,3-dimethylbutan-2-yl)amino)methyl)phenol) 24. To a stirred solution of imine (254 mg, 0.26 mmol) in 5 mL of MeOH : THF (2:3) at 0 °C, $NaBH_4$ (0.5 mmol) was added at portion wise. The reaction mixture was further stirred for 3 h at ambient conditions and quenched with 1N HCl. The solvent was evaporated and the residue was extracted with chloroform (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 (17:3) to give **24**. Pale yellow solid; Mp: 128-131 °C; yield (234 mg, 92%); $[\alpha]_D^{29}$ = +65 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 13.57 (s, 3H), 7.59 (s, 3H), 7.32 (d, J = 1.2 Hz, 3H), 6.98 (d, J = 1.6 Hz, 3H), 4.15 (d, J = 12.8 Hz, 3H), 3.93 (dd, J = 11.3, 3.6 Hz,, 6H), 3.71 (dd, J = 11.3, 4.8 Hz, 3H), 2.36-2.34 (m, 3H) 1.43 (s, 27H), 1.01 (s, 27H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 140.9, 138.3, 133.5, 121.5, 121.3, 121.0, 118.2, 90.5, 86.2, 67.4, 61.5, 53.8, 34.6, 34.3, 29.6, 27.8; FT-IR (KBr): 3470, 2949, 2928, 2881, 2859, 1774, 1709, 1586, 1495, 1465, 1385,

1371, 1334, 1188, 1127, 1100, 1040, 1012, 915, 871, 817, 724, 691, 640, 570, 531 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{63}H_{87}N_3O_6$ 982.6668, found 982.6670.

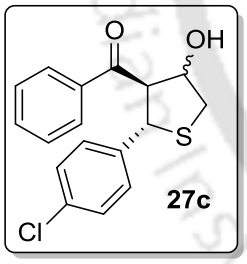
General Procedure for the Synthesis of Tetrahydrothiophenes. A mixture of dendrimer **24** (9.9 mg, 5 mol %) and $FeCl_3$ (4.8 mg, 15 mol %) in 2 mL of toluene : CH_2Cl_2 (2:1) was stirred at room temperature for 10 minutes, then it was cooled to 0 °C. Subsequently, chalcone (0.2 mmol) and 1,4-dithian-2,5-diol (0.2 mmol) were added and the reaction mixture was stirred at 0 °C for 60 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. The reaction mixture was then evaporated on a rotary evaporator to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate (4:1) as eluent.



((2*S*,3*R*)-4-Hydroxy-2-phenyltetrahydrothiophen-3-yl)(phenyl) methanone 27a. White solid; yield (37 mg, 64%); Mp: 106-108 °C; $[\alpha]_D^{29}$ = +90.8 (c = 0.4, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.68-7.67 (d, *J* = 7.8 Hz, 2H), 7.51-7.48 (m, 1H), 7.45-7.44 (m, 2H), 7.35-7.32 (m, 2H), 7.23-7.21 (m, 2H), 7.17-7.14 (m, 1H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.92 (d, *J* = 3.0 Hz, 1H), 4.08 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.60-3.57(m, 2H), 3.18-3.16 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.2, 139.8, 136.8, 133.9, 128.8, 128.5, 128.2, 127.9, 127.6, 77.6, 62.9, 52.1, 41.3; FT-IR (KBr): 3452, 3055, 3024, 2922, 1680, 1596, 1579, 1512, 1447, 1364, 1327, 1299, 1271, 1221, 1180, 1150, 1110, 1035, 1009, 973, 876, 815, 798, 770, 748, 731, 694, 650, 633, 546, 509 cm^{-1}; HPLC: Chiralcel OJ, *n*-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 11.7 min, 20.5 min; 77:23 er; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}O_2S$ 285.0944, found 285.0944.

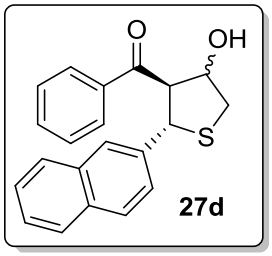


((2*S*,3*R*)-4-Hydroxy-2-(m-tolyl)tetrahydrothiophen-3-yl)(phenyl)methanone 27b. White solid; yield (39 mg, 64%); Mp: 106-108 °C; $[\alpha]_D^{29}$ = +63.4 (c = 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.8, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 6.0 2H), 7.11 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 4.92 (d, *J* = 3.6 Hz, 1H), 4.08 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.57-3.56 (m, 2H), 3.17 (dd, *J* = 12.0, 1.2 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.7, 139.7, 138.2, 136.8, 133.7, 128.8, 128.6, 128.5, 128.5, 128.3, 125.0, 77.5, 62.9, 51.7, 41.1, 21.3; FT-IR (KBr): 3462, 3086, 3060, 3028, 2934, 1680, 1596, 1579, 1540, 1492, 1447, 1391, 1332, 1271, 1220, 1181, 1150, 1075, 1028, 1009, 972, 932, 876, 783, 747, 729, 696, 652, 618, 585, 546 cm^{-1}; HPLC: Chiralcel OJ, n-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 8.1 min, 14.2 min; 77:23 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{18}O_2S$ 299.1100, found 299.1100.

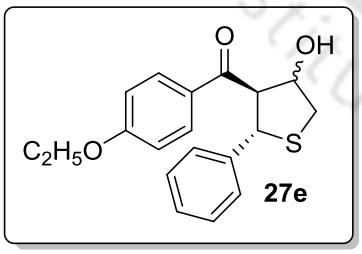


((2*S*,3*R*)-2-(4-Chlorophenyl)-4-hydroxytetrahydrothiophen-3-yl)(phenyl)methanone 27c. Colourless solid; yield (41 mg, 64%); Mp: 134-135 °C; $[\alpha]_D^{29}$ = +103.2 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.55-7.51 (m, 1H), 7.41-7.35 (m, 4H), 7.21-7.18 (m, 2H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 3.2 Hz, 1H), 4.03 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.60 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.44 (d, *J* = 4.4 Hz, 1H), 3.17 (dd, *J* = 11.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 138.4, 136.6, 134.0, 133.4, 129.5, 128.8, 128.8, 128.4, 77.5, 63.2, 51.1, 41.2; FT-IR (KBr): 3440, 3061, 3022, 2933, 1963, 1917, 1681, 1596, 1578, 1490, 1463, 1447, 1383, 1324, 1273, 1217, 1181, 1150, 1108, 1034, 1010, 974, 931, 877, 798, 774, 738, 695, 651, 601, 557 cm^{-1}; HPLC: Chiralcel OJ, *n*-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 01.0 mL/min, retention

time: 10.9 min, 25.0 min; 81:18 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}ClO_2S$ 319.0554, found 319.0556.



((2*S*,3*R*)-4-Hydroxy-2-(naphthalen-2-yl)tetrahydrothiophen-3-yl)(phenyl)methanone 27d. Colourless solid; yield (43 mg, 64%); Mp: 126-128 °C; $[\alpha]_D^{29}$ = +91.4 (c = 0.88, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.77-7.69 (m, 5H), 7.65 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.44-7.40 (m, 3H), 7.28 (dd, *J* = 15.6, 7.8 Hz, 2H), 5.37 (d, *J* = 10.2 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.22 (dd, J = 10.2, 3.0 Hz, 1H), 3.65 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.52 (d, *J* = 3.6 Hz, 1H), 3.23 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.8, 137.0, 136.8, 133.9, 133.3, 133.0, 128.7, 128.4, 127.9, 127.7, 127.3, 126.3, 126.1, 125.5, 77.7, 62.8, 52.1, 41.5; FT-IR (KBr): 3440, 3061, 2932, 2914, 2885, 2848, 1677, 1597, 1580, 1509, 1447, 1367, 1324, 1272, 1223, 1155, 1097, 1078, 1026, 1012, 973, 930, 899, 873, 831, 810, 773, 751, 732, 693, 650, 623, 540, 519 cm^{-1}; HPLC: Chiralcel OJ, *n*-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 0.8 mL/min, retention time: 11.9 min, 18.4 min; 83:17 er; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{18}O_2S$ 335.1100, Found 335.1101



(4-Ethoxyphenyl)((2*S*,3*R*)-4-hydroxy-2-phenyltetrahydrothiophen-3-yl)methanone 27e. Colourless solid; yield (50 mg, 64%); Mp: 131-133 °C; $[\alpha]_D^{29}$ = +44.3 (c = 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.16-7.14 (m, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 1.8 Hz, 1H), 4.06-3.98 (m, 4H), 3.55 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.18 (d, *J* = 11.4 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150

MHz, $CDCl_3$): δ 198.8, 163.6, 139.6, 130.9, 129.4, 128.6, 128.1, 127.7, 114.2, 77.5, 63.9, 61.7, 52.5, 41.1, 14.6; FT-IR (KBr): 3448, 2977, 2932, 1665, 1598, 1573, 1510, 1496, 1476, 1453, 1421, 1395, 1331, 1306, 1262, 1227, 1171, 1119, 1040, 972, 919, 874, 837, 828, 804, 738, 699, 680, 668, 646, 631, 624, 617 cm^{-1}; HPLC: Chiralcel AD-H, *n*-hexane/isopropanol (90:10), λ_{max}: 254 nm, flow rate: 1.0 mL/min, retention time: 13.1 min, 20.3 min; 85:15 ee; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}O_3S$ 329.1206, found 329.1205.

4.4 References

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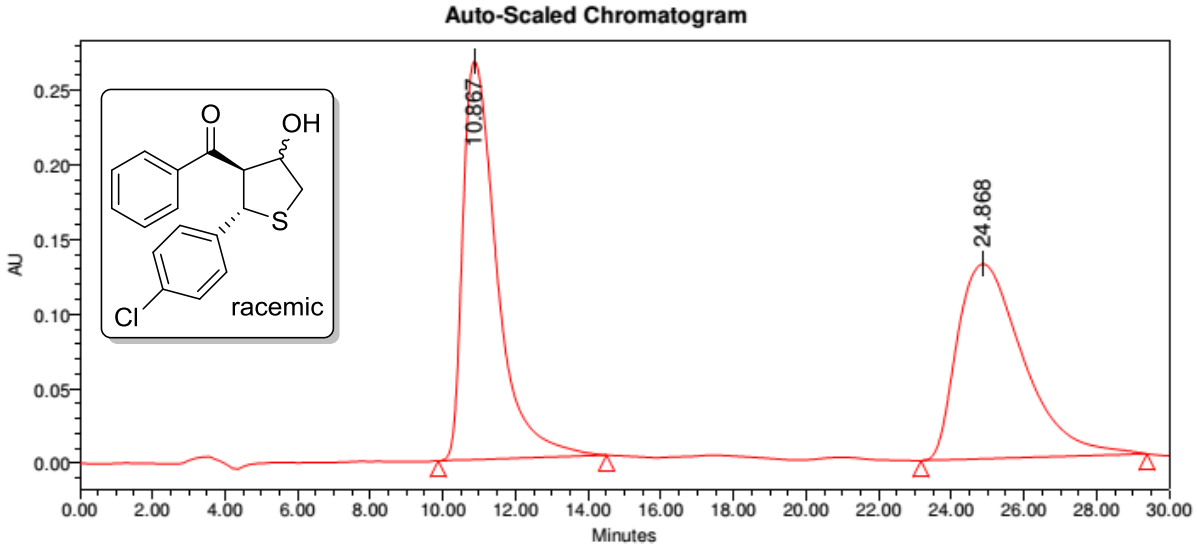
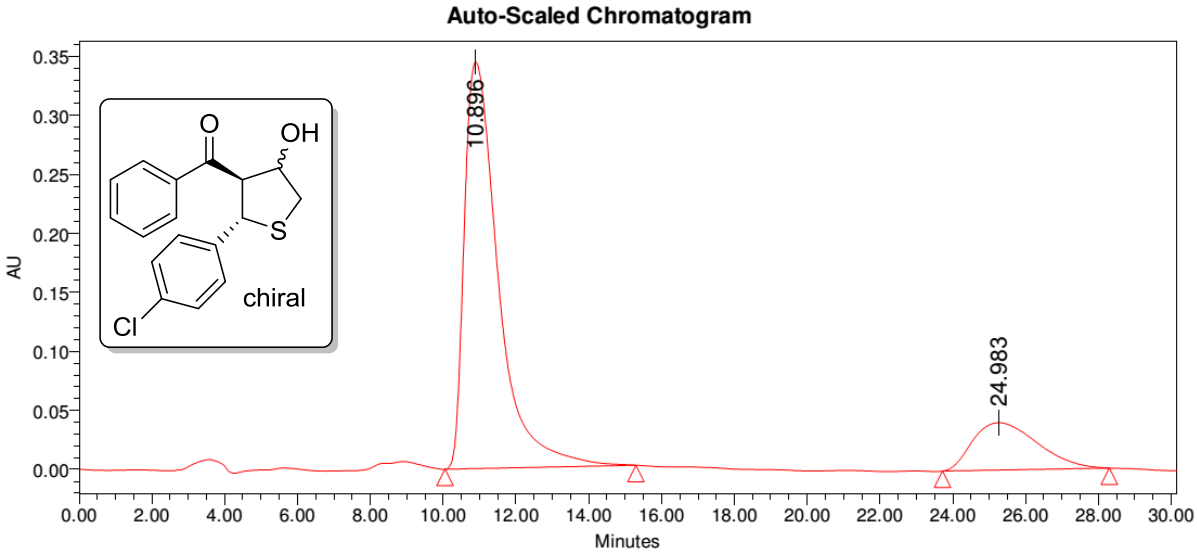
4.5 Selected HPLC Chromatograms



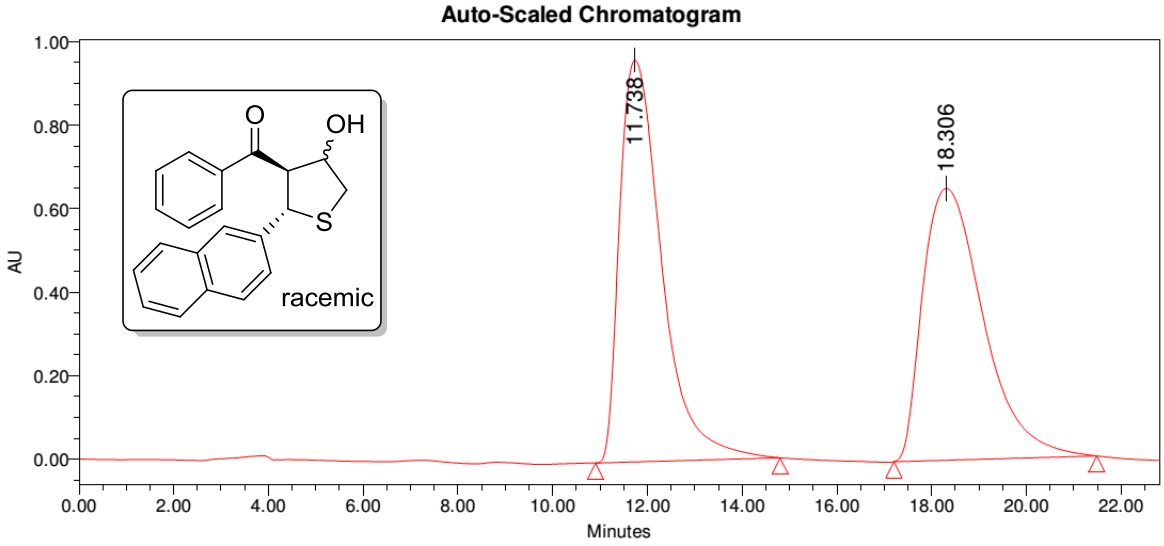
Peak Results

	RT	Height (μV)	% Area
1	10.867	267193	51.30
2	24.868	130461	48.70



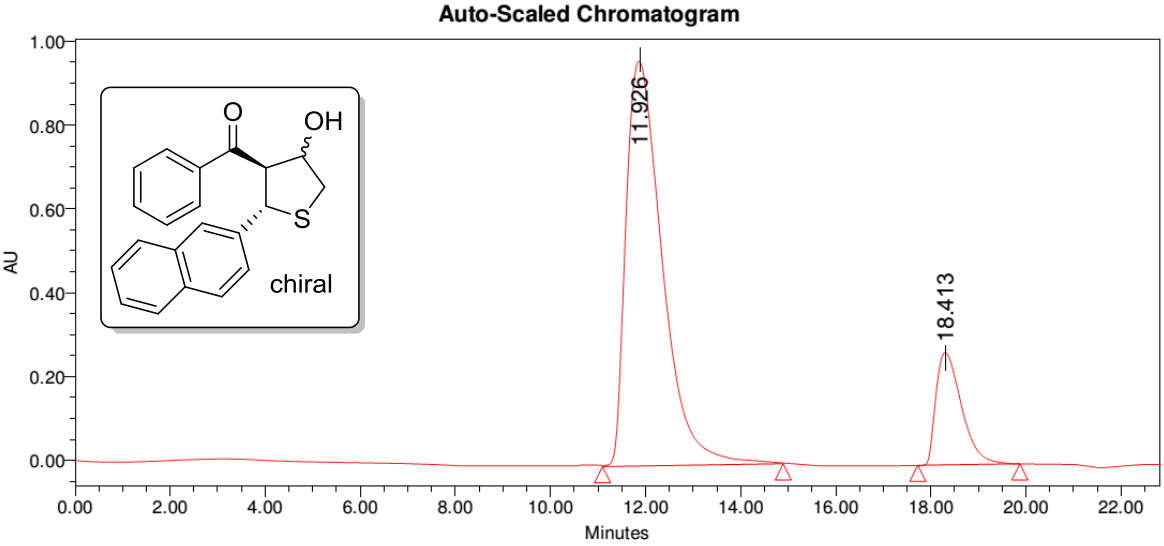
Peak Results

	RT	Height (μV)	% Area
1	10.896	344540	81.83
2	24.983	40116	18.17



Peak Results

	RT	Height (μV)	% Area
1	11.738	963271	50.62
2	18.306	651334	49.38



Peak Results

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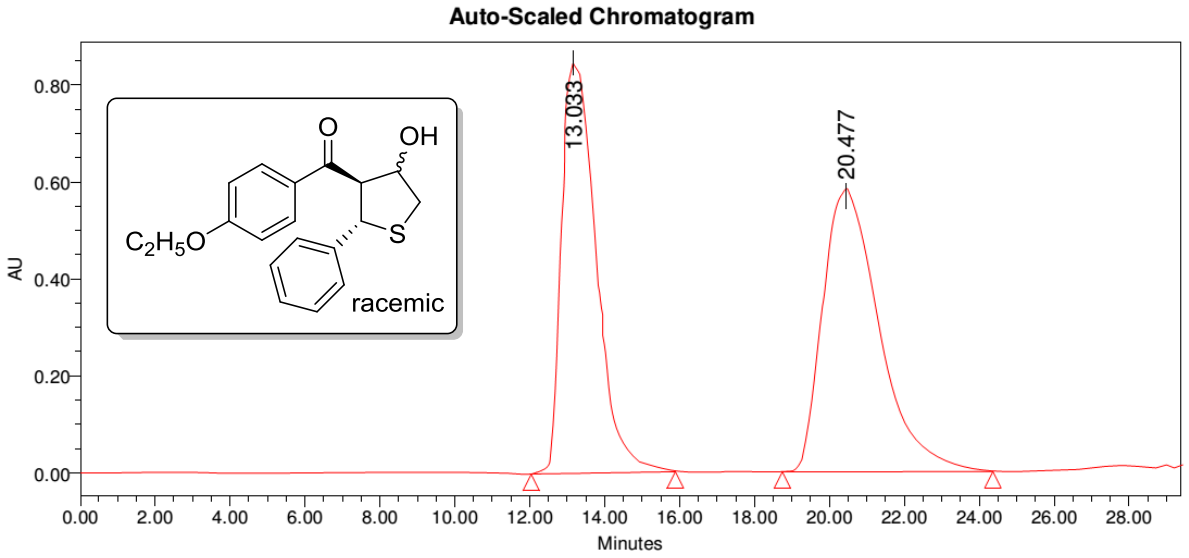
1	11.926	963271	82.62
2	18.413	194334	17.38



Peak Results

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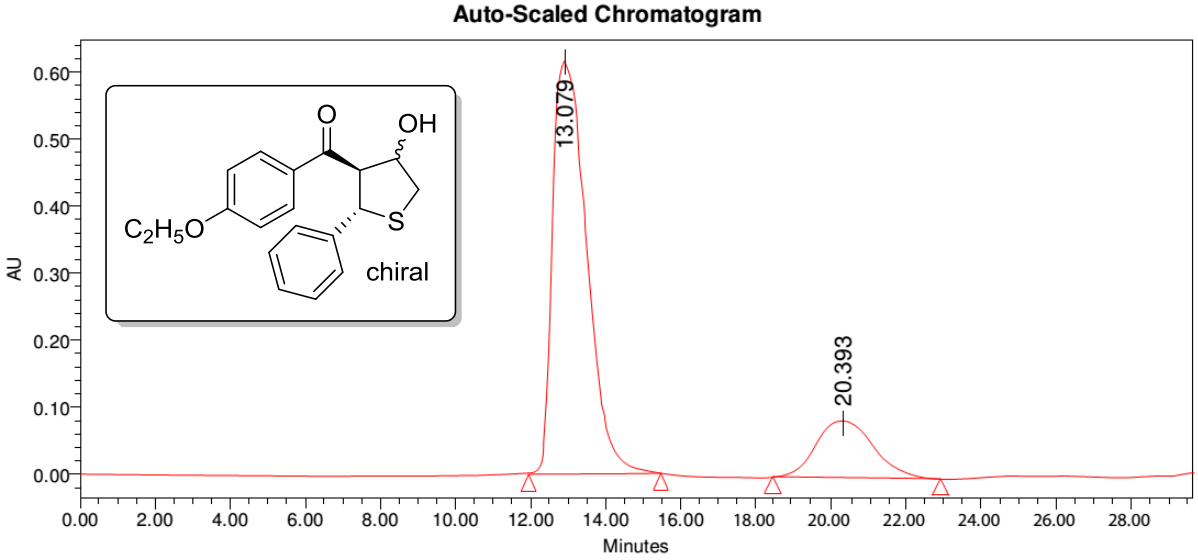
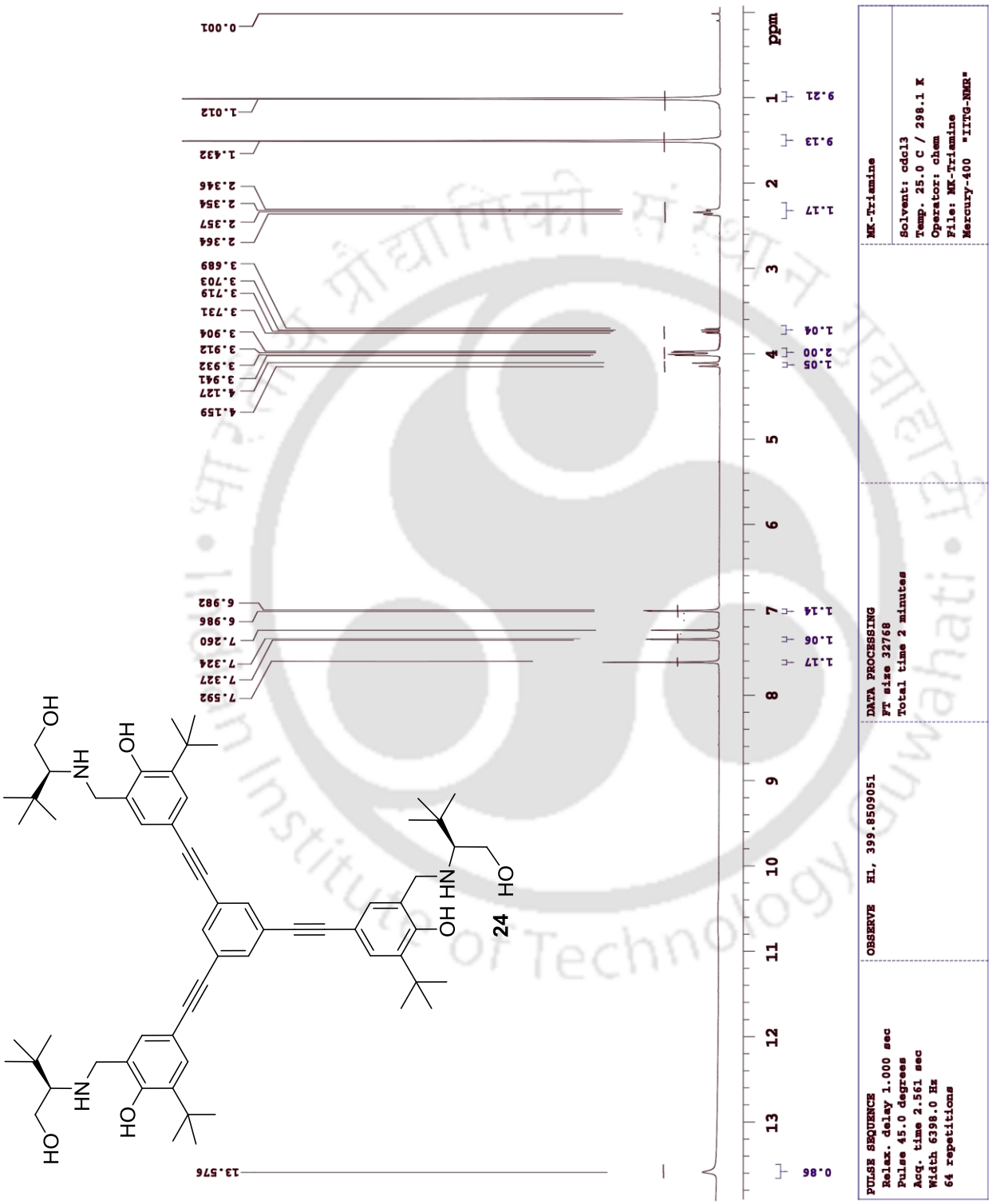
1	13.033	841510	50.45
2	20.477	468527	49.55

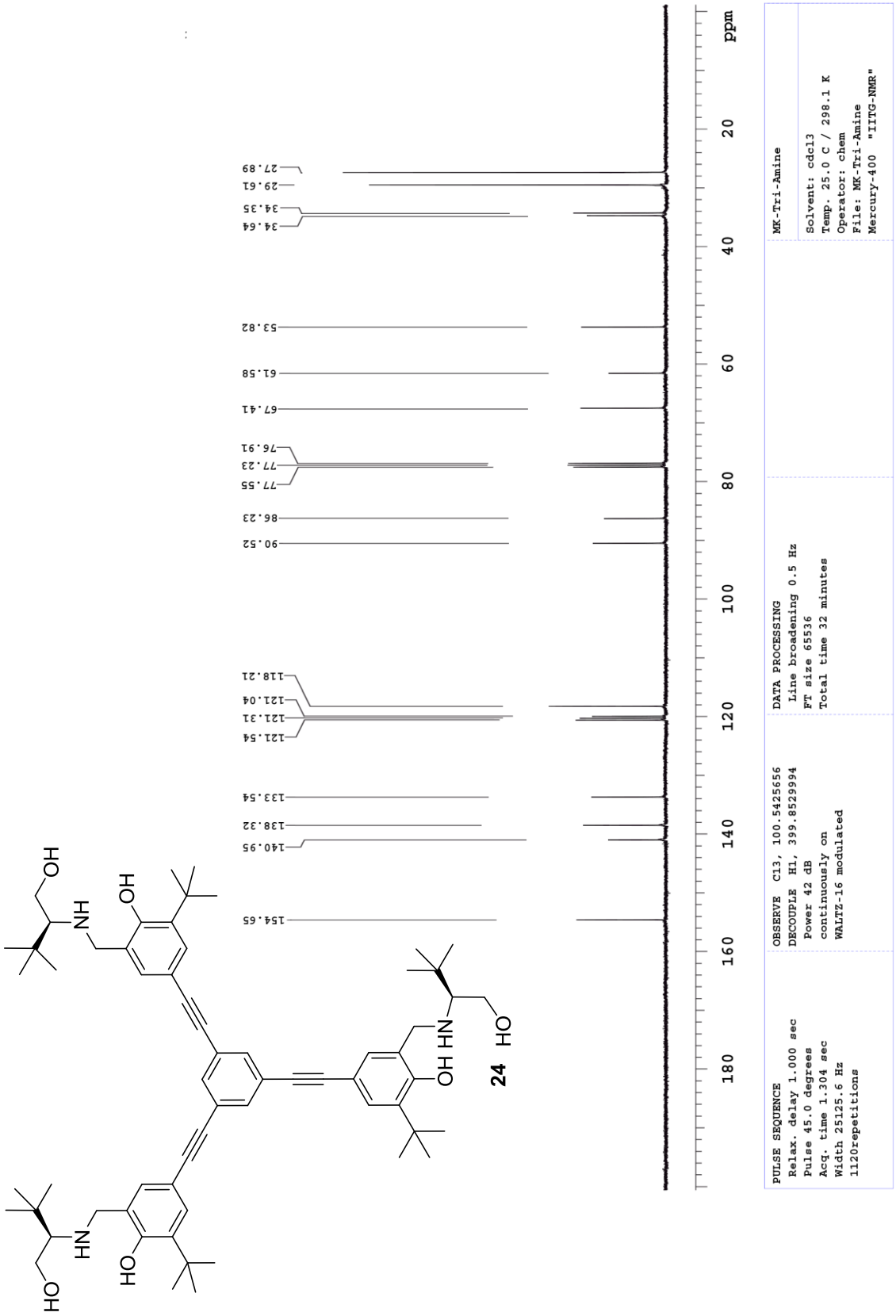


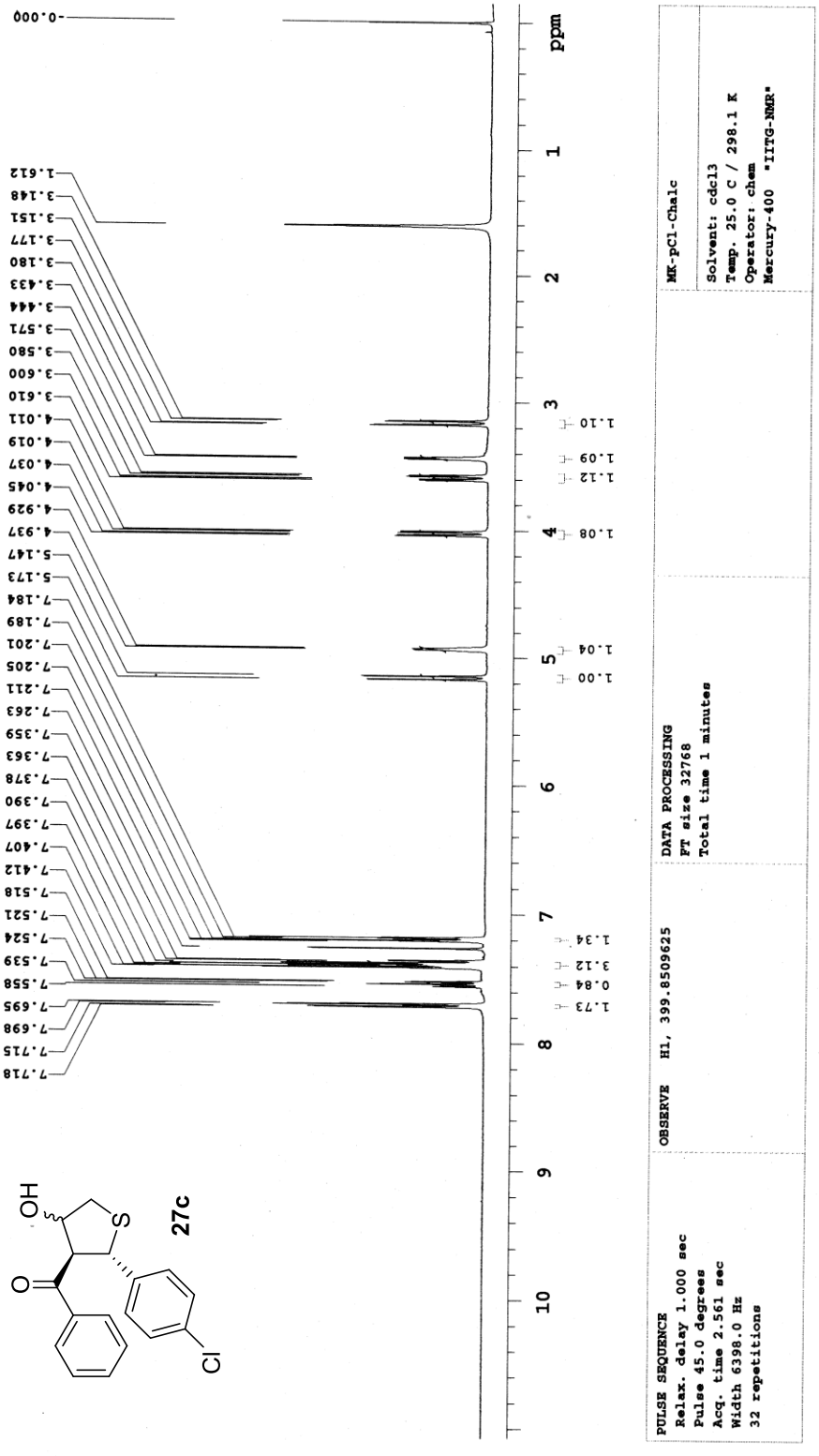
Peak Results

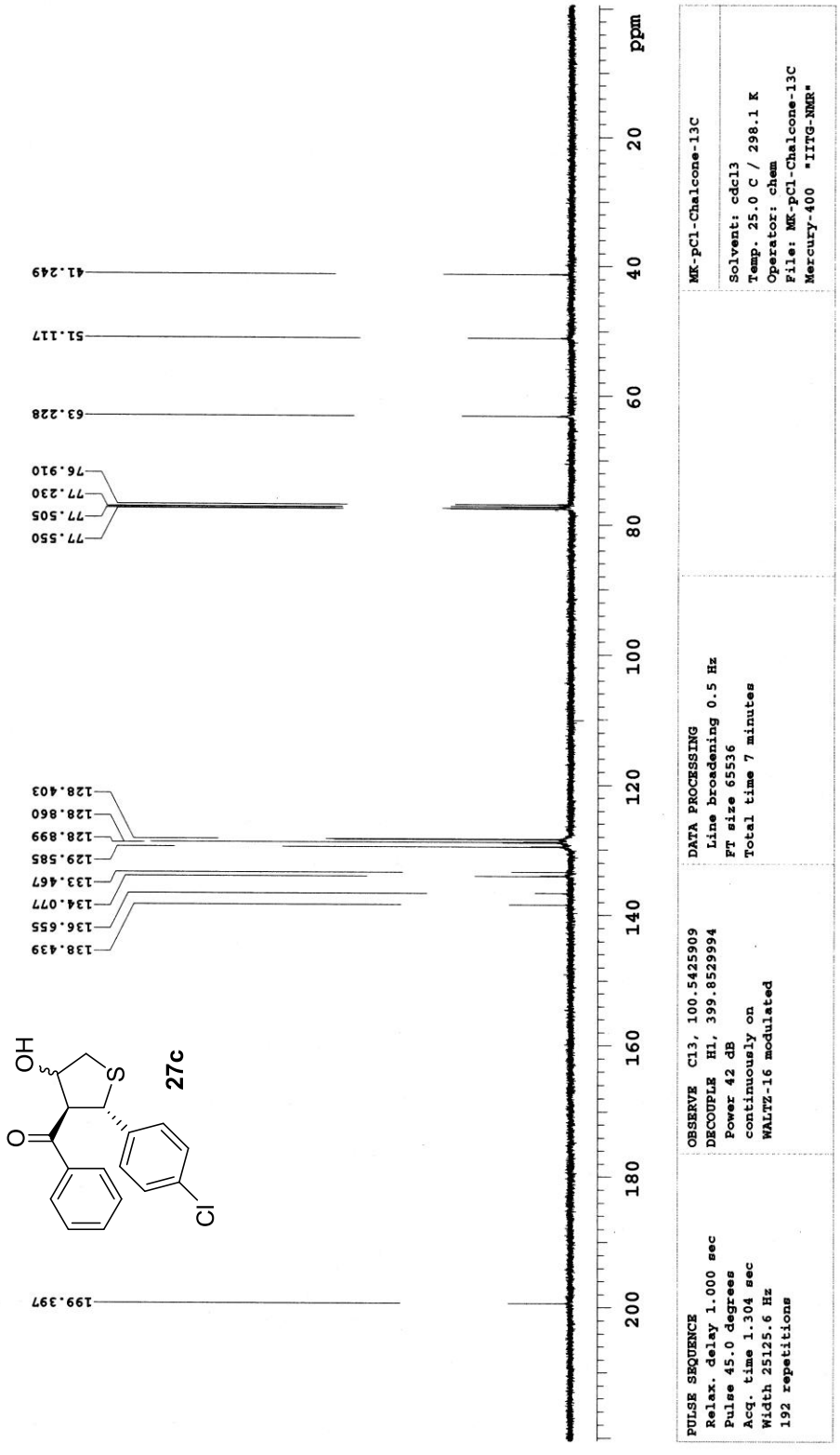
	RT	Height (μV)	% Area
1	13.079	616201	84.62
2	20.393	77694	15.38

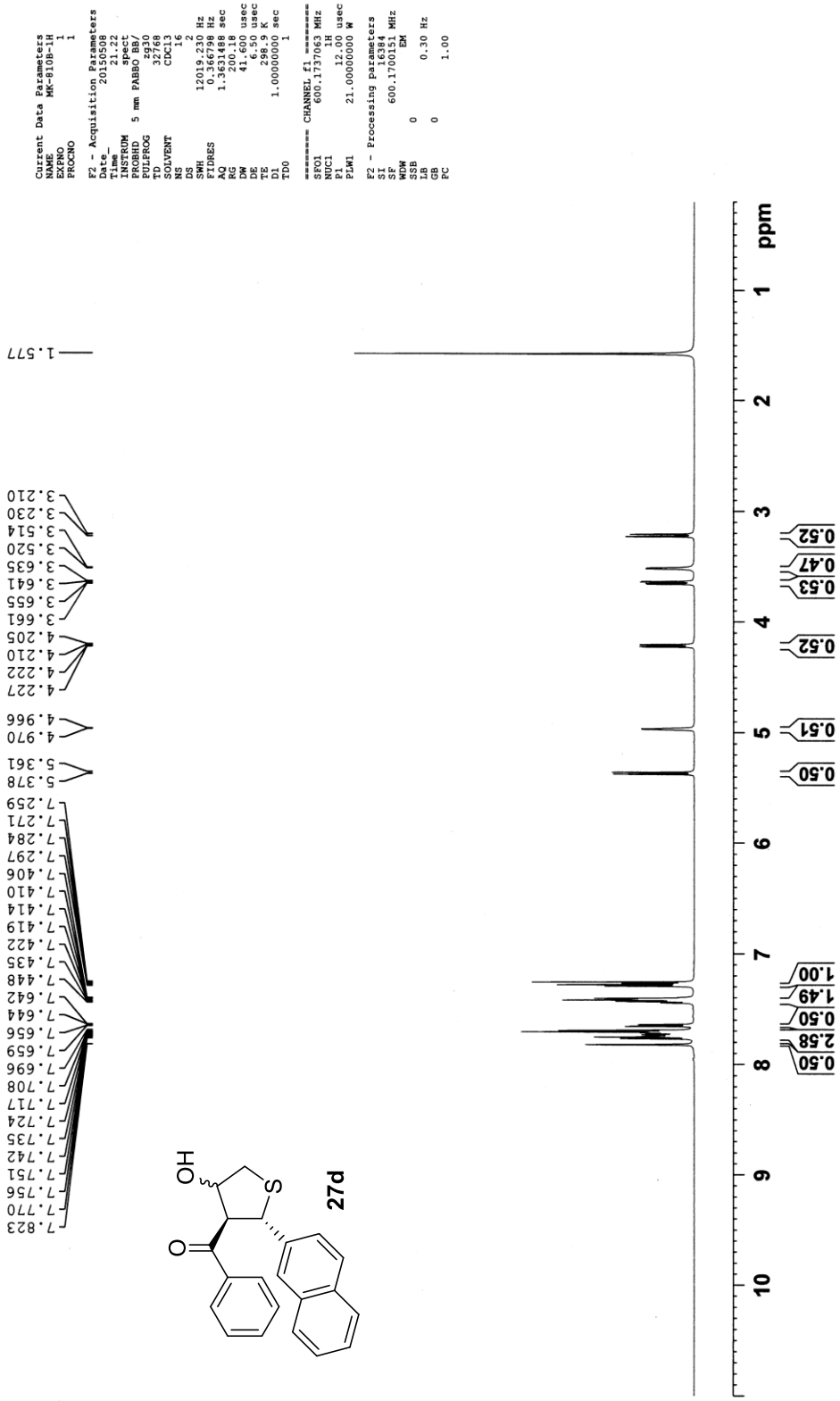
4.6 Selected NMR (^{1}H and ^{13}C) Spectra

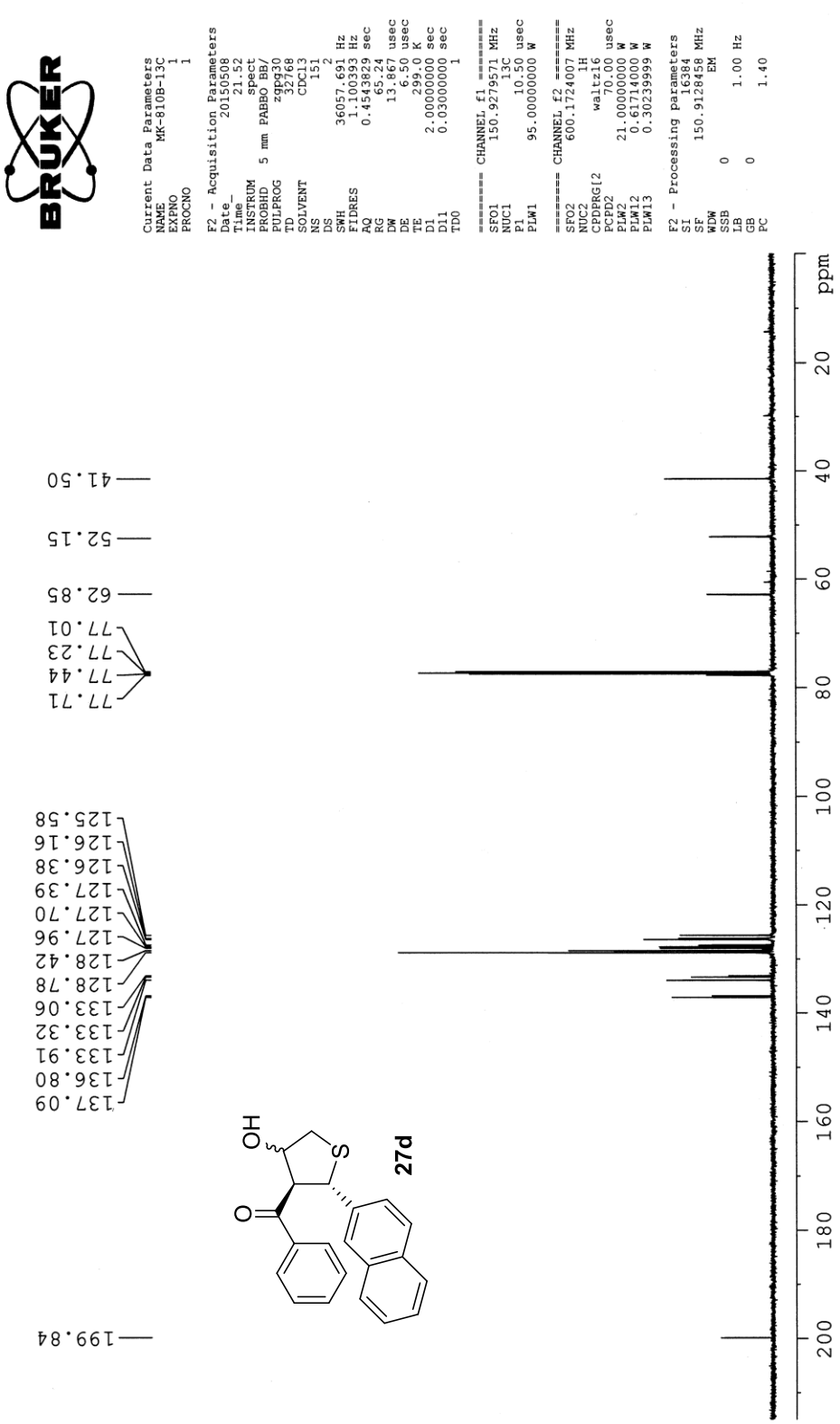


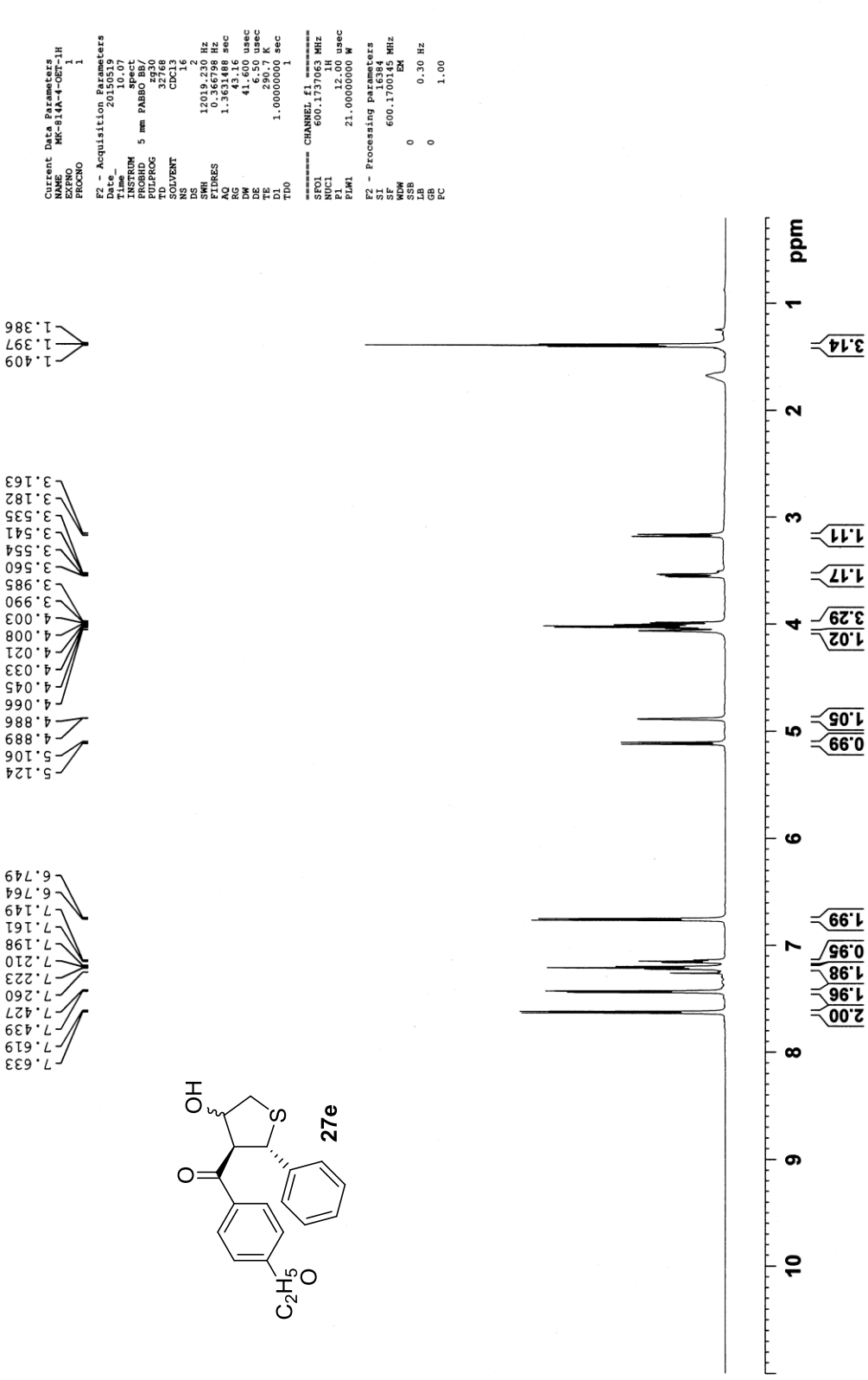


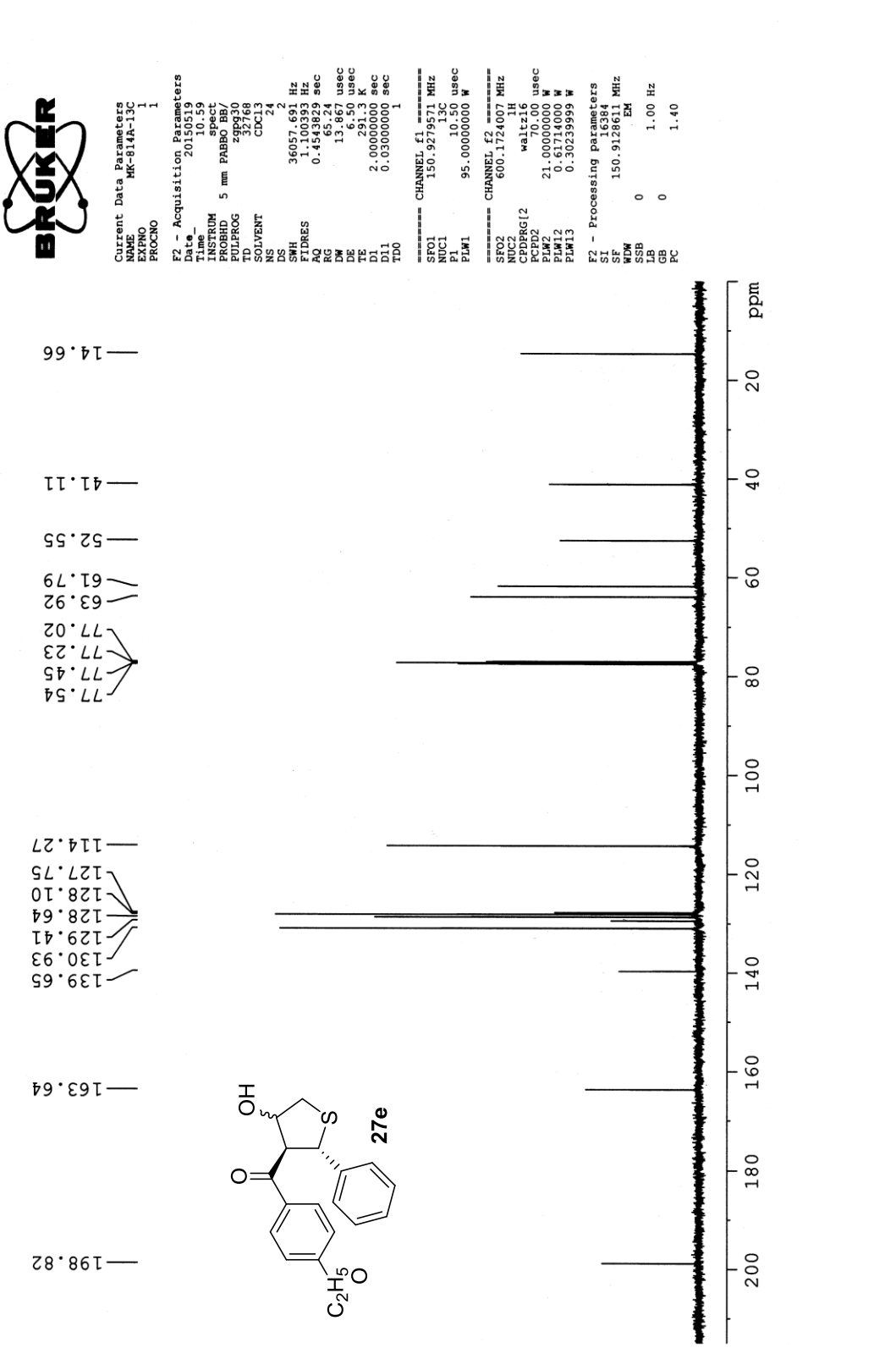












Conclusions

Chapter I describes the synthetic oppurtunities of chiral tetradentate salen, salan, salelan ligands and tridentate *β*-aminoalcohol derived ligands on asymmetric metal catalysis.

Chapter II presents the sythesis of chiral Cu(II)-coplexes bearing salen, salan, salalen and salalan ligands and their application towards enantioselective nitroaldol reaction. The reaction is mild and afforded aryl, heteroaryl, naphthyl and alkyl *β*-nitroalcohols in high enantioselectivities at room temperature without any additivies.

Chapter III demonstrates the synthesis of chiral tetradentate salen ligand and tridentate *β*-aminoalcohol derived ligands for Fe-catalyzed enantioselective thia-Michael-aldol cascade reaction. The reaction proceeded readily between aryl, heteroaryl, alkyl chalcones and 1,4-dithiane-2,5-diol in the presence of Fe-catalyst to afford the corresponding trisubstituted tetrahydrothiophenes in good enantioselectivities.

Chapter IV describes the synthesis of chiral *β*-aminoalcohol derived tridentate dendrimer and their application as a recoverable and recyclable catalyst has been demonstrated for enantioselective thia-Michael-aldol cascade reaction. The system provides the advantages of simplified product isolation, easy recovery and recyclability of the dendrimer Fe(III)-catalyst.

List of Publications

1 Polyaniline.
Punniyamurthy, T.; **Kannan, M.** *Encyclopedia of Reagents for Organic Synthesis*, **2012**.

2 Effect of Ligand N,N-Substituents on the Reactivity of Chiral Copper(II) Salalen, Salan, and Salalan Complexes Toward Asymmetric Nitroaldol Reactions.
Kannan, M.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2014**, *25*, 1331.

3 Expedient Synthesis of Tetrasubstituted Pyrroles *via* Copper-Catalyzed Cascade Inter-/Intramolecular Cyclization of 1,3-Enynes Carry a Nitro Group with Amines
Bharathiraja, G.; **Sengoden, M.**; Kannan, M.; Punniyamurthy, T. *Org. Biomol. Chem.* **2015**, *13*, 2786.

4 Transition-Metal-Mediated Carbon-Heteroatom Cross-Coupling. An Overview; in Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds; Kannan, M.; **Sengoden M.**; Punniyamurthy, T. (Mortier, J. Ed.) Wiley, Hoboken, NJ. 2015, pp. 547-586.

5 Chiral Iron-Catalyzed Enantioselective Synthesis of Tetrahydrothiophenes.
Kannan, M.; Bharathiraja, G.; Punniyamurthy, T. *Manuscript under Preparation.*

Conferences

1 Ligand Substituents Effect on Copper Catalyzed Enantioselective Nitroaldol Reaction, **Kannan M.**; Punniyamurthy, T. *National Conference on Frontiers in Chemical Sciences*, organized by IIT Guwahati, December 04-06, 2014.