Review Paper:
Chiral Salen-metal complexes in asymmetric synthesis

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Abstract
Asymmetric synthesis is the centre of modern organic chemistry as it is the key process in chemical synthesis. Particularly grasped its importance in pharmaceuticals, since the different enantiomers (or) diastereomers differ in the activity. Chiral metal-complexes are the most flexible asymmetric inducers and have wide range of applicability.

Of them, Schiff bases so called salen-ligands co-ordinated with different metals, generate different complexes with broad applicability in asymmetric induction. These are capable in directing the stereoselectivity of the required isomer in good yields. This review mainly focuses on the applications of salen-complexes towards the stereo-controlled reaction methodologies.

Keywords: Enantioselectivity, Asymmetric induction, Salen-metal complex, Stereo controlled catalytic transformations.

Introduction
Organic synthesis is creative in its approach. It is the art of creating molecules. The main aim of organic synthesis is to construct a molecule with the stable methodologies, efficient yields and to endow it with novel structural and functional activity to address the solutions to different abnormalities. Most of the totally synthetic drugs were chiral. Often, only one enantiomer is responsible for the respective pharmacological activity and the opposite one might be a toxic or useless.

Hence, enantiomeric purity is the heart of Pharmaceutical synthesis. Recent advances in organometallic catalysis can address the enantioselectivity. Since the transition metal complexes have wide range of applications, metal mediated enantioselective reactions are the frontier areas of research in organic synthesis.

So far, conventional methods including classical resolution via diastereomers, chemical kinetic resolution, enzymatic resolution and chromatographic resolution have been employed to prepare enantiomerically pure organic compounds. Rather the use of transition metal complexes has achieved the great success towards enantioselectivity. In general, asymmetric catalysts are designed by the chelation of metal ion with a chiral organic ligand. These complexes are selected for specific reactions based on their ability to catalyse reaction and their selectivity as an asymmetric inducer. The first condition could be achieved by the presence of metal coordination site to facilitate the reactant. Asymmetric induction arises due to the chiral vicinity generated by the metal complex and the result will be the response of reaction towards complex.

Chiral Salen ligands: Salen means Schiff's base, metal complexes of the Schiff's base are referred as salen complexes. The copper complex of N,N'-Bis(salicyladehydo) ethylene diamine[9] was the first salen complex synthesized in 1889. This was the milestone for the development of salen complexes towards the efficient and enantioselective reaction methodologies. This review will focus on the recent advances in the development of these complexes towards stereo controlled catalytic transformations.
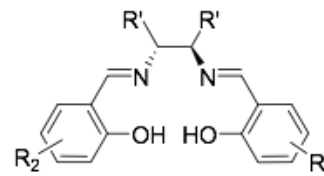
Chiral Salen ligand

Preparations: In the course of salen-complex preparation, first Schiff's base was formed by the condensation of aromatic ortho hydroxy aldehyde with a diamine in 2:1 ratio respectively. The chiral salen ligands are prepared by introducing the asymmetry via aryl component. The steric substituents on the aryl part are responsible for asymmetric induction.

Various methods have been employed for the metalation of metal Ion with a ligand to form a complex. The most often used three methods for synthesizing these complexes include (Method 1), the reaction of respective metal amide *e.g.* $M(NMe_2)_4$ with a ligand to form Bis-amido salen-metal complex followed by chlorination with trimethylsilyl chloride leading to bis-chloro salen-metal complex.

(Method 2) Metal acetates are reacted with ligands under THF reflux for complex formation. (Method 3) For early transition metals, metal halides are often used by direct exchange under basic condition (Scheme 1).

Applications: Metal complexes have been used in asymmetric synthesis since early 1990's and the need of

stereoselective reaction methodologies is everlasting. The structural features of the ligand, oxidation state of the metal and reacting confirmation of the metal complex are the responsible factors for the stereoselectivity of the product. Based on these factors, the chiral salen complexes have numerous applications in stereoselective transformations.
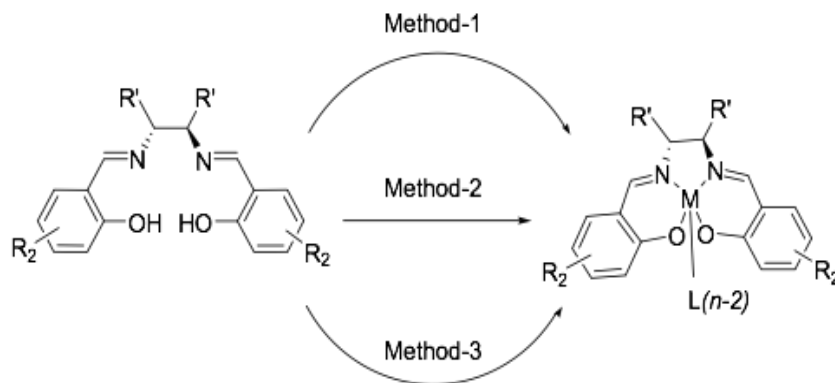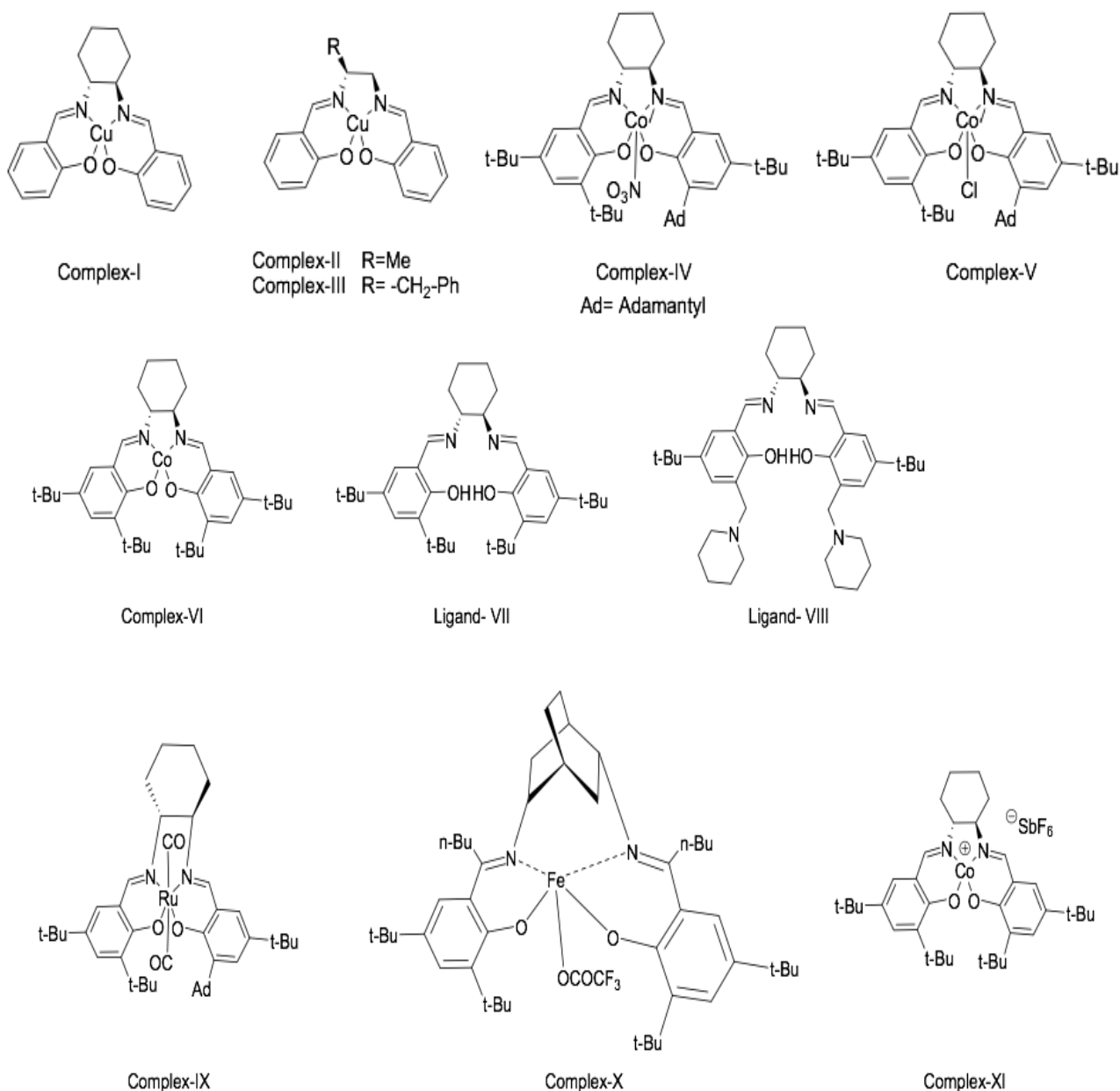

Figure 1: Metalation of salen-ligands

Scheme 1: Complexes studied

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Res. J. Chem. Environ.

Copper-salen complex catalysed asymmetric alkylation of imino esters: Symmetry of these salen complexes plays a vital role for enantioselectivity. This example has demonstrated the importance of symmetry of a complex. Imino ester was alkylated with an alkyl bromide catalysed by copper-salen complex-I with C_2-axis of symmetry resulting in 81% enantiomeric excess, whereas the salen complexes(II-III) with C_1-axis of symmetry yielded 27% enantiomeric excess (Scheme-2)[2,3].
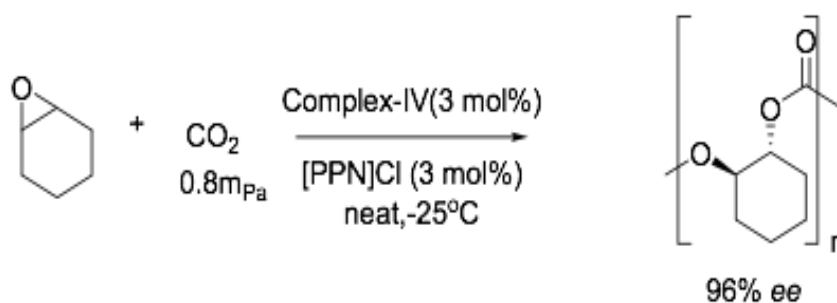
Asymmetric co-polymerization: Carbon dioxide as substrate for "CO" insertion reaction has numerous applications[22]. Chiral polycarbonate could be synthesized by the copolymerisation of monosubstituted epoxides[16,19] catalysed by cobalt salen complex-IV in which Bis (triphenylphosphine) iminium chloride was added as co-catalyst and the reaction resulted in in 96% in enantiomeric excess (Scheme 3)[21,35].
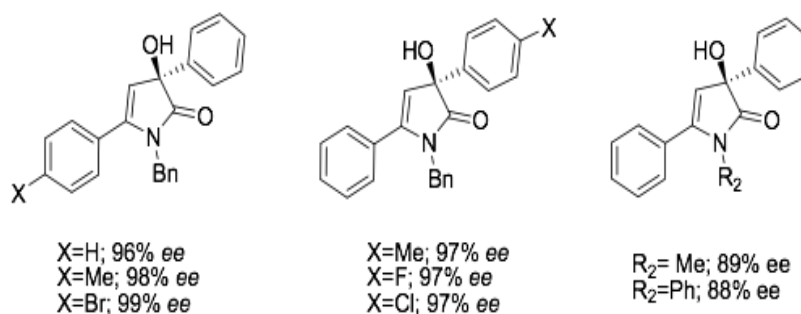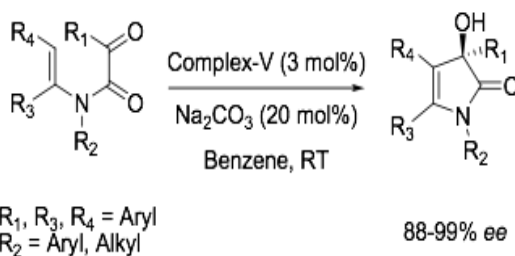
Cyclisation of α-keto enamides: For the synthesis of chiral pyrrolinones (both monocyclic and fused), the use of chromium salen complex-V has resulted in excellent enantioselective yields. α-ketone tertiary enamides cyclized[38] with complex-V in the presence of catalytic amount of sodium carbonate (Scheme 4).
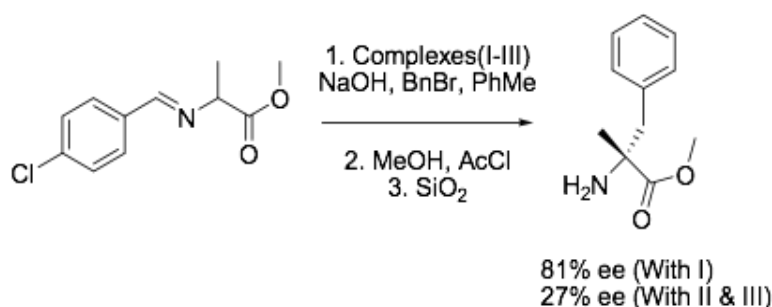
Scheme 2: Copper-salen complex catalyzed asymmetric alkylation of imino esters

Scheme 3: Asymmetric co-polymerization

R1, R3, R4 = Aryl
R2 = Aryl, Alkyl

88-99% ee

X=H; 96% *ee*
X=Me; 98% *ee*
X=Br; 99% *ee*

X=Me; 97% *ee*
X=F; 97% *ee*
X=Cl; 97% *ee*

R2= Me; 89% ee
R2=Ph; 88% ee

**Scheme 4: Cyclisation of keto enamides**

Enantioselective Baeyer-Villiger oxidation: Some general applications of organometallic catalysis are available for the enantioselective oxidation of prochiral ketones to esters and lactones.[5,7,8,12] γ-Lactones can be synthesized by the oxidation of 3-substituted cyclobutanone using cationic Cobalt-salen complex 78% enantiomeric excess product[31,32]. Bicyclic cyclobutanones catalysed by the Zirconium-salen complex yielded the corresponding lactones up to 93% enantiomeric excess[34]. Cobalt salen complex-VI was found to be non-stereoselective for cyclobutanones in organic solvents, appeared to be active by taking the complex in water with surfactant Triron X 114 and yielded the corresponding lactone in 90% enantiomeric excess (Scheme 5)[4].

Conjugate Cyanation of nitro-olefins: The addition reaction of TMSCN and nitro-olefins catalysed by Titanium salen complex-VII resulted in β-nitro nitriles with good yields up to 84% enantiomeric excess. The complex has been generated *in situ* by taking equimolar ratio of Titanium tetraisopropoxide and ligand (Scheme 6)[15].

Asymmetric Addition of Alkynes to Aldehydes: Aldehydes are being converted into chiral alcohols by the addition of alkynes catalysed by a Zinc Salen complex. The complex was generated *in situ* by reacting dimethyl zinc with ligand-VIII (Kozlowsk's Salen Ligand) containing 1-Piperidinyl methyl substituents at C_3 and $C_{3'}$ position of Benzoid Moieties. Propargylic alcohols are obtained in good yield by the addition of Phenyl acetylene to the aldehydes (Scheme 7)[24].

Asymmetric cyclopropanation of alkene with diazoacetates: Ruthenium complexes are found to be excellent catalysts for the efficient conversion of alkenes containing diazoacetates in to cyclopropyl lactones[29,30]. Ruthenium complex-IX catalysed intramolecular cyclopropanation of trans allylic diazoacetates into cyclopropyl-γ-lactones and yielded ≥ 94% *ee* (Scheme 8)[36].
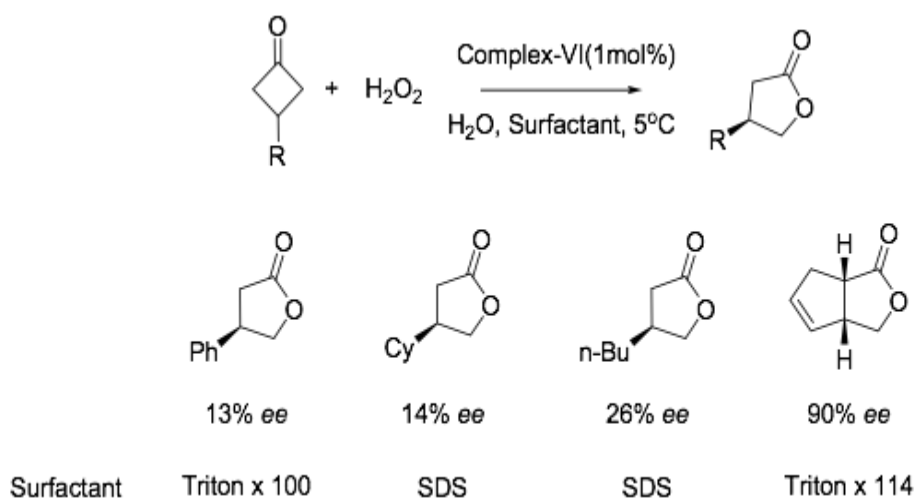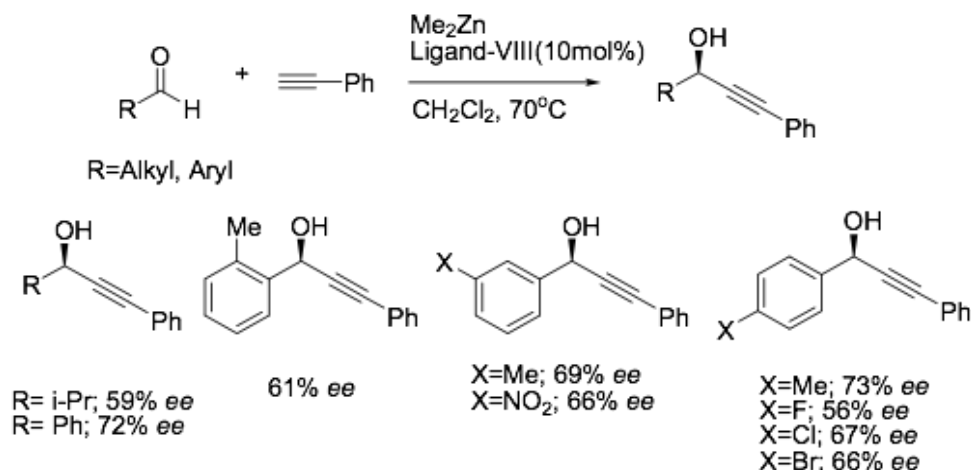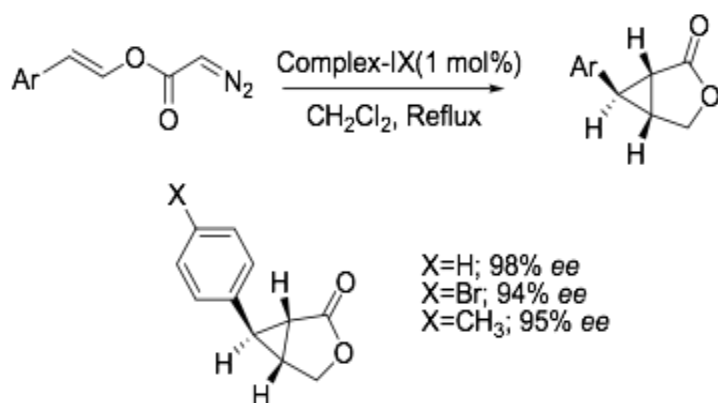

Scheme 5: Enantioselective Baeyer-Villiger oxidation
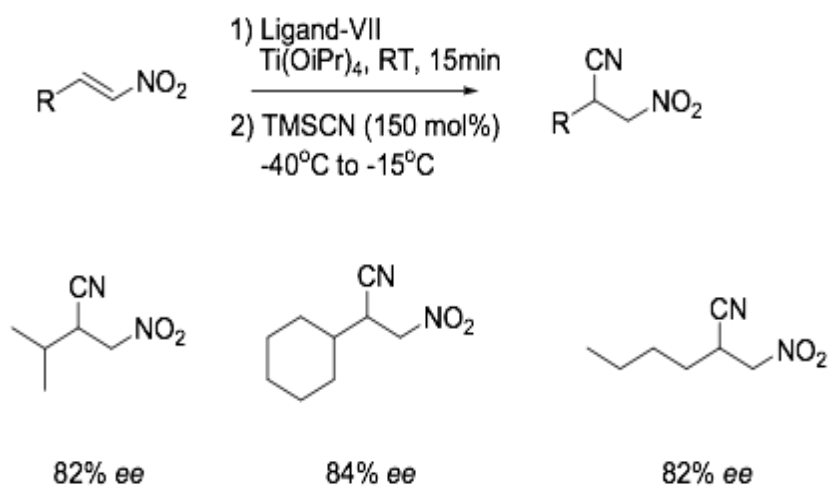
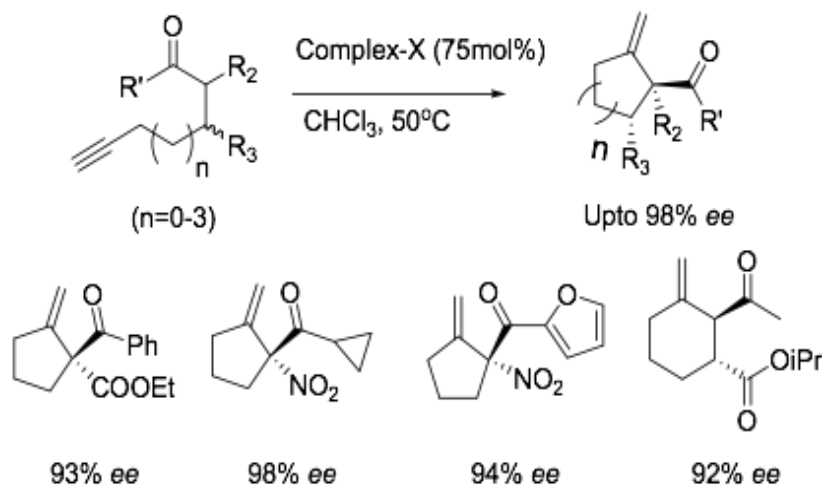(Absolute configuration of the compounds were not determined)

Scheme 6: Conjugate cyanation of nitro-olefins

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Res. J. Chem. Environ.

Scheme 7: Asymmetric Addition of Alkynes to Aldehydes

**Scheme 8: Asymmetric cyclopropanation of alkene with diazoacetates**

Scheme 9: Asymmetric Conia-Ene reaction catalyzed by Iron-salen complex

Asymmetric Conia-Ene reaction catalysed by Iron-salen complex: Enolate adds internally to carbon-carbon multiple bond to form carbocycle with quaternary centre in intramolecular Conia-Ene reaction[11]. The asymmetric induction was achieved in this reaction by introducing the catalyst made of hard and soft Lewis acids[10,17,37]. The Iron-salen complex-X catalysed cyclisation of α-functionalised ketones with inactive terminal alkyne into exo methylene substituted carbocycle with an adjacent quaternary stereo centre and yielded > 90% *ee* (Scheme 9)[23].

Cobalt Salen-complex catalysed Asymmetric Diels-Alder reaction: Diels-Alder cycloaddition is found to be an efficient transmission for the synthesis of cyclohexene with chiral centres. This was applied in natural product synthesis for the stereoselective moieties.
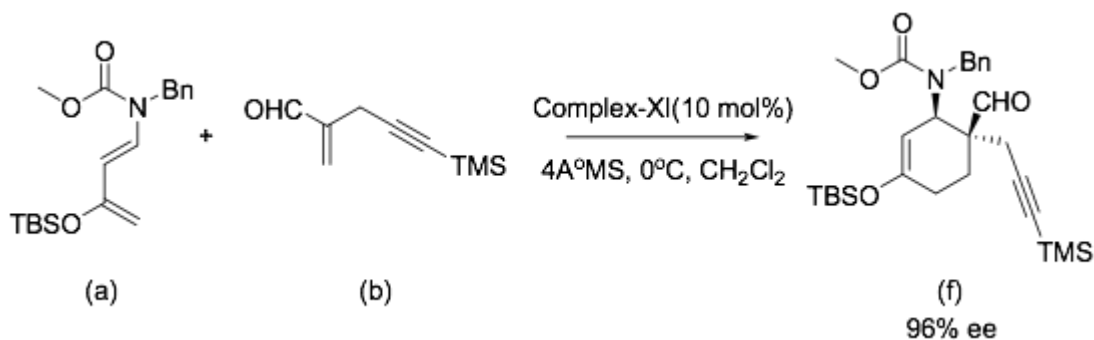
Scheme 10: Cobalt Salen-complex catalyzed Asymmetric Diels-Alder reaction
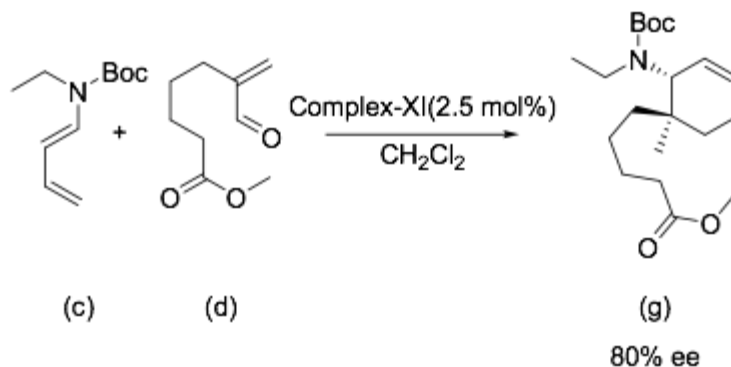
Scheme 11: Cobalt Salen-complex catalyzed Asymmetric Diels-Alder reaction

Salen-metal complexes occupied major role in catalysing the asymmetric Diels-Alder cycloaddition[6]. The Cobalt Salen complex-II catalysed the cycloaddition diene(a) with dienophile(b) and yielded the cycloadduct(F) in 96% *ee* (Scheme- 10)[14,18]. Thus formed cyclohexene derivative was converted into (-)-platencin[20]. The same complex catalysed the cycloaddition of dine(c) with dienophile(d) and yielded the cycloadduct(g) in 80% *ee* (Scheme 11)[25].

Conclusion

Asymmetric reaction methodologies are the highly important areas of study in organic synthesis due to the need of chiral compounds as drug and materials. Since 1970's, the use of chiral metal complexes as efficient catalyst and asymmetric inducers has occupied dominant role in asymmetric synthesis. As of now, wide variety of chiral ligands are available that can encapsulate with a metal ion as a salen complex. There is a better understanding of how the metal site and the structure of ligand contributes for stereoselectivity[33]. Many reactions have been developed with improved level of stereoselectivity, in which some of them have to be understood in mechanistic point of view.

This could be achieved by the in-depth study on spatial orientation of the substrates, physical properties of the metal-ligand coordination and the transition states in the process of asymmetric induction. Furthermore, the complexes in which a ligand can coordinate with different pair of metal sites are also developed[1]. This may lead to the new pathways in asymmetric synthesis. We can expect that the investigators will design new entities with the renowned

applicability. The recent developments in the synthesis of immobilised salen complexes are highly encouraged as they not only incorporate the easier separation of catalyst from the product but also support for the reusability of the catalyst[13,26-28]. The developments in this field are highly appreciable and it is captivating to think as mature field of study.

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