Chapter 1

Introduction: Synthesis and Applications of Oxazolinyl Ligands
Asymmetric catalysis is the phenomenon whereby a chiral catalyst promotes the conversion of an achiral substrate to a chiral product with a preference for the formation of one of the non-superimposable mirror image isomers (enantiomers). The demand for chiral compounds, often as single enantiomer, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavours and fragrances. This widespread demand for chiral compounds has stimulated intensive research to develop improved methods for synthesizing such compounds. Historically, enantiomerically enriched compounds were generated either by chemical transformation of an enantiomerically enriched precursor, often derived directly or indirectly from nature’s chiral pool, or by resolving a 50/50 mixture (racemic) of the two enantiomers. Both of these approaches suffer from potentially severe drawbacks, the former in requiring stoichiometric amounts of a suitable precursor and the latter in typically yielding only up to 50% of the desired enantiomer.

Catalytic asymmetric transformation is an extremely attractive and economical way for producing a large amount of optically pure materials using relatively small quantities of expensive chiral initiators. Generally asymmetric induction is achieved by the use of metal complexes of chiral ligands or by application of organocatalysts in asymmetric organic transformations. The greatest challenge in discovering new asymmetric catalysts is conducting interdisciplinary research that combines organic, inorganic, organometallic, and biomimetic chemistry. To make an efficient transition metal catalyst, the following tasks are generally required: (i) designing and synthesizing chiral ligands (ii) preparing suitable substrates (iii) catalyst precursors and metal ligand complexes (iv) standardising the reaction conditions.

In the mid 80’s Pfaltz has developed a new class of chiral bidentate $N, N$-ligands for asymmetric catalysis, the $C_2$-symmetric semicorrins\(^1\) (X = CH) or 2 [Figure 1].

![Figure 1: C_2-Symmetric ligands](image-url)
In these compounds, the two substituents at the stereogenic centres are located in close proximity to the metal centre and hence they have a distinct, direct effect on a reaction taking place in the coordination sphere. The high enantioselectivities induced by semicorrins in the copper-catalyzed cyclopropanation of olefins$^{1b-e}$ and cobalt-catalyzed conjugate reduction of $\alpha,\beta$-unsaturated carboxylic acid derivatives$^{1a,6h}$, prompted number of scientists to develop structurally related ligands such as the aza-semicorrins 1 (X = N) and 3 as well as the bis(oxazoline)s 4 - 6. Especially bis(oxazoline)s of type 6 have proven to be highly versatile ligands for the enantiocontrol of a wide range of metal-catalyzed processes.$^{1a,b,2}$

The great ability of oxazolines to bind well with metal ions makes them effective ligands in asymmetric synthesis and also the stereogenic centre is quite close to the reactive site of the catalysts. Hence the optically active oxazolines have gained paramount importance as ligands to control the stereochemistry in many asymmetric transformations.$^3$ Along with the catalysis there have been many other synthetic uses of oxazoline compounds in organic synthesis such as protecting group in organic synthesis$^4$ and a fundamental skeleton in many bioactive molecules and natural products [Figure 2].$^5$ The oxazoline structure is present as a functional group in several bioactive species known to inhibit sex pheromone production in bacteria or enzyme like chymotrypsin, cathepsin B and thrombin.

![Figure 2: Bioactive molecules with oxazoline skeleton](image)

Types of oxazoline molecules, their synthesis and applications in organic transformations will be presented in this chapter.

Several methods are known for synthesis of oxazolines from carboxylic acids$^{ba}$, carboxylic esters$^{eb}$, nitriles$^{ec}$, aldehydes$^{ed}$ and amido alcohols.$^{ec}$ Most of the methods utilize complex reagents, strongly acidic conditions and stringent reaction parameters with occasionally low yields of the reaction products. A large number of applications in asymmetric organic transformations such as Asymmetric allylic substitution, allylic oxidation, aziridination of olefins and imines, cyclopropanation, Diel-Alder /hetero Diels-Alder reaction, Mukaiyama aldol reaction, Henry Reaction, aldol reaction, diethylzinc addition to aldehydes, asymmetric Heck type reaction etc. have been well documented in the literature.$^3$
They have been divided into three major classes according to the number of oxazoline ring present in the molecule.

**Types of Oxazolines**

- Mono-Oxazolines
- Bis-Oxazolines
- Tris-Oxazolines

**Mono-Oxazolines:**

Depending upon the coordinating atoms present, generally mono oxazolines have been classified into four groups.

i) \(N,P\)-Ligands;  
ii) \(N,O\)-Ligands

iii) \(N,S\)-Ligands;  
iv) \(N,N\)-ligands

**\(N,P\)-Ligands**

Subsequent to pioneering work of Meyers and Brunner, oxazolines, readily available from amino acids, have found widespread use as chiral nonracemic ligands in asymmetric catalysis. The member of \(N,P\)-Ligands, phosphinooxazoline (PHOX) 9-11 (Figure 3) were first developed in 1993 by Pfaltz, Helmchen and Williams as highly effective non-C\(_2\)-symmetric ligands for asymmetric allylic alkylation and which have been applied with great success in a diverse range of asymmetric reactions. Schematic diagram for the preparation of the Ligands 9 and 11 are shown in [Scheme 1] and [Scheme 2].

**Figure 3:** PHOX ligands developed in 1993-1996

The schematic diagram for preparation of ligands 9 – 11 is shown below.
Scheme 1: Preparation of the PHOX ligands 9a-e and 11 developed by Pfaltz

Scheme 2. Preparation of the PHOX ligand 10 developed by Pfaltz and Helmchen

This type of PHOX ligands have also been applied for variety of asymmetric organic transformations. Few of them are discussed in this chapter.

Most commonly, the Pd-catalyzed enantioselective C-C and C-N bond-forming allylic substitutions are important area of research.\(^\text{11}\) Palladium complexes of PHOX ligands turned out to be very reactive, highly selective catalysts for the allylic substitution of 1,3-diphenyl-2-propenyl acetate 12 with range of carbon and nitrogen nucleophiles.\(^\text{12}\)

The reaction of 1,3-diphenyl-2-propenyl acetate 12 with the sodium salt of dimethyl malonate in the presence of catalytic \([(\pi-C_3H_5)\text{PdCl}_2]\) and the ligands 9a – 9e performed which afforded the allyl substituted product 13 in good yield with high enantioselectivity [Scheme 3]. The reactions were conducted at 20 °C, and were complete within 6 hours.\(^\text{9c}\) All the ligands were almost equally effective.

Scheme 3: Pd-catalyzed allylic substitution of 12 using ligands 9a-e
Mechanistic study for the understanding of the cause of enantioselective step for Pd-catalyzed allylic substitution was developed by Helmchen and Pfaltz.\textsuperscript{10c,d} Rationalization of the steric course of the nucleophilic substitution is difficult because it involves two diastereomeric \( \pi \)-allyl complexes, designated \textit{exo} (A) and \textit{endo} (B) isomers.

![Mechanistic aspect for the selectivity due to PHOX ligands](Chart-1.png)

\textbf{Chart-1:} Mechanistic aspect for the selectivity due to PHOX ligands

As we know the more abundant isomer is the more reactive one. The more abundant is generally the \textit{exo}-isomer [\textbf{Chart-1}]. In conjunction with the known configuration of the products of allylic substitutions, it was deduced that the nucleophile preferentially attacks the carbon \textit{trans} to phosphorus. The structure A clearly shows that the chiral phosphinooxazoline ligand mainly provides interaction at its wings. It appears likely that allylic system with larger substituents, such as phenyl in this case, should display high A (\textit{exo}) : B (\textit{endo}) ratios and enantioselectivity, but system with smaller substituents or cyclic compounds, might responsible for low selectivity.

The same ligands have also been used for enantiocontrol in tungsten-catalyzed allylic alkylations of monosubstituted allylic substrates.\textsuperscript{13} Complex with Ligand 9c was found to be the best which afforded 98\% \textit{ee} of the product.

This type of PHOX ligands not only worked well for Pd-catalyzed allylic substitution reactions but also proved to be efficient ligands for Pd-catalyzed asymmetric Heck reaction.
Using ligands 9, numbers of transition metal catalyzed organic transformations have been reported. Phosphinoxazolines are highly effective ligands for the enantiocontrol in Heck reaction [Scheme 4].

\[
\begin{align*}
\text{14} \quad \text{OTf} \quad \text{15} \quad \text{C}_6\text{H}_{12} \quad 50^\circ\text{C} \quad 69 \text{ h} \\
3 \text{ mol}\% \text{Pd(dba)}_2 \quad 6 \text{ mol}\% \text{Ligands 9} \quad \text{proton sponge} \\
\text{16} \quad \% \text{Conversion} \quad \% \text{ee} \\
\text{With Ligand 9b} \quad 24 \quad 90 \\
\text{With Ligand 9e} \quad 95 \quad 98 \\
\text{17} \quad (<0.1 \% \text{conversion})
\end{align*}
\]

**Scheme 4**: Pd-catalyzed enantioselective intermolecular Heck reaction

The reaction of 2,3-dihydrofuran 14 with cyclohexenyl triflates 15 leads exclusively to the corresponding 2,5-dihydrofuran derivatives 16 with excellent enantioselectivities and high yields. Interestingly, analogous reactions with Pd-BINAP catalysts produce a mixture of the 2,5- 16 and the 2,3-dihydro isomers 17 with the more stable 17 as the main product.\(^{15}\) In contrast to Pd catalysts derived from BINAP, which was previously clearly the best ligand for enantioselective Heck reactions, virtually no C-C double bond migration is observed with Pd-PHOX catalysts. Hence, particularly in cases where double bond migration leads to undesired products or mixtures of isomers, phosphinoxazolines are the ligands of choice. Because the catalysts are deactivated by traces of halides, alkenyl and aryl bromides or iodides give unsatisfactory results, the best selectivities and yields have been obtained in intermolecular reactions of aryl and alkenyl triflates with substrates containing a C-C double bond embedded in a five-member ring. Ripa and Hallberg have also reported an example of an intramolecular Heck reaction where the PHOX ligand 9e gave much higher enantioselectivities and yields than BINAP [Scheme 5].

\[
\begin{align*}
\text{18} \quad \text{Pd} (\text{OAc})_2 \cdot 9e \quad \text{DIPEA toluene} \\
110^\circ\text{C} \quad 48 \text{ h} \\
\text{19} \quad (>98\% (87\% \text{ee}) \\
\text{20} \quad <2\% (>99\% \text{ee})
\end{align*}
\]

**Scheme 5**: Pd-catalyzed intramolecular enantioselective Heck reaction by Ripa and Hallberg

These ligands were also applied for microwave assisted palladium catalyzed asymmetric Heck reaction of 2,3-dihydrofuran (14) and phenyltriflate (21) to afford corresponding product 22 with R enantiomer predominantly [Scheme 6]. Ligand 9c gave 45% yield and 86% ee while 9e resulted with 81% yield and 96% ee.\(^{17}\)
Scheme 6: Microwave assisted Pd-catalyzed asymmetric Heck reaction

Complexes of this type of PHOX ligands with other metals like iridium, rhodium, ruthenium, copper etc have also contributed for the enantioselection in various organic transformations. Ir-PHOX-A complex have emerged as a promising new class of catalysts for the enantioselective hydrogenation of imines and olefins. The COD (cyclooctadiene) complexes, which serve as pre-catalysts, can be readily prepared and easily handled as they are air-stable crystalline compounds. They are very active catalysts for asymmetric hydrogenation of imines and olefins. The encouraging results were obtained with N-phenyl imines 23 derived from acetophenone [Scheme 7], afforded product 24 up to 89% ee with 99% yield at H₂ pressure between 10 and 100 bar and turn over number >1000.

Scheme 7: Ir-catalyzed asymmetric hydrogenation of imines

Even higher catalyst activity were observed in supercritical CO₂ as a solvent which allowed easy recovery and recycling of the catalyst. There was problem of deactivation of the catalyst during the course of reaction which was then solved after a long term experiments by using tetrakis[2,6-bis(trifluoromethyl)phenyl]borate (TFPB) as the counterion instead of more common noncoordinating anions, such as hexafluorophosphate (PF₆⁻) or tetrafluoroborate (BF₄⁻). The TFPB salts displayed much longer lifetime and exhibited high catalytic activity. With Ir-PHOX-9e-TFPB system with ligand 9e almost same
enantioselectivity was achieved for the hydrogenation of trisubstituted 1,2-diarylalkenes in less than 2 h using 0.1 mol% catalyst. [Scheme 8].

![Scheme 8: Ir-catalyzed asymmetric hydrogenation of trisubstituted olefins](image)

Similarly Ir-PHOX catalyst system with ligand 9c worked well for intramolecular enantioselective amination, developed by Helmchen et al afforded product 31 in 99% yield and 88% ee [Scheme 9].

![Scheme 9: Ir-catalyzed intramolecular enantioselective amination](image)

Bolm et al and Hou et al have independently studied Ir-PHOX catalyzed asymmetric hydrogenation of the carbon-carbon double bond of α, β-unsaturated ketone 32 which gave saturated ketone 33 with good to high degree of enantioselectivities in the range 25-98% ee. In this case also ligand 9e was found to be the most stereoselective [Scheme 10].

![Scheme 10: Ir-catalyzed asymmetric hydrogenation of α,β-saturated ketone](image)

Nakamura et al have developed new class of enantioselective C-C bond forming reaction which was useful for the region and enantioselective synthesis of α-allyl-α-fluoro
ketones. A racemic α-fluoro-β-ketoester 34 was converted into the corresponding optically active α-fluoro ketone 35 by Pd-catalyzed extrusion of carbon dioxide [Scheme 11]. Again 9e was found to be the ligand of choice which exhibited 96% ee.22

\[ \text{Pd(dba)}_3 (5 \text{ mol\%}) \quad \text{Ligand 9c-e (12.5 mol\%)} \quad \text{THF rt, 3 h} \]

91-95% Yield; 91-96% ee

**Scheme 11:** Pd-catalyzed decarboxylative allylation of α-fluoro ketone

Ligand 9c and 9e were also screened for the palladium catalyzed asymmetric allylation reaction of fluorinated silyl enol ether 36 using allyl ethyl carbonate 37 resulted with 80% and 92% ee as R enantiomer of the product 38 respectively [Scheme 12].17

\[ \text{OTES} \quad \text{COCOEt} \]

\[ \text{Pd(C_(3)H_(5))Cl}_2 (1.25 \text{ mol\%}) \quad \text{Ligand 9c and 9e (3.1 mol\%)} \quad \text{TBAT (35 mol\%)} \quad \text{Toluene, 40 °C, 16 - 18h} \]

\[ 38 \text{ (R)} \]

**Scheme 12:** Pd-catalyzed asymmetric allylation of fluorinated silyl enol ether

Ligand 9e was also found to be effective for the synthesis of key intermediate 40 which was involved in the enantioselective total synthesis of (+) and (-) Nigellamines 41, alkaloids are associated with potent lipid metabolism-promoting activity.23 Exposure of the lithium enolate of allylic ester 39 to a Pd-9e complex9c resulted in the production of diene 40 in 95% ee as the only reaction product, which is key intermediate for total synthesis of 41 [Scheme 13].

\[ \text{Li(N(TMS))}_2 \quad \text{Pd(dba)}_3 : 9e \]

100% conversion, 95% ee

**Scheme 13:** Use of PHOX-9e in total synthesis of alkaloid 41

41 (+) and (-) - Nigellamine

8 steps
Another class of PHOX ligands 42-46 were also developed by group of scientists [Figure 4].

![Chemical structures of ligands 42-46](image)

**Figure 4:** New class of PHOX ligands developed by Helmchen et al and Froiland et al

Another set of $N,P$-ligands 42-44 were developed by Wiese et al with the assumption that increasing the size of the substituent of the oxazoline moiety leads to an enhanced bending of the chelate ring. Accordingly, larger substituents in the oxazoline moiety should give rise to higher enantioselectivity. $^{24a}$ Ligand 42 stands out as it induces not only the highest selectivity but also the highest reaction rate. Ligand 42 and 45 was prepared by reaction of by reaction of 2-diphenylphosphinobenzonitrile with (2S,3R)-3-hydroxy-bornylamine and (1R,2S)-1-amino-2-indanol [Scheme 14] while ligand 44 was obtained from (1R,2S)-1,2,3,4-tetrahydro-1,2-naphthalindiol by applying a method involving a Ritter-type cyclization with 2-fluorobenzonitrile. The ligand is then obtained by subsequent nucleophilic substitution of fluoride with lithium diphenylphosphide [Scheme 15]. Indeed, the corresponding ligands 9e, 44 furnished up to 89.5% ee for the reaction of 1,3 dimethylallyl acetate with sodium dimethylmalonate.

![Chemical structures of Scheme 14](image)

**Scheme 14:** Preparation of ligands 42 and 43

![Chemical structures of Scheme 15](image)

**Scheme 15:** Preparation of ligand 44
Ligands 9c, 9e and 42-44 were screened for the Pd-catalyzed allylic substitution of 1,3-dimethylallyl acetate 47 with sodium dimethylmalonate to give 48 with excellent conversion ranging from 93 to 97% and good enantiocontrol between 57-85% [Scheme 16]. Results support the assumption, that the enantioselectivity of 48 was increased with the bulk of the substituent on oxazoline ring of the ligands. Amongst 9c and 9e, the ligand with tert-butyl substituent i.e. 9e furnished 48 (S) with better enantioselectivity up to 68% whereas the ligand 9c bearing iso-propyl substituent gave product with same stereochemistry in 57% ee. Similar trend was observed for 42-44 ligands also. In this case maximum enantioselectivity was achieved with ligand 44, 85% ee of 48(R), ligand 43 showed 82% ee of 48(R) and 42 induced 58% ee of 48(S).

![Scheme 16: Pd-catalyzed allylic substitution using ligands 9c, 9e and 42-44](image)

It is well known that most of the earlier phosphinooxazoline ligands possess only one kind of chirality i.e. on oxazoline ring which render the ligands effective for a number of reactions. Ligand 45 and 46 [see Figure 4] were prepared from 2-Iodo benzoyl chloride via amido alcohol intermediate and then nucleophilic substitution of iodide with diphenylphosphine to afforded the desired product in considerably high yield [Scheme 17].

![Scheme 17: Synthesis of ligand 45 and 46](image)

Enantiodiscrimination of ligands 45 and 46 for Pd and Ir-catalyzed allylic substitution was studied by Frölander et al. Catalysts with the methoxy-containing ligand 46 generally
provided products with high ee while use of catalysts prepared from the hydroxy-containing ligand 45 resulted in products with low ee’s or even racemates [Scheme 18].

\[
\begin{align*}
\text{Ligand 45} & \quad \text{Nu} \underset{\text{NaH}}{\xrightarrow{\text{"Pd" or "Ir"}}} \quad \text{Ph} \quad \text{Nu} \\
& \quad \text{Ph} \quad \text{R} \\
\text{Nu} & \underset{\text{"Pd" or "Ir"}}{\xrightarrow{\text{NaH}}} \quad \text{Ph} \\
& \quad \text{Ph} \quad \text{R} \\
\text{Ligand 46} & \quad \text{OAc} \quad \text{Nu} \\
& \quad \text{Ph} \quad \text{R} \\
\end{align*}
\]

Product

\[
\begin{align*}
\text{Nu} & = \text{CH}_2(\text{COOCH}_2)_2 \\
\text{Ligand 45} & \quad \text{Ligand 46} \\
\eta^3-(\text{C}_3\text{H}_5)\text{PdCl}_2 & \quad \eta^3-(\text{C}_3\text{H}_5)\text{IrCl}_2 \\
\text{% Yield} & \quad \% \text{ ee} \quad \% \text{ Yield} \quad \% \text{ ee} \\
12 & \quad >99 \quad 88 \,(S) \quad >99 \quad 99 \,(S) \\
47 & \quad 67 \quad 3 \,(S) \quad 97 \quad 82 \,(R) \\
\end{align*}
\]

**Scheme 18: Comparison of ligands 45 and 46 in Pd and Ir-catalyzed allylic substitution**

It is also well known that most of the earlier oxazoline ligands possess only one kind of chirality on oxazoline rings which render the ligands effective for a number of reactions. Ikeda et al were first to develop diastereomeric N,P-oxazoline ligands 50 [Figure 5] which were having two chiral elements, one was the chiral substituent present on oxazoline ring and the other due to the binaphthyl backbone. It was expected that by the introduction of a chiral binaphthyl backbone in these diphenylphosphinooxazoline ligands some interesting and effective asymmetric inductions may be found.

![Figure 5: N,P-oxazoline ligands with binaphthyl backbone 50](image)

Ligands \((S,aR)-50\) and \((S,aS)-50\) can be synthesized from racemic diphenylphosphinocarboxylic esters 48 which were prepared from racemic binaphthol according to a reported method. After the reaction of racemic 48 with (S)-aminoalcohol, the resulting two diastereomeric amides \((S, aR)-49\) and \((S, aS)-49\) were separated with silica gel column chromatography in 34-39% yields. These amides \((S, aR)-49\) and \((S, aS)-49\) were treated with methanesulfonylchloride in the presence of triethylamine to afford ligands \((S,\)
(aR)-50 and (S, aS)-50 in 68 and 72% yields respectively [Scheme 19]. The absolute configurations of the two diastereomers of 50 were determined in comparison with those prepared from particular optically pure isomer of 1,1'-bi-2-naphthol.

Scheme 19: Preparation of diastereomers of ligand 50

These diastereomeric N,P – chelating ligands were also screened for Pd-catalysed allylic substitution reaction of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate [Scheme 20].

Scheme 20: Pd-catalyzed allylic substitution reaction using ligands 50

It was surprising that the two diastereomers (S,aR)-50 and (S,aS)-50 afforded two enantiomeric products (R)-13 and (S)-13, respectively, with excellent catalytic activities and enantioselectivities, regardless of the identical (S)-oxazoline ring existing in both ligands. It was well known that all of the (S)-oxazoline ligands derived from (S)-amino acids so far afforded an (S)-13 and therefore, this is the first example using an (S)-oxazoline ligand to generate (R)-product for this reaction. In addition, although several oxazoline ligands with multi-chirality have been reported for other reactions, the same enantiomeric product was obtained with both diastereomeric ligands when they have the same chirality on the oxazoline
ring in all of these cases. This result was the first example where the chiral backbone other than the chiral oxazoline group of the ligands played a dominant role in the determination of the chiral sense of the enantioselection.

Results showed that the substituent on the oxazoline ring affected the enantioselectivity and a bulkier group gave a better enantioselection. Thus, as the substituent was changed from iso-propyl to tert-butyl, the ee was changed from 90% to 93% at 25 °C. Like the cases of most other chiral ligands, the base used affected the ee largely and the best result was obtained with N,O-bis(trimethylsilyl)acetamide (BSA) as a base in this case. Reaction temperatures also had some effect on enantioselectivities and up to 96% ee was attained with (S,aR)-50b as a ligand at 0 °C. The enantiomeric excess was determined by 1H-NMR in the presence of shift reagent Eu(tfc)₃ and the absolute stereochemistry of the product was determined by comparison of the optical rotation with literature values.

New class of phosphinooxazoline ligands 51-52 were developed by Gilbertson in which an alkyl chain connects the diphenylphosphino group to an oxazoline ring [Figure 6].

![Figure 6: New class of N,P-oxazoline ligands 51 and 52](image)

These ligands with both one and two stereocentres have been utilized in palladium catalyzed allylic alkylations. Amongst the ligands possessing a stereocentre, ligand 51c with an iso-propyl substituent on oxazoline ring gave the highest enantioselectivity (up to 90% ee) for alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate [Scheme 20].

Interestingly, the introduction of second stereocentre, that on an alkyl chain α to the diphenylphosphine, enhanced the asymmetric induction in the case of the matched diastereomeric ligands (R,Sox)-52a and (R,Sox)-52c gave R enantiomer of 13 in 86 and 80% yield with 94 and 95% ee respectively.

Different from the earlier discussed ligands, Burgess et al have developed another class of phosphinooxazoline ligands 58a-k where diphenylphosphino moiety is incorporated into the chiral substituent at the 4th position of the oxazoline ring by different synthetic methods [Figure 7].
This set of ligands were synthesized by three different methods from the key intermediate 57, which was presynthesized from readily available L-serine 53. L-Serine was converted to N-Boc protected methyl ester 54 which was converted to oxazolidine ester 55 using 2,2-dimethoxypropane and catalytic amount of p-toluenesulphonic acid. Reduction of this ester 55 by lithium borohydride and tosylation using tosyl chloride gave 56 and which on treatment with LiPPh₂ resulted in substitution of tosylate by diphenylphosphine group which was protected immediately by addition of BH₃.THF complex to afford 57 \[\text{Scheme 21}\].

\[\text{Scheme 21: Synthetic route for the preparation of key intermediate 57}\]

Three methods used for the preparation of phosphinoxazolines 58 are shown in scheme [\text{Scheme 24 and 25}].
Scheme 22: Different methods used for the preparation of PHOX ligands 58

Scheme 23: Different methods used for the preparation of PHOX ligands 58

This set of PHOX ligands 58a-k were screened for reactivity and enantioselectivity in the palladium catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate [Scheme 24]. Amongst these set of ligands, the one with bulky adamantyl substituent afforded the highest level of asymmetric induction for 13 i.e. 94% ee.

Scheme 24: Pd-catalyzed allylic alkylation using ligand 58a-k

Another class of phosphinooxazoline ligands is diphenylphosphinoferrocenyloxazolines 63 [Figure 8] which has been developed by Sammakia et al.\textsuperscript{31}
Earlier, ferrocene complexes have been prepared in nonracemic form by classical resolution. However, this method had practical limitations in that the resolution procedure must be modified for each substrate, and is consequently time consuming if a variety of molecules are to be synthesized. Hence the preparative method of 63 from acid chloride 59 developed by Sammakia et al was found to be easier than the earlier reported one [Scheme 25-27].

Scheme 25: Preparation of ferrocene based oxazolines 60

For the practical application of such molecules, efforts have been made to make these ferrocene based oxazolines, as chiral catalysts for various asymmetric transformation, incorporation of chelating centre should be done. Hence Sammakia et al, Richards et al and others have developed a highly diastereoselective lithiation of oxazolinyferrocene compounds. The first reports of this chemistry appeared simultaneously from three groups who examined the ratio of diastereoisomers obtained on addition of n-BuLi or sec-BuLi followed by an appropriate electrophile. Common to all three studies was the iso-propyl and tert butyl substituted ferrocenyl oxazoline 60a,b for which the ratio of lithiated oxazolines 61 to 62 varied from 2.5:1 using n-BuLi at room temperature, through 8:1 with sec-BuLi at −78°C in THF, and finally 39:1 with sec-BuLi again used at −78°C but in Et₂O. These reactions are mediated by nitrogen rather than oxygen directed lithiation. With oxazolines 60a and 60b the observed selectivity may be explained with a model in which the oxazoline substituent is similarly oriented towards the iron, allowing the nitrogen-coordinated alkyl lithium reagent to approach unconstrained from the opposite direction. However, when tert-BuLi is employed in these lithiations, it is possible that the
significantly lower selectivities observed are due to a competing and less sterically encumbered oxygen directed pathway.

Scheme 26: Lithiation of ferrocenyl oxazolines 60a and 60b

With oxazolines 60a and 60b the observed selectivity may be explained with a model in which the oxazoline substituent is similarly oriented towards the iron, allowing the nitrogen-coordinated alkyl lithium reagent to approach unconstrained from the opposite direction. However, when tert-BuLi is employed in these lithiations, it is possible that the significantly lower selectivities observed are due to a competing and less sterically encumbered oxygen directed pathway.

Quenching these lithiated species with chlorodiphenylphosphine has provided exclusively (S,Sp)-diphenylphosphinoferrocenyl oxazoline (DPOF) ligands 63a–d [Scheme 27].

Scheme 27: Preparation of DPOF (S,Sp)-63a–d

The corresponding (S,Rp)-diastereoisomers of 63a–d have also been obtained through initial introduction of a removable trimethylsilyl blocking group [Scheme 28].
Scheme 28: Preparation of DPOF \((S, Rp)-63a-d\) ligands

As a practical application of these DPOF ligands, Ahn et al have reported the Pd-catalyzed allylic alkylation using \((S, Sp)-63a,b\). Since these ligands have different planar chirality, it is of interest to study their effects on the enantioselectivity [Scheme 29].\(^{35}\) DPOF ligand \((S, Sp)-63b\), tert-butyl substituent on oxazoline ring was found to be the best ligand which afforded 99% ee.

Scheme 29: Pd-catalyzed allylic alkylation using \((S, Sp)-63a,b\)

Sammakia and co-workers have also used \((S, Sp)-63b,c\) ligands for Ru-catalyzed transfer hydrogenation using 2-propanol as a hydrogen source to reduce ketones to alcohols [Scheme 30].\(^{31d}\) All of the ligands provided enantioselectivity of 90% while with the tert-butyl- and phenyl-substituted oxazolines, \((S, Sp)-63b\) and \((S, Sp)-63c\) provided 67 with 94% ee.

Scheme 30: Ru-catalyzed transfer hydrogenation of acetophenone using \((S, Sp)-63a,b\)

Ligands \((S, Sp)-63a\) and \((S, Sp)-63c\) have also been applied to rhodium catalysed asymmetric hydrosilylation of acetophenone 66. \((R)-1\text{-phenylethanol} 67\) being formed in 48 and 60% ee respectively.\(^{20}\)
Another type of DPOF ligands 68-73 were developed by Deng et al [Figure 9] for Pd-Catalyzed asymmetric Heck reactions of 2,3-dihydrofuran 14 and phenyltriflate 21 [Scheme 30].

![Chemical Structures]

Figure 9: Another type of new DPOF ligands 68-73

Surprisingly, DPOF (S,Sp)-63a and (S,Sp)-63b had almost no catalytic activity in this reaction even with the reaction time prolonged to 24 h. Use of ligand 68a-d showed good to moderate yield (46–79%) as well as enantioselectivity (42–76%), 68d with benzyl substituent on oxazoline ring showed highest 76% ee. While ligand 69-71 gave better yield ranging from 72-79% while selectivity range was 83-92%, amongst these ligands 70 gave the best enantioselectivity of 88% for R isomer of 22 [Scheme 31]. Improvement was observed with the use of ligands 72 and 73 which gave 80 and 88% yield as well as 75 and 85% enantiomeric excess.

![Scheme 31]

Scheme 31: Pd-catalyzed asymmetric Heck reaction using DPOF ligands 68-73

These type of DPOF ligands were also successfully applied in variety of other asymmetric catalytic transformations, such as Ru-Catalyzed hydrosilylation,^{58} enantioselective ring opening of aza and oxabicyclic alkenes with dimethylzinc reagent.^{59}

Recently, Wang et al have developed C2-symmetric planar chiral ruthenocene based phosphinooxazoline ligand 73 and employed for ruthenium catalyzed asymmetric hydrogenation reaction of ketone 74 to 75 as a key step which was the part of the synthetic route for one of the important biologically active molecules, (R)-(+-)Shikonin 76 with 99.3% ee [Scheme 32].^{40}
Scheme 32: Application of ligand 73 in the total synthesis of (R)-(+) Shikonin 76

**N,O-Ligands**

In 1991 Bolm has synthesized 2-(oxazolinyI)phenolato ligand 79 from 2-hydroxy benzonitrile 77 and L-valinol 78 using ZnCl₂ as Lewis acid catalyst [Scheme 33].

Scheme 33: Preparation of (S)-2-(4-isopropyl-4,5-dihydrooxazol-2-yI)phenol 79

Metal complexes bearing 2-(oxazolinyI)phenolato ligands have been utilized in a number of asymmetric reactions including Baeyer-Villiger oxidations, cyclopropanations, allylic functionalizations and Lewis acid catalyzed C C bond formation.\(^\text{50}\)
In the presence of copper catalyst \((S,S)\)-81 aerobic oxidation of racemic 2-aryl cycloalkanones 80 afforded the corresponding lactones 82 with enantioselectivities of up to 69% ee [Scheme 34]. Alkyl substituted ketones and positional isomers did not react under this condition.\(^{42a}\)

\[
\begin{align*}
\text{Scheme 34: Baeyer-Villiger oxidation using catalyst 81}
\end{align*}
\]

Feng has reported the synthesis of the new derivatives of \(N,O\)-Ligands 83a-f [Figure 10] by the well known method as described in Scheme 33 from appropriate hydroxyl benzonitriles and chiral amino alcohols.

\[
\begin{align*}
\text{Figure 10: New } N,O\text{-Ligands 03a-f}
\end{align*}
\]

The resulting ligands have been used in the Ti-catalyzed oxidation of prochiral sulphides 84 into chiral sulfoxides 85 using \textit{tert}-butyl hydroperoxide (TBHP) [Scheme 35].\(^{46}\)

\[
\begin{align*}
\text{Scheme 35: Ti-catalyzed oxidation of methyl phenyl sulphide 84 using 83b}
\end{align*}
\]
Ligand 83b induced significantly higher enantioselectivities [72% ee for \( R \) isomer] than other ligands for the oxidation of methyl phenyl sulphide 84 with 1.1 equivalent of TBHP in \( CH_2Cl_2/CCl_4 \) at 0 °C for 24 h. An increase in enantioselectivity was observed by increasing the amount of oxidant used [up to 96% ee (\( R \)) with 2.0 equivalent of TBHP]. This could be due of concomitant kinetic resolution of the product sulfoxide 85 by further oxidation to sulfone 86.

Gong has developed a series of \( N,O \)-oxazoline ligands 87-88 [Figure 11] for the addition of diethylzinc to imines.\(^{47}\) Chiral oxazolines with a backbone similar to that found in 87 have three structural characteristics that might enable them to be the promising candidates in competition with aminoalcohols in catalyzing the diethylzinc addition of \( N \)-diphenylphosphinoylimines: (1) They have \( sp^2 \) nitrogens restricted by the oxazoline ring, which probably made the structure of the ligand rigid, so that could minimize the diastereomers formed in the transition state during catalysis. (2) The oxygen in the oxazoline ring is conjugated with C=N, which made the nitrogen to be more Lewis basic so that would change the Lewis acidity and catalytic activity of their zinc complexes. (3) The chiral environment could be systematically modified for the high enantioselectivity by fine-tuning the size of the \( R \) groups in 87.

![Figure 11: New class of \( N,O \)-Ligands 87 and 88](image)

Ligands 87a-e were prepared from (1S,2S)-2-amino-1-phenyl-propan-1,3-diol 89 on treatment with appropriate acid chloride to give amidol derivatives 90a-e, which upon reaction with tosyl chloride in dichloromethane under reflux condition furnished 87a-e in the yield ranging from 51-80% [Scheme 36].\(^{48}\)

![Scheme 36: Synthesis of ligands 87a-e](image)
The chiral oxazoline 87f was prepared from 87a by a Mitsunobu configuration inversion procedure in 20% yield [Scheme 37], in order to investigate the effect of chiral carbon bonded to hydroxyl group on the enantioselectivity.

\[ \text{87a} + \text{COOH} \xrightleftharpoons{\text{Ph}_3\text{P}, \text{DEAD, THF, reflux}} \xrightarrow{\text{i}) \text{K}_2\text{CO}_3, \text{MeOH, rt 20\%}} \text{87f} \]

**Scheme 37:** Synthesis of ligand 87f from 87a via inversion of configuration

Ligands 88 was synthesized from (1S,2S)-2-amino-1-phenyl-propan-1,3-diol 89 by refluxing with benzonitrile in presence of K$_2$CO$_3$ using mixture of ethylene glycol and glycerol as solvent [Scheme 38].

\[ \text{99} + \text{CN} \xrightarrow{\text{K}_2\text{CO}_3, \text{ethylene glycol:glycerol reflux 92\%}} \text{88} \]

**Scheme 38:** Synthesis of ligand 88

In general, high enantioselectivity (81-93% ee) was obtained for the addition of diethylzinc to N-diphenylphosphinoyl benzalimine 91 promoted by stoichiometric amounts of ligands 87 and 88 leading to diphenylphosphinoamide 92 [Scheme 39].

\[ \text{91} \xrightarrow{\text{Et}_2\text{Zn 87 or 88, toluene rt}} \text{92} \]

**Scheme 39:** Enantioselective diethylzinc addition to N-diphenylphosphinoyl benzalimine

It was found that the stereocentre at the carbon atom bearing the hydroxyl group was crucial for high asymmetric induction (ligand 88 lacking this stereocentre gave only 23% ee) and also determined the configuration of the product [92% ee (S) with 87a against 76% ee (R) with 87f].

The application of stereoplanar ferrocenyl based mono(oxazoline) N,O-ligands in asymmetric catalysis has been discussed in a review by Bryce and Sutcliffe. Rechards reported the synthesis of the stereoplanar mimetics 93-96 [Figure 12].
Ligands 93-95 were prepared from the readily available carboxylic acid 97 which on treatment with oxalyl chloride to generate intermediate acid chloride and amide 98 was obtained using (S)-serine methyl ester hydrochloride in the presence of triethylamine. Then dehydrative ring-closure was achieved with DAST to give oxazoline 99 in 93% overall yield. Ligand 93 and 94 was obtained by Grignard reaction of 99 by phenylmagnesium bromide and methylmagnesium bromide respectively. And upon reduction of 99 using lithium aluminium hydride furnished 96 [Scheme 40].

In addition they have synthesised pentaphenylferrocene based N,O-oxazoline ligand 96 from pentaphenylferrocene 100. Direct acylation of 100 with 2-chlorobenzoyl chloride in presence of aluminium chloride cleanly gave aryl ketone 101. Then it got hydrolyzed using 'BuOK in DME to have corresponding carboxylic acid 102. This acid then converted to acid chloride and treatment with (S)-serine methyl ester·HCl gave amidol 103, which ultimately on dehydrative ring closure using DAST and subsequently reduction with lithium aluminium hydride afforded pure ligand 96 in 95% yield [Scheme 41].

Addition of 1.5 equivalents of diethylzinc to benzaldehyde 104 in the presence of 5 mol% of ligands 93-95 resulted in the clear formation of 105, highest enantioselectivities for the R product was obtained by ligand bearing hydroxymethylene group on oxazoline ring 95 (68% ee). While in contrast, the ligand with phenyl and methyl substituent adjacent to the
hydroxyl group in 93 and 94 respectively resulted in erosion of the selectivity compared to the hydrogen. As expected the application of ligand 96 in this reaction exhibited increase in enantioselectivity of the product 105 (R) to 75% ee with the same stereochemistry at the stereocentre [Scheme 42].

**Scheme 41: Synthesis of pentaphenylferrocenyl based N,O-oxazoline ligand 96**

**Scheme 42: Addition of diethylzinc on benzaldehyde using stereoplanar N,O-oxazoline ligands 93-96**

The absolute configuration of the 1-phenylpropanol 105 resulting from these reactions may be rationalised by considering the two alternative reaction pathways A and B [Chart 2]. Orientation of the oxazoline 4-substituent away from the floor defined by the phenyl groups results in a preference for the oxazoline–metalallocene rotamer drawn in both A and B. Following coordination to zinc, the ethyl group to be transferred may be aligned either away (see A) or towards (see B) the alkoxy methylene arm of the oxazoline. In the former, coordination of benzaldehyde from the side opposite to the floor results in ethyl transfer to the Re face and formation of the major R-enantiomer. In the alternative B the coordinated benzaldehyde is in close proximity to the bulky floor unless the oxazoline rotates into an alternative conformation. This may occur to a greater extent when methyl and phenyl groups are adjacent to the zinc coordinated alkoxide, with these substituents favouring alignment of
the transferable ethyl group towards the alkoxyethylene arm. Clearly too much bulk is detrimental to selectivity with this system.

![Chart 2: Explanation for the selectivity in diethylzinc addition reaction using 93-96](image)

The reason for the increase in selectivity might alternatively relate to the size of the floor as defined by the metallocene phenyl substituents.

**N,S-Ligands**

The combination of an oxazoline group with an auxiliary donor atom provides a bidentate ligand which creates an electronic bias in the metal catalyst. However, the precise nature of the auxiliary donor atom will have an influence on the electronic and steric environment around the metal. The bidentate oxazoline N,S-mono(oxazoline) ligands 106-110 [Figure 13](image) developed by Williams and co-workers were among the first mono(oxazoline) ligands containing an auxiliary sulphur donor atom to be applied in asymmetric catalysis.\(^{52}\)

![Figure 13: N,S-monc(oxazoline) ligands 106-110](image)

Ligands 106 were prepared from the reaction of o-fluorobenzonitrile 111 with sodiumthiophenolate afforded the diarylsulfide 112 and subsequent reaction of 112 with
appropriate chiral amino alcohols afforded the oxazolines 106a-e with high yields [Scheme 43].

Scheme 43: Synthesis of N,S-mono(oxazoline) ligands 106a-e

The treatment of thioacetonitriles 113a-b with enantiomerically pure amino alcohols and catalytic amounts of zinc chloride in chlorobenzene at reflux for 48 hours afforded the corresponding oxazolines 107 in good yields [Scheme 44].

Scheme 44: Preparation of ligands 107a-d

Similarly, methylbenzimidate hydrochloride was reacted with methioninol 114 and methyl cysteinol 115 in dichloromethane at reflux for 18 hours to furnish ligands 108 and 109 [Scheme 45].

Scheme 45: Preparation of ligands 108 and 109

The ligands 110a-g were prepared by adaptation of a literature procedure from thiophene-2-carbonitrile 116 and the corresponding amino alcohol by treatment with catalytic amounts of zinc chloride in chlorobenzene at reflux for 48 h [Scheme 46]
Scheme 46: Preparation of thiophene based $N,S$-mono(oxazoline) ligands 110a-g

All these ligands 106-110 have been applied to the Pd-catalyzed allylic substitution reaction of 1,3-diphenylprop-2-enyl-1-acetate 12 with the sodium salt of dimethylmalonate to afford product 13 with good conversion and enantioselectivity, particularly 110e was found to be the most effective ligand inducing 80% ee.52

Another class of $N,S$-mono(oxazoline) ligands, thioglucose-derived oxazoline ligands 117-121 have been developed by Pregosin [Figure 14] 53

Figure 14: Thioglucose base $N,S$-mono(oxazoline) ligands 117-120 and cyclohexyl based ligands 121

Ligands 117-120 were prepared by standard methods, which includes the reaction of optically pure amino alcohols 122 with (chloromethyl)benzoyl chloride to produce amido alcohol 123 which on cyclization using triphenylphosphine, carbontetrachloride, in acetonitrile to give corresponding oxazoline 124, which on coupling with appropriate thioglucose derivatives gave desired thioglucose based $N,S$-mono(oxazoline) ligands 117-120 in good yields [Scheme 47].
Scheme 47: Synthesis of thioglucose based \( N,S \)-mono(oxazine) ligands 117-120

Pregosin has applied these ligands 117-120 in Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate to afford substituted product 13. And the result showed that ligands with bulky pivalate ('BuO-) protecting groups 118 and 120, provided best enantioselectivities of 97% and 96% ee respectively. The lower enantiodiscrimination (75%) obtained with cyclohexane thioether 121 indicated that the sugar moiety was important for good enantioinduction.

Schulz has developed dibenzothiophene based mono(oxazine) ligands 125a,b and benzothiophene based mono(oxazine) ligands 126a-c [Figure 15] and applied them in Pd-catalyzed allylic substitution of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate.

Figure 15: Dibenzothiophene based mono(oxazine) 125a-b and benzothiophene based mono(oxazine) 126a-d

Ligands 125a-b were prepared from dibenzothiophene 127 via ortho lithiation using \( n \)-Butyl lithium and upon quenching with dry ice to afford dibenzothiophene 4-carboxylic acid 128. Initially 128 was converted to corresponding acid chloride on refluxing with thionyl
chloride in presence of DMF as catalyst in chloroform and subsequently the acid chloride was treated with appropriate chiral amino alcohol to give chiral amidol 129 and finally DAST mediated cyclization afforded desired dibenzo thiophene based oxazolines 125a-b in good yields [Scheme 48].

Scheme 48: Synthesis of dibenzo thiophene based mono(oxazoline) ligands 125a-b

Using similar synthetic strategy, benzothiophene based mono(oxazoline)s 126a-c have been prepared form thianaphthene 2-carboxylic acid 130 [Scheme 49].

Scheme 49: Synthesis of benzothiophene based mono(oxazoline) ligands 126a-d

Both ligand classed 125a-b and 126a-c afforded moderate conversions and modest enantioselectivities (up to 41% ee), with six-member chelate ring formation in ligands 125 giving slightly better results.

**N,N-Ligands**

Brunner has reported, the best known N,N-mono(oxazoline) ligands with two coordinating nitrogen donor atoms are the pyridinyl oxazoline ligands 132 and 133 [Figure 16]. The choice of ligands was done on the basis of size of chelate ring generated upon coordination which is responsible for the better results.
These ligands were synthesized by condensation of methyl pyridine-2-carboximidate 135 with the appropriate amino alcohols 136a-g in presence of hydrochloric acid at 80 °C gave the optically active pyridine based oxazolines 132 and 133 in good conversion [Scheme 50].

Scheme 50: Conventional synthesis of pyrindine based $N,N$-mono(oxazoline) ligands

Since being first applied in asymmetric catalysis in 1986 for Cu-catalyzed monophenylation of cis-cyclohexan-1,2-diol 137 with triphenylbismuth diacetate 138 afforded cis-l-phenoxyhexan-2-ol 139 (up to 30% ee for 132e) using 132a-e [Scheme 51] and subsequently with some success in Rh(I) – catalyzed hydroalumination (up to 84% ee), many structural derivatives of these ligands have been used successfully in a range of asymmetric reactions such as asymmetric alkylation.
These ligands and their many structural derivatives have been applied successfully in a range of asymmetric reactions. Jung has reported another application of pyridinyl oxazoline ligands 132c, 132f and 132g in asymmetric intermolecular Heck type reaction of arylboronic acids to acyclic alkenes via oxidative palladium (II) catalysis.\textsuperscript{57} Pd-catalyzed coupling of phenylboronic acid 140 and \textit{trans}-2-methyl-2-butenal 141 produced exclusively the compound 2-methylene-3-phenylbutanal 142 generating new stereogenic centre using bidentate \textit{N},\textit{N}-mono(oxazoline) ligands 132c (25\% \textit{ee}), 132f (21 \% \textit{ee}) and 132g (42\% \textit{ee}) resulted in good conversion as well as selectivity compared to phosphine based ligands which turned out to be inefficient due to the side reactions. Still there was scope for the improvement in terms of selectivity because when reaction was carried out by forming a complex between Pd and 132 the selectivity went up to 42 \% (for 132f). Hence to overcome this shortcoming authors have synthesized, isolated and characterized corresponding palladium catalyst complex 143 and utilized it for the same reaction. With this catalyst the selectivity was improved up to 75\% with \textit{R} configuration of the product 142 [Scheme 52].

![Scheme 52: Pd-catalyzed oxidative Heck type reaction](image)

To study the effect of chelate size, Fryzuk and Zhou has independently reported the synthesis and application of chiral bidentate ligands 144a-g that contain the oxazoliny1 unit and the pyridine separated by a methylene unit in asymmetric transformations. [Figure 17].\textsuperscript{58}

![Figure 17: Pyridine based mono(oxazoline) linked by methylene unit](image)

The preparation of these ligands was done by standard synthetic protocol by refluxing a mixture of 2-cyanomethylpyridine and the appropriate chiral aminoalcohol in chlorobenzene in the presence of a catalytic amount of zinc chloride produced the desired ligand 144a-b.
Ligands 144a and 144b were applied in Rh-catalyzed asymmetric hydrosilylation of acetophenone 66 using diphenylsilane in carbon tetrachloride, followed by acidic work up yielded (R)-1-phenyl ethanol 67 with good conversion but modest enantioselectivity. Ligand 144a gave 67 with maximum 42% of enantioselectivity while 144b produced product 67 with 40% ee [Scheme 53].

Scheme 53: Rh-catalyzed hydrosilylation of acetophenone using ligands 144a-b

The synthesis of chiral pyridinyl-oxazoline ligands 144c-g started from 2-picoline as shown in [Scheme 54]. 2-Chloromethyl pyridine 145 was prepared by oxidation of 2-picoline with hydrogen peroxide to N-oxide 146 and side chain chlorination with phenylsulfonyl chloride to chloromethylated pyridine 147. Substitution of chloride with cyanide followed by methylation with methyl iodide gave 2-methyl-2-pyridinyl propionitrile 149. Ligands 144c-g were produced by condensation of nitrile 149 with optically pure amino alcohol in the presence of one equivalent amount of anhydrous zinc chloride.

Scheme 54: Synthesis of ligands 144c-g

For practical applications these set of ligands were applied to Cu(I)-catalyzed asymmetric cyclopropanation reaction of styrene 150 with ethyl diazoacetate 151 to produce trans-152 and cis-153 with good results [Scheme 55]. Ligands 144c-g have good chemical yields in refluxing CH₂Cl₂, but the enantiomeric excesses were low (maximum 18% ee for trans and 12% ee for cis isomer).
Scheme 55: Cu(I)-catalyzed asymmetric cyclopropanation reaction using ligands 144c-g

Another analogous of the pyridine oxazoline ligands 154a-c and 155a-b have been prepared and screened for Pd-catalyzed asymmetric allylic alkylation reaction by Chelucci [Figure 18].

Figure 18: Another class of N,N-mono(oxazoline) ligands having quinoline ring

Ligands 154 and 155 have been prepared from corresponding cyano derivatives 156 and 157 respectively on treatment with appropriate chiral amino alcohols in presence of anhydrous zinc chloride as catalyst in chlorobenzene under reflux condition [Scheme 56].

Scheme 56: Synthesis of new class of quinoline based N,N-mono(oxazoline) ligands
Application of these ligands 154a-c and 155a-b in Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethylmalonate using O,N-bis(trimethylsilyl)acetamide as a base in dichloromethane at room temperature to afford the product 13 in good yield as well as selectivity [Scheme 57]. Amongst these ligands 154a with iso-propyl substituent on 4-position of oxazole ring gave 13-(S) with 62% ee and 154b having phenyl group at 4-postion of oxazole ring produced 13-(R) with 68% ee, while maximum enantioselectivity 92% was exhibited by ligand 154c which possessed bulky tert-butyl substituent at 4-postion of oxazole ring. Unfortunately there was no significant effect of the ligand 155a-b in this reaction.

Scheme 57: Pd-catalyzed allylic alkylation using ligands 154 and 155

Several derivatives of the 8-quinolinyl-oxazoline class of ligands 158a-i were prepared by Zhou and co-workers [Figure 19]. The idea behind the development of these quinoline based ligand possible formation of six member chelate on coordination with metal against the five member chelate forming pyridine based mono(oxazoline)s 132 and 133. This may influence the stability, efficiency and enantioselectivities of catalysts.

Figure 19: 8-Quinolinyl mono(oxazoline) ligands 158a-i

A series of 8-quinolinyl-oxazolines 158 were synthesized from enantiomerically pure amino alcohols and 8-quinolinecarboxylic acid derivatives 159 in four steps as shown in [Scheme 58]. Intermediate 159 was converted to the corresponding acid chloride 160 with thionyl chloride. After evaporation of excess SOCl2, the chlorides were reacted with the amino alcohols in the presence of triethylamine in chloroform to provide 8-quinolinecarboxamides of type 161. The hydroxy group of the 8-quinolinecarboxamides 161 was converted to chloride 162 by refluxing with SOCl2. The cyclization of chloride derivative 162 with NaOH in refluxing methanol gave the desired ligand 158 good to excellent yield.
Scheme 58: Synthetic route for the synthesis of 8-Quinolinyl mono(oxazoline) ligands 158a-g

These ligands were tested in the asymmetric Cu(I)-catalyzed cyclopropanation of styrene 150 with diethyl diazoacetate 151 [see Scheme 55]. In this reaction, 2-methyl-substituted analogues, with ligand 158g afforded the optimum result (54% ee for both trans-152 and cis-153). Comparison of the results achieved with ligands 158 with high yields and low enantiodiscrimination by pyridinyl oxazoline ligands 144c-g suggested that conjugation between the heteroaryl ring and oxazoline unit is necessary for good enantiocontrol with these types of ligands.

Another application of ligands 158 was reported by the same group for Pd-catalyzed asymmetric hydroarylation of norbornene 163 with aryl iodides 164 yielding corresponding exo product 165 exclusively [Scheme 59].

Scheme 59: Pd-catalyzed asymmetric hydroarylation of norbornene using ligands 158

Amongst these ligands, 158b and 158c with benzyl and iso-Propyl substituent at the oxazoline ring respectively proved to be effective ligand for reaction of Norbornene 163 with
Iodobenzene 164a giving exclusively corresponding exo-product 165a in 73 and 75% ee respectively. It was found that the nature of the hydroarylation agent had significant influence on the reaction. The common arylating agents bromobenzene and phenyl triflate were inactive, and whereas iodobenzene analogues with electron-donating substituent 164b increased the enantioselectivity of the corresponding 165b (75% ee) and those with electron-withdrawing group 164c substantially decreased the enantioselectivity of 165c (53% ee).

Echavarren has applied the platinum complex of ligand 132c in the alkoxycyclization of enyne and although this afforded the cyclized product high yield but the enantiomeric excess obtained was only 10%. Sigman has recently applied ligand 132 and its quinoline analogue 154 in the palladium-catalyzed enantioselective aerobic dialkoxylation of 2-propenyl phenols.

Andersson has reported the synthesis of new 2-aza norbornane ligands 166 and 167 [Figure 20] and studied their applications in the asymmetric transfer hydrogenation of acetophenone 66.

![Figure 20: 2-Aza norbornane based oxazoline ligands 166 and 167](image)

**Figure 20:** 2-Aza norbornane-based oxazoline ligands 166 and 167

The syntheses of 2-aza norbornane-oxazoline ligands 166a-e and 167a-e using a Cbz-protecting group for cyclic secondary nitrogen are shown in [Scheme 60]. The protection of the amino functionality in (1S,3R,4R)-2-azabicyclo[2.2.1]-heptane-3-carboxylic acid 168 was performed using benzyl chloroformate to give 169 in 72% yield. The amide coupling of 169 with appropriate L- and D-aminoalcohols lead to hydroxylamines 170a-c and 171a-c (yield 64–94%). These compounds were converted into protected oxazolines 172a-c and 173a-c by treatment with methanesulfonyl chloride under basic conditions in 65–95% yield after purification. The cleavage of the benzyloxy carbonyl group from the amine was accomplished by hydrogenolysis using palladium on carbon as a catalyst to yield the ligands 166a-c and 167a-c in 55–74%. Ligands 166d-e and 167d-e were prepared in 55–59% yield by the same procedure described in [Scheme 60] with the only one change by using p-nitrobenzyloxy carbonyl as protecting group instead of simple benzyloxy carbonyl.
These diastereomeric pairs of 166a-e and 167a-e were applied to Ir-Catalyzed hydrogen transfer to acetophenone 66. Use of ligands 166a-e produced from L-aminoalcohol leads to (R)-1-phenylethanol 67 formation while (S)-1-phenylethanol 67 is obtained employing the Ir-complex with an oxazoline 167a-e which are synthesized from a D-aminoalcohol. Amongst these ligands, 166b, with hexylpropyl group at the oxazoline moiety gave best selectivity up to 72%. It was found that a further increase in the size of the oxazoline substituent led to a decrease in both conversion and enantioselectivity.
Wipf has prepared a range of chiral cyclohexane ligands 174 and 175 with different oxazoline substituents and sulfanyl nitrogen groups [Figure 21].

![Chemical structures of ligands 174 and 175]

Where Ts= toluenesulfonyl; Mts= 2,4,6-trimethylbenzenesulfonyl; Ns= p-nitrobenzenesulfonyl

**Figure 21:** Cyclohexane basec amino oxazoline ligands 174 and 175

These cyclohexane based amino oxazoline ligands were prepared by following the method as depicted in Scheme 61. Selective saponification of imide 176, followed by modified Curtius rearrangement with diphenylphosphoryl azide (DPPA), provided carbamate 177. Catalytic hydrogenation of the alkene moiety with concomitant removal of the Cbz-group, N-tosylation, and hydrolysis of the methyl ester led to carboxylic acid 178 as the precursor for the introduction of heterocyclic substituents. Upon activation of the acid with oxalyl chloride and condensation with (L)-valinol, the intermediate amide 179 was then cyclodehydrated to give oxazoline 174a in excellent overall yield. Similarly all other structural derivatives [see Figure 21] of this class were prepared by appropriate changes.

![Scheme 61: Schematic diagram for the synthesis of ligand 174a]

These ligands 174 and 175 were screened for asymmetric induction in the addition of diethylzine to benzaldehyde 104 afforded 105 with 12-95% enantioselectivity. Ligands 174
gave $R$-isomeric product and 175 produced $S$-isomer of 105. Amongst all these aminooxazoline ligands 174a was found to be superior with the selectivity of 94% ee.

Guiry has reported the synthesis and application of pyrrolidine-oxazoline containing ligands 180 and 181 [Figure 22] in the asymmetric transfer hydrogenation of acetophenone 66.

![Figure 22: Pyrrolidine based oxazoline ligands 180 and 181](image)

Ligands 180a-e can be prepared by means of a four-step synthesis starting from readily available chiral amino alcohols and proline [Scheme 62]. First, N-carbobenzyloxy(Chz)-protected proline 182 was chlorinated with thionyl chloride and then reacted without purification with an appropriate chiral amino alcohol in the presence of triethylamine to give $\beta$-hydroxyamides 183a-e in moderate to good yield (57–92%). Cyclohexane of 183a-e by treatment with diethylamino-sulfur trifluoride (DAST) afforded excellent yield (75–98%) of the Cbz-protected pyrrolidine-oxazolines 184a-e, which were then deprotected in a transfer hydrogenolysis reaction using Pd/C and cyclohexene afforded the required pyrrolidine-oxazoline ligands 180a-e in moderate yields (40–89%).

![Scheme 62: Synthesis of pyrrolidine based oxazoline ligands](image)
Using \([\text{IrCl(COD)}]_2\) as the metal precursor in the asymmetric hydrogen transfer reaction to acetophenone 66 using 2-propanol as hydrogen source resulted in excellent conversions (up to 96%) but gave only modest enantioselectivities (up to 38% ee). \([\text{Ru}(\mu\text{-cymene})\text{Cl}_2]_2\) was then used as the metal precursor, and the best results were obtained using the iso-propyl substituted ligands 180a and 181a, which gave product 67 with enantiomeric excesses of (R-isomer) 51% and (S-isomer) 61%, respectively.

As optically active proline has been gained paramount importance for asymmetric induction in organic transformations, combination of oxazoline moiety with proline generates efficient asymmetric catalyst. Sigman has developed set of diastereomers of proline based oxazoline ligand 185 [Figure 23] and used for the allylation of benzaldehyde (Nozaki-Hiyama reaction).

![Figure 23: Proline based oxazoline ligands 185a-d](image)

These set of ligands have been synthesized in a three-step process [Scheme 63]. Starting with F-moc protected valine derivative 186 and phenyl alaninol 187, oxazoline ring formed using triphenylphosphine-\(\text{CCl}_4\) system in the presence of DIPEA in dichloromethane to afford F-moc protected oxazoline 188 with good conversion. Then deprotection of 188 was achieved under basic condition by stirring 188 with piperidine in methanol to give amino oxazoline 189 which was then coupled with \(N\)-Boc proline 190 using DCC in dichloromethane to afford desired proline based oxazoline ligand 185d in excellent yield.
Scheme 63: Synthesis of proline based oxazoline ligand 185

Addition of allylhalides to aldehydes is generally referred as Nozaki-Hiyama reaction. Sigman has screened proline based oxazoline ligands 185a-d in Cr(II)-catalyzed addition of allyl bromide 191 to benzaldehyde 104 [Scheme 64]. After screening the series, result showed that the ligand 185d led to the best catalytic system for the reaction, giving a product 192 with 92% ee (R isomer) in 95% isolated yield. It was noted that changing the catalyst diastereomer has much effect on the outcome of the reaction, when ligand 185c where the stereochemistry at proline module was reversed that resulted the product 192 with slightly lower selectivity (89% ee for S-isomer) and a small drop of yield as well.

Scheme 64: Nozaki-Hiyama reaction using proline based oxazoline ligands 185a-d

These ligands worked well for aromatic aldehydes yielding high enantioselectivities where as resulted in poorer selectivity for aliphatic aldehydes. In continuation of the work, Sigman has also developed these type of ligands for allylation of ketones and achieved high stereo selectivity and conversion.$^{66b}$

Another class of amino oxazoline ligands which involves the presence of oxazoline ring to the ortho position of aniline moiety [Figure 24].
These types of oxazolines have four unique properties:

(i) Ease of variation of groups on the oxazoline portion of the molecular framework.
(ii) Facile derivatisation of the \(-\text{NH}_2\) group to modify the reactivity or function of oxazoline.
(iii) Coordination of both the N-atoms to form six member chelate.
(iv) Modification of aromatic ring by substitutions

These unique features make them efficient ligands for the number of organic transformations which will be discussed in this portion.

These type of derivatives have been synthesized by a number of synthetic routes which involves include inorganic clay promoted addition of amino alcohols to isatoic anhydride, Lewis acid catalyzed addition of amino alcohols to 2-cayano anilines, ring closure of (2-anilinyl)amidoalcohols using ethanolic KOH, ortho-metalation of aryl-oxazolines followed by reaction with sodium azide and subsequent treatment with NaBH\(_4\) and treatment of isatoic anhydride with amino alcohols using ZnCl\(_2\).\(^{67}\)

Fujisawa and co-workers have developed 2-[2-[(alkylsulfonyl or arylsulfonyl)amino]phenyl]-4-phenyl-1,3-oxazolines 193a-g [Figure 25] and screen their Mg-complexes for asymmetric Diels-Alder reaction.\(^{66}\)

![Figure 25](image)

The chiral ligand was readily accessible in two step procedure [Scheme 65], involve the reaction of aminobenzenitrile 194 with D-phenylglycinol in presence of catalytic amount of zinc chloride in chlorobenzene to afford 2-(2-amino)phenyl-4-phenyloxazoline 195 which
was converted to corresponding 2-[(alkylsulfonyl or arylsulfonyl)amino]phenyl]-4-phenyl-1,3-oxazolines 193a-g on treatment with appropriate alkyl or arylsulfonyl chloride in presence of catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane.

**Scheme 65:** Synthesis of 2-[(alkyl of arylsulfonyl)amino]phenyl]-4-phenyl-1,3-oxazoline 193a-g

Use of ligands 193a-g in the reaction of 3-(2'-propenoyl)-1,3-oxazolidin-2-one 196 and cyclopentadiene 197 in presence of additive at 0 °C in dichloromethane afforded the Diels-Alder adduct 198-endo in good conversion as well as stereoselectivity [Scheme 66].

**Scheme 66:** Mg-catalyzed Diels-Alder reaction using ligands 193a-g

In this case complex of Mg using Grignard reagent of MeI and particular ligand was prepared prior to the addition of the starting materials for Diels-Alder reaction. Amongst all these ligands 193a-g, one with p-toluene sulfonyl substituent 193a was found to be the best where the endo product was formed in 92% ee, which is exclusively formed in all the cases in this reaction. It is also observed that the use of additive govern the stereoselectivity in this reaction. Quite poor selectivity (7% ee) was observed without additive where as it was dramatically increased to 60% ee on adding silver hexafluoroantimonate. The highest selectivity (92% ee) was obtained with the use of iodine in this reaction.
Chart 3: Model proposed for the selectivity in Diels-Alder reaction using ligands 193a-g

The degree of enantioselection of this Diels-Alder reaction may be explained as follows: The magnesium complexes of ligands 4a-g probably assume an octahedral arrangement. On the other hand, the dienophile assumes an S-cis conformation as shown in A [Chart 3], and the endo-Si-attack of cyclopentadiene from the sterically less-hindered side appears to be favoured, leading to the observed R-configuration of the product. The reversal of enantioselectivity using the magnesium complex derived from trifluoromethyl ligand 4g may be explained as follows: The trifluoromethyl group could coordinate or interact weakly with the magnesium cation. Furthermore, the use of a (trifluoromethyl)sulfonyl group increased the Lewis acidity of the metal centre. In this case, coordination of the fluorine or oxygen presumably occupies one of the equatorial positions, and the dienophile coordinates with the oxygen at the equatorial and axial positions, as depicted in B [Chart 3]. On the basis of this molecular arrangement, the endo-Re attack of the dienes appears to be favoured, providing the S-configuration.

Bedekar and co-workers have developed a series of derivatives of 2-(o-aminophenyl)oxazolines [Figure 26] from the reaction between isatoic anhydride 199 and different achiral as well as chiral aminoalcohols using Kaolinitic clay as catalyst to afford 200a-g in good yield. The optical purity of 200f was checked by the conversion to its tosyl derivative 193a and the optical rotation of which was in accord with the reported value, indicating no loss of optical purity during the reaction. Author’s main aim was to use this methodology for the preparation of heterogeneous catalysts 201a-c [Figure 26] because of certain advantages over classical aminooxazoline based homogeneous catalysts: (1) the ease of separation of the expensive chiral catalyst from the reaction system, and hence the possibility of reutilizing the catalyst for successive reactions, (2) convenient operation in flow reactors or
flow membrane reactors for continuous production and (3) for the development of environmentally safe processes for the production of fine chemicals.

![Diagram of molecular structures 200 and 201](image)

**Figure 26:** List of o-(anilinyl) oxazolines 200a-g and its polymer supported derivatives 201a-c

Polymer supported catalysts 201a-c were prepared according to the route described in Scheme 67. The polymer-supported isatoic anhydride 202 was prepared from chloromethylated styrene–divinylbenzene 203 polymer and isatoic anhydride 199 by the procedure described by Coppola. A sample of 202 was exposed to 2.5 equivalents of appropriate chiral aminoalcohol in presence of catalytic amount of kaolinitic clay in chlorobenzene to afford polymer-anchored amino oxazolines 201a-c.

These polymer-anchored amino-oxazolines 201a and 201b have been applied in the diethylzinc addition reaction of aldehydes. For this study addition of diethylzinc to benzaldehyde 104 was used as standard reaction. It was noted that ligands worked successfully with good results even without addition of any additive such as Lewis acid. Ligands 201a with sec-Bu substituent on oxazoline ring gave product 105-(R) with 89% ee while benzyl substituted ligand 201b produced product 105-(R) with 84% ee. The superiority of heterogeneous catalyst was proved by applying 201a for successive three cycles for the same reaction and produced the product with almost consistent stereo as well as enantioselectivity. These ligands worked well with not only aromatic aldehydes but with aliphatic aldehydes also gave good conversion and enantioselectivity.
Scheme 67: Synthesis of α-(anilinyl) oxazoline 200a-g and polymer supported derivatives 201a-c

Gossage has reported the synthesis and characterization of complexes 206 and 207 which were generated from a new class of pincer ligands derived from the 2-(α-anilinyl)-2-oxazoline 204 and 205 [Figure 27].

Figure 27: Pd-complexes 206 and 207 of α-(anilinyl) oxazoline
Pd-complexes 206 and 207 of the aminooxazolines 204 and 205 were prepared from readily accessible aminooxazolines 200b and 208 [Scheme 68]. The starting material picolinic acid was converted to its acid chloride derivative and subsequently treated with 200b or 208 using DCC-DMAP protocol to give amido oxazolines 204 and 205 with good conversion. Pd-complexes of 204 and 205 were achieved by reaction with Li₂PdCl₄.

Scheme 68: Synthesis of Pd-complexes 204 and 205 of o-(anilinyl) oxazoline

These catalysts 206 and 207 were applied for the Heck reaction of Iodobenzene and styrene to produce stilbene with high yields [Scheme 69].

Scheme 69: Application of Pd-complexes 206 and 207 in Heck reaction

Du has reported combination of two “Privileged Ligands”, one is Schiff-base ligands as they can be easily prepared through the condensation of various aldehydes with primary amines and are able to coordinate with various metals and stabilize them in different oxidation states, which enables the applications of Schiff base metal complexes in a large variety of useful catalytic transformations. It is well established that the oxazolines are another type of ‘privileged ligand’ owing to the ready accessibility, modular nature and successful
applications in various catalytic asymmetric reactions. They have synthesized a number of derivatives of Ligands 210 and 211 [Figure 28] and screened them for Cu-catalyzed asymmetric Henry reaction.\(^\text{72}\)

![Figure 28: Schiff base containing oxazoline ligands 210 and 211](image)

The oxazoline Schiff-base ligands 210 and 211a-b were easily synthesized from corresponding aldehydes and 1,2-amaioalcohols by just physical mixing at ambient conditions. Prepared ligands 210 and 211a-b were applied to the Cu-catalyzed asymmetric Henry reaction of p-Nitrobenzaldehyde 212 and nitromethane 213 in ethanol which resulted in the formation of product 214 with good enantioselectivity [Scheme 70]. Ligand 210 gave product (S)-214 with 82% ee while higher enantioselectivity of the product (S)-214 was obtained up to 88% with 211b.

![Scheme 70: Cu-catalyzed asymmetric Henry reaction using 210 and 211a-b](image)

Guiré has developed ligands 215 [Figure 29] and investigated their application in the Nozaki-Hiyama-Kishi allylation of benzaldehyde 104 using allyl bromide 191 to afford allylated product 194. The product (S)-194 with highest enantioselectivity of 57% was obtained in high isolated yield using the ligand 215f.\(^\text{73}\) For the synthesis of ligands, proline was protected as either the N-carbobenzyloxy (Cbz) or tert-butoxycarbonyl (Boc) under standard conditions in excellent yields which was then activated using chloroethylformate and subsequently reacted with o-anilino–oxazoline 200 to afford desired ligands 215 and 216 in excellent yields.
Bis-Oxazolines:

After a great success of the development of semicorrins for asymmetric catalysis, structurally similar molecules, bis(oxazolines), have been developed for the same purpose.\textsuperscript{1a,2} In recent years chiral bis(oxazolines) have received great attention for being used in asymmetric catalysis due to their coordinating ability with metals.\textsuperscript{2,74} Chiral bis(oxazoline) ligands with a great deal of structural diversity have been introduced since 1989 [Figure 30].

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chiral_semicorrin_bis_oxazoline.png}
\caption{Structurally similar $N,N$-ligands}
\end{figure}

In general bis(oxazoline) ligands with one carbon spacer between the oxazine rings are most frequently utilized. These ligands form a six member metal chelate as well as having the substituents on the ring at close proximity of the metal center which helps to increase the catalytic efficiency in asymmetric synthesis [Figure 31].
In 1991 two communications, one by Evans et al. dealing with asymmetric cyclopropanation of alkenes\textsuperscript{75a} and the other one by Corey et al. about enantioselective Diels-Alder reactions,\textsuperscript{75b} describing the applications of chiral Cu(I)- and Fe(III)-box complexes as catalysts, respectively were published. These two, almost simultaneous, communications induced a small revolution in the field of asymmetric catalysis. The box ligands quickly became widely adopted bidentate ligands due to for their easy and flexible synthesis and for the excellent enantioselectivity induced in variety of asymmetric reactions.

There are number of synthetic procedures are reported for preparation of chiral bis(oxazoline)s. Synthesis of bis(oxazoline)s has been classified roughly into three different categories:

(A) The construction of the oxazolidine rings starting from a symmetrically disubstituted malonic acid derivative (the bis-substituted spacer) and 2 equiv of optically active β-amino alcohol (the chiral messenger), the method followed by Evans and Corey in their pioneering work.

(B) The substitution of two hydrogen atoms with two identical groups on the spacer of a preformed box (followed when the spacer requires substituents other than methyl), a method that is based on the acidity of the methylene protons. This method consists of the formation of a dianion with 2 equiv of NaH or BuLi (rarely with NEt\textsubscript{3}) and in the
nucleophilic substitution either with 2 equiv of alkyl halide or with 1 equiv of alkyl dihalide to construct a ring on the spacer.

The manipulations of either chiral groups on the oxazoline rings or the groups on the spacer, the former being used to introduce hetero atom sometimes useful as internal auxiliary ligands to increase the standard bi-coordination of the box ligand and the latter in general being used to introduce functions suitable for grafting the box ligand to a solid surface.

The preparation of bis(oxazoline) ligands 217a-d and 217e from dimethylmalonyl chloride 220 is shown in scheme 71. For this, dimethylmalonyl chloride was treated with appropriate chiral aminoalcohol in presence of triethylamine as base in dichloromethane to give 221 in quantitative yield. Then it was refluxed in thionyl chloride to produce dichloro derivative 222 followed by base mediated cyclization to afford desired bis(oxazoline) ligands 217a-d in excellent yield.

![Scheme 71: Preparation of bis(oxazoline) ligands 217a-d; (R,R)-217e and (S,S)-217e](image)

Evans et al. have demonstrated that the ligand–metal complexes derived from bis(oxazoline) 217a-d and mild Lewis acid such as Cu(OTf)₂ are very efficient chiral catalysts for the Diels–Alder reaction of 3-(2′-propenoyl)-1,3-oxazolidin-2-one 196 with cyclopentadiene 197. Among these ligands, the ligand 217d with tert-butyl substituent at oxazoline ring consistently provided a very high level of endo/exo selectivity as well as 198-endo enantioselectivity (98% ee with 5–10 mol% catalyst) and chemical yield (82–92%) with a number of substituents [Scheme 72]. The Cu(II) complexes of ligand 217a, 217b and 217c
are not equally effective catalysts as they have shown considerably lower enantioselectivity (30, 82% and 58% ee respectively).

In 1998 Desimoni developed both enantiomers of the bis(oxazoline) ligand 217e, with bulky 2-naphthyl groups at the 4-position of the oxazoline rings. This ligand was examined in the Lewis acid-catalyzed Diels-Alder reaction of 3-(2'-propenoyl)-1,3-oxazolidin-2-one 196 with cyclopentadiene 197. This aim was achieved by using different metal salts [Mg(IIClO₄)₂, Mg(OTf)₂, and Cu(OTf)₂] as Lewis acid catalysts with ligand (R,R)-217e. The catalyst derived from magnesium(II)triflate provided the product 198-endo with the highest levels of asymmetric induction of 94 ee (R) for the reaction of 196 [see Scheme 72]. The opposite enantiomeric product 198-endo-(S) was obtained in 77% ee when the counterion was changed to perchlorate. This reversal of enantioselectivity was attributed to the formation of a tetrahedral complex with magnesium(II)perchlorate and an octahedral complex with magnesium(II)triflate.

![Scheme 72: Cu-catalyzed Diels-Alder reaction using bis(oxazoline) ligands 217a-d](image)

Desimoni et al reported the synthesis of cis and trans-4,5-disubstituted chiral bis(oxazoline) derivatives 218a and 218b from the same optically active 1,2-disubstituted aminoalcohol 223 and dimethylmalonyl chloride 220 [Scheme 75]. As depicted in Scheme 75, the bis(hydroxy)amide 224 was subjected to two different cyclization conditions to effect either retention or inversion of configuration at the C-5 position. Exposure of the bis(hydroxy)amide 224 under the Masamune protocol (Bu₂SnCl₂, reflux) furnished the cis-1,2-disubstituted bis(oxazoline) 218a. On the other hand, formation of the bis-mesylate followed by treatment with base afforded the trans-1,2-disubstituted bis(oxazoline) 218b.
Scheme 73: Synthesis of 4,5-disubstituted bis(oxazoline) derivatives 218a-b

Davies has developed the synthesis of spiro bis(oxazolines) 225a-d [Scheme 74], and explained a direct correlation between the ligand bite angle and enantioselectivity in asymmetric Diels-Alder reaction. [see Scheme 72].

Scheme 74: Synthesis of bis(oxazoline) 219, 228 and spiro bis(oxazoline)s 225a-d

The spiro ligands 225a-d were synthesized in two steps from the readily available (1S,2R)-amino indanol 229 (Scheme 2). Condensation with diethylmalonimide 227 at reflux in 1,2-dichloroethane gave the pivotal bis(oxazoline) 228. Treatment of a mixture of 228 (1 eq.), TMEDA (2 eq.), and diisopropylamine (1 eq.) with butyllithium (2 eq.) at -65 to -20 °C, followed by addition of the appropriate dioxoalkane (1.1 eq.) led to the formation of the spirobis(oxazoline) 225a-d. From 228, on treatment with LDA (2 eq.) followed by addition of methyl iodide (2 eq.) led to the formation of dimethylsubstituted pivotal bis(oxazoline) 219.

Use of ligand 219 in Cu-catalyzed Henry reaction of 4-Nitrobenzaldehyde 212 and nitromethane 213 was resulted in excellent yield for (R)-214 with 81% enantioselectivity [see Scheme 70]. The distorted square-pyramidal configuration can be proposed for the reaction intermediate A, with the nucleophile in the axial position and the electrophile in the ligand.
plane on the basis of both steric and electronic considerations, which accounts for the observed sense of asymmetric induction [Chart 4].

![Chart 4: Model for the selectivity in Henry reaction using ligand 219](image)

Using these bis(oxazoline ligands) for the Diels-Alder reaction of 3-(2'-propenoyl)-1,3-oxazolidin-2-one 196 with cyclopentadiene 197 afforded the exclusively 198-endo product with high enantioselectivity. Results clearly showed that direct effect of ligand bite angle on the enantioselectivity of the product, as or gradual increase of the bite angle of the ligand from 103.7° (in ligand 225d) to 110.6° (in ligand 225a) resulted in the increase in enantioselectivity of the product from 83% (with ligand 225d) to 96% (with 225a).

Nishiyama and co-workers have developed pyridinyl bis(oxazoline) ligands 230 and 231a-c from pyridine 2,6-dicarboxylic acid chloride 232 [Scheme 75].

![Scheme 75: Synthesis of pyridinyl bis(oxazoline) ligands 230 and 231a-c](image)

These type of py-box ligands have been applied to variety of asymmetric transformations. Nishiyama et al have reported the use of Ru(II)-Py-box complexes as excellent catalysts for the enantioselective asymmetric cyclopropanation of styrene 150 with
diazooacetate 234. Amongst these py-box ligands, the Ru-complex formed with ligand 231b was found to be the best system for this reaction giving trans isomeric product 235 predominantly with high enantioselectivity in the range 92-93% depending on the Ru-salt used for the complexation [Scheme 76].

![Scheme 76: Cyclopropanation reaction of styrene using Ru-complex of py-box 231b](image)

Jacobsen has also used these py-box ligands 231a-c in Yb-catalyzed asymmetric ring opening of meso epoxide 236 with TMSCN yielded the β-trimethylsiloxy nitrile ring-opened product 237 with good enantioselectivities (82-93% ee) [Scheme 77]. Complex with ligand 231c gave the best results for this reaction. The reaction exhibits a second-order kinetics dependence on catalyst concentration and a first-order dependence on epoxide concentration, consistent with a bimetallic pathway involving simultaneous activation of epoxides and cyanide.

![Scheme 77: Yb-catalyzed asymmetric ring opening of epoxide using ligands 231a-c](image)

Another class of bis(oxazoline) ligands with cyclic 1,3-dioxolane backbone 238 a-e and 239 a-b [Figure 32] have been developed by Andersson et al in good yields and screened them for Cu-catalyzed cyclopropanation reaction of styrene with ethyl diazooacetate.

![Figure 32: New class of bis(oxazoline) ligands with cyclic 1,3-dioxolane backbone 238 a-e and 239 a-b](image)
The preparation of ligands 238a-e was achieved in four steps from (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester 240 [Scheme 78]. Compound 240 was treated with appropriate L-amino acid in the presence of catalytic amount of NaCN in Methanol at 45°C to afford corresponding dihydroxydiamides 241a-e in good yields which were then converted to their mesylate derivatives using MsCl in presence of triethylamine as base in dichloromethane and subsequently mesylates were cyclised to give desired bis(oxazoline) ligands 238a-e with good conversion. Also the enantiomers 239a-b were prepared from the corresponding (4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester by following the same procedure as described in scheme 78.

Scheme 78: Preparation of bis(oxazolinc) ligands with cyclic 1,3-dioxolane backbone 238a-e

These set of ligands were applied to Cu-catalyzed asymmetric cyclopropanation reaction of styrene 150 with ethyl diazoacetate 242 to give corresponding product 243 with good conversion as well as stereoselectivity [Scheme 79]. Amongst the series 238a-e, ligand with iso-propyl substituent at oxazoline ring 238c yielded product 243 with 70:30 (trans: cis ratio) and enantioselectivity for trans product was 84% and 65% for cis product while from the ligands 239a-b, 239b gave product 243 with same ration i.e. 70:30 (trans: cis ratio) and 84% ee for trans and 85% ee for cis product.
Scheme 79: Cu-catalyzed cyclopropanation of styrene using bis(oxazolines) 238 and 239

Bolm has also developed series of bis(oxazoline) ligands 244-248 [Figure 33] having cyclic backbone and screened them for asymmetric cyclopropanation reaction as well as asymmetric transfer hydrogenation. These ligands have been prepared according to well documented procedures.\(^8^4\)

![Figure 33: Bis(oxazoline) ligands having cyclic backbone](image)

Using these ligands 244-248 for Cu-catalyzed cyclopropanation of styrene 150 with ethyl diazoacetate 242 resulted product with good conversion but with modest selectivity.

Hayashi has developed ligands 249 and 250 containing functional groups in the 3- and 3’-positions of the binaphthyl skeleton [Figure 34].\(^8^5\) Ligands 249 and 250 were examined for asymmetric induction in the palladium(II) catalyzed Wacker-type cyclization of the trisubstituted olefin \((E)-2-(2$\text{-methyl}$-2$\text{-butenyl})$phenol 252, forming the 2,3-dihydrobenzofuran 253 [Scheme 80].
Ligand 250a, with gem-dimethyl groups at the oxazoline 4-positions and methoxycarbonyl groups at the C-3 and C-3’ positions of the binaphthyl skeleton, was optimal, affording product 253 in 90% yield and 67% ee (S) at 60 °C. The enantioselectivity was increased to 96% ee (S) on running the reaction at the reduced temperature of 20 °C with an increased ligand-to-palladium ratio of 3:1, while surprisingly ligand 249a gave only 13% ee for this reaction.

Scheme 80: Pd-catalyzed Wacker type cyclization using ligand 250

1,1’-Bis(diphenylphosphino)-2,2’-bis(oxazolinyloxy)ferrocene ligands 251 [see Figure 34] and its structural analogues were investigated by Park in the palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate 35. The palladium catalysts, generated in situ from ligands 251 and [Pd(η3-C3H5)Cl]2 (1 mol %), was highly efficient, affording product [(S)-13] in almost quantitative yield and with 94% ee.

Dibenzofused heterocycle based bis(oxazoline) ligands 254-257 have been developed by number of research groups independently [Figure 35].
Figure 35: Dibenzo-fuzed heterocycle based bis(oxazoline) ligands 254-257

Pd-allyl complexes ([Pd(η3-C5H5) ligand]PF6) of the (S,S)-DBFOX/Ph ligand *ent-254* and the bis(oxazoline) ligand 255, which contains a diphenyl ether backbone, were applied by Gómez in the Pd-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate.86 The palladium complex (2 mol %) derived from ligand 255 afforded high enantioselectivity, giving 89% ee (S) and complete conversion after 2.5 days at room temperature. In contrast, the palladium allyl complex of ligand *ent-254* was inactive, affording no product after 7 days. This result was in agreement with the inability of this ligand to form stable palladium complexes with 1,3-diphenylallyl substrate 12.

Another class of ligands, carbazole based bis(oxazoline) of type 256 was developed by Nakada for the application in asymmetric Nozaki-Hiyama-Kishi reaction. Using chromium complex of the ligand 256 for the alkylation of benzaldehyde 104 with allyl bromide 191 yielded allylated product 192-(S) with 68% ee.87

Schulz has applied the dibenzo thiophene based bis(oxazoline) ligands 257 in the Pd-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate 12 with dimethyl malonate.88 The (S)-iso-propyl substituted ligand 257a afforded the best result, with 77% ee for R-isomer and complete conversion after 70 h at 40 °C in dichloromethane using 2.5 mol % of [Pd(η3-C5H5)Cl]2 and employing the BSA/KOAc methodology.
Tris-Oxazolines:

There are relatively few examples of metal complexes of tris(oxazoline) ligands being applied in asymmetric catalysis. Representative structures are shown in Figure 36.

![Figure 36: Examples of tris(oxazoline) ligands 258 and 259](image)

Tang has reported the synthesis of tris(oxazoline) ligand 258 from dimethylmalonate 260 in four steps [Scheme 81].\(^8\) Starting from dimethylmalonate 260 which was alkylated with bromomethylacetate in presence of sodium in methanol to give triester 261. Again alkylation of 261 using methyl iodide afforded methylated triester 262 which was then treated with appropriate chiral aminoalcohol to give triamidol product 263 with good conversion. Finally the cyclisation of 262 using PPh₃-CCl₄ system to afford desired tris(oxazoline) ligands 258 with excellent yield.

![Scheme 81: Synthesis of tris(oxazoline) ligands 258a-c](image)
Tang has applied these tris(oxazoline) ligands 258 in the enantioselective Friedel-Crafts reaction between indole 264 and diethyl 2-benzylidene malonate 265. Amongst all these ligands 258a was found to be the best to give product (S)-266 with 93% ee [Scheme 82].

Scheme 82: Cu-catalyzed Friedel-Crafts alkylation of indole using tris(oxazoline) ligand 258

Because of their high affinity for potassium ions, the benzene-based tripodal oxazoline ligands 259 were utilized by Ahn in the enantioselective Michael reaction between methyl phenylacetate 267 and methyl acrylate 268 mediated by catalytic amounts of potassium tert-butoxide gave product 269 [Scheme 83].\textsuperscript{90} The best result for the product 83% yield and 82% ee (R) was afforded by 20 mol % of potassium tert-butoxide and 10 mol % of ligand 259b in toluene at -78 °C.

Scheme 83: Michael addition reaction using tris(oxazoline) ligands 259b

Thus in this chapter a summary of the developments in the field of homogeneous catalysis, using oxazolinyl system is presented, with particular emphasis on the chiral applications.
References


