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 oragnocatalysts 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[1a] **1** (X = CH) or **2** [**Figure 1**].

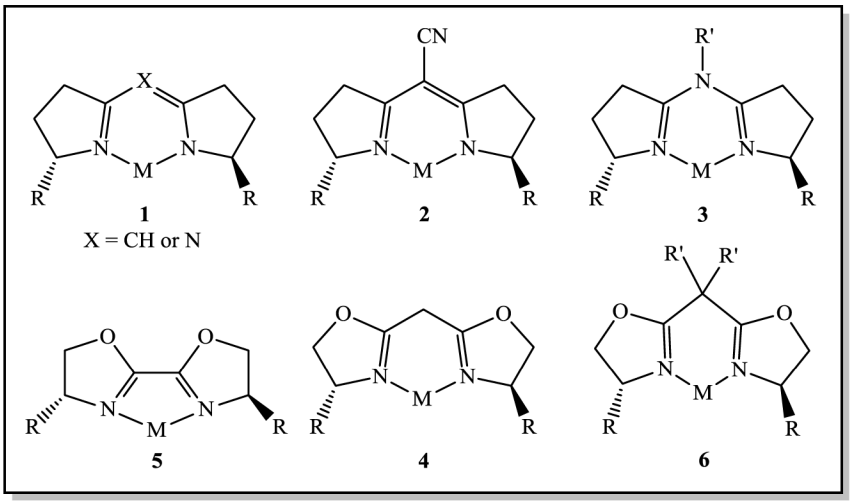


Figure 1: C_2-Symmetric ligands

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 α,β-unsaturated carboxylic acid derivatives[1a,f-h], 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,i, 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.

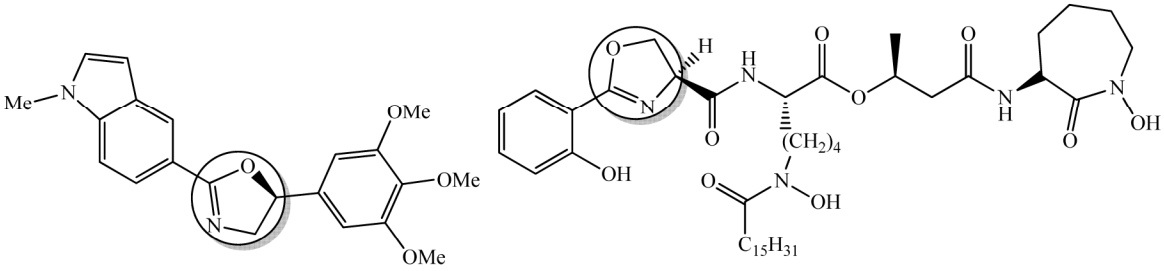
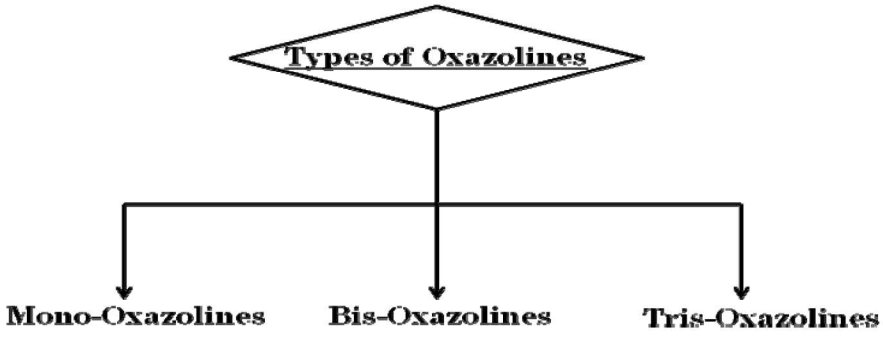


Figure 2: Bioactive molecules with oxazoline skeleton

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[6a], carboxylic esters[6b], nitriles[6c], aldehydes[6d] and amido alcohols.[6e] 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.



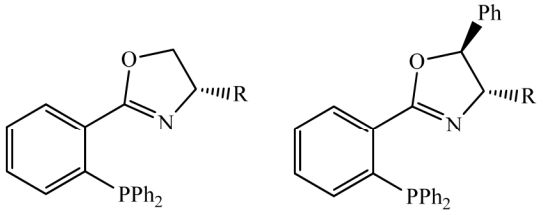
Mono-Oxazolines:

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,[7] oxazolines, readily available from amino acids, have found widespread use as chiral nonracemic ligands in asymmetric catalysis.[8] 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.[9] Schematic diagram for the preparation of the Ligands **9** and **11** are shown in **[Scheme 1]** and **[Scheme 2]**.[10]

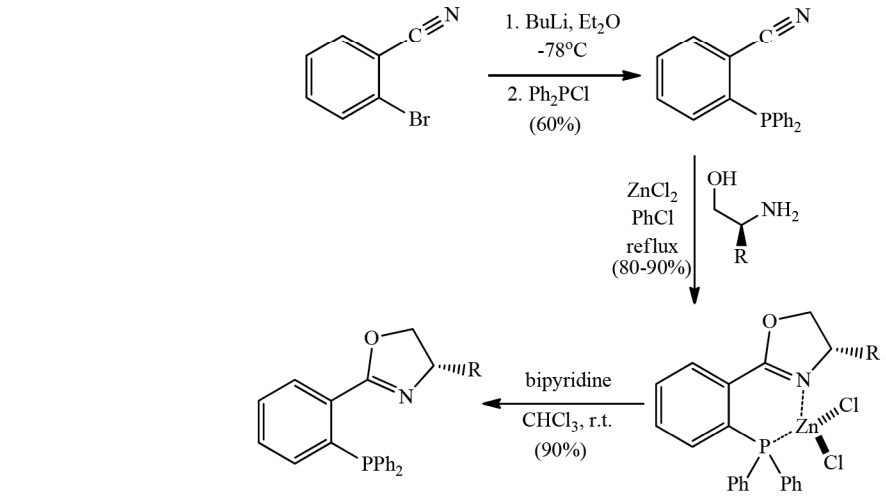


9a (R = Me); 9b (R = Bn); 9c (R = ^{i}Pr); 9d (R = Ph); 9e (^{t}Bu); Ar = Ph
10; Ar = 1-naphthyl; R = ^{i}Pr

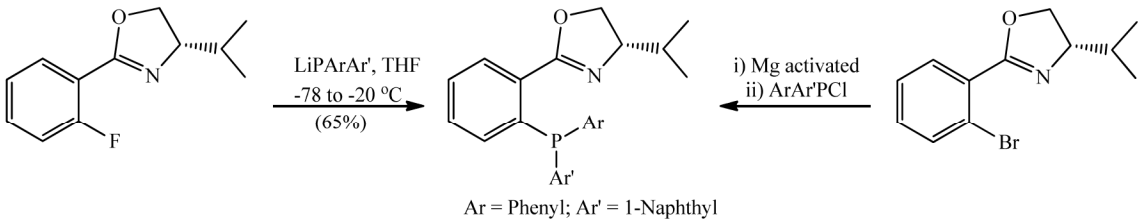
11; R = CH2OSi^{t}BuMe2

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

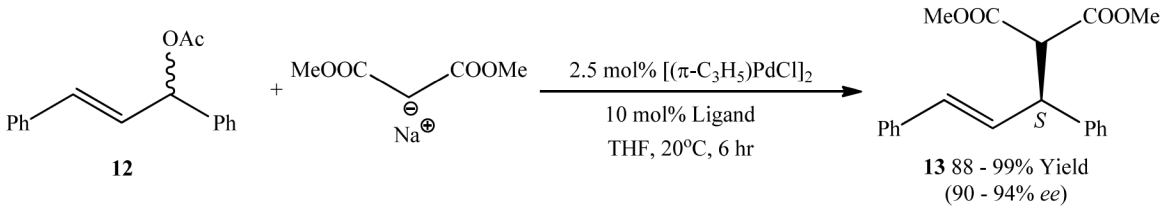


Scheme 2: Preparation of the PHOX ligand **10** developed by Pfaltz and Helmchen

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.[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.[12]

The reaction of 1,3-diphenyl-2-propenyl acetate **12** with the sodium salt of dimethyl malonate in the presence of catalytic $[(\pi\text{-}C_3H_5)PdCl]_2$ 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.[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.[10c,d] Rationalization of the steric course of the nucleophilic substitution is difficult because it involves two diastereomeric π-allyl complexes, designated *exo* (A) and *endo* (B) isomers.

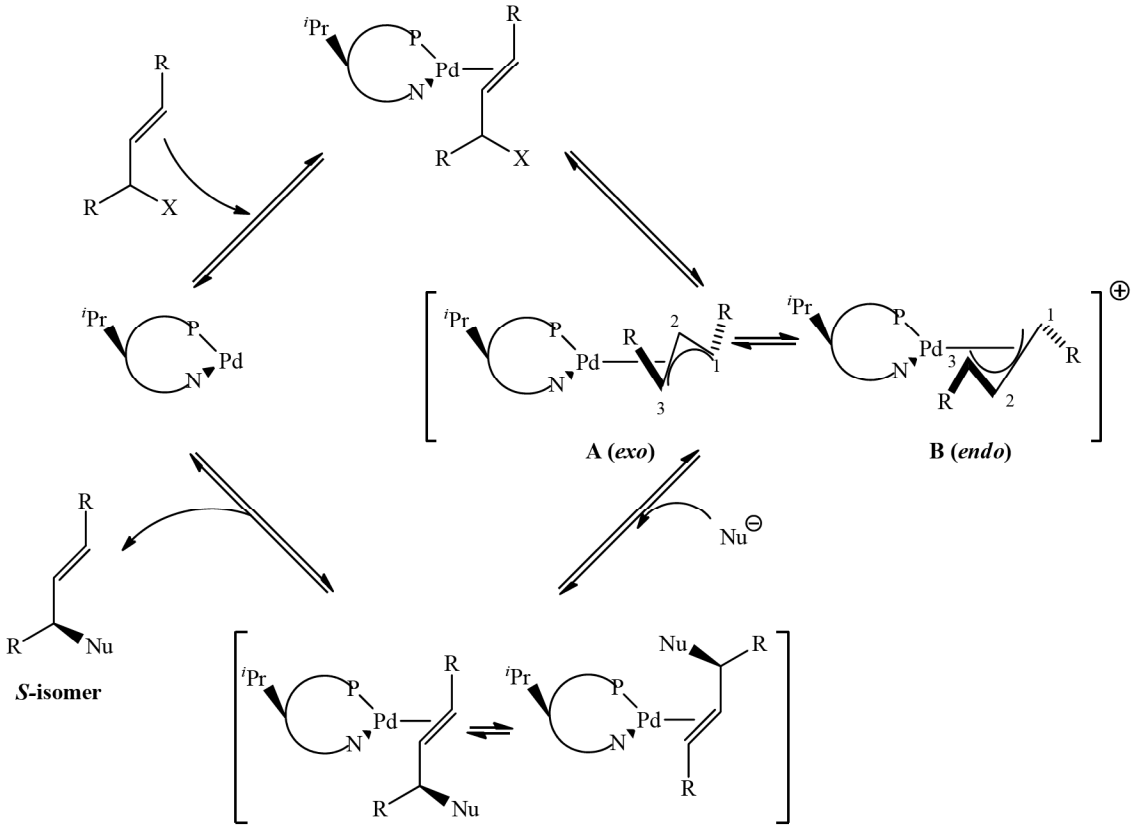


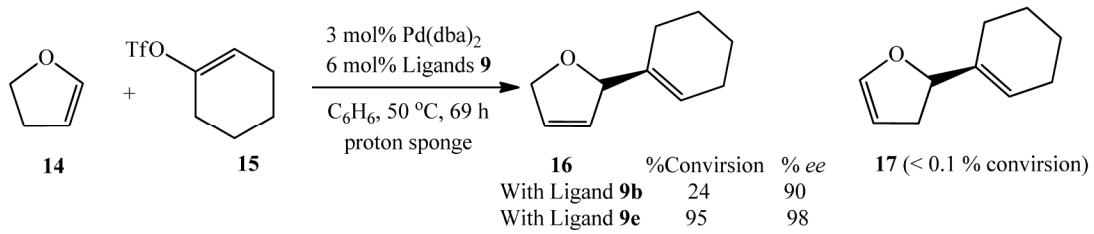
Chart-1: Mechanistic aspect for the selectivity due to PHOX ligands

As we know the more abundant isomer is the more reactive one. The more abundant is generally the *exo*-isomer **[Chart-1]**. In conjunction with the known configuration of the products of allylic substitutions, it was deduced that the nucleophile preferentially attacks the carbon *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 (*exo*) : B (*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.[13] Complex with Ligand **9c** was found to be the best which afforded 98% *ee* of the product.

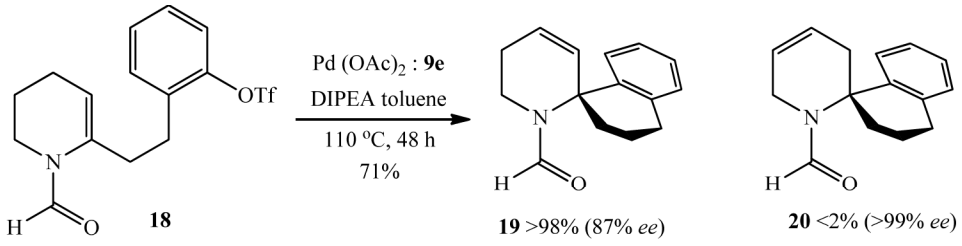
This type of PHOX ligands not only worked well for Pd-catalyzed allylic substitution reactions but also proved to be efficient ligands for Pd-catalyzed asymmetric Heck reaction.

Using ligands **9**, numbers of transition metal catalyzed organic transformations have been reported. Phosphinooxazolines are highly effective ligands for the enantiocontrol in Heck reaction **[Scheme 4]**.[14]



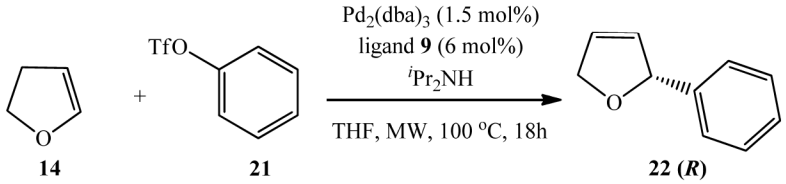
Scheme 4: Pd-catalyzed enantioselective intermolecular Heck reaction

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, phosphinooxazolines 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]**.[16]



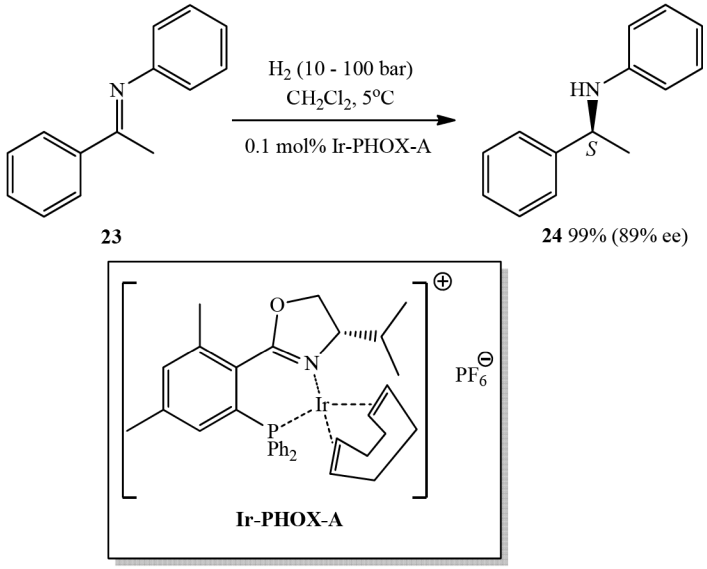
Scheme 5: Pd-catalyzed intramolecular enantioselective Heck reaction by Ripa and Hallberg

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

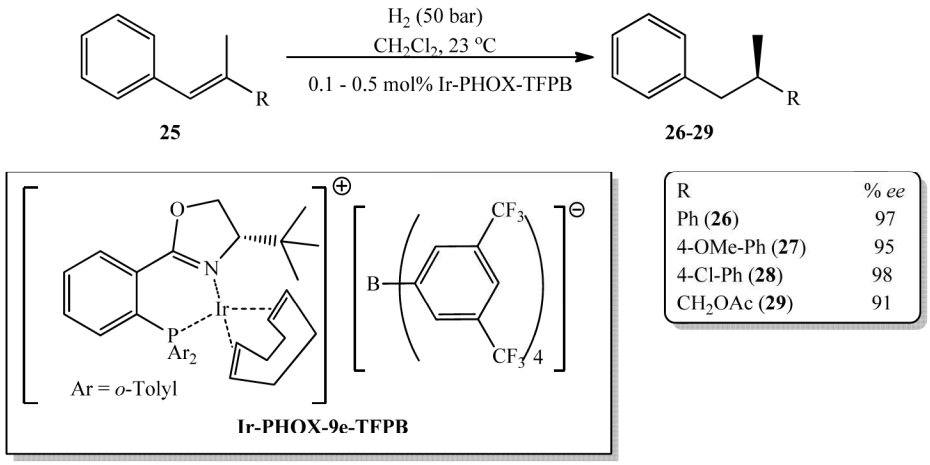
Complexes of this type of PHOX ligands with other metals like iridium, rhodium, ruthenium, copper etc have also contributed for the enantioselection in various organic transformations. Ir-PHOX-A complex have emerged as a promising new class of catalysts for the enantioselective hydrogenation of imines 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 H_2 pressure between 10 and 100 bar and turn over number >1000.



Scheme 7: Ir-catalyzed asymmetric hydrogenation of imines

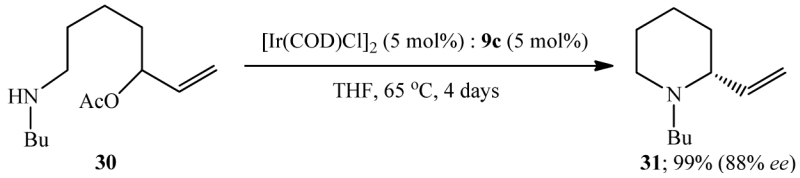
Even higher catalyst activity were observed in supercritical CO_2 as a solvent which allowed easy recovery and recycling of the catalyst.[18] There was problem of deactivation of the catalyst during the course of reaction which was then solved after a long term experiments by using tetrakis[2,6-bis(tifluoromethyl)phenyl]borate (TFPB) as the counterion instead of more common noncoordinating anions, such as hexafluorophosphate (PF_6^-) or tetrafluoroborate (BF_4^-). 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]**.[19]



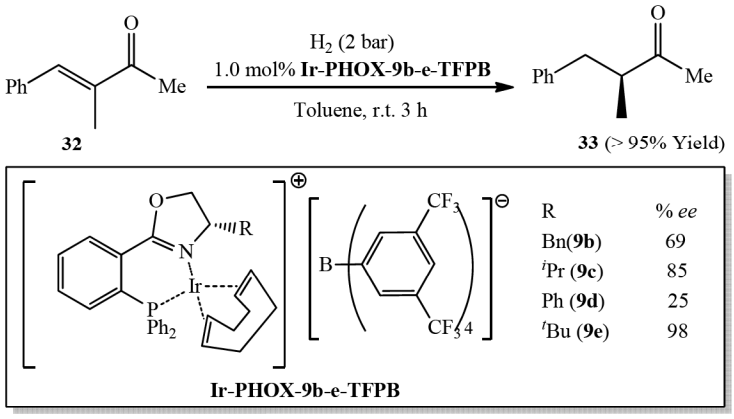
Scheme 8: Ir-catalyzed asymmetric hydrogenation of trisubstituted olefins

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]**.[20]



Scheme 9: Ir-catalyzed intramolecular enantioselective amination

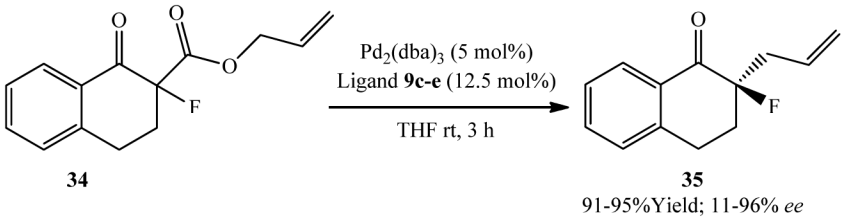
Bolm *et al* and Hou *et al* have independently studied Ir-PHOX catalyzed asymmetric hydrogenation of the carbon-carbon double bond of α, β-unsaturated ketone **32** which gave saturated ketone **33** with good to high degree of enantioselectivities in the range 25-98% *ee*. In this case also ligand **9e** was found to be the most stereoselective **[Scheme 10]**.[21]



Scheme 10: Ir-catalyzed asymmetric hydrogenation of α,β–saturated ketone

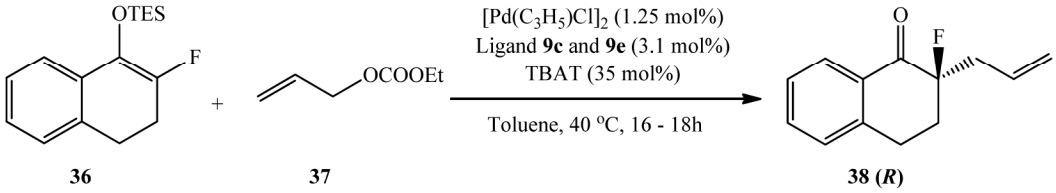
Nakamura *et al* have developed new class of enantioselective C-C bond forming reaction which was useful for the region and enantioselective synthesis of α-allyl-α-fluoro

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]



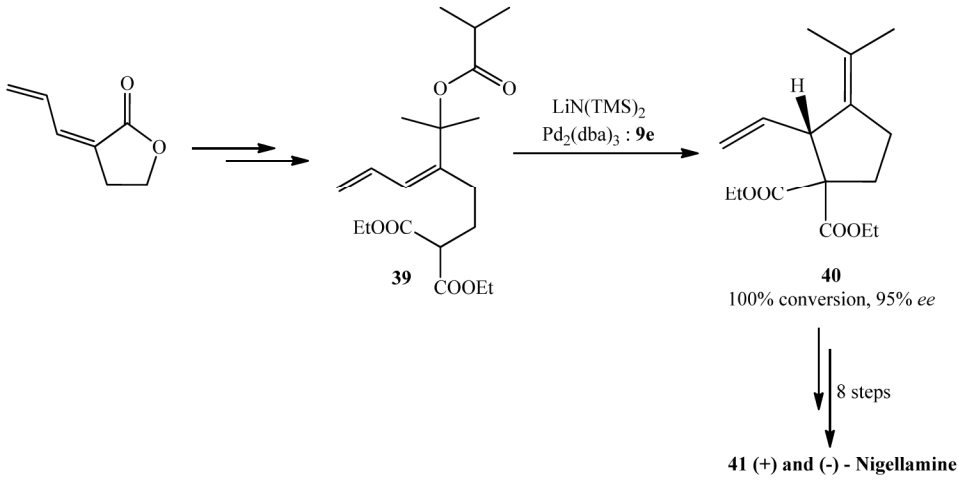
Scheme 11: Pd-catalyzed decarboxylative allylation of α–fluoro ketone

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]



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** complex[9c] 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]**.



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

Another class of PHOX ligands **42-46** were also developed by group of scientists **[Figure 4]**.[24]

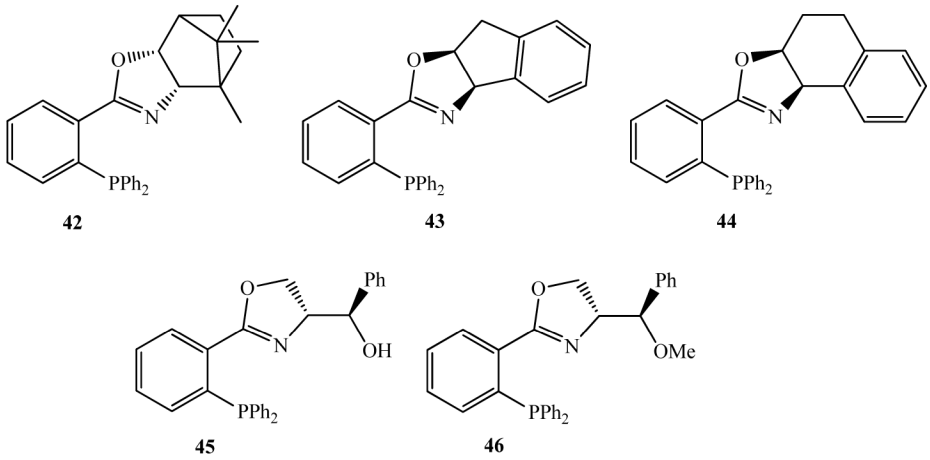
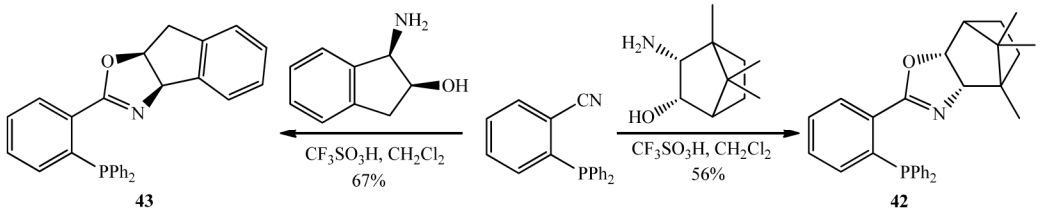
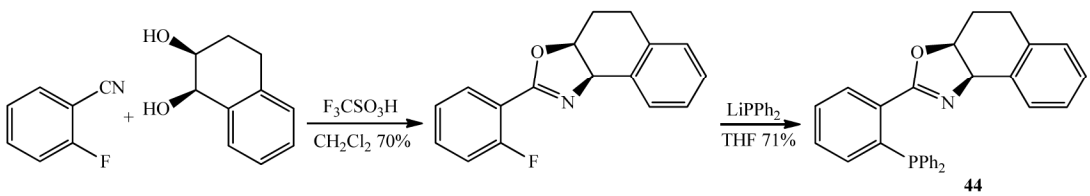


Figure 4: New class of PHOX ligands developed by Helmchen *et al* and Frolander *et al*

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 (2*S*,3*R*)-3-hydroxy-bornylamine and (1*R*,2*S*)-l-amino-2-indanol **[Scheme 14]** while ligand **44** was obtained from (1R,2S)-l,2,3,4-tetrahydro-l,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.

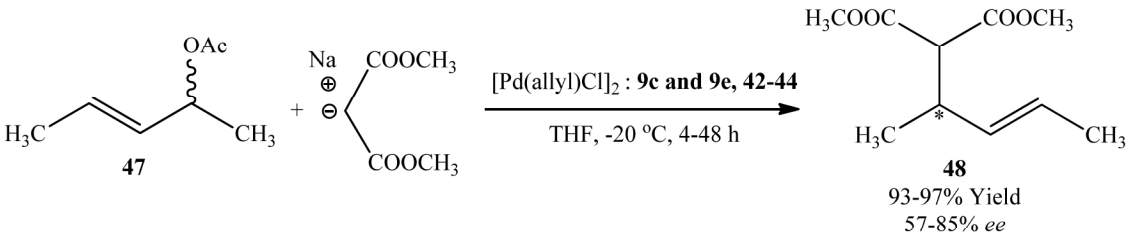


Scheme 14: Preparation of ligands **42** and **43**



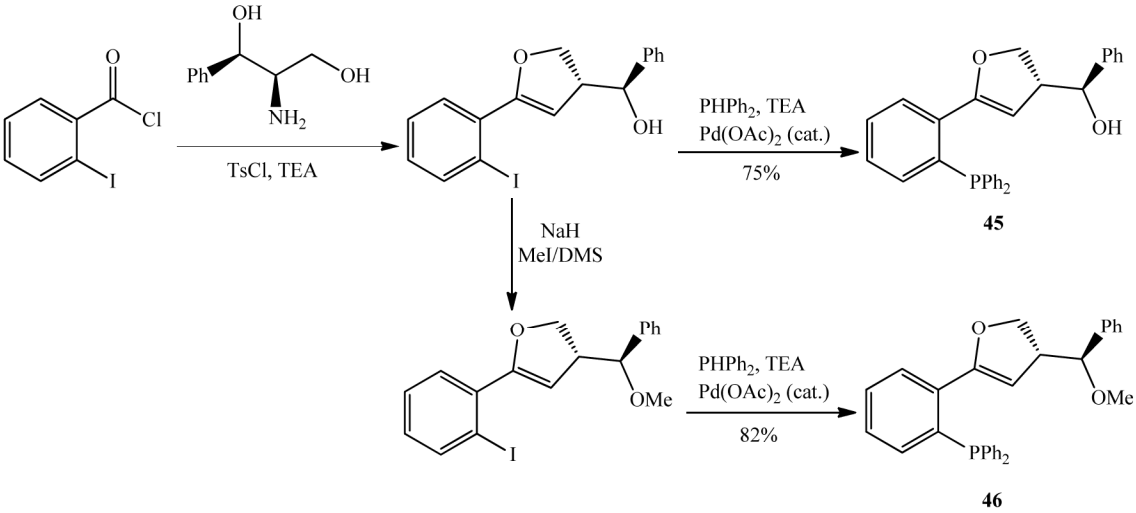
Scheme 15: Preparation of ligand **44**

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**

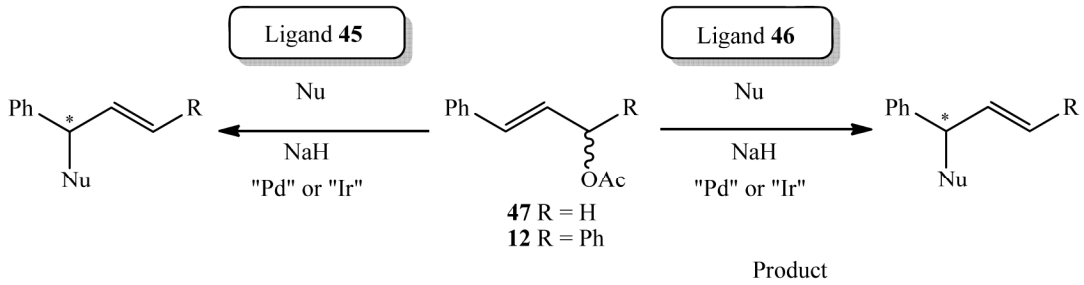
It is well known that most of the earlier phosphinooxazoline ligands possess only one kind of chirality i.e. on oxazoline ring which render the ligands effective for a number of reactions. Ligand **45** and **46** **[**see **Figure 4]** were prepared from 2-Iodo benzoyl chloride via amido alcohol intermediate and then nucleophillic substitution of iodide with diphenylphosphine to afforded the desired product in considerably high yield **[Scheme 17]**.[24b]



Scheme 17: Synthesis of ligand **45** and **46**

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]**.[24b]

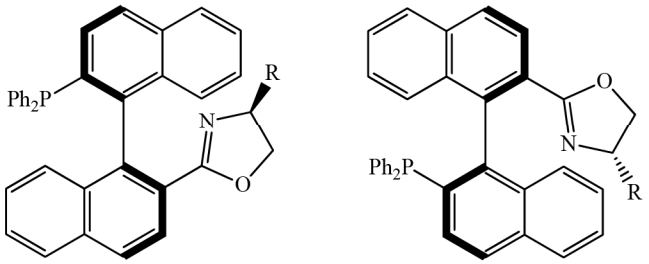


Product

Nu = $CH_2(COOCH_3)_2$		Ligand **45**		Ligand **46**	
		% Yield	% *ee*	% Yield	% *ee*
$[\eta^3-(C_3H_5)PdCl]_2$	**12**	>99	88 (*S*)	>99	99 (*S*)
$[Ir(COD)Cl]_2$	**47**	67	3 (*S*)	97	82 (*R*)

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.[1a,2,25] 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.[26] 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.

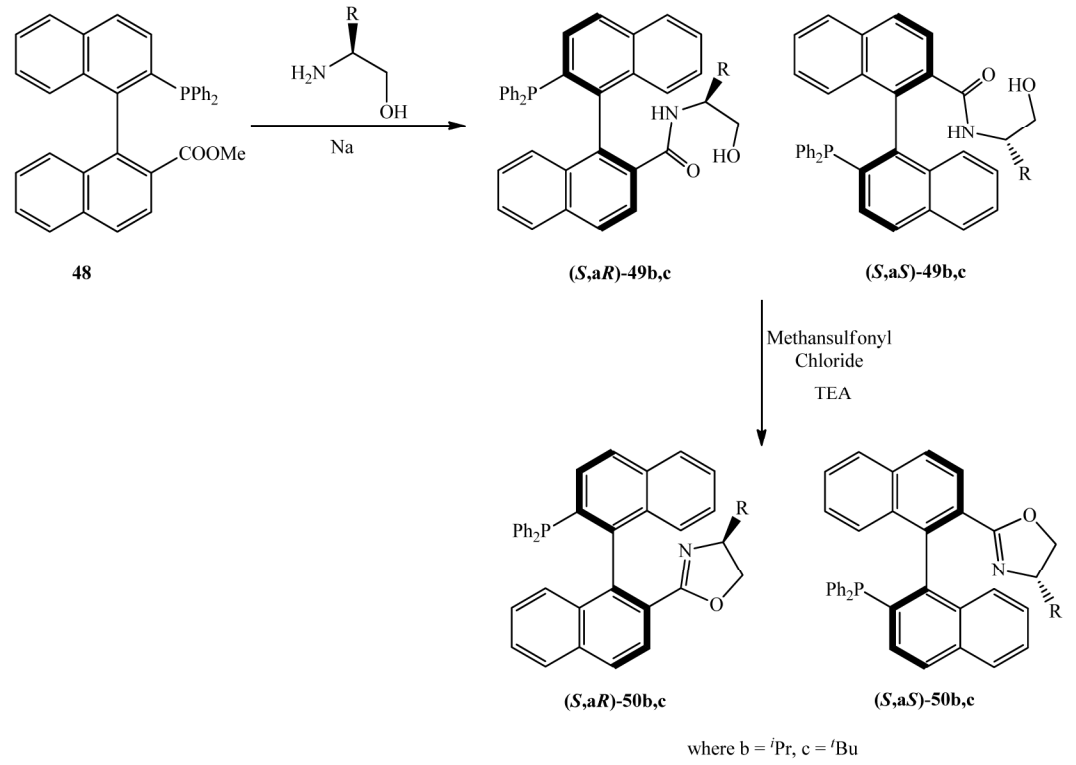


(*S*,a*R*)-50 b; R = ^{i}Pr, c; R = ^{t}Bu **(*S*,a*S*)-50**

Figure 5: N,P-oxazoline ligands with binaphthyl backbone **50**

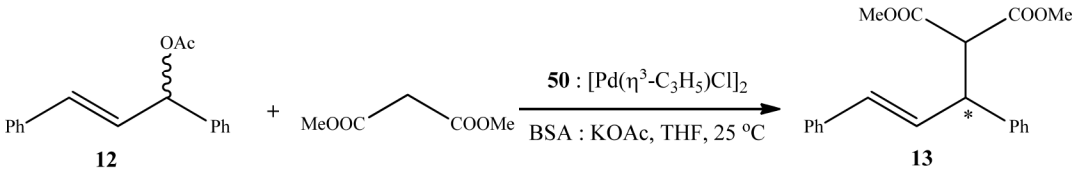
Ligands **(*S,aR*)-50** and **(*S,aS*)-50** can be synthesized from racemic diphenylphosphinocarboxylic esters **48** which were prepared from racemic binaphthol according to a reported method. After the reaction of racemic **48** with (*S*)-aminoalcohol, the resulting two diastereomeric amides **(*S*, a*R*)-49** and **(*S*, a*S*)-49** were separated with silica gel column chromatography in 34-39% yields. These amides **(*S*, a*R*)-49** and **(*S*, a*S*)-49** were treated with methanesulfonylchloride in the presence of triethylamine to afford ligands **(*S*,**

a*R*)-50 and **(*S*, a*S*)-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]**.



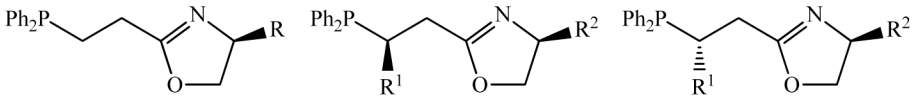
Scheme 20: Pd-catalyzed allylic substitution reaction using ligands **50**

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*)-aminoacids so far afforded an (*S*)-**13**[1a,2,25] 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.[27] 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,[28] 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 ^{o}C. The enantiomeric excess was determined by ^{1}H-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]**.



51
a R = Me
b R = Bn
c R = ^{i}Pr
d R = Ph

(*R,S*$_{ox}$)-52
a R^1 = Me, R^2 = Me
b R^1 = Ph, R^2 = Bn
c R^1 = Ph, R^2 = ^{i}Pr
d R^1 = Ph, R^2 = Ph
e R^1 = Ph, R^2 = ^{t}Bu

(*S,S*$_{ox}$)-52

Figure 6: New class of *N,P*-oxazoline ligands **51** and **52**

These ligands with both one and two stereocentres have been utilized in palladium catalyzed allylic alkylations.[29] 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,S*ox)-52a** and **(*R,S*ox)-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]**.[30]

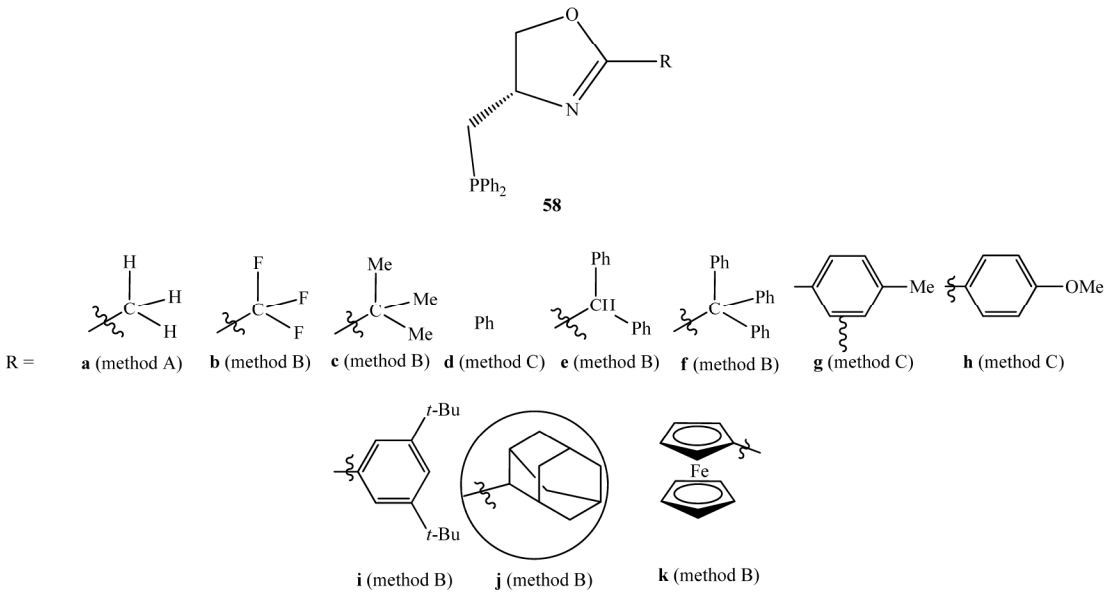
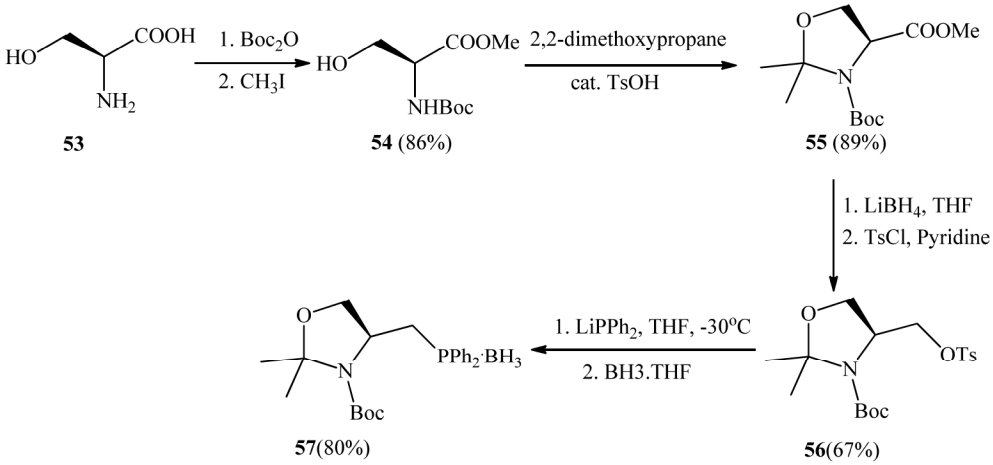


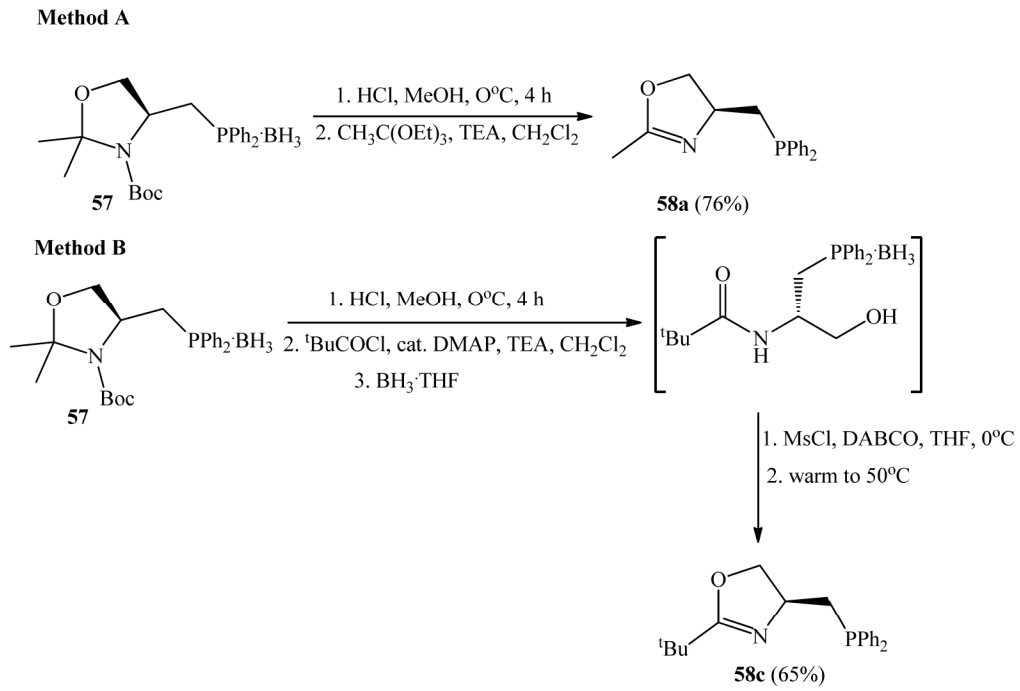
Figure 7: List of ligands developed by Burgess

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 $LiPPh_2$ resulted in substitution of tosylate by diphenylphosphine group which was protected immediately by addition of BH_3.THF complex to afford **57 [Scheme 21]**.

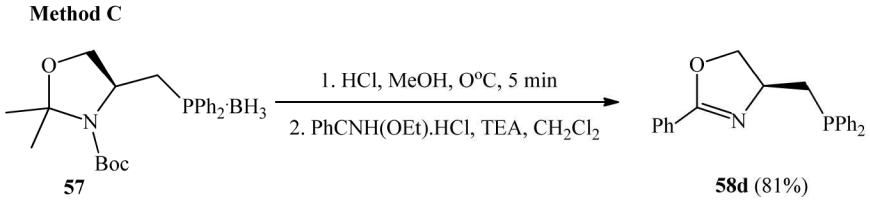


Scheme 21: Synthetic route for the preparation of key intermediate **57**

Three methods used for the preparation of phosphinooxazolines **58** are shown in scheme **[Scheme 24** and **25]**.

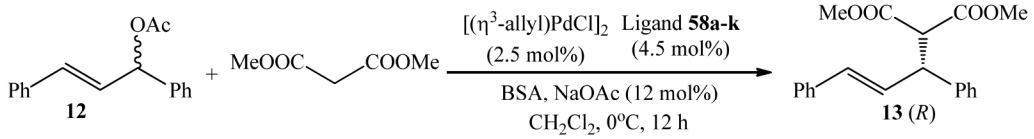


Scheme 22: Different methods used for the preparation of PHOX ligands **58**



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*.



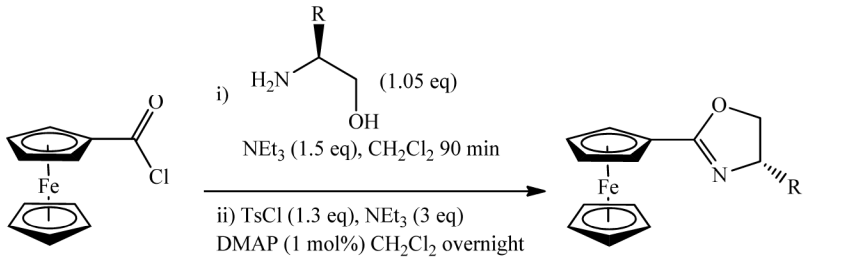
Scheme 24: Pd-catalyzed allylic alkylation using ligand **58a-k**

Another class of phosphinooxazolie ligands is diphenylphosphinoferrocenyl oxazolines **63 [Figure 8]** which has been developed by Sammakia *et al*.[31]

(*S,Sp*)-63 R = iPr (a); tBu (b); Ph (c); Bn (d) **(*S, Rp*)-63** R = iPr (a); tBu (b); Ph (c); Bn (d)

Figure 8: Diphenylphosphinoferrocenyl oxazoline ligands (DPOF) **63**

Earlier, Ferrocene complexes have been prepared in nonracemic form by classical resolution.[32] 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]**.[31d]

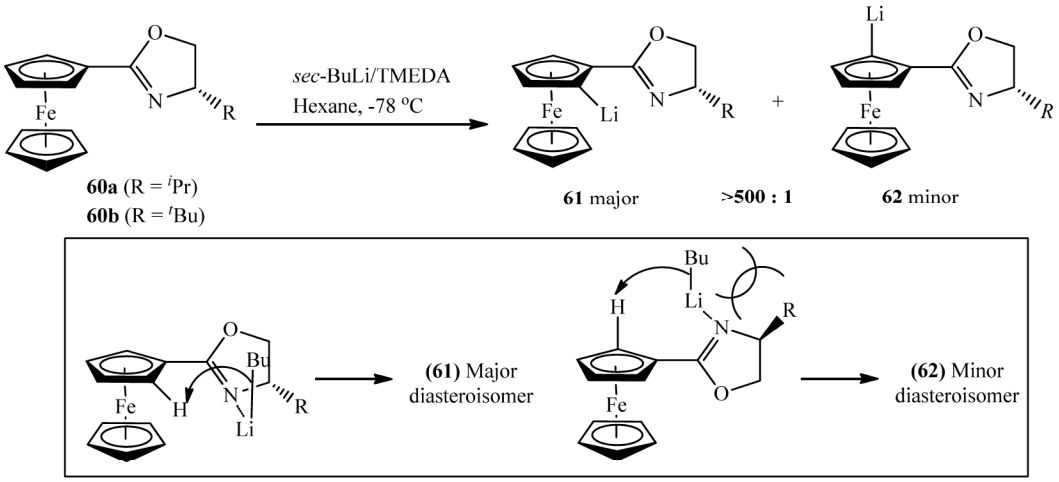


59 **60a-d** R = a (iPr, 82%); b (tBu, 96%) c (Ph, 61%); d (Bn, 70%)

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 oxazolinylferrocene compounds.[33] 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.[31a,33a,b] 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,[33a] through 8:1 with *sec*-BuLi at −78°C in THF,[33b] and finally 39:1 with *sec*-BuLi again used at −78°C but in Et_2O[31a] **[Scheme 26].** These reactions are mediated by nitrogen rather than oxygen directed lithiation.[31c] 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.[33a] However, when *tert*-BuLi is employed in these lithiations, it is possible that the

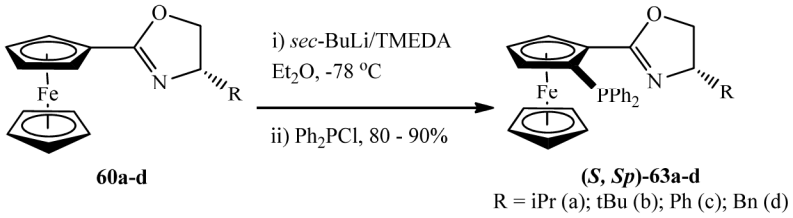
significantly lower selectivities observed are due to a competing and less sterically encumbered oxygen directed pathway.



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

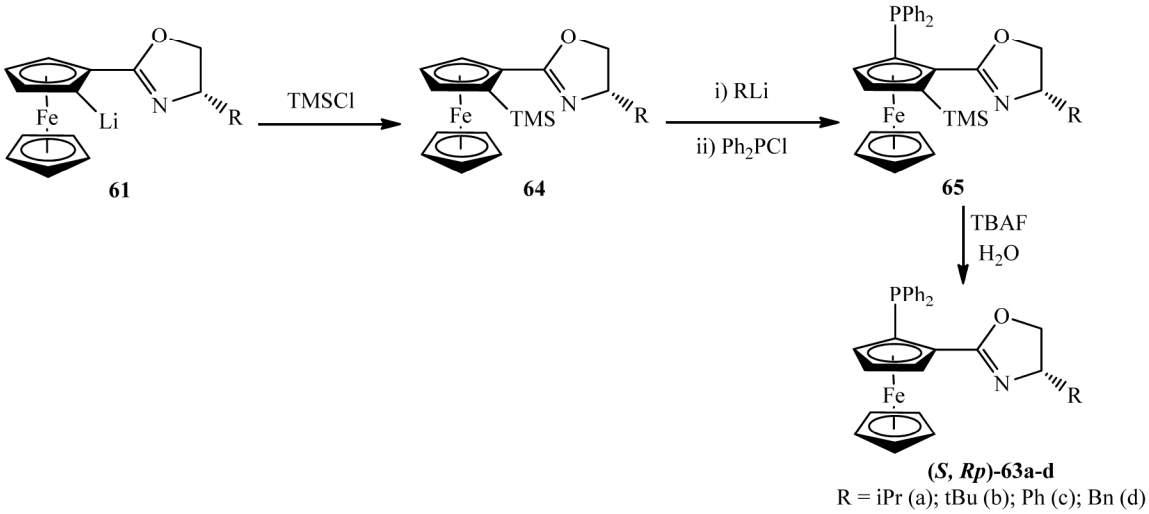
With oxazolines **60a** and **60b** the observed selectivity may be explained with a model in which the oxazoline substituent is similarly oriented towards the iron, allowing the nitrogen-coordinated alkyl lithium reagent to approach unconstrained from the opposite direction.[33a] However, when *tert*-BuLi 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*)-diphenylphosphinoferrocenyloxazoline (DPOF) ligands **63a**–**d [Scheme 27].**



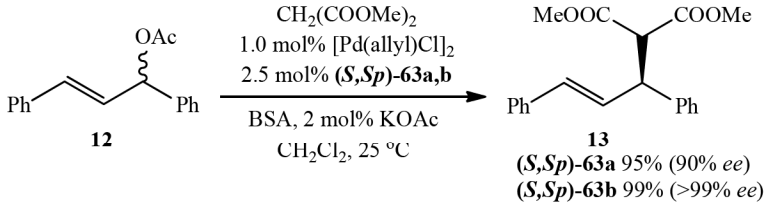
Scheme 27: Preparation of DPOF **(*S,Sp*)-63a-d**

The corresponding (*S*,*Rp*)-diastereoisomers of **63a**–**d** have also been obtained through initial introduction of a removable trimethylsilyl blocking group **[Scheme 28]**.[33d,34]



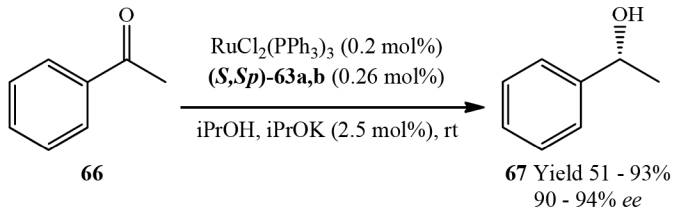
Scheme 28: Preparation of DPOF **(*S,Rp*)-63a-d** ligands

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**

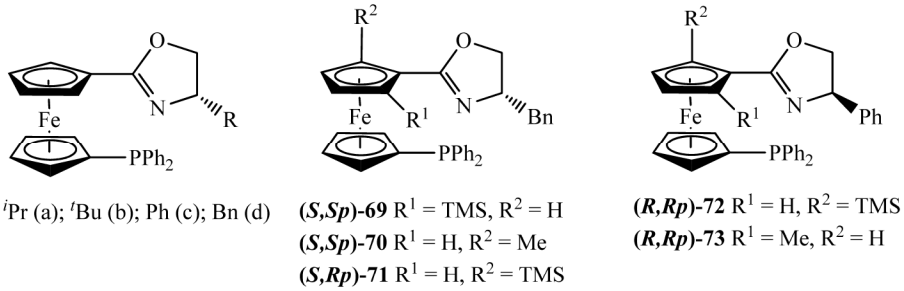
Sammakia and co-workers have also used **(*S,Sp*)-63b,c** ligands for Ru-catalyzed transfer hydrogenation using 2-propanol as a hydrogen source to reduce ketones to alcohols **[Scheme 30]**.[31d] All of the ligands provided enantioselectivity of 90% while with the *tert*-butyl- and phenyl-substituted 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-phenylethanol **67** being formed in 48 and 60% *ee* respectively.[36]

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].**[37]



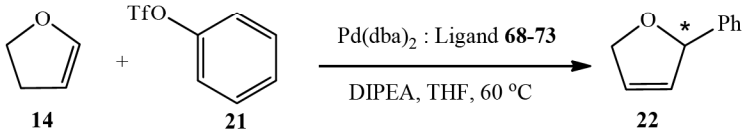
68 R = ^{i}Pr (a); ^{t}Bu (b); Ph (c); Bn (d)

(***S,Sp***)**-69** R^1 = TMS, R^2 = H
(***S,Sp***)**-70** R^1 = H, R^2 = Me
(***S,Rp***)**-71** R^1 = H, R^2 = TMS

(***R,Rp***)**-72** R^1 = H, R^2 = TMS
(***R,Rp***)**-73** R^1 = Me, R^2 = H

Figure 9: Another type f 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.

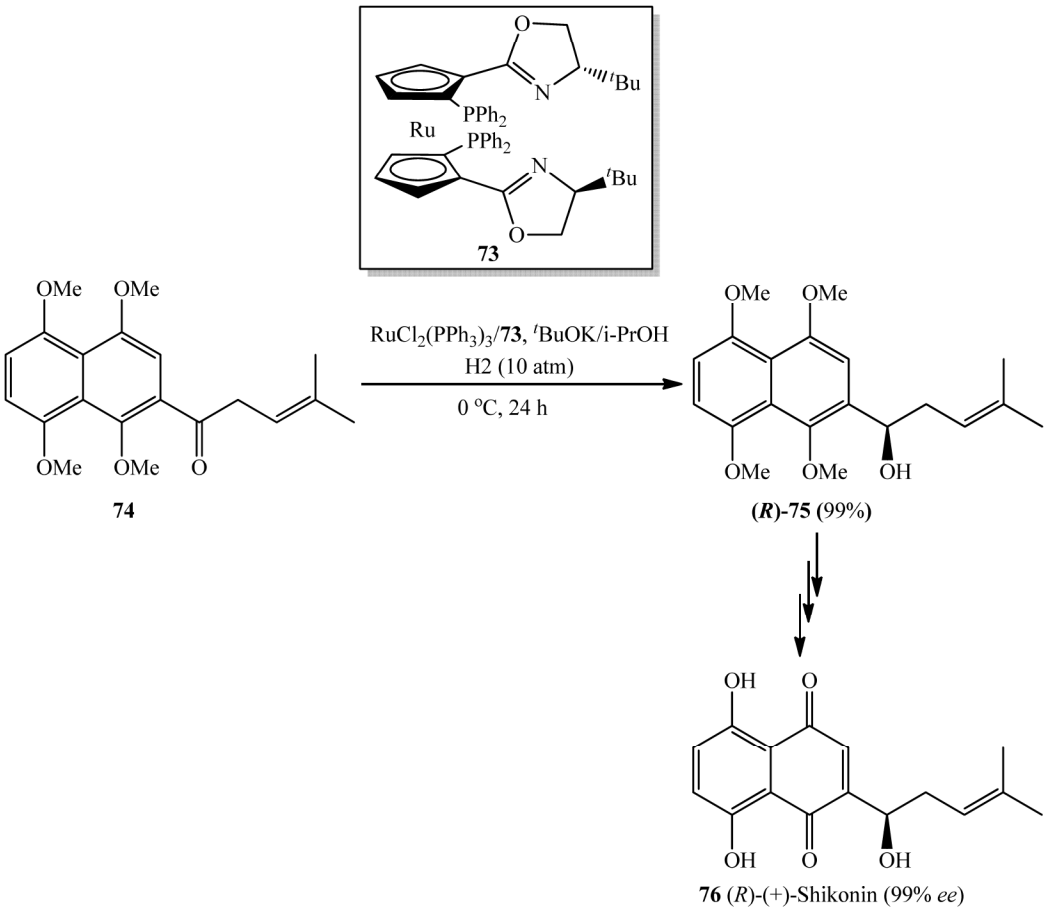


14 **21** **22**

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,[38] enantioselective ring opening of aza and oxabicyclic alkenes with dimethylzinc reagent.[39]

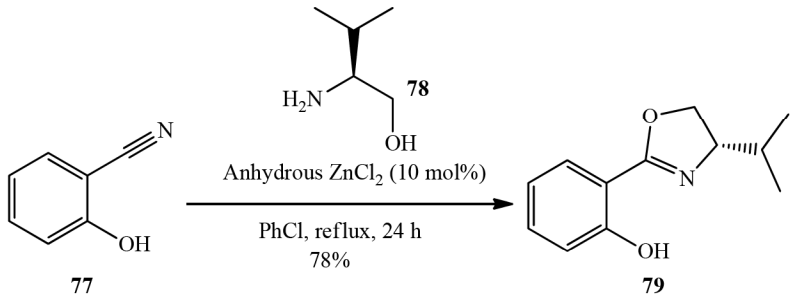
Recently, Wang *et al* have developed C_2-symmetric planar chiral ruthenocene based phosphinooxazoline ligand **73** and employed for ruthenium catalyzed asymmetric hydrogenation reaction of ketone **74** to **75** as a key step which was the part of the synthetic route for one of the important biologically 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**

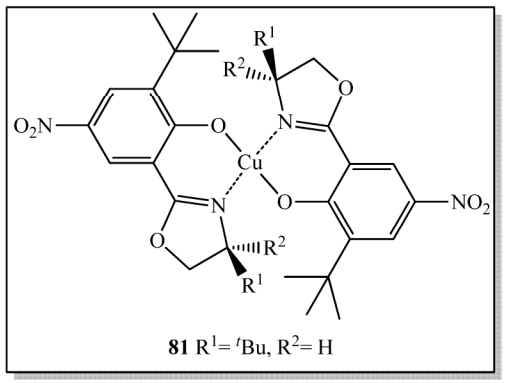
In 1991 Bolm has synthesized 2-(oxazolinyl)phenolato ligand **79** from 2-hydroxy benzonitrile **77** and L-valinol **78** using $ZnCl_2$ as Lewis acid catalyst **[Scheme 33]**.[41]

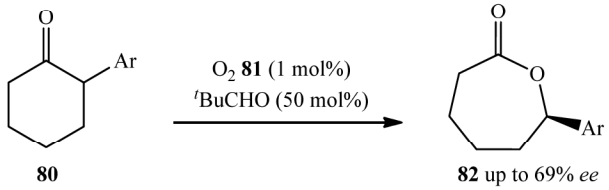


Scheme 33: Preparation of (*S*)-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenol **79**

Metal complexes bearing 2-(oxazolinyl)phenolato ligands have been utilized in a number of asymmetric reactions including Baeyer-Villiger oxidations,[42] cyclopropanations,[43] allylic functionalizations[44] and Lewis-acid catalyzed C-C bond formations.[50]

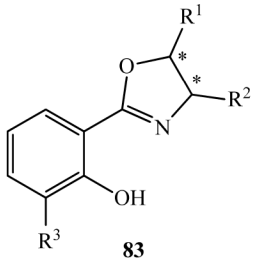
In the presence of copper catalyst **(*S,S*)-81** aerobic oxidation of racemic 2-arylcycloalkanones **80** afforded the corresponding lactones **82** with enantioselectivities of up to 69% *ee* **[Scheme 34]**. Alkylsubstituted ketones and positional isomers did not react under this condition.[42a]





Scheme 34: Baeyer-Villiger oxidation using catalyst **81**

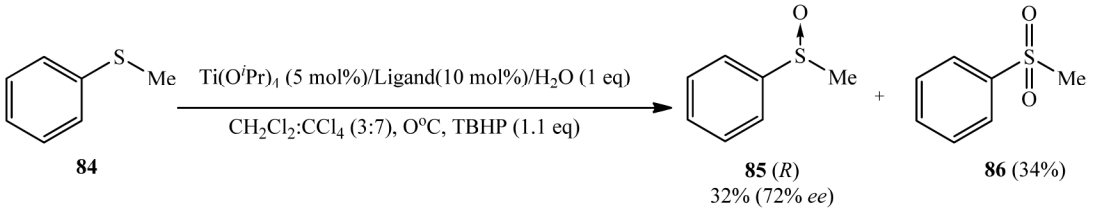
Feng has reported the synthesis of the new derivatives of *N,O*-Ligands **83a-f [Figure 10]** by the well known method as described in **Scheme 33** from appropriate hydroxyl benzonitriles and chiral amino alcohols.



(*4S,5R*)-a R^1=R^2=Ph, R^3=^{t}Bu **(*4S,5S*)-d** R^1=R^2=Ph, R^3=*H*
(*4S,5S*)-b R^1=R^2=Ph, R^3=^{t}Bu **(*4S*)-e** R^1=H, R^2=Ph, R^3=^{t}Bu
(*4S,5R*)-c R^1=R^2=Ph, R^3=H **(*4S*)-f** R^1=H, R^2=Bn, R^3=H

Figure 10: New *N,O*-Ligands **83a-f**

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



Scheme 35: Ti-catalyzed oxidation of methyl phenyl sulphide **84** using **83b**

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**.

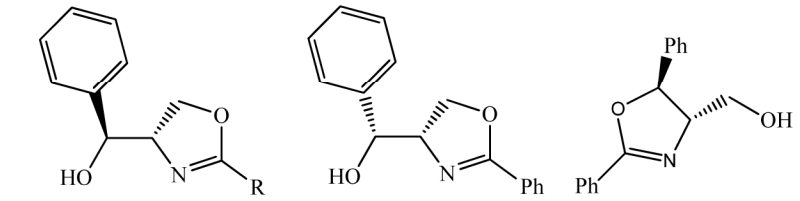
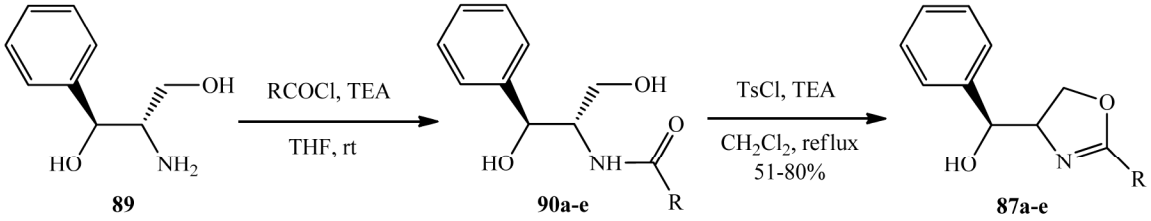


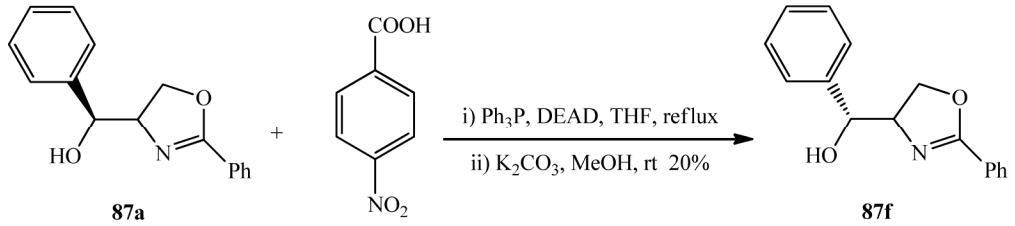
Figure 11: New class of *N,O*-Ligands **87** and **88**

Ligands **87a-e** were prepared from (1*S*,2*S*)-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 tosylchloride in dichloromethane under reflux condition furnished **87a-e** in the yield ranging from 51-80% **[Scheme 36]**.[48]



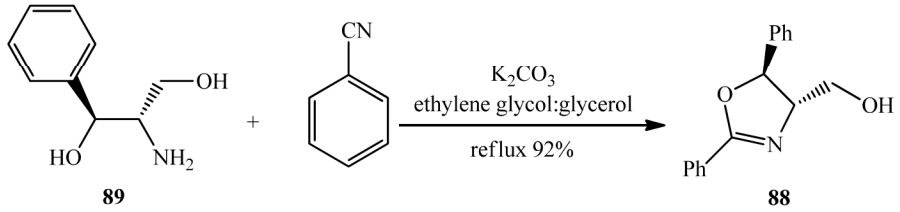
Scheme 36: Synthesis of ligands **87a-e**

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.



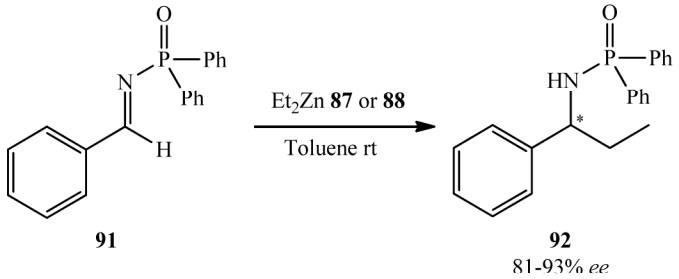
Scheme 37: Synthesis of ligand **87f** from **87a** via inversion of configuration

Ligands **88** was synthesized from (1*S*,2*S*)-2-amino-1-phenyl-propan-1,3-diol **89** by refluxing with benzonitrile in presence of K_2CO_3 using mixture of ethylene glycol and glycerol as solvent **[Scheme 38]**.[49]



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 diphenylphosphinoylamide **92 [Scheme 39]**.



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.[50] Rechards reported the synthesis of the stereoplanar mimetics **93-96 [Figure 12]**.[51]

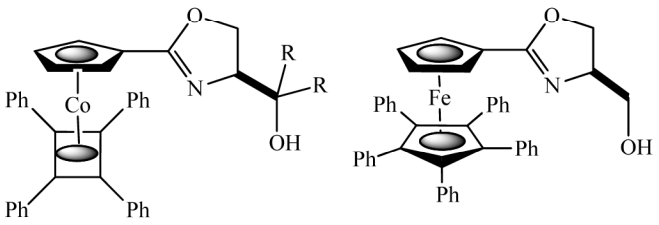
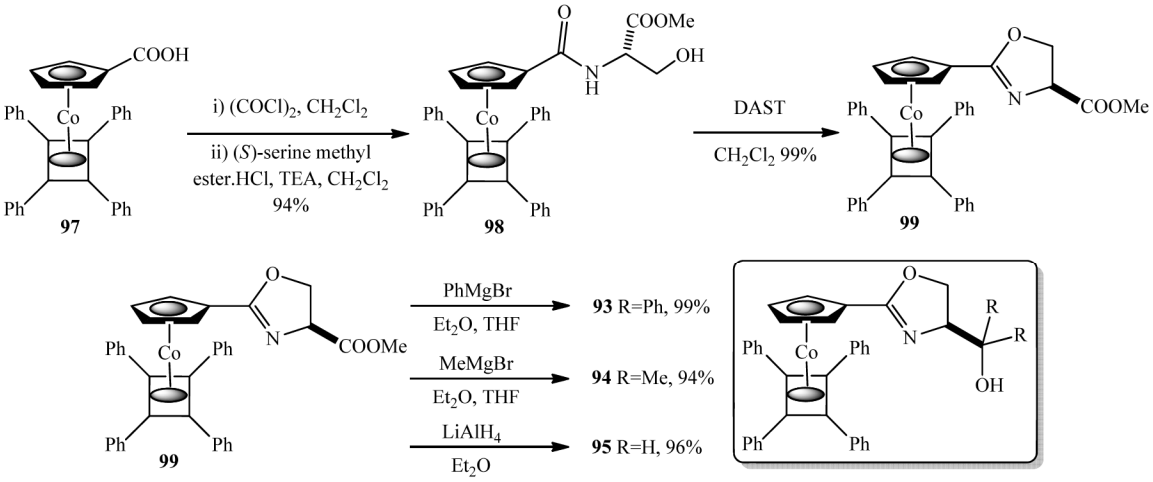


Figure 12: Stereoplanar *N,O*-oxazoline ligands

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]**.

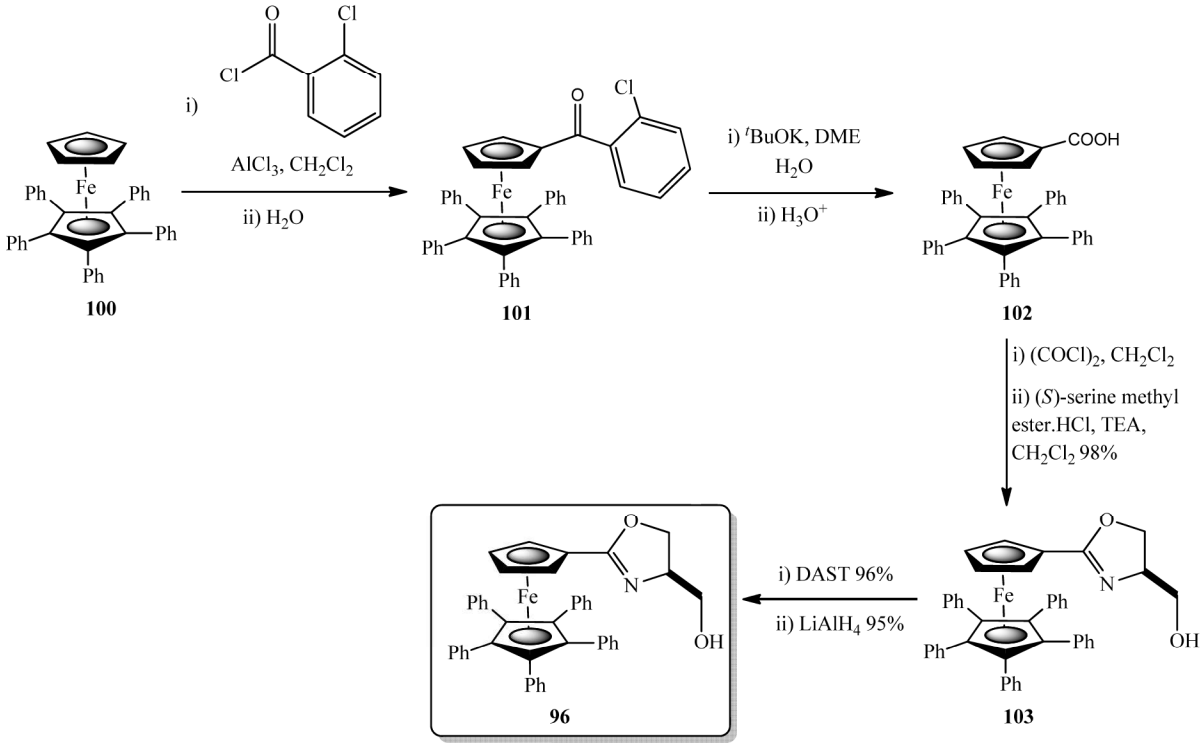


Scheme 40: Synthesis of stereoplanar *N,O*-oxazoline ligands **93-95**

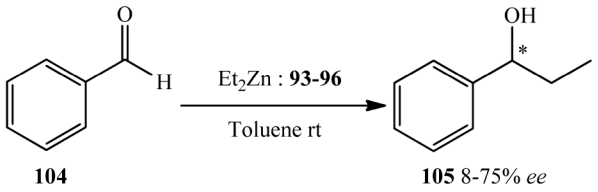
In addition they have synthesised pentaphenylferrocene based *N,O*-oxazoline ligand **96** from pentaphenylferrocene **100**. Direct acylation of **100** with 2-chlorobenzoyl chloride in presence of aluminium chloride cleanly gave aryl ketone **101**. Then it got hydrolyzed using ^{t}BuOK in DME to have 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 clean 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–metallocene 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 alkoxymethylene 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 alkoxymethylene arm. Clearly too much bulk is detrimental to selectivity with this system.

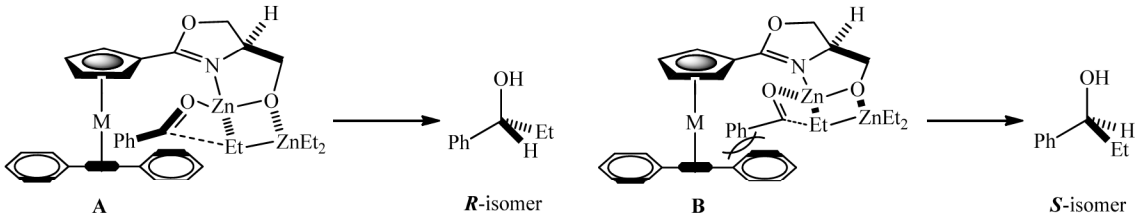


Chart 2: Explanation for the selectivity in diethylzinc addition reaction using **93-96**

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]** 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]

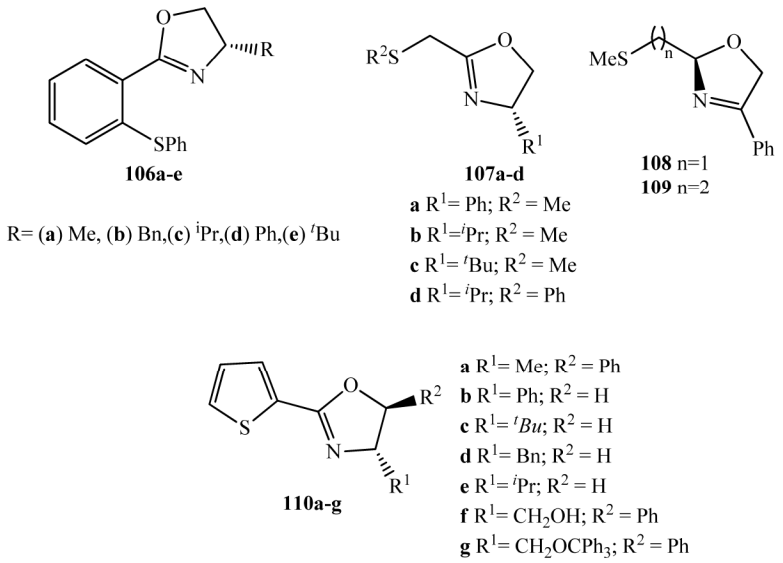
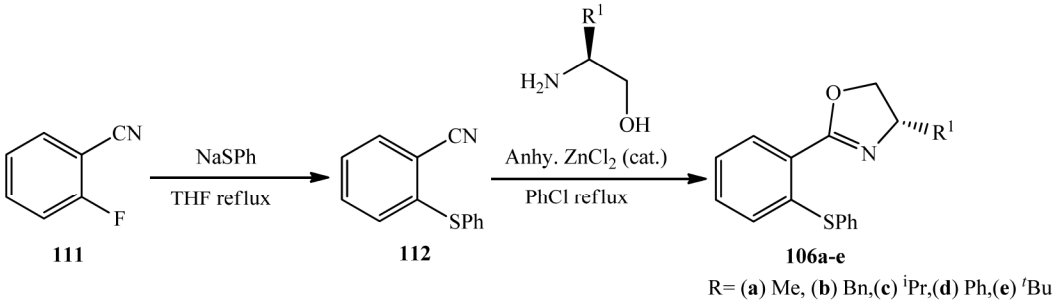


Figure 13: *N,S*-mono(oxazoline) ligands **106-110**

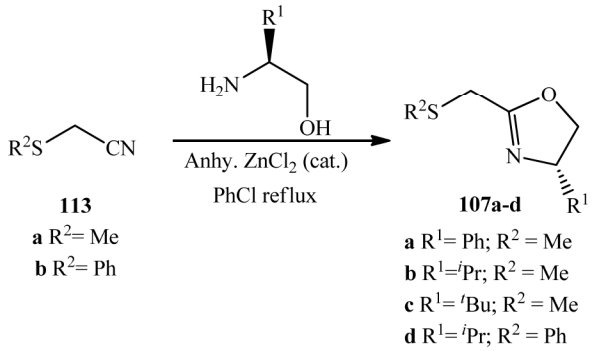
Ligands **106** were prepared from the reaction of *o*-fluorobenzonitrile **111** with sodiumthiophenolate afforded the diarylsulfide **112** and subsequent reaction of **112** with

appropriate chiral amino alcohols afforded the oxazolines **106a-e** with high yields **[Scheme 43]**.



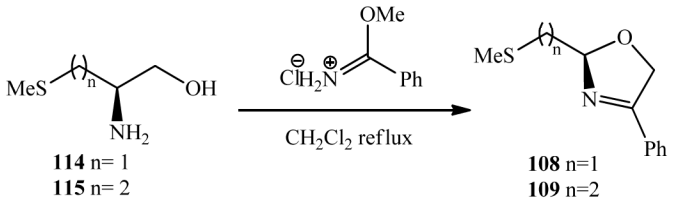
Scheme 43: Synthesis of *N,S*-mono(oxazoline) ligands **106a-e**

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]**.



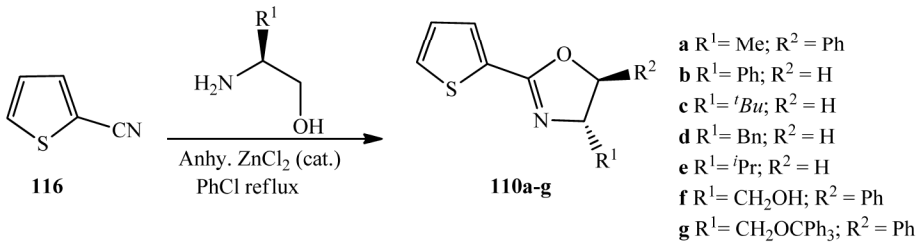
Scheme 44: Preparation of ligands **107a-d**

Simillarly, methylbenzimidate hydrochlonde 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**

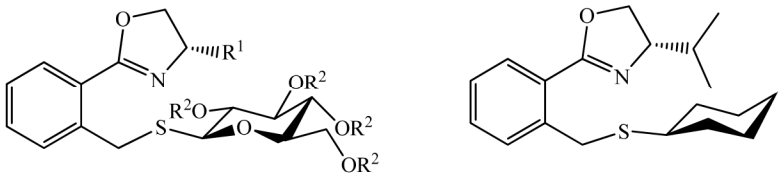
The ligands **110a-g** were prepared by adaptation of a literature procedure[45] from thiophene-2-carbonitrile **116** and the corresponding amino alcohol by treatment with catalytic amounts of zinc chloride in chlorobenzene at reflux for 48 h **[Scheme 46]**



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]

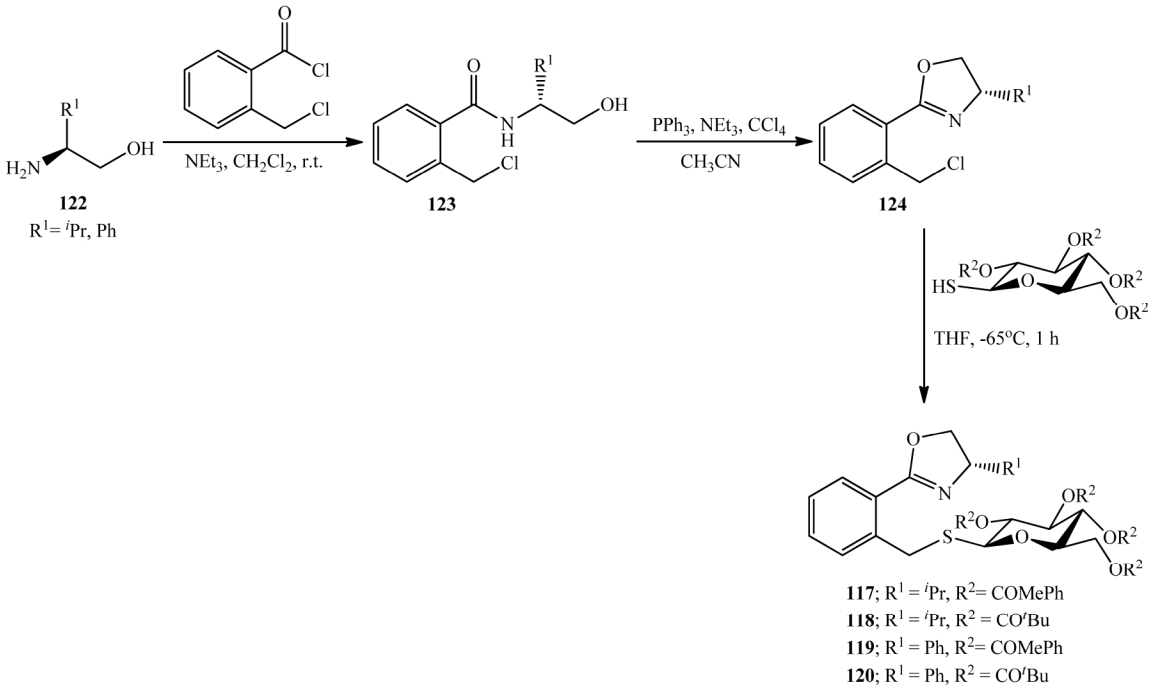
Another class of *N,S*-mono(oxazoline) ligands, thioglucose-derived oxazoline ligands **117-121** have been developed by Pregosin **[Figure 14]**. [53]



117; R^1 = ^{i}Pr, R^2= COMePh
118; R^1 = ^{i}Pr, R^2 = CO^{t}Bu
119; R^1 = Ph, R^2= COMePh
120; R^1 = Ph, R^2 = CO^{t}Bu

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

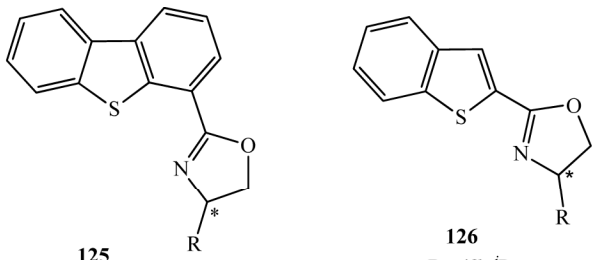
Ligands **117-120** were prepared by standard methods, which includes the reaction of optically pure amino alcohols **122** with (chloromethyl)benzoyl chloride to produce amido alcohol **123** which on cyclization using triphenylphosphine, carbontetrachloride, in acetonitrile to give corresponding oxazoline **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(oxazoline) 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 (^{t}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(oxazoline) ligands **125a,b** and benzothiophene based mono(oxazoline) ligands **126a-c [Figure 15]**[54] and applied them in Pd-catalyzed allylic substitution of 1,3-diphenyl-2-propenyl acetate **12** with dimethyl malonate.



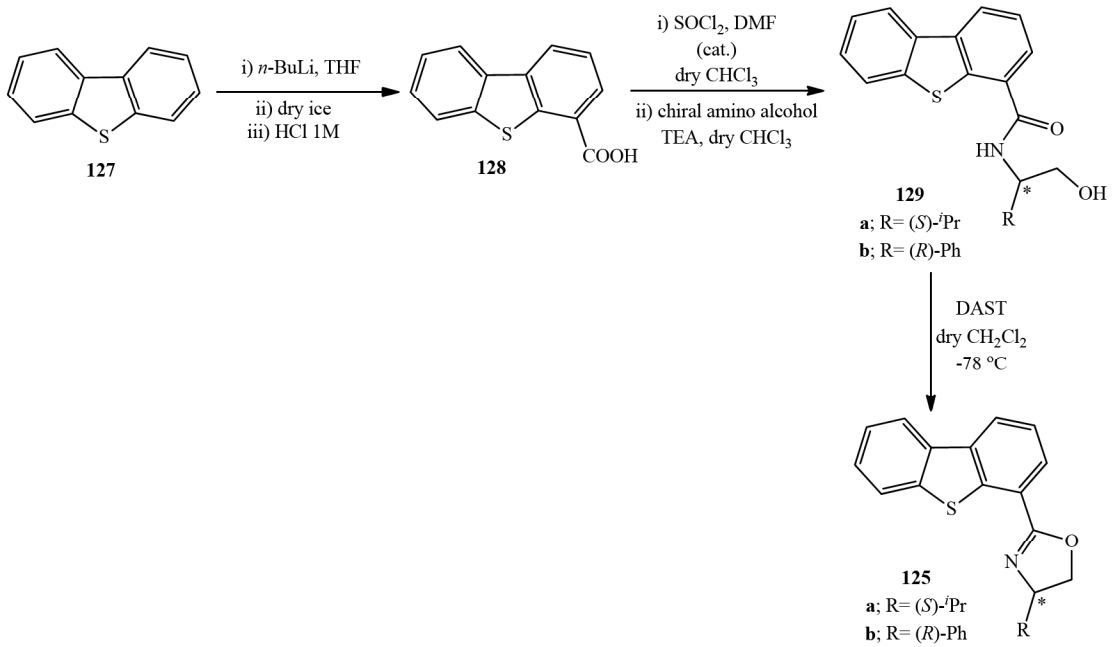
125
a; R= (*S*)-^{i}Pr
b; R= (*R*)-Ph

126
a; R= (*S*)-^{i}Pr
b; R= (*R*)-Ph
c; R= (*S*)-^{t}Bu

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

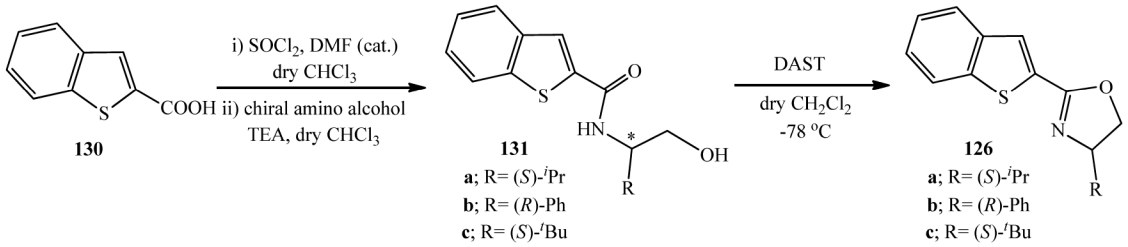
Ligands **125a-b** were prepared from dibenzothiophene **127** via *ortho* lithiation using *n*-Butyl lithium and upon quenching with dry ice to afford dibenzothiophene 4-carboxylic acid **128**. Initially **128** was converted to corresponding acid chloride on refluxing with thionyl

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 dibenzothiophene based oxazolines **125a-b** in good yields **[Scheme 48]**.



Scheme 48: Synthesis of dibenzothiophene 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]**.

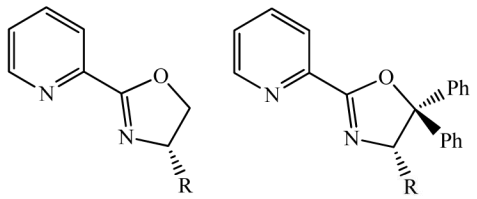


Scheme 49: Synthesis of benzothiophene based mono(oxazoline) ligands **126a-d**

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]**.[55] The choice of ligands was done on the basis of size of chelate ring generated upon coordination which is responsible for the better results.

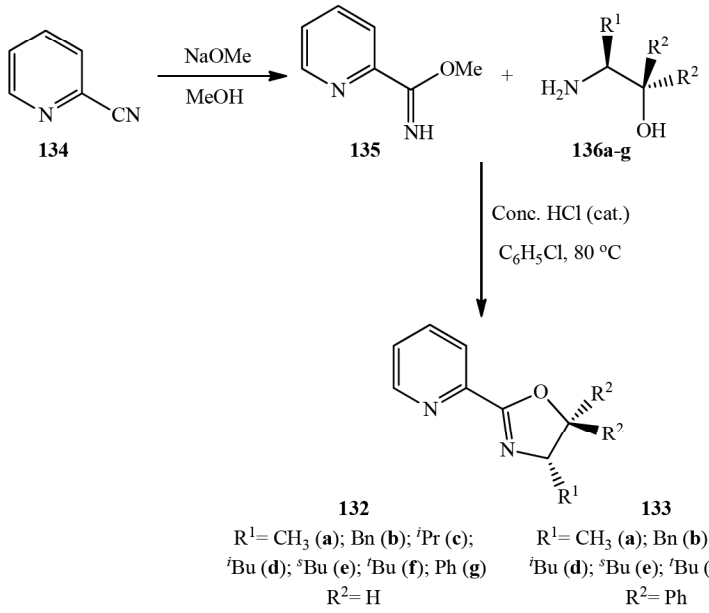


132 **133**

R= CH_3 (**a**); Bn (**b**); ^{i}Pr (**c**); ^{i}Bu (**d**); ^{s}Bu (**e**); ^{t}Bu (**f**); Ph (**g**)

Figure 16: First developed *N,N*-mono(oxazoline) ligands

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 ^{o}C gave the optically active pyridine based oxazolines **132** and **133** in good conversion **[Scheme 50]**.[56a]



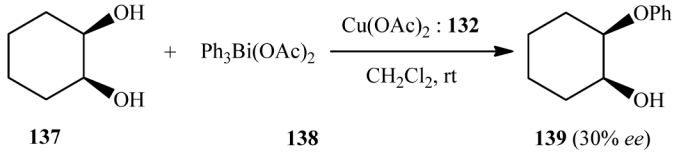
134 **135** **136a-g**

132
R^1= CH_3 (**a**); Bn (**b**); ^{i}Pr (**c**); ^{i}Bu (**d**); ^{s}Bu (**e**); ^{t}Bu (**f**); Ph (**g**)
R^2= H

133
R^1= CH_3 (**a**); Bn (**b**); ^{i}Pr (**c**); ^{i}Bu (**d**); ^{s}Bu (**e**); ^{t}Bu (**f**); Ph (**g**)
R^2= Ph

Scheme 50: Conventional synthesis of pyrinde based *N,N*-mono(oxazoline) ligands

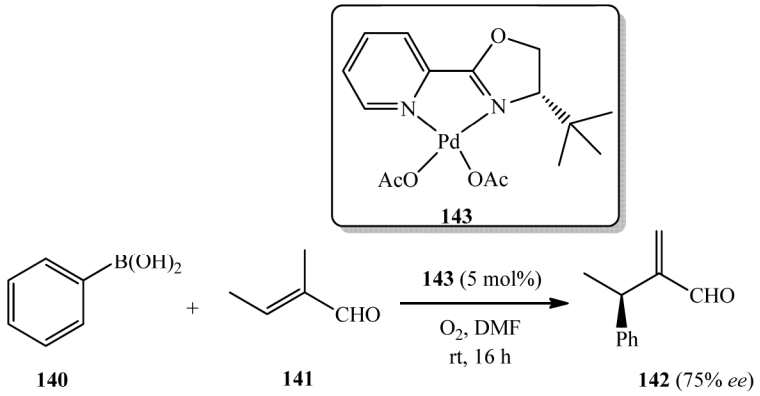
Since being first applied in asymmetric catalysis in 1986 for Cu-catalyzed monophenylation of *cis*-cyclohexan-l,2-diol **137** with triphenylbismuth diacetate **138** afforded *cis*-l-phenoxycyclohexan-2-ol **139** (up to 30% *ee* for **132e**) using **132a-e [Scheme 51]**[55] and subsequently with some success in Rh(I) – catalyzed hydrosilylation (up to 84% *ee*), many structural derivatives of these ligands have been used successfully in a range of asymmetric reactions such as asymmetric alkylation.[56]



137 **138** **139** (30% *ee*)

Scheme 51: Cu-catalyzed monophenylation using ligands **132**

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.[57] Pd-catalyzed coupling of phenylboronic acid **140** and *trans*-2-methyl-2-butenal **141** produced exclusively the compound 2-methylene-3-phenylbutanal **142** generating new stereogenic centre using bidentate *N,N*-mono(oxazoline) ligands **132c** (25% *ee*)**, 132f** (21 % *ee*) and **132g** (42% *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 *R* configuration of the product **142 [Scheme 52]**.



Scheme 52: Pd-catalyzed oxidative Heck type reaction

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 oxazolinyl unit and the pyridine separated by a methylene unit in asymmetric transformations. **[Figure 17]**.[58]

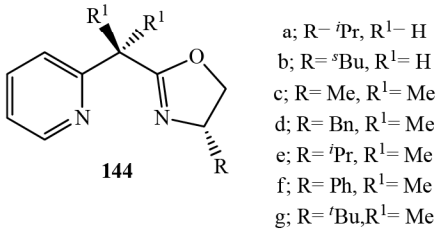
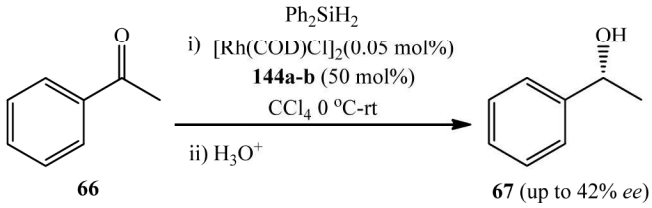


Figure 17: Pyridine based mono(oxazoline) linked by methylene unit

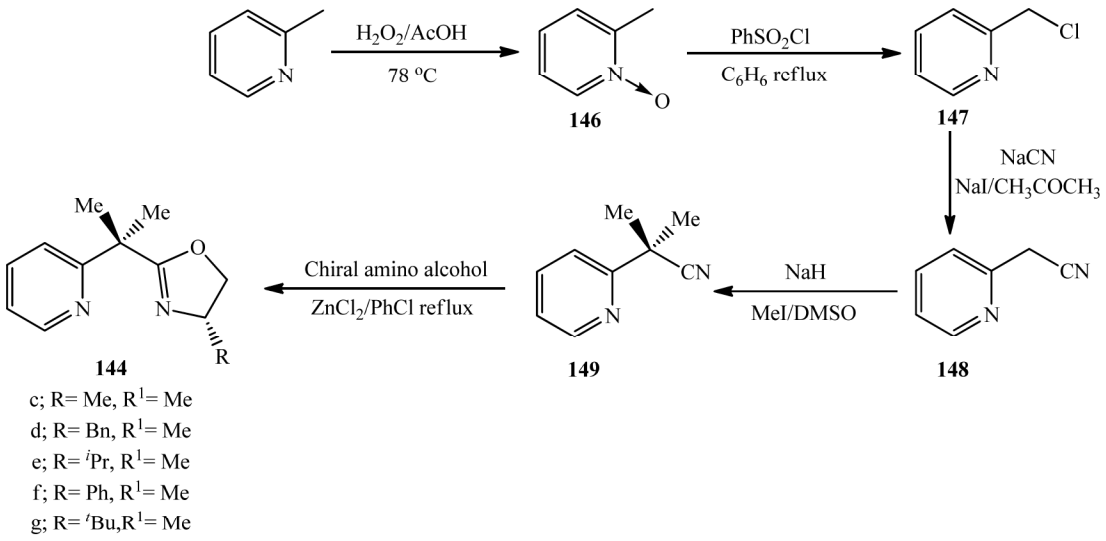
The preparation of these ligands was done by standard synthetic protocol by refluxing a mixture of 2-cyanomethylpyridine and the appropriate chiral aminoalcohol in chlorobenzene in the presence of a catalytic amount of zinc chloride produced the desired ligand **144a-b**.

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]**.[58a]



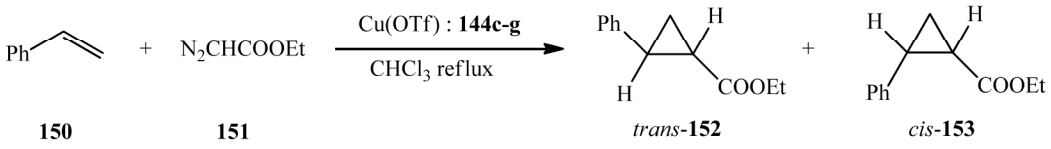
Scheme 53: Rh-catalyzed hydrosilylation of acetophenone using ligands **144a-b**

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**

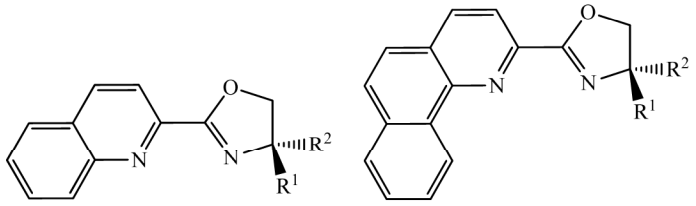
For practical applications these set of ligands were applied to Cu(I)-catalyzed asymmetric cyclopropanation reaction of styrene **150** with ethyl diazoacetate **151** to produce *trans*-**152** and *cis*-**153** with good results **[Scheme 55]**.[58b] Ligands **144c-g** have good chemical yields in refluxing CH_2Cl_2 , but the enantiomeric excesses were low (maximum 18% *ee* for *trans* and 12% *ee* for *cis* isomer).



150 **151** *trans*-**152** *cis*-**153**

Scheme 55: Cu(I)-catalyzed asymmetric cyclopropanation reaction using ligands **144c-g**

Another analogous of the pyrindine oxazoline ligands **154a-c** and **155a-b** have been prepared and screened for Pd-catalyzed asymmetric allylic alkylation reaction by Chelucci **[Figure 18]**.[59]

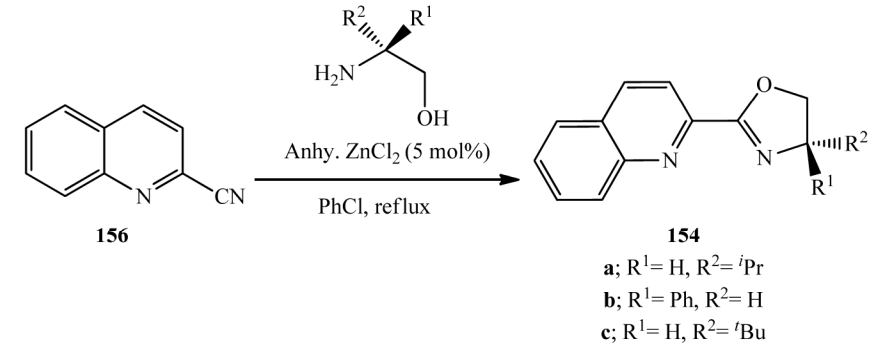


154
a; R^1= H, R^2= ^{i}Pr
b; R^1= Ph, R^2= H
c; R^1= H, R^2= ^{t}Bu

155
a; R^1= H, R^2= ^{i}Pr
b; R^1= Ph, R^2= H

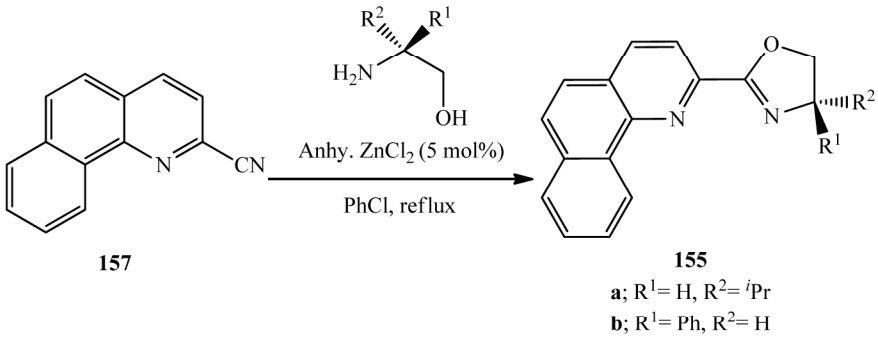
Figure 18: Another class of *N,N*-mono(oxazoline) ligands having quinoline ring

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]**.



156

154
a; R^1= H, R^2= ^{i}Pr
b; R^1= Ph, R^2= H
c; R^1= H, R^2= ^{t}Bu

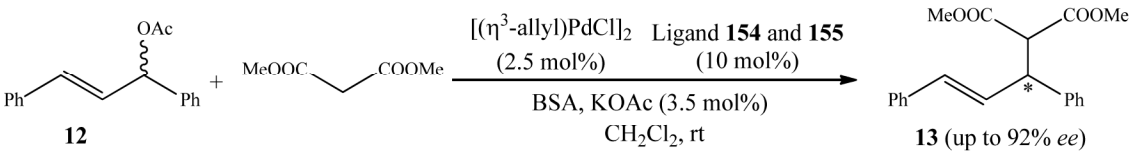


157

155
a; R^1= H, R^2= ^{i}Pr
b; R^1= Ph, R^2= H

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 oxazoline ring gave **13**-(*S*) with 62% *ee* and **154b** having Phenyl group at 4-postion of oxazoline 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 oxazoline 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]**.[60] 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.

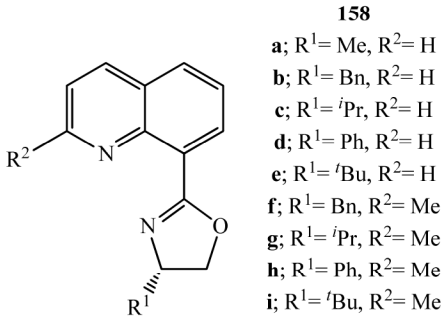
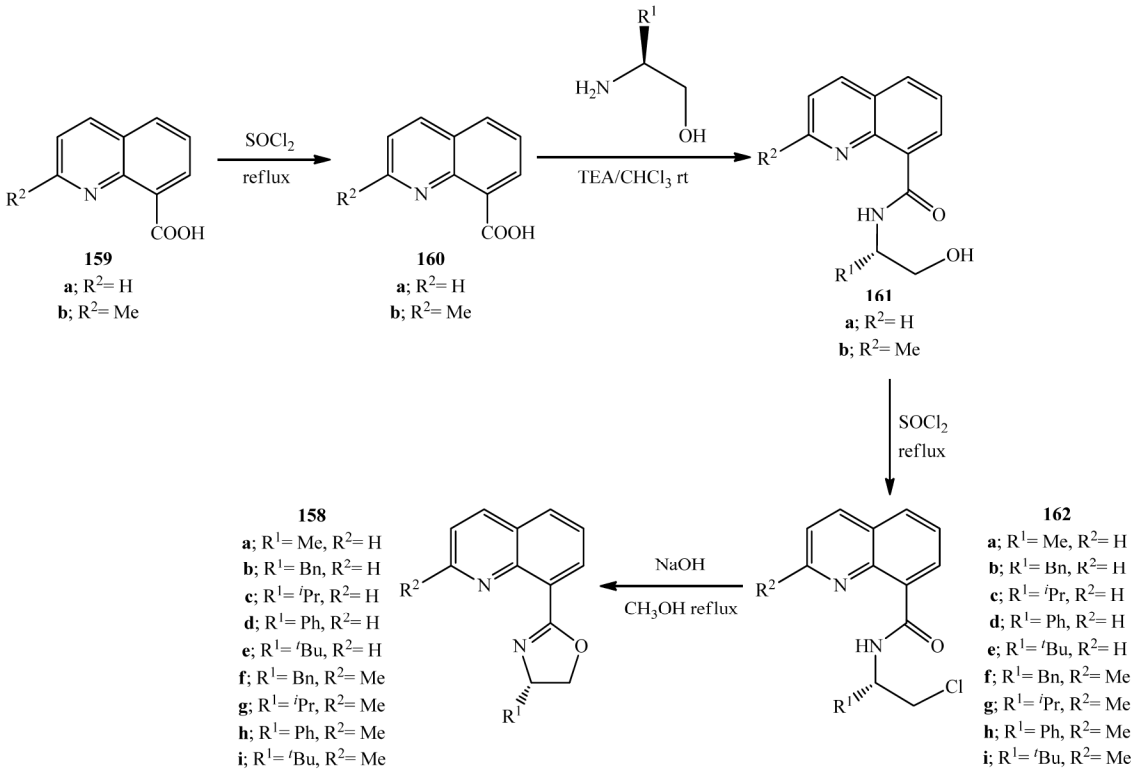


Figure 19: 8-Quinolinyl mono(oxazoline) ligands **158a-i**

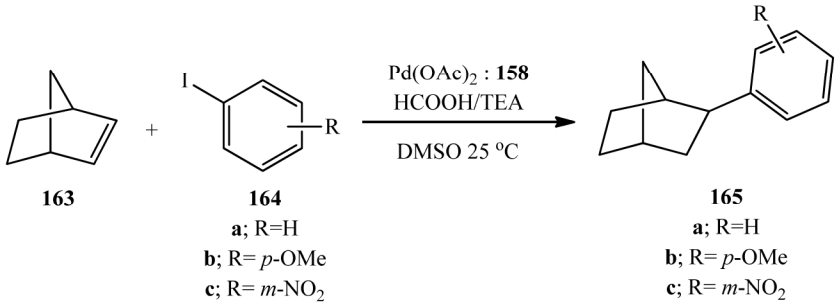
A series of 8-quinolinyl-oxazolines **158** were synthesized from enantiomerically pure amino alcohols and 8-quinolinecarboxylic acid derivatives **159** in four steps as shown in **[Scheme 58]**.[60a] Intermediate **159** wes converted to the corresponding acid chloride **160** with thionyl chloride. After evaporation of excess $SOCl_2$, 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** wes converted to chloride **162** by refluxing with $SOCl_2$. 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]**.[61]



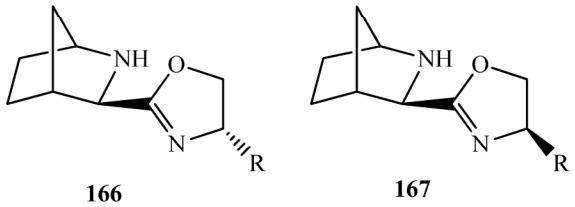
Scheme 59: Pd-catalyzed asymmetric hydroarylation of norborneene using ligands **158**

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 hydroarylating 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%.[62a] Sigman has recently applied ligand **132** and its quinoline analogue **154** in the palladium-catalyzed enantioselective aerobic dialkoxylation of 2-propenyl phenols.[62b]

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**.[63]

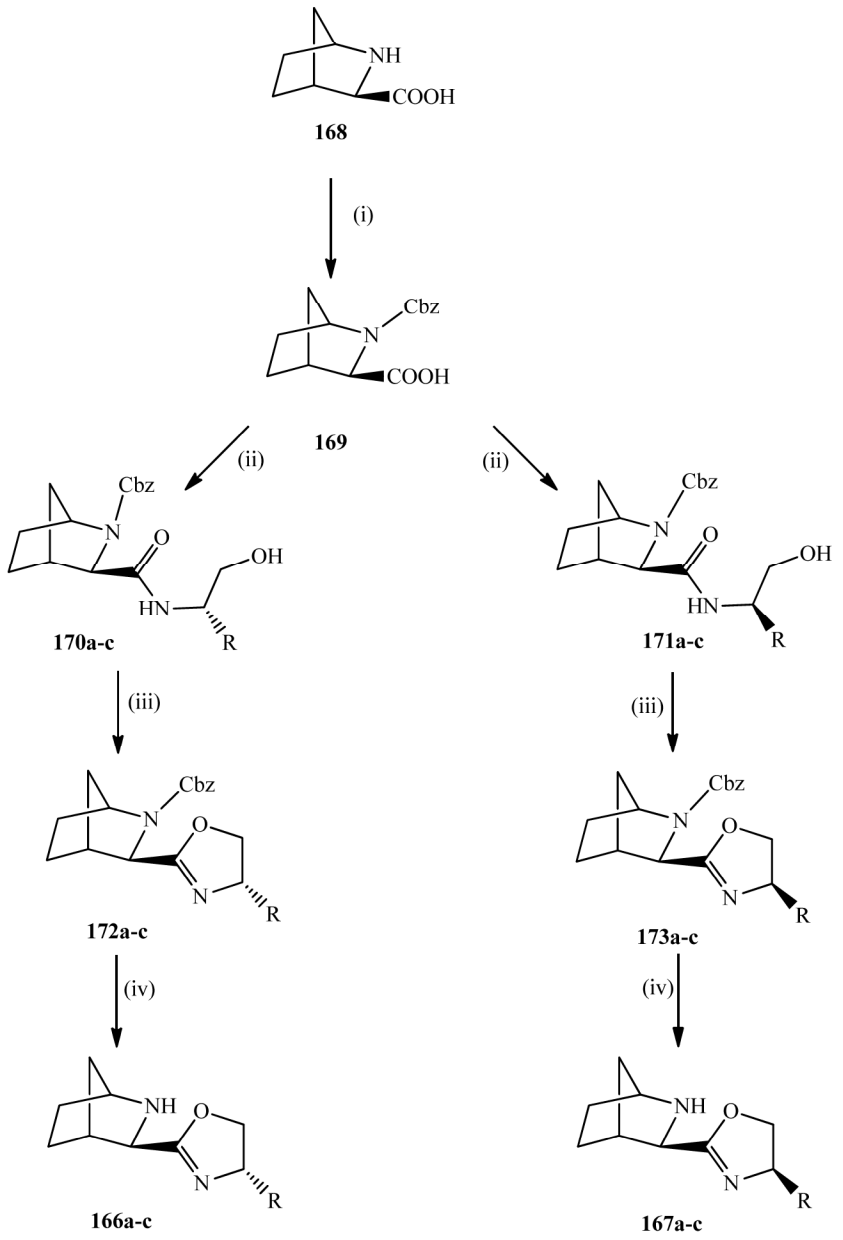


166 **167**

a; R= Me **b**; R= Bn **c**; R= ^{i}Pr **d**; R= Ph **e**; R= ^{t}Bu

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 (1*S*,3*R*,4*R*)-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 benzyloxycarbonyl 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-nitrobenzyloxycarbonyl as protecting group instead of simple benzyloxycarbonyl.

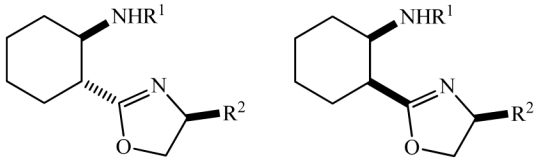


Scheme 60: Synthesis of ligands **166a-c** and **167a-c**

[Conditions and reagents: (i) CbzCl, sat. $NaHCO_3$ in H_2O, rt, 3 h; (ii) EDC, HOBt, aminoalcohol, CH_2Cl_2, rt, overnight; (iii) MsCl, TEA, CH_2Cl_2, 0 ^oC to rt, overnight; (iv) Pd/C (10 wt%), H_2 (1 atm.), EtOH, rt, overnight.

These diastereomeric pairs of **166a-e** and **167a-e** were applied to Ir-Catalyzed hydrogen transfer to acetophenone **66** from 2-propanol [see **Scheme 30**]. 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 *iso*-propyl group at 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 to10 and18% respectively

Wipf has prepared a range of chiral cyclohexane ligands **174** and **175** with different oxazoline substituents and sulfonyl nitrogen groups **[Figure 21]**.[64]



174

a; R^1= Ts, R^2= ^{i}Pr
b; R^1= Ts, R^2= ^{t}Bu
c; R^1= Ts, R^2= Ph
d; R^1= Mts, R^2= ^{i}Pr
e; R^1= Ns, R^2= ^{i}Pr
f; R^1= Tf, R^2= ^{i}Pr

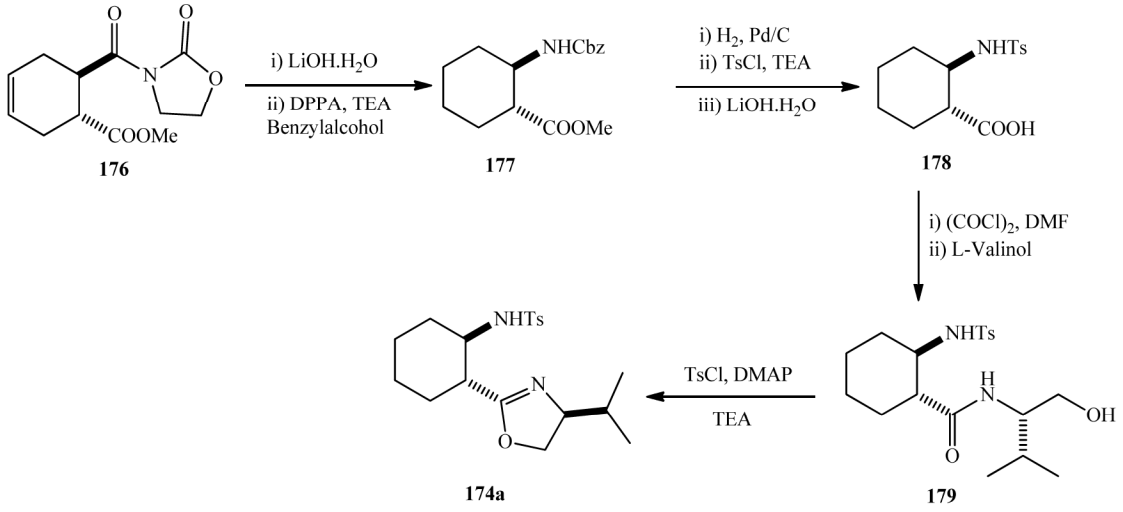
175

a; R^1= Ts, R^2= ^{i}Pr
b; R^1= Ts, R^2= ^{t}Bu
c; R^1= Ts, R^2= Ph

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

Figure 21: Cyclohexane based aminooxazoline 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.



176 **177** **178** **179** **174a**

Scheme 61: Schematic diagram for the synthesis of ligand **174a**

These ligands **174** and **175** were screened for asymmetric induction in the addition of diethylzinc 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.**[65]

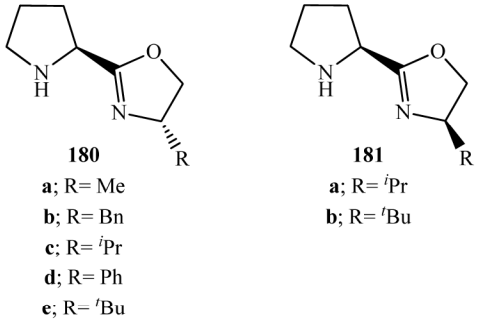
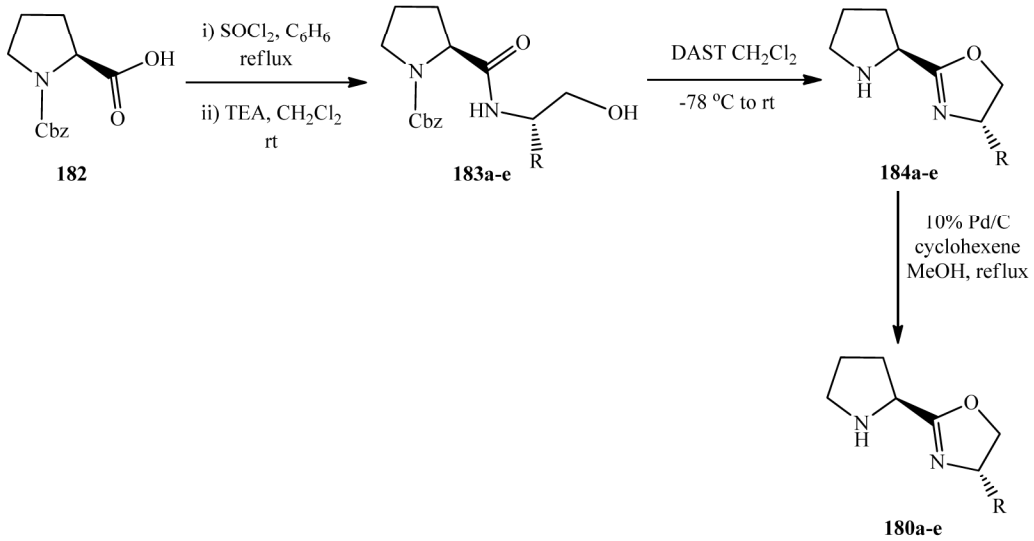


Figure 22: Pyrrolidine based oxazoline ligands **180** and **181**

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(Cbz)-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 β-hydroxyamides **183a-e** in moderate to good yield (57–92%). Cyclodehydration of **183a-e** by treatment with diethylaminosulfur triflouride (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

Using $[IrCl(COD)]_2$ as the metal precursor in the asymmetric hydrogen transfer reaction to acetophenone **66** using 2-propanol as hydrongen source resulted in excellent conversions (up to 96%) but gave only modest enantioselectivities (up to 38% *ee*). [Ru(*p*-cymene)$Cl_2]_2$ 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).[66a]

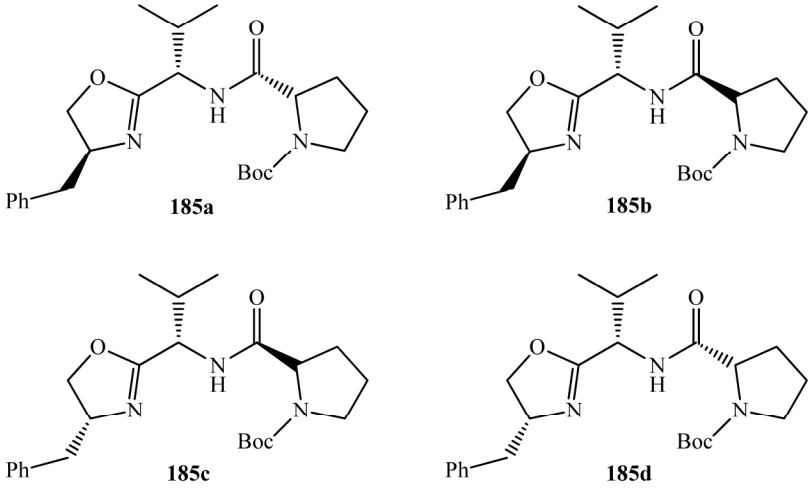
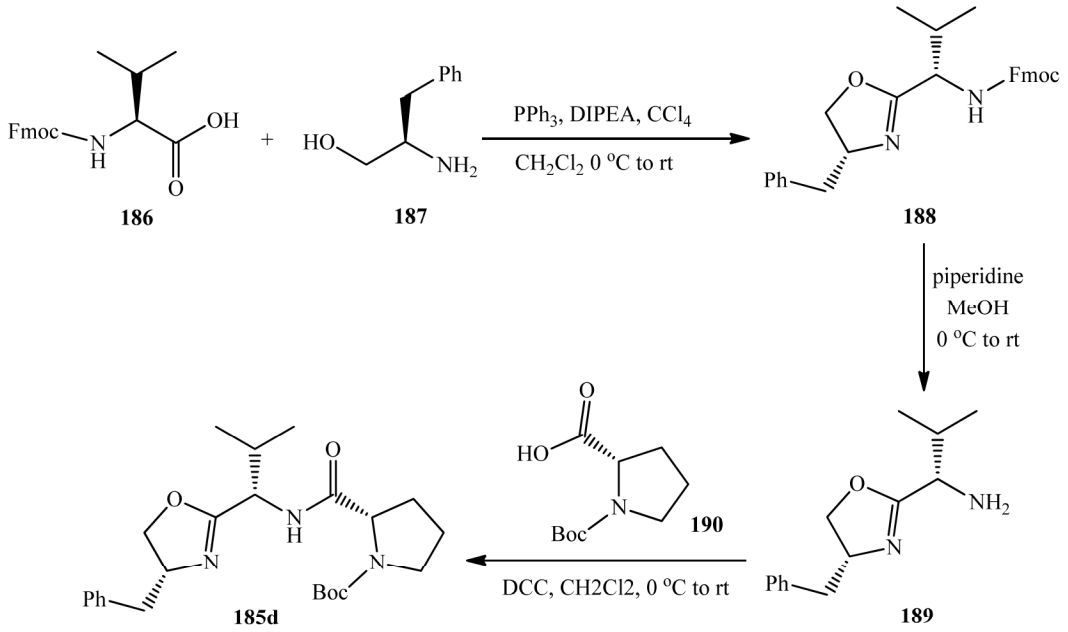


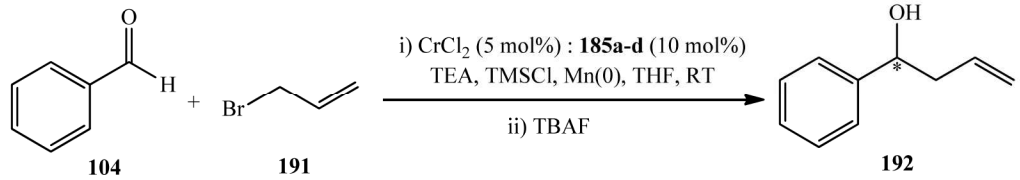
Figure 23: Proline based oxazoline ligands **185a-d**

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-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]**.

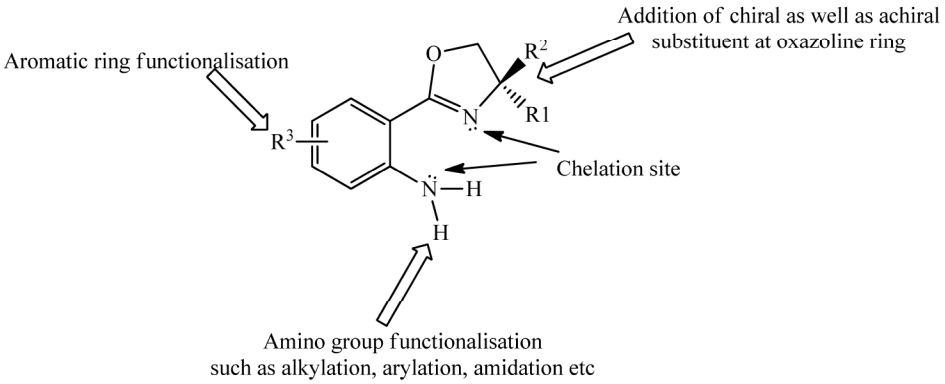


Figure 24: Gerneral features of *o*-(anilinyl)oxazoline derivatives

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 $-NH_2$ 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 isatioic 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]

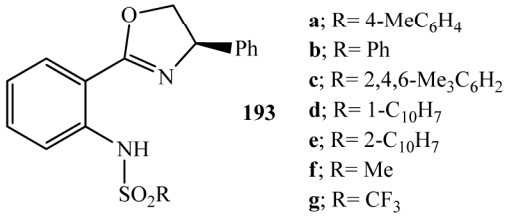
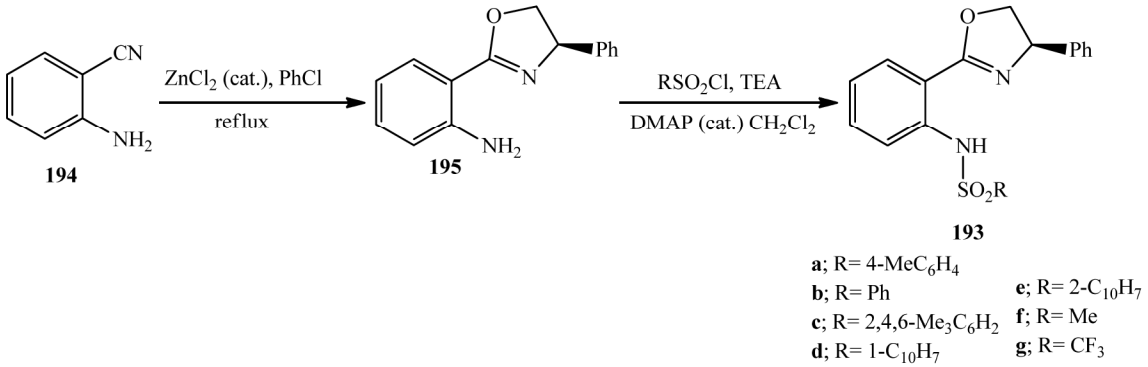


Figure 25: 2-[2-[(alkyl of arylsulfonyl)amino]phenyl]-4-phenyl-1,3-oxazoline **193a-g**

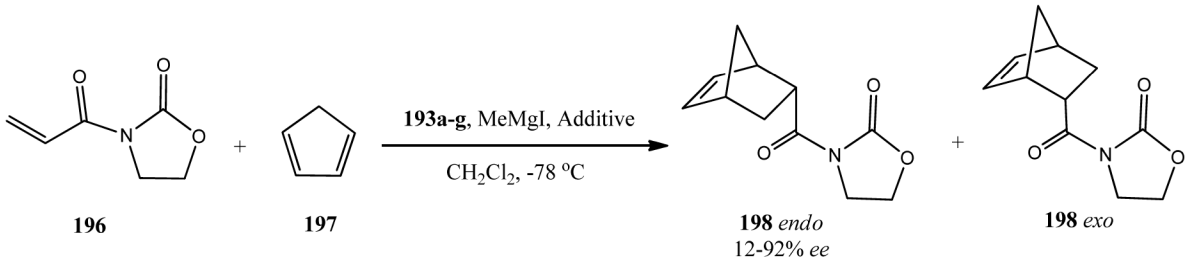
The chiral ligand was readily accessible in two step procedure **[Scheme 65]**, involve the reaction of aminobenzonitrile **194** with D-phenylglycinol in presence of catalytic amount of zinc chloride in chlorobenzene to afford 2-(2-amino)phenyl-4-phenyloxazoline **195** which

was converted to corresponding 2-[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-[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 ^{o}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.

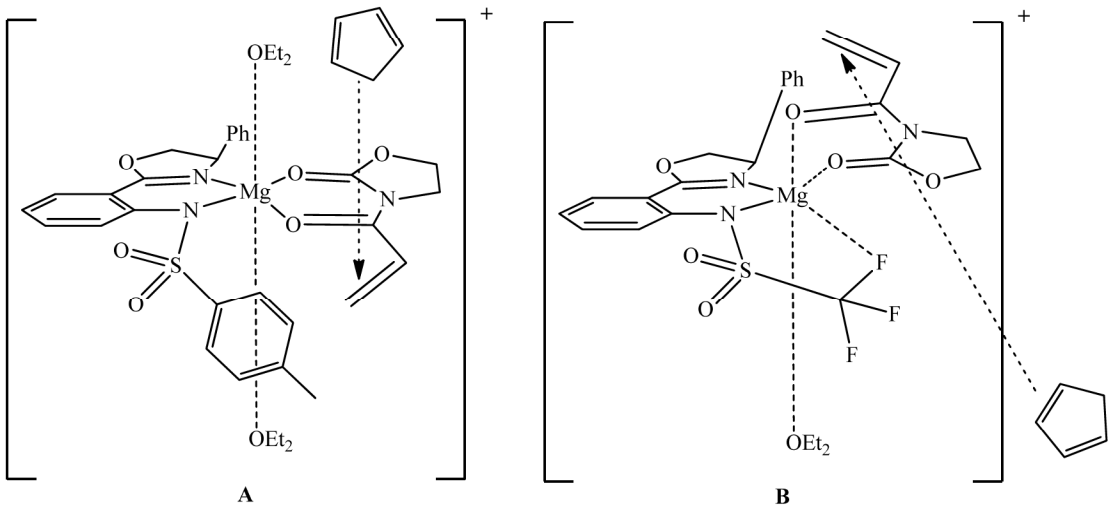
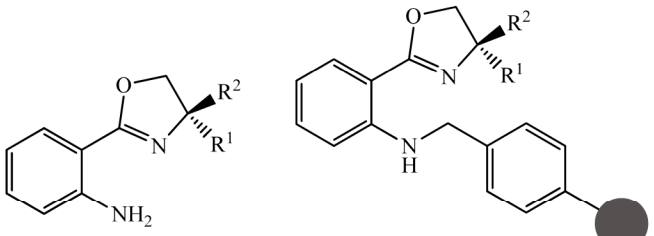


Chart 3: Model proposed for the selectivity in Diels-Alder reaction using ligands **193a-g**

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]**[67a] 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,[66a] 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]**[69] because of certain advantages over classical aminooxzoline 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.



200

a; R^1= H, R^2= H
b; R^1= Me, R^2= Me
c; R^1= ^{i}Pr, R^2= H
d; R^1= ^{s}Bu, R^2= H
e; R^1= Bn, R^2= H
f; R^1= H, R^2= Ph
g; R^1= H, R^2= Et

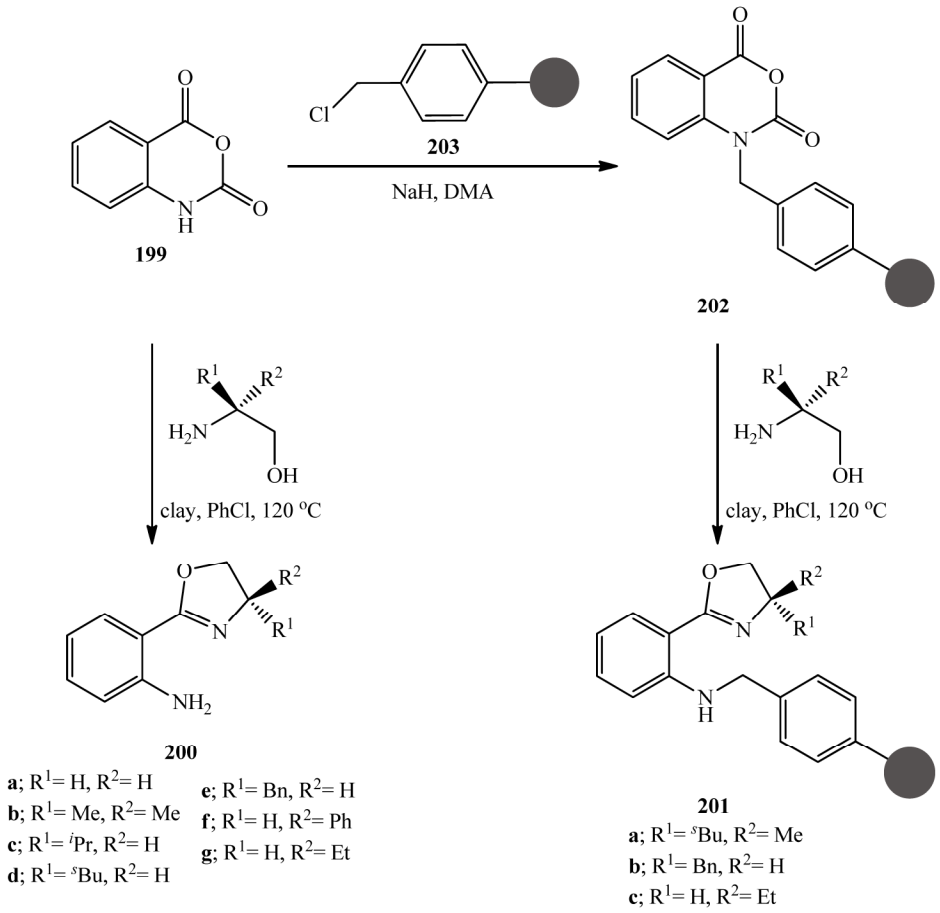
201

a; R^1= ^{s}Bu, R^2= Me
b; R^1= Bn, R^2= H
c; R^1= H, R^2= Et

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.[70] 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 diethylzic 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 *o*-(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-(*o*-anilinyl)-2-oxazoline **204** and **205 [Figure 27]**.[71]

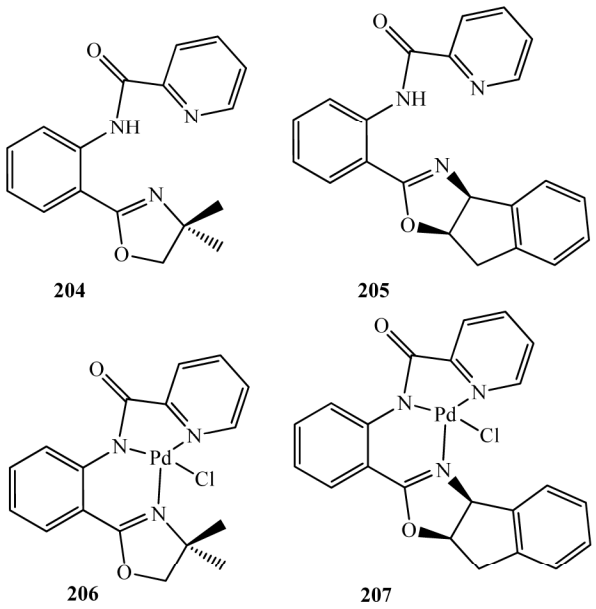
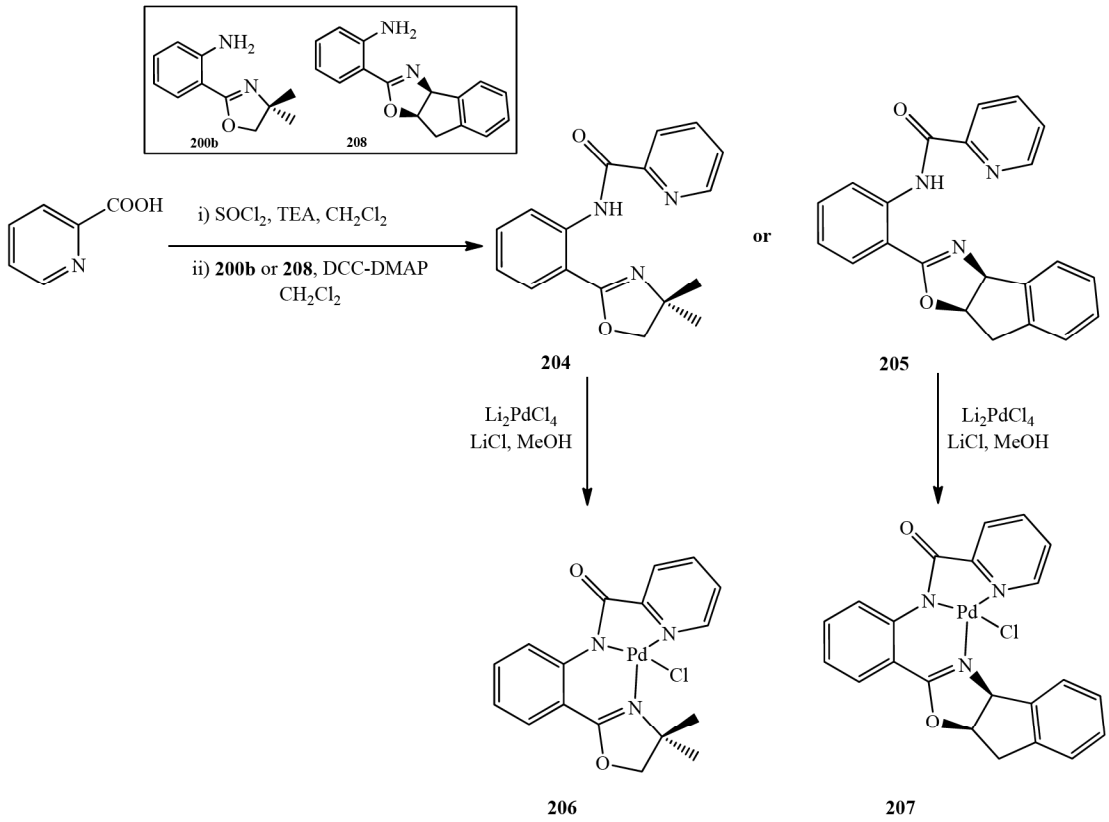


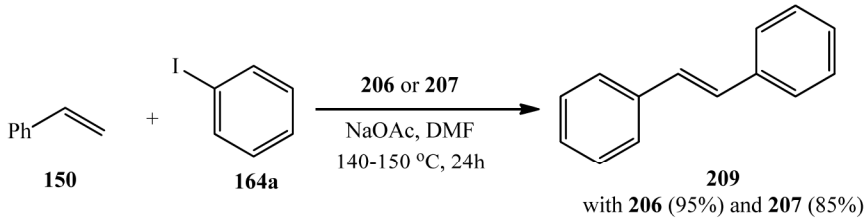
Figure 27: Pd-complexes **206** and **207** of *o*-(anilinyl) oxazoline

Pd-complexes **206** and **207** of the aminooxzolines **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 Li_2PdCl_4.



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

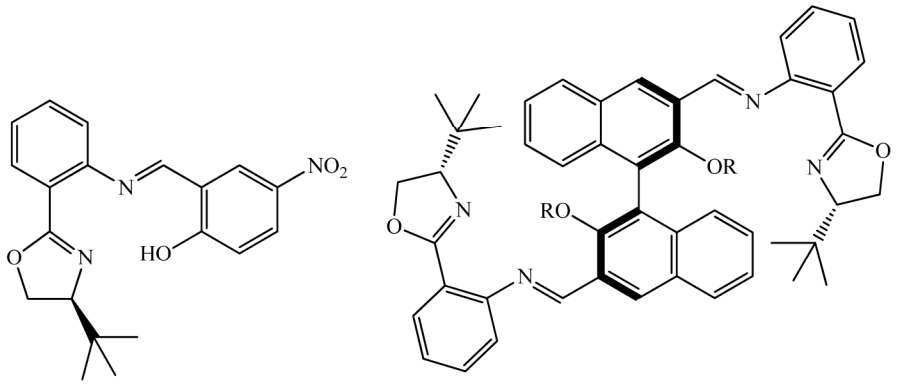
These catalysts **206** and **207** were applied for the Heck reaction of Iodobenzene and styrene to produce stilbene with high yields **[Scheme 69]**.



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

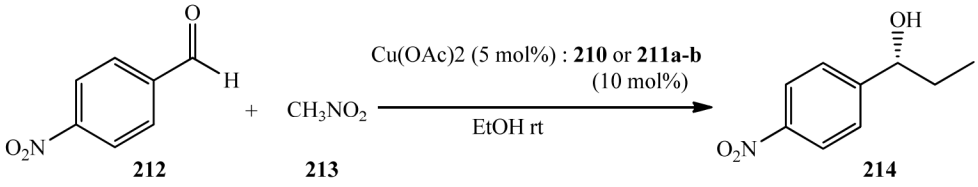
applications in various catalytic asymmetric reactions. They have synthesized a number of derivatives of Ligands **210** and **211 [Figure 28]** and screened them for Cu-catalyzed asymmetric Henry reaction.[72]



210 **211**
a; R= H
b; R= MOM

Figure 28: Schiff base containing oxazoline ligands **210** and **211**

The oxazoline Schiff-base ligands **210** and **211a-b** were easily synthesized from corresponding aldehydes and 1,2-aminoalcohols by just physical mixing at ambient conditions. Prepared ligands **210** and **211a-b** were applied to the Cu-catalyzed asymmetric Henry reaction of p-Nitrobenzalehyde **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**.



212 **213** **214**

Scheme 70: Cu-catalyzed asymmetric Henry reaction using **210** and **211a-b**

Guiry has developed ligands **215 [Figure 29]** and investigated their application in the Nozaki-Hiyama-Kishi allylation of benzaldehyde **104** using allyl bromiode **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**.[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.

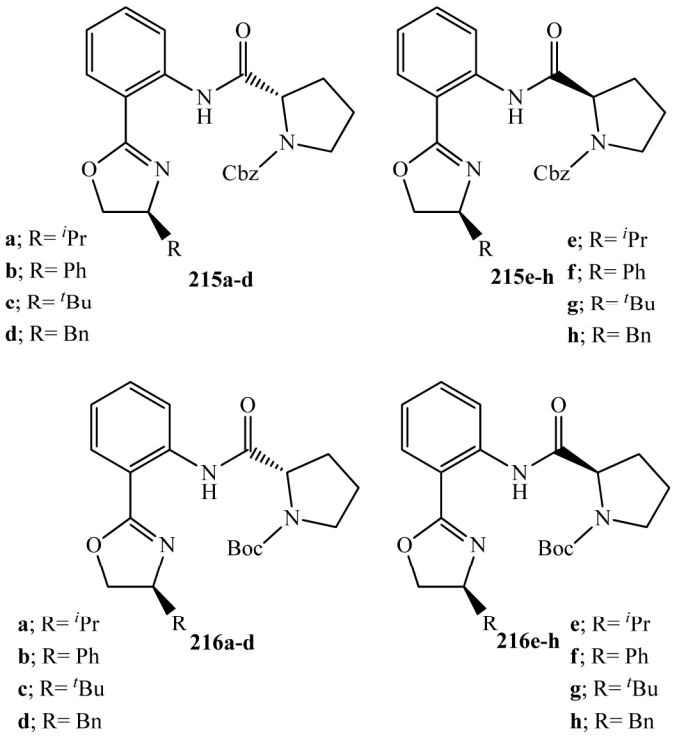


Figure 29: Proline based *o*-(anilinyl) oxazoline ligands **215** and **216**

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.[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.[2,74] Chiral bis(oxazoline) ligands with a great deal of structural diversity have been introduced since 1989 **[Figure 30]**.

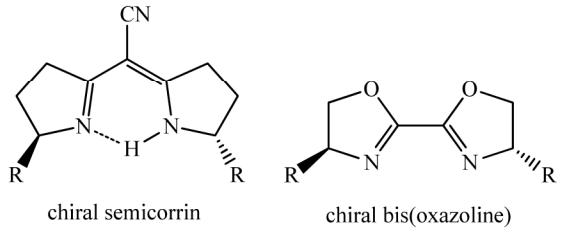
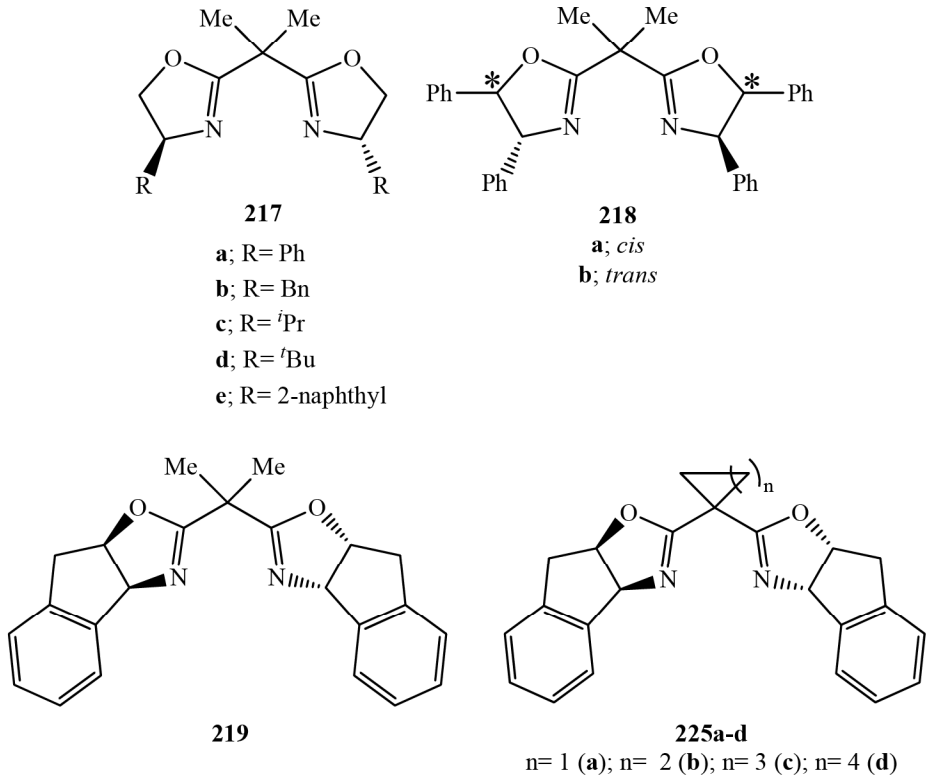


Figure 30: Structurally similar *N,N*-ligands

In general bis(oxazoline) ligands with one carbon spacer between the oxazoline 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]**.



217

a; R= Ph
b; R= Bn
c; R= ^{i}Pr
d; R= ^{t}Bu
e; R= 2-naphthyl

218

a; *cis*
b; *trans*

219

225a-d

n= 1 (**a**); n= 2 (**b**); n= 3 (**c**); n= 4 (**d**)

Figure 31: Two oxazoline rings connected with one carbon spacer

In 1991 two communications, one by Evans *et al.* dealing with asymmetric cyclopropanation of alkenes[75a] and the other one by Corey *et al.* about enantioselective Diels-Alder reactions,[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:

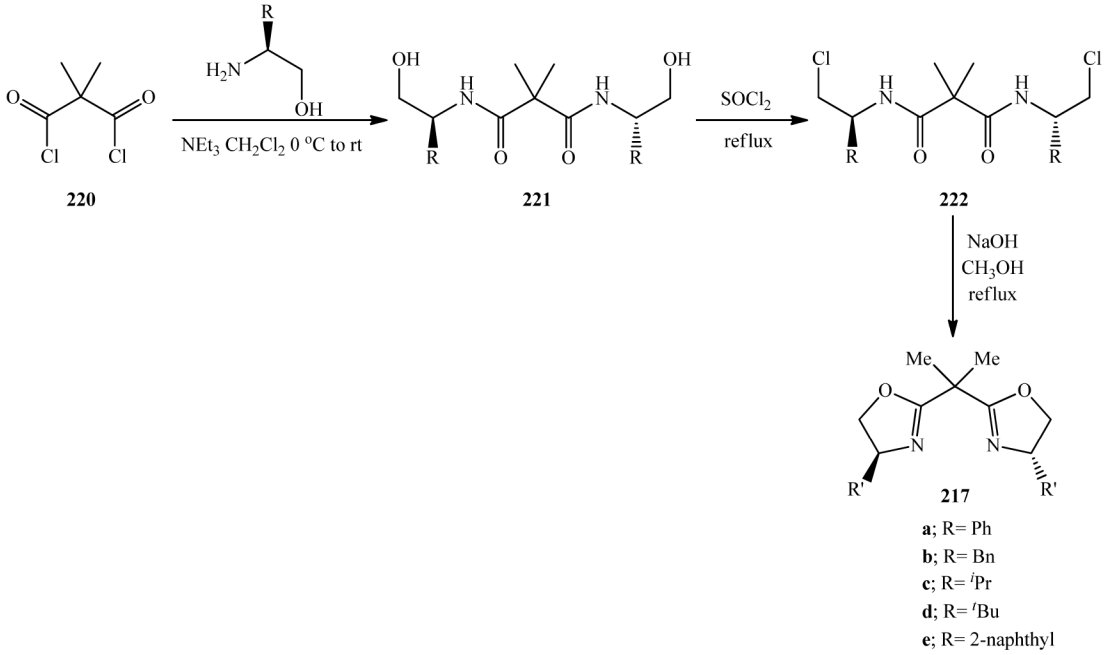
(A) The construction of the oxazolidine rings starting from a symmetrically disubstituted malonic acid derivative (the bis-substituted spacer) and 2 equiv of optically active β-amino alcohol (the chiral messenger), the method followed by Evans and Corey in their pioneering work.

(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_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.

(C) 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 choride **220** is shown in **scheme 71**.[76] 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.

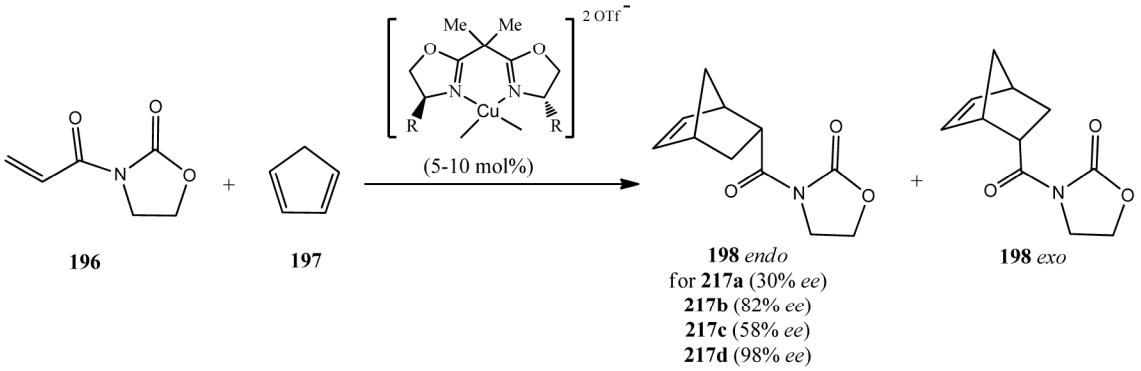


Scheme 71: Preparation of bis(oxazoline) ligands **217a-d**; **(*R,R*)-217e** and **(*S,S*)-217e**

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**.[76] 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**

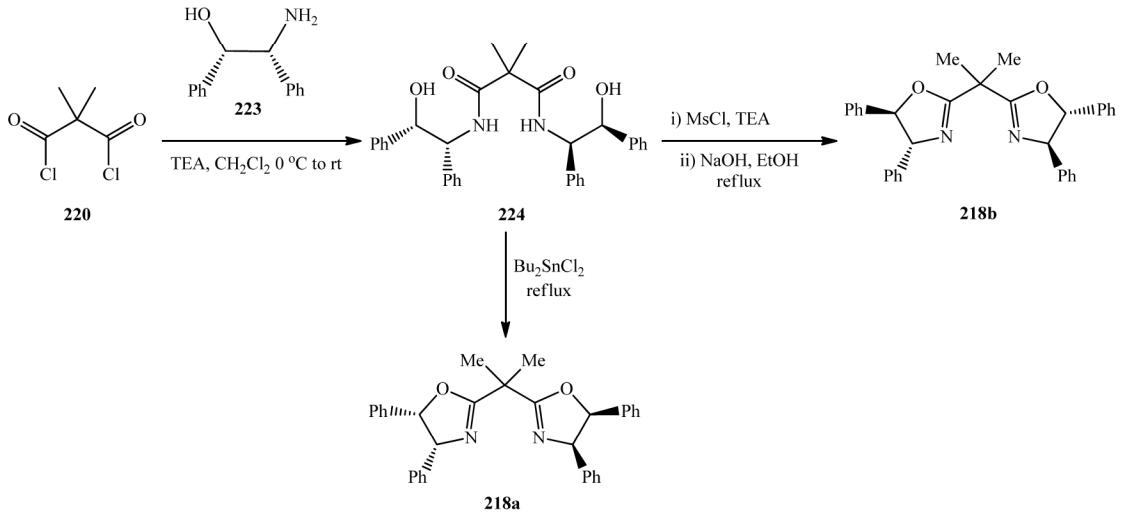
are not equally effective catalysts as they have shown considerably lower enantioselectivity (30, 82% and 58% *ee* respectively).

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.[77] 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 [$Mg(IIClO_4)_2$, $Mg(OTf)_2$, 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.



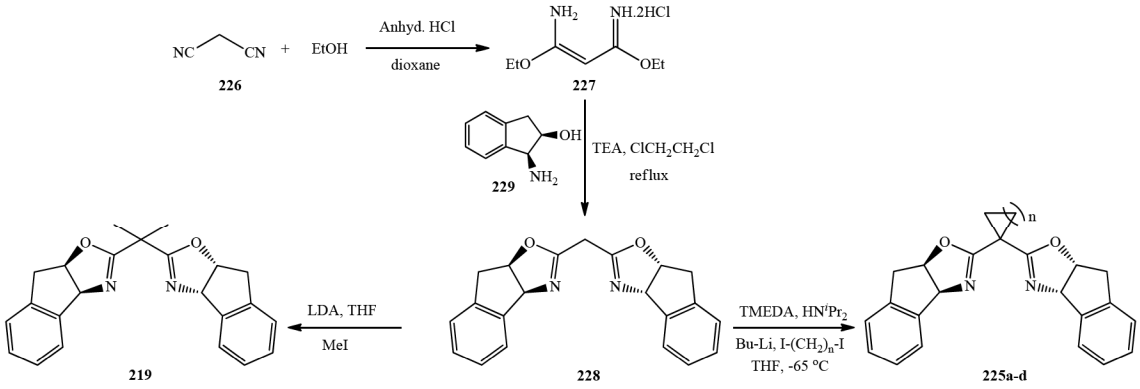
Scheme 72: Cu-catalyzed Diels-Alder reaction using bis(oxazoline) ligands **217a-d**

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 73]**.[77] 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 (Bu_2SnCl_2, reflux) furnished the *cis*-1,2-disubstituted bis(oxazoline) **218a**.[78] 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(oxazo1ines) **225a-d[Scheme 74],** and explained a direct correlation between the ligand bite angle and enantioselectivity in asymmetric Diels-Alder reaction. **[**see **Scheme 72]**.[79a]



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 (1*S*,2*R*)-amino indanol **229** (Scheme 2). Condensation with diethylmalonimidate **227** at reflux in 1,2-dichloroethane gave the pivotal bis(oxazo1ine) **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 diiodoalkane (1.1 eq.) led to the formation of the spirobis(oxazo1ines) **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(oxzoline) **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]**.[79b] 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]**.

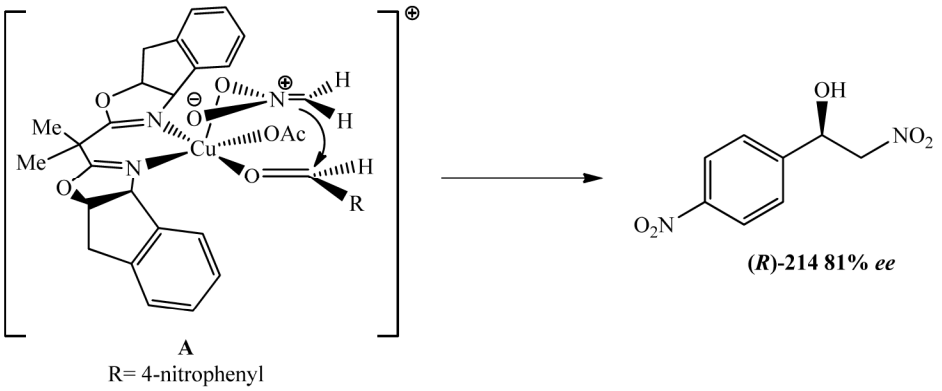
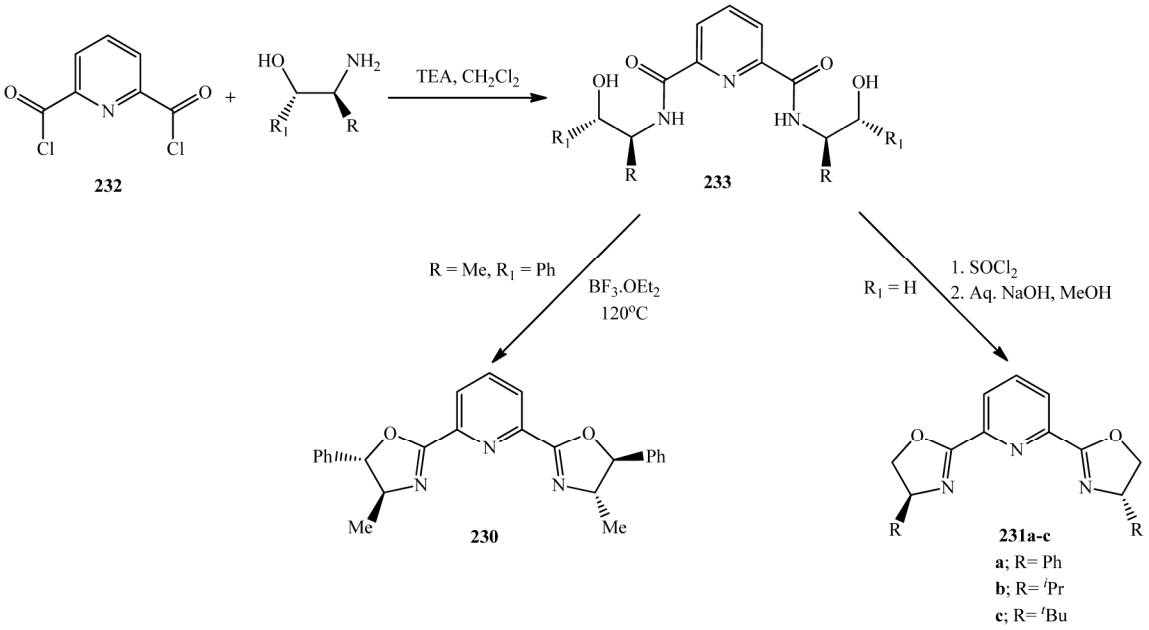


Chart 4: Model for the selectivity in Henry reaction using ligand **219**

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 on 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**).

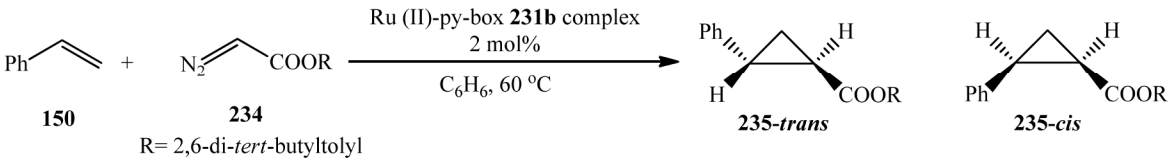
Nishiyama and co-workers have developed pyridinyl bis(oxazoline) ligands **230** and **231a-c** from pyridine 2,6-dicarboxylic acid chloride **232 [Scheme 75]**.[80]



Scheme 75: Synthesis of pyridinyl bis(oxazoline) ligands **230** and **231a-c**

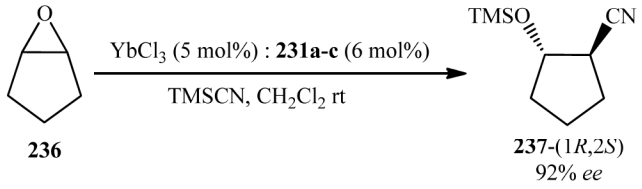
These type of py-box ligands have been applied to variety of asymmetric transformations. Nishiyama *et al* haves reported the use of Ru(II)-Py-box complexes as excellent catalysts for the enantioselective asymmetric cyclopropanation of styrene **150** with

diazoacetate **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 up on the Ru-salt used for the complexation**[Scheme 76]**.[81]



Scheme 76: Cyclopropanation reaction of styrene using Ru-complex of py-box **231b**

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]**.[82] 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**

Another class of bis(oxazoline)ligands with cyclic 1,3-dioxolane backbone **238 a-e** and **239a-b [Figure 32]**[83] have been developed by Andersson *et al* in good yields and screened them for Cu-catalyzed cyclopropanation reaction of styrene with ethyl diazoacetate.

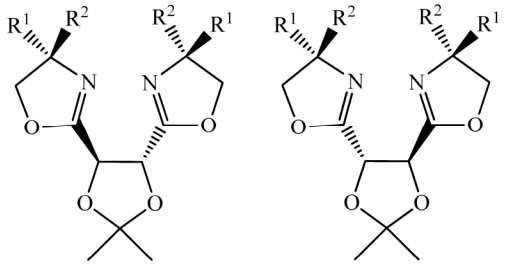
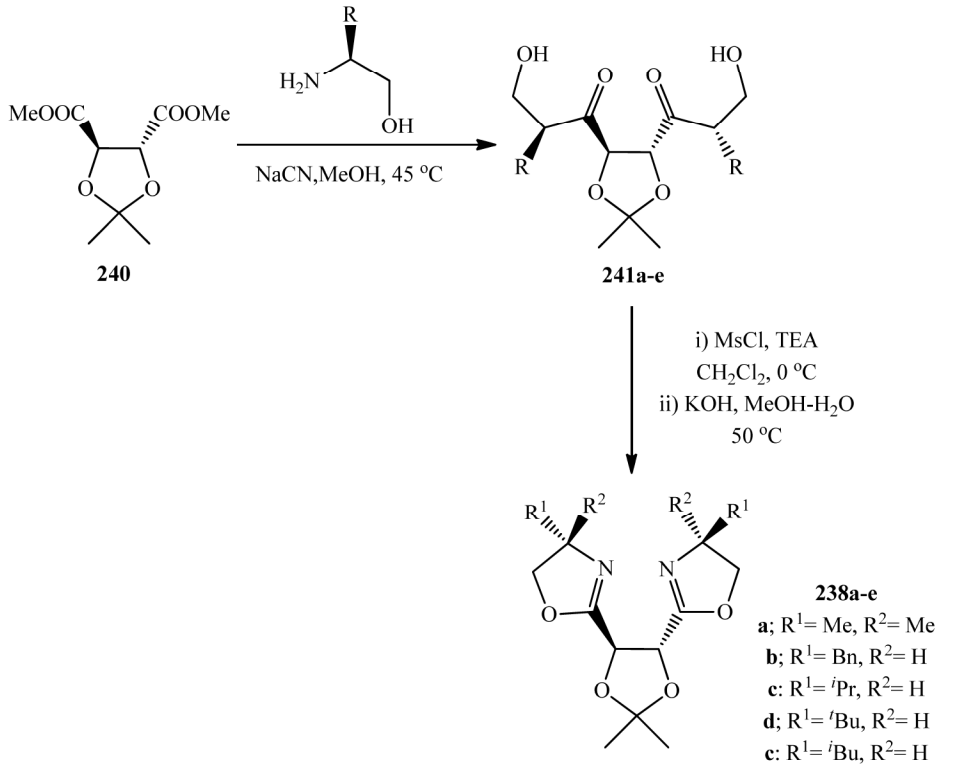


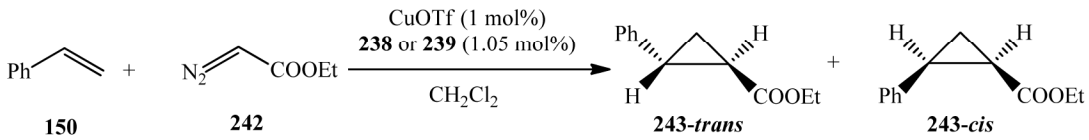
Figure 32: New class of bis(oxazoline) ligands with cyclic 1,3-dioxolane backbone **238a-e** and **239a-b**

The preparation of ligands **238a-e** was achieved in four steps from (4*R*,5*R*)-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 dihydroydiamides **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 (4*S*,5*S*)-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(oxazoline) 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 domented procedures.[84]

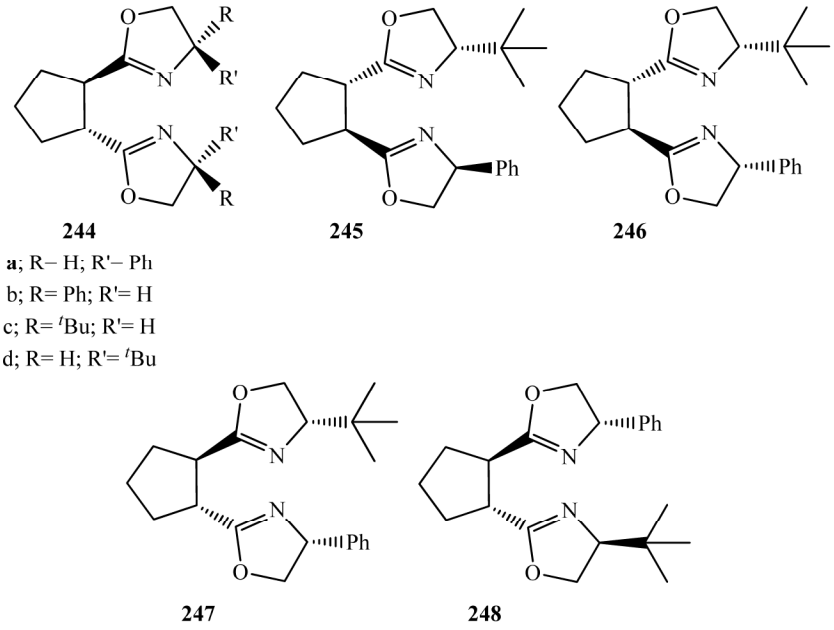
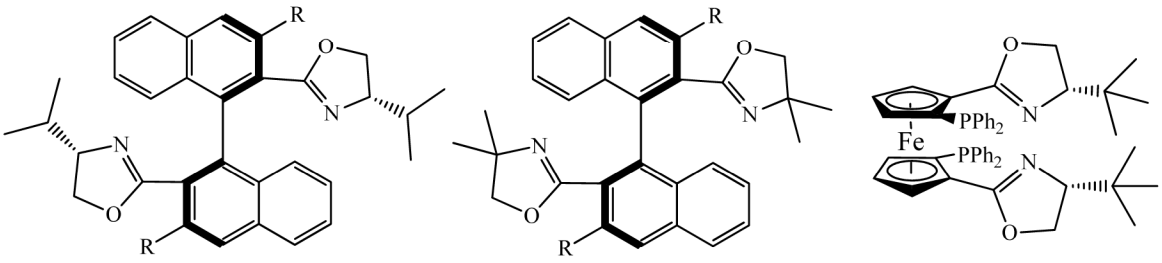


Figure 33: Bis(oxazoline) ligands having cyclic backbone

Using these ligands **244-248** for Cu-catalyzed cyclopropation 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]**.[85] Ligands **249** and **250** were examined for asymmetric induction in the palladium(II) catalyzed Wacker-type cyclization of the trisubstituted olefin (*E*)-2-(2-methyl-2-butenyl)phenol **252**, forming the 2,3-dihydrobenzofuran **253 [Scheme 80]**.

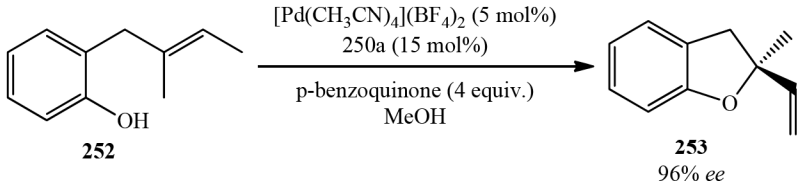


249 **a**; R= COOMe
b; R= TMS
c: R= $CONMe_2$
d; R= CHO
e; R= I

250 **251**

Figure 34: Bis(oxazoline) ligands with stereoaxis **249-250** and with stereoplane **251**

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.



252 **253** 96% *ee*

Scheme 80: Pd-catalyzed Wacker type cyclization usling ligand **250**

1,1'-Bis(diphenylphosphino)-2,2'-bis(oxazolinyl)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 $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (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]**.

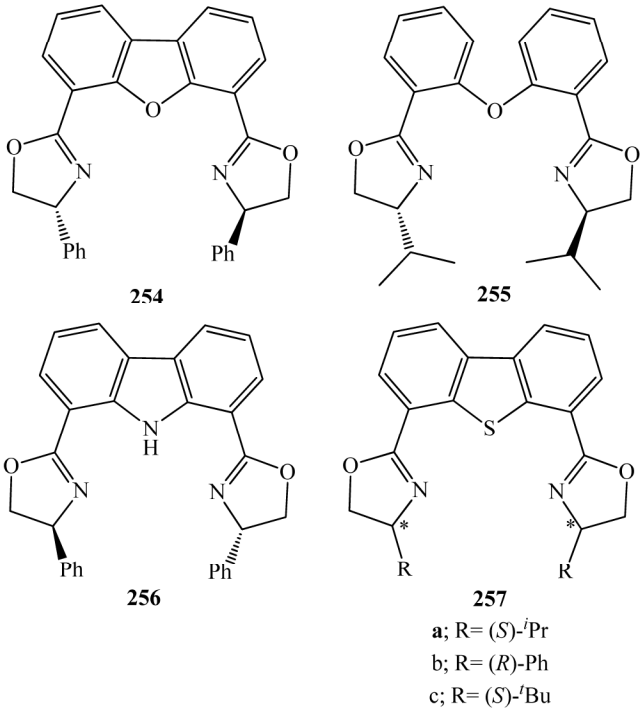


Figure 35: Dibenzofuzed heterocycle based bis(oxazoline) ligands **254**-**257**

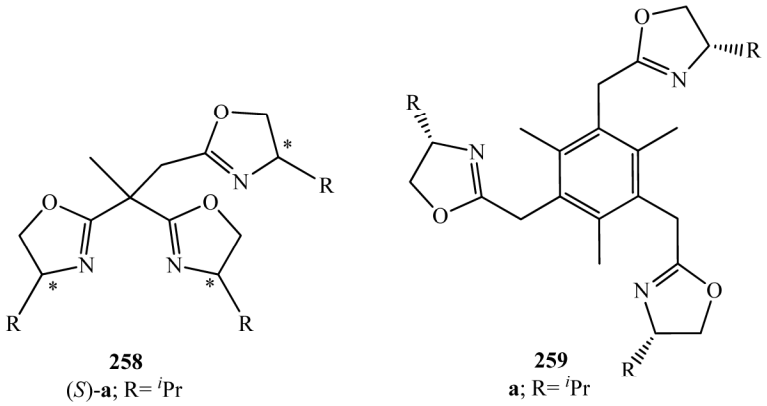
Pd-allyl complexes ([Pd(η^3-C_3H_5) **ligand**]PF_6) of the (*S*,*S*)-DBFOX/Ph ligand *ent*-**254** and the bis(oxazoline) ligand **255**, which contains a diphenyl ether backbone, were applied by Gómez in the Pd-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **12** with dimethyl 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 allylation of benzaldehyde **104** with allyl bromide **191** yielded allylated product **192**-(*S*) with 68% *ee*.[87]

Schulz has applied the dibenzothiophene 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(η^3- C_3H_5)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**.

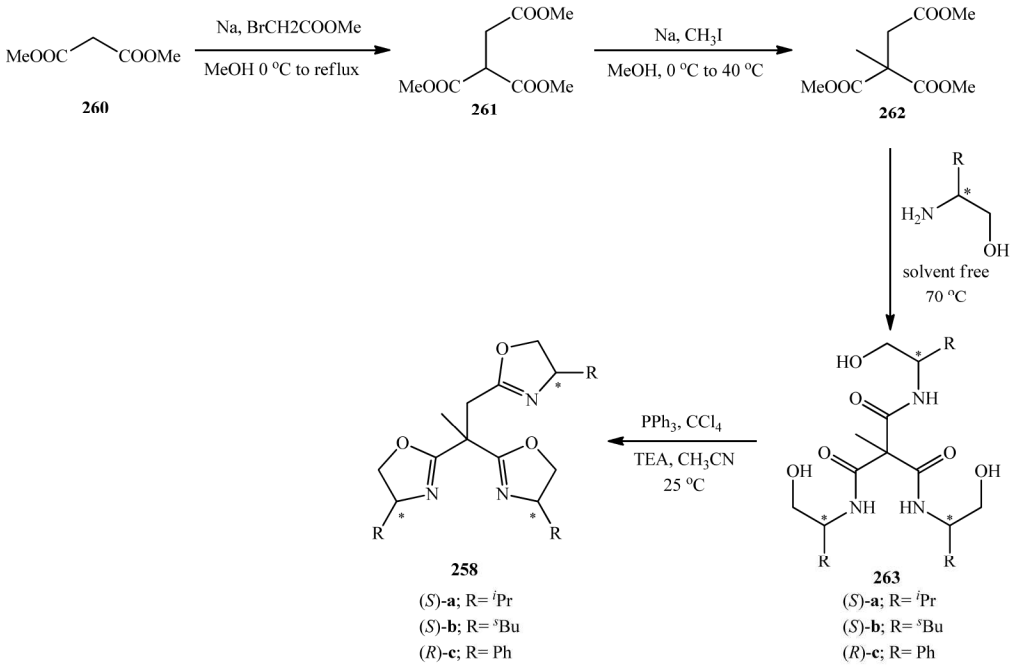


258
(*S*)-**a**; R= ^{i}Pr
(*S*)-**b**; R= ^{s}Bu
(*R*)-**c**; R= Ph

259
a; R= ^{i}Pr
b; R= ^{s}Bu
c; R= Ph

Figure 36: Examples of tris(oxazoline) ligands **258** and **259**

Tang has reported the synthesis of tris(oxazoline) ligand **258** from dimethylmalonate **260** in four steps **[Scheme 81]**.[89] 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 PPh_3-CCl_4 system to afford desired tris(oxazoline) ligands **258** with excellent yield.



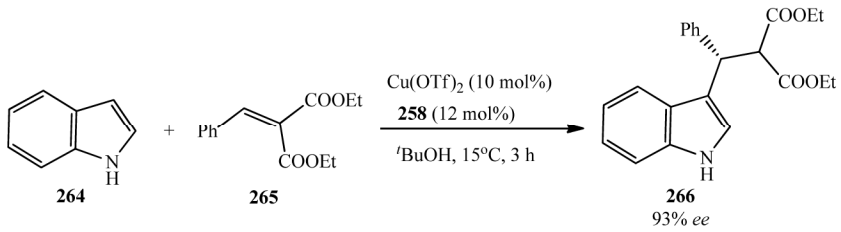
260 **261** **262**

258
(*S*)-**a**; R= ^{i}Pr
(*S*)-**b**; R= ^{s}Bu
(*R*)-**c**; R= Ph

263
(*S*)-**a**; R= ^{i}Pr
(*S*)-**b**; R= ^{s}Bu
(*R*)-**c**; R= Ph

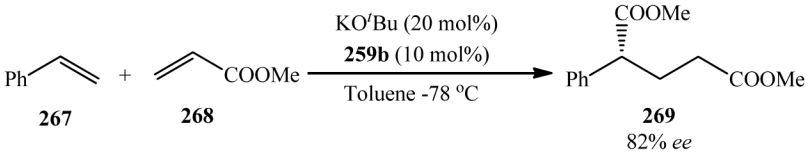
Scheme 81: Synthesis of tris(oxazoline) ligands **258a-c**

Tang has applied these tris(oxazoline) ligands **258** in the enantioselective Friedel-Crafts reaction between indole **264** and diethyl 2-benzylidenemalonate **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]**.[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

1) a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem.* **1986**, *98*, 1028. (c) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1005. (d) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553. (e) Pique, C.; Fahndrich, B.; Pfaltz, A. *Synlett* 1995, 491. (f) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem.* **1989**, *101*, 61. (g) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 60. (h) von Matt, P.; Pfaltz, A. *Tetrahedron: Asymmetry* **1991**, *2*, 691. (i) Pfaltz, A. *Acta Chim. Scand.* **1996**, *50*, 189.

2) A.K. Gosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.

3) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.

4) Green, T. W.; Wutz, P. G.; *Protecting Groups in Organic Synthesis 2: John Wiley and Sons; New York:* **1991.**

5) (a) Prinsep, M. R.; Moore, R. E.; Levine, I. A.; Patterson, G. M. L *J. Nat. Prod.* **1992**, *55*, 140. (b) Kelly, J. W.; You, S. L. *Chem. Eur. J.* **2004**, *10*, 71. (c) Moraski, G. C.; Chang, M.; Villegas-Estrada, A.; Franzblau, S. G.; Mo¨llmann, U; Miller, M. J. *Eur. J. Med. Chem.* **2010**, *45*, 1703.

6) a) Gant, T. G.; Meyers, A. I. *Tetrahedron*, **1994**, *50*, 2297 (b) Lowenthal, R. E.; biko, A.; Masamune, S. *Tetrahedron Lett* **1990**, *31*, 6005. (c) Bolm, J. G.; Aube, J. *J. Org. Chem.* **1996**, *61*, 2484. (d) Witte, H.; Seelinger, W. *Leibigs Ann. Chem*. **1974**, 996. (e) Wipf, P.; Venkatraman, S. *Tetrahedron Lett*. **1996**, *37*, 4659.

7) (a) Brunner, H. *Synthesis* **1988**, 645. (b) Lutomski, K. A., Meyers, A.I. *Asymmetnc Synthesis,* J.D. Morrison (Ed.), Academic, Orlando, **1984**, *3*, 213.

8) (a) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35,* 1523. (b) von Matt, P.; Loiseleur, O.; Koch, G.;. Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573.

9) (a) von Matt, P.; Pfaltz, A.; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.

10) (a) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Prétôt, R.; Pfaltz, A.; Schaffner, S.; Schnider, P.; von Matt, P. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 206. (b) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513. (c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

11) (a) Trost, B. M.; Van Vranken, D. L. Chem. Rev. **1996**, *96*, 395-422. (b) Lautens, M. A.; Pfaltz, A. Allylic Substitution Reactions. In Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 2, Chapter 24.

12) (a) von Matt, P.; Pfaltz, A.; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.

13) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1995**, *34*, 462.

14) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16.

15) (a) Hayashi, T.; Kubo A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421. (b) Shibasaki, M.; Vogl, E. M. In Comperhensive Asymmetric Catalysis; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds. Springer: Heidelberg, **1999**, *chapter 14*.

16) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595.

17) Bélanger, É.; Pouliot, M. F.; Paquin, J. F. *Org. Lett.* **2009**, *11*, 2201.

18) Kainz, S.; Brinkmann, A.; Leiner, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421.

19) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew Chem. Int. Ed.* **1998**, *37*, 2897.

20) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896.

21) Bolm, C.; Lu, S. –M. *Angew. Chem. Int. Ed.* **2008**, *47*, 8920. (b) Lu, W. –J.; Chen, Y, -W.; Hou, X. –L. *Angew. Chem. Int. Ed.* **2008**, *47*, 10133.

22) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem. Int. Ed.* **2005**, *44*, 7248.

23) Bian, J.; Wingerden, M. V.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 7428.

24) (a) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727. (b) Frolander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *J. Org. Chem.* **2005**, *70*, 9882.

25) (a) Bolm, C. *Angew. Chem. Int. Ed. Engl.* **1991**, *30,* 542. (b) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33,* 497.

26) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343.

27) (a) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1997**, *38,* 2681. (b) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36,* 8745. (c) Uozumi, Y.; Kyota, H.: Kishi, E.; Kitayarna, K.; Hayashi, T. *Tetrahedron:Asymmetry* **1996**, *7*, 1603. (d) Uozumi, Y.; Kato, K.; Hayashi, *T. J. Am. Chem. Soc.* **1997**, *119,* 5063. (e) Andrus, M. B.; Asgari, D.; Sclafani, J. A. J. *Org. Chem.* **1997**, *62,* 9365.

28) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96,* 395.

29) Gilbertson, S. R.; Chang, C. –W. T. *J. Org. Chem.* **1998**, *63*, 8424.

30) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180.

31) (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10; (b) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002. (c) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629. (d) Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104.

32) (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389 (b) Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. K. *J. Am. Chem. Soc.***1973**, *95*, 482. (c) Ratajczak, A.; Misterkiewicz, B. *J. Organomet. Chem.* **1975**, *91*, 73. (d) Hayashi, T.; Mise, T.; Kumada, M. *Tetrahedron Lett.* **1976**, *48*, 4351. (e) Wang, Y. -F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. -H. *J. Am. Chem. Soc* **1988**, *110*, 7200. (f) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061.

33) (a) Richards, C.; Damalidis, T.; Hibbs, D. E.; Hursthose, M. B. *Synlett* **1995**, 74; (b) Nishibashi, Y.; Uemura, S. *Synlett* **1995**, 79; (c) Park, J.; Lee, S.; Ahn, K. H.; Cho, C.-W. *Tetrahedron Lett.* **1995**, *36*, 7263; (d) Ahn, K. H.; Cho. C.-W.; Back, H.-H.; Park, J.; Lee, *S. J. Org. Chem.* **1996**, *61,* 4937.

34) Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry*, **1996**, *7*, 1419.

35) Ahn, K. H.; Cho, C. W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179.

36) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics*, **1995**, *14*, 5486.

37) Deng, W. –P.; Hou, X. –L.; Dai. L. –X.; Dong, X. –W. *Chem. Commun.*, **2000**, 1483.

38) (*a*) Nishibayashi, Y.; Segawa, K.; Ohe, K.; Oemura, S. *Organometallics*, **1995**, *14*, 5486; (*b*) Y. Nishibayashi, I. Takei, S. Uemura and M. Hidai, *Organometallics*, **1998**, *17*, 3420; (*c*) Takei, I.; Nishibayashi, Y.; Arikawa, Y.; Oemura, S.; Hidai, M. *Organometallics*, **1999**, *18*, 2271; (*d*) Takei, I.; Nishibayashi, Y.; Mizobe, Y.; Uemura, S.; Hidai, M. *Chem. Commun.* **2001**, 2360.

39) Lautens, M.; Hiebert, S.; Renaud, J. –L. *Org. Lett.* **2000**, *2*, 1971

40) Wang, R.; Guo, H.; Cui, J.; Li, S. *Tetrahedron Lett.* **2012**, *53*, 3977.

41) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

42) (a) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1848. (b) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* **1993**, *34*, 3405. (c) Bolm, C.; Schlingloff, G. *Chem. Commun.* **1995**, 1247.

43) Brunner, H.; Berghofer, J. *J. Organomet. Chem.* **1995**, *501*, 161.

44) Yang, H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1993**, *12*, 3485.

45) Cozzi, P. G.; Floriani, C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2357.

46) Peng, Y.; Feng, X.; Cui, X.; Jiang, Y.; Chang, A. S. C. *Synth. Commun.* **2001**, *31*, 2287.

47) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. *Tetrahedron Lett*. **2002**, *43*, 1535.

48) Poelert, M. A.; Hulshof, L. A.; Kellogg, R. M. *Recl*. *Trav*. *Chim*. *Pays-Bas* **1994**, *113*, 355.

49) Rozwadowska, M. D. *Tetraheron: Asymmetry* **1998**, *9*, 1615.

50) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297.

51) Jones, G.; Butler, D. C. D.; Richards, C. J. *Tetrahedron Lett.* **2000**, *41*, 9351.

52) (a) Allen. J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2065. (b) Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 7793. (c) Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 2015.

53) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, G. *Organometallics* **1998**, *17*, 3254.

54) Voituriez, A.; Schulz, E. *Tetrahedron: Asymmetry* **2003**, *14*, 339.

55) Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1.

56) (a) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499. (b) Brunner, H.; Brandl, P. *Tetrahedron: Asymmetry* **1991**, *2*, 919.

57) Yoo, K. S.; Park, C. P.; Yoon, C. H.; Sakaguchi, S.; O'Neill, J.; Jung, K. W. *Org. Lett.* **2007**, *9*, 3933.

58) (a) Fryzuk, M. D.; Jafarpour, L.; Retting, S. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3191. (b) Wu, X. –Y.; Shen, Y. –Y.; Ma, B.; Zhou, Q. –L.; Chan, A. S. C. *J. Mol. Catal. A* **2000**, *157*, 59.

59) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543.

60) (a) Wu, X. –Y.; Li, X. –H.; Zhou, Q. –L. *Tetrahedron: Asymmetry* **1998**, *9*, 4143. (b) Li, X. –G.; Wang, L. –X.; Zhou, Q. –L. *Chin. J. Chem.* **2002**, *20*, 1445.

61) (a) Wu, X. –Y.; Xu, H. –D.; Tang, F. –Y.; Zhou, Q. –L. *Tetrahedron: Asymmetry* **2001**, *12*, 2565. (b) Wu, X. –Y.; Xu, H. –D.; Tang, F. –Y.; Zhou, Q. –L. Chan, A. S. C. *Tetrahedron: Asymmetry* **2000**, *11*, 1255.

62) (a) Munoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293 (b) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076.

63) Trifonova, A.; Köllström, K. E.; Andersson, P. G. *Tetrahedron* **2004**, *60*, 3393.

64) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197.

65) McManus, H. A.; Barry, S. M.; Andersson, P. G.; Guiry, P. J. *Tetrahedron: Asymmetry* **2004**, *60*, 3405.

66) (a) Lee, J. –Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837. (b) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752.

67) (a) Gajare, A. S.; Shaikh, N. S.; Jnaneshwara, G. K.; Deshpande, V. H.; Ravindranathan, T.; Bedekar, A. V. *J. Chem. Soc., Perkin Trans. 1* **2000**, 999. (b) Reisch, J.; Usifoh, C. O.; Olewadiya, J. O. *J. Heterocyclic Chem.* **1989**, *26*, 1495. (c) Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795. (d) Button, K. M.; Gossage, R. A. *J. Heterocyclic. Chem.* **2003**, *40*, 513.

68) (a) Fujisawa, T.; Ichiyanagi, T.; Shimizu, M. *Tetrahedron Lett.* **1995**, *36*, 5031. (b) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *J. Org. Chem.* **1997**, *62,* 7937.

69) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2002**, *43*, 5587.

70) G. M. Coppola *Tetrahedron Lett.* **1998**, *39*, 8233.

71) Decken, A.; Gossage, R. A.; Yadav, P. N. *Can. J. Chem.* **2005**, *83*, 1185.

72) (a) Yang, W.; Liu, H.; Du, D. –M. *Org. Biomol. Chem.* **2010**, *8*, 2956. (b) Yang, W.; Du, D. –M. *Eur. J. Org. Chem.* **2011**, 1552.

73) Hargaden, G. C.; Muller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2007**, 4235.

74) Gómez, M.; Muller, G.; Rocamora, M. *Coord. Chem. Rev.* **1999**, *193-195*, 769.

75) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Corey E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

76) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc*. **1993**, *115*, 6460.

77) (a) Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron* **1996**, *52*, 13649. (b) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721.

78) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005 (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.

79) (a) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoevena, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753. (b) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.

80) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.

81) (a) Nishiyama, H.; Aoki, K.; Itoh, H.; Iwamura, T.; Sakata, N.; Kurihara, O.; Motoyama, Y. *Chem. Lett*. **1996**, 1071. (b) Park, S.-B.; Sakata, N.; Nishiyama, H. *Chem. Eur. J*. **1996**, *2*, 303. (c) Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487. (d) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, Y.; Itoh, K. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1247. (e) Nishiyama, H.; Itoh, Y.;Matsumoto, H.; Park, S.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223.

82) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.

83) (a) Bedekar, A. V.; Anderson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073. (b) Bedekar, A. V.; Koroleva, E. B.; Anderson, P. G. *J. Org. Chem.* **1997**, *62*, 2518.

84) Atodiresei, I.; Schiffers, I.; Bolm, C. *Tetrahedron: Asymmetry* **2006**, *17*, 620.

85) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620.

86) Gómez, M.; Jansat, S.; Muller, G.; Maestro, M. A.; Mahía, J. *Organometallics* **2002**, *21*, 1077.

87) (a) Suzuki, T.; Kinoshita, A.; Kawada, H.; Nakada, M. *Synlett* **2003**, 570. (b) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140.

88) Voituriez, A.; Fiaud, J.-C.; Schulz, E. *Tetrahedron Lett.* **2002**, *43*, 4907.

89) Ye, M. C.; Jian, B. L.; Zhou, J.; Sun, X. L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6108.

90) Kim, S. –G.; Ahm, K. H. *Tetrahedron Lett.* **2001**, *42*, 4175.