Design and Synthesis of Chiral Spiro Ligands

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Abstract

Tremendous progress has been made in design and synthesis of chiral spiro ligands and researches in finding their utility have led development of several asymmetric- and organo-catalysis. This review describes recent advances in synthesis of chiral spiro ligands.

***Keywords**: asymmetric synthesis, metal catalysis, spiro ligands*

Introduction

The adjective *chiral* is derived from the Greek *cheir* meaning "hand". A hand has no symmetry plane since the right half of a hand is not a mirror image of the left half. Left and right hands are chiral that do not superimpose on each other and are not identical. The phenomenon of handedness or chirality exhibits in many molecules of the Nature and are importantly biologically active. Unfortunately, Nature supplies such bioactive compounds in limited quantities and usually only single isomers are available after tedious isolation processes. Thus the scientific community has focused on asymmetric synthesis of organic compounds through the induction of chirality by employing chiral reagents, where synthesis of all the enantiomers is feasible.[1] In particular, the metal-catalyzed asymmetric synthesis has emerged as a powerful and economic tool for the synthesis of optically active organic compounds of biological importance, in which, the use of a suitable chiral ligand can provide an effective asymmetric environment for chirality induction. The design and synthesis of an efficient chiral ligand, with strong metal affinity and a suitable chiral backbone, is one of the most challenging tasks and plays a central role for the success. Additional benefits are gained when the chiral ligands could easily be modified to achieve high turn over number in the catalytic reactions.

In 1980s, Noyori reported an outstanding diphosphine ligand 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) with a biaryl scaffold, which is one of the most commonly used chiral ligands in the transition metal-catalyzed asymmetric reactions.[2] The configurational stability of this type of ligand depends on the restriction in rotation around the bridged-bond due to the bulk of the *ortho*-substituents and thus exhibits an axial chirality. Searching of new chiral ligands over the past decades has led to synthesis of several bidentate phosphines, diamines, oxazolines and hybrid *P,N* ligands (Figure 1).[3] In contrast, spirane with two rings and one common spiro atom (generally carbon) is rigid. This rigid spirocyclic framework minimizes the number of possible conformations and consequently benefits in selectivity. The parent spiro[4,4]nonane itself is achiral, however, the spirane chirality is observed when suitable substituents are introduced in the perpendicular rings that gives rise C_2-symmetric structural feature (Figure 2). The introduction of substituents in spirane ring for creation of chiral skeleton results in more than one chiral center in the molecule and thereby increases the difficulties in its synthesis and resolution.

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The synthesis of a spiro skeleton can be traced back to the late 1890s.[4] von Baeyer has coined the term "spirocyclane" for the pretzel like bicyclic hydrocarbons in 1900.[5] After one century of its discovery, spiro skeleton has gained interests of scientific community to be used as chiral auxiliaries. The purpose of this review is to summarize the design and synthesis of chiral spiro ligands, which have already been used in metal catalysis.[6]

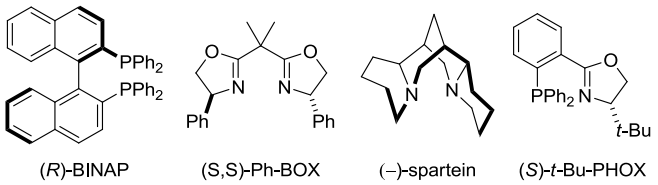


Figure 1: *Representative examples of chiral ligands.*

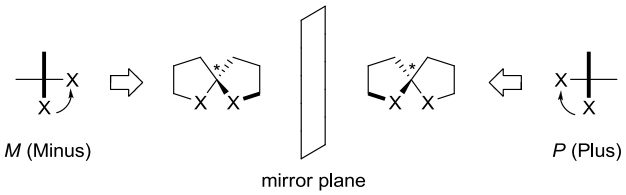


Figure 2: *Spirane chirality.*

[m,n]Alkane-based Spiro Ligands

Spiro[4.4]nonane-1,6-diol (Spirol)

Spiro[4.4]nonane-1,6-diol (Spirol) can exist in three diastereomeric forms: *cis,cis* **1**, *cis,trans* **2** and *trans,trans* **3** (Figure 3). Cram, Gerlach, Harada and their coworkers have independently reported the synthesis of Spirol.[7] In 1993, an improved synthesis of *cis,cis*-**1** was reported by Keay *et al.* (Scheme 1).[8] Alkylation of the anion of ethyl 2-oxocyclopentanecarboxylate (**4**) with ethyl 4-bromobutyrate produced the diester, which subsequently hydrolyzed and decarboxylated by refluxing in 10% HCl to give **5**. The spiro cyclization of **5** was affected by treating with *p*-toluenesulphonic acid in refluxing toluene (through azeotropic removal of the water) producing racemic dione **6**. Treatment of **6** with lithium *tert*-butyldiisobutylaluminium hydride selectively produced *racemic cis,cis*-**1** with 51% yield in four steps. The choice of reducing agent in this step was found crucial for the diastereoselectivity. Chan *et al.* have reported predominantly formation of *cis,trans*-**2** by catalytic hydrogenation of dione **6** in the presence of platinum-charcoal in acetic acid (**1**:**2**:**3**= 24:76:0).[9] Alternatively, in the stoichiometric hydrogenation of **6**, the use of borane in THF was effective (**1**:**2**:**3** = 16:82:2). On the other hand, the chiral oxazaborolidine reagent-catalyzed reduction of dione **6** produced *trans, trans*-**3** stereoselectively. Spirol can be resolved by column chromatographic separation of the diastereomers that obtained by treating with either (+)-camphor and *p*-toluenesulphonic acid[8] or *d*-camphorsulphonyl chloride in pyridine,[9] followed by hydrolysis. Spirols are not explored their selves as chiral ligands in the metal catalysis but are further converted in to the phosphine and nitrogen based ligands and then utilized in metal catalysis.

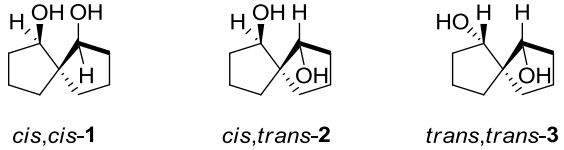
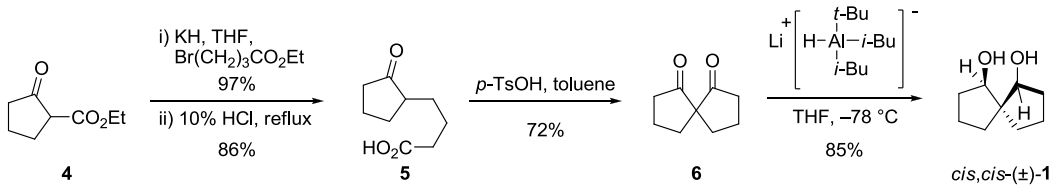


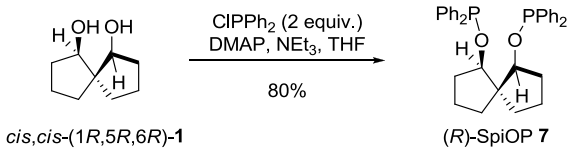
Figure 3: *Three diastereomers of Spirol.*



Scheme 1: *Synthesis of cis,cis-Spirol.*

Spiro bisphosphinite (SpirOP)

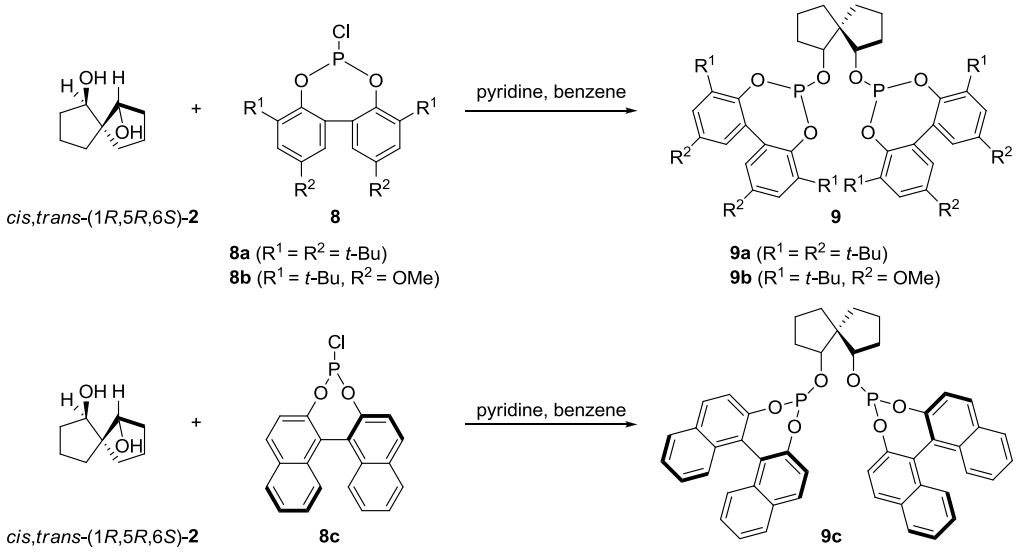
In the pioneering report, Chan and Jiang *et al*. described synthesis of chiral 1,6-spiro bisphosphinite ligand (SpirOP) **7** through the reaction of chlorodiphenylphosphine with optically pure *cis,cis*-(1*R*,5*R*,6*R*)-Spirol **1** in the presence of *N*,*N*-dimethyl-4-diaminopyridine (DMAP) (Scheme 2).[10] SpirOP **7** was utilized in the Rh-catalyzed asymmetric hydrogenation reactions.[11]



Scheme 2: *Synthesis of SpirOP.*

Spiro diphosphite

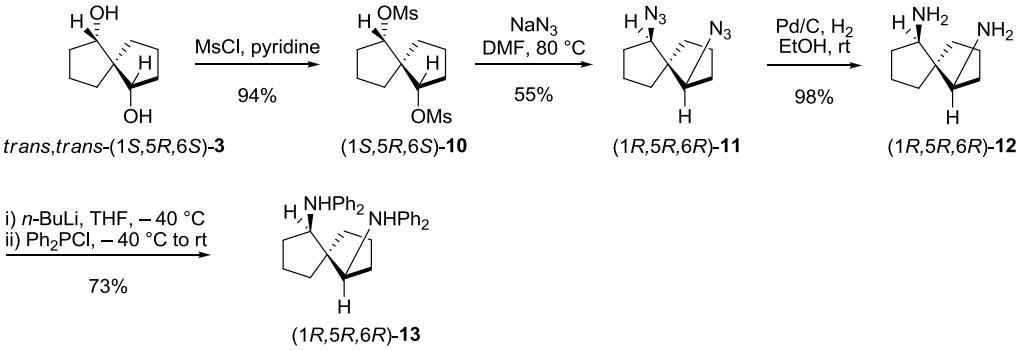
Jiang, Xue and their coworkers have prepared chiral spiro diphosphite ligands **9** by the reaction of *cis,trans*-(1*R*,5*R*,6*S*)-Spirol **2** with chlorophosphites **8** (Scheme 3).[12] Related diphosphites are not produced from *cis,cis*-(1*R*,5*R*,6*R*)-Spirol **1** due to the steric constraints. In the presence of ligands **9** and syn gas ($CO:H_2$ = 1:1), the Rh-catalyzed asymmetric hydroformylation of styrenes is reported.



Scheme 3: *Synthesis of spiro diphosphites.*

Spiro bisphosphinamidite (SpiroNP)

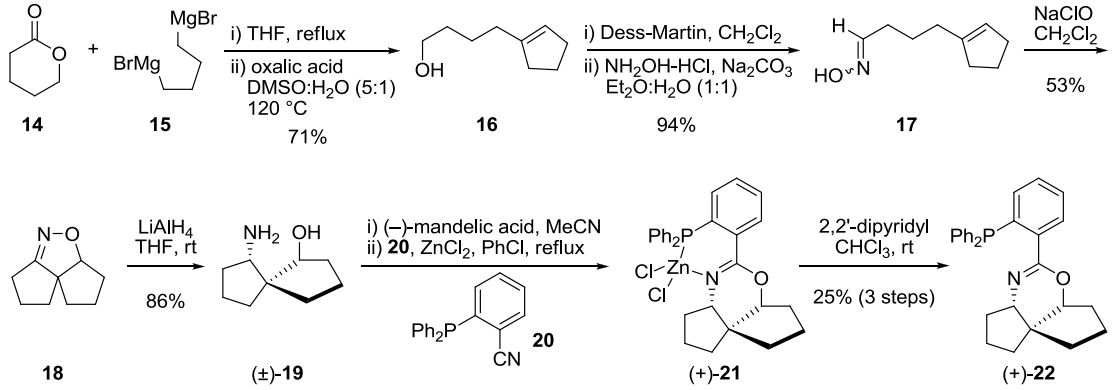
Chan *et al*. have reported chiral spiro bisphosphinamidite ligand (SpiroNP) **13** (Scheme 4).[13] Dimesylate (1*S*,5*R*,6*S*)-**10**, obtained from *trans*,*trans*-(1*S*,5*R*,6*S*)-**3**, upon treatment with sodium azide produced diazide (1*R*,5*R*,6*R*)-**11**. The Pd/C reduction of diazide **11** with molecular hydrogen produced diamine (1*R*,5*R*,6*R*)-**12**. Subsequent lithiation of **12** followed by the addition of Ph_2PCl produced (1*R*,5*R*,6*R*)-**13**. The application of SpiroNP has been shown in the cationic Rh-catalyzed asymmetric hydrogenation reaction.



Scheme 4: *Synthesis of SpiroNP.*

Spiro phosphino-oxazoline

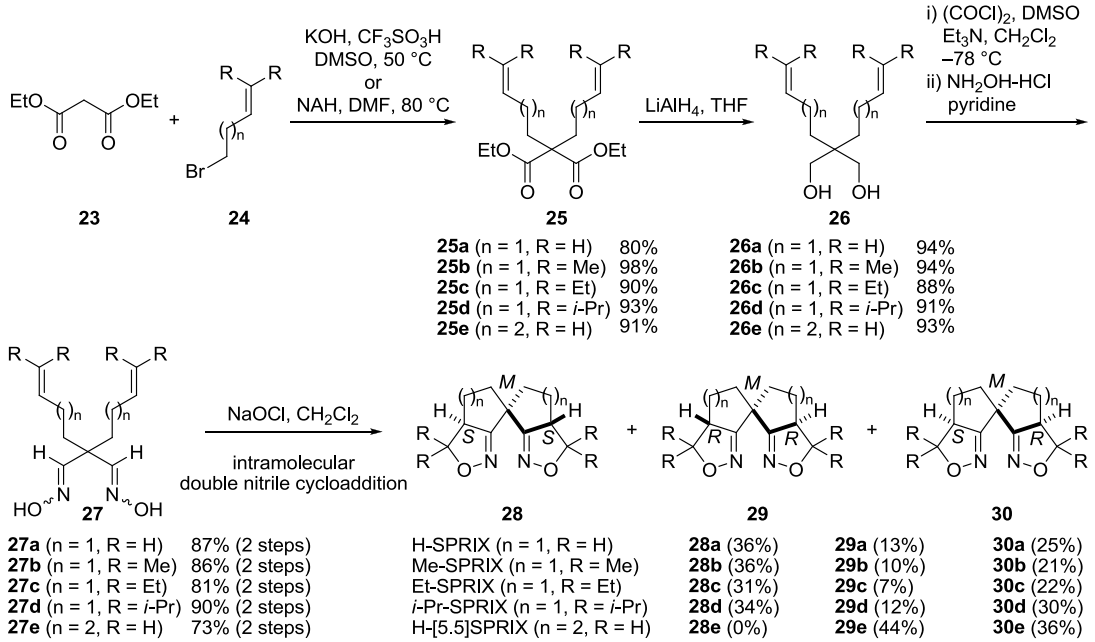
Keay *et al*. have synthesized spiro phosphino-oxazoline **22** (Scheme 5).[14] Addition of lactone **14** to the Grignard reagent produced a diol, which was dehydrated under acidic conditions yielding **16**. Dess-Martin oxidation of **16** followed by oxime formation produced **17**. Oxime **17** was stirred with NaClO to produce a nitrile oxide, which underwent intramolecular 1,3-dipolar cycloaddition giving **18**. $LiAlH_4$ reduction of **18** produced spiro amino alcohol (±)-**19**. Resolution of (±)-**19** with (–)-mandelic acid gave (+)-**19**.[14b] Coupling of (+)-**19** and **20** by refluxing with $ZnCl_2$ produced (+)-**21**, which on treating with 2,2'-dipyridyl gave (+)-**22**. The application of spiro phosphino-oxazoline was shown in the Pd-catalyzed alkylation reaction.[14a]



Scheme 5: *Synthesis of spiro phosphino-oxazoline.*

Spiro bis(isoxazoline) (SPRIX)

In 1999, Sasai *et al.* reported novel chiral spiro bis(isoxazoline) ligands (SPRIXs) **28**-**30** bearing two isoxazoline rings to coordinate with a metal center.[15] SPRIXs **28**-**30** were synthesized starting from diethyl malonate (**23**) *via* intramolecular double nitrile oxide cycloaddition as a key step, which constructs four rings and a spiro backbone in one step (Scheme 6). Compound **23** was treated with alkenyl bromide **24** in the presence of a base to produce malonate **25**, which was subsequently reduced with $LiAlH_4$ producing diol **26**. After Swern oxidation of **26**, the resulting dialdehyde was treated with NH_2OH-HCl in pyridine to produce dioxime **27** as a single isomer. All the possible diastereomers were obtained using intramolecular double nitrile oxide cycloaddition of **27** and each diastereomer was easily separated using silica gel column chromatography. (*M*,*S*,*S*)-H-[5.5]-SPRIX **28e** was not obtained because of a steric repulsion between the two nitrogens of isoxazoline rings.



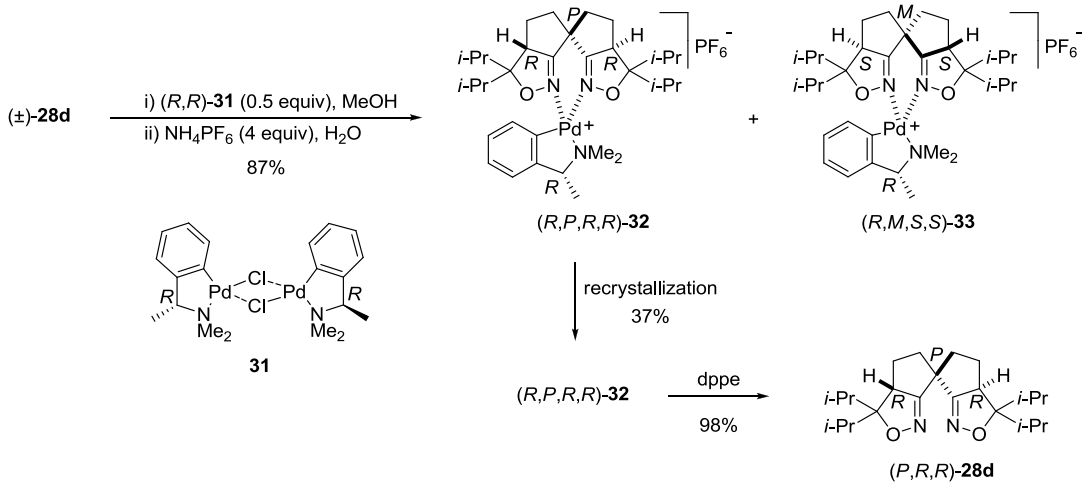
Scheme 6: *Synthesis of SPRIXs.*

Enantiomerically pure SPRIXs were obtained by chiral stationary phase column chromatography [Daicel Chiralpak AD (ø 2 cm × 25 cm)]. Later, tetraisopropyl-substituted spiro bis(isoxazoline) (*i*-Pr-SPRIX, **28d**) was successfully resolved by using *ortho*-palladated benzylamine derivative as a resolving agent *via* the separation of a mixture of the diastereomeric palladium complexes of (±)-**28d** (Scheme 7).[16] The treatment of (±)-**28d** with 0.5 equivalents of di-μ-chlorobis{(*R*)-2-[1-(dimethylamino)ethyl]phenyl-*C*,*N*}dipalladium (II) (*R*,*R*)-**31** followed by addition of 4 equivalents of aqueous NH_4PF_6 in MeOH produced 1:1 diasteromeric mixture of cationic palladium complexes (*R*,*P*,*R*,*R*)-**32** and (*R*,*M*,*S*,*S*)-**33**. After fractional recrystallization from dichloromethane/diethyl ether solution, the pure sample of (*R*,*P*,*R*,*R*)-**32** was obtained as a colorless crystal. Optically pure (*P*,*R*,*R*) enantiomer of *i*-Pr-SPRIX **28d** was obtained by decomplexation from (*R*,*P*,*R*,*R*)-**32** through the ligand exchange reaction using 1,2-bis(diphenylphosphino)ethane (dppe).

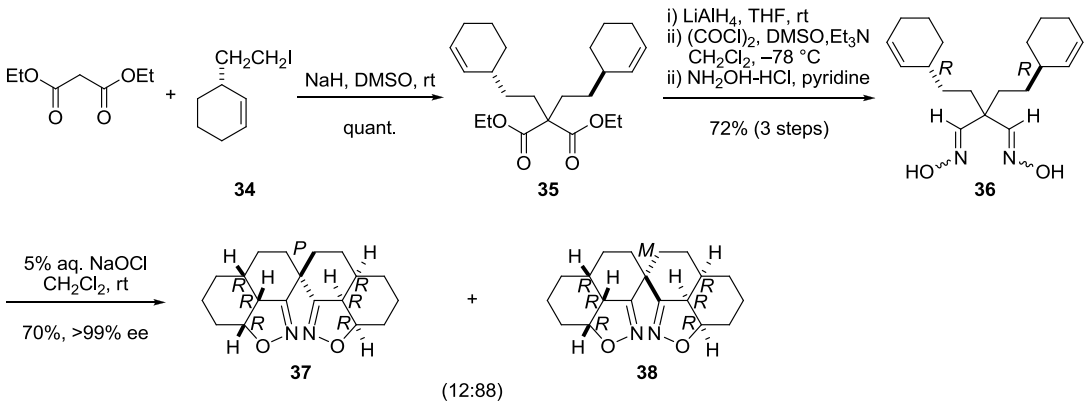
Using SPRIXs, Pd-catalyzed Wacker-type cyclization of alkenyl alcohols and tandem cyclization of dialkenyl alcohols (see: Scheme 12),[17] intramolecular aminocarbonylation of alkenyl amines and

amides,[18] cyclization of (*Z*)-4'-acetoxy-2'-butenyl-2-alkynoates,[19] 5-*endo*-*trig*-type cyclization of β,γ-unsaturated carbonyl compounds[20] were developed. Furthermore, an interesting application of SPRIX has been found in the dicationic palladium-catalyzed enantioselective isotactic copolymerization of CO with styrenes.[21] Recently, the first asymmetric Pd^{II}/Pd^{IV} catalysis was achieved by using a combination of a hypervalent iodine reagent and SPRIX to synthesize bicylo[3.1.0] hexanes *via* oxidative cycliation of enynes.[22]

Next, using an optically pure olefin derivative **34**, new chiral spiro bis(isoxazoline) ligands **37** and **38** were synthesized following the general route (Scheme 8).[23] Only two diastereomers **37** and **38** were obtained with a ratio of 12:88 in overall 51% yield. Importantly, these ligands were obtained in an optically pure form by simple column chromatography. MM2 calculation revealed that **37** have comparably a short *N–N* atomic distance (3.04 Å vs. 4.09 Å of **38**) and a small out-of-plane angle between the two C=N bonds (59.8° vs. 89.5° of **38**) indicating it's potential for a metal coordination. Using ligand **37**, the first example of the bis(isoxazoline) ligand-promoted, Cu-catalyzed gloxylate-ene reaction of olefins to produce alkenoates was reported.



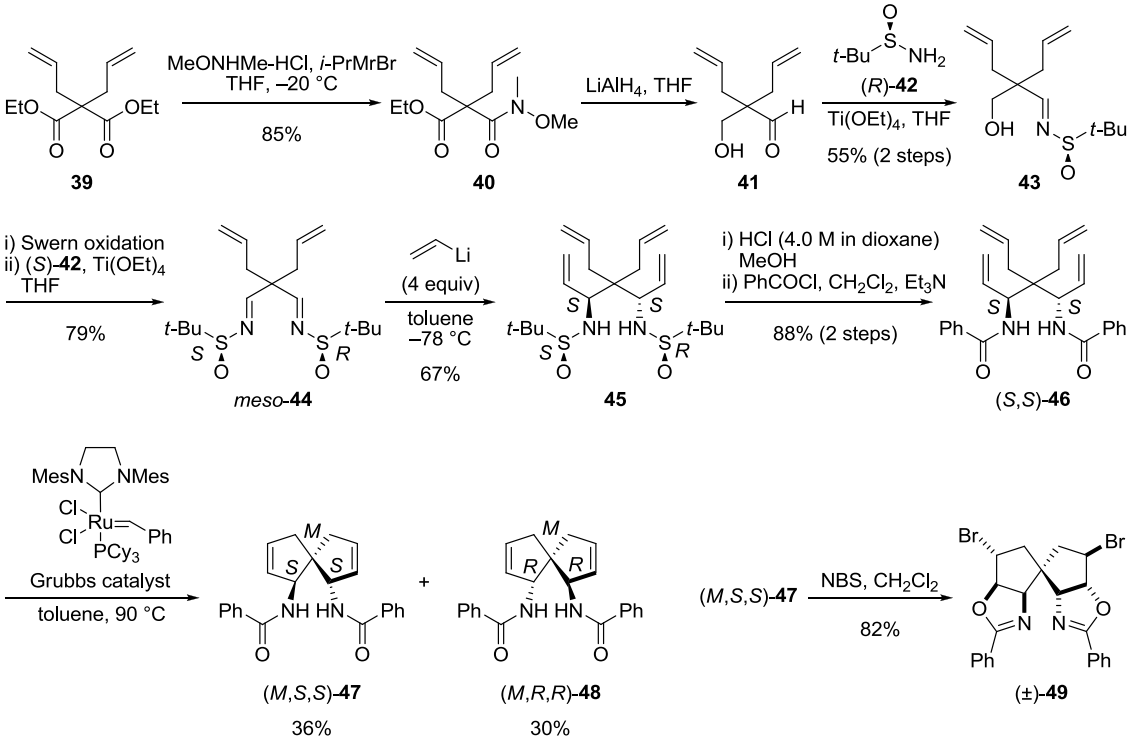
Scheme 7: *Resolution of i-Pr-SPRIX.*



Scheme 8: *Synthesis of the polycyclic spiro bis(isoxazolines).*

Spiro bis(oxazoline)

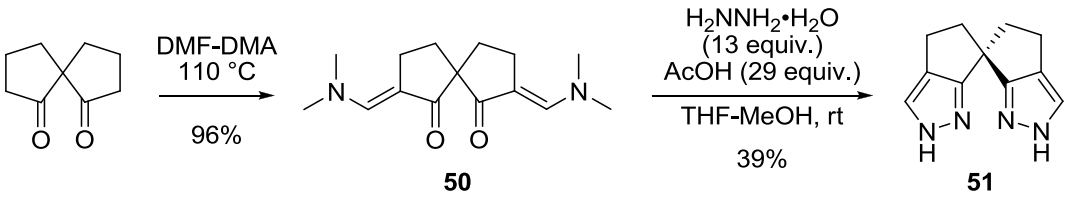
For the synthesis of spiro bis(oxazoline) ligand **49**, diethyl 2,2-diallyl malonate (**39**) was converted to Weinreb amide **40** (Scheme 9).[24] After $LiAlH_4$ reduction followed by condensation with (*R*)-**42** in the presence of $Ti(OEt)_4$ produced **43**. The aldehyde obtained after Swern oxidation of **43** was reacted with (*S*)-**42** to produce *meso*-**44**. Diastereoselective 1,2-addition of vinyl lithium to *meso*-**44** predominantly gave **45**, which was treated with HCl and then reacted with benzoyl chloride to give the cyclization precursor (*S*,*S*)-**46**. Ring closing metathesis of tetraene **46** with Grubbs catalyst produced spiro amides (*M*,*S*,*S*)-**47** and (*M*,*R*,*R*)-**48**. Finally, the desired ligand (±)-**49** was synthesized from (*M*,*S*,*S*)-**47** in 82% yield *via* oxazoline ring formation promoted by *N*-bromosuccinimide (NBS). This reaction proceeded with high diastereoselectivity, with no other diastereomer being observed. After separation by using a chiral stationary phase column [Daicel Chiralpak AD (ø 2 cm × 25 cm)], the enantiopure **49** was used in the Cu-catalyzed glyoxylate-ene and Henry reactions.



Scheme 9: *Synthesis of spiro bis(oxazoline).*

Spiro bis(pyrazole)

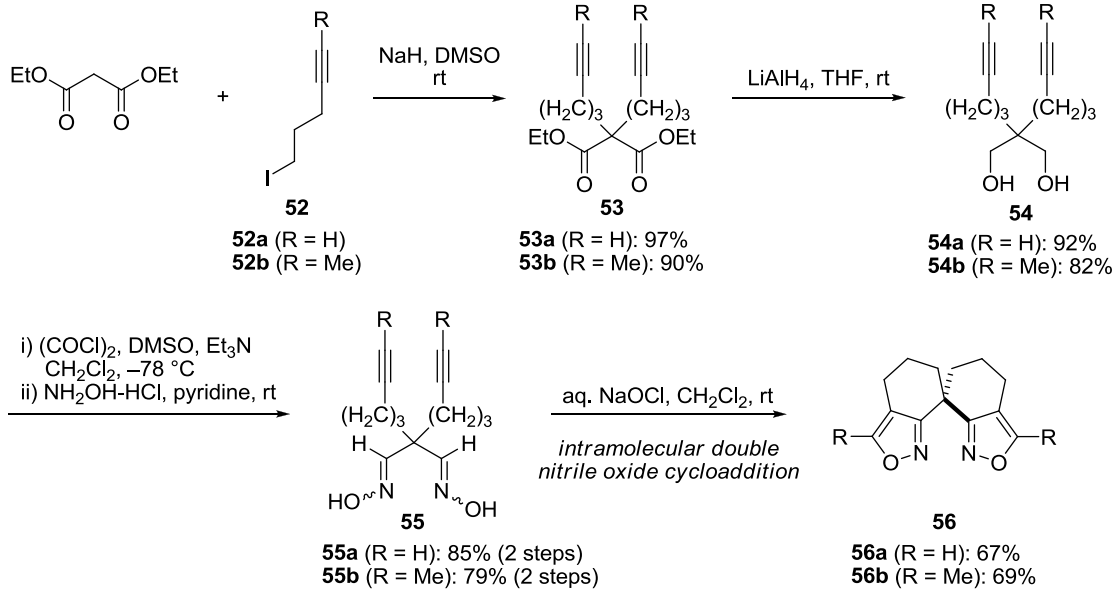
Furthermore, spiro bis(pyrazole) ligand **51** was synthesized by Sasai *et al* (Scheme 10).[25] Heating of a mixture of spiro[4.4]nonane-1,6-dione and *N*,*N*-dimethylformamide dimethyl acetal produced dione **50**. Treatment of **50** with an excess of hydrazine monohydrate and AcOH produced ligand (±)-**51**. Optically pure **51** was obtained by separation with a chiral stationary phase column [Daicel Chiralpak AD (ø 2 cm × 25 cm)] and used in the Cu-catalyzed asymmetric glyoxylate-ene reaction.



Scheme 10: *Synthesis of spiro bis(pyrazole).*

Spiro bis(isoxazole)

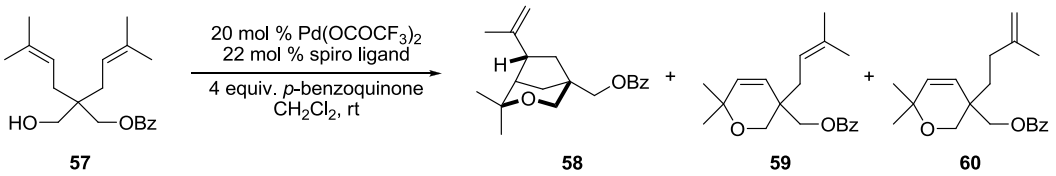
Designing of ligand **56** having isoxazole rings led to the synthesis of dioxime **55** using alkynyl halide **52** by following similar strategy of the SPRIX synthesis (Scheme 11).[26] Intramolecular double nitrile oxide cycloaddition of dioxime **55** produced **56** in 40–51% overall yield. After separation by using a chiral stationary phase column chromatography [Daicel Chiralpak AD (ø 2 cm × 25 cm)], the enantiomerically pure **56a** and **56b** were tested for the catalytic activity in the Pd-catalyzed tandem cyclization of dialkenyl alcohols (see: Scheme 12).



Scheme 11: *Synthesis of spiro bis(isoxazole).*

Spiro (isoxazoline-isoxazole)

A weaker coordinating chiral spiro bis(isoxazoline) ligand (SPRIX) **28** restores the Lewis acidity at the metal center making it more reactive. In contrast, a more weaker coordinating chiral spiro bis(isoxazole) ligands **56** were found ineffective in the Pd-catalyzed tandem cyclization of the dialkenyl alcohol (Scheme 12).



57 **58** **59** **60**

other conditions	58	59	60
(*M*,*S*,*S*)-*i*-Pr-SPRIX **28d** (8 h)	42%, 93% ee	15%	17%
(*M*,*S*,*S*)-*i*-Pr-SPRIX **28d** (85 h at 0°)	65%, 95% ee	5%	26%
(+)-**56a** (17 h)	27%, 56% ee	43%	4%
(+)-**56b** (7 h)	23%, 59% ee	47%	8%

Scheme 12: *Pd-catalyzed tandem cyclization of the dialkenyl alcohol*

We thought that a combination of weakly coordinating groups and more rigid structure would provide optimum benefit in designing a new ligand. Thus we designed a new hybrid spiro isoxazoline-isoxazole ligand containing an unsymmetrical spiro backbone.[27] It was anticipated that in this new design of hybrid ligand, only two diastereomers would be formed and this is advantageous, since in the case of synthesis of SPRIX, three diastereomers were obtained. A computational calculation study of possible diastereomers with varying ring size such as spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane and spiro[4.6]undecane using HF/6-31G* revealed that spiro[4.5]decane skeleton has the most suitable design. And, the isoxazoline and isoxazole rings fused to the 5 and 6 membered spiro rings, respectively, showed the shortest *N–N* distance (3.35 Å) (Figure 4).

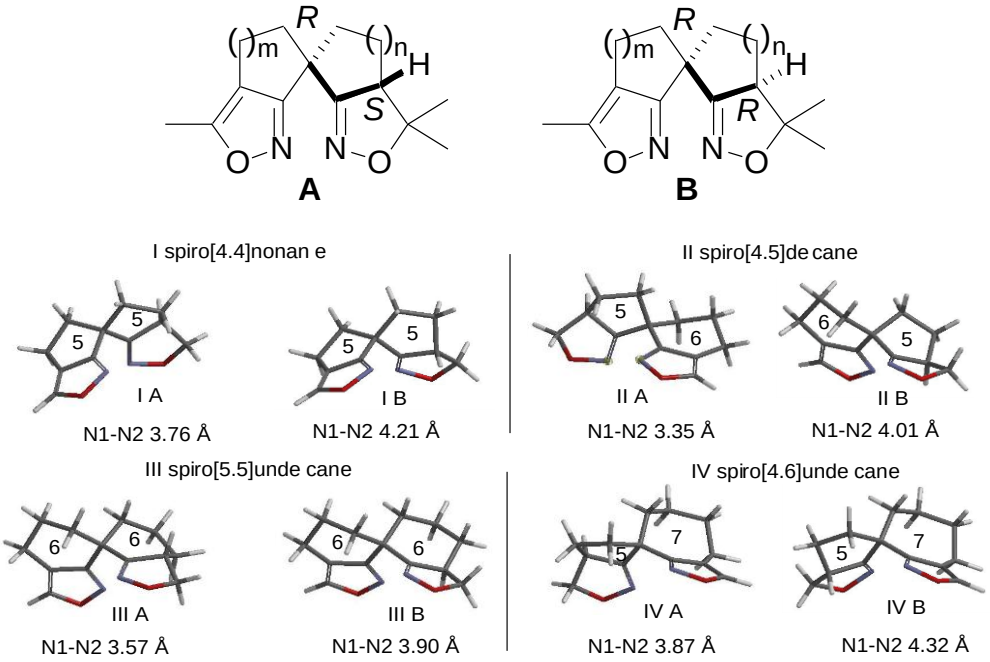


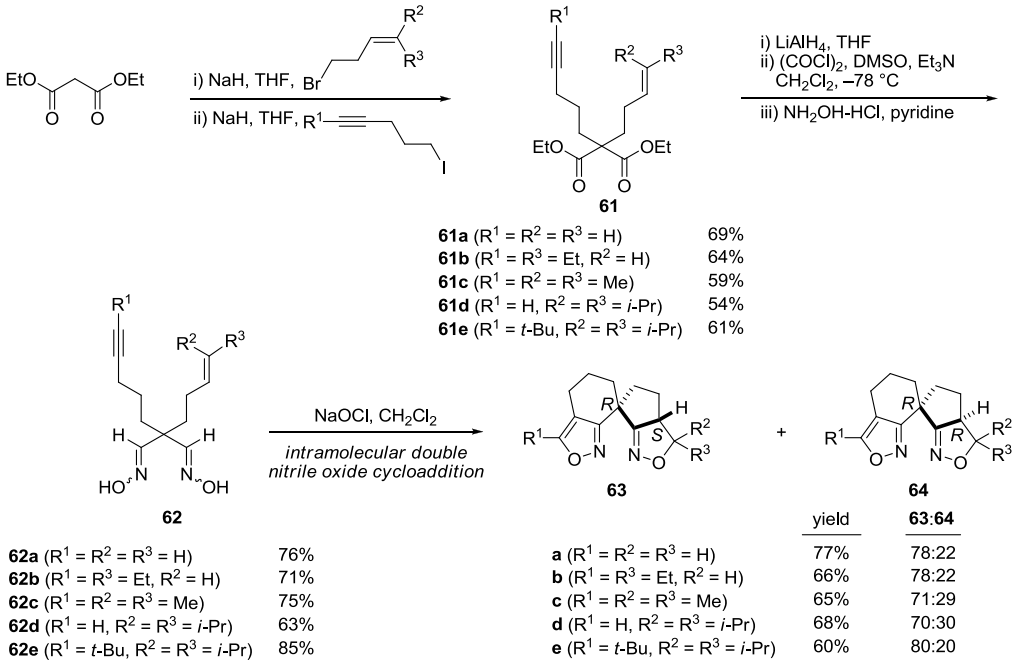
Figure 4: *Optimization of the structures with various ring size.*

After structure optimization, a flexible synthetic route similar to that of SPRIX was employed for the synthesis of the hybrid spiro (isoxazoline-isoxazole) ligands **63** and **64** (Scheme 13). In the initial step, different combinations of alkenyl- and alkynyl halides were used for the alkylation of diethyl malonate to produce differentially substituted diesters **61**. After successive $LiAlH_4$ reduction, Swern oxidation, dioxime formation, followed by intramolecular double nitrile oxide cycloaddition of the dioxime **62** produced **63** and **64** with a high diastereoselectivity. Optically pure ligands were obtained by separation using a chiral stationary phase column chromatography [Daicel Chiralpak AD (ø 2 cm × 25 cm)]. The relative configuration of the spiro skeleton was confirmed by X-ray analysis of **63c** (Figure 5). The distance between the two nitrogens was found to be 3.71 Å, in a close agreement with the calculated value. The hybrid ligands **63** were then used in the Pd-catalyzed asymmetric tandem cyclization of **57**. In accord with our hypothesis, the hybrid ligand **63e** was found more efficient and yielded 74% of the tandem product **58** in 95% ee within 17 hours at 0˚ temperature using a mixed solvent CH_2Cl_2/MeOH (1:1).

Biindane-based Spiro Ligands

Spiro bisphosphinite (SpiroBIP)

Keay *et al.* reported synthesis of *cis*,*cis*-2,2'-spirobiindane-1,1'-diol **70**, beginning with 1-indanone (**65**), in overall 68% yield after four steps (Scheme 14).[28] In the presence of NaH, treatment of **65** with diethyl carbonate produced β-keto ester **66**. Alkylation of **66** with **67** gave diester **68**, which when treated with 70% H_2SO_4 produced dione **69**. Reduction of **69** with lithium *tert*-butyldiisobutylaluminium hydride produced *cis*,*cis*-(±)-**70**. Enatiopure **70** can be obtained by separation of diastereomeric monoesters formed upon treating *cis*,*cis*-(±)-**70** with (*S*)-2-(*tert*-butyldimethylsilyl)-mandeloyl chloride as a chiral auxiliary, followed by hydrolysis.



Scheme 13: *Synthesis of spiro (isoxazoline-isoxazole).*

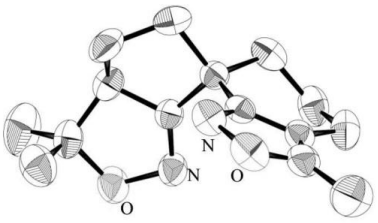
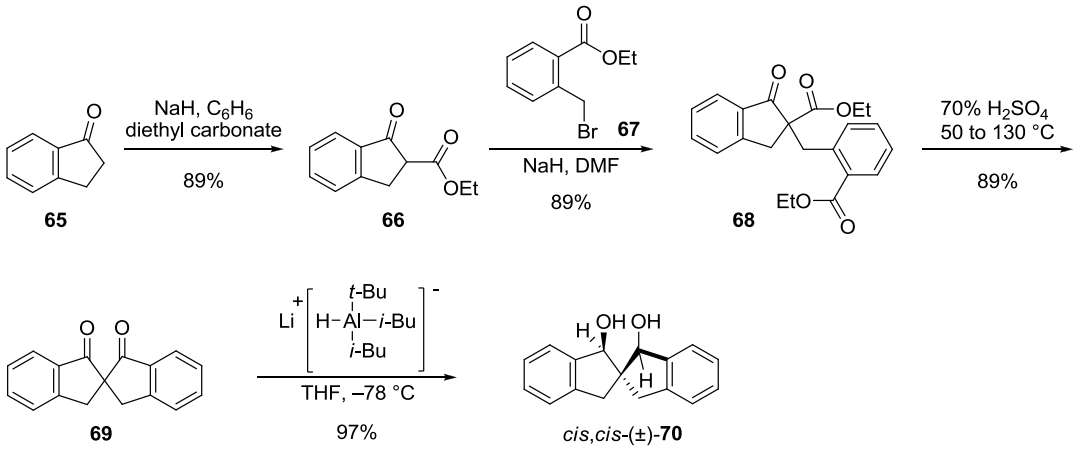
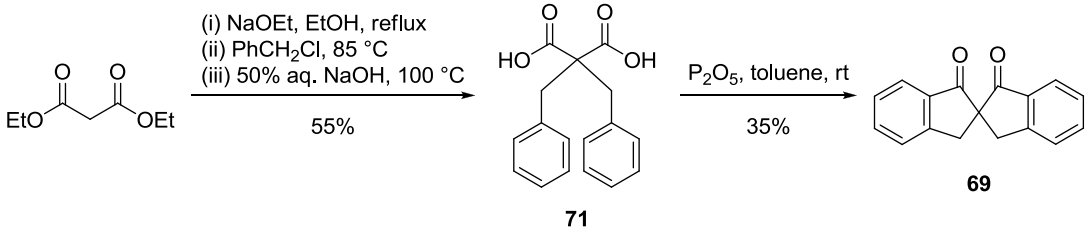


Figure 5: *X-ray structure of* ***63c*** *showing the spiro skeleton (N–N = 3.71 Å).*



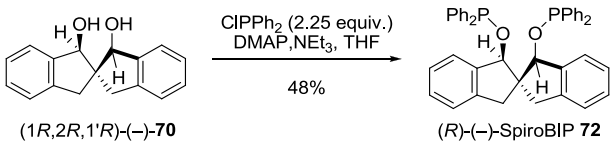
Scheme 14: *Synthesis of cis,cis-2,2'-spirobiindane-1,1'-diol.*

An alternative preparation of *cis,cis*-2,2'-spirobiindane-1,1'-dione **69** *via* dibenzylation of diethylmalonate followed by cyclization is reported by Burk and Harlow (Scheme 15).[29] Following the route, Chen *et al* have reported the synthesis and resolution of *cis,cis*-(±)-**70** after slight modification of Keay's protocol.[30]



Scheme 15: *Synthesis of cis,cis-2,2'-spirobiindane-1,1'-dione.*

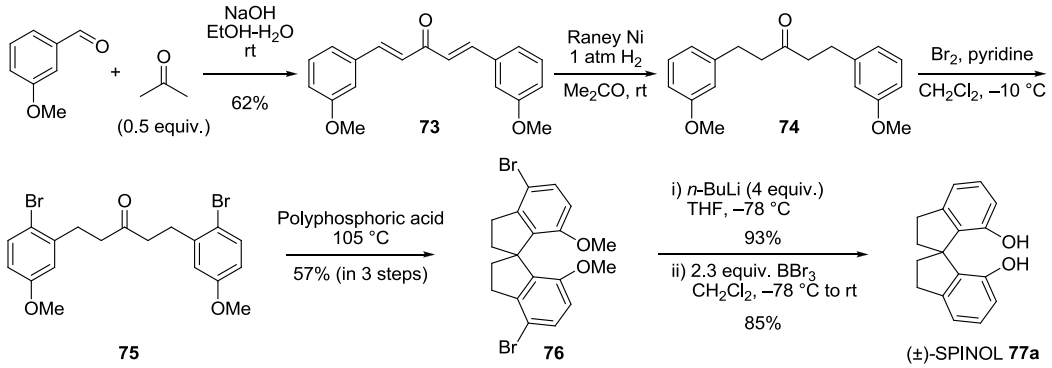
The enantiopure 2,2'-spirobiindane-1,1'-diol **70** was then converted into chiral 1,1'-bis(diphenylphosphinoxy)-2,2'-spirobiindane (SpiroBIP) **72** (Scheme 16).[30] This ligand was used in the Rh-catalyzed asymmetric hydrogenation and found comparatively less efficient than SpirOP **7**, perhaps due to weaker metal coordination executed by the steric hindrance of fused benzene rings.



Scheme 16: *Synthesis of SpiroBIP.*

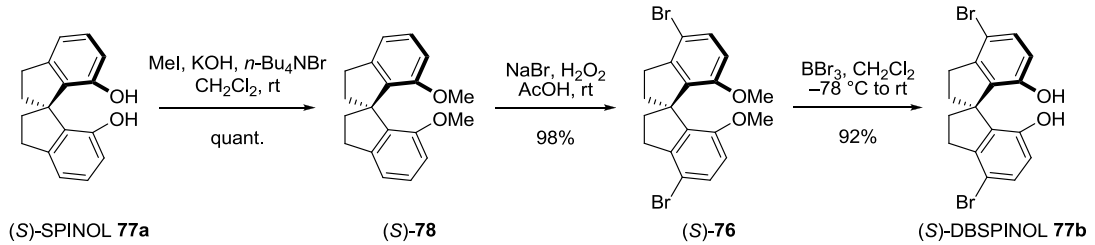
1,1'-Spirobindane-7,7'-diol (SPINOL)

In 1999, Birman *et al*. reported the synthesis of 1,1'-spirobiindane-7,7'-diol (SPINOL) **77a** (Scheme 17).[31] Condensation of *m*-anisaldehyde with acetone followed by hydrogenation produced ketone **74**. In order to direct the bis-cyclization *ortho*- to the methoxy groups, the *para*-positions to the methoxy groups were blocked with removable Br substituent. Treatment of bis-brominated compound **75** with polyphosphoric acid underwent spiro cyclization to give **76**. Debromination of **76** followed by demethylation produced (±)-SPINOL **77a** in 28% overall yield. Pure enantiomers of SPINOL can be obtained by treating (±)-**77a** with (–)-menthyl chloroformate and Et_3N followed by hydrozinolysis of resulting diasteromers using hydrazine hydrate.[31] Alternatively, (±)-**77a** can be resolved by inclusion complexation with *N*-benzylcinchonium chloride.[32]



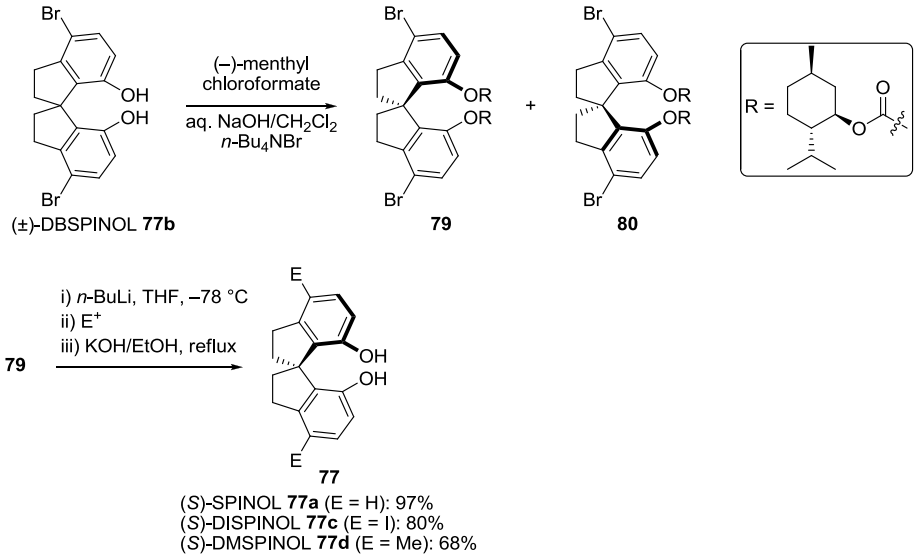
Scheme 17: *Synthesis of SPINOL.*

In 2003, Zhou *et al* have reported synthesis 4,4'-disubstituted-SPINOL from enantiomerically pure SPINOL **77a**.[33] For example; (*S*)-4,4'-dibromo-7,7'-dihydroxy-1,1'-spirobiindane (DBSPINOL) ((*S*)-**77b**) has been synthesized from (*S*)-**77a**. The protection of hydroxy groups of (*S*)-**77a** followed by bromination with NaBr in the presence of H_2O_2 produces dibromide (*S*)-**76**. Deprotection of hydroxyl groups in (*S*)-**76** using BBr_3 produces (*S*)-DBSPINOL **77b** (Scheme 18).



Scheme 18: *Synthesis of DBSPINOL.*

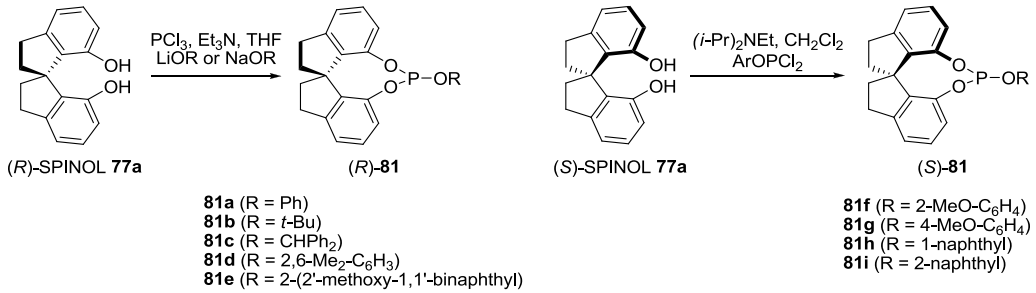
Later in 2004, Wan *et al.* have synthesized (±)-DBSPINOL **77b** through direct demethylation of Birmans's intermediate **76** using BBr_3 and resolved with (–)-menthylchloroformate in the presence of *n*-Bu_4NBr as a phase transfer catalyst, followed by hydrolysis.[34] Through the replacement of two bromine atoms in diastereomer **79** (or **80**) with appropriate electrophiles in the presence of *n*-BuLi can produce enantiopure SPINOL **77a**, DISPINOL **77c** and DMSPINOL **77d** (Scheme 19).[34b] The SPINOL and its 4,4'-substituted derivatives in the form of their Ti-alkoxides were used as catalysts in diethylzinc additions to aromatic aldehydes.[34b]



Scheme 19: *Synthesis of enantiopure SPINOLs.*

Spiro monophosphite (ShiP)

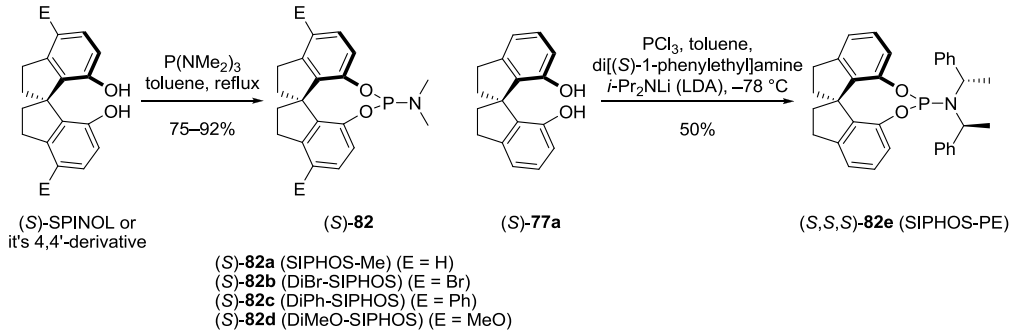
After having enantiomerically pure SPINOLs in hand, Zhou *et al* have synthesized a wide range of 1,1'-spirobindane-7,7'-diol-based chiral ligands. Spiro monophosphite ligands **81** were synthesized starting from **77a** by condensation with PCl_3 followed by treatment with alkoxides or condensation with dichlorophosphites in the presence of diisopropylethyl amine (Scheme 20).[35] These ligands were tested in: (a) Cu-catalyzed allylic alkylation of cinnamyl bromide with diethylzinc,[35a] (b) Pd-catalyzed hydrovinylation of styrene with ethylene,[35b] and (c) Rh-catalyzed addition of arylboronic acids to aldehydes.[35c]



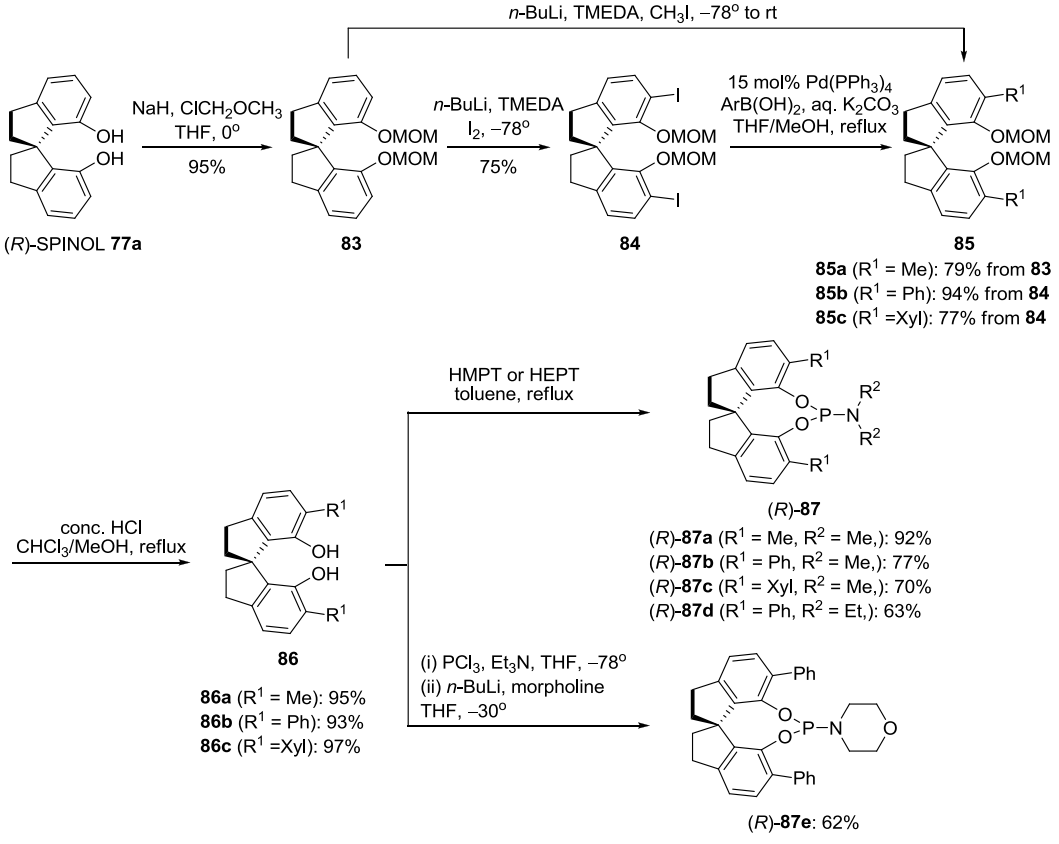
Scheme 20: *Synthesis of spiro monophosphites.*

Spiro phosphoramidite (SIPHOS)

Chiral monodentate spiro phosphoramidite ligands **82** were synthesized from the corresponding enantiomerically pure SPINOLs either by heating with hexamethylphosphorus triamide or condensation with PCl_3 followed by treatment with the lithium dialkylamide (Scheme 21).[33,36] These ligands were used in the asymmetric hydrogenation,[33,36a,36d] hydrosilylation,[37] hydrovinylation,[35b,38] allylic alkylation,[35a] Michael reaction,[36c] Pouson-Khand reaction[39] and desymmetrization of *meso*-oxabicyclic alkenes.[40]



Scheme 21: *Synthesis of spiro phosphoramidites.*

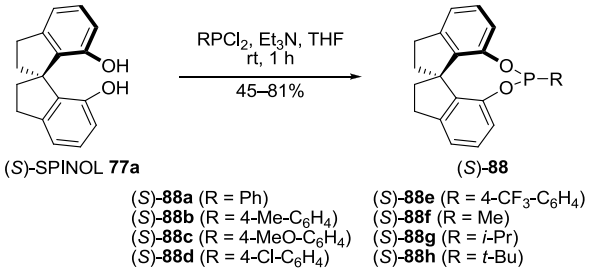


Scheme 22: *Synthesis of 6,6'-disubstituted spirobiindane phosphoramidites.*

The 6,6'-disubstituted spirobiindane phosphoramidites ligands **87** were also synthesized by Zhou *et al* (Scheme 22).[41] First the OH groups of enantiomerically pure (*R*)-SPINOL **77a** were protected with methoxymethane. Iodination of **83** using bases *n*-BuLi and tetramethylethylenediamine (TMEDA) followed by Suzuki coupling installed the aryl groups at 6 and 6' positions as in structure **85**, while methyl groups at the same positions were installed by direct methylation of **83** using methyl iodide. Deprotection of the hydroxy groups produced 6,6'-disubstituted SPINOL **86**. The required 6,6'-disubstituted spirobiindane phosphoramidite ligands were synthesized either by heating with hexamethylphosphorous triamide (HMPT) or hexaethylphosphorous triamide (HEPT) or condensation with PCl_3 followed by treatment with the lithiated amine. These ligands were used in the first Ni-catalyzed asymmetric reductive coupling of 1,3-dienes and aldehydes to yield chiral bishomoallylic alcohols.

Spiro phosphonite (FuP)

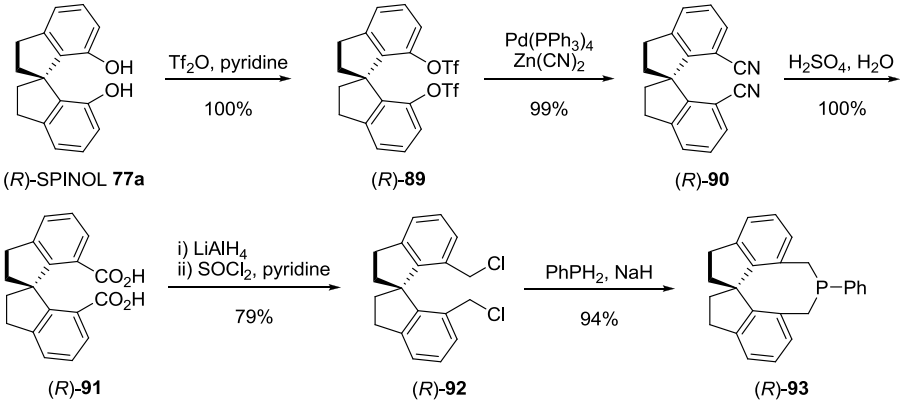
Zhou *et al* have synthesized chiral spiro phosphonites (*S*)-**88** from (*S*)-SPINOL **77a** by treating with the corresponding dichlorophosphine in the presence of Et_3N and used in the Rh-catalyzed asymmetric hydrogenation (Scheme 23).[42]



Scheme 23: *Synthesis of spiro phosphonites.*

Spiro phospholane (SITCP)

Zhou *et al.* have synthesized chiral monodentate phospholane ligand (SITCP) **93** from enantiomerically pure SPINOL in six steps (Scheme 24).[43]

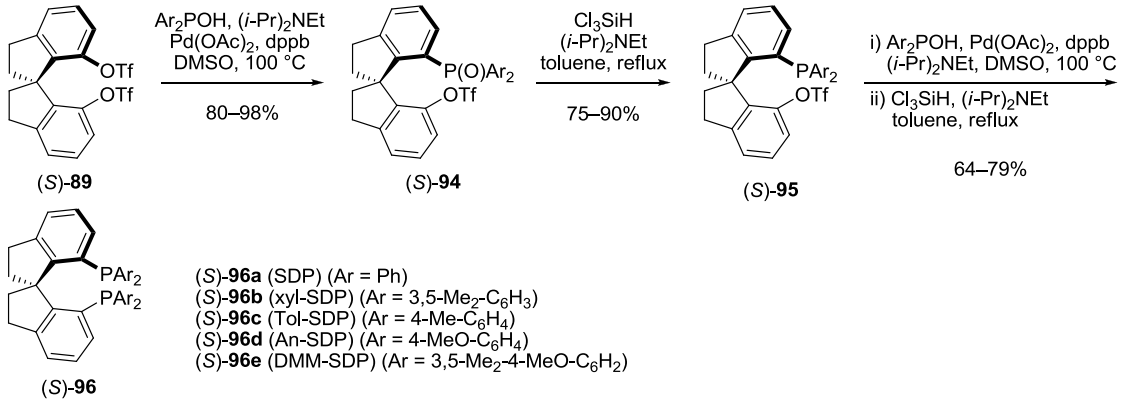


Scheme 24: *Synthesis of spiro phospholane.*

(*R*)-**77a** was converted into ditriflate **89** by ligand exchange and then cynated with $Zn(CN)_2$ catalyzed by $Pd(PPh_3)_4$ to produce dinitrile **90**. Hydrolysis of **90** produced diacid **91**, which after $LiAlH_4$ reduction followed by $SOCl_2$ treatment produced dichloride **92**. The condensation of **92** with phenylphosphine gave phenylphospholane (*R*)-**93**. Spiro phospholane ligand is used in the Pd-catalyzed enantiselective allylations of aromatic, heteroaromatic and aliphatic aldehydes with allylic alcohols.

Spiro diphosphine (SDP)

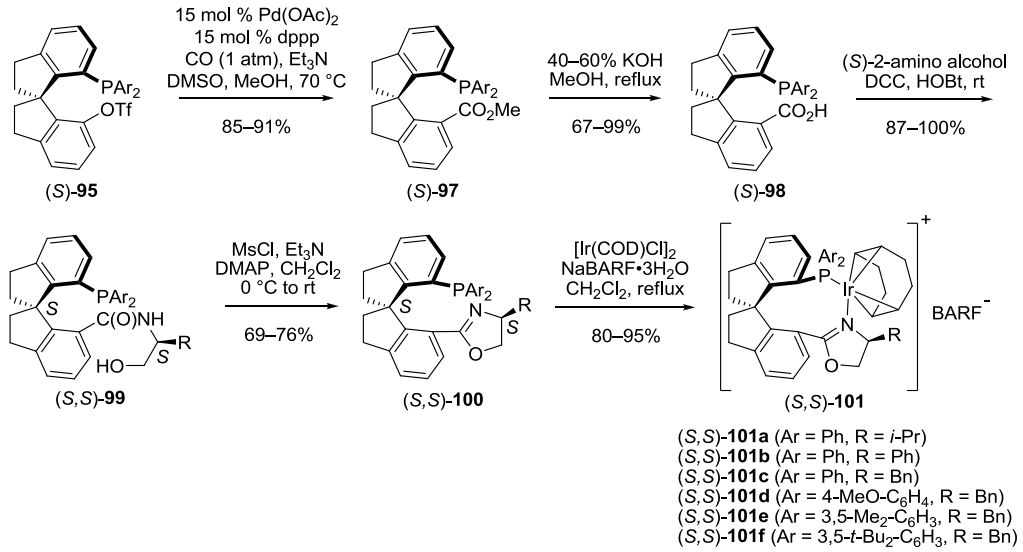
Chiral diphosphine ligands are most popular in asymmetric catalysis. The first example of chiral diphosphine ligands with a spiro skeleton has been reported by Zhou *et al* (Scheme 25).[44] Ditriflate (*S*)-**89**, obtained from (*S*)-SPINOL **77a** (see: Scheme 24), monophosphinylated with diarylphosphine oxide in the presence of $Pd(OAc)_2$-dppb (dppb = 1,4-bis(diphenylphosphino)-butane) followed by reduction with trichlorosilane to produce phosphine monotriflate **95**. The second phosphine group was introduced using the same conditions as for the first by phosphinylation of **95** followed by reduction to give chiral spiro diphosphines (*S*)-**96**. Ruthenium catalyst prepared from the spiro diphosphine ligands were used in the asymmetric hydrogenations of aromatic, heteroaromatic, and α,β-unsaturated ketones.[44a] Spiro diphosphine ligands were further utilized in the Pd-catalyzed allylic alkylation of (±)-1,3-diphenyl-2-propenyl acetate.[44b]



Scheme 25: *Synthesis of spiro diphosphines.*

Spiro phosphine-oxazoline (SIPHOX)

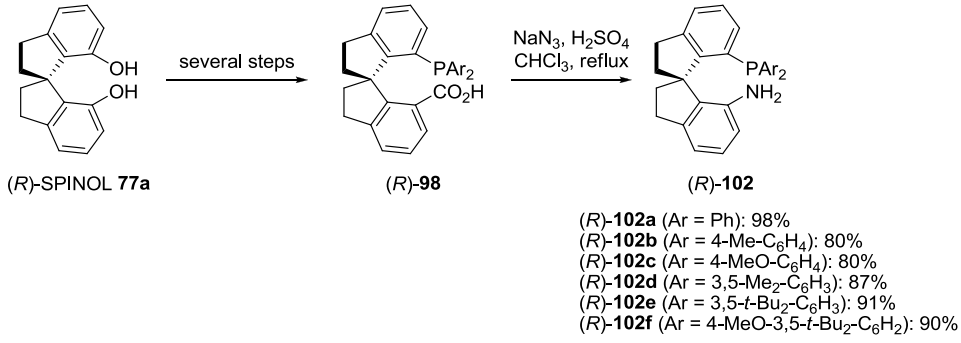
Zhou *et al* further reported spiro phosphine-oxazoline ligands **100** (Scheme 26).[45] In the presence of 1,3-bis(diphenylphosphino)-propane (dppp) ligand, the Pd-catalyzed carbonylation of optically pure **95** produced esters **97**, which after hydrolysis followed by condensation with enatiomerically pure amino alcohols in the presence of 1-hydroxylbenzotriazole (HOBt) and *N,N'*-dicyclohexylcarbodiimide (DCC) gave amides **99**. Cyclization of **99** produced spiro phosphine-oxazoline ligands **100**. Mixing of $[Ir(COD)Cl]_2$ (COD = 1,5-cyclooctadiene), ligand **100** and $NaBARF{\cdot}3H_2O$ (BARF = tetrakis-3,5-bis(trifluoromethyl)-phenylborate) in the ratio 0.5:1:1.5 produced the cationic iridium complex **101**. The Ir-SIPHOX complexes **101** catalyzed asymmetric hydrogenation of acyclic *N*-aryl ketimines under ambient hydrogen pressure providing chiral amines in excellent enatioselectivity. More recently, the application of Ir-SIPHOX complexes has found in enantioselective hydrogenations of α-aryloxy and α-alkoxy-substituted α,β-unsaturated carboxylic acids to produce α-hydroxy acids, after deprotection.[46]



Scheme 26: *Synthesis of spiro phosphine-oxazolines.*

Spiro aminophosphine (SpiroAP)

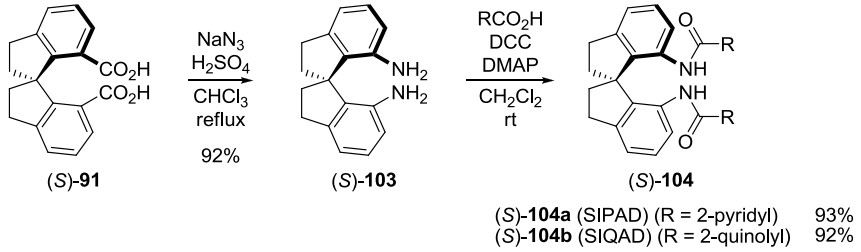
Optically pure (*R*)-SPINOL **77a** was converted into spiro aminophosphine ligands *via* bisarylphosphino-7'-caboxy-1,1'-spirobiindannes (*R*)-**98**, a key intermediate in the synthesis of spiro phosphine-oxazolines (see: Scheme 26).[47] The Schmidt reaction of phosphino acids (*R*)-**98** produced the spiro aminophosphine ligands **102** (Scheme 27). These ligands were used in the Ir-catalyzed hydrogenation of α-arylmethylene cycloalkanones.



Scheme 27: *Synthesis of spiro aminophosphines.*

Spiro bispyridyl diamide (SIPAD) and spiro bisquinolyl diamide (SIQAD)

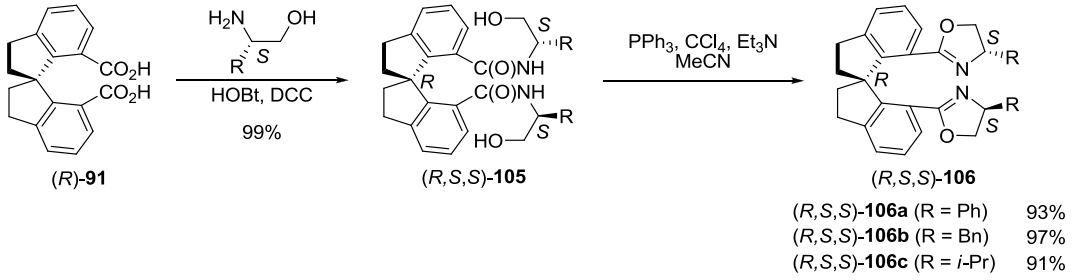
Zhou *et al* synthesized chiral spiro bispyridyl diamide (SIPAD) **104a** and spiro bisquinolyl diamide (SIQAD) **104b** having pyridine and quinoline as coordinating units, respectively (Scheme 28).[48] Curtius rearrangement of (*S*)-**91** (see: Scheme 24) produced diamine (*S*)-**103**, which was treated with picolinic acid or quinoline-2-carboxylic acid in the presence of dicyclohexylcarbodiimide and *N*,*N*-dimethyl-4-diaminopyridine to give corresponding ligands (*S*)-**104a** or (*S*)-**104b**, respectively. The cobalt complexes prepared *in situ* from $Co(OAc)_2$ and SIPAD **104a** showed a moderate enantioselectivity in the asymmetric Michael addition of malonates to chalcone derivatives.



Scheme 28: *Synthesis of SIPAD and SIQAD.*

Spiro bis(oxazoline) (SpiroBOX)

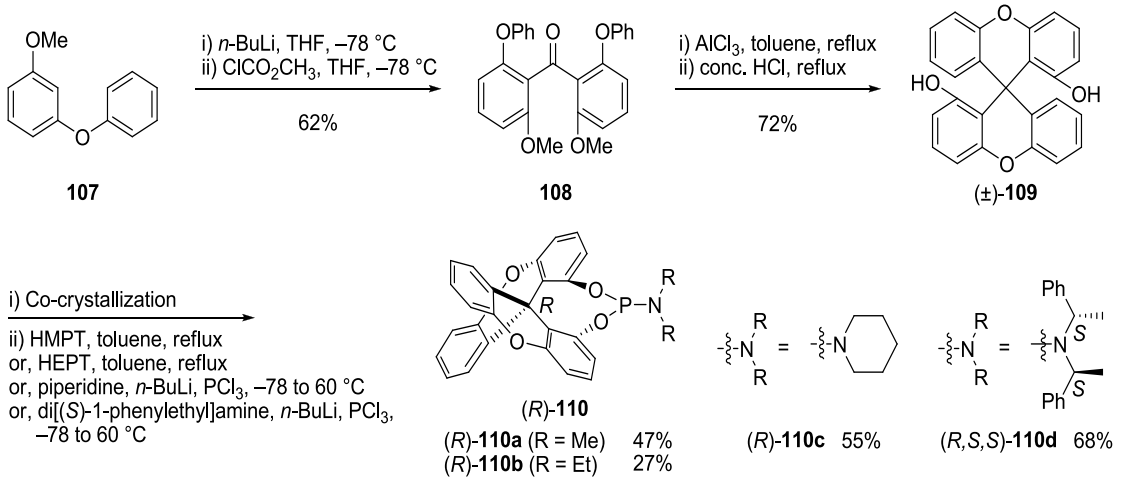
Zhou *et al* have reported synthesis of spiro bis(oxazoline) ligands **106** (Scheme 29).[49] Enantiomerically pure dicarboxylic acid **91** on treating with optically active amino alcohols in the presence of HOBt and DCC gave amides **105**, which was subjected to oxazoline ring formation and produced **106**. The efficiency of the ligands was evaluated in the Cu-catalyzed asymmetric cyclopropanation of styrene derivatives, allylic oxidation of cyclic alkenes and insertion of carbenoids into O–H and N–H bonds.[50] Later Ma *et al* have synthesized more bulkier spiro bis(oxazoline) ligands with α-naphthylmethyl and β-naphtylmethyl substituents following Zhou's protocol and used in the Pd-catalyzed enantioselective cyclization of allenyl hydrazines with aromatic iodides and enantioselective cyclization of allenes with *ortho*-aminoiodobenzenes.[51]



Scheme 29: *Synthesis of spiro bis(oxazoline).*

Bioxanthene-based Spiro Phosphoramidite Ligands

An another variety of chiral phosphoramidite ligands **110** with 9,9'-spirobixanthene backbone was reported by Zhang *et al*.[52] Starting from 3-phenoxyanisole (**107**), symmetric ketone **108** was prepared by linking 2 equivalents of lithiated **107** with methyl chloroformate (Scheme 30). Treatment of **108** with $AlCl_3$ promoted the Friedel-Crafts alkylation as well as deprotection of methyl ether producing *racemic*-9,9'-spriobixanthene-1,1'-diol (±)-**109**. Co-crystallization of (±)-**109** using *N*-benzylcinchonidium chloride gave (*R*)-**109**, while (*S*)-**109** was obtained from the mother liquor by co-crystallization with *N*-benzylquininium chloride. Treatment of (*R*)-**109** with HMPT or HEPT produced (*R*)-**110a** or (*R*)-**110b**, respectively. Ligands (*R*)-**110c** and (*R,S,S*)-**110d** were prepared by reacting the starting amine sequentially with equivalent amounts of *n*-BuLi, PCl_3 and then (*R*)-**109**. The efficiency of the ligands in asymmetric catalysis has demonstrated in the Rh-catalyzed hydrogenation reactions[52a] and the Cu-catalyzed conjugate addition of diethylzinc to cyclic enones.[52b]



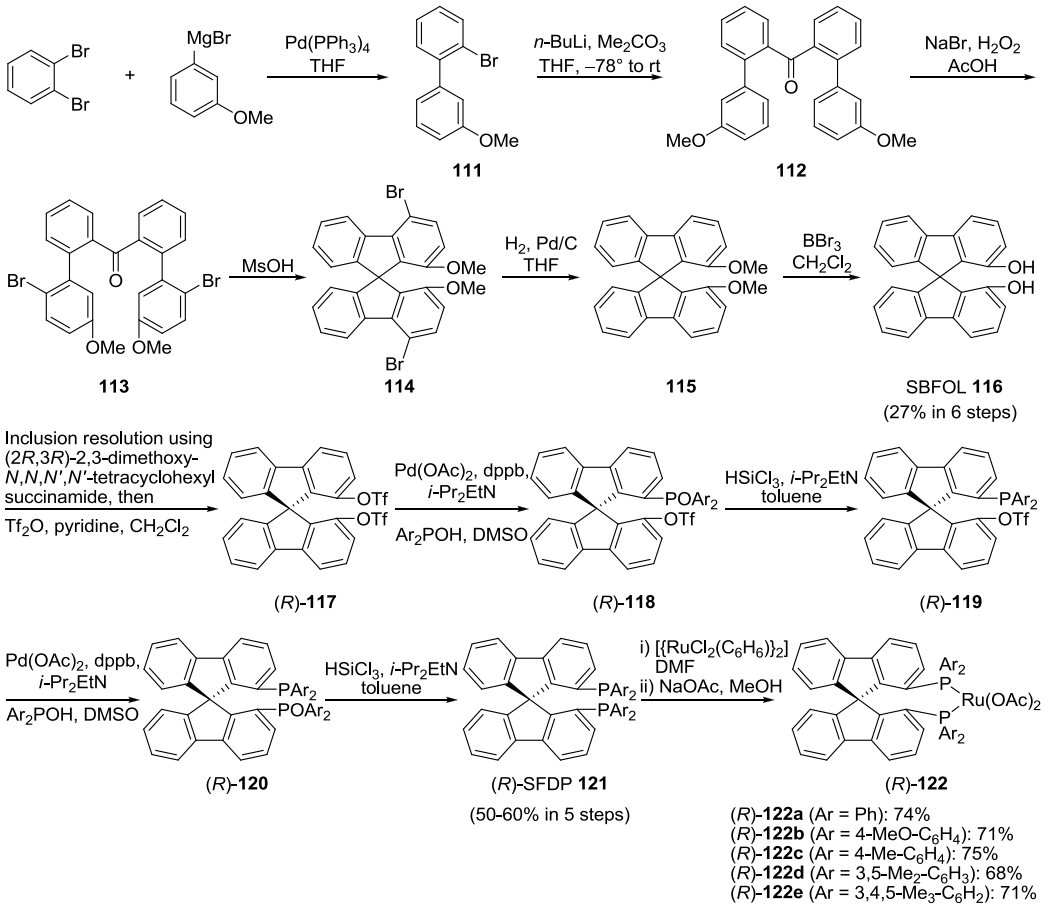
Scheme 30: *Synthesis of 9,9'-spirobioxanthene-based phosphoramidites.*

Bifluorene-based Spiro Diphosphine Ligands (SFDP)

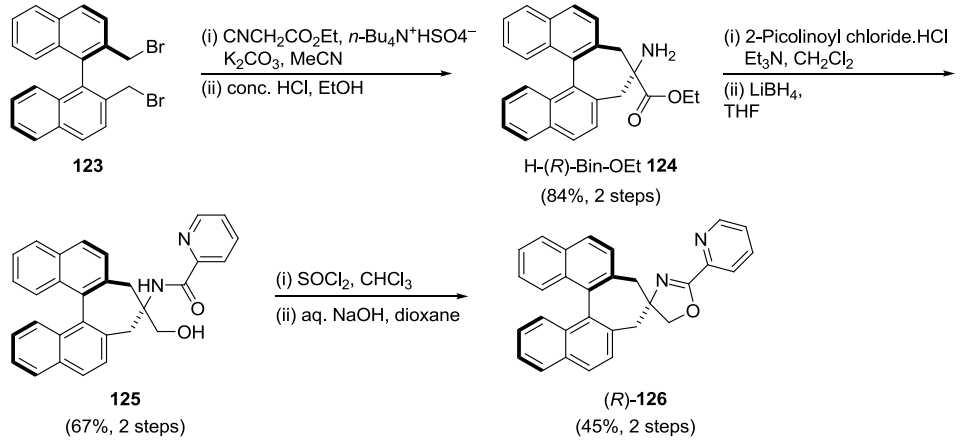
A new variety of spirobifluorene-based diphosphine ligands **121** was reported by Zhou *et al* (Scheme 31).[53] Kumada coupling product of 1,2-dibromobenzene with the Grignard reagent of 3-bromoanisole was treated with dimethyl carbonate in the presence of *n*-BuLi to produce ketone **112**. Bromination followed by cyclization with methane sulphonic acid provided the 9,9'-spirobifluorene compound **114**. Debromination by Pd/C-catalyzed hydrogenation followed by demethylation yielded 9,9'-spirobifluorene-1,1'-diol (SBFOL) **116** in 27% overall yield. Inclusion resolution with (2*R*,3*R*)-2,3-dimethoxy-*N*,*N*,*N'*,*N'*-tetracyclohexyl succinamide provided optically pure (*R*)-SBFOL.[53a] The precursor was converted into the ditriflate (*R*)-**117**. Ni-catalyzed direct diphosphanylation with diarylphosphanes was failed, hence, a stepwise Pd-catalyzed phosphanylation with diarylphosphane oxide followed by reduction with trichlorosilane were carried out to obtain the target diphosphine ligand (*R*)-**121**.[53b] Using the enantiopure spiro diphosphine ligands, Ru-catalysts **122** were prepared and used in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[53c]

Binaphthyl-based Spiro 2-(oxazolinyl)pyridine (SPYMOX)

2-(Oxazolinyl)pyridine ligand **126** having a spiro binaphthyl backbone is recently prepared by Shibatomi *et al* (Scheme 32).[54] Using a phase transfer catalyst, ethyl isocyanoacetate was reacted with (*R*)-2,2'-bis(bromomethyl)-1,1'-binaphthyl (**123**) followed by hydrolysis to afford ethyl ester of 1,1'-binaphthyl-substituted α-amino isobutyric acid (H-[(*R*)-Bin]-OEt) **124**. The condensation of **124** with 2-picolinoyl chloride followed by reduction of the ethyl ester with $LiBH_4$ produced amido alcohol **125**. After chlorination of the primary alcohol, cyclization was achieved under basic condition to give SPYMOX (*R*)-**126**. This ligand was used in the Pd-catalyzed asymmetric allylic alkylation[54a] and the Cu-catalyzed *gem*-chlorofluorination of active methylene compounds.[54b]



Scheme 31: *Synthesis of bifluorene-based spirodiphosphines ligands and their ruthenium complexes.*



Scheme 32: *Synthesis of SPYMOX.*

Conclusion

While designing and synthesis of new chiral ligands, many features are envisioned – an appropriate backbone, effective asymmetric environment, chelating sites, economic synthesis, number of diasteromers, separation, resolution and ease of ligand modification etc. – there by making the task a most challenge. The chiral diphosphine ligand with a biaryl scaffold, BINAP, is one of the most extensively used ligands in the transition-metal catalysis. In search of versatile alternative ligands, a number of research groups are extensively focusing on the development of novel chiral ligands. Among them, chiral spiro ligands with C_2-symmetrical structure are quite interesting since they have displayed unusual and unique reactivity in metal catalysis. The usefulness of chiral spiro ligands has been extensively realized after 1997, when Chan and Jiang have reported the pioneering work on the Rh-catalyzed asymmetric hydrogenation using SpirOP. About the same time, Sasai has designed and synthesized novel chiral spiro ligands bearing nitrogen containing heterocyles (such as SPRIX) and used in several oxidative cyclizations. Extensive reports on the area are due to Zhou and his co-workers. They have developed several chiral spiro ligands with a 1,1'-spirobiindane scaffold and used in new asymmetric transformations. Whereas, 2,2'-spirobiindane scaffold was incorporated by Chen in SpiroBIP. Bioxanthene-, biofluorene- and binaphthyl-based chiral spiro ligands are synthesized by Zhang, Zhou and Shibatomi, respectively. Many of these spiro ligands have shown either unique reactivity or more efficient or comparable to the hitherto known chiral ligands.

Acknowledgement

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