Award Accounts

The Chemical Society of Japan Award for Creative Work for 2005

Development of Chiral Spiro Ligands for Metal-Catalyzed Asymmetric Reactions

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This account focuses our works on the development of chiral spiro ligands bearing N-heterocycles as metal-coordinating units and their applications in the metal-catalyzed asymmetric reactions. The spiro bis(isoxazoline) ligands (SPRIXs), spiro bis(isoxazole) ligands, and spiro (isoxazole–isoxazoline) ligands were readily synthesized through intramolecular double nitrile oxide cycloaddition of the corresponding dioximes as a key step. An unprecedented activation of olefins was displayed by the Pd^{II} complexes of these chiral spiro ligands in the enantioselective oxidative cyclizations, for example; the asymmetric tandem cyclization of dialkenyl alcohol via oxy-palladation produced a bicyclic ether in excellent enantioselectivity and enantioselective version of the aminocarbonylation proceeded for the first time. Other hitherto known chiral ligands we examined failed to promote these reactions.

1. Introduction

Great attention has been paid by the scientific community to metal-catalyzed asymmetric synthesis, since it provides a powerful and economical tool for the synthesis of optically active organic compounds of biological importance. The design and synthesis of novel chiral ligands is one of the most challenging tasks in asymmetric catalysis.[1] An efficient chiral ligand, which has both an appropriate affinity for the metal and a suitable chiral backbone to construct an effective asymmetric environment, is the key for the development of asymmetric catalysts. Novel types of chiral ligands offer an opportunity to realize new asymmetric reactions. The introduction of a new metal-coordinating moiety and/or a new chiral backbone is especially attractive.

Assiduous efforts over the past decades have led to thousands of chiral bidentate phosphines, oxazolines, diamines, and hybrid P,N ligands (Figure 1).[2] With a contrasting structural geometry, spiranes represent a new class of relatively less explored chiral ligands, where suitable substituents in the two perpendicular rings give rise to a unique chirality (Figure 2). These spiro ligands contain a quaternary center, which makes their racemization virtually impossible regardless of the substituent pattern and hence are considerably more rigid. This rigidity of the spirocyclic framework can be expected to minimize the number of possible conformations of the catalytic species consequently benefiting selectivity in the asymmetric synthesis. Due to these distinct advantages associated with a spiro skeleton, we are interested developing chiral spiro ligands for metal-catalyzed asymmetric reactions. In this account, we focus on the results of our studies of the design and synthesis of novel chiral spiro ligands bearing various N-heterocycles, namely isoxazoline, isoxazole, oxazoline, and pyrazole as coordinating units to the metal center. The unique catalytic reactivity of the newly synthesized spiro ligands has enabled us to develop new asymmetric reactions.

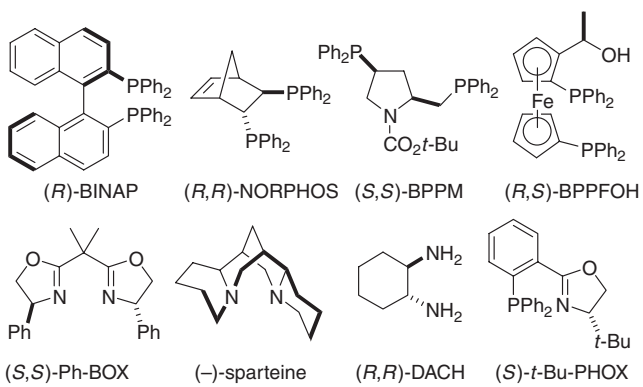


Figure 1. Representative hitherto known chiral ligands.

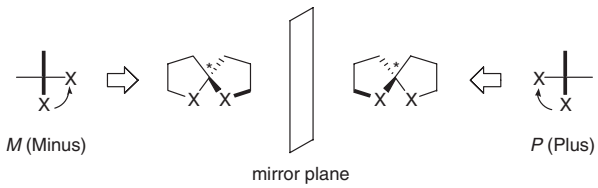
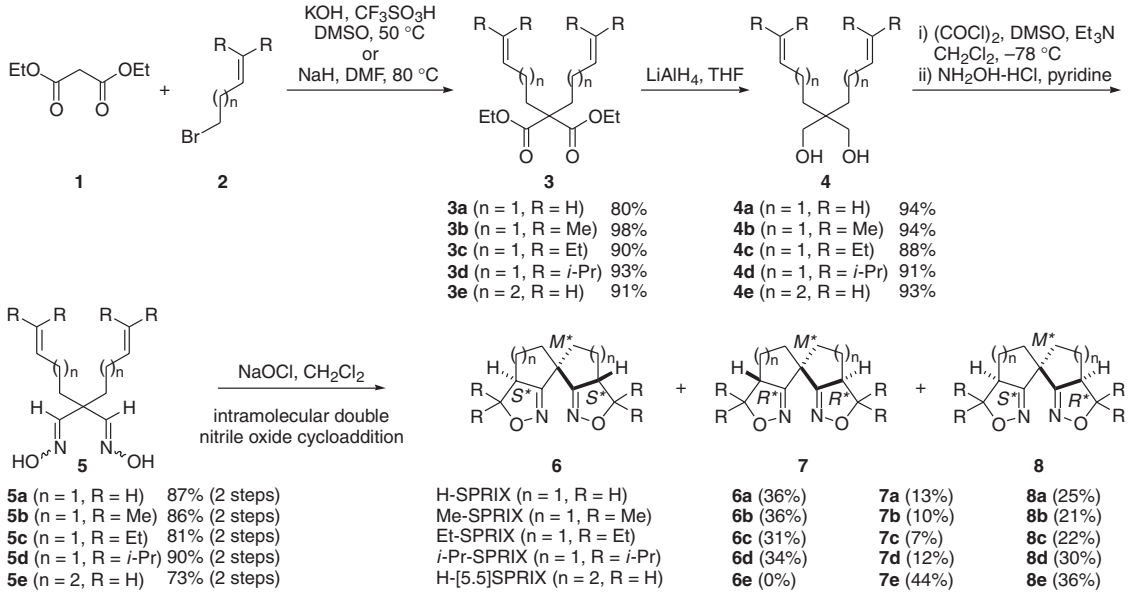


Figure 2. Spirane chirality.

Published on the web March 12, 2009; doi:10.1246/bcsj.82.285



Scheme 1. Synthesis of SPRIX.

2. Spiro Bis(isoxazoline)

In 1999, we reported the first design and synthesis of chiral spiro bis(isoxazoline) ligands (SPRIXs) **6**–**8** bearing a chiral spiro skeleton and two isoxazoline rings to coordinate with a metal center.[3] We envisioned that the rigid spiro backbone in SPRIX could reduce the conformational obscurity in the transition state for the metal-catalyzed reactions, and such compounds would provide a new group of chiral ligands. Judicious placement of substituents in the isoxazoline rings should afford the opportunity to organize the most appropriate asymmetric environment around the metal to achieve high levels of asymmetric induction.

As shown in Scheme 1, SPRIXs **6**–**8** were readily synthesized in multigram scales starting from diethyl malonate (**1**) via intramolecular double nitrile oxide cycloaddition as a key step, which constructs four rings and a spiro backbone in one step.[4] A general synthetic route was adopted to prepare various SPRIXs. Diethyl malonate (**1**) was treated with bromide **2** in the presence of a base to produce malonate **3**, which was subsequently reduced with $LiAlH_4$ to obtain diol **4**. After Swern oxidation of **4**, the resulting dialdehyde was treated with $NH_2OH \cdot HCl$ in pyridine to produce dioxime **5** as a single isomer. All the possible diastereomers of SPRIXs **6**–**8** (except **6e**) were obtained using intramolecular double nitrile oxide cycloaddition of **5** and each diastereomer was easily separated using silica gel column chromatography.

The structure of SPRIX was unequivocally determined by X-ray crystallographic analyses of all three diastereomers of H-SPRIX (Figure 3). Among the three diastereomers of H-SPRIX, **6a** has the shortest N–N atomic distance (3.17 Å) and the smallest out-of-plane angle between two C=N bonds (45.6°). Characteristic color changes upon treatment of H-SPRIXs with several metal complexes such as $Cu(OTf)_2$, CuOTf, $CoCl_2$, $NiCl_2$, and $Pd(OAc)_2$ in an organic solvent indicated its coordinating ability with metal. Using enantiomerically pure H-SPRIXs, which were obtained by optical

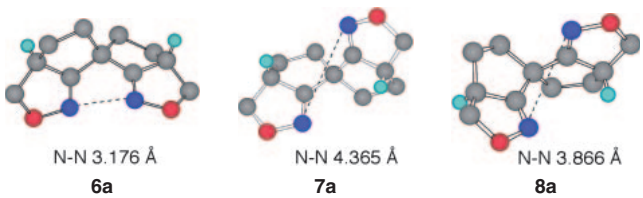
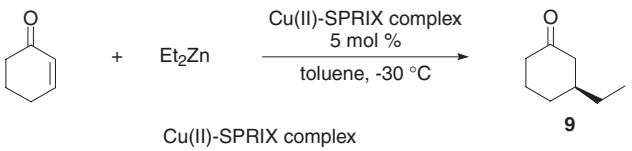


Figure 3. X-ray structures and N–N distances in H-SPRIX.

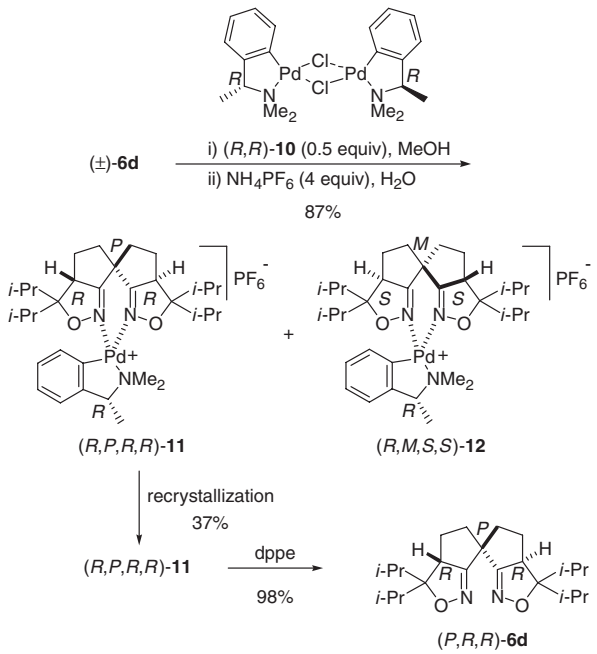


Cu(II)-SPRIX complex	
$Cu(acac)_2$-(*M*,*S*,*S*)-H-SPRIX (**6a**)	68%, 43% ee (4 h)
$Cu(acac)_2$-(*M*,*R*,*R*)-H-SPRIX (**7a**)	35%, 5% ee (31 h)
$Cu(acac)_2$-(*M*,*S*,*R*)-H-SPRIX (**8a**)	39%, 1% ee (31 h)
$Cu(OTf)_2$-(*M*,*S*,*R*)-H-SPRIX (**8a**)	79%, 42% ee (3.5 h)
$Cu(OTf)_2$-(*M*,*S*,*R*)-H-[5.5]-SPRIX (**8e**)	93%, 54% ee (2 h)

Scheme 2.

resolution with a chiral stationary phase column (Daicel Chiralpak AD (ϕ2 cm × 25 cm), EtOH), the first application in the Cu-catalyzed Michael reaction of 2-cyclohexen-1-one with diethylzinc was demonstrated to yield **9** in moderate ee (Scheme 2).[3] It is noteworthy that the ligand can be recovered without obvious decomposition.

Recently, we have succeeded in resolution of *i*-Pr-SPRIX **6d** using ortho palladated benzylamine derivative as a resolving agent via the separation of a mixture of the diastereomeric palladium complexes of (±)-**6d** (Scheme 3).[5] The treatment of (±)-**6d** with 0.5 equivalents of di-μ-chlorobis{(*R*)-2-[1-(dimethylamino)ethyl]phenyl-*C*,*N*}dipalladium(II) ((*R*,*R*)-**10**) followed by addition of 4 equivalents of aqueous NH_4PF_6 in MeOH produced a 1:1 diastereomeric mixture of cationic palladium complexes (*R*,*P*,*R*,*R*)-**11** and (*R*,*M*,*S*,*S*)-**12**. After fractional recrystallization from dichloromethane/diethyl ether



Scheme 3. Resolution of *i*-Pr-SPRIX.

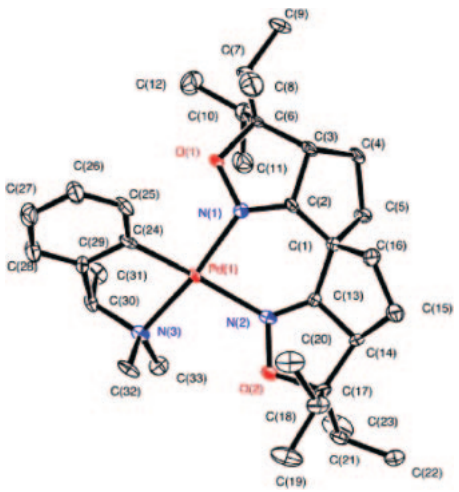
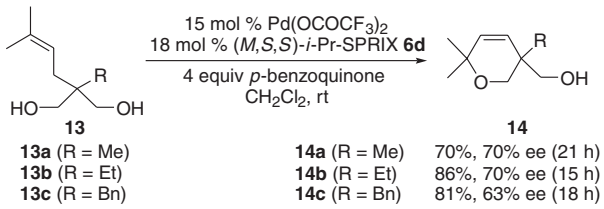


Figure 4. ORTEP plot of (*R*,*P*,*R*,*R*)-**11**. Hydrogen atoms and a counter ion are omitted for clarity (Ref. 5).

solution, the pure sample of (*R*,*P*,*R*,*R*)-**11** was obtained as a colorless crystal. The absolute configuration of (*R*,*P*,*R*,*R*)-**11** was determined by X-ray analysis based on the configuration at the benzylic carbon C(30) to be *R* (Figure 4). The Pd center adopts slightly distorted square-planar geometry, and the angle between the planes of N(1)–Pd(1)–N(2) and N(3)–Pd(1)–C(24) is 13.4°. The geometry around the imino groups is slightly distorted. The dihedral angles of Pd(1)–N(1)–C(2)–C(1), O(1)–N(1)–C(2)–C(3), Pd(1)–N(2)–C(13)–C(1), and O(2)–N(2)–C(13)–C(14) are essentially zero, the dihedral angles of Pd(1)–N(1)–C(2)–C(3), O(1)–N(1)–C(2)–C(1), Pd(1)–N(2)–C(13)–C(14), and O(2)–N(2)–C(13)–C(1) are approximately 20°. Optically pure P,R,R enantiomer of **6d** was obtained by decomplexation from (*R*,*P*,*R*,*R*)-**11** through ligand-exchange reaction using 1,2-bis(diphenylphosphino)ethane (dppe) (Scheme 3).



Scheme 4.

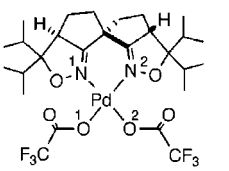
SPRIX ligands are found to be stable under acidic, basic, and oxidative conditions (Acidic conditions: MeOH–aq 1 M HCl (1:1) at rt overnight, Basic conditions: MeOH–aq 1 M NaOH (1:1) at rt overnight, and Oxidative conditions: MeOH–35% aq H_2O_2 (1:1) at rt overnight). In contemplating approaches to catalytic asymmetric reactions, one needs to ensure that the chiral ligands employed are compatible with the reagent such as an oxidant. The stability of SPRIX under oxidative conditions motivated us to carry out Pd-catalyzed asymmetric oxidative reactions. The Pd-catalyzed selective oxidative transformations of alkenes, such as Wacker reaction, have evolved into a highly useful methodology in synthetic organic chemistry because the intramolecular version of Wacker reaction, employing oxygen-containing nucleophiles, can provide various heterocyclic compounds.[6,7] We demonstrated the first example of asymmetric Wacker-type cyclization by employing aliphatic alkenyl alcohols promoted by chiral Pd^{II}–SPRIX catalysts.[8] The catalyst system based on (*M*,*S*,*S*)-SPRIX **6** and $Pd(OCOCF_3)_2$ promoted the asymmetric Wacker-type cyclization of alkenyl alcohol **13** in the presence of *para*-benzoquinone as a reoxidant to give 6-endo cyclized product **14**. Among the three diastereomers of H-SPRIX, the use of enantiomerically pure (*M*,*S*,*S*)-H-SPRIX **6a** showed the highest catalytic activity in the formation of **14a** (83%, 41% ee, after 14 h) [(*M*,*R*,*R*)-H-SPRIX **7a**: 30%, 3% ee, after 30 h; (*M*,*S*,*R*)-H-SPRIX **8a**: 74%, 22% ee, after 28 h]. Moreover, the bulkiness of the R substituent in (*M*,*S*,*S*)-SPRIX **6** affected enantioselectivity of the reaction, and the best result was obtained by using tetra-isopropyl-substituted SPRIX **6d** (Scheme 4). The X-ray crystallographic analysis of a single crystal of the $Pd(OCOCF_3)_2$–**6d** complex revealed that the geometry of the complex is close to an ideal square-planar structure, in which the palladium metal center coordinates with two nitrogen atoms in the isoxazoline rings (Figure 5).

We envisaged that if the alkyl Pd^{II} intermediates resulting from an intramolecular oxy-palladation are trapped by alkenes in a tandem sequence, a variety of polycyclic compounds can be synthesized in a single step.[9] Delightfully, we demonstrated the first example of Pd^{II}-catalyzed enantioselective oxidative tandem cyclization reaction via oxy-palladation by using SPRIX. Compound **15** containing two C–C double bonds was treated with $Pd(OCOCF_3)_2$–**6d** complex prepared in situ by mixing of $Pd(OCOCF_3)_2$ (20 mol %) and (*M*,*S*,*S*)-*i*-Pr-SPRIX **6d** (24 mol %) in CH_2Cl_2 (Table 1, Entry 1). The tandem bicyclic product **16** was obtained as a single diastereomer in 65% yield and 95% ee along with dihydropyrans **17** and **18** in 5% and 26% yields, respectively. The use of MeOH as a solvent increased the ratio of the bicyclic compound **16**, though the ee value was decreased (Entry 2). Balancing the factors of

yield and ee of the product led us to use a mixed CH_2Cl_2/MeOH solvent system (Entry 3). In the mixed solvent system, the reaction proceeded smoothly with 10 mol % of the catalyst. Although *para*-benzoquinone can coordinate to Pd species, it seemed that *para*-benzoquinone has no role in the enantiomeric induction step, since the reaction of **15** in the presence of stoichiometric amounts of $Pd(OCOCF_3)_2$–**6d** complex without using *para*-benzoquinone in CH_2Cl_2 at room temperature produced **16** in 83% ee.

A plausible mechanism of the tandem cyclization is shown in Scheme 5. Intramolecular nucleophilic attack of the hydroxy group at the activated C–C double bond produces alkyl Pd^{II} intermediate **20**. A subsequent C–C bond formation produces tandem bicyclic product **16** through the formation of palladacycle **21** by intramolecular carbopalladation or from a direct insertion intermediate **23**. The reaction without ligand gave only 34% yield of **16** even after 67 h. This result obviously indicated that $Pd(OCOCF_3)_2$–**6d** has sufficient ability to accelerate Wacker-type cyclization. Furthermore the rigid spiro[4.4]nonane skeleton of SPRIX prevented β-elimination from intermediates **20** and **22**, resulting in **17** and **18** as miner products, respectively. The isolated monocyclic product **17** or **18** was recovered without isomerization upon treating under the standard conditions, which indicated that bicyclic product **16** is produced in a sequential reaction.

With the success of the Pd^{II}–SPRIX-catalyzed Wacker-type cyclization of alkenyl alcohols, we envisioned an enantioselective aminopalladation of alkenyl amine derivatives. The



bond lengths and angles	
Pd-N1	2.002 Å
Pd-N2	2.005 Å
Pd-O1	2.002 Å
Pd-O2	2.013 Å
N1-Pd-N2	88.34°
O1-Pd-O2	89.80°

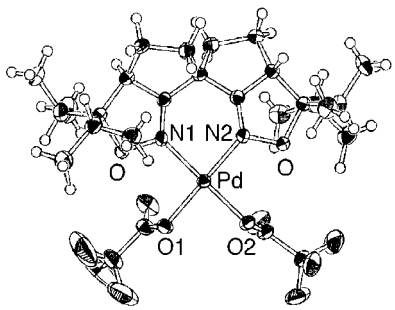
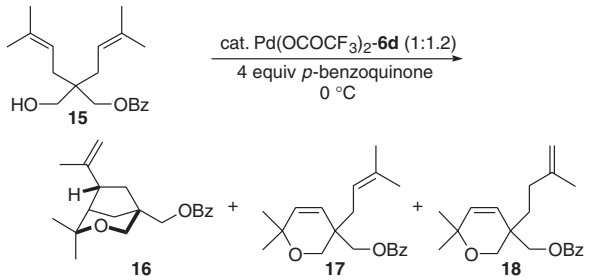


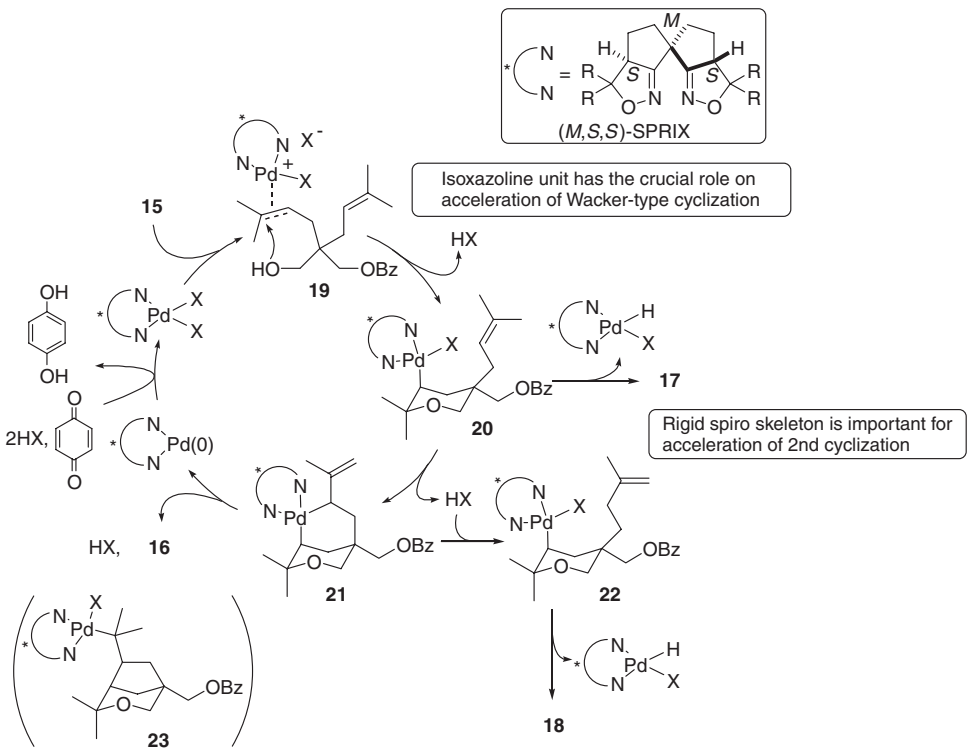
Figure 5. X-ray structure of $Pd(OCOCF_3)_2$–(*M*,*S*,*S*)-*i*-Pr-SPRIX (Ref. 8).

Table 1. Pd^{II}–SPRIX-Catalyzed Asymmetric Tandem Cyclization

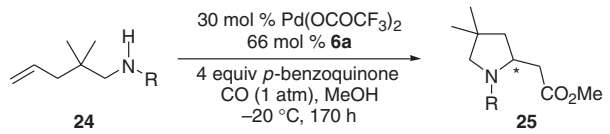


Entry	Conditions[a)]	16 Yield /%	16 Ee /%	17 Yield /%	17 Ee /%	18 Yield /%	18 Ee /%
1	A	65	95	5	45	26	60
2	B	79	68	5	26	11	31
3	C	89	82	3	36	8	57

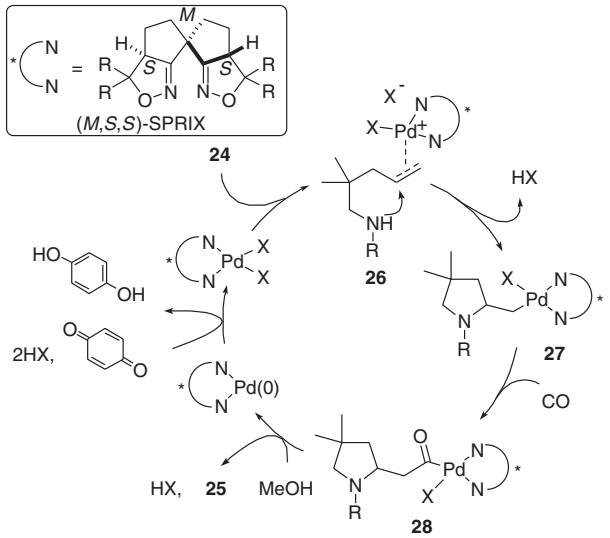
a) Conditions: A: 20 mol % cat., CH_2Cl_2, 85 h. B: 20 mol % cat., MeOH, 24 h. C: 10 mol % cat., CH_2Cl_2/MeOH (1:1), 24 h.



Scheme 5. Plausible mechanism of the tandem cyclization via oxy-palladation.



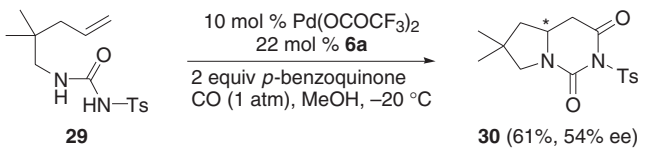
Scheme 6.



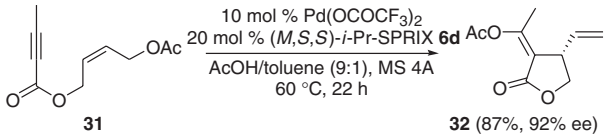
Scheme 7. Plausible mechanism of intramolecular aminocarbonylation.

Pd^{II}-catalyzed intramolecular aminocarbonylation of alkenyl amine derivatives has proven to be one of the most efficient and straightforward methods for constructing biologically important β-amino acid derivatives, alkaloids and related compounds. Tamaru and Kimura have developed efficient Pd^{II}-catalyzed aminocarbonylation reactions,[10] however, no catalytic enantioselective version of this reaction has been reported. We have reported the first example of the enantioselective intramolecular aminocarbonylation of alkenyl amine derivatives **24** promoted by Pd–SPRIX catalyst (Scheme 6).[11] When substrate **24a** was treated with 10 mol % of $Pd(OCOCF_3)_2$ and 22 mol % of (*M*,*S*,*S*)-H-SPRIX **6a** in the presence of 4 equivalents of *para*-benzoquinone under carbon monoxide in MeOH at −20 °C, β-amino acid derivative **25a** was obtained in 53% yield and 52% ee. The three fold excess of catalyst loading afforded **25a** in 83% yield and 53% ee. The use of Pd–**6a** with a ratio of 1:2.2 was found to be essential to improve both yield and ee as compared to a 1:1 ratio, perhaps due to dissociation of the ligand from Pd under a carbon monoxide atmosphere forming undesired catalytic species with the appearance of Pd black that responsible for lowering of ee.

A plausible mechanism of the catalytic enantioselective aminocarbonylation of alkenyl amine **24** is shown in Scheme 7. Intramolecular nucleophilic attack of the amino group at the activated C–C double bond generates alkyl Pd^{II} intermediate **27**. CO insertion in **27** gives acylpalladium intermediate **28** and after alcoholysis produces **25** generating Pd^0. The Pd^0 is oxidized to Pd^{II} by *para*-benzoquinone to complete the catalytic cycle.



Scheme 8.



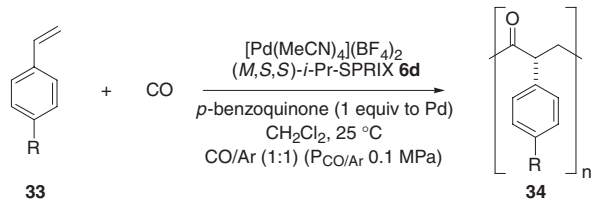
Scheme 9.

Upon treatment of alkenyl urea **29**[10] with $Pd(OCOCF_3)_2$–**6a** catalyst, an interesting bicyclic 5,6-dihydrouracil derivative **30** containing two nitrogen atoms was synthesized as a single product in one step with 54% ee (Scheme 8). Product **30** was derived by intramolecular nucleophilic attack of the tosylamide group on the acylpalladium intermediate.

Continuing to explore the SPRIX ligand, we have reported the $Pd(OCOCF_3)_2$–**6d** catalyzed intramolecular cyclization of (*Z*)-4-acetoxy-2-butenyl 2-alkynoates to afford α-methylene-γ-butyrolactones (Scheme 9).[12] For example, in the presence of $Pd(OCOCF_3)_2$–**6d** catalyst and MS 4A in AcOH:toluene (9:1), substrate **31** was smoothly cyclized to give **32** in 87% yield and 92% ee.

Another interesting application of SPRIX has been found in polymerization. Although several Pd^{II} complexes with weakly coordinating counter anions and C_2-symmetric bidentate nitrogen donors have been developed for CO/styrene copolymerization, reported catalytic systems generally produce the copolymer (CP) in poor chemical yield and formation of fully isotactic polyketones usually results in low molecular weight.[13] We have developed a highly efficient dicationic Pd^{II}–SPRIX complex for alternating copolymerization of CO with styrene derivatives **33** for enantioselective synthesis of polyketones **34**.[14] When styrene and its derivatives were treated with $[Pd(i\text{-Pr-SPRIX})_2](BF_4)_2$ **35**, prepared in situ by mixing $[Pd(MeCN)_4](BF_4)_2$ and (*M*,*S*,*S*)-*i*-Pr-SPRIX **6d** (Pd/L = 1:2), in the presence of *para*-benzoquinone at 25 °C under CO:Ar gas (1:1) produced corresponding polyketones in high molecular weight with full stereoregularity as revealed by the observed molar optical rotation values (Table 2). This catalytic system was effectively used in a large scale copolymerization of styrene with CO by decreasing catalyst loading to 0.01 mol % (Entry 3). The poly(styrene-*alt*-CO) was obtained in an excellent combination of high productivity (445 g CP/g Pd), molecular weight value of 61600 ($M_w/M_n = 1.7$) and stereoregularity ($[\phi] = -505°$), albeit low chemical yield. We succeeded to prepare a single yellow crystal of racemic **35**. X-ray analysis of complex **35** shows a slightly distorted square-planar structure, where the dihedral angles between the planes that consist of Pd and two N atoms of *i*-Pr-SPRIX are approximately 14°, probably due to the intramolecular steric repulsion between the two *i*-Pr-SPRIX ligands (Figure 6). This phenomenon is likely due to the intramolecular steric repulsion between the two *i*-Pr-SPRIX ligands, because the geometry of $Pd(OCOCF_3)_2$–**6d** (Figure 5) is close to an ideal square-planar

Table 2. Pd^{II}–SPRIX-Catalyzed Copolymerization of CO with Styrene Derivatives



33 **34**

Entry	R	Cat /mol %	Time /d	Yield /%	g CP/g Pd	M_w (M_w/M_n)[c]	$[\phi]^{25}_{589}$[d]
1[a]	H	1	2	49	62	35700 (1.2)	−511
2[a]	H	0.25	2	19	97	72600 (1.6)	−538
3[b]	H	0.01	6	4	445	61600 (1.7)	−505
4[a]	Me	1	2	20	28	62000 (1.6)	−404
5[a]	*t*-Bu	1	2	41	74	34000 (1.6)	−376

a) Reaction scale was 0.48 mmol. b) Reaction scale was 48 mmol. c) M_w = weight average molecular weight, M_n = number average molecular weight. d) $[\phi]$ = molar optical rotation.

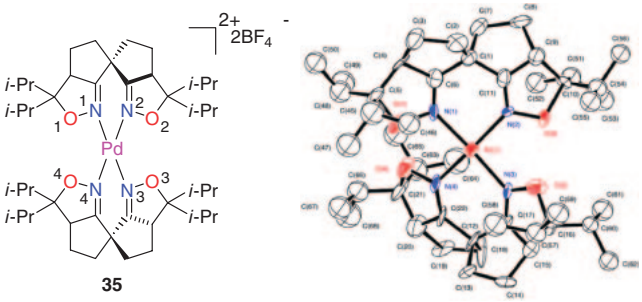
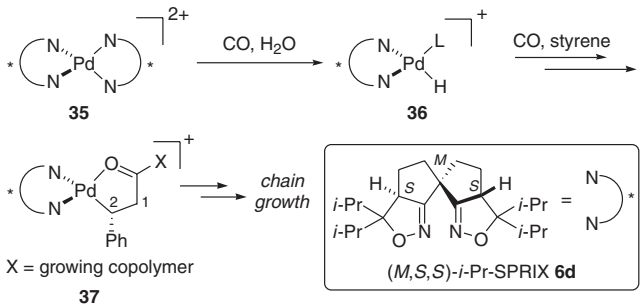
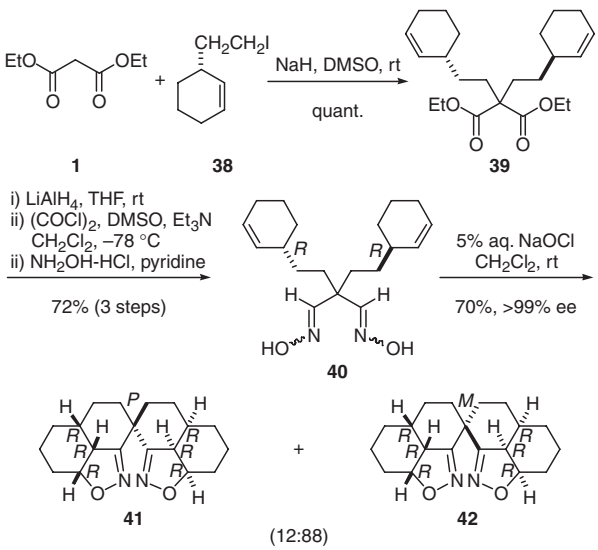


Figure 6. ORTEP plot of $[Pd(i\text{-Pr-SPRIX})_2](BF_4)_2$. The counter anions and all hydrogen atoms are omitted for clarity (Ref. 14).



Scheme 10. Plausible mechanism of the copolymerization.

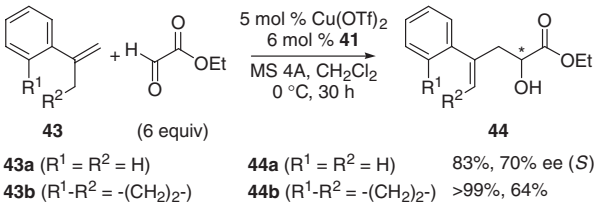


Scheme 11. Synthesis of the polycyclic spiro bis(isoxazoline)s.

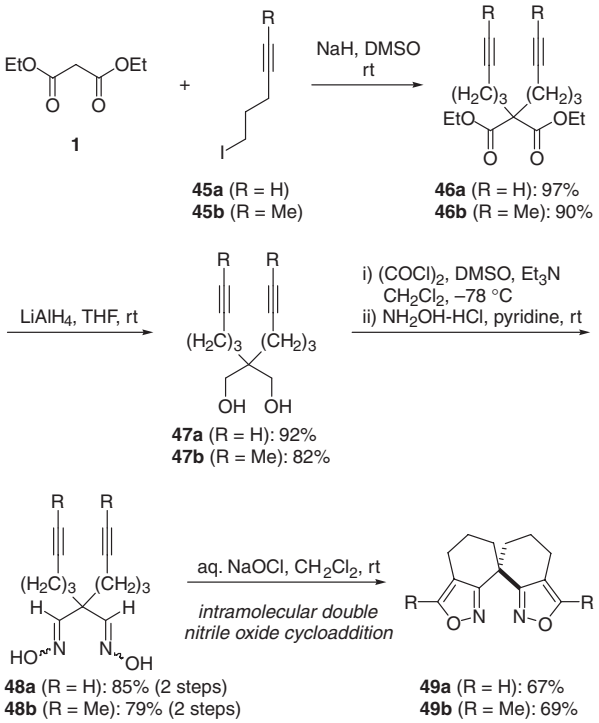
structure. The six-membered diazametallacycles formed by chelate coordination of *i*-Pr-SPRIX nearly lie on the same plane with a dihedral angle between two imino planes of 28.60(8)°. Most of the torsion angles at the trans position around the imino groups are in the range of 157–165°, whereas those at the cis position are less than 7°.

Although further study is necessary to gain insight into the identification of the active initiator in the polymerization process, we speculate that the initiation step involves the formation of a Pd–hydride species **36**, generated via water-gas shift reaction (Scheme 10).[15] Insertion of styrene into **36** generates an alkyl–palladium species. Alternative insertion of CO and styrene produces **37** as the propagating species. Termination is expected to be through β-H elimination.

Using an optically pure olefin derivative **38**, we have sought to develop new chiral spiro bis(isoxazoline) ligands **41** and **42** (Scheme 11).[16] The stereochemistry of chiral olefin **38** was relayed to dioxime **40** following the general route developed for the SPRIX synthesis and the intramolecular double nitrile oxide cycloaddition of **40** produced two diastereomers **41** and **42** with a ratio of 12:88 in overall 51% yield. The most important characteristic in this strategy is ligands **41** and **42** can be obtained in an optically pure form by simple column chromatography and no further optical resolution is necessary. MM2 calculation of ligands **41** and **42** revealed that **41** has comparably a short N–N atomic distance (3.04 Å vs. 4.09 Å of **42**) and a small out-of-plane angle between the two C=N bonds (59.8° vs. 89.5° of **42**), which indicates its potential for a metal coordination. Using ligand **41**, the first example of biisoxazoline ligand-promoted Cu-catalyzed glyoxylate-ene reaction of olefins **43** was demonstrated to produce chiral alkenoates **44** with up to 70% ee (Scheme 12).[17]

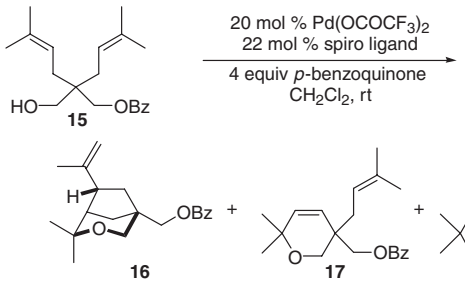


Scheme 12.



Scheme 13. Synthesis of spiro bis(isoxazole).

Table 3. Pd^{II}-Catalyzed Asymmetric Tandem Cyclization (Ligand Comparison: Spiro Bis(isoxazoline) vs. Spiro Bis(isoxazole))



Entry	Ligand used	Time /h	16 Yield /%	16 Ee /%	17 Yield /%	18 Yield /%
1	(*M*,*S*,*S*)-*i*-Pr-SPRIX **6d**	8	42	93	15	17
2	(+)-**49a**	17	27	56	43	4
3	(+)-**49b**	7	23	59	47	8

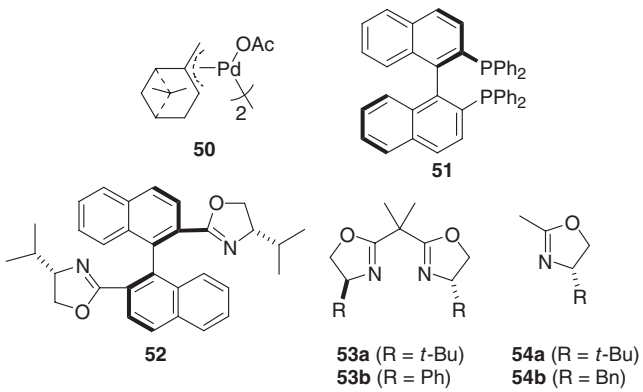


Figure 7. Compounds used in the cyclization reactions.

3. Spiro Bis(isoxazole)

The coordination chemistry of isoxazoles has been studied, however there is no example of their applications as a ligand in enantioselective reactions.[18] We thought to develop chiral spiro bis(isoxazole) ligands **49** in which the isoxazole rings and spiro skeleton would be installed in one step via intramolecular double nitrile oxide cycloaddition of dioxime **48** (Scheme 13).[19] Dioxime **48** was synthesized following the strategy of the SPRIX synthesis by using alkynyl halide **45** in place of alkenyl halide and final spiro cyclization produced **49** in 40–51% overall yield. Since single spiro atom chirality exists in **49**, no other diastereomers are possible, which is different to the synthesis of SPRIX ligand. After separation by using chiral stationary phase column chromatography (Daicel Chiralpak AD (ϕ2 cm × 25 cm), EtOH/hexane), the enantiomerically pure **49a** and **49b** were tested for catalytic activity in the Pd^{II}-catalyzed tandem cyclization of **15** and the results were compared with that of (*M*,*S*,*S*)-*i*-Pr-SPRIX **6d** (Table 3). The cyclization of **15** in the presence of 20 mol % of $Pd(OCOCF_3)_2$–**6d** complex in CH_2Cl_2 at room temperature afforded tandem product **16** as a single diastereomer in 93% ee, together with monocyclized compounds **17** and **18** (Entry 1). When the reaction was carried out using **49a** or **49b**, both the product ratio and enantioselectivity of **16** dropped (Entries 2 and 3). This result suggested that alkylpalladium intermediate attached to Pd^{II}–**49** (see intermediate **20** in Scheme 5) might readily undergo β-hydride elimination to produce **17** because of the flexibility of the spiro[5.5]undecane skeleton of **49**.

4. Spiro (Isoxazole–Isoxazoline)

An unprecedented activation of olefins was displayed by the Pd^{II} complexes of SPRIX in the enantioselective oxidative cyclizations (vide supra). Interestingly, we observed that the use of known asymmetric catalysts, such as [(3,2,10-η^3-pinene)PdOAc]$_2$ **50** and combination of $Pd(OCOCF_3)_2$ with (*R*)-BINAP **51**, (*S*,*S*)-ip-boxax **52**, bis(oxazoline)s **53**, and monodentate oxazoline ligands **54** (Figure 7), were ineffective to promote the cyclizations of alkenyl alcohols **13a**–**13c**, dialkenyl alcohol **15**, and alkenyl amines **24a** and **24b**. We reasoned that this failure was due to a stronger coordinating ability of the ligands. A weaker coordinating SPRIX restores the Lewis acidity at the metal center making it more reactive as well as providing an asymmetric environment. However, much weaker coordinating chiral spiro bis(isoxazole) ligands **49** were ineffective to promote the tandem reaction of dialkenyl alcohol

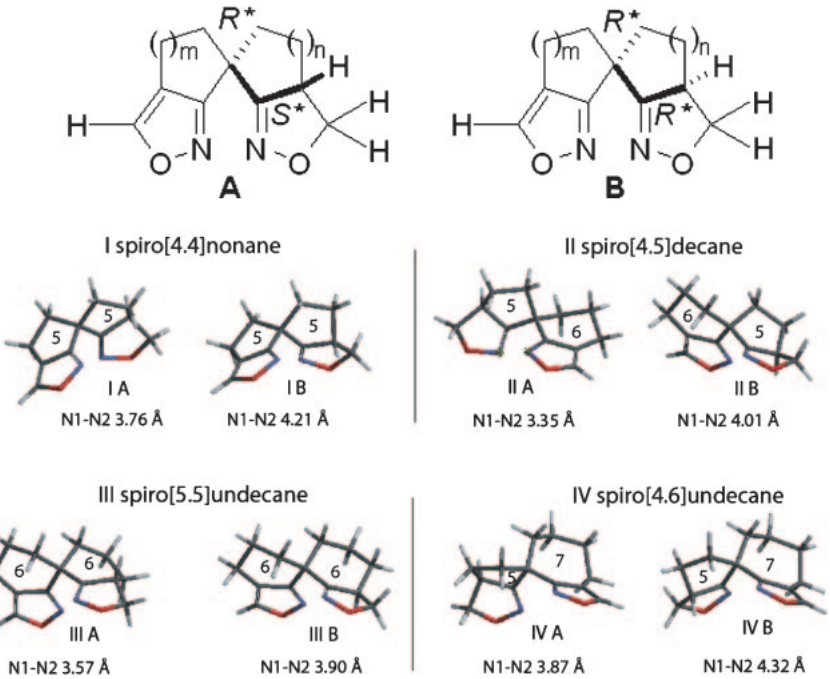


Figure 8. Optimization of the structures with various ring size.

15. It was thought that a proper combination of weakly coordinating groups and rigidity would provide optimum benefit in the design of new ligands. Thus we decided to prepare new hybrid spiro (isoxazole–isoxazoline) ligand containing an unsymmetrical spiro backbone.[20] 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.

The distance between the two coordinating nitrogen atoms of isoxazole and isoxazoline rings plays an important role to act synergistically for binding with the metal center. An optimum flexibility of the rigid spiro backbone for a bidentate coordination to form a square-planar complex with a metal is equally important. 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 (Figure 8). And, the isoxazole and isoxazoline rings fused to the 6- and 5-membered spiro rings, respectively, showed the shortest N–N distance (3.35 Å).

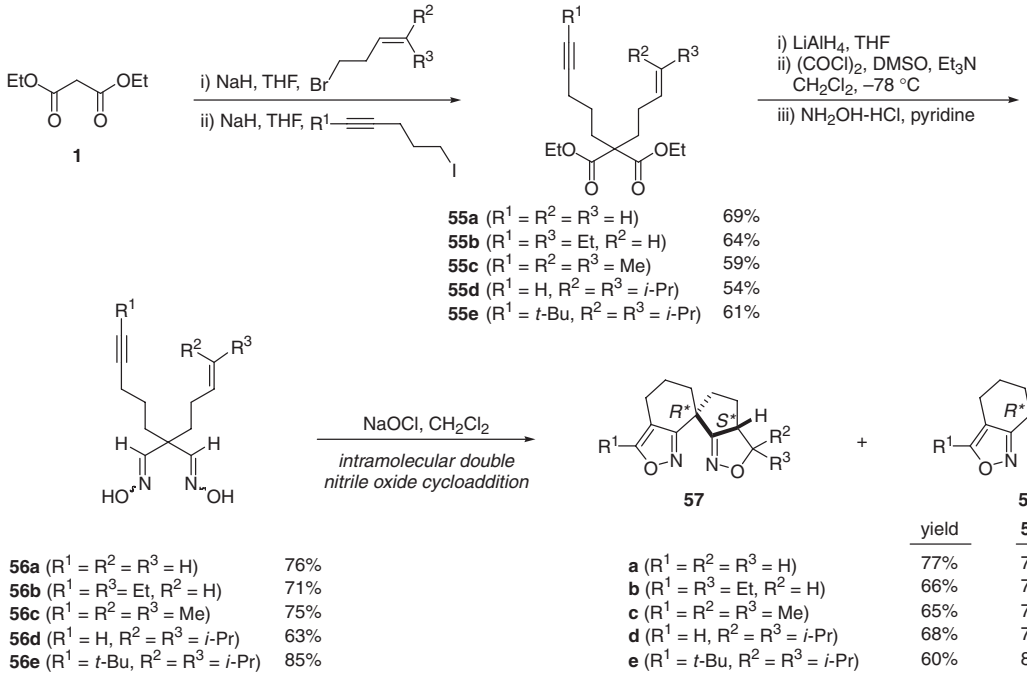
A flexible synthetic route, similar to that of SPRIX, was employed for the synthesis of the designed hybrid spiro (isoxazole–isoxazoline) ligands **57** and **58** (Scheme 14). In the initial step, different combinations of alkenyl and alkynyl halides were used for the alkylation of diethyl malonate (**1**) to produce differentially substituted diesters **55**, which were converted into dioximes **56**. The hybrid spiro (isoxazole–isoxazoline) ligands **57** and **58** were obtained in good yields by an intramolecular double nitrile oxide cycloaddition. The desired diastereomer **57** was preferentially formed over **58** in a ratio of 3:1 to 4:1. Optically pure ligands were obtained by separation using a chiral stationary phase HPLC (Daicel Chiralpak AD (ϕ2 cm × 25 cm), 2-propanol/hexane). The relative configuration of the spiro skeleton was confirmed by X-ray analysis of **57c** (Figure 9). The distance between the two nitrogens was found to be 3.71 Å in close agreement with the calculated value of 3.63 Å by using HF/6-31G*.

The coordination ability of the hybrid spiro (isoxazole–isoxazoline) ligand was evaluated by a ligand-exchange reaction in an NMR tube. When 1 equivalent of (*M*,*S*,*S*)-*i*-Pr-SPRIX **6d** was added to a solution of precomplexed $Pd(OCOCF_3)_2$ and hybrid ligand **57d** in CD_2Cl_2/CD_3OD (9:1), formation of free **57d** and $Pd(OCOCF_3)_2$–**6d** complex were observed indicating a weaker coordinating ability of spiro (isoxazole–isoxazoline) ligand with Pd compared to that of SPRIX (Figure 10).

Hybrid ligands **57a**–**57e** were used in the Pd-catalyzed asymmetric tandem cyclization of **15** (Table 4). Gradual increment in the yield and ee of tandem product **16** was observed as the steric bulk at R^2 and R^3 positions was increased from ligands **57a** to **57e** (Entries 1–5). Although, a high enantiomeric excess of 95% was observed using *i*-Pr-SPRIX **6d** in CH_2Cl_2 (Entry 6), while a mixed solvent CH_2Cl_2/MeOH (1:1) gave a better yield of the tandem product **16** (89% yield), however the enantioselectivity decreased to 82% ee (Entry 7). In accordance with our hypothesis, compared to the result obtained by using *i*-Pr-SPRIX **6d**, the use of hybrid ligand **57e** in the mixed solvent system provided comparable enantioselectivity while still maintaining high product yield as well as regioselectivity in the product distribution (Entry 5).

5. Spiro Bis(oxazoline)

Over the past decade, a large number of chiral oxazoline ligands have been prepared and applied in a variety of asymmetric reactions.[2c–2g] For comparison of the reactivity with SPRIX, we designed and synthesized novel spiro bis(oxazoline) ligand **69** (Scheme 15).[21] Diethyl 2,2-diallyl malonate



		yield	57:58
55a ($R^1 = R^2 = R^3 = H$)	69%		
55b ($R^1 = R^3 = Et$, $R^2 = H$)	64%		
55c ($R^1 = R^2 = R^3 = Me$)	59%		
55d ($R^1 = H$, $R^2 = R^3 = i$-Pr)	54%		
55e ($R^1 = t$-Bu, $R^2 = R^3 = i$-Pr)	61%		
56a ($R^1 = R^2 = R^3 = H$)	76%	**a** ($R^1 = R^2 = R^3 = H$)	77%	78:22
56b ($R^1 = R^3 = Et$, $R^2 = H$)	71%	**b** ($R^1 = R^3 = Et$, $R^2 = H$)	66%	78:22
56c ($R^1 = R^2 = R^3 = Me$)	75%	**c** ($R^1 = R^2 = R^3 = Me$)	65%	71:29
56d ($R^1 = H$, $R^2 = R^3 = i$-Pr)	63%	**d** ($R^1 = H$, $R^2 = R^3 = i$-Pr)	68%	70:30
56e ($R^1 = t$-Bu, $R^2 = R^3 = i$-Pr)	85%	**e** ($R^1 = t$-Bu, $R^2 = R^3 = i$-Pr)	60%	80:20

Scheme 14. Synthesis of spiro (isoxazole–isoxazoline).

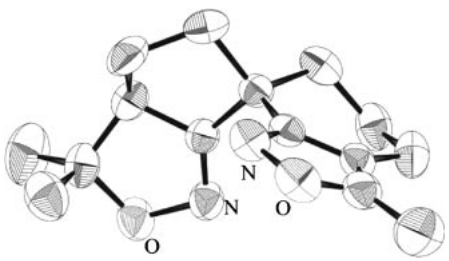


Figure 9. X-ray structure of **57c** showing the spiro skeleton (N–N = 3.71 Å) (Ref. 20).

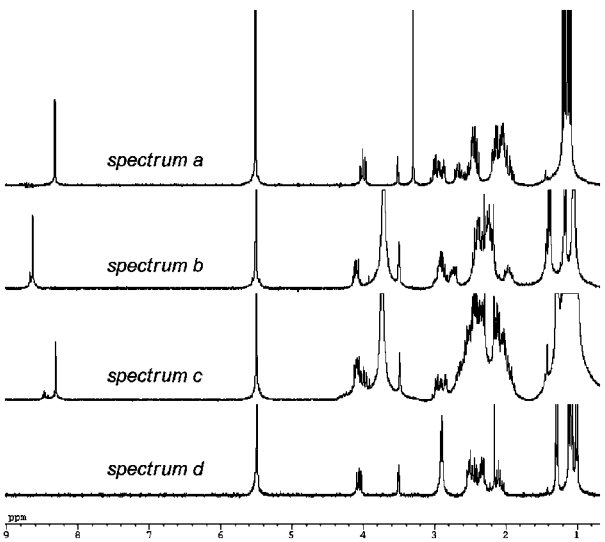
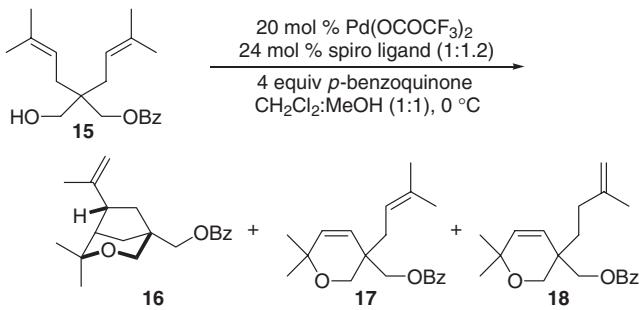


Figure 10. Comparison of coordinating abilities by NMR. (a) free **57d**, (b) $Pd(OCOCF_3)_2$ + **57d** complex, (c) free **57d** and $Pd(OCOCF_3)_2$–**6d** complex were generated upon addition of **6d** to $Pd(OCOCF_3)_2$–**57d** complex, (d) authentic spectrum for $Pd(OCOCF_3)_2$–**6d** complex.

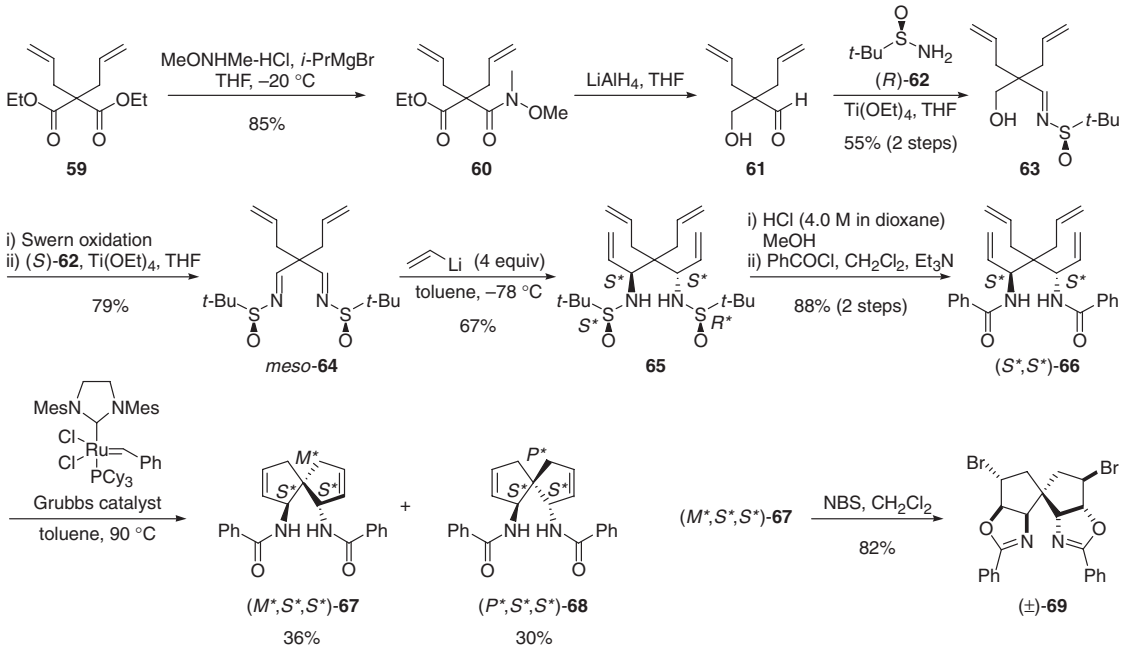
Table 4. Pd^{II}-Catalyzed Asymmetric Tandem Cyclization (Ligand Comparison: Spiro Bis(isoxazoline) vs. Spiro (Isoxazole–Isoxazoline))



Entry	Ligand used	Time /h	16 Yield /%	16 Ee /%	17 Yield /%	18 Yield /%
1	**57a**	72	34	66	14	33
2	**57b**	48	47	69	7	39
3	**57c**	21	54	87	2	32
4	**57d**	17	59	97	5	23
5	**57e**	17	74	95	0	25
6[a)]	*i*-Pr-SPRIX **6d**	85	65	95	5	26
7[b)]	*i*-Pr-SPRIX **6d**	24	89	82	3	8

a) CH_2Cl_2 was used as solvent. b) 10 mol % cat. was used.

(**59**) was converted to amide **60**, which after $LiAlH_4$ reduction, condensation with (*R*)-**62**, Swern oxidation and treatment with (*S*)-**62** produced *meso*-**64**. Diastereoselective 1,2-addition of vinyl lithium to *meso*-**64** followed by treatment with HCl and benzoyl chloride produced the cyclization precursor (*S**,*S**)-**66**. Ring closing metathesis of **66** with Grubbs catalyst produced spiro amides (*M**,*S**,*S**)-**67** and (*P**,*S**,*S**)-**68**. Finally, the desired spiro bis(oxazoline) ligand (±)-**69** was synthesized from (*M**,*S**,*S**)-**67** via oxazoline ring formation



Scheme 15. Synthesis of spiro bis(oxazoline).

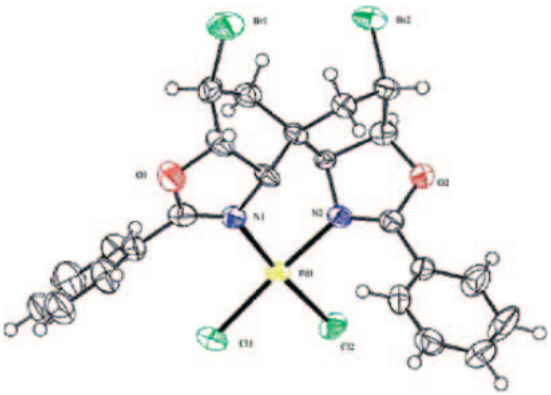
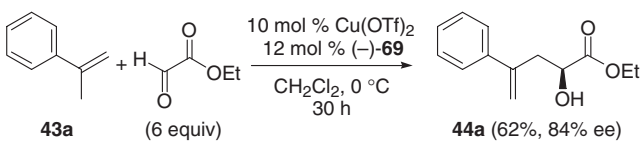


Figure 11. ORTEP drawing of $PdCl_2$–(±)-**69** complex (Ref. 21).

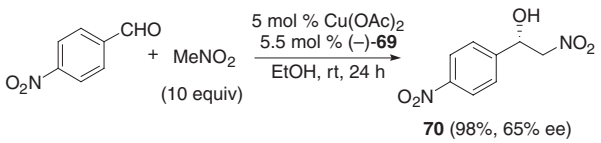
promoted by NBS. This reaction proceeded with high diastereoselectivity, with no other diastereomer being observed. Separation by using a chiral stationary phase column (Daicel Chiralpak AD (ϕ2 cm × 25 cm), 2-propanol/hexane) gave enatiopure **69**.

The X-ray crystallographic analysis of $PdCl_2$–**69**, obtained by recrystallization from a 1:1 mixture of ligand (±)-**69** with $PdCl_2$ in acetone–hexane revealed that **69** works as a bidentate ligand (Figure 11). However, it failed to promote the Pd-catalyzed tandem cyclization of alkenyl alcohol **15** indicating the importance of isoxazoline moieties of SPRIX in this reaction.

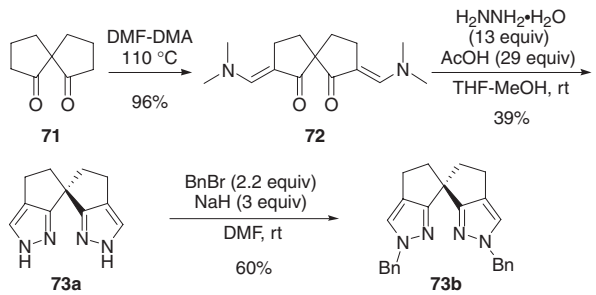
Spiro bis(oxazoline) ligand **69** was found to be effective in the Cu-catalyzed glyoxylate-ene and Henry reactions. In the presence of 10 mol % of $Cu(OTf)_2$–(−)-**69**, the reaction of **43a** with ethyl glyoxylate produced **44a** in 84% ee (Scheme 16). The Henry reaction of *p*-nitrobenzaldehyde with nitromethane was promoted by 5 mol % of $Cu(OAc)_2$–(−)-**69** producing **70** in a high yield and moderate ee (Scheme 17).



Scheme 16.



Scheme 17.



Scheme 18. Synthesis of spiro bis(pyrazole)s.

6. Spiro Bis(pyrazole)

The potential of pyrazole as an efficient coordinating ligand is well-established in inorganic chemistry.[22] We decided to install pyrazole rings in a spiro skeleton and synthesized new spiro bis(pyrazole) ligands **73** (Scheme 18).[23] Heating a mixture of spiro[4.4]nonane-1,6-dione **71**[24h] and *N*,*N*-dimethylformamide dimethyl acetal (DMF–DMA) produced dione **72**. Treatment of **72** with an excess of hydrazine monohydrate and

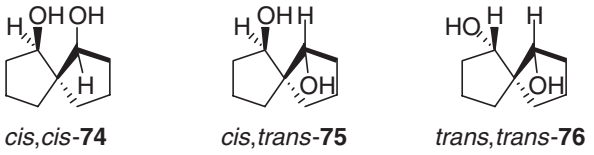
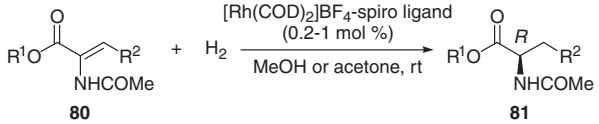
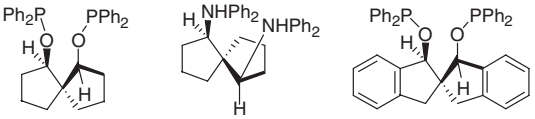


Figure 12. Three diastereomers of spiro[4.4]nonane-1,6-diol (Spirol).



	using **77**	using **78**	using **79**
81a (R^1 = H, R^2 = Ph)	97.9% ee	>98% ee	90% ee
81b (R^1 = H, R^2 = 2-Cl-C_6H_4)	97.3% ee	96% ee	93% ee
81c (R^1 = H, R^2 = 3-Cl-C_6H_4)	97.4% ee	95% ee	94% ee
81d (R^1 = R^2 = H)	99.9% ee	78% ee	74% ee
81e (R^1 = Me, R^2 = H)	99.0% ee	95% ee	80% ee
81f (R^1 = Me, R^2 = Ph)	95.7% ee	>99% ee	94% ee
81g (R^1 = Me, R^2 = 4-Cl-C_6H_4)	94.2% ee	>99% ee	67% ee



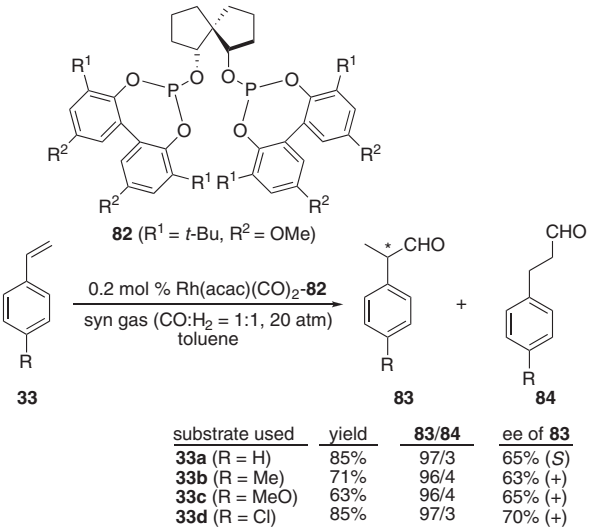
Scheme 19.

AcOH produced ligand (±)-**73a**. The structure of **73a** was confirmed by X-ray crystallographic analysis of **73b**, which was obtained by dibenzylation of **73a**. Enantiomerically pure **73a** was obtained by separation with a chiral stationary phase column (Daicel Chiralpak AD (ϕ2 cm × 25 cm), EtOH/hexane) and used in the $Cu(OTf)_2$-catalyzed asymmetric glyoxylate-ene reaction of **43a** with ethyl glyoxylate, unfortunately an unsatisfactory result (15% ee) was obtained.

7. Other Spiro Ligands

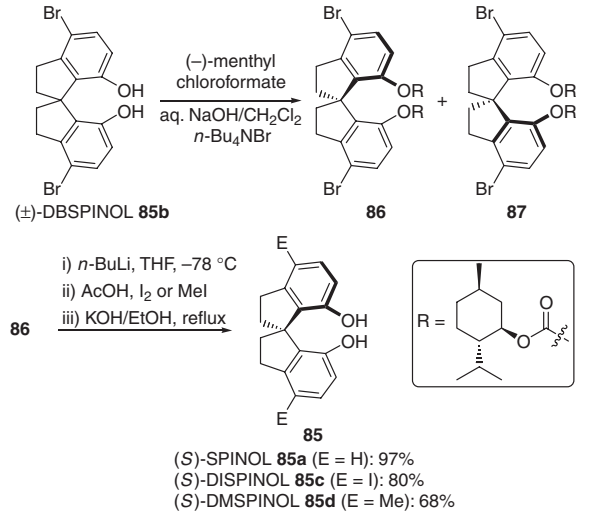
Cram et al., Gerlach and co-worker, Harada et al., Keay et al., and Chan et al. have independently reported the synthesis of spiro[4.4]nonane-1,6-diol (Spirol) (Figure 12).[24] The enantiomerically pure *cis*,*cis*-**74** has been used as a chiral auxiliary in conjugation with $LiAlH_4$ in the asymmetric reduction of phenyl alkyl ketones to produce the corresponding alcohols in up to 90% ee.[25] The mono-pivalate mono-acrylate esters of *cis*,*cis*-**74** have shown their applications in the asymmetric Diels–Alder reaction with cyclopentadiene to produce endo bicyclo adduct in >97% de.[26]

Chan et al. have described synthesis of chiral spiro bis(phosphinite) (SpirOP) ligands **77**[27] and spiro bis(phosphinamidite) (SpirNP) ligands **78**[28] starting from optically pure *cis*,*cis*-spirol **74** and *trans*,*trans*-spirol **76**, respectively. Chen et al. have synthesized chiral 1,1′-bidiphenylphosphinoxy-2,2′-spirobiindane (SpiroBIP) **79** with additionally fused benzene rings.[29] These ligands were employed in asymmetric hydrogenation reactions (Scheme 19).[30] Compared to SpirOP **77**, SpiroBIP **79** exhibited less catalytic activity in the Rh-catalyzed asymmetric hydrogenation of (*Z*)-2-acetamido-3-arylacrylic acids and their methyl ester derivatives **80**.



substrate used	yield	**83**/**84**	ee of **83**
33a (R = H)	85%	97/3	65% (*S*)
33b (R = Me)	71%	96/4	63% (+)
33c (R = MeO)	63%	96/4	65% (+)
33d (R = Cl)	85%	97/3	70% (+)

Scheme 20.

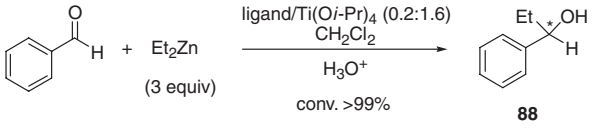


Scheme 21. Synthesis of enantiopure SPINOL and it's 4,4′-derivatives.

Jiang et al. have prepared chiral spiro bis(phosphate) ligands **82** using enantiomerically pure *cis*,*trans*-spirol **75**.[31] The Rh-catalyzed asymmetric hydroformylation of styrene derivatives **33** in the presence of **82** produced branched aldehyde **83** in high regioselectivities and moderate enantioselectivities (Scheme 20).

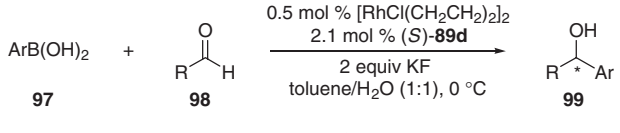
In 1999, Birman et al. reported the first synthesis of 1,1′-spirobiindane-7,7′-diol (SPINOL) **85a**.[32a] Zhou et al. have synthesized enantiomerically pure 4,4′-disubstituted-SPINOL such as 4,4′-dibromo-7,7′-dihydroxy-1,1′-spirobiindane (DBSPINOL) **85b** from SPINOL.[32b,32c] Later, Liang, Wan, and their co-workers demonstrated resolution–protection–deprotection of DBSPINOL through the replacement of two bromine atoms in diastereomer **86** (or **87**) with appropriate electrophiles in the presence of *n*-BuLi followed by cleavage of two menthyl carbonate groups to produce enantiopure SPINOL **85a**, DISPINOL **85c**, and DMSPINOL **85d** (Scheme 21).[32d,32e]

The SPINOL and the corresponding 4,4′-derivatives in the form of their Ti–alkoxides were used as catalysts in the



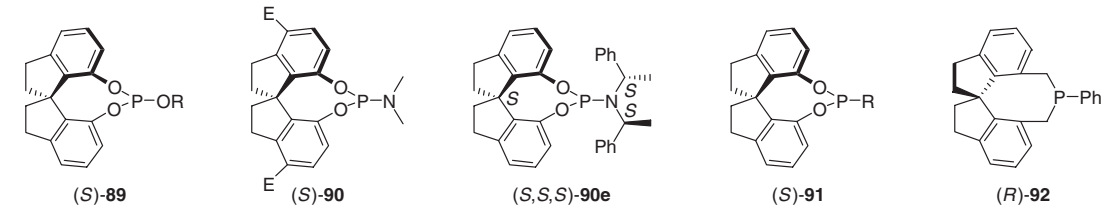
ligand used	ee
(*R*)-SPINOL **85a**	88% (*S*)
(*S*)-DBSPINOL **85b**	84% (*R*)
(*S*)-DISPINOL **85c**	83% (*R*)
(*S*)-DMSPINOL **85d**	84% (*R*)

Scheme 22.



99a (Ar = Ph, R = 4-MeO-C_6H_4)	90%, 65% ee (*R*)
99b (Ar = Ph, R = 4-CF_3-C_6H_4)	96%, 70% ee (*R*)
99c (Ar = Ph, R = *trans*-PhCH=CH)	96%, 75% ee (*S*)
99d (Ar = 4-Ac-C_6H_4, R = 2-Cl-C_6H_4)	88%, 85% ee (*R*)
99e (Ar = 2-thienyl, R = 2-Cl-C_6H_4)	98%, 71% ee (*R*)
99f (Ar = 4-Ph-C_6H_4, R= 2-Br-C_6H_4)	94%, 87% ee (*R*)

Scheme 23.



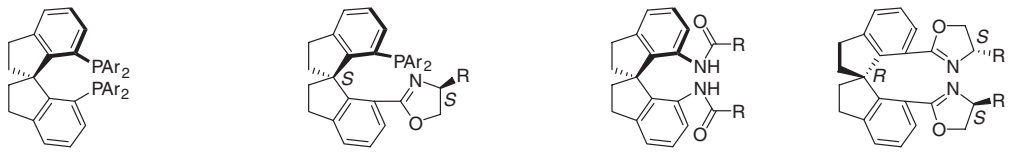
(*S*)-**89**
89a (R = Ph)
89b (R = 4-MeO-C_6H_4)
89c (R = 4-CF_3-C_6H_4)
89d (R = 2-naphthyl)

(*S*)-**90**
90a (E = H)
90b (E = Br)
90c (E = Ph)
90d (E = MeO)

(*S,S,S*)-**90e**

(*S*)-**91**
(*S*)-**91a** (R = Ph)
(*S*)-**91b** (R = Me)
(*S*)-**91c** (R = *i*-Pr)
(*S*)-**91d** (R = *t*-Bu)

(*R*)-**92**



(*S*)-**93**
(*S*)-**93a** (Ar = Ph)
(*S*)-**93b** (Ar = 3,5-Me_2-C_6H_3)
(*S*)-**93c** (Ar = 4-MeO-C_6H_4)
(*S*)-**93d** (Ar = 3,5-Me_2-4-MeO-C_6H_2)

(*S,S*)-**94**
(*S,S*)-**94a** (Ar = Ph, R = *i*-Pr)
(*S,S*)-**94b** (Ar = Ph, R = Ph)
(*S,S*)-**94c** (Ar = 4-MeO-C_6H_4, R = Bn)
(*S,S*)-**94d** (Ar = 3,5-Me_2-C_6H_3, R = Bn)

(*S*)-**95**
(*S*)-**95a** (R = 2-pyridyl)
(*S*)-**95b** (R = 2-quinolyl)

(*R,S,S*)-**96**
(*R,S,S*)-**96a** (R = Ph)
(*R,S,S*)-**96b** (R = Bn)
(*R,S,S*)-**96c** (R = *i*-Pr)

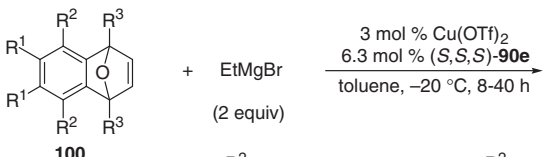
Figure 13. Chiral spiro ligands reported by Zhou et al.

enantioselective addition of diethylzinc to aromatic aldehydes.[32e,33] The addition reaction proceeded smoothly producing secondary alcohols with high conversions and high enantioselectivites (up to 88%) (Scheme 22).

Zhou et al. have synthesized a wide range of chiral spiro ligands **89–96**, which were prepared starting from enantiomerically pure SPINOL **85a** (Figure 13). The Rh-catalyzed asymmetric addition of arylboronic acids **97** to aldehydes in the presence of spiro monophosphite **89d** produced **99** with up to 87% ee (Scheme 23).[34,35]

The chiral monodentate spiro phosphoramidite (SIPHOS) ligands **90** were used in asymmetric hydrogenation,[32c,36a–36c] hydrosilylation,[36d] allylic alkylations,[36e] hydrovinylation,[36f,36g] Michael reactions,[36h] and Pauson–Khand reactions.[36i] The Cu-catalyzed asymmetric ring opening of oxabenzonorbornadienes **100** with Grignard reagents using (*S,S,S*)-SIPHOS-PE **90e** in toluene produced the corresponding ring-opening product alcohols **101** with excellent anti stereoselectivity and high enantioselectivity (Scheme 24).[36j] Coordinating solvents such as THF, DME afforded racemic products.

The Rh-catalyzed asymmetric hydrogenation of 1-(dialkylamino)-1-alkene **102** promoted by chiral spiro phosphonite **91d** produced chiral tertiary amines **103** in high enantioselectivity (Scheme 25).[37] In the presence of $[Rh(COD)_2]BF_4$/(*S*)-**91d**, the use of 2 mol % of I_2 and 20 mol % of AcOH as additives under 10 atm of H_2 were found essential to obtain good enantio-

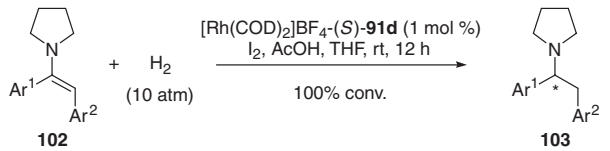


	yield	*anti*/*syn*	ee (anti)
101a (R^1 = R^2 = R^3 = H)	85%	97:3	56%
101b (R^1 = R^2 = H, R^3 = Me)	87%	99:1	88%
101c (R^1 = R^3 = H, R^2 = MeO)	66%	94:6	72%
101d (R^1 = H, R^2 = MeO, R^3 = Me)	90%	99:1	87%

Scheme 24.

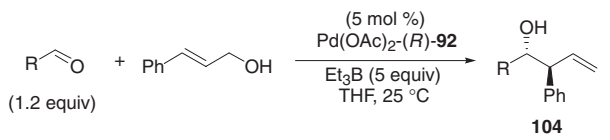
selectivity. The electronic nature of the aryl groups of enamine showed a strong influence on the enantioselectivity. The substrates with an Ar^1 connecting electron-donating group displayed higher enantioselectivity, while a reverse effect was observed on the Ar^2 side.

Spiro phospholane ligand **92** was used in the Pd-catalyzed enantioselective allylation of aromatic, heteroaromatic, and aliphatic aldehydes with allylic alcohols to produce the corresponding allylated products **104** in high yields, excellent



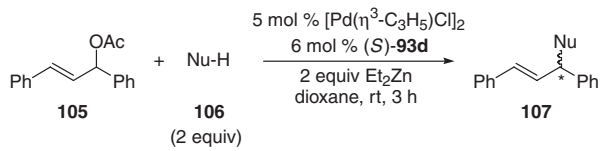
103a (Ar^1 = Ph, Ar^2 = Ph)	87% ee
103b (Ar^1 = 4-Me-C_6H_4, Ar^2 = Ph)	91% ee
103c (Ar^1 = 4-Cl-C_6H_4, Ar^2 = Ph)	73% ee
103d (Ar^1 = Ph, Ar^2 = 4-Me-C_6H_4)	80% ee
103e (Ar^1 = Ph, Ar^2 = 4-Cl-C_6H_4)	96% ee

Scheme 25.



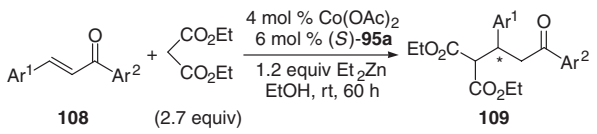
104a (R = Ph)	80%, *anti*/*syn* = 98/2, 82% ee (12 h)
104b (R = 4-MeO-C_6H_4)	97%, *anti*/*syn* = 99/1, 74% ee (48 h)
104c (R = 4-CF_3-C_6H_4)	71%, *anti*/*syn* = 97/3, 58% ee (12 h)
104d (R = 1-naphthyl)	99%, *anti*/*syn* = 99/1, 73% ee (12 h)
104e (R = 2-furyl)	73%, *anti*/*syn* = 99/1, 78% ee (12 h)
104f (R = *c*-C_6H_{11})	50%, *anti*/*syn* = 99/1, 83% ee (32 h)

Scheme 26.



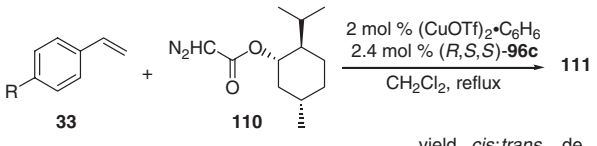
107a (Nu = -$CH(CO_2Me)_2$	96%, 99% ee (*S*)
107b (Nu = -$CMe(CO_2Me)_2$	93%, 97% ee (*S*)
107c (Nu = -(MeCO)C(Me)CO_2Et	90%, 91 & 97% ee (37% de) (36 h)

Scheme 27.



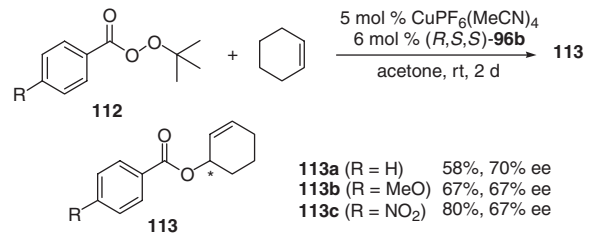
109a (Ar^1 = Ar^2 = Ph)	78%, 50% ee (+)
109b (Ar^1 = 4-Cl-C_6H_4, Ar^2 = Ph)	76%, 57% ee (+)
109c (Ar^1 = Ph, Ar^2 = 4-Cl-C_6H_4)	72%, 49% ee (+)
109d (Ar^1= Ph, Ar^2= 4-MeO-C_6H_4)	72%, 53% ee (+)

Scheme 28.



	yield	*cis*:*trans*	de
111a (R = H)	93%	11:89	70%
111b (R = Me)	67%	18:82	55%
111c (R = MeO)	55%	15:85	53%
111d (R = Cl)	54%	14:86	82%
111e (R = CF_3)	56%	14:86	82%

Scheme 29.



113a (R = H)	58%, 70% ee
113b (R = MeO)	67%, 67% ee
113c (R = NO_2)	80%, 67% ee

Scheme 30.

diastereoselectivities, and good enantioselectivities (up to 83% ee) (Scheme 26).[38] Et_3B was used as an umpolung reagent for π-allylpalladium complex that was generated from allylic alcohol.

Ruthenium catalysts prepared from chiral spiro diphosphine (SDP) ligands **93** were used in the asymmetric hydrogenation of aromatic, heteroaromatic, and α,β-unsaturated ketones.[39a] These ligands were further utilized in the Pd-catalyzed allylic alkylation of (±)-1,3-diphenyl-2-propenyl acetate (**105**) (Scheme 27).[39b] The use of diethylzinc as a base, especially when the reaction was carried out in dioxane, was found to be critical for obtaining high enantioselectivity in the allylic alkylation of **105** with β-dicarbonyl nucleophiles **106**.

The iridium complexes of spiro (phosphine–oxazine) (SIPHOX) ligands **94** catalyzed asymmetric hydrogenation of imines.[40] The cobalt complex prepared in situ from $Co(OAc)_2$ and chiral spiro bispyridine carboxamide (SIPAD) **95a** showed a moderate enantioselectivity in the asymmetric Michael addition of malonates to chalcone derivatives **109** regardless the electronic properties of the substituents (Scheme 28).[41]

The efficiency of spiro bis(oxazoline) (SpiroBOX) ligands **96** was evaluated in the Cu-catalyzed asymmetric cyclopropanation of styrene derivatives with menthyl diazoacetate **110** (Scheme 29) and allylic oxidation of cyclic alkenes with *tert*-butyl perbenzoates **112** (Scheme 30).[42]

Zhang et al. have reported another variety of chiral phosphoramidite ligands **114** with 9,9′-spirobixanthene backbone (Figure 14).[43] These ligands were utilized in Rh-catalyzed hydrogenation[43a] and Cu-catalyzed conjugate addition of diethylzinc to cyclic enones.[43b] Keay et al. have synthesized spiro (phosphine–oxazine) **115** and used it in Pd-catalyzed alkylation reactions.[44] A new variety of spirobifluorene-based diphosphine (SFDP) ligands **116** was reported by Zhou et al. and was used in the Ru-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[45]

Recently, some new spiro ligands have been reported and have shown their coordinating ability with metal complexes (Figure 15). Spiro bispyridines **117** showed their coordinating ability with a copper complex.[46] Spiro bisoxime **118** has been demonstrated as a helical chiral bridging ligand for the preparation of bimetallic compounds.[47] An *ansa*-zirconocene has been synthesized in a spirane scaffold using ligand **119**.[48] Spanning diphosphine (SPANphos) ligands **120** with a spirobichroman backbone were reported as cis chelating ligands with Rh-complexes.[49] Spirocyclic N-heterocyclic carbenes (NHCs) **121** and **122** have been reported in the past year.[50]

Spiro amino alcohol **123** and spiro dione **124** have been used as chiral auxiliaries in asymmetric Diels–Alder reactions.[51] Fructose-derived ketone **125** has been applied to the asymmetric epoxidation of *trans*-olefins.[52]

We recently reported the first example of spiro crown ethers **126** bearing (*S*)-1,1′-spirobiindane as a chiral backbone and used them as phase-transfer catalysts.[53] Heating (*S*)-SPINOL **85a** with 3,6,9,12-tetraoxatetradecamethylene di-*para*-toluenesulfonate in the presence of *tert*-BuOK readily produced (*S*)-**126**. The combination of (*S*)-**126** and KOH promoted the asymmetric alkylation of glycine derivative **127** with benzyl bromide in moderate enantioselectivity (Scheme 31).

More recently, we reported a novel chiral imidazolium salt **129** with a spiro skeleton as chiral ionic liquid and the chiral discrimination abilities were investigated.[54]

8. Conclusion

In the research of asymmetric catalysis, the search for efficient chiral ligands is a central issue. Furthermore, the development of new chiral ligands is a most challenging task where many aspects have to be considered, such as: (a) design of ligand with an appropriate scaffold, (b) economical short step synthesis, (c) formation of a number of diastereomers, separation and resolution, (d) reacting sites, (e) an effective asymmetric environment, (f) ease of ligand modification, etc.

Synthetic chemists who are involved in asymmetric metal catalysis, have used chiral diphosphine ligands with a biaryl scaffold as their first choice. Recently, the use of other types of ligands, such as nitrogen-containing oxazoline ligands, has gained great attention. On the process of development of asymmetric synthesis, new chiral ligands are continuously appearing. In 1997, the pioneering work by Chan and Jiang using spiro bis(phosphinite) ligands (SpirOP) for the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives initiated the search for alternative chiral ligands with a spiro skeleton. At the same time, we realized that spiro ligands can emerge as a new class of chiral ligands in asymmetric catalysis and entered in this field to develop chiral spiro ligands bearing nitrogen-containing heterocycles. In 1999, we reported the first example of chiral spiro bis(isoxazoline) (SPRIX) ligands. We have shown the unusual reactivity and efficiency of SPRIX in Pd^{II}-catalyzed asymmetric oxidative cyclizations. It has been revealed that only Pd^{II}–SPRIX catalysts promote Wacker-type cyclization of alkenyl alcohols, tandem cyclization via oxy-palladation, and aminocarbonylation reactions. The Pd^{II}–SPRIX catalyst system has been found to be efficient in several interesting oxidative cyclizations for the enantioselective synthesis of valuable biologically important heterocycles. We have also developed a highly efficient SPRIX-based dicationic Pd^{II} complex for the enantioselective synthesis of polyketones through alternating copolymerization of CO with styrene derivatives. We have synthesized several novel chiral spiro ligands containing variously substituted N-heterocycles such as isoxazoline, isoxazole, isoxazole–isoxazoline, oxazoline, and pyrazole. These ligands were efficiently coordinated with Pd^{II}, Ni^{II}, and Cu^{II} complexes. Xie and Zhou have developed a number of chiral spiro ligands with a 1,1′-spirobiindane backbone and demonstrated their usefulness in metal-catalyzed asymmetric reactions.[55] The dramatic increment in number of publications that have appeared in the last

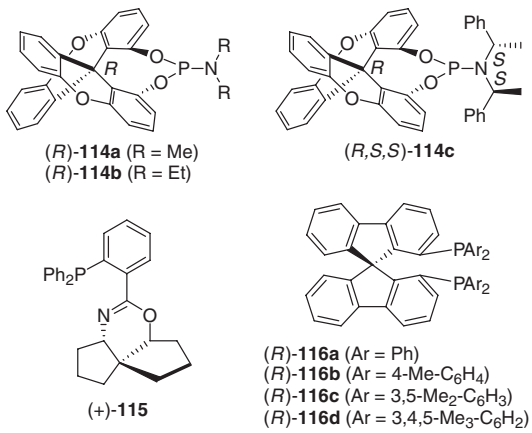
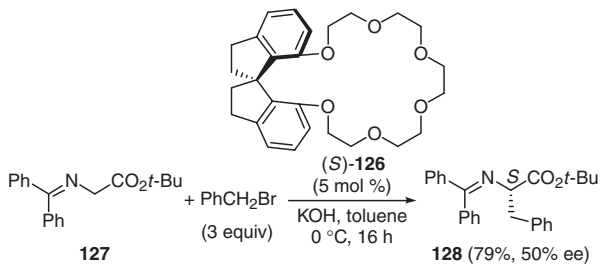


Figure 14. Miscellaneous spiro ligands.



Scheme 31.

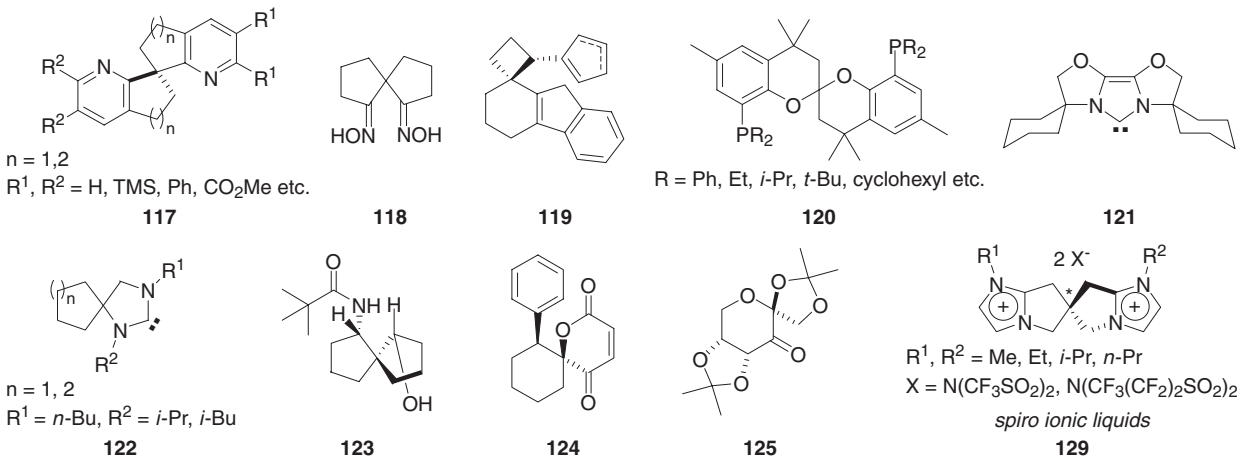


Figure 15. Spiro compounds that displayed coordinating ability.

five years, describing novel design and synthesis of chiral spiro ligands and their utility in metal-catalyzed asymmetric reactions, shows the rapid growth of this research area. Many additional applications of the spiro ligands undoubtedly will be forthcoming.

We gratefully acknowledge financial support of our own research to develop chiral spiro compounds by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. G.B.B. thanks the Japan Society for the Promotion of Science (JSPS) for a post-doctoral research fellowship. We are indebted greatly to co-workers, whose names are shown in the references of our publications.

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