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Design and synthesis of chiral hybrid spiro (isoxazole–isoxazoline) ligands

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Abstract—Novel chiral hybrid ligands containing an unsymmetrical spiro[4.5]decane skeleton with isoxazole and isoxazoline as the two coordinating units have been synthesized. Pd complexes of these ligands were found to be effective in activating olefins towards enantioselective tandem cyclization of a dialkenyl alcohol, providing the cyclized products in up to 97% ee.

1. Introduction

The chiral spiro skeleton has gained much attention from synthetic chemists over the past decade; a family of ligands based on a spiro skeleton with various coordinating units was recently reported.[1] We have been investigating the utility of a spiro skeleton in the design of ligands and have developed several spiro ligands,[2] namely, spiro bis(isoxazolines) (SPRIXs) (Fig. 1),[2a,b,f] spiro bis(isoxazoles),[2c] spiro bis(oxazolines)[2d] and spiro bis(pyrazoles).[2e] An unprecedented enantioselective tandem reaction, in which a dialkenyl alcohol was converted into a unique bicyclic ether via an oxy-palladation process, was achieved in the presence of Pd–SPRIX complex.[3] Interestingly, no previously known catalysts, including $Pd(OCOCF_3)_2$-bis(oxazolinyl) propane,[4] $Pd(OCOCF_3)_2$-(*S*,*S*)-ip-boxax,[5] $Pd(OCOCF_3)_2$-(−)-sparteine,[6] and $[(3,2,10\text{-}\eta^3\text{-pinene})\text{-}PdOAc]_2$[7] could promote this reaction.[3,8] We reasoned that all ligands in these catalysts have a stronger coordinating ability than SPRIX and suppress the Lewis acidity of the catalysts. A weaker coordinating ligand, such as SPRIX, restores the Lewis acidity at the metal centre thus making it more reactive under mild conditions. However chiral spiro bis(isoxazole) ligands, which have weaker coordinating ability than SPRIX, were ineffective to promote the tandem reaction.[2c] Thus it was thought that a combination of weakly coordinating groups and rigidity would be of optimum benefit in the design of new ligands.

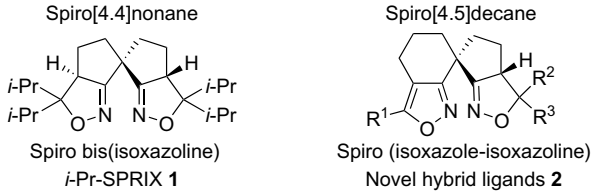

Figure 1. Structure of *i*-Pr-SPRIX and spiro (isoxazole–isoxazoline) ligand.

2. Results and discussion

Herein, we report the design and synthesis of hybrid ligand **2** (Fig. 1), which contains two different coordinating units, isoxazole and isoxazoline, brought together by virtue of a spiro backbone. The distance between two nitrogen atoms of isoxazole and isoxazoline rings plays an important role in acting synergistically for binding with the metal centre. An optimum flexibility of rigid spiro backbone for a bidentate coordination to form a square planar metal complex is equally important. In the search for a suitable ligand, a computational study of varying ring size was carried out to calculate the distance between the two nitrogens.[9] The study revealed that the spiro[4.5]decane skeleton was the most suitable design, with the isoxazole and isoxazoline rings fused to the 6 and 5 membered spiro rings, respectively. In this particular arrangement, the two coordinating nitrogens are placed at an optimum distance for bidentate

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coordination. Replacement of one of the isoxazoline rings in SPRIX with isoxazole alters the coordinating ability, while replacing the spiro[4.4]nonane skeleton with a spiro[4.5]decane skeleton imparts more flexibility to the system, allowing for a bidentate coordination. It was anticipated that in this new design of hybrid ligands, only two diastereomers would be generated. This is advantageous, since in the case of the synthesis of SPRIX ligands, three diastereomers were obtained.[2a,3]

The synthesis of hybrid spiro (isoxazole–isoxazoline) ligands was based on a flexible approach (Scheme 1).[10] Different combinations of alkenyl bromides **4** and alkynyl iodides **5** were used for the alkylations of diethyl malonate **3** to obtain the differentially substituted diesters **6**. Diesters **6** were subsequently converted into dioximes **7** via $LiAlH_4$ reduction and Swern oxidation, followed by treatment with hydroxylamine hydrochloride. The final step involves an intramolecular double nitrile oxide cycloaddition of the dioxime with the alkyne and olefin moieties to furnish the spiro skeleton together with the isoxazole and isoxazoline rings in single operation. The pronounced advantage associated with the synthetic method is the diastereoselectivity in the last step; the diastereomer obtained in excess is the required one (Table 1).[11] Thus, novel hybrid ligands **2a**–**e** were synthesized with varying steric demands.[12] The new design of hybrid ligands resulted in a better synthetic route for obtaining the desired diastereomer as compared to that of SPRIX.[2a,3]

The relative configuration of the spiro skeleton was confirmed by X-ray analysis of **2c** (Fig. 2).[13] The distance between the two nitrogens was found to be 3.71 Å, which is in good agreement with the calculated values using HF/6-31G* (3.63 Å, when $R^1 = R^2 = R^3 = Me$). Enantiomerically pure ligands were obtained by separation using chiral stationary phase HPLC.[14] In an NMR tube, when 1 equiv of *i*-Pr-SPRIX **1** was added to a solution of precomplexed $Pd(OCOCF_3)_2$ and **2d** in CD_2Cl_2/CD_3OD (9:1), the formations of free **2d** and Pd–*i*-Pr-SPRIX complex were observed by ^1H NMR, which indicated that *i*-Pr-SPRIX **1** has a higher coordinating ability when compared to hybrid spiro (isoxazole–isoxazoline) ligand **2d**. This observation proved our hypothesis of the ligand design as expected to make it less coordinating than that of SPRIX.

Table 1. Results of double nitrile oxide cycloaddition reaction of dioxime **7**

Entry	R^1	R^2	R^3	Yield[a] (%)	Ratio of **2**:**2′**[b]
1	H	H	H	77	**2a**:**2a′** (78:22)
2	Et	H	Et	66	**2b**:**2b′** (78:22)
3	Me	Me	Me	65	**2c**:**2c′** (71:29)
4	H	*i*-Pr	*i*-Pr	68	**2d**:**2d′** (70:30)
5	*t*-Bu	*i*-Pr	*i*-Pr	60	**2e**:**2e′** (80:20)

[a] Total isolated yield.
[b] Determined after separation by column chromatography.

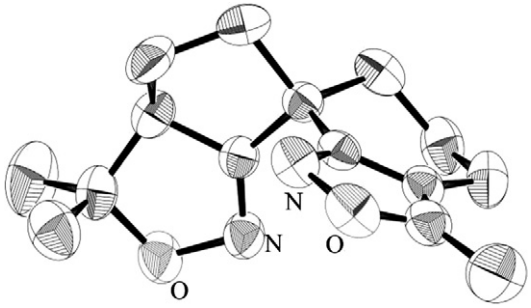
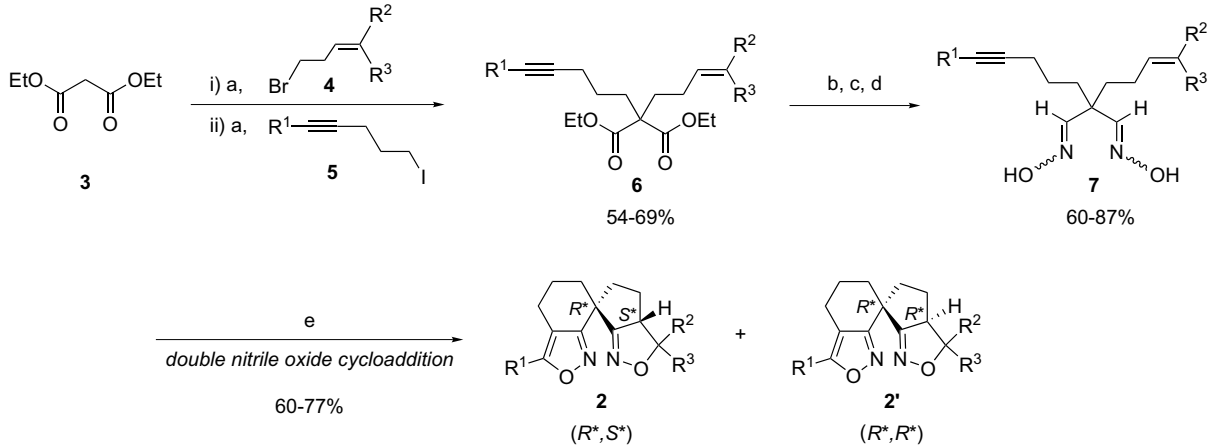


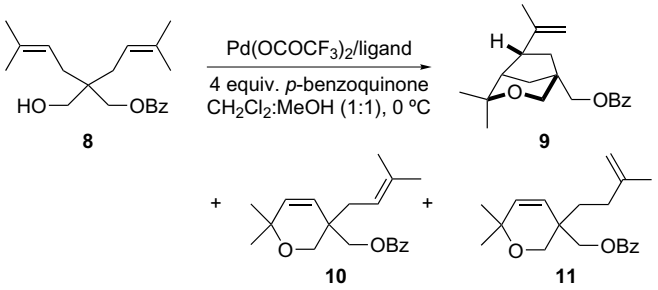
Figure 2. X-ray crystal structure of **2c** showing the spiro skeleton (N–N = 3.71 Å).

The major diastereomers **2** in their enantiopure form were used in the Pd-catalyzed tandem cyclization of dialkenyl alcohol **8**.[3] Standard conditions were applied for the cyclization of **8** at 0 °C.[15] In a controlled reaction without using ligand at room temperature, low yields of cyclic products **9**, **10** and **11** were obtained, where monocyclic product **10** was formed as the major product (22%) (Table 2, entry 1). No reaction took place at 0 °C. However, in the presence of hybrid ligands, the reactions were clearly accelerated even at 0 °C, highlighting the ability of these ligands to fine-tune the properties of the metal. Under the standard conditions, when **2a** was employed, **9** was obtained with a moderate



Scheme 1. Synthetic route of novel spiro (isoxazole–isoxazoline) ligands. Reagents and conditions: (a) NaH (1 equiv), THF, 0 °C then rt; (b) $LiAlH_4$, THF, 0 °C then rt; (c) Swern oxidation. $(COCl)_2$, CH_2Cl_2, DMSO, −78 °C, Et_3N; (d) $NH_2OH{\cdot}HCl$, Py, 0 °C then rt; (e) aq NaOCl, CH_2Cl_2, 0 °C then rt.

Table 2. Pd-catalyzed tandem cyclization of **8** (ligand screening)[a]



Entry	Ligand	Time (h)	Yield (%)			ee of **9**[d] (%)
			9[b]	**10**[c]	**11**[c]	
1[e]	None	15	9	22	3	—
2	**2a**	72	34	14	33	66
3	**2b**	48	47	7	39	69
4	**2c**	21	54	2	32	87
5	**2d**	17	59	5	23	97
6	**2e**	17	74	0	25	95
7	**1**	24	88	3	8	82
8[f]	**1**	85	65	5	26	95

[a] The reaction of **8** (47 μmol) was carried out in the presence of *p*-benzoquinone (4 equiv) using the catalyst prepared in situ with 20 mol % $Pd(OCOCF_3)_2$ and 24 mol % ligand in CH_2Cl_2/MeOH (1:1) (0.05 M) at 0 °C under argon unless otherwise noted.
[b] Isolated yield.
[c] Calculated yield based on the NMR analysis of inseparable mixture of **10** and **11**.
[d] Determined by HPLC [Daicel Chiralpak AD column, hexane/*i*-PrOH (120:1)].
[e] Conducted at room temperature.
[f] CH_2Cl_2 was used as the solvent.

enantiomeric excess of 66% (entry 2). The use of ligands **2b**, **2c** and **2d** led to the improvement of the enantiomeric excess to 69%, 87% and 97%, respectively, while at the same time the yield was also improved (entries 3–5). The best result was obtained when ligand **2e** was used (74% yield of **9**, 95% ee) (entry 6).

Improvements in product yield and the enantiomeric excess were observed as the steric bulk at R^2 and R^3 positions was increased, from ligand **2a** (no substituent) to **2e** (di-*i*-Pr substituent). Comparison of these results with those obtained using *i*-Pr-SPRIX **1** revealed that the use of **2e** improved enantioselectivity while maintaining high product yield (Table 2, entries 6–8).[3] In addition, the use of ligand **2e** afforded only two products **9** and **11**, avoiding production of the β-elimination product **10**.[16] In a separate experiment pure compounds **9** (95% ee), **10** and **11** were subjected individually to the standard reaction conditions; analysis after 12 h showed that the products maintained the same level of enantioselectivity and were recovered essentially in the same amount. Thus the products, once formed, are stable under the reaction conditions and no interconversion among either of them is possible. A time course study showed that the enantiomeric excess of product **9** remains constant throughout the reaction.[17] The ligand could be recovered (80%) after reaction completion, showing that the ligand did not undergo any structural change during the reaction. The reaction was found to be very sensitive to the Pd source used.[18] The amount of *p*-benzoquinone could be reduced to 1 equiv without any loss of enantioselectivity. Oxygen could also be utilized as an oxidant.[19] However, a slightly decreased reactivity was observed and the yield of **9** was compromised (**9**, **10**, **11** = 54%, 0%, 44%, respectively). Nevertheless **9** was obtained with 87% ee.

3. Conclusion

In conclusion, a novel unsymmetrical hybrid spiro (isoxazole–isoxazoline) ligand has been designed, synthesized and shown to efficiently promote a Pd-catalyzed tandem cyclization under mild conditions. This new, weakly coordinating ligand was shown to clearly accelerate the cyclization reaction and was compared with the previously used ligand. Further investigations of possible applications of these ligands in development of asymmetric reactions are currently underway and will be reported in due course.

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9. Structures with various combinations of ring size such as spiro[4.4]nonane, spiro[4.5]decane and spiro[4.6]undecane having unsubstituted isoxazole and isoxazoline moieties were optimized using HF/6-31G*. The optimized structures of these spiro skeletons, in which five membered spiro ring bearing isoxazoline unit, showed the N–N distance of 3.76, 3.35 and 3.87 Å, respectively, for the *R**,*S** diastereomer, and 4.21, 4.01, 4.32 Å, respectively, for the *R**,*R** diastereomer.
10. Concise procedure for the synthesis of hybrid ligands: (a) Diethyl malonate (**3**) was added to a suspension of 60% NaH (1 equiv) in THF at 0 °C. Alkenyl bromide **4** (1 equiv) was added to the solution and allowed to warm to rt. After completion, the reaction was quenched with saturated aq NH_4Cl and extracted with EtOAc. Mono alkenylated product was obtained from the organic layer, after column chromatography. The second alkylation of the mono alkenylated compound was carried out in a similar manner using alkynyl iodide **5** (1 equiv) to give **6**. (b) Diester **6** was reduced with $LiAlH_4$ as usual to produce the diol. (c) The diols were converted into dialdehydes by Swern oxidation. To a solution of $(COCl)_2$ (3.8 equiv) in CH_2Cl_2 was slowly added a solution of DMSO (5.8 equiv) in CH_2Cl_2 at −78 °C and stirred for 40 min. A solution of the diol in CH_2Cl_2 was added and further stirred for 40 min. Et_3N (9 equiv) was then added and allowed to stirred at rt for 1.5 h. After quenching with saturated aq NH_4Cl, the reaction mixture was extracted with CH_2Cl_2 to give crude dialdehyde. (d) The dialdehyde was dissolved in pyridine and treated with $NH_2OH{\cdot}HCl$ (10 equiv) at 0 °C. The reaction mixture was stirred at rt for 6 days with additions of additional $NH_2OH{\cdot}HCl$ (5 equiv) per day. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$ and brine. Dioxime **7** was obtained from the organic layer after purification by silica gel column chromatography. (e) Finally, a solution of dioxime **7** in CH_2Cl_2 was treated with aq NaOCl (2.3 equiv) at 0 °C and the mixture stirred overnight at rt. The reaction was quenched with water and extracted using CH_2Cl_2. The resulting diastereomers **2** and **2′** were easily separated by silica gel column chromatography.
11. The required diastereomer was identified based upon complexation studies of the two diastereomers **2d** and **2d′**. The major diastereomer **2d** formed a single species upon complexation with $Pd(OCOCF_3)_2$. While, the minor diastereomer **2d′** was unable to coordinate in a bidentate fashion to palladium as observed in NMR experiment and GPC analysis. For the other hybrid ligands, the analogy in ^1H NMR analyses and TLC behaviour was used to identify the required diastereomer.
12. Analytical data for both the diastereomers of ligands: *(R*,S*)-3′,3a′,4′,5,5′,6-Hexahydro-4H-spiro[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2a**: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.60–2.45 (m, 7H), 2.50–2.72 (m, 1H), 2.84–2.88 (m, 2H), 3.95–3.97 (m, 2H), 4.55–4.56 (m, 1H), 8.12 (t, $J = 1.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 18.3, 20.1, 27.7, 34.7, 39.0, 44.9, 54.6, 75.3, 114.0, 153.4, 163.8, 175.5. FAB-HRMS calcd for $C_{12}H_{15}N_2O_2$ [M+H$^+$]: 219.1134. Found: 219.1150. Mp 167 °C (recrystallization from hexane/ether). $[\alpha]_D^{29} = -134$ (*c* 0.11, $CHCl_3$) (first peak of HPLC).
(R,R*)-3′,3a′,4′,5,5′,6-Hexahydro-4H-spiro[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2a′**: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.60–2.72 (m, 10H), 2.85–3.92 (m, 1H), 4.25–4.35 (m, 1H), 4.55–4.62 (m, 1H), 8.12 (t, $J = 1.08$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 18.4, 20.6, 25.9, 33.7, 38.8, 44.9, 54.6, 75.3, 114.1, 153.4, 163.0, 174.0. FAB-MS [M+Na$^+$]: 219.2.
(R,S*)-3,3′-Diethyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2b**: ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (t, $J = 7.29$ Hz, 3H), 1.20 (t, $J = 7.29$ Hz, 3H), 1.25–1.40 (m, 1H), 1.60–2.45 (m, 9H), 2.60–2.72 (m, 4H), 3.82–3.93 (m, 1H), 4.38–4.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 10.3, 11.4, 18.6, 19.5, 20.2, 22.8, 23.7, 34.4, 39.2, 45.5, 56.9, 84.8, 108.7, 165.1, 167.8, 174.8. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.68; H, 8.05; N, 9.96. FAB-HRMS Calcd for $C_{16}H_{23}N_2O_2$ [M+H$^+$]: 275.1760; found, 275.1730. Mp 106 °C (recrystallization from hexane/ether). $[\alpha]_D^{29} = -186$ (*c* 0.10, $CHCl_3$) (first peak of HPLC).
(R,R*)-3,3′-Diethyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2b′**: ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (t, $J = 7.56$ Hz, 3H), 1.18 (t, $J = 7.56$ Hz, 3H), 1.22–1.58 (m, 2H), 1.6–1.78 (m, 2H), 1.80–2.45 (m, 6H), 2.46–2.62 (m, 4H), 4.11–4.18 (m, 1H), 4.38–4.47 (m, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 10.5, 11.5, 18.7, 19.5, 20.5, 20.6, 23.8, 29.7, 33.7, 39.1, 44.3, 56.5, 84.2, 109.0, 164.0, 168.0, 173.1. FAB-MS [M+H$^+$]: 275.
(R,S*)-3,3′,3′-Trimethyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro-[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2c**:^1H NMR ($CDCl_3$, 270 MHz) δ 1.26 (s, 3H), 1.53 (s, 3H), 1.70–2.40 (m, 11H), 2.40–2.80 (m, 2H), 3.60–3.64 (m, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 10.9, 18.4, 20.1, 22.2, 22.9, 26.3, 34.1, 39.7, 45.2, 61.9, 87.7, 109.5, 163.1, 164.8, 176.2. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found:C, 68.83; H, 7.60; N, 10.53. FAB-HRMS calcd for $C_{15}H_{21}N_2O_2$ [M+H$^+$]: 261.1603; found, 261.1587. Mp 101 °C (recrystallization from hexane/ether). $[\alpha]_D^{29} = -202$ (*c* 0.095, $CHCl_3$) (first peak of HPLC).
(R,R*)-3,3′,3′-Trimethyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro-[2,1-benzisoxazole-7,6′-3cyclopenta[c]isoxazole]* **2c′**:^1H NMR ($CDCl_3$, 270 MHz) δ 1.23 (s, 3H), 1.53 (s, 3H), 1.7–2.4 (m, 8H), 2.25 (s, 3H), 2.40–2.80 (m, 2H), 3.84 (t, $J = 9.45$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 11.1, 18.7, 20.5, 20.9, 22.3, 27.0, 33.5, 39.9, 44.3, 61.7, 87.5, 109.9, 163.4, 163.9, 174.5. FAB-MS [M+H$^+$]: 261.
(R,S*)-3′,3′-Diisopropyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro-[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2d**: ^1H NMR

($CDCl_3$, 270 MHz) δ 0.91–1.06 (m, 12H), 1.70–2.50 (m, 10H), 2.60–2.90 (m, 2H), 3.75–3.82 (m, 1H), 8.10 (t, $J = 1.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 17.7, 18.2, 18.3, 18.6, 18.8, 20.1, 23.9, 31.3, 31.8, 35.2, 39.1, 44.9, 55.6, 95.7, 114.1, 153.3, 163.8, 172.7. Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.10; H, 8.46; N, 8.97. FAB-HRMS Calcd for $C_{18}H_{27}N_2O_2$ [M+H$^+$]:303.2073; found, 303.2095. Mp 116 °C (recrystallization from hexane/ether).$[\alpha]_D^{29} = -178$ (c 0.11, $CHCl_3$) (first peak of HPLC).

(R,R*)-3′,3′-Diisopropyl-3′,3a′,4′,5,5′,6-Hexahydro-4H-spiro-[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2d′**: ^1H NMR($CDCl_3$, 270 MHz) δ 0.91–1.06 (m, 12H), 1.70–2.50 (m, 10H), 2.60–2.90 (m, 2H), 4.20 (t, $J = 9.72$ Hz, 1H), 8.10 (t, $J = 1.08$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 17.3, 17.9, 18.2, 18.5, 18.7, 20.7, 21.2, 31.7, 33.7, 39.3, 44.1, 54.7, 96.0, 114.0, 153.2, 163.6, 171.7. FAB-MS [M+H$^+$]: 303.

(R,S*)-3-tert-Butyl-3′,3′-diisopropyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2e**: ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90–1.11 (m, 12H), 1.2 (s, 9H), 1.71–2.60 (m, 10H), 2.79–2.87 (m, 2H), 3.76–3.81 (m, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 17.8, 18.4, 18.7, 18.8, 20.4, 20.5, 23.9, 28.6, 31.2, 31.7, 33.8, 34.8, 39.4, 45.2, 55.6, 95.5, 107.5, 164.7, 172.5, 172.8. Anal. Calcd for $C_{22}H_{34}N_2O_2$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.38; H, 9.63; N, 7.41. FAB-HRMS Calcd for $C_{22}H_{35}N_2O_2$ [M+H$^+$]: 359.2699; found, 359.2680. Mp 131 °C (recrystallization from hexane/ether). $[\alpha]_D^{29} = -114$ (c 0.10, $CHCl_3$) (first peak of HPLC).

(R,R*)-3-tert-Butyl-3′,3′-diisopropyl-3′,3a′,4′,5,5′,6-hexahydro-4H-spiro[2,1-benzisoxazole-7,6′-cyclopenta[c]isoxazole]* **2e′**: ^1H NMR ($CDCl_3$, 270 MHz) δ 0.80–1.11 (m, 12H), 1.38 (s, 9H), 1.71–2.60 (m, 10H), 2.60–2.68 (m, 2H), 4.2 (t, $J = 9.72$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 17.4, 17.9, 18.3, 18.7, 20.5, 20.9, 21.1, 28.6, 31.6, 33.1, 33.8, 39.6, 44.2, 54.8, 55.2, 95.9, 107.3, 164.5, 172.0, 172.7. FAB-MS [M+H$^+$]: 359.

13. Crystallographic data (excluding structure factors) for the structure **2c** in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 640619. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. The absolute configurations of ligands **2** and **2′** were not determined.
14. Conditions for HPLC separation [Daicel Chiralpak AD column (2 cm $\Phi \times 25$ cm)]: Compound **2a**; hexane/EtOH (7:3), flow rate = 2.5 mL/min, 34 min, 48 min. Compound **2b**: hexane/*i*-PrOH (9:1), flow rate = 2.5 mL/min, 21 min, 33 min. Compound **2c**: hexane/*i*-PrOH (9:1), flow rate = 2.5 mL/min, 14 min, 22 min. Compound **2d**: hexane/*i*-PrOH (9:1), flow rate = 2.5 mL/min, 10 min, 16 min. Compound **2e**: hexane/*i*-PrOH (9:1), flow rate = 2.5 mL/min, 8 min, 14 min.
15. General procedure for the cyclization of substrate **8**: $Pd(OCOCF_3)_2$ (3.1 mg, 9.4 μmol) and ligand (*R**,*S**) **2e** (4.0 mg, 11.3 μmol) were stirred in 1:1 mixture of CH_2Cl_2/MeOH (0.9 mL, 0.05 M) for 2 h under argon to allow complexation. *p*-Benzoquinone (20.3 mg, 4 equiv) and alkenyl alcohol **8** (15.0 mg, 47 μmol) were added to the complex solution at 0 °C, and the reaction mixture was stirred until the starting material was consumed. After completion, the reaction was quenched by the addition of water, extracted with ethylacetate (3 × 7 mL), washed with brine, dried over Na_2SO_4 and concentrated to obtain the crude mixture. Purification of the products was carried out by silica gel column chromatography [hexane/ethylacetate (30:1)] to give the tandem product **9** (11.0 mg, 74%, 95% ee) and **11** (3.7 mg, 25%). Ee of **9** was determined by HPLC analysis using a chiral stationary phase column [Daicel Chiralpak AD, hexane/*i*-PrOH (100:1)], flow rate = 0.5 mL/min, 16 min and 21 min. The absolute configuration of product **9** was not determined. In the cases of the formation of inseparable monocyclized products **10** and **11**, the ratio was determined by ^1H NMR.
16. A plausible mechanism of the tandem cyclization is discussed in Ref. 3.
17. The ee of product **9**, checked after 2, 8 and 12 h, was found to be constant (95%).
18. The use of $PdCl_2$, $Pd(OAc)_2$, $Pd(acac)_2$ and $Pd(hfacac)_2$ afforded products both in lower yields and ee. Electronically deficient Pd source such as $[Pd(CH_3CN)_4](BF_4)_2$ and $Pd(OCOCF_3)_2$ proved to be the best Pd sources.
19. Reaction conditions: 20 mol % $Pd(OCOCF_3)_2$, 24 mol % ligand **2e**, substrate **8** (47 μmol), 3 Å MS (500 mg/mmol), oxygen balloon (1 atm), CH_2Cl_2/MeOH (1:1), rt, 192 h.