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SPIRO BIS(ISOXAZOLE) AS A NEW CHIRAL LIGAND

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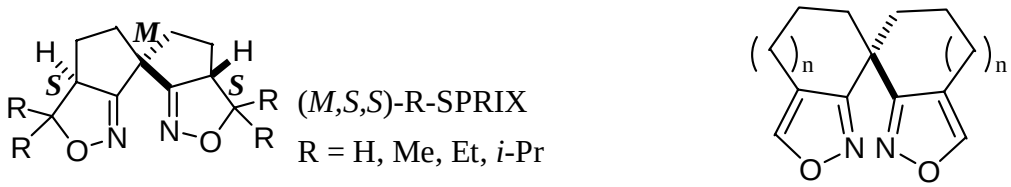
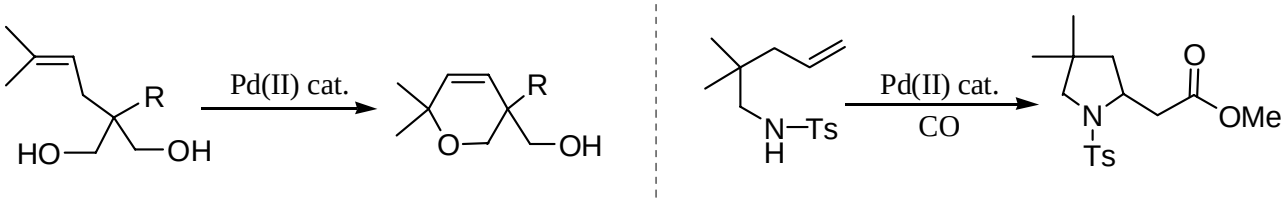
Abstract – A novel bis(isoxazole) ligand, (*M**)-4,4',5,5',6,6',7,7'-octahydro-7,7'-spirobi[benzo[*c*]isoxazole] (**5**) bearing a spiro chirality was designed and synthesized. Characterization of the ligand and its application to the enantioselective tandem cyclizaton of alkenyl alcohol *via* oxy-palladation are described.

Recently, transition metal-catalyzed asymmetric reactions have acquired prominence in synthetic organic chemistry. The design of optically active ligands which have both strong affinity for metal and a chiral backbone to construct an effective asymmetric environment is the key to the development of new enantioselective reactions.[1] Since a chiral spiro skeleton is quite rigid and able to possess unique chirality, several applications of asymmetric spiro ligands have been reported.[2] We have so far reported the novel spiro bis(isoxazoline) ligands (SPRIXs) (Figure 1) bearing a chiral spiro skeleton and two isoxazoline rings, and demonstrated the first example for the use of an isoxazoline ligand in transition metal-catalyzed enantioselective reaction.[3a] Utilizing the good affinity of SPRIXs to Pd(II) salts and the

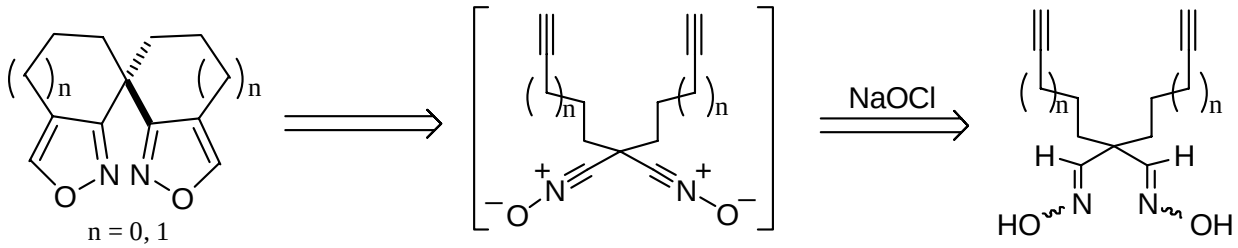


(*M*,*S*,*S*)-R-SPRIX
R = H, Me, Et, *i*-Pr

Figure 1. Spiro bis(isoxazoline) ligands (SPRIXs) and a new spiro bis(isoxazole) ligand



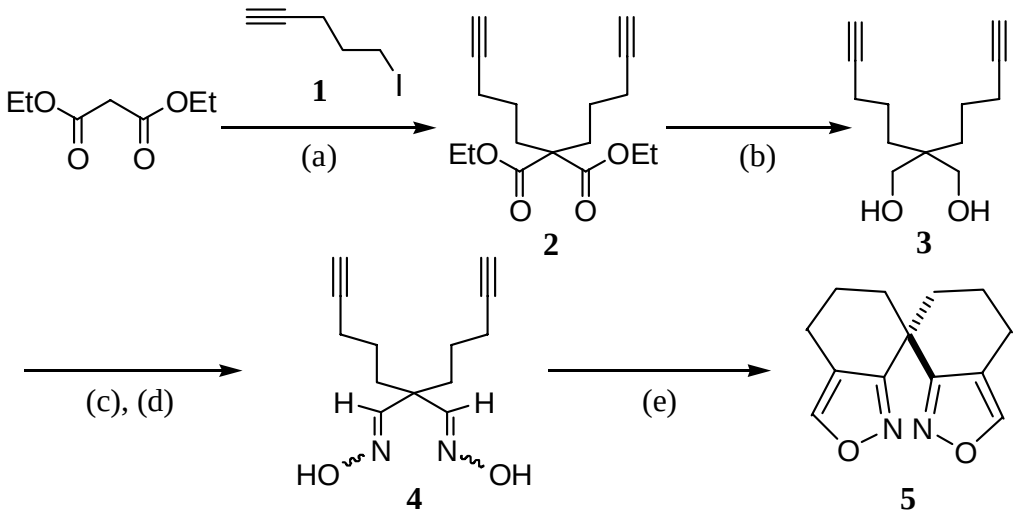
Scheme 1. Pd(II)-catalyzed enantioselective Wacker-type cyclization and aminocarbonylation



Scheme 2. Design of a new spiro bis(isoxazole) ligand

stability of SPRIXs under oxidative conditions, we developed the first enantioselective Wacker-type cyclization of alkenyl alcohols and enantioselective aminocarbonylation of alkenyl amides promoted by Pd(II)-SPRIX catalysts (Scheme 1).[3b,c] Interestingly, these cyclizations are not promoted by hitherto known ligands such as BINAP, bis(oxazolinyl)propane,[4,5] and boxax.[6] We have already reported that the isoxazoline moieties play a crucial role in accelerating these reactions.[3d,7] Having been encouraged by these results using SPRIXs, we designed a new type of spiro ligands. Herein, we report the first synthesis, characterization and applicaton of spiro bis(isoxazole) ligand (Figure 1) which has a single chiral center and two isoxazole units in the molecule.

Isoxazoles are important compounds as synthetic intermediates for functionalized building blocks as well as isoxazolines.[8] Although the coordination chemistry of isoxazoles has been studied,[9,10] no example of their application as a ligand to enantioselective reactions has been reported. For the design of new ligand containing isoxazole, we selected a spiro[5.5]undecane skeleton (n=1 in Scheme 2) which would coordinate to metals in a bidentate manner because of its more appropriate flexibility than that of a spiro[4.4]nonane skeleton. The isoxazole units would exhibit similar affinity toward Pd(II) salts as that



(a) 60% NaH, **1**, DMSO, rt: 97%; (b) $LiAlH_4$, THF, rt: 92%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (d) NH_2OH-HCl, Py, rt: 85% (2 steps); (e) 5% aq. NaOCl, CH_2Cl_2, rt: 67%.

Scheme 3. Synthesis of the spiro bis(isoxazole) ligand (**5**)

of the isoxazoline units of SPRIXs. The ligand (**5**) was synthesized through double intramolecular nitrile oxide cycloaddition as a key reaction, which could construct two isoxazole rings and a spiro backbone in one step (Scheme 2).

The synthesis of spiro bis(isoxazole) ligand (**5**) is shown in Scheme 3. Diethyl malonate was treated with 2 equiv. of 60% NaH and 5-iodopent-1-yne (**1**) successively to afford diethyl 2,2-di(pent-4-ynyl)malonate (**2**) in 97% yield. The malonate (**2**) was reduced with $LiAlH_4$ to give the diol (**3**) in 94% yield. After the Swern oxidation of **3**, the resulting dialdehyde was treated with NH_2OH in pyridine without further purification. The dioxime (**4**) was obtained in 85% yield from **3** in 2 steps. Treatment of dioxime (**4**) with 5% aq. NaOCl afforded the desired spiro bis(isoxazole) ligand, (*M**)-4,4',5,5',6,6',7,7'-octahydro-7,7'-spirobi[benzo[*c*]isoxazole] (**5**) *via* the double intramolecular nitrile oxide cycloaddition in 67% yield. The ligand (**5**) is stable to air and moisture at rt. The structure of racemic **5** was unequivocally determined by X-Ray crystallographic analysis (Figure 2).[11] Optical resolution of **5** was performed with chiral stationary phase column chromatography.

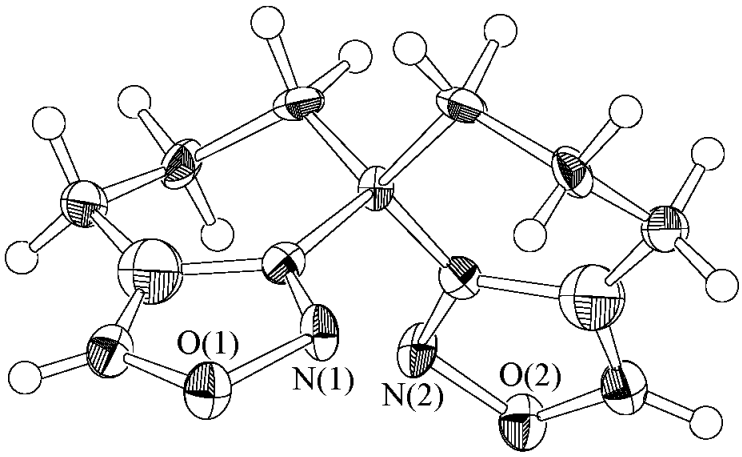
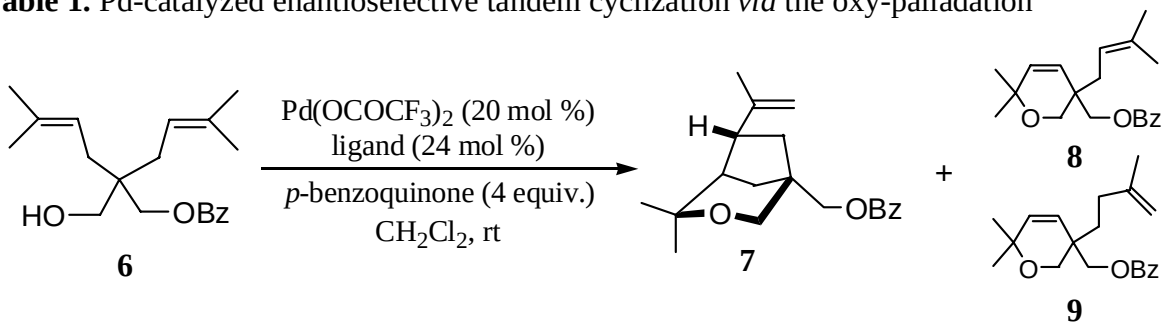


Figure 2. ORTEP drawing of spiro bis(isoxazole) ligand (**5**)

Next, we compared the catalyst activity of the Pd(II)-**5** complex with that of Pd(II)-SPRIX in the tandem cyclization of alkenyl alcohol (**6**) as shown in Table 1. The Pd(II)-SPRIX complex promoted the reaction to afford bicyclic product (**7**) as a single diastereomer with 93% ee, together with monocyclized compounds (**8**) and (**9**) (entry 2). When the reaction was carried out using Pd(II)-**5**, the reaction proceeded to give the cyclized products in 74% yield, including the tandem product (**7**) with 56% ee (entry 3). Since the reaction without ligand gave only 34% yield even after 67 h (entry 1), this result obviously indicated that Pd(II)-**5** complex has the ability to accelerate the Wacker-type cyclization. In comparison with the result of Pd(II)-SPRIX, the ratio of the tandem product (**7**) was reduced by using Pd(II)-**5**. This result suggested that alkylpalladium intermediate attached to Pd(II)-**5** in the second

Table 1. Pd-catalyzed enantioselective tandem cyclization *via* the oxy-palladation[a]



entry	ligand	time (h)	yield (%)[b]	product ratio (ee (%))		
				7[c]	**8**[c]	**9**[c]
1	none	67	34	26	66	8
2[d]	(*M, S, S*)-*i*-Pr-SPRIX	8	73	57 (93)	20 (31)	23 (48)
3	(+)-**5**	17	74	36 (56)	58 (14)	6 (17)

a) Reactions were carried out using 20 mol % of $Pd(OCOCF_3)_2$ and 24 mol % of ligand in the presence of *p*-benzoquinone as a re-oxidant at rt. b) Total yield of Wacker-type cyclization products. c) Absolute configurations of the cyclized products have not been determined. d) The reaction at 0 ^oC for 85 h gave **7** (65%, 95% ee), **8** (5%, 45% ee), and **9** (26%, 60% ee).

cyclization step might readily undergo β-hydride elimination because of the flexibility of spiro[5.5]undecan skeleton of **5**.[12]

In conclusion, the first spiro bis(isoxazole) ligand (**5**) has been synthesized, characterized and shown to act as a chiral ligand for enantioselective catalysis. Determination of the absolute configuration of (+)-**5** using X-Ray crystallographic analysis of Pd(II)-**5** complex, introduction of substituents to the isoxazole rings for the construction of more effective asymmetric environment, and development of new enantioselective reactions using these ligands are in progress.

EXPERIMENTAL

General procedures

^1H and ^{13}C NMR spectra were recorded on JEOL JNM-EX270 (^1H NMR-270 MHz, ^{13}C NMR-67.7 MHz). All signals were expressed as ppm down field from tetramethylsilane used as an internal standard. IR spectra were obtained with SHIMADZU FTIR-8300 instrument. Optical rotations were measured with JASCO P-1030 Polarimeter. Enantiomeric excesses were determined by HPLC analysis equipped with a chiral stationary phase column (DAICEL CHIRALPAK AD). MS spectra were determined on JEOL JMS-600H (FAB-LRMS) and SHIMADZU GCMS-QP 5050A (EI-LRMS).

Elemental analyses were performed with PERKIN-ELMER 2400. X-Ray crystallographic analysis was carried out with RIGAKU AFC-7R, and all calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. Melting point and decomposition point were measured with Yanaco MICRO MELTING POINT APPARATUS MODEL MP-S9. Column chromatography was performed on Kanto Silica Gel 60 (40-100 μm). Merck silica gel 60 F_{254} plates were used for TLC. Anhydrous THF was purchased from Kanto Chemicals, Tokyo. Anhydrous CH_2Cl_2 was distilled from calcium hydride.

Preparation of Diethyl 2,2-Di(pent-4-ynyl)malonate (2) To a suspension of 60% NaH (546 mg, 13.6 mmol) in DMSO (20 mL) was added diethyl malonate (940 μL, 6.20 mmol) slowly, and the mixture was stirred for 30 min. To the mixture was added 5-iodopent-1-yne (**1**) (2.48 g, 13.0 mmol) dropwise through a cannula. After being stirred overnight at rt, the reaction was quenched by the addition of sat. aq. NH_4Cl and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 7/1) to obtain diethyl 2,2-di(pent-4-ynyl)malonate (**2**) (1.76 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.0 Hz, 6H), 1.38-1.49 (m, 4H), 1.95-2.04 (m, 6H), 4.19 (q, *J* = 7.0 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 14.2, 18.8, 23.3, 31.6, 57.0, 61.2, 68.8, 83.6, 171.2. IR (neat): 3292, 2970, 2118, 1724, 1447, 1367, 1300, 1254, 1219, 1175, 1090, 1024, 858, 631 cm^{-1}. FAB-LRMS m/z: 293 $[M+H]^+$. *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.64; H, 8.37.

Preparation of 2,2-Di(pent-4-ynyl)propane-1,3-diol (3) To a solution of **2** (312 mg, 1.06 mmol) in THF (4 mL) was added $LiAlH_4$ (60.3 mg, 1.59 mmol) at 0 °C. The reaction mixture was stirred at rt overnight, quenched by the addition of water (300 μL) to obtain a white precipitate. After being stirred for 1 h, the mixture was filtered through a Celite pad. The filtrate was concentrated, and the residue was chromatographed with silica gel (hexane/ethyl acetate = 1/1) to afford 2,2-di(pent-4-ynyl)propane-1,3-diol (**3**) (208 mg, 94%) as a white solid. mp 60-61 °C (hexane-ether). ^{1}H NMR ($CDCl_3$): δ 1.36-1.56 (m, 8H), 1.97 (t, *J* = 2.3 Hz, 2H), 2.20 (dt, *J* = 6.9, 2.3 Hz, 4H), 2.28 (br s, 2H), 3.58 (br s, 4H). ^{13}C NMR ($CDCl_3$): δ 19.3, 22.2, 30.0, 41.1, 68.6, 68.8, 84.3. IR (neat): 3364, 3304, 2947, 2347, 1460, 1431, 1022, 907, 727, 629 cm^{-1}. FAB-LRMS m/z: 209 $[M+H]^+$. *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.89; H, 9.69.

Preparation of 2,2-Di(pent-4-ynyl)malonaldehyde Dioxime (4) To a solution of $(COCl)_2$ (1.5 mL, 17.1 mmol) in CH_2Cl_2 (13 mL) was added a solution of DMSO (1.7 mL, 23.4 mmol) in CH_2Cl_2 (3 mL) slowly at –78 °C, and the mixture was stirred for 40 min. To the mixture was added a solution of **3** (939

mg, 4.5 mmol) in CH_2Cl_2 (9 mL) dropwise at –78 °C, and the reaction mixture was stirred for 40 min. Et_3N (5.6 mL, 41 mmol) was then added to the reaction mixture at –78 °C. After being stirred for 1.5 h at rt, the reaction was quenched by the addition of sat. aq. NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subsequently dissolved in pyridine (11 mL), and NH_2OH-HCl (3.1 g, 45 mmol) was added at 0 °C. The reaction mixture was stirred for 6 days at rt, to which additional NH_2OH-HCl (625 mg, 9.0 mmol) was added per day. The mixture was diluted with CH_2Cl_2, washed with 1N HCl, sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel chromatography (hexane/ethyl acetate = 3/1 to 2/1) to give 2,2-di(pent-4-ynyl)malonaldehyde dioxime (**4**) (892 mg, 85%) as a white solid. mp 61-63 °C (hexane-ether). ^{1}H NMR ($CDCl_3$): δ 1.48-1.60 (m, 6H), 1.74-1.82 (m, 4H), 1.97 (t, *J* = 2.3 Hz, 2H), 2.20 (dt, *J* = 6.9, 2.3 Hz, 4H), 7.14-7.20 (br s, 2H), 7.41 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 18.8, 23.0, 35.0, 45.5, 69.0, 83.7, 153.6. IR (neat): 3348, 3287, 2949, 2355, 2112, 1460, 1431, 1280, 930, 633 cm^{-1}. FAB-LRMS m/z: 235 $[M+H]^+$. *Anal.* Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.59; H, 7.53; N, 11.78.

Preparation of (*M)-4,4',5,5',6,6',7,7'-Octahydro-7,7'-spirobi[benzo[*c*]isoxazole] (5)** To a solution of **4** (755 mg, 3.2 mmol) in CH_2Cl_2 (64 mL) was added aq. NaOCl (>5.0% chlorine, 6.4 mL) at 0 °C, and the mixture was stirred overnight at rt. The reaction was quenched by the addition of water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was recrystallized from hexane-ether to afford (*M**)-4,4',5,5',6,6',7,7'-octahydro-7,7'-spirobi[benzo[*c*]isoxazole] (**5**) (498 mg, 67%) as a white solid. mp 190 °C (decomp). ^{1}H NMR ($CDCl_3$): δ 1.82-1.93 (m, 4H), 2.07-2.18 (m, 2H), 2.30-2.40 (m, 2H), 2.59-2.78 (m, 4H), 8.13 (t, *J* = 1.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.5, 18.9, 35.2, 36.1, 114.0, 153.1, 164.4. IR (neat): 3096, 2949, 2355, 1605, 1439, 1406, 1097, 854, 590 cm^{-1}. FAB-HRMS. Calcd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134. Found : 231.1155. Each enantiomer was separated using DAICEL CHIRALPAK AD (2 cm ϕ x 25 cm, hexane/*i*-PrOH = 4/1, 5.0 mL/min, 23 min, 33 min). $[\alpha]_D^{25}$ –130° (c 1.01, $CHCl_3$) (first peak on HPLC).

General Procedure for Pd(II)-catalyzed Tandem Cyclization *via* the Oxy-palladation A mixture of ligand (0.024 mmol) and Pd(II)-salt (0.020 mmol) in 0.5 mL of CH_2Cl_2 was stirred at rt for 2 h. To this solution were added the alkenyl alcohol (**6**) (0.10 mmol) and *p*-benzoquinone (43 mg, 0.40 mmol). The reaction mixture was stirred until **6** was completely consumed on TLC. The reaction was quenched by the addition of water and extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate =

30/1) to give the tandem product (**7**) and the mixture of monocyclized products (**8**) and (**9**). The ratio of **7** and monocyclized products (**8**) and (**9**) was determined by isolated yields and ^{1}H NMR spectrometry. The enantiomeric excess of the products were determined by HPLC analysis using chiral stationary phase column (DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 120/1, flow rate = 0.25 mL/min).

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11. Crystal data for **5**: orthorhombic; space group $C222_1$ (#20); a = 9.3193 Å, b = 9.7383 Å, c = 12.5279 Å, V = 1114.98 Å^3, Z = 8; Mo Kα radiation (-75 ^{o}C); R = 0.057, R_w = 0.058; d_{calc} = 1.443 g/cm^3; $F(000)$ = 512.00; 2θ range = 25 (32.6-34.8^o).
12. Plausible mechanism of enantioselective tandem cyclization of **6**.