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SYNTHESIS OF NOVEL CHIRAL SPIRO BIS(PYRAZOLE) LIGANDS

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Abstract – The first synthesis of spiro bis(pyrazole) ligands, 2,2',4,4'-tetrahydro-6,6'-spirobi[5*H*-cycopentapyrazole] (**1a**) and 2,2'-dibenzyl-2,2',4,4'-tetrahydro-6,6'-spirobi[5*H*-cycopentapyrazole] (**1b**) was achieved. The application of spiro bis(pyrazole) ligand to asymmetric catalysis was also examined.

The design of enantiomerically pure chiral ligands is one of the most important challenges in the development of asymmetric catalysis.[1] We have previously reported the first design and synthesis of the chiral spiro bis(isoxazoline) ligands (SPRIXs), which have a chiral spiro skeleton and two isoxazoline rings.[2] (Figure 1) Among the investigation of asymmetric reactions catalyzed by Pd(II)-SPRIXs,[3] the rigidity of spirocyclic framework in the ligands reduces the flexibility of coordinating units for Pd(II) in the transition state and consequently promotes the Pd(II)-mediated enantioselective reactions,[3a] particularly the Wacker-type cyclization of alkenyl alcohols[3b] and the carbonylation of alkenylamines in the presence of carbon monoxide.[3c] These characteristic results of using SPRIXs in the above reactions prompted us to further explore the design of new chiral ligands with spiro skeleton.[4] The potential of pyrazoles as efficient coordinating ligands is well-established in inorganic chemistry.[5] The incorporation of a pyrazole heterocyclic unit into certain chiral molecules would provide new chiral ligands.[6]

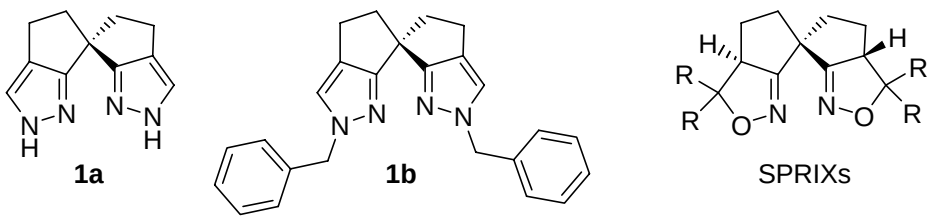
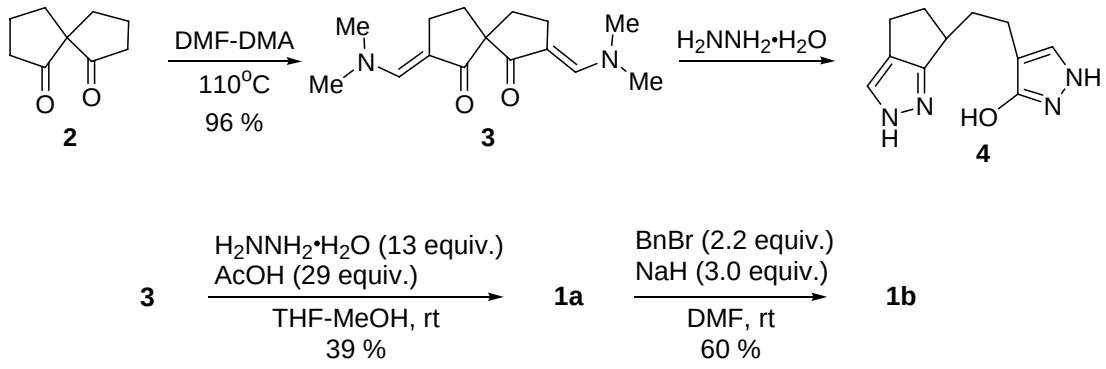


Figure 1. New Spiro bis(pyrazole) ligands and SPRIXs

Herein we wish to report the first synthesis, characterization of spiro bis(pyrazole) ligands, 2,2',4,4'-tetrahydro-6,6'-spirobi[5*H*-cycopentapyrazole] (**1a**) and 2,2'-dibenzyl-2,2',4,4'-tetrahydro-6,6'-spirobi[5*H*-cycopentapyrazole] (**1b**).



Scheme 1. Synthesis of spiro bis(pyrazole) ligands (**1a**) and (**1b**)

The synthesis of spiro bis(pyrazole) ligands (**1a)** and (**1b**) is shown in Scheme 1. A mixture of spiro[4.4]nonane-1,6-dione (**2**)[7] and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) was heated at 110 °C for 24 h. After removing solvents under reduced pressure and washing the residue with Et_2O, 2,7-(*E*)-bisdimethylaminomethylenespiro[4.4]nonane-1,6-dione (**3**) (0.17 g, 0.66 mmol) was obtained in 96 % yield as a yellow solid. Initially we assumed that ligand (**1a**) could be synthesized by double intermolecular cyclization of **3** with hydrazine monohydrate. All attempts for construction of **1a** resulted in 4-[2-(2,4,5,6-tetrahydrocyclopentapyrazol-6-yl)ethyl]-1*H*-pyrazol-3-ol (**4**)[8] as major product with the spiro ring cleaved. However, the use of a large excess of hydrazine monohydrate (13 equiv.) and acetic acid (29 equiv.) for **3** afforded the desired product (**1a**) in 39 % yield. Subsequently **1a** was converted to **1b** by dibenzylation in 60 % yield. The structure of **1b** was determined by X-Ray crystallographic analysis (Figure 2).[9]

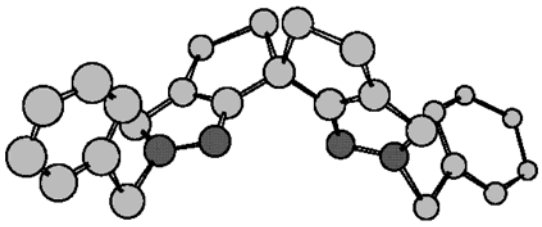
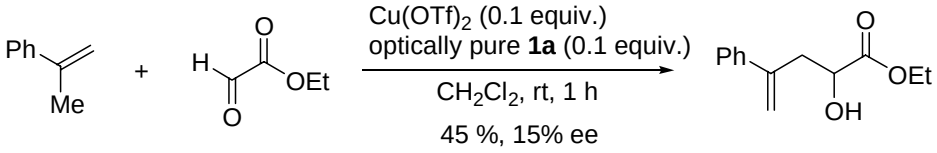


Figure 2. Chem-3D presentation for the X-Ray structure of **1b**

Optically pure **1a** was readily obtained by separation with chiral stationary phase column.[10] To elucidate the ability of optically pure **1a** as a chiral ligand, asymmetric ene reaction of α-methylstyrene

with ethyl glyoxylate was examined.[11] As a preliminary result, the Cu(II)-spiro bis(pyrazole) catalyst generated from $Cu(OTf)_2$ and optically pure **1a** after stirring for 2 h promoted the ene reaction to afford the adduct in 45 % yield with 15% ee (Scheme 2).



Scheme 2

In conclusion novel spiro bis(pyrazole) ligands (**1a**) and (**1b**) were readily synthesized and Cu(II)-spiro bis(pyrazole) complex exhibited activity as asymmetric catalyst in the asymmetric ene reaction. Further studies for development of new asymmetric reaction using spiro bis(pyrazole) ligands are under way.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM-EX270 FT NMR (^{1}H-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 spectral data were obtained on Shimadzu FTIR 8300. Optical rotations were measured with a JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/VIS detector) using a mixture of hexane and *i*-PrOH or EtOH as the eluent. MS spectra were obtained on JEOL JMS-700 (for FAB-MS) and JMS-T100LC (for ESI-MS). Elemental analysis was performed on 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 points were measured with Yanaco MICRO MELTING POINT APPARATUS MODEL MP-S9. Column chromatography was performed using Kanto Silica Gel 60 (40-100 μm). Anhydrous THF and toluene were purchased from Kanto Chemicals, Tokyo.

2,7-(*E*)-Bis-dimethylaminomethylenespiro[4.4]nonane-1,6-dione (3). A mixture of spiro[4.4]nonane-1,6-dione (**2**) (0.11 g, 0.69 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (0.20 mL, 1.5 mmol) was heated at 110 ^{o}C for 24 h. After completion of the reaction, the solvent was removed under reduced pressure. The residue was washed with Et_2O three times, and was purified by recrystalization from AcOEt-hexane to obtain compound (**3**) (0.17 g, 0.66 mmol) in 96 % yield as a yellow solid. mp 69 ^{o}C. IR (neat) 2930, 1724, 1672, 1564, 1431, 1377, 1292, 1267, 1236, 1196, 1109, 1053, 1005, 989, 959, 932, 899, 827, 775, 652, 569 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.59-1.71 (m,

2H), 2.27-2.37 (m, 2H), 2.74-2.84 (m, 2H), 3.01-3.14 (m, 2H), 3.06 (s, 12H), 7.16 (s, 2H). ^{13}C-NMR ($CDCl_3$) δ 25.3, 32.4, 42.2, 63.5, 103.3, 146.9, 204.2. FAB-MS *m/z* 263 ($[M + H]^+$). *Anal.* Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.52; H, 8.33; N, 10.60.

2,2',4,4'-Tetrahydro-6,6'-spirobi[5*H*-cyclopentapyrazole] (1a). To a stirred solution of **3** (51 mg, 0.19 mmol) in THF-MeOH (10:1 v/v) (0.44 mL) was added 1 M hydrazine monohydrate-AcOH (0.46 mL, 2.7 mmol, 1:2.5, v/v) in THF-MeOH (5:1 v/v) (3.0 mL). The reaction mixture was stirred for 8 h at rt. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/AcOEt=1/10) to give the spiro bis(pyrazole) ligand (**1a**) (15 mg, 0.076 mmol) in 39 % as a white solid. mp 231 °C (decomp, recrystalization from AcOEt-hexane). IR (neat) 3101, 2920, 1396, 1178, 1040, 972, 812, 704, 596 cm^{-1}. ^{1}H-NMR (CD_3OD) δ 2.50 (m, 8H), 7.22 (s, 2H). ^{13}C-NMR (CD_3OD) δ 22.6, 47.0, 47.1, 123.8, 125.2, 165.1. FAB-MS *m/z* 201 ($[M + H]^+$). *Anal.* Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.84; H, 6.05; N, 28.19.

2,2'-Dibenzyl-2,2',4,4'-tetrahydro-6,6'-spirobi[5*H*-cyclopentapyrazole] (1b). NaH (60 %, 30 mg, 0.75 mmol) was washed with DMF three times. To the NaH in DMF (0.5 mL) was added spiro bis(pyrazole) ligand (**1a**) (51 mg, 0.25 mmol) at 0 °C. After stirring for 3 h at rt, benzyl bromide (65.4 μL, 0.55 mmol) was added, and the mixture was stirred for 23 h. The reaction mixture was quenched by addition of H_2O, and the mixture was extracted with AcOEt. The combined organic layers were washed with sat. aq. $NaHCO_3$, brine, and dried over Na_2SO_4, filtered and concentrated. The residue was purified by recrystalization from AcOEt to obtain the spiro bis(benzylpyrazole) ligand (**1b**) (57 mg, 0.15 mmol) in 60 % as a colorless crystal. mp 161 °C. IR (neat) 2930, 1568, 1499, 1454, 1433, 1382, 1333, 1150, 1032, 986, 907, 787, 731, 698, 632, 559, 521, 513 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.50-2.84 (m, 8H), 5.25 (dd, *J*=22.4, 15.1 Hz, 4H), 6.92 (s, 2H), 7.18-7.36 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ 22.0, 45.4, 47.4, 56.1, 123.1, 124.3, 127.6, 128.5, 137.2, 164.6. MS (ESI-HRMS) calcd for $C_{25}H_{24}N_4Na$ $[M+Na^+]$: 403.1899, Found: 403.1879.

General procedure for catalytic asymmetric ene reaction using Cu(II)-spiro bis(pyrazole) catalyst. The mixture of optically pure **1a** (2.0 mg, 0.01 mmol) and $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) in CH_2Cl_2 (0.3 mL) was stirred at rt for 2 h. To this solution was added α-methylstyrene (13 μL, 0.1 mmol) and ethyl glyoxylate (60 μL, 0.30 mmol). After the reaction completed, the mixture was directly loaded onto silica gel column and eluted with the solvent (AcOEt/hexane=3/1) to give ethyl 2-hydroxy-4-phenyl-4-pentanoate (9.9 mg, 0.045 mmol) in 45 % as a colorless oil. IR (neat) 3476, 3083, 2982, 2906, 1736, 1445, 1210, 1094, 1029, 905 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.22 (t, *J*=7.1 Hz, 3H), 2.86 (dd, *J*=14.5, 7.6 Hz, 1H), 3.01 (brs, 1H), 3.07 (dd, *J*=14.5, 4.5 Hz, 1H), 4.06 (m, 2H), 4.28 (dd, *J*=7.6, 4.7 Hz, 1H), 5.22 (s, 1H), 5.40 (s, 1H), 7.43-7.31 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 14.0, 40.4, 61.4, 69.1, 116.0, 126.3, 127.6, 128.1, 140.2, 143.5, 174.3. MS (EI-LRMS) 221 $[M^+]$. Enantiomeric excess of

ethyl 2-hydroxy-4-phenyl-4-pentanoate was determined by using DAICEL CHIRALPAK AS (hexane/*i*-PrOH=10/1, 0.5 mL/min, 17.0 min, 23.0 min).

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8. **4-[2-(2,4,5,6-tetrahydrocyclopentapyrazol-6-yl)ethyl]-1*H*-pyrazol-3-ol (4).** brown solid. mp 88 ^{o}C (recrystalization from AcOEt-hexane). IR (neat) 3134, 2920, 1578, 1510, 1406, 1302, 1150,

1026, 970, 719, 546, 515 cm^{-1}. ^{1}H-NMR (CD_3OD) δ 1.64-1.89 (m, 2H), 2.00-2.13 (m, 1H), 2.43-2.65 (m, 5H), 2.88-2.98 (m, 1H), 3.27 (quintet, *J*=1.6 Hz, 1H), 7.14 (s, 1H), 7.22 (s, 1H). ^{13}C-NMR (CD_3OD) δ 21.3, 22.6, 36.3, 37.9, 38.8, 105.6, 124.7, 125.0, 130.8, 161.3, 163.2. FAB-MS *m/z* 219 ($[M + H]^+$). *Anal.* Calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.41; H, 6.72; N, 25.61.

9. The compound (**1b**) crystallizes in the primitive orthorhombic crystal system, space group $P2_12_12$(#18), a=10.707(4) Å, b=18.192(4) Å, c=10.369(5) Å, V=2019(1) $Å^3$, Z=4, d_{calc}=1.251 g/cm^3, *F*(000)=808.00, 2θrange 20(8.6-11.0°), R=0.083.
10. Each enantiomer of **1a** (2.5 mg) was separated by using DAICEL CHIRALPAK AD [2 cm Φ x 25 cm, hexane/EtOH=1/50, 3.0 mL/min, 21 min (1.2 mg), 28 min (1.2 mg)]. mp 95-96 °C (recrystalization from EtOH-hexane). $[\alpha]_D^{23}$ +13.3° (c 0.51, MeOH) (first peak of HPLC), $[\alpha]_D^{23}$ –13.9° (c 0.51, MeOH) (second peak of HPLC).
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