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Optical resolution of tetra isopropyl-substituted spiro bis(isoxazoline)*i*-Pr-SPRIX

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Abstract

The optical resolution of racemic tetra isopropyl-substituted spiro bis(isoxazoline) ligand (*i*-Pr-SPRIX) is achieved by fractional recrystallization of palladium complexes **2a** and **2b** prepared from (±)-SPRIX **1** and di-μ-chlorobis{(*R*)-2-[1-(dimethylamino)ethyl]phenyl-*C*,*N*}dipalladium(II) (*R*,*R*)-**3** followed by the decomplexation from palladium by the treatment with 1,2-bis(diphenylphosphino)ethane. The X-ray crystal structure of the complex **2a** reveals that (−)-*i*-Pr-SPRIX has (*P*,*R*,*R*)-configuration.

Keywords: Optical resolution; Asymmetric ligands; Spiro bis(isoxazoline); *i*-Pr-SPRIX

1. Introduction

The design of enantiomerically pure chiral ligands is one of the most important challenges in the development of new asymmetric catalysis [1]. Recently, we reported the design and synthesis of spiro bis(isoxazolines) ligands (SPRIXs) [2], which structure is shown in Fig. 1. The rigidity of spiro framework in SPRIXs, appears to reduce the conformational obscurity in the transition state and consequently promote the Pd(II)-mediated enantioselective reactions such as the Wacker-type cyclization of alkenyl alcohols [2b] and the carbonylation of alkenylamines in the presence of carbon monoxide [2c]. The above reactions are not promoted by hitherto known ligands including BINAP, bis(oxazolinyl)propane [3], and boxax [4]. The isoxazoline units of the SPRIXs also play a crucial role in accelerating the Pd(II)-mediated reactions [2d]. The efficient catalyst activity of SPRIXs on the reaction is attributable to the higher Lewis acidity of the Pd-SPRIX complexes in comparison with that of oxazolines [2e]. These characteristic results of using SPRIXs in the oxidative cyclizations further prompted us to explore a new class of asymmetric SPRIXs-mediated catalysis. However, despite the unique benefits of SPRIXs, the optical resolution by using chiral stationary phase column is necessary to obtain enantiomerically pure SPRIXs. We present here the resolution of racemic-*i*-Pr-SPRIX (±)-**1**, using optically pure *ortho*-palladated benzylamine derivatives as a resolving agent, via the separation of a mixture of the diastereomeric palladium complexes of (±)-**1**.

2. Results and discussion

Optical resolution of (±)-**1** via the diastereomeric complexation was performed by using di-μ-chlorobis{(*R*)-2-[1-(dimethylamino)ethyl]phenyl-*C*,*N*}dipalladium(II) (*R*,*R*)-**3**, which have been reported to be useful resolving agent of wide range of asymmetric ligands [5]. The resolution procedure is summarized in Scheme 1.

The treatment of (±)-**1** with 0.5 mol equiv. of dimeric palladium complex (*R*,*R*)-**3** in MeOH at room temperature for 2.5 h, followed by the reaction of 4.0 mol equiv. of aq. NH_4PF_6 [6] at room temperature for 30 min produced a 1:1-diastereomeric mixture of cationic palladium complexes **2a** and **2b** in 87% yield, and unreacted (±)-**1** was

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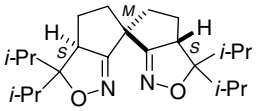


Fig. 1. Spiro bis(isoxazoline) ligands, SPRIXs.

recovered in 13% yield [7]. The ^{1}H NMR spectrum of the mixture **2a** and **2b** exhibited two unique signal, assignable to benzylic proton, with equal intensities at δ 3.44 and 4.70. After recrystallization of **2a** and **2b** from dichloromethane/diethyl ether solution, the intensity of the signal at δ 3.44 was slightly increased compared to that at δ 4.70, suggesting that the content of **2a** was increased. Thus, we performed successive recrystallization and obtained the pure sample of **2a** as a colorless crystal in 32% theoretical yield, which was confirmed by the complete disappearance of the signal at δ 4.70 in the ^{1}H NMR spectrum. Complex **2a** showed $[\alpha]_D^{25}$ −228.4 (*c* 0.38, chloroform) [8].

Single crystals were grown by slow diffusion of hexane into dichloromethane/1,2-dichloroethane solution of **2a**, and X-ray crystallographic analysis was conducted. The molecular structure is given in Fig. 2. The absolute configuration of **2a** was determined based on the configuration at the benzylic carbon C(30) to be *R*. The Pd center adopt slightly distorted square planar geometry, and the angle between the planes of Pd(1)–N(1)–N(2) and Pd(1)–N(3)–C(24) is 13.4°. The two imino groups of the isoxazoline rings twist away in free **1a** [2a]. However, the ideal conformation for *cis* chelate coordination is coplanar. Thus, the geometry around the imino groups is slightly distorted. Although 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)–

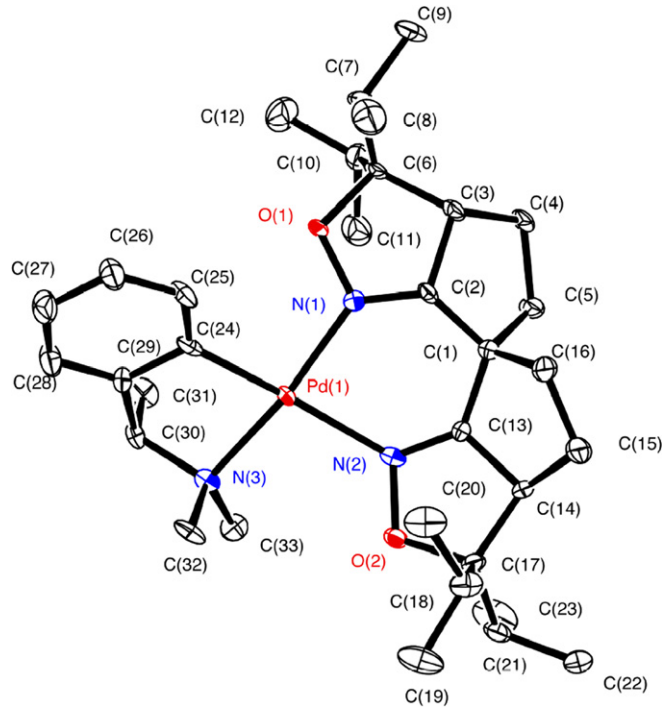
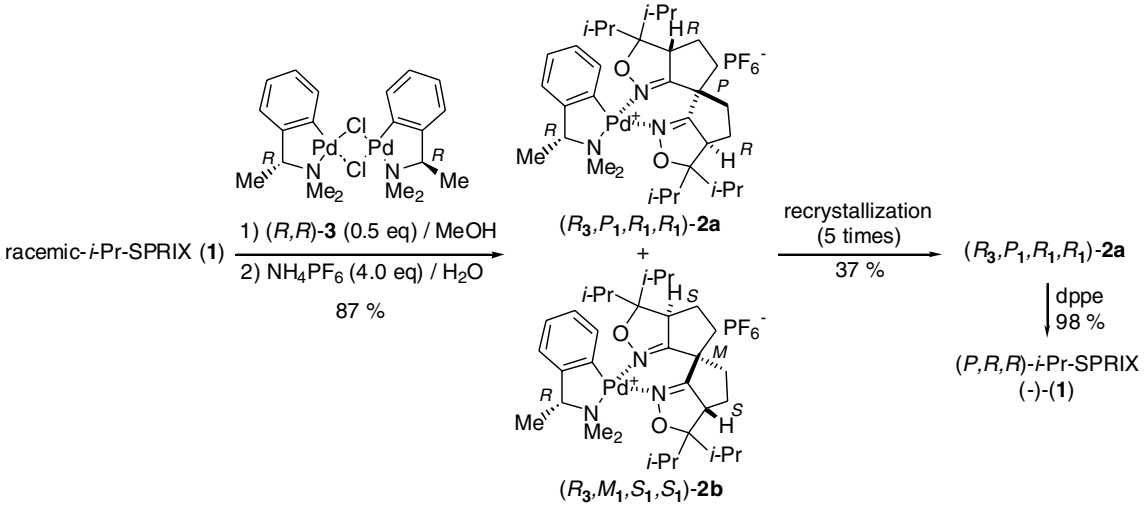


Fig. 2. ORTEP plot of (R_3,P_1,R_1,R_1)-**2a**. Hydrogen atoms and a counter anion are omitted for clarity.



Selected ^{1}H-NMR data[a] of Pd complexes derived from racemic-*i*-Pr-SPRIX (**1**)

Pd complex	NC*H*Me	N	NCH*Me*	*Me*$_a$	N*Me*$_b$
(R_3,P_1,R_1,R_1)-**2a**	3.44 (q, 6.25 Hz)		1.82 (d, 6.25 Hz)	2.83 (s)	2.87 (s)
(R_3,M_1,S_1,S_1)-**2b**	4.70 (q, 6.76 Hz)		1.40 (d, 6.76 Hz)	2.60 (s)	3.14 (s)

[a] In $CDCl_3$ at 270 MHz; chemical shift (ppm) relative to TMS (*J* in Hz).

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°. These structural features may be the origin of the characteristic reactivity of the Pd-SPRIX complex.

Treatment of isolated (R_3,P_1,R_1,R_1)-**2a** with 1,2-bis(diphenylphosphino)ethane (dppe) underwent ligand exchange reaction to afford (−)-**1** and Pd-dppe complex quantitatively. The HPLC analysis showed that the resulting (−)-**1** was enantiomerically pure. This result clearly reveals (−)-*i*-Pr-SPRIX has (*P*,*R*,*R*)-configuration.

In conclusion, racemic-*i*-Pr-SPRIX (±)-**1** has been resolved via the separation of a mixture of the diastereomeric palladium complexes **2a** and **2b**, derived from the reaction of (±)-**1** with di-μ-chlorobis{(*R*)-2-[1-(dimethylamino)ethyl]phenyl-*C*,*N*}dipalladium(II) (*R*,*R*)-**3**. The X-ray crystal structure of **2a** supports that (−)-*i*-Pr-SPRIX has (*P*,*R*,*R*)-configuration. Further investigation on separation of pure **2b** is currently underway [9].

3. Experimental

3.1. General

Commercially available organic and inorganic compounds were used without further purification except for the solvents, which were distilled over sodium/benzophenone or CaH_2. Column chromatography was performed with Kanto Silica Gel 60 (40–100 μm). ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM-EX270 (^{1}H NMR 270 MHz, ^{13}C NMR 67.7 MHz). All signals were expressed as ppm down field from tetramethylsilane, used as internal standard (for ^{1}H and ^{13}C NMR). FT-IR spectra were recorded on a SHIMADZU FTIR-8300. Optical rotations were measured with 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 2-propanol as the eluent. Mass spectra were obtained on JEOL JMS-T100LC (for ESI-TOFMS). X-ray crystallographic analysis was carried out with RIGAKU AFC-7R, and all calculations were performed using the Crystal Structure determination package of Molecular Structure Corporation.

3.2. Palladium complex *2a*

A solution of (±)-**1** (375 mg, 1.0 mmol) and (*R*,*R*)-**3** (290 mg, 0.5 mmol) in MeOH (30 mL) was stirred at room temperature for 2.5 h. A solution of NH_4PF_6 (326 mg, 2.0 mmol) in H_2O (5 mL) was added to the above mixture, and it was stirred at room temperature for 30 min. The reaction mixture was concentrated and the remaining aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Mg_2SO_4 and concentrated in vacuo. The resulting residue was washed with diethyl ether–hexane (1:1) to afford the corresponding diastereomeric palladium complexes **2a** and **2b** (676 mg, 0.87 mmol, 87% yield). (±)-**1** was also recovered in 13% yield from the above diethyl ether–hexane layer. Recrystallization of diastereomeric mixture of palladium complexes **2a** and **2b** (4.35 g, 5.6 mmol) (five times) from dichloromethane/diethyl ether solution produced pure **2a** (1.61 g, 2.08 mmol) in 37% yield as a white crystal; m.p. 235 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ 0.82–1.14 (m, 24H), 1.82 (d, $J = 6.26$ Hz, 3H), 2.00 (m, 4H), 2.30 (m, 6H), 2.75 (m, 2H), 2.83 (s, 3H), 2.87 (s, 3H), 3.44 (q, $J = 6.26$ Hz, 1H), 4.1 (m, 2H), 6.86–7.08 (m, 3H), 7.24 (d, $J = 7.58$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 17.0, 17.3, 17.5, 17.6, 17.8, 18.0, 18.8, 18.8, 18.9, 22.5, 25.8, 31.7, 31.9, 32.1, 32.3, 38.0, 38.9, 45.3, 45.1, 51.1, 51.1, 53.0, 77.2, 102.1, 102.6, 121.1, 124.8, 125.5, 135.7, 144.3, 153.4, 170.1, 172.3. IR (KBr): 840 cm^{-1} (ν_{P-F}). ESI-TOF-MASS (Low). 628. $[\alpha]_D^{18}$ −228.4 (*c* 0.38, $CHCl_3$).

3.3. Palladium complex *2b*

Palladium complex **2b** was prepared by the reaction of pure (+)-**1** with (*R*,*R*)-**3** based on the similar protocol for **2a**. White solid, m.p. 207 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ 0.82–1.14 (m, 24H), 1.40 (d, $J = 6.75$ Hz, 3H), 2.0 (m, 4H), 2.35 (m, 6H), 2.60 (s, 3H), 2.75 (m, 2H), 3.14 (s, 3H), 4.1 (m, 2H), 4.7 (q, $J = 6.75$ Hz, 1H), 6.76 (t, $J = 7.30$ Hz, 1H), 6.94 (t, $J = 7.30$ Hz, 1H), 7.09 (t, $J = 7.30$ Hz, 1H), 7.25 (d, $J = 7.30$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 10.2, 17.0, 17.3, 17.6, 17.7, 17.8, 17.0, 18.7, 18.8, 19.1, 19.2, 31.8, 31.9, 32.2, 32.4, 38.0, 38.9, 43.4, 45.2, 49.5, 51.2, 51.3, 74.6, 101.8, 102.6, 122.7, 125.5, 125.7, 135.3, 147.3, 150.0, 170.2, 172.3. IR (KBr): 841 cm^{-1} (ν_{P-F}). $[\alpha]_D^{22}$ +188.3 (*c* 0.29, $CHCl_3$).

3.4. Ligand exchange reaction of palladium complex *2a* with 1,2-diphenylphosphinoethane (dppe)

A solution of (R_3,P_1,R_1,R_1)-**2a** (1.61 g, 2.08 mmol) and 1,2-bis(diphenylphosphino)ethane (dppe) (830 mg, 2.08 mmol) in CH_2Cl_2(48 mL) was stirred at room temperature for 2 h. The organic solvent was concentrated in vacuo. The resulting residue was filtered through silica gel (CH_2Cl_2/hexane = 1/2) to defecate dppe and then purified by silica gel (acetone/hexane = 1/3) to give (−)-**1** (765 mg, 2.04 mmol) in 98% yield. (−)-**1** was identical in all the respects with our reported spectra [2a].

3.5. Crystallography

X-ray analysis of (R_3,P_1,R_1,R_1)-(−)-**2a** was performed on a colorless needle crystal (0.60 × 0.10 × 0.10 mm) which was obtained by recrystallization from CH_2Cl_2/$(CHCl_2)_2$/hexane: $C_{33}H_{52}F_6N_3O_2PPd$, $M = 774.16$, monoclinic, $P2_1$(#4), $a = 16.094(5)$ Å, $b = 8.905(3)$ Å, $c = 12.387(3)$ Å, $\beta = 94.32(2)°$, $V = 1770.2(9)$ Å^3, $Z = 2$, $D_{calc} = 1.452$ g/cm^3, $F(000) = 804$, $T = -150$ °C, $R = 0.0563$, $R_w = 0.0840$.

4. Supplementary material

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 600190. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk. or www: http://www.ccdc.cam.ac.uk.

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References

[1] (a) E.N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Comprehensive Asymmetric Synthesis I–III, Springer, Berlin, 1999;
(b) I. Ojima (Ed.), Catalytic Asymmetric Synthesis, second ed., Wiley–VCH, New York, 2000;
(c) Y. Kobayashi (Ed.), Latest Frontiers of Organic Synthesis, Research Signpost, Trivandrum, 2002.

[2] (a) M.A. Arai, T. Arai, H. Sasai, Org. Lett. 1 (1999) 1795;
(b) M.A. Arai, M. Kuraishi, T. Arai, H. Sasai, J. Am. Chem. Soc. 123 (2001) 2907;
(c) T. Shinohara, M.A. Arai, K. Wakita, T. Arai, H. Sasai, Tetrahedron Lett. 44 (2003) 711;
(d) T. Shinohara, K. Wakita, M.A. Arai, T. Arai, H. Sasai, Heterocycles 59 (2003) 587;
(e) T. Kato, K. Marubayashi, S. Takizawa, H. Sasai, Tetrahedron: Asymmetry 15 (2004) 3693;
(f) M.A. Arai, T. Shinohara, T. Arai, H. Sasai, J. Synth. Org. Chem. 62 (2004) 59.

[3] (a) E.J. Corey, N. Imai, H.-Y. Zhang, J. Am. Chem. Soc. 113 (1991) 728;
(b) D.A. Evans, K.A. Woerpel, M.M. Hinman, M.M. Faul, J. Am. Chem. Soc. 113 (1991) 726.

[4] Y. Uozumi, H. Kyota, K. Kato, M. Ogasawara, T. Hayashi, J. Org. Chem. 64 (1999) 1620.

[5] (a) S. Otsuka, A. Nakamura, T. Kano, K. Tani, J. Am. Chem. Soc. 93 (1971) 4301;
(b) K. Tani, L.D. Brown, J. Ahmed, J.A. Ibers, M. Yokota, A. Nakamura, S. Otsuka, J. Am. Chem. Soc. 99 (1977) 7876;
(c) K.M. Pietrusiewicz, M. Zablocka, Chem. Rev. 94 (1994) 1375;
(d) S. Gladiali, A. Dore, D. Fabbri, O. De Lucchi, M. Manassero, Tetrahedron: Asymmetry 5 (1994) 511;
(e) A. Miyashita, H. Takaya, T. Souchi, R. Noyori, Tetrahedron 40 (1984) 1245;
(f) R. Schmid, M. Cereghetti, B. Heiser, P. Schönholzer, H.-J. Hansen, Helv. Chem. Acta 71 (1988) 897;
(g) R. Schmid, J. Foricher, M. Cereghetti, P. Schönholzer, Helv. Chem. Acta 74 (1991) 370;
(h) H. Jendralla, C.H. Li, E. Paulus, Tetrahedron: Asymmetry 5 (1994) 1297;
(i) N.W. Alcock, D.I. Hulmes, J.M. Brown, J. Chem. Soc., Chem. Commun. (1995) 395.

[6] N.W. Alock, J.M. Brown, D.I. Hulmes, Tetrahedron: Asymmetry 4 (1993) 743.

[7] The diastereomer ratio of **2a** and **2b** was determined by ^{1}H NMR. The recovered SPRIX as a racemic form was confirmed by HPLC with Daicel Chiralpack AD using hexane/2-propanol (50/1) as an eluent.

[8] Optical purity of (*P*,*R*,*R*)-*i*-Pr-SPRIX after recrystallization of **2a**: 1 time, 37% ee; 2 times, 60% ee; 3 times, 98% ee (determined by HPLC with Daicel Chiralpack AD after the ligand exchange).

[9] The mother liquid after the filtrate fraction (2 times) produced **2b** in 11% theoretical yield with 66% de. Complexes **2a** and **2b** could not be separated by column chromatography.