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Structural Features and Asymmetric Environment of *i*-Pr-SPRIX Ligand

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ABSTRACT Novel chiral diisopropyl spiro bis(isoxazoline) ligands, *anti-i*-Pr-SPRIX and *syn-i*-Pr-SPRIX, were designed and synthesized. Their catalytic utility, X-ray crystallographic analyses, and complexation studies demonstrated the structural features of tetraisopropyl spiro bis(isoxazoline) ligand, *i*-Pr-SPRIX, which is a prominent ligand in various enantioselective Pd catalytic processes: All *i*-Pr groups work in collaboration to create an effective asymmetric environment. *Chirality 27:532–537, 2015*.

KEY WORDS: chiral ligand; spiro framework; isoxazoline; asymmetric environment; palladium; enantioselective catalysis; oxidative cyclization

The development of novel chiral ligands is one of the most imperative tasks in asymmetric catalysis. Notably, chiral spiro ligands have been attracting broad interest, as they exhibit excellent enantioselectivity based on their entirely rigid backbone.[1–7] We have successfully developed unique chiral spiro ligands and have been investigating their utility. A series of spiro bis(isoxazoline) **1**, abbreviated SPRIX, are the first examples of chiral ligands possessing an isoxazoline coordination unit (Fig. 1).[8] Asymmetric synthesis of SPRIX **2** has been achieved by using an optically pure starting material.[9,10] Spiro bis(isoxazole) ligands (**3**)[11] and spiro (isoxazole-isoxazoline) hybrid ligands (**4**)[12,13] have also been prepared.

These chiral ligands exert a peculiar accelerative effect on various Pd-catalyzed oxidative cyclizations stemming from the low σ-donor ability of the isoxazoline and/or isoxazole coordination sites. For example, catalytic reactions through a Pd(II)/Pd(IV) redox couple, which are able to realize unprecedented transformations complementary to the conventional Pd(0)/Pd(II) catalysis, proceed with high enantioselectivity.[14–16] Recently, we succeeded in the development of the cyclative diacetoxylation of alkynyl cyclohexadienones involving an unusual Pd enolate umpolung.[17] In addition, 5-*endo*-*trig*-type cyclization of 3-alkenoic acids,[18,19] oxidative allylic C – H esterification of 4-alkenoic acids,[20] and other asymmetric Pd-catalyzed reactions[21–24] are also feasible. In these processes, *i*-Pr-SPRIX **1d** displayed the best performance. For a better understanding of the notable features of **1d**, we designed *anti-i*-Pr-SPRIX **1e** and *syn-i*-Pr-SPRIX **1f** whose stereoconfiguration at the C5 center of the isoxazoline rings was regulated (Fig. 2). Herein, we report the preparation, properties, and structures of these new SPRIX ligands, which contribute to the development of more valuable SPRIX-type chiral ligands.

MATERIALS AND METHODS

General Information

All reactions were performed with standard Schlenk techniques under nitrogen atmosphere. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECS400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). All signals in the ^{1}H NMR spectra were expressed as chemical shift (δ) in ppm downfield from Me_4Si used as an internal standard (δ = 0.00 ppm). Chemical shifts of the ^{13}C NMR signals are reported as δ referenced to $CDCl_3$ (δ = 77.0 ppm). Electrospray ionization (ESI) mass spectra (MS) were recorded on a Thermo Fisher LTQ ORBITRAP XL spectrometer. Optical rotations were measured with a JASCO P-1030 polarimeter. High-performance liquid chromatography (HPLC) analyses were performed on a JASCO HPLC system (JASCO PU 2080 pump and MD-2010 UV/Vis detector). Melting points were measured with a Yanaco micro melting point apparatus model MP-S9 and were uncorrected. Anhydrous diethyl ether, tetrahydrofuran (THF), and toluene were purchased from Kanto Chemicals and further purified by passage through activated alumina using a GlassContour solvent purification system.[25] Other solvents were purified prior to use by standard techniques.[26] *p*-Benzoquinone was purified by sublimation under vacuum. Compounds **5a** (CAS registry number [134287-57-3])[27] and **5b** (CAS registry number [101971-37-3])[28] were prepared according to previously reported methods. All other chemicals were purchased from commercial suppliers and used as received. Column chromatography was performed using Kishida Silica Gel 60 (63–200 μm). Merck silica gel 60 F_{254} plates were used for TLC.

Synthetic Procedures

Diethyl 2,2-bis((E)-5-methylhex-3-enyl)malonate (7a). To a suspension of NaH (60% in oil, 0.32 g, 7.9 mmol) in dimethyl sulfoxide (DMSO) (7 mL) was added diethyl malonate (**6a**) (0.48 g, 3.0 mmol) at 0 °C, which was then stirred for 1 h at room temperature (rt). To this mixture was added (*E*)-1-bromo-5-methylhex-3-ene (**5a**)[27] solution (1.4 g, 7.9 mmol) in DMSO (3 mL). After being stirred for 24 h at 50 °C, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with 1 M aq. HCl and brine successively and dried over Na_2SO_4. The volatiles were removed by evaporation under reduced pressure, and the residue was purified by column chromatography using silica gel (hexane/EtOAc = 5/1) to give desired compound **7a** (0.73 g, 69%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (dd, J = 15.6 Hz, J = 6.4 Hz, 2H), 5.31 (dt, J = 15.6 Hz, J = 6.4 Hz,

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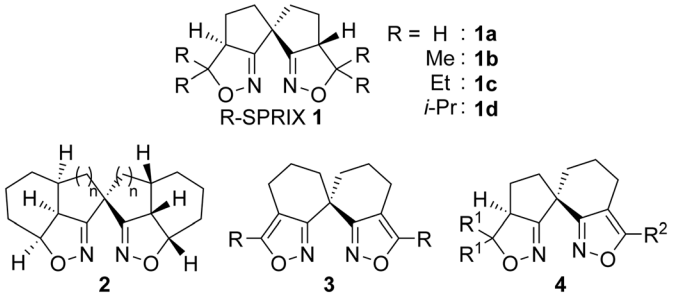


Fig. 1. Structures of spiro bis(isoxazoline) ligand **1** and its derivatives.

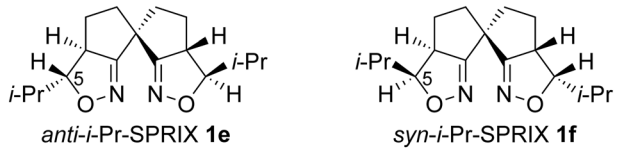


Fig. 2. Structures of *anti-i*-Pr-SPRIX **1e** and *syn-i*-Pr-SPRIX **1 f**.

2H), 4.17 (q, J = 6.9 Hz, 4H), 2.25–2.17 (m, 2H), 1.96–1.92 (m, 4H), 1.89–1.84 (m, 4H), 1.24 (t, J = 6.9 Hz, 6H), 0.95 (d, J = 6.9 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 138.2, 125.8, 61.0, 57.2, 32.3, 31.0, 27.2, 22.5, 14.1. HRMS (ESI): calcd. for $C_{21}H_{36}NaO_4$: *m/z* 375.2511 ($[M + Na]^+$), found: *m/z* 375.2502.

Bis(2,2,2-trifluoroethyl) 2,2-bis((*Z*)-5-methylhex-3-enyl)malonate (7b). To a solution of bis(2,2,2-trifluoroethyl) malonate (**6b**) (1.4 g, 5.2 mmol), (*Z*)-5-methylhex-3-en-1-ol (**5b**)[28] (1.4 g, 12.0 mmol), and Ph_3P (5.7 g, 21.8 mmol) in toluene (45 mL) was added a solution of 1,1′-(azodicarbonyl)dipiperidine (6.0 g, 23.9 mmol) in toluene (75 mL), which was then stirred for 13 h at 50 °C. The resulting mixture was concentrated, and passed through a pad of silica gel and rinsed with CH_2Cl_2. The solvents were evaporated and the residue was purified by column chromatography using silica gel (hexane/EtOAc = 10/1) to give desired compound **7b** (1.7 g, 72%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27–5.16 (m, 4H), 4.52 (q, J = 8.2 Hz, 4H), 2.57–2.45 (m, 2H), 2.04–1.93 (m, 8H), 0.93 (d, J = 6.9 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 139.0, 124.9, 122.7 (q, J = 276 Hz), 61.0 (q, J = 37.4 Hz), 57.4, 32.6, 26.5, 23.0, 22.0. HRMS (ESI): calcd. for $C_{21}H_{30}F_6NaO_4$: *m/z* 483.1946 ($[M + Na]^+$), found: *m/z* 483.1935.

2,2-Bis((*E*)-5-methylhex-3-enyl)propane-1,3-diol (8a). To a solution of $LiAlH_4$ (0.27 g, 7.0 mmol) in THF (14 mL) was added a solution of **7a** (1.21 g, 3.5 mmol) in THF (6 mL) at 0 °C. After being stirred for 4 h at rt, the reaction mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ and Et_2O. The resulting suspension was filtered, and the preciptate was washed with Et_2O. The combined organic layer was concentrated and the residue was purified by column chromatography using silica gel (hexane/EtOAc = 3/1) to give desired compound **8a** (0.74 g, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (dd, J = 15.1 Hz, J = 6.4 Hz, 2H), 5.31 (dt, J = 15.1 Hz, J = 6.0 Hz, 2H), 3.62 (s, 2H), 3.49 (s, 4H), 2.25–2.13 (m, 2H), 1.92–1.86 (m, 4H), 1.30–1.25 (m, 4H), 0.92 (d, J = 6.4 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 127.0, 68.2, 41.0, 30.9, 30.5, 25.9, 22.5. HRMS (ESI): calcd. for $C_{17}H_{32}NaO_2$: *m/z* 291.2300 ($[M + Na]^+$), found: *m/z* 291.2291.

2,2-Bis((*Z*)-5-methylhex-3-enyl)propane-1,3-diol (8b). According to the procedure for the preparation of **8a**, the desired compound **8b** was obtained as a white solid (0.76 g, 77%) using $LiAlH_4$ (0.28 g, 7.4 mmol) and **7b** (1.7 g , 3.7 mmol) in THF (18 + 7 mL). Mp: 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26–5.17 (m, 4H), 3.60 (s, 4H), 2.63–2.54 (m, 2H), 2.15 (s, 2H), 2.03–1.97 (m, 4H), 1.37–1.32 (m, 4H), 0.95 (d, J = 6.9 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 127.1, 69.1, 41.3, 31.1, 26.6, 23.2, 21.0. HRMS (ESI): calcd. for $C_{17}H_{32}NaO_2$: *m/z* 291.2300 ($[M + Na]^+$), found: *m/z* 291.2296.

2,2-Bis((*E*)-5-methylhex-3-enyl)malonaldehyde dioxime (9a). To a solution of oxalyl chloride (1.28 g, 9.9 mmol) in CH_2Cl_2 (6 mL) was slowly added DMSO (1.05 g, 13.5 mmol) at –78 °C, which was then stirred for 30 min. While maintaining the temperature, a solution of **8a** (0.74 g, 2.6 mmol) in CH_2Cl_2 (7 mL) was added and stirred for additional 30 min. To this mixture was added triethylamine (2.39 g, 23.4 mmol) at –78 °C. After being stirring for 1.5 h at rt, the reacion mixture was quenched with saturated aq. NH_4Cl and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. To the crude aldehyde product were added $NH_2OH \cdot HCl$ (0.90 g, 13 mmol) and pyridine (5.2 mL) at 0 °C, which was then stirred for 12 d at rt (further $NH_2OH \cdot HCl$ (0.90 g, 13 mmol) was added after 3 d and 6 d for a total of 2.70 g (39 mmol)). The reaction mixture was diluted with EtOAc, and the organic layer was washed with water and brine, and dried over Na_2SO_4. After evaporation of the volatiles, the residue was purified by column chromatography using silica gel (hexane/EtOAc = 5/1) to give desired compound **9a** (0.74 g, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 2H), 7.40 (s, 2H), 5.39 (dd, J = 15.1 Hz, J = 6.4 Hz, 2H), 5.27 (dt, J = 15.1 Hz, J = 6.4 Hz, 2H), 2.26–2.15 (m, 2H), 2.00–1.95 (m, 4H), 1.73–1.69 (m, 4H), 0.94 (d, J = 6.4 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 138.3, 126.0, 45.7, 36.0, 31.0, 27.0, 22.5. HRMS (ESI): calcd. for $C_{17}H_{30}N_2NaO_2$: *m/z* 317.2205 ($[M + Na]^+$), found: *m/z* 317.2195.

2,2-Bis((*Z*)-5-methylhex-3-enyl)malonaldehyde dioxime (9b). According to the procedure for the preparation of **9a**, the desired compound **9b** was obtained (0.63 g, 75%) as a colorless oil using oxalyl chloride (1.37 g, 10.6 mmol), DMSO (1.13 g, 14.5 mmol), **8b** (0.76 g, 2.85 mmol), triethylamine (2.58 g, 25.2 mmol) CH_2Cl_2 (7 + 7 mL), $NH_2OH \cdot HCl$ (total: 2.99 g, 2.97 mmol), and pyridine (5.2 mL). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 2H), 7.28 (s, 2H), 5.23–5.14 (m, 4H), 2.59–2.50 (m, 2H), 2.07–2.01 (m, 4H), 1.73–1.69 (m, 4H), 0.93 (d, J = 6.9 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 138.3, 126.0, 45.7, 36.0, 30.9, 27.0, 22.5. HRMS (ESI): calcd. for $C_{17}H_{30}N_2NaO_2$: *m/z* 317.2205 ($[M + Na]^+$), found: *m/z* 317.2197.

(*M,S,S*)- and (*P,R,R*)-*Anti-i*-Pr-SPRIX (1e). To a solution of **9a** (0.74 g, 2.3 mmol) in CH_2Cl_2 (46 mL) was added aq. NaOCl (>5.0%, 7.3 mL) at 0 °C, which was then stirred for 4 d at rt. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using silica gel (hexane/EtOAc = 5/1) to give the desired compound *rac*-(*M,S,S*)-**1e** (0.19 g, 28%) as a white solid with a diastereomeric mixture of *rac*-(*M,R,R*)-**1e** and *rac*-(*M,S,R*)-**1e** (0.44 g, 67%). Mp: 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (dd, J = 12.4 Hz, J = 7.3 Hz, 2H), 3.40 (dt, J = 12.4 Hz, J = 7.3 Hz, 2H), 2.54 (dd, J = 12.4 Hz, J = 6.9 Hz, 2H), 2.15 (dt, J = 12.4 Hz, J = 6.9 Hz, 2H), 2.05–1.94 (m, 4H), 1.82–1.72 (m, 2H), 1.05 (d, J = 6.9 Hz, 6H), 0.93 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 94.1, 56.9, 43.7, 41.5, 31.1, 27.5, 19.7, 18.6. HRMS (ESI): calcd. for $C_{17}H_{26}N_2NaO_2$: *m/z* 313.1892 ($[M + Na]^+$), found: *m/z* 313.1883. The enantiomers were separated using a Daicel Chiralpak AD column [2 cm $\Phi \times$ 25 cm, EtOH, 8 mL/min, 223 nm]: T_1 = 8 min for (*P,R,R*)-**1e** and T_2 = 24 min for (*M,S,S*)-**1e**. (*P,R,R*)-**1e**: $[\alpha]_D^{22}$ = –242.9 (c = 0.45, $CHCl_3$). (*M,S,S*)-**1e**: $[\alpha]_D^{23}$ = +248.6 (c = 0.57, $CHCl_3$).

(*M,S,S*)- and (*P,R,R*)-*Syn-i*-Pr-SPRIX (1 f). According to the procedure for the preparation of **1e**, the desired compound *rac*-(*M,S,S*)-**1 f** was obtained as a white solid (0.31 g, 45%) with a diastereomeric mixture of *rac*-(*M,R,R*)-**1 f** and *rac*-(*M,S,R*)-**1 f** (0.36 g, 51%) using **9b** (0.77 g, 2.4 mmol), CH_2Cl_2 (48 mL) and aq. NaOCl (>5.0%, 7.7 mL). Mp: 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (t, J = 10.1 Hz, 2H), 3.83 (ddd, J = 12.4 Hz, J = 10.1 Hz, J = 7.3 Hz, 2H), 2.52 (ddd, J = 12.4 Hz, J = 5.5 Hz, J = 1.8 Hz, 2H), 2.15 (ddd, J = 12.4 Hz, J = 11.4 Hz, J = 7.3 Hz, 2H), 2.05–1.94 (m, 6H), 1.01 (d, J = 6.4 Hz, 6H), 0.79 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 88.5, 57.0, 43.5, 40.3, 27.9, 24.0, 19.2, 18.9; HRMS (ESI): calcd. for $C_{17}H_{26}N_2NaO_2$: *m/z* 313.1892 ($[M + Na]^+$), found: *m/z* 313.1886. The enantiomers were separated using a Daicel Chiralpak AD column [2 cm $\Phi \times$ 25 cm, EtOH, 4 mL/min, 235 nm]:

T_1 = 16 min for (*P,R,R*)-**1 f** and T_2 = 24 min for (*M,S,S*)-**1 f**. (*P,R,R*)-**1 f**: $[\alpha]_D^{22}$ = −115.8 (*c* = 0.82, $CHCl_3$). (*M,S,S*)-**1 f**: $[\alpha]_D^{23}$ = +119.4 (*c* = 0.13, $CHCl_3$).

General Procedure for Enantioselective Pd(II)/Pd(IV) Cyclization of Enyne 10[13]

$Pd(OCOCF_3)_2$ (2.7 mg, 8.0 μmol, 10 mol %) and SPRIX ligand (12 μmol, 15 mol %) were dissolved in a 9:1 mixture of MeCN and AcOH (0.3 mL), which was then stirred at 25 °C for 2 h. To this solution was added 2-methylallyl phenylpropiolate (**10**) (16.0 mg, 0.080 mmol), $PhI(OAc)_2$ (103 mg, 0.32 mmol), and a 9:1 mixture of MeCN and AcOH (0.5 mL). After being stirred at 50 °C for 30 h, the reaction mixture was filtered through a short pad of silica gel and rinsed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography using silica gel (hexane/EtOAc = 4/1) to give 1-benzoyl-5-methyl-3-oxabicyclo[3.1.0]hexan-2-one (**11**).

General Procedure for Enantioselective Allylic C–H Esterification of 4-Alkenoic Acid 12[14]

$Pd(OAc)_2$ (1.1 mg, 5.0 μmol, 10 mol %) and SPRIX ligand (7.5 μmol, 15 mol %) were dissolved in CH_2Cl_2 (0.25 mL), which was then stirred at 25 °C for 2 h. To this solution was added *p*-benzoquinone (10.8 mg, 0.10 mmol, 2 equiv) and 5-methyl-2,2-diphenylhex-4-enoic acid (**12**) (14.0 mg, 0.050 mmol) in CH_2Cl_2 (0.25 mL). After being stirred at 25 °C for 12 h, the reaction mixture was directly filtered through a short pad of silica gel and rinsed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography using silica gel (hexane/EtOAc = 5/1 or CH_2Cl_2) to give 3,3-diphenyl-5-(prop-1-en-2-yl)dihydrofuran-2(3*H*)-one (**13**).

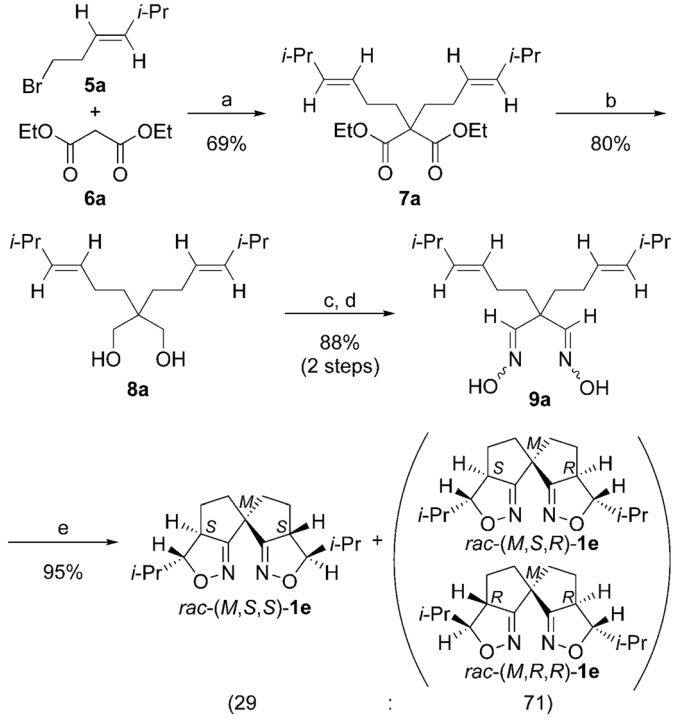
RESULTS AND DISCUSSION

Preparation

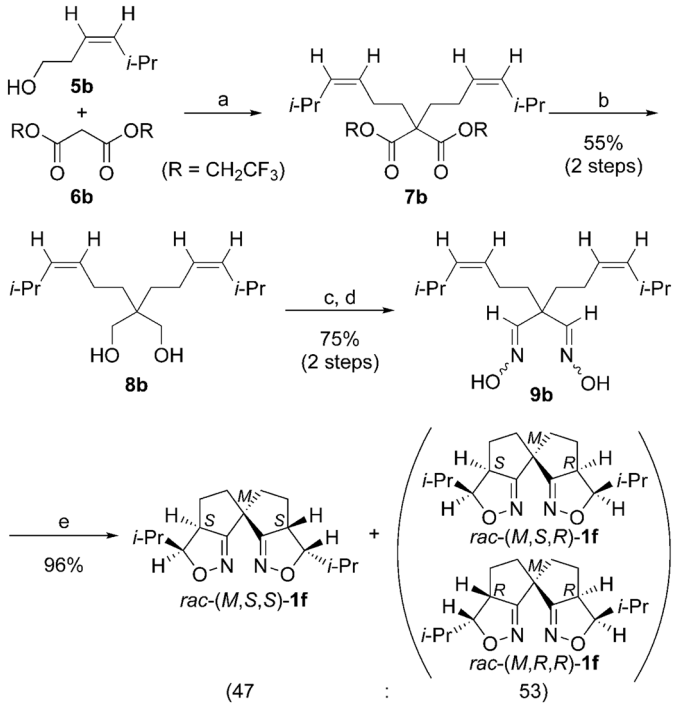
A key step in the preparation of SPRIX is an intramolecular nitrile oxide cycloaddition of dioxime, which is known to be a stereospecific reaction.[29] Target compounds **1e** and **1 f** were obtained using the corresponding homoallyl compounds (*E*)-1-bromo-5-methylhex-3-ene (**5a**)[27] and (*Z*)-5-methylhex-3-en-1-ol (**5b**),[28] respectively. *Anti-i*-Pr-SPRIX **1e** was prepared from **5a** and diethyl malonate (**6a**) in 46% yield over five steps: alkylation in the presence of NaH, reduction with $LiAlH_4$, Swern oxidation, oxime formation by treatment with $NH_2OH \cdot HCl$, and intramolecular double nitrile oxide cycloaddition of dioxime **9a** (Scheme 1). *Syn-i*-Pr-SPRIX **1 f** was prepared from **5b** and bis(2,2,2-trifluoroethyl) malonate (**6b**) in 40% overall yield, where the Mitsunobu reaction was employed as the initial alkylation process (Scheme 2).[10] In each case, the desired *rac*-(*M,S,S*)-isomer was readily separated from other diastereomers by column chromatography using silica gel. The structures of *rac*-(*M,S,S*)-**1e** and *rac*-(*M,S,S*)-**1 f** were identified by NMR spectroscopy and MS. Stereochemistry at C5 of the isoxazoline rings was determined on the basis of the coupling constant between the hydrogen on C5 and the bridgehead hydrogen as well as the chemical shift of C5: $^3J_{HH}$ = 12.4 Hz and 94.1 ppm for *rac*-(*M,S,S*)-**1e**, $^3J_{HH}$ = 10.1 Hz and 88.5 ppm for *rac*-(*M,S,S*)-**1 f**.[30] As with SPRIX ligands **1a–d**, these compounds were stable towards acid (1 M aq. HCl), base (1 M aq. NaOH), and oxidant (30% H_2O_2). Enantiopure materials were isolated through optical resolution using HPLC equipped with a preparative-scale chiral stationary phase column (Daicel Chiralpak AD).

Catalytic Utility

With new SPRIX ligands **1e** and **1 f** in hand, we conducted Pd-catalyzed reactions using them as well as H-SPRIX **1a** and *i*-Pr-SPRIX **1d** to determine the effect of the *i*-Pr group on asymmetric induction. These chiral ligands were first applied



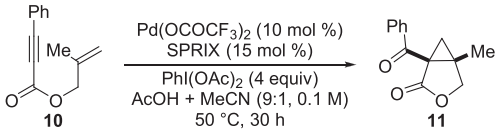
Scheme 1. Synthesis of *anti-i*-Pr-SPRIX **1e**. Reagents and conditions: (**a**) **5a** (2.5 equiv), **6a** (1 equiv), NaH (2.5 equiv), DMSO, 50 °C; (**b**) $LiAlH_4$ (2 equiv), THF, 0 °C to rt; (**c**) $(COCl)_2$ (3.8 equiv), DMSO (5.2 equiv), Et_3N (9 equiv), CH_2Cl_2, −78 °C to rt; (**d**) $NH_2OH \cdot HCl$ (15 equiv), pyridine, rt; (*e*) aq. NaOCl (2.2 equiv), CH_2Cl_2, rt.



Scheme 2. Synthesis of *syn-i*-Pr-SPRIX **1 f**. Reagents and conditions: (**a**) **5b** (2.5 equiv), **6b** (1 equiv), PPh_3 (4.2 equiv), 1,1′-(azodicarbonyl)dipiperidine (4.6 equiv), toluene, 50 °C; (**b**) $LiAlH_4$ (2 equiv), THF, 0 °C to rt; (**c**) $(COCl)_2$ (3.8 equiv), DMSO (5.2 equiv), Et_3N (9 equiv), CH_2Cl_2, −78 °C to rt; (**d**) $NH_2OH \cdot HCl$ (15 equiv), pyridine, rt; (**e**) aq. NaOCl (2.2 equiv), CH_2Cl_2, rt.

to enantioselective Pd(II)/Pd(IV) cyclization of 2-methylallyl phenylpropiolate (**10**), leading to bicyclic lactone **11**.[14] These results are summarized in Table 1. Treatment of **10** with 10 mol %

TABLE 1. Enantioselective Pd(II)/Pd(IV) catalysis of 10



Entry	SPRIX Ligand	Yield (%)[a]	Ee (%)[b]
1	(*M,S,S*)-*anti-i*-Pr-SPRIX **1e**	63	32
2	(*M,S,S*)-*syn-i*-Pr-SPRIX **1f**	62	3
3	(*M,S,S*)-H-SPRIX **1a**	72	4
4	(*M,S,S*)-*i*-Pr-SPRIX **1d**	94	82

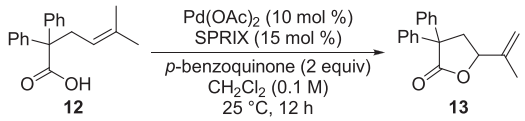
[a]Determined by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard.
[b]Determined by HPLC analysis using a Daicel Chiralpak AS-H column.

of $Pd(OCOCF_3)_2$ and 15 mol % of (*M,S,S*)-*anti-i*-Pr-SPRIX **1e** in the presence of 4 equiv of $PhI(OAc)_2$ in a 9:1 mixture of AcOH and MeCN at 50 °C for 30 h gave product **11** in 63% yield with 32% enantiomeric excess (ee) (entry 1). When (*M,S,S*)-*syn-i*-Pr-SPRIX **1f** was used as the chiral ligand, the selectivity was as low as 3% ee (entry 2). Similar to **1f**, (*M,S,S*)-**1a** scarcely rendered enantioinduction under otherwise identical conditions, most likely due to a nonselective background reaction (entry 3). In the reaction with (*M,S,S*)-**1d**, with four *i*-Pr groups, the enantiopurity of **11** was drastically improved to 82% ee (entry 4).

The same trend was observed for the asymmetric oxidative allylic C – H esterification of 5-methyl-2,2-diphenylhex-4-enoic acid (**12**) (Table 2).[20] Thus, the reaction of **12** with a Pd $(OAc)_2$/(*M,S,S*)-**1e** catalyst system led to the quantitative formation of γ-lactone product **13** with 34% ee, whereas an inferior result was obtained in the presence of (*M,S,S*)-**1f** or (*M,S,S*)-**1a** (entries 1–3). Not surprisingly, (*M,S,S*)-**1d** promoted the reaction in a highly selective manner to give **13** in quantitative yield with 76% ee (entry 4).

From the above observations, *i*-Pr-SPRIX **1d** proved to still be the most effective ligand for Pd-catalyzed asymmetric oxidative cyclizations. Hence, four *i*-Pr groups on the isoxazoline rings are vital to create an effective asymmetric environment for the SPRIX ligand.

TABLE 2. Enantioselective allylic C–H esterification of 12



Entry	SPRIX Ligand	Yield (%)[a]	Ee (%)[b]
1	(*M,S,S*)-*anti-i*-Pr-SPRIX **1e**	>98	34
2	(*M,S,S*)-*syn-i*-Pr-SPRIX **1f**	75	27
3	(*M,S,S*)-H-SPRIX **1a**	37	38
4	(*M,S,S*)-*i*-Pr-SPRIX **1d**	>98	76

[a]Determined by ^{1}H NMR analysis using acetophenone as an internal standard.
[b]Determined by HPLC analysis using a Daicel Chiralpak AD-H column.

Structure

To gain further insight into the role of the *i*-Pr group, we performed X-ray crystallographic analyses of *rac*-(*M,S,S*)-**1e** and *rac*-(*M,S,S*)-**1f** and compared the structures with those of *rac*-(*M,S,S*)-**1d** (Figs. 3 and 4).[31] Conformational differences of the *i*-Pr groups found in the X-ray structures are visualized as a schematic in Figure 5. The *i*-Pr methine protons of **1e** and **1f** were oriented in an antiperiplanar fashion with respect to the C5–H bonds and were considered to be the most stable conformers. Conversely, the *i*-Pr groups in the solid state of **1d** were located at the position rotated by ca. 120° compared to those of **1e** and **1f**. This difference can be attributed mainly to the steric repulsion between the geminal *i*-Pr groups and the 3*a*,4,5,6-tetrahydro-3*H*-cyclopenta[*c*]isoxazole backbone.

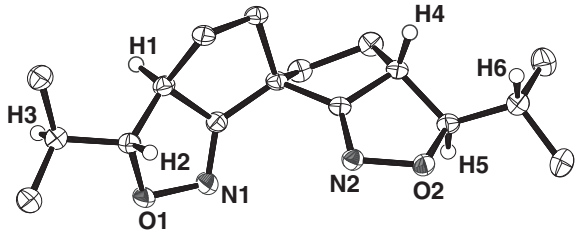


Fig. 3. ORTEP drawing of *rac*-(*M,S,S*)-**1e**. Hydrogen atoms are omitted for clarity, with the exception of methine hydrogens.

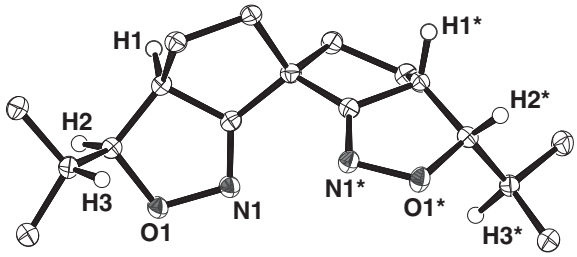


Fig. 4. ORTEP drawing of *rac*-(*M,S,S*)-**1f**. Hydrogen atoms are omitted for clarity, with the exception of methine hydrogens.

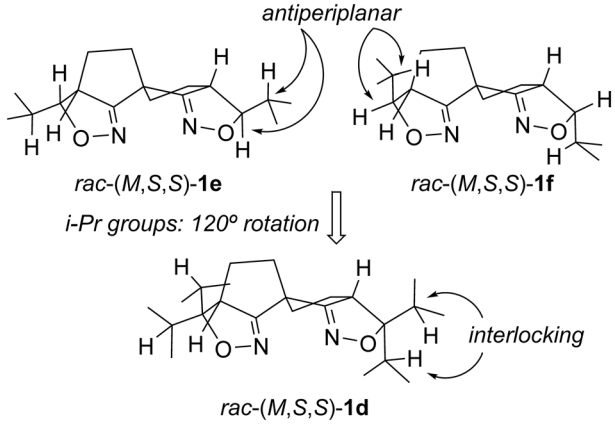


Fig. 5. Schematic for the X-ray structures of **(a)** *rac*-(*M,S,S*)-**1e**, **(b)** *rac*-(*M,S,S*)-**1f** and, **(c)** *rac*-(*M,S,S*)-**1d**.

In addition to the orientation of the *i*-Pr group, there was another structural variation between these SPRIX ligands. Although the N···N distance was nearly identical (3.131 Å for **1d**, 3.213 Å for **1e** and 3.124 Å for **1f**), the dihedral angle consisting of the two C–N double bonds was found to vary significantly depending on the substitution pattern of the *i*-Pr groups. The angle for **1d** was 21.1°, which was narrower than that of **1e** (32.5°) and roughly half that of **1f** (39.4°). This angular difference was seemingly reflected in their complexation behavior. On stirring **1d** with $Pd(OCOCF_3)_2$ in CH_2Cl_2, selective formation of the corresponding chelated complex was confirmed in the ^1H NMR spectrum (Fig. 6). A similar tendency was observed for **1e** (Fig. 7). However, for **1f** and **1a**, unidentified signals also appeared along with peaks assignable to the chelated complex, indicating their ill-defined coordination (Figs. 8 and 9).

Based on these results, functions of the *i*-Pr groups in SPRIX ligands were determined. The two *i*-Pr groups on the same carbon atom most likely interact with each other in an interlocking manner to construct an effective chiral pocket. Moreover, the *i*-Pr group *cis* to the bridgehead hydrogen, which is located at the equatorial position of the isoxazoline ring, is believed to be necessary for chelation to a metal through the adjustment of the C–N dihedral angle. Consequently, *i*-Pr-SPRIX **1d**, bearing four *i*-Pr groups, shows high enantioselectivity in various asymmetric Pd-catalyzed reactions.

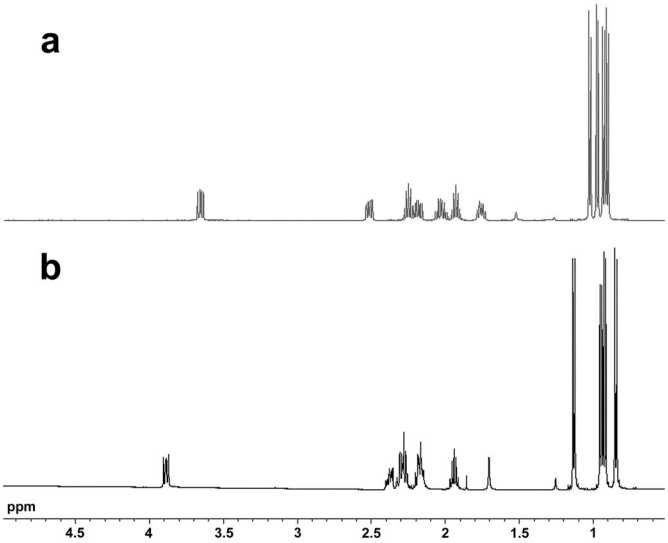


Fig. 6. ^1H NMR spectra of (**a**) *rac*-(*M*,*S*,*S*)-**1d** and (**b**) *rac*-(*M*,*S*,*S*)-**1d** + Pd $(OCOCF_3)_2$.

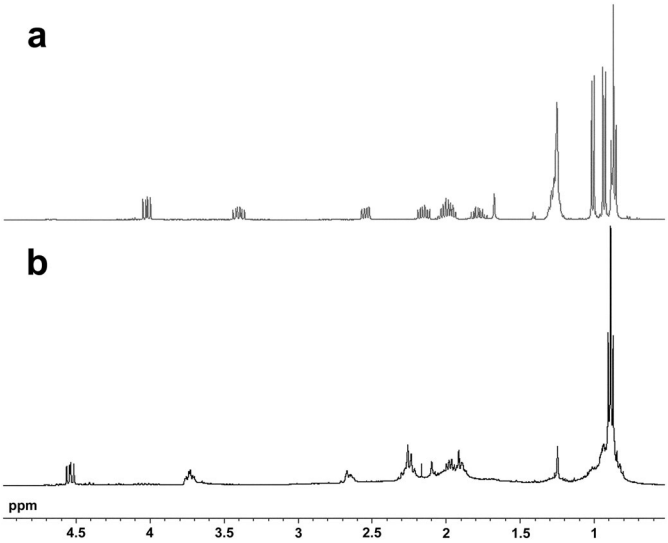


Fig. 7. ^1H NMR spectra of (**a**) *rac*-(*M*,*S*,*S*)-**1e** and (**b**) *rac*-(*M*,*S*,*S*)-**1e** + Pd $(OCOCF_3)_2$.

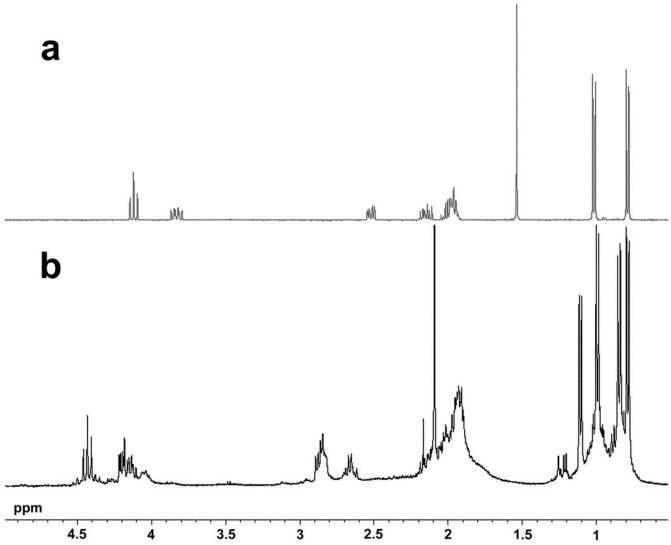


Fig. 8. ^1H NMR spectra of (**a**) *rac*-(*M*,*S*,*S*)-**1f** and (**b**) *rac*-(*M*,*S*,*S*)-**1f** + Pd $(OCOCF_3)_2$.

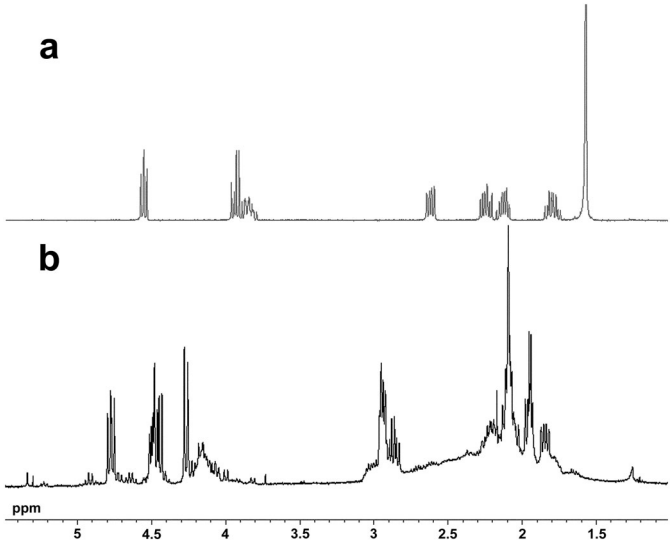


Fig. 9. ^1H NMR spectra of (**a**) *rac*-(*M*,*S*,*S*)-**1a** and (**b**) *rac*-(*M*,*S*,*S*)-**1a** + Pd $(OCOCF_3)_2$.

CONCLUSION

We designed and synthesized novel SPRIX ligands, *anti-i*-Pr-SPRIX **1e** and *syn-i*-Pr-SPRIX **1f**, which possess an *i*-Pr group on each of the isoxazoline donor moieties. Their catalytic application, X-ray structure, and complexation behavior analyses revealed the function of the *i*-Pr substituents on the isoxazoline rings. The four *i*-Pr groups of **1d** work cooperatively to create an effective asymmetric environment, resulting in high enantioselectivity. Based on the present

study, development of a new chiral ligand superior to *i*-Pr-SPRIX **1d** is now in progress.

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