

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 cyclization 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

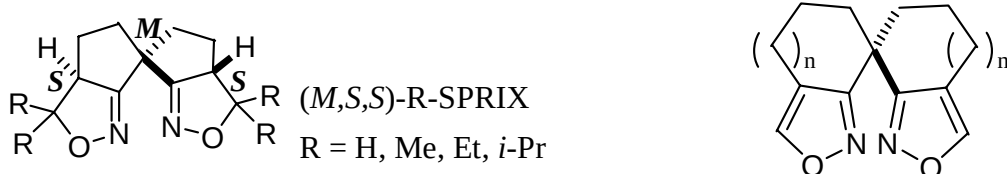
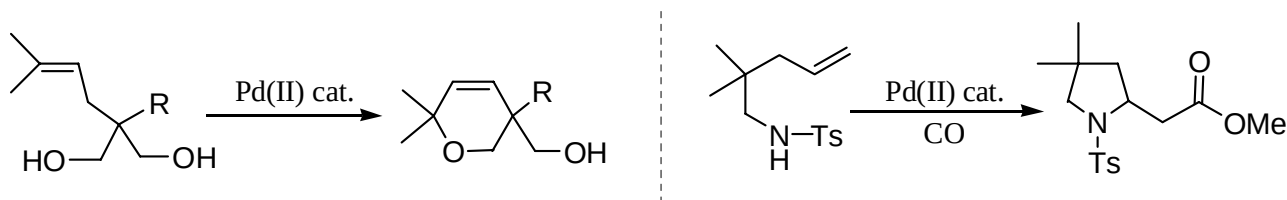
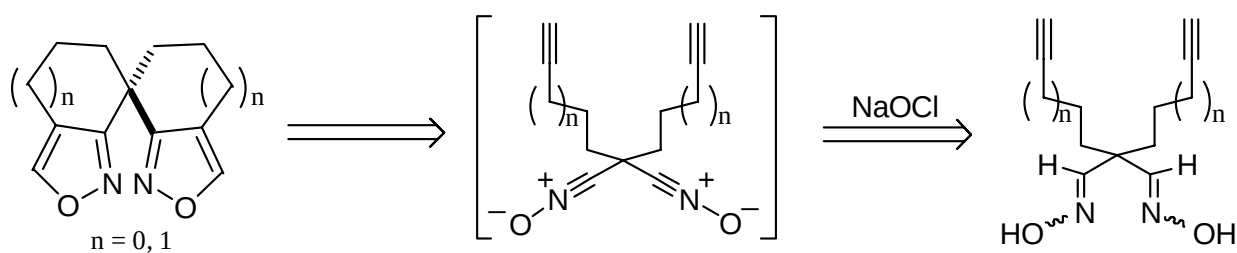


Figure 1. Spiro bis(isoxazoline) ligands (SPRIXs) and a new spiro bis(isoxazole) ligand



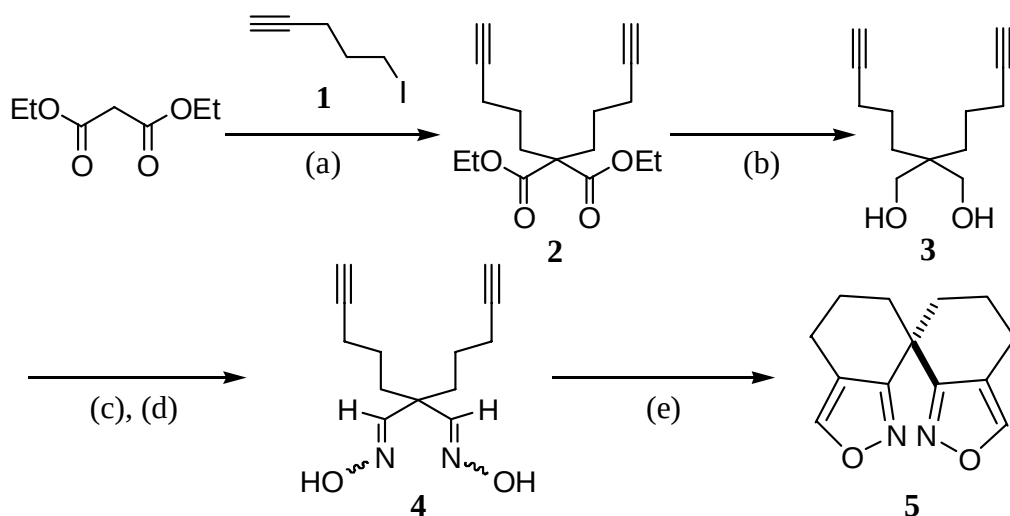
Scheme 1. Pd(II)-catalyzed enantioselective Wacker-type cyclization and aminocarbonylation



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 application 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) LiAlH₄, THF, rt: 92%; (c) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C; (d) NH₂OH-HCl, Py, rt: 85% (2 steps); (e) 5% aq. NaOCl, CH₂Cl₂, 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 LiAlH₄ to give the diol (**3**) in 94% yield. After the Swern oxidation of **3**, the resulting dialdehyde was treated with NH₂OH 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.

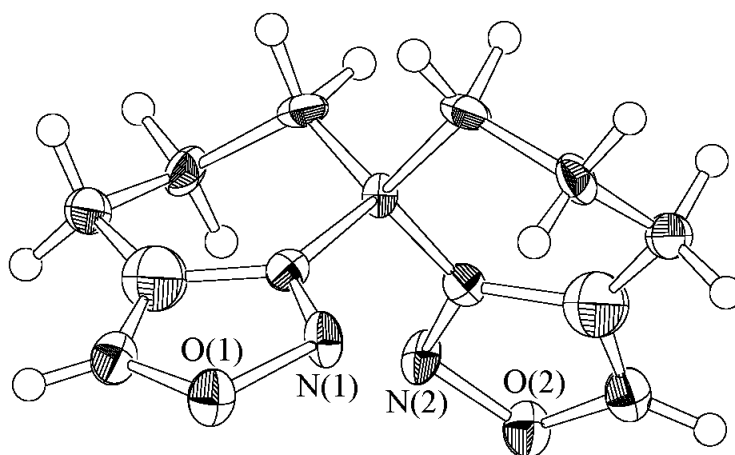
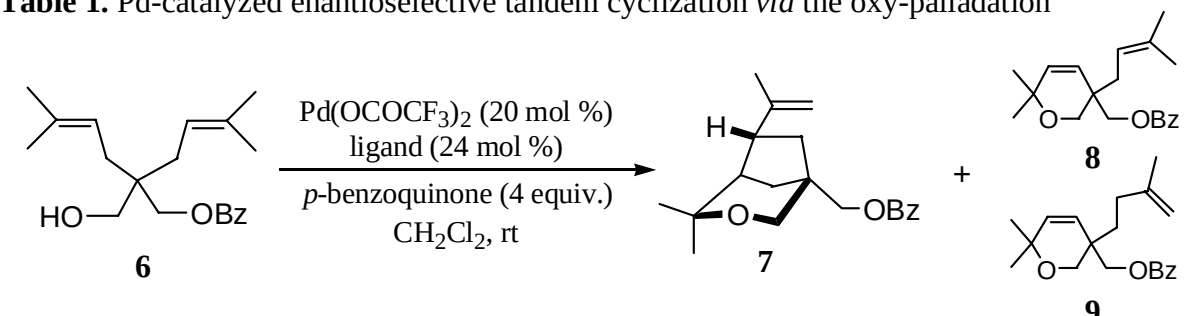


Figure 2. ORTEP drawing of spiro bis(isoxazole) ligand (**5**)

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	(<i>M, S, S</i>)- <i>i</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(OCOCF₃)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 °C 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 ¹³C NMR spectra were recorded on JEOL JNM-EX270 (¹H NMR-270 MHz, ¹³C 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 μ m). Merck silica gel 60 F₂₅₄ plates were used for TLC. Anhydrous THF was purchased from Kanto Chemicals, Tokyo. Anhydrous CH₂Cl₂ 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 μ L, 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. NH₄Cl and extracted with ether. The organic layer was washed with brine, dried over Na₂SO₄, 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. ¹H NMR (CDCl₃): 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). ¹³C NMR (CDCl₃): 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 C₁₇H₂₄O₄: 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 LiAlH₄ (60.3 mg, 1.59 mmol) at 0 °C. The reaction mixture was stirred at rt overnight, quenched by the addition of water (300 μ L) 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). ¹H NMR (CDCl₃): 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). ¹³C NMR (CDCl₃): 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 C₁₃H₂₀O₂: 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 CH₂Cl₂ (13 mL) was added a solution of DMSO (1.7 mL, 23.4 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (9 mL) dropwise at -78 °C, and the reaction mixture was stirred for 40 min. Et₃N (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. NH₄Cl and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄, and concentrated. The residue was subsequently dissolved in pyridine (11 mL), and NH₂OH-HCl (3.1 g, 45 mmol) was added at 0 °C. The reaction mixture was stirred for 6 days at rt, to which additional NH₂OH-HCl (625 mg, 9.0 mmol) was added per day. The mixture was diluted with CH₂Cl₂, washed with 1N HCl, sat. aq. NaHCO₃, brine, dried over MgSO₄, 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). ¹H NMR (CDCl₃): 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). ¹³C NMR (CDCl₃): 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 C₁₃H₁₈N₂O₂: 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 CH₂Cl₂ (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 CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄, 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). ¹H NMR (CDCl₃): 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). ¹³C NMR (CDCl₃): 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 C₁₃H₁₅N₂O₂ [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). [α]_D²⁵ -130° (c 1.01, CHCl₃) (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 CH₂Cl₂ 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 Na₂SO₄ 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 ¹H 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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REFERENCES AND NOTES

1. (a) E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, eds. '*Comprehensive Asymmetric Catalysis I-III*,' Springer, Berlin, 1999. (b) I. Ojima, ed. '*Catalytic Asymmetric Synthesis, 2nd ed.*,' Wiley-VCH: New York, 2000.
2. (a) A. S. C. Chan, W.-H. Hu, C.-C. Pai, C.-P. Lau, Y.-Z. Jiang, A.-Q. Mi, M. Yan, J. Sun, R.-L. Lou, and J.-G. Deng, *J. Am. Chem. Soc.*, 1997, **119**, 9570. (b) Y.-Z. Jiang, S. Xue, Z. Li, J.-G. Deng, A.-Q. Mi, and A. S. C. Chan, *Tetrahedron: Asymmetry*, 1998, **9**, 3185. (c) Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, and Q.-L. Zhou, *Chem. Commun.*, 2002, 480. (d) A.-G. Hu, Y. Fu, J.-H. Xie, H. Zhou, L.-X. Wang, and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2002, **41**, 2348. (e) H. Zhou, W.-H. Wang, Y. Fu, J.-H. Xie, W.-J. Shi, L.-X. Wang, and Q.-L. Zhou, *J. Org. Chem.*, 2003, **68**, 1582. (f) J.-H. Xie, L.-X. Wang, Y. Fu, S.-F. Zhu, B.-M. Fan, H.-F. Duan, and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2003, **125**, 4404.
3. (a) M. A. Arai, T. Arai, and H. Sasai, *Org. Lett.*, 1999, **1**, 1795. (b) M. A. Arai, M. Kuraishi, T. Arai, and H. Sasai, *J. Am. Chem. Soc.*, 2001, **123**, 2907. (c) T. Shinohara, M. A. Arai, K. Wakita, T. Arai, and H. Sasai, *Tetrahedron Lett.*, 2003, **44**, 711. (d) C. Muthiah, M. A. Arai, T. Shinohara, T. Arai, S. Takizawa, and H. Sasai, *Tetrahedron Lett.*, 2003, **44**, 5201.
4. E. J. Corey, N. Imai, and H.-Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728.
5. D. A. Evans, K. A. Woerpel, M. M. Hinman, and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726.
6. (a) Y. Uozumi, H. Kyota, E. Kishi, K. Kitayama, and T. Hayashi, *Tetrahedron: Asymmetry*, 1996, **7**, 1603. (b) Y. Uozumi, K. Kato, and T. Hayashi, *J. Am. Chem. Soc.*, 1997, **119**, 5063. (c) Y. Uozumi, H. Kyota, K. Kato, M. Ogasawara, and T. Hayashi, *J. Org. Chem.*, 1999, **64**, 1620.
7. T. Shinohara, K. Wakita, M. A. Arai, T. Arai, and H. Sasai, *Heterocycles*, 2003, **59**, 587.
8. (a) A. Lang and Y.-I. Lin, '*Comprehensive Heterocyclic Chemistry*,' ed. by A. R. Katritzky, Pergamon Press, Oxford, 1984, Vol. 6, pp. 1-130. (b) M. Sutharchanadevi and R. Murugan,

'Comprehensive Heterocyclic Chemistry II,' ed. by I. Shinkai, Elsevier, Oxford, 1996, Vol. 3, pp. 221-260.

9. M. S. Munsey and N. R. Natale, *Coord. Chem. Rev.*, 1991, **109**, 251 and references therein.
10. A. A. Watson, D. A. House, and P. J. Steel, *Aust. J. Chem.*, 1995, **48**, 1549 and references therein.
11. Crystal data for **5**: orthorhombic; space group $C222_1$ (#20); $a = 9.3193 \text{ \AA}$, $b = 9.7383 \text{ \AA}$, $c = 12.5279 \text{ \AA}$, $V = 1114.98 \text{ \AA}^3$, $Z = 8$; Mo $K\alpha$ radiation (-75°C); $R = 0.057$, $R_w = 0.058$; $d_{\text{calc}} = 1.443 \text{ g/cm}^3$; $F(000) = 512.00$; 2θ range = $25 (32.6\text{--}34.8^\circ)$.
12. Plausible mechanism of enantioselective tandem cyclization of **6**.

