HETEROCYCLES, Vol. 59, No. 2 , 2003, pp. 587 - 593, Received, 7th August, 2002

SYNTHESIS AND CHARACTER OF NEW BIS(ISOXAZOLINE) LIGANDS†

Toshio Shinohara, Kazuhiko Wakita, Midori A. Arai, Takayoshi Arai, and Hiroaki Sasai*

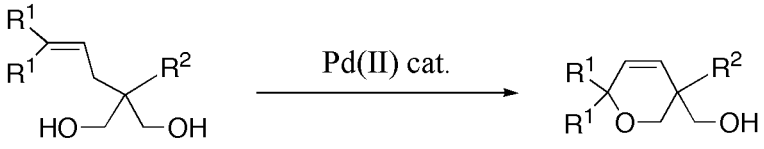
The Institute of Scientific and Industrial Research (ISIR), Osaka University Mihogaoka, Ibaraki, Osaka 567-0047, Japan

Abstract – Synthesis of two kinds of new bis(isoxazoline) ligand, achira 2,2'-bis(isoxazolinyl)propane and (*R*)-2,2'-bis(isoxazolinyl)-1,1'-binaphthyl bearing an axial chirality is described. Both of the bis(isoxazoline) ligands accelerated the Pd(II)-catalyzed Wacker-type cyclization of alkenyl alcohol. The isoxazoline ligands were found to be essential to promote the cyclization.

For the enantioselective reactions promoted by transition metal catalysts, effective optically active ligands are required to achieve high catalyst activity and high stereoselectivity.[1] We have previously reported the novel spiro bis(isoxazoline) ligands (SPRIXs), which have a chiral spiro backbone and isoxazoline units, and succeeded to demonstrate the first example of the use of an isoxazoline ligand for a transition metal-catalyzed asymmetric reaction.[2a] In view of the good affinity of SPRIXs to Pd(II) salts and the stability of SPRIXs under oxidative conditions, we developed a new asymmetric Wacker-type cyclization of alkenyl alcohols promoted by a Pd-SPRIX catalyst (Scheme 1).[2b] It is remarkable that these cyclizations are not promoted

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

Figure 1. Spiro bis(isoxazoline) ligands (SPRIXs)



Scheme 1. Pd(II)-catalyzed asymmetric Wacker-type cyclization

† This paper is dedicated to Professor Yuichi Kanaoka on the occasion of his seventy fifth birthday.

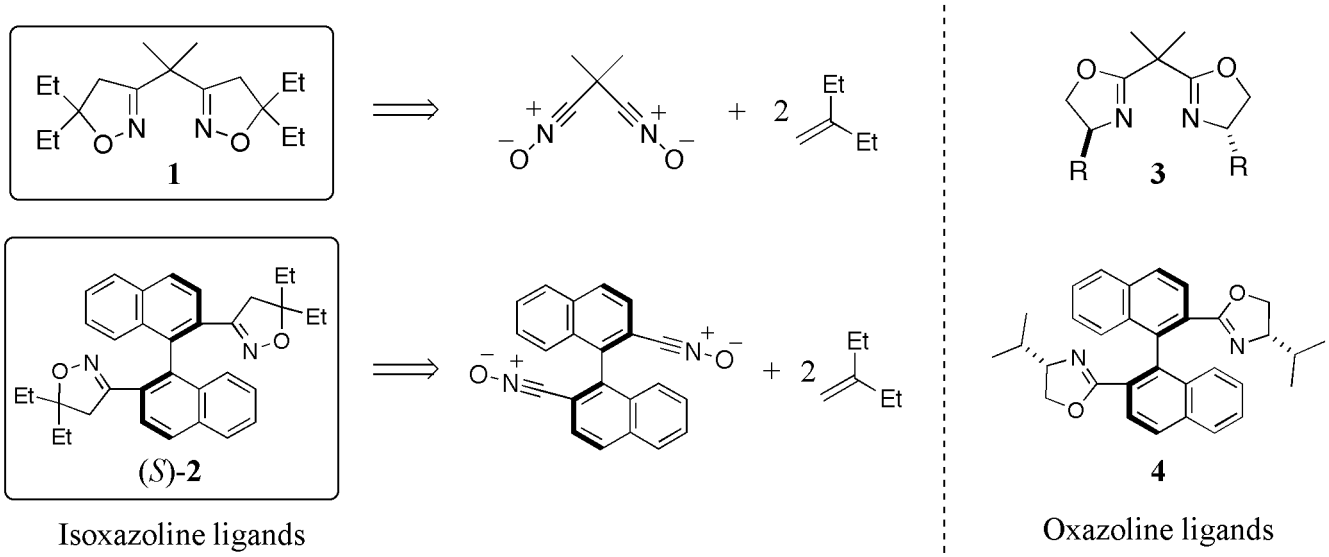
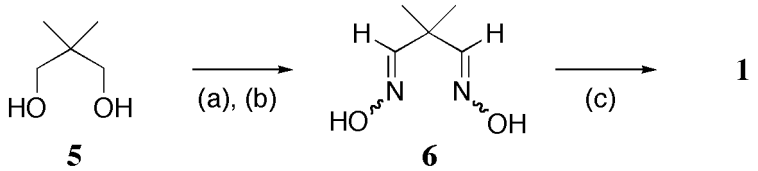


Figure 2. Design of new bis(isoxazoline) ligands

by hitherto known chiral ligands such as boxax,[3a] BINAP, and bis(oxazolinyl)propane.[4,5] For the elucidation of the unique character of SPRIXs in the Wacker-type cyclization, here we report the synthesis of new bis-(isoxazoline) ligands (**1**) and (**2**), and the comparison of ligand-acceleration effects of these isoxazoline ligands.

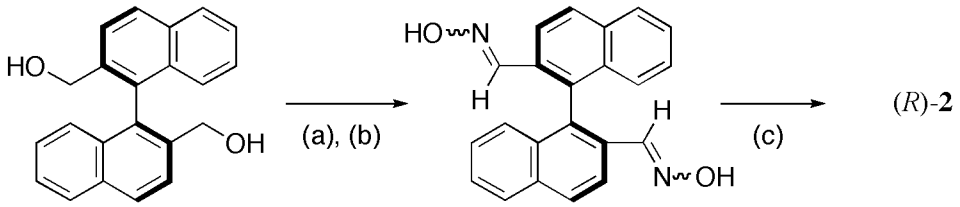
For the design and synthesis of new types of bis(isoxazoline) ligand, the structural similarity of isoxazoline and oxazoline was considered. Thus, the achiral bis(isoxazoline) (**1**) was designed as an analog of the representative bis(oxazoline) ligands (**3**) as shown in Figure 2. In addition, the optically active 2,2'-bis(isoxazolinyl)-1,1'-binaphthyl (**2**) was also set to study because Uozumi and Hayashi reported (*S,S*)-2,2'-bis(4-isopropyloxazolyl)-1,1'-binaphthyl ((*S,S*)-ip-boxax) (**4**) for the Wacker-type cyclization of *o*-allylphenols.[3b,c] Both the new ligands (**1**) and (**2**) were expected to be synthesized by a double intermolecular nitrile oxide cycloaddition.



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C
(b) NH_2OH-HCl, pyridine, rt; 68% (2 steps)
(c) 2-ethyl-1-butene, aq. NaOCl, THF, rt; 70%

Scheme 2. Synthesis of 2,2-bis(isoxazolinyl)propane (**1**)

The synthesis of 2,2'-bis(isoxazolinyl)propane (**1**) is shown in Scheme 2. The 2,2-dimethyl-1,3-propanediol (**5**) was oxidized under Swern oxidation condition, and a subsequent treatment with NH_2OH in pyridine gave 2,2-dimethylmalonaldehyde dioxime (**6**) as a single isomer in 68% yield from diol (**5**). By the treatment of dioxime (**6**) with 2-ethyl-1-butene in aq. NaOCl, bis(isoxazoline) ligand (**1**) was obtained *via* the double intermolecular nitrile oxide cycloaddition in 70% yield.



(*R*)-**7** (*R*)-**8**

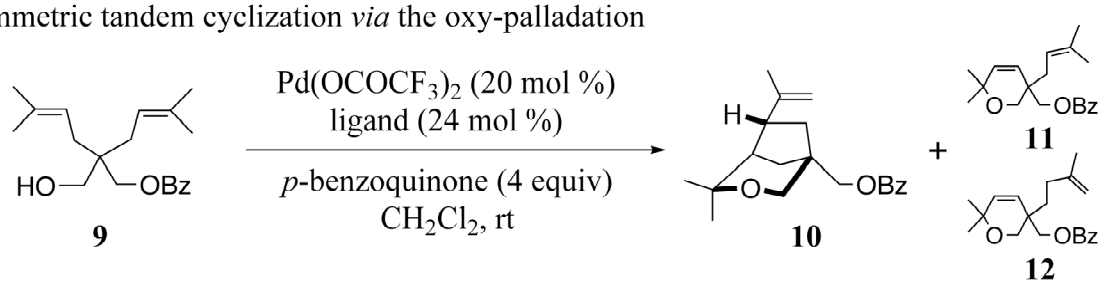
(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C
(b) NH_2OH-HCl, pyridine, CH_2Cl_2, rt; 95% (2 steps)
(c) 2-ethyl-1-butene, aq. NaOCl, THF, rt; 62%

Scheme 3. Synthesis of (*R*)-2,2'-bis(isoxazolinyl)-1,1'-binaphthyl (**2**)

Synthesis of the optically active 2,2'-bis(isoxazolinyl)-1,1'-binaphthyl (**2**) was started from (*R*)-2,2'-bis(hydroxymethyl)-1,1'-binaphthyl (**7**)[6] in a manner similar to that of **1** (Scheme 3). After oxidation of **7** the resulting dialdehyde was directly used in the next dioxime formation. (*R*)-1,1'-Binaphthyl-2,2'-dicarbaldehyde dioxime (**8**) was prepared in 95% yield from **7**. The isoxazoline ring formation was performed by using 2-ethyl-1-butene in aq. NaOCl to give (*R*)-2,2'-bis(isoxazolinyl)-1,1'-binaphthyl (**2**) in 62% yield. Both the bis(isoxazoline) ligands (**1**) and (**2**) are stable to air and moisture at room temperature, and even stable under oxidative conditions.[7]

The coordinating ability of **1** and **2** to palladium(II) was examined by NMR spectrometry. The palladium(II)-bis(isoxazoline) ligands complex (1:1 of $Pd(OCOCF_3)_2$ / ligand) were prepared in $CDCl_3$. In both cases, the

Table 1. Comparison of ligand-acceleration effects of isoxazoline ligands on the Pd-catalyzed asymmetric tandem cyclization *via* the oxy-palladation



entry	ligand	time (h)	yield (%)[a]	product ratio (ee (%))		
				10	**11**	**12**
1	none	67	34	26	66	8
2[b]	(*M,S,S*)-*i*-Pr-SPRIX	8	73	57 (93)	20 (31)	23 (48)
3	**1**	23	91	41	41	18
4	(*R*)-**2**	8	94	13 (63)	50 (5)	37 (54)
5	**3**[c]	45	trace			
6	**4**	45	trace			

a) Total yield of Wacker-type cyclization products b) The reaction at 0 °C for 85 h gave **10** (65%, 95 % ee), **11** (5%, 45% ee), and **12** (26%, 60% ee). c) R = *t*-Bu

^{1}H-NMR spectra showed a significant downfield shift of the peaks corresponding to the methylene protons on isoxazoline ring by the formation of the complex.[8] The ^{13}C-NMR spectra supposed the symmetrical structure of the complexes. These results indicate a spontaneous formation of Pd(II) complex with bis(isoxazoline) ligands (**1**) and (**2**) with bidentate manner.

The accelerating abilities of newly prepared bis(isoxazoline) ligands (**1**) and (**2**) in the tandem cyclization of alkenyl alcohol (**9**) are shown in Table 1. These reactions were examined using 20 mol % of $Pd(OCOCF_3)_2$ and 24 mol % of ligand in the presence of *p*-benzoquinone at room temperature. The Pd(II)-SPRIX complex promoted this reaction to give a bicyclic compound (**10**) as single diastereomer with 93% ee, together with monocyclized compounds (**11**) and (**12**) (entry 2). When the reaction was carried out using ligand (**1**), the cyclized products were obtained in 91% yield (entry 3). In the case of ligand (**2**), the reaction smoothly proceeded to afford the cyclized products in 94% yield, and the tandem product (**10**) was obtained with 63% ee (entry 4). Because the reaction without bis(isoxazoline) ligand gave only 34% yield of products (entry 1),[9] these results clearly indicated that both the bis(isoxazoline) ligands (**1**) and (**2**) have the acceleration effects on the Wacker-type cyclization. It is noteworthy that the known chiral bis(oxazoline) ligands such as bis(oxazolinyl)propane (**3**),[5] and (*S*,*S*)-ip-boxax (**4**) did not promote this cyclization (entries 5 and 6). This is clearly showing that isoxazoline moiety in the ligands plays a key role for promoting the cyclization. In terms of the tandem cyclization, the ratio of the tandem product (**10**) was reduced by using **1** and **2** compared with that obtained by SPRIX. These results indicate that the chiral spiro backbone of SPRIXs is essential to promote the tandem cyclization with high enantioselectivity.

In conclusion, two types of new bis(isoxazoline) ligand, 2,2'-bis(isoxazolinyl)propane (**1**) and (*R*)-2,2'-bis(isoxazolinyl)-1,1'-binaphthyl (**2**) have been prepared and the strong ligand-acceleration effects were demonstrated in Pd(II)-catalyzed Wacker-type cyclization of alkenyl alcohol. The lack of the acceleration effects of oxazoline ligands clearly shows the crucial role of isoxazoline moiety on the Wacker-type cyclization of alkenyl alcohols.

EXPERIMENTAL

General procedures

^{1}H NMR and ^{13}C NMR spectra were recorded on 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 an internal standard. IR spectra were obtained with SHIMADZU FTIR-8300 instrument. Optical rotations were measured with JASCO DIP-370 Polarimeter. Enantiomeric excesses were determined by HPLC analysis equipped with a chiral stationary phased column (DAICEL CHIRALPAK AD). Column chromatography was conducted on Kanto Silica Gel 60 (40-100 μm). Anhydrous THF was purchased from Kanto Chemicals, Tokyo. Anhydrous CH_2Cl_2 was distilled from calcium hydride.

Preparation of 2,2-Dimethylmalonaldehyde Dioxime (6) To a solution of $(COCl)_2$ (3.3 mL, 38 mmol) in CH_2Cl_2 (32 mL) was added a solution of DMSO (3.7 mL, 52 mmol) in CH_2Cl_2 (10 mL) slowly at -78 ^oC, and the mixture was stirred for 40 min. To the mixture was added a solution of 2,2-dimethyl-1,3-propanediol (**5**) (1.04 g, 10 mmol) in CH_2Cl_2 (20 mL) dropwise at -78 ^oC, and the reaction mixture was stirred for 30 min. Then Et_3N (12.5 mL, 90 mmol) was added to the reaction mixture at -78 ^oC. 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. To the crude residue were added NH_2OH-HCl (2.8 g, 40 mmol) and pyridine (40 mL) at 0 ^oC. The reaction mixture was stirred at rt for 1 day. To the reaction mixture was added NH_2OH-HCl (1.4 g, 20.0 mmol) and the whole was stirred for additional two days. The mixture was diluted with diethyl ether, washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give 2,2-dimethylmalonaldehyde dioxime (**6**) (889 mg, 68 % in 2 steps) as a white solid. mp 103-104 ^oC (hexane ether). ^1H NMR (acetone-d_6): □1.21 (s, 6H), 7.35 (s, 2H), 9.72 (s, 2H). ^{13}C NMR (acetone-d_6): δ 24.3, 39.4, 154.5. IR (neat) : 3207, 2978, 1738, 1452, 1364, 1205, 951 cm^{-1}. FAB-HRMS. Calcd for $C_5H_{11}N_2O_2$ $[M+H]^+$: 131.0820. Found : 131.0804.

Preparation of 2,2-Bis(5,5-diethyl-4,5-dihydroisoxazol-3-yl)propane (1) To a solution of **6** (65 mg, 0.5 mmol) in THF (10 mL) were added 2-ethyl-1-butene (1.22 mL, 10.0 mmol) and aq. NaOCl (>5.0% chlorine, 1.0 mL) at 0 ^oC, and the mixture was stirred for 20 h at rt. The reaction was quenched by the addition of water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 25/1 to 5/1) to give 2,2-bis(5,5-diethyl-4,5-dihydroisoxazol-3-yl)propane (**1**) (103 mg, 70 %) as a white solid. mp 35-39 ^oC (hexane ether). ^1H NMR ($CDCl_3$): □0.90 (t, *J* = 7.5 Hz, 12H), 1.59 (s, 6H), 1.63 (q, *J* = 7.5 Hz, 8H), 2.66 (s, 4H). ^{13}C NMR ($CDCl_3$): □8.2, 24.3, 30.6, 38.2, 41.7, 89.8, 160.8. IR (neat) : 2968, 2937, 1460, 1325, 1242, 908, 860, 727, 646 cm^{-1}. *Anal*. Calcd for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found : C, 69.08; H, 10.04; N, 9.17.

Preparation of (*R*)-1,1'-Binaphthyl-2,2'-dicarbaldehyde Dioxime (8) To a solution of $(COCl)_2$ (324 □L, 3.72 mmol) in CH_2Cl_2 (5 mL) was added a solution of DMSO (354 □L, 5.00 mmol) in CH_2Cl_2 (2 mL) slowly at -78 ^oC, and the reaction mixture was stirred for 40 min. To the mixture was added a solution of (*R*)-2,2'-bis(hydroxymethyl)-1,1'-binaphthyl (**7**) (390 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) dropwise at -78 ^oC, and the reaction mixture was stirred for 30 min. Then Et_3N (1.21 mL, 8.68 mmol) was added to the mixture at -78 ^oC. 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 dissolved in CH_2Cl_2 (5 mL) and NH_2OH-HCl (344 mg, 4.96 mmol) and pyridine (5 mL) was added at 0 ^oC. The reaction mixture was stirred at rt for 3 h. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to give (*R*)-1,1'-binaphthyl-2,2'-dicarbaldehyde dioxime (**8**) (400 mg, 95 % in 2 steps) as a white solid. mp 306 – 309 ^oC (hexane–diethyl ether). $[\alpha]_D^{29}$ +74.1^o (c = 1. 04, acetone). ^1H NMR ($CDCl_3$): δ 7.07 (d, *J* = 8.5 Hz, 2H), 7.26 (ddd, *J* = 8.5, 6.9, and 1.3 Hz, 2H), 7.49 (ddd, *J* = 8.0, 6.9, and 1.3 Hz, 2H), 7.62 (s, 2H), 7.85 (s, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 122.1, 126.6, 127.1, 127.1, 128.1, 129.0, 129.3, 133.0, 134.0, 134.8, 148.7. IR (neat) : 3236, 1425, 1323, 972, 951, 816, 785, 741 cm^{-1}. FAB-HRMS. Calcd for $C_{22}H_{17}N_2O_2$ $[M+H]^+$: 341.1290. Found : 341.1300.

Preparation of (*R*)-2,2'-Bis(5,5-diethyl-4,5-dihydroisoxazol-3-yl)-1,1'-binaphthyl (2) To a solution of **8** (92 mg, 0.27 mmol) in THF (6 mL) were added 2-ethyl-1-butene (0.66 mL, 5.4 mmol) and aq. NaOCl (>5.0% chlorine, 0.5 mL) at 0 ^oC, and the whole was stirred for 5 h at room temperature. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1 to 4/1) to give (*R*)-2,2'-bis(5,5-diethyl-4,5-dihydroisoxazol-3-yl)-1,1'-binaphthyl (**2**) as colorless oil (85 mg, 62 %). $[\alpha]_D^{28}$ +33.8^o (c = 1.25, acetone). ^1H NMR ($CDCl_3$): δ 0.38 (t, *J* = 7.6 Hz, 6H), 0.61 (t, *J* = 7.6 Hz, 6H), 1.20 (q, *J* = 7.6 Hz, 4H), 1.33 (q, *J* = 7.6 Hz, 4H), 1.71 (d, *J* = 17.3 Hz, 2H), 2.04 (d, *J* = 17.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.28 (ddd, *J* = 8.3, 6.8, and 1.4 Hz, 2H), 7.49 (ddd, *J* = 8.1, 6.8, and 1.4 Hz, 2H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 7.5, 7.8, 30.3, 30.4, 42.6, 90.6, 125.8, 126.7, 126.9, 127.0, 127.9, 128.6, 129.4, 133.3, 134.56, 156.4. IR (neat) : 3059, 2962, 2926, 1456, 986, 930, 829, 748 cm^{-1}. ESI-HRMS. Calcd for $C_{34}H_{36}N_2NaO_2$ $[M+Na]^+$: 527.2675. Found : 527.2682.

General Procedure for Pd(II)-catalyzed Tandem Cyclization *via* the Oxy-palladation A mixture of bis(isoxazoline) 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 (**9**) (0.10 mmol) and *p*-benzoquinone (43 mg, 0.40 mmol), and the reaction mixture was stirred until **9** was completely consumed on TLC. The reaction was quenched by the addition of H_2O 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 (**10**) and the mixture of monocyclized products (**11** and **12**). The ratio of **10** and monocyclized products (**11** and **12**) was determined by isolated yields. The ratio of **11** and **12** was determined by ^1H NMR spectrometry. The enantiomeric excess of the products was determined by HPLC

analysis using chiral stationary phased column (DAICEL CHIRALPAK AD, hexane/*i*-PrOH = 120/1, flow rate = 0.25 mL/min).

ACKNOWLEDGMENT

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.S. and M.A.A. appreciate Research Fellowships from the Japan Society for the Promotion of Science (JSPS) for Young Scientists. We thank the technical staff at the Materials Analysis Center of ISIR.

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) 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.
3. (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.
4. E. 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. T. Ohta, M. Ito, K. Inagaki, and H. Takaya, *Tetrahedron Lett*., 1993, **34**, 1615.
7. Oxidative conditions: MeOH-35% aq. H_2O_2 (1:1) at room temperature overnight.
8. Downfield shift values: $Pd(OCOCF_3)_2$-**1** (□□: 0.24), $Pd(OCOCF_3)_2$-**2** (□□: 0.70).
9. Reaction using $Pd(OAc)_2$ or $PdCl_2$ without bis(isoxazoline) ligand proceeded very slowly.