Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2569–2573

Application of chiral 2,6-bis(thiazolinyl)pyridines in asymmetric Ru-catalyzed cyclopropanations with diazoesters

Paul Le Maux,[a] Isabelle Abrunhosa,[b] Mathieu Berchel,[a] Gérard Simonneaux,[a,*] Mihaela Gulea[b] and Serge Masson[b,*]

[a]*Laboratoire de Chimie Organométallique et Biologique, UMR CNRS 6509, Université de Rennes 1, 35042 Rennes Cedex, France*
[b]*Laboratoire de Chimie Moléculaire et Thio-organique, UMR CNRS 6507, Université de Caen et ISMRA, F-14050 Caen, France*

Received 10 June 2004; accepted 28 June 2004
Available online 3 August 2004

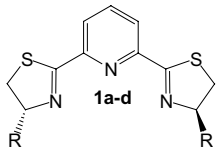
Abstract—Chiral 2,6-bis(thiazolinyl)pyridines were examined as ligands for ruthenium-catalyzed asymmetric catalytic cyclopropanation of olefins with diisopropyl diazomethylphosphonate and ethyl diazoacetate. Enantioselectivities of up to 84% for the *trans*-cyclopropylphosphonate were observed.

1. Introduction

The asymmetric cyclopropanation of alkenes with diazoesters catalyzed by transition metals has been intensively studied since the first report by Nozaki et al.[1] of enantioselective cyclopropanation with a chiral copper(II) chelate. Over the last decade, ruthenium complexes have been redeveloped.[2,3] This is partly due to the design of ruthenium catalysts that possess chiral bis(oxazolinyl)pyridine (Pybox) ligands described by Nishiyama et al.[4] This catalytic system gives high *trans*-selectivity with high enantioselectivity.[4,5] In contrast, a limited number of chiral bis(thiazoline) ligands has been synthesized[6,7] while their uses in catalytic reactions have been rarely examined. Two remarkable exceptions are the Rh(I)-catalyzed asymmetric hydrosilylation of acetophenone[6] and the Pd-catalyzed allylic substitution reaction.[7] Moreover, some of us have recently compared the behaviour of several bis(thiazolines) and the corresponding bis(oxazolines) as ligands in the Pd-catalyzed Tsuji–Trost allylic substitution reaction with important differences concerning the reactivity and asymmetric induction being observed.[8] As part of our continuing efforts to promote ruthenium complexes in asymmetric catalysis,[9] we herein report the use of chiral ruthenium 2,6-bis(thiazolinyl)pyridine complexes as catalysts for the asymmetric cyclopropanation of styrene derivatives using ethyl diazoacetate, as well as diisopropyl diazomethylphosphonate. It should be emphasized that cyclopropylphosphonates display interesting biological activity such as inhibition for deaminases and alanine racemase.[10]

2. Results and discussion

Homochiral 2,6-bis(thiazolinyl)pyridines **1a–c** (Scheme 1) were synthesized from dithioesters and commercial enantiopure 2-aminoalcohols, as previously reported for **1d**.[7]



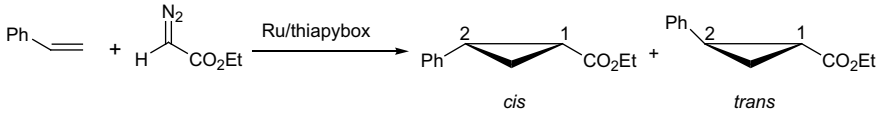
Ligand 1	R	Configuration
1a	Et	*(R,R)*
1b	iPr	*(S,S)*
1c	Bn	*(S,S)*
1d	Ph	*(R,R)*

Scheme 1.

The asymmetric cyclopropanation of styrene and diazoethylacetate was carried out using a solution of the

* Corresponding authors. Tel.: +33-(0)2-99286285; fax: +33-(0)2-99281646; e-mail: simonnea@univ-rennes1.fr

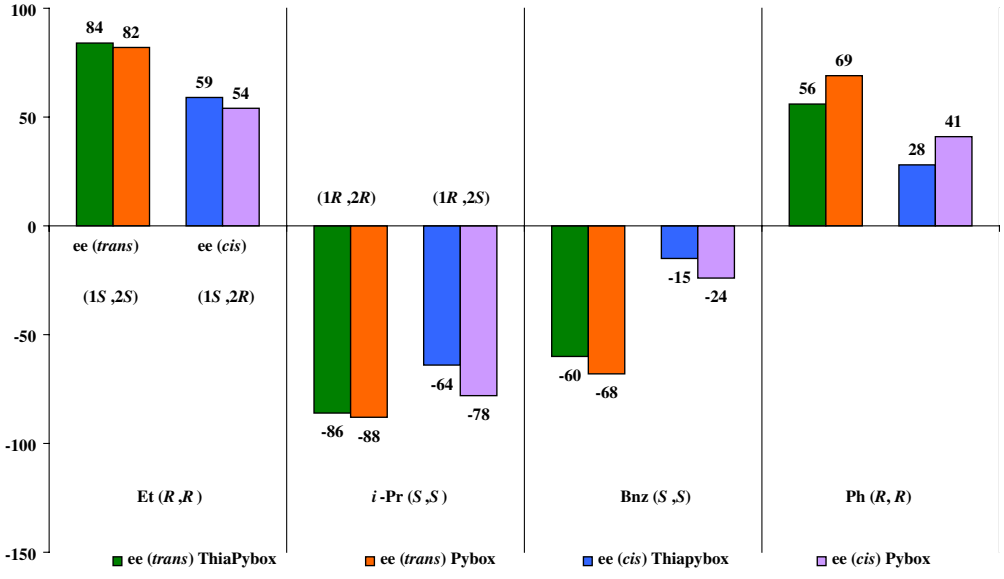
0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.06.039



Scheme 2.

homochiral ligand and $[Ru(p\text{-cymene})Cl_2]_2$[11] as an in situ catalyst, in a protocol similar to that reported for bis(oxazolinyl)Ru complexes (Scheme 2).[4] Four different chiral 2,6-bis(thiazolinyl)pyridines **1a**–**d** were used as ligands (Scheme 1). For example, the addition of homochiral ligand **1a** or **1b** to a solution of $[Ru(p\text{-cymene})Cl_2]_2$ gave a dark red solution, which was stirred for 5 h at room temperature before addition of styrene and diazoacetate. By contrast, 1 h of stirring was only necessary with R = Bn and Ph substituted ligands **1c** and **1d** to obtain the optimal conditions (see Experimental section). The results are reported in Table 1.

As it is evident from the data, the two ligands **1a** (R = Et) and **1b** (R = *i*Pr) are superior to **1c** (R = Bn) and **1d** (R = Ph). In all cases, the cyclopropanation is very selective in favour of the *trans*-isomer, which is also obtained with better enantiomeric excesses than its *cis*-isomer (Scheme 2). With ligands **1a** and **1b** ee >80% are observed and they are comparable to those previously reported for cyclopropanation using ruthenium bis(oxazolinyl) complexes.[5] By contrast, % ee values for **1c** (R = Bn) or **1d** (R = Ph) reached only moderate levels. A diagram allowing a comparison between the two catalytic systems is shown below.



Although we could anticipate a different electronic density between the two ligands that is thia–Pybox and Pybox, due to the presence of a sulfur atom in the five-membered ring of the former, it appears in this Ru-catalyzed cyclopropanation reaction that this modification does not change the preferred configuration and slightly alters the enantiomeric excess of the cyclopropane derivatives. Varying the substituents in the *para*-phenyl position of the styrene does not change significantly the enantiomeric excess, showing the weak electronic effect of the substrate upon enantioselectivity. In contrast, a remote electronic control in asymmetric cyclopropanation with chiral Ru–Pybox was found, with substituted bis(oxazoline)Ru.[12]

These Ru–thia–Pybox complexes can also be applied to catalyze styrene cyclopropanation with diisopropyl diazomethylphosphonate (Scheme 3). Cyclopropylphosphonates are very convenient intermediates for the synthesis of diphenylmethylene-cyclopropane derivatives[13] by the Wadsworth–Emmons reaction.[14] Since our first catalytic enantioselective cyclopropanation of an olefin with diisopropyl diazomethylphosphonate by a chiral porphyrin ruthenium complex,[15] only one study using Ru-bis(oxazoline) catalytic system with diazomethylphosphonate has been mentioned as a work to be published in a review.[16] Good enantiomeric excesses up to 90% were obtain. Herein, with R = Et, the yield and the enantiomeric excesses compare well with those obtained with ethyl diazoacetate (see Table 1). In this case, however, the reaction time is longer (12 h), as we have previously observed with cyclopropanation of styrene catalyzed by ruthenium porphyrins.[15]

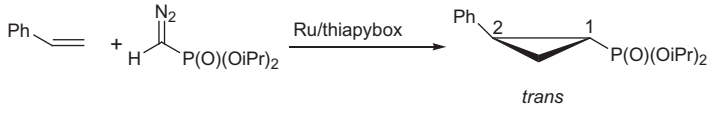
It has already been reported that cyclopropanation with the Pybox-ruthenium system should proceed concertedly via an attack of styrene on the possible intermediate

Table 1. Asymmetric cyclopropanation of styrene and its derivatives with ethyl diazoacetate and isopropyl diazomethylphosphonate catalyzed by Ru/thia–Pybox[a]

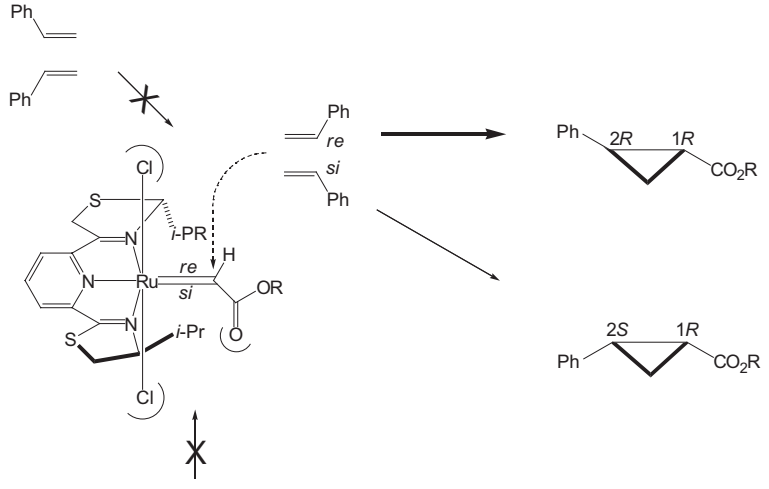
Catalyst L =	Substrate	N_2CHR R =	Products: *trans*- and *cis*-cyclopropyl esters			
			Yield (%)[b]	Selectivity *trans*/*cis*[c]	Ee (config.)	
					trans %[d]	*cis*
Et	Styrene	CO_2Et	87	13.6	84 (1*S*,2*S*)	59 (1*S*,2*R*)
*i*Pr	Styrene	CO_2Et	89	12.4	85 (1*R*,2*R*)	65 (1*R*,2*S*)
Ph	Styrene	CO_2Et	86	8.8	47 (1*S*,2*S*)	20 (1*S*,2*R*)
Bzyl	Styrene	CO_2Et	92	10.1	60 (1*R*,2*R*)	15 (1*R*,2*S*)
Et	*p*-CF_3 styrene	CO_2Et	83	19	83 (1*S*,2*S*)	55 (1*S*,2*R*)
*i*Pr	*p*-CF_3 styrene	CO_2Et	86	12.5	77 (1*R*,2*R*)	48 (1*R*,2*S*)
Ph	*p*-CF_3 styrene	CO_2Et	89	16.2	76 (1*S*,2*S*)	15 (1*S*,2*R*)
Bzyl	*p*-CF_3 styrene	CO_2Et	75	12.1	45 (1*R*,2*R*)	4 (1*R*,2*S*)
Et	*p*-CH_3 styrene	CO_2Et	84	10.5	81 (1*S*,2*S*)	46 (1*S*,2*R*)
*i*Pr	*p*-CH_3 styrene	CO_2Et	72	9.6	81 (1*R*,2*R*)	54 (1*R*,2*S*)
Ph	*p*-CH_3 styrene	CO_2Et	78	8.6	45 (1*S*,2*S*)	20 (1*S*,2*R*)
Bzyl	*p*-CH_3 styrene	CO_2Et	97	11.5	58 (1*R*,2*R*)	2 (1*R*,2*S*)
Et	*p*-OCH_3 styrene	CO_2Et	96	10.5	85 (1*S*,2*S*)	48 (1*S*,2*R*)
*i*Pr	*p*-OCH_3 styrene	CO_2Et	86	11.6	83 (1*R*,2*R*)	64 (1*R*,2*S*)
Ph	*p*-OCH_3 styrene	CO_2Et	81	7.7	53 (1*S*,2*S*)	14 (*1S*,2*R*)
Bzyl	*p*-OCH_3 styrene	CO_2Et	80	7.3	52 (1*R*,2*R*)	4 (1*R*,2*S*)
Et	Styrene	$PO(OiPr)_2$	62	—	84[e]	ND[f]
*i*Pr	Styrene	$PO(OiPr)_2$	35	—	64	ND
Ph	Styrene	$PO(OiPr)_2$	18	—	17	ND
Bzyl	Styrene	$PO(OiPr)_2$	17	—	17	ND

[a] Reactions were performed in CH_2Cl_2 at 35 °C for 1 h with a catalyst:diazo:substrate molar ratio of 1:200:1000.
[b] Isolated yields based on ethyl diazoacetate and isopropyl diazomethylphosphonate.
[c] Determined by chiral GC (chiral column: Chrompack Chirasil-Dex CB) for styrene and *p*-CF_3 styrene and by chiral HPLC (Chiralcel OJ-H column, Daicel) for *p*-CH_3 styrene and *p*-OMe styrene.
[d] The configuration is given in parentheses.
[e] The configuration has not been determined.
[f] The *cis*-cyclopropyl esters were formed in too small quantities to be analyzed.

carbene complex without olefin coordination.[17] Thus carbene ruthenium intermediates can also be suggested in these cyclopropanations as previously demonstrated with bis(oxazoline) analogues.[17] The enantioselectivities for the cyclopropanation observed with catalysts were consistent with the alkene approach trajectories that are depicted in Scheme 4. In these representations, the complex orientates the carbon double bond of the



Scheme 3.



Scheme 4.

substrate to a front side approach of the metallocarbene, as indicated in Scheme 4, yielding to the *trans*-isomer. The reverse approach of the substrate produces the *cis*-isomer. Similar orientations have been previously proposed for the asymmetric cyclopropanation of styrene catalyzed by chiral Ru-bis(oxazoline) complexes. The unexpected decrease in the ees for the *trans*-product with phenyl and benzyl substituted ligands could be explained by the larger steric interactions between the aryl group of the ligand and the phenyl group of the incoming substrate.

3. Conclusion

The most probable mechanism of the transition-metal-complex-catalyzed cyclopropanation is generally divided in two main steps. First, a transition metal complex reacts with diazoacetates to generate a carbene complex as an intermediate and then the intermediate reacts with alkenes to give cyclopropanes. As suggested recently by a theoretical analysis,[18] the nature of the metal–carbene bond may be quite important, in particular in regards to the diastereoselectivity and enantioselectivity. Thus, substituting an oxygen atom by a sulfur atom in the five-membered ring of the chiral ligands could lead to a different situation as has been observed for the bidentate bis(thiazolines) in the Pd-catalyzed allylic alkylation.[8] Comparative evaluation of enantiocontrol for cyclopropanation of styrene with chiral ruthenium bis(oxazoline) and bis(thiazoline) shows many similarities with, in some cases, good enantiomeric excess. These surveys also illustrate that chiral bis(thiazoline) are versatile ligands, which may be used in many different reactions involving carbene transfer. These encouraging results should open up the way to other catalytic systems. Their development should be considerably widened in the future, with application in asymmetric catalysis.

4. Experimental

4.1. General

Reactions were carried out under an argon atmosphere with magnetic stirring. ^{1}H NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 on a Bruker AC 400 spectrometer. The chemical shifts (δ) are expressed in ppm relative to TMS. The coupling constants (J) are given in hertz. Mass spectra were obtained using a Nermag R 10H spectrometer. GC analysis were performed on a VARIAN CP-3380 gas chromatography (using helium as the carrier gas) equipped with a CP-1177 Injector and a Flame Ionization Detector (FID). A WCOT fused silica Chrompack capillary column coating CP-Chirasil-Dex CB (25 m*0.25 mm i.d.; 0.25 μm film thickness) was used. Analytic HPLC data were obtained using a VARIAN Prostar 218 system equipped with a Chiralcel OJ-H column (Daicel, 0.46 cm i.d.*25 cm). IR spectra were recorded on a Perkin–Elmer 16 PC spectrophoto meter, ν (cm^{-1}) are given. Optical rotations were measured on a Perkin–Elmer model 241 polarimeter for the sodium D line at 20 °C. Microanalyses were performed at Caen with an automatic apparatus ThermoQuest. Synthesized products were purified by flash column chromatography on silica gel. Styrene derivatives were purchased from Aldrich, Acros and Lancaster. Before being used, chloroform, dichloromethane and benzene were distilled under argon over K_2CO_3, CaH and Na/benzophenone, respectively.

4.2. Preparation of pyridine-2,6-bis(thiazoline) 1a–d

Pyridine-2,6-bis(thiazoline) **1a–c** have been prepared using the general method already described for analogous compounds with R = *t*Bu, Ph (**1d**),[7] in two steps, starting from dimethyl 2,6-pyridine bis(dithiocarboxylate)[19] and 2 equiv of (*S*)-valinol. They were purified by silica gel flash chromatography (pentane/diethyl ether).

4.2.1. (*R*,*R*)-2,6-Bis[4-ethyl-4,5-dihydro-2-thiazolyl]pyridine 1a. Yellow solid, mp = 179 °C, $[\alpha]_D^{20} = +135$ (*c* 1, acetone), overall yield = 75%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.09 (t, 6H, J_3 = 7.4 Hz, 2 × CH_3CH_2), 1.70–2.00 (m, 4H, 2 × CH_3CH_2), 3.05 (dd, 2H, J_2 = 11 Hz, J_3 = 8.3 Hz, 2 × CHHS), 3.45 (dd, 2H, J_2 = 11.0 Hz, J_3 = 8.7 Hz, 2 × CHHS), 4.67 (dt, 2H, J_3 = 7.4 Hz, J_3 = 8.3 Hz, 2 × CHN), 7.35 (t, 1H, J_3 = 7.6 Hz, H_4), 7.72 (d, 2H, J = 7.6 Hz, H_3 and H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): 11.2 (2 × CH_3CH_2), 28.6 (2 × CH_3CH_2), 35.8 (2 × CH_2S), 80.3 (2 × CHN), 123.8, 137.5, 150.6, 169.1 (S—C═N). IR (KBr): 2950, 2870, 1605 ($\nu_{S-C=N}$), 1460, 1370. Anal. Calcd for $C_{15}H_{19}N_3S_2$: C, 58.98; H, 6.27; N, 13.76; S, 20.99. Found: C, 58.47; H, 6.32; N, 13.48; S, 20.60.

4.2.2. (*S*,*S*)-2,6-Bis[4-isopropyl-4,5-dihydro-2-thiazolyl]pyridine 1b. Yellow solid, mp = 190 °C, $[\alpha]_D^{20} = -125$ (*c* 1, acetone), overall yield = 70%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.04 and 1.13 (2d, 12H, J_3 = 6.7 Hz, 2 × $CH(CH_3)_2$), 2.13 (oct, 2H, J_3 = 6.7 Hz, 2 × $CH(CH_3)_2$), 3.11 (t, 2H, J_2 = 10.4 Hz, J_3 = 9.3 Hz, 2 × CHHS), 3.38 (dd, 2H, J_2 = 10.4, J_3 = 9.3 Hz, 2 × CHHS), 4.53 (td, 2H, J_3 = 9.3, 6.7 Hz, 2 × CHN), 7.83 (t, 2H, J_3 = 7.7 Hz, H_4), 8.16 (d, 2H, J_3 = 7.7 Hz, H_3 and H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.0 and 19.7 (2 × $(CH_3)_2CH$), 33.4 (2 × $CH(CH_3)_2$), 34.1 (2 × CH_2S), 84.0 (2 × CHN), 122.7, 136.9, 150.6, 167.9 (S—C═N). IR (KBr): 2960, 2870, 1600 ($\nu_{S-C=N}$), 1450, 1360, 1310, 1020. Anal. Calcd for $C_{17}H_{23}N_3S_2$: C, 61.22; H, 6.95; N, 12.60. Found: C, 60.91; H, 6.92; N, 12.78.

4.2.3. (*R*,*R*)-2,6-Bis[4-benzyl-4,5-dihydro-2-thiazolyl]pyridine 1c. Yellow solid, mp = 191 °C, $[\alpha]_D^{20} = -102$ (*c* 1, acetone), overall yield = 67%. ^{1}H NMR (400 MHz, $CDCl_3$): 2.88 (dd, 2H, J_2 = 13.6 Hz, J_3 = 9.0 Hz, 2 × CHHPh), 3.14 (dd, 2H, J_2 = 13.6 Hz, J_3 = 8.1 Hz, 2 × CHHPh), 3.33 (dd, 2H, J_2 = 11.3 Hz, J_3 = 8.6 Hz, 2 × CHHS), 3.34 (dd, 2H, J_2 = 11.3 Hz, J_3 = 8.6 Hz, 2 × CHHS), 4.99–5.07 (m, 2H, 2 × CHN), 7.20–7.36 (m, 10H, $2C_6H_5$), 7.86 (t, 1H, J_3 = 7.7 Hz, H_4), 8.16 (d, 2H, J_3 = 7.7 Hz, H_3 and H_5). ^{13}C NMR (62.9 MHz,

$CDCl_3$): 36.1 (CH_2Ph) 40.2 ($2\times CH_2S$), 79.4 ($2\times CHN$), 122.9, 126.5, 128.5, 129.4, 137.1, 138.4, 150.6, 169.6 (S—*C*=N). IR (KBr): 3060, 3020, 2920, 2860, 1600 ($\nu_{S-C=N}$), 1570, 1490, 1450, 1320, 1150, 1030. Anal. Calcd for $C_{25}H_{23}N_3S_2$: C, 69.89; H, 5.40; N, 9.78; S, 14.93. Found: C, 69.84; H, 5.41; N, 9.52; S, 14.11.

4.3. General procedure for the asymmetric catalytic cyclopropanation of olefins and analysis of the products

A solution of complex $[RuCl_2(p\text{-cymene})]_2$ (3.1 mg, 5 μmol) and (*S*,*S*)-2,6-bis[4-isopropyl-4,5-dihydro-2-thiazolyl]pyridine **1b** (4.7 mg, 14 μmol) in dichloromethane (0.1 mL) was stirred at room temperature for 5 h under argon. The reaction mixture was heated at 35 °C and styrene (104 mg, 1 mmol) then added. Ethyl diazoacetate (22.8 mg, 0.2 mmol) in dichloromethane (0.2 mL) was next added over 30 min and the reaction mixture stirred for an additional 30 min. The enantiomeric excess was determined by chiral GC with a Chirasil-Dex CB column (Chrompack, 25 m).

For the *p*-CH_3 styrene and *p*-OMe styrene compounds, the enantiomeric excess was determined by chiral HPLC with a Chiralcel OJ-H column (Daicel, 25 cm). The cyclopropyl esters formed were analyzed by GC and purified by flash chromatography with a suitable mixture of pentane and ether (5:1) as the eluant. The same procedure was applied for the cyclopropanation of styrene with the isopropyl diazophosphonate and a reaction time of 5 h.

The reaction time with the chiral ligand 2,6-pyridyl bisthiazoline and the complex $[RuCl_2(p\text{-cymene})]_2$ was 5 h when the ligand was **1a** (R = Et) and 1 h when the ligand was **1c** (R = Bn) or **1d** (R = Ph).

References

1. Nozaki, H.; Moriuti, S.; Takaya, H.; Nohori, R. *Tetrahedron Lett.* **1966**, 5239–5244.
2. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935.
3. Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183–190.
4. Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S. B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223–2224.
5. Nishiyama, H.; Itoh, Y.; Suwagara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247–1262.
6. Helmchen, G.; Krotz, A.; Ganz, K. T.; Hansen, D. *Synlett* **1991**, 257–259.
7. Abrunhosa, I.; Gulea, M.; Levillain, J.; Masson, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2851–2859.
8. Abrunhosa, I.; Delain-Bioton, L.; Gaumont, A. C.; Gulea, M.; Masson. S. *Tetrahedron*, in press.
9. Simonneaux, G.; Le Maux, P. *Coord. Chem. Rev.* **2002**, *228*, 43–60.
10. Erion, M. D.; Walsh, C. T. *Biochemistry* **1987**, *26*, 3417–3425.
11. Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233–241.
12. Park, S. B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487–2494.
13. Lewis, R. T.; Motherwell, W. B.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1995**, *51*, 3289–3302.
14. Lewis, R. T.; Motherwell, W. B. *Tetrahedron Lett.* **1988**, *29*, 5033–5036.
15. Paul-Roth, C.; De Montigny, F.; Rethoré, G.; Simonneaux, G.; Gulea, M.; Masson, S. *J. Mol. Cat. A: Chem.* **2003**, *201*, 79–91.
16. Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
17. Nishiyama, H.; Aoki, K.; Itoh, H.; Iwamura, T.; Sakata, N.; Kurihara, O.; Motoyama, Y. *Chem. Lett.* **1996**, 1071–1072.
18. Ikeno, T.; Iwakura, I.; Yamada, T. *J. Am. Chem. Soc.* **2002**, *124*, 15152–15153.
19. Abrunhosa, I.; Gulea, M.; Masson, S. *Synthesis* **2004**, *6*, 928–936.