Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 729–733

Novel chiral tetraaza ligands: synthesis and application in asymmetric transfer hydrogenation of ketones

Wei-Yi Shen, Hui Zhang, Hua-Lin Zhang and Jing-Xing Gao*

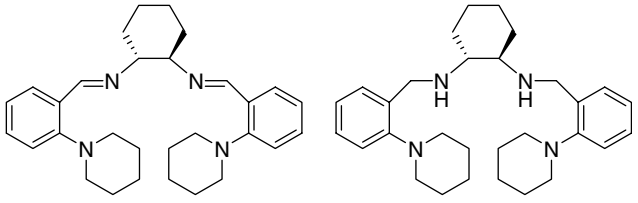
State Key Laboratory of Physical Chemistry of Solid Surfaces and Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, PR China

Received 5 January 2007; accepted 12 March 2007

Abstract—Novel chiral tetraaza ligands, N^1,N^2-bis(2-(piperidin-1-yl)benzylidene)cyclohexane-1,2-diamine **1** and N^1,N^2-bis(2-(piperidin-1-yl)benzyl)cyclohexane-1,2-diamine **2**, have been synthesized and fully characterized by analytical and spectroscopic methods. The structure of (*R*,*R*)-**1** has been established by X-ray crystallography. Asymmetric transfer hydrogenation of aromatic ketones with the catalysts prepared in situ from $[IrHCl_2(COD)]_2$ and the chiral tetraaza ligands in 2-propanol gave the corresponding optically active secondary alcohols in high conversions and good ees (up to 91%) under mild reaction conditions.

1. Introduction

The realization of most homogeneous asymmetric catalysis should need chiral metal complexes, which act as templates to regulate organic reactions.[1] Generally, chiral metal complexes contain various metal centers and chiral organic ligands which allow good stereocontrol and modify the reactivity and selectivity of the metal center in catalytic processes. For the past decades, chiral phosphine ligands are becoming some of the more important and popular ligands in asymmetric catalysis.[2,3] It should be noted, however, in the field of asymmetric transfer hydrogenation reaction, the most used chiral auxiliaries contain nitrogen, not phosphorus, as the donor atom.[4–6] Recently, chiral tetraaza ligands have received much attention because of their simple synthesis from easily available inexpensive precursors, less toxic than phosphine ligands, and providing multi-coordination sites on the metal center.[7] Chiral tetraaza ligands have been successfully used as chiral auxiliaries for a wide range of reactions, such as asymmetric allylic alkylation,[8–12] asymmetric hydrosilylation,[13,14] asymmetric cyanosilylation[15,16] and dialkylzinc addition.[17,18] However, when chiral tetraaza ligands were used for asymmetric transfer hydrogenation of aryl ketones, the results were unsatisfactory, and only gave low enantiomeric excesses.[7,19,20] Recently, we have synthesized two novel chiral tetraaza ligands, N^1,N^2-bis(2-(piperidin-1-yl)benzylidene)-cyclohexane-1,2-diamine **1** and N^1,N^2-bis(2-(piperidin-1-yl)benzyl)cyclohexane-1,2-diamine **2,** which were used in the Ir-catalyzed asymmetric transfer hydrogenation of aromatic ketones, giving the corresponding optically active secondary alcohols in high chemical yields and in fair to good ees.



(*R*,*R*)-**1** (*R*,*R*)-**2**

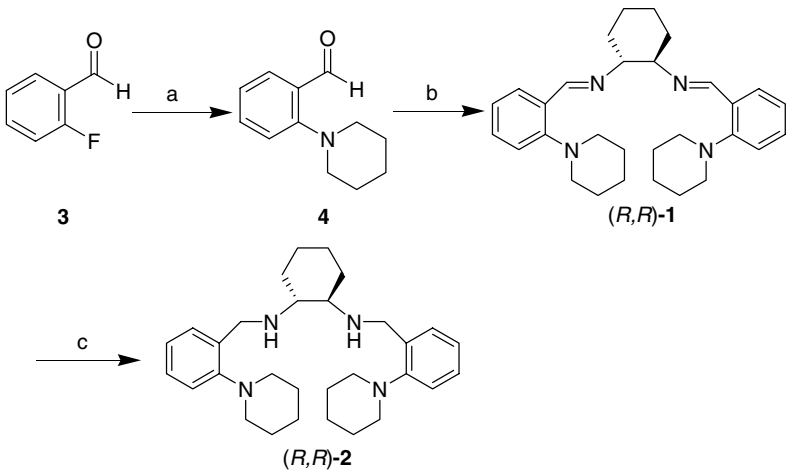
2. Results and discussion

2.1. Synthesis of ligands 1 and 2

The synthesis of chiral tetraaza ligands (*R*,*R*)-**1** and (*R*,*R*)-**2** is outlined in Scheme 1. According to the literature procedure,[21] 2-(piperidin-1-yl)benzaldehyde **4** can be conveniently prepared by nucleophilic displacement of the

* Corresponding author. Tel.: +86 592 2180116; fax: +86 592 2183047; e-mail addresses: jxgao@xmu.edu.cn; cuihua@xmu.edu.cn

0957-4166/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2007.03.013



Scheme 1. Synthesis of tetraaza ligands (*R*,*R*)-**1** and (*R*,*R*)-**2**. Reagents and conditions: (a) K_2CO_3, DMF, piperidine, reflux; (b) (*R*,*R*)-1,2-diaminocyclohexane, CH_3CH_2OH, reflux; (c) $NaBH_4$, CH_3CH_2OH, reflux.

activated fluorine in 2-fluorobenzaldehyde with piperidine in refluxing dimethylformamide (83% yield). The imine ligand (*R*,*R*)-**1** was synthesized by the condensation of (*R*,*R*)-1,2-diaminocyclohexane with **4** in refluxing ethanol (74% yield). Ligand (*R*,*R*)-**1** is stable in air and water. The IR spectrum of (*R*,*R*)-**1** exhibited a strong C=N stretch at 1637 cm^{-1}. The ^1H NMR spectrum presented a singlet at δ 8.55 for the imino protons. The geometry of this compound was confirmed by the X-ray crystal structure analyses (Fig. 1). Reduction of the imino ligand (*R*,*R*)-**1** with excess $NaBH_4$ was carried out in refluxing ethanol to afford the amine ligand (*R*,*R*)-**2** in 70% yield.

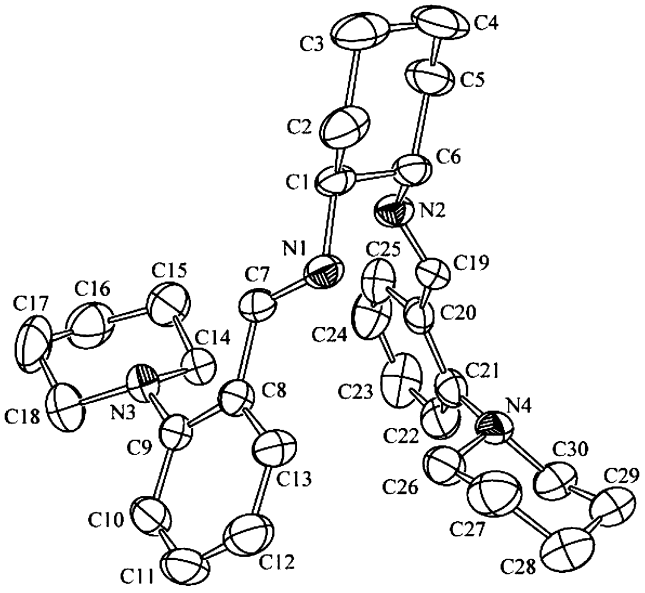


Figure 1. Molecular structure of (*R*,*R*)-**1**.

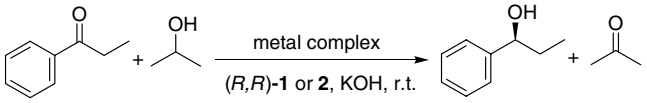
2.2. Asymmetric transfer hydrogenation of various ketones

2.2.1. Asymmetric transfer hydrogenation of propiophenone. In an initial experiment, the transfer hydrogenation of propiophenone was chosen as a model reaction. Some Ru, Rh or Ir complexes with ligand (*R*,*R*)-**1** or (*R*,*R*)-**2** as catalyst precursors have been tested for this reduction. The catalyst systems were generated in situ by mixing ligand (*R*,*R*)-**1** or (*R*,*R*)-**2** and various metal complexes in refluxing 2-propanol, which were directly used for reduction of propiophenone. Typical results are listed in Table 1.

The $Ru(DMSO)_4Cl_2$/(*R*,*R*)-**1** system showed only low activity and enantioselectivity (Table 1, entry 1), while ligand (*R*,*R*)-**2** was used, the activity improved but the ee remained low (Table 1, entry 2). When catalyst systems, coupled with $[RhCl(COD)]_2$ and either (*R*,*R*)-**1** or (*R*,*R*)-**2** were applied, no reaction was observed (Table 1, entries 3 and 4). While iridium complexes $[IrCl(COD)]_2$ or $[IrHCl_2(COD)]_2$ was employed as the metallic precursor, the $[IrHCl_2(COD)]_2$/(*R*,*R*)-**1** system gave the best result (97% yield and 67% ee). We also found this system to be stable in air and the catalytic reactions can be performed under air atmosphere.

2.2.2. Asymmetric transfer hydrogenation of aromatic ketones. The aforementioned catalytic system $[IrHCl_2(COD)]_2$/(*R*,*R*)-**1** has been further examined for the asymmetric transfer hydrogenation of various aromatic ketones. The results are summarized in Table 2. A variety of aromatic ketones can be reduced to the corresponding optically active secondary alcohols with high chemical yields and good enantiomeric excesses under air atmosphere. We found that the reaction rate and enantioselectivity were affected by the steric property of the substrates in alkyl moiety. As the bulkiness of the alkyl group increased from methyl, ethyl, propyl to *n*-butyl, the enantioselectivity gradually increased (76–91% ee, Table 2, entries 1–5), but the reduction of isobutyrophenone proceeded slowly with lower ee (Table 2, entry 6). The electronic properties and position of the groups in ring substituent also affected the enantioselectivity of the reduction reaction. *ortho*-Substituted acetophenone was reduced smoothly with 90% ee (Table 2, entries 7 and 8), while a lower ee for *meta*-methyl acetophenone (Table 2, entry 9) was obtained. The introduction of an electron-donating substituent, such as a

Table 1. Influence of the catalyst precursors on the asymmetric transfer hydrogenation of propiophenone[a]



Entry	Precursor	Ligand	Temperature (°C)	Time (h)	Conversion[b] (%)	ee[b] (%)	Configuration[c]
1	$Ru(DMSO)_4Cl_2$	(*R*,*R*)-**1**	25	24	8	10	(*S*)
2		(*R*,*R*)-**2**	25	6	60	12	(*S*)
3	$[RhCl(COD)]_2$	(*R*,*R*)-**1**	25	3	Trace	—	—
4		(*R*,*R*)-**2**	25	3	Trace	—	—
5	$[IrCl(COD)]_2$	(*R*,*R*)-**1**	25	5	97	57	(*S*)
6		(*R*,*R*)-**2**	25	2	82	55	(*S*)
7	$[IrHCl_2(COD)]_2$	(*R*,*R*)-**1**	25	2	97	67	(*S*)
8		(*R*,*R*)-**2**	25	3	27	56	(*S*)

[a] Reaction conditions: propiophenone, 1.0 mmol; [M]:[ligand]:[KOH]:[propiophenone] = 1:1.2:10:100; 2-propanol, 10 mL.
[b] Conversions and enantiomeric excesses were determined by GC analysis using a chiral G-TA column.
[c] The configurations were determined by comparison of the retention times of the enantiomers on the GC traces with literature values.

meta-methoxyl group in acetophenone gave higher conversion but lower ee (Table 2, entry 10). The ketone having an electron-withdrawing substituent, *ortho*- or *para*-chloroacetophenone gave 99% chemical yield with moderate ee (Table 2, entries 11 and 12).

In order to determine the role of the piperidinyl group in the phenyl ring of ligand **1**, we synthesized the chiral ligand, (1*R*,2*R*)-N^1,N^2-dibenzylidenecyclohexane-1,2-diamine,[22] which does not contain any substituent in the 2-position of the phenyl ring. This ligand has been examined in the asymmetric transfer hydrogenation of 2′-methylacetophenone, with lower conversion and ee achieved (35% conversion, 78% ee). This result indicated that the piperidinyl group in the phenyl ring of ligand **1** played an important role in asymmetric transfer hydrogenations.

3. Conclusion

The new chiral tetraaza ligands (*R*,*R*)-**1** and (*R*,*R*)-**2** have been prepared and the molecular structure of (*R*,*R*)-**1** established. These ligands were employed for the first time to catalyze the enantioselective reduction of a variety of aromatic ketones with high chemical yields and satisfactory enantioselectivities under an air atmosphere. Although the enantioselectivity remains to be further improved, the present study shows that chiral tetraaza ligands can be also used in asymmetric transfer hydrogenation. These results provide a useful insight for the design of more efficient chiral catalytic system, based on C_2-symmetric tetraaza ligands.

4. Experimental

4.1. General methods

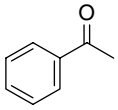
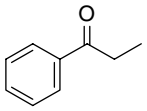
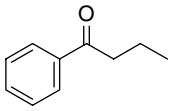
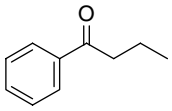
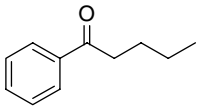
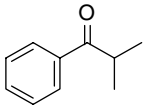
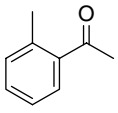
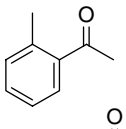
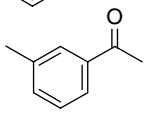
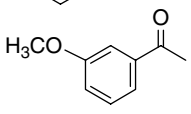
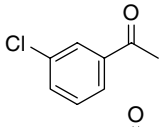
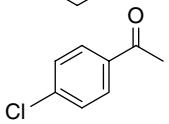
NMR spectra were recorded on a Bruker AV 400 instrument using TMS as an internal standard in $CDCl_3$. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were recorded on a Finnigan LCQ mass spectrometer. Elemental analyzes were carried out on a Carlo Erba 1110 analyzer. The yields and ee values were determined by GC analysis with a chiral G-TA column. Column chromatography was carried out on a silica gel (140 mesh) using ethyl acetate/petroleum ether as eluent. The solvents were dried and purified according to standard methods.

4.2. Synthesis of the chiral tetraaza ligands

4.2.1. 2-(Piperidin-1-yl)benzaldehyde 4. This compound was synthesized according to literature procedures in 83% yield, as a yellow oil (6.28 g, 83% yield).[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62–1.67 (m, 2H), 1.73–1.78 (m, 4H), 3.05 (t, $J = 5.2$ Hz, 4H), 7.04–7.10 (m, 2H), 7.49–7.51 (m, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 10.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.05, 26.20, 55.61, 118.98, 121.95, 128.62, 129.16, 134.81, 156.98, 191.65. IR (neat, NaCl) ν 3067, 2936, 2851, 2701, 1687, 1596, 1482, 1452, 1378, 1283, 1228, 925, 825, 764, 648 cm^{-1}.

4.2.2. (1*R*,2*R*)-N^1,N^2-bis(2-(piperidin-1-yl)benzylidene)cyclohexane-1,2-diamine (*R*,*R*)-1. A solution of (*R*,*R*)-1,2-diaminocyclohexane (0.856 g, 0.0075 mmol) and 2-(piperidin-1-yl)benzaldehyde **4** (2.840 g, 0.015 mmol) in ethanol (20 mL) was refluxed with stirring for 72 h. A yellow solution was obtained and then cooled to room temperature, concentrated under reduced pressure to ca. 5 mL. The residue was then cooled to −18 °C to give acicular crystals (1*R*,2*R*)-N^1,N^2-bis(2-(piperidin-1-yl)benzylidene)cyclohexane-1,2-diamine (*R*,*R*)-**1** (2.74 g, 80% yield). Mp 152–153 °C. $[\alpha]_D^{20} = +85.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.55 (m, 6H), 1.62–1.72 (m, 8H), 1.83–1.90 (m, 6H), 2.79 (s, 8H), 3.48 (s, 2H), 6.91–6.96 (m, 4H), 7.24–7.29 (m, 2H), 7.78 (d, $J = 7.6$ Hz, 2H), 8.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.19, 24.64, 26.27, 33.13, 54.44, 74.54, 118.40, 122.10, 127.84, 129.73, 130.55, 153.96, 159.06. IR (KBr): ν 3067, 2932, 2853, 1637, 1595, 1483, 1449, 1281, 1227, 763 cm^{-1}. EIMS (*m*/*z*): 457 (M+1). Anal. Calcd for $C_{30}H_{40}N_4$: C, 78.90; H,

Table 2. Asymmetric transfer hydrogenation of various ketones catalyzed by $[IrHCl_2(COD)]_2$/**1**[a]

Entry	Substrate	Time (h)	Conversion[b] (%)	ee[b] (%)	Configuration[c]
1		1.3	98	76	(*S*)
2		1.5	97	80	(*S*)
3		1.3	99	88	(*S*)
4[d]		1.3	93	87	(*R*)
5		1	98	91	(*S*)
6		1.6	46	64	(*S*)
7		1.5	94	90	(*S*)
8[d]		1.5	93	90	(*R*)
9		1.3	94	80	(*S*)
10		1.3	97	77	(*S*)
11		1.3	99	70	(*S*)
12		1.3	99	68	(*S*)

[a] Reaction conditions: ligand, (*R*,*R*)-**1**; ketone, 1.0 mmol; [M]:[ligand]:[KOH]:[ketone] = 1:1.2:300:100; 2-propanol, 15 mL; air atmosphere.
[b] Conversions and enantiomeric excesses were determined by GC analysis using a chiral G-TA column.
[c] The configurations were determined by comparison of the retention times of the enantiomers on the GC traces with literature values.
[d] Ligand, (*S*,*S*)-**1**.

8.83; N, 12.27. Found: C, 79.03; H, 8.69; N, 12.28. In an analogous manner, using (*S*,*S*)-1,2-diaminocyclohexane instead of (*R*,*R*)-1,2-diaminocyclohexane, ligand (*S*,*S*)-**1** was also prepared. $[\alpha]_D^{20} = -85.3$ (*c* 1.0, $CHCl_3$).

4.2.3. (1*R*,2*R*)-N^1,N^2-bis(2-(piperidin-1-yl)benzyl)cyclo-hexane-1,2-diamine (*R*,*R*)-2. A solution of (1*R*,2*R*)-N^1,N^2-bis(2-(piperidin-1-yl)benzylidene)cyclohexane-1,2-diamine **1** (2.283 g, 5.0 mmol) and $NaBH_4$ (7.566 g, 200 mmol) in absolute ethanol (60 mL) was refluxed with stirring for 72 h. The solution was cooled to room temperature and H_2O (25 mL) was added to destroy any excess $NaBH_4$. The mixture solution was extracted with CH_2Cl_2 (60 mL × 3). The combined extracts were washed with saturated NH_4Cl solution (15 mL × 3) and the organic layer dried over anhydrous $MgSO_4$, followed by filtration, con-

centrated to ca. 8 mL and cooled to −18 °C to yield a pale yellow solid. Purification of the crude product by flash chromatography (EtOAc/petrol ether 1:1) gave (*R*,*R*)-**2** as a white solid (1.61 g, 70% yield). Mp 52 °C. $[\alpha]_D^{20} = -55.4$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.27 (m, 2H), 1.34–1.61 (m, 14H), 1.75 (d, $J = 7.6$ Hz, 2H), 2.10 (d, $J = 12$ Hz, 2H), 2.37–2.49 (m, 2H), 2.50–2.65 (m, 4H), 2.68–2.88 (m, 4H), 3.76 (d, $J = 12.8$ Hz, 2H), 4.24 (d, $J = 13.2$ Hz, 2H), 7.04–7.13 (m, 4H), 7.18–7.23 (m, 2H), 7.26–7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.95, 24.27, 26.54, 29.10, 47.62, 54.29, 59.31, 121.01, 124.61, 129.44, 130.90, 131.12, 152.99. IR (KBr): 3429, 3060, 3023, 2932, 2852, 2800, 1598, 1491, 1450, 1223, 1104, 1030, 765 cm^{-1}. EIMS (*m*/*z*): 461 (M + 1). Anal. Calcd for $C_{30}H_{44}N_4$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.03; H, 10.16; N, 11.81. When ligand (*S*,*S*)-**1** was reduced with the same manner, the (*S*,*S*)-**2** was also prepared. $[\alpha]_D^{20} = +55.1$ (*c* 1.0, $CHCl_3$).

4.3. X-ray crystallographic study of (*R*,*R*)-1

White crystals of (*R*,*R*)-**1** suitable for X-ray diffraction were grown from ethanol/H_2O as a solvate of stoichiometry (*R*,*R*)-**1**·0.5H_2O. Diffraction data were collected on a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo Kα radiation at 296 K. The structure was solved by SHELXS-97 and refined by full-matrix least-squares procedures with anisotropic thermal parameters for all of the nonhydrogen atoms. Hydrogen atoms were located from a difference Fourier map. All calculations were performed on a microcomputer using SHELXL-97 and SHELXS-97 programs.[23,24]

Crystal data for compound (*R*,*R*)-**1**: space group *C*2, Monoclinic, $a = 27.010(9)$ Å, $b = 9.588(3)$ Å, $c = 11.685(4)$ Å, $\beta = 111.669(6)°$, $V = 2812.2(15)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.097$ g cm^{-3}, $T = 296$ (2) K, $R_1 = 0.0780$, $wR_2 = 0.1968$ [$I > 2\sigma(I)$], $R_1 = 0.0882$, $wR_2 = 0.2054$ for all data.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambrige Crystallographic Data Centre as Supplementary Publication No. CCDC 629600 {(*R*,*R*)-**1**}, which can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambrige CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4. Typical procedure for asymmetric transfer hydrogenation of ketones

A solution of $[IrHCl_2(COD)]_2$ (3.8 mg, 0.005 mmol) and ligand (*R*,*R*)-**1** (5.5 mg, 0.012 mmol) in 2-propanol (10 mL) was heated to 80 °C for 30 min under air atmosphere. After cooling to room temperature, valerophenone (1 mmol) was added, followed by KOH (3 mmol) in 2-propanol (5 mL). The asymmetric transfer hydrogenation was conducted at room temperature for the time indicated (monitored by GC). The resulting solution was quenched with 1 M HCl and the organic phase concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column to afford (*S*)-1-phenylphentan-1-ol in 98% conversion with 91% ee.

Acknowledgements

We would like to thank the National Natural Science Foundation of China (20373056, 20423002), the Fujian Provincial Science and Technology Commission (2005YZ1020) for financial support.

References

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
2. Burnner, H. *Handbook of Enantioselective Catalysis with Transition Metal Compounds*; VCH: Weiheim, 1993.
3. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070.
4. Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069.
5. Fache, F.; Dunjic, B.; Gámez, P.; Lemaire, M. *Top. Catal.* **1997**, *4*, 201–209.
6. Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231.
7. Fonseca, M. H.; König, B. *Adv. Synth. Catal.* **2003**, *345*, 1173–1185.
8. Albano, V. G.; Bandini, M.; Monari, M.; Marcucci, E.; Piccinelli, F.; Umani-Ronchi, A. *J. Org. Chem.* **2006**, *71*, 6451–6458.
9. Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3595–3598.
10. Belda, O.; Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Hallberg, A.; Moberg, C. *J. Org. Chem.* **2000**, *65*, 5868–5870.
11. Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929–1932.
12. Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141–144.
13. Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143–150.
14. Lee, S.-g.; Lim, C. W.; Song, C. E.; Kim, I. O.; Jun, C. H. *Tetrahedron: Asymmetry* **1997**, *8*, 2927–2932.
15. Liu, Y. L.; Liu, X. H.; Xin, J. G.; Feng, X. M. *Synlett* **2006**, *7*, 1085–1089.
16. Xiong, Y.; Huang, X.; Gou, S. H.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *Adv. Synth. Catal.* **2006**, *348*, 538–544.
17. Dangel, B. D.; Polt, R. *Org. Lett.* **2000**, *2*, 3003–3006.
18. Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743–1746.
19. Halle, R.; Bréhéret, A.; Schulz, E.; Pinel, C.; Lemaire, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2101–2108.
20. Marson, C. M.; Schwarz, I. *Tetrahedron Lett.* **2000**, *41*, 8999–9003.
21. Niewiadomski, K. B.; Suschitzky, H. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1679–1682.
22. Shaikh, A. L.; Puranik, V. G.; Deshmukh, A. R. A. S. *Tetrahedron* **2005**, *61*, 2441–2451.
23. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
24. Sheldrick, G. M. SHELX-*97 and* SHELXL-*97, Programs for Solution and Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.