Novel Chiral Aminophosphine Ligand: Synthesis and Application in Asymmetric Catalytic Hydrogenation Reaction

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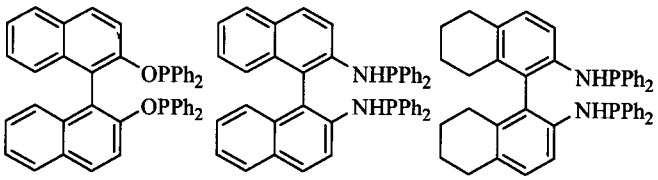
A new chiral aminophosphine ligand 6,6′-dimethoxy-2,2′-bis(diphenylphosphinoamino) biphenyl (DMBDPPABP) was prepared and its rhodium complex was found to be an effective catalyst for the asymmetric hydrogenation of amidoacrylic acid and its derivatives. The effects of solvent and reaction temperature on enantioselectivity were also studied.

Keywords aminophosphine, chiral ligand, 6,6′-dimethoxy-2,2′-bis(diphenylphosphinoamino)biphenyl, asymmetric hydrogenation

Introduction

Transition metal complex catalyzed asymmetric reactions have attracted great attention because of their high efficiency for the preparation of enantiomerically pure compounds, and great efforts have been made towards the design and synthesis of new chiral ligands for this purpose. The C_2-symmetric biaryl diphosphines such as BINAP, BIBHEMP and their analogues have been shown to be highly effective ligands for transition metal catalyzed asymmetric hydrogenation reactions.[1] The most acceptable reason for the success of binaphthalene family chiral ligands such as BINAP comes from the highly skewed and relatively rigid structure when forming complex with transition metals such as rhodium or ruthenium. Furthermore, a molecule with C_2-symmetric axis may reduce the possibility of competing approaches of the substrate towards the catalyst. To this end, large amount of chiral ligands bearing C_2-symmetry have been prepared and used for asymmetric preparation of optically active compounds.

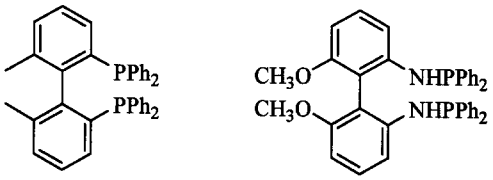
Besides the success of BINAP in asymmetric catalytic hydrogenation reaction, chiral phosphinite or phosphinamidite ligands bearing a binaphthyl backbone, such as BINAPO or BDPAB (Fig. 1), have also proven to be effective ligands in the catalytic hydrogenation of dehydroamino acids, leading to the corresponding chiral amino acids with high *ee* values.[2] Another aminophosphine ligand H_8-BDPAB (Fig. 1) bearing partially hydrogenated binaphthyl structure was found to be more efficient and highly enantioselective in the catalytic hydrogenation of dehydroamino acid derivatives.[3]



BINAPO BDPAB H_8-BDPAB

Fig. 1 Examples of phosphinite and aminophosphine ligands bearing biaryl backbone.

While binaphthyl family chiral ligands such as BINOL or BINAP have attracted great attention, its biphenyl counterparts have been relatively less explored.[4] The optically active diphosphine (BIPHEMP, Fig. 2) bearing biphenyl moiety has been shown to be effective in asymmetric catalytic reactions.[5] To expand the scope of biaryl chemistry in asymmetric catalysis, we designed a novel aminophosphine ligand containing 6,6′-dimethoxybiphenyl moiety (DMBDPPABP, Fig. 2), and studied the asymmetric catalytic reactions using this chiral ligand.



BIPHEMP DMBDPPABP

Fig. 2 Examples of phosphine and aminophosphine ligands bearing biphenyl backbone.

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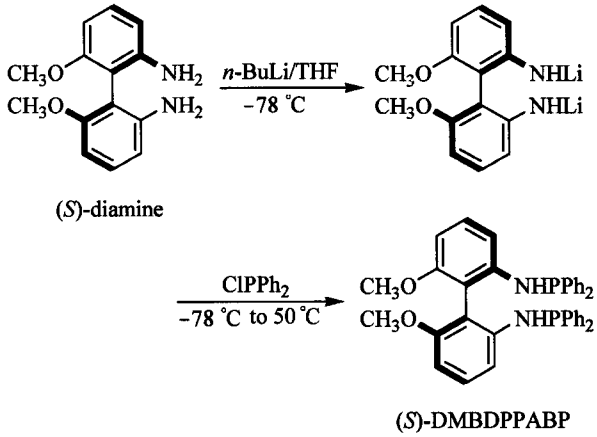
Chiral ligands such as BIPHEMP and DMBDPPABP, like other reported biaryl type chiral ligands, bear the structural feature of C_2-symmetrical axis, and the two phenyl rings may also form a skewed structure as their binaphthyl counterparts do. These biphenyl ligands also have their own uniqueness: since the phenyl group, unlike its binaphthyl counterpart, is less rigid,[5] such structure may offer a special feature by forming more flexible transition state which may allow the optimal orientation of substrates on the catalyst and thus may enhance the stereoselectivity of the reaction.[6]

On one hand, the relatively less rigid structure of the biphenyl system is possibly a disadvantage of this type of ligand. On the other hand, however, the phenyl group may provide some advantage as it can easily be functionalized to give a chiral ligand with variable geometry, steric hindrance and different electronic property upon substitution with different functional groups. Furthermore, bridging the 6,6′-position, for instance, through a 7- or 8-membered ring, would hold the dihedral angle within a limited range, thus restricting torsional mobility and introducing additional rigidity. Taking these advantages, we designed the chiral aminophosphine ligand 6, 6′-dimethoxy-2, 2′-bis (diphenylphosphinoamino) biphenyl (DMBDPPABP) and studied the asymmetric catalytic hydrogenation of dehydroamino acids and their derivatives using the rhodium complex of this ligand as chiral catalyst.

Results and discussion

The chiral aminophosphine ligand (*S*)-DMBDPPABP can be readily prepared from the corresponding diamine[7] first by *n*-BuLi treatment at −78 °C followed by the addition of a solution of chlorodiphenylphosphine in dry THF. The desired chiral ligand (*S*)-DMBDPPABP was obtained in 94% yield (Scheme 1).

Scheme 1



The cationic rhodium complex [Rh(COD)(*S*)-(DMBDPPABP)]BF_4 (Fig. 3) was prepared *in situ* by stirring $[Rh(COD)Cl]_2$, silver tetrafluoroborate with (*S*)-DMBDPPABP ligand in acetone under an inert atmosphere.

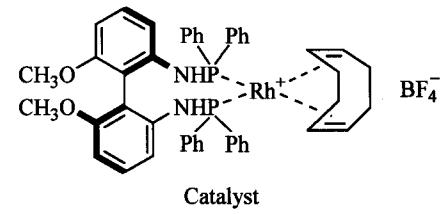
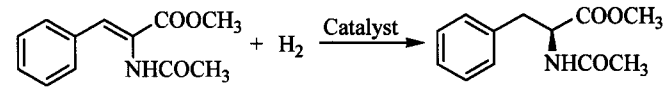


Fig. 3 Cationic rhodium complex of DMBDPPABP as chiral catalyst.

The asymmetric hydrogenation of methyl (*Z*)-2-acylamidocinnamate catalyzed by the complex [Rh(COD)(*S*)-(DMBDPPABP)]BF_4 was carried out at ambient temperature and under 0.68 MPa of hydrogen pressure. Complete conversion with good *ee* values were observed in most cases. Table 1 summarizes the result of the study of the effect of hydrogen pressure and solvent on the hydrogenation of methyl (*Z*)-2-acetoamidocinnamate.

Table 1 Hydrogenation of methyl (*Z*)-2-acetamidocinnamate catalyzed by Rh-DMBDPPABP complex[a]



Entry	Solvent	p_{H_2} (MPa)	Temp. (°C)	Conv. (%)[b]	*ee* (%)[b]	Config.
1	Acetone	0.1	25	93.1	69.7	*S*
2	Acetone	0.68	25	100	73.7	*S*
3	Acetone	1.36	25	100	71	*S*
4	Acetone	3.40	25	100	73	*S*
5	Acetone	6.80	25	100	72.3	*S*
6	Acetone	0.68	0	100	75.4	*S*
7	Acetone	0.68	50	100	72	*S*
8	Acetone	0.68	−20	99.6	76.8	*S*
9	Ethanol	0.68	25	100	70.4	*S*
10	Methanol	0.68	25	100	71.8	*S*
11	*i*-Propanol	0.68	25	100	69	*S*
12	THF	0.68	25	100	46	*S*
13	Benzene	0.68	25	89.1	62.4	*S*
14	Dichloromethane	0.68	25	93.5	66.9	*S*
15	Chloroform	0.68	25	96.3	64.3	*S*

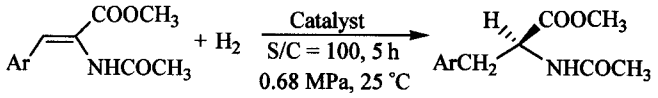
[a] **Reaction conditions**: reaction time, 5 h; S/C (substrate/catalyst) = 100 (mol : mol); solvent, acetone; [b] The *ee* values and conversions were determined by GLC using a chrompack chirasil-*L*-Val column.

It can be concluded from Table 1 that the reaction proceeded smoothly in polar or non-polar solvents with similar enantioselectivity. Enantioselectivites higher than 70% were observed in acetone, ethanol and methanol. Lower enantioselectivity (46%) was found in THF. The results also suggested that the hydrogen pressure had little effect on the enantioselectivity of the reaction. The effect of reaction temperature on the enantioselectivity was not significant within the range of temperature studied (−20—−50 °C).

These results indicated that the catalyst containing DMBDPPABP was effective in catalytic hydrogenation and provided satisfactory results under very different conditions.

Under similar hydrogenation conditions, a series of methyl ester of (*Z*)-2-acetamidocinnamic acids was also hydrogenated and the results was summarized in Table 2.

Table 2 Rh(DMBDPPABP) catalyzed asymmetric hydrogenation of (*Z*)-2-acetamidocinnamic acid methyl ester and its analogs[a]



Entry	Substrate (Ar)	Conversion (%)[b]	*ee* (%)[b]	Config.
1	Ph	100	73.7	*S*
2	4-CH_3Ph	100	71.2	*S*
3	4-CH_3OPh	100	72.7	*S*
4	3,4-OCH_2OPh	100	76.2	*S*
5	4-HOPh	100	74.6	*S*
6	2-ClPh	100	72.0	*S*
7	3-ClPh	100	72.1	*S*
8	4-ClPh	100	74.0	*S*
9	4-FPh	100	73.0	*S*
10	4-NO_2Ph	100	73.4	*S*

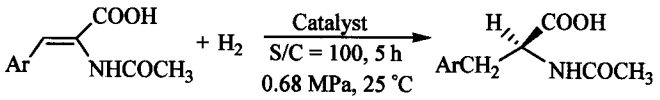
[a]**Reaction conditions**: H_2 pressure, 0.68 MPa; room temperature; reaction time, 5 h; S/C = 100 (mol:mol); solvent, acetone. [b] The *ee* values were determined by GLC using a chrompack chirasil-*L*-Val column, 100% conversion was observed in all cases.

Similar *ee* values of over 70% was observed in the hydrogenation of substituted methyl (*Z*)-2-acetamidocinnamate regardless of the properties of the substituents on the phenyl group. All the reactions were completed in 5 h.

Further studies of the hydrogenation of prochiral amidoacrylic acids showed that the good enantioselectivity of the reaction and high activity of the catalyst were quite general. A variety of (*Z*)-2-acetamido-3-arylacrylic acids were hydrogenated with Rh(S-DMBDPPABP) and in all cases the products were found to have satisfactory *ee* values. More detailed data are shown in Table 3. The data suggested that the substituent group on the aryl moiety had little effect on the enantioselectivity of the catalytic reaction.

In asymmetric hydrogenation, reaction conditions such as hydrogen pressure, solvent, reaction temperature, and substrate-to-catalyst ratio may have substantial impact on both the rates and the stereoselectivities of the reaction. These effects may be attributed either to the formation of different catalytically competing species in solution, or to the operation of kinetically distinct catalytic cycles under different conditions. The solvent employed in asymmetric catalytic reactions may also have a dramatic influence on the reaction rate as well as enantioselectivity, possibly because the solvent molecule is also involved in the catalytic cycle. The goal of asymmetric hydrogenation is to find optimal conditions with a combination of chiral ligand, counterion, metal, solvent, hydrogen pressure and reaction temperature under which the reactivity and the stereoselectivity of the reaction will be jointly maximized. Novel aminophosphine chiral ligand DMBDPPABP has been shown to tolerate the variation of different reaction conditions such as the change of temperature, solvent, substrate-to-catalyst ratio to give similar enantioselectivities. Further study will aim at improving the enantioselectivity of the reaction.

Table 3 Rh[(*S*)-DMBDPPABP] catalyzed asymmetric hydrogenation of (*Z*)-2-acetamido-3-arylacrylicacids[a]



Entry	Substrate (Ar)	Conversion (%)[b]	*ee* (%)[b]	Config.
1	Ph	100	79.6	*S*
2	4-ClPh	100	79.1	*S*
3	3-ClPh	100	76.3	*S*
4	2-ClPh	100	78.1	*S*
5	4-NO_2Ph	100	76.4	*S*
6	3,4-OCH_2OPh	100	80.3	*S*
7	2-CH_3OPh	99.3	79.0	*S*

[a]**Reaction conditions**: H_2 pressure, 0.68 MPa; reaction time, 5 h; S/C = 100 (mol:mol); solvent, acetone. [b] The *ee* values and conversions were determined by GLC using a chrompack chirasil-*L*-Val column.

In conclusion, we have developed a chiral aminophosphine ligand (DMBDPPABP). The rhodium catalyst containing this ligand was highly effective in the asymmetric hydrogenation of dehydroamino acids and their derivatives. The fine tuning of the structure of the chiral ligand to improve the enantioselectivity of the reaction is in progress and the results will be reported in due time.

Experimental

General information

All reactions were carried out under inert atmosphere, and the commercial reagents were used as received without further purification. All solvents used were dried with standard, published methods and were distilled before use. NMR spectra were recorded on a Bruker Dpx-400 spectrometer. Mass analyses were performed on a Model Mat 95 ST spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter. Melting points were determined using an electrothermal 9100 apparatus in capillaries sealed under nitrogen. GLC and HPLC analyses were performed using a Hewlett-Packard Model HP5890 series II GC and a Waters 600E.

(S)-6,6'-Dimethoxy-2,2'-bis(diphenylphosphinoamino)biphenyl [(S)-DMBDPPABP]

A 50-mL flask with a magnetic stirrer was charged with (S)-6,6'-dimethoxy-2,2'-diaminobiphenyl (100 mg, 0.41 mmol) in THF (10 mL) under a nitrogen atmosphere. The solution was cooled to −78 ℃ and *n*-butyllithium in hexane (0.55 mL of 1.6 mol/L solution, 0.84 mmol) was added dropwise. The mixture was stirred for 1 h at −78 ℃ to −50 ℃ followed by the dropwise addition of a solution of chlorodiphenylphosphine (0.16 mL, 0.9 mmol) in THF (5 mL). The system was stirred further for 5 h at this temperature and then was brought to room temperature. The solution was filtered to remove the solid. The solvent was removed *in vacuo* to give 189 mg of (S)-DMBDPPABP. The crude product was dissolved in a mixture of 5 mL of dichloromethane and 5 mL of diethyl ether. The solution was kept at −30 ℃ for 24 h to allow the growth of crystals of (S)-DMBDPPABP. White crystals of (S)-DMBDPPABP were obtained (167 mg, 66.8%). m.p. 112—113.7 ℃, $[\alpha]_D^{20}$ −39.7 (*c* 1.0 g/L, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.58 (s, 6H), 6.41 (d, J = 8.11 Hz, 2H), 7.09—7.36 (m, 24H); ^{31}P NMR (CD_2Cl_2, 162 MHz) δ: 29.68; HRMS calcd for $C_{38}H_{34}N_2O_2P_2$ 612.20955, found 612.20977; microanalysis calcd for $C_{38}H_{34}N_2O_2P_2$: C 74.50, H 5.59, N 4.57; found C 74.41, H 5.62, N 4.61.

[Rh(COD)(S)-DMBDPPABP]BF_4 *complex*

$[Rh(COD)Cl]_2$ (purchased from Stream Chemicals, Inc., Newburyport, Massachusetts) (5.0 mg, 0.01 mmol) and $AgBF_4$ (4.0 mg, 0.03 mmol) in acetone (5 mL) were stirred at room temerature for 30 min under a nitrogen atmosphere. The solution was filtered to remove the solid AgCl. To this filtrate was added chiral ligand (S)-DMBDPPABP (12.3 mg, 0.02 mmol), and the thus formed [Rh(COD)-(S)-(DMBDPPABP)]BF_4 was used as stock solution (0.005 mol/L in acetone). ^{31}P NMR ($CDCl_3$, 162 MHz) δ: 69.47 (d, $J_{Rh\text{-}P}$ = 156.3 Hz).

General procedure for asymmetric hydrogenation

Asymmetric hydrogenation of methyl (Z)-2-acetamidocinnamate catalyzed by [Rh(COD)(S)-DMBDPPABP]BF_4 *complex*

A 50-mL autoclave with a magnetic stirring bar was charged with catalyst Rh(DMBDPPABP) (10 μL, 0.02 mmol/mL) and methyl (Z)-2-acetamidocinnamate (4.4 mg, 0.02 mmol) in acetone (2 mL). The hydrogenation was carried out under 0.68 MPa of hydrogen pressure at room temperature for 5 h. A portion of the reaction mixture was analyzed by gas chromatography on chiral capillary column using a chrompack chirasil-*L*-Val as stationary phase to determine the product composition, and 100% conversion of the starting material to the hydrogenation product and 73.7% *ee* of methyl (S)-2-acetamido-3-phenylpropanoate were observed. Absolute configuration of product was determinied by comparing the observed rotation with the reported value.[8]

Asymmetric hydrogenation of (Z)-2-acetamidocinnamic acid catalyzed by [Rh(COD)(S)-DMBDPPABP]BF_4 *complex*

The process is similar to that for the catalytic hydrogenation of methyl (Z)-2-acetoamidocinnamate, except that 20 μL (0.02 mol/L) of chiral catalyst stock solution was used, and the amount of substrate (Z)-2-acetamidocinnamic acid was 8.2 mg (0.04 mmol). The reaction proceeded with 100% conversion, and the *ee* value of the product was 79.6%. The enantiomeric excess of the product was determined by chiral capillary GC using a chrompack CD-chirasil-DEX CB capillary column as the corresponding methyl ester.

N-Acetylphenylalanine methyl ester[8] (capillary GC, 170 ℃, isothermal) (R) t_1 = 6.54 min, (S) t_2 = 9.44 min; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.24—7.19 (m, 5H), 5.82 (brs, 1H), 4.86—4.78 (m, 1H), 3.64 (m, 3H), 3.13—3.12 (m, 2H), 2.12 (s, 3H).

N-Acetyl-p-fluorophenylalanine methyl ester[8] (capillary GC, 180 ℃, isothermal) (R) t_1 = 5.64 min, (S) t_2 = 7.12 min; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.16—7.08 (m, 4H), 6.02 (brs, 1H), 4.68—4.62 (m, 1H), 3.82 (s, 3H), 3.18—3.14 (m, 2H), 2.10 (s, 3H).

N-Acetyl-o-chlorophenylalanine methyl ester[8] (capillary GC, 180 ℃, isothermal) (R) t_1 = 9.68 min, (S) t_2 = 10.56 min; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.21—7.18 (m, 4H), 6.14 (brs, 1H), 4.70—4.68 (m, 1H), 3.81 (s, 3H), 3.19—3.17 (m, 2H), 2.16 (s, 3H).

N-Acetyl-p-methoxyphenylalanine methyl ester[8] (HPLC, 1.0 mL/min, 10% *i*-PrOH/hexane) (S) t_1 = 63.34 min, (R) t_2 = 68.32 min; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.11—7.08 (m, 2H), 6.76—6.82 (m, 2H) 5.93 (brs, 1H), 4.79—4.71 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 2.98 (dd, J_1 = 2.31 Hz, J_2 = 5.76 Hz, 2H), 1.86 (s, 3H).

Dehydroamino acid derivatives (substrates)

α-Acetamidocinnmic acid was purchased from Aldrich Chemical Co. The other dehydroamino acids were prepared according to reported methods.[9] The corresponding methyl esters were prepared as the following: dehydroamino acid (5.0 mmol) in DMF (10 mL) was stirred with $KHCO_3$ (1.0 g, 10.0 mmol), CH_3I (0.3 mL, 5.0 mmol) was added to the above mixture. The stirring was continued for half an hour, and water (20 mL), ethyl acetate (50 mL) and benzene (10 mL) were added. The organic layer was separated and washed with water (15 mL × 2) and brine (20 mL), dried over anhydrous magnesium sulfate. Evaporating the solvent afforded a white solid which can be recrystallized from the mixture of CH_2Cl_2 and hexane (1:1) to give white crystals. Yields were ranged from 85% to 90%.

References

1 (a) Morrison, J. D. *Asymmetric Synthesis*, Vol. 5, Academic Press, New York, **1985**.
(b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley & Sons, New York, **1994**.
(c) Ojima, I. *Catalytic Asymmetric Synthesis*, VCH, New York, **1993**.
(d) Stephenson, G. R. *Advanced Asymmetric Synthesis*, Chapman & Hall, London, **1996**.
(e) Doyle, M. P. *Advances in Catalytic Processes*, Vol. 1, JAI Press, Greenwich, Connecticut, **1995**.
(f) Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*, Wiley & Sons, New York, **2000**.

2 (a) Miyano, S.; Nawa, M.; Hashimoto, H. *Chem. Lett.* **1980**, 729.
(b) Miyano, S., Nawa, M.; Mori, A.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, 2171.

3 Zhang, F.-Y.; Pai, C.-C. Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808.

4 (a) Rampf, F. A.; Spiegler, M.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *582*, 204.
(b) Delogu, G.; Fabbri, D. *Tetrahedron: Asymmetry* **1997**, *8*, 759.
(c) Lew, D.; Amer, I. *Tetrahedron: Asymmetry* **1993**, *4*, 2147.
(d) Pastor, S. D.; Rodebaugh, R. K.; Odorisio, P. A.; Pugin, B.; Rihs, G.; Togni, A. *Helv. Chim. Acta*. **1991**, *74*, 1175.

5 Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897.

6 (a) Frejd, T.; Klingstedt, T. *Acta Chem. Scand.* **1989**, *43*, 670.
(b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.
(c) Mezzetti, A.; Consiglio, G. *J. Chem. Soc., Chem. Commun*. **1991**, 1675.
(d) Genet. J. P.; Pinel, C.; Ratovelomananavidal, V.; Mallat, S.; Pfister, X.; Bischoff, L.; Deandrade, M. C. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675.
(e) Mezzetti, A.; Tschumper, A.; Consiglio, G. *J. Chem. Soc., Dalton Trans*. **1995**, 49.
(f) Pini, D.; Mandoli, A.; Iuliano, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1031.

7 Chen, Y.-X.; Li, Y.-M.; Lam, K.-H.; Chan, A. S. C. *Chin. J. Chem.* **2001**, *19*, 794.

8 (a) Fryzuk, M, D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.
(b) Burk, M. J.; Feaster, J. E.; Nugtent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
(c) Roberts, N. K.; Wild, S. B. *J. Am. Chem. Soc.* **1979**, *101*, 6254.
(d) Roberts, N. K.; Wild, S. B. *J. Chem. Soc., Dalton Trans*. **1979**, 2015.
(e) Zhu, G. X.; Zhang, X. M. *J. Org. Chem.* **1998**, *63*, 3133.

9 (a) Cereghetti, M.; Rageot, A. *Eur. Pat.* **1992**, 511558.
(b) Jacqueline, H. P. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, John Wiley & Sons, New York, **1995**, p. 57.
(c) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*, John Wiley and Sons, New York, **1981**.
(d) Nogarradi, M. *Stereoselective Synthesis*, 2nd ed., VCH Weinheim, Germany, **1995**.

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