Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 297–304

TETRAHEDRON: *ASYMMETRY*

Structural probing of D-fructose derived ligands for asymmetric addition of diethylzinc to aldehydes

Hanmin Huang, Huilin Chen, Xinquan Hu, Changmin Bai and Zhuo Zheng*

Dalian Institute of Chemical Physics, The Chinese Academy of Sciences, Dalian 116023, PR China

Received 7 November 2002; revised 11 December 2002; accepted 12 December 2002

Abstract—A series of new chiral ligands derived from D-fructose have been synthesized and applied in the enantioselective addition of diethylzinc to aldehydes. Comparison of the enantioselectivities obtained with these ligands demonstrated that the catalytic properties are highly dependent upon the structure of ligands, a rational explanation of the structural effects on the catalytic properties is provided.

1. Introduction

The enantioselective addition of diethylzinc to aldehydes is one of the most important synthetic procedures for obtaining enantiopure secondary alcohols.[1] Since the first report on the asymmetric reaction in 1984 by Oguni and Omi, who used certain β-amino alcohols as catalysts,[2] numerous efforts have been made to search for new effective ligands in the reaction and to elucidate the reaction mechanism.[3] As analogs of β-amino alcohols, pyridyl alcohols should also be effective ligands for this reaction and although a variety of pyridyl alcohols have been synthesized,[4] reported works on the design and development of cheap and effective pyridyl alcohols derived from carbohydrates are scarce.[5] Moreover, to the best of our knowledge, a detailed study aimed at defining the structural features, which are responsible for their efficiency as chiral inducers, is still lacking.

D-Fructose is readily available and its derivatives **1a** and **1b** could be readily prepared[6] (Scheme 1). With the aim of improving their performance and widening their use as ligands in asymmetric catalysis, we report herein the synthesis of chiral ligands **2**–**6** derived from D-fructose and their application as catalysts in the enantioselective addition of diethylzinc to aldehydes. To ascertain the structural features important for chiral recognition, we systematically tuned the ligands. This approach can provide some information about how the different structures affect the enantioselectivity and may also provide some insights for the design of efficient new catalysts based on carbohydrates.

2. Results and discussion

2.1. Synthesis of ligands

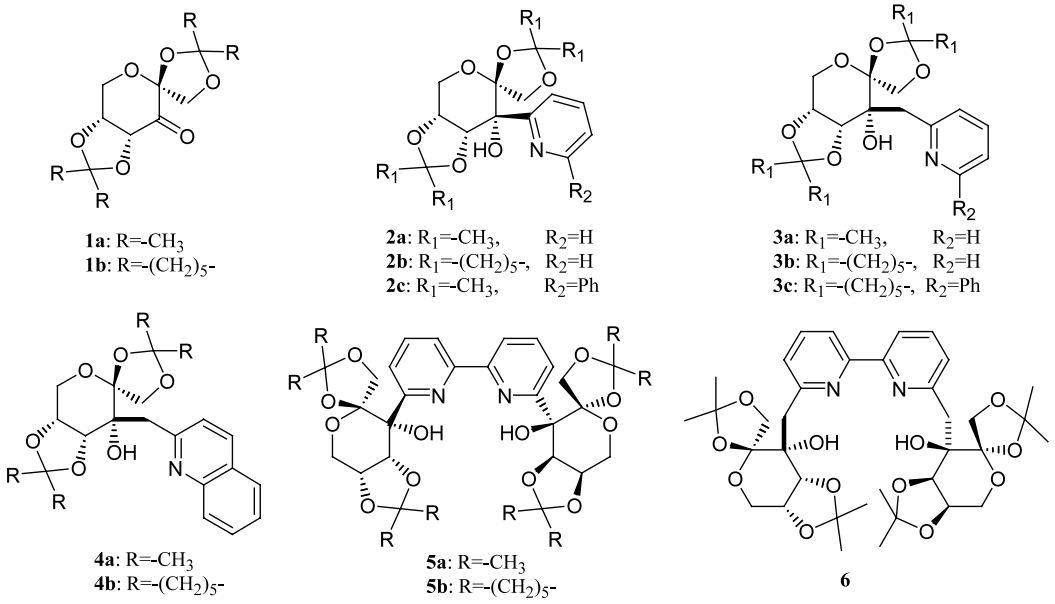
Starting from the commercially available D-fructose, chiral ketones **1a** and **1b** were readily synthesized using known procedures.[6] Thus, the pyridyl alcohols **2a** and **2b** and bromopyridyl alcohols **7** could be prepared easily in moderate yields by monolithiation of 2-bromopyridine and 2,6-dibromopyridine in ether at −78°C followed by treatment with chiral ketones **1a** and **1b** (Scheme 2). The optically active C_2-symmetrical bipyridyl alcohols **5a** and **5b** were then prepared via Ni(0)-mediated homocoupling **7** in 52–55% yields.[7] Suzuki coupling of **7a** with phenylboronic acid afforded ligand **2c** in nearly quantitative yield.[8]

The routes used for the synthesis of chiral ligands **3a**–**c** and **4a**–**b** are shown in Scheme 3, 2-methylpyridine, 2-phenyl-6-methylpyridine **8** and 2-methyquinoline were first lithiated with *n*-BuLi in ether at 0°C to give the corresponding organolithium, followed by trapping with chiral ketone **1a** or **1b** to produce compounds **3a**–**c** and **4a**–**b** in 53–83% yields.

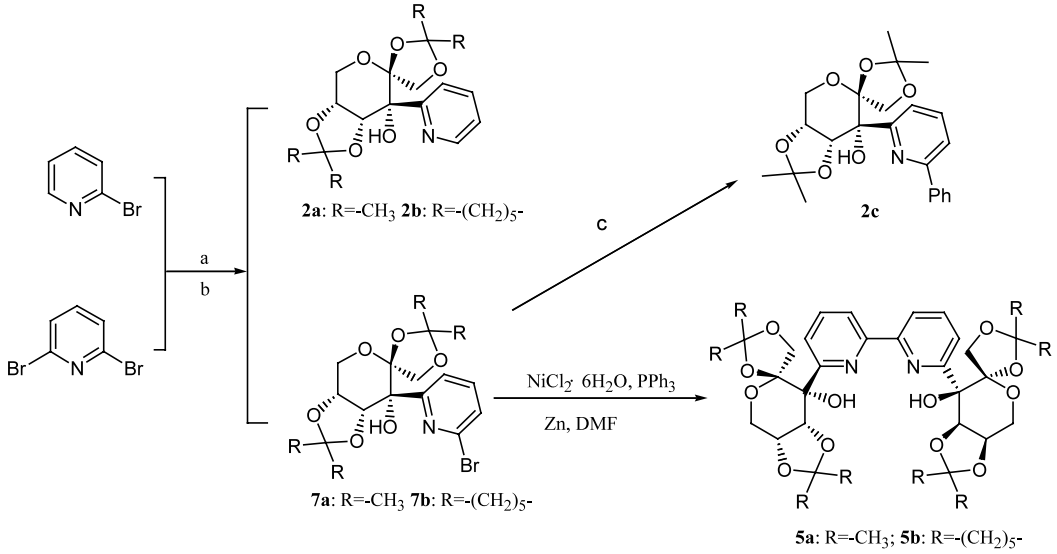
Compounds **2**–**5** were obtained as single diastereomers as shown by NMR analyses. The absolute configuration at C-3 of D-fructose backbone in ligands **2**–**5** was

* Corresponding author. Tel.: +86+411-4379276; fax: +86+411-4684746; e-mail: zhengz@ms.dicp.ac.cn

0957-4166/03/$ - see front matter
PII: S0957-4166(02)00861-3



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) *n*-BuLi, Et_2O, −78 ∼ −45°C; (b) ketone **1**, −78°C ∼ rt; (c) $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, toluene/H_2O, 85°C.

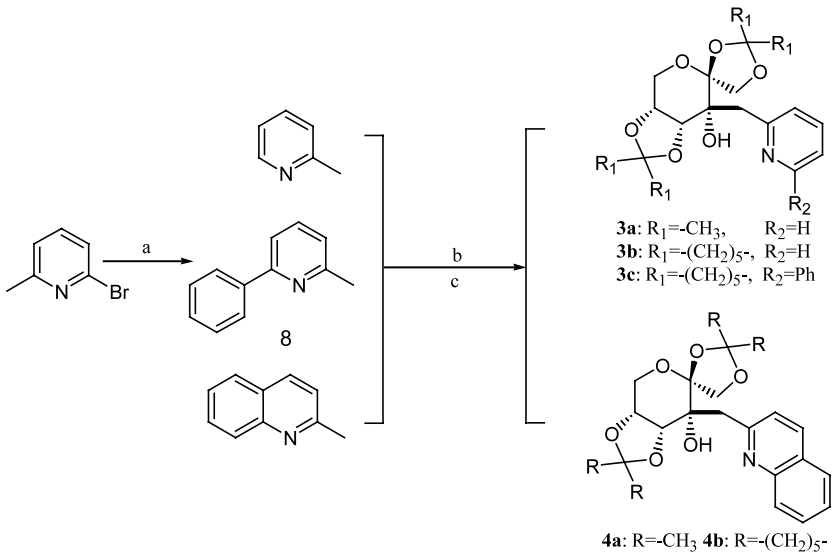
deduced according to the analogous ligands reported previously,[5] whose absolute configuration has previously been determined by X-ray crystallography.

The conformationally flexible C_2-symmetric bipyridyl alcohol **6**, which is the dimer of compound **3a**, can be conveniently prepared in 32% yield by the reaction of 2 equivalents of the chiral ketone **1a** with 6,6′-dimethyl-2,2′-bipyridine in the presence of *n*-BuLi[9] (Scheme 4). NMR and HPLC analyses indicate that compound **6** is formed as two diastereomers in a ratio of 48:52. Several attempts to separate the diastereomers were unsuccessful.

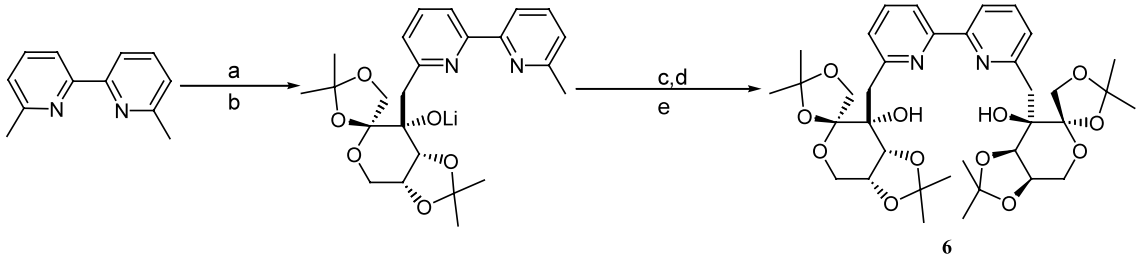
2.2. Enantioselective addition of diethylzinc to aldehydes

In order to examine the effect of ligand structure on the catalytic properties in the enantioselective addition of diethylzinc to aldehydes, the catalytic performance of ligands **2**–**6** was thoroughly examined: In a first set of experiments, we carried out this reaction at 0°C in the presence of a catalytic amount (5 mol%) of various ligands. The results are summarized in Table 1.

As can be seen from Table 1, pyridyl- and quinolyl alcohols derived from the D-fructose proved to be

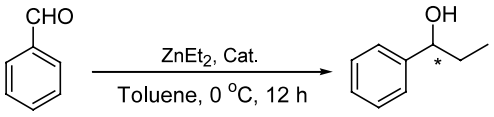


Scheme 3. *Reagents and conditions*: (a) $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, toluene/H_2O, 85°C; (b) *n*-BuLi, Et_2O, 0°C ~ rt; (c): ketone 1, Et_2O, 0°C ~ rt.



Scheme 4. *Reagents and conditions*: (a) *n*-BuLi, Et_2O, 0°C ~ rt; (b) ketone **1a**, −78°C ~ rt; (c) *n*-BuLi, Et_2O, 0°C ~ rt; (d) ketone **1a**, −78°C ~ rt; (e) H_2O.

Table 1. Enantioselective addition of diethylzinc to benzaldehyde promoted by chiral ligands **2**–**6**[a]



Entry	Ligand	Yield (%)[b]	E.e. (%) (config.)[c]
1	**2a**	76	21 (*R*)
2	**2b**	65	25 (*R*)
3	**2c**	50	7 (*R*)
4	**3a**	94	79 (*R*)
5	**3b**	96	82 (*R*)
6	**3c**	94	75 (*R*)
7	**4a**	99	80 (*R*)
8	**4b**	99	83 (*R*)
9	**5a**	65	15 (*R*)
10	**5b**	51	15 (*S*)
11	**6**	97	73 (*R*)

[a] The reactions were carried out in toluene at 0°C for 12 h, benzaldehyde/Et_2Zn/ligand = 1.0/2.2/0.05.

[b] Isolated yields based on the benzaldehyde.

[c] Determined by GC with β-DEX 120 capillary column and the absolute configuration was determined by comparing the sign of specific rotation.[11]

effective catalysts for the addition of diethylzinc to benzaldehyde. It is interesting to point out that 73% e.e. and 97% yield can also be obtained when using the non-diastereomerically pure ligand **6** as catalyst. However, the catalytic properties were found to be influenced dramatically by the structure of the ligands. Firstly, the length of the backbone between the coordinating nitrogen and oxygen atoms in the ligands is crucial to the reactivity and enantioselectivity. It appears that the ligands with longer backbones induce higher enantioselectivity and activity than the ligands with shorter backbones. For example, catalysts **2a**–**c** provided the addition products in less than 25% e.e. (entries 1–3), whereas the catalysts **3a**–**c** and **4a**–**b** with arms of one methylene group longer than **2a**–**c** between the coordinating nitrogen and oxygen atoms gave much higher enantioselectivity (75–83% e.e. entries 4–8). The above tendency was also observed for ligand **6** and **5a** (entry 11 versus entry 9), which have a similar structure but contain different backbone lengths. The different behaviour of these ligands can be explained via conformational analysis of their ethylzinc aminoalkoxide complexes. It is generally recognized that the actual catalyst in this reaction is the ethylzinc aminoalkoxide complex formed in situ. For ligands with a longer backbone (**3a**–**c** and **4a**–**b**), the six-membered ring ethylzinc

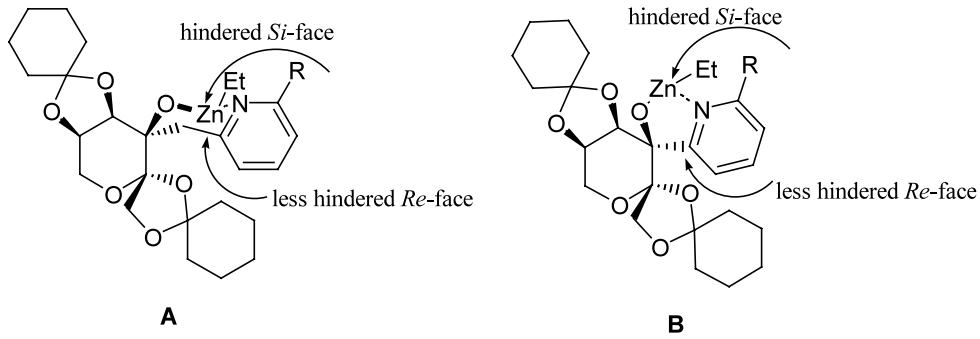


Figure 1. Plausible transition state of catalyst **A** and **B**.

aminoalkoxide **A** can be formed, the O–Zn linkage should be arranged *anti* to of the fructose skeleton due to steric factors. The less hindered *Re*-face of the zinc atom is easy to be coordinated by benzaldehyde, and to give products with the *R* configuration. For the ligands with a shorter backbone (**2a–c**), the five-membered ring ethylzinc aminoalkoxide **B** is formed. As shown in Fig. 1, **B** is more congested and rigid than the ethylzinc aminoalkoxide **A**. Consequently, the reactivity of ligands **2a–c** is lower than ligands with a longer backbone (**3a–c** and **4a–b)**. In additon, there is less difference between the two enantiofaces of catalyst **B** than in catalyst **A**, so the enantioselectivity of catalyst **B** should be expected to be lower.

It is well recognized that the presence of a C_2 symmetry axis within a chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing diastereomeric transition states and thus increases the enantioselectivity. The C_2-symmetric bipyridyl alcohols **5a** and **5b**, which are dimers of **2a** and **2b** (entries 9 and 10), were synthesized by the above methods and applied in this reaction, the results showed that the C_2-symmetrical ligands produced lower chemical yields and enantioselectivities than the corresponding monomeric pyridyl alcohols **2a** and **2b** (entries 9–10 versus entries 1–2). Surprisingly, the sense of asymmetric induction of **5b** is the opposite of all of the other ligands studied. This observation is not easy to interprete, but it may be due to the bulkiness of the ligand, which changes the structure of the active catalyst. Our results, combined with the related other published works,[4e,f,s] indicated that C_2-symmetric dimeric bipyridyl alcohols may act as monomeric pyridyl alcohols. When one part of the ligand coordinates to zinc atoms, the remaining *N*,*O* part of the ligand seems to play a sceening role or coordinates to other zinc atoms during the reaction. Further comparison of the results obtained with non-diastereoisomeric ligand **6** and the corresponding monomeric ligand **3a** provide more information (entry 11 versus entry 5), and might confirm this viewpoint.

The effect of the substituents of the ligands on the reactivity and enantioselectivity was also studied by varying the protecting groups on the D-fructose skeleton and the pyridine ring. The results demonstrated that the sterically more bulky cyclohexanone-protected ligands gave slightly higher enantioselectivity and catalytic activity than the corresponding acetone-protected ligands. A similar tendency has also been observed for ligands **4a** and **4b** derived from 2-methylquinoline, which are more bulky than the 2-methylpyridine-derived ligands **3a** and **3b** (entries 7–8 versus entries 4–5). However, introducing a more bulky substituent (such as a phenyl group) at the 6-position of the pyridine ring of the pyridyl alcohols was detrimental to the enantioselectivity and catalytic activity of the alkylation reaction (21% e.e. for **2a**, entry 1; 7% e.e. for **2c**, entry 3; 82% e.e. for **3b**, entry 5 and 75% e.e. for **3c**, entry 6). These results support the above view that very rigid structures might be deleterious to discrimination of the two enantiotopic faces of the benzaldehyde within the transition state complex.

The effects of different reaction parameters (i.e. solvent, temperature and catalyst loading) were also investigated with the ligands **3b**. The results show that the efficiency of the process depends strongly on the nature of the solvent (Table 2) and toluene was found to be the best solvent. Temperature can also affect the catalytic properties (Table 3), lowing the temperature from +20 to −20°C leads to slightly slower reaction rate but to an increase of asymmetric induction from 79 to 86% e.e. Changing the catalyst loading from 1 to 20% has only a small effect on enantioselectivity but the effect on the yields of the *sec*-alcohols is marked. In terms of reactivity and enantioselectivity, **3b** and **4b** are better chiral catalysts.

Table 2. The effect of solvent on the asymmetric addition of diethylzinc to benzaldehyde with **3b** as ligand[a]

Entry	Solvent	Yield (%)[b]	E.e. (%) (config.)[c]
1	Dichloromethane	66	77 (*R*)
2	Acetonitrile	30	62 (*R*)
3	THF	27	73 (*R*)
4	Diethyl ether	86	71 (*R*)
5	Toluene	96	82 (*R*)
6	Hexane	97	73 (*R*)
7	Toluene/hexane (1:1)	94	75 (*R*)

[a] The reactions were carried out at 0°C for 12 h, benzaldehyde/Et_2Zn/**3b** = 1.0/2.2/0.05.

[b] Isolated yields based on the benzaldehyde.

[c] Determined by GC with β-DEX120 capillary column and the absolute configuration was determined by comparing the sign of specific rotation.[11]

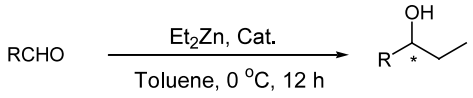
Table 3. The effect of temperature and catalyst loading on the asymmetric addition of diethylzinc to benzaldehyde with **3b** as ligand[a]

Entry	Catalyst loading (mol%)	Temperature (°C)	Yield (%)[b]	E.e. (%) (config.)[c]
1	5	20	99	79 (*R*)
2	5	0	96	82 (*R*)
3	5	−20	91	86 (*R*)
4	2.5	−20	63	84 (*R*)
5	1	−20	35	83 (*R*)
6	10	−20	93	85 (*R*)
7	20	−20	99	86 (*R*)

[a] The reactions were carried out in toluene for 12 h, benzaldehyde/Et_2Zn = 1.0/2.2.
[b] Isolated yields based on the benzaldehyde.
[c] Determined by GC with β-DEX 120 capillary column and the absolute configuration was determined by comparing the sign of specific rotation.[11]

With chiral ligands **3b** and **4b** as catalysts, the enantioselective addition with a few other representative aldehydes have also been investigated using 5 mol% of the ligand **3b** and **4b**. The results are summarized in Table 4. All aromatic aldehydes gave the desired addition products with good e.e. values, no obvious electronic and steric effects were observed. However, with aliphatic aldehydes, the enantioselectivities were moderate or worse.

Table 4. Enantioselective addition of diethylzinc to aldehydes catalyzed by **3b** and **4b**[a]



Entry	Ligand	R	Yield (%)[b]	E.e. (%) (config.)[c]
1	**3b**	C_6H_5	96	82 (*R*)
2	**4b**	C_6H_5	99	83 (*R*)
3	**3b**	*p*-ClC_6H_4	99	81 (*R*)
4	**4b**	*p*-ClC_6H_4	99	80 (*R*)
5	**3b**	*p*-BrC_6H_4	98	80 (*R*)
6	**4b**	*p*-BrC_6H_4	97	79 (*R*)
7	**3b**	*p*-$CH_3C_6H_4$	99	78 (*R*)
8	**4b**	*p*-$CH_3C_6H_4$	96	80 (*R*)
9	**3b**	*p*-$MeOC_6H_4$	99	80 (*R*)
10	**4b**	*p*-$MeOC_6H_4$	95	83 (*R*)
11	**3b**	*o*-$MeOC_6H_4$	99	81 (*R*)
12	**4b**	*o*-$MeOC_6H_4$	99	82 (*R*)
13	**3b**	PhCH=CH	85	34 (*R*)
14	**4b**	PhCH=CH	85	36 (*R*)
15	**3b**	$CH_3(CH_2)_7$	79	15 (*R*)[d]
16	**4b**	$CH_3(CH_2)_7$	81	16 (*R*)[d]
17	**3b**	*c*-C_6H_{11}	78	50 (*R*)[d]
18	**4b**	*c*-C_6H_{11}	75	41 (*R*)[d]

[a] The reactions were carried out in toluene at 0°C for 12 h, aldehyde/Et_2Zn/ligand = 1.0/2.2/0.05.
[b] Isolated yields based on the aldehydes.
[c] Determined by GC with β-DEX 120 capillary column and the absolute configuration was determined by comparing the sign of specific rotation.[11]
[d] Determined by analyzing the acetate derivative of the product on the β-DEX 120 capillary column.

3. Conclusions

In conclusion, a new series of chiral ligands based on D-fructose have been successfully synthesized and applied as catalysts in the asymmetric addition diethylzinc to aldehydes. In these reactions good e.e. values and yields were obtained. The appropriate backbone length between the coordinating nitrogen and oxygen atoms is crucial for highly effective catalysis with these ligands. We also elucidated that the C_2-symmetric bipyridyl alcohols functioned as *N,O* ligands in the reaction. Moreover, good enantiomeric excess can also be obtained in the reaction using non-diastereomerically pure C_2-symmetrical dimeric pyridyl alcohol **6**. Work is now in progress to study the performance of the above compounds as ligands in other catalytic asymmetric reactions.

4. Experimental

4.1. General methods

All reactions were carried out under an N_2 atmosphere. Melting points were measured on a Metter FP5 melting apparatus and are uncorrected. NMR spectra were measured in $CDCl_3$ on a Bruker DRX-400 NMR spectrometer with TMS as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 high sensitive polarimeter. High resolution mass spectra were recorded on Applied Biosystems Mariner System 5303. Enantiomeric excess (e.e.) determination was carried out using GC with a β-DEX 120 capillary column on an Agilent HP-4890 GC instrument with FID as detector. HPLC analyses were performed using an Agilent 1100 Series with Phenomenex ODS column. All solvents were dried and degassed by standard methods. *n*-BuLi was prepared according the standard method, 6-bromo-2-methylpyridine and 6,6′-dimethyl-2,2′-bipyridine were prepared according to the known procedure,[7,10] all other chemicals obtained commercially.

4.2. General procedures for the synthesis of *N,O* ligands 2a–b and 7a–b

To a solution of 2-bromopyridine (10 mmol) in 30 mL diethyl ether under N_2 was added a 2.1 M solution of

n-BuLi (11 mmol) in hexane at −78°C over 30 min. The reaction mixture was allowed to warm to −45°C slowly and stirred for 15 min; a clear yellow solution was observed. The mixture was cooled back to −78°C and chiral ketone (10 mmol) in dry diethyl ether was added dropwise over 10 min. The solution was allowed to warm to room temperature over 1 h and stirred for another 3 h. Quenched the reaction mixture with water. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography.

4.2.1. Synthesis of *N,O* ligand 2a. The above procedure was followed using 2-bromopyridine and chiral ketone **1a**. After work-up, it gave 1.54 g (45%) of **2a**; mp 159–160°C; $[\alpha]_D^{25}=-175.3$ (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.63 (s, 3H), 3.64 (d, 1H, $J=9.2$ Hz), 4.05 (d, 1H, $J=9.6$ Hz), 4.35 (t, 3H, $J=8.0$ Hz), 4.89 (d, 1H, $J=5.6$ Hz), 5.56 (s, 1H), 7.27 (d, 1H, $J=4.0$ Hz), 7.76 (s, 2H), 8.57 (d, 1H, $J=4.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 25.57, 25.73, 25.81, 26.19, 59.73, 71.22, 72.25, 73.31, 75.77, 106.54, 109.33, 112.74, 122.67, 122.87, 136.35, 147.07, 157.38; HRMS (ESI) calcd for $C_{17}H_{23}NO_6$ (M^++1): 338.1525, found: 338.1556.

4.2.2. Synthesis of *N,O* ligand 2b. The above procedure was followed using 2-bromopyridine and chiral ketone **1b**. After work-up, it gave 1.50 g (36%) **2b**; mp 161–162°C; $[\alpha]_D^{25}=-172.0$ (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.19–2.14 (m, 20H), 3.59 (d, 1H, $J=9.6$ Hz), 4.05 (d, 1H, $J=9.2$ Hz), 4.39 (s, 3H), 4.89 (d, 1H, $J=5.2$ Hz), 5.52 (s, 1H), 7.27 (d, 1H, $J=8.8$ Hz), 7.76 (t, 2H, $J=7.0$ Hz), 8.57 (d, 1H, $J=4.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 23.68, 23.89, 24.14, 24.91, 25.15, 25.16, 34.59, 34.96, 35.30, 35.90, 60.04, 70.85, 72.01, 73.31, 75.37, 106.25, 110.09, 113.61, 122.84, 122.93, 136.44, 146.97, 157.72; HRMS (ESI) calcd for $C_{23}H_{31}NO_6$ (M^++1): 418.2151, found: 418.2127.

4.2.3. Synthesis of compound 7a. The above procedure was followed using 2,6-dibromopyridine and chiral ketone **1a**. After work-up, it gave 1.9 g (45%) of **7a**; mp 192–193°C; $[\alpha]_D^{25}=-153.5$ (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.12 (s, 3H), 1.36 (s, 3H), 1.47 (s, 3H), 1.61 (s, 3H), 3.76 (d, 1H, $J=9.6$ Hz), 4.01 (d, 1H, $J=9.6$ Hz), 4.26 (s, 1H), 4.29–4.38 (m, 3H), 5.07 (d, 1H, $J=6.0$ Hz), 7.42 (d, 1H, $J=7.6$ Hz), 7.58 (t, 1H, $J=8.0$ Hz), 7.75 (d, 1H, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 25.41, 25.52, 25.77, 26.04, 59.83, 71.33, 72.03, 73.89, 75.11, 106.21, 109.21, 112.88, 121.55, 127.13, 138.50, 140.24, 159.76.

4.2.4. Synthesis of compound 7b. The above procedure was followed using 2,6-dibromopyridine and chiral ketone **1b**. After work-up, it gave 2.2 g (44%) of **7b**; mp 201–202°C; $[\alpha]_D^{25}=-149.8$ (*c* 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.11–1.72 (m, 20H), 3.72 (d, 1H, $J=9.6$ Hz), 4.02 (d, 1H, $J=9.2$ Hz), 4.21–4.35 (m, 4H), 5.10 (d, 1H, $J=6.8$ Hz), 7.41 (d, 1H, $J=7.6$ Hz), 7.57 (t, 1H, $J=8.0$ Hz), 7.75 (d, 1H, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 23.61, 23.71, 23.90, 24.02, 24.86, 25.06, 34.34, 34.92, 35.40, 35.86, 59.91, 70.82, 71.72, 73.77, 74.57, 105.75, 109.91, 113.75, 121.62, 127.07, 138.43, 140.19, 160.22.

4.3. Synthesis of 2c and 8

A solution of compound **7a** or 2-bromo-6-methylpyridine (6 mmol) and $Pd(PPh_3)_4$ (0.18 mmol) in 13 mL toluene was treated with a degassed solution of Na_2CO_3 (12 mmol) in H_2O (6 mL), followed by a solution of phenylboronic acid (7.2 mmol) in MeOH (4 mL). The mixture was stirred at 85°C for 5 h under N_2. After cooling to room temperature, a solution of concentrated aqueous NH_3 (5 mL) in 35 mL saturated aqueous Na_2CO_3 was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a crude product, which was purified by silica gel chromatography.

4.3.1. Synthesis of *N,O* ligand 2c. The above procedure was followed using compound **7a**. After work-up, it gave 2.39 g (97%) white solid; mp 144–145°C; $[\alpha]_D^{25}=-151.6$ (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 3H), 1.36 (s, 3H), 1.50 (s, 3H), 1.65 (s, 3H), 3.71 (d, 1H, $J=9.6$ Hz), 4.39 (t, 3H, $J=9.4$ Hz), 3.71 (d, 1H, $J=5.6$ Hz), 7.44–7.52 (m, 3H), 7.72 (t, 2H, $J=6.9$ Hz), 7.85 (d, 1H, $J=7.6$ Hz), 7.97 (d, 2H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 25.71, 25.80, 25.86, 26.23, 59.97, 71.38, 72.44, 73.58, 76.05, 106.71, 109.56, 112.80, 120.05, 121.34, 127.03, 128.79, 129.42, 137.78, 154.71, 156.98; HRMS (ESI) calcd for $C_{23}H_{27}NO_6$ (M^++1): 414.1838, found: 414.1863.

4.3.2. Synthesis of compound 8. The above procedure was followed using 2-bromo-6-methylpyridine. After work-up, it gave a colourless oil, yield 85%; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H), 6.85 (d, 1H, $J=7.0$ Hz), 7.28–7.37 (m, 5H), 7.96 (d, 2H, $J=8.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 24.13, 116.81, 120.97, 126.38, 128.07, 128.15, 136.23, 139.05, 156.02, 157.56.

4.4. Synthesis of *N,O* ligands 3a–4b

To a solution of pyridine or quinoline derivatives (10 mmol) in diethyl ether (30 mL) under N_2 was added a solution of *n*-BuLi (2.1 M, 11 mmol) in hexane at 0°C over 30 min. This solution was allowed warm to room temperature and stirred for 1 h. A solution of ketone (10 mmol) in 30 mL diethyl ether was added dropwise over 15 min with vigorous stirring while the temperature cooled back to 0°C. The mixture was stirred for an additional 2 h and hydrolyzed with a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with ether (3×50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography to give a white solid.

4.4.1. Synthesis of *N,O* ligand 3a. The above procedure was followed using 2-methylpyridne and chiral ketone **1a**. After work-up, it gave 2.8 g (80%) of **3a**; mp 121–122°C; $[\alpha]_D^{25}=-41.8$ (*c* 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.16 (s, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.50 (s, 3H), 3.07 (d, 2H, $J=13.6$ Hz), 4.05–4.21 (m, 5H), 4.36 (d, 1H, $J=9.6$ Hz), 7.20 (s, 1H), 7.28 (t, 1H, $J=7.2$ Hz), 7.66 (s, 1H), 8.48 (d, 1H, $J=3.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 25.50, 25.55, 25.77, 26.29, 41.03, 60.22, 71.31, 71.91, 72.30, 75.55, 106.77, 108.72, 111.85, 121.62, 124.93, 136.99, 147.27, 158.17; HRMS (ESI) calcd for $C_{18}H_{25}NO_6$ (M^++1): 352.1682, found: 352.1624.

4.4.2. Synthesis of *N,O* ligand 3b. The above procedure was followed using 2-methylpyridne and chiral ketone **1b**. After work-up, it gave 3.3 g (77%) of **3b**; mp 94–95°C; $[\alpha]_D^{25}=-40.2$ (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.19–1.79 (m, 20H), 3.00 (dd, 2H, $J_1=13.6$ Hz, $J_2=13.6$ Hz), 4.08–4.24 (m, 1H), 4.43 (d, 1H, $J=9.6$ Hz), 5.43 (s, 1H), 7.15–7.18 (m, 1H), 7.26 (t, 1H, $J=6.6$ Hz), 7.61–7.64 (m, 1H), 8.48 (d, 1H, $J=4.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 22.58, 23.52, 23.77, 23.88, 25.02, 31.52, 34.68, 35.12, 35.35, 35.71, 42.25, 60.55, 70.72, 71.66, 72.11, 74.89, 106.38, 109.18, 112.68, 121.41, 124.78, 136.49, 148.10, 158.52; HRMS (ESI) calcd for $C_{24}H_{33}NO_6$ (M^++1): 432.2308, found: 432.2377.

4.4.3. Synthesis of *N,O* ligand 3c. The above procedure was followed using compound **8** and chiral ketone **1b**. After work-up, it gave 2.7 g (53%) **3c**; mp 121–122°C; $[\alpha]_D^{25}=+93.4$ (*c* 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.36–1.74 (m, 20H), 2.58 (d, 1H, $J=13.6$ Hz), 3.07 (d, 1H, $J=14.0$ Hz), 3.69–3.78 (m, 1H), 3.98 (d, 1H, $J=14.0$ Hz), 1.13–4.18 (m, 3H), 4.33 (d, 1H, $J=8.4$ Hz), 7.21 (t, 1H, $J=13.2$ Hz), 7.38–7.47 (m, 3H), 7.58 (d, 1H, $J=7.6$ Hz), 7.69 (t, 1H, $J=7.6$ Hz), 7.87 (d, 2H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 22.50, 23.41, 23.51, 23.65, 23.77, 24.91, 34.66, 35.08, 35.31, 35.69, 41.21, 59.69, 60.64, 70.69, 71.49, 72.31, 75.31, 106.45, 109.16, 112.52, 118.24, 123.01, 126.68, 128.55, 129.02, 137.67, 155.48, 158.41; HRMS (ESI) calcd for $C_{30}H_{37}NO_6$ (M^++1): 508.2621, found: 508.2615.

4.4.4. Synthesis of *N,O* ligand 4a. The above procedure was followed using 2-methylquinoline and chiral ketone **1a**. After work-up, it gave 3.3 g (83%) of **4a**; mp 127–128°C; $[\alpha]_D^{25}=+36.5$ (*c* 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.09 (s, 3H), 1.33 (s, 3H), 1.48 (s, 3H), 1.51 (s, 3H), 3.15 (d, 1H, $J=14.4$ Hz), 3.27 (d, 1H, $J=14.4$ Hz), 4.09–4.23 (m, 5H), 4.43 (d, 1H, $J=9.6$ Hz), 6.84 (br, 1H), 7.35 (d, 1H, $J=9.2$ Hz), 7.49 (t, 1H, $J=7.2$ Hz), 7.67 (t, 1H, $J=7.4$ Hz), 7.78 (d, 1H, $J=8.0$ Hz), 7.97 (d, 1H, $J=8.3$ Hz), 8.09 (d, 1H, $J=8.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 25.50, 25.71, 26.24, 41.33, 60.28, 71.30, 71.85, 72.58, 76.04, 106.82, 108.68, 111.68, 122.84, 125.83, 126.55, 127.40, 128.19, 129.46, 136.95, 146.38, 159.42; HRMS (ESI) calcd for $C_{22}H_{27}NO_6$ (M^++1): 402.1838, found: 402.1857.

4.4.5. Synthesis of *N,O* ligand 4b. The above procedure was followed using 2-methylquinoline and chiral ketone **1b**. After work-up, it gave 3.8 g (79%) **4b**; mp 122–123°C; $[\alpha]_D^{25}=+35.6$ (*c* 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.99–1.01 (m, 3H), 1.31–1.43 (m, 7H), 1.56–1.81 (m, 10H), 3.17 (d, 1H, $J=14.0$ Hz), 3.46 (d, 1H, $J=14.0$ Hz), 4.10–4.21 (m, 4H), 4.28 (d, 1H, $J=5.6$ Hz), 4.49 (d, 1H, $J=9.6$ Hz), 7.38 (d, 1H, $J=8.4$ Hz), 7.49 (t, 1H, $J=7.6$ Hz), 7.67 (t, 1H, $J=7.8$ Hz), 7.79 (d, 1H, $J=8.0$ Hz), 7.98 (d, 1H, $J=8.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 23.37, 23.42, 23.72, 23.85, 24.89, 24.98, 34.57, 35.17, 35.73, 42.32, 60.68, 70.71, 71.55, 72.50, 75.34, 106.46, 109.19, 112.60, 123.12, 125.87, 126.72, 127.37, 128.47, 129.45, 136.29, 146.84, 159.52; HRMS (ESI) calcd for $C_{28}H_{35}NO_6$ (M^++1): 482.2464, found: 482.2464.

4.5. Synthesis of bipyridines 5a–b

To a solution of $NiCl_2{\cdot}6H_2O$ (6 mmol) in degassed DMF (30 mL), triphenylphosphine (24 mmol) was added at 70°C under N_2 to give a blue solution. Zinc powder (13 mmol) was then added and the resulting mixture was stirred for 1 h, which resulted in the formation of a dark brown mixture. Compound **7** (5 mmol) in degassed DMF was added slowly and the mixture was stirred for another 3 h. When the mixture was cooled to room temperature, the 5% aqueous NH_3 (50 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with water. Dried over Na_2SO_4 and removal of the solvent under reduced pressure gave a pale yellow solid, which was purified by silica gel column chromatography (20:1 to 4:1 CH_2Cl_2: ethylacetate) to give a white solid.

4.5.1. Synthesis of bipyridine 5a. The above procedure was followed using the compound **7a**. After work-up, it gave 0.92 g (55%) **5a**; mp 203–204°C; $[\alpha]_D^{25}=-200.6$ (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.10 (s, 6H), 1.36 (s, 6H), 1.49 (s, 6H), 1.64 (s, 6H), 3.72 (d, 2H, $J=9.6$ Hz), 4.05 (d, 2H, $J=9.6$ Hz), 4.40 (t, 6H, $J=11.6$ Hz), 5.04 (d, 2H, $J=5.6$ Hz), 5.30 (s, 2H), 7.81 (d, 2H, $J=8.0$ Hz), 7.93 (t, 2H, $J=8.0$ Hz), 8.38 (d, 2H, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 25.65, 25.76, 25.81, 26.22, 59.91, 71.42, 72.25, 73.78, 75.73, 106.61, 109.42, 112.80, 120.35, 123.07, 137.55, 152.91, 157.05; HRMS (ESI) calcd for $C_{34}H_{44}N_2O_{12}$ (M^++1): 673.2894, found: 673.2889.

4.5.2. Synthesis of bipyridine 5b. The above procedure was followed using the compound **7b**. After work-up, it gave 1.1 g (52%) **5b**; mp 168–169°C; $[\alpha]_D^{25}=-171.2$ (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.24–1.77 (m, 40H), 3.69 (d, 2H, $J=9.6$ Hz), 4.06 (d, 2H, $J=9.2$ Hz), 4.37 (d, 6H, $J=10.4$ Hz), 5.03 (d, 2H, $J=5.6$ Hz), 5.36 (br, 2H), 7.81 (d, 2H, $J=8.0$ Hz), 7.90 (t, 2H, $J=8.0$ Hz), 8.35 (d, 2H, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$): δ 23.85, 23.94, 24.09, 24.90, 25.14, 26.86, 34.66, 35.06, 35.32, 35.88, 60.13, 70.96, 71.96, 73.65, 75.25, 106.29, 110.04, 113.59, 120.28, 123.03, 137.39, 152.97, 157.34; HRMS (ESI) calcd for $C_{46}H_{60}N_2O_{12}$ (M^++1): 833.4146, found: 833.4121.

4.6. Synthesis of ligand 6

A solution of 6,6′-dimethyl-2,2′-bipyridine (5 mmol) in ether (20 mL) was added to *n*-BuLi (2.1 M, 5.1 mmol) in hexane at 0°C over 30 min which was allowed to warm to room temperature slowly and stirred for another 1 h. This orange solution was cooled back to −78°C, and a solution of chiral ketone **1a** (5 mmol) in 30 mL of ether was added dropwise. The mixture was allowed to warm to room temperature and stirred for 30 min, and an additional 5.1 mmol of 2.1 M *n*-BuLi in hexane was introduced, after the mixture was cooled to −78°C again, chiral ketone **1a** (5 mmol) in 30 mL of ether was added dropwise. This mixture was warmed to room temperature and stirred for another 3 h. Water was then added. The yellow organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed by brine and dried over Na_2SO_4, and the solvent was removed, to give a yellow oil which was purified by silica gel column chromatography and recrystallized from CH_2Cl_2/hexane to give a white solid 1.12 g (32%); mp 185–186°C; $[\alpha]_D^{25} = +65.8$ (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.12–1.53 (m, 24H), 3.01–3.15 (m, 4H), 3.88–4.00 (m, 2H), 4.07–4.20 (m, 8H), 4.33–4.45 (m, 2H), 6.80–6.90 (br, 2H), 7.19–7.28 (m, 2H), 7.65–7.77 (m, 2H), 8.04–8.10 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 22.70, 24.92, 25.31, 25.58, 25.91, 26.08, 26.36, 27.29, 29.63, 40.66, 40.88, 42.74, 51.05, 53.28, 60.39, 60.49, 64.82, 70.46, 70.86, 71.32, 71.93, 72.04, 72.40, 75.99, 80.95, 106.87, 108.75, 108.95, 110.27, 111.76, 111.87, 112.78, 118.57, 119.08, 124.49, 124.73, 137.37, 137.95, 153.18, 154.24, 155.29, 157.95, 158.12; HRMS (ESI) calcd for $C_{36}H_{48}N_2O_{12}$ (M^++1): 701.3207, found: 701.3204.

4.7. General procedures for the asymmetric addition of diethylzinc to aldehydes

The chiral ligand (0.05 mmol, 5 mol%) in dry toluene (3 mL) was cooled to 0°C and diethylzinc in hexane (1 M, 2.2 mmol, 2.2 mL) was added slowly. After stirring for 30 min at 0°C, freshly distilled aldehyde (1 mmol) was added and the reaction was monitored by TLC. When the reaction was completed, 1 N aqueous HCl (5 mL) was added. The layers were separated and the aqueous layer was extracted with ether (3×15 mL). The combined organic phases were washed with brine, dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography, the enantiomeric excess was determined by GC.

Acknowledgements

Financial support from the National Science Foundation of China (29933050) is gratefully acknowledged. The authors thank Dr. Yonggui Zhou for helpful discussions.

References

1. For reviews, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (c) Blaser, H. U. *Chem. Rev.* **1992**, *29*, 359; (d) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757.
2. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
3. Corey, E. J.; Yuen, P. W.; Hammon, F. J. D.; Wierda, A. *J. Org. Chem.* **1990**, *55*, 784.
4. (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205; (b) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169; (c) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191; (d) Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235; (e) Collomb, P.; Von Zelewsky, A. *Tetrahedron: Asymmetry* **1998**, *9*, 3911; (f) Kwong, H. L.; Lee, W. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3791; (g) Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411; (h) Ishizaki, M.; Hoshino, O. *Chem. Lett.* **1994**, 337; (i) Williams, D.; Fromhold, M. G. *Synlett* **1997**, 523; (j) Macedo, E.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 549; (k) Kang, J.; Kim, H.-Y.; Kim, J.-H. *Tetrahedron: Asymmetry* **1999**, *10*, 2523; (l) Kotsuki, H.; Nakagawa, Y.; Moriya, N.; Tateishi, H.; Ochi, M.; Suzuki, T.; Isobe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1165; (m) Kotsuki, H.; Hayakawa, H.; Tateishi, H.; Wakao, M.; Shiro, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3203; (n) Wu, Y.; Yun, H.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3543; (o) Yun, H.; Wu, Y.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron Lett.* **2000**, *41*, 10263; (p) Zhang, H.; Xue, F.; Mak, T. C. W.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002; (q) Zhang, H.; Chan, K. S. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 381; (r) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382; (s) Goanvic, D. L.; Holler, M.; Pale, P. *Tetrahedron: Asymmetry* **2002**, *13*, 119.
5. Zhou, Y. G.; Dai, L. X.; Hou, X. L. *Chin. J. Chem.* **2000**, *18*, 121.
6. Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
7. Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1984**, 736.
8. (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513; (b) Alves, T.; de Oliveira, A. B.; Snieckus, V. *Tetrahedron Lett.* **1998**, *29*, 2135; (c) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.
9. Konig, B.; Meetasm, A.; Kellog, R. M. *J. Org. Chem.* **1998**, *63*, 5533.
10. Adams, R.; Miyano, S. *J. Am. Chem. Soc.* **1954**, *76*, 3168.
11. (a) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165; (b) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc. Chem. Commun.* **1994**, 2009; (c) Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218; (d) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.