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Bifunctional pyridyl alcohols with the bicyclo[3.3.0]octane scaffold in the asymmetric addition of diethylzinc to aldehydes

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Abstract—Some new pyridyl alcohols with the *cis*-bicyclo[3.3.0]octane scaffold were synthesized and used as chiral ligands for the enantioselective addition of diethylzinc to aldehydes. Ligands **4** were found to be far superior to the C_2-symmetric ligands **2** in terms of enantioselectivities. Quantitative yields and enantiomeric excesses of up to 92% were obtained when the ligand **4** was used. The carbonyl function in **4** proved to be beneficial for the high enantioselectivities in the addition of diethylzinc to aldehydes. Conversion of the carbonyl group into oxime or oxime ether group led to a sort of more active ligands, which catalyzed the same reaction with rate acceleration.

1. Introduction

Over the past decade, much attention has been paid to the design and synthesis of novel chiral ligands for the asymmetric processes.[1] Among them, the development of bifunctional ligand systems for the asymmetric construction of C–C bonds is of great interest.[2,3] The secondary basic sites in chiral ligands provided an additional interaction between the ligand and the reagent, which usually resulted in an improved reactivity and stereoselectivity.[4]

Amino alcohols catalyzed addition of diethylzinc to aldehydes was so extensively explored that it has become as one of the model reactions in the asymmetric catalysis.[5] It is generally accepted that this reaction proceeds via a dual activation of the aldehyde electrophile and the diethylzinc nucleophile,[6] as shown in transition state **A** in Figure 1. It occurred to us that if there is a secondary basic site (represented as Nu in **B** in Figure 1) in the same ligand well positioned to coordinate with zinc atom Zn(2), the dissociation of Zn(2)–O(2) bond in **A** might occur. Accordingly, the transition state would shift from **A** to **B**, which included a chair-like six-membered ring structure.[7]

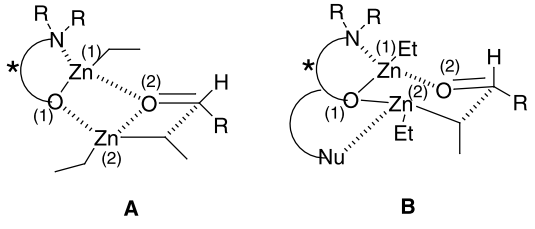

Figure 1.

In our laboratory, we are interested in the application of some structurally interesting molecules for asymmetric synthesis.[8] Synthesis of new chiral ligands bearing the *cis*-bicyclo[3.3.0]octane scaffold and their applications in asymmetric reactions are one of our recent projects.[8c,d] The appealing semi-caged structure of the *cis*-bicyclo[3.3.0]octane framework is anticipated to provide a peculiar chiral environment in asymmetric processes.

In our previous work,[8c] we reported the synthesis of the C_2-symmetric bis-pyridyl alcohol **2** (Scheme 1) and mono-pyridyl alcohol **4** from the chiral diketone **1**[9] which was easily obtained from 1,5-cyclooctadiene, and their application as novel chiral ligands in the enantioselective addition of diethylzinc to aldehydes. To our surprise, C_2-symmetric ligand **2** was found to only induce very low enantioselectivity (7% ee) in the diethylzinc addition to benzaldehyde, while ligand **4**, with a carbonyl group in the bicyclo[3.3.0]octane scafflod, was found much more efficient in catalyzing the same reaction and provided the product with 92% ee in quantitative yield. Similar good ees (89–92%) were observed in the reaction with other aldehydes. To explain these results, we envisioned that the carbonyl group in ligand **4** might be involved in the

Keywords: Bicyclo[3.3.0]octane; Bifunctional ligand; Pyridyl alcohol; Diethylzinc; Secondary basic site.

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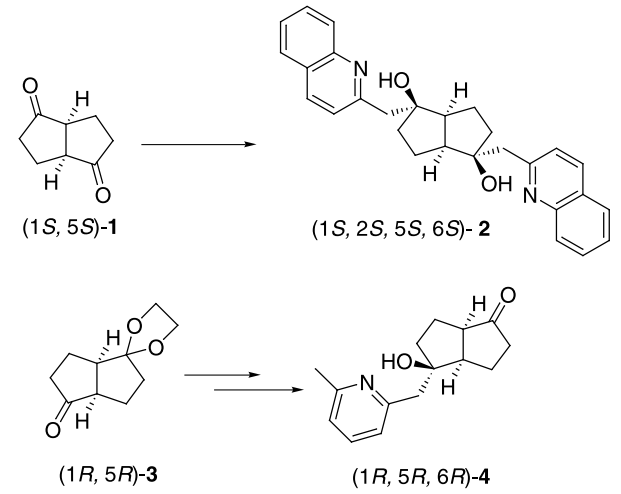
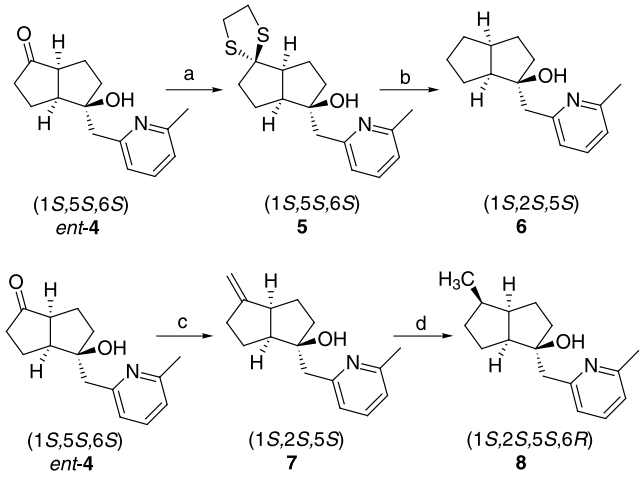


Scheme 1. The synthesis of compounds **2** and **4**.



Scheme 2. The synthesis of compounds **5**, **6**, **7**, and **8**. (a) $HSCH_2CH_2SH$, BF_3OEt_2, CH_2Cl_2, Quant. (b) Raney-nickel, EtOH, reflux, Quant. (c) CH_3PPh_3I, *t*-BuOK, 82%. (d) Pd/C, MeOH, H_2 (1 atm), 85%.

coordination with zinc atom and stabilize the reaction transition state, as depicted in Figure 1.

In this paper, we wish to report our detailed studies. We found that the unmasked carbonyl group in ligand **4** acted as a secondary basic group in this reaction, and was important for maintaining the high stereoselectivities. The modification of **4** by converting the carbonyl function into oxime or oxime ether group led to a kind of more efficient ligands, which catalyzed the addition of diethylzinc to aldehydes with an obvious acceleration effect.

2. Results and discussion

To address whether the carbonyl group in ligand **4** had contribution to the high enantioselectivity observed in the diethylzinc addition to aldehydes, we first consider to convert the carbonyl group into other functions to see if it would result in an apparent impact on the stereoselectivity when applied to the reaction. Reduction of the carbonyl group into methylene moiety was certainly the first choice.

Unfortunately, direct reduction, including Wolff-Kishner–Huang reduction[10] and reduction of tosylhydrazone by sodium cyanoborohydride,[11] was proved to be unsuccessful. Thus, a different approach was then taken. As shown in Scheme 2, by converting the *ent*-**4** (the enantiomer of **4**) into its dithioketal counterpart **5**, followed by the reaction with Raney-nickel in 2-propanol,[12] we successfully obtained the designed compound **6**. In addition, compound **7** and **8**[13] were also synthesized via Wittig reaction of *ent*-**4** with CH_3PPh_3I, followed by the hydrogenation reaction.

With compounds **5**, **6**, **7** and **8** in hand, we investigated their efficiency as chiral ligand respectively in the diethylzinc addition to aldehydes under the same conditions[8c] as ligand

Table 1. Comparison of the stereoselectivity of the product induced by ligand **4** and **5**–**8**[a]

Entry	Ligand	Aldehyde	Yield (%)[b]	ee (%)[c]
1	**4**	Benzaldehyde	>98	92
2	**4**	*p*-Chlorobenzaldehyde	84	91
3	**4**	*p*-Anisaldehyde	>98	91
4	**4**	*p*-Tolualdehyde	>98	91
5	**4**	1-Naphthaldehyde	>98	89
6	**4**	*trans*-Cinnamaldehyde	>98	51
7	**5**	Benzaldehyde	90	78
8	**5**	*p*-Chlorobenzaldehyde	90	76
9	**5**	*p*-Anisaldehyde	85	77
10	**6**	Benzaldehyde	>98	79
11	**6**	*p*-Chlorobenzaldehyde	95	77
12	**7**	Benzaldehyde	88	77
13	**7**	*p*-Chlorobenzaldehyde	93	79
14	**7**	*p*-Anisaldehyde	>98	77
15	**7**	*p*-Tolualdehyde	>98	78
16	**7**	1-Naphthaldehyde	>98	76
17	**7**	*trans*-Cinnamaldehyde	98	33
18	**8**	Benzaldehyde	>98	77
19	**8**	*p*-Chlorobenzaldehyde	>98	78
20	**8**	*p*-Anisaldehyde	>98	75
21	**8**	*p*-Tolualdehyde	98	79
22	**8**	1-Naphthaldehyde	>98	74
23	**8**	*trans*-Cinnamaldehyde	90	33

[a] The absolute configuration of products catalyzed by **4** is *R*, while it is *S* when catalyzed by **5**–**8**.
[b] Isolated yield after the column chromatography.
[c] Determined by chiral HPLC analysis.

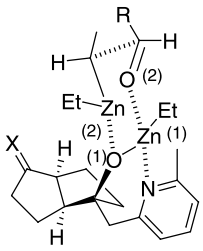


Figure 2. Proposed transition state.

To gain some insight into this interesting phenomena, X-ray analysis of **2** and **4** were performed (Figs. 3 and 5).[14] X-ray analysis of **2** (Fig. 3) revealed that there was a hydrogen bonding between hydroxyl O(2)H and oxygen atom O(1), and the distance between two oxygen atoms was 2.74 Å. The two nitrogen atoms in the quinoline ring were hidden in the back side of the bicyclo[3.3.0]octane framework, and neither of them had a hydrogen bonding with the hydroxy moiety. It was reasonable to assume when **2** was used to catalyze the addition of diethylzinc to aldehyde, the real catalyst could be depicted in Figure 4, wherein zinc atom

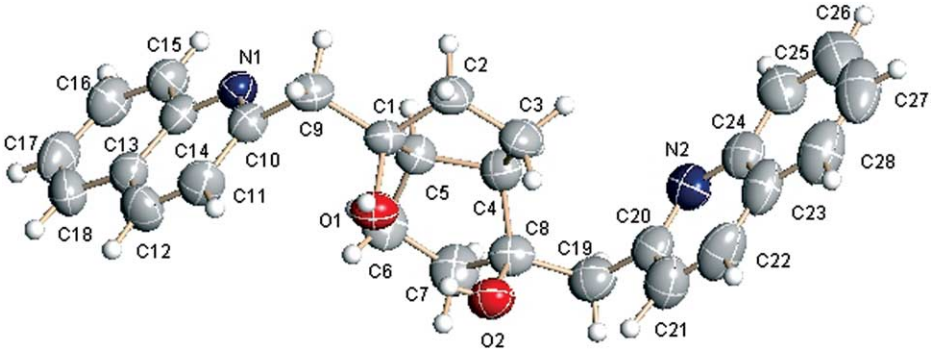


Figure 3. X-ray analysis of ligand **2**.

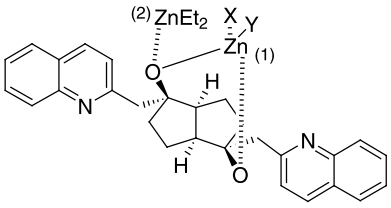


Figure 4. Proposed catalyst when **2** was used as the ligand. X, Y may be the ethyl, aldehyde group, or as part of the oligmer form.

4 was used. The experimental results were summarized in Table 1. As we can see, when the ligand **5**, **6**, **7** or **8** was used, the obtained ee value of the corresponding product was 10% or more lower than that obtained by using ligand **4**. For benzaldehyde (entries 7, 10, 12, 18), substituted benzaldehydes (entries 8, 9, 11, 13, 14, 15, 19, 20, 21) and 1-naphthaldehyde (entries 16, 22), the ee value of the product decreased from 90% level (entries 1–5) to 77% or so. For *trans*-cinnamaldehyde (entries 17, 23) a similar decrease from 51% (entry 6) to 33% was observed. These results indicate that the presence of the carbonyl group in ligand **4** is indeed important for maintaining the high ee in this reaction.

Considering the differences between ligand **4** and **6**–**8**, it might be reasonable to postulate that the carbonyl group in ligand **4** was employed as a secondary basic site, in other words, the reaction might proceed via a transition state as shown in Figure 2 (X=O), where the carbonyl group coordinated with zinc atom Zn(2) to act as a secondary basic group. In the case of ligand **5**, although the sulfur atom could be a secondary basic site, it was still not as effective as ligand **4**, which suggested that the planar conformation of the carbonyl group of ligand **4** was also an important factor for inducing the high enantioselectivity.

Zn(2) did not coordinate with the nitrogen atom. It was obvious that the surroundings of zinc atoms Zn(1) and Zn(2) was free from steric hindrance, which resulted in the low stereo-induction.

On the other hand, the X-ray analysis of **4** (Fig. 5) showed a

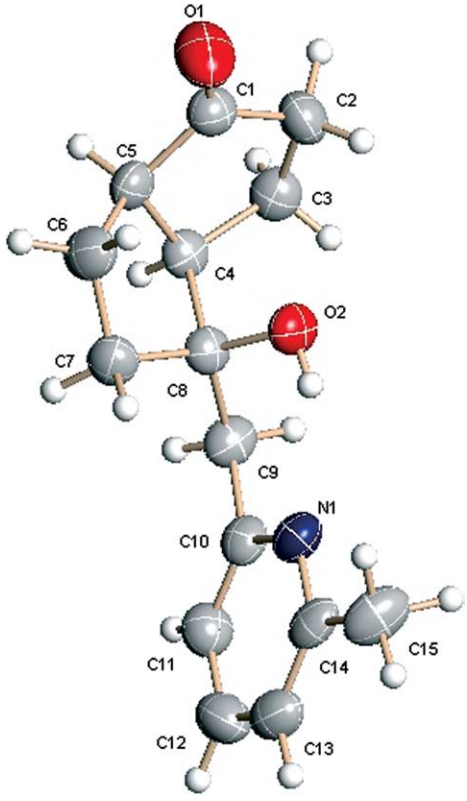
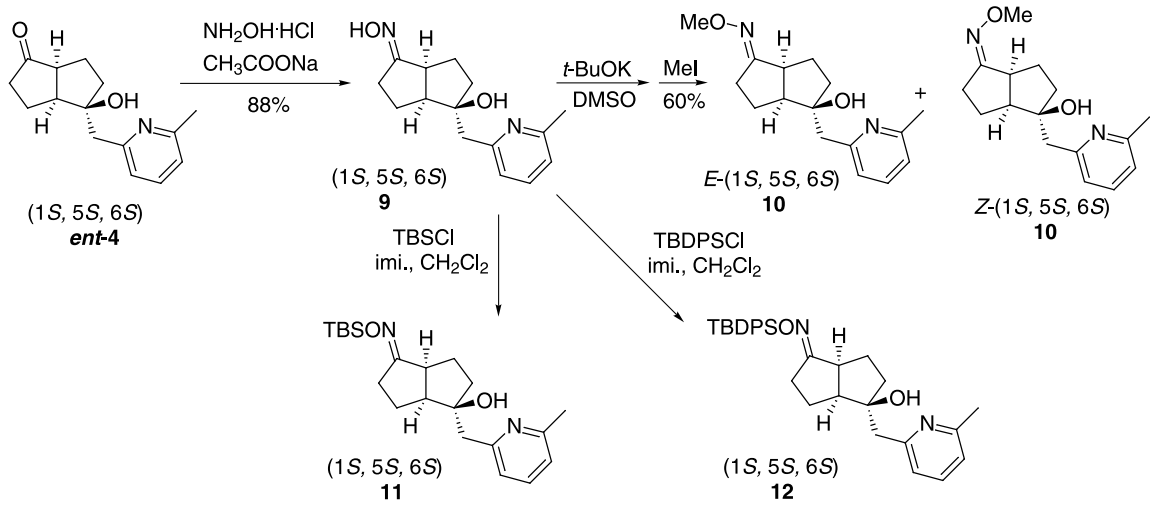


Figure 5. X-ray analysis of ligand **4**.



Scheme 3. The synthesis of ligands **9**–**12**.

hydrogen bonding between the hydroxyl O(2)H and the nitrogen atom in the pyridine ring. When **4** was used to catalyze the addition of diethylzinc to aldehyde, the real catalyst was possible as described in Figure 2. Zinc atom Zn(1) combined with hydroxyl oxygen atom, and coordinated with the nitrogen atom in the pyridine ring. Zinc atom Zn(2) coordinated with hydroxyl oxygen atom. The carbonyl oxygen was also possibly involved in the stabilizing the six-membered chair-like transition state. Taking advantage of the steric hindrance of bicyclo[3.3.0]-octane backbone and methyl group in the pyridine ring, the reaction using ligand **4** gave higher enantioselectivities.

To further prove our hypothesis, we envisioned that if X in the proposed transition state (Fig. 2) is replaced by sulfur atom or nitrogen atom, which will have a more electron-donating potential and thus the ethyl group bound to Zn(2) atom would be more nucleophilic. As a result, an accelerated reaction rate could be observed in the same reaction. Disappointingly, we were unsuccessful in converting the carbonyl group of ligand *ent*-**4** into thiocarbonyl group with Lawesson' reagent or P_2S_5.[15,16] Efforts to convert the carbonyl group into imine analogous also failed, presumably due to the presence of the hydroxy and pyridine moiety within the molecule.

We then turned our attention to the oxime and oxime ether group which were reluctantly used in chiral ligands or auxiliaries due to the usual formation of a mixture of geometric isomers.[17] However, two advantages of oxime and oxime ether are appealing: (1) they are more electron-donating than imine; (2) the high stability toward hydrolytic conditions would allow them for separation via flash column chromatography easily. Keeping these in mind, we prepared the oxime ligand **9** from ligand *ent*-**4**. Methylation of **9** afford the *O*-methyl oxime ether ligand **10** (Scheme 3). The *E*/*Z* isomers of oxime **9** were inseparable by column chromatography. However, the corresponding oxime ether *E*-**10** and *Z*-**10** could be separated by flash column chromatography.[18]

Interestingly, when oxime ligand **9** was used to catalyze the

Table 2. Comparison of the reaction rational catalyzed by ligands **4**, **9**–**12**[a]

Entry	RCHO	Ligand	Catalyst loading (mol%)	Temperature (°C)	Reaction time (h)	Yield (%)[b]	ee (%)[c]
1	Benzaldehyde	**4**	10	0 to rt	24	>98	92
2	Benzaldehyde	**9**	5	0	10	>98	81
3	Benzaldehyde	**9**	10	−20	24	>98	84
4	Benzaldehyde	*Z*-**10**	3	0	10	>98	83
5	Benzaldehyde	*E*-**10**	4	0	10	>98	85
6	Benzaldehyde	**11**	3	0	10	>98	88
7	Benzaldehyde	**11**	5	−20	44	>98	90
8	Benzaldehyde	**12**	2	0	10	>98	86
9	Benzaldehyde	**12**	6	−20	30	>98	88
10	*p*-Chlorobenzl-dehyde	**11**	3.5	0	11	94	87
11	*p*-Anisaldehyde	**11**	4	0	12	>98	88
12	*trans*-Cinnamal-dehyde	**11**	4	0	8	88	51
13	Cyclohexane-carboxyalde-hyde	**11**	4.5	0	11	>98	69[d]

[a] The absolute configuration of all products is *S* except in entry 1 which is *R*.
[b] Isolated yield after the column chromatography.
[c] The ee was determined by chiral HPLC analysis unless otherwise noted.
[d] The ee was determined by comparison of the specific optical rotation with the literature, see Ref. 19.

addition of diethylzinc to benzaldehyde, a distinctive acceleration phenomenon was observed. The reaction was completed in only 10 h at 0 °C with 5 mol% of loading (entry 2, Table 2). In comparison, the reaction needed 24 h at rt for completion when 10 mol% of ligand **4** was used (entry 1, Table 2). Considering a relatively lower ee of 81% was observed, the reaction temperature was reduced to −20 °C (entry 3), which resulted in a prolonged reaction time (24 h) and a slight enhancement of ee to 84%. Similar acceleration effect was also observed when oxime ether *Z*-**10** or *E*-**10** was used as the ligands (entries 4 and 5). It was worth noting that the addition reaction catalyzed by *Z*-**10** or *E*-**10** afforded the product with the same sense and almost the same ee value, which indicated the geometry (*Z* or *E*) of the oxime ether played a minor role in the stereoinduction of this reaction.

Comparison of entry 2 and entries 4, 5 revealed that the oxime ether ligand was more efficient than the corresponding oxime ligand in terms of the enantioselectivity. Therefore, we turned to prepare other oxime ethers with the hope to find more efficient ligands. As shown in Scheme 3, TBS (*t*-butyldimethylsilyl) oxime ether ligand **11** and TBDPS (*t*-butyldiphenylsilyl) oxime ether ligand **12** were synthesized from oxime **9** in quantitative yields. When 3 mol% of **11** was employed as the ligand (entry 6), the reaction was completed within 10 h to furnish the product with a slight increase of ee (88%) than ligand **10**. A decrease in temperature from 0 to −20 °C resulted in a further increase of ee to 90%, in sacrifice of the reaction time (44 h) (entry 7). Attempts to employ compound **12** with a bulkier silyl ether group as the ligand to further increase the ee proved to be unsuccessful (entries 8 and 9). Extension of the substrate to substituted benzaldehydes (entries 10 and 11) and aliphatic aldehydes (entries 12 and 13) using TBS–oxime **11** as ligand also showed an acceleration effect, though the ee of the product decreased slightly in comparison with that induced by ligand **4**.

This acceleration effect is in accordance with our hypothesis. When the carbonyl group in **4** (or *ent*-**4**) was converted into oxime or oxime ether group that had a more electron-donating potential, the ethyl group bound to Zn(2) atom should be more nucleophilic. As a result, an accelerated reaction occurred. Considering the relative position of the carbonyl group and the hydroxyl group in ligand **4** (see X-ray analysis in Figure 5), the lone pair electrons of the carbonyl oxygen atom are almost bisected by the O(1)–O(2) line. So unlikely they could be directed to one zinc atom at the same time. The experimental fact that both *E*- and *Z*-oxime ether (entries 4 and 5, Table 2) gives the same enantioselectivities with the same sense also implies that the lone pair electrons would not be involved in the transition state. Most likely it is the π electrons of the carbonyl group that interact with the zinc atom Zn(2) in the supposed transition state **B** in Figure 1. Clarification of the real mechanism calls for further investigation.

3. Conclusion

In summary, some new pyridyl alcohols with the *cis*-bicyclo[3.3.0]octane scaffold were synthesized and used to catalyze the enantioselective addition of diethylzinc to aldehydes. C_2-symmetric ligand **2** was found less effective than unsymmetric ligand **4**. Over 90% ees were found when **4** was used to catalyze the reactions. The carbonyl group in pyridyl alcohol **4** was evidenced to be important in achieving the high enantioselectivity. Conversion of this carbonyl group into oxime or oxime ether motif led to a kind of more efficient ligand, which catalyzed the same reaction with a higher reaction rate. The work to expand the use of these ligands in other asymmetric reactions is in progress.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ on 300 and 75 MHz FT-spectrometers, respectively, using $SiMe_4$ as the internal reference. IR spectra were recorded on a Bio-Rad FTS-185 IR spectrometer. Mass spectra were recorded by the EI method, and HRMS were measured on a Finnigan MAT-8430 mass spectrometer. Elemental analyses were performed on Heraeus Rapid-CHNO. Enantiomeric excess (ee) determination was carried out using HPLC with Chiralcel OD, AS, AD, OJ columns. The silica gel used for flash chromatography was 300–400 mesh. All solvents were dried by standard methods. Unless otherwise noted, commercially available reagents were used without further purification.

4.1.1. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-ylmethyl)-bicyclo[3.3.0]octan-2-one, ethylene thioketal, 5. Pyridyl alcohol *ent*-**4** (490 mg, 2 mmol) was dissolved in anhydrous dichloromethane (50 mL) in a 100 mL flame-dried three-necked flask under an argon atmosphere, followed by the addition of Boron trifluoride diethyl etherate (1.33 mL, 10 mmol) and 1,2-ethanedithiol (0.32 mL, 4 mmol). This solution was stirred at rt overnight and quenched by the saturated aqueous $NaHCO_3$. The organic layer was separated, and the water layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over with anhydrous Na_2SO_4. Purification by flash column chromatography afforded 630 mg of **5** as a white solid in quantitative yield. Mp 72 °C; $[\alpha]_D^{20}$ +5.3° (*c* 1.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40–1.99 (m, 7H), 2.16 (m, 1H), 2.32 (m, 1H), 2.49 (s, 3H), 2.76 (m, 1H), 2.87 (s, 2H), 3.23 (m, 4H), 6.00–6.60 (br, 1H), 6.89 (d, J= 7.8 Hz, 1H), 7.00 (d, J=8.1 Hz, 1H), 7.50 (td, J=7.8, 1.2 Hz, 1H); FT-IR (KBr, cm^{-1}): 3367, 3062, 2922, 1594, 1576, 1459, 1416; EIMS (*m*/*z*, %): 321 (M^+, 12.85), 303 (M^+-H_2O, 1.93), 262 (15.30), 260 (30.29), 228 (30.13), 162 (12.89), 149 (33.32), 134 (13.55), 107 (100.00), 106 (26.84); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.26, 25.40, 30.08, 38.32, 38.75, 39.94, 42.99, 46.35, 51.26, 56.91, 75.82, 81.90, 120.88, 121.03, 137.11, 157.05, 158.86; HRMS for $C_{17}H_{23}NOS_2$ (M^+), calcd: 321.1221, found 321.1211.

4.1.2. (1*S*,2*S*,5*S*)-2-(6-Methylpyridin-2-ylmethyl)-bicyclo-[3.3.0]octan-2-ol, 6. Thioketal **5** (360 mg, 1.1 mmol) was dissolved in ethanol (20 mL), followed by

the addition of 1 g of Raney nickel. The resulting mixture was then refluxed for 2 h. The cooled solution was filtered through celite and washed with ethanol. Purification by flash column chromatography provided 260 mg of pyridyl alcohol **6** as an oil in quantitative yield. $[\alpha]_D^{20}$ +4.4° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (m, 5H), 1.63 (m, 5H), 2.13 (m, 1H), 2.45 (m, 1H), 2.52 (s, 3H), 2.90 (m, 2H), 6.16 (br, 1H), 6.92 (d, J=7.6 Hz, 1H), 7.02 (d, J=7.7 Hz, 1H), 7.49 (m, 1H); FT-IR (film, cm^{-1}): 3348, 3068, 2948, 1579, 1459, 798; EIMS (*m/z*, %): 231 (M^+, 1.82), 162 (21.33), 149 (34.49), 134 (10.72), 108 (10.59), 107 (100.00), 106 (12.04), 79(6.97), 41(7.16); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.27, 27.31, 27.57, 30.15, 34.43, 39.82, 43.22, 46.46, 52.46, 81.67, 120.85, 120.92, 136.97, 157.04, 159.36; HRMS for $C_{15}H_{21}NO$ (M^+), calcd: 231.1623, found 231.1641.

4.1.3. (1*S*,2*S*,5*S*)-6-Methylene-2-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-ol, 7. To a 100 mL three-necked round-bottomed flask was added PPh_3CH_3I (606 mg, 1.5 mmol) and THF (20 mL) under argon atmosphere at 0 °C. While the mixture was stirred, *t*-BuOK (168 mg, 1.5 mmol) was added. The resulting yellow solution was stirred for 30 min, followed by the slow addition of a solution of 245 mg of pyridyl alcohol *ent*-**4** (1 mmol) in 10 mL of THF. Stirring was continued for 10 h at 0 °C. Then, 10 mL water was added to quench the reaction. Usual workup followed by flash column chromatography afforded **7** (200 mg, yield 82%) as a colorless oil. $[\alpha]_D^{20}$ +80.0° (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.53 (m, 2H), 1.73 (m, 3H), 1.95 (m, 1H), 2.23 (m, 2H), 2.45 (m, 1H), 2.51 (s, 3H), 2.92 (m, 3H), 4.74 (m, 1H), 4.83 (m, 1H), 6.20 (br, 1H), 6.92 (d, J=7.6 Hz, 1H), 7.02 (d, J=7.7 Hz, 1H), 7.52 (t, J=7.6 Hz, 1H); FT-IR (film, cm^{-1}): 3335, 3068, 2951, 1654, 1579, 1459, 877; EIMS (*m/z*, %): 243 (M^+, 8.09), 107 (100.00), 149 (16.99), 162 (16.91), 134 (14.74), 108 (12.09), 79 (10.79), 77 (8.79); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.20, 25.97, 30.51, 34.86, 39.36, 46.05, 47.62, 52.95, 82.04, 103.67, 121.03, 121.05, 137.14, 157.09, 159.17, 159.26; HRMS for $C_{16}H_{19}N$ (M^+-H_2O), calcd.: for 225.1529, found 225.1518.

4.1.4. (1*S*,2*S*,5*S*,6*R*)-6-Methyl-2-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-ol, 8. To a solution of **7** (410 mg, 1.68 mmol) in methanol (20 mL) was added 57 mg of 10% Pd/C. The mixture was hydrogenated for 48 h under 1 atm of H_2, and then filtered through a pad of celite. The filtrate was concentrated and purified by flash column chromatography to give **8** (348 mg, yield 85%) as a colorless oil. $[\alpha]_D^{20}$ +21.8° (*c* 1.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (d, J=6.3 Hz, 3H), 1.13 (m, 2H), 1.39 (m, 4H), 1.56 (m, 2H), 1.75 (m, 1H), 2.14 (t, J=7.5 Hz, 1H), 2.34 (m, 1H), 2.45 (s, 3H), 2.85 (s, 2H), 5.84 (br, 1H), 6.8 (d, J=7.8 Hz, 1H), 6.94 (d, J=7.8 Hz, 1H), 7.45 (t, J=7.8 Hz, 1H); FT-IR (film, cm^{-1}): 3352, 3065, 1595, 1579, 1459, 1097, 795; EI-MS (*m/z*, %): 245 (M^+, 1.19), 227 (M^+-H_2O, 3.74), 162 (18.99), 149 (36.55), 134 (9.67), 108 (10.73), 107 (100.00), 106 (13.13), 79 (5.89), 41 (5.87); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.02, 23.09, 23.31, 25.15, 32.82, 36.54, 39.78, 46.24, 47.27, 51.68, 80.97, 119.85, 119.89, 135.97, 156.12, 158.53; HRMS for $C_{16}H_{23}NO$ (M^+), calcd.: 245.1780, found: 245.1794.

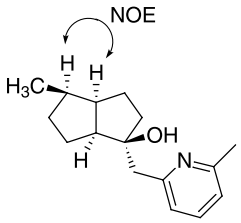


Figure 6. The establishment of the relative configuration of ligand **8** by NOESY analysis.

The relative configuration of **8** was confirmed by its NOESY analysis, see Figure 6.

4.1.5. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-one oxime, 9. To a solution of 37 mg of hydroxylamine hrdrochloride in 5 mL of ethanol was added *ent*-**4** (65 mg, 0.26 mmol) and sodium acetate (43 mg, 0.53 mmol). The resulting mixture was stirred at rt for 30 min. After evaporation of the solvent, the residue was partitioned between CH_2Cl_2 (10 mL) and brine (10 mL). The water layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was purification by flash column chromatography to give **9** (61 mg, yield 88%) as a white solid. $[\alpha]_D^{20}$ +136.7° (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.56–2.05 (m, 6H), 2.06–2.37 (m, 2H), 2.52 (s, 3H), 2.63 (m, 1H), 2.87 (m, 1H), 3.03 (m, 1.5H), 3.40 (m, 0.5H), 6.21 (br, 1H), 6.93 (d, J=7.5 Hz, 1H), 7.02 (d, J=8.1 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H), 8.41 (br, 1H); FT-IR (KBr, cm^{-1}): 3393, 3188, 3075, 2957, 1674, 1597, 1579, 1459, 950; EIMS (*m/z*, %): 260 (M^+, 1.67), 243 (M^+-OH, 19.24), 225 (8.88), 163 (7.04), 162 (17.64), 134 (12.90), 108 (10.95), 107 (100.00), 106 (12.45). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.05; H, 7.72; N, 10.62.

4.1.6. 4.6. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo[3.3.0]octan-2-one *O*-methyl oxime, 10. Potassium *tert*-butoxide (166 mg, 1.48 mmol) was added into a solution of oxime **9** (350 mg, 1.34 mmol) in 15 mL of DMSO. The mixture was stirred at rt for 30 min, followed by the addition of the iodomethane (0.094 mL, 1.48 mmol). After 1 h, the mixture was diluted with ethyl acetate (300 mL) and washed with brine. The residue after concentration was subjected to flash chromatography to afford *Z*-**10** (40 mg), *E*-**10** (50 mg) and a mixture of *Z*-**10** and *E*-**10** (100 mg) with a total yield of 60%. The ratio of *Z*-**10**/*E*-**10** was confirmed to be 1:2 by ^1H NMR analysis of the crude product.

Minor isomer (*Z*, *less polar*). $[\alpha]_D^{20}$ +217.6° (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.49–1.81 (m, 5H), 2.08 (m, 1H), 2.27 (m, 2H), 2.50 (s, 3H), 2.61 (m, 1H), 2.81–2.98 (AB, δ_A=2.84, δ_B=2.96, J_{AB}=14.4 Hz, 2H), 3.30 (m, 1H), 3.80 (s, 3H), 6.24 (br, 1H), 6.90 (d, J=7.6 Hz, 1H), 7.02 (d, J=7.8 Hz, 1H), 7.52 (t, J=7.8 Hz, 1H); FT-IR (film, cm^{-1}): 3324, 2945, 1595, 1577, 1459, 1056; EIMS (*m/z*, %) 275 (M^++H, 100.00), 276 (13.75), 257 (4.67), 244 (3.23), 243 (17.61), 226 (3.74), 225 (10.30), 107 (15.18); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.15, 24.28, 27.68, 31.23, 39.56, 43.72, 45.77, 52.19, 61.22, 82.07, 120.96, 121.12, 137.18, 157.25, 159.07, 170.47.

Major isomer (*E*, *more polar*). $[\alpha]_D^{20}$ +124.3° (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.59–1.71 (m, 3H), 1.87 (m, 2H), 2.05 (m, 1H), 2.35 (m, 1H), 2.40–2.70 (m, 2H), 2.50 (s, 3H), 2.81–3.02 (AB, $\delta_A=2.83$, $\delta_B=2.99$, $J_{AB}=14.4$ Hz, 2H), 3.10 (m, 1H), 3.83 (s, 3H), 6.92 (d, $J=$ 7.8 Hz, 1H), 7.02 (d, $J=7.8$ Hz, 1H), 7.52 (t, $J=7.8$ Hz, 1H); FT-IR (film, $^{-1}$): 3325, 2953, 1596, 1579, 1460, 1053, 756; EIMS (*m*/*z*, %) 275 (M^++H, 7.27), 243 (27.01), 225 (23.85), 162 (21.51), 134 (17.88), 108 (13.61), 107 (100.00), 79 (9.12), 65 (8.12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.78, 24.27, 28.37, 29.09, 39.70, 45.65, 46.16, 61.27, 82.17, 120.99, 121.12, 137.16, 157.27, 159.10, 171.05; HRMS for $C_{16}H_{22}N_2O_2$ (M^+), calcd: 274.1681, found: 274.1719.

4.1.7. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo-[3.3.0]octan-2-one *O*-(*tert*-butyldimethylsilyl) oxime, 11. To a solution of oxime **9** (130 mg, 0.5 mmol) and imidazole (140 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added *tert*-butyldimethylsilyl chloride (151 mg, 1 mmol). The stirring was continued for 4 h at rt. The resulting mixture was diluted with CH_2Cl_2 and washed with brine. Purification by flash column chromatography provided 190 mg of **11** as a colorless oil in quantitative yield. $[\alpha]_D^{20}$ +97.0° (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.08 (s, 6H), 0.85 (s, 4.5H), 0.86 (s, 4.5H), 1.20–1.90 (m, 5H), 1.95–2.20 (m, 1H), 2.26–2.32 (m, 1H), 2.44 (s, 3H), 2.50 (m, 1H), 2.84 (dd, $J=14.7$ Hz, 3.6 Hz, 1H), 2.95 (dd, $J=14.3$, 5.7 Hz, 1H), 3.05 (m, 0.5H), 3.33 (m, 0.5H), 6.25 (br, 1H), 6.85 (m, 1H), 6.96 (d, $J=8.1$ Hz, 1H), 7.45 (t, $J=7.8$ Hz, 1H); FT-IR (film, cm^{-1}): 3335, 2956, 1596, 1579, 1461, 1249, 915, 837, 781; EIMS (*m*/*z*, %): 374 (M^+, 3.01), 318 (18.35), 317 ($M^+-C_4H_9$, 73.64), 225 (35.67), 162 (13.53), 108 (16.21), 107 (100.00), 106 (18.35), 75 (40.24); HRMS. for $C_{21}H_{34}N_2O_2Si$ (M^+), calcd: 374.2390, found 374.2359.

4.1.8. (1*S*,5*S*,6*S*)-6-Hydroxy-6-(6-methylpyridin-2-yl methyl)-bicyclo[3.3.0]octan-2-one *O*-(*tert*-butyldiphenylsilyl) oxime, 12. Prepared from oxime **9** and *tert*-butyldiphenylsilyl chloride in a similar way as described in Section 4.1.7. $[\alpha]_D^{20}$ +84.8° (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.08 (s, 9H), 1.50–2.00 (m, 6H), 2.34 (m, 2H), 2.53 (s, 3H), 2.63–3.09 (m, 3.5H), 3.54 (m, 0.5H), 6.00–6.50 (br, 1H), 6.92 (m, 1H), 7.03 (d, $J=7.2$ Hz, 1H), 7.36 (m, 6H), 7.50 (m, 1H), 7.72 (m, 4H); FT-IR (film, cm^{-1}): 3323, 3072, 2959, 1595, 1579, 1460, 1429, 1114, 914, 740, 701, 506; EIMS (*m*/*z*, %): 498 (M^+, 0.57), 442 (21.89), 441 ($M^+-C_4H_9$, 62.21), 225 (80.36), 199 (70.68), 198 (19.12), 197 (22.14), 107 (100.00), 106 (23.60); HRMS for $C_{31}H_{38}N_2O_2Si$ (M^+), calcd: 498.2703, found 498.2710.

4.2. General procedure for the asymmetric addition of diethyl zinc to arylaldehydes

To a solution of ligand (0.05 mmol) in toluene (2.3 mL) at 0 °C was added 15% wt solution of diethylzinc in hexane (2.3 mL, 2.0 mmol). The resulting mixture was stirred for 30 min at 0 °C, followed by the addition of the freshly distilled benzaldehyde (1.0 mmol). The reaction mixture was stirred at 0 °C to completion, and then quenched with saturated aqueous NH_4Cl. The water layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over with anhydrous Na_2SO_4. Purification by flash column chromatography afforded the addition product. The enantiomeric excess of the obtained product was determined by chiral HPLC analysis.

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References and notes

1. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999.
2. For selective reviews, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236. (b) Groger, H. *Chem. Eur. J.* **2001**, *7*, 5247. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (d) Steinhagen, H.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339.
3. For recent examples, see: (a) Dimauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781. (b) Dimauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (c) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3. (d) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634.
4. (a) Schinnerl, M.; Bohm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765. (b) Dimauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053.
5. For reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
6. (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (b) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (d) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605. (e) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998. (f) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77.
7. (a) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2003**, *125*, 5130. (b) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464. (c) Xu, Q.-Y.; Wang, G.-X.; Pan, X.-F.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 381. (d) Cherng, Y.-J.; Fang, J.-M.; Lu, T.-J. *J. Org. Chem.* **1999**, *64*, 3207.
8. (a) Wang, J.-Q.; Xu, M.-H.; Zhong, M.; Lin, G.-Q. *Chin. Chem. Lett.* **1998**, *9*, 325. (b) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953. (c) Zhong, Y.-W.; Lei, X.-S.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2002**, *13*, 2251. (d) Zhong, Y.-W.; Tian, P.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771.
9. (a) Mehta, G.; Srinivas, K. *Tetrahedron Lett.* **2001**, *42*, 2855. (b) Perard-Viret, J.; Rassat, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1. (c) Lemke, K.; Ballschuh, S.; Kunath, A.; Theil, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2051. (d) Moriarty, R. N.; Duncan, M. P.; Vaid, P. K.; Prakash, R. *Org. Synth.* **1990**, *68*, 175.
10. Huang, M.-L. *J. Am. Chem. Soc.* **1946**, *68*, 2487.

11. Caglioti, L.; *Organic Syntheses*, Collect. Vol. 6; Wiley: New York, 1988 p 62.
12. Paquette, L. A.; *Encyclopedia of Reagents for Organic Synthesis*, Vol. 6; Wiley: New York, 1995 p 4401.
13. Shown in Scheme 2 is the major isomer of **8** whose relative configuration has been evidenced by the NOESY analysis, see Section 4.
14. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 242959 and 242960, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk
15. (a) Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158. (b) Scheibye, S.; Shabana, R.; Lawesson, S.-O. *Tetrahedron* **1982**, *38*, 993. (c) Deng, S.-L.; Chen, R.-Y. *Synthesis* **2002**, 2527. (d) Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N. *Tetrahedron* **1985**, *41*, 2567.
16. Paquette, L. A.; *Encyclopedia of Reagents for Organic Synthesis*, Vol. 6; Wiley: New York, 1995 p 4138.
17. (a) Brunner, H.; Schonherr, M.; Zabel, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2671. (b) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841. (c) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 841.
18. *O*-methylation of oxime (1*S*,5*S*,6*S*)-**9** afforded a mixture of *E* and *Z* isomers of (1*S*,5*S*,6*S*)-**10** in a ratio of 2:1 as determined by ^{1}H NMR analysis. Attempts to assign their configuration by NOESY analysis proved unsuccessful. ^{13}C NMR correlation method adopted by many authors[20] was also abortive in our case. So we tentatively assumed that the major isomer of **10** had the *E* form oxime ether with the methoxy group *anti* to the bridged carbon, and the minor isomer had the *Z* form oxime ether.
19. $[\alpha]_D^{20}$ +3.93° (*c* 3.50, $CHCl_3$). Literature: $[\alpha]_D^{20}=+5.6°$ (*c* 1.09, $CHCl_3$) for *R* enantiomer with 96% ee. Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929.
20. (a) Hawkes, G. E.; Herwig, K.; Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1028. (b) Farser, R. R.; Dhawan, K. L. *J. Chem. Soc. Chem. Commun.* **1976**, 674. (c) Miller, R. J.; Kuliopulos, A.; Coward, J. K. *J. Org. Chem.* **1989**, *54*, 3436.