Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 119–126

Synthesis of novel C_2-symmetric chiral bis(oxazoline) ligands and their application in the enantioselective addition of diethylzinc to aldehydes

Bin Fu, Da-Ming Du* and Jianbo Wang

Department of Chemical Biology, College of Chemistry and Molecular Engineering, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Peking University, Beijing 100871, PR China

Received 6 September 2003; revised 25 October 2003; accepted 10 November 2003

Abstract—Novel chiral bis(oxazoline) ligands bearing dibenzo[*a,c*]cycloheptadiene and a dihydroxy group have been synthesized and their application in the catalytic asymmetric addition of diethylzinc to aldehydes investigated. The enantioselectivities for the aromatic aldehydes are generally high and up to 96% ee was obtained.

1. Introduction

The catalytic enantioselective addition of organozinc reagent to aldehydes is one of the most widely used methodologies in asymmetric carbon–carbon bond formation.[1] Asymmetric organozinc addition to aldehydes provides the synthesis of various chiral alcohols, which are important structural components of natural products and fine chemicals. Over the past decade, many chiral ligands and catalysts have been designed and synthesized, and high enantioselectivities have been achieved.[2] Among the diverse chiral ligand structures, chiral amino alcohols are predominant. In recent years, other types of ligands, such as diols TADDOLs,[3] and BINOLs,[4] amino thiols,[5] iminyl alcohols,[6] carbohydrate derivatives,[7] sulfonamides,[8] and phosphoramide,[9] have also been explored for catalyzing this type of reaction. On the other hand, chiral oxazolines, especially chiral bis(oxazoline), have been widely applied in many catalytic asymmetric reactions as versatile ligands.[10] Recently, oxazoline-based ligands were also found to be effective for the asymmetric addition of diethylzinc to aldehydes.[11] In particular, the ligand combining the oxazoline ring and hydroxy group or an amino group have been reported to show excellent catalytic activity in the asymmetric addition of diethylzinc to aldehydes.[12–15] For example, Ikeda et al.[13] developed the ligands **1**–**3** for the asymmetric addition of diethylzinc to aldehydes and high enantioselectivities were obtained. Ligands **4** and **5**, explored by Bolm et al.[14] and ligand **6** designed by Pastor and Adolfsson,[15] respectively, also showed good catalytic activity (Scheme 1). In these ligands, the oxazoline unit and adjacent hydroxy group function together to control the catalytic process.

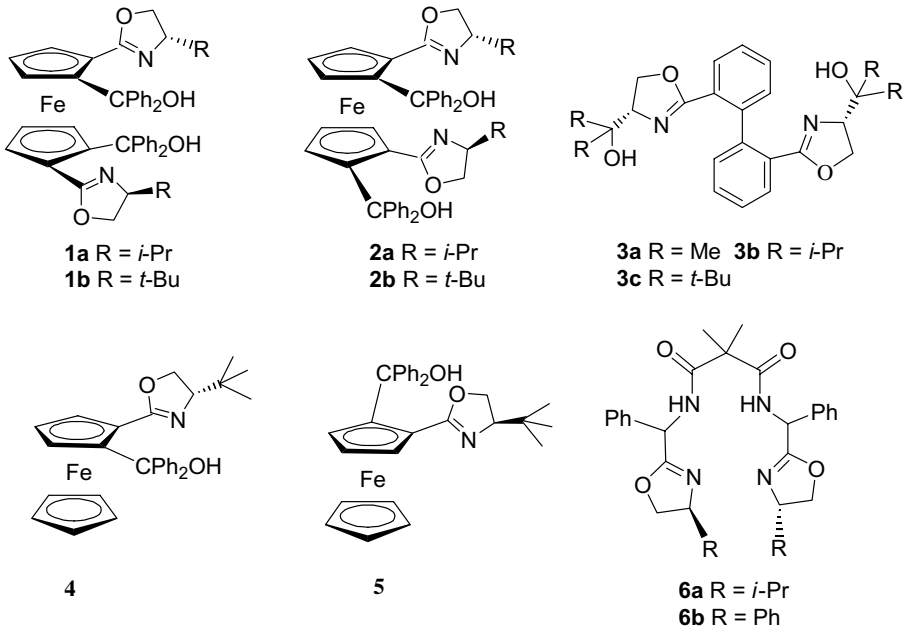
As a continuation of our ongoing project on the development of novel chiral bis(oxazoline) ligands,[16,17] we report herein the synthesis and application of novel C_2-symmetric bis(oxazoline) ligands **11a** and **11b** with dibenzo[*a*,*c*]cycloheptadiene and a hydroxy group as substituents on the oxazoline ring. These ligands were expected to furnish a new chiral environment in asymmetric catalysis reactions by a combination of a hydroxy group, oxazoline ring, and dibenzo[*a*,*c*]cycloheptadiene.

2. Results and discussion

The ligand **11** was synthesized starting from the cyclic diethyl dicarboxylate **7**.[18] The cyclic carboxylate was converted into the dihydroxy diamide **8** by the following procedure: (1) hydrolysis in methanol solution of NaOH; (2) acyl chloride formation with thionyl chloride; and (3) condensation with amino alcohol in the presence of excess Et_3N. The overall yield of three steps was up to 72%. Subsequently, the method explored by Denmark et al.[19] was selected for cyclization. However,

* Corresponding author. Tel.: +86-10-6275-6568; fax: +86-10-6275-1708; e-mail: dudm@pku.edu.cn

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.11.006



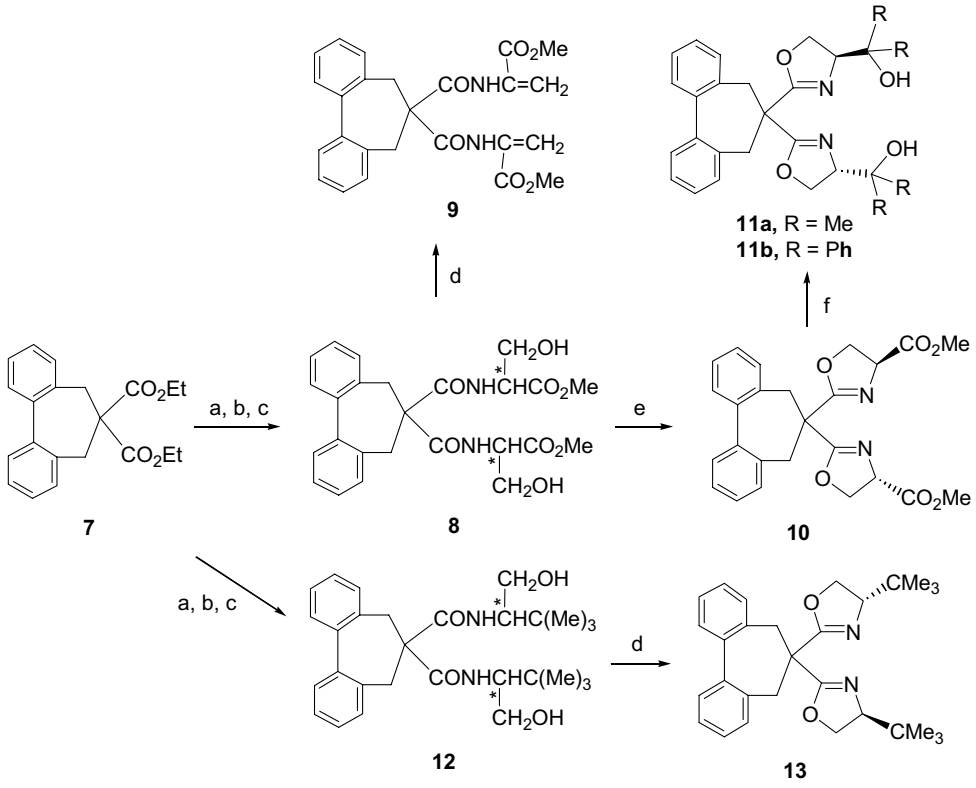
Scheme 1.

the treatment of dihydroxy diamide **8** with mesyl chloride (2.2 equiv) and Et_3N (4.4 equiv) in dichloromethane led to unexpected product **9**. The methanesulfonate is a good leaving group and with assistance of the adjacent carboxylate group, the elimination reaction will be dominant and thus a more stable conjugate product **9** was formed. We then tried a different dehydration reagent, diethylaminosulfur trifluoride (DAST), according to the work of Williams et al.[20] Thus, treatment of the dihydroxy diamide **8** with a slight excess (1.1 equiv) of DAST at −78 °C in CH_2Cl_2, followed by addition of K_2CO_3 and warming to room temperature, afforded the desired bis(oxazoline) biscarboxylate **10** in high yield (86%). Treatment of compound **10** with Grignard reagent (11 equiv) in THF (−78 °C to rt) gave the target bis(oxazoline) ligands **11a**,**b** in good yields (for **11a** 75% and **11b** 71%) (Scheme 2). For comparison, ligands **10** and **13**, which bear CO_2Me and *tert*-butyl on the oxazoline ring, respectively, were also synthesized following the same procedure (Scheme 2). The mono-oxazoline ligand **17** was obtained according to the above similar procedure from mono-acid **14**, which can be obtained by decarbonylation of corresponding diacid (Scheme 3).[18] The structures of these new compounds were characterized by NMR, MS, IR, and elemental analysis.

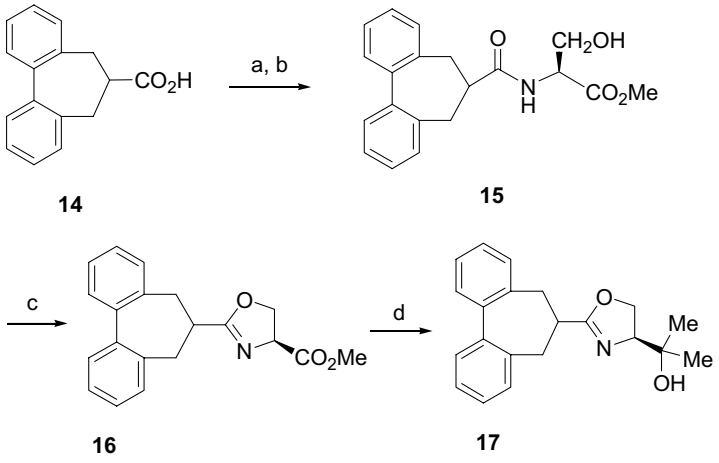
Despite the existence of axial chirality in compound **11**, fast interconversion between (*R*) and (*S*) enantiomers of biphenyl occurs at room temperature owing to the low rotational energy barrier along the 1,1′-bond of biphenyl moiety.[21] Consequently, the chirality of **10**, **11a**,**b**, **13**, **16**, and **17** only derives from the chiral oxazolines. The formation of dibenzo[*a*,*c*]cycloheptadiene ring from linking the biphenyl reduces the difficulty in separating the diastereoisomers from the double chirality of biphenyl backbone and oxazoline ring, and makes the synthesis procedure convenient.

With the ligands in hand, we proceeded to investigate their efficiency in catalytic asymmetric addition of diethylzinc to aldehydes. Catalytic asymmetric addition of diethylzinc to aldehydes is one of most common reactions for carbon–carbon bond formation. At first, we screened the normal reaction conditions for this typical reaction. Thus, the effect of solvent and reaction temperature on the catalytic addition of diethylzinc to benzaldehyde was investigated using 10% mol ligand **11a**. The results are summarized in Table 1. With hexane as the solvent, the reaction was carried at room temperature for 24 h, after work-up and column chromatography, (*R*)-1-phenyl-1-propanol was obtained only in 40% yield with 2% ee (Table 1, entry 1). Although it was reported that hexane is favorable for high enantioselectivity,[22a,b] it seems not to be the case in our reaction system. Subsequently, other solvents were tested (Table 1, entries 2–4). In a mixed solvent of dichloromethane–hexane (1:1), the chemical yield is low (38%), but the enantioselectivity is improved to 65% ee; in THF–hexane (1:1), both chemical yield and ee rise significantly to 68% and 77% ee, respectively. The best solvent system was found to be toluene–hexane (1:1). At room temperature, this solvent system gave 88% chemical yield and 84% ee (Table 1, entry 4). The reaction at low temperature was found to give slightly better results (Table 1, entry 5). However, when the volume ratio of toluene–hexane was changed to 5:1, the yield dropped to 32% and the ee value did not change (86% ee) (Table 1, entry 6). This result is different from the previous observation that dilute toluene solutions give higher yields and enantioselectivities.[23]

The chiral ligand **11b** was found not to be as effective as **11a**. Under the same conditions as entry 5, the ligand **11b** gave only 38% yield and 50% ee (Table 1, entry 7). The electron-rich dimethylhydroxymethyl group in **11a** should increase the Lewis basicity of the alkoxide and



Scheme 2. Reagents and conditions: (a) NaOH, CH_3OH; (b) $SOCl_2$; (c) aminol alcohol, Et_3N, 72%; (d) MsCl, Et_3N; (e) DAST, K_2CO_3, 86%; (f) RMgBr, THF, −78 °C to rt, 71–75%.

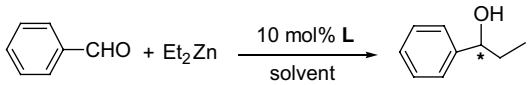


Scheme 3. Reagents and conditions: (a) $SOCl_2$; (b) aminol alcohol, Et_3N, 78%; (c) DAST, K_2CO_3, 85%; (d) MeMgBr, THF, −78 °C to rt, 76%.

enhances the rigidity of the five-membered chelate and thus results in a better stereochemical control.[22e] On the other hand, bis(oxazoline) **10** afforded racemic product in 81% yield (entry 8), while ligand **13** gave only 28% yield and 18% ee (Table 1, entry 9). These results demonstrate that the hydroxyl substituent on the oxazoline ring plays an important role on the catalytic activity. For comparison, the mono-oxazoline **17** was tested under the same conditions, 70% yield and 61% ee are obtained (entry 10).

With the optimized conditions, we then proceeded to examine the addition of diethylzinc to other aldehydes using ligand **11a**. The results are collected in Table 2. As can be seen from Table 2, high yields and enantioselectivities were obtained for most aromatic aldehydes (Table 2, entries 1–7). The additions of diethylzinc to *p*-methoxybenzaldehyde and *p*-chlorobenzaldehyde give high enantioselectivity to afford the corresponding alcohols with 95% ee and 96% ee, respectively. Generally, higher enantioselectivities were obtained with *para*-substituted aryl aldehydes than their *ortho*- and *meta*-substituted analogues. The electronic nature of the substituent also seems to affect the enantioselectivity. A strong electron-withdrawing group such as NO_2 decreases the enantioselectivity (Table 2, entry 8).

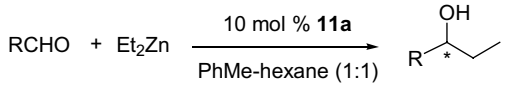
Table 1. Diethylzinc addition to benzaldehyde using ligands **10**, **11a**,**b**, **13**, and **17**



Entry	Ligand[a]	Solvent	Temp.	Yield (%)[c]	Ee (%)[d]	Config.[e]
1	**11a**	Hexane	rt	40	2	*R*
2	**11a**	CH_2Cl_2–hexane (1:1)[b]	rt	38	65	*R*
3	**11a**	THF–hexane (1:1)	rt	68	77	*R*
4	**11a**	Toluene–hexane (1:1)	rt	88	84	*R*
5	**11a**	Toluene–hexane (1:1)	0 °C	86	87	*R*
6	**11a**	Toluene–hexane (5:1)	0 °C	32	86	*R*
7	**11b**	Toluene–hexane (1:1)	0 °C	38	50	*R*
8	**10**	Toluene–hexane (1:1)	0 °C	81	0	—
9	**13**	Toluene–hexane (1:1)	0 °C	28	18	*R*
10	**17**	Toluene–hexane (1:1)	0 °C	70	61	*R*

[a] The reaction was carried out in the presence of 10% ligand for 24 h.
[b] Volume ratio of the solvents.
[c] Isolated yield by column chromatography.
[d] Determined by HPLC on Chiracel OB [hexane–2-propanol 95:5, 0.5 mL/min, t_R 11.1 min (*S*), t_R 12.4 min (*R*)].
[e] Determined by comparison with literature data.[22a,d]

Table 2. Diethylzinc addition to various aldehydes using ligand **11a**[a]



Entry	R	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	*p*-$MeOC_6H_4$	91	95	*R*
2	*m*-$MeOC_6H_4$	88	92	*R*
3	*o*-MeC_6H_4	90	84	*R*
4	*o*-FC_6H_4	92	89	*R*
5	*p*-ClC_6H_4	90	96	*R*
6	*m*-BrC_6H_4	91	94	*R*
7	1-Naphthyl	90	90	*R*
8	*p*-$NO_2C_6H_4$	84	75	*R*
9	*p*-$Me_2NC_6H_4$	86	74	*R*
10	*trans*-PhCH=CH	86	61	*R*
11	3-$PhCH_2CH_2$	82	47	*R*

[a] The reaction were carried out in toluene–hexane at 0 °C for 24 h.
[b] Isolated yields after column chromatography.
[c] Determined by HPLC on Chiracel OD, OB, AD with hexane–2-propanol as eluant.
[d] By comparison with the literature data.[22a,d–f]

However, it was also found that the strong electron-donating group *p*-Me_2N decreases the enantioselectivity (Table 2, entry 9), this may be ascribed to the nitrogen atom of the amino group, which could compete with the hydroxyl group to interact with zinc. The basic dimethylamino group in the substrate and the product may contribute to some minor catalytic pathways. On the other hand, it is worthwhile to note that the addition to *trans*-cinnamaldehyde and phenylpropionaldehyde gave good yields and moderate enantioselectivities (61% ee and 47% ee, respectively) (Table 2, entries 10 and 11). The absolute configurations of the products were determined as *R* for reactions of all aldehydes examined in this study by comparison with the literature data.

The mono-oxazoline **17** is less effective than the corresponding bis(oxazoline) **11a** suggesting a binuclear zinc complex[13b] may be involved in the catalytic cycle. It is necessary to have ligand backbone dibenzo[*a,c*]cycloheptadiene for achieving high enantioselectivity. The ligand **3a** gave 93% yield and 78% ee in the diethylzinc addition to benzaldehyde, the corresponding mono-oxazoline gave 9% yield and 37% ee.[13b] Our ligand **11a** gave 87% ee in the diethylzinc addition to benzaldehyde and 96% ee to *p*-chlorobenzaldehyde. The corresponding mono-oxazoline **17** also can give better enantioselectivity in the diethylzinc addition to benzaldehyde (61% ee).

3. Conclusion

In conclusion, we have synthesized new C_2-symmetric bis(oxazoline) ligands with dibenzo[*a,c*]cycloheptadiene backbone and a hydroxy group as the substituent on the oxazoline ring. The catalytic activity for the asymmetric addition of diethylzinc to aldehydes was investigated. The high enantioselectivities and yields have been obtained for bis(oxazoline) dihydroxy ligand **11a**. These results show that the novel dibenzo[*a,c*]cycloheptadiene bis(oxazoline) dihydroxy ligands have potential for asymmetric reaction. Further studies are in progress in our laboratory in order to expand the application of these chiral ligands to other catalytic asymmetric reactions.

4. Experimental section

Melting points were measured on an XT-4 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Mercury 200 or 300 MHz spectrometer with tetramethylsilane as the internal standard. Infrared spectra were obtained on a Bruker Vector 22 spectrometer. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Optical rotations were measured on

a Perkin–Elmer 341 LC polarimeter. Elemental analyses were carried out on an Elementar Vario EL instrument. The enantiomeric excesses of (*R*)- and (*S*)-alcohols were determined by HPLC analysis over a chiral column (Daicel Chiralcel OB, AD or OD; eluted with hexane–isopropyl alcohol; UV detector, 254 nm). The absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation. Solvents were purified and dried by standard procedures.

4.1. 6,6-Bis[*N*-(1′*S*)-(1′-(methoxycarbonyl)hydroxyethyl)amido]-dibenzo[*a,c*]-1,3-cycloheptadiene 8

To a solution of diethyl dibenzo[*a,c*]-1,3-cycloheptadiene-6,6-dicarboxylate **7** (1.0 g, 2.96 mmol) in CH_3OH (10 mL) was added aqueous NaOH solution (10 mL, 2 N). The mixture was refluxed for 8 h, then the methanol was removed in vacuo. The residue was cooled to 0 °C and acidified with aqueous HCl (6 N). The acidified mixture was extracted with ether (10 mL × 3), the organic layer was dried over anhydrous Na_2SO_4 and evaporated. The obtained white solid was directly refluxed with $SOCl_2$ (5 mL) for 2 h, the excess $SOCl_2$ was removed in vacuo. Anhydrous benzene (10 mL) was added to the above crude diacyl dichloride and the solvent was removed again to dryness (to remove the trace of $SOCl_2$). The diacyl dichloride in CH_2Cl_2 (20 mL) was added dropwise to a solution of L-serine methyl ester hydrochloride (1.0 g, 6.43 mmol) and Et_3N (8 mL, 57.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with water (5 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a crude solid. Purification by silica gel column chromatography (ethyl acetate–petroleum ether 1:1) afforded the dihydroxy diamide **8** (1.04 g, 73%). Mp 82–83.5 °C; $[\alpha]_D^{20} = -15.3$ (*c* 0.30, $CHCl_3$). IR: 3374, 2972, 1737, 1656, 1526, 1439 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.40–7.26 (m, 8H, ArH), 6.97 (s, 2H, NH), 4.63 (t, $J = 3.4$ Hz, 2H, $CHCO_2Me$), 4.06–3.95 (m, 4H, CH_2OH), 3.79 (s, 6H, CO_2Me), 3.52–2.80 (m, 4H, $ArCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.4, 170.6, 140.3, 135.2, 130.2, 127.9, 127.5, 65.5, 61.9, 55.2, 52.7, 36.7; MS (FAB): 485 ($M+H^+$). Anal. Calcd for $C_{25}H_{28}N_2O_8$: C, 61.98; H, 5.82; N, 5.78. Found: C, 62.11; H, 5.92; N, 5.70.

4.2. 6,6-Bis[(4′*S*)-4′-(methoxycarbonyl)oxazolin-2′-yl]-dibenzo[*a,c*]-1,3-cycloheptadiene 10

To a solution of the dihydroxy diamide **8** (0.6 g, 1.24 mmol) in CH_2Cl_2 (30 mL) was added DAST (0.44 g, 2.73 mmol) at −78 °C, after stirring for 1 h, anhydrous K_2CO_3 (50 mg) was added. The mixture was allowed to warm to room temperature and was stirred for another 1 h. The mixture was quenched by 20 mL of saturated $NaHCO_3$ solution. The solution was washed with water (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a pale yellow oil. Purification by silica gel column chromatography (petroleum ether–ethyl acetate 5:1) to afford a colorless viscous oil **10** (0.48 g, 86%). $[\alpha]_D^{20} = +74.9$ (*c* 0.69, $CHCl_3$). IR: 2955, 1741, 1648, 1439, 1357, 1208 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.41–7.21 (m, 8H, ArH), 4.81–4.66 (dd, $J = 7.2$, 2H, 9.8 Hz), 4.63 (m, 2H), 4.45 (dd, $J = 8.8$ Hz, 10.0 Hz, 2H), 3.75 (s, 6H, CO_2Me), 3.40–2.90 (m, 4H, $ArCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 169.1, 140.8, 135.1, 130.0, 127.9, 127.5, 127.2, 70.0, 68.0, 53.3, 52.5, 52.5, 37.6, 37.4; MS (*m/z*, relative intensity): 448 (M^+, 35), 389 (21), 320 (100). HRMS (EI) calcd for $C_{25}H_{24}N_2O_6$: 448.1634. Found: 448.1633.

4.3. 6,6-Bis[(4′*S*)-4′-(isopropanolyl)oxazolin-2′-yl]-dibenzo[*a,c*]-1,3-cycloheptadiene 11a

To a solution of bis(oxazoline) carboxylate **10** (0.5 g, 1.12 mmol) in THF (20 mL) was added a solution of MeMgBr in THF (4.5 mL, 3 M) at −78 °C, the mixture was warmed to room temperature and stirred for 12 h, and then was quenched with saturated NH_4Cl solution. After most solvent was removed in vacuo, water (20 mL) was then added, and the mixture was extracted with CH_2Cl_2 (15 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a pale yellow oil. Purification by silica gel column chromatography (petroleum ether–ethyl acetate 3:2) afforded a colorless viscous oil **11a** (0.38 g, 75%). $[\alpha]_D^{20} = +73.8$ (*c* 0.40, $CHCl_3$). IR: 3448, 2958, 1658, 1448 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42–7.25 (m, 8H, ArH), 4.38–4.33 (t, $J = 7.8$ Hz, 2H), 4.26 (t, $J = 9.0$ Hz, 2H), 4.04 (dd, $J = 7.6$, 9.0 Hz, 2H), 3.22 (s, 2H, CH_2), 2.99 (s, 2H, CH_2), 2.75 (s, 2H, OH), 1.28 (s, 6H, CH_3), 1.13 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 169.2, 140.7, 135.5, 130.1, 128.1, 127.6, 127.3, 74.5, 71.7, 69.3, 54.0, 37.6, 26.8, 25.2; MS (*m/z*, relative intensity): 448 (M^+, 20), 433 (10), 389 (78), 320 (100). HRMS (EI) calcd for $C_{27}H_{32}N_2O_4$: 448.2362. Found: 448.2367.

4.4. Bis[(4′*S*)-4′-(diphenylmethanolyl)oxazolin-2′-yl]-dibenzo[*a,c*]-1,3-cycloheptadiene 11b

The same procedure as for **11a** was followed with PhMgBr in THF (1 M, 6 mL) and bis(oxazoline) carboxylate **8** (0.3 g, 0.67 mmol) as starting material to afford **11b** (0.33 g, 71%). $[\alpha]_D^{20} = -7.8$ (c 0.45, $CHCl_3$). IR: 3452, 2960, 1656, 1642, 1448 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42–6.92 (m, 28H, ArH), 5.34 (t, $J = 7.2$ Hz, 2H), 4.33–4.23 (m, 2H), 4.10 (t, $J = 7.2$ Hz, 2H), 3.23 (s, 2H, CH_2), 3.06 (d, $J = 7.4$ Hz, 2H, CH_2), 2.75 (s, 2H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 144.3, 140.7, 135.6, 130.3, 128.7, 128.3, 127.9, 127.4, 127.2, 127.0, 126.0, 78.9, 71.9, 69.7, 54.1, 37.5; MS (FAB) 697 ($M+H^+$). Anal. Calcd for $C_{47}H_{40}N_2O_4$: C, 81.01; H, 5.79; N, 4.02. Found: C, 81.10; H, 5.82; N, 4.00.

4.5. 6,6-Bis[*N*-(1′*S*)-(1′-(*tert*-butyl)hydroxyethyl)amido]-dibenzo[*a,c*]-1,3-cycloheptadiene 12

From diethyl dibenzo[*a,c*]-1,3-cycloheptadiene-6,6-dicarboxylate **7** (1.0 g, 2.96 mmol), L-*tert*-leucinol (0.75 g, 6.4 mmol), and Et_3N (4 mL, 28.9 mmol), the

same procedure as for **8** afforded the dihydroxy diamide **12** (0.98 g, 68%). Mp 142–144 °C; $[\alpha]_D^{20} = -13.3$ (*c* 0.23, $CHCl_3$). IR (KBr): 3406, 2960, 1638, 1534, 1452, 1264 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.41–7.23 (m, 8H, ArH), 6.41 (s, 2H, NH), 3.92–3.81 (m, 4H), 3.52–3.38 (m, 6H), 2.76 (s, 2H, OH), 0.86 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): 172.7, 140.3, 135.6, 130.5, 127.9, 127.5, 66.2, 62.1, 59.7, 37.4, 33.2, 26.8; MS (FAB): 481 ($M+H^+$). Anal. Calcd for $C_{29}H_{40}N_2O_4$: C, 72.47; H, 8.39; N, 5.83. Found: C, 72.52; H, 8.30; N, 5.61.

4.6. 6,6-Bis[(4′*S*)-4′-(*tert*-butyl)oxazolin-2′-yl]-dibenzo-[*a*,*c*]-1,3-cycloheptadiene 13

To an ice-cooled solution of the dihydroxy diamide **12** (0.60 g, 1.25 mmol) and Et_3N (2 mL, 14 mmol) in CH_2Cl_2 (20 mL) was added MsCl (0.30 g, 2.6 mmol) slowly. The mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was washed with water (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness in vacuo to give the crude bismesylate as yellow oil. The crude bismesylate was dissolved in CH_3OH (20 mL) and was treated with NaOH solution (4 mL, 1 N) at room temperature for 12 h. The methanol was removed in vacuo and 30 mL CH_2Cl_2 was added to it. The solution was washed with water (5 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give pale yellow oil. Purification by silica gel column chromatography (petroleum ether–ethyl acetate 5:1) afforded a colorless viscous oil **13** (0.46 g, 83%). $[\alpha]_D^{20} = -44.6$ ($c = 0.18$, $CHCl_3$). IR (KBr): 3010, 2965, 1654, 1508, 1484 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.47–7.23 (m, 8H, ArH), 4.19 (t, $J = 9.2$ Hz, 2H), 4.08 (t, $J = 7.7$ Hz, 2H), 3.87 (dd, $J = 7.5$, 8.7 Hz, 2H), 3.45–2.69 (m, 4H, $PhCH_2$), 0.81 (s, 18H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.2, 140.8, 135.9, 131.2, 127.9, 127.2, 126.9, 75.6, 68.9, 53.5, 37.5, 33.9, 25.7; MS (*m*/*z*, relative intensity): 444 (M^+, 50), 387 (100), 344 (17). HRMS (EI) calcd for $C_{29}H_{36}N_2O_2$: 444.2777. Found: 444.2774.

4.7. 6,6-Bis[*N*-(1′-(methoxycarbonyl)vinyl)amido]-dibenzo[*a*,*c*]-1,3-cycloheptadiene 9

To an ice-cooled solution of the dihydroxy diamide **8** (0.50 g, 1.03 mmol) and Et_3N (2 mL, 14.5 mmol) in CH_2Cl_2 (20 mL) was added MsCl (0.25 g, 2.17 mmol) slowly. The mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was washed with water (5 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude product as yellow oil. Purification by silica gel column chromatography (petroleum ether–ethyl acetate 10:1) afforded a colorless viscous oil **9** (0.39 g, 85%). IR: 2981, 1750, 1690, 1513, 1316 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.59 (s, 2H, CONH), 7.50–7.25 (m, 8H, ArH), 6.63 (d, $J = 5.6$ Hz, 2H, $=CH_2$), 5.91 (d, $J = 2.0$ Hz, 2H, $=CH_2$), 3.87 (s, 6H, CO_2Me), 3.48 (s, 2H, $ArCH_2$), 2.85 (s, 2H, $ArCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.0, 164.4, 140.4, 136.2, 130.8, 129.2, 128.2, 127.6, 127.2, 106.7, 52.8, 52.5, 34.1; MS (*m*/*z*, relative intensity): 448 (M^+, 30), 320 (18), 219 (100), 191 (60). HRMS (EI) calcd for $C_{25}H_{24}N_2O_6$: 448.1634. Found: 448.1631.

4.8. 6-[*N*-(1′*S*)-(1′-methoxycarbonyl)hydroxyethyl-amido]-dibenzo[*a*,*c*]-1,3-cycloheptadiene 15

Dibenzo[*a*,*c*]-1,3-cycloheptadiene-6,6-dicarboxylic acid 0.80g (2.84 mmol) (prepared from dicarboxylate **7** in Section 4.1) was heated at 160 °C for 1 h and then cooled to room temperature. The white solid mono-acid **14** was obtained and directly refluxed with $SOCl_2$ (4 mL) for 2 h, the excess $SOCl_2$ was removed in vacuo. Benzene (10 mL) was added and the solvent was removed again to dryness to remove the trace of $SOCl_2$ and afford the corresponding acyl chloride. The acyl chloride in CH_2Cl_2 (20 mL) was added dropwise to a solution of L-serine methyl hydrochloride (0.5 g, 3.21 mmol) and Et_3N (4 mL, 28.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. Then the mixture was washed with water (5 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude solid. Purification by silica gel column chromatography (ethyl acetate–petroleum ether 1:1) afforded the hydroxy amide **15** (0.75 g, 78%). Mp 122–124 °C; $[\alpha]_D^{20} = +20.0$ (*c* 0.21, $CHCl_3$). IR: 3401, 3323, 3014, 2951, 1737, 1645, 1526, 1434, 1385, 1348, 1238, 1199, 747 cm^{-1}; ^1H NMR ($CDCl_3$): 7.41–7.25 (m, 8H, ArH), 6.51 (d, $J = 10.8$ Hz, 1H), 4.71–4.66 (m, 1H, CH), 4.05–3.92 (m, 2H, CH_2), 3.80 (s, 3H, CH_3), 3.24–3.14 (m, 1H, CH), 2.87–2.68 (m, 4H, $ArCH_2$), 2.51 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): 175.0, 171.0, 140.6, 136.6, 129.2, 128.4, 127.7, 127.4, 63.5, 54.6, 52.8, 52.7, 51.6, 34.4, 34.2. MS (*m*/*z*, relative intensity): 339 (M^+, 24), 220 (M−119, 15), 192 (100), 178 (50), 165 (25). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.58; H, 6.47; N, 3.91.

4.9. 6-[*N*-(4′*S*)-(4′-methoxycarbonyl)oxazolin-2′-yl]-dibenzo[*a*,*c*]-1,3-cycloheptadiene 16

To a solution of the hydroxy amide **15** (0.42 g, 1.24 mmol) in CH_2Cl_2 (20 mL) was added DAST (0.22 g, 1.37 mmol) at −78 °C, after stirring for 1 h, anhydrous K_2CO_3 (25 mg) was added. The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched by the addition of 20 mL of saturated $NaHCO_3$ solution. The solution was washed with water (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a pale yellow oil. Purification by silica gel column chromatography (petroleum–ethyl acetate 6:1) to afford colorless viscous oil **16** (0.34 g, 85%). $[\alpha]_D^{20} = +27.1$ (*c* 0.15, $CHCl_3$). IR: 2950, 2359, 1741, 1651, 1440, 1208, 1176, 752 cm^{-1}; ^1H NMR ($CDCl_3$): 7.42–7.26 (m, 8H, ArH), 4.75–4.69 (m, 1H, CH), 4.57–4.35 (m, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.40–3.33 (m, 1H, CH), 2.96–2.70 (m, 4H, $ArCH_2$); ^{13}C NMR ($CDCl_3$): 172.1, 171.7, 140.75, 140.72, 136.8, 129.2, 128.2, 127.5, 127.4, 127.2, 69.4, 67.9, 52.5, 43.9, 34.0, 33.98. MS (*m*/*z*,

relative intensity): 321 (M^+, 82), 306 (5), 262 (15), 191 (56), 178 (60), 143 (100). HRMS (EI) calcd for $C_{20}H_{19}O_3N$: 321.1365. Found: 321.1355.

4.10. 6-[*N*-(4′*S*)-(4′-isopropanolyl)oxazolin-2′-yl]-dibenzo[*a*,*c*]-1,3-cycloheptadiene 17

To a solution of oxazoline carboxylate **16** (0.34 g, 1.06 mmol) in THF (20 mL) was added a solution of MeMgBr in THF (1.4 mL, 3 M) at −78 °C, then the mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with saturated NH_4Cl solution. After removing most of the solvent in vacuo, water (20 mL) was then added, and the mixture was extracted with CH_2Cl_2 (15mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a pale yellow oil. Purification by silica gel column chromatography (petroleum–ethyl acetate 3:1) afforded colorless viscous oil **17** (0.26 g, 76%). $[\alpha]_D^{20} = +17.6$ (*c* 0.42, $CHCl_3$). IR: 3410, 2967, 2359, 1658, 1481, 1452, 1377, 1174, 752 cm^{-1}; ^1H NMR ($CDCl_3$): 7.42–7.22 (m, 8H, ArH), 4.29–4.10 (m, 2H, CH_2N), 4.05–3.99 (m, 1H, CH), 3.35–3.25 (m, 1H, CH), 2.86–2.70 (m, 4H, $ArCH_2$), 1.85 (s, 1H, OH), 1.24 (s, 3H, CH_3), 1.10 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 170.49, 140.75, 140.70, 137.11, 136.78, 129.06, 128.18, 127.37, 127.22, 127.10, 74.88, 71.05, 68.56, 43.93, 34.13, 34.02, 26.77, 24.78. MS (*m*/*z*, relative intensity): 321 (M^+, 46), 306 (8), 263 (20), 193 (100), 178 (54). HRMS (EI) calcd for $C_{21}H_{23}O_2N$: 321.1729. Found: 321.1731.

4.11. General procedure for the addition of diethylzinc to aldehyde

To a solution of ligand **11a** (18 mg, 0.04 mmol) in toluene (1 mL) at room temperature was added dropwise a solution of diethylzinc in hexane (1 mL, 15%, 0.88 mmol). The mixture was stirred at room temperature for 15 min. Aldehyde (0.42 mmol) was added in one portion at 0 °C and the reaction mixture was stirred for 24 h at room temperature or at 0 °C. The reaction was then quenched by aqueous HCl solution (2 N, 10 mL) and the mixture was extracted with Et_2O (20 mL × 2). The combined organic extracts were washed with brine (15 mL × 2), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography over silica gel with petroleum–ethyl acetate (8:1 to 5:1) to give the pure alcohol. The enantiomeric excess was determined by HPLC over a chiral column (Daicel Chiralcel OD, OB or AD).

Acknowledgements

We are grateful to the National Natural Science Foundation of China (grant nos. 20172001 and 20372001) and Peking University for financial support.

References and Notes

1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
2. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833; (c) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824.
3. (a) Schmidt, B.; Seebach, D. *Angew Chem., Int. Ed. Engl.* **1991**, *30*, 99–101; (b) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323; (c) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473–7478; (d) Ito, Y. N.; Ariza, X.; Beck, A. K.; Boháč, A.; Ganter, C.; Gawley, R. E.; Kuhnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2210; (e) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363–4384.
4. (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494; (b) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236; (c) Zhang, F. Y.; Yip, C. W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589; (d) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 2161–2164; (e) Huang, W. S.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940; (f) Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433–3436; (g) Shen, X. Q.; Guo, H.; Ding, K. L. *Tetrahedron: Asymmetry* **2000**, *11*, 4321–4327.
5. (a) Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31–34; (b) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009–2010.
6. (a) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 4613; (b) Mino, T.; Oishi, K.; Yamashita, M. *Synlett* **1998**, 965–966; (c) Fleischer, R.; Braun, M. *Synlett* **1998**, 1441–1443.
7. (a) Bauer, T.; Tarasiuk, J.; Paśniczek, K. *Tetrahedron: Asymmetry* **2002**, *13*, 77–82; (b) Cho, B. T.; Chun, Y. S.; Yang, W. K. *Tetrahedron: Asymmetry* **2002**, *11*, 2149–2157; (c) Cho, B. T.; Kim, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2901–2907.
8. (a) Royo, E.; Betancort, J. M.; Davis, T. J.; Caroll, P.; Walsh, P. J. *Organometallics* **2000**, *19*, 4840–4851; (b) Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929–7934; (c) Hwang, C. D.; Uang, B. J. *Tetrahedron: Asymmetry* **1998**, *54*, 8275–8319; (d) Knochel, P.; Perea, J.; Almena, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319; (e) Guo, C.; Qiu, J.; Zhang, X.; Verduge, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145–4158.
9. Shi, M.; Sui, W. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319–3325.
10. For reviews: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
11. (a) Chan, T. H.; Zheng, G. Z. *Can. J. Chem.* **1997**, *75*, 629–633; (b) Zhu, H. J.; Zhao, B. T.; Dai, W. M.; Zhou, J.; Hao, X. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2879–2888; (c) Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699–3702.
12. (a) Allen, J. V.; Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 649–650; (b) Deng, W. P.; Hou, X. L.; Dai, L. X. *Tetrahedron: Asymmetry* **1999**, *10*, 4689–4693.
13. (a) Zhang, W. B.; Yoshinaga, H.; Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**;(10), 1512–1514; (b) Imai, Y.; Matsuo, S.; Zhang, W. B.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**;(2), 239–241.
14. (a) Bolm, C.; Muniz-fernandez, K.; Seger, A.; Raabe, G.; Gunther, J. *J. Org. Chem.* **1998**, *63*, 7860–7867; (b) Bolm, C.; Muniz-fernandez, K.; Hildebrand, J. P. *Org. Lett.* **1998**, *1*, 491–493.

15. Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743–1746.
16. (a) Du, D. M.; Wang, Z. Y.; Xu, D. C.; Hua, W. T. *Synthesis* **2002**, 2347–2352; (b) Wang, Z. Y.; Du, D. M.; Wu, D.; Hua, W. T. *Synth. Commun.* **2003**, *33*, 1275–1283; (c) Xu, D. C.; Du, D. M.; Ji, N.; Wang, Z. Y.; Hua, W. T. *Synth. Commun.* **2003**, *33*, 2563–2574.
17. (a) Du, D. M.; Fu, B.; Hua, W. T. *Tetrahedron* **2003**, *59*, 1933–1938; (b) Fu, B.; Du, D. M. *Chin. J. Chem.* **2003**, *21*, 597–599.
18. (a) Kenner, J. *J. Chem. Soc.* **1913**, 613–627; (b) Dvorken, L. V.; Smyth, R. B.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 486–492.
19. Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884–4892.
20. Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.
21. (a) Mazaleyrat, J. P.; Gaucher, A.; Savrda, J.; Wakselman, M. *Tetrahedron: Asymmetry* **1997**, *8*, 619–631; (b) Gaucher, A.; Bintein, F.; Wakselman, M.; Mazaleyrat, J. P. *Tetrahedron Lett.* **1998**, *39*, 575–578.
22. (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072; (b) Jin, M. J.; Ahn, S. J.; Lee, K. S. *Tetrahedron Lett.* **1996**, *37*, 8767–8770; (c) Watanabe, M. *Tetrahedron Lett.* **1995**, *36*, 8991–8994; (d) Sola, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1998**, *63*, 7078–7082; (e) Dai, W. M.; Zhu, H. J.; Hao, X. J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315–2337; (f) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685–14692.
23. (a) Itsumo, S.; Frechet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140; (b) Ko, D. H.; Kim, K. H.; Ha, D. C. *Org. Lett.* **2002**, *4*, 3759–3762.