Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2879–2888

TETRAHEDRON: *ASYMMETRY*

Chiral ligands derived from abrine. Part 5: Substituent effects on asymmetric induction in enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral oxazolidines possessing an indole moiety

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Received 26 June 1998; accepted 22 July 1998

Abstract

A number of the indole-containing chiral oxazolidines possessing the *gem*-di-*p*-tolyl and *gem*-di-*o*-tolyl groups at C_5 were synthesized from abrine and the effects of the C_5 and C_2 substituents on the asymmetric induction in catalytic enantioselective addition of diethylzinc to benzaldehyde were examined. A working model is proposed to rationalize the asymmetric catalysis by these chiral oxazolidines.

1. Introduction

Enantioselective addition of dialkylzinc to aldehydes catalyzed by chiral β-amino alcohols[1] and other chiral promoters is one of the most extensively investigated asymmetric C–C bond formation reactions in recent years. Extension of this catalytic enantioselective reaction to ketones[2] and C=N[3] functionalities further widens its application to the synthesis of chiral alcohols possessing a stereogenic quaternary carbon center and chiral amines. Our recent work on the alkaloid-based asymmetric synthesis has produced several novel classes of chiral promoters containing an indole moiety.[4] We found that the chiral oxazolidines **1a**–**j** and related compounds, although lacking a hydroxyl group, could catalyze the reaction of Et_2Zn with benzaldehyde in up to 53.8% ee.[4b] We describe herein the synthesis and catalysis of chiral oxazolidines **2a**–**g** having the *gem*-di-*o*-tolyl groups at C_5 and propose a working model to discuss the substituent effect on the catalysis of chiral oxazolidines **1a**–**j** and **2a**–**g** (Fig. 1).

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0957-4166/98/$ - see front matter
PII: S0957-4166(98)00298-5

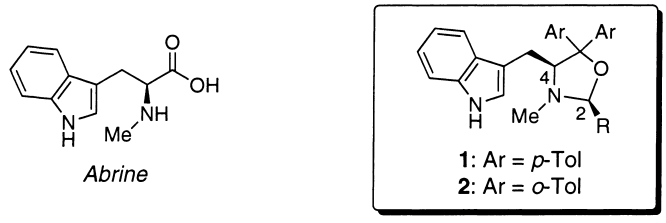
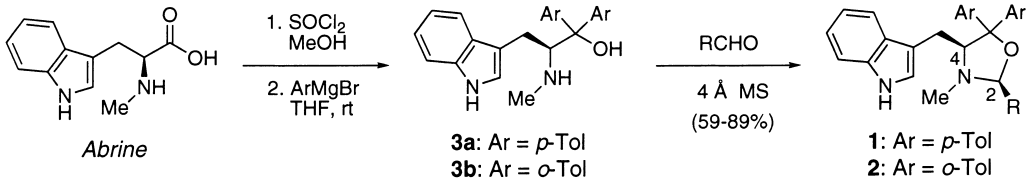


Fig. 1.

2. Results and discussion

Chiral oxazolidines **1**[4b] and **2** were synthesized from the alkaloid, abrine [(*S*)-*N*-methyltryptophan][5] isolated from the seeds of *Abrus precatorius* collected in the Yunnan Province of China (Scheme 1). Reaction of the methyl ester of abrine with excess *p*- or *o*-TolMgBr afforded the corresponding tertiary β-amino alcohols **3a** and **3b**[4a] which were condensed with a number of aldehydes in the presence of 4 Å MS under very mild conditions (CH_2Cl_2, rt or PhH, refluxing) to provide chiral *cis*-2,4-disubstituted oxazolidines **1a–j** and **2a–g** in 59–89% yield (Table 1). The *trans*-isomers of the oxazolidines were not detected from the condensation reaction in most cases.



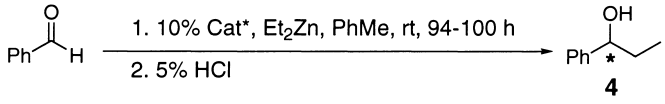
Scheme 1.

Table 1
Synthesis of chiral oxazolidines **1** and **2** from amino alcohols **3a** and **3b**

Entry	R	**1** (Ar = *p*-Tol) from **3a**		**2** (Ar = *o*-Tol) from **3b**	
		Method; *t*; Yield(%)[a]	$[\alpha]_D^{20}$ (c)[b]	Method; *t*; Yield(%)[a]	$[\alpha]_D^{22}$ (c)[b]
a	Me	A; 50 h; 88	-12.4 (1.37)	B; 14 h; 59	-134.2 (0.18)
b	Et	B; 24 h; 67	-60.5 (1.24)	B; 14 h; 76	-199.0 (1.24)
c	*n*-Pr	A; 35 h; 85	-56.0 (1.71)	B; 14 h; 77	-207.1 (0.73)
d	*n*-Bu	A; 48 h; 65	-50.3 (1.89)	B; 14 h; 76	-207.6 (1.89)
e	*n*-Pent	B; 14 h; 70	-50.0 (0.49)[c]	B; 14 h; 71	-206.1 (0.41)
f	*i*-Pr	A; 48 h; 62	-105.5 (1.33)	B; 14 h; 85	-205.2 (0.63)
g	CH_2-*i*-Pr	B; 40 h; 89	-67.4 (1.01)	B; 14 h; 70	-219.7 (1.78)
h	CH_2-*t*-Bu	B; 60 h; 67	-71.7 (1.08)		
i	$(CH_2)_2$Ph	A; 40 h; 86	-82.4 (1.58)		
j	Ph	A; 66 h; 79	-96.0 (1.36)		

[a]Method A: Reaction was carried out in reflexing PhH; Method B: Reaction was performed in CH_2Cl_2 at rt. Yields refer to the isolated homogenous materials. [b]Recorded in $CHCl_3$. [c]Recorded at 22 °C.

Table 2
Reaction of Et_2Zn with benzaldehyde catalyzed by chiral oxazolidines **1** and **2**



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Entry	R	Cat*: **1** (Ar = *p*-Tol)[a]			Cat*: **2** (Ar = *o*-Tol)		
		Yield(%)[b]	ee(%)[c,e]	Configuration[d]	Yield(%)[b]	ee(%)[c]	Configuration[d]
a	Me	57.3	23.4	*S*	60.2	5.5	*R*
b	Et	51.0	26.4	*S*	34.0	17.2	*R*
c	*n*-Pr	57.8	53.8	*S*	46.0	22.6	*R*
d	*n*-Bu	47.2	6.9	*S*	62.2	8.5	*R*
e	*n*-Pent	34.2	3.1	*S*	69.0	18.2	*R*
f	*i*-Pr	56.3	7.4	*R*	56.7	1.4	*R*
g	CH_2-*i*-Pr	52.7	32.1	*S*	38.0	4.7	*R*
h	CH_2-*t*-Bu	50.6	28.2	*S*			
i	$(CH_2)_2Ph$	52.1	5.3	*S*			
j	Ph[f]	45.0	0	----			

[a]Data taken from ref. 4b. [b]Yield is based on the isolated product. Benzyl alcohol was formed in most of the reactions. [c]Determined using HPLC on a CHIRALCEL OD column (*i*-PrOH:Hexane = 95:5, flow rate = 1 mL/min, UV detector at 254 nm). [d]The specific rotation $[\alpha]_D$ +45.6° ($CHCl_3$)[6] for *R* enantiomer of **4** was used to determine the configuration. [e]The values were reexamined. [f]Reaction for 6 days.

The catalytic potency of **1a–j** and **2a–g** was examined using the prototype reaction between Et_2Zn and benzaldehyde with 10 mol% of the catalyst in toluene at room temperature and the results are summarized in Table 2. It is interesting to note that the catalysts **1** induced the formation of the (*S*)-enantiomer of 1-phenyl-1-propanol (−)-**4** in up to 53.8% ee and in 34.2–57.8% yield except for chiral oxazolidine **1f** bearing an isopropyl group at the C_2 position. In contrast, only the (*R*)-enantiomer of 1-phenyl-1-propanol (+)-**4**[6] was formed in up to 22.6% ee and in 34–69% yield under the catalysis of chiral oxazolidines **2a–g**. The opposite asymmetric induction by **1a–e**,**g–j** and **2a–g** is influenced by the *gem*-diaryl groups at C_5. The enantioselectivity is generally high for C_5 *gem*-di-*p*-tolyl-substituted oxazolidines **1** compared with the C_5 *gem*-di-*o*-tolyl-substituted analogs **2**. A plot of the percentage ee versus the carbon number of the substituent R at C_2 of **1a–e** and **2a–e** is given in Fig. 2. It is concluded that: (a) the enantiomeric excess varies with the carbon number of R at C_2 with a maximum value recorded for R=*n*-Pr for both classes of chiral oxazolidines; and (b) the enantioselectivity of the reaction is much more sensitive to the C_2 R group for the catalysts **1a–e** compared with that of **2a–e**, indicating that the C_2 R group in **1a–e** is in close proximity to the reacting centers in the ethyl-transferring transition state. In other words, a loose transition state operates in the reactions catalyzed by chiral oxazolidines **2a–e** and low asymmetric induction is achieved.

Generally speaking, the enantioselectivity induced by chiral oxazolidines **1** and **2** is not very high compared with a variety of hydroxyl group bearing chiral promoters.[1] However, the current work is interesting in the mechanistic aspects of the catalysis. It was reported that chiral diamines[7–9] including

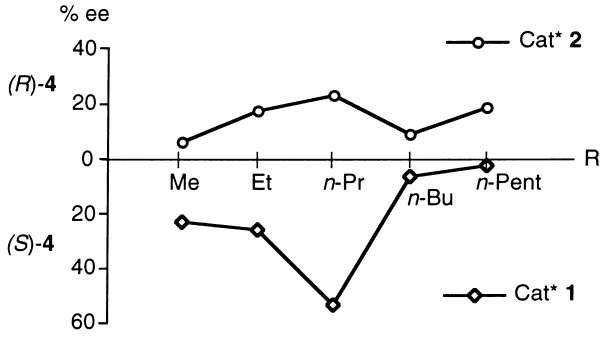

Fig. 2. Relationship between the ees of chiral 1-phenyl-1-propanol (**4**) and the carbon number of R at the C_2 position of chiral oxazolidine promotors **1** and **2** used for enantioselective ethylation of benzaldehyde

tertiary diamines catalyze the addition reactions of Et_2Zn to aldehydes by formation of either the N–Zn complexes or zinc amides.[8b,c10,11] The methoxy group in *o*-anisaldehyde was also reported to form undesirable catalytic species by coordination with Et_2Zn.[9a] The chiral oxazolidines **1a**–**j** and **2a**–**g** have two basic sites, i.e. the nitrogen and oxygen atoms of the oxazolidine ring. If the indole nitrogen could be deprotonated by Et_2Zn, a third basic site might be available for complexation. Nevertheless, we consider that the nitrogen and oxygen atoms of the oxazolidines contribute primarily to the catalysis through the transition state (TS) **5** (Fig. 3). The oxygen-bound zinc species $[(Et_b)_2Zn_b]$ is much more reactive[9a] and will transfer the Et_b group onto the C=O of benzaldehyde complexed with Zn_a, the latter is also coordinated with the nitrogen atom. An alternative to TS **5** is considered by sharing one Et_a group on Zn_a with Zn_b to form a polycyclic assembly (a bridged 5/6/6-ring system) which is likely to be too rigid to work. TS **5** predicts the *si*-face attack at benzaldehyde to give (*S*)-**4** as the major enantiomer which is consistent with our experimental results of **1a**–**e**.[4b] Modification on the *gem*-diaryl groups at C_5 can significantly affect the complexation ability of the oxygen atom. With two bulky *o*-tolyl groups at C_5, TS **5** fails to operate because the oxygen atom is incapable of forming a complex due to the severe steric repulsion. Under this circumstance, the Et-transferring zinc species should attack intermolecularly by another zinc complex of the oxazolidine nitrogen or a zinc amide of the indole[8b,c,10,12] at the Zn_a-coordinated benzaldehyde from the *re*-face (TS **6**) to give (*R*)-**4**. Due to the great separation among the reacting and the C_2/C_4 stereogenic centers, the asymmetric induction of **2a**–**g** should be low and less sensitive to the R group at C_2.

In summary, we have examined a number of chiral oxazolidines **1a**–**j** and **2a**–**g** possessing an indole moiety as promoters in the enantioselective addition of Et_2Zn to benzaldehyde and found that substituents on both C_2 and C_5 positions of the oxazolidine ring significantly influence the asymmetric induction. Based on these results, we propose a transition state **5** for catalysis by **1a**–**e**,**g**–**i**, featuring the coordination of both oxygen and nitrogen atoms of the oxazolidine with the zinc species. Our finding will encourage further study on the use of readily available chiral oxazolidines[10] in asymmetric catalysis.

3. Experimental section

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 or AM-400 NMR instrument. IR spectra were taken on a Bio-Rad FTS-IR spectrophotometer. Mass spectra (MS) were measured on a Finnigan TSQ 7000 mass spectrometer. High resolution mass spectra (HRMS) were measured by a VG Autospec mass spectrometer under FAB^+ conditions. Elemental analysis was performed on a Model 1106 instrument. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. All reactions were

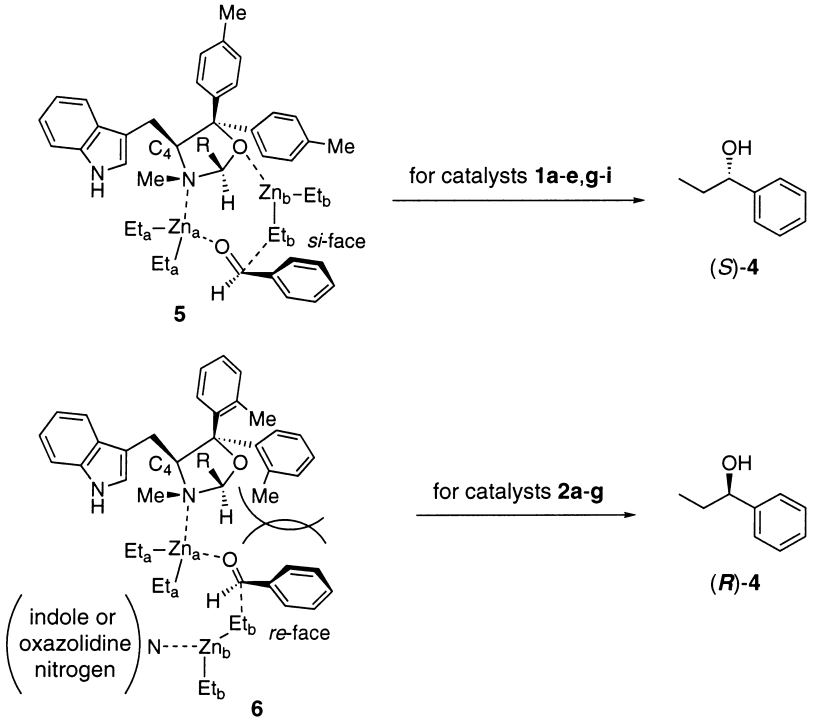

Fig. 3.

carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Abrine was isolated from the extract of the seeds of *Abrus precatorius* collected in the Yunnan Province of China.[5] Amino alcohols **3a** and **3b** were synthesized from abrine according to the known procedure.[4a] Et_2Zn (1.0 M in hexanes) and other reagents were obtained commercially and used as received.

*3.1. Oxazolidines **1a–j** and **2a–g**; general procedure*

Method A: A solution of **3a** (128 mg, 0.33 mmol) and the aldehyde (0.50 mmol) in dry PhH (10 mL) in the presence of powdered 4 Å MS was heated at refluxing temperature until the TLC analysis indicated the completion of the reaction (see Table 1 for reaction times).

Method B: A solution of **3a** or **3b** (128 mg, 0.33 mmol) and the aldehyde (0.50 mmol) in dry CH_2Cl_2 (10 mL) in the presence of powdered 4 Å MS was stirred at room temperature until TLC analysis indicated the completion of the reaction (see Table 1 for reaction times). The reaction mixture was filtered through a pad of Celite with washing by diethyl ether. The combined organic solution was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 14% EtOAc in hexane) to give the oxazolidines. The yields and specific rotation data are summarized in Table 1.

3.1.1. (2S,4S)-4-(Indol-3-yl-methyl)-2,3-dimethyl-5,5-di(p-tolyl)-1,3-oxazolidine ***1a***

Pale yellow foam; IR (KBr) 3420 (br), 2920, 1455, 1350, 820, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.24–7.05 (m, 10H), 6.58 (s, 1H), 4.00 (q, *J*=5.1 Hz, 1H), 3.68 (t, *J*=6.3 Hz, 1H), 2.76 (d, *J*=6.3 Hz, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H), 1.54 (d, *J*=5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 140.5, 136.7, 136.5, 136.2, 128.6, 128.4, 128.1, 127.5, 126.9, 122.7, 121.8, 119.2, 119.0, 113.1, 111.1, 91.5, 88.1, 73.8, 37.8, 29.0, 21.0, 20.9, 19.0; MS (CI^+) *m/z* (relative intensity) 411 (M^++1, 100); HRMS (FAB^+) calcd for $C_{28}H_{31}N_2O$ (M^++1): 411.2436. Found: 411.2484. Anal. calcd for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.82. Found: C, 81.79; H, 7.55; N, 6.50.

3.1.2. (2S,4S)-2-Ethyl-4-(indol-3-yl-methyl)-3-methyl-5,5-di(p-tolyl)-1,3-oxazolidine ***1b***

Pale yellow foam; IR (KBr) 3395, 2920, 1450, 1340, 1230, 1180, 1010, 810, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.60 (d, *J*=7.9 Hz, 1H), 7.36 (d, *J*=8.1 Hz, 1H), 7.26–7.06 (m, 10H), 6.61 (d, *J*=2.3 Hz, 1H), 3.85 (dd, *J*=6.4, 2.9 Hz, 1H), 3.71 (t, *J*=6.4 Hz, 1H), 2.69 (dd, *J*=7.0, 2.3 Hz, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H), 1.90–1.61 (m, 2H), 1.17 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 140.6, 136.5, 136.4, 136.2, 128.7, 128.2, 128.0, 127.6, 126.9, 122.7, 121.8, 119.2, 119.0, 113.5, 111.0, 95.9, 87.8, 73.4, 38.7, 29.4, 26.5, 21.0, 20.9, 9.1; HRMS (FAB^+) calcd for $C_{29}H_{33}N_2O$ (M^++1): 425.2593. Found: 425.2644. Anal. calcd for $C_{29}H_{32}N_2O$: C, 82.04; H, 7.60; N, 6.60. Found: C, 82.13; H, 7.65; N, 6.44.

3.1.3. (2S,4S)-4-(Indol-3-yl-methyl)-3-methyl-2-propyl-5,5-di(p-tolyl)-1,3-oxazolidine ***1c***

Pale yellow foam; IR (KBr) 3400, 2920, 1450, 1350, 1180, 1020, 810, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.58 (d, *J*=7.5 Hz, 1H), 7.35 (d, *J*=7.8 Hz, 1H), 7.26–7.04 (m, 10H), 6.59 (s, 1H), 3.87 (t, *J*=4.5 Hz, 1H), 3.67 (t, *J*=6.3 Hz, 1H), 2.69 (d, *J*=6.0 Hz, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 2.17 (s, 3H), 1.83–1.56 (m, 4H), 1.03 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 140.5, 136.5, 136.4, 136.2, 128.7, 128.2, 128.1, 127.4, 126.9, 122.8, 121.8, 119.2, 119.0, 113.6, 111.0, 95.0, 87.8, 73.5, 38.6, 35.7, 29.3, 21.0, 20.9, 18.3, 14.4; MS (CI^+) *m/z* (relative intensity) 439 (M^++1, 100); HRMS (FAB^+) calcd for $C_{30}H_{35}N_2O$ (M^++1): 439.2749. Found: 439.2720. Anal. calcd for $C_{30}H_{34}N_2O$: C, 82.15; H, 7.81; N, 6.39. Found: C, 82.03; H, 7.99; N, 6.22.

3.1.4. (2S,4S)-2-Butyl-4-(indol-3-yl-methyl)-3-methyl-5,5-di(p-tolyl)-1,3-oxazolidine ***1d***

Pale yellow foam; IR (KBr) 3400, 2920, 1450, 1350, 1180, 1020, 820, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.26–7.05 (m, 10H), 6.58 (s, 1H), 3.86 (dd, *J*=6.0, 3.0 Hz, 1H), 3.68 (t, *J*=6.3 Hz, 1H), 2.70 (d, *J*=6.0 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.18 (s, 3H), 1.84–1.28 (m, 6H), 0.98 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 140.5, 136.5, 136.4, 136.2, 128.7, 128.2, 128.1, 127.6, 126.8, 122.8, 121.8, 119.1, 118.9, 113.3, 111.0, 95.1, 87.8, 73.5, 38.6, 33.3, 29.3, 27.2, 23.0, 21.0, 20.9, 14.1; MS (CI^+) *m/z* (relative intensity) 453 (M^++1, 100); HRMS (FAB^+) calcd for $C_{31}H_{37}N_2O$ (M^++1): 453.2906. Found: 453.2924. Anal. calcd for $C_{31}H_{36}N_2O$: C, 82.26; H, 8.02; N, 6.19. Found: C, 82.15; H, 8.06; N, 6.04.

3.1.5. (2S,4S)-4-(Indol-3-yl-methyl)-3-methyl-2-pentyl-5,5-di(p-tolyl)-1,3-oxazolidine ***1e***

Pale yellow foam; IR (KBr) 3400, 2910, 2840, 1440, 1340, 1320, 1180, 1005, 805, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.60 (d, *J*=7.5 Hz, 1H), 7.33 (d, *J*=7.8 Hz, 1H), 7.30–7.07 (m, 10H), 6.58 (s, 1H), 3.89 (dd, *J*=6.0, 3.0 Hz, 1H), 3.71 (t, *J*=6.2 Hz, 1H), 2.73 (d, *J*=6.0 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 2.00–1.25 (m, 8H), 0.96 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.6, 136.5, 136.4, 136.3, 128.7, 128.2, 128.0, 127.6, 126.7, 122.8, 121.7, 119.1, 118.9, 113.4,

111.0, 95.2, 87.9, 73.4, 38.6, 33.7, 32.1, 29.7, 29.4, 24.6, 22.7, 20.9, 14.0; HRMS (FAB$^+$) calcd for $C_{32}H_{39}N_2O$ (M$^+$+1): 467.3062. Found: 467.3101.

*3.1.6. (2*S*,4*S*)-4-(Indol-3-yl-methyl)-2-isopropyl-3-methyl-5,5-di(*p*-tolyl)-1,3-oxazolidine* ***1f***

Pale yellow foam; IR (KBr) 3395, 2940, 1445, 1340, 1180, 810, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.58 (d, *J*=7.5 Hz, 1H), 7.36–7.08 (m, 11H), 6.73 (d, *J*=2.1 Hz, 1H), 3.80 (dd, *J*=8.1, 5.4 Hz, 1H), 3.75 (d, *J*=3.6 Hz, 1H), 2.58 (dd, *J*=14.4, 8.4 Hz, 1H), 2.52 (dd, *J*=14.1, 5.4 Hz, 1H), 2.32 (s, 6H), 2.04 (s, 3H), 1.95 (d of septet, *J*=3.6, 6.9 Hz, 1H), 1.20 (d, *J*=6.9 Hz, 3H), 1.12 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 140.6, 136.4, 136.1, 136.0, 128.8, 128.3, 127.7, 127.2, 126.7, 122.7, 121.6, 119.0, 118.8, 113.9, 111.0, 99.0, 87.6, 72.4, 40.6, 31.7, 29.8, 21.0, 20.9, 18.7, 16.5; MS (CI$^+$) *m/z* (relative intensity) 439 (M$^+$+1, 100); HRMS (FAB$^+$) calcd for $C_{30}H_{35}N_2O$ (M$^+$+1): 439.2749. Found: 439.2721. Anal. calcd for $C_{30}H_{34}N_2O$: C, 82.15; H, 7.81; N, 6.39. Found: C, 82.11; H, 7.93; N, 6.18.

*3.1.7. (2*S*,4*S*)-4-(Indol-3-yl-methyl)-3-methyl-2-(2-methylpropyl)-5,5-di(*p*-tolyl)-1,3-oxazolidine* ***1g***

Pale yellow foam; IR (KBr) 3400, 2940, 1450, 1340, 1180, 1010, 810, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.37 (d, *J*=8.0 Hz, 1H), 7.24–7.06 (m, 10H), 6.60 (d, *J*=1.8 Hz, 1H), 3.91 (dd, *J*=8.3, 2.4 Hz, 1H), 3.67 (t, *J*=6.5 Hz, 1H), 2.70 (d, *J*=6.5 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.18 (s, 3H), 2.10–1.95 (m, 1H), 1.85–1.76 (m, 1H), 1.70–1.61 (m, 1H), 1.07 (d, *J*=6.7 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 140.6, 136.5, 136.4, 136.2, 128.7, 128.2, 128.1, 127.6, 126.8, 122.7, 121.8, 119.2, 119.0, 113.4, 111.0, 93.9, 88.0, 73.4, 42.9, 38.5, 29.4, 25.2, 23.8, 22.6, 21.0, 20.9; HRMS (FAB$^+$) calcd for $C_{31}H_{37}N_2O$ (M$^+$+1): 453.2906. Found: 453.2978. Anal. calcd for $C_{31}H_{36}N_2O$: C, 82.26; H, 8.02; N, 6.19. Found: C, 82.25; H, 8.06; N, 6.06.

*3.1.8. (2*S*,4*S*)-4-(Indol-3-yl-methyl)-3-methyl-2-(2,2-dimethylpropyl)-5,5-di(*p*-tolyl)-1,3-oxazolidine* ***1h***

Pale yellow foam; IR (KBr) 3430, 2960, 1420, 1320, 840, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.61 (d, *J*=7.7 Hz, 1H), 7.37 (d, *J*=8.0 Hz, 1H), 7.26–7.06 (m, 10H), 6.62 (d, *J*=2.2 Hz, 1H), 3.92 (dd, *J*=8.0, 1.0 Hz, 1H), 3.65 (t, *J*=6.5 Hz, 1H), 2.68 (d, *J*=6.4 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H), 1.85 (dd, *J*=14.3, 8.2 Hz, 1H), 1.72 (d, *J*=14.3 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 140.8, 136.4, 136.3, 136.0, 128.7, 128.2, 128.1, 127.7, 126.9, 122.7, 121.8, 119.2, 119.0, 113.4, 111.0, 93.1, 88.5, 72.7, 47.3, 38.3, 30.2, 29.8, 29.5, 21.0, 20.9; HRMS (FAB$^+$) calcd for $C_{32}H_{39}N_2O$ (M$^+$+1): 467.3062. Found: 467.3129. Anal. calcd for $C_{32}H_{38}N_2O$: C, 82.36; H, 8.21; N, 6.00. Found: C, 82.20; H, 8.28; N, 5.90.

*3.1.9. (2*S*,4*S*)-4-(Indol-3-yl-methyl)-3-methyl-2-(2-phenylethyl)-5,5-di(*p*-tolyl)-1,3-oxazolidine* ***1i***

Pale yellow foam; IR (KBr) 3400, 2940, 1455, 1355, 830, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.60 (d, *J*=7.8 Hz, 1H), 7.37–7.07 (m, 16H), 6.62 (d, *J*=1.8 Hz, 1H), 3.95 (dd, *J*=6.3, 2.7 Hz, 1H), 3.73 (t, *J*=6.3 Hz, 1H), 3.17–3.04 (m, 1H), 2.96–2.82 (m, 1H), 2.69 (d, *J*=6.3 Hz, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H), 2.23–2.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 142.5, 140.5, 136.6, 136.5, 136.2, 128.7, 128.5, 128.3, 128.2, 128.0, 127.5, 126.9, 125.7, 122.7, 121.8, 119.2, 118.9, 113.4, 111.0, 94.3, 88.1, 73.2, 38.7, 35.3, 31.0, 29.5, 21.0, 20.9; MS (CI$^+$) *m/z* (relative intensity) 501 (M$^+$+1, 100); HRMS (FAB$^+$) calcd for $C_{35}H_{37}N_2O$ (M$^+$+1): 501.2906. Found: 501.2976. Anal. calcd for $C_{35}H_{36}N_2O$: C, 83.96; H, 7.25; N, 5.60. Found: C, 83.77; H, 7.39; N, 5.43.

*3.1.10. (2S,4S)-4-(Indol-3-yl-methyl)-3-methyl-2-phenyl-5,5-di(*p*-tolyl)-1,3-oxazolidine* ***1j***

Pale yellow foam; IR (KBr) 3410, 2940, 2870, 1670, 1460, 1355, 830, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.71 (d, *J*=6.3 Hz, 2H), 7.58 (d, *J*=7.8 Hz, 1H), 7.49–7.07 (m, 14H), 6.59 (d, *J*=1.5 Hz, 1H), 4.72 (s, 1H), 3.87 (t, *J*=6.3 Hz, 1H), 2.81 (ABX, *J*=11.1, 6.9 Hz, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 140.4, 139.0, 136.6, 136.5, 136.2, 129.0, 128.8, 128.4, 128.4, 128.2, 128.2, 127.5, 127.1, 122.8, 121.8, 119.2, 118.9, 113.2, 111.1, 96.4, 88.9, 72.9, 37.8, 29.4, 21.0, 20.9; MS (CI^+) *m/z* (relative intensity) 473 (M^++1, 50), 211 (100); HRMS (FAB^+) calcd for $C_{33}H_{33}N_2O$ (M^++1): 473.2593. Found: 473.2611. Anal. calcd for $C_{33}H_{32}N_2O$: C, 83.86; H, 6.82; N, 5.93. Found: C, 83.79; H, 6.98; N, 5.71.

*3.1.11. (2S,4S)-4-(Indol-3-yl-methyl)-2,3-dimethyl-5,5-di(*o*-tolyl)-1,3-oxazolidine* ***2a***

Pale yellow foam; IR (KBr) 3250, 2925, 1457, 1341, 1234, 1140, 1071, 750, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.60 (d, *J*=7.7 Hz, 1H), 7.49 (d, *J*=6.3 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.18–6.99 (m, 9H), 6.80 (s, 1H), 4.28 (d, *J*=8.7 Hz, 1H), 3.76 (q, *J*=5.0 Hz, 1H), 2.36 (dd, *J*=11.3, 8.7 Hz, 1H), 2.26 (d, *J*=11.3 Hz, 1H), 2.08 (s, 6H), 2.00 (s, 3H), 1.37 (d, *J*=5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.1, 136.4, 133.2, 131.6, 128.5, 127.6, 127.2, 125.1, 124.0, 121.6, 119.2, 118.7, 111.1, 90.3, 89.5, 67.6, 38.4, 29.7, 21.8, 14.1; HRMS (FAB^+) calcd for $C_{28}H_{31}N_2O$ (M^++1): 411.2436. Found: 411.2347.

*3.1.12. (2S,4S)-2-Ethyl-4-(indol-3-yl-methyl)-3-methyl-5,5-di(*o*-tolyl)-1,3-oxazolidine* ***2b***

Pale yellow foam; IR (KBr) 3424, 2967, 2930, 1484, 1456, 1353, 1230, 1068, 1014, 751, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.59 (d, *J*=7.7 Hz, 1H), 7.53 (d, *J*=7.0 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.21–7.00 (m, 9H), 6.85 (s, 1H), 4.34 (d, *J*=8.7 Hz, 1H), 3.65 (dd, *J*=5.8, 2.8 Hz, 1H), 2.36 dd, *J*=12.2, 8.7 Hz, 1H), 2.21 (d, *J*=12.2 Hz, 1H), 2.08 (s, 6H), 2.04 (s, 3H), 1.78–1.60 (m, 2H), 1.08 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.1, 136.3, 134.8, 133.1, 131.4, 129.0, 128.3, 127.9, 127.4, 126.9, 124.9, 123.7, 123.0, 121.5, 119.0, 118.8, 114.2, 111.0, 94.4, 89.8, 66.8, 38.9, 31.2, 27.2, 22.3, 21.7, 8.7; HRMS (FAB^+) calcd for $C_{29}H_{33}N_2O$ (M^++1): 425.2593. Found: 425.2681.

*3.1.13. (2S,4S)-4-(Indol-3-yl-methyl)-3-methyl-2-propyl-5,5-di(*o*-tolyl)-1,3-oxazolidine* ***2c***

Pale yellow foam; IR (KBr) 3421, 3259, 2959, 1457, 1356, 1233, 1137, 1016, 754, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.60 (d, *J*=7.7 Hz, 1H), 7.53 (d, *J*=6.9 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.22–7.00 (m, 9H), 6.83 (s, 1H), 4.32 (d, *J*=8.6 Hz, 1H), 3.66 (dd, *J*=5.6, 2.7 Hz, 1H), 2.34 (dd, *J*=12.1, 8.6 Hz, 1H), 2.22 (d, *J*=12.1 Hz, 1H), 2.09 (s, 6H), 2.05 (s, 3H), 2.03–1.46 (m, 4H), 1.00 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.1, 136.3, 134.8, 133.0, 131.4, 129.0, 128.4, 127.9, 127.4, 126.9, 124.9, 123.7, 123.0, 121.5, 119.0, 118.8, 114.2, 111.0, 93.6, 89.7, 66.7, 38.9, 36.9, 31.2, 22.3, 21.6, 18.0, 14.4; HRMS (FAB^+) calcd for $C_{30}H_{35}N_2O$ (M^++1): 439.2749. Found: 439.2809.

*3.1.14. (2S,4S)-2-Butyl-4-(indol-3-yl-methyl)-3-methyl-5,5-di(*o*-tolyl)-1,3-oxazolidine* ***2d***

Pale yellow foam; IR (KBr) 3226, 2954, 2928, 1458, 1353, 1234, 1131, 1017, 754, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.52 (d, *J*=6.7 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.21–7.00 (m, 9H), 6.83 (s, 1H), 4.31 (d, *J*=8.6 Hz, 1H), 3.65 (dd, *J*=6.0, 2.9 Hz, 1H), 2.34 (dd, *J*=11.8, 8.6 Hz, 1H), 2.20 (d, *J*=11.8 Hz, 1H), 2.16 (s, 6H), 2.04 (s, 3H), 2.03–1.32 (m, 6H), 0.95 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 139.1, 136.3, 133.3, 131.6, 128.4, 127.7, 127.2, 125.1, 123.9, 121.6, 119.2, 118.4, 111.2, 94.0, 90.1, 67.5, 38.9, 33.5, 27.1, 22.8, 22.5, 21.6, 14.1; HRMS (FAB^+) calcd for $C_{31}H_{37}N_2O$ (M^++1): 453.2906. Found: 453.2885.

3.1.15. (2S,4S)-4-(Indol-3-yl-methyl)-3-methyl-2-pentyl-5,5-di(o-tolyl)-1,3-oxazolidine ***2e***

Pale yellow foam; IR (KBr) 3221, 2953, 2928, 1458, 1353, 1129, 1017, 754, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.52 (d, *J*=6.7 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.21–7.00 (m, 9H), 6.83 (s, 1H), 4.31 (d, *J*=8.6 Hz, 1H), 3.65 (dd, *J*=6.0, 2.9 Hz, 1H), 2.34 (dd, *J*=11.8, 8.6 Hz, 1H), 2.20 (d, *J*=11.8 Hz, 1H), 2.16 (s, 6H), 2.04 (s, 3H), 2.03–1.32 (m, 8H), 0.90 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.1, 136.3, 135.0, 133.1, 131.4, 129.0, 128.4, 127.7, 127.4, 126.7, 124.9, 123.7, 122.9, 121.5, 119.0, 118.9, 114.3, 111.0, 93.8, 89.8, 66.9, 38.9, 34.4, 31.2, 24.4, 23.0, 22.3, 21.7, 14.2; HRMS (FAB^+) calcd for $C_{32}H_{39}N_2O$ (M^++1): 467.3062. Found: 467.3066.

3.1.16. (2S,4S)-4-(Indol-3-yl-methyl)-2-isopropyl-3-methyl-5,5-di(o-tolyl)-1,3-oxazolidine ***2f***

Pale yellow foam; IR (KBr) 3417, 3392, 2960, 2927, 1456, 1357, 1230, 1054, 1023, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.57 (d, *J*=7.5 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 1H), 7.30–7.00 (m, 9H), 6.95 (s, 1H), 4.42 (br s, 1H), 3.51 (d, *J*=3.4 Hz, 1H), 2.44 (br s, 1H), 2.19 (d, *J*=13.2 Hz, 1H), 2.13 (s, 3H), 2.06 (s, 6H), 2.00–1.80 (m, 1H), 1.16 (d, *J*=6.8 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 139.2, 136.3, 134.6, 133.2, 131.4, 129.1, 128.2, 127.8, 127.5, 127.0, 125.0, 123.7, 123.2, 121.5, 119.1, 118.6, 114.1, 111.1, 98.0, 89.4, 66.8, 40.2, 31.7, 30.8, 29.7, 22.3, 21.5, 18.7; HRMS (FAB^+) calcd for $C_{30}H_{35}N_2O$ (M^++1): 439.2749. Found: 439.2685.

3.1.17. (2S,4S)-4-(Indol-3-yl-methyl)-3-methyl-2-(2-methylpropyl)-5,5-di(o-tolyl)-1,3-oxazolidine ***2g***

Pale yellow foam; IR (KBr) 3428, 2954, 2928, 1456, 1355, 1232, 1014, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.59 (d, *J*=7.7 Hz, 1H), 7.51 (d, *J*=7.2 Hz, 1H), 7.32 (d, *J*=7.9 Hz, 1H), 7.25–7.00 (m, 9H), 6.87 (br s, 1H), 4.44 (br s, 1H), 3.70 (d, *J*=7.3 Hz, 1H), 2.40 (br s, 1H), 2.25 (d, *J*=13.4 Hz, 1H), 2.11 (s, 3H), 2.04 (s, 6H), 2.00–1.50 (m, 3H), 1.01 (d, *J*=6.7 Hz, 3H), 0.86 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.0, 136.3, 133.2, 131.5, 128.8, 128.5, 127.5, 127.0, 125.0, 123.8, 123.3, 121.6, 119.1, 118.7, 111.0, 92.9, 90.0, 67.0, 43.9, 38.8, 29.7, 25.1, 23.7, 22.7, 22.4, 21.6; HRMS (FAB^+) calcd for $C_{31}H_{37}N_2O$ (M^++1): 453.2906. Found: 453.2948.

3.2. A typical procedure for the catalytic addition of Et_2Zn to bezaldehyde

To a solution of the chiral oxazolidine **1** or **2** (0.18 mmol) in dry PhMe (8 mL) under a nitrogen atmosphere cooled in an ice–water bath (ca. 0°C) was added a solution of Et_2Zn (4 mL, 1 M in hexanes) via a syringe. After stirring for 10 min, freshly distilled benzaldehyde (0.20 mL, 1.80 mmol) was added into the mixture via another syringe. The resultant mixture was allowed to warm up to room temperature and stirring was continued for 94–100 h. The reaction mixture was cooled in an ice–water bath and quenched with 5% HCl aqueous solution. The mixture was extracted with diethyl ether (3×20 mL), washed with brine, dried over anhydrous $MgSO_4$, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexane) to give chiral 1-phenyl-1-propanol (**4**). The yields and enantiomeric excess data are summarized in Table 2.

Acknowledgements

This work was supported by a Young Investigator Grant of The Science and Technology Commission of Yunnan Province of China to H.-J. Zhu, The National Foundation Grant for Outstanding Young Scientists to X.-J. Hao, and the Department of Chemistry, HKUST.

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