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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2643–2648

Synthesis of novel chiral oxazoline ligands and application in the highly enantioselective diethylzinc addition to *N*-diphenylphosphinoylimines

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Received 3 September 2007; accepted 22 October 2007

Abstract—Two sets of novel chiral oxazoline ligands were designed and conveniently prepared from readily available L-aspartic acid and evaluated in enantioselective diethylzinc addition to *N*-diphenylphosphinoyl imines. In the presence of stoichiometric amounts of these ligands, high enantioselectivities (up to 95% ee) and yields (up to 85%) were achieved for several aromatic imines in toluene at room temperature. Furthermore, the effect of the structure of the ligand on the reaction was studied.

1. Introduction

Chiral amines are pivotal intermediates for the synthesis of natural products, physiologically active substances and pharmaceutical compounds.[1] Enantioselective diorganozinc addition to imines is among the most convenient approaches to the preparation of chiral amines.[2] Various chiral N,O-ligands[3] and chiral Lewis acids[4] were employed to promote enantioselective diorganozinc addition to imines. In the past few years, our group has been engaged in research regarding enantioselective dialkylzinc addition to imines.[5] Besides derivatives of chiral aminoalcohols, chiral oxazolines **1**–**2** (Fig. 1) were firstly developed by our group and employed in promoting enantioselective diethylzinc addition to *N*-diphenylphosphinoylimines.[5b,d]

Generally, these structurally rigid and conformationally restricted oxazoline ligands were proved to be efficient and highly enantioselective in the title reaction. However, they are still not in competition with chiral amino alcohols in promoting enantioselective diethylzinc addition to *N*-diphenylphosphinoylimines, especially ligand **2**, which exhibited only moderate enantioselectivity as well as poor reactivity. One of the most important rules in the design of a chiral ligand is the incorporation of rigidity and flexibility. Therefore, we designed and synthesized two sets of

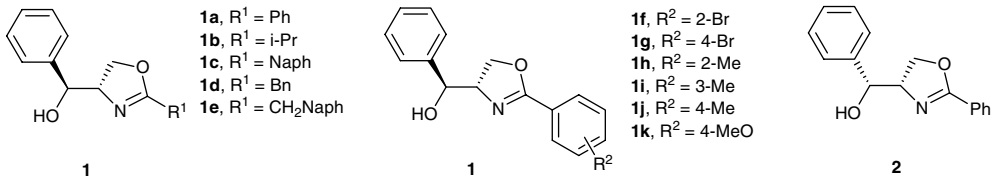

Figure 1. Oxazoline ligands **1** and **2** developed by our group previously.

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doi:10.1016/j.tetasy.2007.10.035

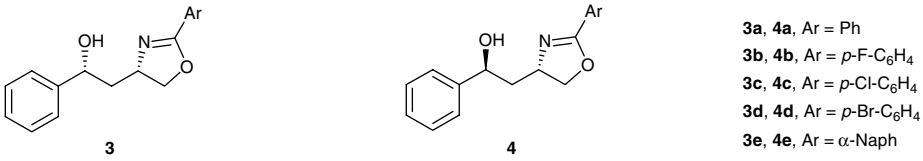


Figure 2. Oxazoline ligands **3** and **4** synthesized and evaluated in the present study.

novel chiral oxazoline ligands **3** and their diastereomers **4** (Fig. 2). Compared with chiral oxazolines **1**–**2**, **3**–**4** retain the rigid oxazoline ring but are more flexible around the hydroxyl moiety. We suggest that these novel chiral oxazoline ligands might provide better results in activating enantioselective diethylzinc addition to imines.

2. Results and discussion

As depicted in Scheme 1, L-aspartic acid **5** was treated with phosphorus trichloride to give anhydride **6**. Friedel–Crafts acylation of benzene with anhydride **6** provided amino acid hydrochloride **7**.[6] Reduction of both the carbonyl group and the carboxylic group of **7** with sodium borohydride and iodine generated a mixture of two diastereomers of amino diol **8**. Acylation of the amino group of **8** facilitated a mixture of two diastereomers of amide **9**. Tosylation of the primary hydroxyl group of **9** and subsequent in situ cyclization accomplished the formation of oxazolines **3** and **4**. The configuration of **3a** was determined by X-ray analysis of its crystal structure (Fig. 3). Herein, we report the application of chiral oxazolines **3** and **4** in catalyzing the addition of diethylzinc to *N*-diphenylphosphinoylimines which gave interesting results compared with chiral oxazolines **1**–**2**.

First, *N*-diphenylphosphinoyl benzalimine **10a** was used as the standard substrate to check the effect of ligands. The results of diethylzinc addition to imine **10a** in the presence of stoichiometric amounts of **3** and **4** are summarized in

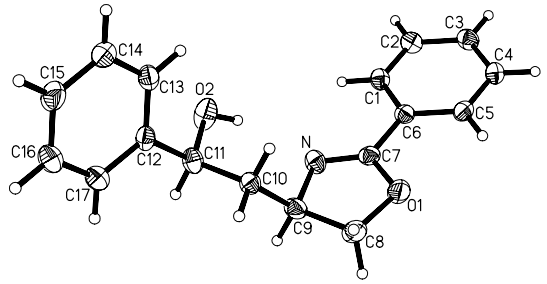
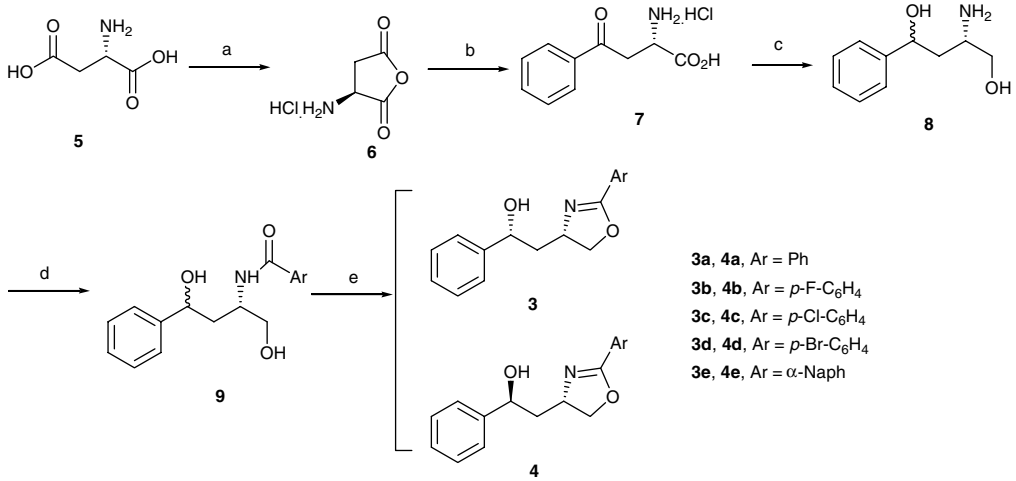


Figure 3. X-ray crystal structure of **3a**.

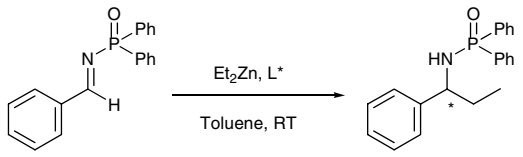
Table 1. Most of the ligands exhibited good reactivities and high enantioselectivities for the title reaction. Ligands **3e** and **4e** gave slightly lower yields and enantioselectivities (Table 1, entries 9 and 10) perhaps due to the bulkier substituent on 2′ carbon of the oxazoline ring. It is noteworthy that **3b** and **4b** delivered dramatically low yields as well as poor enantioselectivities (Table 1, entries 3 and 4). Maybe this results from the strong electron-withdrawing *p*-fluoro substituent on the phenyl group on 2′ carbon of the oxazoline ring which made it difficult for the ligand to coordinate with zinc.

It was found that the configuration of the product was determined by the configuration of the carbon bonded to the hydroxyl group in the ligand. When the configuration of this carbon was inverted, but that of the carbon bonded to nitrogen in the oxazoline ring maintained, the configuration of the product was inverted. According to Table 1,



Scheme 1. Reagents and conditions: (a) PCl_3 (1 equiv), THF, rt, quant.; (b) $AlCl_3$ (2.6 equiv), benzene, $MeNO_2$, reflux, 4 M HCl, 0 °C, 65%; (c) $NaBH_4$ (4 equiv), I_2 (1.1 equiv), THF, reflux, 76% (two diastereomers); (d) ArCOCl (1 equiv), $NaHCO_3$ (1.5 equiv), THF, rt, 80–90% (two diastereomers); (e) TsCl (1 equiv), Et_3N, CH_2Cl_2 or THF, reflux, 70–90% (two diastereomers), silica gel chromatography (molar ratio **3**:**4** ≈ 5:6).

Table 1. Enantioselective diethylzinc addition of *N*-diphenylphosphinoyl benzalimine **10a** in the presence of chiral oxazolines **3** and **4**[a]



10a **11a**

Entry	Ligands	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**3a**	80	91	*S*
2	**4a**	89	85	*R*
3	**3b**	19	70	*S*
4	**4b**	13	50	*R*
5	**3c**	86	89	*S*
6	**4c**	82	83	*R*
7	**3d**	79	90	*S*
8	**4d**	78	86	*R*
9	**3e**	74	85	*S*
10	**4e**	75	83	*R*
11	**1a**[5b]	77	91	*S*
12	**2**[5b]	56	76	*R*

[a] Unless specified otherwise, reactions were carried out in the presence of stoichiometric amounts of oxazoline and 5.0 equiv of Et_2Zn on 0.1 mmol scale in 2.0 mL of toluene at room temperature for 48 h.
[b] Isolated yield based on imine.
[c] Determined by HPLC (Chiralcel OD).
[d] Determined by comparison of the retention time with the literature values.[6]

(*R*,*S*)-**3** resulted in *S*-**11a**, (*S*,*S*)-**4** gave *R*-**11a**. Meanwhile, the configuration of the carbon bonded to nitrogen in the oxazoline ring affected the enantioselectivities. In general, (*R*,*S*)-**3** resulted in higher enantioselectivities than their diastereomers (*S*,*S*)-**4** (Table 1, entries 1–10). Interestingly, on the contrary, (*S*,*S*)-**1a** gave much higher yield as well as enantioselectivity than its diastereomer (*R*,*S*)-**2** (Table 1, entries 11 and 12).[5b] It might be reasoned from the different catalytic intermediates generated from the different catalytic systems (Fig. 4). (*R*,*S*)-**3** coordinates with zinc to form a stable six-membered ring in which both the phenyl group and the oxazoline ring are situated in an equatorial location. Whereas (*S*,*S*)-**4** coordinates with zinc to form a less stable five-membered ring in which the phenyl group is situated in an axial location. (*S*,*S*)-**1a** coordinates with zinc to form a stable five-membered ring in which both the phenyl group and the oxazoline ring are situated in equatorial location. Whereas (*R*,*S*)-**2** coordinates with zinc to form a less stable five-membered ring in which the phenyl group is situated in an axial location. Hence, (*R*,*S*)-**3** and (*S*,*S*)-**1a** delivered higher enantioselectivities than their diastereomers. On the other hand, owing to the flexibility of (*R*,*S*)-**3**-ZnEt and (*S*,*S*)-**4**-ZnEt, ligand **4** exhibited almost the same reactivities with ligands **3** and slightly lower enantioselectivities than ligands **3**. However, ligand **2** gave much lower yield as well as enantioselectivity than ligand **1a** due to the rigidity of (*S*,*S*)-**1a**-ZnEt and (*R*,*S*)-**2**-ZnEt.

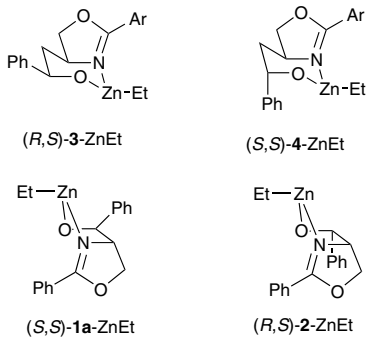
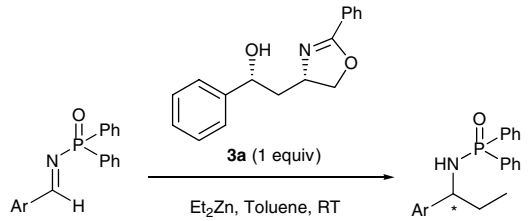


Figure 4. Catalytic intermediates generated from (*R*,*S*)-**3**, (*S*,*S*)-**4**, (*S*,*S*)-**1a**, (*R*,*S*)-**2** and diethylzinc.

Afterwards, the optimal ligand **3a** was applied to promote diethylzinc addition of various *N*-diphenylphosphinoylimines (Table 2). As shown in Table 2, most of the substrates underwent the title reaction smoothly to give the corresponding products in good yields ranging from 76% to 85% and high enantioselectivities ranging from 86 to 95%. However, imine **10b** was almost unreactive. Once again, the *p*-fluoro substituent on the phenyl group of the substrate exhibited a deleterious effect on the reaction.

Table 2. Enantioselective diethylzinc addition of *N*-diphenylphosphinoylimine **10** in the presence of chiral oxazolines **3a**[a]



10 **11**

Ar	Imine	Yield[b] (%)	ee[c] (%)
Ph	**10a**	80	91
p-FC_6H_4–	**10b**	Trace	—
p-ClC_6H_4–	**10c**	76	88
p-BrC_6H_4–	**10d**	85	94
p-$MeOC_6H_4$–	**10e**	78	94
p-$BnOC_6H_4$–	**10f**	81	95
Piperonyl	**10g**	83	92
β-Naphthyl	**10h**	84	86

[a] Unless specified otherwise, reactions were carried out in the presence of stoichiometric amounts of oxazoline and 5.0 equiv of Et_2Zn on 0.1 mmol scale in 2.0 mL of toluene at room temperature for 48 h.
[b] Isolated yield based on imine.
[c] Determined by HPLC (Chiralcel OD or AX).

3. Conclusion

In conclusion, two sets of chiral oxazolines were designed and prepared from L-aspartic acid conveniently. Their application in promoting diethylzinc addition of various *N*-diphenylphosphinoylimines provided corresponding chiral amines in good yields of 76–85% and high enantioselectivities of 88–95%. The configuration of the product was determined by the configuration of the carbon bonded to the hydroxyl group in the ligand. Ligands (*R*,*S*)-**3** resulted in higher enantioselectivities than ligands (*S*,*S*)-**4**. The fact was explained by comparing the catalytic intermediate generated from the (*R*,*S*)-**3** and diethylzinc with the catalytic intermediate generated from the (*S*,*S*)-**4** and diethylzinc.

4. Experimental

4.1. General methods

All starting materials were of the highest commercially available grade and used without further purification. All solvents were purified and dried according to standard methods prior to use. THF (Na, benzophenone), toluene (Na, benzophenone), CH_2Cl_2 (CaH_2) were distilled under argon from the drying agents indicated prior to use. Reactions were monitored by thin layer chromatography using Silica Gel HSGF254 plates. Melting points were measured on an electrothermal digital melting point apparatus. Optical rotations were measured on a Perkin–Elmer 341 Polarimeter at $\lambda = 589$ nm (cg/100 mL). IR spectra were measured with a NICOLET MX-1E FT-IR spectrometer. ^1H and ^{13}C NMR (300 MHz and 75 MHz, respectively) spectra were recorded in $CDCl_3$. ^1H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, $\delta = 7.26$ ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, $\delta = 77.0$ ppm). HRMS-ESI spectra were recorded on BioTOF Q. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak OD, AS columns were purchased from Daicel Chemical Industries (Hong Kong, China). All enantiomer-ratios have been controlled by co-injections of the pure sample with the racemic substrates. All imines were prepared according to the general procedure[7] and their ^1H NMR data matched the literature data.

4.2. Synthesis of oxazolines 3a–3e and 4a–4e

4.2.1. General procedure. Compounds 6 and 7 were synthesized according to the literature[6]

4.2.1.1. (*S*)-3-Amino-dihydrofuran-2,5-dione hydrochloride 6. To a suspension of L-aspartic acid **5** (13.3 g, 0.1 mol, 1 equiv) in THF (60 mL) (0 °C) was added PCl_3 (8.3 mL, 0.1 mol, 1 equiv) dropwise. The mixture was warmed up to room temperature and stirred for additional 6 h. The resulting solid was filtered, washed with THF and dried in vacuo to afford the L-aspartic anhydride hydrochloride **6** (15.2 g, 0.1 mol, quant.) as white crystals.

4.2.1.2. (*S*)-2-Amino-4-oxo-4-phenylbutanoic acid hydrochloride 7. Anhydrous $AlCl_3$ (34.7 g, 0.26 mol, 2.6 equiv) was dissolved in dry $MeNO_2$ (40 mL) and dry benzene (120 mL) at 0 °C. The above anhydride **6** (15.2 g, 0.1 mol, 1 equiv) was added in portionwise. The resulting brown suspension was stirred for 30 min at 0 °C. Then the mixture was refluxed for about 15 h. After cooling to 0 °C, 4 M aqueous HCl (100 mL) was added to the solution and the resulting mixture was stirred for 2 h, during which a dark solid precipitated. After filtration, the residue was purified by recrystallization from mixture of H_2O (20 mL) and acetone (100 mL) to give the desired amino acid hydrochloride **5** (15.0 g, 0.065 mol, 65%) as an off-white solid.

4.2.1.3. (*S*)-3-Amino-1-phenylbutane-1,4-diol 8. Amino acid hydrochloride **7** (15.0 g, 0.065 mol, 1 equiv) was suspended in dry THF (200 mL). $NaBH_4$ (9.9 g, 0.26 mol, 4 equiv) was added slowly at 0 °C. Afterwards the reaction mixture was cooled with an ice-salt bath, then I_2 (18.1 g, 0.0715 mol, 1.1 equiv) in dry THF (40 mL) was added dropwise. After refluxing for 10 h at 70 °C, the mixture was quenched with MeOH (50 mL). The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (100 mL). The resulting solution was added NaOH (13.0 g, 0.325 mol, 5 equiv) and stirred for 5 h at 50 °C. The aqueous solution was extracted with EtOAc and CH_2Cl_2 (EtOAc/CH_2Cl_2 = 1:1, 3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. Silica gel chromatography (gradient elution, EtOAc, EtOAc/EtOH = 3:1 to 1:1) afforded amino diols **8** (two diastereomers, 8.25 g, 0.0455 mol, 70%) as a colourless oil.

4.2.1.4. Amides 9. The above amino diols **8** (two diastereomers, 8.25 g, 0.0455 mol, 1 equiv) and $NaHCO_3$ (5.7 g, 0.068 mol, 1.5 equiv) was dissolved or suspended in dry THF (100 mL). The resulting solution was added the corresponding acid chloride ArCOCl (0.0455 mol, 1 equiv) at 0 °C, after which warmed to ambient temperature and stirred for 5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (50 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Column chromatography on silica gel (petroleum ether/EtOAc = 1:1) afforded amides **9** (two diastereomers, 80–90%) as a foam solid.

4.2.1.5. Oxazolines 3 and 4. To a stirred solution of the amides **9** (two diastereomers, 1 equiv) in dry CH_2Cl_2 (100 mL) and dry Et_3N (40 mL) was added TsCl (1 equiv). The reaction mixture was stirred for 3 h at 0 °C, then heated up to 60 °C and kept refluxing for 5 h. The solvent was evaporated under reduced pressure and flash chromatography on silica gel (petroleum ether/EtOAc = 4:1) afforded oxazolines **3** and **4** (two diastereomers, 70–90%) as a white needle-like crystal. Further purification by column chromatography on silica gel (CH_2Cl_2) giving the pure oxazolines **3** and **4** (molar ratio **3**:**4** = ca. 5:6), respectively.

4.2.2. (*R*)-1-Phenyl-2-((*S*)-2-phenyl-4,5-dihydrooxazol-4-yl)ethanol 3a. Mp 101–103 °C; $[\alpha]_D^{20} = +79.3$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3337, 3204, 1638, 1494, 1448, 1363, 1101, 1063, 950, 758, 689, 565; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.98–7.95 (m, 2H), 7.52–7.29 (m, 8H), 5.32 (s, 1H), 5.12 (dd, $J = 10.0$ Hz, 2.3 Hz, 1H), 4.65–4.60 (m, 1H), 4.60–4.53 (m, 1H), 4.04–3.95 (m, 1H), 2.09–2.03 (m, 1H), 1.99–1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.0, 144.3, 131.7, 128.4, 128.4, 128.3, 127.3, 127.0, 125.7, 74.2, 73.2, 66.5, 45.9; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{17}NNaO_2$, 290.1157; found, 290.1145.

4.2.3. (*S*)-1-Phenyl-2-((*S*)-2-phenyl-4,5-dihydrooxazol-4-yl) ethanol 4a. Mp 64–66 °C; $[\alpha]_D^{20} = -142.0$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3338, 3203, 1638, 1494, 1448, 1363,

1101, 1063, 950, 758, 689, 565; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.96–7.92 (m, 2H), 7.50–7.29 (m, 8H), 5.15 (dd, $J = 10.3$ Hz, 5.9 Hz, 1H), 4.77 (d, $J = 6.2$ Hz, 1H), 4.51 (dd, $J = 9.6$, 7.7 Hz, 1H), 4.45–4.37 (m, 1H), 4.01 (dd, $J = 7.7$, 7.7 Hz, 1H), 2.17–2.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.0, 144.5, 131.6, 128.4, 128.3, 127.1, 125.7, 125.6, 73.0, 72.2, 63.1, 44.1; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{17}NNaO_2$, 290.1157; found, 290.1140.

4.2.4. (*R*)-2-((*S*)-2-(4-Fluorophenyl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 3b. Mp 92–94 °C; $[\alpha]_D^{20} = +75.3$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3377, 3206, 1643, 1601, 1508, 1357, 1227, 1153, 1079, 1057, 844, 751, 700, 556; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.98–7.94 (m, 2H), 7.43–7.29 (m, 5H), 7.14–7.08 (m, 2H), 5.19 (s, 1H), 5.11 (dd, $J = 10.0$ Hz, 2.5 Hz, 1H), 4.65–4.54 (m, 2H), 4.01–3.97 (m, 1H), 2.09–2.02 (m, 1H), 1.97–1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.6, 163.3, 163.1, 144.2, 130.8, 130.6, 127.6, 127.3, 125.7, 123.3, 123.3, 115.7, 115.4, 74.2, 73.3, 66.5, 45.8; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{16}FNNaO_2$, 308.1063; found, 308.1055.

4.2.5. (*S*)-2-((*S*)-2-(4-Fluorophenyl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 4b. Mp 84–86 °C; $[\alpha]_D^{20} = -148.7$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3333, 3190, 1642, 1604, 1508, 1365, 1236, 1152, 1073, 1011, 956, 841, 761, 698, 561; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.94–7.89 (m, 2H), 7.46–7.28 (m, 5H), 7.09–7.03 (m, 2H), 5.12 (dd, $J = 10.5$ Hz, 5.8 Hz, 1H), 4.56–4.47 (m, 2H), 4.44–4.37 (m, 1H), 4.01 (dd, $J = 7.9$ Hz, 7.9 Hz, 1H), 2.12–2.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.5, 163.2, 163.1, 144.5, 130.7, 130.6, 128.4, 127.1, 125.6, 123.5, 123.5, 115.6, 115.3, 73.2, 72.1, 63.1, 44.2; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{16}FNNaO_2$, 308.1063; found, 308.1043.

4.2.6. (*R*)-2-((*S*)-2-(4-Chlorophenyl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 3c. Mp 114–116 °C; $[\alpha]_D^{20} = +82.0$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3304, 3242, 1644, 1595, 1489, 1355, 1271, 1090, 1055, 1012, 836, 750, 699, 563; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.90–7.87 (m, 2H), 7.43–7.26 (m, 7H), 5.15 (s, 1H), 5.10 (dd, $J = 9.9$ Hz, 2.4 Hz, 1H), 4.64–4.53 (m, 2H), 3.99 (dd, $J = 7.5$ Hz, 7.5 Hz 1H), 2.08–2.02 (m, 1H), 1.98–1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.2, 144.1, 138.0, 129.7, 128.5, 128.3, 127.3, 125.7, 125.5, 74.1, 73.3, 66.5, 45.7; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{16}ClNNaO_2$, 324.0767; found, 324.0760.

4.2.7. (*S*)-2-((*S*)-2-(4-Chlorophenyl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 4c. Mp 122–124 °C; $[\alpha]_D^{20} = -154.0$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3424, 3290, 1636, 1596, 1489, 1403, 1365, 1092, 1074, 1013, 953, 833, 730, 693, 566; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.86–7.83 (m, 2H), 7.45–7.28 (m, 7H), 5.11 (dd, $J = 10.6$ Hz, 5.8 Hz, 1H), 4.53–4.35 (m, 3H), 4.01 (dd, $J = 7.8$ Hz, 7.8 Hz, 1H), 2.11–2.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.2, 144.5, 137.8, 129.7, 128.6, 128.4, 127.2, 125.8, 125.6, 73.2, 72.0, 63.2, 44.3; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{16}ClNNaO_2$, 324.0767; found, 324.0756.

4.2.8. (*R*)-2-((*S*)-2-(4-Bromophenyl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 3d. Mp 132–134 °C; $[\alpha]_D^{20} = +67.0$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3374, 3252, 1644, 1590, 1485, 1355, 1271, 1079, 1055, 1010, 834, 750, 700, 561; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83–7.81 (m, 2H), 7.58–7.55 (m, 2H), 7.43–7.29 (m, 5H), 5.11 (dd, $J = 10.4$ Hz, 2.4 Hz, 1H), 5.08 (s, 1H), 4.65–4.51 (m, 2H), 4.00 (dd, $J = 7.5$ Hz, 7.5 Hz, 1H), 2.09–2.03 (m, 1H), 1.98–1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.3, 144.1, 131.7, 129.9, 128.4, 127.4, 126.5, 126.0, 125.7, 74.2, 73.4, 66.6, 45.8; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{16}BrNNaO_2$, 368.0262; found, 368.0274.

4.2.9. (*S*)-2-((*S*)-2-(4-Bromophenyl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 4d. Mp 135–137 °C; $[\alpha]_D^{20} = -142.7$ (*c* 0.3, CH_2Cl_2); IR(Nicolet, cm^{-1}) 3296, 1637, 1592, 1485, 1399, 1366, 1095, 1075, 1011, 833, 728, 694, 564; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.82–7.79 (m, 2H), 7.56–7.53 (m, 2H), 7.45–7.25 (m, 5H), 5.11 (dd, $J = 10.2$ Hz, 6.0 Hz, 1H), 4.50 (dd, $J = 10.4$ Hz, 8.2 Hz, 1H), 4.42–4.32 (m, 1H), 4.23 (d, $J = 6.2$ Hz, 1H), 4.02 (dd, $J = 8.1$ Hz, 8.1 Hz, 1H), 2.19–2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.3, 144.4, 131.6, 129.9, 128.4, 127.2, 126.3, 126.2, 125.6, 73.2, 72.1, 63.3, 44.2; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{17}H_{16}BrNNaO_2$, 368.0262; found, 368.0273.

4.2.10. (*R*)-2-((*S*)-2-(Naphthalen-1-yl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 3e. Mp 124–126 °C; $[\alpha]_D^{20} = +131.7$ (*c* 0.3, CH_2Cl_2); IR(Nicolet, cm^{-1}) 3383, 1639, 1587, 1510, 1340, 1194, 1127, 1053, 996, 806, 777, 699, 560; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.07–9.04 (m, 1H), 8.14–8.12 (m, 1H), 8.01–7.98 (m, 1H), 7.91–7.88 (m, 1H), 7.63–7.28 (m, 8H), 5.18 (dd, $J = 9.4$ Hz, 2.9 Hz, 1H), 5.05 (s, 1H), 4.78–4.62 (m, 2H), 4.00 (dd, $J = 7.8$ Hz, 7.8 Hz, 1H), 2.18–2.11 (m, 1H), 2.07–1.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 164.1, 144.3, 133.7, 132.4, 131.1, 129.4, 128.5, 128.4, 127.5, 127.4, 126.2, 126.1, 125.7, 124.6, 123.8, 74.1, 72.1, 67.1, 45.9; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{21}H_{19}NNaO_2$, 340.1313; found, 340.1309.

4.2.11. (*S*)-2-((*S*)-2-(Naphthalen-1-yl)-4,5-dihydrooxazol-4-yl)-1-phenylethanol 4e. Mp 101–102 °C; $[\alpha]_D^{20} = -82.7$ (*c* 0.3, CH_2Cl_2); IR (Nicolet, cm^{-1}) 3400, 1637, 1587, 1509, 1355, 1193, 1131, 1088, 998, 810, 780, 699, 570; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.07–9.04 (m, 1H), 8.11–8.08 (m, 1H), 7.99–7.96 (m, 1H), 7.90–7.88 (m, 1H), 7.65–7.29 (m, 8H), 5.21–5.15 (m, 1H), 4.61–4.49 (m, 2H), 4.12–4.05 (m, 1H), 4.01 (d, $J = 6.0$ Hz, 1H), 2.26–2.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.9, 144.5, 133.6, 132.0, 131.0, 129.1, 128.4, 128.3, 127.3, 127.1, 126.0, 126.0, 125.5, 124.5, 124.2, 72.1, 72.0, 64.0, 44.6; HRMS-ESI (*m*/*z*): ($M+Na^+$) calcd for $C_{21}H_{19}NNaO_2$, 340.1313; found, 340.1315.

4.3. General procedure for the asymmetric diethylzinc addition to imines

Imine **10a** (30.5 mg, 0.1 mmol) and oxazoline **3a** (26.7 mg, 0.1 mmol) were dissolved in toluene (2 mL) under argon. To the mixture was added Et_2Zn in hexane (1 M, 0.5 mL,

0.5 mmol) at rt. After stirring for 48 h, the reaction was quenched with saturated aqueous ammonium chloride, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified through column chromatography on silica gel to give **11a** (26.8 mg, 0.08 mmol, 80%) as a white powder. The enantiomeric excess of the *S*-isomer 91% (major) was determined by HPLC (Chirapak OD column, hexane/propan-2-ol = 95:5; flow rate 1 mL/min; *R*-isomer, t_R 10.87 min and *S*-isomer, t_R 15.21 min).

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (Project 20572109) and Sichuan Youth Science and Technology Foundation.

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