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A new chiral sulfonamide ligand based on tartaric acid: synthesis and application in the enantioselective addition of diethylzinc to aldehydes and ketones

Ailing Hui, Jintang Zhang, Jinmin Fan and Zhiyong Wang*

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

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Abstract—A new sulfonamide ligand based on L-tartaric acid was synthesized and was employed as a chiral ligand in the enantioselective addition of diethylzinc to aldehydes, giving rise to the best enantiomeric excess up to 83% with 5 mol % of catalyst loading. Moreover, the addition of diethylzinc to ketones can also be achieved with good to excellent enantioselectivities by employing 7 mol % of the catalyst under mild conditions.

1. Introduction

Chiral alcohols are ubiquitous in the structures of natural products and drug compounds, and are also important precursors for many other functional organic molecules. One of the most useful methods for the asymmetric preparation of *sec*-alcohols and *tert*-alcohols is the enantioselective addition of dialkylzinc reagents to carbonyl compounds with chiral ligands.[1] Although many existing chiral ligands can induce good to excellent selectivity, it is still desirable to develop new chiral ligands for high enantioselectivity. Due to the two stereogenic centers, tartaric acid has attracted much attention recently. However, only a few chiral ligands derived from tartaric acid were found to be effective in promoting the asymmetric addition of dialkylzinc reagents to aldehydes.[2] To the best of our knowledge, there is no successful example of a tartaric acid-derived chiral ligand used for asymmetric addition of diethylzinc to ketones until now. Since a variety of sulfonamide ligands have been reported to be effective in the enantioselective addition of dialkylzinc reagents to aldehydes[3] or ketones,[4,5] we focused our research on the synthesis of sulfonamide ligands based on tartaric acid and their application in the addition of diethylzinc to carbonyl compounds. Herein, we report an efficient synthesis method for a new chiral sulfonylamide ligand based on tartaric acid and its application to the enantioselective addition of diethylzinc to aldehydes and ketones.

2. Results and discussion

2.1. Synthesis of the chiral ligand

Initially, L-tartaric acid was easily transformed into its ester, which was reacted with acetone to generate **1**. Subsequently, compound **1** was converted to amide **2** and then reduced to amine **3**. After that, diamine **3** was reacted with camphor sulfonyl chloride to give compound **4**. The final ligand **5** was obtained by the reduction of sulfonamide **4**, as shown in Scheme 1.

2.2. Asymmetric addition of diethylzinc to aldehydes

Once ligands **4** and **5** were prepared, they were tested in a standard enantioselective addition of diethylzinc to *p*-chloro benzaldehyde with a 5 mol % of ligand loading in toluene. The experimental results are listed in Table 1. From Table 1 it can be seen that ligand **4** gave a poor enantiomeric excess (20% ee, entry 1 in Table 1), while ligand **5** can achieve moderate enantioselectivity under the same condition (70% ee, entry 2 in Table 1). Therefore, ligand **5** was chosen as a catalyst model for further optimizing the conditions. When toluene was replaced with hexane or ether, the reaction also gave high yields, but the ee val-

* Corresponding author. Tel./fax: +86 551 3603185; e-mail: zwang3@ustc.edu.cn

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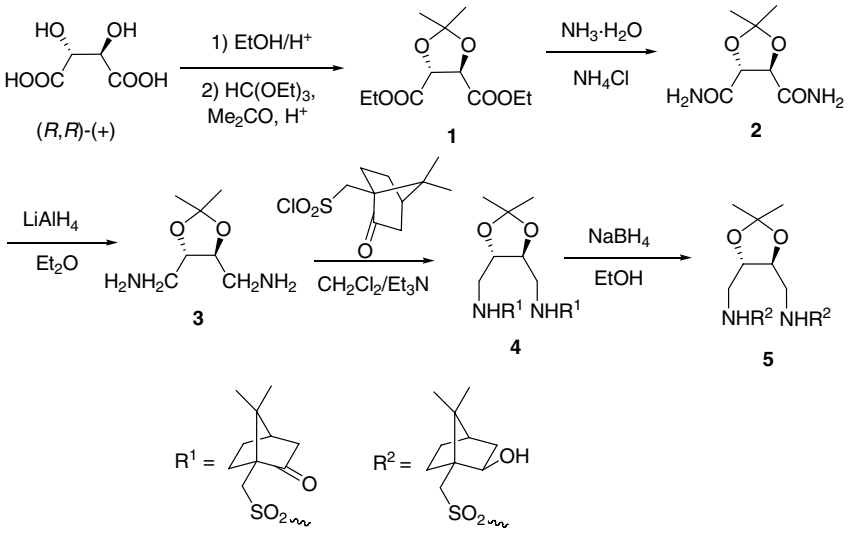
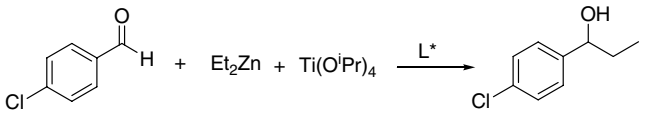


Scheme 1. Synthesis of the chiral ligands.

Table 1. Enantioselective addition of diethylzinc to aldehydes under different conditions

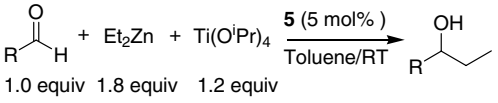


Entry	Ligand	mol %	Solvent	T (°C)	Time (h)	Yield (%)	ee[a] (%)
1	**4**	5	Toluene	20	1	85	20
2	**5**	5	Toluene	20	1	95	70
3	**5**	5	Hexane	20	2	93	64
4	**5**	5	Et_2O	20	5	95	62
5	**5**	5	THF	20	10	—	—
6	**5**	5	CH_2Cl_2	20	4	70	43
7	**5**	10	Toluene	20	1	96	58
8	**5**	15	Toluene	20	3	90	63
9	**5**	3	Toluene	20	18	82	64
10	**5**	5	Toluene	0	4	90	58
11	**5**	5	Toluene	−20	18	84	41
12	**5**	5	Toluene	−35	24	75	13
13	**5**	5	Toluene	40	1	95	60
14	**5**	5	Toluene	60	1	95	60

[a] The enantiomeric excess was determined by chiral HPLC.

ues decreased slightly (entries 3 and 4 in Table 1). When the reaction was carried out in tetrahydrofuran under the same conditions, no desired product was obtained (entry 5 in Table 1). Neither the reaction yield nor the enantiomeric excess can be obtained satisfactorily when the reaction was performed in dichloromethane (entry 6 in Table 1). The optimization for the catalyst loading showed that a 5 mol % of ligand loading was the best compromise for reaction yield and enantioselectivity (entries 2, 7–9 in Table 1). Optimization of the reaction temperature indicated that room temperature favored a higher enantiomeric excess. Either elevation or decrease in reaction temperature would lower the enantioselectivity (entries 10–14 in Table 1). The reaction conditions in entry 2 were chosen as the optimal conditions for this type of asymmetric addition. Having established the optimal conditions, different aldehydes were submitted to the addition with ligand **5**. The results are presented in Table 2. As illustrated in Table 2, in all cases tested, the reactions gave the desired products in high yields. The addition of diethylzinc to benzaldehyde gave the expected product with moderate enantioselectivity (entry 1 in Table 2). Electron-withdrawing substituents at the *para*-position of benzaldehyde were favorable to the reaction yield and enantioselectivity of this addition (entries 2 and 3 in Table 2) while electron-donating substituents at the *para*-position of benzaldehyde disfavored the ee value in comparison with benzaldehyde (entries 4, 5 vs entry 1, Table 2). The *ortho*-substituents in benzaldehyde gave lower ee values regardless of whether this substituent was electron-withdrawing or electron-donating, as shown in entries 7, 9, and 10 in Table 2. However, 2-methylbenzaldehyde bearing a methyl group at the *ortho*-position

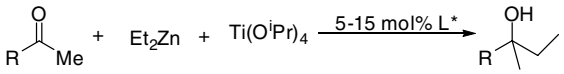
Table 2. The addition of diethylzinc to aldehydes in the presence of ligand **5**



Entry	R	Yield[a] (%)	Time (h)	ee[b] (%)
1	C_6H_5	90	2	65
2	4-FC_6H_4	93	1	75
3	4-ClC_6H_4	95	1	70
4	4-MeC_6H_4	81	12	60
5	4-$MeOC_6H_4$	83	12	58
6[c]	4-$MeOC_6H_4$	97	2	63
7	2-ClC_6H_4	92	3	38
8	2-MeC_6H_4	96	2	81
9	2-$MeOC_6H_4$	90	3	54
10[c]	2-$MeOC_6H_4$	95	2	63
11	1-Naphthyl	85	3	83
12	Cinnamyl	95	3	31

[a] Isolated yields.
[b] The ee values were determined by chiral OD-H column.
[c] 3 equiv Et_2Zn was used.

Table 3. Enantioselective addition of diethylzinc to ketones in the presence of ligand **5**



1.0 equiv 1.8 equiv 1.2 equiv

Entry	R	mol % L*	Solvent	*T* (°C)	Time (h)	Yield[a] (%)	ee (config.)[b]
1	4-ClC_6H_4	5	Toluene	20	48	60	58
2	4-ClC_6H_4	5	Hexane	20	50	72	76
3	4-ClC_6H_4	10	Hexane	20	50	73	80
4	4-ClC_6H_4	10	Tol/hex[c]	20	50	72	81
5	4-ClC_6H_4	15	Tol/hex	20	50	75	81
6	4-ClC_6H_4	7	Tol/hex	20	50	73	81
7	4-ClC_6H_4	7	Tol/hex	0	50	62	80
8	4-ClC_6H_4	7	Tol/hex	40	36	65	79
9	4-FC_6H_4	7	Tol/hex	20	40	78	83
10	4-BrC_6H_4	7	Tol/hex	20	40	78	80
11	C_6H_5	7	Tol/hex	20	50	70	99 (*S*)
12	4-$MeOC_6H_4$	7	Tol/hex	20	56	68	35
13	4-MeC_6H_4	7	Tol/hex	20	48	70	70
14	4-PhC_6H_4	7	Tol/hex	20	40	80	78
15[d]	2-Furan	7	Tol/hex	20	36	88	10
16[d]	2-Thiophene	7	Tol/hex	20	40	75	18
17	2-Naphthyl	7	Tol/hex	20	48	80	82

[a] Isolated yields.
[b] The ee were determined by chiral HPLC using OD-H column or OJ-H column.
[c] Mixed solvents were used with the ratio of 1:6.
[d] 3 equiv Et_2Zn was used in the reaction.

improved the ee value up to 81% in this addition reaction (Table 2, entry 8). Usually it is assumed that this addition involves a transition state, which is a titanium complex containing the corresponding ligand and the coordinated carbonyl compound.[6] A higher electronegative substitution at the *ortho*-position of benzaldehyde would have a great influence on the coordination of the carbonyl compound to the titanium center possibly due to the electrostatics or a hydrogen bond between the *ortho*-substituent and coordinated heteroatoms such as oxygen and nitrogen atoms in this complex. Therefore, 2-chloro and 2-methoxy substitution has a electrostatic effect or an hydrogen bond with coordinated oxygen or nitrogen in this complex besides steric hindrance while 2-methyl substitution has only steric hindrance, resulting in the difference of the substitution effect on the ee value. In comparison with benzaldehyde, sterically demanding 1-naphthaldehyde gave better enantioselectivity of 83% ee (Table 2, entry 11). Increasing the amount of diethylzinc enhanced both the reaction yield and ee value in this addition reaction (Table 2, entries 6 and 10). Cinnamaldehyde also gave the desired product in high yield but with a poor enantioselectivity (Table 2 entry 12).

2.3. Asymmetric addition of diethylzinc to ketones

On the basis of the good efficiency of ligand **5** for the asymmetric addition of diethylzinc to aldehydes, we tried to employ the sulfonamide **5** in the addition of diethylzinc to ketones, in order to extend the scope of the reaction substrate and to synthesize chiral building blocks containing a quaternary stereogenic carbon center. First of all, *p*-chloro acetophenone was chosen as a standard substrate for studying the effect of solvent, catalyst loading and temperature (entries 1–8 in Table 3). After optimization, it was found that hexane-toluene (mixed solvent with the ratio 6:1), 7 mol % of catalyst loading and room temperature were the best options in all the conditions tested (Table 3, entry 6) and as a result were adopted in experimental manipulation. Subsequently, different substrates were tested under these conditions. All the experimental results are listed in Table 3. From Table 3 it was found that acetophenone gave the best enantioselectivity, being up to 99% with a good yield (entry 11 in Table 3). The electronic properties of the substituents had a great influence on the reaction yield and ee value. The electron-withdrawing group on the aromatic ring of the substrate increased the reaction enantiomeric excess (Table 3, entries 6, 9, and 10) while electron-donating substitution disfavored the enantioselectivity (Table 3, entries 12–14). In addition, heteroaromatic ketone derivatives, such as 2-acetyl furan and 2-acetylthiophene, also gave good yields but with a poor enantioselectivity in the presence of 3 equiv of Et_2Zn (entries 15 and 16 in Table 3). In comparison with acetophenone, the more sterically demanding 2-acetylnaphthalene gave good enantiomeric excess (entry 17), which implied that steric hindrance in this substrate helped increase the ee value.

3. Conclusion

We have described a new C_2-symmetric chiral sulfonamide ligand, which can be easily prepared from L-tartaric acid and camphor sulfonyl chloride. This ligand has been successfully used in the asymmetric addition of diethylzinc

to aldehydes and ketones in the presence of titanium tetraisopropoxide under mild conditions, affording the corresponding chiral alcohols in high yields with good ee values. Further investigation on the scope of the reaction and the mechanism of the catalytic species is currently in progress.

4. Experimental

4.1. General

Unless other indicated, all reactions using diethylzinc and $Ti(O^iPr)_4$ were carried out in dry glassware under nitrogen. Hexane, tetrahydrofuran, ethyl ether, and toluene were freshly distilled from sodium and benzophenone. Dichloromethane was freshly distilled from CaH_2. Titanium tetraisopropoxide was freshly distilled under reduced pressure. Triethylamine was distilled and stored in 4 Å MS. Ethyl zinc solution was 1.5 M in hexane and used directly. Reactions were monitored by thin-layer chromatography (TLC) analysis. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 FT (^1H: 300 MHz, ^{13}C: 75.46 MHz) or AC-400 FT (^1H: 400 MHz, ^{13}C: 100 MHz) using TMS as internal reference. The chemical shifts (δ) and coupling constants (J) were expressed in parts per million and hertz, respectively. IR spectra were recorded on a Perkin–Elmer 2000 FTIR. High resolution mass spectra were obtained on GCT-TOF spectrometer. Optical rotations were measured on a WZZ-2 polarimeter. Chiral HPLC was performed in an Agilent 1100 series instrument equipped with a diode array detector. Chiralcel OD-H column and Chiralcel OJ-H column were purchased from Daicel chemical industries with 0.46 cm $\varnothing \times 25$ cm. Retention times (t) for HPLC are given in minutes.

4.2. Preparation of chiral ligand

The syntheses of compounds **1**–**5** are already described in the literature.[7]

Spectral and physical data for compound **4**: Yellowish solid, yield: 90%; mp = 126–127 °C; $[\alpha]_D^{25} = +25.0$ (c 0.8, $CHCl_3$); IR 3449, 3287, 2957, 1745, 1146 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.91 (6H, s), 1.02 (6H, s), 1.44–1.50 (6H and 2H, s and m overlap), 1.90–2.22 (10H, m), 2.30–2.40 (2H, m), 2.95 (2H, d, $J = 15.0$ Hz), 3.38–3.49 (2H and 4H overlap, d and m, $J = 15.0$ Hz), 4.18 (2H, m), 5.53–5.55 (2H, m) ppm; ^{13}C NMR (75.5 Hz, $CDCl_3$) 20.0, 20.4, 27.0, 27.6, 43.3, 43.4, 43.7, 49.3, 50.3, 59.6, 76.2, 78.0, 109.8, 217.1 ppm.

Spectral and physical data for compound **5**: white foam solid, yield: 40%; mp = 83–84 °C; $[\alpha]_D^{25} = -42.6$ (c 0.5, $CHCl_3$); IR 3450, 2920, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.84 (6H, s), 1.07 (6H, s), 1.11–1.16 (2H, m), 1.42 (6H, s), 1.44–1.48 (2H, m), 1.72–1.82 (10H, m), 2.50 (2H, br), 2.94 (2H, d, $J = 13.8$ Hz), 3.43 (4H, m), 3.53 (2H, d, $J = 13.8$ Hz), 4.01 (2H, m), 4.06–4.09 (2H, q), 4.92 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 20.0, 20.7, 27.2, 27.5, 30.5, 39.3, 44.3, 44.5, 48.9, 50.5, 52.8, 76.5, 77.1, 109.9 ppm; m/z (HPLC–ESI/MS) 591 $(M-H)^-$. Anal. Calcd for $C_{27}H_{48}N_2O_8S_2$: C, 54.70; H, 8.16; N, 4.73. Found: C, 54.58; H, 8.12; N, 4.71.

4.3. General procedure for enantioselective addition of diethylzinc to aldehydes

Ligand **5** (15 mg, 0.025 mmol, 0.05 equiv) and $Ti(O^iPr)_4$ (175 mg, 0.6 mmol, 1.2 equiv) were dissolved in toluene (2 ml) or other solvents under nitrogen. The resulting mixture was stirred for 10 min at room temperature (20 °C). Diethylzinc solution (0.6 ml, 0.9 mmol, 1.5 M in hexane, 1.8 equiv) was added to the above flask and the color of the solution became orange-green. After 2 min, the corresponding aldehyde (0.5 mmol, 1 equiv, diluted with 0.5 ml toluene or dissolved in 0.5 ml toluene) was added at this temperature. The reaction was stirred for the appointed time indicated in Table 1 or 2 until it was quenched with diluted hydrochloric acid. The resulting mixture was filtered through silica gel, extracted with ethyl acetate (3×10 ml), and the organic layer dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography column to afford the expected *sec*-alcohol. The enantiomeric excess was determined by chiral HPLC.

4.3.1. 1-Phenyl-1-propanol (entry 1 in Table 2). Colorless oil, $[\alpha]_D^{25} = -32.5$ (c 1.0, $CHCl_3$); IR 3383, 3029, 2965, 2933 cm^{-1}; ^1H NMR 0.91 (3H, t, $J = 7.4$ Hz), 1.70–1.87 (3H, m and s overlap), 4.59 (1H, t, $J = 6.4$ Hz), 7.25–7.36 (5H, m) ppm; ^{13}C NMR 10.1, 31.8, 75.8, 126.0, 127.3, 128.3, 144.7 ppm; HRMS calcd for $C_9H_{12}O$ 136.0888, found 136.0884; HPLC (chiralcel OD-H):, *n*-hexane/^{i}PrOH = 97:3 (v/v), flow rate = 0.5 ml/min, 25 °C, 254 nm, $t_1 = 20.2$ min, $t_2 = 22.9$ min.

4.3.2. 1-(4-Fluorophenyl)propan-1-ol (entry 2 in Table 2). Colorless oil, $[\alpha]_D^{25} = -28.0$ (c 1.0, $CHCl_3$); IR 3383, 2967, 1605 cm^{-1}; ^1H NMR 0.90 (3H, t, $J = 7.4$ Hz), 1.67–1.85 (2H, m), 1.94 (1H, s), 4.58 (1H, t, $J = 6.6$ Hz), 6.99–7.05 (2H, m), 7.28–7.32 (2H, m) ppm; ^{13}C NMR 10.0, 31.9, 75.3, 115.0, 115.2, 127.6, 127.7, 140.4, 140.4, 160.5, 163.8 ppm; HRMS calcd for $C_9H_{11}FO$ 154.0794 found 154.0796; HPLC (chiralcel OD-H column): hexane/^{i}PrOH = 99.5:0.5; 0.4 ml/min, 25 °C, 270 nm, $t_1 = 68.3$ min, $t_2 = 71.6$ min.

4.3.3. 1-(4-Chlorophenyl)-1-propanol (entry 3 in Table 2). Colorless oil, $[\alpha]_D^{25} = -18.0$ (c 1.0, benzene); IR 3374, 2966, 2933, 2877 cm^{-1}; ^1H NMR 0.90 (3H, t, $J = 7.4$ Hz), 1.69–1.81 (2H, m), 1.84 (1H, s), 4.58 (1H, t, $J = 6.4$ Hz), 7.25–7.33 (4H, m) ppm; ^1H NMR 10.0, 31.9, 75.1, 127.4, 128.4, 133.0, 143.1 ppm; HRMS calcd for $C_9H_{11}ClO$ 170.0498, found 170.0493; HPLC (chiralcel OD-H): hexane/^{i}PrOH = 99:1, flow rate = 0.5 ml/min, 25 °C, 254 nm; $t_1 = 38.2$ min, $t_2 = 40.3$ min.

4.3.4. 1-(4-Methylphenyl)-1-propanol (entry 4 in Table 2). Colorless oil, $[\alpha]_D^{25} = -25.0$ (c 1.0, benzene); IR 3381, 2966, 2933, 2875 cm^{-1}; ^1H NMR 0.90 (3H, t, $J = 7.4$ Hz), 1.70–1.84 (3H, m and s overlap), 2.34 (3H, s), 4.55 (1H, t, $J = 6.6$ Hz), 7.13–7.25 (4H, m) ppm; ^{13}C NMR 10.1, 21.0, 31.7, 75.7, 126.0, 128.9, 136.8,

141.8 ppm; HRMS calcd for $C_{10}H_{14}O$ 150.1045, found 150.1048; HPLC (chiralcel OD-H): *n*-hexane/^{i}PrOH = 99.5:0.5, flow rate = 0.4 ml/min, 25 °C, 254 nm, t_1 = 67.1 min, t_2 = 70.1 min.

4.3.5. 1-(4-Methoxyphenyl)-1-propanol (entry 5 in Table 2). Colorless oil, $[\alpha]_D^{25} = -21.0$ (*c* 1.0, benzene); IR 3405, 2963, 2934 cm^{-1}; ^{1}H NMR 0.89 (3H, t, J = 7.4 Hz), 1.69–1.84 (3H, m and s overlap), 3.80 (3H, s), 4.54 (1H, t, J = 6.7 Hz), 6.86–6.89 (2H, m), 7.25–7.27 (2H, m) ppm; ^{13}C NMR 10.1, 31.7, 55.2, 75.4, 113.7, 127.2, 136.9, 158.8 ppm; HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0996; HPLC (chiralcel OD-H): *n*-hexane/^{i}PrOH = 97:3, flow rate = 0.5 ml/min, 25 °C, 270 nm, t_1 = 28.5 min, t_2 = 31.9 min.

4.3.6. 1-(2-Chlorophenyl)-1-propanol (entry 7 in Table 2). Colorless oil, $[\alpha]_D^{25} = -17.5$ (*c* 2.0, $CHCl_3$); IR 3383, 3068, 2967, 2934 cm^{-1}; ^{1}H NMR 0.96 (3H, t, J = 7.4 Hz), 1.65–1.83 (2H, m), 1.93 (1H, s), 5.03 (1H, dd, J = 4.9, 7.5 Hz), 7.15–7.50 (4H, m) ppm; ^{13}C NMR 10.0, 30.5, 71.9, 127.0, 127.3, 128.3, 129.3, 132.0, 142.1 ppm; HRMS calcd for $C_9H_{11}ClO$ 170.0498, found 170.0492; HPLC (chiralcel OD-H): *n*-hexane/^{i}PrOH = 99:1, flow rate = 0.5 ml/min, 25 °C, 270 nm, t_1 = 30.5 min, t_2 = 31.5 min.

4.3.7. 1-*o*-Tolylpropan-1-ol (entry 8 in Table 2). Colorless oil, $[\alpha]_D^{25} = -43.0$ (*c* 0.5, benzene); IR 3357, 2964, 1460 cm^{-1}; ^{1}H NMR 0.98 (3H, t, J = 7.4 Hz), 1.72–1.81 (3H, m and s overlap), 2.34 (3H, s), 4.87 (1H, t, J = 6.3 Hz), 7.12–7.26 (3H, m), 7.44–7.47 (1H, m) ppm; ^{13}C NMR 10.3, 19.0, 30.9, 71.8, 125.3, 126.1, 127.0, 130.2, 134.5, 142.8 ppm; HRMS calcd for $C_{10}H_{14}O$ 150.1045, found 150.1040; HPLC (chiralcel OD-H column): hexane/^{i}PrOH = 98:2, flow rate = 0.3 ml/min; 254 nm, 25 °C, t_1 = 40.5 min, t_2 = 44.0 min.

4.3.8. 1-(2-Methoxyphenyl)-1-propanol (entry 9 in Table 2). Colorless oil, $[\alpha]_D^{25} = -36.0$ (*c* 1.0, toluene); IR 3406, 2964 cm^{-1}; ^{1}H NMR 0.95 (3H, t, J = 7.4 Hz), 1.77–1.86 (2H, m), 2.40 (1H, br), 3.84 (3H, s), 4.78 (1H, t, J = 6.6 Hz), 6.86–6.95 (2H, m), 7.23–7.30 (2H, m) ppm; ^{13}C NMR 10.4, 30.2, 55.3, 72.1, 110.5, 120.7, 127.0, 128.2, 132.6, 156.6 ppm; HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0997; HPLC (chiralcel OD-H): *n*-hexane/^{i}PrOH = 98:2, flow rate = 0.5 ml/min, 254 nm, 25 °C, t_1 = 26.9 min, t_2 = 28.9 min.

4.3.9. 1-(1-Hydroxypropyl) naphthalene (entry 11 in Table 2). Yellow oil, $[\alpha]_D^{25} = -53.5$ (*c* 0.5, $CHCl_3$); IR 3384, 3052, 2966, 2929 cm^{-1}; ^{1}H NMR 1.03 (3H, t, J = 7.1 Hz), 1.85 (1H, s), 1.88–2.07 (2H, m), 5.40 (1H, dd, J = 5.1, 7.4 Hz), 7.47–8.10 (7H, m) ppm; ^{13}C NMR 10.5, 31.1, 72.5, 123.0, 123.3, 125.4, 125.5, 125.9, 127.8, 128.9, 130.6, 133.9, 140.3 ppm; HRMS calcd for $C_{13}H_{14}O$ 186.1045, found 186.1054; HPLC (chiralcel OD-H): *n*-hexane/^{i}PrOH = 91:9, flow rate = 0.5 ml/min, 254 nm, 25 °C, t_1 = 16.3 min, t_2 = 27.8 min.

4.3.10. (*E*)-1-Phenylpent-1-en-3-ol (entry 11 in Table 2). Yellow oil, $[\alpha]_D^{25} = -2.4$ (*c* 3.0, $CHCl_3$); IR 3374, 2964, 1600 cm^{-1}; ^{1}H NMR 0.97 (3H, t, J = 7.4 Hz), 1.59–1.74 (3H, m and s overlap), 4.21 (1H, q, J = 6.5 Hz), 6.21 (1H, dd, J = 6.7, 15.9 Hz), 6.57 (1H, d, J = 15.9 Hz), 7.21–7.39 (5H, m) ppm; ^{13}C NMR 9.8, 30.3, 74.4, 126.5, 127.6, 128.6, 130.4, 132.4, 136.9 ppm; HRMS calcd for $C_{11}H_{14}O$ 162.1045 found 162.1052; HPLC (chiralcel OD-H column): hexane/^{i}PrOH = 91:9, flow rate = 0.5 ml/min, 260 nm, 25 °C, t_1 = 16.1 min, t_2 = 24.1 min.

4.4. General procedure for enantioselective addition of diethylzinc to ketones

Ligand **5** (21 mg, 0.035 mmol, 0.07 equiv) and Ti(O^{i}Pr)$_4$ (175 mg, 0.6 mmol, 1.2 equiv) were dissolved in hexane (2.5 ml) under nitrogen. The resulting mixture was stirred for 2 min at room temperature (20 °C). A diethylzinc solution (0.6 ml, 0.9 mmol, 1.5 M in hexane) was added to the above flask causing the color of the solution to turn orange-green. After 2 min, the corresponding ketone (0.5 mmol, 1 equiv, dissolved in 0.5 ml toluene or diluted with 0.5 ml toluene) was added at this temperature. The reaction was stirred for the appointed time mentioned in Table 3 until it was quenched with diluted hydrochloric acid. The resulting mixture was filtered through silica gel, extracted with ethyl acetate (3 × 10 ml) and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash chromatography column to afford the expected *tert*-alcohol. The enantiomeric excess was determined by chiral HPLC.

4.4.1. 2-Phenyl-butan-2-ol (entry 11 in Table 3). Colorless oil, $[\alpha]_D^{25} = -15.7$ (*c* 0.70, acetone); IR 3399, 2967, 1645 cm^{-1}; ^{1}H NMR 0.80 (3H, t, J = 7.4 Hz), 1.55 (3H, s), 1.68 (1H, s), 1.80–1.88 (2H, m), 7.23–7.44 (5H, m) ppm; ^{13}C NMR 8.4, 29.5, 36.7, 74.9, 125.0, 126.5, 128.1, 147.9 ppm; HRMS calcd for $C_{10}H_{14}O$ 150.1045, found 150.1046; HPLC (chiralcel OD-H column): hexane/isopropanol = 99:1, flow rate = 0.3 ml/min, 254 nm, 25 °C, t_1 = 45.3 min, t_2 = 49.3 min.

4.4.2. 2-(4-Chloro-phenyl)-butan-2-ol (entry 6 in Table 3). Colorless oil, $[\alpha]_D^{25} = -14.1$ (*c* 1.5, MeOH); IR 3411, 2972, 1648, 1164 cm^{-1}; ^{1}H NMR 0.79 (3H, t, J = 7.4 Hz), 1.53 (3H, s), 1.69 (1H, s), 1.77–1.83 (2H, m), 7.28–7.38 (4H, m) ppm; ^{13}C NMR 8.3, 29.6, 36.7, 74.7, 126.6, 128.2, 132.3, 146.4 ppm; HRMS calcd for $C_{10}H_{13}ClO$ 184.0655, found 184.0658; HPLC (chiralcel OJ-H column): hexane/isopropanol = 99:1, flow rate = 0.3 ml/min, 254 nm, 25 °C, t_1 = 55.5 min, t_2 = 66.2 min.

4.4.3. 2-(4-Fluoro-phenyl)-butan-2-ol (entry 9 in Table 3). Colorless oil, $[\alpha]_D^{25} = -6.5$ (*c* 3.0, MeOH); IR 3418, 2973, 1603, 1161 cm^{-1}; ^{1}H NMR 0.79 (3H, t, J = 7.4 Hz), 1.53 (3H, s), 167 (1H, s), 1.77–1.86 (2H, m), 6.98–7.03 (2H, m), 7.37–7.41 (2H, m) ppm; ^{13}C NMR 8.3, 29.6, 36.9, 74.7, 114.6, 114.9, 126.7, 126.8, 143.6, 143.6, 160.0, 163.3 ppm; HRMS calcd for $C_{10}H_{13}FO$ 168.0950, found 168.0948; HPLC (chiralcel OJ-H column): hexane/isopropanol = 99:1, flow rate = 0.3 ml/min, 270 nm, 25 °C, t_1 = 44.0 min, t_2 = 48.9 min.

4.4.4. 2-(4-Bromo-phenyl)-butan-2-ol (entry 10 in Table 3). Colorless oil, $[\alpha]_D^{25} = -10.0$ (*c* 2.0, MeOH); IR 3416, 2971, 1164 cm^{-1}; ^1H NMR 0.79 (3H, t, $J = 7.4$ Hz), 1.52 (1H, s), 1.66 (1H, s), 1.76–1.85 (2H, m), 7.29–7.32 (2H, m), 7.44–7.47 (2H, m) ppm; ^{13}C NMR 8.3, 29.5, 36.6, 74.7, 120.4, 126.9, 131.1, 146.9 ppm; HRMS calcd for $C_{10}H_{13}BrO$ 228.0150 found 228.0152; HPLC (chiralcel OJ-H column): hexane/isopropanol = 99:1, flow rate = 0.3 ml/min, 270 nm, 25 °C, $t_1 = 65.8$ min, $t_2 = 85.1$ min.

4.4.5. 2-(4-Methoxy-phenyl)-butan-2-ol (entry 12 in Table 3). Colorless oil, $[\alpha]_D^{25} = -5.7$ (*c* 3.0, $CHCl_3$); IR 3448, 2971, 1611 cm^{-1}; ^1H NMR 0.79 (3H, t, $J = 7.4$ Hz), 1.53 (3H, s), 1.65 (1H, s), 1.77–1.86 (2H, m), 3.80 (3H, s), 6.85–6.89 (2H, m), 7.32–7.37 (2H, m) ppm; ^{13}C NMR 8.5, 29.6, 36.8, 55.3, 74.7, 113.5, 126.2, 140.1, 158.3 ppm; HRMS calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1153; HPLC (chiralcel OD-H column): hexane/isopropanol = 99:1, flow rate = 0.4 ml/min, 225 nm, 25 °C, $t_1 = 46.6$ min, $t_2 = 54.7$ min.

4.4.6. 2-*p*-Tolyl-butan-2-ol (entry 13 in Table 3). Colorless oil, $[\alpha]_D^{25} = -2.1$ (*c* 3.0, EtOH); IR 3454, 2972, 1729 cm^{-1}; ^1H NMR 0.78 (3H, t, $J = 7.5$ Hz), 1.51 (3H, s), 1.64 (1H, s), 1.81 (2H, q, $J = 7.5$ Hz), 2.32 (3H, s), 7.13 (2H, $J = 7.9$ Hz), 7.30 (2H, $J = 8.0$ Hz); ^{13}C NMR 8.4, 21.0, 29.6, 36.7, 74.9, 124.9, 128.9, 136.0, 145.0 ppm; HRMS calcd for $C_{11}H_{16}O$ 164.1201 found 164.1200; HPLC (chiral OD-H column): hexane/isopropanol = 99.5:0.5, flow rate = 0.4 ml/min, 270 nm, 25 °C, $t_1 = 38.7$ min, $t_2 = 41.7$ min.

4.4.7. 2-Biphenyl-4-yl-butan-2-ol (entry 14 in Table 3). Colorless oil, $[\alpha]_D^{25} = -17.0$ (*c* 1.5, acetone); IR 3422, 2971, 1163 cm^{-1}; ^1H NMR 0.84 (3H, t, $J = 7.5$ Hz), 1.56 (3H, s), 1.66 (1H, s), 1.83–1.89 (2H, m), 7.24–7.58 (9H, m) ppm; ^{13}C NMR 8.4, 29.5, 36.7, 74.8, 125.5, 126.8, 127.0, 127.2, 128.8, 139.3, 140.9, 147.0 ppm; HRMS calcd for $C_{16}H_{18}O$ 226.1358, found 226.1351; HPLC (chiralcel OD-H column): hexane/isopropanol = 98:2, flow rate = 0.4 ml/min, 270 nm, 25 °C, $t_1 = 32.6$ min, $t_2 = 43.0$ min.

4.4.8. 2-Furan-2-yl-butan-2-ol (entry 15 in Table 3). Yellow oil, $[\alpha]_D^{25} = -0.5$ (*c* 5.0, acetone); IR 3405, 2973, 1160 cm^{-1}; ^1H NMR 0.79 (3H, t, $J = 7.4$ Hz), 1.43 (3H, s), 1.55 (1H, s), 1.70–1.87 (2H, m), 6.18 (1H, d, $J = 3.7$ Hz), 6.30 (1H, dd, $J = 1.8$, 3.7 Hz), 7.34 (1H, d, $J = 1.8$ Hz) ppm; ^{13}C NMR 8.5, 25.8, 34.4, 71.9, 104.6, 109.9, 141.4, 159.5 ppm; HRMS calcd for $C_8H_{12}O_2$ 140.0837, found 140.0838; HPLC (chiralcel OD-H column): hexane/isopropanol = 98:2, flow rate = 0.3 ml/min, 220 nm, 25 °C, $t_1 = 30.1$ min, $t_2 = 32.1$ min.

4.4.9. 2-Thiophen-2-yl-butan-2-ol (entry 16 in Table 3). Yellow oil, $[\alpha]_D^{25} = -1.8$ (*c* 3.0, acetone); IR 3406, 2972, 1160 cm^{-1}; ^1H NMR 0.90 (3H, t, $J = 7.5$ Hz), 1.60 (3H, s), 1.70 (1H, s), 1.78–1.91 (2H, m), 6.85–6.95 (2H, m), 7.15–7.20 (1H, m) ppm; ^{13}C NMR 8.5, 29.6, 37.4, 74.1, 122.3, 123.7, 126.6, 153.2 ppm; HRMS calcd for $C_8H_{12}OS$ 156.0609, found 156.0608; HPLC (chiralcel OD-H column): hexane/isopropanol = 98:2, flow rate = 0.4 ml/min, 254 nm, 25 °C, $t_1 = 26.6$ min, $t_2 = 29.4$ min.

4.4.10. 2-Naphthalen-2-yl-butan-2-ol (entry 17 in Table 3). Colorless oil, $[\alpha]_D^{25} = -11.5$ (*c* 2.0, MeOH); IR 3424, 2971, 1130 cm^{-1}; ^1H NMR 0.81 (3H, t, $J = 7.4$ Hz), 1.64 (3H, s), 1.75 (1H, s), 1.84–2.00 (2H, m), 7.25–7.54 (3H, m), 7.80–7.90 (4H, m) ppm; ^{13}C NMR 8.4, 29.5, 36.5, 75.0, 123.3, 123.9, 125.6, 126.0, 127.4, 127.8, 128.2, 132.3, 132.2, 145.2 ppm; HRMS calcd for $C_{14}H_{16}O$ 200.1201, found 200.1200; HPLC (chiralcel OD-H column): hexane/isopropanol = 98:2, flow rate = 0.4 ml/min, 270 nm, 25 °C, $t_1 = 52.1$ min, $t_2 = 61.9$ min.

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