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The first catalytic asymmetric addition of diethylzinc to aldehyde promoted by chiral thiourea

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Abstract

A series of C_2-symmetric and asymmetric chiral thiourea derivatives were synthesized from commercial L-phenylalanine. All of the new compounds have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, MS spectra and elemental analyses. The chiral thioureas were used as chiral ligands in the catalytic enantioselective ethylation of aldehydes with diethylzinc, the corresponding sec-alcohols were gained with excellent enantioselectivities (up to 87.1% *ee*) and high yields (up to 76.7%) after the conditions were optimized.

Keywords: Chiral thiourea; Diethylzinc; Amino alcohol; C_2-symmetric; Enantioselective addition

Over the last decade, chiral thioureas have been intensively studied as prominent asymmetric catalyst due to their strong double hydrogen-bonding interaction with reactants. Since the pioneering work of Jacobson [1], extensive studies have been carried out in this area. A number of chiral thiourea derivatives have been synthesized and successfully applied in several types of asymmetric reactions, such as Strecker reactions [2], Henry [3] and aza-Henry reactions [4], Mannich [5] and nitro-Mannich reactions [6], Michael [7] and nitro-Michael additions [8], Morita-Baylis-Hillman reactions [9], dynamic kinetic resolution [10], etc. However, to the best of our knowledge, there are no reports about the enantioselective alkylation of aldehydes by using thiourea [11,12]. To further extend the scope of applications of thiourea, we firstly report herein the preparation of these easy accessible thiourea ligands and their applications in the reaction of diethylzinc with aldehyde.

As to the synthetic procedure, thioureas were commonly prepared from the reaction of amine with thiophosgene, isothiocyanate or dithiocarbamates and related salts [13–15]. But these typical procedures must use isothiocyanate, thiophosgene and dithiocarbamate, which were not agreement with the principle of environmentally friendly and large-scale synthesis. So, the thiourea bifunctional compounds were prepared from the reaction of amine with carbon disulfide or by substitution [16,17] as depicted in Scheme 1. The amino alcohols were gained according to the literature methods [18], which were derived from L-phenylalanine and converted into the thioureas **3** and **4** with carbon

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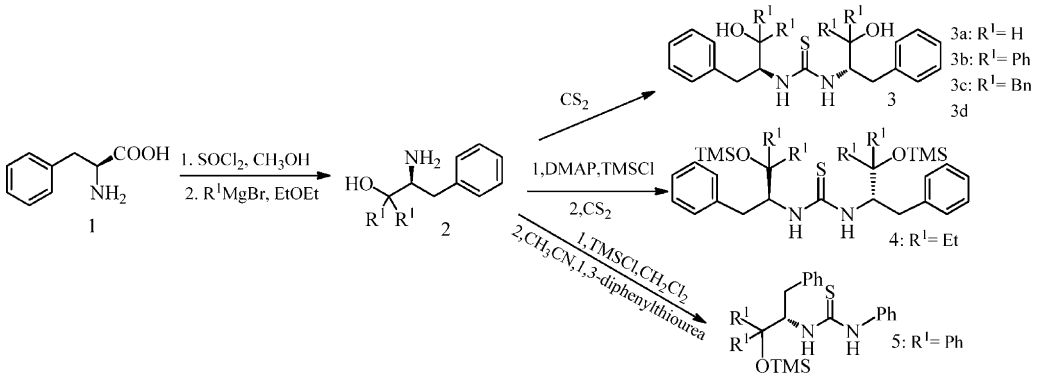


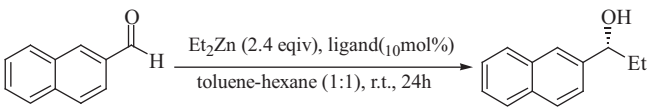
Scheme 1. Synthesis of asymmetric chiral thiourea organocatalyst.

disulfide in 53–91% yield, **3d** was derived from L-(−)-ephedrine. Reaction of 1, 3-diphenylthiourea with (*S*)-1, 1, 4-triphenyl-1-((trimethylsilyl)-oxy)-butan-2-amine in CH_3CN gave **5** in 76% yields [21].

In order to evaluate the catalytic potential of these ligands, our initial experiments in the asymmetric addition of diethylzinc to 2-naphthaldehyde involve the presence of 10% mol of ligands **3–5** in toluene at room temperature for 24 h, the results were listed in Table 1. The results of **5** and **6** demonstrated that the hydrogen atom of the hydroxy group play a vital role in the enantioselectivity ethylation of 2-naphthaldehyde, which can not afforded the alkylated products smoothly after the hydrogen atoms were substituted by -OTMS (Table 1, entries 1–4 *vs* 5–6). The C_2-symmetric chiral thioureas **3a–3d** gave moderate to good yield and enantioselectivity. After verified the effectiveness of the chiral thioureas **3a–3d** with modifying the bulkiness of R^1 with H (**3a**), Ph (**3b**) to Bn (**3c**) and **3d**, the best results were achieved by the catalyst **3b** with 65.7% *ee* (R^1 = Ph, Table 1, entry 2).

To determine the optimum conditions, **3b** was chosen as a model compound for the asymmetric addition of diethylzinc to 2-naphthaldehyde. The results were listed in Table 1 and depicted that the solvent played an important

Table 1
Asymmetric addition of diethylzinc to 2-naphthaldehyde.



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Entry	Ligand	Ligand (mol%)	Solvent	Temp (°C)	Yield (%)[a]	Ee (%)[b]
1	**3a**	10	Toluene	r.t.	16.1	7.6
2	**3b**	10	Toluene	r.t.	50.3	65.7
3	**3c**	10	Toluene	r.t.	55.5	46.1
4	**3d**	10	Toluene	r.t.	62.1	60.7
5[c]	**4**	10	Toluene	r.t.	n.d.	n.d.
6[c]	**5**	10	Toluene	r.t.	n.d.	n.d.
7	**3b**	10	Toluene:THF = 1:1	r.t.	36.1	14.2
8	**3b**	10	Toluene:CH_2Cl_2 = 1:1	r.t.	88.7	13.1
9	**3b**	10	Toluene:Et_2O = 1:1	r.t.	4.8	16.8
10	**3b**	10	Toluene:hexane = 2:1	r.t.	90.5	54.9
11	**3b**	10	Toluene:hexane = 1:1	r.t.	87.1	76.7
12	**3b**	10	Toluene:hexane = 1:2	r.t.	70.9	61.3
13	**3b**	3	Toluene:hexane = 1:1	r.t.	20.1	13.9
14	**3b**	5	Toluene:hexane = 1:1	r.t.	29.1	22.0
15	**3b**	15	Toluene:hexane = 1:1	r.t.	97.3	49.5
16	**3b**	10	Toluene:hexane = 1:1	0	46.9	85.1

[a] Isolated yield after flash chromatography.
[b] Values were determined by HPLC with a Chiralcel AD-H or OJ-H column [18–20].
[c] n.d.: not determined.

Table 2
Asymmetric addition of diethylzinc to aldehydes using ligand **3b**.

Entry	RCHO	Yield (%)[a]	*ee* (%)[b]
1	2-Naphthaldehyde	76.7	87.1
2	C_6H_5CHO	74.3	63.7
3	Furfural	64.7	76.1
4	3, 5-$(MeO)_2C_6H_3CHO$	82.1	71.9
5	*p*-BrC_6H_4CHO	72.5	82.3
6	*p*-ClC_6H_4CHO	42.3	38.3
7	2-ClC_6H_4CHO	67.2	31.1
8	4-Bromothiophene-2-carboxaldehyde	55.2	28.9

[a] Isolated yield after flash chromatography.
[b] Values were determined by HPLC with a chiralcel AD-H or OJ-H column [18–20].

role in the enantioselective process (Table 1, entries 7–12). When the reaction performed in toluene/hexane (1:1, v/v), the best results with 87.1% yield and 76.7% *ee* achieved (Table 1, entry 11). Increasing of toluene or combining of Et_2O, THF or CH_2Cl_2 lowered the *ee* values of the resulting alcohol (Table 1, entries 7–10). Furthermore, lowered the reaction temperature and shifted the loading of the catalyst cannot provide better results (Table 1, entries 13–16). Therefore, the reaction condition of entry 11 was chosen as the optimal conditions for the following reactions.

Under the optimal reaction conditions, the scope of the utility of **3b** was extended. A variety of aldehydes were tested and moderate to excellent enantioselectivity were observed, the results were summarized in Table 2. All of the alkylated products were affirmed R-configuration by comparison to the known values in the literatures [18–20].

In conclusion, we have prepared a series of chiral thioureas organocatalysts by efficient synthetic routes from commercial and inexpensive amino acids. We firstly performed these thioureas as ligands to asymmetric addition of diethylzinc to aldehydes showed a great catalytic potential. Further studies on their applications are in progress in our laboratories, and the results will be reported in due course.

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[21] Data of products. **3a**: white crystal. Yield 56%. mp 92–95° C. IR (KBr): 3165, 3025, 1528, 1454, 1330, 1268, 1091, 703, 678 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.57 (s, 2H, OH), 3.01 (d, 2H, J = 7.5 Hz, $PhCH_2$), 3.35 (m, 2H, J_1 = 11.0 Hz, J_2 = 4.0 Hz, $HOCH_2$), 3.63 (dd, 2H, J_1 = 11.0 Hz, J_2 = 3.5 Hz, $HOCH_2$), 4.46 (p, 2H, J = 7.3 Hz, C*H), 7.08 (s, br, 2H, NH), 7.37–7.21 (m, 10H, PhH). **3b**: white crystal. Yield 67%. mp 112–115 °C. IR (KBr): 3335, 3024, 1531, 1199, 749, 702, 678 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, br, 2H, OH), 2.69–2.15 (m, 4H, $PhCH_2$), 4.18 (dd, 1H, J_1 = 2.5 Hz, J_2 = 10.8 Hz, C*H), 4.84 (dd, 1H, J_1 = 3.2 Hz, J_2 = 11.6 Hz, C*H), 6.73 (s, br, 2H, NH), 7.65–7.13 (m, 30H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.7, 38.9, 58.1, 65.3, 95.5, 125.3, 125.7, 126.0, 126.4, 126.5, 126.7, 127.5, 128.2, 128.4, 128.6, 128.7, 128.8, 129.0, 129.2, 136.1, 138.2, 139.6, 140.9, 144.3, 146.7,187.9. MS (EI): *m/z* (%) 346 (100.0), 286 (23.0), 269 (24), 194 (63), 91 (15). Anal. calcd. for $C_{43}H_{40}N_2O_2S$ (648.28): C, 79.60; H, 6.21; N, 4.32. Found: C, 79.54; H, 6.16; N, 4.25. **3c**: yellow crystal. Yield 80%. mp 124–126 °C. IR (KBr): 3161, 3026, 1602, 1521, 1454, 1196, 730, 648 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.59 (s, 2H, OH), 2.79–2.75 (m, 4H, $PhCH_2$ C*), 2.82 (d, 2H, J = 14.6 Hz, $PhCH_2$ C*), 2.89 (d, 2H, J = 14.2 Hz, $PhCH_2$ C*), 3.11 (d, 2H, J = 14.6 Hz, $PhCH_2$ C*), 3.48 (d, 2H, J = 14.2 Hz, $PhCH_2$ C*), 4.14–4.09 (m, 2H, C*H), 6.46 (s, br, 2H, NH), 7.43–7.07 (m, 30H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.1, 39.8, 41.4, 63.0, 92.5, 126.9, 127.1, 127.3, 127.5, 128.4, 128.5, 128.6, 129.2, 130.5, 131.1, 134.2, 134.4, 136.0, 187.9. MS (EI): *m/z* (%) 373(53), 282(100), 222(17), 205(34), 91(48). Anal. calcd. for $C_{47}H_{48}N_2O_2S$ (704.34): C, 80.08; H, 6.86; N, 3.97. Found: C, 79.98; H, 6.76; N, 3.85. **3d**: white solid. Yield 91%. mp 82–85 °C. IR (KBr): 3193, 3038, 2979, 1523, 1330, 1168, 727, 658 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (d, 6H, J = 6.6 Hz, CH_3), 4.44–4.39 (m, 2H, CH_3C*H), 5.95 (d, 2H, J = 8.6 Hz, Ph C*H), 7.43–7.26 (m, 10H, PhH), 7.69 (s, br, 2H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6, 56.0, 86.6, 126.2, 128.6, 128.9, 133.6, 189.1. MS (EI): *m/z* (%) 193 (100.0), 150 (42), 132 (46), 117 (24), 77 (23). Anal. calcd. for $C_{19}H_{24}N_2O_2S$ (344.16): C, 66.25; H, 7.02; N, 8.13. Found: C, 66.13; H, 6.86; N, 8.02. **4**: yellow solid. Yield 53%. mp 68–70 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 0.99 (t, 6H, J_1 = J_2 = 7.5 Hz, CH_2CH_3), 1.09 (t, 6H, J_1 = J_2 = 7.4 Hz, CH_2CH_3), 2.04–1.75 (m, 8H, CH_3CH_2), 2.88–2.72 (m, 4H, $PhCH_2$), 3.92 (dd, 2H, J_1 = 3.4 Hz, J_2 = 11.4 Hz, $PhCH_2$ C*H), 6.63 (s, br, 2H, NH), 7.38–7.17 (m, 10H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.4, 7.7, 24.9, 29.1, 36.3, 64.4, 94.6, 127.4, 128.7, 129.2, 136.2, 188.1. MS (EI): *m/z* (%) 249 (70), 158 (100), 98 (63), 91 (64). Anal. calcd. for $C_{33}H_{56}N_2O_2SSi_2$ (600.36): C, 65.94; H, 9.39; N, 4.66. Found: C, 65.83; H, 9.24; N, 4.48. **5**: white solid. Yield 76%. mp 116 °C. IR (KBr): 3229, 3026, 2979, 1603, 1584, 1199, 835, 751, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ −0.22 (s, 9H, CH_3), 1.29–1.23 (m, 2H, $PhCH_2$), 1.62 (s, br, 1H, OH), 2.20 (dd, 1H, J_1 = 8.3 Hz, J_2 = 14.1 Hz, C*H), 5.89 (s, br, 2H, NH), 7.48–6.87 (m, 20H, PhH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 1.7, 37.9, 61.1, 84.2, 126.1, 126.5, 127.4, 127.8, 128.0, 128.6, 130.0, 130.1, 135.4, 138.1, 143.5, 143.7, 180.7. MS (EI): *m/z* (%) 328 (20), 255 (100), 120 (46), 91 (11), 73 (35). Anal. calcd. for $C_{31}H_{34}N_2OSSi$ (510.22): C, 72.90; H, 6.71; N, 5.48. Found: C, 72.78; H, 6.57; N, 5.39.