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Thiazolidine Derivatives as Chiral Catalysts in the Enantioselective Addition of Diethylzinc to Benzaldehyde

Qing Lin MENG, Yue Lan LI, Yan HE, Ye Di GUAN*

Department of Chemistry, Peking University, Beijing 100871
State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071

Abstract: Four types of chiral thiazolidine derivatives were synthesized conveniently from natural L-cysteine and showed good enantioselectivity in up to 90% ee in the addition of diethylzinc to benzaldehyde. Their enantioselectivity was affected by the bulkiness of R and the thiazolidine ring systems in their molecules.

Keywords: Chiral catalysts, enantioselective addition, % ee (enantiomeric excess), thiazolidine derivatives.

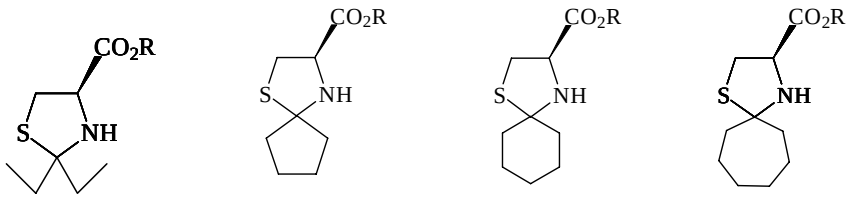
Enantioselective addition of dialkylzinc to aldehydes in the presence of catalytic amounts of chiral catalysts is one of the most important asymmetric C-C bond formation reactions. In most cases chiral β-amino alcohols or their analogies were used as efficient catalysts in this reaction[1].

Several chiral catalysts based on the thiazolidine ring have been reported, which showed moderate enantioselectivity[2]. While esters or their derivatives were seldom used as efficient catalysts. But in our previous work we have reported the ethylation of benzaldehyde with diethylzinc catalyzed by (R)-thiazolidine-4-carboxylic acid esters which do not contain hydroxyl group[3]. Here we wish to report other four types of thiazolidine derivatives **1**~**4** (**Scheme 1**), which were obtained from natural L-cysteine in moderate yields. **1**~**4** were synthesized by esterification with anhydrous alcohol ROH first and then cyclisation with corresponding ketone catalyzed by p-toluenesulfonic acid. **1**~**4** also have ester group but no hydroxyl group in their molecules and they catalyzed the enantioselective addition of diethylzinc to benzaldehyde in 65~99% yields and 72~90% ee, exhibiting good enantioselectivity as chiral catalysts.

The catalytic reactions were generally carried out in toluene-hexane (1:1) at room temperature for 48 hours and the results are summarized in **Table 1**. As can be seen, the bulkiness of R do affect the enantioselectivity of **1**~**4**. The larger R became (Me→Et→i-Pr), the higher enantioselectivity the catalysts usually showed. On the other hand, the enantioselectivity of the catalysts were also influenced by different thiazolidine ring

systems in **1**~**4**. It can be seen clearly that **1** and **4** always exhibited higher enantioselectivity than corresponding **2** and **3**.

Scheme 1 Thiazolidine derivatives **1**~**4**

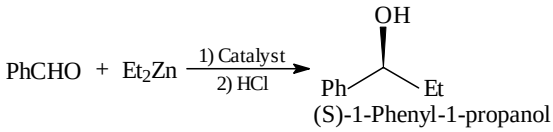


1 a, R=Me
b, R=Et
c, R= i-Pr

2 a, R=Me
b, R=Et
c, R= i-Pr

3 a, R=Me
b, R=Et
c, R= i-Pr

4 a, R=Me
b, R=Et
c, R= i-Pr



(S)-1-Phenyl-1-propanol

Table 1 Enantioselective addition of diethylzinc to benzaldehyde catalyzed by **1**~**4**

Entry	Catalyst	mol%	Yield(%)[a]	%ee[b]
1	1a	8	74	85
2	1b	8	70	88
3	1c	2	78	72
4	1c	4	99	88
5	1c	8	98	90
6	2a	8	65	79
7	2b	8	67	82
8	2c	8	77	89
9	3a	8	83	79
10	3b	8	90	80
11	3c	8	74	81
12	4a	8	99	87
13	4b	8	90	89
14	4c	8	90	89

a) Yields were based on the isolated products. b) Determined by using HPLC on a CHIRALCEL OJ column. c) The specific rotation $[\alpha]_D^{20}$=-47 (c=2.25, hexane) [4] for S enantiomer of the product was used to determine the configuration. d) The mole ratio of PhCHO: Et_2Zn: Catalyst is usually 1: 2.4: 0.08.

In conclusion, the thiazolidine derivatives **1**~**4**, as ester compounds in structure, have been successfully used as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde, although they do not belong to amino alcohol compounds. Our work will encourage further study on the use of thiazolidine derivatives as chiral catalysts. Further studies in preparation of efficient catalysts from L-cysteine are in

progress.

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References and notes

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5. ^{1}H NMR (200MHz, $CDCl_3$) and IR (film) data of the thiazolidine derivatives **1**~**4**:
1a: ^{1}H NMR: δ 4.03 (dd, J=6.4, 9.4Hz, 1H), 3.79 (s, 3H), 3.30 (dd, J=6.4, 10.2Hz, 1H), 2.84 (dd, J=9.6, 10.2Hz, 1H), 2.42 (s, 1H), 1.67-1.99 (m, 4H), 1.04 (t, J=7.2Hz, 3H), 0.92 (t, J=7.2Hz, 3H); IR: 3309, 2967, 1744, 1436, 1347, 1273, 1226, 1175, 847 cm^{-1}.
1b: ^{1}H NMR: δ 4.22 (dq, J=2.0, 7.2Hz, 2H), 4.00 (dd, J=7.0, 9.6Hz, 1H), 3.30 (dd, J=6.6, 10.4Hz, 1H), 2.84 (dd, J=9.4, 10.2Hz, 1H), 2.43 (s, 1H), 1.67-1.99 (m, 4H), 1.24 (t, J=7.2Hz, 3H), 1.04 (t, J=7.2Hz, 3H), 0.92 (t, J=7.2Hz, 3H); IR: 3309, 2969, 1740, 1459, 1371, 1337, 1223, 1179, 1027, 850 cm^{-1}.
1c: ^{1}H NMR: δ 5.09 (m, 1H), 3.98 (dd, J=6.8, 9.2Hz, 1H), 3.29 (dd, J=6.6, 10.4Hz, 1H), 2.82 (dd, J=9.4, 10.4Hz, 1H), 2.44 (s, 1H), 1.70-1.99 (m, 4H), 1.28 (dd, J=3.6, 6.0Hz, 6H), 1.05 (t, J=7.2Hz, 3H), 0.93 (t, J=7.2Hz, 3H); IR: 3310, 2971, 1736, 1458, 1375, 1320, 1226, 1177, 1107, 851 cm^{-1}.
2a: ^{1}H NMR: δ 3.94 (dd, J=7.0, 9.4Hz, 1H), 3.79 (s, 3H), 3.38 (dd, J=6.8, 10.2Hz, 1H), 2.99 (dd, J=9.2, 10.2Hz, 1H), 2.51 (s, 1H), 1.75-2.17 (m, 8H); IR: 3302, 2955, 1744, 1437, 1343, 1227, 1168, 835 cm^{-1}.
2b: ^{1}H NMR: δ 4.24 (dq, J=1.8, 7.2Hz, 2H), 3.92 (dd, J=7.2, 9.2Hz, 1H), 3.39 (dd, J=7.2, 10.4Hz, 1H), 2.98 (dd, J=9.4, 10.0Hz, 1H), 2.51 (s, 1H), 1.78-2.17 (m, 8H), 1.31 (t, J=7.2Hz, 3H); IR: 3302, 2962, 1739, 1446, 1370, 1335, 1224, 1166, 1027, 831 cm^{-1}.
2c: ^{1}H NMR: δ 5.10 (m, 1H), 3.90(dd, J=7.2, 9.2Hz, 1H), 3.38 (dd, J=7.2, 10.4Hz, 1H), 2.96 (dd, J=9.2, 10.2Hz, 1H), 2.54 (s, 1H), 1.73-2.31 (m, 8H), 1.28 (dd, J=2.6, 6.0Hz, 6H); IR: 3303, 2962, 1735, 1450, 1361, 1325, 1127, 1169, 1107, 822 cm^{-1}.
3a: ^{1}H NMR: δ 4.07 (dd, J=6.8, 9.4Hz, 1H), 3.79 (s, 3H), 3.30 (dd, J=6.6, 10.4Hz, 1H), 2.88 (dd, J=9.6, 10.4Hz, 1H), 2.43 (s, 1H), 1.29-1.91 (m, 10H); IR: 3300, 2931, 1744, 1437, 1348, 1232, 1199, 1157, 878, 802 cm^{-1}.
3b: ^{1}H NMR: δ 4.26 (dq, J=2.0, 7.2Hz, 2H), 4.04 (dd, J=6.6, 9.6Hz, 1H), 3.30 (dd, J=6.6, 10.4Hz, 1H), 2.87 (dd, J=9.6, 10.2Hz, 1H), 2.43 (s, 1H), 1.46-1.91 (m, 10H), 1.31 (t, J=7.2Hz, 3H); IR: 3301, 2932, 1739, 1447, 1371, 1341, 1191, 1157, 1026, 880, 800 cm^{-1}.
3c: ^{1}H NMR: δ 5.10 (m, 1H), 4.01(dd, J=6.6, 9.4Hz, 1H), 3.29 (dd, J=6.4, 10.2Hz, 1H), 2.84 (dd, J=9.4, 10.0Hz, 1H), 2.44 (s, 1H), 1.46-1.92 (m, 10H), 1.28 (dd, J=3.4, 6.2Hz, 6H); IR: 3301, 2932, 1736, 1448, 1362, 1232, 1194, 1158, 1107, 878, 801 cm^{-1}.
4a: ^{1}H NMR: δ 4.02 (dd, J=6.6, 9.2Hz, 1H), 3.78 (s, 3H), 3.34 (dd, J=6.8, 10.6Hz, 1H), 2.91 (dd, J=9.6, 10.6Hz, 1H), 2.48 (s, 1H), 1.58-2.15 (m, 12H); IR: 3305, 2928, 2855, 1744, 1437, 1345, 1220, 1170, 1007, 942, 852, 789 cm^{-1}.
4b: ^{1}H NMR: δ 4.20 (dq, J=2.0, 7.2Hz, 2H), 3.98 (dd, J=6.8, 9.2Hz, 1H), 3.33 (dd, J=6.4,

10.2Hz, 1H), 2.89 (dd, J=9.2, 10.2Hz, 1H), 2.35 (s, 1H), 1.66-2.14 (m, 12H), 1.31 (t, J=7.2Hz, 3H); IR: 3305, 2928, 2856, 1739, 1458, 1370, 1337, 1212, 1178, 1026, 853, 789 cm^{-1}.
4c: ^1H NMR: δ 5.09 (m, 1H), 3.95 (dd, J=6.8, 9.2Hz, 1H), 3.32 (dd, J=6.8, 10.2Hz, 1H), 2.86 (dd, J=9.2, 10.4Hz, 1H), 2.41 (s, 1H), 1.57-2.14 (m, 12H), 1.28 (dd, J=2.6, 6.2Hz, 6H); IR: 3306, 2929, 2856, 1736, 1458, 1373, 1322, 1220, 1178, 1107, 852, 797 cm^{-1}.

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