Enantioselective Addition of Diethylzinc to Aldehydes with Easily Prepared Chiral Thiazolidine Catalysts

Myung-Jong Jin* **and Sang-Han Kim**

School of Chemical Science & Engineering, Inha University, Inchon 402-751, Korea
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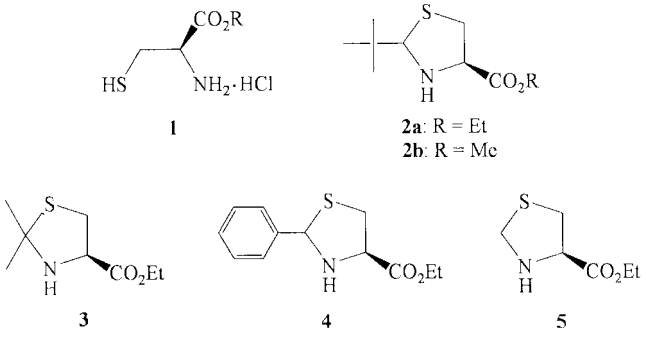
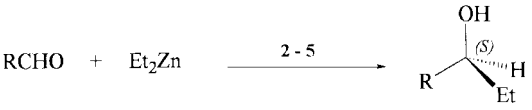
Asymmetric metal catalysis is now recognized as the most promising area in the synthesis of optically active organic compounds. One attractive method that leads to the formation of optically active secondary alcohols is catalytic enantioselective addition of dialkylzinc reagent to aldehydes.[1] Numerous elegant and efficient catalysts have been developed for this purpose, in which most of them are based on amino alcohols,[2] diols,[3] diamines,[4] and their derivatives.[5] In spite of the variety of chiral catalysts, the develoment of catalysts obtainable by simple synthetic routes remains still as an active research subject. We have easily prepared 4-carboethoxy-1,3-thiazolidines **2-5** from L-cysteine ester through one step. Previously, thiazolidine **4** was found to catalyze the dialkylzinc-aldehyde addition.[6] Following on from previous work, we wish to report the results on the enantioselective dialkylzinc-aldehyde addition in the presence of several N,S-chelate thiazolidine ligands.



Chiral thiazolidines **2-5** were easily prepared by condensation of L-cysteine ester **1** with the corresponding carbonyl compounds. Thiazolidines **2** and **4** were obtained as inseparable *ca*. 1:1.9 diastereomeric mixtures.[7] (2R,4R)-*cis*-Thiazolidines were assigned to be major diastereomers on a combination of the ^{1}H NMR data and the previous studies.[8] The catalytic behavior of the ligands **2-5** for the diethylzinc-aldehyde addition was then examined. The reaction conditions and results are summarized in Table 1. All the aldehydes were converted to the corresponding (*S*)-alcohols with moderate to excellent enantiomeric excess in high yields. Enantioselectivity was somewhat dependent on the amount of the ligand. Increasing the amount of ligand from 4 to 8% led to a small increase in the enantioselectivity (entries 1-3) and 6 mol% of ligand was enough to afford good enantioselectivity and reactivity. It is noteworthy that the ee

Table 1. Enantioselective Addition of Diethylzinc to Aldehydes[a]



Entry	R^1	Ligand (mol%)	Time (h)	Yield[b] (%)	e.e.[c] (%)
1[d]	Ph	**2a** (4)	4	95	87
2	Ph	**2a** (6)	4	99	90
3	Ph	**2a** (8)	4	99	90
4[d]	*p*-ClC_6H_4	**2a** (6)	4	100	95
5	*p*-$MeOC_6H_4$	**2a** (6)	4	99	94
6	*o*-$MeOC_6H_4$	**2a** (6)	4	100	90
7	*cyclo*-C_6H_{11}	**2a** (6)	4	100	92
8	2-naphtyl	**2a** (6)	4	100	90
9	Ph	**2b** (6)	4	98	86
10	*p*-ClC_6H_4	**2b** (6)	4	100	92
11	Ph	**3** (4)	6	94	87
12	Ph	**3** (6)	6	99	90
13	*p*-ClC_6H_4	**3** (6)	6	99	90
14	*p*-$MeOC_6H_4$	**3** (6)	6	100	82
15	Ph	**4** (6)	12	84	80
16	*p*-ClC_6H_4	**4** (6)	6	98	87
17	*p*-$MeOC_6H_4$	**4** (6)	12	90	76
18	Ph	**5** (6)	12	90	67
19	*p*-ClC_6H_4	**5** (6)	12	95	72

[a]Reactions were carried out in hexane at 0 °C → RT. Molar ratio, Et_2Zn : aldehyde : ligand = 2 : 1 : 0.04-0.08. Absolute configuration was assigned by the sign of the optical rotation and elution order from a chiral column. [b]Measured as %-conversion into the product by GC. [c]determined by HPLC analysis (chiralcel OD column) or GC analysis (*β*-DEX chiral column).

of the product depends on the size of substituents on thiazolidine ring. Thiazolidine **2a** having larger carboalkoxy moiety showed higher enantioselectivity than **2b** (entries 2, 4 versus 9, 10). Although R group affects the enantioselectivity, the bulkiness of C2-substituent on the thiazolidine ring is more important. Higher enantioselectivity was obtained with increasing size of the C2-substituent. Introduction of *tert*-butyl group on C2 led to the most improved enantioselectivity in the range of 90-95% ee. It is interesting that high enantioselectivity could be obtained with diastereomeric mixture **2**. This result suggests that the chirality of substituent on C2 is less important role for the stereochemical outcome. Each of diasteromers that differ in the

configuration at C2 would generate similar asymmetric induction environment. Accordingly, diastereomerically pure ligand is not necessarily required in order to obtain high enantioselectivity.[2d,9]

In conclusion, we have prepared chiral thiazolidines **2-5** derived from L-cysteine ethyl ester. In particular **2a** could catalyze efficiently the enantioselective addition of dialkylzinc to aldehydes.

Experimental Section

Reactions were carried out under an inert nitrogen atmosphere using dried glassware. All the commercially available reagents were used without further purification. NMR spectra were recorded on a Bruker AC 250 NMR spectrometer. Optical rotation were measured with a Perkin-Elmer 241 polarimeter. IR spectra were obtained on a Bruker IFS-48.

Preparation of 2-substituted-1,3-thiazolidines-4-carboxylate 2-5. Thiazolidines **2a**[6,8] and **4**[9] have been previously reported. According to the previous method, **2-5** were prepared by the reaction of L-cysteine ester hydrochloride with the corresponding carbonyl compounds.

2-tert-Butyl-4-carboethoxy-1,3-thiazolidine (2a). Yield 93%; colorless liquid; $[\alpha]_D^{20}$ -153.2 (c=1.0, $CHCl_3$); major diastereomer: ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 4.40 (s, 1H, SC*H*N), 4.18 (q, *J* = 7.3 Hz, 2H, OC*H*$_2$CH$_3$), 3.72 (dd, *J* = 8.3, 6.8 Hz, 1H, SCH$_2$C*H*), 3.23 (dd, *J* = 8.4, 6.8 Hz, 1H, SC*H*$_2$CH), 2.62 (t, *J* = *J'* = 10.0 Hz, 1H, SC*H*$_2$CH), 2.17 (br, 1H, NH), 1.24 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.02 (s, 9H, C(CH$_3$)$_3$); minor diasteromer: 4.40 (s, 1H, SC*H*N), 4.15 (q, *J* = 5.3 Hz, 2H, OC*H*$_2$CH$_3$), 4.04 (t, *J* = *J'* = 6.0 Hz, 1H, SCH$_2$C*H*), 3.07 (dd, *J* = 8.6, 6.4 Hz, 1H, SC*H*$_2$CH), 2.94 (dd, *J* = 8.2, 6.0 Hz, 1H, SC*H*$_2$CH), 2.17 (br, 1H, NH), 1.23 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 0.92 (s, 9H, C(C*H*$_3$)$_3$); IR (neat) $\upsilon_{C=O}$ 1736 cm^{-1}; MS (EI) *m/z* 217 (M$^+$).

2,2-Dimethyl-4-carboethoxy-1,3-thiazolidine (3). yield 81%; colorless liquid, $[\alpha]_D^{20}$ -178.6 (c=1.4, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 4.18 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.02 (dd, *J* = 9.1, 7.0 Hz, 1H, SCH$_2$C*H*), 3.38 (dd, *J* = 10.5, 7.0 Hz, 1H, SC*H*$_2$CH), 2.95 (br, 1H, N*H*), 2.96 (dd, *J* = 10.3, 9.2 Hz, 1H, SC*H*$_2$CH), 1.65 (s, 3H, CCH$_3$), 1.47 (s, 3H, CC*H*$_3$), 1.24 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); IR (neat) $\upsilon_{C=O}$ 1742 cm^{-1}; MS (EI) *m/z* 189 (M$^+$).

4-Carboethoxy-1,3-thiazolidines (5). yield 67%; colorless liquid, $[\alpha]_D^{20}$ -145.4 (c=1.1, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 4.35 (d, *J* = 9.6 Hz, 1H, SC*H*$_2$N), 4.20 (q, *J* = 7.5 Hz, 2H, OC*H*$_2$CH$_3$), 4.08 (d, *J* = 9.6, Hz, 1H, SC*H*$_2$N), 3.79 (t, *J* = *J'* = 7.5 Hz, 1H, SCH$_2$C*H*), 3.22 (dd, *J* = 10.0, 4.5 Hz, 1H, SC*H*$_2$CH), 2.82 (dd, *J* = 13.8, 8.0 Hz, 1H, SC*H*$_2$CH), 2.32 (br, 1H, N*H*), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); IR (neat) $\upsilon_{C=O}$ 1736 cm^{-1}; MS (EI) *m/z* 161 (M$^+$).

General Procedure for the enantioselective addition of diethylzinc to aromatic aldehydes. To a solution of thiazolidine (0.06 mmol) in hexane (2.0 mL) was added Et_2Zn (2.0 mL, 1.0 M in hexane) at 0 °C. The mixture was allowed to warm to RT. Aldehyde (1.0 mmol) was added dropwise and the reaction mixture was stirred at RT for a given time, observing the progress of the reaction by GC. The reaction was quenched at 0 °C by addition of 1.0 M HCl and the resulting mixture was extracted with CH_2Cl_2. After removal of solvent, the residue was purified by flash chromatography on silica gel (hexane/AcOEt=8/2). The enantiomeric excess was determined by HPLC (chiralcel OD column) or GC (β-DEX chiral column).

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