# Enantioselective Addition of Diethylzinc to α-Branched Aldehydes

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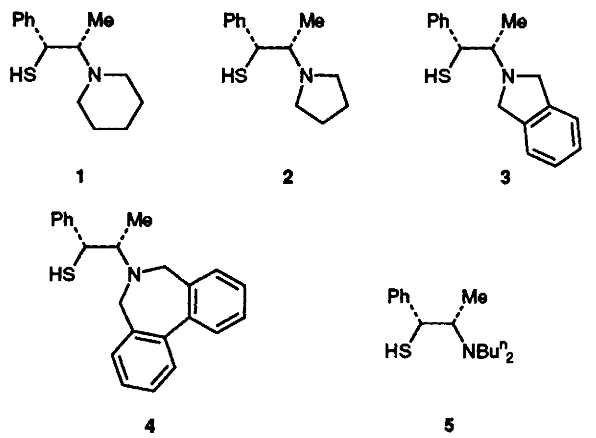
Reaction of diethylzinc with α-branched aldehydes in the presence of a catalytic amount of (1*R*,2*S*)-(−)-1-phenyl-2-piperidinopropane-1-thiol **1** provided the corresponding secondary alcohols in almost 100% enantiomeric excess.

Considerable efforts have been devoted to the asymmetric additions of dialkylzinc reagents to aldehydes in the presence of a catalytic amount of β-amino alcohols.[1–3] The quest for a catalyst system which would give complete optical purity (100% e.e.) continues. To this end, we sought better ligands for this reaction and decided on chiral *cyclic amino thiols*, which have the following features: (*i*) enhanced polarizability of sulfur (thiol) as compared to oxygen (alcohol), (*ii*) the heterocyclic nature of the ligand ring as a face blocker, (*iii*) high affinity of thiol and thiolate toward metals, especially zinc, and (*iv*) lower tendency of metal thiolates to diminish the Lewis acidity of the metal as compared to metal alcoholate.



Scheme 1

Among various amino thiols studied (**1–5**),[†] with which the reactions were faster than with the corresponding amino alcohols, (1*R*,2*S*)-(−)-1-phenyl-2-piperidinopropane-1-thiol **1** gave the best results.[‡§] Optimization showed toluene or ether to be the optimal solvent, which was gratifying since it opens up the possibility of utilization of other commercially unavailable dialkylzinc reagents, which can be prepared from alkyllithium, Grignard reagents or alkyl iodides.[4] Under the standard condition [Et$_2$Zn (2 equiv.), solvent: ether or toluene, 5% (mol/mol) of the ligand **1**, 0 °C], all the aromatic aldehydes examined afforded the corresponding secondary alcohols with the (*R*)-configuration (Scheme 1) in high optical purity (more than 98:1 enantiomer ratio). Similarly, cyclohexanecarbaldehyde and pivalaldehyde were ethylated in 100% e.e. (Table 1). To the best of our knowledge, such a degree of asymmetric induction has not been achieved with other ligand systems.

However, hexanal and *trans*-cinnamaldehyde could only be ethylated in moderate enantioselectivity (62–77% e.e.) at various temperature and in various solvents. Consequently, for good asymmetric induction with the present system, the aldehyde should be α-branched. Aromatic aldehydes may be considered to have an α-alkyl group (hydrogen).

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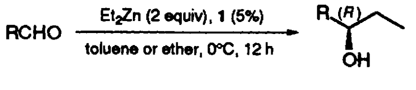
**Table 1** Enantioselective addition of diethylzinc to aldehydes in the presence of **1**[a]

| R in RCHO | Yield (%)[b] | E.e. (%) | Rotation, $[\alpha]^{25}_{D}$ |
|---|---|---|---|
| Ph | 94, 92[c] | 100[d] | +46.0 (*c* 5.2, CHCl$_3$)[j] |
| 2-MeOC$_6$H$_4$ | 96, 90[c] | 100[d] | +53.3 (*c* 3.0, toluene)[k] |
| 4-MeOC$_6$H$_4$ | 95, 96[c] | 100[d] | +35.5 (*c* 4.1, benzene)[l] |
| 4-ClC$_6$H$_4$ | 99 | 100[d] | +28.0 (*c* 5.0, benzene)[m] |
| 4-FC$_6$H$_4$ | 92 | 100[d] | +51.2 (*c* 2.5, CHCl$_3$)[n] |
| 2-Naphthyl | 98 | 99[e] | +29.8 (*c* 4.7, benzene)[o] |
| 1-Naphthyl | 100 | 99[e] | +55.6 (*c* 2.4, CHCl$_3$)[p] |
| Ferrocenyl | 98[q] | 98[f] | −57.5 (*c* 1.1, benzene)[r] |
| Bu$^t$ | 94[s] | 100[g] | |
| Cyclohexyl | 97 | 100[g] | |
| *n*-Pentyl | 92–96 | 62–65[h] | |
| *trans*-PhCH=CH | 92–98 | 68–77[i] | |

[a] Absolute configuration was determined by comparison of the optical rotation with the literature value. [b] Isolated yield, in toluene. [c] In ether. [d] GC, Chiraldex B-PH. [e] HPLC, Daicel Chiralcel OB. [f] HPLC, Daicel Chiralcel OF. [g] GC of benzoate, Chiraldex B-PH. [h] GC of MTPA ester, Chiraldex B-PH. [i] HPLC, Daicel Chiralcel OD. [j] Lit. for (*S*)-isomer $[\alpha]^{25}_{D}$ −45.45 (*c* 5.2, CHCl$_3$).[5] [k] Lit. $[\alpha]^{25}_{D}$ + 47.0 (*c* 1.2, toluene) for 87% e.e.[6] [l] Lit. for (*S*) isomer of 51% e.e. $[\alpha]^{25}_{D}$ −17.2 (*c* 5, benzene).[7] [m] Lit. for (*S*) isomer of 43% e.e. $[\alpha]^{25}_{D}$ −10.4 (*c* 5, benzene).[7] [n] Configuration presumed.[8] [o] Lit. for (*S*)-isomer of 97% e.e., $[\alpha]^{25}_{D}$ −26.6 (*c* 3.35, benzene)[9]. [p] Lit. $[\alpha]^{25}_{D}$ +36.3 (*c* 2.14, CHCl$_3$) for 62% e.e.[10] [q] Reaction at 20 °C. [r] Lit. $[\alpha]^{25}_{D}$ −57.5 (*c* 1.0, benzene) for 96% e.e.[11] [s] Determined by GC using *n*-dodecane as an internal standard.



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## Footnotes

[†] (1*R*,2*S*)-(−)-Norephedrine was alkylated with 2 equiv. of the α,ω-dibromoalkane or Bu$^n$Br in refluxing ethanol in the presence of 5 equiv. of potassium carbonate. The resulting amino alcohols were mesylated; subsequent displacement with potassium thioacetate gave the corresponding thioacetate with retention of configuration. Treatment of the thioacetate with Bu$^i_2$AlH in toluene provided the pure β-amino thiols **1–5** which were stored under nitrogen in benzene below 0 °C.

[‡] For the amino thiol **1**, alkylation (70%), thioacetate (89%) and hydrolysis of thioacetate (97%), bp 105 °C at 0.1 mmHg, $[\alpha]^{25}_{D}$ −67.0 (*c* 2.25, CHCl$_3$). Spectral data: IR (neat ν/cm$^{-1}$ 3068.8, 2932.5, 2792.7 and 2643.3; $^1$H NMR (200 MHz, CDCl$_3$) δ 7.18–7.40 (m, 5H), 4.16 (d, *J* 7.2 Hz, 1H), 2.87 (dq, *J* 7.2, 6.6 Hz, 1H), 2.32–2.54 (m, 4H), 1.26–1.49 (m, 6H), 1.11 (d, *J* 6.6 Hz, 3H); MS (EI): *m/z* 202 (M$^+$ −33, 3.6%), 121 (16), 112 (100).

[§] Professor Kellogg and colleagues have recently reported thiol analogues of *N*-alkylephedrine as ligands for the present reaction. However, the best ligands in their case were the corresponding disulfides of the *N*-methyl and *N*-isopropyl analogues, which gave the corresponding alcohol in only 90% e.e. R. P. Hof, M. A. Poelert, N. C. M. W. Peper and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1994, **5**, 31.

## References

1 T. Sato, K. Soai, K. Suzuki anbd T. Mukaiyama, *Chem. Lett.*, 1978, 601; T. Mukaiyam, K. Soai, T. Sato, H. Shimizu and K. Suzuki, *J. Am. Chem. Soc.*, 1979, **101**, 1455; N. Oguni and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823.

2 For reviews on catalytic addition of organozinc reagents to carbonyl compounds, see R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49, K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833. See also N. Oguni, Y. Matsuda and T. Kaneko, *J. Am. Chem. Soc.*, 1988, **110**, 7877; G. B. Hones and S. B. Heaton, *Tetrahedron: Asymmetry*, 1993, **4**, 261; J. M. J. Williams, J. V. Allen and C. G. Frost, *Tetrahedron: Asymmetry*, 1993, **4**, 649.

3 M. Kitamura, S. Suga, K. Kawai and R. Noyori, *J. Am. Chem. Soc.*, 1986, **108**, 6071; K. Soai, A. Okawa, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.

4 D. Seebach, L. Behrendt and D. Felix, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1008; H. Stadtmüller, R. Lentz, C. E. Tucker, T. Stüdemann, W. Dörner and P. Knochel, *J. Am. Chem. Soc.*, 1993, **115**, 7027.

5 R. H. Richard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115.

6 J. Capillon and J. Guette, *Tetrahedron*, 1979, **35**, 1817.

7 A. Smaardijk and H. Wynberg, *J. Org. Chem.*, 1987, **52**, 135.

8 K. Soai, Y. Hirose and S. Niwa, *J. Fluorine Chem.*, 1992, **59**, 5.

9 M. Watanabe, S. Araki, Y. Butsugan and M. Uemura, *J. Org. Chem.*, 1991, **56**, 2218.

10 S. Niwa and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2717.

11 Y. Natsumoto, A. Ohno, S. Lu and T. Hayashi, *Tetrahedron: Asymmetry*, 1993, **4**, 1763.