

The Steric Effect of *trans*-(1*S*,2*S*)-1-Substituted-2-(*N,N*-dialkylamino)-1-indanol Derivatives as Chiral Ligands in the Catalytic Enantioselective Addition of Diethylzinc to Aldehydes

Qian Yong XU^{1,2*}, Hong Fang YANG², Xin Fu PAN², Guang Ming ZHU³

¹Northwest Institute of Nuclear Technology, P. O. Box 69, Xi'an 710024

²Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000

³Department of Chemical Engineering, Northwestern Polytechnic University, Xi'an 710062

Abstract: Optically active *trans*-(1*S*,2*S*)-1-substituted-2-(*N,N*-dialkylamino)-1-indanol derivatives have been prepared and used in the asymmetric addition of diethylzinc to aldehydes to give *sec*-alcohol in good yield with up to 93.1% enantiomeric excess.

Keywords: Diethylzinc, enantioselective alkylation, indanol derivative.

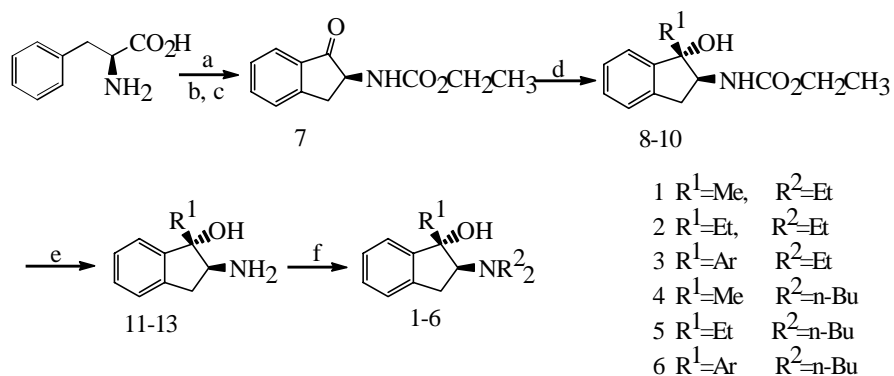
The catalytic enantioselective addition of dialkylzinc to aldehydes has attracted much attention in recent years because of its potential in the preparation of optically active secondary alcohol¹. Among the chiral ligands used, a myriad of β -amino alcohols have been especially investigated as catalysts because they are readily accessible in an enantiomeric purity in a few steps from natural precursors, *i.e.* α -amino acids^{1,2}. However amino indanol, although has been widely applied in the asymmetric reduction of prochiral ketones to secondary alcohols³, has rarely been used as catalysts in the enantioselective addition of dialkylzinc to aldehydes⁴. In this paper, we report the syntheses of *trans*-(1*S*,2*S*)-1-substituted-2-(*N,N*-dialkylamino)-1-indanol derivatives⁵ **1-6** (Scheme 1) and initial results on the catalytic activity of these chiral catalysts in the enantioselective addition of diethylzinc to aldehydes (Table 1).

L-Phenylalanine was first protected as *L*-*N*-ethoxycarbonyl-phenylalanine with ethyl chloroformate in quantitative yield. The ethoxycarbonyl derivative was transformed to acid chloride by PCl₅, followed by Friedel-Crafts cyclization to give (*S*)-2-[(ethoxycarbonyl)amino]-1-indanone **7**⁶. The key intermediate **7** was converted by Grignard reagents to *trans*-(1*S*,2*S*)-1-substituted-2-[(*N*-ethoxycarbonyl)amino]-1-indanol **8-10**. The configurations of **8-10** were determined by NMR techniques; specifically, NOE was not observed between H-2 and R¹ (R¹=CH₃) (Figure 1). Accordingly, the (1*S*,2*S*)-configuration was deduced. **8-10** were then deprotected with KOH/C₂H₅OH solution to produce **11-13**, alkylated by iodoethane or 1-iodobutane to

*E-Mail: nintzhang@hz163.net

give *trans*-(1*S*,2*S*)-1-substituted-2-(*N,N*-dialkylamino)-1-indanol **1-6**⁵.

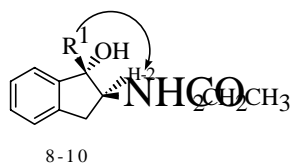
Scheme 1



Reagents and conditions: a) CH₃CH₂OCOC/MeOH, 0°C, 1 h, 100% yield; b) PCl₅, 0°C, 1 h, 100% yield; c) AlCl₃, 0°C, 2 h, 61% yield; d) R¹MgX/ether, rt, 10 h, 53-57% yield; e) KOH/C₂H₅OH, reflux, 4 h, 94-98% yield; f) R²I, K₂CO₃, reflux, 12 h, 37-85% yield.

Figure 1

not observed



The results indicated that the chiral *trans*-(1*S*,2*S*)-1-substituted-2-(*N,N*-dialkylamino)-1-indanol derivatives **1-6** catalyze efficiently the addition of diethylzinc to benzaldehyde and afforded 1-phenyl-1-propanol in high yields with good enantiomeric excesses (entries 1-6). The enantioselectivity of the reaction is very sensitive to the structure of chiral catalyst. The enhancement of the bulkiness of substituents on the nitrogen-atom induced an increasing of the enantioselectivity (entries 1 vs 4, or 2 vs 5, or 3 vs 6). Anymore, the enantioselectivity also increased with the increasing bulkiness of substituents on hydroxy-bearing carbon (entries 1-3 vs 4-6) and with the chiral ligand **6**, which has bulkiness substituents both on nitrogen atom and hydroxy-bearing carbon, gave the best reactivity and enantioselectivity. When chiral ligand **6** was used as catalyst in the enantioselective addition of diethylzinc to various aldehydes, high enantioselectivities were generally obtained for aromatic aldehydes (entries 6-15) except for 4-pyridinecarboxaldehyde, which gave much low enantiomeric excess (entries 16). For this substrate, the nitrogen atom on heterocyclic ring and its corresponding addition product, *sec*-alcohol, might promote the non-enantioselective ethylation reaction of 4-pyridinecarboxaldehyde with diethylzinc. It then reduced the overall enantioselectivity⁷. A reasonably enantioselective (45.4~58.2% e.e.) addition products were obtained for aliphatic aldehydes (entries 17-20).

Table 1 The enantioselective addition of diethylzinc to aldehydes^a

Entry	Substrate	Catalyst	Yield (%) ^b	E.e. (%) (Config.) ^c
1	Benzaldehyde	1	91	81.9 (R)
2	Benzaldehyde	2	94	78.9 (R)
3	Benzaldehyde	3	89	90.7 (R)
4	Benzaldehyde	4	87	88.5 (R)
5	Benzaldehyde	5	90	88.2 (R)
6	Benzaldehyde	6	90	93.1 (R)
7	<i>p</i> -Anisaldehyde	6	91	89.7 (R)
8	<i>o</i> -Chlorobenzaldehyde	6	90	90.6 (R)
9	<i>p</i> -Chlorobenzaldehyde	6	90	86.2 (R)
10	<i>p</i> -Tolualdehyde	6	83	92.3 (R)
11	3,4-Dimethoxybenzaldehyde	6	96	83.0 (R) ^d
12	1-Naphthaldehyde	6	91	86.7 (R) ^d
13	2-Naphthaldehyde	6	95	84.1 (R) ^d
14	<i>p</i> -Morphinobenzaldehyde	6	90	87.6 (R) ^d
15	4-(Dimethylamino) benzaldehyde	6	94	76.4 (R) ^d
16	4-Pyridinecarboxaldehyde	6	79	8.2 (R) ^d
17	<i>trans</i> -Cinnamaldehyde	6	93	45.4 (R) ^d
18	Dodecylaldehyde	6	80	55.8 (R) ^e
19	Nonylaldehyde	6	77	50.2 (R) ^e
20	Cyclohexanecarboxaldehyde	6	86	58.2 (R) ^e

a) The reactions were carried out in toluene/hexane (v/v, 1/4) at 0°C with 20 % mol chiral ligand, ZnEt₂/aldehyde = 10.0/5.0 (mmol). b) Based on isolated product. c) Except as noted, the e.e. values were determined by GLC with Chrompack CP-Chirasil-DEX CB capillary column and the configurations were determined by comparison the specific rotation with known compounds. d) The e.e. values were determined by HPLC with a Chiralcel-OD column. e) The e.e. values were determined by GLC after acetylation.

In conclusion, we have demonstrated that ligands **1-6** were efficient chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde and chiral ligand **6**, which has bulkiness substituents both on hydroxy-bearing carbon and nitrogen atom, gives the best enantiomeric excess. This chiral ligand promoted the ethylation with good enantioselectivities for a number of aromatic aldehydes and with reasonable enantioselectivities for aliphatic aldehydes.

References and Notes

- For review see: R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, **1994**, pp. 255-297.
- a) Q. Xu, G. Wang, X. Pan, A. S. C. Chan, *Tetrahedron: Asymmetry*, **2001**, *12*, 381; b) Q. Xu, H. Wang, X. Pan, A. S. C. Chan, T. K. Yang, *Tetra. Lett.*, **2001**, *42*, 6171.
- a) A. K. Ghosh, S. Fidanze, C. H. Senanayake, *Synthesis*, **1998**, 937; b) Y. Hong, Y. Gao, X. Nie, C. M. Zepp, *Tetra. Lett.*, **1994**, *35*, 6631; c) R. Hett, C. H. Senanayake, S. A. Wald, *Tetra. Lett.*, **1998**, *39*, 1705; d) B. Kaptein, H. Elsenberg, A. J. Minnaard, Q. B. Broxterman, L. A. Hulshof, J. Koek, T. R. Vries, *Tetrahedron: Asymmetry*, **1999**, *10*, 1413; e) M. P. Sibi, G. R.

- Cook, P. Liu, *Tetra. Lett.*, **1999**, *40*, 2477; f) S. Jones, J. C. C. Atherton, *Tetrahedron: Asymmetry*, **2000**, *11*, 4543.
- a) B. D. Simone, D. Savoia, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron: Asymmetry*, **1995**, *6*, 301; b) L. Sola, A. Vidal-Ferran, A. Moyano, M. A. Pericas, A. Rier, *Tetrahedron: Asymmetry*, **1997**, *8*, 1559.
 - Compound **1**: white solid, Mp. 63~64°C; $[\alpha]_{\text{D}}^{20} = +34.6$ (c 0.55, CH₃OH); ¹H NMR (400 MHz, DMSO-⁶d): 1.00 (t, 6H, *J* = 7.2 Hz), 1.27 (s, 3H), 2.67 (dd, 1H, *J* = 10.2, 14.9 Hz), 2.76 (m, 2H), 2.94 (m, 3H), 3.24 (dd, 1H, *J* = 7.4, 10.2 Hz), 7.12-7.29 (m, 4H); ¹³C NMR (DMSO-⁶d): 10.94, 23.32, 34.98, 43.84, 73.29, 82.92, 123.19, 124.95, 127.35, 127.98, 138.62, 151.24. Compound **2**: pale yellow liquid, $[\alpha]_{\text{D}}^{20} = +35.8$ (c 0.53, CH₃OH); ¹H NMR (400 MHz, DMSO-⁶d): 0.86-1.01 (m, 9H), 1.57 (m, 1H), 1.84 (m, 1H), 2.56 (dd, 1H, *J* = 9.8, 14.6 Hz), 2.76 (m, 2H), 2.92 (m, 3H), 3.26 (dd, 1H, *J* = 7.2, 9.8 Hz), 7.16-7.27 (m, 4H); ¹³C NMR (DMSO-⁶d): 8.01, 10.99, 28.04, 35.07, 44.02, 74.17, 85.14, 124.89, 125.08, 126.70, 128.04, 139.57, 148.87. Compound **3**: pale yellow liquid, $[\alpha]_{\text{D}}^{20} = -31.6$ (c 0.49, CH₃OH); ¹H NMR (400 MHz, DMSO-⁶d): 0.76 (t, 6H, *J* = 6.9 Hz), 2.34 (m, 2H), 2.57 (m, 2H), 2.86 (dd, 1H, *J* = 10.8, 15.4 Hz), 3.03 (dd, 1H, *J* = 7.2, 15.4 Hz), 3.70 (dd, 1H, *J* = 7.2, 10.8 Hz), 7.13-7.26 (m, 9H); ¹³C NMR (DMSO-⁶d): 12.35, 33.77, 44.43, 76.55, 86.53, 125.04, 125.25, 126.94, 127.78, 127.80, 127.85, 128.48, 140.63, 145.19, 149.83. Compound **4**: Pale yield liquid, $[\alpha]_{\text{D}}^{20} = +26.9$ (c 0.64, CH₃OH); ¹H NMR (400 MHz, DMSO-⁶d): 0.91 (t, 6H, *J* = 7.4 Hz), 1.27 (m, 7H), 1.44 (m, 4H), 2.67 (m, 2H), 2.80 (m, 3H), 2.93 (dd, 1H, *J* = 7.2, 14.9 Hz), 3.28 (dd, 1H, *J* = 7.2, 9.0 Hz), 7.12-7.34 (m, 4H); ¹³C NMR (DMSO-⁶d): 14.46, 21.34, 23.32, 29.00, 34.68, 51.38, 74.11, 82.92, 123.21, 125.02, 127.38, 128.03, 138.91, 151.28. Compound **5**: Pale yield liquid, $[\alpha]_{\text{D}}^{20} = +41.4$ (c 0.72, CH₃OH); ¹H NMR (400 MHz, DMSO-⁶d): 0.84-0.93 (m, 9H), 1.30 (m, 4H), 1.45-1.59 (m, 5H), 1.88 (m, 1H), 2.66 (m, 2H), 2.81 (m, 3H), 2.94 (dd, 1H, *J* = 7.3, 14.9 Hz), 3.31 (dd, 1H, *J* = 7.3, 10.1 Hz), 7.14-7.26 (m, 4H); ¹³C NMR (DMSO-⁶d): 8.01, 14.48, 21.35, 27.98, 28.89, 34.90, 51.42, 74.87, 85.11, 124.83, 125.05, 126.67, 127.99, 130.64, 148.86. Compound **6**: Pale yellow liquid, $[\alpha]_{\text{D}}^{20} = -21.2$ (c 0.64, CH₃OH); ¹H NMR (400 MHz, DMSO-⁶d): 0.76 (t, 6H, *J* = 7.3 Hz), 1.07 (m, 4H), 1.24 (m, 4H), 2.21 (m, 2H), 2.41 (m, 2H), 2.91 (dd, 1H, *J* = 10.1, 15.5 Hz), 2.99 (dd, 1H, *J* = 7.6, 15.5 Hz), 3.72 (dd, 1H, *J* = 7.6, 10.1 Hz), 7.15-7.27 (m, 9H); ¹³C NMR (DMSO-⁶d): 14.37, 21.07, 29.23, 30.48, 51.79, 76.93, 86.20, 125.06, 125.28, 127.00, 127.79, 127.98, 128.47, 140.77, 145.22, 149.73.
 - a) D. E. McClure, B. H. Arison, J. H. Jones, J. J. Baldwin, *J. Org. Chem.*, **1981**, *46*, 2431; b) D. E. McClure, P. K. Lumma, B. H. Arison, J. H. Jones, J. J. Baldwin, *J. Org. Chem.*, **1983**, *48*, 2675.
 - a) S. J. Li, Y. Z. Jiang, A. Q. Mi, G. Yang, *J. Chem. Soc., Chem. Commun.*, **1993**, 885; b) K. Ding; A. Ishii, K. Mikami, *Angew. Chem., Int. Ed. Engl.*, **1999**, *38*, 497; c) H. C. Zhang, F. Xue, T. C. W. Mak, K. S. Chan, *J. Org. Chem.*, **1996**, *61*, 8002.

Received 10 January, 2002