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Synthesis of C_2-symmetrical bis-β-amino alcohols and their application in the enantioselective addition of diethylzinc to aldehydes

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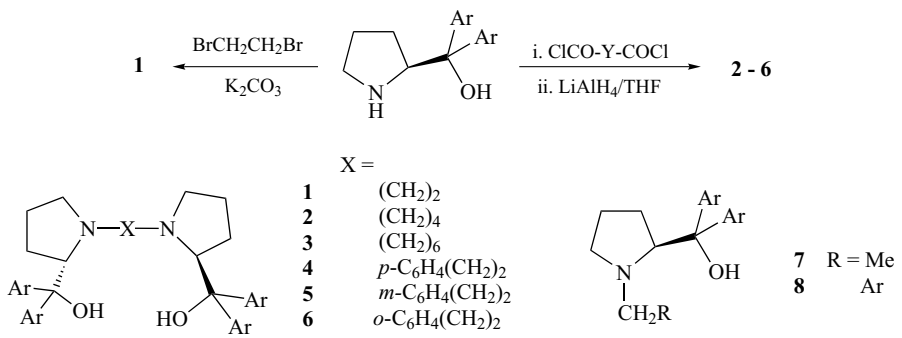
Abstract—The C_2-symmetrical bis-β-amino alcohols **1**–**6** were prepared and especially attention is focused on bridges, which link the two β-amino alcohol units. These ligands have been applied as chiral catalysts in the asymmetric addition of diethylzinc to aldehydes. *sec*-Alcohols have been obtained in good yields with up to 95.4% enantiomeric excess.

Enantioselective addition of organometallic reagents to carbonyl compounds is one of the most efficient methods for generating optically active secondary alcohols.[1] Among the possible reactions, catalytic enantioselective addition of dialkylzinc to aldehydes has attracted much attention.[2] A wide variety of chiral catalysts, i.e. amino alcohols,[3] diamines,[4] disulfonamides,[5] and diols[6] have been used successfully to promote the enantioselective alkylation. Among them, β-amino alcohols are the most often used chiral auxiliaries. Since it was reported that the presence of C_2 axis within a chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing diastereomeric transition states,[7] many C_2-symmetrical auxiliaries have been synthesized and applied in the catalytic enantioselective reaction.[4–6] However, to our knowledge, there are few C_2-symmetrical bis-β-amino alcohols being studied so far.[8] Here, we report easily available and efficient C_2-symmetrical bis-β-amino alcohols for the asymmetric addition of diethylzinc to aldehydes.

C_2-Symmetrical bis-β-amino alcohol **1**[9] was obtained by dimerization of L-prolinol[10] via 1,2-dibromoethane/potassium carbonate in dry acetonitrile[8a] (Scheme 1) and C_2-symmetrical bis-β-amino alcohols **2**–**6**[11] were



Scheme 1. Synthesis of chiral ligands **1**–**8**.

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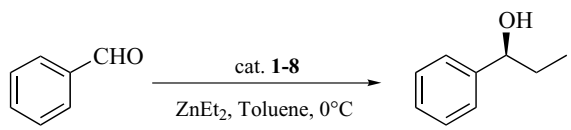
prepared from chloride of dibasic acids in benzene to give diamides followed by reduction with $LiAlH_4$ in THF. In order to compare the effect of asymmetric induction, 'monomeric' β-amino alcohol analogous **7**[11] and **8**[10] were synthesized in a manner similar to that for the synthesis of ligands **2**–**6**. The catalytic asymmetric addition of diethylzinc to the model substrate benzaldehyde was first investigated in toluene at 0°C and the results are summarized in Table 1.

As can be seen from the results, (*S*)-1-phenylpropanol is preferentially obtained with catalysts **1**–**8** in 87–95% yields and the enantiomeric excesses vary from 2.9 to 95.4%. Interestingly, for corresponding alkylene-bridged C_2-symmetrical bis-β-amino alcohols **1**–**3**, the enantioselectivities decrease when compared with their 'monomeric' β-amino alcohol analogous **7** (entries 1–5 via 11). On the other hand, for xylylene-bridged C_2-symmetrical bis-β-amino alcohols, enantioselectivities increase for ligand **6** and decrease for ligands **4** and **5** when compared with their 'monomeric' β-amino alcohol analogous **8** (entries 6–10 via 12). It was expected that chiral ligands **3** and **4**, which have longer bridges, give high enantioselectivities, because the two β-amino alcohol groups have less interaction and act as two 'monomeric' β-amino alcohol independently. However, it is chiral ligand **6**, which has a much crowd structure, to give better enantioselectivity. Thus, a sterically more demanding structure in C_2-symmetrical bis-β-amino alcohol seems to be crucial for enhancing the enantioselectivity of catalytic asymmetric addition of diethylzinc to aldehydes. Anymore, by varying the catalysts' loading of **1** and **6**, there is no effect both on the yields and enantioselectivities in the studying range (entries 1–3 and 8–10).

With chiral ligand **6** being the best catalyst, a few other representative aldehydes have also been investigated in the enantioselective addition reaction by using 2.5% mol of the ligand **6** and the results are summarized in Table 2. Chemical yields of the *sec*-alcohols were good and enantioselectivities were all lower than benzaldehyde with (*S*)-configuration products (entries 1–8). In the case of *trans*-cinnamaldehyde and aliphatic aldehydes, although the yields were still high, selectivities were moderate (entries 9–11).

In conclusion, we have successfully synthesized six C_2-symmetric bis-β-amino alcohols and the more crowd chiral ligand **6** is the most efficient catalyst in these series when they were applied in the enantioselective addition of diethylzinc to aldehydes. Enantiomeric excess of up to 95.4% was observed with good yield. Elucidation of the mechanism and further application of these ligands in other catalytic asymmetric reactions are in progress.

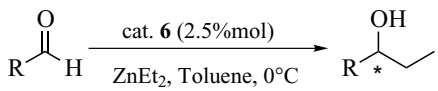
Table 1. Enantioselective addition of diethylzinc to benzaldehyde promoted by chiral ligands **1**–**8**[a]



Entry	Ligand (mol%)	Yield (%)[b]	E.e. (%) (config.)[c]
1	**1** (2.5)	87	64.9 (*S*)
2	**1** (5.0)	86	57.3 (*S*)
3	**1** (10.0)	89	60.0 (*S*)
4	**2** (2.5)	92	57.8 (*S*)
5	**3** (2.5)	89	60.1 (*S*)
6	**4** (2.5)	87	28.6 (*S*)
7	**5** (2.5)	88	2.9 (*S*)
8	**6** (2.5)	92	94.7 (*S*)
9	**6** (5.0)	95	95.2 (*S*)
10	**6** (10.0)	93	95.4 (*S*)
11	**7** (5.0)	88	87.0 (*S*)
12	**8** (5.0)	89	39.9 (*S*)

[a] The reactions were carried out in toluene at 0°C. Benzaldehyde/$ZnEt_2$ = 5.0/10.0 (mmol).
[b] Based on isolated product.
[c] The e.e. values were determined by GC with Chrompack CP-Chirasil-DEX CB capillary column and the configuration was determined by comparison of the sign of the specific rotation with the known compound.

Table 2. The enantioselective addition of diethylzinc to aldehydes catalyzed by **6**[a]



Entry	Substrate	Yield (%)[b]	E.e. (%) (config.)[c]
1	Benzaldehyde	92	94.7 (*S*)
2	*o*-Anisaldehyde	89	89.7 (*S*)
3	*p*-Anisaldehyde	79	84.3 (*S*)
4	*o*-Chlorobenzaldehyde	90	85.0 (*S*)
5	*p*-Chlorobenzaldehyde	81	82.3 (*S*)
6	3,4-Dimethoxybenzaldehyde	78	83.3 (*S*)[d]
7	1-Naphthaldehyde	81	85.0 (*S*)[d]
8	2-Naphthaldehyde	83	86.7 (*S*)[d]
9	*trans*-Cinnamaldehyde	79	63.3 (*S*)[d]
10	Dodecylaldehyde	83	59.8 (*S*)[e]
11	Cyclohexanecarboxaldehyde	86	65.0 (*S*)[e]

[a] The reaction were carried out in toluene at 0°C with **6**:aldehyde:diethylzinc = 0.125:5.0:10.0 (mmol).
[b] Based on isolated yield.
[c] Except as note, the e.e. values were determined by GC with Chrompack CP-Chirasil-DEX CB capillary column and the configurations were determined by comparison of the sign of the specific rotation with the known compounds.
[d] Determined by HPLC with a Chiralcel-OD column from Daicel with hexane/2-propanol as eluent.
[e] Determined by GC with Chrompack CP-Chirasil-DEX CB capillary column after acetylation.

References

1. (a) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp. 255–297; (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49; (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
2. (a) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605; (b) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.
3. (a) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293; (b) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108.
4. (a) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717; (b) Pini, D.; Mastantuono, A.; Uccello-Barretta, G.; Iuliano, A.; Salvadori, P. *Tetrahedron* **1993**, *49*, 9613; (c) Rosini, C.; Franzini, L.; Luliano, A.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **1991**, *2*, 363.
5. (a) Paquette, L. A.; Zhou, R.-J. *J. Org. Chem.* **1999**, *64*, 7929; (b) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657.
6. (a) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957; (b) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651.
7. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
8. (a) Wassmann, S.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4437; (b) Bastin, S.; Delebecque, N.; Agbossou, F.; Brocard, J.; Pelinski, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1647; (c) Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1409; (d) Soai, K.; Nishi, M.; Lto, Y. *Chem. Lett.* **1987**, 2405; (e) Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523.
9. Compound **1**: Mp 174–175°C; $[\alpha]_D^{20} = -5.6$ (*c* 1.05, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.38–1.62 (m, 6H), 1.65–1.70 (m, 2H), 1.72–1.97 (m, 4H), 2.16–2.22 (m, 2H), 2.32–2.39 (m, 2H), 3.69–3.75 (dd, $J = 9.4$, 4.8 Hz, 2H), 4.75–4.90 (br, 2H), 7.08–7.32 (m, 12H), 7.48–7.53 (m, 4H), 7.64–7.68 (m, 4H).
10. Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.* **1988**, *97*, 691.
11. Compound **2**: Mp 163–164°C; $[\alpha]_D^{20} = +7.0$ (*c* 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.61–0.98 (m, 4H), 1.55–1.70 (m, 8H), 1.80–1.92 (m, 4H), 2.24–2.32 (m, 2H), 3.05–3.14 (m, 2H), 3.68–3.74 (dd, $J = 9.4$, 4.8 Hz, 2H), 4.6–5.0 (br, 2H), 7.11–7.31 (m, 12H), 7.50–7.59 (m, 8H). Compound **3**: Mp 127–128°C; $[\alpha]_D^{20} = +12.6$ (*c* 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.59–0.75 (m, 4H), 1.02–1.15 (m, 4H), 1.61–1.68 (m, 6H), 1.77–1.95 (m, 6H), 2.28–2.36 (m, 2H), 3.16–3.21 (m, 2H), 3.73–3.79 (dd, $J = 9.4$, 4.8 Hz, 2H), 4.94 (br, 2H), 7.06–7.31 (m, 12H), 7.51–7.61 (m, 8H). Compound **4**: Mp 226–227°C; $[\alpha]_D^{20} = +25.6$ (*c* 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.60–1.68 (m, 4H), 1.74–1.81 (m, 2H), 1.93–2.01 (m, 2H), 2.31–2.37 (m, 2H), 2.87–2.91 (m, 2H), 2.98, 3.17 (AB system, $J = 12.5$ Hz, 4H), 3.96–3.99 (dd, $J = 9.4$, 4.8 Hz, 2H), 4.95 (br, 2H), 6.93 (s, 4H), 7.11–7.21 (m, 4H), 7.28–7.34 (m, 8H), 7.60–7.74 (m, 8H). Compound **5**: Mp 170–171°C; $[\alpha]_D^{20} = +18.8$ (*c* 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.58–1.68 (m, 4H), 1.73–1.80 (m, 2H), 1.92–2.00 (m, 2H), 2.27–2.40 (m, 2H), 2.83–2.88 (m, 2H), 2.95, 3.16 (AB system, $J = 12.6$ Hz, 4H), 3.95–4.02 (dd, $J = 9.4$, 4.8 Hz, 2H), 4.95 (br, 2H), 7.05–7.37 (m, 16H), 7.54–7.71 (m, 8H). Compound **6**: Mp 110–112°C; $[\alpha]_D^{20} = +4.5$ (*c* 0.53, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.60–1.68 (m, 4H), 1.70–1.80 (m, 2H), 1.92–2.06 (m, 2H), 2.18–2.30 (m, 2H), 2.73–2.80 (m, 2H), 2.95, 3.08 (AB system, $J = 12.6$ Hz, 4H), 3.96–4.00 (dd, $J = 9.4$, 4.8 Hz, 2H), 4.80 (br, 2H), 7.05–7.37 (m, 16H), 7.54–7.71 (m, 8H). Compound **7**: Mp 78–79°C; $[\alpha]_D^{20} = +6.3$ (*c* 0.64, CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.78 (t, $J = 7.2$ Hz, 3H), 1.62–1.76 (m, 3H), 1.84–2.08 (m, 3H), 2.33–2.45 (m, 1H), 3.17–3.27 (m, 1H), 3.76–3.80 (dd, $J = 9.2$, 4.8 Hz, 1H), 4.70–5.15 (br, 1H), 7.11–7.32 (m, 6H), 7.52–7.62 (m, 4H).