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Reversal of enantioselectivity using catalysts containing multiple stereogenic centres

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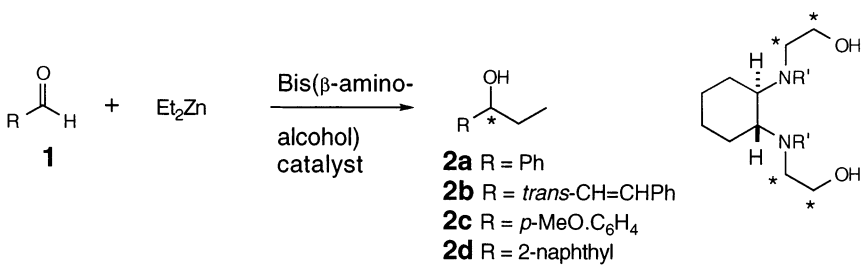
Abstract—*N*-Methylation of ligands with multiple stereogenic centres is shown to provide the product of the opposite configuration in significant enantiomeric excess (e.e.), in the addition of diethylzinc to aldehydes. The catalysts possess stereogenic centres appended to a *trans*-1,2-cyclohexanediamine core. © 2001 Elsevier Science Ltd. All rights reserved.

Catalytic asymmetric formation of carbon–carbon bonds is a field of major contemporary interest in organic synthesis.[1] Within this area, the addition of diethylzinc to aldehydes[2] provides a yardstick for the efficiency and enantioselectivity of a catalyst, since the rate of the reaction in the absence of a catalyst is low and catalytic effects can be substantial.[3,4] The β-amino alcohol moiety has been extensively studied as a ligand in the asymmetric addition of dialkylzinc reagents to carbonyl compounds,[2b,4,5] and mechanistic features have been thoroughly investigated.[4] Such asymmetric additions to carbonyl compounds have also used the well studied *trans*-1,2-cyclohexanediamine systems as catalysts.[6] We sought to develop new catalysts that include both a *trans*-1,2-diaminocyclohexyl subunit and vicinal β-amino alcohol moieties, partly because few ligands capable of tetradentate coordination are known. These ligands possess an extended array of up to six stereogenic centres (Scheme 1) and the predominant enantioselection they induce is shown to be reversed upon *N*-methylation.[7]

The bis(β-aminoalcohol) catalysts were synthesised according to Scheme 2. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane[8] was dialkylated with 2-bromoethanol (water, reflux, 12 hours) to give **4a** (30%),[9] which was *N*,*N*′-dimethylated using HCHO–HCOOH in an Eschweiler–Clarke procedure,[10] but in the presence of the hydrogen donor sodium formate[11] to give **4b** (95%). That route provided the unadorned basic ligand. Ligands **5** and **7** (56 and 50%, respectively), possessing additional stereogenic centres, were prepared by activation of the requisite enantiomer of mandelic acid with DCC in the presence of *N*-hydroxysuccinimide and then reaction with **3**.[12] Reduction[13] of amides **5** and **7** gave the secondary amines **6a** (32%) and **8a** (25%), respectively, which were also subjected to Eschweiler–Clarke *N*,*N*′-dimethylation in the above manner to give the tertiary amines **6b** and **8b**[14] quantitatively. Lastly, systems with six stereogenic centres were obtained by heating **3** with cyclohexene oxide to give **9a** (30%), which was also reacted with HCHO–HCOOH in the presence of



Scheme 1. Extended polyheteroatomic chiral systems as enantioselective catalysts.

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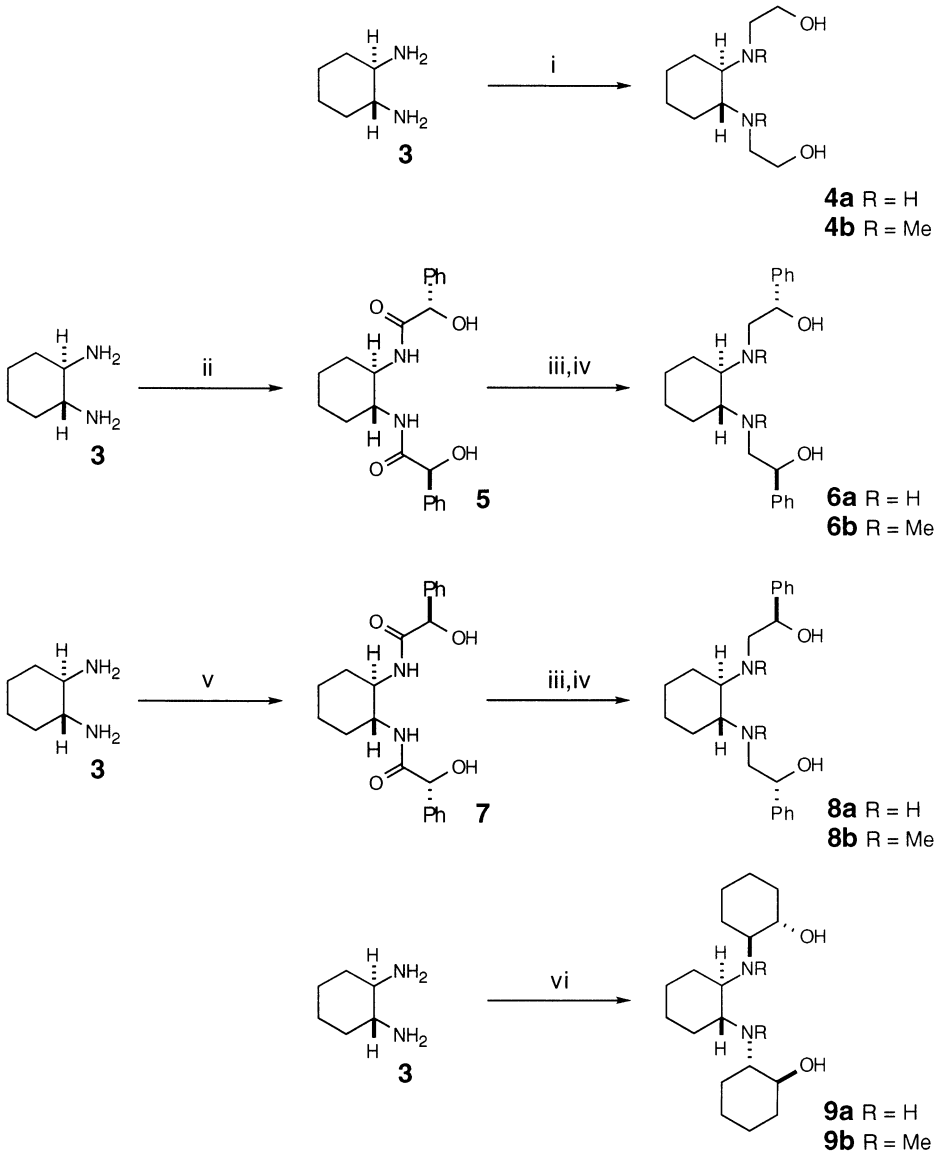

Scheme 2. Synthesis of *trans*-1,2-diaminocyclohexane catalysts with extended chiral systems. *Reagents*: (i) 2-bromoethanol (2 mol equiv.), reflux in water; (ii) (*S*)-(+)-mandelic acid, DCC (2.5 mol equiv.), *N*-hydroxysuccinimide (2.5 mol equiv.), THF; (iii) $Me_2S{\cdot}BH_3$ (3.3 mol equiv.), $Et_2O{\cdot}BF_3$ (4 mol equiv.), THF; (iv) 37% HCHO (2 mol equiv.), 90% HCOOH (3 mol equiv.); (v) (*R*)-(−)-mandelic acid, DCC (2.5 mol equiv.), *N*-hydroxysuccinimide (2.5 mol equiv.), THF; (vi) cyclohexene oxide (3 mol equiv.), EtOH, reflux.

sodium formate to give the corresponding tertiary amine **9b** quantitatively.

Only the racemic **9a** has been prepared previously, and the relative configuration was established by X-ray crystallography.[15] We also obtained only a single diastereoisomer[16] from the reaction of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane with cyclohexene oxide, as had been found in a previous study using the racemic diamine.[15] Such directed stereochemical control during the reaction, undoubtedly assisted by hydrogen bonding networks, has features in common with adducts formed from the co-crystallisation of enantiopure 1,2-diaminocyclohexane with cyclohexane-1,2-diols.[17]

While *N*,*N*-dimethylation can lead to reversal of enantioselectivity,[18] previous work has described only low e.e.'s with the secondary amine ligands.[18,19] Thus, it is noteworthy that the secondary amine catalyst **9a** affords 80% e.e. (Table 1, entry 5). While the *N*-methylated catalysts **6b**, **8b** and **9b** all give greater amounts of (*S*)-1-phenylpropan-1-ol, the effect is greatest with **9b**, a catalyst with six stereogenic centres. However, with **9b** and 2-naphthaldehyde, there was no detectable yield of the aryl alcohol, presumably because of steric hindrance of approach to the catalyst. With a *trans*-1,2-diaminocyclohexane as part of a salen ligand, e.e.'s of 30–70% were obtained for the addition of diethylzinc to benzaldehyde;[20] our ligands **9** compare favourably, and show that systems based on a *trans*-1,2-diaminocyclohexane, but with extended chirality, can deliver significantly high e.e.'s in the enantioselective addition to carbonyl compounds. In contrast, the amines **4a** and **4b**, lacking additional chirality, did not give satisfactory

Table 1. Reaction of aldehydes with diethylzinc in toluene[a]

Entry	Ligand	Aldehyde	Temp. (°C)	Yield (%)[b]	E.e. (%)[c]	Configuration
1	**6a**	PhCHO	−30	40	23	(*R*)
2	**6b**	PhCHO	−30	55	54	(*S*)
3	**8a**	PhCHO	−30	42	45	(*S*)
4	**8b**	PhCHO	−30	51	16	(*R*)
5	**9a**	PhCHO	−30	50	80	(*R*)
6	**9b**	PhCHO	−30	25	92	(*S*)
7	**9a**	PhCHO	0	99	64	(*R*)
8	**9b**	PhCHO	0	68	75	(*S*)
9	**9a**	*p*-MeO·C_6H_4CHO	−30	74	56	(*R*)
10	**9b**	*p*-MeO·C_6H_4CHO	−30	18	52	(*S*)
11	**9a**	2-Naphthaldehyde	0	95	60	(*R*)

[a] The *trans*-1,2-diaminocyclohexane ligand (10 mol%), and 2.2 equiv. of diethylzinc were used. Reactions were maintained at −30 or 0°C for 4 h, then allowed to warm to 20°C over a subsequent period of 12 h.
[b] Yields were determined by ^{1}H NMR spectroscopy.
[c] The absolute configurations of the alcohols were determined using a Chiralcel OD column.[21]

results (**4a** gave 30% of **2a** in 8% e.e., but **4b** gave no **2a**).

In asymmetric additions to aldehydes, the nature of the *N*-substituent can substantially affect the enantioselectivities. Thus, depending on the nature of the dialkyl substituent, *N*,*N*-dialkylnorephedrine derivatives afforded (*S*)-5-methylhexan-3-ol in e.e.s of 53–83%.[4b] However, no reversal of e.e. was noted and a tertiary amine was needed, as is often the case. The absolute configurations obtained with catalysts **9a** and **9b**, as well as the fact that **9b** favours the (*S*)-configuration of 1-arylpropan-1-ol (compared with **9a**) can be accounted for by a model in which the aldehyde presents to the pocket of the catalyst defined by the flanking wall of the aminocyclohexanol ring and the basal plane that includes two zinc and two oxygen atoms. Interaction of the carbonyl group of the aldehyde with the zinc atom coordinated to the diamine unit prior to alkyl transfer from the other zinc atom (presumed to be bound to the two oxygen atoms) has been previously postulated.[2a,22] For **9a**, the NH group is sufficiently small to allow the aryl ring to reside nearby, leading to the attack of the *Re*-face of the aldehyde. Conversely, for **9b**, the bulk of the *N*-methyl group is presumed to be sufficient to hinder location of the aryl group as above, thereby leading to addition to the *Si*-face and predominantly the (*S*)-1-arylpropan-1-ol. However, further investigations are needed before these tentative proposals can be fully substantiated.

These results show that introduction of new stereogenic centres at the β-amino alcohol carbon atoms of **4** can lead to improved e.e.s in the addition of Et_2Zn to aldehydes. A cyclohexane backbone, as in **9**, gave the highest e.e.s of those catalysts studied, as well as affording the products with the opposite configuration in high e.e., simply by *N*,*N*′-dimethylation of the ligand.[23]

Acknowledgements

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References

1. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994; (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388–401.
2. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188; (d) Ref. 1a pp. 260–278.
3. (a) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841; (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
4. (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; (b) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264–4268.
5. Jian, L. S.; Yaozhong, J.; Aiqiao, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1467–1474.
6. Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195.
7. The *N*-benzyl analogues of ligands **6b** and **8b** were shown to give (*R*)-2-phenylcyclohexanone in 41 and 2% e.e., respectively, when used in the enantioselective protonation of the samarium enolate: Mikami, K.; Yamaoka, M.; Yoshida, A.; Nakamura, Y.; Takeuchi, S.; Ohgo, Y. *Synlett* **1998**, 607–608. Those examples employing stoichiometric amounts of ligand appear to be the other use of the ligands described in the present catalytic asymmetric study.
8. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane was obtained by resolution using L-(+)-tartaric acid according to: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939–1942.
9. Atoh, M.; Sørensen, H. O.; Andersen, P. *Acta Chem. Scand.* **1997**, *51*, 1169–1177.
10. Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829–832.

11. (a) Cantarelli, G. *Farmaco Ed. Sci.* **1970**, 248–252; (b) Rajagopal, S.; Spatola, A. F. *J. Org. Chem.* **1995**, *60*, 1347–1355.
12. All compounds gave satisfactory spectral data (^{1}H and ^{13}C NMR, IR and MS), and all new compounds gave satisfactory analytical data or HRMS. Procedures for acylation of **3** with (*R*)- and (*S*)-mandelic acid were adapted from: Ho, P. T.; Ngu, K. *J. Org. Chem.* **1993**, *58*, 2313–2316.
13. Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 996–997.
14. For a synthesis of **8b** using (*R*)-(+)-styrene oxide, see: Cross, R. J.; Farrugia, L. J.; Newman, P. D.; Peacock, R. D.; Stirling, D. *Inorg. Chem.* **1999**, *38*, 1186–1192.
15. De Sousa, A. S.; Hancock, R. D.; Reibenspies, J. H. *J. Chem. Soc., Dalton Trans.* **1997**, 2831–2835.
16. **(1*R*,2*R*)-*N*,*N*′-Bis((3*S*,4*S*)-4-hydroxycyclohexyl)-*trans*-1,2-diaminocyclohexane 9a**. To a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.80 g, 42.0 mmol) in anhydrous ethanol (100 mL) under an inert atmosphere at 20°C was added cyclohexene oxide (17.3 mL, 171 mmol) via a pressure-equalising dropping funnel over a period of 20 min. Upon complete addition, the mixture was heated under reflux for 16 h. After this time, the pale yellow solution was allowed to cool to 20°C, whereupon the solvent was evaporated to give a brown oil that was acidified to pH 2 with 2 M aqueous hydrochloric acid and the aqueous layer extracted with chloroform (2×50 mL) which was discarded. The aqueous layer was then basified to pH 11 with 2 M aqueous sodium hydroxide and the aqueous layer was again extracted with chloroform (2×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The resulting yellow–orange oil was subjected to purification by flash column chromatography, initially with methanol:chloroform (1:4 v/v), then followed by methanol:chloroform (1:19 v/v) to give a clear oil that was dissolved in hot petroleum ether (40–60°C). On cooling, small glassy needles deposited which were isolated and recrystallised from cyclohexane to give **9a** as small glassy needles (3.90 g, 30%), mp 129–130°C; IR (thin film) ν_{max} 3126, 2926, 2854, 1446, 1369, 1105 cm^{-1}; $[\alpha]_D$ = +11.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (2H, br, OH), 3.49 (2H, m, C_1HOH), 2.43 (2H, m, $C_{1'}HNH$), 2.29 (2H, m, C_2HNH), 2.01 (2H, m), 1.91 (2H, m), 1.67 (6H, m), 1.64 (2H, m), 1.30–1.18 (10H, m), 0.99 (2H, m), 0.65 (2H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 77.46, 65.58, 65.44, 35.25, 33.19, 32.57, 25.59, 25.46, 24.33. HRMS calcd for $C_{18}H_{35}N_2O_2$ (MH^+) 311.2699. Found: 311.2699. FAB MS (%) 311 (MH^+, 100), 196 (52), 115 (42). Anal. calcd for $C_{18}H_{34}N_2O_2$ C, 69.62; H, 11.04; N, 9.03. Found: C, 69.42; H, 11.14; N, 8.93%.
(1*R*,2*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis((3*S*,4*S*)-4-hydroxycyclohexyl)-*trans*-1,2-diaminocyclohexane 9b. Diamine **9a** (0.556 g, 1.80 mmol) was dissolved in formaldehyde (37% by wt, 4.0 mmol, 6.0 mL) and formic acid (96% v/v, 0.22 mol, 7.8 mL) and the resulting solution heated to 90°C. Sodium formate (7.40 mmol, 0.50 g) was then added in one portion and the resulting solution was stirred at 90°C for 16 h. After this time, the solution was cooled to 20°C and then basified, with cooling, to pH 12 with 2 M aqueous sodium hydroxide. The aqueous layer was washed with diethyl ether (3×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a clear oil (0.58 g, 95%) that required no further purification; $[\alpha]_D$ = +42.2 (*c* 0.53, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$, 300 MHz) δ 3.23 (2H, m, C_1HOH), 2.45 (2H, m, $C_{1'}HNH$), 2.30 (2H, m, C_2HNH), 2.09 (6H, s, CH_3), 2.02 (2H, m), 1.86 (2H, m), 1.75–1.63 (8H, m), 1.64–1.18 (12H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.59, 67.77, 66.55, 34.00, 29.31, 28.78, 27.80, 26.57, 26.33, 24.87. HRMS calcd for $C_{20}H_{38}N_2O_2$ (MH^+) 339.3012. Found: 339.3009. FAB MS (%) 339 (MH^+, 100), 210 (22), 112 (19).
17. Hanessian, S.; Simard, M.; Roelens, S. *J. Am. Chem. Soc.* **1995**, *117*, 7630–7645.
18. Kimura, K.; Sugiyama, E.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1992**, *33*, 3147–3150.
19. Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *Tetrahedron* **1995**, *51*, 165–172.
20. Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 4613–4616.
21. Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979–3984. Representative conditions for the addition of diethylzinc to aldehydes: (*S*)- and/or (*R*)-1-phenylpropan-1-ol **2**. Typical procedure. Ligand **9a** (0.06 g, 0.20 mmol, 10 mol%) was dissolved with stirring in freshly distilled toluene (9 mL) under an atmosphere of nitrogen at 20°C. Freshly distilled benzaldehyde (0.20 mL, 2.0 mmol) was then injected by syringe and the resulting solution stirred for 15 min. The mixture was then cooled to −30°C (cooling bath) and a solution of diethylzinc in toluene (1.1 M, 3.6 mL, 4 mmol) was injected by syringe, ensuring that the tip of the needle was below the surface of the solution. The mixture was stirred at −30°C for 16 h. Aqueous hydrochloric acid solution (1 M, 10 mL) was added slowly (CAUTION: vigorous reaction). The aqueous layer was extracted with diethyl ether (2×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a turbid oil that was further purified by flash column chromatography (ethyl acetate, petroleum ether 40–60°C, 3:17 v/v) to give a clear oil (0.135 mg, 50%). Enantiomeric excess was determined using a Chiracel OD column. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (5H, m, Ar-H), 4.56 (1H, t, *J* 7.3, C*H*OH), 2.43 (1H, br, OH), 1.78 (2H, m, CH_2), 1.43 (3H, t, *J* 7.3, CH_3).
22. Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5237–5240.
23. The 2-pyrrolidinylmethanol system provides a rare example of an NH catalyst being active (36% e.e.) *and* the corresponding (*N*-benzyl) tertiary amine affording predominantly the opposite enantiomer (82% e.e.): Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K. *Tetrahedron: Asymmetry* **1999**, *10*, 133–138.