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An Amino Alcohol Ligand for Highly Enantioselective Addition of Organozinc Reagents to Aldehydes: Serendipity Rules

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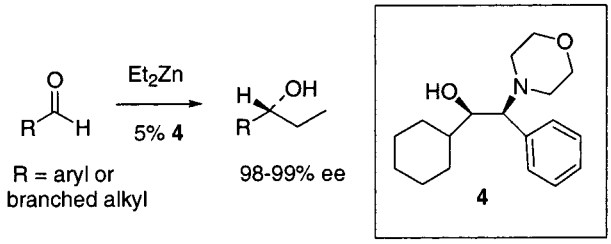
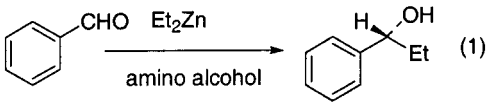
ABSTRACT



Amino alcohol 4 (or its enantiomer) is prepared in two simple steps. Commercial (1*R*,2*S*)-2-amino-1,2-diphenylethanol is dialkylated with bis(2-bromoethyl) ether. Subsequent hydrogenation over 5% Rh on alumina in the presence of morpholine unexpectedly stops at the hexahydro derivative 4. Amino alcohol 4 promotes the enantioselective addition of diethylzinc to aldehydes at room temperature in up to 99% enantiomeric excess.

The enantioselective addition of organozinc reagents to aldehydes[1] catalyzed by enantiopure β-amino alcohols remains the focus of much research activity as evidenced by hundreds of research papers and several comprehensive review articles.[2] Perhaps because of its archetypical nature—this transformation represents the enantioselective counterpart of the Grignard addition reaction[3]—it remains a favored testing ground for novel amino alcohol ligands.

Several years ago we reported[4] the use of parallel synthesis techniques to explore the structure−activity relationship of β-amino alcohol ligands in asymmetric catalysis. The reaction selected for study was the addition of diethylzinc to benzaldehyde (eq 1). Some relevant observations from that study



are shown in Figure 1. For the series of amino alcohols in our study, we found that a six-membered ring on nitrogen (piperidinyl or morpholinyl) in the tertiary amine substructure was optimal in all cases. As might be expected, both the N-terminal and O-terminal substituents play a significant role in controlling the enantioselectivity of eq 1. The prototypical "stripped down" ligand **1** provided virtually no enantioselectivity. Introduction of a phenyl group at the N-terminal position (ligand **2**) sharply increases enantioselectivity to 83% while sterically "inflating" the methyl group of **1** to the level of a cyclohexyl substituent (ligand **3**) increases the enantioselectivity to 67%. This led to the proposal that ligand **4**, which incorporates both of these structural features, might provide even higher ee values for eq 1.

(1) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
(2) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. Soai, K. Niwa, S. *Chem Rev.* **1992**, *92*, 833. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 5.
(3) Grignard, V. *C. R. Hebd. Sceances Acad. Sci.* **1900**, *130*, 1322.
(4) Nugent, W. A.; Licini, G.; Bonchio, M.; Bortolini, O.; Finn, M. G.; McClelland, B. W. *Pure Appl. Chem.* **1998**, *70*, 1071.

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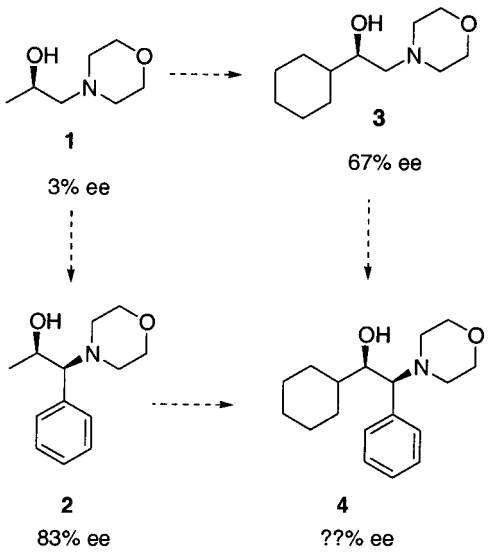
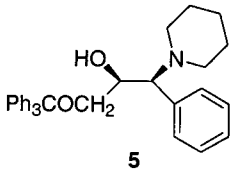


Figure 1. Observed enantioselectivity for addition of diethylzinc to benzaldehyde (eq 1) using a series of β-amino alcohols prepared in parallel synthesis studies.

This would be the case if we assume that the contributions from the O-terminal and N-terminal substituents are independent and additive. This concept was first applied to modular ligand design by Snapper and Hoveyda[5] who noted "The described strategy assumes that the influence of each ligand subunit is independent and additive: it is impossible to rule out cooperative effects without individually testing each combination".

In fact, the literature contains examples of ligands which share the flat/bulky structural motif with **4** and which provide high enantiomeric excesses in eq 1. A notable example is ligand **5** which was reported[6] by Pericas and co-workers to



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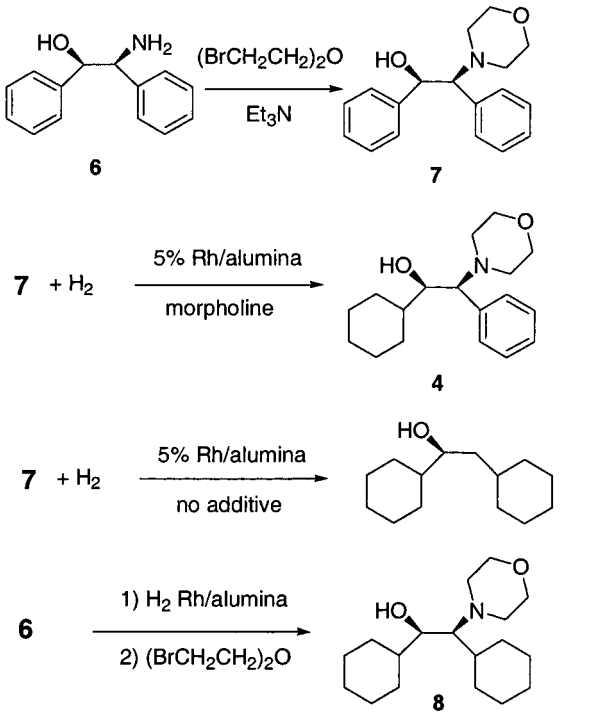
promote eq 1 at room temperature in 91% enantiomeric excess. The synthesis of **4** appeared complicated compared with known ligands such as **5** and was not pursued in our initial report. However, we have subsequently prepared **4** as a result of a "happy accident".

We previously described[4] the synthesis of amino alcohol **7** by reaction of morpholine with enantiopure stilbene oxide (90 °C, 7 d). More recently, we developed a faster route as shown in Scheme 1. Treatment of commercial (1*R*,2*S*)-2-amino-1,2-diphenylethanol with 2-bromoethyl ether in the

Scheme 1. Preparation of Amino Alcohol **4** and Its Fully Hydrogenated Analogue **8**



presence of triethylamine (DMSO, 25 °C) resulted in dialkylation of the amine nitrogen to afford (1*R*,2*S*)-**7** in 74% yield after crystallization from hot toluene. Attempted hydrogenation of both phenyl rings of **7** using 5% Rh/alumina catalyst (4% HOAc/MeOH, 25 °C, 60 psi) in the presence of morpholine (1 equiv) instead reproducibly afforded **4** (71% yield after crystallization from heptane). For details, see the Supporting Information.

In the absence of the morpholine additive, hydrogenation of **7** was sluggish. Complete conversion was achieved by raising the reaction temperature to 50 °C but the product was that derived from benzylic C−N cleavage, 1,2-dicyclohexylethanol. The fully saturated dicyclohexyl amino alcohol **8** could be prepared by reversing the order of the steps, i.e., hydrogenation of **6**[7] followed by dialkylation with 2-bromoethyl ether.

A sample of (1*S*,2*R*)-**4** was prepared in analogous fashion from (1*S*,2*R*)-**6**. An X-ray crystal structure (Figure 2) confirmed that hydrogenation had occurred at the O-terminal end, leaving the N-terminal phenyl ring intact.

Ligand **4** promotes the enantioselective addition of diethylzinc to benzaldehyde (eq 1). Using a 2-fold excess of diethylzinc in 2:1 hexane/toluene and 5% of **4** as ligand, the addition proceeded in 98% yield and 99% enantiomeric excess (ee) Under identical conditions, ligands **7** and **8** promoted eq 1 in 89% and 92% ee, respectively.

The addition of diethylzinc to a series of aldehydes using (1*R*,2*S*)-**4** as catalyst is summarized in Table 1. The reactions

(5) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A. Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668.

(6) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970.

(7) Complete hydrogenation of 2-amino-1,2-diphenylethanol to its dicyclohexyl analogue has been reported: Pankova, M.; Sicher, J. *Collect. Czech. Chem. Commun.* **1965**, *30*, 388.

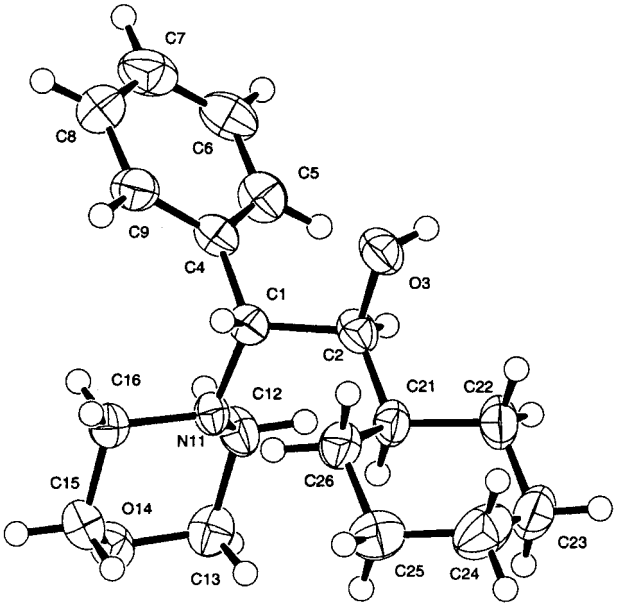


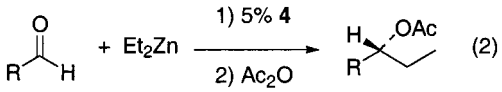
Figure 2. ORTEP diagram of amino alcohol (1*S*,2*R*)-**4** showing *erythro* structure and location of cyclohexyl substituent.

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

entry	aldehyde in eq 2	yield (%)[b]	ee (%)
1	benzaldehyde	98	99
2	*m*-tolualdehyde	97	99
3	*p*-tolualdehyde	96	98
4	*m*-anisaldehyde	97	98
5	*p*-fluorobenzaldehyde	98	99
6	*p*-chlorobenzaldehyde	97	98
7	isobutyraldehyde	93	98
8	2-ethylbutyraldehyde	91	99
9	cyclohexanecarboxaldehyde	93	98
10	trimethylacetaldehyde[c]	73	99
11	2,2-dimethyl-4-pentenal[c]	78	99
12	3-thiophenecarboxaldehyde	94	96
13	methacrolein	95	94
14	hexanal[d]	96	87

[a] All reactions contained aldehyde (3.0 mmol), Et_2Zn (6.0 mmol), amino alcohol (1*R*,2*S*)-**4** (0.15 mmol), and *tert*-butylbenzene as internal standard (300 μL) in 2:1 hexane−toluene (9 mL) at room temperature for 3 h except as indicated; for details, see the Supporting Information. [b] Yield and ee determined by gas chromatography on Cyclodex B stationary phase (J&W Scientific). [c] 24 h run at room temperature. [d] 3 h run at 0 °C.

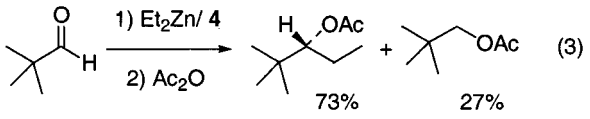
in Table 1 were quenched by addition of acetic anhydride (eq 2), which quantitatively converts the intermediate zinc



(2)

alkoxides to the corresponding acetate esters and allows direct analysis of the product mixtures by chiral capillary column gas chromatography.[8] As exemplified by entries 1−6, addition of diethylzinc to aromatic aldehydes proceeds in high yield and with enantioselectivities in the range 98% to 99% ee. Several α-branched aliphatic aldehydes (entries 7−11) also afforded the corresponding acetates in 98% to 99% ee.

The diminished yield in the case of the tertiary alkyl derivatives (entries 10 and 11) is the result of the ubiquitous competing reductive pathway shown in eq 3. This side reaction was intitially noted by Noyori and co-workers[9] for the case of diethylzinc addition to benzaldehyde. In our experience, detectable amounts of primary alcohols are always formed during the addition of organozinc reagents to aldehydes in the presence of β-amino alcohols. This pathway represents a significant side reaction in the case of sterically bulky aldehydes bearing tertiary alkyl substituents.



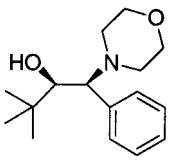
(3)

In an effort to identify the limitations of ligand **4**, we extended our studies to include a heterocyclic aldehyde (entry 12) and an α,β-unsaturated aldehyde[10] (entry 13); somewhat surprisingly, these additions still proceeded with synthetically useful enantiomeric excesses. Only in the case of a straight-chain aliphatic aldehyde (entry 14) did the ee drop below 90%.

To determine the absolute stereochemistry of eq 2, the product acetate esters were isolated in three cases where the sign of optical rotation for the product has been assigned. The products from benzaldehyde, hexanal, and cyclohexanecarboxaldehyde all exhibited (+)-rotation, indicating that the (*R*)-enantiomer had been formed in each case.[11] On the basis of the consistent order of elution observed for the product enantiomers in Table 1, these are also tentatively assigned as having (*R*)-stereochemistry.

The success of the flat/bulky structural motif for organozinc additions raised the question of whether further increasing the steric bulk of the O-terminal substituent might further enhance enantioselectivity. To this end, amino alcohol **9** was prepared from *trans*-β-bromostyrene by a sequence of Ni-catalyzed cross-coupling with *tert*-BuMgCl, MCPBA epoxidation, ammonia addition, and resolution (mandelic acid) followed by alkylation with 2-bromoethyl ether. (The complexity of this synthesis further underscores the efficiency of our serendipitous route to **4**.) Using representative aldehydes and the standard conditions of Table 1, enantio-

(8) Nugent, W. A. *Chem. Commun.* **1999**, 1369.
(9) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.
(10) Oguni and co-workers have previously reported enantioselective addition of organozinc reagents to methacrolein using amino alcohol catalysts: Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25.
(11) For assignments see, the following. (*R*)-(+)-1-Phenyl-1-propyl acetate: Faraldos, J.; Arroyo, E.; Herradon, B. *Synlett* **1997**, 367. (*R*)-(+)-3-Octyl acetate: Mihailovic, M. Lj.; Mamuzic, R. I.; Zigic-Mamuzic, Lj.; Bosnjak, J.; Cekovic, Z. *Tetrahedron* **1967**, *23*, 215, (*S*)-(−)-1-Cyclohexyl-1-propyl acetate: Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1932**, *97*, 379.



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selectivities for addition of diethylzinc were generally lower for ligand **9** than those observed for ligand **4**. For details, see the Supporting Information.

The reason hydrogenation of **7** stops at the stage of the mono-cyclohexyl derivative **4** is unclear at this point. The formation of 1,2-dicyclohexylethanol as the overwhelming product in the absence of morpholine is especially striking when one considers that *morpholine is the expected coproduct of this hydrogenolysis*. (The importance of morpholine as an additive came to light when we changed the synthesis of **7** as noted above. Evidently, excess morpholine in the crude **7** used in initial studies was sufficient to promote the selective hydrogenation.) Conceivably, the directing effect[12] of the hydroxyl group provides a significant acceleration for hydrogenation of the O-terminal phenyl ring in the presence of the morpholine catalyst poison.

Both enantiomers of 2-amino-1,2-diphenylethanol are commercially available. As noted above, **4** can also be prepared[13] from enantiopure *trans*-stilbene oxide and excellent methods[14] are now available to prepare this epoxide. In addition to organozinc additions, β-amino alcohols are broadly useful chiral auxiliaries in asymmetric synthesis[15] and we anticipate additional uses for **4**, reflecting its ready synthesis. In truth—at least in this case—serendipity rules.

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Supporting Information Available: Detailed descriptions of experimental procedures, characterization of new compounds, and X-ray data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(13) Although addition of morpholine to *trans*-stilbene oxide was rather slow at 90 °C in our initial studies, a subsequent report by Pericas suggests that this addition may be greatly accelerated in the presence of lithium perchlorate. We have not yet tested this possibility. Sola, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Rieras, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078.

(14) See, for example: Chang, H.-T.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 6456. Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937.

(15) For a review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.