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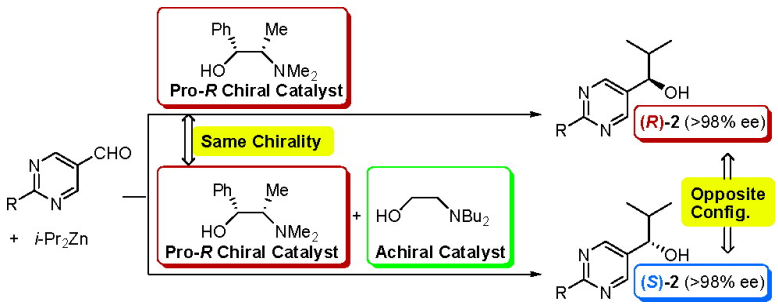

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Small Amounts of Achiral β-Amino Alcohols Reverse the Enantioselectivity of Chiral Catalysts in Cooperative Asymmetric Autocatalysis

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The process that led to the natural homochirality of biomolecules has been a long-standing puzzle.[1] Although several origins of chirality have been proposed, the enantiomeric excesses induced by such origins of chirality have usually been very low, except when in conjunction with amplification of chirality by such methods as asymmetric autocatalysis.[2,3] However, a major question remains unsolved: why are L-amino acids, and not D-amino acids, predominant in nature? The essential point consists of understanding the factors that determine the absolute configuration of an initially formed chiral compound in an environment, including several chiral sources in competition. To address this issue, we recently carried out an asymmetric autocatalytic reaction in the presence of two competing chiral catalysts. The major configuration of the product corresponds to the catalyst bearing the highest ability to control the absolute configuration of the product, the highest "asymmetric power".[4]

Recently, the use of achiral additives in asymmetric organometallic catalysis was shown to be a promising approach for the optimization of the enantioselectivity of chiral catalysts.[5,6] In addition, achiral additives may sometimes reverse the enantioselectivity of a chiral catalyst,[6] although these catalytic systems generally afford products with moderate enantiomeric excesses. In these rare examples, however, the achiral additives have different functional groups from the chiral catalyst or bear no catalytic activity.[6]

We here report an unexpected reversal of the enantiofacial selectivity of chiral β-amino alcohol catalysts by a smaller amount of achiral β-amino alcohol catalysts during the enantioselective addition of diisopropylzinc (*i*-Pr_2Zn) to pyrimidine-5-carbaldehyde **1**, leading to highly enantioenriched pyrimidyl alkanol **2** with the opposite absolute configuration to that expected considering the absolute configuration of the chiral catalyst (Scheme 1).

The addition of *i*-Pr_2Zn to aldehyde **1** using a catalytic amount (20 mol %) of chiral (1*R*,2*S*)- or (1*S*,2*R*)-*N*,*N*-dimethylnorephedrine (DMNE **3**, >99.5% ee) alone afforded (*R*)- or (*S*)-alkanol **2** with 98.7% ee (Table 1, run 1) and 98.8% ee (run 2), respectively. To evaluate the impact of achiral catalysts, the same reaction was then catalyzed by a mixture of chiral (1*R*,2*S*)-DMNE **3** (0.5 mol %) and achiral *N*,*N*-dibutylaminoethanol (DBAE **6d**, 19.5 mol %) in hexane, and alkanol **2** with 95.2% ee was obtained, but with *S* (!) configuration (run 3). The reversal of the sense of enantioselectivity was also observed by using the chiral catalyst with the opposite enantiomer, that is, (1*S*,2*R*)-DMNE, and achiral DBAE, (*R*)-**2** being obtained with 94.8% ee (run 4). Thus, the enantiofacial selectivity of the chiral catalyst was reversed by the achiral catalyst **6d**.

This inversion phenomenon seems to be quite general, as it was also observed with other achiral amino alcohols, such as *N*,*N*-dimethylaminoethanol (DMAE **6a**) (run 5) and *N*,*N*-dioctylaminoethanol (DOAE **6e**) (run 6), in other solvents such as toluene (runs 7 and 8) and dibutyl ether (runs 9 and 10), or other chiral catalysts,

Scheme 1

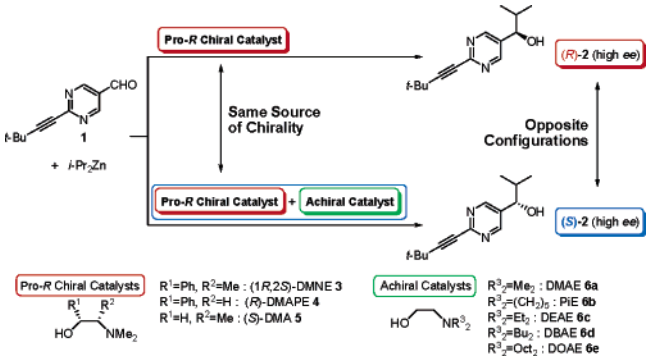

Table 1. Reversal of Enantioselectivity by Achiral Amino Alcohols in Asymmetric Autocatalysis Initiated Using Chiral and Achiral Amino Alcohols

	Catalytic Mixture			Product **2**		
run	chiral catalyst	achiral catalyst	solvent	yield (%)	ee (%)	effect of the achiral catalyst
1[a]	(1*R*,2*S*)-DMNE **3**	none	hexane	96	98.7 (*R*)	
2[a]	(1*S*,2*R*)-DMNE **3**	none	hexane	98	98.8 (*S*)	
3[b]	(1*R*,2*S*)-DMNE **3**	DBAE **6d**	hexane	95	95.2 (*S*)	reversal
4[b]	(1*S*,2*R*)-DMNE **3**	DBAE **6d**	hexane	95	94.8 (*R*)	reversal
5[b]	(1*R*,2*S*)-DMNE **3**	DMAE **6a**	hexane	94	91.8 (*S*)	reversal
6[b]	(1*R*,2*S*)-DMNE **3**	DOAE **6e**	hexane	95	96.0 (*S*)	reversal
7[a]	(1*S*,2*R*)-DMNE **3**	none	toluene	96	97.7 (*S*)	
8[b]	(1*S*,2*R*)-DMNE **3**	DBAE **6d**	toluene	98	92.0 (*R*)	reversal
9[a]	(1*S*,2*R*)-DMNE **3**	none	dibutyl ether	92	98.9 (*S*)	
10[b]	(1*S*,2*R*)-DMNE **3**	DBAE **6d**	dibutyl ether	96	96.6 (*R*)	reversal
11[a]	(*R*)-DMAPE **4**	none	hexane	94	98.2 (*R*)	
12[b]	(*R*)-DMAPE **4**	DBAE **6d**	hexane	92	94.0 (*S*)	reversal
13[a]	(*S*)-DMA **5**	none	hexane	96	97.3 (*R*)	
14[b]	(*S*)-DMA **5**	DBAE **6d**	hexane	92	92.9 (*S*)	reversal

[a] Molar ratio of aldehyde **2**:*i*-Pr_2Zn:chiral catalyst = 1.0:2.0:0.2. [b] Molar ratio of aldehyde **2**:*i*-Pr_2Zn:chiral catalyst:achiral catalyst = 1.0:2.0:0.005:0.195.

such as (*R*)-2-*N*,*N*-(dimethylamino)-1-phenylethanol (DMAPE **4**) (runs 11 and 12) or (*S*)-*N*,*N*-dimethylalaninol (DMA **5**) (runs 13 and 14).

After these surprising preliminary observations, a more detailed study was carried out. The addition of *i*-Pr_2Zn to **1** was catalyzed by a mixture of (1*S*,2*R*)-DMNE **3** and DBAE **6d** in various proportions in toluene. The total concentration of amino alcohols (20 mol %), however, was kept constant with respect to the concentration of aldehyde. The variation in the enantiomeric excess and the absolute configuration of the product **2** with the composition of the catalytic mixture are shown in Figure 1. (1*S*,2*R*)-DMNE **3** alone afforded (*S*)-**2** (Table 1, run 7). When the reaction was carried out in the presence of achiral DBAE **6d** and (1*S*,2*R*)-DMNE **3** in a ratio of 65:35, (*S*)-**2** was obtained. In sharp contrast, when the

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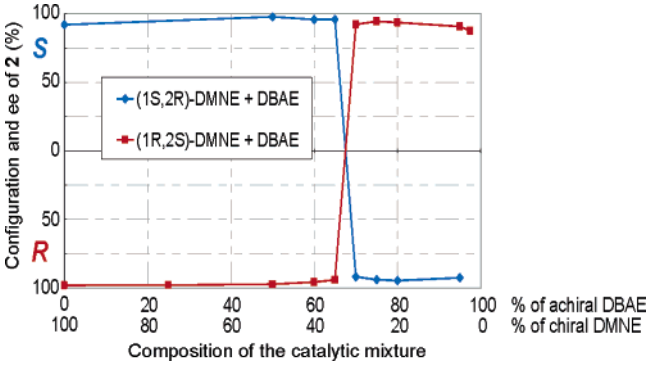

Figure 1. Asymmetric autocatalysis initiated by a mixture of chiral DMNE **3** and achiral DBAE **6d** of various ratios in toluene.

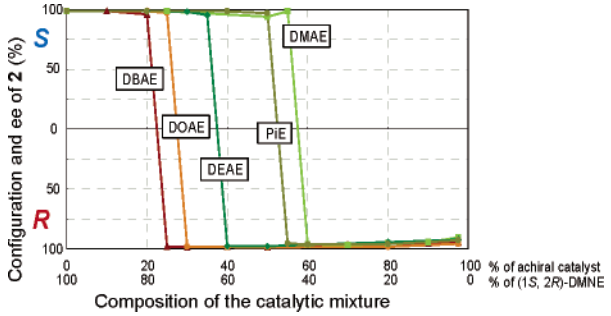

Figure 2. Asymmetric autocatalysis initiated by a catalyst mixture of (1*S*,2*R*)-DMNE **3** and various achiral **6a**−**e** in hexane.

ratio was slightly changed to 70:30, a sudden reversal of the enantioselectivity occurred and (*R*)-**2** was formed in high enantiomeric excess. It should be noted that almost symmetrically opposite results were obtained by using a mixture of chiral (1*R*,2*S*)-DMNE and achiral DBAE (Figure 1).

The most significant reversal of enantioselectivity by achiral catalysts was observed in hexane (Figure 2). Even a smaller amount of achiral DBAE **6d** than (1*S*,2*R*)-DMNE (DBAE:DMNE = 25:75; i.e, 5 and 15 mol %, respectively) reversed the enantioselectivity of DMNE to afford (*R*)-**2** with high (98.3%) ee. Similarly, the reversal occurred in the presence of smaller ratios of achiral DOAE **6e** or *N*,*N*-diethylaminoethanol (DEAE **6c**) than chiral (1*S*,2*R*)-DMNE, respectively, to give the product with *S* configuration. Thus, the use of achiral *N*,*N*-dialkylaminoethanols associated with a unique chiral catalyst results in obtaining either enantiomeric form of the product with high enantiomeric excess by just changing their ratio.

The exact origin of this reversal of enantioselectivity remains unclear. However, (1*R*,2*S*)-DMNE **3** alone affords (*R*)-**2**. As (*S*)-**2** is formed by using a mixture of chiral and achiral catalysts, this clearly shows that the chiral and achiral catalysts interact and form a new catalytic species that promotes the formation of the opposite (*S*)-**2**. Whatever the exact structure of this complex, these observations prove that a mixed aggregate is catalytically active.[7] Because only monomeric species were believed to be catalytically active in dialkylzinc addition to aldehydes catalyzed by β-amino alcohols,[5d,8] our observations may bring some new insights to the mechanism of the β-amino alcohol catalyzed addition of dialkylzincs to aldehydes. These reversal phenomena imply that, in the presence of achiral and chiral catalysts, the achiral one may also have played an essential role to control the absolute configuration of the initial product in the chemical evolution of chirality. An explanation of the observations is currently being investigated.

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Supporting Information Available: Typical experimental procedures are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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