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DRAMATIC REVERSAL OF ENANTIOSELECTIVITY IN β-AMINOALCOHOL-CATALYZED ADDITION OF DIETHYLZINC TO ALDEHYDES

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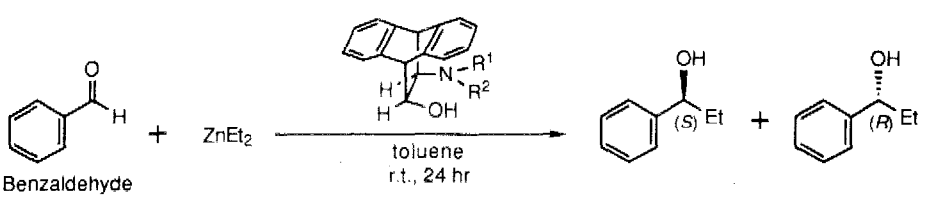
Summary: β-Aminoalcohols sterically constrained by a dibenzobicyclo[2.2.2] ring system serve well as chiral catalysts in highly enantioselective additions of diethylzinc to aldehydes (up to 98% e.e.). A dramatic reversal of the enantioselectivity is observed when the *N,N*-dimethyl (**2a**) and *N*-sulfonyl-β-aminoalcohols (**2c-2e**) are used as catalysts.

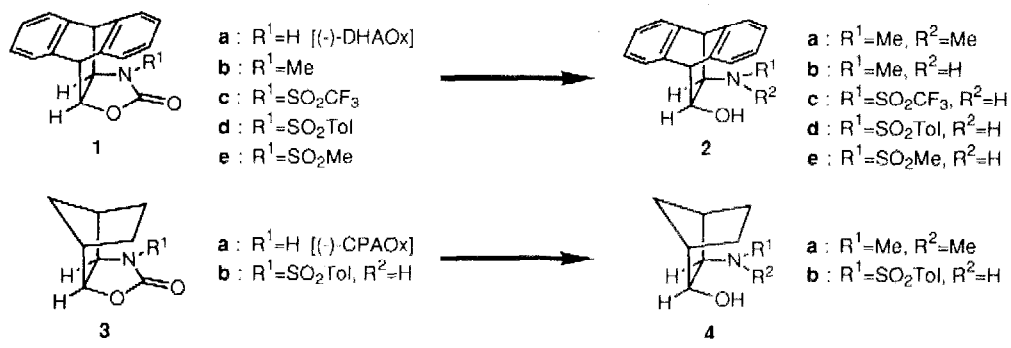
There has been an explosive growth in research on catalytic asymmetric processes for carbon-carbon bond formations, and a great variety of strategies have proved to be successful in providing high levels of enantioselection.[1] Among such highly enantioselective reactions developed so far, nucleophilic addition of alkylmetals to carbonyl compounds in the presence of chiral ligands has been one of the most extensively explored.[2] Various types of chiral aminoalcohols[2] as well as diamines with C_2-symmetry[3] have been developed as excellent chiral ligands in the enantioselective catalytic alkylation of aldehydes with organozincs.[2]

In this paper we describe the use of 2-aminoalcohols conformationally fixed by bicyclo[2.2.2] and bicyclo[2.2.1] ring systems as chiral ligands in the alkylation of aldehydes with diethylzinc, and show that *opposite enantioselectivities* are observed when catalytic amounts of the 2-dimethylamino (**2a**) and 2-sulfonamidoalcohols (**2c**) are used (Scheme 1).



2a : R^1=R^2=Me 91% (98 : 2)

Scheme 1 **2c** : R^1=SO_2CF_3, R^2=H 80% (1 : 99)



Scheme 2

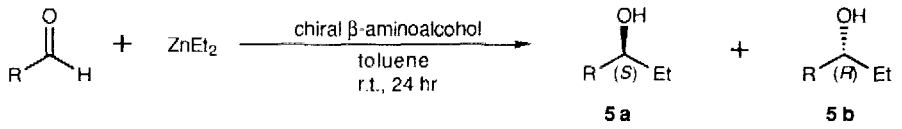
The sterically constrained 2-aminoalcohols examined as catalysts in this study, *i.e.*, *N*-substituted 1,2-(9,10-dihydro-9,10-anthraceno) (**2**) and 1,2-(1,3-cyclopentano)-2-aminoethanols (**4**),[4] are readily obtainable from the chiral 4,5-disubstituted-2-oxazolidinones ,**1** (R^1=H) and **3** (R^1= H), of which both enantiomers were recently introduced as the highly promising chiral auxiliaries in Evans' asymmetric strategy.[5]

Thus, ring-opening of the *N*-methyl, *N*-tosyl, *N*-mesyl and *N*-triflyl (trifluoromethanesulfonyl)-2-oxazolidinones (**1b**-**1e** and **3b**) smoothly proceeded under hydrolytic conditions with barium hydroxide and cesium carbonate to give quantitative yields of the *N*-methyl (**2b**) and the corresponding *N*-sulfonyl-2-aminoalcohols (**2c**-**2e** and **4b**). The *N,N*-dimethyl derivatives (**2a** and **4a**) were readily obtained by reductive cleavage of the *N*-methyl-2-oxazolidinones with $LiAlH_4$ or dimethylation of the parent aminoalcohols. All of the chiral aminoalcohols thus obtained are easy to handle, due to their high crystallinity. The chiral β-aminoalcohols of conformational rigidity have a precedent of camphor-derived auxiliaries.[2,6]

Alkylations of both aromatic and aliphatic aldehydes with organozincs catalyzed by such aminoalcohol derivatives proceeded with satisfactory enantioselectivity of up to 98% e.e., as indicated in the Table. When benzaldehyde was treated with diethylzinc (1.2 mol equiv.) in toluene at room temperature in the presence of a catalytic amounts (0.2 mol equiv.) of (1*S*,2*R*)-*N,N*-dimethylanthraceno-2-aminoethanol (**2a**), (*S*)-1-phenylpropanol was produced with 96% e.e. in 91% yield. The additions catalyzed by the *N*-monomethyl aminoalcohols (**2b**) gave much lower enantioselectivity of only 20% e.e. and low yield (22%) under the same conditions, as might be anticipated.[2] The use of the *N*-sulfonyl-aminoalcohols (**2c**-**2e**) surprisingly resulted in the opposite enantiofacial selection, and among the examined *N*-sulfonyl catalysts the *N*-triflyl derivative (**2c**) gave the highest selectivity (98% e.e.) of the antipodal (*R*)-1-phenylpropanol.[7] Similar reversal in the enantioselectivity were obtained in the alkylations of aliphatic aldehyde such as heptanal catalyzed by *N,N*-dimethyl (**2a**) and *N*-triflyl (**2c**) auxiliaries.

On the other hand, in the reactions catalyzed by the cyclopentano-aminoalcohols (**4**), such a reversal in the enantioselectivity was not observed and the *N,N*-dimethyl (**4a**) and *N*-tosyl derivatives (**4b**) gave 97% e.e. and 79% e.e. of (*S*)-1-phenylpropanol, respectively. As shown in the

Table. Enantioselective Alkylation of Aldehydes with Diethylzinc Catalyzed by Chiral β-Aminoalcohols.



Entry	R	β-aminoalcohol	Yield (%)[a]	**5a** (*S*) : **5b** (*R*)[b]
1	Ph-	**2a**	91	98 : 2
2	$CH_3(CH_2)_5$-	**2a**	81	94 : 6[c]
3	Ph-	**2b**	22	60 : 40
4	Ph-	**2c**	80	1 : 99
5	$CH_3(CH_2)_5$-	**2c**	70	17 : 83[c]
6	Ph-	**2d**	63	6 : 94
7	Ph-	**2e**	60	11 : 89
8	Ph-	**4a**	96	97 : 3
9	Ph-	**4b**	69	79 : 21
10	Ph-	(1*S*,2*R*)-*N*-tosyl norephedrine	25	46 : 54
11	Ph-	(1*S*,2*R*)-*N*,*N*-dibutyl norephedrine	100	95 : 5[d]

a) Isolated yields.

b) Determined by direct HPLC analysis using a chiral column (DAICEL CHIRALCEL OD).

c) Determined by HPLC analysis of the corresponding (*R*)-1-(1-naphthyl)ethyl carbamate.

d) Taken from reference 8.

table for comparison, the *N*-tosylnorephedrine was not effective for the asymmetric induction, while the *N*,*N*-dibutyl derivative was reported to be quite fruitful.[8]

Elucidation of the mechanism of the enantioselectivity reversal will require further study.[2a,2b,9]

In conclusion, we present a new class of aminoalcohols (**2a** and **2c**) which serve as excellent catalysts for the selective preparation of each of the enantiomeric alcohols with 96-98% e.e. in the addition of diethylzinc to aldehydes.

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4) **2a** : mp. 195°C (from EtOH), $[\alpha]_D$= -32.1° (c.1.0, $CHCl_3$).
2b : mp. 164°C (from EtOH), $[\alpha]_D$= +16.5° (c.1.0, MeOH).
2c : mp. 81°C (from CCl_4), $[\alpha]_D$= -7.4° (c.1.0, $CHCl_3$).
2d : mp. 200°C (from EtOH), $[\alpha]_D$= -35.1° (c.1.0, $CHCl_3$).
2e : mp. 178°C (from MeOH), $[\alpha]_D$= +8.2° (c.1.0, $CHCl_3$).
4a : mp. 85°C (from hexane), $[\alpha]_D$= -7.0° (c.1.0, $CHCl_3$).
4b : mp. 116°C (from EtOH), $[\alpha]_D$= -47.0° (c.1.0, EtOH).

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