Stereoselective Synthesis of Optically Active *syn*- and *anti*-1,3-Diols by the Catalytic Alkylation of a β-Alkoxy Aldehyde

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Diastereodivergent synthesis of optically active *syn*- and *anti*-1,3-diols is achieved by the alkylation of the β-alkoxy aldehyde **1** with dialkylzinc reagents using chiral catalysts, providing the first example of the *syn*-selective alkylation of **1**.

Diastereoselective synthesis of 1,3-diols has attracted much attention because the 1,3-diol function is involved in the structures of polyenemacrolide antibiotics such as mycoticin A and roflamycoin.[1] Compared to the synthesis of 1,3-diols by the *reduction* of β-hydroxy ketones,[1] there have been only a few reports on the synthesis of (mono-protected) 1,3-diols by the *alkylation* of β-alkoxy aldehydes.[2] The origin of the diastereoselectivity in the alkylation method is the chirality at the β-position of the β-alkoxy aldehyde, *i.e.* 1,3-asymmetric induction. The applicability of the alkylation method is limited

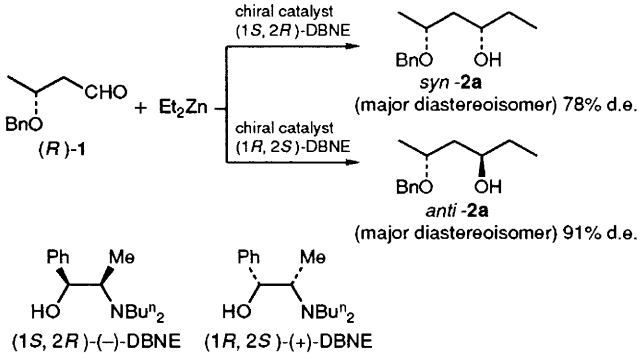
Table 1 Stereoselective synthesis of optically active *anti*- and *syn*-monoprotected 1,3-diols **2** by the alkylation of racemic **1** with dialkylzinc reagents using chiral catalysts[a]

				Product **2**			
						E.e.[b] (%)	
Entry	R_2Zn	Catalyst	*t*/h		Yield (%)	*anti*	*syn*
1	Et_2Zn	(1*S*,2*R*)-DBNE	20	**2a**	57 (58/42)	81	85
2	Et_2Zn	(1*S*,2*R*)-DHNE[d]	17	**2a**	76 (59/41)	78	88
3	Et_2Zn	(*S*)-DPMPM[e]	14	**2a**	80 (55/45)	64	70
4	Me_2Zn	(1*S*,2*R*)-DBNE	15	**2b**	34 (67/33)	61	74

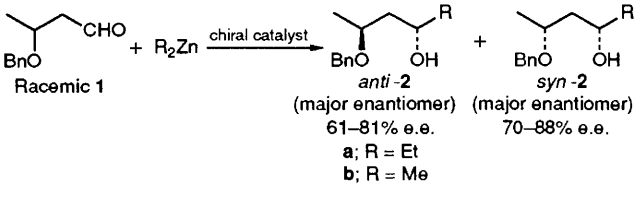
[a] Reactions were run in hexane at room temperature. Molar ratio: **1**: R_2Zn: catalyst = 1:2.2:0.1–0.2. [b] Determined by HPLC analyses of the corresponding esters with (−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA esters). Chiral column: Chiralcel OD; eluent: 0.25% propan-2-ol in hexane; flow rate: 0.5 ml min^{-1}; column temperature: room temperature (*ca.* 32 °C); 254 nm UV detector; retention time (*t*/min): for **2a**, 18.7 (3*R*,5*R*)-minor *anti*, 21.5 (3*S*,5*S*)-major *anti*, 27.0 (3*R*,5*S*)-minor *syn*, and 29.4 (3*S*,5*R*)-major *syn*; for **2b** column temperature 40 °C), 18.4 (2*R*,4*R*)-minor *anti*, 22.4 (2*S*,4*S*)-major *anti*, 24.8 (2*R*,4*S*)-minor *syn*, and 33.4 (2*S*,4*R*)-major *syn*. [c] Isolated yield. Figures in parentheses are *anti*/*syn* ratios. [d] *N*,*N*-Di(n-hexyl)norephedrine (ref. 4*b*). [e] Diphenyl(1-methylpyrrolidin-2-yl)methanol (ref. 5).

to the synthesis of (mono-protected) *anti*-1,3-diols. Thus, the diastereoselective synthesis of (mono-protected) *syn*-1,3-diols by the alkylation of β-alkoxy aldehyde is a challenging problem. The enantioselective addition of dialkylzinc reagents to aldehydes using chiral catalysts has been reported recently.[3]

We now report the first synthesis of (mono-protected) *syn*-1,3-diols by the alkylation of a β-alkoxy aldehyde with dialkylzinc reagents using chiral catalysts. When (*R*)-3-benzyloxybutanal **1**† was treated with Et_2Zn using (1*S*,2*R*)-(−)-*N*,*N*-dibutylnorephedrine (DBNE)[4] as a chiral catalyst, (3*S*,5*R*)-5-benzyloxyhexan-3-ol **2a** (mono-protected *syn*-1,3-diol) was obtained in 43% yield with 78% diastereoisomeric excess (d.e. was determined by HPLC analysis using a chiral column) (Scheme 1).‡ On the other hand, when (1*R*,2*S*)-(+)-DBNE (the opposite enantiomer) was used as a catalyst, (3*R*,5*R*) **2a** (the mono-protected *anti*-1,3-diol) was obtained in 45% yield with 91% d.e. The present diastereodivergency reveals that, unlike the conventional 1,3-asymmetric induction,[2] the origin of the stereoselectivity is the chirality of the chiral catalyst and not the chirality of **1**.§



Scheme 1 Bn = $PhCH_2$



Scheme 2

† (*R*)-**1** was prepared from commercially available (3*R*)-ethyl 3-hydroxybutanoate *via* the following steps: (i) $NaBH_4$–Bu^tOH–MeOH (K. Soai and H. Oyamada, *Synthesis*, 1984, 605); (ii) Ph_3CCl, pyridine (K. Mori and M. Miyake, *Tetrahedron*, 1987, **43**, 2229); (iii) $PhCH_2Br$, NaH; (iv) 3 mol dm^{-3} HCl, tetrahydrofuran (THF); (v) pyridinium dichromate (E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399).

‡ *Procedure*: To a solution of (*R*)-**1** (0.045 g, 0.25 mmol) and (−)-DBNE (0.0128 g, 0.049 mmol) in 1.45 ml of hexane was added a hexane solution (1.0 mol dm^{-3}) of Et_2Zn (0.55 mmol, 0.55 ml) at room temperature. After the mixture had been stirred at room temperature for 39 h, the reaction was quenched with 1 mol dm^{-3} HCl (4 ml). The mixture was extracted with dichloromethane, dried (anhydrous Na_2SO_4), and purified by silica gel TLC (developing solvent: dichloromethane). Compound **2a** was obtained (0.022 g) in 43% yield. HPLC analysis of **2a** using a chiral column (Chiralcel OB; eluent: 0.5% propan-2-ol in hexane: flow rate: 1.0 ml min^{-1}; 254 nm UV detector) showed a retention time of 24.0 min for the minor (*anti*) isomer and 28.9 min for major (*syn*) isomer.

Authentic samples of *anti*- and *syn*-**2a**,**b** were prepared by the *anti*-selective reaction of racemic **1** with R_2Zn–$TiCl_4$.[2b]

§ However, if the stereocontrol was completely catalyst dependent, d.e. of *syn*-**2a** (78% d.e.) with (1*S*,2*R*)-DBNE and *anti*-**2a** (91% d.e.) with (1*R*,2*S*)-DBNE should be the same. The results indicate that the original stereochemistry of (*R*)-**1** may still play a part.

It was also found that optically active *syn*- and *anti*-1,3-diols were obtained from the stereoselective addition of dialkylzinc reagents to *racemic* **1** using (1*S*,2*R*)-(−)-DBNE as a catalyst (Scheme 2). As shown in Table 1, both *syn*- [85% enantiomeric excess (e.e.)] and *anti*-1,3-diols (81% e.e.) were synthesized by the reaction with Et_2Zn. Reactions with other combinations of dialkylzinc reagents and chiral catalysts also afforded diols with good to high e.e. Formation of these optically active isomers is the result of the selective addition of dialkylzinc reagents to racemic **1** from the *Si*-face regardless of the configuration of **1**. Thus, optically active alcohols **2** were synthesized even from racemic **1** using chiral catalysts, and this cannot be achieved by the conventional 1,3-asymmetric induction.[2]

The selective addition of dialkylzinc reagents to β-alkoxy aldehydes using a chiral catalyst thus provides a useful

diastereodivergent synthesis of optically active *syn*- and *anti*-1,3-diols.

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