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Direct Enantioselective Synthesis of *syn*-1,3-Diols by the Reaction of Aldehydes with Enol Silyl Ethers in the Presence of a Chiral Borane Complex. Successive Asymmetric Aldol Reaction and Asymmetric Reduction with One Promoter[1]

Yuichi Kaneko, Takao Matsuo, and Syun-ichi Kiyooka*

Department of Chemistry, Kochi University
Akebono-cho, Kochi 780, Japan

Key words: enantioselectivity; *syn*-1,3-diol; asymmetric aldol reaction; chiral borane

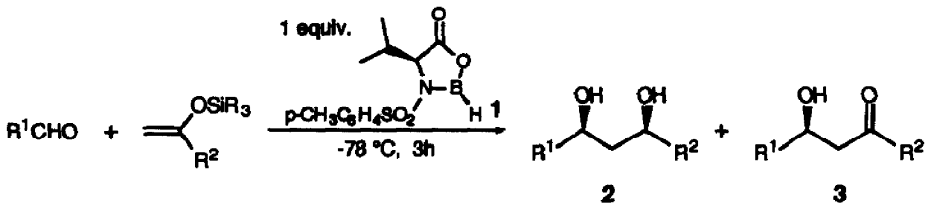
Abstract: A stoichiometric amount of the chiral borane 1 turned out to successively promote the asymmetric aldol reaction of aldehydes with enol silyl ethers and the following asymmetric reduction in one pot to afford *syn*-1,3-diols with high enantioselectivity.

The chiral 1,3-diol system is one of the most important fundamental units present in a number of natural products (e.g., polyene macrolides). A variety of synthetic approaches toward such a unit have been investigated and one of them, the 1,3-asymmetric reduction of β-hydroxy ketones, has effectively addressed the diastereoselective synthesis of 1,3-diol units. Although the chiral 1,3-diol units have been introduced by using optically active β-hydroxy ketone synthons thus far,[2,3] the direct enantioselective synthesis from achiral starting compounds is intrinsically more attractive. We have already reported that the reaction of aldehydes with TBDMS ketene acetals in the presence of a stoichiometric amount of the chiral borane complex 1, prepared from *p*-toluenesulfonamide of (*S*)-valine and BH_3·THF,[4] where β-hydroxy-TBDMS acetals were obtained via the unexpected reduction of the reaction intermediates. Under similar conditions, enol silyl ethers were found to successfully undergo both aldol addition and reduction to afford the corresponding 1,3-diols. We disclose herein the direct enantioselective synthesis of *syn*-1,3-diols.

A typical experimental procedure is as follows. To a solution of *N*-*p*-toluenesulfonyl-(*S*)-valine (1 mmol) in propionitrile (3 mL) was added a 1 M THF solution of BH_3·THF (1 mL, 1 mmol) over 5 min under Ar. The solution was then stirred for 30 min at 0 °C. After stirring for an additional 30 min at ambient temperature, the solution was cooled to -78 °C. To this solution was added the aldehyde (1 mmol) in propionitrile, followed by the addition of the enol silyl ether (1.1 mmol). The reaction mixture was stirred for 3 h at -78 °C and then quenched at that temperature by the introduction of buffer solution (pH 6.8) (10 mL). The mixture was extracted with ether and the organic layer was washed with saturated aqueous $NaHCO_3$ solution. The extract was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to obtain crude products. After flash column chromatography, the products having a trimethylsilyloxy group were desilylated by treatment with a

0.3 M THF solution of *n*-Bu_4NF. The diastereoselectivity and enantioselectivity of the 1,3-diols and aldols were determined using ^1H and ^{19}F NMR and HPLC analyses. The results are summarized in Table 1.

Table 1. Enantioselective *syn*-1,3-Diol Synthesis in the Reaction of Aldehydes with Enol Silyl Ethers



(1)

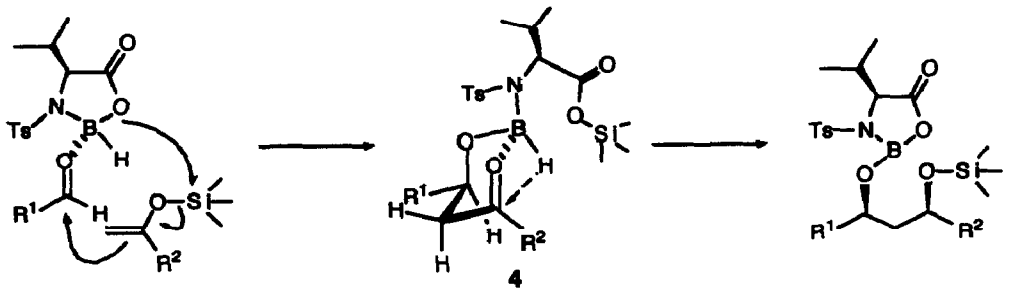
entry	solvent	aldehyde R^1	enol silyl ether R^2	enol silyl ether SiR_3	diol 2 %yield	diol 2 %ee (syn)	aldol 3 %yield	aldol 3 %ee
1	CH_2Cl_2	i-Pr	Ph	TMS	60 (95/5)[a]	94[b]	21	50[b] (S)[c]
2	Toluene	i-Pr	Ph	TMS	55 (98/2)[a]	87[b]	6	68[b] (S)[c]
3	C_2H_5CN	i-Pr	Ph	TMS	65 (97/3)[a]	99[b]	17	60[b] (S)[c]
4	CH_2Cl_2	i-Pr	Ph	TBDMS	62 (75/25)[a]	98[b]	9	43[b] (S)[c]
5	CH_2Cl_2	i-Pr	$BnOCH_2CH_2$	TMS	55 (89/11)[a]	86	15	67[b]
6	C_2H_5CN	i-Pr	n-Hex	TMS	70 (91/9)[a]	99[d]	23	60[d] (S)[e]
7	C_2H_5CN	n-Pr	Ph	TMS	63 (91/9)[a]	96[b] (R, R)[e]	22	39[b] (R)[e]
8	C_2H_5CN	n-Pr	n-Hex	TMS	66 (90/10)[a]	98[c]	25	49[d]
9	CH_2Cl_2	Ph	n-Hex	TMS	53 (97/3)[a]	85	18	72[b]

[a] Diastereomer ratio (syn/anti). [b] Enantiomeric excess was determined by HPLC analysis with a Daicel Chiralcel OD column. [c] Absolute configurations were determined by ^1H NMR of their MTPA esters. [d] Enantiomeric excess was determined by ^{19}F NMR of their MTPA esters (ref. 6). [e] Absolute configuration was determined by comparision of the specific rotation value with the literature one (Narasaka, K.; Miwa, T.; Hayashi, H.; Ohta, M. *Chem. Lett.* **1984**, 1399).

With a variety of aldehydes, 1,3-diols were obtained in moderate yields (53 - 70 %) with high syn-diastereoselectivity. The *syn*-1,3-diols prepared from aliphatic aldehydes in the reaction (C_2H_5CN) were almost enantiomerically pure (96 - 99 %ee). Propionitrile was the best solvent for the reaction selectivity. The TBDMS substituent of enol silyl ether reduced the syn selectivity.

The notable point is that good to excellent diastereo- and enantioselectivities are simultaneously achieved on the 1,3-diols while the enantioselectivity of the β-hydroxy ketones is considerably lower. Such observations

on the selectivity of the products suggested that the syn selective reduction of the reaction intermediate takes place after the enantioselective aldol addition.



Scheme 1

On the basis of our working hypothesis for the aldol reaction mechanism,[4] the reduction is by an intramolecular hydride transfer as **4** (Scheme 1),[5] which is accelerated by a matching mode between the promoter's chirality and the newly formed aldol's chirality. More experimentation will be necessary to determine the reaction mechanism including the aldol reaction stages.

This reaction is an example in which the double asymmetric inductions are effectively accomplished by only one promoter, which provides a promising direct way to optically active *syn*-1,3-diols from achiral starting materials. Further studies are in progress on the reaction mechanism as well as the application to the synthesis of natural products.

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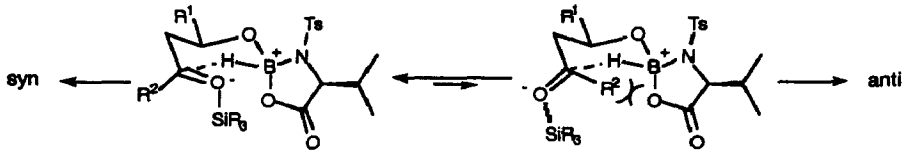
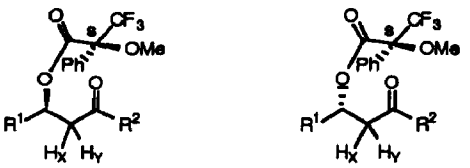
5. The boron chelation requires our hypothetical silyl group shuttling mechanism on the aldol reaction using promoter **1** (ref. 4). An alternative mechanism without chelation is also possible involving hydride delivery to the preferred *O*-silyl oxocarbenium ion comformer as shown below.



6. ^{1}H NMR and ^{19}F NMR data of MTPA esters.



a b

MTPA ester		^{1}H NMR						^{19}F NMR
R^1	R^2	δ_{aHx}	δ_{bHx}	δ_{aHx}-δ_{bHx}	δ_{aHy}	δ_{bHy}	δ_{aHy}-δ_{bHy}	δ_a-δ_b
i-C_3H_7	C_6H_5	3.38	3.42	-0.04	3.02	3.03	-0.01	-0.21
n-C_3H_7	C_6H_5	3.43	3.48	-0.05	3.04	3.08	-0.04	-0.14

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