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LETTERS

Attainment of *Syn*-Selectivity for Boron-Mediated Asymmetric Aldol Reactions of Carboxylic Esters[1]

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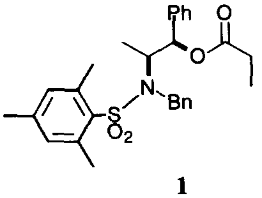
Abstract: *A new chiral reagent for syn-selective aldol reactions has been developed based on the recent finding that the stereochemistry of the boron-mediated aldol reaction of a carboxylic ester is controlled by the bulkiness of the alcohol moiety of the ester, by the proper choice of reagents, and by the enolization conditions. This readily available, inexpensive reagent has been utilized in studies directed towards the synthesis of the macrolide tedanolide.*

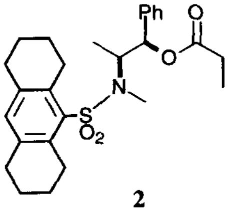
Efforts continue to develop efficient, practical reagents for the aldol reaction.[3] Our recent work concerning the boron-mediated aldol reaction of propionate esters has demonstrated that several parameters are critically important in terms of stereochemical control.[4] These parameters are (1) the steric size of the alcohol moiety of the ester, (2) the proper choice of reagents and (3) the conditions selected for enolization of the ester. Based on these findings, we have already succeeded in developing a chiral propionate ester **1** as an *anti*-selective aldol reagent with high diastereofacial selectivity.[5] There was reason to believe that ester **1** could be modified to obtain a *syn*-selective reagent with high diastereofacial selectivity. We herein describe the development of such a reagent, ester **2**, which is derived from ephedrine. Ester **2**, with **1**, constitutes a pair of reagents for the extension of either the *syn* or *anti* propionate unit. The application of ester **2** in studies towards the synthesis of the macrolide tedanolide is also shown as an example.

Figure 1



1

Anti aldol reagent



2

Syn aldol reagent

Ester **2** was readily prepared from commercially available ephedrine[6] in two steps (Scheme 1): (1) selective sulfonylation of the amino group with 1,2,3,4,6,7,8,9-octahydroanthracenesulfonyl chloride (**3**)[7] and

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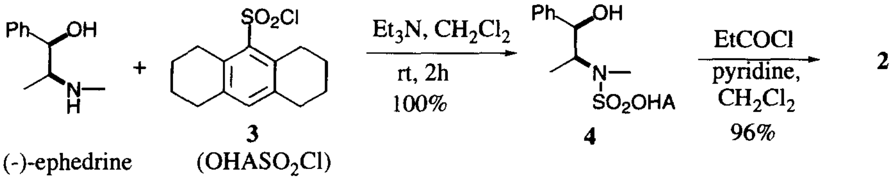
triethylamine gave alcohol **4**, (2) acylation of alcohol **4** with propionyl chloride and pyridine afforded **2** $[\alpha]_D$= -8.42 (c 1.40, $CHCl_3$); *ent*-**2** $[\alpha]_D$= 8.40 (c 1.50, $CHCl_3$). The overall yield is greater than 96%.

Scheme 1



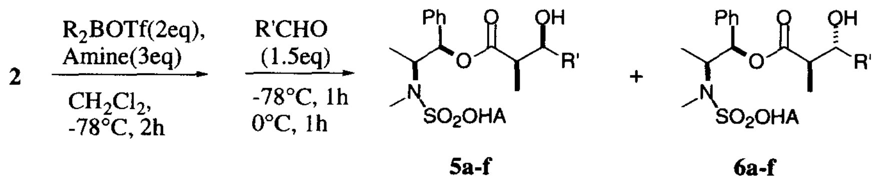
The aldol reaction of **2** was investigated using two different combinations of enolization reagents: dibutylboron triflate / diisopropylethylamine (Table 1, left) and dicyclohexylboron triflate / triethylamine (Table 1, right). These are the typical combinations for the *syn*-selective and *anti*-selective aldol reactions, respectively.[4] Thus, enolization of **2** with dibutylboron triflate / diisopropylethylamine, followed by reaction with a series of representative aldehydes (Scheme 2) afforded the corresponding aldol products uniformly in greater than 93% yield. Ester **2** showed high diastereofacial selectivity for the *syn* isomer (~97:3). It should be noted that ester **2** provided high *syn*-selectivity in all cases, whereas with ester **1** under the same conditions the selectivity was low (syn:anti = 87:13 with isobutyraldehyde).[5]

Table 1. Boron Aldol Reaction of Ester **2** [a,b]

	n-Bu_2BOTf/i-Pr_2NEt				c-Hex_2BOTf/Et_3N			
Aldehyde	syn:anti	ds for syn	yield %	major prod.	anti:syn	ds for anti	yield %	major prod.
EtCHO	93:7	97:3	95	**5a**	>98:2	86:14	95	**6a**
PrCHO	94:6	>97:3	93	**5b**	>98:2	85:15	95	**6b**
i-PrCHO	95:5	97:3	98	**5c**	>98:2	89:11	96	**6c**
(*E*)-CH_3CH=CHCHO	93:7	>97:3	98	**5d**	>98:2	83:17	94	**6d**
t-BuCHO	92:8	97:3	97	**5e**	>98:2	85:15	93	**6e**
PhCHO	94:6	95:5	97	**5f**	>98:2	78:23	97	**6f**

a) Enolization: Propionate ester (1 equiv) with boron triflate (2 equiv) and amine (3 equiv) in CH_2Cl_2 at -78 °C for 2 h. Aldol reaction: Aldehyde (1.5 equiv) at -78 °C for 1 h and at 0 °C for 1 h. b) Yield and ratio determined by HPLC and ^1H NMR.

Scheme 2

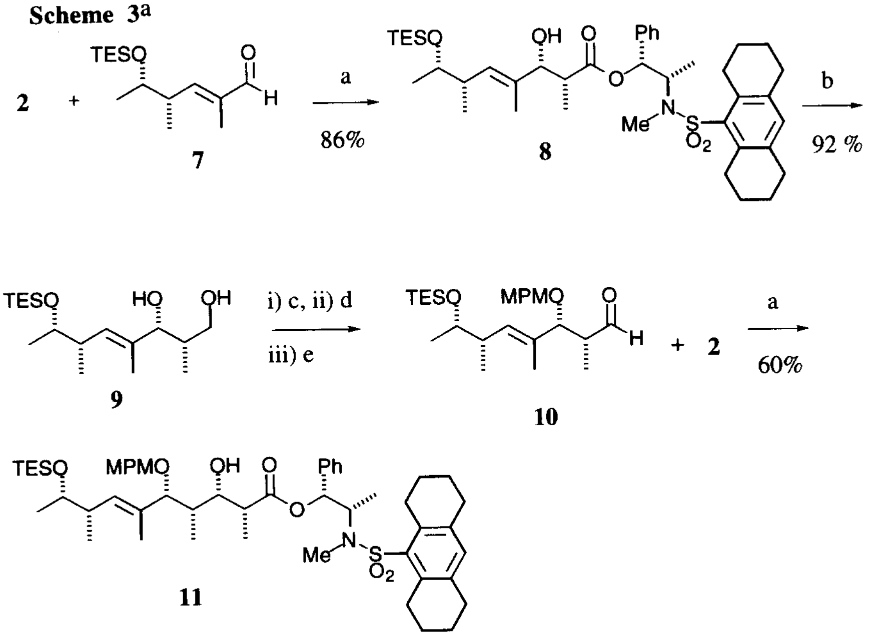


For comparative purposes, the *anti*-aldol reaction of ester **2** was also carried out with dicyclohexylboron triflate / triethylamine used as the enolization reagents (See Table 1, right). Like ester **1**, ester **2** showed high *anti*-selectivity. However, ester **2** had lower diastereofacial selectivity for the *anti*-isomer than ester **1** did.[5] The major *syn*- and *anti*-products were proven to be **5** and **6** (*vide infra*). (See Scheme 2)

Reductive cleavage[4,5] of the purified aldol products with either $LiAlH_4$, $LiBH_4$ or DIBAL-H gave recovered auxiliary as well as enantiomerically pure 1,3-diols. Alternatively, mild saponification[5] of the aldol products gave recovered auxiliary and enantiomerically pure carboxylic acids. The absolute stereochemistry of the products was confirmed by comparing their optical rotations with reference values.[8]

To demonstrate its usefulness, ester **2** was applied in studies towards the synthesis of tedanolide, a marine natural product with interesting biological activities.[9] The key steps are shown in Scheme 3.

Scheme 3^a



^{a}Reagents and conditions: a) **2** (1 equiv), n-Bu_2BOTf (2 equiv), *i*-Pr_2NEt (2.4 equiv), -78 °C, 2 h, then aldehyde; b) DIBAL-H or $LiBH_4$; c) dimethyl acetal of *p*-anisaldehyde, cat. PPTS, CH_2Cl_2, 85%, 5% recovered st.m.; d) DIBAL-H, CH_2Cl_2, 0 °C, 87%; e) Dess-Martin periodinane, pyridine, CH_2Cl_2, rt, quant.

Under the standard conditions for the *syn*-aldol reaction, ester **2** reacted with aldehyde **7** to give the *syn*-aldol product **8** with a selectivity of 95:5 (**8**:other isomers) and good yield. Cleavage of the auxiliary followed by protecting group manipulation and then oxidation with Dess-Martin periodinane afforded aldehyde **10**. Another *syn*-aldol reaction gave **11** with a selectivity of 93:7 (**11**:other isomers) and moderate yield. The reactivity and selectivity are very high considering the fact that the auxiliary has to override the inherent selectivity of the α-chiral center[10] of aldehyde **10** (mismatched reaction). Compound **11** represents the C(3) - C(12) portion of tedanolide.

In conclusion, synthetically useful diastereo- and diastereofacial selectivities have now been achieved in a practical way through the enolization of reagents **1** and **2** with different combinations of dialkylboron triflate and amine. These reagents are readily available, inexpensive to prepare, and easily enolized under mild boron-mediated conditions. All these features make esters **1** and **2** easily applicable in natural product synthesis. The new reagent **2** is a useful alternative to the existing reagents for *syn*-selective aldol reactions.[3a]

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References and Notes:

1. Part of this work was carried out at the Institute for Fundamental Research, Kao Corporation, Ichikai-machi, Haga-gun, Tochigi, 321-34, JAPAN.
2. The current address for Z.P. is Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Drive, Abbott Park, IL 60064.
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