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A practical synthesis of essentially enantiopure *syn*-propionate aldols using a chiral oxazaborolidinone-promoted asymmetric aldol reaction coupled with radical reduction

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Abstract

Essentially enantiopure *syn*-propionate aldols (>98% ee) were prepared by a chiral oxazaborolidinone-promoted asymmetric aldol reaction, followed by a diastereoselective radical reduction with Bu_3SnH and Et_3B, which was carried out under chelation control.

Keywords: asymmetric aldol reaction; chiral Lewis acid; diastereoselective radical reduction.

Diastereoselectively divergent synthesis of essentially enantiopure *syn*- and *anti*-propionate aldols using chiral Lewis acid mediated asymmetric aldol reactions has not been realized yet.[1] If such a diastereoselective synthesis is possible, the reaction might provide to be the most reliable and powerful means of constructing chiral acyclic skeletons biosynthetically incorporating propionate moieties from the viewpoint of practical synthesis, compared with the asymmetric aldol reactions with chiral auxiliaries. During the course of applying our chiral oxazaborolidinone-promoted asymmetric aldol reaction to enantioselective acyclic stereoselection,[2] it occurred to us to expand this convenient reaction into a diastereoselective synthesis of *syn*- and *anti*-propionate aldols with high enantioselectivity. A preliminary trial could be achieved by using a silyl ketene acetal (*E*:*Z*=1:3), derived from ethyl 2-(methylthio)propionate, to give essentially enantiopure *syn*- and *anti*-propionate aldols but without diastereoselection.[2d] The problem of non-diastereoselection in the reaction was addressed by focusing on a clue to the solution in the desulfurization process but several trials for the stereoselective desulfurization resulted in failure. We disclose herein a versatile solution toward a practical synthesis of essentially enantiopure *syn*-propionate aldols, which was achieved by using a new silyl nucleophile **2** giving an α-bromo substituent in the resulting aldol in the asymmetric aldol reaction (Scheme 1).

The bromo substituent in 2-bromo-1-ethoxy-2-methyl-1-trimethylsiloxyethane **2** (74–75°C/15 mmHg, *E*:*Z*=1:2) has dual roles; the first is a suitable steric bulkiness of the silyl nucleophile in order to achieve

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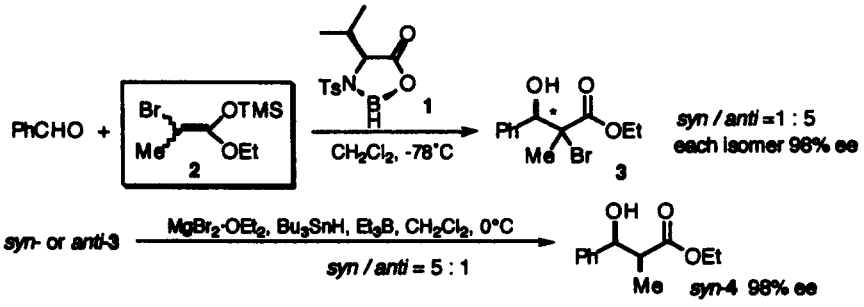
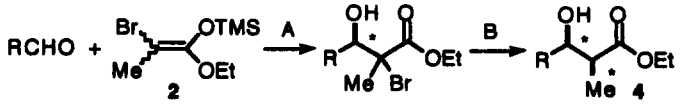


Scheme 1.

Table 1
Synthesis[a] of essentially enantiopure *syn*-propionate aldols through the asymmetric aldol reaction (A) and the following radical reduction with Bu_3SnH (B)



Entry	Aldehyde (R)	Yield[b] (%)	*syn*-4 / *anti*-4	% ee of *syn* isomer[c]
1	Ph	87	5 : 1	>98
2	$(CH_3)_2CH$	83	>70 : 1	>98
3	$PhCH_2CH_2$	80	6 : 1	>98
4	$CH_3CH_2CH_2$	79	5 : 1	>98

[a] Both processes, A and B, were carried out without separation of α-bromo aldol isomers. Chiral borane 1 was used in the aldol reaction (A). Reactions (0°C) (B) of non-protected bromo aldols were carried out with 2 equiv of Bu_3Sn and 0.2 equiv of Et_3B, and 5 equiv of $MgBr_2$·OEt_2 in CH_2Cl_2. [b] Isolated overall yields. [c] Determined by HPLC analysis of propionate aldols using a Daicel Chiralcel OD column with 0.2 - 5% 2-propanol in hexane.

very high enantioselectivity in the aldol condensation process[2] and the second is a promising eliminable function of the resulting aldol intermediate in the radical reduction process.[3] The asymmetric aldol reaction of benzaldehyde with **2** smoothly proceeded (–78°C, 3 h) in the presence of a stoichiometric amount of chiral oxazaborolidinone **1** to give a mixture of α-bromo aldol **3** (each isomer 98% ee) in 89% yield with *anti* selectivity (5:1). [4] The following radical reductions of the separated *syn*- and *anti*-**3** were carried out according to the conditions reported by Guindon[3] in the radical reduction of a series of α-bromo-β-alkoxy esters with Bu_3SnH and catalytic Et_3B in the presence of $MgBr_2 \cdot OEt_2$ (chelation control). Each reduction resulted in *syn* selection with almost the same level. The stereocenter at the α of **3** scarcely affected the stereochemical outcome in the radical process. It is noteworthy, from the standpoint of practical synthesis, that the chelation conditions are valid for the case involving β-hydroxy function like **3** without protection.

The results obtained with a variety of aldehydes are summarized in Table 1; in each run essentially enantiopure *syn*-propionate aldols were diastereoselectively obtained in good overall yield. The chelation-control conditions in process B surely guaranteed the expected moderate *syn* selection. When the steric branch of the R group was increased, the *syn* selectivity was substantially enhanced (entry 2).

In conclusion, we have achieved an effective access to the practical synthesis of essentially enantiopure *syn*-propionate aldols by using a chiral oxazaborolidinone-mediated aldol reaction coupled with a

stereoselective radical reduction. Further investigation to search for *anti* diastereoselectivity in our system is now underway.

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4. After separation with silica gel flash column chromatography, *syn*- and *anti*-**3** both showed 98% ee, determined by HPLC with Daicel Chiralcel AD and OD columns. The assignment of *syn* and *anti* configurations was confirmed by NOE experiments of the acetonide derivatives obtained after reduction of the ester moiety.