The Anti-Selective Boron-Mediated Asymmetric Aldol Reaction of Carboxylic Esters

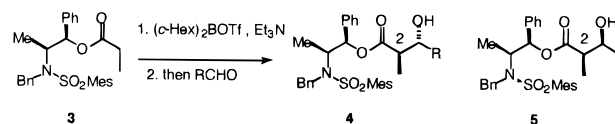Atsushi Abiko,*,† Ji-Feng Liu,† and Satoru Masamune*,‡

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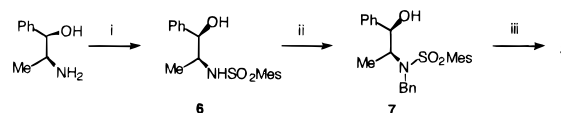Technology, 77 Massachusetts Avenue
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Natural products of propionate origin such as macrolide antibiotics often contain both *anti-* and *syn*-3-hydroxy-2-methylcarbonyl units (**1** and **2**) in their structural framework. While the efficient construction of the syn unit **2** can now be readily achieved through an asymmetric aldol reaction,[1] efforts still continue to explore the synthetic method for the anti unit **1**.[2] Several methods for anti-aldols thus far recorded in the literature include (1) the use of the boron, titanium, or tin(II) enolate carrying chiral ligands,[3] (2) an asymmetric version of the Lewis acid catalyzed aldol reaction generally categorized as the Mukaiyama aldol reaction,[4] and (3) the use of the metal enolate derived from a chiral carbonyl compound.[5] In many cases these methods provide anti-aldols with high enantioselectivities but appear to present problems in terms of the availability of reagents, the generality of reactions, or conditions required for reactions. Because of its proven reliability,[1] we have focussed on the boron-mediated aldol reaction and disclose

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(4) For Si enolates, see: (a) Helmchen, G.; Leikauf, U.; Taufer-Knopfel, I. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 874. (b) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (c) Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699. (d) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61. (e) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321. For B enolates, see: (f) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. (g) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (h) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.* **1996**, *61*, 2038. For Ti enolates, see: (i) Ghosh, A. K.; Ohnishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527.

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(6) The titanium enolates derived from the propionates of two related chiral sulfonamide-alcohols have been reported to undergo Lewis-acid mediated aldol reactions. One set of aldol reactions proceeded syn-selectively (Xiang, Y.-B.; Olivier, E.; Ouimet, N. *Tetrahedron Lett.* **1992**, *33*, 457) and the other anti-selective (4i) even under similar conditions.

Scheme 1

Scheme 2[a]

[a] (i) MesSO2Cl, Et3N, CH2Cl2, 100%; (ii) BnBr, K2CO3, MeCN, reflux, 7 h, 95%; (iii) EtCOCl, py., CH2Cl2, 0 °C to room temperature, 100%.

herein the finding that the aldol reaction of the chiral ester **3** with a wide variety of aldehydes proceeds anti-selectively with excellent diastereofacial selectivity.[6]
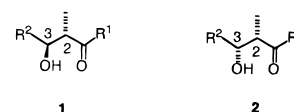
The design of ester **3** originates from our recent observations that (1) *carboxylic esters* can be converted under the standard conditions (dialkylboron triflate and amine) into the corresponding boron enolates which react with aldehydes to yield aldol products in high yield and (2) more importantly the syn- and anti-stereochemistry of the aldol products can be controlled by the proper choice of reagents and enolization conditions.[7] Thus, the reaction of an ester consisting of a sterically bulky alcohol with dicyclohexylboron triflate and triethylamine led to the predominant formation of the *anti*-aldols. After extensive screening of the propionate esters of chiral (enantio-pure or racemic) alcohols, the ester **3** was found to be a superb stereocontrolling reagent in terms of both simple diastereo- and diastereofacial selectivities. Both enantiomers of the propionate **3** were prepared from commercially available (+)- or (−)-norephedrine in three steps: (1) selective sulfonylation of the amino group with mesitylenesulfonyl chloride and triethylamine,[8] (2) selective N-alkylation with benzyl bromide in the presence of base (K2CO3 in CH3CN),[9] and (3) acylation with propionyl chloride and pyridine. **3**: mp 147 °C,[10] [α]D 11.1 (c 2.24, CHCl3). *Ent*-**3**: mp 147 °C,[10] [α]D −11.2 (*c* 2.38, CHCl3).

The stereoselectivity of the aldol reaction of ester **3** (with isobutyraldehyde) was crucially influenced by the reaction parameters involved in the generation of the enolates (Table 1). As expected from our earlier observation,[7] the combination of dibutylboron triflate and triethylamine failed to enolize **3** (entry 1). The use of diisopropylethylamine, instead of triethylamine, effected the syn-selective aldol reaction (syn:anti = 7:1; ds for the syn-isomer >97:3) (entry 2). Dicyclopentylboron triflate and triethylamine behaved similarly to the case of dibutylboron triflate (entry 3), whereas the use of diisopropylethylamine afforded the *anti*-aldol product with high diastereofacial selectivity (entry 4). The use of dicyclohexylboron triflate and triethylamine improved both reactivity and selectivity (entry 5), which indicated that this combination would represent a synthetically useful method (see also Table 2 for the stereoselectivity). It should be noted that the *E(O)*-enolate, which

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(9) Under other conditions such as Cs2CO3 in CH3CN (reflux, 0.5 h) or KOt-Bu in DMF (room temperature, 3 h), the reaction also proceeded well.

(10) Compound **3** and *ent*-**3** exist in polymorphic form: lower mp 124 °C.

Table 1. Aldol Reaction of Ester **3**[a]

entry	R$_2$BOTf	amine	temp, time	yield (%)	4c[b]	4′c[b]	5c[b]	5′c[b]
1	Bu$_2$BOTf	Et$_3$N	−78 °C, 2 h	<3				
2	Bu$_2$BOTf	i-Pr$_2$EtN	−78 °C, 2 h	80	12	1	85	2
3	c-Pen$_2$BOTf	Et$_3$N	−78 °C, 2 h	8				
4	c-Pen$_2$BOTf	i-Pr$_2$EtN	−78 °C, 2 h	68	93	4	2	1
5	c-Hex$_2$BOTf	Et$_3$N	−78 °C, 2 h	98	98	2	0	0
6	c-Hex$_2$BOTf	i-Pr$_2$EtN	−78 °C, 2 h	70	97	3	0	0
7	c-Hex$_2$BOTf	Et$_3$N	−78 °C, 2 h; 0 °C, 1 h	97	66	2	31	1

[a] Enolization: **3** (1 equiv) was treated with R$_2$BOTf (2 equiv) and amine (2.4 equiv) in CH$_2$Cl$_2$ under the conditions (temp. and time) indicated in the table. Aldol reaction with i-PrCHO (1.2 equiv): at −78 °C for 1 h and then 0 °C for 1 h. Yield and product ratio by HPLC analysis. [b] **4c** (R = i-Pr; 2R,3R), **4′c** (R = i-Pr; 2S,3S), **5c** (R = i-Pr; 2R,3S), **5′c** (R = i-Pr; 2S,3R).

Table 2. Enolization of Ester **3** with Dicyclohexylboron Triflate[a]

entry	c-Hex$_2$BOTf (equiv)	Et$_3$N (equiv)	enolization time	yield[b]	ds (4c:4′c)
1	1.0	1.2	2 h	67	97.3:2.7
2	1.5	1.8	2	91	97.2:2.8
3[c]	2.0	2.4	2	98	97.7:2.3
4	1.7	2.0	0.5	56	95.9:4.1
5	1.7	2.0	1	73	97.4:2.6

[a] After the enol borinate was formed at −78 °C, i-PrCHO (1.2 equiv) was added at −78 °C. Aldol conditions: at −78 °C for 1 h and then 0 °C for 1 h. Yield and isomer ratio by HPLC analysis. [b] Yields of syn isomers (**5c** and **5′c**) < 2%. [c] See Table 1, entry 5 .

formed at −78 °C, isomerized to a mixture of *E(O)*- and *Z-(O)*-enolates (anti:syn = ~2:1) upon warming to 0 °C for 1 h (entry 7). Rather unexpectedly, the absolute configuration of the C-2 carbon of the major syn isomer **5c** was the same as that of the anti-isomer **4c**. This shows that the *E(O)*- and *Z-(O)*-enolates behave differently in the sense of facial selection when they react with an aldehyde.[11]

The c-Hex$_2$BOTf-Et$_3$N combination was further investigated. As shown in Table 2, entries 1−3, 2 equiv of the boron triflate was necessary to complete enolization of **3** (1 equiv), and we conclude that the optimal enolization condition is achieved with the use of 2 equiv of c-Hex$_2$BOTf and 2.4 equiv of Et$_3$N in CH$_2$Cl$_2$ at −78 °C for 2 h (entry 3). It is noted that the change in the equivalent amount of the boron triflate (1−2 equiv) did not affect the selectivity, and this fact rules out the possibility that the formation of the *anti*-aldols proceeds through Lewis-acid catalysis.

The optimal conditions defined above for the aldol reaction were used for representative aldehydes. As shown in Table 3, the excellent anti-selectivity (anti:syn = >98:2) and diastereo-facial selectivity for anti-isomers (>95:5) were achieved for all of the aliphatic, aromatic, and α,β-unsaturated aldehydes

Table 3. Aldol Reaction of Ester **3** and *ent-***3** with Representative Aldehyde[a]

entry	RCHO	product[b]	yield[c] (%)	ds for anti(4:4′)
1	EtCHO	**4a**	90	96.1:3.9
2	PrCHO	**4b**	95	95.2:4.8
3[d]	i-PrCHO	**4c**	98	97.7:2.3
4	c-HexCHO	**4d**	91	95.2:4.8
5	t-BuCHO	**4e**	96	99.4:0.6
6	PhCHO	**4f**	93	94.7:5.3
7	(E)-MeCH=CHCHO	**4g**	96	98.0:2.0
8	CH$_2$=C(Me)CHO	**4h**	97	95.8:4.2
9	BnOCH$_2$CH$_2$CHO	**4i**	94	94.8:5.2
10	BnOCH$_2$C(Me)$_2$CHO	**4j**	98	95.7:4.3
11[e]	i-PrCHO	*ent-***4c**	91	97.7:2.3
12[e]	PhCHO	*ent-***4f**	95	94.6:5.4

[a] After an enol borinate was formed at −78 °C, aldehyde (1.2 equiv) was added at −78 °C. Aldol conditions: at −78 °C for 1 h and then 0 °C for 1 h. Yield and the isomer ratio by HPLC analysis. [b] **4a** (R = Et), **4b** (R = n-Pr), **4c** (R = i-Pr), **4d** (R = c-Hex), **4e** (R = t-Bu), **4f** (R = Ph), **4g** (R = E-MeCH=CH−), **4h** [R = CH$_2$=C(Me)], **4i** (R = BnOCH$_2$CH$_2$−), **4j** [R = BnOCH$_2$C(Me)$_2$−]. [c] Yields of syn isomers (**5** and **5′**) < 2%. [d] See Table 1, entry 5. [e] *ent-***3** used.

examined. The diastereoselectivity of the reaction was measured by HPLC and ^{1}H NMR analyses. The purified aldol products were converted to the corresponding alcohols (LiAlH$_4$, THF, 0 °C, 1 h) and/or carboxylic acids (LiOH, THF-H$_2$O, 3 days)[4c] without loss of the stereochemical integrity.[12] The absolute stereochemistry of the major product was determined by comparison of the optical rotation data of the corresponding diols or methyl esters with the literature values. The chiral auxiliary could be recovered by silica gel chromatography nearly quantitatively and reused.

In conclusion, we have successfully devised a highly efficient, reliable method for the stereoselective construction of the *anti*-3-hydroxy-2-methylcarbonyl system, a task that has challenged us for many years. It should be emphasized that the ready availability of the auxiliary group, the ease of the operation, and the mildness of the boron aldol reaction render this method advantageous and practical.

Supporting Information Available: The general experimental procedure for the preparation of **3**, the general procedure for the aldol reaction, general procedures for the hydrolysis of the aldol products, and characterization of all new compounds (11 pages). See any current masthead page for ordering and Internet access instructions.

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(12) See Supporting Information for complete experimental details on the hydrolysis of the aldol products.