Boron-Mediated Aldol Reaction of Carboxylic Esters†

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Received October 7, 2003

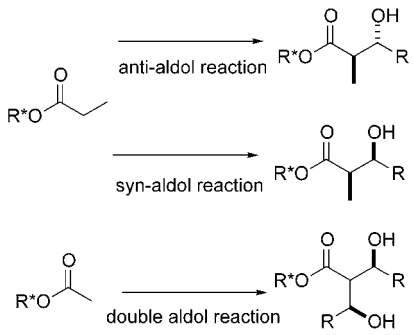
ABSTRACT
This Account outlines the unique features of the boron-mediated aldol reaction of carboxylic esters, which include (i) facile isomerization of *E*-enolate to *Z*-enolate and (ii) formation of a doubly borylated enolate upon enolization of acetate esters. The first carbon-bound boron enolates were spectroscopically characterized, and they appeared to be responsible for these unique properties. Furthermore, complementary anti- and syn-selective boron-mediated asymmetric aldol reactions of chiral propionate esters have been developed. A novel double aldol reaction of acetate esters has been discovered, and a plausible mechanism of the double aldol reaction is proposed.

Introduction

After evolution of the modern aldol technique, the aldol reaction has contributed to the development of organic synthesis as one of the most versatile and reliable carbon−carbon bond forming reactions.[1] Over the last two decades, tremendous efforts have resulted in the development of many highly sophisticated and efficient protocols of stereoselective aldol reactions in enantio- and diastereoselective manners.[2] Among them, the boron-mediated aldol reaction has demonstrated its power and efficiency, especially in the field of total synthesis of complex natural products.[3] The characteristic features of the boron-mediated aldol reactions compared to those of lithium-mediated ones can be summarized as follows: (i) The reacting boron enolate species in solution appears to be homogeneous and uncomplicated in terms of aggregation, while lithium enolates usually exist as aggregates. (ii) The B−O and B−C bonds are shorter than Li−O and Li−C bonds, which makes the transition state more compact. (iii) Nucleophilicity (or basicity) of the boron enolate is less pronounced, which reduces the possible side reactions such as proton transfer reactions. With these characteristics, the stereochemical information in the boron enolates is faithfully reflected in the aldol products, and many boron-based asymmetric aldol reagents have been developed.[4]

Carboxylic esters have been paid little attention as a substrate for boron-mediated aldol reactions. Our recent research on the boron-mediated aldol reaction of carboxylic esters revealed that they were, in fact, as good substrates as other carbonyl compounds. This work led to the development of complementary anti- and syn-selective asymmetric aldol reactions and the discovery of a novel double aldol reaction of acetate esters (Scheme 1). Furthermore, the first carbon-bound boron enolate was characterized as a key player in the unique properties of the boron enolates of carboxylic esters. In this Account, we summarize our findings on the boron-mediated aldol reaction of carboxylic esters.

Scheme 1



Boron-Mediated Aldol Reaction of Propionate Esters

Enolization of Propionate Esters with Boron Triflate and Amine. Since the discovery of a convenient and reliable procedure for the enolization of carbonyl compounds with dialkylboron triflate and a tertiary amine,[5] the boron-mediated aldol reaction has been undoubtedly one of the most successful variants of the modern aldol methodology. As a substrate of the boron-mediated aldol reaction, however, carboxylic esters have been scarcely used compared to ketones, thioesters, or imides. At the very early stage of the boron aldol history, it was documented that enolization of methyl propionate failed with a combination of a boron triflate and an amine as enolization reagents.[6] Since then, carboxylic esters have long been assumed to be inactive under these enolization conditions. Only a few examples of the boron-mediated aldol reaction of carboxylic esters using special reagents or conditions have been recorded.[7]

In 1996, we found[8] that treatment of benzyl propionate with certain pairs of a dialkylboron triflate and an amine provided the corresponding aldol product in high yield (Table 1). The reaction was sensitive to the choice of enolization reagents, and the steric size of the amine was especially important for the success of the enolization. A very large or a very small amine, such as triisopropylamine or 1-methylpyrrolidine, was ineffective for enolization. The failure of enolization with a very small amine is presumably due to formation of a very tight boron triflate−amine complex, and that with a very large amine (*i*-Pr_3N) is due to steric hindrance. It is interesting to note that the

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† This paper is dedicated with respect and affection to the memory of Professor Satoru Masamune, who passed away on November 9, 2003.

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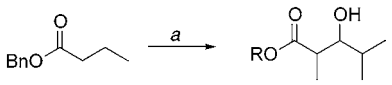
10.1021/ar030249w CCC: $27.50
Published on Web 05/21/2004

Table 1. Boron Aldol Reaction of Benzyl Propionate



amine	yield (%)[b] Et_2BOTf	Bu_2BOTf	*c*-Hex_2BOTf
i-Pr_3N	0	0	0
i-Pr_2NEt	96 (92:8)	97 (95:5)	84 (90:10)
c-Hex_2NMe	93 (95:5)	95 (95:5)	
c-$HexNEt_2$		78 (94:6)	88 (98:2)
Bu_3N	0	<10	
Et_3N	0	<10	92 (10:90)
$(CH_2)_4NMe$	0	0	0

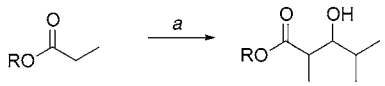
[a] (1) R_2BOTf (1.3 equiv), Et_3N (1.5 equiv); (2) *i*-PrCHO, −78 °C for 1 h, 0 °C for 1 h. [b] syn/anti ratio in parentheses.

combination of a smaller boron triflate (Et_2BOTf, Bu_2BOTf) and a smaller amine (Et_3N, Bu_3N) led to the failure of enolization of the ester. The fact that the same combination of reagents (Bu_2BOTf−Et_3N) effects the enolization of ketones, imides, thioesters, or methyl acetate implies that the inactivity toward propionate esters should be attributed to the insufficient basicity of the amine to deprotonate an α-proton of the propionate from a propionate−boron triflate complex. More interestingly, with *c*-Hex_2BOTf and Et_3N the anti aldol isomer was obtained as a major product; otherwise the syn isomer predominates.

The Anti- and Syn-Selective Asymmetric Aldol Reaction. The aldol reaction of propionyl derivatives (propionate ester, ethyl ketone, propanethioate, *N*-propionyloxazolidinone, etc) with aldehydes produce *syn*- and *anti*-*β*-hydroxy-α-methyl carbonyl compounds. During these two decades, control of the stereochemistry of the aldol reaction in diastereo- or enantioselective manners or both has been a subject of intense research.[9] Following the Zimmerman−Traxler six-membered chairlike transition state model, the stereochemistry of the aldol product (syn or anti) is determined by the configuration of the enolate: the *Z*-enolate leads to the *syn*-aldol, and the *E*-enolate produces the *anti*-aldol. The boron-mediated aldol reaction has an advantage over other aldol variants in its higher stereospecificity due to the shorter bond length (B−O and B−C) and a tighter transition state. Several factors affecting the stereochemistry of the enolization of propionyl derivatives have been studied,[6,7b,10] and diastereoselective and enantioselective syn- or anti-selective boron-mediated aldol reactions have been reported.[6,11,12] Although there are reliable and practical procedures for the syn-selective asymmetric aldol reactions available, most of the reported anti-selective asymmetric aldol reactions suffer from serious disadvantages such as insufficient selectivity, harsh reaction conditions, lack of generality of the substrate, or laborious reagent preparation.

Using two sets of enolization reagents, Bu_2BOTf−*i*-Pr_2EtN and *c*-Hex_2BOTf−Et_3N, we subjected a series of propionate esters to the aldol reaction (Table 2). It was interesting to find that with *c*-Hex_2BOTf−Et_3N, more anti-isomer was produced than from the reactions with Bu_2BOTf−*i*-Pr_2EtN (compare entries 2 and 8, 3 and 10, 4 and 12). The diastereoselectivity of *c*-Hex_2BOTf−Et_3N reaction was sensitive to the alcohol residue of the ester as well as the reaction temperature; the bulkier the ester, the more anti-isomer was produced (entries 6, 8, 10, 12, and 14), and at higher temperature, the syn-isomers became predominant (entries 5, 7, and 11). Formation of the anti-isomer should be attributed to the kinetic formation of *E*-enolate, because isomerization of the enolate was observed under the enolization conditions (Table 3, entries 3−5). Thus, the aldol reaction at −95 °C afforded the anti-aldol product (>97:3), which implies the intermediate enolate consisted of >97% *E*-enolate. When the enolate solution was warmed to 0 °C before addition of aldehyde, the syn-aldol product was obtained as a major product. This facile isomerization is particularly noteworthy in comparison with an enolate of propiophenone. Although the isomer ratio of the aldol products altered depending on the reaction temperature, it did not change with warming of the enolate mixture (Table 3, entries 6−10). The geometry of the enolate of propiophenone was

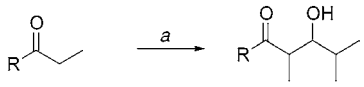
Table 2. Boron Aldol Reaction of Propionate Esters



entry	propionate ester	enolization reagents	conditions	yield (%)	syn/anti
1	$EtCO_2Me$	Bu_2BOTf−*i*-Pr_2EtN	−78 °C, 1 h	85	>97:3
2	$EtCO_2Et$		−78 °C, 1 h	81	95:5
3	$EtCO_2CH_2$*c*-Hex		−78 °C, 1 h	89	80:20
4	$EtCO_2$*i*-Pr		−78 °C, 1 h	65	75:25
5	$EtCO_2Me$	*c*-Hex_2BOTf−Et_3N	0 °C, 0.5 h	64	>97:3
6	$EtCO_2Me$		−78 °C, 1 h	84	>97:3
7	$EtCO_2Et$		0 °C, 0.5 h	77	70:30
8	$EtCO_2Et$		−78 °C, 1 h	86	60:40
9	$EtCO_2Et$		−95 °C, 1 h	75	7:93
10	$EtCO_2CH_2$*c*-Hex		−78 °C, 1 h	92	30:70
11	$EtCO_2$*i*-Pr		0 °C, 0.5 h	90	96:4
12	$EtCO_2$*i*-Pr		−78 °C, 1 h	63	30:70
13	$EtCO_2$*i*-Pr		−95 °C, 1 h	86	18:82
14	$EtCO_2$*t*-Bu		−78 °C, 1 h	69	3:>97

[a] (1) R'_2BOTf (1.3 equiv), Et_3N (1.5 equiv); (2) *i*-PrCHO, −78 °C for 1 h, 0 °C for 1 h.

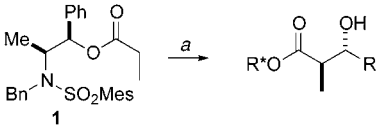
Table 3. Isomerization of the Boron Enolate



entry	R	enolization conditions	yield (%)	syn/anti
1	BnO	0 °C, 0.5 h	94	90:10
2		−78 °C, 0.5 h	92	10:90
3		−95 °C, 1 h	80	3:>97
4		−95 °C, 1 h; 0 °C, 0.5 h	84	67:33
5		−95 °C, 1 h; 0 °C, 2 h	90	90:10
6	Ph	0 °C, 0.5 h	97	95:5
7		−78 °C, 0.5 h	92	73:27
8		−78 °C, 0.5 h; 0 °C, 0.5 h	92	75:25
9		−95 °C, 1 h,	84	67:33
10		−95 °C, 1 h; 0 °C, 0.5 h	92	74:26

[a] (1) *c*-Hex_2BOTf (1.3 equiv), Et_3N (1.5 equiv); (2) *i*-PrCHO, −78 °C for 1 h, 0 °C for 1 h.

Table 4. anti-Selective Asymmetric Aldol Reaction of Compound 1



RCHO	yield (%)	ds for anti[b]
MeCHO	92	97:3
EtCHO	90	96:4
n-PrCHO	95	95:5
i-PrCHO	95	98:2
c-HexCHO	91	95:5
t-BuCHO	96	>99:1
PhCHO	93	95:5
(*E*)-CH_3CH=$CHCHO$	96	98:2
CH_2=$C(CH_3)CHO$	97	96:4
$BnOCH_2CH_2CHO$	94	95:5
$BnOCH_2C(CH_3)_2CHO$	98	96:4

[a] *c*-Hex_2BOTf (2.0 equiv), Et_3N (2.4 equiv), −78 °C for 2 h; then RCHO, −78 °C for 1 h, 0 °C for 1 h. [b] anti/syn = >98:2; ds = diastereoselectivity.

determined at the enolization stage and the configuration did not change under the enolization conditions.[6,13]

The results in Tables 1 and 2 demonstrate the possibility of controlling the stereochemical course of the aldol reaction by the judicious choice of enolization conditions. To develop an asymmetric aldol reagent, chiral propionate esters were tested for the anti- and syn-selective aldol reaction with *c*-Hex_2BOTf−Et_3N and Bu_2BOTf−*i*-Pr_2EtN conditions, respectively.

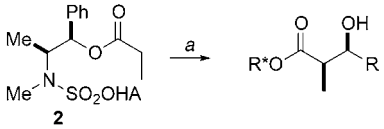
We found that compound **1** exhibited excellent diastereo- and diastereofacial selectivities for the anti-selective asymmetric aldol reaction.[14] Under carefully optimized reaction conditions, the anti-selective asymmetric aldol reaction of compound **1** proceeded with excellent diastereo- (>98:2) and diastereofacial (>95:5) selectivities with all of aldehydes examined, including aliphatic aldehydes of various steric bulkiness and aromatic and α,β-unsaturated aldehydes (Table 4). This wide applicability as well as ready availability of both enantiomeric reagents[15] and operational simplicity of the reaction demonstrate the practical merit of this procedure.

Compound **1** showed high diastereofacial selectivity (97:3) for the syn-selective asymmetric aldol reaction using Bu_2BOTf/*i*-Pr_2EtN; however, the diastereoselectivity of the reaction was only marginal (syn/anti = 87:13). The structurally related compound **2** exhibited excellent selectivity in both diastereo- and diastereofacial manners with a wide range of aldehydes (Table 5).[14b,16] This reaction provides an alternative to the existing syn-selective aldol reactions.

Boron-Mediated Aldol Reaction of Acetate Esters

The Double Aldol Reaction. An extension of this investigation would naturally include an acetate aldol reaction utilizing a chiral ester. The reaction of ester **3** proceeded in an unusual manner to afford a substantial amount of the unexpected bis-aldol products **5**, along with the expected mono-aldol product **4** (Scheme 2).[17]

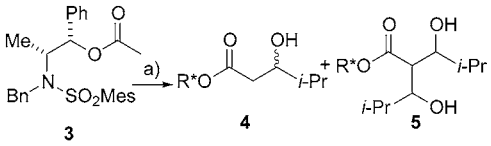
Table 5. syn-Selective Asymmetric Aldol Reaction of Compound 2



RCHO	yield (%)	ds for syn[b]
EtCHO	95	97:3
n-PrCHO	93	>97:3
i-PrCHO	98	97:3
t-BuCHO	97	97:3
PhCHO	97	95:5
(*E*)-CH_3CH=$CHCHO$	98	>97:3

[a] Bu_2BOTf (2.0 equiv), Et_3N (2.4 equiv), −78 °C, 2 h; then RCHO, −78 °C for 1 h, 0 °C for 1 h. [b] syn/anti = >95:5; ds = diastereoselectivity.

Scheme 2

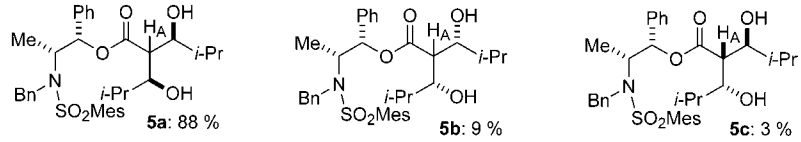


Optimization of a variety of reaction parameters led to the establishment of conditions for almost exclusive formation of **5** (**4**/**5** = <5:95). Treatment of compound **3** with *c*-Hex_2BOTf (2.5 equiv) and Et_3N (3.0 equiv) at −78 °C for 15 min, followed by reaction with isobutyraldehyde (−78 °C, 10 min; then rt, 30 min), afforded product **5** in over 95% yield with a diastereomer ratio of **5a**/**5b**/**5c** = 90:8:2. The fourth possible isomer was not detected. The major bis-aldol product **5a**, obtained as a pure crystalline compound, has been fully characterized by NMR as well as X-ray crystallography. Stereochemistry of other isomers was determined as their acetonides (Chart 1). The stereochemistry of the newly formed stereocenters in **5a** is the same as that of the anti-selective aldol reaction, which suggests that both aldol reactions proceed through *E*-enolate.[18] At higher reaction temperature, **5b** became a major product (0 °C; **5a**/**5b**/**5c** = 23:67:10), due to isomerization of the *E*-enolate to the *Z*-enolate.

The double aldol reaction proceeded in high selectivity with a variety of aldehydes (Table 6). Taking advantage of the embedded "chiral bis-carbinol moiety", we synthesized chiral triols of C_3-symmetry[19] in a straightforward manner (Scheme 3).

The Characteristic Features of the Double Aldol Reaction. Unique features of the boron-mediated aldol reaction of carboxylic esters and the unusual behavior of the boron-containing intermediate are the following. (1) While double aldol reactions proceed with an acetate ester as the enolate source, this double aldol reaction does *not* occur with other carbonyl compounds such as methyl ketones, acetate thioesters, and propionate esters under the reaction conditions. (2) When acetate ester **3** was enolized with *less* than 2 equiv of dialkylboron triflate, both bis-aldol products **5** and recovered starting material were obtained. Therefore, the formation of bis-aldol products is not solely due to the ratio of the excess

Chart 1



5a: 88 %
*acetonide
H_A: δ 2.74, J=4.8, 7.8 Hz

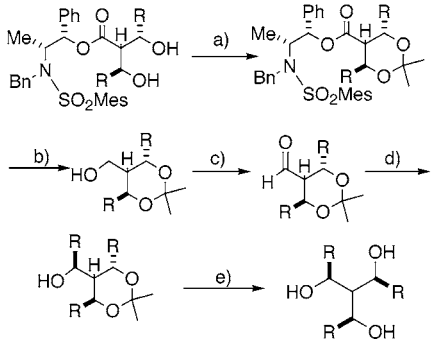
5b: 9 %
*acetonide
H_A: δ 2.65, J=4.6, 7.5 Hz

5c: 3 %
*acetonide
H_A: δ 2.56, t, J=2.7 Hz

Table 6. Asymmetric Double Aldol Reaction

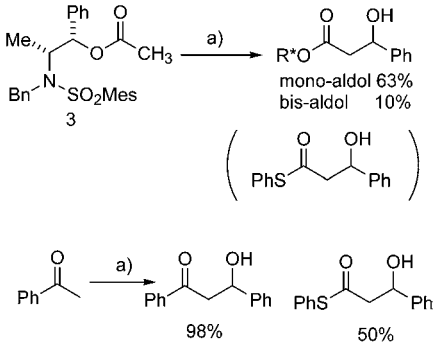
RCHO	chiral-a/chiral-b/meso-c
i-PrCHO	88:9:3
EtCHO	90:4:6
MeCHO	94:4:2
PhCHO	84:3:13
$C_{10}H_{23}CHO$	95:0:5
$CH_2{=}C(CH_3)CHO$	90:4:6

Scheme 3[a]



[a] (a) 2,2-dimethoxypropane, PTS; (b) $LiAlH_4$; (c) PHSNH*t*-Bu, NCS, K_2CO_3; (d) RMgBr; (e) H_3O^+.

Scheme 4[a]



[a] (a) (1) *c*-Hex_2BOTf (2.0 equiv), Et_3N (2.4 equiv), CH_2Cl_2, −78 °C, 0.5 h; (2) $PhSCOCH_3$ (1 equiv); (3) PhCHO.

dialkylboron triflate to ester. (3) When the enolate of compound **3** (1 equiv), prepared with *c*-Hex_2BOTf (2 equiv) and Et_3N (2.5 equiv), was mixed with *S*-phenyl thioacetate (1 equiv), no enolization of *S*-phenyl thioacetate occurred. This result is in contrast to the same experiment with acetophenone in place of compound **3**, in which the aldol product of the thioester was obtained in ∼50% yield (Scheme 4). These results demonstrate that in the ester aldolization the "second equivalent of boron triflate" is neither free boron triflate nor an equilibrium form of boron triflate. (4) Subjection of an equimolar mixture of compounds **3** and **4′** (dr = 3:1) under the optimized double aldol reaction conditions afforded **5a**−**c** in the same ratio as shown above, while **4′** was recovered unchanged, quantitatively (Scheme 5). This result implies that the conventionally assumed boron aldolate **6** is not a precursor to the double aldol reaction.

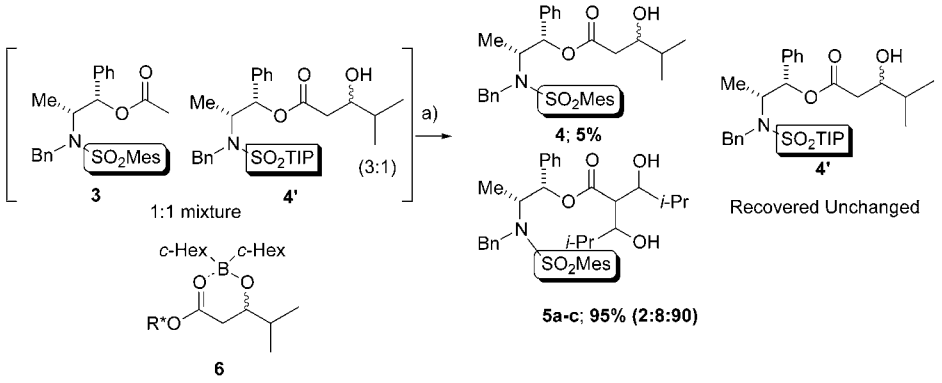
It is now a distinct possibility that two kinds of boron species are involved in the boron-mediated aldol reaction of carbonyl compounds. The first boron species exists with ketones and thioesters and leads to the *single* aldol reaction. The second boron species exists with acetate esters and leads to the *double* aldol reaction with the stoichiometry of carbonyl/boron = 1:2.

The Doubly Borylated Enolate as an Intermediate of the Double Aldol Reaction.[20] To elucidate the pathway of the double aldol reaction, the reaction was monitored by NMR spectroscopy. When methyl acetate (1.0 equiv, Figure 1a) and *c*-Hex_2BOTf (2.5 equiv) were mixed in $CDCl_3$, the ^1H NMR spectrum showed a downfield shift of the chemical shift due to complexation (Figure 1b). Addition of Et_3N (3.0 equiv) to the mixture resulted in clean conversion to a new species, which was determined to be the doubly borylated enolate **7** (Figure 1c,d). The structure of compound **7** was unequivocally established using modern NMR techniques. Compound **7**, in turn, was proved to be an intermediate in the double aldol reaction by its reaction with isobutyraldehyde to give compound **8** (Figure 1e). The doubly borylated enolate is unusual in that two dicyclohexylboron moieties are incorporated in the enolate involving formation of a carbon−boron bond. It should be added that the corresponding doubly borylated enolates could be prepared from methyl acetate with *n*-Bu_2BOTf, 9-BBN triflate or *c*-Hex_2BI under the same reaction conditions.

NMR Spectroscopic Characterization of a Carbon-Bound Boron Enolate.[21] Mechanistic considerations concerning the formation of a doubly borylated enolate naturally led to the assumption of the intermediacy of an α-borylester. From a structural point of view, three distinct types of "enolate" are possible depending on the nature of the metal−enolate bond; an oxygen-bound enolate, an α-metalocarbonyl compound (a carbon-bound enolate), and a η^3-oxaallyl complex. Although α-borylcarbonyl compounds have been described as a hypothetical intermediate in certain reactions,[22] boron enolates are believed to exist only as oxygen-bound enolates, and carbon-bound boron enolates have never been characterized as such.

Assuming a two-step enolization process toward doubly borylated enolates, treatment of an acetate ester with a decreased amount of boron triflate should produce an intermediate monoboron enolate. From an extensive survey of acetate esters with the purpose of detecting the possible "carbon-bound boron enolate" intermediate, we

Scheme 5[a]



[a] (a) (1) *c*-Hex$_2$BOTf (2.5 equiv), Et$_3$N (3 equiv), CH$_2$Cl$_2$, −78 °C, 0.5 h; (2) *i*-PrCHO (3 equiv), −78 °C to rt.

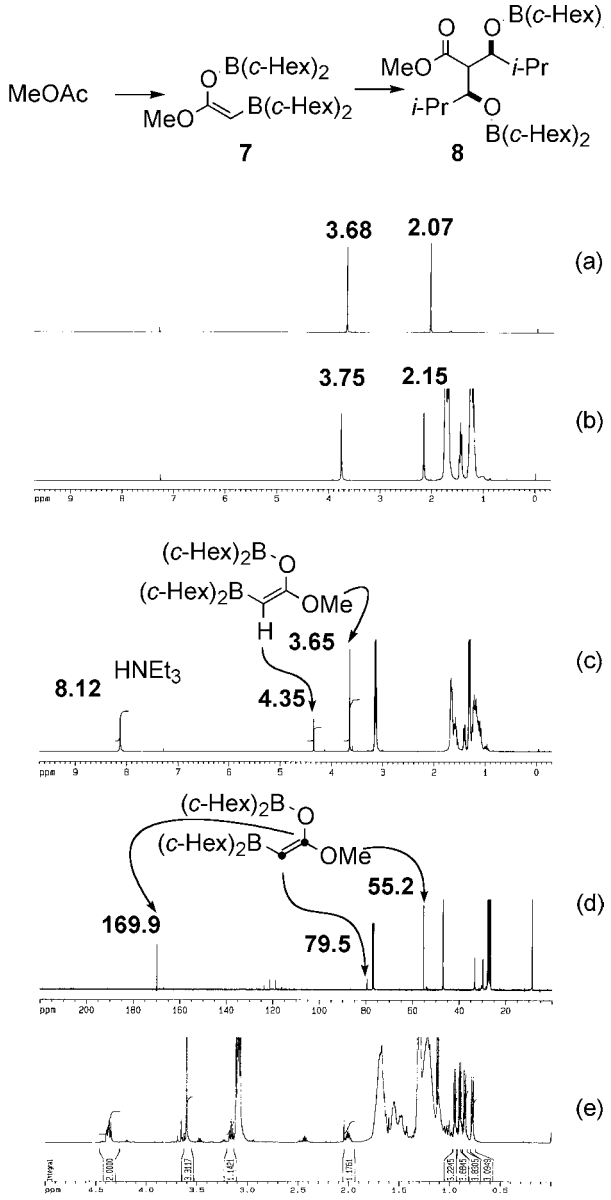


FIGURE 1. NMR trace of the double aldol reaction of methyl acetate: (a) ^{1}H NMR of methyl acetate; (b) ^{1}H NMR of methyl acetate + *c*-Hex$_2$BOTf (2.5 equiv); (c) ^{1}H NMR of methyl acetate + *c*-Hex$_2$BOTf (2.5 equiv) + Et$_3$N (3 equiv); (d) ^{13}C NMR of methyl acetate + *c*-Hex$_2$BOTf (2.5 equiv) + Et$_3$N (3 equiv), (e) ^{1}H NMR of methyl acetate + *c*-Hex$_2$BOTf (2.5 equiv) + Et$_3$N (3 equiv) + *i*-PrCHO (3 equiv).

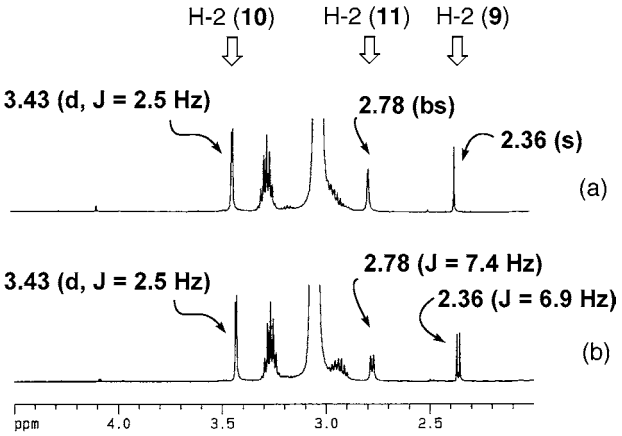
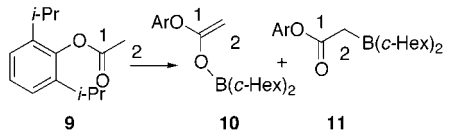


FIGURE 2. ^{1}H NMR of enolate mixture derived from **9** (a) and 1-^{13}C-**9** (b).

Scheme 6



found that certain aryl acetates afforded the corresponding monoboron enolates as a mixture of oxygen- and carbon-bound forms. When 2,6-diisopropylphenyl acetate (**9**) was treated with 1.3 equiv of *c*-Hex$_2$BOTf and 1.5 equiv of Et$_3$N in CDCl$_3$ at 0 °C, the ^{1}H NMR spectrum showed formation of two enolate species (oxygen- (**10**) and carbon-bound (**11**) enolates, Scheme 6) in a 7:2 ratio with 90% conversion (see signals at 3.43 and 2.78 ppm in Figure 2a, respectively).

The major species exhibited a set of doublets (J = 2.5 Hz) at 3.43 and 3.06 (concealed) ppm (C=CH_2), suggesting the structure of the oxygen-bound enolate (**10**, Scheme 6). The minor component, carbon-bound enolate **11**, exhibited a broad singlet at 2.78 ppm (COCH_2B), the assignment of which was confirmed by the ^{1}H NMR of the enolate sample derived from 1-^{13}C-**9** (doublet at 2.78 ppm, J = 7.4 Hz, Figure 2b). The structures of these enolates were determined using two-dimensional NMR techniques. This represents the first spectroscopic characterization of a carbon-bound boron enolate.

Table 7. Enolization of Acetate Esters[a]

entry	aryl acetate **9** (R^1; R^2)	product composition (%) **9**	**10**	**11**	**12**[b]
1	R^1 = H; R^2 = H	54	0	0	46 (5:1)
2	R^1 = Me; R^2 = H	17	52	14	17 (9:1)
3	R^1 = Et; R^2 = H	10	56	15	19 (9:1)
4	R^1 = *i*-Pr; R^2 = H	7	71	20	2 (>20:1)
5	R^1 = Ph; R^2 = H	10	46	43	1 (1:1)
6	R^1 = Me; R^2 = *t*-Bu	27	37	13	23 (4:1)
7	R^1 = Me; R^2 = Br	11	63	15	18 (9:1)
8	R^1 = Me; R^2 = MeO	18	46	13	3 (12:1)

[a] A solution of acetate ester (0.5 mmol) and Et_3N (0.75 mmol) in $CDCl_3$ (2.5 mL) was treated with *c*-Hex_2BOTf (0.65 mmol) at 0 °C. After 5 min, the product composition was determined by ^1H NMR. [b] Isomer ratio (stereochemistry not determined) in parentheses.

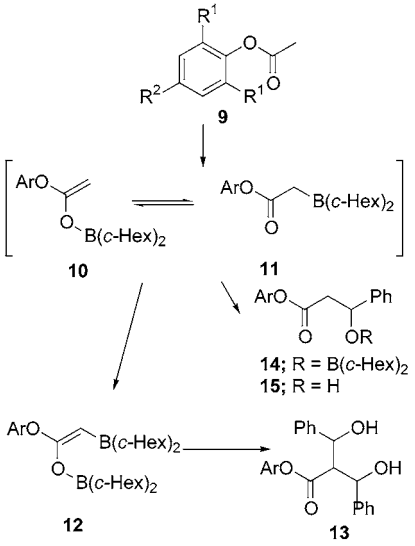
The degree of formation of monoenolate was highly dependent on the steric factor of the acetate. Formation of the monoenolate became less favorable with the less sterically demanding substituents on the 2- and 6-positions; the lower analogues (2,6-diethyl and 2,6-dimethylphenyl acetates) gave less monoenolates (Table 7, entries 2 and 3), and phenyl acetate did not afford the monoenolate (entry 1). This difference can be attributed to steric factors; for the bulkier esters, the coordination of the second molecule of a boron triflate to the carbonyl group of the α-borylester becomes unfavorable making the lifetime of the monoenolate longer. 2,6-Dimethylphenyl esters with the substituents of different electronic nature on the 4-position gave the monoenolate in comparable yields (entries 2 and 6−8).

Chemical Properties of the Carbon-Bound Boron Enolate. Carbon- and oxygen-bound enolates may exist as separable, interconvertible species (e.g., silicon enolates[23]) or equilibrium mixtures (e.g., tin enolates[24]) depending on the metals. To elucidate the nature of the carbon-bound boron enolate species, the chemical reactivity of the enolate mixture was examined. With an additional 1.3 equiv of *c*-Hex_2BOTf (and 1.5 equiv of Et_3N), the monoenolate mixture of **10** and **11** was quantitatively converted to the doubly borylated enolate **12**. When the same monoenolate mixture was treated with 0.5 equiv of benzaldehyde at 0 °C, ^1H NMR showed formation of the boron aldolate **14** (43%) leaving **10** (37%) and **11** (10%), whereas the treatment with 1.3 equiv of benzaldehyde afforded the monoaldol product **15** in 71% yield after workup (Scheme 7).

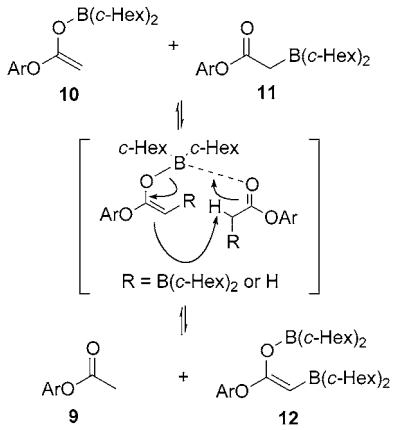
The aldol reaction presumably proceeds via the oxygen-bound enolate.[25] Thus, the indistinguishable reactivity of the oxygen- and carbon-bound boron enolates in these reactions suggests rapid equilibrium between them, and this was confirmed by variable-temperature NMR experiments at −43 to 27 °C. The equilibrium was established within the NMR acquisition time, and the ratio of the oxygen- and carbon-bound enolates at equilibrium was dependent only on the temperature but not on time; at higher temperatures, the enolate mixture consisted of more oxygen-bound enolate.

The monoenolates of aryl acetates were reasonably stable but underwent disproportionation via an equilibrium process between the oxygen- and the carbon-bound enolates (and also between the doubly borylated enolate and the acetate) to produce the starting acetate and the doubly borylated enolates upon standing (Scheme 8). The rate of disproportionation was affected by the steric factor of the substrate.

Scheme 7



Scheme 8



Doubly Borylated Enolate Formation from Various Carbonyl Compounds. The doubly borylated enolate chemistry was further examined (Table 8). Upon treatment with *c*-Hex_2BOTf (2.5 equiv) and Et_3N (3.0 equiv) in $CDCl_3$ at 0 °C for 5 min (condition A), a variety of carbonyl compounds, such as methoxyacetone, acetic acid, dimethylacetamide, 2-acetylpyridine, and 3-acetyl-2-oxazolidinone,[26] gave the corresponding doubly borylated enolates. Only an oxygen-bound monoenolate, however, was detected from $PhSCOCH_3$, acetophenone, 2-butanone, 4-methoxyacetophenone, or 2-methoxyacetophenone. It is interesting to note that with 1 equiv of the boron triflate, methoxyacetone and 3-acetyl-2-oxazolidinone afforded the oxygen-bound monoenolate in >98% and 72% yields, respectively (condition B), and the monoenolate of $PhSCOCH_3$ and 2-methoxyacetophenone were slowly converted to the doubly borylated enolates after prolonged reaction at 0 °C with excess boron triflate (condition C).

Scheme 9

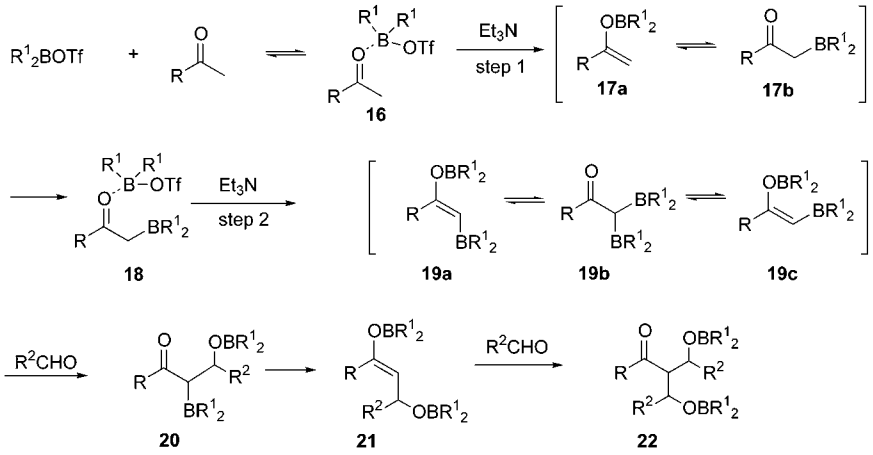
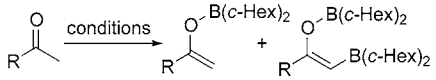


Table 8. Enolization of Acetyl Derivatives



R	conditions[a]	yield (%) monoenolate	yield (%) DBE[c]
$MeOCH_2$	A	0	>98
HO	A[b]	0	>98
Me_2N	A	0	>98
2-Py	A	0	>98
2-oxazolidione	A	0	>98
PhS	A	>98	0
Ph	A	>98	0
Et	A	>98	0
2-MeO-C_6H_4	A	>98	0
4-MeO-C_6H_4	A	>98	0
2-oxazolidione	B	72	11[d]
$MeOCH_2$	B	>98	0
PhS	C	0	>98
2-MeO-C_6H_4	C	0	>98

[a] Conditions: (A) carbonyl compound (1.0 equiv), *c*-Hex_2BOTf (2.5 equiv), and Et_3N (3.0 equiv) in $CDCl_3$ at 0 °C, 5 min; (B) carbonyl compound (1.0 equiv), *c*-Hex_2BOTf (1.0 equiv), and Et_3N (1.3 equiv) in $CDCl_3$ at −65 °C, 10 min; (C) carbonyl compound (1.0 equiv), *c*-Hex_2BOTf (3.5 equiv), and Et_3N (4.0 equiv) in $CDCl_3$ at 0 °C, 24 h. [b] *c*-Hex_2BOTf (4.0 equiv) and Et_3N (5.0 equiv) were employed. [c] Doubly borylated enolate. [d] Starting material = 17%.

From these results, it is conceivable that the formation of the doubly borylated enolate and the success of the double aldol reaction should be attributed to the stability of the carbon-bound boron enolate species.[27] Resonance stabilization of the carbon-bound enolates of carboxylic ester, thioester, and ketone diminished in this order, and the nearby chelating functional group stabilized the carbon-bound enolate intermediate of methoxyacetone, 2-acetylpyridine, and 2-methoxyacetophenone.

A plausible pathway of the double aldol reaction can be summarized as shown in Scheme 9. A boron triflate reversibly forms a complex with both a carbonyl compound and an amine. When the boron triflate−carbonyl compound complex **16** is more favorable than boron triflate−amine complex **and** the acidity of the α-proton of the boron−carbonyl complex is high enough to be deprotonated with the amine, enolization proceeds (step 1). The initial product, an oxygen-bound monoenolate **17a**, rapidly equilibrates with the carbon-bound enolate **17b**, and the latter is again enolized with the aid of boron triflate and amine (step 2). This second enolization proceeds with an acetate ester (and a thioacetate, acetyl-2-oxazolidinone, and certain ketones) irrespective of the amount of the carbon-bound enolates. For acetates with a smaller alcohol residue, step 2 is faster than step 1; thus, only the doubly borylated enolate is produced even with 1 equiv of boron triflate. For larger esters, step 2 becomes slower due to steric hindrance. For acetophenone or 2-butanone, the concentration of the carbon-bound enolate is too low to form **18** for the further enolization to the doubly borylated enolate. In the case of enolization of acetate esters with sufficiently large R, the configuration of the initially formed doubly borylated enolate is *E* (**19a**) at low temperature, which may isomerize to *Z*-isomer (**19c**) upon warming. The facile isomerization implies that it also proceeds through a carbon-bound boron enolate (**19b**). The aldol reaction naturally proceeds in a stepwise manner to afford α-boryl *β*-boryloxy carbonyl intermediate **20**, which isomerizes to the second (oxygen-bound) enolate with *E* configuration **21**. Then the bis-aldol **22** is produced after reaction with the second equivalent of the aldehyde.

Conclusion

From the research on the boron-mediated aldol reaction of carboxylic esters reported here, we have found that carbon-bound boron enolates have a crucial role in the boron enolate chemistry. The carbon-bound enolate is responsible for a variety of unusual and unique properties of boron aldol reaction of carboxylic esters, such as facile isomerization of *E*-enolate to *Z*-enolate or doubly borylated enolate formation. Contribution of a carbon-bound enolate to the boron enolate of carboxylic esters would suggest new uses of boron enolate chemistry in other synthetic reactions than aldol reactions. A bonus of the present research includes development of complementary anti- and syn-selective asymmetric aldol reactions and discovery of the new double aldol reaction. The anti aldol reaction is especially valuable for natural product synthesis, and the double aldol reaction provides a convenient access to chiral triols of C_3-symmetry, which would

be useful chiral building blocks for asymmetric molecular recognition.

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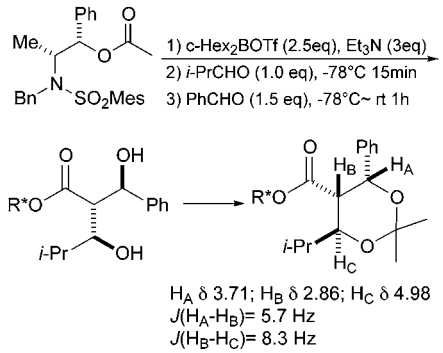

H_A δ 3.71; H_B δ 2.86; H_C δ 4.98
$J(H_A\text{-}H_B)$= 5.7 Hz
$J(H_B\text{-}H_C)$= 8.3 Hz

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