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Mechanism of the Double Aldol Reaction: The First Spectroscopic Characterization of a Carbon-Bound Boron Enolate Derived from Carboxylic Esters

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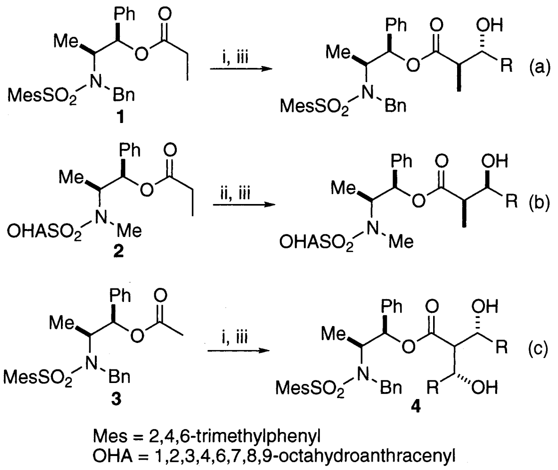
Received February 22, 2002

Abstract: The novel doubly borylated enolate is identified as an intermediate of the double aldol reaction of acetate esters. As a precursor to the formation of the doubly borylated enolate, carbon-bound boron enolates of carboxylic esters are spectroscopically characterized for the first time. When 2,6-diisopropylphenyl acetate (**10d**) is treated with *c*-Hex$_2$BOTf (1.3 equiv) and triethylamine (1.5 equiv) in CDCl$_3$, the corresponding mono-enolate is formed as a mixture of oxygen- (**11d**) and carbon-bound (**12d**) forms in 71% and 20% yields, respectively. The structures of these enolates have been unambiguously determined by NMR spectroscopy. Investigation of the enolization of a series of substituted aryl acetates shows that the steric factor of the acetate affects the degree of the mono-enolate (as a mixture of oxygen- and carbon-bound enolates) and the doubly borylated enolate formation. Studies also revealed that oxygen- and carbon-bound boron enolates exist as equilibrium mixtures and that a proton transfer process occurs between oxygen- and carbon-bound enolates. The doubly borylated enolate formation is general for a variety of carbonyl compounds. Besides acetate esters, carbonyl containing compounds, such as acetic acid, dimethylacetamide, methoxyacetone, and 3-acetyl-2-oxazolidinone, also produce the doubly borylated enolates when treated with *c*-Hex$_2$BOTf (2.5 equiv) and triethylamine (3.0 equiv). A plausible pathway of the double aldol reaction involving a carbon-bound boron enolate as a key intermediate is proposed.

Introduction

Since the discovery of a convenient and reliable procedure for the enolization of carbonyl compounds with dialkylboron triflate and a tertiary amine,[1] the boron-mediated aldol reaction has been undoubtedly one of the most successful variants of the modern aldol methodology. As a substrate of this reaction, however, carboxylic esters have been scarcely used, as compared with ketones, thioesters, or imides. Recently, we have found that there are a number of unique features to the boron-mediated aldol reaction of carboxylic esters,[2a] which are summarized as follows: (i) the stereochemistry of an enolate of propionate ester could be controlled by the judicious selection of the enolization conditions, (ii) facile isomerization of an *E*-enolate[3] to the *Z*-enolate was observed, and (iii) the boron-mediated aldol reaction of acetate esters proceeded in an unusual manner to produce bis-aldols. More specifically, we have reported that anti- and syn-β-hydroxy-α-methyl carbonyl adducts can be constructed from chiral propionate esters **1**[2b,d] and **2**[2c,d] (Scheme 1a and 1b), and acetate ester **3** undergoes novel double aldol reaction to give **4** selectively (Scheme 1c).[4] Furthermore, bis-aldol **4** provided an efficient route to chiral triols of C$_3$-symmetry.

Scheme 1



[a] (i) *c*-Hex$_2$BOTf (2.5 eq), Et$_3$N (3 eq), (ii) RCHO. [b](i) *n*-Bu$_2$BOTf (2.5 eq), *i*-Pr$_2$EtN (3 eq), (ii) RCHO. Mes = 2,4,6-trimethylphenyl, OHA = 1,2,3,4,6,7,8,9-octahydroanthracenyl

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(1) Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

(2) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590. (b) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (c) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (d) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250.

(3) In this paper the *Z* and *E* stereochemical descriptors of enol borinates are defined on the assignment of the highest priority designation to the OBR$_2$ group.

(4) Abiko, A.; Liu, J.-F.; Buske, D. C.; Moriyama, S.; Masamune, S. *J. Am. Chem. Soc.* **1999**, *121*, 7168.

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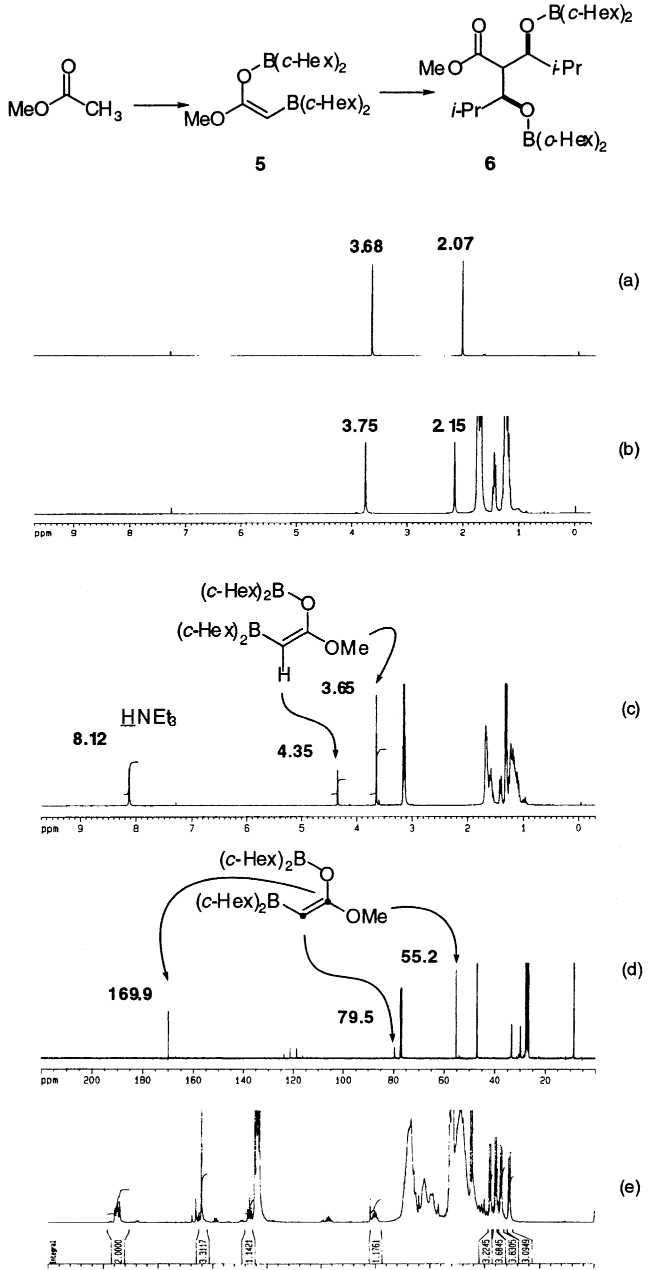


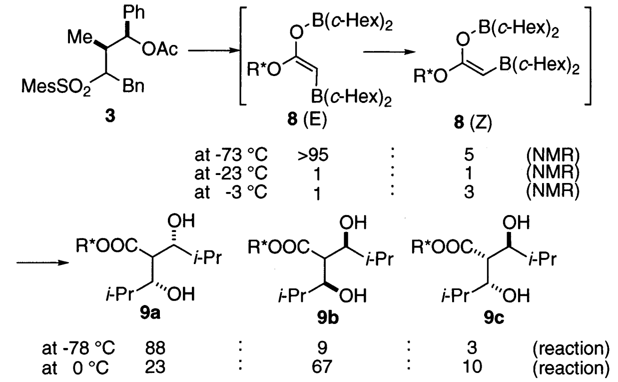
Figure 1. (a) ^{1}H NMR of methyl acetate, (b) ^{1}H NMR of (a) + *c*-Hex$_2$-BOTf (2.5 eq), (c) ^{1}H NMR of (b) + Et$_3$N (3 eq), (d) ^{13}C NMR of (b) + Et$_3$N (3 eq), (e) ^{1}H NMR of (c) + *i*-PrCHO (3 eq).

From the detailed investigation of the double aldol reaction of methyl acetate, the novel doubly borylated enolate **5** was identified as an intermediate enolate species (Figure 1). Herein, we disclose further efforts to delineate the mechanism of the double aldol reaction, including the characterization of the first carbon-bound boron enolate of carboxylic esters. Part of the work appeared earlier in preliminary form.[5]

Results and Discussion

The Doubly Borylated Enolate as an Intermediate of the Double Aldol Reaction. 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$_2$BOTf (2.5 equiv) were mixed in CDCl$_3$ (0.27 M for MeOAc, 0.68 M for *c*-Hex$_2$BOTf), the ^{1}H NMR spectrum showed a downfield shift of the chemical shift because of complexation (Figure 1b). Addition of triethylamine (3.0 equiv) to the mixture produced the doubly borylated enolate **5** (Figure 1c and d). The structure of **5** was unequivocally established using modern NMR techniques.[5] (Detailed discussion is given in ref 5.) The order of mixing of the reagents (acetate, boron triflate, and amine) did not affect the results. **5**, in turn, was proved to be an intermediate of the double aldol reaction by the reaction with isobutyraldehyde to give **6** (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. Double borylation in the doubly borylated enolate was further confirmed by a deuteration experiment. When the corresponding doubly borylated enolate derived from benzyl acetate was treated with D$_2$O-MeOD two deuteriums were incorporated in the recovered acetate at the acetyl group quantitatively. The corresponding doubly borylated enolates could be prepared from methyl acetate with *n*-Bu$_2$BOTf, 9-BBN triflate, or *c*-Hex$_2$BI under the same reaction conditions.

Scheme 2



Chiral acetate ester **3** also afforded the doubly borylated enolate **8** with *c*-Hex$_2$BOTf (2.5 equiv) and triethylamine (3.0 equiv) (Scheme 2). At −73 °C in CD$_2$Cl$_2$–CDCl$_3$, **8-*E*** was formed as a single isomer, which isomerized to a mixture of **8-*E*** and **8-*Z*** upon warming; **8-*E***: **8-*Z*** = 1:1 at −23 °C, 1:3 at −3 °C (Figure 2). The facile isomerization of the doubly borylated enolate is particularly noteworthy (vide infra). The similar *Z*-isomer preference on the isomerization of the boron enolate was observed for the chiral propionate ester **1**. The *E*:*Z* ratios of **8** at −73 °C (**8-*E*** only) and −3 °C (**8-*E***: **8-*Z*** = 1:3) were in good agreement with the ratios of the double aldol products obtained by enolization at −78 °C (**9a**:**9b**:**9c** = 88:9:3) and at 0 °C (**9a**:**9b**:**9c** = 23:67:10) (Scheme 2). **8-*E*** mainly produced **9a**, whereas **8-*Z*** afforded **9b** as a major product. Thus, the same chiral auxiliary group exhibited the oposite sense of diastereofacial selection with its *E* and *Z* enolates. The similar reversal of the facial selectivity was observed in the related anti- and syn-selective asymmetric aldol reactions (see Scheme 1i and ii).[2b]

NMR Spectroscopic Characterization of a Carbon-Bound Boron Enolate. 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 "enolates" are possible depending on the nature of the metal-enolate bond; an oxygen-bound enolate, an α-metalocarbonyl compound (a

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(5) Abiko, A.; Inoue, T.; Furuno, H.; Schwalbe, H.; Fieres, C.; Masamune, S. *J. Am. Chem. Soc.* **2001**, *123*, 4605.

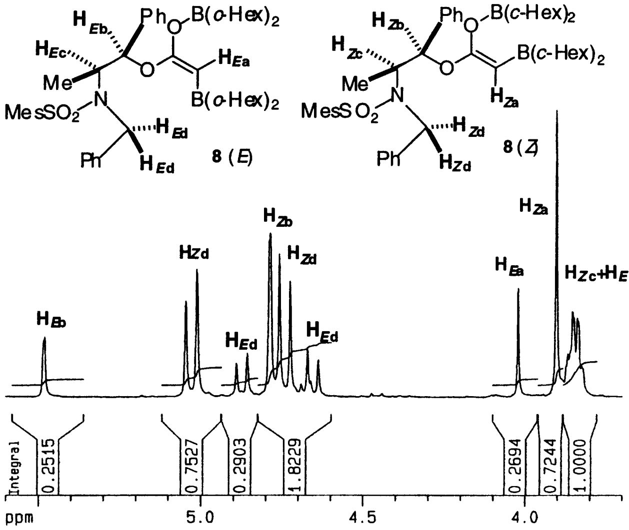
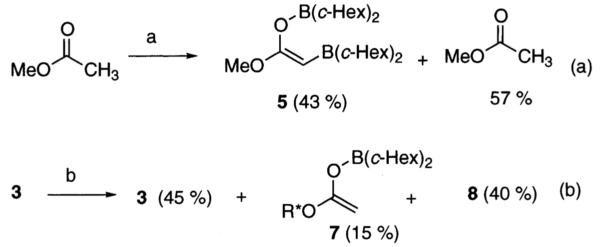


Figure 2. ^{1}H NMR spectrum (partial) of the doubly borylated enolate mixture (**8**) from **3**.

Scheme 3



[a] c-Hex$_2$BOTf (1.0 eq), Et$_3$N (1.3 eq), CDCl$_3$ 0 °C 5 min. [b] c-Hex$_2$BOTf (1.0 eq), Et$_3$N (1.3 eq), CDCl$_3$ −65 °C 5 min

carbon-bound enolate), and a η^3-oxaallyl complex. Although α-borylcarbonyl compounds have been described as a hypothetical intermediate of certain reactions,[6] boron enolates are believed to exist only as oxygen-bound enolates, and carbon-bound boron enolates have never been characterized as such.[7]

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 mono-boron enolate. Unexpectedly, when methyl acetate was treated with 1.0 equiv of *c*-Hex$_2$BOTf and 1.3 equiv of triethylamine, the ^{1}H NMR spectrum showed the formation of the doubly borylated enolate **5** (43%) and unreacted acetate (57%) (Scheme 3a). In contrast to this, by the same treatment of **3** at −65 °C, the intermediate mono-enolate **7**[8] could be detected in the reaction mixture [**7**, 15%; **8**, 40% (*E*:*Z* = 1:2); **3**, 45%] (Scheme 3b).[9] The difference in the product distribution (the degree of the mono-enolate formation) between these substrates is noteworthy (vide infra). In both cases, the mixture was quantitatively converted to the doubly borylated enolate with another 1.3 equiv of *c*-Hex$_2$BOTf. This indicates that the doubly borylated enolate is formed in a stepwise manner via a mono-enolate, presumably via a carbon-bound enolate, and that the difference in the distribution of mono- and doubly borylated enolates is attributable to the difference in the rate of the first and the second enolization steps (see below for detailed discussion).

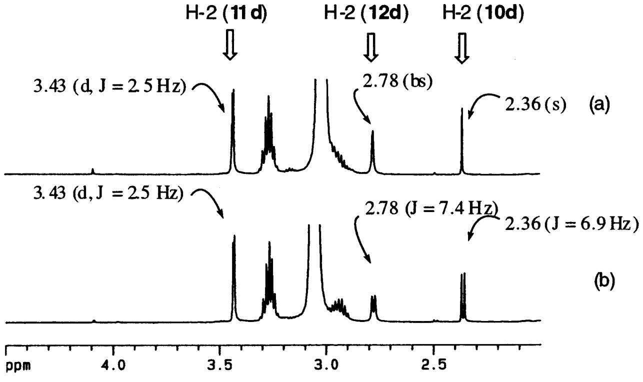
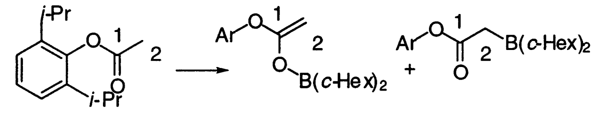


Figure 3. (a) Enolate mixture derived from **10d**, *c*-Hex$_2$BOTf (1.3 eq), Et$_3$N (1.5 eq). (b) Enolate mixture derived from 1-^{13}C-**10d**, *c*-Hex$_2$BOTf (1.3 eq), Et$_3$N (1.5 eq).

Scheme 4



10d **11d** **12d**

From an extensive survey of acetate esters with the purpose of detecting the possible “carbon-bound boron enolate” intermediate, we found that certain aryl acetates afforded the corresponding mono-boron enolates as a mixture of oxygen- and carbon-bound forms. When 2,6-diisopropylphenyl acetate (**10d**) was treated with 1.3 equiv of *c*-Hex$_2$BOTf and 1.5 equiv of triethylamine in CDCl$_3$ at 0 °C, the ^{1}H NMR spectrum showed formation of two enolate species (oxygen- (**11d**) and carbon-bound (**12d**) enolates) in a 7:2 ratio with 90% conversion (see signals at 3.43 and 2.78 ppm in Figure 3 a, respectively) (Scheme 4).The structures of these enolates were determined using two-dimensional NMR techniques. The major species exhibited a set of doublets (J = 2.5 Hz) at 3.43 and 3.06 (concealed) ppm ($C{=}C\underline{H}_2$), which correlated to the ^{13}C signal at 68.1 ppm ($C{=}\underline{C}H_2$) in the [^{13}C, ^{1}H] COSY and [^{1}H, ^{13}C] HMBC spectra (^1J doublet) [(a) in Figure 4a and 4b], suggesting the structure of the oxygen-bound enolate (**11d**) (Scheme 4). Because the $^2J_{\text{C}-1\,\text{H}-2}$ is nearly 0 Hz, the [^{1}H, ^{13}C] HMBC cross-peak between C-1 (161.1 ppm) and H-2 (3.43 and 3.06 ppm) could not be observed (Figure 4b). The presence of the keteneacetal substructure was proved using 1-^{13}C-**10d**, where C-2 appeared as a doublet (J = 100 Hz) at 68.1 ppm (see Supporting Information) and H-2 appeared as a doublet ($^2J_{\text{C}-1\,\text{H}-2}$ = 0 Hz) at 3.43 ppm (Figure 3b). The minor component exhibited a broad singlet at 2.78 ppm ($COC\underline{H}_2B$), which correlated to the ^{13}C signal at 32.7 ppm ($CO\underline{C}H_2B$) in the [^{13}C, ^{1}H] COSY spectra [(b) in Figure 4a] and to the ^{13}C signals at 35.7 ppm ($COCH_2B\underline{C}H$) and 172.1 ($\underline{C}OCH_2B$) in the [^{1}H, ^{13}C] HMBC spectra [(b) and (c) in Figure 4b, respectively]. The assignment of this peak was confirmed by the ^{1}H NMR of the enolate sample derived from 1-^{13}C-**10d** (doublet at 2.78 ppm, J = 7.4 Hz) (Figure 3b). The ^{13}C signal at 35.7 ppm ($COCH_2B\underline{C}H$) showed a cross-peak between a proton around

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(6) (a) Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 6218. (b) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (c) Brown, H. C.; Rogic, M. M.; Rathke, M. W. Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 818. (d) Pasto, D. J.; Wojtkowski, P. W. *J. Org. Chem.* **1971**, *36*, 1790. (e) Mukaiyama, T.; Murakami, M.; Oriyama, T.; Yamaguchi, M. *Chem. Lett.* **1981**, 1193.

(7) Computational study of *O*- and *C*-bound boron enolate, see Ibrahim, M. R.; Bühl, M.; Knab, R.; von Rague Schleyer, P. *J. Comput. Chem.* **1992**, *13*, 423.

(8) Because of a minute quantity and instability of **7**, the structure was determined using a ^{13}C-enriched sample.

(9) To obtain a higher yield of **7**, the enolization was conducted at −65 °C. NMR spectra were recorded at −23 °C for better resolution. The *E*:*Z* ratio of **8** slowly changed to 1:3 upon standing at −23 °C. See above.

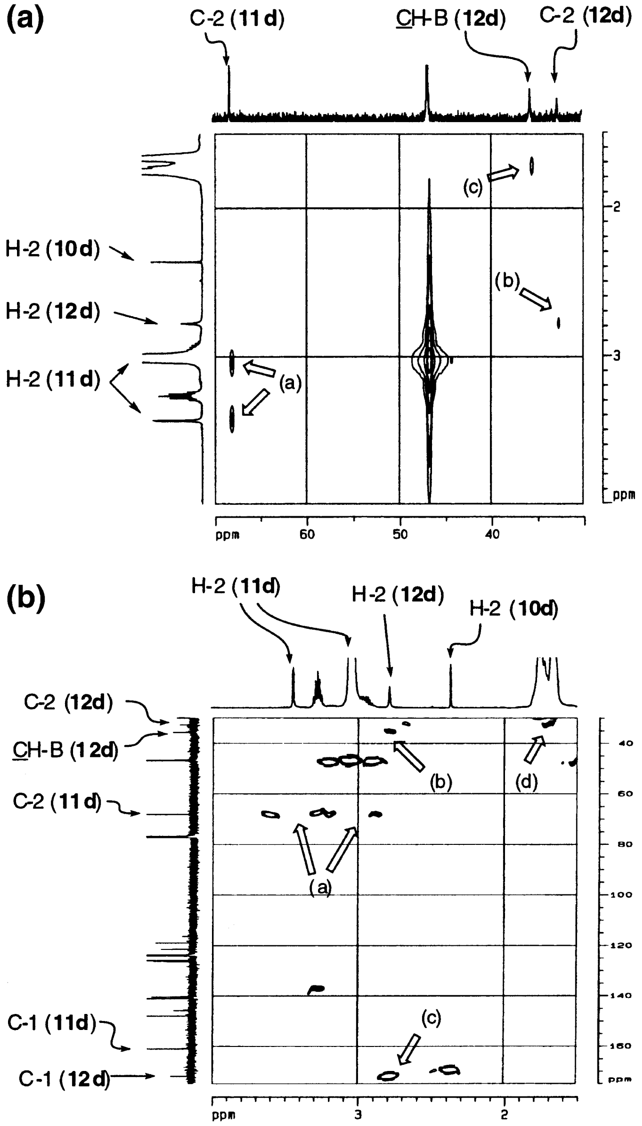


Figure 4. (a) $[^{13}C, ^{1}H]$ COSY of the enolate mixture. (b) $[^{1}H, ^{13}C]$ HMBC of the enolate mixture.

Table 1. Enolization of Acetate Esters[a]

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

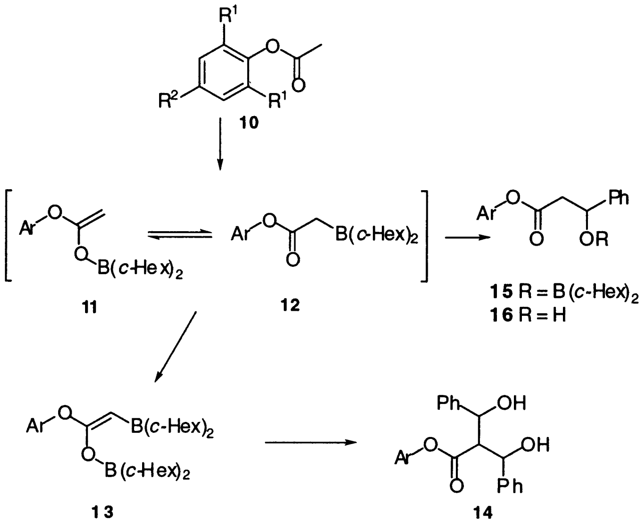
[a] A solution of acetate ester (0.5 mmol) and Et_3N (0.75 mmol) in $CDCl_3$ (2.5 mL) was treated with *c*-Hex_2BOTf (0.65 mmol) at 0 °C. After 5 min, the product composition was determined by ^{1}H NMR. [b] Isomer ratio (stereochemistry not determined) in parentheses.

1.7 ppm ($COCH_2BC\underline{H}$) in the $[^{13}C, ^{1}H]$ COSY spectra [(c) in Figure 4a], proving the methine of the cyclohexyl group, while a $[^{1}H, ^{13}C]$ HMBC cross-peak was observed between ~1.7 ($COCH_2BC\underline{H}$) and 32.7 ppm ($CO\underline{C}H_2BCH$) [(d) in Figure 4b]. Accordingly, the structure was assigned as carbon-bound enolate **12d** (Scheme 4).

As were the cases of methyl acetate and **3**, the degree of formation of mono-enolate was highly dependent on the steric factor of the acetate. Formation of the mono-enolate became less favorable with the less sterically demanding substituents on the 2- and 6-positions; the lower analogues (2,6-diethyl- (**10c**) and 2,6-dimethylphenyl (**10b**) acetates) gave less mono-enolates (Table 1, entries 2 and 3) and phenyl acetate (**10a**) did not afford the mono-enolate (Entry 1).[10] This difference can be attributed to steric factors; for the bulkier esters, the coordination of the second molecule of boron triflate to the carbonyl group of the α-borylester becomes too unfavorable to allow the mono-enolate to persist. 2,6-Dimethylphenyl esters with the substituents of different electronic nature on the 4-position gave the mono-enolate 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., Si enolates[11]) or equilibrium mixtures (e.g., Sn enolates[12]) 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 additional 1.3 equiv of *c*-Hex_2BOTf (and 1.5 equiv of Et_3N), the mono-enolate mixture of **11d** and **12d** (prepared as described above, see Table 1, entry 4) was quantitatively converted to the doubly borylated enolate **13d** (1:3, stereochemistry not determined).[13] When the same mono-enolate mixture was treated with 0.5 equiv of benzaldehyde at 0 °C, ^{1}H NMR showed formation of the boron aldolate **15d** (43%) leaving **11d** (37%) and **12d** (10%), whereas the treatment with 1.3 equiv of benzaldehyde afforded the mono-aldol product **16d** in 71% yield after workup (Scheme 5).

Scheme 5



The aldol reaction presumably proceeded via the oxygen-bound enolate.[14] Thus, the indistinguishable reactivity of **11d**

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(10) With 2,6-di-*tert*-butylphenyl acetate (**10i**), the enolization proceeded up to the mono-enolate stage, and none of the doubly borylated enolate was observed even with excess amount of *c*-Hex_2BOTf (3 equiv, 98% conversion after 2 h).

(11) Rearrangement of α-silyl carbonyl to silyl enol ether; e.g., Kwart, H.; Barnette, W. E. *J. Am. Chem. Soc.* **1977**, *99*, 614 and references therein.

(12) Pereyre, M.; Bellegrade, B.; Mendelsohn, J.; Valade J. *J. Organomet. Chem.* **1968**, *11*, 97. Kobayashi, K.; Kawanisi, M.; Hitomi, T.; Kozima S. *Chem. Lett.* **1984**, 4971. Yasuda, M.; Katoh, Y.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda N. *J. Org. Chem.* **1994**, *59*, 4386.

(13) **13d** afforded **14d** in 76% yield (meso: dl = 2:1) after addition of benzaldehyde.

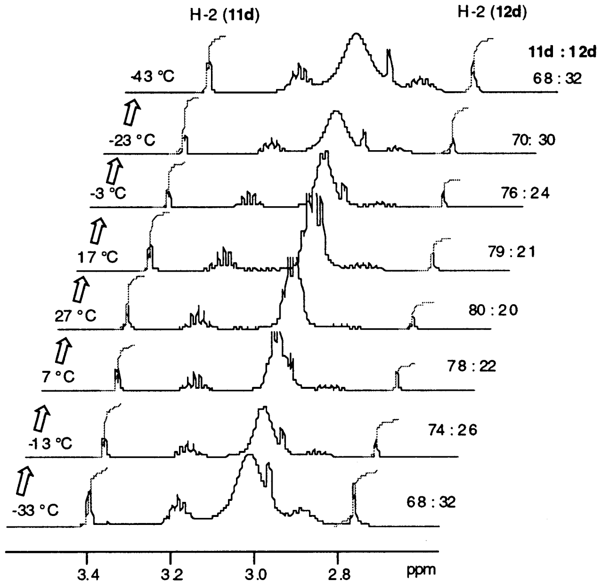
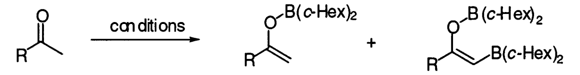


Figure 5. VT-NMR experiment of the enolate mixture prepared from **10d**.

Table 2. Enolization of Acetyl Derivatives[a]



R	conditions[a]	mono-enolate	doubly borylated enolate
R = $MeOCH_2$	[A]	0%	>98%
R = HO	[A][b]	0%	>98%
R = Me_2N	[A]	0%	>98%
R = 2-Py	[A]	0%	>98%
R = 2-Oxazolidione	[A]	0%	>98%
R = PhS	[A]	>98%	0%
R = Ph	[A]	>98%	0%
R = Et	[A]	>98%	0%
R = 2-$MeOC_6H_4$	[A]	>98%	0%
R = 4-$MeOC_6H_4$	[A]	>98%	0%
R = 2-Oxazolidione	[B]	72%	11%[c]
R = $MeOCH_2$	[B]	>98%	0%
R = PhS	[C]	0%	>98%
R = 2-$MeOC_6H_4$	[C]	0%	>98%

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

and **12d** in these reactions suggests rapid equilibrium between the oxygen- and carbon-bound boron enolates, and this was confirmed by the variable temperature NMR experiments. The oxygen and carbon-bound enolates existed as an equilibrium mixture at −43 to ~27 °C for **11d** and **12d** (Figure 5).[15] The equilibrium was established within the NMR acquisition time and the ratio of **11d** and **12d** at equilibrium was only dependent on the temperature and not on time; at higher temperatures the enolate mixture consisted of more oxygen-bound enolate **11d**. These results imply that the activation energy of the isomerization is very small and the product ratios are mostly determined by the difference in the stability of both forms of the enolates.[16]

Doubly Borylated Enolate Formation from Various Carbonyl Compounds. The doubly borylated enolate chemistry was further examined (Table 2). 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,[17] gave the corresponding doubly borylated enolates. Only an oxygen-bound mono-enolate, however, was detected from $PhSCOCH_3$, acetophenone, 2-butanone, 4-methoxyacetophenone, or 2-methoxyacetophenone. With 1 equiv of the boron triflate, methoxyacetone and 3-acetyl-2-oxazolidinone afforded the oxygen-bound mono-enolate in >98% and 72% yields, respectively (condition [B]). The mono-enolate 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]). 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.[18] 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.

Proton-Transfer Process in the Boron Enolate. The mono-enolates of aryl acetates were reasonably stable but underwent disproportionation to produce the starting acetate and the doubly borylated enolates upon standing (Table 3, Scheme 6).[21] The rate of disproportionation was affected by the steric factor of the substrate. Thus, a 15:56:14:15 mixture of **10c**:**11c**:**12c**:**13c** changed to a 35:30:8:27 mixture after 6 h, whereas a 6:72:20:2 mixture of **10d**:**11d**:**12d**:**13d** changed to a 22:53:15:10 mixture after 24 h. The ratio of oxygen- and carbon-bound enolates was constant during the disproportionation process.

When 1-^{13}C-**10d** (1 equiv) was added to the enolate mixture prepared from 1-^{12}C-**10d** (cf. Table 1, entry 4), ^{1}H NMR showed gradual formation of 1-^{13}C-**12d** and 1-^{12}C-**10d**. The disproportionation was suppressed at 24 h (Table 4). It is evident from these results that there exists an equilibrium process between the oxygen- and the carbon-bound enolates (and also between the doubly borylated enolate and the acetate) via proton transfer as described in Scheme 6.

Plausible Pathway of the Double Aldol Reaction. Now a plausible pathway of the double aldol reaction can be summarized as shown in Scheme 7. A boron triflate forms a complex with both a carbonyl compound and an amine reversibly. When the boron triflate−carbonyl compound complex **17** is more

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(14) The higher reactivity of oxygen-bound metal enolates toward aldol reactions has been reported. For Si enolate: Hong, Y.; Norris, D. J.; Collins, S. *J. Org. Chem.* **1993**, *58*, 359. For Sn enolate: Kobayashi, K.; Kawanisi, M.; Hitomi, T.; Kozima, S. *Chem. Lett.* **1983**, 851. Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329.

(15) The similar results were obtained with the enolate of **10e**. See Supporting Information.

(16) From the data in Figure 5, thermodynamic parameters were calculated: $\Delta S_0 = -0.013$ kcalmol^{-1} and $\Delta H_0 = -2.81$ kcalmol^{-1}.

(17) The asymmetric double aldol reaction of chiral acetyloxazolidinones proceeded with high selectivity. Furano, H.; Inoue, T.; Abiko, A. Submitted for publication.

(18) It is known that the carbon-bound silyl enolate of esters are more stabilized than those of ketones presumably by resonance stabilization. See Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 248.

(19) The boron enolate of ketones were reported to isomerize under rather forcing conditions; (a) Masamune, S.; Mori, S.; van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(20) The double aldol reaction of **3** can be done with two different aldehydes in a stepwise manner. See ref 4.

(21) During the disproportionation process, more starting acetates than the doubly borylated enolates were produced. The reason of this phenomena is not clear.

Table 3. Disproportionation of Enolates[a]

time	product composition [%]			
	10c	**11c**	**12c**	**13c**
5 min	15	56	14	15
1 h	15	57	15	13
2 h	22	48	13	17
4 h	31	35	10	24
6 h	35	30	8	27
24 h	44	17	4	35

time	product composition [%]			
	10d	**11d**	**12d**	**13d**
5 min	6	72	20	2
1 h	6	71	20	3
4 h	10	68	18	4
8 h	13	63	17	7
12 h	16	59	16	9
24 h	22	53	15	10

[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. The product composition was determined by ^1H NMR at the indicated times.

Scheme 6

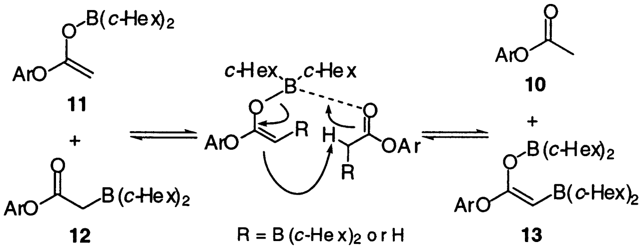


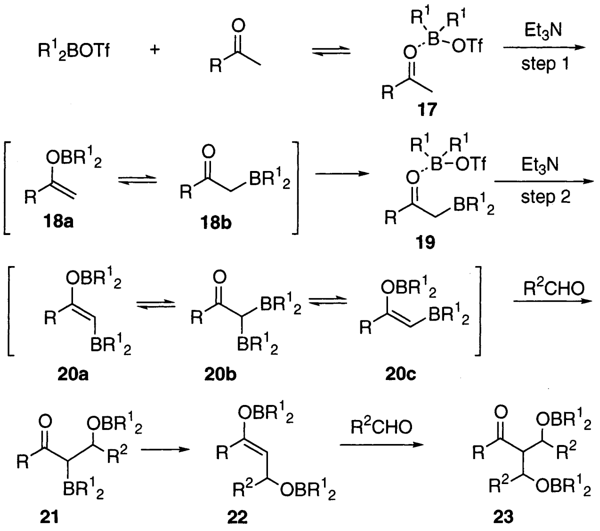
Table 4. Disproportionation of Enolates of **10d** with 1-^{13}C-**10d**[a]

time	product composition [%]					
	1-^{13}C-**10d**	1-^{12}C-**10d**	**11d**[b]	1-^{12}C-**12d**	1-^{13}C-**12d**	**13d**
5 min	50	8	32	9		1
1 h	50	10	30	7	2	1
4 h	46	14	30	6	3	1
8 h	44	19	27	5	4	1
12 h	44	22	26	4	3	1
24 h	42	25	24	4	4	1

[a] **10d** (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 being stirred for 5 min, 1-^{13}C-**10d** (0.5 mmol) was added to the reaction mixture. Then, ^1H NMR was recorded at the indicated times. [b] 1-^{13}C- and 1-^{12}C-**11d** are indistinguishable in ^1H NMR ($J_{\mathrm{C-1\,H-1}} = 0$ Hz).

favorable than the 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 mono-enolate **18a**, rapidly equilibrates with the carbon-bound enolate **18b**, 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 smaller alcohol residue, "step 2" is faster than "step 1", thus only the doubly borylated enolate is produced even with 1 equivalent of boron triflate. For larger esters, "step 2" becomes slower because of steric hindrance. For acetophenone or 2-butanone, the concentration of the carbon-bound enolate is too small to form **19** for further enolization to the doubly borylated enolate. In the enolization of acetate esters with sufficiently large R, the configuration of the initially formed doubly borylated enolate is *E* (**20a**) at low temperature, which may isomerize to *Z*-isomer (**20c**) upon warming. This facile isomerization[19] implies that it also proceeds through a carbon-bound boron enolate (**20b**). The aldol reaction naturally proceeds in a stepwise manner to afford α-boryl *β*-boryloxy carbonyl intermediate **21**, which isomerizes to the second (oxygen-bound) enolate with *E* configuration **22**.[20] Then the bis-aldol **23** is produced after reaction with the second equivalent of the aldehyde.

Scheme 7. A Plausible Pathway of the Double Aldol Reaction



Summary

Mechanistically, the boron-mediated aldol reaction has been considered a "straightforward reaction". However, our recent research on the boron aldol reaction of carboxylic esters has revealed its rather complex nature and, more importantly, dramatically expanded its utility toward complementary anti- and syn- selective asymmetric aldol reactions and the double aldol reaction, with the identification of a "carbon-bound boron enolate" as a key player. Further studies on the boron-enolate chemistry are in progress in our laboratory.

Acknowledgment. A.A. was supported by a grant from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Grant-in-Aid 10640578 and 13640533).

Supporting Information Available: Experimental detail and NMR spectra (^1H, ^{13}C, [^{13}C, ^1H] COSY, [^1H, ^{13}C] HMBC) of enolate mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0260014