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The First Doubly Borylated Enolate as an Intermediate of the Double Aldol Reaction

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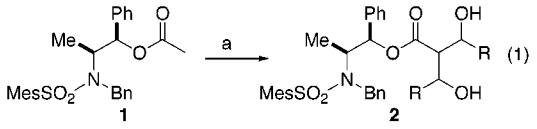
Recently we have reported a new asymmetric boron-mediated double aldol reaction (eq 1).[1] The characteristic features of this novel reaction have been summarized as follows: (1) the double aldol reaction is specific to acetate esters, not to ketones or thioesters, (2) the stoichiometry of the boron triflate to acetate ester is 2:1 to achieve enolization of the acetate ester, (3) the second equivalent of the boron triflate is active for the double aldol reaction but inactive for enolization of an external thioester, (4) a β-boryloxyester, which is an intermediate of the single (conventional) aldol reaction, is not an intermediate of the double aldol reaction.



(1)

(a) i) *c*-Hex$_2$BOTf (2.5 eq), Et$_3$N (3 eq), ii) RCHO

To delineate the mechanism of the double aldol reaction, we have investigated the intermediate enolate species. The structures of metal enolates can be categorized in three types, depending on the nature of the metal−enolate bond: (1) an oxygen-bound enolate, (2) a η^1-carbon-bound enolate, and (3) a η^3-oxaallyl complex. The boron enolate is believed to exist only as an oxygen-bound enolate,[2] and aldol reactions involving boron enolates are now widely used as one of the most reliable carbon−carbon bond-forming reactions.[3] Herein, we elaborate on the characterization of the unprecedented doubly borylated enolate, which is found to be involved in the aldol reaction as an intermediate.

The double aldol reaction was monitored by NMR. When triethylamine (3.0 equiv) was added to a mixture of methyl acetate (1.0 equiv) and *c*-Hex$_2$BOTf (2.5 equiv) in CDCl$_3$ (0.27 M for MeOAc, 0.68 M for *c*-Hex$_2$BOTf), the ^{1}H NMR showed the following changes indicative for a clean formation of a single species: (1) an upfield shift of the methoxy signal (from 3.75 to 3.65 ppm), (2) the disappearance of the acetyl methyl signal at 2.15 ppm, (3) the appearance of new signals at 4.35 (integrated as 1H) and 8.12 ppm (integrated as 2H), the latter being assigned as an ammonium proton of Et$_3$NH$^+$. The ^{13}C NMR proved the formation of an enolate by the two diagnostic peaks at 169.9 and 79.5 ppm as a keteneacetal. The [^{13}C,^{1}H] COSY and the DEPT spectra revealed that the olefinic carbon at 79.5 ppm has only one proton (4.35 ppm) (**a** in Figure 1), and confirmed the assignment of the methoxy group (3.65 ppm; 55.3 ppm) (**b** in Figure 1) and methine groups (^{1}H, 1.1 and 1.6 ppm; ^{13}C, 29.8 and 33.3 ppm, respectively) of the cyclohexyl moieties (**c** in Figure 1). Furthermore, the [^{1}H,^{13}C] HMBC (delay time 65 ms) showed the correlation between the methine proton (1.6 ppm) of a cyclohexyl group and the carbon at 79.5 ppm (**a** in Figure 2), the olefinic proton (4.35 ppm) and the methine carbon of the cyclohexyl group at 33.3 ppm (**b** in Figure 2), and the same olefinic proton (4.35 ppm) and the acetal carbon at 169.9 ppm (**c** in Figure 2). The acetal carbon furthermore showed a correlation peak to the methoxy protons (**d** in Figure 2). The [^{1}H,^{13}C] constant time HSQC spectra[4] (Figure 3) unambiguously proved the η^1 coordination of the dicyclohexylboron moiety to the olefinic carbon of 79.5 ppm. The cross-peak of the carbon of 79.5 ppm and the proton of 4.35 ppm increased 3.7 times of its amplitude upon decoupling of ^{11}B, demonstrating partial elimination of the quadrupolar effect of ^{11}B nuclei on the connecting carbon atom. These spectral data establish the presence of the substructure (MeO)(−O)C═CH−B(*c*-Hex)$_2$.

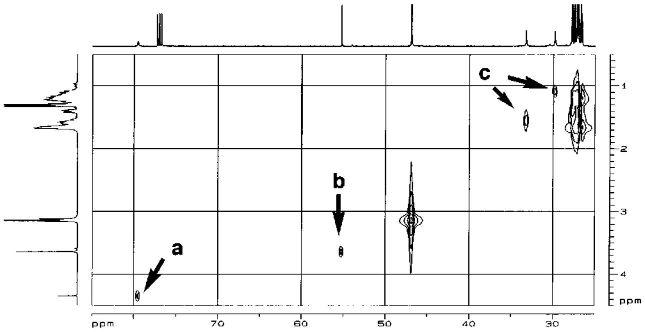


Figure 1. [^{13}C,^{1}H] COSY of **3**.

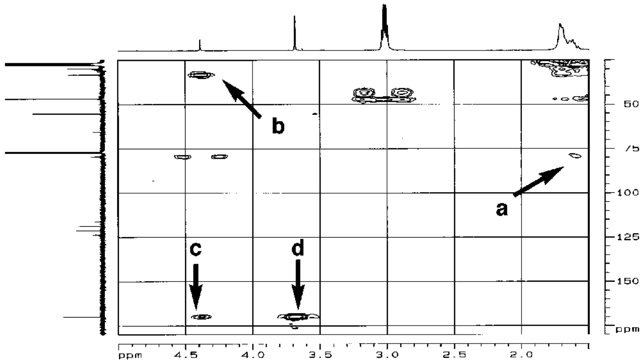


Figure 2. [^{1}H,^{13}C] HMBC of **3**.

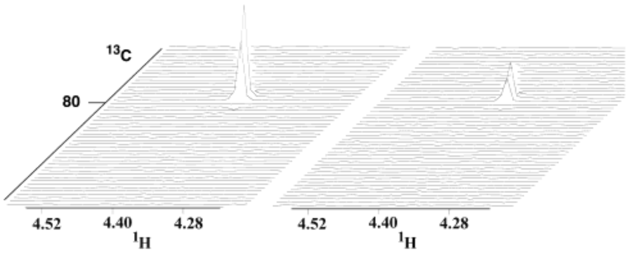


Figure 3. [^{1}H,^{13}C] *constant time* HSQC of **3** with (left) and without (right) decoupling of ^{11}B.

The existence of two kinds of boron species was shown by two ^{11}B NMR signals at 74 and 56 ppm with equal intensity.

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[1] Abiko, A.; Liu, J.-F.; Buske, D. C.; Moriyama, S.; Masamune, S. *J. Am. Chem. Soc.* **1999**, *121*, 7168.

[2] α-Borylcarbonyl compounds have been proposed as intermediates of certain reactions: (a) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (b) Brown, H. C.; Logić, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 6218.

[3] For review of aldol reactions involving boron enolates: (a) Braun, M. *Advances in Carbanion Chemistry*; 1992; Vol. 1, pp 177−247. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

[4] For detail of this NMR experiment, see Supporting Information.

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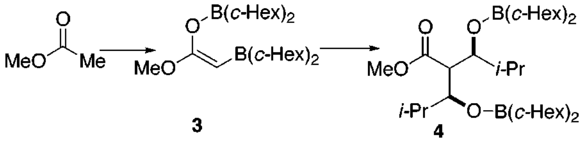
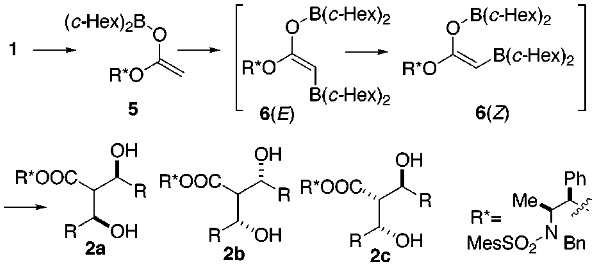
Scheme 1



The stereochemistry of the enolate was determined in a NOESY experiment by observation of a cross-peak between the methoxy protons and the methine proton. Therefore, the structure of the intermediate was formulated as **3** (Scheme 1). This structure is unique in that two dicyclohexylboron moieties are incorporated in the enolate, involving formation of a carbon−boron bond. **3** could quantitatively be transformed into **4** after addition of isobutyraldehyde.[5] Thus, this transformation leads to the conclusion that **3** is an intermediate of the double aldol reaction (Scheme 1).[6]

NMR experiments were then conducted on the double aldol reaction of chiral acetate **1**. Similar spectral characteristics were observed, except for the presence of an isomeric doubly borylated enolate. At −73 °C (in CD_2Cl_2−$CDCl_3$), ^{1}H and ^{13}C NMR showed unresolved spectra, but the presence of ammonium proton (integrated as 2H relative to the starting ester) and two carbon signals assignable to the keteneacetal (165.2 and 87.4 ppm). When the spectra were recorded at −43 °C, another set of the keteneacetal signals appeared at 166.4 and 84.6 ppm. The latter isomer increased to 1:1 at −23 °C, and the two sets of distinctly resolved signals (1:3) were observed at −3 °C. Two species were assigned spectroscopically as isomers of the doubly borylated enolate **6**(*E*) and **6**(*Z*).[7] The *E*:*Z* ratio was in good agreement with the ratios of the double aldol products obtained by enolization at −78 °C, **2a**:**2b**:**2c** = 88:9:3,[1] and at 0 °C, **2a**:**2b**:**2c** = 23:67:10 (Scheme 2).[8] The facile isomerization of the doubly borylated enolate would be particularly noteworthy.[9] When **1** was treated with 1.0 equiv of *c*-Hex_2BOTf and 1.3 equiv of triethylamine at −65 °C, the intermediate mono-enolate **5**[10] could be detected in the reaction mixture at −23 °C (**5**, 15%; **6**, 40% (*E*:*Z* = 1:2); **1**, 45%).[11] This mixture was converted **6** with another equivalent of *c*-Hex_2BOTf. This indicated that the doubly borylated enolate was formed in a stepwise manner.

Scheme 2



The doubly borylated enolate chemistry was further examined. Under the standard conditions[12] a variety of doubly borylated enolates were formed from methoxyacetone, dimethylacetamide, and acetic acid, and with *n*-Bu_2BOTf, 9-BBN triflate or *c*-Hex_2BI from methyl acetate. Only a “conventionally” assumed boron enolate, however, was detected from $PhSCOCH_3$, 4-methoxyacetophenone, or 2-methoxyacetophenone. 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 (4.5 equiv, 24 h, 100%).[13] The difference in the formation of the doubly borylated enolate would be closely related with the rate of formation and stability of a carbon-bound boron enolate as an intermediate.[14]

In summary, we characterized an unprecedented doubly metalated boron enolate as an intermediate of the double aldol reaction using ^{1}H,^{13}C,^{11}B NMR. To our best knowledge, this is the first example for characterizing a “carbon-bound boron enolate” as well as a doubly metalated enolate species from a carbonyl compound under conventional conditions for enolate preparation. Further investigation of the chemistry of the doubly metalated enolate and the double aldol reaction are underway in our laboratories.

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Supporting Information Available: Experimental procedures and spectral data, and NMR spectra of **3**, **6**, and the doubly borylated enolates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[5] When the corresponding doubly borylated enolate derived from benzyl acetate was treated with D_2O−MeOD, two deuteriums were incorporated at the acetyl group quantitatively.

[6] **3** was not stable enough to obtain accurate elemental analysis nor mass spectra under various ionization conditions. The double aldol reaction in the absence of the ammonium salt and excess reagents led to the same results.

[7] In this paper, the highest priority is designated to the OBR_2 group for the descriptor of the stereochemistry of boron enolates.

[8] The stereochemical outcome is in good agreement to the propionate aldol reaction with the same auxiliary. The opposite sense of the facial selectivity from the enolate of different configuration (*E* and *Z*) was observed for the *anti* and *syn* aldol reactions using the same auxiliary. See, Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873.

[9] The similar *Z*-isomer preference on the isomerization of the boron enolate of propionate esters was reported. Abiko, A.; Liu, J.-F.; Masamune S. *J. Org. Chem.,* **1996**, *61*, 2590.

[10] Because of a minute quantity and instability of **5**, the structure was determined using a ^{13}C-enriched sample. See Supporting Information.

[11] The *E*:*Z* ratio of **6** slowly changed to 1:3 upon standing at −23 °C.

[12] The carbonyl compound was mixed with boron reagent (2.5 equiv) and Et_3N (3.0 equiv) in $CDCl_3$ at 0 °C for 5 min, and then the reaction was monitored by NMR at 23 °C. *c*-Hex_2BOTf (4.0 equiv) and Et_3N (5.0 equiv) were employed for acetic acid.

[13] Formation of the doubly borylated enolate appears more general than previously thought. Detailed discussion of the double aldol reaction of these doubly borylated enolates will be reported in due course.

[14] It is well-known that carbon-bound enolate is more favorable for carboxylic esters than ketones, presumably due to the resonance stabilization. See, e.g. Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 2418.