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A New Look at Boron Enolate Chemistry: Aminative C–C Bond Formation Using Diaminoboron Enolate with Aldehyde

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ABSTRACT

Unlike ordinary boron enolates, such as dialkylboryl (R_2B) and dialkoxyboryl ($(RO)_2B$) derivatives, reactions of diaminoboryl ($(R_2N)_2B$) enolates with aldehydes proceed with the concurrent transfer of amino and enoxy groups from the boron to the aldehyde carbon, yielding *β*-amino ketones in a selective manner.

Boron enolate is one of the most versatile reagents for the aldol-type C−C bond formation reactions.[1] Its reactions with aldehydes proceed via compact cyclic transition states, which are believed to be crucial for the high stereoselectivity of the aldol formation.[2,3] To attain the Lewis acidity of the boron centers, dialkylboron (**1a**) and dialkoxyboron (**1b**) derivatives are usually employed (Figure 1). In contrast, diaminoboron derivatives (**2**) have attracted less attention, partly because of the low acidity of their boron center. The donation of the nonbonding lone pair on the nitrogen atom to the vacant boron *p*-orbital makes a carbonyl−boron interaction unfavorable.

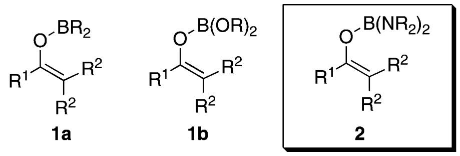
1a **1b** **2**

Figure 1.

Recently, we reported that bis(dialkylamino)cyanoboranes served as a highly efficient reagent for Strecker-type aminative cyanation of aldehydes.[4] The concurrent transfer of both the amino and the cyano group to the carbonyl carbon was so efficient that stoichiometric reaction of the aminocyanoborane afforded the corresponding α-amino nitrile in near-quantitative yields.[5] Remarkably, no cyanohydrin was formed by simple cyanation. On consideration of the reaction mechanism, it occurred to us that replacing the cyano group of the aminocyanoboranes with another nucleophilic group

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[1] Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2., p 239.

[2] For diastereoselectivity in boron-mediated aldol reactions, see: (a) Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, *20*, 1665. (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

[3] For asymmetric aldol reactions using boron enolates, see: (a) Masamune, S.; Sato, T.; Kim, B.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (b) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (c) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (d) Review: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

[4] Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **2002**, 1392.

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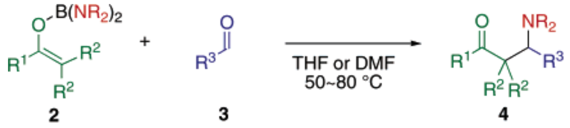
would lead to the development of new aminative C−C formation reactions.[6] Herein, we report on a Mannich-type reaction of bis(dialkylamino)boron enolates **2** with aldehydes, which leads to the highly selective formation of β-amino ketones.[7]

There are a few precedents of reactions of aminoboron enolates with aldehydes. It has been reported that ordinary aldol products were obtained in good yields in the reaction of cyclohexenoxybis(dimethylamino)borane with aldehydes.[8] Similarly, chloro(dialkylamino)boron enolates have been reported to yield aldol products in their reaction with aldehydes.[9] Despite these rather discouraging precedents, we carried out experiments to verify our hypothesis.

We prepared bis(diethylamino)boron enolate **2a** by reacting the lithium enolate of acetophenone with chlorobis(diethylamino)borane. The boron enolate was isolated by distillation in a high yield. Although the reaction of **2a** with benzaldehyde (2 equiv) was sluggish at room temperature in THF, heating the reaction mixture to 50 °C for 5 h led to the complete consumption of **2a**. We found that β-amino ketone was formed in a good yield, with no formation of the corresponding aldol product (Table 1, entry 1). Furthermore, the reactions of p-substituted benzaldehydes with **2a** afforded the corresponding β-amino ketones **3b** and **3c** in high yields (entries 2 and 3). Boron enolate **2a** also reacted with paraformaldehyde to afford **4ad** in a high yield (Table 1, entry 4).

Table 1. Reactions of Diaminoboron Enolates **2** with Aldehydes[a]



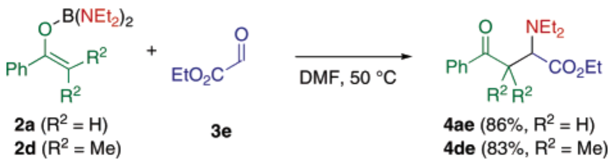
entry	enolate ($\mathrm{R^1, R^2, NR_2}$)	aldehyde ($\mathrm{R^3}$)	% yield[b]
1	**2a** (Ph, H, $\mathrm{NEt_2}$)	**3a** (Ph)	84 (**4aa**)
2	**2a**	**3b** (p-$\mathrm{MeOC_6H_4}$)	87 (**4ab**)
3	**2a**	**3c** (p-$\mathrm{NCC_6H_4}$)	97 (**4ac**)
4[c]	**2a**	**3d** (H)[d]	90 (**4ad**)
5[c]	**2b** (Ph, H, $\mathrm{N(allyl)_2}$)	**3a**	88 (**4ba**)
6[c]	**2c** (Ph, H, pyrrolidino)	**3a**	66 (**4ca**)
7[c,e]	**2d** (Ph, Me, $\mathrm{NEt_2}$)	**3a**	63 (**4da**)
8	**2e** (Me, H, $\mathrm{NEt_2}$)	**3a**	84 (**4ea**)

[a] A mixture of boron enolate **2** (0.25 mmol) and aldehyde **3** (0.5 mmol) in THF (0.5 mL) was stirred at 50 °C for 5 h unless otherwise noted. [b] NMR yield (2,6-dimethylanisol or benzyl acetate as an internal standard). [c] In DMF. [d] Paraformaldehyde. [e] At 80 °C.

Reactions of a series of aminoboron enolates **2b**−**e** with benzaldehyde **3a** were also tested.[10] Acetophenone-derived boron enolates **2b** and **2c** bearing diallylamino and pyrrolidino groups successfully afforded the corresponding amino ketones (entries 5 and 6). In these reactions, use of DMF as a solvent moderately accelerated the Mannich-type reaction, allowing the reaction to proceed to completeness within 2 h at 50 °C. It is important to note, however, that the decomposition of the β-amino ketone products to α,β-unsaturated ketones via the elimination of amines becomes the dominant reaction in DMF if long reaction times or higher reaction temperatures are used.[11] Remarkably, aminative C−C bond formation also took place at the geminally disubstituted carbon atom of enolate **2d** (entry 7). In this particular case, use of DMF as a solvent at 80 °C was essential to drive the reaction to completion. Boron enolate **2e**, derived from acetone, also reacted with benzaldehyde to afford good yields (entry 8).

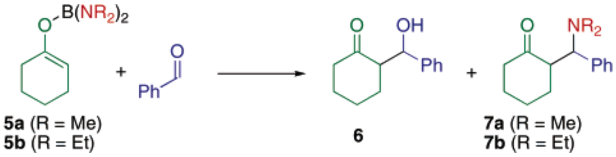
It is interesting to note that the α-amino acid derivatives bearing γ-keto functions were synthesized by this reaction protocol. Thus, reactions of **2a** and **2d** with polymeric glyoxylic acid ethyl ester (**3e**) in DMF at 50 °C led to the formation of **4ae** and **4de**, respectively, in high yields (Scheme 1).

Scheme 1



These results prompted us to reinvestigate Hoffmann's aldol system, in which boron enolate **5a** was reacted with benzaldehyde in THF (Table 2).[8] We did reproduce their results, in which the aldol product **6** was obtained as the

Table 2. Reactions of Diaminoboron Enolates **2** with Aldehydes[a]



entry	boron enolate	solvent	T, °C	% yield[b] **6**	% yield[c] **7**
1	**5a** (R = Me)	THF	−78∼20	63	trace
2	**5a**	THF	50	57	trace
3	**5a**	DMF	−70 to 20	61	20
4	**5a**	DMF	50	5	50
5	**5b** (R = Et)	THF	−78 to 20	47	28
6	**5b**	DMF	50		**72**

[a] Boron enolate **5** (0.25 mmol), benzaldehyde **3a** (0.5 mmol), and the solvent (0.5 mL) were used. [b] NMR yield (using 2,6-dimethylanisol or benzyl acetate as an internal standard). The diastereomeric ratios were 10:1−15:1. [c] NMR yield. The diastereomeric ratios were in the range 2.5:1∼1:1.

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(6) Sugasawa, T.; Toyoda, T. *Synth. Commun.* **1979**, *9*, 553.

(7) Recent review of the Mannich reaction: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1044.

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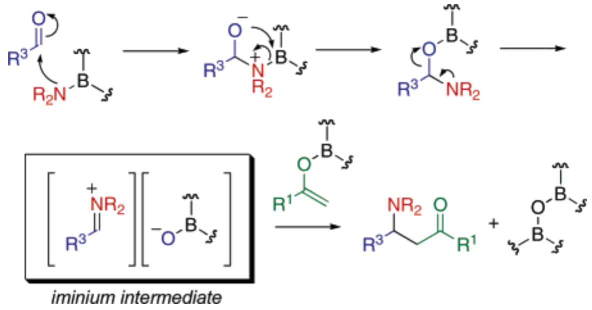
(9) Sugasawa, T.; Toyoda, T.; Sakakura, K. *Synth. Commun.* **1979**, *9*, 583.

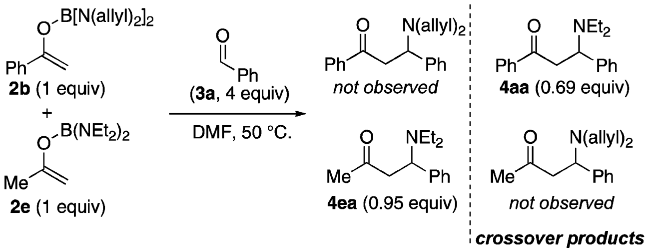
major product (entry 1). In the reaction mixture, however, a trace amount of β-dimethylamino ketone **7a** was also detected. This preference for the formation of the aldol product was unchanged either by using a higher reaction temperature (50 °C, 5 h) (entry 2) or by use of DMF as a solvent at low temperature (−70 to 20 °C, 18 h) (entry 3). To our surprise, however, a dramatic change of the reaction course was observed when the reaction was carried out in DMF at 50 °C (1.5 h). The amino ketone **7a** was obtained as the major product with a minor formation of **6** (**6**:**7a** = 1:10) (entry 4). We also observed that the corresponding diethylamino derivative **5b** favored the amino ketone formation more than **5a**. Even when using Hoffmann's conditions (i.e., THF and low temperature), the ratio of **7b** to **6** was found to be greater than 1:2 (entry 5). Applying the optimized conditions (DMF, 50 °C) increased the yield of **7b** to 72%, without any detectable formation of **6** (entry 6). We confirmed that **7** and **6** are derived by independent reaction pathways. Thus, before aqueous treatment of the reaction mixture obtained under the reaction conditions for entry 5 (Table 2), the solvent (THF) was replaced with DMF, and the resultant DMF solution was heated at 50 °C for 1.5 h. Aqueous workup resulted in the major formation of the aldol product **6** in a ca. 2:1 ratio (**6**:**7**).

We propose the following explanation for the observed Mannich-type reaction. A direct aldol-type reaction via a cyclic transition state may be suppressed by the unfavorable coordination of the carbonyl group to the di(amino)boron center as a result of its low Lewis acidity. Instead, an iminium intermediate is generated via nucleophilic attack of the boron-bound nitrogen to the aldehyde followed by deoxygenation, with corresponding formation of a B−O bond (Scheme 2). A boron enolate then attacks the iminium intermediate, for which a cyclic transition state is unlikely. The existence of the iminium ion pair may be supported by the crossover experiment shown in Scheme 3. Thus, a mixture of the boron enolates **2b** and **2e** (1:1) was reacted with excess benzaldehyde in DMF at 50 °C for 2 h. It had been confirmed that no exchange of the amino groups between the two boron enolates took place in the *absence* of the aldehyde under otherwise identical reaction conditions. The reaction of benzaldehyde with the mixture of the boron enolates yielded two β-amino ketones. One of these β-amino ketones was **4ea**, in which both functionalities were derived solely from the boron enolate **2e**. Unexpectedly, the other product was found to be a crossover product **4aa**, whose amino and carbonyl functionalities were derived from **2e** and **2b**, respectively. No amino ketones bearing the diallylamino group were detectable. The selective transfer of a diethylamino group over a diallylamino group was also observed in the reaction of benzaldehyde with the (diallylamino)(diethylamino)boron enolate of acetophenone. The boron enolate with mixed amino groups yielded diethylamino ketone **4aa** exclusively in good yield.The formation of **4aa** suggests that the amino and enoxy groups are derived from two independent boron components, as shown in Scheme 2.

Scheme 2



Scheme 3



In summary, we have reported a new Mannich-type reaction using bis(amino)boron enolates, which yield synthetically useful β-amino ketones. In addition to their synthetic importance, this demonstrates the generality of the aminative C−C bond formations using diaminoboryl-substituted nucleophiles. We are currently investigating the mechanistic details to expand the scope of the reaction.

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Supporting Information Available: Experimental procedures and spectral data for new compounds This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The boron enolates **2a**, **2b**, **2d**, and **2e** were prepared from the corresponding lithium enolates with chlorobis(dialkylamino)boranes and used after distillation. The enolate **2c** was prepared via amino exchange by reaction of **2a** with pyrrolidine (3−4 equiv). The boron enolates generated by the amino exchange reaction were used after evaporation of volatile materials in vacuo.

(11) All of the β-amino ketones reported in this work decompose gradually on storage at room temperature, even under an inert atmosphere. Moreover, owing to chromatographic instability, the amino ketones could not be isolated in the pure state. The yields were determined by ^{1}H NMR with an internal standard for crude β-amino ketones, which were obtained by acid/base extraction (see Supporting Information). In all cases, a purity >90% was achieved.