

Aminoboranes as “Compatible” Iminium Ion Generators in Aminative C–C Bond Formations

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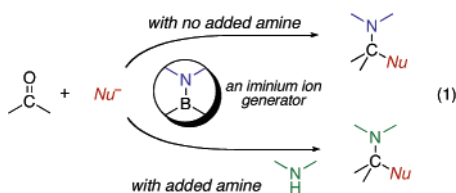
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The Mannich reaction is recognized as a highly important method to access functionalized amines.^{1,2} The original three-component protocol uses amines, non-enolizable aldehydes, and active methylene compounds, including ketones, under rather harsh acidic conditions. The reaction efficiency is improved by using two-component systems, which use preformed imines or iminium salts. Recent developments of asymmetric variants using a two-component protocol have made the Mannich reaction very valuable.³

However, a two-component system is not always ideal. In the synthesis of a large number of derivatives, it is preferable to use a three-component strategy, involving the in situ formation of iminium intermediates from aldehydes and amines, which are easily available with wide structural variations. Although new three-component systems have been reported recently, these mostly involve the use of primary anilines, which readily form imines.^{4,5} Exploitation of new reagents for the efficient generation of iminium intermediates is crucial to expand the scope of three-component systems.

We recently reported that bis(dialkylamino)boron cyanide⁶ and enolates⁷ react with carbonyl compounds yielding Strecker and Mannich-type products, respectively, via aminative C–C bond formation processes. We presumed that a common role of the boron reagents was in the generation of reactive iminium intermediates, which undergo further nucleophilic addition of the cyanide or enolate. This idea prompted us to develop new boron-based iminium ion generators that would work under mild reaction conditions. Here, we report a new three-component Mannich-type reaction using aminoboranes as efficient iminium ion generators that are compatible with acid-sensitive functionalities (eq 1).



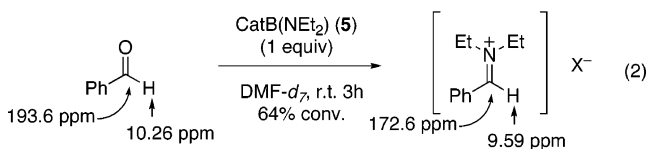
Reactions of benzaldehyde (2.0 equiv) with silyl ketene acetal **7** (1.0 equiv) were carried out in the presence of aminoboranes **1–6** (1.0 equiv) in dry *N*-methylpyrrolidinone (NMP) at 30 °C (Table 1, entries 1–6). In all cases, the β -amino ester **8** was obtained selectively, although the yields varied significantly with the structure of the aminoboranes. It should be noted that no Mannich product was detected in the presence of the corresponding stannylamine, silylamine, or free amine in place of the borylamines under otherwise identical reaction conditions (entries 7–9). Among the aminoboranes tested, the salicyl alcohol derivative **6** exhibited the highest reactivity, yielding **8** in a 95% yield. We also found that the presence of a sub-stoichiometric amount of a secondary amide (0.2 equiv), such as 2-piperidinone, significantly accelerated the reaction, lowering the reaction temperature to 20 °C or below (entries 2, 3, 5, and 6).

Table 1. Reactions of Silyl Ketene Acetal **7** with Benzaldehyde in the Presence of Aminoboranes **1–6** or Other Amino Sources^a

entry	iminium ion generator	%yield of 8 ^b
1	B(NEt ₂) ₃ (1)	31
2	<i>i</i> -PrOB(NEt ₂) ₂ (2)	88 (94 ^c)
3	PhB(NEt ₂) ₂ (3)	74 (66 ^c)
4		34
5		83 (70 ^c)
6		95 (99 ^c)
7	Me ₃ SnNEt ₂	0
8	Me ₃ SiNEt ₂	0
9	HNEt ₂	0

^a **7** (1.0 equiv), aldehyde (2.0 equiv), and aminoborane (1.0 equiv) in *N*-methylpyrrolidinone (0.5 mL) were reacted at 30 °C for 3 h unless otherwise noted. ^b NMR yield. ^c Yields in parentheses were obtained with use of 2-piperidinone (0.2 equiv) at room temperature.

Our proposed mechanism, involving the formation of the iminium salt with the aminoborane, is supported by the results of NMR experiments. Upon a 1:1 mixing of **5** with benzaldehyde in DMF-*d*₇, new distinctive signals were observed at 9.59 and 172.6 ppm in the ¹H and ¹³C NMR spectra, respectively (eq 2). These chemical



shifts can be assigned to the iminium proton and the carbon atom from previously reported values of 9.18 and 171.3 ppm, respectively, for dimethyl(*p*-methylbenzylidene)ammonium methoxytrifluoroborate in DMSO-*d*₆.^{8,9} It should be noted that the iminium intermediate had not been observed in our previous aminative C–C bond formations, because the aminoborane reagents inevitably possess carbon nucleophiles on their boron atoms.^{6,7}

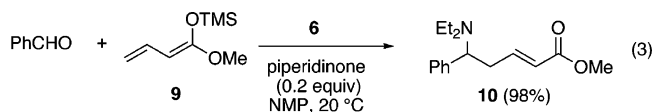
The reactions of some other aldehydes with silyl ketene acetals were examined in the presence of aminoborane **2** or **6** acting as new iminium ion generators (Table 2). Enolizable butyraldehyde successfully afforded the corresponding Mannich product in a high yield (entry 1). In a reaction with 5-tetrahydropyranyloxypentanal, aminoborane **6** gave the corresponding product in a high yield (entry 2). Under the same reaction conditions, Boc-protected aliphatic and

Table 2. Reactions of Aldehydes with Silyl Ketene Acetals in the Presence of Aminoboranes^a

$\text{R}^1\text{CHO} + \text{R}^2\text{C}(\text{OSiMe}_2\text{R}^5)=\text{C}(\text{R}^3)\text{R}^4 \xrightarrow[\text{NMP, 20 } ^\circ\text{C}]{\text{NEt}_2\text{B-R}^5 \text{ (2 or 6)}, \text{ piperidinone (0.2 equiv)}} \text{R}^1\text{CH}(\text{Et}_2\text{N})\text{C}(\text{R}^2)(\text{R}^3)\text{C}(\text{R}^4)=\text{O}$				
entry	nucleophile	aldehyde	aminoborane	%yield ^b
1	7	<i>n</i> -PrCHO	2	96
2	7	THPO(CH ₂) ₅ CHO	6	98
3	7	BocNHCH ₂ CH ₂ CHO	6	64
4	7	<i>p</i> -BocNHC ₆ H ₄ CHO	6	94
5		PhCHO	6	88
6		PhCHO	2	77

^a Silyl ketene acetals or a silyl enol ether (1.0 equiv), aldehyde (2.0 equiv), and aminoborane (1.0 equiv) with 2-piperidinone (0.2 equiv) in *N*-methylpyrrolidine (0.5 mL) were reacted at 20 °C for 1–3 h. ^b Isolated yield.

aromatic aldehydes afforded the corresponding Mannich products (entries 3 and 4). These examples using aldehydes bearing acid-sensitive functionalities clearly demonstrate the mildness of the present iminium generation conditions. β,β -Disubstituted silyl ketene acetal afforded the corresponding β -amino ester in a high yield (entry 5), and silyl enol ether also successfully afforded the corresponding β -amino ketone in a high yield (entry 6). The vinylogous Mannich reaction² with silyl ketene acetal **9** was also examined. Only the γ -addition product **10** with trans geometry was obtained stereoselectively in a high yield with no formation of the α -adduct (eq 3).



We then focused our attention on the use of free secondary amines as the source of the amino group via the in situ formation of the requisite aminoborane. We prepared the (diisopropylamino)-borane derivatives **11** and **12**, and the bulky aminoboranes sluggishly afforded Mannich products bearing a diisopropylamino group using the reaction conditions shown above. However, when free secondary amines, such as diethylamine (1 equiv), were added to the reaction mixture, Mannich products derived from the added amines were isolated in high yields (Table 3, entry 1). In a similar manner, (*p*-methoxybenzyl)methylamine, acetal-protected piperidin-4-one, and pyrrolidine afforded the corresponding products in good yields (entries 2–4). In the reaction of pyrrolidine with an aliphatic aldehyde, aminoborane **12** gave a slightly higher yield than **11** did (94% versus 86%, respectively) (entry 5). In the reaction of optically pure 2-methoxymethylpyrrolidine, one diastereoisomer was obtained selectively in a high yield (entry 6). It should be noted that the same strategy was applicable to aliphatic and aromatic aldehyde bearing acid-sensitive functionalities (entries 7 and 8). A successful three-component coupling reaction relies upon the amino group exchange reaction on the boron atom, producing a more reactive, (i.e., less bulky) aminoborane in a reversible manner. A remarkable feature of this three-component coupling reaction seems to be the mildness of the reaction conditions, which results in a high compatibility with the functional groups. The applicability of the reaction to enolizable aldehydes is also noteworthy.

In summary, we have established that aminoboranes serve as efficient iminium ion generators in Mannich-type reactions. The synthetically useful three-component coupling of aldehydes, sec-

Table 3. Aminoborane-Mediated Coupling of Aldehyde, Silyl Ketene Acetal, and Secondary Amine^a

$\text{R}^1\text{CHO} + \text{R}^2\text{C}(\text{OTBS})=\text{C}(\text{OMe})\text{R}^3 + \text{HNR}^2\text{R}^3 \xrightarrow[\text{NMP, 20 } ^\circ\text{C}]{\text{piperidinone (0.2 equiv), 11 (n=0) or 12 (n=1)}} \text{R}^1\text{CH}(\text{R}^2)(\text{R}^3)\text{C}(\text{OMe})=\text{C}(\text{R}^2)\text{R}^3$				
entry	HNR ² R ³	R ¹ CHO	amino-borane	%yield ^b
1	Et ₂ NH	PhCHO	11	99
2	(PMB)MeNH ^c	PhCHO	11	71
3		PhCHO	11	83
4		PhCHO	11	96
5		<i>n</i> -PrCHO	12	94
6 ^d		PhCHO	12	88 (91:9)
7	Et ₂ NH	THPO(CH ₂) ₅ CHO	12	73
8	Et ₂ NH	BocNHC ₆ H ₄ CHO	12	98

^a **7** (1.0 equiv), aldehyde (1.5 equiv), secondary amine (1.0 equiv), and aminoborane (1.0 equiv) with 2-piperidinone (0.2 equiv) in *N*-methylpyrrolidine (0.5 mL) were reacted at 20 °C for 1–3 h. ^b Isolated yield. ^c PMB, *p*-methoxybenzyl. ^d The reaction was carried out at –10 to 20 °C.

ondary amines, and silyl ketene acetals is mediated by common boron reagents bearing a bulky diisopropylamino group on the boron atom. Investigation into the application of this reaction system to other nucleophiles, including organometallic species, is now being undertaken in our laboratory.

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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>.

References

- (1) Kleinman, E. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 893.
- (2) For recent advances in the Mannich reaction, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
- (3) For examples of asymmetric Mannich reactions using the two-component protocol, see: (a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (e) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. For reviews, see: (f) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 954. (g) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
- (4) For recent examples of three-component Mannich reaction, see: (a) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545. (c) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. (d) Loh, T.-P.; Liung, S. B. K. W.; Tan, K.-L.; Wei, L.-L. *Tetrahedron* **2000**, *56*, 3227. For the asymmetric version, see: (e) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.
- (5) For some examples for the use of enolizable aldehydes in the three-component Mannich reactions, see: (a) Arend, M.; Risch, N. *Synlett* **1997**, 974. (b) Zarghi, A.; Naimi-Jamal, M. R.; Webb, S. A.; Balalaie, S.; Saidi, M. R.; Ipaktschi, J. *Eur. J. Org. Chem.* **1998**, 197. (c) Loh, T. P.; Chen, S. L. *Org. Lett.* **2002**, *4*, 3647.
- (6) Sugimoto, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **2002**, 1392.
- (7) Sugimoto, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* **2004**, *6*, 1167.
- (8) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121.
- (9) See also: (a) Mayr, H.; Ofial, A. R.; Würthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, *119*, 12727. (b) Jochims, J. C.; Glocker, M. O.; Hofmann, J.; Fischer, H. *Tetrahedron* **1991**, *47*, 205. (c) Keenan, T. R.; Leonard, N. J. *J. Am. Chem. Soc.* **1971**, *93*, 6567.

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