Alkenyl and Aryl Boronates—Mild Nucleophiles for the Stereoselective Formation of Functionalized *N*-Heterocycles

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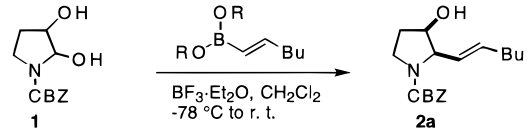
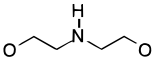
Nucleophilic additions to *N*-acyliminium ions[1] constitute an important method for the synthesis of alkaloids[2] and other biologically active nitrogen heterocycles. Intermolecular reactions with a variety of different classes of carbon-based nucleophiles are possible, including allylsilanes,[3] other allylmetals,[4] alkyl- and arylmetals,[3e,5] alkynylmetals,[6] TMSCN,[3d,7] isonitriles,[7c] enol derivatives,[3d,7c,8] and aromatics.[9] While a wide variety of nucleophiles are known to attack *N*-acyliminium ions, there are few reactions with alkenyl[3e,10] or arylmetal derivatives, and we are not aware of any reported examples of additions of organoboronic acids or esters.[11] Such additions would be attractive because of the good air and water stability of boronic acid or ester derivatives.[12] Petasis and co-workers have recently developed a three-component coupling reaction of alkenyl- and arylboronic acids with aldehydes and amines, for the synthesis of allylamines and α-amino acids.[13] This reaction was demonstrated not to occur via direct addition to free iminium ions.[13a] However, we considered that the greater reactivity of *N*-acyliminium ions could enable reaction with boronic acids and esters. We now report the first examples of the reaction of alkenyl- and arylboronic acids and esters with *N*-acyliminium ions.

Table 1. Addition of Hexenyl Boronates to Pyrrolidine **1**[a]



OR, OR	Yield (%)	OR, OR	Yield (%)
OH, OH	57 (77)[b]		24
$O(CMe_2)_2O$	66		
^{i}PrO, ^{i}PrO	75		85
		$O(CH_2)_2O$	93

[a] 1.4 equiv of boronate or acid, 4 equiv of $BF_3{\cdot}Et_2O$, −78 °C, 2.5 h, then warm to room temperature, 2.5 h. [b] 3 equiv of boronic acid.

3-Hydroxypyrrolidines were chosen as target structures, since this motif is present in the polyhydroxylated indolizidine and pyrrolizidine alkaloid families,[14] which include many examples of biologically active natural products, such as swainsonine, castanospermine, retronecine, and australine. Pyrrolidine **1** was therefore chosen as an *N*-acyliminium ion precursor. Oxidation and protection of pyrrolidine according to the method of Kraus and Neuenschwander gave *N*-Cbz-2-pyrroline.[15] Dihydroxylation using OsO_4 catalysis then afforded the desired precursor **1**.[16] Reaction of **1** with *E*-hexenyl boronic acid in the absence of a Lewis acid did not lead to the desired adducts, but instead resulted in esterification of the boronic acid by **1**. However, addition of the Lewis acid, boron trifluoride etherate, promoted addition of the boronic acid to give **2a** (Entry 1, Table 1). Prior esterification of the boronic acids as the corresponding boronates has a pronounced effect on the efficacy of addition (Entries 2−6, Table 1). Use of the pinacol or diisopropyl boronates produced a slight improvement in yield, whereas the catechol boronates were poor substrates. Both the diethanolamine and ethylene glycol boronates gave excellent yields of **2a**. In all cases **2a** was formed as a single diastereomer (>98:2 *cis*:*trans* by ^{1}H NMR).[17]

The reaction is amenable to a range of alkenyl- and arylboronates, producing exclusively the *cis*-2,3-substituted products (Table 2).[18] Simple alkyl- and phenyl-substituted *E*-alkenyl boronates give adducts having an *E*-alkene geometry (Entries 1−3, Table 2). The alkene stereochemistry is maintained in the products,

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(17) The diastereomer of **2a** was prepared via Mitsonobu reaction (see Supporting Information), and was not found in crude reaction mixtures.

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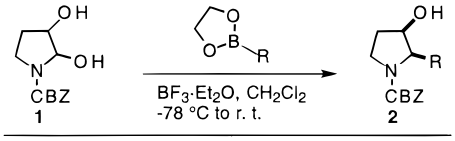
Table 2. Addition of Aryl and Alkenyl Boronates



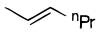
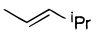
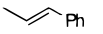
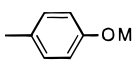
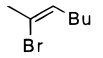
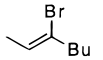
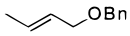
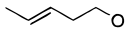
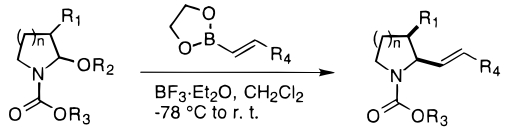
Entry	R	Product	Yield (%)
1		**2b**	91
2		**2c**	81
3		**2d**	64
4		**2e**	80
5		**2f**	70
6		**2g**	83
7		**2h**	98
8		**2i**	77
9		**2j**	99
10		**2k**	81

Table 3. Addition of Alkenyl Boronates to *N*-Acyliminium Ions



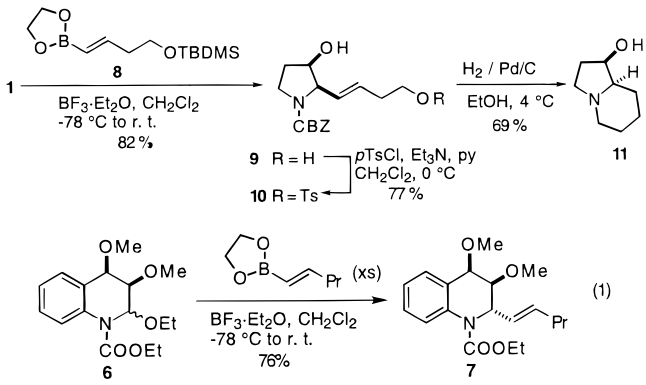
Entry	n	R_1	R_2	R_3	R_4	product	yield (%)
1	1	OH	Me	Bn	Pr	**2b**	91
2	1	OMe	Me	Bn	Bu	**3**	84
3	1	H	H	Bn	Bu	**4**	25
4	2	OH	H	Me	Pr	**5**	77

as was shown by the exclusive formation of the *Z*-alkenyl-substituted product in the addition of the *Z*-alkenyl boronate (Entry 4, Table 2). Aryl boronates will also add, such as the phenyl and *p*-methoxyphenyl boronates (Entries 5 and 6, Table 2). Importantly, functionalized boronates also add successfully, leading to products ready for subsequent synthetic manipulations (Entries 7−10, Table 2).

We next explored the scope of the reaction with respect to the *N*-acyliminium ion partner (Table 3). Compound **1** was derivatized as its 2-methoxy analogue and its 2,3-dimethoxy analogue. Use of either substrate as the *N*-acyliminium ion precursor did not have a strong effect on the efficacy of the reaction, and again only *cis*-2,3-substituted products resulted (Entries 1 and 2). When a substrate without functionality at the 3-position was employed (Entry 3), adduct **4** was obtained in 25% yield. We have also found the reaction is successful for elaboration of piperidine substrates (Entry 4), again proceeding with exclusive *cis* stereoselectivity. By contrast, addition to tetrahydroquinoline **5** (eq 1) proceeds to give **6**, the result of addition *trans* to the 3- and 4-methoxy groups.

As a preliminary demonstration of the utility of this methodology, we undertook the synthesis of the fungal metabolite (1*R**,-8a*R**)-1-hydroxyindolizidine **11** (Scheme 1).[19] Addition of TBS-protected boronate[20] **8** to **1** occurred with concomitant deprotection

Scheme 1



of the silyl ether furnishing diol **9** as a single diastereomer. Selective tosylation of the primary alcohol afforded **10**, which on hydrogenation underwent cyclization to afford **11**.

Although the mechanism for the addition reaction has not been proven, the requirement for Lewis acidic activation strongly implies the intermediacy of *N*-acyliminium ions. The boronate attacks *N*-acyliminium ions derived from pyrrolidine and piperidine substrates exclusively from the face bearing the *β*-oxygen, which can be rationalized by a mechanism involving coordination of boron to oxygen, producing an activated tetracoordinate species.[21] Further experiments will be required to elucidate the origin of stereoselectivity reversal for addition to tetrahydroquinoline **6**. Two additional features of these reactions warrant further comment. First, whereas most *N*-acyliminium ion precursors require protection of hydroxyl functionality, the addition of boronic ester nucleophiles tolerates free hydroxyl functionality. Second, the highly stereoselective nature of these additions is unusual for the formation of 2,3-disubstituted heterocycles. For instance, additions of trimethylallylsilane, trimethylsilyl cyanide, and alkyl copper reagents under Lewis acidic catalysis to the 3-OAc and 3-OTBS analogues of **1** provide mixtures of trans and cis products.[3a−c,7a,10b]

In conclusion, functionalized *N*-heterocycles are efficiently formed by the reaction of alkenyl- and arylboronates with activated *N*-acyliminium ion precursors under Lewis acidic catalysis. This methodology is advantageous relative to many *N*-acyliminium ion based strategies, because of the ready availability, stability, low toxicity, and mildly nucleophilic character of organoboronates. Further studies and applications of this reaction will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of **1**−**11** and precursors, the diastereomer of **2a** and derivatization of **2f** and **5**, and representatitve procedures for the preparation of boronates; ^{1}H NMR and ^{13}C NMR spectra of **2a**−**k**, **3**−**5**, **7**, **9**−**11**, the diastereomer of **2a**, and NOESY of **7**; X-ray data of derivatives of **2f** and **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) A crystal structure was obtained of (2*R**,3*R**)-3-hydroxy-2-phenylpyrrolidine (the pyrrolidine derived from CBZ deprotection of phenyl adduct **2e**: see Supporting Information). The authors have deposited atomic coordinates for this compound with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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(20) Protection of the alcohol as its TBS ether facilitated boronate synthesis.

(21) For the nucleophilic addition of allenylboronic acid to a *β*-hydroxy ketone, possibly involving hydroxyl mediated delivery, see: Ikeda, N.; Omori, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1175−1178.