ORGANIC
LETTERS

XXXX
Vol. XX, No. XX
000–000

Synthesis of Amines with Pendant Boronic Esters by Borrowing Hydrogen Catalysis

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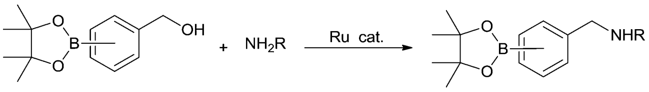
Received August 9, 2013

ABSTRACT



Amine alkylation reactions of alcohols have been performed in the presence of boronic ester groups to provide products which are known to have use as molecular sensors. The boronic ester moiety could be present in either the alcohol or amine starting material and was not compromised in the presence of a ruthenium catalyst.

In recent years a great deal of attention has been focused on the alkylation reaction of amines, particularly the reaction of an amine with an alkyl halide which is an electrophilic alkylating agent.[1] However, alkylation reactions can prove difficult to control and the product is often over alkylated.[2]

There has been significant recent interest in the alkylation of amines with alcohols using hydrogen transfer catalysts as an alternative to conventional alkylation procedures.[3,4]

The hydrogen transfer catalysts operate by an activation of the alcohol to an aldehyde in a process that we have termed "Borrowing Hydrogen Methodology".[5]

The borrowing hydrogen method typically uses ruthenium or iridium as the catalyst and takes the hydrogen from the alcohol **1** to form the aldehyde **2**. This aldehyde can react with an amine to form an imine **3**, and the hydrogen is then returned to give a C−N bond in product **4** (Scheme 1).[1e,5e,6]

This methodology generates water as the only reaction byproduct and allows alcohols to replace more conventional, but often toxic, alkyl halides as the alkylating agent.

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10.1021/ol402271a

Scheme 1. Borrowing Hydrogen Strategy in the Alkylation of Amines with Alcohols

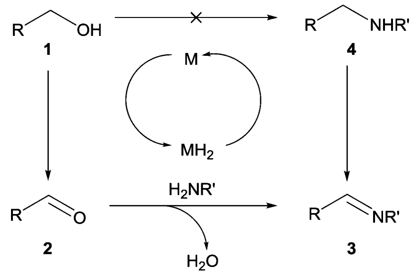
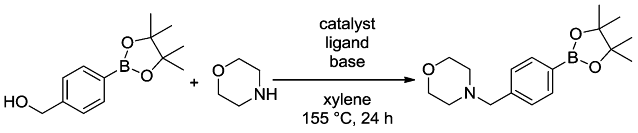


Table 1. Alkylation of Morpholine by Boronic Ester Alcohol **5a**[a]



5a **6** **7**

entry	catalyst[b]	mol %	ligand	mol %	yield (%)[c]
1	none	–	none	–	0
2	Ru	1	none	–	0
3	Ru	1	DPEphos	2	40
4	Ru	2.5	DPEphos	5	84
5	Ru	1	Dppf	2	16
6	Ru	2.5	Dppf	5	62

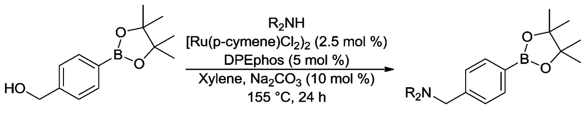
[a] The reaction was carried out with boronic ester alcohol (1.0 mmol) with morpholine (1.0 mmol), catalyst (2.5 mol %), and base Na_2CO_3 (10 mol %) at 155 °C for 24 h. [b] Ru = $[Ru(p\text{-cymene})Cl_2]_2$. [c] Isolated yield by recrystallization.

Herein we report a simple one-pot reaction to generate amines with pendant boronic acid derivatives, using either an alcohol tethered to a boronic ester with an amine or an amine tethered to a boronic ester with an alcohol. These reactions are catalyzed by $[Ru(p\text{-cymene})Cl_2]_2$ in the presence of a bidentate phosphine ligand to form secondary or tertiary amines containing a boronic ester moiety.

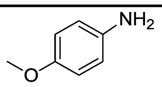
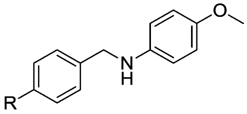
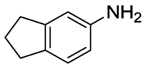
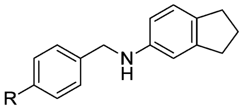
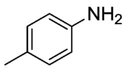
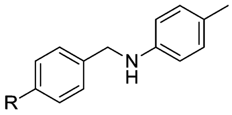
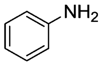
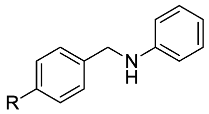
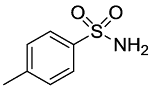
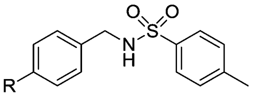
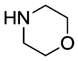
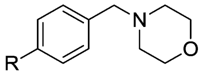
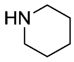
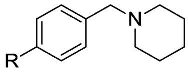
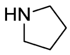
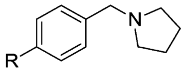
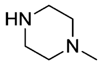
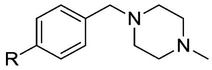
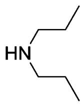
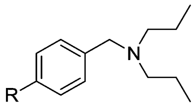
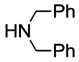
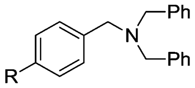
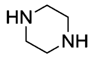
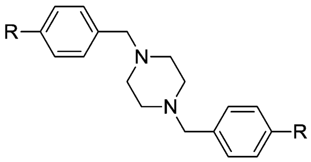
In order to simplify handling and reaction workup we protected boronic acid with pinacol using standard methodology.[7]

We wanted to explore the use of Borrowing Hydrogen Methodology for the preparation of boronic acid building blocks which have been extensively used in the construction of sensors for saccharides and anions.[8] We chose to investigate the coupling of boronic ester containing alcohol **5a** with morpholine **6**.

Table 2. Formation of Amines Containing a *p*-Boronic Ester Group[a]



5a

Entry	Amine	Product[c]	Yield (%)[d]
1			72
2			72
3			70
4			52
5			21[e]
6			84
7			80
8			75
9			83
10			87
11			59
12[b]			65

[a] The reaction was carried out with boronic ester alcohol (1.0 mmol) with amine (1.0 mmol). [b] Boronic ester alcohol/amine (2:1), 5 mol % catalyst, 10 mol % ligand, and 20 mol % base. [c] R = B-pinacolato. [d] Isolated yield by recrystallization. [e] Percentage conversion since the product could not be isolated cleanly.

As shown in Table 1, the reaction was unsuccessful in the absence of a catalyst or ligand (entries 1 and 2). However, the use of either DPEphos or dppf led to good conversions into the corresponding coupled product **7**. We were particularly pleased that the boronic ester survived the reaction

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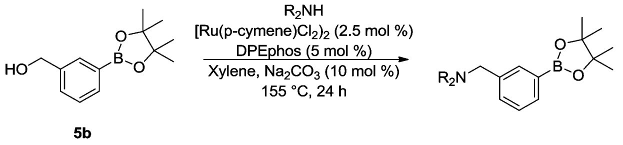
Table 3. Formation of Amines Containing a *m*-Boronic Ester Group[a]



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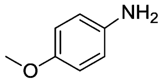
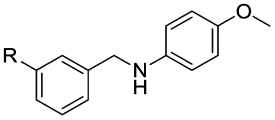
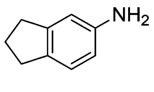
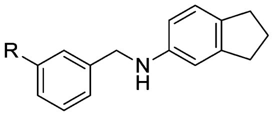
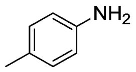
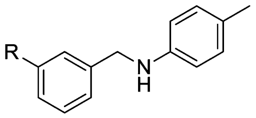
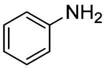
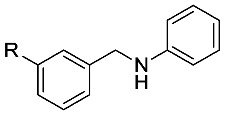
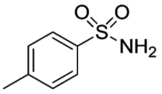
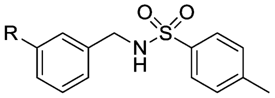
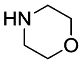
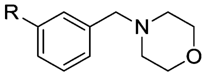
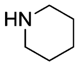
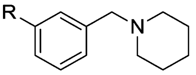
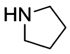
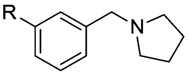
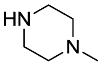
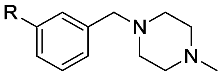
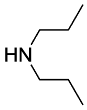
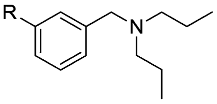
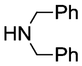
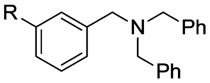
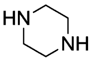
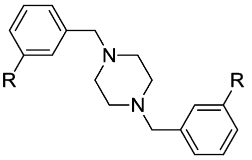
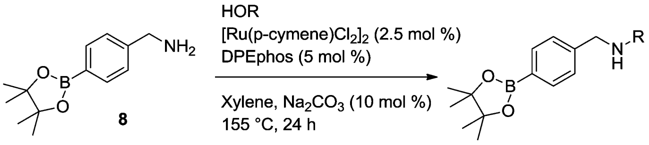
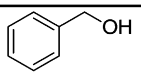
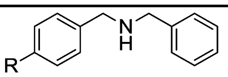
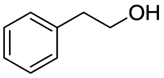
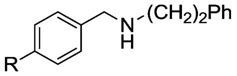
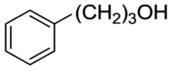
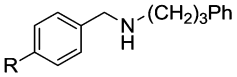
1			66
2			71
3			62
4			43
5			18[e]
6			80
7			79
8			78
9			80
10			69
11			65
12[b]			60

[a] The reaction was carried out with boronic ester alcohol (1.0 mmol) with amine (1.0 mmol). [b] Boronic ester alcohol/amine (2:1), 5 mol % catalyst, 10 mol % ligand, and 20 mol % base. [c] R = B-pinacolato. [d] Isolated yield by recrystallization. [e] Percentage conversion since the product could not be isolated cleanly.

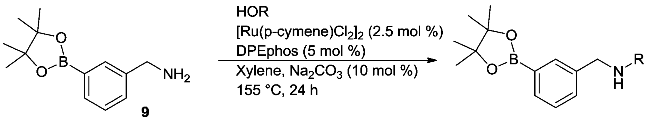
Table 4. Formation of *p*-Boronic Ester Amine by *N*-Alkylation with Alcohols[a]

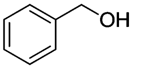
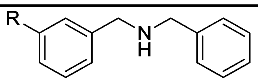
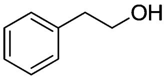
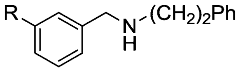
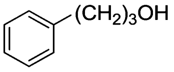
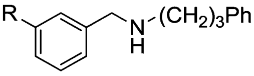


Entry	Alcohol	Product[b]	Yield (%)[c]
1			60
2			61
3			64

[a] The reaction was carried out with boronic ester amine (1.0 mmol) with alcohol (1.0 mmol). [b] R = B-pinacolato. [c] Isolated yield by recrystallization.

Table 5. Formation of *m*-Boronic Ester Amine by *N*-Alkylation with Alcohols[a]



Entry	Alcohol	Product[b]	Yield (%)[c]
1			61
2			53
3			60

[a] The reaction was carried out with boronic ester amine (1.0 mmol) with alcohol (1.0 mmol). [b] R = B-pinacolato. [c] Isolated yield by recrystallization.

conditions, since boronic acid derivatives have well-established chemistry with many transition metal catalysts.[3c,9] Yet, more forcing reaction conditions were required than those for substrates which do not contain boronic esters.

$[Ru(p\text{-cymene})Cl_2]_2$ is a simple, commercially available catalyst precursor, and we chose to use the $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos combination for the N-alkylation of other alcohols.[10] Table 2 contains the results obtained when the *para*-substituted boronic ester substrate **5a** was used. Table 3 contains the results obtained when the *meta*-substituted boronic ester substrate **5b** was used. The corresponding

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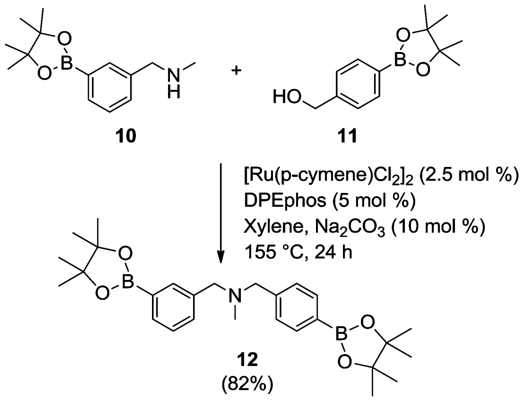
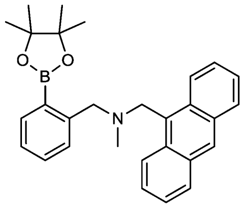
(9) (a) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358–2364. (b) Kranenburg, M.; Vanderburgt, Y. E. M.; Kamer, P. C. J.; Vanleeuwen, P.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089. (c) Lamb, G. W.; Williams, J. M. J. *Chim. Oggi.* **2008**, *26*, 17–19.

(10) (a) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 5662–5663. (b) Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2006**, *47*, 6787–6789.

Scheme 2. Formation of an Unsymmetrical Bis-boronic Ester





13

Figure 1. Sensor **13**.

ortho-substituted boronic ester did not undergo clean amination under these reaction conditions.

We were pleased to find that alcohol **5a** and **5b** were successfully aminated with a range of amines, with good isolated yields being achieved in most cases. The use of a sulfonamide (Table 2, entry 5) was an exception to this, and this was also found to be the case in the amination of the corresponding *m*-substituted product (Table 3, entry 5). Nevertheless, other amines, including anilines, could be used in the reaction.

The general applicability of the reaction was further confirmed by condensation of the *para*-boronic ester alcohol **10** and *meta*-boronic ester amine **11** (Tables 4 and 5) to form *bis*-boronic ester **12** (Scheme 2).

We also used the strategy to prepare a known saccharide sensor **13**[12] in 84% yield (Figure 1; the success of this reaction is probably due to the use of the less sterically demanding methyl substituted secondary amine); the unprotected sensor was prepared for comparison using a standard reductive amination procedure in 54% yield. Identical fluorescence behavior of the two sensors with added saccharides was observed (the protecting group is displaced under the measurement conditions)[13] and clearly demonstrates the validity of our new synthetic procedure in the preparation of fluorescence sensors for saccharides (Supporting Information). We are currently exploring the use of our procedure in the preparation of novel imprinted material based sensors.

In summary, the [Ru(*p*-cymene)Cl$_2$]$_2$/DPEphos/Na$_2$CO$_3$ conditions were found to be effective for the synthesis of amines with pendant boronic ester groups. These compounds and their derivatives have important applications as sensors.

Supporting Information Available. Experimental procedures and characterization of compounds are available with copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] (a) Tsuji, Y.; Huh, K. T.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 377–380. (b) Tsuji, Y.; Huh, K. T.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673–1680. (c) Tsuji, Y.; Huh, K. T.; Yokoyama, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1575–1576. (d) Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* **1996**, *61*, 4214–4218.

[12] James, T. D.; Sandanayake, K. R. A. S.; Iguchi, R.; Shinkai, S. *J. Am. Chem. Soc.* **1995**, *117*, 8982–8987.

[13] Xing, Z.; Wang, H.-C.; Cheng, Y.; Zhu, C.; James, T. D.; Zhao, J. *Eur. J. Org. Chem.* **2012**, 1223–1229.

The authors declare no competing financial interest.