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Deprotection of pinacolyl boronate esters by transesterification with polystyrene–boronic acid

Thomas E. Pennington,[a] Cynantya Kardiman[b] and Craig A. Hutton[a,b,*]

[a]*School of Chemistry, The University of Sydney, NSW 2006, Australia*
[b]*School of Chemistry, The University of Melbourne, VIC 3010, Australia*

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Abstract—Mild deprotection of pinacolyl boronate esters to the corresponding boronic acids was achieved in the presence of excess polystyrene–boronic acid via a transesterification process. The procedure allows for the cleavage of pinacolyl boronate esters in the presence of sensitive functional groups.

The utility of organoboronic acids in organic synthesis has flourished in recent years, particularly through developments in Miyaura–Suzuki couplings,[1] allylborations,[2] copper-catalysed arylboronic acid–heteroatom couplings,[3] and the Petasis reaction.[4] Pivotal to the rapid advancement in organoboron chemistry has been the accessibility of organoboron compounds under mild conditions enabled by Miyaura's borylation of aryl- and vinyl-halides in the presence of a palladium catalyst and bis(pinacolato)diboron.[5] The product pinacolyl organoboronate esters are themselves suitable substrates in Miyaura–Suzuki couplings, thereby negating the need for conversion to the corresponding boronic acids. However, several reactions of organoboron reagents require, or proceed most efficiently with, boronic acids.

The arylation of phenols and a variety of nitrogen nucleophiles in the presence of arylboronic acids and Cu(I) or Cu(II) catalysts has been fine tuned over recent years to represent one of the best methods for heteroatom arylation.[3] However, these reactions proceed in very low yields with pinacolyl boronate esters.[6,7] Similarly, the three-component coupling of an aldehyde, amine and organoboron species (Petasis reaction) can proceed with a pinacolyl boronate ester in some circumstances, but is higher yielding and more general with boronic acid substrates.[8] Hence, the conversion of pinacolyl organoboronate esters to the corresponding organoboronic acids is of much interest.

Several general methods for the deprotection of hindered organoboronate esters are known, but they often employ harsh, acidic or oxidising conditions. Organoboronate esters can be converted to diethanolamine boro- nates by treatment with diethanolamine, with subsequent hydrolysis under acidic or basic conditions generating the boronic acid.[9] Boronate esters can be oxidatively cleaved by treatment with periodate.[10,11] Boron tribromide has also been used to deprotect pinacolyl boronate esters (with concomitant cleavage of a Boc-protected amino group).[12] One of the milder methods for the conversion of pinacolyl organoboronate esters is transesterification in the presence of excess phenylboronic acid. This process is most effective under phase-transfer conditions where the resultant organoboronic acid is water soluble and is separated from the excess organic-soluble phenylboronic acid, such as in the preparation of α-amino organoboronic acids.[11] Transesterification can be used under homogeneous conditions, but is limited by either the difficulties in separating large quantities of phenylboronic acid (if a large excess is used) or incomplete conversion (if only a moderate excess is used). An example of such an approach was reported by Decicco et al.[7] in the deprotection of phenylalanine- and tyrosine-derived pinacolyl boronate esters. Typically 2 equiv of phenylboronic acid were used, with the desired organoboronic acid isolated in ~60% yield and the starting boronate ester recovered in up to 25% yield.

We hereby report the use of polystyrene–boronic acid as a useful reagent for the conversion of pinacolyl boronate esters to the corresponding boronic acids via

* Corresponding author. Tel.: +61-3-8344-6482; fax: +61-3-9347-5180; e-mail: chutton@unimelb.edu.au

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transesterification. The advantages of solid-phase reagents in synthetic transformations are well established: primarily the ability to use a large excess of reagent due to the ease of removal of excess reagent by filtration.[13] We envisaged that the use of a polymer-supported arylboronic acid would allow an excess of reagent to be used in a boronate transesterification reaction, thereby driving the reaction towards complete conversion while also enabling simple removal of the reagent and isolation of the product boronic acid.

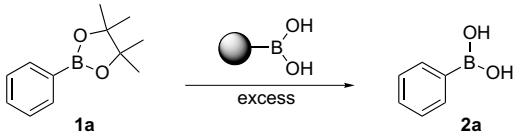
Polystyrene–boronic acid is available commercially (Lancaster) or from bromopolystyrene according to the methods of Farral and Frechet[14] and Hodge et al.[15] Initial attempts to prepare polystyrene–boronic acid using *n*-butyllithium/trimethylborate according to the conditions of Hodge et al. did not provide a high loading of boronic acid functionality. However, using triisopropyl borate in place of trimethyl borate gave polystyrene–boronic acid with higher loading and with greater reproducibility. Whereas Hodge et al. determined the loading by boron elemental analysis, we employed a titration-type procedure, which can be performed in the laboratory, is cost effective, and we believe gives a more accurate reflection of 'available' boronic acid functionality. The polystyrene–boronic acid is treated with 2–3 equiv of pinacol in THF for 16 h such that available boronic acid groups are converted to pinacolyl boronate esters. The polymer is removed by filtration and the solvent is evaporated to leave the excess pinacol. Simple calculation of the amount of pinacol retained by the polymer then provides a measure of the loading, which was typically ~2 mmol/g.

Deprotection of phenyl pinacolyl boronate **1a** was investigated in various solvents in the presence of acid catalysts. Two procedures emerged as being most suitable. Acetonitrile appeared to be the best solvent, with either trifluoroacetic acid or aqueous hydrochloric acid as additives. The acetonitrile/TFA procedure was initially optimised for the deprotection of phenyl pinacolyl boronate **1a** (see Table 1). Acetonitrile was a superior solvent to dichloromethane and chloroform (entries 1–3), and concentrations of TFA greater than 2% did not improve yields (entries 4–6). The use of ~9 equiv of polystyrene–boronic acid in refluxing conditions resulted in virtually complete deprotection of the pinacolyl boronate ester in 6 h (entry 9). Optimised conditions for the HCl/acetonitrile procedure were the use of 9:1 acetonitrile/1 M HCl, at room temperature in the presence of ~5 equiv of polystyrene boronic acid (Scheme 1).

Various aryl pinacolyl boronate esters **1** were then deprotected using these conditions, as shown in Table 2. In general higher yields were obtained using the acetonitrile/1 M HCl method, in many cases giving the boronic acids **2** in >90% yield. In such cases chromatography was unnecessary, and simple removal of the solvent after filtration provided the near-pure boronic acid with only a trace of the pinacolyl boronate ester detectable. It should be noted that the lower yields using the acetonitrile/TFA method represent lower conversions, with the remainder of the boronate ester being recovered.

The results shown in Table 2 indicate that functional groups such as nitro groups, ketones, carbamates, esters and alkenes tolerate these conditions. Of note is that the Boc-group of a protected aniline derivative was stable under these conditions, with the protected arylboronic acid isolated in 78% yield after chromatography (entry 12). The procedure is also applicable to the deprotection of more complex pinacolyl boronate esters such as a protected tyrosine-3-boronate derivative[16] (entry 14). Treatment of the boronate ester with 5 equiv of polystyrene–boronic acid in acetonitrile/1 M HCl (9:1) for 18 h yielded 99% of the corresponding boronic acid. Vinyl pinacolyl boronate esters can also be deprotected under these conditions (entry 13) (Scheme 2).

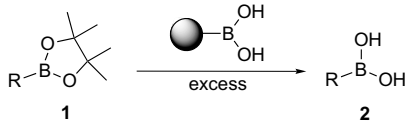
As a large excess of polymer-supported reagent is used, the recovered reagent can be used several times without drastic loss of activity. For example, the resin recovered from the deprotection of the *m*-tolyl and *p*-methoxyphenylboronates (entries 3 and 5, method B) was reused in identical reactions and still gave good yields of the corresponding boronic acids (second run yields in brackets), the yields of the second runs being ~90% of the first run. Ultimately, though, regeneration of the polystyrene–boronic acid was deemed necessary to make this



Scheme 1.

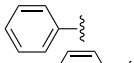
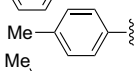
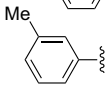
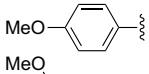
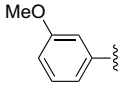
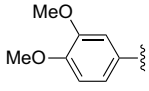
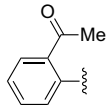
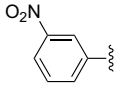
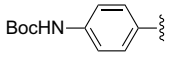
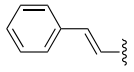
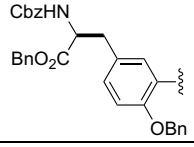
Table 1. Optimisation of deprotection of phenyl pinacolyl boronate ester in acetonitrile/TFA

Entry	Polystyrene–boronic acid	Solvent	Temp	Time	Conv. (%)
1	3 equiv	CH_2Cl_2/1%TFA	25 °C	14 d	13
2	3 equiv	$CHCl_3$/1%TFA	25 °C	14 d	36
3	3 equiv	CH_3CN/1%TFA	25 °C	14 d	98
4	3 equiv	CH_3CN/1%TFA	25 °C	5 d	27
5	3 equiv	CH_3CN/2%TFA	25 °C	5 d	37
6	3 equiv	CH_3CN/5%TFA	25 °C	5 d	36
7	9 equiv	CH_3CN/2%TFA	25 °C	5 d	97
8	9 equiv	CH_3CN/2%TFA	Reflux	3 h	78
9	9 equiv	CH_3CN/2%TFA	Reflux	6 h	98
10	9 equiv	CH_3CN/2%TFA	Reflux	18 h	100



Scheme 2.

Table 2. Deprotection of pinacolyl organoboronate esters

Entry	Substrate (R)	Yield of boronic acid (method A)[a]	Yield of boronic acid (method B)[b]
1		98	94
2		78	94
3		85	95 (87)[c]
4		90	90
5		88	99 (90)[c]
6		98	90
7		92	95
8		85	95
9		82	95
10		99	96
11		80	88
12		37	78
13		67	94
14		52	99

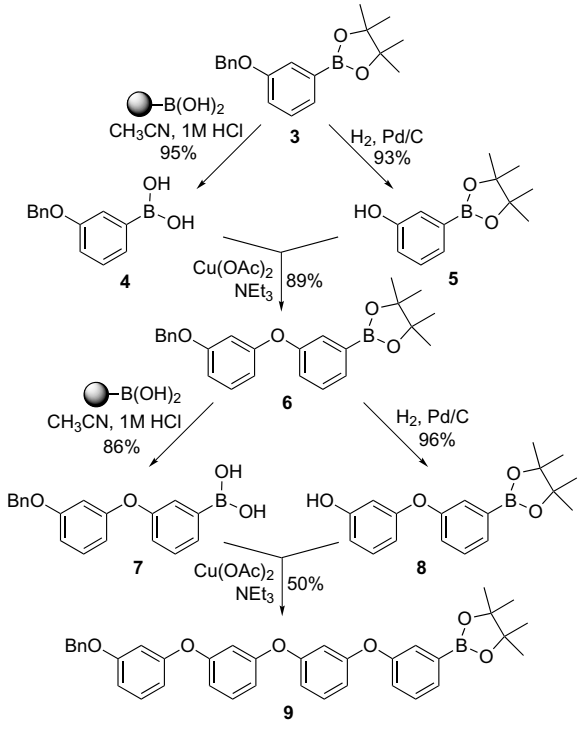
[a] CH_3CN/2% TFA, 9 equiv polystyrene boronic acid, reflux, 18 h.
[b] 9:1 CH_3CN/1 M HCl, 5 equiv polystyrene–boronic acid, room temp, 18 h.
[c] Second run.

method cost effective. Accordingly, used resin was treated with excess diethanolamine in THF, followed by treatment with 1 M HCl/acetonitrile, in order to convert resin-bound pinacolyl boronate ester groups to free boronic acid groups. The used resin recovered after two rounds of deprotection of *p*-methoxyphenyl pinacolyl boronate (entry 5) was regenerated using this procedure, then resubjected to the deprotection reaction conditions. The yield of *p*-methoxyphenylboronic acid was 91%, indicating that the regenerated resin had >90% activity of the fresh resin.

The development of an efficient, mild method for the deprotection of pinacolyl boronate esters enables this group to be used as a true protecting group, rather than simply as a blocking group introduced during the preparation of the organoboron species. Accordingly, we have utilised our method in the synthesis of the polyarylether **9** (Scheme 3).

m-Benzyloxyphenyl pinacolyl boronate ester **3** was converted to either the phenol **5** (by hydrogenolysis of the benzyl ether) or the boronic acid **4** (by employing the polystyrene–boronic acid deprotection procedure described above). Coupling of the phenol **5** and boronic acid **4** in the presence of $Cu(OAc)_2$ gave the biaryl ether **6** in 89% yield. Samples of the biarylether **6** were likewise converted to the corresponding phenol **8** (by hydrogenolysis) and boronic acid **7** (by polystyrene–boronic acid deprotection of the pinacolyl boronate) in good yields. Subsequent Cu(II)-catalysed coupling of compounds **7** and **8** gave the tris(biaryl ether) **9**. The pinacolyl boronate ester group is used as a true protecting group in this sequence, being both orthogonal to the benzyl ether group and preventing reactivity of the boron substituent in the Cu-catalysed phenol–boronic acid coupling reactions.

In conclusion, the use of polystyrene–boronic acid resin in acidic acetontrile provides a mild, high-yielding method for the deprotection of pinacolyl boronate esters. This method allows for the simple isolation of the product boronic acid and tolerates numerous functional and protecting groups.



Scheme 3.

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