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Virtues of Volatility: A Facile Transesterification Approach to Boronic Acids

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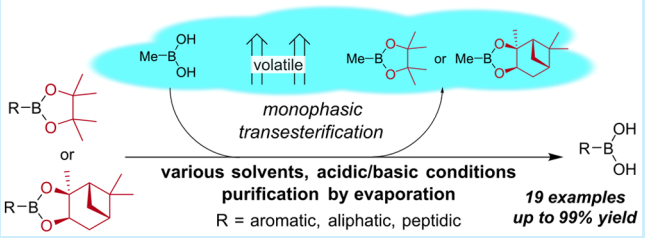
Supporting Information

ABSTRACT: Boronic acids are an increasingly important compound class for many applications, including C−C bond formation reactions, medicinal chemistry, and diagnostics. The deprotection of boronic ester intermediates is frequently a problematic and inefficient step in boronic acid syntheses. We describe an approach that highly facilitates this transformation by leveraging the volatility of methylboronic acid and its diol esters. The method is performed under mild conditions, provides high yields, and eliminates cumbersome and problematic purification steps.



Various synthetic procedures, such as metal-catalyzed CH-activations,[1] asymmetric hydroborations,[2−4] or decarboxylative borylations,[5−7] have been recently developed to provide access to a promising chemical space.[8] Most modern procedures rely on diboron compounds, such as B_2pin_2, to afford stable boronic esters as key intermediates after C−B bond formation. Stereoselective borylations like the well-known Matteson homologation use the pinanediol group as a protecting group and chiral auxiliary.[9] However, the deprotection of those intermediates can be very troublesome. The recently emerged borylation reactions and the increasingly recognized value of boronic acid derivatives in medicine and diagnostics provide considerable incentive to develop efficient, versatile, and technically feasible deprotection approaches.

Established deprotection methods for boronic esters can be classified into the "harsh deprotections" and "biphasic transesterifications" (Scheme 1). The harsh approaches include the transborylation with boron trichloride,[10−13] reductive cleavage with lithium aluminum hydride,[14,15] oxidative cleavage with sodium periodate,[16,17] or the hydrolysis with potassium hydrogen difluoride.[18−23] However, these reagents are hazardous and not tolerant of many functional groups, causing limitations in scope and technical applicability. In addition, subsequent purification steps by chromatography can be problematic because of limited on-column stability and polarity of the products.

Similar difficulties are inherent to biphasic transesterification methods that involve phenylboronic acid or isobutylboronic acid, whose application is limited to polar reactants, because substrate and product must be soluble in the aqueous or methanolic phase.[16,24] However, even during synthesis of polar peptide boronic acids, e.g. the proteasome inhibitor bortezomib or ixazomib, the yields can be low.[25−27]

Transesterifications with diethanolamine are highly dependent on polarity differences between the corresponding diethanolamine salt and the free boronic acid, which results in a narrow substrate scope.[28−30] A solid-phase transesterification using polystyrene-boronic acid has also been

Scheme 1. Representative Procedures for the Deprotection of Boronic Esters

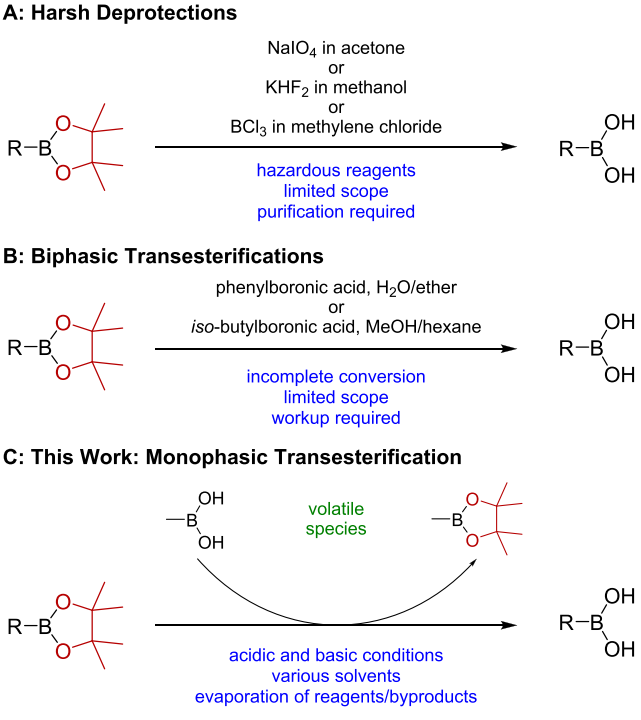


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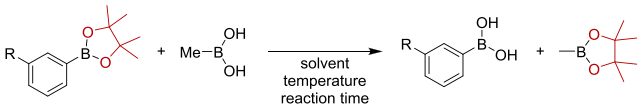
Table 1. Optimization of Reaction Parameters[a]



entry	R	equiv of $MeB(OH)_2$	solvent	conditions	conversion[b] (%)
1	H	0	DMF	rt, on	0
2	H	3	DMF	rt, on	2
3	H	2	5% TMP/DMF	rt, 2 h	56
4	H	2	5% TMP/DMF	rt, on	75
5	H	3	5% DIPEA/DMF	rt, on	15
6	H	1	5% DIPEA/DCM	rt, on	40
7	H	3	5% DIPEA/DCM	rt, on	80
8	H	5	5% DIPEA/DCM	rt, on	95
9	NH_2	2	5% DIPEA/DCM	rt, on	49
10	NH_2	10	5% TMP/DMF	rt, 17 h	40
				rt, 23 h	57
				rt, 42 h	76
				rt, 50 h	89
11	NH_2	10	5% TMP/DMF	40 °C, 17 h	80
				40 °C, 23 h	86
				40 °C, 42 h	89
				40 °C, 50 h	89
12	NH_2	0	5% TFA/DCM	rt, on	0
13	NH_2	5	DCM	rt, on	7
14	NH_2	2	5% TFA/DCM	rt, 2 h	83
15	NH_2	3	5% TFA/DCM	rt, 2 h	95
16	H	3	5% TFA/DCM	rt, on	99 (97)[c]
17	NH_2	3	5% TFA/DCM	rt, on	99 (99)[c]

[a]Reactions were performed on 0.2 mmol scale. [b]Determined by proton NMR of the crude reaction mixture. [c]Isolated yield, based on free boronic acid; on: overnight.

reported, but an excess of expensive resin is required and the protocol is mainly restricted to aromatic substrates.[31]

In an ongoing project that involves the synthesis of boronic acid building blocks for drug discovery,[32,33] we recently struggled with the deprotection of boronic acid pinacol esters. Neither the biphasic transesterification with phenylboronic acid nor the transborylation with boron trichloride or the diethanolamine protocol gave the desired products, mostly due to polarity issues or functional group incompatibilities. In order to circumvent these issues, we investigated other possibilities to develop a protocol that should be applicable to a wide range of pinacol and pinanediol esters. The aim was to devise a mild and efficient method that does not require any chromatographic purification or time-consuming workup procedures. We focused on the transesterification strategy, keeping in mind that the method should be insensitive to choice of solvent to ensure wide applicability. One idea was to involve a separation procedure, such as evaporation, that is orthogonal to other approaches. This could be realized by introducing a volatile transesterification reagent whose volatility is increased upon esterification with a pinacol unit. We reasoned that this should drive the equilibrium to completion by consecutive evaporation of byproducts and excess reagent. A convenient reagent was found in the form of the inexpensive (~1 $/€ per gram; see the SI for details) and nonhazardous methylboronic acid, a semivolatile solid. The corresponding pinacol ester was described as a liquid with a boiling point of 120−122 °C under atmospheric pressure.[34] For the exploration of this idea, we chose phenylboronic acid pinacol ester and its meta-substituted amino derivative as model compounds due to their stability and suitability for NMR reaction controls (see Figure S-1 in the SI for further details).

On first attempts, DMF was chosen as solvent with a high boiling point to allow evaporation of the methylboronic pinacol ester from a liquid phase. Unfortunately, no significant conversion under neutral conditions was observed (Table 1, entries 1−2). However, the addition of small amounts of 2,4,6-trimethylpyridine (TMP) increased the conversion rate considerably (Table 1, entries 3−4). The use of DIPEA resulted in lower conversions (Table 1, entry 5), but switching to methylene chloride as solvent resulted in conversion rates up to 95% (Table 1, entries 6−9), indicating that the choice of base is not crucial. It was also shown that an increase of reaction temperature accelerates the transesterification process without influencing the equilibrium (Table 1, entries 10−11). However, under basic conditions, workup steps would have to be introduced since methylboronic acid and the product itself would be prone to salt formation with the respective base.

Therefore, acidic conditions were tested, and almost complete conversion was achieved using 5% trifluoroacetic acid in methylene chloride after 2 h (Table 1, entries 14−15). Without the addition of TFA, transesterification remained negligible (Table 1, entry 13). No conversion occurred in TFA/DCM in the absence of methylboronic acid (Table 1, entry 12), demonstrating that transesterification is indeed the underlying mechanism. The equilibrium was usually reached within a few hours as exemplified in Figure 1. Since methylboronic acid is less volatile than its pinacol ester, the reaction was driven to completeness during the evaporation process, providing the pure desired product after removal of

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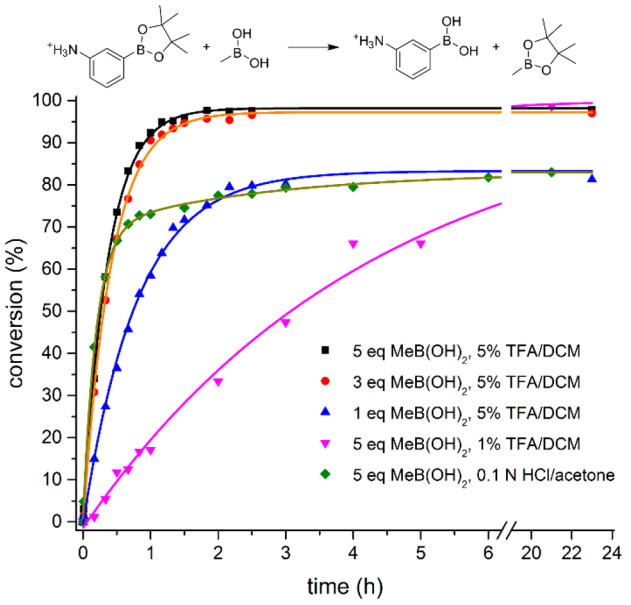


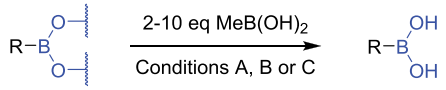
Figure 1. Time dependency of the transesterification progress. Reactions were performed on 0.2 mmol scale in the respective solvent (100 mM) at room temperature. Quantification was done by proton NMR of the crude reaction mixture.

excess methylboronic acid, the byproduct, and the solvent from the reaction vessel.

Occasionally, NMR signals that resembled residual methylboronic acid, resistant to evaporation, persisted in the product. We hypothesized that these signals originate from mixed anhydrides, such as heteroboroxines,[35] that are formed during the evaporation process. Fortunately, this issue could easily be resolved by adding 0.1 N hydrochloric acid to the crude product and repeated evaporation. This led to the disappearance of contaminant methyl group signals, indicating—as expected—complete reversibility of the anhydride formation and removal of residual methylboronic acid without chromatography or extraction. It was therefore straightforward to deprotect both model compounds in quantitative yields with no further purification steps (Table 1, entries 16–17). Final compounds were therefore obtained as hydrochloride salts if they contained basic groups.

With suitable reaction conditions in hand, the scope of the protocol was examined. Aromatic derivatives **1a**, **2a**, **3a**, **4a**, **5a**, and **6a** could be transformed easily and quantitatively into their corresponding acids (Table 2, conditions A). No difference in efficacy was observed between ortho-, meta-, and para-substituted aromatic compounds. Moreover, compound **1a** was transesterified quantitatively in a gram-scale experiment, thereby demonstrating the utility of the reaction for technical processes. Aliphatic compound **7a** was deprotected exceptionally fast, since the product was insoluble in methylene chloride, driving the equilibrium to completion within 30 min. Boronic ester **8a** could also be transesterified completely, but the isolated yield was slightly lower due to product volatility. For the deprotection of thiophene-2-boronic acid pinacol ester (**9a**) under conditions A, only degradation products were obtained (data not shown). We reasoned that trifluoroacetic acid might promote protodeboronation and therefore switched the solvent system to a binary mixture of 0.1 N hydrochloric acid and acetone (conditions B). With these conditions, the desired product **9** could be isolated in 96% yield. Similar results were achieved with the deprotection of vinylic compound **10a** and α-aminoboronic ester **11a**.

Table 2. Scope of the Monophasic Transesterification



substrate	cond.	product	yield[a] (%)
1a	A	**1**	99
1b	A		94
2a	A	**2**	97
3a	A	**3**	93
4a	A	**4**	99
5a	A	**5**	93
6a	A	**6**	93
7a	A	**7**	99
8a	A	**8**	76
9a	B	**9**	96
10a	B	**10**	84
11a	B	**11**	99
12a	B	**12**	94
12b	B		92
13a	B	**13**	93
13b	B		92
14a	B	**14**	90
15a	B	**15**	94
16a	C	**16**	97

[a]Isolated yield, based on free boronic acid. A: 5% TFA/DCM. B: 0.1 N HCl/acetone (1:1, v/v). C: 0.1 N NaOH/acetone (1:1, v/v). pin: pinacol; pnd: (+)-pinanediol. Detailed synthetic procedures are provided in the Supporting Information.

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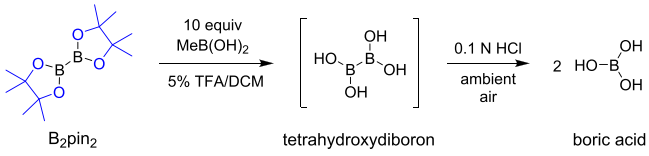
Since the synthesis of peptide boronic acids recently became a prominent field, especially in medicinal chemistry, we included the synthesis of the approved proteasome inhibitors bortezomib (**12**) and ixazomib (**13**) in our studies. The pinacol and pinanediol esters of both peptides were synthesized and deprotected using conditions B in excellent yields. Even the exceptionally stable pinanediol esters **12b** and **13b** could be readily deprotected, however with slightly longer reaction times compared to the respective pinacol esters **12a** and **13a**. If done on scale, valuable chiral auxiliaries like the pinanediol group could also be recovered by employing literature-known methods.[36] However, we did not attempt or pursue this for the examples in Table 2.

Using the new deprotection procedure, we did not encounter any problems deprotecting the initially desired building blocks *N*-Fmoc-(2-aminoethyl)boronic acid pinacol ester (**14a**) and *N*-Fmoc-(4-aminobenzyl)boronic acid pinacol ester (**15a**) in excellent yields. It should be noted that our efforts to generate tertiary aliphatic boronic acids failed, likely due to their limited stability and high susceptibility to autoxidation processes.

To gain access to the deprotection of acid-sensitive substrates we also developed a protocol using basic conditions. Using a binary solvent mixture of 0.1 N sodium hydroxide solution and acetone, the Boc protected derivative **16a** was transesterified completely overnight. The solution was carefully neutralized with 0.1 N hydrochloric acid and concentrated to dryness. The remaining residue was resuspended in acetone, allowing the sodium chloride precipitate to be easily filtered off to obtain the pure product in 97% yield after solvent evaporation (Table 2).

To investigate the behavior of diboron compounds, B_2pin_2 was treated with methylboronic acid under conditions A. It was shown that B_2pin_2 can be converted into 2 equiv of water-soluble boric acid, presumably *via* tetrahydroxydiboron as an intermediate that readily decomposes in aqueous acidic media under ambient atmosphere (Scheme 2). The transesterification

Scheme 2. Double Transesterification of B_2pin_2 Yields Boric Acid Which Is Easily Removable from Crude Reaction Mixtures



can therefore facilitate the purification after borylation reactions, since diboron compounds are being used in excess throughout modern borylation reactions, but often remain persistent as impurities even after column chromatography.

In conclusion, we have developed a versatile protocol for the deprotection of boronic esters that can be adapted to its substrate in terms of solvent choice, equivalents of methylboronic acid, and reaction time, leading to exceptionally high yields. Due to the easy workup procedure, it can also be implemented into high-throughput synthesis protocols. It is expected that the monophasic transesterification approach described here will facilitate the synthesis of boronic acids and thereby augment their utility in cross-coupling reactions and for the identification of new lead structures in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00584.

Full synthetic procedures and analytical data of all intermediates and final compounds; ^{1}H, ^{13}C, and ^{11}B NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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