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# A novel redox-sensitive protecting group for boronic acids, MPMP-diol

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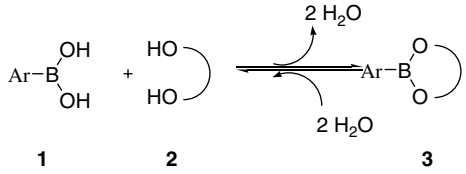
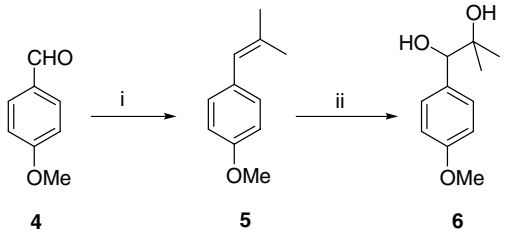
**Abstract**—A new boronic acid protecting group, 1-(4-methoxyphenyl)-2-methylpropane-1,2-diol (MPMP-diol), has been developed. Both protection and deprotection can be accomplished under mild conditions with quantitative conversions. The deprotection can be carried out using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).


Boronic acids have a wide variety of applications in organic synthesis,[1] medicinal chemistry,[2] and carbohydrate sensor design.[3–5] Our laboratory has had a long-standing interest in using the boronic acid moiety for the preparation of carbohydrate sensors and lectin mimetics.[5] In the preparation of boronic acids or reactions involving boronic acids, often the protected form is used for easy purification and to avoid side reactions. An ideal protecting group has the following characteristics: (1) easy protection, (2) stable under normal purification conditions, and (3) readily cleavable when needed under mild conditions. In this regard, the pinacol, neopentylglycol, or diethanolamine boronate esters are commonly used. Between the first two, the pinacol protected form of boronic acids is generally more useful because of its higher stability under column chromatography conditions. However, for the same reason the pinacol boronic esters are rather difficult to deprotect because the deprotection relies on driving the equilibrium (shown in Scheme 1) in the reverse direction. $BCl_3$ and $NaIO_4$ have been used to either trap ($BCl_3$) or destructively remove the pinacol protecting group ($NaIO_4$) in order to drive the reaction to completion.[6,7] In many cases, these methods do not work very well in removing the protecting group, presumably because the obligatory first step, dissociation, is negatively affected by the high association constants between boronic acids and pinacol under the cleavage conditions.




**Scheme 1.** The equilibrium between boronic acids and corresponding esters.

The diethanolamine (sometimes *N*-methyldiethanolamine) protecting group has the unique advantage of being able to crystallize most, not all, of the esters for purification.[8] However, it does not allow for easy column purification because of the high polarity of the protected form. Herein, we report a new protecting group, 1-(4-methoxy-phenyl)-2-methyl-propane-1,2-diol (MPMP-diol) (**6**, Scheme 2), that forms a stable ester




**Scheme 2.** Preparation of 1-(4-methoxy-phenyl)-2-methyl-propane-1,2-diol. Reagents and conditions: (i) isopropyltriphenylphosphonium iodide, *n*-butyllithium, THF, 0 °C, 96%; (ii) osmium tetroxide, 4-methylmorpholine *N*-oxide, acetone–$H_2O$ (10:1), 90%.

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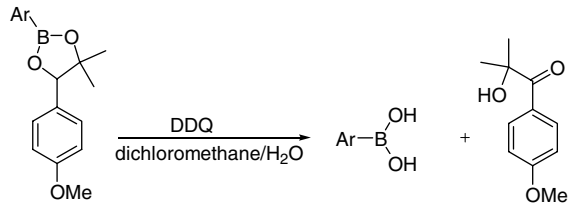


**Scheme 3.** Deprotection of the boronic ester.

with the boronic acid moiety, and can be deprotected readily under mild oxidative conditions using reagents such as 2,3-dichloro-5,6-dicyano-1,-4-benzoquinone (DDQ) (Scheme 3). The deprotection reaction does not rely on the equilibrium described in Scheme 1, that is, dissociation is not an obligatory step as it is in the cleavage of the pinacol ester. Therefore, the high stability of the boronic ester has no negative impact on the ease of cleavage. Such an orthogonal protecting method allows for the optimization of the cleavage conditions independent of the binding constants.

The design takes advantage of the known oxidative cleavage of methoxybenzyl ethers, generating the corresponding aldehyde or ketone, by DDQ.[9] Similar reactions have been studied and used extensively in organic synthesis.[10,11] Such reactions occur under very mild conditions with high efficiency. With this reaction in mind, compound **6** (Scheme 2) was designed as a new boronic acid protecting group.

In this design, the vicinal diol in **6** was expected to bind to boronic acids to give a stable cyclic boronic ester structure; and the trisubstitution pattern was expected to help stabilize the boronic ester. DDQ-mediated cleavage of the benzyl ether linkage to give the corresponding carbonyl group should allow for the deprotection of the boronic acid. Again, in the cleavage step, dissociation is not necessary. The presence of a *para*-methoxy group on the phenyl ring was designed to facilitate the oxidative cleavage.

1-(4-Methoxyphenyl)-2-methylpropane-1,2-diol (**6**) was prepared as described in Scheme 2 starting with commercially available 4-methoxylbenzaldehyde through a Wittig reaction followed by dihydroxlation with catalytic amount of osmium tetraoxide in the presence of 4-methylmorpholine-*N*-oxide.[12] The overall yield was about 85%.

To examine the applicability of this diol for the protection of boronic acids, we have studied a series of five arylboronic acids (Table 1), which include phenylboronic acid, arylboronic acids that have an electron-withdrawing group (nitro and ester), and those that have an electron-donating group (methoxy and alkyl groups).

All the boronic esters were prepared under similar conditions at room temperature except for the reaction time; and all reactions achieved quantitative conversions based on TLC. The isolated yields ranged from 91% to 95%, and the reaction time ranged from 2 to 6 h. The protection step can be accomplished using the following typical procedure: To a solution of boronic acid in anhydrous THF were added MPMP-diol (1.2 equiv) and $MgSO_4$. The mixture was stirred at room temperature until TLC indicated complete conversion (2–6 h), and then filtrated. Then, solvent was evaporated to give the crude product, which was purified by silica gel column chromatography to give the corresponding boronic ester.

These products, boronic esters, are quite stable in water and methanol. For example, when the esters were stirred in aqueous methanol (methanol–water = 9:1) solution overnight at room temperature under both neutral and acidic conditions (pH = 3), no dissociation was observed based on TLC.

Regeneration of the boronic acids was achieved by oxidative cleavage upon treatment with DDQ. Specifically, to a solution of the ester in a mixture of methylene chloride–$H_2O$ (9:1) was added DDQ in portions. The amount of DDQ added ranged from 1.2 to 3 equiv. After stirring for a certain period of time (until TLC indicated completion of the reaction), the reaction solution was concentrated, and the residue was purified by column chromatography to give the corresponding boronic acid. Table 1 lists the specific deprotection conditions and isolated yield for each boronic acid. Although the isolated yields ranged from 65% to 85%, it is important to note that complete deprotection was observed for all the tested boronic esters based on TLC. The discrepancy reflects the difficulty in recovering 100% of free boronic acids on silica gel column.

The experimental results indicate that the new protecting group can be completely removed with a mild oxidative reagent, DDQ. Normally, due to the enhanced B–O bond strengths and increased binding constants,[5] deprotection of arylboronic esters with a strong electron-withdrawing group is quite difficult. Sometimes, even $NaIO_4$ cannot remove the pinacol protecting group. The results in Table 1 indicate that the MPMP-diol protecting group works very well for boronic acids with either a strong electron-withdrawing or a strong electron-donat-

**Table 1.** Oxidative cleavage of boronic esters

| Boronic acid | Reaction time/h | Reaction temperature | Yield (%) |
|---|---|---|---|
| Phenylboronic acid | 8 | rt | 81 |
| 3-Nitrophenylboronic acid | 24 | 50 °C | 65 |
| 4-Methoxy-phenylboronic acid | 24 | rt | 80 |
| 3-*N*-BOC-aminomethylphenylboronic acid | 24 | rt | 77 |
| 3-Methoxycarbonyl-phenylboronic acid | 6 | rt | 85 |

ing group. This is because the deprotection does not involve an obligatory dissociation step.

In conclusion, we have developed 1-(4-methoxy-phenyl)-2-methylpropane-1,2-diol (MPMP-diol) as a new redox-sensitive protecting group for arylboronic acids, which has the following desirable characteristics: (1) easy and high yield protection, (2) stable under normal handling conditions, (3) easy cleavage under mild oxidative conditions, and (4) works with arylboronic acids with either an electron-withdrawing or electron-donating group. It is worth noting that the protecting group has a chiral center and is in the racemic form. Therefore, in the protection of a boronic acid with an existing chiral center, diasteroisomers are expected.

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## Supplementary data

Supplementary data are available with this paper including experimental procedures and spectroscopic data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.010.

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