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Published on Web 10/07/2008

Multistep Synthesis of Complex Boronic Acids from Simple MIDA Boronates

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Received August 12, 2008; E-mail: burke@scs.uiuc.edu

Boronic acids are tremendously useful building blocks for organic synthesis.[1] However, to avoid incompatibilities with most synthetic reagents, it is typically necessary to introduce the boronic acid group just prior to its utilization. Because most of the methods for achieving this have limited functional group tolerance, accessing structurally complex boronic acids can be very challenging. A variety of sterically bulky boronic esters are more compatible with synthetic reagents than their boronic acid counterparts.[2] However, liberation of the boronic acid usually requires harsh conditions that can be incompatible with complex substrates. Trifluoroborate salts can in many cases serve as highly effective surrogates for boronic acids.[3] These compounds are also stable to a variety of common reaction conditions and benchtop storage, thus providing novel access to many important organoboranes.[3,4] However, a lack of compatibility with chromatography can significantly limit the utility of trifluoroborate salts in the multistep synthesis of structurally and/or stereochemically complex building blocks.

In addition to being unreactive under anhydrous cross-coupling conditions, we have recently reported that *N*-methyliminodiacetic acid (MIDA) boronates[5] are universally compatible with chromatography, exceptionally stable to benchtop storage, and easily hydrolyzed using mild conditions to liberate the corresponding boronic acids.[6,7] MIDA boronates thus represent a potentially general building block platform with distinct advantages over boronic acids and other surrogates. Greatly expanding access to these materials, we herein report the discovery that MIDA boronates are compatible with a wide range of common synthetic reagents. As demonstrated with the total synthesis of (+)-crocacin C, this finding now makes it possible to reliably transform simple B-containing starting materials into structurally complex boronic acid building blocks via multistep synthesis pathways (Scheme 1a).

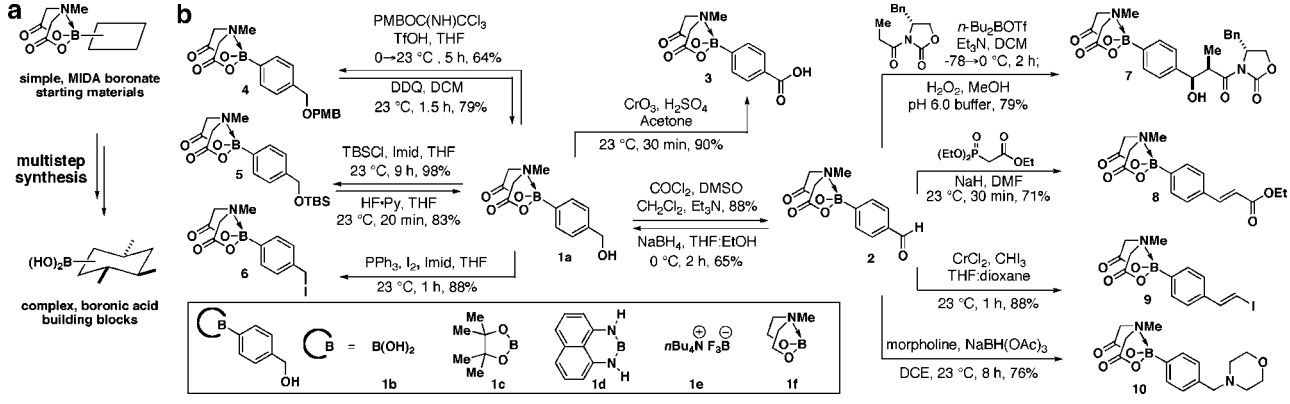
Due to a lack of the p-orbital that is typically involved in the reactivity of boronic acids, we anticipated that pyramidalized MIDA boronates might be relatively stable to some mild reagents. We first explored the compatibility of the model substrate *p*-hydroxymethylphenyl MIDA boronate **1a** to a range of oxidants and found the conditions of Swern afforded the desired benzaldehyde **2** in good yield (Scheme 1b). PDC, TPAP/NMO, and Dess−Martin periodinane were also well-tolerated. Expecting to identify the limits of this stability, we exposed MIDA boronate **1a** to the very strongly acidic and oxidizing Jones conditions (H_2SO_4/CrO_3). However, we were surprised to find a 90% yield of benzoic acid **3**. The corresponding boronic acid **1b**, pinacol boronic ester **1c**, 1,8-diaminonaphthalene adduct[8] **1d**, trifluoroborate salt[4] **1e**, and *N*-methyldiethanolamine boronate[9,10] **1f** all decomposed under Jones conditions.[8]

To gain understanding of the dramatic difference in reactivity for the structurally related MIDA (**1a**) and *N*-methyldiethanolamine (**1f**) adducts, we carried out single crystal X-ray analysis of both complexes which revealed no major differences in bond lengths, bond angles, or tetrahedral character at the two boron centers (Supporting Information). In contrast, and consistent with studies of related complexes,[5,10] variable temperature NMR of a solution of **1f** in d_6-DMSO revealed coalescence of the diastereotopic methylene protons of the diethanolamine backbone upon heating from 23 to 60 °C, while the same experiment with the MIDA boronate **1a** yielded no coalescence upon heating to 150 °C. These data are consistent with the conclusion that the N→B bond in **1f** is dynamic which renders the boron p-orbital and nitrogen lone pair vulnerable to attack, whereas in the MIDA boronate **1a** these potentially reactive sites are kinetically not accessible at <150 °C.

Encouraged by the unique stability of the MIDA boronate group to these strongly acidic and oxidative conditions, we explored its compatibility with a variety of common reagents (Scheme 1b). Remarkably, even TfOH (pK_a −14) was tolerated, enabling the acid-catalyzed *p*-methoxybenzylation of **1a** to yield **4**, which was then smoothly debenzylated with DDQ to regenerate **1a**. Alcohol **1a** was also reversibly silated under standard conditions (**1a** → **5**; **5** → **1a**) or converted into the bifunctional halo MIDA boronate **6** upon treatment with PPh_3/I_2. The compatibility with soft nucleophiles suggested by the latter encouraged us to explore a series of C−C bond-forming reactions with benzaldehyde **2**. The Evans aldol, Horner−Wadsworth−Emmons olefination, and Takai olefination reactions were all found to be well-tolerated. Aldehyde **2** was also reductively aminated to form **10** or reduced with $NaBH_4$ to regenerate **1a**.

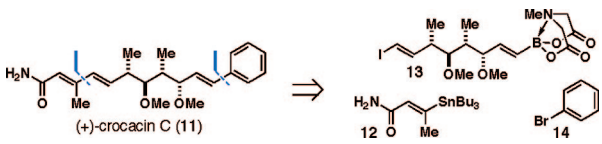
In the course of these studies, we found that MIDA boronates are tolerant to a variety of workup/extraction solutions including water, pH 7 buffer, brine, aq. HCl, aq. NH_4Cl, aq. NaS_2O_3, and aq. hydrogen peroxide at pH 6. Surprisingly, saturated aqueous $NaHCO_3$ is also well-tolerated, except in the presence of alcoholic solvents. Despite this

Scheme 1

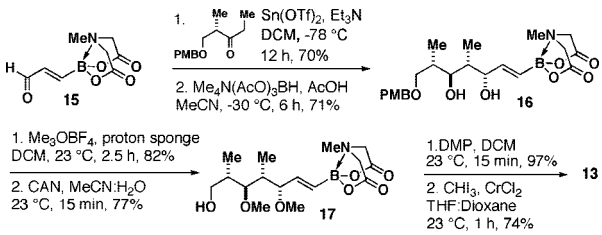


10.1021/ja8063759 CCC: $40.75

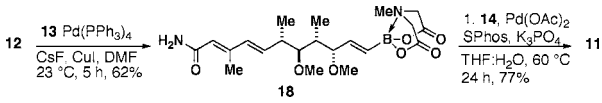
Scheme 2



Scheme 3



Scheme 4



widespread stability, MIDA boronates **1**−**5** and **7**−**10** were all conveniently transformed into the corresponding boronic acids using mild aqueous base (aq. NaOH/THF, 23 °C, 10 min, or aq. $NaHCO_3$/MeOH, 23 °C, 3.5 h, Supporting Information).[6−8] Consistent with a focused sensitivity to hard nucleophiles, we found that MIDA boronates are generally incompatible with $LiAlH_4$, DIBAL, TBAF, and a variety of metal alkoxides.[11] Importantly, compounds **1a**−**10** are all crystalline solids, compatible with chromatography, and stable to long-term benchtop storage under air.

Inspired by the simplicity and flexibility of peptide coupling, we recently reported a potentially general strategy for small molecule synthesis involving the iterative cross-coupling (ICC) of MIDA-protected haloboronic acids.[6−8] In an ideal ICC-based pathway, building blocks having all of the required functional groups preinstalled in the correct oxidation state and with the desired stereochemical relationships are brought together using only stereospecific cross-coupling reactions. We recognized that the newfound reagent compatibilities of MIDA boronates should enable structurally and/or stereochemically complex haloboronic acid building blocks to be readily prepared from simple MIDA boronate starting materials via multistep synthesis. To evaluate this potential, we targeted the total synthesis of the natural product (+)-crocacin C[12] (**11**) via ICC.

Retrosynthetic fragmentation of **11** via recursive cross-coupling generates known building blocks **12**[12b] and **14** and the structurally complex, B-protected haloboronic acid **13** (Scheme 2). As shown in Scheme 3, the synthesis of **13** commenced with acrolein MIDA boronate **15**, which was prepared from the known boronic acid.[13] A Paterson aldol reaction followed by diastereoselective reduction of the resulting β-hydroxyketone[12d] yielded diol **16**. Harnessing a key advantage of MIDA boronates, silica gel chromatography was utilized to remove the small amounts of diastereomeric byproducts that are typically generated during these types of reactions. Permethylation of **16** with Meerwein's salt and cleavage of the resulting PMB ether using CAN afforded primary alcohol **17**. DMP oxidation followed by Takai olefination[12d] of the resulting aldehyde afforded bifunctional building block **13**. Notably, **15**, **13**, and all intermediates are crystalline solids, compatible with chromatography, and stable to benchtop storage under air. With building block **13** in hand, a CsF/CuI-promoted Stille coupling[14] with **12** followed by *in situ* boronic acid generation[15] and Pd/SPhos[16]-promoted cross-coupling between **18** and **14** completed the synthesis of (+)-crocacin C (Scheme 4). Enabled by the ability to carry a boron functional group through multiple synthetic steps, this ICC-based route is short (nine steps in the longest linear sequence) and readily amenable to analogue synthesis via incorporation of modified building blocks into the same pathway.

As demonstrated herein, the stability of MIDA boronates to a broad range of common reaction conditions and the unique compatibility of these materials with chromatography collectively make it now possible to reliably prepare complex boronic acid building blocks from simple B-containing starting materials[17] via multistep synthesis pathways. Because of this and many other highly enabling features,[6,7] MIDA boronates represent a uniquely promising platform for the preparation, storage, and utilization of organoborane building blocks in organic synthesis.

Acknowledgment. We gratefully acknowledge the NSF (CAREER 0747778) and the Dreyfus Foundation for financial support, Sigma-Aldrich for gifts of reagents, and S. Wilson for X-ray analysis. M.D.B. is a Beckman Young Investigator.

Supporting Information Available: Procedures, spectral data, spectra, and X-ray crystallographic data (cif) for **1a** and **1f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA8063759