Published in final edited form as:
Tetrahedron. 2013 September 9; 69(36): . doi:10.1016/j.tet.2013.05.050.

(1-bromovinyl)-MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis

Eric M. Woerly, **Jonathan E. Miller**, and **Martin D. Burke**
Howard Hughes Medical Institute, Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801

Martin D. Burke: burke@scs.uiuc.edu

Keywords

MIDA boronates; Iterative cross-coupling; 1,1-disubstituted boronates; 1,1-disubstituted olefins

1. Introduction

The substantial level of inherent modularity present in most small molecules suggests that a generalized building block based approach may be applicable to the laboratory synthesis of many of these compounds. In an idealized form of this approach, stable subunits having all of the required functional groups preinstalled in the correct oxidation states and with the desired stereochemical relationships are linked using only one reaction. As a roadmap for creating a general strategy for small molecule synthesis, we aim to identify common substructural motifs that are prevalent in a wide range of natural products and transform them into shelf-stable building blocks that are compatible with iterative assembly.

In this vein, 1,1-disubstituted olefins are prevalent in small molecule pharmaceuticals[1] and natural products derived from a wide range of biosynthetic pathways (Figure 1).[2] In addition, they are useful synthetic intermediates. [3] Some common strategies for the synthesis of 1,1-disubstituted olefins include the Wittig reaction of methyltriphenylphosphonium bromide and a ketone,[4] the Heck reaction of an organohalide or triflate and monosubstituted olefin,[5] and other metal catalyzed couplings between a halide or halide surrogate and an organometallic reagent.[6]

Of particular interest, the 1,1-disubstituted alkenyl boronate motif is an attractive intermediate for the preparation of 1,1-disubstituted olefins because of the versatility of the vinyl boron moiety. [7] While methods for the synthesis of 1,2-disubstituted alkenyl boronates are abundant,[8] the methods for the preparation of 1,1-disubstituted alkenyl boronates have been limited. [9] Recent methods for the preparation of these motifs include the copper catalyzed hydroboration of aryl and heteroaryl substituted alkynes.[9a] Alternatively, aryl substituted vinyl boronates can be prepared from the corresponding vinyl halide via a

Correspondence to: Martin D. Burke, burke@scs.uiuc.edu.

Dedicated to Professor Paul Wender with deepest admiration on his receipt of the 2012 Tetrahedron Prize for Creativity in Organic Chemistry.

Miyaura borylation[9c] or a lithiation/trap sequence.[9d,9e] However, the synthesis of the requisite vinyl halide can be challenging and often uses conditions that are not compatible with acid-sensitive functionalities. To address these challenges, we envision that a B-protected 1,1-disubstituted halo boronate building block would be extremely useful for the modular synthesis of targets containing a 1,1-disubstituted olefin motif (Scheme 1).

Along these lines, we are developing a platform of *N*-methyliminodiacetic acid (MIDA) boronate building blocks.[10,11,12,13,14,15,16,17,18,19,20,21,22,23,24] MIDA boronates have many desirable properties that render them exceptionally useful as synthetic intermediates. They are uniformly air-stable, non-toxic, highly crystalline, and monomeric free-flowing solids that are fully compatible with silica gel chromatography. Many methods now exist for preparing MIDA boronates from a wide range of different starting materials, including boronic acids,[10,11,12,13,19,25] haloboranes,[11,13] boronic esters,[16] trialkoxyborate salts,[14–17,19] organohalides,[19] organolithium reagents,[19,23] and Grignard reagents.[15,16] The MIDA boronate functional group is inert to anhydrous cross-coupling conditions, yet can be readily transformed into a fully reactive boronic acid or ester using mild conditions.[10,14,17] These features enable the simple, efficient, and highly flexible synthesis of a wide range of complex small molecules via iterative cross-coupling of MIDA-protected haloboronic acids.[10,11,12,16,17,21,22,24] Finally, a large and growing collection of MIDA boronates are now commercially available.[26] Taking advantage of all of these properties, we herein report a 1,1-disubstituted halo MIDA boronate building block, which upon selective functionalization, allows ready access to a variety of 1,1-disubstituted alkenyl boronate motifs with the potential for iterative cross-coupling for the preparation of 1,1-disubstituted olefins.

2. Results

Bromination-elimination reactions provide a convenient method for the synthesis of vinyl halides.[27] In particular, 1,1-disubstituted olefins can be prepared from terminal alkenes via this type of transformation.[28] With this strategy in mind, vinyl MIDA boronate **1** is an attractive starting point. This building block can easily be prepared on large scale from inexpensive starting materials (Scheme 2), and is now commercially available on both the gram and kilogram scales.[29] Bromination of **1** followed by treatment of the resulting vicinal dibromide intermediate with DBU in MeCN provides a very convenient route to (1-bromovinyl)-MIDA boronate **2** in 67% overall yield. Moreover, **2** can be prepared on the decagram scale and isolated in pure form without the use of column chromatography. Building block **2** is also now commercially available.[26]

With a readily scalable synthesis of **2** in hand, we have preliminarily explored its utility in the preparation of a range of new 1,1-disubstituted alkenyl boronate building blocks en route to 1,1-disubstituted olefins. In this vein, our initial attempt to couple **2** with phenyl boronic acid under anhydrous cross-coupling conditions surprisingly formed a mixture of products identified as the desired 1,1-disubstituted boronate **3** and the *trans*-1,2-disubstituted product **4** in a 1:4 ratio (Scheme 3).

We hypothesized that **4** is formed through a competitive reaction pathway involving oxidative addition of the palladium catalyst to **2** followed by β-hydride elimination, reinsertion of the Pd-H species to form a *trans*-1,2-disubstituted olefin, transmetalation with the boronic acid, and reductive elimination (Figure 2, pathway 2). Guided by this hypothesis, we explored reaction conditions that could limit the β-hydride elimination pathway (pathway 2) and/or accelerate the rate of the desired transmetalation reaction that leads to pathway 1 (Figure 2).

Along these lines, silver salts have been proposed to increase the rate of transmetalation in the Suzuki-Miyaura cross-coupling reaction.[30] To test if this could favor pathway 1 over pathway 2, we employed silver oxide as the base (Table 1, entry 1) in combination with $Pd(OAc)_2$ and tricyclohexylphosphine (Cy_3P) and observed **3** as the major product (3:1), although with low conversion (30%). Alternatively, the use of silver carbonate (entry 2) produced **3** in a slightly better ratio (4:1) and with greater conversion (60%). As a second variable, bidentate ligands, such as 1,1′-bis(diphenylphosphino)ferrocene (dppf), have been used to limit β-hydride elimination pathways in cross-coupling reactions.[31] Use of $PdCl_2$dppf (entry 3) with silver carbonate provided **3** as the major product (4:1) with greatly improved conversion over previous reaction conditions. A survey of other bidentate phosphine ligands revealed 1,5-bis(diphenylphosphino)pentane (dppp, entry 4) as a ligand that provided **3** in a 10:1 ratio. As a final variable, ancillary ligands were investigated. A survey of various palladium sources revealed that Pd_2dba_3 combined with 1,6-bis(diphenylphosphino)hexane (dpph, entry 6) provided **3** in a >20:1 ratio and with excellent conversion. Interestingly, during the course of this study, we also found that exclusive formation of the *trans* product **4** can be achieved in 85% conversion using $Pd(OAc)_2$, SPhos, and K_3PO_4 in THF (entry 7).

These optimized conditions for the formation of 1,1-disubstituted boronate **3** have proven to be scalable. On a 1 mmol scale, cross-coupled product **3** was obtained in 61% isolated yield as a single isomer (Scheme 4). We further explored the utility of **2** as a substrate for iterative cross-coupling (ICC) reactions. The in situ hydrolysis of **3** followed by cross-coupling of the resulting boronic acid with aryl iodide **5** yielded **6** as a single isomer.

We next tested the generality of the optimized cross-coupling conditions with a variety of aryl, heteroaryl, and vinyl boronic acids (Table 2). Good to moderate conversions were observed in all cases. The coupling of boronic acids with electron neutral (entries 1–3), withdrawing (entries 4–6), and donating (entires 7–8) groups formed the desired product in all cases. Specifically, the coupling of 4-vinylphenylboronic acid **7a** and *m*-tolylboronic acid **7b** proceeded with excellent selectivity (>20:1), high conversion (>95%), and a 81% isolated yield for **8a** and 90% isolated yield for **8b**. Furthermore, boronic acids with ortho substituents, such as **7c**, are tolerated, providing the cross-coupled product **8c** in >20:1 selectivity and 50% isolated yield. However, the presence of electron withdrawing groups, including 4-methoxycarbonyl, 4-cyano, 4-fluoro, and 4-trifluoromethoxy (entries 4–6), resulted in moderate selectivities (10:1 to 4:1) albeit still with good conversions (70–90%). The electron withdrawing groups on the boronic acid may reduce the rate of the desired transmetalation reaction (Figure 2, pathway 1), therefore making the β-hydride elimination pathway more competitive (pathway 2). In contrast, electron donating groups, including 3,5-dimethoxy and 4-dimethylamino (entries 7–8) provided the cross-coupled products with excellent selectivity (>20:1) and a 66% isolated yield for **8g**. Additionally, the coupling of 2-heterocyclic boronic acids, including 2-benzofuranboronic acid **7i** and 2-thiopheneboronic acid **7j** produced the 1,1-product in >20:1 in both cases and a 82% isolated yield for **8i**. Finally, the coupling of vinyl boronic acids also produced the 1,1-product in >20:1 and 76% isolated yield for **8k** and 65% isolated yield for **8l**.

3. Summary and conclusions

Access to a wide range of bifunctional building blocks representing motifs that commonly appear in small molecules stands to greatly increase the efficiency and flexibility of the synthesis of this broadly important class of compounds. The 1,1-disubstituted olefin represents a very important substructure that appears in a wide range of pharmaceuticals and natural products. We herein described a very practical and scalable synthesis of the bifunctional building block **2** and demonstrated its utility for the synthesis of a wide range of

1,1-disubstituted boronates. Collectively, these findings expand the utility of ICC with MIDA boronates as a simple and flexible platform for the efficient synthesis of a wide range of functional small molecules.

4. Experimental

4.1. Materials

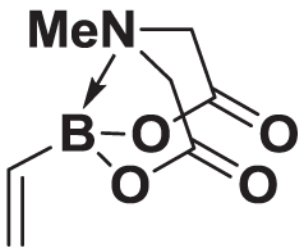
Commercial reagents were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI America, Strem Chemicals Inc., or Frontier Scientific and were used without further purification unless otherwise noted. Solvents were purified via passage through packed columns as described by Pangborn and coworkers[32] (THF, Et_2O, CH_3CN, CH_2Cl_2: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q5 reactant; DMSO, DMF: activated molecular sieves). All water was deionized prior to use.

4.2. General experimental procedures

Unless noted, all reactions were performed in flame-dried round bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 35 – 40 °C. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F_{254} plates (0.25mm). Compounds were visualized by exposure to a UV lamp (λ = 254 nm) and/or a solution of basic $KMnO_4$ followed by brief heating using a Varitemp heat gun. MIDA boronates are compatible with standard silica gel chromatography, including standard loading techniques. Column chromatography was performed using standard methods[33] or on a Teledyne-Isco CombiFlash R_f purification system using Merck silica gel grade 9385 (60Å, 230–400 mesh). For loading, compounds were adsorbed onto non acid-washed Celite *in vacuo* from an acetone solution. Specifically, for a 1 g mixture of crude material the sample is dissolved in reagent grade acetone (25 to 50 mL) and to the flask is added Celite 545 Filter Aid (5 to 15 g). The mixture is then concentrated *in vacuo* to afford a powder, which is then loaded on top of a silica gel column. The procedure is typically repeated with a small amount of acetone (5 mL) and Celite (2 g) to ensure quantitative transfer.

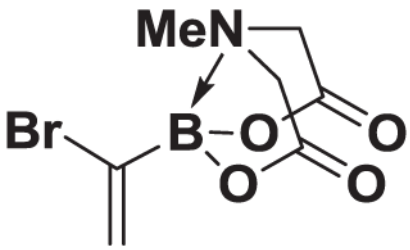
4.3. Structural analysis

^1H NMR spectra were recorded at 23 °C on one of the following instruments: Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB. Chemical shifts (δ) are reported inparts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent ($CHCl_3$, δ = 7.26; CD_2HCN, δ = 1.94, center line; d_6-acetone, δ = 2.05, center line) or to added tetramethylsilane (δ = 0.00). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad, app = apparent), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra were recorded at 23 °C on a Varian Unity 400 or Varian Unity 500. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.0, center line; $\mathbf{C}D_3CN$, δ = 1.30, center line; d_6-acetone, δ = 29.80, center line) or to added tetramethylsilane (δ = 0.00). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun, Haijun Yao, and Beth Eves at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory. X-ray crystallographic analyses were carried out by Dr. Danielle Gray at the University of Illinois George L. Clark X-Ray facility.



4.4. MIDA boronate 1

To a 3 L 3-neck round bottom flask equipped with a stir bar was added $B(OMe)_3$ (94 mL, 840 mmol) and THF (600 mL). The solution was cooled to −78 °C. Vinylmagnesium bromide (1.0 M in THF, 800 mL, 800 mmol) was added dropwise *via* cannula over 2 h 45 min. The resulting solution was stirred at −78°C for 15 min, followed by stirring at 23 °C for 2 h 30 min. In a separate 2 L 3-neck round bottom flask equipped with a stir bar, internal thermometer, and distillation apparatus was added dry MIDA (235.0 g, 1.6 mol) and DMSO (600 mL). The solution was heated with an oil bath to an internal temperature of 110 – 115 °C. The borate suspension was added dropwise to the hot MIDA solution via a Teflon cannula dropwise over 2 h 10 min, keeping the internal temperature between 105 and 115 °C. After full addition of the borate solution, the reaction solution was cooled to 23 °C. The resulting solution was transferred to a separatory funnel containing H_2O (1 L), brine (1 L), EtOAc (1.5 L) and acetone (1 L). The mixture was shaken and the aqueous layer was removed and extracted with EtOAc:acetone (2:1, 2 × 600 mL). The combined organic layers were washed with H_2O (2 × 500 mL). The combined water washes were back extracted with EtOAc:acetone (2:1, 2 × 300 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was suspended in 300 mL acetone and 4 L Et_2O was added to precipitate the product. The resulting solid was collected by vacuum filtration to yield vinyl MIDA boronate **1** as a white solid (81.2 g, 55%). Spectral data for **1** were consistent with those previously reported from our laboratories.[13]



4.5. MIDA boronate 2

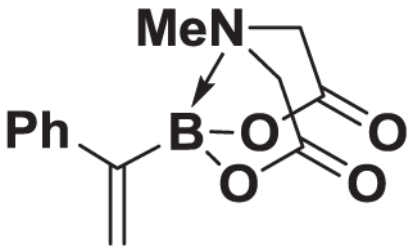
To a 2 L round bottom flask equipped with a stir bar and charged with vinyl MIDA boronate **1** (25.0 g, 137 mmol) was added CH_2Cl_2 (1.2 L). The resulting clear, colorless solution was cooled to 0 °C in an ice bath. Neat bromine (12.5 mL, 239 mmol) was added dropwise over 5 min to give a cloudy orange solution. The solution was warmed to 23 °C over 30 min. The resulting orange solution was concentrated *in vacuo* to give a yellow solid. Residual bromine was removed by azeotroping with CH_2Cl_2 (2 × 100 mL). The resulting solid was suspended in MeCN (1 L). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 51.0 mL, 342 mmol) was added in one portion. The resulting mixture stirred at 23 °C for 1 h. The solution was poured into 1 M aq. HCl (1 L) and diluted with EtOAc:acetone (3:1, 1 L). After shaking, the layers were separated. The organic layer was washed with saturated aqueous sodium bisulfite:brine (3:2, 1 × 500 mL) and brine (1 × 250 mL). The organic layer was dried over

$MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was passed through a plug of silica, eluting with acetone. The resulting solid was suspended in THF (50 mL) onto which Et_2O (1.8 L) was layered to precipitate the product. The product **2** was collected by vacuum filtration (24.0 g, 67%).

^{1}H NMR (500 MHz, d_6-acetone) δ 6.39 (bs, 1H), 6.19 (bs, 1H), 4.37 (d, *J* = 17.0 Hz, 2H), 4.16 (d, *J* = 17.0 Hz, 2H), 3.16 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.4, 129.5, 63.4, 47.2. HRMS (ESI^+) calculated for $C_7H_{10}BBrNO_4$ $(M+H)^+$: 261.9886. Found: 261.9873. X-ray quality crystals were grown by vapor diffusion of Et_2O into a dissolved solution of **2** in acetone.[34] MIDA boronate **2** is commercially available.[26]

4.6. General procedure for Table 1

In a glovebox, to a 7 mL vial containing a stir bar and silver salt (0.4 mmol, 4.0 eq) was added a 0.25 mL aliquot of each of the following three stock solutions: 1) 262 mg MIDA boronate **2** in 2.5 mL THF (0.1 mmol, 1.0 eq of **2** added to each reaction); 2) 183 mg phenylboronic acid in 2.5 mL THF (0.15 mmol, 1.5 eq of boronic acid added to each reaction); 3) A solution of 0.05 mmol palladium salt and 0.2 mmol ligand in 2.5 mL THF was prepared and stirred at 23 °C for 30 min. before adding an aliquot to the reaction vials (0.005 mmol, 0.05 eq of palladium added to each reaction and 0.02 mmol, 0.2 eq of ligand added to each reaction). An additional 0.25 mL of THF was added to each reaction. The vials were capped, removed from the glovebox, and placed in a 40 °C heating block with stirring for 24 h. The crude reaction mixtures were filtered through a plug of Celite, concentrated *in vacuo*, and analyzed by ^{1}H NMR.



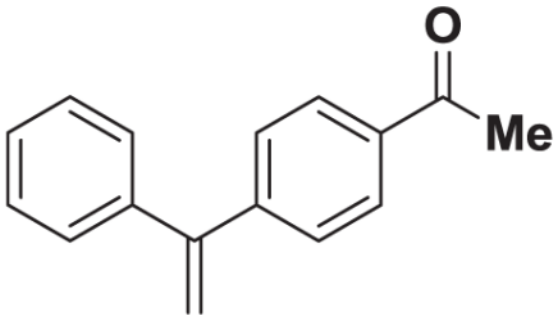
4.7. MIDA boronate 3

Preparation of catalyst solution—In a glovebox, to a 7 mL vial charged with dpph (90.9 mg, 0.20 mmol) and Pd_2dba_3 (45.8 mg, 0.05 mmol) was added THF (5.0 mL). The solution was stirred at 23 °C for 30 min.

The freshly prepared catalyst solution was used in the following reaction—In a glovebox, to a 20 mL vial with stir bar, charged with MIDA boronate **2** (261.9 mg, 1.0 mmol) was added Ag_2CO_3 (1.10 g, 4.0 mmol). Phenylboronic acid (182.8 mg, 1.5 mmol) was added as a solution in THF (5.0 mL). The prepared catalyst solution was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. The solution was stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo*, dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et_2O:MeCN 100:0 → 80:20) to afford MIDA boronate **3** (158.0 mg, 61%).

^{1}H NMR (400 MHz, d_6-acetone) δ 7.42–7.38 (m, 2H), 7.33–7.28 (m, 2H), 7.26–7.21 (m, 1H), 5.73 (bd, *J* = 3.0 Hz, 1H), 5.69 (bs, 1H), 4.23 (d, *J* = 17.0 Hz, 2H), 3.85 (d, *J* = 17.0 Hz, 2H), 2.82 (s, 3H). ^{13} C NMR (125 MHz, d_6-acetone) δ 168.9, 145.2, 129.1, 128.3, 128.1, 127.3, 62.6, 47.6. HRMS (ESI^+) calculated for $C_{13}H_{15}BNO_4$ $(M+H)^+$: 260.1094.

Found: 260.1094. TLC (Et_2O:MeCN 6:1) R_f = 0.44, visualized by short wave UV. MIDA boronate **3** is commercially available.[26]



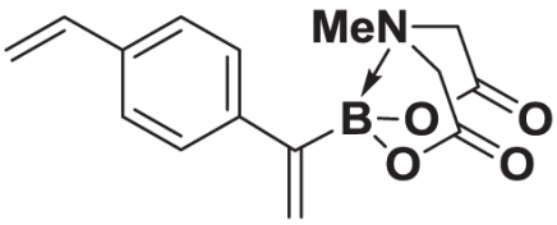
4.8. 1,1-disubstituted olefin 6

In a glovebox, to a 20 mL vial with stir bar, charged with MIDA boronate **3** (100.0 mg, 0.39 mmol, 1.0 eq) was added 4-iodoacetephenone (113.9 mg, 0.46 mmol, 1.2 eq), 2nd gen. SPhosPd cycle (20.9 mg, 0.029 mmol, 0.075 eq), and THF (3.5 mL). The vial was sealed with a septum cap and removed from the glovebox. To the reaction solution was added 1 M aq. NaOH via syringe (2.9 mL, 2.9 mmol). The solution was stirred at 23 °C for 4 h. The reaction mixture was poured into a separatory funnel containing aqueous sodium phosphate buffer (0.5 M, pH 7.0, 10 mL) and diluted with Et_2O (10 mL). The mixture was shaken and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organics were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude material was dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (hexane:EtOAc 100:0 → 90:10) to afford 1,1-disubstituted olefin **6** (63.5 mg, 74%). Spectral data for **6** were consistent with those previously reported.[35]

4.9. General procedure for Table 2

Preparation of catalyst solution—In a glovebox, to a 20 mL vial charged with dpph (136.4 mg, 0.30 mmol) and Pd_2dba_3 (68.7 mg, 0.075 mmol) was added THF (7.5 mL). The solution was stirred at 23 °C for 30 min.

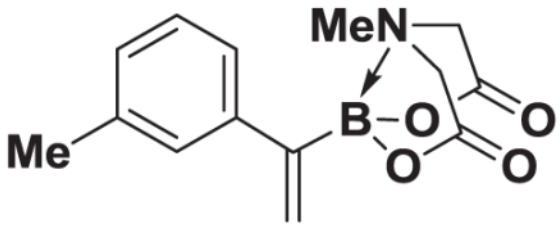
The freshly prepared catalyst solution was used in the following reactions—In a glovebox, to a 7 mL vial with stir bar, charged with MIDA boronate **2** (26.2 mg, 0.1 mmol) was added Ag_2CO_3 (110.0 mg, 0.4 mmol). Boronic acid (0.15 mmol) was added, followed by THF (0.50 mL). An aliquot of the prepared catalyst solution (0.50 mL) was added in one portion. The vial was sealed with a septum cap and removed from the glovebox. The solution was stirred at 40 °C for 24 h. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo*, and analyzed by ^{1}H NMR. Select samples were dry loaded onto Celite from an acetone solution, and purified via flash chromatography on silica (Et_2O:MeCN 100:0 → 80:20) to afford the MIDA boronate **8**.



4.10. MIDA boronate 8a

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to >95% conversion and a >20:1 of **8:9** was obtained. **8a** was isolated by column chromatography to provide 57.8 mg (0.25 mmol reaction), 81% yield.

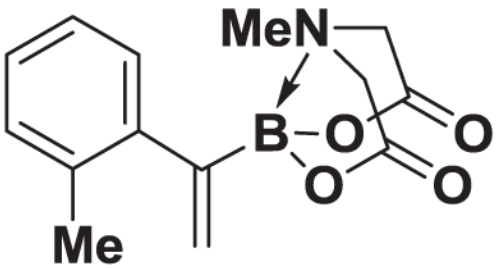
^{1}H NMR (400 MHz, d_6-acetone) δ 7.71–7.33 (m, 4H), 6.85–6.68 (m, 2H), 5.90–5.68 (m, 2H), 5.29–5.17 (m, 1H), 4.25 (d, *J* = 17.0 Hz, 2H), 3.88 (d, *J* = 17.0 Hz, 2H), 2.81 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.9, 137.4, 136.7, 135.2, 128.5, 128.0, 127.0, 113.7, 62.6, 47.6. HRMS (ESI$^+$) calculated for $C_{15}H_{17}BNO_4$ $(M+H)^+$: 286.1251. Found: 286.1248. TLC (Et_2O:MeCN 6:1) R_f = 0.44, visualized by short wave UV.



4.11. MIDA boronate 8b

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to >95% conversion and a >20:1 of **8:9** was obtained. **8b** was isolated by column chromatography to provide 61.1 mg (0.25 mmol reaction), 90% yield.

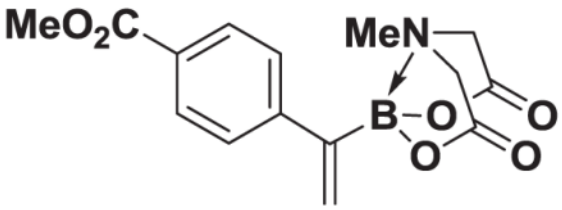
^{1}H NMR (500 MHz, d_6-acetone) δ 7.24 (m, 1H), 7.21–7.18 (m, 2H), 7.10–7.05 (m, 1H), 5.73 (bd, *J* = 3.0 Hz, 1H), 5.68 (bs, 1H), 4.23 (d, *J* = 17.0 Hz, 2H), 3.83 (d, *J* = 17.0 Hz, 2H), 2.83 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.7, 145.2, 138.3, 128.9, 128.8, 127.9, 127.6, 125.3, 62.6, 47.4, 21.4. ^{11}B NMR (128 MHz, d_6-acetone) δ 11.4. HRMS (ESI$^+$) calculated for $C_{14}H_{17}BNO_4$ $(M+H)^+$: 274.1251. Found: 274.1245. TLC (Et_2O:MeCN 6:1) R_f = 0.44, visualized by short wave UV.



4.12. MIDA boronate 8c

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to >95% conversion and a >20:1 of **8:9** was obtained. **8c** was isolated by column chromatography to provide 68.6 mg (0.50 mmol reaction), 50% yield.

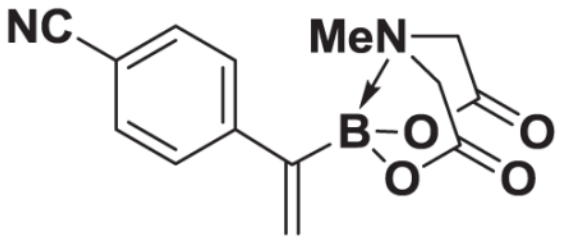
^{1}H NMR (400 MHz, d_6-acetone) δ 7.18–7.04 (m, 4H), 5.84 (d, *J* = 3.5 Hz, 1H), 5.52 (bs), 4.19 (d, *J* = 17.0 Hz, 2H), 3.88 (d, *J* = 17.0 Hz, 2H), 3.03 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.7, 144.9, 136.2, 130.9, 128.5, 128.3, 127.0, 126.1, 62.6, 47.4, 20.6. HRMS (ESI$^+$) calculated for $C_{14}H_{17}BNO_4$ $(M+H)^+$: 274.1251. Found: 274.1252. TLC (Et_2O:MeCN 6:1) R_f = 0.44, visualized by short wave UV.



4.13. MIDA boronate 8d

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 85% conversion and a 10:1 of **8:9** was obtained. **8d** and **9d** were isolated by column chromatography as an inseparable mixture of isomers to provide 60.6 mg (0.50 mmol reaction), 45% yield.

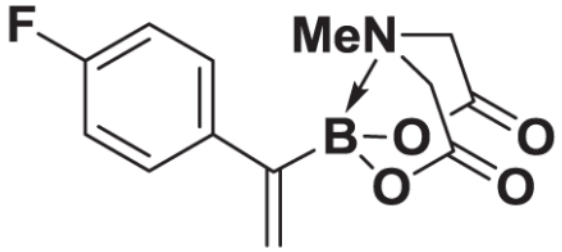
^{1}H NMR (400 MHz, d_6-acetone) δ 7.70–7.36 (m, 4H), 5.77 (bd, *J* = 3.0 Hz, 1H), 5.73 (bs, 1H), 4.25 (d, *J* = 17.0 Hz, 2H), 3.91 (d, *J* = 17.0 Hz, 2H), 3.85 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.8, 167.1, 134.9, 130.2, 129.2, 129.0, 128.5, 62.7, 52.2, 47.7. HRMS (ESI^{+}) calculated for $C_{15}H_{17}BNO_6$ $(M+H)^{+}$: 318.1149. Found: 318.1143. TLC (Et_2O:MeCN 6:1) R_f = 0.32, visualized by short wave UV.



4.14. MIDA boronate 8e

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 70% conversion and a 8:1 of **8:9** was obtained. **8e** and **9e** were isolated by column chromatography as an inseparable mixture of isomers to provide 57.6 mg (0.50 mmol reaction), 39% yield.

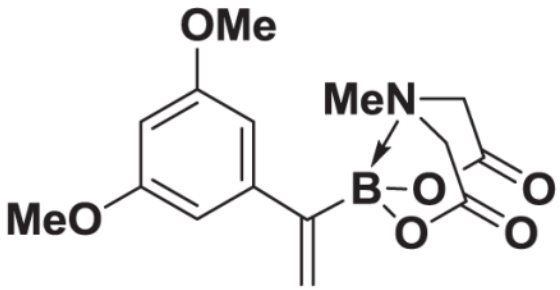
^{1}H NMR (400 MHz, d_6-acetone) δ 7.79–7.52 (m, 4H), 5.82 (bd, *J* = 3.0 Hz, 1H), 5.79 (bs, 1H), 4.27 (d, *J* = 17.0 Hz, 2H), 3.95 (d, *J* = 17.0 Hz, 2H), 2.82 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.8, 134.2, 132.9. 130.4, 129.3, 119.4, 111.0, 62.6, 4d7.7. HRMS (ESI^{+}) calculated for $C_{14}H_{14}BN_2O_4$ $(M+H)^{+}$: 285.1047. Found: 285.1038. TLC (Et_2O:MeCN 6:1) R_f = 0.32, visualized by short wave UV.



4.15. MIDA boronate 8f

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 90% conversion and a 4:1 of **8:9** was obtained. **8f** and **9f** were isolated by column chromatography as an inseparable mixture of isomers to provide 59.1 mg (0.50 mmol reaction), 43% yield.

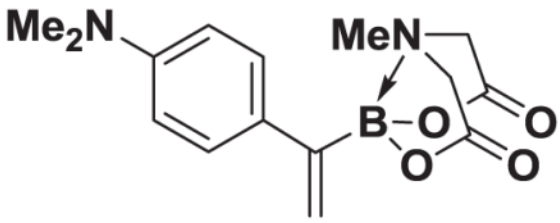
^{1}H NMR (400 MHz, d_6-acetone) δ 7.49–7.00 (m, 4H), 5.70 (bd, *J* = 3.0 Hz, 1H), 5.67 (bs, 1H), 4.23 (d, *J* = 17.0 Hz, 2H), 3.88 (d, *J*= 17.0 Hz, 2H), 2.80 (s, 3H). ^{13} C NMR (125 MHz, d_6-acetone) δ 163.6, 130.2, 130.1, 129.2, 128.4, 115.8, 62.6, 47.6. HRMS (ESI^{+}) calculated for $C_{13}H_{14}BFNO_4$ $(M+H)^{+}$: 278.1000. Found: 278.0994. TLC (Et_2O:MeCN 6:1) R_f = 0.37, visualized by short wave UV.



4.16. MIDA boronate 8g

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 85% conversion and a >20:1 of **8:9** was obtained. **8g** was isolated by column chromatography to provide 21.1 mg (0.1 mmol reaction), 66% yield.

^{1}H NMR (500 MHz, d_6-acetone) δ 6.59 (d, *J* = 2.5 Hz, 2H), 6.38 (t, *J* = 2.5 Hz, 1H), 5.75 (m, 2H), 4.24 (d, *J* = 17.0 Hz, 2H), 3.84 (d, *J* = 17.0 Hz, 2H), 3.77 (s, 6H), 2.86 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 169.0, 161.7, 147.4, 127.8, 106.3, 99.7, 62.9, 55.5, 47.6. ^{11}B NMR (128 MHz, d_6-acetone) δ 11.3. HRMS (ESI^{+}) calculated for $C_{15}H_{19}BNO_6$ $(M+H)^{+}$: 320.1305. Found: 320.1295. TLC (Et_2O:MeCN 6:1) R_f = 0.31, visualized by short wave UV.

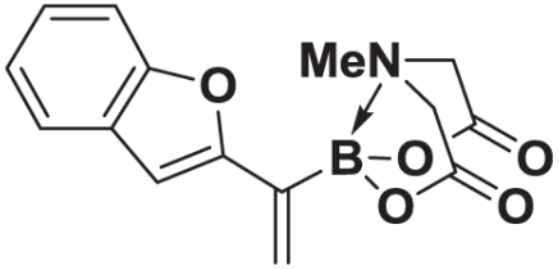


4.17. MIDA boronate 8h

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 50% conversion and a >20:1 of **8:9** was obtained. **8h** was isolated by column chromatography to provide 40.4 mg (0.50 mmol reaction), 28% yield.

^{1}H NMR (400 MHz, d_6-acetone) δ 7.35–7.00 (m, 4H), 5.58 (bs, 1H), 5.55 (bd, *J* = 3.0 Hz, 1H), 4.18 (d, *J* = 17.0 Hz, 2H), 3.79 (d, *J* = 17.0 Hz, 2H), 3.12 (s, 6H), 2.75 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.3, 129.5, 128.9, 128.4, 125.2, 113.2, 62.7, 47.5, 40.5.

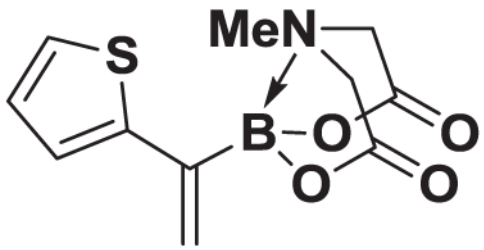
HRMS (ESI$^+$) calculated for $C_{15}H_{20}BN_2O_4$ $(M+H)^+$: 303.1516. Found: 303.1524. TLC (Et_2O:MeCN 6:1) R_f = 0.31, visualized by short wave UV.



4.18. MIDA boronate 8i

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 95% conversion and a >20:1 of **8:9** was obtained. **8i** was isolated by column chromatography to provide 24.6 mg (0.1 mmol reaction), 82% yield.

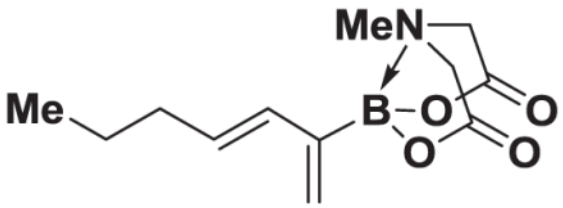
^{1}H NMR (500 MHz, d_6-acetone) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.0 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 6.45 (s, 1H), 5.80 (d, *J* = 2.5 Hz, 1H), 4.41 (d, *J* = 17.0 Hz, 2H), 4.23 (d, *J* = 17.0 Hz, 2H), 3.03 (s, 3H). ^{13}C NMR (125 MHz, d_6-acetone) δ 168.9, 158.4, 154.8, 129.8, 126.5, 125.0, 123.3, 121.7, 111.2, 104.5, 62.9, 47.7. ^{11}B NMR (128 MHz, d_6-acetone) δ 11.3. HRMS (ESI$^+$) calculated for $C_{15}H_{15}BNO_5$ $(M+H)^+$: 300.1043. Found: 300.1049.



4.19. MIDA boronate 8j

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 50% conversion and a >20:1 of **8:9** was obtained. **8j** was isolated by column chromatography to provide 31.3 mg (0.50 mmol reaction), 24% yield.

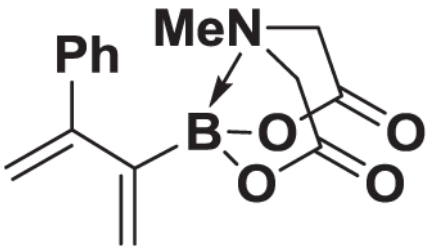
^{1}H NMR (400 MHz, d_6-acetone) δ 7.80–7.00 (m, 3H), 5.83 (bs, 1H), 5.56 (bs, 1H), 4.30 (d, *J* = 17.0 Hz, 2H), 4.00 (d, *J* = 17.0 Hz, 2H), 3.13 (s, 3H). ^{13} C NMR (125 MHz, d_6-acetone) δ 168.3, 129.5, 128.5, 126.1, 125.7, 125.3, 62.9, 47.8. HRMS (ESI$^+$) calculated for $C_{11}H_{13}BNO_4S$ $(M+H)^+$: 266.0658. Found: 266.0647. TLC (Et_2O:MeCN 6:1) R_f = 0.39, visualized by short wave UV.



4.20. MIDA boronate 8k

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 90% conversion and a >20:1 of **8:9** was obtained. **8k** was isolated by column chromatography to provide 47.7 mg (0.25 mmol reaction), 76% yield.

^{1}H NMR (500 MHz, d_6-acetone) δ 6.20 (d, *J* = 15.0 Hz, 1H), 5.90 (dt, *J* = 15.0 Hz, 6.5 Hz, 1H), 5.61 (bs, 1H), 5.34 (bd, *J* = 3.5 Hz, 1H), 4.25 (d, *J* = 17.0 Hz, 2H), 4.01 (d, *J* = 17.0 Hz, 2H), 2.97 (s, 3H), 2.06 (m, 2H), 1.41 (s, *J* = 7.0 Hz, 2H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 132.9, 132.8, 125.9, 61.9, 47.0, 35.4, 22.5, 13.7. ^{11}B NMR (128 MHz, $CDCl_3$) δ 10.7. HRMS (ESI^+) calculated for $C_{12}H_{19}BNO_4$ $(M+H)^+$: 252.1407. Found: 252.1405. TLC (Et_2O:MeCN 6:1) R_f = 0.48, visualized by short wave UV.



4.21. MIDA boronate 8l

Based on the ^{1}H NMR of the crude reaction mixture, the reaction proceeded to 80% conversion and a >20:1 of **8:9** was obtained. **8l** was isolated by column chromatography to provide 46.3 mg (0.25 mmol reaction), 65% yield.

^{1}H NMR (400 MHz, d_6-acetone) δ 7.47–7.19 (m, 5H), 5.58 (d, *J* = 2.0 Hz, 1H), 5.31 (d, *J* = 2.0 Hz, 1H), 5.25 (d, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 2.0 Hz, 1H), 4.16 (d, *J* = 17.0 Hz, 2H), 3.91 (d, *J* = 17.0 Hz, 2H), 3.05 (s, 3H). ^{13} C NMR (125 MHz, d_6-acetone) δ 168.6, 154.5, 142.3, 129.1, 128.8, 128.2, 128.1, 113.9, 62.7, 47.5. HRMS (ESI^+) calculated for $C_{15}H_{17}BNO_4$ $(M+H)^+$: 286.1251. Found: 286.1244. TLC (Et_2O:MeCN 6:1) R_f = 0.36, visualized by short wave UV.

Acknowledgments

We gratefully acknowledge the NIH for funding (R01 GM080436). E.M.W. is an NSF Graduate Fellow and M.D.B. is an Early Career Scientist of the Howard Hughes Medical Institute.

References

1. (a) Boehm MF, Zhang L, Badea BA, White SK, Mais DE, Suto CM, Goldman ME, Heyman RA. J Med Chem. 1994; 37:2930–2941. [PubMed: 8071941] (b) Carney JR, Krenisky JM, Williamson RT, Luo J. J Nat Prod. 2002; 65:203–205. [PubMed: 11858757] (c) Borris RP, Cordell GA. J Nat

Prod. 1984; 47:270–278. [PubMed: 6736968] (d) Jarboe CH, Porter LA, Buckler RT. J Med Chem. 1968; 11:729–731. [PubMed: 5671231]

2. (a) Arnone A, Dimodugno V, Nasini G, Depava OV. Gazz Chim Ital. 1990; 120:397.(b) Corey EJ, Roberts BE. J Am Chem Soc. 1997; 119:12425–12431.(c) Oppolzer W, Thirring K. J Am Chem Soc. 1982; 104:4978–4979.(d) Ghosh AK, Wang Y. J Am Chem Soc. 2000; 122:11027–11028.
3. (a) Organ MG, Bratovanov S. Tetrahedron Lett. 2000; 41:6945–6949.(b) Taber DF, Christos TE, Neubert TD, Batra D. J Org Chem. 1999; 64:9673–9678.(c) Tiefenbacher K, Mulzer J. Angew Chem, Int Ed. 2008; 47:2548–2555.
4. Hamze A, Giraud A, Messaoudi S, Provot O, Peyrat JF, Bignon J, Liu JM, Wdzieczak-Bakala J, Thoret S, Dubois J, Brion JD, Alami M. ChemMedChem. 2009; 4:1912. [PubMed: 19790205]
5. (a) Dounay AB, Overman LE. Chem Rev. 2003; 103:2945–2963. [PubMed: 12914487] (b) Cabri W, Candiani I, DeBernardinis S, Francalanci F, Penco S. J Org Chem. 1991; 56:5796–5800.
6. (a) Sabarre A, Love J. Org Lett. 2008; 10:3941–3944. [PubMed: 18702501] (b) Hamze A, Brion JD, Alami M. Org Lett. 2012; 14:2782–2785. [PubMed: 22616778] (c) Bhilare SV, Darvatkar NB, Deorukhkar AR, Raut DG, Trivedi GK, Salunkhe MM. Tetrahedron Lett. 2009; 50:893.(d) Hashimoto T, Kutubi S, Izumi T, Rahman A, Kitamura TJ. Organomet Chem. 2011; 696:99.(e) Li R, Wang SR, Lu W. Org Lett. 2007; 9:2219. [PubMed: 17474753] (f) Reetz MT, Sommer K. Eur J Org Chem. 2003:3485.
7. (a) Miyaura N, Suzuki A. Chem Rev. 1995; 95:2457–2483.(b) Hall, DG. Boronic Acids. Wiley-VCH; Weinheim, Germany: 2005.
8. (a) Zweifel G, Brown HC. Org React. 1963; 13:1.(b) Miyaura, N.; Maruoka, K. Synthesis of Organometallic Compounds. Wiley; Chichester, UK: 1997.
9. (a) Jang H, Zhugralin AR, Lee Y, Hoveyda AH. J Am Chem Soc. 2011; 133:7859–7871. [PubMed: 21526827] (b) Gao F, Hoveyda AH. J Am Chem Soc. 2010; 132:10961–10963. [PubMed: 20698643] (c) Takagi J, Takahashi K, Ishiyama T, Miyaura N. J Am Chem Soc. 2002; 124:8001–8006. [PubMed: 12095344] (d) Morrill C, Funk TW, Grubbs RH. Tetrahedron Lett. 2004; 45:7733–7736.(e) Moran WJ, Morken JP. Org Lett. 2006; 8:2413–2415. [PubMed: 16706539] (f) Takahashi K, Ishiyama T, Miyaura N. J Organomet Chem. 2001; 625:47–53.
10. Gillis EP, Burke MD. J Am Chem Soc. 2007; 129:6716–6717. [PubMed: 17488084]
11. Lee SJ, Gray KC, Paek JS, Burke MD. J Am Chem Soc. 2008; 130:466–468. [PubMed: 18081295]
12. Gillis EP, Burke MD. J Am Chem Soc. 2008; 130:14084–14085. [PubMed: 18837550]
13. Uno BE, Gillis EP, Burke MD. Tetrahedron. 2009; 65:3130–3138.
14. Knapp DM, Gillis EP, Burke MD. J Am Chem Soc. 2009; 131:6961–6963. [PubMed: 19405470]
15. Struble JR, Lee SJ, Burke MD. Tetrahedron. 2010; 66:4710–4718.
16. Woerly EM, Cherney AH, Davis EK, Burke MD. J Am Chem Soc. 2010; 132:6941–6943. [PubMed: 20441218]
17. Lee SJ, Anderson TM, Burke MD. Angew Chem Int Ed. 2010; 49:8860–8863.
18. Ballmer SG, Gillis EP, Burke MD. Org Syn. 2009; 86:344–359.
19. Dick GR, Knapp DM, Gillis EP, Burke MD. Org Lett. 2010; 12:2314–2317. [PubMed: 20465293]
20. Woerly EM, Struble JR, Palyam N, O'Hara SP, Burke MD. Tetrahedron. 2011; 67:4333–4343. [PubMed: 22753994]
21. Fujii S, Chang SY, Burke MD. Angew Chem Int Ed. 2011; 50:7862–7864.
22. Li J, Burke MD. J Am Chem Soc. 2011; 133:13774–13777. [PubMed: 21823591]
23. Dick GR, Woerly EM, Burke MD. Angew Chem Int Ed. 2012; 51:2667–2672.
24. Gray KC, Palacios DS, Dailey I, Endo MM, Uno BE, Wilcock BC, Burke MD. Proc Natl Acad Sci USA. 2012; 109:2234–2239. [PubMed: 22308411]
25. Mancilla T, Contreras R, Wrackmeyer B. J Organomet Chem. 1986; 307:1–6.
26. www.aldrich.com/mida
27. (a) see references 13 and 17Brown HC, Subrahmanyam C, Hamaoka T, Ravindran N, Bowman DH, Misumi S, Unni MK, Somayaji V, Bhat NG. J Org Chem. 1989; 54:6068–6075.Morrill C, Grubbs RH. J Org Chem. 2003; 68:6031–6034. [PubMed: 12868943]

28. For examples see Chauvelier J. Ann Chim. 1948; 12:393–444.Mitchell RH. Can J Chem. 1977; 55:210–219.(c) reference 7.

29. Sigma Aldrich: 704415; AllyChem: AC111044; BoroPharm

30. (a) Uenishi Y, Beau JM, Armstrong RW, Kishi Y. J Am Chem Soc. 1987; 109:4756–4758.(b) Weibel JM, Blanc A, Pale P. Chem Rev. 2008; 108:3149–3173. [PubMed: 18616324]

31. (a) Driver MS, Hartwig JF. J Am Chem Soc. 1996; 118:7217–7218.(b) Alcazar-Roman LM, Hartwig JF, Rheingold AL, Liable-Sands LM, Guzei IA. J Am Chem Soc. 2000; 122:4618–4630. (c) Birkholz MN, Freixa Z, van Leeuwen PWNM. Chem Soc Rev. 2009; 38:1099–1118. [PubMed: 19421583]

32. Pangborn AB, Giardello MA, Grubbs RH, Rosen RK, Timmers FJ. Organometallics. 1996; 15:1518.

33. Still WC, Kahn M, Mitra A. J Org Chem. 1978; 43:2923.

34. CCDC 937425 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.cdcc.cam.ac.uk/data_request.cif

35. Xu ZH, McArthur CR, Leznoff CC. Can J Chem. 1983; 61:1405–1409.

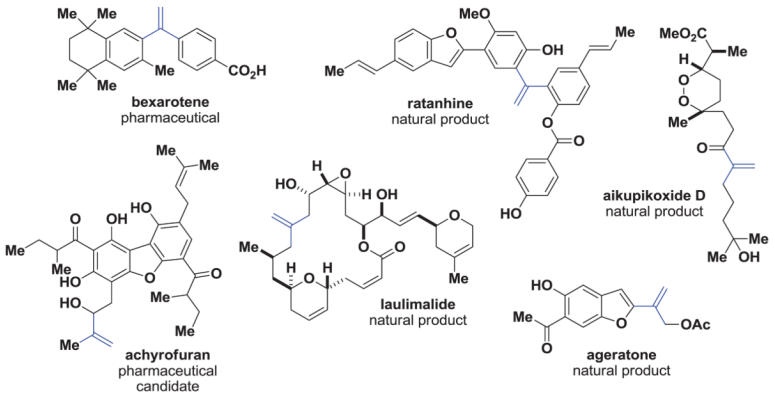


Figure 1.
1,1-Disubstituted olefins are abundant in pharmaceuticals and natural products.

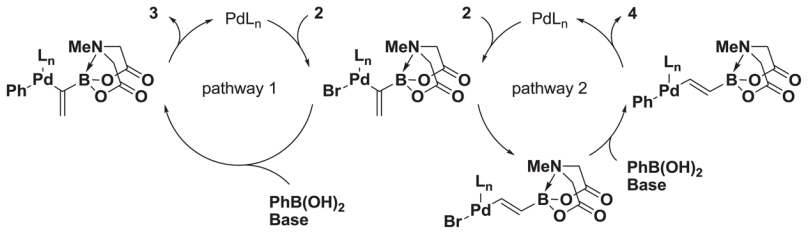
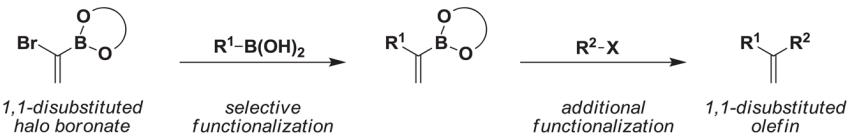
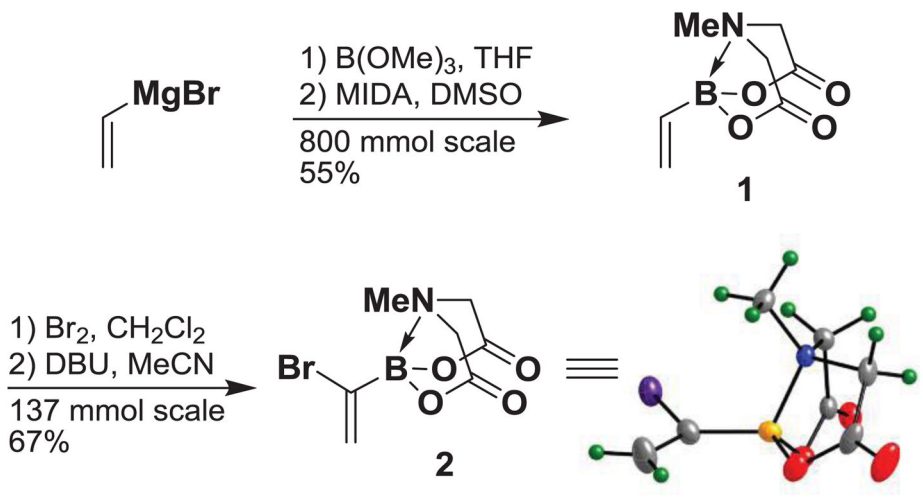


Figure 2.
Proposed mechanism for the formation of 1,1-disubstituted product **3** and 1,2-disubstituted product **4**.

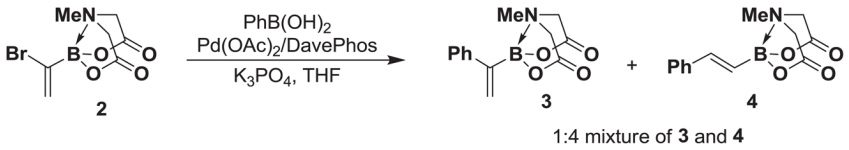


Scheme 1.

A 1,1-disubstituted halo boronate building block as a useful reagent for the preparation of 1,1-disubstituted olefins.

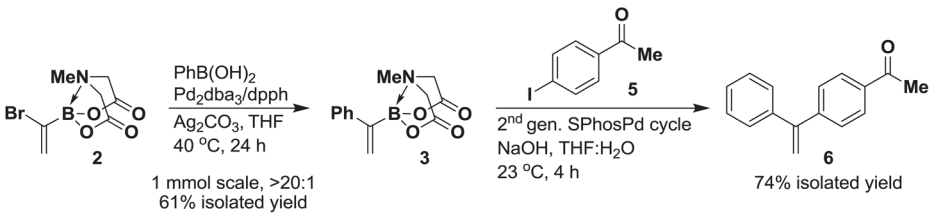


Scheme 2.
Synthesis of (1-bromovinyl)-MIDA boronate **2**.



Scheme 3.

The unoptimized coupling of building block **2** with phenyl boronic acid provides a mixture of products.

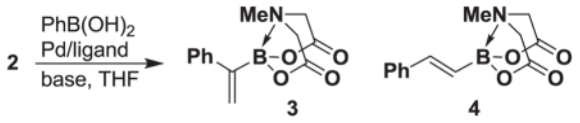


Scheme 4.

MIDA boronate **2** is a substrate for iterative Suzuki-Miyaura coupling reactions.

Table 1

Optimization studies for the coupling of **2**.

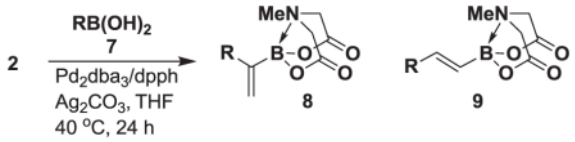


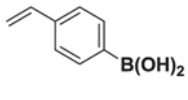
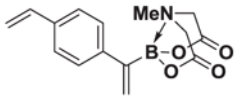
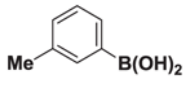
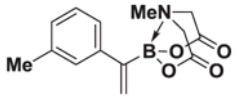
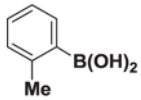
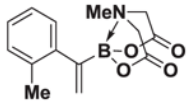
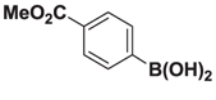
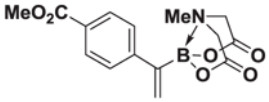
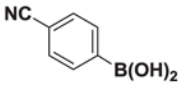
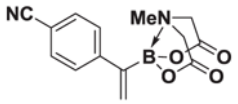
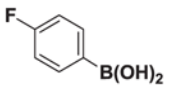
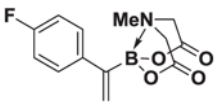
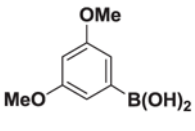
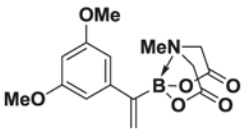
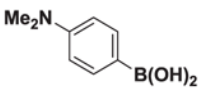
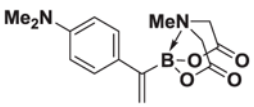
entry	Pd/ligand	base	% conversion[a]	3:4[a]
1	$Pd(OAc)_2/Cy_3P$	Ag_2O	30	3:1
2	$Pd(OAc)_2/Cy_3P$	Ag_2CO_3	60	4:1
3	$PdCl_2$dppf	Ag_2CO_3	>95	4:1
4	$Pd(OAc)_2$/dppp	Ag_2CO_3	70	10:1
5	Pd_2dba_3/dppp	Ag_2CO_3	70	12:1
6	Pd_2dba_3/dpph	Ag_2CO_3	>95	>20:1
7	$Pd(OAc)_2$/SPhos	K_3PO_4	85	1:20

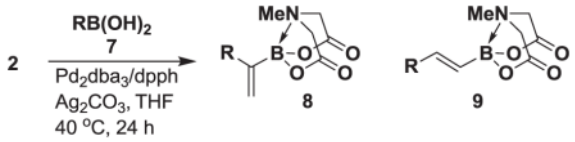
[a]The reaction conversion and ratio of **3:4** was determined based on the ^{1}H NMR of the crude reaction mixture.

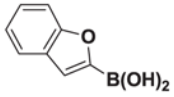
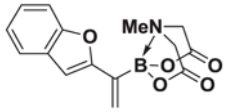
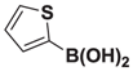
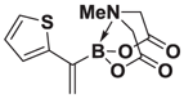
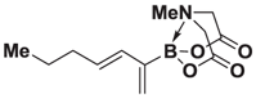
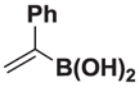
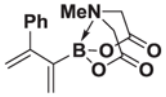
Table 2

Substrate scope under the optimized reaction conditions.



entry	7	8	8:9	% conversion[a] (isolated yield)
1	 **7a**	 **8a**	>20:1	>95 (81%)
2	 **7b**	 **8b**	>20:1	>95 (90%)
3	 **7c**	 **8c**	>20:1	>95 (50%)
4	 **7d**	 **8d**	10:1	85 (45%)[b]
5	 **7e**	 **8e**	8:1	70 (39%)[b]
6	 **7f**	 **8f**	4:1	90 (43%)[b]
7	 **7g**	 **8g**	>20:1	85 (66%)
8	 **7h**	 **8h**	>20:1	50 (28%)



entry	7	8	8:9	% conversion[a] (isolated yield)
9	 **7i**	 **8i**	>20:1	95 (82%)
10	 **7j**	 **8j**	>20:1	50 (24%)
11	 **7k**	 **8k**	>20:1	90 (76%)
12	 **7l**	 **8l**	>20:1	80 (65%)

[a] The reaction conversion and ratio of **8:9** was determined based on the ^{1}H NMR of the crude reaction mixture.

[b] Isolated yield as an inseparable mixture of isomers.