



Ethynyl MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis

Justin R. Struble, Suk Joong Lee, Martin D. Burke*

Howard Hughes Medical Institute, Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana–Champaign, Urbana, IL 61801, USA

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ABSTRACT

Ethynyl *N*-methyliminodiacetic acid (MIDA) boronate is a very useful building block for small molecule synthesis. This compound can serve as both a bifunctional acetylene equivalent with the capacity for terminus-selective bis-functionalization and a versatile starting material for the preparation of a wide range of other MIDA boronate building blocks.

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1. Introduction

Many powerful strategies have been developed to advance the facility with which small molecules can be prepared in the laboratory. Of these, that which is sometimes called ‘the building block approach’¹ can be particularly enabling. In one idealized version of this strategy,² a collection of pre-assembled building blocks having all of the required functional groups pre-installed in the correct oxidation states and with the desired stereochemical relationships are brought together using only one stereospecific reaction in an iterative fashion. The inherent modularity of most small molecule natural products and pharmaceuticals suggests that the theoretical scope of this approach is substantial.

With the goal of maximally enabling such a strategy, we are developing a platform of *N*-methyliminodiacetic acid (MIDA) boronate³ building blocks.² MIDA boronates have a wide range of favorable chemical and physical properties that collectively render them highly useful in this context. Specifically, these compounds are air-stable, monomeric, highly crystalline, free-flowing solids that can be stored indefinitely on the benchtop under air, are soluble in many organic solvents, and are uniformly compatible with silica gel chromatography.^{2,4–8} With respect to reactivity, the MIDA boronate functional group is inert toward cross-coupling under anhydrous

conditions but can be readily hydrolyzed with mild aqueous base to yield a reactive boronic acid.^{4,5} This enables the iterative cross-coupling (ICC) of bifunctional MIDA boronates bearing a halide or pseudohalide. MIDA boronates are also stable to a wide range of other common reaction conditions, making it possible to utilize multistep synthesis pathways to prepare complex organoborane building blocks from simple MIDA boronate starting materials.^{6,7} In addition, the in situ rate-controlled hydrolysis of MIDA boronates in the presence of aqueous base can produce dramatic improvements in the yields of cross-coupling reactions.⁸ This ‘slow-release’ methodology has transformed even some of the most notoriously unstable boronic acids into air-stable and highly effective cross-coupling partners. Given the favorable features of this platform, the development of highly versatile MIDA boronate building blocks represents an important goal.

In this vein, ethynyl MIDA boronate **1** was very attractive. First, the ethyne subunit appears in wide range of natural products, pharmaceuticals, and materials. Thus, a simple, non-toxic, and air-stable bifunctional ethyne equivalent with the capacity for terminus-selective bis-functionalization would be of substantial utility (Fig. 1A). Moreover, given the compatibility of MIDA boronates with many common reaction conditions^{6,7} and the considerable versatility of the alkyne functional group, we recognized that **1** could potentially serve as a very effective starting material for the preparation of many other types of useful MIDA boronate building blocks (Fig. 1B).⁹

* Corresponding author. E-mail address: burke@scs.uiuc.edu (M.D. Burke).

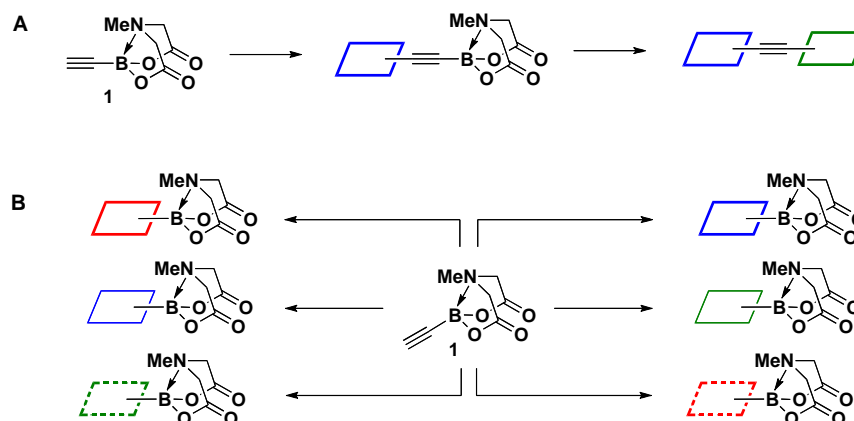
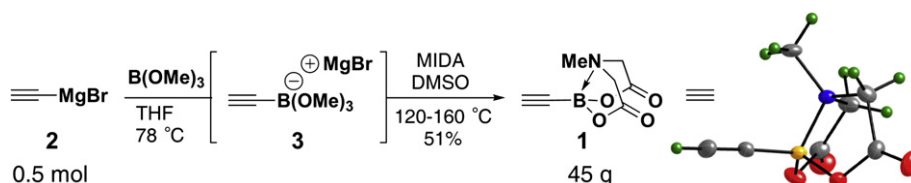


Figure 1. **A.** Ethynyl MIDA boronate **1** is an air and chromatographically stable, highly crystalline solid that can serve as a bifunctional surrogate for acetylene. **B.** This compound also represents a highly versatile starting material for the preparation of a range of other types of useful MIDA boronate building blocks.

As part of our efforts to prepare a wide range of bifunctional haloalkenyl MIDA boronate building blocks for the stereospecific synthesis of polyene motifs via ICC, we recently reported that **1** can be prepared via the trimethylborate salt derived from reacting ethynylmagnesium bromide **2** with trimethylborate (Scheme 1).¹⁰ We further discovered that running this MIDA transligation reaction at $>115\text{ }^{\circ}\text{C}$ ¹¹ can provide good yields of **1** on the decagram scale.¹⁰ Importantly, all of the reagents used in this synthesis are environmentally friendly and can be accessed on very large scale for very low cost, including the MIDA ligand. Specifically, MIDA can be prepared on the kilogram scale from the commodity chemicals iminodiacetic acid, formic acid, and formaldehyde.^{12,13} Iminodiacetic acid is a starting material used to make herbicides (e.g., Round-up[®]), environmental metal chelating reagents, and surfactants. As a result, tens of thousands of metric tons of iminodiacetic acid are produced annually¹⁴ and this material is very inexpensive.¹⁵ MIDA is also biodegradable.¹⁶



Consistent with many other MIDA boronates that we have prepared and studied, **1** is an air-stable, monomeric, highly crystalline, free-flowing solid that is soluble in many common organic solvents and fully compatible with silica gel chromatography.¹⁰ We attribute the stability of this building block (in contrast to the corresponding highly unstable boronic acid) to the pyramidalized and rigid MIDA boronate functional group lacking a reactive p-orbital on the boron atom^{4,6} (see Scheme 1 for crystal structure). We herein describe the utility of **1** in both ICC and building block synthesis applications.

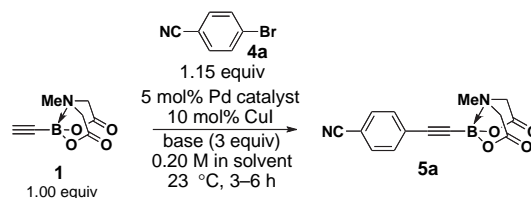
2. Results

The utility of **1** as a bifunctional acetylene equivalent with the capacity for sequential, distinct derivitization of the two alkyne termini was first explored.¹⁷ There are a few prior reports of Sonogashira couplings with ethynyl boranes that proceed with specialized substrates.¹⁸ As shown in Table 1, only low yields were

observed when **1** was coupled to 1-bromo-4-cyano benzene using $\text{Pd}(\text{PPh}_3)_4$ as catalyst and piperidine as base in THF (Table 1, entry 1). Alternatively, switching to $\text{PdCl}_2(\text{PPh}_3)_2$ and triethylamine led to a substantial improvement in yield (entry 2). A survey of solvents revealed that while both DMSO and CH_3CN led to inferior results (entries 3 and 4), an excellent isolated yield (93%) was observed when this reaction was performed in DMF (entry 5).

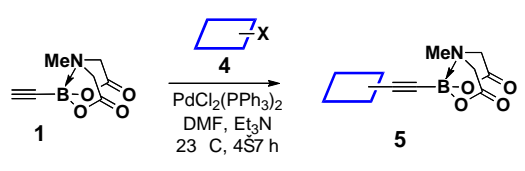
The scope of aryl halides amenable to Sonogashira coupling with **1** under these standard conditions is very good. Specifically, as shown in Table 2, a series of electron-deficient aryl bromides **4a–g** (entries 1–7), electron neutral or rich aryl iodides **4i–l** (entries 9–12), as well as 2-heterocyclic bromides **4m** and **4n** (entries 13 and 14) all provided good to excellent yields of the desired coupling products **5a–m**. Under these conditions, electron rich aryl bromides (e.g., **4h**, entry 8) were competent electrophiles but were less effective than the corresponding iodides (e.g., **4i**, entry 9).

Table 1



Entry	Pd catalyst	Base	Solvent	% Yield
1	$\text{Pd}(\text{PPh}_3)_4$	Piperidine	THF	30
2	$\text{PdCl}_2(\text{PPh}_3)_2$	Et_3N	THF	78
3	$\text{PdCl}_2(\text{PPh}_3)_2$	Et_3N	DMSO	47
4	$\text{PdCl}_2(\text{PPh}_3)_2$	Et_3N	CH_3CN	59
5	$\text{PdCl}_2(\text{PPh}_3)_2$	Et_3N	DMF	93

Table 2



Entry	4	5	Isolated yield (%)
1			93
2			95
3			92
4			69
5			80
6			65
7			72
8			33
9			80
10			75
11			88
12			88
13			67
14			55

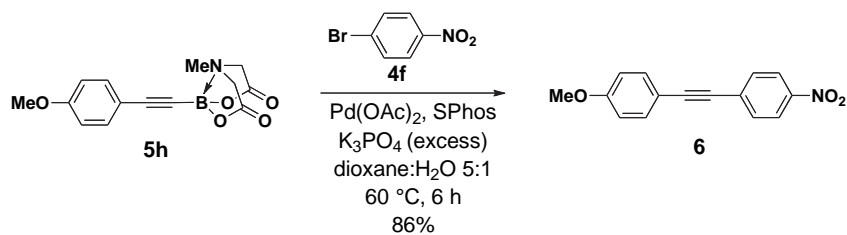
To complete the proposed sequential bis-functionalization of **1**, we tested the capacity of alkynyl MIDA boronates to undergo cross-coupling with organohalides. Suzuki–Miyaura couplings with alkynyl boronic acids are rare,¹⁹ presumably due to the instability of these intermediates. However, there are several reports with more stable alkynyl boronic esters,²⁰ alkynyl(triisopropoxy)borate salts,^{21,22} and trifluoroborate salts.²³ We wanted to determine whether it might be possible to achieve good yields in the cross-coupling of alkynyl boronic acids via employment of the corresponding alkynyl MIDA boronates such as **5j** under ‘slow-release’ cross-coupling conditions.⁸ Specifically, we have determined that exposure of MIDA boronates to K_3PO_4 in organic solvent/water mixtures leads to a slow hydrolysis of the MIDA boronate over the course of several hours producing a constant supply of fresh boronic acid in the reaction mixture. If the rate of cross-coupling is fast relative to the rate of boronic acid release, then the boronic acid is rapidly consumed in a productive coupling reaction thereby avoiding its undesired in situ decomposition.

To test the hypothesis that alkynyl boronic acids could also benefit from this slow-release methodology, **5h** and *p*-nitrobenzene were treated with $Pd(OAc)_2$, SPhos, and aq K_3PO_4 in dioxane: H_2O 5:1 at 60 °C for 6 h (Scheme 2), and an 86% isolated yield was observed. Thus, building block **1** has the potential to serve as a very useful bifunctional acetylene equivalent.

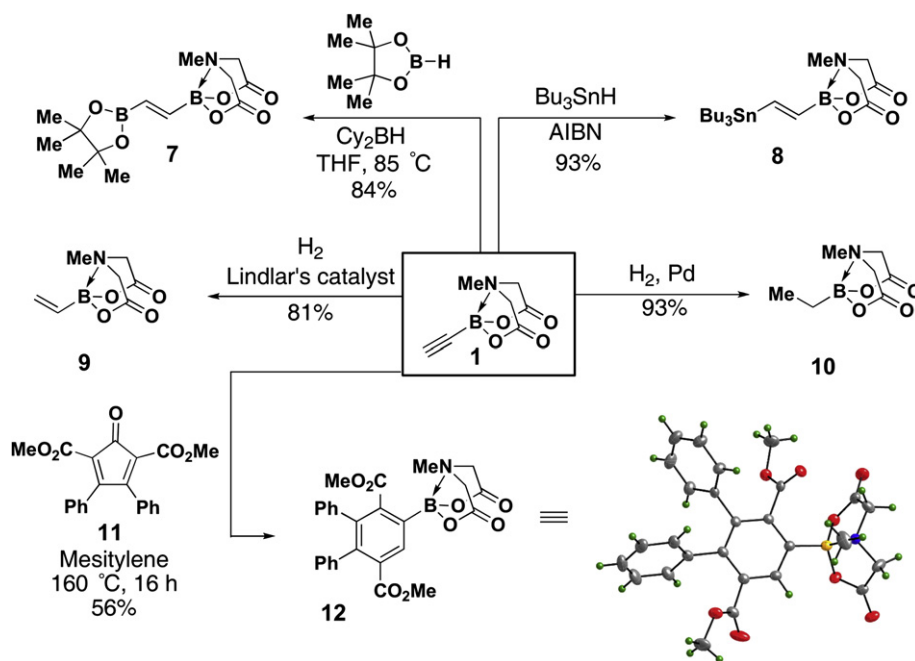
The utility of **1** as a versatile starting material for the preparation of other MIDA boronate building blocks was also explored. As described above, in addition to being unreactive under a wide range of anhydrous cross-coupling conditions, the MIDA boronate functional group is stable to many common synthetic reagents.^{6,7,24} Previous reports have demonstrated that these reagents include oxidants, reductants, soft nucleophiles, electrophiles, acids, and a wide range of anhydrous bases. Given these compatibilities and the remarkable versatility of alkynes, we investigated whether a range of previously unexplored reactions could be performed on the ethyne subunit of **1** while similarly leaving the MIDA boronate functional group intact.

As shown in Scheme 3, dicyclohexyl borane-catalyzed hydroboration with pinacol borane²⁵ proceeded smoothly to generate the very useful bis-borylated ethylene equivalent **7**.^{5,26} This differentially ligated diboron reagent has the capacity for selective cross-coupling of the sp^2 -hybridized pinacol ester terminus while the sp^3 -hybridized MIDA boronate remains inert.^{5,27} Relative to that previously reported,⁵ the hydroboration of **1** to generate **7** represents a more efficient and practical route to this very useful building block. As communicated recently,¹⁰ **1** can also be transformed into *trans*-1-iodo-2-ethenyl MIDA boronate via a one-pot hydrostannylation/iododestannylation sequence. We herein demonstrate that intermediate, 1-tributylstannyl-2-ethenyl MIDA boronate **8**, can be isolated in excellent yield. Lynchpin reagents **7** and **8** both possess substantial potential for terminus-selective double functionalizations via ICC.

The compatibility of **1** with alkyne reduction was also explored (Scheme 3).²⁸ For example, providing an alternative synthesis of vinyl MIDA boronate **9**,^{7,8} **1** underwent efficient semireduction in the presence of Lindlar’s catalyst and 1 atm of hydrogen without



Scheme 2.



Scheme 3.

perturbing the MIDA boronate functional group. Alternatively, complete reduction to the corresponding alkane **10** was achieved with unpoisoned Pd under a H_2 pressure of 200 psi. When combined with the capacity for Sonogashira coupling described above, this demonstrated compatibility of the MIDA boronate functional group with hydrogenative reduction might prove useful in the preparation of a range of new alkenyl and alkyl MIDA boronate building blocks.

As a final example, we found that **1** also smoothly undergoes Diels–Alder cycloaddition⁹ with diene **11**²⁹ followed by spontaneous extrusion of carbon monoxide to generate the pentasubstituted aryl MIDA boronate **12** (Scheme 3, the structure of **12** was confirmed via single crystal X-ray analysis). It is notable that the MIDA boronate proved to be stable even when this cycloaddition was executed at 160°C for 16 h. Collectively, the compatibility of **1** with hydroboration, radical-mediated hydrostannylation, hydrogenative reduction, and cycloaddition demonstrate that this MIDA boronate possesses substantial utility in the synthesis of building blocks for small molecule synthesis.

3. Summary and conclusions

Maximally harnessing the building block approach for small molecule synthesis requires access to a range of air-stable, highly versatile, and ideally commercially-available building blocks representing the substructural elements that most commonly appear in natural products and pharmaceuticals. MIDA boronates represent a very promising platform for this type of synthesis strategy. The results disclosed herein demonstrate that ethynyl MIDA boronate **1** can serve as a bifunctional acetylene equivalent for the controlled assembly of disubstituted alkynes via ICC. Moreover, executing a range of transformations on the alkyne subunit while leaving the MIDA boronate functionality intact represents a promising approach for preparing a range of other useful building blocks. Several of the MIDA boronates described herein, including **1**, are now commercially-available.³⁰ Collectively, these findings help expand the utility of ICC with MIDA boronates as a versatile

platform for the synthesis of a wide range of pharmaceuticals, natural products, and materials.

4. Experimental

4.1. Materials

Commercial reagents were purchased from Sigma–Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted. Palladium(II) acetate and *trans*-dichlorobis(triphenylphosphine) palladium(II) were purchased from Strem and used without further purification. Copper(I) iodide was purchased from Strem and purified according to Ref. 34. Solvents were purified via passage through packed columns as described by Pangborn and co-workers³¹ (THF, Et_2O , 1,4-dioxane, 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. Triethylamine was freshly distilled under an atmosphere of nitrogen from CaH_2 .

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 in oven-dried (125°C , $>2\text{ h}$) vials under an atmosphere of argon. Organic solutions were concentrated via rotary evaporation under reduced pressure with a bath temperature of 40°C . Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F₂₅₄ plates (0.25 mm). Compounds were visualized by exposure to a UV lamp ($\lambda=254\text{ nm}$), a solution of KMnO_4 or an acidic solution of *p*-anisaldehyde, followed by brief heating using a Varitemp heat gun. MIDA boronates are compatible with standard silica gel chromatography,³² including standard loading techniques.

4.3. Structural analysis

^1H NMR spectra were recorded at 20 °C on one of the following instruments: Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CD_2HClN , $\delta=1.93$, center line; acetone- d_6 $\delta=2.04$, center line; $\text{DMSO}-d_6$, $\delta=2.05$, center line). 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 on a Varian Unity 500 or ^{13}C NMR spectra for compounds **5a–m**, **6**, and **12** were recorded at 20 °C on a Varian Unity 600 using a d_1 relaxation time of 20 s. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent (CD_3CN , $\delta=1.30$, center line, acetone- d_6 , $\delta=29.80$, center line, $\text{DMSO}-d_6$, $\delta=39.50$, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation). High resolution mass spectra (HRMS) were performed by Furong Sun and Dr. Steve Mullen at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory. X-ray crystallographic analyses of **1** and **12** were carried out by Dr. Danielle Gray and Amy Fuller at the University of Illinois George L. Clark X-ray facility.

4.4. General procedure A: Sonogashira coupling

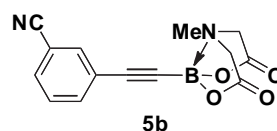
In a glove box, a 7-mL vial equipped with a stir-bar was charged with CuI (10 mol%), $\text{PdCl}_2(\text{PPh}_3)_4$ (5 mol%), ethynyl MIDA boronate **1** (0.300 mmol, 1.00 equiv), and the aryl halide (0.345 mmol, 1.15 equiv). The vial was sealed with a PTFE-lined septum screw-cap and removed from the glove box. Under a positive pressure of $\text{Ar}(\text{g})$, DMF (1.50 mL), and NEt_3 (0.125 mL, 8.98 mmol, 2.99 equiv) were added via syringe. The reaction was allowed to stir at 23 °C for 4–7 h, absorbed onto silica gel using acetone, loaded onto a silica gel column and purified by flash column chromatography to afford the desired compound. When necessary, recrystallization was performed by layering Et_2O onto a concentrated solution of the MIDA boronate in CH_2Cl_2 . The crystalline solid was collected by vacuum filtration and washed with Et_2O .

4.5. General procedure B: Sonogashira coupling

In a glove box, a 7-mL vial equipped with a stir-bar was charged with CuI (10 mol%), $\text{PdCl}_2(\text{PPh}_3)_4$ (5 mol%), and ethynyl MIDA boronate **1** (0.300 mmol, 1.00 equiv). The vial was sealed with a PTFE-lined septum screw-cap and removed from the glove box. Under a positive pressure of $\text{Ar}(\text{g})$, the aryl halide (0.345 mmol, 1.15 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 2.99 equiv) were added via syringe. The reaction was allowed to stir at 23 °C for 4–7 h, absorbed onto silica gel using acetone, loaded onto a silica gel column and purified by flash column chromatography to afford the desired compound. When necessary, recrystallization was performed by layering Et_2O onto a concentrated solution of the MIDA boronate in CH_2Cl_2 . The crystalline solid was collected by vacuum filtration and washed with Et_2O .

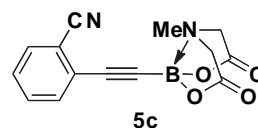
4.5.1. MIDA boronate (5a). Prepared according to general procedure A using CuI (6.1 mg, 0.0320 mmol, 0.106 equiv), $\text{PdCl}_2(\text{PPh}_3)_4$ (11.6 mg, 0.0165 mmol, 0.0546 equiv), ethynyl MIDA boronate **1** (54.7 mg, 0.302 mmol, 1.00 equiv), 4-bromobenzonitrile (61.7 mg, 0.339 mmol, 1.12 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 2.97 equiv). The reaction was allowed to stir at 23 °C for 4 h. Purification via flash chromatography (SiO_2 ; gradient: 1:1 \rightarrow 3:1 $\text{EtOAc}/\text{Et}_2\text{O}$) afforded **5a** as a white crystalline solid (80 mg, 93%).

^1H NMR (500 MHz, acetonitrile- d_3) δ 7.71 (d, $J=8.0$ Hz, 2H), 7.62 (d, $J=8.0$ Hz, 2H), 4.04 (d, $J=17.0$ Hz, 2H), 3.92 (d, $J=17.0$ Hz, 2H), 3.09 (s, 3H). ^{13}C NMR (150 MHz, acetone- d_6) δ 168.4, 133.3, 133.0, 128.5, 118.8, 112.7, 98.6, 62.4, 48.5. HRMS (EI^+) calculated for $\text{C}_{14}\text{H}_{11}\text{BN}_2\text{O}_4$ (M^+): 282.0812, found: 282.0804.



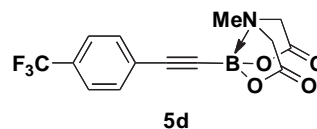
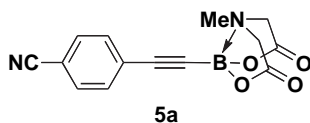
4.5.2. MIDA boronate (5b). Prepared according to general procedure A using CuI (6.4 mg, 0.0336 mmol, 0.114 equiv), $\text{PdCl}_2(\text{PPh}_3)_4$ (10.1 mg, 0.0144 mmol, 0.0490 equiv), ethynyl MIDA boronate **1** (53.2 mg, 0.294 mmol, 1.00 equiv), 3-bromobenzonitrile (64.8 mg, 0.356 mmol, 1.21 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 3.05 equiv). The reaction was allowed to stir at 23 °C for 4.5 h. Purification via flash chromatography (SiO_2 ; gradient: 1:1 \rightarrow 3:1 $\text{EtOAc}/\text{Et}_2\text{O}$) afforded **5b** as a white crystalline solid (79 mg, 95%).

^1H NMR (500 MHz, acetonitrile- d_3) δ 7.87–7.86 (m, 1H), 7.77 (dt, $J=8.0, 1.2$ Hz, 1H), 7.73 (td, $J=1.2, 8.0$ Hz, 1H), 7.55–7.52 (m, 1H), 4.04 (d, $J=17$ Hz, 2H), 3.93 (d, $J=17$ Hz, 2H), 3.10 (s, 3H). ^{13}C NMR (150 MHz, acetonitrile- d_3) δ 168.7, 136.9, 136.1, 133.2, 130.6, 124.9, 118.9, 113.5, 98.5, 62.5, 48.8. HRMS (EI^+) calculated for $\text{C}_{14}\text{H}_{11}\text{BN}_2\text{O}_4$ (M^+): 282.0812, found: 282.0815.



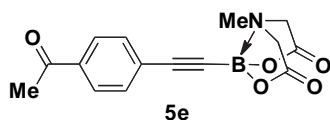
4.5.3. MIDA boronate (5c). Prepared according to general procedure A using CuI (6.1 mg, 0.0320 mmol, 0.108 equiv), $\text{PdCl}_2(\text{PPh}_3)_4$ (10.5 mg, 0.0150 mmol, 0.0507 equiv), ethynyl MIDA boronate **1** (53.5 mg, 0.296 mmol, 1.00 equiv), 2-bromobenzonitrile (70.0 mg, 0.384 mmol, 1.30 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 3.05 equiv). The reaction was allowed to stir at 23 °C for 5 h. Purification via flash chromatography (SiO_2 ; gradient: 1:1 \rightarrow 3:1 $\text{EtOAc}/\text{Et}_2\text{O}$) afforded **5c** as an off-white solid (77 mg, 92%).

^1H NMR (500 MHz, acetonitrile- d_3) δ 7.74 (d, $J=7.5$ Hz, 1H), 7.68–7.63 (m, 2H), 7.54–7.50 (m, 1H), 4.08 (d, $J=17.0$ Hz, 2H), 3.95 (d, $J=17.0$ Hz, 2H), 3.18 (s, 3H). ^{13}C NMR (150 MHz, acetonitrile- d_3) δ 168.6, 133.9, 133.8, 133.5, 130.3, 127.0, 118.5, 115.8, 96.8, 62.5, 49.0. HRMS (EI^+) calculated for $\text{C}_{14}\text{H}_{11}\text{BN}_2\text{O}_4$ (M^+): 282.0812, found: 282.0818.



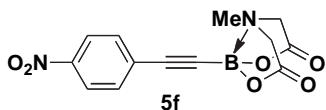
4.5.4. MIDA boronate (5d). Prepared according to general procedure B using CuI (5.8 mg, 0.0304 mmol, 0.100 equiv), PdCl₂(PPh₃)₄ (10.9 mg, 0.0155 mmol, 0.0512 equiv), ethynyl MIDA boronate **1** (54.8 mg, 0.303 mmol, 1.00 equiv), 4-bromobenzotrifluoride (48 μL, 0.348 mmol, 1.15 equiv), DMF (1.50 mL), and NEt₃ (0.125 mL, 0.898 mmol, 2.96 equiv). The reaction was allowed to stir at 23 °C for 5.5 h. Purification via flash chromatography (SiO₂, 1:1 EtOAc/Et₂O) followed by recrystallization afforded **5d** as a white crystalline solid (68 mg, 69%).

¹H NMR (500 MHz, acetone-*d*₆) δ 7.71 (app s, 4H), 4.36 (d, *J*=17.0 Hz, 2H), 4.20 (d, *J*=17.0 Hz, 2H), 3.35 (s, 3H). ¹³C NMR (150 MHz, acetone-*d*₆) δ 168.5, 133.2 (t, *J*=16 Hz), 130.5 (q, *J*=32 Hz), 128.0, 126.2 (q, *J*=4 Hz), 125.0 (q, *J*=270 Hz), 98.8, 62.4, 48.5. HRMS (EI⁺) calculated for C₁₄H₁₁BF₃NO₄ (M)⁺: 325.0733, found: 325.0748.



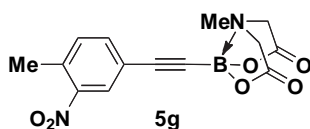
4.5.5. MIDA boronate (5e). Prepared according to general procedure A using CuI (5.9 mg, 0.0310 mmol, 0.102 equiv), PdCl₂(PPh₃)₄ (15.5 mg, 0.0192 mmol, 0.0634 equiv), ethynyl MIDA boronate **1** (54.9 mg, 0.303 mmol, 1.00 equiv), 4-bromoacetophenone (55.0 mg, 0.476 mmol, 1.57 equiv), DMF (1.50 mL), and NEt₃ (0.125 mL, 0.898 mmol, 2.96 equiv). The reaction was allowed to stir at 23 °C for 4 h. Purification via flash chromatography (SiO₂, 1:1 EtOAc/Et₂O) afforded **5e** as a light yellow solid (72 mg, 80%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.96 (d, *J*=8.5 Hz, 2H), 7.63 (d, *J*=8.5 Hz, 2H), 4.33 (d, *J*=17.0 Hz, 2H), 4.16 (d, *J*=17.0 Hz, 2H), 3.09 (s, 3H), 2.58 (s, 3H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 197.3, 168.7, 136.4, 131.8, 128.4, 126.1, 98.5, 61.5, 48.0, 26.8. HRMS (ESI⁺) calculated for C₁₅H₁₄BNO₅ (M)⁺: 299.0965, found: 299.0970.



4.5.6. MIDA boronate (5f). Prepared according to general procedure A using CuI (5.5 mg, 0.0289 mmol, 0.0973 equiv), PdCl₂(PPh₃)₄ (10.3 mg, 0.0147 mmol, 0.0495 equiv), ethynyl MIDA boronate **1** (53.7 mg, 0.297 mmol, 1.00 equiv), 4-bromoacetophenone (40.7 mg, 0.340 mmol, 1.14 equiv), DMF (1.50 mL), and NEt₃ (0.125 mL, 0.898 mmol, 3.02 equiv). The reaction was allowed to stir at 23 °C for 4 h. Purification via flash chromatography (SiO₂; gradient: 1:1→3:1 EtOAc/Et₂O) followed by recrystallization afforded **5f** as an orange crystalline solid (58 mg, 65%).

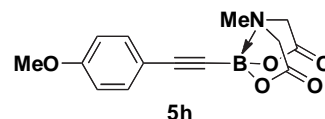
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.23 (d, *J*=8.5 Hz, 2H), 7.76 (d, *J*=9.0 Hz, 2H), 4.35 (d, *J*=17.0 Hz, 2H), 4.17 (d, *J*=17.0 Hz, 2H), 3.11 (s, 3H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 168.7, 147.0, 132.8, 129.1, 123.8, 97.4, 61.6, 48.0. HRMS (EI⁺) calculated for C₁₃H₁₁BN₂O₆ (M)⁺: 302.0710, found: 302.0706.



4.5.7. MIDA boronate (5g). Prepared according to general procedure A using CuI (6.2 mg, 0.0325 mmol, 0.102 equiv), PdCl₂(PPh₃)₄ (10.9 mg, 0.0155 mmol, 0.0489 equiv), ethynyl MIDA boronate **1**

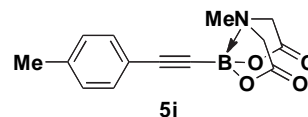
(57.3 mg, 0.317 mmol, 1.00 equiv), 4-bromo-2-nitrotoluene (86.5 mg, 0.400 mmol, 1.26 equiv), DMF (1.50 mL), and NEt₃ (0.125 mL, 0.898 mmol, 2.83 equiv). The reaction was allowed to stir at 23 °C for 6 h. Purification via flash chromatography (SiO₂, 1:1 EtOAc/Et₂O) followed by recrystallization afforded **5g** as an orange crystalline solid (72 mg, 72%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.08 (d, *J*=1.0 Hz, 1H), 7.73 (dd, *J*=8.0, 1.5 Hz, 1H), 7.53 (d, *J*=8.0 Hz, 1H), 4.33 (d, *J*=17.0 Hz, 2H), 4.15 (d, *J*=17.0 Hz, 2H), 3.08 (s, 3H), 2.51 (s, 3H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ 168.7, 148.9, 135.8, 133.4, 133.2, 127.1, 121.3, 96.9, 61.5, 47.9, 19.4. HRMS (EI⁺) calculated for C₁₄H₁₃BN₂O₆ (M)⁺: 316.0867, found: 316.0862.



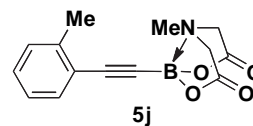
4.5.8. MIDA boronate (5h). Prepared according to general procedure A using CuI (5.7 mg, 0.0299 mmol, 0.100 equiv), PdCl₂(PPh₃)₄ (10.2 mg, 0.0145 mmol, 0.0486 equiv), ethynyl MIDA boronate **1** (54.0 mg, 0.298 mmol, 1.00 equiv), 4-iodoanisole (81.7 mg, 0.349 mmol, 1.17 equiv), DMF (1.50 mL), and NEt₃ (0.125 mL, 0.898 mmol, 3.01 equiv). The reaction was allowed to stir at 23 °C for 6.5 h. Purification via flash chromatography (SiO₂, 1:1 EtOAc/Et₂O) followed by recrystallization afforded **5h** as a tan crystalline solid (69 mg, 80%).

¹H NMR (500 MHz, acetonitrile-*d*₃) δ 7.54 (d, *J*=8.5 Hz, 2H), 7.01 (d, *J*=8.5 Hz, 2H), 4.14 (d, *J*=17.0 Hz, 2H), 4.02 (d, *J*=17.0 Hz, 2H), 3.90 (s, 3H), 3.19 (s, 3H). ¹³C NMR (150 MHz, acetonitrile-*d*₃) δ 168.8, 161.0, 134.2, 115.5, 115.0, 101.1, 62.4, 56.0, 48.7. HRMS (ESI⁺) calculated for C₁₄H₁₅BNO₅ (M+H)⁺: 288.1043, found: 288.1043.



4.5.9. MIDA boronate (5i). Prepared according to general procedure A using CuI (5.2 mg, 0.0273 mmol, 0.0872 equiv), PdCl₂(PPh₃)₄ (10.8 mg, 0.0154 mmol, 0.0492 equiv), ethynyl MIDA boronate **1** (56.7 mg, 0.313 mmol, 1.00 equiv), 4-iodotoluene (76.1 mg, 0.349 mmol, 1.12 equiv), DMF (1.50 mL), and NEt₃ (0.125 mL, 0.898 mmol, 2.86 equiv). The reaction was allowed to stir at 23 °C for 4.5 h. Purification via flash chromatography (SiO₂, 1:1 EtOAc/Et₂O) followed by recrystallization afforded **5i** as white crystalline solid (64 mg, 75%).

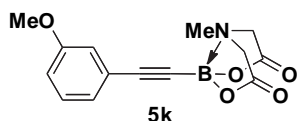
¹H NMR (500 MHz, acetone-*d*₆) δ 7.37 (d, *J*=8.0 Hz, 2H), 7.18 (d, *J*=8.0 Hz, 2H), 4.32 (d, *J*=17.0 Hz, 2H), 4.16 (d, *J*=17.0 Hz, 2H), 3.30 (s, 3H), 2.33 (s, 3H). ¹³C NMR (150 MHz, acetone-*d*₆) δ 168.6, 139.6, 132.4, 129.9, 120.9, 100.7, 62.2, 48.4, 21.3. HRMS (EI⁺) calculated for C₁₄H₁₄BNO₄ (M)⁺: 271.1016, found: 271.1005.



4.5.10. MIDA boronate (5j). Prepared according to general procedure B using CuI (5.5 mg, 0.0289 mmol, 0.0941 equiv), PdCl₂(PPh₃)₄ (11.1 mg, 0.0158 mmol, 0.0515 equiv), ethynyl MIDA boronate **1** (55.5 mg, 0.307 mmol, 1.00 equiv), 2-iodotoluene

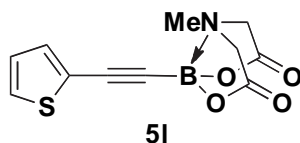
(45 μ L, 0.354 mmol, 1.15 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 2.92 equiv). The reaction was allowed to stir at 23 $^\circ\text{C}$ for 5.5 h. Purification via flash chromatography (SiO_2 , 1:1 EtOAc/ Et_2O) afforded **5j** as a white crystalline solid (73 mg, 88%).

^1H NMR (500 MHz, acetone- d_6) δ 7.44 (d, $J=8.0$ Hz, 1H), 7.27–7.24 (m, 2H), 7.19–7.17 (m, 1H), 4.34 (d, $J=17.0$ Hz, 2H), 4.19 (d, $J=17.0$ Hz, 2H), 3.34 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, acetone- d_6) δ 168.6, 140.9, 132.8, 130.2, 129.5, 126.4, 123.6, 99.3, 62.3, 48.5, 20.8. HRMS (EI^+) calculated for $\text{C}_{14}\text{H}_{14}\text{BNO}_4$ (M^+): 271.1016, found: 271.1020.



4.5.11. MIDA boronate (5k). Prepared according to general procedure B using CuI (6.4 mg, 0.0336 mmol, 0.110 equiv), $\text{PdCl}_2(\text{PPh}_3)_4$ (10.7 mg, 0.0152 mmol, 0.0508 equiv), ethynyl MIDA boronate **1** (55.2 mg, 0.305 mmol, 1.00 equiv), 3-iodoanisole (42 μ L, 0.353 mmol, 1.16 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 2.94 equiv). The reaction was allowed to stir at 23 $^\circ\text{C}$ for 7 h. Purification via flash chromatography (SiO_2 , 1:1 EtOAc/ Et_2O) afforded **5k** as a white crystalline solid (69 mg, 90%).

^1H NMR (500 MHz, acetone- d_6) δ 7.27 (app t, $J=8.0$ Hz, 1H), 7.07–7.03 (m, 2H), 6.95 (ddd, $J=8.5$, 2.5, 1.0 Hz, 1H), 4.33 (d, $J=17.0$ Hz, 2H), 4.18 (d, $J=17.0$ Hz, 2H), 3.80 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (150 MHz, acetone- d_6) δ 168.5, 160.3, 130.4, 130.3, 124.8, 117.3, 115.8, 100.5, 62.3, 55.5, 48.4. HRMS (EI^+) calculated for $\text{C}_{14}\text{H}_{14}\text{BNO}_5$ (M^+): 287.0965, found: 287.0953.



4.5.12. MIDA boronate (5l). Prepared according to general procedure B using CuI (6.0 mg, 0.0315 mmol, 0.107 equiv), $\text{PdCl}_2(\text{PPh}_3)_4$ (11.4 mg, 0.0162 mmol, 0.0549 equiv), ethynyl MIDA boronate **1** (53.4 mg, 0.295 mmol, 1.00 equiv), 2-bromothiazole (35 μ L, 0.362 mmol, 1.23 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 3.04 equiv). The reaction was allowed to stir at 23 $^\circ\text{C}$ for 6 h. Purification via flash chromatography (SiO_2 , EtOAc) followed by recrystallization afforded **5l** as a light-yellow crystalline solid (52 mg, 67%).

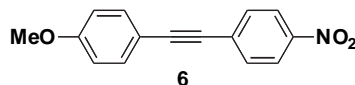
^1H NMR (500 MHz, acetone- d_6) δ 7.38 (dd, $J=5.0$, 1.0 Hz, 1H), 7.19 (dd, $J=3.8$, 1.0 Hz, 1H), 6.94 (dd, $J=5.0$, 3.8 Hz, 1H), 4.22 (d, $J=17.0$ Hz, 2H), 4.08 (d, $J=17.0$ Hz, 2H), 3.18 (s, 3H). ^{13}C NMR (150 MHz, acetone- d_6) δ 168.5, 133.6, 128.7, 128.0, 123.6, 93.1, 62.4, 48.4. HRMS (EI^+) calculated for $\text{C}_{11}\text{H}_{10}\text{BNO}_4\text{S}$ (M^+): 263.0424, found: 263.0441.



4.5.13. MIDA boronate (5m). Prepared according to general procedure B using CuI (6.0 mg, 0.0315 mmol, 0.100 equiv), $\text{PdCl}_2(\text{PPh}_3)_4$ (10.6 mg, 0.0151 mmol, 0.0479 equiv), ethynyl MIDA boronate **1** (57.0 mg, 0.315 mmol, 1.00 equiv), 2-bromopyridine

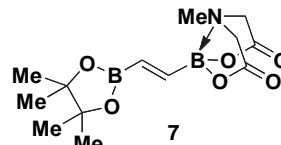
(34 μ L, 0.349 mmol, 1.11 equiv), DMF (1.50 mL), and NEt_3 (0.125 mL, 0.898 mmol, 2.85 equiv). The reaction was allowed to stir at 23 $^\circ\text{C}$ for 6 h. Purification via flash chromatography (SiO_2 , 3:2 Et_2O : CH_3CN) followed by recrystallization afforded **5m** as a pale-green crystalline solid (45 mg, 55%).

^1H NMR (500 MHz, acetonitrile- d_3) δ 8.58 (br s, 1H), 7.75 (dt, $J=8.0$, 1.5 Hz, 1H), 7.54 (d, $J=3.8$, 1.0 Hz, 1H), 7.35–7.33 (m, 1H), 4.33 (d, $J=17.0$ Hz, 2H), 4.18 (d, $J=17.0$ Hz, 2H), 3.12 (s, 3H). ^{13}C NMR (150 MHz, DMSO- d_6) δ 168.7, 150.0, 142.1, 136.7, 127.6, 123.9, 98.9, 61.6, 48.0. HRMS (ESI^+) calculated for $\text{C}_{12}\text{H}_{12}\text{BN}_2\text{O}_4$ ($\text{M}+\text{H}^+$): 259.0890, found: 259.0885.



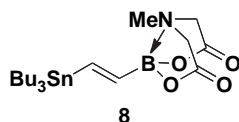
4.5.14. 1-Methoxy-4-((4-nitrophenyl)ethynyl)benzene (6). Under ambient atmosphere a 40-mL vial was equipped with a magnetic stir-bar and charged with $\text{Pd}(\text{OAc})_2$ (2.8 mg, 0.0125 mmol, 0.050 equiv), SPhos (10.5 mg, 0.0256 mmol, 0.100 equiv), 1-bromo-4-nitrobenzene (50.3 mg, 0.249 mmol, 1.00 equiv), and MIDA boronate **1** (76.8 mg, 0.300 mmol, 1.20 equiv). The vial was sealed with a PTFE-lined septum screw-cap and placed under an atmosphere of $\text{Ar}(\text{g})$. To the vial was added 1,4-dioxane (9.0 mL) via syringe and the resulting mixture stirred for 10 min at 23 $^\circ\text{C}$. To the vial was added aq K_3PO_4 (degassed by sparging with $\text{Ar}(\text{g})$ for 45 min; 3.0 M, 1.8 mL, 5.4 mmol, 21.6 equiv). The vial was placed in a 60 $^\circ\text{C}$ oil bath with stirring for 6 h. The mixture was allowed to cool to 23 $^\circ\text{C}$, transferred to a separatory funnel and diluted with aq NaOH (1.0 M, 8 mL). The mixture was extracted with Et_2O (3×10 mL). The combined organic fractions were washed with brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. The crude orange residue was purified via flash chromatography (SiO_2 ; gradient: 100:0 \rightarrow 19:1 hexanes/ EtOAc) to provide **6** as a bright yellow crystalline solid (54 mg, 86%).

^1H NMR (500 MHz, acetone- d_6) δ 8.25 (d, $J=9.0$ Hz, 2H), 7.75 (d, $J=9.0$ Hz, 2H), 7.54 (d, $J=9.0$ Hz, 2H), 7.00 (d, $J=9.0$ Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (150 MHz, acetone- d_6) δ 161.5, 147.7, 134.2, 132.9, 131.2, 124.5, 115.2, 114.7, 95.5, 87.2, 55.7. HRMS (EI^+) calculated for $\text{C}_{15}\text{H}_{11}\text{NO}_3$ (M^+): 253.0739, found: 253.0744.



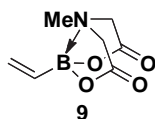
4.5.15. MIDA boronate (7)⁵. To a 40-mL flame-dried vial equipped with a magnetic stir-bar was added ethynyl MIDA boronate **1** (500 mg, 2.8 mmol, 1.0 equiv). The vial was taken into a glove box where solid dicyclohexylborane³³ (98 mg, 0.55 mmol, 20 mol %) was added. The vial was capped with a PTFE-lined septa cap, removed from the glove box, and placed under N_2 . To the vial was added THF (5.5 mL, 0.50 M) and neat pinacolborane (480 μ L, 3.3 mmol, 1.2 equiv). The vial was sealed under N_2 and placed in an 85 $^\circ\text{C}$ heating block. The solution turned clear, colorless within 20 min. After stirring at 85 $^\circ\text{C}$ for 17 h, the crude reaction solution was concentrated in vacuo. The resulting solid was dry loaded onto Celite from an acetone solution and purified via flash chromatography

(SiO₂; gradient: 100:0→2:1 Et₂O/acetone) to afford bisborylated MIDA boronate **7** as a white solid (717 mg, 84%).

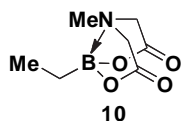


4.5.16. MIDA boronate (8). A dry 25-mL Schlenk flask equipped with a magnetic stir-bar was charged with ethynyl MIDA boronate **1** (182 mg, 1.0 mmol, 1.0 equiv) and 2,2'-azobis(2-methylpropionitrile) (16 mg, 0.10 mmol, 1.0 equiv) and was then placed under N₂ atm. To the flask was added THF (5.0 mL) followed by HSnBu₃ (0.40 mL, 1.5 mmol, 1.5 equiv). The flask was fitted with a reflux condenser vented to N₂ atmosphere. The solution was heated to 65 °C internal temp (70 °C oil bath) with stirring for 18 h. The solution was allowed to cool to 23 °C and was transferred to a 60-mL separatory funnel using Et₂O (15 mL). The solution was washed with aq 1 M HCl (10 mL), satd aq NaHCO₃ (10 mL), and brine (5 mL). The solution was dried over MgSO₄, filtered, and concentrated in vacuo to afford a colorless oil that was purified via flash chromatography (SiO₂; gradient: 100:0→5:1 Et₂O:MeCN) to afford the title compound as a colorless solid (441 mg, 93%).

¹H NMR (500 MHz, acetone-*d*₆) δ 6.99 (app sext, *J*=22.0 Hz, 1H), 6.43 (app sext, *J*=22.0 Hz, 1H), 4.19 (d, *J*=17.0 Hz, 2H), 3.97 (d, *J*=17.0 Hz, 2H), 2.98 (s, 3H), 1.55 (m, 6H), 1.33 (app sext, *J*=7.5 Hz, 6H), 0.94 (t, *J*=7.5 Hz, 6H), 0.89 (t, *J*=7.5 Hz, 9H). ¹³C NMR (125 MHz, acetone-*d*₆) δ 169.2, 147.6, 62.3, 47.5, 29.9 (app hept), 27.9 (t), 14.0, 9.8 (t). HRMS (ESI⁺) calculated for C₁₉H₃₇BNO₄Sn (M+H)⁺: 474.1855, found: 474.1838.



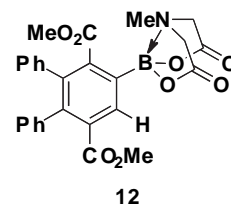
4.5.17. Ethynyl MIDA boronate (9)⁷. An oven-dried 7-mL vial equipped with a magnetic stir-bar was charged with ethynyl MIDA boronate **1** (45 mg, 0.25 mmol, 1.0 equiv), Lindlar's cat. (2.5 mg), and 1,4-dioxane (1.5 mL). Quinoline (0.015 mL, 0.125 mmol, 0.50 equiv) was added and the vial sealed with a PTFE-lined plastic screw-cap. The vial was filled with hydrogen gas using a balloon and the reaction mixture was stirred at 23 °C for 3.5 h. The reaction mixture was diluted with acetonitrile (1.0 mL) and filtered through Celite[®]. The crude product was purified via flash chromatography (SiO₂, 19:1 EtOAc/MeCN) to afford **9** as a colorless crystalline solid (37 mg, 81%).



4.5.18. Ethyl MIDA boronate (10). An oven-dried 7-mL vial equipped with a magnetic stir-bar was charged with ethynyl MIDA boronate **1** (45 mg, 0.25 mmol, 1.0 equiv), Lindlar's cat. (5.0 mg), and 1,4-dioxane (1.0 mL). The vial containing this reaction mixture was placed in a hydrogenation bomb and the hydrogen pressure was adjusted to 200 psi. The reaction mixture was allowed to stir at 23 °C for 15 h. The reaction mixture was diluted with acetonitrile

(1.0 mL) and filtered through Celite[®]. The resulting colorless solution was concentrated in vacuo to provide **10** as a colorless crystalline solid (43 mg, 93%).

¹H NMR (500 MHz, acetonitrile-*d*₃) δ 3.92 (d, *J*=16.5 Hz, 2H), 3.76 (d, *J*=16.5 Hz, 2H), 2.84 (s, 3H), 0.89 (t, *J*=8.0 Hz, 3H), 0.58 (q, *J*=8.0 Hz, 2H). ¹³C NMR (100 MHz, acetonitrile-*d*₃) δ 169.1, 62.6, 46.3, 8.0. HRMS (ESI⁺) calculated for C₇H₁₃BNO₄ (M+H)⁺: 186.0938, found: 186.0946.



4.5.19. MIDA boronate (12). A 5-mL round-bottom flask was equipped with a magnetic stir-bar and charged with ethynyl MIDA boronate **1** (172 mg, 0.950 mmol, 1.00 equiv), dimethyl 2-oxo-4,5-diphenylcyclopenta-3,5-diene-1,3-dicarboxylate **11** (460 mg, 1.32 mmol, 1.40 equiv), and mesitylene (1.0 mL). The flask was equipped with a water-jacketed reflux condenser and an Ar(g) inlet. The reaction was allowed to stir in a 160 °C oil bath for 16 h. The black reaction mixture was allowed to cool to 23 °C, absorbed onto silica gel using acetone, and semi-purified via flash chromatography (SiO₂, 5:4 EtOAc/Et₂O). The semi-purified brown powder was dissolved in a minimal volume of acetone and then precipitated by the addition of Et₂O with vigorous stirring. Collection by vacuum filtration and washing with Et₂O afforded **12** as a white powder (269 mg, 56%).

¹H NMR (500 MHz, acetone-*d*₆) δ 8.00 (s, 1H), 7.14–7.12 (m, 6H), 7.00–6.99 (m, 4H), 4.43 (d, *J*=17.5 Hz, 2H), 4.25 (d, *J*=17.5 Hz, 2H), 3.48 (s, 3H), 3.30 (s, 3H), 3.11 (s, 3H). ¹³C NMR (150 MHz, acetone-*d*₆) δ 172.6, 169.4, 169.3, 142.2, 142.1, 139.9, 139.7, 139.1, 134.3, 134.1, 131.0, 130.4, 128.0, 127.9, 127.6, 127.4, 64.7, 52.4, 52.1, 50.2. HRMS (EI⁺) calculated for C₂₇H₂₄BNO₈ (M)⁺: 501.1595, found: 501.1586.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.020.

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