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

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Dedicated to Professor Justin Dubois to celebrate his receipt of the Tetrahedron Young Investigator Award and his inspirational contributions to molecule making

ABSTRACT

Iterative cross-coupling represents a potentially general approach for the simple, efficient, and flexible construction of natural products, pharmaceuticals, and materials. *N*-Methyliminodiacetic acid (MIDA) boronates represent a promising platform for the development of this type of synthesis strategy. This report describes the discovery that vinyl MIDA boronate (**1**) is an air- and chromatographically stable compound that can be conveniently prepared on a multigram scale and serve as a versatile starting material for the preparation of a range of new MIDA boronate building blocks. Analogous to *tert*-butylethylene, **1** is also an excellent substrate for olefin cross-metathesis, providing access to a range of *trans*-alkenyl MIDA boronates as single stereoisomers. An improved synthesis of the very versatile bifunctional building block *trans*-(2-bromovinyl) MIDA boronate (**2**) is also described. Collectively, these results contribute to the expanding generality of the iterative cross-coupling approach.

1. Introduction

State-of-the-art syntheses of peptides, oligonucleotides, many oligosaccharides, and various types of materials are based on the stepwise, iterative coupling of pre-assembled building blocks.[1] These processes are simple, efficient, and flexible, and can now be executed in a fully automated fashion. In contrast, syntheses of 'small molecules', such as natural products and man-made pharmaceuticals, tend to be much more complex and, as a result, less efficient and less flexible. Although it is true that small molecules are very diverse in structure, most share in common a highly modular constitution. This is because many natural products are in fact biosynthesized via iterative bond formation between bifunctional building blocks, e.g., malonyl-CoA or methylmalonyl-CoA units for polyketides, amino acids for non-ribosomal peptides, isopentenyl pyrophosphate or dimethylallyl pyrophosphate for polyterpenes, and malonyl-CoA for fatty acids.[2] In addition, many synthetic pharmaceuticals are derived from small building blocks (cyclic and heterocyclic fragments and associated appendages) that are typically brought together using a variety of different reactions. Thus, there are particular structural motifs that appear with remarkable frequency in both natural products and pharmaceuticals. With the goal of more effectively harnessing this inherent modularity, we have established a research program that aims to develop a wide range of shelf-stable building blocks representing these common structural motifs and the chemistry that will enable their simple and flexible union via iterative, metal-mediated cross-coupling reactions.

N-Methyliminodiacetic acid (MIDA) boronates[3] represent a highly promising platform for this type of synthesis strategy.[4] In contrast to many boronic acids, MIDA boronates are monomeric, air- and chromatographically stable, highly crystalline, free-flowing solids. Moreover, the MIDA boronate functional group is stable to a wide range of common synthetic reagents, enabling the multistep synthesis of complex B-containing building blocks from simple MIDA boronate starting materials.[4c] In addition, MIDA boronates are unreactive toward cross-coupling under anhydrous conditions, yet can be easily hydrolyzed using mild aqueous base to reveal the corresponding boronic acid.[4]

Collectively, these features have enabled the development of a potentially general approach for the synthesis of a wide range of natural products, pharmaceuticals, and materials. Analogous to the construction of peptides via the iterative coupling of suitably protected amino acids, MIDA-protected *haloboronic acids* can be precisely assembled into small molecules via iterative cycles of transition metal-mediated cross-coupling followed by boronic acid deprotection.[4,5] In the idealized form of this iterative cross-coupling (ICC)-based approach, a collection of building blocks having all of the required functional groups pre-installed in the correct oxidation state and with the desired stereochemical relationships are brought together using only stereospecific cross-coupling reactions. This strategy has already been harnessed to achieve efficient and flexible syntheses of the natural products ratanhine, all-*trans*-retinal, β-parinaric acid, crocacin C, and half of the amphotericin B macrolide skeleton.[4]

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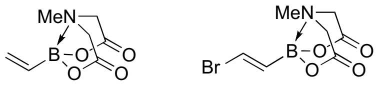
With the goal of maximizing the generality of this approach, we seek to enable the efficient preparation of a wide range of new MIDA boronate building blocks. In this regard, a very stable and chemically robust vinyl borane could serve as a valuable starting material. In fact, there are promising examples demonstrating that vinyl boranes can be compatible with chemical transformations on the vinyl moiety;[6–12] however, limited stabilities of most boranes to chromatography and/or long-term storage have thus far precluded the widespread utilization of this approach. Overcoming these limitations, we herein report that vinyl MIDA boronate **1** (Fig. 1) is an air- and chromatographically stable, highly crystalline, free-flowing solid. We have developed a convenient and scalable synthesis of this building block from the corresponding inexpensive and readily available commercial reagent vinyltrimethylsilane. We further demonstrate that **1** can serve as a versatile starting material for the preparation of a variety of new MIDA boronate building blocks that are uniformly air- and chromatographically stable. Finally, we report a new and operationally more convenient synthesis of the very versatile bifunctional halo MIDA boronate **2**,[4b] also from the corresponding commercially available trimethylsilane. Importantly, both **1** and **2** are now commercially available as well.[13]

2. Results

A wide variety of MIDA boronates can be easily prepared by complexing the corresponding boronic acids with MIDA under Dean–Stark-type conditions.[3,4] However, our initial efforts to prepare vinyl MIDA boronate **1** using this approach were thwarted by rapid decomposition of vinyl boronic acid[14] during purification and/or MIDA complexation. An alternative approach was suggested by our previous experience in preparing *trans*-(2-bromovinyl) MIDA boronate **2**,[4b] where we found that trapping (*E*)-(2-bromoethenyl)-dibromoborane[15,10b] with a DMSO suspension of MIDA in the presence of 2,6-lutidine was effective. We therefore attempted to prepare **1** via BBr_3-promoted transmetalation[16,17,10g] of the readily available vinyltrimethylsilane **3** into the corresponding dibromoborane intermediate **4**,[18,17,10g] followed by trapping of **4** with MIDA in the presence of 2,6-lutidine and DMSO (Table 1, entry 1). We were encouraged to observe the formation of significant quantities of **1** using this protocol, yet important limitations still remained. Specifically, in addition to providing only moderate yield, this procedure requires the utilization of 2 equiv of 2,6-lutidine to scavenge the HBr generated upon MIDA complexation. We reasoned that alternatively trapping this same intermediate **4** with the pre-formed bis-sodium salt of MIDA ($MIDA^{2-}Na^{+}_2$, **6**)[19] would instead generate NaBr as a stoichiometric byproduct and thereby obviate the use of 2,6-lutidine. This approach was not very successful when using DMSO as solvent (entry 2). However, switching to CH_3CN resulted in a robust and high-yielding synthesis of **1** (entry 3).

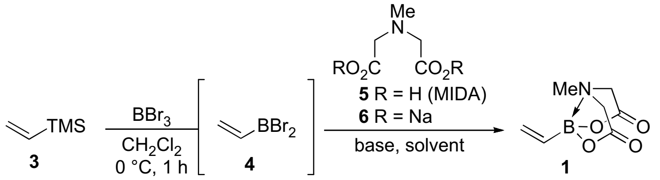
Given the simple and convenient nature of this procedure, we decided to explore its scalability. We first developed a convenient, >100 g scale procedure for transforming MIDA into the corresponding bis-sodium salt **6** via the treatment with aqueous sodium hydroxide followed by a simple filtration procedure (Scheme 1).[19] Having secured large scale access to $MIDA^{2-}Na^{+}_2$, we translated the conditions described above for the synthesis of **1** to the 30 mmol scale (Scheme 2). The product was purified and isolated as a colorless, free-flowing, crystalline solid using a simple and convenient recrystallization procedure. Single crystal X-ray analysis confirmed the predicted structure of **1** having a pyramidalized boron center (Scheme 2). We have stored this novel vinyl borane on the benchtop under air for more than 3 months without any noticeable decomposition.



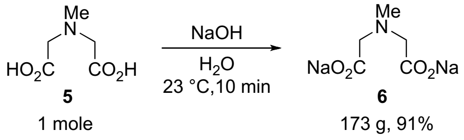
1 2

Figure 1. Air-stable alkenyl MIDA boronate building blocks for small molecule synthesis.

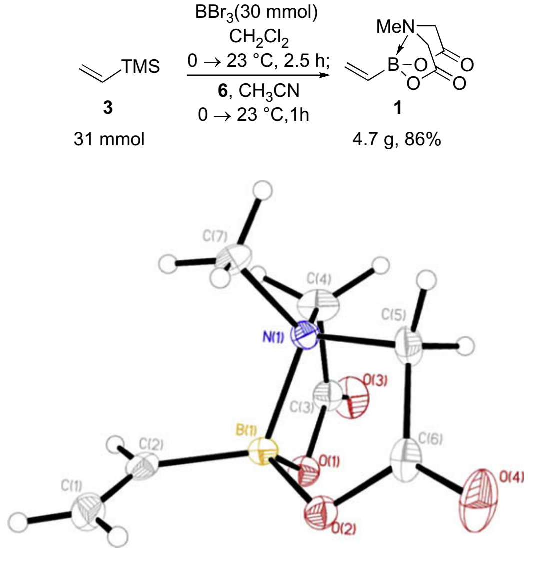
Table 1
Synthesis of **1** from vinyltrimethylsilane (**3**)



Entry	Ligand	Base	Solvent	% Yield
1	**5**	2,6-Lutidine	DMSO	51
2	**6**	None	DMSO	18
3	**6**	None	CH_3CN	86



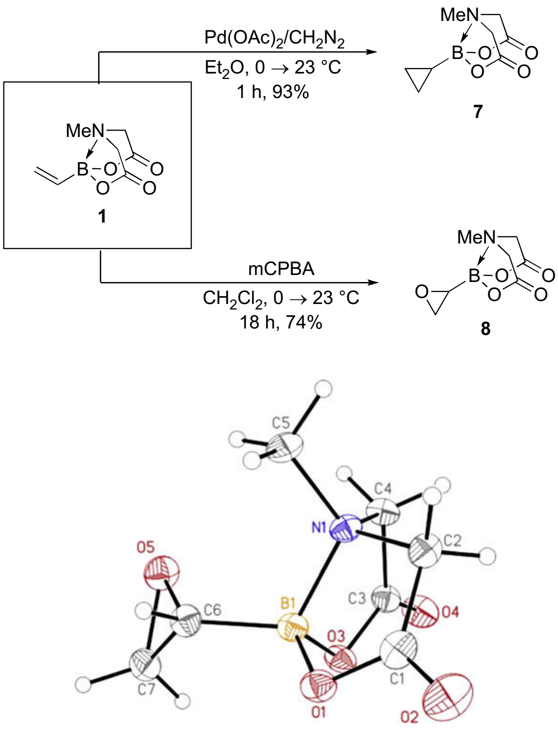
Scheme 1.



1

Scheme 2.

With a simple and readily scalable synthesis of **1** in hand, we have preliminarily explored its utility as a starting material for the preparation of a range of new MIDA boronate building blocks. For example, due to its sensitivity to protodeboronation, cyclopropyl boronic acid can be difficult to synthesize and store.[20] Circumventing this challenge, the cyclopropanation[9] of **1** proceeds in excellent yields using $Pd(OAc)_2$ and diazomethane to yield cyclopropyl MIDA boronate **7** as an air- and chromatographically stable solid (Scheme 3). The success of this formal [2+1] cycloaddition prompted us to consider the related epoxidation reaction. In pioneering studies, Molander and co-workers have demonstrated the compatibility of substituted alkenyltrifluoroborate salts with epoxidation mediated by DMDO.[21] mCPBA was also effective in these studies, but the incompatibility of trifluoroborate salts with chromatography precluded the separation of the epoxide products from the benzoic acid byproducts.[21] In contrast, mCPBA promoted the epoxidation of **1** and, remarkably, the resulting novel oxiranyl MIDA boronate **8** is stable to silica gel chromatography and can be isolated in pure form. We are unaware of any prior synthesis of an unsubstituted oxiranylborane. Single crystal X-ray analysis confirmed unambiguously the structure of this very interesting and potentially highly versatile new building block.

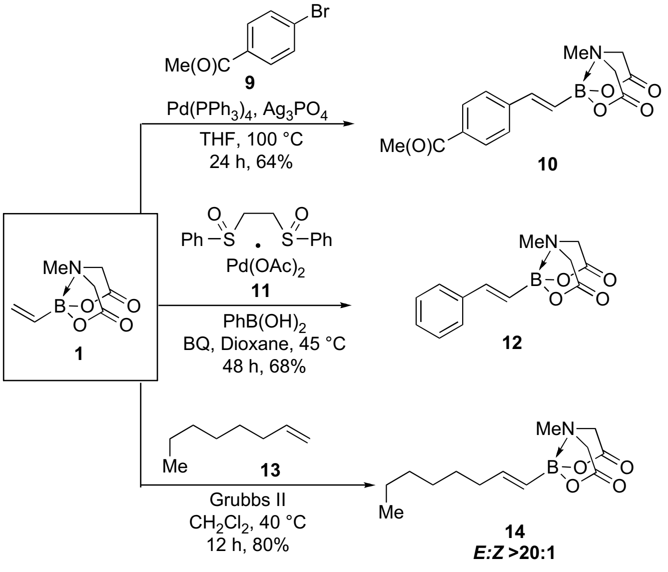


8

Scheme 3.

We further explored the compatibility of **1** with a series of transition metal-mediated transformations of the vinyl moiety (Scheme 4). Whiting and co-workers have developed a series of selective Heck-type couplings of aryl and vinyl halides with sterically bulky vinyl boronic esters to generate styrenyl and polyenyl boranes, respectively.[6] We have found that in the absence of water MIDA boronates are unreactive toward cross-coupling,[4] which led us to question whether it might be possible to similarly achieve high selectivity for a Heck reaction between organohalides and **1** under anhydrous conditions. In fact, as shown in Scheme 4, *p*-bromoacetophenone **9** readily coupled with **1** with to yield MIDA boronate **10** as a single regio and stereoisomer.

The oxidative Heck reaction[22,7] provides a complementary opportunity to generate similar products from boronic acid rather than organohalide starting materials. For example, it has been demonstrated that tolylboronic acid and vinyl pinacol boronic ester can be effectively coupled using this reaction manifold.[7] The White catalyst (**11**)[23] was recently found to be a powerful and highly selective promoter of oxidative Heck reactions with a wide range of aryl and alkenyl boranes.[24] We found that **11** also promotes the oxidative coupling of **1** and phenylboronic acid to yield styrenyl MIDA boronate **12** as a single regio and stereoisomer. Importantly, products **10** and **12** retain the capacity for subsequent cross-coupling via the MIDA boronate-masked boronic acid. In this way, **1** represents a new type of bifunctional MIDA boronate building block, rich with potential for a variety of iterative cross-coupling based applications.



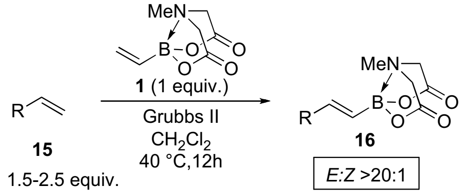
Scheme 4.

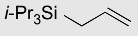
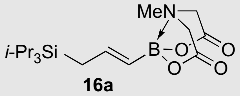
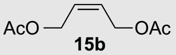
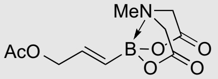
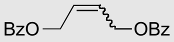
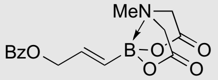
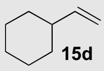
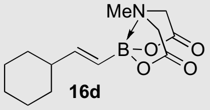
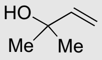
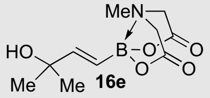
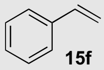
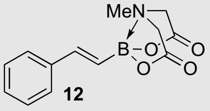
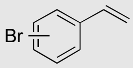
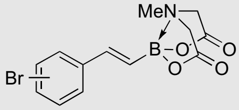
The cross-metathesis of terminal olefins developed by Grubbs and co-workers with vinyl or propenyl pinacol boronic esters[8] represents a powerful approach for the preparation of alkenyl boranes with many advantages over conventional methods, including the use of readily available and chemically robust terminal olefins as starting materials, excellent functional group compatibility, and generally good yields and stereoselectivities. However, there are some important limitations of this method, including instabilities of many alkenyl pinacol boronic esters to long-term storage and/or silica gel chromatography,[8b] and suboptimal *E*:*Z* ratios for cross-metathesis with some important olefin classes, including unfunctionalized terminal olefins.[8b]

Given that alkenyl MIDA boronates are invariably stable to benchtop storage under air and chromatography,[4] we were attracted to the use of **1** as an alternative vinyl borane for cross-metathesis applications. Moreover, we hypothesized that the sterically bulky nature of the MIDA boronate group would cause **1** to behave like a type III olefin[25] (analogous to *tert*-butylethylene), thereby avoiding any homodimerization and providing high yields and stereoselectivities with many classes of alkenes. Our initial experiments indicated that this approach was very promising. For example, as shown in Scheme 4, cross-metathesis between **1** and unfunctionalized terminal olefin **13** generated the corresponding octenyl MIDA boronate **14** as an air- and chromatographically stable crystalline solid in good yield and with a >20:1 *E*:*Z* ratio (the *Z* isomer was not observed by ^{1}H NMR). A similar cross-metathesis reaction using propenyl pinacol boronic ester has been reported to proceed with only a 9:1 *E*:*Z* ratio.[8b] Moreover, the alkenyl pinacol boronic ester products are somewhat unstable to silica gel chromatography.[8b]

Encouraged by the exceptional yield and stereoselectivity observed for the preparation of **14**, we decided to preliminarily explore the scope of the cross-metathesis with **1**. As shown in Table 2, this reaction is in fact highly effective with a range of olefin

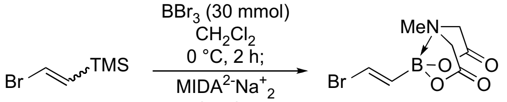
Table 2



Entry	Cross partner	Cross Product	Isolated yield (%)
1	 **15a**	 **16a**	85
2	 **15b**	 **16b**	84
3	 **15c** (*E*:*Z*1:1)	 **16c**	98
4	 **15d**	 **16d**	96
5	 **15e**	 **16e**	94
6	 **15f**	 **12**	93
7 8 9	 **15g** (*ortho*) **15h** (*meta*) **15i** (*para*)	 **16g** (*ortho*) **16h** (*meta*) **16i** (*para*)	81 91 89

substrates, invariably providing the corresponding alkenyl MIDA boronates in good to excellent yields and outstanding stereoselectivities (all >20:1, i.e., *Z* isomers were not observed by ^{1}H NMR). Specifically, cross-metathesis with allyltriisopropylsilane (entry 1) and a pair of 2-butenediol derivatives (entries 2–3) were all highly effective, yielding a new collection of potentially bifunctional MIDA boronate building blocks **16a–16c**. As is common with many cross-metathesis reactions,[8,25] increased substitution at the allylic position was also well tolerated (entries 4 and 5) and styrene derivatives proved to be excellent substrates (entries 6–9). Specifically, all the regioisomers of bromostyrene were successfully employed to yield a series of halo MIDA boronates **16g–16i** (entries 7–9), which represent excellent building blocks for iterative cross-coupling applications.[4a] Moreover, given that alkenyl MIDA boronates can be readily converted into the corresponding boronic acids under mild conditions (NaOH/THF or $NaHCO_3$/MeOH)[4] or used directly as cross-coupling partners under aqueous basic Suzuki–Miyaura conditions,[26,4b,c] cross-metathesis with **1** represents an excellent entry into these valuable building blocks for synthesis.

Finally, given the successful synthesis of **1** via trapping of an intermediate dibromoborane with $MIDA^{2-}Na^{+}{}_2$, we questioned whether it might be possible to develop a more operationally convenient synthesis of the very versatile building block *trans*-(2-bromovinyl) MIDA boronate **2**[4b,27] from the readily available silane **17**[28] (Scheme 5). Although **17** is typically prepared (or purchased) as a mixture of *E* and *Z* isomers, it has been previously observed that transmetalation of *Z*-alkenyl silanes with BBr_3 yields predominantly the corresponding *E*-alkenyl boranes (*E*:*Z* ~9:1).[10g] Fortuitously, we found that transmetalation of **17** (*E*:*Z* 9:1) with BBr_3 at 0 °C followed by trapping with $MIDA^{2-}Na^{+}{}_2$ yields *trans*-(2-bromovinyl) MIDA boronate **2** as a single stereoisomer (Scheme 5).[29] We have run this reaction on 30 mmol scale to prepare 4.8 g of **2** in a single step. Although the overall yield for this new procedure is comparable to that previously reported,[4b] this protocol is much more convenient,[27] providing scalable access to this very versatile building block.



17 (*E*:*Z* 9:1)

2 (*E* only)
4.8 g, 18.3 mmol, 61%

Scheme 5.

3. Summary and conclusions

Iterative cross-coupling represents a potentially general strategy for the simple, efficient, and flexible construction of a wide range of small molecules, and the many enabling features of MIDA boronates make them particularly useful for this type of synthesis. In this report, we demonstrate that vinyl MIDA boronate **1** is a readily accessible and highly versatile building block with a range of potential applications. Its synthesis can be readily achieved on the multigram scale from vinyltrimethylsilane, BBr_3, and $MIDA^{2-}Na^{+}{}_2$. Obviating a boronic acid intermediate, this procedure has the potential to provide access to a wide range of MIDA boronates for which the corresponding boronic acids are unstable and/or difficult to prepare. In addition, the compatibility of this protocol with organohalides makes it particularly attractive as a convenient way to access a variety of halo MIDA boronates (e.g., **2**, Scheme 5).

We further demonstrate that **1** has broad potential utility as a starting material for the preparation of many types of interesting MIDA boronate building blocks, including cyclopropyl and oxiranyl derivatives. Compatibility with the Heck and oxidative Heck-type reactions opens opportunities for new types of iterative cross-coupling sequences. Finally, cross-metathesis reactions with **1** proceed in high yields and outstanding stereoselectivities for a broad range of alkenes, thereby providing a very convenient and accessible new route to alkenyl MIDA boronates. Importantly, MIDA boronates can be readily converted into the corresponding boronic acids using mild conditions (1 M aq NaOH/THF or saturated aq $NaHCO_3$/MeOH), or used directly in the Suzuki–Miyaura reaction under aqueous basic conditions.[26,4b,c]

As demonstrated herein, concerted efforts to substantially expand the available pool of MIDA boronate building blocks and enable their highly efficient iterative coupling are currently underway in our laboratories. As a result of our preliminary studies in this area, a large collection of MIDA boronates are now commercially available, including **1** and **2**.[13,30] Collectively, this program aims ultimately to advance the iterative cross-coupling strategy into a simple, general, and automated process for the laboratory construction of small molecules.

4. Experimental

4.1. Materials

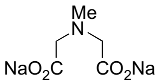
Commercial reagents were purchased from Sigma–Aldrich, Fisher Scientific, Alfa Aesar, TCI America, or Frontier Scientific, and were used without further purification unless otherwise noted. Solvents were purified via passage through packed columns as described by Pangborn and co-workers[31] (THF, Et_2O, 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. Triethylamine, diisopropylamine, diethylamine, pyridine, 2,6-lutidine, and ethanol were freshly distilled under an atmosphere of nitrogen from CaH_2. Grubbs II catalyst (Aldrich 569747) and Quadrasil (Aldrich 680427) silica supported Ru scavenger kits [TA (Aldrich 679496), MTU (Aldrich 679518), MP (Aldrich 679526), and AP (Aldrich 679534)] were generous gifts from Sigma–Aldrich (Milwaukee, WI).

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. 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 F_{254} plates (0.25 mm). Compounds were visualized by exposure to a UV lamp (λ=254 nm), a glass chamber containing iodine, and/or a solution of $KMnO_4$, an acidic solution of *p*-anisaldehyde, or a solution of ceric ammonium molybdate (CAM) followed by brief heating using a Varitemp heat gun. MIDA boronates are compatible with standard silica gel chromatography,[32] including standard loading techniques. For this study, chromatography was performed on a Teledyne-Isco Combi-Flash R_f purification system using Merck silica gel grade 9385 (60 Å, 230–400 mesh). For loading, compounds were adsorbed onto Celite in vacuo from an acetone solution. Specifically, for a 1 g mixture of crude material the sample is dissolved in reagent grade acetone (25–50 mL) and to the flask is added Celite 545 Filter Aid (5–15 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. Purification was generally performed using a gradient of $Et_2O \rightarrow Et_2O/CH_3CN$ 3:2.

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 in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent ($CHCl_3$, δ=7.26; CD_2HCN, δ=1.93, center line; acetone-d_6 δ=2.04, 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, sept=septet, m=multiplet, br=broad, app=apparent), coupling constant (*J*) in hertz (Hz), and integration. ^{13}C NMR spectra were recorded at 23 °C on a Varian Unity 500. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent ($CDCl_3$, δ=77.0, center line; CD_3CN, δ=1.30, center line, acetone-d_6 δ=29.80, center line) or to added tetramethylsilane (δ=0.00). Carbons bearing boron substituents were not observed (quadrupolar relaxation). ^{11}B NMR were recorded using a General Electric GN300WB instrument and referenced to an external standard of ($BF_3 \cdot Et_2O$). 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. Infrared spectra were collected from a thin film on NaCl plates (a solution of each compound was placed on the salt plate and then evaporated to dryness) on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). X-ray crystallographic analyses of **1** and **8** were carried out by Dr. Scott Wilson and Mr. Heath Timmons at the University of Illinois George L. Clark X-ray facility.

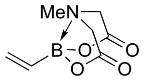


6

4.4. Dibasic sodium *N*-methyliminodiacetic acid (6)

Under ambient atmosphere, to a 500 mL round-bottom flask equipped with a stir bar was added water (300 mL), NaOH (120 g, 3.00 mol), and *N*-methyliminodiacetic acid (MIDA, 147 g, 1.00 mol). *CAUTION*: An exotherm was observed as the contents dissolved to form a clear, light yellow solution. The solution was concentrated to dryness in vacuo followed by addition of MeOH (300 mL). The MeOH solution was then heated to reflux and filtered while hot through a glass-fritted funnel. The reflux/filtration process was repeated twice. Residual solvent was removed via co-evaporation with MeCN (×3) and lyophilization overnight to yield **6** as a white powder (173 g, 91%).

^{1}H NMR (500 MHz, CD_3OD) δ 2.95 (s, 4H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 179.2, 63.7, 43.9. Elemental analysis: calculated 31.43% *C*, 3.69% *H*, 7.33% *N*. Found: 31.08% *C*, 3.54% *H*, 6.75% *N*.

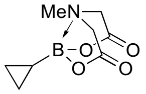


1

4.5. Vinyl MIDA boronate (1) (Scheme 2)

A 50 mL Schlenk flask equipped with a stir bar was charged with BBr_3 (1.0 M in CH_2Cl_2, 30 mmol) and the solution was cooled to 0 °C. To this solution was added dropwise vinyltrimethylsilane (4.49 mL, 31.5 mmol). The solution was maintained at 0 °C for 20 min and then was allowed to warm to 23 °C with stirring for an additional 2 h. The resulting solution was added dropwise via cannula to a suspension of sodium salt **6** (5.73 g, 30.0 mmol) in MeCN (50 mL) stirred at 0 °C. The rate of addition was controlled such that the internal temperature did not exceed 5 °C. Following the addition, the mixture was allowed to warm to 23 °C with stirring for 1 h. The resulting white suspension was filtered through a pad of Celite and the filter cake was extracted three times with acetone. To the orange filtrate was added Et_2O causing the crystallization of **1** as a colorless solid (4.74 g, 86%). This building block is now commercially available from Sigma–Aldrich (704415).

^{1}H NMR (500 MHz, acetone-d_6) δ 5.96 (dd, J=19.0, 13.5 Hz, 1H), 5.72–5.63 (m, 2H), 4.21 (d, J=17.0 Hz, 2H), 4.01 (d, J=17.0 Hz, 2H), 3.0 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 168.3, 128.7, 61.6, 46.7. HRMS (EI$^+$) calculated for $C_7H_{10}BNO_4$ (M)$^+$: 183.0703. Found: 183.0700. TLC (EtOAc) R_f=0.26, visualized by $KMnO_4$. IR (thin film, cm^{-1}) 3063, 2997, 2960, 1755, 1617, 1455, 1420, 1345, 1312, 1251, 1175, 1155, 1134, 1117, 1090, 1033, 987, 964, 951, 865.

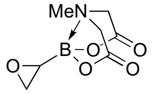


7

4.6. MIDA boronate 7

To a 100 mL Schlenk flask equipped with a stir bar was added vinyl MIDA boronate **1** (183 mg, 1.00 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), and THF (40 mL). The solution was cooled to 0 °C. To the solution was added dropwise diazomethane (0.3 M in Et_2O, 5 mmol, freshly prepared) and the resulting solution was stirred for 10 min. To the flask was added additional $Pd(OAc)_2$ (18 mg, 0.080 mmol) and diazomethane (0.3 M in Et_2O, 5 mmol). The solution was allowed to warm to 23 °C with stirring for 1 h. The solution was sparged with N_2 and was further quenched via the addition of glacial acetic acid (0.5 mL). The dark mixture was concentrated in vacuo and the resulting residue was purified via flash chromatography (SiO_2, Et_2O/CH_3CN) to yield **7** as a colorless crystalline solid (187 mg, 93%).

^{1}H NMR (500 MHz, CD_3CN) δ 3.92 (d, J=17.0 Hz, 2H), 3.80 (d, J=17.0 Hz, 2H), 2.98 (s, 3H), 0.46 (dq, J=9.5, 3.0 Hz, 2H), 0.12 (m, 2H), −0.33 (m, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.0, 62.7, 46.8, 1.2. ^{11}B NMR (96 MHz, CD_3CN) δ 13.2. HRMS (FAB$^+$) calculated for $C_8H_{13}BNO_4$ (M+H)$^+$: 198.0938. Found: 198.0937. IR (thin film, cm^{-1}) 2998, 1744, 1457, 1358, 1337, 2197, 1246, 1129, 1048, 985, 956, 892, 880, 845, 704.

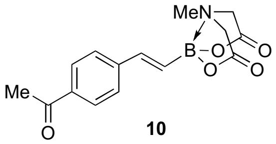


8

4.7. MIDA boronate 8

A 50 mL Schlenk flask equipped with a stir bar was charged with vinyl MIDA boronate **1** (183 mg, 1.00 mmol) and CH_2Cl_2 (20 mL) and the resulting suspension was cooled to 0 °C. To this suspension was added in one portion solid 3-chloroperbenzoic acid (77% mCPBA, 713 mg, 3.18 mmol). The mixture was allowed to warm to 23 °C with stirring for 18 h. The mixture was poured into a separatory funnel charged with satd aq $NaHCO_3$ (10 mL) and the mixture was diluted with EtOAc (40 mL). The mixture was shaken and the phases were separated. The aqueous phase was extracted with EtOAc (2×40 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified via flash chromatography (SiO_2, $Et_2O \rightarrow Et_2O/CH_3CN$ 3:2) to yield **8** as a colorless crystalline solid (147 mg, 74%).

^{1}H NMR (500 MHz, acetone-d_6) δ 4.29 (d, J=17.0 Hz, 1H), 4.21 (d, J=17.0 Hz, 1H), 4.13 (d, J=17.0 Hz, 1H), 3.93 (d, J=17.0 Hz, 1H), 3.27 (s, 3H), 2.76 (dd, J=6.0, 5.0 Hz, 1H), 2.56 (dd, J=6.5, 3.5 Hz, 1H), 2.24 (t, J=4.0 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.4, 168.1, 62.9, 62.7, 46.8, 44.9. HRMS (EI$^+$) calculated for $C_7H_{10}BNO_5$ (M)$^+$: 199.0652. Found: 199.0570. TLC (EtOAc) R_f=0.25, visualized by $KMnO_4$.

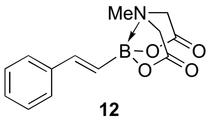


10

4.8. MIDA boronate 10

In a glove box, to a 20 mL vial equipped with a stir bar was added vinyl MIDA boronate **1** (183 mg, 1.00 mmol), 4-bromoacetophenone (198 mg, 1.00 mmol), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol), Ag_3PO_4 (838 mg, 2.00 mmol), and THF (5 mL). The vial was sealed with a PTFE-lined cap, removed from the glove box, and maintained in a 100 °C oil bath with stirring for 24 h. The mixture was concentrated in vacuo and the resulting residue was purified via flash chromatography (SiO_2, Et_2O/MeCN) to yield **10** as a colorless, crystalline solid (193 mg, 64%).

^{1}H NMR (500 MHz, acetone-d_6) δ 7.97 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.5 Hz, 2H), 7.03 (d, J=18.0 Hz, 1H), 6.55 (d, J=18.0 Hz, 1H), 4.29 (d, J=17.0 Hz, 2H), 4.12 (d, J=17.0 Hz, 2H), 3.09 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 197.3, 169.0, 143.4, 141.7, 137.3, 129.4, 127.5, 62.4, 47.4, 26.6. HRMS (EI$^+$) calculated for $C_7H_{10}BNO_4$ (M)$^+$: 301.1122. Found: 301.1126.



12

4.9. MIDA boronate 12

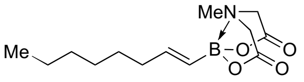
Under ambient atmosphere, to a 7 mL vial equipped with a stir bar was added vinyl MIDA boronate **1** (183 mg, 1.00 mmol), phenylboronic acid (305 mg, 2.50 mmol), 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (White catalyst, 25 mg, 0.050 mmol), benzoquinone (216 mg, 2.00 mmol), glacial acetic acid (0.23 mL, 4.0 mmol), and dioxane (3.0 mL). The vial was sealed with a PTFE-lined cap and maintained in a 45 °C oil bath for 48 h. The solution was concentrated in vacuo and the resulting residue was purified via flash chromatography (SiO_2, Et_2O/CH_3CN) to yield **12** as a colorless, crystalline solid (183 mg, 68%).

^1H NMR (500 MHz, acetone-d_6) δ 7.51 (d, J=9.0 Hz, 2H), 7.33 (m, 3H), 6.94 (d, J=18.0 Hz, 1H), 6.35 (d, J=18.5 Hz, 1H), 4.25 (d, J=17.0 Hz, 2H), 4.07 (d, J=17.0 Hz, 2H), 3.05 (s, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ 169.6, 143.3, 139.0, 129.5, 129.0, 127.6, 62.3, 47.6. HRMS (EI^+) calculated for $C_{13}H_{14}BNO_4$ $(M)^+$: 259.1016. Found: 259.1017.

^{13}C NMR (125 MHz, acetone-d_6) δ 169.2, 142.9, 139.3, 129.4, 128.8, 127.5, 62.4, 47.5.

4.10. General procedure for olefin cross-metathesis with boronate ester 1

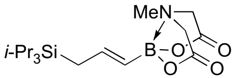
In a glove box, to a 25 mL Schlenk flask equipped with a stir bar was added vinyl MIDA boronate **1** (183 mg, 1.00 mmol), Grubbs II catalyst (85 mg, 0.10 mmol) and olefin (1.50–2.50 mmol). The flask was sealed with a septum and removed from the glove box. To the flask was added CH_2Cl_2 (10 mL). The flask was fitted with a water-cooled reflux condenser and the reaction was heated to reflux with stirring for 24 h. The mixture was cooled to 23 °C and to the mixture was added 400 mg of Quadrasil (TA, MTU, or AP) silica supported metal scavenger (Sigma–Aldrich), which caused significant decolorization. The mixture was stirred for 15 min and was then concentrated in vacuo. The resulting residue was purified via flash chromatography (SiO_2, $Et_2O \rightarrow Et_2O/CH_3CN$ 3:2). The products were thus obtained as colorless, crystalline solids. Some of the purified alkenyl MIDA boronate products contained small amounts of styrenyl MIDA boronate (**12**), presumably derived from reactions with the initial catalyst complex.



14

4.11. MIDA boronate 14

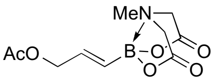
The general procedure was followed using 1-octene (280 mg, 2.50 mmol) to yield **14** (214 mg, 80%). ^1H NMR (500 MHz, acetone-d_6) δ 6.07 (dt, J=17.5, 6.5 Hz, 1H), 5.46 (d, J=17.5 Hz 1H), 4.16 (d, J=17.0 Hz, 2H), 3.97 (d, J=17.0 Hz, 2H), 2.97 (s, 3H), 2.10 (q, J=7.0 Hz, 2H), 1.40 (m, 2H), 1.29 (m, 6H), 0.86 (t, J=5.0 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.0, 146.0, 62.1, 47.3, 36.1, 32.4, 32.2, 30.5, 23.2, 14.3. HRMS (EI^+) calculated for $C_{13}H_{22}O_4NB$ $(M)^+$: 267.1642. Found: 267.1644.



16a

4.12. MIDA boronate 16a

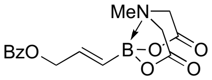
The general procedure was followed using allyltriisopropylsilane (496 mg, 2.50 mmol) to yield **16a** (299 mg, 85%). ^1H NMR (500 MHz, acetone-d_6) δ 6.19 (dt, J=17.5, 8 Hz, 1H), 5.38 (d, J=17.5 Hz, 1H), 4.15 (d, J=17.0 Hz, 2H), 3.93 (d, J=17.0 Hz, 2H), 2.97 (s, 3H), 1.78 (dd, J=10.0, 1.0 Hz, 2H), 1.07 (s, 18H), 1.07 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.1, 143.2, 62.3, 47.2, 20.2, 19.0, 11.7. HRMS (EI^+) calculated for $C_{17}H_{32}O_4NSiB$ $(M)^+$: 353.2194. Found: 353.2193.



16b

4.13. Boronate ester 16b

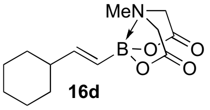
The general procedure was followed using *cis*-1,4-diacetoxy-2-butene (431 mg, 2.50 mmol) to yield **16b** (213 mg, 84%). ^1H NMR (500 MHz, acetone-d_6) δ 6.12 (dt, J=17.5, 5.0 Hz, 1H), 5.76 (dt, J=18.0, 1.5 Hz, 1H), 4.58 (dd, J=5.0, 1.5 Hz, 2H), 4.21 (d, J=17.0 Hz, 2H), 4.02 (d, J=17.0 Hz, 2H), 2.99 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 170.6, 168.9, 139.8, 66.3, 62.3, 47.4, 20.7. HRMS (EI^+) calculated for $C_{10}H_{14}O_6NB$ $(M)^+$: 255.09142. Found: 255.09137.



16c

4.14. MIDA boronate 16c

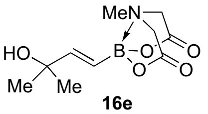
The general procedure was followed using 1,4-dibenzoyloxy-2-butene (E:Z ~1:1, 444 mg, 1.50 mmol) to yield **16c** (310 mg, 98%). ^1H NMR (500 MHz, acetone-d_6) δ 8.05 (d, J=8.5 Hz, 2H), 7.63 (tt, J=7.0, 1.5 Hz, 1H), 7.51 (t, J=7.5 Hz, 2H), 6.28 (dt, J=18.0, 5.0 Hz, 1H), 5.90 (dt, J=16.0, 1.5 Hz, 1H), 4.87 (dd, J=4.5, 1.0 Hz, 2H), 4.23 (d, J=17.0 Hz, 2H), 4.04 (d, J=17.0 Hz, 2H), 3.01 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.0, 166.4, 139.0, 133.9, 131.2, 130.2, 129.4, 66.9, 62.3, 47.4. HRMS (EI^+) calculated for $C_{15}H_{16}O_6NB$ $(M)^+$: 317.10707. Found: 317.10738.



16d

4.15. MIDA boronate 16d

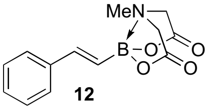
The general procedure was followed using vinylcyclohexane (165 mg, 1.50 mmol) to yield **16d** (253 mg, 96%). ^1H NMR (500 MHz, acetone-d_6) δ 6.03 (dd, J=18.0, 6.5 Hz, 1H), 5.42 (dd, J=18.0, 1.5 Hz, 1H), 4.17 (d, J=17.0 Hz, 2H), 3.97 (d, J=17.0 Hz, 2H), 2.96 (s, 3H), 1.99 (m, 1H), 1.71 (m, 4H), 1.62 (m, 1H), 1.28 (m, 2H), 1.20–1.05 (m, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.1, 151.4, 62.1, 47.3, 43.7, 43.2, 33.2, 26.8. HRMS (EI^+) calculated for $C_{13}H_{20}O_4NB$ $(M)^+$: 265.1485. Found: 265.1488.



16e

4.16. MIDA boronate 16e

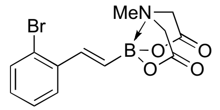
The general procedure was followed using 2-methylbut-3-en-2-ol (215 mg, 2.50 mmol) to yield **16e** (227 mg, 94%). ^1H NMR (500 MHz, acetone-d_6) δ 6.22 (d, J=18.0 Hz, 1H), 5.63 (d, J=18.0 Hz, 1H), 4.18 (d, J=17.0 Hz, 2H), 3.98 (d, J=17.0 Hz, 2H), 3.46 (s, 1H), 2.97 (s, 3H), 1.23 (s, 6H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.2, 153.7, 71.1, 62.1, 47.3, 30.6.



12

4.17. MIDA boronate 12

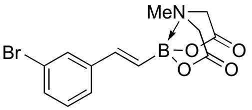
The general procedure was followed using styrene (260 mg, 2.50 mmol) to yield **12** (240 mg, 93%). For characterization of **12**, see above.



16g

4.18. MIDA boronate 16g

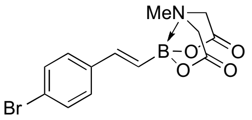
The general procedure was followed using 2-bromostyrene (275 mg, 1.50 mmol) to yield **16g** (274 mg, 81%). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.73 (dd, J=7.5, 1.5 Hz, 1H), 7.59 (dd, J=8.0, 1.0 Hz, 1H), 7.36 (t, J=7.5 Hz, 1H), 7.29 (d, J=18.0 Hz, 1H), 7.20 (td, J=7.5, 1.5 Hz, 1H), 6.36 (d, J=18.0 Hz, 1H), 4.29 (d, J=17.0 Hz, 2H), 4.11 (d, J=17.0 Hz, 2H), 3.09 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.0, 140.9, 138.8, 133.7, 130.3, 128.6, 128.3, 124.1, 62.4, 47.5. HRMS (EI$^+$) calculated for $C_{13}H_{13}O_4NBrB$ (M$^+$): 337.0121. Found: 337.0124.



16h

4.19. MIDA boronate 16h

The general procedure was followed using 3-bromostyrene (275 mg, 1.50 mmol) to yield **16h** (305 mg, 91%). For characterization of **16h** see Ref. 4a.

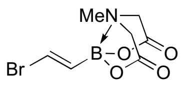


16i

4.20. MIDA boronate 16i

The general procedure was followed using 4-bromostyrene (275 mg, 1.50 mmol) to yield **16i** (240 mg, 93%).

^{1}H NMR (500 MHz, acetone-d_6) δ 7.52 (d, J=8.5 Hz, 2H), 7.47 (d, J=8.5 Hz, 2H), 6.91 (d, J=18.0 Hz, 1H), 6.39 (d, J=18.0 Hz, 1H), 4.26 (d, J=17.0 Hz, 2H), 4.08 (d, J=17.0 Hz, 2H), 3.06 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6) δ 169.1, 141.4, 138.3, 132.3, 129.2, 121.9, 62.3, 47.4. HRMS (EI$^+$) calculated for $C_{13}H_{13}O_4NBrB$ (M$^+$): 337.0121. Found: 337.0119.



2

4.21. MIDA boronate 2

To a 500 mL Schlenk flask equipped a stir bar was added BBr_3 (1.0 M in CH_2Cl_2, 30 mmol) and CH_2Cl_2 (270 mL) and the solution was cooled to 0 °C. To the solution was added dropwise 2-bromovinyltrimethylsilane (5.0 mL, 33 mmol). The stirred solution was maintained at 0 °C for 3 h and then added dropwise via cannula to a mixture of sodium salt **6** (10.0 g, 52.3 mmol) in MeCN (300 mL) stirred at 0 °C. The rate of addition was controlled such that the internal temperature did not exceed 5 °C. Following the addition, the mixture was stirred at 0 °C for 30 min and was then filtered through a fine glass-fritted funnel. The filter cake was extracted with acetone. The filtrate was concentrated in vacuo and the resulting residue was purified via flash chromatography (SiO_2, $Et_2O \rightarrow Et_2O$/MeCN 65:45) to yield **2** as a colorless, crystalline solid (4.79 g, 60%). For characterization of **2** see Ref. 4b. This building block is now commercially available from Sigma–Aldrich (703478).

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