# A Mild and Simple Method for Making MIDA Boronates

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**Abstract:** The use of methyliminodiacetic acid (MIDA) boronates as protected boronic acids has broadly enabled the automatable lego-like synthesis of many different types small organic molecules and materials. However, many MIDA boronate building blocks remain challenging to access. This is because the current best approach for making them is harsh and operationally complex, which limits both the types of boronic acids that can be employed and the types of people that can do it. Specifically, the current approach involves condensing a boronic acid and MIDA with concomitant removal of two equivalents of water at 110 °C using a specialized Dean-Stark apparatus. To improve and democratize this process, we found that a pre-dried form of MIDA, MIDA anhydride **1**, can serve as both the reagent and *in situ* desiccant to promote a mild and simple MIDA boronate synthesis procedure that is much more effective with a range of sensitive boronic acid substrates. Leveraging the unique solubility and chromatographic profile of MIDA boronates and the operational simplicity of this approach, we have further developed a "MIDA Boronate Maker Kit" which only requires heating and centrifugation equipment that is widely available in many labs not specialized in organic synthesis.

Methyliminodiacetic acid (MIDA) boronates are bench stable building blocks[1] that have found widespread use, in automated lego-like small molecule synthesis,[2] including synthesis of many different types of natural products[3] and drug candidates[4] for a range of biological targets which include cancer[3a,4l,m] Parkinson's disease,[4n] fibrosis,[4g] bacterial infections,[3c] and HIV[4j], polymer science,[5] preparation of complex boronic acids,[6] ligands for characterization of approved pharmaceutical ingredients,[7] liquid crystal technology,[8] and numerous other applications.[9] However, access to many MIDA boronates remains limited by the harsh and complex method that is typically used to make them. Specifically, the most widely used procedure involving condensation of a boronic acid with the diacid MIDA, requires the use of high temperatures and a Dean-Stark apparatus to remove two equivalents of water and thus drive the reaction forward. These harsh acidic conditions can lead to competitive protodeboronation[10] and are thus incompatible with many types of boronic acids.[11] Moreover, the specialized glassware and nature of this procedure limits its accessibility to only those labs that specialize in organic synthesis.[11] To overcome both of these limitations, we sought a new method for making MIDA boronates that is milder and simpler.

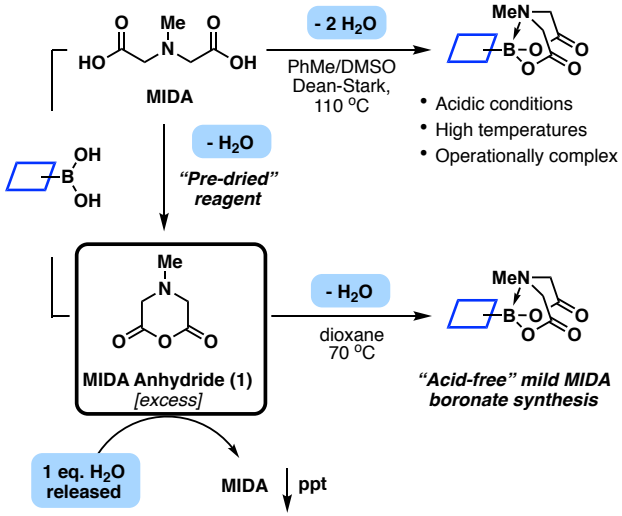
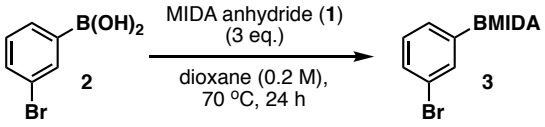



**Figure 1.** Sensitive boronic acid building blocks are incompatible with the harsh conditions for dehydrative MIDA boronate synthesis. The pre-dried reagent MIDA anhydride **1** pre-loads one of the two required dehydrations and acts as an *in situ* desiccant rendering MIDA boronate synthesis mild and simple.

We hypothesized that a pre-dried form of MIDA, MIDA anhydride (**1**),[12] could act as both a source of the MIDA ligand and an internal desiccant to promote the conversion of boronic acids to MIDA boronates (**Figure 1**). If **1** were to be used in excess, we reasoned that the only byproduct generated would be a single equivalent of MIDA, which might be selectively precipitated depending on the solvent used. Such a procedure could significantly reduce acid-mediated decomposition pathways and render MIDA boronate synthesis both mild and simple.

After a series of exploratory studies with model bifunctional haloboronic acid **2,** we found that 3 equivalents of MIDA anhydride in dioxane at 70 °C for 24 h led to formation of the desired MIDA boronate **3** in excellent yield (**Figure 2**, entry 1). With this substrate, the same yield was achieved after only 3 h (entry 2). Two equivalents of **1** were also effective and provided modestly reduced yield (90%, entry 3). These complexations




| Entry | Deviation from Standard Conditions | Yield of **3** |
|---|---|---|
| 1 | none | >95% |
| 2 | 3 h | >95% |
| 3 | 2 eq. of **1** | 90% |
| 4 | RT | 30% |
| 5 | RT, 48 h | 66% |
| 6 | DMSO | >95% |
| 7 | DMF | >95% |
| 8 | MeCN | 91% |
| 9 | THF (65 °C) | 65% |

**Figure 2.** Deviation from standard conditions in the preparation of MIDA boronate **3** using MIDA anhydride **1** (0.5 mmol of **2**).

could also be run at room temperature, but longer reaction times were required to achieve good yields (entries 4 and 5). Other polar aprotic solvents such as DMSO, DMF, MeCN, and THF were also effective (entries 6-9). From all of these studies, we noted that the one equivalent of MIDA formed during this reaction was insoluble in dioxane. This solvent was thus chosen for further studies with more sensitive substrates to minimize the potential negative impact of the generated diacid.

We tested the effectiveness of this new method with the synthesis of MIDA boronates from sensitive boronic acids that are largely incompatible with the high temperature, acidic conditions associated with standard Dean-Stark complexations (**Figure 3**). Polyfluorinated boronic acids are notoriously sensitive to protodeboronation.[10c] Unsurprisingly, pentafluorophenylboronic

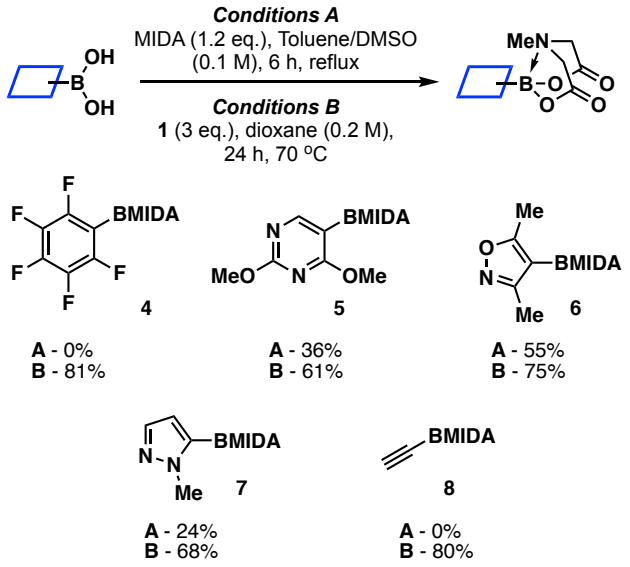



**Figure 3.** MIDA anhydride **1** enables direct preparation of bench stable MIDA boronates from sensitive boronic acids which decompose under Dean-Stark conditions.

acid was found to decompose and provided no yield of the targeted MIDA boronate when using the harsh Dean-Stark protocol. In contrast, using the mild and non-acidic MIDA anhydride method pentafluorophenyl MIDA boronate **4** was isolated in 81% yield.

Heterocyclic boronic acids are an important class of building blocks for the synthesis of pharmaceuticals and functional materials but they are also known to be susceptible to protodeboronation,[10a] requiring the development of highly specialized methods to access these challenging heterocyclic MIDA boronate building blocks.[11a] Using our mild MIDA anhydride protocol we were able to isolate pyrimidine **5**, isoxazole **6** and *N*-methylpyrazole **7** in substantially improved yields compared to the corresponding Dean-Stark complexations.

As a final demonstration of the enabling capacity of **1,** we targeted ethynyl MIDA boronate **8** as it has been shown to be a highly versatile bench stable equivalent of the exceptionally unstable ethynyl boronic acid.[11e, 13] The Dean-Stark approach previously proved to be ineffective, and the preparation of **8** required development an alternative highly specialized procedure.[11e] Using the mild conditions enabled by **1**, we developed a convenient process involving reaction of readily available ethynyl magnesium bromide and trimethylborate followed by hydrolysis mild aqueous acid,[14] and then treatment of the resulting solution with **1** under Conditions B to yield ethynyl MIDA boronate **8** in 80% yield (Fig. 3). Attempts to alternatively make **8** from the same intermediate using Dean-Stark conditions (Conditions A) gave a 0% yield.

As progress toward automated lego-like synthesis of small molecules continues to be made,[2,15] it will also be impactful to enable non-specialists in organic synthesis to access many different types of building blocks for specific projects. Notably, more than 14,000 boronic acids are currently commercially available. Thus, having demonstrated the superior capacity of this mild method to convert boronic acids into their MIDA boronate counterparts, we next sought to leverage the simplicity of this process to make it broadly accessible to non-specialists in organic synthesis.

Many labs that do not have rotary evaporators do have centrifuges. And many of those same labs have experience using kits, such as Qiagen® kits,[16] to prepare and purify DNA, RNA and other biological reagents. We thus sought to develop an analogous MIDA boronate maker kit that only requires standard heating and centrifugation equipment. Advantageously, MIDA boronates have a unique binary affinity for silica gel: they are minimally mobile in $Et_2O$ and rapidly eluted with THF, and this feature was previously harnessed to enable the automated iterative assembly of MIDA boronate building blocks.[2] Notably, Qiagen kits® use a related binary affinity of DNA for silica gel to easily extract DNA in pure form using a wash-elution-precipitation sequence and a centrifuge.[16] We accordingly developed a similar centrifuge-based method to simplify the purification of MIDA boronates (**Figure 4**).

Specifically, a crude reaction mixture from the complexation of **2** with **1** was poured into a prepacked silica gel centrifuge column containing hexane/$Et_2O$ (1:1). Centrifugation was used to remove the solvent and solubilized impurities while the MIDA boronate was caught on the silica gel in the cartridge and/or precipitated above (**Catch**).[17] The centrifuge column was then washed with $Et_2O$ and centrifuged three times to elute excess MIDA anhydride and residual boronic acid (**Wash**). Finally, we

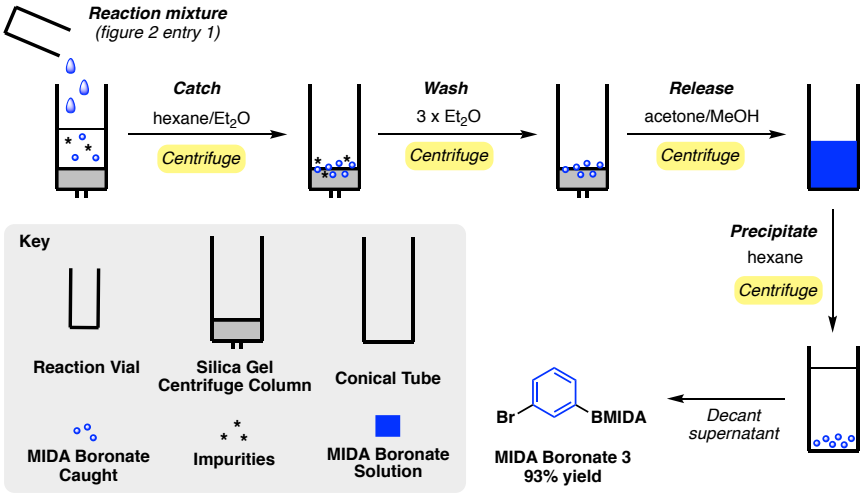



**Figure 4** Centrifuge purification of crude MIDA boronate **3** using a catch-release-precipitate protocol.

found that addition of 1% MeOH in acetone followed by centrifugation caused elution of a solution of the desired MIDA boronate (**Release**) [see Supplementary Figure 1]. To avoid any requirement for evaporation steps and thereby maximize the operational simplicity of this protocol, the product solution was then diluted with hexane causing precipitation of the desired MIDA boronate (**Precipitate**). Pelleting of the resultant precipitate by a final centrifugation step followed by decantation of the supernatant and air drying overnight afforded clean MIDA boronate product **3** in 93% isolated yield. Importantly, this approach to MIDA boronate purification uses only solvent transfers and centrifugation – rendering this procedure highly accessible to non-specialists in organic synthesis.

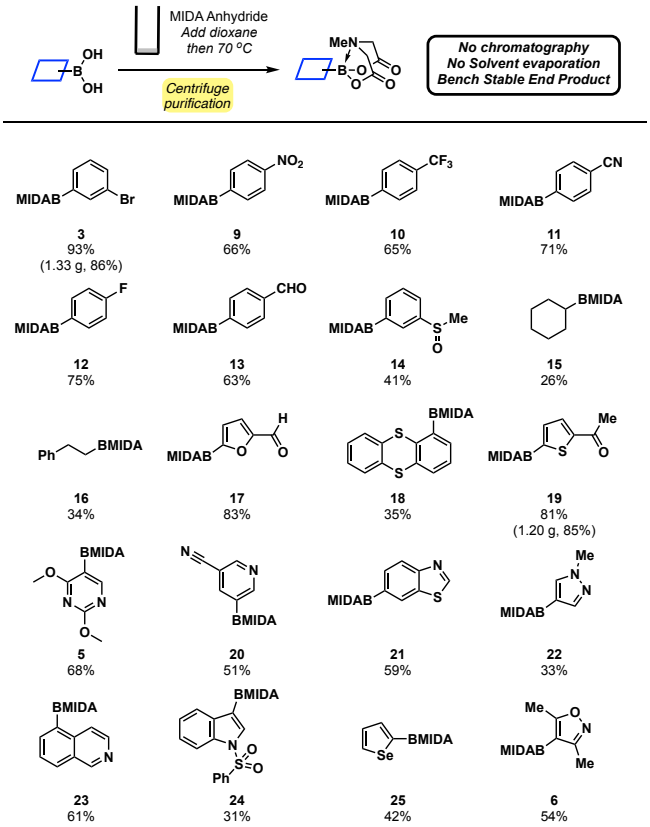



**Figure 5** Synthesis of MIDA boronates using MIDA anhydride with catch-release-precipitate centrifuge purification on a 0.5 mmol scale.

Leveraging the simplicity of this method and new purification process, we prepared a "MIDA Boronate Maker Kit" (**Figure 6**).[18] Using only these kits, a standard stirrer/hot plate, and a centrifuge, a wide range of structurally distinct boronic acids were readily transformed into their MIDA boronate counterparts in preparatively useful yields. The process involves mixing reagents and solvents, heating, and centrifuging per simple kit instructions (See Supporting Information).[18] The building blocks that were formed included a range of aryl (**3**, **9**-**13**), alkyl (**15**, **16**) and heterocyclic (**5**, **6**, **17**-**25**) MIDA boronates (**Figure 5**). This protocol was also easily scaled tenfold (5 mmol) to provide gram quantities of MIDA boronates **3** and **19**. Importantly, the same catch-release-precipitate approach to MIDA boronate isolation provided pure product regardless of the identity of the organic fragment attached to the MIDA boronate motif. This process also does not require any specialist-dependent synthetic manipulations such as aqueous workup, column chromatography, or rotary evaporation.

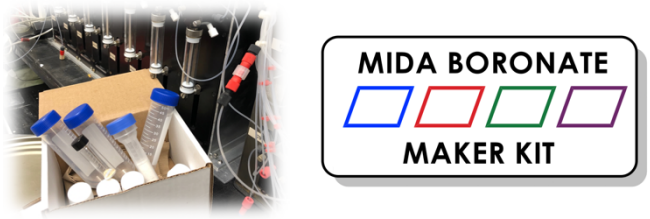



**Figure 6** The MIDA Boronate Maker Kit fits within a single 6"x4"x4" box and contains all the necessary components to synthesize and isolate a MIDA boronate from a boronic acid.

In summary, we have developed a mild and simple method for the synthesis of MIDA boronates. This process expands the scope of boronic acids that can be readily converted into their MIDA boronate counterparts. Moreover, we leveraged this new method to create a MIDA Boronate Maker Kit (**Figure 6**) which will empower non-specialists to more readily participate in the molecular innovation process.

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**Keywords:** boron • centrifuge purification • heterocycles • MIDA boronates • synthesis kit

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[12] MIDA Anhydride is available from Sigma Aldrich (734217). Alternatively, MIDA anhydride can be prepared from MIDA which is widely available for ~0.5$/g (OR-0737, Combi-Blocks). On a laboratory scale we have prepared >200 g of MIDA anhydride from MIDA using only the commodity chemicals acetic anhydride and pyridine, requiring only a crystallization for purification. See Supporting Information for details.

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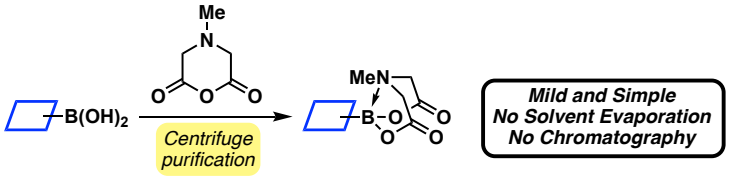
[17] During the catch step for some MIDA boronates varying degrees of precipitated MIDA boronate product remained on top of the silica gel column.

[18] See Supporting Information for the contents and step-by-step instructions for use of the MIDA Boronate Maker Kit.

## Entry for the Table of Contents




Existing methods for making MIDA boronates require harsh conditions and complex procedures to achieve dehydration. Here we disclose that a pre-dried form of MIDA, MIDA anhydride, acts as both a source of the MIDA ligand and an in situ desiccant to enable a mild and simple MIDA boronate synthesis procedure. This method expands the range of sensitive boronic acids that can be converted into their MIDA boronate counterparts. Further utilizing unique properties of MIDA boronates, we have developed a MIDA Boronate Maker Kit which enables the direct preparation and purification of MIDA boronates from boronic acids using only heating and centrifuge equipment that is widely available in labs that do not specialize in organic synthesis.

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