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Authors: Andrei K. Yudin, Aleksandra Holownia, Chieh-Hung Tien, Diego B Diaz, and Reed T Larson

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Carboxyboronate: A Versatile C1 Building Block

Aleksandra Holownia, Chieh-Hung Tien, Diego B. Diaz, Reed T. Larson and Andrei K. Yudin*

Abstract: The synthesis and applications of carboxy-MIDA-boronate, a novel C1 building block, are described. This molecule is accessible via a ruthenium tetraoxide-mediated cleavage of commercially available ethynyl-MIDA-boronate. In the course of this study, carboxy-MIDA-boronate was found to possess ambident reactivity towards nucleophiles. Carboxylic acid derivatization produces a broad range of previously unknown carbamoyl-, oxycarbo- and thiocarboboronates. Carboxy-MIDA-boronate and its derivatives undergo condensations to access borylated heterocycles with boron at positions that are difficult to access using alternate methods. The resulting heterocycles participate in the Suzuki-Miyaura cross-coupling reaction, enabling entry into diverse bis(heteroaryl) motifs. The carbon monoxide-releasing capacity of carboxy-MIDA-boronate was also examined and applied in palladium-catalyzed carbonylation.

Introduction

Functional groups (FGs) are defined as combinations of atoms with distinct chemical properties.[1] An *sp*^{2}-hybridized carbon atom bound to heteroatoms is a common constituent of FGs in organic chemistry. While it is tempting to assume that all possible frameworks bearing carbon and heteroatoms have been explored, the reality is far from it. To illustrate this point, we have considered combinations between *sp*^{2}-hybridized carbon and its neighbors from the periodic table. The connectivity maps identified in Figure 1a correspond to FGs that are present in hundreds of thousands of known molecules, whereas the ones depicted in Figure 1b have little precedent. Driven by finding new applications for boron in organic chemistry,[2] our interest has been to find synthetic solutions towards underappreciated and new FGs, such as those shown in Figure 1b, and explore their potential in synthesis. This manuscript outlines our efforts toward the carboxyboronate FG, a combination of the boronate and carboxylic acid functionalities.

In 1967, Malone and Parry isolated boranocarbonate (BH_3COONa_2).[3] Synthesis of this molecule was achieved through the generation of the pyrophoric H_3B–CO complex at low temperatures, followed by hydrolysis under strongly basic conditions.[4] In 1976, Spielvogel developed the synthesis of R_3NBH_2COOH in four steps from sodium cyanoborohydride.[5] Transformation of both boranocarbonate and carboxyborane to more synthetically useful boron analogues has not been realized. Later, Nozaki generated a five-membered diazaborole featuring the boron and carboxylic acid linkage from the corresponding boryllithium and carbon dioxide (CO_2) gas at low temperature and inert atmosphere.[6] Interestingly, Nozaki's derivative was prone to decomposition via the bora-Brook rearrangement, resulting in the formation of the corresponding hydroxyboron species.[7] Application of that derivative in synthesis has not been reported.

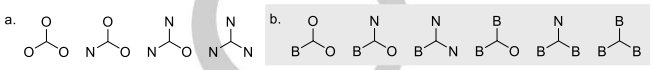

Figure 1. Connectivity maps of *sp*^{2}-hybridized carbon bound to 2nd row heteroatoms from the periodic table.

As part of an ongoing research effort in the area of ambident reactivity, we sought to exploit the hemilabile nature of the *N*-methyliminodiacetate (MIDA)[8,9] ligand in order to define new boron-based ambident FGs. In a recent report, we showed that hemilability enables boron to possess either nucleophilic or electrophilic character depending on the reaction conditions.[10] Herein, we demonstrate that by merging the MIDA boronate and carboxylic acid FGs we were able to generate a one carbon unit (C1) building block with ambident properties.

Results and Discussion

We initiated our studies by subjecting phenyl-MIDA-boronate to a modified RuO_4-mediated C-C bond cleavage (Table 1a, Entry 1).[11,12] Full conversion of the starting material was achieved within 30 minutes and a novel boron-containing species was observed. The resulting compound exhibited IR stretches at 3183 and 1703 cm^{-1}, a broad ^{1}H NMR chemical shift at 9.07 ppm, and a ^{11}B NMR chemical shift at 5.4 ppm,[13] consistent with carboxy-MIDA-boronate **1** (Table 1b). To improve on the initially low NMR yield of **1**, several commercially available MIDA boronates were screened, along with solvents and co-oxidants. Ethynyl MIDA boronate was found to deliver the desired product most efficiently (Entry 3). A simple work-up protocol provides **1** as a bench stable, white solid in 62% isolated yield. The reaction can be conducted up to an 11.0 mmol scale.

In order to demonstrate the synthetic potential of carboxy-MIDA-boronate, we evaluated its chemical reactivity. Studies were commenced by subjecting **1** to standard amide coupling conditions (Scheme 1a). The formation of carbamoylboronate **2a** was observed in an initially modest NMR yield of 54%. In addition to desired product **2a**, spectroscopic analysis revealed that a second boron-MIDA (BMIDA) containing species (**3**) was generated in 27% (Scheme 1b). When the reaction was repeated in the absence of amine, carboxy-MIDA-boronate was completely consumed and converted into the previously observed side-product **3**. Isolation and structural characterization by spectroscopic analysis (Scheme 1c) and X-ray crystallography

[a] A. Holownia, C. -H. Tien, D. B. Diaz, A. K. Yudin
Davenport Research Laboratories, Department of Chemistry
University of Toronto
80 St. George., Toronto, ON, M5S 3H6 (Canada)
E-mail: ayudin@chem.utoronto.ca
[b] R. T. Larson
Process Research & Development, MRL
Merck & Co
Kenilworth, NJ 07033, USA

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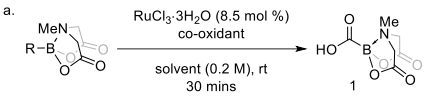
Table 1. a. Optimization of carboxy-MIDA-boronate (**1**) preparation; b. ^{1}H and ^{11}B NMR spectra of **1**.

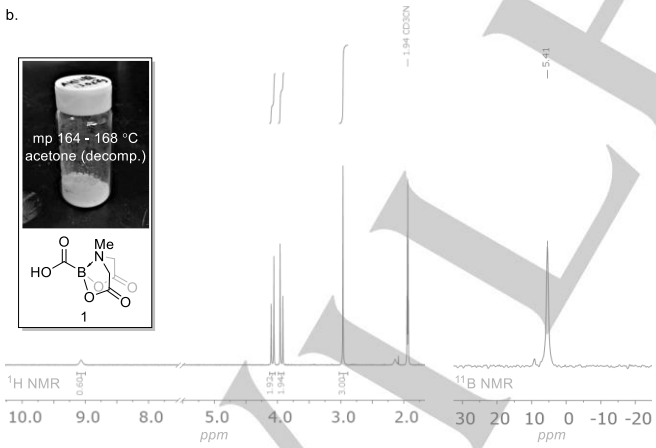
a.



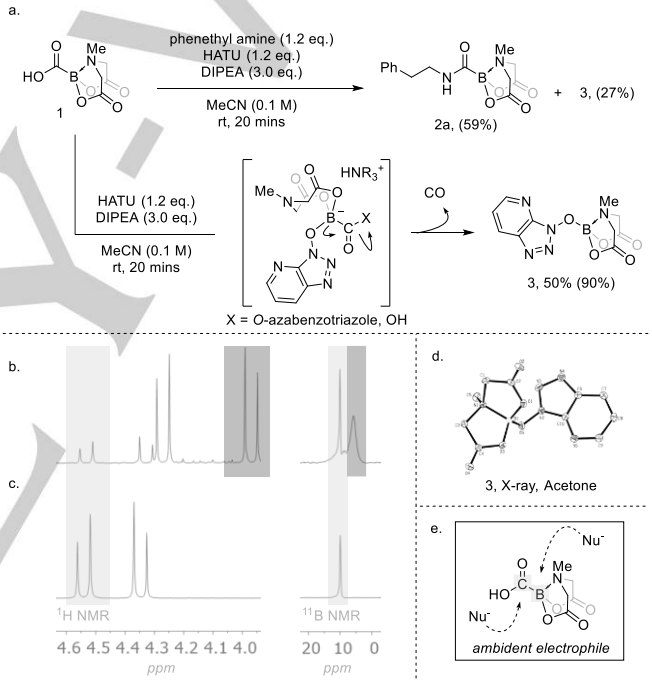
Entry[a]	R	Solvent	Co-oxidant	Yield (%)[b]
1[c]	phenyl	MeCN	H_5IO_6	42
2	vinyl	MeCN	H_5IO_6	31
3	ethynyl	MeCN	H_5IO_6	>95(62)[e]
4	ethynyl	MeCN	$NaIO_4$	NR
5	ethynyl	MeCN	$KHSO_5$	NR
6[d]	ethynyl	1:1 MeCN:H_2O	$NaIO_4$	trace
7[d]	ethynyl	1:1 MeCN:H_2O	H_5IO_6	trace
8[d]	ethynyl	9:1 MeCN:H_2O	H_5IO_6	82

[a] Reaction condition: MIDA boronate (0.1 mmol, 1.0 eq.) and co-oxidant (0.4 mmol, 4 eq.) were combined with solvent (0.2 M). $RuCl_3·3H_2O$ (8.5 mol %) was added and the reaction was stirred for 45 mins at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [c] 15.0 eq. of co-oxidant was used. [d] Reaction was stirred for 5 minutes. [e] Isolated yield. NR = no reaction. MeCN = acetonitrile.

b.



(Scheme 1d) confirmed the identity as B–O adduct **3**.[14] The identification of **3** suggests that during the reaction a BMIDA-containing intermediate undergoes a *C*-to-*O* migration to yield the corresponding *O*-borylated azabenzotriazole. To gain some insight into the mechanism of the migration, the headspace of the reaction was analyzed by gas chromatography-thermal conductivity detection (GC-TCD) and it was found that the generation of **3** is coupled with the release of carbon monoxide (CO) gas (see Supplementary Information for details). Based on the previous demonstration of BMIDA hemilability in the presence of nucleophiles, the formation of **3** is hypothesized to arise via an *O*-azabenzotriazole mediated displacement of the MIDA amine (Scheme 1a).[10,15] Overall, this result demonstrates that under HATU-mediated coupling conditions carboxy-MIDA-boronate displays ambident reactivity towards nucleophiles: **1** can generate products that contain nucleophiles bound at either the carbonyl or boron atom (Scheme 1e). In order to improve the reaction selectivity for **2**, several modifications to the standard condition were evaluated (see Supplementary Information for details). We found that decreasing the amount of *N,N*-diisopropylethylamine (DIPEA) to 2.0 equivalents and conducting the reaction at 0 °C suppressed the formation of 3 and generated **2a** in 94% NMR yield.



Scheme 1. a. Observation of *O*-borylated azabenzotriazole (**3**) byproduct suggests a *C*-to-*O* migration of the hemilabile BMIDA group; the reaction is coupled with CO release; b. Crude ^{1}H and ^{11}B NMR spectral analysis of HATU mediated coupling reveals two competing reactions: generation of **2a** (highlighted in dark grey) and **3** (highlighted in light grey); c. ^{1}H and ^{11}B NMR spectra of isolated **3**; d. X-ray crystal structure of **3**; e. Ambident reactivity of **1**. NMR yields in brackets. HATU = hexafluorophosphate azabenzotriazole tetramethyl uranium.

The optimized conditions were then used to generate a scope of carbamoylboronates (Scheme 2a). Electron-neutral and electron-rich aromatic amines were well tolerated (**2b**-**d**), while electron-poor aromatic amines led to an increased formation of **3**. Decreasing the equivalents of DIPEA to 1.0 and increasing the amount of *p*-chloroaniline to 3.0 equivalents minimized the formation of **3** and increased the overall yield to 80% (**2e**). Furthermore, we were successful in generating the primary carbamoylboronate (**2f**). Aliphatic primary and secondary amines

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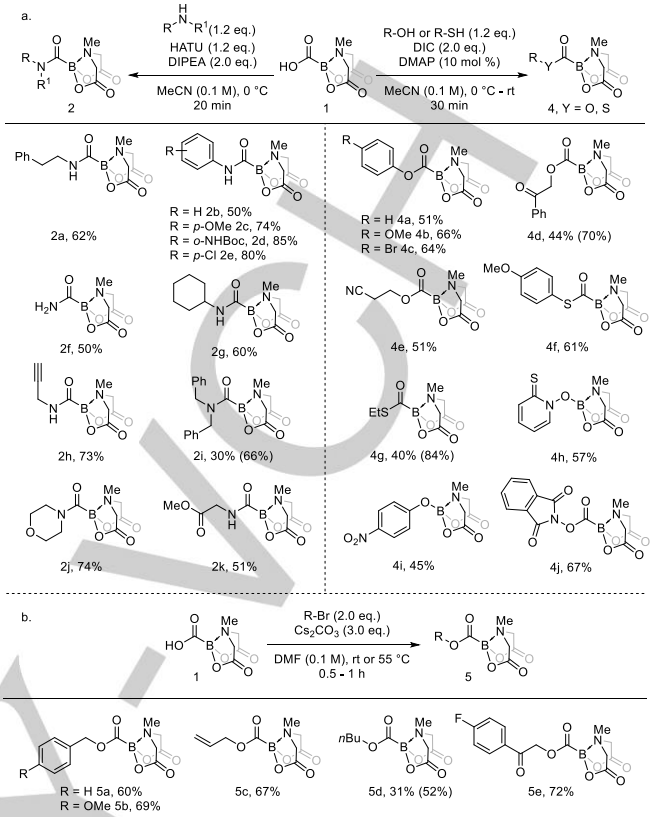
were also well tolerated (**2g**-**k**). This methodology was then applied to the synthesis of oxycarbo- and thiocarboboronate derivatives. Unfortunately, the HATU conditions were not ideal for the reaction and led to poor conversion. After screening a series of coupling agents, *N,N'*-diisopropylcarbodiimide (DIC) with 4-dimethylaminopyridine (DMAP) were found to cleanly deliver the desired compounds. Phenols containing electron-rich, neutral and poor groups transformed **1** into the desired oxycarboboronates in good yields (**4a**-**c**). Aliphatic alcohols were also tolerated (**4d**-**e**). Likewise, aromatic and aliphatic thiols provided the target thiocarboboronate derivatives (**4f**-**g**). Interestingly, under the standard reaction conditions, attempts to generate the Barton ester were unsuccessful. Instead, the reaction yielded borylated analogue **4h**, which is likely formed through a BMIDA *C*-to-*O* migration as previously described in Scheme 1a. Decreasing the equivalents of 2-mercaptopyridine *N*-oxide did not yield the desired oxycarboboronate.[16] This unusual reactivity was also observed between **1** and *p*-nitrophenol (**4i**). These results, coupled with the generation of **3** under HATU conditions, imply that the generation of highly activated derivatives of **1** might be enhancing the electrophilic character of boron, promoting boron migration. In contrast, the reaction with 1.0 eq. of *N*-hydroxylphthalimide led to isolation of **4j** in good yield.[17] The success of these transformations and stability of the coupled products led us to assess **1** in other carboxylic acid-based transformations (Scheme 2b). The cesium salt of **1** was generated in situ and further reacted with various alkyl bromides giving access to alkoxycarboboronates (**5a**-**5e**) in modest to good yields in 30 minutes to 1 hour.

Carboxy-MIDA-boronate and its derivatives were also amenable to condensation chemistry, yielding several borylated heterocycles in a regioselective fashion (Scheme 3). Borylated thiazole **7** was generated through a trans-thioesterification of **4f** to generate **6** in situ, followed by condensation to deliver product in 94% isolated yield (Scheme 3a). Borylated oxazole **8** was synthesized by a gold-catalyzed cyclization of **2h** and was isolated in 88% yield (Scheme 3b).[19] Oxadiazole **10a** and **10b** were obtained in 64% and 56% yield, respectively, from a one-pot *p*-toluenesulfonyl chloride (*p*-TsCl) mediated cyclization of the in situ generated **9** (Scheme 3c).[20] Synthesis of borylated imidazole **11** was achieved through a trifluoroacetic acid (TFA)-mediated deprotection of **2e**, followed by a heat-induced cyclization, delivering product in 34% yield (Scheme 3d). To obtain triazole **13**, carbamoylboronate **2g** was initially transformed into the corresponding thiocarbamoylboronate **12**. Compound **12** was subsequently subjected to a silver-promoted condensation reaction with formic hydrazide, leading to the generation of **13** in 54% isolated yield (Scheme 3e). Synthesis of thiadiazole **15** was accomplished in 40% yield through the in situ generation of **14**, followed by cyclization at room temperature (Scheme 3g). These examples highlight the capacity of carboxyboronate to yield a diverse array of heterocycles using straightforward and mild conditions.[21] In the process of these investigations, an X-ray crystal structure of **12** was obtained, thereby confirming that boron is bound to an sp^2-hybridized carbon (Scheme 3f).[22]



Scheme 2. a. Synthesis of carbamoylboronates[18] using HATU-mediated coupling conditions; synthesis of oxycarbo- and thiocarboboronates using DIC-mediated coupling; b. Synthesis of alkyloxycarboboronates via cesium salt of **1**. NMR yields in brackets. Compounds purified via silica-gel column chromatography. DMF = dimethylformamide.

Given the importance of bis(heterocyclic) frameworks in pharmaceutical targets and biologically relevant molecules,[23] we assessed the viability of the borylated heterocycles generated from **1** as partners in the Suzuki-Miyaura cross-coupling (SMCC) reaction.[24] It is well established that heteroatom-rich cycles are challenging substrates for cross-coupling.[25] Based on the number of heteroatoms present in our compounds and their proximity to boron,[26] we suspected that protodeboronation would pose a significant challenge. Previously developed techniques to attenuate decomposition of boronate intermediates during cross-coupling include the application of highly tuned catalysts[27] and the use of additives, such as copper salts.[9f,28] At the outset of our investigation, **7** was selected for the optimization of the SMCC reaction. Utilizing XPhos-G2-Palladacycle (XPhosPdG2) with $Cu(OAc)_2 \cdot H_2O$ as the stoichiometric additive, trace amounts of **16a** were detected by ^1H NMR (Table 2, Entry 1).[29] Changing the solvent mixture from MeCN to DMF led to an increase in yield (Entry 2), which is likely the result of the enhanced solubility of **7** in DMF. Replacing isopropyl alcohol (IPA) with *t*-amyl alcohol[30] gave a similar yield (Entry 3), while addition of water to the solvent mixture led to quantitative protodeboronation (Entry 4).

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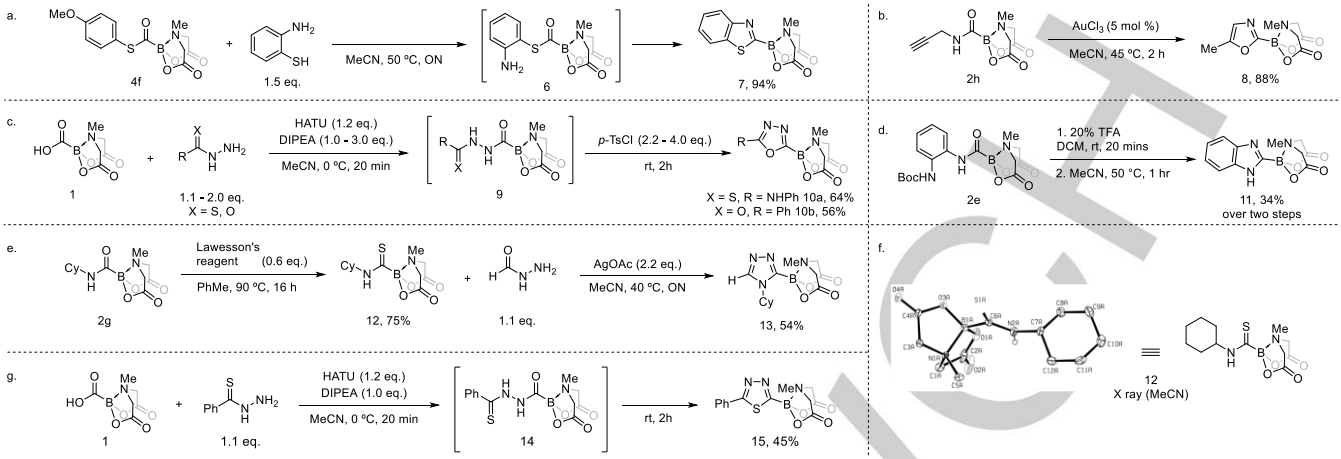
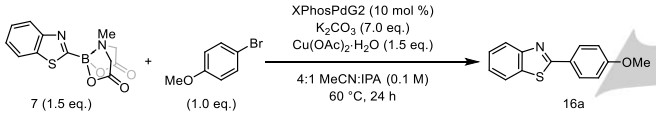


Scheme 3. a. Synthesis of 2-borylated benzothiazole **7** via trans-thioesterification of **4f** with 2-aminothiophenol; b. Gold-catalyzed formation of 2-borylated 1,3-oxazole **8** from **2h**; c. One-pot, two-step approach to borylated 1,3,4-oxadiazoles **10a** and **10b** from **1**; d. TFA-mediated deprotection of **2e**, followed by condensation yields imidazole **11**; e. Synthesis of triazole **13** via a Ag-promoted condensation between thiocarboboronate **12** and formic hydrazide; f. X-ray crystal structure of **12**; g. Synthesis of borylated thiadiazole **15** via the cyclization of intermediate **14**. PhMe = toluene.

Table 2. Optimization of the SMCC reaction of thiazole **7** with an arylbromide.



Entry[a]	Variation from Standard	Yield (%)[b]
1	None	trace
2	DMF instead of MeCN	15
3	4:1 DMF:*t*-Amyl-OH instead of 4:1 MeCN:IPA	15
4	4:1 DMF:H_2O instead of 4:1 MeCN:IPA	trace
5[c]	100 °C instead of 60 °C	51
6[d],[e]	CuCl instead of $Cu(OAc)_2·H_2O$	16
7[d],[e]	CuI instead of $Cu(OAc)_2·H_2O$	27
8[c],[e]	$Cu(OAc)_2$ instead of $Cu(OAc)_2·H_2O$	64
9[c],[e],[f]	5.0 eq. of K_2CO_3 instead of 7.0 eq.	65

[a] Reaction condition: MIDA boronate (0.05 mmol, 1.5 eq.), XPhosPdG2 (0.003 mmol, 10 mol %) and [Cu] (0.05 mmol, 1.5 eq.) were combined in a flame-dried 0.5-dram vial under nitrogen atmosphere. Solvent (0.1 M) was added followed by 4-bromoanisole (0.03 mmol, 1.0 eq.) and K_2CO_3 (0.21 mmol, 7.0 eq.). The reaction was capped and stirred for 24 h at 60 °C. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as internal standard. [c] Reactions were carried out in a 4:1 DMF:*t*-Amyl-OH solvent mixture. [d] Reactions were carried out in a 4:1 DMF:IPA solvent mixture. [e] Reactions were carried-out at 100 °C for 16 hours. [f] Reaction carried out with $Cu(OAc)_2$.

Increasing the temperature to 100°C significantly increased the yield and lowered the reaction time (Entry 5). $Cu(OAc)_2$ was found to be the most optimal additive (Entry 8), whereas other additives (Entry 6-7) led to depressed yields of formation of **16a**. In the absence of copper, the formation of **16a** was not observed and protodeboronation of **7** was significant (See Supplementary Information for details), which emphasizes the importance of copper in reducing the rate of protodeboronation.[9f,28] Product formation was likewise not detected when the pre-catalyst was removed (See Supplementary Information for details). Lastly, varying the amount of base in the reaction mixture had little impact on the reaction (Entry 9).

The optimized reaction conditions were utilized to explore the scope between the borylated heterocycles generated from **1** and challenging halide coupling partners (Scheme 4). Encouragingly, the methodology proved to be highly general among the heterocyclic boronates and aryl bromides selected. For example, **7** was successfully coupled with 2-bromopyridine, delivering product in 62% yield (**16b**). Oxazole **8** was coupled with electron-rich (**17a-c**) (het)aryl bromides in good yields. Oxadiazole **10b** and thiadiazole **15** were both efficiently coupled with 3-bromopyridine (**18a** and **20a**) and 5-bromopyrimidine (**18b** and **20b**). Imidazole **11** was coupled with 4-bromothiazole providing access to thiabendazole (Mintezol™), a commercially available antihelmintic agent. Overall, this strategy offers a complementary approach to existing methodologies because it allows coupling with substrates that would be difficult to achieve selectively under standard conditions.[31] For example, the aryl bromides utilized to obtain compounds **18b**, **19**, and **20b** have multiple sites of reactivity, which would limit selectivity under standard C–H activation conditions. We anticipate that application of the borylated heterocycles in the SMCC will enable the modular installation of a wide variety of privileged scaffolds[32] across diverse molecular architectures. A more comprehensive analysis and scope is currently underway in our laboratory.

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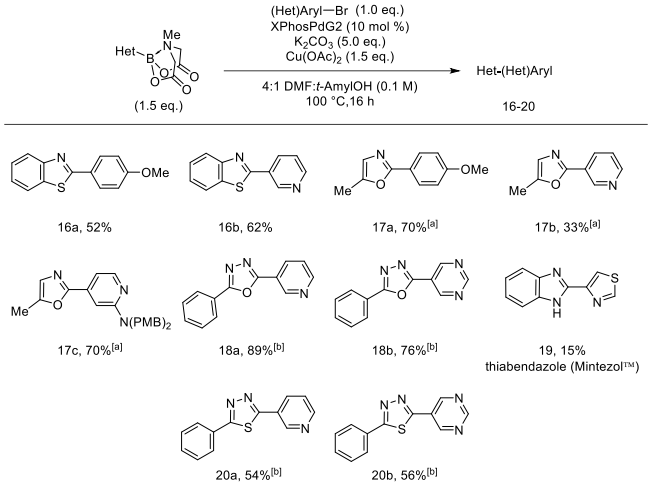
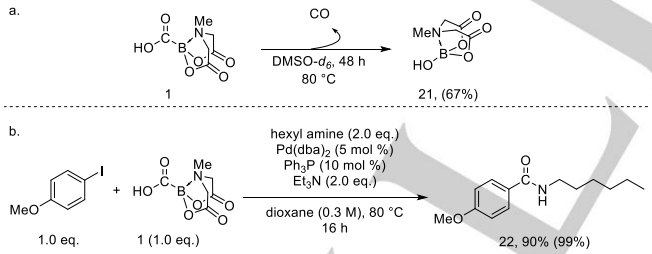


Scheme 4. Scope of the Pd-catalyzed SMCC of carboxy-MIDA-boronate-derived heterocycles. [a] CuCl (1.5 eq.) and 4:1 DMF:IPA were utilized. [b] 9:1DMF:*t*-amyl alcohol was used. Isolated yields.

Intrigued by the CO detected in the course of the generation of **3**, we were interested in exploring conditions to directly induce CO release from **1**. In general, research efforts have been dedicated to designing small molecules that can controllably and efficiently release CO, thereby limiting exposure to toxic levels of CO and enabling the generation of CO in stoichiometric quantities.[33-35] While investigating the thermal stability profile of **1**, we found that heating at 80°C for 48 hours led to decomposition of **1** and detection of hydroxy-MIDA-boronate **21** (Scheme 5a). Generation of **21** suggests that the carboxylic acid moiety may interact with boron, and facilitate a 1,2-bora-Brook type rearrangement, which is coupled with the release of CO.[6,7,10]



Scheme 5. a. Thermally induced CO-extrusion from **1**; b. Application of **1** as a CO surrogate during a palladium-catalyzed carbonylation reaction. NMR yields in brackets. $Pd(dba)_2$ = palladium(0) bis(dibenzylideneacetone); Ph_3P = triphenylphosphine; Et_3N = triethylamine.

To showcase the efficiency of gas released upon heating, we subjected 1.0 equivalent of **1** to a Pd-catalyzed amino-carbonylation reaction using a two-chamber approach (Scheme 5b).[35g] The corresponding amide (**22**) was obtained in 99% NMR yield, emphasizing the efficient conversion and uptake of CO from carboxy-MIDA-boronate.

Conclusion

In closing, we have successfully merged the carboxylic acid and boronate FGs and developed a novel C1-building block, carboxy-MIDA-boronate. Carboxy-MIDA-boronate can undergo reactions analogous to organic carboxylic acids, providing access to carbamoyl-, oxycarbo- and thiocarboboronates. In the process of evaluating the corresponding reactivity, we found that carboxy-MIDA-boronate can react with nucleophiles to give products bound to either the carboxylate carbon or boron centers. We attribute this observation to the hemilabile nature of the MIDA ligand, which allows boron to behave as either a nucleophile or electrophile. Furthermore, we demonstrated the ability of carboxy-MIDA-boronate and the corresponding derivatives to participate in condensation-driven reactions to access various borylated heterocycles. The borylated heterocycles were found to be efficient coupling partners in the SMCC reaction under one general set of conditions. These couplings provide expedient access to compounds of chemical and pharmaceutical relevance in a single step from readily available aryl bromides. Furthermore, this strategy offers a complementary approach to existing methods, allowing the synthesis of bis(heteroaryl) motifs that would be difficult to access through established means. Lastly, we showcase that carboxy-MIDA boronate can reliably store and release CO for applications such as carbonylative coupling chemistry. Mechanistic studies and further applications of carboxy-MIDA-boronate are currently being pursued in our lab. We anticipate that carboxy-MIDA-boronate will find application in multiple disciplines within the chemistry community.

Acknowledgements

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Keywords: carboxyboronate • ambident electrophile • C1 building block • heterocycles • cross-coupling

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[15] Another plausible mechanism involves a 1,2-bora-Brook type rearrangement of the carbonyl bound *O*-azabenzotriazole via a three-membered transition state (see references 6 and 7).

[16] Efforts to demonstrate that the Barton ester is a transient intermediate to **4h** were unsuccessful. However, we were able to show that **4h** could be generated from **4f** and mercaptopyridine *N*-oxide, suggesting that the Barton ester may be a short-lived intermediate to **4h**. See Supplementary Information for details.

[17] Reaction with greater than 1.0 eq. of *N*-hydroxyphthalimide led to formation of the corresponding *O*-borylated product.

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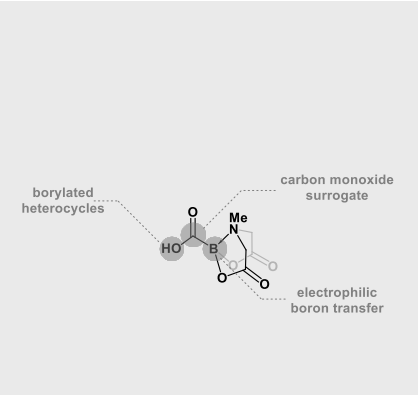
RESEARCH ARTICLE

The scalable and straightforward synthesis of carboxy-MIDA-boronate, one of the simplest boron-containing building blocks, is described. Carboxy-MIDA-boronate can undergo a diverse range of transformations, providing access to an extensive scope of borylated products. In the course of this study, carboxy-MIDA-boronate was found to possess unusual reactivity towards nucleophiles.



*Aleksandra Holownia, Chieh-Hung Tien, Diego B. Diaz, Reed T. Larson, Andrei K. Yudin**

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