Synthetic Methods

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Oxidative Geminal Functionalization of Organoboron Compounds**

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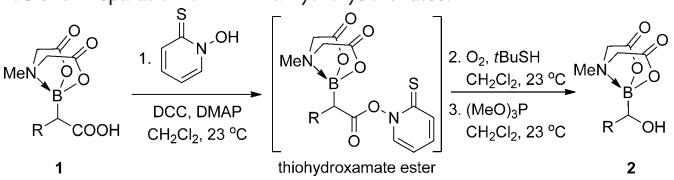
Dedicated to Professor George A. Olah on the occasion of his 85th birthday

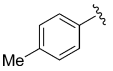
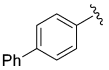
Organoboronic acids and their derivatives are widely utilized building blocks in chemical synthesis.[1] The reactivity of these molecules is due to the accessibility of the vacant p orbital at the trivalent boron center. This Lewis acidity, however, is a "double-edged sword", since sp^2-hybridized boron species are often too reactive to survive chemical transformations during late-stage functional-group manipulation. The emergence of stable tetracoordinate organoboron derivatives, such as organotrifluoroborates[2] and *N*-methyliminodiacetyl (MIDA) boronates,[3] as boronic acid surrogates has opened up new opportunities to address this problem. The corresponding organoboron compounds are stable under a variety of conditions wherein other functional groups are chemoselectively transformed, thereby leaving the boryl functionality available for downstream transformations.[4,5] The tetracoordinate nature of the sp^3 boron center in these molecules inhibits undesired reactions typical of trivalent organoboron compounds.

Recent development of MIDA boronate derived α-boryl aldehydes/carboxylic acids[6] and their pinene analogues[7] has further highlighted the prominent effect of sp^3 boron centers in chemoselective transformations. While functional-group manipulations remote to the tetracoordinate boryl groups are well-documented, geminal functionalization, particularly oxidative transformation directly at the α-position of the boron center, has remained underexplored.[4r,5g] Herein, we describe a decarboxylative conversion of α-boryl carboxylic acids to α-hydroxyboronates that have enabled access to stable MIDA acylboronates through oxidation of the hydroxy group. This new class of acylboronates was found to be suitable for chemoselective synthesis of a range of heterocyclic boronate building blocks. Of note is the facility with which functionalities that are sensitive to classical lithiation–borylation protocols (for instance, unprotected amines) can be handled by using this new method. Our work should encourage the development of additional examples where boron-containing heterocycles are accessed by means other than established metal-based approaches.

In our recent contribution, we described the preparation of configurationally stable α-boryl acids.[6] In the present study, we opted to utilize the Barton radical decarboxylation,

Table 1: Preparation of MIDA α-hydroxyboronates.[a]



Starting Material	R	Product	Yield [%][b]
1a		**2a**	73
1b		**2b**	70
1c		**2c**	50
1d		**2d**	70
1e		**2e**	71
1f		**2f**	32
1g		**2g**	32
1h		**2h**	35
1i		**2i**	29

[a] The reactions were carried out using: step 1) α-borylcarboxylic acid (1.0 equiv), *N*-hydroxypyridine-2-thione (1.2 equiv), DCC (1.2 equiv), and DMAP (0.05 equiv) in anhydrous CH_2Cl_2 at 23 °C for 12 h; step 2) O_2 bubbling, *t*BuSH (9.0 equiv), irradiation with 250 W tungsten-halogen light at 23 °C for 2–8 h; step 3) $(MeO)_3P$ (2.0 equiv) at 23 °C for 2 h. [b] Yields of isolated products after silica gel chromatography. DCC = *N*,*N*′-dicyclohexylcarbodiimide. DMAP = 4-dimethylaminopyridine.

which is a well-established method to replace carboxylic acids with other functional groups,[8,9] as a test reaction to evaluate the feasibility of α-hydroxyboronate preparation. MIDA α-borylcarboxylic acid **1a** (Table 1, entry 1) was first converted to the corresponding thiohydroxamate ester under standard DCC/DMAP coupling conditions. The resulting bright-yellow ester solution was then bubbled with O_2 gas in the presence of *t*BuSH while being irradiated under tungsten-halogen light. Upon irradiation, the α-boryl radical species derived from the photoinduced decomposition of the thiohydroxamate ester was trapped by molecular oxygen and converted to the α-boryl hydroperoxide intermediate. The final reductive treatment of the reaction mixture with trimethylphosphite

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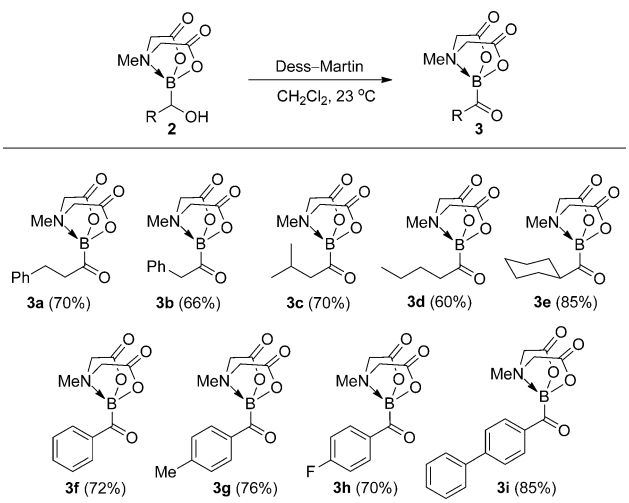
afforded the desired MIDA α-hydroxyboronate **2a** in 73% yield. Although compounds containing a *gem*-hydroxyboron motif have been reported,[10] these molecules equipped with a tetracoordinate boron center are unprecedented.

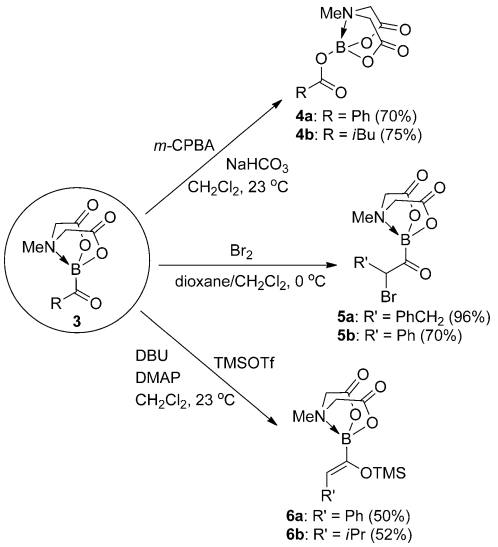
The successful synthesis of compound **2a** prompted us to expand the scope of the preparative procedure (Table 1). It was found that alkyl-substituted substrates generally afforded the desired MIDA α-hydroxyboronates in good yields. However, the starting α-borylcarboxylic acids with aryl substituents resulted in the isolation of products with low yields (29–35%), which are possibly due to delocalization of the α-boryl radical to the aromatic ring, thereby triggering the generation of unidentified by-products. It is worth pointing out that, although the carbon-centered radicals with ordinary trivalent α-boronic ester substituents are known intermediates in a range of reactions,[11] ours is the first report of a chemical transformation involving α-boryl radicals connected to the sp^3 boron center.

With α-hydroxyboronates in hand, we questioned the possibility of alcohol oxidation as a general means of accessing acylboronic compounds, a class of scarce but highly valuable synthetic building blocks.[12] Tetracoordinate boron centers have been shown to be stable under oxidative conditions leading to the formation of remote aldehyde or ketone functionalities from alcohols;[4p,5h] however, the corresponding oxidation at the carbon atom equipped with the boryl group is unprecedented. To examine the feasibility of this novel transformation, α-hydroxyboronate **2a** was first subjected to the Ley oxidation (TPAP/NMO; TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide).[13] Encouragingly, the desired MIDA acylboronate **3a** was isolated from the reaction by using a large amount of TPAP (50 mol%). Lower TPAP loading (e.g. 5 mol%) failed to afford the desired product. An increase in reactiom time led to significant decomposition. The inefficiency of this process prompted us to examine milder oxidants. To our delight, the reaction between **2a** and a stoichiometric amount of Dess–Martin periodinane[14] in CH_2Cl_2 smoothly afforded the acylboronate **3a** as a white powder that was stable in air after silica gel chromatography in 70% yield (Scheme 1). To test the generality of this process, different α-hydroxyboronates were also subjected to the Dess–Martin oxidation (Scheme 1). Alkyl- and aryl-substituted substrates were all tolerated and the corresponding acylboronates were isolated in good yields. Importantly, no oxidative cleavage of the carbon–boron bond was observed in this process.

We next turned our attention to the stability and reactivity of MIDA acylboronates. To test the tolerance of their carbon–boron bonds towards chemical transformations, various MIDA acylboronates were subjected to a range of conditions (Scheme 2). Treatment of compounds **3c** and **3f** with *m*-CPBA afforded good yields of stable acyloxyboronate products **4b** and **4a**, respectively. Unlike ordinary acyloxyboranes, which are a class of unstable strong Lewis acids,[15] compounds **4a** and **4b** are stable in air and can be purified using silica gel chromatography. These results unambiguously indicated the occurrence of a Baeyer–Villiger transformation that proceeded by the migration of the boryl group, thus



Scheme 1. Preparation of MIDA acylboronates through Dess–Martin oxidation. The reactions were carried out using α-hydroxyboronate (1.0 equiv), Dess–Martin periodinane (1.1 equiv) in CH_2Cl_2 at 23 °C for 0.5 h. All yields in parentheses are yields of isolated products after silica gel chromatography.



Scheme 2. Transformations of MIDA acylboronates. *m*-CPBA = *meta*-chloroperoxybenzoic acid. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

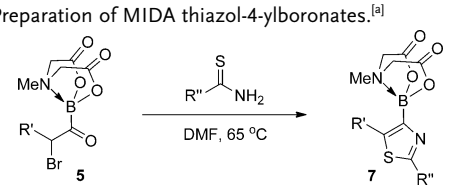
revealing a stronger migratory aptitude of the tetracoordinate MIDA boron center compared to alkyl or aryl substituents. Given the fact that an analogous 1,2-boryl migration also took place in the BF_3-promoted rearrangement of oxiranyl MIDA boronates to generate α-boryl aldehydes,[6c] the MIDA boryl group is likely to find additional applications in organic synthesis owing to its potential in migratory transformations.

The exposure of acylboronates **3a** and **3b** to strong oxidant Br_2 in dioxane/CH_2Cl_2 resulted in the corresponding α-bromination products **5a** and **5b** in good yields with the carbon–boron bond remaining intact. The ease of α-bromination of MIDA acylboronates attests to their enolization capability. For further validation, the 1-(silyloxy)vinylboronates **6a** and **6b** were synthesized by treating the starting

acylboronates **3b** and **3c** with TMSOTf in the presence of DBU.

The facile access to α-bromocarbonyl compounds **5a** and **5b** encouraged us to examine their potential in downstream transformations leading to heterocycles. We were pleased to observe that the reaction of **5a** or **5b** with thioamides in DMF at 65 °C afforded a range of 4-borylated thiazoles in good yields (Table 2, entries 1–4). Replacement of thioamide with

Table 2: Preparation of MIDA thiazol-4-ylboronates.[a]

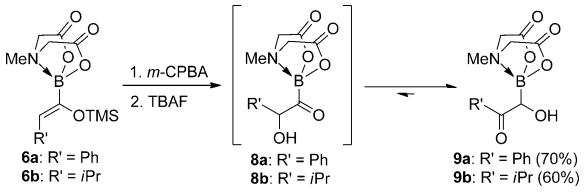


Entry	R′	R″	Product	Yield [%][b]
1	$PhCH_2$	Me	**7a**	50
2	$PhCH_2$	Ph	**7b**	66
3	Ph	Me	**7c**	33
4	Ph	Ph	**7d**	66
5	$PhCH_2$	NH_2	**7e**	88
6	Ph	NH_2	**7f**	61

[a] Reactions were carried out using α-bromoacylboronate (1.0 equiv), thioamide or thiourea (1.2 equiv) in anhydrous DMF at 65 °C for 6 h. [b] Yields of isolated products after silica gel chromatography.

thiourea in the reaction also resulted in the smooth generation of thiazol-2-amine products (Table 2, entries 5–6). Significantly, no cleavage of the boryl group was observed in these reactions. The thiazolylboronates, which are stable in air and difficult to obtain with established borylation methodologies,[16,17] are valuable building blocks for cross-coupling reactions[18] in the synthesis of active pharmaceutical ingredients.

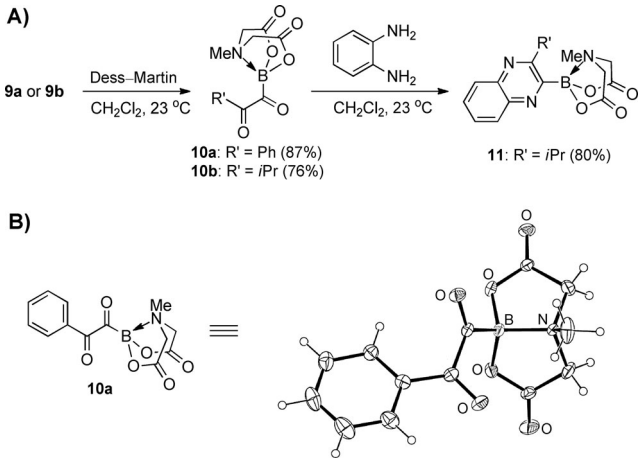
Successful preparation of thiazolylboronates aroused our curiosity to further explore new possibilities towards borylated heterocyclic compounds from MIDA acylboronates and their derivatives. We envisioned the conversion of 1-(silyloxy)vinylboronates to α-hydroxyacylboronates. Upon subjecting compounds **6a** and **6b** to the Rubottom oxidation (a continuous treatment with *m*-CPBA and TBAF),[19] α-hydroxy-α-boryl ketones **9a** and **9b**, respectively, were isolated (Scheme 3). It is likely that the initially formed α-hydroxyacylboronates **8a/b** isomerized to their more stable isomers **9a/b** through a proton transfer process. Indeed, in the case of vinylboronate **6b**, a 1:1 mixture of the corresponding α-hydroxyacylboronate **8b** and the rearranged α-boryl ketone



Scheme 3. Generation of α-hydroxy-α-boryl ketones. TBAF = tetra-*n*-butylammonium fluoride.

9b was isolated after the TBAF desilylation. Upon standing in solvents (e.g. DMSO, MeCN, $CHCl_3$), the mixture spontaneously converted to pure compound **9b** within hours, thus further underscoring the relative instability of the acylboronate unit. This could be attributed to the inefficient interaction between the π* orbital of the carbonyl group and the low-lying σ_{B-N} and σ_{B-O} orbitals on the MIDA boryl substituent. The corresponding interaction between the π* orbital of the carbonyl group and the σ_{C-B} orbital in compound **9** contribute stronger stabilization to the system.

We further subjected **9a** and **9b** to the Dess–Martin oxidation (Scheme 4 A). Gratifyingly, the oxidation smoothly afforded the desired 2-oxo-acylboronate products **10a** and **10b** as solids that are stable in air. The 1,2-diketo compounds equipped with boryl groups are hitherto unknown. The X-ray structure of **10a** (Scheme 4 B)[20] revealed that the bond



Scheme 4. A) Synthesis of 2-oxo-acylboronates and their transformation to quinoxaline derivatives. B) Crystal structure of **10a**. Thermal ellipsoids are set at 50% probability.

length of its two C=O bonds is between 1.22 and 1.23 Å, thus indicating a set of ordinary 1,2-diketone carbonyl groups. The smooth transition of **10b** to a 2-borylated quinoxaline derivative **11** upon treatment with *o*-phenylenediamine (Scheme 4 A) further corroborated the potential of this class of molecules in heterocyclic boronate synthesis. Given the existence of quinoxaline subunits in many bioactive compounds,[21] direct access of boronic acid building blocks of this sort through 2-oxo-acylboronates is of particular importance for medicinal chemistry research.

In summary, we have demonstrated a facile oxidative installation of a hydroxy group geminal to the MIDA boryl moiety through a Barton radical decarboxylation from α-borylcarboxylic acids. The resulting α-hydroxyboronates were subsequently transformed to a novel class of acylboronates that are stable in air through the Dess–Martin oxidation. These carbonyl-based building blocks are capable of generating a range of functionalized boron derivatives, including acyloxyboranes, α-bromoacylboronates, 1-(silyloxy)vinylboronates, α-hydroxy-α-boryl ketones, and 2-oxo-acylboronates. Exemplified by the successful downstream preparation of a series of borylated thiazoles and quinoxalines, MIDA

acylboronates and their derivatives have proven their potential in the construction of stable 2-heterocyclic MIDA boronates that are useful because of their general capacity for slow-release cross-coupling reactions.[18] In view of the tolerance of MIDA boronates towards a wide range of chemical transformations, chemoselective late-stage functionalization of these building blocks that are stable in air provides opportunities to synthesize boron-containing heterocycles through condensation reactions; this approach is conceptually different from established metalation procedures.

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