

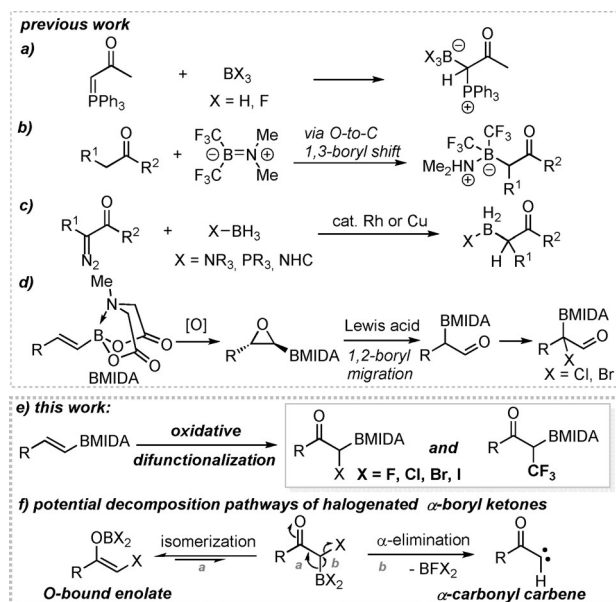
Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201604898
Internationale Ausgabe: DOI: 10.1002/anie.201604898Oxidative Difunctionalization of Alkenyl MIDA Boronates: A Versatile Platform for Halogenated and Trifluoromethylated α -Boryl KetonesWen-Xin Lv⁺, Yao-Fu Zeng⁺, Qingjiang Li, Yunyun Chen, Dong-Hang Tan, Ling Yang, and Honggen Wang*

Abstract: The synthesis of halogenated and trifluoromethylated α -boryl ketones via a one-pot oxidative difunctionalization of alkenyl MIDA boronates is reported. These novel densely functionalized organoborons bearing synthetically and functionally valuable carbonyl, halogen/ CF_3 and boronate moieties within the same molecule are synthetically challenging for the chemist, but have great synthetic potential, as demonstrated by their applications in a straightforward synthesis of borylated furans. The generality of this reaction was extensively investigated. This reaction is attractive since the starting materials, alkenyl MIDA boronates, are easily accessible.

Organoborons are among the most frequently used compounds in organic synthesis and organometallic chemistry,^[1] with uses in other fields such as medicine and materials science,^[2] enabling diverse and useful chemical transformations, with some of the most well-known and important examples being the Suzuki–Miyaura^[3] and Chan–Evans–Lam^[4] couplings, the Petasis reaction^[5], and the Hayashi–Miyaura conjugate addition.^[6] Despite their importance, the preparation of organoborons is not trivial in organic synthesis and this is particularly true for multi-functionalized organoborons consisting of sensitive functional groups.^[1,2] With regards to enolizable carbonyls that can generate boron enolates, there is a rapid equilibrium between the O- and C-bound forms, with the latter being much less thermodynamically stable because of the stronger O–B bonds over C–B bonds.^[7] Hence, the formation of C-boron enolates (α -boryl carbonyls) provides a greater challenge to the synthetic chemist.^[8] However, they have potentially good synthetic value because they are kinetically amphoteric, meaning that they contain a nucleophilic site adjacent to an electrophilic center (the nucleophilic boronate and the electrophilic carbonyl) and hence exhibit multiple modes of reactivity.^[9]

Generally, the formation of stable, isolable α -boryl carbonyls remains an underexplored area of research, despite the fact that they have been suggested or (in some cases) shown to be implicated as reactive intermediates in many transformations.^[9] One of the simplest examples for the formation of α -boryl ketones is the reaction of ylides and boranes (Figure 1a).^[10] Furthermore, Bürger and co-workers have

Figure 1. α -Boryl ketone synthesis.

observed that α -bis(trifluoromethyl)boryl ketones can be formed through a O-to-C 1,3-boryl shift by reacting $(\text{F}_3\text{C})_2\text{B}=\text{NMe}_2$ with ketones (Figure 1b).^[11] Recently, several groups have reported elegant syntheses of α -boryl carbonyls.^[12] Transition-metal-catalyzed carbene-directed B–H insertion can take place starting from diazocarbonyl compounds and stabilized borane adducts (Figure 1c). Furthermore, Yudin^[13] and Burke^[14] independently reported the preparation of α -boryl aldehydes by a two-step synthesis that consisted of the epoxidation of alkenyl MIDA (*N*-methyliminodiacetyl) boronates followed by a Lewis acid-promoted 1,2-boryl migration (Figure 1d). The resulting α -boryl aldehydes could be halogenated to provide α -haloacylboronates, which have been demonstrated to be versatile synthons in the synthesis of borylated heterocycles.^[13,15]

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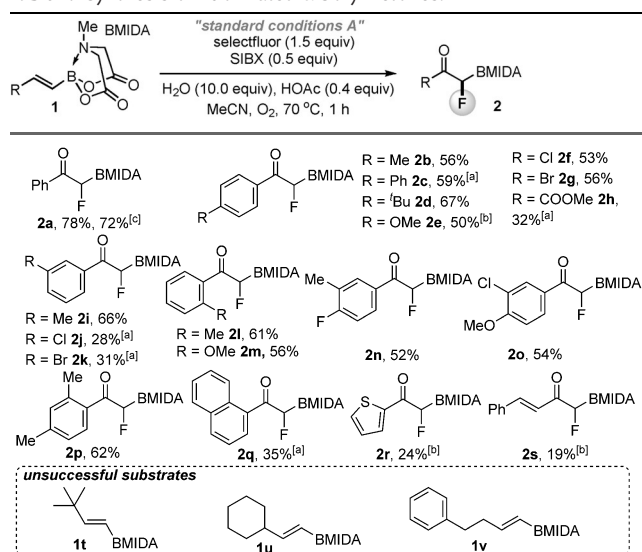
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Alkenyl MIDA boronates,^[16] which are easily accessible using several synthetic routes^[17,18a] and are bench-top stable, consist of an unreactive boronate and a synthetically transformable alkenyl group. We envisioned that these characteristics make them a great platform for complex organoborate synthesis.^[13,14,18] Herein, we report an oxidative difunctionalization of alkenyl MIDA boronates for the assembly of five types of functionalized α -boryl ketones in a single synthetic operation (Figure 1e).^[19] These densely functionalized organoborons bearing valuable functional groups (carbonyl, boronate and halogen/CF₃) within the same molecule have great synthetic potential but have been nonetheless synthetically challenging thus far. The rapid C-to-O 1,3-boryl shift of a C-boron enolate (Figure 1f, left) and the potential undesired α -elimination to produce the α -carbonyl carbene might account for the sparsity of these compounds in the literature (Figure 1f, right).^[9] The success of our attempts in developing this reaction might hinge on the barrier imposed for the tautomerization of electron-rich tetracoordinated sp³-hybridized MIDA borons compared to their sp²-hybridized counterparts.^[8b,9]

There is a growing interest in fluorine-containing building blocks as a result of the unique properties conferred by fluorine.^[20] The oxidative fluorination of alkenyl MIDA boronates was thus initially investigated.^[21] It was found that fluorinated α -boryl ketone **2a** could be obtained in 78 % yield by reacting styrenyl MIDA boronate **1a** with selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) under the optimized reaction conditions: selectfluor (1.5 equiv), SIBX^[22] (0.5 equiv), H₂O (10.0 equiv), HOAc (0.4 equiv) in CH₃CN, 70 °C, under O₂ atmosphere (1 atm) (Table 1).^[23] The reaction is highly regioselective, with the fluorine atom being found exclusively α to the boryl group. The structure of **2a** was confirmed unambiguously by X-ray analysis.^[24] Interestingly, a literature survey showed that this type of compounds has been

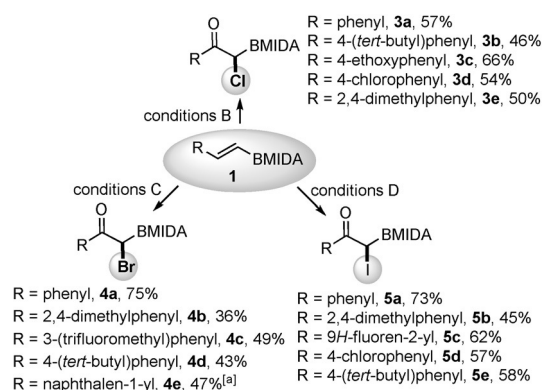
Table 1: Synthesis of fluorinated α -boryl ketones.



[a] SIBX (1.0 equiv) was used. [b] At 50 °C. [c] Gram-scale preparation, 1.06 g of **2a** was obtained.

inaccessible thus far. The generality of this reaction was then explored. We were gratified to find that the phenyl group could be substituted with a variety of functionalities, such as methyl (**2b**, **2i**, **2l**, **2n**, **2p**), phenyl (**2c**), *tert*-butyl (**2d**), methoxy (**2e**, **2m**, **2o**), fluoro (**2n**), chloro (**2f**, **2j**, **2o**), bromo (**2g**, **2k**), and ester (**2h**) groups, providing opportunities for further derivatization of the products. Importantly, *ortho*-substituents did not hamper the reactivity (**2l,m**). Notably, for electron-deficient substrates, a higher amount (1.0 equiv) of oxidant was required to improve the product yield (**2c**, **2h**, **2j**, **2k**). In contrast, for electron-rich substrates, it was found that slightly lowering the temperature to 50 °C minimized side reactions (**2e**, **2r**). Along with phenyl-substituted vinyl MIDA boronates, the reaction is also compatible with naphthalen-1-yl and thiophen-2-yl aromatic substituents, although these substrates lead to lower yields of products **2q** and **2r**. The difunctionalization with the optimized reaction conditions is also a viable reaction with the introduction of an additional conjugated vinyl group: 4-phenylbuta-1,3-dien-1-yl MIDA boronate yields the corresponding product **2s**, albeit in lower yield than other analogues. The unreactive nature of alkyl vinyl MIDA boronates **1t**, **1u**, and derivative **1v** with an aromatic substituent, which resulted in the starting materials being left largely unreacted, demonstrates that the reaction requires an aromatic substituent conjugated with the terminal vinyl group (compare **2s** with **1v**) at a position close to the boron center (hence the decreased yield of **2s**). The practical utility of the transformation for large-scale processes was confirmed by carrying out a gram-scale reaction without modification of the optimized conditions, with the product **2a** being obtained in 72 % yield, comparable to that obtained in the smaller-scale reaction.

The success of the above oxidative fluorination of vinyl MIDA boronates encouraged us to explore the feasibility of other halogenation reactions.^[13,15] Gratifyingly, the reaction was also amenable for the formation of chlorinated,^[25] brominated,^[26] and iodinated^[25] α -boryl ketones using NaClO₂, NBS, and I₂ as the halogen sources, respectively (Scheme 1).^[13,15] In general, moderate to good yields were obtained and decent functional group tolerance was observed.

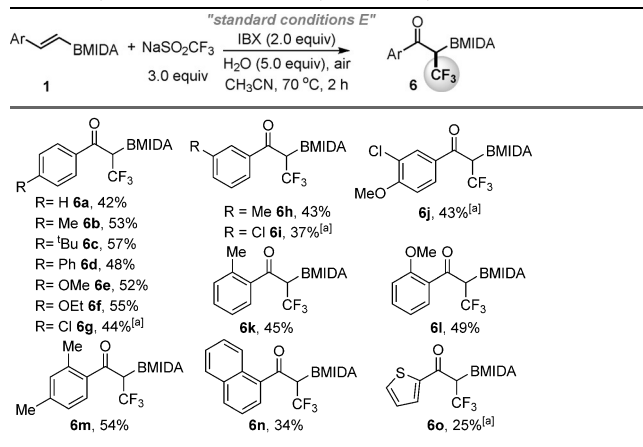


Scheme 1. Scope of the oxidative halogenation reactions. Conditions B: NaClO₂ (3.0 equiv), CCl₃CO₂H (3.0 equiv), DCM, air, rt, 4 h. Condition C: NBS (1.5 equiv), IBX (1.5 equiv), H₂O (5.0 equiv), toluene, air, 70 °C, 30 min. Conditions D: I₂ (1.0 equiv), IBX (1.0 equiv), H₂O (1.0 equiv), CH₃CN, air, 70 °C, 30 min. [a] In MeCN.

The versatility of Cl, Br, and I in chemical transformations offers additional value to these compounds.

To further demonstrate the value of this oxidative difunctionalization of alkenyl MIDA boronates, we investigated the oxidative trifluoromethylation reactions, expecting to obtain trifluoromethylated α -boryl ketones (Table 2).^[27] As with the formation of the fluorinated α -

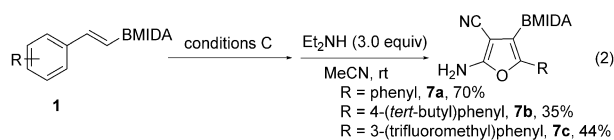
Table 2: Synthesis of trifluoromethylated α -boryl ketones.



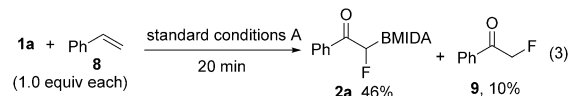
[a] At 80 °C.

boryl ketones, to the best of our knowledge, no synthetic method has thus far been reported for their synthesis. We were delighted to find that these products are indeed accessible through a variation of the reaction conditions described above. For example, trifluoromethylated boronate **6a** was formed in 42% yield with Langlois' reagent (NaSO_2CF_3)^[28] as the source of the trifluoromethyl group and IBX as the oxidant, in the presence of 5.0 equivalents of H_2O in CH_3CN .^[23] The scope of this oxidative trifluoromethylation reaction was then explored. A variety of substrates bearing aryl groups with both electron-donating and mildly electron-withdrawing substituents were subjected to the reaction conditions and generally formed the oxidized and trifluoromethylated products in moderate yields (**6b–m**). Furthermore, naphthalen-1-yl (**6n**) and thiophen-2-yl (**6o**) vinyl MIDA boronates are also substrates amenable to oxidation/trifluoromethylation.

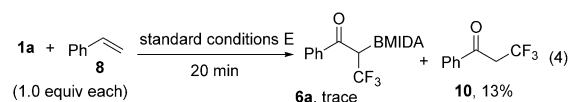
The synthetic utility of the products was demonstrated by the transformation of brominated α -boryl ketones **4** to borylated furans. Thus, the reaction of **4a** and malononitriles in the presence of diethylamine furnished the borylated 2-amino-3-furonitrile **7a** in 86% yields [Eq. (1)].^[29] Furthermore, a telescoping synthesis of **7** was also possible starting from **1** without the isolation of intermediate **4**, giving the corresponding products in acceptable to good yields [Eq. (2)].



Preliminary mechanistic studies were conducted to shed light on the fluorination and trifluoromethylation reaction. Competition experiments showed that the alkenyl MIDA boronate **1a** is more reactive than styrene **8** in the fluorination reaction [Eq. (3)]. This result suggests that the presence of the



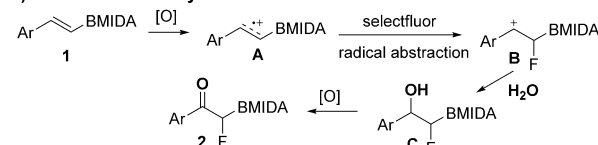
MIDA boronate increases the reactivity of the starting material. In contrast, in the trifluoromethylation reaction, **1a** remained largely untouched probably because of the steric hindrance induced by the MIDA boronate [Eq. (4)]. It was



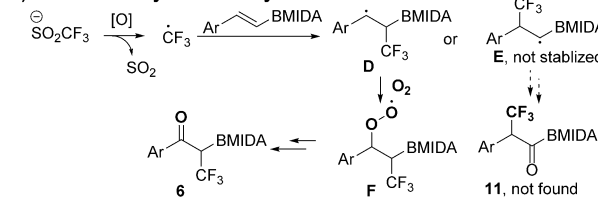
found that the addition of the radical scavenger TEMPO or BHT inhibited both reactions,^[30] suggesting that radical pathways are indeed operative. In addition, ^{18}O -labeling experiments clearly demonstrated that H_2O is the oxygen source for the fluorinated product; however, the oxygen in the carbonyl group of trifluoromethylated α -boryl ketones was derived from atmospheric oxygen.^[30]

Based on the above experimental observations and literature precedents, plausible mechanisms were proposed as outlined in Scheme 2. In the oxidative fluorination reaction (Scheme 2a), the oxidation of **1** by single-electron transfer [SET] generates radical cation **A**,^[21,31] which can abstract

a) fluorinated α -boryl ketones



b) trifluoromethylated α -boryl ketones



Scheme 2. Mechanistic rationale.

a fluorine atom from selectfluor to form benzylic carbocation **B**. The attack of water then delivers the intermediate alcohol **C**, which is further oxidized to yield the final product **2**.^[32] For the synthesis of trifluoromethylated α -boryl ketones, the reaction is initiated by the trifluoromethyl radical, generated by the oxidation of NaSO_2CF_3 , with concomitant release of SO_2 (Scheme 2b). This radical then adds to the vinyl double bond to form the stabilized benzylic radical intermediate **D** or the non-stabilized radical **E**. Mechanistic studies clearly evidenced that atmospheric oxygen is the source of the carbonyl group. Thus, in this case, **D** undergoes attack by O_2 , forming peroxy radical **F** which is further transformed into final product. The exclusive formation of **3** rather than its regioisomer **11** is consistent with a recent theoretical calculation that alkyl radicals are destabilized by an adjacent MIDA boronate.^[18d]

In summary, we have developed a one-pot oxidative difunctionalization of alkenyl MIDA boronates for the formation of densely functionalized halogenated and trifluoromethylated α -boryl ketones. The presence of synthetically valuable carbonyl, boronate and halogen/ CF_3 groups within the same molecule confers on these products great synthetic utility. It is worth noting that all the products formed were found to be bench-stable, which increases the ease with which these compounds can be handled. The transformation of brominated α -boryl ketones to borylated furans was demonstrated. Furthermore, the reaction also offers the advantage that the alkenyl MIDA boronate starting materials are easily accessible.

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