

Photochemical Organocatalytic Borylation of Alkyl Chlorides, Bromides, and Sulfonates

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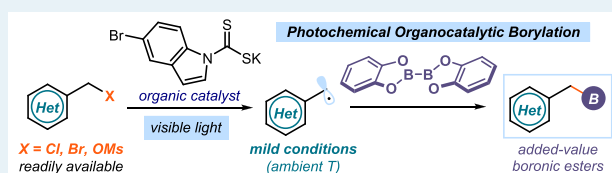
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Supporting Information

ABSTRACT: Reported herein is a photochemical strategy for the borylation of alkyl halides using bis(catecholato)diboron as the boron source. This method exploits the ability of a nucleophilic dithiocarbonyl anion organocatalyst to generate radicals via an S_N2-based photochemical catalytic mechanism, which is not reliant on the redox properties of the substrates. Therefore, it grants access to alkyl boronic esters from readily available but difficult-to-reduce electrophiles, including benzylic and allylic chlorides, bromides, and mesylates, which were inert to or unsuitable for previously reported metal-free borylation protocols.

KEYWORDS: borylation, organocatalysis, photochemistry, radicals, S_N2 chemistry



Boronic acids and esters are extensively used in material science,¹ chemosensing,² and medicinal chemistry.³ They are also extremely valuable synthetic precursors that can be readily transformed to a variety of useful functional groups.⁴ For example, the prominence of the Suzuki–Miyaura reaction^{4a} has established the crucial synthetic importance of aromatic boronic acids and esters. Therefore, there are well-developed synthetic protocols for making aromatic derivatives.⁵

Alkyl boronic acids and esters are also highly useful intermediates,⁶ which justifies the recent interest in developing effective methods for their preparation. Traditionally, they have been accessed via the hydroboration of alkenes or from organo-lithium and organo-magnesium reagents via transmetalation.⁵ Both strategies suffer from regioselectivity issues and functional group incompatibility. A more effective approach relies on the transition-metal-catalyzed borylation of alkyl halides with diborons (Figure 1a, left arrow). While most resulting strategies require the use of alkyl bromides or iodides,⁷ a few catalytic systems based on manganese^{8a} and copper^{8b} have been described for the borylation of unactivated alkyl chlorides. These protocols, although effective, require the use of transition-metal catalysts, which might be incompatible with N-heterocycle-containing substrates because of deleterious heteroatom-catalyst binding effects. Indeed, N-heterocyclic moieties, which are common motifs in drug molecules, generally represent a significant tolerability challenge for synthetic methods.⁹ As a result, few metal-based borylation methods compatible with heteroarenes containing multiple

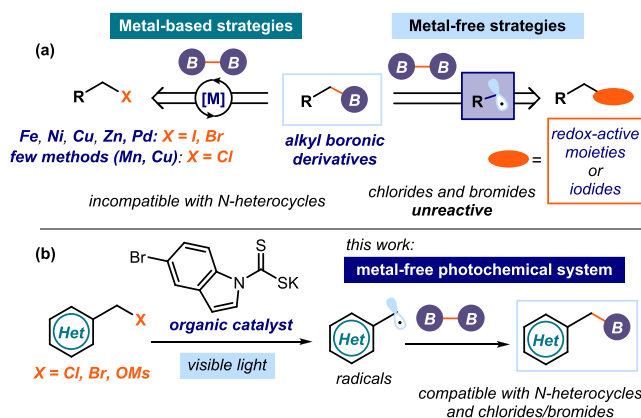


Figure 1. (a) Previous catalytic borylation strategies require either the use of metals (left panel), which complicates the compatibility with N-heterocycle-containing substrates, or of radical precursors containing redox active moieties and alkyl iodides (right panel). (b) The photochemical strategy presented herein uses a nucleophilic organic catalyst and visible light for the borylation of redox-inert alkyl electrophiles, including chlorides. It is compatible with N-heterocyclic moieties.

heteroatoms and high nitrogen content have been reported so far.¹⁰

Received: April 10, 2019

Revised: May 24, 2019

Published: May 28, 2019

More recent borylation methods have sought to overcome these limitations by using metal-free and functional group tolerant conditions. In this context, radical-mediated processes, in which alkyl radicals are borylated with diboranes, have become increasingly important (Figure 1a, right arrow).¹¹ However, these methodologies generally require the use of tailored substrates, purposely adorned with redox-active moieties.¹² This is because a redox event is needed to trigger the formation of the reactive C(sp^3)-centered radicals. Studer recently developed a metal-free photochemical borylation of alkyl iodides, where light is responsible for radical formation by eliciting homolytic carbon–iodine bond cleavage.¹³ Despite the clear improvement, in terms of atom economy, this borylation process is limited to the use of highly reactive and unstable iodide derivatives.

Here, we report a visible-light-mediated organocatalytic system capable of borylating a wide range of readily available and stable benzylic and allylic chlorides, bromides, and mesylates, which were inert to other metal-free borylation protocols (Figure 1b). Importantly, the method's high functional group tolerance allows us to easily prepare alkyl boronic esters adorned with *N*-heterocycles, which would not be compatible with strong redox-active reagents or metal-based protocols.

This research endeavor was motivated by our interest in using the photochemical reactivity of organocatalytic intermediates to generate radicals under mild conditions.¹⁴ Specifically, our laboratory¹⁵ recently reported a visible-light-mediated catalytic strategy that uses a dithiocarbonyl (DTC) anion **A**, adorned with an indole chromophoric unit (Figure 2a). This nucleophilic organic catalyst **A**¹⁷ can activate alkyl electrophiles by displacing a variety of leaving groups via an S_N2 pathway, including chlorides. The resulting photon-absorbing intermediates **I** afford C(sp^3)-centered radicals upon excitation by visible light and homolytic cleavage of the weak C–S bond.¹⁸ This catalytic S_N2 -based strategy, which is not reliant on the redox properties of the radical precursor, grants access to open-shell intermediates from substrates generally inert to classical radical-generating strategies.¹⁹

Cognizant of the ability of the commercially available bis(catecholato)diboron (B_2cat_2) **2** to intercept carbon radicals,^{11–13} we wondered if our photochemical strategy could serve for the borylation of readily available alkyl chlorides, bromides, and alcohol derivatives, such as mesylates. As detailed in Figure 2b, we envisioned that, upon S_N2 displacement and photolysis of **I**, the C(sp^3)-centered radical **II** could react with B_2cat_2 **2** to forge a C–B bond. The ensuing boron-centered radical **IV** is then intercepted by dimethylformamide (DMF) to afford intermediate **V**.¹³ **V** collapses to afford the target alkyl boronic ester product **3**, along with the DMF-complexed boryl radical **VI**. The open-shell intermediate **VI** ($E_{1/2} = -1.53$ V in MeCN vs SCE)^{12d} can then perform a single electron reduction of the dithiocarbonyl radical **III** (the ethyl xanthogenate anion, where Z = OEt, has a reduction potential of E_{red} (**III/A**) = +0.04 V vs SCE)²⁰ to close the catalytic cycle and turn over the catalyst **A**.²¹

To test the feasibility of our borylation strategy, we selected the commercially available 1-(chloromethyl)-1H-benzotriazole **1a** as the radical precursor (Table 1). This choice was informed by our desire to develop a metal-free protocol that could (i) activate alkyl chlorides and (ii) tolerate *N*-heterocyclic moieties. The experiments were conducted in DMF at ambient temperature using 2 equiv of B_2cat_2 **2**, 10 mol

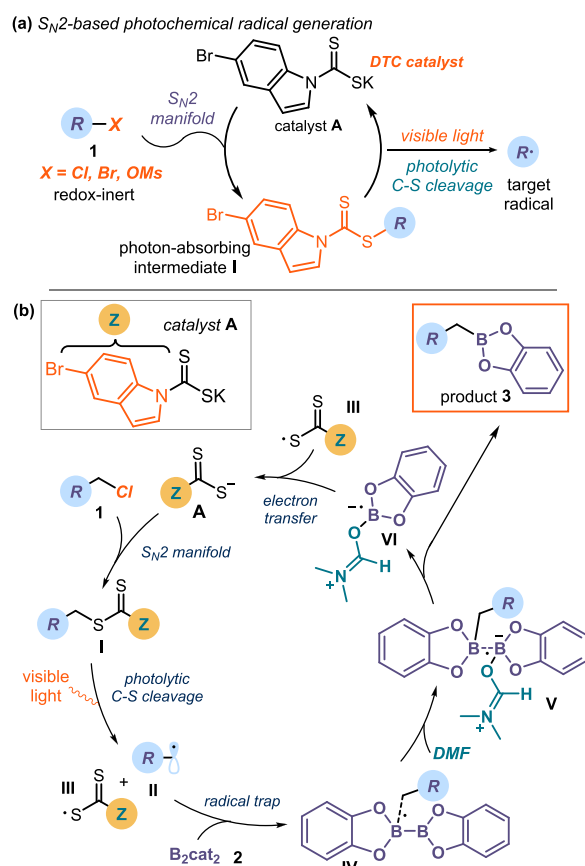


Figure 2. (a) Our recently developed S_N2 -based method for photochemically generating radicals from alkyl chlorides. (b) Proposed mechanism for the visible-light-driven borylation of alkyl halides (Z = chromophore).

Table 1. Optimization Studies^a

entry	deviation from the standard conditions	yield of 3a ^b (%)
1	none	>95 (83)
2	DMA instead of DMF	>95 (82)
3	DMSO or ACN instead of DMF	0
4	1.5 equiv of B_2cat_2 2	65
5	no light	0
6	no catalyst A	0
7	5 mmol scale reaction	55 (52)

^aReactions performed in DMF (0.4 mL) at ambient temperature for 16 h on a 0.2 mmol scale under illumination by blue LED strips ($\lambda_{max} = 465$ nm) and using catalyst **A** (10 mol %) and 2 equiv of **2**. ^bYield of **3a** determined by ¹H NMR analysis of the crude mixture using nitromethane as the internal standard; the value shown in parentheses refers to the yield of isolated **3a** after chromatographic purification on silica gel. [Legend: DMF, dimethylformamide; DMA, dimethylacetamide; ACN, acetonitrile; DMSO, dimethyl sulfoxide; MIDA, methyliminodiacetic acid.]

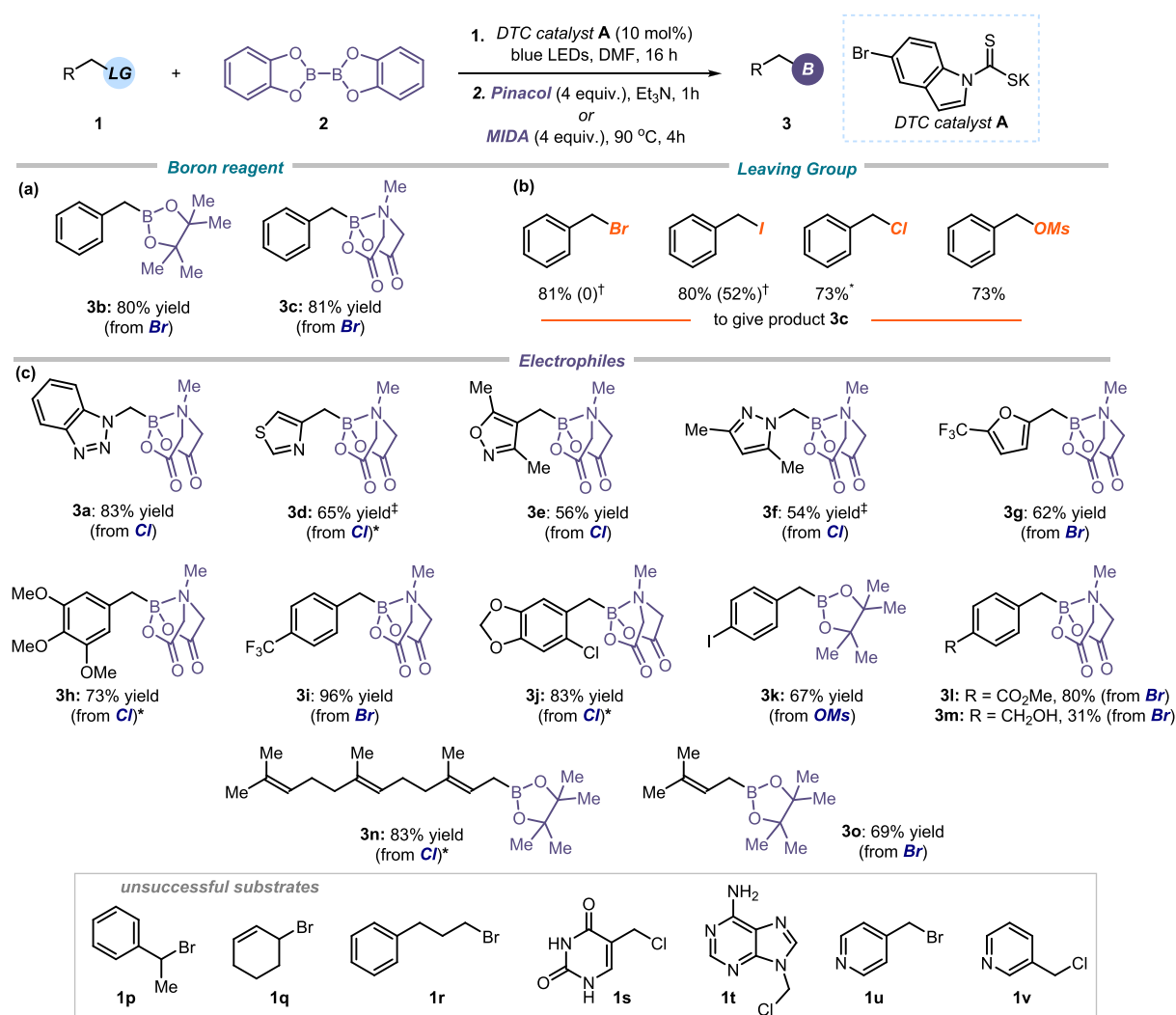


Figure 3. Survey of the electrophiles **1** that can participate in the photochemical borylation reaction. Reactions performed on a 0.2 mmol scale using 2 equiv bis(catecholato)diboron **2** in 0.4 mL of DMF. Yields of the isolated products **3** are indicated below each entry. [Asterisk symbol (*) denotes 2 equiv of NaBr. Superscripted dagger symbol (†) indicates that the yields in parentheses refer to the reaction performed in the absence of catalyst **A**. Superscripted double dagger symbol (‡) denotes the presence of 1 equiv of 2,6-lutidine. MIDA = methyliminodiacetic acid.]

% of the indole-containing dithiocarbamate catalyst **A**, and blue LEDs emitting at 465 nm (see Table 1). After 16 h, the reaction was treated with 4 equiv of methyliminodiacetic acid (MIDA) and heated at 90 °C to perform ligand exchange and generate the more-stable MIDA boronate **3a**. These conditions furnished the borylation product **3a** in high chemical yield (83%, entry 1 in Table 1).

The use of a different coordinating solvent, such as dimethylacetamide (DMA, entry 2 in Table 1), elicited a similar reactivity, while acetonitrile (ACN) or dimethyl sulfoxide (DMSO) completely inhibited the reaction (Table 1, entry 3). These results are consistent with the need to stabilize the radical intermediate **V** (see Figure 2).²² Further variations of the initial conditions, including a lower amount of **2** (Table 1, entry 4), led to poorer results. Control experiments established that both catalyst **A** and light are required for the reaction to proceed (Table 1, entries 5 and 6). A 25-fold scaleup of the reaction (Table 1, entry 7, 5 mmol scale) delivered product **3a** in 52% yield (750 mg) using the same standard experimental setup as for the 0.2 mmol process. This

experiment indicates that this procedure is also relevant to preparative-scale reactions.

Adopting the optimized conditions described in entry 1 in Table 1, we focused on the generality of this photochemical borylation protocol. The process allows the use of both MIDA and pinacol as chelating agents for boron (Figure 3a). Because of the superior stability of the corresponding adducts, we preferentially used MIDA. However, we note that pinacol in triethylamine can be used in all cases to provide the corresponding pinacol boronic esters of type **3b**. As for the radical precursors, this photochemical strategy is suitable for substrates bearing different leaving groups, which can undergo S_N2 activation from the organic catalyst **A**. For example, benzyl bromide, iodide, chloride, and mesylate can all be used to deliver the benzyl borylated product **3c** (Figure 3b). In some cases, the activation of benzylic chlorides required the addition of sodium bromide, which was necessary to generate the corresponding bromide in situ (see, for example, products **3d**, **3h**, **3j**, **3n**).

As for the scope of the process (Figure 3c), a wide array of heteroaromatic derivatives can be efficiently functionalized,

further highlighting the tolerance of this procedure for unprotected polar functional groups. More specifically, this protocol efficiently delivers borylated building blocks featuring a benzotriazole (adduct **3a**), thiazole (**3d**), oxazole (**3e**), pyrazole (**3f**), and furan (**3g**) moiety. Since this S_N2 -based radical-generation strategy is not reliant on the redox properties of the radical precursors, it could tolerate benzylic substrates bearing electron-donating (product **3h**) or electron-withdrawing (**3i**) moieties in the aryl ring. The process is also effective in delivering the desired compounds with high selectivity: an aryl iodide (adduct **3k**), an ester (**3l**), and an unprotected alcohol (**3m**) were all tolerated and activated exclusively at the desired benzylic position. In addition to benzylic electrophiles, allyl substrates could be activated because both farnesyl (**3n**) and prenyl (**3o**) derivatives could be successfully borylated. As a limitation of the system, alkyl bromides leading to secondary radicals (**1p** and **1q**) or nonstabilized primary radicals (**1r**) could not be activated, while substrates containing a uracil (**1s**) or an adenine moiety (**1t**) afforded the dehalogenated products exclusively. Also pyridine derivatives (**1u** and **1v**) did not provide the corresponding borylation products. A complete list of moderately successful and unsuccessful substrates for this radical borylation strategy is reported in section C4, Figure S3, in the Supporting Information.

Cognizant that our S_N2 -based radical-generation strategy can also produce electrophilic radicals,¹⁵ we explored the feasibility of implementing a three-component reaction,²³ where the generated open-shell intermediate is intercepted by an olefin (Figure 4). The newly generated radical would

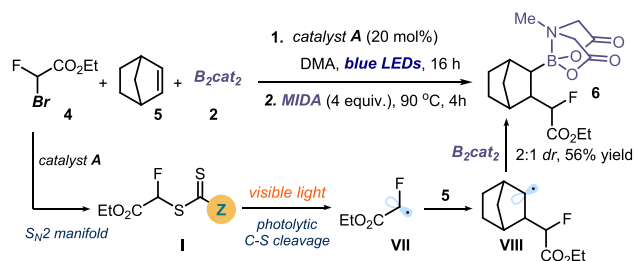


Figure 4. Implementation of a light-driven radical three-component reaction catalyzed by **A** (**Z** = indole chromophore within **A**).

then possess the right polarity (nucleophilic radical) to react with B_2cat_2 , delivering a difunctionalized product. In consonance with this plan, the activation of fluorobromoacetate **4** with catalyst **A** delivered the electrophilic radical **VII**. A sequential trap with norbornene **5** afforded radical **VIII**, which could engage in a C–B bond formation with B_2cat_2 . The difunctionalized product **6** was isolated in 56% yield.

In summary, we have developed a catalytic borylation strategy that uses an easily available organic catalyst and mild reaction conditions, including visible-light illumination and ambient temperature. The chemistry exploits an S_N2 -based radical-generation strategy, which is not reliant on the redox properties of the radical precursors. Therefore, it grants access to alkyl boronic esters from readily available electrophiles that are difficult to reduce. These include benzylic and allylic chlorides, bromides, and mesylates, which are generally inert to previously reported metal-free borylation protocols. In addition, the redox neutral conditions of this process make it

tolerant of redox-sensitive substrates and allow the borylation of heterocyclic-containing substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b01482.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by MICIU (No. CTQ2016-75520-P), the AGAUR (Grant No. 2017 SGR 981), and the European Research Council (No. ERC-2015-CoG 681840-CATA-LUX). D.M. thanks H2020-MSCA-ITN-2016 (No. 722591-PHOTOTRAIN) for a predoctoral fellowship.

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