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Decarboxylative Borylation of Stabilized and Activated Carbon Radicals

Qiang Zhang, Xiaojuan Li, Weigang Zhang, Shengyang Ni, Yi Wang,* and Yi Pan

Abstract: Redox-active esters (RAEs) as active radical precursors have been extensively studied for C-B bond formations. However, the analogous transformations of stabilized radicals from the corresponding acid precursors remain challenging due to the strong preference towards single-electron oxidation to the stable carbocations. This work describes a general strategy for rapid access to various aliphatic and aromatic boronic esters by mild photoinduced decarboxylative borylation. Both aryl and alkyl radicals could be generated from the leaving group-assisted *N*-hydroxybenzimidoyl chloride esters, even α-CF_3 substituted substrates could be activated for further elaboration.

Boronic acids are versatile organic synthons[1] that transform to various functionalities via Suzuki coupling[2] and found useful in pharmaceutical[3] and material industry.[4] Activated radical precursors to access boronic acids include Katrizky salts,[5] (pseudo)halides,[6] carboxylic acids[7] and their redox-active esters.[8] However, carboxylic acids with distinctive structural features could not deliver the desired boronic ester products, such as benzylic and trifluoromethylated substrates, mainly because the putative intermediate carbon radicals are favored to undergo single-electron transfer to afford carbocation/carbanion rather than borylation.[7a] Therefore, the decarboxylative borylation of stabilized and activated radicals has remained challenging in terms of reactivity and much effort has been devoted to harness those species for further derivatization.

Trifluoroethyl radicals are useful fluorinated synthons for incorporating CF_3 functionality into aliphatic systems. We envisioned that α-CF_3 carboxylic acids, which are readily accessed from radical addition or carbometallation of commercial 2-(trifluoromethyl)acrylic acid (TFMAA),[9] can serve as a reliable source of trifluoroethyl radical to access trifluoromethylated boronates. However, such moiety has been proven difficult to activate under strong oxidants, heat, light or transition-metal catalysts due to their unique electronic properties. The few accounts for the generation of trifluoroethyl radical suffered from synthetic hassle and restricted reaction scope. The activation of trifluoroethyl halides needed metal and heat that often caused β-fluoride elimination of M-F moiety.[10] The CF_3-containing sulfinates required multi-step procedures from Barton esters of the corresponding carboxylic acids.[11] (Figure 1A) Current approaches towards geminal trifluoromethyl organoborons were limited to hydroboration of CF_3-substituted olefins[12] and nucleophilic substitution of highly reactive trifluorodiazoethane with boronic acids.[13] Thus, a general and practical strategy for decarboxylative borylation, especially for that of stabilized radicals is in high demand.

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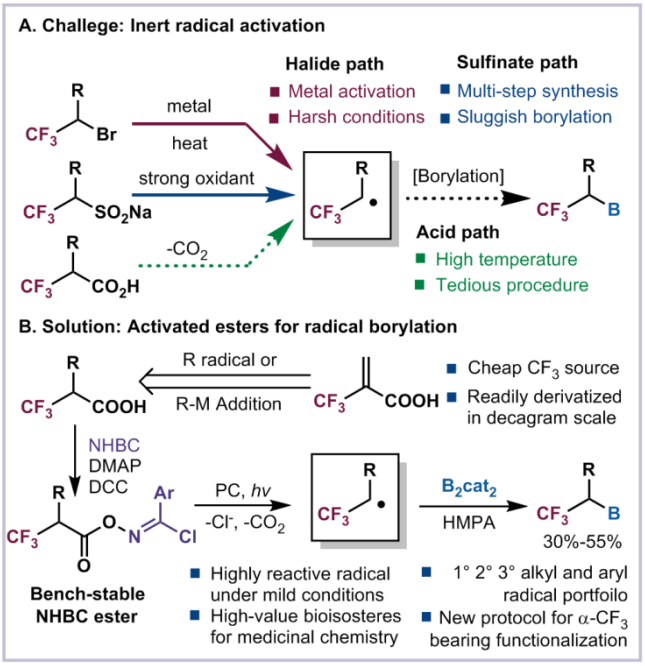
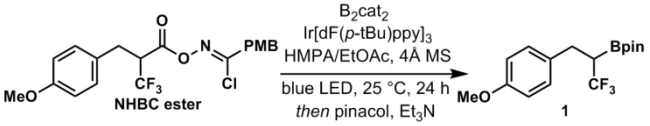


Figure 1. Origin of the Reaction Design.

We speculate that the activation of α-CF_3 carboxylic ester would lead to a highly deshielded secondary radical, which can be captured by diboronates. Therefore, we have tested several plausible pathways for decarboxylative borylation. The NHPI ester of trifluoropropionic acid resulted in low conversion of the product.[7a] We then turned our way to the *N*-hydroxybenzimidoyl chloride (NHBC) esters that developed in our laboratory.[14] The leaving-group assisted redox-active ester could successfully harness the strong electron-withdrawing effect of CF_3 group to generate trifluoroethyl radical under the irradiation of blue LEDs. Herein, we report a universal decarboxylative borylation protocol of alkyl and aryl carboxylic acids with the activation of NHBC (Figure 1B).

Table 1. Optimizations of the Reaction Conditions.



Entry	Deviation from the reaction conditions	Yield [%][b]
1	N/A	51
2	NHPI instead of NHBC	18
3	B_2pin_2 instead of B_2cat_2	0
4	w/o HMPA	0
5	DMAc instead of HMPA/EtOAc	trace
6	w/o 4Å MS	40
7	w/o Ir[dF(*p*-tBu)ppy]$_3$	0
8	in darkness	0

[a] Reaction conditions: **1a** (0.1 mmol), B_2cat_2 (2.5 equiv), Ir[dF(P-tBu)ppy]$_3$ (0.5 mol %), HMPA (5.0 equiv), EtOAc (1.5 mL), r.t., Ar, 24 h. [b] Crude yields were determined by ^{19}F NMR using trifluoromethoxybenzene as internal standard.

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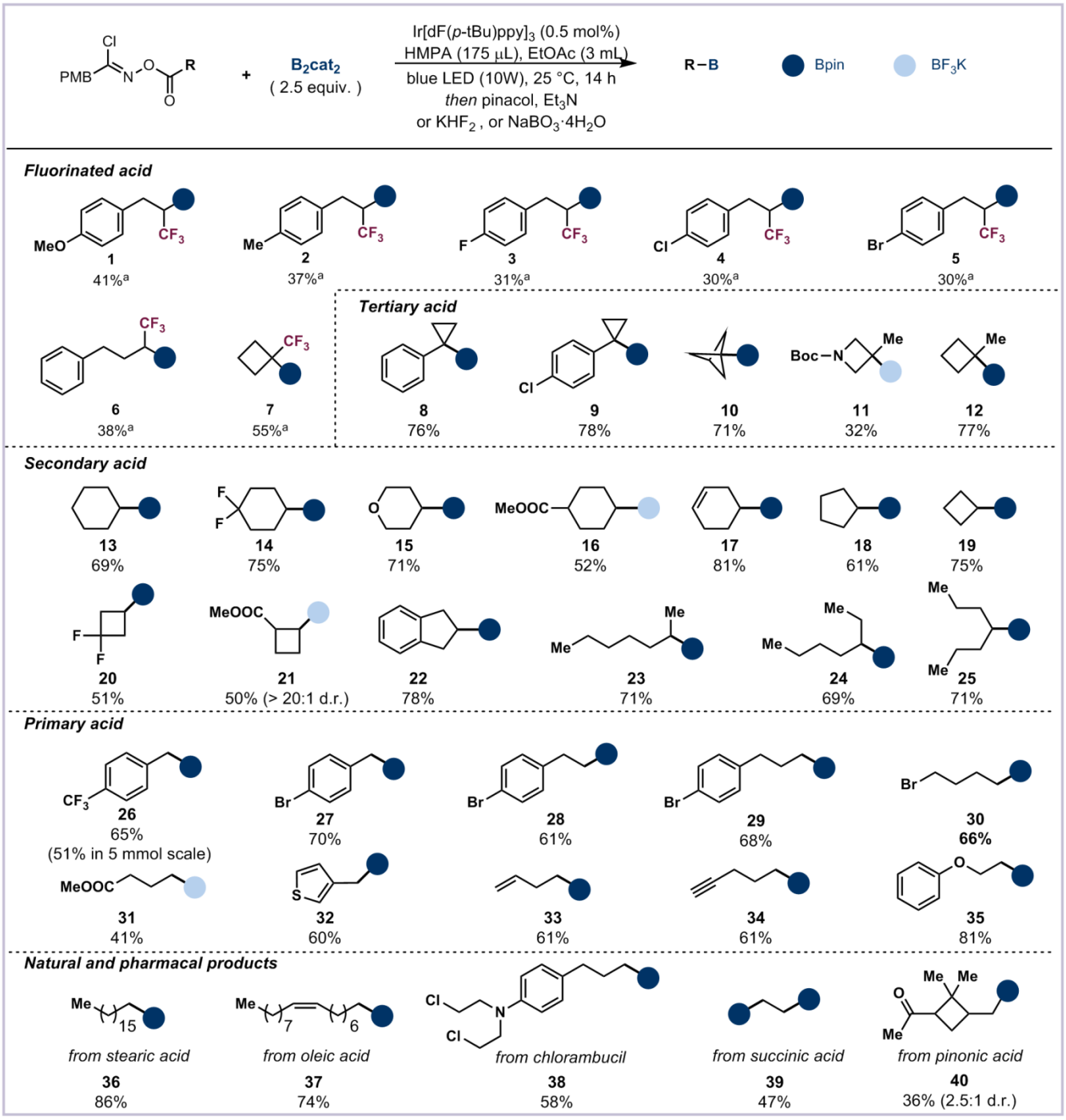
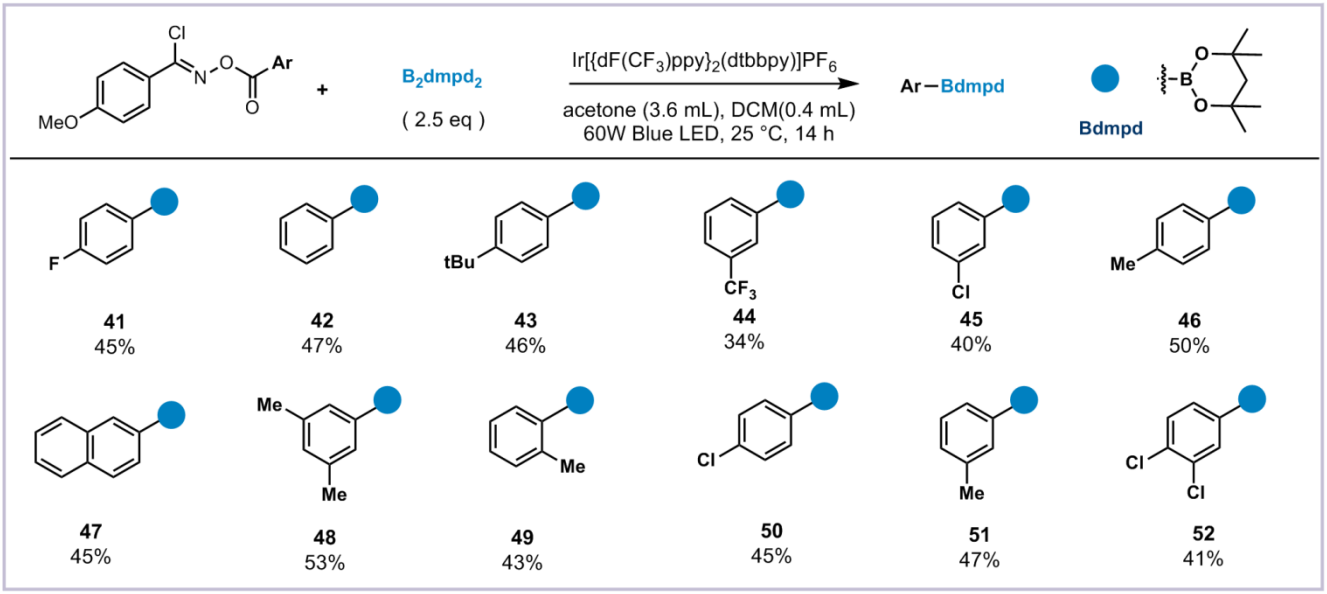


Scheme 1. Substrate Scope of the Aliphatic Acids. [a] The reaction was conducted for 24 h with 50 mg 4 Å MS and the isolated yield was determined from the corresponding hydroxylated product.

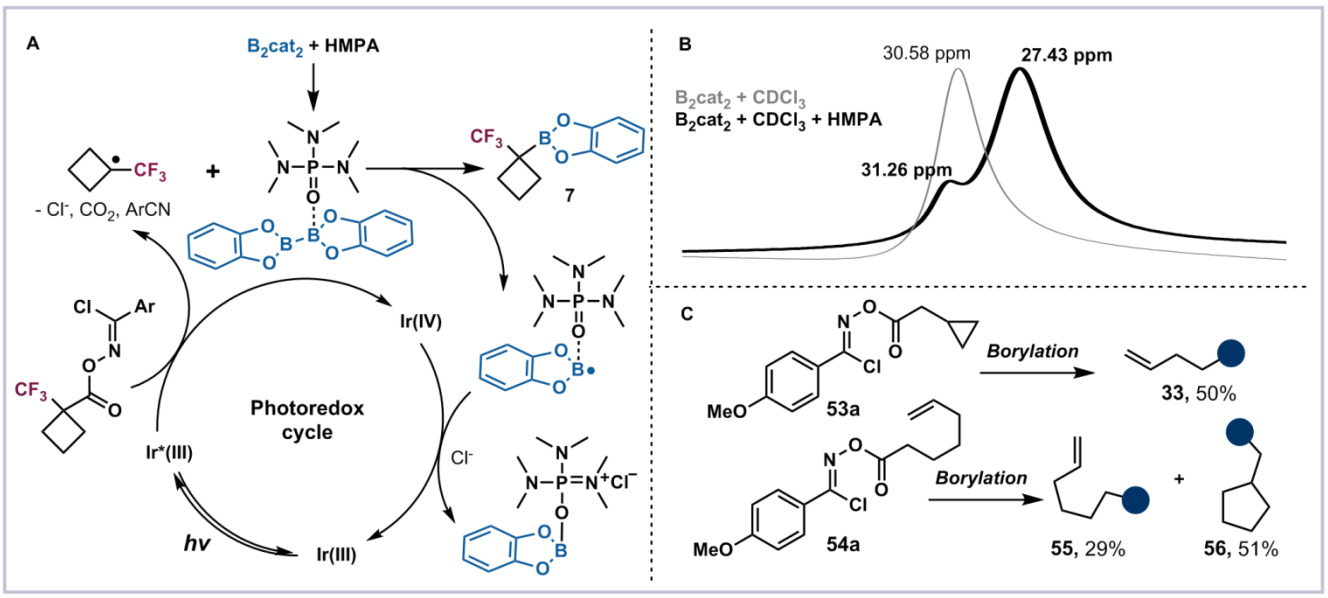
We evaluated the conditions for this decarboxylative borylation reaction and found out in the presence of 0.5 mol% Ir[dF(*p*-tBu)ppy]$_3$ catalyst and B_2cat_2 (2.5 equiv.) in HMPA/EtOAc (3 mL) at ambient temperature, the desired CF_3-boronate was obtained in 51% yield under irridation of blue LEDs (Table 1, entry 1). Since the catechol boronate product is not stable, the crude reaction mixture was converted to the corresponding pinacol boronate, potassium trifluoroborate or alcohol. The use of NHPI ester afforded the product in very low yield (entry 2). Other diboron reagents, such as B_2pin_2, did not provide the corresponding carboboration product (entry 3). Control experiment shows that photocatalyst, HMPA and light are necessary (entries 4-8). The use of other solvents such as CH_2Cl_2, MeCN, THF and MeOH did not lead to any product (see Supporting Information).

With the optimized reaction conditions, we examined the substrate scope of the aliphatic acids for this radical borylation (Scheme 2). Both linear and cyclic CF_3-bearing carboxylic acids are tolerated to access *gem*-CF_3-boronate moieties (**1-7**). Tertiary carboxylic acids bearing strained ring systems could also furnish the borylated products in good yields (**8-12**). Secondary carboxylic acids appended to a variety of cyclic functionalities include cyclohexyl (**13-17**), cyclopentyl (**18, 22**) and cyclobutyl (**19-21**) groups furnished the corresponding boronates. Acyclic acids (**23-25**) were converted into the corresponding boronic esters or potassiunm trifluoroborate salts in good yield. Primary carboxylic acids including benzylic

substrates (**26** and **27**), different aryl moieties on the carbon chains (**28** and **29**), carbonbromine (**30**), ester (**31**), 2-thiophenyl (**32**), alkene (**33**), alkyne (**34**), and ether (**35**), were readily



Scheme 2. Substrate Scope of the Aromatic Acids.



Scheme 3. Mechanistic study. (A) Proposed mechanism for the decarboxylative borylation of NHBC esters. (B) ^{11}B NMR spectra of HMPA and $CDCl_3$ solutions of B_2cat_2. (C) Radical clock reactions

transformed into primary pinacol boronic or potassium trifluoroborate salts in high yields. To showcase the utility of the transformation for diversifying natural-product carboxylic acids, we prepared various NHBC esters and subjected to the standard conditions. Stearic acid (**36**) and oleic acid (**37**) derivatives were obtained in good to high yields. Borylation of the diester of succinic acid furnished the corresponding 1,2-bis(boronic ester) (**38**) in 47% yield. Bioactive Chlorambucil (**39**) and pinonic acid (**40**) were also converted into the corresponding boronic esters.

In the attempt of expending the reaction scope to aryl boronic esters, we setup the reactions using B_2dmpd_2 as boron source in acetone and dichloromethane under the irradiation of blue LEDs (see SI). Aryl boronic esters with electron-donating and electron-withdrawing groups were afforded in good yields. Halogenated aryl boronic esters (**41**, **44**, **45**, **50** & **52**) were also tolerated. Naphthyl-substituted ester was also performed well in the reaction (**47**).

Recent investigations have revealed that *N*-heterocycles and amides are suitable Lewis bases for stabilizing boryl radicals.[7a,15] We found out phosphoramides promote this radical borylation even more efficiently. Comparing the ^{11}B NMR spectrum of B_2cat_2 in $CDCl_3$ with that in HMPA (Scheme 3B), the former shows a single signal at 30.58 ppm, whereas the latter shows one upfield signal (27.43 ppm). The upfield shifting and broadening of the peak supports the ligation of HMPA with diboron species. To confirm the radical mechanism, further radical clock reactions were carried out. Under the standard conditions, ethyl cyclopropyl *N*-hydroxybenzoimidyl chloride **53a** formed homoallylic boronic ester **33** in 50% yield. 5-Hexenyl *N*-hydroxybenzoimidyl chloride **54a** was also subjected to the borylation reaction and 5-hexenyl radical intermediate

underwent cyclization to the more thermodynamically stable cyclopentylmethyl primary radical. The ratio of 5-hexenyl **55** (linear) and cyclopentyl methyl boronic ester **56** (cyclic) in the mixture was determined as ~1:2 (Scheme 3C). On the basis of the above results, a plausible mechanism for the decarboxylative borylation is illustrated (Scheme 3A). The transformation is initiated by the irritation of photocatalyst Ir(III) to Ir(III)* and the activation of NHBC ester releases benzonitrile, chloride, CO_2 and generates trifluormethyl cyclobutyl radical. The HMPA binds to the boron centers of B_2cat_2 and forms a heteroleptic complex. This species captures the alkyl radical to generate the desired boronic ester **7** and cleavage of the B–B bond forms the HMPA-stabilized boryl radical. This intermediate is then oxidized to a neutral complex and terminates the radical chain. Further Stern-Volmer quenching experiment is performed and quantum yield measurement shows that a radical chain mechanism is also possible (see SI for details).[7a]

In conclusion, we have developed a decarboxylative borylation reaction of both stabilized and activated carbon radicals. A range of functionalities including *gem*-CF_3 substituted boronates can be readily accessed from alkyl and aryl derived leaving-group assisted redox-active carboxylic esters under this mild photocatalytic framework for further elaboration.

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Keywords: borylation • photoredox • inert radicals• imidoyl chloride

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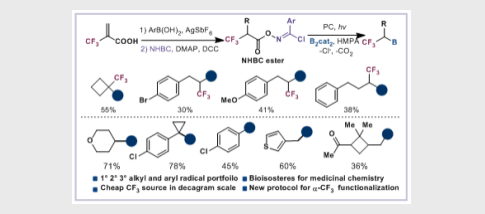

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