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Organocatalytic Decarboxylative Alkylation of N-Hydroxyphthalimide Esters Enabled by Pyridine-Boryl Radicals

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The decarboxylative alkylation of N-hydroxyphthalimide (NHPI) based reactive esters with olefins has been achieved *via* an organocatalytic strategy. Control experiments and density functional theory calculations suggest that these reactions involve a boryl-radical mediated decarboxylation pathway, which is different from the single electron transfer involved decarboxylative alkylation reactions reported previously. This metal-free decarboxylative alkylation reaction features good functional compatibility, and broad substrate scope illustrated by the transformations of both the alkyl and aryl carboxylic acid derivatives.

The decarboxylative alkylation *via* the addition of carbon radicals to olefins is one of the most useful tools to construct C-C bonds, due to the broad sources of carboxylic acids and olefins. Recently, photoredox-mediated decarboxylation of aliphatic acids[1] or its activated esters,[2] provide a facile access for the C-C bond formation *via* the decarboxylation-radical addition reaction of alkyl carboxylic acids to activated alkenes (Fig. 1a). In addition, Ni-catalyzed decarboxylation Giese reaction developed by Baran et al[3] provides a thermally induced radical pathway for the decarboxylative alkylation of aliphatic acids with Michael acceptors. In photoredox catalysis[4-5] or transition-metal catalysis,[6] N-(acyloxy)phthalimide can accept an electron to form a radical anion, which is then fragmented to afford alkyl radicals. These alkyl radicals would then undergo conjugate addition with electron-deficient olefins to provide conjugated addition products. Although the photoredox- or Ni-catalyzed decarboxylative alkylation reaction has been well established, the scope of carboxylic acids is still limited to aliphatic acids. In this regard, the development of a new protocol utilizing both alkyl and aryl radicals from their N-hydroxyphthalimide (NHPI) esters derivatives in decarboxylative alkylation is still desirable.

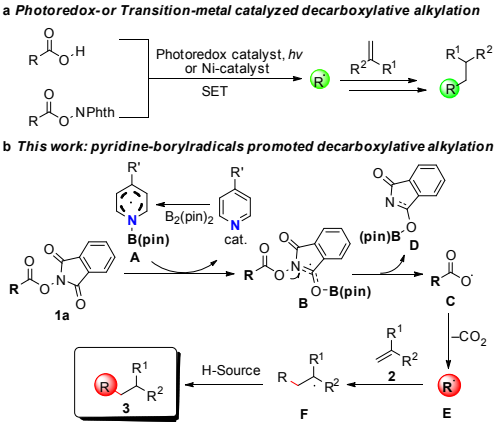

Figure 1. Decarboxylative alkylation reactions.

Herein, we report an organocatalytic decarboxylative alkylation of N-(acyloxy)phthalimides esters with alkenes (Fig. 1b), which, to the best of our knowledge, has not been reported previously. This strategy is inspired by recent reports that the carbonyl group of ketones or aldehydes is readily associated pyridine-boryl radicals to initiate a radical addition reaction[7] and a recent pyridine-catalyzed decarboxylative borylation of NHPI esters reported by Fu's group.[8] In Fu's work, the NHPI ester and a pyridine were assumed to be first coordinated to the diboron complex, and then the B-B bond is cleaved to generate a pyridine-boryl radical and a carboxylate radical simultaneously *via* an intramolecular single electron transfer step. However, we think that the NHPI ester is very likely to coordinate with the pyridine-boryl radical (**A**) to form a radical intermediate, which may trigger the fragmentation of NHPI esters to generate a carbon radical for subsequent radical addition reactions. The pyridine-boryl radical can be easily generated using readily available (pinacolato)diboron (B_2pin_2) and pyridines.[7, 9-10] This strategy would provide an alternative strategy for the decarboxylative alkylation using

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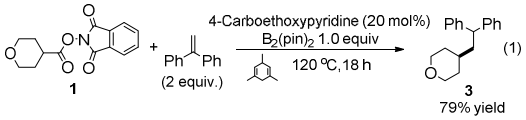
alkenes and readily available NHPI esters. In this work, a broad range of aliphatic or aryl carboxylic acid based reactive esters and alkenes are suitable in this transformation, affording the $C(sp^3)$-$C(sp^3)$ or $C(sp^3)$-$C(sp^2)$ coupling products. We have also demonstrated the utility of this method in the late-stage modification of drug-relevant molecules. This protocol provides a new approach for the construction of C-C bonds from readily available materials without the use of transition-metal or photoredox catalysts.

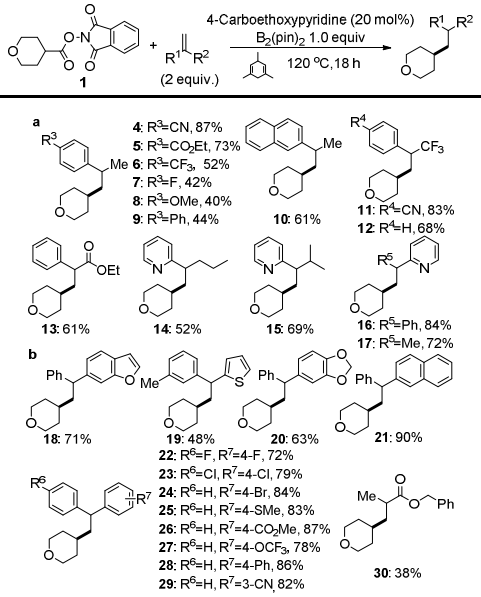
Our proposed catalytic cycle consists of the following steps (Fig. 1b): (1) the generation of the pyridine-boryl radical **A** from B_2pin_2 and pyridine *via* the cooperative catalysis of two pyridine molecules; (2) the migration of the pyridine-boryl radical **A** to N-(acyloxy)phthalimide (1a) to form the radical species **B**; (3) the dissociation of the pyridine molecule from the radical **B** to regenerate the catalyst; (4) the homolytic cleavage of the N-O bond in **B** to afford the aroyloxy radical **C** and phthalimide-B(pin) **D**; (5) the extrusion of CO_2 from **C** to provide the carbon radical **E**; (6) the formation of the radical intermediate **F** from the addition of the carbon radical **E** to alkene; and (7) the hydrogen abstraction of the intermediate **F** from a hydrogen source to give the desired decarboxylative-radical addition product. Although 4-cyanopyridine has been demonstrated to be a suitable Lewis base for the generation of the pyridine-boryl radical **A**,[7, 11] here other pyridines with various substituents will also be explored experimentally.



To explore the possibility of the proposed reaction, we began our study by evaluating the reaction of N-(acyloxy)phthalimides **1** and 1,1-diphenylethylene **2** as the substrates (see Table S1 in Supporting Information for details). In the presence of B_2pin_2 and 1,3,5-trimethyl-1,4-cyclohexadiene, the optimal reaction conditions was achieved through the use of 20 mol% of 4-carboethoxypyridine as the catalyst and $PhCF_3$ as the solvent, the decarboxylative alkylation product **3** could be obtained in 79% yield (see Eq. 1). The use of 1,3,5-trimethyl-1,4-cyclohexadiene is crucial to suppress the disproportionation of the diaryl radical intermediate (**F**).[7c]

After identifying the optimal conditions, the substrate scope of alkenes was investigated with **1** as the substrate (Table 1). A broad variety of α-methylstyrenes, with withdrawing groups and electron-donating group at the para-position of arene moiety, could be used as radical acceptors to form the corresponding adducts **4**-**7** and **8**-**9**. Additionally, α-trifluoromethyl styrenes, α-ester styrenes and 2-vinylsubstituted naphthalene could also be used with similar efficiency, as shown by the formation of **10**-**13**. Good to excellent yields of decarboxylative adducts (**4**-**6**, **11**) were generally obtained for styrenes bearing withdrawing groups. Heterocyclic structure is an important class of structural unit found in drugs and other bioactive molecules, and the synthesis of diverse functionalized heterocycle containing compounds in a metal-free manner is attractive. Notably, our method tolerates a wide range of 1,1-disubstituted olefins containing heterocyclic moiety, including 2-pyridine (**14**-**16**), 4-pyridine (**17**), benzofuran (**18**), thiophene (**19**), and benzo[d][1,3]dioxole (**20**). In addition, other 1,1-diarylethylenes with various substituents such as Br (**24**), SMe (**25**), CO_2Et (**26**) and OCF_3 (**27**) also reacted with 1, giving the dicarboxylative adducts (**21**-**29**) in 72-90% yields. Other alkenes such as benzyl methacrylate could also be employed as the radical acceptor, as demonstrated by the formation of **30** in acceptable yield.

Table 1. Substrate scope of alkene substrates.[a]



[a]Reaction conditions: NHPI ester **1** (0.2 mmol), $B_2(pin)_2$ (0.2 mmol), 4-carboethoxypyridine (0.04 mmol), alkenes (0.4 mmol), $PhCF_3$ (1.0 ml), 1,3,5-trimethyl- 1,4-cyclohexadiene (0.3 mmol), 18 hours.

Different N-(acyloxy)phthalimides could be used as substrates to react with 1,1-disubstituted olefins (Table 2). These thermally induced radical reactions could be compatible with a wide range of functional groups, including halogens (F (**32**, **41**), Cl (**35**), Br (**33**)), heterocycles (pyridine (**35**), piperidines (**42**, **43** and **50**), indole (**68**)), esters (**48**), alkenes (**36**, **40**), amides (**42**-**44**, **50**), hydroxyl (**52**), ketone (**73**), suggesting that this protocol can serve as a versatile platform for further modification. The primary (Table 2a), secondary carboxylic acids (Table 2b) are good alkyl radical precursors to form the 1,1-diarylalkane derivatives in good to excellent yields. The use of tertiary carboxylic acids (Table 2c) could offer the 1,1-diarylalkane compounds with quaternary carbon center with high levels of efficiency (**46**-**52**) in 48-91% yield. Since 1,1-diaryl motif is an important moiety in medicinal chemistry,[12] our method could provide a straightforward way for the generation of a library of drug relevant molecules containing 1,1-diarylalkanes. More importantly, some electron deficient aromatic carboxylic acid reactive esters (derived from pyridine, isoquinoline or benzene carboxylic acids) could also be used as coupling partners to generate the radical adducts (**53**-**67**) in moderate yields (Table 2d). In contrast, the aromatic carboxylic acids or their reactive eaters have not been used in photoredox- or Ni-catalyzed decarboxylative alkylation reaction with alkenes.[2d, 3, 4c] In addition, this method is also applicable in the late-stage structural modification of drug molecules (Table 2e). N-(acyloxy)phthalimides derived from

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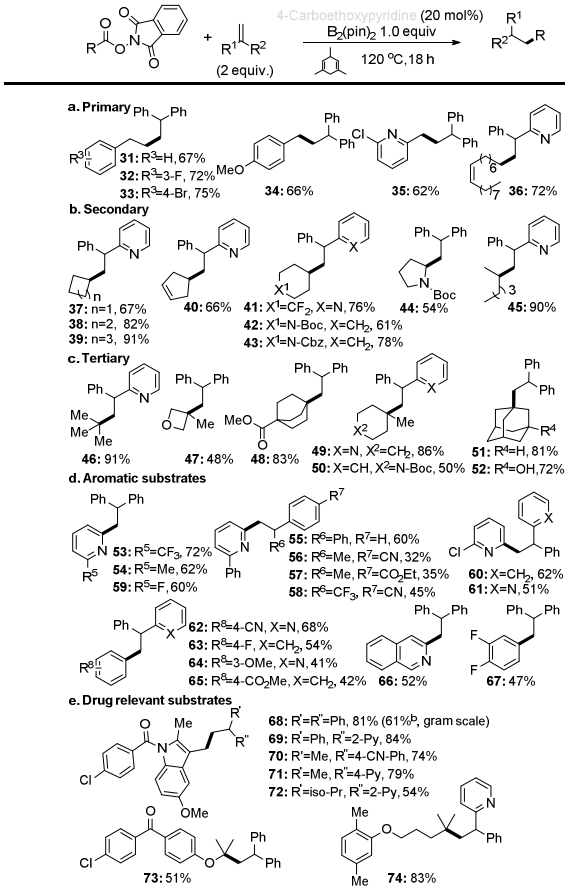
some drug molecules (indometacin, fenofibric acid and gemfibrozil), were all converted to the corresponding decarboxylative adducts (**58**-**74**) in 51-84% yield. Decarboxylative alkylation of the NHPI ester derived from indometacin to form **68** was successfully scaled up to 2.4 mmol, with the product **68** in 61% yield.

Table 2. Substrate scope of NHPI esters.[a]



[a]Reaction conditions: NHPI ester (0.2 mmol), $B_2(pin)_2$ (0.2 mmol), 4-carboethoxypyridine (0.04 mmol), alkenes (0.4 mmol), $PhCF_3$ (1.0 ml), 1,3,5-trimethyl-1,4-cyclohexadiene (0.3 mmol), 18 hours. [b]Performed at 2.4 mmol scale for 18 hours.

With 1,3,5-trimethyl-1,4-cyclohexadiene as a hydrogen source, we have computationally investigated the free energy profile of the reaction between 1,1-diphenylethylene, NHPI ester **1** and the pyridine-boryl radical (**A**) along the pathway proposed in Figure 1b with DFT calculations (with the M06-2X functional).[13] Our calculations suggest that the formation of the pyridine-boryl radical **A** from 4-carboethoxypyridine and $B_2(pin)_2$ is exothermic by 14.9 kcal/mol, with a free energy barrier of 24.6 kcal/mol (see Fig. S1 for computational details). For the reaction among 1,1-diphenylethylene, NHPI ester **1** and the pyridine-boryl radical **A**, the calculated free energy profile is shown in Fig. 2. It can be seen that the six steps proposed above are supported by our calculations. Among six steps, two steps have relatively large activation barriers. The homolytic cleavage of the O-N bond in **B** to form a carboxylate radical **C** *via* TS_{B-C} involves a barrier of 21.8 kcal/mol (relative to the reactants **1** and **A**). Nevertheless, the rate-determining step is the hydrogen abstraction from 1,3,5-trimethyl-1,4-cyclohexadiene to afford the radical species **F** *via* TS_{F-3}, with a barrier of 24.8 kcal/mol (relative to the radical **F**). The whole reaction is strongly exothermic by 50.5 kcal/mol. These results are in qualitative accord with the experimental condition (120 °C is used). In addition, our DFT calculations suggest that the direct SET process from the pyridine-boryl radical to the NHPI ester is highly endergonic by 55.8 kcal/mol (see Figure S3). Thus, the SET pathway for the activation of the NHPI ester to form a carboxylate radical can be excluded.

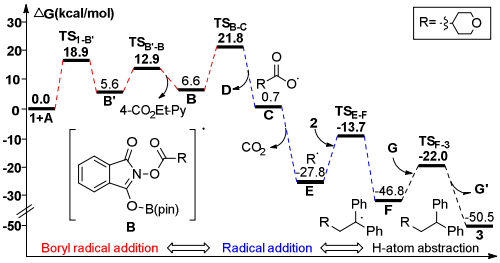


Figure 2. Gibbs free energy profile of the proposed pathway

Furthermore, we performed several control experiments to verify the proposed pathway (Fig. 3 and Fig. S4). First, the intermediacy of the pyridine-boryl radical can be confirmed by the detection of EPR signal from the mixture of 4-carboethoxypyridine/$B_2(pin)_2$ (g = 2.0031, 298 K) (see Fig. S4). The EPR parameters obtained from simulations of the experiment spectra are listed in Table S2. The SOMO picture from our calculations shows that the unpaired electron of this radical (**A**) is mainly delocalized over the pyridine ring (Fig. S4). Then, the formation of the alkyl radical *via* the decarboxylation of N-(acyloxy)phthalimides was verified by a radical-clock experiment using **75** as the substrate (Fig. 3a). The isolation of 5-exo cyclization related product (**76**) in 65% yield indicates that the direct addition of the alkyl radical to alkenes is much slower than the intramolecular radical addition step within the alkyl radical (see Fig. S5).[14] The direct hydrogen abstraction reaction of the decarboxylative carbon radical from 1,3,5-trimethylcycylohexandiene is also possible. As expected, when the substrate **77** was subjected to the standard condition in the absence of alkenes, the decaboxylative reduction product **78** was isolated in 79% yield, and only trace amount of the C-B coupling product **79** was detected by GC-MS analysis (Fig. 2b, see Fig. S6 for details). In contrast, when the 1,1-diphenylethylene was added, the decarboxylative adduct (**80**) was formed in 76% yield (Fig. 2b). These results suggest that the addition of the carbon radical to 1,1-disubstituted ethylene is more favorable than the hydrogen abstraction from 1,3,5-trimethyl-1,4-cyclohexadiene in the reaction. In addition, the formation of the key intermediate, phthalimide-B(pin) (**D**), could be detected by crude HRMS analysis of the reaction mixture of **77** and 1,1-diphenylethylene (see Fig. S7). Finally, we also found that the pyridine/B_2pin_2 system was even compatible with some classical electron acceptors (which are easily reduced *via* a SET pathway). For example, with N-tosylindole **81**, Weinreb amide **82** or aryl iodides **83a-b** as additives, the decarboxylative radical addition related product (**3** and **3'**) could be formed as expected, leaving these electron acceptors untouched (see Table S3).[10b,15] These control experiments also revealed that this decarboxylative alkylation is likely to proceed *via* a pyridine-boryl radical association-

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triggered NHPI ester fragmentation pathway rather than a SET process.

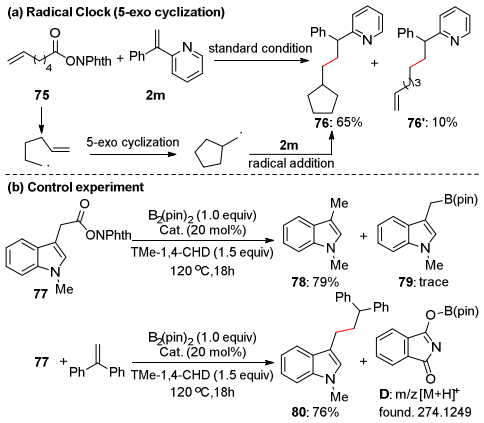

Figure 3. Mechanistic investigations.

In summary, we have established an organocatalytic decarboxylative alkylation of N-hydroxyphthalimide based reactive esters with olefins using 4-carboethoxypyridine as the catalyst. DFT calculations and control experiments suggest that the formation of alkyl or aryl radicals in this decarboxylation alkylation process is induced by the association of the pyridine-boryl radicals with NHPI esters. This metal-free strategy offers an alternative decarboxylative alkylation protocol, different from existing photoredox or transition-metal catalyzed decarboxylative alkylation protocols. This pyridine-boryl radical promoted decarboxylation protocol provides a facile access to a variety of alkyl and aryl radicals from readily available N-hydroxyphthalimide based reactive esters. Moreover, this protocol exhibits broad substrate scope and good functional group compatibility. The potential of this protocol in late-stage modifications of drug molecules has been demonstrated. We hope that our present work might stimulate more studies on radical chemistry.

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Conflicts of interest

There are no conflicts to declare.

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