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Decarboxylative N-Alkylation of Azoles through Visible-Light-Mediated Organophotoredox Catalysis

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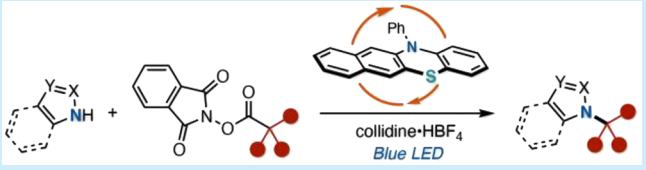
ABSTRACT: An organophotoredox-catalyzed decarboxylative cross-coupling between azole nucleophiles and aliphatic carboxylic acid-derived redox-active esters is demonstrated. This protocol efficiently installs various tertiary or secondary alkyl fragments onto the nitrogen atom of azole nucleophiles under mild and transition-metal-free conditions. The pyridinium additive successfully inhibits the formation of elimination byproducts from the carbocation intermediate. This reaction is applicable to the synthesis of a protein-degrader-like molecule containing an azole and a thalidomide.

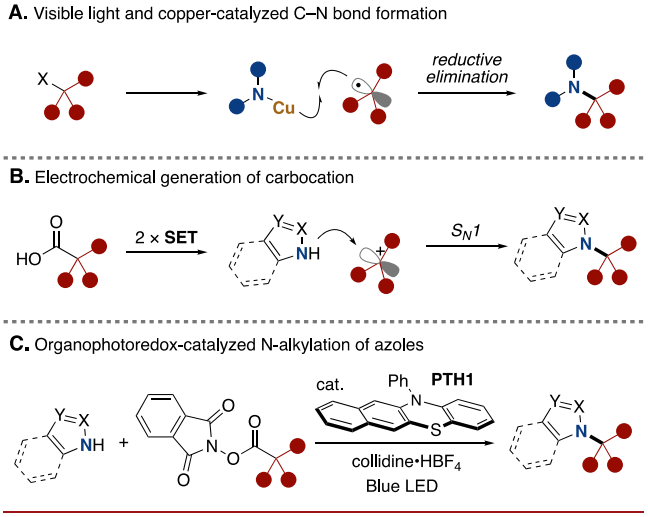


Azoles are an important class of scaffolds found in many pharmaceutical compounds and drug candidates, including antifungal drugs.[1] Among them, N-alkylated azoles have gained much attention in recent medicinal chemistry.[2] To this end, a variety of synthetic methods for N-alkylation of azoles have been developed. For the introduction of primary or secondary alkyl groups to azoles, nucleophilic substitution with alkyl electrophiles, including the Mitsunobu reaction, are commonly employed.[3] An alternative approach is the oxidative N-alkylation of azoles using hydrocarbons bearing weak C−H bonds and reactive oxidants.[4] On the other hand, the introduction of tertiary alkyl groups onto azoles depends on conventional S_N1-type reactions using tertiary alkyl halides or tertiary alcohols with strong acids.[5] Because of the difficulty of substrate preparation and the poor functional group tolerance, tertiary N-alkylation of azoles remains a key challenge for medicinal chemists.

Recently, alkyl-radical-mediated N-alkylation of azoles under mild reaction conditions has been intensively studied. MacMillan and co-workers demonstrated that a copper catalyst enabled the connection of nitrogen nucleophiles and alkyl radicals generated from aliphatic carboxylic acid-derived hypervalent iodine reagents with metallaphotoredox catalysis (Scheme 1A).[6] This approach enables the installation of various primary, secondary, and tertiary alkyl groups onto the nitrogen atom of nitrogen-based nucleophiles, including azoles. Although a few examples of tertiary alkylation were demonstrated, the scope of alkyl fragments was restricted.[7] Against this background, Baran and co-workers expanded the synthetic toolbox by employing electrochemical generation of carbocations from aliphatic carboxylic acids to achieve N-alkylation of azoles (Scheme 1B).[8]

We previously reported visible-light-mediated organophotoredox catalysis for alkylation of heteroatom nucleophiles using aliphatic carboxylic acid-derived redox-active esters as an alkylation source.[9] The reaction proceeds through a redox-neutral radical−polar crossover mechanism.[10] Therein a photoinduced single electron transfer (SET) from the catalyst *N*-phenylbenzo[*b*]phenothiazine (**PTH1**)[11] to a redox-active ester[12] produces a **PTH1** radical cation and a radical anion form of the redox-active ester, which releases an alkyl radical with carbon dioxide and phthalimide anion. The resultant alkyl radical is oxidized by the **PTH1** radical cation to give the

Scheme 1. N-Alkylation of Azoles



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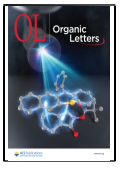
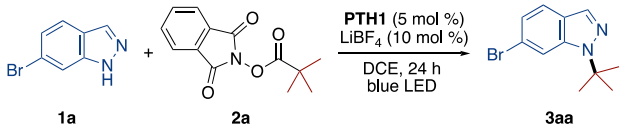


corresponding alkylsulfonium intermediate, which engages with various heteroatom nucleophiles.

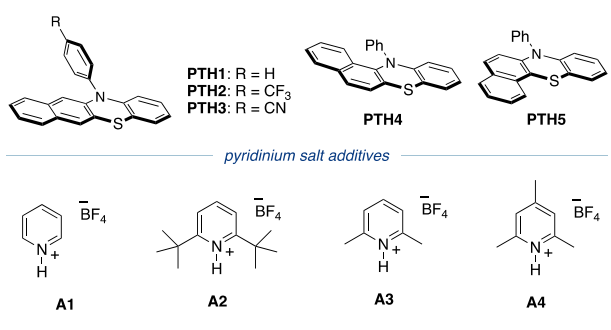
In this work, we extended this visible-light-mediated organophotoredox protocol to N-alkylation of azoles (Scheme 1C). Various tertiary and secondary benzyl fragments were efficiently transferred from carboxylic acid-derived redox-active esters to azoles under mild and transition-metal-free conditions. This protocol provides an alternative synthetic tool for N-alkylation of azoles.

The optimization of the reaction conditions for N-alkylation of azoles was explored with 6-bromoindazole (**1a**) and pivalic acid-derived redox-active ester **2a**. After a quick screening, the reaction of **1a** and **2a** was found to proceed in the presence of **PTH1** and lithium tetrafluoroborate salt as cocatalysts in 1,2-dichloroethane under blue LED irradiation for 24 h to produce the N-alkylated product **3aa** in 20% yield (Table 1, entry 1). MeCN, which was found to be the best reaction medium in our previous report on etherification reactions, did not give the desired product at all (entry 2). THF afforded the coupling product **3aa** in low yield (entry 3). Although other halogenated solvents such as 1,2-dichlorobenzene and DCM were examined, the reaction efficiency was not improved (entries 4 and 5).

Table 1. Screening of the Reaction Conditions[a]



Entry	Change from standard conditions	Yield of **3aa** (%)[b]
1	none	20
2	MeCN instead of DCE	0
3	THF instead of DCE	10
4	1,2-dichlorobenzene instead of DCE	7
5	DCM instead of DCE	14
6	**PTH2** instead of **PTH1**	19
7	**PTH3** instead of **PTH1**	11
8	**PTH4** instead of **PTH1**	0
9	**PTH5** instead of **PTH1**	6
10	**A1** (15 mol %) instead of $LiBF_4$ (10 mol %)	20
11	**A2** (15 mol %) instead of $LiBF_4$ (10 mol %)	19
12	**A3** (15 mol %) instead of $LiBF_4$ (10 mol %)	29
13	**A4** (15 mol %) instead of $LiBF_4$ (10 mol %)	29
14	**A4** (2 equiv.), and **2a** (2 equiv.) instead of $LiBF_4$ (10 mol %), 8 h	59
15	entry 14 in 1 mmol scale	53



[a]The reaction was carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), **PTH1** (0.01 mmol), and $LiBF_4$ (0.02 mmol) in solvent (0.5 mL) under blue LED irradiation for 24 h. [b]^{1}H NMR yields.

Other phenothiazine catalysts were examined (Table 1, entries 6–9). Incorporation of an electron-deficient group on the N-substituent of the benzo[*b*]phenothiazine catalyst did not improve the yield of N-alkylated product (entries 6 and 7). The reactions employing isomers of the benzophenothiazine core as the organophotoredox catalyst did not proceed well (entries 8 and 9).

The identity of the additive had an immense effect on the formation of the desired product (Table 1, entries 10–14). We assumed that the phthalimide anion generated from single-electron reduction of a redox-active ester would act as a base to promote the unproductive elimination (E1/E2) reaction. To suppress this side reaction, a series of pyridinium salts (pK_a = 3.4 for pyridinium in DMSO[13]) bearing a lower pK_a than phthalimide (pK_a = 8.3[14]) were examined. Unfortunately, pyridinium tetrafluoroborate did not improve the product yield (entry 10). A 2,6-di-*tert*-butylpyridine-derived HBF_4 salt showed comparable reactivity to $LiBF_4$ (entry 11). Further screening of pyridinium salts revealed that pyridinium salts derived from 2,6-lutidine or 2,4,6-collidine increased the product yield (entries 12 and 13). Finally, increasing the amount of **A4** and **2a** drastically improved the yield of **3aa** (entry 14). This protocol was equally applicable on a 1 mmol scale with a limited impact on the yield (entry 15).

With the optimal reaction conditions established, the scope of azoles was investigated with *tert*-butyl redox-active ester **2a** (Figure 1, top). A simple indazole also participated in the reaction as an azole donor (**3ba**). Ester- or amide-substituted indazoles were found to be suitable substrates (**3ca**–**3ea**). The reaction with 4-methylindazole afforded the *N*-*tert*-butylated product, although the yield was low (**3fa**). The reaction with benzotriazole gave a mixture of regioisomers (**3ga**). A pyrazole substrate efficiently coupled with **2a** to give the desired product (**3ha**). The scope of azoles was also evaluated with tertiary benzylic redox-active ester **2b**. In comparison with **2a**, the reactions with **2b** gave the coupling products in relatively high yields (**3ab**, **3ib**, and **3db**). A highly functionalized pyrazole was also identified as a suitable substrate (**3jb**). When a purine derivative and 5-azaindole were used as reaction substrates, the corresponding coupling products **3kb** and **3lb**, respectively, were obtained in moderate yields. These substrates did not give any coupling product with **2a** (data not shown). As with **3ga**, the reactions with benzotriazole **1g** gave a mixture of regioisomers (**3gb**). This protocol was not applicable to other heteroatomatics containing carbazoles and indoles (data not shown).

Our attention turned to the scope of aliphatic redox-active esters (Figure 1, bottom). An acyclic aliphatic substituent could be readily introduced (**3dc** and **3bd**). The low yield of **3bd** was thought to be due to the competitive elimination reaction. Our protocol facilitated the installation of various 1-methylcycloalkyl groups on the nitrogen atom of an indazole fragment (**3be**–**bg**). The carboxylic acid moiety of gemfibrozil was transformed into an azole group using this organophotoredox catalytic method (**3bh**). Both acyclic and cyclic tertiary benzylic redox-active esters worked as N-alkylating reagents (**3bb**, **3di**, **3dj**, **3bk**, and **3bl**). Secondary benzylic azoles could be prepared using the corresponding carboxylic acids, including ketoprofen (**3gm**, **3bn**, and **3bo**). Although we tested the reactions with unactivated secondary or primary redox-active esters, the desired product were not obtained

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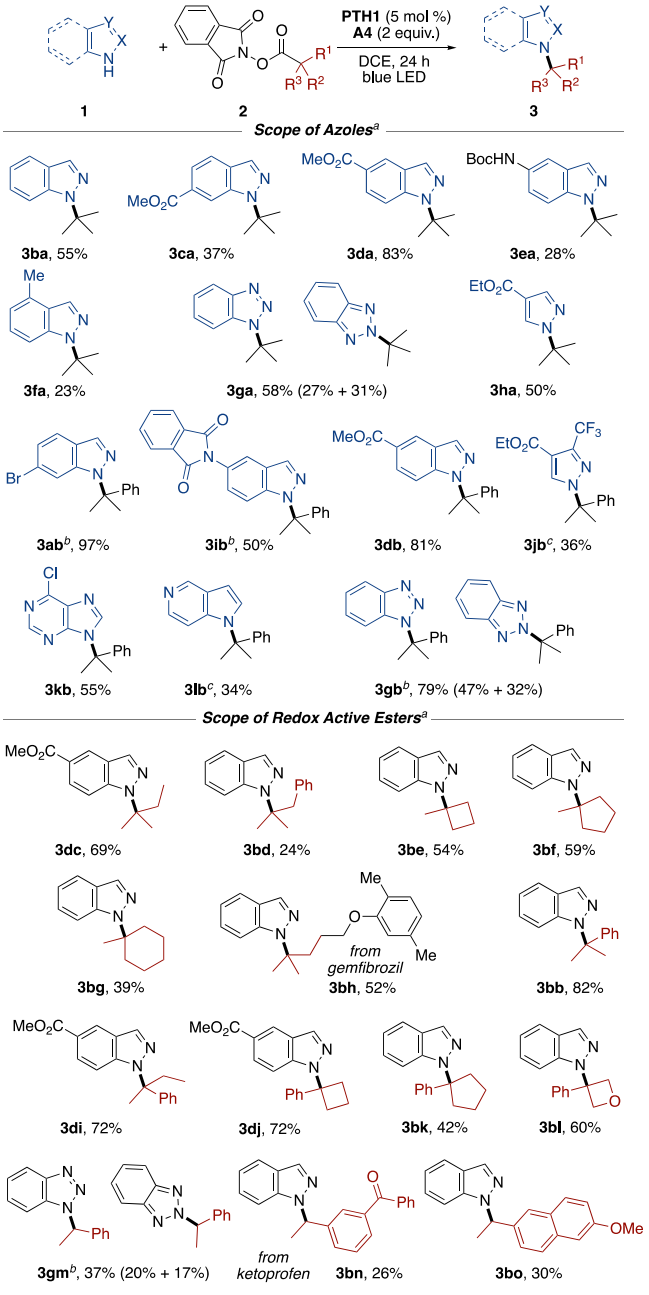


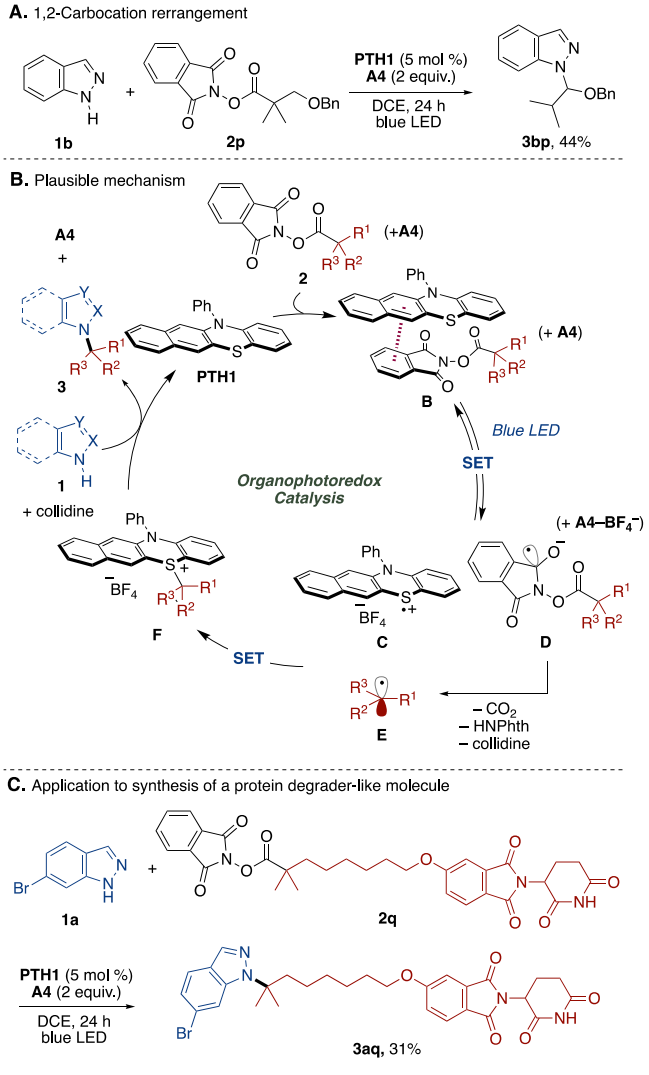
Figure 1. Substrate scope. Notes: [a]The reaction was carried out with **1** (0.2 mmol), **2** (0.4 mmol), **PTH1** (0.01 mmol), and **A4** (0.4 mmol) in DCE (0.5 mL) under blue LED irradiation for 24 h. [b]The reaction was carried out with **1** (0.2 mmol), **2** (0.3 mmol), **PTH1** (0.01 mmol), and $LiBF_4$ (0.02 mmol) in AcOEt (0.5 mL) under blue LED irradiation for 24 h. [c]See the Supporting Information for the details.

(data not shown), possibly because of the slow formation of the corresponding alkyl radicals.

To shed light on the reaction mechanism, various studies were conducted. First, the reaction of **1b** and redox-active ester **2p** bearing a β-alkoxy substituent was conducted (Scheme 2A). The alkylation occurred at the α-alkoxy position and not at the original α-carbonyl position. This 1,2-carbocation rearrangement supported the hypothesis that a carbocation intermediate or an equivalent species plays a role in this catalytic cycle.

The role of additive **A4** was also investigated. First, to see whether **A4** inhibits the elimination (E1/E2) reaction, the product ratio of the reactions of **1b** and **2h** with or without **A4**

Scheme 2. Mechanistic Studies and Application to the Synthesis of a Protein-Degrader-like Molecule



was checked (Figure S4). As a result, the formation of the alkene was suppressed, albeit slightly. Next, cyclic voltammetry experiments on **A4** and **2a** were carried out (see Figures S5 and S6). The CVs of **A4** and **2a** showed irreversible waves (E_{pc} = −1.62 and −1.33 V vs SCE, respectively). Upon the addition of **A4** to **2a**, the reduction wave of **2a** slightly moved to E_{pc} = −1.12 and −1.22 V vs SCE (Figure S7). Following our previous report, we investigated whether **A4** is involved in the formation of a charge-transfer complex between **PTH1** and the redox-active ester. The UV−vis absorption spectra for various combinations of **PTH1**, **2a**, and **A4** were measured under the optimal reaction conditions (Figure S8). No significant shift of the absorption band was observed when **A4** was added to the mixture of **PTH1** and **2a**. These observations above suggested that **A4** possibly acts as a Brønsted acid that facilitates the electron transfer from **PTH1** to the redox-active ester and traps the catalytically generated phthalimide anion.

On the basis of the mechanistic studies shown above, the proposed mechanism for the organophotoredox-mediated radical−polar crossover is summarized in Scheme 2B. First, **PTH1** and redox-active ester **2** assemble to form charge-transfer complex **B**. Blue LED irradiation induces SET from **PTH1** to **2** to afford the radical cation form of **PTH1** (**C**) and

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Org. Lett. 2021, 23, 5415−5419

the radical anion form of **2** (**D**). In the presence of collidine HBF_4 (**A4**), **D** generates alkyl radical **E** with the release of carbon dioxide, phthalimide, and collidine. Recombination of **C** and **E** through SET followed by complexation affords alkylsulfonium intermediate **F**, which then reacts with azole nucleophile **1** in the presence of collidine to give the N-alkylated product **3** and regenerate **A4** and **PTH1**.

To demonstrate the synthetic utility of this decarboxylative alkylation, this protocol was applied to synthesis of a protein-degrader-like molecule[15] (Scheme 2C). For this purpose, a partial protein-degrader-like precursor **2q** bearing a thalidomide as an E3 ligase ligand moiety and a tertiary redox-active ester as a cross-linker moiety was prepared. The reaction of **1a** and **2q** under the standard reaction conditions proceeded to afford the coupling product **3aq**.

In conclusion, we have developed a synthetic tool for N-alkylation of azole compounds using visible-light-mediated organophotoredox catalysis. The collidine HBF_4 additive acts as a Brønsted acid that efficiently inhibits the elimination reaction of the carbocation intermediate caused by the phthalimide anion. Notably, this reaction does not require transition metals, external oxidants/reductants, and strong acids, which have been utilized in previously reported methods. The high functional group tolerance of this protocol was demonstrated through the application of this reaction to the synthesis of a protein-degrader-like molecule. On the basis of this achievement, our group is aiming to expand the scope of amine nucleophiles that can be employed in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01745.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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