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Cross Coupling of Alkyl Redox-Active Esters with Benzophenone Imines via Tandem Photoredox and Copper Catalysis

Runze Mao, Jonathan Balon, and Xile Hu*

Abstract: Alkyl amines are an important class of organic compounds in medicinal and materials chemistry. Until now very few methods exist to synthesize alkyl amines by metal-catalyzed cross coupling of alkyl electrophiles with nitrogen nucleophiles. Described here is an approach to employ tandem photoredox and copper catalysis to enable the cross coupling of alkyl *N*-hydroxyphthalimide esters, readily derived from alkyl carboxylic acids, with benzophenone imines. Hydrolysis of the coupling products furnish alkylated primary amines. Primary, secondary, and tertiary alkyl groups can be transferred, and the coupling tolerates a diverse set of functional groups. The method allows rapid functionalization of natural products and drugs, and can be used for expedite syntheses of pharmaceuticals from readily available chemical feedstock.

Alkyl amines are prevalent in synthetic intermediates and bio-active molecules.[1-2] Although certain alkyl amines can be conveniently prepared by direct substitution of alkyl halides with nitrogen nucleophiles,[3] the substitution is difficult or even impossible for bulky secondary and tertiary alkyl halides. Moreover, elimination and overalkylation are common pitfalls of substitution. Transition metal catalyzed C(sp^3)-N cross coupling has the potential to overcome the shortcomings of direct substitution. However, this coupling method is only at its infancy.[4-12] β-H elimination from metal alkyl intermediates and difficulty in C(sp^3)-N reductive elimination are two perceived problems.

The groups of Baran[13] and others[14] have reported remarkable applications of alkyl redox-active esters in C-C cross coupling reactions. These esters can be easily prepared from alkyl carboxylic acids, which are readily available, stable, and non-toxic. Due to the challenge in C(sp^3)-N cross coupling described above, alkyl redox active esters have not been widely used for C-N coupling.[7, 12, 15] Fu, Peters, and co-workers[7] developed photoindued, Cu-catalyzed intramolecular decarboxylative C-N coupling of primary and secondary alkyl *N*-hydroxyphthalimide (NHPI) esters, a prototypical class of redox-active esters, to give alkyl phthalimides (Fig. 1A). However, only primary and secondary alkyl NHPI esters could be coupled. We reasoned that the inability to couple tertiary alkyl NHPI esters in this method might be due to steric hindrance or difficulty in reductive elimination.

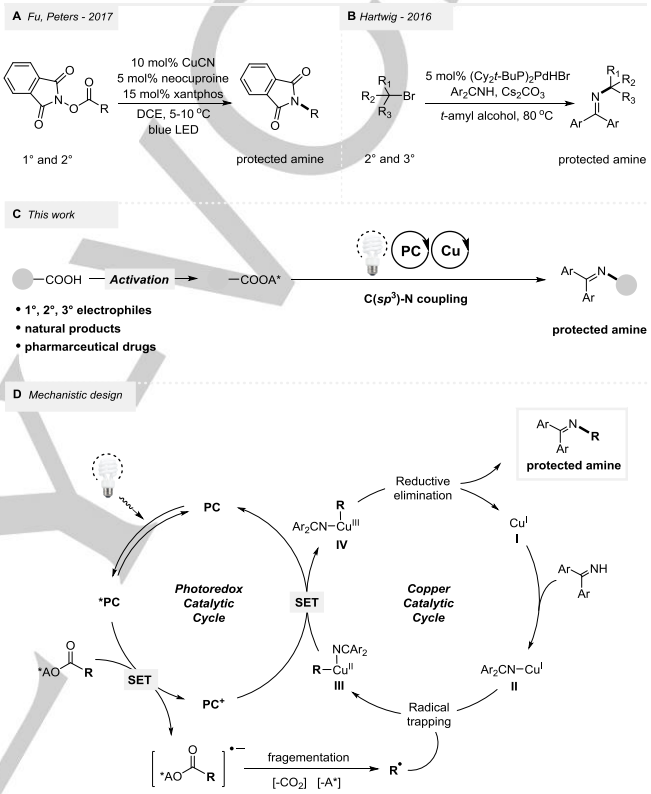

Figure 1. (A) A previous method for the intramolecular C-N coupling of alkyl NHPI esters (B) A previous method for the cross coupling of alkyl bromides with benzophenone imines (C) Reaction scheme for the present C-N coupling method. (D) Design of tandem photoredox and Cu catalysis for the present C-N coupling method.

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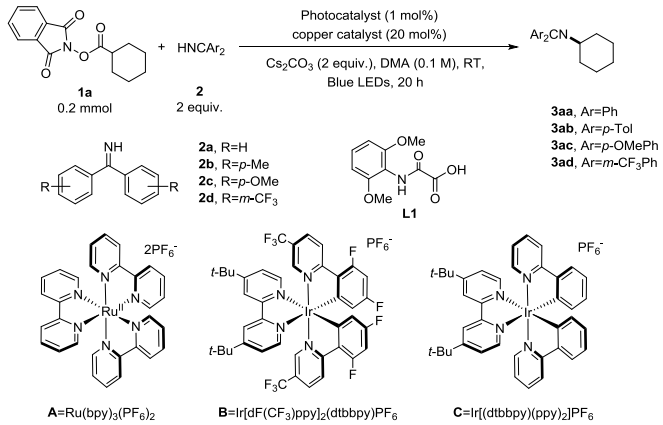
Table 1. Summary of the effects of reaction parameters and conditions on the reaction efficiency



Entry	Imine	PC	Copper catalyst	Yield (%)[a]
1[b]	**2a**	**A**	CuBr/**L1**	30
2[b]	**2a**	**A**	$Cu(MeCN)_4PF_6$	32
3[c]	**2a**	**A**	$Cu(MeCN)_4PF_6$	19
4	**2a**	**A**	$Cu(MeCN)_4PF_6$	39
5[d]	**2a**	**A**	$Cu(MeCN)_4PF_6$	trace
6[e]	**2a**	**A**	$Cu(MeCN)_4PF_6$	trace
7	**2a**	**B**	$Cu(MeCN)_4PF_6$	40
8	**2a**	**C**	$Cu(MeCN)_4PF_6$	49
9	**2a**	**C**	Cu (100 mol%)	24
10	**2a**	**C**	$CuCl_2$	28
11	**2b**	**C**	$Cu(MeCN)_4PF_6$	33
12	**2c**	**C**	$Cu(MeCN)_4PF_6$	29
13	**2d**	**C**	$Cu(MeCN)_4PF_6$	70
14	**2d**	none	$Cu(MeCN)_4PF_6$	trace
15	**2d**	**C**	none	trace
16[f]	**2d**	**C**	$Cu(MeCN)_4PF_6$	trace

[a] Corrected GC yield using *n*-dodecane as an internal standard. [b] Same condition as the optimized reaction condition in reference 12. Reaction was carried out with **1a** (0.2 mmol), **2a** (2 equiv.), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuBr (20 mol%), **L1** (7.5 mol%), Et_3N (5 equiv.) and MeCN (2.0 mL). [c] MeCN (0.1 M). [d] K_2CO_3 (2 equiv.) as the base. [e] KO^{t}Bu (2 equiv.) as the base. [f] No light. **PC**=photocatalyst; **A**=$Ru(bpy)_3(PF_6)_2$; **B**=$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$; **C** =$Ir[(dtbbpy)(ppy)_2]PF_6$; DMA=*N,N*-dimethylacetamide.

These issues might be solved using a benzophenone imine nucleophile with a sp^2-hybridized nitrogen, which is sterically more accessible and more prone to reductive elimination.[16] The benzophenone imine group in the products can be easily hydrolyzed or transaminated to give primary amines[10, 17-18] Furthermore, Hartwig and co-workers[10] showed that benzophenone imines could be coupled to secondary and tertiary alkyl bromides to give protected amines (Fig. 1B). However, coupling to primary alkyl bromides was not reported.

Here we report the successful development of a method that indeed allows the intermolecular coupling of alkyl NHPI esters with benzophenone imines (Fig. 1C). This method works with primary, secondary and tertiary alkyl electrophiles, which provides a clear advantage over reductive amination and substitution (not suitable for tertiary alkyl groups). Broad scope, highly functional group tolerance, and applications in medicinal chemistry have been demonstrated.

We envisioned the following tandem photoredox and copper catalysis[19-20] for the decarboxylative coupling of alkyl NHPI esters with benzophenone imines (Figure 1D). Initially, the coordination of the benzophenone imines with a low-valent copper catalyst (**I**) followed by deprotonation would form the copper(I)-amido species (**II**). Concurrently, excitation of a photocatalyst (PC) would generate a photoexcited complex (PC*), which could reduce the NHPI ester through a single-electron transfer (SET), affording an alkyl radical upon fragmentation. Subsequent capture of the alkyl radical by **II** would yield intermediate (**III**). Oxidation of **III** by the oxidized photocatalyst (PC^+) forms a high-valent metal alkyl amido complex **IV** and regenerates the PC. **IV** is expected to undergo reductive elimination to give the desired coupling product and regenerate a low-valent Cu species (**I**), closing the copper catalytic cycle. In this design, the photoredox catalysis has two important roles: generation of an alkyl radical from an alkyl NHPI ester and one-electron oxidation of a Cu alkyl amido complex. The former is necessary because metal amido species has not been shown to activate alkyl NHPI ester under thermal conditions. The latter is intended to facilitate the difficult C(sp^3)-N reductive elimination.

We recently applied a similar design for the decarboxylative coupling of alkyl NHPI esters with anilines.[12] Using the optimized conditions in that study, however, the coupling of cyclohexyl NHPI ester **1a** with benzophenone imine **2a** was inefficient (Table 1, entry 1). Optimization was conducted to search for the best conditions for this coupling (Table 1; SI, Table S1). After various ligands were screened, it was found that ligand-less conditions gave even slighly higher yields (Table 1, entry 2; SI, Table S1, entries 1-10). Among various copper salts, $Cu(MeCN)_4PF_6$ gave the best yield (SI, Table S1, entries 7-10). Cs_2CO_3 was the best base (Table 1, entries 2-6; SI, Table S1, entries 11-17), probably due to coordination the NHPI ester with Cs_2CO_3 as proposed in a previous study.[21] Dimethylacetamide (DMA) was the best solvent (Table 1, entries 3-4; SI, Table S1, entries 12, 18-20). By changing the photocatalyt from $Ru(bpy)_3(PF_6)_2$ (**A**) to an Ir(III) complex such as $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**B**) or $Ir[(dtbbpy)(ppy)_2]PF_6$ (**C**), the yield was improved (Table 1, entries 4, 7-8; Table S1, entries 21-23). An optimized yield of 49% was obtained using **1a** (0.2 mmol), benzophenone imine (**2a**, 2 equiv.), $Ir[(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $Cu(MeCN)_4PF_6$ (20 mol%), Cs_2CO_3 (2 equiv.), and DMA (0.1 M) under blue LED irradiation for 20 h at room temperature (Table 1, entry 8). Interestingly, when the Cu(I) complex $Cu(MeCN)_4PF_6$ (20 mol%) was replaced by either a Cu metal (100 mol%) or a Cu(II) salt $CuCl_2$ (20 mol%), the coupling product was also obtained, but with lower yields (Table 1, entries 9-10). The Cu metal might be oxidized by the excited Ir photocatalyst to Cu(I), generating the Ir(II) form of the photocatalyst which upon reducing the NHPI ester regenerates the photocatalyst. Likewise, $CuCl_2$ might be reduced by the excited Ir photocatalyst to Cu(I), while the resulting Ir(IV) species might be reduced to the Ir(III) photocatalyst by the solvent. In these cases, a catalytic cycle similar to Fig. 1D is operating. Alternatively when $CuCl_2$ is used as catalyst, the catalytic might occur via an alternative pathway where Cu(II) imine species

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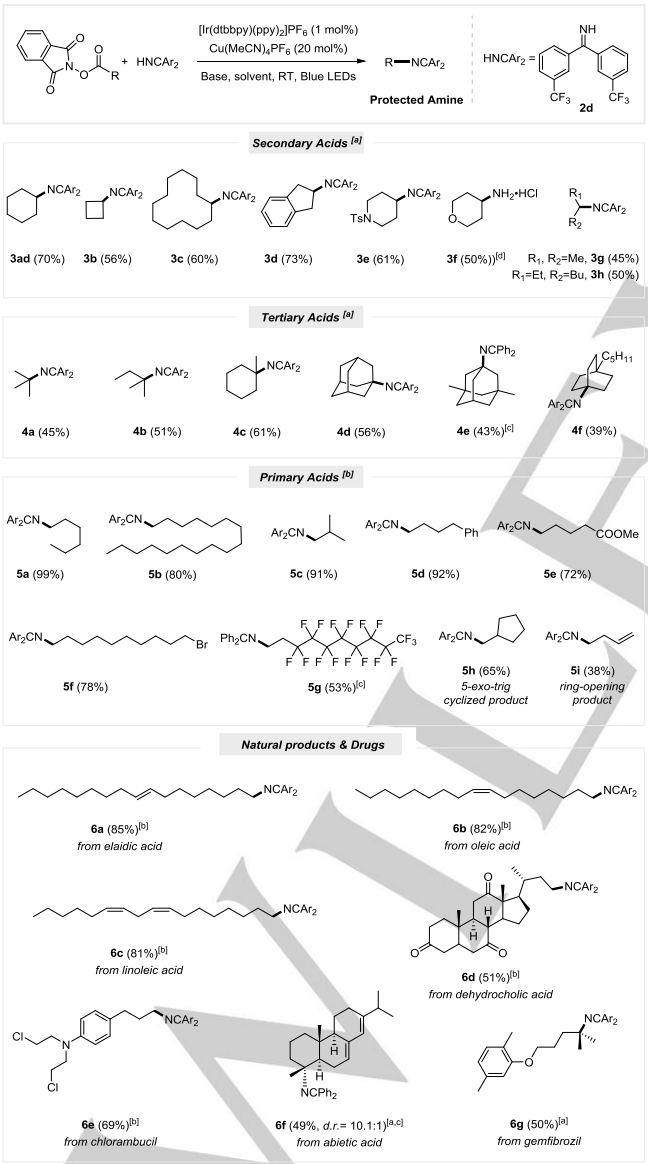
captures the alkyl radical from the NHPI ester to give the key Cu(III) intermediate,[15] which upon reductive elimination gives the C-N coupling product (Fig. S1, SI).

Different substituted benzophenone imines were then explored as the imine partners (Table 1, entries 8, 11-13). The coupling of the electron-deficient imine **2d** (Table 1, entry 13) gave a higher yield (70%) than that of electron-rich imines **2b** and **2c** as well as the parent imine **2a** (Table 1, entries 8, 11-12). An added advantage of using **2d** is that the products are less sensitive to silica gel chromatography. Thus, **2d** was chosen as the preferred nitrogen nucleophile. Photocatalyst, copper catalyst and light are all essential for the coupling. Without any one of the three elements, no coupling was obtained (Table 1, entries 14-16).

Table 2. Scope of the cross coupling of alkyl NHPI esters with substituted benzophenone imines



[a] General conditions for secondary and tertiary NHPI ester: NHPI ester (1 equiv.), **2d** (2 equiv.), $Ir[(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $Cu(MeCN)_4PF_6$ (20 mol%), and Cs_2CO_3 (2 equiv.) in DMA (0.1 M), irradiated at room temperature for 20 h, isolated yield. [b] General conditions for primary NHPI ester: NHPI ester (2 equiv.), **2d** (1 equiv.), $Ir[(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $Cu(MeCN)_4PF_6$ (20 mol%) and diisopropylamine (2 equiv.) in MeCN (0.1 M), irradiated at room temperature for 16 h, isolated yield. [c] **2a** as the nucleophile. [d] Following acidic work-up was conducted.

The optimal reaction conditions in Table 1 (entry 4) could be applied to the coupling of a wide range of secondary alkyl NHPI esters (Table 2). Cyclic alkyl groups including small and large rings (**3ad**-**3c**), indane group (**3d**) and heterocyclic alkyl group (**3e-3f**), as well as acyclic secondary alkyl groups (**3g**-**3h**) were all successfully coupled. Tertiary alkyl electrophiles are challenging substrates in cross-coupling reactions due to their bulky nature. To our delight, tertiary alkyl NHPI esters are viable substrates as well (Table 2). Protected amines substituted by acyclic (**4a**-**4b**), cyclic (**4c**) alkyl groups as well as those containing relatively complex skeletons such as adamantane (**4d-4e**) and a bridged bicyclic structure (**4f**) could be obtained in synthetically useful yields.

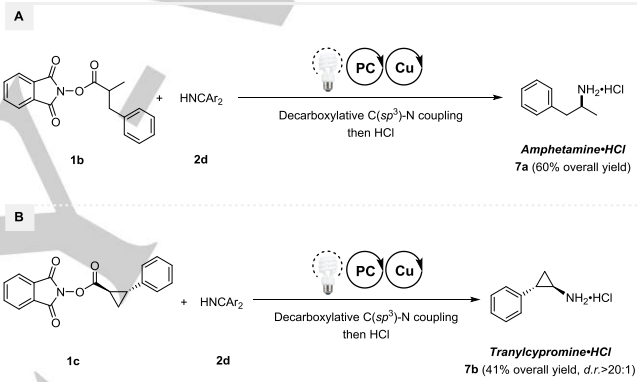


Figure 2. Synthesis of amine drugs using the present coupling method.

The coupling of primary alkyl NHPI esters was also possible, but required a slight modification of reaction conditions (SI, Table S2). The optimized conditions employed the same reaction stroichiometry, photocatalyst, and Cu catalyst as in the coupling of secondary alkyl NHPI esters, but the base was changed to diisopropylamine (2 equiv) and the solvent was changed to acetonitrile (MeCN). The modified conditions were successfully applied to the coupling of various primary alkyl NHPI esters (**5a**-**5i**, Table 2) in moderate to excellent yields. Functional groups such as aryl, ester and bromo groups were tolerated (**5d-5f**). A polyfluorinated alkly ester could also be coupled (**5g**), providing a convenient route to a polyfluorinated alkyl amine, which can be difficult to access otherwise. Coupling of the esters derived from 6-heptenoic acid and cyclopropylacetic acid, which served as radical-clock probes, gave the 5-exo-trig cyclized and ring-opening products **5h** and **5i**, respectively. This result indicates the intermediacy of alkyl radicals. This decarboxylative amination method also enabled the synthesis of protected primary amines substituted by a complex alkyl group, derived from natural resources and known drugs (Table 2). For example, NHPI esters from fatty acids such as elaidic acid, oleic acid, and linoleic acid could be used to give the corresponding coupling products in good yields (**6a**-**6c**), without isomerization or oxidation of the

olefin group. Drugs and natural products such as dehydrocholic acid (**6d**), chlorambucil (**6e**), abietic acid (**6f**) and gemfibrozil (**6g**) were easily transformed into their protected amine derivatives, demonstrating the potential of the method in post-synthetic drug and natural product modification. The cases of **5f, 6d** and **6e** highlight the orthogonal functional group compatibility of the present method compared to direct alkylation and reductive amination: **5f** has a bromo group and **6e** has two chloro groups which are incompatible with direct alkylation; **6d** has three keto groups which are incompatible with reductive amination. It is important to note that multiple stereocenters are conserved in **6d** and **6f**.

To further demonstrate the synthetic utility of the present coupling method, it was applied for the synthesis of two drugs: amphetamine and tranylcypromine. As shown in Figure 2, both cases were successful, and following acidic deprotection of the imine group, amphetamine•HCl and tranylcypromine•HCl were obtained in 60% (**7a**) and 41% (**7b**, *d.r.* > 20:1) overall yields, respectively.

In summary, tandem photoredox and Cu catalysis has been developed to enable the cross coupling of alkyl NHPI esters with benzophenone imines. The method allows the rapid transformation of readily available alkyl carboxylic acids into alkylated primary amines, which are important compounds in medicinal and materials chemistry. The work significantly expands the scope of C(sp^3)-N coupling. Analogous tandem photoredox and Cu catalysis may find further applications in C-C and C-heteroatom coupling reactions.

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Keywords: photoredox · decarboxylation · C-N coupling · copper catalysis · alkylation

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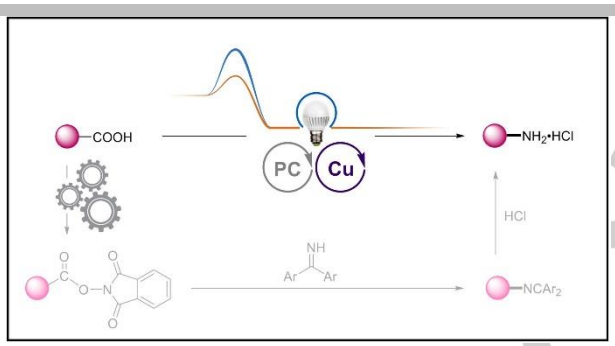
A tandem photoredox and Cu catalysis has been developed to enable the cross coupling of alkyl NHPI esters with benzophenone imine derivatives.



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