Decarboxylative C(sp^3)-N Cross Coupling via Synergetic Photoredox and Copper Catalysis

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ABSTRACT: Amines are a quintessential moiety in bioactive molecules, pharmaceuticals, and organic materials. Transition metal catalyzed C-N coupling of aryl electrophiles has been established as a powerful and reliable method for amine synthesis. However, the analogous C-N coupling of alkyl electrophiles is largely underdeveloped, due to decomposition of metal alkyl intermediates by β-H elimination and difficulty in C(sp^3)-N reductive elimination. Here we provide a general strategy for amination of alkyl electrophiles by merging photoredox and copper catalysis. The photoredox catalysis allows the use of alkyl redox-active esters, recently established as a superior class of alkyl electrophiles, whereas copper catalysis enables the C(sp^3)-N cross coupling. The decarboxylative amination can be used for the synthesis of a diverse set of alkyl anilines with high chemoselectivity and functional group compatibility. Rapid functionalization of amino acid, natural products, and drugs are demonstrated.

Introduction

Amines are one of the most important structural motifs in pharmaceuticals, agrochemicals, and organic materials.[1,2] While traditional alkylation and reductive amination reactions are still commonly used to prepare and modify amines, and new methods derived from reductive amination such as borrowing hydrogen[3] strategy has been reported.[4-7] The most significant development in amine synthesis has been transition metal catalyzed C-N coupling of aryl electrophiles (halides and pseudo halides) with amine nucleophiles.[8-11] (Figure 1A) The C-N coupling of alkyl electrophiles, however, is largely underdeveloped (Figure 1A). A perceived difficulty is β-hydrogen elimination from a metal alkyl intermediate originated from oxidative addition of the alkyl electrophile, which has posed considerable challenges in analogous C-C cross coupling of alkyl electrophiles.[12-14] Moreover, the product yielding Csp^3-N reductive elimination step is rarely demonstrated.[15] A notable exception is the light induced, copper-catalyzed C-N coupling of alkyl halides recently developed by the groups of Peters and Fu.[16-18] Nevertheless, the scope of amine nucleophiles is limited to carbazoles[16,18] and amides[17,19]. Alternative, formal C-N coupling of alkyl electrophiles via addition of alkyl radicals to nitroarenes has been reported.[20,21]

The group of Baran has recently trailblazed the use of redox-active esters (RAEs) derived from alkyl carboxylic acids as superior surrogates of alkyl halides in decarboxylative C-C cross-coupling reactions.[22-24] Extension to decarboxylative C-heteroatom, particularly C-B bond formation has also been reported.[19,25-29] The key attributes of alkyl carboxylic acids[30,31] are their unparalleled availability, stability, and non-toxic nature, which are in stark contrast with alkyl halides, ketones, and aldehydes. While several precedents of decarboxylative imidation[32] and amination[19,33] are known, they are limited to a narrow scope of very special substrates or intramolecular reactions. A general metal-catalyzed decarboxylative C-N coupling of RAEs with anilines will provide a valuable methodology for the synthesis of alkylated anilines (Figure 1B), which requires alkyl halides and carbonyl compounds[6] as starting reagents using the currently standard methods of alkylation and reductive amination, respectively. Further foreseen advantages of such a decarboxylative amination include applicability to bulky primary and secondary alkyl groups and immunity to over alkylation, both of which are major limitations of direct alkylation (Figure 1B). Despite its conceptual simplicity and resemblance to decarboxylative C-C coupling, the intermolecular decarboxylative C-N coupling of redox active esters poses significant hurdles. The activation principle of redox active esters originates from amide-bond synthesis, thus, amide formation can compete when amine nucleophiles are used. Moreover, decarboxylative C-C coupling reactions of redox active esters are until now all initiated by electron transfer from an organometallic nickel or iron species,[22-24,34] but the analogous electron transfer from metal amido species is unprecedented. The result of the reaction of cyclohexyl NHPI ester **1a** with aniline **2a** under conditions similar to those of Baran decarboxyative C-C coupling[22,23] seemed to substantiate these concerns (Figure 1C). No amine was formed; instead, side products originated from decomposition of esters (**1b**-**1e**), amide formation (**1g**), and amine substitution of *N*-phenylphthalimide (**1f**) were observed.

Okada and Overman applied photoredox chemistry to generate alkyl radicals from alkyl redox active esters for subsequent Michael addition reactions,[35,36] while Fu used a similar approach for decarboxylative alkynylation of α-amino acid derivatives.[37] In view of the difficulty to activate redox active esters by metal amides, we envisioned a synergetic photoredox and metal catalysis for C-N coupling of redox active esters with anilines (Figure 1D). Visible-light excitation of a photocatalyst generates an excited-state complex, which reduces a redox-active ester via a single-electron transfer (SET). The reduced ester then undergoes decarboxylation to give an alkyl radical, which is trapped by a low-valent metal amido complex (**I**) to give intermediate (**II**). The photocatalytic cycle is closed by a single-electron transfer from intermediate **II** to the oxidized photocatalyst, yielding at the same time a high-valent metal alkyl amido complex (**III**). C-N reductive elimination from **III** then gives the desired amine product and liberates a low-valent metal species (**IV**). The latter reacts with an aniline to give complex **I** and completes the metal catalytic cycle. This type of relay between photoredox catalysis with nickel catalysis has been exploited for C-C coupling,[30,38,39] and electron-transfer via photoredox catalysis is reported to promote $C(sp^2)$-N reductive elimination.[40,41] However, a similar strategy has not been demonstrated for $C(sp^3)$-N coupling.

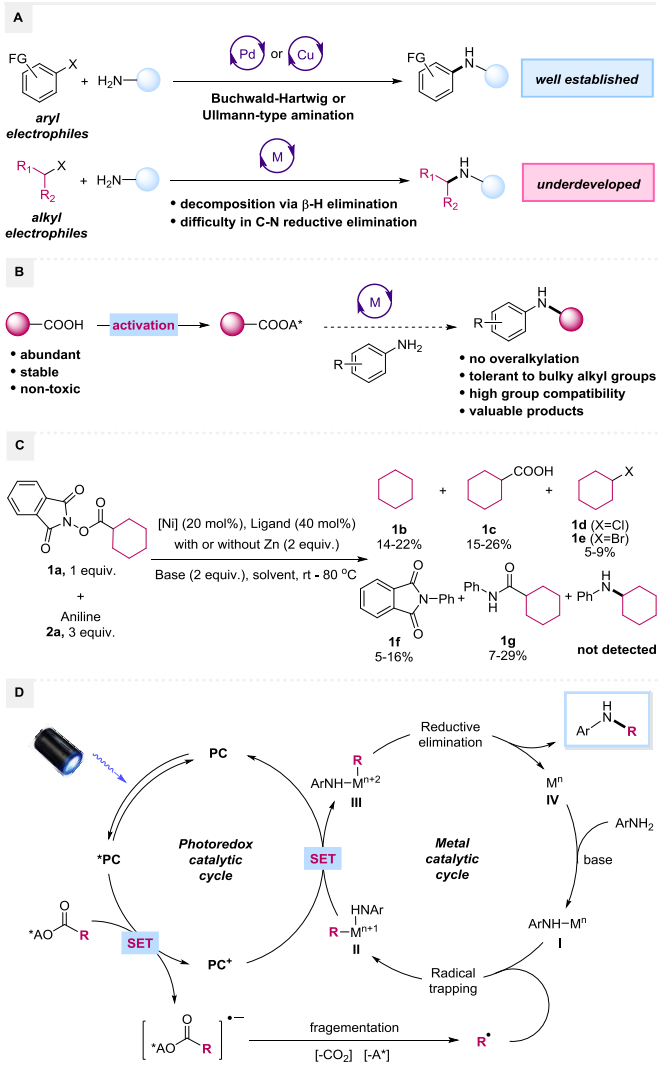


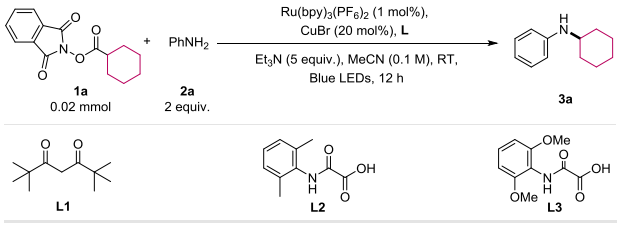
Figure 1. Reaction development. (A) Comparison of transition metal catalyzed C-N coupling of aryl and alkyl electrophiles with amine nucleophiles. (B) Advantages of metal-catalyzed decarboxylative C-N coupling. (C) Unsuccessful decarboxylative C-N coupling using methods for Ni-catalyzed decarboxylative C-C coupling. (D) Mechanistic design for decarboxylative amination via synergetic photoredox and transition metal catalysis.

Here we report the successful development of synergetic photoredox and copper catalysis for amination of alkyl redox-active esters. The catalysis allowed the synthesis of a diverse set of alkyl anilines with high chemoselectivity and functional group compatibility and rapid functionalization of amino acid, natural products, and drugs.

Results

Screening of reaction conditions. Based on mechanistic design (Figure 1D), our initial efforts were placed on the optimization of reaction conditions for the coupling of cyclohexyl NHPI ester **1a** with aniline **2a** (Table 1). Although Pd catalysis has been extensively used for C-N coupling, we targeted Fe, Co, Ni, and Cu-based catalysts because these base metals are not only more cost-effective, but also more prone to single-electron transfer reactions. Only Cu catalysis yielded an appreciable amount of amination product. The optimization required a significant amount of experimental work, which is described in Supplementary Tables 1-7, and Table 1 gives a brief summary of this optimization. Using $Ru(bpy)_3(PF_6)_2$ (1 mol%) as photoredox catalyst, CuBr (20 mol%) as metal catalyst, and Et_3N (5 equiv.) as base, MeCN (0.1 M) as solvent, the desired coupled amine **3a** was obtained in 15% yield under blue LED irradiation at room temperature after 12 h (Table 1, entry 1). Various ligands were then screened in order to increase the yields (Supplementary Table 1), and 2,2,6,6-Tetramethyl-3,5-heptanedione **(L1,** 30 mol%) was the best among the first set of 20 ligands, giving **3a** in 58% yield (Table 1, entry 2). Ma recently developed a modular ligand system based on oxoacetic acids and oxalamides for Cu-catalyzed amination of aryl chlorides.[42,43] When oxalamides were used for our reaction, yields were modest, probably due to poor solubility (Supplementary Table 1) However, when 2-(2,6-dimethylphenylamino)-2-oxoacetic acid (DMPAO, **L2**) was used, the yield was significantly improved to 71% (Table 1, entry 3). Encouraged by this result, we systematically varied the aromatic substituents of **L2**. The best ligand was 2-(2,6-dimethoxylphenylamino)-2-oxoacetic acid **L3**, which gave a yield of 91% (Table 1, entry 4). From the optimization results (Supplementary Table 1), especially considering the comparisons of **L2**, **L3**, **L28**-**L30**, we propose that *ortho*-disubstitution at the aryl rings of the ligands is important to enforce a steric bulkiness, favoring C-N reductive elimination. Additionally, electron-rich groups lead to a more electron-rich Cu center, favoring oxidation. Both factors are beneficial for the catalysis according to the proposed catalytic cycle (Figure 1D).

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



entry	variation [a]	yield (%)[b]
1	No **L**	15
2	**L1** (30 mol%)	58
3	**L2** (30 mol%)	71
4	**L3** (30 mol%)	91
5	**L3** (7.5 mol%)	94
6	no light	0
7	no $Ru(bpy)_3(PF_6)_2$	0
8	no CuBr	0

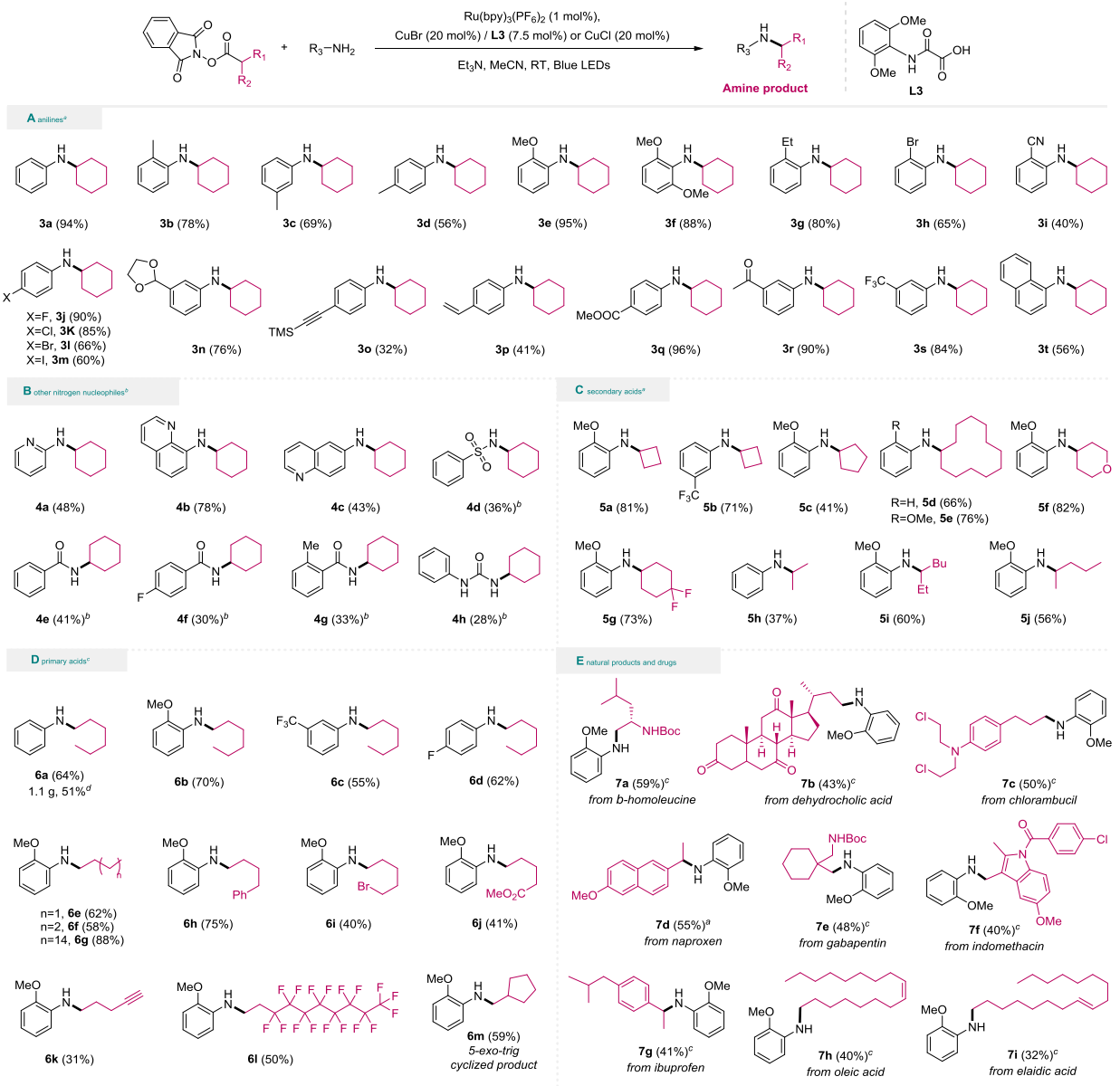
[a]Reaction conditions: **1a** (0.02 mmol), **2a** (2 equiv.), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuBr (20 mol%), ligand, and Et_3N (5 equiv.) in the solution of MeCN (0.1 M) under the irradiation of blue LED at room temperature for 12 h. [b]Corrected GC yield using *n*-dodecane as an internal standard.

As a preliminary mechanistic investigation suggests the binding of Cu ion to the redox-active esters (see below), the ratio of ligand to metal was decreased from 1:1 to liberate some "free" Cu ions to promote the binding to the esters (Supplementary Table 2). This turned out to be beneficial, and at 7.5 mol% loading of **L3**, the yield reached 94% (Table 1, entry 5). $Ru(bpy)_3(PF_6)_2$ was the best photocatalyst (Supplementary Table 3) and CuBr was the best metal catalyst (Supplementary Table 4). Additionally, the reaction was best run at room temperature (Supplementary Table 5) and Et_3N was the best base. Inorganic bases commonly used for Ullman coupling tent to give amidation rather than amination products, while Hunig´s base (N, N-Diisopropylethylamine) was ineffective probably due to reaction with the excited state of $Ru(bpy)_3(PF_6)_2$. Light, $Ru(bpy)_3(PF_6)_2$, and a copper salt are all essential. Without any of the three, no amination product was formed (Table 1, entries 6-8). Under the optimized reaction conditions, besides the desired amine product **3a** (94%), phthalimide (61%), **2a** (59%), **1f** (7%), *N*-cyclohexylphthalimide (less than 2%) and **1e** (less than 1%) were observed via GC analysis after reaction (Supplementary Figure 1). The rest of the phthalimide (< 30%) probably coordinates with copper.

Scope of the decarboxylative C-N coupling. The optimal reaction conditions could be applied for the coupling of a diverse set of secondary alkyl redox-active esters with anilines. The scope of anilines was explored. *Ortho*-, *meta*-, and *para*-toluidine all coupled with **1a** to give the corresponding amines in good yields (Table 2A, **3b**-**3d**). Sterically hindered *ortho*-substituted anilines which bearing mono-methoxy (**3e**), di-methoxy (**3f**), ethyl (**3g**), bromo (**3h**) or cyano (**3i**) groups were all suitable amine substrates. Halogen substituents such as fluoro, chloro, bromo, even reactive iodo groups were tolerated in the anilines, with high chemoselectively and good yields (**3j**-**3m**). Synthetically useful functional group, such as cyano (**3i**), protected aldehyde (**3n**), acetylene (**3**), vinyl (**3p**), ester (**3q**), ketone (**3r**), trifluoromethyl (**3s**), were all compatible. To further probe the limit of functional group compatibility, the reaction in Table 1 was conducted in the presence of small molecule additives containing alpha-beta unsaturated ester, aldehyde, NMe-indole, NH-indole, secondary alkyl amide, or unprotected alcohol using the method developed by Glorius.[44] NMe-indole, and free alcohol were well tolerated, NH-indole and aldehyde were modestly compatible, and alpha-beta unsaturated ester and secondary alkyl amide inhibited the reactions to about 25% yields (Supplementary Table 10)

Challenging substrates such as **3t** (sterically hindered), **4a** (pyridine), **4b** (sterically hindered quinoline) and **4c** (quinoline) were applicable. Other nitrogen nucleophiles were also tested, which revealed some limitations of the current method. While sulfonamide (**4d**), amide (**4e**-**4g**), urea (**4h**) were coupled in modest yields (Table 2B), nitrogen heterocyclic such as indole and imidazole could not be coupled. Alkyl amines tend to give amidation products, while methanesulfonamide and acetamide were coupled in low yields (about 10%, **S1**-**S2**, Supplementary Information). Secondary amines have low conversions and yields. We tentatively attribute the limitation in nitrogen nucleophiles to steric factors as anilines are the least bulky substrates. The scope of secondary alkyl redox active esters was significant. Cyclic alkyl groups (Table 2C) including small and large rings (**5a**-**5e**), heterocyclic alkyl group (**5f**), and fluorinated alkyl group (**5g**), as well as acyclic secondary alkyl groups (**5h**-**5j**) were all amenable to the coupling. When a tertiary alkyl redox active ester, activated 1-adamantanecarboxylic acid, was coupled to aniline, *N*-phenyladamantan-1-amine (Supplementary Figure 2) was obtained in only 9%, consistent with the challenge in cross-coupling of the very bulky tertiary alkyl groups.

Table 2. Scope of the C-N coupling of alkyl redox-active esters



[a]General conditions: NHPI ester (1 equiv.), aniline (2 equiv.), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuBr (20 mol%), **L3** (7.5 mol%) and Et_3N (5 equiv.) in MeCN (0.1 M), irradiated at room temperature for 12 h, isolated yield. [b] $Cu(MeCN)_4PF_6$ (50 mol%), **L3** (20 mol%), 20 h, isolated yield. [c]General conditions: NHPI ester (2 equiv.), aniline (1 equiv.), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuCl (20 mol%) and Et_3N (3 equiv.) in MeCN (0.1 M), irradiated at room temperature for 12 h, isolated yield. [d]Gram-scale conditions: Aniline (12.2 mmol), NHPI ester (1.5 equiv), $Ru(bpy)_3(PF6)_2$ (1 mol%), CuCl (20 mol%) and Et_3N (3 equiv) in MeCN (0.2 M), irradiated at room temperature for 12 h.

Primary alkyl carboxylic acids are inexpensive and abundant reagents. The C-N coupling of redox-active esters derived from primary alkyl carboxylic acids was possible, but required a slight modification of reaction conditions. Unexpectedly, higher yields were obtained under ligand-less conditions (Supplementary Table 9) The modified conditions were successfully applied to the coupling of various

primary alkyl redox-active esters (Table 2D). NHPI esters derived from simple primary carboxylic acids were coupled with different anilines in good yields (**6a**-**6g**). To showcase the scalability of this process, a gram-scale reaction was performed to deliver **6a**. Gratifyingly, a satisfactory 51% isolated yield could be obtained. Moreover, NHPI esters bearing phenyl, bromo ester and acetylene groups were coupled chemoselectively in synthetically useful yields (**6h**-**6k**). Polyfluorinated alkly group was viable (**6l**), providing a convenient route to polyfluorinated amines, which are difficult to access otherwise. Coupling of an activated 6-heptenoic acid, a radical-clock probe, gave the 5-exo-trig cyclized product (**6m**), consistent with the intermediacy of alkyl radical. Importantly, multi-alkylation was not detected in all these reactions, which represented an important advantage over direct alkylation.

Synthetic applications. The decarboxylative amination method is applicable for the synthesis of complex alkyl anilines with impressive chemoselectivity and functional group compatibility (Table 2E). For example, NHPI esters from an amino acid, β-homoleucine (**7a**), and a natural product, dehydrocholic acid (**7b**) were aminated in reasonable yields. Drugs containing alkyl carboxylic acid groups could be transformed into their amine derivatives in one-step (**7c**-**7g**), demonstrating the potential of this method for rapid, post-synthetic drug modification. NHPI esters from sensitive fatty acids, such as oleic acid and elaidic acid, could also be used to deliver the corresponding amines without significant isomerization or oxidation of olefin groups, albeit in modest yields (**7h**-**7i**). The successful coupling of dehydrocholic acid and chlorambucil derivatives highlight the orthogonal functional group compatibility of our decarboxylative amination method compared to the methods of reductive amination and direct alkylation: dehydrocholic acid has three ketone groups which are incompatible with reductive amination, while chlorambucil has two alkyl choro groups which are incompatible with direct alkylation.

To demonstrate its potential utility for medicinal chemistry, this decarboxylative amination method was applied for the synthesis of the core skeleton of a drug candidate. Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi (T. cruzi)*, is an increasing threat to global health. To our delight, the key intermediate **8a** to an inhibitor of *Trypanosoma cruzi* (*T. cruzi*)[45] was synthesized with a yield of 75% yield in only one step employing this amination method (Figure 2).

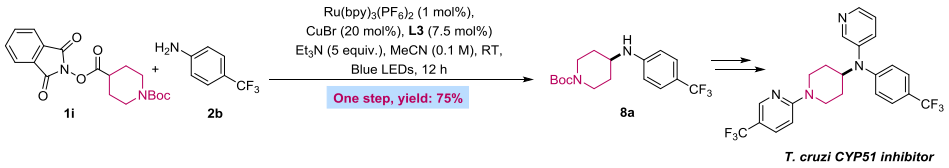


Figure 2. Synthesis of 8a, the skeleton of a *T. cruzi* CYP51 inhibitor.

Mechanistic investigation. A series of fluorescence quenching experiments (Supplementary Figure 3) showed that the electron transfers between the photoexcited complex $*Ru(bpy)_3^{2+}$ and a NHPI ester was significantly promoted by CuBr, suggesting the activation of NHPI ester by coordination to a Cu(I) ion. The amination was quenched in the presence of (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), and O-alkylated TEMPO (**S4**) was formed in 57% yield(Supplementary Information). This result is consistent with the formation of alkyl radical in the amination reaction. Experiments were conducted to probe whether alkyl radical reacts with Cu species prior the formation of Cu amine/amido species (Figure 3). Under standard conditions (12h), amination product had a yield of 94% (8% in 2 h) while bromocyclohexane **1e** was formed in less than 1% (trace product in 2 h). However, in the absence of aniline, **1e** was obtained in 12% yield (1.4 % in 2 h). This result suggests that if an alkyl radical reacts with a Cu(I) species without amine coordination, then a non-negligible amount of alkyl bromide would be formed from a putative Cu(II) alkyl bromide intermediate. As only a trace amount of alkyl bromide was

formed in the catalysis, it is more likely that the alkyl radical is trapped by a Cu amine/amido intermediate.

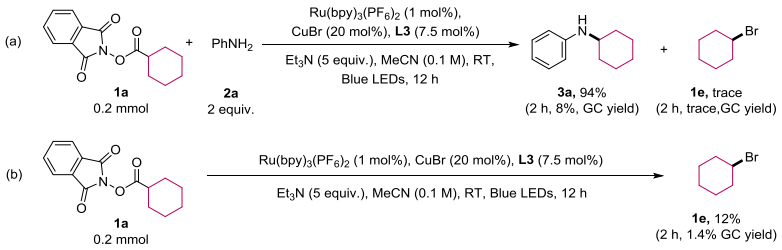


Figure 3. Reactions of 1a with and without aniline under catalytically relevant conditions.

Following the mechanistic hypothesis in Figure 1D, the Cu catalytic cycle starts with binding and deprotonation of an aniline on a Cu(I) center to give the Cu(I) amido intermediate (**I**, M = Cu). Trapping of an alkyl radical from an NHPI ester by Cu(I) amido intermediate gives the Cu(II) alkyl amido complex (**II**, M = Cu), which is oxidized by $Ru(bpy)_3^{3+}$ to give the Cu(III) alkyl amido intermediate (**III**, M = Cu). C-N reductive elimination becomes viable at this high-valent complex to furnish the desired amination product.

An alternative Cu catalytic cycle is the oxidation of a Cu(I) amido species by $Ru(bpy)_3^{3+}$ to a Cu(II) amido species, which then accepts the alkyl radical to give the Cu(III) alkyl amido complex, followed by reductive elimination to give the amine product and a Cu(I) species that can bind the amine and re-enter the catalytic cycle. To test whether the alkyl radical is trapped by a Cu(I) or Cu(II) amido species, we prepared a Cu(II) amine complex (**9a**) (Figure 4 and Supplementary Information) and reacted with **1a** under conditions relevant to the C-N coupling. Both in the absence and presence of **L3**, the amination yield was about 10%. The corresponding Cu(I) amine complex could not be isolated probably due to its instability; however, an in-situ prepared Cu(I) amine species (**9b**) reacted with **1a** under conditions relevant to the C-N coupling to give the amine in 41-46% yield. This result suggests that the catalysis more likely involves the trapping of alkyl radical by a Cu(I) amide intermediate, consistent with our mechanistic proposal. However, more experiments are required to confirm this, and to elucidate the mechanistic details.

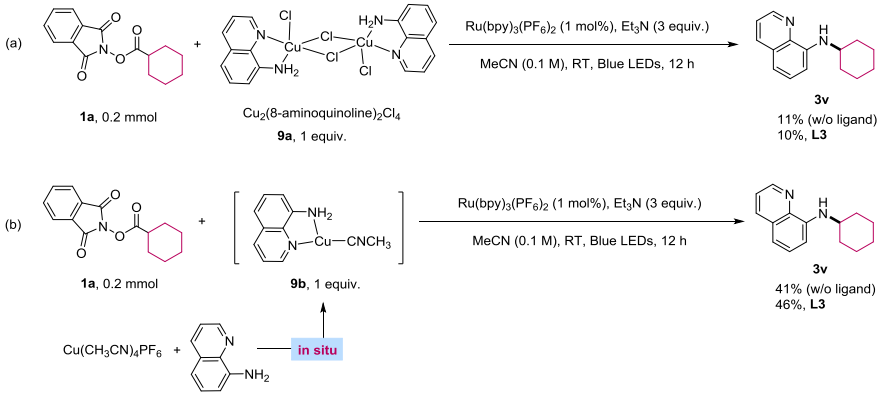


Figure 4. Reactions of Cu amine complexes with a redox-active ester.

Conclusions

In summary, tandem photoredox and Cu catalysis enables the decarboxylative amination of alkyl redox-active esters with anilines. This method significantly expands the scope of metal-catalyzed C(sp^3)-N coupling, which remains under-explored. Thanks to the consequential advantages of alkyl carboxylic acids over alkyl halides in availability, stability, and toxicity, the method and its underlying strategy are expected to have widespread use in amine synthesis. The unique activity of Cu-based catalysts in this decarboxylative C-N coupling contrasts the reign of Ni catalysis in analogous C-C coupling via tandem photoredox/metal catalysis,,[30,38,39] underscoring their important divergences.

Methods

General. Supplementary Methods for experimental details and characterization data, Supplementary Tables for the results of optimization of reactions, Supplementary Figures for results of additional reactions and NMR spectra can be found in the Supplementary Information.

General procedure for *N*-hydroxyphthalimide (NHPI) ester synthesis. A 100 mL round-bottom flask was charged with (if solid) carboxylic acid (1.0 equiv.), nucleophile (*N*-hydroxyphthalimide, 1.0 equiv.) and DMAP (0.1 equiv.). Dichloromethane was added (0.2 M), and the mixture was stirred vigorously. Carboxylic acid (1.0 equiv) was added via syringe (if liquid). DIC (1.1 equiv) was then added dropwise via syringe, and the mixture was allowed to stir until the carboxylic acid was consumed (determined by TLC). Typical reaction times were between 0.5 h and12 h. After the reaction, the mixture was filtered over Celite and rinsed with additional CH_2Cl_2. The solvent was removed under reduced pressure, and purification by column chromatography afforded corresponding activated esters, which were used without further purification unless otherwise noted.

General procedure for branched alkyl aryl amine synthesis. An oven-dried 15 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was sequentially charged with NHPI ester (1 equiv., 0.2 mmol), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuBr (20 mol%), **L3** (7.5 mol%), acetonitrile solvent (2 mL), aniline (2 equiv), Et_3N (5 equiv) in the glove box. The vial was sealed with a screw cap and removed from the glove box**.** The vigorously stirred solution was irradiated with blue LED light under table fan cooling for 12 h. After the reaction, the reaction mixture was acidified with saturated NH_4Cl solution and then neutralized with saturated $NaHCO_3$ solution. The crude product in the aqueous fraction was extracted with ethyl acetate. The combined organic fractions were concentrated *in vacuo* with the aid of a rotary evaporator. The crude product residue was purified by preparative thin layer chromatography (pretreated with 3% triethylamine in hexanes) using a solvent mixture (ethyl acetate, hexanes) as an eluent to afford the purified amine products.

General procedure for linear alkyl aryl amine synthesis. An oven-dried 15 mL re-sealable screw-cap test tube equipped with a Teflon-coated magnetic stir bar was sequentially charged with aniline ((1 equiv., 0.2 mmol)), NHPI ester ((2 equiv., 0.4 mmol)), $Ru(bpy)_3(PF_6)_2$ (1 mol%), CuCl (20 mol%), acetonitrile solvent (2 mL), Et_3N (3 equiv) in the glove box. The vial was sealed with a screw cap and removed from the glove box**.** The vigorously stirred solution was irradiated with blue LED light under table fan cooling for 12 h. After the reaction, the reaction mixture was acidified with saturated NH_4Cl solution and then neutralized with saturated $NaHCO_3$ solution. The crude product in the aqueous fraction was extracted with ethyl acetate. The combined organic fractions were concentrated *in vacuo* with the aid of a rotary evaporator. The crude product residue was purified by preparative thin layer chromatography (pretreated with 3% triethylamine in hexanes) using a solvent mixture (ethyl acetate, hexanes) as an eluent to afford the purified amine products.

Dada availability

Crystallographic data for the structure **9a** reported in this Article has been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 1586680. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk. All other data supporting the findings of this study, including experimental procedures and compound characterization, are available within the Article and its Supplementary Information, or from the corresponding author upon reasonable request.

Author contributions

R.M. and X.H. conceived and designed the study. R.M. designed and optimized the synthetic method, studied the scope, application and mechanism. A.F. and J.B. contributed to the scope and application. R.M. and X.H. wrote the manuscript. X.H. directed the research.

Competing financial interests

The authors declare no competing financial interests.

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