Decarboxylative C(sp^3)-O Cross Coupling

Runze Mao, Jonathan Balon, and Xile Hu*

Abstract: Alkyl aryl ethers are an important class of compounds in medicinal and agro chemistry. Catalytic C(sp^3)-O cross coupling of alkyl electrophiles with phenols is an unexplored disconnection strategy to the synthesis of alkyl aryl ethers, with the potential to overcome some of the major limitations of existing methods such as C(sp^2)-O cross coupling and S_N2 reactions. Here we employ tandem photoredox and copper catalysis to achieve decarboxylative C(sp^3)-O coupling of alkyl *N*-hydroxyphthalimide (NHPI) esters with phenols under mild conditions. This method could be used to synthesize a diverse set of alkyl aryl ethers using readily available alkyl carboxylic acids, including many natural products and drug molecules. Complementarity in scope and functional group tolerance to existing methods was demonstrated.

Alkyl aryl ether linkages are ubiquitous in natural products,[1] pharmaceuticals[2] and agrochemicals.[3] Transition-metal-catalyzed C(sp^2)-O cross coupling has been developed into a valuable method for the synthesis of alkyl aryl ethers, overcoming the limitations in scope and functional group tolerance of traditional approaches such as nucleophilic substitution (S_N2)[4-5] and nucleophilic aromatic substitution (S_NAr).[6] However, these coupling reactions are typically conducted under elevated temperatures due to certain difficult elemental steps in the catalytic cycle. For Pd[7-10] and Ni[11] catalysis, oxidative addition of aryl halides is facile but C(sp^2)-O reductive elimination is problematic (Fig. 1A). Thus, sterically demanding and complicated phosphine ligands are employed to promote C(sp^2)-O reductive elimination. For Cu catalysis, C-O reductive elimination is straightforward but oxidative addition of aryl electrophiles is challenging (Fig. 1A). As a result, the scope of electrophiles is largely restricted to aryl iodides and activated aryl bromides. In an elegant study, MacMillan and co-workers[12] employed photoredox catalysis to transiently oxidize an Ni(II)(aryl)(alkoxide) intermediate to Ni(III), thereby facilitating C(sp^2)-O reductive elimination. The C(sp^2)-O coupling occurred at room temperature. Nevertheless, the electrophiles were limited to (hetero)aryl bromides. This photoredox/Ni dual-catalyzed approach has also been applied to other C-heteroatom (S, P, N) coupling reactions.[13-16]

Catalytic C(sp^3)-O coupling of alkyl electrophiles with phenols is an intriguing alternative for the synthesis of alkyl aryl ethers. The catalytic version of Williamson ether synthesis has the potential to overcome some of its inherent shortcomings such as forcing conditions, narrow scope, and poor tolerance. Moreover, if alkyl electrophiles other than halides can be used as the coupling partners, base-catalyzed elimination from alkyl electrophiles will no longer be a major side reaction. In this context we considered alkyl redox-active esters derived from alkyl carboxylic acids as desirable alkyl electrophiles (Fig. 1A).

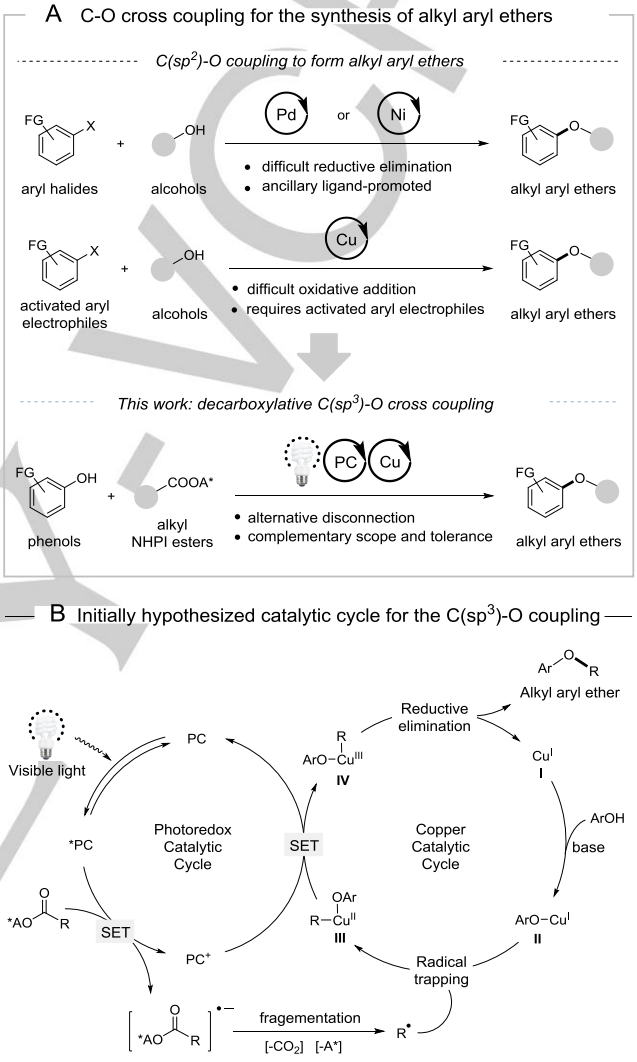

Figure 1. (A) Comparison of C-O cross coupling methodologies for the synthesis of alkyl aryl ethers; (B) The initially hypothesized catalytic cycle for decarboxylative C(sp^3)-O coupling. FG = functional group, SET = single electron transfer.

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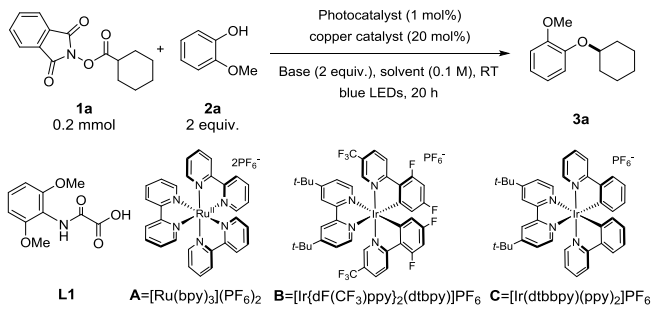
Table 1. Summary of the effects of reaction parameters and conditions on the reaction efficiency[a]



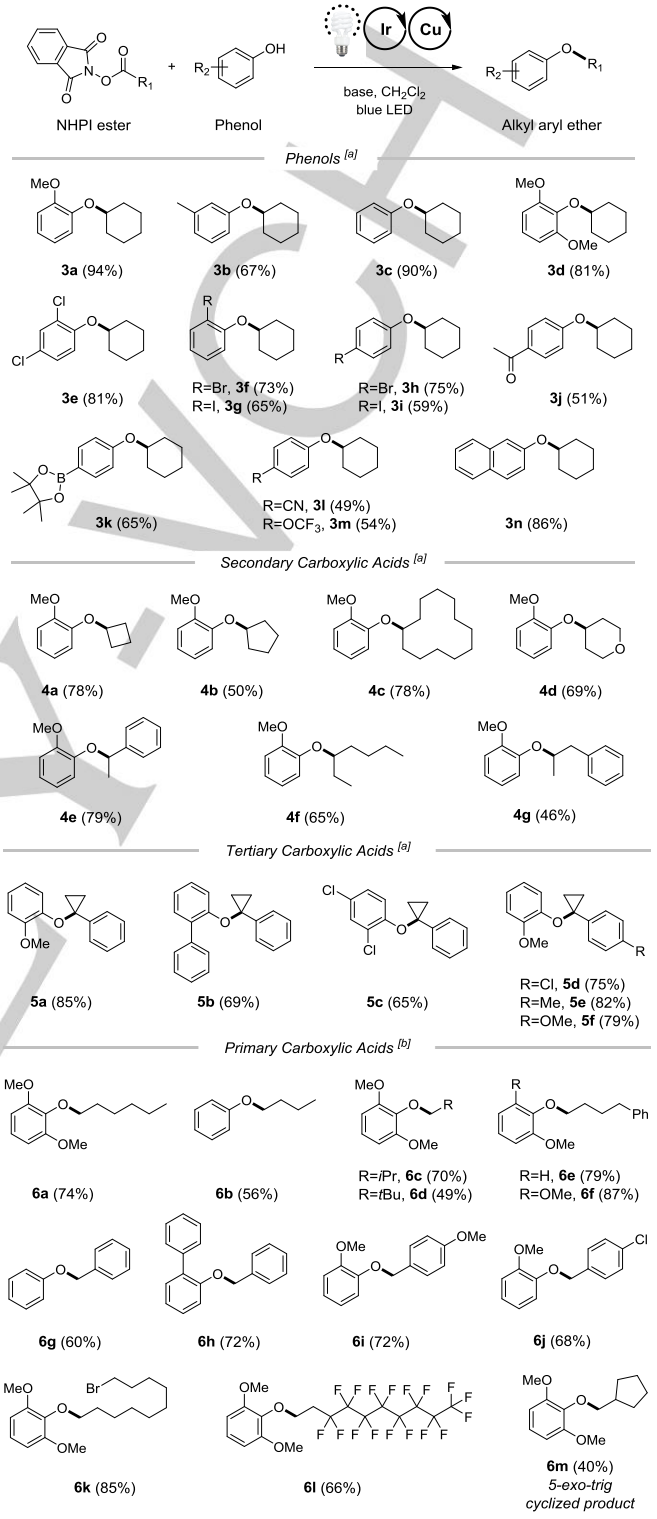
Entry	PC	Cu catalyst	Base	Solvent	Yield
1[b]	**A**	CuBr/L1	Et_3N	MeCN	16%
2[c]	**A**	CuBr	Et_3N	MeCN	19%
3[c]	**A**	CuCl	Et_3N	MeCN	22%
4[c,d]	**A**	Cu	Et_3N	MeCN	5%
5[c]	**A**	$CuCl_2$	Et_3N	MeCN	9%
6[e]	**A**	CuCl	Cs_2CO_3	MeCN	trace
7[c]	**A**	CuCl	Et_3N	DMF	trace
8[c]	**A**	CuCl	Et_3N	DCM	32%
9	**A**	CuCl	Et_3N	DCM	44%
10	**B**	CuCl	Et_3N	DCM	21%
11	**C**	CuCl	Et_3N	DCM	62%
12[f]	**C**	$(CuOTf)_2•C_6H_6$	Et_3N	DCM	82%
13[f,g]	**C**	$(CuOTf)_2•C_6H_6$	Et_3N	DCM	94%
14[f,h]	**C**	$(CuOTf)_2•C_6H_6$	Et_3N	DCM	0%
15[f]	none	$(CuOTf)_2•C_6H_6$	Et_3N	DCM	0%
16	**C**	none	Et_3N	DCM	0%

[a] Calibrated GC yield using *n*-dodecane as an internal standard. [b] Same condition as the optimized reaction condition in reference 21. Reaction was carried out with **1a** (0.2 mmol), **2a** (2 equiv.), **A** (1 mol%), CuBr (20 mol%), **L1** (7.5 mol%), Et_3N (5 equiv.) and MeCN (2 mL). [c] Et_3N (5 equiv.). [d] Cu (100 mol%). [e] Yield of the *O*-acylation product is 85%. [f] $(CuOTf)_2•C_6H_6$ (10 mol%). [g] DCM (0.05 M). [h] No light. RT = room temperature, PC = photocatalyst, DMF = *N,N*-dimethylformamide, DCM = dichloromethane, $(CuOTf)_2•C_6H_6$ = copper(I) trifluoromethanesulfonate benzene complex.

These redox-active esters have been employed for remarkable decarboxylative C-C[17-21] and C-heteroatom (B, Si, N)[22-29] cross-coupling reactions. However, analogous C-O cross coupling is hitherto unknown. Our group recently developed synergetic photoredox and copper catalysis for decarboxylative C(sp^3)-N cross coupling[28-29] We reasoned that a similar strategy might provide access to the elusive C(sp^3)-O coupling due to the more facile C-O reductive elimination on Cu.[30]

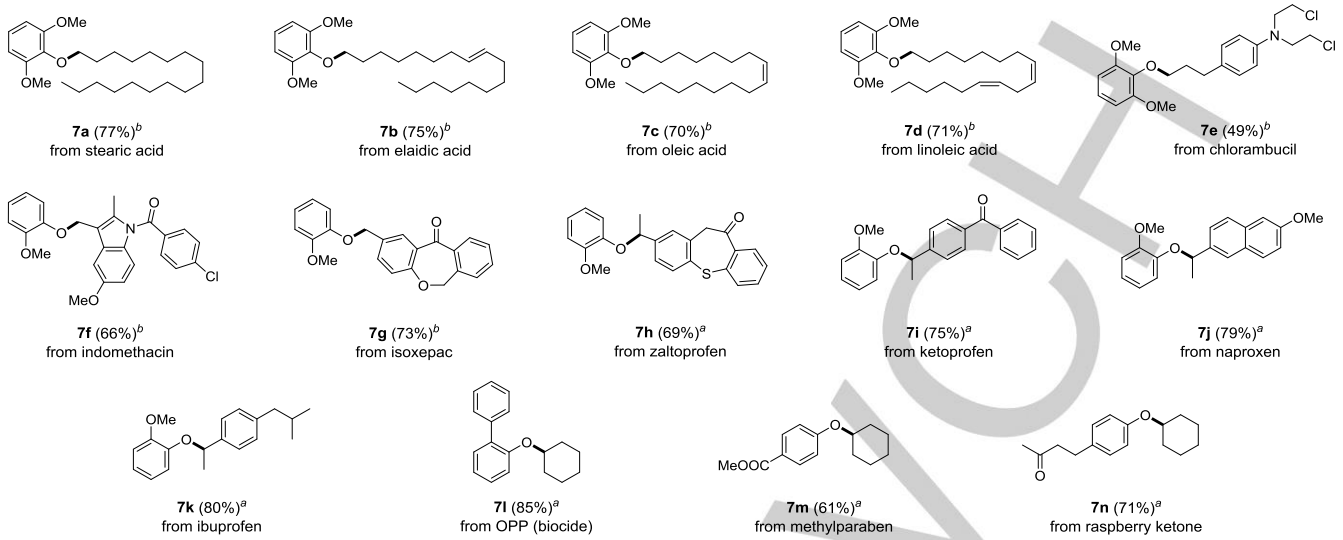
Following the previous C-N coupling, we hypothesized (Figure 1B) that binding of the phenol substrate to a Cu(I) species (**I**) followed by deprotonation would generate a Cu^I-alkoxide intermediate (**II**). This intermediate can trap the alkyl radical generated by oxidative quenching of the excited photocatalyst (*PC) with an alkyl NHPI ester to yield a Cu(II) intermediate (**III**). The oxidized photocatalyst (PC^+) then oxidizes **III** to give a Cu^{III}

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



[a] NHPI ester (1 equiv.), phenol (2 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $(CuOTf)_2•C_6H_6$ (10 mol%) and Et_3N (2 equiv.) in CH_2Cl_2 (0.05 M), irradiated at room temperature for 20 h, isolated yield. [b] NHPI ester (2 equiv.), phenol (1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $Cu(MeCN)_4OTf$ (40 mol%) and *N*-isopropyl-*N*-methyl-*tert*-butylamine (1 equiv.) in CH_2Cl_2 (0.05 M), irradiated at 0-RT for 20 h, isolated yield.

Table 3. Late-Stage decarboxylative etherification of natural products and drugs containing carboxylic acids



[a] NHPI ester (1 equiv.), phenol (2 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $(CuOTf)_2{\bullet}C_6H_6$ (10 mol%) and Et_3N (2 equiv.) in CH_2Cl_2 (0.05 M), irradiated at room temperature for 20 h, isolated yield. [b] NHPI ester (2 equiv.), phenol (1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), $Cu(MeCN)_4OTf$ (40 mol%) and *N*-Isopropyl-*N*-Methyl-*tert*-butylamine (1 equiv.) in CH_2Cl_2 (0.05 M), irradiated at 0-RT for 20 h, isolated yield.

alkyl alkoxide intermediate (**IV**) and regenerates the PC. **IV** should readily undergo C(sp^3)-O reductive elimination to give the alkyl aryl product while regenerating the initial Cu^I catalyst (**I**). Here we report the successful development of such a C(sp^3)-O cross coupling methodology, which exhibits attractive features such as mild conditions, no ancillary ligand, broad scope, and functional group tolerant. Furthermore, the method could be applied for late-stage functionalization of various natural products and drug molecules.

We began our investigation by subjecting cyclohexyl NHPI ester **1a** and guaiacol **2a** to the conditions previously employed for decarboxylative C(*sp*^{3})-N cross coupling of NHPI esters with anilines[21] (Table 1, entry 1; and Table S1, entry 1). The desired ether **3a** was formed, albeit in a low yield (16%). The coupling was then optimized by varying reaction parameters (Table S1, SI) and a summary of key observations is shown in Table 1. Interestingly, omission of the ligand was slightly beneficial (Table 1, entry 2). Although various Cu(I) salts could serve as catalysts, the nature of their counter anions had an influence in the yields (Table 1, entries 2-3; Table S1, entries 7-10). CuCl was the best copper catalyst among preliminary optimization (Table 1, entry 3). Cu(II) and Cu(0) catalysts gave lower yields (Table 1, entries 4-5). When Et_3N was replaced by an inorganic base, Cs_2CO_3, *O*-acylation of phenol instead of *O*-alkylation was observed (Table 1, entry 6). CH_2Cl_2 was the best solvent (Table 1, entries 6-8; Table S1, entries 19-21), and decreasing the amount of base increased the yield (Table 1, entry 9). Changing the photocatalyst from $[Ru(bpy)_3](PF_6)_2$ to an Ir-based photocatalyst could be beneficial (Table 1, entries 9-11; Table S1, entries 23-26), and the best photocatalyst was $[Ir(dtbbpy)(ppy)_2]PF_6$ (Table 1, entry 11). Further optimization indicated $(CuOTf)_2{\bullet}C_6H_6$ (10 mol%) and decreased concentration further improved the yield (Table 1, entries 12-13). The best conditions were $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%) as the photocatalyst, $(CuOTf)_2{\bullet}C_6H_6$ (10 mol%) as the copper catalyst, triethylamine (2 equiv.) as the base, and CH_2Cl_2 (0.05 M) as the solvent, blue LED irradiation, 20 h. A yield of 94% was obtained under these conditions (Table 1, entry 13). Light, photocatalyst, and copper catalyst were all essential for the coupling (Table 1, entries 14-16).

The scope of the decarboxylative C(*sp*^{3})-O cross coupling method was explored employing the optimized conditions described above. As shown in Table 2, a myriad of phenols containing electron-donating (**3a**-**3d**), electron-neutral (**3c**), and electron-withdrawing (**3e**-**3j**) substituents were coupled to give the corresponding ethers in moderate to excellent yields. Notably, aryl halide (**3e**-**3i**) or aryl boronic ester (**3k**) groups were tolerated in the coupling, demonstrating its excellent chemoselectivity and orthogonal functional group compatibility relative to C(sp^2)-O coupling methods. Other important functional groups such as ketone (**3j**), cyano (**3l**), trifluoromethoxyl (**3m**), and polycyclic aromatic ring (**3n**) were also tolerated. Although GC (Gas Chromatography) analysis indicated a high yield of **3m**, its volatile nature led to a decreased isolated yield (54%). The modest yield of **3l** (49%) was probably due to coordination of copper by the cyano group of the substrate. The coupling was successful for various secondary alkyl NHPI esters, including those containing cyclic alkyl groups (**4a**-**4c**), heterocyclic alkyl group (**4d**), and acyclic alkyl groups (**4e**-**4g**). To our delight, some tertiary NHPI esters, which generated non-planarizable radicals, could be coupled in good to excellent yields (**5a**-**5f**). These bulky ether products would be difficult to access using using classic Williamson ether synthesis. Planarizable radical sources, like NHPI esters derived from pivalic acid and 1-methylcyclohexanoic acid, only afforded the desired products in less than 30% yields.

For the coupling of primary alkyl NHPI esters, a modification of reaction conditions was necessary (Table S2). The optimized conditions were NHPI ester (2 equiv.), phenol (1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%) as the photocatalyst, $Cu(MeCN)_4OTf$ (40 mol%) as the copper catalyst, and *N*-isopropyl-*N*-methyl-*tert*-butylamine (1 equiv.) as the base in

CH_2Cl_2 (0.05 M), irradiated at 0-R.T. for 20 h. Under these conditions, various primary alkyl NHPI esters were successfully coupled (**6a**-**6m**). Both non-activated alkyl (**6a**-**6f**) and benzyl groups (**6g**-**6j**) were compatible. Alkyl bromide (**6k**) and perfluoroalkyl (**6l**) groups were tolerated, demonstrating the orthogonal functional tolerance of the current method relative to S_N2 reactions. Note that alkyl aryl ethers containing bulky *ortho*,*ortho*-disubstituted aryl groups (**6a**, **6c**-**6f**, **6h**-**6m**) were readily obtained using this coupling method. These products are diffuclt to access using C(sp^2)-O coupling methods which are inefficient for the activation of bulky aryl halides. Coupling of the NHPI ester of 6-heptenoic acid, a radical-clock probe, gave the 5-*exo-trig* cyclized product (**6m**), suggesting the intermediacy of alkyl radical.

The use of alkyl NHPI esters instead of alkyl halides as electrophiles makes the current decarboxylative C(sp^3)-O coupling method amenable to the rapid, late-stage modification of many carboxylic acid-containing natural products and drug molecules (Table 3). Indeed, fatty acids such as stearic acid (**7a**), elaidic acid (**7b**), oleic acid (**7c**) and linoleic acid (**7d**) were etherified with ease. Moreover, drugs such as chlorambucil (**7e**), indomethacin (**7f**), isoxepac (**7g**), zaltoprofen (**7h**), ketoprofen (**7i**), naproxen (**7j**) and ibuprofen (**7k**) underwent smooth esterification as well. Natural phenolic compounds such as *o*-phenylphenol (OPP, **7l**), methylparaben (**7m**) and raspberry ketone (**7n**) could also be used as coupling partners. The successful late-stage functionalization of these natural products and drugs, many of which contain sensitive alkene, carbonyl, halide, and heterocyclic groups, underscores the high chemoselectivity and functional group tolerance of the current method.

While the detailed mechanism warrants a dedicated study, a few experiments were conducted to give preliminary insights. Surprisingly, the fluorescence of $[Ir(dtbbpy)(ppy)_2]PF_6$ was not quenched by guaiacol (**2a**), triethylamine (Et_3N), $Cu(MeCN)_4PF_6$, NHPI ester (**1a**), mixture of $Cu(MeCN)_4PF_6$ and NHPI ester (**1a**), or mixture of $Cu(MeCN)_4PF_6$ and guaiacol (**2a**) (Fig. S1, SI). On the other hand, the fluoresence was quenched by the mixture of $Cu(MeCN)_4PF_6$ and Et_3N (Fig. S2, SI) with defined Stern-Volmer kinetics (Fig. S3, SI). These results suggest that due to the change of photocatalyst (Ru to Ir) and solvent, the initial step of the photocatalysis in the present C-O coupling is different from that of analogous C-N coupling[28] The excited state $*Ir^{III}$ complex ($E_{1/2}$ [$*Ir^{III}/Ir^{II}$] = +0.66 vs SCE in MeCN)[31] first reacts with a Cu(I)-Et_3N complex **A** to give a copper(II) species **B** (Fig. 2). The unique function of Et_3N compared to other bases is evident here. The NHPI ester ($E_{1/2}^{red}$ < -1.28 vs SCE in MeCN)[32] would then be reduced by the newly formed Ir^{II} spieces ($E_{1/2}$ [Ir^{II}/Ir^{III}] = -1.51 vs SCE in MeCN), regenerating the ground-state of the photocatalyst and producing a carboxyl radical, which upon fragmentation, yields the alkyl radical. The product from a radical clock probe substrate (**6m**) agreed with this hypothesis, which was further supported by the inhibition of the catalysis by a radical scavenger, 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO). The alkyl-TEMPO adduct was detected (SI). The alkyl radical is trapped by the Cu(II) species, which is likely coordinated by an aryloxide from the phenol substrate, to yield a Cu(III) alkyl aryloxide intermediate **C**. C-O reductive elimination then furnishes the coupling product and regenerate the Cu(I) catalyst (Fig. 2).

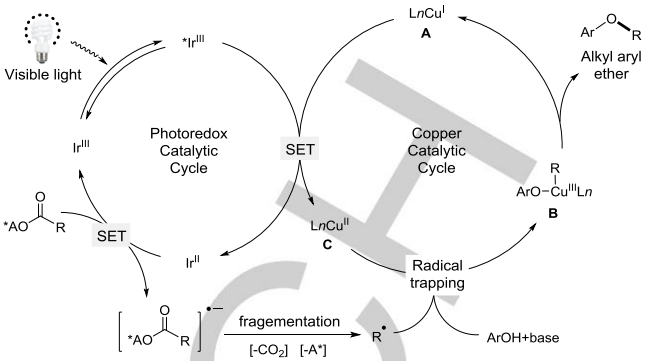


Figure 2. Proposed catalytic cycle for decarboxylative C(sp^3)-O coupling.

In summary, decarboxylative C(sp^3)-O coupling of alkyl NHPI esters has been achieved using tandem photoredox and Cu catalysis. This coupling method allows for the rapid transformation of readily available alkyl carboxylic acids into alkyl aryl ethers, which are important compounds in medicinal chemistry. The method provides a new disconnection strategy and exhibits complementary scope and functional group tolerance compared to traditional C(sp^2)-O coupling and S_N2 reactions.

Acknowledgements

This work is supported by the NoNoMeCat Marie Skłodowska-Curie training network funded by the European Union under the Horizon 2020 Program (675020-MSCA-ITN-2015-ETN). We thank Dr. Lei Zhang (EPFL) for assistance in conducting mechanistic study.

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

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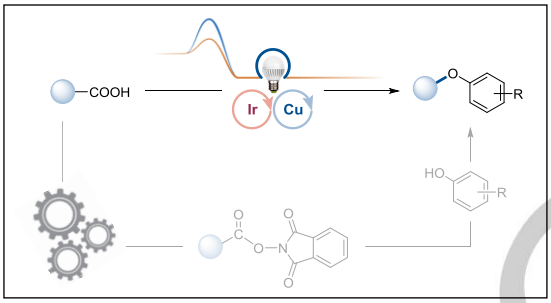
COMMUNICATION

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



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