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A General Copper Catalyst for Photoredox Transformations of Organic Halides

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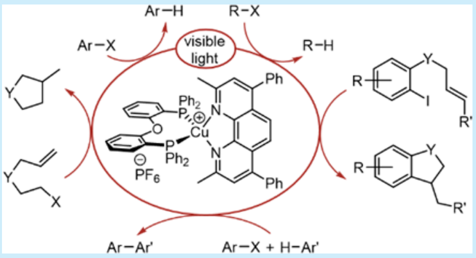
Supporting Information

ABSTRACT: A broadly applicable copper catalyst for photoredox transformations of organic halides is reported. Upon visible light irradiation in the presence of catalytic amounts of [(DPEphos)(bcp)Cu]PF_6 and an amine, a range of unactivated aryl and alkyl halides were shown to be smoothly activated through a rare Cu(I)/Cu(I)*/Cu(0) catalytic cycle. This complex efficiently catalyzes a series of radical processes, including reductions, cyclizations, and direct arylation of arenes.



The development of photoredox catalysis has recently enabled the design of remarkably powerful synthetic tools, notably based on the generation of radical species under mild, safe, and environmentally friendly conditions.[1] Following pioneering studies reported at the end of 20th century, spectacular applications of photoredox catalysis were developed in the past decade. This field has been largely dominated by ruthenium and iridium complexes associated with π-deficient ligands whose main features encompass strong absorption in the visible region, high oxidation and reduction potentials, and long-lived excited states (typically in the μs range).[1]

The main alternatives mostly rely on the use of organic dyes[2] or photoactivatable gold complexes[3] that were introduced more recently. In sharp contrast, much less attention has been devoted to copper complexes, despite their strong potential as cheaper catalysts and for the activation of a broader range of substrates. Despite the early work of Kutal,[4] Mitani,[5] and Sauvage[6] and the recent remarkable reports by Peters and Fu[7] and Reiser,[8] who demonstrated their unique potential, copper complexes have been scarcely used in photoredox transformations,[9,10] which can mostly be attributed to their short-lived excited states. Based on our recent interest in copper-catalyzed radical processes,[11] we report here a broadly applicable copper catalyst for photoredox transformations of organic halides.

We initiated our studies by identifying a copper complex that could activate the carbon−halogen bond in a representative unactivated organic halide possessing a highly negative reduction potential and whose activation is therefore known to be challenging.[12,13] The model reduction of aryl iodide **1a** was evaluated in the presence of excess triethylamine as the sacrificial reductant in acetonitrile at rt for 16 h under irradiation at 420 nm and in the presence of various photoactivatable copper complexes: results from these studies are collected in Table 1 (entries 1−12). After the little success met with a series of homoleptic complexes of phenanthroline and diphosphine derivatives (Table 1, entries 1−5), we next moved to heteroleptic complexes,[14] combining both one-electron-deficient phenanthroline and one-electron-rich chelating diphosphine[10a,15] or bis(isonitrile)[8c] (Table 1, entries 6−12). Among all heteroleptic complexes evaluated, [(DPEphos)(bcp)Cu]PF_6, whose efficiency as a photosensitizer for the photocatalytic reduction of water[15b] and carbon dioxide[15c] had been previously demonstrated, proved to be superior. Further optimization of the sacrificial reductant revealed the higher efficiency of Hünig's base, which enabled a clean reduction of **1a** in 93% yield with a decreased catalyst loading of 5 mol % (Table 1, entry 14). Control experiments demonstrated the strict requirement of both catalyst and light for the reaction to occur (Table 1, entries 15 and 16), the heteroleptic complex being also responsible for the catalysis and not the corresponding homoleptic complexes that might result from a poorly controlled speciation in solution (entry 12 vs entries 4 and 5). Finally, note that the reaction can also be performed by using simple blue LEDs to promote the reaction (Table 1, entry 17) with only a slight erosion of the yield, and that oxygen or TEMPO was highly detrimental (50 and 0% yields, respectively).

With these optimized conditions in hand, and to gain insights into the substrates that could be activated under these conditions, we next moved to the study of the scope and limitation of the light-mediated, [(DPEphos)(bcp)Cu]PF_6-catalyzed reduction of a series of aryl halides possessing representative substituents and substitution patterns (Figure 1).[12] Reduction of various aryl iodides **1** was first evaluated and found to proceed smoothly in all cases, providing the corresponding hydrodeiodinated arenes **2a-h** in good yields regardless of the substitution pattern and electronic properties of the starting aryl iodide. Notably, the reaction was found to be compatible with a range of functional groups, including a boronate **2e**, and could also be extended to heteroaryl iodides **2h**.

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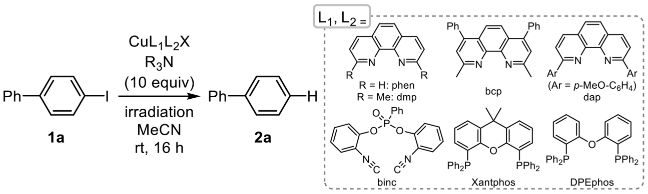
Table 1. Optimization of the Copper-Catalyzed Photoredox Reduction of Aryl Halides



entry	catalyst CuL_1L_2X	R_3N	irradiation	yield[a] (%)
1	$[(phen)_2Cu]Cl$ (10 mol %)	Et_3N	420 nm	–
2	$[(dmp)_2Cu]Cl$ (10 mol %)	Et_3N	420 nm	–
3	$[(dap)_2Cu]Cl$ (10 mol %)	Et_3N	420 nm	–
4	$[(DPEphos)_2Cu]PF_6$ (10 mol %)	Et_3N	420 nm	–
5	$[(bcp)_2Cu]PF_6$ (10 mol %)	Et_3N	420 nm	–
6	$[(binc)(dmp)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	–
7	$[(binc)(dap)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	–
8	$[(Xantphos)(dmp)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	58
9	$[(Xantphos)(bcp)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	65
10	$[(DPEphos)(dap)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	–
11	$[(DPEphos)(dmp)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	60
12	$[(DPEphos)(bcp)Cu]PF_6$ (10 mol %)	Et_3N	420 nm	70
13	$[(DPEphos)(bcp)Cu]PF_6$ (10 mol %)	iPr_2NEt	420 nm	88
14	$[(DPEphos)(bcp)Cu]PF_6$ (5 mol %)	iPr_2NEt	420 nm	93
15	no catalyst	iPr_2NEt	420 nm	–
16	$[(DPEphos)(bcp)Cu]PF_6$ (5 mol %)	iPr_2NEt	no light	–
17	**$[(DPEphos)(bcp)Cu]PF_6$ (5 mol %)**	**iPr_2NEt**	**blue LEDs**	85

[a]NMR yield with p-anisaldehyde as internal standard.

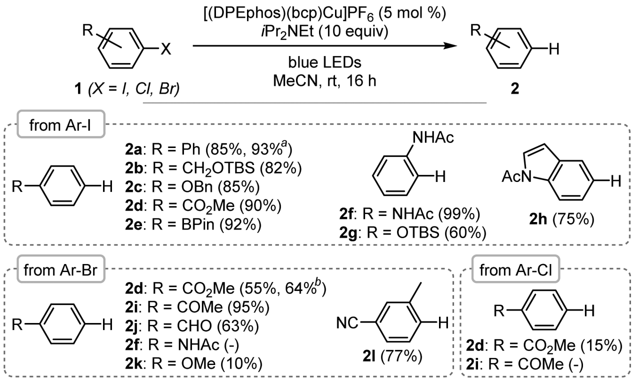


Figure 1. Scope of the copper-catalyzed photoredox reduction of aryl halides. Yields determined by ^{1}H NMR analysis of crude reaction mixtures using p-anisaldehyde as internal standard ([a]on a 1.0 mmol scale; [b]using 10 mol % of catalyst).

We next evaluated the reduction of aryl bromides, which is known to be much more challenging due to the slow C−Br bond cleavage kinetics.[12a,16] The reaction was efficient with electron-poor substrates (**1d,i,j**, X = Br), and the presence of electron-donating substituents strongly hampered the reaction (**1f,k**, X = Br). Aryl chlorides, even activated, were found to be poor reaction partners.

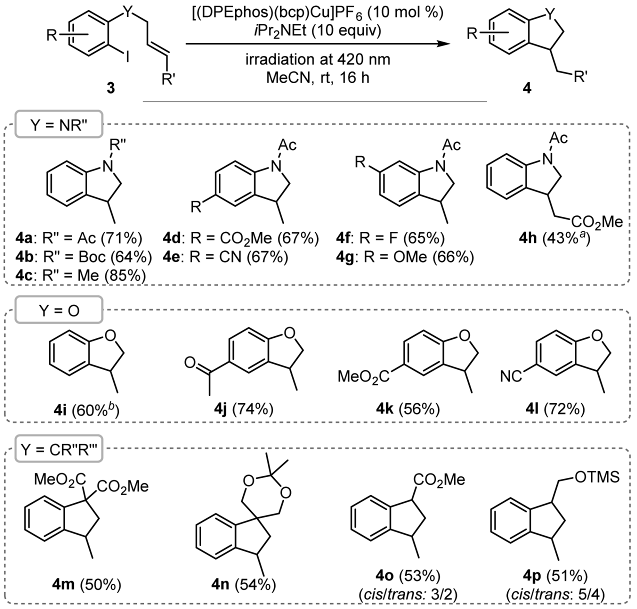


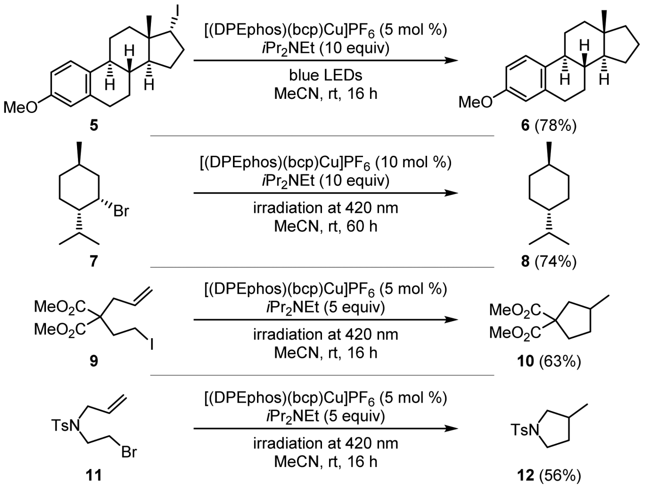
Figure 2. Copper-catalyzed photoredox cyclization of aryl iodides ([a]irradiation with blue LEDs; [b] ^{1}H NMR yield).

To further test the efficiency and usefulness of our procedure for the activation of aryl halides, we further studied its use for the formation of C−C bonds in intramolecular processes. The reductive radical cyclization of N-allyl-o-iodoanilines (Figure 2, **3**, Y = NR′′) afforded the corresponding polysubstituted indolines **4a-h**[3,12a,b] in fair to good yields if 10 mol % of $[(DPEphos)(bcp)Cu]PF_6$ was used in combination with irradiation in a photoreactor at 420 nm (50 W/m^2), which proved to be slightly superior to the use of blue LEDs. A range of substituents were well-tolerated on the nitrogen atom, including alkyl and common protecting groups (**4a-c**), on the aromatic ring (**4d-g**), and on the alkene (**4h**), although the reaction was less efficient in the last case. This cyclization could be extended to the preparation of a series of dihydrobenzofurans **4i-l**[3,12a,c,d] and indanes **4m-p** starting from the corresponding allylaryl ethers and homoallylarenes, respectively, with similar efficiency. Various substituents were found to be compatible with the reaction conditions in all cases, and the yields of the cyclized products compared well with the ones obtained through other procedures, clearly demonstrating the broad applicability of $[(DPEphos)(bcp)Cu]PF_6$ as a catalyst for photoredox transformations of aryl halides.

Having confirmed the applicability of $[(DPEphos)(bcp)Cu]PF_6$ in photoredox processes with aryl halides, we finally evaluated the reductive cleavage of alkyl halides. Alkyl iodides and bromides, even embedded in a complex structure such as **5**, were smoothly reduced under our standard conditions, yielding the corresponding derivatives **6** and **8** in 78 and 74% yields, respectively (Scheme 1). The copper catalyst can also initiate radical cyclizations from suitably functionalized alkyl halides such as **9** and **11**, yielding the corresponding carbo- and heterocycles **10** and **12** with reasonable efficiency if the amount of Hünig's base was decreased to minimize the competing reduction.

Next, we focused on an especially challenging transformation, the direct arylation of C(sp^2)−H bonds in arenes. Whereas various photoredox processes have been recently reported for this reaction, which affords a remarkably direct entry to biaryls,[13,17] they mostly rely on the use of diazonium salts,[18a−d] diaryliodonium triflates,[18e] or aryl sulfonyl chlorides.[18f] Although more challenging due to their potential competitive reduction,

Scheme 1. Copper-Catalyzed Photoredox Transformations of Alkyl Halides



aryl halides are considerably more practical and attractive readily available arylation reagents.[12c,19] To check whether our copper-based catalytic system could efficiently promote this reaction, we selected pyrroles as substrates as they are known to have high reaction rates in the addition of radical species.[12c] Initial studies revealed that the competitive reduction of the aryl halide by Hünig's base was a serious side reaction which could be suppressed using dicyclohexylisobutylamine.[19d] Biphenyl iodide **1a** was found to smoothly react with an excess of *N*-methylpyrrole, with the excess of the arene being required in most processes reported to date, in the presence of 10 mol % of [(DPEphos)(bcp)Cu]PF_6, 0.5 equiv of $\mathrm{Cy}_2\mathrm{N}i\mathrm{Bu}$, and 2 equiv of potassium carbonate in acetonitrile at rt for 3 days to afford the corresponding C2-arylated pyrrole **15a** in 66% yield (Figure 3).

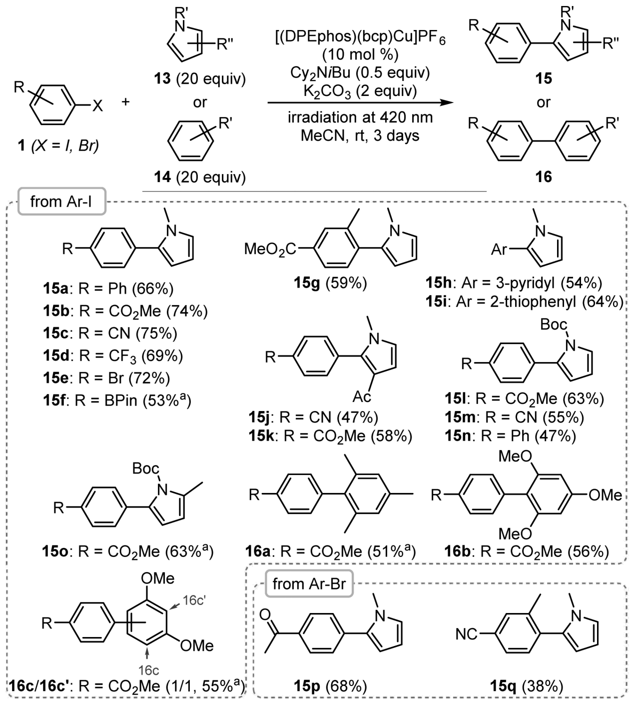


Figure 3. Copper-catalyzed photoredox direct arylation of (hetero)-arenes with aryl halides ([a]during 5 days).

The scope of this copper-catalyzed photoredox direct arylation was next explored starting with the arylation of *N*-methylpyrrole with various representative aryl iodides **1**. As demonstrated in Figure 3, the reaction was found to be rather general, the corresponding arylated pyrroles **15** being obtained in fair to good yields. Interestingly, aryl iodides substituted with a bromide or a boronate could be smoothly and selectively used as arylating reagents, therefore providing a useful handle for subsequent functionalization and diversification of corresponding products **15e** and **15f**. Heteroaryl iodides performed equally well, as demonstrated with their use in arylation of *N*-methylpyrrole to corresponding 2-pyridyl and 2-thiophenyl derivatives **15h** and **15i**. Other pyrroles also reacted smoothly, including Boc-protected ones, and direct arylation could be extended to electron-rich benzene derivatives **16**. Finally, electron-poor aryl bromides could be used for the direct arylation, as demonstrated with the synthesis of **15p** and **15q**.

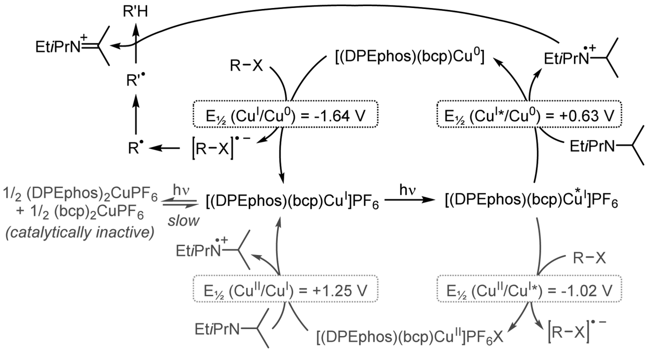


Figure 4. Mechanistic proposal, stability, and photophysical properties of [(DPEphos)(bcp)Cu]PF_6.

Photophysical studies of [(DPEphos)(bcp)Cu]PF_6, which was shown to be perfectly stable in the dark and afford only minor amounts of catalytically inactive homoleptic complexes upon irradiation, revealed a luminescence lifetime of 819 ns, which is in the high range for a heteroleptic copper complex, and an oxidation potential in the excited state of −1.02 V vs SCE.[20] This value is in accordance with recently reported ones[15c] and clearly demonstrates the inability of the excited copper catalyst to reduce an organic halide by a Cu(I)/Cu(I)*/Cu(II) oxidative quenching cycle (Figure 4, bottom). A rare Cu(I)/Cu(I)*/Cu(0) catalytic cycle[21] (Figure 4, top) might then account for the ability of [(DPEphos)(bcp)Cu]PF_6 to catalyze photoredox transformations of organic halides. The reaction would be initiated by reduction of [(DPEphos)(bcp)Cu]PF_6* with $i\mathrm{Pr}_2\mathrm{NEt}$, a transformation which is supported by the reduction potential in the excited state for this complex of +0.63 V vs SCE[20] and by the reported oxidation potential of $i\mathrm{Pr}_2\mathrm{NEt}$ (+0.68 V vs SCE),[22a] generating a transient copper(0) complex [(DPEphos)(bcp)Cu] whose oxidation potential was measured to be −1.64 V vs SCE.[20] Whereas this value might seem rather high for this complex to be able to reduce unactivated aryl iodides (reduction potentials of −1.2 to −0.33 V vs SCE for alkyl iodides[22b] and −1.91 V vs SCE for iodobenzene[7]), similar results have been reported for iridium complexes such as *fac*-Ir(ppy)$_3$, whose excited state (with an oxidation potential of −1.73 V vs SCE) was shown to be quenched by compounds with reduction potentials lower than −2.00 V vs SCE.[12a,22c] Moreover, formation of copper nanoparticles/mirrors in the presence of unreactive organic halides and strong quenching of [(DPEphos)-

(bcp)Cu]PF_6* by $i$$Pr_2$NEt ($k_q$ = 3.4 × 10^7 M^{-1} s^{-1})[20] strongly support this elementary step. Limited quenching of [(DPEphos)(bcp)Cu]PF_6* by iodobenzene (k_q = 6.9 × 10^6 M^{-1} s^{-1})[20] also supports this mechanism. Reduction of the organic halide R−X by single electron transfer from [(DPEphos)(bcp)Cu] regenerates the copper(I) catalyst and initiates generation of a radical $R^\bullet$, and upon its further cyclization in the presence of a suitably placed functional group or its addition to a radical acceptor such as an arene, yielding another radical species $R'^\bullet$. This radical is finally reduced by the amine radical cation to afford the final product. In the case of the direct arylation of $C(sp^2)$−H bonds in arenes, a reductant is not formally needed. The final rearomatization can indeed be triggered by reduction of the resulting radical species by either the amine radical cation or [(DPEphos)(bcp)Cu]PF_6*. In the last case, a substoichiometric amount of the amine is sufficient for the reaction to occur, which accounts for the successful use of only 0.5 equiv of Cy_2NiBu, which, combined with its low solubility,[19d] minimizes the competitive reduction of the starting halide.

In conclusion, we have reported a general and broadly applicable copper catalyst enabling photoredox transformations of organic halides. Both aryl and alkyl halides were found to be readily transformed to the corresponding radicals upon reaction with catalytic amounts of [(DPEphos)(bcp)Cu]PF_6 in the presence of an amine. A rare Cu(I)/Cu(I)*/Cu(0) catalytic cycle was shown to be involved with this photocatalyst, whose excited state was also shown to be long-lived. Besides providing an excellent alternative to iridium and ruthenium complexes, this opens new perspectives in the use of copper complexes for photoredox transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01518.

Photophysical studies of [(DPEphos)(bcp)Cu]PF_6, experimental procedures, characterization, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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