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Benzylic C–H Esterification with Limiting C–H Substrate Enabled by Photochemical Redox Buffering of the Cu Catalyst

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Abstract

Copper-catalyzed radical-relay reactions provide a versatile strategy for selective C–H functionalization; however, reactions with peroxide-based oxidants often require excess C–H substrate. Here, we report a photochemical strategy to overcome this limitation by using a Cu/2,2'-biquinoline catalyst that supports benzylic C−H esterification with limiting C−H substrate. Mechanistic studies indicate that blue-light irradiation promotes carboxylate-to-copper charge transfer, reducing resting-state Cu^{II} to Cu^{I}, which activates the peroxide to generate an alkoxyl radical hydrogen-atom transfer species. This "photochemical redox buffering" introduces a unique strategy to sustain the activity of Cu catalysts in radical-relay reactions.

Graphical Abstract

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ASSOCIATED CONTENT
SUPPORTING INFORMATION
The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxx
Experimental details with supplemental notes, characterization data, and NMR spectra (PDF).
CCDC 2232435 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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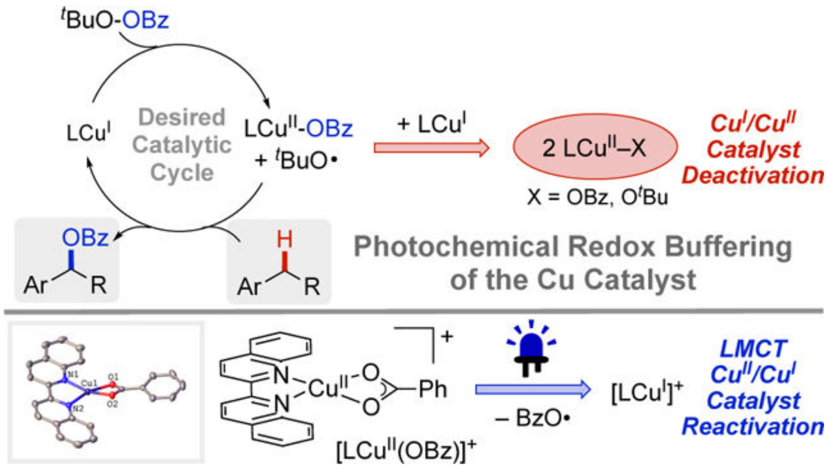

Keywords

Kharasch-Sosnovsky reaction; C─H functionalization; photochemistry

The Kharasch-Sosnovsky (K-S) reaction, first reported in 1958, uses a copper catalyst and peroxyester oxidant to convert alkenes to allylic esters (Figure 1A).[1,2] This seminal reaction is a prototype for contemporary radical-relay C(sp^3)–H functionalization methods.[3,4] The proposed mechanism for K-S reactions begins with activation of *tert*-butyl peroxybenzoate (TBPB) by $\mathrm{Cu^I}$ to generate a *tert*-butoxyl radical and $\mathrm{Cu^{II}}$benzoate (Figure 1B). The *tert*-butoxyl radical promotes hydrogen-atom transfer (HAT) from the allylic C─H bond, generating an allylic radical that reacts with a $\mathrm{Cu^{II}}$-benzoate species to form the C─O bond. While reviewing previous fundamental studies,[5–7] it became apparent that this simplified mechanism cannot account for key experimental observations. The reported activation barriers for steps 1–3 (Figure 1B) suggest the reaction should proceed within seconds at room temperature; however, K-S reactions and later variations that form C–O, [8] C–N [9] and C–C [10] bonds often require elevated temperatures (80–120 °C) and/or long (sometimes multi-day) reaction times. Here, we offer mechanistic hypotheses explain these observations, providing the foundation for development of Cu-catalyzed benzylic esterification reactions compatible with use of the C–H substrate as the limiting reagent (Figure 1C).

Studies of other radical-relay C–H oxidation reactions[10b,11] help to rationalize the unexplained features of K-S reactions. $\mathrm{Cu^I}$ often reacts rapidly with the peroxide in a 2:1 stoichiometry, converting all $\mathrm{Cu^I}$ to $\mathrm{Cu^{II}}$. Warren and coworkers characterized this reactivity between a diketiminate-$\mathrm{Cu^I}$ complex and ^{t}BuOO^{t}Bu (DTBP),[8b] and we have observed similar behavior in reactions of $\mathrm{Cu^I}$ with *N*-fluorobenzenesulfonimide (NFSI),[11] another common oxidant in radical-relay reactions. Since $\mathrm{Cu^{II}}$ does not react with peroxides under these conditions, radical generation relies on thermal O–O bond homolysis when $\mathrm{Cu^I}$ is depleted. At high temperatures needed to initiate the reaction, however, *tert*-butoxyl radical decomposes via *β*-methyl scission, producing methyl radical and acetone.[12] Use of excess C─H substrate (3–10 equiv) enables the bimolecular HAT step to compete with unimolecular decomposition of *tert*-butoxyl radical; however, this approach reduces the synthetic utility of the reaction. HAT gains a competitive advantage over *β*-scission at lower temperature.[6a,12b] We recently used photochemistry to support O–O cleavage under ambient conditions, leveraging triplet energy-transfer (EnT) with an Ir-based photocatalyst, $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ [Ir-F; $dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-(5-trifluoromethyl)pyridine]. [13] This approach proved more effective than direct photolysis of the peroxide[14–16] in C–H methylation reactions with DTBP.[17] We initiated the present study with the goal of developing K-S-type benzylic esterification using a similar photocatalytic EnT concept; however, we instead discovered a photoactive Cu/2,2'-biquinoline (biq) catalyst system that does not require the Ir photocatalyst. The results outlined below demonstrate a new "photochemical redox-buffering" mechanism to enable Cu-catalyzed radical-relay C–H functionalization.

Initial efforts probed the reaction of ethylbenzene (**1a**) with TBPB (**2**), using **1a** as the limiting reagent. Thermal K-S conditions with $[Cu(MeCN)_4]PF_6$ and a bidentate nitrogen ligand as the catalyst, including 1,10-phenanthroline (phen), 2,2'-bipyridine (bpy) and biq, led to negligible or low yields of the esterification product **3a** at 40 and 80 °C (Table 1, entries 1–6). The reactions were reassessed in the presence of the Ir-F photocatalyst while irradiating with 450 nm LEDs. A 20% yield of **3a** was observed with the biq/Cu^I catalyst (Table 1, entry 9). Control experiments, in which the reaction solution was irradiated in the absence of Ir-F, led to an even better yield with biq/Cu^I (39% **3a**). Optimized conditions afforded a 74% yield of **3a** (Table 1, entry 11) (see Supporting Information for full screening data).

The optimized conditions were tested with other substrates. Secondary benzylic C–H bonds proved particularly effective (Figure 2). Ethyl- and *n*-alkylbenzene derivatives, including those with electron-rich and -deficient aromatic substituents and 1° alkyl halides, proceeded in good yield (59−79%, **3b**−**3n**). The reaction was also effective with a substituted diarylmethane (**3s**),[18] and benzofuran and thiophene substrates (**3p**, **3r**).[19] The pyridine-containing substrate **2q** exhibited high conversion, but did not afford the desired product **3q** (see Figure S7 for additional unsuccessful substrates). More complex substrates also proved effective, including celestolide (85%, **3t**), ibuprofen methyl ester (58%, **3u**); and benzbromarone methyl ether (55%, **3v**), a derivative of a xanthine oxidase inhibitor.[20]

No reactivity was observed at the 3° benzylic C–H bond of the ibuprofen derivative (**3u**); however, this site is electronically deactivated by the adjacent carbonyl group.[21] Substrates with electronically unbiased 3° C–H bonds showed good reactivity (Figure 3A, **3w**–**3y**). In substrates with more than one benzylic C–H bond or both benzylic and tertiary aliphatic C–H bonds, the reaction favors 2° benzylic reactivity (Figure 3, **3z**–**3ac**). This selectivity likely reflects steric effects favoring the less hindered site and electronic effects favoring the more substituted sites (i.e., more electron-rich and/or weaker C–H bonds).[22] Collectively, the reactions in Figures 2 and 3 provide a means to access benzylic alcohols via benzylic C–H oxygenation, without over-oxidation to the corresponding ketones. This outcome may be realized via C–H esterification, followed by hydrolysis, without isolation of the intermediate ester (**4r**–**4ae**, Figure 3B).

Subsequent efforts probed how the biq/Cu^I catalyst system differs from more conventional Cu catalyst systems, such as those with phen and bpy. The reaction of TBPB with

$[Cu(MeCN)_4]PF_6$ and 1.5 equiv of phen, bpy, or biq was monitored by UV-visible spectroscopy (Figure 4A). The phen- and bpy-ligated Cu^I complexes react rapidly with TBPB, undergoing full oxidation of Cu^I within seconds after mixing (Figures 4A–1 and 4A-2). The reaction of biq/Cu^I with TBPB is more complex, with rapid partial reaction of Cu^I observed immediately after mixing, followed by very slow oxidation of the remaining Cu^I over several days (Figure 4A–3). Biq is known to form tetrahedral $[biq_2Cu^I]^+$ complexes,[23,24] and this species exhibits the absorption feature centered at 549 nm. Ligand titration, however, revealed that $[(biq)_2Cu^I]^+$ does not begin to appear until nearly a full equivalent of biq is added (see Figure S4). Therefore, the optimized catalyst system, with a 1.5:1 biq/Cu ratio, will have both mono- and bis-ligated biq/Cu^I complexes in the reaction mixture. A 1:1 mixture of biq/$[Cu(MeCN)_4]PF_6$ reacts very rapidly with TBPB, while a 2:1 mixture of biq/$[Cu(MeCN)_4]PF_6$ shows negligible reactivity (Table S7). TBPB titration experiments show that the rapid oxidation of Cu^I reaches completion with only 0.5 equiv of TBPB (Figure 4B). These data show that phen/Cu^I and bpy/Cu^I and 1:1 biq/Cu^I undergo very rapid oxidation by TBPB, while the 2:1 biq/Cu^I species is nearly inert under analogous conditions.

We then probed the reactivity of biq/Cu^I (1.5:1) with TBPB during blue LED irradiation. Analysis of this reaction by UV-vis spectroscopy showed partial disappearance of the $[(biq)_2Cu^I]^+$ species over the first 5–6 min, consistent with oxidation of Cu^I by TBPB; however, $[(biq)_2Cu^I]^+$ reappeared over the next 6 min (Figure 4C). The initial phase of this reactivity suggests that irradiation enhances the rate of $[(biq)_2Cu^I]^+$ oxidation by TBPB, albeit more slowly than reaction of TBPB with the 1:1 biq/Cu^I species. Reappearance of $[(biq)_2Cu^I]^+$ during irradiation is notable and implicates light-promoted reduction of a biq/Cu^{II} species.

Reaction of 0.5 equiv of TBPB with biq/Cu^I (cf. Figure 4B) is expected to form Cu^{II}–OBz and Cu^{II}–O^{t}Bu species.[8b] While the latter species are thermally unstable,[9b, 25] X-ray quality crystals of $[(biq)Cu^{II}(OBz)]PF_6$ (**Cu^{II}-OBz**) were obtained from the reaction (Figure 4D, left). A catalytically relevant mixture of 1.5:1 biq/Cu^I was then fully oxidized by TBPB. Irradiation of this mixture with blue LEDs led to photoinduced reduction of Cu^{II} and appearance of $[(biq)_2Cu^I]^+$ (Figure 4D, right). When biq was replaced by phen or bpy in this sequence, no photoreduction of Cu^{II} was observed (Figure S6). To probe photoreduction of biq/Cu^{II} further, **Cu^{II}-OBz** in CH_2Cl_2 was irradiated in the absence of substrate. Analysis of the organic products by ^{1}H NMR spectroscopy revealed the presence of $PhCO_2H$ and 1,1,2,2-tetrachloroethane in 80% and 10% yields with respect to the initial **Cu^{II}-OBz** (Figure 4E). These products are consistent with photoinduced ligand-to-metal charge transfer (LMCT) in **Cu^{II}-OBz** and release of benzoyloxyl radical, resembling reactivity reported in other recent reports.[26] Benzoyloxyl radical-promoted HAT from CH_2Cl_2 solvent accounts for tetrachloroethane formation (Figure 4E). [27] A separate control experiment confirmed that **Cu^{II}-OBz** is a competent catalyst precursor (Figure 4F), indicating that this species can undergo in situ activation by blue LED irradiation without requiring addition of a Cu^I source.

The above insights are rationalized by the following mechanistic proposal. The $[(biq)Cu^I]^+$ species reacts rapidly with TBPB to generate $[(biq)Cu^{II}(OBz)]^+$ and a *tert*-butoxyl radical.

Ideally, the *tert*-butoxyl radical promotes HAT from the C–H substrate (Figure 5, blue arrow), but it can be quenched by a second equivalent of Cu^I when relatively high concentrations of $[(biq)Cu^I]^+$ are present (Figure 5, red arrow). [28] The accumulation of Cu^{II} species generated by this reaction accounts for the negligible product formation in the absence of blue LED irradiation (cf. Table 1, entries 3 and 6) because Cu^{II} does not activate TBPB under these mild conditions. Blue LED irradiation regenerates Cu^I, which can promote reductive activation of TBPB to generate a *tert*-butoxyl radical. The mild reaction temperature and negligible Cu^I present during the steady-state reaction conditions means that *tert*-butoxyl radical can promote HAT from the C–H substrate with minimal competition from β-methyl scission and/or quenching by Cu^I.

These results introduce “photochemical redox-buffering” as a new strategy to support Cu-catalyzed radical-relay C–H oxidation reactions (Figure 5A). This process, in which irradiation of the reaction mixture generates Cu^I from restingstate Cu^{II} species, resembles the chemical redox buffering pathways first established in Cu-catalyzed C–H oxidation with NFSI as the oxidant,[11a] which also proceed under mild conditions and using limiting C–H substrate. Studies of the latter reactions showed that Cu^I reacts rapidly with NFSI to generate Cu^{II} species that cannot support catalysis unless a sacrificial reductant is present to regenerate Cu^I.[11a] This reductant could be the coupling partner (Figure 5B; e.g., TMSCN and $ArB(OH)_2$ reduce Cu^{II} via homocoupling to cyanogen or biaryl),[29,30] or a separate reagent when the coupling partner is not an effective reductant for Cu^{II} (Figure 5C).[11,31–33]

The observations outlined herein provide an important starting point for further development of Kharasch-Sosnovsky and other Cu-catalyzed radical-relay reactions. Reactions of this type require both Cu^I and Cu^{II} to support formation and functionalization of the organic radical, respectively; however, oxidants such as peroxides and NFSI rapidly convert all of the Cu^I to Cu^{II}, deactivating the catalyst and quenching the HAT species. The present study shows that visible light irradiation may be used as an alternative to chemical reagents to buffer the redox state of the Cu catalyst and support catalytic turnover under mild reaction conditions and with the C–H substrate as the limiting reagent. Efforts have been initiated to elaborate on these concepts in an effort to explore new substrate classes and catalyst systems, including variations with chiral ligands, that will expand the synthetic utility of this reactivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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27. Inclusion of ethylbenzene and 4-ethylanisole in the reaction shown in Figure 4E led to only minor conversion of the benzylic substrate (0% and 13%, respectively). This observation suggests most benzylic reactivity under catalytic conditions originates from reaction with tert-butoxyl radical. See Section 8, Experiment S11 in the Supporting Information for details.

28. We note that the bis-ligated $[(biq)_2CuI]^+$ species appears largely inert under the reaction conditions; however, it could serve as a reservoir for additional CuI via ligand exchange. For example, we find that addition of $[(biq)Cu^{II}(OBz)]^+$ to a solution of $[(biq)_2CuI]^+$ results in a decrease in the absorbance of the latter species, implicating dissociation of one of the biq ligands from this species. See, Figure S5 and associated experimental description in the Supporting Information.$_2{}^{+II+}{}_2{}^+$

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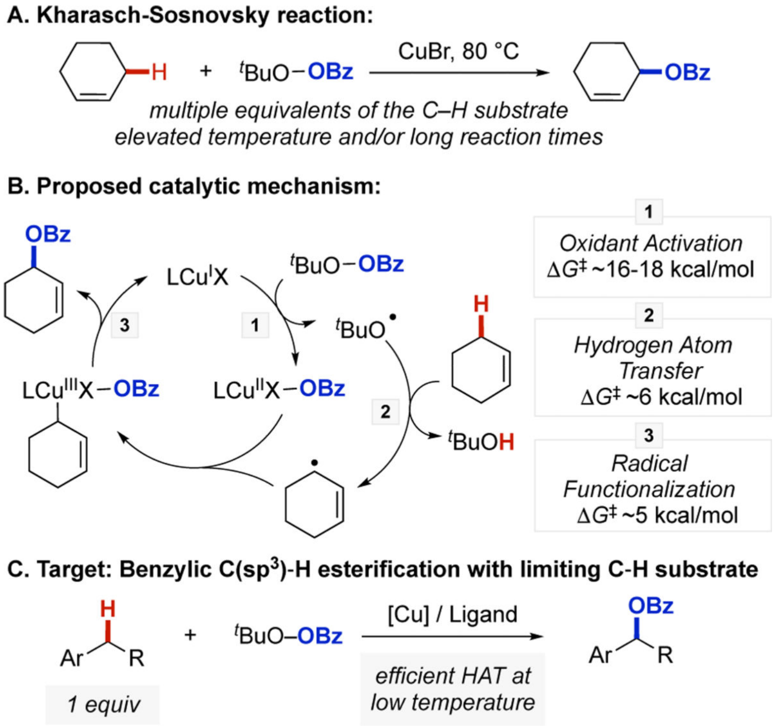


Figure 1.

(A) Kharasch-Sosnovsky (K-S) allylic C–H esterification. (B) Proposed catalytic mechanism for the K-S reaction and estimated activation barriers for individual steps. (C) Focus of this study is to develop a K-S-type benzylic esterification, capable of using the C–H substrate as a limiting reagent.

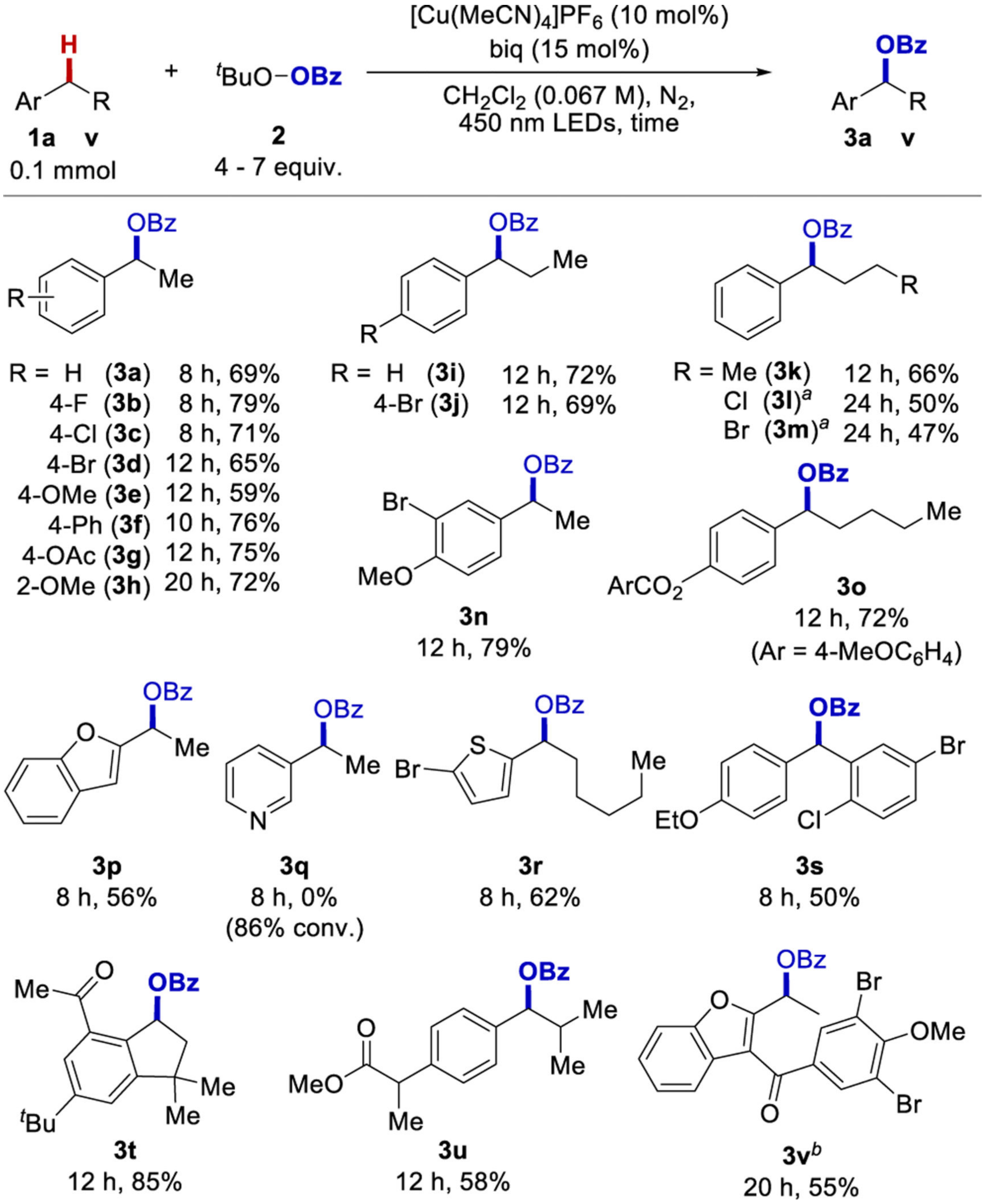


Figure 2.

Reactions of diverse 2° benzylic C─H substrates. [a]Conducted with 10 equiv TBPB. [b]Conducted with 2 equiv dibenzoyl peroxide.

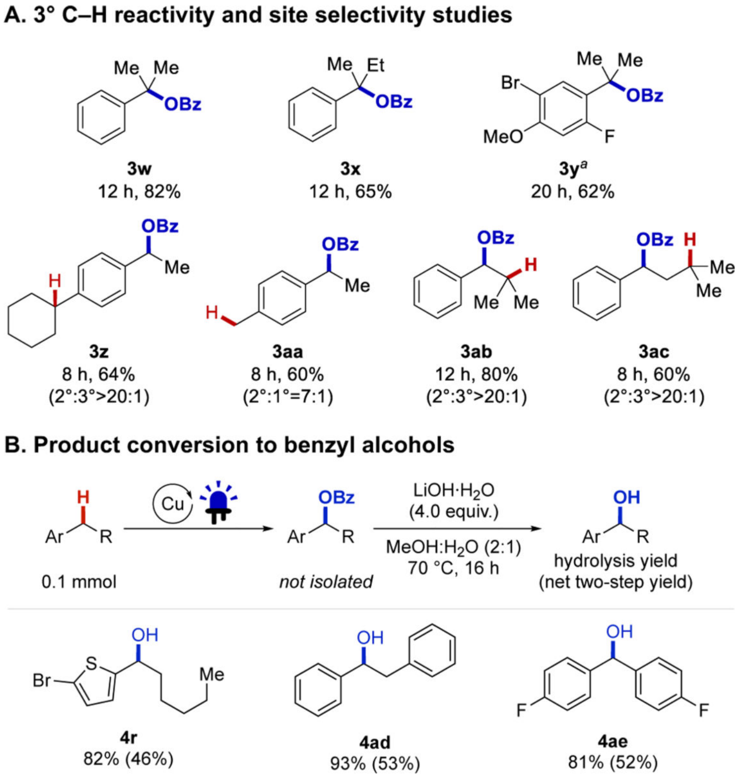


Figure 3.

(A) Reactivity of 3° benzylic substates and assessment of benzylic site-selectivity under the conditions defined in Figure 2, and (B) sequential esterification/deprotection of benzylic C−H substrates.

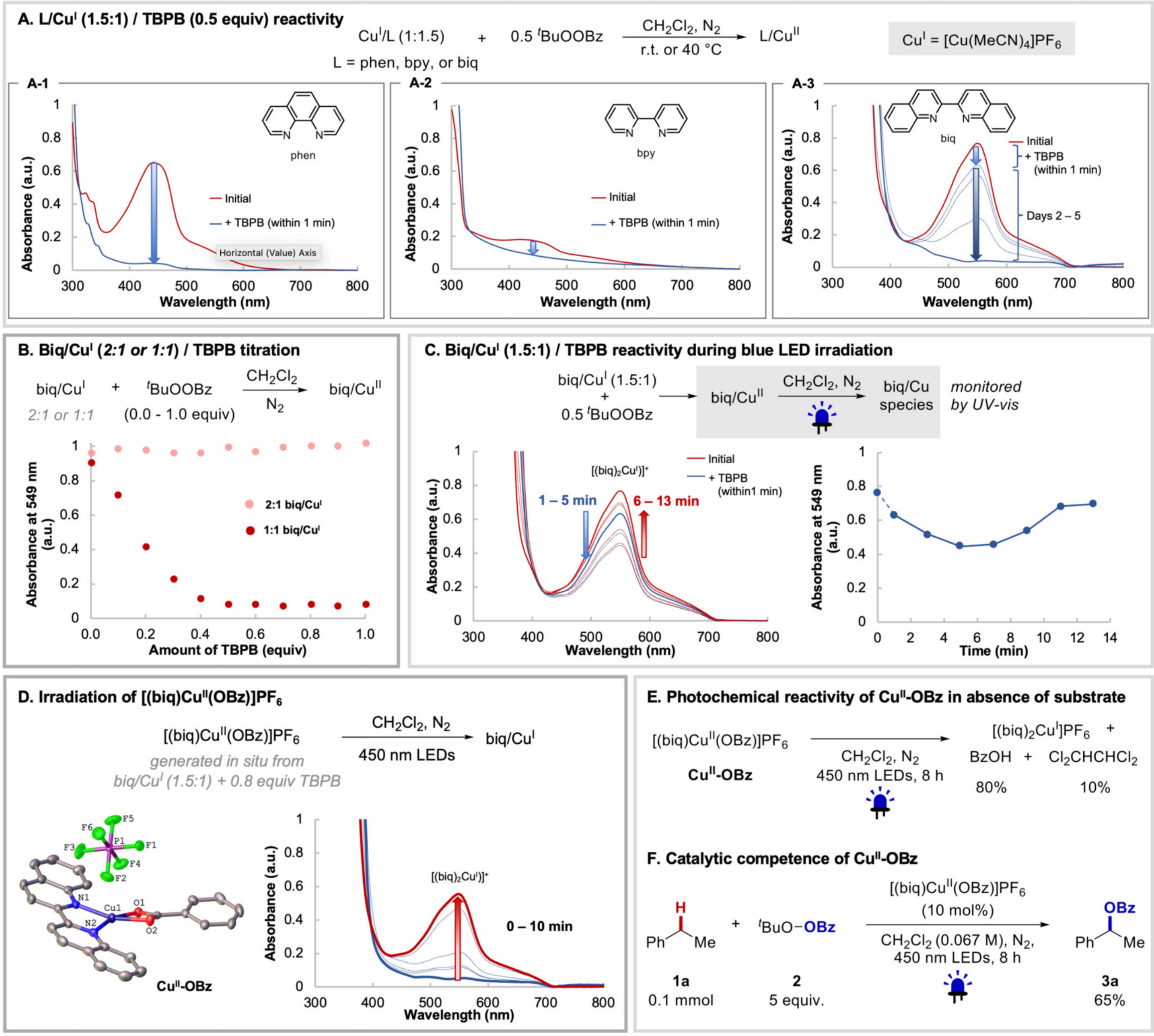


Figure 4.

(A) UV-visible absorption spectra for oxidation of Cu^{I} complexes with phen (r.t.), bpy (r.t.), and biq (40 ^{O}C) ligands without irradiation. (B) TBPB titration experiment with 2:1 biq/Cu^{I} and 1:1 biq/Cu^{I} with 30s mixing after every addition. (C) UV-visible absorption spectrum for oxidation of biq/Cu^{I} under irradiation. (D) UV-visible absorption spectrum of photochemical reduction of biq/Cu^{II}. Reaction of 1:1 biq/Cu^{I} with TBPB to afford [(biq)Cu^{II}(OBz)]PF_6. For clarity, hydrogen atoms are not shown in the X-ray structure. (E) Photochemical reactivity of **Cu^{II}-OBz** in absence of a C–H substrate. (F) Catalytic reactivity of **Cu^{II}-OBz** under standard reaction condition.

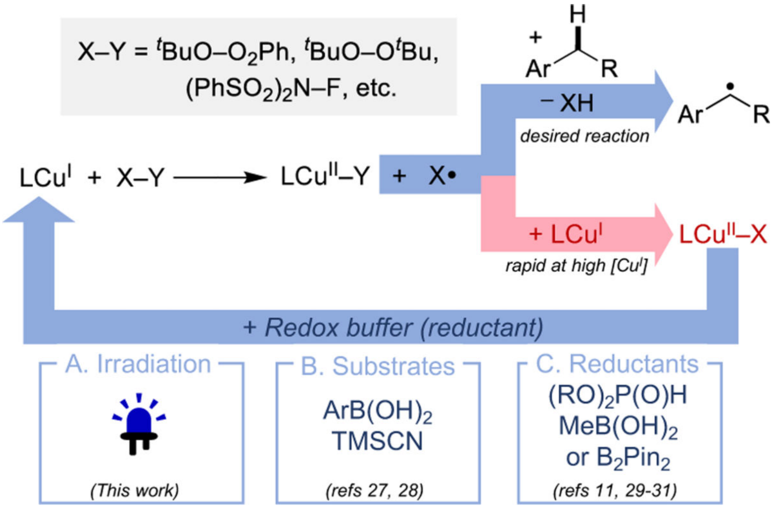
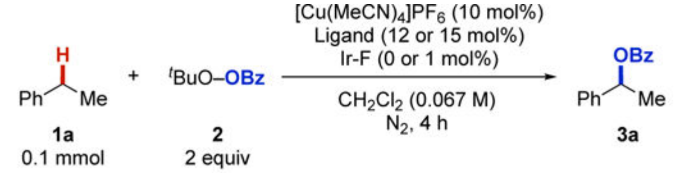


Figure 5.

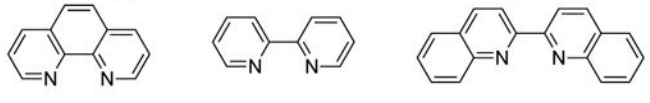
Redox buffering pathway for Cu-catalyzed C–H functionalization reactions. Cu^{II} reduction can be promoted by light (A), coupling partners (B), or sacrificial reagents (C).

Table 1.

Reaction optimization for photo-promoted benzylic esterification.



Entry	Ligand (mol%)	Ir-F[a] (mol%)	Temp (°C)	Conv. of **1a**[b] (%)	Yield of **3a**[b] (%)
Thermal: 40 or 80 °C					
1	phen (12)	0	40	0	0
2	bpy (12)	0	40	0	0
3	biq (12)	0	40	0	0
4[c]	phen (12)	0	80	3	3
5[c]	bpy (12)	0	80	6	0
6[c]	biq (12)	0	80	13	13
Photochemical: 450 nm LED irradiation at 40 °C					
7	phen (12)	1	40	11	0
8	bpy (12)	1	40	4	0
9	biq (12)	1	40	33	20
10	biq (12)	0	40	57	39
11[d]	**biq (15)**	**0**	**40**	**99**	**74**



phen **bpy** **biq**

[a] Ir-F = $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$.

[b] ^{1}H NMR spectroscopy; yield determined using mesitylene as ext. std.

[c] 1,2-dichloroethane used as the solvent.

[d] Reaction run for 8 h with 5 equiv of TBPB (**2**).