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Copper-mediated etherification via aryl radicals generated from triplet states

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Carbon–heteroatom (C–X) cross-coupling is a common method for bond-forming reactions in chemistry but the more electronegative the heteroatom X is, the more challenging the bond formation becomes. Although reductive elimination from Cu(III) intermediates to form C–X bonds is generally a facile reaction, oxidative addition of Cu(I) into the carbon–(pseudo)halide bond of aryl (pseudo)halides is energetically challenging. Therefore, cross-coupling reactions of aryl halides with a variety of nucleophiles is currently out of reach for methods based on copper. Here we present a strategy to bypass the high-barrier oxidative addition step to aryl halides by the generation of aryl radicals from triplet states. Photoinduced energy transfer to, or direct excitation of, aryl halides even enables the use of aryl chlorides as electrophilic coupling partners. This strategy allows for the use of alcohols, amines and fluoride as nucleophiles and expands the scope of copper-mediated cross-coupling chemistry.

The arylation of alcohols is one of the most widely utilized organic reactions in the pharmaceutical industry according to a big data analysis of pharmaceutical patents over the past 40 years[1]. Copper-mediated C–O bond formation from aryl halides has the potential to provide a convenient and efficient protocol to realize etherification due to the low toxicity and cost of copper and the existence of readily accessible haloarenes. However, copper cannot generally be used in cross-coupling reactions due to the lack of efficient oxidative addition of aryl (pseudo)halides to Cu(I)[2]. While palladium(0) is efficient for oxidative addition due to the development of suitable ligands, product-forming C–X bond reductive elimination from Cu(III) is typically more facile than from Pd(II) (refs. [2,3]). Merging photoredox and metal catalysis is promising for the construction of carbon–heteroatom bonds because photoexcited catalysts can result in synthetically useful oxidation states of transition metals that are not easily accessible with conventional transition-metal catalysis[4–11]; excited-state organometallic intermediates can enable transformations not currently accessible by organometallics in the ground state[12]. However, a general strategy to access aryl ethers, transition-metal-catalysed or metallaphotoredox-catalysed, has not been developed from aryl halides based on copper. Here we report a conceptually different and general approach to activate aryl halides for copper-mediated carbon–heteroatom bond formation reactions by energy transfer to, or direct excitation of, aryl halides. In contrast to current photoredox-based strategies, our approach increases the range of suitable electrophiles to encompass aryl iodides, bromides and even chlorides, and the scope of nucleophiles, for example, to functionalized alcohols, which has not been achieved by photoinduced Ullmann-type C–O coupling reactions of aryl halides[13,14]. The approach was further extended to other nucleophiles such as amines and fluoride, showcasing the potential of the energy transfer and direct excitation strategy in combination with copper.

Over the past two decades, different transition-metal-promoted reactions[15], such as Chan–Lam couplings[16], palladium-catalysed C–O bond-forming reactions[17], Ullmann-type reactions[2,18–22] and various others[7,14], have been developed to construct C–O bonds. However, Chan–Lam couplings require arylboronic acids as starting materials, which are often less available than the corresponding halides. For palladium-catalysed coupling reactions, the scope has become more and more general upon extensive ligand development[17]. However, basic conditions and high temperature promote competitive β-hydride elimination and diminish the applicability of the reaction. Copper-catalysed or copper-mediated Ullmann-type reactions were discovered as early as 1903[2], but usually require harsh reaction conditions due to the high barrier of the copper aryl halide oxidative addition step. With alcohol nucleophiles, high reaction temperature (>110 °C) or solvent amounts of alcohol are required[18]. Additionally, the substrate scope is often restricted to aryl iodides[18,19]. To achieve a broader substrate scope and milder reaction conditions, various ligands were developed to tackle the slow rate of oxidative addition to other aryl halides. For example, Buchwald and co-workers developed diamine ligands[20], and Ma and Hartwig developed oxalic diamide and oxalohydrazide ligands[21,22], which enable a broader substrate scope but still mostly for simple alcohols and aryl iodides and bromides. Extension of the concept of metallaphotoredox catalysis to copper and aryl halides is promising but has not yet resulted in a general strategy that would also encompass aryl ether bond formation. For example, the generation of synthetically useful aryl radicals from aryl halides can achieve the formation of synthetically useful arylcopper species[10,13,14], but the generation of aryl radicals through this process is challenging[10,13,23]. In 2018, MacMillan and co-workers developed a photoredox strategy to generate [L_nNuCu^{III}Ar] intermediates via bromine atom abstraction from aryl halides by a silyl radical abstraction process (Fig. 1a)[10]. The atom transfer activation mode, however, has not yet been generalized, for example, to etherification or fluorination of aryl halides, possibly due to undesired side reactions between silanes and the nucleophile[24]. Aryl chlorides are still out of reach for that chemistry based on copper. Another promising approach involves single-electron transfer (SET) to aryl halides to generate aryl radicals by mesolytic bond cleavage that can then undergo oxidative ligation to copper. Fu and Peters reported that excited [L_nCu^{I}Nu] species could undergo SET with aryl halides (Fig. 1b). To excite the [L_nCu^{I}Nu] species, the nucleophiles are usually substrates with a π system such as phenol, carbazole and indole[13,14]. Other photoredox

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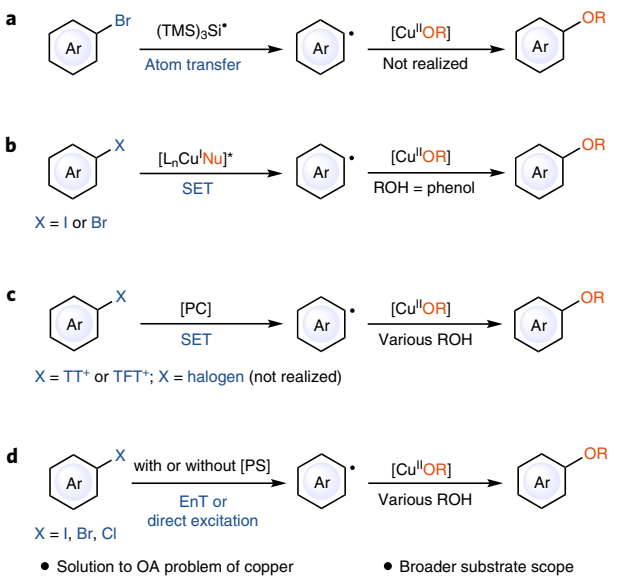


Fig. 1 | Generation of aryl radicals from aryl (pseudo)halides in copper-mediated etherification reactions. a–c, Previous strategies: activation of aryl bromides via atom transfer with silyl radical[10] (**a**), activation of aryl halides via SET with excited-state [Cu^{I}] species[13,14] (**b**) and activation of aryl sulfonium salts via SET with photocatalyst[26–29] (**c**). **d**, This work: activation of aryl halides via energy transfer or direct excitation. PC, photocatalyst; TT, thianthrenium; TFT, tetrafluorothianthrenium; PS, photosensitizer; EnT, energy transfer; OA, oxidative addition.

catalysts have not been identified to generally access aryl radicals from aryl halides under conditions that are suitable for productive reductive elimination from high-valent copper. The low oxidation potentials of aryl halides that require strongly reducing excited states are usually not compatible with high-valent copper species[23]. Our group has addressed this challenge by photoredox-mediated generation of aryl radicals from aryl thianthrenium salts, which can be prepared site selectively from complex arenes[25] and have substantially lower oxidation potentials and higher mesolytic cleavage rates than aryl halides (Fig. 1c)[26]. Based on this approach, we achieved visible-light-induced radical oxygenation[27], amination[28], trifluoromethylation[29] and fluorination reactions[26]. However, while thianthrenium salt formation from complex small molecules is often superior to halogenation, thousands of aryl halides are commercially available but out of reach for this chemistry. Therefore, to realize a general copper-mediated carbon–heteroatom bond formation reaction from aryl halides, we sought to develop a new strategy to activate aryl halides that is compatible with high-valent copper intermediates and various nucleophiles. The approach bypasses the energetically challenging oxidative addition process by copper through generation of aryl radicals from triplet-state aryl halides, as opposed to photoredox catalysis, which is compatible with facile C–X bond formation from high-valent copper (Fig. 1d).

Results and discussion

Generally, SET for activation of Ar–X bonds (X = (pseudo)halogen) requires transfer of an external electron to a π^* orbital of the haloarene to form a radical anion species. Subsequently, the radical anion can further undergo C–X bond mesolytic cleavage to form an aryl radical and a halide anion[30]. The external single electron donor, a strong reductant, is commonly incompatible with high-valent copper intermediates, especially for the strong single-electron reductants required for SET to aryl halides. In contrast, energy transfer[31,32] is initiated by absorption of a photon of a photosensitizer, which leads to excitation from the ground state (S_0) to the first excited singlet state (S_1), followed by intersystem crossing (ISC), for an ideal photosensitizer in high quantum yield, to the lowest triplet state (T_1). From T_1, the photosensitizer can transfer its energy to an aryl halide, resulting in a triplet-state aryl halide. The sensitization process requires no external electron or high reduction potential and therefore has the potential to be compatible with high-valent metal intermediates. Based on this analysis, we designed a catalytic cycle that does not involve photoredox processes but instead direct energy transfer (EnT, Fig. 2a). While energy transfer is a well-established photophysical process, it does not appear to have been used as a substrate-activation strategy for metal-mediated cross-coupling chemistry. Radiative emission from the triplet state is spin-forbidden, so that homolytic cleavage of the C–X bond can occur to form two radicals[33–36]. The halogen atom could oxidize or oxidatively ligate[37] to Cu(I) in the presence of nucleophiles to form a [L_nCu^{II}Nu] intermediate and a halide anion. Oxidative ligation of the aryl radical to [L_nCu^{II}Nu] (refs. [38–42]) would form the high-valent [L_nNuCu^{III}Ar] intermediate, from which fast reductive elimination[2] would occur to form product and regenerate Cu(I).

A typical energy transfer process is depicted in the Jablonski diagram in Fig. 2b (left). For the energy transfer to occur effectively, a close spatial encounter between an excited photosensitizer of sufficient triplet energy and the substrate must occur. Therefore, the energy transfer mechanism is only applicable to aryl halide substrates whose triplet energy is lower than or similar to that of the photosensitizer. We selected thioxanthone (TXO) as photosensitizer due to its triplet state energy of $E_T = 64.5$ kcal mol^{-1} (ref. [31]) and 4-iodobiphenyl (**1**) with a reported triplet energy of $E_T = 62.5$ kcal mol^{-1} (ref. [32]) to evaluate the desired etherification reaction of **1** and obtained 70% yield of azetedinyl ether upon irradiation with a 400 nm light-emitting diode (LED) (Fig. 2c). CuTC was identified as the best copper source, while copper halides performed worse and produce dehalogenation species as major side products (Supplementary Table 2). Because copper halides are probably produced as by-products in the cross-coupling reactions of aryl halides, stoichiometric amounts of CuTC afforded higher product yields but copper catalysis can be achieved upon addition of halide scavengers. For example, addition of 0.5 equiv. of Ag_2O enabled the CuTC catalyst loading to be reduced to 5 mol% and unambiguously established the presence of a catalytic copper redox cycle (Fig. 2c). Given that CuTC is rather inexpensive (US$2.2 g^{-1}) and no expensive ligand is required, we identified both the reaction with 1 equiv. of CuTC and the reaction conditions with 5 mol% as practical and synthetically useful.

The triplet energy of aryl halides is highly dependent on the conjugated π system. For example, phenyl halides have triplet energies of $E_T = 78–82$ kcal mol^{-1} (ref. [32]), which is too high for excitation by common photosensitizers such as benzophenone ($E_T = 69.1$ kcal mol−1)[31]. Therefore, to evaluate whether the substrate scope of our approach could be extended to aryl halides without additional conjugated π systems, we attempted direct excitation of those aryl halides to access their triplet states under otherwise identical reaction conditions (Fig. 2b, right). For example, 4-bromo- and 4-chloroanisole (**4b**, **4c**) have the same triplet energy of 78.1 kcal mol^{-1} (ref. [32]), and could be excited with ultraviolet light to afford the desired etherification product **5** in good yield (Fig. 2d). Although ultraviolet irradiation must be used, the engagement of unactivated aryl chlorides for copper-mediated cross-coupling is a fundamental advance that has not been achieved with conventional or metallaphotoredox approaches under mild conditions as of yet. In addition, we show that the requirement for ultraviolet irradiation does not preclude the use of functionalized small molecules, even those with other chromophores on either aryl halide or the alcohol reaction partner.

Experiments with respect to the mechanism of the etherification are consistent with our design (Fig. 3). First, inter- and intramolecular radical-trapping experiments results indicate the formation of aryl

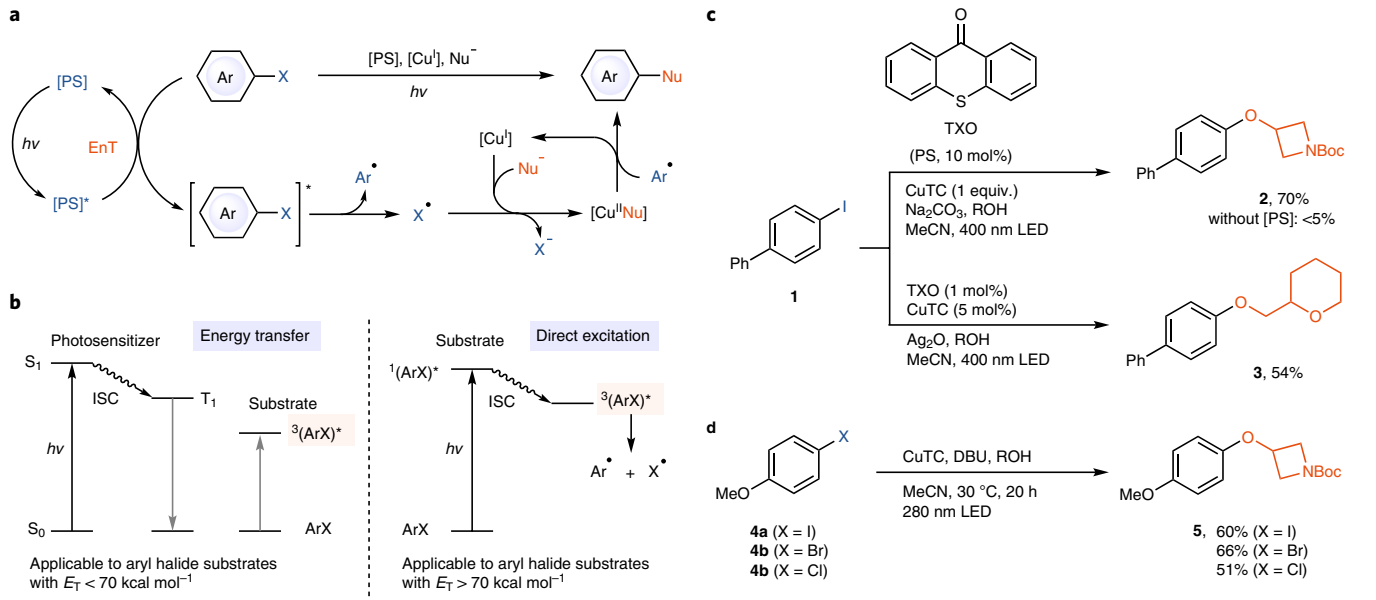


Fig. 2 | Functionalization of aryl halides via energy transfer or direct excitation mechanism. a, The catalytic cycle for the functionalization reaction of aryl halides via energy transfer. **b**, The activation process of aryl halides via energy transfer or direct excitation. **c**, Etherification reaction of 4-iodobiphenyl via energy transfer. **d**, Etherification reaction of halogenated anisole via direct excitation. PS, photosensitizer; Nu, nucleophile; CuTC, copper(I) thiophene-2-carboxylate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

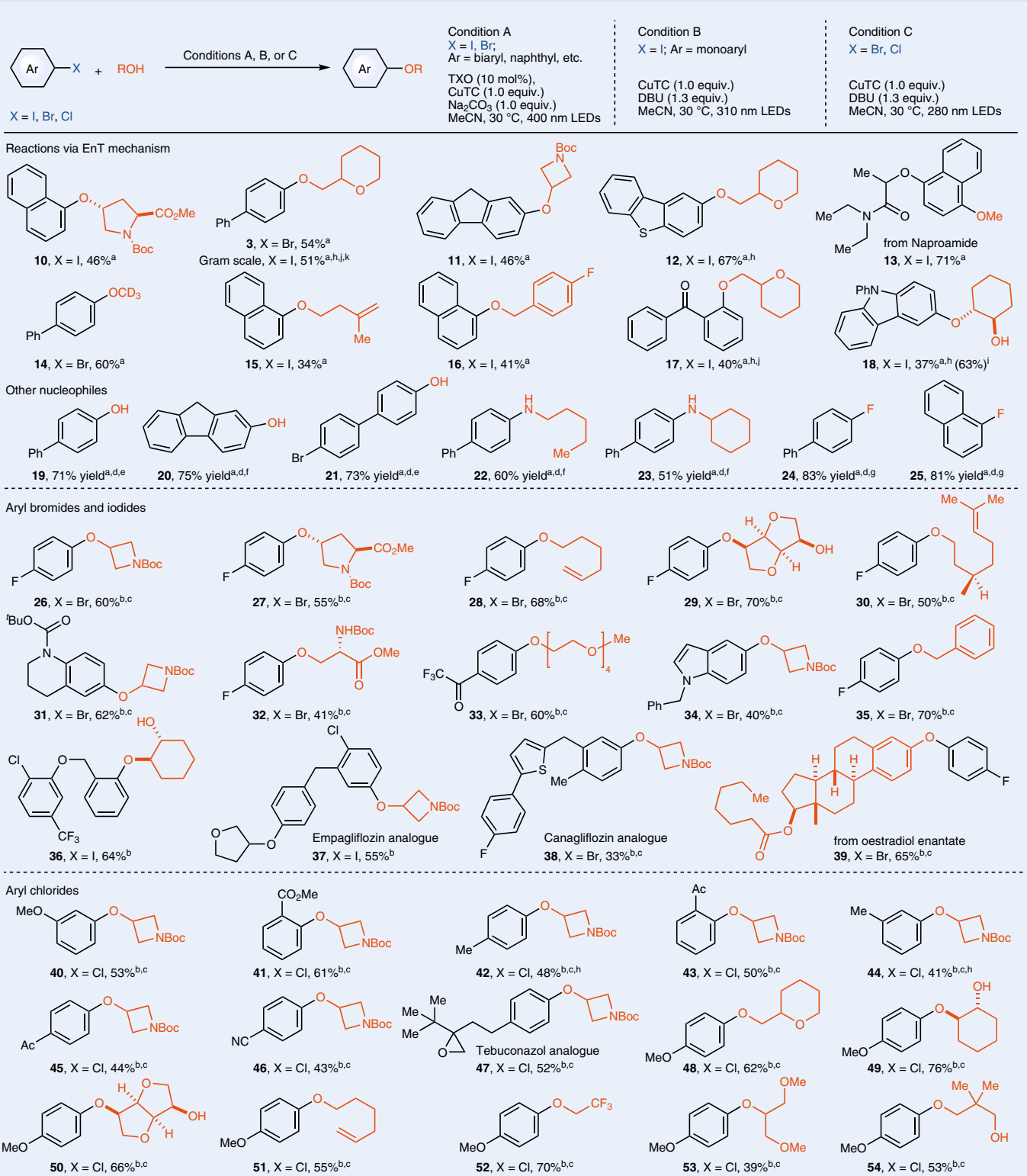
radicals during the cross-coupling reaction. Upon addition of styrene to the otherwise unchanged reaction set-up, the radical adduct 4-styryl-1,1′-biphenyl (**6**, Fig. 3a) could be isolated. Additionally, upon addition of different amounts of THF to the etherification reaction, the product distribution changed linearly with THF concentration towards arene (Ar–H), consistent with hydrogen atom transfer from the typical hydrogen atom donor THF to the in situ formed aryl radical (Fig. 3b). By employing THF-d_8, we determined a primary kinetic isotope effect of 2.2, also consistent with the involvement of the aryl radical intermediates. Furthermore, when prenyl ether **7** was subjected to the standard conditions, cyclization products **8a** and **8b** were observed in a 40% combined yield (Fig. 3c). To probe the hypothesis of an operating energy transfer mechanism, we irradiated the reaction mixture of 1-iodonaphthalene (**9**) in the absence of copper sources and nucleophile to a conversion of 50% and observed the formation of 40% naphthalene and 38% molecular iodine (yield based on the mass of iodine), which would not be expected for an SET mechanism (Fig. 3d); in the presence of stoichiometric CuTC, formation of iodine was not observed, consistent with oxidation to Cu(II) by the halogen radical. Reactions with excess halogen scavenger 2-methyl-2-butene and an oxidant did not work (Supplementary Table 2), possibly because halogen radical reacts with CuTC more efficiently than alkenes[37]. The etherification reaction efficiency correlates with the triplet state energy of the photosensitizer but not with its reduction potential, which is in agreement with an energy transfer mechanism and would be unusual for an SET mechanism (Fig. 3e). Additionally, a Stern–Volmer analysis revealed an effective quenching of the photoexcited sensitizer's luminance by 1-iodonaphthalene (**9**) but not by CuTC or CuTC in the presence of alcohol, also consistent with energy transfer to substrate (Fig. 3f and Supplementary Fig. 12).

The merger of triplet-state aryl halides and copper redox chemistry is successful in engaging a variety of challenging nucleophiles for copper-mediated cross-coupling reactions (Table 1). Primary alcohols, including methanol-d_4 (**14**), 4-fluorobenzyl alcohol (**16**) and alcohols of higher complexity (**3**, **15**, **28**, **30**, **32**, **33**, **52**, **54**), can undergo coupling reactions with aryl halides in 34–71% yield. Due to synthetic practicality and its low cost, we employed 1 equiv. of CuTC for these examples but also demonstrate a small-scale experiment to synthesize **17** and a scale-up experiment to produce 1.37 g of **3** with 5 mol% CuTC as catalyst. Secondary alcohols including *N*-Boc protected 3-hydroxyazetidine, 1,2-cyclohexanediol (**18**) and 1,3-dimethoxy-2-propanol (**53**), and carbohydrates (**29**) or amino acid derivatives were also found to be effective coupling partners for the etherification reactions. Tertiary alcohols did not participate in the reaction, but a complex phenol (**39**) was an effective coupling partner. The basic reaction conditions and high reaction temperatures commonly used for other transition-metal-catalysed etherification reactions usually lead to side reactions such as transesterification[19], epimerization[15] or β-hydride elimination[17]. The comparatively mild conditions of our reaction protocol therefore enable conversion of substrates that are not tolerated by conventional methods[15]. For example, alcohols with base-sensitive esters are tolerated (**10**, **27**, **32**) and no epimerization or racemization was observed. Additionally, an alcohol bearing a terminal olefin (**28**), which is challenging in, for example, palladium-catalysed C–O cross-coupling, could be arylated under our reaction conditions.

The generality of our approach goes beyond etherification; activation by energy transfer is also suitable for the construction of other carbon–heteroatom bonds (**19**–**25**). Water, amines and especially fluoride are challenging coupling partners for cross-coupling reactions but can participate smoothly via energy transfer in hydroxylation (**19**–**21**), amination (**22**, **23**) and fluorination (**24**, **25**) reactions with virtually identical reaction conditions. Aryl halides without additional conjugated π systems can also be aminated or fluorinated under direct excitation conditions (Supplementary Table 4), the ability to couple various challenging nucleophiles in synthetically useful yields via energy transfer is a consequence of the design and distinguishes our protocol from other contributions in this field.

We subsequently evaluated the generality with respect to the aryl halide coupling partner through either energy transfer or direct excitation (Table 1), applying one of a selection of three different reaction conditions, namely, 400 nm, 310 nm or 280 nm light irradiation, respectively. The appropriate condition can be deduced from

Table 1 | Dehalogenative functionalization



[a]Condition A: aryl halide, ROH, CuTC (1 equiv.), Na_2CO_3 (1 equiv.), TXO (10 mol%), MeCN (0.2 M), 400 nm LED (10 W), borosilicate glass reaction vessel, 30 °C, 20 h. [b]Condition B: aryl halide, ROH, CuTC (1 equiv.), DBU (1.3 equiv.), MeCN (0.2 M), 310 nm LED (3 W), quartz reaction vessel, 30 °C, 20 h. [c]Condition C: change light source to 280 nm LED (10 W). [d]Change CuTC to $Cu(MeCN)_4BF_4$. [e]Change ROH and Na_2CO_3 to water. [f]Change ROH to amine. [g]Change ROH and Na_2CO_3 to KF. [h]Reaction time: 40 h. [i]Yield based on recovered starting material. [j]Change Na_2CO_3 to Ag_2O (0.5 equiv.), with CuTC (5 mol%), TXO (1 mol%). [k]Gram-scale (10 mmol) synthesis of **3**: 1.37 g.

the triplet energy but also intuitively selected based on the simple selection criteria provided in Table 1. Aryl chlorides are challenging substrates for copper-mediated cross-coupling reactions because oxidative addition of Cu(I) into aryl chloride is slow and cannot be achieved by copper-mediated cross-coupling under mild conditions. Our reaction, however, can activate aryl chlorides smoothly

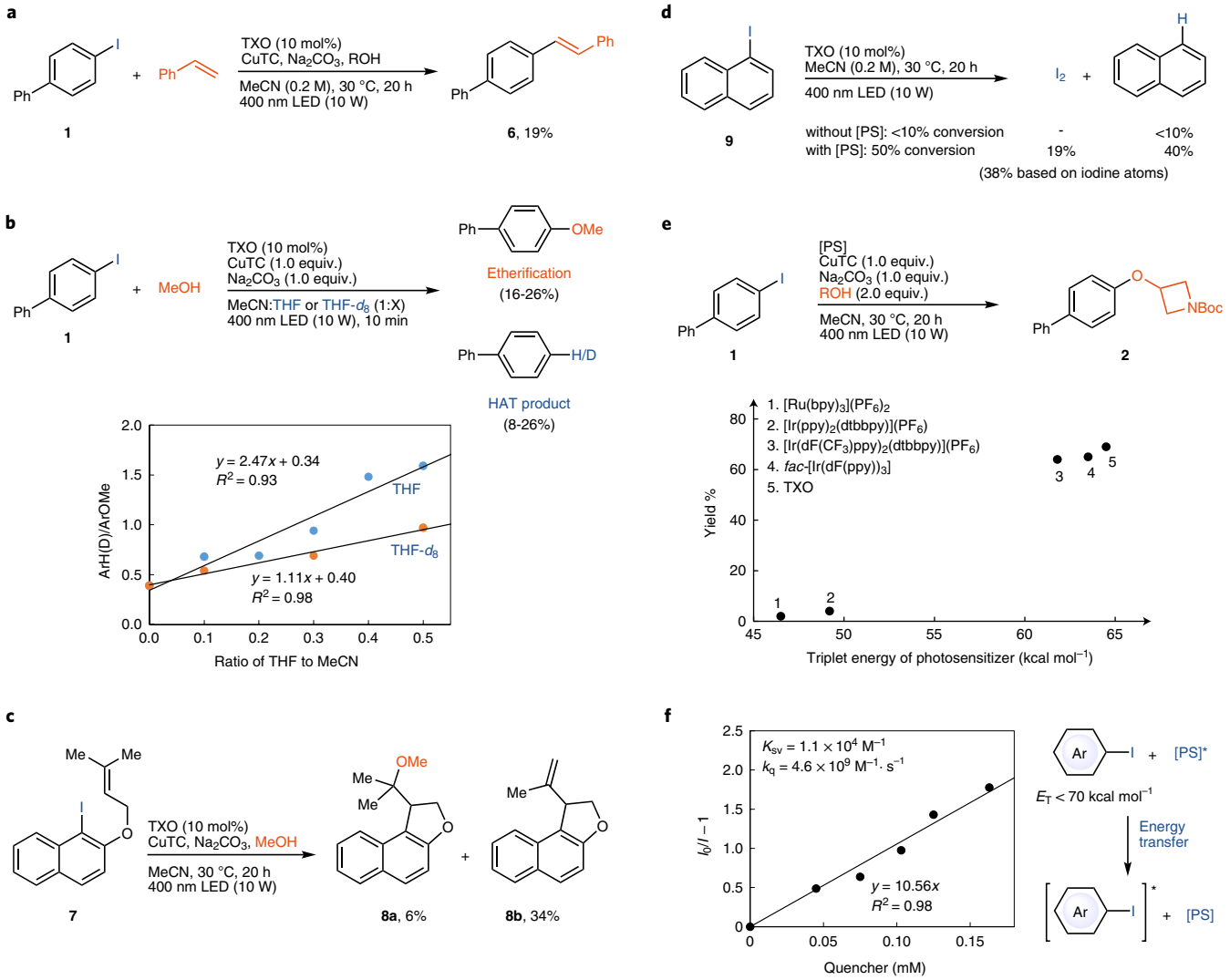


Fig. 3 | Mechanistic investigation. a, Intermolecular radical-trapping experiment. **b**, Competition kinetics between etherification and hydrogen atom transfer reaction. **c**, Intramolecular radical-trapping experiment. **d**, C–I bond homolytic cleavage via energy transfer. **e**, Relationship between triplet energy of photosensitizer and yield. **f**, Stern–Volmer analysis between excited state photosensitizer and 1-iodonaphthalene. I_0, luminescence intensity without quencher; I, luminescence intensity with quencher; K_{SV}, Stern–Volmer constant; k_q, quenching rate constant.

under ultraviolet light irradiation, without deleterious effect on the substrate scope of the alcohol coupling partner (**40**–**54**). A range of functional groups, including esters (**41**), nitriles (**46**), ketones (**43**, **45**), carbamates (**31**), amides (**13**), trifluoromethyl (**36**), and heterocycles (**12**, **18**, **34**, **38**), are all tolerated in the etherification reactions. Ambient reaction temperature and high functional group tolerance render the method useful for late-stage functionalization, as demonstrated for the drug-like molecules **13**, **36**–**39** and **47**. Other chromophores, such as functionalized aryl (**36**, **37**), biaryl (**38**), benzyl (**34**, **35**) and phenol (**39**) groups, are tolerated and the reaction is chemoselective for the aryl halide in such cases.

Conclusions

Generation of aryl radicals from triplet-state aryl halides provides a solution to tackle the energetically challenging oxidative addition problem of copper. The value of our contribution is also to provide a conceptually different strategy to activate aryl halides that is compatible with high-valent copper intermediates. The approach substantially expands the accessible universe of reactivity to aryl halides and a variety of nucleophiles that have been out of reach for modern cross-coupling and metallaphotoredox approaches with copper.

Methods

General procedure for the etherification reaction under visible light. In an anhydrous-nitrogen-filled glovebox, a 4 ml borosilicate vial equipped with a magnetic stir bar was charged with copper(I) thiophene-2-carboxylate (38.1 mg, 0.200 mmol, 1.00 equiv.), alcohol (0.400 mmol, 2.00 equiv.), Na_2CO_3 (21.2 mg, 0.200 mmol, 1.00 equiv.), aryl halide (0.200 mmol, 1.00 equiv.) and TXO (4.2 mg, 20 μmol, 10 mol%). Dry MeCN (1 ml, 0.2 M) was then added into the vial. The vial was sealed with a Teflon cap, and then transferred out of the glovebox. The reaction mixture was stirred at 23 °C for 2 h, then the vial was placed onto an aluminium plate fitted with a 10 W high-power single LED plate (Zerodis LED chip; size, 10 × 10 mm, λ_{max} = 400 nm) which is driven by a constant current power supply (9–12 V, 900 mA). An aluminium block was used to hold the vial. The temperature was kept at approximately 30 °C through the use of a cooling fan. The reaction mixture was stirred for 20 h with 400 nm LED irradiation, and then diluted with CH_2Cl_2 (2 ml). The reaction mixture was filtered through a short pad of silica using CH_2Cl_2 (25 ml) as eluent. The filtrate was collected and concentrated in vacuo, and the residue was then purified by flash column chromatography on silica gel to afford the ether.

Note: The reaction is moisture sensitive and therefore the use of anhydrous MeCN, Na_2CO_3 and CuTC is important for the reaction. When wet MeCN was used, or Na_2CO_3 and CuTC were weighed without further drying under ambient atmosphere, the yield of the etherification product was lower and hydroxylation product could be observed. For simplicity, all reaction components were stored and weighed in a nitrogen-filled glovebox, although the reactions can be performed outside of a glovebox by using Schlenk techniques to avoid moisture.

Data availability

The data reported in this paper are available in the main text or the Supplementary Information.

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Author contributions

L.Z. conceived the project and developed the etherification reactions. L.Z. and E.I. conducted the mechanistic studies. L.Z., E.I. and J.Y. explored the substrate scope. L.Z. and T.R. wrote the manuscript with input from all authors. T.R. directed the project.

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