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Aminoalkyl radicals as halogen-atom transfer agents for activation of alkyl and aryl halides

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Abstract: Organic halides are important building blocks in synthesis but their use in (photo)redox chemistry is limited by their low reduction potentials. Halogen-atom transfer still remains the most reliable approach to exploit these substrates in radical processes despite its requirement for hazardous reagents and initiators such as tributyltin hydride. Herein, we demonstrate that α -aminoalkyl radicals, easily accessible from simple amines, promote the homolytic activation of carbon–halogen bonds with a reactivity profile mirroring that of classical tin radicals. This strategy conveniently engages alkyl and aryl halides in a wide range of redox transformations to construct sp^3 – sp^3 , sp^3 – sp^2 and sp^2 – sp^2 carbon–carbon bonds under mild conditions with high chemoselectivity.

One Sentence Summary: α -Aminoalkyl radicals enable halogen-atom abstraction from unactivated alkyl and aryl halides with a reactivity profile analogous to the one of tin radicals.

Main Text: Carbon radicals are versatile synthetic intermediates central to the preparation of high-value compounds (1, 2). The advent of visible-light photoredox catalysis (3) has offered a broadly applicable radical generation protocol, transforming a variety of redox-active precursors into open-shell intermediates by single-electron transfer (SET) and fragmentation (4-6). However, photoredox activation has thus far rarely extended to organic halides, one of the largest class of building blocks available to organic chemists. The current synthetic gap is especially evident in the case of unactivated alkyl halides, where only dehalogenation and intramolecular cyclization of iodides have been reported (7-10). The difficulties in engaging these feedstocks in redox chemistry arise from their highly negative reduction potentials ($E_{red} < -2$ V vs SCE for unactivated alkyl and aryl iodides), which in turn necessitate the use of strongly reducing systems (11, 12) (Fig. 1A). Furthermore, the mechanisms involved in photoredox reactions are often uncertain (9), displaying large redox mismatches (> 1 V) for SET activation, which has in turn thwarted the exploitation of the carbon radicals accessed in this manner.

This lack of synthetic applicability stands in stark contrast to the fundamental role alkyl and aryl halides have played in the development of radical chemistry. Methods based on tin/silicon reagents and trialkylboranes– O_2 have proven to be highly reliable in accessing carbon radicals from organic halides, generating the open-shell intermediate by homolytic carbon–halogen bond cleavage via

halogen-atom transfer (XAT) (13-15). However, the toxic, hazardous nature of these reagents and initiators is problematic and has been one of the main drives towards the identification of alternative precursors and chemical strategies for carbon radical generation. Nevertheless, silicon radicals has been recently used in metallaphotoredox catalysis to overcome sluggish carbon-halogen oxidative additions with transition metals (16, 17).

We questioned whether α -aminoalkyl radicals could serve as a distinct class of halogen-abstracting reagents (Fig. 1B). Our idea for this reactivity stemmed from the fact that although classical XAT processes benefit from the formation of strong halogen-tin/silicon bonds, it is the high degree of charge-transfer in the transition state that facilitates halogen-atom abstraction by these nucleophilic radicals (18). We therefore reasoned that strongly nucleophilic α -aminoalkyl radicals might benefit from related kinetic polar effects and manifest the same reactivity. Such radicals can be easily generated from simple amines, a class of abundant and inexpensive reagents that would offer ample opportunity for fine steric and electronic tuning.

Here, we report the successful realization of this concept and its implementation as part of a mild and general strategy for the engagement of unactivated alkyl and aryl halides in redox chemistry (Fig. 1C). As α -aminoalkyl radicals display a reactivity profile similar to that of tin radicals, their capacity to abstract iodine and bromine atoms has enabled the development of deuteration, cross-electrophile coupling, Heck-type olefination and aromatic C-H alkylation protocols.

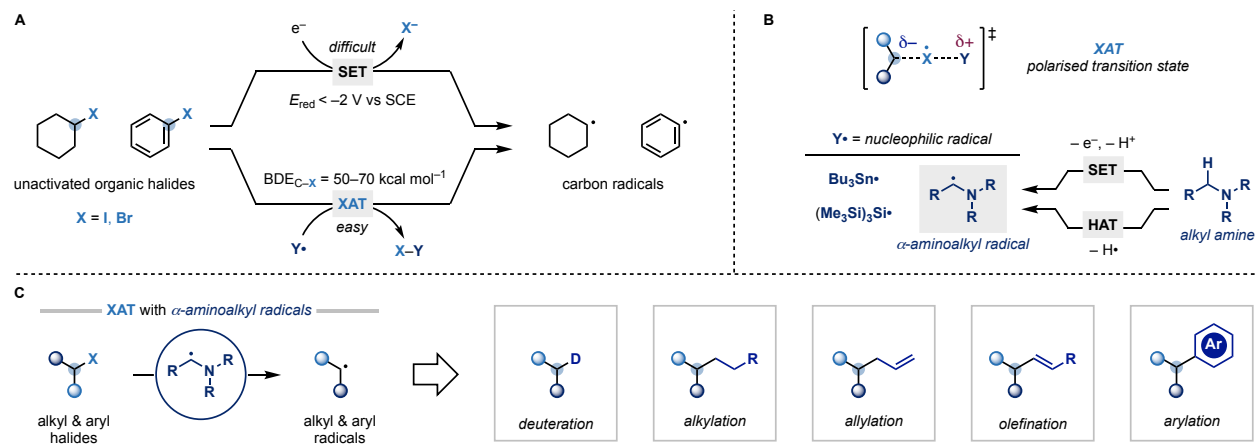


Figure 1. Homolysis of carbon-halogen bonds by α -aminoalkyl radicals. (A) Activation modes for the generation of carbon radicals from alkyl and aryl halides. (B) Nucleophilic α -aminoalkyl radical abstracts halogen atoms (X) through polarized transition states in analogy to tin and silicon radicals. (C) Outline of the transformations possible using alkyl and aryl halides activated via α -aminoalkyl radical-mediated XAT.

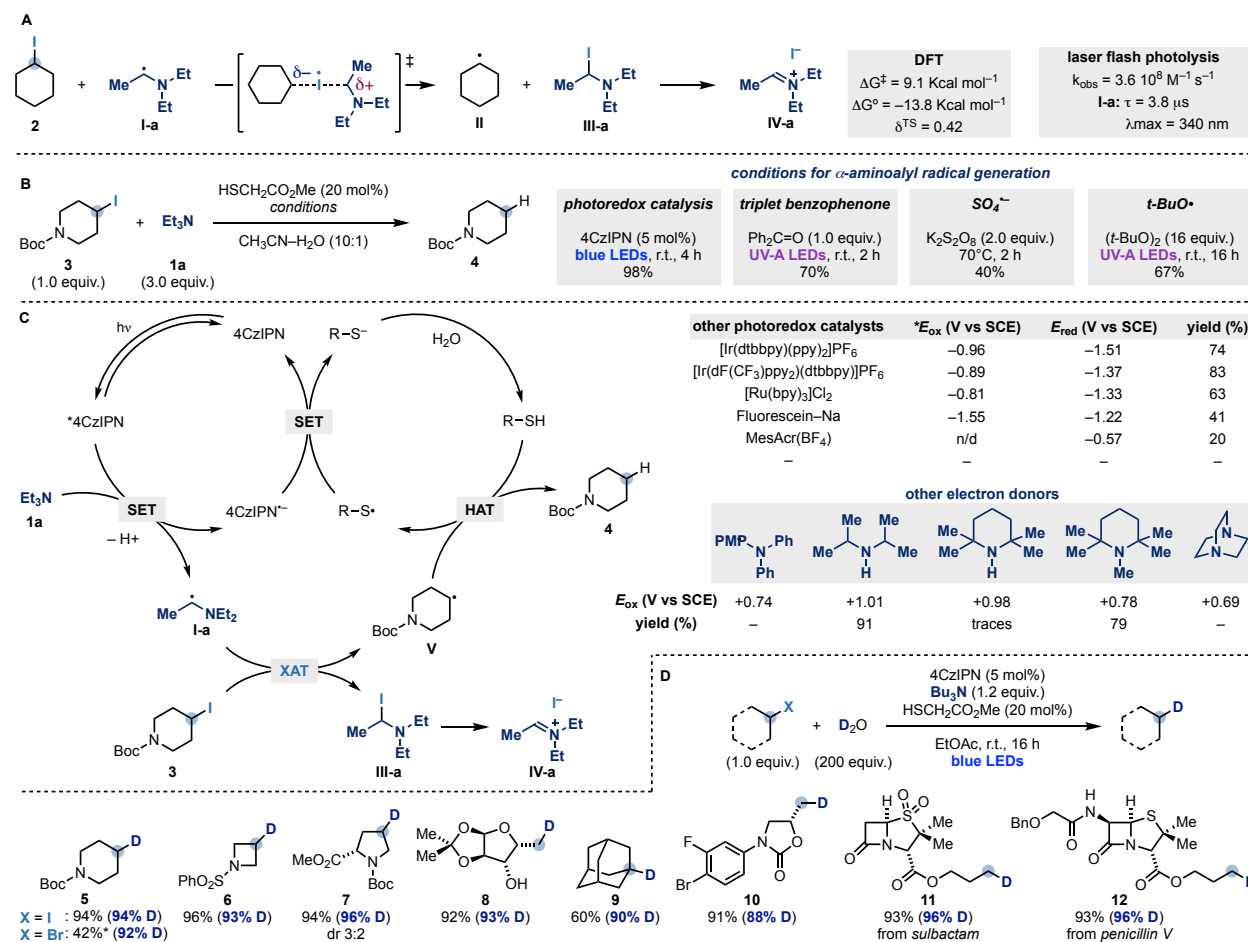
We initiated our study by evaluating the iodine-atom transfer reaction from cyclohexyl iodide **2** to the α -aminoalkyl radical **I-a**, derived from triethylamine (Et_3N , **1a**) (Fig. 2A). Density functional theory (DFT) calculations predicted this XAT to be kinetically feasible, involving a polarized transition state with a notable charge-transfer character ($\delta^{TS} = 0.42$), which supports the anticipated

interplay of polar effects. Although the XAT is only slightly exothermic,⁽¹⁹⁾ it is the fast and irreversible dissociation of the resulting α -iodo-amine **III-a** into the iminium iodide **IV-a** that provides the thermodynamic driving force to the process. To gather direct experimental evidence, we generated and monitored **I-a** using laser flash photolysis (20, 21) and observed a noticeable reactivity towards **2**. Data analysis provided a fast rate constant ($k_{\text{XAT}} = 3.6 \cdot 10^8 \text{ M}^{-1} \text{ s}^{-1}$) that is just one order of magnitude slower than reported rates for I-abstraction by $\text{Bu}_3\text{Sn}\cdot$ and $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ ($\sim 10^9 \text{ M}^{-1} \text{ s}^{-1}$) (22), showing promising potential for implementation in synthetic radical chemistry. To explore the applicability of this strategy in radical reactions, we chose the dehalogenation of 4-iodo-*N*-Boc-piperidine **3** using Et_3N as XAT-agent precursor and methyl thioglycolate– H_2O as the H-atom donor (Fig. 2B). At the outset, we were particularly interested to evaluate if the various modes for α -amino-radical generation, photochemical or thermal, could be recruited for XAT reactivity. We therefore started by testing four known systems based on amine SET oxidation (Et_3N : $E_{\text{ox}} = +0.77 \text{ V}$ vs SCE) followed by deprotonation (i.e. photoredox catalysis (23), triplet benzophenone (24) and $\text{SO}_4^{\cdot-}$ (25)) or direct H-atom transfer (HAT) (Et_3N : α -*N*-C–H BDE = 91 kcal mol⁻¹) using *t*-BuO \cdot (26). The desired product **4** was obtained in all cases in excellent to good yields, exemplifying the ample variety of conditions for α -amino-radical generation and ensuing XAT.

The proposed mechanism under photoredox conditions is depicted in Fig. 2C. Upon blue light irradiation, the excited organic photocatalyst 4CzIPN ($*E_{\text{red}} = +1.35 \text{ V}$ vs SCE) oxidizes **1a** which, after subsequent deprotonation, furnishes the key α -aminoalkyl radical **I-a**. This species undergoes XAT with **3** and the resulting alkyl radical **V** provides the product **4** by a favorable HAT from methyl thioglycolate (S–H BDE = 87 kcal mol⁻¹). Lastly, SET between the thiyl radical and 4CzIPN $^{\cdot-}$, followed by protonation with H_2O , regenerate the thiol along with the ground-state photocatalyst. The choice of 4CzIPN and Et_3N is relevant to our mechanistic hypothesis because neither the excited nor the reduced state of the photocatalyst ($*E_{\text{ox}} = -1.04 \text{ V}$; $E_{\text{red}} = -1.21 \text{ V}$ vs SCE (27)) nor **I-a** ($E_{\text{ox}} = -1.12 \text{ V}$ vs SCE (26)) are strong enough to promote direct SET reduction of **3** ($E_{\text{red}} = -2.35 \text{ V}$ vs SCE). This means that the carbon-radical generation is now dissected by the redox requirements of the system and therefore the reductive ability of the photocatalyst is not crucial to the outcome of the reaction. Indeed, this process can be achieved with a diverse range of photocatalysts including those of limited reductive power (e.g. Fukuzumi's acridinium; $*E_{\text{ox}} = -0.57 \text{ V}$ vs SCE). The replacement of Et_3N with other common electron donors (e.g. $\text{Ph}_2\text{N}(\text{PMP})$, sodium ascorbate or Hantzsch ester) suppressed the reactivity, despite all effectively quenching the excited photocatalyst.⁽¹⁹⁾ Moreover, other alkyl amines were tested but crucially only those able to generate an α -aminoalkyl radical promoted the desired reactivity.⁽¹⁹⁾ These results suggest alkyl iodide activation via a reductive-quenching photoredox cycle is not operative and that the amine plays a fundamental role in the C–I bond cleavage that goes beyond its capacity to act as an electron donor.

The high yields obtained with the photoredox system along with the use of H_2O as stoichiometric H-atom source prompted exploration of dehalogenation-deuteration reactions using D_2O (Fig. 2D). After optimization, we achieved efficient deuteration of primary, secondary and tertiary alkyl

iodides in nearly quantitatively yields (**5–12**). The mild reaction conditions tolerated multiple functional groups showcasing the strong chemoselectivity of this XAT approach. Activation of alkyl bromides is still a challenging task in radical chemistry and, for example, it is considered unfeasible using trialkyl borane–O₂ systems (28). We were pleased to see that our α-aminoalkyl radical-based XAT strategy was applicable to bromides albeit in lower conversion compared to the iodides.



The XAT strategy generates carbon radicals from organic halides oxidatively, which represents an umpolung approach relative to the natural redox requirement for SET activation of these building blocks. We posited that the generated radicals could therefore be used in similar mechanistic scenarios to carboxylic acids or potassium trifluoroborates, allowing their modular application in net reductive processes, such as cross-electrophile couplings (29, 30).

We explored this premise by developing Giese-type hydroalkylation of electron-poor olefins. Although these transformations have been performed with the aid of nickel catalysis, they typically require the use of stoichiometric metal reductants (e.g. Mn^0 , Zn^0) or silane H-donors (31, 32). In our case, as α -aminoalkyl radicals have been used as substrates in Giese additions (33), the success of this strategy hinged on their capacity to undergo preferential XAT over their known reaction with the olefin. Exploration began with 3-iodo-*N*-Boc-azetidine in the presence of Et_3N and 4CzIPN under blue light irradiation (Fig. 3A see Fig. S10 for a proposed mechanism). A diverse range of electron poor olefins were efficiently converted into the corresponding products in high to excellent yields (13–23). A variety of functionalities were readily accommodated including polar groups such as free carboxylic acid, primary amide, pyridine and boronic ester. When the same reactions were attempted using 3-bromo-*N*-Boc-azetidine, no desired product was obtained and a significant amount of the adduct arising from the direct addition of **I-a** to the olefin acceptor was identified (Fig. 3B). In this case, owing to the stronger nature of the C–Br bond, XAT is slower thus rendering the direct Giese reaction of **I-a** with the acceptor competitive ($k_{\text{obs}} \sim 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (21)). We therefore reasoned that the modulation of the electronic and steric properties of the α -aminoalkyl radical could be used to tune its reactivity. Indeed, by using tribenzylamine (**1b**) we restored XAT as the favored pathway for reactions of unactivated alkyl bromides in these hydroalkylations. As the stabilized α -aminoalkyl radical **I-b** was essentially unreactive towards electron poor olefins ($k_{\text{calc}} \sim 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ (21)), bromine abstraction was now possible providing the desired products in good yields.

We next explored the alkyl iodide scope using Boc-protected dehydroalanine as olefin acceptor, providing convenient access to unnatural amino acids (24–35). Also in this case, a wide variety of organyl groups bearing common functionalities such as free alcohol, alkyl chloride, silane and terminal alkyne were compatible, reflecting the mildness of the reaction conditions. Furthermore, this protocol has also been carried out at gram-scale without erosion in yield. The ability to generate primary alkyl radicals complements approaches using oxalates and trifluoroborates which are known to suffer from sluggish fragmentations (34, 35). When alkyl halides activated towards $\text{S}_{\text{N}}2$ attack by Et_3N were employed (e.g. **29** and **32**), not surprisingly the desired products were obtained in low yields. This hurdle was addressed by adjusting the steric properties of the XAT-reagent: using the bulkier amine 1,2,2,6,6-pentamethylpiperidine (**1c**), efficient couplings were achieved. We have also been able to extend this methodology to unactivated aryl iodides using the more hindered but less stabilized α -aminoalkyl radical derived from triisobutylamine (**1d**). These conditions enabled direct access to aryl radicals by sp^2 C–I bond cleavage and were applied to the one-pot transformation of tosylated serine into phenylalanine derivatives (36–39). Overall, these results illustrate how the large structural diversity of available tertiary amines facilitates the

rational tailoring of the α -aminoalkyl radical reactivity to address different challenges in carbon–halogen bond activation.

The XAT strategy for cross-electrophile coupling is not restricted to electron poor olefins. We also achieved efficient allylation of alkyl/aryl halides using simple allyl chlorides and other pseudohalides (**40–50**) (Fig. 3C, see Fig. S12 for a proposed mechanism). This approach bypasses the conventional conversion of one of the two coupling partners into a Grignard/organozinc reagent (**36**) and therefore tolerates functionalities, such as free alcohol and ketone, that are often troublesome with organometallics.

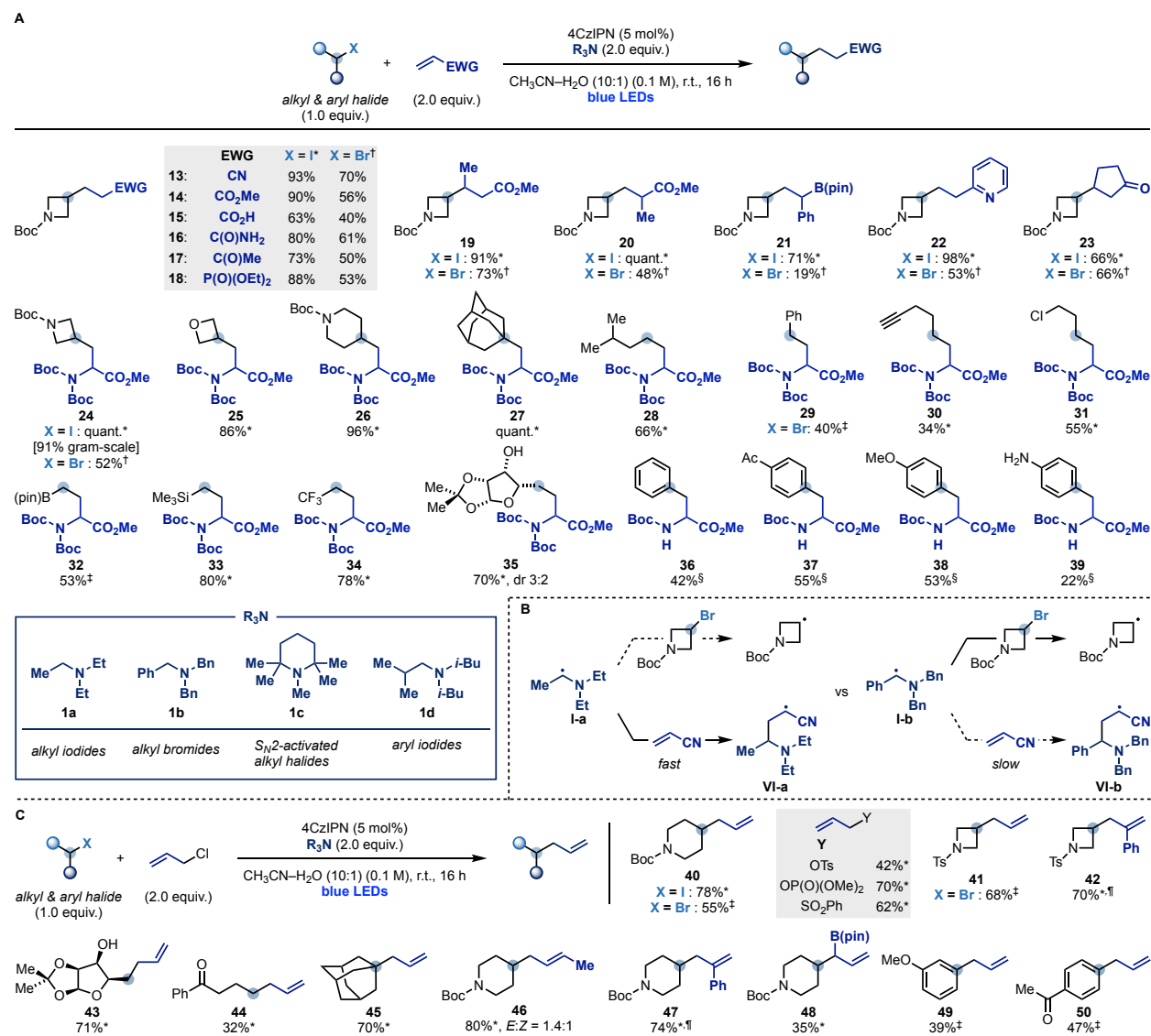


Figure 3. Application to hydroalkylation and allylation. (A) Scope for the alkylation of alkyl iodides, alkyl bromides and aryl iodides. (B) Tailoring XAT reactivity by modifying the α -aminoalkyl radical structure. (C) Scope for the allylation of alkyl iodides, alkyl bromides and aryl iodides. All yields are isolated. * **1a** was used as the amine. [†] **1b** was used as the amine. [‡] **1c** was used as the amine. [§] **1d** was used as the amine. [¶] The corresponding allyl sulfone was used.

To further demonstrate the versatility of this activation mode, we sought to adapt it to target the use of alkyl halides in Heck-type olefinations, a long-standing challenge in conventional palladium catalysis due to undesired β -hydride-elimination (37-39). Specifically, we questioned whether, after addition of alkyl radicals to suitable olefins (VII), a cobaloxime co-catalyst might trigger a dehydrogenation reaction (40), thus leading to sp^3 - sp^2 C-C bond formation (via VIII) without the need for precious metals (see Fig. S14 for a proposed mechanism). As shown in Fig. 4A, we found this dual XAT-[Co] protocol feasible thus allowing the direct olefination of primary, secondary and tertiary alkyl iodides and bromides exclusively as the *E*-isomers (51-74) (with the exception of 54 and 62). The broad functional group compatibility was demonstrated with the successful engagement of substrates containing phenol, aniline and benzoic acid moieties as well as aryl bromide, boronic acid and phosphine groups that could limit application under transition metal catalysis. The olefination was also very effective in intramolecular settings as showcased by the construction of tricyclic 75 in good yield. Couplings with aryl iodides were attempted but generally resulted in low yields.

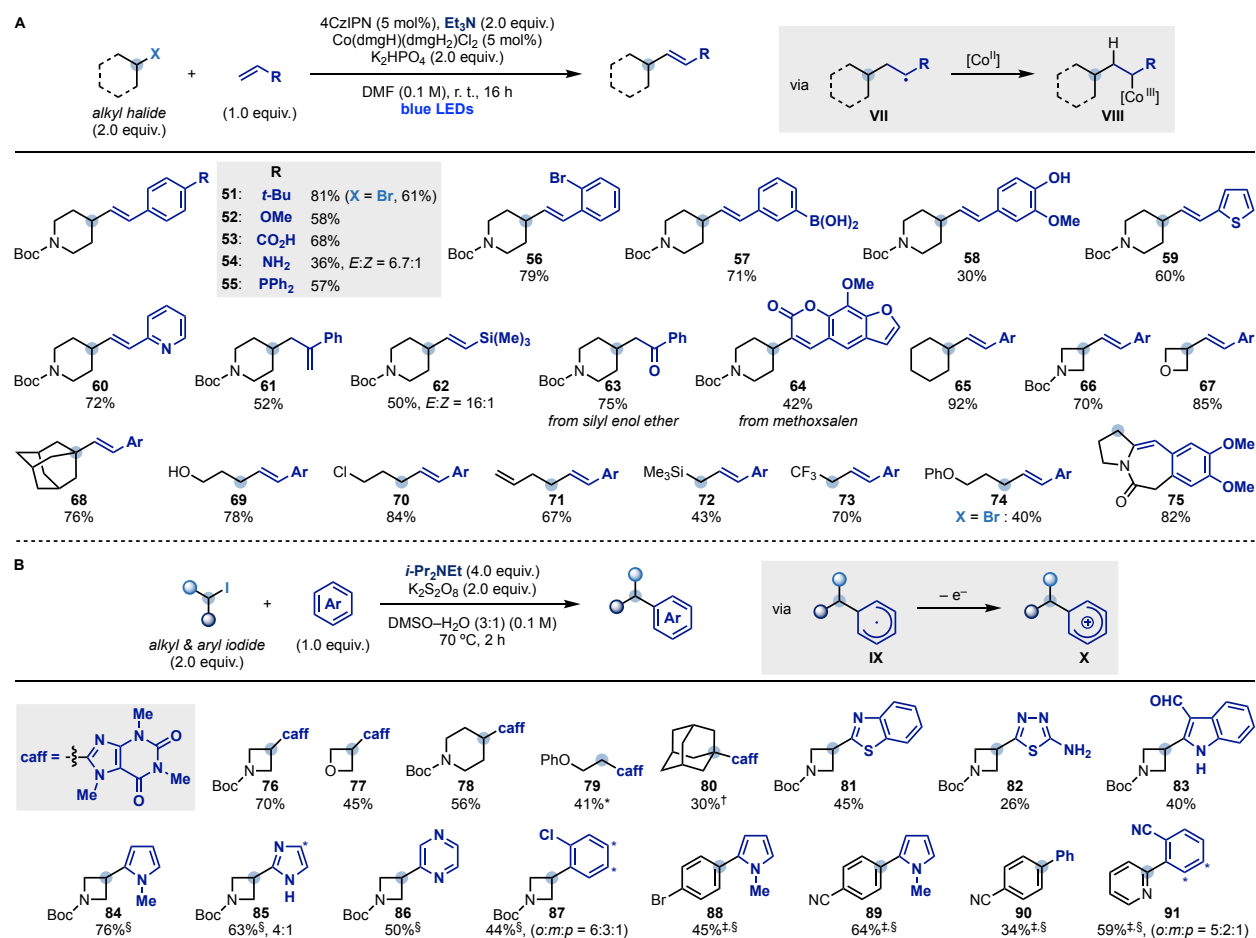


Figure 4. Application to olefinations and arylations. (A) Scope for olefination of alkyl iodides and alkyl bromides. (B) Scope for the C-H alkylation and arylation of aromatics. All yields are

isolated. * **1c** was used as the amine. † Me₃N was used as the amine. ‡ Bu₃N was used as the amine.
§ The reaction was run with 50 equiv. of the arene.

5 In a final effort to establish the generality of this XAT strategy, we turned our attention to the
direct aromatic C–H alkylation via radical intermediates (Fig. 4B, see Fig. S15 for a proposed
mechanism). Recently, the use of zinc-alkylsulfonates has provided a powerful and effective
10 solution to this synthetic challenge (41, 42). However, as these reagents are often prepared from
the corresponding halides, a methodology that directly used these building blocks would obviate
multistep synthesis of any reactive intermediate. In this case however, a photoredox system for α -
aminoalkyl radical generation is difficult to implement due to the mechanistic requirement of a
15 second oxidation after radical addition to the arene in order to allow re-aromatization (**IX**→**X**).
The broad set of reactivity modes for α -aminoalkyl radical generation enabled identification of
simple thermal, net oxidative conditions for the direct alkylation of caffeine with alkyl iodides
without the need for light or catalysts (76–80). This manifold for aromatic C–H alkylation was
20 compatible with the installation of primary, secondary and tertiary alkyl groups and could be
extended to other heteroarenes commonly found in bioactive molecules such indole and azoles as
well as benzenoids (43) (81–87). Furthermore, we demonstrated that aryl iodide activation and
subsequent sp²–sp² coupling (44) is also possible, as shown by the successful preparation of **88**–
25 **91**.

The results presented here demonstrate that alkyl and aryl halides can be converted into carbon-
radicals by halogen-atom transfer using α -aminoalkyl radicals. We believe that the broad scope,
functional group tolerance and modularity of this approach for carbon–halogen bond activation
will be of great utility to chemists working in both academia and industry.

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designed the project and wrote the manuscript. T. C., M. Z., A. R. and F. J. performed all the
30 experiments. N. S. S. performed the computational studies. All the authors analyzed the results;
Competing interests: Authors declare no competing interests. **Data and materials availability:**
All data are available in the main text or the supplementary materials.

Supplementary Materials

Materials and Methods

Figures S1 to S24

Tables S1 to S16

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