



Letter

# Coupling Photocatalysis and Substitution Chemistry to Expand and Normalize Redox-Active Halides

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**ABSTRACT:** Photocatalysis can generate radicals in a controlled fashion and has become an important synthetic strategy. However, limitations due to the reducibility of alkyl halides prevent their broader implementation. Herein we explore the use of nucleophiles that can substitute the halide and serve as an electron capture motif that normalize the variable redox potentials across substrates. When used with photocatalysis, bench-stable, commercially available collidinium salts prove to be excellent radical precursors with a broad scope.



he use of visible light to drive reactions has the potential to be energy-efficient and green and can reveal new mechanistic possibilities that enable synthesis.<sup>1-4</sup> Often central to these methods is the controlled generation of radicals, which are the critical reactive intermediates  $5^{-13}$  whose formation is enabled and governed by absorption of a photon by the photocatalyst.<sup>14</sup> Some substrates that can be reductively activated by single electron transfer (SET) include aryl halides<sup>15</sup> and pseudohalides.<sup>16–20</sup> Reaction is possible because of the relatively low-lying unoccupied  $\pi^*$  orbitals of the aromatic system into which an electron is transferred. En route to radical formation, intramolecular ET to the C–X  $\sigma^*$  orbital takes place, allowing the critical mesolytic fragmentation that yields the halide ion and carbon-centered radical.<sup>21–23</sup> The rate of this intramolecular ET is dependent on a number of factors, including the energy of the  $\pi^*$  orbitals and the electronic overlap with the fragmenting groups.<sup>22,24–30</sup> Practically speaking, useful rates of radical anion fragmentation are observed for ipso-substituted halides and  $\alpha$ -halo species but decrease with greater structural separation, representing a real mechanistic limitation of the radical anion fragmentation mechanism. This sensitivity to structure is particularly revealing in the case of benzylic halides, in which the rate of fragmentation becomes highly dependent on the structure and functional groups attached to the aromatic component, resulting in significant variation in the reduction potential and the nature of the orbitals involved.<sup>26,27</sup> In general, the substantial variation in reduction potential of the substrates (Scheme 1d) prevents the development of broadly applicable methodology.

Recently, several diverse strategies have been explored to engage such aliphatic halides that would otherwise be hard to directly engage photocatalytically. Evolution of the photocatalyst structure aimed at pushing the reduction limits has been pursued by several groups<sup>31–34</sup> (Scheme 1a). Alternatively, Leonori recently proposed the use of  $\alpha$ -amino radicals to facilitate halogen transfer (Scheme 1b).<sup>35</sup> More relevant to this work, Melchiorre identified a clever system that capitalizes on the electrophilicity of alkyl halides to be displaced by a nucleophilic chromophore (Scheme 1c).<sup>36</sup> Upon displacement of the halide with a nucleophilic chromophore, the alkyl substrate becomes photoactive and upon absorption of a photon undergoes homolysis of the inherently weak C–S bond. One potential liability of this conceptually elegant approach is the inherent coupling of the nucleophilic and chromophoric capacities of the catalyst, which may limit both the scope of reactions and the range of mechanistically diverse reactions that would be possible if these two aspects of the catalysts operated independently.

Thus, we set out to develop a conceptually related idea  $(Scheme 1d)^{37-40}$  that capitalized on the electrophilicity of alkyl halides but decoupled the photon-absorbing aspects of the catalyst from its nucleophilic aspects. Our objective was to identify a nucleophile that upon addition to the alkyl halide would serve as the electron-capturing component where the halide failed and ultimately would level the substrate reduction potentials. Thus, we began our studies by exploring a Giese-type

Received: January 16, 2021 Published: February 26, 2021







reaction<sup>41-44</sup> using benzyl bromide-derived salts and conditions that have been used for reductive coupling in our lab<sup>45-48</sup> (Scheme 2). We found that quaternary ammonium, imidazolium, and phosphonium salts showed no reactivity under these conditions. The molecular orbitals obtained using semiempirical Hückel calculations demonstrate that the LUMO lies primarily on the fluorobenzene fragment rather than on the added nucleophilic component, which explains the lack of reactivity

#### Scheme 2. Search for Redox-Active Salts<sup>c</sup>



<sup>*a*</sup>The reaction went to completion within 8 h. <sup>*b*</sup>The reaction did not go to completion and reached 79% conversion after 72 h. <sup>*c*</sup>Conversion was determined by <sup>19</sup>F NMR spectroscopy.

(see the Supporting Information). In contrast, pyridinium 1d, which displays LUMO density on the pyridinium motif, provided the product, albeit in low yield (12%).

Inspection of the corresponding reaction mixtures by GC-MS suggested that the formation of fluorobenzylated pyridine byproducts was a major contributor to the mass balance. Thus, we speculated that fluorobenzyl radical formed under reaction conditions and either attacked the pyridinium salt (1d) or the resulting pyridine in a Minisci-type reaction.<sup>49,50</sup> Indeed, when the 4-position was blocked (1e and 1f), we observed a slightly improved albeit still meager yield. 1g resulted in the formation of a colored electron donor-acceptor complex that was consumed but did not result in product formation. We next explored both collidinium (1h) and Katritzky<sup>51</sup> (1i) salts, whose susceptible positions were blocked. In both cases, the Minisci product could not be detected, and the yield nearly doubled. A direct comparison with the corresponding benzyl bromide revealed the enhanced reactivity of the pyridinium-derived salts, suggesting that electron capture could be enhanced by substitution.

Encouraged by the positive results of our initial exploration and those of Glorius,<sup>52–54</sup> Lautens,<sup>53</sup> and Aggarwal,<sup>55</sup> who used Katritzky salts in deaminative couplings of primary amines via photoredox catalysis, and related work<sup>56,57</sup> that provided strong precedent, we set out to optimize the reaction conditions (Table 1). While both the trimethyl- (**1h**) and triphenylpyridinium (**1i**)

#### Table 1. Optimization Table

F	$\begin{array}{c c} & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$	py)3 (0.25 CN (0.1 M EA (2 equ r, Blue LF	5 mol%) 1) iv) 2Ds F		→ CN ;a
entry	modification	time	conv%ª	3a%ª	3a/3a'+3a''
1	none	6 h	100%	23%	0.37
2	MeCN (0.05 M)	10 h	100%	38%	1.36
3	Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbbpy)PF <sub>6</sub>	46 h	50%	38%	3.5
4	[Ru(bpy) <sub>3</sub> ]PF <sub>6</sub>	44 h	1%	0%	0
5	Entry 3 (0.5 mol% photocatalyst)	48 h	70%	52%	5.2
6	Entry 3 (0.05 mol% photocatalyst)	48 h	85%	19%	0.3
7	Entry 3 MeCN (0.05 M)	72 h	39%	33%	5.2
8	Entry 3, NBu <sub>3</sub> instead of DIPEA	48 h	65%	34%	3.4
9	Entry 3, DIPEA 3 equiv	47 h	79%	66%	6.6
10	Entry 3, DIPEA 4 equiv	16 h	100%	77%	9.63
11	Entry 10, H <sub>2</sub> O 5 equiv	12 h	100%	85%	21.25
12	Entry 10, H <sub>2</sub> O 10 equiv	12 h	100%	88%	29.3
13	No amine, no photocatalyst, no light	24 h	0	0	0
	F	CI	N ÇN	CI	n çn çn



 $^a\mathrm{Conversions}$  and product ratios were determined by  $^{19}\mathrm{F}$  NMR spectroscopy.

salts resulted in higher yields compared with less substituted versions, a closer inspection of the <sup>19</sup>F NMR spectra of the reaction mixtures revealed that trimethylpyridinium **1h** produced far fewer side products (see the SI). Given this and the fact that triphenylpyridinium **1i** is derived from the corresponding expensive oxopyrylium salt (\$2376/mol) rather

than inexpensive collidine (\$29/mol), we elected to continue optimization using collidinium salt **1h**.

With reductive conditions, which included catalytic  $Ir(ppy)_{3}$ , DIPEA, and blue light, we observed complete conversion within 6 h, but the desired product was a minor product (23%) (Table 1, entry 1). While minor amounts of radical termination products were identified (3' and 3''), we were encouraged to see that the majority of the mass balance appeared to be derived from a benzyl radical that had formed the desired C-C bond and could, if nudged in the right mechanistic direction, lead to product. More specifically, it appeared that rather than terminating to give the desired product, it underwent one or two propagation steps to give products 3a' and 3a". Dilution of the reaction mixture (entry 2) helped somewhat, giving a correspondingly higher yield, but slowed the reaction. Together these experiments suggested that controlling the rate of termination would be vital to achieving product selectivity. We postulated that identification of the appropriate catalyst could facilitate reduction of the intermediate radical.58,59 Indeed, a photocatalyst screen (see the SI) showed that while the iridium catalyst  $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$  gave more sluggish conversion (entry 3), the critical ratio of desired to undesired products improved by an order of magnitude. Furthermore, increasing or decreasing the photocatalyst loading increased (entry 5) or decreased the product ratio (entry 6), respectively.

Changing the catalyst to Ru(bpy)<sub>3</sub> (Table 1, entry 4), which has a similar reduction potential  $(E_{1/2}(II/I) = -1.33 \text{ V vs SCE})$ gave very sluggish conversion and no detectable product formation, suggesting that the photocatalyst plays a nuanced role in the reaction. Attempts to use NBu<sub>3</sub> (entry 8) instead of DIPEA (entry 3) led to slightly faster conversion but gave substantial amounts of a compound derived from combination of the amine and nitrile.<sup>60,61</sup> Speculating that the off-cycle use of the amine retarded the reaction at higher conversions, we investigated the use of more amine (entry 3 vs entries 9 and 10). Indeed, moving from 2 to 4 equiv increased the conversion from 50% to 100% and decreased the reaction time from 46 to 16 h. Importantly, as the desired reaction was able to take place throughout the entirety of the reaction period, the product distribution shifted in favor of the desired product. With evidence suggesting the involvement of the photocatalyst in the termination step, we investigated the effect of water on the reaction (entries 11 and 12). Indeed, the inclusion of 10 equiv of H<sub>2</sub>O further enhanced the product distribution to 29.3:1 and accelerated the reaction (12 h), resulting in an 88% yield. Finally, individual control studies evidenced the critical aspect of each reaction component (entry 13).

Having identified the optimal conditions (Table 1, entry 12), we examined the scope of collidinium salts with acrylonitrile (Scheme 3). A broader range of collidinium salts was prepared (see the SI). The reaction worked well for benzylic collidinium salts with electron-withdrawing groups (3a, 3d, and 3f), electron-neutral groups (3b, 3c, and 3g), and electron-donating groups (3i and 3j), which would have been a challenging feat for the corresponding halides. This strategy could be extended to sterically demanding, ortho-flanked benzylic substrates (3e and 3k) by use of the 4-methylpyridine-derived salts. Apparently, the bulk of the benzyl component, which made nucleophilic substitution more challenging, also served to protect these salts from undergoing the Minisci-type benzylation that we had observed earlier with less sterically demanding benzylpyridinium salts. Furthermore, the 4-methylpyridinium salt of a

## Scheme 3. Scope Studies<sup>d</sup>



 $^a{\rm The}$  4-methylpyridinium salt was used.  $^b{\rm The}$  catalyst loading was 0.5 mol %.  $^{c19}{\rm F}$  NMR yield.  $^d{\rm Yields}$  are of isolated products, unless otherwise noted.

secondary benzylic substrate (31) also gave a good yield, highlighting the ability to rapidly and significantly modify the carbon framework of the substrate. The mild reaction conditions are compatible with a wide range of functional groups, such as nitrile (3f), ester (3d), ether (3j), and bromide (3b and 3c). Importantly, all of these substrates were engaged photocatalytically using the same conditions-a feat that would have been challenging using the corresponding halides. The collidinium salts offer protection to otherwise-sensitive heterocycles such as thiophene<sup>62</sup> (3m) and naphthalene<sup>63</sup> (3h), which might be expected to undergo radical addition. We expect the broad functional group tolerance to facilitate further synthetic elaboration. Other electron-deficient alkenes worked well in the reaction (3n-s), with the ester substituent of acrylates exhibiting minimal influence (3n and 3o) while methacrylate (3p) was slightly more prone to propagation. Similarly, cinnamate (3s) gave the product in modest yield. Cyclic enones proved to be competent (3q, and 3r), giving the fluorobenzylated products in good yields. Other alkenes also proved to be competent (see the SI). Interestingly, the use of  $\alpha$ -methylstyrene resulted in the formation of product (3t) and higher-order oligiomers. The scope suggests that different reaction mechanisms may be operative depending on the alkene. The use of the bench-stable crystalline collidinium salts also facilitates workup of the reaction. Simple extraction followed by acidic washes removes any excess DIPEA, collidine byproduct, and (if present) any unreacted collidinium salts. This is in stark contrast to the Katritzky salt, which produces triphenylpyridine, which must be removed chromatographically. Likewise, if the benzyl halide were used, any excess would also be expected to require removal from the organic extracts.

Our working mechanism of the reaction is shown in Scheme 4. The reaction begins with absorption of a blue photon to give

### Scheme 4. Working Mechanism<sup>a</sup>



<sup>*a*</sup>(A) Our current understanding of the mechanism. (B) Literature redox values of  $lr[dF(CF_3)ppy]_2(dtbbpy)pF_6$ . (C) Fluorescence quenching experiments on  $lr[dF(CF_3)ppy]_2(dtbbpy)PF_6$  (1.25  $\mu$ M) using collidinium salt ([**1h**] = 25 mM) and amine ([DIPEA] = 25 mM). All spectra were recorded in MeCN in a 1 cm path length quartz cuvette at 25 °C.

strongly oxidizing Ir(III)\* [Ir\*(III)/Ir(II) = 1.21 V vs SCE in CH<sub>3</sub>CN],<sup>64</sup> followed by reductive quenching by the amine<sup>65,66</sup> (NR<sub>3</sub>  $\approx$  0.50 V vs SCE).<sup>67,68</sup> This is supported by Stern–Volmer analysis (**5a**). Next, the reduced Ir(II) undergoes SET to collidinium salt **1h**<sup>69,70</sup> (Ir(II/III) = -1.37 V vs SCE;<sup>64</sup> estimated  $E_{1/2} = -1.27$  V vs SCE in DMF),<sup>71</sup> giving collidinium radical I and completing cycle A. Subsequently, I undergoes unimolecular fragmentation<sup>72</sup> to give collidine and benzylic radical II. Addition of II to acrylonitrile generates radical intermediate III. Hydrogen atom transfer (HAT) from the amine radical cation yields the product (path a).

However, several observations called this explanation into question, namely, the effect of the photocatalyst loading on the product distribution (Table 1, entries 1, 5 and 6) and the enhanced rate and selectivity upon addition of water (Table 1, entry 12). Indeed, we observed a solvent kinetic isotope effect of  $k_{\rm H}/k_{\rm D}$  = 2.0 when we used 10 equiv of D<sub>2</sub>O (Scheme 5).

#### Scheme 5. Isotope Experiments



Furthermore, the deuterium incorporation experiment (Scheme 5) revealed that the use of D<sub>2</sub>O resulted in only partial incorporation of the deuterium (30%) in the  $\alpha$ -position of the nitrile product. On the basis of the O–H bond strength of water (118.8 kcal/mol)<sup>73</sup> and the C $_{\alpha}$ -H bond strength of the product (89.0 kcal/mol),<sup>74</sup> HAT from water is improbable. However, protium incorporation (70%) in the presence of D<sub>2</sub>O suggests that HAT (path a) indeed occurs, with the likely donor being DIPEA radical cation.<sup>3,75</sup> The observed rate enhancement of the desired reaction upon inclusion of water may be due to proton-coupled electron transfer (PCET) (path B) that facilitates

reduction of the radical to carbanion **IV** (estimated reduction potential  $\approx -0.9$  to -1.1 V vs SCE).<sup>76,77</sup> The photocatalyst concentration is expected to influence the lifetime of **III**, which may also undergo oligimerization; therefore, it is expected to impact product distribution, which we observed.

Returning to our initial goal of dual catalysis, in a preliminary catalytic experiment with 2-(chloromethyl)-1,3,5-trimethylbenzene (Scheme 6), we observed that a 20 mol % loading of 4-

# Scheme 6. Preliminary Attempt to Achieve Catalytic Activation



<sup>a</sup>Assay yield determined by GC–MS. <sup>b</sup>Without 4-methylpyridine, the conversion was 38% after 26 h.

methylpyridine is capable of achieving catalytic turnover and significantly enhancing the rate of benzylation. While some background reaction was observed, it was substantially slower (38% vs 100% conversion; see the SI for more details). This result supports the validity of the underlying concept and provides an initial point for further investigation of nucleophiles that can strike the appropriate balance of nucleophilicity and reducibility to allow the catalytic transformation of non-redoxactive electrophiles.

In conclusion, we have demonstrated that the use of commercially available collidinium salts is a viable strategy that enables photoredox catalysis to mildly and efficiently engage previously sluggish and unreactive alkyl halides. While this study focused on the stoichiometric work, we have shown that dual catalysis is feasible and that further development is warranted. Pragmatically, collidinium salts are easy-to-make, easy-tohandle, photochemically stable, and bench-stable crystalline salts that are redox-active alternatives to halides. Furthermore, all of the reaction components are water-soluble, which facilitates product isolation and potentially allows their use in complex settings.

#### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00173.

FAIR data, including the primary NMR FID files, for compounds 1a, 1e-t, and 3a-t (ZIP)

Procedures, spectra, and additional experiments (PDF)

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#### Notes

The authors declare the following competing financial interest(s): The authors have licensed collidinium salt technology to Weaver Labs, LLC, of which J.D.W. has ownership.

#### ACKNOWLEDGMENTS

We thank the NSF (CHE-1453891).

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