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

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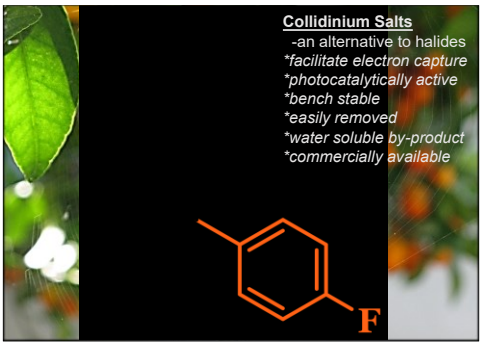
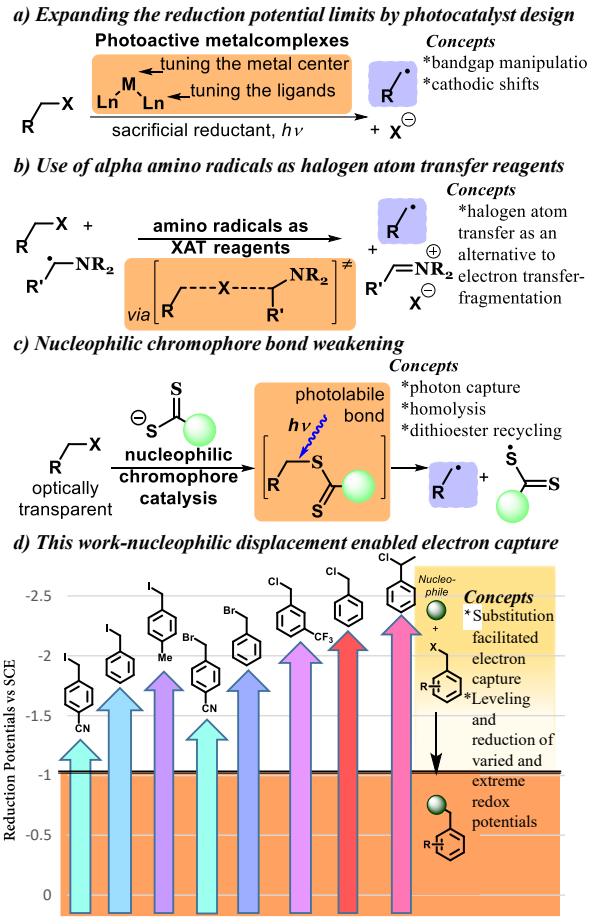


ABSTRACT: Photocatalysis can generate radicals in a controlled fashion and has become an important synthetic strategy. Limitations owing to the reducibility of alkyl halides, however, prevent their broader implementation. Herein, we explore the use of nucleophiles that can substitute the halide and serve 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.

The use of visible light to drive reactions has the potential to be energy efficient, green, and can reveal new mechanistic possibilities that enable synthesis.[1-4] 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.[14] Some substrates that can be reductively activated by SET include aryl halides[15] and pseudo-halides.[16-20] Reaction is possible due to the relatively low-lying unoccupied pi* orbitals of the aromatic system into which an electron is transferred. En route to radical formation, an intramolecular electron transfer (ET) to the C–X sigma* orbital takes place, allowing the critical mesolytic fragmentation which yields the halide ion and carbon centered radical.[21-23] The rate of this intramolecular ET is dependent on a number of factors, including the energy of the pi*-orbitals, and electronic overlap with the fragmenting groups, among other factors.[22,24-30] Practically speaking, useful rates of radical anion fragmentation are observed for ipso substituted halides, and alpha halo species, but drops with greater structural separation, and represents a real mechanistic limitation of 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 which result in significant variation in the reduction potential and the nature of the orbitals involved.[26,27] In general, the substantial variation in reduction potential (Scheme 1d) of the substrates 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[31-34] (Scheme 1a). Alternatively, Leonori has recently proposed the use of alpha amino radicals to facilitate halogen transfer (1b).[35] More relevant to this work, Melchiorre has identified a clever system that capitalizes on the electrophilicity of alkyl halides to be displaced by a nucleophilic chromophore (1c).[36] 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

Scheme 1. Emerging strategies for radical formation.

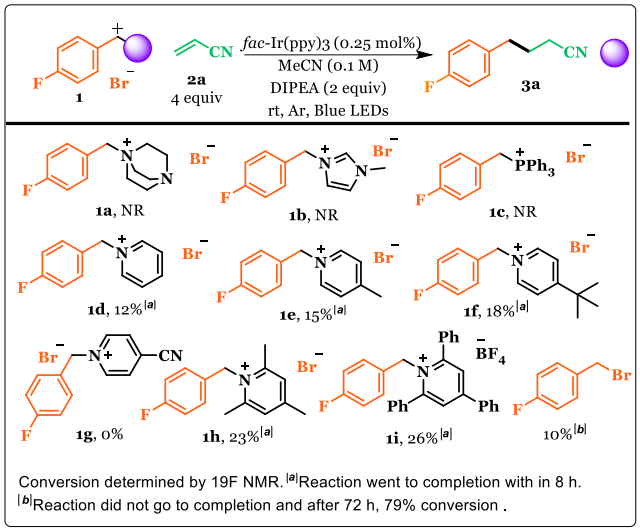


potential liability of this conceptually elegant approach is the inherent coupling of the nucleophilic and the chromophoric capacities of the catalyst, which may limit both the scope of reactions and the range of mechanistically diverse reactions that would be possible if these two aspects of the catalysts operated independently.

Thus, we set about to develop a conceptually related idea (1d) [37-40] that capitalized on the electrophilicity of alkyl halides but one that 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, level substrate reduction potentials. Thus, we began our studies by exploring a Giese type reaction[41-44] using benzyl bromide derived salts and conditions that have been used for reductive coupling in our lab.[45-48]

We found that quaternary ammonium, imidazolium, and phosphonium salts showed no reactivity under these conditions. Calculation of the molecular orbitals using semi-empirical Hückel calculations demonstrate that the LUMO orbital lies primarily on the fluorobenzene fragment rather than on the added nucleophilic component and explains a lack of reactivity (see SI). In contrast, pyridinium **1d**, which displays LUMO density on the pyridinium motif, provided the product, albeit in low yield (12%).

Scheme 2. Search for redox active salts.



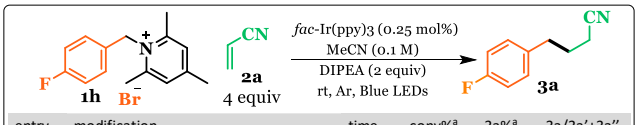
Inspection of the corresponding reaction mixtures by GCMS suggested the formation of fluorobenzylated pyridine byproducts were a major contributor to the mass balance. Thus, we speculated that fluorobenzyl radical was forming under reaction conditions and either attacking the pyridinium salt (**1d**)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

Encouraged by the positive results of our initial exploration and that of Glorius,[52-54] Lautens,[53] and Aggarwal,[55] whose efforts to use of Katritzky salts in deaminative couplings of primary amines via photoredox catalysis, and related work[56,57] that provided strong precedent, we set out to optimize the reaction conditions (**Table 1**).

While both the trimethyl- (**1h**) and triphenyl-pyridinium (**1i**) salts resulted in the higher yields compared to less substituted versions, a closer inspection of the 19F NMR spectra of the reaction mixtures revealed that the trimethyl-pyridinium (**1h**) produced far fewer side products (see SI). Given this and that triphenyl-pyridinium (**1i**) is derived from the corresponding expensive oxopyrylium salt ($2,376/mol) rather than inexpensive collidine ($29/mol), we elected to continue optimization using the collidinium salt, **1h**.

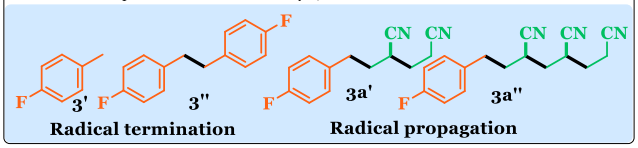
With reductive conditions, that included catalytic $Ir(ppy)_3$, DIPEA, and blue light, we observed complete conversion within 6 h, but the desired product was minor (23%, entry 1). While minor amounts of radical termination products were identified (**3'** and **3''**), we were encouraged to see that the majority of the mass balance appeared to 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 and gave a corresponding 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 SI) showed that while 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 had improved by an order of magnitude. Furthermore, increasing or decreasing the photocatalyst loading increased (entry 5) or decreased the product ratio (entry 6).

Table 1. Optimization table.



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	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	46 h	50%	38%	3.5
4	$[Ru(bpy)_3]PF_6$	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_3 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_2O 5 equiv	12 h	100%	85%	21.25
12	Entry 10, H_2O 10 equiv	12 h	100%	88%	29.3
13	No amine, no photocatalyst, no light	24 h	0	0	0

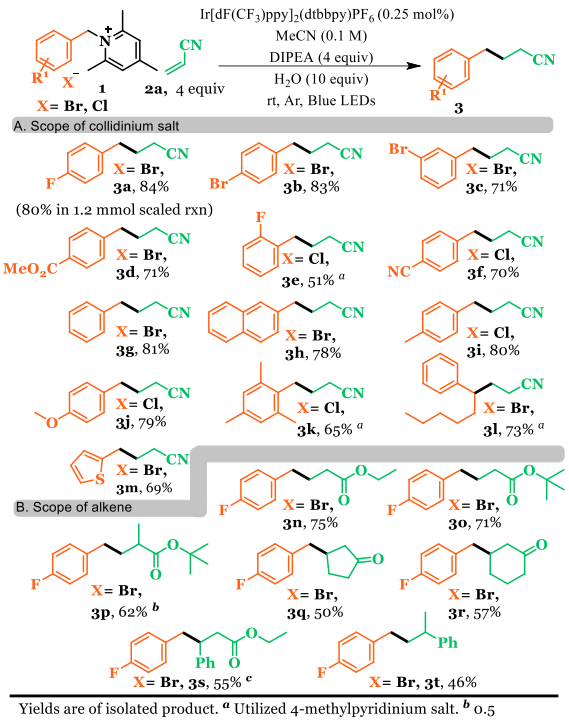
[a]Conversion and product ratio determined by 19F NMR.



Changing the catalyst to $Ru(bpy)_3$ (entry 4) which has a similar reduction potential ($E_{1/2}$(II/I) -1.33 V vs SCE)[1a] gave very sluggish conversion and no detectable product formation, suggesting that the photocatalyst plays a nuanced role in the reaction. Attempts to use NBu_3 (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.[60,61] Speculating that the off cycle use of the amine was resulting in reaction retardation at higher conversions, we investigated the use of more amine (entry 3 vs 9 and 10). Indeed, moving from 2 to 4 equivalents increased the conversion from 50% to 100% and decreased the reaction time from 46 h to 16 h. Importantly, as the desired reaction was able to take place throughout the entirety of the reaction, the product distribution shifted in favor of the desired product. With evidence suggesting the involvement of photocatalyst in the termination step, we investigated the effect of water on the reaction (entry 11 and 12). Indeed, the inclusion of 10 equivalents of H_2O 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).

Scheme 3. Scope studies.

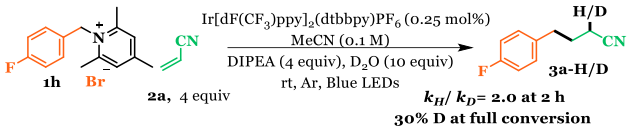


Yields are of isolated product. [a] Utilized 4-methylpyridinium salt. [b] 0.5 mol% of catalyst loading. [c] 19F NMR yield.

Having identified optimal conditions (entry 12 in **Table 1**), we examined the scope of collidinium salts with acrylonitrile (**Scheme 3**). A broader range of collidinium salts was prepared (see SI). The reaction worked well for benzylic collidinium salts with electron withdrawing - (**3a**, **3d**, and **3f**) neutral-groups (**3b**, **3c**, and **3g**) and electron-donating (**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-methyl pyridine derived salts. Apparently, the bulk of benzyl component, which made nucleophilic substitution more challenging, also served to protect these salts from undergoing Minisci-type benzylation which we had observed earlier with less sterically demanding benzyl pyridinium salts. Furthermore, 4-methyl pyridinium salt of a secondary benzylic substrate (**3l**) also gave a good yield, highlighting the ability to rapidly and significantly modify the carbon framework of substrates. The mild reaction conditions are compatible with a wide range of functional groups such as a nitrile (**3f**), ester (**3d**), ethers (**3j**) and bromides (**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[62] (**3m**) and naphthalene[63] (**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-3s**), with 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 competent (**3q**, and **3r**), giving the fluorobenzylated products in good yield. Other alkenes also proved competent (see SI). Interestingly, the use of α-methylstyrene resulted in the formation of product (**3t**) and higher order oligiomers. The scope suggests different reaction mechanisms may be operative depending on alkene. The use of the bench stable, crystalline collidinium salts also facilitate workup of the reaction. Simple extraction followed by acidic washes removes any excess DIPEA, collidine by-product, and, if present, any unreacted collidinium salts. This is in stark contrast to the Katritzky salt which produces triphenyl pyridine which must be removed chromatographically. Likewise, if the benzyl halide were used, any excess would also be expected to need to be removed from the organic extracts.

Our understanding of the reaction (**Scheme 5**) begins by absorption of a blue photon to give strongly oxidizing Ir(III)* [(Ir*(III)/(Ir(II) = 1.21 V vs SCE in CH_3CN)],[64] followed by reductive quenching by the amine[65,66] (NR_3 ~0.50 V).[67,68] This is supported by Stern-Volmer analysis (**5a**).

Scheme 4. Isotope experiments.

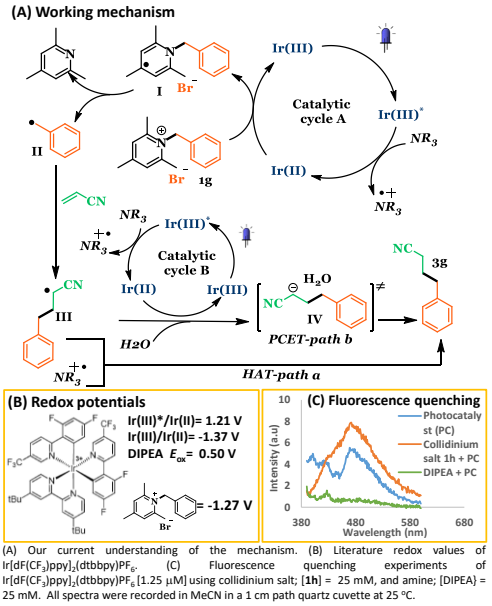


Next, the reduced Ir(II) undergoes SET to the collidinium salt **1h**,[69,70] (Ir(II/III) = -1.37 V vs SCE[64] $E_{1/2}$ = estimated -1.27 V vs SCE in DMF)[71] giving the collidinium radical, **I**, and completing **Cycle A**. Subsequently, **I** undergoes unimolecular fragmentation[72] to give collidine and benzylic radical, **II**. Addition of **II** to acrylonitrile generates radical intermediate **III**. HAT from the amine radical cation yields product (path a). However, several observations called this explanation into question, namely, the effect of photocatalyst loading on the product distribution (**Table 1**, entries 1, 5 and 6), and enhanced rate and selectivity upon addition of water (entry 12). Indeed, we observed a solvent kinetic isotope effect of k_H/k_D = 2.0 when we used 10 equivalents of D_2O (**Scheme 4**). Furthermore, the deuterium incorporation experiment (Scheme 4) revealed that use of D_2O resulted in only partial incorporation of the deuterium (30%) in the alpha position of the nitrile product. Given the O–H bond strength of water (118.8 kcal/mol)[73] and the C_{alpha}–H bond strength of the product (89.0 kcal/mol),[74] HAT from water is improbable. However, protium incorporation (70%) in the presence of D_2O, suggests that HAT (path a) is indeed occurring-the likely donor being the DIPEA radical cation.[3,75] The observed rate enhancement of the desired reaction upon inclusion of water may be due to a proton-coupled electron transfer (path B) that facilitates a reduction of the radical to carbanion **IV** (estimated reduction potential ~ -0.9- -1.1).[76,77] 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 observe.

Returning to our initial goal of dual catalysis, in a preliminary catalytic experiment with 2-(chloromethyl)-1,3,5-trimethylbenzene

(**Scheme 6**), we have seen that 20 mol% of 4-methylpyridine is capable of achieving catalytic turnover and significantly enhancing

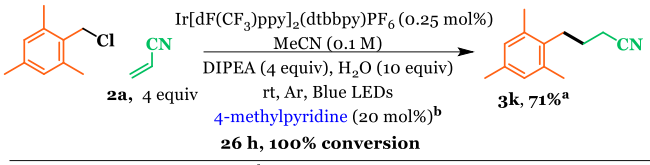
Scheme 5. Working mechanism.



(A) Our current understanding of the mechanism. (B) Literature redox values of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$. (C) Fluorescence quenching experiments of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ [1.25 μM] using collidinium salt; [**1h**] = 25 mM, and amine; [DIPEA] = 25 mM. All spectra were recorded in MeCN in a 1 cm path quartz cuvette at 25 °C.

the rate of benzylation. While some background reaction was observed, it was substantially slower (38% vs 100% conversion, see 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-redox active electrophiles.

Scheme 6. Preliminary attempt to achieve catalytic activation.



[a]Assay yield determined by GCMS. [b]Without 4-methylpyridine gave 38% conversion (26 h)

In conclusion, we have demonstrated that the use of commercially available collidiniums salts are a viable strategy that enable 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 further development is warranted. Pragmatically, collidinium salts are easy to make, handle, photochemically- and bench-stable, crystalline salts, which are redox active alternatives to halides. Furthermore, all reaction components are water soluble which facilitates product isolation, and potentially allows their use in complex settings.

ASSOCIATED CONTENT

Supporting Information

Procedures, spectra, references, and additional experiments.

The Supporting Information is available free of charge on the ACS Publications website. Supporting information (PDF)
FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds [1a, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n, 1o, 1p, 1q, 1r, 1s, 1t, 3a, 3b, 3c,3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l, 3m, 3n, 3o, 3p, 3q, 3r, 3s, 3t]

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

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ABBREVIATIONS

HAT, hydrogen atom transfer; SET, single electron transfer.

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