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Communication

Photoredox Catalysis

The Alkylation and Reduction of Heteroarenes with Alcohols Using Photoredox Catalyzed Hydrogen Atom Transfer via Chlorine Atom Generation

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Abstract: Radical additions to heteroaromatic bases are frequently employed for the rapid synthesis of complex products using C–H functionalization strategies. The conditions that are commonly employed are typically harsh, routinely requiring stoichiometric oxidants and other additives. In search for milder reaction environments allowing late-stage functionalization, we present the alkylation of N-heteroarenes using primary alcohols and ethers as radical precursors, where the corresponding alkyl radical is formed via hydrogen atom transfer process with a photoredox catalyzed chlorine atom generation as HAT agent. Furthermore, we explore the reduction of the heteroarenes in moderate to high yields when using secondary alcohols.

Introduction

Recent advancements in photoredox catalysis have led to a rapid increase of method development in organic synthesis.[1] The use of transition metal catalysts and organic dyes in photoredox mediated processes has been proven to be an effective alternative to classical radical formation.[2] Eliminating the need for initiators, harsh reaction conditions, and stoichiometric additives has resulted in robust organic transformations that are mild and highly efficient. The conversion of photons into potential energy has captivated chemists in search of new activation models for synthesis, in by the light-harvesting biomolecules found in nature.[3]

Hydrogen atom transfer (HAT) reactions are widely used processes in synthesis and have been an emerging strategy for method development in photoredox catalysis.[4] These processes can be achieved via photocatalyst-mediated HAT with tetra-*n*-butylammonium decatungstate (TBADT)[4a–4c] and Eosin Y[4d] as well as in dual photoredox catalysis processes using additives/catalysts such as thiols, amines, amides, and phosphates.[4e–4s] The catalytic generation of atomic halogens (chlorine or bromine) for HAT processes in synthetic applications is largely unexplored. Recently, Molander and Doyle have made advances in Ir^{III}/Ni^{0} dual photoredox HAT catalysis that have allowed the cross-coupling of alkanes with haloarenes through the generation of atomic halogens.[5] Our group and others have explored the photoredox mediated catalytic generation of chlorine atoms for the functionalization of a variety of alkanes.[6] Herein, we describe the photoredox mediated activation of alcohols and ethers using an Ir-based polypyridyl complex for the alkylation and reduction of heteroarenes. The transformation is mediated by the generation of chlorine atoms, a highly reactive intermediate seldom utilized in organic synthesis that undergoes HAT processes.

The alkylation of electron-deficient heteroarenes has been developed by Minisci.[7] The initial protocol utilized silver-mediated decarboxylation processes to produce alkyl radicals. Persulfate additives were necessary to oxidize the silver catalyst as well as the corresponding radical cation subsequent to radical addition to the heteroarene.

Although great success has been achieved with this strategy, many cases suffer from lower yields and the formation of multiple by-products. To circumvent these restrictions and harsh conditions, photoredox mediated strategies have been employed to create broad methodologies for the alkylation of heteroarenes.[8]

The use of alcohols in the photo-mediated alkylation of heteroarenes was developed over half a century ago, however, these protocols were met with low yields and functionality tolerance due to the requirement of forcing conditions.[9] In 2015, MacMillan and co-workers used the concept of polarity reversal catalysis to alkylate heteroarenes using alcohols (Scheme 1a).[10a] In a collaborative effort with the Scaiano group, we detailed the photo-mediated (UVA) methylation of heteroarenes using MeOH as alkylating agent with no need for extraneous additives, where a report from the Li group also appeared during this time (Scheme 1b).[6a,10b] Most recently, Glorius and co-workers has developed a photoredox catalyzed methylation process using DMSO as the alkylating agent (Scheme 1c).[10c] In order to overcome the challenges encountered in our previous methodology, we report the development of a photoredox process that improves on several factors: 1) using visible light mediated activation to negate UV-mediated decomposition pathways, 2) having alcohol as a reagent

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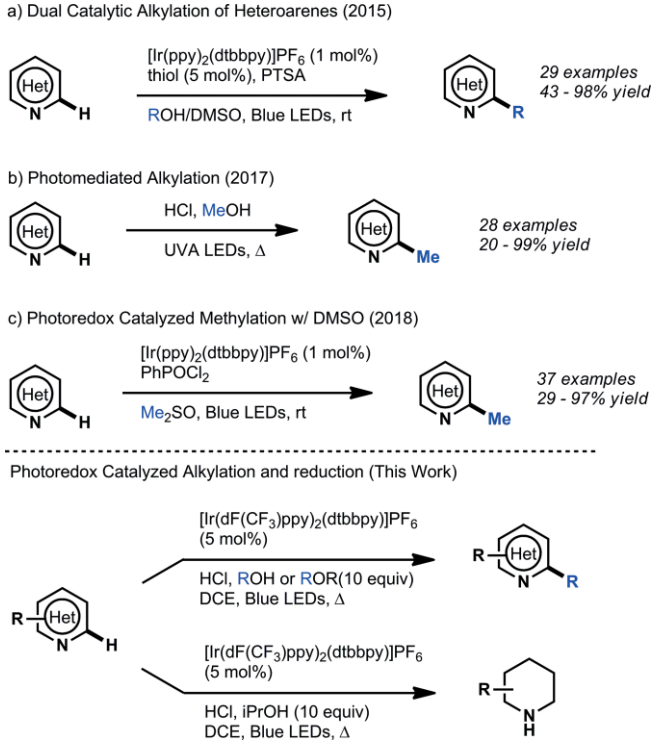
avoids its use as a solvent, and 3) increasing the scope of the transformation from methanol to longer chain alcohols.

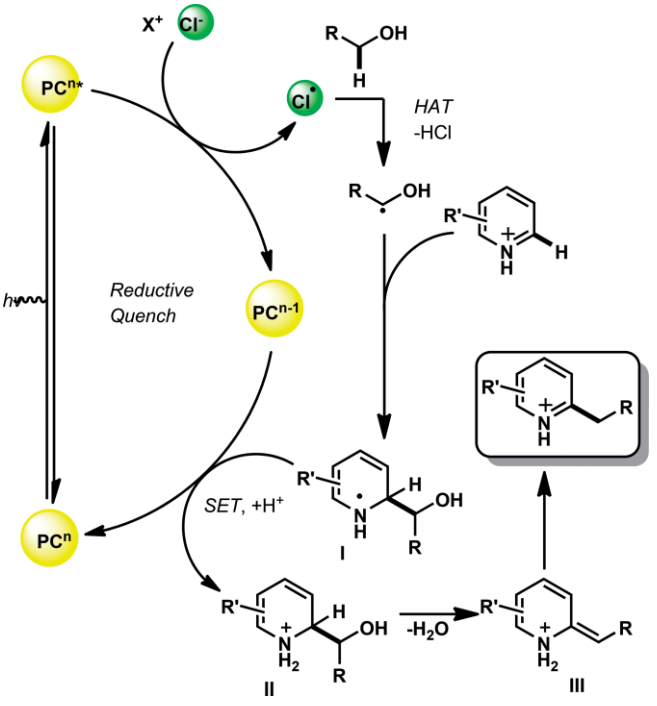


Scheme 1. Photo-mediated heteroarene alkylation.

Results and Discussion

We envisioned alkylation of heteroarenes via a photo-catalyzed HAT reaction using organic dyes or Ir-based polypyridyl complexes. Mechanistically, we hypothesized that a redox neutral alkylation strategy that merged photomediated single electron transfer (SET) and HAT processes would allow for the desired methodological improvements (Scheme 2). We propose that upon excitation of the photo-catalyst [PC]* would go through a reductive quench to oxidize chloride into a chlorine atom. The latter would then abstract a hydrogen atom from the alkylating agent at the most hydridic position. The resulting nucleophilic radical could then add to the heteroarene to generate intermediate **I**, where the radical cation that is produced would get reduced by the $[PC]^{n-1}$ species, giving intermediate **II**. After the elimination of water, the corresponding enamine (**III**) will tautomerize to give the desired product.

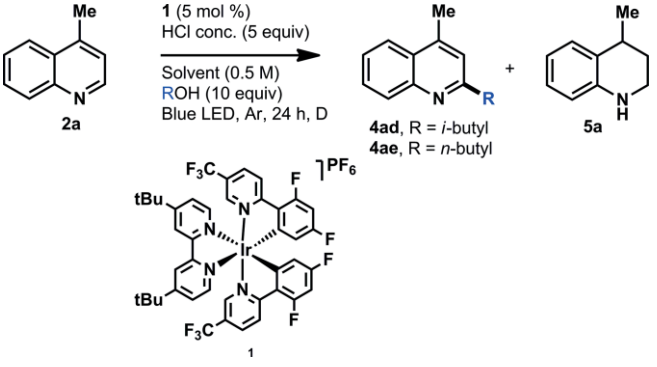
After initial screening of different organic photocatalysts such as substituted diphenylquinolines and acridinium salts, we found that the Ir-based polypyridyl complex, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**1**), proved to be compatible in the methodology. Using *i*BuOH (**3d**) as an alkylating agent, we began the optimization of this process by exploring the catalyst loading necessary to achieve the desired reactivity (Table 1). Using 5 mol-% of 1 with lepidine (**2a**) in the presence of HCl (5 equiv.) and **3d** (10 equiv.) in DCE gave a 50 % yield of **4ad** and 28 % of the reduced starting material (**5a**, entry 1). Reduction of the catalyst loading to 2 mol-% did not change the amount of by-product



Scheme 2. Proposed mechanism.

formed (entry 2). The reaction was performed in other solvents as $CHCl_3$, MeCN and DCM, but lower yields were obtained (entries 3–5). Interestingly, using DMSO as solvent did not produce the desired alkylated product, but instead the methylated prod-

Table 1. Optimization of reaction conditions.



entry	**1** [mol-%]	solvent	**4** [%][a]	**5a** [%][a]
1	5	DCE	**4ad**, 50	28
2	2	DCE	**4ad**, 41	30
3	5	$CHCl_3$	**4aa**, 38	21
4	5	MeCN	**4ad**, 27	10
5	5	DCM	**4ad**, 41	10
6	5	DMSO	**4aa**, 41	0
7	5	DCE	**4ae**, 64 (49)	7
8	0	DCE	0	0
9	5	DCE	0[b]	0
10	5	DCE	0[c]	0
11	5	DCE	0[d]	0

[a] NMR yield using mesitylene as internal standard. [b] In absence of light and heat. [c] With catalyst and heat in the absence of light. [d] At room temperature.

uct **4aa** in 41 % (entry 6). It was hypothesized that DMSO acts as alkylating agent and it could be reacting through a similar pathway as described by Glorious and co-workers. Trying to avoid product **5a** we changed the alkylating agent from a branched *i*BuOH **3d** to linear *n*BuOH **3e**. It proved to be successful and **5a** was lowered to 7 % and **4ae** increased to 64 % yield (49 % isolated) (entry 7). Lowering the acid and alcohol equivalents did not favor the reaction and full conversion was achieved only when an excess of HCl and alcohol was employed. Finally, control experiments showed that light and photocatalyst and heat were essential for the reaction to progress (Entries 8 and 9).

After establishing the reaction conditions, we investigated the reaction scope using different primary alcohols **3a**–**3g** and ethers **3h**–**3k** with lepidine to produce alkylated lepidines 4 (Table 2). Since the reaction did not need the alkylating agent as solvent, longer chained alcohols were compatible with this methodology; only primary and secondary alcohols could be used in accordance to the proposed mechanism. Starting with primary alcohols, it was found that shorter chains **3a** and **3b** gave the corresponding alkylated lepidines **4aa** and **4ab** in 77 % yields whereas the longer chain alcohols **3c** and **3e** produced lepidines **4ac** and **4ae** in 49 % yields. Alkylation using branched primary alcohols such **3d** gave the desired product **4ad** in 41 % isolated yield along with a significant amount of **5a** (see Table 1). Photoredox reactions with primary diols **3f** and **3g** provided alcohols **4af** [R = $(CH_2)_2CH_2OH$] and **4ag** [R = $(CH_2)_3CH_2OH$] in 66 % and 61 % yields, respectively. Cyclic ethers **3h** and **3i** gave **4ah** [R = $(CH_2)_3CH(OH)CH_2OH$] and **4ag** in 76 % and 71 % yields whereas acyclic **3k** ether led to the formation of **4ae** in 80 % yield. A lower yield was observed with pyran **3j**. Interestingly, the formation of **4ah** was selective as only one C-H position reacted. One can explain the exclusive regioselectivity by the subtle inductive effect of neighbouring oxygen atoms on C–H bond dissociation energy.

While studying the heteroarene scope, we found that a variety of quinolines were compatible with the methodology (Table 3). In general, the light-enabled addition of butyl to quinolines using dibutyl ether gave the desired compounds in yields ranging from 24 to 72 %. When 6-functionalized quinolines where used only degradation was observed. We found that lowering the equivalents of HCl to 2 equivalent and the reaction was completed after 2 h, giving quinolines **4ek**–**4gk** in 24 %, 72 %, and 60 %, respectively.

Table 2. Scope of the photoredox-catalyzed alkylation of heteroarenes using alkyl alcohols and ethers.

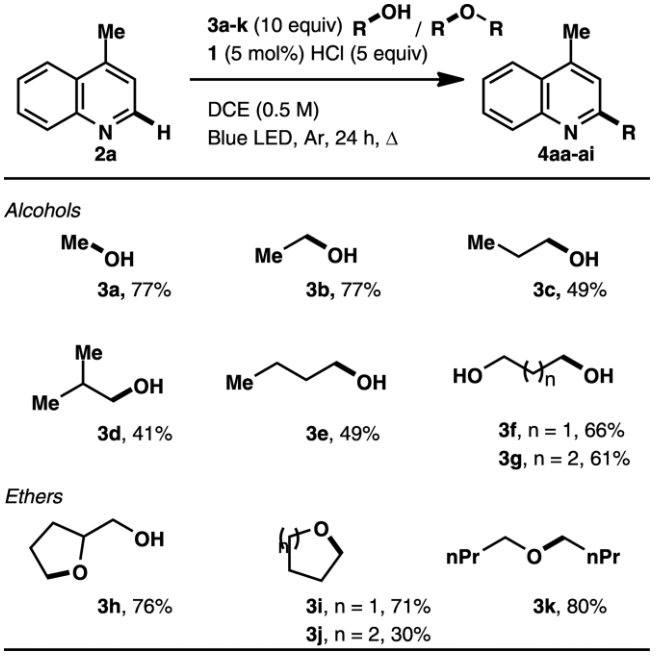
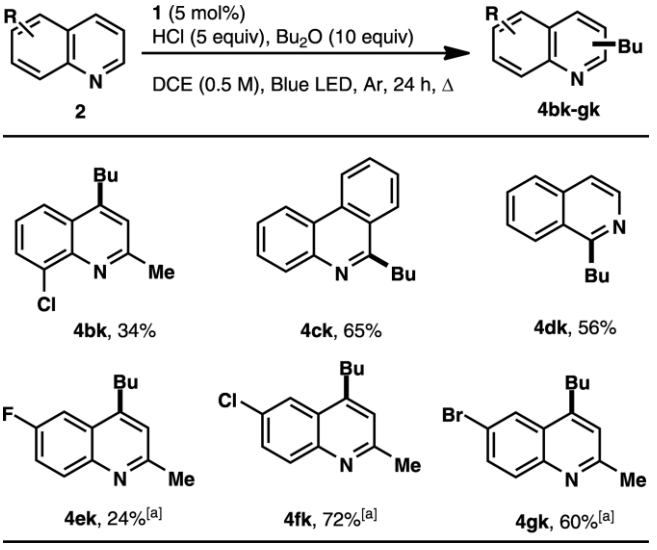


Table 3. Photoredox-catalyzed alkylation of various heteroarenes.

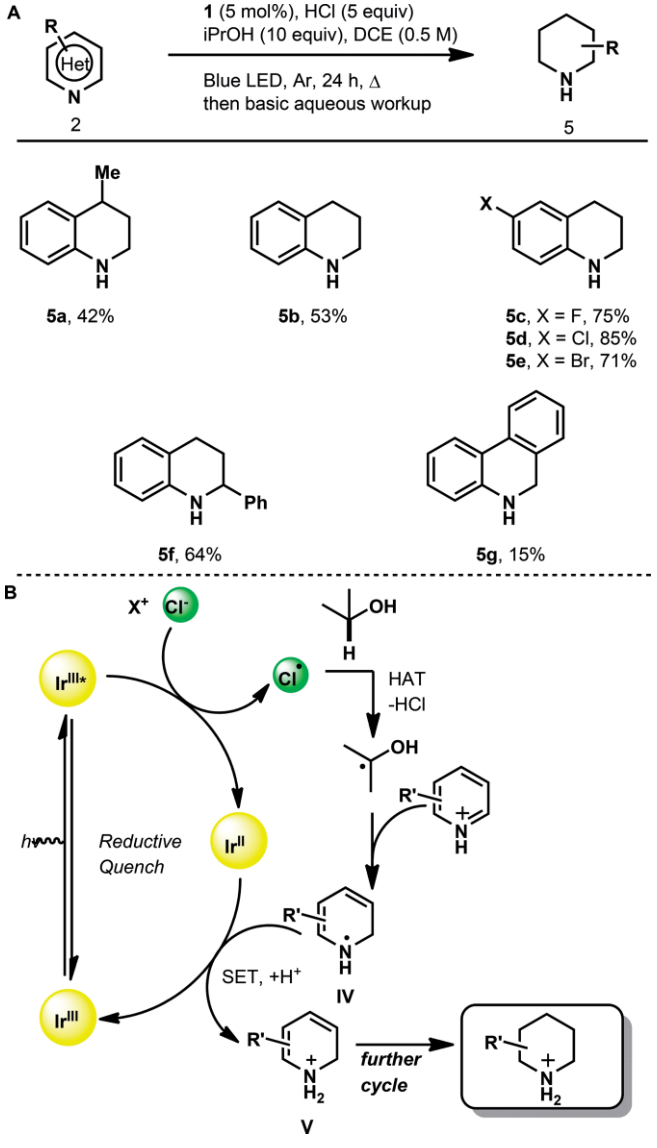


[a] 2 equiv. of HCl were used, full conversion in 2 h.

When *i*PrOH was used as the alkylating agent, the major product was the reduced heteroarene **5**. This result led us to explore the reduction of heteroarenes using these conditions (Scheme 3). It was observed that electron-poor and electron neutral quinolines gave the reduced product **5a**–**f** in good yields (Scheme 3, A). In the case of the reduction of phenanthridine **2c** 15 % of **5g** was observed. This can be attributed to the highly aromatic nature of phenanthridine and its resistance to lose this aromaticity.

A similar mechanism to the alkylation of heteroarenes is proposed for this reaction (Scheme 3, B). When the chlorine atom undergoes HAT with *i*PrOH, the corresponding ketyl radical gives an electron to the heteroarene to form radical cation **IV** and acetone as the by-product. One can suggest that the reaction is driven by the strong reducing nature of the ketyl radical that is formed. Then, the [Ir^{II}] species will also give an electron to the heterocycle, giving intermediate **V**. In its resonance-stabilized form, the species will undergo the catalytic cycle once more to get fully reduced.

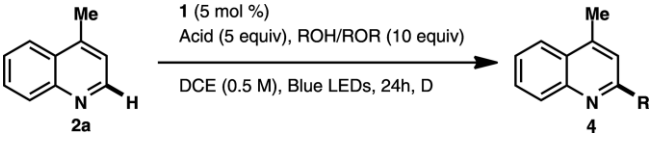
To obtain more information on the mechanism of the transformation, deuterated studies were performed (Table 4). As expected, when submitting fully deuterated conditions CD_3OD and DCl in D_2O we obtained **d_3-4aa** in 20 % yield. Using CD_3OH and HCl in H_2O the product found was **d_2-4aa** in 16 % yield.



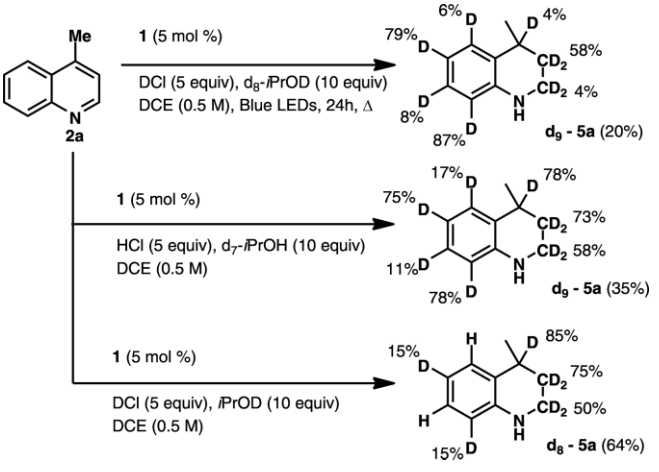
Scheme 3. Photoredox mediated reduction of heteroarenes and its proposed mechanism.

When CH_3OD with DCl in D_2O was used, **d-4aa** in 60 % yield was obtained (entries 1–3). These studies are in support with the proposed mechanism and the irreversible tautomerization of the enamine since no deuterium scrambling was observed. Furthermore, when a mixture of CD_3OH and CH_3OH (1:1) a ratio of products **4aa:d$_2$-4aa** was found (1.17:1) giving a kinetic isotope effect (KIE) of 1.17 (entry 4). Doing similar studies with THF gave analogous results, albeit in higher yields (entries 5–7). Submitting a mixture of THF and [D_8]THF (1:1) provided a mixture of **d-4ai** and **d$_7$-4ai** (1.19:1) in 88 % yield and provided a KIE of 1.19 (entry 8). Similar steps were taken to study the reaction with *i*PrOH (Scheme 4). Using fully deuterated conditions with d_8-*i*PrOD and DCl in D_2O gave product **d$_9$-5a** in 20 % yield. When using [D_7]*i*PrOH with HCl in H_2O, **d$_9$-5a** in 35 % yield was obtained. Finally, when *i*PrOD with DCl in D_2O was used, **d$_8$-5a** was observed in 64 % yield. The amount of deuterium scrambling observed in these products could be indicative of the resonance structures possible *en route* to the fully reduced desired products. To gain insight on the nature of the photochemical trans-formation, Stern-Volmer quenching experiments were performed to probe the excited-state reactivity of the photocatalyst (See Supporting Information).

Table 4. Deuterium labelling experiments.



entry	acid	ROH/ROR	yield [%]
1	DCl in D_2O	[D_4]MeOD	**d$_3$-4aa**, 20
2	HCl in H_2O	[D_3]MeOH	**d$_2$-4aa**, 16
3	DCl in D_2O	MeOD	**d-4aa**, 60
4	HCl in H_2O	MeOD/MeOH	**d-4aa/4aa**, 45, KIE = 1.17
5	DCl in D_2O	[D_8]THF	**d$_8$-4ai**, 76
6	HCl in H_2O	[D_8]THF	**d$_7$-4ai**, 90
7	DCl in D_2O	THF	**d-4ai**, 77
8	HCl in H_2O	[D_8]THF/THF	**d$_7$-4ai/4ai**, 88, KIE = 1.19



Scheme 4. More deuterium labelling experiments.

Evaluating the quenching rate determined by Doyle and co-workers for the Ir complex **1** (kqTBACl = 5.3×10^4 M^{-1} s^{-1}), we were interested in comparing the quenching with the alcohol substrate.[6b] First, we explored the quenching of the **1-PF$_6$** counterion. Little quenching was observed and when plotting the corresponding Stern-Volmer data; a Stern-Volmer constant (KSV) 0.038 was found. Using the excited-state lifetime (τ= 2.3×10^{-6} s) of **1**, a rate of quenching $<10^5$ M^{-1} s^{-1} was obtained.[1f] Since our conditions require a large excess of HCl, **1-Cl** was synthesized as well to see how it differed from its PF_6 salt.[6c] In MeCN, the quenching experiment was done using MeOH and quenching of the catalyst was observed (KSV = 0.29, kqMeOH = 1.3×10^5 M^{-1} s^{-1}).[11] In our hands, kqTBACl = 1.1×106 M^{-1} s^{-1} in MeCN was found for complex **1-PF$_6$**.[6a] This mechanistic data supports the proposed mechanism.

Conclusions

In conclusion, a redox neutral photoredox mediated protocol has been developed to alkylate functionalized quinolines from

alcohols and ethers. Furthermore, a photocatalytic reduction using *i*PrOH has been described. Deuterium labelling studies helped to determine that the mechanism was indeed going through an enamine intermediate, with the formation of the CD_3, CD_2H and CDH_2 adducts. The formation of the chlorine atom can be broadly applied to other HAT substrates and its use in other catalytic systems are currently being explored in our laboratory and will be discussed in due course.

Experimental Section

To an oven dried 8 mL Pyrex screw-top reaction vessel was added the heteroarene (0.2 mmol, 1.0 equiv.), ROH (2 mmol, 10.0 equiv.), concentrated HCl (1 mmol, 5 equiv.), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (0.01 mmol, 0.05 equiv.), DCE (0.4 mL, 0.5 M). The reaction vessel was capped, degassed with argon by sparging for 5 minutes (volatile alkyl alcohols were added after sparging), then irradiated with a blue (465 nm) LED (2–2.4 W) at an approximate distance of 1–5 mm for 24 hours. The resulting mixture was poured into DCM and extracted with NaOH (1 M) in a separatory funnel, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was further purified by flash chromatography (0–100 % EtOAc/hexanes), where relevant fractions were combined, concentrated, and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

Conflict of Interest

The authors declare no competing financial interest.

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Keywords: Photoredox · Photocatalysis · Heterocycles · Alkylation · Redox-neutral

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[11] Stern-Volmer quenching was conducted in MeCN due to solubility issues caused by DCE.

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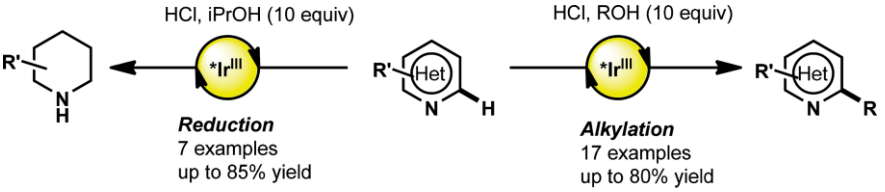
Photoredox Catalysis



The alkylation of N-heteroarenes using primary alcohols and ethers as radical precursors. The corresponding alkyl radical is formed via hydrogen atom transfer (HAT) process with a photoredox catalyzed chlorine atom generation as HAT agent. Furthermore, we explore the reduction of the heteroarenes when secondary alcohols are employed, giving moderate to high yields.

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