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Visible-Light-Induced $C(sp^3)$−H Oxidative Arylation with Heteroarenes

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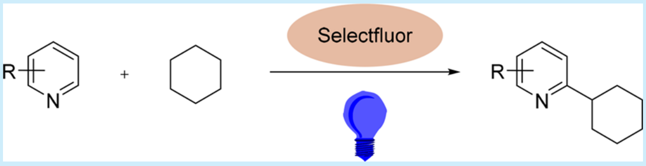
Supporting Information

ABSTRACT: Considering the ubiquitous $C(sp^3)$−H and the important value of alkylated heteroarenes, developing a universal method for $C(sp^3)$−H arylation with heteroarenes is significant. Herein, we proposed a method where Selectfluor can promote the oxidative $C(sp^3)$−H arylation with heteroarenes without external photocatalysis under visible-light irradiation. By EPR study, the N−F activation of Selectfluor by blue LED irradiation can generate the N radical cation, which is the key step for this conversion.



Alkanes, ethers, and methylarenes are ubiquitous bulk chemicals whose $C(sp^3)$−H functionalization to value-added compounds is significant. Over the past decades, oxidation-induced $C(sp^3)$−H functionalization served as a general route to forge C−C and C−X (N, S, O, etc.).[1] Oxidative cross-coupling between two C−H compounds is the most step- and atom-economical method to construct a C−C bond.[2] Considering that alkylated heteroarenes are widespread constituents of medicines and materials,[3] numerous impressive works for the synthesis of these valuable compound have been reported.[4] With the development of photocatalysis,[5] $C(sp^3)$−H arylation with heteroarenes is usually achieved by the combination of a photocatalyst and stoichiometric peroxides,[6] which can effectively avoid high temperatures. Because different types of $C(sp^3)$−H may have different physical properties,[7] such as cyclohexane, tetrahydrofuran, and toluene, their bond dissociation energies (BDEs) are different (Figure 1a). Therefore, a novel and universal method for these $C(sp^3)$−H arylations is highly desired.

Selectfluor is known as a powerful fluorination regent and oxidant.[8] A one-electron reduction event is considered the key step for the N−F breakage of Selectfluor, delivering an N radical cation and F anion. Direct photoinduced N−F activation of Selectfluor to generate the N radical cation and F radical is unknown (Figure 1b). Herein, we demonstrate a visible-light-induced Selectfluor-mediated selective $C(sp^3)$−H arylation by using heteroaromatic compounds as the aryl source (Figure 1c). The electron paramagnetic resonance (EPR) experiments evidence that visible light can induce the N−F activation of Selectfluor, which is the key step for this transformation. A series of alkanes, ethers, and methylbenzenes exhibit good reactivities and delivery of desired alkylated heteroarenes.

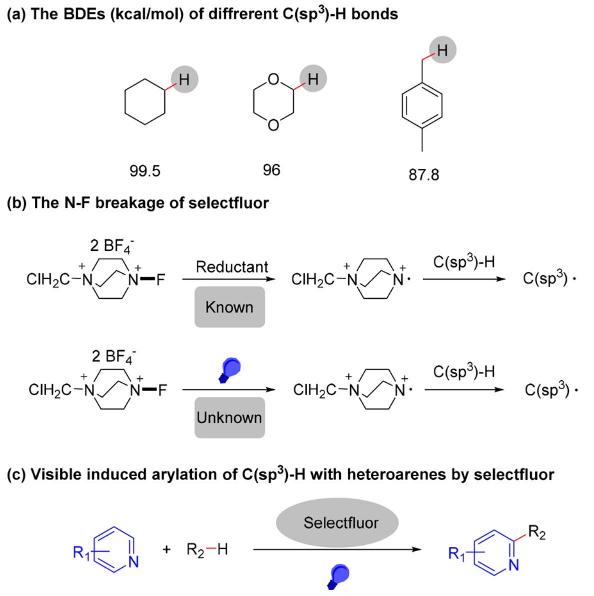


Figure 1. Oxidative $C(sp^3)$−H arylation with heteroarenes.

Initially, we chose isoquinoline **1a** and cyclohexane **2a** as the model substrates to investigate these visible-light-induced oxidative $C(sp^3)$−H arylation conditions. An excellent yield of 95% was observed when Selectfluor was employed as an effective oxidant under blue LED irradiation, and trifluoroacetic acid (TFA) was served as a suitable acid (Table 1, entry 1). It was notable that blue-light irradiation was necessary because no product was detected when the reaction mixture was treated under green LED irradiation or darkness (entries 2 and 3), implying that the longer wavelength visible light could not induce N−F activation and led to the failure of this transformation. Even when the reaction system was heated to 80 °C under darkness, the reactivity was still poor (entry 4). In contrast, *N*-fluorobenzenesulfonimide (NFSI), as the analogue

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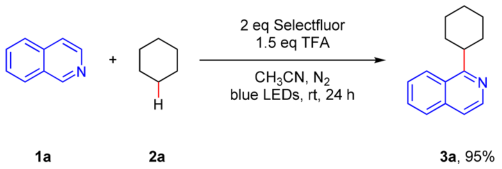
Table 1. Investigation of the Reaction Conditions[a]



entry	variation from the standard conditions	yield (%)
1	none	95
2	green LEDs instead of blue LEDs	nd
3	darkness	nd
4	80 °C instead of blue LEDs	trace
5	$K_2S_2O_8$ instead of Selectfluor	trace
6	NSFI instead of Selectfluor	37
7	CH_3COOH instead of TFA	20

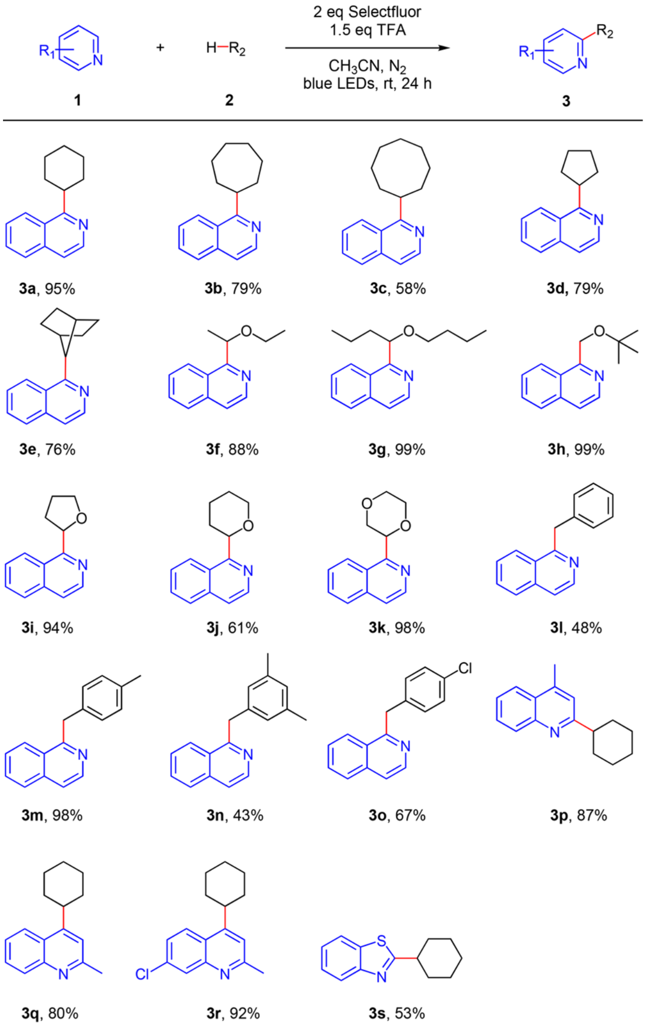
[a]Conditions: **1a** (0.3 mmol), **2a** (1.5 mL), Selectfluor (0.6 mmol), TFA (0.45 mmol) in 2.0 mL of CH_3CN under a nitrogen atmosphere, irradiated by 3 W blue LEDs, rt, 24 h; isolated yields.

of Selectfluor, provided a low yield of 37% under the standard conditions (entry 5). We proposed that the N−F activation of NFSI may be more difficult than that of Selectfluor because the BDE of NFSI is higher than that of Selectfluor.[9] Commonly used chemical oxidant potassium superoxide ($K_2S_2O_8$) was unable to drive the conversion under blue LED irradiation (entry 6). When TFA was placed into acetic acid (CH_3COOH), the yield dropped rapidly (entry 7), which indicated that TFA can effectively achieve the protonation of heteroarenes.

With the suitable conditions in hand, we hoped that various C(sp^3)−H with heteroarenes could be efficiently transformed into the corresponding alkylated heteroarenes by use of our method (Scheme 1). Other cycloparaffins like cycloheptane, cyclooctane, and cyclopentane could also successfully deliver oxidative C(sp^3)−H arylation products in good yields (**3b−d**). Notably, a single site-selectivity for the more contorted C(sp^3)−H of norbornane was observed under the standard conditions (**3e**). Subsequently, we attempted to expand the simple C(sp^3)−H to ethers. Not only did the chain ethers such as ethoxyethane, 1-butoxybutane, and *tert*-butyl methyl ether show excellent reactivity (**3f−h**) but also cyclic ethers like tetrahydrofuran, tetrahydro-2*H*-pyran, 1,4-dioxane proceeded in high efficiency (**3i−k**). At the same time, a series of methylarenes were examined. It was delightful that toluene was smoothly compatible with this system, providing the desired benzylic C(sp^3)−H arylation product (**3l**). Furthermore, *p*-xylene and mesitylene were competent substrates (**3m** and **3n**). The functional group on the toluene moiety (Cl) was well tolerated (**3o**), providing the potential chance for further chemical transformation. To extend the synthetic utility of this methodology, other electron-deficient heteroarenes as aryl source were investigated with cyclohexane to synthesize those valuable alkylated heteroarenes. The quinolines with different substituents could be converted into the desired products in good yields under the same conditions (**3p−r**). Moreover, benzothiazole behaved a satisfactory reactivity for the oxidative C(sp^3)−H arylation (**3s**).

Additionally, the gram-scale synthesis experiment was carried out (see the Supporting Information for details). A comparable yield 82% was obtained when the model reaction was performed in 10 mmol scale, providing promising application in preparative synthesis (Figure 2).

Scheme 1. Substrate Scope for the Oxidative C(sp^3)−H Arylation with Heteroarenes[a]



[a]Conditions: **1** (0.3 mmol), **2** (1.5 mL), Selectfluor (0.6 mmol), TFA (0.45 mmol) in 2.0 mL of CH_3CN under a nitrogen atmosphere, irradiated by 3 W blue LEDs, rt, 24 h; isolated yields.

1a 10 mmol **2a** **3a**, 82%, 1.74g

Figure 2. Gram-scale synthesis experiment.

To get a deeper understanding about this protocol, an intermolecular kinetic isotope effect experiment was carried out. A kinetic isotope effect (KIE) value of 3.00 was observed, revealing that the cleavage of C(sp^3)−H might be the rate-determining step (see the Supporting Information for details). When 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as a radical-trapping reagent was subjected to the standard reaction conditions, the oxidative C(sp^3)−H arylation of alkane was totally suppressed, which indicated a radical pathway might be involved (see the Supporting Information for details).

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To reveal the detail mechanism of the blue-light-induced Selectfluor-promoted oxidative C(sp^3)−H arylation, the electron paramagnetic resonance (EPR) experiments were designed to observe the behavior of Selectfluor under blue-light irradiation and darkness (Figure 3). When Selectfluor in acetonitrile was irradiated by blue LEDs, two kinds of radical signals were detected by utilizing 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a radical scavenger. One of the radicals was confirmed as the radical adduct between two fluorine radicals and DMPO, while the other one resulted from the oxidation of DMPO, whose ratio is 3:8.10.[10] In contrast, we did not detect the radical adduct between two fluorine radicals and DMPO in the dark.

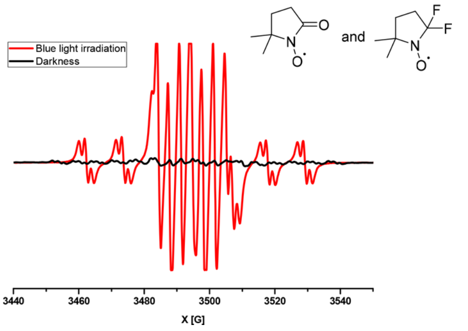

Figure 3. EPR spectra of Selectfluor under blue LED irradiation and darkness.

Finally, the intermolecular competition experiments were designed to explore the preferred C(sp^3)−H under this oxidative C(sp^3)−H arylation condition. As shown in Figure 4, the reaction rate of benzyl C(sp^3)−H is much faster than alkanes and ethers, while alkanes behaved a slower reactivity than ethers.

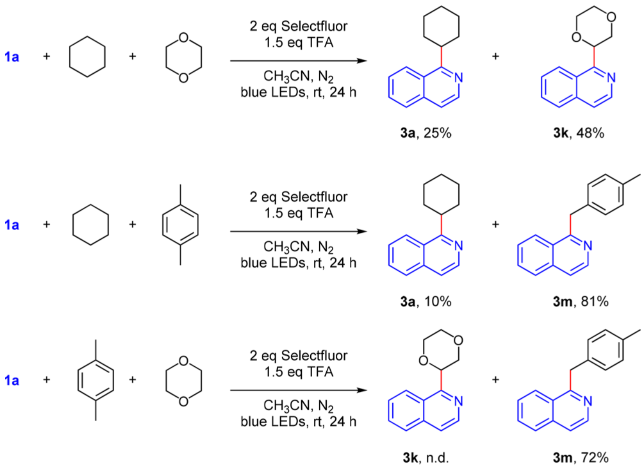

Figure 4. Intermolecular competition experiments.

On the basis of the above study, a plausible reaction mechanism is shown in Figure 4. The N−F homolytic cleavage of Selectfluor under blue LEDs irradiation can be achieved, delivering the corresponding N radical cation **4** and F radical **5** (Figure 5a). The generated N radical cation is capable of abstracting the sp^3 C−H of cyclohexane to product the corresponding alkyl radical **7** (Figure 5b). Then the electron-deficient heteroarenes protonated by TFA can capture the nucleophilic radical and generate the radical adducts **8** (Figure 5c). Finally, further oxidation and deprotonation of this radical adduct by another Selectfluor would then afford the C(sp^3)−H arylation product **3** (Figure 5d). Light on/off experiments indicated that the radical-chain process might be impossible (see the Supporting Information for details).

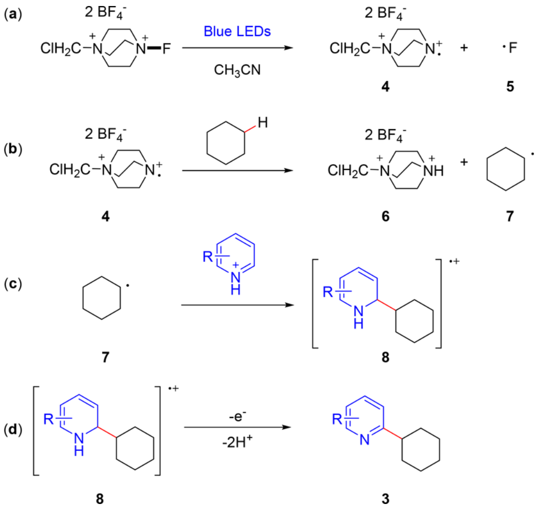

Figure 5. Proposed mechanism for the oxidative C(sp^3)−H arylation with heteroarenes.

In conclusion, we have developed an intriguing and efficient method for oxidative C(sp^3)−H arylation with heteroarenes, which was mediated by Selectfluor under blue LED irradiation. The C(sp^3)−H of simple alkanes, ethers, and methylarenes under these special oxidative condition could be well tolerated. The blue-light-induced N−F activation of Selectfluor evidenced by EPR study is key for this transformation. The intermolecular competition experiments indicated that oxidative methylarenes C(sp^3)−H arylation are faster than ethers and alkanes. The observed reactivity may have important implications for chemical transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00744.

Full experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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