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Catalyst-Free and Redox-Neutral Innate Trifluoromethylation and Alkylation of Aromatics Enabled by Light

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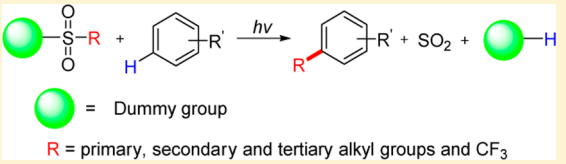
Supporting Information

ABSTRACT: The Minisci alkylation is useful to functionalize aromatics via alkyl radical addition. Current approaches to prepare alkyl radicals follow either oxidative or reductive pathways from various functional groups. Developing new strategy beyond these traditional methods remains elusive yet highly significant. In this article, we present a redox-neutral and catalyst-free protocol to engender alkyl radicals in the context of trifluoromethylation and general alkylation of arenes. This protocol, via the Norrish type I concept to produce alkyl radicals, accommodates various functional groups and delivers the product in good yields. This method identified a series of compounds as the trifluoromethylation and alkylation reagents assisted by light. It is expected that these compounds can find potential applications in other radical-involved reactions.



1. INTRODUCTION

The Minisci alkylation is a powerful tool to functionalize aromatics via alkyl radical addition.[1−4] Complementary to the Friedel−Crafts alkylation, it is particularly effective to functionalize electron-deficient aromatics. The original Minisci protocol employs aliphatic carboxylic acids to generate alkyl radicals through the oxidative decarboxylation.[4] Numerous other methods to prepare alkyl radicals have since been invented in the context of Minisci alkylation. Current approaches to access alkyl radicals consist of two general strategies: (a) the oxidative and (b) the reductive approaches. Besides Minisci's seminal oxidative decarboxylation protocol using silver catalyst and persulfate, other decarboxylative protocols were also established, such as Barton's decarboxylation,[5−8] photoredox,[9−18] and hypervalent iodine-based protocols.[19,20] Besides aliphatic carboxylic acids, other functional groups, including sulfinates,[21−27] boronates,[28−36] and even carbon−hydrogen bonds[37−48] among others,[49] can also serve as the radical precursors for the oxidative strategy.[50,51] On the other hand, the reductive strategy also found wide applications based on various functional groups, including alkyl halides,[52−59] sulfonyl halides,[60−63] and olefins.[64−67] In addition, another useful strategy involving alkyl halides to generate alkyl radicals is via the homolytic radical substitution (S_H2); for example, alkyl iodides can be converted into alkyl radicals in the presence of more reactive methyl or phenyl radicals to alkylate protonated heteroaromatics in synthetically useful yields[68−71] (Figure 1).

In terms of the redox-economy toward more sustainable synthesis,[72] the above-mentioned methods to access alkyl radicals are not satisfying because of the involvement of harsh oxidants and reductants. These redox reagents, often used in superstoichiometric amount (> 3 equiv), not only impair the substrate scope and evoke chemoselectivity issues but also generate obnoxious byproducts especially for large scale synthesis. Therefore, redox-neutral protocols obviating these external oxidizing and reducing reagents are desirable.[73] In the past few years, the photoredox catalysis is very successful along this line.[74−77] Nevertheless, various photocatalysts are mandated to initiate the single electron transfer process, and

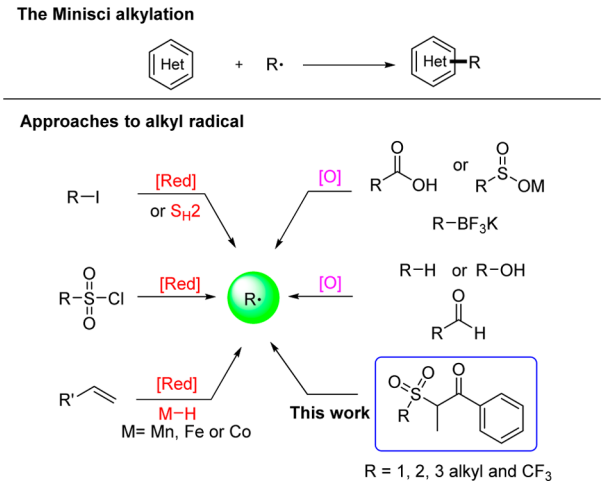


Figure 1. Different approaches to access alkyl radicals for the Minisci alkylation.

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the generation of alkyl radicals in these protocols still follows either reductive or oxidative mechanism. Accessing alkyl radicals in a redox-neutral manner without external redox reagents or photocatalysts remains unexplored yet highly significant. In this article, we wish to report such an approach enabled by a series of α-methyl-α-sulfone phenyl methyl ketones as the alkylation regents assisted by light irradiation (Figure 1).

2. RESULTS AND DISCUSSION

2.1. Research Design. It is well-established that alkyl halides can undergo homolytic cleavage under light irradiation to generate alkyl radicals in a redox-neutral manner.[78−81] This light-promoted approach is not applicable to the Minisci alkylation[82] due to two reasons: (1) insufficient concentration of alkyl radical due to its reversible combination with halogen radical generated simultaneously; (2) the more reactive halogen radical would compete with the less reactive alkyl radical, which makes the side reactions predominate.[83] Therefore, to utilize light to homolytically generate alkyl radical in a synthetically useful way without the assistance of halogen radical trapper,[84] the following criteria should be met: (1) the undesired twin radical is less reactive than the target alkyl radical; (2) the reversible reaction of homolytic cleavage should be inferior to the desired Minisci alkylation. We hypothesized that these requirements can be met when the undesired radical is also a carbon radical: (1) since they are both carbon radicals, the target alkyl radical would at least bear a comparable reactivity with the undesired carbon radical; (2) the reactivity of the undesired carbon radical could be further diminished through modulating its electronics and sterics thanks to the wealth of knowledge of carbon radical.[66,85−89]

The Norrish type I reaction refers to the homolytic α-cleavage of carbonyls.[90] This reaction engenders a pair of carbon radicals, one of which is an acyl radical (Figure 2a). The acyl radical further undergoes decarbonylation to produce another alkyl radical. Such a reaction is valuable to construct carbon−carbon bonds via intramolecular decarbonylation as only one potential product can be formed (Figure 2b).[91,92] In contrast, its intermolecular counterpart is typically not synthetically useful due to the presence of multiple radicals (Figure 2c). Inspired by Garcia-Garibay's elegant work on engineering Norrish I reaction[93−99] and the so-called "captodative effect",[100,101] we considered that using a stabilized dummy substituent R^1 might solve the regioselectivity issue: (1) the α-cleavage would prefer the pathway to produce the more stable dummy radical R^1, which generates the desired radical in a more selective way; (2) the more stable dummy radical R^1 is less reactive, which could not compete with the target radical to react with the aromatics and the desired Minisci product would prevail (Figure 2d). Therefore, a hypothesis to alkylate aromatics based on the Norrish I concept can be proposed (Figure 2e). With these in mind, we embarked on identifying a proper dummy substituent R.[1]

2.2. Library Screening for Trifluoromethylation. In surveying the context of Minisci alkylation, we recognized that trifluoromethylation is a good starting point. Trifluoromethylation of aromatics is highly important in the pharmaceutical industry and material chemistry.[102−109] Various trifluoromethylation protocols have been developed via using electrophilic, nucleophilic, and radical trifluoromethyl reagents. Considering the mild conditions, broad functional group compatibility and avoidance of prefunctionalization and directing groups, innate

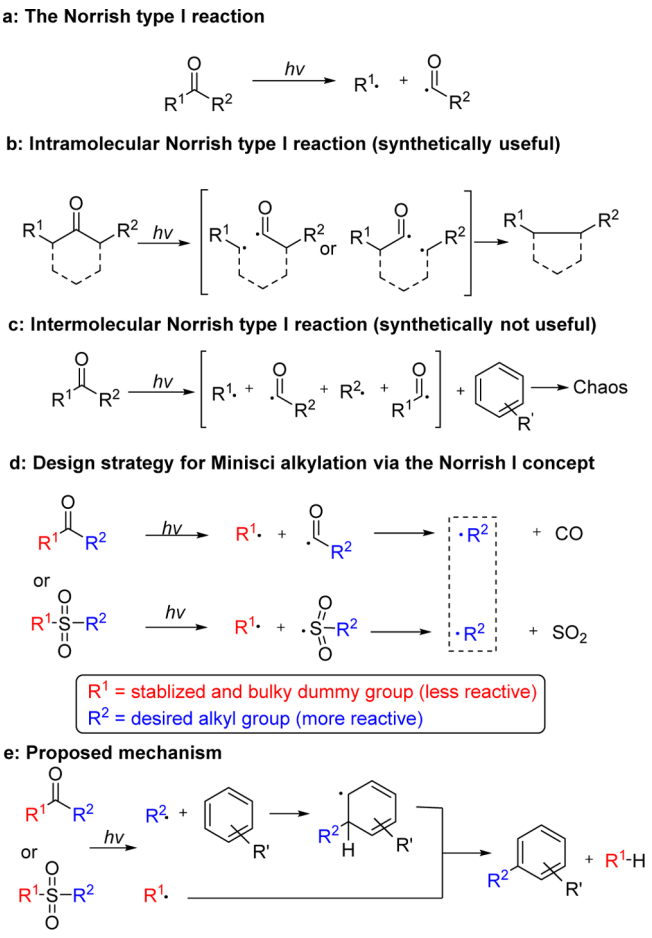

Figure 2. Norrish type I reactions toward the Minisci alkylation.

trifluoromethylation of aromatics via radical addition is superior to other metal-involved approaches.[106,110−112] In this regard, the state-of-the-art methods are represented by exploiting metal trifluoromethylsulfinates under oxidative conditions[21,113] and photoredox catalysis via CF_3SO_2Cl and others under reductive conditions.[60,114−116] Despite there being some early reports about homolytically generating CF_3 radical via using CF_3I,[117−121] bis(trifluoromethyl)peroxide,[122] or CF_3SO_2Cl[123] under thermal or light conditions, the reactions are extremely sluggish perhaps due to the interference of untamed halogen radicals. Moreover, the gaseous CF_3I, bis(trifluoromethyl)-peroxide, and volatile CF_3SO_2Cl are not convenient to store and handle, especially in the pharmaceutical industry. Therefore, developing a readily synthesized and stable CF_3 radical source, which can be used in a redox-neutral reaction, is both conceptually important and synthetically practical.

Following the hypothesis demonstrated in Figure 2d, a library comprising a wide array of trifluoromethyl compounds was constructed. Given the ease of structural analysis, 1,3,5-trimethoxybenzene was selected as the substrate to evaluate the feasibility of different trifluoromethylation reagents (Table 1). Under light irradiation, regular ketones, esters, and oxime[124] with CF_3 group did not produce any product (**1**−**6**) and α-diketone **7** only delivered the product in 9% yield. Considering the lower carbon−sulfur bond strength than carbon−carbon bond and more rapid kinetics of desulfonylation than decarbonylation,[125,126] we turned our attention to trifluoromethyl sulfones.[127−129] Although sulfone **8** failed to give any product, a 10% yield could be detected with **9** as the CF_3

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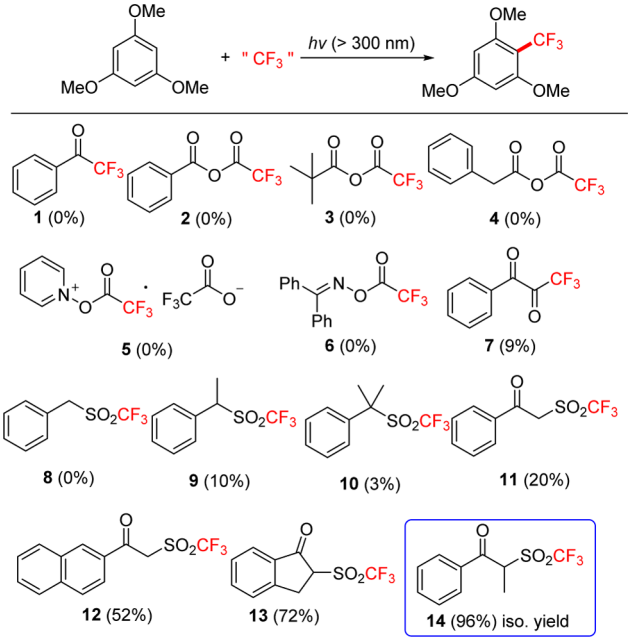
Table 1. Evaluations of Different Trifluoromethyl Compounds

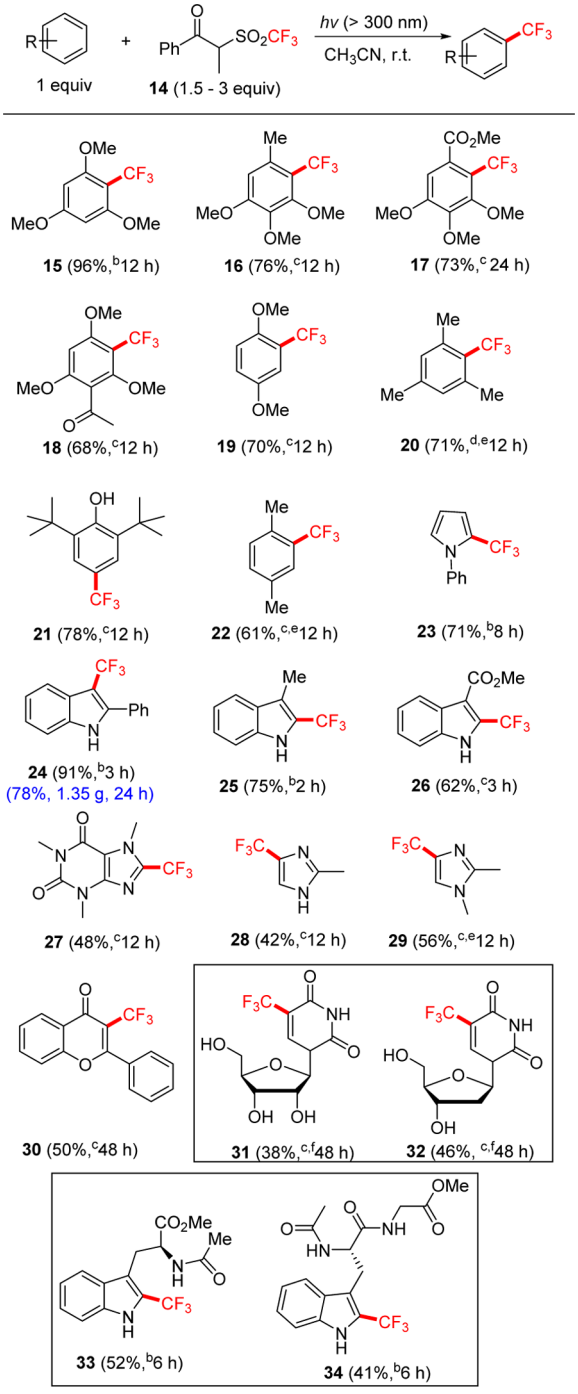


[a]All the reactions were conducted with 1,3,5-trimethoxybenzene (0.05 mmol) and CF_3 source (0.075 mmol) in 0.25 mL of CH_3CN under argon for 12 h at rt (ca. 25 °C), and the reaction yields were quantified by ^1H NMR via mesitylene as the internal standard except **14**.

source. Introducing a second methyl group did not increase the yield (**10**). Fortunately, when the dummy groups were aryl methyl ketones (**11**–**13**), the yields were significantly enhanced (20%–72%).[130] Further adding one methyl group to the methylene carbon of **11** raised the isolated yield of the desired trifluoromethyl product to 96% (**14**). The high reactivity of **14** is attributed to the stabilizing effect of both carbonyl and methyl groups (the so-called "captodative effect"),[100,101] as well as the steric bulkiness. The stabilizing effect induces the ease to undergo the homolytic cleavage, and the bulky environment induces its lower capacity to react with the aromatic than with trifluoromethyl radical.

After identifying the appropriate compound (**14**), we further evaluated the scope of this trifluoromethylation reagent toward both aromatics and heteroaromatics (Table 2). To our delight, they were both compatible with our protocol. With respect to the aromatics, we observed good to excellent yields with many functional groups such as methoxy (**15**, **19**), benzylic methyl (**16**), ester (**17**), ketone (**18**), and phenol (**21**). Not only the electron-rich aromatics but also regular aromatics without electron donating groups can deliver the trifluoromethylation products smoothly (**20**, **22**). Regarding the heteroaromatics, pyrrole (**23**), unprotected indoles (**24**, **25**, and **26**), caffeine (**27**), imidazoles (**28**, **29**), flavonoid (**30**), nucleosides (**31**, **32**), and even amino acid (**33**) and peptide (**34**) were applicable. The broad functional group compatibility suggests the usefulness of this reagent in the context of trifluoromethylation. Moreover, UV–vis spectrum indicates that this trifluoromethylation reagent **14** has light absorption around 380 nm (UVA region) (Figure 3), which overlaps with the emission spectrum of a household compact fluorescence lamp (CFL).[131] To further demonstrate the flexibility and robustness of this reagent, we found that a simple household CFL could be employed as the light source to promote the reactions (Table

Table 2. Scope of the Arenes for the Trifluoromethylation[a]



[a]All the reactions were conducted with arene (0.1 mmol), CH_3CN (0.5 mL), and 300 W xenon lamp under argon with specified amount of CF_3 source **14** at rt (ca. 25 °C), and the yields are isolated ones. [b]1.5 equiv of **14**. [c]3.0 equiv of **14**. [d]2.0 equiv of **14**. [e]Yields were quantified by GC-MS due to volatility of products. [f]H_2O, 0.1 mL, was added into 0.5 mL of CH_3CN.

3). The lower yields driven by CFL than those by regular xenon lamp can be attributed to the lower conversion of the starting material. Prolonging the reaction time can enhance the conversion rate and consequently the reaction yields.

2.3. Application to the Alkylation. After successfully applying **14** to trifluoromethylate aromatics, we decided to further extend this concept into a more general strategy for the

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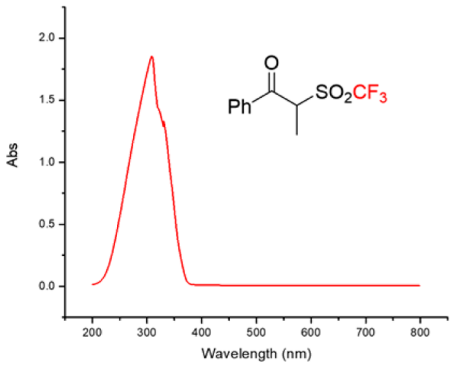
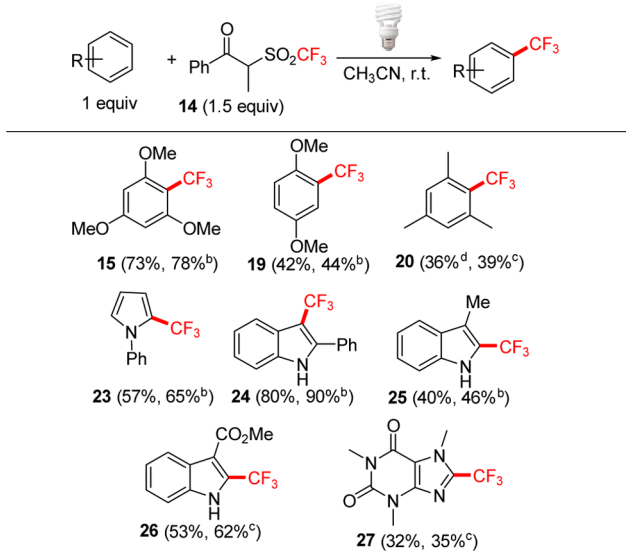


Figure 3. UV−vis of **14**.

Table 3. Household CFL as light source to promote the trifluoromethylation[a]

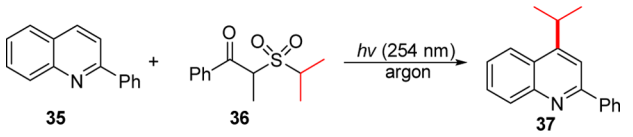


[a]All the reactions were conducted with arene (0.1 mmol), **14** (0.15 mmol), CH_3CN (0.5 mL), and 45 W CFL under argon for 48 h, and the yields are isolated ones, which are followed by the conversion in the parentheses. [b]The conversion was calibrated by ^1H NMR. [c]The conversion was calibrated by GC/MS. [d]This yield was determined by GC/MS due to its volatility.

alkylation.[32,132] Different from the electrophilic CF_3 radical, the nucleophilic alkyl radical tends to react with the electron-deficient heteroaromatics in acidic conditions. Therefore, the reaction between 2-phenyl quinoline **35** and isopropyl radical source **36** was selected as the model considering the significance of the quinoline scaffold in oncology drug discovery[133] (Table 4). Initially, the same solvent, CH_3CN, for the trifluoromethylation was employed with 1 equiv of TFA at rt. To our delight, the desired alkylation product could be detected in 7% yield (entry 1). When the solvent was switched to acetone, the product was obtained in 13% yield (entry 2). Further increasing the temperature to 50 °C raised the yield to 22% (entry 3). Moreover, increasing the amount of TFA would boost the yield to 68% (entries 4 and 5). In addition, solvent screening indicated that acetone was the best solvent (entries 6−11). A higher temperature of 80 °C would enhance the yield to 75% (entry 12). Finally, it was found that more TFA would result in the product in the yield of 81% (entry 13).

After the optimized reaction conditions of isopropylation were established, the scope of the heteroaromatics was

Table 4. Optimization for the Isopropylation of 2-Phenylquinoline



entry[a]	solvent	TFA (equiv)	T (°C)	yield (%)[b]
1	CH_3CN	1	rt	7
2	acetone	1	rt	13
3	acetone	1	50	22
4	acetone	3	50	51
5	acetone	10	50	68
6	CH_3CN	10	50	19
7	DCM	10	50	12
8	DMF	10	50	3
9	DMSO	10	50	10
10	EtOAc	10	50	19
11	MeOH	10	50	15
12	acetone	10	80	75
13	**acetone**	**20**	**80**	**81**

[a]All the reactions were conducted with 0.1 mmol of **35** and 0.15 mmol of **36** in 0.5 mL solvent with a 300 W mercury lamp under argon for 10 h. [b]The yield was determined by GC/MS.

examined (Table 5). Different substituents such as phenyl (**37**), methyl (**38**), methoxy (**39**, **40**), ester (**41**), −CN (**42**), and −Cl (**45**) can all be tolerated. Both the 2 and 4 positions of the quinoline can be alkylated in good yields (**44**−**49**). Besides the quinoline, a wide range of heteroarenes such as pyridine (**50**), benzothiazole (**51**), acridine (**52**), phenanthridine (**53**), caffeine (**54**), and purine (**55**) can also be tolerated. Unfortunately, the regular electron-deficient arenes such as ethyl benzoate and benzonitrile are not applicable to this protocol. Regarding the substrates with more than one reactive site, different regioisomers could be detected (**56**, **57**) (Table 5).

Subsequently, other alkyl substituents were also evaluated (Table 6). It was found that primary (**58**−**60**, **68**), secondary (**61**, **65**−**67**), and tertiary alkyl groups (**62**) can all alkylate the heteroarenes in good yields (32−72%) even with only 1.5 equiv of alkylation reagents. Interestingly, benzyl (**63**) and methyl groups (**64**) are not applicable in this alkylation reaction. The failure to produce **63** is perhaps due to the relative high stability of benzyl radical, which would undergo other side reactions faster than the desired radical addition. The fact that methyl radical is not suitable in this reaction (**64**) is perhaps due to its high energy, which makes its generation via this approach difficult.[134]

3. CONCLUSION

Although the Norrish type I reaction has been uncovered for more than 80 years, synthetic examples to apply this reaction, especially in an intermolecular version, are rare. Herein, we demonstrated such a synthetic application via the Norrish type I concept. The benefit via the Norrish type I process is to generate alkyl radical without redox process, implying that the SET initiators and external redox reagents can be avoided. Consequently, a general approach to trifluoromethylate and alkylate (hetero)aromatics in a redox-neutral manner without any catalyst was developed. Notably, the trifluoromethylation can be conducted at room temperature via a household CFL as

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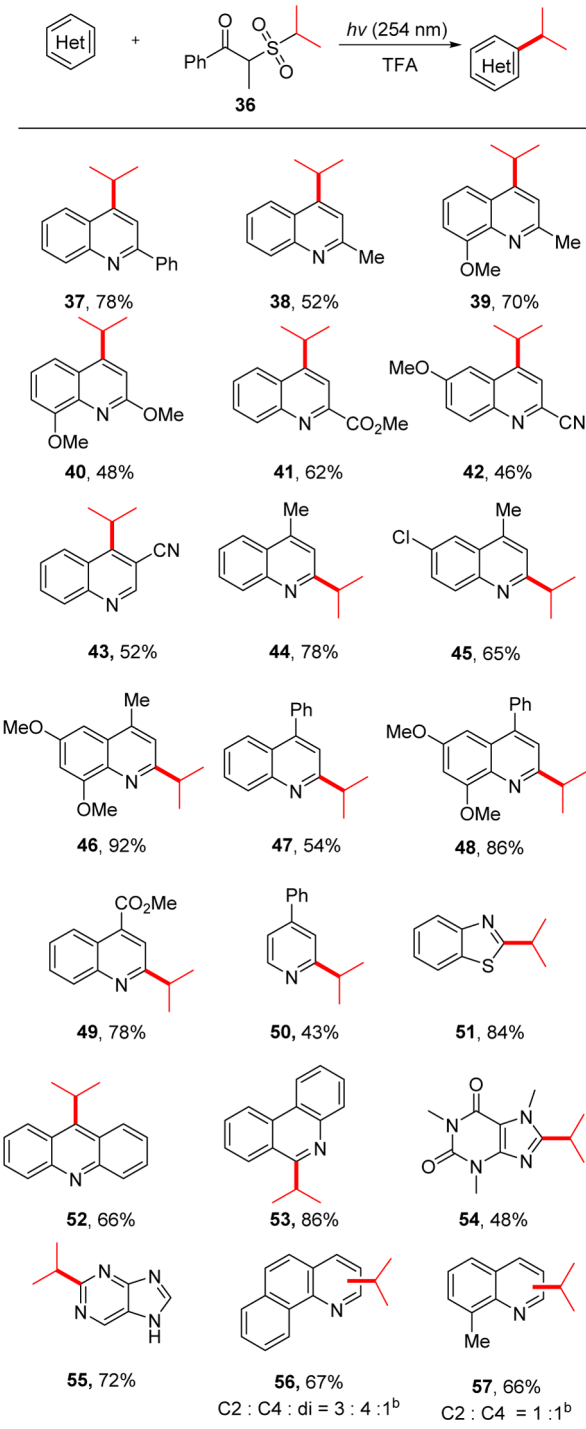
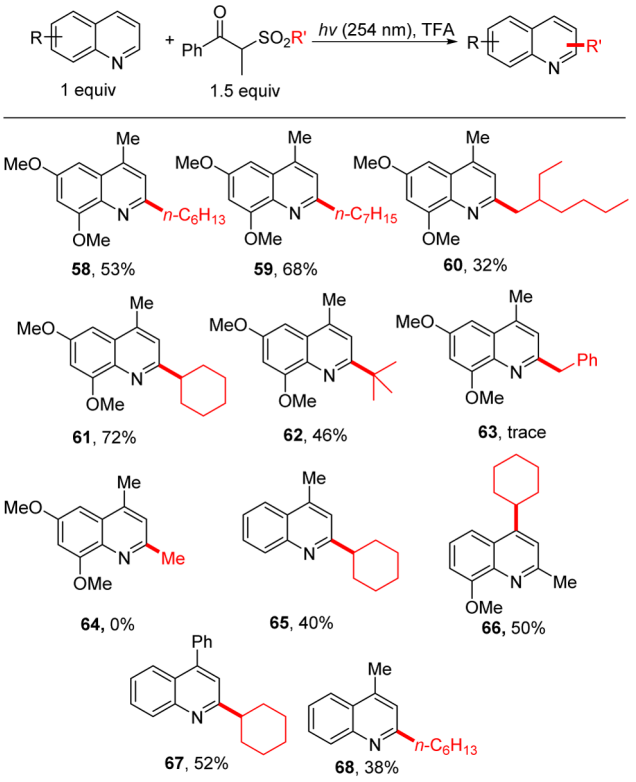
Table 5. Scope of the Heteroarenes for the Alkylation[a]



[a]All the reactions were conducted with 0.1 mmol heteroarene, 0.12 mmol of **36** in 0.5 mL of acetone with a 300 W mercury lamp under argon for 10 h. [b]isolated yield and the ratio of different isomers for **56** and **57** was determined by GC/MS.

Table 6. Scope of the Alkyl Groups for the Alkylation[a]



[a]All the reactions were conducted with 0.1 mmol of heteroarene and 0.15 mmol of alkylation reagents in 0.5 mL of acetone with a 300 W mercury lamp under argon for 10 h, and the yields are isolated ones.

the light source. The success of this approach hinges upon the identification of a series of sulfone compounds, which can be homolytically cleaved under light irradiation. These trifluoromethylation and alkylation reagents are stable to air and water, are soluble in all common organic solvents, and can be readily synthesized from cheap starting materials.[130,135−139] Despite these advantages, some limitations are still associated with this protocol, one of which is the involvement of UV light. The generation of UV light requires relatively special equipment compared to the photoredox chemistry. Reagents that are active under the visible light region are more ideal. Nonetheless, it is hoped that these compounds would find potential applications in other radical-involved reactions with the benefit to avoid the catalysts and external oxidants or reductants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b08685.

Experimental procedures, characterization data, NMR spectra, photographs of lamp used in the study, UV-vis absorption spectrum of compound **36**, and optimization of trifluoromethylation with CFL light source (PDF)

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Author Contributions

[§]P. Liu and W. Liu contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(82) For example, in ref 52, in order to use alkyl bromide as the alkyl radical source under UV light, gold photocatalyst has to be present to reduce the bromine radical to bromide, which would not compete with alkyl radical. The control experiments show that the absence of gold photoredox catalyst would not produce any Minisci product.
(83) These side reactions include (1) aromatic halogenation and (2) hydrogen abstraction by the halogen radical. Both side reactions would consume the starting materials, which make the reaction mixture messy.
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