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Author manuscript
Chem Commun (Camb). Author manuscript; available in PMC 2020 July 07.

Published in final edited form as:
Chem Commun (Camb). 2019 July 07; 55(53): 7599–7602. doi:10.1039/c9cc04265b.

Metal-Free Defluorinative Arylation of Trifluoromethyl Alkenes via Photoredox Catalysis

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Abstract

Literature methods to access *gem*-difluoroalkenes are largely limited to harsh, organometallic-based methods, and known photoredox mediated processes are not amenable to aryl radical addition to trifluoromethyl alkenes. A mild, metal-free, functional group-tolerant method for the preparation of benzylic *gem*-difluoroalkenes is described. The combination of organic dye photocatalyst and silanol reductant enables halogen atom abstration from (hetero)aryl halides to generate aryl radicals that undergo a defluorinative arylation of α-trifluoromethyl alkenes. A breadth of electronically disparate aryl radicals and α-trifluoromethyl alkenes are effective under the developed conditions, which demonstrates high functional group compatibility and allows access to structures previously untenable under traditional transition metal-mediated methods.

Introduction

The incorporation of fluorinated motifs into organic structures is an ever-growing field of organic chemistry. It is a well-established and often-utilized strategy to introduce fluorine into organic molecules to impart desirable pharmacological properties. These properties include increased metabolic stability, enhanced lipophilicity, and improved bioavailability.[1] As such, methods for the synthesis of new and unusual fluorinated groups continue to increase in relevance.[2] Most importantly, there is a great need for methods that afford the incorporation or modification of fluorinated groups under mild conditions to maximize potential feasibility in late-stage functionalization.

One functional group of interest for medicinal chemistry is the geminally-substituted difluoroalkene. These structures are postulated as isosteres for carbonyl groups, and are particularly attractive when metabolism at a carbonyl is a point of undesirable metabolic degradation.[3] Although methods for the synthesis of *gem*-difluoroalkenes have been described,[4] they rely on two-electron chemistry and can be largely classified as either the direct conversion of carbonyls into *gem*-difluoroalkenes or as the modification of an existing fluorinated group. In the context of the addition of aryl groups to trifluoromethyl alkenes, these methods are limited to two-electron additions of organometallic species such as

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Conflicts of interest
There are no conflicts to declare.

phenyllithium and phenylcopper reagents.[5] To date, milder, more functional group-tolerant arylation conditions have not been described, representing an important methodological gap.

Recent work by our group and others has included the development of photoredox-mediated approaches for the synthesis of *gem*-difluoroalkenes.[6] Several classes of radical precursors have been leveraged through this approach, including alkyltrifluoroborates, alkylbis(catecholato)silicates, α–silylamines, and alkyl carboxylate salts (Scheme 1). These radical precursors are effective for the generation of alkyl radicals displaying diverse functional groups; however, these methods are not feasible for arylation, as aryl radicals have elevated oxidation potentials outside the range of many common photocatalysts.[7] The present work demonstrates the first photoredox-catalyzed arylation of trifluoromethyl alkenes using (hetero)aryl halides as a radical source.

An established pathway for the formation of aryl radicals in photoredox catalysis follows a one-electron reduction of aryl halides (**I**), facilitated by oxidative quenching of an excited photocatalyst ([**PC**]*) (Scheme 2).[8] As demonstrated by the groups of Jui, Lee, and others, these reductively generated radicals (**II**) can engage in Giese-type additions to alkenes.[8,9] Then, in a redox-neutral radical polar crossover (RPC) manifold, the photocatalyst cycle is completed by oxidation of radical intermediate **III** to regenerate the photocatalyst and form cationic species **IV**.[9,10] Intermediate **IV** could then react further by either a base-mediated elimination to re-form an alkene or by nucleophilic attack at the cationic carbon. However, a cationic intermediate would not be viable for the E1cb fluoride elimination needed to produce the desired *gem*-difluoroalkene product.

To access the anionic intermediate necessary for fluoride elimination (Scheme 3, **XI**) we envisioned generating aryl radicals through a net reductive pathway. A recent report by the MacMillan group demonstrated the feasibility of using tris(trimethylsilyl)silanol (**V**) as an activator of aryl halides (Ep = +1.54 V versus SCE).[11] We proposed that use of **V**, which alters the sequence of single electron transfer (SET) events so that a reductive quenching photocatalytic cycle occurs, would generate aryl radicals in a reducing environment capable of accessing the anionic intermediate **XI** needed for fluoride elimination.

We proposed that the catalytic cycle would be initiated by base-mediated deprotonation of silanol **V** to give **VI**. Then, oxidation by the photocatalyst followed by a radical Brook rearrangement generates silyl radical **VIII**. The silyl radical next abstracts a halogen atom from aryl halide **I** to afford aryl radical **II**, which adds to the trifluoromethyl alkene **IX**. The photocatalytic cycle is closed by a reduction of species **X** to the α–trifluoromethyl anion **XI**, and finally an E1cb elimination of fluoride generates the desired product **XII**.[12]

With the aid of high throughput experimentation, the reaction conditions were evaluated (Table 1) (see Supporting Information for additional details). Photocatalyst screening revealed the organic photocatalyst 2,4,5,6-tetrakis(3,6-dichloro-9H-carbazol-9-yl)isophthalonitrile (Cl-4CzIPN, Ep = +1.71 V versus SCE) gave the highest formation of desired product, even when compared to commonly used iridium photocatalysts.[13] The evaluation of various solvents identified polar aprotic solvents as most suitable, with DMSO giving the highest conversion. A screening of inorganic bases saw Na_2CO_3 provide optimal product formation. Control studies confirmed the necessity of each reaction component. Without photocatalyst or silanol, no reaction, whether undesired or otherwise, was observed. Without base, which is important for silanol activation, only trace product was formed. Finally, when the reaction was allowed to run in ambient light, no reactivity was observed.

Having identified optimal conditions, the scope of the reaction was evaluated (Table 2). The reaction was optimized with the electron deficient aryl nitrile (**2a**), and as expected good reactivity was observed with other electron-poor substrates such as an aryl ketone (**2g**) and ester (**2l**). The reaction was also amenable to the addition of several electron-rich aryl radicals (**2d**, **2h**, **2i**). Further experiments demonstrated moderate to good yields with meta- and para-substituted aryl methoxy halides (**2h** and **2i**), albeit with marginally lower isolated yields. More impressively, the conditions were also amenable toward a variety of heteroaryl halides, including several substituted pyridines (**2b**, **2c**, **2f**, **2j**, **2k**) and even an unprotected indole (**2d**). Importantly, both aryl iodides and -bromides are substrates, allowing facile, direct access to numerous aryl radicals from commercially available reagents. Example **2k** demonstrates the selectivity observed in the presence of both aryl bromides and -iodides, with radical generation in the ratio of 7.6:1 favoring reactivity at the iodide.

We then sought to explore the scope of the method with respect to the trifluoromethyl alkene substrate. In addition to the dioxole substrate used in optimization, the standard conditions were applicable to other electron-rich trifluoromethylalkenes. These included dimethoxy- (**2s**), dimethylamino- (**2t**), thioether- (**2o**), and *tert*-butyl-substituted (**2u**) trifluoromethyl alkenes. Electron poor substrates were also reactive, affording the corresponding products in moderate to good yields. The dichloro-substituted alkene (**2m**) is one example of this, and also demonstrates that the method is chemoselective for the activation of aryl iodides and bromides in the presence of aryl chlorides.[14] The reaction also tolerated an appended alkyne (**2v**) and carboxylic acid (**2x**), with no evidence of undesired side-reactivity. Additionally, this method is viable on substrates with unprotected alcohols (**2p**). Other notable examples of the substrate scope include the expansion of this method to heteroaryl trifluoromethyl alkenes (**2q**, **2r**, **2w**). The reaction was also successful when performed on a 2.5 mmol scale, although a longer reaction time was necessary (**2a**, Table 2).

During the course of the scope exploration, interesting reactivity was noted in the case of the exceptionally electron deficient example **2b** (Scheme 4). When the standard conditions using two equivalents of aryl bromide were used, a significant portion of double addition product was observed (**3a**). This product results from the addition of a second aryl radical to the *gem*-difluoroalkene, where reduction and a second fluoride elimination furnishes the monofluoroalkene. Fluorinated triarylalkenes are themselves relevant to medicinal chemists as they are known anticancer agents in the family of tamoxifen derivatives.[15] A second interesting observation was made while developing the reaction workup conditions. It was found that when electron poor compounds were eluted through a plug of KF/alumina, a rearrangement occurred to convert the *gem*-difluoroalkene to a difluoromethyl-substituted internal alkene (**3b**). Moderate amounts of this alkene rearrangement was observed even when exposure to the KF/alumina was limited to only 30 s. When the sample was stirred in KF/alumina for 3 h, complete conversion to the internal alkene was observed. These two products demonstrate the utility of the trifluoromethyl alkenes prepared here as starting materials for a diverse array of functionalization reactions.

Conclusions

Methods to access structurally diverse fluorinated molecules have gained significant prominence in recent years. Photoredox catalysis has offered unique opportunities for achieving such transformations with mild reaction conditions and high functional group compatibility. The reported method offers an efficient, metal-free approach to achieve the arylation of trifluoromethyl alkenes to make a new class of substituted *gem*-difluoroalkenes that were previously inaccessible under such mild conditions, and thus represents a step forward in our ability to synthesize and modify useful fluorinated motifs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We sincerely thank Dr. John Milligan of the University of Pennsylvania and Dr. Christopher Kelly of Virginia Commonwealth University for useful discussion. We thank Dr. Charles Hendrick for his assistance in the Penn Merck High Throughput Experimentation Center. We thank Dr. Charles W. Ross, III for assistance in obtaining HRMS data. We thank Dr. Jun Gu and Prof. Bill Dailey for helpful insight into ^{19}F NMR data.

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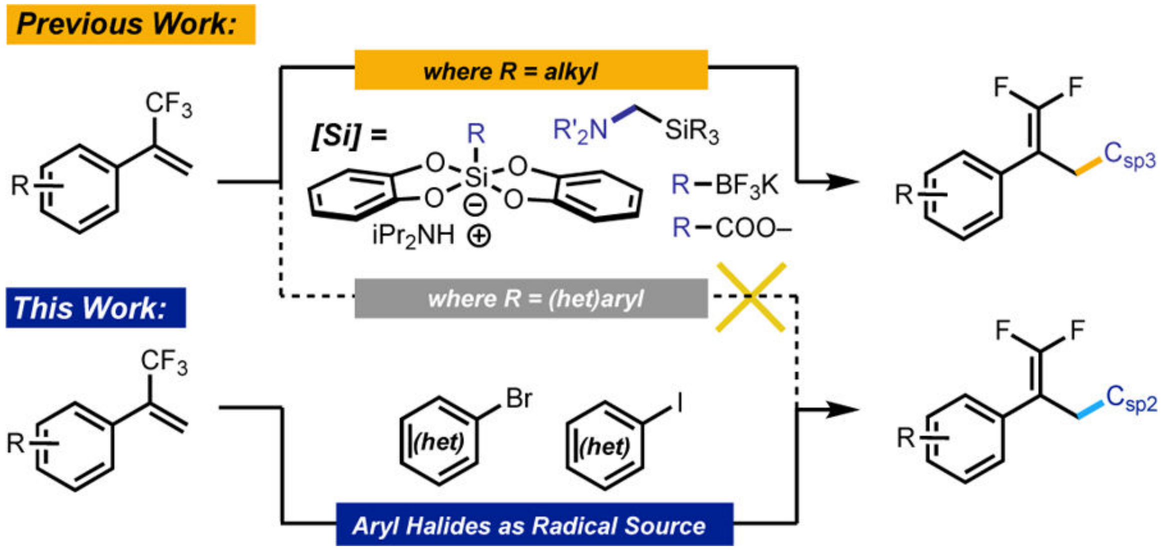
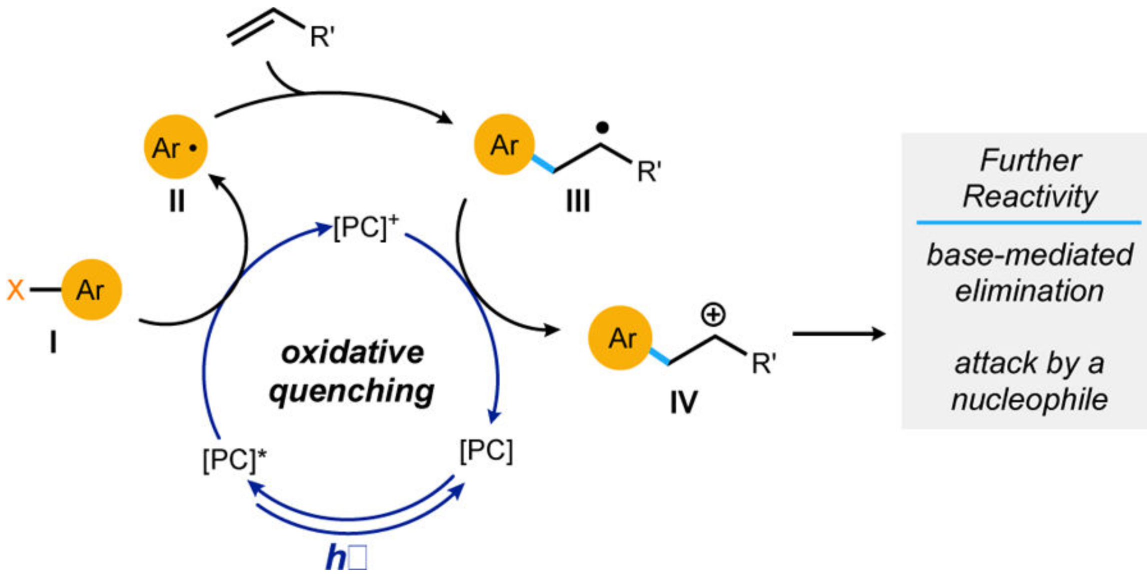
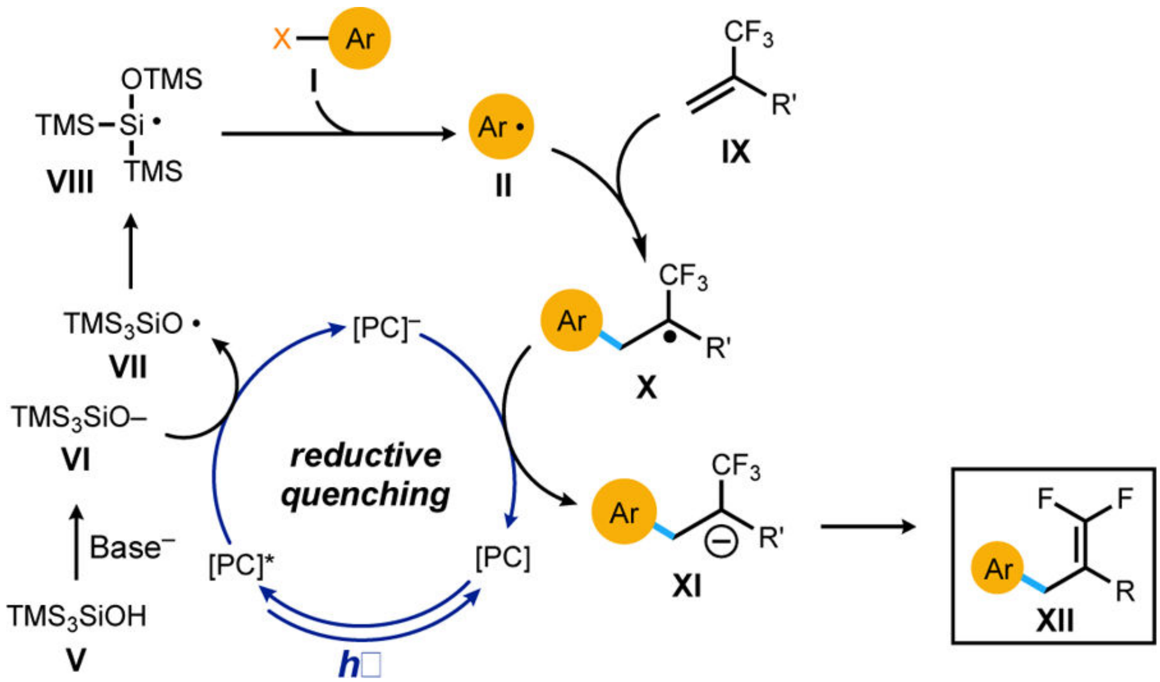


Scheme 1.

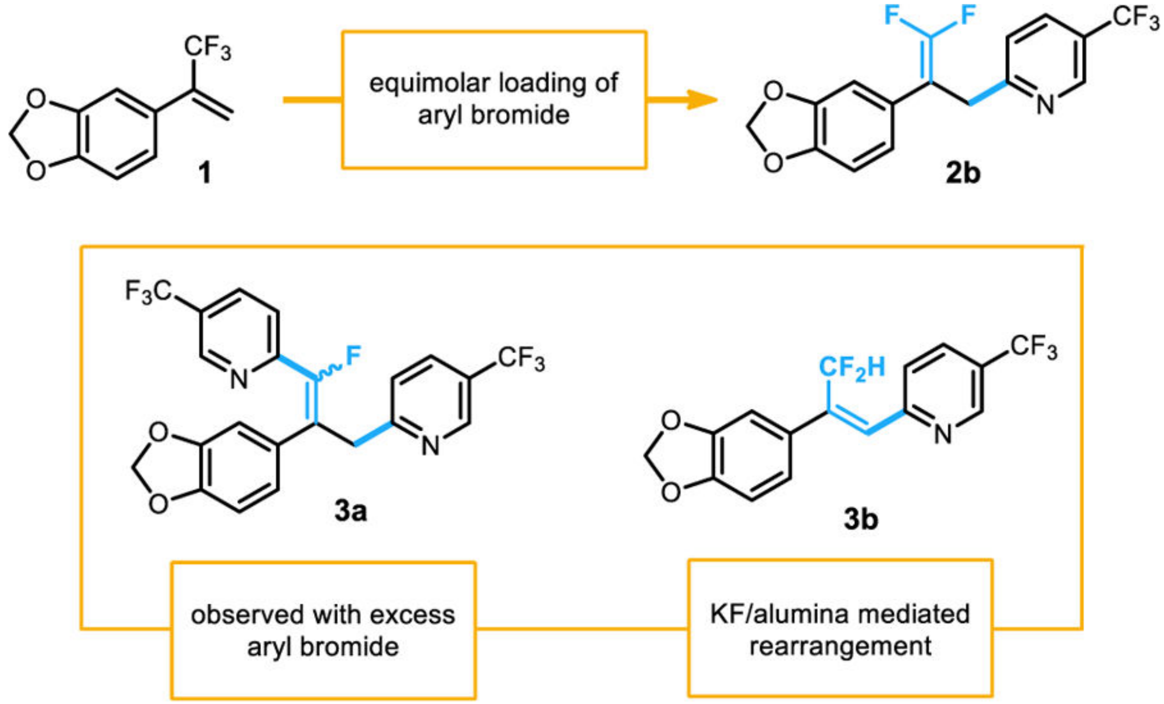
Arylation of trifluoromethyl alkenes through a new pathway



Scheme 2.
Net-neutral radical polar crossover via oxidative quenching photocatalysis



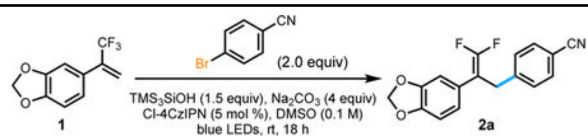
Scheme 3.
Mechanism for silanol-mediated radical polar crossover



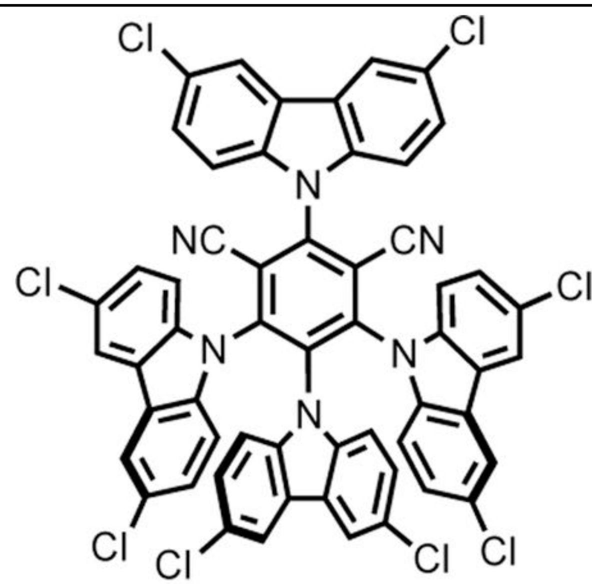
Scheme 4.
Unusual experimental observations and side reactivity

Table 1.

Reaction optimization and control studies



Entry	Deviation from Standard	Conversion[a]
1	**None**	**92**
2	**[Ir{dF(CF_3)ppy}$_2$(dCF_3bpy)](PF_6)**	**59**
3	**acetone**	**77**
4	MeCN	**32**
5	DMF	**32**
6	NaOAc	**92**[b]
7	K3PO4	**49**
8	None	**98**
9	NO CI-4CzIPN	**0**
10	NO TMS_3SiOH	**0**
11	**No base**	**< 5**
12	**No LEDs**	**0**



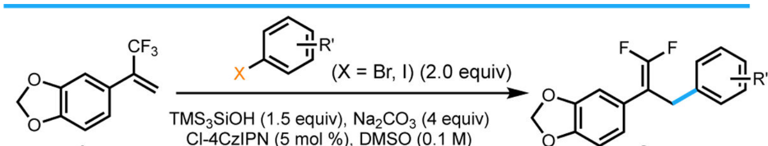
Cl-4CzIPN

[a]Conversions determined by ^{19}F NMR of crude reaction mixtures.

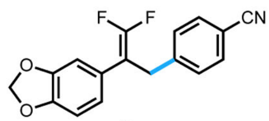
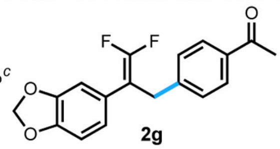
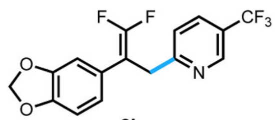
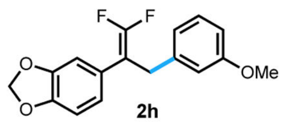
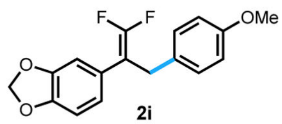
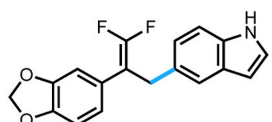
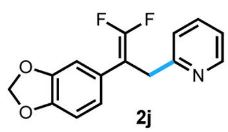
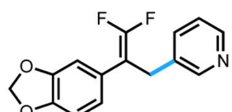
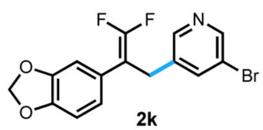
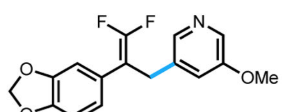
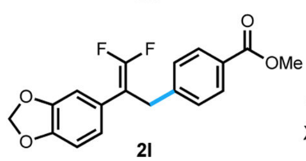
[b]Conversion to product was observed with full consumption of starting materials with the formation of unidentified reaction byproducts.

Table 2.

Aryl radical scope[a,b]



1 → 2

Product	Yield	Product	Yield
 **2a**	75%, 70%[c] X = Br	 **2g**	73%[g] X = I
 **2b**	71%[e,h] X = Br	 **2h**	60%[e] X = Br
 **2c**	82% X = Br	 **2i**	63%[d] X = Br
 **2d**	79%[d,f] X = I	 **2j**	67%[e,h] X = I
 **2e**	79%[d,g] X = I	 **2k**	46%[f,i] X = I
 **2f**	60% X = Br	 **2l**	78%[d] X = Br

[a]All values indicate the yield of the isolated product.

[b]General reaction conditions: aryl halide (2.0 equiv, 1.0 mmol), alkene (1.0 equiv, 0.50 mmol), Cl-4CzIPN (5 mol %, 0.025 mmol), TMS_3SiOH (1.5 equiv, 0.75 mmol), Na_2CO_3 (4 equiv, 2.0 mmol), DMSO (0.1 M), 18 h, irradiating with blue LEDs (30 W). See the Supporting Information for details.

[c]Isolated yield on 2.5 mmol scale; reaction run for 5 d.

[d]Isolated on 1.0 mmol scale.

[e]Isolated yield on 0.3 mmol scale.

[f]Conducted using 10 mol % Cl-4CzIPN.

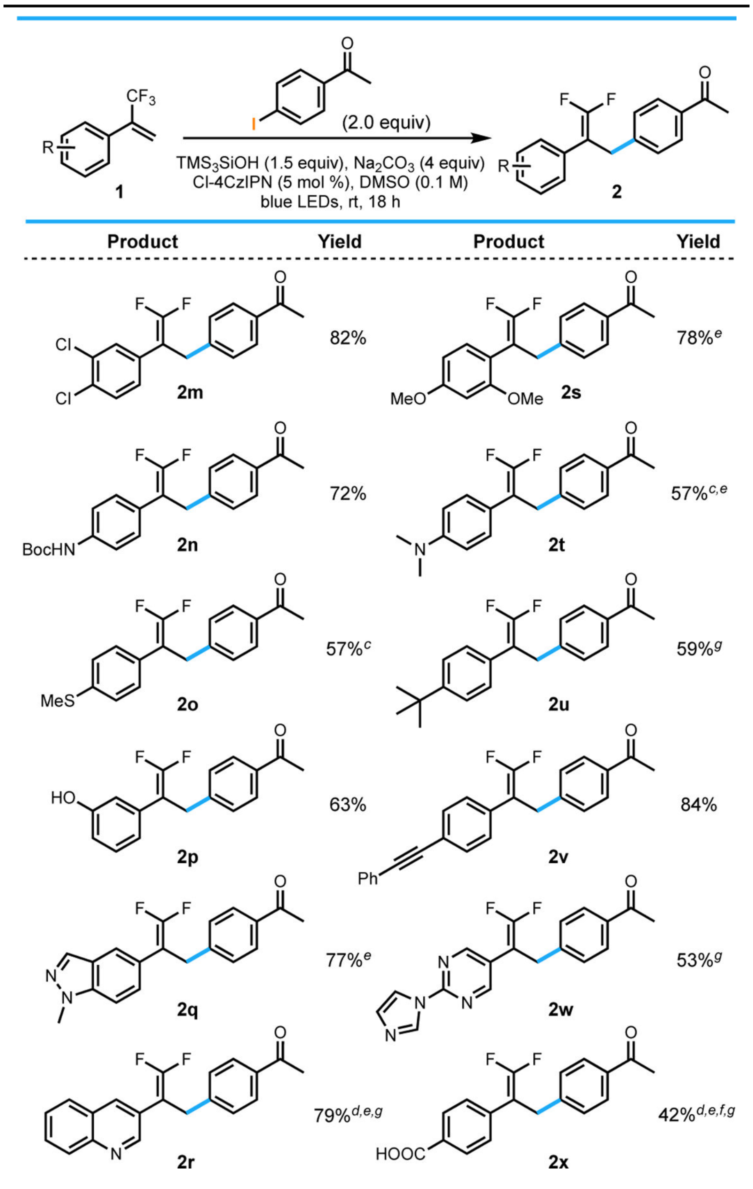
[g]Reaction run for 2 d.

[h]Conducted using 1 equiv Ar–X. [h]Isolated with <5% impurity of alkene.

[i]Isolated as a 7.6:1 mixture of Br:I arene.

Table 3.

Trifluoromethyl alkene scope.[a,b]



[a] All values indicate the yield of the isolated product.

[b] General reaction conditions: aryl halide (2.0 equiv, 1.0 mmol), alkene (1.0 equiv, 0.50 mmol), Cl-4CzIPN (5 mol %, 0.025 mmol), TMS_3SiOH (1.5 equiv, 0.75 mmol), Na_2CO_3 (4 equiv, 2.0 mmol), DMSO (0.1 M), 18 h, irradiating with blue LEDs (30 W). See the Supporting Information for details.

[c] Isolated on 1.0 mmol scale.

[d] Conducted using 10 mol % Cl-4CzIPN.

[e] Reaction run for 2 d.

[f]Conducted using 3 equiv Ar–X and 2.0 equiv TMS_3SiOH.

[g]Isolated with <5% impurity of alkene.