CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201302407

# Visible-Light-Induced Trifluoromethylation of *N*-Aryl Acrylamides: A Convenient and Effective Method To Synthesize $CF_3$-Containing Oxindoles Bearing a Quaternary Carbon Center

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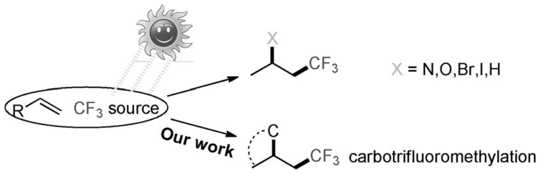
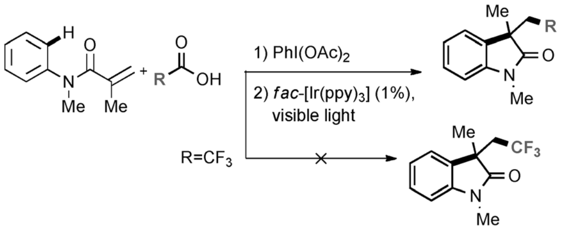
The incorporation of the trifluoromethyl group into organic molecules has becoming a hot topic, as trifluoromethylated compounds possess unique physical properties and biological activities.[1] Over the past decade, various trifluoromethylation strategies have been reported using "$CF_3^+$" or "$CF_3^-$" reagents,[2] and these strategies can be mainly classified into three types: nucleophilic,[3] electrophilic,[4] and radical trifluoromethylation.[5] Among these protocols, radical transformation has been developed as a highly promising synthetic transformation and attracted considerable attention.

In the past 5 years, visible-light photoredox catalysis has emerged as a powerful and ecofriendly synthetic tool from the viewpoint of cost, safety, and availability.[6] Visible-light-induced radical difunctionalization of alkenes serves as an efficient and feasible method to introduce the trifluoromethyl group into molecular skeletons.[7] Despite extensive progress in alkene difunctionalization, transformations involving $C_{sp^3}$–$CF_3$ bond formation are limited to halotrifluoromethylation,[7a,b] oxytrifluoromethylation,[7d,f] aminotrifluoromethylation,[7f,i] and hydrotrifluoromethylation[7g,j] (Scheme 1). To the best of our knowledge, visible-light-promoted carbotrifluoromethylation of electron-withdrawing alkenes has not been reported.[8] Herein, we document our recent studies on the visible-light-promoted tandem carbotrifluoromethylation of *N*-aryl acrylamide derivatives.



Scheme 1. Visible-light-induced radical addition to alkenes involving $C_{sp^3}$–$CF_3$ bond formation.

Very recently, we have reported an excellent visible-light-driven protocol for the formation of oxindoles containing a quaternary carbon atom by coupling diverse aliphatic carboxylic acids with *N*-aryl acrylamide derivatives (Scheme 2).[9a,b,10] Trifluoroacetic acid was examined under the optimized reaction conditions. Unfortunately, no expected product was obtained. As the importance of $CF_3$-containing oxindoles containing a quaternary carbon atom in natural products[11] and our continuing interest in photoredox catalysis,[12] we focused our attention on Togni's reagent,[13] an easy-to-handle $CF_3^+$ reagent, which has been reported to generate a $CF_3$ radical in the presence of photoredox catalysts.[7d] When a solution of *N*-aryl acrylamide **1a** and Togni's reagent in *N*,*N*-dimethylformamide (DMF) was irradiated by 5 W blue LEDs (light-emitting diode strips, $\lambda_{max} = 455$ nm) in the presence of $[Ru(bpy)_3Cl_2]$ (bpy = 2,2′-bipyridine) as a catalyst, the tandem trifluoromethylation/arylation reaction occurred with a low yield of 32% (Table 1, entry 1). Encouraged by this delightful result, the influence of photocatalysts and solvents on the tandem trifluoromethylation/arylation reaction was further investigated.



Scheme 2. Visible-light-mediated protocol for preparing oxindoles bearing a quaternary carbon atom.

Firstly, DMF was used as solvent, and the corresponding results were listed in Table 1. Among the photocatalysts tested, *fac*-$[Ir(ppy)_3]$ and $[Ru(phen)_3Cl_2]$ (phen = phenanthroline) showed the best catalytic efficiency (Table 1, entries 1–5). Considering the lower cost of ruthenium, $[Ru(phen)_3Cl_2]$ was the preferred catalyst. The choice of sol-

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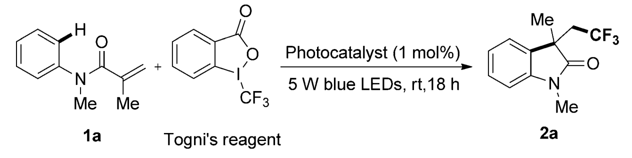
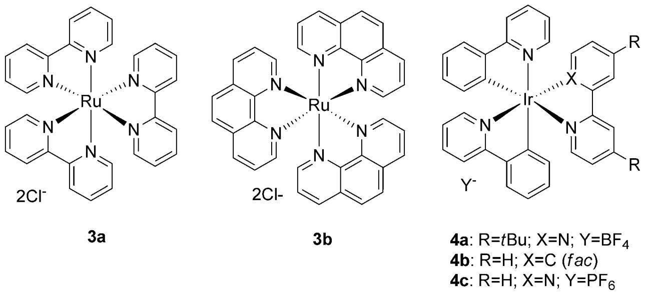
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302407.

Table 1. Optimization of reaction conditions.[a]





| Entry | Photocatalyst | Solvent | Yield [%][b] |
|---|---|---|---|
| 1 | **3a** | DMF | 32 |
| 2 | **3b** | DMF | 73 |
| 3 | **4a** | DMF | 36 |
| 4 | **4b** | DMF | 73 |
| 5 | **4c** | DMF | 50 |
| 6 | **3b** | $CH_2Cl_2$ | 86 (82)[c] |
| 7 | **3b** | DMSO | 51 |
| 8 | **3b** | $CH_3CN$ | 23 |
| 9[d] | **3b** | $CH_2Cl_2$ | 76 |
| 10[e] | **3b** | $CH_2Cl_2$ | 83 |
| 11[f] | **3b** | $CH_2Cl_2$ | 74 |
| 12[g] | **3b** | $CH_2Cl_2$ | 0 |
| 13 | – | $CH_2Cl_2$ | 0 |

[a] Reaction conditions: **1a** (0.2 mmol), Togni's reagent (0.4 mmol), photocatalyst (1 mol %), solvent (2 mL), 5 W blue LEDs light, RT. [b] Determined by $^{19}$F NMR analysis of the reaction mixture using 4-(trifluoromethyl)-acetophenone as an internal standard. [c] Yield of isolated product. [d] 35 W fluorescent light bulb was used instead of 5 W blue LEDs. [e] 1 equiv $Na_2HPO_4$ was added. [f] 1 equiv $Et_3N$ was added. [g] In the dark. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

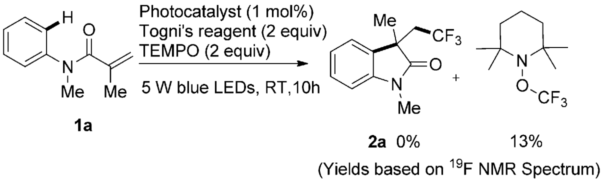
vents was important for the transformation. It was found that when $CH_2Cl_2$ was used as the solvent, a satisfactory yield of 83 % could be obtained (Table 1, entries 6–8). The use of a fluorescent light bulb (35 W) did not improve the reaction (Table 1, entry 9). When additives ($Na_2HPO_4$ and $Et_3N$) were used, the yield was somewhat decreased (Table 1, entries 10 and 11). Control experiments indicated that both light and photocatalyst were essential to the success of the tandem trifluoromethylation/arylation reaction (Table 1, entries 12 and 13). Consequently, the optimized reaction conditions are the use of 1 mol % [Ru(phen)$_3$Cl$_2$], a 5 W blue LED, and $CH_2Cl_2$ as solvent.

With the optimized reaction conditions established, we turned our attention to an evaluation of the scope of the visible-light-promoted process with a range of different *N*-aryl acrylamide derivatives (Table 2). Substrates with different N-protecting groups were employed and the desired products could be obtained in 72–88 % (**2a**–**e**). Much to our surprise, the use of a secondary aryl amide did not work at all (**2 f**). Subsequently, the effect of substituents at the N-aryl moiety was examined. The experimental results showed that several *para*-position substituents, such as Cl, Br, I, alkyl, and MeO groups, were well tolerated under the optimized reaction conditions and **2g**–**k** were obtained in high yields. With substituent groups at the *ortho* position of the *N*-aryl acrylamides, a lower yield was observed owing to the strong steric-bulk effect (**2l**). In addition, substrates bearing a *meta* substituent (**1m** and **1n**) showed good reactivity; however, although the transformation in the case of **1n** was regioselective, giving **2n** in 85 % yield, that for **1m** was poorly regioselective in that isomers **2m** and **2m′** were obtained in a ratio of 1:1. Moreover, 3,5-disubstituted *N*- aryl amides also underwent the tandem reaction smoothly (**2o** and **2p**). When an N-naphthalene amide was used as a substrate, desired oxindole **2q** could be isolated in 70 % yield.

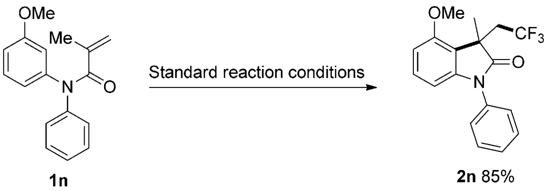
Next, various substituted alkenes were investigated. The use of α-substituted olefins bearing different functional groups, such as benzyl (**2r**), phenyl (**2s**), hydroxy (**2t**), ester (**2u**), and phthalimide (**2v**) groups did not uniformly furnish the desired products in good yields. Notably, the tandem radical-addition process had excellent chemoselectivity. Only the desired product was obtained when using a substrate containing two different alkene groups (**2w**). Lastly, using heterocyclic substrates **2x** and **2y**, the tandem trifluoromethylation/arylation reaction proceeded to give the desired products in moderate yields.

To demonstrate the scalability of this protocol, the reaction was carried out on a mole scale under the standard reaction conditions. The reaction could also be obtained with a moderate yield (see the Supporting Information, Scheme S1).

To get an insight into the possible mechanism, the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added in the reaction system. It was found that little product was detected, a result that gave further support to the addition to the alkene being a radical process (see [Eq. (1)] and the Supporting Information, Scheme S2. Then, **1n** was chosen as a substrate for an intramolecular competition experiment [Eq. (2)]. The cyclization reaction involved functionalization of the aromatic ring bearing the electron-donating methoxy group and gave a single product, **2n**, in

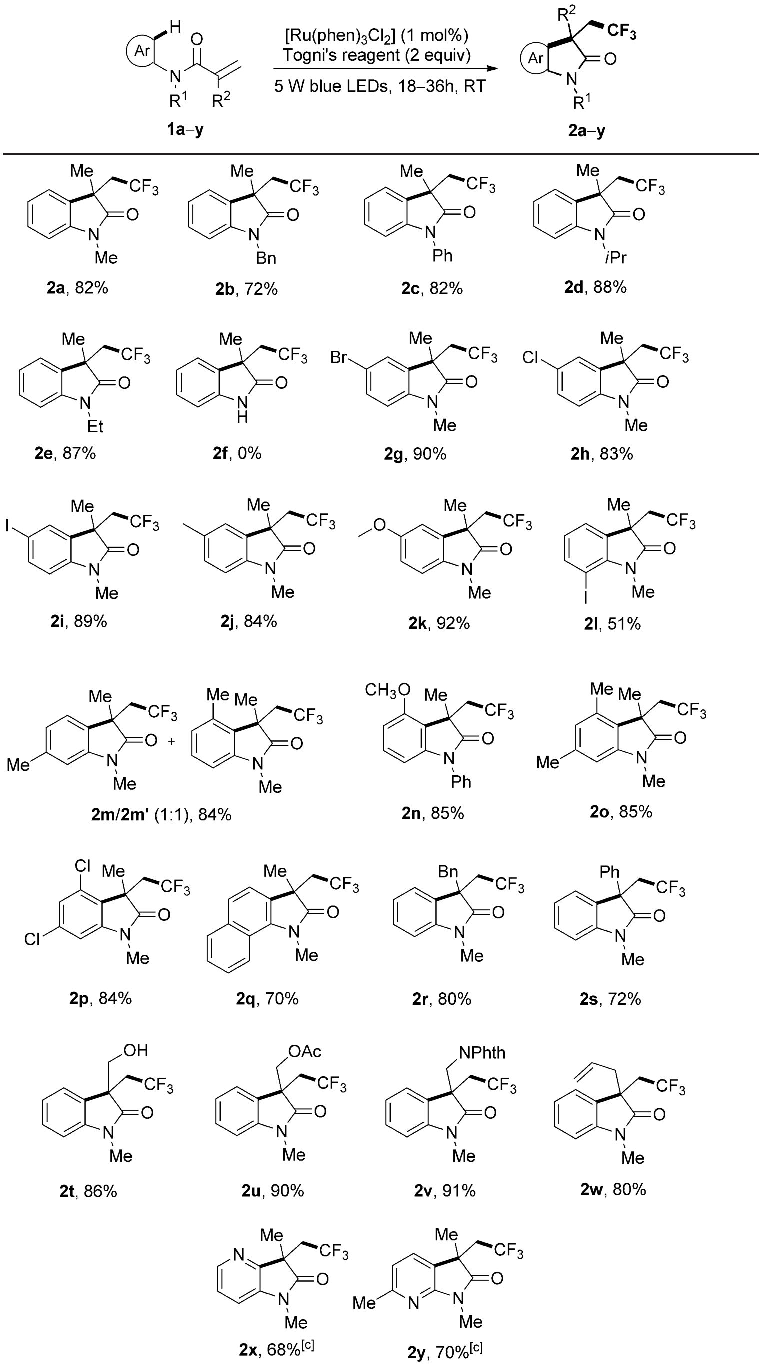


(1)



(2)

Table 2. Scope of substrates.[a,b]



[a] The reactions were carried out with [Ru(phen)$_3$Cl$_2$] (1 mol%) and Togni's reagent (2 equiv) in CH$_2$Cl$_2$ at room temperature, 5 W blue LEDs, 18 h, unless otherwise mentioned. [b] Yield of isolated product. [c] 36 h.

85% yield. This regioselectivity suggested that the catalytic cycle may involve a cationic intermediate whose stability was effected by the substituents on the aromatic ring and that the process of generating this cationic intermediate may be the rate limiting.

Based on the above results, a possible reaction mechanism is shown in Scheme 3. Firstly, the excited state, [Ru(phen)$_3$]$^{2+*}$ (**5**), is formed under the irradiation by visible light.[14] Togni's reagent is then reduced by **5** to generate the corresponding radical anion, **6**. Rapid collapse of **6** gives 2-iodobenzoate **7** and the relatively stable CF$_3$ radical, **8**. Subsequently, the CF$_3$ radical may undergo a radical C−H functionalization cascade, forming radical intermediate **10**, which is ultimately oxidized to the give key carbocation **11** through a single-electron transfer (SET) process. Finally, deprotonation of **11** by 2-iodobenzoate **7** gives the trifluoromethylation/arylation product **2a**. The generated 2-iodobenzoic acid (**12**) in the last step was detected by $^1$H NMR spectroscopy, a result that supports our hypothesis. Alternatively, a radical chain propagation mechanism cannot be ruled out. However, the transformation requires continuous irradiation of visible light, indicating that chain propagation may be not a mechanistic pathway (Figure 1).

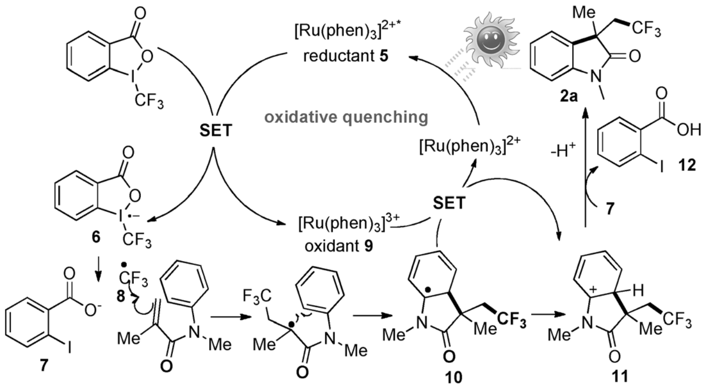
In summary, we have developed the first visible-light-induced tandem trifluoromethylation/arylation of electron-withdrawing alkenes. It provides an effective method to synthesize a variety of CF$_3$-containing oxindoles bearing a quaternary carbon center. Importantly, this protocol is an improvement over existing protocols for the introduction of a trifluoromethyl group through visible-light-induced radical addition to alkenes, because it can be performed at room temperature with a low catalyst loading and without additives. Further explorations on visible-light-mediated trifluoromethylation and associated mechanisms are currently being investigation in our laboratory.

## Experimental Section

**General procedure**: **1a–y** (0.2 mmol), [Ru(phen)$_3$Cl$_2$] (0.01 equiv), Togni's reagent (2.0 equiv) and dichloromethane (2 mL) were added to an oven-dried Schlenk tube (20 mL) equipped with a magnetic stir bar. The tube was degassed by alternating vacuum evacuation (5 min) and argon backfill (three times). The tube was placed at a distance of ca. 5 cm from the 5 W blue LEDs and the resulting red solution was stirred at ambient temperature under visible-light irradiation. When the reaction finished, the mixture was purified directly by flash chromatography (eluent: petroleum ether 60–90/EtOAc, 5:1–2:1 *v*/*v*) on silica gel, yielding the pure product **2a–y**.

## Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21172106, 21074054), the National Basic Research Program of China (2010CB923303), and the Research Fund for the Doctoral Program of Higher Education of China (20120091110010) for their financial support. J. Xie acknowledges receipt of an academic scholarship for doctoral candidates from MOE.



Scheme 3. Proposed mechanism of radical tandem trifluoromethylation/arylation of **1a**, as catalyzed by [Ru(phen)$_3$Cl$_2$].

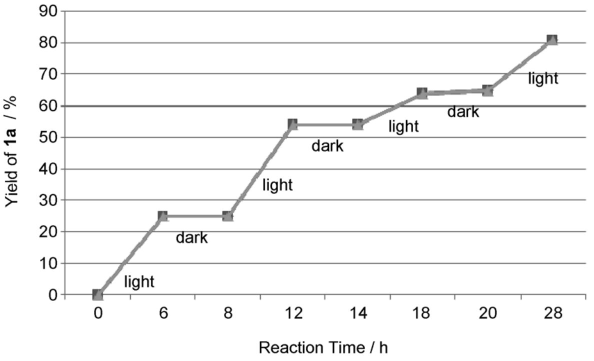


Figure 1. Time profile of trifluoromethylation/arylation of **1a** in the presence and in the absence of light.

**Keywords:** alkenes · photocatalysis · radical addition · synthetic methods · trifluoromethylation

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Received: June 24, 2013