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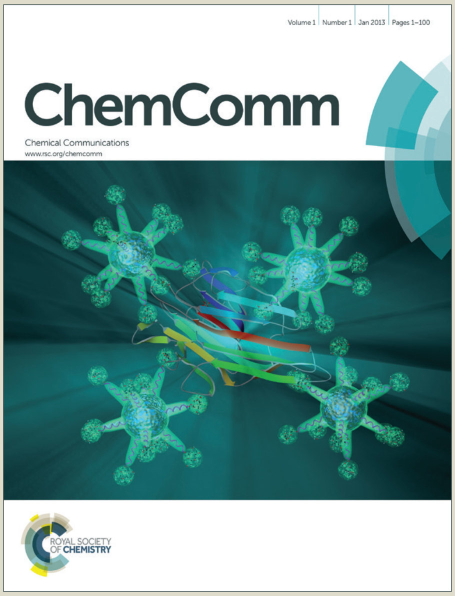

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One pot and selective intermolecular aryl- and heteroaryl-trifluoromethylation of alkenes by photoredox catalysis

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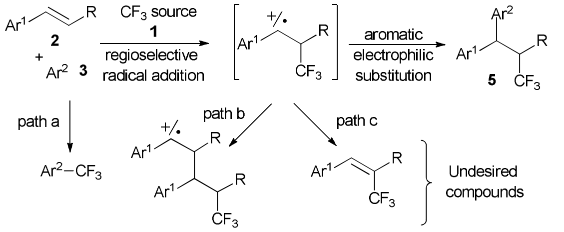
We report herein the first photoredox-catalyzed intermolecular aryl- and heteroaryltrifluoromethylation of alkenes. Under the optimized conditions using Umemoto's reagent as CF_3 source, a wide range of styrenes can be readily difunctionalized, affording the corresponding trifluoromethylated adducts in up to 99% yield.

Tandem vicinal difunctionalization of carbon–carbon double bonds has recently become an attractive and efficient strategy for the construction of two new σ bonds in one step.[1] Among these methods, vicinal trifluoromethylfunctionalization of alkenes[2] has attracted much attention due to the CF_3 group which imparts profound changes in physical, chemical, and biological properties of organic molecules.[3] Thus, many radical trifluoromethylation reactions have been developed in the presence of various nucleophiles, allowing the concomitant formation of C-O,[4] C–X (X = halogen),[5] C–N,[6] or C–H bonds[7] via the trapping of the radical intermediate (or its corresponding oxidized electrophilic cation). The carbotrifluoromethylation, which involves a carbon nucleophile in such radical-cationic processes, has also been studied, especially with arenes as nucleophiles.[8] Although intramolecular aryltrifluoromethylation using photo-[8a,b,d-f] or metal-[8h-j] catalysis have been reported, the development of an intermolecular version of these reactions remains a significant challenge due to: (a) a potential competition between both reactive species (arenes and alkenes) during the trifluoromethylation process (Scheme 1, path a);[9] (b) a problem of polymerization or elimination reaction of the radical or carbocation intermediate (Scheme 1, path b and c). Only one example of intermolecular aryltrifluomethylation of alkenes with aryl boronic acid catalysed by copper with broad scope has been very recently described by Liu et *al.*[10] To our knowledge, the use of arenes as nucleophiles in the intermolecular trifluoromethylation has not been reported. Based on our experience in intermolecular cyanotrifluoromethylation of alkenes using photoredox catalysis,[4k,11,12,13] we envisioned a scenario in which the CF_3 radical generated by visible light photoreduction could selectively react with alkenes and the resulting radical or carbocation intermediate could be trapped by a suitable aryl nucleophile. To this end, we selected styrenes as alkenes. Indeed, the more stable radical or carbocation in benzylic position would be favourably generated, thus allowing a regio- and chemoselective tandem difunctionalization (Scheme 1). In addition, this approach would result in the efficient synthesis of 1,1-diarylalkane motif which is often present in various biologically active compounds.[14] We report herein the first photomediated intermolecular aryltrifluoromethylation of a wide range of styrene derivatives. Importantly, extension of this efficient three-component process to the more challenging heteroaryltrifluoromethylation is furthermore presented.



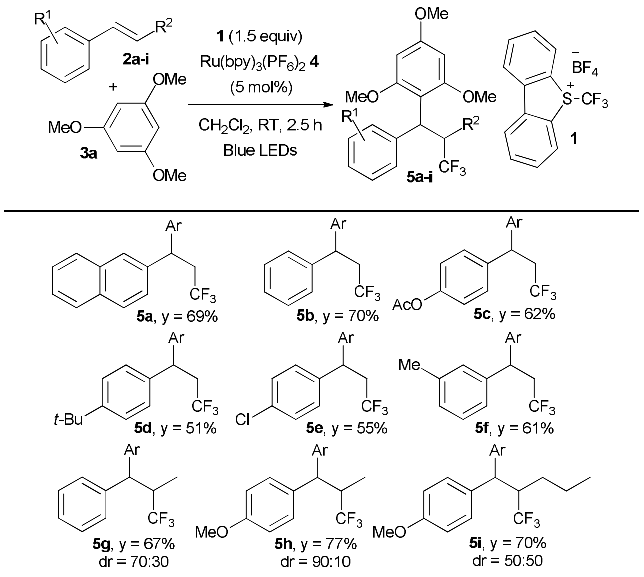
Scheme 1 Synthetic approach and potential side-reactions

Firstly, we examined the reaction of 2-vinylnaphthalene (**2a**), 1,3,5-trimethoxybenzene TMB (**3a**) and Umemoto's reagent **1**[15] as CF_3 source, in presence of $Ru(bpy)_3(PF_6)_2$ photocatalyst **4** under visible light irradiation (5W blue LEDs). After surveying the reaction conditions by varying the catalyst, solvent, temperature, and stoichiometry, we were pleased to find that the reaction performed in CH_2Cl_2 in the presence of 5 mol % of catalyst **4** afforded compound **5a** in 69% yield (see the Supporting Information for details).

With these optimized reaction conditions, the scope of this photoredox-catalyzed intermolecular aryltrifluoromethylation was investigated and the results are summarized in Table 1. The reaction was first performed with styrene derivatives **2a-f** bearing various substituents on the aromatic ring, including electron-withdrawing and electron-donatong groups. Pleasingly, they were all suitable partners for this reaction, leading to the expected α-aryl β-trifluoromethyl products **5a-f** in up to 70% yield.[16] Noteworthy is the perfect regioselectivity observed in the reaction of internal alkenes, such as **2g-i**. Moreover, these styrenes bearing a methyl or propyl group in β position exhibited a slightly higher reactivity compared to terminal alkenes, and reacted smoothly to afford the corresponding trifluoromethylarylated adducts **5g-i** in good yields (67-77%) with moderate diastereoselectivity (from 50:50 to 90:10 dr). It is also worth noting that a variety of functional groups, such as halogen and ester, are compatible with the reaction conditions.

Pleasingly, this novel multi-component protocol was found to be successful with other various nucleophilic aromatic partners

Table 1 Substrate scope of styrene derivatives **2** with TMB[a,b,c]



5a, y = 69%; **5b**, y = 70%; **5c**, y = 62%; **5d**, y = 51%; **5e**, y = 55%; **5f**, y = 61%; **5g**, y = 67%, dr = 70:30; **5h**, y = 77%, dr = 90:10; **5i**, y = 70%, dr = 50:50

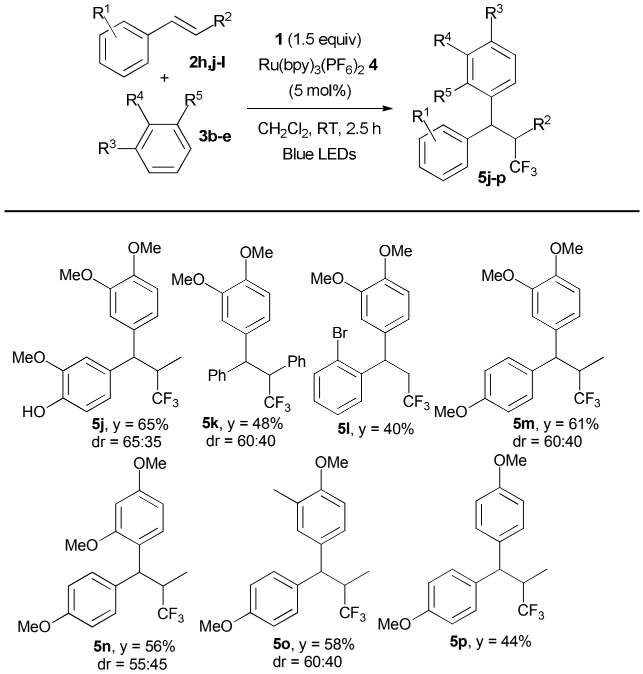
[a] Reaction conditions: styrene **2** (0.10 mmol), **1** (0.15 mmol), TMB **3a** (3 equiv), **4** (0.05 equiv), in CH_2Cl_2 (2.0 mL) irradiated at RT for 2.5 h. [b] Yields referred to chromatographically pure product. [c] dr determined by ^{19}F-NMR analysis of crude mixtures.

(Table 2). Notably, 1,2-dimethoxybenzene (**3b**) readily participated in the reaction with terminal or internal alkenes and afforded the expected α-aryl β-trifluoromethyl compounds **5j-m** in up to 65% yield as single *meta-para* regioisomers. Other nucleophiles such as 1,3-dimethoxybenzene (**3c**) or *ortho*-methylanisole (**3d**) were also efficiently used in this photocatalyzed process, leading to the corresponding aryltrifluoromethylated adducts **5n-o** in 56-58% yield, once again with complete regioselectivity. Remarkably, this reaction could be performed with the less nucleophilic anisole **3e**, albeit with a lower yield (44%). Furthermore, even though an excess of arenes was used, only traces of trifluoromethylated arene were obtained (<15%), which demonstrates the high chemoselectivity and efficiency of our sequence.

Encouraged by these results, we next sought to extend the methodology to "privileged" heteroaryl nucleophiles found in medicinal drugs and natural products such as indoles.[17] To the best of our knowledge, the use of heteroarene partners has never been reported in the case of aryltrifluoromethylation reactions. The results are summarized in Table 3. To our delight, unprotected indole (**3f**) smoothly reacted with *trans*-anethole (**2i**) and Umemoto's reagent **1**, and gave the 3-alkylated indole adduct **5q** in 62% yield. Various substituents in position 5 of the indole scaffold, such as bromine, methoxy or nitro groups, were compatible with the reaction conditions. We observed that the more nucleophilic electron-rich indoles exhibited a better reactivity than electron-poor ones (52 to 66% yield). More interestingly, this photo-catalyzed process was even more efficient with indoles **3j** and **3k** bearing a phenyl or a methyl group in position 2, respectively. We were pleased to see that the expected products **5u-v** were obtained in up to 99% yield.

Additionally, the reaction scope was broadened to other heteroarenes such as benzofuran (**3l**) and pyrrole (**3m**), furnishing the desired trifluoromethylated adducts **5w-x** in up to 50% yield.

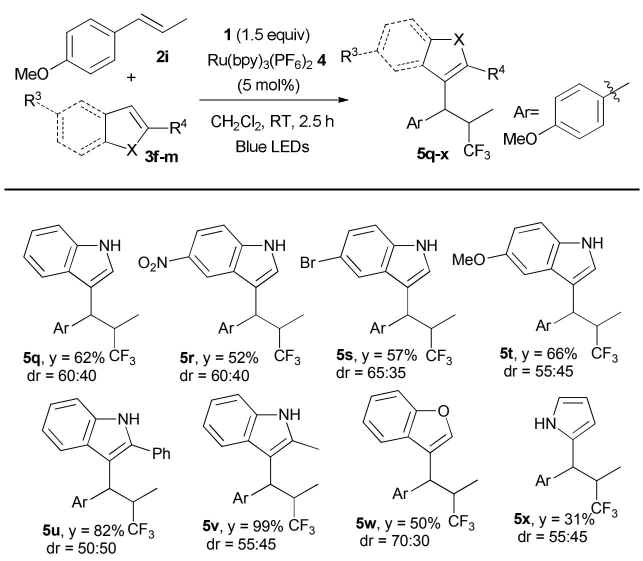
Table 2 Scope of aryl derivatives **3**[a,b,c]



5j, y = 65%, dr = 65:35; **5k**, y = 48%, dr = 60:40; **5l**, y = 40%; **5m**, y = 61%, dr = 60:40; **5n**, y = 56%, dr = 55:45; **5o**, y = 58%, dr = 60:40; **5p**, y = 44%

[a] Reaction conditions: styrene **2** (0.10 mmol), **1** (0.15 mmol), aryl derivative **3** (3 equiv), **4** (0.05 equiv), in CH_2Cl_2 (2.0 mL) irradiated at RT for 2.5 h. [b] Yields referred to chromatographically pure product. [c] dr determined by ^{19}F-NMR analysis of crude mixtures.

Table 3 Scope of heteroaryl derivatives **3**[a,b,c]

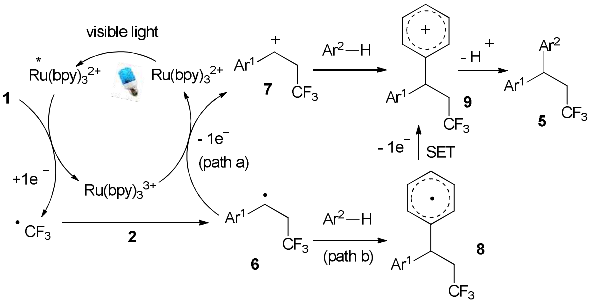


5q, y = 62%, dr = 60:40; **5r**, y = 52%, dr = 60:40; **5s**, y = 57%, dr = 65:35; **5t**, y = 66%, dr = 55:45; **5u**, y = 82%, dr = 50:50; **5v**, y = 99%, dr = 55:45; **5w**, y = 50%, dr = 70:30; **5x**, y = 31%, dr = 55:45

[a] Reaction conditions: styrene **2i** (0.10 mmol), **1** (0.15 mmol), aryl derivative **3** (3 equiv), **4** (0.05 equiv), in CH_2Cl_2 (2.0 mL) irradiated at RT for 2.5 h. [b] Yields referred to chromatographically pure product. [c] dr determined by ^{19}F-NMR analysis of crude mixtures.

Remarkably, even though an excess of heteroaryl nucleophiles was used, only traces of trifluoromethylated benzofuran, indole or pyrrole derivatives were observed (<10%), once again pointing out the high chemoselectivity of this multi-component process.

The following control experiments were carried out to gain some mechanistic insight. No reaction took place in the absence of irradiation and/or [Ru(bpy)$_3$(PF$_6$)$_2$] **4**. Moreover, the formation of **5** was inhibited in the presence of radical scavengers such as TEMPO, suggesting that a radical/cationic process is involved in this reaction. On the basis of the above results as well as other reports, a plausible reaction mechanism is shown in Scheme 2. First, irradiation with visible light excites $Ru(bpy)_3^{2+}$ into a strong reductant species $^*Ru(bpy)_3^{2+}$, which performs a single electron transfer (SET) to generate CF_3 from Umemoto's reagent **1**.[4a,6a,7a,18] Subsequent regioselective addition of electrophilic CF_3 radical to styrene **2** furnishes the benzylic radical **6**. This latter species can either be oxidized into cation **7** by SET from $Ru(bpy)_3^{3+}$ (path a), or directly trapped by (hetero)aryl nucleophile **3**, giving radical species **8** (path b). Then, Friedel-Crafts-type alkylation of **3** by carbocation **7**, or oxidation of radical **8** by $Ru(bpy)_3^{3+}$, leads to cation **9** which, after rearomatization, affords the desired α-(hetero)aryl β-trifluoromethyl adduct **5**. While the exact mechanism has not been fully elucidated, the failure with electron deficient arenes is in favour of the path a mechanism. Furthermore, the observed regioselective alkylation in C3-position of indoles **3f-i** also supports this mechanism, as radical alkylation of indoles (path b) would generally lead to the C2-alkylated regioisomer.[9a,19,20] In addition, oxidation of radical species **6** or **8** by Umemoto's reagent **1** to regenerate CF_3 radical (radical chain propagation) was excluded, as the reaction requires continuous irradiation.



Scheme 2 Plausible reaction mechanism

Conclusions

In conclusion, we have successfully developed the first intermolecular aryltrifluoromethylation of styrenes using visible-light-driven photoredox catalyst $[Ru(bpy)_3(PF_6)_2]$ under mild conditions. This difunctionalization protocol is suitable for the completely regioselective synthesis of a wide range of α-aryl β-trifluoromethyl products with good functional group compatibility. Terminal alkenes as well as internal alkenes are compatible with this radical/ionic process. This method provides a simple and efficient route to various carbotrifluoromethylated compounds which have many potential synthetic applications. Remarkably, this method was, for the first time, successfully extended to the preparation of valuable functionalized heteroaromatic compounds in good to excellent yields.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. See DOI: 10.1039/b000000x/

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