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Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications

www.rsc.org/chemcomm

ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

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DOI: 10.1039/C8CC01096J

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Combining Photoredox and Silver Catalysis for Azidotrifluoromethoxylation of Styrenes

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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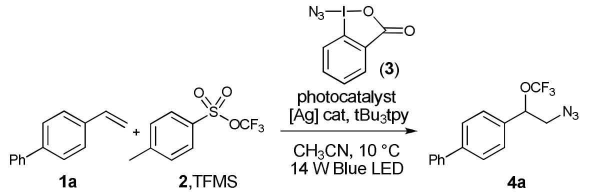
The first example of an azidotrifluoromethoxylation of styrenes has been achieved by synergistic visible-light-mediated photoredox and silver catalysis. Trifluoromethyl arylsulfonate (TFMS) and the Zhdankin reagent were used as the trifluoromethoxylation reagent and azide source, respectively. A good functional group tolerance and mild reaction conditions of this method is applicable to late-stage azidotrifluoromethoxyaltion of complex small molecules. Furthermore, the mechanistic investigations indicate the single-electron transfer involved in the reaction.

The incorporation of a trifluoromethoxy group (OCF_3) into drugs and agrochemicals has received much attention due to its strongly electron-withdrawing nature and high lipophilicity.[1] Therefore, great efforts have been devoted to the development of new methods for the synthesis of trifluoromethyl ethers.[2] Recently, photoredox catalysis employing visible light has emerged as a valuable platform for the synthesis of fluorinated compounds.[3] However, methods for the synthesis of trifluoromethyl ethers by photoredox catalysis remain extremely rare, due to the reversible decomposition of trifluoromethoxide anion and limited trifluoromethoxylation reagents.[4] To the best of our knowledge, only two methods have been reported by Ngai and co-workers for the construction of trifluoromethoxylated aromatic compounds by photoredox catalysis.[5] Herein, we reported the first example of an azidotrifluoromethoxylation of styrenes by synergistic visible-light-mediated photoredox and silver catalysis under mild reaction conditions, with trifluoromethyl arylsulfonate (TFMS)[2v,9] and the Zhdankin reagent[6] as the trifluoromethoxylation reagent and azide source, respectively.

The traditional methods for the trifluoromethoxylation of alkenes have been achieved using trifluoromethyl hypofluorite or trifluoromethyl hypochloride.[7] However, the toxic and potential explosiveness of these reagents are major drawbacks. Recently, palladium-catalyzed intramolecular aminotrifluoromethoxylation and intermolecular ditrifluoromethoxylation of unactivated alkenes with $AgOCF_3$ as the trifluoromethoxylation reagent was reported by Liu and co-workers.[8] With the TFMS, our group has reported an asymmetric silver-catalyzed bromotrifluoromethoxylation of alkenes.[9] Although the progress has been made for the synthesis of trifluoromethyl ethers from alkenes, methods for the trifluoromethoxylation of alkenes are limited. Furthermore, the merger of photocatalysis and transition metal catalysis (termed metallaphotocatalysis) has recently received much attention as a versatile platform for new methods development,[10] and no example was reported for trifluoromethoxylation with metallaphotocatalysis. Therefore, the development of a new method for the trifluoromethoxylation of alkenes by metallaphotocatalysis is highly desirable.

Considering the importance of the azide group as a stable precursor of amines,[11] we envisioned an azidotrifluoromethoxylation of styrenes with a photoredox system and transition metal catalysis. Inspired by recent studies that $\bullet N_3$ was generated from the Zhdankin reagent (**3**) with photoredox catalyst,[12] we hypothesized that the merger of visible-light photocatalysis (to generate $\bullet N_3$) with silver catalysis (to generate reactive $AgOCF_3$ species)[9] might provide a mild and general method for the azidotrifluoromethoxylation of styrenes. Our initial investigations focused on the azidotrifluoromethoxylation of 4-vinylbiphenyl in the presence of photoredox catalyst and silver salts with TFMS (**2**) and Zhdankin reagent (**3**). As briefly illustrated in Table 1, the use of a photoredox

Table 1. Optimization of the reaction conditions. [a]

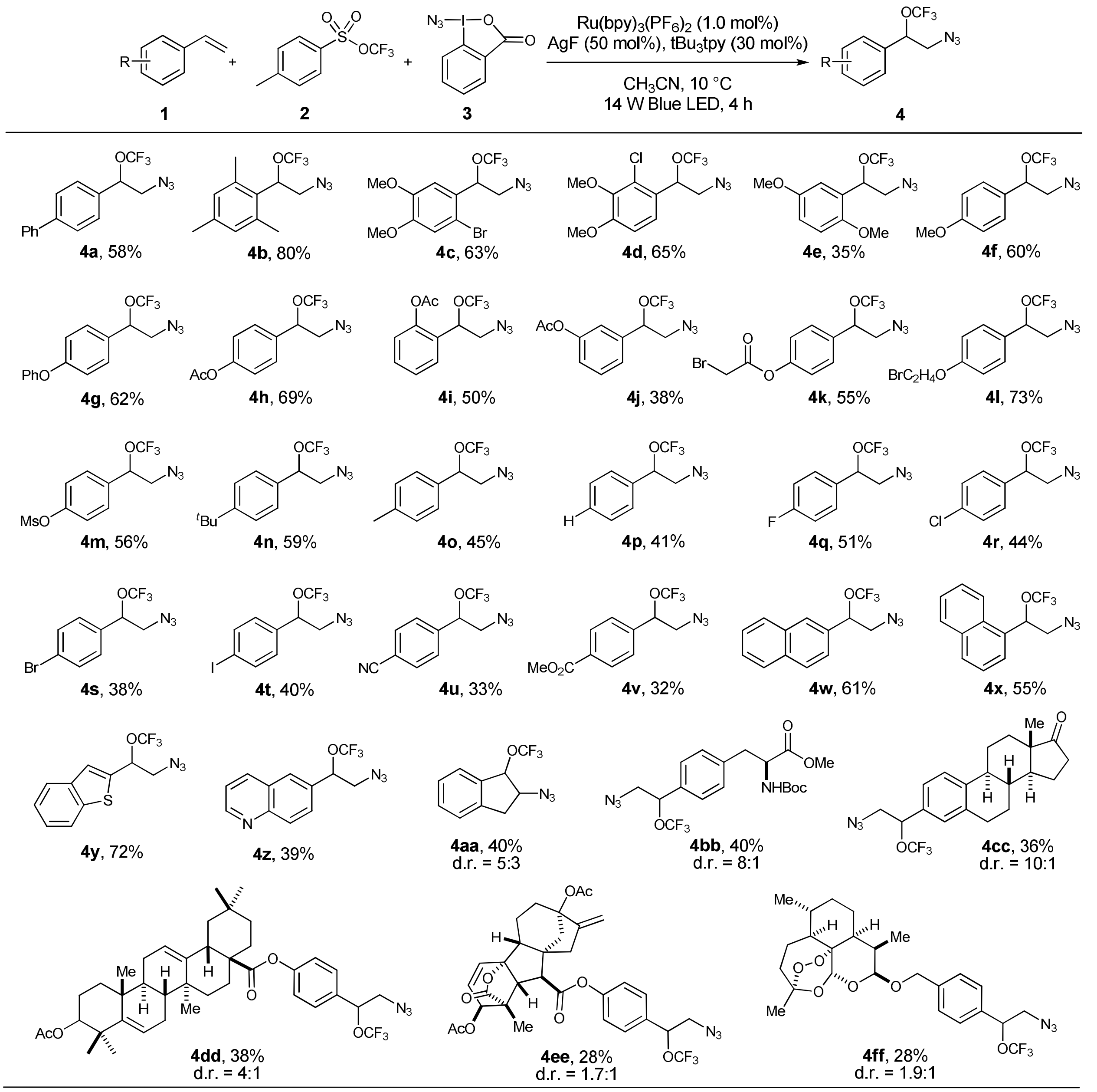


Entry	Photocatalyst	Silver salts	Yield(%)[d]
1	*fac*-$Ir(ppy)_3$	AgF	2
2	$[Ir(ppy)_2(dtbbpy)](PF_6)_2$	AgF	2
3	Eosin Y	AgF	0
4	Fluorescein	AgF	0
5	$[Ru(bpz)_3](PF_6)_2$	AgF	0
6	$[Ru(phen)_3](PF_6)_2$	AgF	36
7	$[Ru(bpy)_3](PF_6)_2$	AgF	52
8	$[Ru(bpy)_3](PF_6)_2$	AgOTf	5
9	$[Ru(bpy)_3](PF_6)_2$	AgOAc	39
10[b]	$[Ru(bpy)_3](PF_6)_2$	AgF	63
11	$[Ru(bpy)_3](PF_6)_2$	none	1
12	none	AgF	2
13[c]	$[Ru(bpy)_3](PF_6)_2$	AgF	0

[a] General conditions: **1a** (0.05 mmol), **2** (0.15 mmol), **3** (0.10 mmol), photocatalyst (1 mol%) , silver salts (50 mol%), tBu_3tpy (30 mol%), degassed CH_3CN, 10 °C, 4 h, 14 W blue LED. [b] 5.0 equiv of TFMS (**2**) was used. [c] In the dark, temperature is 60ºC. [d] Yields were determined by ^{19}F NMR with benzotrifluoride as a standard.

DOI: 10.1039/C8CC01096J

Table 2. Substrate scope for Ag/Ru-catalyzed azidotrifluoromethoxylation of styrenes [a]



[a] Reaction conditions: **1** (1.0 equiv), **2** (2.0 equiv), **3** (5.0 equiv), $[Ru(bpy)_3](PF_6)_2$ (1 mol%) , AgF (50 mol%), tBu_3tpy (30 mol%), CH_3CN, N_2 atmosphere, 10 °C, 4 h, 14 W blue LED. Yields of isolated products are given. tBu_3tpy = 4,4',4''-tri-tert-butyl-2,2':6'2''-terpyridine.

catalyst is crucial for achieving an efficient transformation in the presence of AgF, and $[Ru(bpy)_3](PF_6)_2$ was found to give the highest yield (entries 1-7). Changing the photocatalyst to fac-$Ir(ppy)_3$, $[Ir(ppy)_2(dtbbpy)](PF_6)_2$ or other organic photocatalysts resulted in less than 5% yield of desired product formation. Next, different silver salts were evaluated and AgF was found to give the highest yield (entries 7-9). A further improvement was observed when 5.0 equiv of TFMS was used (entry 10). Importantly, photoredox catalyst, silver salt, and visible light were all critical for this transformation. Significantly reduced yields of **4a** (<1%) were observed in the absence of these components. Also, no desired products were found in the dark and thermal conditions (entry 11 to 13). Finally, extensive optimization with various solvents, ligands and temperatures (See more details in the supporting information), revealed that product **4a** could be obtained in the highest yield when the reaction of 1a was conducted with 1.0 mol% $[Ru(bpy)_3](PF_6)_2$, 50 mol% AgF and 30 mol% tBu_3tpy, 5.0 equiv of TFMS (**2**), 2 equiv of Zhdankin reagent (**3**) in MeCN under N_2 atmosphere at 10°C under 14W blue LED light irradiation for four hours.

Adopting the optimum conditions, we explored the substrate scope of the transformation (Table 2). First, styrene derivatives **1a-1v** bearing electron-donating to electron-withdrawing substituents on aryl rings were successfully converted to the desired products with isolated yields ranging from 32% to 80%. In general, styrenes with electron-donating groups gave higher yields compared to styrenes with electron-withdrawing groups. It was worth mentioning that bulky ortho-substituents such as the mesityl derivative **1b** yielded

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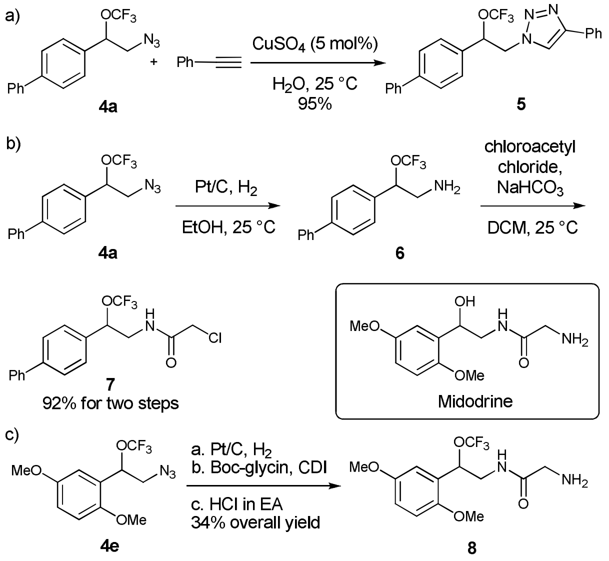
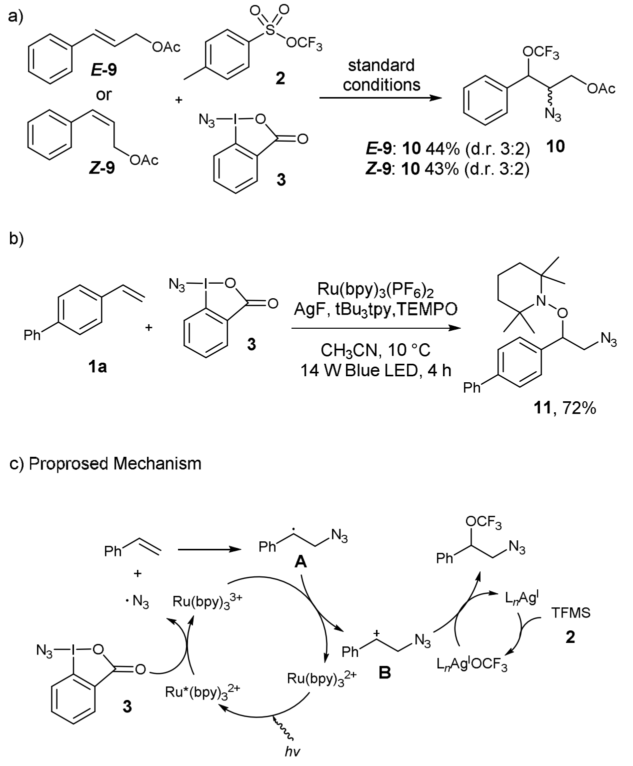
the desired product **4b** in 80% yield. Notably, thianaphthene analogues (**1y**) and quinolone analogues (**1z**) could be employed to provide the corresponding products (**4y**, **4z**). This method could also be applied to the azidotrifluoromethoxylation of an amino acid derivative and provided the corresponding product (**4bb**) in 40% yield. In addition, the reaction was compatible with a good range of functionalities, including ether, ester, amide, nitrile, sulfonyl, fluoro, chloro, bromo, and even iodo. Encouraged by these results, more complex substrates were employed and gave the corresponding products (**4dd** to **4ff**) with moderate yields. For example, artemisinin derivative (**1ff**), which contains a peroxide bridge, proceeded successfully to provide the desired product **4ff** in 28% isolated yield. Furthermore, in order to demonstrate scalability of this method, we prepared **4a** on a gram scale under the standard reaction conditions in 67% isolated yield. The limitation of this method was that low yields were observed with aliphatic alkenes.



Scheme 1. Further transformation of the azidotrifluoromethoxylated products.

Further transformation of the azidotrifluoromethoxylated products were investigated (Scheme 1). For instance, click reaction was employed to yield trifluoromethoxylated triazole **5** in 95% yield. In addition, the azide **4a** could be reduced and protected to deliver trifluoromethoxylated amine derivatives **7** in excellent yield. Furthermore, compound **8**, an analogue to drug Midodrine hydrochloride, which is a vasopressor/antihypotensive, was afforded via the reduction of the azide and subsequent amidation. These representative transformations demonstrated the versatilities of the azidotrifluoromethoxylated compounds in organic chemistry.

To get some insight into the mechanism, some preliminary studies were conducted (See more details in the supporting infor-mation). Firstly, (*E*) and (*Z*)-cinnamyl acetate ***E*-9** and ***Z*-9** were evaluated under the standard conditions, providing the same dia-stereoselectivities (3:2) and similar yields (Scheme 2a). In addition, when 2.0 equiv of TEMPO was added, no azidotrifluoromethoxylated product was observed, the TEMPO-N_3 adduct **11** was isolated in 6% yield and 90% of styrene was recovered. In the absence of TFMS, 72% yield of TEMPO-N_3 adduct **11** was isolated (Scheme 2b).[13] These results indicated that a N_3 radical was involved in the reaction, and a benzyl radical species was formed through the addition of N_3 radical to styrene. To verify the effect of photo irradiation, light/dark experiments were investigated. When the LED lamp was switched off, the reaction didn't proceed during the "off" periods, which suggested the visible light was essential. Moreover, the quantum yield of this photocatalytic reaction was determined. The value of Φ was estimated to be 0.55. Furthermore, to probe the detail electron transfer among the catalyst and substrates, a series of luminescence quenching experiments were conducted. The Zhdankin reagent (**3**) is the only molecular entity in the reaction system that quenches the excited photocatalyst.



Scheme 2. Mechanism studies and proposed mechanism.

Based on these mechanistic studies, we proposed the mechanism depicted in Scheme 2c, under visible-light irradiation, the photocatalyst $[Ru(bpy)_3]^{2+}$ is exited providing $[Ru^*(bpy)_3]^{2+}$, which is then oxidatively quenched by the Zhdankin reagent (**3**) to deliver an oxidizing $[Ru(bpy)_3]^{3+}$ and the azide radical (•N_3) via single electron transfer. The azide radical subsequently react with styrene generated a benzyl radical intermediate (**A**), which was further oxidized to benzyl carbocation intermediate (**B**) by the $[Ru(bpy)_3]^{3+}$. Concurrently, the ligated Ag(I) trifluoromethoxide, which is generated in situ via ligated Ag(I) and TFMS (**2**), was intercept benzyl carbocation intermediate (**B**) to give the desired product **4**. The intermediate (**B**) could be captured by 2-iodobenzoate remaining from the Zhdankin reagent to form the 2-azido-1-phenyl 2-iodobenzoate as the major byproduct.

Conclusions

In conclusion, we have developed a novel silver and visible-light-mediated photoredox dual-catalytic system, which has been applied to the azidotrifluoromethoxylation of styrene with trifluoromethyl arylsulfonate (TFMS) and the Zhdankin reagent. This new method takes advantage of visible-light photoredox catalysis to generate the azide radical under mild conditions and merges it with silver-catalyzed trifluoromethoxylation reaction. This method tolerates a

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wide range of functional groups and is applicable to late-stage azidotrifluoromethoxylation of complex small molecules. Furthermore, it represents a first example of combining organometallic and photoredox catalysis to achieve the trifluoromethoxylation reaction, which could lead to the development of a wide range of novel, dual-catalyzed new trifluoromethoxylation reactions in the future.

Acknowledgements

We gratefully acknowledge the State Key Laboratory of Elemento-organic Chemistry for generous start-up financial support. This work was supported by the National Key Research and Development Program of China (2016YFA0602900), NFSC (21421062, 21522205, 21672110).

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[†] Electronic Supplementary Information (ESI) available: Data for new compounds and experimental procedures. See DOI: 10.1039/c000000x/

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