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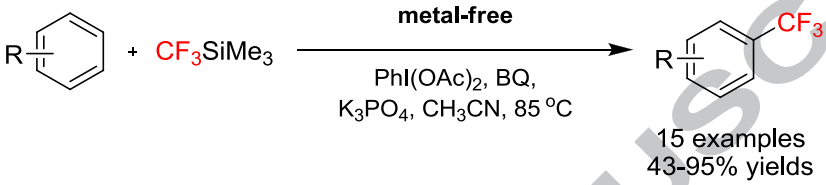

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$PhI(OAc)_2$-Mediated Oxidative Trifluoromethylation of Arenes with CF_3SiMe_3 under Metal-Free Conditions

Xinyue Wu[a], Lingling Chu[a], and Feng-Ling Qing[a,b,*]

[a] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China*
[b] *College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China*

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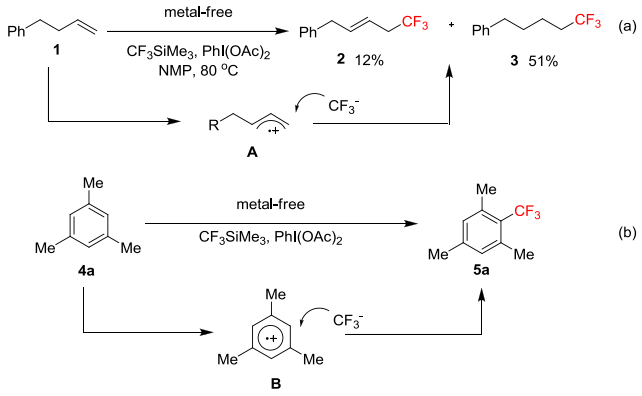
ABSTRACT

A $PhI(OAc)_2$-mediated oxidative trifluoromethylation of arenes with CF_3SiMe_3 under metal-free conditions has been described. This protocol precludes the need of substrate pre-functionalization and metal catalysts, enabling a direct access to a series of trifluoromethylated arenes and heterocycles containing common functional groups in moderate and good yields.

Trifluoromethylated arenes are widely prevalent in pharmaceuticals and argochemicals because of the metabolic stability, lipophilicity, and electron-withdrawing character of the trifluoromethyl group (CF_3-).[1] As a result, it has been of great synthetic interest to develop mild and efficient methods for the incorporation of the CF_3 moiety into aromatic compounds. Over the past five years, significant advances have been made in transition-metal-mediated or -catalyzed trifluoromethylation of aryl halides,[2] boronic acids,[3] and even C-H bonds.[4] Of particularly importance is the direct trifluoromethylation of aryl C-H bonds, which is more staightforward and more economical trifluoromethylation protocols because it does not require the pre-functionalized starting materials.[4] In addition, this method provides a more precise installation of the trifluoromethyl group than the radical trifluoromethylation of simple arenes.[5] Despite of these tremendous progress, current direct trifluoromethylation methods are limited by some combination of expensive reagents, high temperatures, and limited substrate scope. Particularly, transition metal catalysts are required for these reactions, resulting in heavy-metal contamination of the products and complicating the purification for pharmaceutical applications. Thus, a more general direct trifluoromethylation of aryl C-H bonds under metal-free and mild conditions is highly desirable.

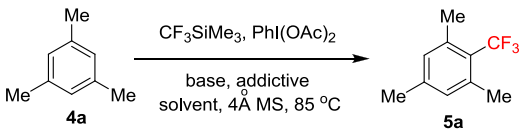
Recently, we reported copper-catalyzed oxidative trifluoromethylation of terminal alkenes with CF_3SiMe_3 in the presence of $PhI(OAc)_2$, allowing efficient access to a wide range of trifluoromethylated allylic compounds.[6] It was significant to observe that the oxidative trifluoromethylation of **1** proceeded smoothly under metal-free conditions by the action of $PhI(OAc)_2$ to afford the side product **3** in 51% yield along with the desired product **2** in 12% yield (Scheme 1a). We surmised that this transformation occurred via $PhI(OAc)_2$-induced oxidation of terminal alkene and then formation of the radical cation intermediate **A** as a key intermediate. On the basis of this work and previous reports on hypervalent iodine-induced functionalization of arenes, [7] we envisaged that $PhI(OAc)_2$-mediated oxidative trifluoromethylation of arenes under metal-free conditions would be possible if an analogous aromatic radical cation intermediate **B** was formed (Scheme 1b). Herein, we report a facile method to access trifluoromethylated arenes through $PhI(OAc)_2$-mediated oxidative trifluoromethylation of arenes with CF_3SiMe_3 under metal-free conditions.



Scheme 1. $PhI(OAc)_2$-Mediated Oxidative Trifluoromethylation under Metal-Free Conditions

To test our hypothesis on the metal-free oxidative trifluoromethylation of arenes, mesitylene **4a** was initially employed to react with CF_3SiMe_3 using $PhI(OAc)_2$ as an oxidant and K_2CO_3 as a base under the same conditions of metal-free oxidative trifluoromethylation of alkenes (Table 1).[6] Gratifyingly, the desired product **5a** was obtained in 29% yield (Table 1, entry 1). Exploration of bases revealed that K_3PO_4 was more effective than other bases, such as NaOAc and CsF, while *t*-BuOK was completely ineffective with almost no formation of the desired product (entries 1-5). We also screened the solvent and found that besides NMP, CH_3CN also provided an acceptable yield of product **5a**, while reactions conducted in DMF, DMSO, or 1,2-dichloroethane (DCE) gave low yields (entries 6-9). Considering the convenience of reaction workup, we continued our studies by using CH_3CN as the optimal solvent. Substrate concentration was found to be important in facilitating this transformation. As the concentration of substrate **4a** was increased from 0.3 M to 1 M, the yield of the trifluoromethylated product was increased to 70%, however, further increase in concentration was not beneficial for the reaction (entries 9-11). Reducing the amount of CF_3SiMe_3 and K_3PO_4 from 4.0 equiv to 2.4 euqiv and $PhI(OAc)_2$ from 2.0 equiv to 1.2 equiv has no significant impact on the reaction efficiency, and the desired product was obtained without any loss in yield (entry 12). To further increase the reaction efficiency, a series of Lewis acids, which are known to be able to activate the hypervalent iodine(III) reagents,[7d,8] were screened (entries 13-17). However, most of Lewis acids we tested, including $BF_3{\cdot}Et_2O$, $Cu(OAc)_2$, $FeCl_3$, and $In(OTf)_3$, were ineffective in the current reaction (entries 13-16). Recently, Sanford and Brase independently reported Ag-mediated trifluoromethylation of aromatic substrates using nucleophilic CF_3SiMe_3 as a trifluoromethylating reagent, abeit 4.0 equiv Ag salts are required to facilitate these transformations.[4d,4g] Inspired by these results, we surmised that the addition of AgOTf might be helpful in enhancing the reaction efficiency. Experimentally, the desired product **5a** was obtained in 85% yield in the presence of catalytic AgOTf (entry 17). We also examined the reactivity of AgOTf under these conditions. As shown in entry 18, stoichiometric AgOTf provided only 14% yield of product **5a**, precluding the possibility of AgOTf-mediated oxidative trifluoromethylation in the current reaction. This result further indicates that this pathway might not involve a trifluoromethyl radical intermediate, which has been proposed by Sanford and Brase in Ag-mediated trifluoromethylation.[4d,4g] Interestingly, the highest yield of **5a** was achieved in the presence of catalytic amount of benzoquinonine (BQ) (entry 19). However, no product was observed when stoichiometric amount of BQ instead of $PhI(OAc)_2$ was employed as an oxidant under otherwise identical conditions (entry 20). At this stage, the role of BQ remains to be elucidated.

Table 1. Optimization of Oxidative Trifluoromethylation of Mesitylene[a]



Entry	Base (equiv)	Solvent	Additive (equiv)	Yield of **5a** (%)[b]
1[c]	K_2CO_3 (4.0)	NMP [0.3M]	/	29
2[c]	K_3PO_4 (4.0)	NMP [0.3M]	/	43
3[c]	NaOAc (4.0)	NMP [0.3M]	/	29
4[c]	CsF (4.0)	NMP [0.3M]	/	29
5[c]	*t*-BuOK (4.0)	NMP [0.3M]	/	trace
6[c]	K_3PO_4 (4.0)	DMF [0.3M]	/	28
7[c]	K_3PO_4 (4.0)	DMSO [0.3M]	/	29
8[c]	K_3PO_4 (4.0)	DCE [0.3M]	/	26
9[c]	K_3PO_4 (4.0)	MeCN [0.3M]	/	41
10[c]	K_3PO_4 (4.0)	MeCN [1.0M]	/	70
11[c]	K_3PO_4 (4.0)	MeCN [2.0M]	/	45
12	K_3PO_4 (2.4)	MeCN [1.0M]	/	70
13	K_3PO_4 (2.4)	MeCN [1.0M]	$BF_3{\cdot}Et_2O$ (1.0)	46
14	K_3PO_4 (2.4)	MeCN [1.0M]	$Cu(OAc)_2$ (0.1)	63
15	K_3PO_4 (2.4)	MeCN [1.0M]	$FeCl_3$ (0.1)	46
16	K_3PO_4 (2.4)	MeCN [1.0M]	$In(OTf)_3$ (0.1)	62
17	K_3PO_4 (2.4)	MeCN [1.0M]	AgOTf (0.1)	85
18[d]	K_3PO_4 (2.4)	MeCN [1.0M]	AgOTf (1.2)	14
19	**K_3PO_4 (2.4)**	**MeCN [1.0M]**	**BQ (0.2)**	**95**
20[d]	K_3PO_4 (2.4)	MeCN [1.0M]	BQ (1.2)	none

[a] Reaction conditions: **4a** (0.3 mmol), CF_3SiMe_3 (0.72 mmol, 2.4 equiv), $PhI(OAc)_2$ (0.36 mmol, 1.2 equiv), base (0.72 mmol, 2.4 equiv), 4Å MS (50 mg), addictive, solvent, 85 °C, 6h.

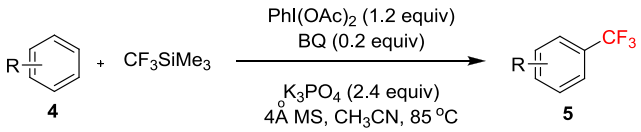
[b] Yields of **5a** were determined by ^{19}F NMR with fluorobenzene as an internal standard.

[c] CF_3SiMe_3 (1.2 mmol, 4.0 equiv), $PhI(OAc)_2$ (0.6 mmol, 2.0 equiv), base (1.2 mmol, 4.0 equiv).

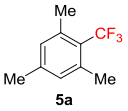
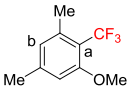
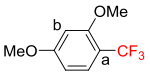
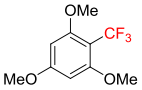
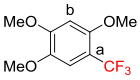
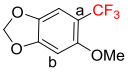
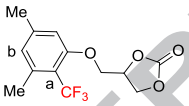
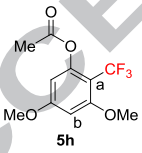
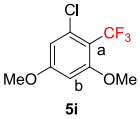
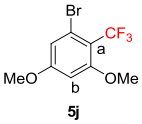
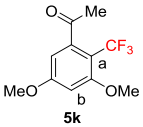
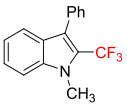
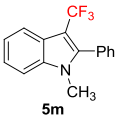
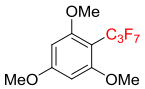
[d] In the absence of $PhI(OAc)_2$.

With the optimized reaction conditions in hand (Table 1, entry 19), the substrate scope of the $PhI(OAc)_2$-mediated oxidative trifluoromethylation of arenes under metal-free conditions was then investigated. As shown in Table 2, a series of electron-rich arenes bearing electron-donating alkyl and alkoxy groups (**4a**-**4h**) were good for this transformation, affording the corresponding products in moderate to excellent yields (Table 2, entries 1-8). This oxidative trifluoromethylation reaction also proceeded successfully with aromatic substrates containing an electron-withdrawing group such as Cl (**4i**), Br (**4j**), or keto groups (**4k**) to give the trifluoromethylated products in moderate to good yields (entries 9-11). Several common functional groups, including ester, keto, Cl and Br, are tolerated under the reaction conditions, providing opportunities for further transformations (entries 7-11). Importantly, the heterocycles such as indoles (**4l**-**4m**) and *N*-methyl pyrrole (**4n**) were also amenable to this oxidative trifluoromethylation protocol and useful yields were obtained under the standard reaction conditions (entries 12-14). In most cases, mixtures of regioisomers were produced in these transformations, albeit with a moderate regioselectivity (Table 2). Some regioisomers can be separated by chromatography to provide the single trifluoromethylated products (entries 5, 9-10). Notably, the current oxidative protocol can be easily extended to the direct perfluoroalkylation of arenes to give the perfluoroalkylated product **5o** in good yield (entry 15).

Table 2. $PhI(OAc)_2$-Mediated Oxidative Trifluoromethylation of Arenes[a]



4 5

Entry	Substrate **4**	Product **5**	Isolated yield
1	**4a**	 **5a**	95%[b]
2	**4b**	 **5b**	72% (a : b= 1.5 : 1)
3	**4c**	 **5c**	59% (a : b= 1.4 : 1)
4	**4d**	 **5d**	78%
5	**4e**	 **5e**	73% (a : b = 11 : 1)
6	**4f**	 **5f**	43% (a : b = 8 : 1)
7	**4g**	 **5g**	55% (a : b = 1.3 : 1)
8	**4h**	 **5h**	56% (a : b = 1.5 : 1)
9	**4i**	 **5i**	79% (a : b = 3.2 : 1)
10	**4j**	 **5j**	50% (a : b = 1 : 1)
11	**4k**	 **5k**	56% (a : b = 3.3 : 1)
12	**4l**	 **5l**	72%
13	**4m**	 **5m**	62%
14	**4n**	 **5n**	94% (a : b = 6.4 : 1)[b]
15	**4o**	 **5o**	86%

[a] Reaction conditions: **4** (0.5 mmol), CF_3SiMe_3 (1.2 mmol, 2.4 equiv), $PhI(OAc)_2$ (0.6 mmol, 1.2 equiv), K_3PO_4 (1.2 mmol, 2.4 equiv), BQ (0.1 mmol, 0.2 equiv), 4Å MS (80 mg), CH_3CN [1.0 M], 85 °C, 6h. Isolated yields. Isomer ratios were determined by ^{19}F NMR spectroscopy.

[b] Yields were determined by ^{19}F NMR spectroscopy with fluorobenzene as an internal standard.

In summary, a $PhI(OAc)_2$-mediated oxidative trifluoromethylation of arenes with CF_3SiMe_3 under metal-free conditions has been developed, providing a direct method for synthesizing trifluoromethylated arenes without the need of pre-functionalization. A variety of trifluoromethylated arenes and heterocycles were obtained under mild conditions in moderate to good yields. This method is amenable to normal benchtop setup and tolerates a range of functional groups. The optimized conditions for the oxidative trifluoromethylation of arenes were also effective for the oxidative perfluoroalkylation.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.....

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