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Silver-catalysed trifluoromethylation of arenes at room temperature†

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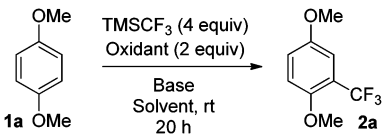
A variety of heteroarenes and electron rich arenes can be trifluoromethylated at room temperature with $TMSCF_3$, catalytic silver and $PhI(OAc)_2$.

The trifluoromethyl group is valued for its ability to modulate the properties of diverse materials such as pharmaceuticals, agrochemicals and polymers. Aryl CF_3 groups are electron-withdrawing, hydrophobic and generally very stable, all properties that can be harnessed in the design of biologically active molecules and functional materials. Synthetic methods for aryl and heteroaryl trifluoromethylation are thus critical to the discovery and production of new molecules of high value to society.[1] Recent developments in metal-mediated trifluoromethylation have produced significant advances in this area,[2] with common functional groups such as aryl boronic acids and halides undergoing efficient trifluoromethylation under palladium and copper catalysis.[3] Metal-catalysed trifluoromethylation of unactivated C–H positions, by contrast, is significantly less developed and has great potential for accelerating medicinal and agrochemical syntheses. Despite some recent groundbreaking developments in this area,[4] there is still great demand for the development of catalytic C–H trifluoromethylation methods that function under mild and simple conditions.

We were interested in developing a catalytic trifluoromethylation based on silver; in contrast to its Group 11 neighbour copper there have been few reports on silver-mediated trifluoromethylation[4g,k,5] and none that we are aware of using silver catalysis. The redox catalysis of silver, comprising one electron steps between 0, +1, +2 and +3 oxidation states, has been scarcely exploited in synthesis relative to other late TMs[6,7] and could offer productive catalytic pathways for trifluoromethylation. We have recently developed silver-catalysed decarboxylative C–H cross-coupling under oxidative radical conditions,[8] and were keen to see if a similar approach was viable for C–H trifluoromethylation.

We started with a screen of reaction conditions based around $TMSCF_3$ as the trifluoromethylating agent.[9] The groups of Sanford, Bräse and Wang have recently demonstrated the compatibility of this reagent with stoichiometric silver salts,[4g,k,5c] encouraging us that it could form the basis of a catalytic system. Using 1,4-dimethoxybenzene (**1a**) as the substrate, we conducted an initial solvent screen using combinations of AgF, $TMSCF_3$ and $PhI(OAc)_2$ (Table 1). We worked at room temperature under air throughout, with the aim of developing a mild reaction with as broad a functional group tolerance as possible. The reaction proved sensitive to solvent choice with initially only MeCN from a selection of common organic solvents producing any reaction (entries 1 and 2). DMSO proved more effective still, affording the trifluoromethylated compound **2a** in 51% conversion (entry 3). Fluoride was not a requirement, with Ag_2CO_3 being similarly effective at promoting reaction (entry 4). Alternative oxidants did not improve on $PhI(OAc)_2$ (entries 5 and 6), and the use of a

Table 1 Ag-catalysed trifluoromethylation: reaction optimisation



Entry[a]	Catalyst (equiv.)	Oxidant	Solvent	Yield[b] (%)
1	AgF (1)	$PhI(OAc)_2$	Solvent[c]	0
2	AgF (1)	$PhI(OAc)_2$	MeCN	26
3	AgF (1)	$PhI(OAc)_2$	DMSO	51
4	Ag_2CO_3 (0.5)	$PhI(OAc)_2$	DMSO	48
5	AgF (1)	$PhI(TFA)_2$	DMSO	5
6	AgF (1)	$K_2S_2O_8$	DMSO	20
7[d]	AgF (1)	$PhI(OAc)_2$	DMSO	35
8[e]	AgF (0.25)	$PhI(OAc)_2$	DMSO	55
9[e,f]	AgF (0.25)	$PhI(OAc)_2$	DMSO	55 (58[g])
10[e,h]	AgF (0.25)	$PhI(OAc)_2$	DMSO	60

[a] 1,4-Dimethoxybenzene **1a** (0.3 mmol), $TMSCF_3$ (1.2 mmol), oxidant (0.6 mmol), F^- source or base, solvent (1.0 mL), room temperature, 20 h. [b] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [c] THF, 1,4-dioxane, MeOH, $(CF_3)_2CHOH$, DCE, DCM. [d] Under N_2. [e] Slow addition of AgF to the stirring mixture of **1a**, $TMSCF_3$ and $PhI(OAc)_2$ in DMSO. [f] 2 equiv. of $TMSCF_3$. [g] Isolated yield. [h] $TESCF_3$ (2 equiv.) instead of $TMSCF_3$.

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nitrogen atmosphere led to a reduction in yield (entry 7). Crucially, sub-stoichiometric amounts of silver salts proved equally effective (entries 8–10), indicating that a catalytic reaction was feasible. We settled on conditions of AgF (25 mol%) with $TMSCF_3$ (2 equiv.) and $PhI(OAc)_2$ (2 equiv.), at room temperature (entry 9) to take forward. The use of the more stable (and expensive) $TESCF_3$ reagent gave only marginal improvement (entry 10), so we continued with the cheaper $TMSCF_3$ reagent.

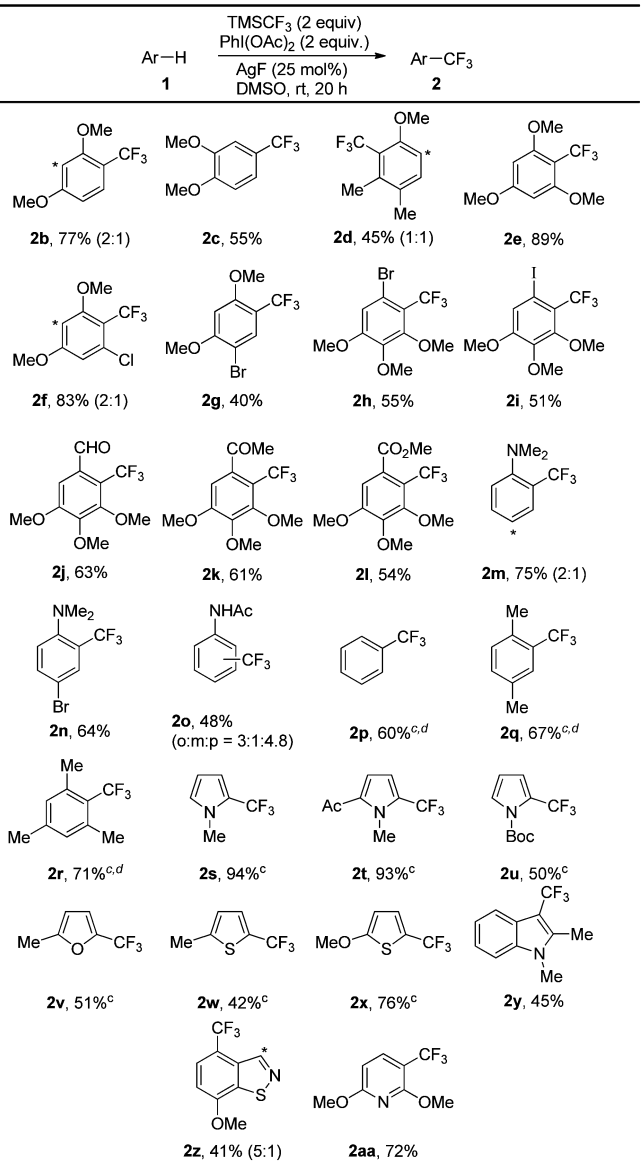
Substrate scope investigations established that the procedure was effective for a variety of electron rich arenes with broad substrate scope tolerance (Table 2). For unsymmetrical substrates isomeric mixtures were generally observed, with regioselectivities consistent with radical $S_{Ar}H$ addition (*vide infra*). Importantly, the reaction was compatible with halogen groups, illustrating an orthogonal reactivity to conventional C–X trifluoromethylations whereby neighbouring C–H bonds undergo preferential reaction. The useful building blocks **2f**, **2g**, **2h** and **2i** were prepared in this fashion. Electron-withdrawing groups such as aldehyde (**2j**), ketone (**2k**) and ester (**2l**) were likewise tolerated without problem. Importantly, dialkylanilines could be trifluoromethylated, a key class of building block that has rarely featured in C–H trifluoromethylation reports.[4i,10] A slight preference for *ortho* over *para* selectivity was observed for simple dimethylamine (**2m**), with bromo substitution also tolerated (**2n**) along with N-acylation (**2o**). We were pleased to observe that the reaction was also effective for un-activated arenes (**2p**, **2q** and **2r**), although these substrates did require an excess of the arene and the reaction temperature raised to 70 °C.

The reaction could be extended to heteroarenes with N–Me pyrroles in particular being excellent substrates (**2s**, **2t**). Electron-withdrawing groups on the heteroarene nucleus were well-tolerated (**2t**), but on nitrogen less so (N–Boc, **2u**). Furans (**2v**), thiophenes (**2w**, **2x**) and indoles (**2y**) were all productive, indicating that the method is viable for the major classes of π-excessive heterocycle. π-Deficient heteroarenes, by contrast, were not generally effective in the reaction but could be efficiently captured by masking the azine nucleus with electron-donating groups (**2aa**).

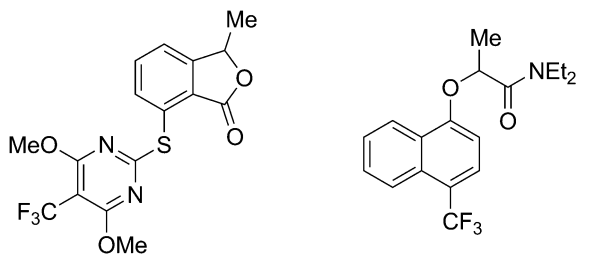
We next turned to the trifluoromethylation of more complex, biologically active molecules – a major driver for the development of new methods in this area. Introduction of the CF_3 group at unactivated C–H positions represents a very versatile approach to fluorine incorporation for modulation of biological activity,[4c,d,j] demanding mild reaction conditions that are tolerant of functional groups and reasonable stoichiometries with respect to the (often valuable) C–H substrate. Accordingly, we extended the reaction to trifluoromethylate some more complex molecules in the agrochemistry field, an area where the CF_3 group is particularly prevalent. We could successfully incorporate the CF_3 group into the commercial herbicides pyriftalid[11] and napropamide[12] (Scheme 1). The functional group tolerance of the reaction was illustrated by sulfide, lactone and α-hydroxyamide functionality all being stable to the reaction conditions (Scheme 1, **3** and **4**).

A radical mechanism is implicated for the trifluoromethylation reaction,[13] as radical quenching reactions using TEMPO and galvinoxyl radical both shut down the reaction, with the TEMPO–CF_3 adduct being clearly observed in the crude ^{19}F NMR. The electrophilic CF_3 radical usually (but with some exceptions)[4c,j] displays a marked preference for electron rich substrates, as seen here, underlining the likelihood of a radical pathway. A possible

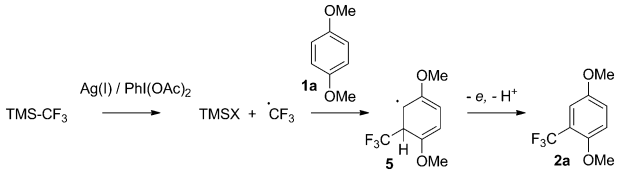
Table 2 Ag-catalysed trifluoromethylation: substrate scope[a,b]



[a] **1** (0.3 mmol), $TMSCF_3$ (0.6 mmol), $PhI(OAc)_2$ (0.6 mmol), AgF (0.075 mmol), DMSO (1.0 mL), room temperature, 20 h. [b] Isolated yields. For isomer mixtures, the minor regioisomeric position is labeled with *. [c] Yields determined by ^{19}F NMR using 4-fluoroanisole as the internal standard. [d] Reaction conducted at 70 °C, 5–10 equiv. of arene.



Scheme 1 Agrochemical trifluoromethylation.



Scheme 2 Silver-catalysed radical trifluoromethylation.

mechanism is shown in Scheme 2 whereby $TMSCF_3$ is oxidised to the CF_3 radical, followed by $S_{Ar}H$ addition, then a second one electron oxidation and proton loss to give the product **2**. Control experiments to investigate the role of silver in the first step of the proposed mechanism indicated that AgF alone was insufficiently oxidizing to generate $CF_3^{\bullet}$ (mixing AgF with $TMSCF_3$ in the presence of TEMPO in DMSO at room temperature gave only trace quantities of TEMPO–CF_3). $PhI(OAc)_2$ alone was moderately effective (44% NMR yield of TEMPO–CF_3) and the combination of $PhI(OAc)_2$ and AgF highly effective (91% NMR yield).[14] The background oxidizing activity of the hypervalent iodine reagent could be quantified in the trifluoromethylation of 1,4-dimethoxybenzene **1a** in the absence of any silver salt, producing a low conversion to the trifluoromethylated product **2a** (26% NMR yield).

Alternative mechanisms were investigated by treating dimethoxyanisole **1a** with *in situ* prepared $AgCF_3$[5b] in both MeCN and DMSO as solvents. No reaction could be observed in each case, suggesting organometallic $AgCF_3$ intermediates are not participating under our reaction conditions. A further control experiment with Togni's reagent[4a] in DMSO at room temperature gave no reaction, ruling out simple S_EAr attack on an electrophilic CF_3 source. Finally, we considered the possibility of initial arene oxidation by $PhI(OAc)_2$, followed by CF_3 anion addition to a cationic arene intermediate. Extensive work by Kita has demonstrated the C–H functionalization of electron rich arenes using $PhI(TFA)_2$ in the presence of stoichiometric $BF_3{\cdot}OEt_2$ and nucleophiles.[15] It seems the present conditions are not sufficiently oxidizing to enable an analogous pathway, as a control reaction in the absence of $TMSCF_3$ gave no reaction, where some degree of homocoupling would be expected if this mechanism was in operation.

In conclusion, we have developed a silver-catalysed trifluoromethylation system for electron rich aromatic and heteroaromatic substrates. The reaction works at room temperature under air, does not require excessive stoichiometries of substrate or reagent, and is operationally simple to carry out. The application of this chemistry to new trifluoromethylation substrates will be the subject of future work in our laboratory.

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