Silver-Mediated Trifluoromethylation of Arenes Using TMSCF$_3$

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ABSTRACT

The silver-mediated C−H trifluoromethylation of aromatic substrates using TMSCF$_3$ is described. The development, optimization, and scope of these transformations are reported. AgCF$_3$ intermediates are proposed.

Trifluoromethylated aromatic compounds are widely prevalent in pharmaceuticals, agrochemicals, and organic materials.[1] As a result, the development of transition-metal-mediated/catalyzed methods for introducing CF$_3$ groups into organic molecules has been the subject of intense research. Over the past 5 years a variety of Pd[2,3] and Cu[4,5]-based protocols have been developed for the trifluoromethylation of aryl halides, aryl boronic acids, and aromatic carbon−hydrogen bonds. In addition, several free radical approaches are available for arene trifluoromethylation.[6,7] Despite this extensive progress, current trifluoromethylation methods have significant limitations. Some systems utilize expensive trifluoromethylating reagents (*e.g.*, *S*-(trifluoromethyl)thiophenium salts,[3a,4f,5d] Togni's reagent,[5b,e] or TESCF$_3$).[3b,5a] Others involve

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(6) Examples of arene/heteroarene trifluoromethylation with CF$_3$•: (a) Wakselman, C.; Tordeux, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1701. (b) Akiyama, T.; Kato, K.; Kajitani, M.; Sakaguchi, Y.; Nakamura, J.; Hayashi, H.; Sugimori, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3531. (c) Sawada, H.; Nakayama, M. *J. Fluorine Chem.* **1990**, *46*, 423. (d) Kirk, K. L.; Nishida, M.; Fujii, S.; Kimoto, H. *J. Fluorine Chem.* **1992**, *59*, 197. (e) McClinton, M. A.; McClington, D. A. *Tetrahedron* **1992**, *48*, 6555. (f) Kamigata, N.; Ohtsuka, T.; Fukushima, T.; Yoshida, M.; Shimizu, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1339. (g) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98. (h) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411.

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temperatures greater than 100 °C[2b,3a,b,4d] and/or exhibit modest substrate scope/generality.[3c,5a,b,6] Free radical based methods often require inconvenient electrochemical or photochemical activation procedures[6b,d,e] or utilize potentially explosive reagents like peroxides at elevated temperatures.[6c,g] Additionally, C−H bond trifluoromethylation methods (which are particularly attractive because they do not require prefunctionalized starting materials) remain especially limited in substrate scope.[3a,d,6]

We were interested in the possibility of addressing some of these limitations by identifying metals other than Cu or Pd that could promote the formation of benzotrifluorides. We were attracted to Ag based on the fact that it is readily available, is directly below Cu on the periodic table (suggesting the potential for similar reactivity), and has recently proven a useful promotor for other organometallic reactions.[8] There are also a number of reports describing the synthesis of AgCF$_3$ complexes.[9,10] However, the reactivity of these species has not been explored extensively,[9,10] thereby suggesting opportunities for new reaction discovery. We report herein that the combination of AgOTf, KF, and TMSCF$_3$ can be used for the C−H trifluoromethylation of aromatic substrates under mild conditions. The development, scope, and mechanism of this transformation are discussed herein.

Scheme 1. Reaction of AgCF$_3$ with PhI and Benzene
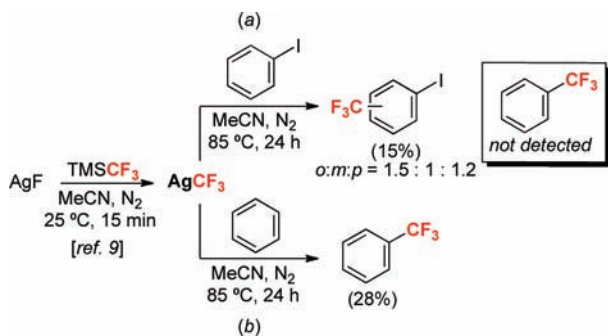
CuCF$_3$ complexes are well-known to react with aryl iodides to afford benzotrifluoride products.[4] Thus, we first sought to examine the reactivity of AgCF$_3$ with PhI (Scheme 1a). AgCF$_3$ was generated *in situ* from the reaction of AgF with TMSCF$_3$ in MeCN for 15 min at 25 °C using the procedure of Tyrra and Naumann.[9] PhI (20 equiv) was then added, and the reaction was heated at 85 °C for 24 h. ^{19}F NMR spectroscopic analysis of the crude reaction mixture did not show the presence of PhCF$_3$. Instead, three isomeric C−H trifluoromethylation products were observed in 15% total yield based on

TMSCF$_3$ (*o*: *m*: *p* ratio = 1.5: 1: 1.2). This result clearly demonstrates the orthogonal reactivity of AgCF$_3$ and CuCF$_3$ reagents with aryl−H versus aryl−I bonds. Conducting this same procedure with benzene in place of PhI afforded the C−H trifluoromethylation product PhCF$_3$ in 28% yield (Scheme 1b).

This Ag-mediated C−H trifluoromethylation reaction was optimized using benzene (20 equiv) as the substrate and DCE as the solvent (see Supporting Information for evaluation of other solvents). Since this is a net $2e^-$ oxidation reaction (where Ag^I is presumably acting as the terminal oxidant), our optimization studies began with 2 equiv of various Ag^I salts. As shown in Table 1, the use of 2 equiv of AgF, AgNO$_3$, or AgOTf in the presence of 2 equiv of KF afforded trifluorotoluene in modest yield, with AgOTf providing the best result (entries 3−5). In contrast, AgOAc and Ag$_2$O generated < 10% product under analogous conditions (entries 1 and 2). Moving from 2 to 4 equiv of AgOTf/KF improved the yield from 68 to 87% (entries 5 and 6). Importantly, KF is required for the AgOTf reaction (entry 7), presumably to activate the TMSCF$_3$. For comparison, we also examined the reactivity of Cu^I salts like [CuOTf]$_2$·C$_6$H$_6$ and CuI under these conditions. As shown in entries 9 and 10, they provided none of the C−H trifluoromethylation product, again highlighting the complementarity of this Ag-based method versus more traditional Cu-mediated trifluoromethylation protocols.

Table 1. Optimization of Trifluoromethylation Reaction[a,b]

entry	metal salt	metal salt/ KF equiv	yield (%)
1	AgOAc	2/2	6
2	Ag$_2$O	2/2	6
3	AgNO$_3$	2/2	40
4	AgF	2/2	45
5	AgOTf	2/2	68
6	AgOTf	4/4	87
7[c]	AgOTf	4/0	0
8[d]	AgOTf	4/4	53
9	[CuOTf]$_2$·C$_6$H$_6$	2/2	0
10	CuI	4/4	0

[a] General conditions: C$_6$H$_6$ (20 equiv), TMSCF$_3$ (1 equiv) in DCE at 85 °C for 24 h. [b] Yields determined by ^{19}F NMR analysis. [c] No KF. [d] Conditions: C$_6$H$_6$ (1 equiv), TMSCF$_3$ (5 equiv), AgOTf (4 equiv), KF (4 equiv) in DCE at 85 °C for 24 h.

The final optimized conditions (20 equiv of benzene, 4 equiv of AgOTf and KF, 1 equiv of TMSCF$_3$ at 85 °C for 24 h) were readily scalable, affording trifluorotoluene in 87%, 84%, and 87% yield on 0.08, 0.5, and 1 mmol scales, respectively. Notably, the use of benzene as the limiting

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reagent (1 equiv) along with 5 equiv of TMSCF$_3$ also led to an acceptable 53% yield (entry 8).

This Ag-mediated C−H trifluoromethylation reaction was applicable to a variety of different arene substrates. As shown in Table 2, arenes bearing electron-donating alkyl or alkoxy substituents reacted in good to excellent yield (entries 1−10). In general, these transformations proceeded with a modest preference for trifluoromethylation at C−H sites *ortho* and *para* to the electron-donating alkyl or alkoxy groups. Heteroaromatics like *N*-methyl pyrrole, thiophene, and caffeine were also good substrates for C−H trifluoromethylation and reacted with moderate to excellent site selectivity (entries 12, 13, and 15).[11] Under our optimal conditions PhI reacted to form a mixture of the *o*-, *m*-, and *p*-trifluoromethylated isomers in 46% total yield (entry 11). The trifluoromethylation of naphthalene proceeded in good yield with modest selectivity for the α-position (entry 14).

The optimal reaction conditions were also effective for transfer of other perfluoroalkyl groups. For example, the AgOTf/KF-mediated reaction of benzene with TMSC$_3$F$_7$ afforded (heptafluoropropyl)benzene in 60% yield (Scheme 2).

Scheme 2. Ag-Mediated Perfluoroalkylation of Benzene
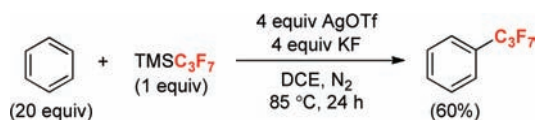
We initially hypothesized that this transformation proceeded via a pathway involving Ag-promoted generation of a trifluoromethyl radical (CF$_3$•) (Scheme 3, step *a*), which then participates in a radical aromatic substitution reaction. Addition of CF$_3$• to the aromatic ring to generate intermediate **A** (step *b*) followed by SET from **A** to a second equivalent of Ag^I (step *c*) would release the product along with HOTf and Ag^0. Importantly, free radical arene trifluoromethylation[6] and perfluoroalkylation[7] have significant precedent in the literature. Most commonly, CF$_3$• is generated from CF$_3$Br or CF$_3$I either photochemically or electrochemically.[6b,d,e] A more recent report by Yamakawa and co-workers demonstrated radical trifluoromethylation of aromatic compounds using CF$_3$I, Fe^{II}, and H$_2$O$_2$.[6g] However, to our knowledge, the use of TMSCF$_3$ as a precursor to radical arene trifluoromethylation has not been reported.

To test for the possibility of CF$_3$• intermediates, we examined the AgOTf/KF-promoted reaction of benzene with TMSCF$_3$ in the presence of a variety of radical initiators/inhibitors. In the presence of light (which is frequently used to promote radical reactions), the reaction

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(11) Several other heteroaromatics, including furan (16% yield), 2-methylfuran (7% yield), pyridine (2% yield, 2 isomers), and 1-methyl-limidazole (3% yield, 3 isomers), afforded low yields of monotrifluoromethylated products under our standard conditions.

Table 2. Substrate Scope of Silver-Mediated Trifluoromethylation[a,b]
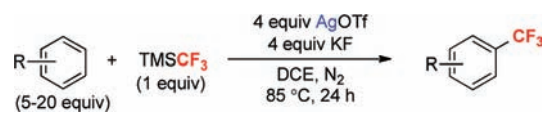
entry	substrate	major product	yield (%)	isomer ratio
1[c]			87	---
2			81	a : b : c 2.7 : 1.4 : 1
3			76	---
4			76	a : b : c 5.2 : 3.5 : 1
5			65	a : b 1.4 : 1
6			78	---
7			87	a : b : c 2.7 : 1.2 : 1
8[c]			88	---
9			85	a : b : c 13 : 7.3 : 1
10			70	a : b 4 : 1
11[c]			46	a : b : c 1.7 : 1.2 : 1
12[c]			44	a : b >20 : 1
13			72	a : b 8 : 1
14[d]			70	a : b 4.8 : 1
15[d]			42	---

[a] General conditions: substrate (10 equiv), TMSCF$_3$ (1 equiv) in DCE at 85 °C for 24 h. [b] Yield and selectivity determined by ^{19}F NMR analysis of the crude reaction mixtures. [c] 20 equiv of substrate used. [d] 5 equiv of substrate used.

Scheme 3. Possible Free Radical Pathway for Ag-Mediated Trifluoromethylation
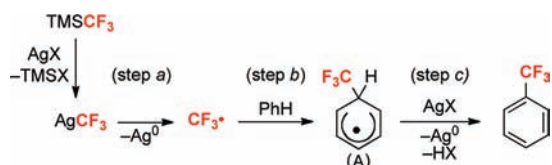
proceeded in a slightly lower yield (75% versus 87%). This may be due to the light sensitivity of Ag salts.[12] The addition of azobisisobutyronitrile (AIBN), a radical initiator, led to a moderate decrease in the overall yield of the reaction. The use of 20 mol % of AIBN resulted in a 77% yield of PhCF$_3$, while a 57% yield was obtained upon addition of 1 equiv of this additive.[12] Nitrobenzene has been employed previously as an inhibitor of SET steps (like step c in Scheme 3) during free radical trifluoromethylation.[6a] Interestingly, the addition of 1 equiv of NO$_2$Ph had little effect on the Ag-mediated reaction of benzene with TMSCF$_3$ (85% versus 87% yield in the absence of this additive). TEMPO has been utilized in the literature as a trap for CF$_3^{\bullet}$.[3c] The addition of 1 equiv of TEMPO led to a dramatic reduction in yield (to 7%) under otherwise analogous conditions.

Because the results with the radical inhibitors/initiators were somewhat ambiguous, we next sought to compare the site selectivity of TMSCF$_3$/AgOTf/KF-mediated trifluoromethylation to that of a known CF$_3^{\bullet}$ reaction. Under the reaction conditions described by Yamakawa and co-workers,[6g] anisole reacted with *in situ* generated CF$_3^{\bullet}$ to form a 7.5:1:5 ratio of $o/m/p$ trifluoromethylated products (Scheme 4). This reaction shows significantly higher o/p selectivity compared to our Ag-mediated transformation (where $o/m/p$ = 2.7:1:1.2). Veratrole also reacted with different site selectivity for trifluoromethylation with CF$_3^{\bullet}$ versus TMSCF$_3$/AgOTf/KF (Scheme 4).[13] While further studies are needed to gain a complete mechanistic picture of the TMSCF$_3$/AgOTf/KF-mediated reaction, these results suggest against a purely free radical pathway.

The involvement of caged and/or Ag-associated radicals is a likely possibility. Notably, Kamigata has proposed a mechanism involving "radical intermediates confined in the coordination sphere of Ru" for related transformations.[6f]

Scheme 4. Comparison of Reactivity and Selectivity of Radical Trifluoromethylation
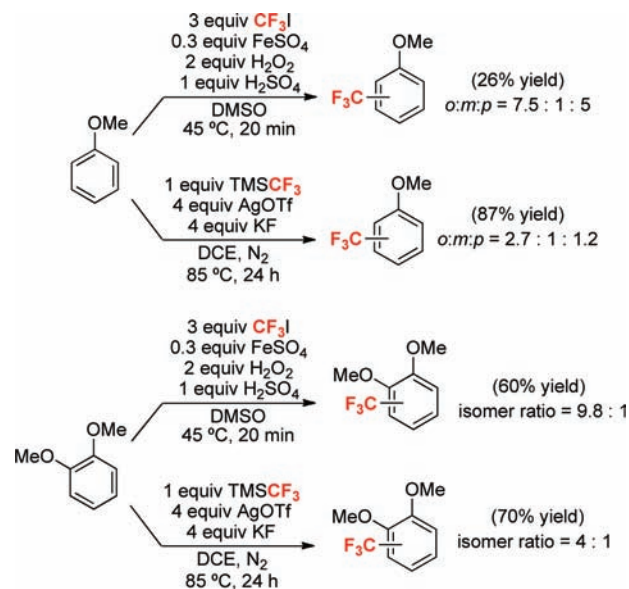
In conclusion, this report describes the silver-mediated trifluoromethylation of aromatic substrates with TMSCF$_3$. These reactions are proposed to proceed via a AgCF$_3$ intermediate, and preliminary studies suggest against free CF$_3^{\bullet}$ as an intermediate. Importantly, these Ag-mediated reactions proceed with complementary reactivity to analogous transformations of CuCF$_3$ reagents. Ongoing studies are focused on probing the mechanism and developing related Ag-catalyzed trifluoromethylation reactions.

(12) It is possible that light/AIBN do not have an effect on this system because they are not capable of promoting the Ag−CF$_3$ bond homolysis (step a in Scheme 3).

(13) The different selectivity with CF$_3^{\bullet}$ does not appear to be a temperature or solvent effect. For example, when the Fe-catalyzed reaction of CF$_3^{\bullet}$ with veratrole (Scheme 4) was conducted at 85 °C, it afforded 10.2:1 selectivity (67% yield). Similarly, when DCE was used as the solvent in place of DMSO, the product was obtained with 7.7:1 selectivity (4% yield).