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Silver-Mediated Trifluoromethylation of Arenes using $TMSCF_3$

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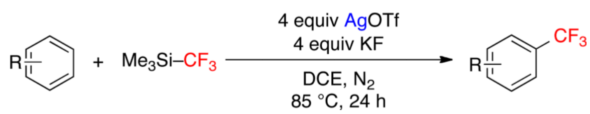
Abstract



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 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 pre-functionalized 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.

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Supporting Information Available. Experimental procedures along with experimental and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

$CuCF_3$ 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_2O generated <10% product under analogous conditions (entries 1 and 2). Moving from 2 equiv 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 (Table 1, entry 7), presumably to activate the $TMSCF_3$. For comparison, we also examined the reactivity of Cu^I salts like $[CuOTf]_2{\cdot}C_6H_6$ 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.

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 reagent (1 equiv) along with 5 equiv of $TMSCF_3$ also led to an acceptable 53% yield (Table 1, 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 and 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 afforded 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 $TMSC_3F_7$ afforded (heptafluoropropyl)benzene in 60% yield (Scheme 2).

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] has significant precedent in the literature. Most commonly, CF_3• is generated from CF_3Br or CF_3I either photochemically or electrochemically.[6b,d,e] A more recent report by Yamakawa and coworkers demonstrated radical trifluoromethylation of aromatic compounds using CF_3I, Fe^{II} and H_2O_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 proceeded in 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 77% yield of $PhCF_3$, while a 57% yield was obtained in upon addition of 1 equiv of this additive.[12] Nitrobenzene has been employed previously as an inhibitor of SET transfer steps (like step *c* in Scheme 3) during free radical trifluoromethylation.[6a] Interestingly, the addition of 1 equiv of NO_2Ph 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•.[3c] The addition of 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• reaction. Under the reaction conditions described by Yamakawa and coworkers,[6g] anisole reacted with *in situ*-generated CF_3• 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• 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]

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• 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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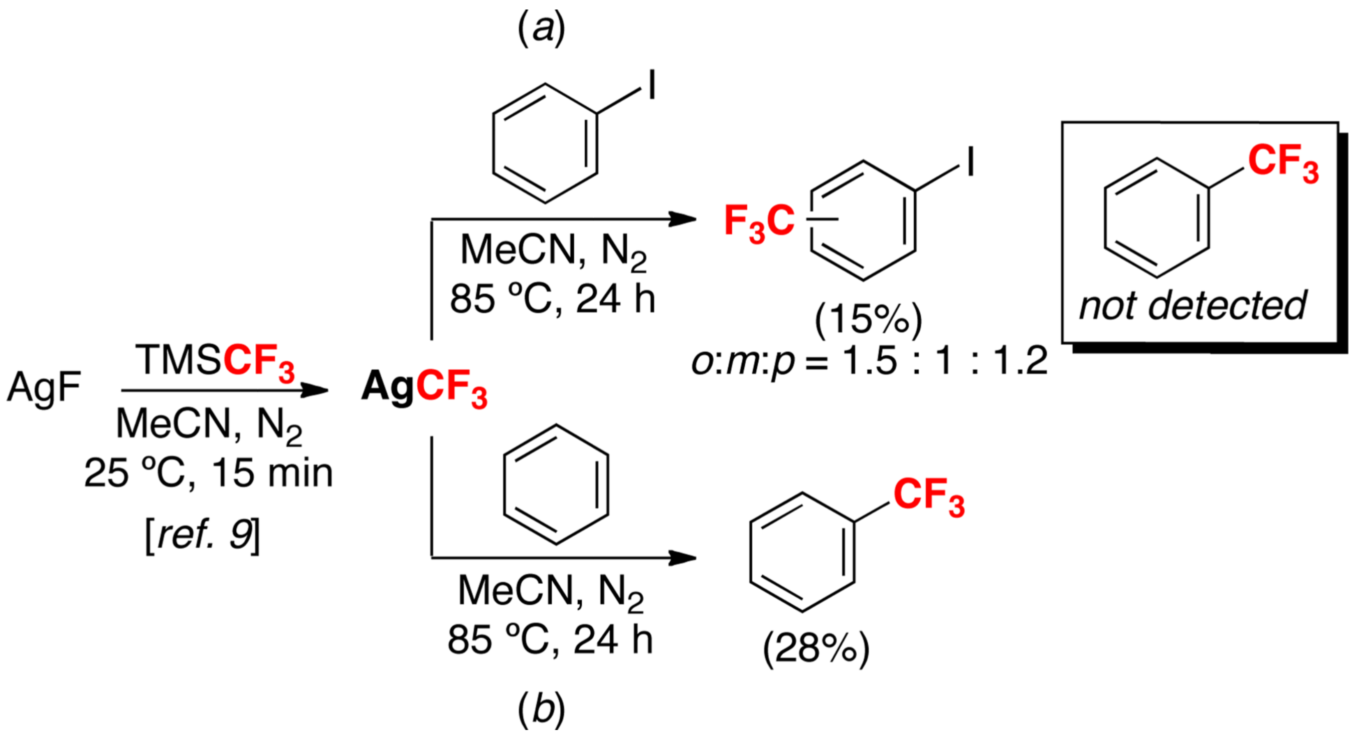
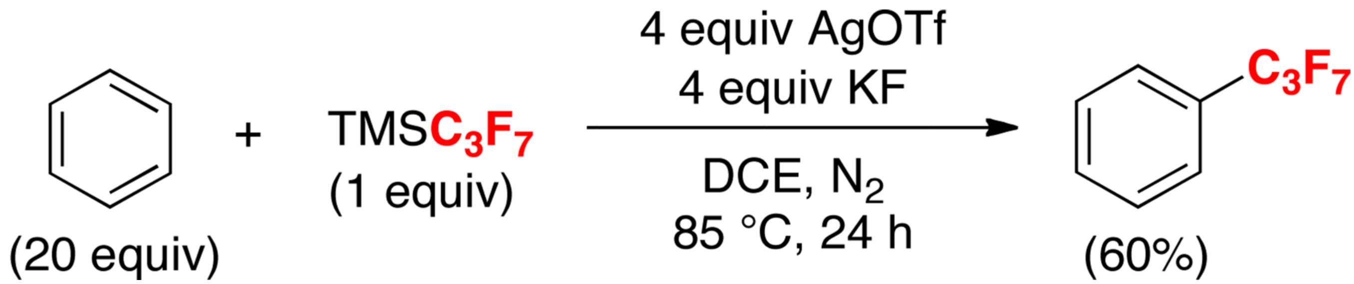
11. Several other heteroaromatics, including furan (16% yield), 2-methylfuran (7% yield), pyridine (2% yield, 2 isomers), and 1-methylimidazole (3% yield, 3 isomers), afforded low yield of mono-trifluoromethylated products under our standard conditions.
12. It is possible that light/AIBN do not have an effect on this system because they are just not capable of promoting the Ag–CF_3 bond homolysis (step *a* in Scheme 3).
13. The different selectivity with CF_3• does not appear to be a temperature or solvent effect. For example, when the Fe-catalyzed reaction of CF_3• with veratrole ([a] in 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).



Scheme 1.
Reaction of $AgCF_3$ with PhI and Benzene



Scheme 2.
Ag-Mediated Perfluoroalkylation of Benzene

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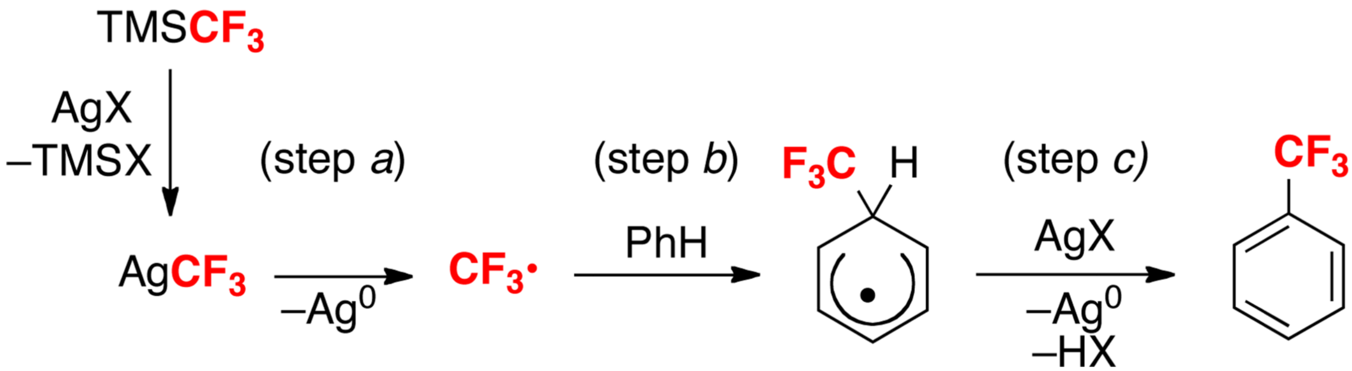
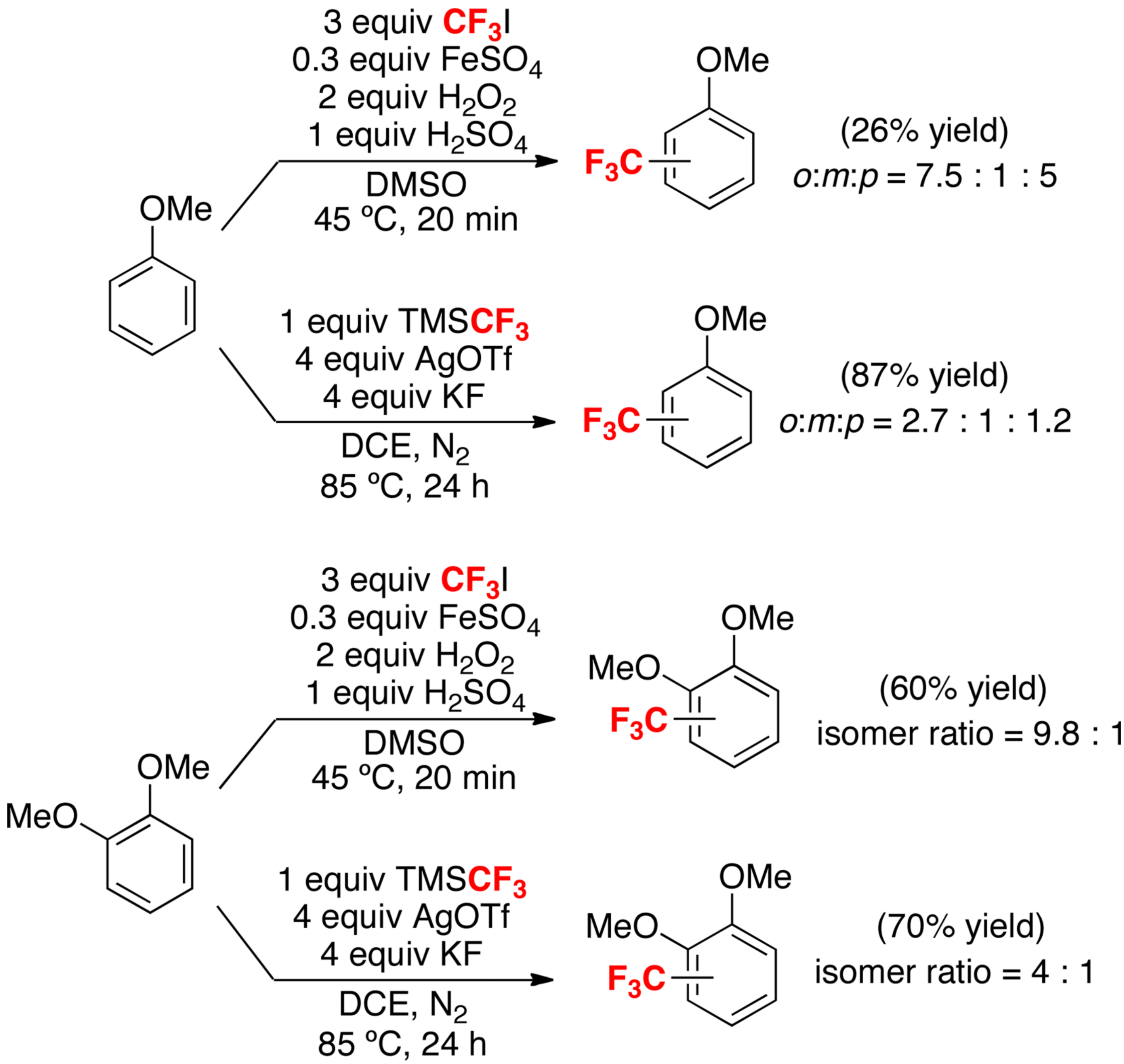


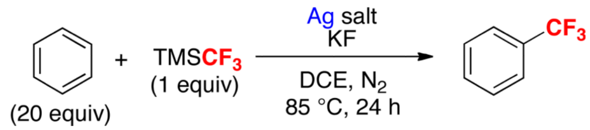
Scheme 3.
Possible Free Radical Pathway for Ag-Mediated Trifluoromethylation



Scheme 4.
Comparison of Reactivity and Selectivity of Radical Trifluoromethylation

Table 1

Optimization of Trifluoromethylation Reaction[a][b]



entry	metal salt	metal salt/ KF equiv	yield (%)
1	AgOAc	2/2	6
2	Ag_2O	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	$[CuOTf]_2{\cdot}C_6H_6$	2/2	0
10	CuI	4/4	0

[a] General conditions: C_6H_6 (20 equiv), $TMSCF_3$ (1 equiv) in DCE at 85 °C for 24 h.

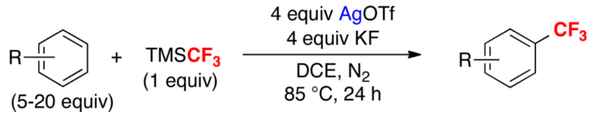
[b] Yields determined by ^{19}F NMR analysis.

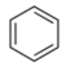
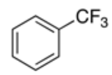
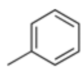
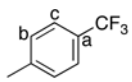
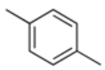
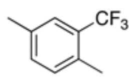
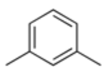
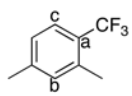
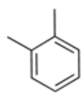
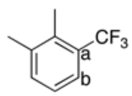
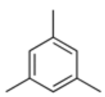
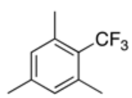
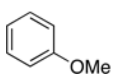
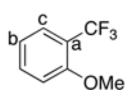
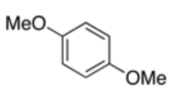
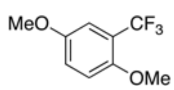
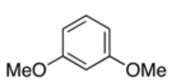
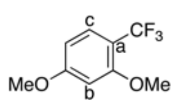
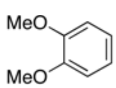
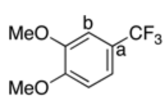
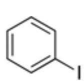
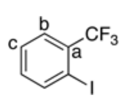
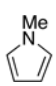
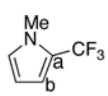
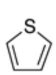
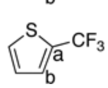
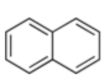
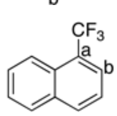
[c] No KF.

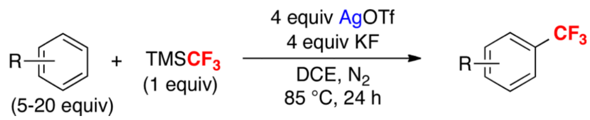
[d] Conditions: C_6H_6 (1 equiv), $TMSCF_3$ (5 equiv), AgOTf (4 equiv), KF (4 equiv) in DCE at 85 °C for 24 h.

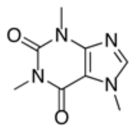
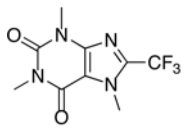
Table 2

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



entry	substrate	major product	yield (%)	isomer ratio
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 substrate used.

[d]5 equiv substrate used.