

Silver-Mediated Trifluoromethylation–Iodination of Arynes

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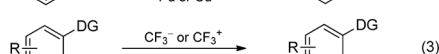
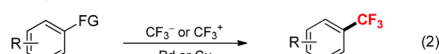
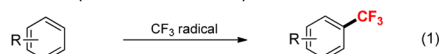
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Supporting Information

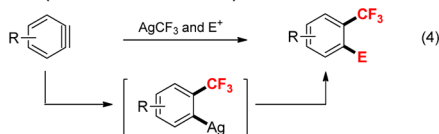
ABSTRACT: An unprecedented silver-mediated vicinal trifluoromethylation–iodination of arynes that quickly introduces CF₃ and I groups onto aromatic rings in a single step to give *o*-trifluoromethyl iodoarenes has been developed. A new reactivity of AgCF₃ has been revealed, and 2,2,6,6-tetramethylpiperidine plays an important role in this difunctionalization reaction.

Trifluoromethylated arenes are intriguing compounds for the development of new pharmaceuticals, agrochemicals, and functional materials because of their unique properties such as increased stability, lipophilicity, and bioavailability.¹ As a result, much effort has been exerted to develop efficient methods of introducing CF₃ group(s) onto aromatic rings.² The previously known methods for this transformation can be divided into three categories: (a) methods involving CF₃ radicals³ (eq 1); (b)

Previous work (monofunctionalization):



This work (vicinal difunctionalization):



methods involving transition-metal-mediated^{4,5} cross-couplings with aryl halides^{4a–d,5a,b} or arylboron reagents^{4e–j} using nucleophilic or electrophilic CF₃ sources (eq 2); and (c) methods involving arene C–H activation followed by Pd(IV)-mediated trifluoromethylation^{5c,d} (eq 3). However, all of these trifluoromethylation methods feature *monofunctionalization* (trifluoromethylation) of aromatic compounds. In this communication, we disclose a new trifluoromethylation protocol, namely, vicinal *difunctionalization* of arenes via Ag-mediated one-step trifluoromethylation–iodination of arynes (eq 4).

Benzyne, with its low-lying LUMO, offers the strategic advantage of enabling the rapid construction of multifunctionalized arenes that are otherwise difficult to synthesize.^{6,7} Previously, during our investigation of the hard/soft nature of α -fluoro carbanions,⁸ we found that nucleophilic trifluoromethylation of benzyne failed, presumably because of the low

stability of “CF₃[–]” (generated from TMSCF₃/F[–]) and the mismatch between the soft benzyne and the hard “CF₃[–]” species.^{8a} We envisioned that this synthetic problem might be solved by using a proper trifluoromethylmetallic species (MCF₃), with the hope that the MCF₃ species would possess increased stability and softness in comparison with the previously used “CF₃[–]”,^{8a} which would enable it to react with arynes. This would allow an in situ-generated aryne species to be trapped by MCF₃ to form an *o*-(trifluoromethyl)arylmatal complex, which would further react with electrophiles to give vicinally difunctionalized arenes (eq 4). *o*-CF₃-containing functionalized arenes can serve as highly useful synthetic building blocks for many applications.

We began by mixing various MCF₃ species with benzyne to see whether trifluoromethylation would take place (Table 1).

Table 1. Reaction of Benzyne, Trifluoromethylmetals, and Various Electrophiles^a

entry	MCF ₃	electrophile	R	yield (%) ^b
1	CuCF ₃	none	H	0
2	Zn(CF ₃) ₂	none	H	0
3	AgCF ₃	none	H	80
4	AgCF ₃	PhCHO	H	82
5	AgCF ₃	NCS	Cl (H)	6 (31)
6	AgCF ₃	NBS	H	5
7	AgCF ₃	NIS	H	15
8	AgCF ₃	<i>n</i> -BuSnCl	H	20
9	AgCF ₃	(<i>n</i> -Bu ₃ Sn) ₂	H	24
10	AgCF ₃	allyl chloride	H	0
11	AgCF ₃	allyl bromide	H	6
12	AgCF ₃	Ph–C≡C–Br	H	69
13	AgCF ₃	Ph–C≡C–I	I (H)	31 (43)

^aReaction conditions: **1a** (0.1 mmol), CsF (0.4 mmol), MCF₃ (freshly prepared, 0.2 mmol), and electrophile (0.2 mmol) in MeCN (4 mL).

^bDetermined by ¹⁹F NMR spectroscopy using [–]OTf (a fragment of **1a**) as an internal standard.

Initially, we examined the reaction of CuCF₃, 2-trimethylsilylphenyl triflate (**1a**) as a benzyne precursor,^{7a} and CsF; however, no trifluoromethylation product was observed (entry 1). Replacing CuCF₃ by Zn(CF₃)₂ gave a similar result (entry 2). Gratifyingly, we found that trifluoromethylsilver (AgCF₃) can smoothly react with benzyne to form PhCF₃ in 80% yield (entry

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3). AgCF_3 was prepared by mixing TMSCF_3 and AgF in 1:1 ratio in acetonitrile at room temperature (rt) for 30 min.^{9a} It is noteworthy that although AgCF_3 is known to be an effective nucleophilic trifluoromethylating agent for certain activated organohalides⁹ and a precursor of CF_3 radical,^{3d,f} its reaction with benzyne has never been reported. To take advantage of benzyne as a vicinally difunctionalizable substrate, a series of electrophiles were added in the reaction to trap the *o*-(trifluoromethyl)-arylsilver intermediate (entries 4–13). While benzaldehyde was unreactive (entry 4), *N*-chlorosuccinimide (NCS) gave *o*-chlorotrifluoromethylbenzene in 6% yield along with a 31% yield of PhCF_3 (entry 5). *N*-Bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) failed to give the desired *o*-halogenated trifluoromethylbenzenes, and only a small amount of PhCF_3 was formed in each case (entries 6 and 7). Our attempts to obtain transmetalation products by using organotin reagents also failed (entries 8 and 9). Allyl chloride and bromide were found to be unsuitable electrophiles for the reaction (entries 10 and 11). Other mild X^+ reagents such as 1-bromophenylacetylene (entry 12) and 1-iodophenylacetylene (entry 13) were tried, and to our delight, the latter one gave the desired iodination product in 31% yield along with a 43% yield of the protonated product PhCF_3 .¹¹

Encouraged by the iodination result (Table 1, entry 13), we further optimized the reaction conditions, mainly focusing on suppressing the undesired protonation product PhCF_3 . Our initial attempts to suppress the undesired protonation process completely¹⁰ by carrying out all of the operations under anhydrous conditions were unsuccessful. Therefore, we tried a new strategy, namely, adding an external additive/ligand to accelerate the iodination process, thus enhancing the ratio of iodinated to protonated product (Table 2). After a quick screening (entries 1–6), we concluded that alkylamines are suitable ligands for promoting the iodination. Further studies

showed that the hindered secondary amine 2,2,6,6-tetramethylpiperidine (TMP) could serve as a privileged ligand for the reaction (entries 7–13), affording a 70% yield of the iodinated product with complete suppression of the undesired protonation (no PhCF_3 was observed; see entry 13). Finally, after further tuning of the reaction parameters, the best result (82% yield of *o*-iodotrifluoromethylbenzene with no formation of PhCF_3) was obtained by using **1a** (0.1 mmol), CsF (0.4 mmol), freshly prepared AgCF_3 (0.3 mmol), **3** (0.3 mmol), and TMP (0.3 mmol) in MeCN (4 mL) (Table 2, entry 14).

Having the optimized reaction conditions in hand, we then examined the scope of the reaction using a variety of structurally diverse aryne precursors (Table 3). It was found that substrates

Table 2. Optimization of the Trifluoromethylation–Iodination of Benzyne by Screening of External Ligands^a

$\text{R}-\text{C}_6\text{H}_3(\text{TMS})(\text{OTf}) + [\text{AgCF}_3] + \text{Ph}-\text{C}\equiv\text{C}-\text{I} \xrightarrow[\text{MeCN, 50 }^\circ\text{C, 5 h}]{\text{CsF, ligand}} \text{R}-\text{C}_6\text{H}_3(\text{CF}_3)(\text{I})$			
entry	ligand	yield (%) ^b	
		R = H	R = I
1	MeOH	33	35
2	PPh_3	0	0
3	PhSMe	0	16
4	pyridine	14	30
5	phen	4	50
6	<i>n</i> -PrNH ₂	2	59
7	(<i>n</i> -Pr) ₂ NH	9	43
8	(<i>n</i> -Pr) ₃ N	6	6
9	Et_2NH	0	54
10	Et_3N	0	11
11	piperidine	0	32
12	PMP ^c	50	29
13	TMP	0	70
14 ^d	TMP	0	82

^aReaction conditions: **1a** (0.1 mmol), CsF (0.4 mmol), **2** (freshly prepared, 0.2 mmol), **3** (0.2 mmol), and ligand (0.2 mmol) in MeCN (4 mL). ^bDetermined by ^{19}F NMR spectroscopy using ^-OTf (a fragment of **1a**) as an internal standard. ^c1,2,2,6,6-Pentamethylpiperidine. ^dOptimized conditions: **1a** (0.1 mmol), CsF (0.4 mmol), **2** (freshly prepared, 0.3 mmol), **3** (0.3 mmol), and TMP (0.3 mmol) in MeCN (4 mL).

Table 3. Scope of Silver-Mediated Trifluoromethylation–Iodination of Arynes^a

$\text{R}-\text{C}_6\text{H}_3(\text{TMS})(\text{OTf}) + [\text{AgCF}_3] + \text{Ph}-\text{C}\equiv\text{C}-\text{I} \xrightarrow[\text{MeCN, 50 }^\circ\text{C, 5 h}]{\text{CsF, TMP}} \text{R}-\text{C}_6\text{H}_3(\text{CF}_3)(\text{I})$			
entry ^a	substrates (1)	product (4)	yield (%) ^b
1	1a	4a	71
2	1b	4b	72
3	1c	4c	86
4	1d	4d	43
5	1e	4e (50 : 50) ^c	94
6	1f	4f	37
7	1g	4g (50 : 50) ^c	61
8	1h	4h	51
9	1i	4i	35
10	1j	4j	53

^aThe reaction was conducted on a 0.5 mmol scale under the optimized conditions. ^bIsolated yields. ^cThe ratio of regioisomers was determined by ^{19}F NMR spectroscopy prior to isolation.

bearing electron-donating groups (entries 3 and 6) are amenable to the present Ag-mediated trifluoromethylation–iodination process. Functional groups such as acetal, bromo, and allyl are compatible with this reaction (entries 3, 9, and 10). Noteworthy is the perfect regioselectivity observed in the reaction with 3-substituted benzyne, as **4f**, **4i**, and **4j** were formed as single isomers. In contrast, the reactions with 4-phenylbenzyne and 4-

methylbenzynes gave almost 1:1 ratios of regioisomeric products **4e** and **4g** in yields of 94 and 61%, respectively.

To gain more insights into the present trifluoromethylation–iodination reaction, we carried out preliminary mechanistic studies. First, we examined the interaction between AgCF_3 and TMP (Figure 1).⁹ Naumann et al.^{9b} reported that there is an

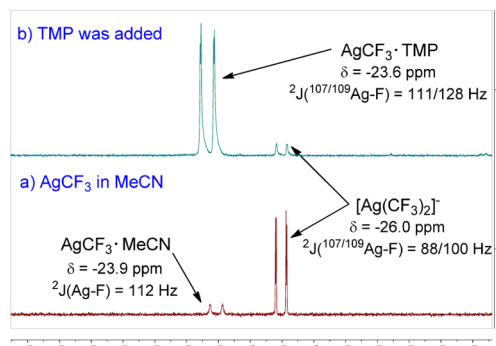
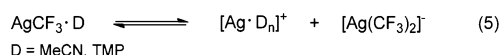


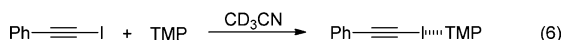
Figure 1. ^{19}F NMR monitoring of the coordination between AgCF_3 and TMP at rt.

equilibrium between the neutral species $\text{AgCF}_3\cdot\text{D}$ and the ionic species $[\text{Ag}(\text{CF}_3)_2]^-$ (eq 5) and that the equilibrium constant



depends on the solvent. We found that the $\text{AgCF}_3\cdot\text{MeCN}/[\text{Ag}(\text{CF}_3)_2]^-$ ratio was 1:3.8 in MeCN (Figure 1a). However, upon addition of TMP to AgCF_3 (in a 1:1 ratio), the new complex $\text{AgCF}_3\cdot\text{TMP}$ was instantaneously formed (as monitored by ^{19}F NMR spectroscopy), and the $\text{AgCF}_3\cdot\text{TMP}/[\text{Ag}(\text{CF}_3)_2]^-$ ratio was 18.8:1 (Figure 1b). It is reasonable to assume that the new complex $\text{AgCF}_3\cdot\text{TMP}$ has better reactivity than $[\text{Ag}(\text{CF}_3)_2]^-$ toward benzyne because of the increased electron density on the silver atom resulting from TMP coordination.

We also investigated the interaction between TMP and 1-iodophenylacetylene (eq 6). Although the halogen bonding



between 1-iodoacetylene and various donors has been extensively studied by Laurence and co-workers¹² and Goroff and co-workers¹³ using IR and ^{13}C NMR spectroscopies, the donor–acceptor interaction between 1-iodophenylacetylene and TMP in MeCN has never been reported. Indeed, our ^{13}C NMR study showed a strong halogen-bonding interaction between TMP and 1-iodophenylacetylene, as the C1 atom in 1-iodophenylacetylene was significantly deshielded (Figure 2).¹³

To probe whether the present trifluoromethylation–iodination reaction involves a radical process, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a well-known radical scavenger, was added to the reaction under the standard conditions (Table 2, entry 14). The desired product was still formed in 80% yield (eq 7), suggesting that a mechanism involving a radical pathway is less likely.¹⁴ We also studied the feasibility of deprotonation of TMP under the standard reaction conditions. When AgCF_3 , CsF, and deuterated TMP were mixed, CHF_3 and CDF_3 were slowly generated (eq 8), indicating that deprotonation of TMP during the reaction is possible. Furthermore, as shown in Table 2,

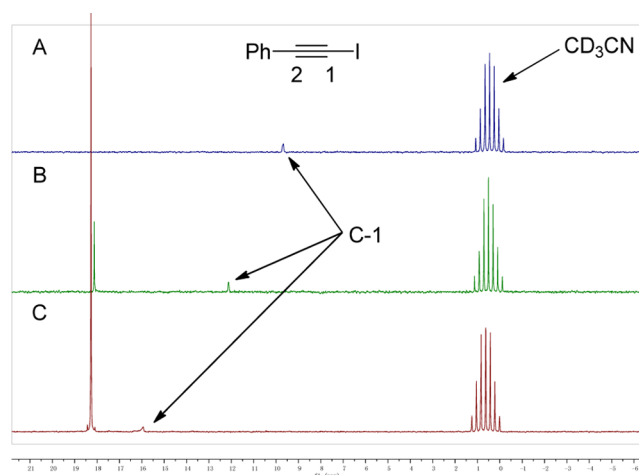
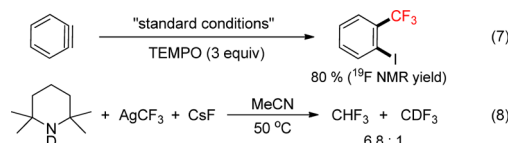


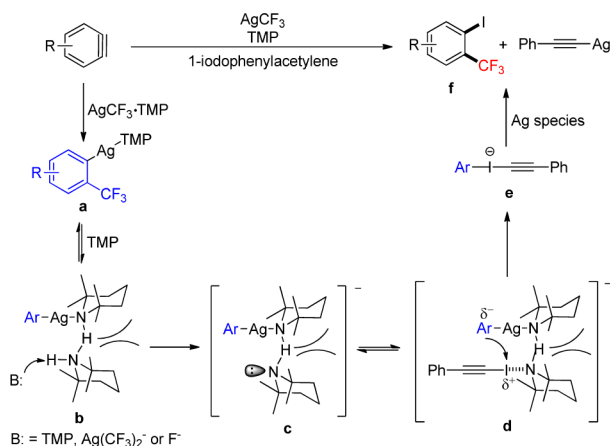
Figure 2. ^{13}C NMR monitoring of the halogen bonding between 1-iodophenylacetylene and TMP at rt. A: 1-iodophenylacetylene (0.188 mmol) in 0.5 mL of CD_3CN ; B: 1-iodophenylacetylene (0.188 mmol) and TMP (1 equiv) in 0.5 mL of CD_3CN ; C: 1-iodophenylacetylene (0.188 mmol) and TMP (5 equiv) in 0.5 mL of CD_3CN .



tertiary amines are far less effective than primary and secondary amines in promoting the iodination (entries 6–13); therefore, hydrogen bonding may play an important role in the reaction. In addition, the great difference between piperidine and TMP (entries 11 and 13) indicates that the reaction is also sensitive to the steric bulk of the ligand.

With the aforementioned experimental results and mechanistic considerations, we propose a plausible reaction mechanism for this unprecedented Ag-mediated and TMP-promoted trifluoromethylation–iodination process (Scheme 1). The in situ-generated aryne reacts with $\text{AgCF}_3\cdot\text{TMP}$ via a carboargenation step to afford intermediate **a**,¹⁵ which forms hydrogen bonds with another TMP to give **b**.¹⁶ Intermediate **b** undergoes deprotonation to generate anionic intermediate **c**, which can be stabilized by charge delocalization. Subsequent coordination of **c**

Scheme 1. Proposed Mechanism for Ag-Mediated Trifluoromethylation–Iodination of Arynes



with iodophenylacetylene via halogen bonding gives rise to intermediate **d**,^{12,13} from which ate complex **e** is formed by intramolecular nucleophilic attack.¹⁷ Complex **e** readily produces substituted *o*-iodotrifluoromethylbenzene **f** and silver phenylacetylide¹⁸ as a byproduct in the presence of silver species.¹⁹ The beneficial effects of TMP may be summarized as follows: (a) TMP may increase the electron density on Ag and thus enhance the nucleophilicity of AgCF₃;²⁰ (b) TMP may reduce the energy barrier of the iodination step through the formation of a six-membered ring by hydrogen bonding and halogen bonding (see **d** in Scheme 1); and (c) steric hindrance due to TMP may enhance the rigidity of the transition state and therefore increase the proximity between the aryl group and the iodine atom (see **d** in Scheme 1 and Table 2, entries 11 and 13).

In conclusion, we have developed an unprecedented one-step protocol for trifluoromethylation–iodination of arynes. This method provides a simple and efficient route to various *o*-trifluoromethylated iodoarenes that are otherwise difficult to synthesize by traditional methods²¹ but have many potential synthetic applications in life- and materials-science-related fields. Additionally, the new reactivity of AgCF₃ reported herein promises to trigger further development of silver-mediated fluoroalkylation reactions, which is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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