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New Reagent for Highly Efficient Synthesis of Trifluoromethyl-Substituted Arenes and Heteroarenes

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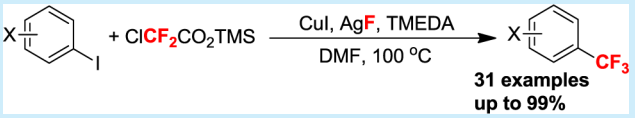
Supporting Information

ABSTRACT: A new reagent trimethylsilyl chlorodifluoroacetate (**TCDA**) is reported for the introduction of a $-CF_3$ group to arenes and heteroarenes. Compared with current known reagents, **TCDA** shows very broad scope with respect to electron-deficient, -neutral, and -rich aryl/heteroaryl iodides as well as excellent functional group tolerance, including ester, amide, aldehyde, hydroxyl, and carboxylic acid.

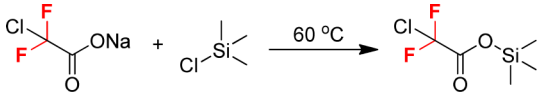


Fluorinated organic compounds play a key role in medicinal, agricultural, and material sciences.[1,2] For example, in small molecule drug discovery, CF_3 is a popular functional group because it can improve the binding affinity, physicochemical properties, and metabolic stability of molecules.[3] As such, several top-selling drugs contain a CF_3 group, such as sitagliptin (Januvia), celecoxib (Celebrex), and emtricitabine (Atripla). In general, the chemistry to incorporate this important motif can be classified into three categories: electrophilic ($+CF_3$), nucleophilic ($-CF_3$), and radical ($^{\bullet}CF_3$) reactions. The more widely used electrophilic trifluoromethylating reagents include trifluoromethylsulfonium salts such as Umemoto's salt and Togni's hypervalent iodine $-CF_3$.[4,5] Nucleophilic reagents are usually derived from fluoroform and (trialkylsilyl)-trifluoromethanes including Ruppert–Prakash's $TMSCF_3$.[6,7] Additionally, methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2CH_3$) and methyl chlorodifluoroacetate ($ClCF_2CO_2Me$) can also be considered nucleophilic trifluoromethylation reagents.[8,9] In this case, the reaction proceeds via a difluorocarbene intermediate followed by the formation of a $^{-}CF_3$ anion either by the reagent itself or in the presence of KF and CuI. Langlois and Baran have reported the use of trifluoromethane sulfinate salt as a radical C–H trifluoromethylation reagent.[10,11] In 2011, MacMillan's group described the photoredox trifluoromethylation reaction of CF_3SO_2Cl with a Ru(II) or Ir(III) complex as a photosensitizer.[12] However, with the exception of methyl chlorodifluoroacetate,[13] none of the above-reported reagents can be utilized for the introduction of $[^{18}F]CF_3$. We designed a new reagent, **TCDA**, which has been demonstrated to efficiently introduce a CF_3 group via cooperative interaction of AgF and CuI. In addition, **TCDA** can be potentially used as an alternative of $ClCF_2CO_2Me$ to incoporate $[^{18}F]CF_3$ in one-pot synthesis under milder conditions due to the formation of a favorable strong Si–F bond, AgCl, and CO_2 gas.

Herein, we report the synthesis, reaction optimization and application of this new reagent for the introduction of a trifluoromethyl group. The scope of this transformation, which is tolerant to alcohol, aldehyde, phenol, Boc-protected amine, and carboxylic acid groups, is also explored and discussed. In terms of the trifluoromethylation of protic substrates, only a few examples in the presence of a carboxylic acid have been demonstrated to date by Baran and MacMillan;[11,12] however, regioselectivity is often an issue due to the C–H-activated radical reaction. Another publication from Hartwig et al. has described a copper-catalyzed trifluoromethylation of iodoarenes containing a hydroxyl-alkyl group.[14]

As shown in Scheme 1, **TCDA** is prepared in a one-step process by mixing sodium chlorodifluoroacetate and chlorotrimethylsilane without the need for a solvent. Distillation affords the compound as a colorless liquid with greater than 95% purity and in 43% yield. The reaction was run on a ≥20 g scale, and the purification required only one distillation. As such, **TCDA** is very convenient to prepare on scale. Both starting materials are cheap and commercially available. In terms of chemical stability, the **TCDA** was stored under nitrogen at 5 °C for a week, and it displayed reactivity similar to that of freshly prepared material. Both ^{1}H and ^{19}F NMR spectra exhibited no obvious decomposition.

Scheme 1. Synthesis of TCDA



Before exploring the broader reactivity of **TCDA**, we wanted to establish optimal reaction conditions. In theory, at least 2 equiv of AgF should be used together with **TCDA** in order to introduce a CF_3 group. The silver-mediated C–H trifluoromethylation was reported by Sanford and Bräse et al., and Hu's group also described a similar trifluoromethylation for the iodination of arynes, in which $AgCF_3$ is proposed to be the intermediate.[15,16] Using this as a starting point, we first tried using AgF and **TCDA** to trifluoromethylate an aryl iodide.

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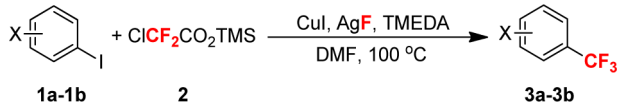
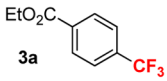
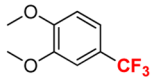
$AgCF_3$ was assumed to be formed under the reaction conditions, followed by reaction with 4-iodobenzoate or dimethoxybenzene iodide. However, no desired product was formed either with or without TMEDA as a ligand (entries 1 and 2, Table 1). The use of stoichiometric amounts of CuI, AgF, and TMEDA allowed us to obtain the trifluoromethylated product in 57% and 17% yields (entries 4 and 11, Table 1).

Table 1. Optimization of the Molar Ratio of Reagents[a]



1a-1b 2 3a-3b

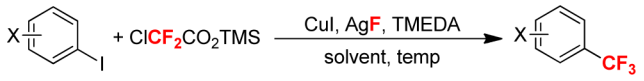
entry	product	2/CuI/AgF/TMEDA (equiv)	yield [%]
1		1.5:0:3:0	0
2		1.5:0:3:1.5	0
3		1:0.1:2:0.1	5
4		1:1:2:1	57
5		1.5:1.5:3:1.5	69
6		2:2:4:2	95
7		2.5:2.5:5:2.5	91
8		1.5:0:3:0	0
9		1.5:0:3:1.5	0
10		1:0.1:2:0.1	0
11		1:1:2:1	17
12		1.5:1.5:3:1.5	33
13		2:2:4:2	51
14		2.5:2.5:5:2.5	66

[a]Reaction conditions: **1a,b** (0.5 mmol), CuI, AgF, TMEDA, and **2** in DMF (1 mL) were stirred at 100 °C under nitrogen in a sealed vial for 1 h. Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. The yield was reported as an average of two runs.

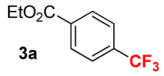
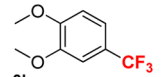
In order to identify general reaction conditions, we optimized the trifluoromethylation using both electron-poor 4-iodobenzoate and electron-rich dimethoxybenzene iodide as substrates. Considering the potential radiochemistry and the half-life of ^{18}F (110 min), the desired optimized reaction time was set at 1 h. Initial optimization experiments starting with catalytic CuI and TMEDA led to either very low yield when using electron-poor 4-iodobenzoate or no desired product in the case of electron-rich dimethoxybenzene iodide (entries 3 and 10, Table 1). Increasing the molar ratio of **TCDA**, CuI, AgF, and TMEDA to 1.5:1.5:3:1.5 afforded a moderate yield of 69% for the electron-deficient aryl iodide in 1 h and 33% for the electron-rich aryl iodide (entries 5 and 12, Table 1). As indicated in Table 1, a good yield was obtained in the case of the electron-poor iodobenzoate when the molar ratio was raised to 2:2:4:2 or 2.5:2.5:5:2.5 (entries 6 and 7, Table 1). However, the higher loading of 2.5:2.5:5:2.5 was required to give a good yield (66%) for electron−rich dimethoxybenzene iodide, and consequently, these conditions were selected in order to optimize solvent and temperature.

As indicated in Table 2, no desired product was formed when DMSO was used as solvent, and a lower yield was observed in NMP at 100 °C relative to DMF (entries 5 and 10), which proved to be the solvent of choice. In terms of reaction temperature, higher yields were obtained at 100 °C as opposed to either 90 or 110 °C (entries 1−3 and 6−8). After this

Table 2. Optimization of the Temperature and Solvent[a]



1a-1b 2 3a-3b

entry	product	temp °C	yield [%]
1		90	66
2		100	91
3		110	76
4		100	0 (DMSO)
5			57 (NMP)
6		90	32
7		100	66
8		110	52
9		100	0 (DMSO)
10			57 (NMP)

[a]Reaction conditions: **1a,b** (0.5 mmol), **2**, CuI, AgF, and TMEDA (2.5:2.5:5:2.5) in DMF (1 mL) were stirred at different temperatures under nitrogen in a sealed vial for 1 h. Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. The yield was reported as an average of two runs.

process of optimization, the preferred reaction conditions appeared to be a molar ratio of 2.5:2.5:5:2.5 (TCDA/CuI/AgF/TMEDA) in DMF at 100 °C. These conditions were applied while carrying out reaction scope explorations.

Having optimized reaction conditions, we turned our attention to investigate the scope of this transformation. A broad range of aryl iodide coupling partners were explored with reactions being analyzed at different reaction time points (1, 2, and occasionally 6 h depending on the substrate). As shown in Table 3, it is clear that ring electronics do not effect the reaction yield. Under identical reaction conditions, use of electron-deficient, -neutral or -rich aryl iodides gave high yields of trifluoromethylated product, although the reaction proceeded faster for electron-poor aryl iodides. In many cases, we experienced difficulties in isolating the trifluoromethylated products either in high yield or in pure form, probably due to their high volatility or similar polarity to the iodoarene starting materials. For example, in the case of compounds **3c** and **3k**, the isolated yields of 79% and 27% are much lower than those detected by NMR spectroscopy (entries 3 and 11, Table 3). Furthermore, the low yield observed with ortho-substituted aryl iodides, such as seen for entry 8 (28%), is likely due to the steric hindrance, which could also explain low yield of 35% for entry 27. Nonetheless, the reaction is tolerant of a wide range of aryl iodides containing reactive functional groups, such as nitro, ester, formyl, cyano, amide, hydroxyl, and carboxylic acid groups (entries 1, 3−7, 9−10, and 13−15, Table 3). The high yield (57−99%) for reactions with pyrimidine, quinoline, thiophene, and pyrazole is also very encouraging (entries 22−26 and 29−31, Table 3). Also of interest is that trifluoromethylation of bromo- and chloro-substituted iodoarenes **3k** and **3w** selectively takes place at the iodide.

Although the electron-neutral and electron-rich iodoaryls reacted slowly with **2**, excellent yields were also obtained in 2 or 6 h (**3b**, **3r**, **3s**, **3t**, Table 3). Good yields were also obtained for the reaction of **2** with iodoarenes containing protic functional groups, such as carboxylic acid, hydroxyl, and Boc-protected amine (**3j**, **3m**, **3n**, and **3o**). The reaction of aniline did not afford the desired product (entry 16, Table 3). Instead, the compound **3p** was formed, probably as a result of further reaction of the trifluoromethylated aniline with DMF. This was supported by ^1H NMR and LCMS spectra and is consistent with the published data.[17] The excellent tolerance of protic

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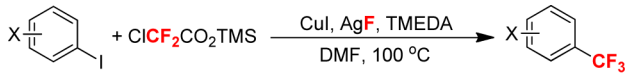
Table 3. Substrate Scope of the Trifluoromethylation[a]



1a-1ae 2 3a-3ae

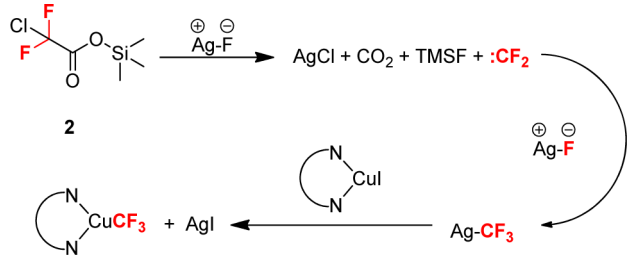
entry	product	yield [%] 1 h	yield [%] 2 h	entry	product	yield [%] 1 h	yield [%] 2 h	entry	product	yield [%] 1 h	yield [%] 2 h
1	3a	91	98 (82)[b]	12	3l	43	49	23	3w	98	
2	3b	66	72(91)[c]	13	3m	31	40(66)[c]	24	3x	56	57
3	3c	99 (79)[b]		14	3n	27	32	25	3y	44	46(69)[c]
4	3d (90 °C)	63	65 (43) [b]	15	3o	52	64(87)[c]	26	3z	74	74(99)[c]
5	3e	78	87 (75)[b]	16	3p [d]	6	17	27	3aa	29	35
6	3f	63	62(87)[c]	17	3q (90 °C)	33	42	28	3ab	16	29
7	3g	88	95	18	3r	47	56(97)[c]	29	3ac	52	65
8	3h	26	28	19	3s	47	56(91)[c]	30	3ad	56	91
9	3i	58	70 (50)[b]	20	3t	40	51(95)[c]	31	3ae	82	85
10	3j	47	64 (53)[b]	21	3u	48	61				
11	3k	77	84 (27)[b]	22	3v	76	83				

[a]Reaction conditions: **1a−ae** (0.5 mmol), CuI (1.25 mmol), AgF (2.5 mmol), TMEDA (1.25 mmol), and **2** (1.25 mmol) in DMF (1 mL) were stirred at 100 °C unless specified under nitrogen in a sealed tube. Yields were determined by ^{19}F NMR spetroscopy using $PhCF_3$ as an internal standard. The yield was reported as an average of two runs. [b]Isolated yield. [c]Yield after 6 h. [d]**1** was 4-iodoaniline, **2**/CuI/AgF/TMEDA = 3:2.5:6:2.5, DMF as solvent.

fuctionality is particularly interesting. Given the simplicity and efficiency of this method, we expect the incorporation of a CF_3 group at a late stage in a synthetic sequence should be possible, even in highly functionalized molecules. This would be of particular use in PET labeling chemistry to introduce $[^{18}F]CF_3$ for PET-imaging studies of clinical compounds.

The reaction is believed to occur in a stepwise manner as shown in Scheme 2. In the first step, **TCDA** reacts with AgF to produce difluorocarbene, with the formation of AgCl, a strong Si−F bond, and CO_2 gas as the driving force. The CF_2 carbene then reacts with fluoride provided by second equivalent of AgF to form trifluoromethyl anion $^-CF_3$. The presence of the $^-CF_3$ intermediate was recently confirmed by Prakash and Olah et al.[18] The resulting $AgCF_3$ exchanges a ligand with a copper iodide complex to give AgI and $CuCF_3$.[19] It is well accepted that $CuCF_3$ is the reactive complex formed in copper-catalyzed trifluoromethylation reactions, and once generated, the reaction

Scheme 2. Proposed Reaction Mechanism



with iodoaryls or iodoheteroaryls follows the well-established mechanism to provide trifluoromethylated products.[20]

In summary, we have shown the design, synthesis, and application of an easily accessible and relatively inexpensive reagent to introduce a trifluoromethyl group under mild conditions. The reagent **TCDA** provides good conversion of electron-deficient, -neutral, and -rich substrates in comparison

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to current alternative methods, and it exhibits remarkably high functional group tolerance. Further studies focusing on trifluoromethylation reactions with **TCDA** in the context of radiolabeling (i.e., introducing $[^{18}F]CF_3$) are ongoing in our group and shall be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization. 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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