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Trifluoromethylation of aryl and heteroaryl halides

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1. Introduction

The trifluoromethyl group (CF_3) is an important structural moiety present in diverse classes of bioactive organic molecules including novel pharmaceuticals and agrochemicals.[1–4] In fact, several commercially available pharmaceuticals such as Prozac and Celebrex contain an aryl-trifluoromethyl group (Fig. 1). The benefit of introducing the trifluoromethyl group in prospective drug candidates is well documented[2] and it is reasonable to predict that more trifluoromethylated drugs will be developed in the future.

Bearing strong electronegativity and having a size roughly twice that of a methyl group,[2a] the trifluoromethyl functionality is often used in medicinal chemistry to impart substantial changes in physiochemical, biological, and pharmacological properties for 'drug-like' molecules. The lipophilic nature of the trifluoromethyl group can increase lipid solubility of drugs, thus enhancing their ability to penetrate through the cell membrane. Many CNS active drugs contain a trifluoromethyl group, which enhances penetration of the drug molecule through the blood–brain barrier in sufficient concentration to create the desired level of biological activity. Interestingly, the presence of a 3,5-di(trifluoromethyl)phenyl group significantly increases the binding affinity of many neurokinin 1 (NK1) antagonists ('magic bullets').[5] The strong C–F bond in the trifluoromethyl group in aromatics or heteroaromatics imparts increased metabolic stability of these molecules. Overall, this unique functionality has been frequently used to enhance binding selectivity, elevate lipophilicity, and improve metabolic stability in the prospective drug candidates.[2,5]

Extensive efforts have led to new methods for the introduction of the trifluoromethyl group onto aromatic and heteroaromatic ring systems. The most synthetically useful method of effecting this transformation is the coupling of the corresponding aryl and heteroaryl halides with a trifluoromethylcopper species.[1] This enables one to conveniently incorporate the trifluoromethyl group at the later stage of a synthetic sequence rather than relying on commercially available CF_3-containing building blocks, which would be

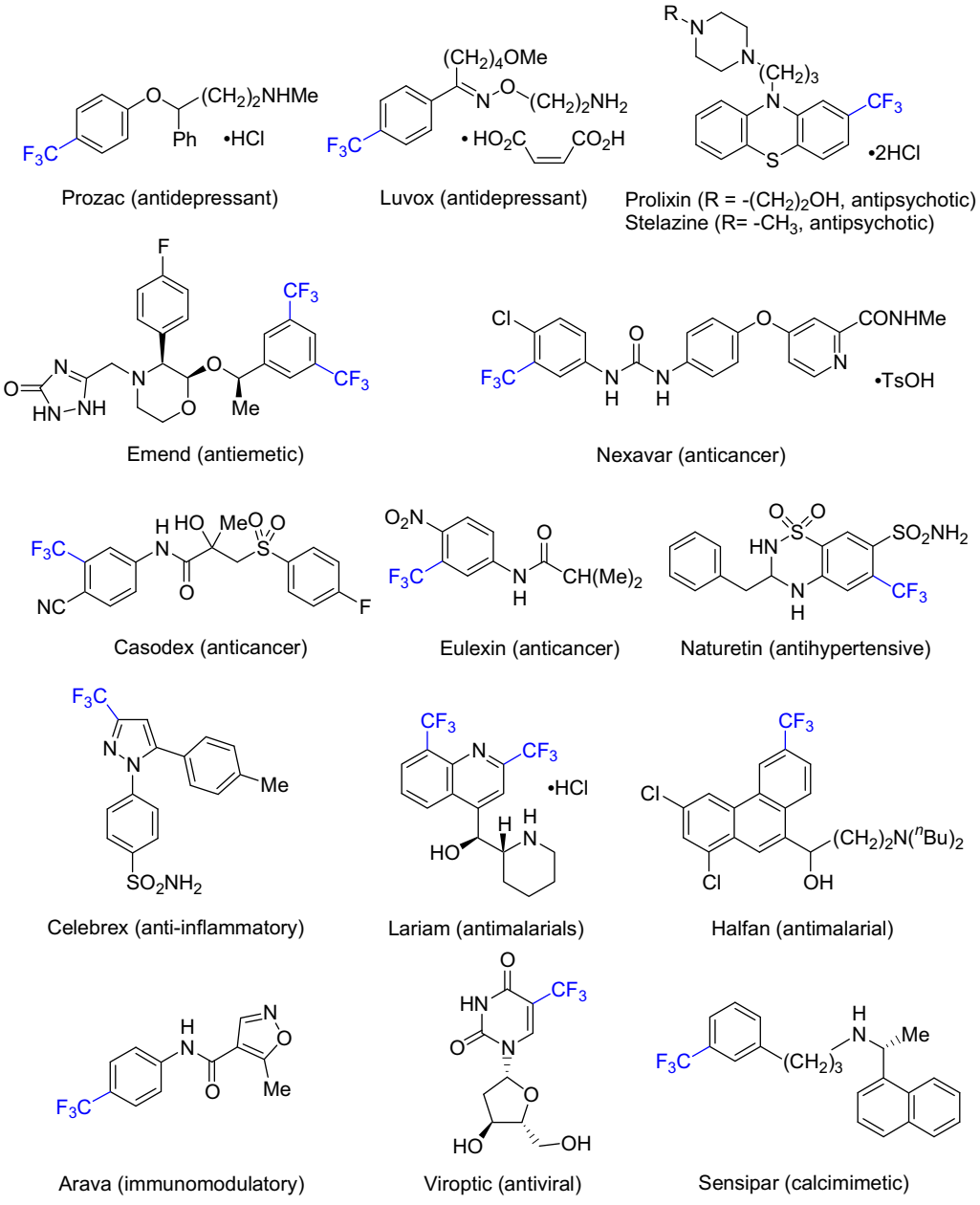


Fig. 1.

a limiting factor in exploring diversity space. Although other methods are available for the preparation of trifluoromethylated aromatics and heteroaromatics,[6] they have limited substrate scope and the *selective* introduction of trifluoromethyl functionality cannot be controlled in most cases. Therefore, trifluoromethylation of aryl and heteroaryl halides has become an important reaction type in synthetic organic chemistry.

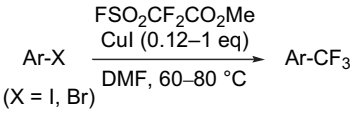
In this review, we will focus our attention on the regioselective trifluoromethylation of aryl and heteroaryl halides. These halides regularly find utility for the preparation of simple trifluoromethyl building blocks as well as serving to directly introduce a CF_3 group into advanced intermediates at the late stage. We survey what has been successfully achieved with various aromatic and heterocyclic halide substrates as well as functional groups that can tolerate this transformation.

Aryl and heteroaryl iodides are the preferred substrates among all halides for common copper-mediated trifluoromethylation reactions based on the order of reactivity iodide>bromide≫chloride. Different aryl and heteroaryl iodides have been efficiently converted to the corresponding trifluoromethyl derivatives. Aryl bromides have also been successfully used in trifluoromethylation reactions to replace a bromine atom with a CF_3 group. Although trifluoromethylation of aryl iodides would seem to be the most attractive reaction, utilization of aryl bromides is highly useful due to the greater commercial availability of bromide building blocks as compared to the number of commercially available aryl iodides. Yields that are not listed in this review were not reported in the paper.

2. Trifluoromethylation using methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$)

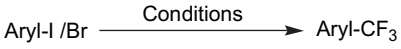
2.1. Reactions of $FSO_2CF_2CO_2Me$ with aryl iodides and bromides

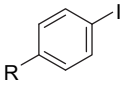
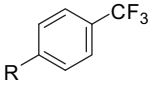
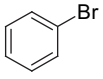
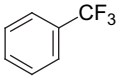
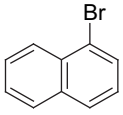
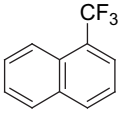
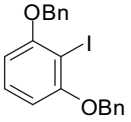
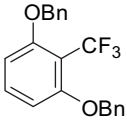
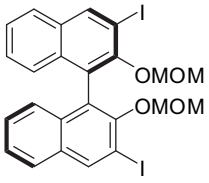
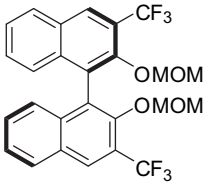
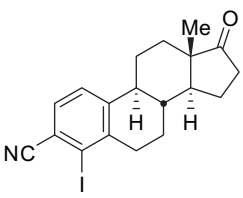
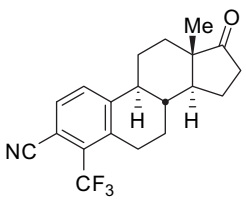
Chen and Wu first reported a convenient trifluoromethylation of aromatic iodides using methyl fluorosulfonyldifluoroacetate [methyl 2,2-difluoro-2-(fluorosulfonyl)acetate].[7] Thus, treatment of aryl iodides with methyl fluorosulfonyldifluoroacetate (MFSDA, 2 equiv) in the presence of catalytic copper(I) iodide (12 mol %) in either DMF or DMSO at 60–80 °C for 2–6 h gave the desired products in excellent yield (Scheme 1, Table 1, entry 1). These researchers also demonstrated the successful trifluoromethylation of aryl bromides using MFSDA (entries 2 and 3). This procedure was also applied to related allyl halides (X=I, Br) and benzyl halides (X=I, Br, Cl) to prepare the corresponding trifluoromethyl compounds in 53–81% yields. Copper(I) iodide was found to be essential for this reaction; no conversion to the desired benzotrifluorides was observed in absence of CuI or by replacement with potassium iodide. These observations validate the existence of the active trifluoromethylcopper species in this process.



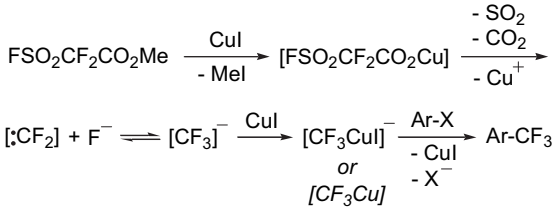
Scheme 1.

Table 1



Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		$FSO_2CF_2CO_2Me$, CuI, DMF, 70 °C		R=H (84%)[7] R=Cl (78%)[7]
2		$FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C		(61%)[7]
3		$FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C		(70%)[7]
4		$FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 80 °C		(82%)[8]
5		$FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 70 °C		(93%)[9]
6		$FSO_2CF_2CO_2Me$, CuI, DMF, 110 °C		(76%)[10]

The authors propose that the copper salt [$FSO_2CF_2CO_2Cu$], formed initially by the coupling of MFSDA and CuI, decarboxylates readily to yield difluorocarbene [:CF_2] and fluoride ion, which are in equilibrium with trifluoromethide anion [CF_3]$^-$ (Scheme 2). The [CF_3]$^-$ in the presence of CuI readily forms [CF_3CuI]$^-$, thus shifting the equilibrium in the forward direction. The nucleophilic attack of [CF_3CuI]$^-$ on the aryl halide provides the desired product. The intermediacy of [CF_3CuI]$^-$ instead of [CF_3CuI]$^\bullet$ was further confirmed when no effect was observed upon the addition of 20 mol % *p*-dinitrobenzene (single-electron transfer scavenger) to the reaction medium during the conversion of 1-iodo-4-nitrobenzene to its benzotrifluoride derivative (80% yield with 95% conversion in both cases). Also, addition of 2,3-dimethylbut-2-ene (a trapping agent for difluorocarbene) to the reaction mixture of 1-iodo-4-nitrobenzene did not furnish any cyclopropane derivative, only the 4-nitrobenzotrifluoride was obtained. It was reasoned that the difluorocarbene generated during the reaction could not be trapped by the alkene since CuI readily combines with [CF_3]$^-$ to drive the equilibrium toward the formation of trifluoromethylcopper complex.



Scheme 2.

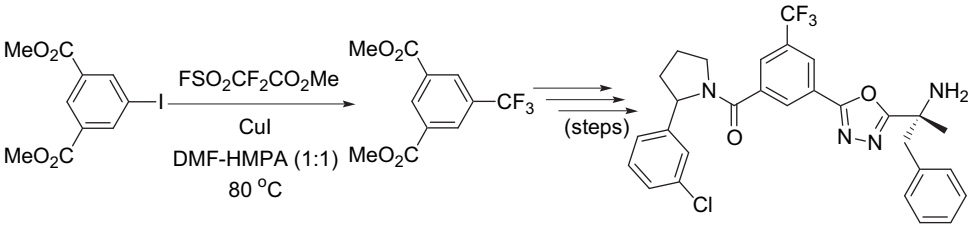
Methyl fluorosulfonyldifluoroacetate is an air- and moisture-stable, commercially available liquid that is easily handled without the use of specialized equipment or handling techniques. The use of this non-expensive fluorinating agent and the convenience to carry out this reaction with regular laboratory apparatus has made this method an attractive choice for medicinal chemists. However, dry solvents and anhydrous conditions are necessary for the success of the reaction.

With MFSDA as a trifluoromethylating agent in the presence of CuI, iodobenzene having a bis-*O*-benzyl neighboring group was efficiently converted to the corresponding trifluoromethyl analog by Aicher and co-workers (Table 1, entry 4).[8] They heated the mixture of aryl iodide with MFSDA (5 equiv) in the presence of CuI (1.2 equiv) and HMPA (5 equiv) in DMF at 80 °C for 18 h. Similarly, MFSDA–CuI mediated trifluoromethylation of a 1,1′-binaphthyl derivative that contains labile MOM protecting groups was achieved by Chong without difficulty (entry 5).[9] In this example, a mixture of diiodide, MFSDA (4 equiv), CuI (2.4 equiv), and HMPA (4 equiv) in DMF was stirred at 70 °C for 6 h under argon. In these cases, HMPA was used to stabilize the trifluoromethylcopper complex. During the preparation of novel 17-α-substituted steroids as modulators of systematic antiandrogens and selective androgen receptors, Labrie reported successful incorporation a trifluoromethyl group onto an iodo-cholesterol core in high yield even without using the carcinogenic HMPA (entry 6).[10]

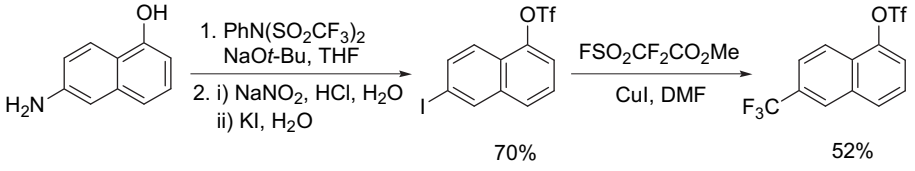
In a search for β-secretase inhibitors for the treatment of Alzheimer's disease, Merck researchers reported the conversion of dimethyl 5-iodoisophthalate to its trifluoromethyl derivative by using MFSDA (5 equiv) and CuI (5 equiv). The trifluoromethyl compound was subsequently modified to provide the final product (Scheme 3).[11]

While evaluating substituted naphthyl piperazines (known ligands for several CNS targets) as inhibitors of the 5-HT transporter, Lilly researchers treated 6-iodonaphthalen-1-yl trifluoromethanesulfonate with MFSDA in the presence of CuI to yield the target compound in 52% yield (Scheme 4).[12] Of particular importance was the finding that the triflate group was relatively stable under the reported reaction conditions.

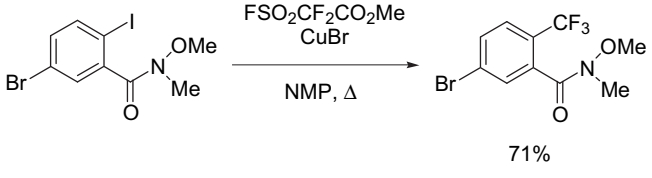
A chemoselective trifluoromethylation of *N*-methoxy-*N*-methyl-5-bromo-2-iodobenzamide was achieved by Nomura and co-workers using MFSDA (1.5 equiv) in the presence of catalytic copper (I) bromide (12 mol %) (Scheme 5).[13] The desired product was obtained in high yield.



Scheme 3.



Scheme 4.



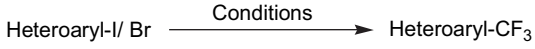
Scheme 5.

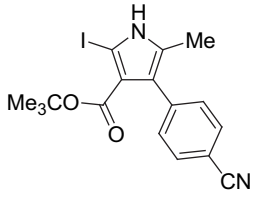
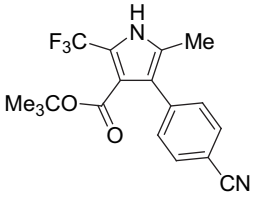
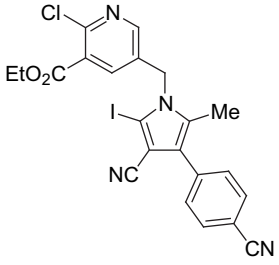
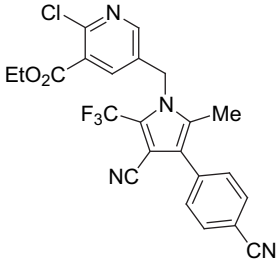
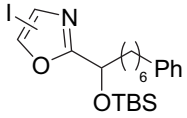
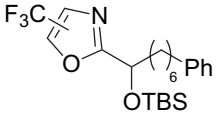
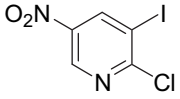
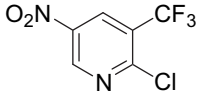
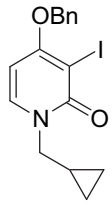
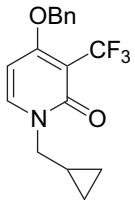
2.2. Reactions of $FSO_2CF_2CO_2Me$ with heteroaryl iodides and bromides

While preparing novel pyrrole derivatives as androgen receptor antagonists, Ito reported trifluoromethylation of a tetra-substituted *NH*-free pyrrole using MFSDA (Table 2, entry 1).[14a] On a gram-scale

reaction, the 2-iodopyrrole was heated with MFSDA (3 equiv) and copper(I) iodide (1.1 equiv) in DMF at 80 °C for 14 h to give the desired product in 71% yield. Similar trifluoromethylation of a *N*-substituted pyrrole was also reported by the same research group in comparable yield (entry 2).[14b] In a series of publications, Boger reported the preparation of 2- and 3-trifluoromethyloxazole derivatives as inhibitors of the enzyme fatty acid amide hydrolase (FAAH), a potential treatment for anxiety and nociception.[15] In these reports, iodooxazole, containing an OTBS protecting group, was treated with MFSDA in the presence of CuI in HMPA–DMF to provide the targeted product in low to moderate yields (entry 3). However, for the trifluoromethylation of a 5-bromooxazole derivative, Doi and Takahashi reported an 81% yield using similar conditions.[16] As an intermediate for the synthesis of inhibitors of dehydroorotate dehydrogenase (DHODH), Laria and co-workers prepared 2-chloro-5-nitro-3-trifluoromethylpyridine by treating the corresponding iodide with MFSDA (0.75 equiv) and CuI (15 mol%) (entry 4).[17] Although the yield was low (30%), presumably due to the use of less MFSDA, access to this important intermediate was achieved. Using similar conditions, Cid-Nunez reported trifluoromethylation on a substituted 3-iodopyridinone while preparing a series of novel 2-pyridinones as positive allosteric modulators of mGluR2 subtype of metabotropic receptors (entry 5).[18a] These pyridinones are potentially useful for the prevention of certain neurological and psychiatric disorders. In this case, the iodopyridinone was treated with MFSDA (2 equiv) and copper(I) iodide (2 equiv) in DMF at 100 °C for 5 h to furnish the desired product in excellent yield. A series of diaryl ether substituted 4-pyridones have been synthesized by GSK researchers as a potential treatment for malaria where they reported that 3-iodopyridin-4(1*H*)-one can be trifluoromethylated using MFSDA and copper(I) iodide, albeit in low yield (entry 6).[18b] Successful trifluoromethylation of a highly substituted benzimidazole was reported by Gerspacer and Weiler where a 4-iodobenzimidazole core was heated with MFSDA (3 equiv) and a catalytic amount of CuI (10 mol%) in DMF at 120 °C for 2 h (entry 7).[19] Notably, the aromatic aldehyde functionality tolerated this transformation. While preparing novel derivatives with potential indications toward orexin receptor antagonists, Aissaoui reported trifluoromethylation of a Boc-protected dihydroimidazopyrazine iodide (entry 8).[20] Trifluoromethylation of a highly substituted 5-bromopyrimidine was carried out by Coteron and co-workers using MFSDA–CuI to afford novel heteroaryl nitrile derivatives as cysteine protease inhibitors (entry 9).[21] The preparation of a 3-trifluoromethyl-2*H*-indazole, bearing a *para*-methoxyphenyl (PMP) protecting group, was reported by the Katzenellenbogen group where they treated the corresponding bromide with MFSDA (5 equiv) and CuI (1 equiv) in DMF at 80 °C for 2 h. A low yield was obtained in this case (entry 10).[22]

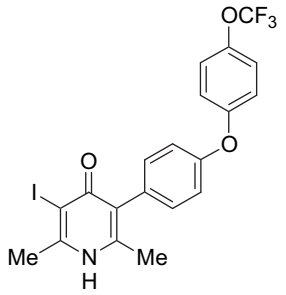
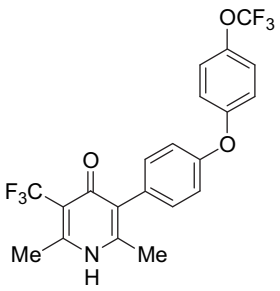
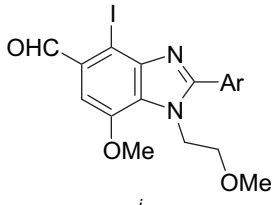
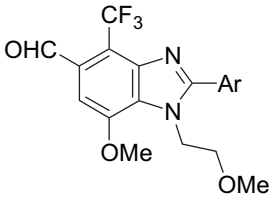
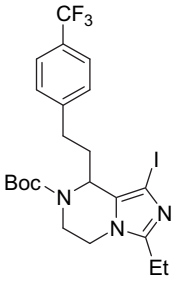
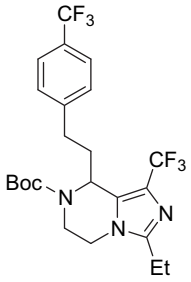
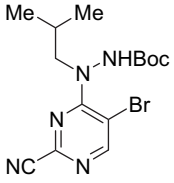
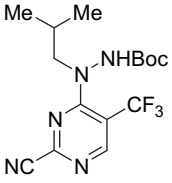
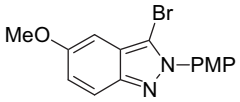
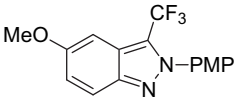
Table 2



Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		$FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C		71%[14a]
2		$FSO_2CF_2CO_2Me$, CuI, DMF, 100 °C		(63%)[14b]
3		$FSO_2CF_2CO_2Me$, CuI, HMPA-DMF, 70 °C		(25–55%)[15]
4		$FSO_2CF_2CO_2Me$, CuI, DMF, 70 °C		(30%)[17]
5		$FSO_2CF_2CO_2Me$, CuI, DMF, 100 °C		(89%)[18a]

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl iodide	Condition	Product	Yield[Ref]
6		$FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 70 °C		(41%)[18b]
7	 Ar = (4-^{i}Pr)Ph	$FSO_2CF_2CO_2Me$, CuI, DMF, 120 °C	 Ar = (4-^{i}Pr)Ph	(86%)[19a]
8		$FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 80 °C		(57%)[20]
9		$FSO_2CF_2CO_2Me$, CuI, HMPA, DMF, 80 °C		(—)[21]
10		$FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C		(34%)[22]

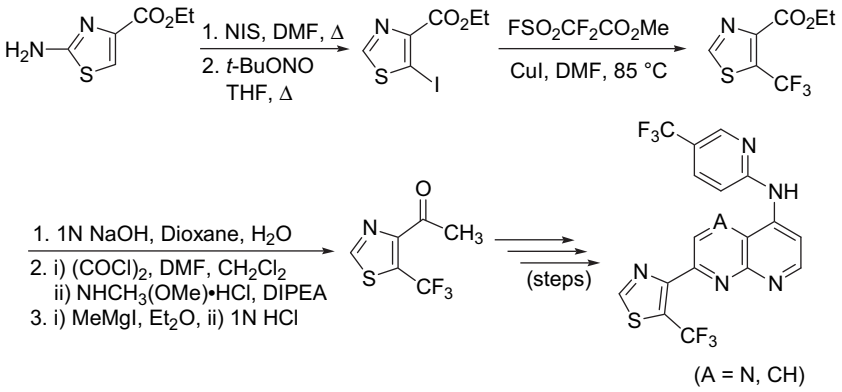
Caldwell reported the synthesis of novel heteroaryl substituted quinolin-4-ylamine analogs where trifluoromethylation of a 5-iodothiazole scaffold was attained using MFSDA. The trifluoromethylated subunit was then subsequently modified to build the targeted products that are useful for treating medical conditions related to capsaicin receptor activation (Scheme 6).[23]

Several simple tetrahydroisoquinolines (THIQ) were synthesized by the Grunewald group as potent inhibitors of phenylethanolamine *N*-methyltransferase (PNMT) where they have utilized MFSDA–CuI system to install a trifluoromethyl group in the tetrahydroisoquinolinone ring (Scheme 7).[24] The tetrahydroisoquinolinone was then efficiently reduced to the desired tetrahydroisoquinoline in excellent yield.

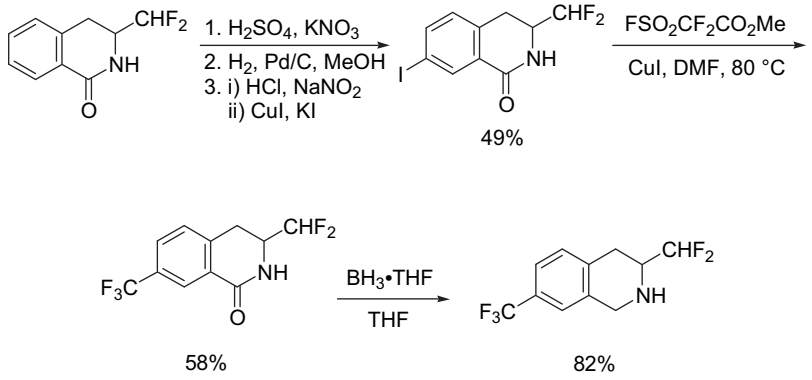
Lilly researchers reported the trifluoromethylation of a tetrahydrobenzoazepine nucleus in the course of preparing novel 5-HT_{2c} receptor agonists. Thus, 7-iodo-tetrahydro-1*H*-benzo[*d*]azepine was heated with MFSDA (8 equiv), CuI (1.6 equiv), and HMPA (8 equiv) in DMF at 70 °C for 5.5 h (Scheme 8).[25] The desired product was obtained in a low yield and 59% of the iodide starting material was recovered after purification. Here, the iodide precursor was prepared in two steps by NIS-iodination followed by protection by Tf_2O.

In order to study the anticancer activity of some simple chrysin derivatives, both mono- and bis(trifluoromethylation) on the chromone nucleus were carried out by the Qing group using MFSDA and CuI (Scheme 9).[26] Similar trifluoromethylations on an isocoumarin nucleus were reported by both the Katzenellenbogen and Larock groups where the desired products were obtained in high yields by heating a solution of iodide with MFSDA and CuI (Scheme 9).[27,28]

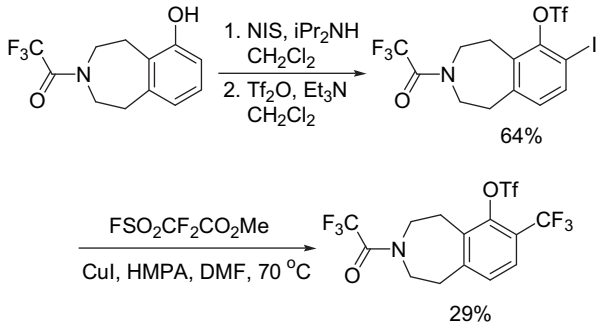
Representative practical procedure[9]. Chong and co-workers stirred a mixture of (*R*)-3,3′-diiodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (3.2 mmol), $FSO_2CF_2CO_2Me$ (12.8 mmol), CuI (7.7 mmol), and HMPA (12.8 mmol) in DMF (40 mL) under argon for 6 h at 70 °C. After being cooled to room temperature, the mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography gave the desired product in 93% yield.



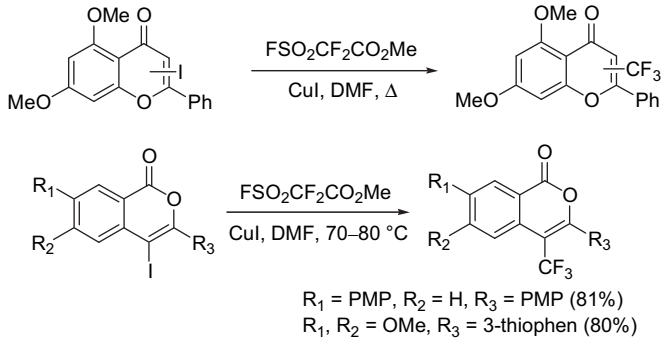
Scheme 6.



Scheme 7.



Scheme 8.

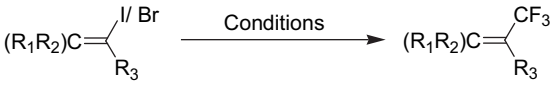


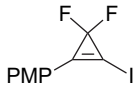
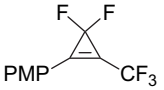
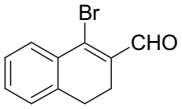
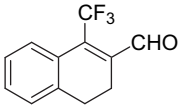
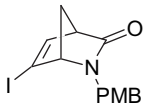
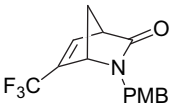
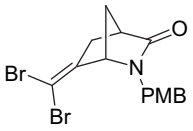
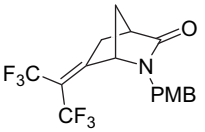
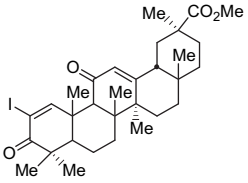
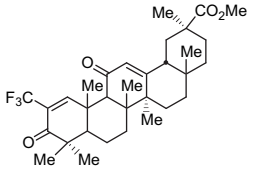
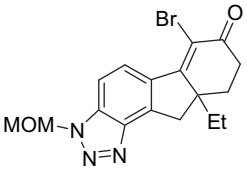
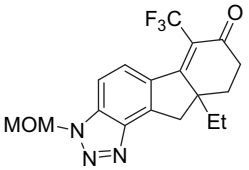
Scheme 9.

2.3. Reactions of $FSO_2CF_2CO_2Me$ with related vinylic iodides and bromides

Trifluoromethylation of 3,3-difluoro-1-iodocyclopropenes was achieved by the Chen group using MFSDA (2 equiv) in the presence of 12 mol % CuI (Table 3, entry 1).[29] Likewise, trifluoromethylation of 4-bromo-1,2-dihydronaphthalene using MFSDA (2.2 equiv) and catalytic CuI afforded the desired product in 45% yield (entry 2).[30] Trifluoromethyl derivatives of conformationally restricted γ-aminobutyric acids are known to be useful as aminotransferase inhibitors, and were prepared by the Silverman group from the corresponding PMB-protected iodide leaving the PMB protecting group on the nitrogen unaffected during the transformation. For this purpose, a solution of MFSDA (2.5 equiv) in anhydrous DMF was added dropwise over 1 h to a suspension of PMB-protected iodide (1 equiv) and CuI (1.2 equiv) in a mixture of anhydrous DMF–HMPA (2:1) to furnish the desired product in high yield (entry 3).[31] Similar double-trifluoromethylation of a dibromomethylene moiety using the MFSDA–CuI reagent was also reported by Lu and Silverman (entry 4). Safe reported the conversion of a triterpenoid iodide to the corresponding trifluoromethylated triterpenoid with MFSDA and CuI (entry 5).[32] In their search for novel triazolo-tetrahydrofluorenone derivatives as selective estrogen receptor beta agonists, Merck researchers used MFSDA to trifluoromethylate a substituted bromoenone (entry 6).[33] Of note, they used Hunig's base to prevent the loss of MOM group during the course of the reaction and subsequent triazole methylation (by methyl iodide, which is generated in situ).

Table 3

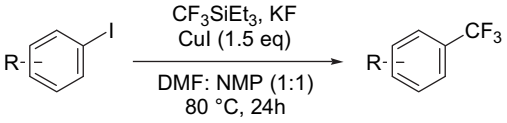


Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		$FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C		(71%)[29]
2		$FSO_2CF_2CO_2Me$, CuI, DMF, 80 °C		(45%)[30]
3		$FSO_2CF_2CO_2Me$, CuI, DMF-HMPA (2:1), 75 °C		(75%)[31]
4		$FSO_2CF_2CO_2Me$, CuI, DMF-HMPA (2:1), 75 °C		(82%)[31]
5		$FSO_2CF_2CO_2Me$, CuI, DMF-HMPA, 70 °C		(—)[32]
6		$FSO_2CF_2CO_2Me$, CuI, DIPEA DMF, 80 °C		(—)[33]

3. Trifluoromethylation using (trifluoromethyl)trialkylsilane (CF_3SiR_3)

3.1. Reactions of CF_3SiEt_3 with aryl and heteroaryl iodides

Urata and Fuchikami reported the first trifluoromethylation studies of aryl iodides using (trifluoromethyl)triethylsilane (CF_3SiEt_3 or CF_3TES).[34] They used the CF_3SiR_3/F^- system, developed by Prakash and Olah,[35] in the presence of copper(I) to convert a variety of aryl iodides to the corresponding benzotrifluorides in good yields (Scheme 10). This procedure was also successfully applied to the related benzyl and vinyl bromides. At least a stoichiometric amount of copper(I) iodide was needed for an optimum yield while a significant decrease in reaction yield was observed with lesser amounts of CuI. Although other copper(I) salts, such as CuBr, CuCl and CuCN, were found to be quite effective, copper(II) salts as well as Zn and Ni salts were ineffective for this transformation. Although KF afforded superior results when used as the fluoride ion source, NaF and CsF provided only small amounts of the desired products. Furthermore, TBAF as the fluoride source, which is particularly useful in nucleophilic trifluoromethylation of aldehydes and ketones, was found to be completely ineffective in this case. DMSO was found to be less attractive as a choice of solvent, providing the desired products in lesser yields than DMF and NMP. In a typical procedure, iodide was heated with CF_3TES (1.2 equiv) in the presence of CuI (1.5 equiv) and KF (1.2 equiv) in DMF–NMP (1:1) at 80 °C for 24 h to yield the desired products. KF is hygroscopic and must be fully dried before the reaction for the best results.

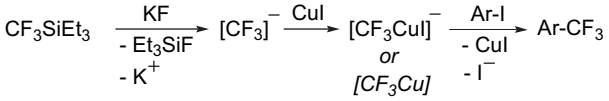


R = 4-NO_2 (99%), R = 2-Me (86%)
R = CO_2Et (94%), R = 3-Me (78%)
R = COMe (45%), R = 4-OMe (48%)

Scheme 10.

The reaction is initiated by attack of fluoride ion on the silicon center, thereby generating the highly unstable trifluoromethide anion $[CF_3]^-$ that then forms the active trifluoromethylcopper complex with a copper(I) salt (Scheme 11). This active copper species then displaces the iodide, as before, to form the benzotrifluorides. Although aromatic trifluoromethylation was predominant for a 4′-iodoacetophenone substrate, nucleophilic trifluoromethylation at the carbonyl center also occurred providing 1,1,1-trifluoro-2-(4-iodo-phenyl)-propan-2-ol and 1,1,1-trifluoro-2-(4-trifluoromethyl-phenyl)-propan-2-ol in 17% and 6% yields, respectively, as the by-products. For relatively electron-

rich 4-iodoanisole substrates, 4-pentafluoroethylanisole was obtained in 18% yield as a by-product along with the desired 4-trifluoromethylanisole. This is in agreement with Burton's report[36] about the formation of pentafluoroethylcopper(I) species from the unstable trifluoromethylcopper(I) complex ([CF_3Cu]+[:CF_2]→[CF_3CF_2Cu]) at higher temperature, especially in the absence of suitable(/strongly electrophilic) substrates.



Scheme 11.

Smith and co-workers used this method to install trifluoromethyl functionality onto a thiophene ring while preparing certain aminopyridines useful for treating diseases mediated by polo-like kinase 1 (Plk1) (Scheme 12).[37] During their synthesis of a series of novel butenolides as seed germination stimulants, researchers at the DuPont crop protection center also utilized CF_3TES in the presence of KF and CuI to incorporate CF_3 group into butenolides (Scheme 13).[38] The iodide handle was first installed on the butenolide by treatment with NIS and then conveniently replaced by the trifluoromethyl group. The desired product was isolated in 50% yield.

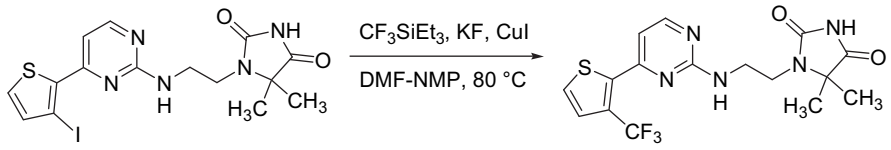
3.2. Reactions of CF_3SiMe_3 with aryl iodides

Following Urata and Fuchikami's methods, researchers have widely used (trifluoromethyl)trimethylsilane (CF_3SiMe_3 or CF_3TMS), a congener of CF_3TES, for the same purpose. (Trifluoromethyl)trimethylsilane (TFMTMS) is also known as Ruppert's reagent that was originally used by Prakash and Olah for their fluoride-induced trifluoromethylation of carbonyls.[35] CF_3TMS has a lower boiling point than CF_3TES. Thus, CF_3TES could be preferable for a reaction that requires higher temperature unless the reaction is performed in a pressure vessel. Both CF_3TMS and CF_3TES are commercially available as colorless liquids.

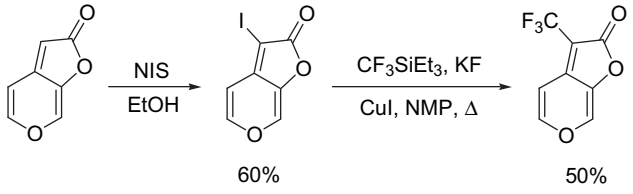
Berkessel reported the successful conversion of an iodoacetal to its trifluoromethyl derivative, using CF_3TMS in the presence of CuI and KF, in nearly quantitative yield (Table 4, entry 1).[39] Interestingly, attempts to introduce the CF_3 group in the presence of the analogous aldehyde were unsuccessful; protecting the aldehyde as the cyclic acetal was key to facilitating this reaction. While preparing a series of novel substituted acylpiperazine derivatives, broadly useful in the neurological diseases, Roche researchers reported a small scale (~50 mg) trifluoromethylation of aryl iodide in excellent yield when the iodide was stirred in with CF_3TMS (2 equiv), CuI (1.6 equiv), KF (1.4 equiv) in NMP–DMF (1:1) in a sealed tube at room temperature for 17 h (entry 2).[40] Notably, an excellent yield was reported even though the reaction was carried out at room temperature. Schlosser later demonstrated the chemoselective trifluoromethylation of dihalonaphthalenes using similar conditions (entries 3 and 4).[41] Importantly, he successfully carried out these reactions on a relatively large (17–37 g) scale. In contrast, a low yield was reported by Takizawa for the trifluoromethylation of 2-(2,4-difluoro-3-iodophenyl)pyridine using this protocol (entry 5).[42] Kim and Shreeve reported first Cu(I)-mediated nucleophilic trifluoromethylation in ionic liquid [*N*-2-(2-ethoxyethoxy)ethyl-*N*-methylmorpholinium bis(trifluoromethanesulfonyl)amide] using CF_3TMS–KF–CuI condition where 1-iodo-4-trifluoromethylbenzene was obtained as the major product, albeit in low yield (38%, GC yield) from the corresponding 1,4-diiodobenzene (entry 6).[43]

3.3. Reactions of CF_3SiMe_3 with heteroaryl iodides

Schlosser extensively studied the trifluoromethylation reaction on halopyridines using CF_3TMS (or TFMTMS) in the presence of KF and CuI (Table 5, entries 1 and 2).[44] Again, these reactions were successfully carried out on a relatively large (~21 g) scale. Substitution at C-2 was found to be more favorable than at other positions. However, due to volatility of the products, substantial loss was



Scheme 12.



Scheme 13.

suspected during the reaction work-up and purification, thus affecting the yields in many cases. As seen before, the displacement was found to follow the order of reactivity of I≫Br in the dihalopyridine system and occurred exclusively on the iodine to furnish the corresponding trifluoromethylated products. These researchers have also extended the procedure to trihalopyridines, where the reaction was carried out on a 32 g scale of the pyridine precursor and selective trifluoromethylation was observed (entry 3).[45] In the course of the synthesis of novel peroxisome proliferator-activated receptor (PPAR) ligands, the Schlosser conditions were used by Guillaumet for the synthesis of 5-bromo-2-trifluoromethylpyridine.[46] Using the CF_3TMS–KF–CuI protocol, Bruton reported chemoselective trifluoromethylation of 5-bromo-2-iodopyrimidine (on a 6.5 g scale) at room temperature where the desired product was obtained in 46% yield (entry 4).[47] As an extension of their work on selective trifluoromethylation of dihalopyridines, Schlosser investigated trifluoromethylation of a dihaloquinoline system.[48] As observed before, the displacement of iodides occurred chemoselectively (entries 5 and 6). As in previous cases, these reactions were also carried out on a relatively large (~40 g) scale and the desired products were obtained in good yield using relatively mild conditions (50 °C for 20 h). While preparing novel piperazine-piperidine compounds as 5-HT_{1A} binding agents, useful in the treatment of CNS disorders, Wyeth researchers reported the chemoselective trifluoromethylation of 8-bromo-3-iodoquinoline using Schlosser's conditions to afford the trifluoromethyl derivative in 73% yield.[49] In the quest for new insecticides, Bayer researchers have conducted trifluoromethylation of a 4-iodopyrazole derivative using the standard CF_3TMS–KF–CuI protocol. However, the isolated yield was reported to be only 20% after heating the reaction mixture in DMF at 100 °C for 8 h (entry 7).[50] Ebenbeck and co-workers have carried out a relatively large scale

Table 4

Aryl-I $\xrightarrow{\text{Conditions}}$ Aryl-CF_3

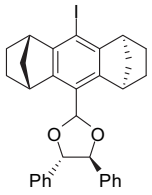
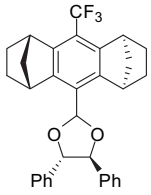
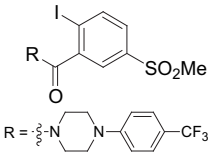
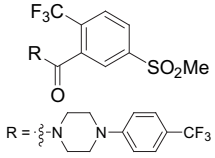
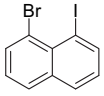
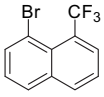
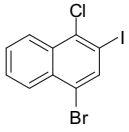
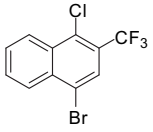
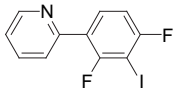
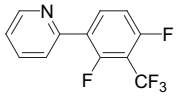
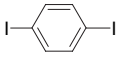
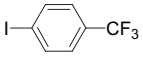
Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		CF_3SiMe_3, KF, CuI, DMF, HMPA, 70 °C		(96%)[39]
2		CF_3SiMe_3, KF, CuI, DMF, NMP, rt		(90%)[40]
3		CF_3SiMe_3, KF, CuI, NMP, 75 °C		(92%)[41]
4		CF_3SiMe_3, KF, CuI, NMP, 50 °C		(54%)[41]
5		CF_3SiMe_3, KF, CuI, NMP		(32%)[42]
6		CF_3SiMe_3, KF, CuI, ionic liquid, 80 °C		(38%)[43]

Table 5

Het-Ar-I $\xrightarrow{\text{Conditions}}$ Het-Ar-CF_3

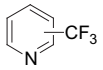
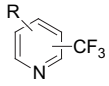
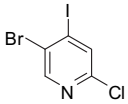
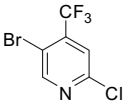
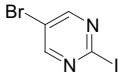
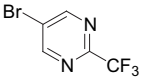
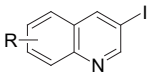
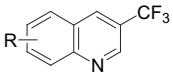
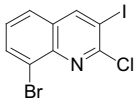
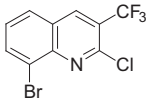
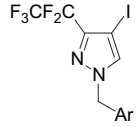
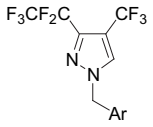
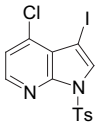
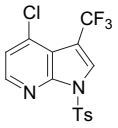
Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		CF_3SiMe_3, KF, CuI, DMF-NMP, 25 °C		2-CF_3 (68%)[44] 3-CF_3 (23%)[44] 4-CF_3 (25%)[44]
2		CF_3SiMe_3, KF, CuI, DMF-NMP, 25 °C		5-Br, 2-CF_3 (69%)[44] 2-Br, 6-CF_3 (79%)[44] 2-Br, 5-CF_3 (29%)[44] 2-Cl, 4-CF_3 (68%)[44]
3		CF_3SiMe_3, KF, CuI, NMP, 50 °C		(64%)[45]
4		CF_3SiMe_3, CuI, KF, DMF:NMP (1:1), rt		(46%)[47]
5		CF_3SiMe_3, KF, CuI NMP, 50 °C		R=2-Cl (80%)[48] R=4-Cl (79%)[48]
6		CF_3SiMe_3, KF, CuI NMP, 50 °C		(64%)[48]

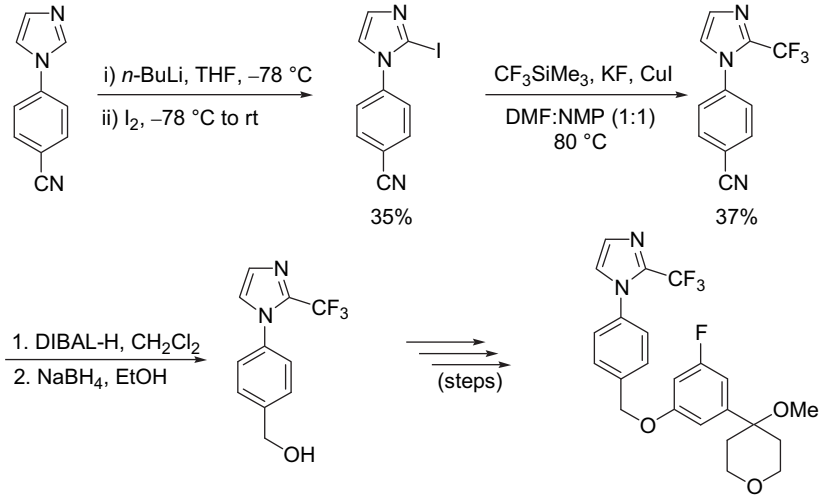
Table 5 (*continued*)

Entry	Aryl iodide	Condition	Product	Yield[Ref]
7	 Ar = 3-Me-4-NO_2-Ph	CF_3SiMe_3, KF, CuI, DMF, 100 °C	 Ar = 3-Me-4-NO_2-Ph	(20%)[50]
8		CF_3SiMe_3, KF, CuI, DMF:NMP (1:1), rt		(67%)[51]

(~86 g) trifluoromethylation reaction to prepare novel pyrrolo[2,3-*b*]pyridines.[51] Thus, the iodide was treated with CF_3TMS (2.2 equiv) in the presence of a mixture of KF (2 equiv) and CuI (2 equiv) at room temperature to yield the corresponding trifluoromethyl derivative in moderate yield (entry 8). In many cases, a mixture of KF and CuI was first heated together under high vacuum that was then subsequently used in the trifluoromethylation reactions.[47,51]

While evaluating novel imidazole compounds as potent, orally active inhibitors of 5-lipoxygenase, Pfizer researchers converted a 2-iodoimidazole, bearing an aryl nitrile functionality, to the corresponding trifluoromethyl derivative using CF_3TMS in the presence of CuI and KF (Scheme 14).[52] The prerequisite iodide starting material was prepared via lithium–halogen exchange followed by iodination. The trifluoromethyl product was subsequently converted to the target molecule.

Representative practical procedure[41]. Schlosser and co-workers thoroughly mixed 'spray-dried' KF (50 mmol) and CuI (50 mol) and then heated the mixture under vacuum (1 mmHg) with a Bunsen burner under gentle shaking until a homogeneous greenish color was obtained. After the addition of NMP (100 mL) and CF_3TMS (50 mmol), the slurry was heated to 75 °C over the course of 45 min before 1-bromo-8-iodonaphthalene (50 mmol) was added. After 20 h, the mixture was cooled to room temperature, poured into 12% aqueous ammonia, and extracted with Et_2O. The combined organic extracts were washed consecutively with 12% aqueous ammonia, 2 M HCl, saturated aqueous $NaHCO_3$ solution, and brine. After drying and concentration, recrystallization from hexanes gave the desired product in 92% yield.



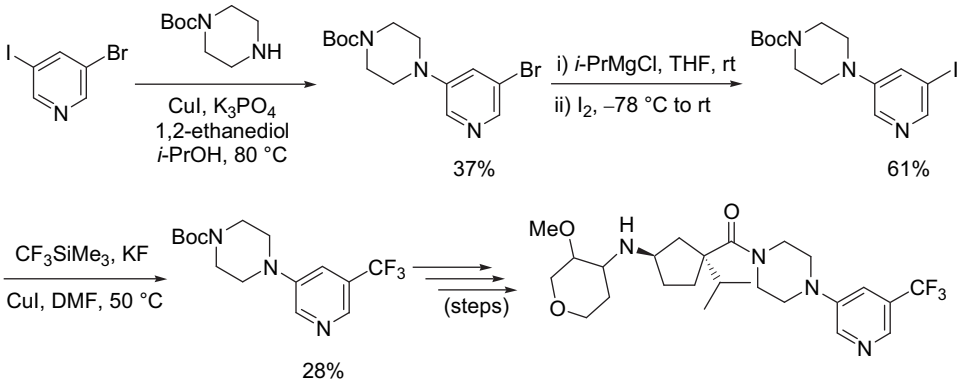
Scheme 14.

Xue and co-workers treated a 3-iodopyridine, containing a Boc-piperazine subunit, with CF_3TMS (2.6 equiv) in the presence of KF (2.6 equiv) and CuI (2.6 equiv) in the course of synthesis of novel piperazinyl-pyridinyl derivatives as antagonist inhibitors of CCR2 and CCR5 receptors (Scheme 15).[53] Interestingly, the desired product was isolated in only 28% yield even with excess reagents, which is in agreement with Schlosser's observation of low yielding trifluoromethylation with simple 3-iodopyridines utilizing this method. Here, the iodide starting material was prepared in two steps from 3-bromo-5-iodopyridine. Similar trifluoromethylation of another 3-iodopyridine, bearing an *N*-Boc piperidine ring, was reported by Blackaby while preparing inhibitors of glycine transporters (GlyT1) for the treatment in neurological and psychiatric disorders (Scheme 16).[54]

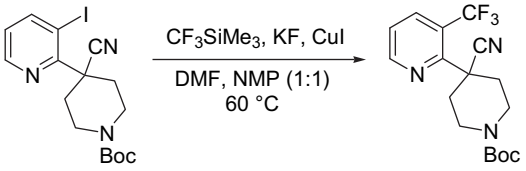
4. Trifluoromethylation using methyl chlorodifluoroacetate ($ClCF_2CO_2Me$)

4.1. Reactions of $ClCF_2CO_2Me$ with aryl iodides

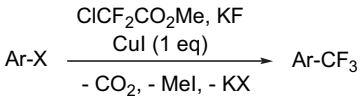
The Chen group has demonstrated a convenient conversion of aromatic iodides to the corresponding benzotrifluorides using methyl chlorodifluoroacetate (Scheme 17).[55] Methyl chlorodifluoroacetate is also commercially available as a liquid. In these gram-scale syntheses, the iodides were heated with methyl chlorodifluoroacetate (2 equiv) in the presence of CuI (1 equiv) and dry KF (1 equiv) in DMF at 100–120 °C for 8 h (Table 6, entry 1). Use of HMPA as solvent instead of DMF gave a slightly lower yield. Although only one example of aromatic trifluoromethylation with an



Scheme 15.



Scheme 16.



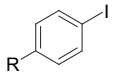
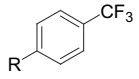
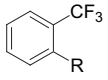
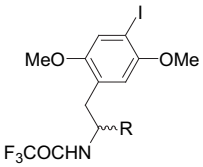
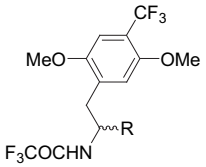
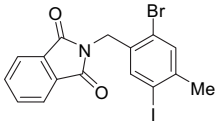
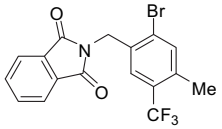
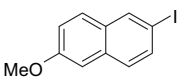
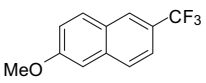
Scheme 17.

aryl bromide substrate was reported, aryl chlorides are presumably inert under this condition. Thus, chemoselectivity was observed when 1-chloro-4-iodobenzene was subjected to the reaction, providing exclusively 1-chloro-4-trifluoromethylbenzene in 81% yield; no 1,4-bis-trifluoromethylbenzene was detected. However, the method was also shown to be effective for benzyl, vinyl, and allyl bromide substrates (56–84% yields) and even with benzyl chloride, which gave the desired product in 46% yield.

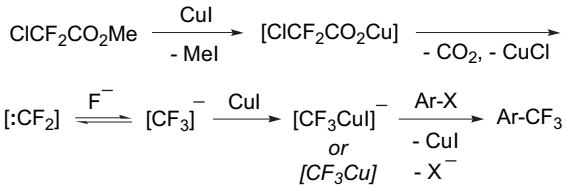
Similar to other aromatic trifluoromethylations, the authors proposed the generation of a difluorocarbene intermediate [:CF_2] from the CuI-assisted decomposition of methyl chlorodifluoroacetate, which then combines with the fluoride ion to form trifluoromethide anion $[CF_3]^-$ (Scheme 18). CuI readily drives the equilibrium toward $[CF_3CuI]^-$ that reacts with aryl halides to furnish the trifluoromethyl products. Similar to the MFSDA–CuI mediated trifluoromethylation, the use of 2,3-dimethylbut-2-ene (a trapping agent for difluorocarbene) in the reaction of iodobenzene with $ClCF_2CO_2Me$ using the conditions mentioned above did not furnish a cyclopropane. Furthermore, CuCl instead of CuI was found to be completely ineffective, and $ClCF_2CO_2Me$ was recovered

Table 6

Aryl-I —Conditions→ Aryl-CF_3

Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		$ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C		R=H (88%)[55] R=Cl (81%)[55]
2		$ClCF_2CO_2Me$, CuI, KF, DMPU, 120 °C		R=H (62%)[56] R=Me (52%)[56]
3		$ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C		R=H (72%)[58] R=Me (75%)[58]
4		$ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C		(40%)[59]
5		$ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C		(78%)[60]

without decomposition. Also, at least 1 equiv of KF was found to be essential in order to obtain a good yield of the desired product, indicating that the reaction is not catalytic in KF. The gas that evolved from the reaction mixture was identified by GC–MS as mostly MeCl (or a mixture of MeCl and MeBr for aryl bromide substrates). The absence of HCF_2Cl and compounds having a CF_2Cl group revealed the nonexistence of $[CF_2Cl]^-$ in the reaction pathway; thus, it was proposed that the decomposition of the copper salt is a concerted rather than a stepwise process. Although CuCl is inactive for the decomposition of $ClCF_2CO_2Me$, the presence of MeCl in the reaction mixture suggested that MeI reacted with generated CuCl forming MeCl and regenerating the CuI. Also, they observed the formation of trace $CF_2{=}CF_2$ from the decomposition of the pentafluoroethylcopper(I) species that was generated in situ from the trifluoromethylcopper(I) complex ($[CF_3CuI]^- + [:CF_2] \rightarrow [CF_3CF_2CuI]^- \rightarrow CF_2{=}CF_2 + F^- + CuI$). As in other cases, the formation of HCF_3 was observed due to protonation of trifluoromethide anion (CF_3^-) by trace water.



Scheme 18.

Later in the same year, Burton reported the generation of the trifluoromethylcopper species by the decarboxylation of $ClCF_2CO_2Me$ that was also used in the trifluoromethylation of aryl iodides.[56] In comparison to Chen's method, Burton utilized DMPU (*N*,*N*′-dimethylpropylene urea) as a solvent instead of DMF and also used excess KF. Thus, in similar gram-scale syntheses, iodides were treated with $ClCF_2CO_2Me$ (1 equiv) in the presence of CuI (1 equiv) but with excess KF (5 equiv) in DMPU 120 °C for 4 h to give the desired products in moderate to good yield (Table 6, entry 2). Burton proposed the formation of the difluorocarbene intermediate via a fluoride-induced decomposition of methyl chlorodifluoroacetate similar to what they observed earlier in the presence of LiCl–HMPA or KF–18-crown-6;[57] therefore suggesting the use of excess KF for this transformation. However, many researchers later successfully conducted similar trifluoromethylations in high yields with 1–2 equiv of KF.

Following this trifluoromethylation method, Nichols reported the synthesis of 1-((2,5-dimethoxy)-4(trifluoromethyl)phenyl)-2-aminopropane derivatives as potent serotonin 5-$HT_{2A/2C}$ agonists (Table 6, entry 3).[58] Thus, methyl chlorodifluoroacetate was added via a syringe pump over 3 h to a solution of iodide, CuI and KF in anhydrous DMF at 120 °C. A low concentration of the reagent is essential for the success of this reaction, which was achieved by the slow addition of $ClCF_2CO_2Me$. Using similar conditions, Pfizer researchers selectively carried out the trifluoromethylation of a 1-bromo-4-iodobenzene derivative while preparing dibenzylamine compounds to treat diseases exacerbated by low levels of HDL-cholesterols and/or high levels of LDL-cholesterols/triglycerides (entry 4).[59] The desired product was obtained in 40% isolated yield. The low yield could be attributed to the undesired side reaction on the bromine as reported by Chen for unsubstituted bromobenzene.[55] Hoveyda and co-workers have reported the trifluoromethylation of an iodonaphthalene using methyl chlorodifluoroacetate (entry 5).[60] Accordingly, $ClCF_2CO_2Me$ (2.4 equiv) was added to a mixture of 2-methoxy-6-iodonaphthalene, CuI (1.2 equiv), and KF (1.2 equiv) in DMF at 120 °C for 20 h. The reaction was performed on a 6 g scale and a high yield (78%) of the corresponding trifluoromethylated product was obtained.

4.2. Reactions of $ClCF_2CO_2Me$ with heteroaryl iodides

Ple and co-workers used methyl chlorodifluoroacetate as a trifluoromethylating agent on a variety of heteroaryl iodides such as pyrimidine, pyrazine, and pyridazine ring systems.[61] Thus, a mixture of the heteroaryl iodide, CuI (1.5 equiv), anhydrous KF (2 equiv), and methyl chlorodifluoroacetate (2 equiv) in DMF was heated at 115 °C for 3–10 h. These reactions were carried out on a 1–5 g scale and the desired products were obtained in moderate to good yields (Table 7, entries 1–3). Researchers at AstraZenecca have carried out a trifluoromethylation reaction during their synthesis of novel isoindolone compounds as metabotropic glutamate receptor modulators for the treatment of neurological and psychiatric disorders.[62] The desired 7-trifluoromethylisoindolone was obtained in a 41% yield employing $ClCF_2CO_2Me$–CuI–KF (entry 4). During the search for simple indoline derivatives as 5-HT_{2C} receptor agonists, Bentley reported the synthesis of a 6-trifluoromethylindole in excellent yield from the corresponding 6-iodoindole using $ClCF_2CO_2Me$ as the trifluoromethylating reagent.[63] Notably, *N*-Boc-protecting groups are stable under these reaction conditions (entry 5). Dade reported the trifluoromethylation of quinolines using methyl chlorodifluoroacetate where 2-propyl-3-trifluoromethylquinoline was prepared in moderate yield (entry 6).[64] While preparing novel aryl sulfonamide and sulfonyl compounds as peroxisome proliferator activated receptor (PPAR) modulators for the treatment of metabolic disorders, Zhao and co-workers carried out trifluoromethylation of an iodopyridazine on a relatively large scale (12 g). Instead of $ClCF_2CO_2Me$, they used $ClCF_2CO_2Et$ in the presence of KF and CuI to trifluoromethylate the iodopyridazine. Ethyl chlorodifluoroacetate is also commercially available as a colorless liquid but has a higher boiling point than its methyl analog. However, the product was obtained in only 32% yield (entry 7).[65a] Smith later reported a 20% yield for the same conversion using $ClCF_2CO_2Me$ under similar conditions during their preparation of novel triazolopyridazines as protein kinase modulators.[65b]

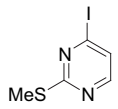
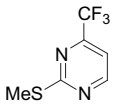
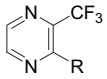
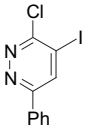
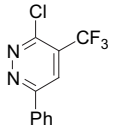
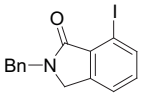
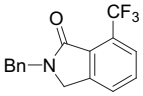
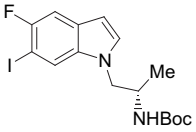
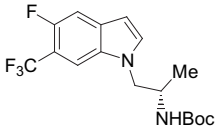
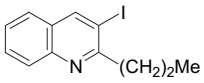
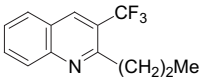
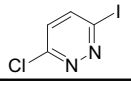
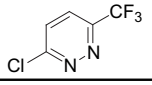
In their quest for novel thiophene derivatives as immunosuppressive agents, Bolli and colleagues reported a relatively large scale (~18 g) trifluoromethylation of 3-iodo-*N*-methoxy-*N*,5,5-trimethyl-4,5,6,7-tetrahydrobenzo[*c*]thiophene-1-carboxamide with methyl chlorodifluoroacetate (2.4 equiv), CuI (1.6 equiv), and KF (1.6 equiv) in DMF at 134 °C (Scheme 19).[66] Here, $ClCF_2CO_2Me$ was added at 134 °C over a period of 4 h to keep it at a low concentration and the corresponding trifluoromethyl product was obtained in 91% yield. The product was then converted to the targeted compound. Here, the iodide precursor was conveniently prepared from the corresponding acid in two steps.

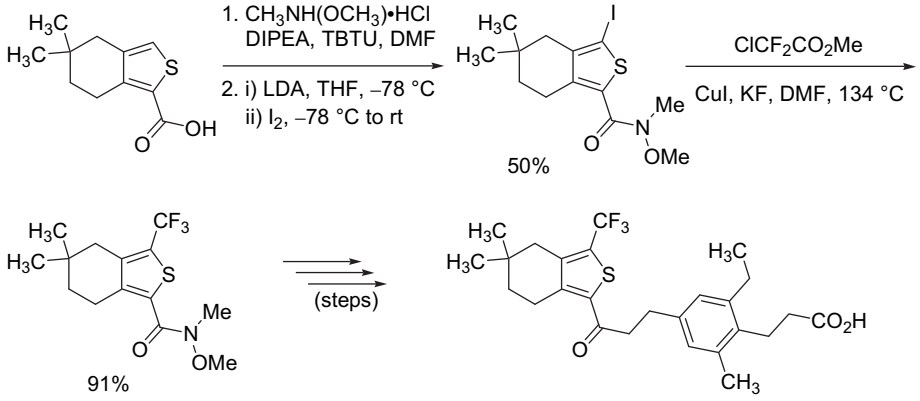
Apart from the initial report by Chen, aryl or heteroaryl bromides were not routinely used as substrates for the trifluoromethylation reaction using the $ClCF_2CO_2Me$–CuI–KF protocol. One such example was reported by Zeng where they trifluoromethylated a bromide in the course of synthesizing novel pyrazinyl-piperazine-piperidines as CXCR3 antagonists for the treatment of chemokine mediated diseases (Scheme 20).[67] However, the desired product was isolated in a low yield even after heating the reaction mixture at 110 °C for 24 h.

Representative practical procedure[58]. Nichols and co-workers added $ClCF_2CO_2Me$ (15 mmol) to a mixture of CuI (11 mmol), dry KF (11 mmol), and 1-(2,5-dimethoxy-4-iodophenyl)-2-(trifluoroacetamido)propane (7.2 mmol) in DMF (15 mL) at 120 °C, via a syringe pump over 3 h. After the addition was complete, the mixture was stirred at 120 °C for 4 h after which it was poured into water. The precipitate was collected by vacuum filtration, the solid filter cake was suspended in $CHCl_3$ and filtered through Celite. The filtrate was washed with 2 N HCl, water, brine, dried over $MgSO_4$, and concentrated. Recrystallization gave the desired product in 75% yield.

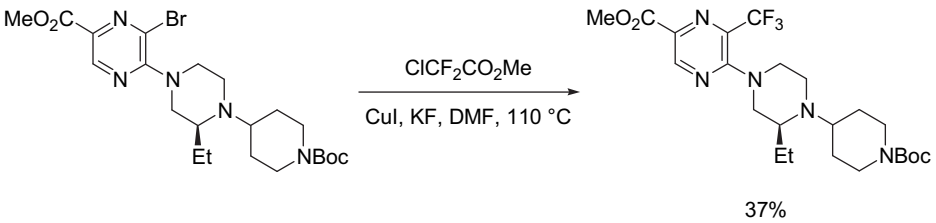
Table 7

Het-Ar-I —(Conditions)→ Het-Ar-CF_3

Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		$ClCF_2CO_2Me$, CuI, KF, DMF, 115 °C		(68%)[61]
2		$ClCF_2CO_2Me$, CuI, KF, DMF, 115 °C		R=Cl (50%)[61] R=SPh (63%)[61]
3		$ClCF_2CO_2Me$, CuI, KF, DMF, 115 °C		(65%)[61]
4		$ClCF_2CO_2Me$, CuI, KF, DMF, 140 °C		(41%)[62]
5		$ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C		(84%)[63]
6		$ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C		(57%)[64]
7		$ClCF_2CO_2Et$, CuI, KF, DMF, 120 °C		(32%)[65a]



Scheme 19.

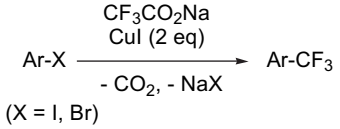


Scheme 20.

5. Trifluoromethylation using sodium trifluoroacetate (CF_3CO_2Na)

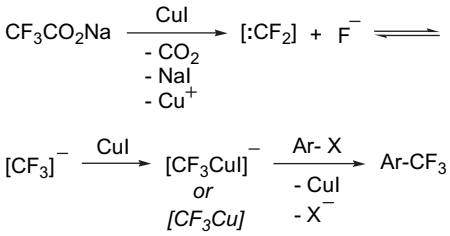
5.1. Reactions of CF_3CO_2Na with aryl iodides and bromides

Matsui and co-workers reported a convenient trifluoromethylation of aromatic iodides with sodium trifluoroacetate (Scheme 21).[68] Sodium trifluoroacetate is commercially available as a white powder. They heated a mixture of iodobenzene with sodium trifluoroacetate (4 equiv) and CuI (2 equiv) in NMP at 160 °C for 4 h (Table 8, entry 1). *N*,*N*-Dimethylacetamide (DMAC) and HMPA were also acceptable solvents. A few years later, Chambers and co-workers further developed this copper-assisted trifluoromethylation using sodium trifluoroacetate.[69] Notably, *ortho* and *para*-chloroiodobenzene selectively gave the trifluoromethylated product in almost quantitative yields (entry 2, GC yield). They extended their method to aromatic bromides (entry 3, GC yield); however, slightly lower yields were observed when compared with the results for the corresponding iodo series. Use of excess sodium trifluoroacetate was also suggested by both Matsui and Chambers since fluoroform was produced as a by-product from the trace moisture present in the reaction medium. Chambers also reported that copper(I) iodide is more effective than copper(I) bromide and a stoichiometric amount of copper salts should be used to maximize the yields. Evolution of carbon dioxide (due to the decomposition of CF_3CO_2Na) was observed to start at 140 °C, indicating that the mixture must be heated higher than 140 °C for the success of this reaction. Requirement of the high temperature is a small drawback for this method, especially for thermally sensitive substrates.



Scheme 21.

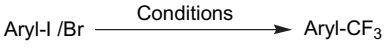
Similar to the previous cases, CuI-assisted decomposition of sodium trifluoroacetate generates the trifluoromethylcopper species, which nucleophilically reacts with aryl/heteroaryl iodides and bromides to provide the trifluoromethylated aromatics and heteroaromatics (Scheme 22). Chambers also confirmed the anionic nature of the copper complex $[CF_3CuI]^-$ (as compared to $[CF_3CuI]^{\bullet}$) that is responsible for the nucleophilic of attack on the aryl halides.

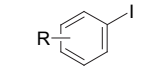
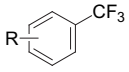
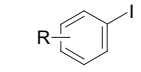
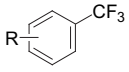
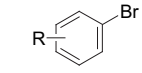
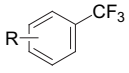
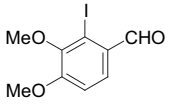
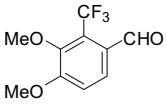
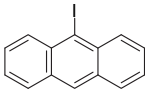
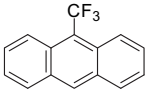
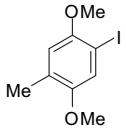
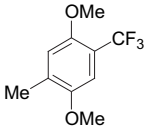


Scheme 22.

Similarly, Miller utilized CF_3CO_2Na–CuI to convert 2-iodo-3,4-dimethoxybenzaldehyde to its trifluoromethyl analog in 40% yield (Entry 4).[70] However, Ammann reported only a 25% yield for the same reaction in their asymmetric synthesis of (*R*)- and (*S*)-2-trifluoromethylepinephrine.[71] As in previous cases of trifluoromethylations, it was noted that rigorously anhydrous conditions are needed to prevent the undesired formation of veratraldehyde, the dehalogenated/reduced starting material.[70] Toyota and co-workers also exploited this methodology by converting 9-iodoanthracene to its trifluoromethyl derivative (entry 5).[72] Notably, Matsui reported a 78% yield for the similar trifluoromethylation of 1-iodonaphthalene.[68] On a 17 g scale, Hunig reported a 67% yield of the trifluoromethyl product when 1-iodo-2,5-dimethoxy-4-methylbenzene was heated with CF_3CO_2Na (3 equiv) and CuI (2 equiv) in a DMAC–toluene solvent system at reflux for 6–8 h (entry 6).[73] Toluene was distilled-off during the course of reaction to remove

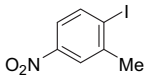
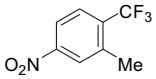
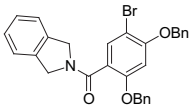
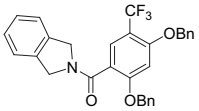
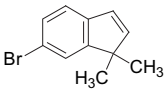
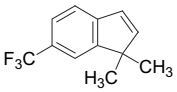
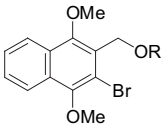
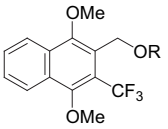
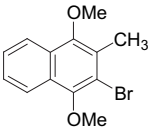
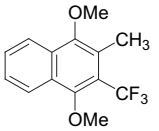
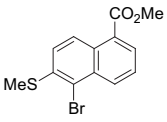
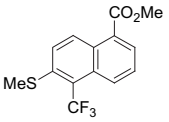
Table 8



Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		CF_3CO_2Na, CuI, NMP, 160 °C		R=4-NO_2 (39%)[68] R=4-OMe (42%)[68]
2		CF_3CO_2Na, CuI, NMP, 160 °C		R=H (87%)[69] R=2-Cl (87%)[69] R=4-Cl (98%)[69]
3		CF_3CO_2Na, CuI, NMP, 160 °C		R=H (68%)[69] R=3-Me (78%)[69]
4		CF_3CO_2Na, CuI, NMP, 175 °C		(25–40%)[70, 71]
5		CF_3CO_2Na, CuI, NMP, 160 °C		(—)[72]
6		CF_3CO_2Na, CuI, DMAC–toluene, reflux		(67%)[73]

(*continued on next page*)

Table 8 (*continued*)

Entry	Aryl iodide	Condition	Product	Yield[Ref]
7		CF_3CO_2Na, CuI, NMP, 160 °C		(37%)[74]
8		CF_3CO_2Na, CuI, DMF, 150 °C		(29%)[75]
9		CF_3CO_2Na, CuI, NMP, 160 °C		(100%)[76]
10		CF_3CO_2Na, CuI, DMF–toluene, 170 °C		R=Bn (84%)[77] R=PMB (78%)[77]
11		CF_3CO_2Na, CuI, DMAC–toluene, 170 °C		(46%)[78]
12		CF_3CO_2Na, CuI, NMP, 180 °C		(77%)[79]

traces of water and the temperature was increased to 152–153 °C. While preparing C3A receptor antagonists, Claffey reported the use of this method to prepare 3-methyl-4-trifluoromethyl nitrobenzene from the corresponding iodide precursor.[74] Despite the addition of excess CF_3CO_2Na and CuI in portions, only a modest 37% yield was obtained for the desired product (entry 7). In their search for novel inhibitors of Hsp 90, Chessari and co-workers were able to use CF_3CO_2Na to replace the bromide of bis-*O*-benzyl-protected benzamide with a trifluoromethyl group, albeit in low yield (entry 8).[75] On the contrary, a quantitative yield of the desired trifluoromethyl product was reported by Buckle when a 6-bromoindene was heated at 160 °C with sodium CF_3CO_2Na (4 equiv) and CuI (4 equiv) in NMP for 6 h (entry 9).[76] Pure product was easily isolated just after simple aqueous work-up and filtration. De Kimpe also explored the use of sodium trifluoroacetate to trifluoromethylate a variety of electron-rich 3-substituted 1,4-dimethoxynaphthalenes.[77] Heating the bromide with CF_3CO_2Na, CuI in DMF–toluene (2:1) at 170 °C for 12 h gave trifluoromethylnaphthalenes in 74–96% yield, depending on the 2-alkoxy substituents (entry 10). These naphthalene derivatives were converted to the bioactive naphthoquinones using CAN. Charvet and coworkers also used CF_3CO_2Na on a similar electron-rich bromonaphthalene system while preparing antimalarial compounds based on potent inhibitors of glutathione reductase.[78] However, the desired trifluoromethylnaphthalene was isolated only in 46% yield along with 33% of the unreacted bromide starting material (entry 11). Continuous azeotropic removal of water (that might be present in trace amounts in the reaction solvent) using a Dean–Stark apparatus also failed to significantly improve the overall yield in this case. While preparing analogs of Tolrestat (orally active aldose reductase inhibitors), Wrobel reported the successful trifluoromethylation of a bromonaphthalene that contained both an ester and thiomethyl ether groups.[79] For this purpose, a suspension of bromide, CuI (4 equiv), and sodium trifluoroacetate (8 equiv) in NMP was heated at 180 °C for 2.5 h. After aqueous work-up and chromatographic purification, the desired product was isolated in 77% yield (entry 12).

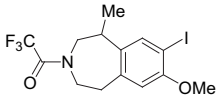
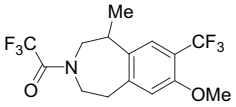
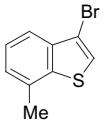
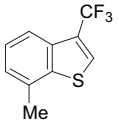
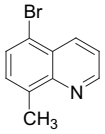
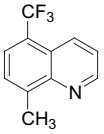
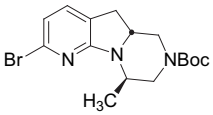
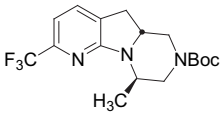
5.2. Reactions of CF_3CO_2Na with heteroaryl iodides and bromides

Behan utilized sodium trifluoroacetate for the trifluoromethylation of a tetrahydrobenzoazepine nucleus while preparing novel 5-HT_{2c} receptor agonists.[80] In this case, the trifluoromethylated product was isolated in only 12% yield (Table 9, entry 1). As observed in a previous report (using MFSDA–CuI protocol) by the Lilly researchers,[25] trifluoromethylation of an iodide containing a trifluoromethylacetamide protecting group gave a low yield of the desired product even with CF_3CO_2Na–CuI conditions. Stütz reported CF_3CO_2Na–CuI mediated trifluoromethylation of a benzo[*b*]thiophene bromide.[81] The resulting product was isolated in 54% yield in this case (entry 2). Grigg reported that 5-bromoquinoline can be trifluoromethylated with sodium trifluoroacetate and copper(I) iodide.[82] After heating the reaction mixture at 160 °C for 5 days, the desired trifluoromethylated product was isolated by these researchers in 59% yield (entry 3). In an effort to synthesize compounds as selective 5-HT_{2c} receptor agonists for potential treatment of obesity, Richter reported the trifluoromethylation of a hexahydropyridopyrrolo[1,2-*a*]pyrazine bromide with CF_3CO_2Na and CuI (entry 4).[83] Although the yield of this particular step was not reported separately, a combined yield of 20% was reported for the *NH*-free product after Boc-deprotection by TFA starting from the Boc-protected bromo precursor.

Representative practical procedure[77]. De Kimpe and co-workers heated a mixture of 2-(benzyloxymethyl)-3-bromo-1,4-dimethoxynaphthalene (2.6 mmol), CF_3CO_2Na (5.2 mmol), CuI (5.2 mmol) in DMF (10 mL) and toluene (5 mL) at 170 °C for 12 h under nitrogen.

Table 9

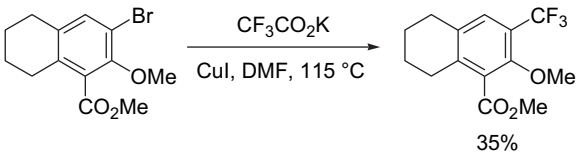
Heteroaryl-I/ Br —Conditions→ Heteroaryl-CF_3

Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		CF_3CO_2Na, CuI, DMF, 155 °C		(12%)[80]
2		CF_3CO_2Na, CuI, NMP, 160–180 °C		(54%)[81]
3		CF_3CO_2Na, CuI, NMP, 160 °C		(59%)[82]
4		CF_3CO_2Na, CuI, NMP, 180 °C		(—)[83]

After being cooled to room temperature, the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was washed with 12 M HCl, 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. Purification via silica gel chromatography gave the desired product in 84% yield.

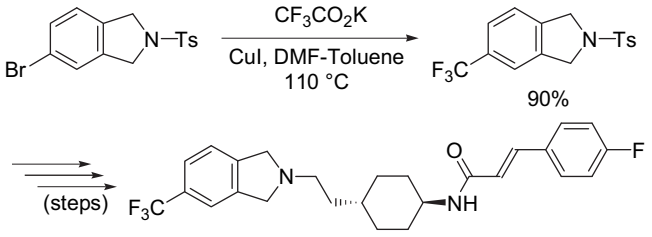
5.3. Reactions of related CF_3CO_2K/$CF_3CO_2(NH_3)_4$ with aryl/heteroaryl bromides

Analogous to sodium trifluoroacetate, commercially available potassium trifluoroacetate was also used in the CuI-assisted trifluoromethylation reactions in very few cases. An example of CF_3CO_2K–CuI mediated trifluoromethylation on a tetrahydronaphthalene system was published by Bernstein during the synthesis of novel aryl glycinamide derivatives as potential NK1 antagonists and serotonin reuptake inhibitors.[84] Thus, heating the bromide with CF_3CO_2K and CuI in DMF at 115 °C for 2 days furnished the CF_3-analog in a 35% yield (Scheme 23). Another example of CF_3CO_2K as a trifluoromethylating agent was reported by Branch in a synthesis of novel 2,3-dihydro-1*H*-isoindoles as selective dopamine D_3 receptor compounds.[85] In contrast to the previous case, 5-trifluoromethyl-2,3-dihydro-1*H*-isoindole was obtained in excellent yield by heating the reaction mixture at 110 °C for only 1.5 h (Scheme 24). It is particularly important to note the high degree of stability of the *N*-tosyl protecting group under these reaction conditions.



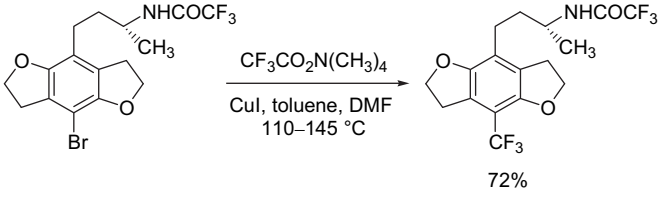
Scheme 23.

Nichols reported the use of tetramethylammonium trifluoroacetate as a potential trifluoromethylating agent while preparing novel 5-$HT_{2A/2C}$ receptor agonists.[86] Thus, starting with a dihydrobenzofuran bromide, successful trifluoromethylation was carried out using $CF_3CO_2NMe_4$ (4.8 equiv) and CuI (5.5 equiv)



Scheme 24.

(Scheme 25). In this case, the halide precursor with a trifluoroacetamide moiety gave the desired product in high yield. As in previous cases, the intial solvent toluene was distilled-off using a Dean–Stark trap followed by the addition of DMF to the reaction mixture, which was then heated at higher temperature. Although $CF_3CO_2NMe_4$ is not widely available, it can be easily prepared using literature procedures.[87]

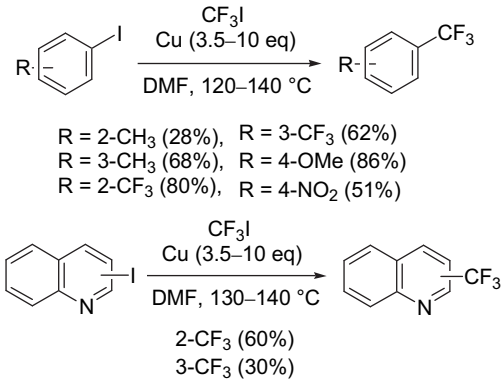


Scheme 25.

6. Trifluoromethylation using trifluoromethyl iodides (CF_3I)

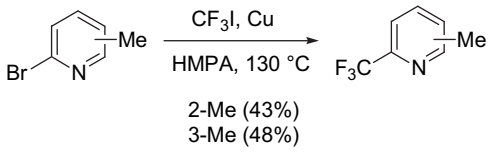
One of the earliest trifluoromethylations of an aryl iodide was reported by Kobayashi and co-workers using trifluoromethyl iodide (Scheme 26).[88] However, the handling of gaseous trifluoromethyl iodide reduces the usefulness and ease of conducting this reaction. Nonetheless, reactions of aryl halides with trifluoromethyl iodide (3.5–10 equiv) in the presence of copper powder in DMF at 120–130 °C for 11–30 h gave the corresponding trifluoromethylated

derivatives in modest to good yield (only GC yields were provided for all cases). These researchers also reported that copper powder prepared from an aqueous solution of copper sulfate and zinc powder gave a much better yield than either commercial copper or copper bronze. They have extended the use of trifluoromethyl iodide to heteroaryl systems, specifically for quinoline cores. Presumably, the reaction proceeds through the formation of trifluoromethylcopper(I) and, thus, the ease of nucleophilic attack at the C-2-position of quinoline by $[CF_3CuI]^-$ gave a higher yield of the desired product compared to the C-3 substituted product under the same condition. Use of HMPA was found to be beneficial in some cases, especially with the bromide precursors, which gave poor (trace) yields in DMF; thus, 3-(trifluoromethyl)quinoline was obtained in 74% yield (GC yield) from 3-bromoquinoline when the reaction was carried out in HMPA instead of DMF. Similarly, the use of pyridine as solvent was useful in few instances.



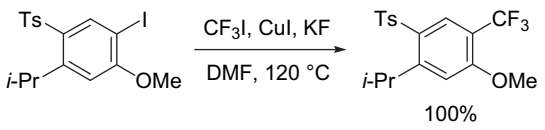
Scheme 26.

Fukaya and co-workers have isolated trifluoromethyl picolines from the corresponding bromo precursors in moderate yields using CF_3I–CuI conditions (Scheme 27).[89] Suschitzky reported the use of this procedure to a pyranoquinoline system, but obtained a very low yield of the desired product after heating the mixture of bromide, CF_3I (0.9 equiv), and activated copper powder in HMPA for 3 h (Scheme 28).[90] However, running the reaction for only 3 h and using less than a stoichiometric amount of CF_3I probably indicates the instability of the starting material under these conditions, which also accounts for the low yield obtained in this case.



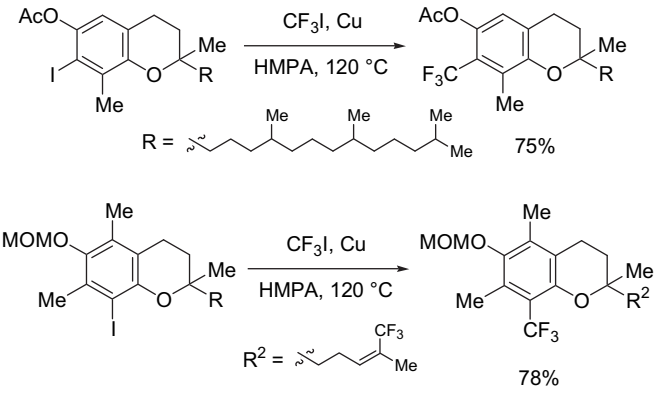
Scheme 27.

In later years, Broka demonstrated similar trifluoromethylation of an aryl iodide using trifluoromethyl iodide but with KF and CuI instead of copper powder (Scheme 29).[91] He reported that the tosyl group is well tolerated under the reaction conditions and the desired product was isolated in quantitative yield.

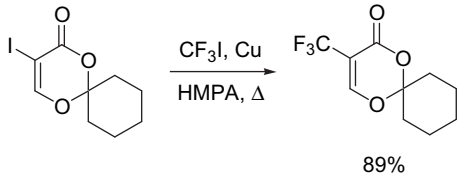


Scheme 29.

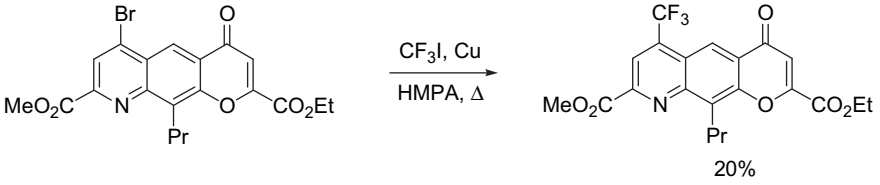
Kumadaki used the CF_3I–Cu system to introduce the trifluoromethyl functionality onto tocopherols.[92] Thus, heating the iodides with CF_3I in the presence of copper powder in HMPA gave trifluoromethylated tocopherols in good yields (Scheme 30). No significant steric effect was observed for the introduction of the CF_3 group between the adjacent OAc and Me groups. Reaction with a similar bromo precursor also gave the desired product in comparable yield under these conditions. Furthermore, trifluoromethylation in the presence of a labile MOM-protected hydroxyl group gave the desired 8-(trifluoromethyl)benzopyran derivative in 78% yield. Iwaoka reported the preparation of a 5-trifluoromethyldioxinones using CF_3I–CuI.[93] The reaction was carried out on a ~4.5 g scale of iodide and the desired product was obtained in excellent yield (Scheme 31).



Scheme 30.



Scheme 31.

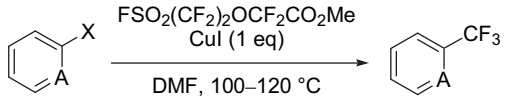


Scheme 28.

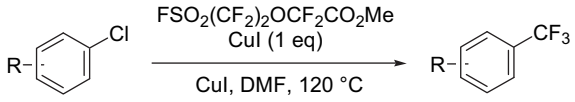
7. Trifluoromethylation of aryl/heteroaryl iodides, bromides and chlorides using other trifluoromethylation agents

7.1. Methyl 3-oxo-ω-fluorosulfonylperfluoropentanoate

Chen and Duan reported the trifluoromethylation of aromatic iodides, bromides, and chlorides using methyl 3-oxo-ω-fluorosulfonylperfluoropentanoate (Scheme 32).[94] Thus, treatment of aromatic halides with $FSO_2(CF_2)_2OCF_2CO_2Me$ (1 equiv) in the presence of CuI (1 equiv) in DMF at 100–120 °C for 6–10 h gave the desired products in excellent yield. Most importantly, various substituted chlorobenzenes, which are normally unreactive under various trifluoromethylation conditions, were converted to their corresponding trifluoromethyl derivatives in 32–72% yields. Aldehydes, ester and nitro functionalities tolerated this transformation. This procedure worked well with simple 2-halopyridines without any activating group, which were known to be difficult in some instances; thus providing the 2-trifluoromethylpyridine in 64–70% yield. Furthermore, this method was also effective for benzyl, allyl, and vinyl iodide and bromide substrates. Although $FSO_2(CF_2)_2OCF_2CO_2Me$ is not commercially available, this useful trifluoromethylating agent can be prepared in high yield by treating commercially available tetrafluoro-2-(tetrafluoro-2-iodoethoxy) ethanesulfonyl fluoride (5-iodooctafluoro-3-oxapentanesulfonyl fluoride) with SO_3 followed by quenching with methanol.[95]



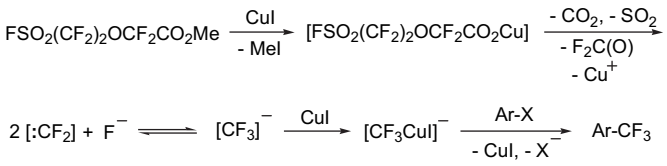
A = CH, X = I (80%), A = N, X = Br (70%)
A = CH, X = Br (73%), A = N, X = Cl (64%)



R = H (52%), R = 4-CO_2Et (52%)
R = 2-Me (32%), R = 3-NO_2 (72%)
R = 4-CHO (56%), R = 4-OMe (37%)

Scheme 32.

Authors proposed the mechanism for this transformation to be similar to that of MFSDA: initial reaction of CuI with $FSO_2(CF_2)_2OCF_2CO_2Me$ forms the usual copper salt that decarboxylates in a concerted manner to furnish the difluorocarbene and fluoride ion (along with elimination of CO_2, SO_2 and difluorophosgene) that are in equilibrium with trifluoromethide ion (Scheme 33). In the presence of CuI, the equilibrium readily shifts toward the formation of $[CF_3CuI]^-$ that then adds nucleophilically onto aromatics displacing the halide.

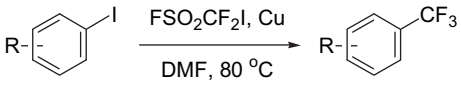


Scheme 33.

The authors observed the formation of CO_2 and SO_2 in a 2:1 molar ratio, which was rationalized by the possible reaction of difluorophosgene and DMF (reaction solvent) providing another equivalent each of CO_2 and F^- (Scheme 34). Fluoride ion adds to the second equivalent of difluorocarbene; thus providing 2 equiv of trifluoromethide ion from 1 equiv of trifluoromethylating agent. One obvious advantage of this trifluoromethylating agent is to produce a higher concentration of difluorocarbene intermediate and fluoride ion in situ. Thus, the benzotrifluoride was obtained in a reasonable yield (61%) from the iodobenzene even when it was treated with only 50 mol % of $FSO_2(CF_2)_2OCF_2CO_2Me$ in the presence of CuI (1 equiv). Similarly, 1,4-bis(trifluoromethyl)benzene was obtained as the sole product in 62% yield from the corresponding 1,4-diiodobenzene using $FSO_2(CF_2)_2OCF_2CO_2Me$ (1 equiv) and CuI (1 equiv). Displacement of the chloride in 1-chloro-4-iodobenzene, which was known to be difficult even using excess of many other common trifluoromethylating agents, was effected with 2 equiv of $FSO_2(CF_2)_2OCF_2CO_2Me$ in the presence of CuI (1 equiv) to provide the 1,4-bis(trifluoromethyl)benzene as the sole product in 52% yield. However, only mono-substitution in 1-chloro-4-iodobenzene was observed with 1 equiv of $FSO_2(CF_2)_2OCF_2CO_2Me$ under the same conditions, furnishing 1-chloro-4-trifluoromethylbenzene in 82% yield. This reagent is superior to many other trifluoromethylating agents due to its ability to convert aryl chlorides, even the unactivated ones, to the corresponding trifluoromethyl derivatives.

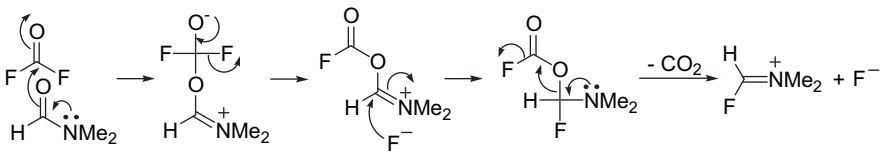
7.2. Fluorosulfonyldifluoromethyl iodide

Chen and Wu reported the use of fluorosulfonyldifluoromethyl iodide in the copper-mediated trifluoromethylation reaction.[96] In a typical procedure, iodobenzene (2 equiv) was treated with FSO_2CF_2I (1 equiv) in presence of Cu powder (2.2 equiv) in DMF at 80 °C for 7 h to provide the benzotrifluoride in 80% yield (Scheme 35). This procedure was also applied to benzyl, styryl, and allyl iodides and bromides and the corresponding trifluoromethyl products were obtained in 72–90% yields (based on used FSO_2CF_2I). The optimum ratio for FSO_2CF_2I–Cu was 1:2.2. Aryl bromides were equally effective: reaction of 1-bromonaphthalene (2.5 equiv) with FSO_2CF_2I (1 equiv) under similar conditions gave 78% yield of the desired product. On the contrary, aryl chlorides were found to be completely inert; thus, substitution occurred exclusively at the iodo-center of 1-chloro-4-iodobenzene even with 3 equiv of the trifluoromethylating agent. A copper SET-induced mechanism was proposed for this transformation where difluorocarbene (and fluoride ion) was generated from $[FSO_2CF_2]^-$ after the elimination of SO_2. This $[FSO_2CF_2]^-$ was in turn generated, via the intermediacy of $[FSO_2CF_2]^{\bullet}$, from FSO_2CF_2I through a series of single-electron transfer sequences. Finally, $[:CF_2]$ and F^- together generate $[CF_3]^-$, which then forms the active trifluoromethylcopper(I) species responsible for aromatic trifluoromethylation.



R = H (80%)
R = 4-NO_2 (83%)

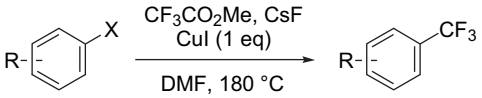
Scheme 35.



Scheme 34.

7.3. Methyl trifluoroacetate

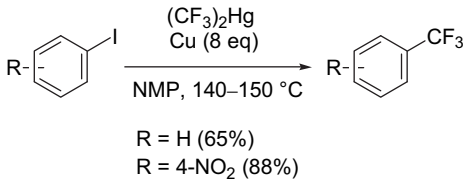
Langlois and Roques showed that commercially available methyl trifluoroacetate (MTFA) also can be used as a trifluoromethylating agent under suitable conditions in place of the commonly used methyl chlorodifluoroacetate (Scheme 36).[97] Thus, reaction of 4-iodoanisole with CF_3CO_2Me (5 equiv) in the presence of CsF (2.5 equiv) and CuI (1 equiv) at 180 °C for 8 h furnished the corresponding benzotrifluoride in 75% yield (100% conversion of iodide was observed). The same benzotrifluoride was obtained from the corresponding bromo precursor in 56% yield (73% conversion). 2-Bromopyridine was also trifluoromethylated, providing the desired product in 42% yield. Use of sub-stoichiometric amount of CuI decreased the conversion of the substrate as well as lowered the yield of the trifluoromethyl product. These researchers also found that 2.5 equiv of cesium fluoride could be conveniently replaced with 1 equiv of cesium chloride providing a similar conversion for 4-iodoanisole. This was rationalized by the better solubility of CsCl than CsF although the possibility of a slightly different mechanism involving CsCl was not ruled out. Other cesium halides gave lower conversion than CsCl (CsCl>CsBr>CsI). Also, KF was found to be ineffective due to low solubility. Sulfolane (tetrahydrothiophene 1,1-dioxide or tetramethylene sulfone) was found to be an attractive solvent for this transformation as it was effective in the temperature range of 140–180 °C, whereas DMF was quite inefficient at 140 °C for the trifluoromethylation using MTFA. This difference was rationalized by the better chelation of Cu(I) by sulfolane, which facilitates the decarboxylation of cuprous trifluoroacetate. Despite this activating effect by sulfolane, a stoichiometric amount of CuI was still needed for the transformation. The authors reasoned that the rate of the oxidative addition of $[CF_3CuI]^-$ to Ar–X bond is much slower than the rate of decarboxylation of $[CF_3CO_2Cu]$ species; thus generating unstable $[CF_3]^-$ at a much faster rate that needs to be accumulated and stabilized by equal amounts of Cu(I) before it reacts in the oxidative addition process to furnish the benzotrifluorides.



Scheme 36.

7.4. Bis(trifluoromethyl)mercury

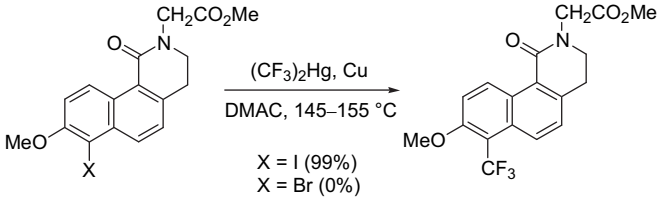
Yagupolskii first reported the use of bis(trifluoromethyl)mercury for trifluoromethylation of aromatic iodides. For this purpose, the aryl iodide was heated with $(CF_3)_2Hg$ (2 equiv) and activated copper powder (8 equiv) in NMP (or DMAC) at 150 °C to yield the desired products in 65–88% yields (Scheme 37).[98] In some cases, somewhat higher yields (10–20%) were obtained when a filtrate (obtained by filtration of $(CF_3)_2Hg$ and Cu mixture after heating in NMP at 140 °C) was used for the reaction with the iodide, instead of the direct presence of $(CF_3)_2Hg$ and Cu powder in the reaction medium. Presumably, the active trifluoromethylcopper(I) complex



Scheme 37.

in the filtrate efficiently drives the desired trifluoromethylation. This protocol was also applied to 2-iodopyridine, which upon heating with $(CF_3)_2Hg$ and Cu powder in DMAC furnished the corresponding product in 74% yield. [CAUTION: It is important to note that dimethyl mercury is an extremely toxic and potentially lethal reagent and should be handled with extreme care].

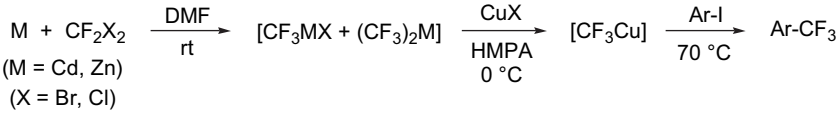
Later, Wrobel reported this method for trifluoromethylating a naphthalene-fused lactam ring while preparing these compounds as novel aldose reductase inhibitors (Scheme 38).[99] As suggested by Yagupolskii, the trifluoromethylcopper (I) species was first generated in situ by pre-heating a solution of $(CF_3)_2Hg$ (0.6 equiv) and activated copper powder (2.4 equiv) in DMAC at 145 °C after which the iodide was added dropwise and stirred at 150–155 °C for 1 h. The desired product was isolated in nearly quantitative yield. The authors reported that the corresponding bromide precursor completely failed to give the desired product under the same reaction conditions, indicating that aryl bromides are not attractive substrates for this trifluoromethylation method.



Scheme 38.

7.5. Difluorodihalomethanes

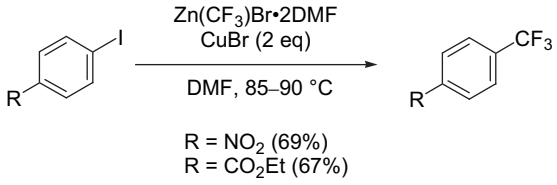
Burton reported the simple, one-pot in situ preparation of (trifluoromethyl)copper species via metathesis of (trifluoromethyl)cadmium and (trifluoromethyl)zinc reagents with copper(I) salts (such as CuBr, CuI, CuCl, and CuCN) (Scheme 39).[36,100] (Trifluoromethyl) cadmium and (trifluoromethyl)zinc reagents were, in turn, prepared in situ from the reaction of activated (acid washed) cadmium and zinc powders with difluorodihalomethanes, such as CF_2Br_2 (or CF_2Cl_2 and CF_2BrCl) in high yields. The authors reported that the trifluoromethylcopper species can be stabilized by the addition of HMPA and no significant change was observed at room temperature. However, in the absence of HMPA, the $[CF_3Cu]$ species was slowly converted to the $[CF_3CF_2Cu]$ species (presumably, $[CF_3Cu]+[:CF_2]\rightarrow[CF_3CF_2Cu]$) in almost quantitative yield after 11 h at room temperature. Nonetheless, the authors have been able to successfully demonstrate the use of trifluoromethylcopper generated by this method to effect the trifluoromethylation of some representative aryl iodides in 72–84% isolated yields.



Scheme 39.

7.6. $Zn(CF_3)Br\cdot 2DMF$ complex

Kremlev recently employed the solid $Zn(CF_3)Br\cdot 2DMF$ complex along with copper(I) bromide for the trifluoromethylation of aryl and heteroaryl iodides.[101] First, $Zn(CF_3)Br\cdot 2DMF$ was stirred with copper (I) bromide (2 equiv) at room temperature for about 30 min to form the trifluoromethylcopper species in situ. To this solution, the aryl iodide was added and then the mixture was heated at 85–90 °C for 8 h to give the corresponding trifluoromethyl product in good yields (Scheme 40). Similarly, 2-iodothiophene and electron-deficient 2-iodopyridine gave the corresponding 2-trifluoromethyl derivatives in 60% and 93% yields, respectively. In most cases small amounts of pentafluoroethyl derivatives were isolated as by-products. As initially reported by Burton, the authors also observed the formation of $[C_2F_5-Cu]$ when the $[CF_3Cu]$ species was left to stir at 50 °C for 4 h, which then subsequently reacted with aryl iodides to give corresponding pentafluoroethyl derivatives.



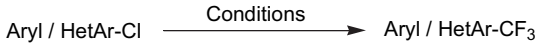
Scheme 40.

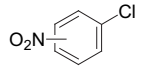
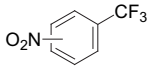
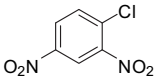
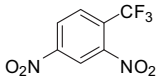
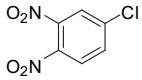
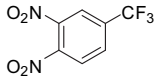
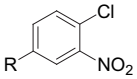
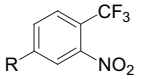
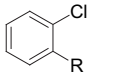
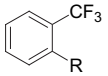
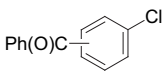
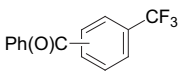
8. Effect of an *ortho*-nitro group and trifluoromethylation of aryl chlorides using copper reagents

Trifluoromethylation of aromatic and heteroaromatic chlorides is not very common. As discussed, methyl 3-oxo-ω-fluorosulfonylperfluoropentanoate is one of the very few reagents that have been consistently useful in converting the aryl chlorides to the corresponding trifluoromethyl derivatives. The higher bond-strength of a carbon–chlorine bond compared to a carbon–bromine or carbon–iodine bond makes the aryl or heteroaryl chloride less labile toward trifluoromethylation. Nevertheless, strongly electrophilic aryl or heteroaryl chlorides are prone to nucleophilic attack by $[CF_3CuI]^-$ as compared to less electrophilic analogs. Thus, trifluoromethylation of chlorides has been achieved with electron-deficient aromatics and heteroaromatics, especially when a nitro group is present on the ring.[102] Otherwise, the presence of a non-labile group *ortho* to the chlorine that can coordinate with the active trifluoromethyl species generally favors this otherwise difficult trifluoromethylation reaction with a trifluoromethylcopper species.

Clark and co-workers have extensively investigated the trifluoromethylation of various aryl chlorides using commercially available dibromodifluoromethane (CF_2Br_2).[102] In a typical procedure, aryl chlorides were treated with dibromodifluoromethane (2.2 equiv) in the presence of copper powder (6 equiv) in DMAC at 100 °C for 8 h to furnish the corresponding benzotrifluorides (Table 10, entries 1–10, only GC yields were provided for all cases). Electron-withdrawing groups at the *ortho* position gave higher yields than those at the *meta* and the *para* positions. Trifluoromethylation of 2-nitrochlorobenzene and 4-nitrochlorobenzene gave 59% and 8% yields, respectively, whereas there was no reaction for 3-nitrochlorobenzene (Table 10, entry 1). Thus, the order of reactivity of substrates toward trifluoromethylation under these conditions: 2-chloronitrobenzene ≫4-chloronitrobenzene>3-chloronitrobenzene. An excellent yield of the trifluoromethylated product was obtained for the 2,4-dinitrochlorobenzene (entry 2) but a very low yield was obtained for 3,4-dinitrochlorobenzene (entry 3). This *ortho*-effect was rationalized by the coordination of the copper to the nitro group, which stabilizes the trifluoromethylcopper complex as well as holds the copper species in the *correct geometry* to place it close to the reaction site. Chlorobenzenes bearing electron-withdrawing but *non-chelating* substituents (such as CF_3, in 2-chlorobenzotrifluoride) were ineffective in this reaction (entry 5). Although the nitrile functionality is capable of coordinating with the copper center, 2-chlorobenzonitrile was unreactive due to the

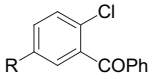
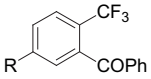
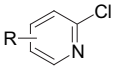
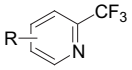
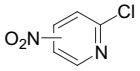
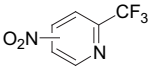
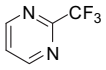
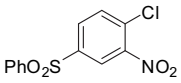
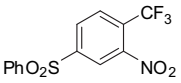
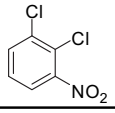
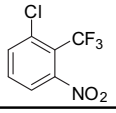
Table 10



Entry	Aryl iodide	Condition	Product	Yield[Ref]
1		CF_2Br_2, Cu, DMAC, 100 °C		2-NO_2 (59%)[102] 3-NO_2 (0%)[102] 4-NO_2 (8%)[102]
2		CF_2Br_2, Cu, DMAC, 100 °C		(100%)[102]
3		CF_2Br_2, Cu, DMAC, 100 °C		(8%)[102]
4		CF_2Br_2, Cu, DMAC, 100 °C		R=CF_3 (97%)[102] R=CHO (100%)[102]
5		CF_2Br_2, Cu, DMAC, 100 °C		R=CF_3 (0%)[102] R=CN (0%)[102] R=OMe (0%)[102] R=CO_2Me (17%)[102] R=CHO (16%)[102]
6		CF_2Br_2, Cu, DMAC, 100 °C		4-COPh (0%)[102] 2-COPh (7%)[102]

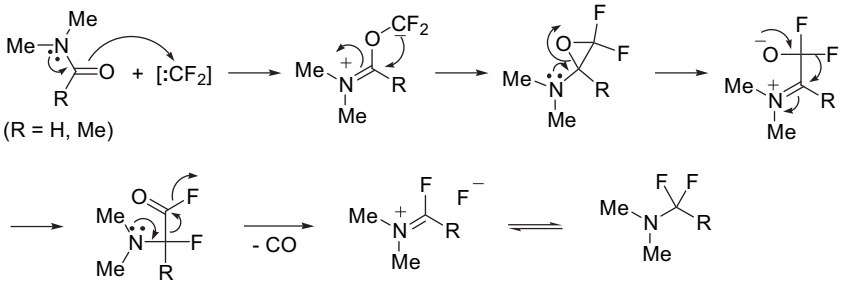
(*continued on next page*)

Table 10 (*continued*)

Entry	Aryl iodide	Condition	Product	Yield[Ref]
7		CF_2Br_2, Cu, DMAC, 100 °C		R=NO_2 (100%)[102]
8		CF_2Br_2, Cu, DMAC, 100 °C		R=H (13%)[102] R=3-CF_3 (19%)[102]
9		CF_2Br_2, Cu, DMAC, 100 °C		3-NO_2 (93%)[102] 5-NO_2 (48%)[102]
10		CF_2Br_2, Cu, DMAC, 100 °C		(46%)[102]
11		CF_2Br_2, Cu, DMAC, 100 °C		(55%)[103]
12		CF_2Br_2, Cu, DMAC, 75 °C		(74%)[104]

incorrect geometry in the transition state. Relatively weak electron-withdrawing functional groups that can hold the copper species in the correct transition state geometry showed some reactivity. Thus, chlorobenzenes with ester and carbonyl functionality at the *ortho* position gave the trifluoromethylated product in low yields (entries 5 and 6). However, an *ortho* keto-substrate, bearing the strongly electron-withdrawing nitro group, furnished the desired product in excellent yield (entry 7) due to increased electronic activation of the aryl chloride substrate in combination with an *ortho*-effect. Clark also applied this procedure to the electrophilic 2-chloropyridine and 2-chloropyrimidine, which were transformed to the corresponding 2-trifluoromethyl derivatives in low to moderate yield (entries 8–10). In contrast, dual assistance by the *ortho*-effect and electronic activation of the substrate due to the presence of the nitro group again enhanced the yield of the desired product (entry 9).

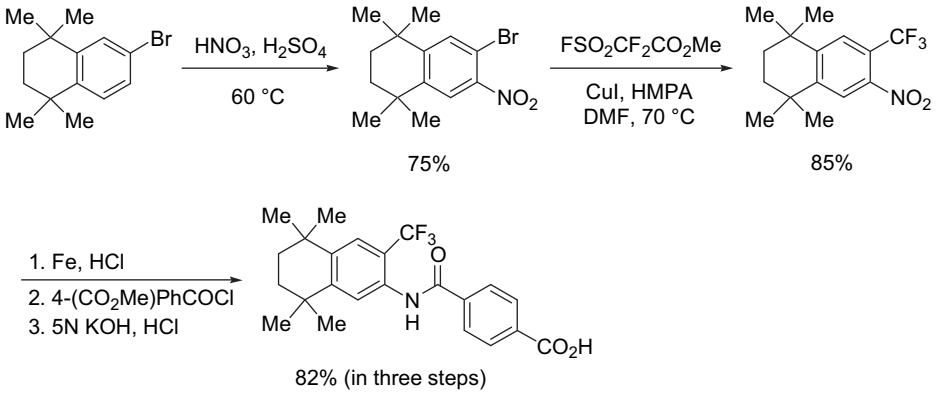
Clark and co-workers also examined the role for an amide solvent in this reaction since the formation of trifluoromethylcopper presumably involves the generation of difluorocarbene from CF_2Br_2–Cu, which then reacts with the amide solvent to provide a difluoroalkylamine that acts as a source of fluoride ion (Scheme 41). Reaction of F^- with [:CF_2] forms $[CF_3]^-$, which finally forms the active trifluoromethylcopper(I) complex, as seen in other cases. Indeed, DMSO and sulfolane were not suitable for this reaction due to their inability to generate fluoride ion; thus validating the proposed mechanism for this transformation. Interestingly, the use of stoichiometric DMF (as a reagent) with chlorobenzene (as bulk solvent) gave the desired 2,4-dinitrobenzotrifluoride from the 2,4-dinitrochlorobenzene model substrate, but at a slower rate and a less efficient conversion to the desired product. Other aromatic solvents such as nitrotoluene or toluene with stoichiometric DMF were considerably less effective. Moreover, the use of DMPU (*N*,*N*′-dimethylpropylene urea) as solvent offered the fastest reaction rate. However, DMAC was superior for the best combination of reaction rate and efficiency. Notably, addition of KF to the reaction mixture, as an additional fluoride source, unexpectedly decreased the reaction rate for 2,4-dinitrochlorobenzene and also generated 2,4-dinitrofluorobenzene. This inhibition was very prominent with less reactive substrates; for example, addition of 10% KF completely inhibited the trifluoromethylation reaction of 2-chlorobenzaldehyde. The significant formation of the fluorinated product from 2,4-dinitrochlorobenzene was rationalized by the precipitation of copper salts due to increased anion concentration in the reaction medium. A similar effect was observed with the addition of KI where the formation of fluoroaromatics was accounted for by the competitive formation of KF from KI plus F^- present in the system. Interestingly, 2-bromonitrobenzene and 2-iodonitrobenzene were unreactive under this CF_2Br_2–Cu–DMAC protocol (30% and 6% GC yields for benzotrifluoride, respectively). Biphenyl products, generated from Ullmann coupling, were obtained. Thus, Clark's method is largely complementary to the other common trifluoromethylation methods involving iodides and bromides and suitable choice of conditions would lead to the desired benzotrifluorides from the available set of iodides, bromides, or activated chlorides.



Scheme 41.

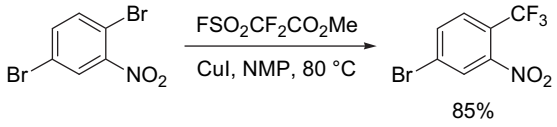
Following Clark's method, Commons and Mewshaw reported the trifluoromethylation of an *ortho*-nitrochlorobenzene during the preparation of novel aryl sulfonamide derivatives as modulators of secreted frizzled-related protein-1 for the treatment of several bone-related diseases (Table 10, entry 11).[103] Thus, exposing the aryl chlorides to CF_2Br_2 and copper powder in dry DMAC at 100 °C gave the desired products in 55–58% yields. On a 300 g scale, Favor and co-workers carried out a regioselective trifluoromethylation of 2,3-dichloronitrobenzene during the preparation of novel isoindole derivatives useful in the treatment of various CNS disorders (e.g., schizophrenia).[104] Thus, dibromodifluoromethane (2 equiv) was added dropwise to a mixture of aryl chloride and copper (6 equiv) in dimethylacetamide after which the mixture was heated at 75 °C for 20 h. The chlorine next to nitro group was displaced exclusively and the desired product was isolated in 74% yield (entry 12). Of note, Clark earlier reported an 86% yield (GCyield) for this particular transformation in a ~1 g scale (at 100 °C). Thus, the procedure is scalable to a very large scale of aryl chloride substrates.

Qing and Fan successfully carried out the trifluoromethylation of a tetrahydronaphthalene in the presence of an *ortho*-nitro group using excess MFSDA–CuI (Scheme 42).[105] The desired product was obtained in excellent yield from the activated bromide substrate at relatively mild temperature. The trifluoromethyl product was then rapidly converted to the desired target molecule that is an analog of Am 80, a selective inhibitor for certain retinoid receptors.

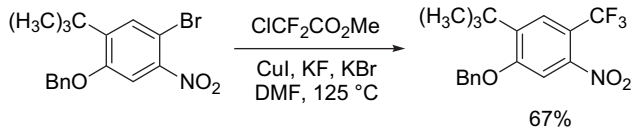


Scheme 42.

Parrish and Dhanak reported a regioselective trifluoromethylation of 1,4-dibromo-2-nitrobenzene on a five-gram scale while preparing inhibitors of mitotic kinesin KSP that are useful for treating cellular proliferative diseases such as cancer.[106] A mixture of the dibromide and MFSDA (2 equiv) in the presence of catalytic copper(I) iodide (25 mol %) was heated at 80 °C for 24 h (Scheme 43). Despite the use of catalytic CuI, the desired product was obtained in 85% isolated yield, presumably due to the effect of the *ortho*-nitro group to stabilize and position the copper species near to the reaction site, thereby facilitating the reaction with MFSDA–CuI. Ruah reported the preparation an *ortho*-nitrotrifluoromethylbenzene that is an important intermediate for the preparation of novel modulators of ATP-Binding Cassette (ABC) transporters as well as cystic fibrosis conductance regulators.[107] In this case, heating a mixture of the aryl bromide with methyl chlorodifluoroacetate in the presence of CuI, KF, and KBr furnished the desired product in moderate yield (Scheme 44).

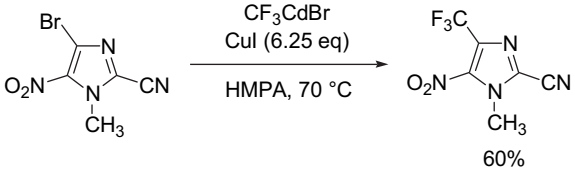


Scheme 43.



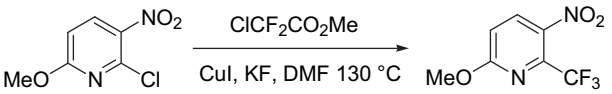
Scheme 44.

Chauviere used trifluoromethylcadmium bromide to convert a bromoimidazole to its trifluoromethyl derivative by treating the aryl bromide with this cadmium salt (2.5 equiv) with CuI (6.25 equiv) in HMPA at 70 °C (Scheme 45).[108]



Scheme 45.

Arvanitis reported the conversion of 2-chloro-6-methoxy-3-nitropyridine to the corresponding 2-(trifluoromethyl)pyridine (Scheme 46).[109] Although a similar protocol has been successfully used for the trifluoromethylation of similar aryl iodides and bromides, trifluoromethylation of aryl chlorides under these conditions was unprecedented. Presumably, doubly activation by the pyridine ring and the nitro functionality facilitated this transformation, as reported by Clark for their CF_2Br_2–Cu–DMAC system.

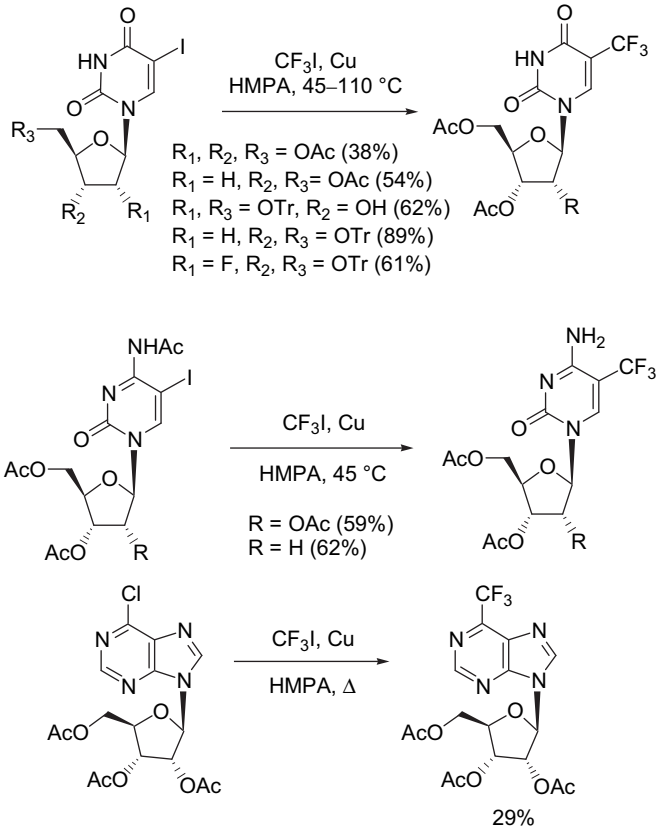


Scheme 46.

9. Trifluoromethylation of halo-nucleosides

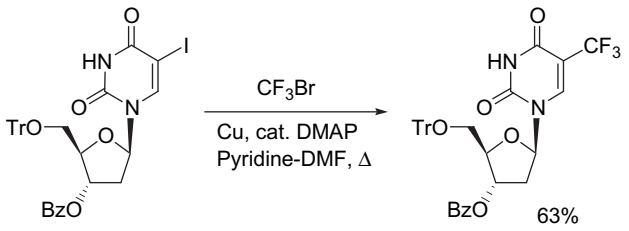
Kobayashi reported the trifluoromethylation of 5-iodouridine and 5-iododeoxyuridine using trifluoromethyl iodide and CuI (Scheme 47).[110] Both *O*-acetyl and *O*-trityl protecting groups were well tolerated under the reported conditions and moderate to excellent yields of the desired products were obtained. Generally, reactions were performed at lower temperature (45 °C) for *O*-acetyl protected compounds and at higher temperature (110 °C) for

O-trityl protected compounds, thus furnishing higher yields for the *O*-trityl protected compounds. Similarly, trifluoromethylation was achieved with cytidine and adenosine iodides, however the *N*-acetyl protecting group was apparently unstable in the reaction work-up and resulted in formation of the free amine. Similarly, bromoadenosine and bromoinosine were trifluoromethylated to their corresponding trifluoromethyl derivatives in moderate yield. Kobayashi also investigated trifluoromethylation of a 6-chloropurine riboside using these conditions; however, a lower yield was obtained for the corresponding 6-trifluoromethyl purine analog due to lower reactivity of the chloride substrate. Watanabe later used similar conditions with arabinofuranosyluracil iodide to yield the desired product in 61% yield.[111]



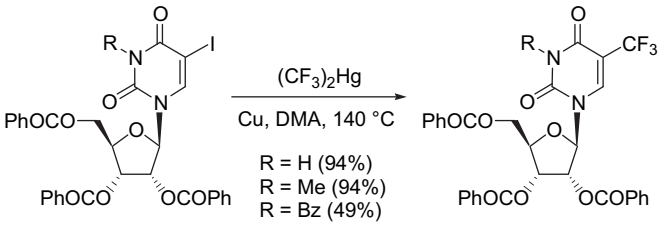
Scheme 47.

Instead of using CF_3I, Yamashita and co-workers used CF_3Br in the presence of Cu powder and catalytic DMAP in pyridine/DMF for the trifluoromethylation of 5-iododeoxyuridine (Scheme 48).[112] Interestingly, the desired product was obtained in comparable yield to that observed for the trifluoromethylation of similar 5-iododeoxyuridines.



Scheme 48.

Nowak and Robins utilized $(CF_3)_2Hg$ and activated copper powder for the trifluoromethylation of 5-iodouracil nucleosides (Scheme 49).[113] The desired 5-trifluorouracil derivatives were generally obtained in excellent yields, except in one case where the *N*-benzoyl protecting group was found to be cleaved to produce the free NH analog as a major by-product of this reaction. [CAUTION: It is important to note that dimethylmercury is an extremely toxic and possibly lethal reagent and should be handled with extreme care].



Scheme 49.

Jacobson reported the trifluoromethylation of an adenine nucleoside using Burton's procedure (Scheme 50).[114] In the event, the 2-iodopurine unit of the nucleoside was efficiently converted to the corresponding trifluoromethyl analog in 77% yield using the trifluoromethylcopper species that was generated in situ from CF_2Br_2 and Zn in DMF, followed by the addition of CuI and HMPA, as discussed before. Earlier, Nair and Buenger had reported the synthesis of 2-(trifluoromethyl)adenosine in 63% yield from the corresponding 2-iodoadenosine using a similar procedure.[115]

Beal and co-workers investigated the synthesis of 6-trifluoromethylpurine ribonucleoside from the corresponding 6-bromopurine by two methods (Scheme 51).[116] Notably, both Chen's method (MFSDA–CuI) or a variation of Burton's procedure (CF_3I–Zn–CuI) gave an excellent yield of the desired product.

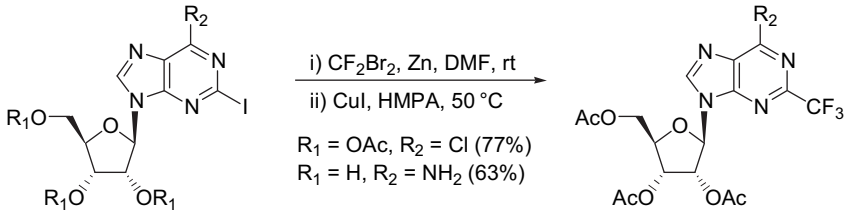
10. Aromatic trifluoromethylation using microwave heating

Microwave heating has been safely used in a few instances in place of conventional heating to obtain the trifluoromethylated products from the corresponding iodides and bromides. For example, Barbosa reported trifluoromethylation of a 4-bromothiazole with sodium trifluoroacetate and CuI under microwave irradiation (Scheme 52).[117] Despite using 2 equiv of CF_3CO_2Na and CuI, only a low yield of desired product was obtained. A similar low yield was obtained by the same group for the trifluoromethylation of a related aryl bromide under microwave conditions.[118] Presumably, low solubility of CF_3CO_2Na in toluene–DMF is responsible for lower yields in these cases. Of note, these compounds were developed for treating neurological and psychiatric disorders, acting as corticotrophin releasing factor 1 (CRF1) receptor antagonists.

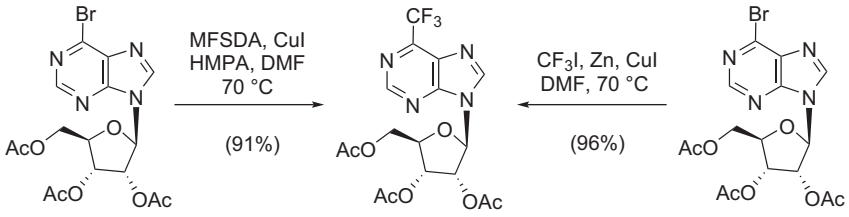
Jones reported the trifluoromethylation of an isonicotinamide while preparing novel HIV integrase inhibitors (Scheme 53).[119] Following Kobayashi's procedure, a solution of heteroaryl iodide in pyridine was heated under microwave with a large excess of iodotrifluoromethane and a stoichiometric amount of copper powder to yield the desired product.

11. Electrochemical aromatic trifluoromethylation using a sacrificial copper anode

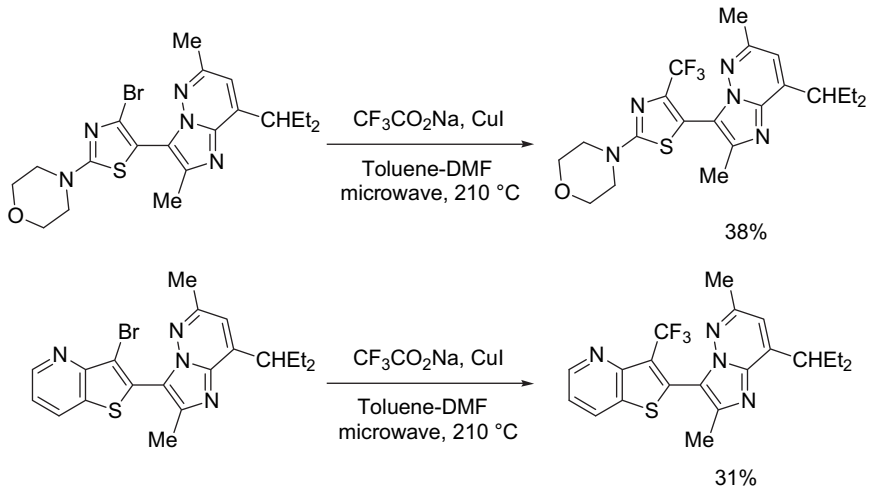
Paratian reported an electrochemical trifluoromethylation for aryl iodides and bromides where the trifluoromethylcopper(I) complex was generated utilizing a copper anode in the presence of excess CF_3Br, TMEDA (4 equiv), and catalytic Bu_4NBr (5 mol %) in DMF (Scheme 54).[120] Use of ligands such as TMEDA, PPh_3, PBu_3, or



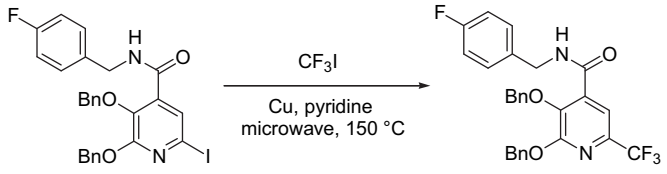
Scheme 50.



Scheme 51.

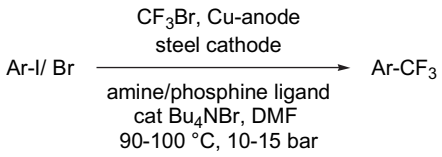


Scheme 52.



Scheme 53.

2,2′-bipyridine (bpy) was essential to avoid the precipitation of copper(I) bromide. Importantly, ^{19}F NMR indicated complexation of these ligands with the organocopper species, which presumably assisted the trifluoromethylation process by stabilizing the trifluoromethylcopper species. On a 10–20 mmol scale, benzotrifluorides were obtained in 32–98% yield (only GC yields were provided for all cases) under these conditions. Aryl iodides were more reactive than the bromides, and a 90% yield was obtained with 4-iodoanisole despite the presence of the electron-donating methoxy group. The strongly electron-withdrawing nitro group (and cyano in some cases) favored the trifluoromethylation reaction. Thus, benzotrifluoride was obtained in moderate yield (55%) from 4-chloronitrobenzene in the presence of the PBu_3 (2 equiv) ligand under similar conditions. Choice of ligands was found to be crucial for the success in some cases as the use of TMEDA (even with 5 equiv) with the same 4-chloronitrobenzene substrate gave only a trace amount of the desired product. Using TMEDA (4 equiv) ligand, 2- and 3-bromopyridines as well as 3-bromoquinoline furnished the desired products in 95–98% yield. Notably, similar yields were obtained with lesser equivalents of the phosphine ligand (2 equiv of PBu_3) compared to the 4–5 equiv of TMEDA from 2-bromopyridine. Despite the low applicability of carrying out this transformation under simple laboratory set-ups routinely, this work provided important insights on the use of amine and phosphine ligands in the trifluoromethylation process.

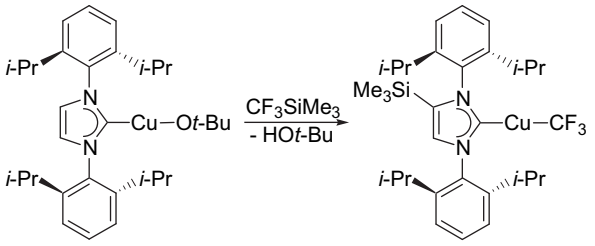


Scheme 54.

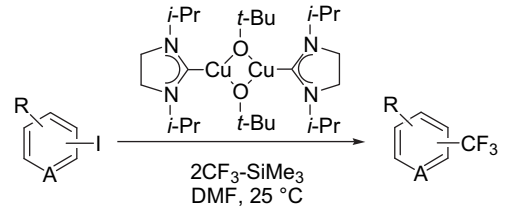
12. Isolable Cu(I)–CF_3 complex

Vicic reported the first example of a well-defined and stable CF_3–Cu(I) complex that has been subsequently used for the trifluoromethylation of aryl iodides (Scheme 55).[121] The authors observed that the reaction of CF_3TMS with a known *N*-heterocyclic carbine (NHC)–copper complex yielded the desired CF_3–Cu(I) complex along with the unexpected incorporation of a TMS group into the backbone of the NHC-ligand. Nonetheless, this was the first example of the preparation of an isolable trifluoromethylcopper complex, the structure of which was confirmed by X-ray crystallography. The CF_3–Cu(I) complex is stable at room temperature and no evidence of aggregation was found even in solution, presumably due to the steric bulk of the IPr [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] ligand. However, when this Cu(I)–CF_3 complex was treated with neat iodobenzene at room temperature for 44 h, the desired trifluoromethylated product was produced in only 33% yield. Upon heating the reaction mixture, the formation of $PhCF_3$ is competitive with the decomposition of the Cu(I)–CF_3 complex and the formation of both L–Cu–CF_2CF_3 (as observed previously for solvated trifluoromethylcopper species) and TMS–F was observed. The presence of TMS–F as a major by-product in the decomposition mixture prompted the use of a non-silylated NHC–Cu(I)–CF_3 complex in the trifluoromethylation reaction, because the silylated carbene ring in the Cu(I)–CF_3 complex could be the cause for the low yield. To prevent the silylation at the 4-position of the imidazole ring, as observed in the previous case, the authors used an NHC-ligand with a saturated backbone. Thus, treatment of an NHC–copper complex, containing the saturated SI^{i}Pr [1,3-diisopropylimidazolin-2-ylidene] ligand, with CF_3TMS provided the desired analogous Cu(I)–CF_3 complex, but without any incorporation of the TMS group into the Cu(I)–CF_3 complex. Furthermore, the new CF_3–Cu(I) complex was expected to be more efficient than the previous case due to greater accessibility of the copper center due to a less sterically demanding SI^{i}Pr ligand. This assumption was supported by the dimeric nature of the L–Cu–O^{t}Bu starting material containing the SI^{i}Pr ligand compared to the monomeric nature of the L–Cu–O^{t}Bu used in the previous case. The SI^{i}Pr–Cu–CF_3 complex was prepared in 91% yield by treating the SI^{i}Pr–Cu–O^{t}Bu dimer with CF_3TMS in THF at room temperature and, as expected, the new Cu(I)–CF_3 complex provided excellent yields of the desired trifluoromethyl product when treated with aryl iodides at room temperature (Scheme 56). However, the Cu(I)–CF_3 complex with the SI^{i}Pr ligand is extremely air-sensitive and, thus, it was more convenient to generate this complex in situ from the corresponding precursor using CF_3TMS. Also, the DMF solvent greatly enhances the efficiently of the trifluoromethylation reaction in this case. Using these conditions to generate the NHC–Cu–CF_3 complex in situ and subsequent reaction of this complex with the representative iodobenzenes and iodopyridines afforded the desired benzotrifluorides in almost quantitative yields (yields were measured by ^{19}F NMR). However, the examples were limited to aryl iodides, which should be used in excess amounts (5 equiv) for the best results. Also, an attempt to employ catalytic conditions using 1 equiv of KO^{t}Bu to regenerate the SI^{i}Pr–Cu–O^{t}Bu complex was ineffective. Although this method is not catalytic and a full equivalent of copper is still required, it presents the advantage of trifluoromethylation at room temperature and could be particularly useful for the synthesis of thermally sensitive starting materials.

In continuation of their effort to develop active systems for trifluoromethylation reactions, Vicic and co-workers reported the effect of the SIMes (1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) ligand on the reactivity L–Cu(I)–CF_3.[122] The SIMes ligand was chosen due to its size, which is between the size of the SI^{i}Pr and IPr ligands. Treatment of (SIMes)–Cu–O^{t}Bu with CF_3TMS afforded



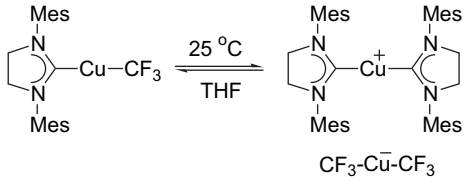
Scheme 55.



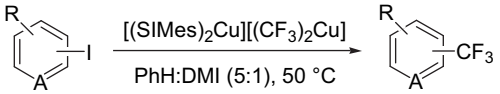
A = CH, R = H (94%)
A = CH, R = 4-Ph (99%)
A = CH, R = 4-OMe (91%)
A = N, R = H, 3-CF_3 (94%)
A = N, R = H, 4-CF_3 (99%)

Scheme 56.

the desired SIMes–Cu–CF_3 complex in high yield. However, in THF solution at room temperature, it was in equilibrium with another new species that was later identified by X-ray crystallography as a cuprate salt [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] (Scheme 57). [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] was found to be quite stable in the solid state and no decomposition was observed over an extended period of time. Apart from the success with iodobenzenes, [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] was also found to be effective for the conversion of aryl bromides to benzotrifluorides in good yields. However, higher temperature (85–90 °C) was required for the bromide substrates compared to the room temperature reaction with iodides. Thus, reaction of [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] with *neat* 4-methoxybromobenzene at 85 °C for 2 h afforded the trifluoromethylated product in 72% yield (compared to 37% yield using the [(SI^{i}Pr)Cu-CF_3] complex under similar conditions; yields were determined by ^{19}F NMR). The reaction was optimized to suppress the formation of the [CF_3CF_2Cu] species. Representative aryl iodides and bromides (e.g., 2-bromopyrimidine) were trifluoromethylated using solid [(SIMes)$_2$Cu][(CF$_3$)$_2$Cu] in benzene–DMI (5:1) solvent (DMI=1,3-dimethyl-2-imidazolidinone) at 50 °C for 28 h (Scheme 58) in moderate to high yield, except for the case of 5-bromopyrimidine, which failed to give the desired product. As in previous cases, a stoichiometric amount of copper salt was needed for these reactions.



Scheme 57.



A = CH, R = H (86%)
A = CH, R = 4-Ph (93%)
A = CH, R = 4-OMe (89%)
A = N, R = H, 3-CF_3 (88%)
A = N, R = H, 4-CF_3 (57%)

Scheme 58.

Notably, Vicic and co-workers also reported the preparation of various nickel-trifluoromethyl complexes, such as (BOXAM)$NiCF_3$ [BOXAM=bis[((4-isopropyl)-4,5-dihydrooxazol-2yl)phenyl]amine]; however, successful aromatic trifluoromethylation using such Ni-complexes is yet to be reported.[123]

13. Trifluoromethylation using catalytic copper reagent

Recently, Amii and co-workers reported the first systematic study of copper-catalyzed aromatic trifluoromethylation.[124] Considering the Urata and Fuchikami's trifluoromethylation method (CuI–CF_3SiEt_3–KF), they have hypothesized that the rate of regeneration of the CuI from the σ-bond metathesis between CF_3Cu and Ar–I is much slower than the rate of decomposition of CF_3TES to form the trifluoromethide ion. Therefore, the net transformation cannot regenerate sufficient CuI that would enter into the catalytic cycle by reacting with $[CF_3]^-$ before its decomposition. Thus, a stoichiometric amount of CuI is needed. Notably, Langlois and Roques proposed similar kinetics for their methyl trifluoroacetate mediated trifluoromethylation reaction (Fig. 2).[97]

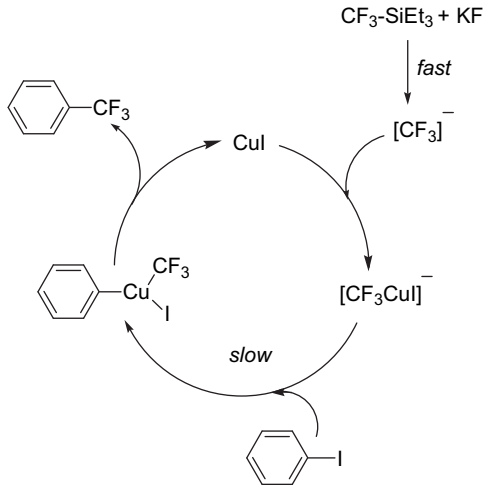


Fig. 2.

In a simplified scenario, Amii and co-workers envisioned a copper(I)-diamine complex (L_2Cu–I) for the trifluoromethylation because the bidentate diamine ligand would increase the electron density at the metal center in the $L_2Cu(I)$–CF_3 complex, thereby enhancing the nucleophilicity of the CF_3 moieties that would react with Ar–I at a faster rate, accelerating the rate of regeneration of L_2Cu–I (Fig. 3). In this regard, a few diamine ligands such as 1,10-phenanthroline (phen) gave excellent results. Of note, Paratian and co-workers have used similar bidentate amine ligands during their electrochemical aromatic trifluoromethylation.[120]

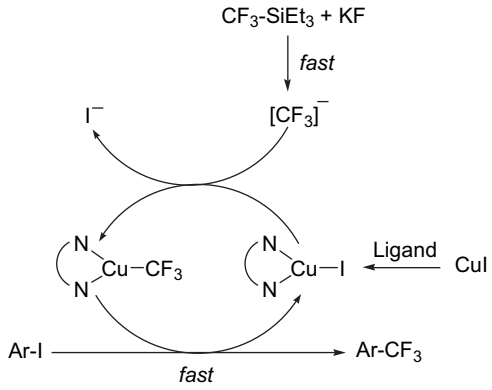
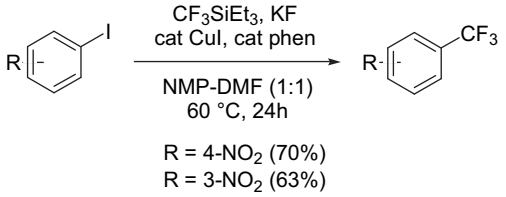


Fig. 3.

With 10 mol % of the L_2Cu–I complex (prepared in situ from 10 mol % CuI and 10 mol % of 1,10-phenanthroline), aryl and heteroaryl iodides were trifluoromethylated with CF_3TES (2 equiv) and KF (2 equiv) in NMP–DMF (1:1) (Scheme 59). The desired products were obtained in moderate to excellent yields with only small amounts (<3%) of the pentafluoroethylated (Ar–CF_2CF_3) by-product. As expected, iodoarenes with electron-withdrawing groups worked better in this catalytic nucleophilic process. Notably, 2-(trifluoromethyl)quinoline was isolated in 95% yield from 2-iodoquinoline under these conditions. However, an attempt to decrease the catalyst loading gave a lower yield of the 4-(trifluoromethyl)nitrobenzene from 4-nitroiodobenzene under similar conditions. Also, other copper(I) salts, such as CuBr and CuCl, in conjugation with the 1,10-phenanthroline ligand, gave the desired benzotrifluoride product, but in slightly lower yields. Although this method is currently limited to iodides, it is an important breakthrough in aromatic trifluoromethylation as a catalytic process in copper. Notably, a Japanese patent for this purpose utilizing Cu–aminopyridine complexes has appeared at a similar time by a different research group.[125]

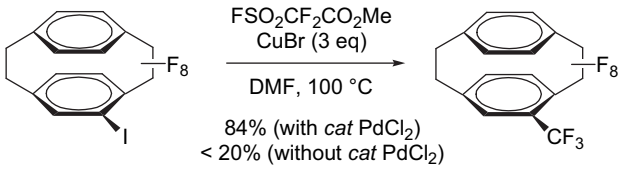


Scheme 59.

Representative practical procedure[124]: Amii and co-workers heated a mixture of CuI (0.1 mmol), 1,10-phenanthroline (0.1 mmol), KF (2.0 mmol), 4-iodonitrobenzene (1.0 mmol), and CF_3TES (2.0 mmol) in NMP–DMF (2 mL, 1:1) at 60 °C for 24 h under nitrogen. After being cooled to room temperature, the mixture was quenched with water, extracted with Et_2O, dried over Na_2SO_4, and concentrated. Purification via silica gel chromatography gave the desired product in 70% yield.

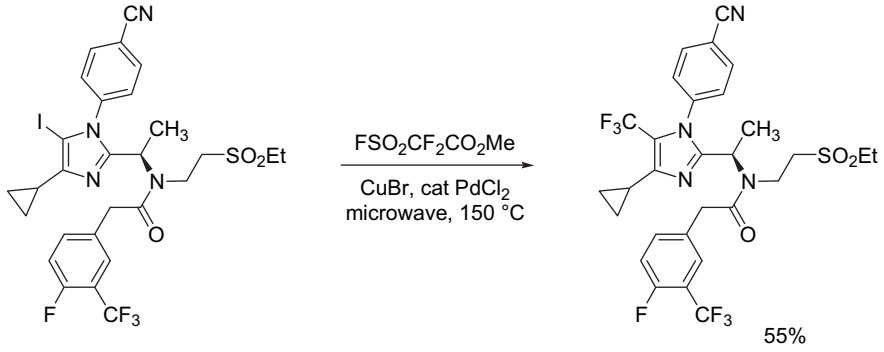
14. Palladium-catalyzed copper-mediated trifluoromethylation

Dolbier reported the effect of catalytic $PdCl_2$ (10 mol %) in Cu(I)-mediated aromatic trifluoromethylation reactions.[126] He observed that the yields of trifluoromethylated octafluoro[2.2]paracyclophanes (OFP) can be greatly enhanced in the presence of catalytic $PdCl_2$ (Scheme 60). Thus, trifluoromethylation of iodo-OFP using MFSDA, copper(I) bromide, and 10 mol % of $PdCl_2$ gave the desired product in 84% yield, while the same product was produced in <20% yield in the absence of $PdCl_2$ using MFSDA–CuI conditions. In the following year, Dolbier extended this modification to the trifluoromethylation of pseudo-*meta* and pseudo-*para* OFP diiodides. Similar effects on the reaction yield were observed using catalytic $PdCl_2$, furnishing the desired products in high yields (68–80%). These substrates were difficult to trifluoromethylate under standard copper-mediated trifluoromethylation, but the use of $PdCl_2$ as a catalyst was clearly beneficial to yield the desired benzotrifluorides.



Scheme 60.

Subsequently, Du and co-workers used catalytic $PdCl_2$ in their copper-mediated microwave-assisted trifluoromethylation while preparing novel imidazole derivatives as potent CXCR3 antagonists.[127] In the event, the iodoimidazole was microwaved at 150 °C using MFSDA, CuBr, and catalytic $PdCl_2$. A moderate yield (55%) of the desired product was obtained despite the presence of several other labile functionalities in the molecule (Scheme 61).

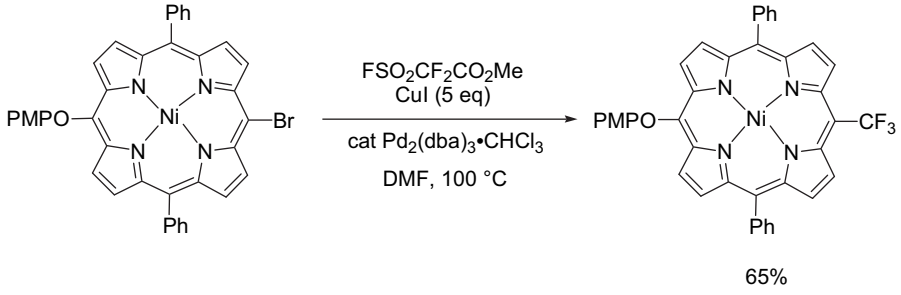


Scheme 61.

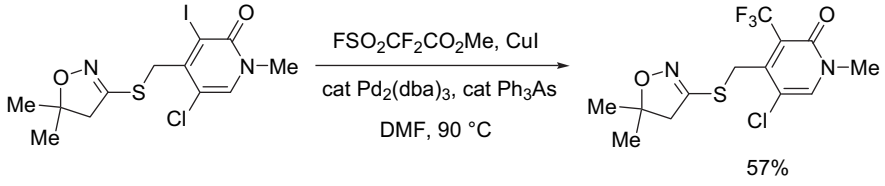
While performing trifluoromethylation on a bromoporphyrin, the Chen group used catalytic tris(dibenzylideneacetone)dipalladium(0) along with MFSDA and CuI (Scheme 62).[128a] A mixture of bromoporphyrin, MFSDA (10 equiv), CuI (5 equiv), and catalytic $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol%) was heated at 100 °C for 8 h to provide the corresponding trifluoromethylated product in 65% yield. Interestingly, the trifluoromethylcopper species was totally inert toward bromoporphyrins without the palladium catalyst and no reaction was observed.[128b] They proposed that oxidative addition of Pd(0) to bromoporphyrin generates a (porphyrin)Pd(II) complex that undergoes transmetalation with $[CF_3CuI]^-$ to form the (trifluoromethylatedporphyrin)Pd(II) complex, which finally furnishes the desired product after reductive elimination to regenerate the Pd (0) species for the catalytic cycle.[128b]

15. Palladium-catalyzed aromatic trifluoromethylation

Although the copper-mediated aromatic trifluoromethylation reaction was highly successful in many cases, attempts to achieve this conversion with palladium catalysis have been of interest to organic chemists for long time. Palladium-catalyzed cross-coupling reactions are now ubiquitous in synthesis, but only limited success has been achieved for the palladium-catalyzed trifluoromethylation reaction until recently. In 1982, Kitazume and Ishikawa reported the first palladium-catalyzed aromatic trifluoromethylation without the use of copper(I).[130] Thus, iodobenzene could be easily trifluoromethylated in high yield using CF_3I and zinc powder in the presence of $PdCl_2(PPh_3)_2$ under ultrasonic irradiation for 30 min (Scheme 64). They proposed the formation of trifluoromethylzinc iodide (CF_3ZnI) that entered the catalytic cycle as $[CF_3]^-$. However, no reaction was observed without ultrasonic irradiation under the same conditions.



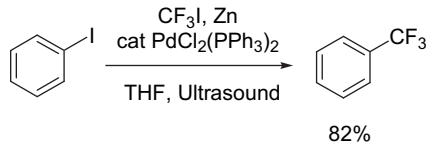
Scheme 62.



Scheme 63.

Following the Chen's method,[128b] Smith and co-workers recently used 40 mol% triphenylarsine along with 5 mol% $Pd_2(dba)_3$, CuI (5 equiv), and MFSDA (5 equiv) in DMF in the trifluoromethylation of

Although Kitazume and Ishikawa proposed in 1982 a classical Pd (0)–Pd(II) catalytic cycle for their method (Fig. 4),[130] no report appeared for a long time of another palladium catalyzed



Scheme 64.

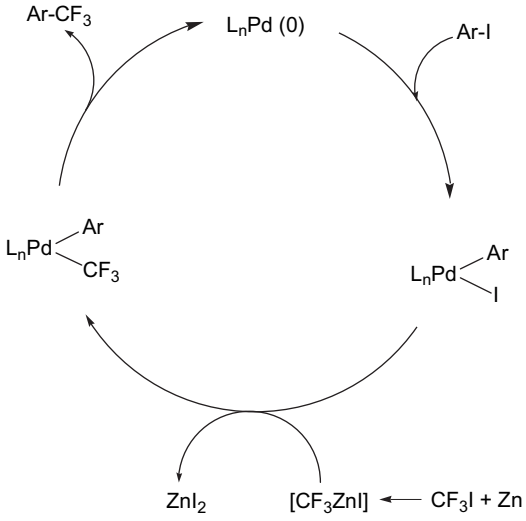
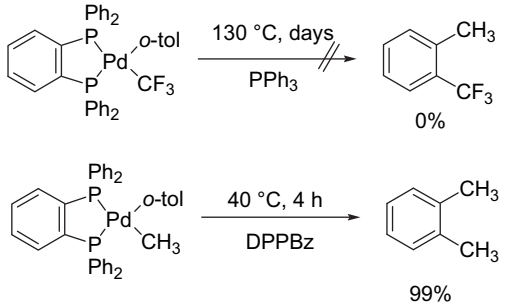


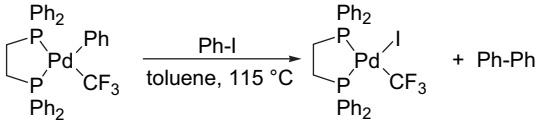
Fig. 4.

trifluoromethylation. Almost 22 years later, Culkin and Hartwig reported that reductive elimination from a $L_nPd(Ar)CF_3$ complex (to form the corresponding Ar–CF_3 compound) is much more difficult than it is from the related $L_nPd(Ar)CH_3$ complex (Scheme 65).[131] The latter researchers have extensively studied the C–C bond-forming reductive elimination from the *isolated* arylpalladium complexes. Interestingly, no reductive elimination was observed from the isolated (dppbz)Pd(*o*-tol)–CF_3 complex upon heating at 130 °C for several days [dppbz=1,2-bis(diphenylphosphino)benzene], whereas the related $L_nPd(o\text{-tol})–CH_3$ complex underwent facile reductive elimination to form *o*-xylene in 99% yield.[132] Also, the related (dppbz)Pd(*p*-tol)–CH_2CF_3 complex underwent reductive elimination to form the corresponding Ar–CH_2CF_3 compound in 96% yield in 36 h upon heating at 110 °C in the presence of PPh_3. This clearly indicated the difficulty (high activation barrier) in forming the C–C bond during the reductive elimination from a Pd (II) center to furnish the corresponding Ar–CF_3 compounds.



Scheme 65.

While attempting the reductive elimination from the (dppe)Pd(Ph)CF_3 complex in the presence of iodobenzene (to trap the resulting Pd(0) species), Grushin and Marshall surprisingly obtained biphenyl instead of the desired trifluoromethylbenzene (Scheme 66).[133] They rationalized these unexpected results by the formation of (dppe)Pd(0) complex in the presence of trace water in the catalytic cycle, as shown in Fig. 5.



Scheme 66.

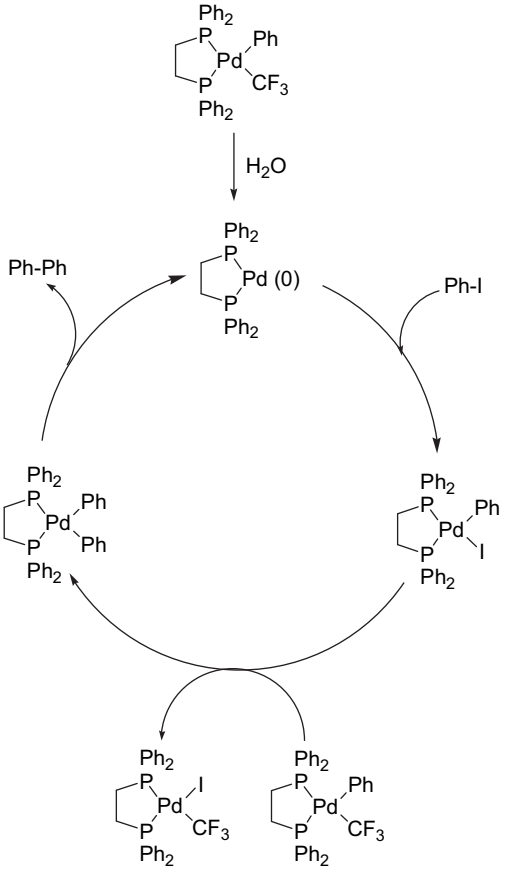
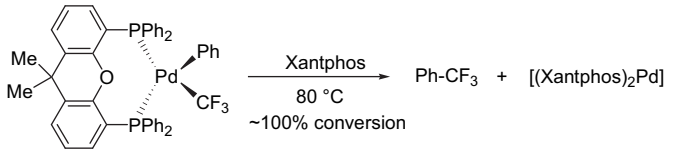


Fig. 5.

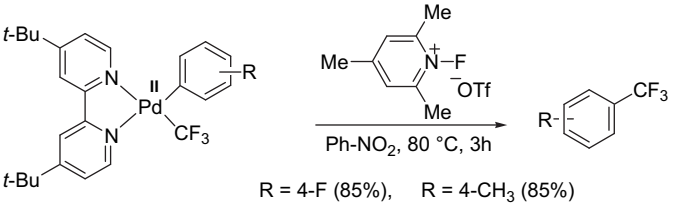
In order to screen other ligands for this purpose, Grushin and Marshall studied reductive elimination from [$(PPh_3)_2$Pd(Ph)CF_3] and [(xantphos)Pd(Ph)CF_3] in order to obtain the desired benzotrifluoride.[134] Instead of strongly chelating bidentate ligands, triphenylphosphine was chosen as a monodentate ligand due to the success with the $PdCl_2(PPh_3)_2$ catalyst in Kitazume and Ishikawa's trifluoromethylation studies.[130] Xantphos was selected for its large bite angle that is known both to facilitate the reductive elimination and to form cis- and trans-chelating isomers.[135] Although the desired product was not obtained by heating [$(PPh_3)_2$Pd(Ph)CF_3] at 60 °C in presence of PhI or PPh_3, [(xantphos)Pd(Ph)CF_3] successfully underwent clean reductive elimination to furnish the desired trifluoromethylbenzene when heated at 80 °C for 3 h with an extra equivalent of xantphos (Scheme 67). The prerequisite [(xantphos)Pd(Ph)CF_3] complex was prepared in 88% yield (without the isolation of fluoride intermediate) by treating [(xantphos)Pd(Ph)I] with AgF/ultrasound in benzene[136] followed by the addition of CF_3TMS to the reaction filtrate.[137] Although this conversion was extremely sensitive to the nature of the ancillary ligand on the Pd^{II}

complex and only xantphos was shown to be effective at promoting the reaction, this was the first example of a facile Ar–CF_3 bond-forming reductive elimination from a '*well-defined*' $L_2Pd^{II}(Ar)CF_3$ complex.



Scheme 67.

Since Ar–CF_3 bond-forming reductive elimination from most $Pd^{II}(Ar)CF_3$ complexes are challenging, Sanford reasoned that $2e^-$ oxidation of the Pd(II) complex should yield Pd^{IV} species that are known to participate in certain obstinate reductive elimination reactions.[138] They found that the treatment of $L_2Pd^{II}(Ar)CF_3$ complexes with *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT) afforded the desired Ar–CF_3 products in high yields (Scheme 68). The conversions were effective for both electron-donating and electron-withdrawing arene substituents (yields were determined by ^{19}F NMR spectroscopy). Although (^{i}Bu-bpy)Pd(Ph)CF_3, (^{i}Bu-bpy)Pd(4-F–Ph)CF_3, and (TMEDA)Pd(4-F–Ph)CF_3 complexes gave 83–89% yields of the corresponding benzotrifluorides, only 29% yield was obtained from the related (dppe)Pd(Ph)CF_3 complex under the same conditions. These $L_2Pd^{II}(Ar)CF_3$ complexes were, in turn, prepared from the corresponding $L_2Pd^{II}(Ar)I$ complexes by reaction with CsF followed by treatment with CF_3TMS.



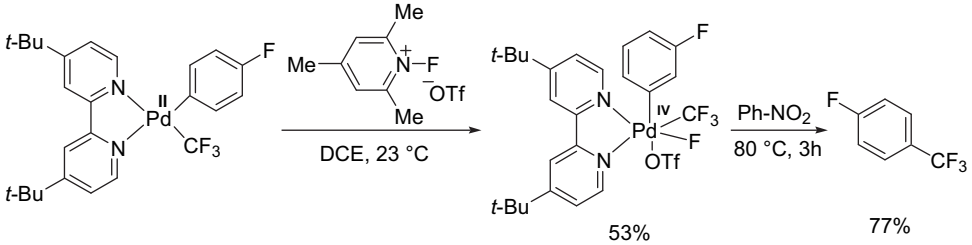
Scheme 68.

Sanford and co-workers isolated a Pd^{IV} complex and confirmed the octahedral structure by X-ray crystallography.[138] This isolated complex underwent a facile Ar–CF_3 bond-forming reaction when heated at 80 °C in nitrobenzene for 3 h (Scheme 69). No Ar–X (X=F, OTf) products were detected, in contrast to the cases where PhI$(OAc)_2$, NCS, or NBS oxidants gave Ar–X (X=OAc, Cl, Br) as the major products from $L_2Pd^{II}(Ar)CF_3$ complexes, which is due to faster Ar–X bond-forming reductive elimination than Ar–CF_3 coupling. Although these results were only reported for limited substrates (*para*-substituted arenes), this was the first example of facile Ar–CF_3 bond-forming reductive elimination from a $Pd^{IV}(Ar)CF_3$ complex.

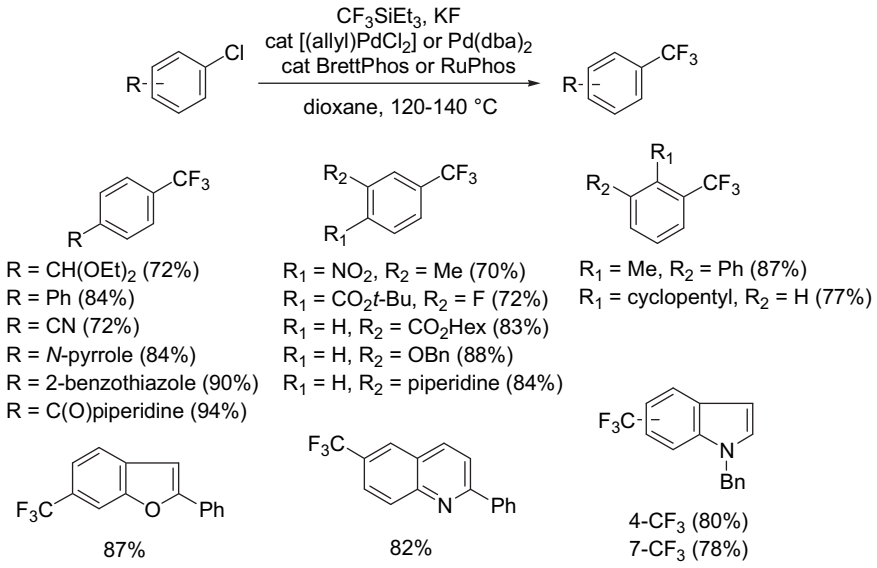
Very Recently, Buchwald reported the first palladium-catalyzed trifluoromethylation of aryl and heteroaryl chlorides.[139] He found that various aryl and heteroaryl chlorides were successfully trifluoromethylated using CF_3TES (2 equiv) and KF (2 equiv) in the presence of 3–6 mol % $[(allyl)PdCl]_2$ or $Pd(dba)_2$ and 9–12 mol % of BrettPhos or RuPhos (Pd:ligand=1:1.5) in dioxane at 120–140 °C for 6–20 h (Scheme 70). BrettPhos was chosen as a ligand due to previous success with the challenging amination and fluorination cross-coupling reactions.[140] Less bulky RuPhos was employed for *ortho*-substituted substrates for which BrettPhos failed to provide high yields. Among the screened CF_3SiR_3–MF system, the CF_3TES–KF combination was found to be the best transmetalating agent. Although most other monodentate biarylphosphine ligands provided small amounts of trifluoromethylated product, xantphos failed to furnish the desired product. Chlorides of both electron-rich and electron-deficient arenes, such as esters, acetals, amides, nitriles, ethers, dialkylamines, as well as indoles, carbazoles, quinolines, and benzofurans gave the corresponding trifluoromethylated products. However, substrates with aldehyde and ketone functionalities were not appropriate for this conversion. Also, chloride precursors containing unprotected NH and OH groups were not suitable presumably due to protonation of the $[CF_3]^-$ nucleophile, and/or reaction at the silicon center of CF_3TES, and/or competing coordination to the palladium center. The authors proposed the classical Pd(0)–Pd(II) catalytic cycle for this transformation, as shown in Fig. 6. Under the optimized reaction conditions and at high temperature, both transmetalation and reductive elimination proceed faster to form Ar–CF_3 bonds through the catalytic cycle. Although the reactions were reported thus far for only 1–5 mmol substrates, this method demonstrates great potential in terms of substrate scope and should be valuable for the late-stage introduction of CF_3 functionality in advanced intermediates.

Representative practical procedure[139]. Buchwald and co-workers heated a mixture of KF (10 mmol), hexyl 4-chlorobenzoate (5.0 mmol), $[(allyl)PdCl]_2$ (0.1 mmol), BrettPhos (0.3 mmol), and CF_3TES (10 mmol) in dioxane (16.6 mL) at 120 °C for 12 h under nitrogen. After being cooled to room temperature, the mixture was diluted with Et_2O, filtered through a silica gel plug, and concentrated. Purification via silica gel chromatography gave the desired product in 85% yield.

In summary, numerous aryl and heteroaryl iodides and bromides are documented in the literature to be efficiently converted to their corresponding trifluoromethyl derivatives. Although many of these reactions are robust, all of them need to be performed under rigorously anhydrous reaction conditions since the reduction of aryl halides to the dehalogenated aromatics (Ar–I to Ar–H; as well as $[CF_3]^-$ to HCF_3) will occur in the presence of trace water, thereby diminishing the yield of the desired trifluoromethylated product. These reactions are generally carried out in dry polar aprotic solvents under argon (or nitrogen) atmosphere. In many cases, especially with unactivated substrates, a small amount of the pentafluoroethylated product (Ar–CF_2CF_3) is obtained along with the desired Ar–CF_3 product due to conversion of unstable $[CF_3Cu]$ to $[C_2F_5CuI]$. As revealed in our review, the typical reagents for generating the active trifluoromethylcopper(I) species are



Scheme 69.



Scheme 70.

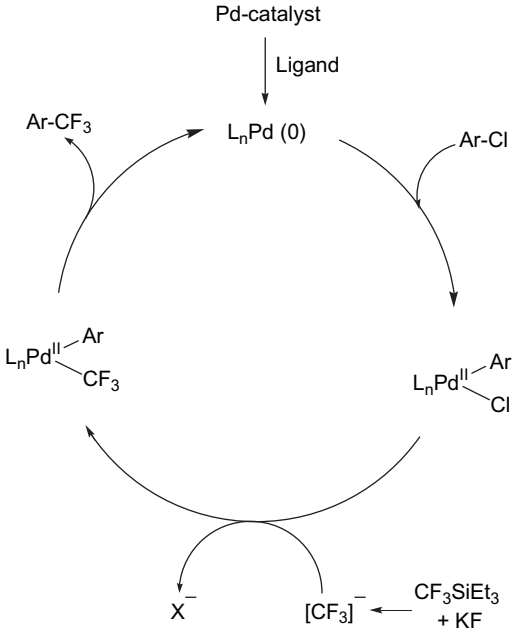


Fig. 6.

$FSO_2CF_2SO_2Me$, CF_3SiR_3 (R=Me, Et), $ClCF_2CO_2Me$, CF_2CO_2Na, and CF_3I. When gaseous CF_3I is used in presence of copper powder, a high temperature is generally required. Higher temperature is also generally required for the decomposition of CF_2CO_2Na in the presence of CuI to effect the desired trifluoromethylation. This particular method suffers from the low solubility of sodium trifluoroacetate, which is also required in excess amounts. However, with $ClCF_2CO_2Me$ in the presence of CuI and KF, trifluoromethylation can be achieved at a relatively lower temperature. The trifluoromethylating agent, CF_3TMS, which is used in the presence of CuI and KF is effective at low temperatures in many cases. The combination of $FSO_2CF_2SO_2Me$ and CuI also works well at relatively lower temperatures. Although necessary in excess to attain higher yields, the commercial availability and ease of handing liquid MFSDA, as well as milder reaction conditions required for trifluoromethylation coupled with the relatively inert nature of MFSDA toward sensitive functional groups makes it a popular reagent. Use of a Pd-catalyst in combination with the MFSDA–CuI system is useful in certain cases where this transformation is difficult to achieve otherwise. Furthermore, both copper-catalyzed and palladium-catalyzed versions of this transformation have been developed using the CF_3TES–KF system in combination with suitable catalysts and ancillary ligands. Therefore, numerous examples of trifluoromethylation of aryl and heteroaryl halides are expected to be reported in the future, reaffirming the significance of this vital reaction in medicinal chemistry.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.002.

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Biographical sketch

Sudipta Roy completed his undergraduate studies in Chemistry (Honors) at Presidency College—Calcutta, India. Thereafter, he received his master's degree from Indian Institute of Technology (IIT)—Bombay. He obtained his Ph.D. degree in Organic Chemistry from Dartmouth College in 2006, working under the supervision of Professor Gordon Gribble. After his post-doctoral work with Professors Richard Larock and George Kraus at Iowa State University, he joined AMRI in 2008. His current research interests include development of new synthetic methodologies, heterocyclic chemistry, organometallic chemistry, organofluorine chemistry, natural product synthesis, and medicinal chemistry.

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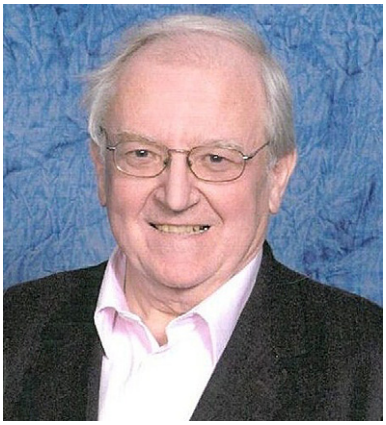

Gordon W. Gribble is a native of San Francisco, California, and completed his undergraduate education at the University of California at Berkeley in 1963. He earned a Ph.D. in organic chemistry at the University of Oregon in 1967. After a National Cancer Institute Postdoctoral Fellowship at the University of California, Los Angeles, he joined the faculty of Dartmouth College in 1968 where has been Full Professor of Chemistry since 1980. He served as Department Chair from 1988 to 1991. In 2005, he was named to the ignaugral endowed Chair as 'The Dartmouth Professor of Chemistry.' Dr. Gribble has published 320 papers in natural product synthesis, synthetic methodology, heterocyclic chemistry, natural organohalogen compounds, and synthetic triterpenoids, one of which is currently in Phase 3 clinical trials for the treatment of chronic kidney disease. Since 1995 he has co-edited the annual series 'Progress in Heterocyclic Chemistry', and the second edition of 'Palladium in Heterocyclic Chemistry', co-authored with Jack Li, was published in 2007. As a home winemaker for the past 30 years, he has a strong interest in the chemistry of wine and winemaking.

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