Trifluoromethylation

Sandmeyer Trifluoromethylation of Arenediazonium Tetrafluoroborates**

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The development of methods for the introduction of trifluoromethyl groups into functionalized molecules is of great importance due to their presence in many top-selling pharmaceuticals, agrochemicals, and functional materials. Trifluoromethyl groups are known to impart desirable properties, such as higher metabolic stability, increased lipophilicity, and stronger dipole moments to druglike molecules.[1] Celecoxib, dutasteride, fluoxetine, and sitagliptin are some examples of top-selling pharmaceuticals featuring trifluoromethyl groups, and beflubutamid, diflufenican, and norfluazon examples of agrochemicals.[2] However, traditional methods to access benzotrifluorides, for example, the Swarts reaction, typically require harsh conditions and have a low substrate scope, so that they are confined to the beginning of a synthetic sequence (Scheme 1a).[3]

Building on pioneering work on Cu– and Pd–perfluoroalkyl complexes by McLoughlin, Yagupolskii, Burton, Chambers, Grushin, and others, substantial progress has recently been made in the development of trifluoromethylation reactions that allow the selective introduction of CF$_3$ groups into functionalized, late-stage synthetic intermediates.[4] A wealth of new reactions has been disclosed, which can be roughly divided into five categories (Scheme 1b–f).[5] The first are couplings of aryl halides with nucleophilic CF$_3$ reagents (reaction type b), usually copper–CF$_3$ complexes in stoichiometric amounts.[5b,d,6] These complexes may also be generated in situ from copper salts and Ruppert's reagent (CF$_3$SiMe$_3$),[7] fluoroform,[8] potassium (trifluoromethyl)trimethoxyborate,[9] trifluoroacetate salts,[5e,10] methyl trifluoroacetate,[11] or fluorosulfonyldifluoroacetic acid.[12] Grushin,[5d] Sanford,[13] and Buchwald[14] also disclosed trifluoromethylations of aryl halides based on palladium complexes.

Palladium complexes also promote C–H functionalizations of arenes with trifluoromethylating reagents (reaction type c). Examples are the *ortho*-trifluoromethylation of donor-substituted arenes with Umemoto's reagent described by Yu et al.[15] and the Pd-catalyzed coupling of arenes with perfluoroalkyl iodides reported by Sanford et al.[16] C–H trifluoromethylations of heteroarenes have recently been reported also with nucleophilic trifluoromethylation reagents under oxidative conditions.[17] Examples of couplings of aryl nucleophiles with electrophilic CF$_3$ sources (reaction type d) include the coupling of arylboronic acids with Togni's and Umemoto's reagent disclosed by Shen and Liu, respectively.[18] Sanford et al. employed a copper/ruthenium photocatalyst system to promote a radical trifluoromethylation of boronic acids.[19]

The copper-catalyzed syntheses of benzotrifluorides from boronic acids and CF$_3$SiMe$_3$ or K$^+$[CF$_3$B(OMe)$_3$]$^-$ developed by Qing et al.[20] and ourselves[21] exemplify oxidative couplings of aryl nucleophiles with nucleophilic CF$_3$ reagents (reaction type e). The radical trifluoromethylation of arenes (reaction type f) was pioneered by Langlois.[22] Baran[23] and MacMillan[24] recently reported modern variants of this reaction concept based on peroxide or ruthenium initiators.

From a practical standpoint, nucleophilic reagents are appealing for the introduction of trifluoromethyl groups for the following reasons. CF$_3$SiMe$_3$ and K$^+$[CF$_3$B(OMe)$_3$]$^-$ are available in large quantities for a reasonable price, and are easy to store and handle. They are accessible not only from halofluorocarbons, but also from fluoroform, a by-product in the production of Teflon.[25] One of the most widely used methods for the introduction of halides and related nucleophiles is the Sandmeyer reaction.[26] Aromatic amines, which are available in great structural diversity, are diazotized using, for example, NaNO$_2$ or organic nitrites. Upon treatment with the appropriate copper(I) halides, nitrogen gas is released, and a halide group is installed regiospecifically in the position
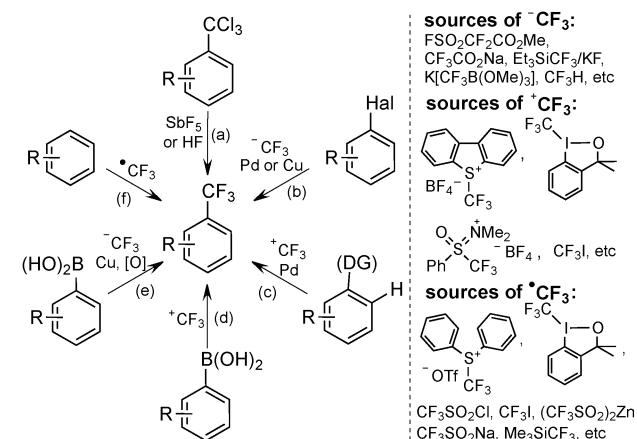
**Scheme 1.** Strategies for the introduction of trifluoromethyl groups.

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of the former amino group. Based on our experiences with copper-catalyzed trifluoromethylations of aryl iodides, we were convinced that a similar strategy should also allow the synthesis of benzotrifluorides from aromatic amines (Scheme 2).[27,28]

In order to probe the viability of this approach, we treated 4-methoxybenzenediazonium tetrafluoroborate (**1**) with K+-
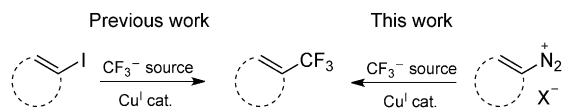
Scheme 2. Trifluoromethylations with nucleophilic reagents.

$[(CF_3)B(OMe)_3]^-$ in the presence of 20 mol% of CuI and phenanthroline in DMSO at 60°C, conditions previously optimized for the trifluoromethylation of aryl iodides.[9] The trifluoromethylated product was indeed observed in modest yield, along with the protodediazotization product, anisole. Encouraged by these results, we systematically optimized the reaction conditions for this model reaction (Table 1).

A decisive increase in the yields was obtained when the diazonium salt was added to a trifluoromethyl–copper species preformed from a copper salt and $K^+[(CF_3)B(OMe)_3]^-$ (Table 1, entry 1). A combination of Ruppert's reagent (TMSCF$_3$)[29] and cesium fluoride was found to provide higher yields than the milder borate reagent (Table 1, entry 2), which led us to continue our optimization work

with the latter reagent. The desired product was obtained in 63% yield when a copper(I) iodide solution in acetonitrile was stirred with TMSCF$_3$ and cesium fluoride for 10 min at room temperature, followed by addition of the diazonium salt and continued stirring for 12 h (Table 1, entry 2).

The main by-product observed was the iodinated arene. For this reason, we replaced copper iodide by copper salts with other counterions (Table 1, entries 3–5). Among them, copper thiocyanate was most effective. The desired benzotrifluoride **2** was obtained in almost quantitative yield (Table 1, entry 5). Using this copper source, neither the proto-dediazotization product anisole nor the aryl thiocyanate were observed. The only detectable side product was di(p-methoxy)azobenzene (2% yield).

Copper(0) and copper(II) salts were less effective which supports our theory that this is a Sandmeyer-type reaction (Table 1, entries 6 and 7). Similarly to related reactions of diazonium salts, acetonitrile was the most effective solvent (see the Supporting Information). Several additives besides CsF were investigated for promoting the transfer of the CF$_3$ group from silicon to the copper. Among the fluoride salts tested, only CsF was effective (Table 1, entries 5, 8, and 9). When the counterion on the cesium was varied, we found that carbonate and fluoride are similarly effective, while other counterions gave inferior results (Table 1, entries 5 and 10). Control experiments confirmed that the reaction does not proceed without either copper or basic additives (Table 1, entries 11 and 12). The amount of copper could be decreased to 60 mol% without negatively impacting the yield (Table 1, entry 13). With this prototype system, further reduced catalyst loadings resulted in incomplete conversions. However, the observation that full conversions can be reached with substoichiometric amounts of copper nurtures the hope that this reaction can be made truly catalytic in copper in the near future. When the p-methoxyaniline was diazotized with tert-butyl nitrite/p-toluenesulfonic acid (pTSA) and the resulting diazonium salt solution subjected to the reaction conditions without intermediary workup, the product was obtained in 72% based on the aniline (Table 1, entry 14).

Having thus found an effective protocol for the Sandmeyer trifluoromethylation, we next investigated its scope. Various arenediazonium tetrafluoroborates were smoothly converted into the corresponding benzotrifluorides in high yields (Scheme 3). Only for some simple, low-boiling substrates, the products could not be isolated in the high yields observed by in situ spectroscopic analysis due to their volatility. Both electron-rich and electron-deficient substrates gave similarly high yields. Many common functionalities were tolerated including ester, ether, amino, keto, carboxylate, cyano, and even iodo groups. This demonstrates the utility of the new reaction for the late-stage trifluoromethylation of complex, highly functionalized intermediates. Various heterocycles were also trifluoromethylated in good yields. Most products were obtained in sufficiently pure form to allow for straightforward isolation. Only for a few substrates was it necessary to subject the product to elaborate separation procedures to remove traces of the protodediazotization products.

Table 1: Optimization of the reaction conditions.[a]

Entry	[Cu]	Additive	Yield of **2** [%][b]
1[c]	CuI	CsF	30[d]
2	CuI	CsF	63
3	[Cu(MeCN)$_4$]BF$_4$	CsF	62
4	CuOAc	CsF	81
5	CuSCN	CsF	98
6	Cu	CsF	0
7	Cu(OAc)$_2$	CsF	21
8	CuSCN	KF	traces
9	CuSCN	NaF	0
10	CuSCN	Cs$_2$CO$_3$	98
11	CuSCN	–	0
12	–	Cs$_2$CO$_3$	0
13[e]	CuSCN	Cs$_2$CO$_3$	98
14[f]	CuSCN	Cs$_2$CO$_3$	72

[a] Reaction conditions: 0.75 mmol of TMSCF$_3$, 0.75 mmol of [Cu], 0.75 mmol of additive, 1 mL of MeCN, 10 min, RT, followed by dropwise addition of 0.50 mmo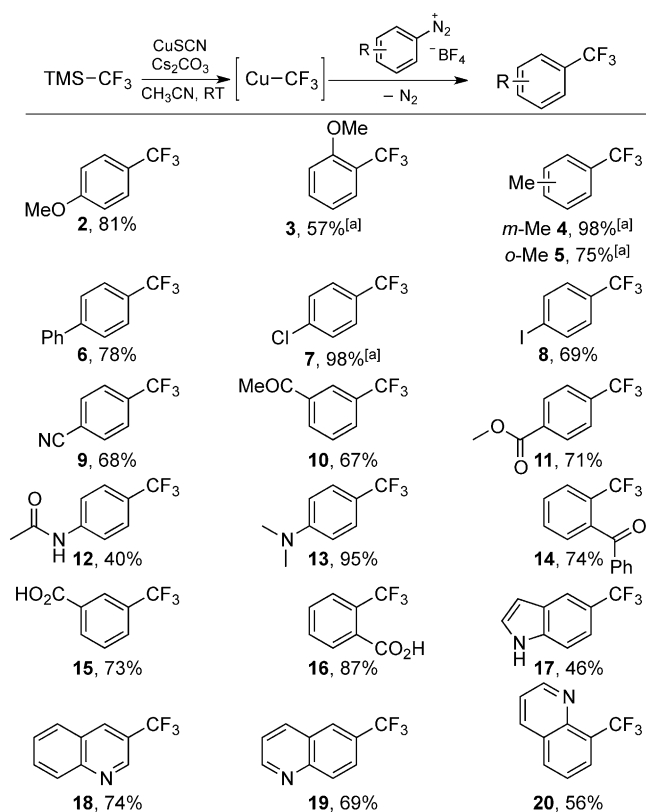l of **1** in 1 mL of solvent, 12 h, room temperature. [b] Yields were determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [c] Using KCF$_3$B(OMe)$_3$ instead of TMSCF$_3$ at 60°C. [d] Yield was determined by ^{19}F NMR spectroscopy using 1,3-difluorobenzene as an internal standard. [e] Using 0.3 mmol of CuNCS. [f] With in situ diazotization of p-anisidine using tert-butyl nitrite/pTSA. TMS = trimethylsilyl, pTSA = p-toluenesulfonic acid.

Scheme 3. Scope of the Sandmeyer trifluoromethylation. Reaction conditions: 1.5 mmol of TMSCF₃, 0.6 mmol of CuSCN, 1.5 mmol of Cs₂CO₃, 2 mL of MeCN, 10 min, RT, followed by dropwise addition of 1.0 mmol of arenediazonium tetrafluoroborate in 2 mL of MeCN, 12 h, room temperature; yield of isolated product. [a] Yield determined by ¹⁹F NMR spectroscopy using trifluoroethanol as an internal standard.

We assume that the reaction proceeds analogously to Sandmeyer halogenations of diazonium salts, which are generally believed to proceed via radical intermediates (Scheme 4).[30] It is plausible that the trifluoromethyl copper(I) species, generated from the copper precursor and TMSCF₃ in the presence of the cesium base, transfers one electron to the diazonium salt. The resulting diazo radical releases nitrogen with formation of an aryl radical, which abstracts the trifluoromethyl group from the copper(II) intermediate to form the trifluoromethylated product along with a copper(I) species.

In conclusion, the newly discovered Sandmeyer trifluoromethylation allows the straightforward synthesis of trifluoromethylated compounds from the corresponding aromatic amines under mild conditions at room temperature. Ongoing research is directed towards combining the diazotization and
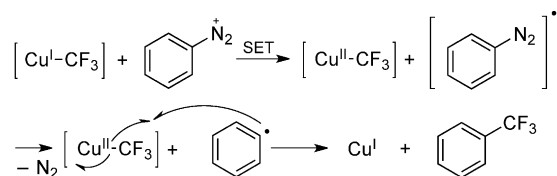
Scheme 4. Proposed mechanism.

the Sandmeyer reaction into a one-pot procedure, and towards reducing the amount of copper to truly catalytic quantites.

Experimental Section

Standard procedure for the synthesis of benzotrifluorides from the corresponding arenediazonium salts: An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanate (73.5 mg, 0.60 mmol) and cesium carbonate (489 mg, 1.50 mmol) under an atmosphere of dry nitrogen. Acetonitrile (2 mL) and trifluoromethyltrimethylsilane (240 μL, 1.50 mmol) were added by syringe. The resulting suspension was stirred at room temperature for 10 min and a solution of the arenediazonium tetrafluoroborate (1 mmol) in acetonitrile (2 mL) was added dropwise by syringe. The reaction mixture was stirred at ambient temperature for 16 h. The resulting mixture was filtered through a pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO₂, pentane/diethyl ether gradient), yielding the corresponding benzotrifluoride.

[1] T. Yamazaki, T. Tagauchi, I. Ojima in *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**, pp. 3–46.

[2] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; b) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.

[3] a) F. Swarts, *Bull. Acad. R. Belg.* **1892**, *24*, 309–314; b) J. H. Simons, C. J. Lewis, *J. Am. Chem. Soc.* **1938**, *60*, 492–492; c) G. A. Boswell, W. C. Ripka, R. M. Scribner, C. W. Tullock, *Org. React.* **1974**, *21*, 30–44; d) H. Sawada, M. Nakayama, M. Yoshida, T. Yoshida, N. Kamigata, *J. Fluorine Chem.* **1990**, *46*, 423–431.

[4] Reviews of trifluoromethylations: a) A. T. Osleya, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; d) Z. Jin, G. B. Hammond, B. Xu, *Aldrichimica Acta* **2012**, *45*, 67–83; copper-mediated trifluoromethylations: e) T. Liu, Q. Shen, *Eur. J. Org. Chem.* **2012**, 6679–6687; radical-trifluoromethylations: f) A. Studer, *Angew. Chem.* **2012**, *124*, 9082–9090; *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958; trifluoromethylations via C-H activation: g) H. Liu, Z. Gu, X. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 617–626.

[5] a) C. C. R. McLoughlin, J. Thrower, *Tetrahedron* **1969**, *25*, 5921–5940; b) N. V. Kondratenko, E. P. Vechirko, L. M. Yagupolskii, *Synthesis* **1980**, 932–933; c) K. Matsui, E. Tobita, M. Ando, K. Kondo, *Chem. Lett.* **1981**, 1719–1720; d) D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832–834; e) D. E. Carr, R. D. Chambers, T. F. Holmes, *J. Chem. Soc. Perkin Trans. 1* **1988**, 921–926; f) F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 327–330; g) V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644–12645.

[6] a) O. A. Tomashenko, E. C. Escudero-Adán, M. Martínez Belmonte, V. V. Grushin, *Angew. Chem.* **2011**, *123*, 7797–7801; *Angew. Chem. Int. Ed.* **2011**, *50*, 7655–7659; b) H. Morimoto, T.

Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem.* **2011**, *123*, 3877 – 3882; *Angew. Chem. Int. Ed.* **2011**, *50*, 3793 – 3798.

[7] a) H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, *32*, 91 – 94; b) G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600 – 8601; c) G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233 – 6235.

[8] A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901 – 20913.

[9] T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 2689 – 2697.

[10] K. A. McReynolds, R. S. Lewis, L. K. G. Ackerman, G. G. Dubinina, W. W. Brennessel, D. A. Vicic, *J. Fluorine Chem.* **2010**, *131*, 1108 – 1112.

[11] a) B. R. Langlois, N. Roques, *J. Fluorine Chem.* **2007**, *128*, 1318 – 1325; b) T. Schareina, X.-F. Wu, A. Zapf, A. Cotté, M. Gotta, M. Beller, *Top. Catal.* **2012**, *55*, 426 – 431.

[12] Q. Y. Chen, S. W. Wu, *J. Chem. Soc. Chem. Commun.* **1989**, 705 – 706.

[13] N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 2878 – 2879.

[14] a) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679 – 1681; b) B. S. Samant, G. W. Kabalka, *Chem. Commun.* **2011**, *47*, 7236 – 7238.

[15] X. Wang, L. Truesdale, J. Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648 – 3649.

[16] R. N. Loy, M. S. Sanford, *Org. Lett.* **2011**, *13*, 2548 – 2551.

[17] L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298 – 1304.

[18] a) T. Liu, Q. Sheng, *Org. Lett.* **2011**, *13*, 2342 – 2345; b) J. Xu, D. Luo, B. Xiao, Z. Liu, T. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300 – 4302.

[19] a) Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034 – 9037; b) Y. Ye, S. A. Künzi, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4979 – 4981.

[20] L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060 – 5063.

[21] B. A. Khan, A. E. Buba, L. J. Gooßen, *Chem. Eur. J.* **2012**, *18*, 1577 – 1581.

[22] a) B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525 – 7528; b) J.-B. Tommasino, A. Brondex, M. Médebielle, M. Thomalla, B. R. Langlois, T. Billard, *Synlett* **2002**, 1697 – 1699.

[23] a) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95 – 99; b) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411 – 14415.

[24] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224 – 228.

[25] a) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324 – 1327; b) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848 – 8856.

[26] a) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633 – 1635; b) H. H. Hodgson, *Chem. Rev.* **1947**, *40*, 251 – 277; c) A. Roglans, A. Pla-Quintana, M. Moreno-Mañas, *Chem. Rev.* **2006**, *106*, 4622 – 4643.

[27] For the trifluoromethylations of α-diazoesters, see: M. Hu, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 15257 – 15260.

[28] During the reviewing process, a similar trifluoromethylation based on Umemoto's reagent was reported: J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, DOI: 10.1021/ja404217t.

[29] G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757 – 786.

[30] a) J. K. Kochi, *J. Am. Chem. Soc.* **1957**, *79*, 2942 – 2948; b) C. Galli, *Chem. Rev.* **1988**, *88*, 765 – 792.