CuI-Mediated Trifluoromethylations with Stannanes

Preliminary Communication

by **Italo A. Sanhueza**, **Mads C. Nielsen**, **Marcel Ottiger**, and **Franziska Schoenebeck***

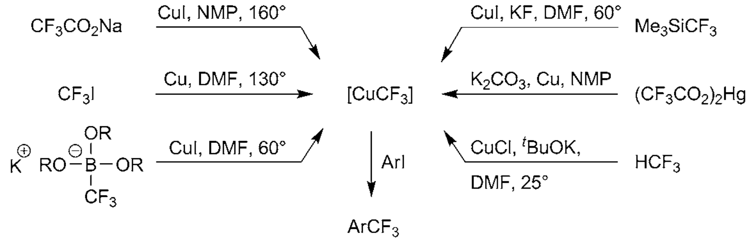
Laboratory for Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich,
Wolfgang-Pauli-Strasse 10, CH-8093 Zürich
(e-mail: schoenebeck@org.chem.ethz.ch; homepage: http://www.schoenebeck.ethz.ch/)

Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

(Trifluoromethyl)stannane reagents such as Bu_3SnCF_3 are effective in CuI-mediated trifluoromethylation reactions of aryl iodides. The reactions proceed *via* the intermediacy of $[CuCF_3]$ species.

The introduction of CF_3 groups into molecules has a tremendous influence on the properties of compounds [1]. Considerable efforts have, therefore, been made to develop new reactions for the introduction of CF_3 groups [2]. Various transition metal-mediated transformations of ArX [3] or ArH [4] to $ArCF_3$ have been reported in this context. Alternative methods [5], such as those involving electrophilic [6] or radical-based [7] trifluoromethylation processes, have also been developed. One of the most effective methods for aromatic trifluoromethylations involves Cu [8]. Such transformations generally occur *via* reaction of aryl iodides with a $[CuCF_3]$ species [9]. The latter are either pre-synthesized [10] or formed *in situ* (see *Scheme 1*). The use of *Ruppert*'s reagent (Me_3SiCF_3) along with KF and CuI constitutes one of the most widely applied methods to form $[CuCF_3]$[11][12]. A similarly mild method was recently reported by *Gooßen* and co-workers, involving borate salts (see *Scheme 1*) [13]. In addition, CHF_3 can readily be converted to $[CuCF_3]$, as recently shown by *Grushin* and co-workers [14].

Scheme 1. *Examples of Syntheses of $[CuCF_3]$ and Its Reaction with ArI*



We herein report our finding that tributyl(trifluoromethyl)stannane, Bu_3SnCF_3, is also efficient in Cu-mediated trifluoromethylation reactions. We found that using CuI,

Bu_3SnCF_3, and KF along with a coordinating solvent, such as the mixture DMF/*N*-methylpyrrolidin-2-one (NMP) 1:1, allows the conversion of a variety of aryl iodides to $ArCF_3$ under relatively mild conditions in 24 h. *Table 1* gives a compilation of stoichiometric experiments that we performed in this context. Electron-rich as well as electron-deficient aryl iodides were trifluoromethylated in good yields.

Table 1. *Examples of ArI Couplings under Stoichiometric Reaction Conditions*

$$\text{Ar–I} + \underset{(1.5\text{ equiv.})}{CF_3SnBu_3} \xrightarrow[\text{NMP/DMF (1:1 }v/v\text{)}\atop 80°,\ 24\text{ h}]{\text{CuI (2 equiv.)}\atop \text{KF (2 equiv.)}} \text{Ar–}CF_3$$

Entry	Ar	Yield [%] of product[a]
1	4-NO_2–C_6H_4	87
2	4-BnO_2C–C_6H_4	91
3	4-MeO–C_6H_4	96
4	4-Me–C_6H_4	99
5	4-Cl–C_6H_4	95
6	Naphthalen-1-yl	98
7	Pyridin-3-yl	96
8	4-[$Ph(CH_2)_3O$]–C_6H_4	87
9	4-^{t}Bu–C_6H_4	82

[a]) Determined by ^{19}F-NMR *vs.* internal standard (4,4′-difluoro-1,1′-biphenyl).

With ^{19}F-NMR studies, we observed that [$CuCF_3$] species form readily at room temperature under these reaction conditions (CuI, Bu_3SnCF_3, KF), indicating that the CuI-mediated trifluoromethylation involving stannane proceeds *via* the intermediacy of [$CuCF_3$]. We observed peaks at δ -29.3 ppm and -32.2 ppm in (D_7)DMF which are similar to those signals reported previously by *Kolomeitsev* and co-workers for [$CuCF_3$], *i.e.*, -28.8 ppm for ($CF_3Cu \cdot KBr$) and -32.4 ppm for $[(CF_3)_2Cu]^- K^+$ [15][16][1]). In the absence of a fluoride salt, the signals associated with [$CuCF_3$] are observed only at higher temperature (75°).

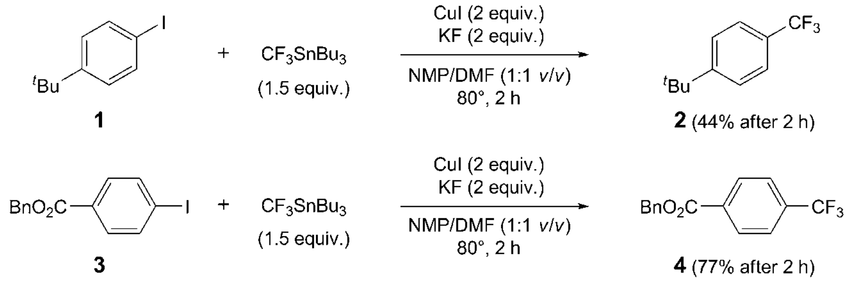
In the presence of KF, we found that the subsequent reaction of [$CuCF_3$] with ArI to $ArCF_3$ is the more difficult step and requires elevated temperature for efficient conversion. Electron-poor aryl iodides react more rapidly with [$CuCF_3$] than electron-rich analogs: after 2 h reaction time at 80°, 1-(*tert*-butyl)-4-iodobenzene (**1**) showed 44% conversion, while benzyl 4-iodobenzoate (**3**) was nearly fully consumed (75%) in the same time (see *Scheme 2*; the remaining material was predominantly unreacted starting material, and less than 2% of side-products (*e.g.*, $ArCF_2CF_3$) were detected).

The trifluoromethylations with stannane, therefore, seem to mirror the reactivity of the CuI-mediated trifluoromethylations of aryl iodides involving *Ruppert*'s reagent [11][12]. Given that the analogous reactivity is observed as with *Ruppert*'s reagent, we were intrigued to compare the relative reactivity of the stannane reagent with *Ruppert*'s reagent, testing *i*) the relative ease of [$CuCF_3$] formation and *ii*) the overall efficiency of the reaction. In *Scheme 3*, the results are outlined. After 20 min at room

---

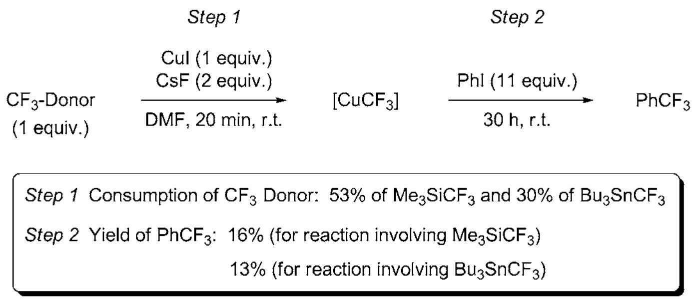
[1]) Using CuBr instead of CuI, we also observed the peak at 29.3 ppm in ^{19}F-NMR.

Scheme 2. *Reactivity Comparison of Electron-Rich* vs. *Electron-Deficient ArI*



temperature, 53% of *Ruppert*'s reagent had been consumed, while, under identical conditions, only 30% of the Bu_3SnCF_3 had reacted. This suggests that $[CuCF_3]$ formation proceeds slightly more readily in the case of *Ruppert*'s reagent. However, after 30 h reaction time with PhI at room temperature (*Scheme 3*), almost identical overall conversions to $ArCF_3$ had taken place (13–16% yield), indicating that the stannane is similarly effective as *Ruppert*'s reagent in CuI-mediated trifluoromethylations of ArI.

Scheme 3. *Comparison of the Reactivity of* Me_3SiCF_3 vs. Bu_3SnCF_3, *Testing the Ease of Formation of* $[CuCF_3]$ (*Step 1*) *and Overall Reaction Efficiency* (*Step 2*)

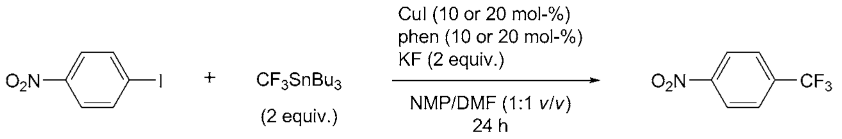


Step 1 Consumption of CF_3 Donor: 53% of Me_3SiCF_3 and 30% of Bu_3SnCF_3

Step 2 Yield of $PhCF_3$: 16% (for reaction involving Me_3SiCF_3)
13% (for reaction involving Bu_3SnCF_3)

In a manner similar to the reactions performed with *Ruppert*'s reagent, drawbacks also apply for the stannane-mediated trifluoromethylations, *i.e.*, moisture sensitivity (protonation of $[CuCF_3]$) and a tendency to undergo side-reactions are encountered. For example, $ArCF_2CF_3$ side-products were detected. It has previously been suggested that these form as a consequence of $[CuCF_3]$ decomposition to CF_2 carbenes, which in turn react with $[CuCF_3]$ to give pentafluoro derivatives [2][8]. This side-reaction was also encountered under catalytic reaction conditions. In *Table 2*, our preliminary, unoptimized experiments, involving 10–20 mol-% loading of CuI together with phenanthroline and KF in a mixture of NMP and DMF, are compiled. A reaction temperature of 50° was found to give the best conversions (*ca.* 60% yield of $ArCF_3$; see *Entries 4* and *5*). *Amii* and co-workers previously demonstrated such catalytic conditions to be effective for trifluoromethylations with *Ruppert*'s reagent [12].

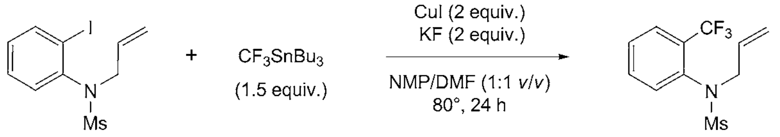
Table 2. *CuI-Catalyzed Trifluoromethylation of ArI Involving Bu_3SnCF_3*



Entry	Catalyst loading [mol-%]	Temperature [°]	Yield [%] of product
1	10	80	30
2	20	80	37
3	10	25	21
4	10	50	56
5	20	50	60

To gain further mechanistic insights and to test for the potential intermediacy of radicals, we applied our reaction conditions to aryl iodide **5** (*Scheme 4*). Substrate **5** was previously shown to undergo a very rapid cyclization upon aryl radical formation (generated either *via* electron-transfer-induced reductive bond cleavage of C–I or through reaction with a radical-chain carrier) [17]. However, no cyclized product was detected in our hands, and uncyclized product **6**, arising from direct trifluoromethylation of the C–I bond, was isolated instead[2]), indicating that, if aryl radicals were to be involved in the mechanism, their lifetime would be extremely short. This suggests that trifluoromethylation is likely to occur *via* σ-bond methathesis or direct oxidative addition of the nucleophilic [$CuCF_3$] species to C–I.

Scheme 4. *Test for the Intermediacy of Radicals*



5

6 (90%)

In conclusion, it was demonstrated that (trifluoromethyl)stannane reagents, such as Bu_3SnCF_3, are effective trifluoromethylation agents in CuI-mediated transformations of ArI. The reactions proceed *via* the [$CuCF_3$] intermediates and show promise for catalytic reaction conditions. The formation of organocopper species has frequently been implicated in cross-coupling reactions, such as the *Stille* reaction [18]. Our direct detection of [$CuCF_3$] species and their facile formation from a stannane precursor may provide support of the latter proposals.

REFERENCES

[1] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359.

[2] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475.

---

[2]) The side-product $ArCF_2CF_3$ (5%) was also detected.

[3] V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644; V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 4632; G. G. Dubinina, W. W. Brennessel, J. L. Miller, D. A. Vicic, *Organometallics* **2008**, *27*, 3933; V. V. Grushin, *Acc. Chem. Res.* **2012**, *43*,160; E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679.

[4] X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648; N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 2878; N. D. Ball, J. B. Gary, Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 7577.

[5] F. Swarts, *Bull. Acad. R. Med. Belg.* **1892**, *24*, 309; H. S. Booth, H. M. Elsey, P. E. Burchfield, *J. Am. Chem. Soc.* **1935**, *57*, 2066; Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464.

[6] T. Umemoto, S. Ishihara, *Tetrahedron Lett.* **1990**, *31*, 3579; T. Umemoto, *Chem. Rev.* **1996**, *96*, 1757; S. G. K. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757; J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119; I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem., Int. Ed.* **2007**, *46*, 754; J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1.

[7] A. P. Stefani, M. Szwarc, *J. Am. Chem. Soc.* **1962**, *84*, 3661; J. M. Birchall, G. P. Irvin, R. A. Boyson, *J. Chem. Soc., Perkin Trans. 2* **1975**, 435; H. Kimoto, S. Fujii, L. A. Cohen, *J. Org. Chem.* **1984**, *49*, 1060; Y. Girard, J. G. Atkinson, P. C. Bélanger, J. J. Fuentes, J. Rokach, C. S. Rooney, D. C. Remy, C. A. Hunt, *J. Org. Chem.* **1983**, *48*, 3220; B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525; D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224; Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411; N. Iqbal, S. Choi, E. Ko, E. J. Cho, *Tetrahedron Lett.* **2012**, *53*, *2005*; E. Mejía, A. Togni, *ACS Catal.* **2012**, *2*, 52; Y. Li, A. Studer, *Angew. Chem., Int. Ed.* **2012**, *51*, 8221.

[8] V. C. R. McLoughlin, J. Thrower, *Tetrahedron* **1969**, *25*, 5921; Y. Kobayashi, I. Kumadaki, *Tetrahedron Lett.* **1969**, *10*, 4095; D. J. Burton, Z.-Y. Yang, *Tetrahedron* **1992**, *48*, 189; M. A. McClinton, D. A. McClinton, *Tetrahedron* **1992**, *48*, 6555; D. J. Burton, L. Lu, *Top. Curr. Chem.* **1997**, *193*, 45; M. Schlosser, *Angew. Chem., Int. Ed.* **2006**, *45*, 5432; S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161; K. Sato, A. Tarui, M. Omote, A. Ando, I. Kumadaki, *Synthesis* **2010**, 1865.

[9] D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc.* **1986**, *108*, 832.

[10] Y. Usui, J. Noma, M. Hirano, S. Komiya, *Inorg. Chim. Acta* **2000**, *309*, 151; G. G. Dubinina, H. Furutachi, D. A. Vicic, *J. Am. Chem. Soc.* **2008**, *130*, 8600; G. G. Dubinina, J. Ogikubo, D. A. Vicic, *Organometallics* **2008**, *27*, 6233; I. Kieltsch, G. G. Dubinina, C. Hamacher, A. Kaiser, J. Torres-Nieto, J. M. Hutchison, A. Klein,Y. Budnikova, D. A. Vicic, *Organometallics* **2010**, *29*, 1451; O. A. Tomashenko, E. C. Escudero-Adán, M. Martínez Belmonte, V. V. Grushin, *Angew. Chem., Int. Ed.* **2011**, *50*, 7655; H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem., Int. Ed.* **2011**, *50*, 3793.

[11] H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, *32*, 91; F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 327.

[12] M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909.

[13] T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. – Eur. J.* **2011**, *17*, 2689; B. A. Khan, A. E. Buba, L. J. Gooßen, *Chem. – Eur. J.* **2012**, *18*, 1577.

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

[15] A. Kütt, V. Movchun, T. Rodima, T. Dansauer, E. B. Rusanov, I. Leito, I. Kaljurand, J. Koppel, V. Pihl, I. Koppel, G. Ovsjannikov, L. Toom, M. Mishima, M. Medebielle, E. Lork, G.-V. Röschenthaler, I. A. Koppel, A. A. Kolomeitsev, *J. Org. Chem.* **2008**, *73*, 2607.

[16] M. M. Kremlev, W. Tyrra, A. I. Mushta, D. Naumann, Y. L. Yagupolskii, *J. Fluorine Chem.* **2010**, *131*, 212.

[17] J. A. Murphy, T. A. Khan, S.-Z. Zhou, D. W. Thomson, M. Mahesh, *Angew. Chem., Int. Ed.* **2005**, *44*, 1356; T. A. Khan, R. Tripoli, J. J. Crawford, C. G. Martin, J. A. Murphy, *Org. Lett.* **2003**, *5*, 2971.

[18] N. J. Long, C. K. Williams, *Angew. Chem., Int. Ed.* **2003**, *42*, 2586; Y. Fujikura, K. Sonogashira, N. Hagihara, *Chem. Lett.* **1975**, 1067; K. Osakada, T. Yamamoto, *Coord. Chem. Rev.* **2000**, *198*, 379; P.

Espinet, A. M. Echavarren, *Angew. Chem., Int. Ed.* **2004**, *43*, 4704; L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260; Y. Wang, D. J. Burton, *Org. Lett.* **2006**, *8*, 1109.

Received August 10, 2012