CuI-Mediated Trifluoromethylations with Stannanes

Preliminary Communication

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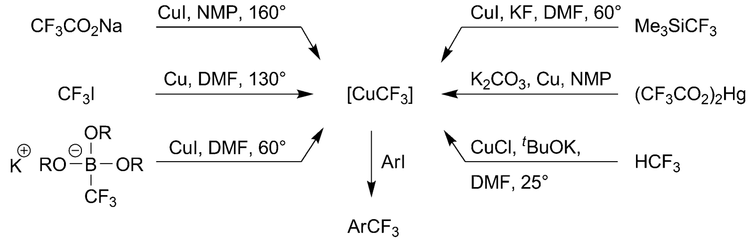
Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

(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].

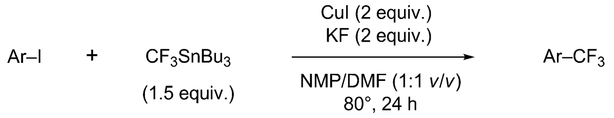
Scheme 1. *Examples of Syntheses of $[CuCF_3]$ and Its Reaction with ArI*



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*



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

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$(CH_2)_3$O]–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

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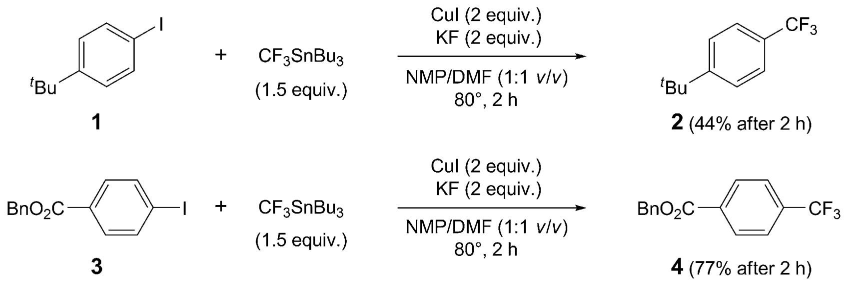
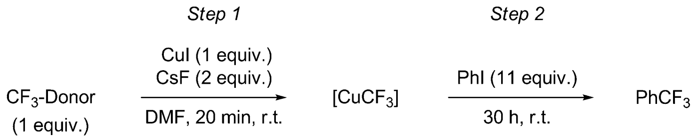
[1]) Using CuBr instead of CuI, we also observed the peak at 29.3 ppm in ^{19}F-NMR.

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*)

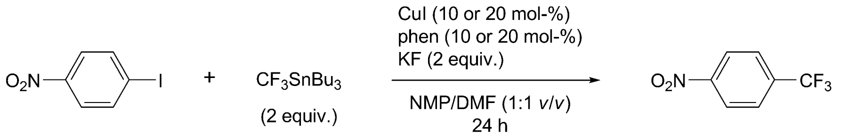


Step 1 Consumption of CF_3 Donor: 53% of Me_3SiCF_3 and 30% of Bu_3SnCF_3

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].

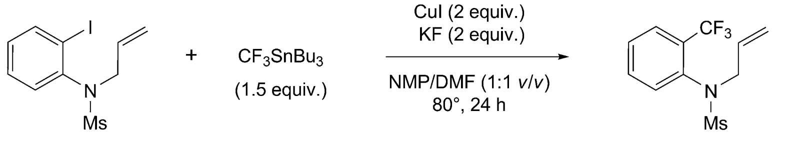
Table 2. *CuI-Catalyzed Trifluoromethylation of ArI Involving Bu_3SnCF_3*



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 instead2), 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.

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

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Received August 10, 2012