Organofluorine Compounds

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Copper-Mediated Difluoromethylation of (Hetero)aryl Iodides and β-Styryl Halides with Tributyl(difluoromethyl)stannane**

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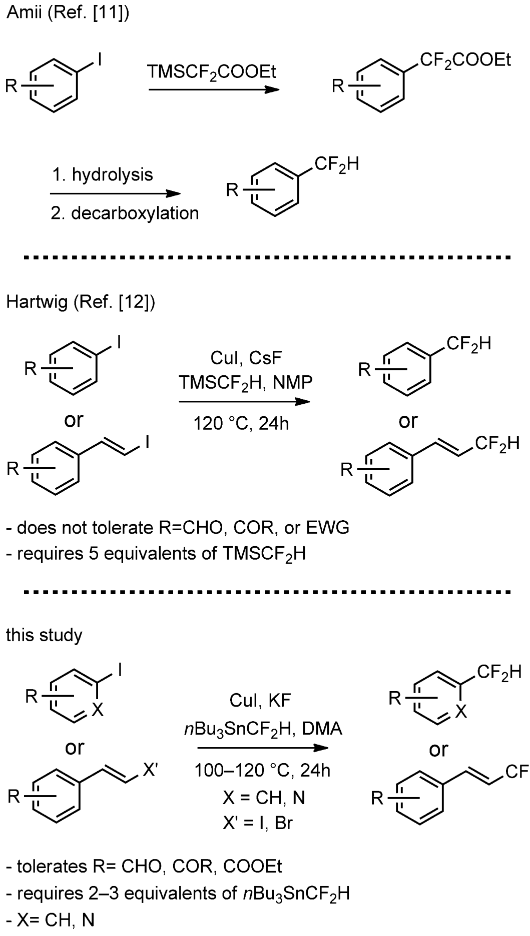
Organofluorine compounds have found application in a wide variety of fields. They occur, for example, in pharmaceuticals, agrochemicals, materials, surfactants, and catalysts.[1] The selective introduction of the difluoromethyl group (CF_2H) into organic molecules is of interest owing to the special biological properties of this group, such as its enhancement of membrane permeability, binding affinity, and bioavailability.[2] The CF_2H functionality is isosteric and isopolar with the hydroxy (OH) group and is reasonably lipophilic.[3] At the same time, the CF_2H group is weakly acidic and capable of participating in weak hydrogen-bonding interactions. Because of these properties, the CF_2H group is found in various biologically active compounds, such as enzyme inhibitors, sugars,[4] and agrochemicals.[5]

Several methods have been developed for the preparation of CF_2H-containing compounds, including the deoxofluorination of aldehydes with SF_4, *N*,*N*-diethylaminosulfur trifluoride (DAST), and derivatives of DAST.[6] The magnesium-metal-mediated reductive difluoromethylation of chlorosilanes with difluoromethyl sulfides, sulfoxides, and sulfones has been reported,[7] as has the nucleophilic introduction of a CF_2H group into carbonyl compounds with difluoromethyl phenyl sulfone,[8] (difluoromethyl)dimethylphenylsilane, and (chlorodifluoromethyl)trimethylsilane.[3,9] The direct transfer of a difluoromethyl group to a heteroarene with zinc difluoromethanesulfinate (DFMS), which is believed to proceed by a radical pathway, was reported by the Baran research group.[10] However, direct access to regiospecifically difluoromethylated arenes has been a challenge until recently.

Amii and co-workers reported a CuI-catalyzed three-step approach for the synthesis of difluoromethyl aromatic and heteroaromatic compounds by a C–C coupling reaction between an aryl iodide and an α-silyldifluoroacetate, followed by hydrolysis and decarboxylation (Scheme 1).[11] Fier and Hartwig reported a one-step copper-mediated (CuI) nucleophilic difluoromethylation of iodoarenes with $TMSCF_2H$.[12] Although the products were obtained in excellent yields, the latter method requires a significant excess of $TMSCF_2H$, is limited to electron-rich and electron-neutral iodoarenes, and is not compatible with aldehydes and ketones owing to competitive nucleophilic addition at the carbonyl center.[13]



Scheme 1. Methods for difluoromethylation. EWG = electron-withdrawing group, TMS = trimethylsilyl.

Herein we report the synthesis of tributyl(difluoromethyl)stannane and its application in the copper-mediated difluoromethylation of iodoarenes and β-styryl halides. This methodology has been extended to the difluoromethylation of both activated and deactivated iodoarenes (iodoheteroarenes), including those with carbonyl substituents, in moderate to good yields, and the difluoromethylation of β-styryl halides in good to excellent yields.

Our research group recently demonstrated that singlet CF_2 carbene can be generated from $TMSCF_3$ in the presence

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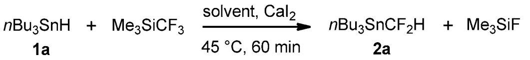
of tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) and NaI.[14] This carbene adds readily across an alkene or alkyne by a [2+1] cycloaddition reaction. We wanted to use this methodology to insert a CF_2 carbene into a metal–hydrogen bond. While screening various compounds containing metal–hydrogen bonds, we observed that the CF_2 carbene could be readily inserted into the Sn–H bond of nBu$_3$Sn–H to afford nBu$_3$SnCF$_2$H under mild conditions in over 80 % yield.

Cullen et al. had previously reported the insertion of CF_2 carbene generated from Me_3SnCF_3 into the Sn–H bond of trimethyltin hydride under harsh conditions (150 °C, 24 h); the insertion product was obtained in 63 % yield.[15] We found calcium iodide to be an ideal initiator. In the presence of CaI_2, CF_2 carbene could be generated from $TMSCF_3$ at 45 °C to give nBu$_3$SnCF$_2$H (**2a**) as the major product in less than an hour. The reaction proceeds in a variety of polar aprotic solvents, such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and *N*-methylpyrrolidone (NMP; Table 1).

Table 1: Optimization of the synthesis of nBu$_3$SnCF$_2$H with the initiator CaI_2.[a]



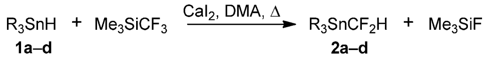
$$\underset{\textbf{1a}}{n\text{Bu}_3\text{SnH}} + \text{Me}_3\text{SiCF}_3 \xrightarrow[45\ ^\circ\text{C, 60 min}]{\text{solvent, CaI}_2} \underset{\textbf{2a}}{n\text{Bu}_3\text{SnCF}_2\text{H}} + \text{Me}_3\text{SiF}$$

Me_3SiCF_3 [equiv]	Solvent	Yield of **2a** [%][b]
2.25	DMA	85
2.25	DMF	72
2.25	NMP	86
2.25	THF	0
2.25	THF/HMPA (1:1)	0
2.25	DMSO	0
1.1	NMP	63
1.4	NMP	79
1.7	NMP	82

[a] Reaction conditions: nBu$_3$SnH: 8.68 mmol, CaI_2: 0.34 mmol, solvent: 4 mL. [b] The yield was determined by ^{19}F NMR spectroscopy. DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoramide.

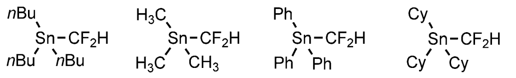
This procedure is quite general for the transformation of compounds of type R_3SnH into R_3SnCF_2H (Table 2). However, we focused on the use of **2a** owing to its ease of synthesis, nonvolatile nature, and stability in air. Furthermore, unlike most tin hydrides, such as Ph_3SnH, Cy_3SnH, and Me_3SnH, the starting tributyltin hydride is inexpensive, has relatively low toxicity (because of its low volatility), and is stable. The insertion reaction can be carried out on a multigram scale by this simple method to yield pure **2a**, **2c**, and **2d** in an inert environment. The isolation of trimethyl(difluoromethyl)stannane (**2b**) proved to be a challenge and was not pursued further. Compound **2a** is readily purified and can be stored in air for long periods of time (weeks to months at least) without decomposition.

Table 2: Conversion of R_3SnH into R_3SnCF_2H.[a]



$$\underset{\textbf{1a–d}}{\text{R}_3\text{SnH}} + \text{Me}_3\text{SiCF}_3 \xrightarrow{\text{CaI}_2\text{, DMA, }\Delta} \underset{\textbf{2a–d}}{\text{R}_3\text{SnCF}_2\text{H}} + \text{Me}_3\text{SiF}$$

Product, yield[b]



2a 80% (86%) **2b** (54%) **2c** 54% (65%) **2d** 57% (67%)

[a] Reaction conditions: R_3SnH (5 g), $TMSCF_3$ (2.2 equiv), CaI_2 (0.07 equiv), DMA (8 mL), 45–50 °C, 1 h. [b] The yield of the isolated product is given where applicable. The yield determined by ^{19}F NMR spectroscopy is given in parentheses. Cy = cyclohexyl.

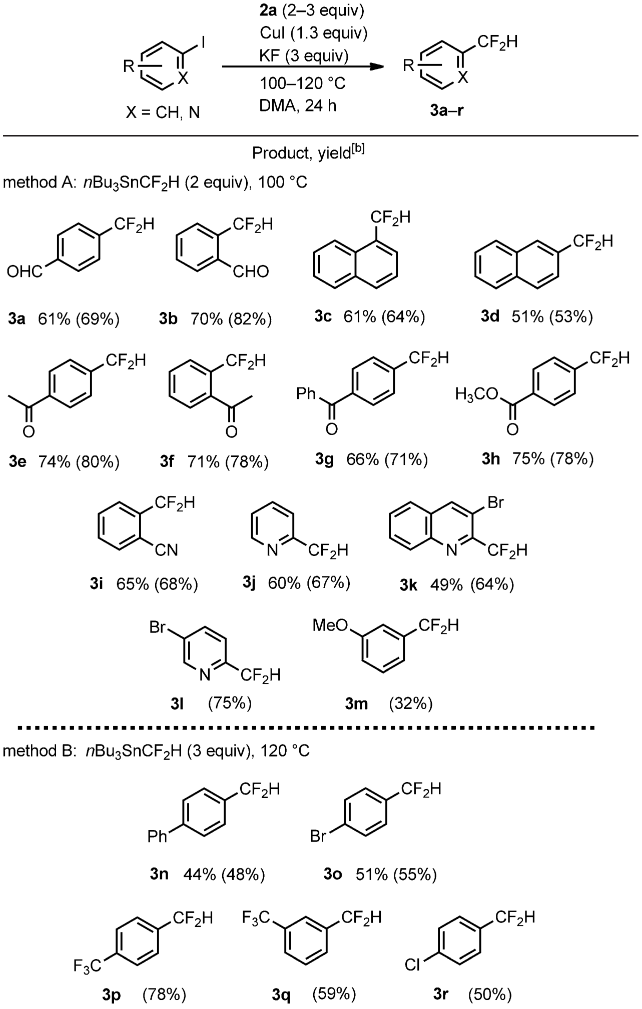
After extensive screening studies to determine conditions suitable for the copper-mediated difluoromethylation of iodoarenes, we observed the desired product when CuI was used in DMA with KF as an initiator. The reaction was found to be sensitive to the amounts of CuI, KF, and **2a** used, and the ratio of KF to CuI. We adopted two sets of optimized conditions: method A, in which the starting material, a β-styryl halide, iodonaphthalene, or iodo-substituted aldehyde/ketone, is treated with 1.3 equivalents of CuI, 3 equivalents of KF, and 2 equivalents of **2a** for 24 h at 100 °C, and method B, which is effective for Br-, Cl-, Ph-, and CF_3-substituted iodoarenes and calls for 1.3 equivalents of CuI, 3 equivalents of KF, and 3 equivalents of **2a**, a reaction temperature of 120 °C, and a reaction time of 24 h. When CsF was used as the initiator, the desired product was formed in lower yield. Only traces of the desired product were observed when other Cu^I halides, such as CuBr and CuCl, were used. Less than 5 % yield of the product was observed by ^{19}F NMR spectroscopy in the control reactions when no KF was added.

A series of iodoarenes (iodoheteroarenes) were converted into the respective CF_2H-substituted arenes (heteroarenes) in the solvent DMA (Table 3). The products were formed in slightly higher yields in DMA than in analogous solvents, such as DMF, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and NMP. Although yields vary, the method is extremely selective and amenable to a variety of functionalities, including aldehydes, ketones, esters, and other halides. Iodo-substituted heteroarenes were also converted into the desired products (**3j**, **3k**, and **3l**). Reactions with bromoarenes as the starting material proceeded only in low yields, rarely above 5 %. In products **3k**, **3l**, and **3o**, the bromo substitutent remained intact. This selectivity could be exploited by the use of bromides such as **3k**, **3l**, and **3o** as starting materials in coupling reactions to generate more complex difluoromethylated molecules. Compounds **3l**, **3m**, and **3p–r** were not isolated because of their volatility or relatively low yield.

Owing to the success of this copper-catalyzed *ipso*-substitution reaction, we assumed that β-styryl substituents should undergo a similar reaction. Our findings support this premise: the corresponding products were formed in yields 20–30 % higher than those observed for similar iodoarenes (Table 4). β-Styryl bromides also gave the desired products, albeit in slightly lower yields than their iodo counterparts. No isomerization of the double bond was observed during the reaction with the β-styryl halides, which indicates that the reaction proceeds with retention of configuration. Substituted styryl iodides (*cis*, *trans*, electron-rich, and electron-poor) showed similar reactivity; the desired products were formed by method A in good to excellent yields (60–85 %; Table 4).

Both computational and experimental methods were used to study the mechanism of the reaction. We based our

Table 3: Difluoromethylation of iodoarenes with **2a**.[a]

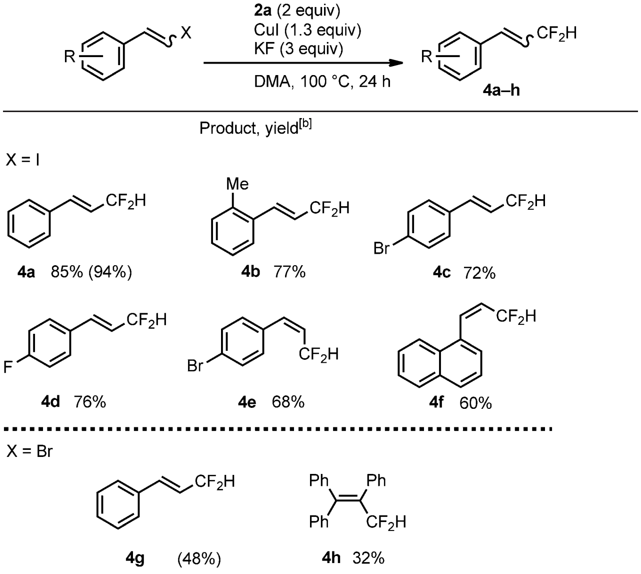


[a] Reaction conditions: iodoarene (0.5 mmol), **2a** (1–1.5 mmol), CuI (0.65 mmol), KF (1.5 mmol), DMA (4 mL), N_2 atmosphere, 20 mL microwave vial, 100–120 °C, 24 h. [b] The yield of the isolated product is given where applicable. The yield determined by ^{19}F NMR spectroscopy is given in parentheses.

computational studies on the reaction in DMF, because this solvent is easier to model than DMA. We also simplified the substituents on our tin reagent from *n*-butyl to methyl. All calculations were conducted with the Gaussian 09[16] computational package at the B3LYP/cc-pVTZ level of theory for neutral reactions and at the B3LYP/aug-cc-pVDZ level of theory for reactions involving anions. Further computational details, Cartesian coordinates, and the energies for all structures can be found in the Supporting Information.

Rather than attempt to predict energies exactly, we followed our reasoning that trends determined computationally could help us understand the reaction better, and we attempted to back up our computationally derived mechanism with experimental data. The addition of a single DMF molecule into the calculation (with the oxygen atom interacting with the copper center) proved to stabilize the $CuCF_2H$ species by 14.1 kcal mol^{-1}. Additional solvent molecules did not yield stable structures, so from this point forward we used a single DMF molecule in all calculations with only one formal ligand of a copper(I) species.

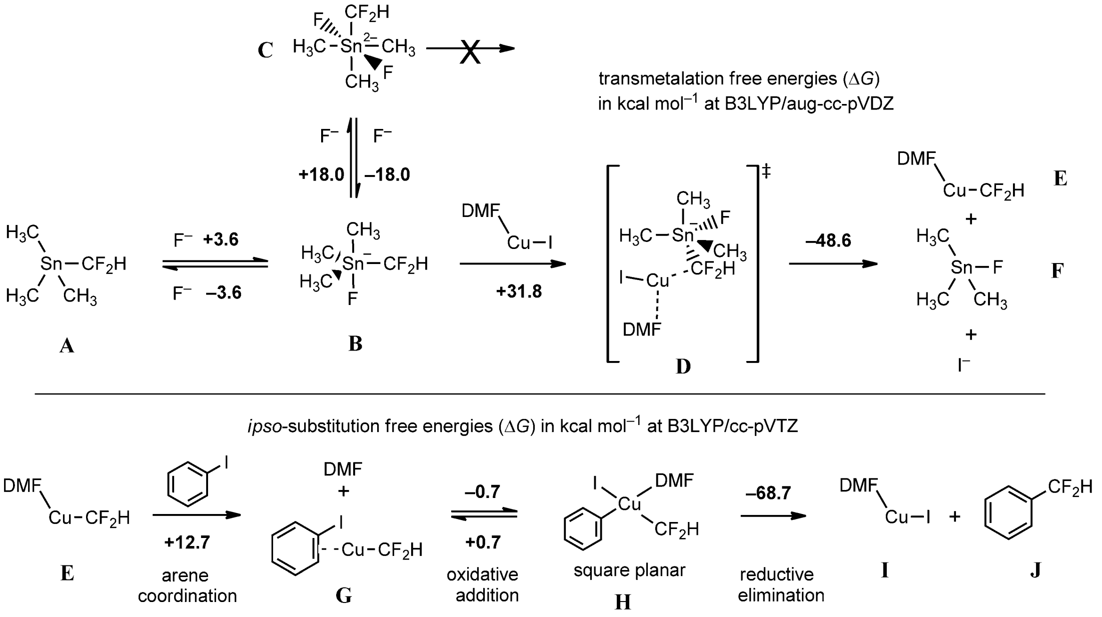
Table 4: Difluoromethylation of β-styryl halides with **2a**.[a]



[a] Reaction conditions: β-styryl halide (0.5 mmol), **2a** (1 mmol), CuI (0.65 mmol), KF (1.5 mmol), DMA (4 mL), N_2 atmosphere, 20 mL microwave vial, 100 °C, 24 h. [b] The yield of the isolated product is given where applicable. Yields in parentheses were determined by ^{19}F NMR spectroscopy.

Since an unstable CF_2H^- anion is not likely to exist independently in solution (especially as we did not observe nucleophilic addition to carbonyl groups), we then tried to identify a reasonable mechanism for the transfer of a CF_2H group from the tin reagent **2a** to a Cu–CF_2H species similar to that reported in the literature.[17] Interestingly, no transition state could be found by simply combining the CF_2H-substituted tin reagent (structure **A** in Scheme 2) with CuI (or $CuCF_2H$) in a plausible way. Only when we first formed the pentacoordinate anion **B** were we able to successfully optimize a transition state involving CuI (structure **D**). Similarly, we were unable to find a suitable transition state involving CuI when we started with the octahedral dianion **C**. If no productive transition states exist when **A** or **C** are used as starting points, then the necessary amounts of CuI and KF should be closely tied, as we have confirmed experimentally.[18]

The ^{19}F NMR spectrum of **2a** at −30 °C[19] in [D$_7$]DMF with a substoichiometric amount of tetramethylammonium fluoride (TMAF)[20] showed two distinct peaks at $\delta = -136.7$ and −148.1 ppm, which we assign to Sn–F species owing to the large ^1J coupling constant (1780 and 2024 Hz, respectively) of the ^{119}Sn satellites observed. Additional overlapping peaks observed in the region between −125.5 and −126.2 ppm, where we generally detect **2a**, indicated that we had potentially formed an activated CF_2H species (Scheme 2, structure **B**). Unfortunately, this region of the spectrum was too crowded for the various species present to be identified and quantified. Under these conditions, we did not detect CF_2H_2 (which was observed after heating to room



Scheme 2. DFT calculations for copper-mediated difluoromethylation.

temperature); thus, we could conclude that **2a** had not yet decomposed to tri-*n*-butyltin fluoride.

The proposed mechanism involves two steps. The transmetalation step involves the transfer of CF_2H from tin to copper and is likely to be rate-determining on the basis of our computational studies, whereas the *ipso* substitution involves the reaction between the proposed $CuCF_2H$ species and the starting material. The direct observation of $CuCF_2H$ was unsuccessful, probably as a result of the short half-life of the species at higher temperatures (−30 °C), as reported previously.[17b] The ^{19}F NMR peak assigned to $Cu(CF_2H)_2$ by Fier and Hartwig[12] for difluoromethylation with $TMSCF_2H$ was not observed when **2a** was used. Therefore, we propose that difluoromethylation with **2a** is mechanistically different from difluoromethylation with $TMSCF_2H$. This mechanistic difference is highlighted by the preference of $TMSCF_2H$ for iodobenzenes with electron-donating groups as opposed to the preference of **2a** for iodobenzenes with electron-withdrawing groups. The highest-energy transition state for *ipso* substitution could be either the coordination of $CuCF_2H$ to the starting material or the oxidative addition. There are two competing pathways for the reaction of $CuCF_2H$, namely, decomposition[17b] and coordination to the starting material. This competition is the likely cause of the varying yields of the difluoromethylated products. The product of oxidative addition is formally a copper(III) species, which seems unusual at first, but has been postulated before as a reactive intermediate in copper-mediated coupling reactions.[21]

Although CuI should be catalytic (as we start and end with it in our mechanism), we did not find good experimental evidence to suggest that the reaction is truly catalytic in CuI. At best, one could describe the reaction as substoichiometric in CuI, depending on the reaction conditions. Thus, there may be other pathways for decomposition of the copper species to insoluble (aggregates) or otherwise unreactive products.

In summary, we have developed an efficient procedure for the preparation of difluoromethylated tin compounds from $TMSCF_3$. We have demonstrated a single-step copper-mediated transformation of iodoarenes and iodoheteroarenes into their CF_2H-substituted counterparts with tributyl(difluoromethyl)stannane. The protocol gives even higher yields with β-styryl halides, the reactivity of which is such that bromides can be used to give the desired products in reasonable yields. We have also proposed a mechanism for the formation and utilization of CF_2H via a copper intermediate. The choice of solvent is critical in this reaction because the solvent molecules must directly stabilize the Cu−CF_2H species.

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[18] Extensive experimental screening showed a high degree of correlation between the amounts of KF and CuI required in the reaction. High concentrations of KF relative to CuI left the reagent unreacted, whereas high concentrations of CuI relative to KF led mostly to by-products, such as CF_2H_2. We take these results as evidence that the reaction is highly dependent on the amount of an "active" reagent, which, on the basis of computational modeling, we believe to be $[n\mathrm{Bu}_3\mathrm{SnCF}_2\mathrm{HF}]^-$.

[19] We resorted to low-temperature studies as a result of the fast exchange of F^- ions at high temperatures.

[20] TMAF was used instead of KF as a result of its solubility in DMF at low temperatures.

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