

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

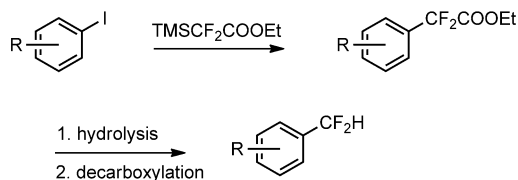
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Organofluorine compounds have found application in a wide variety of fields. They occur, for example, in pharmaceuticals, agrochemicals, materials, surfactants, and catalysts.^[1] The selective introduction of the difluoromethyl group (CF_2H) into 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]

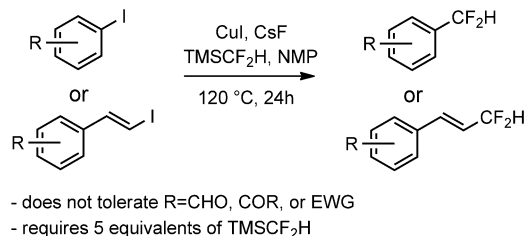
Several methods have been developed for the preparation of CF_2H -containing compounds, including the deoxofluorination of aldehydes with SF_4 , *N,N*-diethylaminosulfur trifluoride (DAST), and derivatives of DAST.^[6] The magnesium-metal-mediated reductive difluoromethylation of chlorosilanes with difluoromethyl 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 difluoromethanesulfonate (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

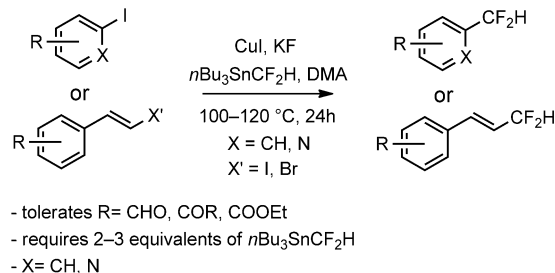
Amii (Ref. [11])



Hartwig (Ref. [12])



this study



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

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]

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 CF₂ carbene into a metal–hydrogen bond. While screening various compounds containing metal–hydrogen bonds, we observed that the CF₂ carbene could be readily inserted into the Sn–H bond of *n*Bu₃Sn–H to afford *n*Bu₃SnCF₂H under mild conditions in over 80 % yield.

Cullen et al. had previously reported the insertion of CF₂ carbene generated from Me₃SnCF₃ 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 CaI₂, CF₂ carbene could be generated from TMSCF₃ at 45 °C to give *n*Bu₃SnCF₂H (**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 *n*Bu₃SnCF₂H with the initiator CaI₂.^[a]

$n\text{Bu}_3\text{SnH} + \text{Me}_3\text{SiCF}_3 \xrightarrow[45^\circ\text{C, 60 min}]{\text{solvent, CaI}_2} n\text{Bu}_3\text{SnCF}_2\text{H} + \text{Me}_3\text{SiF}$		
Me ₃ SiCF 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: *n*Bu₃SnH: 8.68 mmol, CaI₂: 0.34 mmol, solvent: 4 mL. [b] The yield was determined by ¹⁹F NMR spectroscopy. DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoramide.

This procedure is quite general for the transformation of compounds of type R₃SnH into R₃SnCF₂H (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 Ph₃SnH, Cy₃SnH, and Me₃SnH, the starting tributyltin hydride is inexpensive, has relatively low toxicity (because of its low volatility), and is

Table 2: Conversion of R₃SnH into R₃SnCF₂H.^[a]

$\text{R}_3\text{SnH} + \text{Me}_3\text{SiCF}_3 \xrightarrow[\Delta]{\text{CaI}_2, \text{DMA}} \text{R}_3\text{SnCF}_2\text{H} + \text{Me}_3\text{SiF}$		
1a–d		
Product, yield ^[b]		
$\begin{array}{c} n\text{Bu} \\ \\ \text{Sn}-\text{CF}_2\text{H} \\ \\ n\text{Bu} \end{array}$	$\begin{array}{c} \text{H}_3\text{C} \\ \\ \text{Sn}-\text{CF}_2\text{H} \\ \\ \text{H}_3\text{C} \end{array}$	$\begin{array}{c} \text{Ph} \\ \\ \text{Sn}-\text{CF}_2\text{H} \\ \\ \text{Ph} \end{array}$
2a 80% (86%)	2b (54%)	2c 54% (65%)
		2d 57% (67%)

[a] Reaction conditions: R₃SnH (5 g), TMSCF₃ (2.2 equiv), CaI₂ (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 ¹⁹F NMR spectroscopy is given in parentheses. Cy = cyclohexyl.

stable. The insertion reaction can be carried out on a multi-gram 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.

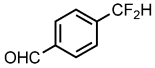
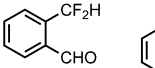
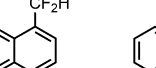
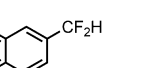
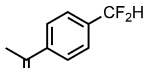
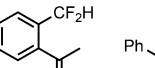
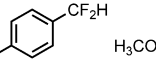
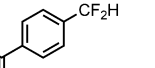
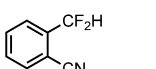

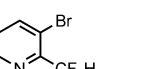
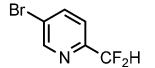
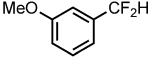
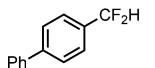
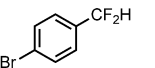
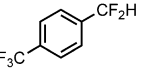
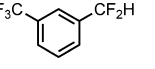
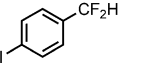
After extensive screening studies to determine conditions suitable for the copper-mediated difluoromethylation of iodoarenes, we observed the desired product when CuI was used in DMA with KF as an initiator. The reaction was found to be sensitive to the amounts of CuI, KF, and **2a** used, and the ratio 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 CF₃-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 ¹⁹F NMR spectroscopy in the control reactions when no KF was added.

A series of iodoarenes (iodoheteroarenes) were converted into the respective CF₂H-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 substituent 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]

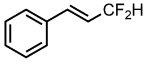
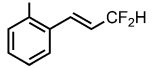
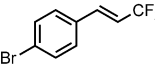
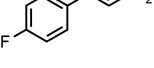
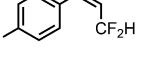
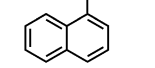
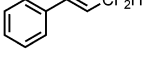
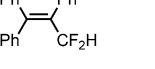
$\text{R}-\text{C}_6\text{H}_4-\text{I} \xrightarrow[\text{DMA, 24 h}]{\text{2a (2–3 equiv), CuI (1.3 equiv), KF (3 equiv), 100–120 }^\circ\text{C}}$ $\text{R}-\text{C}_6\text{H}_4-\text{CF}_2\text{H}$	
X = CH ₃ , N	3a–r
Product, yield ^[b]	
method A: <i>n</i> Bu ₃ SnCF ₂ H (2 equiv), 100 °C	
	3a 61% (69%)
	3b 70% (82%)
	3c 61% (64%)
	3d 51% (53%)
	3e 74% (80%)
	3f 71% (78%)
	3g 66% (71%)
	3h 75% (78%)
	3i 65% (68%)
	3j 60% (67%)
	3k 49% (64%)
	3l (75%)
	3m (32%)
method B: <i>n</i> Bu ₃ SnCF ₂ H (3 equiv), 120 °C	
	3n 44% (48%)
	3o 51% (55%)
	3p (78%)
	3q (59%)
	3r (50%)

[a] Reaction conditions: iodoarene (0.5 mmol), **2a** (1–1.5 mmol), CuI (0.65 mmol), KF (1.5 mmol), DMA (4 mL), N₂ 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 ¹⁹F 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 Gaussian09^[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 CuCF₂H species by 14.1 kcal mol^{−1}. Additional solvent molecules did not yield stable structures, so from this point forward we used

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

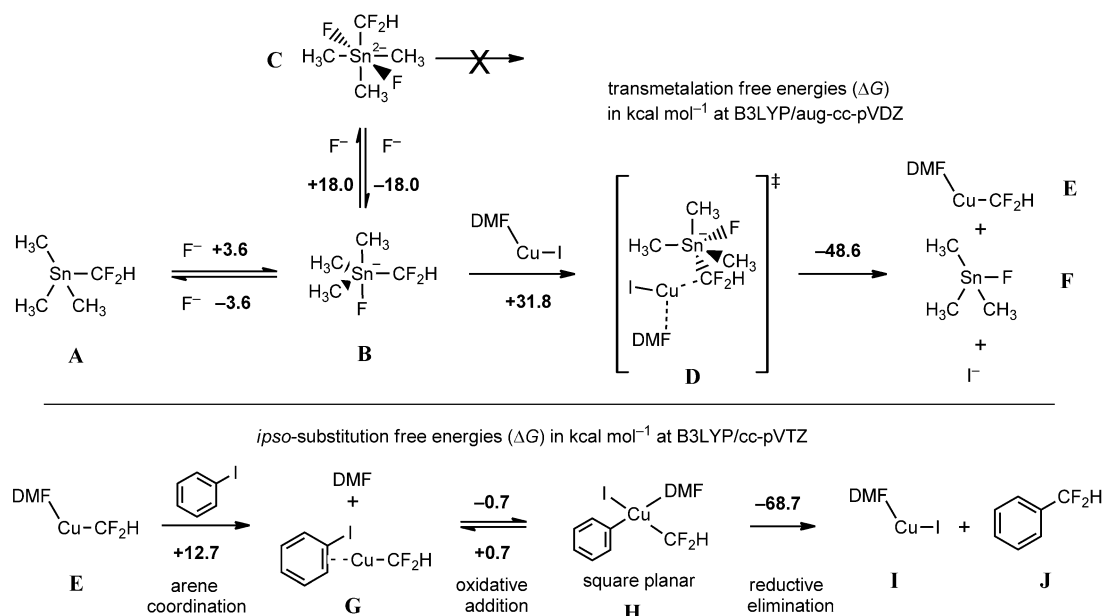
$\text{R}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{X} \xrightarrow[\text{DMA, 100 }^\circ\text{C, 24 h}]{\text{2a (2 equiv), CuI (1.3 equiv), KF (3 equiv)}}$ $\text{R}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CF}_2\text{H}$	
X = I	4a–h
Product, yield ^[b]	
	4a 85% (94%)
	4b 77%
	4c 72%
	4d 76%
	4e 68%
	4f 60%
X = Br	
	4g (48%)
	4h 32%

[a] Reaction conditions: β-styryl halide (0.5 mmol), **2a** (1 mmol), CuI (0.65 mmol), KF (1.5 mmol), DMA (4 mL), N₂ 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 ¹⁹F NMR spectroscopy.

a single DMF molecule in all calculations with only one formal ligand of a copper(I) species.

Since an unstable CF₂H[−] 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 CF₂H group from the tin reagent **2a** to a Cu–CF₂H species similar to that reported in the literature.^[17] Interestingly, no transition state could be found by simply combining the CF₂H-substituted tin reagent (structure **A** in Scheme 2) with CuI (or CuCF₂H) 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 ¹⁹F NMR spectrum of **2a** at −30 °C^[19] in [D₇]DMF with a substoichiometric amount of tetramethylammonium fluoride (TMAF)^[20] showed two distinct peaks at δ = −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 ¹¹⁹Sn 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 CF₂H 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 CF₂H₂ (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 CF₂H 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 CuCF₂H species and the starting material. The direct observation of CuCF₂H was unsuccessful, probably as a result of the short half-life of the species at higher temperatures (−30 °C), as reported previously.^[17b] The ¹⁹F NMR peak assigned to Cu(CF₂H)₂ by Fier and Hartwig^[12] for difluoromethylation with TMSCF₂H was not observed when **2a** was used. Therefore, we propose that difluoromethylation with **2a** is mechanistically different from difluoromethylation with TMSCF₂H. This mechanistic difference is highlighted by the preference of TMSCF₂H 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 CuCF₂H to the starting material or the oxidative addition. There are two competing pathways for the reaction of CuCF₂H, 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 TMSCF₃. We have demonstrated a single-step copper-mediated transformation of iodoarenes and iodoheteroarenes into their CF₂H-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 CF₂H via a copper intermediate. The choice of solvent is critical in this reaction because the solvent molecules must directly stabilize the Cu–CF₂H species.

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