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Copper Mediated Difluoromethylation of Aryl and Vinyl Iodides

Patrick S. Fier and **John F. Hartwig**
Department of Chemistry, University of California, Berkeley, California 94720, United States.

Abstract

Selectively fluorinated molecules are important as materials, pharmaceuticals, and agrochemicals, but their synthesis by simple, mild, laboratory methods is challenging. We report a straightforward method for the cross-coupling of a difluoromethyl group with readily available reagents to form difluoromethylarenes. The reaction of electron-neutral, electron-rich, and sterically hindered aryl and vinyl iodides with the combination of CuI, CsF and $TMSCF_2H$ leads to the formation of difluoromethylarenes in high yield with good functional group compatibility. This transformation is surprising, in part, because of the prior observation of the instability of $CuCF_2H$.

The unique stability, reactivity and biological properties of fluorinated compounds contribute to their widespread use in many chemical disciplines. Compounds containing a triflurometyhl group have been studied extensively. Compounds containing partially fluorinated alkyl groups, such as a difluoromethyl group, should be similarly valuable for medicinal chemistry because such groups could act as lipophilic hydrogen bond donors and as bio-isosteres of alcohols and thiols.[1,2] However, methods for the introduction of a difluoromethyl group are limited, and methods for the introduction of a difluoromethyl group onto arenes are even more limited. Hence there is a current need for new procedures to generate difluoromethylarenes.[3]

Most current syntheses of difluoromethylarenes require hazardous reagents or multi-step sequences (Scheme 1). Fluorodeoxygenation of aldehydes with sulfur tetrafluoride or amino-sulfurtrifluorides (DAST, Deoxofluor) is the most common route to difluoromethyl compounds. However, these reagents release hydrogen fluoride upon contact with water and may undergo explosive decomposition when heated.[4] Amii and coworkers recently reported a three-step route to difluoromethylarenes; however, the final step of this process only occurred with electron-deficient aryl iodides, and the three-step process with electron-poor arenes occurred in modest overall yields (Scheme 1).[5] Baran recently reported a new reagent that leads to the addition of difluoromethyl radicals to heteroaromatic systems under mild conditions.[6] However, reactions with arenes were not reported. Thus, methods for the introduction of a difluoromethyl group onto arenes and methods for the introduction of the difluoromethyl group with regioselectivities that complement those resulting from radical-based reactions are needed.

In contrast to the recent success in developing copper mediated trifluoromethylation of aryl halides[7] methods for related copper-mediated difluoromethylation of aryl halides have not been developed. Difluoromethyl copper complexes are much less stable than trifluoromethyl copper complexes and are known to be unstable toward the formation of tetrafluoroethane

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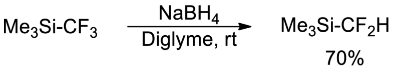
Correspondence to: John F. Hartwig.
Corresponding Author jhartwig@berkeley.edu.

ASSOCIATED CONTENT
Supporting Information.
Experimental procedures and characterization of all new compounds including ^1H, ^{13}C, and ^{19}F NMR spectra.

and *cis*-difluoroethylene.[3,8] Despite this instability, we have identified conditions for copper-mediated difluoromethylation of aryl iodides. We report our results on this difluoromethylation process. The difluoromethylation reaction occurs with aryl iodides containing a wide range of functional groups, as well as vinyl iodides, in a single step with inexpensive and readily available reagents.

We chose to develop difluoromethylations with trimethylsilyl difloromethane ($TMSCF_2H$) as the source of the CF_2H group because fluoroalkylsilanes are accessible, commercially available, stable, and readily prepared on large scale. Most important for the current work, $TMSCF_2H$ is accessible on multi-gram scale, as shown in eq 1, by sodium borohydride reduction of the Ruppert-Prakash reagent ($TMSCF_3$).[9] Initial attempts to extend our previously published work on the trifluoromethylation of aryl iodides[10] with (1,10-phenanthroline)$CuCF_3$ to the difluoromethylation of aryl iodides with pre-formed or *in-situ* generated (1,10-phenanthroline)$CuCF_2H$ gave large amounts of arene. Only trace amounts of the difluoromethylarene product were formed. Reactions of 1-butyl-4-iodobenzene conducted with *tert*butoxide or fluoride to activate the silane and a broad range of copper (I) sources and exogenous ligands gave similar product distibutions.



$$Me_3Si\text{-}CF_3 \xrightarrow[\text{Diglyme, rt}]{NaBH_4} \underset{70\%}{Me_3Si\text{-}CF_2H} \tag{1}$$

However, reactions conducted without added ligand resulted in high conversion to the difluoromethylarene. Various copper(I) sources were found to mediate the difluoromethylation of 1-butyl-4-iodobenzene, but reactions conducted with CuI provided higher yields than did those with CuBr, $CuBr\text{-}SMe_2$, or CuCl (Table 1). Reactions conducted with cesium fluoride led to transfer of the difluoromethyl group from $TMSCF_2H$ without significant background decomposition of the silane. Studies with various ratios of reagents showed that reactions with 1 equiv of CuI, 3 equiv of CsF and 5 equiv of $TMSCF_2H$ occurred in reproducibly high yields. Reactions conducted with less CsF or $TMSCF_2H$ resulted in moderate to good yields (Table 1, entries 6-8). The excess $TMSCF_2H$ in the reaction likely converts $CuCF_2H$ to the cuprate, $Cu(CF_2H)_2^-$ (vide infra).

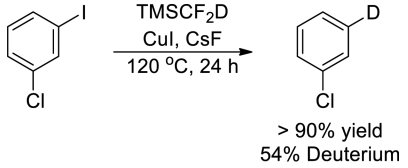
The reaction conditions developed for the difluoromethylation of 1-butyl-4-iodobenzene were suitable for the conversion of a range of aryl iodides **1** to difluoromethylarenes **2** (Table 2). Electron-neutral, electron-rich, and sterically hindered aryl iodides reacted in high yield. Amine, ether, amide, ester, aromatic bromide and protected alcohol functionality were tolerated under the standard reaction conditions. While ketones and aldehydes underwent competing direct addition of the difluoromethyl group,[11] acetal-protected ketone **1h** gave quantitative conversion to difluoromethylarene **2h**. In contrast to reactions of electron-rich and electron-neutral aryl iodides, reactions of electron-deficient aryl iodides formed arene as the major product, along with trace amounts of trifluoromethyl and tetrafluoroethylarene. The latter products, presumably, form by a sequence similar to the one that forms pentafluoroethylarenes during copper-mediated trifluoromethylation of aryl halides involving difluorocarbene.[7] The volatility of difluoromethylarenes and the similar polarity of the difluoromethylarene to side-products made the yields of isolated material lower than the yields determined by NMR spectroscopy in some cases..

This difluoromethylation protocol was also suitable for the difluoromethylation of vinyl iodides **3** to prepare allylic difluorinated alkenes **4** (Table 3). This family of products has been prepared by the reaction of sulfur tetrafluoride or aminosulfurtrifluorides and α-ß unsaturated aldehydes; however formation of products from allylic substitution and rearrangements of reaction intermediates occur in these systems, resulting in a mixture of isomers.[4] In addition, the cross-coupling of vinyl iodides with $TMSCF_2H$ avoids the use of hazardous sulfurfluoride reagents and reactive, electrophilic α,ß-unsaturated aldehydes. *Cis* and *trans* alkenes, as well as styrenyl iodides, reacted in good yield to give a single stereoisomer of the coupled product.

Reactions of aryl halides with Cu(I) species have been proposed in some cases to occur by radical intermediates[12] and in other cases to occur through Cu(III) intermediates formed by oxidative addition of organic halides to a Cu(I) intermediate.[13] Although the current evidence disfavors radical reactions of aryl halides with copper complexes containing neutral dative nitrogen ligands,[14] the difluoromethylation in the current work occurs through complexes lacking such ligands and, therefore, could follow a different pathway. To probe the potential inter-mediacy of aryl radicals during this difluoromethylation reaction, we conducted the difluoromethylation of 1-(allyloxy)-2-iodobenzene (Scheme 2). The corresponding aryl radical undergoes 5-exo-trig cyclization with a rate constant of 10^{10} s^{-1} to form 3-methyl-2,3-dihydrobeznofuran after hydrogen atom abstraction from the solvent.[15] Thus, if products from cyclization are not observed, then the reaction of the aryl radical with the fluoroalkyl species must occur with an effective first order rate constant of 10^{12} s^{-1} – 10^{13} s^{1}, which approaches the time scale of a vibration and the diffusion-controlled limit. The reaction of 1-(allyloxy)-2-iodobenzene with CuI, CsF and $TMSCF_2H$ did not give any products resulting from cyclization. Instead, this reaction formed allyloxybenzene and the difluoromethylarene. Although the yield of difluoromethylarene was low (13%), in agreement with the result from the reaction of ortho iodoansole, this result argues against a mechanism involving an aryl radical intermediate.

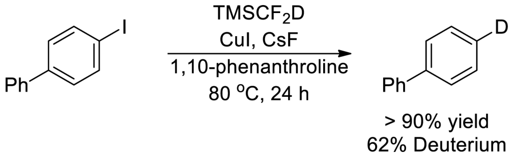
Reactions of vinyl iodides also provide evidence against a radical intermediate. The difluoromethylation of Z-1-iodo-1-octene formed the difluoroallyl product with complete retention of the olefin geometry. Because of the configurational instability of vinyl radicals a mixture of stereoisomers of the coupled products would be expected to form if a vinyl radical were formed. Only one stereoisomer was observed (Scheme 2).

An unusual feature of the scope of this coupling process is the higher yields obtained from reactions of electron-rich aryl iodides than from reactions of electron-poor aryl iodides. Most often, electron-deficient electrophiles react faster and in higher yields than electron-rich electrophiles in cross-coupling reactions. To elucidate the origin of the effect of arene electronics on the yield of the difluoromethylation reaction, we conducted experiments with deuterium labeled $TMSCF_2D$, prepared from $TMSCF_3$ and $NaBD_4$. The reaction of 1-chloro-3-iodobenzene with CuI, CsF and $TMSCF_2D$ resulted in greater than 50% deuterium incorporation at the iodide position of the arene product (eq 2). Thus, the arene product appears to form, at least in part, by an overall hydride transfer from trimethyl(difluoromethyl)silane.



(2)

Similar results were obtained from reactions conducted with exogenous ligand. The reaction of 4-iodo-1,1'-biphenyl with $TMSCF_2D$ in the presence of CuI, CsF and 1,10-phenanthroline formed arene in greater than 90% yield, and the arene contained greater than 60% deuterium at the iodide position (eq 3). Reactions conducted in deuterated solvent did not lead to incorporation of deuterium into the arene, showing that the solvent is not a source of hydrogen for the hydrodehalogenation process.



(3)

The observation of tetrafluoroethyl and trifluoromethyl side products from reactions of electron-deficient aryl iodides suggests that difluorocarbene may be formed under the reaction conditions (vide supra). However, reactions conducted with added cyclohexene or styrene to trap difluorocarbene gave only trace amounts or no detectable amount of products resulting from cyclopropanation, respectively.

Difluoromethylcopper(I) has been reported to undergo a combination of disproportionation and homo-coupling to form *cis*-difluoroethylene and 1,1,2,2-tetrafluoroethane, even below room temperature.[8] If the reaction we report occurs through $CuCF_2H$, the reaction of this complex with aryl iodide must be faster than decomposition. However, the reactions of aryl iodides with Cu(I) species typically require elevated temperatures, and electron-poor aryl iodides typically react with Cu(I) faster than electron-rich aryl iodides.[16] Thus, we suggest that two different reaction pathways are likely to form the difluoromethylarene and the arene, and the rate of formation of arene would be faster with electron-poor arenes than with electron-rich arenes.

To assess the identity of the difluoromethyl copper species that could react with the aryl iodide, we combined CuI, CsF, and $TMSCF_2H$ and heated the mixture at 120 °C in the absence of aryl iodide. Within 5 min, this reaction formed a product with ^{19}F NMR chemical shift and $J_{H\text{-}F}$ values (-116.6 ppm, $J = 44$ Hz) that matched those reported previously for the cuprate $Cu(CF_2H)_2^-$.[8,17, 18] This difluoromethylcuprate species in this difluoromethylation reaction is clearly more stable than the neutral $CuCF_2H$.

Although speculative, we provide a rationalization of our ability to develop copper-mediated difluoromethylation, despite the instability of $CuCF_2H$. We suggest that $Cu(CF_2H)_2^-$ acts as a stable reservoir for the neutral $CuCF_2H$. Because prior studies have shown that two-coordinate cuprates react more slowly with haloarenes than do neutral complexes,[14a-c] we suggest that $CuCF_2H$ reacts with the haloarene. The low concentrations of $CuCF_2H$ should decrease the rate of bimolecular decomposition, relative to reaction with the haloarene. Future studies will assess these mechanistic hypotheses.

In summary, we have described a one-step procedure for the difluoromethylation of aryl and vinyl iodides that occurs with readily available and non-hazardous reagents. This reaction tolerates amine, ether, amide, ester, aromatic bromide and protected alcohol functionalities and occurs in high yield with sterically hindered aryl iodides. The simplicity and generality of this method makes it attractive for the introduction of a CF_2H group into functionally diverse iodoarenes. Work is ongoing to develop conditions for difluormethylation of electron-poor aryl iodides, to develop reactions of heteroaryl iodides, and to develop reactions of higher difluoroalkyl groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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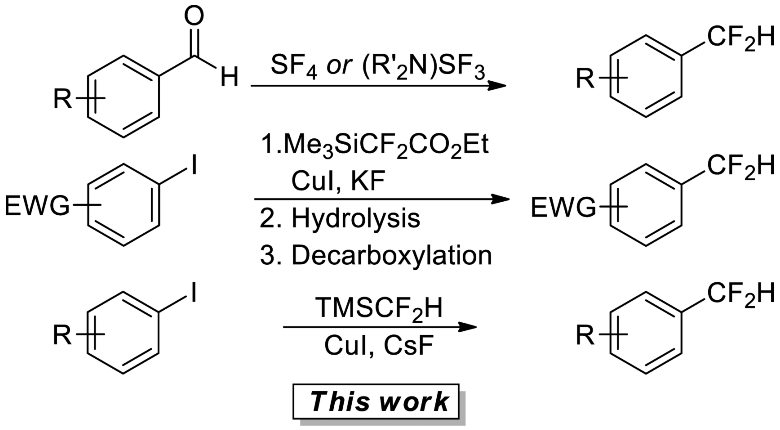
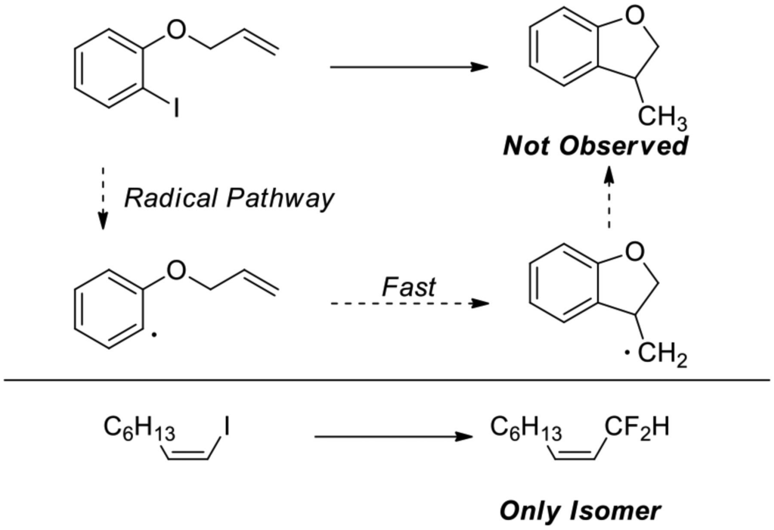


Scheme 1.
Preparation of Difluoromethylarenes

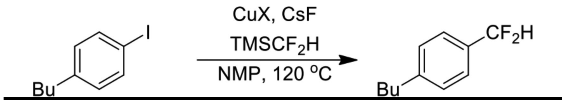


Scheme 2.

Evidence against aryl and vinyl radical intermediates

Table 1

Effect of Copper Source and Reagent Ratios on the Difluoromethylation of 1-butyl-4-iodobenzene[a]

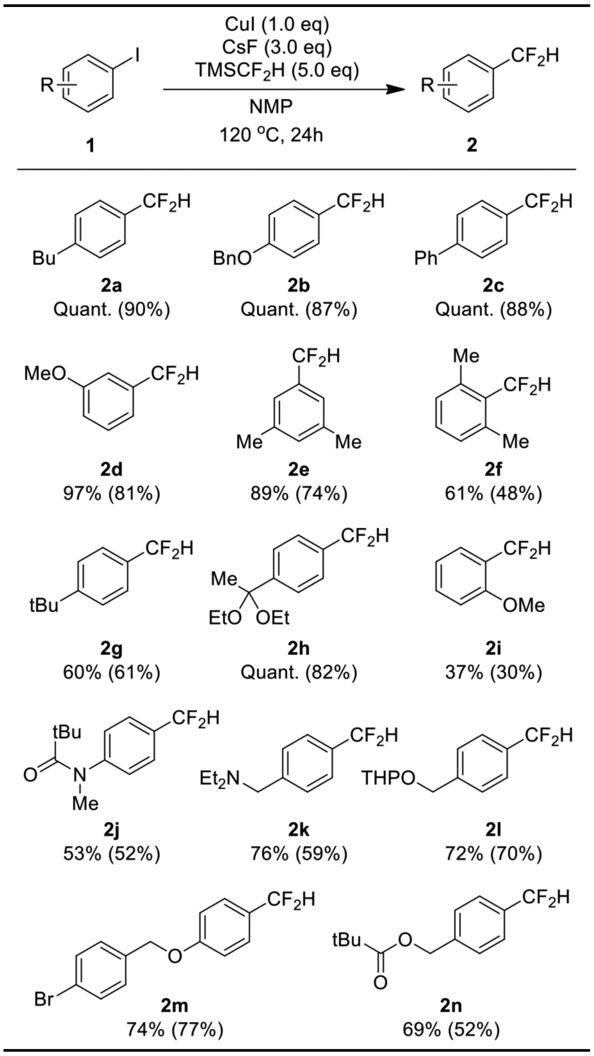


Entry	CuX (eq)	CsF (eq)	TMSCF$_2$H (eq)	yield (%)
1	CuBr (1.0)	2.0	5.0	84
2	CuBr-SMe$_2$ (1.0)	2.0	5.0	70
3	CuCI (1.0)	2.0	5.0	53
4	Cul (1.5)	1.5	1.5	26
5	Cul (3.0)	3.0	3.0	36
6	Cul (1.0)	1.0	5.0	55
7	Cul (1.0)	2.0	5.0	91
8	Cul (1.0)	3.0	3.0	75
9	Cul (1.0)	3.0	5.0	100

[a] Reactions were performed with 0.1 mmol of 1-butyl-4-iodobenzene in 0.5 mL of NMP for 24 hours. The yield was determined by ^{19}F NMR with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

Table 2

Difluoromethylation of Aryl Iodides with $TMSCF_2H$ Mediated by Copper Iodide[a]

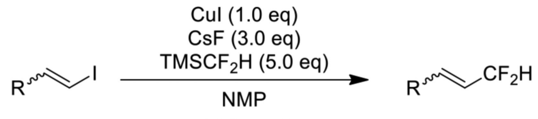


1		**2**
2a Quant. (90%)	**2b** Quant. (87%)	**2c** Quant. (88%)
2d 97% (81%)	**2e** 89% (74%)	**2f** 61% (48%)
2g 60% (61%)	**2h** Quant. (82%)	**2i** 37% (30%)
2j 53% (52%)	**2k** 76% (59%)	**2l** 72% (70%)
2m 74% (77%)	**2n** 69% (52%)	

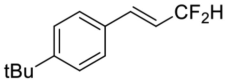
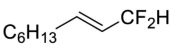
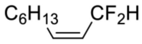
[a] Reactions were performed with 0.1 mmol of aryl iodide to determine ^{19}F NMR yields with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. Isolated yields, shown in parenthesis, were obtained from reactions performed with 0.5 mmol of aryl iodide.

Table 3

Difluoromethylation of Vinyl Iodides with $TMSCF_2H$ Mediated by Copper Iodide.[a]



3 **4**

		
4a	**4b**	**4c**
82% (80%)	Quant. (91%)	47% (42%)

[a] Reactions were performed with 0.1 mmol of vinyl iodide to determine ^{19}F NMR yields with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. Isolated yields, shown in parenthesis, were obtained from reactions with 0.5 mmol of vinyl iodide.