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A New Method for Aromatic Difluoromethylation: Copper-Catalyzed Cross-Coupling and Decarboxylation Sequence from Aryl Iodides

Kenichi Fujikawa,[†] Yasutaka Fujioka,[†] Akira Kobayashi,[‡] and Hideki Amii*[,†,‡]

Department of Chemistry, Graduate School of Science, Kobe University, Kobe 657-8501, Japan and Department of Chemistry and Chemical Biology, Graduate School of Engineering, Gunma University, Kiryu, Gunma 376-8515 Japan

amii@chem-bio.gunma-u.ac.jp

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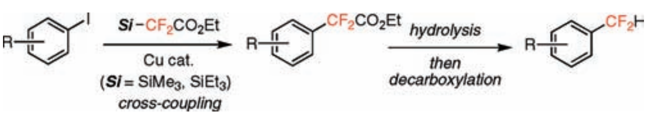
ABSTRACT



A new methodology for aromatic difluoromethylation is described. Aryl iodides reacted with α-silyldifluoroacetates upon treatment with copper catalyst in DMSO or DME to give the corresponding aryldifluoroacetates in moderate to good yields. The subsequent hydrolysis of aryldifluoroacetates and KF-promoted decarboxylation afforded a variety of difluoromethyl aromatics.

Fluorinated organic compounds play a key role in the remarkable progress of medicinal, agricultural, and material sciences.[1] Difluoromethylene compounds have been considerable synthetic targets because of their wide utility.[2,3] Among them, difluoromethylated aromatic compounds (Ar−CF_2H) have received a great deal of attention in the design and development of bioactive agents.[4,5] For instance, certain difluoromethylated aromatics show potential inhibitory activities against VanX (a zinc-dependent D-Ala-D-Ala dipeptidase)[6] and CETP (cholesteryl ester transfer protein).[7] Although fluorination of aromatic aldehydes (Ar−CHO) by the use of a nucleophilic fluorinating agent such as SF_4, DAST, and its derivatives is an orthodox method to construct Ar−CF_2H skeletons,[8,9] an alternative approaches for selective introduction of CF_2H groups into aromatic compounds have been a topic of considerable interest.

Fluoroalkyl cross-coupling is one of the most versatile methods to produce fluoromethylated aromatics. Copper-mediated cross-coupling reactions for aromatic trifluoromethylation have been widely investigated.[10−14] Recently,

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[†] Kobe University.

[‡] Gunma University.

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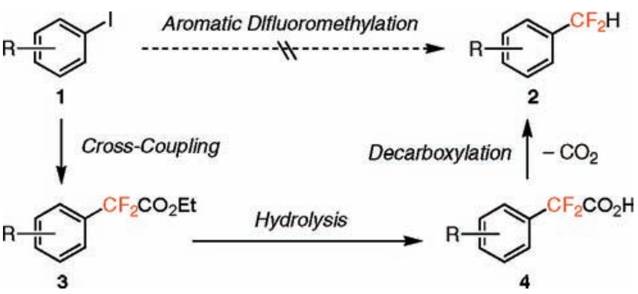
we demonstrated that a small amount of CuI−phenanthroline complex engenders the cross-coupling reactions of aryl/heteroaryl iodides with CF_3SiEt_3[14a] and fluoral derivatives[14b] to deliver trifluoromethylated arenes. Trifluoromethyl copper intermediates (CF_3CuL) contribute to these transformations (both stoichimetric and catalytic in copper). Compared with the chemistry of trifluoromethylation, that of difluoromethylation has been much less studied. The use of difluoromethyl copper (HCF_2Cu) is anticipated to yield difluoromethylated aromatic compounds ($Ar-CF_2H$). There have been few reports on the reactions of HCF_2Cu species with electrophiles such as allylic, propargylic, alkynyl, and benzyl halides.[15,16] However, to the best of our knowledge, the cross-coupling of HCF_2Cu with aromatic halides has never been accomplished due to the lack of thermal stability of HCF_2Cu species. Herein, we describe a new reaction sequence leading to an efficient synthesis of difluoromethylated aromatic compounds **2** from aryl iodides **1** *via* 2-aryl-2,2-difluoroacetates **3** (Scheme 1).

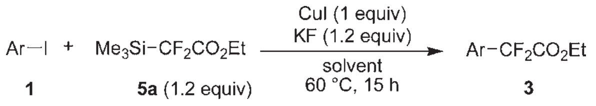
Scheme 1



Initially, Cu-promoted cross-coupling reactions of aryl iodides **1** with α-silyldifluoroacetates (**5**)[17] were examined. A mixture of 4-iodobenzonitrile (**1a**) and ethyl 2-(trimethylsilyl)-2,2-difluoroacetate (**5a**) in DMF was heated at 60 °C for 15 h in the presence of CuI (1.0 equiv) and KF (1.2 equiv) to afford aryldifluoroacetate **3a** in only 8% NMR yield (Table 1, entry 1). After the survey of reaction media (entries 2−4), DMSO was found to be an effective solvent for the Cu-mediated transformation (entry 4).

Other examples of the selective formation of 2-aryl-2,2-difluoroacetates **3** are given in Table 1 (entries 5−14). Upon treatment with a stoichiometric amount of CuI, a wide repertoire of aromatic iodides **1** bearing electron-withdrawing or -donating substituents underwent cross-coupling reactions to provide the corresponding *gem*-difluoroesters **3** in high yields (entries 4−14). En passant, aryldifluoroacetates **3** have been used for several applications.[18] To date, the reductive cross-coupling reactions of bromo- or iododifluoroacetates with aryl harides by the use of copper bronze are one of the most reliable methods to prepare 2-aryl-2,2-difluoroacetates **3**.[19−22] In these transformations, 2 equiv of copper are required to generate $Cu-CF_2CO_2R$ intermediates,[19b] which participate in cross-coupling with aryl halides. Compared to the

Table 1. Cross-Coupling of Aryl Iodides **1** with α-Silyldifluoroacetate **5a** (Stoichiometric in Copper)



$$\underset{\mathbf{1}}{\text{Ar}-\text{I}} + \underset{\mathbf{5a}\ (1.2\ \text{equiv})}{\text{Me}_3\text{Si}-\text{CF}_2\text{CO}_2\text{Et}} \xrightarrow[\text{solvent}\ 60\ {}^\circ\text{C},\ 15\ \text{h}]{\text{CuI (1 equiv)}\ \text{KF (1.2 equiv)}} \underset{\mathbf{3}}{\text{Ar}-\text{CF}_2\text{CO}_2\text{Et}}$$

entry	Ar	solvent	yield/%[a,b]
1	4-NC-C_6H_4 (**1a**)	DMF	8
2	4-NC-C_6H_4 (**1a**)	CH_3CN	12
3	4-NC-C_6H_4 (**1a**)	DME	72
4	4-NC-C_6H_4 (**1a**)	DMSO	88 (71)
5	3-NC-C_6H_4 (**1b**)	DMSO	85 (69)
6	2-NC-C_6H_4 (**1c**)	DMSO	57 (44)
7	4-O_2N-C_6H_4 (**1d**)	DMSO	41 (29)
8	4-EtO_2C-C_6H_4 (**1e**)	DMSO	81 (73)
9	3,4-Cl_2-C_6H_3 (**1f**)	DMSO	84 (73)
10	4-Br-C_6H_4 (**1g**)	DMSO	76 (54)
11	4-Ph-C_6H_4 (**1h**)	DMSO	78 (68)
12	Ph (**1i**)	DMSO	75[c] (40)
13	4-EtO-C_6H_4 (**1j**)	DMSO	78 (72)
14	2-quinolyl (**1k**)	DMSO	88 (87)

[a] NMR yields, which were calculated by ^{19}F NMR integration of products **3** relative to the 2,2,2-trifluoroethanol internal standard. [b] The values in parentheses indicate the isolated yields of **3**. [c] Determined by GC analysis using biphenyl as an internal standard.

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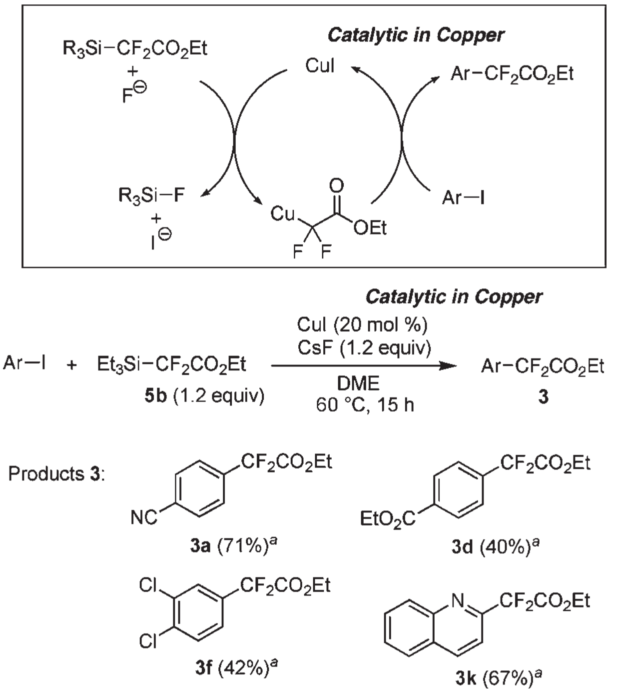
previously available methods, our transmetalation methodology has several advantages: (i) the cross-coupling participants **5** (2-silyl-2,2-difluoroacetates) are stable and readily available directly from trifluoroacetates or chlorodifluoroacetates;[17,23] (ii) with a high level of functional group tolerance, the reactions proceeded smoothly under mild conditions; and (iii) fine-tuning of the reaction conditions rendered a reaction catalytic in copper possible (Scheme 2).[24,25]

Scheme 2

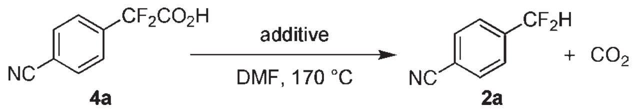


[a] Determined by ^{19}F NMR (CF_3CH_2OH was used as internal standard).

When a mixture of **1a**, $Me_3Si-CF_2CO_2Et$ (**5a**), and KF in DMSO was heated at 60 °C for 15 h in the presence of a catalytic amount of CuI (0.2 equiv to **1a**) under an argon atmosphere, the cross-coupling reaction proceeded to give ester **3a** in 38% NMR yield. To improve the chemical yields of cross-coupling using a small amount of CuI, various screening experiments were undertaken. After systematical optimization, the use of 2-(triethylsilyl)-2,2-difluoroacetates (TES-CF_2CO_2Et, **5b**) instead of **5a** as a coupling partner and DME as a solvent was shown to be effective for the selective formation of aryldifluoroacetate **3** in moderate yields at a 20 mol % catalyst loading (Scheme 2).

Next, we explored decarboxylation of 2-aryl-2,2-difluoroacetic acids **4**, which were readily obtained by alkaline hydrolysis of esters **3**. Upon heating a DMF solution of aryl-2,2-difluoroacetic acid **4a** at 170 °C (without any catalyst), decarboxylation took place to give difluoromethyl arene **2a** in 19% yield (Table 2, entry 1). Interestingly, a significant change was observed when the reaction was conducted in the presence of NaF to provide the decarboxylation product **2a** in 60% yield (entry 2). Heating of a DMF solution of **4a** with KF[26] (2 equiv to **4a**) led to formation of difluoromethyl arene **2a** in 93% yield (entry 4). The use of metal fluorides such as NaF, KF, and CsF was found to be effective for decarboxylation of **4a** (entries 2−7). In contrast, addition of KBr instead of KF gave a poor result for decarboxylation (entry 7).

Table 2. Additive Effect on Decarboxylation of **4a**



entry	additive (amount)	time/h	yield/%[a]
1	none	1	19
2	NaF (1 equiv)	1	60
3	KF (1 equiv)	1	64
4	KF (2 equiv)	1	87
5	KF (2 equiv)	2	93
6	CsF (1 equiv)	1	95
7	KBr (1 equiv)	1	17

[a] Determined by ^{19}F NMR analysis (CF_3CH_2OH was used as internal standard).

Hydrolysis of **3** with aqueous K_2CO_3 followed by decarboxylation of **4** gave difluoromethyl arenes **2**. Without

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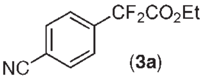
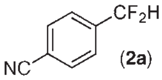
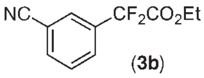
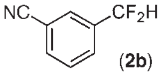
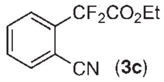
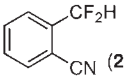
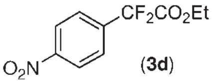
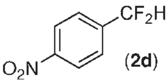
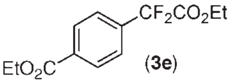
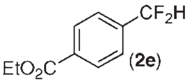
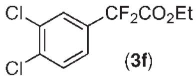
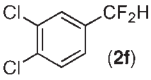
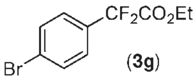
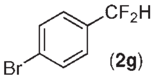
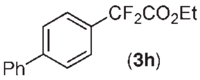
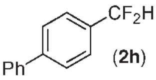
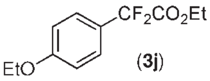
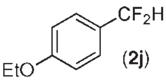
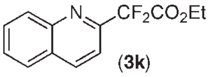
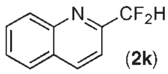
(23) α-Silyldifluoroacetates **5** were readily prepared in good yields by Mg-promoted reductive transformation of ethyl chlorodifluoroacetate in the presence of Me_3SiCl or Et_3SiCl.

(24) Pd-catalyzed cross-coupling of aryl bromides with enol ethers of difluoroketones: (a) Guo, Y.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583–3585. (b) Guo, Y.; Twamley, B.; Shreeve, J. M. *Org. Biomol. Chem.* **2009**, *7*, 1716–1722.

Table 3. Synthesis of Difluoromethylated Aromatics **2**

$$\underset{\mathbf{3}}{\text{Ar}-\text{CF}_2\text{CO}_2\text{Et}} \xrightarrow[\text{MeOH/H}_2\text{O, rt, 1–2 h}]{\text{K}_2\text{CO}_3} \underset{\mathbf{4}}{\text{Ar}-\text{CF}_2\text{CO}_2\text{H}} \xrightarrow[\text{DMF or NMP, conditions}]{\text{KF (or CsF)}} \underset{\mathbf{2}}{\text{Ar}-\text{CF}_2\text{H}}$$

entry[a]	esters **3**	conditions (**4**→**2**)	**2**	yield/%[b]
1	 (**3a**)	DMF 170 °C, 2 h	 (**2a**)	84
2	 (**3b**)	NMP 200 °C, 5 h	 (**2b**)	57
3	 (**3c**)	NMP 200 °C, 2 h	 (**2c**)	67
4	 (**3d**)	DMF 170 °C, 3 h	 (**2d**)	81
5	 (**3e**)	DMF 170 °C, 12 h	 (**2e**)	74
6	 (**3f**)	DMF 170 °C, 12 h	 (**2f**)	77
7[c]	 (**3g**)	NMP 200 °C, 48 h	 (**2g**)	59
8[c]	 (**3h**)	NMP 200 °C, 24 h	 (**2h**)	62
9[c]	 (**3j**)	DMF 170 °C, 12 h	 (**2j**)	–[d]
10	 (**3k**)	DMF 170 °C, 12 h	 (**2k**)	89

[a] In each reaction, KF (5 equiv) was used unless noted. [b] Isolated yields (from esters **3**). [c] These reactions were carried out by the use of CsF (5 equiv) instead of KF. [d] The decarboxylation reaction did not occur.

isolation of the intermediate carboxylic acid **4a**, difluoroester **3a** was converted cleanly to **2a** in 84% overall yield via a hydrolysis–decarboxylation sequence. Representative results are summarized in Table 3. Under the optimized reaction conditions, KF-promoted decarboxylation worked well for various aryldifluoroacetic acids **4**. Difluoroesters **3a**–**f** endowed with electron-withdrawing groups on the aryl rings underwent KF-catalyzed decarboxylation smoothly to provide the desired difluoromethyl arene **2** in good yields (entries 1–6). The decarboxylation reactions of **3g** and **3h** possessing Br or phenyl groups required the utilization of CsF under the harsh conditions (at 200 °C, in NMP) (entries 7 and 8). In contrast, decarboxylation of **3j** bearing an electron-donating substituent such as an ethoxy group on the aryl ring did not occur at 200 °C even in the presence of CsF (entry 9). Furthermore, heteroarene **3k** partook in the KF-catalyzed decarboxylation to afford difluoromethylated quinoline **2k** in high yield (entry 10).

In conclusion, we have developed a convenient route to difluoromethyl arenes from aryl iodides. In the first cross-coupling reactions, α-silyldifluoroacetates **5** served as a donor of the difluoromethylene component to aromatics. For the subsequent decarboxylation step, KF was found to be a good promoter. The stepwise conversion of the iodo moieties in **1** to CF_2H groups was successfully accomplished.[27] Thereby, the design of the reaction sequences enables the development of various practical transformations, with potential biological and chemical utility.

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Supporting Information Available. Details of experimental procedures and characterization data (^{1}H, ^{13}C, and ^{19}F NMR; IR; and mass spectrometry) for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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