ACS Catalysis

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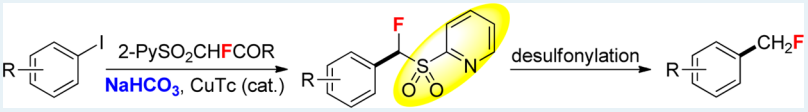
Copper-Catalyzed Debenzoylative Monofluoromethylation of Aryl Iodides Assisted by the Removable (2-Pyridyl)sulfonyl Group

Yanchuan Zhao, Chuanfa Ni, Fanzhou Jiang, Bing Gao, Xiao Shen, and Jinbo Hu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

Supporting Information



ABSTRACT: A new method for aromatic monofluoromethylation was developed. Aryl iodides can be efficiently transformed into the corresponding monofluoromethylated products by a copper-catalyzed debenzoylative fluoroalkylation with 2-$PySO_2CHFCOR$ and subsequent reductive desulfonylation. The (2-pyridyl)sulfonyl moiety plays an important role in the copper-catalyzed cross-coupling, and it can be removed easily through Bu_3SnH-mediated desulfonylation.

KEYWORDS: *monofluoromethylation, copper catalysis, (2-pyridy)sulfonyl group, cross-coupling, fluorine*

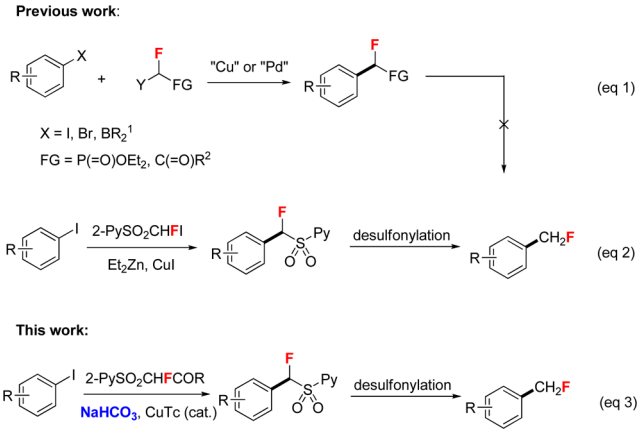
Fluoroalkylated aromatic compounds are of great synthetic interest because of their wide applications in pharmaceutical and materials research.[1−3] Transition metal (TM)-mediated or catalyzed fluoroalkylations of aryl halides or boronic acids are generally employed to construct the R_f-C (sp^2) linkage, among which copper- and palladium-catalyzed processes are the most extensively investigated as a result of the wide scope and high efficiency.[4−13] Despite the fact that the TM-catalyzed coupling reaction between a trifluoromethyl group and an aryl group has been well documented,[4−13] the analogous methods for the incorporation of partially fluorinated methyl groups into arenes remain largely unexplored.[14,15]

Recently, Amii et al. reported a three-step preparation of difluoromethylated aromatics by copper-catalyzed cross-coupling reaction with Me_3SiCF_2COOEt and subsequent decarboxylation.[16] Moreover, the copper-mediated direct difluoromethylation of aryl iodides with Me_3SiCF_2H and Bu_3SnCF_2H was reported by Hartwig et al. and Prakash et al., respectively.[17,18] However, despite the various applications of monofluoromethylated compounds in different fields,[19−23] efficient methods for monofluoromethylation of aromatic halides or boronic acids are scarce.[24] Direct introduction of a CH_2F group was reported by Suzuki et al. in 2009 by the cross-coupling reaction between CH_2FI and pinacol phenylboronate; however, the method employed a large excess amount of pinacol phenylboronate (40 equiv) and the yield was low.[25] Furthermore, a series of functionalized monofluoromethyl groups (CFR^1R^2) could be introduced by coupling of aryl halides (or boronic acids) with α-fluoro phosphonates, ketones (or enolates), and esters, but further transformation of the products in these reactions to monofluoromethylated compound is difficult (Scheme 1, eq 1).[26−30]

Recently, we became interested in investigating the versatile chemical behaviors of fluoroalkyl 2-pyridyl sulfone reagents.[31−35] We discovered that a monofluoromethylation of aryl iodide could be achieved by a copper-mediated fluoroalkylation with 2-$PySO_2CFHI$ and subsequent desulfonylation (Scheme 1, eq 2).[33] Herein, we report a new monofluoromethylation of aryl iodides by a Hurtley-type debenzoylative cross-coupling with an α-fluorinated active methylene compound and subsequent desulfonylation. It was found that the copper-catalyzed debenzoylative cross-coupling proceeded smoothly in the presence of CuTc (copper thiophene-2-carboxylate) and $NaHCO_3$ with the aid of the removable (2-pyridyl)sulfonyl group (Scheme 1, eq 3).

The Hurtley reaction is a well established method for cross-coupling of aryl halides and active methylene compounds under basic conditions. In the presence of a suitable ancillary ligand,

Scheme 1. Transition Metal-Mediated Cross-Coupling To Introduce a Functionalized Monofluoromethyl Group

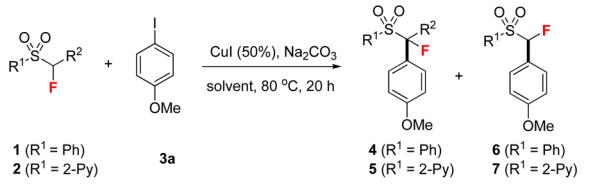


Received: January 26, 2013
Revised: February 28, 2013
Published: March 4, 2013

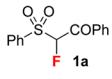
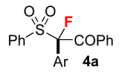
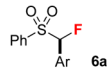
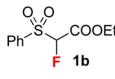
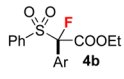
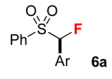
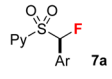
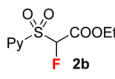
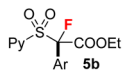
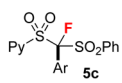
the coupling reaction could proceed under mild reaction conditions with a wide substrate scope;[36] however, couplings with activated α-fluoro methylene compounds are rarely explored.[37] Generally, it is difficult for α-substituted substrates to participate in a Hurtley reaction. For instance, the reaction with diethyl 2-methylmalonate was reported to give a trace amount of product.[38] Moreover, an α-fluoroalkyl anion tends to decompose under elevated temperatures. These restrictions make it challenging to achieve efficient Hurtley reactions with fluorinated active methylene compounds.

We first focused on the copper-catalyzed cross-coupling reaction between various phenylsulfonyl-substituted active methylene compounds (**1a**−**1c**) and aryl iodide using 1-iodo-4-methoxybenzene (**3a**) as a model substrate in the presence of 50% CuI under slightly basic conditions. The results are shown in Table 1. To our surprise, only a trace amount of product was

Table 1. Survey of Various Methylene Compounds



1 (R^1 = Ph) **2** (R^1 = 2-Py) **3a** **4** (R^1 = Ph) **5** (R^1 = 2-Py) **6** (R^1 = Ph) **7** (R^1 = 2-Py)

entry[a]	nucleopile	coupling product		yield (%)[b]
1	 **1a**	 **4a**	 **6a**	**4a:** trace **6a:** trace
2	 **1b**	 **4b**	 **6a**	**4b:** 0 **6a:** 0
3	 **1c**	 **4c**	 **6a**	**4c:** 0 **6a:** 0
4	 **2a**	 **5a**	 **7a**	**5a:** 23 **7a:** 72
5	 **2b**	 **5b**	 **7a**	**5b:** 60 **7a:** <1
6	 **2c**	 **5c**	 **7a**	**5c:** 0 **7a:** 0

[a]Unless otherwise stated, the reactions were run on a 0.2 mmol scale in DMSO (2 mL) at 80 °C for 20 h in the presence of Na_2CO_3 (0.2 mmol) and CuI (0.1 mmol). [b]The yield of coupling product based on the amount of **3a**, which was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

observed when employing reagent **1a** (substituted with benzoyl group), and no desired product was obtained when the reactions were carried out with reagents **1b** and **1c** (substituted with an ester and sulfonyl group, respectively). Despite the long history of the Hurtley reaction, the scope of the CH-acid is still largely restricted to a specific type of active methylene compound that is likely to serve as a chelating ligand for copper under basic conditions.[39] In 2002, Buchwald et al. developed an efficient arylation of diethyl malonate in the presence of CuI and 2-phenylphenol; however, arylation of cyclic malonate ester and cyclic diketones was unsuccessful under the reaction system. The authors thus proposed that a bidentate binding of enolate to copper is crucial to the reaction.[40] Unlike carbonyl compounds and esters, sulfones could not form "enolates" and are generally less efficient in coordinating to a metal catalyst.[41] As a result, sulfones are challenging substrates in transition metal-catalyzed C−C bond formation reactions,[42] although the sulfonyl group possesses a good ability to enhance the acidity of the substrate that is beneficial to the reaction.

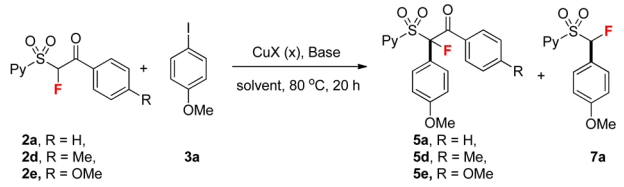
In our previous work, we discovered that the (2-pyridyl)-sulfonyl group played an important role in copper-mediated fluoroalkylations. The reactions with (2-pridyl)sulfones gave much better yields than those with (phenyl)sulfones.[33] In light of the result, we envisioned that a copper-catalyzed Hurtley-type reaction with α-fluorinated active methylene compound might also be achieved by introducing the (2-pyridyl)sulfonyl group as a coordinating group. A series of (2-pyridyl)sulfonyl-substituted CHF acids were then synthesized to investigate their behavior in the current copper-catalyzed fluoroalkyations.[43] To our delight, reaction with (2-pyridyl)sulfonyl CHF acids **2a** and **2b** gave good yields of the coupling products (entries 4 and 5), which suggested the (2-pyridyl)sulfonyl group promoted the reaction efficiently. It should be noted that no desired product was obtained when employing **2c** as a reagent, which indicated the presence of carbonyl or ester group is still necessary to the success of the reaction. Interestingly, both expected coupling product **5a** and debenzoylative product **7a** were observed when the reaction was carried out with **2a**, but only the expected coupling product **5b** was obtained when employing **2b** as a reagent. This result is probably due to the different electrophilicities of the carbonyl and ester groups. Because debenzoylation of **5a** could proceed in the presence of Na_2CO_3 in DMSO, the product **7a** is likely to be generated through subsequent debenzoylation of **5a**.[44,45]

With the suitable reagent **2a**, we further optimized other reaction parameters. K_2CO_3 and Cs_2CO_3 were found to be less effective than Na_2CO_3 in the current reaction (Table 1, entry 4; Table 2, entries 1 and 2). This is probably due to the tendency of decomposition (via debenzoylation and defluorination) of the reagent **2a** under highly basic conditions. Interestingly, the reaction could also proceed in the presence of *N*-ethyl-diisopropylamine, which was reported to inhibit the Hurtley reaction by saturating the coordination sphere of copper (Table 2, entry 3). Highly polar solvents DMSO and NMP were beneficial to the reaction (Table 2, entry 5). A trace amount of the desired product was observed when the reaction was carried out in less-polar solvent 1,4-dioxane (Table 2, entry 6). CuTc was found to be more effective than CuI in promoting the current cross-coupling reaction (Table 2, entries 7 and 8). The introduction of electron-donating groups into the phenyl ring of reagent **2a** was found to retard the debenzoylation of reagent **2** and improve the total yield of product **5** and **7** (Table 2, entries 8−10). Finally, we found a highly selective debenzoylative fluoroalkylation could be achieved by switching the base to $NaHCO_3$ (Table 2, entry 11). The small amount of **5** could be easily converted into **7** by heating with $NaHCO_3$ in MeOH.

With the optimized reaction conditions in hand (Table 2, entry 11), we next explored the scope of the current copper-catalyzed debenzoylative fluoroalkylation. As shown in Table 3, various aryl iodides were converted to the corresponding fluoroalkylated products in moderate to good yields (63−85%). The method is amenable to a variety of functionalities, including esters, ketones, and halides. The reactions with aryl

dx.doi.org/10.1021/cs4000574 | ACS Catal. 2013, 3, 631−634

Table 2. Survey of the Reaction Conditions

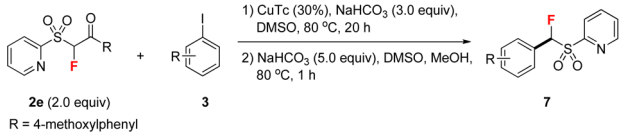


2a, R = H, **2d**, R = Me, **2e**, R = OMe — **3a** — **5a**, R = H, **5d**, R = Me, **5e**, R = OMe — **7a**

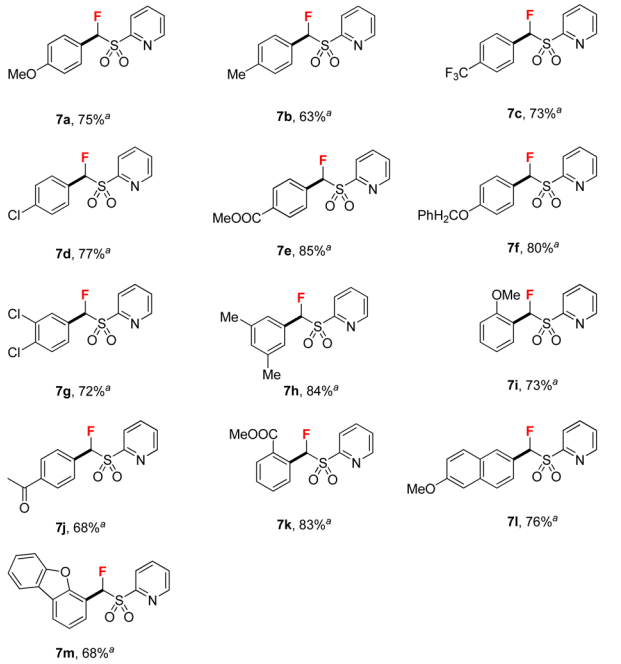
entry[a]	base	solvent	CuX	*x*, %	yield (%)[b]
1	K_2CO_3	DMSO	CuI	50	**5a**, 14; **7a**, 52
2	Cs_2CO_3	DMSO	CuI	50	**5a**, 17; **7a**, 20
3	*i*-Pr_2NEt	DMSO	CuI	50	**5a**, 45; **7a**, 0
4	Na_2CO_3	DMF	CuI	50	**5a**, 9; **7a**, trace
5	Na_2CO_3	NMP	CuI	50	**5a**, 2; **7a**, 51
6	Na_2CO_3	dioxane	CuI	50	**5a**, trace; **7a**, 0
7	Na_2CO_3	DMSO	CuI	20	**5a**, 12; **7a**, 53
8	Na_2CO_3	DMSO	CuTc	20	**5a**, 19; **7a**, 63
9[c]	Na_2CO_3	DMSO	CuTc	20	**5d**, 25; **7a**, 60
10[d]	Na_2CO_3	DMSO	CuTc	20	**5e**, 37; **7a**, 53
11[d]	$NaHCO_3$	DMSO	CuTc	30	**5e**, 1; **7a**, 90

[a]Unless otherwise stated, the reactions were run on a 0.2 mmol scale in solvent (2 mL) at 80 °C for 20 h. [b]Yield of coupling product based on the amount of **3a**, which was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c]**2d** was used instead of **2a**. [d]**2e** was used instead of **2a**.

Table 3. Copper-Catalyzed Debenzoylative Fluoroalkylation of Aryl Iodides 3



2e (2.0 equiv), R = 4-methoxylphenyl — **3** — **7**

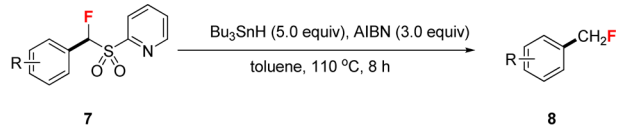


[a]Isolated yield.

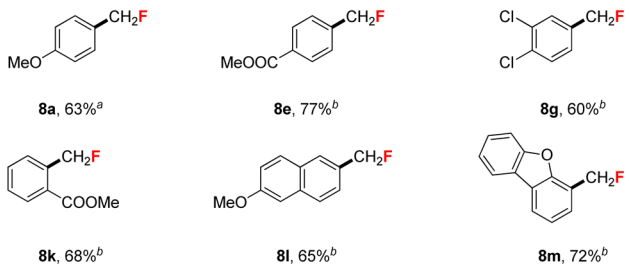
iodides bearing either an electron-donating (including **7a**, **7f**, **7i**) or electron-withdrawing group (**7c**) furnished satisfactory yields of products. For ortho-substituted aryl iodides, a small amount (5−10%) of undebenzoylative products **5** was obtained in a cross-coupling reaction, probably as a result of steric hindrance. The products **5** were subsequently converted to the debenzoylative products **7** by treating with $NaHCO_3$ and MeOH.

Reductive desulfonylation of **7** with Bu_3SnH/AIBN enabled facile access to monofluoromethylated arenes.[46,47] Representative results are illustrated in Table 4. The reactions worked well

Table 4. Reductive Desulfonylation of 7



7 — **8**



[a]Yield determined by ^{19}F NMR spectroscopy of the reaction mixture using $PhCF_3$ as an internal standard. [b]Isolated yields.

with structurally diverse (2-pyridyl)sulfonylfluoromethylated arenes **7** and smoothly gave the corresponding monofluoromethylated products **8** in moderate to good yields (60−77%). It should be mentioned that an excess amount of AIBN is necessary to drive the reaction to completion. The ipso substitution of the (2-pyridyl)sulfonyl group by a tributylstannyl radical is likely involved in the reaction, which is supported by the observation of 2-(tributylstannyl)pyridine as a byproduct in the reaction.

In conclusion, we have developed monofluoromethylation of aryl iodides via a copper-catalyzed Hurtley-type debenzoylative fluoroalkylation and subsequent desulfonylation. The (2-pyridyl)sulfonyl group played an important role in promoting the copper-catalyzed cross-coupling and could be removed easily via a Bu_3SnH-mediated desulfonylation. The use of $NaHCO_3$ as a base allowed a highly selective debenzoylative cross-coupling reaction. Further explorations of the applications of the (2-pyridyl)sulfonyl group in fluoroalkylation reactions and a detailed mechanistic study are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jinbohu@sioc.ac.cn.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/cs4000574 | *ACS Catal.* 2013, 3, 631−634

■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2012CB821600, 2012CB215500), the National Natural Science Foundation of China (20825209, 21202189), and the Chinese Academy of Sciences.

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