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Copper-Promoted Reductive Coupling of Aryl Iodides with 1,1,1-Trifluoro-2-iodoethane

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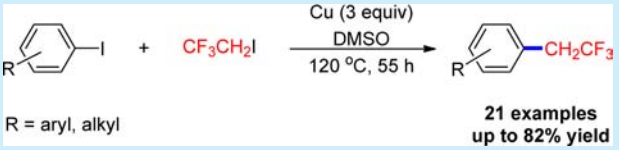
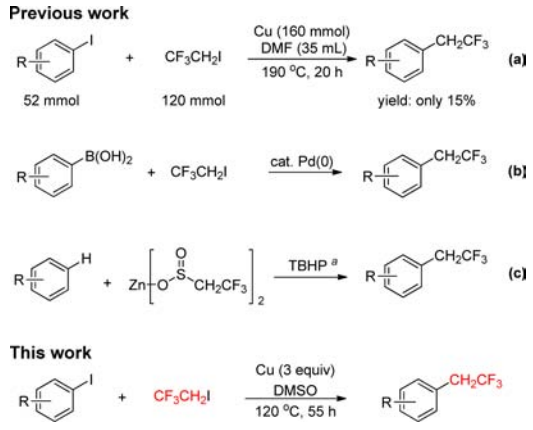
Supporting Information

ABSTRACT: An efficient Cu-promoted reductive coupling of aryl iodides with 1,1,1-trifluoro-2-iodoethane has been developed. This reaction could occur in good yields under milder conditions as compared with previous studies. The reaction tolerated nitro, formyl, ester, ether, carbonyl, sulfonyl, and even azo groups.



The introduction of fluorine atoms into organic molecules can substantially change their properties such as metabolic stability and bioavailability.[1] In recent years, the trifluoromethyl group has attracted more attention due to the functional group's strong electron-withdrawing property and hydrophobicity. In addition to the many studies on trifluoromethylation of aromatic compounds,[2] the preparation of (2,2,2-trifluoroethyl)arenes has also gained attention.[3] However, few direct methods for the introduction of the CH_2CF_3 group on the aromatic ring have been reported. For example, the copper-promoted reductive coupling of aryl iodides with 1,1,1-trifluoro-2-iodoethane was reported for the first time in 1969 (Scheme 1a).[4] Although in only 15% yield, this reaction offered a new method for trifluoroethylation. Lately, Hu reported the palladium-catalyzed 2,2,2-trifluoroethylation of organo boronic acids and esters (Scheme 1b).[5] Soon after, similar work was published by Zou.[6] Recently, it was reported that zinc sulfonate salts can be used to transfer alkyl radicals to heterocycles, which involved introduction of the trifluoroethyl on the aromatic ring (Scheme 1c).[7]

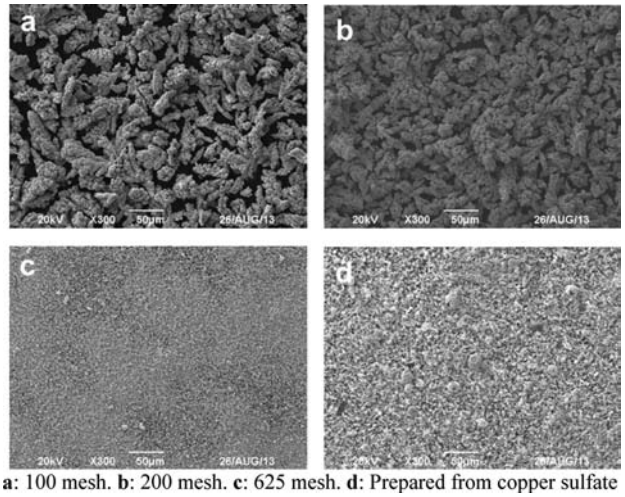
Scheme 1. Direct Synthesis of 2,2,2-Trifluoroethylated Arenes



[a]TBHP = *tert*-butyl hydroperoxide.

Based on the study of McLoughlin and Thrower on the copper-promoted 2,2,2-trifluoroethylation of arenes using the cheap and available reagent CF_3CH_2I as the source of the CH_2CF_3 group, further study was undertaken by us. The reaction is simple and nontoxic. In our investigation, we were surprised to find that the copper powder with a bigger particle size will significantly promote the reaction process. Herein, we reported an efficient protocol for the reductive coupling between aryl iodides and 1,1,1-trifluoro-2-iodoethane.

Our study began with the reductive couping of ethyl 4-iodobenzoate (**I**) with CF_3CH_2I. We initially used the copper powder **b** (200 mesh, Figure 1b) as a reductant and 4 equiv of CF_3CH_2I at 120 °C. DMF was used as the solvent according to the previous work.[4] To our disappointment, it only gave a trace amount of the desired product **II** (Table 1, entry 1). Then, a



a: 100 mesh. **b**: 200 mesh. **c**: 625 mesh. **d**: Prepared from copper sulfate

Figure 1. TEM images of copper powder.

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Table 1. Reductive-Coupling of I and CF_3CH_2I[a]

I II

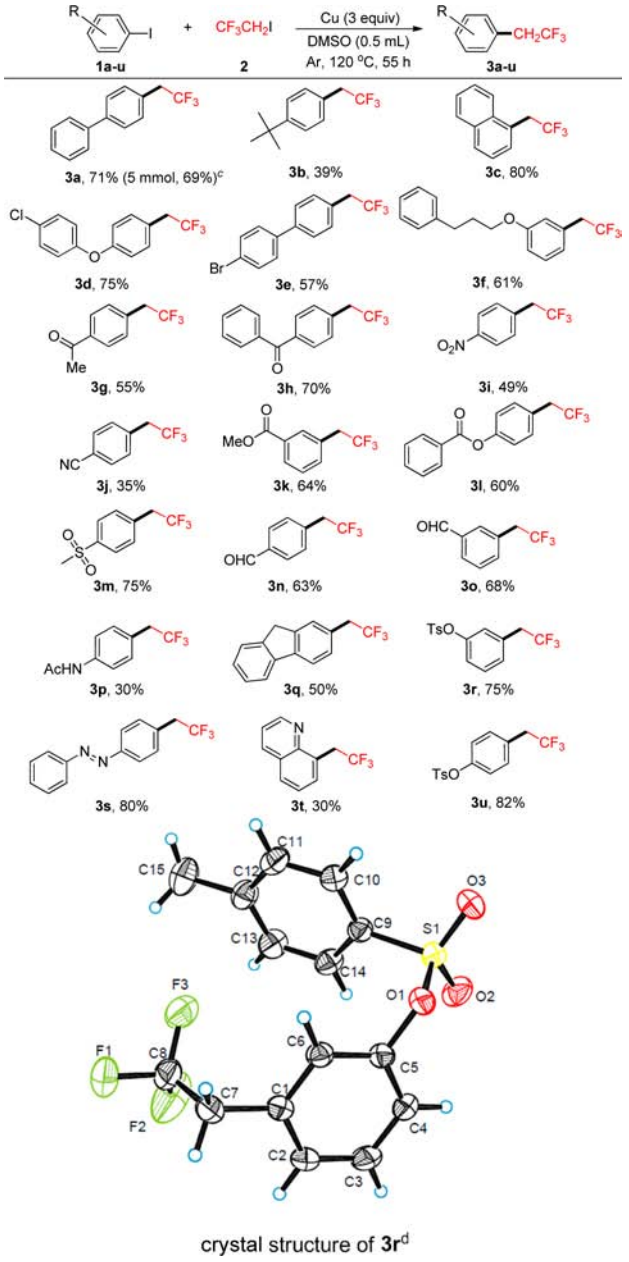
entry	copper (equiv)	temp (°C)	time (h)	solvent	yield (%)[b]
1	3	120	24	DMF	trace
2	3	120	24	DME	NR
3	3	120	24	mesitylene	NR
4	3	120	24	sulfolane	NR
5	3	120	24	water	NR
6	3	120	24	NMP	trace
7	3	120	24	DMI	trace
8	3	120	24	EG	trace
9	3	120	24	HMPA	18
10	3	120	24	DMAC	26
11	3	120	24	DMSO	43
12	3	140	24	DMSO	40
13	3	100	24	DMSO	23
14	3	80	24	DMSO	trace
15	1	120	24	DMSO	18
16	2	120	24	DMSO	38
17	4	120	24	DMSO	42
18	3	120	36	DMSO	58
19	3	120	48	DMSO	69
20	3	120	55	DMSO	73
21	3	120	60	DMSO	73
22[c]	3	120	55	DMSO	78
23[d]	3	120	55	DMSO	27
24[e]	3	120	55	DMSO	40

[a]Unless otherwise stated, the reaction was conducted with **I** (0.25 mmol), CF_3CH_2I (4 equiv), copper powder **b** (3 equiv), anhydrous DMSO (0.5 mL) under Ar, 120 °C, 55 h. [b]Yield determined by GC. [c]Copper powder **a**. [d]Copper powder **c**. [e]Copper powder **d**. DMF = dimethylformamide, DME = dimethyl ether, NMP = 1-methyl-2-pyrrolidinone, DMI = *N*,*N*′-dimethylethyleneurea, EG = ethylene glycol, HMPA = hexamethylphosphoramide, DMAC = *N*,*N*-dimethylacetamide, DMSO = dimethyl sulfoxide.

series of solvents, such as DME, mesitylene, sulfolane, water, NMP, DMI, EG, HMPA, DMAC, and DMSO, were screened. DMSO was found to be the most effective solvent, while the others were not as effective (Table 1, entries 2−11). Next we studied the reaction by varying the reaction temperature. Unfortunately, the reaction was not significantly improved (Table 1, entries 12−14). Furthermore, the yield decreased when the copper powder was reduced or increased (Table 1, entries 15−17). To further improve the reaction outcome, the reaction time was extended. Gratifyingly, the desired product was obtained in 73% yield in 55 h (Table 1, entries 18−21). Finally, under the present conditions, we investigated the influence of particle size of the copper powder on the reaction. Interestingly, the yield increased to 78% when copper powder **a** (100 mesh, Figure 1a) was used. Unexpectedly, only 27% and 40% yields were obtained when copper powders **c** (625 mesh, Figure 1c) and **d** (prepared from copper sulfate,[8] Figure 1d) were used. We identified the sediments of the reactions (entries 22−23) at 36 h by X-ray diffraction (XRD). According to these results, the sediments of reaction using copper powder **a** (entry 22) remain as a large amount of CuI, CuO, and unreacted copper powder, but the sediments of reaction using copper powder **c** (entry 23) only remain as CuI and CuO (see Supporting Information). These findings indicate that copper powder with a smaller particle size may be oxidated or undergo side reactions easily during the course of a reaction because of its activity. These competitive side reactions will influence the yield of the reaction due to its slower reaction rate. The above results showed that copper powder with a bigger particle size promoted the reaction effectively. Additionally, we found the aryl iodides were easily protonated even though the reaction was carried out as anhydrous as possible.

With the optimized reaction conditions in hand, we examined the scope of the reaction in order to establish the generality of the protocol. As shown in Table 2, many

Table 2. Screening Scope of Substrates[a,b]



crystal structure of **3r**[d]

[a]Reaction conditions: **1** (0.25 mmol), **2** (4 equiv), copper powder **a** (3 equiv) in DMSO (0.5 mL) at 120 °C under an argon atmosphere for 55 h. [b]Isolated yields on **1**. [c]Reaction conditions in parentheses: **1** (5 mmol) in DMSO (2 mL) at 120 °C under argon atmosphere for 55 h. [d]The X-ray crystal structure of **3r** is shown with the thermal ellipsoids set at 35% probability.

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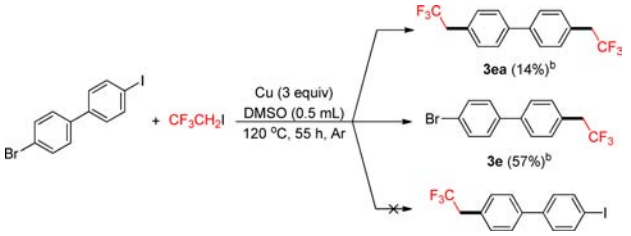
synthetically important functional groups including ether (**1d**, **1f**), carbonyl (**1g**−**1h**), ester (**1k**−**1l**, **1r**, **1u**), cyano (**1j**), aldehyde (**1n**−**1o**), and fluorene (**1q**) groups were well tolerated in the transformation. Moreover, both electron-donating (**1a**−**1f**) and electron-withdrawing (**1g**−**1m**) aryl iodides were trifluoroethylated smoothly to give the corresponding products in 35−82% yields. Significantly, the leaving group containing compounds (**3r**, **3u**) exhibited very good reactivity to afford the products in good yields (75−82%). To our delight, the reaction conditions were also compatible with the azobenzene dye (**3s**) that could be readily reduced under the alkaline conditions.[9] However, the presence of acetamide (**3p**) and quinoline (**3t**) groups lead to low yields (30%). Unfortunately, the ortho-substituted aryl iodides were not suitable for the reaction due to the steric effect.

We subjected 4-bromo-4′-iodo-1,1′-biphenyl to selective reductive coupling at the C−I site under the optimal conditions (Scheme 2). As expected, an iodo group reacted in preference

Scheme 2. Site-Selective Reductive Coupling[a]

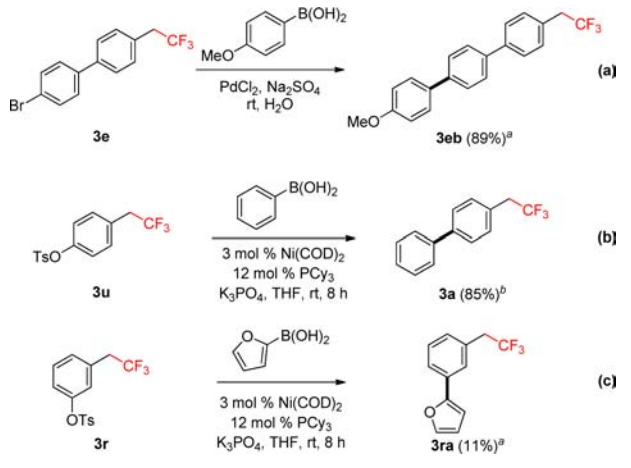


[a]Reaction conditions: 4-bromo-4′-iodo-1,1′-biphenyl (0.25 mmol), CF_3CH_2I (1 mmol), copper powder **a** (0.75 mmol). [b] Isolated yield.

to a bromo group, providing the 4-bromo-4′-(2,2,2-trifluoroethyl)-1,1′-biphenyl in moderate yield (**3e**) and the 4,4′-bis(2,2,2-trifluoroethyl)-1,1′-biphenyl (**3ea**) in only 14%. This chemoselectivity enabled the design of sequential coupling reactions on the aromatic ring.

Note that a series of (2,2,2-trifluoroethyl)arenes were obtained with a leaving group in Table 2 that may be further functionalized through cross-coupling. Cu-promoted reductive couping at the C−I site of 4-bromo-4′-iodo-1,1′-biphenyl was followed by palladium-catalyzed cross-coupling at the C−Br site (Scheme 3a).[10] Next, phenyl and furyl were successfully

Scheme 3. Further Functionalization of Some Products

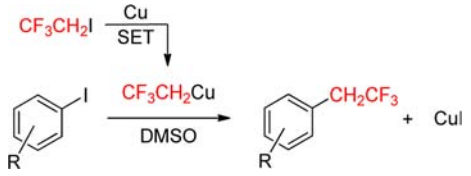


[a]Isolated yield. [b] GC yield.

introduced to (2,2,2-trifluoroethyl)arenes at the C-OTs site of 4-(2,2,2-trifluoroethyl)phenyl 4-methylbenzenesulfonate (Scheme 3b) and 3-(2,2,2-trifluoroethyl)phenyl 4-methylbenzene-sulfonate (Scheme 3c) through sequential transition-metal-catalyzed cross-coupling reactions.[11] Thus, it provides a practical method for the preparation of complex target molecules carrying (2,2,2-trifluoroethyl)phenyl.

Finally, to gain more insight into the mechanism of this reaction, a radical scavenger, (2,2,6,6-tetramethyl-piperidin-1-yl)oxidanyl (TEMPO) was added to the reaction and only a trace amount of product was detected. When another radical trapping agent, 1,1-diphenylethylene, was used, only a 29% yield was obtained. So the reaction may follow a radical and single electron transfer (SET) mechanism as has been reported for similar reactions.[12] As previously mentioned, the copper particles translate into CuI after a successful reaction. So we deduced the reaction may proceed through the mechanism shown in Scheme 4. In the metalation stage, copper-mediated

Scheme 4. Proposed Mechanism



SET in CF_3CH_2I produces the CF_3CH_2 radical, which then reacts with copper to generate CF_3CH_2Cu. In the second stage, CF_3CH_2Cu reacts with aromatic iodide to give the desired product.

In conclusion, the copper powder with a bigger particle size was found to promote the reductive-coupling reaction of aryl iodides with CF_3CH_2I efficiently. Due to the neutral conditions employed, the reaction tolerated numerous sensitive functional groups. We believed that this protocol is useful for the trifluoroethylation of arene.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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