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Copper-Mediated Fluoroalkylation of Aryl Iodides Enables Facile Access to Diverse Fluorinated Compounds: The Important Role of the (2-Pyridyl)sulfonyl Group

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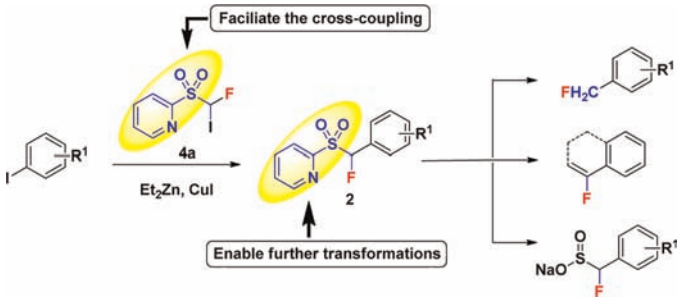
ABSTRACT



The (2-pyridyl)sulfonyl group was found to be a multifunctional group in the preparation of structurally diverse fluorinated products. It not only facilitates the copper-mediated (or catalyzed) cross-coupling reaction between α-fluoro sulfone 4a and aryl iodides, but also enables further transformations of the coupling products 2.

Fluorinated organic compounds have received increasing attention during the past years because of their indispensable role in the progress of various fields. This is largely due to the beneficial changes that fluorine imparts to organic molecules.[1] As aryl−fluoroalkyl linkages are widely found in pharmaceuticals, fluoroalkylated aromatics are of intense synthetic interest,[2] and in this context, copper-mediated (or catalyzed) processes are generally employed to prepare fluoroalkylated aromatics. It is now possible to efficiently install trifluoromethyl (CF_3), difluoromethyl (CF_2H), and functionalized difluoromethyl groups [CF_2X, X = C(O)R, P(O)$(OEt)_2$] onto aromatic rings via copper-mediated (or catalyzed) fluoroalkylations.[3] However, the introduction of a fluoromethyl (CH_2F) or functionalized fluoromethyl (CFR^1R^2) group by copper-mediated process remains an interesting challenge possibly due to the decreased stability of the corresponding organocopper species. The only example of copper-mediated monofluoroalkylation of aryl iodides was reported by Burton and co-workers in 1999 using [$(EtO)_2$P(O)CHFBr], while the yield was strongly dependent on the electronic nature of the substrates.[4] Therefore, it is highly desired to develop a new

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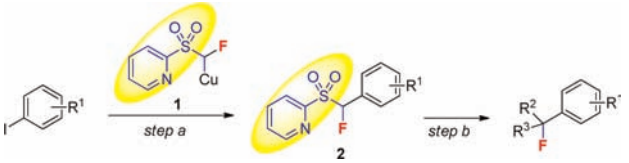
protocol for the copper-mediated fluoroalkylation of aryl iodides to introduce a fluoromethyl or functionalized fluoromethyl group in terms of both synthetic and mechanistic aspects.[5]

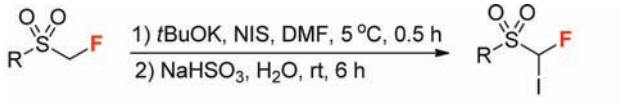
We envisioned that the stability and/or reactivity of (monofluoroalkyl)copper intermediates could be tuned by introducing an intramolecular coordinating group, as organocuprates bearing a neighboring *N*-atom were reported to react with a variety of electrophiles efficiently.[6] Based on our experience on the nucleophilic fluoroalkylation and olefination with fluoroalkyl 2-pyridyl sulfones,[7] we assumed that [(2-pyridyl)sulfonyl]fluoromethylcopper species (**1**) could serve as a good monofluoroalkylating agent to react with aryl iodides, since the (2-pyridyl)-sulfonyl group may act as an intramolecular ligand by coordinating to copper catalyst with its nitrogen atom (Scheme 1, step a). Furthermore, given the versatile chemical behaviors of the fluoroalkyl 2-pyridyl sulfones in fluoroalkylations and fluoroolefinations,[7] the copper-mediated coupling products **2** could be further transformed into structurally diverse monofluorinated organic compounds (Scheme 1, step b).

Scheme 1. Copper-Mediated Monofluoroalkylation Assisted by the Multifunctional (2-Pyridyl)sulfonyl Group



At the onset of our investigation, we speculated that the reactive species [2-PySO$_2$CHFCu] used in the cross-coupling reaction with aryl iodides could be prepared by a transmetalation between CuI and [2-PySO$_2$CHF]ZnX, and the latter species could be furnished by metal−halide exchange between the corresponding iodide (2-PySO$_2$CHFI) (**4a**) and Et$_2$Zn under mild conditions.[8] Furthermore, other structurally similar compounds RSO$_2$CHFCI (R ≠ 2-Py) species were also prepared and used to examine their reactivity in the copper-mediated monofluoroalkylation (Scheme 2).

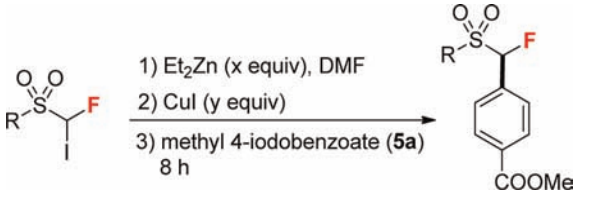
Scheme 2. Synthesis of Different Fluoroiodomethyl Sulfones **4**



3a, R = 2-Py (2-pyridyl) — **4a**, R = 2-Py, 72%
3b, R = Ph (Phenyl) — **4b**, R = Ph, 74%
3c, R = BT (1,3-benzothiazol-2-yl) — **4c**, R = BT, 70%
3d, R = TBT (1-*tert*-butyl-1H-tetrazol-5-yl) — **4d**, R = TBT, 75%

With a series of different fluoroiodomethyl sulfones **4a**−**d** in hand, we first examined their reactivity in the Cu(I)-mediated cross-coupling reaction using methyl 4-iodobenzoate (**5a**) as a model substrate. Et$_2$Zn was added to a solution of fluoroiodomethyl sulfone (**4a**−**d**) in DMF at room temperature, and CuI and **5a** were added subsequently. The results are illustrated in Table 1. It was found that sulfone **4b** bearing a phenyl moiety displayed low reactivity under the current reaction conditions (Table 1, entry 1), and the product yield was

Table 1. Survey of Reaction Conditions[a]



entry	R	x	y	ligand	yield[f] (%)
1	Ph	1.2	2.0		34
2[b]	Ph	1.2	2.0	phen	23
3	2-Py	1.2	2.0		90
4	BT	1.2	2.0		trace
5	TBT	1.2	2.0		trace
6	2-Py	2.0	2.0		87
7[c]	2-Py	1.2	2.0		>95 (92)
8	2-Py	1.2	0.2		48
9[d]	2-Py	1.2	0.3		80
10[d,e]	2-Py	1.2	0.3		90 (80)

[a] Unless otherwise stated, the reactions were run on a 0.25 mmol scale in DMF (3 mL) at rt. [b] 1,10-Phenanthroline (20%) was added as a ligand. [c] [2-PySO$_2$CFHCu] species was prepared at −15 °C. [d] The reaction was heated to 60 °C after **5a** was added. [e] NMP was used as a solvent instead of DMF. [f] Yield of coupling product based on the amount of **5a**, which was determined by ^{19}F NMR spectroscopy using PhCF$_3$ as an internal standard; data in parentheses refers to the yield of isolated coupling product.

similar to that for the reported monofluoroalkylation with [(EtO)$_2$P(O)CHFCu].[4] It is surprising that the reactions with nitrogen-containing heteroaryl sulfones **4c** and **4d** (with BT and TBT groups substituted at sulfur atom, respectively) only gave a trace amount of the corresponding products (Table 1, entries 4 and 5). The addition of 1,10-phenanthroline, which was shown to be very effective in promoting the copper-catalyzed trifluoromethylation,[3] did not improve the yield (Table 1, entry 2). To our delight, the reaction employing 2-pyridyl sulfone (**4a**) gave much better results (entries 3 and 6−10). The coordination of the

(5) Although palladium-catalyzed monofluoroalkylation of aryl halides (or boronic acids) with α-fluoro ketones (or enolates) and esters are known, further transformations of the corresponding monofluorinated products are limited. See: (a) Guo, C.; Wang, R.-W.; Guo, Y.; Qing, F.-L. *J. Fluorine Chem.* **2012**, *133*, 86. (b) Guo, C.; Yue, X.; Qing, F.-L. *Synthesis* **2010**, 1837. (c) Guo, Y.; Twamley, B.; Shreeve, J. M. *Org. Biol. Chem.* **2009**, *7*, 1716. (d) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.

(6) Dieter, R. K. N-Functionalized Organocuprates. In *The Chemistry of Organocopper Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2009 and references cited therein.

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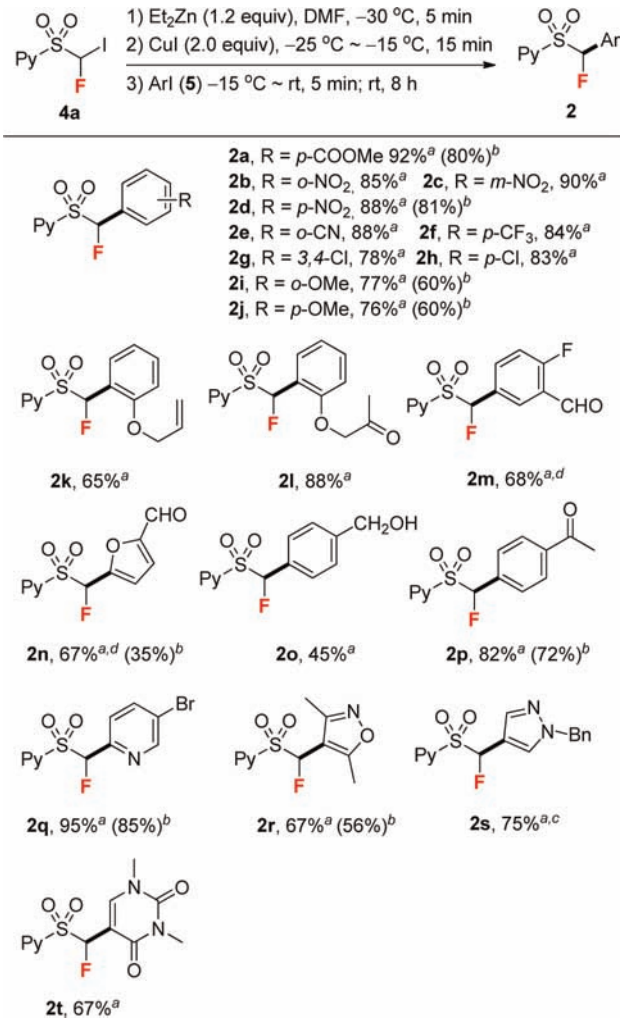
neighboring 2-pyridyl group to a metal catalyst is extensively involved in transition-metal-catalyzed reactions.[9] Although the exact role of the 2-pyridyl group in the current reaction has not been fully elucidated at the current stage, we believe that it could accelerate the rate of transmetalation between $[RSO_2CHF]ZnX$ species and CuI, and enhance the reactivity of $[RSO_2CHFCu]$ species by electron-donation from nitrogen to copper. It should be mentioned that only 0.3 mmol of Et_2Zn was needed for the full conversion of 0.5 mmol of 2-$PySO_2CFIH$ in the current reaction, which suggests that $[2\text{-}PySO_2CHF]_2Zn$ (rather than $[2\text{-}PySO_2CHF]ZnEt$) is probably involved in the current reaction. Furthermore, it was found that generation of $[2\text{-}PySO_2CHFCu]$[10] species at low temperature (−15 °C) further improved the yield, and we could isolate the product **2a** in 92% yield under the optimized reaction conditions (Table 1, entry 7). Moreover, the reaction could also proceed smoothly with *catalytic* amount of CuI (30%) at elevated temperature (60 °C) without significant loss of the product yield (Table 1, entry 10). It should be noted that no ligand is needed in our catalytic reaction, which is different from the recently developed copper-catalyzed fluoroalkylations in the presence of catalytic amount of copper.[3a,g,i] This result suggests the (2-pyridyl)sulfonyl group may serve as an "intramolecular ligand" in the current reaction.

Considering the low cost of CuI and mild reaction conditions when employing a stoichiometric amount of copper, we first examined the substrate scope of the copper-mediated cross-coupling reaction between 2-$PySO_2CFHI$ **4a** and aryl iodides **5** by using reaction conditions as described in Table 1, entry 7 as standard (reactant ratio **4a**:**5** = 2:1). As shown in Scheme 3, the reactions with iodoarenes containing either electron-withdrawing [including ester (**5a**), nitro (**5b**−**5d**), cyano (**5e**)] or electro-donating groups [including methoxyl (**5i** and **5j**)] afforded the desired products in 76−92% yields. The reaction tolerates several reactive functionalities, such as hydroxyl (**5o**), aldehydes (**5m** and **5n**), and ketones (**5l** and **5p**). Bromo- and chloro-substituted iodoarenes (**5g**, **5h**, and **5q**) reacted selectively at the aryl−I bond. It should be mentioned that, in the reaction with 2-(allyloxy)iodobenzene (**5k**), no cyclized product 3-methyl-2,3-dihydrobenzofuran was observed. This result suggests that the involvement of aryl radicals (possibly generated from cleavage of C−I bond) in the current copper-mediated cross-coupling reaction with **4a** is unlikely. Moreover, the *catalytic version* of this reaction (as those for Table 1, entry 10)

Scheme 3. Copper-Mediated or -Catalyzed Fluoromethylation of Aryl Iodides[a]



[a] Copper-mediated process: **4a** (0.5 mmol), ArI **5** (0.25 mmol), CuI (0.5 mmol), Et_2Zn (0.3 mmol) in DMF (3 mL) at rt for 8 h, isolated yield is reported. [b] Copper-catalyzed process: **4a** (0.5 mmol), ArI **5** (0.25 mmol), CuI (0.075 mmol), Et_2Zn (0.3 mmol) in NMP (3 mL) at 60 °C for 8 h, isolated yield is reported. [c] The reaction was heated to 60 °C. [d] CuI (0.65 mmol) was employed in the reaction.

also proceeded smoothly to give the products in satisfactory yields (**5a**,**d**,**i**,**j**,**n**,**p**−**r**). It is striking that even the acetyl (**5p**) and formyl group (**5n**) are tolerated in the current copper-catalyzed reaction.

Taking advantage of the versatile chemical behavior of the 2-pyridylsulfonyl group, the present copper-mediated fluoroalkylation with **4a** was further used to prepare a variety of structurally diverse and potentially useful fluorinated compounds (as shown in Scheme 4).[7] Biologically active 3-fluoromethyl-3-deoxylestrone (**7**) was obtained with satisfactory yield in two steps from the corresponding iodide (**6**) by our CuI-mediated cross-coupling with 2-$PySO_2CHFI$ and subsequent desulfonylation with

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(10) The "copper reagent" exhibited a broad ^{19}F NMR signal at −216 ppm, and the signal gradually decreased after aryl iodide was added.

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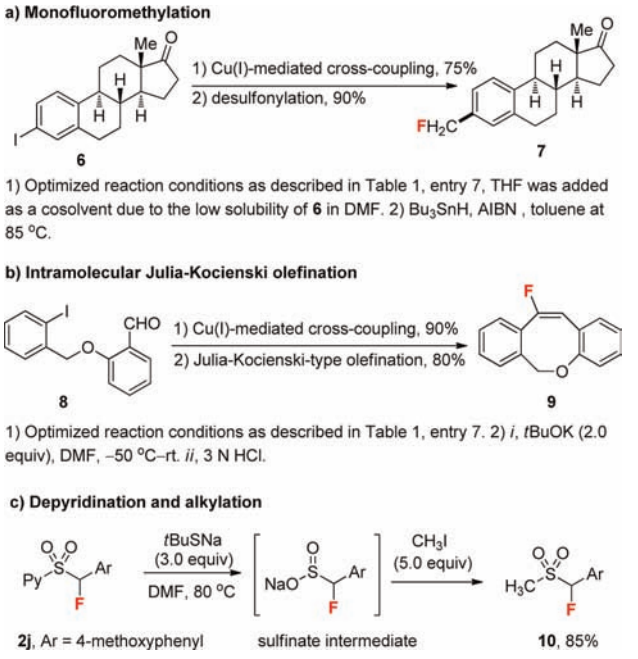
Scheme 4. Synthetic Application of the Products of the Copper-Mediated Cross-Coupling Reactions



Bu_3SnH and AIBN (Scheme 4, a).[11] The method thus enabled a quick access to fluoromethylarenes from the corresponding iodoarenes. Moreover, Julia–Kocienski olefination is generally employed to stereoselectively construct alkenes; however, for designing an intramolecular version of Julia–Kocienski olefination, the introduction of the heterosulfone functional group often suffers from multistep procedures and poor functional group tolerance.[12] In our case, direct introduction of the (2-pyridylsulfonyl)fluoromethyl group in the presence of the formyl group smoothly gave the precursor of an *intramolecular* Julia–Kocienski olefination. Simple treatment of the product with *t*-BuOK in DMF furnished the desired monofluoroalkene with an eight-member ring in 80% yield (Scheme 4, b).[7a] Moreover, the fluorinated sulfinates are important precursors for fluorinated sulfonic acids and fluorinated sulfones, which found wide application in modern functional materials and biologically active compounds.[13] Monofluorinated sulfinate could be easily generated by a *t*-BuSNa-mediated depyridination and could be trapped in situ with CH_3I to furnish the corresponding methyl sulfone (**10**) in 85% yield (Scheme 4, c).[7c]

In conclusion, a copper-mediated monofluoroalkylation of aryl iodides has been successfully developed using fluoroiodomethyl 2-pyridyl sulfone **4a**. With this method, a wide range of aryl iodides bearing various functional groups were efficiently converted into the desired monofluoroalkylated products employing either stoichiometric or catalytic amount of copper. The method is amenable to the late-stage fluoromethylation of biologically active molecules (as demonstrated in Scheme 4, a). Not only does the presence of the (2-pyridyl)sulfonyl group play a crucial role in the copper-mediated cross-coupling reaction, it also facilitates further transformations of the obtained products, such as desulfonylation, intramolecular Julia–Kocienski olefination, and depyridination.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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