JOC Article
pubs.acs.org/joc

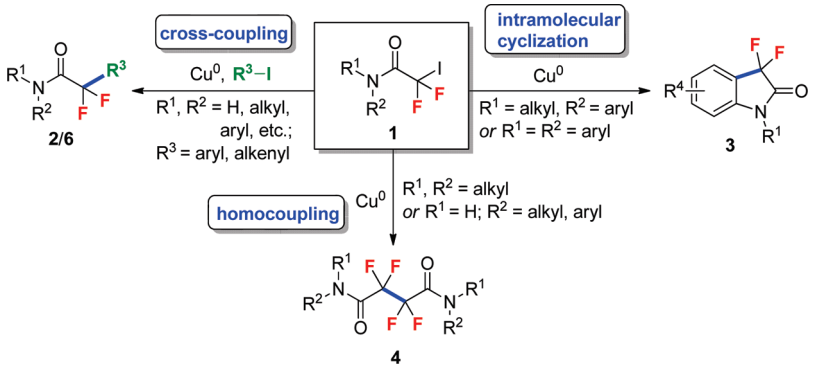
Copper-Mediated Fluoroalkylation Reactions with Iododifluoroacetamides: Controlling the Selectivity among Cross-Coupling, Intramolecular Cyclization, and Homocoupling Reactions

Jieming Zhu, Wei Zhang, Laijun Zhang, Jun Liu, Ji Zheng, and Jinbo Hu*

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

jinbohu@sioc.ac.cn

Received March 23, 2010



Cu-mediated fluoroalkylation reactions with iododifluoroacetamides **1** have been systematically investigated. It was found that three types of reactions may coexist in Cu-mediated reactions between iododifluoroacetamides and aryl/alkenyl iodides: cross-coupling, intramolecular cyclization, and homocoupling reactions. The selectivity among these three types of reactions could be controlled by tuning the substituents on the nitrogen atom of iododifluoroacetamides, and/or by removing the cross-coupling reaction partner (aryl/alkenyl halides). The general rule is as follows: (a) in the presence of proper aryl/alkenyl iodides, the cross-coupling products **2** (or **6**) are generally formed as the major products; (b) in the absence of aryl/alkenyl iodides, and when R^1 = alkyl and R^2 = aryl groups, or when R^1 = R^2 = aryl groups, the intramolecular cyclization products **3** can be formed predominantly; and (c) in the absence of aryl/alkenyl iodides, and when $R^1 = R^2$ = alkyl groups, or when R^1 = H and R^2 = alkyl, aryl groups, the homocoupling products **4** can be formed dominantly. Our experimental results also indicate that in many cases when cross-coupling, homocoupling, and intramolecular cyclization reactions coexist in the Cu-mediated reaction system, the reactivity decreases in the following order: cross-coupling > intramolecular cyclization > homocoupling.

Introduction

Selective fluoroalkylation, such as tri-, di-, monofluoromethylation, and perfluoroalkylation, typically involving the transfer of a fluorinated alkyl group R_f (the reaction usually occurred on the fluorine-substituted carbon atom of R_f) to a substrate, has become one of the most important and widely used methods to synthesize fluorinated organic

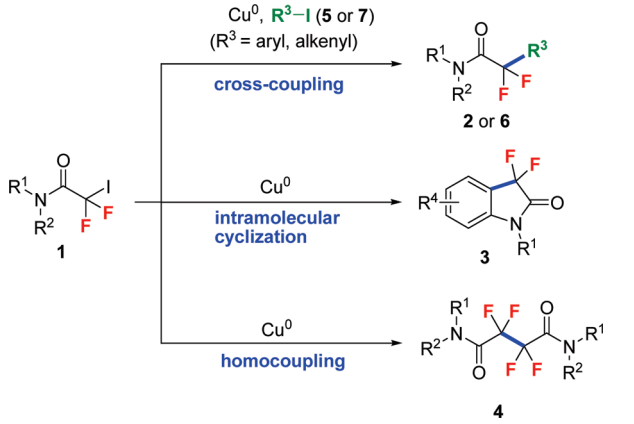
(1) (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2008. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. (c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2004. (d) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, U.K., 2004. (e) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000.

(2) For reviews on nucleophilic fluoroalkylations, see: (a) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921–930. (b) Prakash, G. K. S.; Hu, J. New Nucleophilic Fluoroalkylation Chemistry. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, DC, 2005. (c) Prakash, G. K. S.; Chacko, S. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 793–802. (d) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123–131. (e) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786. (f) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632. (g) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185–194. (h) Médebielle, M.; Dolbier, W. R., Jr. *J. Fluorine Chem.* **2008**, *129*, 930–942. (i) Uno, H.; Suzukib, H. *Synlett* **1993**, 91–96. (j) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666.

DOI: 10.1021/jo1005262 Published on Web 07/21/2010

compounds.[1] Fluoroalkylation reactions are commonly divided into nucleophilic, electrophilic, and free radical fluoroalkylations, and a variety of fluoroalkylating reagents have been developed over the past three decades.[1−7] However, most fluoroalkylation methods are limited in the construction of sp^3 C−R_f bonds and not capable to facilitate the efficient formation of sp^2 C−R_f bonds. Although the transition metal-catalyzed C−C cross-coupling reaction between organometallic reagents and aryl (or alkenyl) halides are well-developed,[8] the similar type of fluoroalkyl cross-coupling (sp^2 C−R_f bond formation) reactions are much less explored.[9−13] Currently, the most widely used synthetic method for the construction of sp^2 C−R_f bonds is the cross-coupling reaction between fluoroalkyl iodides (R_fI) and aryl (or alkenyl) halides in the presence of a stoichiometric amount of copper powder, which was discovered in the late 1960s.[14−16] This copper-mediated fluoroalkyl cross-coupling reaction was believed to be involving a "R_f−Cu" species,[17] and several modified Cu-mediated sp^2 C−R_f bond formation reactions have been developed.[16,18]

SCHEME 1. Three Types of Reactions Involving Iododifluoroacetamides 1



It should be noted that, although Cu-mediated trifluoromethylation and other perfluoroalkylations of aryl (or alkenyl) halides are well documented,[16] the corresponding difluoromethylation involving a "RCF_2−Cu" intermediate was less studied, with the only two examples being alkoxycarbonyldifluoromethylation[19] and (diethoxyphosphinyl)-difluoromethylation with XCF_2COOR and $XCF_2P(O)(OR)_2$ reagents (X = I and Br).[20] Recently, as our continuing effort in developing selective difluoromethylation methodologies,[2a,7] we embarked on the previously unknown Cu-mediated cross-coupling reaction between iododifluoroacetamides **1** and aryl (and alkenyl) halides. It was found that, unlike previously known alkoxycarbonyldifluoromethylation[19] and (diethoxyphosphinyl)difluoromethylation,[20] the reaction with an iododifluoroacetamide **1** could give three types of products: cross-coupling product **2**, intramolecular cyclization product **3**, and homocoupling product **4** (Scheme 1). More importantly, the selectivity among these three products could be controlled by tuning the substituents on the nitrogen atom of compound **1**, which makes the reaction practically useful for the synthesis of *gem*-difluorinated compounds **2**−**4**.

Results and Discussion

1. Cross-Coupling Reaction between Iododifluoroacetamides (1) and Aryl/Alkenyl Halides. Iododifluoroacetamides **1** were prepared according to Huang's procedure.[21] First, we examined the Cu-mediated cross-coupling reaction under different conditions, using *N*,*N*-diethyl iododifluoroacetamide (**1a**) and 1-iodo-4-nitrobenzene (**5a**) as model substrates (Table 1). It turned out that the product yield was sensitive

(3) For reviews on electrophilic fluoroalkylations, see: (a) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777. (b) Umemoto, T. Recent Advances in Perfluoroalkylation Methodology. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, DC, 2005. (c) Kieltsch, I.; Eisenberger, P.; Stanek, K.; Togni, A. *Chimia* **2008**, *62*, 260–263.

(4) For review on chemistry of fluoroalkyl radicals, see: Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *66*, 1557–1584.

(5) For recent examples of radical fluoroalkylations, see: (a) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98–105. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877. (c) Shustova, N. B.; Popov, A. A.; Mackey, M. A.; Coumbe, C. E.; Phillips, J. P.; Stevenson, S.; Strauss, S. H.; Boltalina, O. V. *J. Am. Chem. Soc.* **2007**, *129*, 11676–11677. (d) Antonietti, F.; Gambarotti, C.; Mele, A.; Minisci, F.; Paganelli, R.; Punta, C.; Recupero, F. *Eur. J. Org. Chem.* **2005**, 4434–4440. (e) Antonietti, F.; Mele, A.; Minisci, F.; Punta, C.; Recupero, F.; Fontana, F. *J. Fluorine Chem.* **2004**, *125*, 205–211. (f) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489–2492. (g) Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. *J. Org. Chem.* **2007**, *72*, 5824–5877. (h) Jin, L.-M.; Chen, L.; Yin, J.-J.; Guo, C.-C.; Chen, Q.-Y. *J. Fluorine Chem.* **2005**, *126*, 1321–1326. (i) Jin, L.-M.; Chen, L.; Guo, C.-C.; Chen, Q.-Y. *J. Porphyrins Phthalocyanines* **2005**, *9*, 109–120.

(6) (a) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633–2644. (b) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996. (c) Prakash, G. K. S.; Hu, J. Trihalomethyl Compounds. In *Science of Synthesis*; Charette, A. B., Ed.; Thieme: New York, 2005; Vol. 22. (d) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146.

(7) For reviews on difluoromethylation and monofluoromethylation, see: (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465–7478. (b) Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130–1139.

(8) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(9) Copper-catalyzed Aryl−R_f coupling reaction: Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909–1911.

(10) Palladium-catalyzed Aryl−R_f coupling reaction: (a) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 137–140. (b) Guo, Y.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583–3585. (c) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679–1681.

(11) (a) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600–8601. (b) Dubinina, G. G.; Ogikubo, J.; Vicic, D. A. *Organometallics* **2008**, *27*, 6233–6235. (c) Dubnina, G. G.; Brennessel, W. W.; Miller, J. L.; Vicic, D. A. *Organometallics* **2008**, *27*, 3933–3938.

(12) (a) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 12644–12645. (b) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 4632–4641. (c) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398–3416. (d) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878–2879.

(13) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160–171.

(14) (a) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921–5940. (b) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, *10*, 4095–4096.

(15) Burton, D. J.; Lu, L. Fluorinated Organofluorine Compounds. In *Organofluorine Chemistry, Techniques and Synthons*; Chambers, R. D., Ed.; Springer: New York, 1997.

(16) For a review on fluoroalkyl organometallic compounds, see: Burton, D. J.; Yang, Z.-Y. *Tetrahedron* **1992**, *48*, 189–275.

(17) (a) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832–834. (b) Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1633–1634.

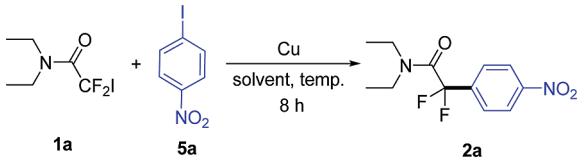
(18) (a) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014–5015. (b) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Chem. Commun.* **1989**, 705–706. (c) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2385–2387. (d) MacNeil, J. G., Jr.; Burton, D. J. *J. Fluorine Chem.* **1991**, *55*, 225–227. (e) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91–94. (f) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 327–330. (g) References 9, 11, and 17.

(19) (a) Taguchi, T.; Kitagawa, O.; Morikawa., T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 6103–6106. (b) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2004**, *125*, 509–515.

(20) (a) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. *J. Org. Chem.* **1996**, *61*, 7207–7211. (b) Yokomatsu, T.; Murano, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1997**, *53*, 815–822.

(21) (a) Zhang, Y. F.; Lu, L.; Huang, W. Y. *Youji Huaxue* **1989**, *9*, 441–444. (b) Huang, W.-Y.; Lu, L.; Zhang, Y.-F. *Chin. J. Chem.* **1990**, 68–74. (c) Hung, M.-H.; Lu, L.; Yang, Z.-Y. *J. Org. Chem.* **2004**, *69*, 198–201.

TABLE 1. Survey of Cross-Coupling Reaction Conditions



entry	solvent	temp (°C)	molar ratio (**1a**: **5a**: Cu)	yield (%)[a]
1	DMSO	50	1:1:2	51
2	DMF	50	1:1:2	0
3	CH_3CN	50	1:1:2	31
4	HMPA	50	1:1:2	0
5[b]	DMSO	50	1:1:2	17
6[c]	DMSO	50	1:1:2	53
7	DMSO	30	1:1:2	0
8	DMSO	70	1:1:2	40
9	DMSO	50	1.5:1:3	59
10	DMSO	50	1.5:1:1.5	30
11	DMSO	50	1.5:1:4.5	62
12	DMSO	50	1.5:1:6	70

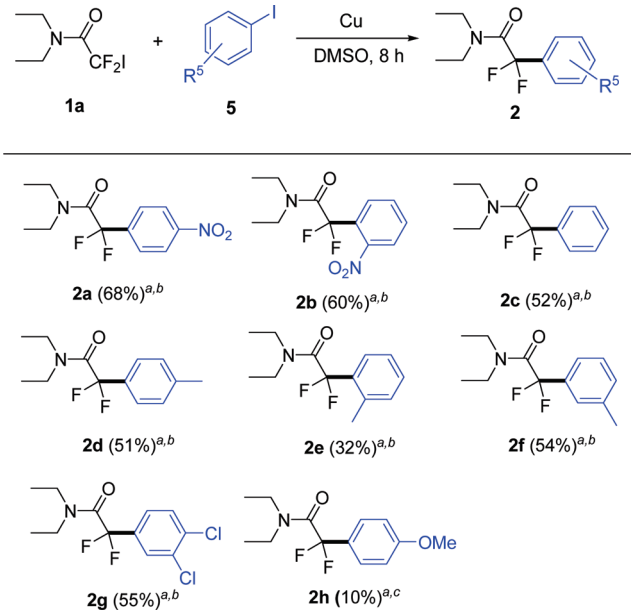
[a]Determined by ^{19}F NMR by using $PhCF_3$ as internal standard. [b]The reaction time was 5 h. [c]The reaction time was 10 h.

to the reaction parameters such as solvent, reaction time, temperature, and reactant ratio. The reaction could proceed in both DMSO and CH_3CN, while it provided better yield of product in DMSO (Table 1, entries 1 and 3). However, the cross-coupling reaction did not occur in solvents such as DMF and HMPA (entries 2 and 4), both of which are commonly used in other Cu-mediated perfluoroalkyl cross-coupling reactions.[16,18] We found that the proper reaction time was 8 h, and prolonged reaction time did not significantly improve the product yield (compare entries 1, 5, and 6). Furthermore, both low temperature (30 °C) and high temperature (70 °C) led to either no or low product yield (entries 7 and 8), and the medium temperature (50 °C) was chosen as the optimal reaction temperature. Finally, after a quick scanning of the reactant ratio, an optimal yield of **2a** (70%) was obtained when the reaction proceeded in DMSO at 50 °C for 8 h with a molar ratio **1a**:**5a**:Cu = 1.5:1:6 (entry 12).

By choosing the above reaction condition (Table 1, entry 12) as a standard, we next investigated the scope of the cross-coupling reaction with **1a**. As showed in Table 2, a variety of structurally diverse aryl iodides **5** were able to react with **1a** to give the corresponding fluoroalkylated products **2a**−**h**. It was found that the electronic nature of the R^5 group in aryl iodides **5** remarkably affects the product yield, and generally the reactions with electron-poor aryl iodides gave better yields than those with electron-rich ones (Table 2). Next, we further examined the Cu-mediated crossing-coupling reactions between **1a** and various alkenyl iodides **7** (Table 3). To our delight, the reactions with alkenyl iodides generally gave higher yields than those with aryl iodides (compare Tables 2 and 3), and products **6** were obtained with the retention of *Z*/*E* configuration of the alkene functionality. Both electronic and steric natures of alkenyl iodides did not significantly influence the product yields.

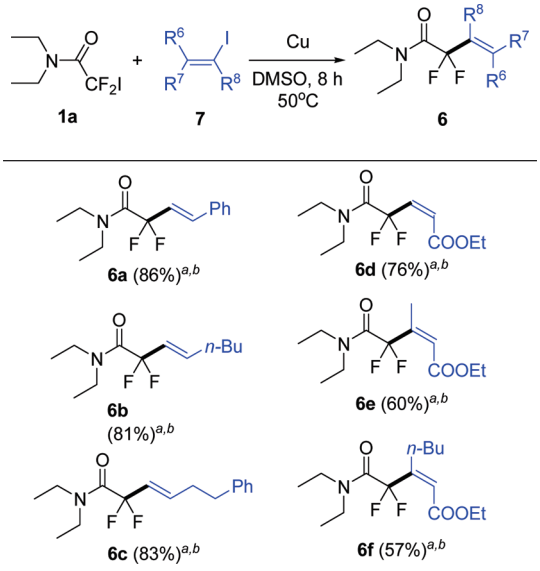
To gain insights into the structure−reactivity relationship of iododifluoroacetamides **1**, we prepared structurally diverse iododifluoroacetamides **1** (with different substituents R^1, R^2 on the nitrogen atom), and applied them in the Cu-mediated cross-coupling reaction with 1-iodo-4-nitrobenzene

TABLE 2. Cross-Coupling of 1a and Aryl Iodides



[a]All the reactions were performed with 0.5 mmol of aryl iodide, 0.75 mmol of **1a**, and 3.0 mmol of Cu in 2.0 mL of DMSO at 50 °C for 8 h. [b]Isolated yield. [c]Determined by ^{19}F NMR with $PhCF_3$ as internal standard.

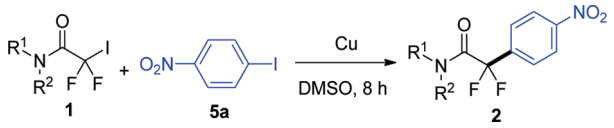
TABLE 3. Cross-Coupling of 1a and Alkenyl Iodides

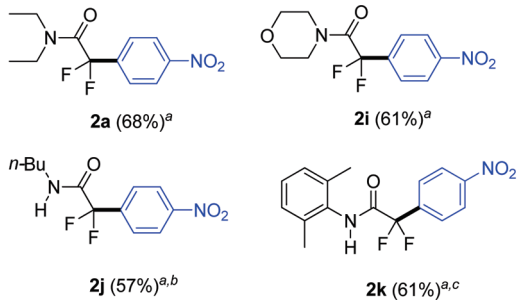


[a]All the reactions were performed with 0.5 mmol of alkenyl iodide, 0.75 mmol of **1a**, and 3.0 mmol of Cu in 2.0 mL of DMSO at 50 °C for 8 h. [b]Isolated yield.

(**5a**) and (*E*)-*β*-iodostyrene (**7a**), respectively (Tables 4 and 5). It was found that when both R^1 and R^2 were alkyl groups, the cross-coupling product yields were generally good (Table 4, **2a** and **2i**; Table 5, **6a** and **6h**); and when R^1 = H and R^2 = alkyl group, the cross-coupling reaction became sluggish and a prolonged reaction time (24 h) was needed (Table 4, **2j**; Table 5, **6g** and **6n**). However, when R^1 = H and R^2 = aryl group, the reaction could complete within 8 h (Table 4, **2k**; Table 5, **6i**).

TABLE 4. Cross-Coupling of Iododifluoroacetamides 1 and 5a



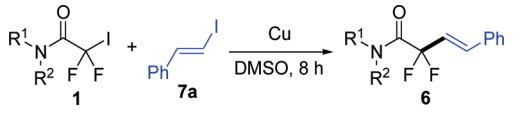


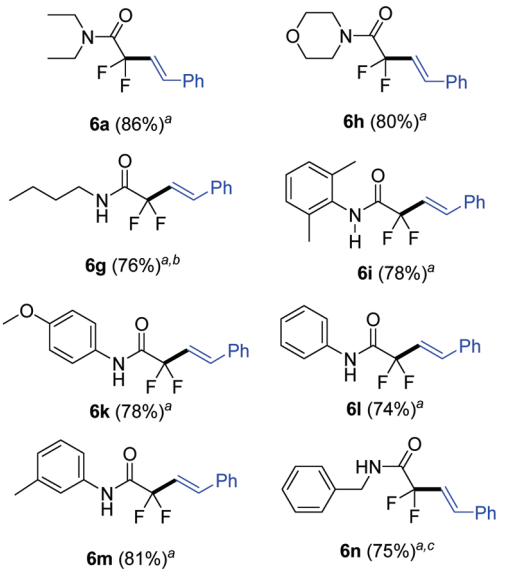
[a]All the reactions were performed with 0.5 mmol of **5a**, 0.75 mmol of **1**, 3.0 mmol of Cu in 2.0 mL of DMSO at 50 °C. [b]The reaction time was 24 h. [c]Determined by LC-MS.

Amides are important compounds in life sciences-related applications,[22] and introduction of fluorine atoms into the α-position of amide functionality may lead to an enhancement of bioactivity of the target molecule. Compound **11** is an amide derivative of benzylpiperazine, which possesses antidepressant activity.[23] We applied the Cu-mediated cross-coupling reaction in the synthesis of *gem*-difluorinated compound **6j**, a fluorine-substituted analogue of compound **11**. As shown in Scheme 2, compound **1e** was prepared from piperazine in 42% overall yield, and cross-coupling between **1e** and (*E*)-(2-iodovinyl)benzene in the presence of copper powder in DMF at 50 °C proved to be successful, and the desired product **6j** was obtained in 80% isolated yield.

2. Intramolecular cyclization of Iododifluoroacetamides 1. Many synthetic methodologies have been devised for the synthesis of indoles and continue to be developed.[24] Oxindoles, especially fluorinated oxindole derivatives, have received relatively little attention, for the lack of efficient synthetic methodologies.[25] When we used **1f** to cross-couple with **5a**, besides the cross-coupling product **2*l***, an unexpected cyclized product 3,3-difluoro-1-methylindolin-2-one **3a** was formed (Scheme 3). The addition reaction of perfluoroalkyl radical

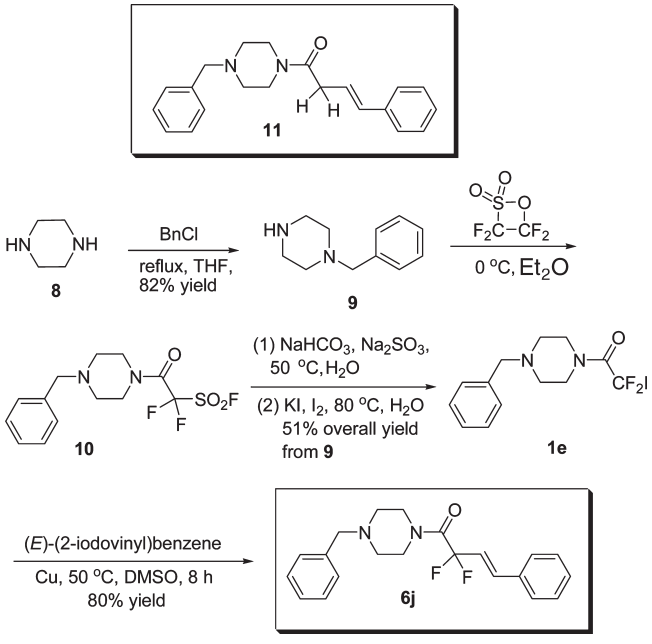
TABLE 5. Cross-Coupling of Iododifluoroacetamides 1 and 7a





[a]All the reactions were performed with 0.5 mmol of **7a**, 0.75 mmol of **1**, and 3.0 mmol of Cu in 2.0 mL of DMSO at 50 °C. [b]The reaction time was 24 h. [c]The reaction time was 10 h, and a mixture of **6n** and **1** (6:1) was obtained.

SCHEME 2



to electron-rich aromatic ring is well-known, but the similar reaction with a difluoroalkyl radical has been much less explored.[26] On the basis of this phenomenon (Scheme 3), we turned our interest to examine the intramolecular cyclization of iododifluoroacetamides.

The intramolecular cyclization reactions of structurally different iododifluoroacetamides **3a**−**e** were performed in

(22) (a) Farrell, E. K.; Merkler, D. J. *Drug Discovery Today* **2008**, *13*, 558–568. (b) Mosley, C. A.; Myers, S. J.; Murray, E. E.; Santangelo, R.; Tahirovic, Y. A.; Kurtkaya, N..; et al. *Bioorg. Med. Chem.* **2009**, *17*, 6463–6480. (c) Kowalchick, J. E.; Leiting, B.; Pryor, K.; Marsilio, F.; Wu, J. K.; He, H..; et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5934–5939.

(23) Younnes-El Hage, S.; Labssita, Y.; Baziard-Mouysset, G.; Payard, M.; Caignard, D.-H.; Rubat, C. *Ann. Pharm. Fr.* **2000**, *58*, 254–259.

(24) (a) Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442–2469. (b) Chen, Y.; Wang, Y. J.; Sun, Z. M.; Ma, D. W. *Org. Lett.* **2008**, *10*, 625–628. (c) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1–8.

(25) (a) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883–2887. (b) Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 6263–6267.

(26) (a) Cao, H.-P.; Xiao, J.-C.; Chen, Q.-Y. *J. Fluorine Chem.* **2006**, *127*, 1079–1086. (b) Ma, W. P.; Wang, W.; Huang, W. Y. *Chin. J. Chem.* **1990**, *8*, 175–181. (c) Ma, W. P.; Huang, W. Y. *Chin. J. Chem.* **2001**, *10*, 180–185. (d) Bravo, A.; Bjorsvik, H.-R.; Fontana, F.; Liguori, L.; Mele, A.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 7128–7136. (e) Matsugi, M.; Hasegawa, M.; Hasebe, S.; Takai, S.; Suyama, R.; Wakita, Y.; Kudo, K.; Imamura, H.; Hayashi, T.; Haga, S. *Tetrahedron Lett.* **2008**, *49*, 4189–4191. (f) Chen, L.; Jin, L.-M.; Xiao, J.-C.; Guo, C.-C.; Chen, Q.-Y. *Synlett* **2007**, 2096–2100. (g) Fuchikami, T.; Ojima, I. *J. Fluorine Chem.* **1983**, *22*, 541–556.

SCHEME 3

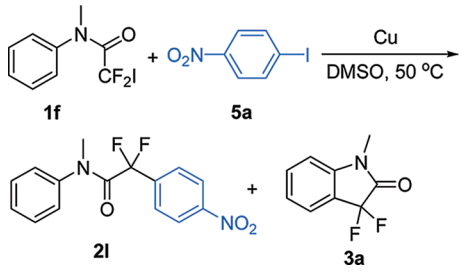
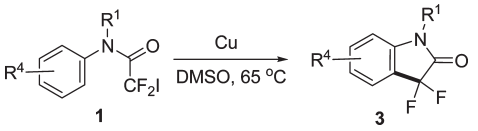
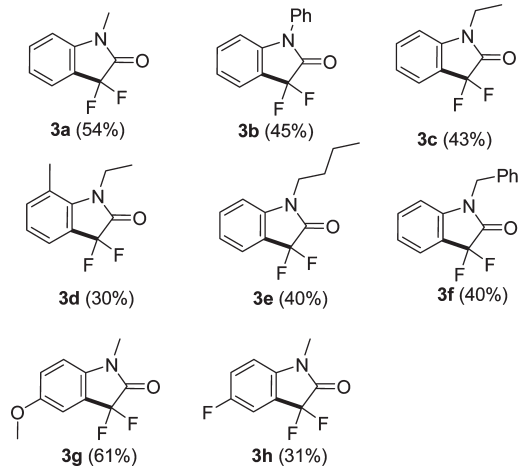


TABLE 6. Intramolecular cyclization of Iododifluoroacetamides 1[a]



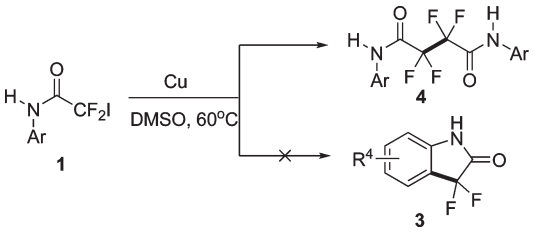


[a]All the reactions were performed with 0.5 mmol of **1**, 1.0 mmol of Cu in 2.5 mL of DMSO at 65 °C.

DMSO at 65 °C. As shown in Table 6, when R^1 = alkyl or aryl groups, intramolecularly cyclized products **3** were formed in moderate yields. Different alkyl substituents (methyl, ethyl, and *n*-butyl groups) on the nitrogen atom of **1** did not significantly influence the product yields (Table 6, **3a**, **3c**, and **3e**). However, the electronic nature of the aromatic substituent on the nitrogen atom of **1** had a remarkable effect on the reaction. When R^4 = methoxy group, the cyclization product **3g** was obtained in 61% yield; however, when R^4 = F, the yield of product **3h** was significantly lower (31%). It is interesting that when R^1 = H, homocoupling reaction occurred instead of intramolecular cyclization (Scheme 4). It is likely that when R^1 = H, the aromatic ring in compound **1** is less electron-rich, which significantly decreases the reaction rate of intramolecular cyclization, and enables the homocoupling reaction to become a major reaction pathway (Scheme 4). It may also be possible that the enhanced acidity of the N−H group (through the strong electron-withdrawing difluoroacetyl group) permits the formation of the corresponding Cu(I) salt and therefore modifies the reactivity of

(27) Tsukamoto, T.; Kitazume, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, *10*, 1177–1182.

SCHEME 4



SCHEME 5

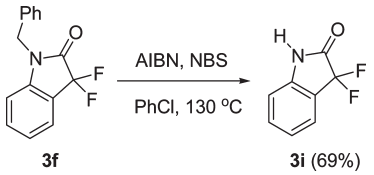
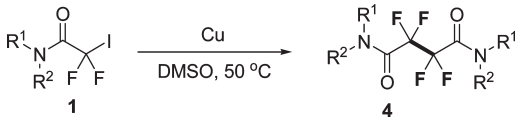
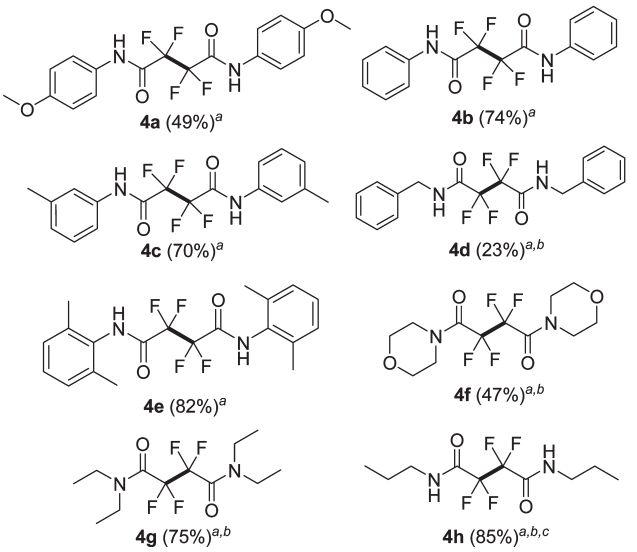


TABLE 7. Homocoupling of Iododifluoroacetamides 1





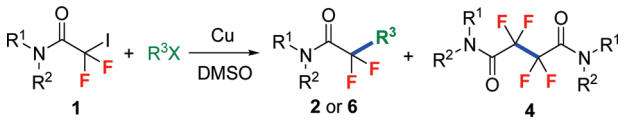
[a]All the reactions were performed with 1.0 mmol of **1**, 2.0 mmol of Cu in 2.5 mL of DMSO at 50 °C. [b]Determined by ^{19}F NMR by with $PhCF_3$ as internal standard. [c]The reaction time was 24 h.

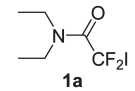
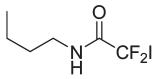
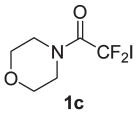
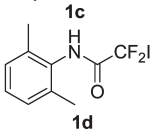
the molecule avoiding the intramolecular cyclization and/or favoring the cross-coupling reaction.[28] To achieve the synthesis of *N*-unprotected difluorooxindole, we used *N*-benzyl-protected iododifluoroacetamide to undergo intramolecular cyclization reaction to give product **3f** (Table 6), and compound **3f** could be successfully deprotected by AIBN/NBS reagent to give *N*-unprotected difluorooxindole compound **3i** (Scheme 5).

(28) We thank one of the reviewers for the comment on this possibility.

3. Homocoupling of Iododifluoroacetamides 1. According to aforementioned results (Scheme 4), we studied the scope of the homocoupling reaction of iododifluoroacetamides **1**.

TABLE 8. Comparison between Cross-Coupling and Homocoupling



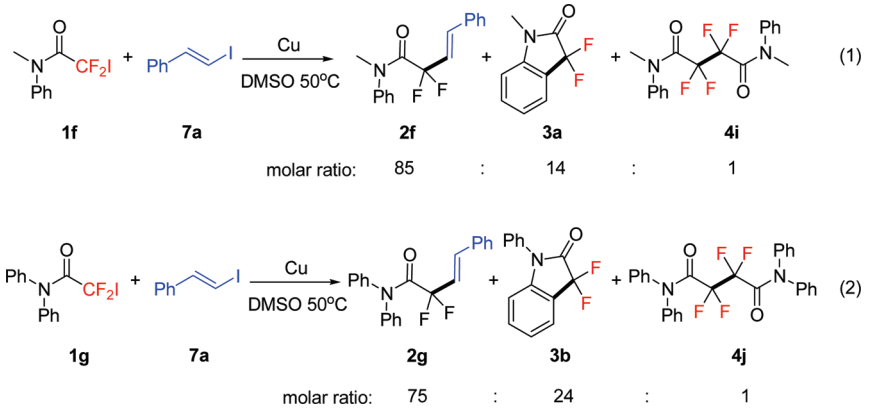
substant	R^3X^a	product ratio[b]
 **1a**	A	**2a** : **4a** = 92 : 8
	B	**6a** : **4a** = 99 : 1
 **1b**	A	**2b** : **4b** = 80 : 20
	B	**6b** : **4b** = 95 : 5
 **1c**	A	**2c** : **4c** = 93 : 7
	B	**6c** : **4c** = 99 : 1
 **1d**	A	**2d** : **4d** = 87 : 13
	B	**6d** : **4d** = 99 : 1

[a]Reactant A = 1-iodo-4-nitrobenzene; reactant B = (*E*)-(2-iodovinyl) benzene. [b]Determined by ^{19}F NMR.

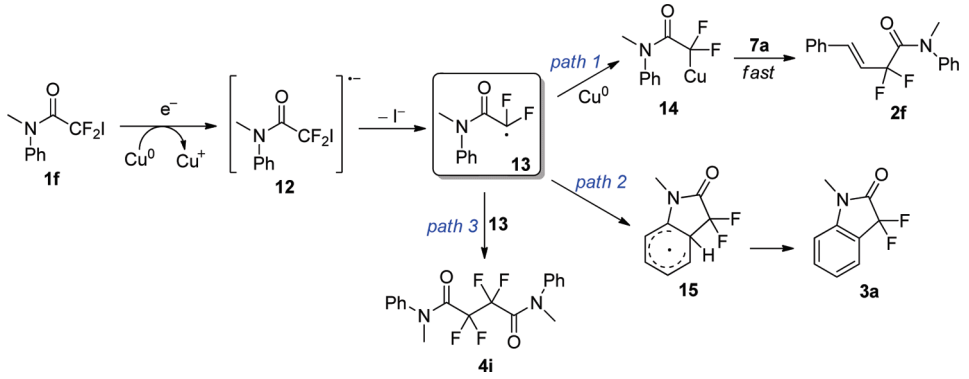
The results are shown in Table 7. It was found that, when R^1 = H and R^2 = alkyl or aryl group, or when R^1, R^2 = alkyl groups, the homocoupling reaction occurred smoothly to give products **4** in moderate to good yields (Table 7). It should be noted that, when R^1 = aryl group and R^2 = alkyl or aryl groups, the homocoupling reaction became negligible and the intramolecular cyclization reaction dominated (as shown in Table 6).

Considering that homocoupling may coexist in any Cu-mediated cross-coupling reaction between iododifluoroacetamides **1** and aryl/alkenyl iodides, we carefully investigated some cross-coupling reactions between iododifluoroacetamides **1a**−**d** and 1-iodo-4-nitrobenzene or (*E*)-(2-iodovinyl)-benzene (Table 8). It was found that, in all reactions we studied, the cross-coupling products dominated. When R^1 = H, the ratios of the homocoupling/cross-coupling products increase (Table 8, **1b** and **1d**). Furthermore, to gain more insights into this Cu-mediated reaction with iododifluoroacetamides, we designed two sets of reactions to determine the relative reactivity (and selectivity) of cross-coupling, intramolecular cyclization and homocoupling reactions (Scheme 6). In the case of a reaction between iododifluoroacetamide **1f** and (*E*)-(2-iodovinyl)benzene (**7a**), the ratio of cross-coupling, intramolecular cyclization, and homocoupling products **2f**:**3a**:**4i** = 85:14:1 (Scheme 5, eq 1). Even when *N*,*N*-diphenyliododifluoroacetamide (**1g**) was used to react with (*E*)-(2-iodovinyl)-benzene (**7a**), cross-coupling product **2g** still dominated (**2g**:**3b**:**4j** = 75:24:1; see Scheme 5, eq 2). This suggests that in many cases when cross-coupling, homocoupling, and

SCHEME 6



SCHEME 7



intramolecular cyclization reactions coexist in one reaction system involving iododifluoroacetamides **1** (such as the reaction between **1f**/**1g** and **7a**), the reactivity decreases in the following order: cross-coupling > intramolecular cyclization > homocoupling.

Finally, a plausible reaction mechanism is proposed, using **1f** as a model compound (as shown in Scheme 7). A single electron transfer (SET) process between Cu^0 and **1f** gives a radical anion species **12**, which undergoes elimination of an iodide ion to afford *gem*-difluoromethyl radical **13**. There are three possible pathways for the synthetic utility of difluorinated radical species **13**: copper-mediated cross-coupling reaction with akenyl (or aryl) halides, which is a fast process (path 1);[16−18] intramolecular cyclization (path 2);[29] and homocoupling reaction (path 3).[30]

Conclusion

In conclusion, Cu-mediated fluoroalkylation reactions with iododifluoroacetamides **1** have been systematically investigated for the first time. It was found that three types of reactions may coexist in Cu-mediated reactions between iododifluoroacetamides and aryl/alkenyl iodides: cross-coupling, intramolecular cyclization, and homocoupling reactions (see Scheme 1). The selectivity among these three types of reactions could be controlled by tuning the substituents on the nitrogen atom of iododifluoroacetamides, and/or by removing the cross-coupling reaction partner (aryl/alkenyl halides). The general rule is as follows: (a) in the presence of proper aryl/alkenyl iodides, the cross-coupling products **2** (or **6**) are generally formed as the major products; (b) in the absence of aryl/alkenyl iodides, and when R^1 = alkyl and R^2 = aryl groups, or when $R^1 = R^2$ = aryl groups, the intramolecular cyclization products **3** can be formed predominantly; and (c) in the absence of aryl/alkenyl iodides, and when $R^1 = R^2$ = alkyl groups, or when R^1 = H and R^2 = alkyl, aryl groups, the homocoupling products **4** can be formed dominantly. Our experimental results also indicate that in many cases when cross-coupling, homocoupling, and intramolecular cyclization reactions coexist in the Cu-mediated reaction system, the reactivity decreases in the following order: cross-coupling > intramolecular cyclization > homocoupling.

Experimental Section

Typical Procedure for the Preparation of 2,2-Difluoro-2-iodoacetamide 1. Into a 250-mL round-bottomed flask was added tetrafluoroethane-β-sultone (36 g, 0.2 mol) and diethyl ether (150 mL). While the solution was vigorously stirred, diethylamine (42 mL, 0.4 mol) was slowly added into the flask at 10 °C. The mixture was then stirred for an additional 4 h, followed by quenching with H_2O (20 mL). The ether phase was washed with H_2O twice, then dried over anhydrous Na_2SO_4. After filtration and solvent removal, the crude product was purified by vacuum distillation to give 2-(diethylamino)-1,1-difluoro-2-oxoethanesulfonyl fluoride (35 g), bp 70−72 °C/2 mm.

A mixture of 2-(diethylamino)-1,1-difluoro-2-oxoethanesulfonyl fluoride (4.6 g, 20 mmol), $NaHCO_3$ (4.0 g, 48 mmol), Na_2SO_3 (3.0 g, 24 mmol), and H_2O (60 mL) was stirred at 50 °C for 4 h, and KI (5.0 g, 30 mmol) and I_2 (10.0 g, 39 mmol) were added in three portions. The reaction mixture was stirred at 80 °C for an additional 2 h. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (30 mL) three times. The combined organic phase was washed with aqueous Na_2SO_3 solution, then dried over anhydrous Na_2SO_4. After filtration and solvent removal, the crude product was purified by silica gel chromatography (petroleum ether/acetone, 10:1 v/v) to give product **1a** (3.2 g, 58% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.23−3.16 (m, 4H), 1.25−1.19 (m, 6H); ^{19}F NMR ($CDCl_3$, 270 MHz) δ −56.8 (s, 2F). The characterization data are consistent with those in a previous report.[21a]

Typical Procedure for Cross-Coupling Reaction between 2,2-Difluoro-2-iodoacetamide 1 and Aryl Iodides (or Alkenyl Iodides). Under N_2 atmosphere, into a 10-mL Schlenk flask was added *N*,*N*-diethyl-2,2-difluoro-2-iodoacetamide (**1a**) (207 mg, 0.75 mmol), 1-iodo-4-nitrobenzene (125 mg, 0.5 mmol), Cu powder (190 mg, 3.0 mmol), and DMSO (2.0 mL). The reaction mixture was vigorously stirred at 50−60 °C for 8 h. After cooling to room temperature, the reaction mixture was quenched by adding H_2O (10 mL) and extracted with diethyl ether (10 mL) three times. The combined organic phase was washed with H_2O, then dried over anhydrous Na_2SO_4. After filtration and solvent removal, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 10:1 v/v) to give product *N*,*N*-diethyl-2,2-difluoro-2-(4-nitrophenyl)acetamide **2a** (92 mg, 68% yield) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 3.38−3.31 (m, 4H), 1.18−1.08 (m, 6H); ^{19}F NMR ($CDCl_3$, 270 MHz) δ −96.5 (s, 2F); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.4, 149.1, 140.5, 126.9, 123.7, 115.1 (t, J = 223.8 Hz), 42.1, 41.8, 14.1, 12.2; IR (film) 3119, 2980, 2941, 2879, 1670, 1532, 1450, 1353, 1178, 1099 cm^{-1}; MS (ESI, *m*/*z*) 273 (M + H$^+$). Anal. Calcd for $C_{12}H_{14}F_2N_2O_3$: C, 52.94; H, 5.18; F, 13.96; N, 10.29; O, 17.63. Found: C, 52.92; H, 5.44; N, 9.86.

Typical Procedure for Intramolecular Cyclization of 2,2-Difluoro-2-iodoacetamide 1. Under N_2 atmosphere, into a 10-mL Schlenk flask was added 2,2-difluoro-2-iodo-*N*-methyl-*N*-phenylacetamide (156 mg, 0.5 mmol), Cu powder (64 mg, 1.0 mmol), and DMSO (2.5 mL). The reaction mixture was vigorously stirred at 60−70 °C for 7 h. After cooling to room temperature, the reaction mixture was quenched by adding H_2O (10 mL) and extracted with diethyl ether (10 mL) three times. The combined organic phase was washed with H_2O, then dried over anhydrous Na_2SO_4. After filtration and solvent removal, the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 20:1 v/v), to give product 3,3-difluoro-1-methylindolin-2-one **3a** (44 mg, 54% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.42 (m, 2H), 7.11 (t, J = 8.7 Hz, 1H), 6.85 (d, J = 9.2 Hz, 1H), 3.15 (s, 3H); ^{19}F NMR ($CDCl_3$, 270 MHz) δ −112.3 (s, 2F). The characterization data are consistent with those in a previous report.[27]

Typical Procedure for Homocoupling Reaction of 2,2-Difluoro-2-iodoacetamide 1. Under N_2 atmosphere, into a 10-mL Schlenk flask was added 2,2-difluoro-2-iodo-*N*-(4-methoxyphenyl)-acetamide (327 mg, 1.0 mmol), Cu powder (128 mg, 2.0 mmol), and DMSO (2.0 mL). The reaction mixture was vigorously stirred at 50 °C for 8 h. After cooling to room temperature, the reaction mixture was quenched by adding H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL) three times. The combined organic phase was washed with H_2O, then dried over anhydrous Na_2SO_4. After filtration and solvent removal, the crude product was purified by silica gel chromatography (petroleum ether/acetone, 3:1 v/v) to

(29) See previous examples of cyclization reaction between a fluorinated alkyl radical and an aromatic ring: (a) Zeng, Z.; Liu, C.; Jin, L. M.; Guo, C. C.; Chen, Q. Y. *Eur. J. Org. Chem.* **2005**, 306–316. (b) Chen, L.; Jin, L. M.; Guo, C. C.; Chen, Q. Y. *Synlett* **2005**, 963–970. (c) Reference 26a.

(30) See previous examples of homocoupling of fluorinated alkyl free radicals, see: (a) Arimistu, S.; Xu, B.; Kishbaugh, T. L. S.; Griffin, L.; Hammond, G. B. *Tetrahedron Lett.* **2004**, *125*, 641–645. (b) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547–6552. (c) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457–4463.

give product 2,2,3,3-tetrafluoro-N^1,N^4-bis(4-methoxyphenyl)succinamide **4a** (98 mg, 49% yield) as a white solid. Mp 248−250 °C; ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.65 (d, J = 9.3 Hz, 4H), 6.93 (d, J = 9.0 Hz, 4H), 3.79 (s, 6H); ^{19}F NMR (CD_3COCD_3, 270 MHz) δ −115.4 (s, 4F); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 157.2, 130.0, 123.6, 113.4, 109.4 (tt, J = 264.3 Hz, J = 30.2 Hz); IR (film) 3301, 1691, 1532, 1251, 1156, 1028, 820, 707 cm^{-1}; MS (ESI, m/z) 401 (M + H$^+$); HRMS (ESI) calcd for $C_{18}H_{17}F_4N_2O_4$ (M + H$^+$) 401.1135, found 401.1119.

Typical Procedure for Deprotection of 1-Benzyl-3,3-difluoroindolin-2-one 3f. A solution of **3f** (100 mg, 0.39 mmol) in chlorobenzene (8 mL) containing NBS (86 mg, 0.46 mmol) and AIBN (15 mg, 0.09 mmol) was heated to reflux under a nitrogen atmosphere. After 4 h AIBN (3 mg, 0.02 mmol) and NBS (20 mg, 0.11 mmol) were added. The solution was heated overnight then cooled to room temperature. Diethyl ether (10 mL) and water (20 mL) were added to the solution, which was stirred for 4 h, then the organic layerwas separated, dried over anhydrous Na_2SO_4, and evaporated and the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3:1 v/v) to give 3,3-difluoroindolin-2-one **3i** (42 mg, 69%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (br s, 1H), 7.70−7.46 (m, 3H), 7.37 (t, J = 7.1 Hz 1H); ^{19}F NMR ($CDCl_3$, 270 MHz) δ −110.9 (s, 2F).

Acknowledgment. We gratefully thank the National Natural Science Foundation of China (20502029, 20772144, 20825209, 20832008), Shanghai Rising-Star Program (06QA14063), and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for funding.

Supporting Information Available: General experimental details, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.