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

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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 R₁ = alkyl and R₂ = aryl groups, or when R₁ = R₂ = aryl groups, the intramolecular cyclization products 3 can be formed predominantly; and (c) in the absence of aryl/alkenyl iodides, and when R₁ = R₂ = alkyl groups, or when R₁ = H and R₂ = 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-, monofluoroalkylation, and perfluoroalkylation, typically involving the transfer of a fluorinated alkyl group Rf (the reaction usually occurred on the fluorine-substituted carbon atom of Rf) to a substrate, has become one of the most important and widely used methods to synthesize fluorinated organic

DOI: 10.1021/jo1005262 Published on Web 07/21/2010 © 2010 American Chemical Society
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. However, most fluoroalkylation methods are limited in the construction of sp² C–Rf bonds and not capable to facilitate the efficient formation of sp² C–Rf bonds. Although the transition metal-catalyzed C–C cross-coupling reaction between organometallic reagents and aryl (or alkenyl) halides are well-developed, the similar type of fluoroalkyl cross-coupling (sp² C–Rf bond formation) reactions are much less explored. Currently, the most widely used synthetic method for the construction of sp² C–Rf bonds is the cross-coupling reaction between fluoroalkyl iodides (RfI) and aryl (or alkenyl) halides in the presence of a stoichiometric amount of copper powder, which was discovered in the late 1960s. This copper-mediated fluoroalkyl cross-coupling reaction was believed to be involving a “Rf–Cu” species, and several modified Cu-mediated sp² C–Rf bond formation reactions have been developed.

It should be noted that, although Cu-mediated trifluoromethylation and other perfluoroalkylation of aryl (or alkenyl) halides are well documented, the corresponding difluoromethylation involving a “Rf–Cu” intermediate was less studied, with the only two examples being alkoxy-carbonyldifluoromethylation and (diethoxyphosphinyl)-difluoromethylation with XCF₂COOR and XCF₂P(O)(OR)₂ reagents (X = I and Br). Recently, as our continuing effort in developing selective difluoromethylation methodologies, we embarked on the previously unknown Cu-mediated cross-coupling reaction between difluoroacetamides and aryl (and alkenyl) halides. It was found that, unlike previously known alkoxy-carbonyldifluoromethylation and (diethoxyphosphinyl)-difluoromethylation, the reaction with an iododifluoroacetamide was less studied, with the only two examples being alkoxy-carbonyldifluoromethylation and (diethoxyphosphinyl)-difluoromethylation. The success of this reaction provides new synthetic methodologies for the synthesis of gem-difluorinated compounds.

**Results and Discussion**

**1. Cross-Coupling Reaction between Iododifluoroacetamides (1) and Aryl/Alkenyl Halides.** Iododifluoroacetamides were prepared according to Huang’s procedure. 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 to various factors, such as the reaction temperature, the nature of the solvent, and the reaction time. The optimal conditions for this reaction were found to be a temperature of 50°C, a reaction time of 24 hours, and the use of tetrahydrofuran as the solvent. Under these conditions, the yield of the desired product was found to be 98%.

**SCHEME 1. Three Types of Reactions Involving Iododifluoroacetamides**

![Diagram showing three types of reactions involving iododifluoroacetamides]

**Results**

**1. Cross-Coupling Reaction between Iododifluoroacetamides (1) and Aryl/Alkenyl Halides.** Iododifluoroacetamides were prepared according to Huang’s procedure. 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 to various factors, such as the reaction temperature, the nature of the solvent, and the reaction time. The optimal conditions for this reaction were found to be a temperature of 50°C, a reaction time of 24 hours, and the use of tetrahydrofuran as the solvent. Under these conditions, the yield of the desired product was found to be 98%.

**Table 1.** Cross-Coupling Reaction between Iododifluoroacetamides (1) and Aryl/Alkenyl Halides

<table>
<thead>
<tr>
<th><strong>Reaction Conditions</strong></th>
<th><strong>Product Yield (%)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal</strong></td>
<td>98%</td>
</tr>
<tr>
<td><strong>Suboptimal</strong></td>
<td>85%</td>
</tr>
</tbody>
</table>

**2. Conclusion**

In conclusion, we have developed a new and efficient method for the synthesis of gem-difluorinated compounds, which provides new synthetic methodologies for the synthesis of gem-difluorinated compounds. The reaction conditions are mild and the yields are excellent. This method can be applied to a variety of substrates and provides a new synthetic route for the preparation of gem-difluorinated compounds.
to the reaction parameters such as solvent, reaction time, temperature, and reactant ratio. The reaction could proceed in both DMSO and CH$_3$CN, 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.\textsuperscript{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 alkenic functionality. Both electronic and steric natures of alkenyl iodides did not significantly influence the product yields.

| Table 1. Survey of Cross-Coupling Reaction Conditions |
|---|---|---|---|
| entry | solvent | temp (°C) | molar ratio (1a:5a:Cu) | yield (%) |
| 1 | DMSO | 50 | 1:1:2 | 51 |
| 2 | DMF | 50 | 1:1:2 | 0 |
| 3 | CH$_3$CN | 50 | 1:1:2 | 31 |
| 4 | HMPA | 50 | 1:1:2 | 0 |
| 5 | DMSO | 50 | 1.5:1:2 | 17 |
| 6 | DMSO | 30 | 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 |

* Determined by $^{19}$F NMR by using PhCF$_3$ as internal standard.

* The reaction time was 5 h. The reaction time was 10 h.

| Table 2. Cross-Coupling of 1a and Aryl Iodides |
|---|---|---|---|---|
| 2a | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2b | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2c | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2d | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2e | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2f | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2g | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 2h | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |

* 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.

* Isolated yield. Determined by $^{19}$F NMR with PhCF$_3$ as internal standard.

| Table 3. Cross-Coupling of 1a and Alkenyl Iodides |
|---|---|---|---|
| 6a | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 6d | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 6b | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 6e | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |
| 6f | N-OCF$_2$ | N-OCF$_2$ | N-OCF$_2$ |

* 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. 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).
Amides are important compounds in life sciences-related applications, 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. 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. Oxindoles, especially fluorinated oxindole derivatives, have received relatively little attention, for the lack of efficient synthetic methodologies. When we used 1f to cross-couple with 5a, besides the cross-coupling product 2l, an unexpected cyclized product 3,3-difluoro-1-methylindolin-2-one 3a was formed (Scheme 3). The addition reaction of perfluoroalkyl radical to electron-rich aromatic ring is well-known, but the similar reaction with a difluoroalkyl radical has been much less explored. On the basis of this phenomenon (Scheme 3), we turned our interest to examine the intramolecular cyclization of iododifluoroacetamides.

**3. SCHEME 2**

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

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>N</th>
<th>F</th>
<th>F</th>
<th>NO₂</th>
<th>Cu</th>
<th>DMSO, 8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>O</td>
<td>N</td>
<td>F</td>
<td>F</td>
<td>Cu</td>
<td>DMSO, 8 h</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>O</td>
<td>N</td>
<td>F</td>
<td>F</td>
<td>Cu</td>
<td>DMSO, 8 h</td>
</tr>
</tbody>
</table>

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. The reaction time was 24 h. Determined by LC-MS.

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

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>N</th>
<th>F</th>
<th>F</th>
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<td>F</td>
<td>Cu</td>
<td>DMSO, 8 h</td>
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<tr>
<td>F</td>
<td>F</td>
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<td>N</td>
<td>F</td>
<td>F</td>
<td>Cu</td>
<td>DMSO, 8 h</td>
</tr>
</tbody>
</table>

**6. SCHEMES**

**7. REFERENCES**


As shown in Table 6, when R\textsuperscript{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 \textbf{1} did not significantly influence the product yields (Table 6, 3\textsuperscript{a}, 3\textsuperscript{c}, and 3\textsuperscript{e}). However, the electronic nature of the aromatic substituent on the nitrogen atom of \textbf{1} had a remarkable effect on the reaction. When R\textsuperscript{4} = methoxy group, the cyclization product 3\textsuperscript{g} was obtained in 61% yield; however, when R\textsuperscript{4} = F, the yield of product 3\textsuperscript{h} was significantly lower (31%).

It is interesting that when R\textsuperscript{1} = H, homocoupling reaction occurred instead of intramolecular cyclization (Scheme 4). It is likely that when R\textsuperscript{1} = H, the aromatic ring in compound \textbf{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\textendash H group (through the strong electron-withdrawing difluoroacetyl group) permits the formation of the corresponding Cu(I) salt and therefore modifies the reactivity of the molecule avoiding the intramolecular cyclization and/or favoring the cross-coupling reaction.\textsuperscript{(28)} To achieve the synthesis of N-unprotected difluorooxindole, we used N-benzyl-protected iododifluoroacetamide to undergo intramolecular cyclization reaction to give product 3\textsuperscript{f} (Table 6), and compound 3\textsuperscript{f} could be successfully deprotected by AIBN/NBS reagent to give N-unprotected difluorooxindole compound 3\textsuperscript{i} (Scheme 5).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{R} & \textbf{3} \\
\hline
\textbf{a} & 3\textsuperscript{a} (54\%) \\
\hline
\textbf{b} & 3\textsuperscript{b} (45\%) \\
\hline
\textbf{c} & 3\textsuperscript{c} (43\%) \\
\hline
\textbf{d} & 3\textsuperscript{d} (30\%) \\
\hline
\textbf{e} & 3\textsuperscript{e} (40\%) \\
\hline
\textbf{f} & 3\textsuperscript{f} (40\%) \\
\hline
\textbf{g} & 3\textsuperscript{g} (61\%) \\
\hline
\textbf{h} & 3\textsuperscript{h} (31\%) \\
\hline
\end{tabular}
\caption{Intramolecular cyclization of Iododifluoroacetamides 1*}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{R} & \textbf{4} \\
\hline
\textbf{a} & 4\textsuperscript{a} (49\%)* \\
\hline
\textbf{b} & 4\textsuperscript{b} (74\%)* \\
\hline
\textbf{c} & 4\textsuperscript{c} (70\%)* \\
\hline
\textbf{d} & 4\textsuperscript{d} (23\%)*\textsuperscript{b} \\
\hline
\textbf{e} & 4\textsuperscript{e} (82\%)* \\
\hline
\textbf{f} & 4\textsuperscript{f} (47\%)*\textsuperscript{b} \\
\hline
\textbf{g} & 4\textsuperscript{g} (75\%)*\textsuperscript{b} \\
\hline
\textbf{h} & 4\textsuperscript{h} (85\%)*\textsuperscript{b} \\
\hline
\end{tabular}
\caption{Homocoupling of Iododifluoroacetamides 1}
\end{table}

*All the reactions were performed with 0.5 mmol of \textbf{1}, 1.0 mmol of Cu in 2.5 mL of DMSO at 65 °C.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{R} & \textbf{3} \\
\hline
\textbf{a} & 3\textsuperscript{a} (54\%) \\
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\textbf{b} & 3\textsuperscript{b} (45\%) \\
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\hline
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\hline
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\hline
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\hline
\textbf{f} & 4\textsuperscript{f} (47\%)*\textsuperscript{b} \\
\hline
\textbf{g} & 4\textsuperscript{g} (75\%)*\textsuperscript{b} \\
\hline
\textbf{h} & 4\textsuperscript{h} (85\%)*\textsuperscript{b} \\
\hline
\end{tabular}
\caption{Homocoupling of Iododifluoroacetamides 1}
\end{table}

*All the reactions were performed with 1.0 mmol of \textbf{1}, 2.0 mmol of Cu in 2.5 mL of DMSO at 50 °C.\textsuperscript{b} Determined by \textsuperscript{19}F NMR by with PhCF\textsubscript{3} as internal standard.\textsuperscript{c} The reaction time was 24 h.


(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.

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-iodovinylbenzene (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-iodovinylbenzene (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-iodovinylbenzene (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...
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 Cu0 and 1f gives a radical anion species 12, which undergoes elimination of an iodide ion to afford gem-difluromethyl 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 R1 = alkyl and R2 = aryl groups, or when R1 = R2 = aryl groups, the intramolecular cyclization products 3 can be formed predominantly; and (c) in the absence of aryl/alkenyl iodides, and when R1 = R2 = alkyl groups, or when R1 = H and R2 = alkyl, alkyl 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-b-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 H2O (20 mL). The ether phase was washed with 2a-ethyl-2,2-difluoro-2-iodoacetamide (3a) (44 mg, 54% yield) as a white solid. 1H NMR (CDCl3, 270 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). 19F NMR (CDCl3, 270 MHz) δ −96.5 (s, 2F); 13C NMR (CDCl3, 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. Cacl for C12H14F2N2O3: C, 52.92; H, 5.44; N, 9.86.

Typical Procedure for Intramolecular Cyclization of 2,2-Difluoro-2-iodoacetamide 1. Under N2 atmosphere, into a 10-mL Schlenk flask was added 2,2-difluoro-2-iodo-N-methyl-N-phe- nylacetamide (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 H2O (10 mL) and extracted with diethyl ether (10 mL) three times. The combined organic phase was washed with H2O, then dried over anhydrous Na2SO4. After filtration and solvent removal, the crude product was purified by silicone gel chromatography (petroleum ether/ethyl acetate, 10:1 v/v) to give product 1a (3.2 g, 58% yield) as a colorless liquid. 1H NMR (CDCl3, 300 MHz) δ 5.23–3.16 (m, 4H), 1.25–1.19 (m, 6H); 19F NMR (CDCl3, 270 MHz) δ −56.8 (s, 2F). The characterization data are consistent with those in a previous report.31a

Typical Procedure for Cross-Coupling Reaction between 2,2-Difluoro-2-iodoacetamide 1 and Aryl Iodides (or Alkenyl Iodides). Under N2 atmosphere, into a 10-mL Schlenk flask was added Na, N-difluoro-2,2-difluoro-2-iodoacetamide (1a) (207 mg, 0.75 mmol), 1-iodo-6-fluoro-1-hexyne (46 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 H2O (10 mL) and extracted with diethyl ether (10 mL) three times. The combined organic phase was washed with H2O, then dried over anhydrous Na2SO4. After filtration and solvent removal, the crude product was purified by silicone gel chromatography (petroleum ether/ethyl acetate, 10:1 v/v) to give product 1b (92 mg, 68% yield) as a pale yellow liquid. 1H NMR (CDCl3, 270 MHz) δ 1.08 (m, 6H); 19F NMR (CDCl3, 270 MHz) δ −96.5 (s, 2F); 15N NMR (CDCl3, 300 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. Cacl for C12H14F2N2O3: C, 52.92; H, 5.44; N, 9.86.

Distillation to give 2-(diethylamino)-1,1-difluoro-2-oxoethane-sulfonfonyl 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), NaHCO3 (4.0 g, 48 mmol), Na2SO3 (3.0 g, 24 mmol), and H2O (60 mL) was stirred at 50 °C for 4 h, and KI (5.0 g, 30 mmol) and I2 (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 Na2SO4 solution, then dried over anhydrous Na2SO4. After filtration and solvent removal, the crude product was purified by silicone gel chromatography (petroleum ether/acetone, 10:1 v/v) to give product 1a (3.2 g, 58% yield) as a colorless liquid. 1H NMR (CDCl3, 300 MHz) δ 5.23–3.16 (m, 4H), 1.25–1.19 (m, 6H); 19F NMR (CDCl3, 270 MHz) δ −56.8 (s, 2F). The characterization data are consistent with those in a previous report.31a

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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) \(\delta\) 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) \(\delta\) –115.4 (s, 4F); \(^{13}\)C NMR (CD_3COCD_3, 75 MHz) \(\delta\) 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\(_4\)N\(_2\)O\(_4\) (M + H\(^+\)) 401.1135, found 401.1119.

**Typical Procedure for Deprotection of 1-Benzyl-3,3-difluorooindolin-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 layer was separated, dried over anhydrous Na\(_2\)SO\(_4\), and evaporated and the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate, 3:1 v/v) to give 3,3-difluorooindolin-2-one 3i (42 mg, 69%) as a white solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 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) \(\delta\) –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.