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Letter

Generation of Carbocations under Photoredox Catalysis: Electrophilic Aromatic Substitution with 1-Fluoroalkylbenzyl Bromides

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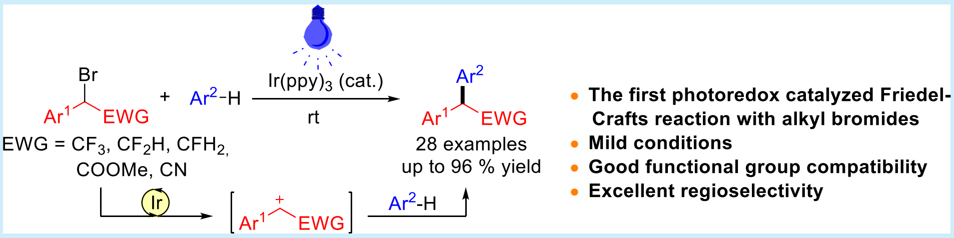
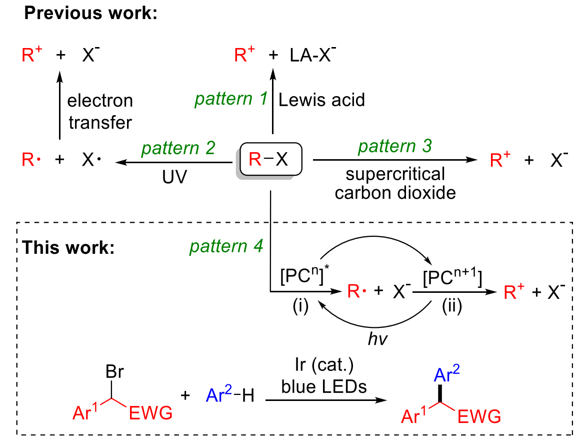


ABSTRACT: A novel Friedel−Crafts-type alkylation of arenes to access valuable 1-fluoroalkyl-1,1-biaryl compounds is established under mild conditions. The key to success is the efficient generation of a destabilized benzylic carbocation intermediate via two consecutive single-electron transfer processes by virtue of visible-light photoredox catalysis. This unique activation pattern avoids using strong Lewis acids and high temperatures that are required for generation of destabilized carbocations in traditional Friedel−Crafts reactions. This protocol demonstrates the first example of photoredox-catalyzed heterolysis of electronically deactivated benzylic C−Br bonds for the formation of destabilized carbocation intermediates.

The applications of fluorine-containing organic molecules in pharmaceuticals and materials[1] have attracted much attention due to their unique physical, chemical, and biological properties.[2] As ubiquity of the 1,1-diaryl motif in drug target[3] and the profound changes can be imparted by the introduction of fluorine-containing moieties, it is of particular interest to access 1-fluoroalkyl-1,1-diaryl compounds. However, there are only limited methods available to achieve this goal. The groups led by Molander, Loh, Tredwell, and Shen demonstrated that the cross-coupling reactions under nickel or palladium catalysis represent a powerful strategy to synthesize 1-fluoroalkyl-1,1-diaryl compounds,[4] but the facile β-fluoride elimination of benzylpalladium intermediates bearing CF_2H and CFH_2 motifs[4c] and the lower efficiency with nickel catalysts[4a,d] limited their practicability in synthesis. An alternative approach was reported by Moran and co-workers using a Friedel−Crafts-type reaction,[5] but the functional group tolerance was low because of the harsh reaction conditions (high temperature and strong acid).[6] Therefore, the development of a new strategy to synthesize 1-fluoroalkyl-1,1-diaryl compounds with broad substrate scope and good functional group compatibility under mild conditions is highly desirable.

Friedel−Crafts alkylation is a powerful method for the construction of 1,1-diaryl motifs from benzylic halides.[7] However, traditional methods are depending predominantly on the use of strong acids such as $AlCl_3$ to activate C−X bonds to deliver the key carbocation intermediate (Scheme 1, pattern 1).[8] Moreover, the use of high temperature[5] or stoichiometric amount of a silver salt[9] is necessary for the generation of a destabilized carbocation that is adjacent to an electron-

Scheme 1. Generation of Carbocations by Activation of the C−X Bond



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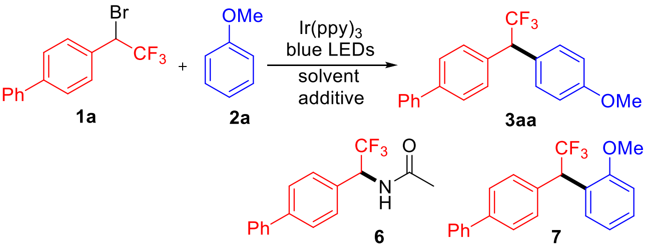
withdrawing group. The heterolysis of C−X bond to generate carbocation intermediates has also been reported under ultraviolet light (pattern 2)[10] or supercritical carbon dioxide (pattern 3)[11] conditions; however, uncontrollable side reactions and harsh conditions have limited their applications. Given the facts that carbocations possess diverse reactivity and are widely utilized in organic synthesis, developing a novel protocol to forge carbocations, especially the destabilized ones under mild conditions, is of great significance.

Recently, remarkable progress has been made in photoredox-catalyzed reactions.[12] In these reactions, the generation of radicals reduced from C−X bonds (pattern 4, step i) was studied extensively,[13] but the further oxidation process between the newly born radicals and photocatalysts was rarely explored[14] (pattern 4, step ii). Based on the roles (both as a reductant and an oxidant) of a photocatalyst played in a photoredox-catalyzed reaction, we surmised that a photocatalyst-promoted C−X bond heterolysis to generate a carbocation might be possible via an initial reduction followed by a subsequent oxidation process (pattern 4). In this regard, we envisioned that two challenges might exist in the whole process: (a) the reversed electronic demand on the substrate during the reduction and oxidation processes is an unmet challenge[15] and (b), with the high reactivity of radical intermediates, how to avoid the radicals-involved side reactions (such as homocoupling and hydrogen abstraction) before the subsequent oxidation by a photocatalyst is another concern. Despite these difficulties, herein we report our success in the formation of destabilized carbocations via C−Br bond cleavage by means of photoredox catalysis, followed by a subsequent reaction with a variety of arenes (Scheme 1, this work). The key to success lies in the appropriate electronic density of substrates and the enough lifetime of radical intermediates (via the stabilization with an aryl group and the steric hindrance of the secondary alkyl radical). To the best of our knowledge, this represents the first example of Friedel−Crafts-type alkylation reaction between electronically deactivated benzylic bromides and arenes enabled by photoredox catalysis.

Initially, α-trifluoromethyl 4-phenylbenzyl bromide **1a**, which is slow to generate a carbocation by traditional means due to the strong electron-withdrawing ability of the α-trifluoromethyl group[16] (for details, see Scheme S1, eq 3), and methoxybenzene **2a** were selected as the model substrates to investigate the photoredox-catalyzed Friedel−Crafts reaction. To our delight, the *para*-alkylated product **3aa** was observed in 81% yield at room temperature by using Ir(ppy)$_3$ as the photocatalyst, ZnF$_2$ as the additive, and CH$_3$CN as the solvent (Table 1, entry 1). Meanwhile, the product **7** with *ortho*-selectivity was only detected in 3% yield. The reaction was accomplished smoothly with a catalytic amount of ZnF$_2$ (entries 2−4), but an extraordinary low reaction rate was observed without ZnF$_2$ (entry 5), indicating the critical role of ZnF$_2$ played in the reaction. As Ritter-type reaction product **6** is the major side product, higher efficiency might be obtained by increasing the loading of **2a** or the concentration of the reactants **1a** and **2a** (entries 6−9). Gratifyingly, 91% yield was obtained when the reaction was carried out in higher concentration (entry 9). Further additive screening revealed that ZnF$_2$ was the optimal Lewis acidic additive (entries 10−14). Solvent screening revealed that both a less polar solvent such as CH$_2$Cl$_2$ or dioxane and a more polar solvent such as DMF were not suitable, giving the desired product in low or no yield (entry 15−17). Therefore, acetonitrile was still proved to be the optimal solvent even though Ritter-type reaction byproduct **6** was inevitably formed. Notably, decreasing the photocatalyst loading to 0.5 mol % had no obvious influence on the yield (entry 18). Finally, the control experiments without either Ir(ppy)$_3$ or light irradiation (entry 19−20) revealed that ZnF$_2$ alone could not catalyze the Friedel−Crafts reaction.

Table 1. Optimization of Reaction Conditions[a]

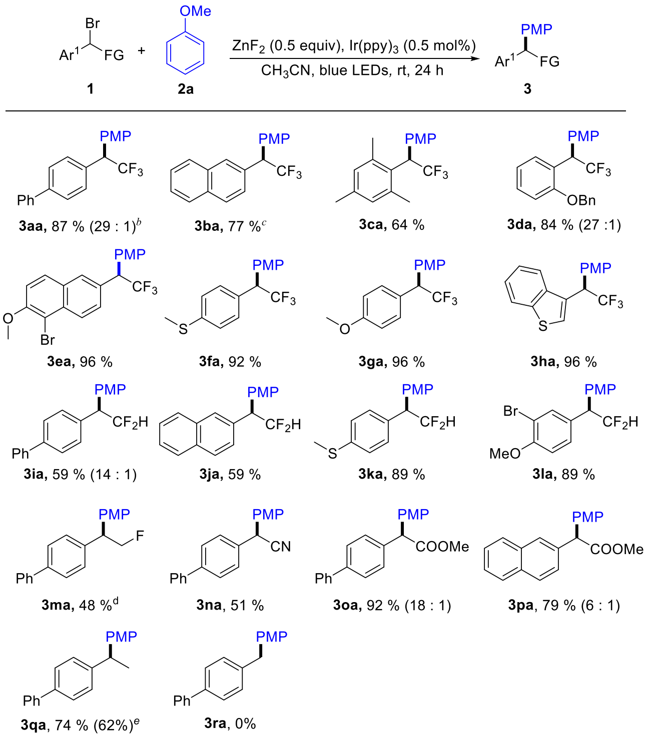


entry	equiv of **2a**	additive (equiv)	solvent	**3aa** (%)	**6** (%)	**7** (%)
1	5	ZnF$_2$ (1)	CH$_3$CN	81	9	3
2	5	ZnF$_2$ (0.5)	CH$_3$CN	81	10	3
3	5	ZnF$_2$ (0.2)	CH$_3$CN	74	8	3
4	5	ZnF$_2$ (0.1)	CH$_3$CN	60	7	2
5	5	none	CH$_3$CN	3	trace	trace
6	8	ZnF$_2$ (0.5)	CH$_3$CN	91	6	3
7	6	ZnF$_2$ (0.5)	CH$_3$CN	88	8	3
8	2	ZnF$_2$ (0.5)	CH$_3$CN	73	24	2
9[b]	5	ZnF$_2$ (0.5)	CH$_3$CN	91	6	3
10	5	AlF$_3$ (0.5)	CH$_3$CN	<5	trace	trace
11	5	TiF$_4$ (0.5)	CH$_3$CN	<5	trace	trace
12[b]	5	ZnBr$_2$ (0.5)	CH$_3$CN	55	26	2
13[b]	5	MgF$_2$ (0.5)	CH$_3$CN	10	trace	trace
14[b]	5	Li$_2$CO$_3$ (0.5)	CH$_3$CN	12	trace	trace
15[b]	5	ZnF$_2$ (0.5)	CH$_2$Cl$_2$	20	0	1
16[b]	5	ZnF$_2$ (0.5)	1,4-dioxane	7	0	trace
17[b]	5	ZnF$_2$ (0.5)	DMF	0	0	0
18[b,c]	5	ZnF$_2$ (0.5)	CH$_3$CN	90	7	3
19[d]	5	ZnF$_2$ (1)	CH$_3$CN	0	0	0
20[e]	5	ZnF$_2$ (1)	CH$_3$CN	0	0	0

[a]Reactions of **1a** (0.2 mmol), **2a**, Ir(ppy)$_3$ (1 mol %), additive, and solvent (2 mL) were irradiated by blue LEDs at room temperature for 24 h. Yields were determined by ^{19}F NMR yield with PhOCF$_3$ as an internal standard. ppy = phenylpyridine. [b]**1a** (0.25 mmol) in 1 mL of solvent. [c]0.5 mol % of Ir(ppy)$_3$. [d]Without Ir(ppy)$_3$. [e]Without blue LED irradiation.

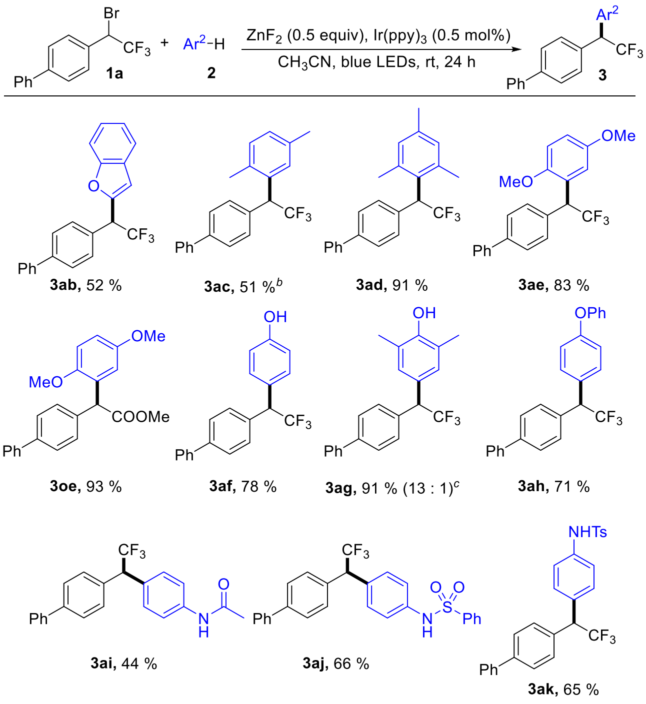
With the optimized conditions in hand (Table 1, entry 18), various electronically deactivated benzylic bromides were tested first to evaluate the practicability of this methodology. With **2a** as the model substrate, a variety of α-trifluoromethyl benzylic bromides **1** bearing electron-rich and electron-neutral substituents could be transformed to the desired products in high yields and with good *para*/*ortho* selectivity (Scheme 2, **3aa**−**3ha**). However, α- trifluoromethyl benzylic bromide with an electron-withdrawing group on the phenyl ring (**1t**) was not an amenable substrate, giving rise to the homocoupling product as the main product, and no desired product was detected (Scheme S3). It is noteworthy that α-difluoromethyl (CF$_2$H) and α-monofluoromethyl (CH$_2$F) groups were also amenable to this reaction, affording the arylation products (**3ia**−**3ma**; these are difficult to prepare by other methods[4]) in moderate to high yields. Remarkably, apart from fluorinated

Scheme 2. Scope of Benzyl Bromides[a]



[a] Reactions of **1** (0.5 mmol), **2** (5 equiv), ZnF$_2$ (0.5 equiv), Ir(ppy)$_3$ (0.5 mol %), and CH$_3$CN (2 mL) were irradiated by blue LEDs at room temperature for 24 h. The *para-/ortho*-isomer ratio of isolated products is shown in parentheses. For those without an isomer ratio, only the para-isomer was isolated. PMP = 4-methoxyphenyl. [b] 6 h, Ir(ppy)$_3$ (0.2 mol %). [c] 12 h. [d] No reaction without Ir(ppy)$_3$. [e] Yield determined by ^{1}H NMR without Ir(ppy)$_3$ is shown in parentheses.

Scheme 3. Scope of Arenes[a]



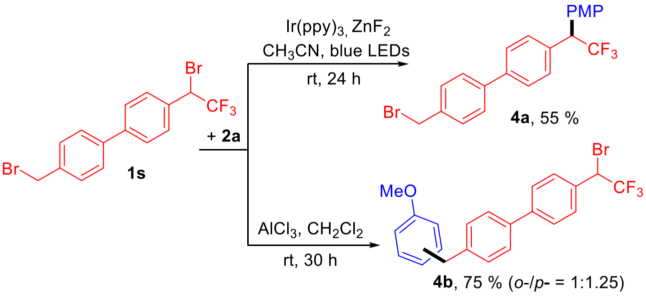
[a] Reactions of **1** (0.5 mmol), **2** (5 equiv), ZnF$_2$ (0.5 equiv), Ir(ppy)$_3$ (0.5 mol %) and CH$_3$CN (2 mL) were irradiated by blue LEDs at room temperature for 24 h. Ts = *p*-toluenesulfonyl. [b] 1 mL of *p*-xylene. [c] The *para*/*meta* regioisomer ratio of isolated products is shown in parentheses. For those without an isomer ratio, only the *para*-isomer was isolated.

methyl groups, the benzylic bromides bearing other electron-withdrawing functionalities such as CN (**3na**) and COOMe (**3oa**–**3pa**), adjacent to the benzylic carbon, underwent reactions smoothly. Furthermore, electron-rich *α*-methyl 4-phenylbenzyl bromide **1q** was also a viable substrate, leading to the desired product **3qa** in 74% yield; however, the control experiment in the absence of the photocatalyst Ir(ppy)$_3$ supports the important role of ZnF$_2$. Interestingly, 4-phenylbenzyl bromide **1r** remains mostly under the present reaction conditions (for more discussions, see Scheme S4).

Next, our attention was turned to the scope of arenes with **1a** as a model substrate (Scheme 3). Generally, electron-rich arenes could provide the products smoothly (**3ab**–**ah**). C-Alkylation products were formed in good yields and with good selectivity with phenols (**3af** and **3ag**). Amides, which are usually incompatible with traditional Friedel–Crafts reactions[5,6] because of the strong coordination of amides to Lewis acids, were amenable to the current reaction (**3af** and **3ag**), highlighting the mildness of our new method.

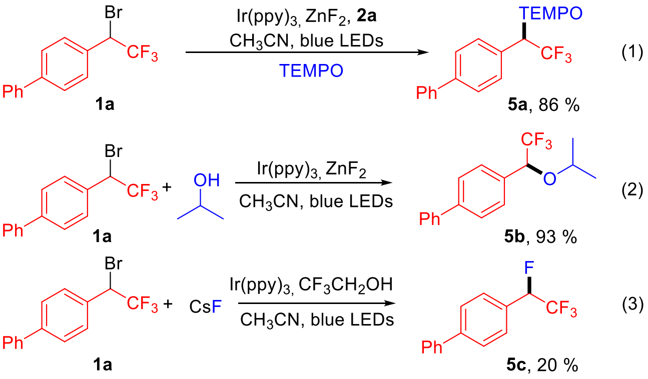
As a normal benzylic bromide such as 4-phenylbenzyl bromide was not reactive under photoredox-catalyzed conditions and destabilized benzylic carbocation was difficult to generate under traditional Friedel–Crafts conditions (see Schemes S1 and S4), we surmised that orthogonal transformation of the ambident substrate that contains electronically biased benzylic bromide might be possible. As expected, when **1s** was subjected to the photoredox-catalyzed conditions, selective arylation of deactivated benzylic bromide to give **4a** was observed; however, under traditional Friedel–Crafts conditions using AlCl$_3$ as Lewis acid, selective arylation of relatively electron rich primary benzylic bromide to form **4b** was observed (Scheme 4). This orthogonal reactivity indicates that our photoredox catalyzed Friedel–Crafts alkylation is suitable for electron-deficient benzyl bromides, while traditional Friedel–Crafts conditions prefer less electron-deficient benzyl bromides.

Scheme 4. Orthogonal Transformation of Electronically Biased Benzyl Bromides

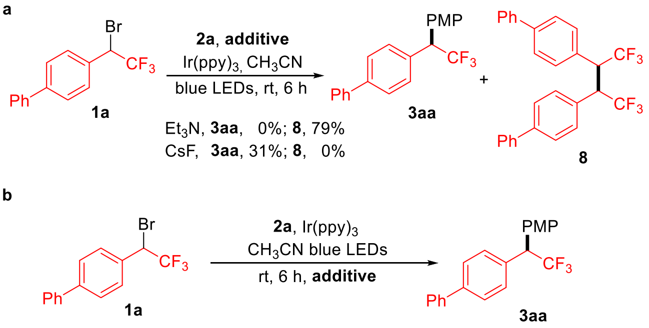


To gain mechanistic understandings of the reaction, a series of experiments were conducted (Schemes 5 and 6 and the Supporting Information). When the reaction was carried out in the presence of TEMPO as a radical scavenger, no desired product **3aa** was formed and product **5a** was detected in 86% yield (Scheme 5, eq 1), suggesting the presence of benzylic radical intermediate. When 2-propanol or fluoride was used instead of *p*-methoxybenzene, the corresponding product **5b** or

Scheme 5. Mechanistic Studies



Scheme 6. Role of ZnF_2



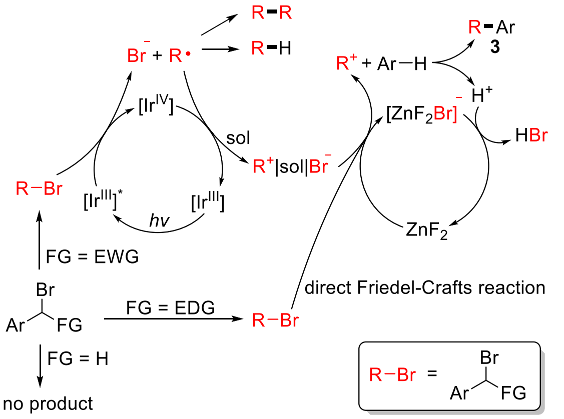
equiv of ZnF_2	equiv of NaBr	1a	3aa
0	0	95 %	3 %
0.2	0	13 %	77 %
0.2	1	82 %	13 %
1.5	1	0 %	84 %

5c was isolated in 93% (Scheme 5, eq 2) and 20% yield (Scheme 5, eq 3), respectively, suggesting the presence of benzylic carbocation intermediate (for more detailed discussions, see Scheme S6).

The role of ZnF_2 was also investigated (Scheme 6; for details, see the Supporting Information). When triethylamine was used instead of ZnF_2, the radical homocoupling product **8** was formed in 79% yield, and when CsF was used instead of ZnF_2, the desired product **3aa** was formed in 31% yield (Scheme 6a). These results indicate that ZnF_2 was not essential for the generation of both benzylic radical and benzylic carbocation. In the absence of ZnF_2, the rate of transformation of **1a** to **3aa** was quite low, and adding 0.2 equiv of ZnF_2 enhanced the rate significantly. However, addition of 1.0 equiv of NaBr decreased the reaction rate until more amount of ZnF_2 was added (Scheme 6b). These data suggest that ZnF_2 may function as a bromide anion scavenger, preventing the recombination of bromide anion and the newly generated carbocation.

On the basis of mechanistic studies, a possible mechanism is proposed (Scheme 7).[17] For substrates in which FG = EDG (**1q**), ZnF_2 itself is enough for the generation of benzylic cation. For substrate in which FG = H (**1r**), because of the absence of α-electron-withdrawing group, reduction of benzylic bromide failed, leading to no desired product. For substrates in which FG = EWG, reduction of this type of benzylic bromides by excited $[Ir^{III}]^*$ gives radical anions, which decompose to radicals and bromide ion. Oxidation of the radicals by $[Ir^{IV}]$ regenerates the $[Ir^{III}]$ catalyst and produce the key carbocation intermediates, which are separated with bromide by the solvent. Capture of bromide by ZnF_2 inhibits the recombination of carbocations with bromide, thus increasing the reaction rate. The carbocations add to arenes to give the desired products after deprotonation. Finally, reaction of $[ZnF_2Br]^-$ with H^+ regenerates the ZnF_2 catalyst.[18]

Scheme 7. Proposed Mechanism



In conclusion, a new method to generate deactivated carbocations, which is previously difficult to access, for Friedel−Crafts-type alkylation of electron-rich arenes has been developed under mild conditions (at room temperature and without strong acid). A myriad of structurally diverse 1-fluoroalkyl-1,1-diarylmethanes can be smoothly obtained, which are useful scaffolds in drug development. The key to success is the generation of deactivate carbocation intermediates via C−Br bond heterolysis, which is enabled by two consecutive single-electron transfer processes by virtue of photoredox catalysis. Our protocol not only provides a novel method for the formation of deactivated carbocation intermediates, but also demonstrates the new application of photoredox catalysis from radical generation to carbocation generation. Further efforts to extend the deactivated carbocation chemistry and make use of the unique activation pattern under photoredox catalysis in carbocation formation are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03258.

Detailed experimental procedures, characterization data, and copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor Youyou Tu, the 2015 Nobel Prize laureate of physiology or medicine, on the occasion of her 90th birthday.

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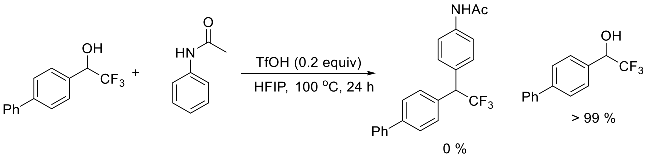
(6) The catalytic amount of strong acid is easy to coordinate with basic functional group. One example is shown in Scheme S2.



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(15) The reduction process prefers electron-deficient substrates, while the oxidation process prefers electron-rich ones. Therefore, it is generally difficult to oxidize a radical (in situ generated by reduction) to give a carbocation species. For example, an electron-deficient radical reduced from **1t** (Scheme S3) can not be oxidized (Scheme 1d, step ii), and **1r** (Scheme S4) can not be reduced to a radical (Scheme 1d, step i).

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(17) For more discussion on ruling out other pathways, see the Supporting Information.

(18) There are two possible catalytic cycles for ZnF_2: $[ZnF_2Br]^-$/ ZnF_2 or $[ZnF_2Br_2]^{2-}$/ $[ZnF_2Br]^-$. One of them is illustrated in Scheme 7.