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Synthesis of Difluoroalkylated Benzofuran, Benzothiophene, and Indole Derivatives via Palladium-Catalyzed Cascade Difluoroalkylation and Arylation of 1,6-Enynes

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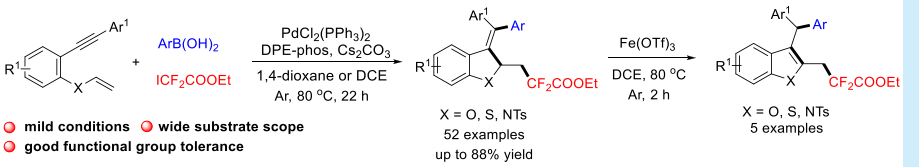
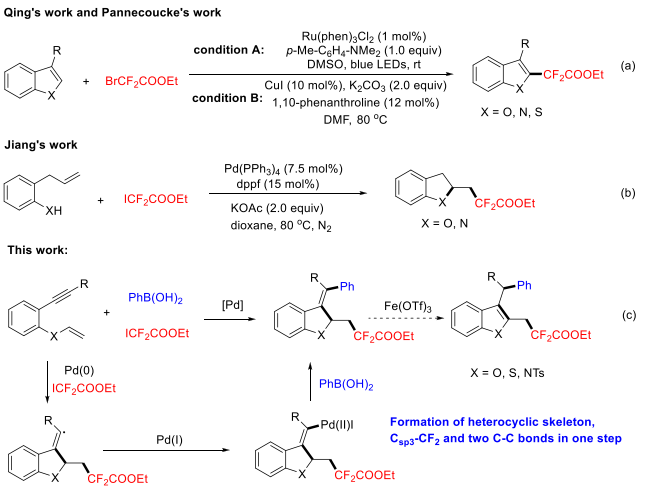


ABSTRACT: A novel and efficient method for the synthesis of difluoroalkylated benzofuran, benzothiophene, and indole derivatives via palladium-catalyzed aryldifluoroalkylation of 1,6-enynes with ethyl difluoroiodoacetate and arylboronic acids has been established. High reaction efficiency, mild conditions, broad substrate scope, and good functional group tolerance are the features of this protocol. Notablely, the resultant products can be smoothly converted into CF_2-containing benzofurans, benzothiophenes and indoles through an isomerization process catalyzed by $Fe(OTf)_3$.

Benzofuran, benzothiophene, and indole derivatives are ubiquitous in bioactive molecules, natural products, pharmaceuticals and functional materials.[1] Therefore, extensive attention has been paid to develop the versatile methods for the synthesis of these structurally diverse heterocycles.[2] As an important fluorine-containing group, the difluoromethylene group (CF_2), which could be regarded as a bioisostere for an oxygen atom or a carbonyl group, exhibits unique properties in drug design.[3] To meet the increasing demand of drug discovery, there is no doubt that the incorporation of difluoromethylene group to heterocyclic skeletons including benzofuran, benzothiophene, and indole derivatives to adjust their chemical and biological properties is of great value. However, efficient approaches to synthesis of these difluoroalkylated heterocycles are very limited.[4−6] For example, the Qing[4] and Pannecoucke groups[5] independently reported the direct C-2 difluoromethylation of indoles and benzofurans utilizing visible-light-mediated photoredox or copper catalysis (Scheme 1a). In addition, Jiang's group[6] developed a palladium-catalyzed fluoroalkylative cyclization of olefins with the formation of C_{sp3}−CF_2 and C−O/N bonds in one step to obtain difluoroalkylated 2,3-dihydrobenzofuran and indolin derivatives (Scheme 1b). In order to improve the molecular diversity, it is still highly desirable to develop practical methods for the construction of heterocycle frameworks and introduction of the difluoromethylene group with broader generality.

In 2015, the Zhang group first reported a palladium-catalyzed fluoroalkylation of alkenes to access fluoroalkylated alkenes via a radical pathway.[7] In addition, they made many original contributions in the field of transition-metal-catalyzed cross couplings of difluoroalkyl halides with arylboron reagents and aryl halides, which facilitate the synthesis of highly desirable difluoroalkylated arenes.[8] Nowadays, great progress has been made in the field of CF_2-radical-initiated difluoroalkylation−arylation of alkenes or alkynes, which provided a

Scheme 1. Strategies for the Synthesis of Difluoroalkylated Heterocycles



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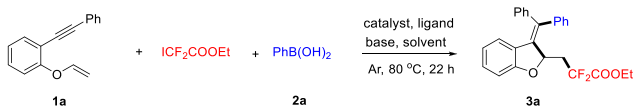
step- and atom-economic means to access various fascinating CF_2-containing compounds.[9] Fluoroalkylation−borylation of alkynes has also been reported by Zhang's group, and the mechanistic studies suggested that trans-fluoroalkylated alkenyl iodide is a key intermediate.[10] Meanwhile, radical cascade of phenol-linked 1,6-enynes has been one of the most efficient routes for the construction of functionalized benzofuran derivatives.[11] Inspired by these advances and our previous work,[12] we envisaged that difluoroalkylated benzofuran derivative would be constructed via palladium-catalyzed cascade difluoroalkylation-arylation of 1,6-enyne and difluoroalkylated benzofuran could be further afforded through an isomerization process catalyzed by $Fe(OTf)_3$ (Scheme 1c).[13] Furthermore, we expected this methodology could be extended to the synthesis of difluoroalkylated benzothiophene and indole derivatives.

To test the hypothesis, our study was carried out by employing phenol-linked 1,6-enyne **1a** as the model substrate, ethyl difluoroiodoacetate (1.5 equiv) as the fluoroalkylating reagent, and phenyl boronic acid **2a** (2.0 equiv) as the coupling partner in the presence of Cs_2CO_3 (2.0 equiv) and $PdCl_2(PPh_3)_2$ (10 mol %) in 1,4-dioxane at 80 °C for 22 h. Gratifyingly, the desired product **3a** was obtained in 55% yield (Table 1, entry 1). In order to improve the yield, a series of

Table 1. Optimization of Reaction Conditions[a]



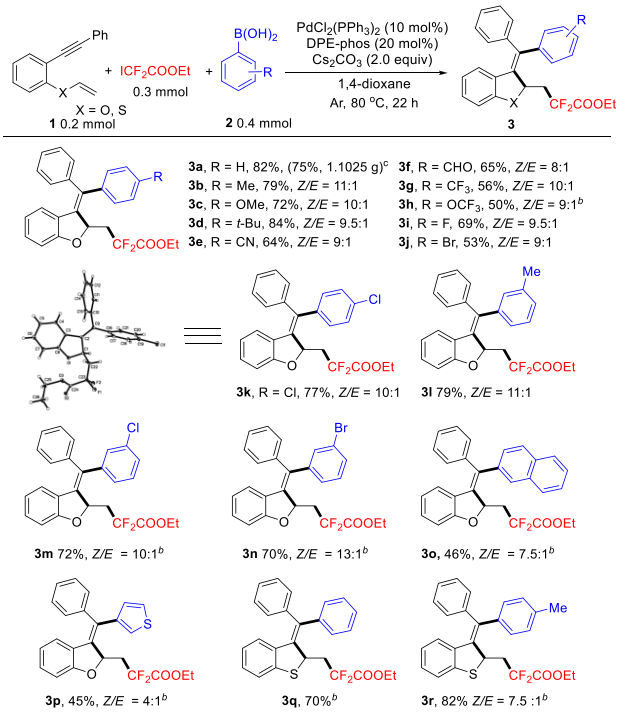
entry	catalyst	ligand	base	solvent	yield (%)
1	$PdCl_2(PPh_3)_2$		Cs_2CO_3	dioxane	55
2	$PdCl_2(PPh_3)_2$	PCy_3	Cs_2CO_3	dioxane	47
3	$PdCl_2(PPh_3)_2$	PPh_3	Cs_2CO_3	dioxane	65
4	**$PdCl_2(PPh_3)_2$**	**DPE-phos**	**Cs_2CO_3**	**dioxane**	**82**
5		DPE-phos	Cs_2CO_3	dioxane	0
6	$PdCl_2(PPh_3)_2$	DPE-phos		dioxane	0
7	$PdCl_2(PPh_3)_2$	DPE-phos	K_2CO_3	dioxane	46
8	$PdCl_2(PPh_3)_2$	DPE-phos	Na_2CO_3	dioxane	trace
9	**$PdCl_2(PPh_3)_2$**	**DPE-phos**	**Cs_2CO_3**	**DCE**	**82**
10	$PdCl_2(PPh_3)_2$	DPE-phos	Cs_2CO_3	MeCN	78

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), ethyl difluoroiodoacetate (0.3 mmol), catalyst (10 mol %), ligand (20 mol %), base (0.4 mmol) in solvent (2.0 mL), stirring at 80 °C under Ar for 22 h. Isolated yields.

ligands were screened, and the results indicated that the product **3a** could be isolated in a high yield of 82% by using DPE-phos as the ligand (Table 1, entries 2−4). Better results were not observed when other Pd catalysts such as $Pd(TFA)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $PdCl_2$, and $Pd(OAc)_2$ were detected (see the Supporting Information (SI) for details). No reaction occurred in the absence of a catalyst or a base, illustrating their necessity in this transformation (Table 1, entries 5 and 6, see the SI for details). Switching Cs_2CO_3 to other bases resulted in a lower yield (Table 1, entries 7 and 8, see the SI for details). A brief survey of the solvents revealed that DCE was also suitable solvent for the reaction as the same yield of **3a** was observed (Table 1, entries 9 and 10, see the SI for details). Reducing the reaction temperature to 60 °C or raising to 90 °C led to a lower yield (see the SI for details).

With the optimized reaction conditions established, we first investigated the scope of various arylboronic acids (Scheme 2).

Scheme 2. Substrate Scope of Arylboronic Acids[a]



[a]Yields of the isolated products. The *Z*/*E* values were determined by ^{19}F NMR and ^1H NMR analysis. [b]DCE as the solvent. [c]The yield was obtained on a 3.5 mmol scale.

To our delight, substrates with both electron-donating and electron-withdrawing substituents at the *para*-position of the phenyl ring were successfully aryldifluoroalkylated. For example, methyl, methoxy, *tert*-butyl, nitrile, formyl, trifluoromethyl, trifluoromethoxy, and halide (F, Cl and Br) groups were well tolerated, affording the corresponding products **3b**−**3k** in moderate to high yields. The structure and the *Z*/*E* conformation of **3k** was implied by X-ray crystal structure analysis. *m*-Methyl-, -bromo-, and -chloro-substituted arylboronic acids could also generate the desired products **3l**−**3n** in 70−79% yields. In addition, 2-naphthylboronic acid and 3-thiopheneboronic acid were also capable and produced the target products **3o** and **3p** in 46% and 45% yields, respectively. Notablely, the reaction of arylboronic acids with thiophenolic 1,6-enyne and ethyl difluoroiodoacetate proceeded smoothly to deliver the desired benzo[*b*]thiophene derivatives **3q** and **3r** in good yields, respectively.

Next, the scope of different phenolic 1,6-enyne derivatives was evaluated, and the results are summarized in Scheme 3. Various substituent groups on the benzene ring attached at the terminal alkyne were first examined under the optimized conditions, and most of them were compatible with the protocol. For the *para*-position of the phenyl ring, substrates substituted with electron-donating groups including methyl, ethyl, phenyl, *tert*-butyl, and methoxy smoothly converted into products **3ba**−**3fa** in 51−88% yields. Gratifyingly, compounds with electron-withdrawing groups such as acetyl, ether, nitrile, and trifluoromethyl also afforded the corresponding products

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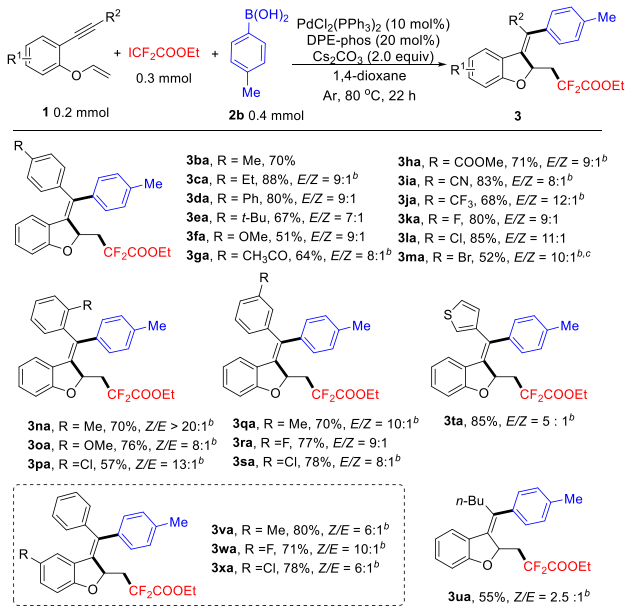
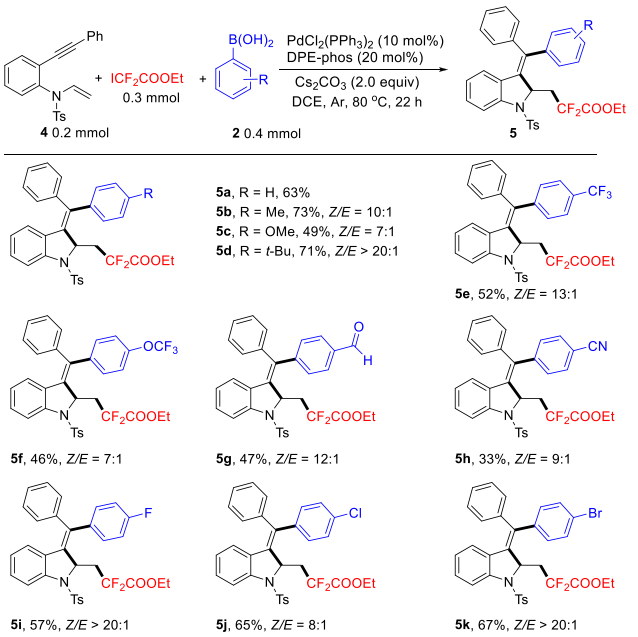
Scheme 3. Substrate Scope of Phenolic 1,6-Enynes[a]



[a]Yields of the isolated products. The *Z*/*E* values were determined by ^{19}F NMR and ^{1}H NMR analysis. [b]DCE as the solvent. [c]**2b** (0.24 mmol).

Scheme 4. Aryldifluoromethylation of Anilinic 1,6-Enyne[a]



[a]Yields of the isolated products. The *Z*/*E* values were determined by ^{19}F NMR and ^{1}H NMR analysis.

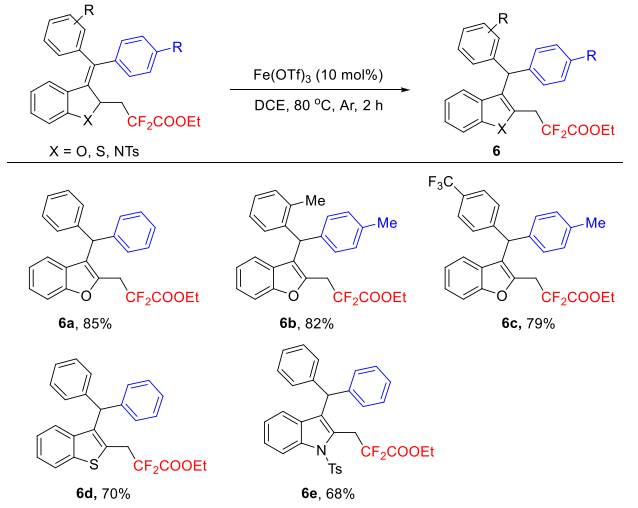
3ga–**3ja** in good yields, demonstrating the generality of this method.

Moreover, halogens including fluorine, chlorine, and bromine showed good compatibility in the reaction, and the products **3ka**–**3ma** were obtained in 52–85% yields, which provided good opportunities for further synthetic transformations. Substrates with functional groups at the *ortho*- or *meta*-position of the benzene ring were also examined and generated the desired products **3na**–**3sa** in satisfactory yields, illustrating that the reaction was not markedly affected by the steric hindrance. For example, the products **3na**, **3oa**, and **3pa** with 2-methyl, 2-methoxy, and and 2-chlorine substituents were obtained in 70%, 76%, 57% yields, respectively. The products **3qa**, **3ra**, and **3sa** with 3-methyl, 3-fluoro, and 3-chloro substituents were also provided in 70%, 77%, and 78% yields, respectively. It is notable that substrates with a 3-thienyl group or *n*-butyl group on the terminal alkyne proceeded well and generated the desired products **3ta** and **3ua** in 85% and 55% yields, respectively. In addition, substrates with methyl, fluoro, and chloro substituents on the phenolic ring were explored, all of which showed high efficiency to give the corresponding products **3va**–**3xa** in 71–80% yields.

In order to extend this protocol to the synthesis of difluoroalkylated indole derivatives, *N*-tosyl (Ts)-protected anilinic 1,6-enyne **4** was prepared and then reacted with a variety of arylboronic acids and ethyl difluoroiodoacetate under the standard conditions. As demonstrated in Scheme 4, the difluoroalkylated indolin **5a** could be afforded in 63% yield by employing phenylboronic acid as the substrate. Moreover, electron-donating and electron-withdrawing group and halogen atom substituted arylboronic acids also underwent the aryldifluoroalkylation process to produce the corresponding products **5b**–**5h** in 33–73% yields.

As 3-substituted indoles and benzofurans could be generated by Fe(OTf)$_3$-catalyzed isomerization of 3-methyleneindoline and benzofuran derivatives,[13] we expected to synthesize difluoroalkylated benzofuran, benzothiophene, and indole through the aromatization of products **3** and **5** under Fe catalysis (Scheme 5). Gratifyingly, the difluoroalkylated

Scheme 5. Fe(OTf)$_3$-Catalyzed Isomerization of 3 and 5[a]



[a]Reaction conditions: **3** or **5** (0.2 mmol), Fe(OTf)$_3$ (10 mol %) in 1,2-dichloroethane (2 mL), stirring at 80 °C under Ar for 2 h. Yields of the isolated products.

benzofurans **6a**–**6c** were generated in good yields. In addition, difluoroalkylated benzothiophene **6d** and indole **6e** were provided in 70% and 68% yields, respectively.

To further demonstrate the utility of this new methodology, late-stage functionalization of bioactive molecules was examined (Scheme 6). Treatment of diacetone-D-glucofuranose-derived 1,6-enyne **1y** with ethyl difluoroiodoacetate and phenyl boronic acid under standard conditions generated the corresponding aryldifluoroalkylated product **3ya** in 80% yield

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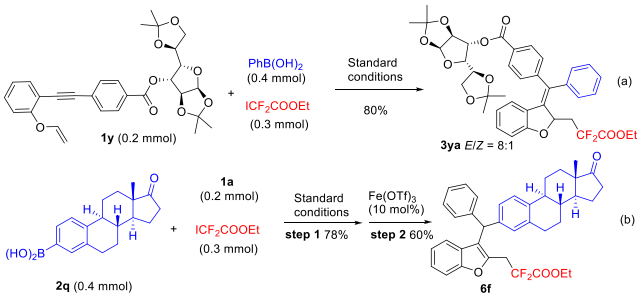
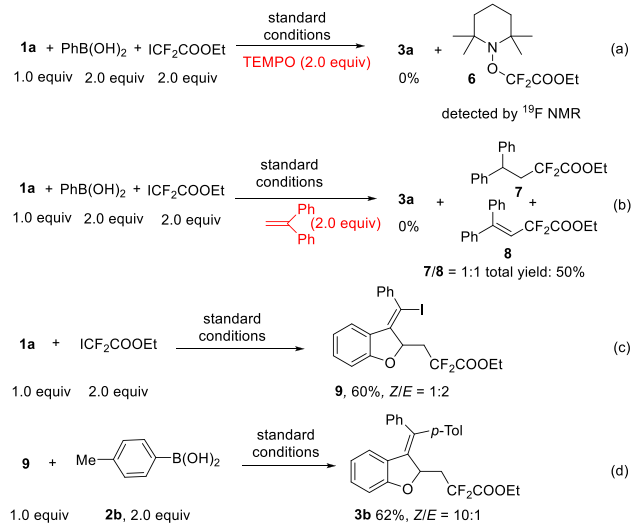
Scheme 6. Late Stage Functionalization of Biologically Active Compounds



(Scheme 6a). Moreover, reaction of **1a** with estrone-derived boronic acid **2q** and ethyl difluoroiodoacetate followed by $Fe(OTf)_3$-catalyzed isomerization produced the desired difluoroalkylated product **6f** with high efficiency (Scheme 6b).

To gain insights into the reaction pathways, several control experiments were conducted (Scheme 7). It was found that the

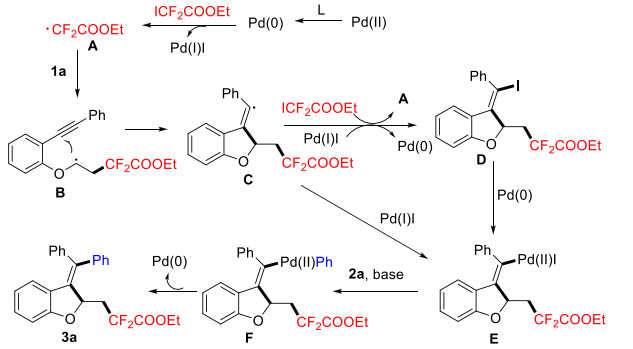
Scheme 7. Control Experiments



formation of product **3a** was completely suppressed when the radical scavengers 2,2,6,6-teramethyl-1-piperidinyloxy (TEMPO) was added under the standard conditions, and the TEMPO−CF_2COOEt adduct **6** was detected by ^{19}F NMR (Scheme 7a). The transformation was also performed in the presence of 1,1-diphenylethylene, and a mixture of **7** and **8** with a 1:1 ratio was isolated in 50% yield without the formation of **3a** (Scheme 7b). As we previously demonstrated, these results indicated that a difluoroalkyl radical might be involved in this aryldifluoroalkylation process. Moreover, treatment of **1a** with ethyl difluoroiodoacetate in the absence of phenylboronic acid gave the iododifluoroalkylation product **9** in 60% yield with a *Z*/*E* ratio of 2:1(Scheme 7c). Interestingly, when the mixture **9** was used to react with **2b**, the product **3b** could be obtained in 62% yield and the *Z*/*E* ratio was 10:1, and this could be explained by the involving of an isomerization *via* $TS_{syn\text{-}anti}$ in this cross-coupling process (Scheme 7d).[14] Although the compound **3b** was afforded in a lower yield than that in the one-pot process, a vinyl iodide intermediate **9** should be considered to be involved.

In light of the control experiments and previous work,[10] a plausible mechanism is proposed in Scheme 8. First, the Pd(0)

Scheme 8. Proposed Mechanism



species is produced by the reduction of Pd(II) and then reacts with ethyl difluoroiodoacetate to generate Pd(I) and difluoroalkyl radical **A**. The radical **A** attacks the vinyl moiety of **1a** to form the alkyl radical intermediate **B**, followed by cyclization to give vinyl radical **C**. Subsequently, vinyl iodide intermediate **D** could be formed via atom transfer of iodine from ICF_2COOEt or Pd(I) species with the release of Pd(0). Oxidative addition of Pd(0) to vinyl iodide **D** leads to the intermediate **E**, which also could be afforded by the direct reaction of vinyl radical **C** with Pd(I) species. Palladium(II) aryl complex **F** is then generated via a transmetalation process between the intermediate **E** and phenylboronic acid **1a** in the presence of the base. Finally, reductive elimination of **F** delivers the desired product **3a** and regenerates the Pd(0) species simultaneously.

In summary, we have successfully developed a palladium-catalyzed cascade difluoroalkylation and arylation of 1,6-enynes for the convenient synthesis of biologically important difluoroalkylated benzofuran, benzothiophene, and indole derivatives. In this reaction, the heterocyclic skeleton, one $C_{sp3}-CF_2$ bond, and two C−C bonds could be formation in one step. Furthermore, the corresponding difluoroalkylated benzofurans, benzothiophenes, and indoles could be afforded via a $Fe(OTf)_3$-catalyzed isomerization process. Good functional group tolerance and easily available starting materials make this protocol a general methodology to access difluoroalkylated advance heterocyclic molecules. The detailed mechanistic investigations and applications of this reaction are currently underway 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.9b04681.

General procedure, characterization data, ^1H, ^{13}C and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 1967789 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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