JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2019, 84, 8345−8359
Featured Article
pubs.acs.org/joc

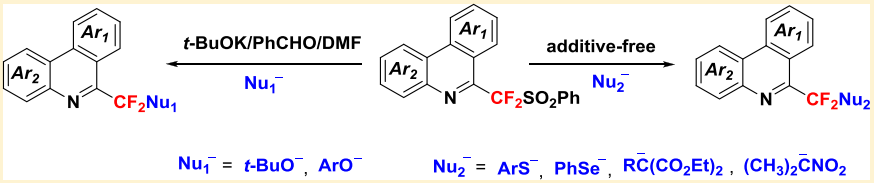
Fluoroalkylation of Various Nucleophiles with Fluoroalkyl Sulfones through a Single Electron Transfer Process

Pan Xiao,[†,‡] Chuanfa Ni,[†] Wenjun Miao,[†] Min Zhou,[†] Jingyu Hu,[†] Dingben Chen,[†] and Jinbo Hu*[,†,‡]

[†]Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

[‡]School of Physical Science and Technology, ShanghaiTech University, 100 Haike Road, Shanghai 201210, China

Supporting Information



ABSTRACT: The fluoroalkylation of various nucleophilic reagents with (phenylsulfonyl)difluoromethyl ($PhSO_2CF_2$)-substituted phenanthridines was achieved to give fluorinated phenanthridine derivatives, which enables the construction of both carbon−heteroatom and carbon−carbon bonds via the substitution of the phenylsulfonyl group. Mechanistic studies indicated that these reactions proceed through a unimolecular radical nucleophilic substitution ($S_{RN}1$) mechanism. It is worthwhile noting that in the cases of O-nucleophiles (*t*-BuO^- and PhO^-), the addition of *t*-BuOK/PhCHO could significantly promote the reactions, due to the in situ formation of a highly reactive electron donor species through the interaction of *t*-BuOK, PhCHO, and the solvent DMF, which can effectively initiate the single electron transfer process.

INTRODUCTION

Recently, organofluorine chemistry has been a research field of great interest as fluorine plays conspicuous and increasingly important roles in pharmaceuticals, agrochemicals, as well as in materials science.[1,2] Therefore, the quest for new reagents and methodologies to efficiently introduce various fluorine-containing moieties into structurally diverse nonfluorinated organic compounds makes this research area very attractive to scientists.[3] Meanwhile, nitrogen-containing heterocycles are a class of important chemical structures,[4] among which the phenanthridine core is commonly present in many biologically active and medicinally useful natural products.[5] In addition, some phenanthridine derivatives have been used as luminescent materials.[6] In this context, selectively incorporating organofluorine functionalities into phenanthridine rings may significantly improve their biological activity and optoelectronic property due to the unique role of fluorine substitution.[1c,2a,7,8]

Fluoroalkyl phenyl sulfones (R_fSO_2Ph) have been developed as versatile fluoroalkylation reagents and used for introducing diverse fluoroalkyl groups into organic molecules by us and others.[9−11] It has been reported that R_fSO_2Ph can be converted to R_fTMS (TMS = trimethylsilyl)[9a] or R_fH[9b−f] under the reduction of magnesium. Besides, R_fSO_2Ph can be attacked by alkoxide or hydroxide to remove the $PhSO_2$ group and to give rise to fluoroalkyl carbanions, which further react with electrophiles such as PhSSPh and PhCHO or are cuprated by Cu(I) salt to generate R_fCu.[10] Furthermore, R_fSO_2Ph can be transformed to fluorinated olefins under certain conditions.[11] However, the use of R_fSO_2Ph for radical fluoroalkylation by R_f-SO_2Ph bond cleavage to form $R_f\bullet$ is still underdeveloped due to the weak electron transfer ability of many conventional radical initiators toward R_fSO_2Ph.[12] Indeed, it was only in early 2016 that synthetically useful radical fluoroalkylations with fluorinated sulfones were reported by virtue of heteroaryl sulfone reagents.[13] Recently, we have disclosed a method to prepare phenylsulfonyldifluoromethyl ($PhSO_2CF_2$)-substituted phenanthridines such as **1a** (Scheme 1) by the process of radical fluoroalkylation with difluoromethyl phenyl sulfone ($PhSO_2CF_2H$).[14] To expand the application of **1a** and its derivatives, it is of great interest to further modify these compounds by developing new desulfonative transformations. Herein, we report the radical difluoroalkylation reactions of 6-[difluoro(phenylsulfonyl)-methyl]phenanthridines with various nucleophiles through a unimolecular radical nucleophilic substitution ($S_{RN}1$) mechanism, which represents a new reaction mode of R_fSO_2Ph.

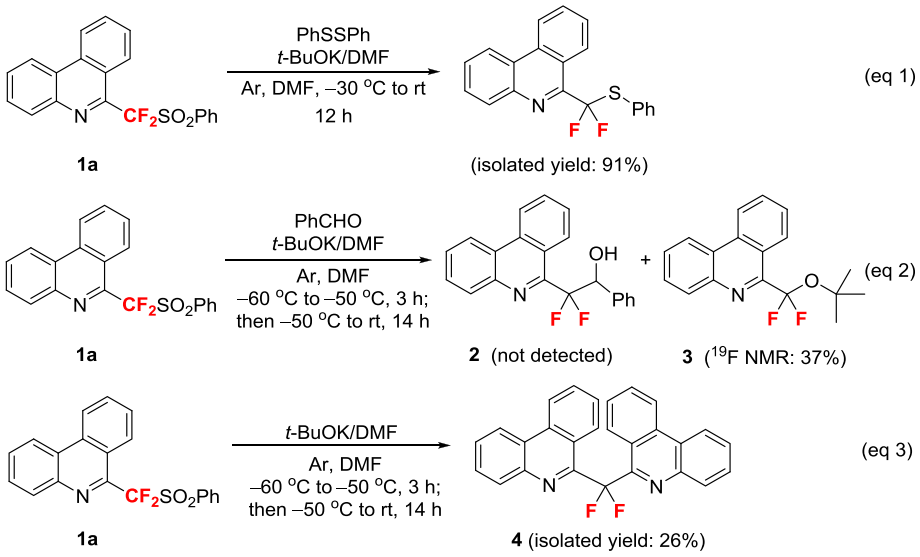
RESULTS AND DISCUSSION

Initial Results. Recently, we accomplished the substitution of the $PhSO_2$ group in **1a** with the PhS group using PhSSPh as the electrophilic reagent under the attack of *t*-BuOK (Scheme 1, eq 1),[14] which was shown to proceed through a fluoroalkyl

Received: February 12, 2019
Published: May 14, 2019

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

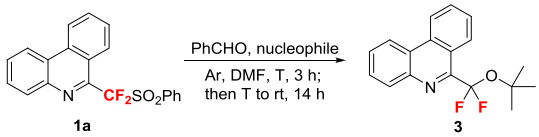
Scheme 1. Desulfonative Transformations of 1a



carbanion intermediate.[10a,b] However, when PhCHO was used instead of PhSSPh as an electrophile, it was surprising to observe that the O-fluoroalkylation product **3** rather than the expected alcohol **2** was formed (Scheme 1, eq 2). This unusual result indicates that the reaction of **1a** with *t*-BuOK and PhCHO did not involve a fluoroalkyl carbanion intermediate. On the contrary, in the absence of PhCHO or any other electrophiles, **1a** underwent attack by *t*-BuOK and further reacted with another molecule of itself to generate **4** (instead of **3**) as the main product (Scheme 1, eq 3),[14] thus revealing that the addition of PhCHO plays an important role in the formation of the O-fluoroalkylation product **3**. Inspired by previous reports in which a single electron transfer (SET) pathway may be involved in the Cannizzaro reaction,[15] we envisioned that the reaction of **1a** with *t*-BuOK in the presence of PhCHO may proceed through a unimolecular radical nucleophilic substitution ($S_{RN}1$) process, where the combination of *t*-BuOK/PhCHO serves as the initiator. The unprecedented reactivity of **1a** toward potassium *tert*-butoxide demonstrated a proof of concept for further development of radical transformation of R_fSO_2Ph with a series of nucleophiles. To our knowledge, there has been no report describing the $S_{RN}1$ reaction between a fluoroalkyl sulfone and a nucleophilic reagent. Previously, fluoroalkyl halides rather than fluoroalkyl sulfones were normally used for the fluoroalkylation of nucleophilic reagents.[16]

Alcoholates as Nucleophiles. Our investigation for the desulfonative fluoroalkylations started from the optimization of the reaction conditions for the generation of compound **3** by using **1a** as the substrate, *t*-BuOK as the nucleophile, PhCHO as the additive, and DMF as the solvent (Table 1). When the molar ratio of **1a**/*t*-BuOK/PhCHO was 1.0:2.0:1.0, we examined the effect of temperature on the reaction. As is shown in Table 1, it is clear that the starting temperature significantly affected the reaction. The yield of **3** decreased significantly as the starting temperature was increased to room temperature, and temperatures between −60 and −50 °C were the optimal starting temperatures for the reaction (Table 1, entries 1−4). When *t*-BuONa was used instead of *t*-BuOK as the nucleophile, the reaction became very sluggish, which revealed the importance of the countercation effect in the reaction (Table 1, entry 5). Subsequently, we screened the equivalents of *t*-BuOK and found that 2.5 equiv of *t*-BuOK was optimal for the formation of **3** (Table 1, entries 1, 6−8). In addition, the amounts of PhCHO could also affect the reaction significantly, with 1.0 equiv being the optimal amount (Table 1, entries 7, 9−12). It is noteworthy that the desired O-fluoroalkylation reaction was very sluggish in the absence of PhCHO (Table 1, entry 9), thus demonstrating that PhCHO plays a crucial role in the generation of **3**.

Table 1. Optimization of Reaction Conditions for the Formation of 3[a]



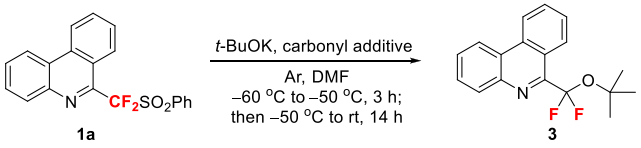
entry	nucleophile	1a/nucleophile/PhCHO	T (°C)	3 (%)[b]
1	*t*-BuOK[c]	1.0:2.0:1.0	−60 to −50	52
2	*t*-BuOK[c]	1.0:2.0:1.0	−30	42
3	*t*-BuOK[c]	1.0:2.0:1.0	rt	11
4	*t*-BuOK[c]	1.0:2.0:1.0	50	17
5	*t*-BuONa[d]	1.0:2.0:1.0	−60 to −50	6
6	*t*-BuOK[c]	1.0:1.5:1.0	−60 to −50	22
7	***t*-BuOK**[c]	**1.0:2.5:1.0**	**−60 to −50**	**67**
8	*t*-BuOK[c]	1.0:3.0:1.0	−60 to −50	54
9	*t*-BuOK[c]	1.0:2.5:0	−60 to −50	3
10	*t*-BuOK[c]	1.0:2.5:0.5	−60 to −50	59
11	*t*-BuOK[c]	1.0:2.5:1.5	−60 to −50	57
12	*t*-BuOK[c]	1.0:2.5:2.0	−60 to −50	39

[a]Reaction conditions: **1a** (0.1 mmol), DMF (0.8 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [c]*t*-BuOK/DMF (1.0 M) was prepared by dissolving *t*-BuOK in DMF and was then added dropwise into the reaction system. [d]*t*-BuONa/DMF (1.0 M) was used.

We also investigated the influence of other carbonyl compounds by replacing PhCHO with additives including aromatic aldehydes, aliphatic aldehydes, and aromatic ketones (Table 2). Compared with PhCHO (Table 2, entry 1), electron-rich aromatic aldehydes (Table 2, entries 2−6), benzaldehydes bearing weak electron-withdrawing groups

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

Table 2. Screening of Carbonyl Additives[a]



1a 3

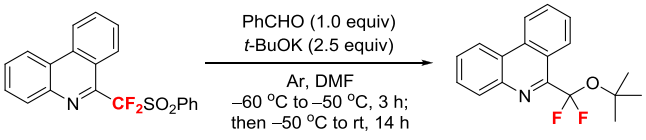
entry	carbonyl additive	3, yield (%)[b]
1	PhCHO	67
2	2-Me-C_6H_4CHO	44
3	3-Me-C_6H_4CHO	56
4	4-Me-C_6H_4CHO	53
5	2-MeO-C_6H_4CHO	59
6	4-MeO-C_6H_4CHO	46
7	2-CHO-C_6H_4CHO	58
8	3-CHO-C_6H_4CHO	50
9	4-CHO-C_6H_4CHO	35
10	3-O_2N–C_6H_4CHO	17
11	4-O_2N–C_6H_4CHO	0
12	4-NC-C_6H_4CHO	20
13	2-naphthaldehyde	57
14	cinnamaldehyde	46
15	isobutyraldehyde	16
16	benzophenone	18

[a]Reaction conditions: **1a** (0.1 mmol), aldehyde (1.0 equiv), *t*-BuOK (2.5 equiv), DMF (0.8 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

(Table 2, entries 7 and 8), and 2-naphthaldehyde (Table 2, entry 13) had a negative, but relatively small effect on the reaction. However, 1,4-phthalaldehyde (Table 2, entry 9) and benzaldehydes with strong electron-withdrawing groups such as $-NO_2$ and $-CN$ (Table 2, entries 10–12) remarkably decreased the yields of **3**. In addition to aromatic aldehydes, cinnamaldehyde could also give rise to moderate yield (Table 2, entry 14), but isobutyraldehyde could only afford a low yield of product (Table 2, entry 15). When benzophenone was used instead of PhCHO, the reaction proceeded in quite low efficiency (Table 2, entry 16). In general, among all the carbonyl compounds examined, PhCHO was identified to be the most effective additive (Table 2, entry 1).

However, the "hard" nature of alkoxides (such as *tert*-butoxide) could lead to the competitive consumption of the starting material **1a** by the nucleophilic attack of an alkoxide toward $PhSO_2$, which restricted the improvement of the yield of the O-fluoroalkylation product. In our case, a full consumption of sulfone **1a** led to the desired product **3** only in moderate yield even under the optimized conditions, where the remainder of the mass balance was attributed to the unidentified decomposition of **1a** as well as the formation of trace amounts of 6-(difluoromethyl)phenanthridine and compound **4**. Moreover, the yield of **3** decreased significantly (Scheme 2) when the reaction was scaled up from 0.1 mmol

Scheme 2. Synthesis of 3 from 1a and *t*-BuOK



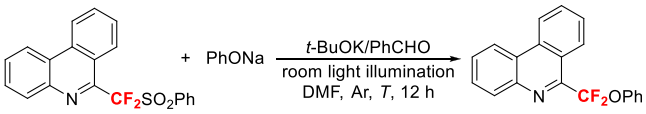
1a (0.2 mmol) **3** (48%)

scale to 0.2 mmol scale, probably due to the increasingly competitive nucleophilic attack of *tert*-butoxide toward $PhSO_2$ to release $ArCF_2^-$.

To overcome the above-mentioned limitations of the substitution reaction of **1a** with alkoxides (such as *t*-BuOK), we turned our attention to the use of "soft" nucleophiles with the hope that we can develop more effective $S_{RN}1$ transformations of **1a**. Indeed, in 1974, Kornblum and co-workers reported the substitution reactions of α-nitrosulfone with several soft carbon nucleophiles via the SET process, which encouraged us to pursue nucleophilic reactions with fluoroalkyl sulfones.[17]

Phenolates as Nucleophiles. Phenolates have been used for the smooth displacement of the halogen atom (X) of some fluoroalkyl halides (R_f–X; X = I, Br, Cl) under additive-free conditions;[16d–f] however, PhONa failed to react with **1a** under similar conditions, even at increased temperatures (Table 3,

Table 3. Optimization of Reaction Conditions for the Formation of 6a[a]



1a 5a 6a

entry	1a/PhONa	t-BuOK/PhCHO	T (°C)	6a, yield (%)[b]
1	1:2		–50 to rt	trace
2	1:2		80	trace
3	1:2		100	trace
4	1:2	1.0:1.0	rt	68
5	1:3	1.0:1.0	rt	88
6	1:4	1.0:1.0	rt	88
7[c,d]	1:3	1.0:1.0	rt	>99 (93[e])
8[c]	1:3	0:1.0	rt	trace
9[c]	1:3	1.0:0	rt	17

[a]Reaction conditions: **1a** (0.1 mmol), DMF (1.0 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [c]A DMF solution of *t*-BuOK was added dropwise into the reaction system. [d]Reaction conditions: **1a** (0.2 mmol), DMF (2.0 mL), under argon atmosphere. [e]Isolated yield.

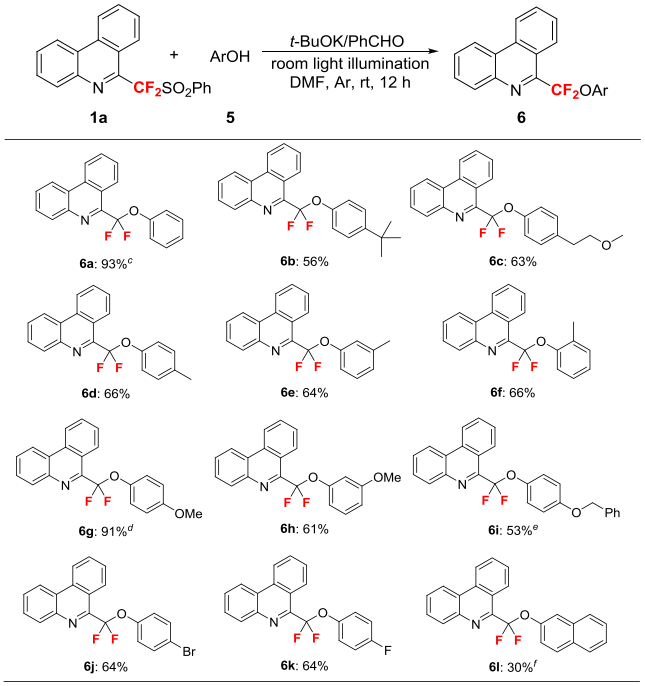
entries 1–3), indicating that the direct electron transfer from the phenoxide ion to **1a** is inefficient. Considering that the addition of PhCHO could promote the reaction between **1a** and *t*-BuOK, we tried the reaction between **1a** and PhONa in the presence of *t*-BuOK and PhCHO. To our delight, when *t*-BuOK (1.0 equiv) and PhCHO (1.0 equiv) were added, the reaction proceeded smoothly at room temperature and the desired product **6a** was observed in 68% ^{19}F NMR yield (Table 3, entry 4). A screening of the amount of PhONa showed that 3.0 equiv is optimal for the reaction (Table 3, entries 4–7). In the above-mentioned conditions, *t*-BuOK was added in solid form. An optimization of the experimental procedures showed that the dropwise addition of the DMF solution of *t*-BuOK could result in a yield of **6a** (>99% yield based on ^{19}F NMR, 93% yield after isolation) that was much higher than that of the addition of the *t*-BuOK solid in one portion (88% yield based on ^{19}F NMR) (Table 3, entries 5 and 7). Control experiments in the presence of either *t*-BuOK or PhCHO afforded product **6a** in only trace to low yields, demonstrating that the

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345–8359

interaction between *t*-BuOK and PhCHO plays a crucial role (Table 3, entries 8 and 9).

Encouraged by the above results, we investigated the scope of the phenolate nucleophiles by slightly modifying the optimized reaction conditions shown in entry 7 of Table 3. Although phenolates can be used as isolated reagents, we chose phenols **5** as the pronucleophiles due to their ready availability; meanwhile, *t*-BuOK was used as both the base for deprotonation and one of the components of the initiator (Table 4).

Table 4. Substitution Reactions of 1a with Phenol Derivatives 5[a,b]

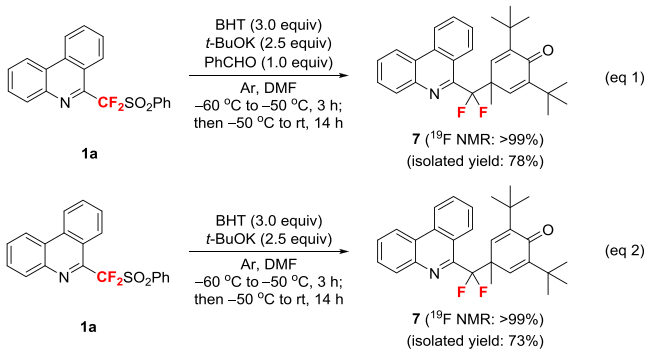


[a]Reaction conditions: **1a** (0.2 mmol), **5** (2.7 equiv), *t*-BuOK (3.6 equiv), PhCHO (1.0 equiv), DMF (2.0 mL), under argon atmosphere, 12 h (unoptimized reaction time). [b]Isolated yields. [c]Reaction conditions: **1a** (0.2 mmol), PhONa (3.0 equiv), *t*-BuOK (1.0 equiv), PhCHO (1.0 equiv), under argon atmosphere. [d]Containing 4% of side product **2**. [e]Isolated yield was given by recrystallization. [f]Yield was determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

The reaction proved to be general and amenable to a range of structurally diverse phenols **5**, and the desired products **6** were obtained in moderate to excellent yields. We found that the electronic nature of the phenols can significantly affect the reaction, with the electron-rich phenols (**6b**–**6i**) being more reactive than the electron-deficient one (**6l**). In the cases of methyl-substituted phenols, the substitution site of methyl had little influence on the outcome (**6d**–**6f**), whereas in the case of methoxy-substituted phenols, the *para*-substituted one (**6g**) was found to be more reactive than the *meta*-substituted one (**6h**). It is of note that some phenols with a halogen substituent are also viable pronucleophiles in the current reaction (**6j** and **6k**), probably due to the π-electron-donating (resonance) effect of the halogen atom. In most cases, the decrease of the yields probably arose from the side reaction of **1a** induced by *t*-BuOK.

Interestingly, when the salt of an antioxidant, butylated hydroxytoluene (BHT), was used as the nucleophilic reagent, the C-alkylation product **7** was isolated in 78% yield. Moreover, the same reaction proceeded smoothly even in the absence of PhCHO (Scheme 3, eqs 1 and 2). Here, the

Scheme 3. Substitution Reaction of 1a with BHT

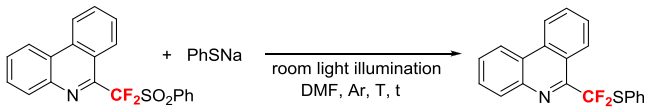


extremely electron-rich phenolate anion derived from BHT serves as the reducing agent, which transfers a single electron to **1a** to afford a difluoroalkyl radical ($ArCF_2\bullet$) and an aryloxy radical (ArO•). The following step may proceed either through the combination of two radicals or through an $S_{RN}1$ mechanism, where the C-alkylation selectivity can be explained by the steric hindrance of the aryloxy radical or anion.

Thiolates and Selenolates As Nucleophiles. Thiolate and selenolate anions are softer nucleophiles than alcoholate and phenolate anions. On the basis of the successful reaction of **1a** with a wide variety of phenolates, we further explored the reactivity of **1a** toward thiolates and selenolates.

The reaction of PhSNa and **1a** in a molar ratio of 1:2 in DMF was chosen as the model reaction (Table 5). It was

Table 5. Optimization of Reaction Conditions for the Formation of 9a[a]



entry	**1a**/PhSNa	*T* (°C)	*t* (h)	**9a**, yield (%)[b]
1	1:2	rt	24	83
2	1:2	80	24	86
3	1:2	110	8	98
4	**1:4**	**rt**	**12**	**>99**

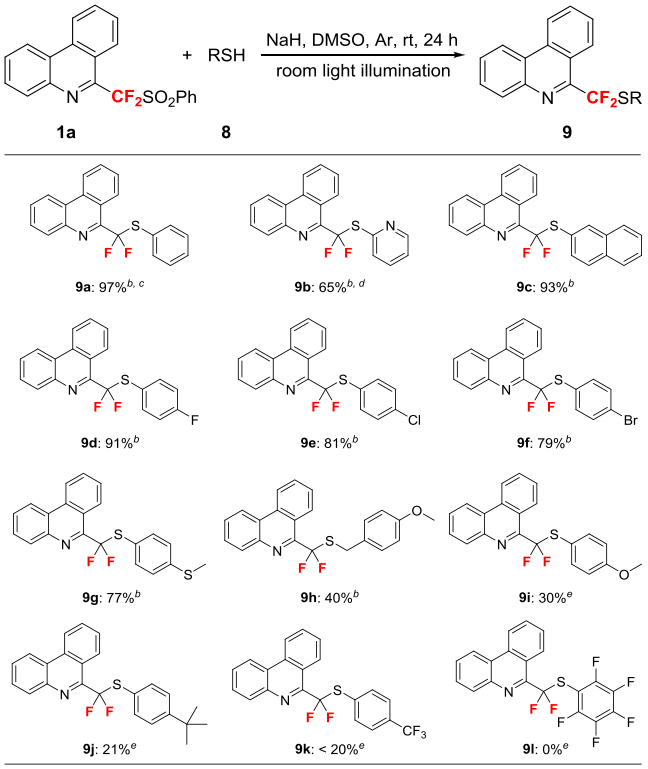
[a]Reaction conditions: **1a** (0.1 mmol), DMF (1.0 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

found that the displacement of the $PhSO_2$ group with the PhS group could readily occur at room temperature in the absence of any additive (Table 5, entry 1), which can be attributed to the strong single electron-donating ability of PhS^- endowed by the high electronic polarizability of the sulfur atom. A quick optimization of the reaction conditions showed that there are two viable methods for improving the yields of **9a**: increasing the reaction temperature from room temperature to 110 °C (Table 5, entry 3) or increasing the amount of PhSNa from 2 to 4 equiv (Table 5, entry 4); the latter method can lead to slightly higher yield of **9a**.

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345–8359

After achieving the fluoroalkylation of PhSNa with **1a**, we investigated the scope of the thiolate nucleophiles (Table 6).

Table 6. Substitution Reactions of 1a with Thiolates[a]

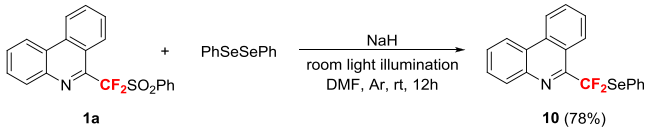


[a]Reaction conditions: **1a** (0.2 mmol), **8** (4.0 equiv), NaH (4.0 equiv), DMSO (2.0 mL), under argon atmosphere. [b]Isolated yields. [c]Reaction conditions: **1a** (0.2 mmol), PhSNa (4.0 equiv), DMF (2.0 mL), under argon atmosphere. [d]Reaction conditions: **1a** (0.2 mmol), 2-PySH (3.5 equiv), *t*-BuOK (4.4 equiv), PhCHO (1.0 equiv), DMSO, under argon atmosphere, 72 h. [e]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

For convenience, the thiolates were in situ prepared by deprotonation of the corresponding thiols with NaH (95%) or *t*-BuOK. When 2-mercaptopyridine was used as the pronucleophile, we found that DMSO was superior to DMF with respect to promoting the reaction (**9b**). Therefore, in the subsequent investigation, DMSO was used as the solvent to conduct the reactions of **1a** with thiolates. For most of the thilolates tested, their reactions proceeded smoothly to afford **9** in moderate to excellent yields (**9a**–**9h**). Electron-neutral aryl-substituted thiolates such as PhSNa and 2-naphthalenethiol exhibited the highest reactivity (**9a** and **9c**), whereas the substitution of thiophenolate with a weak electron-withdrawing group such as F, Cl, and Br slightly decreased the efficiency of the reaction (**9d**–**9f**). However, further enhancing the electron-withdrawing ability of the substituent on the thiophenolates by incorporating CF_3 or five fluorine atoms dramatically or even completely inhibited the reaction (**9k** and **9l**) due to the decreased single electron-donating ability of the thiloates, as is indicated by the low conversion of **1a**. Similarly, *para* electron-donating groups such as MeS, MeO, and *t*-Bu also showed inhibition effect on the desired reaction (**9g**, **9i**, and **9j**). However, the MeS group showed less significant influence than MeO and *t*-Bu groups. In the cases of MeO- and *t*-Bu-substituted thiolates, the low yields of **9** mainly arose from the decomposition of **1a**. In addition, a benzylmercaptan could also take part in the reaction, affording product **9h** in only moderate yield.

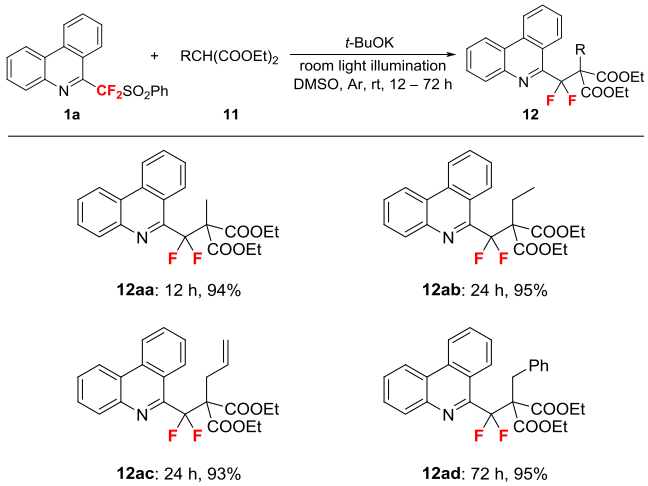
Selenolates are also viable nucleophilic reagents. The fluoroalkylation of PhSeNa that was in situ generated from the reduction of PhSeSePh with NaH[18] afforded the desired product **10** in 78% isolated yield by conducting the reaction of **1a**, PhSeSePh, and NaH in a molar ratio of 1:4:8 in DMF (Scheme 4).

Scheme 4. Substitution Reaction of 1a with in Situ Generated PhSeNa



Salts of Diethyl Malonate Derivatives As Nucleophiles. A screening of carbon nucleophiles showed that the salts of monosubstituted diethyl malonates could react with **1a** efficiently, thus consisting of a new protocol for the construction of FC–C bonds with the displacement of the sulfonyl group. We compared the reactivity of several α-monosubstituted diethyl malonates **11** toward **1a** with *t*-BuOK as the base and DMSO as the solvent and found that the steric hindrance of **11** had a remarkable effect on this reaction (Table 7). The reaction of **1a** with the potassium salt of $CH_3CH(COOEt)_2$ (**11a**) proceeded smoothly in 12 h, and the desired product **12aa** was obtained in 94% yield. However, the reaction rate decreased gradually as the steric hindrance of pronucleophiles **11** increased, and a reaction time of 24 h was needed to achieve a full conversion of the potassium salts of **11b** and **11c** (**12ab**, **12ac**). In the case of pronucleophile **11d** with an α-benzyl substituent, much longer reaction time (72 h) was required to complete the reaction (**12ad**). The diethyl malonate derivatives bearing more sterically hindered α-

Table 7. Substitution Reactions of 1a with the Salts of Diethyl Malonate Derivatives 11[a,b]



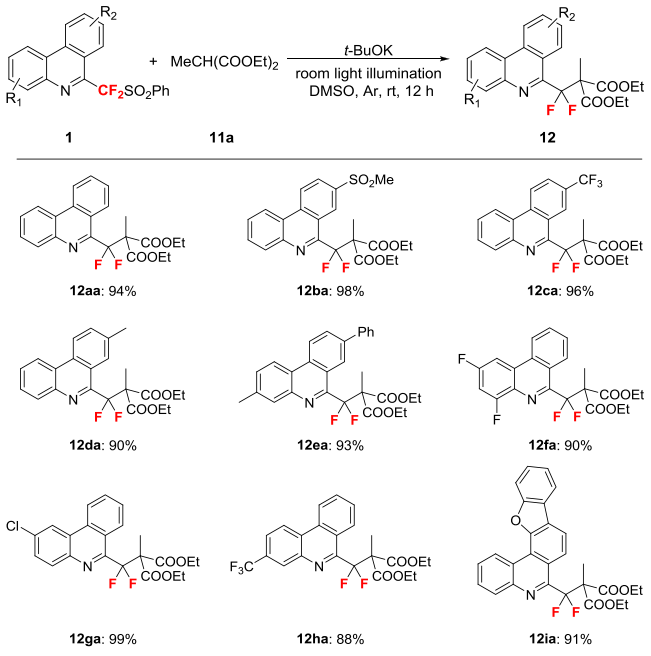
[a]Reaction conditions: **1a** (0.2 mmol), **11** (4.0 equiv), *t*-BuOK (4.0 equiv), DMSO (2.0 mL), under argon atmosphere. [b]Isolated yields.

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345–8359

substituents such as *i*-Pr, COOEt, and $COCH_3$ could not undergo this reaction. Moreover, the salt of nonsubstituted diethyl malonate also failed to react with **1a**, probably arising from its poor single electron-donating ability.

We also investigated the scope of $PhSO_2CF_2$-substituted phenanthridines by using $CH_3CH(COOEt)_2$ (**11a**) as a representative pronucleophile and found that a variety of previously prepared[14] 6-[difluoro(phenylsulfonyl)methyl]-phenanthridine derivatives (**1a–1j**) bearing either electron-withdrawing or electron-donating groups could be transformed into the corresponding products **12** in excellent yields (Table 8). This desulfonative difluoroalkylation reaction tolerates various functional groups on **1**, such as sulfonyl, trifluoromethyl, methyl, phenyl, fluoride, and chloride. In the cases of sulfonyl-, fluoro- and chloro-substituted phenanthridines that were susceptible to undergo nucleophilic aromatic substitution (S_NAr), the reaction only took place at the $PhSO_2CF_2$ group.

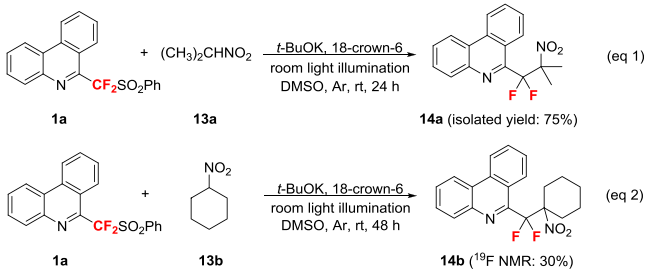
Table 8. Substitution Reactions of 1 with the Salt of 11a[a,b]



[a]Reaction conditions: **1** (1.0 equiv), **11a** (4.0 equiv), *t*-BuOK (4.0 equiv), DMSO, under argon atmosphere. [b]Isolated yields.

Salt of 2-Nitropropane as Nucleophile. 2-Nitropropane (**13a**) could be deprotonated by *t*-BuOK and then reacted with **1a** to give the corresponding product **14a**. However, the relatively low solubility of the in situ generated potassium salt of **13a** in DMSO led to a slow reaction rate at room temperature, thus the desired product **14a** was observed in a quite low yield (29% based on ^{19}F NMR spectroscopy) after 24 h. We found that the addition of 18-crown-6 could effectively improve the yield of **14a**, and we obtained **14a** in 75% isolated yield when 2.4 equiv of 18-crown-6 was used (Scheme 5, eq 1). On this basis, we further explored the reaction of **1a** with nitrocyclohexane (**13b**) at room temperature. The result turned out to be unsatisfactory, with only 30% yield of the desired product **14b** being observed by ^{19}F NMR spectroscopy even when the reaction time was prolonged to 48 h (Scheme 4, eq 2). The significant decrease of the yield reveals that increased steric hindrance was detrimental to the substitution reaction.

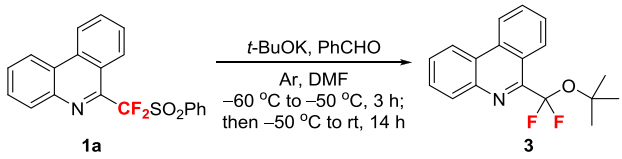
Scheme 5. Substitution Reactions of 1a with the Salt of Nitroalkanes 13



Mechanistic Investigations. To gain more insights into the present desulfonative fluoroalkylation reaction, we carried out mechanistic investigations.

First, to probe the possibility of a radical mechanism, we tested the retarding effect of several radical inhibitors on the standard reactions of **1a** with various nucleophiles. The results are summarized in Table 9 and Tables S1–S5 (see the Supporting Information).

Table 9. Control Experiments of 1a with *t*-BuOK[a]



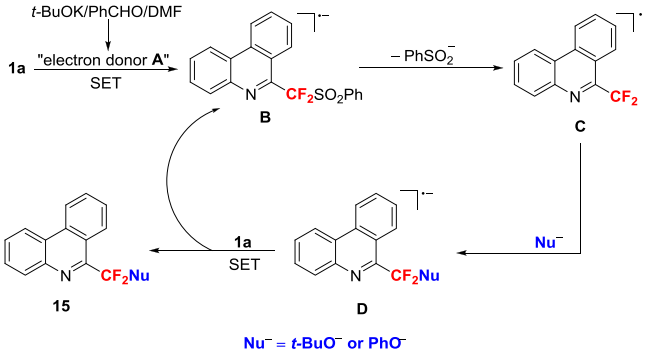
entry	change of standard conditions	**3**, yield (%)[b]
1		67
2	in the presence of *m*-dinitrobenzene (1.0 equiv)	4
3	in the presence of *p*-dinitrobenzene (1.0 equiv)	6
4	in the presence of TEMPO (3.0 equiv)	0
5	replacing argon (Ar) with O_2	0

[a]Reaction conditions: **1a** (0.1 mmol), PhCHO (1.0 equiv), *t*-BuOK/DMF (1.0 M) (0.25 mL), DMF (0.8 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

As is shown in Table 9, the reaction of **1a** with *t*-BuOK was largely or completely inhibited by single electron transfer inhibitors such as *m*-dinitrobenzene and *p*-dinitrobenzene and free radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and O_2. The reaction of **1a** with PhONa in the presence of *t*-BuOK/PhCHO was retarded similarly (see Supporting Information, Table S1). Taken together with our initial understanding on the role of *t*-BuOK/PhCHO, we believed that the reaction proceeded through a SET chain process that was initiated by an electron donor species related to PhCHO (Scheme 6). Initially, "electron donor **A**" that is formed by the interaction of *t*-BuOK/PhCHO acts the initiator and donates a single electron to **1a** to generate the radical anion **B**. Then the resulting radical anion **B** undergoes a fragmentation to release difluoroalkyl radical **C** and $PhSO_2^-$. Subsequently, the combination of **C** with a nucleophile (Nu^- = *t*-BuO^-, PhO^-) leads to the formation of a new radical anion **D**. Finally, intermediate **D** transfers a single electron to another molecule of **1a** to produce product **15** and regenerate intermediate **B**.

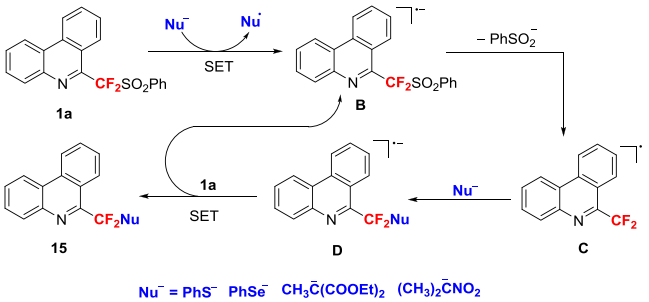
DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345–8359

Scheme 6. Plausible Mechanism of the Reaction of 1a with *t*-BuOK (or PhONa)



Radical inhibition experiments (see the Supporting Information, Tables S2–S5) also support a $S_{RN}1$ mechanism in the reactions of **1a** with other nucleophilic species (PhS^-, $PhSe^-$, $^-CCH_3(COOEt)_2$, and $^-C(CH_3)_2NO_2$) (Scheme 7).

Scheme 7. Plausible Mechanism of the Reaction of 1a with Other Nucleophiles



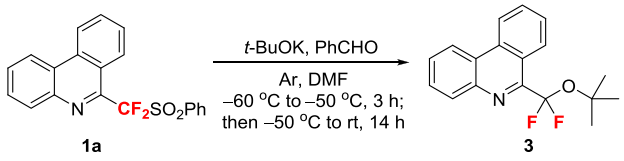
In these cases, the nucleophile itself can act as the initiator to trigger the propagation step. The radicals ($Nu^•$) derived from these nucleophiles should end up with a homocoupling reaction.

Second, to understand the exact role of light, we conducted the control experiments both under room light illumination and in the dark (see the Supporting Information, Tables S1–S5). It was found that room light illumination is necessary in the reactions of PhSNa, PhSeNa, and a malonate salt $KC(Me)(CO_2Et)_2$ with the sulfone **1a** (Tables S2–S4). The same reactions in the absence of room light were found to be very sluggish. The promoting role of room light can be explained by the formation of a charge transfer complex of **1a** and the nucleophile (Nu^-) and its subsequent activation by the visible light to afford $\mathbf{1a}^{•-}$ and Nu•.[19]

However, when PhONa was used as the nucleophile (with *t*-BuOK/PhCHO/DMF as the initiator) (Table S1), the reaction in DMF completed in 1 h, giving the desired product in high yield both in the presence and in the absence of the light. This indicates that room light has little influence on the reaction of phenolates.

Third, to figure out the possible initiator in the reaction of **1a** with *t*-BuOK or PhONa, we investigated the roles of both the intermediates and the possible final products that are related to the Cannizzaro reaction between *t*-BuOK and PhCHO (Table 10). To evaluate the role of the Cannizzaro reaction intermediates, the mixture of *t*-BuOK and PhCHO in DMF was prestirred for 1 or 2 h before adding **1a**. However,

Table 10. Study of Intermediates in the Reaction System of 1a with *t*-BuOK[a]



entry	change of standard conditions	3, yield (%)[b]
1		67
2	the mixture of *t*-BuOK and PhCHO was prestirred for 1 h before adding **1a**	56
3	the mixture of *t*-BuOK and PhCHO was prestirred for 2 h before adding **1a**	59
4	replacing PhCHO with $PhCH_2OH$ (1.0 equiv)	10
5	replacing PhCHO with $PhCO_2t$-Bu (1.0 equiv)	2
6	replacing PhCHO with $PhCO_2H$ (1.0 equiv)	0
7	replacing PhCHO with benzoin (1.0 equiv)	0

[a]Reaction conditions: **1a** (0.1 mmol), PhCHO (1.0 equiv), *t*-BuOK/DMF (1.0 M) (0.25 mL), DMF (0.8 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

the thus-formed reaction mixture could also promote the reaction of *t*-BuOK with **1a** smoothly, albeit with slightly lower yields (Table 10, entries 2 and 3), indicating that the initiator might be the final products rather than the intermediates. Accordingly, we replaced PhCHO with $PhCH_2OH$ and $PhCO_2t$-Bu (the main products of the Cannizzaro reaction of PhCHO) and found that the reaction yield was remarkably decreased (Table 10, entries 4 and 5). Also, $PhCO_2H$ resulting from either the autoxidation of PhCHO or hydroxide-promoted Cannizzaro reaction of PhCHO could not promote the reaction (Table 10, entry 6). Thus, we ruled out the participation of either the intermediates or the final products of the Cannizzaro reaction in triggering the SET process. The participation of benzoin condensation is also unlikely, as the formation of **3** was not observed when benzoin was used instead of PhCHO (Table 10, entry 7).

Recently, Murphy and co-workers made an elegant investigation on *t*-BuOK-promoted SET processes and disclosed that the dimerization of formamides can afford strong organic electron donors such as **G** and **H** (Scheme 8, eq 1),[20] which inspired us to take into account the combinational effect of *t*-BuOK, PhCHO, and DMF in our reaction system. We envisioned that the addition of the acyl anion derived from DMF to PhCHO followed by proton transfer should lead to the generation of electron donor $\mathbf{A_1}$, and further deprotonation of $\mathbf{A_1}$ should afford $\mathbf{A_2}$ with stronger electron-donating ability (Scheme 8, eq 2). To confirm this assumption, we separately prepared the precursor of intermediate **I**, α-hydroxyl amide **16** by reacting PhCHO and DMF with LDA as the base (Scheme 8, eq 3)[21] and examined its influence on the reaction of **1a** with *t*-BuOK and PhONa, respectively (Tables 11 and 12). Gratifyingly, by using **16** instead of PhCHO, the reaction of **1a** with *t*-BuOK afforded **3** in 47% yield when 0.4 equiv of **16** was loaded (Table 11, entry 4). For the reaction system of PhONa, only 0.2 equiv of **16** was needed to achieve an excellent conversion of **1a** (Table 12, entries 1–3). In addition, *t*-BuOK also played an important role in the reaction, as is demonstrated by the dramatic decrease of the yield of **6a** when less than 1 equiv of *t*-BuOK was used (Table 12, entries 3–5).

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345–8359

Scheme 8. Possible Structure of "Electron Donor A"

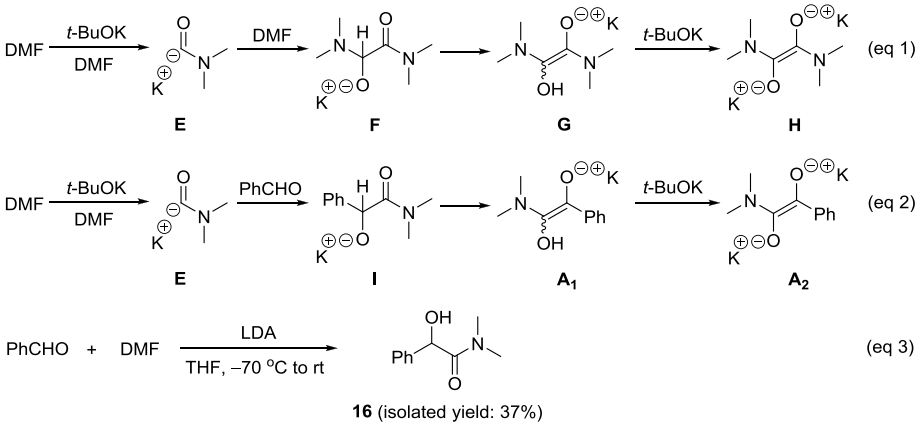
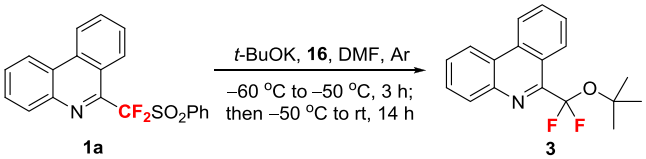


Table 11. Effect of Compound 16 on the Reaction of 1a with *t*-BuOK[a]

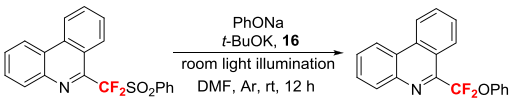


1a 3

entry	1a/*t*-BuOK/16[b]	3 (%)[c]
1	1.0:2.5:0	trace
2	1.0:2.5:0.2	11
3	1.0:2.5:0.3	26
4	1.0:2.5:0.4	47
5	1.0:2.5:0.5	46
6	1.0:2.5:0.6	40
7	1.0:2.5:1.0	28

[a]Reaction conditions: **1a** (0.1 mmol), DMF (0.8 mL), under argon atmosphere. [b]*t*-BuOK (1.0 M in DMF) was prepared by dissolving *t*-BuOK in DMF just before the reaction and was then dropped slowly into the reaction system. [c]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Table 12. Effect of Compound 16 on the Reaction of 1a with PhONa[a]



1a 6a

entry	1a/*t*-BuOK/16	6a (%)[b]
1	1.0:0:0	trace
2	1.0:1.0:0	17
3	1.0:1.0:0.2	96
4	1.0:0.5:0.2	38
5	1.0:0.2:0.2	6

[a]Reaction conditions: **1a** (0.1 mmol), PhONa (3.0 equiv), DMF (1.0 mL), under argon atmosphere. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

It is clear that *t*-BuOK not only promoted the deprotonation of **16** to generate intermediate **I** (Scheme 8) but also facilitated the formation of enolate $\mathbf{A_1}$ and dianion $\mathbf{A_2}$, which should serve as key electron donors in the reaction system.[20]

Finally, to investigate the influence of the π-system connecting to the difluoromethylene group on the single electron transfer process, we conducted the reaction of 2-$PyCF_2SO_2Ph$ and $PhCF_2SO_2Ph$ with the most challenging nucleophile, *t*-BuOK. Interestingly, none of them could undergo the desired nucleophilic substitution reaction, indicating that a large conjugated structure is beneficial for the reaction. We also measured the first reduction potentials of the phenanthridine derivative **1a** (−1.20 V vs SCE), 2-$PyCF_2SO_2Ph$ (−1.44 V vs SCE), and $PhCF_2SO_2Ph$ (−1.55 V vs SCE) by cyclic voltammetry and found that the single electron transfer reactivity of **1a** toward *t*-BuOK is consistent with its highest first reduction potential.[22]

CONCLUSIONS

In summary, we have developed the desulfonative fluoroalkylation of various nucleophiles with 6-[difluoro(phenylsulfonyl)methyl]phenanthridine and its derivatives, leading to the formation of new carbon−heteroatom bonds and carbon−carbon bonds with the removal of the phenylsulfonyl group. A process of single electron transfer is likely to be involved in our reaction system. In particular, the interaction of *t*-BuOK, PhCHO, and DMF might facilitate the formation of "electron donors", which then initiate the reaction between the substrate and the nucleophiles such as *t*-BuOK and PhONa, which are difficult to donate a single electron.

EXPERIMENTAL SECTION

General Methods. Unless otherwise mentioned, all manipulations were conducted with a standard Schlenk tube under argon atmosphere, and reagents were purchased from commercial sources and used without further purification. Dry DMF and DMSO were distilled over CaH_2 and stored over activated molecular sieves. NMR spectra were obtained on a Bruker AV400 or Agilent MR400 (400 MHz for ^{1}H; 376 MHz for ^{19}F; 100 MHz for ^{13}C). ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.00 ppm or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26 ppm. ^{13}C NMR chemical shifts were determined relative to internal $CDCl_3$ at δ 77.0 ppm. ^{1}H, ^{13}C, and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of quartets (tq), multiplet (m), and broad resonance (br). All the melting points were uncorrected. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the DART positive mode.

Preparation of Starting Material 6-(Difluoro(phenylsulfonyl)methyl)phenanthridine Derivatives 1. All of the compounds **1a−1i** (for a list, see the Supporting Information) are known and prepared according to our reported procedures.[14]

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

Compounds **1b**−**1i** were prepared on 0.2 mmol scale in similar yields as previously reported.[14] Compound **1a** was prepared on gram scale by a modification of the purification procedure as follows.

To an oven-dried 300 mL Schlenk tube were added (diacetoxyiodo)benzene (17.8766 g, 55.5 mmol, 6.0 equiv) and cesium carbonate (3.0138 g, 9.25 mmol, 1.0 equiv) in a glovebox. Under argon atmosphere, iodine (I_2, 469.5 mg, 1.85 mmol, 0.2 equiv) was added quickly and DMF (40 mL) was injected into the flask. The reaction mixture was stirred, and then the tube was cooled to −50 to −60 °C with a dry ice/acetone cold bath. After the addition of difluoromethyl phenyl sulfone (3.5550 g, 18.5 mmol, 2.0 equiv), a DMF (15 mL) solution of sodium *tert*-butoxide (2.6665 g, 27.75 mmol, 3.0 equiv) was added dropwise into the reaction system. Then a DMF (10 mL) solution of 2-isocyano-1,1′-biphenyl (1.6579 g, 9.25 mmol, 1.0 equiv) was injected with a syringe, followed by the slow addition of another portion of sodium *tert*-butoxide (2.6665 g, 27.75 mmol, 3.0 equiv) in DMF (15 mL). The resulting reaction mixture was stirred at −50 to −60 °C under Ar atmosphere for 2 h. Then the mixture was warmed to room temperature, and water (150 mL) was added. The aqueous layer was extracted with ethyl acetate (EtOAc) (150 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and preliminarily purified by column chromatography on silica gel by using PE/EtOAc as eluent (20:1−5:1, v/v) to provide crude product of **1a**, which was further recrystallized with EtOAc/petroleum ether (PE) to provide **1a** as white crystals (1.4692g, 43%): mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (t, J = 8.8 Hz, 2H), 8.61−8.59 (m, 1H), 8.29−8.13 (m, 1H), 8.09 (d, J = 7.8 Hz, 2H), 7.91 (t, J = 7.6 Hz, 1H), 7.80−7.74 (m, 4H), 7.61 (t, J = 7.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −95.7 (s, 2F). All the characterization data are consistent with previous report.[14]

Procedures for the Preparation of 6-(*tert*-Butoxydifluoromethyl)phenanthridine (3) (Scheme 2). To an oven-dried 10 mL Schlenk tube was added 6-(difluoro(phenylsulfonyl)methyl)phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv), and then the flask was evacuated and backfilled with argon three times. PhCHO (21.2 mg, 0.2 mmol, 1.0 equiv) mixed with DMF (1.6 mL) was added via syringe in one portion. The reaction mixture was stirred, and then the tube was cooled to −50 to −60 °C with a dry ice/acetone cold bath. A DMF solution of *t*-BuOK (1.0 mol/L, 0.5 mL, 0.5 mmol), which was prepared just before the experiment, was added dropwise into the reaction system. The resulting reaction mixture was stirred at −50 to −60 °C under Ar atmosphere for 3 h and was stirred further at room temperature for 14 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (40:1−20:1, v/v) as eluent to provide **3** as pale yellow solid (28.9 mg, 48%): mp 59−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1H), 8.58 (t, J = 7.0 Hz, 2H), 8.29 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 7.8 Hz, 1H), 7.78−7.70 (m, 3H), 1.66 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.8 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.3 (t, J = 33.1 Hz), 142.0, 134.1, 131.0, 130.7, 129.0, 128.3, 127.6, 127.3, 125.0, 122.5, 122.2, 122.0, 121.9 (t, J = 264.2 Hz), 83.3, 30.4 (t, J = 1.9 Hz); IR (KBr) 3084, 2994, 2929, 1579, 1469, 1372, 1247, 1183, 1165, 1152, 1120, 1046, 1028, 968, 884, 758, 729, 717 cm^{-1}; MS (ESI, m/z) 302.1 (M + H$^+$); HRMS (DART) calcd for $C_{18}H_{18}F_2NO^+$ (M + H$^+$) 302.1351, found 302.1349.

Procedures for the Preparation of 6-(Difluoro(phenoxy)-methyl)phenanthridine (6a) (Table 4). To an oven-dried 10 mL Schlenk tube were added 6-(difluoro(phenylsulfonyl)methyl)-phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv) and PhONa (69.7 mg, 0.6 mmol, 3.0 equiv) in a glovebox. Then the flask was moved out of the glovebox and was evacuated and backfilled with pure argon three times. PhCHO (21.2 mg, 0.2 mmol, 1.0 equiv) in DMF (1.0 mL) was added via syringe in one portion. The reaction mixture was stirred, and then a DMF (1.0 mL) solution of *t*-BuOK (22.4 mg, 0.2 mmol, 1.0 equiv), which was prepared just before the experiment, was added dropwise into the reaction system. The resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 12 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (100:1−80:1, v/v) as eluent to provide **6a** as white solid (59.5 mg, 93%): mp 77−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, J = 6.8 Hz, 2H), 8.61−8.59 (m, 1H), 8.33−8.31 (m, 1H), 7.92−7.88 (m, 1H), 7.82−7.74 (m, 3H), 7.43−7.36 (m, 4H), 7.25−7.21 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.8 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.6, 149.4 (t, J = 31.6 Hz), 142.0, 134.2, 131.23, 131.16, 129.7, 129.2, 128.9, 127.8, 127.1 (t, J = 2.9 Hz), 125.8, 125.2, 122.52, 122.50, 122.1, 121.8, 120.5 (t, J = 264.7 Hz); IR (film) 3067, 2929, 1590, 1491, 1465, 1374, 1250, 1201, 1156, 1134, 1066, 968, 753, 726, 689 cm^{-1}; MS (ESI, m/z) 322.1 (M + H$^+$); HRMS (DART) calcd for $C_{20}H_{14}F_2NO^+$ (M + H$^+$) 322.1038, found 322.1040.

General Procedures for the Preparation of Compounds 6b−6k (Table 4). To an oven-dried 10 mL Schlenk tube A was added *t*-BuOK (107.7 mg, 0.96 mmol) in a glovebox, and then the flask was moved out of the glovebox. Under argon atmosphere, DMF (0.3 mL) was injected and the reaction mixture was stirred. ArOH (**5b**−**k**) (0.72 mmol) was dissolved in DMF (0.9 mL) and was added dropwise into the reaction system. The resulting reaction mixture was stirred at room temperature for 30 min and was left to be used.

To another oven-dried 10 mL Schlenk tube B was added 6-(difluoro(phenylsulfonyl)methyl)phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv), and then the flask was evacuated and backfilled with pure argon three times. PhCHO (21.2 mg, 0.2 mmol, 1.0 equiv) mixed with DMF (1.0 mL) was added via syringe in one portion, and the reaction mixture was stirred. Next, 1.0 mL of the reaction mixture [containing ArOK (0.53 mmol, 2.7 equiv) and *t*-BuOK (0.18 mmol, 0.9 equiv)] was taken out from the Schlenk tube A and was added dropwise into the reaction system of Schlenk tube B. Then, the resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 12 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (80:1, v/v) as eluent to provide compounds **6b**−**6k**.

6-((4-(*tert*-Butyl)phenoxy)difluoromethyl)phenanthridine (6b) (Table 4): Pale yellow solid (37.9 mg, 56%); mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, J = 9.8 Hz, 2H), 8.58 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.90−7.86 (m, 1H), 7.81−7.73 (m, 3H), 7.42 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 1.34 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.0 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.5 (t, J = 31.4 Hz), 148.7, 148.2 (t, J = 1.8 Hz), 142.0, 134.2, 131.2, 131.1, 129.2, 128.8, 127.7, 127.2 (t, J = 2.9 Hz), 126.5, 125.1, 122.49, 122.45, 122.1, 121.2, 120.4 (t, J = 265.0 Hz), 34.6, 31.5; IR (film) 3080, 2963, 2906, 1619, 1510, 1465, 1446, 1373, 1332, 1250, 1209, 1173, 1137, 1103, 1067, 1017, 968, 856, 788, 762, 727, 559 cm^{-1}; MS (ESI, m/z) 378.1 (M + H$^+$); HRMS (DART) calcd for $C_{24}H_{22}F_2NO^+$ (M + H$^+$) 378.1664, found 378.1662.

6-(Difluoro(4-(2-methoxyethyl)phenoxy)methyl)-phenanthridine (6c) (Table 4): Yellow oil (48.0 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70−8.67 (m, 2H), 8.61−8.59 (m, 1H), 8.34−8.31 (m, 1H), 7.92−7.88 (m, 1H), 7.82−7.74 (m, 3H), 7.34 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 3.60 (t, J = 7.0 Hz, 2H), 3.36 (s, 3H), 2.88 (t, J = 7.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.9 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.4 (t, J = 31.6 Hz), 148.9, 142.0, 136.7, 134.1, 131.12, 131.09, 130.0, 129.2, 128.8,

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

127.7, 127.1 (t, J = 2.8 Hz), 125.1, 122.4, 122.1, 121.7, 120.4 (t, J = 264.8 Hz), 73.5, 58.8, 35.6; IR (film) 3067, 3028, 2925, 2870, 1612, 1573, 1532, 1508, 1465, 1446, 1374, 1333, 1307, 1250, 1204, 1156, 1067, 1019, 967, 852, 762, 727 cm^{-1}; MS (ESI, m/z) 380.1 (M + H^+); HRMS (DART) calcd for $C_{23}H_{20}F_2NO_2^+$ (M + H^+) 380.1457, found 380.1455.

6-(Difluoro(*p*-tolyloxy)methyl)phenanthridine (6d) (Table 4): White solid (44.2 mg, 66%); mp 88−90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 8.65 (d, J = 8.4 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.33 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.89−7.85 (m, 1H), 7.81−7.71 (m, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 2.34 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.8 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.5 (t, J = 31.5 Hz), 148.3, 142.0, 135.5, 134.1, 131.14, 131.07, 130.1, 129.2, 128.8, 127.7, 127.1 (t, J = 2.9 Hz), 125.1, 122.46, 122.44, 122.1, 121.7, 120.4 (t, J = 264.3 Hz), 20.9; IR (film) 3076, 3050, 2924, 1617, 1573, 1507, 1465, 1446, 1374, 1333, 1307, 1250, 1203, 1169, 1134, 1066, 967, 819, 758, 724, 555 cm^{-1}; MS (ESI, m/z) 336.1 (M + H^+); HRMS (DART) calcd for $C_{21}H_{16}F_2NO^+$ (M + H^+) 336.1194, found 336.1192.

6-(Difluoro(*m*-tolyloxy)methyl)phenanthridine (6e) (Table 4): Yellow oil (42.9 mg, 64%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.67−8.62 (m, 2H), 8.54 (d, J = 8.0 Hz, 1H), 8.31 (dd, J = 8.0, 1.2 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.78−7.69 (m, 3H), 7.29−7.21 (m, 3H), 7.04−7.02 (m, 1H), 2.36 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.8 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.5 (t, J = 1.7 Hz), 149.4 (t, J = 31.4 Hz), 142.0, 139.8, 134.1, 131.10, 131.06, 129.3, 129.1, 128.8, 127.7, 127.1 (t, J = 2.9 Hz), 126.6, 125.1, 122.44, 122.42, 122.07, 120.4 (t, J = 265.1 Hz), 118.7, 21.5; IR (film) 3080, 2915, 1612, 1587, 1529, 1488, 1464, 1446, 1373, 1333, 1252, 1187, 1157, 1066, 970, 762, 730, 687 cm^{-1}; MS (ESI, m/z) 336.1 (M + H^+); HRMS (DART) calcd for $C_{21}H_{16}F_2NO^+$ (M + H^+) 336.1194, found 336.1195.

6-(Difluoro(*o*-tolyloxy)methyl)phenanthridine (6f) (Table 4): White solid (44.1 mg, 66%); mp 103−105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.4 Hz, 1H), 8.65 (d, J = 8.4 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 8.8 Hz, 1H), 7.86 (t, J = 7.8 Hz, 1H), 7.79−7.70 (m, 3H), 7.55 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.8 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 2.32 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.2 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6 (t, J = 31.9 Hz), 149.2, 142.1, 134.2, 131.5, 131.2, 131.1, 131.0, 129.2, 128.8, 127.7, 127.2 (t, J = 3.3 Hz), 126.9, 125.6, 125.1, 122.49, 122.47, 122.1, 121.5, 120.7 (t, J = 265.2 Hz), 16.9; IR (film) 3080, 2963, 2933, 1614, 1588, 1528, 1493, 1465, 1446, 1374, 1333, 1307, 1250, 1221, 1189, 1155, 1136, 1111, 1066, 1044, 968, 762, 746, 725 cm^{-1}; MS (ESI, m/z) 336.1 (M + H^+); HRMS (DART) calcd for $C_{21}H_{16}F_2NO^+$ (M + H^+) 336.1194, found 336.1192.

6-(Difluoro(4-methoxyphenoxy)methyl)phenanthridine (6g) (Table 4): White solid (66.3 mg, contaminated by 4% of side product **2** according to ^{19}F NMR spectroscopic analysis, calcd 91% yield). An analytically pure sample of compound **6g** was obtained after recrystallization from EtOAc/PE; mp 87−88 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.8 Hz, 2H), 8.61−8.59 (m, 1H), 8.34−8.31 (m, 1H), 7.92−7.88 (m, 1H), 7.82−7.74 (m, 3H), 7.34 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.9 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5, 149.5 (t, J = 31.6 Hz), 143.9 (t, J = 1.9 Hz), 142.1, 134.2, 131.2, 131.1, 129.2, 128.8, 127.8, 127.2 (t, J = 3.0 Hz), 125.1, 123.2, 122.54, 122.51, 122.1, 120.5 (t, J = 263.9 Hz), 114.6, 55.7; IR (film) 3076, 2963, 2933, 2837, 1612, 1575, 1506, 1465, 1445, 1374, 1333, 1307, 1247, 1200, 1154, 1134, 1103, 1065, 1035, 967, 844, 790, 761, 732, 724 cm^{-1}; MS (ESI, m/z) 352.0 (M + H^+); HRMS (DART) calcd for $C_{21}H_{16}F_2NO_2^+$ (M + H^+) 352.1144, found 352.1144.

6-(Difluoro(3-methoxyphenoxy)methyl)phenanthridine (6h) (Table 4): Yellow oil (42.6 mg, 61%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.65−8.63 (m, 2H), 8.56−8.54 (m, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.88−7.83 (m, 1H), 7.79−7.70 (m, 3H), 7.28−7.23 (m, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.78−6.75 (m, 1H), 3.77 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.8 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.6, 151.5 (t, J = 1.7 Hz), 149.3 (t, J = 31.3 Hz), 142.0, 134.1, 131.1, 130.0, 129.2, 128.8, 127.8, 127.0 (t, J = 2.9 Hz), 125.1, 122.5, 122.4, 122.1, 120.4 (t, J = 265.3 Hz), 113.8, 111.6, 107.8, 55.5; IR (film) 3084, 2946, 2850, 1608, 1590, 1490, 1465, 1446, 1373, 1333, 1311, 1286, 1248, 1193, 1155, 1131, 1067, 1044, 1001, 972, 858, 800, 763, 730, 684 cm^{-1}; MS (ESI, m/z) 352.1 (M + H^+); HRMS (DART) calcd for $C_{21}H_{16}F_2NO_2^+$ (M + H^+) 352.1144, found 352.1142.

6-((4-(Benzyloxy)phenoxy)difluoromethyl)phenanthridine (6i) (Table 4): White solid (45.5 mg, 53%; isolated yield was given by recrystallization); mp 108−110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71−8.68 (m, 2H), 8.60 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 7.6 Hz, 1H), 7.92−7.88 (m, 1H), 7.82−7.74 (m, 3H), 7.45−7.35 (m, 7H), 6.98 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.9 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.7, 149.5 (t, J = 31.6 Hz), 144.09, 144.07, 142.0, 136.9, 134.2, 131.2, 131.1, 129.2, 128.8, 128.7, 128.2, 127.8, 127.6, 127.1 (t, J = 2.9 Hz), 125.1, 123.2, 122.5, 122.1, 120.4 (t, J = 264.3 Hz), 115.6, 70.5; IR (film) 3067, 3028, 2868, 1612, 1588, 1504, 1465, 1446, 1375, 1335, 1307, 1247, 1196, 1154, 1134, 1065, 1010, 967, 843, 761, 726, 697 cm^{-1}; MS (ESI, m/z) 428.1 (M + H^+); HRMS (DART) calcd for $C_{27}H_{20}F_2NO_2^+$ (M + H^+) 428.1457, found 428.1456.

6-((4-Bromophenoxy)difluoromethyl)phenanthridine (6j) (Table 4): Yellow solid (51.3 mg, 64%); mp 63−66 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.4 Hz, 1H), 8.62−8.58 (m, 2H), 8.32−8.30 (m, 1H), 7.89 (t, J = 7.8 Hz, 1H), 7.82−7.74 (m, 3H), 7.49 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.8 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 148.9 (t, J = 31.2 Hz), 142.0, 134.2, 132.7, 131.21, 131.18, 129.3, 129.0, 127.9, 126.9 (t, J = 3.0 Hz), 125.1, 123.5, 122.6, 122.4, 122.1, 120.4 (t, J = 265.5 Hz), 119.0; IR (film) 3076, 1614, 1580, 1528, 1485, 1465, 1446, 1374, 1333, 1251, 1204, 1154, 1102, 1068, 1012, 967, 848, 827, 761, 726, 492 cm^{-1}; MS (ESI, m/z) 401.9 (M + H^+); HRMS (DART) calcd for $C_{20}H_{13}BrF_2NO^+$ (M + H^+) 400.0143, found 400.0140.

6-(Difluoro(4-fluorophenoxy)methyl)phenanthridine (6k) (Table 4): White solid (43.5 mg, 64%); mp 148−150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (t, J = 8.2 Hz, 2H), 8.57 (d, J = 7.6 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.81−7.73 (m, 3H), 7.40−7.37 (m, 2H), 7.07 (t, J = 8.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.9 (s, 2F), −117.3 (s, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4 (d, J = 243.3 Hz), 149.07 (t, J = 31.5 Hz), 146.3 (q, J = 2.2 Hz), 141.9, 134.1, 131.15, 131.12, 129.2, 128.9, 127.8, 126.9 (t, J = 3.1 Hz), 125.1, 123.6 (d, J = 8.4 Hz), 122.5, 122.4, 122.1, 120.4 (t, J = 265.0 Hz), 116.3 (d, J = 23.3 Hz); IR (film) 3067, 1619, 1532, 1502, 1463, 1446, 1376, 1333, 1251, 1195, 1130, 1044, 974, 795, 755, 719, 542 cm^{-1}; MS (ESI, m/z) 340.1 (M + H^+); HRMS (DART) calcd for $C_{20}H_{13}F_3NO^+$ (M + H^+) 340.0944, found 340.0942.

Procedures for the Preparation of 2,6-Di-*tert*-butyl-4-(difluoro(phenanthridin-6-yl)methyl)-4-methylcyclohexa-2,5-dienone (7) (Scheme 3). To an oven-dried 10 mL Schlenk tube were added 6-(difluoro(phenylsulfonyl)methyl)phenanthridine (**1a**) (36.9 mg, 0.1 mmol, 1.0 equiv) and butylated hydroxytoluene (BHT, 66.1 mg, 0.3 mmol, 3.0 equiv). The flask was evacuated and backfilled with pure argon three times, and then DMF (0.8 mL) was added via syringe. The reaction mixture was stirred, and then the tube was cooled to −50 to −60 °C with a dry ice/acetone cold bath. A DMF solution of *t*-BuOK (1.0 mol/L, 0.25 mL, 0.25 mmol), which was prepared just before the experiment, was added dropwise into the reaction system. The resulting reaction mixture was stirred at −50 to −60 °C under argon atmosphere for 3 h and was stirred further at room temperature for 14 h. After the reaction was complete, the mixture was quenched with H_2O (2 mL). The aqueous layer was extracted with EtOAc (4 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography to provide **7** as off-white solid (32.5 mg, 73%): mp 157−158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.55−8.53 (m, 1H), 8.00−7.98 (m, 1H), 7.84 (t, J = 7.4 Hz, 1H), 7.72−

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

7.68 (m, 3H), 6.87 (s, 2H), 1.63 (s, 3H), 1.09 (s, 18H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −99.3 (s, 2F). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 186.1, 151.0 (t, J = 28.7 Hz), 147.1, 141.4, 140.8 (t, J = 2.9 Hz), 133.8, 130.7, 130.6, 129.0, 128.6, 127.6, 127.5 (t, J = 8.2 Hz), 124.5, 123.2 (t, J = 1.7 Hz), 122.8 (t, J = 253.2 Hz), 122.6, 122.0, 47.6 (t, J = 23.3 Hz), 34.9, 29.3, 21.4 (t, J = 4.8 Hz); IR (film) 3080, 2957, 2867, 1662, 1642, 1485, 1460, 1446, 1372, 1364, 1249, 1170, 1141, 1095, 1068, 1047, 930, 914, 903, 881, 761, 742, 727 cm^{-1}; MS (ESI, m/z) 448.2 (M + H$^+$); HRMS (DART) calcd for $C_{29}H_{32}F_2NO^+$ (M + H$^+$) 448.2446, found 448.2446.

Procedures for the Preparation of 6-(Difluoro(phenylthio)-methyl)phenanthridine (9a)[14] (Table 6). To an oven-dried 10 mL Schlenk tube was added 6-(difluoro(phenylsulfonyl)methyl)-phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv), and then the flask was evacuated and backfilled with pure argon three times. Under argon atmosphere, PhSNa (105.7 mg, 0.8 mmol, 4.0 equiv) was added quickly and DMF (2.0 mL) was injected into the flask. The resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 24 h. After the reaction was complete, the mixture was diluted with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (100:1, v/v) as eluent to provide **9a** as white solid (65.2 mg, 97%): mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.4 Hz, 1H), 8.61−8.55 (m, 2H), 8.31−8.28 (m, 1H), 7.89−7.68 (m, 6H), 7.52−7.43 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.0 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2 (t, J = 27.9 Hz), 141.8, 137.3, 134.1, 131.1, 131.0, 130.0, 129.7 (t, J = 277.1 Hz), 129.2, 129.1, 128.9, 127.7, 127.5, 127. (t, J = 5.4 Hz), 125.1, 122.5, 122.1, 122.0; IR (KBr) 3084, 2920, 1585, 1478, 1365, 1311, 1133, 1052, 1011, 879, 759, 508 cm^{-1}; MS (ESI, m/z) 338.0 (M + H$^+$); HRMS (DART) calcd for $C_{20}H_{14}F_2NS^+$ (M + H$^+$) 338.0810, found 338.0802. All the characterization data are consistent with previous report.[14]

Procedures for the Preparation of 6-(Difluoro(pyridin-2-ylthio)methyl)phenanthridine (9b) (Table 6). To an oven-dried 5 mL Schlenk tube A was added t-BuOK (134.7 mg, 1.2 mmol) in a glovebox, and then the flask was moved out of the glovebox. Under argon atmosphere, 2-mercaptopyridine (**8b**, 106.7 mg, 0.96 mmol) was added quickly and then DMSO (1.2 mL) was injected. The resulting reaction mixture was stirred at room temperature for 30 min and was left to be used.

To another oven-dried 10 mL Schlenk tube B was added 6-(difluoro(phenylsulfonyl)methyl)phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv), and then the flask was evacuated and backfilled with argon three times. PhCHO (21.2 mg, 0.2 mmol, 1.0 equiv) mixed with DMSO (1.0 mL) was added via syringe in one portion, and the reaction mixture was stirred. Next, 1.0 mL of the reaction mixture [containing 2-PySK (0.71 mmol, 3.5 equiv) and t-BuOK (0.18 mmol, 0.9 equiv)] was taken out from the Schlenk tube A and was added dropwise into the reaction system of Schlenk tube B. Then, the resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 72 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (20:1, v/v) as eluent to provide **9b** as pale yellow solid (43.7 mg, 65%): mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 4.0 Hz, 1H), 8.61 (d, J = 8.4 Hz, 2H), 8.53−8.51 (m, 1H), 8.25−8.23 (m, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.77−7.67 (m, 4H), 7.28 (dd, J = 7.4, 5.4 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.1 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.8, 150.7 (t, J = 27.4 Hz), 150.4, 141.7, 137.1, 134.1, 131.2, 130.9, 130. Five (t, J = 279.0 Hz), 129.6, 129.2, 128.9, 127.8, 126.9 (t, J = 5.3 Hz), 125.1, 123.2, 122.5, 122.1, 121.8 (d, J = 1.9 Hz); IR (film) 3063, 1614, 1572, 1561, 1128, 1491, 1450, 1420, 1365, 1309, 1283, 1242, 1225, 1134, 1095, 1050, 1039, 1011, 989, 976, 877, 845, 780, 758, 722, 675, 650, 508, 423 cm^{-1}; MS (ESI, m/z) 339.0 (M + H$^+$); HRMS (DART) calcd for $C_{19}H_{13}F_2N_2S^+$ (M + H$^+$) 339.0762, found 339.0761.

General Procedures for the Preparation of Compounds 9c−9h (Table 6). To an oven-dried 10 mL Schlenk tube was added NaH (95% purity, 20.2 mg, 0.8 mmol, 4.0 equiv) in a glovebox, and then the flask was moved out of the glovebox. Under argon atmosphere, DMSO (0.4 mL) was injected and the reaction mixture was stirred. Thiol (**8c−8h**) (0.8 mmol, 4.0 equiv) was dissolved in DMSO (1.6 mL) and was added dropwise into the reaction system. The resulting reaction mixture was stirred at room temperature for 30 min. Under argon atmosphere, 6-(difluoro(phenylsulfonyl)methyl)phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv) was added quickly into the reaction system. The resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 24 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (200:1−100:1, v/v) as eluent to provide compounds **9c−9h**.

6-(Difluoro(naphthalen-2-ylthio)methyl)phenanthridine (9c) (Table 6): White solid (72.3 mg, 93%); mp 135−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.4 Hz, 1H), 8.62−8.59 (m, 2H), 8.36 (s, 1H), 8.33−8.31 (m, 1H), 7.92−7.85 (m, 5H), 7.83−7.75 (m, 2H), 7.74−7.70 (m, 1H), 7.60−7.53 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.2 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.1 (t, J = 27.8 Hz), 141.7, 137.5, 134.1, 133.7, 133.5, 133.2, 131.1, 130.9, 129.9 (t, J = 277.3 Hz), 129.1, 128.8, 128.6, 128.2, 127.8, 127.7, 127.3, 126.9 (t, J = 5.2 Hz), 126.6, 125.0, 124.8, 122.4, 122.1, 121.9; IR (KBr) 3054, 2963, 1584, 1362, 1262, 1130, 1093, 1049, 1036, 875, 842, 818, 752, 722, 672, 656, 478 cm^{-1}; MS (ESI, m/z) 388.0 (M + H$^+$); HRMS (DART) calcd for $C_{24}H_{16}F_2NS^+$ (M + H$^+$) 388.0966, found 388.0965.

6-(Difluoro((4-fluorophenyl)thio)methyl)phenanthridine (9d) (Table 6): White solid (65.0 mg, 91%); mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.67−8.63 (m, 1H), 8.55 (d, J = 7.6 Hz, 2H), 8.29−8.27 (m, 1H), 7.89−7.84 (m, 1H), 7.80−7.68 (m, 5H), 7.17−7.11 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.7 (s, 2F), −111.3 (s, 1F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.3 (d, J = 249.0 Hz), 151.0 (t, J = 28.0 Hz), 141.7, 139.4 (d, J = 8.5 Hz), 134.1, 131.2, 130.9, 129.6 (t, J = 277.0 Hz), 129.2, 128.9, 127.8, 126.9 (t, J = 5.3 Hz), 125.1, 122.8, 122.5, 122.1, 121.9, 116.28 (d, J = 21.7 Hz); IR (film) 3084, 1589, 1529, 1490, 1463, 1445, 1397, 1362, 1228, 1158, 1134, 1097, 1052, 1014, 913, 876, 833, 760, 725, 677, 650, 614, 521 cm^{-1}; MS (ESI, m/z) 356.0 (M + H$^+$); HRMS (DART) calcd for $C_{20}H_{13}F_3NS^+$ (M + H$^+$) 356.0715, found 356.0716.

6-(((4-Chlorophenyl)thio)difluoromethyl)phenanthridine (9e) (Table 6): White solid (60.6 mg, 81%); mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.4 Hz, 1H), 8.56−8.53 (m, 2H), 8.28−8.26 (m, 1H), 7.87−7.83 (m, 1H), 7.80−7.67 (m, 5H), 7.44−7.41 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.2 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.9 (t, J = 28.1 Hz), 141.7, 138.4, 136.6, 134.1, 131.2, 130.9, 129.8 (t, J = 277.5 Hz), 129.3, 129.2, 129.0, 127.8, 126.8 (t, J = 5.4 Hz), 126.1, 125.1, 122.5, 122.1, 121.9 (t, J = 2.0 Hz); IR (film) 3079, 1902, 1611, 1586, 1572, 1527, 1487, 1475, 1462, 1445, 1389, 1363, 1305, 1261, 1226, 1164, 1133, 1097, 1050, 1038, 1015, 875, 845, 822, 760, 746, 725, 677, 649, 614, 581, 505 cm^{-1}; MS (ESI, m/z) 371.9 (M + H$^+$); HRMS (DART) calcd for $C_{20}H_{13}ClF_2NS^+$ (M + H$^+$) 372.0420, found 372.0421.

6-(((4-Bromophenyl)thio)difluoromethyl)phenanthridine (9f) (Table 6): White solid (65.5 mg, 79%); mp 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (t, J = 7.8 Hz, 1H), 8.54 (t, J = 7.4 Hz, 2H), 8.27 (d, J = 8.0 Hz, 1H), 7.88−7.66 (m, 6H), 7.58 (d, J = 8.4 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.1 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.8 (t, J = 28.1 Hz), 141.7, 138.7, 134.1, 132.3, 131.2, 130.9, 129.7 (t, J = 277.6 Hz), 129.2, 129.0, 127.8, 126.81 (t, J = 5.3 Hz), 126.75, 125.1, 125.0, 122.5, 122.1, 121.8

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

(t, J = 1.9 Hz); IR (film) 3080, 1611, 1585, 1574, 1565, 1528, 14898, 1473, 14638, 1444, 1386, 1363, 1307, 1261, 1166, 1133, 1095, 1066, 1050, 1037, 1009, 876, 843, 819, 758, 724, 675, 647, 511 cm^{-1}; MS (ESI, m/z) 415.9 (M + H^+); HRMS (DART) calcd for $C_{20}H_{13}BrF_2NS^+$ (M + H^+) 415.9915, found 415.9914.

6-(Difluoro((4-(methylthio)phenyl)thio)methyl)-phenanthridine (9g) (Table 6): White solid (58.9 mg, 77%); mp 137−140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.0 Hz, 1H), 8.58−8.53(m, 2H), 8.28 (d, J = 7.6 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.79−7.67 (m, 5H), 7.29 (d, J = 8.4 Hz, 2H), 2.50 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.8 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.1 (t, J = 27.9 Hz), 141.8, 141.7, 137.5, 134.1, 131.1, 130.9, 129.5 (t, J = 277.1 Hz), 129.1, 128.9, 127.7, 127.0 (t, J = 5.4 Hz), 126.3, 125.0, 123.0, 122.5, 122.1, 121.9, 15.3; IR (film) 3080, 2928, 1575, 1477, 1444, 1387, 1365, 1242, 1186, 1132, 1105, 1095, 1052, 1012, 875, 844, 818, 759, 724, 679, 646, 511 cm^{-1}; MS (ESI, m/z) 384.0 (M + H^+); HRMS (DART) calcd for $C_{21}H_{16}F_2NS_2^+$ (M + H^+) 384.0687, found 384.0685.

6-(Difluoro((4-methoxybenzyl)thio)methyl)phenanthridine (9h) (Table 6): Off-white solid (30.5 mg, 40%); mp 123−126 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (t, J = 8.4 Hz, 2H), 8.58−8.55 (m, 1H), 8.24−8.22 (m, 1H), 7.88 (t, J = 7.8 Hz, 1H), 7.78−7.72 (m, 3H), 7.36 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.29 (s, 2H), 3.79 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.8 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0, 151.2 (t, J = 27.4 Hz), 141.9, 134.1, 131.1, 131.0, 130.6 (t, J = 275.8 Hz), 130.5, 129.1, 128.8, 128.4, 127.7, 127.2 (t, J = 5.1 Hz), 125.1, 122.5, 122.1, 122.0, 114.2, 55.4, 32.4 (t, J = 3.8 Hz); IR (film) 3080, 3002, 2937, 2837, 1611, 1512, 1463, 1444, 1363, 1302, 1248, 1176, 1131, 1095, 1052, 1040, 1000, 918, 880, 840, 762, 726, 677 cm^{-1}; MS (ESI, m/z) 382.1 (M + H^+); HRMS (DART) calcd for $C_{22}H_{18}F_2NOS^+$ (M + H^+) 382.1072, found 382.1072.

Procedures for the Preparation of 6-(Difluoro-(phenylselanyl)methyl)phenanthridine (10)[14] (Scheme 4). To an oven-dried 10 mL Schlenk tube was added NaH (95% purity, 40.4 mg, 1.6 mmol, 8.0 equiv) in a glovebox, and then the flask was moved out of the glovebox. Under argon atmosphere, the solid of PhSeSePh (249.7 mg, 0.8 mmol, 4.0 equiv) was added quickly and then DMF (2.0 mL) was injected. After being stirred at room temperature for 30 min, to the reaction system was added 6-(difluoro(phenylsulfonyl)-methyl)phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv). The resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 12 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (ether ~50:1, v/v) as eluent to provide **10** as white solid (60.2 mg, 78%): mp 141−144 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.91−7.88 (m, 3H), 7.81−7.74 (m, 2H), 7.71−7.68 (m, 1H), 7.50−7.41 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.3 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.8 (t, J = 26.9 Hz), 141.8, 138.0 (t, J = 4.6 Hz), 134.3, 131.3, 130.8, 129.43, 129.39 (t, J = 291.5 Hz), 129.2, 129.1, 128.9, 127.9, 126.8 (t, J = 5.3 Hz), 125.9, 125.3, 122.5, 122.2, 121.5 (t, J = 2.0 Hz); IR (KBr) 3076, 1585, 1478, 1443, 1365, 1305, 1132, 1100, 1048, 1035, 1024, 870, 835, 759, 742, 725, 693 cm^{-1}; MS (ESI, m/z) 386.0 (M + H^+); HRMS (DART) calcd for $C_{20}H_{14}F_2N^{74}Se^+$ (M + H^+) 380.0314, found 380.0317.

General Procedures for the Preparation of Compounds 12 (Tables 7 and 8). To an oven-dried 10 mL Schlenk tube was added *t*-BuOK (0.8 mmol, 89.8 mg, 4.0 equiv) in a glovebox, and then the flask was moved out of the glovebox. Under argon atmosphere, DMSO (0.4 mL) was injected and the reaction mixture was stirred. $RCH(COOEt)_2$ (**11**) (0.8 mmol, 4.0 equiv) was dissolved in DMSO (1.6 mL) and was added dropwise into the reaction system. The resulting reaction mixture was stirred at room temperature for 30 min. Under argon atmosphere, 6-(difluoro(phenylsulfonyl)methyl)-phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv) was added quickly into the reaction system. The resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 12 h (24 or 72 h). After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3) and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (20:1, v/v) as eluent to provide compound **12.**

Diethyl 2-(difluoro(phenanthridin-6-yl)methyl)-2-methyl-malonate (12aa) (Table 7): Yellow solid (75.8 mg, 94%); mp 79−80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 8.4 Hz, 2H), 8.58−8.56 (m, 1H), 8.06−8.03 (m, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.75−7.72 (m, 3H), 4.31−4.19 (m, 4H), 2.06 (s, 3H), 1.18 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −90.3 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7 (t, J = 2.3 Hz), 150.3 (t, J = 31.1 Hz), 141.0, 134.2, 131.0, 130.3, 129.0, 128.6, 127.8, 127.3 (t, J = 6.2 Hz), 124.7, 122.8 (t, J = 2.2 Hz), 122.5, 122.14, 122.10 (t, J = 251.2 Hz), 61.9, 61.1 (t, J = 21.1 Hz), 18.8 (t, J = 4.4 Hz), 14.0; IR (film) 3080, 2982, 2903, 1749, 1616, 1489, 1465, 1447, 1465, 1269, 1113, 1095, 1074, 1049, 1021, 945, 763, 728, 683, 565 cm^{-1}; MS (ESI, m/z) 402.1 (M + H^+); HRMS (DART) calcd for $C_{22}H_{22}F_2NO_4^+$ (M + H^+) 402.1511, found 402.1514.

Diethyl 2-(difluoro(phenanthridin-6-yl)methyl)-2-ethylmal-onate (12ab) (Table 7): Off-white solid (79.0 mg, 95%); mp 74−77 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.0 Hz, 1H), 8.63 (d, J = 8.0 Hz, 1H), 8.55−8.52 (m, 1H), 8.07−8.05 (m, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.73−7.68 (m, 3H), 4.31−4.19 (m, 4H), 2.61 (q, J = 7.3 Hz, 2H), 1.28 (t, J = 7.4 Hz, 3H), 1.17 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −88.4 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1 (t, J = 2.4 Hz), 150.6 (t, J = 31.3 Hz), 141.0, 134.1, 130.9, 130.1, 129.0, 128.7, 127.7, 127.2 (t, J = 6.4 Hz), 124.7, 122.7, 122.5 (t, J = 252.1 Hz), 122.4, 122.1, 65.1 (t, J = 20.2 Hz), 61.5, 25.7 (t, J = 4.2 Hz), 14.0, 10.6; IR (film) 3084, 2981, 2941, 2904, 1736, 1612, 1532, 1465, 1446, 1367, 1317, 1241, 1125, 1055, 1028, 960, 885, 826, 263, 728, 566 cm^{-1}; MS (ESI, m/z) 416.1 (M + H^+); HRMS (DART) calcd for $C_{23}H_{24}F_2NO_4^+$ (M + H^+) 416.1668, found 416.1666.

Diethyl 2-allyl-2-(difluoro(phenanthridin-6-yl)methyl)-malonate (12ac) (Table 7): White solid (79.5 mg, 93%); mp 96−97 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (t, J = 9.6 Hz, 2H), 8.57−8.54 (m, 1H), 8.08−8.06 (m, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.73−7.70 (m, 3H), 6.36−6.26 (m, 1H), 5.21 (d, J = 16.8 Hz, 1H), 5.12 (d, J = 10.0 Hz, 1H), 4.29−4.17 (m, 4H), 3.31 (d, J = 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −88.4 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7, 150.5 (t, J = 31.4 Hz), 141.0, 134.2, 134.1, 131.0, 130.1, 129.0, 128.8, 127.7, 127.2 (t, J = 6.3 Hz), 124.7, 122.7 (t, J = 2.2 Hz), 122.5, 122.1, 122.0 (t, J = 252.4 Hz), 118.6, 65.1 (t, J = 20.3 Hz), 61.7, 37.0, 14.0; IR (film) 3084, 2983, 1738, 1638, 1610, 1530, 1465, 1446, 1367, 1310, 1293, 1248, 1221, 1167, 1145, 1127, 1044, 931, 891, 763, 728, 684, 644, 566 cm^{-1}; MS (ESI, m/z) 428.1 (M + H^+); HRMS (DART) calcd for $C_{24}H_{24}F_2NO_4^+$ (M + H^+) 428.1668, found 428.1668.

Diethyl 2-benzyl-2-(difluoro(phenanthridin-6-yl)methyl)-malonate (12ad) (Table 7): Off-white solid (91.1 mg, 95%); mp 102−105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.0 Hz, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.55−8.53 (m, 1H), 8.09−8.07 (m, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.74−7.69 (m, 3H), 7.53 (d, J = 7.2 Hz, 2H), 7.23 (t, J = 7.2 Hz, 2H), 7.16 (t, J = 7.0 Hz, 1H), 4.12−4.00 (m, 4H), 3.92 (s, 2H), 1.01 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −88.2 (s, 2F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.6, 150.5 (t, J = 31.1 Hz), 141.0, 137.0, 134.2, 131.5, 131.0, 130.2, 129.0, 128.8, 127.8, 127.3 (t, J = 6.1 Hz), 126.7, 124.7, 122.7 (t, J = 253.1 Hz), 122.5, 122.1, 66.4 (t, J = 20.2 Hz), 61.6, 37.9 (t, J = 3.9 Hz), 13.8; IR (film) 3067, 2982, 1739, 1608, 1578, 1532, 1495, 1465, 1446, 1367, 1326, 1242, 1200, 1152, 1098, 1079, 1040, 892, 861, 763, 728, 700, 683, 657, 584, 561, 536 cm^{-1}; MS (ESI, m/z) 478.1 (M + H^+);

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

HRMS (DART) calcd for $C_{28}H_{26}F_2NO_4^+$ (M + H$^+$) 478.1824, found 478.1823.

Diethyl 2-(difluoro(8-(methylsulfonyl)phenanthridin-6-yl)-methyl)-2-methylmalonate (12ba) (Table 8): Prepared from compound **1b** (0.17 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (78.7 mg, 97%); mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (d, J = 2.0 Hz, 1H), 8.78 (d, J = 8.8 Hz, 1H), 8.55−8.53 (m, 1H), 8.30 (dd, J = 8.8, 1.6 Hz, 1H), 8.02−8.00 (m, 1H), 7.80−7.73 (m, 2H), 4.27−4.16 (m, 4H), 3.14 (s, 3H), 2.01 (s, 3H), 1.16 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −89.7 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.3 (t, J = 2.6 Hz), 150.3 (t, J = 31.2 Hz), 141.7, 139.4, 137.2, 130.8, 130.4 (d, J = 2.2 Hz), 129.7, 128.0, 127.6 (td, J = 6.8, 3.1 Hz), 124.3, 123.4, 122.8, 122.1 (d, J = 1.9 Hz), 121.6 (t, J = 251.0 Hz), 62.0, 60.9 (t, J = 21.2 Hz), 44.6, 18.5 (t, J = 4.4 Hz), 14.0; IR (film) 3074, 2987, 2935, 1747, 1610, 1467, 1402, 1378, 1363, 1314, 1271, 1154, 1095, 1073, 1049, 961, 866, 831, 758, 736, 649, 584, 558, 537 cm^{-1}; MS (ESI, m/z) 480.1 (M + H$^+$); HRMS (DART) calcd for $C_{23}H_{24}F_2NO_6S^+$ (M + H$^+$) 480.1287, found 480.1280.

Diethyl 2-(difluoro(8-(trifluoromethyl)phenanthridin-6-yl)-methyl)-2-methylmalonate (12ca) (Table 8): Prepared from compound **1c** (0.05 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (22.6 mg, 96%); mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.77 (d, J = 8.8 Hz, 1H), 8.60−8.57 (m, 1H), 8.07−8.05 (m, 2H), 7.83−7.76 (m, 2H), 4.32−4.20 (m, 4H), 2.06 (s, 3H), 1.19 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9 (s, 3F), −90.0 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5 (t, J = 2.5 Hz), 150.3 (t, J = 31.4 Hz), 141.6, 136.3, 130.5, 130.3, 129.6 (q, J = 32.6 Hz), 129.4, 126.9 (q, J = 3.1 Hz), 125.0−124.8 (m), 124.0 (q, J = 270.8 Hz), 123.8, 123.6, 122.5, 122.1 (t, J = 2.2 Hz), 121.8 (t, J = 251.1 Hz), 62.0, 61.0 (t, J = 21.1 Hz), 18.7 (t, J = 4.5 Hz), 14.0; IR (film) 3078, 2985, 2913, 1733, 1630, 1538, 1465, 1378, 1316, 1178, 1049, 1022, 952, 866, 837, 766, 735, 648, 566 cm^{-1}; MS (ESI, m/z) 470.1 (M + H$^+$); HRMS (DART) calcd for $C_{23}H_{21}F_5NO_4^+$ (M + H$^+$) 470.1385, found 470.1382.

Diethyl 2-(difluoro(8-methylphenanthridin-6-yl)methyl)-2-methylmalonate (12da) (Table 8): Prepared from compound **1d** (0.16 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (60.0 mg, 90%); mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50−8.47 (m, 2H), 8.42 (s, 1H), 8.03−7.99 (m, 1H), 7.69−7.63 (m, 3H), 4.32−4.20 (m, 4H), 2.57 (s, 3H), 2.08 (s, 3H), 1.19 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −90.5 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.7 (t, J = 2.1 Hz), 149.8 (t, J = 31.0 Hz), 140.6, 137.7, 132.7, 132.0, 130.1, 128.6, 128.5, 126.5 (t, J = 5.9 Hz), 124.7, 122.8, 122.3, 122.2 (t, J = 251.2 Hz), 121.9, 61.8, 61.1 (t, J = 21.1 Hz), 21.9, 18.9 (t, J = 4.3 Hz), 14.0; IR (film) 3082, 2983, 2939, 1750, 1577, 1536, 1467, 1369, 1269, 1117, 1096, 1074, 1048, 957, 881, 829, 764, 738, 647, 573 cm^{-1}; MS (ESI, m/z) 416.1 (M + H$^+$); HRMS (DART) calcd for $C_{23}H_{24}F_2NO_4^+$ (M + H$^+$) 416.1668, found 416.1662.

Diethyl 2-(difluoro(3-methyl-8-phenylphenanthridin-6-yl)-methyl)-2-methylmalonate (12ea) (Table 8): Prepared from compound **1e** (0.05 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (22.8 mg, 93%); mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 1.2 Hz, 1H), 8.68 (d, J = 8.8 Hz, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.10 (dd, J = 8.6, 1.4 Hz, 1H), 7.84 (s, 1H), 7.76 (d, J = 7.2 Hz, 2H), 7.58−7.50 (m, 3H), 7.43 (t, J = 7.4 Hz, 1H), 4.32−4.20 (m, 4H), 2.59 (s, 3H), 2.07 (s, 3H), 1.19 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −90.2 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.8 (t, J = 2.2 Hz), 150.3 (t, J = 31.0 Hz), 141.2, 140.4, 140.1, 139.4, 133.3, 130.7, 130.3, 129.7, 129.1, 128.0, 127.7, 125.2 (t, J = 6.1 Hz), 122.89, 122.86, 122.3, 122.2 (t, J = 251.1 Hz), 121.9, 61.9, 61.1 (t, J = 21.1 Hz), 21.6, 18.9 (t, J = 4.4 Hz), 14.1; IR (film) 3039, 2996, 2952, 2931, 1738, 1481, 1463, 1266, 1123, 1096, 1074, 1046, 953, 814, 762, 695 cm^{-1}; MS (ESI, m/z) 492.2 (M + H$^+$); HRMS (DART) calcd for $C_{29}H_{28}F_2NO_4^+$ (M + H$^+$) 492.1981, found 492.1975.

Diethyl 2-((2,4-difluorophenanthridin-6-yl)difluoromethyl)-2-methylmalonate (12fa) (Table 8): Prepared from compound **1f** (0.2 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (78.7 mg, 90%); mp 151−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 8.4 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 9.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 9.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 4H), 2.07 (s, 3H), 1.26 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −90.1 (s, 2F), −106.6 (q, J = 8.6 Hz, 1F), −117.4 (t, J = 9.0 Hz, 1F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.4 (t, J = 2.5 Hz), 161.7 (dd, J = 249.2, 12.0 Hz), 159.5 (dd, J = 260.0, 13.4 Hz), 149.9 (t, J = 31.4 Hz), 132.8, 131.4, 128.9, 127.7 (d, J = 12.2 Hz), 127.4 (t, J = 6.2 Hz), 127.3 (d, J = 1.8 Hz), 123.2, 122.9, 122.1 (t, J = 250.8 Hz), 104.5 (dd, J = 28.0, 22.3 Hz), 103.0 (dd, J = 23.2, 4.5 Hz), 61.9, 61.0 (t, J = 20.9 Hz), 18.7 (t, J = 4.4 Hz), 13.9; IR (film) 3113, 2987, 2909, 1739, 1629, 1588, 1530, 1499, 1444, 1419, 1376, 1272, 1230, 1134, 1099, 1091, 1048, 1001, 866, 771, 682, 603 cm^{-1}; MS (ESI, m/z) 438.1 (M + H$^+$); HRMS (DART) calcd for $C_{22}H_{20}F_4NO_4^+$ (M + H$^+$) 438.1323, found 438.1323.

Diethyl 2-((2-chlorophenanthridin-6-yl)difluoromethyl)-2-methylmalonate (12ga) (Table 8): Prepared from compound **1g** (0.2 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (86.1 mg, 99%); mp 88−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.44 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 4.31−4.19 (m, 4H), 2.05 (s, 3H), 1.18 (t, J = 7.2 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −90.5 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5 (t, J = 2.3 Hz), 150.5 (t, J = 31.2 Hz), 139.3, 134.8, 133.0, 131.5, 131.2, 129.6, 128.3, 127.2 (t, J = 6.1 Hz), 125.7, 122.8, 122.4, 121.9 (t, J = 251.2 Hz), 121.8, 61.8, 61.0 (t, J = 21.2 Hz), 18.7 (t, J = 4.4 Hz), 14.0; IR (film) 3087, 2982, 2905, 1732, 1602, 1525, 1488, 1448, 1415, 1365, 1267, 1176, 1049, 1020, 945, 868, 828, 771, 683 cm^{-1}; MS (ESI, m/z) 436.1 (M + H$^+$); HRMS (DART) calcd for $C_{22}H_{21}ClF_2NO_4^+$ (M + H$^+$) 436.1122, found 436.1116.

Diethyl 2-(difluoro(3-(trifluoromethyl)phenanthridin-6-yl)-methyl)-2-methylmalonate (12ha) (Table 8): Prepared from compound **1h** (0.08 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (33.0 mg, 88%); mp 102−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71−8.65 (m, 3H), 8.27 (s, 1H), 7.92 (t, J = 8.0 Hz, 2H), 7.79 (t, J = 7.6 Hz, 1H), 4.33−4.21 (m, 4H), 2.07 (s, 3H), 1.22 (t, J = 7.2 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8 ((s, 3F), −90.7 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5 (t, J = 2.5 Hz), 152.1 (t, J = 31.0 Hz), 140.3, 133.4, 131.7, 131.1 (q, J = 32.9 Hz), 129.0, 127.7−127.5 (m), 127.1, 124.6 (q, J = 3.1 Hz), 123.9 (q, J = 270.7 Hz), 123.4, 122.9, 121.8 (t, J = 251.5 Hz), 62.0, 61.1 (t, J = 21.1 Hz), 18.7 (t, J = 4.5 Hz), 14.0; IR (film) 3087, 2991, 2918, 1739, 1629, 1612, 1532, 1462, 1445, 1335, 1272, 1239, 1175, 1126, 1098, 1074, 1052, 951, 884, 840, 777, 734, 691 cm^{-1}; MS (ESI, m/z) 470.1 (M + H$^+$); HRMS (DART) calcd for $C_{23}H_{21}F_5NO_4^+$ (M + H$^+$) 470.1385, found 470.1383.

Diethyl 2-(benzofuro[3,2-*k*]phenanthridin-6-yldifluoro-methyl)-2-methylmalonate (12ia) (Table 8): Prepared from compound **1i** (0.08 mmol, 1.0 equiv), following the procedures for the preparation of **12aa**; white solid (35.6 mg, 91%); mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (t, J = 8.2 Hz, 1H), 8.63−8.61 (m, 1H), 8.17−8.13 (m, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.97 (t, J = 8.2 Hz, 1H), 7.84−7.75 (m, 2H), 7.70 (t, J = 8.4 Hz, 1H), 7.53−7.48 (m, 1H), 7.39−7.34 (m, 1H), 4.35−4.23 (m, 4H), 2.13 (s, 3H), 1.22 (t, J = 7.2 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −90.0 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.8 (t, J = 2.7 Hz), 156.6, 152.0, 149.9 (t, J = 31.1 Hz), 141.3, 129.8, 129.12, 129.06, 128.2, 127.2, 125.4, 123.6, 123.2, 122.8, 122.3 (t, J = 252.0 Hz), 122.2, 121.9 (t, J = 6.7 Hz), 121.8, 121.1, 120.0, 112.1, 61.9, 61.3 (t, J = 21.1 Hz), 19.0 (t, J = 4.2 Hz), 14.1; IR (film) 3074, 2987, 2900, 1747, 1625, 1457, 1419, 1370, 1269, 1204, 1189, 1106, 1084, 1050, 997, 860, 767, 749, 733, 628, 582 cm^{-1}; MS (ESI, m/z) 492.1 (M + H$^+$); HRMS (DART) calcd for $C_{28}H_{24}F_2NO_5^+$ (M + H$^+$) 492.1617, found 492.1612.

Procedures for the Preparation of 6-(1,1-Difluoro-2-methyl-2-nitropropyl)phenanthridine (14a) (Scheme 5). To an oven-dried 10 mL Schlenk tube were added *t*-BuOK (89.8 mg, 0.8 mmol,

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

4.0 equiv) and 18-crown-6 (126.9 mg, 0.48 mmol, 2.4 equiv) in a glovebox, and then the flask was moved out of the glovebox. Under argon atmosphere, DMSO (0.4 mL) was injected and the reaction mixture was stirred. Me_2CHNO_2 (**13a**) (71.3 mg, 0.8 mmol, 4.0 equiv) was dissolved in DMSO (1.6 mL) and was added dropwise into the reaction system. The resulting reaction mixture was stirred at room temperature for 30 min. Under argon atmosphere, the solid of 6-(difluoro(phenylsulfonyl)methyl)phenanthridine (**1a**) (73.9 mg, 0.2 mmol, 1.0 equiv) was added quickly into the reaction system. The resulting reaction mixture was stirred at room temperature and room light illumination under argon atmosphere for 24 h. After the reaction was complete, the mixture was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (8 mL × 3), and the combined organic layer was dried over anhydrous $MgSO_4$. After the solution was filtered, the solvent was evaporated under reduced pressure and the residue was mixed with silica gel and purified by column chromatography on silica gel by using PE/EtOAc (30:1, v/v) as eluent to provide **14a** as off-white solid (47.2 mg, 75%): mp 131−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (t, J = 9.0 Hz, 2H), 8.49−8.47 (m, 1H), 8.02−7.99 (m, 1H), 7.83 (t, J = 8.2 Hz, 1H), 7.71−7.67 (m, 3H), 2.11 (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −94.6 (s, 2F); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.1 (t, J = 30.5 Hz), 140.9, 134.2, 131.0, 130.7, 129.03, 128.99, 127.7, 126.8 (t, J = 6.3 Hz), 124.7, 122.9, 122.5, 122.0, 120.2 (t, J = 250.3 Hz), 89.2 (t, J = 25.3 Hz), 23.3 (t, J = 3.6 Hz); IR (KBr) 3080, 3002, 2955, 1616, 1552, 1445, 1397, 1369, 1350, 1236, 1132, 1102, 1090, 1053, 954, 886, 847, 761, 723, 678, 575 cm^{-1}; MS (ESI, m/z) 317.1 (M + H$^+$); HRMS (DART) calcd for $C_{17}H_{15}F_2N_2O_2^+$ (M + H$^+$) 317.1096, found 317.1094.

Procedures for the Preparation of 2-Hydroxy-*N*,*N*-dimethyl-2-phenylacetamide (16) (Scheme 8). The preparation of **16** was based on reported procedures:[21] white solid (200 mg, 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 5.19 (d, J = 6.4 Hz, 1H), 4.74 (d, J = 6.4 Hz, 1H), 3.02 (s, 3H), 2.76 (s, 3H). The characterization data are consistent with previous report.[21]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00419.

List of compounds **1**; control experiments of the reactions between **1a** and nucleophiles; cyclic voltammetry study; and ^{1}H, ^{19}F, and ^{13}C NMR spectra of isolated compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jinbohu@sioc.ac.cn.

ORCID

Jinbo Hu: 0000-0003-3537-0207

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2015CB931900, 2016YFB0101200), the National Natural Science Foundation of China (21632009, 21421002), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), and the Special Financial Grant from the China Postdoctoral Science Foundation (2017T100312 to D.C.). We thank Yue Fu for providing partial data on the dark reactions of **1a** with PhONa, PhSNa, and KC(Me)$(CO_2Et)_2$, and Ling Deng for cyclic voltammetry measurements.

■ REFERENCES

(1) (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004. (b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2013.

(2) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (b) Stuart, A. C.; Tumbleston, J. R.; Zhou, H.; Li, W.; Liu, S.; Ade, H.; You, W. Fluorine Substituents Reduce Charge Recombination and Drive Structure and Morphology Development in Polymer Solar Cells. *J. Am. Chem. Soc.* **2013**, *135*, 1806−1815. (c) Tirotta, I.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo, G.; Bombelli, F. B.; Metrangolo, P.; Resnati, G. ^{19}F Magnetic Resonance Imaging (MRI): From Design of Materials to Clinical Applications. *Chem. Rev.* **2015**, *115*, 1106−1129. (d) Kirsch, P. Fluorine in Liquid Crystal Design for Display Applications. *J. Fluorine Chem.* **2015**, *177*, 29−36. (e) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359. (f) Preshlock, S.; Tredwell, M.; Gouverneur, V. ^{18}F-Labeling of Arenes and Heteroarenes for Applications in Positron Emission Tomography. *Chem. Rev.* **2016**, *116*, 719−766. (g) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.

(3) (a) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264 and references cited therein . (b) Gouverneur, V.; Seppelt, K. Introduction: Fluorine Chemistry. *Chem. Rev.* **2015**, *115*, 563−565. (c) Liu, Q.; Ni, C.; Hu, J. China's Flourishing Synthetic Organofluorine Chemistry: Innovations in the New Millennium. *Natl. Sci. Rev.* **2017**, *4*, 303−325 and references cited therein .

(4) (a) Taylor, E. C.; Saxton, J. E. *The Chemistry of Heterocyclic Compounds*; Wiley-Interscience: New York, 1994. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell: Oxford, 2000. (c) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, Germany, 2003. (d) Süzen, S. Antioxidant Activities of Synthetic Indole Derivatives and Possible Activity Mechanisms. *Top. Heterocycl. Chem.* **2007**, *11*, 145−178. (e) Zhang, B.; Studer, A. Recent Advances in the Synthesis of Nitrogen Heterocycles *via* Radical Cascade Reactions Using Isonitriles as Radical Acceptors. *Chem. Soc. Rev.* **2015**, *44*, 3505−3521.

(5) (a) Rafiee, F. Synthesis of Phenanthridine and Phenanthridinone Derivatives based on Pd-Catalyzed C-H Activation. *Appl. Organomet. Chem.* **2017**, *31*, No. e3820, and references cited therein . (b) Tumir, L.-M.; Radic Stojković, M.; Piantanida, I. Come-Back of Phenanthridine and Phenanthridinium Derivatives in the 21st Century. *Beilstein J. Org. Chem.* **2014**, *10*, 2930−2954. (c) Ishikawa, T. Benzo[*c*]phenanthridine Bases and Their Antituberculosis Activity. *Med. Res. Rev.* **2001**, *21*, 61−72.

(6) (a) Zhang, J.; Lakowicz, J. R. Enhanced Luminescence of Phenyl-phenanthridine Dye on Aggregated Small Silver Nanoparticles. *J. Phys. Chem. B* **2005**, *109*, 8701−8706. (b) Stevens, N.; O'Connor, N.; Vishwasrao, H.; Samaroo, D.; Kandel, E. R.; Akins, D. L.; Drain, C. M.; Turro, N. J. Two Color RNA Intercalating Probe for Cell Imaging Applications. *J. Am. Chem. Soc.* **2008**, *130*, 7182−7183.

(7) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881−1886. (b) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359−4369. (c) O'Hagan, D. Understanding Organofluorine Chemistry. An Introduction to the C−F Bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319.

(8) (a) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. The Synthesis and Metal Binding Characteristics of Novel, Isopolar Phosphonate Analogs of Nucleotides. *J. Chem. Soc., Perkin Trans. 1* **1984**, *1*, 1119−1125. (b) Berkowitz, D. B.; Bose, M. (α-Monofluoroalkyl)-

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359

phosphonates: A Class of Isoacidic and "Tunable" Mimics of Biological Phosphates. *J. Fluorine Chem.* **2001**, *112*, 13. (c) O'Hagan, D.; Wang, Y.; Skibinski, M.; Slawin, A. M. Z. Influence of the Difluoromethylene Group (CF_2) on the Conformation and Properties of Selected Organic Compounds. *Pure Appl. Chem.* **2012**, *84*, 1587−1595.

(9) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. Preparation of Tri- and Difluoromethylsilanes *via* an Unusual Magnesium Metal-Mediated Reductive Tri- and Difluoromethylation of Chlorosilanes Using Tri- and Difluoromethyl Sulfides, Sulfoxides, and Sulfones. *J. Org. Chem.* **2003**, *68*, 4457−4463. (b) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. Nucleophilic Difluoromethylation of Primary Alkyl Halides Using Difluoromethyl Phenyl Sulfone as a Difluoromethyl Anion Equivalent. *Org. Lett.* **2004**, *6*, 4315−4317. (c) Ni, C.; Hu, J. Nucleophilic Difluoromethylation of Carbonyl Compounds Using $TMSCF_2SO_2Ph$ and Mg^0-mediated Desulfonylation. *Tetrahedron Lett.* **2005**, *46*, 8273−8277. (d) Surya Prakash, G. K.; Hu, J.; Wang, Y.; Olah, G. A. Convenient Synthesis of Difluoromethyl Alcohols from Both Enolizable and Non-Enolizable Carbonyl Compounds with Difluoromethyl Phenyl Sulfone. *Eur. J. Org. Chem.* **2005**, *2005*, 2218−2223. (e) Zhu, J.; Wang, F.; Huang, W.; Zhao, Y.; Ye, W.; Hu, J. Copper-Mediated Fluoroalkylation Reactions with [(Phenylsulfonyl)-difluoromethyl]trimethylsilane: Synthesis of $PhSO_2CF_2$-Containing Allenes and Alkynes. *Synlett* **2011**, *2011*, 899−902. (f) Li, X.; Zhao, J.; Hu, M.; Chen, D.; Ni, C.; Wang, L.; Hu, J. Copper-mediated Aerobic (Phenylsulfonyl)difluoromethylation of Arylboronic Acids with Difluoromethyl Phenyl Sulfone. *Chem. Commun.* **2016**, *52*, 3657−3660.

(10) (a) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. Difluoromethyl Phenyl Sulfone as a Selective Difluoromethylene Dianion Equivalent: One-Pot Stereoselective Synthesis of *anti*-2,2-Difluoropropane-1,3-diols. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216−5219. (b) Prakash, G. K. S.; Hu, J.; Olah, G. A. Alkoxide- and Hydroxide-Induced Nucleophilic Trifluoromethylation Using Trifluoromethyl Sulfone or Sulfoxide. *Org. Lett.* **2003**, *5*, 3253−3256. (c) Li, X.; Zhao, J.; Zhang, L.; Hu, M.; Wang, L.; Hu, J. Copper-Mediated Trifluoromethylation Using Phenyl Trifluoromethyl Sulfoxide. *Org. Lett.* **2015**, *17*, 298−301.

(11) (a) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. Difluoromethyl Phenyl Sulfone, A Difluoromethylidene Equivalent: Use in the Synthesis of 1,1-Difluoro-1-alkenes. *Angew. Chem., Int. Ed.* **2004**, *43*, 5203−5206. (b) Ni, C.; Hu, M.; Hu, J. Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis. *Chem. Rev.* **2015**, *115*, 765−825 and references cited therein .

(12) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. Difluorophenylsulfanylmethyl Radical and Difluoromethylene Diradical Synthons: *gem*-Difluoromethylene Building Block. *J. Org. Chem.* **2004**, *69*, 6913−6915.

(13) (a) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743−2747. (b) Rong, J.; Ni, C.; Wang, Y.; Kuang, C.; Gu, Y.; Hu, J. Radical Fluoroalkylation of Aryl Alkenes with Fluorinated Sulfones by Visible-Light Photoredox Catalysis. *Huaxue Xuebao* **2017**, *75*, 105−109. (c) Miao, W.; Zhao, Y.; Ni, C.; Gao, B.; Zhang, W.; Hu, J. Iron-Catalyzed Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone. *J. Am. Chem. Soc.* **2018**, *140*, 880−883. (d) Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D.-H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Nuhant, P.; Baran, P. S. Modular Radical Cross-coupling with Sulfones Enables Access to sp^3-Rich (Fluoro)alkylated Scaffolds. *Science* **2018**, *360*, 75−80. (e) Yu, J.; Wu, Z.; Zhu, C. Efficient Docking-Migration Strategy for Selective Radical Difluoromethylation of Alkenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 17156−17160.

(14) Xiao, P.; Rong, J.; Ni, C.; Guo, J.; Li, X.; Chen, D.; Hu, J. Radical (Phenylsulfonyl)difluoromethylation of Isocyanides with $PhSO_2CF_2H$ under Transition-Metal-Free Conditions. *Org. Lett.* **2016**, *18*, 5912−5915.

(15) (a) Haber, F.; Willstatter, R. Unpairedness and Radical Chains in the Reaction Mechanism of Organic and Enzymic Processes. *Ber. Dtsch. Chem. Ges. B* **1931**, *64*, 2844−2856. (b) Kharasch, M. S.; Foy, M. The Peroxide Effect in the Cannizzaro Reaction. *J. Am. Chem. Soc.* **1935**, *57*, 1510−1510a. (c) Weiss, J. Mechanism of the Cannizzaro Reaction and Some Allied Processes. *Trans. Faraday Soc.* **1941**, *37*, 782−791. (d) Chung, S.-K. Mechanism of the Cannizzaro Reaction: Possible Involvement of Radical Intermediates. *J. Chem. Soc., Chem. Commun.* **1982**, 480−481. (e) Ashby, E. C.; Coleman, D. T., III; Gamasa, M. P. Evidence Supporting a Single Electron Transfer Pathway in the Cannizzaro Reaction. *Tetrahedron Lett.* **1983**, *24*, 851−854. (f) Ashby, E. C.; Coleman, D.; Gamasa, M. Single-Electron Transfer in the Cannizzaro Reaction. *J. Org. Chem.* **1987**, *52*, 4079−4085.

(16) (a) Feiring, A. E. Perfluoroalkylation of the 2-Nitropropyl Anion. Evidence for an $S_{RN}1$ Process. *J. Org. Chem.* **1983**, *48*, 347−354. (b) Koshechko, V. G.; Kiprianova, L. A.; Fileleeva, L. I.; Rozhkova, Z. Z. Electrochemical Initiation by Sulfur Dioxide of Radical-chain Trifluoromethylation Processes of Thiophenols with Bromotrifluoromethane. *J. Fluorine Chem.* **1995**, *70*, 277−278. (c) Yoshida, M.; Morishima, A.; Suzuki, D.; Iyoda, M.; Aoki, K.; Ikuta, S. One-Electron Reductive Cleavage of the C−Cl Bond of $ArCF_2Cl$: Convenient Route for the Synthesis of $ArCF_2$ Derivatives. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2019−2023. (d) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. Nucleophilic Substitution Reactions by Electron Transfer. *Chem. Rev.* **2003**, *103*, 71−167. (e) Rossi, R. A.; Postigo, A. Recent Advances on Radical Nucleophilic Substitution Reactions. *Curr. Org. Chem.* **2003**, *7*, 747−769. (f) Guidotti, J.; Schanen, V.; Tordeux, M.; Wakselman, C. Reactions of (Chlorodifluoromethyl)-benzene and (Chlorodifluoromethoxy)benzene with Nucleophilic Reagents. *J. Fluorine Chem.* **2005**, *126*, 443−447.

(17) Kornblum, N.; Boyd, S. D.; Ono, N. Displacement of the Sulfone Group from α-Nitro Sulfones. *J. Am. Chem. Soc.* **1974**, *96*, 2580−2587.

(18) Krief, A.; Trabelsi, M.; Dumont, W. Syntheses of Alkali Selenolates from Diorganic Diselenides and Alkali Metal Hydrides: Scope and Limitations. *Synthesis* **1992**, *1992*, 933−935.

(19) Kornblum, N.; Stuchal, F. W. New and Facile Substitution Reactions at Tertiary Carbon. The Reactions of Amines with *p*-Nitrocumyl Chloride and *α,p*-Dinitrocumene. *J. Am. Chem. Soc.* **1970**, *92*, 1804−1806.

(20) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. KO*t*Bu: A Privileged Reagent for Electron Transfer Reactions? *J. Am. Chem. Soc.* **2016**, *138*, 7402−7410 and references cited therein .

(21) Ragno, D.; Zaghi, A.; Di Carmine, G.; Giovannini, P. P.; Bortolini, O.; Fogagnolo, M.; Molinari, A.; Venturini, A.; Massi, A. Cross-Benzoin and Stetter-Type Reactions Mediated by KO*t*Bu-DMF *via* an Electron-Transfer Process. *Org. Biomol. Chem.* **2016**, *14*, 9823−9835.

(22) Based on the reduction potential of **1a** (−1.20 V vs SCE) and the nucleophile scope of its substitution reaction, we can predict that many soft nucleophiles (good electron donors), including PhSNa, PhSeNa, and $KC(Me)(CO_2Et)_2$, may be reactive not only toward fluorinated sulfones with first reduction potential higher than that of **1a** but also toward fluorinated sulfones with a first reduction potential somewhat lower than that of **1a**, such as $2\text{-}PyCF_2SO_2Ph$ (−1.44 V vs SCE) and $PhCF_2SO_2Ph$ (−1.55 V vs SCE). For a list of other possible fluorinated sulfones that may undergo SET reaction with soft nucleophiles such as PhSNa, PhSeNa, and $KC(Me)(CO_2Et)_2$, see ref 13a and the Supporting Information.

DOI: 10.1021/acs.joc.9b00419
J. Org. Chem. 2019, 84, 8345−8359