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Synthesis of Polycyclic Furan and Chromene Derivatives *via* Cascade Reactions Enabled by Cleavage of Multiple C(sp^3)-F Bonds

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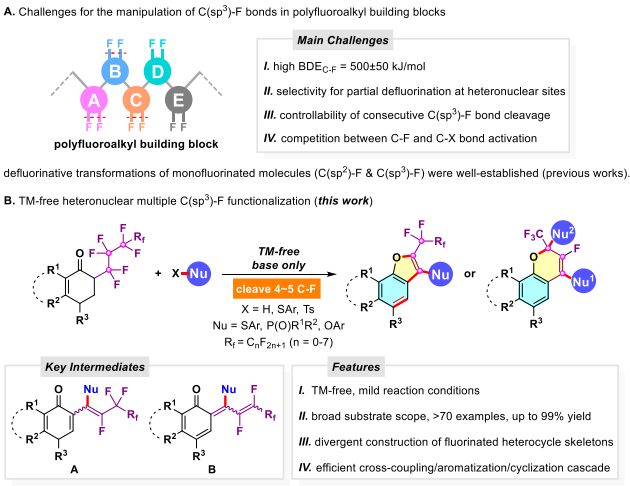
Abstract. The strong and unreactive C-F bond makes polyfluorocarbons extremely long-lived and potentially toxic. A successive selective and controllable C(sp^3)-F functionalization of polyfluoroalkylated ketones with *S*- and *O*-nucleophiles to enable efficient synthesis of pharmaceutically important fluorine- and sulfur-containing polycyclic furan and chromene derivatives under transition metal-free conditions is demonstrated here. The combination of C-S/C-O coupling, aromatization, and cyclization cascade contribute to the accurate four/five C(sp^3)-F bond cleavage at two different sites of perfluoroalkyl chain. The formation of reactive quinoid intermediates and the necessity of using TBAB (tetrabutylammonium bromide) as additive and Cs_2CO_3 as base were identified by detailed mechanistic studies.

Keywords: C(sp^3)-F bond functionalization; cascade reaction; furan; transition metal-free; defluorination

Introduction

Organofluorine chemistry increasingly exerts a profound influence on the vital areas such as healthcare, energy, and food.[1-3] The substantial demands for the development of efficient approaches to incorporate fluorinated fragments into organic molecules reflect the importance of the C-F bonds in synthetic chemistry. Among countless applications, over 25% of the modern pharmaceuticals, ~50% of agrochemicals, and numerous materials contain such important fluorine-containing functionalities in their structural scaffolds,[4-5] this is because the presence of fluorinated moieties usually imparts unique physical and chemical benefits to these parent molecules.

Among the various methods known to access oligofluorine- or perfluorine-bearing compounds,[6-14] one promising strategy involves the derivatization of readily available prefluorinated entities *via* selective cleavage of carbon–fluorine bond.[15-20] C-F bond conversions in this context may lead to new C-X (X = C, N, O, S, P, *etc.*) bond formation and precise retention of partially fluorinated scaffold, although most of the advances focus on the manipulation of single C-F bond. Compared with more activated aromatic[21-25] or vinylic analogues,[26-33] selective



Scheme 1. C-F bond functionalization of polyfluorinated building blocks to access fluoro-organic molecules. TM-free = transition metal-free.

aliphatic C(sp^3)-F functionalization of unreactive perfluoroalkyl substance with multiple C-F bonds attached remote to π-system is relatively uncommon.[34-47] The successful realization of this

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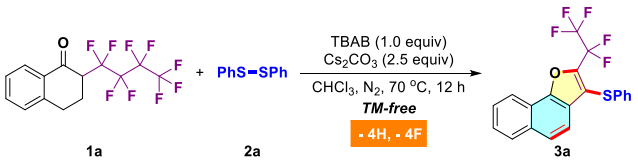
challenging issue is complicated by several apparent factors (Scheme 1A). First, the high strength and activation barrier of C-F bond (BDE_{C-F} = 500±50 kJ/mol) result in chemical robustness of fluorocarbon in terms of thermodynamic stability and kinetic inertness.[48] Second, a distinction must be preferentially made between various C-F bonds with extremely slight reactivity difference, namely, the selectivity for partial defluorination at two different sites of perfluoroalkyl chain is fundamentally considered to be difficult. Third, since the reactivity of multifluorocarbons decrease along with an increase in the number of geminal fluorine atoms, consecutive C(sp^3)-F bonds cleavage are frequently prone to proceed out of control. And last but not least, competitive activation between C-F and other C-X (X = C or other heteroatom) bond is also an intractable issue, especially under metal catalysis.[49] Therefore, the continuing augmentation of chemical toolboxes by exploring distinctive C-F bond functionalization manifolds may allow flexible modulations of fluoro-organic molecules and simultaneously exclude the interference from applying exogenously sensitive fluorinating sources. Meanwhile, evidence of environmental impacts and toxic effects of some multifluorocarbons have urged us to seek innovative techniques for exploiting perfluorinated chemicals.[50]

Herein, we report a successive quadruple/quintuple C(sp^3)-F bond cleavage mode enabled cross-coupling-aromatization-cyclization cascade of polyfluoroalkylated ketones with *S*- and *O*-nucleophiles (Scheme 1B). It was proposed that the divergent defluorinative construction of perfluoroalkylated furan and chromene derivatives typically rely on the key unsaturated ketone intermediates **A** and **B**. The combination of TBAB (tetrabutylammonium bromide) with Cs_2CO_3 contribute to the intermolecular C-S/C-O couplings and subsequent ring-closure.

Results and Discussion

To begin with, we examined the multiple C(sp^3)-F bond heterolysis of 2-(perfluorobutyl)-3,4-dihydronaphthalen-1(2*H*)-one (**1a**) (Table 1, also see Table S1-S7 in Supporting Information for details). In an initial screening of potential nucleophilic partners, we identified 1,2-diphenyldisulfane (**2a**) as a suitable substrate for C-S bond forging in view of the wide utilities of organosulfur derivatives in organic synthesis.[51] Gratifyingly, reacting **1a** and **2a** together with TBAB (1.0 equiv.) and excess Cs_2CO_3 (2.5 equiv.) in chloroform at 70 °C for 12 h led to the desired densely functionalized naphtho[1,2-*b*]furan product **3a**[52,53] in 73% NMR yield (60% isolated yield, entry 1). Control experiments showed the necessity of using TBAB as an additive and Cs_2CO_3 as a base for the present transformation (entries 2- 3). Other solvents, such as DCE, toluene, DMSO, and MeCN, were found to be less effective than $CHCl_3$ (entries 4-7). In addition, no product **3a** was produced when the titled reaction was performed by replacing Cs_2CO_3 with K_2CO_3, NaOH, ^{t}BuOK, or DABCO, suggesting the specificity of Cs_2CO_3 for effecting this

Table 1. TM-free quadruple C(sp^3)-F bonds cleavage: optimization of reaction conditions.[a]



Entry	Deviation from standard reaction conditions	Yield (%)[b]
1	none	73 (60)[c]
2	without TBAB	trace
3	without Cs_2CO_3	0
4	DCE instead of $CHCl_3$	trace
5	toluene instead of $CHCl_3$	38
6	DMSO instead of $CHCl_3$	48
7	MeCN instead of $CHCl_3$	53
8	K_2CO_3 instead of Cs_2CO_3	0
9	NaOH instead of Cs_2CO_3	0
10	^{t}BuOK instead of Cs_2CO_3	0
11	DABCO instead of Cs_2CO_3	0
12	TBAI instead of TBAB	trace
13	NBS instead of TBAB	0
14	KBr instead of TBAB	0
15	TBAHS instead of TBAB	41

[a] Standard reaction conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), TBAB (0.3 mmol), and Cs_2CO_3 (0.75 mmol) in $CHCl_3$ (2.0 mL) at 70 °C for 12 h under N_2.
[b] Yields were determined by NMR analysis with 1,4-dimethoxybenzene as an internal standard.
[c] Isolated yield.

tandem defluorination (entries 8-11). Furthermore, after systematic evaluation of various additives, such as TBAI (tetrabutylammonium iodide), NBS (*N*-bromosuccinimide), KBr, and ^{n}Bu$_4$NHSO$_4$ (TBAHS), TBAB still emerged as the most beneficial promoter for the cascade reaction to generate C2-perfluoroehtylated naphtho[1,2-*b*]furan **3a** (entries 12-15).

With the optimal reaction conditions in hand, substrate scope with regard to various disulfides was investigated (Table 2). An array of commercially available aryl disulfides bearing diverse substituents, including halide (Br, Cl, F) and methyl group, efficiently underwent the present cyclization to afford naphthofuran **3b-3e** in moderate to good yields. In a similar manner, heteroaryl disulfide was found to be compatible with the mild reaction conditions to furnish the corresponding heterocyclic variant **3f** in 57% yield. It should be noted that when 1,2-dipropyldisulfane (**2g**) was applied to the reaction, an unexpected product **3g** with an internal C-C double bond was obtained in 17% yield.[54] Unfortunately, as for substrate **2** bearing a benzyl substituent, it was not suitable for the reaction system (**3h**).

With the success of the above transformations, the synthetic utility of the present strategy was further extended to the quadruple C(sp^3)-F bond functionalization of perfluorobutylated **1a** with simple mercaptans. As summarized in Table 3, both electron-deficient (**5a-5f**) and electron-rich (**5g-5k**) aryl mercaptans were well demonstrated to be appropriate candidates for the reactions. Additionally, substrates

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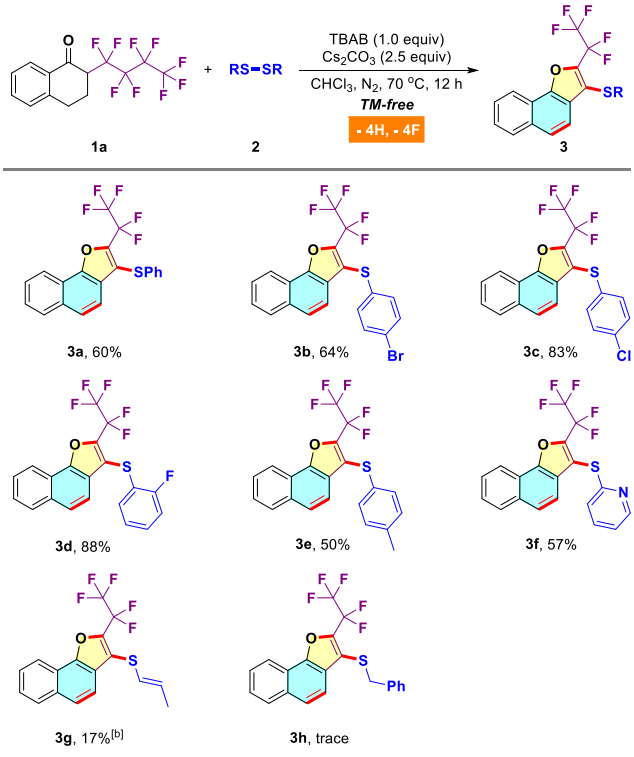
possessing Br, F, or OMe substituents at *ortho*-position were proven to be suitable substrates for the current transition metal-free couplings (84-92% yields, **5c**, **5f**, and **5i**). Moreover, a 1 mmol scale reaction was also successfully achieved for the synthesis of product **5c** (84% yield). More importantly, naphthalene, 1,3,4-thiadiazole, and pyridine could be facilely incorporated into the family of these fused heterocycles, which greatly streamlined access to potential electroluminescence materials (**5l**–**5n**).[55] Interestingly, thiophen-2-ylmethanethiol could be installed as well, albeit furnishing the corresponding product **5o** in a low yield (12% yield). It should be mentioned that alkenyl intermediate **5g'** was obtained as the main product when the reaction was performed under the standard conditions, and the formation of product **5g** could be successfully achieved by performing the reaction in DMSO with the use of 5.5 equiv. of Cs_2CO_3.

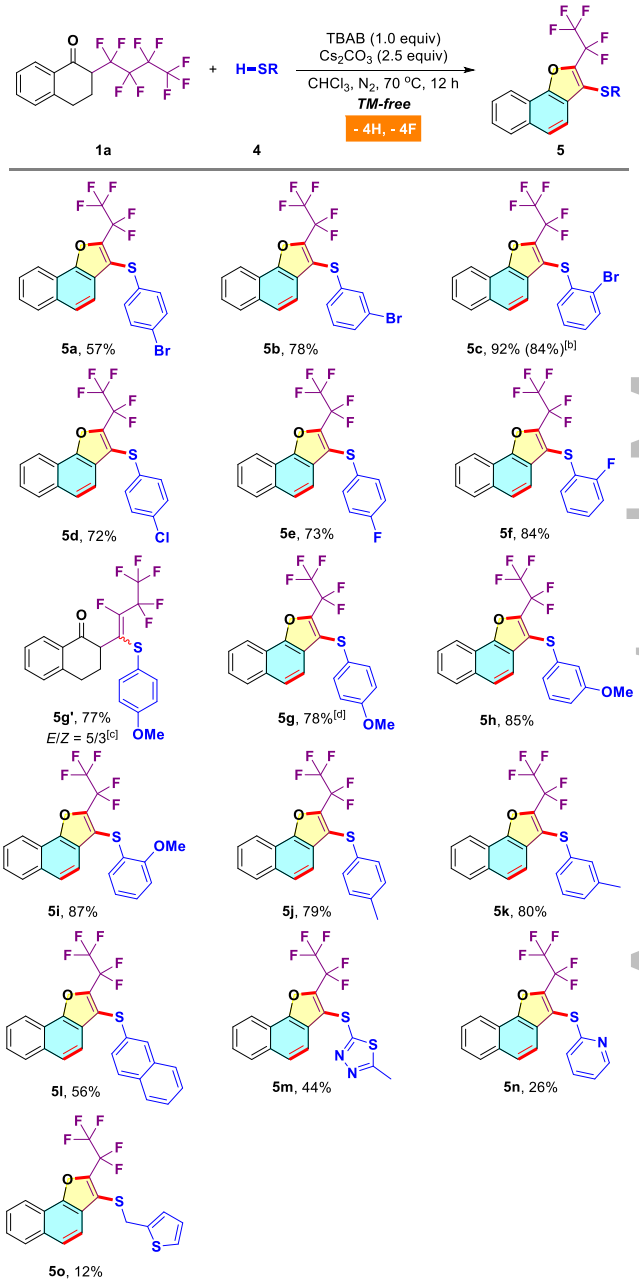
Table 2. Substrate scope of disulfides.[a]



[a] Standard reaction conditions; isolated yields.
[b] 1,2-Dipropyldisulfane (**2g**) was used.

Next, we set out to study the scope of this tandem protocol with respect to structurally varied fluorocarbons **1**, and the results are listed in Table 4. Generally, perfluorobutyl tetralones containing different substituents of varying electronic character and steric hindrance on the phenyl moieties smoothly coupled with 2-bromobenzenethiol (**4c**) to deliver the expected products **6a-6f** in 58%-83% yields. It was found that reaction partners **1** possessing an aryl or alkyl group at the *C*4-position did not have significant influence on the reaction efficiency, giving rise to the desired products **6g** and **6h** in 74% and 75% yields, respectively. Moreover, heteroaromatic analogue of 5-(perfluorobutyl)-6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one worked equally well under the optimized conditions (**6i**, 81% yield). It is worth mentioning that we could successfully obtain a series of site-specific fluoroalkylated benzofuran derivatives **6j-6l**, which is difficult to synthesize by traditional fluoroalkylation methods.[53] Impressively, apart from perfluorobutyl group, the substrates with perfluoroalkyl chain length ranging from ten to three carbons were also compatible with the mild reaction conditions and reacted in a similar fashion (**6m-6p**, 80-93% yield).[52] In all cases, a highly regioselective C-F bond cleavage was observed, favoring the sequence of coupling, aromatization, and annulation cascade.

Table 3. Substrate scope of thiophenols.[a]



[a] Standard reaction conditions; isolated yields.

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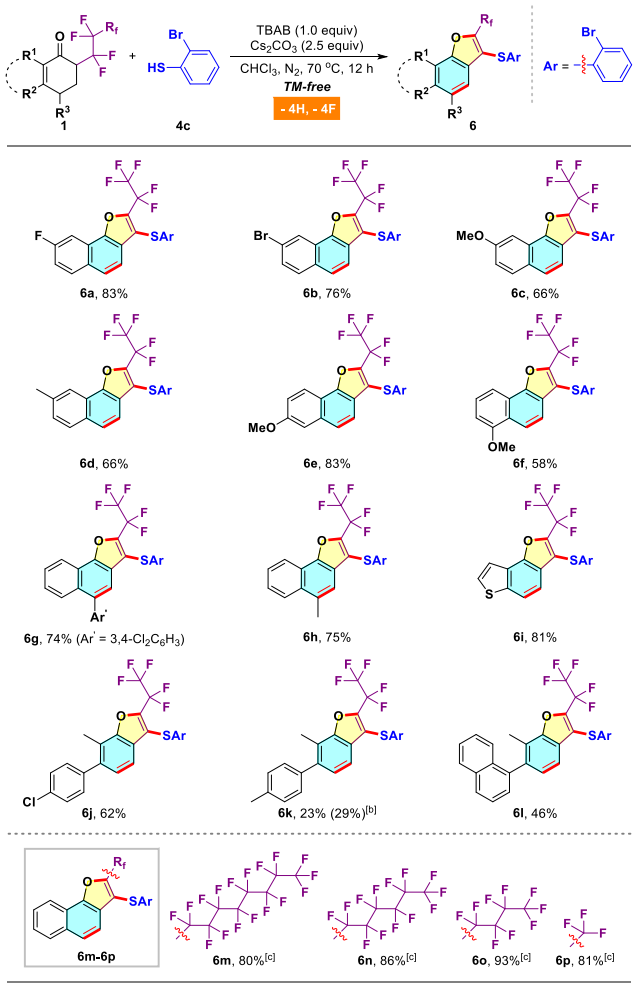
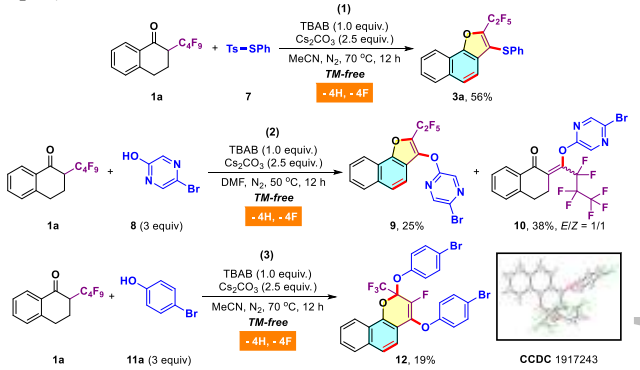
[b] 1 mmol scale.
[c] The ratio of *E*/*Z* isomers were determined by ^{19}F NMR.
[d] Cs_2CO_3 (5.5 equiv.) was used in DMSO.

Table 4. Substrate scope of prefluoralkylated ketones.[a]

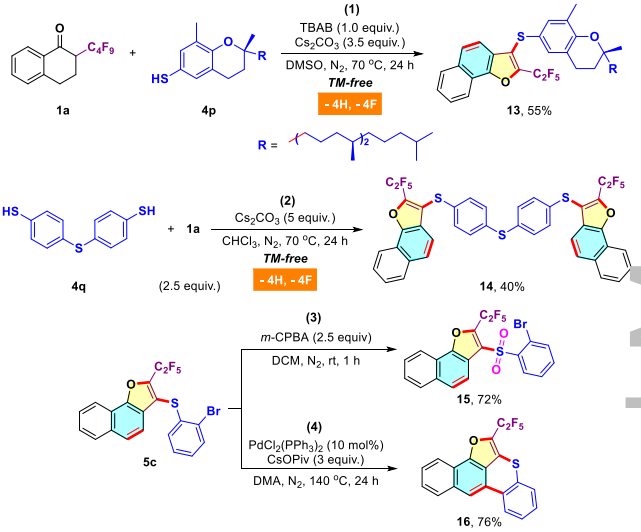


[a] Standard reaction conditions; isolated yields.
[b] At 50 °C for 24 h.
[c] 0.2 mmol scale.

When *S*-phenyl 4-methylbenzenesulfonothioate (**7**) was reacted with ketone **1a**, the corresponding product **3a** was delivered in 56% yield, implying the general applicability of different *S*-sources (Scheme 2, eq. 1). Then, the significance of the coupling partner was further demonstrated through the fact that the use of reagent **8** only led to a mixture of targeted ether **9** and uncyclized byproduct **10** in 25% and 38% yields, respectively (Scheme 2, eq. 2). Interestingly, an unexpected difunctionalized chromene **12** (CCDC 1917243;[56] also see Supporting Information for details) was formed in 19% yield when 4-bromophenol (**11a**) was subjected to reaction with **1a** in a slightly modified reaction system (Scheme 2, eq. 3). The introduction of additional mercaptan **4p** derived from tocopherol and di-nucleophilic 4,4'-thiodibenzenethiol (**4q**) were also proven to be successful for the transformation (Scheme 3, eq. 1 and eq. 2). Finally, we found that the presynthesized product **5c** could be effectively transformed into fluoroalkylated sulfone **15** (72% yield) and polycyclic heteroaromatic ring **16** (76% yield), which would provide chemists an alternative platform for preparing these intriguing fused molecules (Scheme 3, eq. 3 and eq. 4).



Scheme 2. TM-free quadruple C(sp^3)-F bonds cleavage using other nucleophiles.



Scheme 3. Further transformations.

To gain insight into the mechanism of the reaction, several control experiments were conducted in Scheme 4. Firstly, the necessity of the phenyl ring or conjugate C=C bond adjacent to the carbonyl group in the α-perfluoroalkyl ketone **1** was ascertained by using 2-(perfluorobutyl)cyclohexan-1-one (**17**) as a reactant, where no anticipated product **18** was detected (Scheme 4, eq. 1). Secondly, our efforts to use seven-membered **19** as a possible substrate proved futile, revealing that the autoaromatization of the dihydronaphthalenone might become a vital course for the observed successive four C(sp^3)-F bonds cleavage (Scheme 4, eq. 2). Thirdly, it was found that α,β-desaturation of starting material **1a** was enabled by eliminating a molecule of HF under basic conditions to form defluorinated intermediate **22** with *E*/*Z* = 1/1 (Scheme 4, eq. 3). Notably, the generation of product **5c** was completely inhibited in the absence of additive TBAB (only obtained compound **23** in 27% yield with *E*/*Z* = 13/10) which indicated that

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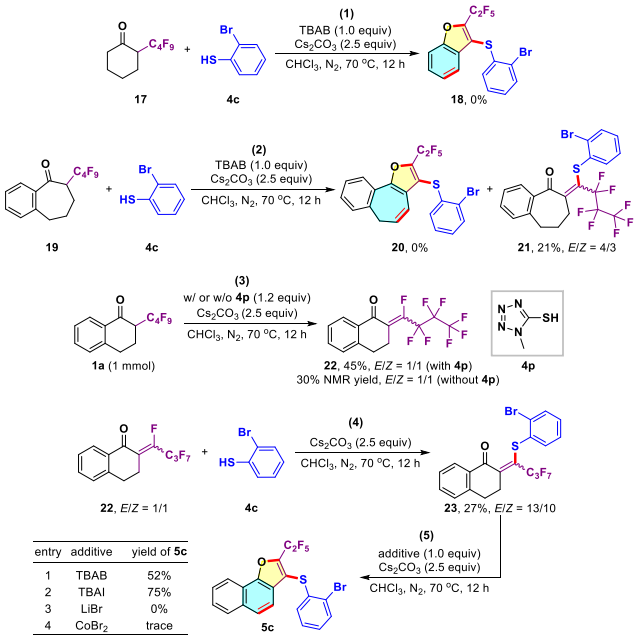
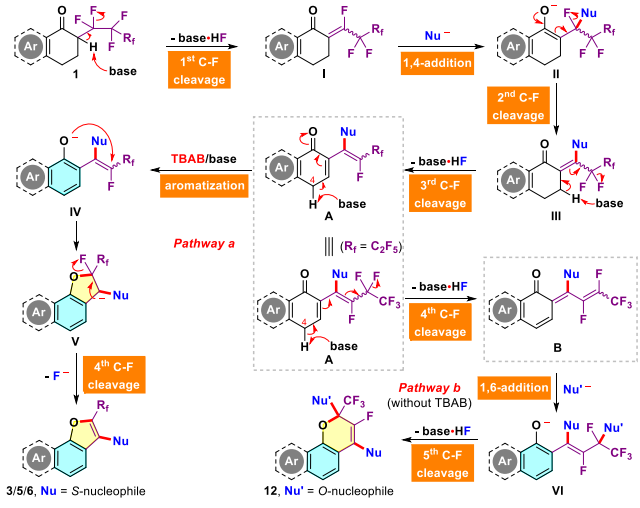
TBAB might favor the intramolecular C-O bonding for ring-closure (Scheme 4, eq. 4).[57] Moreover, unsaturated compound **23** could be eventually converted to the corresponding product **5c** in 52% yield under the standard conditions (Scheme 4, eq. 5). Interestingly, the control reactions using TBAI as additive could proceed to produce product **5c** in 75% yield. However, LiBr and $CoBr_2$ could not promote the desired intramolecular cyclization. These results suggested that the cation of TBAB (or TBAI) is important for the intramolecular cyclization, which might be due to the possibility that the formed TBA-enolate is more nucleophilic than potassium or cesium enolate.[57]



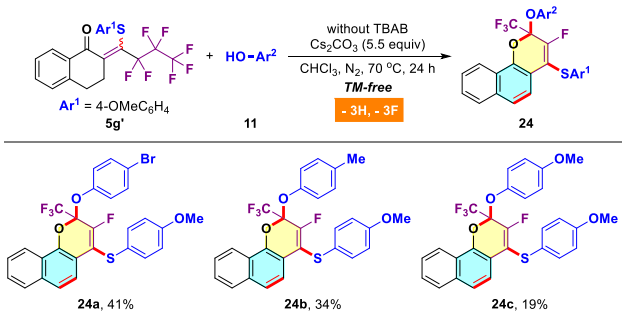
Scheme 4. Control experiments.



Scheme 5. Proposed reaction mechanism.

On the basis of previously reported C-F bond activation modes[15,16,58-61] and above control experiments, a mechanism involving Cs_2CO_3-promoted/TBAB-assisted multiple C(sp^3)-F cleavage is proposed (Scheme 5). The base initially abstracts a molecule of HF from polyfluoroalkylated ketone **1** to deliver an unsaturated ketone **I** which, as a Michael-type acceptor, subsequently reacts with *S*-/*O*-nucleophile in a 1,4-addition manner and followed by the cleavage of the second C-F bond to afford the nascent β-coupled intermediate **III**.[62] The extrusion of third fluoride anion through β,γ-desaturation of **III** readily proceeds under basic conditions, producing the unstable endocyclic naphthalen-1(4*H*)-one **A**, mainly owing to the π-conjugated effect. Subsequently, autoaromatization takes place easily to release a transient naphthol/phenol anion **IV** upon a base-assisted elimination of a proton at *C*4-position from intermediate **A**. The existence of TBAB might contribute to the autoaromatization.[57] Finally, C-F bond heterolysis *via* an intramolecular nucleophilic 5-*endo-trig* cyclization furnishes the ring-closure product (pathway a).[63,64] The possibility that the formed TBA-enolate is more nucleophilic than potassium or cesium enolate cannot be ruled out.[57] We believed that TBAB additive would accelerate both the events of intermolecular C-S/C-O bond formation and intramolecular C-O coupling, but the detailed mode of this action remained elusive. Simultaneously, an additional possible species **VI** might be formed by the Cs_2CO_3-promoted defluorination of intermediate **A** followed by trapping another nucleophile (Nu') *via* 1,6-addition pathway (*via* intermediate **B**). An intramolecular nucleophilic substitution of the resultant **VI** eventually provides the fused chromene product in the absence of TBAB (pathway b). Notably, both the amounts of the Cs_2CO_3 and the type of nucleophiles have dramatic effects on the product outcomes.[65] The change of reaction pathways a and b depends on the presence or the absence of TBAB and the stability of intermediates **IV** and **VI**.

Table 5. Chromene derivatives synthesis.[a]



[a] Reaction conditions: **5g'** (0.2 mmol), **11** (0.6 mmol), and Cs_2CO_3 (1.1 mmol) in $CHCl_3$ (2.0 mL) at 70 °C under N_2 for 24 h; isolated yield.

Base on the mechanistic assumption, the formation of five-membered furan cycles would be suppressed in the absence of TBAB additive. Consequently, under slightly modified reaction conditions (without TBAB), functionalized chromene derivatives **24a-24c** were synthesized by using pre-synthesized

intermediate **5g'** as the substrate and phenol compounds as the coupling partners (Table 5).

Conclusion

In summary, a novel protocol for the highly selective functionalization of C(sp^3)-F bonds, which allows for the divergent synthesis of partially fluorinated sulfur-containing polycyclic furan and chromene derivatives starting from readily available polyfluorinated ketones and various nucleophiles, was established. The versatility of the present methodology is demonstrated for thiolation and phenolation, which makes possible the synthesis of focused chemical libraries of medicinally relevant molecules. In addition to its excellent substrate scope and good functional group compatibility, late-stage applications for the modification of complex compounds, such as mercaptan derived from tocopherol and di-nucleophilic 4,4'-thiodibenzenethiol, were also feasible. Mechanistically, the product selectivity is controlled by the formation of two different reactive quinoid intermediates. Key to the success of the present method mainly relies on the well-controlled sequence of successive four/five C-F bond cleavage consisting of cross-couplings, aromatization, and cyclization in the presence of an efficient combination of TBAB and Cs_2CO_3, which inarguably provides chemists a unique entry to manipulate multiple inert C(sp^3)-F bonds at two different sites of perfluoroalkyl chain.

Experimental Section

General procedures for the synthesis of perfluoroalkylated naphtho[1,2-*b*]furan/benzofuran derivatives

A solution of α-perfluoroalkyl ketone **1** (0.3 mmol), *S*-nucleophile **2**/**4** (0.36 mmol), tetrabutylammonium bromide (97 mg, 0.3 mmol, TBAB), and Cs_2CO_3 (244 mg, 0.75 mmol) in $CHCl_3$ (2.0 mL) was stirred under nitrogen atmosphere at 70 °C for 12 h. The reaction was then quenched by saturated NH_4Cl solution (20 mL) and diluted with EtOAc (20 mL). The organic layer was washed with saturated brine twice, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (300-400 mesh) using petroleum ether/ethyl acetate or dichloromethane/methanol as eluent to afford the pure products **3**/**5**/**6**.

The reaction of unsaturated 2,2,3,3,4,4,4-heptafluoroketone (5g') with *O*-nucleophile

A solution of 2-(2,2,3,3,4,4,4-heptafluoro-1-((4-methoxyphenyl)thio)butylidene)-3,4-dihydronaphthalen-1(2*H*)-one (**5g'**, 0.2 mmol, 93 mg), *O*-nucleophile (**11**, 0.6 mmol), and Cs_2CO_3 (359 mg, 1.1 mmol) in $CHCl_3$ (2.0 mL) was stirred under nitrogen atmosphere at 70 °C for 24 h. The reaction was then quenched by saturated NH_4Cl solution (20 mL) and diluted with EtOAc (20 mL). The organic layer was washed with saturated brine twice, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (300-400 mesh) using petroleum ether as eluent to afford the pure product (**24**).

Acknowledgements

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FULL PAPER

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