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PAPER

Efficient synthesis of unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts for electrophilic bromodifluoromethylating reagents†

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A series of unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts **1** were readily synthesized by treatment of corresponding (bromodifluoromethyl)arylsulfoxides **2** and substituted benzenes **3** with triflic anhydride in moderate to good yields. The unsymmetrical sulfonium salts **1** with different aryl groups having electron-donating or electron-withdrawing substituents can be nicely constructed depending on the choice of **2** and **3**. Bromodifluoromethylation of alkynes was evaluated by using the selected diarylsulfonium salts **1** to provide the desired bromodifluoromethylated alkynes in moderate to good yields.

Introduction

Fluoro-organic compounds play an important role in the development of pharmaceuticals, agrochemicals, and advanced materials.[1] According to a survey, around 20% of drugs on the market contain fluorine(s) and more than 30% of crop protection agents are organofluorine compounds.[2] Among several strategies for the synthesis of organofluorine compounds, the direct introduction of a fluoromethyl group into common non-fluorinated organic molecules is principally advantageous since the method can be performed at a later stage of the total synthesis of target compounds. The direct fluoromethylation of organic compounds can be approached by nucleophilic, radical, and electrophilic ways.[3] Over the past two decades, electrophilic fluoromethylation has attracted considerable attention.[4–6] A series of electrophilic fluoromethylation reagents have been extensively designed and synthesized, including for trifluoromethylation ($^{+}CF_3$),[4] difluoromethylation ($^{+}CHF_2$)[5] and monofluoromethylation ($^{+}CH_2F$)[6] reactions. As a part of our research program for the development of direct fluoromethylation reactions and the synthesis of biologically attractive organofluorine compounds, we required electrophilic bromodifluoromethylating reagents ($^{+}CBrF_2$). While only dozens of organofluorine compounds are available in nature, more than 1600 naturally occurring organobromine compounds have been found, in particular from marine sources, and a large number of these organobromines are biologically attractive. Therefore, the bromodifluoromethylation of common organic molecules could potentially be the strategy after trifluoromethylation for the development of novel pharmaceuticals and agrochemicals. In addition to this, bromodifluoromethylated compounds have another advantage as intermediates, which can be derived into *gem*-difluoromethylene compounds ($-CF_2-$)[7] or compounds having a terminal difluoromethyl group ($-CHF_2$).[8] In 2011, Xiao *et al.* reported the synthesis of a symmetrical *S*-(bromodifluoromethyl)diphenylsulfonium salt for electrophilic bromodifluoromethylating reagent from sodium bromodifluoromethanesulfinate, benzene and triflic anhydride in dichloromethane.[9] Although it is a simple, one-pot procedure, the method cannot be applied to the synthesis of structurally fine-tuned, unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts which might give improved results in electrophilic bromodifluoromethylation processes that at present give only modest yields. Indeed, for trifluoromethylation, the unsymmetrical reagents have much more success than symmetrical ones.[4a,j–l] Prakash *et al.* also show the success of unsymmetrical reagents for mono- and ditrifluoromethylation reactions.[5a,6a] Magnier and co-workers reported electrophilic bromodifluoromethylating reagents based on a sulfoximine skeleton.[10] However, the reagents performed ineffectively in the bromodifluoromethylating reaction. Herein, we disclose the efficient synthesis of a series of unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts **1** as electrophilic bromodifluoromethylating reagents by treatment of aryl bromodifluoromethylsulfoxides **2** with substituted benzenes in the presence of triflic anhydride. *S*-(Bromodifluoromethyl)(2-bromophenyl)(2,3,4,5-tetramethylphenyl)sulfonium triflate **1i′** was found to be most effective for the electrophilic bromodifluoromethylation of alkynes amongst the 5 novel unsymmetrical diarylsulfonium salts prepared (Scheme 1).

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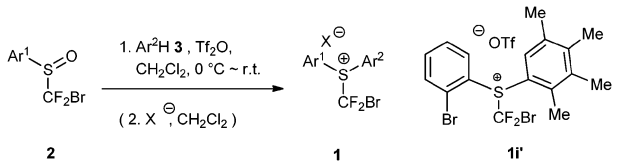


Scheme 1 Synthesis of unsymmetrical *S*-(bromodifluoromethyl)diarylsulfonium salts **1**.

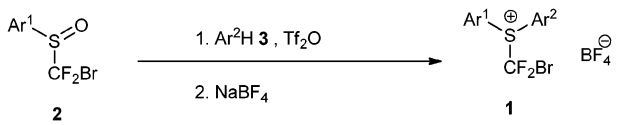
Results and discussion

Synthesis of a series of unsymmetrical *S*-(bromodifluoromethyl)-diarylsulfonium salts **1** were examined by the reaction of aryl bromodifluoromethylsulfoxides with substituted benzene derivatives in the presence of triflic anhydride at 0 °C to room temperature. The starting aryl bromodifluoromethyl sulfoxides were readily prepared from the corresponding sodium arylthiolates with dibromodifluoromethane followed by oxidation using *m*-CPBA in good overall yields. All the salts were obtained as triflates and they were converted into tetrafluoroborates . The results are summarized in Table 1.

First, the reaction of bromodifluoromethyl phenyl sulfoxide **2a** and various benzene derivatives (Ar^2H **3**) having electron-donating or electron-withdrawing groups was examined. 1,2,3,4-Tetramethylbenzene (**3a**, entry 1), 1,3,5-trimethylbenzene (**3f**, entry 7) and 1,3,5-trimethoxybenzene (**3g**, entry 8) were smoothly reacted with **2a** in good to excellent yields. A mixture of *o*-methoxy and *p*-methoxy isomers **1b** was obtained in 89% yield when the reaction of **2a** was carried out with anisole (**3b**, entry 3). A longer reaction time of 48 h was required for the reaction of **2a** with fluorobenzene (**3c**, entry 4). The single, *p*-substituted *S*-(bromodifluoromethyl)-*p*-fluorophenylphenylsulfonium salt **1c** was obtained. However, the reaction of **2a** with *p*-dibromobenzene (**3d**) or *p*-dinitrobenzene (**3e**) failed (entries 5 and 6). These results indicate that electron-donating groups on Ar^2H **3** promoted the reaction while electron-withdrawing groups on Ar^2H **3** intensely decrease the reactivity. The problem of synthesis of diarylsulfonium salts having electron-withdrawing groups can be overcome by the use of a different combination of sulfoxides with electron-withdrawing groups and benzene derivatives. Thus, *p*-nitrophenyl sulfoxide **2b**, when reacted with 1,3,5-trimethoxybenzene **3h**, gave the reagent **1h** in 49% (entry 9). Interestingly, *o*-bromophenyl sulfoxide **2c** reacted with **3i** and **3j** in high yields (71% and 76%, respectively; entries 10 and 12).

With these *S*-(bromodifluoromethyl)diarylsulfonium salts **1** in hand, the electrophilic bromodifluoromethylation of acetylides was examined. Optimization of the reaction was first conducted using *p*-methoxyphenylacetylene (**4a**) as a model substrate, and sulfonium salts (tetrafluoroborates or triflates), **1a**, **1a′**, **1h**, **1i** and **1i′** were taken as examples, resulting in the protocol summarized in Table 2, which shows that sulfonium salt **1i′** had the highest reactivity and gave the desired product **5a** in isolated yield of 72% under the optimized reaction conditions (entry 5). The reason of the better reactivity of triflate **1i′** than tetrafluoroborate **1i** for the transformation of **4a** to **5a** is not clear. The similar counteranion effect is also observed for the monofluoromethylation reagent.[6b] It might be the difference of solubility of **1i** and **1i′** (**1i′** is a bit more soluble in organic solvent than **1i**), although it is not certain. Subsequently, with the best reaction conditions, we screened the scope of acetylenes with **1i′** as a bromodifuoromethylating reagent. The results are summarized in Table 3. All the arylalkynes **4** proceeded with good yields. Heteroaryl alkyne **4j** also is tolerated with a

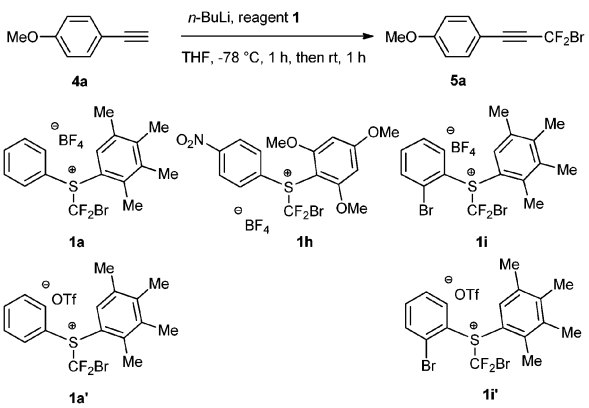
Table 1 Synthesis of unsymmetrical *S*-(bromodifluoromethyl) -diarylsulfonium salts[a]



Entry	2	Ar^1	Ar^2H **3**	*t*/h	1	Yield[b]
1	**2a**	Ph	1,2,3,4-Me_4Ph **3a**	12	**1a**	62
2[c]	**2a**	Ph	1,2,3,4-Me_4Ph **3a**	12	**1a′**	66
3[d]	**2a**	Ph	MeO-Ph **3b**	10	**1b**	89
4[e]	**2a**	Ph	F-Ph **3c**	48	**1c**	81
5	**2a**	Ph	1,4-Br_2Ph **3d**	48	**1d**	NR
6	**2a**	Ph	1,4-$(NO_2)_2$Ph **3e**	48	**1e**	NR
7	**2a**	Ph	1,3,5-Me_3Ph **3f**	10	**1f**	72
8	**2a**	Ph	1,3,5-$(MeO)_3$Ph **3g**	12	**1g**	89
9[f]	**2b**	*p*-NO_2Ph	1,3,5-$(MeO)_3$Ph **3h**	12	**1h**	49
10	**2c**	*o*-BrPh	1,2,3,4-Me_4Ph **3i**	17	**1i**	68
11[c]	**2c**	*o*-BrPh	1,2,3,4-Me_4Ph **3i**	17	**1i′**	71
12[c]	**2c**	*o*-BrPh	1,3,5-$(MeO)_3$Ph **3j**	3	**1j**	76

[a] The reaction of **2** with **3** (1.5 equiv.) was carried out in the presence of Tf_2O (1.5 equiv.) in CH_2Cl_2 at 0 °C to room temperature. For detailed reaction conditions, see the ESI. [b] Isolated yield. [c] TfO salt. [d] The product is a mixture of *o*-methoxy and *p*-methoxy derivatives which cannot be separated. [e] Fluorobenzene was used as the solvent. [f] 5.0 equiv. Tf_2O was used.

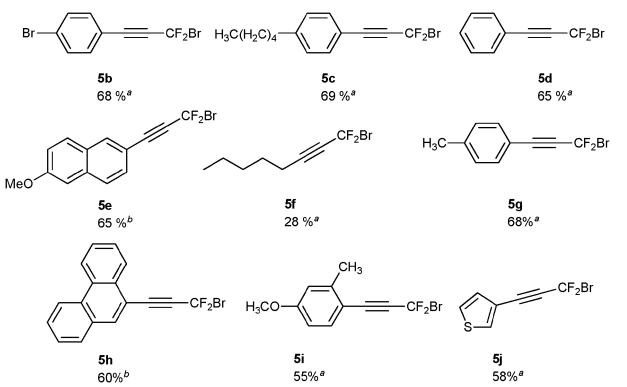
Table 2 Optimization of bromodifluoromethylating reaction[a]



Entry	**1** (equiv.)	*n*-BuLi (eq.)	Yield[b]
1	**1a** (1.3)	1.2	66
2	**1a′** (1.3)	1.2	57[c]
3	**1b** (1.3)	1.2	37
4	**1i** (1.3)	1.2	46[c]
5	**1i′** (1.3)	1.2	72
6	**1i′** (1.0)	1.0	21
7	**1i′** (1.0)	1.2	39

[a] Lithium acetylides were first generated in the reaction of **4** with *n*-BuLi at −78 °C. Then the bromodifluoromethylating agent **1** was added and the reaction system was stirred for 1 h at −78 °C, and then warmed to room temperature. For detailed reaction conditions, see the ESI. [b] Isolated yield. [c] Determined by ^{19}F NMR using trifluorotoluene as the internal standard.

Table 3 Scope of alkynes



[a] Determined by ^{19}F NMR using trifluorotoluene as the internal standard. [b] Isolated yield.

moderate yield (58%), but aliphatic alkyne, hept-1-yne (**4f**) gave the desired product **5f** in low yield (28%).

The bromodifluoromethyl compound **5e** was successfully transformed into *gem*-difluoromethylene ether **6** by the reaction with sodium *p*-nitrophenolate in DMF at room temperature. **5e** also reacted nicely with phenethyl aldehyde under the conditions using Zn and $HgCl_2$ in THF to provide α-difluoromethylene alcohol derivative **7** in 63% (Scheme 2).

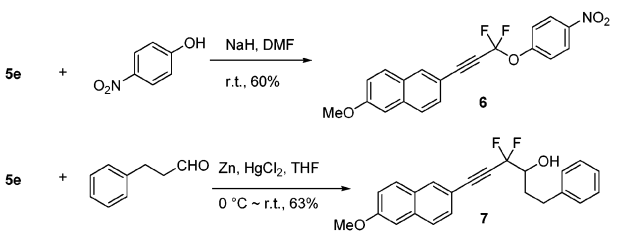
Conclusions

In summary, a series of unsymmetrical *S*-(bromodifluoromethyl)-diarylsulfonium salts were conveniently synthesized in moderate to good yields by treatment of corresponding bromodifluoromethyl arylsulfoxides and a variety of substituted benzenes with triflic anhydride. These sulfonium salts proved to be effective for the electrophilic bromodifluoromethylation reaction of lithium acetylides. The resulting bromodifluoromethyl compounds were successfully used for synthesis of *gem*-difluoromethylene-containing compounds. Study of the utility of the *S*-(bromodifluoromethyl)diarylsulfonium salts for other bromodifluoromethylation reactions is currently in progress in our laboratory.

Experimental section

General

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in oven-dried glassware under a positive pressure of nitrogen. Reaction mixtures were stirred magnetically. Solvents were transferred *via* syringe and were introduced into the reaction vessels though a rubber septum. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or $KMnO_4$ in water/heat. Column chromatography was carried out on a column packed with silica-gel 60 N spherical neutral size 63–210 μm. The ^1H-NMR (300 MHz) and ^{19}F-NMR (282.3 MHz) spectra was recorded on a Varian Mercury 300. The ^{13}C-NMR (150.9 MHz) was recorded on a Bruker Avance 600. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz. All the melting points are uncorrected. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A. Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer.



Scheme 2 Synthesis of *gem*-difluoromethylene-containing compounds **6** and **7**.

General procedure for the preparation of (bromodifluoromethyl)arylsulfoxide 2. Method A

To a solution of aryl bromodifluoromethylsulfide in dichloromethane, *m*-CPBA (1.0 equiv.) was added in four portions over a period of four hours at 0 °C, and the mixture was stirred overnight at room temperature. The resulting solution was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted twice again with dichloromethane. The combined extracts were washed with water and brine, and dried over anhydrous Na_2SO_4. After the drying agent was filtered off and the solvent was removed in vacuum, the residue was directly subjected to the silica-gel column chromatography using appropriate eluent to afford the title compound **2**.

(Bromodifluoromethyl)phenylsulfoxide 2a. Colorless liquid, 89% yield, eluent: hexane/dichloromethane = 4 : 1. The characterization data was consistent with the previous report.[13]

(Bromodifluoromethyl)(*o*-bromophenyl)sulfoxide 2c. White solid, 96% yield, eluent: hexane/dichloromethane = 4 : 1. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.0 (d, J = 9.0 Hz, 1H), 7.49–7.67 (m, 3H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −50.2 (dd, J = 587.2 Hz, 152.4 Hz, 2F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 122.4, 128.5, 129.0, 130.3(dd, J = 683.2 Hz, 663.4 Hz), 133.7, 134.9, 137.9 (d, J = 5.6 Hz); IR (KBr) 2924, 1561,1449, 1428, 1064, 1023, 836, 753 cm^{-1}; mp = 51–53 °C; HRMS (ESI) calcd. for $[C_7H_4F_3OF_2SBr_2Na]^+$: 354.8215, found: 354.8217.

Preparation of (bromodifluoromethyl)(*p*-nitrophenyl)sulfoxide (2b). Method B

To a solution of *p*-nitrophenyl bromodifluoromethyl sulfide (2.13 g, 7.5 mmol) in dichloromethane, *m*-CPBA (0.62 g, 0.25 equiv.) was added at 0 °C. The mixture was stirred for 2 h at room temperature. The same procedure above was repeated three times (3 × 0.25 equiv.). The resulting solution was quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted twice again with dichloromethane. The combined extracts were washed with water and brine, and dried over anhydrous Na_2SO_4. After the drying agent was filtered off and the solvent was removed in vacuum,

the residue was directly subjected to the silica-gel column chromatography (hexane/dichloromethane = 2 : 1) to afford **2b** (1.3 g, 58%) as light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (dd, J = 6.6 Hz, 1.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −51.9 (dd, J = 677.5 Hz, 169.4 Hz, 2F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 124.4, 127.7, 127.8 (d, J = 362.2 Hz), 143.9 (d, J = 3.0 Hz), 151.0; IR (KBr) 3110, 2853, 1603, 1524, 1366, 1343, 1316, 1149,1112, 1089, 829, 723, 548, 507, 417 cm^{-1}; mp = 106–108 °C; HRMS (EI) calcd. for $[C_7H_4NO_3F_2SBr]^+$: 298.9063, found : 298.9072

Preparation of *S*-(bromodifluoromethyl)diarylsulfonium salts 1

To a solution of sulfoxide **2** (0.25 mmol, 1 equiv.) and substituted benzene **3** (0.375 mmol, 1.5 equiv.) in 1 mL dry dichloromethane (fluorobenzene was used as solvent for entry 4 in Table 1) was added dropwise Tf_2O (1.5 equiv., 5.0 equiv. was used for entry 9 in Table 1) at 0 °C under nitrogen atmosphere. After the resulting reaction was performed for a appropriate time at 0 °C to room temperature, the solvent and excess Tf_2O were evaporated off under vacuum and the residue was directly subjected to silica-gel column chromatography (dichloromethane/CH_3CN = 4 : 1) to afford corresponding *S*-(bromodifluoromethyl)diarylsulfonium triflate. The triflate salt was dissolved in 10 mL dichloromethane, and extracted with $NaBF_4$ solution (1 M, 4 × 5 mL). After drying (using anhydrous Na_2SO_4) and evaporation, the residue was dried under vacuum to give corresponding tetrafluoroborate salts **1**.

***S*-Bromodifluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenyl-sulfonium tetrafluoroborate (1a).** White solid, 62% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, J = 8.1 Hz, 2H), 7.83–7.91 (m, 3H), 7.45 (s, 1H), 2.75 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −35.0 (dd, J = 366.7 Hz, 125.9 Hz, 2F), −152.6 (s 1F), −152.7 (s, 3F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 17.5, 17.7, 19.0, 21.7, 114.9, 117.2 (t, J = 356.1 Hz), 120.0, 128.9, 132.6, 133.3, 137.0, 139.3, 140.8, 141.3, 147.0; IR (KBr) 3430, 3082, 2930, 1451, 1272, 1255, 1217, 1063, 823, 757, 686, 523 cm^{-1}; mp = 170–172 °C; MS (ESI, m/z): 370.7500 $[C_{17}H_{18}F_2SBr]^+$; HRMS calcd. for $[C_{17}H_{18}F_2SBr]^+$: 371.0281, found: 371.0283.

***S*-Bromodifluoromethyl-*S*-*p*-nitrophenyl-2,4,6-trimethoxy-phenylsulfonium tetrafluoroborate (1h).** Brown solids, 49% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 9.0 Hz, 2H), 6.44 (s, 1H), 4.05 (s, 3H), 4.00 (s, 6H),; ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −26.4 (dd, J = 429.9 Hz, 107.8 Hz, 2F), −153.0 (s 1F), −153.1 (s, 3F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 58.1, 58.4, 81.7, 94.5, 118.4, 117.2 (dd, J = 366.7 Hz, 356.1 Hz), 126.7, 128.5, 132.9, 152.4, 165.2, 173.2; IR (KBr) 3110, 1600, 1532, 1422, 1345, 1240, 1086, 1059, 1029, 818, 490 cm^{-1}; mp = 170–172 °C; MS (ESI, m/z) : 449.5000 $[C_{16}H_{15}NO_5F_2SBr]^+$; HRMS calcd. for $[C_{16}H_{15}NO_5F_2SBr]^+$: 449.9822, found: 449.9825.

***S*-Bromodifluoromethyl-*S*-*o*-bromophenyl-2,3,4,5-tetramethyl-phenylsulfonium triflate (1i′).** White solids, 71% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (d, J = 8.1 Hz, 1H), 8.07 (t, J = 8.1 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.40 (s, 1H), 2.78 (s, 3H), 2.38 (s, 6H),2.33 (s, 3H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −33.9 (dd, J = 140.6 Hz, 124.8 Hz, 2F), -78.6 (t, J = 20.9 Hz, 3F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 17.2, 17.4, 18.4, 21.1, 114.1, 115.9 (t, J = 357.6 Hz), 121.7, 122.0 (t, J = 319.9 Hz), 126.0, 129.1, 133.3, 136.0, 138.0, 140.1, 140.3, 140.4,147.6; IR (KBr) 3067, 2978, 1450, 1248, 1168, 1097, 1026, 810, 635 cm^{-1}; mp = 143–147 °C; MS (ESI, m/z) : 449.2500 $[C_{17}H_{17}F_2SBr_2]^+$; HRMS calcd. for $[C_{17}H_{17}F_2SBr_2]^+$: 448.9386, found : 448.9390.

Bromodifluoromethylation of alkynes using *S*-bromodifluoromethyl-*S*-*o*-bromophenyl-2,3,4,5-tetramethylphenylsulfonium triflate 1i′

n-BuLi (2.6M in THF, 1.3 equiv.) was added dropwise to a solution of alkyne (0.1 mmol) in 1 mL anhydrous THF at −78 °C under nitrogen atmosphere, the resulting mixture was maintained for 30 min at the same temperature. Then **1i′** was added in one portion at −78 °C, and the reaction mixture was performed for 1 h at the same temperature , followed warming to room temperature for additional 1 h. The reaction mixture (1 equiv. trifluorotoluene was added to reaction mixture as internal standard to determine the yield of desired product) was quenched with aqueous NH_4Cl and extracted 3 times with hexane. The combined extracts were washed with water and brine, and then dried over anhydrous Na_2SO_4. After filtering off the drying agent, the solvent was evaporated off carefully in vacuum, and the residue was subjected to flash silica-gel column chromatography using hexane as eluent to afford corresponding title product **5**.

5a–5b, 5d–5g, 5i. The characterization data was consistent with the previous report.[9–12]

1-(3-Bromo-3,3-difluoroprop-1-ynyl)-4-pentylbenzene (5c). Colorless liquid, 69% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 2.63 (t, J = 7.2 Hz, 2H), 1.56–1.66 (m, 2H), 1.25–1.37 (m, 4H), 0.89 (t, J = 6.9 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −31.3 (s, 2F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 14.1, 22.6, 30.9, 31.5, 36.1, 80.7 (t, J = 38.0 Hz), 90.6, 102.3, 116.0, 128.9, 132.3, 146.6; IR (NaCl) 2930, 2251, 2221, 1511, 1298, 1136, 1090, 939, 817 cm^{-1}; HRMS (EI) calcd. for $[C_{14}H_{15}F_2Br]^+$: 300.0325, found: 300.0317.

9-(3-Bromo-3,3-difluoroprop-1-ynyl)phenanthrene (5h). Off-white solid, 60% isolated yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66–8.72 (m, 2H), 8.26–8.29 (m, 1H), 8.14 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.72–7.77 (m, 3H), 7.64 (t, J = 7.5 Hz, 1H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −31.6 (s, 2F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 85.0 (t, J = 37.7 Hz), 89.1 (t, J = 6.0 Hz), 102.3 (t, J = 289.7 Hz), 115.4, 123.0, 123.2, 126.4, 127.5, 127.8, 127.9, 129.1, 129.3, 130.2, 130.4 130.6 131.4, 134.8 (t, J = 1.5 Hz); IR (KBr) 2924, 2226, 1451, 1322, 1241, 1181, 1090, 1036, 910, 862, 765, 750 cm^{-1}; mp = 83–85 °C; HRMS (EI) calcd. for $[C_{17}H_9BrF_2]^+$: 329.9856, found: 329.9887.

Synthesis of 2-[3,3-difluoro-3-(4-nitrophenoxy)prop-1-ynyl]-6-methoxynaphthalene (6)

To a suspension of sodium hydride (60% suspension in oil, 16 mg, 4 equiv.) in 0.5 mL dry DMF was added *p*-nitrophenol

(55.6 mg, 4 equiv.) at room temperature under nitrogen atmosphere, and the resulting mixture was stirred for 1 h at room temperature. A solution of **5e** (31 mg, 1 equiv.) in 0.5 mL dry DMF was added dropwise at room temperature. After stirring for 36 h at room temperature, the reaction mixture was poured into 20 ml water and extracted 3 times (3 × 10 mL) with ethyl acetate. The combined extracts were washed with water and brine, and then dried over anhydrous Na_2SO_4. After filtering off the drying agent, the solvent was evaporated off in vacuum and the crude was purified on silica-gel chromatography (flash, hexane/ethyl acetate = 8 : 1) to afford desired product **6** as white solid (22 mg, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26–8.31 (m, 2H), 7.94 (s, 1H), 7.68–7.72 (m, 2H), 7.38–7.45 (m, 3H), 7.17–7.21 (m, 1H), 7.11 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −51.3 (s, 2F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 55.6, 88.4 (t, J = 6.0 Hz), 106.0, 113.4, 114.5 (t, J = 247.5 Hz), 120.3, 121.4, 125.6, 127.4, 128.2, 128.4, 129.8, 133.4, 135.6, 145.3, 155.5, 159.5; IR (KBr) 3077, 2237, 1625, 1522, 1348, 1308, 1265, 1205, 1146, 1116, 1046, 853 cm^{-1}; mp = 112–114 °C; HRMS (ESI) calcd. for $[C_{20}H_{13}F_2NO_4S + Na]^+$: 392.0710, found: 392.0716.

Synthesis of 4,4-difluoro-6-(6-methoxynaphthalen-2-yl)-1-phenylhex-5-yn-3-ol (7)

A solution of **5e** (31 mg, 1 equiv.) in 0.3 mL dry THF was added to a mixture of $HgCl_2$ (8 mg, 0.3 equiv.), Zn powder (20 mg, 3 equiv.) and 3-phenylpropionaldehyde (22 mg, 1.5 equiv., 90%) in 0.3 mL dry THF at 0 °C under nitrogen atmosphere, then allowed to warm to room temperature. After vigorously stirring for 24 h at room temperature, all the **5e** was consumed. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and extracted with ethyl acetate (3 × 10 mL). the combined extracts were washed with water and brine, then dried over anhydrous Na_2SO_4, filtered and evaporated off the solvent, the residue was subjected to flash silica-gel chromatography (hexane/ethyl acetate = 8 : 1) to afford the desired product **7** as light yellow solid (23 mg, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (s, 1H), 7.68–7.72 (m, 2H), 7.46 (d, J = 8.7 Hz, 1H), 7.16–7.33 (m, 7H), 7.11 (s, 1H), 3.92 (s, 3H), 2.94–3.04 (m, 1H), 2.74–2.87 (m, 1H), 2.30 (s, 1H), 1.95–2.21 (m, 2H); ^{19}F NMR ($CDCl_3$, 282.3 MHz) δ −95.1 (ddd, J = 282.3 Hz, 260.3 Hz, 7.9 Hz, 2F); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 31.5, 32.1, 55.6, 73.6 (t, J = 30.2 Hz), 79.1 (t, J = 39.2 Hz), 89.8 (t, J = 6.0 Hz), 106.0, 114.7, 115.3 (t, J = 236.9 Hz), 120.1, 126.3, 127.2, 128.3, 128.7 (d, J = 4.5 Hz), 129.7, 133.0, 135.2, 141.2, 159.2; IR (KBr) 3427, 2927, 2239, 1627, 1604, 1499, 1390, 1262, 1162, 1073, 1032, 855, 701 cm^{-1}; mp = 78–81 °C; HRMS (ESI) calcd. for $[C_{23}H_{20}F_2O_2 + Na]^+$: 389.1329, found: 389.1324.

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Notes and references

1 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, 2004; (*b*) A. M. Rhayer, *Chem. Eng. News*, 2006, **84**, 15; (*c*) N. Divid A. and M. Divid W. C., *Nature*, 2011, **480**, 224; (*d*) Y. Huang, S. Wolf, D. Koes, G. M. Popowicz, C. J. Camacho, T. A. Holak and A. Dömling, *ChemMedChem*, 2012, **7**, 49; (*e*) K. L. Kirk, *J. Fluorine Chem.*, 2008, **127**, 1013; (*f*) C. Isanbora and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303.
2 (*a*) A. Togni, *Adv. Synth. Catal.*, 2010, **352**, 2689; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
3 T. Umemoto, *Chem. Rev.*, 1996, **96**, 1757.
4 (*a*) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156; (*b*) J. J. Yang, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1998, **63**, 2656; (*c*) P. Eisenberger, S. Gischig and A. Togni, *Chem.–Eur. J.*, 2006, **12**, 2579; (*d*) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.*, 2007, **46**, 754; (*e*) K. Stanek, R. Koller and A. Togni, *J. Org. Chem.*, 2008, **73**, 7678; (*f*) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann and A. Togni, *Angew. Chem., Int. Ed.*, 2009, **48**, 4332; (*g*) S. Noritake, N. Shibata, S. Nakamura, T. Toru and M. Shiro, *Eur. J. Org. Chem.*, 2008, 3465; (*h*) A. Matsnev, S. Noritake, Y. Nomura, E. Tokunaga, S. Nakamura and N. Shibata, *Angew. Chem., Int. Ed.*, 2010, **49**, 572; (*i*) E. Magnier, J.-C. Blazejewski, M. Tordeux and C. Wakselman, *Angew. Chem., Int. Ed.*, 2006, **45**, 1279; (*j*) Y. Macé, B. Raymondeau, C. Pradet, J.-C. Blazejewski and E. Magnier, *Eur. J. Org. Chem.*, 2009, 1390; (*k*) L. M. Yagupolskii, A. V. Matsnev, R. K. Orlova, B. G. Deryabkin and Y. L. Yagupolskii, *J. Fluorine Chem.*, 2008, **129**, 131; (*l*) J.-J. Yang, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1998, **63**, 2656.
5 (*a*) G. K. S. Prakash, C. Weber, S. Chacko and G. A. Olah, *Org. Lett.*, 2007, **9**, 1863; (*b*) W. Zhang, F. Wang and J. Hu, *Org. Lett.*, 2009, **11**, 2109; (*c*) W. Zhang, W. Huang and J. Hu, *Angew. Chem., Int. Ed.*, 2009, **48**, 9858.
6 (*a*) G. K. S. Prakash, I. Ledneczki, S. Chacko and G. A. Olah, *Org. Lett.*, 2008, **10**, 557; (*b*) Y. Nomura, E. Tokunaga and N. Shibata, *Angew. Chem., Int. Ed.*, 2011, **50**, 1885.
7 (*a*) S. Arimitsu and G. B. Hammond, *J. Org. Chem.*, 2006, **71**, 8665; (*b*) S. Fustero, B. Fernández, P. Bello, C. d. Pozo, S. Arimitsu and G. B. Hammond, *Org. Lett.*, 2007, **9**, 4251; (*c*) R. Surmont, G. Verniest and N. D. Kimpe, *Org. Lett.*, 2009, **11**, 2920; (*d*) Y. Hanzawa, K. Inazawa, A. Kon, H. Aoki and Y. Kobayashi, *Tetrahedron Lett.*, 1987, **28**, 659; (*e*) G. B. Hammond, *J. Fluorine Chem.*, 2006, **127**, 476; (*f*) J. Hao, L. Sun, W. Wan, H. Jiang, Faming Zhuanli Shenqing Gongkai Shuomingshu, CN101265232, 2008; (*g*) H. Barry, G. Michael, S. Eduardo, R. Michael*PCT Int. Appl.*, WO2010056877, 2010; (*h*) B. Xu and G. B. Hammond, *Angew. Chem., Int. Ed.*, 2005, **44**, 7404; (*i*) G. K. S. Prakash, Y. Wang, J. Hu and G. A. Olah, *J. Fluorine Chem.*, 2006, **126**, 1361.
8 (*a*) C. Zhang, Q. Chen, J. Xiao and Y. Gu, *J. Fluorine Chem.*, 2009, **130**, 671; (*b*) J. L. Howell, B. J. Muzzi, N. L. Rider, E. M. Aly and M. K. Abouelmagd, *J. Fluorine Chem.*, 1995, **72**, 61; (*c*) D. V. Avila, K. U. Ingold, J. Lusztyk, W. R. Dolbier, Jr., H. Pan and M. Muir, *J. Am. Chem. Soc.*, 1994, **116**, 99.
9 C. Zhang, H. Cao, Z. Wang, C. Zhang, Q. Chen and J. Xiao, *Synlett*, 2010, **7**, 1089.
10 (*a*) C. Urban, Y. Macé, F. Cadoret, J. C. Blazejewski and E. Magnier, *Adv. Synth. Catal.*, 2010, **352**, 2805; (*b*) C. Urban, F. Cadoret, J. C. Blazejewski and E. Magnier, *Eur. J. Org. Chem.*, 2011, 4862.
11 S. Fustero, B. Fernández, P. Belle, C. del Pozo, S. Arimitsu and G. B. Hammond, *Org. Lett.*, 2007, **9**, 4251.
12 G. B. Hammond, *J. Fluorine Chem.*, 2006, **127**, 476.
13 C. Zhang, Z. Wang, Q. Chen, C. Zhang and J. Xiao, *J. Fluorine Chem.*, 2010, **131**, 433.