Cite this paper: Hu, J.; Yang, Y.; Lou, Z.; Ni, C.; Hu, J. *Chin. J. Chem.* **2018**, *36*, 1202—1208.

Concise Report

DOI: 10.1002/cjoc.201800426

Fluoro-Hydroxylation of *gem*-Difluoroalkenes: Synthesis of ^{18}O-labeled α-CF_3 Alcohols†

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ABSTRACT In this paper, a fluoro-hydroxylation of *gem*-difluoroalkenes is demonstrated. This protocol uses sequential electrophilic fluorination with Selectfluor and nucleophilic hydroxylation with $H_2{}^{18}O$, which can be used to prepare ^{18}O-labeled α-CF_3 alcohols from *gem*-difluorostyrenes. The reaction is typically carried out at room temperature within 4 h in good to excellent yields. Other nucleophiles (besides $H_2{}^{18}O$), such as alcohols, carboxylic acid, acetonitrile and *N,N*-dimethylformamide, are also suitable for this difunctionalization of *gem*-difluoroalkenes.

KEYWORDS *gem*-difluoroalkene, difunctionalization, electrophilic fluorination, ^{18}O-labeling, trifluoromethyl carbinol

Introduction

Recent years have witnessed the flourishing organofluorine chemistry, and fluoroorganics are widely applied in the fields of pharmaceuticals, agrochemicals and advanced materials.[1] In this context, *gem*-difluoroalkenes have attracted much attention in organic synthesis,[2-7] given the fact that the double bond of a *gem*-difluoroalkene is highly polarized and the electrophilic difluoromethylene carbon atom can be easily attacked by nucleophiles.[1a,8]

Considering the significant applications of trifluoromethyl (CF_3) group,[9] fluorination of *gem*-difluoroalkenes with additional nucleophilic fluoride sources has been proved to be an effective pathway to supplement the typical trifluoromethylation reactions.[10] In 1997, Burton and co-workers reported the nucleophilic fluorination of *gem*-difluoroalkenes using wet KF.[10a] The newly generated α-trifluorocarbanion in this reaction was unstable and spontaneously quenched by proton abstraction.[10a-10c] This protocol was further developed by Riss and co-workers to prepare the [^{18}F]CF_3-containing compounds for PET imaging in 2011.[10d] Our group discovered a AgF-mediated fluorinative homocoupling of *gem*-difluoroalkenes and cross-coupling of two olefins in 2014 and 2015, respectively, taking advantage of the rapid homolysis of the C—Ag^{I} bond to produce the α-CF_3 benzyl radical intermediate.[10e-10f] Loh and co-workers further expanded this strategy and succeeded in the palladium-catalyzed fluorinative allylation and arylation reactions in 2016 and 2017, respectively.[10g-10h]

In contrast to the prosperous progress of the nucleophilic fluorination of *gem*-difluoroalkenes, the electrophilic fluorination of *gem*-difluoroalkenes is much less studied.[11,12] Because of the electron-deficient nature of the *gem*-difluoroalkenes, their reactions with electrophiles normally proceed in the presence of strong Brønsted acids[11] or Lewis acids,[12] and the undesired defluorination reaction is inevitable. During the preparation of this manuscript, Wang and co-workers reported the aminofluorination of *gem*-difluoroalkenes with the F^+ source. They used CH_3CN as nucleophile to accomplish the Ritter-type amination reactions, with moderate to good yields of products being obtained.[13] As our continuing effort in the functionalization of *gem*-difluoroalkenes, we have carried out the 1,2-difunctionalization of *gem*-difluoroalkenes *via* electrophilic fluorination with Selectfluor followed by nucleophilic quenching with various *O*- and *N*-nucleophiles. By using this protocol, we were able to synthesize a series of ^{18}O-labled α-CF_3 alcohols in excellent yields and with high efficiency of ^{18}O-isotope incorporation.[14]

Results and Discussion

Our research was inspired by the strong oxidation ability that Selectfluor showed in the reactions with styrenes.[15] The mechanism of this reaction was believed to involve a single electron transfer (SET) process.[16] However, challenges still exist for Selectfluor-mediated electrophilic fluorination of *gem*-difluoroalkenes, which are more electron-deficient than their non-fluorinated analogous. Whether the SET-fluorination process between *gem*-difluoroalkenes and Selectfluor (producing α-CF_3 carbocation intermediate) could occur smoothly or not, remains a question. Therefore, we began our study using tetrasubstituted alkene **1a** as a model substrate. On one hand, the alkyl substituent of **1a** makes the double bond of *gem*-difluoroalkenes less electron-deficient; on the other hand, the carbocation intermediate could be further stabilized by the alkyl substituent. We chose acetonitrile and H_2O as co-solvent (9 : 1), and found that the corresponding α-CF_3 alcohol product was obtained in 96% ^{19}F NMR yield. Realizing that the α-CF_3 alcohol products are generally synthesized *via* the nucleophilic addition reactions to carbonyl compounds (Scheme 1),[17,18] we envisioned that our electrophilic fluorination protocol may have its own synthetic merit that the traditional nucleophilic reactions cannot achieve.[19] In 2017, deutetrabenazine (Austedo), as the first deuterated drug to reach the market,[20] encouraged the research work on stable isotope-labeled compounds.[21] However, we found there was no report on the preparation of ^{18}O-labeled α-CF_3 alcohols, and the characteristics of these compounds were undefined either. Hence, the development of a convenient protocol to synthesize the ^{18}O-labeled α-CF_3 alcohols with high ^{18}O-labled ratio would be highly useful to understand and apply these compounds (Scheme 1).

Considering the relatively high price of $H_2{}^{18}O$, we used initially H_2O to screen the reaction conditions (Table 1). Besides Selectfluor, other F^+ reagents such as NFSI and 1-fluoro-2,4,6-trimethylpridinium triflate were also surveyed, but the latter two failed to give any desired products (entries 11—12, Table 1). We also found that the yield of **2a** increased along with the increase of the amount of H_2O in the reaction system (Table 1). Finally, we chose the optimized reaction conditions as follows: **1a** (1.0 equiv.), H_2O (8.0 equiv.), and Selectfluor (1.3 equiv.) were reacted in CH_3CN under room temperature for 4 h (entry 7, Table 1). The replacement of H_2O by $H_2{}^{18}O$ made no difference in the yield, and product **2a** was obtained in 91% isolated yield while reagent **1a** was fully consumed (entry 10, Table 1).

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† Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

Scheme 1 Methods to prepare ^{18}O-labeled α-CF_3 alcohols

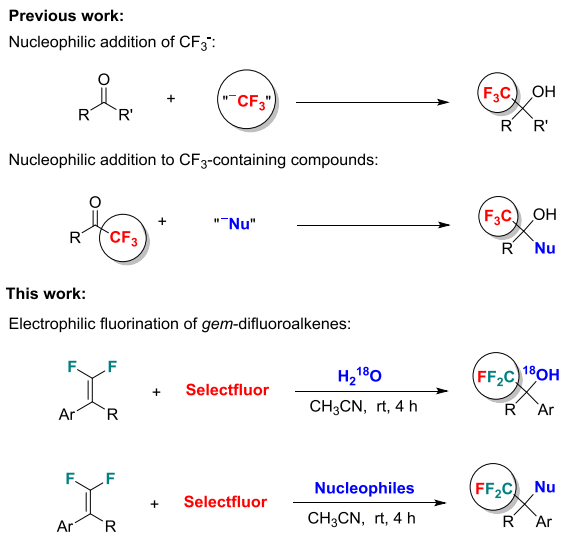
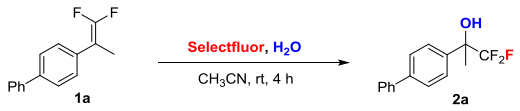


Table 1 Screening of reaction conditions

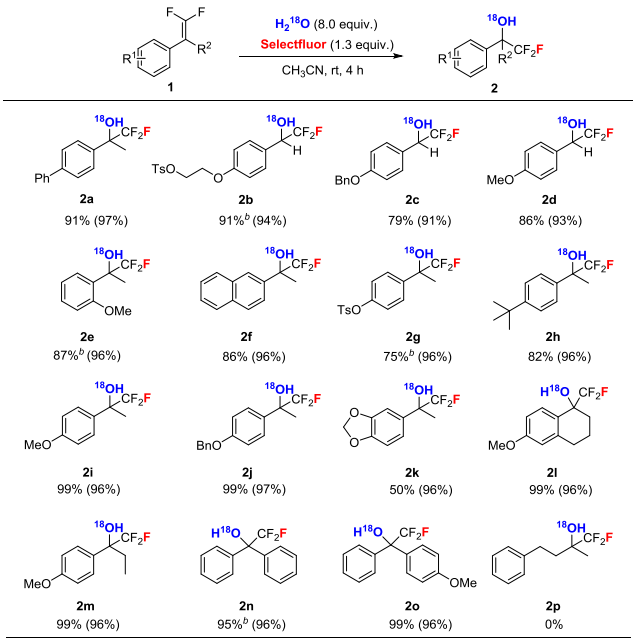


Entry	Selectfluor (*x* equiv.)	H_2O (*y* equiv.)	CH_3CN/mL	Conversion/%	Yield[a]/%
1	1.5	27.8 (0.2 mL)	2.0	100	96
2	1.5	2.0	2.0	92	76
3	1.5	5.0	2.0	97	88
4	1.5	8.0	2.0	100	92
5	1.5	10.0	2.0	100	93
6	1.5	8.0	1.5	100	92
7	**1.3**	**8.0**	**1.5**	**100**	**92**
8[b]	1.2	8.0	1.5	98	91
9[b]	1.1	8.0	1.5	97	90
10[c]	1.3	8.0	1.5	100	92 (91)
11[d]	1.5	8.0	1.5	2	—
12[e]	1.5	8.0	1.5	4	—

[a] **1a** (0.4 mmol, 1.0 equiv.), yield was determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] 8 h. [c] $^{18}H_2O$ instead of H_2O, isolated yield in parathesis. [d] NFSI instead of Selectfluor. [e] 1-Fluoro-2,4,6-trimethylpridium triflate instead of Selectfluor.

With the optimized conditions in hand, we examined the scope of this electrophilic fluoro-hydroxylation reaction. As shown in Scheme 2, both tri-substituted (**1b—1d**) and tetra-substituted (**1a**, **1e—1o**) *gem*-difluorostyrenes gave corresponding products in good to excellent yields. Tri-substituted *gem*-difluorostyrenes bearing electro-donating group generally gave good yields (**1b—1d**), and electron-neutral tetra-substituted *gem*-difluorostyrenes gave excellent yields of products (**1a**, **1f** and **1n**). Tetra-substituted *gem*-difluorostyrenes bearing weak electron-withdrawing group (**1g**), weak electron-donating group (**1h**) or strong electron-donating groups (**1e**, **1i—1j**, **1m—1l**, **1o**) were all amenable to this fluoro-hydroxylation protocol. However, if the aryl group of the *gem*-difluorostyrene is too electron-rich, lower yield of the desired product was obtained, probably due to incompatibility between the substrate and the strong oxidative reaction system (**1k**). The steric hindrance of *gem*-difluorostyrenes had little influence on the efficiency (**1l—1m**). The diaryl *gem*-difluorostyrenes were ideal substrates for this reaction (**1n—1o**), because the carbocation intermediate could be stabilized by two aromatic rings and the generation of minor trifluoromethylated alkene byproducts from β-H elimination was blocked. For some less reactive substrates, which gave low conversions under room temperature, increasing the reaction temperature to 40 °C could increase the conversions as well as the yields (**1b**, **1e**, **1g** and **1n**). However, the reactions of electron-neutral tri-substituted *gem*-difluorostyrenes (such as 4-(2,2-difluorovinyl)-1,1'-biphenyl) and tetra-substituted *gem*-difluorostyrenes bearing electron-withdrawing groups (such as 1-bromo-4-(1,1-difluoroprop-1-en-2-yl)-benzene) afforded complex mixtures. As expected, *gem*-difluoroalkene without aryl substituent (**1p**) gave no corresponding α-CF_3 alcohol product at all. The ^{18}O-isotopic purity [$^{18}OH/(^{18}OH+^{16}OH)$] of the isolated α-$CF_3$ alcohols was measured by mass spectroscopic analysis and shown in Scheme 2. It should be noted that the ^{18}O-isotopic purity in the $H_2{}^{18}O$ starting material was 97%, and as a result, the ^{18}O-isotopic purities of the products were similar, ranging from 91% to 97%.

Scheme 2 Variation of the *gem*-difluorostyrenes for the preparations of ^{18}O-labled α-CF_3 alcohols[a]

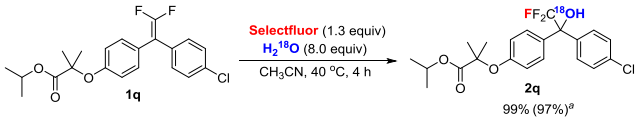


[a] Isolated yield. ^{18}O-isotopic purity is shown in parentheses, which was determined by MS analysis. Reaction conditions (unless otherwise noted): **1** (0.4 mmol), Selectfluor (1.3 equiv.), $H_2{}^{18}O$ (8.0 equiv.), CH_3CN (1.5 mL), rt, 4 h. [b] 40 °C.

To further demonstrate the synthetic application of our fluoro-hydroxylation protocol, we applied this method to the functionalization of difluorovinyl derivative of Fenofibrate, which could be used to treat high cholesterol and high triglyceride levels.[22] We carried out the fluoro-hydroxylation of **1q** under the standard reaction conditions, and the corresponding ^{18}O-labled α-CF_3 alcohol of Fenofibrate (**2q**) was obtained in 99% yield (Scheme 3).

After we accomplished the preparation of a series of ^{18}O-labled α-CF_3 alcohols with $H_2{}^{18}O$ as the nucleophile, we began to investigate the feasibility of other nucleophiles in this difunctionalization of *gem*-difluoroalkenes (Scheme 4). We found that both primary and secondary alcohols were suitable nucleophiles in this fluoro-functionalization reaction (**3a—3e**). The amount of

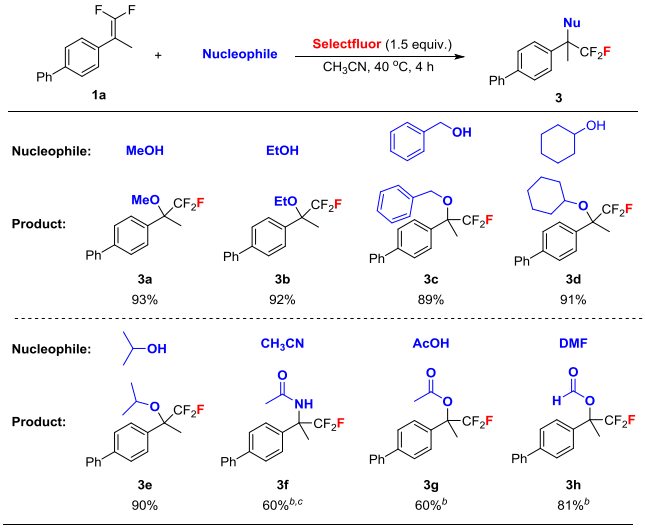
Scheme 3 The preparation of ^{18}O-labled α-CF_3 alcohol derivative of Fenofibrate



[a] Isolated yield. The ^{18}O-isotopic purity is shown in parentheses, which was determined by MS analysis. Reaction conditions: **1q** (0.4 mmol), Selectfluor (1.3 equiv.), $H_2{}^{18}O$ (8.0 equiv.), CH_3CN (1.5 mL), 40 °C, 4 h.

alcohols could be decreased to 5.0 equiv., but heating the reaction system to 40 °C is necessary. When there was no additional nucleophile, the solvent CH_3CN could serve as a nucleophile and the Ritter-type amination reaction occurred (**3f**). Other nucleophiles, such as AcOH and DMF, could also be applied to produce the corresponding α-CF_3 esters (**3g—3h**). In the case of DMF, the formate probably arises from an imidate salt that can undergo hydrolysis during aqueous workup (**3h**).

Scheme 4 Variation of the nucleophiles in the fluoro-functionalization reaction



[a] Isolated yield. Reaction conditions (unless otherwise noted): **1a** (0.4 mmol, 1.0 equiv.), nucleophiles (5.0 equiv.), Selectfluor (1.5 equiv.), CH_3CN (1.5 mL), 40 °C, 4 h. [b] rt. [c] No additional nucleophile was added.

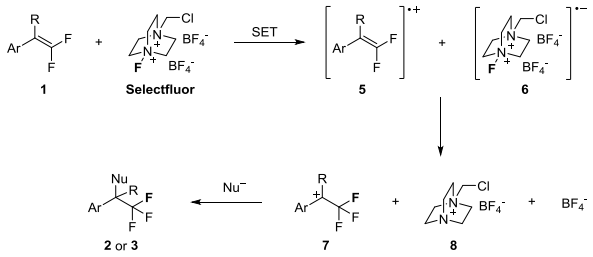
In addition to the preparation of ^{18}O-labeled compounds, this protocol could also be used to synthesize deuterium-labeled trifluoromethyl compounds (Scheme 5). When CD_3OD was used as the nucleophile, the *D*-labeled α-CF_3 ether compound could be obtained in excellent yield. Moreover, the reaction could be scaled up to 4.0 mmol without loss of the efficiency, indicating the high practical applicability of the current synthetic method.

Scheme 5 The preparation of *D*-labeled α-CF_3 derivative

[a] Isolated yield. The deuterated purity is shown in parentheses, which was determined by MS. Reaction conditions: **1a** (4.0 mmol, 1.0 equiv.), CD_3OD (5.0 equiv.), Selectfluor (1.5 equiv.), CH_3CN (15 mL), 40 °C, 4 h.

Finally, a reaction mechanism for the fluoro-functionalization of *gem*-difluoroalkenes is proposed. The reaction mechanism is based on the substrate preference we observed as well as previous reports.[16a,16d] As shown in Scheme 6, an SET process takes place between the *gem*-difluoroalkene **1** and Selectfluor to give the radical cation of *gem*-difluoroalkene (**5**) and the radical anion of Selecfluor (**6**), then the radical cation **5** abstracts a fluorine atom from **6** to give α-trifluoromethyl carbocation **7**. Further trapping of carbocation **7** with the nucleophile affords the desired product **2** or **3**. The electronic nature of the aryl substituent of *gem*-difluorostyrenes could significantly influence the single electron transfer process, the stabilization of the radical cation **5**, as well as the reactivity of α-trifluoromethyl carbocation **7**.

Scheme 6 Proposed mechanism for the fluoro-functionalization of *gem*-difluoroalkenes



Conclusions

In conclusion, we have developed an efficient electrophilic fluorination-driven difunctionalization of *gem*-difluorostyrenes. This protocol provides facile access to ^{18}O-labeled α-CF_3 alcohols in high ^{18}O-labeling efficiency under mild conditions, which are otherwise difficult to prepare. Using Selectfluor as fluorine source and $H_2{}^{18}O$ as a nucleophile, various *gem*-difluorostyrenes could deliver the corresponding desired products in moderate to excellent yields. Besides $H_2{}^{18}O$, other nucleophiles were also investigated. We found that primary and secondary alcohols, CH_3CN, acetic acid and DMF were all suitable nucleophiles in the reaction. This protocol was also successfully used in the preparation of deuterium-labeled α-CF_3 derivatives.

Experimental

General Information. Unless otherwise mentioned, reagents were purchased from commercial sources and used without further purification. CH_3CN (Acetonitrile) was dried from CaH_2 and purified by distillation before being used. The water was used after distillation. All the melting points were uncorrected. ^{1}H NMR spetra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz. ^{19}F NMR spectra were recorded at 376 MHz. ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$(TMS) at δ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to external $CFCl_3$ at δ 0.0. Data for ^{1}H, ^{13}C and ^{19}F NMR are recorded as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, br = broad). Mass spectra were obtained on a mass spectrometer. High resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. All reactions were monitored by TLC, ^{19}F NMR spectroscopy, or GC-MS.

General procedure for the synthesis of ^{18}O-labeled α-CF_3 alcohols 2. Selectfluor (184.1 mg, 0.52 mmol, 1.3 equiv.), and *gem*-difluoroalkene **1** (0.40 mmol, 1.0 equiv.) were added in turn to an oven-dried 10-mL Schlenk tube equipped with a stir bar under an argon atmosphere. The reactants were dissolved in CH_3CN (1.5 mL), followed by the addition of $H_2{}^{18}O$ (64.0 mg, 3.2 mmol, 8.0 equiv.). The reaction mixture was stirred at room tem-

perature or 40 °C for 4 h. The completion of the reaction could be monitored by ^{19}F NMR. The reaction mixture was diluted with ethyl acetate (20.0 mL) and transferred to a flask. The solvent was evaporated under vacuum. The residue was subjected to silica gel column chromatography (petroleum ether: ethyl acetate = 30 : 1) to give product **2**.

2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoropropan-2-ol-^{18}O (2a). Performed with 4-(1,1-difluoroprop-1-en-2-yl)-1,1'-biphenyl (**1a**) at room temperature; 97.6 mg, 91% yield, 97% ^{18}O-isotopic purity. White solid. Mp.: 79—80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72—7.60 (m, 6H), 7.54—7.45 (m, 2H), 7.43—7.37 (m, 1H), 2.53 (s, 1H), 1.84 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.89 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.5, 140.4, 137.3, 128.8, 127.6, 127.2, 127.0, 126.5, 125.6 (q, J = 286.5 Hz), 74.8 (q, J = 29.3 Hz), 23.9. MS (EI, *m*/*z*, %): 268 (M^+, 54.12), 199 (100), 45 (10.82). HRMS (EI): calcd. for $C_{15}H_{13}{}^{18}OF_3$: 268.0961 (M); found: 268.0956. IR (film) *v*: 3363.0, 1489.5, 1487.6, 1408.3, 1375.7, 1287.0, 1218.0, 1179.2, 1165.6, 1109.0, 1080.9, 1068.3, 1006.9, 924.4, 841.1, 829.9, 768.0, 734.1, 714.6, 696.9, 638.0, 610.0 cm^{-1}.

2-(4-(2,2,2-Trifluoro-1-(hydroxy)ethyl)phenoxy-^{18}O)ethyl 4-methylbenzene sulfonate (2b). Performed with **1b** at 40 °C; 142.7 mg, 91% yield, 94% ^{18}O-isotopic purity. White solid. Mp.: 69—71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, J = 8.3 Hz, 2H), 7.33 (dd, J = 8.4, 6.6 Hz, 4H), 6.78 (d, J = 8.7 Hz, 2H), 4.94 (qd, J = 6.7, 4.1 Hz, 1H), 4.38—4.29 (m, 2H), 4.16—4.10 (m, 2H), 3.10 (d, J = 4.5 Hz, 1H), 2.43 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −78.54 (d, J = 6.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.7, 145.2, 132.6, 129.9, 128.8, 127.9, 127.1, 124.4 (q, J = 282.1 Hz), 114.5, 72.1 (q, J = 32.1 Hz), 68.2, 65.4, 21.6. MS (EI, *m*/*z*, %): 392 (M^+, 23.26), 199 (100), 155 (42.72). HRMS (EI): calcd. for $C_{17}H_{17}{}^{16}O_4{}^{18}OF_3S$: 392.0791 (M); found: 392.0797. IR (film) *v*: 3489.9, 2928.1, 1613.6, 1598.2, 1514.8, 1455.4, 1402.6, 1355.6, 1252.6, 1175.0, 1126.7, 1020.7, 931.7, 815.7, 781.4, 691.8, 664.7, 621.2, 576.2 cm^{-1}.

1-(4-(Benzyloxy)phenyl)-2,2,2-trifluoroethan-1-ol-^{18}O (2c). Performed with **1c** at room temperature; 89.7 mg, 79% yield, 91% ^{18}O-isotopic purity. White solid. Mp.: 93—95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58—7.27 (m, 7H), 7.00 (d, J = 8.6 Hz, 2H), 5.07 (s, 2H), 4.93 (q, J = 6.3 Hz, 1H), 2.58 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −78.53 (d, J = 6.7 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.9, 136.8, 130.8, 128.6, 128.1, 127.5, 127.5, 125.6 (q, J = 285.2 Hz), 114.5, 74.5 (q, J = 29.5 Hz), 70.0, 23.8. MS (EI, *m*/*z*, %): 284 (M^+, 7.15), 91 (100), 65 (10.82). HRMS (EI): calcd. for $C_{15}H_{13}{}^{16}O^{18}OF_3$: 284.0910 (M); found: 284.0908. IR (film) *v*: 3398.9, 2913.8, 2861.1, 1612.7, 1585.7, 1515.9, 1454.6, 1387.6, 1303.4, 1252.6, 1199.9, 1126.9, 1049.0, 1009.1, 916.0, 874.5, 811.7, 749.0, 698.6 cm^{-1}.

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethan-1-ol-^{18}O (2d). Performed with **1d** at room temperature; 71.5 mg, 86% yield, 93% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.95 (q, J = 6.7 Hz, 1H), 3.82 (s, 3H), 2.72 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −78.59 (d, J = 6.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.4, 128.8, 126.1, 124.3 (q, J = 281.9 Hz), 114.0, 72.4 (q, J = 32.0 Hz), 55.3. MS (EI, *m*/*z*, %): 208 (M^+, 32.02), 139 (100), 109 (28.37). HRMS (EI): calcd. for $C_9H_9{}^{16}O^{18}OF_3$: 208.0597 (M); found: 208.0590. IR (film) *v*: 3433.0, 2940.9, 2839.1, 2036.7, 1614.2, 1587.6, 1516.6, 1465.9, 1355.7, 1252.0, 1167.8, 1125.6, 1058.4, 1031.0, 870.9, 817.6, 777.6, 692.5 cm^{-1}.

1,1,1-Trifluoro-2-(2-methoxyphenyl)propan-2-ol-^{18}O (2e). Performed with **1e** at 40 °C; 77.3 mg, 87% yield, 96% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42—7.29 (m, 2H), 7.06—6.96 (m, 2H), 6.13 (s, 1H), 3.94 (s, 3H), 1.77 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.48 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.1, 130.3, 129.4, 126.0 (q, J = 287.8 Hz), 125.8, 121.5, 112.5, 76.3 (q, J = 29.6 Hz), 56.2, 22.4. MS (EI, *m*/*z*, %): 222 (M^+, 26.48), 153 (100), 105 (48.9). HRMS (EI): calcd. for $C_{10}H_{11}{}^{16}O^{18}OF_3$: 222.0754 (M); found: 222.0762. IR (film) *v*: 3458.7, 3006.3, 2950.8, 2847.1, 1602.6, 1584.6, 1494.2, 1465.3, 1438.6, 1376.6, 1287.2, 1241.3, 1162.0, 1134.5, 1122.6, 1090.2, 1059.9, 1042.8, 1022.0, 931.0, 860.7, 843.1, 785.0, 755.2, 723.4, 644.1, 611.0, 580.2 cm^{-1}.

1,1,1-Trifluoro-2-(naphthalen-2-yl)propan-2-ol-^{18}O (2f). Performed with **1f** at room temperature; 83.3 mg, 86% yield, 96% ^{18}O-isotopic purity. White solid. Mp.: 56—58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.98—7.81 (m, 3H), 7.69 (d, J = 8.8 Hz, 1H), 7.60—7.47 (m, 2H), 2.60 (s, 1H), 1.90 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: − 80.62 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.8, 133.1, 132.8, 128.5, 128.1, 127.5, 126.7, 126.4, 125.7 (q, J = 285.4 Hz), 125.6, 123.5, 75.0 (q, J = 29.3 Hz), 24.0. MS (EI, *m*/*z*, %): 242 (M^+, 72.29), 173 (100), 45 (58.84). HRMS (EI): calcd. for $C_{13}H_{11}{}^{18}OF_3$: 242.0804 (M); found: 242.0811. IR (film) *v*: 3450.6, 3062.2, 3000.2, 1601.2, 1508.6, 1462.4, 1384.7, 1384.7, 1287.7, 1159.8, 1126.8, 1091.4, 1062.0, 955.1, 925.2, 858.4, 819.2, 804.3, 748.3, 717.5, 667.0, 597.3 cm^{-1}.

4-(1,1,1-Trifluoro-2-(hydroxy)propan-2-yl)phenyl 4-methylbenzenesulfonate (2g). Performed with **1g** at 40 °C; 108.6 mg, 75% yield, 96% ^{18}O-isotopic purity. White solid. Mp.: 88—89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 2.56 (s, 1H), 2.45 (s, 3H), 1.74 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.26 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.6, 145.5, 137.2, 132.2, 129.8, 128.4, 127.6, 125.2 (q, J = 286.8 Hz), 122.1, 74.4 (q, J = 29.8 Hz), 23.9, 21.7. MS (EI, *m*/*z*, %): 362 (M^+, 14.62), 91 (100), 155 (73.24). HRMS (EI): calcd. for $C_{16}H_{15}{}^{16}O_3{}^{18}OF_3$: 362.0686 (M); found: 362.0682. IR (film) *v*: 3499.1, 3006.1, 1597.6, 1504.5, 1458.7, 1372.3, 1291.4, 1179.1, 1158.2, 1093.2, 1017.8, 928.3, 870.2, 814.8, 759.3, 710.6, 665.2, 610.5, 569.1 cm^{-1}.

2-(4-(*tert*-Butyl)phenyl)-1,1,1-trifluoropropan-2-ol-^{18}O (2h). Performed with **1h** at room temperature; 81.4 mg, 82% yield, 96% ^{18}O-isotopic purity. White solid. Mp.: 39—41 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 2.47 (s, 3H), 1.78 (s, 1H), 1.35 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.96 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 151.6, 135.4, 125.7, 125.6 (q, J = 285.2 Hz), 125.3, 74.7 (q, J = 29.3 Hz), 34.5, 31.2, 23.8. MS (EI, *m*/*z*, %): 248 (M^+, 18.9), 233 (100), 179 (39.16). HRMS (EI): calcd. for $C_{13}H_{17}{}^{18}OF_3$: 248.1274 (M); found: 248.1275. IR (film) *v*: 3463.8, 2964.9, 2907.0, 2870.3, 1517.8, 1463.4, 1411.3, 1383.3, 1364.6, 1287.8, 1271.5, 1163.3, 1113.4, 1062.9, 1017.7, 922.0, 840.5, 824.4, 696.7 cm^{-1}.

1,1,1-Trifluoro-2-(4-methoxyphenyl)propan-2-ol-^{18}O (2i). Performed with **1i** at room temperature; 87.9 mg, 99% yield, 96% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 3.82 (s, 3H), 2.54 (s, 1H), 1.77 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.26. ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.7, 130.5, 127.4, 125.6 (q, J = 285.2 Hz), 113.6, 74.5 (q, J = 29.2 Hz), 55.3, 23.8. MS (EI, *m*/*z*, %): 222 (M^+, 22.86), 153 (100), 45 (57.04). HRMS (EI): calcd. for $C_{10}H_{11}{}^{16}O^{18}OF_3$: 222.0754 (M); found: 222.0758. IR (film) *v*: 3455.4, 3001.4, 2941.8, 2841.5, 1613.0, 1584.9, 1515.6, 1465.3, 1418.6, 1382.6, 1288.5, 1254.8, 1160.7, 1107.8, 1090.4, 1065.9, 1031.1, 921.2, 854.4, 828.2, 792.9, 734.1, 719.0, 614.9, 592.0 cm^{-1}.

2-(4-(Benzyloxy)phenyl)-1,1,1-trifluoropropan-2-ol-^{18}O (2j). Performed with **1j** at room temperature; 118.0 mg, 99% yield, 97% ^{18}O-isotopic purity. White solid. Mp.: 66—67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, J = 8.5 Hz, 2H), 7.48—7.39 (m, 4H), 7.39—7.32 (m, 1H), 7.01 (d, J = 8.9 Hz, 2H), 5.09 (s, 2H), 2.47 (s, 1H), 1.77 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.20 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.9, 136.8, 130.8, 128.6, 128.1, 127.5, 127.5, 125.6 (q, J = 285.2 Hz), 114.5, 74.5 (q, J = 29.5 Hz), 70.0, 23.8. MS (EI, *m*/*z*, %): 298 (M^+, 14.39), 91 (100), 92 (9.66). HRMS (EI): calcd. for $C_{16}H_{15}{}^{16}O^{18}OF_3$: 298.1067 (M); found: 298.1065. IR (film) *v*: 3437.9, 2916.5, 2871.7, 1611.2, 1513.9, 1454.3, 1416.3, 1383.2, 1289.9, 1255.1, 1177.9, 1110.3, 1092.7, 1014.1, 919.2, 828.4, 750.5, 734.9, 698.7, 644.3, 609.5 cm^{-1}.

2-(Benzo[d][1,3]dioxol-5-yl)-1,1,1-trifluoropropan-2-ol-^{18}O (2k). Performed with **1k** at room temperature; 47.2 mg, 50% yield,

96% ^{18}O-isotopic purity. Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (s, 1H), 7.05 (d, J=8.2 Hz, 1H), 6.82 (d, J=8.2 Hz, 1H), 5.98 (s, 2H), 2.45 (s, 1H), 1.75 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –81.23 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.7 (d, J=2.8 Hz), 132.2, 125.5 (q, J=285.2 Hz), 119.7, 107.9, 107.5 (d, J=1.7 Hz), 101.3, 74.6 (q, J=29.2 Hz), 24.0. MS (EI, *m/z*, %): 236 (M^+, 80.01), 45 (100), 167 (93.83). HRMS (EI): calcd. for $C_{10}H_9{}^{16}O_2{}^{18}OF_3$: 236.0546 (M); found: 236.0538. IR (film) *v*: 3485.8, 2998.2, 2901.5, 2122.2, 1848.7, 1704.6, 1634.4, 1505.5, 1492.0, 1438.5, 1349.7, 1288.9, 1245.2, 1168.5, 1100.0, 1039.3, 932.4, 899.6, 869.5, 811.0, 734.8, 716.9, 664.5, 577.3 cm^{-1}.

6-Methoxy-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol-^{18}O (2l). Performed with **1l** at room temperature; 98.2 mg, 99% yield, 96% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, J=8.8 Hz, 1H), 6.80 (dd, J=8.8, 2.7 Hz, 1H), 6.66 (d, J=2.6 Hz, 1H), 3.80 (s, 3H), 2.87—2.69 (m, 2H), 2.38 (s, 1H), 2.21 (ddd, J=12.9, 9.6, 3.1 Hz, 1H), 2.11—1.93 (m, 2H), 1.91—1.76 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –78.16 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.7, 140.5, 128.7 (q, J=2.8 Hz), 126.3 (q, J=286.1 Hz), 125.4, 113.7, 112.8, 72.7 (q, J=28.2 Hz), 55.2, 32.6, 30.0, 18.7. MS (EI, *m/z*, %): 248 (M^+, 3.72), 179 (100), 121 (22.93). HRMS (EI): calcd. for $C_{12}H_{13}{}^{16}O^{18}OF_3$: 248.0910 (M); found: 248.0916. IR (film) *v*: 3438.7, 2944.9, 5843.2, 1609.7, 1577.2, 1504.3, 1465.8, 1322.3, 1286.7, 1246.4, 1154.5, 1124.6, 1082.9, 1039.8, 1012.9, 989.3, 960.8, 930.3, 893.3, 874.5, 810.3, 745.2, 724.9, 713.7, 640.0 cm^{-1}.

1,1,1-Trifluoro-2-(4-methoxyphenyl)butan-2-ol-^{18}O (2m). Performed with **1m** at room temperature; 93.5 mg, 99% yield, 96% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, J=8.5 Hz, 2H), 6.93 (d, J=8.9 Hz, 2H), 3.82 (s, 3H), 2.38 (d, J=7.5 Hz, 1H), 2.22 (dq, J=15.0, 7.6 Hz, 1H), 2.03 (dq, J=14.6, 7.3 Hz, 1H), 0.81 (t, J=7.4 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –80.37 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.5, 128.1, 127.7, 127.3 (q, J=286.5 Hz), 113.6, 77.4 (q, J=27.8 Hz), 55.2, 28.0, 6.5. MS (EI, *m/z*, %): 236 (M^+, 31.62), 167 (100), 137 (49.64). HRMS (EI): calcd. for $C_{11}H_{13}{}^{16}O^{18}OF_3$: 236.0910 (M); found: 236.0917. IR (film) *v*: 3465.6, 2979.7, 2943.5, 2841.1, 1613.0, 1584.9, 1515.7, 1465.4, 1384.1, 1302.8, 1277.6, 1252.7, 1156.6, 1110.2, 1091.4, 1033.0, 986.3, 957.4, 933.3, 903.0, 830.0, 806.2, 778.4, 735.2, 715.8, 641.1, 632.2, 589.8 cm^{-1}.

2,2,2-Trifluoro-1,1-diphenylethan-1-ol-^{18}O (2n). Performed with **1n** at 40 °C; 96.5 mg, 95% yield, 96% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52—7.45 (m, 4H), 7.38—7.31 (m, 6H), 3.53 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –74.26 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.3, 128.6, 128.3, 127.4 (q, J=1.9 Hz), 125.3 (q, J=286.3 Hz), 79.4 (q, J=28.6 Hz). MS (EI, m/z, %): 254 (M^+, 10.41), 185 (100), 107 (82.8). HRMS (EI): calcd. for $C_{14}H_{11}{}^{18}OF_3$: 254.0804 (M); found: 254.0800. IR (film) *v*: 3531.9, 3063.1, 3032.5, 2927.7, 1601.4, 1497.5, 1450.5, 1341.5, 1274.4, 1155.6, 1090.6, 1044.0, 1028.8, 1002.0, 951.1, 926.3, 901.8, 757.8, 732.0, 698.1, 666.9, 647.3 cm^{-1}.

2,2,2-Trifluoro-1-(4-methoxyphenyl)-1-phenylethan-1-ol-^{18}O (2o). Performed with **1o** at room temperature; 112.5 mg, 99% yield, 96% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56—7.47 (m, 2H), 7.45—7.33 (m, 5H), 6.88 (d, J=9.0 Hz, 2H), 3.80 (s, 3H), 2.93 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –74.48 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.6, 139.5, 131.5, 128.8 (q, J=1.9 Hz), 128.6, 128.2, 127.4, 125.7 (q, J=287.5 Hz), 113.6, 79.2 (q, J=28.5 Hz), 55.2. MS (EI, *m/z*, %): 284 (M^+, 15.41), 215 (100), 107 (63.68). HRMS (EI): calcd. for $C_{15}H_{13}{}^{16}O^{18}OF_3$: 284.0910 (M); found: 284.0903. IR (film) *v*: 3440.4, 2937.7, 1610.7, 1514.5, 1464.1, 1450.2, 1255.4, 1159.8, 1032.2, 935.0, 906.9, 830.1, 762.4, 724.5, 698.9, 657.5, 605.3 cm^{-1}.

Isopropyl 2-(4-(1-(4-chlorophenyl)-2,2,2-trifluoro-1-(hydroxy)ethyl)phenoxy)-2-methylpropanoate (2q). Performed with **1q** at 40 °C; 171.15 mg, 99% yield, 97% ^{18}O-isotopic purity. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J=8.5 Hz, 2H), 7.30 (d, J=8.7 Hz, 4H), 6.78 (d, J=9.0 Hz, 2H), 5.03 (hept, J=6.3 Hz, 1H), 3.13 (s, 1H), 1.58 (s, 6H), 1.18 (dd, J=6.3, 1.9 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –74.60 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.4, 155.9, 137.8, 134.6, 132.2, 129.0 (d, J=1.9 Hz), 128.3, 128.3, 125.1 (q, J=286.2 Hz), 118.1, 79.2, 78.8 (q, J=28.9 Hz), 69.1, 25.3, 21.5. MS (EI, *m/z*, %): 432 (M^+, 6.93), 235 (100), 345 (35.88). HRMS (EI): calcd. for $C_{21}H_{22}{}^{16}O_3{}^{18}OF_3Cl$: 432.1201 (M); found: 432.1203. IR (film) *v*: 3447.5, 2984.7, 2939.1, 1727.2, 1609.2, 1509.8, 1493.2, 1467.3, 1385.2, 1289.4, 1248.9, 1157.3, 1100.6, 1056.7, 1015.7, 957.6, 913.7, 825.7, 742.8 cm^{-1}.

General procedure for the synthesis of α-CF_3 compounds 3. Selectfluor (212.6 mg, 0.60 mmol, 1.5 equiv.), and 4-(1,1-difluoroprop-1-en-2-yl)-1,1'-biphenyl (**1a**) (92.0 mg, 0.40 mmol, 1.0 equiv.) were added in turn to an oven-dried 10-mL Schlenk tube equipped with a stir bar under an argon atmosphere. The reactants were dissolved in CH_3CN (1.5 mL), followed by the addition of alcohol, HOAc, or DMF (2.0 mmol, 5.0 equiv.). The reaction mixture was stirred at 40 °C for 4 h. The completion of the reaction could be monitored by ^{19}F NMR. The reaction mixture was diluted with ethyl acetate (10.0 mL), transferred to a flask, and treated with brine (10.0 mL). The resulting mixture was extracted with ethyl acetate (10.0 mL x 3). The combined organic solvent was washed with brine (10.0 mL x 3) and then dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The residue was subjected to silica gel column chromatography (Petroleum ether : ethyl acetate=50 : 1) to give product **3**.

4-(1,1,1-Trifluoro-2-methoxypropan-2-yl)-1,1'-biphenyl (3a). Performed with MeOH/CH_3CN; 104.2 mg, 93% yield. White solid. Mp.: 92—94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69—7.55 (m, 6H), 7.52—7.44 (m, 2H), 7.43—7.33 (m, 1H), 3.29 (s, 3H), 1.84 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –79.88 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.7, 140.3, 134.9, 128.8, 128.3, 127.6, 127.1, 127.0, 126.6 (q, J=285.8 Hz), 79.6 (q, J=28.1 Hz), 51.0, 17.7 (d, J=1.8 Hz). MS (EI, *m/z*, %): 280 (M^+, 15.04), 211 (100), 181 (24.36). HRMS (EI): calcd. for $C_{16}H_{15}OF_3$: 280.1075 (M); found: 280.1081. IR (film) *v*: 3083.5, 3014.3, 2949.1, 2851.3, 1461.1, 1448.9, 1408.2, 1379.7, 1312.7, 1261.8, 1164.0, 1141.4, 1113.3, 1097.7, 1070.4, 1047.8, 891.6, 828.4, 762.0, 733.9, 711.6, 650.2, 610.5 cm^{-1}.

4-(2-Ethoxy-1,1,1-trifluoropropan-2-yl)-1,1'-biphenyl (3b). Performed with EtOH/CH_3CN; 109.4 mg, 92% yield. White solid. Mp.: 74—75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66—7.54 (m, 6H), 7.51—7.42 (m, 2H), 7.42—7.34 (m, 1H), 3.53 (dq, J=8.6, 6.9 Hz, 1H), 3.32 (dq, J=8.6, 7.0 Hz, 1H), 1.82 (s, 3H), 1.28 (t, J=7.0 Hz, 3H). ^{9}F NMR (376 MHz, $CDCl_3$) δ: –79.78 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.6, 140.4, 135.8, 128.8, 128.1, 127.6, 127.1, 127.0, 125.2 (q, J=284.9 Hz), 79.3 (q, J=28.1 Hz), 58.9, 18.4, 15.5. MS (EI, *m/z*, %): 294 (M^+, 25.61), 225 (100), 197 (40.36). HRMS (EI): calcd. for $C_{17}H_{17}OF_3$: 294.1232 (M); found: 294.1243. IR (film) *v*: 3074.7, 3042.2, 3026.4, 2989.4, 2948.8, 2887.8, 1949.2, 1918.6, 1884.1, 1488.2, 1464.7, 1446.9, 1404.2, 1375.5, 1305.1, 1236.1, 1171.0, 1145.3, 1129.1, 1107.4, 1067.6, 1052.5, 955.6, 873.8, 858.0, 824.9, 762.9, 733.9, 709.8, 662.6 cm^{-1}.

4-(2-(Benzyloxy)-1,1,1-trifluoropropan-2-yl)-1,1'-biphenyl (3c). Performed with BnOH/CH_3CN; 126.8 mg, 89% yield. White solid. Mp.: 77—78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72—7.59 (m, 6H), 7.49 (t, J=7.5 Hz, 2H), 7.46—7.38 (m, 5H), 7.37—7.30 (m, 1H), 4.56 (d, J=11.4 Hz, 1H), 4.44 (d, J=11.4 Hz, 1H), 1.96 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –79.41 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.8, 140.3, 137.9, 135.3, 128.9, 128.5, 128.3, 127.7, 127.6, 127.2, 127.1, 125.2 (q, J=285.0 Hz), 79.9 (q, J=28.3 Hz), 65.3, 18.6. MS (EI, *m/z*, %): 356 (M^+, 6.47), 91 (100), 250 (23.29). HRMS (EI): calcd. for $C_{22}H_{19}OF_3$: 356.1388 (M); found: 356.1393. IR (film) *v*: 3062.8, 3032.2, 3001.7, 2918.1, 1600.6, 1487.7, 1454.8, 1406.5, 1386.9, 1302.0, 1238.5, 1167.5, 1116.9, 1072.0, 1027.3, 1007.9, 917.5, 830.0, 766.9, 735.4, 696.6, 566.4 cm^{-1}.

4-(2-(Cyclohexyloxy)-1,1,1-trifluoropropan-2-yl)-1,1'-biphe-

nyl (3d). Performed with cyclohexanol/CH_3CN; 126.7 mg, 91% yield. White solid. Mp. 87—88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75—7.69 (m, 2H), 7.69—7.61 (m, 4H), 7.53—7.46 (m, 2H), 7.44—7.36 (m, 1H), 3.54 (tt, J=9.3, 3.8 Hz, 1H), 2.01—1.84 (m, 4H), 1.85—1.68 (m, 3H), 1.63—1.40 (m, 3H), 1.36—1.13 (m, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –79.60 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.4, 140.4, 137.3, 128.8, 128.4, 127.6, 127.1, 126.6, 125.4 (q, J=286.0 Hz), 79.1 (q, J=27.7 Hz), 72.8, 34.7, 34.5, 25.5, 24.4, 18.9. MS (EI, *m*/*z*, %): 348 (M^+, 7.9), 197 (100), 249 (35.75). HRMS (EI): calcd. for $C_{21}H_{23}OF_3$: 348.1701 (M); found: 348.1707. IR (film) *v*: 3034.6, 3014.3, 2935.0, 2856.8, 1601.4, 1487.7, 1464.0, 1449.4, 1406.2, 1371.6, 1300.1, 1237.7, 1162.5, 1115.4, 1071.5, 1046.8, 1024.3, 1007.8, 984.9, 904.1, 863.2, 848.9, 827.1, 765.7, 735.6, 712.7, 697.1, 658.0 cm^{-1}.

4-(1,1,1-Trifluoro-2-isopropoxypropan-2-yl)-1,1'-biphenyl (3e). Performed with isopropanol/CH_3CN; 110.9 mg, 90% yield. White solid. Mp.: 49—50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=8.4 Hz, 2H), 7.63 (d, J=8.3 Hz, 4H), 7.47 (t, J=7.6 Hz, 2H), 7.42—7.35 (m, 1H), 3.83 (hept, J=6.1 Hz, 1H), 1.88 (d, J=1.3 Hz, 3H), 1.27 (d, J=6.1 Hz, 3H), 1.17 (d, J=6.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –79.56 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.5, 140.4, 137.1, 128.8, 128.4, 127.6, 127.1, 126.7, 125.3 (q, J=285.8 Hz), 79.2 (q, J=27.7 Hz), 67.1, 24.6, 24.4, 18.9 (d, J=1.9 Hz). MS (EI, *m*/*z*, %): 308 (M^+, 18.7), 197 (100), 239 (28.35). HRMS (EI): calcd. for $C_{18}H_{19}OF_3$: 308.1388 (M); found: 308.1386. IR (film) *v*: 3031.8, 2979.8, 2934.5, 1600.5, 1488.5, 1465.0, 1406.6, 1383.0, 1302.7, 1236.1, 1164.8, 1114.0, 1071.1, 1008.1, 984.7, 898.1, 834.3, 765.9, 736.4, 697.6 cm^{-1}.

***N*-(2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoropropan-2-yl)acetamide (3f).** Performed with CH_3CN only at room temperature; 73.7 mg, 60% yield. White solid. Mp.: 158—160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J=8.2 Hz, 4H), 7.48 (d, J=8.3 Hz, 2H), 7.43 (t, J=7.6 Hz, 2H), 7.35 (t, J=6.8 Hz, 1H), 6.49 (s, 1H), 2.08 (s, 3H), 2.01 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –78.73 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.3, 141.2, 140.4, 135.3, 128.8, 127.5, 127.2, 127.1, 127.1, 125.4 (q, J=285.2 Hz), 62.2 (q, J=26.9 Hz), 24.0, 19.7. MS (EI, *m*/*z*, %): 307 (M^+, 35.6), 196 (100), 248 (33.75). HRMS (EI): calcd. for $C_{17}H_{16}NOF_3$: 307.1184 (M); found: 307.1192. IR (film) *v*: 3272.7, 3069.0, 1659.4, 1560.2, 1488.4, 1457.3, 1406.2, 1374.7, 1284.3, 1192.8, 1155.6, 1122.5, 1103.6, 1075.2, 1007.3, 974.7, 918.1, 825.0, 765.3, 735.8, 710.0, 696.9, 599.3, 574.9 cm^{-1}.

2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoropropan-2-yl acetate (3g). Performed with HOAc/CH_3CN at room temperature; 73.9 mg, 60% yield. White solid. Mp. 115—117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65—7.57 (m, 4H), 7.53—7.43 (m, 4H), 7.41—7.33 (m, 1H), 2.20 (s, 3H), 2.17 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –81.05 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.1, 141.8, 140.3, 134.3, 128.8, 127.6, 127.2, 127.1, 126.9, 122.8 (q, J=284.5 Hz), 81.6 (q, J=29.3 Hz), 21.8, 18.6. MS (EI, *m*/*z*, %): 308 (M^+, 42.55), 197 (100), 152 (37.53). HRMS (EI): calcd. for $C_{17}H_{15}O_2F_3$: 308.1024 (M); found: 308.1019. IR (film) *v*: 3358.1, 3067.2, 3032.3, 2919.6, 2849.9, 1758.8, 1657.3, 1631.4, 1600.7, 1488.3, 1457.8, 1408.0, 1369.6, 1298.7, 1229.3, 1173.6, 1112.1, 1075.5, 1007.9, 953.8, 888.6, 856.0, 822.0, 756.9, 737.0, 698.1, 604.7 cm^{-1}.

2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoropropan-2-yl formate (3h). Performed with DMF/CH_3CN at room temperature; 95.3 mg; 81% yield. White solid. Mp.: 91—92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.67—7.58 (m, 4H), 7.53 (d, J=8.2 Hz, 2H), 7.50—7.43 (m, 2H), 7.42—7.35 (m, 1H), 2.22 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –80.99 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.9, 142.2, 140.1, 133.4, 128.8, 127.7, 127.2, 127.2, 127.1, 125.3 (q, J=284.8 Hz), 82.2 (q, J=29.8 Hz), 18.9. MS (EI, *m*/*z*, %): 294 (M^+, 100), 197 (99.91). HRMS (EI): calcd. for $C_{16}H_{13}O_2F_3$: 294.0868 (M); found: 294.0869. IR (film) *v*: 2932.8, 1743.4, 1585.1, 1566.8, 1449.5, 1406.2, 1385.9, 1297.7, 1189.8, 1150.7, 1111.0, 1091.8, 1076.9, 888.0, 831.4, 790.5, 756.9, 765.9, 727.3, 693.1, 630.0, 601.7 cm^{-1}.

General procedure for the synthesis of *D*-labeled α-CF_3 compounds 4. Selectfluor (2.126 g, 6.0 mmol, 1.5 equiv.), and 4-(1,1-difluoroprop-1-en-2-yl)-1,1'-biphenyl (**1a**) (920.0 mg, 4.0 mmol, 1.0 equiv.) were added in turn to an oven-dried 25-mL Schlenk tube equipped with a stir bar under an argon atmosphere. The reactants were dissolved in CH_3CN (15.0 mL), followed by the addition of CD_3OH (700.0 mg, 20.0 mmol, 5.0 equiv.). The reaction mixture was stirred at 40 °C for 4 h. The completion of the reaction could be monitored by ^{19}F NMR. The reaction mixture was diluted with ethyl acetate (30.0 mL), transferred to a flask, and treated with brine (30.0 mL). The resulting reaction mixture was extracted with ethyl acetate (30.0 mL x 3). The combined organic solvent was washed with brine (50.0 mL x 3) and then dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The residue was subjected to silica gel column chromatography (petroleum ether : ethyl acetate=50 : 1) to give product **4a** (1.076 g, 95% yield, 99% D).

4-(1,1,1-Trifluoro-2-(methoxy-d_3)propan-2-yl)-1,1'-biphenyl (4a). White solid. Mp.: 90—92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69—7.55 (m, 6H), 7.46 (t, J=7.5 Hz, 2H), 7.38 (t, J=7.3 Hz, 1H), 1.82 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –79.81 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.72 , 140.39 , 135.04 , 128.89 , 128.33 , 127.67 , 127.19 , 127.08 , 125.27 (q, J=284.9 Hz), 79.54 (q, J=28.0 Hz), 54.15—45.64 (m), 17.69 (d, J=1.8 Hz). MS (EI, *m*/*z*, %): 283 (M^+, 18.84), 214 (100). HRMS (EI): calcd. for $C_{16}H_{12}D_3OF_3$: 283.1263 (M); found: 283.1267. IR (film) *v*: 3076.0, 2959.7, 2076.1, 1446.4, 1404.2, 1380.6, 1306.1, 1265.6, 1235.3, 1172.8, 1149.2, 1117.8, 1107.8, 1072.3, 1017.6, 963.5, 866.3, 827.4, 762.1, 733.0. 710.1, 695.6, 644.3, 607.7, 527.0, 512.4 cm^{-1}.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.201800426.

Acknowledgement

This work was supported by the National Key Research and Development Program of China (Nos. 2015CB931900, 2016YFB0101200), the National Natural Science Foundation of China (Nos. 21632009, 21421002, 21472221), the Key Programs of the Chinese Academy of Sciences (No. KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (No. QYZDJ-SSW-SLH049), and Shanghai Science and Technology program (No. 16QA1404600).

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Manuscript received: September 12, 2018
Manuscript revised: October 11, 2018
Manuscript accepted: October 12, 2018
Accepted manuscript online: October 16, 2018
Version of record online: October 25, 2018

