Pd-catalyzed arylation of silyl enol ethers of substituted α-fluoroketones†

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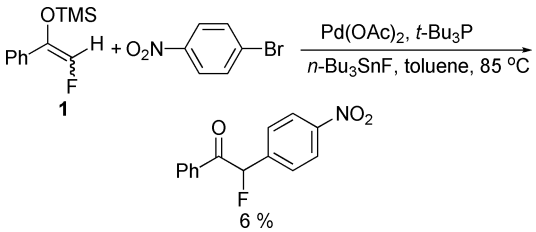
α-Fluoro-α-aryl-ketones were synthesized by the Pd-catalyzed cross-coupling of aryl bromides with either α-fluoroketones or their corresponding silyl enol ethers. The direct arylation with an α-fluoroketone requires a strong base, such as potassium *tert*-butoxide, and under these conditions the presence of a base-sensitive functional group is not compatible. However, good functional tolerance was achieved when the anionic coupling moieties were generated from the silyl enol ethers obtained by reacting α-fluoroketones with tetrabutylammonium (triphenylsilyl)difluorosilicate (TBAT) as the fluoride source under nearly neutral conditions. The aryl halides with a carbmethoxy, nitro, cyano or carbonyl group were used. The reaction with nonfluorinated silyl enol ether **1h** gave a cross-coupling product in low yield.

Introduction

Fluoroorganic chemistry provides surprising and intellectual stimulation in theoretical, synthetic, and biomedical chemistry, and materials science.[1] Tertiary α-fluorinated ketones have received much attention recently because compounds having an α-fluorocarbonyl moiety exhibit interesting biological activity, such as effective mimics of α-hydroxy ketones, useful probes for various biological processes, and enzyme inhibitors.[2] Electrophilic fluorination of a ketone[3] and functionalization of a fluorinated building block[4] give rise to two main strategies for the preparation of tertiary α-fluorinated ketones as well as a few other systems.[5] However, limited reports of methods to prepare α-aryl-α-fluorocarbonyl compounds,[5d] especially synthetic routes to α-aryl-α-fluoroketones, are available. Reactivities of fluorinated substrates were often found to be different and sometimes unexpected compared to their nonfluorinated analogues.[6] Thus, although we developed an approach to α,α-difluoroketones from difluoroenol silyl ethers,[7] it was still interesting to observe the arylation of the substituted α-monofluoroketones even though there have been a few reports of coupling reactions of nonfluorinated enol silyl ethers.[8]

Result and discussion

Palladium-catalyzed cross-coupling reactions of α-aryl-β,β-difluoroenol silyl ethers with aryl bromides proceed smoothly with good functional compatibility in the presence of tri-*tert*-butylphosphine and tri-*n*-butyltin fluoride using palladium acetate as catalyst.[7] However, the yield decreased dramatically when α-phenyl-β-fluoroenol silyl ether **1** reacted with 1-bromo-4-nitrobenzene under similar conditions (Scheme 1).



Scheme 1 The reaction of fluorinated silyl enol ether with 1-bromo-4-nitrobenzene.

In order to expand the utilization of both silyl enol ethers and functionalized halides, the reaction conditions of silyl enol ether **1b** with halides was screened. Selected conditions were depicted in Table 1. Initially the Pd-Bu_3SnF system[7] was used (Entry 6). However, only a small amount of **3b** was obtained. Therefore, several other fluorides were tried. The arylation of enol silyl α-monofluoroketone **1b** was catalyzed by 3.75 mol% bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and 7.5 mol% *t*-Bu_3P in the presence of tetrabutylammonium (triphenylsilyl)difluorosilicate (TBAT) in toluene at elevated temperature. A moderate yield of **3b** resulted (Table 1, Entry 1). The ketone which results from the hydrolysis of silyl enol ether **1a** was formed as the major side product. Several reactions were carried out in order to determine how to reduce its formation. The yield was slightly improved when the aryl iodide was used instead of bromide since the iodide is more reactive (Entry 2); however, slightly larger amounts of hydrolysis products were found. With increase in concentration of the palladium catalyst and phosphine, the yield of aryl product was increased, and the hydrolysis reaction was reduced. Tetrabutylammonium difluorophenylstannate, a fluoride source similar to TBAT, showed poor results (Entry 5). In all cases, we found the biaryl in a low yield.[9]

The time at which the silyl enol ether was introduced into the reaction mixture after reaction initiation appears to be important in some cases. For example, with bromobenzene the results were independent of the time of addition of silyl enol ether (Table 2). However, for reasons which are not entirely clear, the yield of **3** was reduced when addition of the silyl enol ether to a

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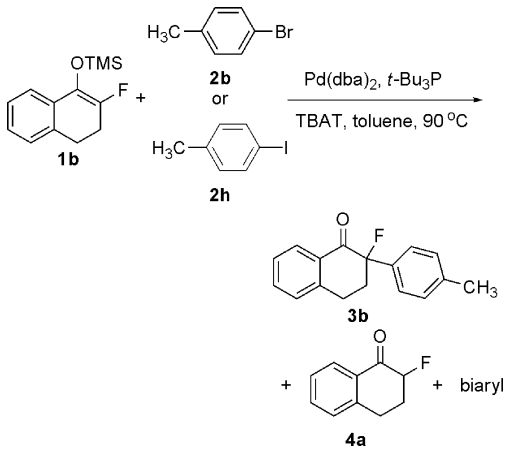
† Electronic supplementary information (ESI) available: All spectroscopic data of new compounds and single-crystal X-ray diffraction analyses of compound **3e**. CCDC reference number 715296. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b900311h

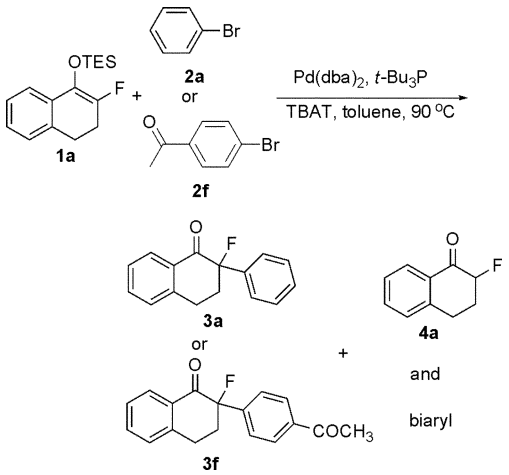
Table 1 Screen of conditions of silyl enol ether **1b** with halides



Entry	Halide	Mol% $Pd(dba)_2$	Mol% t-Bu_3P	% Yield **3b**	% Yield **4a**	% Yield of biaryl
1	**2b**	3.75	7.5	44	41	7
2	**2h**	3.75	7.5	45	50	9
3	**2b**	7.5	15	60	26	9
4	**2b**	15	30	73	13	12
5[b]	**2b**	3.75	7.5	28	65	12
6[c,d]	**2b**	3.75	7.5	25	52	2

[a] Conditions: in toluene (0.7 mL), at 90 °C for 20 min, silyl enol ether of ketone (0.33 mmol), aryl halides (0.66 mmol), TBAT (0.40 mmol). [b] Tetrabutylammonium difluorophenylstannate $[Bu_4N][Ph_3SnF_2]$ (0.40 mmol) instead of TBAT. [c] 3 eq n-Bu_3SnF was used instead of TBAT. [d] Reaction time was 10 hours.

Table 2 Influence of preheating time[a]



Entry	Halide	Preheating time (min)	**3** : **4a**	% Yield of biaryl
1	**2a**	0	(**3a** : **4a**) 64 : 36	n.d.[b]
2	**2a**	2	(**3a** : **4a**) 61 : 39	n.d.
3	**2f**	0	(**3f** : **4a**) 69 : 31	14
4	**2f**	2	(**3f** : **4a**) 57 : 43	17
5	**2f**	3	(**3f** : **4a**) 41 : 59	14

[a] Conditions: in toluene (0.7 mL), at 90 °C for 20 min, silyl enol ether **1a** (0.33 mmol), aryl halides (0.66 mmol), TBAT (0.40 mmol), and $Pd(dba)_2$ (0.05 mmol, 15 mol%), t-Bu_3P (30 mol%). [b] n.d. – not determined.

reaction mixture which contained halide **2f** was further (0 min *vs* 2, 3 min) into the heating cycle. Interestingly, the extent of self-coupling of the halide did not change (Table 2, Entries 3 to 5).

After the optimization of reaction conditions, various silyl enol ethers and halides were studied (Table 3). Unlike the reactions of difluoro[7] or nonfluorinated enol silyl ethers,[8] this route avoids using toxic tri-*n*-butyltin fluoride, which makes the reaction more environmentally friendly. It was found that an excess of aryl halide was necessary to ensure arylation; hydrolysis of the silyl enol ether gave rise to the main side product and biaryls were also formed. Several silyl enol ethers were tested. Triethylsilyl (TES) and trimethylsilyl (TMS) reagents gave similar results (Entry 7). In most cases, TES-substituted silyl enol ethers were used because of the ease of separation of reaction mixtures and of the lower decomposition when subjected to column chromatography on silica gel. The reaction rate of **1d** (seven-membered ring) was observed to be slower than that of **1a** (six-membered ring), thus the reaction was carried out with more TBAT for a prolonged period of time. The reactions of cyclic silyl enol ethers apparently proceeded more efficiently than that of acyclic ethers such as **1f**. The (*E*)-structure of silyl enol ether of **1f** was confirmed by the NOE effect.[10]

The product was an α,α-difluoroketone **5** when difluoroenol silyl ether **1g** was used. The current reaction conditions are not suited for further coupling of **5**. We have reported cross-coupling reactions of **5** with many aryl halides.[7] The reaction mechanism may differ for each.

A remarkable feature of the reaction is the good tolerance to electron-withdrawing base-sensitive functional groups, *e.g.*, carbmethoxy, nitro, cyano or carbonyl group. Single-crystal X-ray diffraction of **3e** confirmed the structure (Fig. 1; CCDC 715296). The 4-nitrophenyl group is introduced at the same carbon with fluorine. When non-fluorinated **1h** was used, the cross-coupling product **3m** was formed in a 15% yield. In Scheme 2, an equal number of equivalents of **1a** and **1h** were used. The unusual fact that compound **1h** (with less steric hindrance) gave a

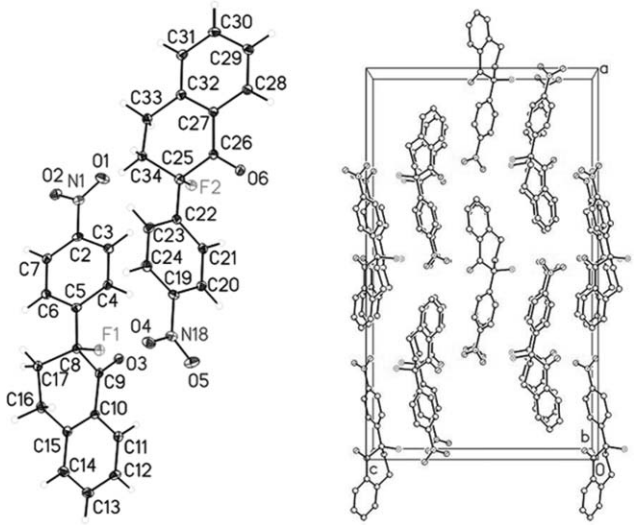
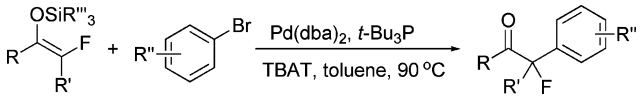


Fig. 1 Single-crystal X-ray structure of **3e**.

Table 3 Arylation of enol silyl ethers of substituted α-monofluoroketones



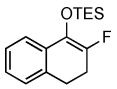
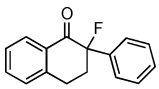
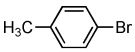
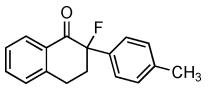
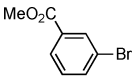
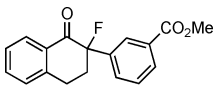
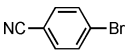
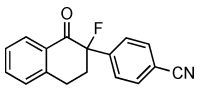
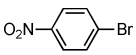
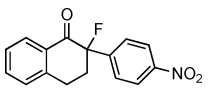
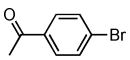
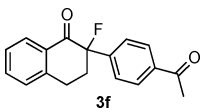
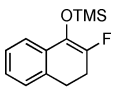
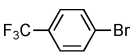
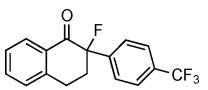
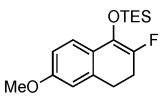
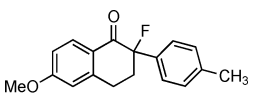
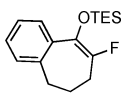
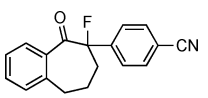
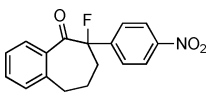
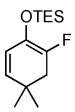
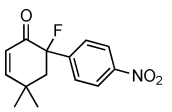
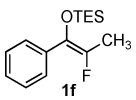
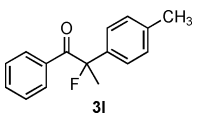
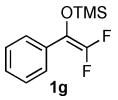
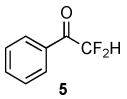
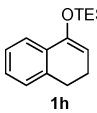
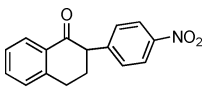
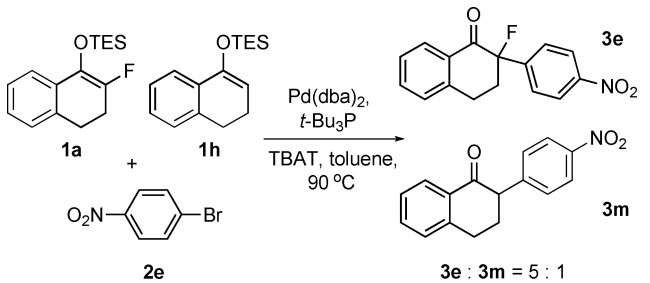
Entry	Silyl enol other	Aryl bromide	Product	% Yield[a]
1	 **1a**	 **2a**	 **3a**	64
2	**1a**	 **2b**	 **3b**	73
3	**1a**	 **2c**	 **3c**	67
4	**1a**	 **2d**	 **3d**	61
5	**1a**	 **2e**	 **3e**	61
6	**1a**	 **2f**	 **3f**	61
7	 **1b**	 **2g**	 **3g**	66
8	 **1c**	**2b**	 **3h**	62
9	 **1d**	**2d**	 **3i**	55[b]
10	**1d**	**2e**	 **3j**	57[b]
11	 **1e**	**2e**	 **3k**	65
12	 **1f**	**2b**	 **3l**	25

Table 3 *(Contd.)*

Entry	Silyl enol other	Aryl bromide	Product	% Yield[a]
13	 **1g**	**2b**	 **5**	90
14	 **1h**	**2e**	 **3m**	15[c]

[a] Conditions: in toluene (0.7 mL), at 90 °C for 20 min, silyl enol ether of ketones (0.33 mmol), aryl halides (0.66 mmol), TBAT (0.40 mmol), and $Pd(dba)_2$ (0.05 mmol, 15 mol%), *t*-Bu_3P (30 mol%). [b] Run with TBAT (0.66 mmol) for 2 h. [c] The yield was determined by ^1H NMR.



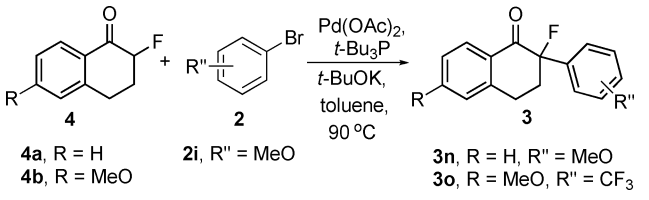
Scheme 2 Comparison of reactivity of non-fluorinated and fluorinated silyl enol ketones.

smaller quantity of the coupling product may be explained by the ease of hydrolysis of **1h**. The introduction of fluoride seemed to stabilize the enolate, thus markedly reducing the generation of the hydrolysis product compared to the non-fluorinated compound. As a result, additional amounts of the coupling product were formed.

For the first time an extensive method has been developed for the synthesis of aryl-substituted tertiary α-fluoroketones by Pd-catalyzed cross-coupling reactions. Traditionally, tertiary α-fluoroketones were synthesized by electrophilic fluorination.[3] However, most electrophilic reagents tend to be expensive and/or difficult to prepare, and often the functional groups of the reactants are incompatible with the electrophiles. We are aware that the enantioselective Pd-catalyzed allylation reaction of fluorinated silyl enol ethers[4] in a previous example avoided electrophilic fluorination in the final step in the synthesis of tertiary α-fluoroketones. However, the advantage of mild conditions and good functional tolerance can not be fully embodied when the substrates were limited to allyl ethyl carbonate and its analogues. Thus, the discovery that a variety of aryl halides with diverse functional groups are compatible in Pd-catalyzed cross-coupling reactions of fluorinated silyl enol ethers has expanded the scope of substrates. At the same time, this methodology will be useful for the enantioselective synthesis of α-aryl α-fluoroketones. The reduction of reactivity from cyclic fluorinated silyl enol ethers to acyclic moieties is common in arylation and allylation.[4]

Since the silyl enolates tended to hydrolyze to generate ketones, and aryl halides tended to generate biaryls, finding favourable

Table 4 Arylation of cyclic monofluoroketones



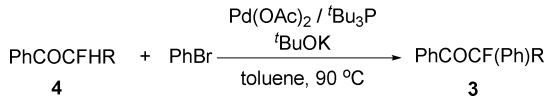
Entry	Ketone	Aryl halide	Product	% Conversion of ketone	% Yield of **3**[a]
1	**4a**	**2a**	**3a**	100	73[b]
2	**4a**	**2b**	**3b**	100	72[b]
3	**4a**	**2i**	**3n**	100	67[b]
4	**4a**	**2g**	**3g**	75	84[b]
5	**4a**	**2g**	**3g**	100	85[c]
6	**4a**	**2c**	**3c**	80	11[c]
7	**4a**	**2d**	**3d**	74	11[c]
8	**4a**	**2f**	**3f**	57	4[c]
9	**4b**	**2b**	**3h**	100	70[b]
10	**4b**	**2g**	**3o**	100	65[c]

[a] Yield based on converted ketone. [b] Conditions: in toluene (0.5 mL), at 90 °C for 1 h, ketone (0.33 mmol), aryl halides (0.36 mmol), *t*-BuOK (0.36 mmol), and $Pd(OAc)_2$ (0.0165 mmol, 5 mol%), *t*-Bu_3P (5 mol%). [c] Aryl halides (0.45 mmol).

conditions that would lead to cross-coupling while concomitantly preventing the formation of the two side products was key to the reaction. It is very important to control the relative speed of the generation of enolate anion and the insertion of palladium into the halide in order to achieve the maximum amount of desired cross-coupling product, *e.g.*, α-aryl-α-fluoroketones. The $Pd(dba)_2$/*t*-Bu_3P/TBAT system gave moderate yields of the products. The nearly neutral reaction conditions not only increases the functionality application, but also provides the possibility of chiral synthesis.

Starting from ketones rather than *via* a silyl enol ether, it is also possible to synthesize α-aryl-α-fluoroketones. The results appear in Table 4. The reaction was catalyzed by palladium acetate and tri-*tert*-butyl phosphine in the presence of potassium *tert*-butoxide. With 1.1 equivalents of monobromobenzene, 4-bromotoluene, or 4-methoxyl-1-bromobenzene, the ketone (**4a** or **4b**) was converted completely (Entries 1, 2, 3 and 9). In order to realize full conversion of the ketone, 1.5 equivalent of 4-bromobenzotrifluoride was

Table 5 Arylation with an acyclic α-fluoroketone



Entry	R	% Conversion of **4**	% Yield of **3**
1	H (**4h**)	90	17
2	CH_3 (**4f**)	67	24
3	F (**4g**)	50	0

required (Entry 4 *vs* Entry 5). However, the conversion and yield were poor even with excess of halide in entries 6 to 8, due to the base-sensitive functional group. It was necessary to employ nearly neutral conditions for those compounds, and using the silyl enol ether was an effective way of doing this, as described above.

Table 5 shows the limitation of the reaction. When using the open-chain monofluoroketone (**4h** or **4f**), **3** was obtained in low yield. There are a number of mysterious features of these reactions. For example, we currently have no good explanation for the difference in levels of yield and conversion observed for the reactions of **4a** and **4h** under identical reaction conditions. Like its enolate from silyl enol ether (Entry 12, Table 3), ketone **4f** gave a poor yield of coupling product (Entry 2, Table 5). Arylation of the difluoroketone did not occur, and as a result none of the coupling product was obtained.

In summary, the synthesis of tertiary α-fluoroketones by palladium-catalyzed arylation was successful. By using silyl enol ethers, a wide range of halides with good functionality tolerance can be utilized. With base-insensitive halides, fluoroketones rather than silyl enol ethers can be used directly to achieve coupling.

Experimental section

General methods

Silyl enol ethers[4a] were prepared by literature methods. Selectfluor® was used as fluoride source for the preparation of fluorinated silyl enol ethers. TBAT was synthesized from Ph_3SiF and tetrabutylammonium and difluorophenylstannate was prepared from Ph_3SnF.[11,12] A 1M toluene solution of P(*t*-Bu)3 was purchased from Aldrich Chemical Co. and used as received or was made by diluting pure tri-*tert*-butylphosphine from Alfa Aesar with dry toluene. Toluene was distilled under nitrogen over sodium prior to use. All other chemicals were used as received from commercial sources. ^1H and ^{19}F NMR spectra were obtained on a 300- or 500-MHz spectrometer, and chemical shifts were recorded relative to tetramethylsilane, and $CFCl_3$, respectively. The solvent was $CDCl_3$ unless otherwise stated. The purity of products was determined by C, H, and N elemental analyses.

General procedure for the arylation of silyl enol ether

To a mixture of $Pd(dba)_2$ (28 mg, 0.05 mmol), TBAT (210 mg, 0.40 mmol) and aryl halide **2e** (133mg, 0.66 mmol), was added freshly dried toluene (0.7 mL) and *t*-Bu_3P (0.1 mL of 1 M toluene solution, 0.1 mmol) at 90 °C under a nitrogen atmosphere. Silyl enol ether **1a** (92 mg, 0.33 mmol) was added *via* syringe with stirring. After 20 minutes, the mixture was cooled and passed through a short pad of silica gel. The precipitate was washed with ethyl acetate. The solvent was removed under reduced pressure. The desired product **3e** (57 mg, 61%) was isolated by flash chromatography using 10% ethyl acetate/hexane.

2-Fluoro-2-phenyl-1-tetralone (3a). IR (film): 1699 cm^{-1}; ^1H NMR δ 2.70–2.85 (m, 3H), 3.08–3.14 (m, 1H), 7.24 (d, $J = 7.6$ Hz, 1H), 7.32–7.38 (m, 5H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.53 (td, $J = 7.6$, 1.2 Hz, 1H), 8.18 (dd, $J = 7.6$, 1.2, 1H). ^{19}F NMR δ −145.6 (t, $J =$ 11.3 Hz). EI-MS (*m*/*z*, relative intensity): 240 (M^+, 29), 118 (100), 90 (45). Anal. Calcd for $C_{16}H_{13}FO$ (FW 240.3): C, 79.98; H, 5.45. Found: C, 80.00; H, 5.40.

2-Fluoro-2-(4-methylphenyl)-1-tetralone (3b). IR (film): 1699 cm^{-1}; ^1H NMR δ 2.33 (s, 3H), 2.63–2.87 (m, 3H), 3.05–3.13 (m, 1H), 7.14–7.26 (4H), 7.21 (d, $J = 7.5$ Hz, 1H), 7.38 (t, $J =$ 7.5 Hz, 1H), 7.52 (t, $J = 7.5$ Hz, 1H), 8.16 (d, $J = 7.5$ Hz, 1H); ^{19}F NMR δ −142.7 (t, $J = 9.9$ Hz). EI-MS (*m*/*z*, relative intensity): 254 (M^+, 15), 118 (100), 90 (36). Anal. Calcd for $C_{17}H_{15}FO$ (FW 254.3): C, 80.29; H, 5.95. Found: C, 80.09; H, 5.85.

Ethyl 3-(1,2,3,4-tetrahydro-2-fluoro-1-oxo-2-naphthalenyl)benzonate (3c). IR (film): 1721, 1699 cm^{-1}; ^1H NMR δ 2.68–2.89 (m, 3H), 3.19 (dt, $J = 16$, 4.5, 3H), 3.90 (s, 3H), 7.26 (d, $J = 7.7$ Hz, 1H), 7.40–7.46 (m, 2H), 7.51–7.55 (m, 2H), 8.04 (d, $J = 7.7$ Hz, 1H), 8.09 (s, 1H), 8.17 (d, $J = 7.7$ Hz, 1H); ^{19}F NMR δ: −147.8 (dd, $J = 17$, 11 Hz). EI-MS (*m*/*z*, relative intensity): 283 (M^+-Me, 0.68), 86 (16), 41 (100). Anal. Calcd for $C_{18}H_{15}FO_3$ (FW 298.3): C, 72.47; H, 5.07. Found: C, 72.20; H, 5.17.

4-(1,2,3,4-Tetrahydro-2-fluoro-1-oxo-2-naphthalenyl)benzonitrile (3d). IR (film): 2230, 1695, 1602, 1233 cm^{-1}; ^1H NMR δ 2.58–2.76 (m, 2H), 2.81–2.93 (m, 1H), 3.26 (dt, $J = 17.5$, 6.0 Hz, 1H), 7.30 (d, $J = 7.7$ Hz, 1H), 7.39–7.81 (m, 6H), 8.15 (d, $J = 7.7$ Hz, 1H). ^{19}F NMR δ −153.0 (dd, $J = 19.7$, 11.3 Hz). EI-MS (*m*/*z*, relative intensity): 265 (M^+, 20), 118 (100), 90 (44).Anal. Calcd for $C_{17}H_{12}FNO$ (FW 265.3): C, 76.97; H, 4.56, N,5.28. Found: C, 77.20; H, 4.47, N, 5.46.

2-Fluoro-2-(4-nitrophenyl)-1-tetralone (3e). IR (film): 1698, 1603, 1522, 1349 cm^{-1}; ^1H NMR δ 2.65–2.76 (m, 2H), 2.84–2.94 (m, 1H), 3.29 (dt, $J = 17.1$, 5.5 Hz, 1H), 7.31 (d, $J = 7.6$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.59 (td, $J = 7.6$, 1.3 Hz, 1H), 8.14 (dd, $J = 7.6$, 1.3 Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 2H); ^{19}F NMR δ −153.5 (dd, $J = 19.7$, 11,3 Hz). EI-MS (*m*/*z*, relative intensity): 285 (M^+, 31), 118 (100), 90 (48). Anal. Calcd for $C_{16}H_{12}FNO_3$ (FW 285.3): C, 67.36; H, 4.24; N, 4.91. Found: C, 67.47; H, 4.23, N, 5.24.

2-Fluoro-2-(4-acetylphenyl)-1-tetralone (3f). IR (film): IR (film): 1679 cm^{-1}; ^1H NMR δ 2.59 (s, 3H), 2.65–2.91 (m, 3H), 3.20 (dt, $J = 16.1$, 5.0 Hz, 1H), 7.28 (d, $J = 7.6$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.57 (td, $J =$ 7.6, 1.2 Hz, 1H), 7.95 (d, $J = 8.2$ Hz, 2H), 8.17 (dd, $J = 7.6$, 1.2 Hz, 1H); ^{19}F NMR δ −151.4 (t, $J = 14.1$ Hz). EI-MS (*m*/*z*, relative intensity): 282 (M^+, 23), 118 (100), 90 (43). Anal. Calcd for $C_{18}H_{15}FO_2$ (FW 282.3): C, 76.58; H, 5.36. Found: C, 76.45; H, 5.43.

2-Fluoro-2-(4-trifluoromethylphenyl)-1-tetralone (3g). IR (film): 1699, 1333, 1125 cm^{-1}; ^1H NMR δ 2.67–2.92 (m, 3H), 3.23 (dt, $J = 16.7$, 5.1 Hz, 1H), 7.29 (d, $J = 7.7$ Hz, 1H), 7.39–7.65 (m, 6H), 8.17 (d, $J = 7.7$ Hz, 1H); ^{19}F NMR δ -63.2 (s, 3F), −151.8 (t, $J = 14.1$ Hz, 1F); EI-MS (*m*/*z*, relative intensity): 308 (M^+ − HF, 23), 118 (100), 90 (44). Anal. Calcd for $C_{17}H_{12}F_4O$ (FW 328.3): C, 66.23; H, 3.92. Found: C, 66.10; H, 3.88.

2-Fluoro-2-(4-methylphenyl)-6-methoxy-1-tetralone (3h). IR (film): 1690, 1599, 1256 cm^{-1}; ^1H NMR δ 2.35 (s, 3H), 2.65–2.85 (m, 3H), 2.95–3.15 (m, 1H), 3.88 (s, 3H), 6.68 (d, $J = 2.3$ Hz, 1H), 6.92 (dd, $J = 8.8$, 2.3 Hz, 1H), 7.16–7.28 (4H), 8.17 (d, $J = 8.8$ Hz, 1H); ^{19}F NMR δ −143.2 (t, $J = 9.9$ Hz). EI-MS (*m*/*z*, relative intensity): 284 (M^+, 13), 264 (37), 221 (13), 148 (100), 120 (18). Anal. Calcd for $C_{18}H_{17}FO_2$ (FW 284.3): C, 76.04; H, 6.03. Found: C, 76.50; H, 6.03.

4-(6-Fluoro-6,7,8,9-tetrahydro-5-oxo-5H-benzocycloheptenyl)-benzonitrile (3i). IR (film): 2230, 1699 cm^{-1}; ^1H NMR δ 1.92–2.06 (m, 1H), 2.21–2.60 (m, 3H), 2.96–3.06 (m, 1H), 3.23–3.33 (m, 1H), 7.26–7.32 (m, 2H), 7.38–7.48 (m, 2H), 7.58 (d, $J = 8.6$ Hz, 2H), 7.69 (d, $J = 8.6$ Hz, 2H). ^{19}F NMR δ −153.9 (dd, $J = 38.7$, 17.8 Hz). EI-MS (*m*/*z*, relative intensity): 279 (M^+, 17), 251 (10), 160 (100), 129 (50), 104 (53), 91 (51), 77 (33). Anal. Calcd for $C_{18}H_{14}FNO$ (FW 279.3): C, 77.40; H, 5.05; N, 5.01. Found: C, 77.23; H, 5.09; N, 5.40.

2-Fluoro-2-(4-nitrophenyl)- 2-fluoro-2-(4-nitrophenyl)-1-benzo-suberone (3j). IR (film): 1699, 1522, 1348 cm^{-1}; ^1H NMR δ 1.93–2.08 (m, 1H), 2.33–2.63 (m, 3H), 2.99–3.07 (m, 1H), 3.25-–3.34 (m, 1H), 7.26–7.33 (m, 2H), 7.39–7.49 (m, 2H), 7.65 (d, $J = 9.0$ Hz, 2H), 8.25 (d, $J = 9.0$ Hz, 2H). ^{19}F NMR δ -153.4 (dd, $J = 39.3$, 17.9 Hz). EI-MS (*m*/*z*, relative intensity): 229 (M^+, 20), 281 (45), 225 (18), 207 (55), 91 (42), 73 (100). Anal. Calcd for $C_{17}H_{14}FNO_3$ (FW 299.3): C, 68.22; H, 4.71; N, 4.68. Found: C, 68.19; H, 4.74; N, 5.23.

6-Fluoro-6-(4-nitrophenyl)-4,4-dimethylcyclohex-2-enone (3k). IR (film): 1690, 1604, 1522, 1348 cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.39 (s, 3H), 2.27–2.45 (m, 2H), 6.15 (d, $J = 10.3$ Hz, 1H), 6.90 (d, $J = 10.3$, 1.5 Hz, 1H), 7.49 (d, $J = 8.5$ Hz, 2H), 8.24 (d, $J = 8.5$ Hz, 2H). ^{19}F NMR δ −150.5 ($J = 37.4$, 16.4 Hz). Anal. Calcd for $C_{14}H_{14}FNO_3$ (FW 263.3): C, 63.87; H, 5.39; N, 5.32. Found: C, 63.92; H, 5.34; N, 5.31.

2-Fluoro-2-(4-methylphenyl)-1-phenyl-1-propanone (3l). IR (film): 1687 cm^{-1}; ^1H NMR δ 1.90 (d, $J = 23.1$ Hz, 3H), 2.34 (s, 3H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.32–7.38 (m, 4H), 7.45–7.50 (m, 1H), 7.88–7.92 (m, 2H); ^{19}F NMR δ −149.1 (q, $J = 23.1$ Hz). EI-MS (*m*/*z*, relative intensity): 242 (M^+, 1.6), 137 (87), 105 (100), 77 (30). Anal. Calcd for $C_{16}H_{15}FO$ (FW 242.3): C, 79.32; H, 6.24. Found: C, 78.94; H, 6.29.

General procedure for the arylation of monofluoroketone

To a mixture of $Pd(OAc)_2$ (3.7 mg, 0.0165 mmol), *t*-BuOK (37 mg, 0.36 mmol), ketone **4a** (54 mg, 0.33 mmol) and aryl halide **2a** (57 mg, 0.36 mmol) was added freshly dried toluene (0.5 mL) and *t*-Bu_3P (0.0165 mL of 1 M toluene solution, 0.0165 mmol) at 90 °C under nitrogen atmosphere. After 1 hour, the mixture was cooled and passed through a short pad of silica gel. The precipitate was washed with ethyl acetate. The solvent was removed under reduced pressure. The desired product **3a** (58 mg, 73%) was isolated by flash chromatography using 5% ethyl acetate/hexane.

2-Fluoro-2-(4-methoxyphenyl)-1-tetralone (3n). IR (film): 1697 cm^{-1}; ^1H NMR δ 2.65–2.90 (m, 3H), 3.04–3.12 (m, 1H), 3.79 (s, 3H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.21 (d, $J = 7.6$ Hz, 1H), 7.29–7.41 (m, 3H), 7.52 (td, $J = 7.6$, 1.3 Hz, 1H), 8.17 (dd, $J = 7.6$, 1.3 Hz, 1H); ^{19}F NMR δ −140.7 (t, $J = 8.5$ Hz, 1H). EI-MS (*m*/*z*, relative intensity): 250 (M^+ − HF, 100), 235 (18), 207 (25), 178 (39). Anal. Calcd for $C_{17}H_{15}FO_2$ (FW 270.3): C, 75.54; H, 5.59. Found: C, 75.19; H, 5.51.

2-Fluoro-2-(4-trifluoromethylphenyl)-6-methoxy-1-tetralone (3o). IR (film): 1680, 1599 cm^{-1}; ^1H NMR δ 2.63–2.86 (m, 3H), 3.10–3.25 (m, 1H), 3.88 (s, 3H), 6.72 (d, $J = 2.2$ Hz, 1H), 6.93 (dd, $J = 8.8$, 2.2 Hz, 1H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.63 (d, $J = 8.2$ Hz, 2H), 8.14 (d, $J = 8.8$ Hz, 1H); ^{19}F NMR δ −62.1 (s, 3F), −150.5 (t, $J = 13.8$ Hz, 1F). EI-MS (*m*/*z*, relative intensity): 338 (M^+, 25), 319 (3.46), 148 (100), 120 (28). Anal. Calcd for $C_{18}H_{14}F_4O_2$ (FW 338.3): C, 63.91; H, 4.17. Found: C, 64.15; H, 4.11.

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10 Compound **1f** is relatively unstable. ^{1}H NMR δ 0.60 (q, J = 7.7 Hz, 6H), 0.92 (t, J = 7.9 Hz, 9H), 2.03 (d, J = 18.1 Hz, 3H), 7.15–7.39 (m, 5H). ^{19}F NMR δ −119.6 (q, J = 17.9 Hz). ROSEY showed the correlation of signal at 2.03 ppm with 0.60 and 0.92 ppm, respectively.

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