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Palladium catalyzed direct α-arylation of α,α-difluoroketones with aryl bromides

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ABSTRACT

The palladium-catalyzed direct α-arylations of α,α-difluoroketones with diverse aryl bromides have been developed by using *rac*-BINAP as ligand and Cs_2CO_3 as a mild base in xylene. This method provides an efficient and straightforward access to a variety of α-aryl-α,α-difluoroketones with broad substrate scope.

1. Introduction

The modification of organic molecules with fluorine can alter their physical and chemical properties and biological activities in a dramatic way. As a result, fluorinated compounds have been widely used as pharmaceuticals and agrochemicals [1]. Especially, incorporation of a *gem*-difluoromethylene group into an organic molecule has also been used as a strategy for modification of biologically active compounds [2]. The *gem*-difluoromethylene group (CF_2) not only enhances the acidity of its vicinal hydroxyl, amino and thiol groups, but also may significantly improve the biological stability. For example, α,α-difluoroketone A79285 is an excellent inhibitor of HIV-1 aspartic protease, as the strong electron withdrawing CF_2 group dramatically increases the electronphilicity of its vicinal carbonyl group, and then the readily hydrated difluoroketone could mimic the tetrahedral intermediate that formed during biological hydrolysis of the peptide bond (Fig. 1) [3].

Among *gem*-difluoromethylene-containing compounds, quaternary α-aryl-α,α-difluoroketone could be an important moiety in many compounds of biological activities. Accordingly, several methods had been developed for the preparation of quaternary α-aryl-α, α-difluoroketones via direct fluorination methods or building block strategies (Scheme 1). Electrophilic fluorination of carbonyl compounds (including their equivalents such as imines) [4], acetylenes [5] and alkenyl diboronate esters [6] using a variety of N-F reagents [7] is one of important methods for the preparation of quaternary α-aryl-α,α-difluoroketones (Scheme 1, Path 1). Nucleophilic fluorination of α-diketones [8], their α-monohydrazone [9] or α-dithiane [10] derivatives with *N,N*-diethylaminosulfur trifluoride (DAST), bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor), IF or BrF_3 produces a variety of quaternary α-aryl-α,α-fluoroketones (Scheme 1, Path 2). Pummerer-type desulfurization–fluorination of α-thiocarbonyl compounds [11] and fluorination of α-diazo compounds [12] by IF_5 or F_2 had also been reported for the synthesis of α-aryl-α,α-difluoroketones. These transformations, however, have some practical drawbacks, such as poor functional compatibility and the use of expensive fluorinating reagents.

An alternative strategy employed fluorinated building blocks for the synthesis of α-aryl-α,α-difluoroketones (Scheme 1, Path 3). Biju had developed a simple methodology for the synthesis of various α-(hetero)aryl-α,α-difluoroketones by the reaction of organolithium reagents with α,α-difluoro-*N*-methoxy-*N*-methyl amides (Weinreb amides) [13]. Pd-catalyzed arylation of α,α-difluorosilyl enol ethers in the presence of P(*t*-Bu)$_3$ and Bu_3SnF had been investigated for the synthesis of α-aryl-α,α-difluoroketones by Shreeve's group [14]. However, silyl enol ethers are unstable and excess amount of them are required in the coupling reaction to achieve good yields.

The palladium-catalyzed direct α-arylation of carbonyl compounds [15] has become a general method for the synthesis of α-aryl ketones, α-aryl esters, α-aryl lactones, α-aryl amides and α-aryl aldehydes [16]. Recently, we have developed a practical and efficient route to α-aryl-α-fluoroketones by palladium-catalyzed direct α-arylation of α-monofluorinated ketones with structurally

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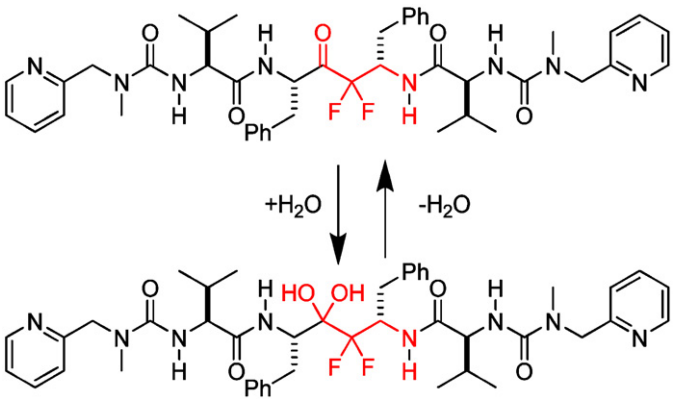


Fig. 1. Structure of A79285, a difluoroketone inhibitor of HIV-1 protease in dehydrated and hydrated form [3a].

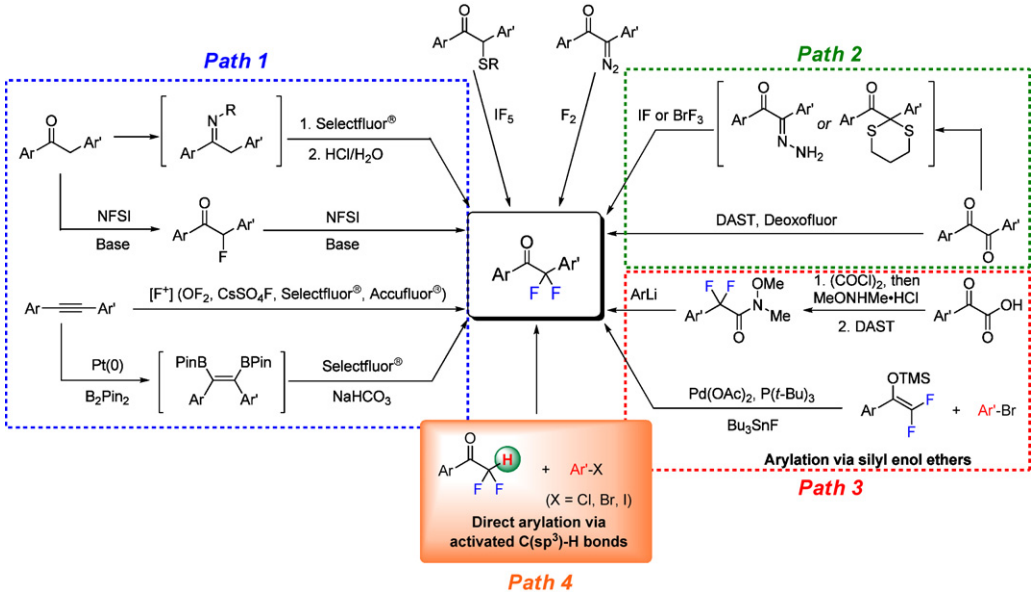
diverse aryl bromides [17]. Encouraged by these results, we envisioned that the palladium-catalyzed arylations of α,α-difluoroketones could provide an atom-economic access to α-aryl-α,α-difluoroketones by C–H bond functionalization (Scheme 1, Path 4). Herein, we describe the direct α-arylation of α, α-difluoroketones with aryl halides as a straightforward route for synthesis of α-aryl-α,α-difluoroketones.

2. Results and discussion

We began our study with the α-arylation of α, α-difluoro-1-phenylethanone **1** with bromobenzene as a model reaction (Table 1). Our initial efforts were focused on base screening using $Pd(OAc)_2$ (10 mol%)/RuPhos (20 mol%) as the catalytic system, as the catalytic system $Pd(OAc)_2$ (10 mol%)/RuPhos (20 mol%) was high efficient for direct α-arylation of α-monofluorinated ketones [17]. As shown in Table 1, when $K_3PO_4{\cdot}3H_2O$ and anhydrous K_3PO_4 were used as base, the Pd-catalyzed arylation in xylene at 130 °C led to the formation of the arylation product **2a** in low yield, and only half amount of **1** was converted (Table 1, entries 1–2). It is noteworthy that two hemiacetals [18] **3** and **4** were produced easily as the hydrated byproduct from starting material **1** and product **2a** respectively. Starting material **1** remained intact in the presence of mild bases Na_2CO_3 and K_2CO_3 (entries 3–4). Cs_2CO_3 promoted the arylation effectively to give **2a** in 39% yield (entry 5). In the case of strong base sodium *tert*-butoxide, hemiacetal **3** was the dominant species and compound **5** was also formed in 11% yield from self-Aldol reaction of **1** [19].

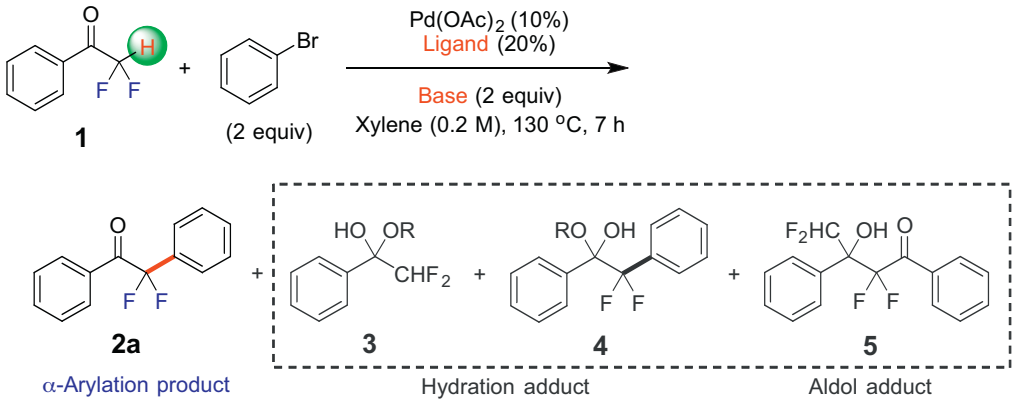
Recently, it has been found that ligands profoundly alter the stability, selectivity and reactivity of transition metal complexes catalyzed reaction [20]. To improve both the conversion of **1** and yield of **2a**, we next examined a series of phosphine ligands. The use of bulky and electron-rich Buchwald ligands SPhos and XPhos [21] significantly promoted the α-arylation of **1** and the hydrated by-products were inhibited simultaneously, but starting material **1** was not completely consumed yet (entries 8–9). The use of DavePhos and JohnPhos resulted in lower yield of **2a** (entries 10–11). Monodentate ligands and bidentate ligands showed similar catalytic efficiencies as SPhos and XPhos in the α-arylation reactions (entries 12–16), although they could promote the reductive elimination of fluoroalkyl palladium(II) intermediates [22]. To our delight, when BINAP [23] was used as the ligand, the desired product **2a** was formed in 90% yield with full conversion of **1** (entry 17). When the arylation was carried out at 100 °C, both the conversion of **1** and yield of **2a** were decreased (entry 18).

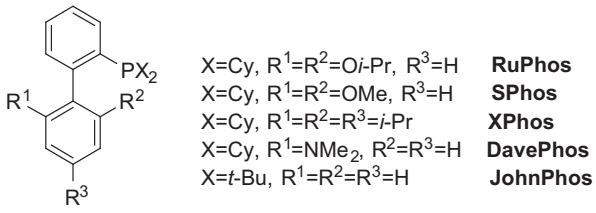
With the optimized reaction conditions in hand, the scope of the direct α-arylation reaction of α,α-difluoro-1-phenylethanone **1** with aryl bromides was investigated. As shown in Table 2, this method was applicable to a wide variety of substituted aryl bromides with either electron-withdrawing or electron-donating substitutions, providing α-aryl-α,α-difluoro-1- phenylethanones **2a**–**2k** in moderate to good yields. Surprisingly, when 4-bromotoluene, 4-*tert*-butylbromobenzene and 1-bromo-4-methoxybenzene were used as the coupling partner, the arylation of α,α-difluoro-1-phenylethanone **1** gave the desired products **2b**, **2c** and **2f** respectively, but compound **2a** was formed as the by-product. Compound **2f** was isolated from **2a** by silica-gel column chromatography. Compounds **2b** and **2c** were not separable from **2a** as they have very similar polarities, and were eventually identified by GC–MS. The mechanism for the formation of side-product **2a** in these reactions is not well understood at this point. When *di*-halo-substituted benzenes (1-fluoro-4-bromobenzene and 1-chloro-4-bromobenzene) were used as substrates, the cross-coupling products (**2g** and **2h)** were formed via the activation of C–Br bond selectively with small amount of **2a** as inseparable contaminant. The reaction of **1** with 1,4-dibromobenzene gave

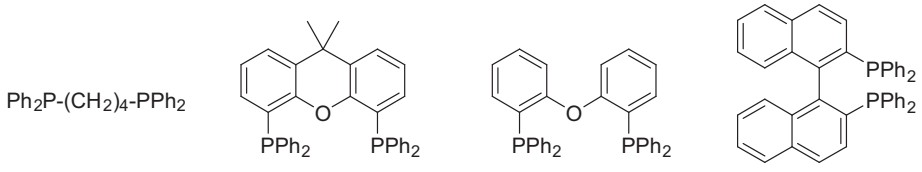


Scheme 1. Synthetic strategies to α-aryl-α,α-difluoroketones.

Table 1
Evaluation of bases and supporting ligands for Pd-catalyzed α-arylation of α,α-difluoroketone **1** with bromobenzene.[a]







Entry	Base	Ligand	Conversion of **1** (%)[b]	Yield of **2a** (%)[b]
1	$K_3PO_4·3H_2O$	RuPhos	57	14
2	K_3PO_4	RuPhos	56	15
3	Na_2CO_3	RuPhos	54	Trace
4	K_2CO_3	RuPhos	51	8
5	Cs_2CO_3	RuPhos	74	39
6	CsOAc[c]	RuPhos	53	0
7[d]	*t*-BuONa	RuPhos	86	9
8	Cs_2CO_3	SPhos	83	57
9	Cs_2CO_3	XPhos	87	64
10	Cs_2CO_3	DavePhos	65	16
11	Cs_2CO_3	JohnPhos	63	18
12	Cs_2CO_3	PPh_3[e]	78	51
13	Cs_2CO_3	P(*t*-Bu)$_3$[e]	75	40
14	Cs_2CO_3	Dppb	75	43
15	Cs_2CO_3	Xantphos	76	47
16	Cs_2CO_3	DPEphos	82	53
17	Cs_2CO_3	BINAP	100	90
18[f]	Cs_2CO_3	BINAP	62	25

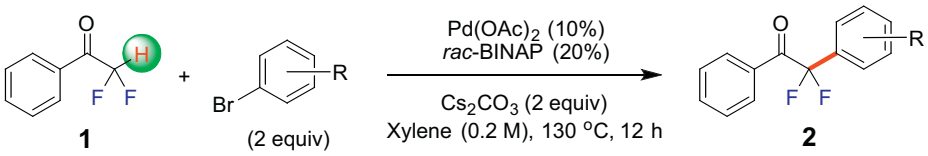
^{19}F NMR data: δ (ppm) **2a**: −96.9 (s); **3**: −130.1, −131.5 (AB, *J* = 277, 56 Hz); **4**: −108.7, −109.6 (AB, *J* = 245 Hz); **5**: −115.6, −117.6 (AB, *J* = 282 Hz), −129.8, −131.4 (AB, *J* = 290, 54 Hz).

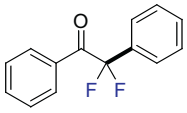
[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), **1** (1 equiv.), bromobenzene (2 equiv.), base (2 equiv.), xylene (0.2 M of **1**), 130 °C, 7 h.
[b] Determined by ^{19}F NMR using fluorobenzene as internal standard.
[c] Generated in situ by Cs_2CO_3 (2 equiv.) and AcOH (4 equiv.).
[d] 11% Aldol adduct **5** was observed.
[e] 40% Ligand was used.
[f] Toluene used as solvent at 100 °C.

mono-arylated compound **2i** in 83% yield without the formation of double-arylated compound. The arylation of **1** with sterically hindered 2-bromotoluene also proceeded smoothly to afford product **2k** in 52% yield.

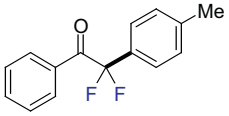
The scope of the α-arylation of α,α-difluoroketones **6** and **8** had also been investigated and the results were summarized in Table 3. Under the standard reaction conditions, the α-arylations of α,α-difluoro-1-(naphthalen-2-yl)ethanone **6** with diverse aryl bromides gave α-aryl-α,α-difluoro-1-(naphthalen-2-yl) ethanones **7a–7h** in moderate to good yields. It was also found that **7a** was formed as a by-product in the case of using 4-bromotoluene, 4-*tert*-butylbromobenzene and 1-bromo-4-methoxybenzene as coupling

Table 2
Pd-catalyzed direct α-arylation of **1** with structurally diverse aryl bromides.[a]

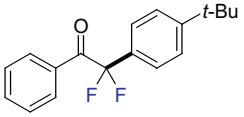




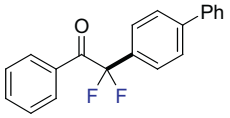
2a: 88%



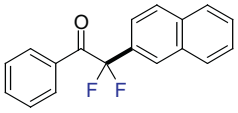
2b: 79%[c] (17% **2a**)



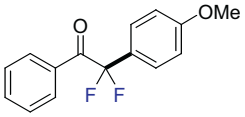
2c: 72%[c] (16% **2a**)



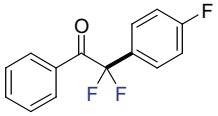
2d: 85%



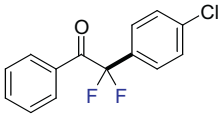
2e: 90%



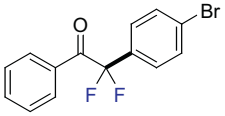
2f: 53%[d] (17% **2a**)



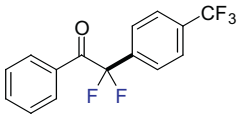
2g: 61%[c] (7% **2a**)



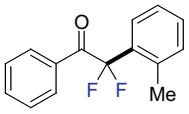
2h: 60%[c] (trace **2a**)



2i: 83%[e]



2j: 68%



2k: 52%

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), BINAP (20 mol%), **1** (1 equiv.), aryl bromide (2 equiv.), Cs_2CO_3 (2 equiv.), xylene (0.2 M of **1**), 130 °C, 12 h.
[b] Isolated yield.
[c] Inseparable with **2a** by silica-gel column chromatography.
[d] Separable with **2a** by column chromatography.
[e] No double-arylated product was found.

partners. The α-arylation of α,α-difluoroketone **8** failed at 130 °C. Fortunately, the cross-coupling reaction of **8** with aryl bromides proceeded smoothly in mesitylene at 160 °C to afford a series of α-aryl-α,α-difluoro-1-(4-methoxyphenyl) ethanones **9** in good yields. Similarly, compound **9a** was formed as a by-product when 4-bromotoluene, 4-*tert*-butylbromobenzene and 1-bromo-4-methoxybenzene were used as coupling partners for α-arylation of α,α-difluoroketone **8**.

3. Conclusion

In summary, we have developed a versatile method to prepare α-aryl-α,α-difluoroketones in moderate to good yields by palladium-catalyzed direct α-arylation of α,α-difluoroketones with structurally diverse aryl bromides. This method provides a practical and straightforward synthetic route to α-aryl-α,α-difluorocarbonyl compounds.

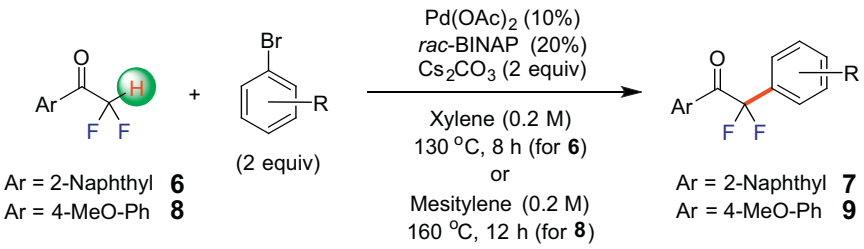
4. Experimental

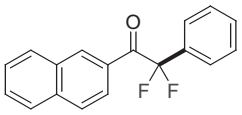
4.1. General

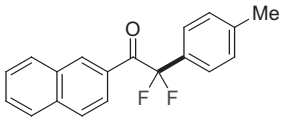
All reactions were carried out under an argon atmosphere. All commercially available reagents were used without further purification, unless specified otherwise. α,α-Difluoroketones **1**, **6** and **8** were prepared according to literature procedures [**4d**].

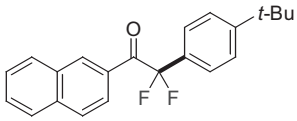
All new compounds were characterized by ^1H NMR, ^{19}F NMR, ^{13}C NMR, and IR spectroscopy, in addition to high-resolution mass spectroscopy. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer and Varian MR-400, respectively. All ^1H NMR experiments are reported in parts per million (ppm) downfield of TMS. All ^{13}C NMR spectra are reported in ppm and were obtained with ^1H decoupling. ^{19}F NMR spectra were recorded on a Bruker AM-300 spectrometer ($CFCl_3$ as outside standard and low field is positive). The following abbreviations were used to

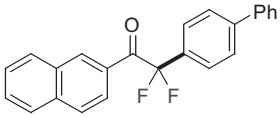
Table 3
Substrate scope of palladium catalyzed α-arylation of α,α-difluoroketones **6** and **8**.[a]

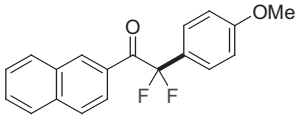


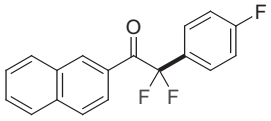

7a: 85%

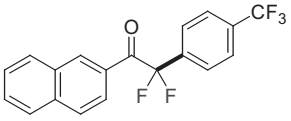

7b: 63%[c] (16% **7a**)

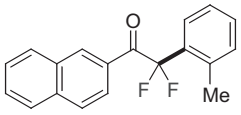

7c: 65%[c] (16% **7a**)

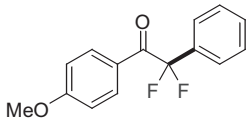

7d: 74%

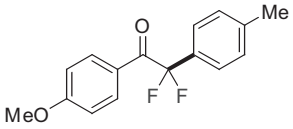

7e: 56%[d] (22% **7a**)

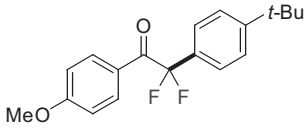

7f: 73%

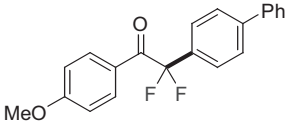

7g: 64%

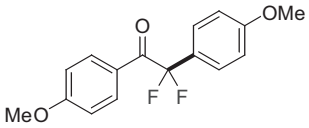

7h: 65%

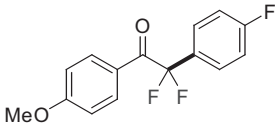

9a: 63%

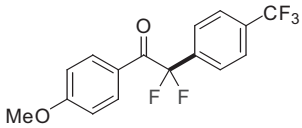

9b: 80%[e] (16% **9a**)


9c: 82%[f] (13% **9a**)


9d: 77%


9e: 69%[f] (22% **9a**)


9f: 75%


9g: 52%

[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), BINAP (20 mol%), **6** or **8** (1 equiv.), aryl bromide (2 equiv.), Cs_2CO_3 (2 equiv.), xylene (0.2 M), 130 °C, 8 h (for **6**) or mesitylene (0.2 M), 160 °C, 12 h (for **8**).
[b] Isolated yield.
[c] Inseparable with **7a** by silica-gel column chromatography.
[d] Separable with **7a** after column chromatography.
[e] Inseparable with **9a** by silica-gel column chromatography.
[f] Separable with **9a** after column chromatography.

explain the multiplicities: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet. Infrared spectra were recorded on a Bio-Rad FTS-185 system. LRMS analyses were performed on Agilent 5973N (EI, 70 eV) and HRMS on Waters Micromass GCT Premier.

4.2. General procedure for Pd-catalyzed α-arylation of α,α-difluoroketone with aryl bromides

An oven-dried Schlenk tube containing a magnetic stirring bar was charged with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), *rac*-BINAP (62.3 mg, 0.10 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon for three times. Xylene (2.5 mL) was added through the septum via syringe and the resulting mixture was stirred at room temperature for 15 min. Then α,α-difluoroketone (0.5 mmol) and aryl bromide (1.0 mmol) were added. The Schlenk tube was sealed and the reaction mixture was heated at 130 °C with vigorous stirring for 12 h. The reaction mixture was cooled to room temperature and quenched with H_2O (20 mL). The solution was extracted with ether (3 × 10 mL), and the combined organic layers were washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using petroleum ether/diethyl ether (40/1) as eluent.

4.2.1. 2,2-Difluoro-1,2-diphenylethanone (2a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.56–7.63 (m, 3H), 7.41–7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (t, *J* = 30.6 Hz), 134.2, 133.2 (t, *J* = 25.5 Hz), 132.2, 130.9, 130.3 (t, *J* = 2.9 Hz), 128.9, 128.7, 125.7 (t, *J* = 5.9 Hz), 117.0 (t, *J* = 252.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.2 (s, 2F). IR (neat, cm^{-1}): 1704, 1597, 1450, 1255, 1135. MS (EI): *m*/*z* (%) 77 (43), 105 (100), 127 (10), 232 (0.23, M^+). HRMS: Calcd. for $C_{14}H_{10}F_2O$: 232.0700; found: 232.0702. Anal. Calcd. for $C_{14}H_{10}F_2O$: C, 72.41; H, 4.34. Found: C, 72.49; H, 4.37.

4.2.2. 2,2-Difluoro-1-phenyl-2-p-tolylethanone (2b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.40–7.62 (m, 5H), 7.25 (d, *J* = 8.1 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (t, *J* = 30.6 Hz), 141.2, 134.1, 130.3 (t, *J* = 2.9 Hz), 130.0, 128.9, 128.7, 128.6, 125.6 (t, *J* = 5.9 Hz), 117.1 (t, *J* = 251.6 Hz), 21.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.5 (s, 2F). IR (neat, cm^{-1}): 1701, 1597, 1259, 1123, 817. MS (EI): *m*/*z* (%) 77 (31), 105 (100), 141 (9), 246 (2, M^+). HRMS: Calcd. for $C_{15}H_{12}F_2O$: 246.0856; found: 246.0857. Anal. Calcd. for $C_{15}H_{12}F_2O$: C, 73.16; H, 4.91. Found: C, 73.61; H, 5.00.

4.2.3. 2-(4-tert-Butylphenyl)-2,2-difluoro-1-phenylethanone (2c)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.41–7.63 (m, 7H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (t, *J* = 30.6 Hz), 154.3, 134.1, 130.3 (t, *J* = 2.9 Hz), 128.9, 128.6, 125.8, 125.4 (t, *J* = 5.8 Hz), 117.2 (t, *J* = 251.6 Hz), 34.9, 31.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.4 (s, 2F). IR (neat, cm^{-1}): 1704, 1597, 1266, 1124. MS (EI): *m*/*z* (%) 77 (29), 105 (100), 183 (6), 288 (1, M^+). HRMS: Calcd. for $C_{18}H_{18}F_2O$: 288.1326; found: 288.1327. Anal. Calcd. for $C_{18}H_{18}F_2O$: C, 74.98; H, 6.29. Found: C, 75.44; H, 6.18.

4.2.4. 2-(Biphenyl-4-yl)-2,2-difluoro-1-phenylethanone (2d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.38–7.68 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (t, *J* = 30.6 Hz), 134.2, 132.0 (t, *J* = 24.8 Hz), 130.3 (t, *J* = 2.9 Hz), 128.9, 128.8, 128.7, 128.6, 128.0, 127.6, 127.3, 126.2 (t, *J* = 5.8 Hz), 117.1 (t, *J* = 251.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.7 (s, 2F). IR (neat, cm^{-1}): 1702, 1613, 1243, 1050. MS (EI): *m*/*z* (%) 77 (34), 105 (100), 130 (16), 308 (2, M^+). HRMS: Calcd. for $C_{20}H_{14}F_2O$: 308.1013; found: 308.1010.

4.2.5. 2,2-Difluoro-2-(naphthalen-2-yl)-1-phenylethanone (2e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85–8.12 (m, 6H), 7.40–7.68 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1 (t, *J* = 31.3 Hz), 134.2, 132.6, 132.3, 130.3 (t, *J* = 2.9 Hz), 129.0, 128.8, 128.7, 127.9, 127.8, 127.0, 126.0 (t, *J* = 6.6 Hz), 122.1 (t, *J* = 6.1 Hz), 117.2 (t, *J* = 251.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.4 (s, 2F). IR (neat, cm^{-1}): 1707, 1596, 1188, 1107. MS (EI): *m*/*z* (%) 77 (32), 105 (100), 177 (13), 282 (4, M^+). HRMS: Calcd. for $C_{18}H_{12}F_2O$: 282.0856; found: 282.0853.

4.2.6. 2,2-Difluoro-2-(4-methoxyphenyl)-1-phenylethanone (2f)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.52–7.59 (m, 3H), 7.42 (t, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (t, *J* = 31.4 Hz), 161.6, 134.1, 132.3, 130.3 (t, *J* = 2.9 Hz), 128.6, 127.3 (t, *J* = 5.8 Hz), 125.2 (t, *J* = 24.8 Hz), 117.1 (t, *J* = 250.9 Hz), 114.3, 55.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.9 (s, 2F). IR (neat, cm^{-1}): 2928, 1704, 1600, 1508, 1264, 1178. MS (EI): *m*/*z* (%) 77 (30), 105 (74), 157 (100), 262 (5, M^+). HRMS: Calcd. for $C_{15}H_{12}F_2O_2$: 262.0805; found: 262.0807. Anal. Calcd. for $C_{15}H_{12}F_2O_2$: C, 68.70; H, 4.61. Found: C, 69.02; H, 4.94.

4.2.7. 2,2-Difluoro-2-(4-fluorophenyl)-1-phenylethanone (2g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.58–7.63 (m, 3H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8 (t, *J* = 31.4 Hz), 164.2 (d, *J* = 249.3 Hz), 134.4, 132.1, 130.3 (t, *J* = 2.9 Hz), 128.7, 128.1 (dt, *J* = 8.8, 5.8 Hz), 125.7 (t, *J* = 5.9 Hz), 116.7 (t, *J* = 252.3 Hz), 116.0 (d, *J* = 22.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −92.7 (s, 2F), −105.2 (s, 1F). IR (neat, cm^{-1}): 1701, 1607, 1511, 1237, 1134. MS (EI): *m*/*z* (%) 77 (42), 105 (100), 145 (11), 250 (0.16, M^+). HRMS: Calcd. for $C_{14}H_9F_3O$: 250.0605; found: 250.0602.

4.2.8. 2-(4-Chlorophenyl)-2,2-difluoro-1-phenylethanone (2h)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.42–7.63 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 (t, *J* = 30.6 Hz), 137.3 (t, *J* = 2.2 Hz), 134.4, 132.0, 131.7 (t, *J* = 25.5 Hz), 130.3 (t, *J* = 2.9 Hz), 129.2, 128.8, 127.3 (t, *J* = 5.8 Hz), 116.7 (t, *J* = 253.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.8 (s, 2F). IR (neat, cm^{-1}): 1702, 1598, 1492, 1252, 1135. MS (EI): *m*/*z* (%) 77 (38), 105 (100), 161 (6). HRMS: Calcd. for $C_{14}H_9ClF_2O$: 266.0310; found: 266.0306.

4.2.9. 2-(4-Bromophenyl)-2,2-difluoro-1-phenylethanone (2i)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.2 Hz, 2H), 7.59–7.62 (m, 3H), 7.44–7.49 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 (t, *J* = 30.6 Hz), 134.4, 132.1, 130.3 (t, *J* = 2.9 Hz), 128.8, 127.5 (t, *J* = 5.9 Hz), 125.6, 116.7 (t, *J* = 252.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.0 (s, 2F). IR (neat, cm^{-1}): 1692, 1594, 1252, 1122. MS (EI): *m*/*z* (%) 77 (29), 105 (100), 205, 207 (3), 310, 312 (0.19, M^+). HRMS: Calcd. for $C_{14}H_9BrF_2O$: 309.9805; found: 309.9801.

4.2.10. 2,2-Difluoro-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethanone (2j)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.74 (s, 4H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4 (t, *J* = 31.3 Hz), 136.8 (t, *J* = 24.0 Hz), 134.6, 133.1 (d, *J* = 32.8 Hz), 131.9, 130.3 (t, *J* = 2.9 Hz), 128.8, 126.5 (t, *J* = 5.9 Hz), 125.8 (q, *J* = 3.6 Hz), 123.6 (q, *J* = 270.5 Hz), 116.5 (t, *J* = 253.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −63.5 (s, 3F), −98.3 (s, 2F). IR (neat, cm^{-1}): 1713, 1596, 1337, 1121, 1072. MS (EI): *m*/*z* (%) 77 (35), 84 (100), 86 (60), 105 (75), 281 (0.75, $[M–F]^+$). HRMS: Calcd. for $C_{15}H_9F_4O$ $[M–F]^+$: 281.0590; found: 281.0589. Anal. Calcd. for $C_{15}H_9F_5O$: C, 60.01; H, 3.02. Found: C, 60.55; H, 3.24.

4.2.11. 2,2-Difluoro-1-phenyl-2-o-tolylethanone (2k)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.22–7.64 (m, 7H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8

(t, J = 31.4 Hz), 136.9 (t, J = 3.7 Hz), 134.1, 132.4, 132.0, 131.8, 130.8, 130.3 (t, J = 3.0 Hz), 128.6, 126.1 (t, J = 8.0 Hz), 125.9, 117.6 (t, J = 251.5 Hz), 20.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.5 (s, 2F). IR (neat, cm^{-1}): 1701, 1597, 1448, 1237, 1117. MS (EI): m/z (%) 77 (29), 105 (100), 141 (7), 246 (2, M^+). HRMS: Calcd. for $C_{15}H_{12}F_2O$: 246.0856; found: 246.0859.

*4.2.12. 2,2-Difluoro-1-(naphthalen-2-yl)-2-phenylethanone (**7a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.83–7.93 (m, 3H), 7.46–7.68 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9 (t, J = 30.6 Hz), 135.9, 133.4 (t, J = 24.8 Hz), 133.0, 132.3, 131.0, 130.1, 129.5, 129.4, 128.9, 128.6, 127.8, 127.0, 125.7 (t, J = 5.8 Hz), 125.0, 117.2 (t, J = 251.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.5 (s, 2F). IR (neat, cm^{-1}): 1701, 1627, 1266, 1108, 926, 699. MS (EI): m/z (%) 127 (65), 155 (100), 282 (4, M^+). HRMS: Calcd. for $C_{18}H_{12}F_2O$: 282.0856; found: 282.0857.

*4.2.13. 2,2-Difluoro-1-(naphthalen-2-yl)-2-p-tolylethanone (**7b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.80–7.85 (m, 2H), 7.46–7.59 (m, 4H), 7.25 (d, J = 8.7 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1 (t, J = 31.4 Hz), 141.3, 135.9, 133.0, 132.3, 131.0, 130.5 (t, J = 26.3 Hz), 130.1, 129.6, 129.3, 128.9, 128.5, 127.8, 127.0, 125.7 (t, J = 5.8 Hz), 125.1, 117.4 (t, J = 252.3 Hz), 21.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.9 (s, 2F). IR (neat, cm^{-1}): 1706, 1627, 1266, 1043, 765. MS (EI): m/z (%) 127 (62), 155 (100), 296 (2, M^+). HRMS: Calcd. for $C_{19}H_{14}F_2O$: 296.1013; found: 296.1014.

*4.2.14. 2-(4-tert-Butylphenyl)-2,2-difluoro-1-(naphthalen-2-yl)ethanone (**7c**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.81–7.86 (m, 2H), 7.46–7.61 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1 (t, J = 30.6 Hz), 154.3, 135.9, 133.0 (t, J = 3.6 Hz), 132.3, 130.7 (t, J = 24.8 Hz), 130.1, 129.6, 129.3, 128.9, 128.5, 127.8, 127.0, 125.9, 125.5 (t, J = 5.8 Hz), 125.1, 117.4 (t, J = 251.6 Hz), 34.9, 31.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.8 (s, 2F). IR (neat, cm^{-1}): 2964, 1701, 1626, 1270, 1107. MS (EI): m/z (%) 127 (70), 155 (100), 173 (17), 338 (0.58, M^+). HRMS: Calcd. for $C_{22}H_{20}F_2O$: 338.1482; found: 338.1486.

*4.2.15. 2-(Biphenyl-4-yl)-2,2-difluoro-1-(naphthalen-2-yl)ethanone (**7d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.85–7.91 (m, 2H), 7.38–7.76 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9 (t, J = 31.6 Hz), 143.9, 140.0, 136.0, 133.0 (t, J = 4.0 Hz), 132.3, 132.1 (t, J = 25.3 Hz), 130.1, 129.6, 129.4, 128.9, 128.6, 128.0, 127.8, 127.6, 127.3, 127.0, 126.2 (t, J = 5.5 Hz), 125.0, 117.3 (t, J = 252.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −97.1 (s, 2F). IR (neat, cm^{-1}): 1698, 1627, 1266, 1049, 747. MS (EI): m/z (%) 127 (65), 155 (100), 203 (7, $[M–NapCO]^+$). HRMS: Calcd. for $C_{13}H_9F_2$ $[M–NapCO]^+$: 203.0672; found: 203.0675.

*4.2.16. 2,2-Difluoro-2-(4-methoxyphenyl)-1-(naphthalen-2-yl)ethanone (**7e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.84–7.88 (m, 2H), 7.52–7.65 (m, 4H), 6.96 (d, J = 8.7 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2 (t, J = 31.3 Hz), 161.6, 135.9, 132.9 (t, J = 3.6 Hz), 132.3, 130.0, 129.6, 129.3, 128.5, 127.8, 127.3 (t, J = 5.8 Hz), 127.0, 125.4 (t, J = 24.8 Hz), 125.1 (t, J = 2.2 Hz), 117.3 (t, J = 250.8 Hz), 114.3, 55.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.0 (s, 2F). IR (neat, cm^{-1}): 1697, 1614, 1519, 1275, 1180. MS (EI): m/z (%) 127 (18), 135 (100), 155 (30), 312 (1, M^+). HRMS: Calcd. for $C_{19}H_{14}F_2O_2$: 312.0962; found: 312.0963.

*4.2.17. 2,2-Difluoro-2-(4-fluorophenyl)-1-(naphthalen-2-yl)ethanone (**7f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.83–7.88 (m, 2H), 7.52–7.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7 (t, J = 30.6 Hz), 164.2 (d, J = 251.5 Hz), 136.0, 133.0 (t, J = 3.6 Hz), 132.3, 130.1, 129.5, 129.3, 128.6, 128.0–128.2 (m), 127.8, 127.1, 124.9 (t, J = 2.2 Hz), 116.9 (t, J = 252.2 Hz), 116.1, 115.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.3 (s, 2F), −109.4 (m, 1F). IR (neat, cm^{-1}): 1705, 1624, 1514, 1228, 591. MS (EI): m/z (%) 127 (69), 155 (100), 300 (2, M^+). HRMS: Calcd. for $C_{18}H_{11}F_3O$: 300.0762; found: 300.0759.

*4.2.18. 2,2-Difluoro-1-(naphthalen-2-yl)-2-(4-(trifluoromethyl)phenyl)ethanone (**7g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.86–7.92 (m, 2H), 7.73–7.81 (m, 4H), 7.55–7.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3 (t, J = 30.8 Hz), 136.9 (t, J = 25.3 Hz), 136.1, 133.0 (t, J = 3.9 Hz), 132.3, 130.1, 129.6, 129.1, 128.8, 127.8, 127.2, 126.5 (t, J = 6.4 Hz), 125.8 (q, J = 4.0 Hz), 124.8, 123.6 (q, J = 270.1 Hz), 116.7 (t, J = 253.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ −63.5 (s, 3F), −97.7 (s, 2F). IR (neat, cm^{-1}): 1712, 1333, 1121, 1070. MS (EI): m/z (%) 127 (71), 145 (17), 155 (100), 350 (1, M^+). HRMS: Calcd. for $C_{19}H_{11}F_5O$: 350.0730; found: 350.0736.

*4.2.19. 2,2-Difluoro-1-(naphthalen-2-yl)-2-o-tolylethanone (**7h**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.83–7.93 (m, 3H), 7.70 (d, J = 7.5 Hz, 1H), 7.51–7.64 (m, 2H), 7.22–7.40 (m, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7 (t, J = 31.4 Hz), 137.0 (t, J = 2.9 Hz), 135.9, 133.0 (t, J = 2.9 Hz), 132.3, 132.1, 132.0 (t, J = 22.6 Hz), 130.8, 130.1, 129.6, 129.3, 128.5, 127.8, 127.0, 126.2 (t, J = 8.0 Hz), 126.0, 125.0, 117.4 (t, J = 251.6 Hz), 20.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.9 (s, 2F). IR (neat, cm^{-1}): 1701, 1626, 1460, 1227, 1104. MS (EI): m/z (%) 127 (71), 155 (100), 296 (2, M^+). HRMS: Calcd. for $C_{19}H_{14}F_2O$: 296.1013; found: 296.1017.

*4.2.20. 2,2-Difluoro-1-(4-methoxyphenyl)-2-phenylethanone (**9a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 9.0 Hz, 2H), 7.60–7.62 (m, 2H), 7.45–7.47 (m, 3H), 6.91 (d, J = 9.3 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.4 (t, J = 29.9 Hz), 164.4, 133.6 (t, J = 24.8 Hz), 132.9 (t, J = 2.9 Hz), 130.8, 128.8, 125.6 (t, J = 5.9 Hz), 125.1, 117.1 (t, J = 250.8 Hz), 114.0, 55.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.7 (s, 2F). IR (neat, cm^{-1}): 2928, 1696, 1601, 1264, 1128. MS (EI): m/z (%) 77 (24), 92 (15), 135 (100), 262 (0.31, M^+). HRMS: Calcd. for $C_{15}H_{12}F_2O_2$: 262.0805; found: 262.0803.

*4.2.21. 2,2-Difluoro-1-(4-methoxyphenyl)-2-p-tolylethanone (**9b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5 (t, J = 29.9 Hz), 164.3, 132.9 (t, J = 2.9 Hz), 130.8 (t, J = 24.8 Hz), 129.5, 128.8, 125.5 (t, J = 5.9 Hz), 125.1, 117.2 (t, J = 250.8 Hz), 114.0, 55.5, 21.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.3 (s, 2F). IR (neat, cm^{-1}): 2936, 1698, 1600, 1264, 1121. MS (EI): m/z (%) 77 (14), 92 (10), 135 (100), 276 (0.31, M^+). HRMS: Calcd. for $C_{16}H_{14}F_2O_2$: 276.0962; found: 276.0965.

*4.2.22. 2-(4-tert-Butylphenyl)-2,2-difluoro-1-(4-methoxyphenyl)ethanone (**9c**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6 (t, J = 30.6 Hz), 164.3, 154.1, 132.9 (t, J = 2.9 Hz), 130.6 (t, J = 24.8 Hz), 125.8, 125.4 (t, J = 5.9 Hz), 125.1, 117.3 (t, J = 250.8 Hz), 114.0, 55.5, 34.9, 31.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −98.6 (s, 2F). IR (neat, cm^{-1}): 2963, 1696, 1601, 1508, 1263, 1140. MS (EI): m/z (%) 77

(12), 92 (8), 135 (100), 318 (0.16, M^+). HRMS: Calcd. for $C_{19}H_{20}F_2O_2$: 318.1431; found: 318.1435.

*4.2.23. 2-(Biphenyl-4-yl)-2,2-difluoro-1-(4-methoxyphenyl)ethanone (**9d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 8.7 Hz, 2H), 7.67 (s, 4H), 7.57 (d, J = 7.8 Hz, 2H), 7.37–7.47 (m, 3H), 6.92 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.4 (t, J = 29.8 Hz), 164.5, 143.8, 140.0, 132.9 (t, J = 2.9 Hz), 132.4 (t, J = 24.8 Hz), 129.0, 128.0, 127.5, 127.3, 126.1 (t, J = 5.9 Hz), 125.0, 117.2 (t, J = 251.6 Hz), 114.1, 55.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −96.5 (s, 2F). IR (neat, cm^{-1}): 1694, 1602, 1270, 1177. MS (EI): m/z (%) 77 (16), 92 (10), 135 (100), 338 (0.26, M^+). HRMS: Calcd. for $C_{21}H_{16}F_2O_2$: 338.1118; found: 338.1115.

*4.2.24. 2,2-Difluoro-1,2-bis(4-methoxyphenyl)ethanone (**9e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.6 (t, J = 30.6 Hz), 164.3, 161.4, 132.9 (t, J = 2.9 Hz), 127.2 (t, J = 5.9 Hz), 125.7 (t, J = 25.5 Hz), 125.1, 117.2 (t, J = 250.9 Hz), 114.2, 114.0, 55.5, 55.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.3 (s, 2F). IR (neat, cm^{-1}): 2925, 1689, 1600, 1255, 1175. MS (EI): m/z (%) 77 (15), 92 (11), 135 (100), 292 (1, M^+). HRMS: Calcd. for $C_{16}H_{14}F_2O_3$: 292.0911; found: 292.0915.

*4.2.25. 2,2-Difluoro-2-(4-fluorophenyl)-1-(4-methoxyphenyl)ethanone (**9f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 8.7 Hz, 2H), 7.57–7.62 (m, 2H), 7.14 (t, J = 8.4 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.1 (t, J = 30.6 Hz), 164.5, 164.1 (d, J = 249.4 Hz), 132.9 (t, J = 3.0 Hz), 129.5 (d, J = 26.2 Hz), 127.9–128.1 (m), 124.9, 116.8 (t, J = 252.3 Hz), 116.0, 115.8, 114.1, 55.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −95.6 (s, 2F), −108.9 (m, 1F). IR (neat, cm^{-1}): 2925, 1691, 1601, 1509, 1264, 1133. MS (EI): m/z (%) 77 (20), 92 (14), 135 (100), 280 (0.17, M^+). HRMS: Calcd. for $C_{15}H_{11}F_3O_2$: 280.0711; found: 288.0713.

*4.2.26. 2,2-Difluoro-1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)ethanone (**9g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 8.7 Hz, 2H), 7.73 (s, 4H), 6.94 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.7 (t, J = 29.9 Hz), 164.7, 137.2 (t, J = 24.7 Hz), 132.9 (t, J = 2.9 Hz), 126.4 (t, J = 5.9 Hz), 125.7 (q, J = 3.6 Hz), 124.7, 123.6 (q, J = 270.5 Hz), 116.6 (t, J = 253.8 Hz), 114.2, 55.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.7 (s, 3F), −97.2 (s, 2F). IR (neat, cm^{-1}): 2936, 1693, 1601, 1326, 1267, 1131, 616. MS (EI): m/z (%) 77 (15), 92 (11), 135 (100), 330 (0.12, M^+). HRMS: Calcd. for $C_{16}H_{11}F_5O_2$: 330.0679; found: 330.0675.

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