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p-Toluenesulfonic Acid Induced Conversion of Fluorinated Trimethylsilylethynylanilines into Aminoacetophenones: Versatile Precursors for the Synthesis of Benzoazaheterocycles

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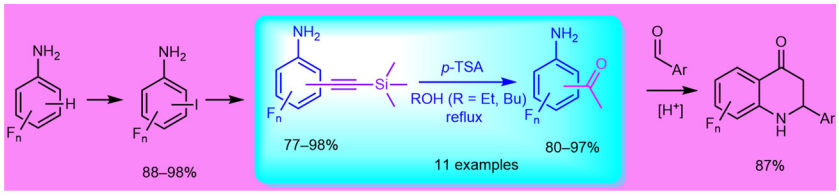

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Abstract A simple and efficient approach to the synthesis of fluorinated amino-substituted acetophenones in good to excellent yields is reported. The heart of the proposed method consists of conversion of a $Me_3Si–C≡C–$ moiety into a MeC(=O)– group in the presence of *p*-toluenesulfonic acid (*p*-TSA) passing a stage of ethynylaniline formation. The reaction is metal-free, proceeds under mild conditions, and uses readily available starting compounds (trimethylsilylarylacetylene derivatives). The reaction provides access to amino-substituted acetophenones, which may serve as precursors for the synthesis of polyfluorinated azaheterocycles, having potential anticarcinogenic activity.

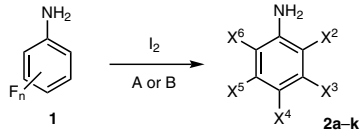
Key words alkynes, hydration, polyfluoroarenes, aryl methyl ketones, polyfluorinated azaheterocycles

Alkynes, a major class of organic compounds, have been extensively used as building blocks and multipurpose synthons in organic synthesis. In all cases, transformation of alkynes into carbonyl compounds through hydration is a key conversion in organic synthesis with perfect atom economy.[1] This reaction has been known since the 19th century,[2] but has yet to gain popularity in the industry and among academic laboratories. The classical synthetic procedure requires a stoichiometric amount of mercury under acidic conditions.[3] The toxicity of mercury and the necessity of a strong acid have limited the applications of this procedure. In recent years, numerous attempts were made to develop mercury-free alkyne hydration methods. As a result, new procedures of alkyne hydration in the presence of metal complexes containing Pt,[4] Au,[5] Ru,[6] Rh,[7] Pd,[8] Tl,[9] Ir,[10] Zr,[11] Ag,[12] Co,[13] or Fe[14] ions have been elaborated. Nevertheless, the use of substantial amounts of expensive noble-metal catalysts limits the practical utility of most of these methods. Other alternatives require the presence of a strong acid such as H_2SO_4,[15] HCO_2H,[16] TfOH,[17] or Tf_2NH,[17a] which may not be compatible in terms of selectivity in the case of functionalized substrates.

Recently, *p*-toluenesulfonic acid (*p*-TSA)-catalyzed hydration of various unsymmetrical arylated alkynes was devised.[18] The process consists of a reaction in a boiling aqueous or alcoholic medium in the presence of *p*-TSA. This new convenient procedure – which is characterized by the mildness of reaction conditions, inexpensive reactants, and excellent functional-group tolerance – allows for the formation of the corresponding Markovnikov adducts in good to excellent yields.[18,19]

We are currently investigating efficient strategies for the preparation of polyfluorinated heterocyclic derivatives (indoles[20,21] and 2,3-dihydroquinolinones[22]), via the development of methods based on transformations of alkynylanilines. Given that the polyfluorinated scaffolds often show more pronounced cytotoxic activity in comparison with less fluorinated analogues,[22] synthesis of new heterocyclic fluorinated structures having potentially biological activity is a challenging synthetic task. Here we describe a simple and effective pathway of conversion of fluorinated iodoanilines into trimethylsilyl derivatives and further to aminoacetophenones. The pathway includes an improved method of transformation of $Me_3Si–C≡C–$ moiety into acetyl group in the presence of *p*-TSA[18b,19a,c] to give fluorinated aminoacetophenones. This one-pot synthesis allows to avoid the hydrolysis of trimethylsilylethynylanilines.[16a] The synthesized aminoacetophenones may serve as 'off-the-shelf compounds' for preparation of five- or six-membered azaheterocycles via condensation reactions with aldehydes,[23] hydrazines,[24] or cynamides,[25] and the whole process represents a convenient approach to the conversion of ketones into cyclic derivatives.

The starting materials for this study (a representative series of iodoanilines fluorinated to various degrees: **2a–k**) were prepared according to our earlier published procedures[20–22,26] (Scheme 1).



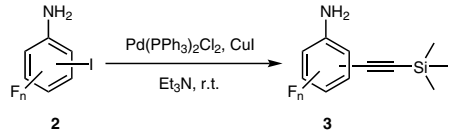
	X²	X³	X⁴	X⁵	X⁶		
a	I	H	F	F	H	(B)[26]	
b	I	H	F	H	F	(A)[26]	
c	I	F	F	H	F	(A)[26]	
d	I	H	F	F	F	(A)	88%
e	I	F	F	F	F	(A)[26]	
f	I	F	CF_3	F	F	(A)[26]	
g	H	H	I	F	H	(B)[22]	
h	F	H	I	F	H	(B)[21]	
i	F	F	I	F	F	(A)[21]	
j	I	H	I	F	H	(B)[22]	
k	I	F	I	H	F	(A)	98%

Scheme 1 Preparation of the starting materials **2a–k** (A: HIO_3/1,4-dioxane/H_2O, reflux; B: $NaHCO_3$/H_2O, r.t.)

The Sonogashira conditions and bis(triphenylphosphine)palladium dichloride and copper(I) iodide as catalysts in anhydrous triethylamine as a solvent caused the cross-coupling of iodoanilines **2a–k** with the trimethylsilylacetylene, thus yielding arylacetylenes **3a–k**. The reactions were carried out at room temperature in a tightly closed Schlenk flask in an argon atmosphere. In each case, the reaction was terminated after disappearance of ^{19}F NMR signals belonging to the starting compounds. Deactivated aryl iodides **2c**, **2e**, **2f**, and **2i** were also successfully coupled with trimethylsilylacetylene (Table 1, entries 3, 5, 6, and 9), but more than 70 hours were required for complete conversion. The data on optimized experimental conditions and the yields of the products formed are summarized in Table 1. Target compounds **3** were isolated by thin-layer chromatography.

Successful preparation of trimethylsilylarylacetylenes **3a–k** allowed us to examine their reactivity in the *p*-TSA/alcohol media. As shown in Table 2, in most cases, the reaction was conducted in refluxing EtOH for 10 hours. Under these conditions, the triple bond was regioselectively hydrated with simultaneous leaving of the Me_3Si group, thus giving polyfluorinated amino-substituted acetophenones **4** in good yields. Compound **3f** was found to have low reactivity and remained unchanged at reflux in EtOH in the presence of *p*-TSA. Nevertheless, harsher conditions (boiling BuOH) produced ketone **4f** in 95% yield (Table 2, entry 6).

Table 1 Synthesis of Fluorinated Trimethylsilylarylacetylenes **3a–k**



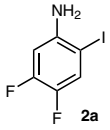
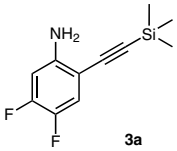
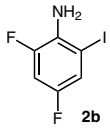
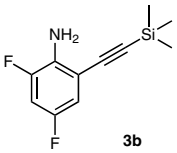
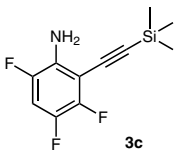
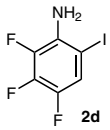
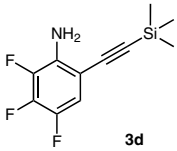
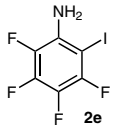
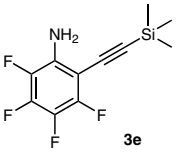
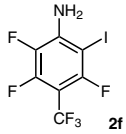
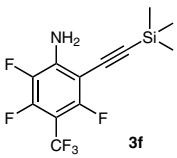
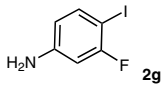
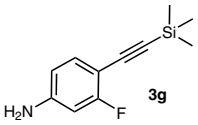
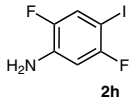
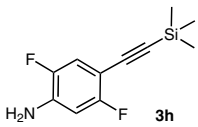
Entry	Iodoaniline **2**	Arylacetylene **3**	Time (h)	Yield (%)
1	 **2a**	 **3a**	20	89
2	 **2b**	 **3b**	20	77
3	 **2c**	 **3c**	97	92
4	 **2d**	 **3d**	42	91
5	 **2e**	 **3e**	72	88
6	 **2f**	 **3f**	117	93
7	 **2g**	 **3g**	46	97
8	 **2h**	 **3h**	20	97

Table 1 (continued)

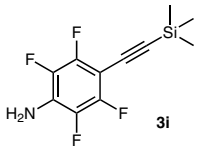
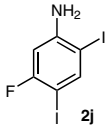
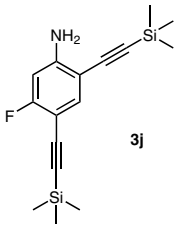
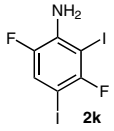
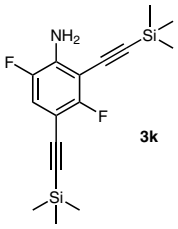
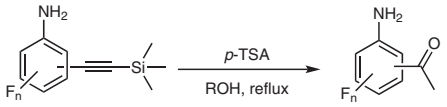
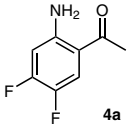
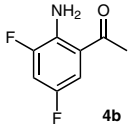
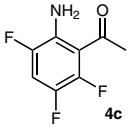
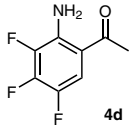
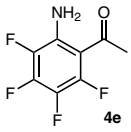
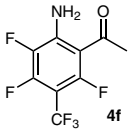
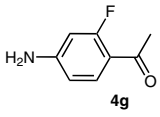
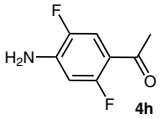
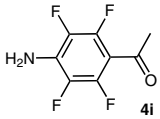
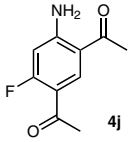
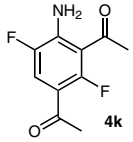
Entry	Iodoaniline **2**	Arylacetylene **3**	Time (h)	Yield (%)
9	 **2i**	 **3i**	115	98
10	 **2j**	 **3j**	48	98
11	 **2k**	 **3k**	20	88

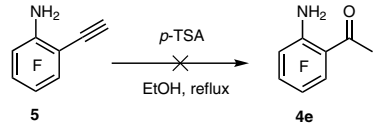
Table 2 Synthesis of Fluorinated Methyl Aryl Ketones **4a–k**



3 **4**

Entry	Acetylene **3**	Aryl ketone **4**	ROH R	Yield (%)
1	**3a**	 **4a**	Et	93
2	**3b**	 **4b**	Et	91
3	**3c**	 **4c**	Et	93
4	**3d**	 **4d**	Et	97
5	**3e**	 **4e**	Et	83
6	**3f**	 **4f**	*n*-Bu	95
7	**3g**	 **4g**	Et	85
8	**3h**	 **4h**	Et	96
9	**3i**	 **4i**	Et	96
10	**3j**	 **4j**	Et	80
11	**3k**	 **4k**	Et	83

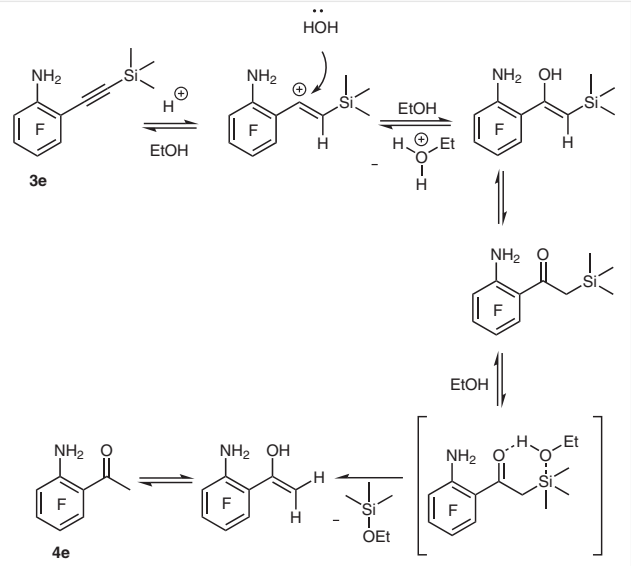
It should be noted that the trimethylsilyl group effectively activates the triple bond in arylacetylenes **3** for the hydration reaction (in comparison with the hydrogen atom). Thus, 2-ethynyl-3,4,5,6-tetrafluoroaniline (**5**), prepared as described elsewhere,[26] remained intact at reflux in EtOH for 20 hours in the presence of *p*-TSA (Scheme 2).



5 **4e**

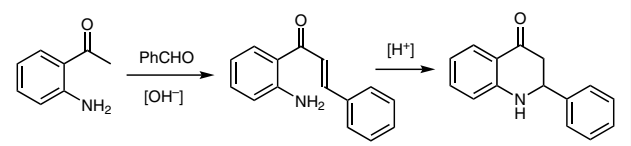
Scheme 2 Inertness of 2-ethynyltetrafluoroaniline **5** toward hydration in system *p*-TSA/EtOH

The proposed mechanism for the formation of methyl aryl ketone **4e** from trimethylsilylarylacetylene **3e** is shown in Scheme 3. Initially, the protonation of the alkynylaniline gives the vinyl carbocation stabilized by the *o*-amino-group effect. Subsequent addition of a water molecule yields an enol tautomerizing into the more stable keto form. At the next step, the alcohol's O atom attacks the electrophilic Si atom. The process is assisted by formation of the intramolecular hydrogen bond and proceeds via the corresponding enol into aryl ketone **4e**.



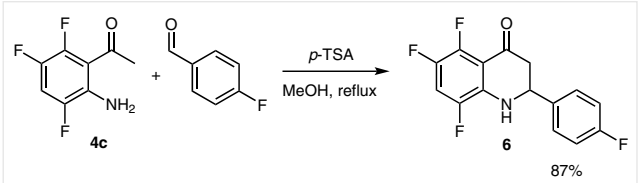
Scheme 3 Proposed mechanism for the formation of **4e**

It is known that amino-substituted acetophenones are valuable precursors for the synthesis of medicinally important substances such as 2-arylquinolin-4(1*H*)-ones and their analogues.[23,27] In recent years, interest in these compounds prompted extensive studies on their properties, such as toxicity to human tumor cell lines and tubulin polymerization inhibition.[28,29] The method most widely used to prepare 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones includes a two-step sequence consisting of base-catalyzed aldol condensation of 2-aminoacetophenone and aldehyde and then acid-catalyzed cyclization of the corresponding 2-aminochalcones thus formed via an intramolecular aza-Michael reaction[27,29,30] (Scheme 4).



Scheme 4 Synthesis of a typical 2-aryl-2,3-dihydroquinolin-4-one[27,29,30]

We evaluated the possibility of synthesis of polyfluorinated 2-aryl-2,3-dihydroquinolin-4(1*H*)-one **6** directly from 2-aminoacetophenone **4c** and *p*-fluorobenzaldehyde in one step, using *p*-TSA as the catalyst and MeOH as the solvent. Fortunately, the desired product **6** was formed in good yield (87%; Scheme 5).



Scheme 5 Preparation of 5,6,8-trifluoro-2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (**6**)

Due to ease and high efficiency, this method shows promise for the synthesis of a large series of bioactive fluorinated 2-aryl-2,3-dihydro-4-quinolones, thereby facilitating biological and medicinal studies on such compounds.

In conclusion, we have shown possibilities of a simple and efficient one-pot transformation of a $Me_3Si–C≡C–$ moiety into a MeC(=O)– group in the presence of *p*-TSA. This conversion was successfully employed for the synthesis of a broad family of fluorinated amino-substituted acetophenones. The presence of the Me_3Si-group at the triple bond leads to selective formation of exclusively carbonyl compounds, unlike transformations that can be realized with the participation of arylalkynes in similar reaction conditions (*p*-TSA/alcohol).[19a,31] The obtained acetophenones could be used for preparation of a diverse and potentially biologically important fluorinated heterocyclic library. In this work, it was exemplified by the synthesis of a fluorinated 2-aryl-2,3-dihydro-4-quinolone.

All solvents were purified using standard procedures. Et_3N was distilled and kept over CaH_2 before use. The starting materials were synthesized according to previously described methods. Other chemicals were obtained from commercial sources and were used without further purification. Preparative TLC was performed on Merck precoated silica gel 60 PF_{254} containing gypsum. Visualization of the developed chromatograms was performed by UV light. To obtain analytically pure samples, the solid synthesized compounds were crystallized from hexane. NMR spectra were recorded on a Bruker Avance-300 (300.13 MHz for ^1H and 282.37 MHz for ^{19}F), Avance-400 (400.13 MHz for ^1H, 376.44 MHz for ^{19}F and 100.62 MHz for ^{13}C), and DRX-500 (500.13 MHz for ^1H, 125.76 MHz for ^{13}C) spectrometers. $CDCl_3$ and acetone-d_6 were used as solvents, with residual $CHCl_3$ (δ_H = 7.26) or $CDCl_3$ (δ_C = 77.0) and acetone (δ_H = 2.15) or acetone-d_6 (δ_C = 28.6 and 205.0) being employed as internal standards. C_6F_6 (δ_F = 163.0) was used as external reference for recording the ^{19}F NMR spectra. ^{13}C NMR spectra were recorded with C–H spin decoupling. Masses of molecular ions were determined by HRMS on a DFS Thermoscientific instrument (EI, 70 eV). Melting points were recorded on a Mettler-Toledo FP81 Thermosystem apparatus. The IR spectra were recorded on a

Bruker Vector 22 spectrometer (KBr or thin film). Elemental analyses were performed on a Euro EA-3000 CHNS analyzer, or on Carlo Erba 1106 CHN elemental analyzer.

Iodoanilines 2; General Procedure

To a stirred solution of aniline **1** (8 mmol) in 1,4-dioxane (60 mL) were added a solution of HIO_3 (2.8 g, 16 mmol) in H_2O (20 mL) and then finely ground I_2 (2.0 g, 8 mmol). The reaction mixture was refluxed for 5 h, cooled to r.t., poured into H_2O (50 mL), and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with sat. aq $Na_2S_2O_3$ (2 × 50 mL), H_2O (2 × 70 mL), dried ($MgSO_4$), and purified by flash chromatography on Al_2O_3 using CH_2Cl_2 as the eluent.

2,3,4-Trifluoro-6-iodoaniline (2d)

Brown oil; yield: 1.90 g (88%).

IR (neat): 3475, 3379, 1595, 1502, 1477, 1335, 1296, 1151, 1038, 995, 850, 787, 706, 530 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.17 [m, J (H^5,F^4) = 9.8 Hz, J (H^5,F^3) = 7.7 Hz, J (H^5,F^2) = 2.5 Hz, 1 H, H^5], 4.50 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 143.0 [dm, ^1J (C^4,F^4) = 241.9 Hz, ^2J (C^4,F^3) = 10.7 Hz, C^4], 140.3 [dm, ^1J (C^3,F^3) = 248.4 Hz, ^2J (C^3,F) = 14.0 Hz, C^3], 138.6 [dm, ^1J (C^2,F^2) = 246.0 Hz, ^2J (C^2,F^3) = 12.4 Hz, C^2], 135.0 [d, ^2J (C^1,F^2) = 10.8 Hz, C^1], 120.5 [dd, ^2J (C^5,F^4) = 9.9 Hz, ^3J (C^5,F^3) = 3.6 Hz, C^5], 73.7 (m, C^6).

^{19}F NMR (282 MHz, acetone-d_6): δ = –149.4 [dd, J (F^4,F^3) = 20.6 Hz, J (F^4,H^5) = 9.7 Hz, 1 F, F^4], –150.4 (dm, J (F^2,F^3) = 19.0 Hz, J (F^2,H^5) = 2.5 Hz, F^2], –159.6 [ddd, J (F^3,F^4) = 20.6 Hz, J (F^3,F^2) = 19.0 Hz, J (F^3,H^5) = 7.7 Hz, 1 F, F^3].

HRMS (EI): m/z $[M]^+$ calcd for $C_6H_3F_3IN$: 272.9257; found: 272.9256.

Anal. Calcd for $C_6H_3F_3IN$: C, 26.40; H, 1.11; N, 5.13. Found: C, 26.73; H, 1.26; N, 5.10.

3,6-Difluoro-2,4-diiodoaniline (2k)

Yellowish solid; yield: 2.99 g (98%); mp 68.1–68.9 °C.

IR (KBr): 3448, 3398, 3304, 3184, 1718, 1622, 1581, 1484, 1408, 1325, 1288, 1209, 1180, 1097, 858, 839, 748, 712, 646, 607, 492 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.41 [dd, J (H^5,F^6) = 10.1 Hz, J (H^5,F^3) = 5.8 Hz, 1 H, H^5], 5.28 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 157.1 [d, ^1J (C^3,F^3) = 233.0 Hz, C^3], 145.8 [d, ^1J (C^6,F^6) = 243.1 Hz, C^6], 139.2 [dd, ^2J (C^1,F^6) = 15.2 Hz, ^3J (C^1,F^3) = 4.9 Hz, C^1], 123.4 [dd, ^2J (C^5,F^6) = 23.0 Hz, ^3J (C^5,F^3) = 3.1 Hz, C^5], 69.6 [dd, ^2J (C^2,F^3) = 34.0 Hz, ^3J (C^2,F^6) = 2.8 Hz, C^2], 59.1 [dd, ^2J (C^4,F^3) = 32.9 Hz, ^3J (C^4,F^6) = 8.2 Hz, C^4].

^{19}F NMR (282 MHz, acetone-d_6): δ = –76.4 [dd, J (F^3,F^6) = 12.3 Hz, J (F^3,H^5) = 5.8 Hz, 1 F, F^3], –132.2 [dd, J (F^6,F^3) = 12.3 Hz, J (F^6,H^5) = 10.1 Hz, 1 F, F^6].

HRMS (EI): m/z $[M]^+$ calcd for $C_6H_3F_2I_2N$: 380.8317; found: 380.8319.

Trimethylsilylarylacetylenes 3; General Procedure

To a solution of iodoaniline **2** (5.00 mmol) and ethynyltrimethylsilane (1.47 g, 15.00 mmol) in Et_3N (10 mL) in a Schlenk flask under argon were added $Pd(PPh_3)_2Cl_2$ (175 mg, 0.25 mmol) and CuI (95 mg, 1.50 mmol). The reaction mixture was heated at 40 °C for the required period (Table 1) with stirring. Then, the mixture was diluted with CH_2Cl_2 (10 mL). The suspension was placed directly onto a chromatography plate (silica gel) and air-dried. The trimethylsilanyl ethynylanilines **3** were isolated by TLC using EtOAc/hexane as the eluent.

4,5-Difluoro-2-[(trimethylsilyl)ethynyl]aniline (3a)

Brown oil; yield: 1.00 g (89%); R_f = 0.56 (EtOAc/hexane, 1:7).

IR (neat): 3485, 3388, 2960, 2901, 2148, 1628, 1599, 1516, 1437, 1348, 1298, 1252, 1227, 1182, 1122, 870, 845, 762, 629 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.07 [dd, J (H^3,F^4) = 10.8 Hz, J (H^3,F^5) = 8.8 Hz, 1 H, H^3], 6.63 [dd, J (H^6,F^5) = 12.7 Hz, J (H^6,F^4) = 7.1 Hz, 1 H, H^6], 5.01 (s, 2 H, NH_2), 0.26 (s, 9 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 152.0 [dd, ^1J (C^5,F^5) = 247.3 Hz, ^2J (C^5,F^4) = 13.8 Hz, C^5], 147.9 [d, ^3J (C^1,F^5) = 10.0 Hz, C^1], 142.3 [dd, ^1J (C^4,F^4) = 235.5 Hz, ^2J (C^4,F^5) = 13.9 Hz, C^4], 120.1 [dd, ^2J (C^3,F^4) = 19.0 Hz, ^3J (C^3,F^5) = 2.0 Hz, C^3], 103.1 [m, ^3J (C^2,F^4) = 7.2 Hz, C^2], 102.8 [d, ^2J (C^6,F^5) = 21.0 Hz, C^6], 103.1 (m, C≡C), 100.3 (m, C≡C), 0.0 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –134.4 [ddd, J (F^5,F^4) = 22 Hz, J (F^5,H^6) = 12.7 Hz, J (F^5,H^3) = 8.8 Hz, 1 F, F^5], –153.2 [ddd, J (F^4,F^5) = 22.4 Hz, J (F^4,H^3) = 10.8 Hz, J (F^4,H^6) = 7.1 Hz, 1 F, F^4].

HRMS (EI): m/z $[M]^+$ calcd for $C_{11}H_{13}F_2NSi$: 225.0780; found: 225.0781.

2,4-Difluoro-6-[(trimethylsilyl)ethynyl]aniline (3b)

Brown oil; yield: 0.87 g (77%); R_f = 0.82 (EtOAc/hexane, 1:10).

IR (neat): 3487, 3388, 3304, 3088, 2962, 2152, 1703, 1606, 1581, 1489, 1448, 1304, 1252, 1200, 1146, 1117, 989, 966, 847, 762 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 6.93 [m, J (H^3,F^2) = 11 Hz, J (H^3,F^4) = 8.7 Hz, J (H^3,H^5) = 2.8 Hz, 1 H, H^3], 6.85 [dm, J (H^5,F^4) = 8.8 Hz, J (H^5,H^3) = 2.8 Hz, 1 H, H^5], 4.81 (s, 2 H, NH_2), 0.28 (s, 9 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 154.2 [dd, ^1J (C^4,F^4) = 235.5 Hz, ^3J (C^4,F^2) = 12.2 Hz, C^4], 151.6 [dd, ^1J (C^2,F^2) = 241.2 Hz, ^3J (C^2,F^4) = 12.7 Hz, C^2], 136.4 [dm, ^2J (C^1,F^2) = 13.8 Hz, C^1], 114.3 [dm, ^2J (C^5,F^4) = 23.3 Hz, C^5], 110.1 [dd, ^3J (C^6,F^4) = 10.8 Hz, ^3J (C^6,F^2) = 7.1 Hz, C^6], 106.1 [dd, ^2J (C^3,F^4) = 27.1 Hz, ^2J (C^3,F^2) = 23.0 Hz, C^3], 102.8 (s, C≡C), 100.9 (m, C≡C), 0.6 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –125.6 [t, J (F^4,H^3) ≈ J (F^4,H^5) = 9 Hz, 1 F, F^4], –129.2 [d, J (F^2,H^3) = 11 Hz, 1 F, F^2].

HRMS (EI): m/z $[M]^+$ calcd for $C_{11}H_{13}F_2NSi$: 225.0780; found: 225.0781.

The analytical and spectral data correspond with those reported in the literature.[32]

3,4,6-Trifluoro-2-[(trimethylsilyl)ethynyl]aniline (3c)

Pink oil; yield: 1.12 g (92%); R_f = 0.72 (EtOAc/hexane, 1:10).

IR (neat): 3496, 3396, 3306, 2962, 2901, 2156, 1649, 1606, 1587, 1500, 1385, 1284, 1252, 1153, 1117, 1009, 980, 912, 847, 762 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.17 [td, J (H^5,F^2) ≈ J (H^5,F^4) = 10.7 Hz, J (H^5,F^3) = 7.3 Hz, 1 H, H^5], 5.10 (s, 2 H, NH_2), 0.29 (s, 9 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 148.4 [dm, ^1J (C^3,F^3) = 236.3 Hz, ^2J (C^3,F^4) = 13.8 Hz, C^3], 146.5 [dm, ^1J (C^6,F^6) = 239.8 Hz, ^3J (C^6,F^4) = 10.6 Hz, C^6], 141.4 [dm, ^1J (C^4,F^4) = 236.1 Hz, ^2J (C^4,F^3) = 13.8 Hz, C^4], 136.8 [dm, ^2J (C^1,F^6) = 15.3 Hz, C^1], 108.6 (m, C≡C), 100.2 [m, ^2J (C^5,F^4) ≈ ^2J (C^5,F^6) = 24.0 Hz, C^5], 100.2 [dm, ^2J (C^2,F^3) = 17.5 Hz, ^3J (C^2,F^4) = 6.9 Hz, C^2], 94.3 (m, C≡C), 0.4 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –135.7 [m, J (F^6,F^3) = 13.7 Hz, J (F^6,H^5) = 11.0 Hz, J (F^6,F^4) = 3.0 Hz, 1 F, F^6], –140.6 [m, J (F^3,F^4) = 22 Hz, J (F^3,F^6) = 13.7 Hz, J (F^3,H^5) = 7.3 Hz, 1 F, F^3], –151.8 [ddd, J (F^4,F^3) = 21.8 Hz, J (F^4,H^5) = 10.5 Hz, J (F^4,F^6) = 3.0 Hz, 1 F, F^4].

HRMS (EI): m/z $[M]^+$ calcd for $C_{11}H_{12}F_3NSi$: 243.0686; found: 243.0687.

2,3,4-Trifluoro-6-[(trimethylsilyl)ethynyl]aniline (3d)

Yellow oil; yield: 1.11 g (91%); R_f = 0.78 (EtOAc/hexane, 1:7).

IR (neat): 3493, 3392, 2962, 2901, 2152, 1587, 1520, 1483, 1371, 1300, 1252, 1203, 1165, 1020, 918, 847, 762, 727 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 6.98 [m, J (H^5,F^4) = 10.4 Hz, J (H^5,F^3) = 7.9 Hz, J (H^5,F^2) = 2.2 Hz, 1 H, H^5], 5.04 (s, 2 H, NH_2), 0.26 (s, 9 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 141.8 [dm, ^1J (C^4,F^4) = 236.8 Hz, ^2J (C^4,F^3) = 10.9 Hz, C^4], 140.9 [dm, ^1J (C^3,F^3) = 249.5 Hz, ^2J (C^3,F) = 16.8 Hz, C^3], 139.5 [dm, ^1J (C^2,F^2) = 241.8 Hz, ^2J (C^2,F^3) = 12.2 Hz, C^2], 136.4 [dm, ^2J (C^1,F^2) = 10.7 Hz, C^1], 113.9 [dd, ^2J (C^5,F^4) = 19.1 Hz, ^3J (C^5,F^3) = 3.5 Hz, C^5], 102.6 (m, C^6), 101.1 (d, C≡C), 98.6 (m, C≡C), –0.9 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –151.6 [dd, J (F^4,F^3) = 21.4 Hz, J (F^4,H^5) = 10.4 Hz, 1 F, F^4], –156.8 [dd, J (F^2,F^3) = 20 Hz, J (F^2,H^5) = 2.2 Hz, 1 F, F^2], –159.3 [m, J (F^3,F^4) = 21.4 Hz, J (F^3,F^2) = 20 Hz, J (F^3,H^5) = 7.9 Hz, 1 F, F^3].

HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{12}F_3NSi$: 243.0686; found: 243.0684.

2,3,4,5-Tetrafluoro-6-[(trimethylsilyl)ethynyl]aniline (3e)

Yellow solid; yield: 1.15 g (88%); R_f = 0.57 (EtOAc/hexane, 1:7); mp 48.4–51.2 °C.

IR (neat): 3500, 3398, 2962, 2902, 2160, 1659, 1599, 1518, 1502, 1433, 1304, 1252, 1171, 1115, 993, 945, 845, 760, 700, 673, 588 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 5.38 (s, 2 H, NH_2), 0.26 (s, 9 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 148.7 [dm, ^1J (C^5,F^5) = 245.0 Hz, C^5], 142.4 [dm, ^1J (C^3,F^3) = 249.0 Hz, C^3], 136.7 [dm, ^2J (C^1,F^2) = 11.6 Hz, C^1], 136.6 [dm, ^1J (C^2,F^2) = 238.0 Hz, C^2], 132.3 [dm, ^1J (C^4,F^4) = 238.2 Hz, C^4], 108.0 (m, C≡C), 94.3 [dm, ^2J (C^6,F^5) = 17.8 Hz, C^6], 92.5 (m, C≡C), –0.2 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –138.3 [ddd, J (F^5,F^4) = 22.0 Hz, J (F^5,F^2) = 9.5 Hz, J (F^5,F^3) = 2.6 Hz, 1 F, F^5], –156.6 [td, J (F^3,F^4) ≈ J (F^3,F^2) = 20.7 Hz, J (F^3,F^5) = 2.6 Hz, 1 F, F^3], –161.8 [ddd, J (F^2,F^3) = 19.9 Hz, J (F^2,F^5) = 9.5 Hz, J (F^2,F^4) = 6.6 Hz, 1 F, F^2], –175.2 [td, J (F^4,F^5) ≈ J (F^4,F^3) = 21.5 Hz, J (F^4,F^2) = 6.6 Hz, 1 F, F^4].

HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{11}F_4NSi$: 261.0591; found: 261.0593.

2,3,5-Trifluoro-4-(trifluoromethyl)-6-[(trimethylsilyl)ethynyl]aniline (3f)

Yellowish solid; yield: 1.45 g (93%); R_f = 0.78 (EtOAc/hexane, 1:10); mp 55.4–58.2 °C.

IR (KBr): 3518, 3410, 2962, 2158, 1651, 1605, 1502, 1342, 1248, 1171, 1120, 939, 879, 647, 762, 723, 642 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 6.20 (s, 2 H, NH_2), 0.26 (s, 9 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 158.0 [dm, ^1J (C^5,F^5) = 254.4 Hz, C^5], 149.4 [dm, ^1J (C^3,F^3) = 255.9 Hz, C^3], 144.8 [m, ^2J (C^1,F^2) = 12.0 Hz, C^1], 136.6 [dm, ^1J (C^2,F^2) = 237.8 Hz, ^2J (C^2,F^3) = 14.9 Hz, C^2], 123.5 [q, ^1J (CF_3,F) = 271.2 Hz, CF_3], 113.7 [dm, ^2J (C^6,F^5) = 23.9 Hz, C^6], 108.5 (m, C≡C), 95.7 (m, C^4), 92.5 (m, C≡C), 0.3 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –53.7 [t, J (CF_3,F^3) ≈ J (CF_3,F^5) = 21.4 Hz, 3 F, CF_3], –113.4 [dq, J (F^5,CF_3) = 21.6 Hz, J (F^5,F^2) = 10.8 Hz, 1 F, F^5], –137.6 [m, J (F^3,CF_3) ≈ J (F^3,F^2) = 20.6 Hz, 1 F, F^3], –163.2 [dd, J (F^2,F^3) = 19.4 Hz, J (F^2,F^5) = 10.8 Hz, 1 F, F^2].

HRMS (EI): m/z [M]$^+$ calcd for $C_{12}H_{11}F_6NSi$: 311.0560; found: 311.0561.

3-Fluoro-4-[(trimethylsilyl)ethynyl]aniline (3g)

Brown solid; yield: 1.00 g (97%); R_f = 0.47 (EtOAc/hexane, 1:10, 2 ×); mp 91.8 °C (dec.).

IR (KBr): 3495, 3468, 3394, 3371, 3207, 2958, 2150, 1628, 1560, 1508, 1448, 1331, 1252, 1223, 1174, 1122, 960, 860, 843, 760, 702, 633, 609 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.15 [t, J (H^5,F^3) ≈ J (H^5,H^6) = 8.7 Hz, 1 H, H^5], 6.48–6.41 (m, 2 H, H^6 + H^2), 5.38 (s, 2 H, NH_2), 0.21 (s, 9 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 165.1 [d, ^1J (C^3,F^3) = 246.8 Hz, C^3], 152.4 (d, ^3J (C^1,F^3) = 11.6 Hz, C^1], 135.2 [d, ^3J (C^5,F^3) = 3.5 Hz, C^5], 110.9 (d, ^4J (C^6,F^3) = 2.1 Hz, C^6], 101.0 [d, ^2J (C^2,F^3) = 24.3 Hz, C^2], 100.7 (s, C≡C), 99.0 [d, ^2J (C^4,F^3) = 16.5 Hz, C^4], 96.2 (d, C≡C), 0.1 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –109.8 [dd, J (F^3,H^2) = 11.9 Hz, J (F^3,H^5) = 8.2 Hz, 1 F, F^3].

HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{14}FNSi$: 207.0874; found: 207.0871.

2,5-Difluoro-4-[(trimethylsilyl)ethynyl]aniline (3h)

Brown oil; yield: 1.09 g (97%); R_f = 0.50 (EtOAc/hexane, 1:7, 2 ×).

IR (neat): 3498, 3400, 3207, 3078, 2960, 2901, 2154, 1641, 1524, 1437, 1358, 1304, 1244, 1217, 1173, 1119, 872, 843, 760, 723, 638, 442 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.17 [dd, J (H^3,F^2) = 11.2 Hz, J (H^3,F^5) = 6.4 Hz, 1 H, H^3], 6.74 [dd, J (H^6,F^5) = 10.5 Hz, J (H^6,F^2) = 7.5 Hz, 1 H, H^6], 5.31 (s, 2 H, NH_2), 0.38 (s, 9 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 160.8 [d, ^1J (C^5,F^5) = 244.6 Hz, C^5], 147.0 [d, ^1J (C^2,F^2) = 235.1 Hz, C^2], 139.3 [dd, ^2J (C^1,F^2) = 15.0 Hz, ^3J (C^1,F^5) = 11.9 Hz, C^1], 119.1 [dd, ^2J (C^3,F^2) = 21.8 Hz, ^3J (C^3,F^5) = 3.4 Hz, C^3], 102.8 [dd, ^2J (C^6,F^5) = 27.1 Hz, ^3J (C^6,F^2) = 4.5 Hz, C^6], 99.1 (s, C≡C), 98.6 [dd, ^2J (C^4,F^5) = 19.0 Hz, ^3J (C^4,F^2) = 8.6 Hz, C^4], 97.4 (d, C≡C), 0.0 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –116.2 [m, J (F^5,F^2) = 14.2 Hz, J (F^5,H^6) = 10.6 Hz, J (F^5,H^3) = 6.4 Hz, 1 F, F^5], –143.1 [m, J (F^2,F^5) = 14.2 Hz, J (F^2,H^3) = 11.2 Hz, J (F^2,H^6) = 7.5 Hz, 1 F, F^2].

HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{13}F_2NSi$: 225.0780; found: 225.0781.

2,3,5,6-Tetrafluoro-4-[(trimethylsilyl)ethynyl]aniline (3i)

Yellow oil; yield: 1.28 g (98%); R_f = 0.47 (EtOAc/hexane, 1:7).

IR (neat): 3505, 3412, 3204, 2963, 2903, 2857, 2168, 1665, 1607, 1518, 1503, 1310, 1252, 1173, 1109, 986, 939, 922, 847, 802, 762, 673, 619 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.13 (s, 2 H, NH_2), 0.24 (s, 9 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0 [dm, ^1J (C^3,F^3) = 252.4 Hz, C^5 + C^3], 135.5 [dm, ^1J (C^2,F^2) = 238.6 Hz, C^2 + C^6], 126.7 [tm, ^2J (C^1,F^2) = 14.1 Hz, C^1], 104.6 (t, C≡C), 91.2 [tm, ^2J (C^4,F^3) = 18.1 Hz, C^4], 89.0 (t, C≡C), –0.7 (s, CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –140.2 [dm, J (F^3,F^2) = 23 Hz, 2 F, F^3 + F^5], –163.7 [dm, J (F^2,F^3) = 23 Hz, 2 F, F^2 + F^6].

HRMS (EI): m/z [M]$^+$ calcd for $C_{11}H_{11}F_4NSi$: 261.0591; found: 261.0586.

5-Fluoro-2,4-bis[(trimethylsilyl)ethynyl]aniline (3j)

Brown oil; yield: 1.48 g (98%); R_f = 0.67 (EtOAc/hexane, 1:10).

IR (neat): 3489, 3388, 2958, 2899, 2150, 1626, 1603, 1564, 1502, 1431, 1308, 1252, 1228, 1190, 877, 841, 760, 698, 633 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.32 [d, J (H^3,F^5) = 7.8 Hz, 1 H, H^3], 6.51 [d, J (H^6,F^5) = 11.5 Hz, 1 H, H^6], 5.54 (s, 2 H, NH_2), 0.24 (s, 9 H, CH_3), 0.21 (s, 9 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 164.3 [d, ^1J (C^5,F^5) = 251.1 Hz, C^5], 152.3 [d, ^3J (C^1,F^5) = 12.4 Hz, C^1], 138.0 [d, ^3J (C^3,F^5) = 3.8 Hz, C^3], 104.0 (d, C^2), 100.6 (s, C≡C), 100.6 [d, ^2J (C^6,F^5) = 25.3 Hz, C^6], 100.0 [d, ^2J (C^4,F^5) = 17.7 Hz, C^4], 99.7 (d, C≡C), 99.1 (s, C≡C), 96.7 (d, C≡C), 0.1 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –106.4 [dd, J (F^5,H^6) = 11.6 Hz, J (F^5,H^3) = 7.8 Hz, 1 F, F^5].

HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{22}FNSi_2$: 303.1269; found: 303.1267.

3,6-Difluoro-2,4-bis[(trimethylsilyl)ethynyl]aniline (3k)

Brown oil; yield: 1.41 g (88%); R_f = 0.75 (EtOAc/hexane, 1:7).

IR (neat): 3502, 3396, 3302, 2960, 2901, 2158, 1633, 1595, 1491, 1444, 1298, 1250, 1142, 1003, 914, 847, 760, 700, 644 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.03 [dd, J (H^5,F^6) = 11.2 Hz, J (H^5,F^3) = 6.2 Hz, 1 H, H^5], 5.45 (s, 2 H, NH_2), 0.29 (s, 9 H, CH_3), 0.24 (s, 9 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 160.8 [d, ^1J (C^3,F^3) = 250.2 Hz, C^3], 146.3 [d, ^1J (C^6,F^6) = 236.3 Hz, C^6], 140.7 [dm, ^2J (C^1,F^6) = 15.7 Hz, C^1], 118.8 [d, ^2J (C^5,F^6) = 21.3 Hz, C^5], 106.9 (s, C≡C), 98.5 [dm, ^2J (C^4,F^3) = 21.1 Hz, C^4], 98.0 [d, ^2J(C^2,F^3) = 14.3 Hz, C^2], 93.9 (s, C≡C), 89.0 (s, C≡C), 86.1 (s, C≡C), 0.0 (s, CH_3), –0.1 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –109.5 [dd, J (F^3,F^6) = 14.3 Hz, J (F^3,H^5) = 6.2 Hz, 1 F, F^3], –137.7 [dd, J (F^6,F^3) = 14.3 Hz, J (F^6,H^5) = 11.2 Hz, 1 F, F^3].

HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{21}F_2NSi_2$: 321.1175; found: 321.1171.

Methyl Aryl Ketones 4; General Procedure

To a solution of trimethylsilylarylacetylene **3** (0.50 mmol) in EtOH (10 mL) (BuOH for **3f**) was added *p*-TSA monohydrate (95 mg, 0.50 mmol), and the mixture was heated under reflux for 10 h with stirring. The mixture was allowed to cool to r.t., placed directly onto a chromatography plate (silica gel) and air-dried. The methyl aryl ketone **4** was isolated by TLC using EtOAc/hexane as an eluent.

1-(2-Amino-4,5-difluorophenyl)ethanone (4a)

Yellowish solid; yield: 80 mg (93%); R_f = 0.50 (EtOAc/hexane, 1:5); mp 74.2–75.3 °C.

IR (KBr): 3522, 3417, 3361, 3298, 3180, 3062, 2928, 1647, 1589, 1558, 1516, 1439, 1381, 1362, 1269, 1244, 1196, 1159, 1041, 949, 893, 872, 839, 644, 598, 538, 467 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.70 [dd, J (H^6,F^5) = 12.0 Hz, J (H^6,F^4) = 9.0 Hz, 1 H, H^6], 7.08 (s, 2 H, NH_2), 6.67 [dd, J (H^3,F^4) = 13.0 Hz, J (H^3,F^5) = 7.0 Hz, 1 H, H^3], 2.51 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 199.7 (s, C=O), 155.6 [dd, ^1J (C^4,F^4) = 251.6 Hz, ^2J (C^4,F^5) = 14.4 Hz, C^4], 150.8 [d, ^3J (C^2,F^4) = 11.2 Hz, C^2], 141.8 [dd, ^1J (C^5,F^5) = 234.0 Hz, ^2J (C^5,F^4) = 13.8 Hz, C^5], 120.9 [dd, ^2J (C^6,F^5) = 17.5 Hz, ^3J (C^6,F^4) = 3.1 Hz, C^6], 114.4 (m, C^1), 105.1 [d, ^2J (C^3,F^4) = 20.0 Hz, C^3], 28.5 (s, CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –127.8 [ddd, J (F^4,F^5) = 22 Hz, J (F^4,H^3) = 11.3 Hz, J (F^4,H^6) = 9.0 Hz, 1 F, F^4], –152.3 [ddd, J (F^5,F^4) = 22.3 Hz, J (F^5,H^6) = 10.5 Hz, J (F^5,H^3) = 6.3 Hz, 1 F, F^5].

HRMS (EI): m/z $[M]^+$ calcd for $C_8H_7F_2NO$: 171.0490; found: 171.0486.

1-(2-Amino-3,5-difluorophenyl)ethanone (4b)

Yellowish solid; yield: 78 mg (91%); R_f = 0.56 (EtOAc/hexane, 1:5); mp 92.3 °C (dec.).

IR (KBr): 3439, 3333, 3063, 2928, 2857, 1653, 1599, 1560, 1464, 1431, 1362, 1273, 1205, 1119, 989, 966, 856, 800, 634, 594, 575, 552 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.45 [dm, J (H^6,F^5) = 9.8 Hz, J (H^6,H^4) = 2.8 Hz, J (H^6,F^3) = 1.8 Hz, 1 H, H^6], 7.20 [m, J (H^4,F^3) = 11.3 Hz, J (H^4,F^5) = 8.4 Hz, J (H^4,H^6) = 2.8 Hz, 1 H, H^4], 6.72 (s, 2 H, NH_2), 2.59 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 200.6 (s, C=O), 152.5 [dm, ^1J (C^5,F^5) = 234 Hz, C^5], 152.3 [dm, ^1J (C^3,F^3) = 243 Hz, C^3], 138.1 [d, ^2J (C^2,F^3) = 12.8 Hz, C^2], 119.6 [t, ^3J (C^1,F^5) ≈ ^3J (C^1,F^3) = 6.8 Hz, C^1], 113.4 [dd, ^2J (C^6,F^5) = 21.9 Hz, C^6], 109.4 [dd, ^2J (C^4,F^5) = 27.9 Hz, ^2J (C^4,F^3) = 22.7 Hz, C^4], 28.7 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –127.7 [dd, J (F^5,H^6) = 9.8 Hz, J (F^5,H^4) = 8.4 Hz, 1 F, F^5], –131.3 [dd, J (F^3,H^4) = 11.3 Hz, J (F^3,H^6) = 1.8 Hz, 1 F, F^3].

HRMS (EI): m/z $[M]^+$ calcd for $C_8H_7F_2NO$: 171.0490; found: 171.0487.

1-(2-Amino-3,5,6-trifluorophenyl)ethanone (4c)

Yellowish solid; yield: 88 mg (93%); R_f = 0.67 (EtOAc/hexane, 1:10); mp 79.6–81.0 °C.

IR (KBr): 3433, 3323, 3080, 3009, 2928, 1649, 1599, 1564, 1471, 1390, 1369, 1327, 1271, 1171, 1113, 982, 930, 864, 723, 613, 523, 501 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.38 [m, J (H^4,F^3) = 11.0, J (H^4,F^5) = 10.2 Hz, J (H^4,F^6) = 7.5 Hz, 1 H, H^4], 6.71 (s, 2 H, NH_2), 2.58 (d, J = 8 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 198.1 (m, C=O), 148.5 [dm, ^1J (C^6,F^6) = 247.0 Hz, ^2J (C^6,F^5) = 13.3 Hz, C^6], 146.7 [dm, ^1J (C^3,F^3) = 238.9 Hz, ^3J (C^3,F^5) = 9.8 Hz, C^3], 139.7 [dm, ^1J (C^5,F^5) = 235.2 Hz, ^2J (C^5,F^6) = 16.4 Hz, C^5], 137.7 [dm, ^2J (C^2,F^3) = 15 Hz, C^2], 110.3 2 [dm, ^2J (C^1,F^6) = 15 Hz, C^1], 109.4 [tm, ^2J (C^4,F^3) ≈ ^2J (C^4,F^5) = 25 Hz, C^4], 33.1 (d, J = 11.3 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –136.5 [m, J (F^3,F^6) = 14.6 Hz, J (F^3,H^4) = 11.0 Hz, J (F^3,F^5) = 3.5 Hz, 1 F, F^3], –138.6 [m, J (F^6,F^5) = 23 Hz, J (F^6,F^3) = 15 Hz, J (F^6,H^4) = 7.5 Hz, 1 F, F^6], –154.3 [ddd, J (F^5,F^6) = 23.0 Hz, J (F^5,H^4) = 10.2 Hz, J (F^5,F^3) = 3.5 Hz, 1 F, F^5].

HRMS (EI): m/z $[M]^+$ calcd for $C_8H_6F_3NO$: 189.0396; found: 189.0393.

Anal. Calcd for $C_8H_6F_3NO$: C, 50.80; H, 3.20. Found: C, 50.76; H, 3.18.

1-(2-Amino-3,4,5-trifluorophenyl)ethanone (4d)

Yellowish solid; yield: 92 mg (97%); R_f = 0.61 (EtOAc/hexane, 1:5); mp 133.8–134.1 °C.

IR (KBr): 3429, 3319, 2926, 2854, 1657, 1591, 1568, 1522, 1462, 1427, 1387, 1362, 1284, 1209, 1016, 953, 864, 850, 681, 596, 517, 467 cm^{-1}.

^1H NMR (500 MHz, acetone-d_6): δ = 7.64 [m, J (H^6,F^5) = 11.7 Hz, J (H^6,F^4) = 8.3 Hz, J (H^6,F^3) = 2.3 Hz, 1 H, H^6], 6.93 (s, 2 H, NH_2), 2.55 (s, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 199.6 (s, C=O), 143.8 [dm, ^1J (C^4,F^4) = 253.5 Hz, ^2J (C^4,F^3) = 17.0 Hz, ^2J (C^4,F^5) = 13.0 Hz, C^4], 141.2 [dm, ^1J (C^5,F^5) = 235 Hz, ^2J (C^5,F^4) = 10.6 Hz, C^5], 140.5 [dm, ^1J (C^3,F^3) = 242.5 Hz, ^2J (C^3,F^4) = 11.4 Hz, C^3], 139.3 [dm, ^2J (C^2,F^3) = 10.5 Hz, C^2], 114.5 [dm, ^2J (C^6,F^5) = 13 Hz, C^6], 113.8 (m, C^1), 28.1 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –153.0 [ddd, J (F^5,F^4) = 21.8 Hz, J (F^5,H^6) = 11.7 Hz, J (F^5,F^3) = 2.9 Hz, 1 F, F^5], –153.7 [m, J (F^4,F^5) = 21.8 Hz, J (F^4,F^3) = 18.1 Hz, J (F^4,H^6) = 8.3 Hz, 1 F, F^4], –157.3 [dt, J (F^3,F^4) = 18.1 Hz, J(F^3,F^5) ≈ J (F^3,H^6) = 2.6 Hz, 1 F, F^3].

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_6F_3NO$: 189.0396; found: 189.0395.

Anal. Calcd for $C_8H_6F_3NO$: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.93; H, 3.15; N, 7.43.

1-(2-Amino-3,4,5,6-tetrafluorophenyl)ethanone (4e)

Yellowish solid; yield: 86 mg (83%); R_f = 0.64 (EtOAc/hexane, 1:5); mp 103.4–104.5 °C.

IR (KBr): 3425, 3315, 3146, 3012, 2928, 2854, 1668, 1649, 1578, 1523, 1473, 1406, 1371, 1336, 1273, 1223, 1082, 993, 962, 858, 742, 619, 590, 561, 503 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.08 (s, 2 H, NH_2), 2.57 (d, J = 8.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 197.0 (s, C=O), 148.9 [dm, ^1J (C^6,F^6) = 248.7 Hz, C^6], 143.2 [dm, ^1J (C^4,F^4) = 252.6 Hz, C^4], 137.6 (m, C^2), 135.9 [dm, ^1J (C^3,F^3) = 239.3 Hz, C^3], 130.6 [dm, ^1J (C^5,F^5) = 237.4 Hz, C^5], 104.7 [dm, ^2J (C^1,F^6) = 14.8 Hz, C^1], 32.2 (d, J = 11.6 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –135.7 [m, J (F^6,F^5) = 24 Hz, J (F^6,F^4) = 8 Hz, 1 F, F^6], –152.2 [m, J (F^4,F^3) ≈ J (F^4,F^5) = 21 Hz, J (F^4,F^6) = 8 Hz, 1 F, F^4], –163.1 [m, J (F^3,F^4) = 19.9 Hz, J (F^3,F^6) = 9.6 Hz, J (F^3,F^5) = 7.8 Hz, 1 F, F^3], –177.8 [m, J (F^5,F^6) = 24.2 Hz, J (F^5,F^4) = 21.6 Hz, J (F^5,F^3) = 7.8 Hz, 1 F, F^5].

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_5F_4NO$: 207.0302; found: 207.0297.

1-[2-Amino-3,4,6-trifluoro-5-(trifluoromethyl)phenyl]ethanone (4f)

White solid; yield: 122 mg (95%); R_f = 0.56 (EtOAc/hexane, 1:7); mp 85.5–85.9 °C.

IR (KBr): 3410, 3307, 3228, 3163, 1659, 1589, 1497, 1427, 1394, 1375, 1352, 1309, 1252, 1146, 1126, 976, 897, 822, 702, 604, 575, 553 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.74 (s, 2 H, NH_2), 2.58 (d, J = 8.9 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 198.1 (s, C=O), 159.4 [dm, ^1J (C^6,F^6) = 258.5 Hz, C^6], 149.8 [dm, ^1J (C^4,F^4) = 259.7 Hz, C^4], 145.7 (m, C^2), 136.6 [dm, ^1J (C^3,F^3) = 238.2 Hz, ^2J (C^3,F^4) = 14.0 Hz, C^3], 123.0 [q, ^1J (CF_3,F) = 271.2 Hz, CF_3], 106.7 [dm, ^2J (C^1,F^6) = 18.0 Hz, C^1], 93.9 (m, C^5), 33.4 (d, J = 12.3 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –53.5 [t, J (CF_3,F^6) ≈ J (CF_3,F^4) = 22.7 Hz, 3 F, CF_3], –109.2 (m, 1 F, F^6), –134.5 [m, J (F^4,CF_3) ≈ J (F^4,F^3) = 22 Hz, 1 F, F^4], –164.0 [dd, J (F^3,F^4) = 19.2 Hz, J (F^3,F^6) = 11.2 Hz, 1 F, F^3].

HRMS (EI): m/z [M]$^+$ calcd for $C_9H_5F_6NO$: 257.0270; found: 257.0268.

Anal. Calcd for $C_9H_5F_6NO$: C, 42.04; H, 1.96; N, 5.45. Found: C, 41.75; H, 1.80; N, 5.49.

1-(4-Amino-2-fluorophenyl)ethanone (4g)

White solid; yield: 65 mg (85%); R_f = 0.39 (EtOAc/hexane, 1:5, 5 ×); mp 113.1 °C (dec.) (Lit.[33] mp 110–112 °C).

IR (KBr): 3408, 3333, 3219, 1659, 1639, 1599, 1562, 1510, 1458, 1422, 1364, 1277, 1171, 1136, 1065, 1026, 966, 856, 818, 745, 635, 598, 542 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.65 [t, J (H^6,F^2) ≈ J (H^6,H^5) = 8.7 Hz, 1 H, H^6], 6.52 [dd, J (H^5,H^6) = 8.7 Hz, J (H^5,H^3) = 2.2 Hz, 1 H, H^5], 6.39 [dd, J (H^3,F^2) = 14.4 Hz, J (H^3,H^5) = 2.2 Hz, 1 H, H^3], 5.79 (s, 2 H, NH_2), 2.43 (d, J = 5.2 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 193.0 (d, 3.7 Hz, C=O), 165.4 [d, ^1J (C^2,F^2) = 251.1 Hz, C^2], 156.2 [d, ^3J (C^4,F^2) = 13 Hz, C^4], 132.8 [d, ^3J (C^6,F^2) = 4.8 Hz, C^6], 114.6 [d, ^2J (C^1,F^2) = 13.0 Hz, C^1], 110.8 (s, C^5), 100.2 [d, ^2J (C^3,F^2) = 27.5 Hz, C^3], 30.8 (d, J = 7.6 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –107.5 [m, J (F^2,H^6) = 9 Hz, 1 F, F^2].

HRMS (EI): m/z [M]$^+$ calcd for C_8H_8FNO: 153.0584; found: 153.0581.

Anal. Calcd for C_8H_8FNO: C, 62.74; H, 5.26; N, 9.15. Found: C, 62.84; H, 4.97; N, 9.13.

1-(4-Amino-2,5-difluorophenyl)ethanone (4h)

White solid; yield: 82 mg (96%); R_f = 0.58 (EtOAc/hexane, 1:5, 5 ×); mp 129.3–129.7 °C.

IR (KBr): 3373, 3321, 3211, 3047, 2706, 2669, 1668, 1620, 1518, 1450, 1365, 1315, 1257, 1188, 1165, 1082, 1043, 1022, 974, 901, 850, 816, 739, 673, 625, 573, 449 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.44 [dd, J (H^6,F^5) = 12.1 Hz, J (H^6,F^2) = 6.7 Hz, 1 H, H^6], 6.59 [dd, J (H^3,F^2) = 12.9 Hz, J (H^3,F^5) = 7.1 Hz, 1 H, H^3], 5.84 (s, 2 H, NH_2), 2.46 (d, J = 5.4 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 192.5 (d, J = 3.6 Hz, C=O), 161.0 [d, ^1J (C^2,F^2) = 248.3 Hz, C^2], 147.7 [d, ^1J (C^5,F^5) = 235.7 Hz, C^2], 144.0 [m, ^2J (C^4,F^5) = 14.3 Hz, C^4], 115.8 [dd, ^2J (C^6,F^5) = 21.2 Hz, ^3J (C^6,F^2) = 5.2 Hz, C^6], 113.6 [dd, ^2J (C^1,F^2) = 15.7 Hz, ^3J (C^1,F^5) = 4.7 Hz, C^1], 102.3 [dd, ^2J (C^3,F^2) = 30.6 Hz, ^3J (C^3,F^5) = 4.3 Hz, C^3], 30.8 (d, J = 8 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –111.8 [m, J (F^2,F^5) = 15 Hz, J (F^2,H^3) = 13 Hz, J (F^2,H^6) = 6.7 Hz, 1 F, F^2], –140.8 [m, J (F^5,F^2) = 15.1 Hz, J (F^5,H^6) = 12.1 Hz, J (F^5,H^3) = 7.1 Hz, 1 F, F^5].

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_7F_2NO$: 171.0490; found: 171.0493.

1-(4-Amino-2,3,5,6-tetrafluorophenyl)ethanone (4i)

White solid; yield: 99 mg (96%); R_f = 0.42 (EtOAc/hexane, 1:10, 2 ×); mp 110.5–110.6 °C.

IR (KBr): 3491, 3338, 3211, 3012, 2928, 2775, 2671, 1686, 1639, 1585, 1537, 1491, 1385, 1362, 1304, 1223, 1174, 1101, 999, 926, 862, 669, 613, 590, 488, 424 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.06 (s, 2 H, NH_2), 2.51 (t, J = 2.7 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, acetone-d_6): δ = 191.5 (t, J = 2.1 Hz, C=O), 146.7 [dm, ^1J (C^2,F^2) = 249.9 Hz, C^2 + C^6], 136.5 [dm, ^1J (C^3,F^3) = 238.4 Hz, C^3 + C^5], 132.5 [tm, ^2J (C^4,F^3) = 14.3 Hz, C^4], 105.6 [tm, ^2J (C^1,F^2) = 14.7 Hz, C^1], 32.5 (t, J = 3.6 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –143.4 [dm, J (F^2,F^3) = 13 Hz, 2 F, F^2 + F^6], –162.7 [dm, J (F^3,F^2) = 13 Hz, 2 F, F^3 + F^5].

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_5F_4NO$: 207.0302; found: 207.0304.

1,1′-(4-Amino-6-fluoro-1,3-phenylene)diethanone (4j)

Yellowish solid; yield: 78 mg (80%); R_f = 0.39 (EtOAc/hexane, 1:5, 10 ×); mp 173.9 °C (dec.).

IR (KBr): 3421, 3317, 3007, 2928, 2854, 2499, 1662, 1616, 1587, 1545, 1458, 1427, 1360, 1323, 1250, 1230, 1178, 1057, 1034, 976, 943, 918, 841, 640, 609, 565, 546, 449 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 8.39 [d, J (H^2,F^6) = 8.5 Hz, 1 H, H^2], 6.52 [d, J (H^5,F^6) = 14.1 Hz, 1 H, H^5], 2.90 (s, 2 H, NH_2), 2.57 (s, 3 H, CH_3), 2.46 (d, J = 5.1 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 200.5 (s, C=O), 293.2 (d, J = 4.0 Hz, C=O), 166.3 [d, ^1J (C^6,F^6) = 258.2 Hz, C^6], 157.4 [d, ^3J (C^4,F^6) = 14.5 Hz, C^4], 138.2 [d, ^3J (C^2,F^6) = 6.3 Hz, C^2], 115.3 (s, C^3), 114.1 [d, ^2J (C^1,F^6) = 14.9 Hz, C^1], 102.4 [d, ^2J (C^5,F^6) = 27.0 Hz, C^5], 30.6 (d, J = 7.3 Hz, CH_3), 27.8 (s, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –102.5 [m, J (F^6,H^5) = 14 Hz, J (F^6,H^2) = 9 Hz, 1 F, F^6].

HRMS (EI): m/z [M]$^+$ calcd for $C_{10}H_{10}FNO_2$: 195.0690; found: 195.0688.

1,1′-(4-Amino-2,5-difluoro-1,3-phenylene)diethanone (4k)

Yellowish solid; yield: 88 mg (83%); R_f = 0.44 (EtOAc/hexane, 1:5); mp 114.6–115.8 °C.

IR (KBr): 3415, 3304, 3172, 3095, 3009, 2931, 2486, 1657, 1628, 1593, 1479, 1423, 1362, 1327, 1281, 1215, 1024, 970, 901, 862, 831, 723, 687, 621, 575 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.57 (s, 2 H, NH_2), 7.52 [dd, J (H^6,F^5) = 12.0 Hz, J (H^6,F^2) = 6.4 Hz, 1 H, H^6], 2.59 (d, J = 9.1 Hz, 3 H, CH_3), 2.51 (d, J = 6.3 Hz, 3 H, CH_3).

^{13}C NMR (126 MHz, acetone-d_6): δ = 199.0 (s, C=O), 192. 4 (s, C=O), 162.3 [d, ^1J (C^2,F^2) = 258.0 Hz, C^2], 147.9 [d, ^1J (C^5,F^5) = 238.4 Hz, C^5], 145.9 (m, C^4), 117.4 [dd, ^2J (C^6,F^5) = 21.1 Hz, ^3J (C^6,F^2) = 6.5 Hz, C^6], 111.9 [dd, ^2J (C^1,F^2) = 18.2 Hz, ^3J (C^1,F^5) = 4.7 Hz, C^1], 109.3 [d, ^2J(C^3,F^2) = 20.5 Hz, C^3], 33.4 (d, J = 12.7 Hz, CH_3), 31.2 (d, J = 8.7 Hz, CH_3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –104.9 (m, 1 F, F^2), –138.6 [dd, J (F^5,F^2) = 16.6 Hz, J (F^5,H^6) = 12.0 Hz, 1 F, F^5].

HRMS (EI): m/z [M]$^+$ calcd for $C_{10}H_9F_2NO_2$: 213.0596; found: 213.0598.

Anal. Calcd for $C_{10}H_9F_2NO_2$: C, 56.34; H, 4.26; N, 6.57. Found: C, 56.58; H, 4.55; N, 6.69.

5,6,8-Trifluoro-2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (6)

To a solution of **4c** (50 mg, 0.26 mmol) in MeOH (5 mL) was added *p*-TSA monohydrate (148 mg, 0.78 mmol) and the mixture was heated at reflux for 20 h with stirring. The mixture was allowed to cool to r.t., placed directly onto a chromatography plate (silica gel) and air-dried. The 2,3-dihydroquinolinone **6** was isolated by TLC using EtOAc/hexane as an eluent; yellowish solid; yield: 66 mg (87%); R_f = 0.37 (EtOAc/hexane, 1:10, 3 ×); mp 146.7 °C (dec.).

IR (KBr): 3396, 3063, 2897, 1678, 1647, 1605, 1508, 1390, 1329, 1296, 1259, 1225, 1196, 1155, 1140, 1113, 1014, 985, 916, 899, 837, 796, 731, 719, 592, 559, 538, 503, 476, 428 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.53 (m, 2 H, H_m), 7.42 [m, J (H^7,F^8) ≈ J (H^7,F^6) = 10.6 Hz, J (H^7,F^5) = 7.0 Hz, 1 H, H^7], 7.13 (m, 2 H, H_o), 6.31 (s, 1 H, NH), 4.92 [dm, J (H^2,H^3) = 11.8 Hz, J (H^2,$H^{3'}$) = 4 Hz, 1 H, H^2], 2.95 [dd, J (H^3,$H^{3'}$) = 15.8 Hz, J (H^3,H^2) = 11.8 Hz, 1 H, H^3], 2.77 [dm, J ($H^{3'}$,H^3) = 15.8 Hz, J ($H^{3'}$,H^2) = 4.2 Hz, 1 H, $H^{3'}$].

^{13}C NMR (126 MHz, acetone-d_6): δ = 190.2 (m, C=O), 163.8 [d, ^1J (C^{12},F^{12}) = 244.4 Hz, C^{12}], 147.1 [dm, ^1J (C^8,F^8) = 250 Hz, C^8], 146.9 [dm, ^1J (C^5,F^5) = 258 Hz, C^5], 141.7 [dm, ^1J (C^6,F^6) = 238 Hz, C^6], 139.2 [dm, ^2J (C^{8a},F^8) = 14.2 Hz, C^{8a}], 138.4 (d, J = 3.1 Hz, C^9), 130.2 [d, ^3J (C^{10},F^{12}) = 8.3 Hz, C^{10}], 116.7 [d, ^2J (C^{11},F^{12}) = 21.6 Hz, C^{11}], 111.1 [tm, ^2J (C^7,F^8) ≈ ^2J (C^7,F^6) = 23.7 Hz, C^7], 110.9 [dm, ^2J (C^{4a},F^5) = 10 Hz, C^{4a}], 57.5 (s, C^2), 47.8 (s, C^3).

^{19}F NMR (282 MHz, acetone-d_6): δ = –114.2 (m, 1 F, F_p), –134.8 [m, J (F^8,F^5) = 17.0 Hz, J (F^8,H^7) = 10.8 Hz, J (F^8,F^6) = 2.7 Hz, 1 F, F^8], –145.8 [m, J (F^5,F^6) = 19.8 Hz, J (F^5,F^8) = 17.0 Hz, J (F^5,H^7) = 7.0 Hz, 1 F, F^5], –152.4 [ddd, J (F^6,F^5) = 19.8 Hz, J (F^6,H^7) = 10.4 Hz, J (F^6,F^8) = 2.7 Hz, 1 F, F^6].

HRMS (EI): m/z [M]$^+$ calcd for $C_{15}H_9F_4NO$: 295.0615; found: 295.0616.

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Supporting Information

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