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ARTICLE

Aryltrifluoromethylative Cyclization of Unactivated Alkenes by the Use of $PhICF_3Cl$ under Catalyst-Free Condition

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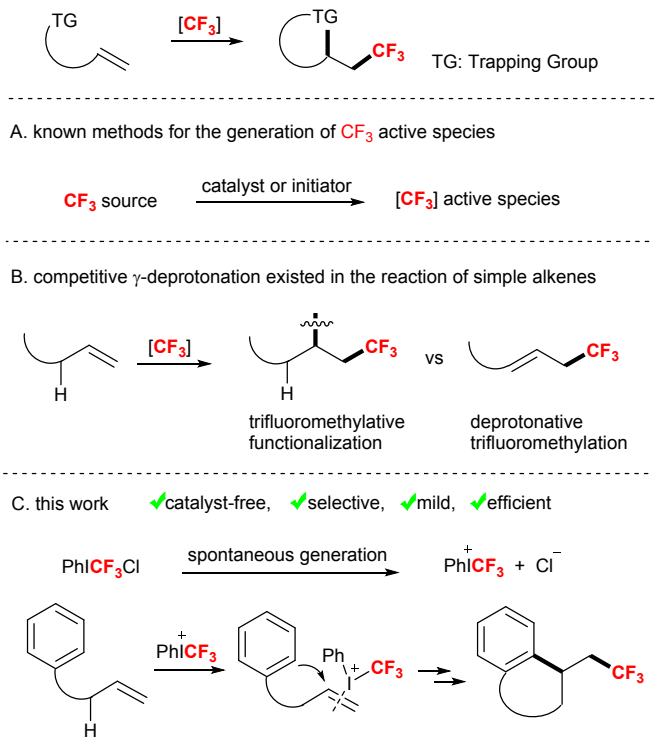
A concise and catalyst-free aryltrifluoromethylative cyclization of unactivated alkenes has been developed herein. The use of $PhICF_3Cl$ as powerful trifluoromethylating agent allows the easy transformations. A set of trifluoroethylated carbocycles and aza-hereocycles were efficiently synthesized in good yield and selectivity. Broad substrate scope, mild reaction conditions, and easy operation would make the method well-suited for applications.

Introduction

The introduction of the trifluoromethyl group into organic molecules is one of the hottest topics in current organic synthesis[1,2] due to the presence of CF_3 framework in a striking number of pharmaceuticals, agrochemicals, and materials.[3] Many elegant trifluoromethylation reactions have been developed but most of them occurred in the presence of at least a catalyst or an activator. In view of the practicability, mild and catalyst-free methods would be a synthetically enabling strategy for simplifying access to trifluoromethylated compounds. To achieve this purpose, the use of a readily available and capable trifluoromethylating agent is undoubtedly a key factor.

Recently, trifluoromethylation-triggered cyclization of alkenes has emerged as a convenient access to trifluoroethylated cyclic compounds of commercial and physiological importance.[2] It is true that known approaches for the generation of the active CF_3 initiator from a trifluoromethylating reagent require the assistance of a catalyst or an activator (Scheme 1A).[4-9] Catalyst-free process remains challenge. For example, when hypervalent iodine-based CF_3 reagents, the Togni's reagents, were used for such cyclizations, they were generally reduced to be a CF_3 radical by accepting an electron from the catalyst and then participated in the reaction.[4a-o] In a few cases, electrophilic CF_3 species was also proposed to undergo an ionic cyclization pathway.[4p-t]



Scheme 1 Trifluoromethylation-triggered cyclization of alkenes.

On the other hand, trifluoromethylative difunctionalization reactions of activated alkenes, such as acryloanilides and styrenes, have been proven to afford the desired difunctionalized products efficiently. By comparison, the reactions of unactivated alkenes bearing an allylic proton would encounter a competitively deprotonative trifluoromethylation (Scheme 1B).[10] In 2012, Buchwald successfully used 2,2'-biquinoline ligand to inhibit such allylic trifluoromethylation in their trifluoromethylation-oxycyclization of unsaturated acids/alcohols.[4a] And in 2013,

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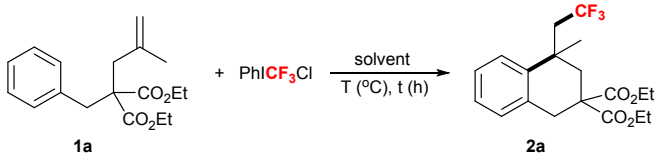
Sodeoka suggested that the well orbital interactions between the alkene and aryl group could make the intramolecular aryltrifluoromethylation of unconjugated alkenes linked by an aryl group the predominant process in the Cu(I)/Togni II catalytic system.[4q]

We recently prepared a CF_3-based λ^3-iodane, $PhICF_3Cl$, by a ligand exchange reaction of $PhI(OCOCF_3)_2$, $TMSCF_3$, and NaCl for the first time.[11] Compared with neutral cyclic analogs (the Togni's reagents[1c]), noncyclic $PhICF_3Cl$ has been proved to have an enhanced CF_3-transfer ability in electrophilic trifluoromethylation reactions.[11,12] With the aim of developing $PhICF_3Cl$ to be efficient and readily available trifluoromethylating reagent, we further explored its synthetic applications. Considering its innate electrophilicity, we envisioned a cyclization of alkenes including a sequential trifluoromethylation and arylation process by using $PhICF_3Cl$ as the electrophilic initiator (Scheme 1C). Herein, we report this catalyst-free and selective cyclization process with a broad range of unactivated alkene substrates.

Results and discussion

We set out to study the trifluoromethylation-cyclization of 5-arylpentenes **1a** using $PhICF_3Cl$ as the electrophile (Table 1). The reaction could give the desired product **2a** in different solvents without any catalyst at 60 °C (entries 1–6), among which DMF led to the best result. Lower temperature (entries 7-9) and shorter reaction time (entries 10, 11) proved to decrease the yield of **2a**. Furthemore, nitrogen atmosphere achieved better transformation of **1a** to **2a** (entry 6 versus 12).

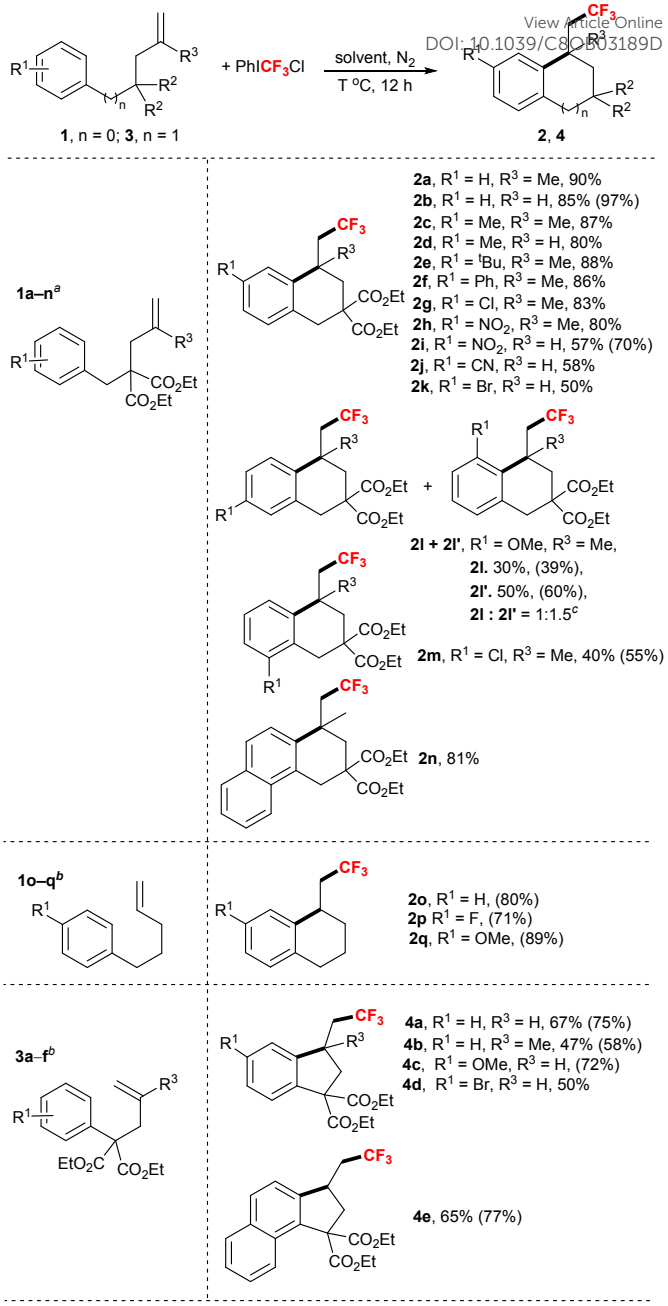
Table 1 Screen of the reaction conditions[a]



1a **2a**

Entry	Solvent	T (°C)	t (h)	Yield (%)[b]
1	MeCN	60	12	25
2	NMP	60	12	31
3	THF	60	12	44
4	1,4-dioxane	60	12	73
5	DCM	60	12	78
6	DMF	60	12	98
7	DMF	50	12	88
8	DMF	40	12	78
9	DMF	30	12	18
10	DMF	60	10	87
11	DMF	60	8	79
12[c]	DMF	60	12	51

Reaction conditions: [a] **1a** (0.1 mmol), $PhICF_3Cl$ (0.15 mmol), solvent (1 mL). [b] ^{19}F NMR yields using $PhCF_3$ as an internal standard. [c] In the air.



Scheme 2. Aryltrifluoromethylation of arylalkenes. **1/3** (0.3 mmol), DMF (3 mL). Isolated yields. Yields in brackets are ^{19}F NMR yields using $PhCF_3$ as an internal standard. [a] With 1.5 equivalent $PhICF_3Cl$. [b] With 2.0 equivalent $PhICF_3Cl$. [c] The ratio of **2l** to **2l'** was determined by ^{19}F NMR spectroscopy.

Then, we investigated the scope of trifluoromethylative cyclizations of **1** under the optimal reaction conditions (table 1, entry 6). To our delight, when 5-arylpentenes **1b**–**n** were tested, all the desired trifluoroethylated tetrahydronaphthalenes **2b**–**n** were obtained in good isolated yields, respectively, in which alkenes **1b, 1d** and **1i**–**k** without R^3-susbtituent could also give corresponding **2** efficiently. Among them, **1l** afforded two isomers of 2l and 2l' as the products. The lower yield was obtained for the substrate that

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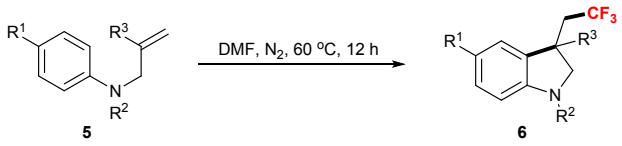
possessed ortho-substitution to the desired product. For alkenes **1o**–**q**, the conversions of them into **2o**–**q** were efficient, while they were not completely separated from the reaction mixture. Similar to the work of Sodeoka, dihydroindenes **4a**–**e** could be obtained as the main products but in relatively lower yields when 4-arylbutenes **3a–f** were selected towards the catalyst-free conditions. Additionally, we tested the reactions of ((3-methylbut-3-en-1-yl)oxy)benzene and (3-methylbut-3-en-1-yl)(phenyl)sulfane with $PhICF_3Cl$ under the standard reaction conditions, respectively. But no desired cyclic products were detected in this case.

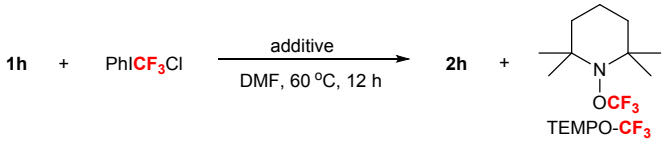
As described above, an efficient catalyst-free intramolecular aryltrifluoromethylation of arylalkenes **1** and **3** has been developed by using $PhICF_3Cl$ as the CF_3 reagent. Next, we extended the method to *N*-allylanilines **5** to synthesize trifluoromethylated indoline derivatives. As presented in Scheme 3, the reactions of **5** and $PhICF_3Cl$ could also proceed under catalyst-free conditions and deliver **6a–i** as the trifluoromethylative cyclization products in 64-90% isolated yields, respectively. By comparison, our method could not be applied to *N*-allylanilines **5** with no R^2 substituent. And substrate **5g** without R^3 substituent also gave **6g** in lower yield.



6a, R^1 = Me, R^2 = Ts, R^3 = Me, 86%
6b, R^1 = OMe, R^2 = Ts, R^3 = Me, 78%
6c, R^1 = Br, R^2 = Ts, R^3 = Me, 71%
6d, R^1 = Me, R^2 = Boc, R^3 = Me, 88%
6e, R^1 = Cl, R^2 = Boc, R^3 = Me, 87%
6f, R^1 = OMe, R^2 = Boc, R^3 = Me, 90%
6g, R^1 = Me, R^2 = Boc, R^3 = H, 64%
6h, R^1 = H, R^2 = Ph, R^3 = Me, 75%
6i, R^1 = OMe, R^2 = Bz, R^3 = Me, 71%

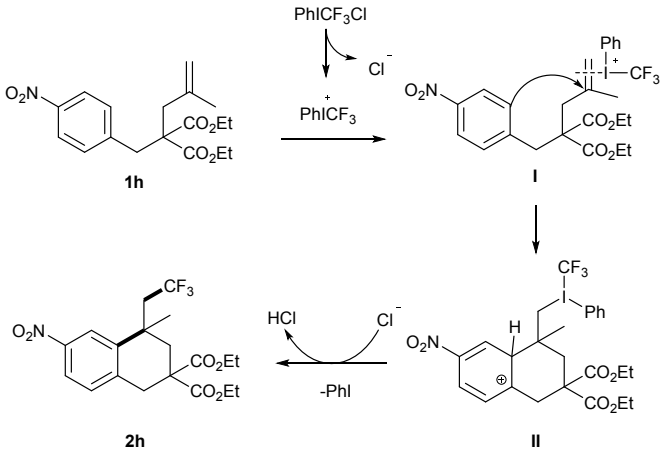
Scheme 3. Aryltrifluoromethylation of N-allylanilines. **5** (0.3 mmol), $PhICF_3Cl$ (1.5 eq.), DMF (3 mL). Isolated yields. Yields in brackets are ^{19}F NMR yields using $PhCF_3$ as an internal standard.

To elucidate the reaction mechanism, control experiments were performed (Scheme 4). The Reactions of **1h** and $PhICF_3Cl$ in the presence of 1.5 equivalents of BHT were conducted. By the analysis of ^{19}F NMR spectroscopies, **2h** could be obtained, in yields almost comparable to those obtained under the standard conditions. Comparatively, the addition of 1.5 equivalents of TEMPO into the reaction mixture could not completely suppress the desired reaction and product **2h** was obtained in 59% yield. The corresponding TEMPO–CF_3 adduct could not be detected in this case (entry 3). The decrease of the reaction yield may be due to the consumption of oxidative $PhICF_3Cl$ for the formation of oxoammonium salt and hydroxylamine from TEMPO.[13] According to the experimental results, an ionic process is proposed to include the activation of the olefin bond by electrophilic $[PhICF_3]^+$ species affording iodonium complex **I**. Then exo-cyclization occurs via an attack of the aryl group affording cyclic intermediate **II**. Finally, the deprotonation of **II** gives trifluoromethylated product **2h** along with the elimination of PhI (Scheme 5). The same as the experimental results reported by Sodeoka, the formations of tetrahydronaphthalenes **2** were more efficient than that of dihydroindenes **4**. The arylative cyclization was suggested to be the rate determining step.[4q]



entry	additive	equiv	yield of **2h**	TEMPO-CF_3
1	--	--	91%	--
2	BHT	1.5	90%	--
3	TEMPO	1.5	59%	0

Scheme 4. Mechanism studies with radical scavenger. **1h** (0.3 mmol), $PhICF_3Cl$ (0.45mmol). DMF (3.0 mL). ^{19}F NMR yields using $PhCF_3$ as an internal standard.



Scheme 5. Possible Mechanism.

Conclusions

In summary, a catalyst-free aryltrifluoromethylative cyclization of unactivated alkenes was disclosed herein. The use of $PhICF_3Cl$ as powerful trifluoromethylating agent enables an easy process for constructing a set of trifluoroethylated carbocycles and aza-hereocycles. The trifluoromethylation reaction has been proven to occur in good selectivity. Control experiments support the suggested ionic mechanism. Broad substrate scope, mild reaction conditions, and easy operation make the method well-suited for wide applications.

Experimental

Typical procedures for catalyst-free intramolecular aryltrifluoromethylation of unactivated alkenes (taking 1a as an example):

To a dried polytetrafluoroethene (PTFE) sealed pressure tube was added **1a** (91.3 mg, 0.3 mmol), $PhICF_3Cl$ (184.8 mg, 4.5 mmol) and anhydrous DMF (3.0 mL) in sequence under N_2. After the reaction mixture was stirred at 60 °C for 12 h, $PhCF_3$ (30 μL, 0.24 mmol) was added as the internal standard and the NMR yield of **2a** was calculated from ^{19}F-NMR integrals. Then the mixture was washed with water and brine, extracted by CH_2Cl_2. The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduce pressure. The residue was purified by silica column chromatography (eluent: petroleum ether/EtOAc = 20/1 to 15/1, v/v) to give **2a** (100.5 mg, 90%) as a yellow oil.

Characterization data for new products:

Diethyl-4,6-dimethyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2c). 113.1 mg, 87% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.05 (dd, *J* = 13.2 Hz, 7.8 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 4.06 - 4.24 (m, 4H), 3.26 (d, *J* = 15.6 Hz, 1H), 3.09 (d, *J* = 15.6 Hz, 1H), 2.63 (d, *J* =15.0 Hz, 1H), 2.47 - 2.56 (m, 1H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.33 - 2.38 (m, 1H), 2.30 (s, 3H), 1.40 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.7, 171.3, 140.6, 136.3, 130.0, 129.0, 127.7, 126.5, 126.5 (q, *J* = 278.1 Hz), 61.7, 61.4, 52.5, 40.6 (q, *J* = 25.7 Hz), 39.6, 35.2 (q, *J* = 0.8 Hz), 34.8, 29.5, 21.3, 13.9, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -58.8 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{20}H_{25}F_3O_4$, M+Na]$^+$: 409.1597, measured: 459.1606.

Diethyl-6-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2d). 89.3 mg, 80% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.05 - 7.08 (m, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 4.19 - 4.24 (m, 2H), 4.05 - 4.15 (m, 2H), 3.28 - 3.33 (m, 2H), 3.15 (t, *J* = 13.8 Hz, 1H), 2.83 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 2.76 - 2.79 (m, 1H), 2.30 (d, *J* = 6.0 Hz, 3H), 2.21 - 2.27 (m, 1H), 1.94 (dd, *J* = 13.8 Hz, 10.2 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.16 (dt, *J* = 22.2 Hz, 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.6, 170.4, 136.4, 135.9, 133.2, 130.0, 128.9, 128.3 (q, *J* = 269.7 Hz), 127.6, 61.7, 61.4, 53.7, 41.0 (q, *J* = 27.2 Hz), 38.4, 34.8, 30.5 (q, *J* = 2.3 Hz), 21.2, 14.0, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -63.5 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{19}H_{23}F_3O_4$, M+Na]$^+$: 395.1440, measured: 395.1444.

Diethyl-6-(tert-butyl)-4-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2e). 115.7 mg, 88% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 4.07 - 4.24 (m, 4H), 3.27 (d, *J* = 16.2 Hz, 1H), 3.12 (d, *J* = 16.2 Hz, 1H), 2.64 (d, *J* =14.4 Hz, 1H), 2.46 - 2.54 (m, 1H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.33 - 2.40 (m, 1H), 1.42 (s, 3H), 1.29 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.8, 171.3, 149.5, 140.1, 130.0, 128.7, 126.5 (q, *J* = 277.7 Hz), 123.9, 122.7, 61.7, 61.4, 52.4, 45.9 (q, *J* = 25.5 Hz), 39.7, 35.4 (q, *J* = 0.9 Hz), 34.7, 34.6, 31.4 (3C), 29.5, 13.9, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -58.7 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{23}H_{31}F_3O_4$, M+Na]$^+$: 451.2067, measured: 451.2072.

Diethyl-4-methyl-6-phenyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2f). 115.6 mg, 86% yield. White solid. mp 125-126 ºC. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.4 Hz, 2H), 7.42 - 7.45 (m, 3H), 7.39 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 4.09 - 4.26 (m, 4H), 3.36 (d, *J* = 16.2 Hz, 1H), 3.18 (d, *J* = 16.2 Hz, 1H), 2.69 (d, *J* = 15.0 Hz, 1H), 2.54 - 2.62 (m, 1H), 2.40 - 2.48 (m, 2H), 1.47 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.7, 171.3, 141.1, 140.0, 132.3, 129.6, 128.8 (2C), 127.4, 127.2, 127.1 (2C), 126.4 (q, *J* = 277.5 Hz), 125.8, 124.0, 61.8, 61.5, 52.5, 45.9 (q, *J* = 25.7 Hz), 39.7, 35.4 (q, *J* = 0.9 Hz), 34.9, 29.7, 13.9, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -58.7 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{25}H_{27}F_3O_4$, M+Na]$^+$: 471.1574, measured: 471.1761.

Diethyl-6-chloro-4-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2g). 101.1 mg, 83% yield. White solid. mp 99-100 ºC. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 4.20 - 4.25 (m, 2H), 4.07 - 4.19 (m, 2H), 3.39 (d, *J* = 16.2 Hz, 1H), 3.15 (d, *J* = 16.2 Hz, 1H), 2.68 (d, *J* = 14.4 Hz, 1H), 2.46 - 2.54 (m, 1H), 2.37 - 2.45 (m, 2H), 1.43 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.1, 170.8, 142.1, 139.3, 130.3, 130.1, 130.1, 125.9 (q, *J* = 277.4 Hz), 111.0, 62.1, 61.8, 52.2, 45.5 (q, J = 26.0 Hz), 39.4, 35.4 (q, *J* = 1.1 Hz), 35.2, 29.8, 13.9, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -58.9 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{19}H_{22}F_3ClO_4$, M+Na]$^+$: 429.1050, measured: 429.1045.

Diethyl-4-methyl-6-nitro-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2h). 100.1 mg, 80% yield. Yellow solid. mp 74-75 ºC. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 4.24 (q, *J* = 8.4 Hz, 2H), 4.08 - 4.19 (m, 2H), 3.45 (d, *J* = 16.2 Hz, 1H), 3.17 (d, *J* = 16.2 Hz, 1H), 2.71 (d, *J* = 14.4 Hz, 1H), 2.52 - 2.60 (m, 1H), 2.43 - 2.50 (m, 2H), 1.47 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.0, 170.7, 147.1, 142.3, 141.4, 130.2, 125.9 (q, *J* = 277.5 Hz), 121.8, 121.6, 62.1, 61.9, 52.2, 45.6 (q, *J* = 26.1 Hz), 39.2, 35.7 (q, *J* = 0.8 Hz), 35.2, 30.0, 13.9, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -58.8 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{19}H_{22}F_3NO_6$, M+Na]$^+$: 440.1291, measured: 440.1293.

Diethyl-6-nitro-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2i). 68.9 mg, 57% yield. Yellow oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.08 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.09 - 4.19 (m, 2H), 3.45 (d, *J* = 16.8 Hz, 1H), 3.38 (q, *J* = 8.4 Hz, 1H), 3.25

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(d, *J* = 16.8 Hz, 1H), 2.88 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 2.78 - 2.84 (m, 1H), 2.33 - 2.42 (m, 1H), 2.03 (dd, *J* = 13.2 Hz, 10.8 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 170.8, 169.8, 147.0, 142.1, 137.9, 130.3, 124.6 (q, *J* = 276.0 Hz), 121.9, 121.9, 62.1, 61.9, 53.3, 40.1 (q, *J* = 27.8 Hz), 35.2, 34.1, 30.8 (q, *J* = 2.1 Hz), 14.0, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -63.2 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{18}H_{20}F_3NO_6, M+Na]^+$: 426.1135, measured: 426.1135.

Diethyl-6-cyano-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2j). 66.7mg, 58% yield. Yellow oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.07 - 4.17 (m, 2H), 3.31 (d, *J* = 15.6 Hz, 2H), 3.13 (d, *J* = 16.2 Hz, 1H), 2.83 (dd, *J* = 13.8 Hz, 7.2 Hz, 1H), 2.68 - 2.76 (m, 1H), 2.24 - 2.34 (m, 1H), 1.95 (dd, *J* = 13.2 Hz, 3.0 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.2, 170.1, 138.1, 132.6, 132.6, 130.6, 127.0, 126.6 (q, *J* = 277.7 Hz), 126.9, 115.7, 61.9, 61.6, 53.5, 40.7 (q, *J* = 27.6 Hz), 34.6, 34.5, 30.6 (q, *J* = 2.3 Hz), 14.0, 13.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -63.5 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{19}H_{20}F_3NO_4, M+Na]^+$: 406.1236, measured: 406.1239.

Diethyl-7-methoxy-4-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2l). 36.2mg, 30% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.4 Hz, 1H), 6.69 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.00 - 4.17 (m, 4H), 3.71 (s, 3H), 3.20 (d, *J* = 15.6 Hz, 1H), 3.04 (d, *J* = 16.2 Hz, 1H), 2.56 (d, *J* = 14.4 Hz, 1H), 2.36 - 2.45 (m, 1H), 2.33 (d, *J* = 15.0 Hz, 1H), 2.22 - 2.31 (m, 1H), 1.31 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 171.6, 171.2, 157.9, 134.4, 132.9, 127.2, 126.3 (q, *J* = 277.9 Hz), 113.2(2C), 61.7, 61.4, 55.1, 52.4, 46.0 (q, *J* = 25.5 Hz), 39.6, 35.3, 34.7, 29.7, 13.9(2C). **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -58.9 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{20}H_{25}F_3O_5, M+Na]^+$: 425.1546, measured: 425.1538.

Diethyl-5-methoxy-4-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2l'). 60.3mg, 50% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.14 - 4.24 (m, 3H), 4.05 - 4.10 (m, 1H), 3.80 (s, 3H), 3.33 (dd, *J* = 15.6 Hz, 2.4 Hz, 1H), 2.99 (d, *J* = 15.6 Hz, 1H), 2.74 - 2.80 (m, 2H), 2.72 (d, *J* = 14.4 Hz, 1H), 2.39 (dd, *J* = 14.4 Hz, 2.4Hz, 1H), 1.40 (s, 3H), 1.27 (t, *J* = 6.6 Hz, 3H), 1.21 (t, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.6, 171.2, 158.1, 135.5, 127.6, 127.3, 126.9 (q, *J* = 279.4 Hz), 122.0, 109.6, 61.6, 61.3, 55.0, 51.8, 42.7 (q, *J* = 25.2 Hz), 41.7 (q, *J* = 1.8 Hz), 36.1, 35.2, 27.1, 14.0, 13.9. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -59.3 (t, *J* = 11.8 Hz). HRMS (ESI): Calcd for $[C_{20}H_{25}F_3O_5, M+Na]^+$: 425.1546, measured: 425.1538.

Diethyl-8-chloro-4-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (2m). 48.7mg, 40% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.26 - 7.29 (m, 1H), 7.13 - 7.19 (m, 2H), 4.06 - 4.26 (m, 4H), 3.68 (dd, *J* = 16.0 Hz, 1.2 Hz, 1H), 3.04 (d, *J* = 16.8 Hz, 1H), 2.64 (d, *J* = 14.8 Hz, 1H), 2.33 - 2.53 (m, 3H), 1.41 (s, 3H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.5, 171.1, 143.1, 134.2, 131.4, 127.7, 127.3, 126.2 (q, *J* = 279.2 Hz), 124.6, 61.9, 61.6, 52.0, 45.9 (q, *J* = 26.1 Hz), 39.0, 35.6, 32.0, 29.7, 13.9, 13.9. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -58.8 (t, *J* = 12.2 Hz). HRMS (ESI): Calcd for $[C_{19}H_{22}ClF_3O_4, M+Na]^+$: 429.1056, measured: 429.1040.

Diethyl-1-methyl-1-(2,2,2-trifluoroethyl)-1,4-dihydrophenanthrene-3,3(2H)-dicarboxylate (2n). 115.6 mg, 81% yield. Yellow oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 4.23 - 4.29 (m, 2H), 4.10 - 4.20 (m, 2H), 3.84 (d, *J* = 16.8 Hz, 1H), 3.41 (d, *J* = 16.2 Hz, 1H), 2.80 (d, *J* = 14.4 Hz, 1H), 2.60 - 2.68 (m, 1H), 2.57 (d, *J* = 14.4 Hz, 1H), 2.37 - 2.45 (m, 1H), 1.49 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 171.9, 171.4, 137.4, 132.2, 131.8, 128.4, 128.2, 127.3, 126.5, 126.5 (q, J = 277.7 Hz), 125.7, 123.8, 123.4, 61.9, 61.5, 52.1, 45.9 (q, *J* = 25.7 Hz), 38.6, 35.6 (d, *J* = 0.9 Hz), 30.8, 29.4, 13.9, 13.9. **^{19}F-NMR** (600 MHz, $CDCl_3$): δ = -58.6 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{23}H_{25}F_3O_4, M+Na]^+$: 445.1597, measured: 445.1596.

Diethyl-3-methyl-3-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-indene-1,1-dicarboxylate (4b). 50.5 mg, 47% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 4.20 - 4.27 (m, 4H), 3.03 (d, *J* = 14.4 Hz, 1H), 2.69 (d, *J* = 14.4 Hz, 1H), 2.37 - 2.52 (m, 2H), 1.42 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (600 MHz, $CDCl_3$): δ = 170.7, 170.6, 150.3, 137.5, 129.3, 127.8, 127.1, 126.6 (q, *J* = 277.2 Hz), 122.6, 64.5, 62.0, 61.9, 45.7, 44.5 (q, *J* = 26.1 Hz), 43.9 (q, *J* = 1.5 Hz), 27.3, 14.0, 14.0. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -59.9 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{18}H_{21}F_3O_4, M+Na]^+$: 381.1284, measured: 381.1292.

Diethyl-5-bromo-3-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-indene-1,1-dicarboxylate (4d). 63.3 mg, 50% yield. Colourless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.47 (d, J = 7.8 Hz, 1H),7.44 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.14 - 4.22 (m, 2H), 3.59 - 3.63 (m, 1H), 3.08 (dd, J = 13.8 Hz, 10.2 Hz, 1H), 2.61 - 2.70 (m, 1H), 2.44 (dd, J = 13.2 Hz, 7.8 Hz, 1H), 2.24 - 2.33 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 170.0, 169.6, 147.0, 138.1, 131.0, 128.5, 126.8, 126.5 (q, J = 277.4 Hz), 123.3, 64.4, 62.1, 62.1, 40.6, 39.0 (q, J = 28.2 Hz), 36.9 (q, J = 2.6 Hz), 14.1, 14.0. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -64.4 (t, J= 10.7 Hz). HRMS (ESI): Calcd for $[C_{17}H_{18}BrF_3O_4, M+Na]^+$: 445.0233, measured: 445.0246.

3,5-Dimethyl-1-tosyl-3-(2,2,2-trifluoroethyl)indoline (6a). 98.8 mg, 86% yield. Yellow oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 3.92 (d, *J* = 10.8 Hz, 1H), 3.67 (d, *J* = 11.4 Hz, 1H), 2.37 (s, 3H), 2.24 - 2.32 (m, 4H), 1.93 - 2.01 (m, 1H), 1.21 (s, 3H). **^{13}C-NMR** (151 MHz,

$CDCl_3$): δ = 144.3, 138.1, 138.1, 133.8, 129.7 (2C), 129.4, 127.7, 127.3 (2C), 126.0 (q, *J* = 278.7 Hz), 123.3, 114.9, 61.4, 42.7 (q, *J* = 26.9 Hz), 41.0 (q, *J* = 1.5 Hz), 25.1, 21.5, 21.0. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.4 (t, *J* = 10.7 Hz). HRMS (ESI): Calcd for $[C_{19}H_{20}F_3NO_2S$, M+Na$]^+$: 406.1059, measured: 406.1069.

5-Methoxy-3-methyl-1-tosyl-3-(2,2,2-trifluoroethyl)indoline (6b). 93.4 mg, 78% yield. Yellow oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.79 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 3.94 (d, *J* = 11.4 Hz, 1H), 3.77 (s, 3H), 3.67 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3H), 2.17 - 2.27 (m, 1H), 1.86 - 1.94 (m, 1H), 1.18 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 156.9, 144.3, 139.7, 133.8, 133.7, 129.7 (2C), 127.3 (2C), 125.9 (q, *J* = 277.1 Hz), 116.2, 113.6, 109.0, 61.5, 55.7, 42.7 (q, *J* = 26.9 Hz), 42.2 (q, *J* = 1.7 Hz), 25.0, 21.5. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.4 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{19}H_{20}F_3NO_3S$, M+Na$]^+$: 422.1008, measured: 422.1008.

5-Bromo-3-methyl-1-tosyl-3-(2,2,2-trifluoroethyl)indoline (6c). 95.2 mg, 71% yield. Yellow oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8,4 Hz, 1H), 7.36 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 1.8 Hz, 1H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.68 (d, *J* = 10.8 Hz, 1H), 2.39 (s, 3H), 2.23 - 2.31 (m, 1H), 1.98 - 2.06 (m, 1H), 1.23 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 144.7, 140.1, 139.8, 133.6, 131.8, 129.9 (2C), 127.2 (2C), 125.8 (q, *J* = 276.9 Hz), 126.1, 116.5, 116.5, 61.4, 42.6 (q, *J* = 28.4 Hz), 41.1 (q, *J* = 1.7 Hz), 25.2, 21.5. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.4 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{18}H_{17}BrF_3NO_2S$, M+Na$]^+$: 470.0008, measured: 470.0007.

***Tert*-butyl-3,5-dimethyl-3-(2,2,2-trifluoroethyl)indoline-1-carboxylate (6d).** 98.7 mg, 88% yield. Colorless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.33 - 7.80 (br. 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.89 (s, 1H), 4.00 (d, *J* = 10.2 Hz, 1H), 3.74 (s, 1H), 2.46 - 2.54 (m, 1H), 2.35 - 2.44 (m, 1H), 2.30 (s, 3H), 1.56 (s, 9H) 1.42 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 152.4, 137.3, 132.1, 129.0, 127.3, 125.4, 122.8, 126.3 (q, *J* = 277.0 Hz), 80.7, 60.1, 43.3 (q, *J* = 26.6 Hz), 28.5 (3C), 26.0, 26.0, 20.9. **^{19}F-NMR** (565 MHz, $CDCl_3$): δ = -60.4 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{17}H_{22}F_3NO_2$, M+Na$]^+$: 352.1495, measured: 352.1490.

***Tert*-butyl-5-chloro-3-methyl-3-(2,2,2-trifluoroethyl)indoline-1-carboxylate (6e).** 91.3 mg, 87% yield. Colorless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.37 - 7.80 (br. 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 4.03 (d, *J* = 10,8 Hz, 1H), 3.77 (s, 1H), 2.38 - 2.52 (m, 2H), 1.56 (s, 9H), 1.43 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 152.1, 140.1, 138.9, 128.5, 127.5, 126.1 (q, *J* = 278.7 Hz), 122.6, 116.0, 81.5, 60.1, 43.2 (q, *J* = 27.0 Hz), 28.4 (3C), 26.1, 26.1. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -60.4 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{16}H_{19}ClF_3NO_2$, M+Na$]^+$: 371.0996, measured: 371.1005.

***Tert*-butyl-5-methoxy-3-methyl-3-(2,2,2-trifluoroethyl)indoline-1-carboxylate (6f).** 99.4 mg, 90% yield. Colorless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.36 - 7.77 (br. 1H), 7.75 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 4.01 (s, 1H), 3.74 - 3.78 (m, 4H), 2.37 - 2.53 (m, 2H), 1.55 (s, 9H), 1.43 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 155.7, 152.4, 138.6, 138.2, 126.3 (q, *J* = 278.6 Hz), 115.6, 112.8, 109.0, 80.7, 60.1, 55.8, 43.2 (q, *J* = 26.9 Hz), 28.5 (3C), 25.9, 25.9. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -60.4 (t, *J* = 11.3 Hz). HRMS (ESI): Calcd for $[C_{17}H_{22}F_3NO_3$, M+Na$]^+$: 368.1444, measured: 368.1447.

3-Methyl-1-phenyl-3-(2,2,2-trifluoroethyl)indoline (6h). 65.5 mg, 75% yield. Colorless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.36 (t. *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.12 - 7.16 (m, 2H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.81 (t, *J* = 7.2 Hz, 1H), 3.98 (d, *J* = 9.6 Hz, 1H), 3.73 (d, *J* = 9.6 Hz, 1H), 2.46 – 2.60 (m, 2H), 1.50 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 145.5, 143.6, 137.4, 129.3 (2C), 128.1, 126.6 (q, *J* = 278.9 Hz), 122.6, 121.5, 119.3, 118.0 (2C), 108.5, 64.1, 42.5 (q, *J* = 26.7 Hz), 40.7 (q, *J* = 1.1 Hz), 24.7. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -60.3 (t, *J* = 12.2 Hz). HRMS (ESI): Calcd for $[C_{17}H_{16}F_3N$, M+Na$]^+$: 313.1174, measured: 313.1167.

(5-Methoxy-3-methyl-3-(2,2,2-trifluoroethyl)indolin-1-yl)(phenyl)methanone (6i). 74.4 mg, 71% yield. Colorless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.26 - 7.29 (m, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 3.94 (d, *J* = 12.6 Hz, 1H), 3.83 (s, 3H), 3.74 (d, *J* = 12.6 Hz, 1H), 2.51 – 2.70 (m, 2H), 1.60 (s, 3H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 164.0, 158.1, 144.0, 135.4, 132.6, 129.4, 128.4, 127.8, 126.6 (2C), 126.1 (q, *J* = 282.5 Hz), 124.5, 114.0 (2C), 59.0, 55.5, 41.3 (q, *J* = 25.4 Hz), 35.6, 22.3. **^{19}F-NMR** (470 MHz, $CDCl_3$): δ = -59.6 (t, *J* = 12.2 Hz). HRMS (ESI): Calcd for $[C_{19}H_{18}F_3NO_2$, M+Na$]^+$: 372.1182, measured: 372.1190.

Conflicts of interest

There are no conflicts to declare.

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