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Synthesis of CF_3-Containing 3,3′-Cyclopropyl Spirooxindoles by Sequential [3 + 2] Cycloaddition/Ring Contraction of Ylideneoxindoles with 2,2,2-Trifluorodiazoethane

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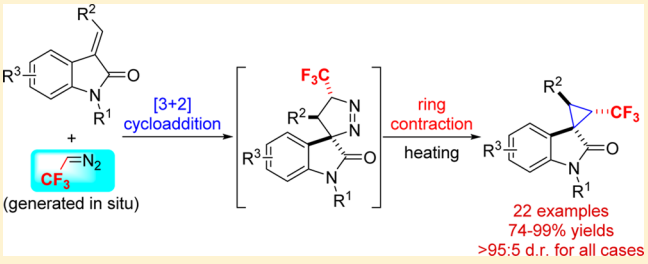
Supporting Information

ABSTRACT: A [3 + 2] cycloaddition/ring contraction sequence of ylideneoxindoles with in situ-generated 2,2,2-trifluorodiazoethane without the use of any transition-metal catalyst has been developed. The reaction provides efficient access to biologically important and synthetically useful CF_3-containing 3,3′-cyclopropyl spirooxindoles in high yield (74−99%) with high diastereoselectivity (>95:5 d.r.).



Spirocyclic oxindoles, especially 3,3′-cyclopropyl spirooxindoles, represent a ubiquitous class of biologically important compounds. They can be also widely found in various natural products and pharmaceuticals.[1−3] For example, many compounds containing the 3,3′-cyclopropyl spirooxindole moiety exhibit interesting biological activities, and some have been identified as powerful HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) as well as kinase and arginine vasopressin inhibitors (Scheme 1).[4] On the other hand, enriching the repertoire of fluorine-containing carbo- and heterocycles has attracted extensive research efforts from synthetic and medical chemists over the past decade because of the unique fluorine effect on the physiochemical properties of pharmaceuticals and drug candidates.[5] In this context, the search for efficient and powerful methodologies for the construction of highly substituted and functionalized carbo- and heterocyclic rings bearing CF_3 moieties has recently become an attractive research topic, since the incorporation of CF_3 groups into drugs always leads to significant improvements in lipophilicity, binding selectivity, and metabolic stability compared with the parent molecules.[6]

Recently, the highly reactive compound 2,2,2-trifluorodiazoethane (CF_3CHN_2) has been identified as a robust C_1 unit for the synthesis of CF_3-containing cyclopropane derivatives.[7] Notably, Carreira and co-workers have demonstrated that this type of reagent can be easily generated in situ from commercially available $CF_3CH_2NH_2$·HCl in the presence of $NaNO_2$.[8] Accordingly, harsh reaction conditions and direct handling of toxic, gaseous, and explosive CF_3CHN_2 can be avoided by using this strategy. As a result, a wide range of transition-metal-promoted cyclopropanations of various terminal olefins and alkynes have been accomplished, providing efficient access to the corresponding structurally diverse CF_3-containing small-ring molecules with high reaction efficiency (Scheme 2, eq 1). Other impressive work has come from the Mykhailiuk group, who reported the cycloaddition of in situ-generated CF_3CHN_2 with α-methylene aminocarboxylates to prepare 1-amino-2-(trifluoromethyl)cyclopropane-1-carboxylic esters, albeit with relatively low diastereoselectivity.[9] Quite recently, the Ma group developed the Ag_2O-mediated [3 + 2] cycloaddition reaction of in situ-generated CF_3CHN_2 with terminal alkynes, which furnishes a diverse set of biologically important 3-(trifluoromethyl)pyrazoles in good yields (Scheme 2, eq 2).[10] Despite the advances being made, trisubstituted electron-deficient alkenes still remain rarely exploited in cycloaddition reactions with the use of CF_3CHN_2 as a CF_3 synthon. As part of our ongoing research program on developing new cascade reactions to construct carbo- and heterocyclic systems,[11] we have developed a highly efficient sequential [3 + 2] cycloaddition/ring contraction reaction of CF_3CHN_2 with ylideneoxindoles under metal-free conditions. The reaction provides access to densely functionalized CF_3-containing 3,3′-cyclopropyl spirooxindoles in high yields and stereoselectivities (Scheme 2, eq 3).

Initially, ethyl (*E*)-2-(1-methyl-2-oxoindolin-3-ylidene)-acetate (**1a**) was chosen as the model substrate to react with CF_3CHN_2, which was generated in situ from $CF_3CH_2NH_2$·HCl and $NaNO_2$ in DCM/H_2O at 0 °C. To our delight, the initial [3 + 2] cycloaddition occurred smoothly to give the corresponding cycloadduct **3a** in 87% isolated yield with excellent regioselectivity and diasteroselectivity (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by single-crystal X-ray analysis.[12] Significantly, the subsequent ring

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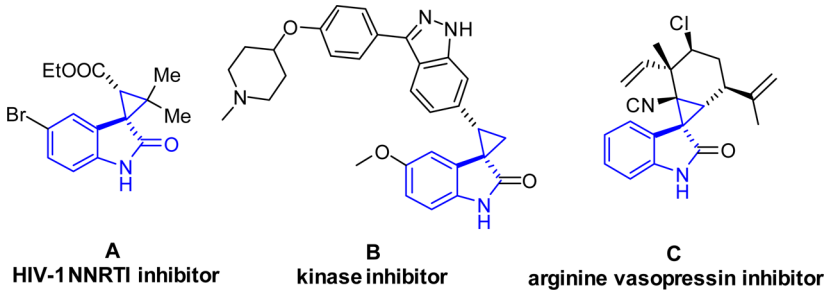
Scheme 1. Representative Therapeutic Agents Containing 3,3′-Cyclopropyl Spirooxindole Scaffolds



A HIV-1 NNRTI inhibitor | **B** kinase inhibitor | **C** arginine vasopressin inhibitor

Scheme 2. Design of the [3 + 2] Cycloaddition/Ring Contraction Sequence for the Synthesis of CF_3-Containing 3,3′-Cyclopropyl Spirooxindoles

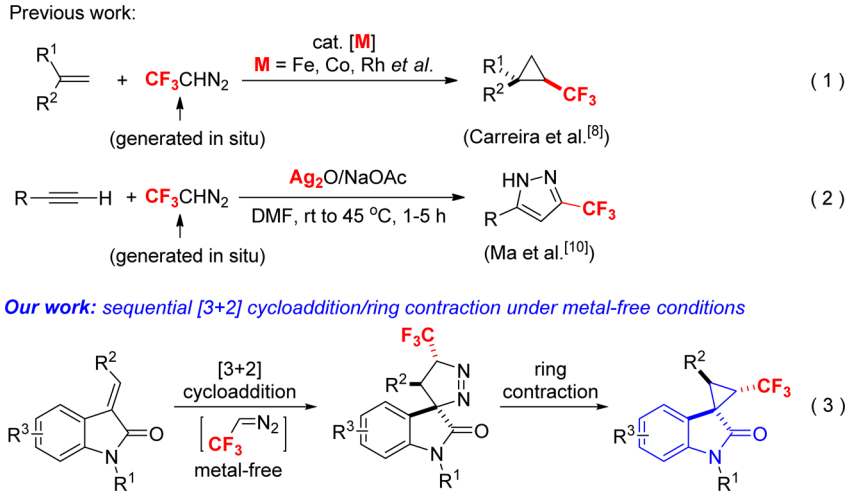
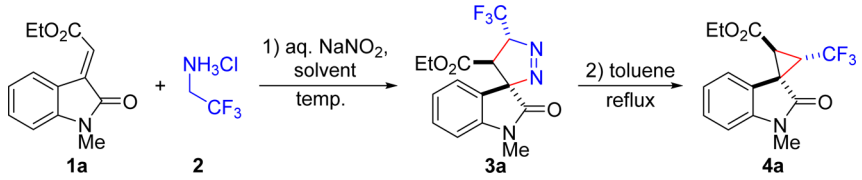


Table 1. Optimization of the Reaction Conditions[a]



entry	T (°C)	solvent	t (h)	yield of **3a** (%)[b]	d.r. of **3a**[c]	yield of **4a** (%)[b]
1	0	DCM	72	87	>95:5	87
2	25	DCM	60	87	>95:5	n.d.[d]
3	40	DCM	48	81	>95:5	n.d.
5	25	$CHCl_3$	36	92	>95:5	n.d.
6	25	DCE	48	83	>95:5	n.d.
7	25	toluene	36	90	>95:5	n.d.
8[e]	**25**	**toluene**	**36**	**n.d.**[e]	**>95:5**	**91**
9[e,f]	25	toluene	96	n.d.[e]	>95:5	84

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), $CF_3CH_2NH_2$·HCl (5 equiv), $NaNO_2$ (6 equiv), solvent (3.0 mL), H_2O (0.2 mL). [b]Isolated yields based on **1a**. [c]Determined by ^1H NMR analysis. [d]n.d. = not determined. [e]The reaction mixture was directly warmed to reflux for 1 h upon complete consumption of **1a**. [f]**2**/$NaNO_2$ (0.6/0.72 mmol, 3/3.6 equiv) were used.

contraction reaction of **3a** also worked very well in refluxing toluene to afford the final CF_3-substituted 3,3′-cyclopropyl spirooxindole **4a** in 87% overall yield with excellent diasteroselectivity. These results encouraged us to investigate other reaction parameters to further improve the reaction efficiency. It was found that the reaction at room temperature gave a comparable yield of **3a** with reduced reaction time, while elevating the temperature to 40 °C resulted in somewhat inferior results, probably because of the instability and volatility of CF_3CHN_2 (Table 1, entry 2 vs entry 3). A brief screen of reaction media showed that toluene was the best solvent of choice (Table 1, entry 7). Notably, the sequential [3 + 2] cycloaddition/ring contraction reaction could be carried out in a one-pot fashion in toluene, affording the desired product **4a** in 91% overall yield (Table 1, entry 8). The reaction with reduced amounts of $CF_3CH_2NH_2$·HCl and $NaNO_2$ led to a slight drop in the overall yield (Table 1, entry 9).[12]

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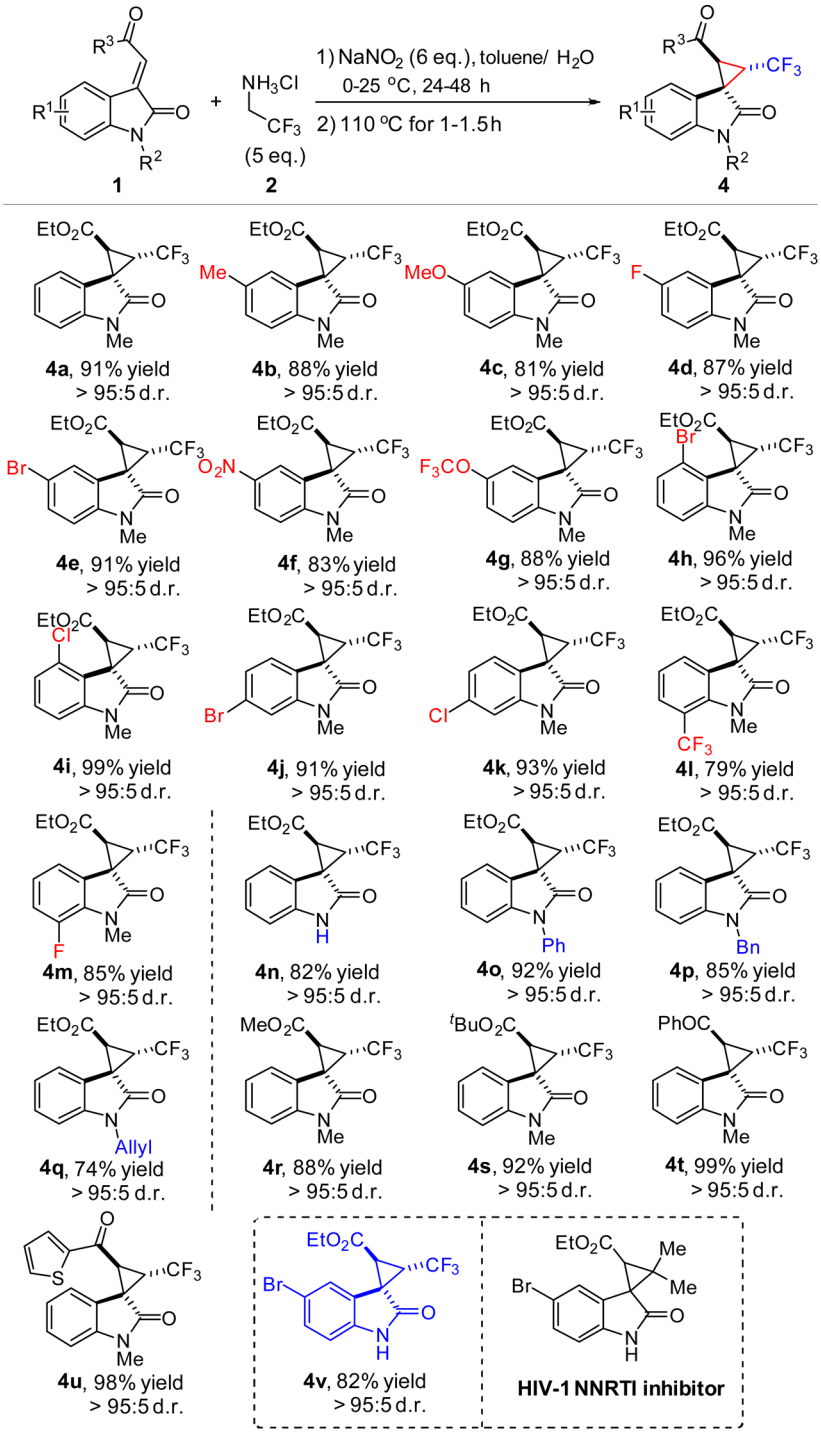
Scheme 3. Scope of the [3 + 2] Cycloaddition/Ring Contraction Sequence[a]



[a]Reaction conditions: see entry 8 of Table 1. Yields of isolated products are shown; all of the d.r. values were determined by ^{1}H NMR analysis.

With the optimized conditions in hand, we then investigated the substrate scope of this tandem reaction. As shown in Scheme 3, a wide range of 3-ylideneoxindoles were found to be suitable for the reaction. Both electron-donating groups (e.g., Me and MeO) and electron-withdrawing groups (e.g., F, Br, NO_2, CF_3O, Cl, and CF_3) were well-tolerated under the reaction conditions, and the corresponding CF_3-containing 3,3′-cyclopropyl spirooxindoles **4a**−**m** were obtained in 79−99% yield with >95:5 dr. Importantly, the above-mentioned halo-substituted products allowed for further transformations through transition-metal-catalyzed cross-coupling reactions. Notably, the products bearing CF_3O, CF_3, and F groups on the aromatic ring (**4g**, 88% yield; **4l**, 79% yield; **4m**, 85% yield; Scheme 3) should also be of significant interest to medicinal chemists because of the potential effect of fluorine on the physiochemical properties of these molecules.

Moreover, the effects of varying the N-protecting group and the ester moiety of the 3-ylideneoxindole were examined. As shown in Scheme 3, 3-ylideneoxindoles with N-protecting groups such as Ph (**1o**), Bn (**1p**), allyl (**1q**) or without a

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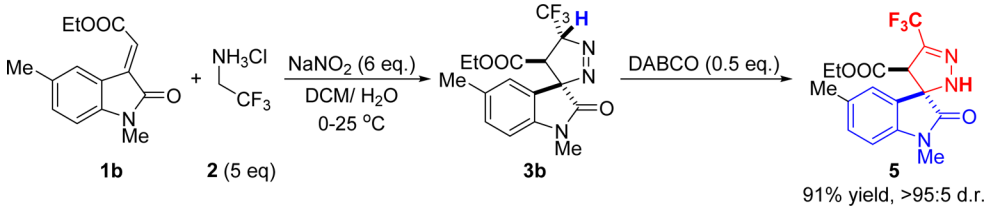
Scheme 4. Sequential [3 + 2] Cycloaddition/1,3-H Shift Reaction for the Synthesis of CF_3-Containing Spiropyrazoline Oxindole 5



protecting group could participate in this reaction very well, providing the corresponding products **4n−q** in 74−92% yield. Variation of the ester moiety (e.g., Me, Et, or ^{t}Bu) had less effect on both the reaction efficiency and stereoselectivity. Remarkably, the reaction was also successfully extended to 3-ylideneoxindoles with (hetero)aromatic carbonyl substituents. For example, the reactions with phenyl- and 2-thiophene-substituted carbonyl groups worked very well, producing **4t** and **4u** in 99% and 98% yield, respectively. Perhaps more importantly, spirooxindole **4v**, an analogue of an HIV-1 NNRTI, was successfully synthesized in one step from ethyl (*E*)-2-(5-bromo-2-oxoindolin-3-ylidene)acetate by this methodology, which further highlights the synthetic potential of this transformation.[4] All of these products were fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS analysis. The structure and stereochemistry of product **4c** were also unambiguously confirmed by single-crystal X-ray analysis.[12]

Interestingly, an alternative sequential [3 + 2] cycloaddition/1,3-H shift reaction was also disclosed during optimization of the reaction conditions. As shown in Scheme 4, in the case of ethyl (*E*)-2-(1,5-dimethyl-2-oxoindolin-3-ylidene)acetate (**1b**), the reaction formed CF_3-substituted spiropyrazoline oxindole **5** with high diastereoselectivity when DABCO was used as the base (91% yield, >95:5 d.r.; Scheme 4). It is noteworthy that this process provides a complementary method to synthesize compounds bearing both oxindole and pyrazoline skeletons.[13]

In summary, we have developed the first example of a sequential [3 + 2] cycloaddition/ring contraction reaction of 3-ylideneoxindoles with in situ-generated CF_3CHN_2 under transition-metal-free conditions. This method provides a straightforward approach to highly substituted and functionalized CF_3-containing 3,3′-cyclopropyl spirooxindole derivatives in excellent yields with great diastereoselectivities. Significantly, a CF_3-substituted analogue of an HIV-1 NNRTI can be synthesized in one step by this methodology. Moreover, a sequential [3 + 2] cycloaddition/1,3-H shift reaction promoted by DABCO was also disclosed, providing a new access to CF_3-containing spiropyrazoline oxindoles.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All of the solvents were treated according to known methods.

General Procedure for the Synthesis of 3-Ylideneoxindoles. To a stirred solution of ethyl 2-(triphenylphosphoranylidene)acetate (22 mmol, 1.1 equiv) in anhydrous THF (50 mL) was added *N*-methylindoline-2,3-dione (20 mmol, 1.0 equiv) at 0 °C. The mixture was stirred at the same temperature until the reaction was complete, as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1). Compound **1a** was obtained as a red solid (1.74 g, 86% yield). The other 3-ylideneoxindoles were prepared according to the above procedure using the corresponding acetates and diones.

General Procedure for the Sequential [3 + 2] Cycloaddition/Ring Contraction Reaction of Alkylenyloxindoles with in Situ-Generated CF_3CHN_2. $CF_3CH_2NH_2$·HCl (135.5 mg, 1.0 mmol, 5 equiv), $NaNO_2$ (83 mg, 1.2 mmol, 6 equiv), and H_2O (0.2 mL) were stirred in 3.0 mL of toluene at 0 °C for 1 h in a 10 mL Schlenk tube under Ar. Then alkylenyloxindole **1** (0.20 mmol) was added, and the reaction mixture was stirred at room temperature for 36 h. The mixture was then heated to reflux for 1.5 h with vigorous stirring. Upon completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and then directly subjected to column chromatography to afford the desired product **4**.

General Procedure for the Sequential [3 + 2] Cycloaddition/1,3-H Shift Reaction for the Synthesis of CF_3-Containing Spiropyrazoline Oxindoles with in Situ-Generated CF_3CHN_2. $CF_3CH_2NH_2$·HCl (135.5 mg, 1.0 mmol, 5 equiv), $NaNO_2$ (83 mg, 1.2 mmol, 6 equiv), and H_2O (0.2 mL) were stirred in 3.0 mL of DCM at 0 °C for 1 h in a 10 mL Schlenk tube under Ar. Then DABCO (11.2 mg, 0.1 mmol) (0.5 equiv) was added, followed by alkylenyloxindole **1** (0.20 mmol), and the reaction mixture was stirred at room temperature for 48 h. Upon completion of the reaction (as monitored by TLC), the reaction mixture was cooled to room temperature and then directly subjected to column chromatography to afford the desired product **5**.

*Ethyl 1-Methyl-2-oxo-5′-(trifluoromethyl)-4′,5′-dihydrospiro-[indoline-3,3′-pyrazole]-4′-carboxylate (**3a**).* 48 h, white solid (59.4 mg, 87% yield), mp 120.6 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 5.96−5.89 (m, 1H), 3.93−3.72 (m, 2H), 3.64 (d, J = 9.1 Hz, 1H), 3.38 (s, 3H), 0.68 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 166.8, 144.4, 131.6, 124.5, 123.2, 123.0 (q, J = 277 Hz), 120.6, 108.9, 99.4, 91.8 (q, J = 28.7 Hz), 61.9, 45.0, 26.9, 13.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.06. MS (EI): m/z 341.03 (M^+). HRMS (ESI-TOF) for $C_{15}H_{14}F_3N_3O_3$ [M + Na]$^+$: calcd 364.0879, found 364.0885.

*Ethyl 1′-Methyl-2′-oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4a**).* 48 h, colorless oil (56.9 mg, 91% yield), d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 4.25−4.13 (m, 2H), 3.38 (d, J = 7.7 Hz, 1H), 3.33 (s, 3H), 3.20−3.14 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 166.2, 144.0, 128.9, 123.5, 123.3 (q, J = 274 Hz), 122.5, 122.4, 108.3, 62.0, 36.2, 35.3 (q, J = 41.0 Hz), 34.9 (d, J = 3 Hz), 26.8, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.17. MS (EI): m/z 313.23 (M^+). HRMS (ESI-TOF) for $C_{15}H_{14}F_3NO_3$ [M + H]$^+$: calcd 314.0999, found 314.1000.

*Ethyl 1′,5′-Dimethyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4b**).* 48 h, white solid (57.6 mg, 88% yield), mp 107.9 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (d, J = 7.9 Hz, 1H), 7.12 (s, 1H), 6.80 (d, J = 7.9 Hz, 1H), 4.24−4.10 (m, 2H), 3.34 (d, J = 7.7 Hz, 1H), 3.28 (s, 3H), 3.14−3.09 (m, 1H), 2.33 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.2, 141.7, 132.1, 129.1, 123.5, 123.4 (q, J = 273 Hz), 123.1, 108.1, 62.0, 36.2, 35.2 (q, J = 40.7 Hz), 34.8, 26.7, 21.1, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.29. MS (EI): m/z 327.27 (M^+). HRMS (ESI-TOF) for $C_{16}H_{16}F_3NO_3$ [M + H]$^+$: calcd 328.1155, found 328.1155.

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*Ethyl 5′-Methoxy-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4c**).* 48 h, yellow solid (55.6 mg, 81% yield), mp 90.9 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.96 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 4.23−4.11 (m, 2H), 3.78 (s, 3H), 3.35 (d, *J* = 7.8 Hz, 1H), 3.27 (s, 3H), 3.13−3.08 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 166.1, 155.8, 137.5, 124.6, 123.3 (q, *J* = 273 Hz), 113.5, 109.7, 108.7, 62.1, 55.7, 36.4, 35.4 (q, *J* = 41.0 Hz), 34.8, 26.8, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.28. MS (EI): *m*/*z* 344.0 (M^+). HRMS (ESI-TOF) for $C_{16}H_{16}F_3NO_4$ $[M + H]^+$: calcd 344.1104, found 344.1107.

*Ethyl 5′-Fluoro-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4d**).* 36 h, yellow solid (57.7 mg, 87% yield), mp 87.4 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 7.08−7.02 (m, 1H), 6.84 (dd, *J* = 8.6 Hz, 4.2 Hz, 1H), 4.27−4.13 (m, 2H), 3.37 (d, *J* = 7.8 Hz, 1H), 3.29 (s, 3H), 3.15−3.08 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 166.0, 158.9 (d, *J* = 239 Hz), 140.1 (d, *J* = 1 Hz), 125.0 (d, *J* = 10 Hz), 123.2 (q, *J* = 273 Hz), 115.1 (d, *J* = 23 Hz), 111.0 (d, *J* = 27 Hz), 108.8 (d, *J* = 8 Hz), 62.3, 36.3, 35.7 (q, *J* = 41.0 Hz), 34.9 (d, *J* = 3 Hz), 26.9, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.35, −119.99. MS (EI): *m*/*z* 331.26 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}F_4NO_3$ $[M + H]^+$: calcd 332.0904, found 332.0893.

*Ethyl 5′-Bromo-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4e**).* 36 h, white solid (71.4 mg, 91% yield), mp 90.0 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.26−4.15 (m, 2H), 3.36 (d, *J* = 7.8 Hz, 1H), 3.28 (s, 3H), 3.15−3.10 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 165.9, 143.1, 131.7, 125.7, 125.4, 123.1 (q, *J* = 274 Hz), 115.1, 109.7, 62.3, 35.8, 35.6 (q, *J* = 39.7 Hz), 35.0, 26.8, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.01. MS (EI): *m*/*z* 391.21 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}BrF_3NO_3$ $[M + H]^+$: calcd 392.0104, found 392.0090.

*Ethyl 1′-Methyl-5′-nitro-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4f**).* 36 h, yellow solid (59.4 mg, 83% yield), mp 143.1 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.6 Hz, 1H), 8.28 (s, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.28−4.17 (m, 2H), 3.42 (d, *J* = 7.9 Hz, 1H), 3.38 (s, 3H), 3.31−3.26 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 165.6, 149.4, 143.3, 125.8, 124.2, 122,9 (q, *J* = 275 Hz), 118.8, 108.0, 62.6, 35.9 (q, *J* = 41 Hz), 35.6 (d, *J* = 2 Hz), 35.4 (d, *J* = 2 Hz), 27.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.54. MS (EI): *m*/*z* 359.15 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}F_3N_2O_5$ $[M + H]^+$: calcd 359.0849, found 359.0856.

*Ethyl 1′-Methyl-2′-oxo-5′-(trifluoromethoxy)-3-(trifluoromethyl)-spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4g**).* 36 h, white solid (70.0 mg, 88% yield), mp 69.2 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.27−4.11 (m, 2H), 3.38 (d, *J* = 7.7 Hz, 1H), 3.31 (s, 3H), 3.20−3.12 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 165.9, 144.5, 142.8, 124.9, 123.1 (q, *J* = 274 Hz), 122.9 (q, *J* = 256 Hz), 122.1, 116.9, 108.7, 62.4, 36.0 (d, *J* = 2 Hz), 35.7 (q, *J* = 41 Hz), 35.1 (d, *J* = 3 Hz), 26.9, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.31, −58.83. MS (EI): *m*/*z* 398.0 (M^+). HRMS (ESI-TOF) for $C_{16}H_{13}F_6NO_4$ $[M + H]^+$: calcd 398.0822, found 398.0826.

*Ethyl 4′-Bromo-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4h**).* 48 h, yellow solid (75.3 mg, 96% yield), mp 107.2 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 4.44 (d, *J* = 8.4 Hz, 1H), 4.29−4.22 (m, 2H), 3.25 (s, 3H), 3.06−3.01 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 165.3, 146.6, 129.9, 128.0, 123.8 (q, *J* = 273 Hz), 120.4, 118.1, 107.9, 62.0, 37.7, 36.9 (q, *J* = 41.3 Hz), 29.0, 26.9, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −56.99. MS (EI): *m*/*z* 391.1 (M^+), 393.1 ($[M + 2]^+$). HRMS (ESI-TOF) for $C_{15}H_{13}BrF_3NO_3$ $[M + H]^+$: calcd 392.0104, found 392.0095.

*Ethyl 4′-Chloro-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4i**).* 48 h, yellow solid (69.0 mg, 99% yield), mp 88.6 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.29−4.21 (m, 3H), 3.26 (s, 3H), 3.09−3.04 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 165.2, 146.3, 130.0, 129.7, 124.5, 123.7 (q, *J* = 272 Hz), 118.9, 107.3, 61.9, 36.8, 36.5 (q, *J* = 41.0), 29.2, 26.9, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.71. MS (EI): *m*/*z* 347.25 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}ClF_3NO_3$ $[M + H]^+$: calcd 348.0609, found 348.0608.

*Ethyl 6′-Bromo-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4j**).* 36 h, white solid (71.5 mg, 91% yield), mp 129.5 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 2.6 Hz, 1H), 7.18 (s, 2H), 7.06 (s, 1H), 4.23−4.10 (m, 2H), 3.34 (d, *J* = 7.8 Hz, 1H), 3.28 (s, 3H), 3.14−3.10 (m, 1H), 1.24 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 166.0, 145.3, 125.3, 123.8, 123.1 (q, *J* = 274 Hz), 122.6, 122.3, 111.8, 62.2, 35.9, 35.3 (q, *J* = 40.7 Hz), 34.9, 26.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.36. MS (EI): *m*/*z* 391.24 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}BrF_3NO_3$ $[M + H]^+$: calcd 392.0104, found 392.0094.

*Ethyl 6′-Chloro-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4k**).* 48 h, yellowish solid (64.8 mg, 93% yield), mp 102.5 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 4.45 (d, *J* = 8.4 Hz, 1H), 4.30−4.21 (m, 2H), 3.25 (s, 3H), 3.06−3.01 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 165.2, 146.6, 129.9, 128.0, 123.8 (q, *J* = 273 Hz), 120.4, 118.1, 107.9, 62.0, 37.6, 36.8 (q, *J* = 41 Hz), 28.9, 26.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.03. MS (EI): *m*/*z* 348.0 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}ClF_3NO_3$ $[M + H]^+$: calcd 348.0609, found 348.0599.

*Ethyl 1′-Methyl-2′-oxo-3,7′-bis(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4l**).* 36 h, red oil (60.3 mg, 79% yield), d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.50 (s, 1H), 7.12 (s, 1H), 4.23−4.13 (m, 2H), 3.51 (s, 3H), 3.40 (s, 1H), 3.19 (s, 1H), 1.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 165.8, 142.0, 126.8 (q, *J* = 5.7 Hz), 125.8, 125.7, 123.4 (q, *J* = 270 Hz), 123.1 (q, *J* = 274 Hz), 121.8, 112.9 (q, *J* = 33 Hz), 62.4, 36.1, 35.9 (q, *J* = 41 Hz), 35.0, 29.6 (q, *J* = 6.3 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −53.64, −58.47. MS (EI): *m*/*z* 382.0 (M^+). HRMS (ESI-TOF) for $C_{16}H_{13}F_6NO_3$ $[M + H]^+$: calcd 382.0872, found 382.0879.

*Ethyl 7′-Fluoro-1′-methyl-2′-oxo-3-(trifluoromethyl)spiro-[cyclopropane-1,3′-indoline]-2-carboxylate (**4m**).* 36 h, white solid (56.4 mg, 85% yield), mp 89.0 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 7.06 (d, *J* = 12.4 Hz, 1H), 7.03−6.92 (m, 1H), 4.26−4.10 (m, 2H), 3.51 (s, 3H), 3.36 (d, *J* = 7.8 Hz, 1H), 3.16−3.09 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 165.9, 147.7 (d, *J* = 242 Hz), 130.8 (d, *J* = 9 Hz), 126.2 (d, *J* = 4 Hz), 123.2 (q, *J* = 273 Hz), 123.0 (d, *J* = 6 Hz), 118.3 (q, *J* = 3 Hz), 116.9 (d, *J* = 19 Hz), 62.2, 36.2, 35.8 (q, *J* = 41 Hz), 35.4, 29.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.35, −136.56. MS (EI): *m*/*z* 331.28 (M^+). HRMS (ESI-TOF) for $C_{15}H_{13}F_4NO_3$ $[M + H]^+$: calcd 332.0904, found 332.0891.

*Ethyl 2′-Oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4n**).* 48 h, white solid (49.2 mg, 82% yield), mp 153.1 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 4.26−4.11 (m, 2H), 3.36 (d, *J* = 7.8 Hz, 1H), 3.18−3.13 (m, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 166.1, 141.5, 128.9, 124.0, 123.4 (q, *J* = 273 Hz), 122.6, 122.5, 110.5, 62.2, 36.7, 35.6 (q, *J* = 41.0 Hz), 35.0, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.21. MS (EI): *m*/*z* 300.1 (M^+). HRMS (ESI-TOF) for $C_{14}H_{12}F_3NO_3$ $[M + H]^+$: calcd 300.0842, found 300.0846.

*Ethyl 2′-Oxo-1′-phenyl-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4o**).* 36 h, white solid (69.1 mg, 92% yield), mp 90.9 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.5 Hz, 2H), 7.45−7.39 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.30−4.12 (m, 2H), 3.45 (d, *J* = 7.7 Hz, 1H), 3.25−3.18 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 166.2, 144.0, 134.0, 129.6, 128.8, 128.3, 126.5, 123.4, 123.3 (q, *J* = 274 Hz), 123.0, 122.8, 109.7, 62.2, 36.4 (d, *J* = 2 Hz), 36.0 (q, *J* = 41.3 Hz), 35.3 (d, *J* = 3 Hz), 14.0. ^{19}F NMR (376

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MHz, $CDCl_3$): δ −58.17. MS (EI): *m/z* 376.1 (M^+). HRMS (ESI-TOF) for $C_{20}H_{16}F_3NO_3$ [M + H]$^+$: calcd 376.1155, found 376.1158.

*Ethyl 1′-Benzyl-2′-oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4p**).* 36 h, white solid (66.3 mg, 85% yield), mp 108.2 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37−7.24 (m, 7H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 4.87 (d, *J* = 15.6 Hz, 1H), 4.26−4.11 (m, 2H), 3.46−3.43 (m, 1H), 3.19−3.17 (m, 1H), 1.25 (t, *J* = 8.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 166.2, 143.2, 135.4, 128.8, 128.8, 127.7, 127.2, 123.6, 123.4 (q, *J* = 274 Hz), 122.6, 122.5, 109.3, 62.1, 44.3, 36.2 (d, *J* = 3 Hz), 35.7 (q, *J* = 40.7 Hz), 35.0 (d, *J* = 3 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.19. MS (EI): *m/z* 390.1 (M^+). HRMS (ESI-TOF) for $C_{21}H_{18}F_3NO_3$ [M + H]$^+$: calcd 390.1312, found 390.1317.

*Ethyl 1′-Allyl-2′-oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4q**).* 48 h, purple solid (50.1 mg, 74% yield), mp 89.9 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33−7.29 (m, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.89−5.83 (m, 1H), 5.25 (s, 1H), 5.23 (d, *J* = 4.7 Hz, 1H), 4.48−4.36 (m, 2H), 4.25−4.10 (m, 2H), 3.38 (d, *J* = 7.7 Hz, 1H), 3.17−3.13 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 166.2, 143.2, 131.0, 128.8, 123.5, 123.3 (q, *J* = 274 Hz), 122.5, 122.5, 117.8, 109.2, 62.1, 42.9, 36.1, 35.6 (q, *J* = 40.7 Hz), 34.9, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.37. MS (EI): *m/z* 340.1 (M^+). HRMS (ESI-TOF) for $C_{17}H_{16}F_3NO_3$ [M + H]$^+$: calcd 340.1155, found 340.1165.

*Methyl 1′-Methyl-2′-oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4r**).* 36 h, purple solid (52.6 mg, 88% yield), mp 94.6 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.72 (s, 3H), 3.37 (d, *J* = 7.7 Hz, 1H), 3.30 (s, 3H), 3.18−3.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.7, 144.1, 128.9, 123.4, 123.3 (q, *J* = 273 Hz), 122.6, 122.4, 108.4, 52.8, 36.3 (d, *J* = 3 Hz), 35.3 (q, *J* = 40.7 Hz), 34.7 (d, *J* = 3 Hz), 26.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.43. MS (EI): *m/z* 300.0 (M^+). HRMS (ESI-TOF) for $C_{14}H_{12}F_3NO_3$ [M + H]$^+$: calcd 300.0842, found 300.0849.

*tert-Butyl 1′-Methyl-2′-oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4s**).* 48 h, white solid (62.8 mg, 92% yield), mp 101.2 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 10.0 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 1H), 3.10−3.05 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 165.0, 144.0, 128.7, 123.6, 123.5 (q, *J* = 274 Hz), 122.4, 122.3, 108.3, 83.1, 35.9, 35.1 (q, *J* = 40.7 Hz), 27.9, 26.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.26. MS (EI): *m/z* 342.2 (M^+). HRMS (ESI-TOF) for $C_{17}H_{18}F_3NO_3$ [M + H]$^+$: calcd 342.1312, found 342.1313.

*2-Benzoyl-1′-methyl-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indolin]-2′-one (**4t**).* 48 h, orange solid (68.7 mg, 99% yield), mp 129.0 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 6.6 Hz, 1H), 7.43 (t, *J* = 6.9 Hz, 2H), 7.27 (t, *J* = 6.7 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.28 (d, *J* = 7.5 Hz, 1H), 3.51−3.46 (m, 1H), 3.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 170.3, 143.7, 135.9, 134.1, 128.8, 128.7, 128.5, 123.7 (q, *J* = 273 Hz), 123.3, 122.7, 122.1, 108.3, 38.3, 37.9, 34.9 (q, *J* = 40.3 Hz), 26.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.27. MS (EI): *m/z* 346.0 (M^+). HRMS (ESI-TOF) for $C_{19}H_{14}F_3NO_2$ [M + H]$^+$: calcd 346.1049, found 346.1058.

*1′-Methyl-2-(thiophene-2-carbonyl)-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indolin]-2′-one (**4u**).* 48 h, yellow solid (68.5 mg, 98% yield), mp 137.3 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.68 (d, *J* = 3.9 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.10 (s, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 4.17 (d, *J* = 7.6 Hz, 1H), 3.47−3.42 (m, 1H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.5, 170.2, 143.8, 143.3, 135.6, 133.6, 128.8, 128.5, 123.6 (q, *J* = 273 Hz), 123.3, 122.7, 122.5, 108.3, 38.7, 38.1, 34.9 (q, *J* = 40.3 Hz), 26.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.25. MS (EI): *m/z* 352.1 (M^+). HRMS (ESI-TOF) for $C_{17}H_{12}F_3NO_2S$ [M + H]$^+$: calcd 352.0614, found 352.0612.

*Ethyl 5′-Bromo-2′-oxo-3-(trifluoromethyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**4v**).* 36 h, white solid (61.7 mg, 82% yield), mp 187.8 °C, d.r. >95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.45 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.26−4.20 (m, 2H), 3.35 (d, *J* = 7.2 Hz, 1H), 3.21−3.12 (m, 1H), 1.27 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 165.8, 140.5, 131.8, 126.0, 125.9, 123.1 (q, *J* = 273 Hz), 115.2, 112.0, 62.5, 36.5, 35.9 (q, *J* = 41.0 Hz), 35.2 (d, *J* = 2 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −58.33. MS (EI): *m/z* 377.32 (M^+). HRMS (ESI-TOF) for $C_{14}H_{11}BrF_3NO_3$ [M + H]$^+$: calcd 377.9947, found 377.9955.

*Ethyl 1,5-Dimethyl-2-oxo-5′-(trifluoromethyl)-2′,4′-dihydrospiro[indoline-3,3′-pyrazole]-4′-carboxylate (**5**).* 72 h, white solid (63.0 mg, 91% yield), mp 135.0 °C, d.r. >95:5. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.17 (d, *J* = 7.9 Hz, 1H), 7.10 (s, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.17 (s, 1H), 4.58 (s, 1H), 3.91−3.81 (m, 2H), 3.24 (s, 3H), 2.31 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 165.1, 140.9, 137.2 (q, *J* = 38 Hz), 133.1, 131.3, 125.4, 125.1, 119.8 (q, *J* = 269 Hz), 108.4, 73.1, 61.6, 58.6 (d, *J* = 3.0 Hz), 26.7, 20.8, 13.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.45. MS (EI): *m/z* 355.12 (M^+). HRMS (ESI-TOF) for $C_{16}H_{16}F_3N_3O_3$ [M + Na]$^+$: calcd 378.1036, found 378.1036.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details, spectroscopic data for **4** and **5**, and CIF files for **3a** and **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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