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Cu-Catalyzed Carbenoid Functionalization of Indoles by Methyl 3,3,3-Trifluoro-2-diazopropionate

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An efficient protocol for the direct CH-functionalization of indole and its derivatives has been developed by using $Cu(F_3\text{-acac})_2$-catalyzed insertion of CF_3-carbene derived from methyl 3,3,3-trifluoro-2-diazopropionate. The reaction proceeds with high regioselectivity within a few minutes under low catalyst loading and allows the introduction of CF_3 and carboxylate functions simultaneously into the 3- or 2-position of the indole core. This method can be successfully applied for the synthesis of trifluoromethyl-containing paullones, which are new members of the known family of potent inhibitors of cyclin-dependent kinases.

Introduction

The incorporation of fluorine functionalities into bioactive compounds has become an important tool in the drug discovery process.[1] Particular attention is focused on trifluoromethyl-containing compounds due to the unique properties of the CF_3 group, such as high electronegativity, relatively low steric bulk, and hydrophobic character, which can profoundly improve the efficacy of the therapeutic agent.[2] Consequently, there is considerable interest in developing new methods for the selective introduction of the CF_3 group into organic molecules.

On the other hand, indoles and their derivatives are found in many bioactive substances, originating from both natural and synthetic sources.[3] Among synthetic strategies for the construction of substituted indoles, the direct functionalization of a preformed indole core seems to be a remarkably efficient approach to structurally diverse indoles[4] including their fluorinated derivatives.[5] In this context, insertion of carbenoids generated from the metal-catalyzed decomposition of diazo compounds[6] represents one of the most attractive and straightforward tools for easy access to a variety of functionalized indoles. The result of such transformation strictly depends on the original substrate substitution patterns.[7] Rhodium carboxylates,[8] copper salts,[9] indium bromide,[10] iron complexes,[11] and, more recently, ruthenium complexes[12] have all been found to be efficient catalysts for the process. Despite a number of reports on metal-carbenoid functionalization of indoles, most are associated with donor–acceptor carbenoids. To the best of our knowledge, only two more reactive acceptor–acceptor carbenoids derived from methyl diazomalonate under Rh-[8b] and Cu-[9b] catalysis, respectively, have been utilized for direct CH-functionalization of the indole core.

Alkyl 3,3,3-trifluorodiazopropionates have recently been recognized as attractive reagents for simultaneous introduction of trifluoromethyl and carboxylic functionalities into a diverse range of organic molecules. On copper- or rhodium-catalyzed extrusion of nitrogen, the resulting highly electrophilic acceptor–acceptor carbenoid has been shown to be effective at cycloaddition,[13] ylide generation,[14] ring expansion[15] as well as X–H[16] insertion. In the course of our ongoing studies on the development of new methods for selective introduction of CF_3 groups into bioactive compounds by means of appropriate building blocks[17] including α-CF_3-diazo compounds,[18] herein, we report our findings on the direct carbenoid CH-functionalization of indoles by using methyl trifluorodiazopropionate (**1**).

Results and Discussion

The investigation of CF_3-carbenoid functionalization of indoles commenced with a study on the reactions of unsubstituted indole with diazopropionate **1**.[13a] In our initial attempts, we examined rhodium(II) acetate as one of the most active catalysts commonly used for the mild diazo decomposition. As a result, we found that the reaction of equimolar amounts of the reagents took place only under heating in toluene at 90 °C in the presence of 5 mol-% $Rh_2(OAc)_4$ and proceeded to completion within 30 min, giving a mixture of N1, C2 and C3 insertion products in comparable ratio (Scheme 1). These products were separated by using column chromatography on silica gel and

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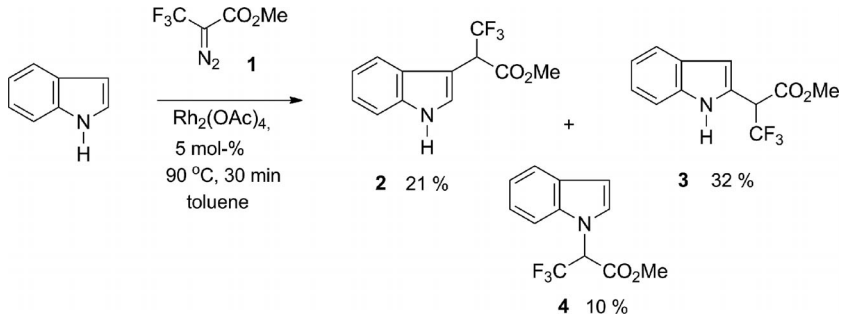
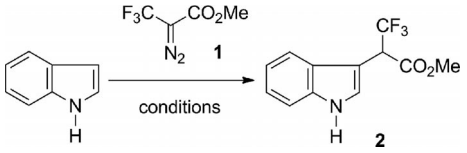


Scheme 1. Rh-catalyzed functionalization of indole by **1**.

fully characterized by NMR spectroscopic and elemental analyses. It should be noted that a similar regioselectivity was previously observed in the reaction of NH-indoles activated by alkyl groups in the 3- or 2-positions with methyl diazomalonate under Rh-catalysis.[8b]

Encouraged by a more recent report by Johansen and Kerr,[9b] wherein better selectivity was found in the same reaction under Cu catalysis, we tested the activity of Cu(acac)$_2$ along with (commercially available) copper trifluoroacetylacetonate [Cu(F$_3$-acac)$_2$] in the reaction of indole with CF$_3$-substituted diazopropionate **1**. The reactions were performed in either dichloromethane or toluene with the catalyst loading in a range of 0.2–5 mol-% (Table 1). Heating of the reagents in CH_2Cl_2 in the presence of 5 mol-% Cu(acac)$_2$ gave none of the desired product even after extended reaction time (entry 3), as was established for the Rh-catalyzed reaction (entry 1). However, the application of more drastic conditions led to the formation C3 insertion product **2** in appreciable yield (entry 4). In this case, approximately 9% of the C2 insertion byproduct **3** was detected in the reaction mixture (based on ^{19}F NMR spectroscopic analysis before isolation).

Table 1. Optimization of reaction conditions.



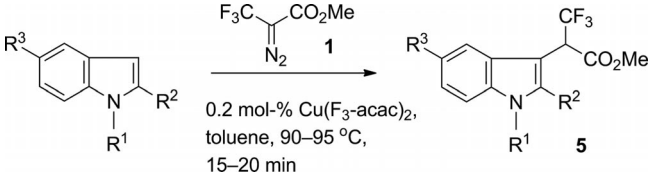
Entry	Solvent	Temp. [°C]	Time [min]	Catalyst (mol-%)	**2** [%][a]
1	CH_2Cl_2	40	24 h	$Rh_2(OAc)_4$ (5)	n.r.
2	toluene	90	30	$Rh_2(OAc)_4$ (5)	21
3	CH_2Cl_2	40	24 h	Cu(acac)$_2$ (5)	n.r.
4	toluene	95	30	Cu(acac)$_2$ (5)	68
5	toluene	95	35	Cu(acac)$_2$ (1)	65
6	toluene	95	40	Cu(acac)$_2$ (0.2)	60
7	CH_2Cl_2	40	24 h	Cu(F$_3$-acac)$_2$ (5)	n.r.
8	toluene	95	15	Cu(F$_3$-acac)$_2$ (5)	77
9	toluene	95	20	Cu(F$_3$-acac)$_2$ (1)	75
10	toluene	95	20	Cu(F$_3$-acac)$_2$ (0.2)	75

[a] Isolated yield after column chromatography on silica gel; n.r.: no reaction.

Similar results were obtained with decreased catalyst loading (Table 1, entries 5 and 6). We were pleased to find that the substitution of Cu(acac)$_2$ for Cu(F$_3$-acac)$_2$ led to notably better yields (entries 8 and 9) in reduced reaction times, even with the lowest catalyst loading (entry 10). The content of byproduct **3** in the reaction mixtures was found to be less than 5% in all these cases. Carbene insertion into the NH-bond was not observed under any of these conditions.

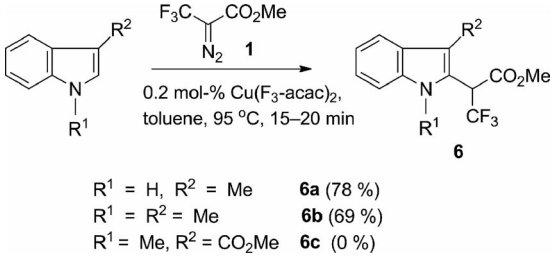
With optimal conditions in hand, we performed CF$_3$-carbene functionalization of commercially available indoles bearing different substituents at the 1-, 2- and 5-positions to afford the corresponding C3 insertion products **5** in good to excellent yields (Table 2). The nature of the substituents and their position in the indole core did not significantly affect the outcome of the reaction. The only exception was

Table 2. Cu-catalyzed selective C(3)H functionalization of indoles.

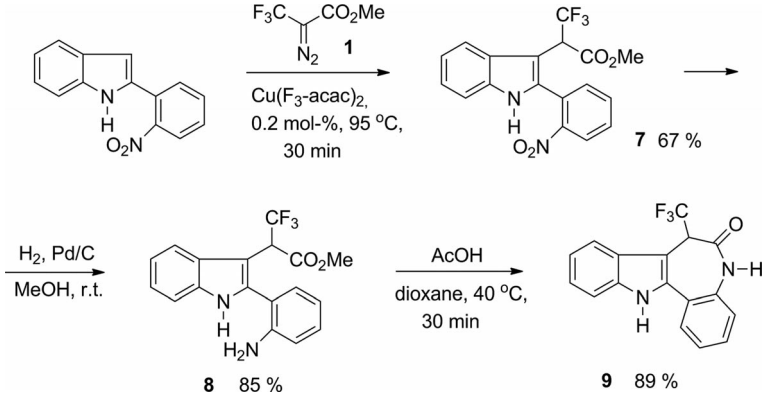


Entry	R^1	R^2	R^3	Product	Yield [%][a]
1	Me	H	H	**5a**	98
2	H	Ph	H	**5b**	93
3	H	Me	H	**5c**	85
4	Me	Ph	H	**5d**	88
5	Me	Me	H	**5e**	97
6	Me	H	Br	**5f**	91
7	H	H	NO_2	**5g**	72
8	H	Me	OMe	**5h**	80
9	H	H	CO_2Me	**5i**	79
10	Boc	H	H	**5j**	n.r.

[a] Isolated yield after column chromatography on silica gel.



Scheme 2. Cu-catalyzed C(2)H functionalization of indoles.



Scheme 3. Synthesis of CF_3-paullone.

found for N-Boc derivative (entry 10); in this case, a complex mixture of products was formed, which can be rationalized by a decreased reactivity of the indole due to the electron-withdrawing influence of the Boc group.

These conditions could also be applied for the functionalization of skatole and *N*-methylskatole to give good yields of C2-substitution products **6a** and **6b** (Scheme 2). However, a *N*-methylindole derivative deactivated by an electron–acceptor methoxycarbonyl group at the 3-position appeared to be completely inactive towards carbene insertion even with increased catalyst loading.

Having established an efficient CF_3-carbenoid C3 functionalization of indoles, we investigated the feasibility of applying this method for the construction of CF_3-containing paullones. The paullones are known inhibitors of cyclin-dependent kinases (CDKs).[19] Over the past decade, numerous derivatives of paullone have been found to possess antitumor,[20] antiproliferative,[21] and antileishmanial[22] activities, and to inhibit glycogen synthase kinase-3 (GSK-3), which may be important for the treatment of diabetes.[23] As such, significant effort has been directed towards efficient syntheses of new representatives of this class of compounds.[24]

For this purpose, we accomplished the synthesis of indole **7** from available 2-(*ortho*-nitrophenyl)indole[25] and diazo compound **1** by applying the same protocol for selective CF_3-carbene insertion (Scheme 3). Subsequent Pd-catalyzed hydrogenation of the NO_2 group of **7** was performed in methanol at room temperature for 24 h, furnishing amino-derivative **8**. Finally, the intramolecular cyclization of **8** was achieved by acidolysis in dioxane at 40 °C for 30 min to afford the desired CF_3-paullone **9** in high yield.

Conclusions

We have developed an efficient protocol for the direct CH-functionalization of indole and its derivatives through $Cu(F_3\text{-acac})_2$-catalyzed insertion of CF_3-carbene derived from methyl 3,3,3-trifluoro-2-diazopropionate. The reaction proceeds with high regioselectivity within a few minutes under low catalyst loading and allows CF_3 and carboxylate functions to be introduced simultaneously into the 3- or 2-position of the indole core. This method can be successfully applied for the synthesis of trifluoromethyl-containing paullones, which are new representatives of a known family of potent inhibitors of cyclin-dependent kinases.

Experimental Section

General Remarks: All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. Analytical TLC was performed with Merck silica gel 60 F_{254} plates; visualization was accomplished with UV light or spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. Chromatography was carried out by using Merck silica gel (Kieselgel 60, 0.063–0.200 mm) and petroleum ether/ethyl acetate as eluent. IR spectra were measured with a Fourier spectrometer Nicolet 6700. NMR spectra were obtained with Bruker AV-300 and AV-600 spectrometers operating at 300 and 600 MHz, respectively, for ^1H (TMS reference), at 150 MHz for ^{13}C, and at 282 MHz for ^{19}F (CF_3COOH reference).

General Procedure for Cu-Catalyzed CH-Functionalization of Indoles: To a solution of the corresponding indole (2.56 mmol, 1 equiv.) in anhydrous toluene (10 mL), diazo compound **1** (2.82 mmol, 1.1 equiv.) and copper trifluoroacetylacetonate (0.5 mmol, 0.2 mol-%) were added sequentially. The reaction mixture was stirred under heating (90–95 °C) for 15–30 min. Upon completion of the reaction (monitored by TLC) the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate).

Methyl 3,3,3-Trifluoro-2-(1*H*-indol-3-yl)propanoate (2): Eluent petroleum ether/ethyl acetate, 3:1, yield 75%; pink solid; m.p. 92–94 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 4.75 (q, $^3J_{H,F}$ = 8.5 Hz, 1 H, CH), 7.24–7.34 (m, 2 H, Ar), 7.46–7.48 (m, 2 H, Ar), 7.73 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ar), 8.39 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.61 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 47.4 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.9, 103.9, 111.6, 118.6, 120.6, 122.8, 124.3 (q, $^1J_{C,F}$ = 280 Hz, CF_3), 124.9, 126.4, 135.9, 167.6 ppm. $C_{12}H_{10}F_3NO_2$ (257.21): calcd. C 56.04, H 3.92, N 5.45; found C 55.97, H 3.72, N 5.25.

Methyl 3,3,3-Trifluoro-2-(1*H*-indol-2-yl)propanoate (3): Eluent petroleum ether/ethyl acetate, 10:1 then 5:1, yield 32%; orange solid; m.p. 75–76 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 4.71 (q, $^3J_{H,F}$ = 8.3 Hz, 1 H, CH), 6.67 (s, 1 H, C(3)-*H*),

7.21 (t, $^3J_{H,H}$ = 9 Hz, 1 H, Ar), 7.29–7.34 (m, 1 H, Ar), 7.47 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.69 (d, $^3J_{H,H}$ = 9 Hz, 1 H, Ar), 8.82 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 10.09 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 49.8 (q, $^2J_{C,F}$ = 30 Hz, CH), 53.5, 102.6, 105.4, 111.4, 120.3, 120.4, 120.8, 123.8 (q, $^1J_{C,F}$ = 279 Hz, CF_3), 127.5, 136.7, 166.2 ppm. $C_{12}H_{10}F_3NO_2$ (257.21): calcd. C 56.04, H 3.92, N 5.45; found C 56.02, H 3.99, N 5.70.

Methyl 3,3,3-Trifluoro-2-(1*H*-indol-1-yl)propanoate (4): Eluent petroleum ether/ethyl acetate, 20:1, yield 10%; pink oil. IR (Nujol): $\tilde{\nu}_{max}$ = 3418, 1755, 1612, 1522, 1118, 1001, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OCH_3), 5.65 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 6.73 (d, $^3J_{H,H}$ = 3 Hz, 1 H, C(3)-*H*), 7.26 (t, $^3J_{H,H}$ = 9 Hz, 1 H, Ar),7.33–7.35 (m, 1 H, Ar), 7.38 (s, 1 H, C(2)-*H*), 7.41–7.44 (m, 1 H, Ar), 7.73 (d, $^3J_{H,H}$ = 9 Hz, 1 H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 6.83 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 53.7, 58.4 (q, $^2J_{C,F}$ = 33 Hz, CH), 104.8, 108.5, 120.9, 121.5, 122.4 (q, $^1J_{C,F}$ = 281 Hz, CF_3), 122.9, 126.5, 128.6, 136.7, 163.9 ppm. $C_{12}H_{10}F_3NO_2$ (257.21): calcd. C 56.04, H 3.92, N 5.45; found C 56.21, H 3.84, N 5.38.

Methyl 3,3,3-Trifluoro-2-(1-methyl-1*H*-indol-3-yl)propanoate (5a): Eluent petroleum ether/ethyl acetate, 20:1, yield 98%; white solid; m.p. 69–70 °C. ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 3.76 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 5.04 (q, $^3J_{H,F}$ = 8.9 Hz, 1 H, CH), 7.19 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, Ar), 7.27 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ar), 7.43 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, Ar), 7.46 (s, 1 H, C(2)-*H*), 7.80 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.45 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, [D$_6$]acetone): δ = 32.1, 46.8 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.1, 102.2, 109.9, 118.8, 119.9, 122.1, 125.7 (q, $^1J_{C,F}$ = 278 Hz, CF_3), 127.1, 129.8, 139.9, 167.1 ppm. $C_{13}H_{12}F_3NO_2$ (271.24): calcd. C 57.57, H 4.46, N 5.16; found C 57.81, H 4.41, N 5.29.

Methyl 3,3,3-Trifluoro-2-(2-phenyl-1*H*-indol-3-yl)propanoate (5b): Eluent petroleum ether/ethyl acetate, 20:1, yield 93%; white solid; m.p. 136–137 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, OCH_3), 4.79 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 7.24 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, Ar), 7.29 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, Ar), 7.39 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, Ar), 7.57–7.45 (m, 1 H, Ar), 7.60 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, Ar), 7.92 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, Ar), 8.44 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 11.46 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 47.49 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.7, 101.1, 111.1, 120.9, 122.9, 124.7 (q, $^1J_{C,F}$ = 279 Hz, CF_3), 126.8, 127.2, 128.4, 129.1, 129.2, 131.4, 135.7, 139.4, 167.2 ppm. $C_{18}H_{14}F_3NO_2$ (333.30): calcd. C 64.86, H 4.23, N 4.20; found C 64.67, H 4.09, N 4.11.

Methyl 3,3,3-Trifluoro-2-(2-methyl-*1H*-indol-3-yl)propanoate (5c): Eluent petroleum ether/ethyl acetate, 5:1, yield 85%; gray solid; m.p. 116–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.62 (q, $^3J_{H,F}$ = 8.9 Hz, 1 H, CH), 7.17–7.25 (m, 2 H, Ar), 7.32–7.38 (m, 1 H, Ar), 7.69 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, Ar), 8.12 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 10.13 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.7, 47.0 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.6, 100.3, 110.6, 118.8, 120.4, 121.8, 124.7 (q, $^1J_{C,F}$ = 280 Hz, CF_3), 127.2, 135.0, 135.2, 167.4 ppm. $C_{13}H_{12}F_3NO_2$ (271.24): calcd. C 57.57, H 4.46, N 5.16; found C 57.47, H 4.27, N 4.87.

Methyl 3,3,3-Trifluoro-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)propanoate (5d): Eluent petroleum ether/ethyl acetate, 15:1, yield 88%; white solid; m.p. 106–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, N-CH_3), 3.76 (s, 3 H, OCH_3), 4.49 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 7.28 (t, $^3J_{H,H}$ = 6.9 Hz, 1 H, Ar), 7.37 (t, $^3J_{H,H}$ = 6.9 Hz, 1 H, Ar), 7.43–7.51 (m, 3 H, Ar), 7.60 (br. s, 3 H, Ar), 7.91 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.87 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.0, 47.8 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.6, 101.3, 109.6, 120.5, 120.7, 122.4, 124.7 (q, $^1J_{C,F}$ = 280 Hz, CF_3), 125.8, 128.6, 128.9, 129.3, 130.1, 130.3, 130.9, 137.1, 142.0, 167.3 ppm. $C_{19}H_{16}F_3NO_2$ (347.33): calcd. C 65.70, H 4.64, N 4.03; found C 65.66, H 4.58, N 4.04.

Methyl 2-(1,2-Dimethyl-1*H*-indol-3-yl)-3,3,3-trifluoropropanoate (5e): Eluent petroleum ether/ethyl acetate, 15:1, yield 97%; orange solid; m.p. 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.5 (s, 3 H, CH_3), 3.76 (s, 3 H, N-CH_3), 3.80 (s, 3 H, OCH_3), 4.65 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 7.19 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.27 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.35 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ar), 7.69 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 10.02 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 10.4, 29.8, 47.2 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.6, 99.5, 109.0, 118.8, 120.1, 121.4, 124.7 (q, $^1J_{C,F}$ = 280 Hz, CF_3), 126.4, 136.6, 136.7, 167.4 ppm. $C_{14}H_{14}F_3NO_2$ (285.26): calcd. C 58.95, H 4.95, N 4.91; found C 58.78, H 4.81, N 4.93.

Methyl 2-(5-Bromo-1-methyl-1*H*-indol-3-yl)-3,3,3-trifluoropropanoate (5f): Eluent petroleum ether/ethyl acetate, 20:1, yield 91%; pink solid; m.p. 103–104 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 4.63 (q, $^3J_{H,F}$ = 8.5 Hz, 1 H, CH), 7.20 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, Ar), 7.30 (s, 1 H, C(2)-*H*), 7.36 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, Ar), 7.81 (s, 1 H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.46 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 33.2, 47.1 (q, $^2J_{C,F}$ = 30 Hz, CH), 53.0, 101.9, 111.2, 113.7, 121.3, 124.9 (q, $^1J_{C,F}$ = 278 Hz, CF_3), 125.3, 128.6, 130.4, 135.4, 167.1 ppm. $C_{13}H_{11}BrF_3NO_2$ (350.13): calcd. C 44.59, H 3.17, N 4.00; found C 44.39, H 3.07, N 4.10.

Methyl 3,3,3-Trifluoro-2-(5-nitro-1*H*-indol-3-yl)propanoate (5g): Eluent petroleum ether/ethyl acetate, 6:1 then 3:1, yield 72%; yellow solid; m.p. 130–131 °C. IR (Nujol): $\tilde{\nu}_{max}$ = 3367, 1753, 1623, 1521, 1332, 1240, 1112, 1038, 1008, 818 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 4.78 (q, $^3J_{H,F}$ = 8.3 Hz, 1 H, CH), 7.54 (d, $^3J_{H,H}$ = 9 Hz, 1 H, Ar), 7.68 (s, 1 H, C(2)-*H*), 8.23 (d, $^3J_{H,H}$ = 8.9 Hz, 1 H, Ar), 8.72 (s, 1 H, Ar), 8.88 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.73 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 46.6 (q, $^2J_{C,F}$ = 30 Hz, CH), 53.2, 106.4, 111.9, 116.1, 118.3, 124.6 (q, $^1J_{C,F}$ = 278 Hz, CF_3), 126.1, 128.3, 139.0, 142.4, 166.8 ppm. $C_{12}H_9F_3N_2O_4$ (302.21): calcd. C 47.69, H 3.00, N 9.27; found C 47.46, H 3.34, N 8.99.

Methyl 3,3,3-Trifluoro-2-(5-methoxy-2-methyl-1*H*-indol-3-yl)propanoate (5h): Eluent petroleum ether/ethyl acetate, 5:1, yield 80%; white solid; m.p. 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.59 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 6.88 (dd, $^3J_{H,H}$ = 9, $^3J_{H,H}$ = 3 Hz, 1 H, Ar), 7.17 (s, 1 H, Ar), 7.23 (d, $^3J_{H,H}$ = 9 Hz, 1 H, Ar), 8.07 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 10.27 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.7, 47.0 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.6, 55.8, 99.9, 101.1, 111.3, 111.6, 124.8 (q, $^1J_{C,F}$ = 280 Hz, CF_3), 127.7, 130.1, 135.9, 154.5, 167.4 ppm. $C_{14}H_{14}F_3NO_3$ (301.26): calcd. C 55.81, H 4.65, N 4.65; found C 55.97, H 4.69, N 4.57.

Methyl 3-(1,1,1-Trifluoro-3-methoxy-3-oxopropan-2-yl)-1*H*-indole-5-carboxylate (5i): Eluent petroleum ether/ethyl acetate, 8:1, yield 79%; white solid; m.p. 149–150 °C. IR (Nujol): $\tilde{\nu}_{max}$ = 3292, 1755, 1739, 1694, 1616, 1293, 1253, 1153, 1100, 745 cm^{-1}. ^{1}H NMR (600 MHz, [D$_6$]acetone): δ = 3.78 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.22 (q, $^3J_{H,F}$ = 8.9 Hz, 1 H, CH), 7.59 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, Ar), 7.72 (s, 1 H, C(2)-*H*), 7.91 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, Ar), 8.57 (s, 1 H, Ar), 10.93 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz,

$CDCl_3$): δ = 9.58 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, [D_6]-acetone): δ = 46.7 (q, $^2J_{C,F}$ = 30 Hz, CH), 51.2, 52.3, 104.9, 111.7, 121.7, 122.2, 123.2, 124.7 (q, $^1J_{C,F}$ = 279 Hz, CF_3), 126.3, 127.7, 139.0, 166.9, 167.2 ppm. $C_{14}H_{12}F_3NO_4$ (315.24): calcd. C 53.33, H 3.81, N 4.44; found C 53.14, H 3.68, N 4.47.

Methyl 3,3,3-Trifluoro-2-(3-methyl-1*H*-indol-2-yl)propanoate (6a): Eluent petroleum ether/ethyl acetate, 20:1, yield 78%; white solid; m.p. 90–91 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 4.81 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 7.24 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.33 (s, 1 H, Ar), 7.45 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.66 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 8.72 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 10.27 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 8.4, 47.4 (q, $^2J_{C,F}$ = 31.5 Hz, CH), 53.4, 111.2, 112.9, 119.2, 119.7, 120.7, 122.5 (q, $^1J_{C,F}$ = 279 Hz, CF_3), 123.3, 128.0, 135.9, 166.5 ppm. $C_{13}H_{12}F_3NO_2$ (271.24): calcd. C 57.57, H 4.46, N 5.16; found C 57.41, H 4.45, N 5.48.

Methyl 2-(1,3-Dimethyl-1*H*-indol-2-yl)-3,3,3-trifluoropropanoate (6b): Eluent petroleum ether/ethyl acetate, 20:1, yield 69%; white solid; m.p. 96–97 °C. IR (Nujol): $\tilde{\nu}_{max}$ = 2857, 1750, 1469, 1269, 1244, 1149, 1117, 1109, 1022, 895, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 4.81 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 7.19–7.24 (m, 1 H, Ar), 7.32–7.40 (m, 2 H, Ar), 7.66 (d, $^3J_{H,H}$ = 9 Hz, 1 H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 11.83 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 8.8, 30.2, 46.7 (q, $^2J_{C,F}$ = 30 Hz, CH), 53.0, 109.5, 112.8, 119.5, 119.9, 122.9, 123.5, 123.7 (q, $^1J_{C,F}$ = 277.5 Hz, CF_3), 127.7, 137.3, 165.9 ppm. $C_{14}H_{14}F_3NO_2$ (285.26): calcd. C 58.95, H 4.95, N 4.91; found C 59.04, H 4.97, N 4.71.

Methyl 3,3,3-Trifluoro-2-[2-(2-nitrophenyl)-1*H*-indol-3-yl]propanoate (7): Eluent petroleum ether/ethyl acetate, 20:1, yield 67%; orange solid; m.p. 171–172 °C. IR (Nujol): $\tilde{\nu}_{max}$ = 3368, 1731, 1525, 1261, 1111, 1002, 869, 787 cm^{-1}. ^1H NMR (600 MHz, [D_6]acetone): δ = 3.68 (s, 3 H, OCH_3), 4.58 (br. s, 1 H, CH), 7.16 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.24 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.49 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.74 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.79 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.85 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.93 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 8.25 (d, $^3J_{H,H}$ = 6 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 10.98 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, [D_6]acetone): δ = 47.0 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.0, 101.9, 111.5, 120.1, 120.2, 122.6, 124.8 (q, $^1J_{C,F}$ = 278 Hz, CF_3), 124.9, 126.1, 126.3, 130.8, 133.4, 133.8, 134.9, 136.5, 149.7, 166.5 ppm. $C_{18}H_{13}F_3N_2O_4$ (378.30): calcd. C 57.15, H 3.46, N 7.41; found C 57.09, H 3.79, N 7.27.

Methyl 2-[2-(2-Aminophenyl)-1*H*-indol-3-yl]-3,3,3-trifluoropropanoate (8): To a solution of indole **7** (0.35 g, 0.93 mmol) in methanol (20 mL), 10% Pd/C (0.038 g, 0.36 mmol) was added and the resulting suspension was stirred at room temperature under a hydrogen atmosphere (1 atm). When TLC indicated no starting material remained (24 h), the mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 4:1), yield 85%; white solid; m.p. 126–127 °C. IR (Nujol): $\tilde{\nu}_{max}$ = 3376, 3367, 1731, 1616, 1260, 1156, 1008, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OCH_3), 3.89 (br. s, 2 H, NH_2), 4.62 (q, $^3J_{H,F}$ = 9 Hz, 1 H, CH), 6.86 (d, $^3J_{H,H}$ = 9 Hz, 1 H, Ar), 6.93 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.26–7.39 (m, 5 H, Ar), 7.86 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 8.52 (br. s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 11.48 (d, $^3J_{H,F}$ = 8.5 Hz, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 47.5 (q, $^2J_{C,F}$ = 30 Hz, CH), 52.8, 102.9, 111.2, 115.8, 115.9, 118.6, 120.4, 120.8, 122.8, 124.5 (q, $^1J_{C,F}$ = 278 Hz, CF_3), 126.4, 130.8, 131.6, 135.9, 136.4, 145.7, 167.4 ppm. $C_{18}H_{15}F_3N_2O_2$ (348.32): calcd. C 62.07, H 4.34, N 8.04; found C 62.19, H 4.47, N 8.25.

7-(Trifluoromethyl)-7,12-dihydrobenzo[2,3]azepino[4,5-*b*]indol-6(5*H*)-one (9): Indole **8** (0.077 g, 0.48 mmol) was dissolved in anhydrous dioxane (2 mL) under an argon atmosphere, then AcOH (300 μL) was added and the resulting mixture was stirred at 40 °C for 30 min. After cooling, saturated aqueous $NaHCO_3$ (10 mL) was added, the aqueous phase was extracted with EtOAc, and the organic phase was dried with $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization (hexane) to give the final product (60 mg, 89%) as a white solid; m.p. 285–286 °C. ^1H NMR (300 MHz, [D_6]acetone): δ = 5.25 (q, $^3J_{H,F}$ = 6 Hz, 1 H, CH), 7.21 (t, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.27–7.32 (m, 2 H, Ar), 7.43 (d, $^3J_{H,H}$ = 6 Hz, 2 H, Ar), 7.55 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.88 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 7.93 (d, $^3J_{H,H}$ = 6 Hz, 1 H, Ar), 9.88 (s, 1 H, NH), 11.06 (s, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.46 (s, 3 F, CF_3) ppm. ^{13}C NMR (150 MHz, [D_6]acetone): δ = 49.9 (q, $^2J_{C,F}$ = 30 Hz, CH), 101.9, 111. 6, 117.7, 120.3, 121.5, 121.8, 123.3, 124.2, 125.5 (q, $^1J_{C,F}$ = 282 Hz, CF_3), 126.6, 128.0, 128.8, 133.9, 134.8, 137.7, 164.5 ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3329, 3188, 2357, 1647, 1575, 1368, 1254, 1165, 1117, 738 cm^{-1}. $C_{17}H_{11}F_3N_2O$ (316.28): calcd. C 64.56, H 3.51, N 8.86; found C 64.45, H 3.69, N 8.60.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds

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