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Note

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En Route to 2-(Cyclobuten-1-yl)-3-(trifluoromethyl)-1*H*-indole

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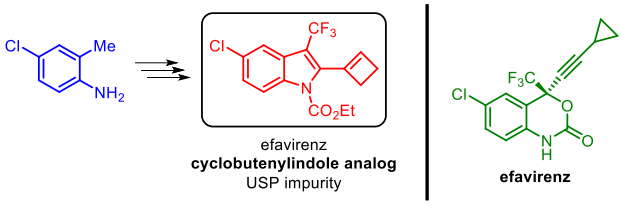
TOC Graphics



Abstract:

A six-step synthetic route from 4-chloro-2-methylaniline to 5-chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole (**1**) has been reported. Compound **1** is a key impurity of reverse transcriptase inhibitor efavirenz, an important anti-HIV/AIDS drug. Synthetic challenges, dead ends and detours are discussed.

5-Chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole derivative **1a**[1] (Chart 1) has been identified as a key impurity of reverse transcriptase inhibitor efavirenz,[2] which is one of the most important anti-HIV/AIDS drugs. In USP monograph for efavirenz drug substance as well as in the monographs for efavirenz capsules and tablets, compound **1a** has been listed as a "cyclobutenylindole analog" impurity with the specified low acceptance limit of 0.10% for drug substance.[1] The specifications for impurities given in pharmacopeial monographs represent official quality standards. Thus, in order to assure a complete regulatory compliance, an adequate testing of drug substance and drug product must be performed by using high quality analytical standards of efavirenz and its impurities.[3] Since compound **1a** represents a strategic molecule for quality compliance testing of efavirenz, elaboration of its synthesis is of key importance. Surprisingly, there is no scientific or patent literature for the preparation of compound **1a** neither is commercially available. In addition, to the best of our knowledge, the synthesis of 2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-

indole scaffold is unprecedented whereas there is only one report describing 2-(cyclobut-1-en-1-yl)-1*H*-indole.[4]

Constructing an enormous body of natural products and finding myriad applications in pharmaceutical, material and other sciences,[5,6] indole, as a privileged class of compounds,[7] inspired synthetic organic and pharmaceutical chemists to develop powerful methodologies for the ring generation as well as functional group introduction and modification procedures.[8,9] Thus, having this pool of knowledge at hand any single desired indole product appears "accessible à la carte" in timely, controlled and predictable way. At the first glance the simplicity in the structure of **1** (Chart 1) promised for relatively trivial synthetic approach; however, by implementing the precedent knowledge at the bench we came across some unexpected observations. Eventually, we identified the route to the target compound. Along with disclosing the successful procedure, we believe a brief overview of dead ends and detours discussed herein will be beneficial to the chemists working in the field.

In contrast to the synthesis of drug substances, where overall yield, environmental impact and scalability of reactions play important role in the viability of the overall synthetic process, the synthesis of key impurities of drug substance is not subjected to these requirements, since they are usually required in milligram quantities. Conversely, synthetic approaches to drug substance impurities used in compliance testing should be as concise as possible, providing reliable access to high purity material. Therefore, the synthesis of **1** could be tackled by two possible routes as shown in Chart 1. Route *a)* would start from a commercially available indole-2-carboxylic acid derivative **2a**, which should after couple of functional group interconversions, including trifluoromethylation, undergo olefination into methylenecyclopropane derivative and subsequent ring enlargement into cyclobutene product. Considering a potential lability of these two highly strained rings, trifluoromethyl group should preferably be introduced in an early synthetic step. If either the trifluoromethyl or the cyclobutene group introduction in route *a)* fails, then route *b)*, an indole '2,3' C–C disconnection, should offer an alternative scenario. Taking into account the commercial availability of the starting materials and keeping the synthetic steps at minimum we began our investigation with route *a).*

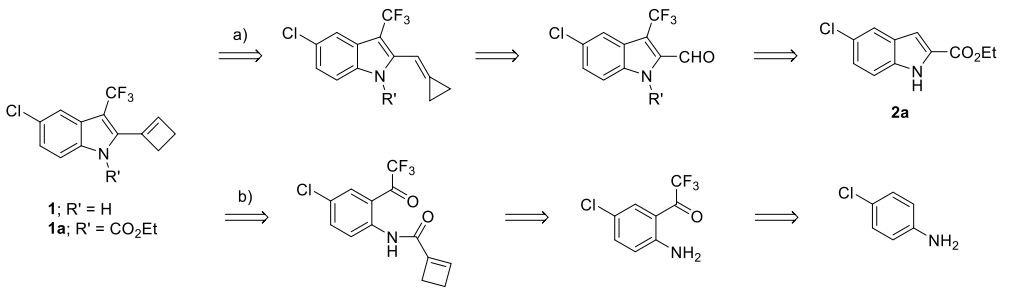
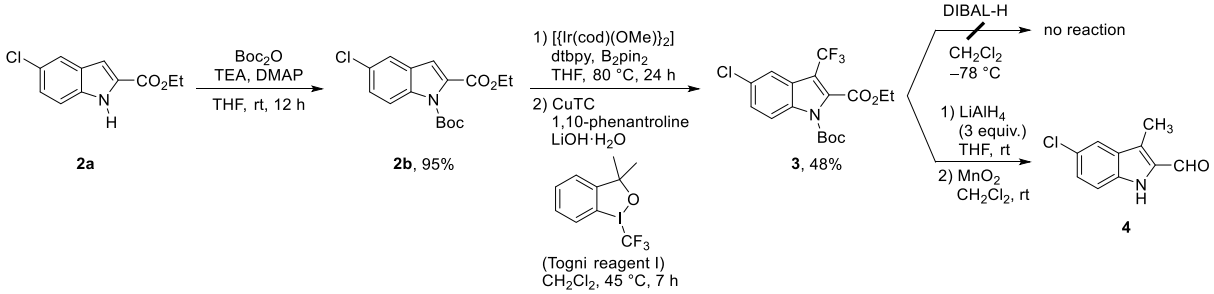


Chart 1. Retrosynthetic considerations.

The group of Shen recently reported a highly efficient tandem C–H activation/trifluoromethylation procedure for the synthesis of *N*-Boc protected 3-(trifluoromethyl)indole.[10] By applying this protocol, the borylation of Boc-indole **2b** with bis(pinacolato)diboron (B_2pin_2) in the presence of [{Ir(cod)(OMe)}$_2$] (cod = 1,5-cyclooctadiene) and di-*tert*-butylbipyridine (dtbpy), followed by trifluoromethylation of the pinacolboronate intermediate with Togni reagent I, we obtained the desired C-3 trifluoromethyl derivative **3** in acceptable 48% yield (Scheme 1). Unfortunately, all attempts to reduce the ester group in **3** with DIBAL-H failed, returning the unreacted starting material. Surprisingly, subjecting ester **3** to $LiAlH_4$ reduction and subsequent MnO_2 oxidation resulted in 5-chloro-3-methyl-1*H*-indole-2-carbaldehyde (**4**), where the desired ester reduction was accompanied by Boc-deprotection and "defluorination".

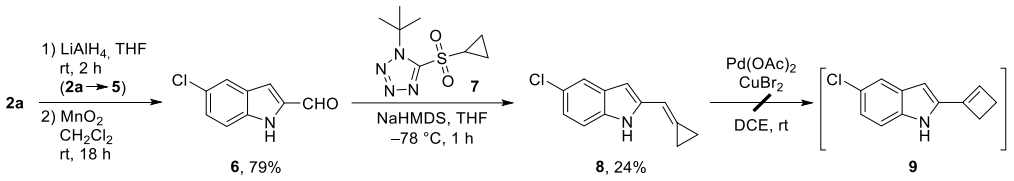
Scheme 1. Attempted synthesis of 1*H*-indole-2-carbaldehyde derivative



Having realized that the C-3 trifluoromethyl group (in **3**) renders the C-2 ethoxycarbonyl group inert towards DIBAL-H, while it is incompatible with $LiAlH_4$, prompted us to test an alternative approach where the CF_3 group is introduced in a later stage of the reaction sequence. This pathway begun with $LiAlH_4$ reduction of ester **2a** into alcohol **5**, and subsequent MnO_2 oxidation into aldehyde **6** (Scheme 2).[11,12] Exposure of the latter to cyclopropyl sulfone **7** in the presence of NaHMDS as a base in THF at low temperature, a variant of the Julia-Kocienski olefination,[13] produced methylenecyclopropane derivative **8**. A

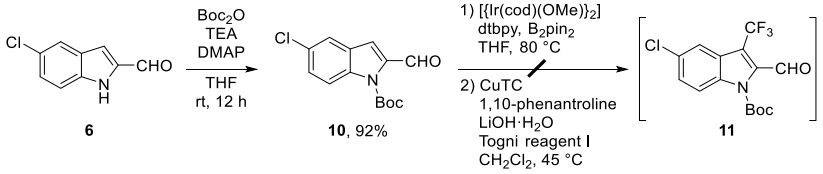
palladium-catalyzed ring enlargement of methylenecyclopropane **8** in the next step was expected to provide cyclobutene derivative **9**. This method, developed by Shi et al., has been documented on a variety of aryl-substituted methylenecyclopropanes to afford 1-arylcyclobutenes under mild conditions.[14] Unfortunately, all attempts to achieve rearrangement of **8** into **9** failed, consistently returning complex mixtures of decomposition and polymerization products as judged by TLC, NMR and MS analyses (Scheme 2).

Scheme 2. Attempted synthesis of cyclobutene derivative **9**



Hoping that the installment of the C-2 cyclobutene ring would eventually be possible, with aldehyde **6** in hands, we were prompted to test the above-mentioned Shen's trifluoromethylation procedure. Unfortunately, exposure of Boc protected indole-2-carbaldehyde **10** to B_2pin_2/[{Ir(cod)(OMe)}$_2$]/dtbpy and then to Togni reagent I did not give product **11**. It turned out that already the C-3 borylation failed to proceed in this case (Scheme 3).

Scheme 3. Attempted instalment of trifluoromethyl group at **10**

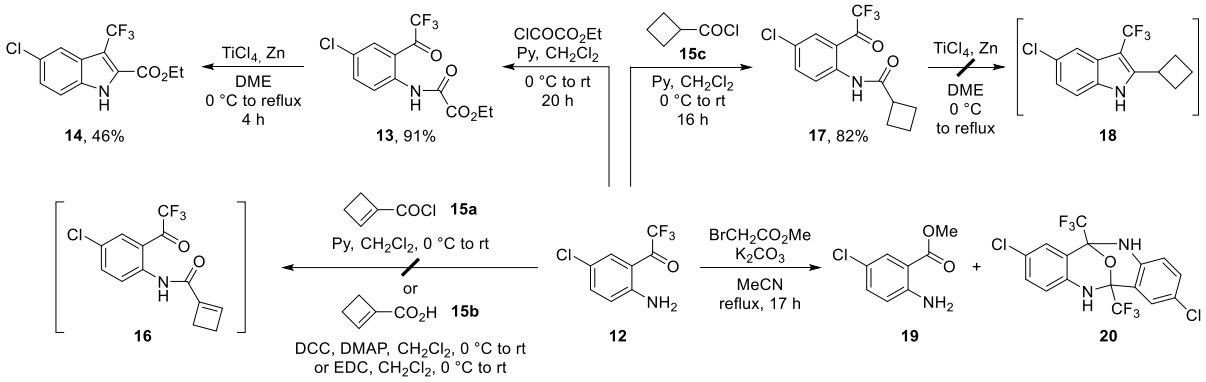


The failure in functionalizing the indole core with trifluoromethyl and cyclobutene groups called for a tactical change. Seeking for the alternative that would allow construction of the indole skeleton at the appropriate trifluoromethyl and cyclobutene pre-functionalized substrate led us to route *b)* from Chart 1.

A low-valent titanium reductive dimerization of aldehydes and ketones to alkenes, known as McMurry reaction,[15] has been developed by Fürstner and co-workers[16] to a convenient and flexible method for the construction of indole scaffold starting form *N*,2-diacetylanilines. To assess this idea, the required starting 4-chloro-2-trifluoroacetylaniline (**12**) was provided from the commercial 4-chloroaniline by known procedure.[17] *N*-Acylation

of **12** with ethyl oxalylchloride gave carbamate **13**, which, as expected, cyclized into indole **14** on treatment with $TiCl_4$ and zinc dust in refluxing DME (Scheme 4).

Scheme 4. Transformations of 4-chloro-2-trifluoroacetylaniline (**12**)



Thus, the process, successfully tested in the model system of **13** → **14**, seemed to be promising for the synthesis of the target compound **1**. Disappointingly, however, all attempts to assemble **12** either with 1-cyclobutenecarboxylic acid chloride (**15a**) or with 1-cyclobutenecarboxylic acid (**15b**)[18] in the presence of DCC or EDC coupling reagents into amide **16** failed. 1-Cyclobutenecarboxylic acid chloride (**15a**) is highly unstable and we carefully prepared and used this compound as described by Parker, Sampson and co-worker.[19] Likewise, DCC coupling had previously proved to form esters from 1-cyclobutenecarboxylic acid (**15b**).[18] In contrast to the above, aniline **12** could only be coupled with cyclobutanecarbonyl chloride (**15c**) into the saturated analogue **17**. This was deemed as a valuable detour since reliable procedures for dehydrogenation of cyclobutane into cyclobutene ring are available (vide infra). Yet, treatment of **17** with $TiCl_4$ and zinc dust in refluxing DME afforded a complex reaction mixture in which the desired indole product **18** could not be detected.

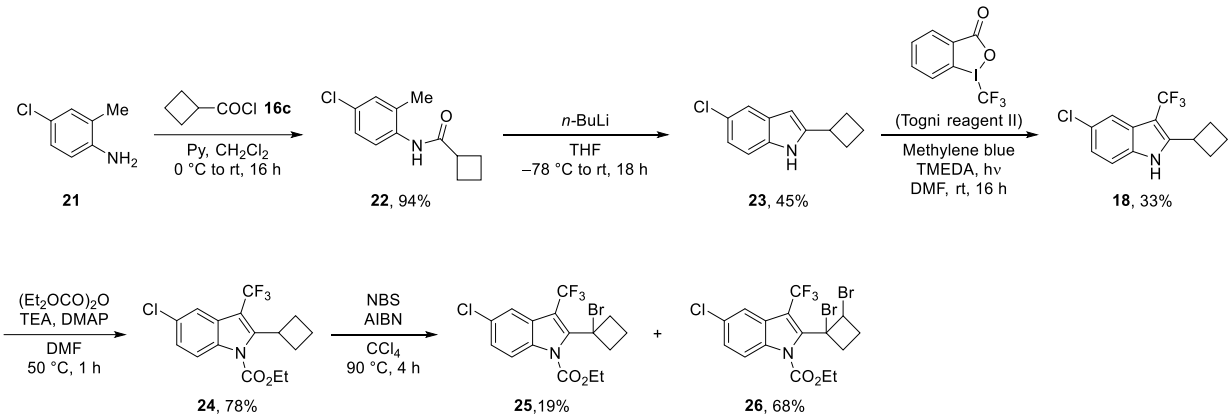
Another protocol for the indole ring formation from precursor **12** was examined at this point. Based on a recent patent,[20] on heating with methyl bromoacetate and K_2CO_3 in refluxing acetonitrile, 2-trifluoroacetylaniline provides methyl 3-(trifluoromethyl)-1*H*-indole-2-carboxylate in 56% yield. In our hands, with 4-chloro-2-trifluoroacetylaniline (**12**), this procedure returned a mixture of methyl 2-amino-5-chlorobenzoate (**19**) and bridging dimer of **12**, epoxy dibenzo[*b*,*f*][1,5]diazocine **20**. No methyl 5-chloro-3-(trifluoromethyl)-1*H*-indole-2-carboxylate could be detected in the crude reaction mixture. Compound **20** has been recently reported by Griffiths and Warm as a side product formed by treatment of **12** with

much stronger bases, such as Grignard reagents or BuLi, in the synthesis of efavirenz.[21]

N-Acylated *o*-toluidines are known to undergo lithiation on treatment with organolithium reagents, which is followed by intramolecular condensation of the resulting lithio species into 2-substituted indoles in good yields.[22] Indeed, *N*-acylation of commercial 4-chloro-2-methylaniline (**21**) with cyclobutanecarbonyl chloride (**15c**) into amide **22** followed by treatment with *n*-BuLi led to indole derivative **23** in 45% yield (Scheme 5).

Out of the methods available for trifluoromethylation[10,23] at this point we decided to test metal-free photocatalytic radical reaction with methylene blue as a photo-catalyst coupled with Togni hypervalent-iodine compounds, developed by the group of Scaiano.[23] Using this protocol, but employing more easily accessible Togni reagent II[24] in place of Togni reagent I, compound **23** was transformed into desired C-3 trifluoromethyl derivative **18**. The latter was *N*-protected with diethyl pyrocarbonate into **24**.[25]

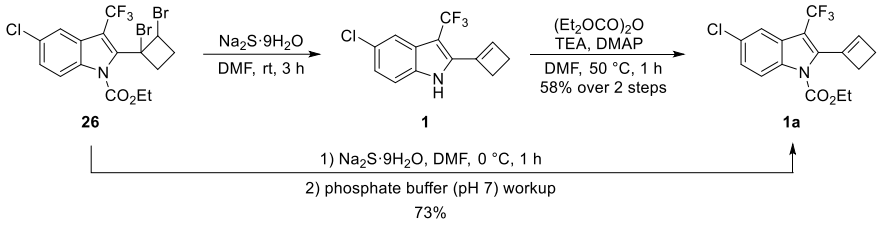
Scheme 5. Synthesis of dibromocyclobutane derivative **26**



Dehydrogenation of the cyclobutane ring in **24** should be possible by radical monobromination with NBS in the presence of AIBN and subsequent elimination of HBr with KOH as reported by Jung and Deng.[18] Interestingly, although working well in the preparation of **15b**, the above NBS/AIBN conditions transformed cyclobutane **24** into a mixture of monobrominated product **25** and vicinal dibromide **26**. Attempted dehydrobromination[26] of **25** by KO*t*Bu in dry THF returned complex mixture of decomposition products and no desired **1a** or **1**. On the other hand, debromination of **26** with sodium sulfide in DMF by the procedure of Fukunaga[27] furnished *N*-deprotected cyclobutene derivative **1**, which could be re-protected with diethyl pyrocarbonate into **1a** in 58% yield over two steps from **26** (Scheme 6). This undesired step was avoided by employing a modified procedure by using buffer (pH = 7) in the isolation workup, which prevented hydrolysis of the base-sensitive carbamate *N*-

protection. Compound **26** was thus transformed into the target **1a** in one step, in 73% yield. Noteworthy, compound **1a** is also extremely sensitive to silica gel chromatography undergoing rapid decomposition into a complex mixture of products unless the eluent consists of sufficient amount of base like NEt_3.

Scheme 6. Synthesis of target compound **1a**



In conclusion, exemplified by compound **1a**, we have developed the first synthesis of 2-(cyclobuten-1-yl)-3-(trifluoromethyl)-1*H*-indole scaffold. Our synthetic approach is based on lithium-inducted intramolecular condensation of *N*-(4-chloro-2-methylphenyl)cyclobutanecarboxamide (**22**) into indole **23**. The installment of the C-3 trifluoromethy group into **18** was possible through the photocatalytic radical reaction with methylene blue and Togni reagent II. Finally, the cyclobutane ring was transformed into the cyclobutene ring by dibromination/debromination reaction sequence. Interestingly, several well established reactions failed in producing intermediates along the synthetic pathway into **1a**.

Experimental Section

General Information

All reactions were performed in oven-dried glassware under argon atmosphere. All reagents purchased commercially were used without further purification unless noted otherwise. Toluene and tetrahydrofuran were distilled over sodium wire. Dichloromethane and acetonitrile were distilled over calcium hydride. Melting points were determined on a micro-hot-stage apparatus and are uncorrected. Thin-layer chromatography (TLC) analysis was performed on Fluka Silica gel on TLC Al foils (silica gel matrix, with fluorescent indicator, 60 Å medium pore diameter). Visualization of compounds was done by illumination with a UV lamp (254 nm) or by using a solution of $KMnO_4/K_2CO_3$/NaOH in water (prepared by dissolving 1.5 g of $KMnO_4$, 10 g K_2CO_3 and 1.25 mL 10% NaOH in 200 mL of water) followed by heating. Silica gel column chromatography was carried out on silica gel 60N. IR

spectra were recorded on a FT-IR spectrometer using ATR. ^{1}H, ^{13}C and ^{19}F spectra were recorded with a Bruker Avance III 500 MHz NMR (500 MHz, 126 MHz and 471 MHz) instrument at 300 K. Some ^{1}H and ^{13}C spectra were recorded with a Bruker Avance DPX 300 spectrometer (300 MHz and 76 MHz) at 302 K. Proton spectra were referenced to TMS as an internal standard. Carbon chemical shifts were determined relative to the ^{13}C signal of $CDCl_3$ (77.0 ppm). Assignments of some proton and carbon resonances were performed by 2D NMR techniques ($^{1}H–^{1}H$ *gs*-COSY, $^{1}H–^{13}C$ *gs*-HSQC, $^{1}H–^{13}C$ *gs*-HMBC and $^{1}H–^{31}P$ *gs*-HMBC). Coupling constants (*J*) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) or br (broadened). HRMS spectra were recorded on a time-of-flight (TOF) mass spectrometer equipped with a double orthogonal electrospray source at atmospheric pressure ionization (ESI) coupled to an HPLC instrument.

1-(*tert*-Butyl)-5-(cyclopropylsulfonyl)-1*H*-tetrazole (**7**) was prepared by the literature procedure.[28] 1-(2-Amino-5-chlorophenyl)-2,2,2-trifluoroethan-1-one (**12**) was prepared as described in the literature[29] (**CAUTION: by adding ethyl trifluoroacetate or trifluoroacetic anhydride into the reaction mixture, the pressure in the reaction vessel increases severely**).

1-(*tert*-Butyl) 2-ethyl 5-chloro-1*H*-indole-1,2-dicarboxylate (2b). To a solution of ethyl 5-chloro-1*H*-indole-2-carboxylate (**2a**, 2.24 g, 10.0 mmol) in THF (30 mL) were added di-*tert*-butyl dicarbonate (Boc_2O, 2.19 g, 10.0 mmol), 4-dimethylaminopyridine (DMAP, 150 mg, 1.2 mmol), and Et_3N (1.40 mL, 10.0 mmol) at room temperature. After stirring the reaction mixture for 12 h at room temperature, the volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1/7) to afford **2b** (3.07 g, 95%) as a pale yellow oil. R_f 0.44 (EtOAc/petroleum ether 1/5). IR (ATR): 2981, 1728, 1539, 1444, 1318, 1227, 1188, 1156, 1139, 1067 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 8.9 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 8.9, 2.1 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 1.62 (s, 9H), 1.39 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5, 148.8, 135.9, 131.9, 128.8, 128.6, 126.8, 121.4, 116.0, 113.3, 85.0, 61.5, 27.7, 14.2. HMRS (ESI+): *m*/*z* calcd for $C_{12}H_{11}ClNO_4^+$ $[M - i\text{-}C_4H_8 + H]^+$ 268.0371, found 268.0367.[30]

1-(*tert*-Butyl) 2-ethyl 5-chloro-3-(trifluoromethyl)-1*H*-indole-1,2-dicarboxylate (3). Compound **3** was prepared from **2b** by a modified literature procedure for the trifluoromethylation.[10]

An Ace pressure tube was charged with [{Ir(cod)(OMe)}$_2$] (21 mg, 0.03 mmol, 1 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (18 mg, 0.06 mmol, 2 mol%), and bis(pinacolato)diboron (506 mg, 2.0 mmol) under argon atmosphere. Dry THF (6.0 mL) and 1-(*tert*-butyl) 2-ethyl 5-chloro-1*H*-indole-1,2-dicarboxylate (**2b**, 957 mg, 3.0 mmol) were added under a flow of argon gas, and the reaction mixture was stirred at 80 °C for 24 h. After filtration through a short pad of celite, the volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (12 mL) and the solution was transferred by a syringe, under argon atmosphere, into an oven-dried Ace pressure tube, pre-charged with copper(I) thiophene-2-carboxylate (60 mg, 0.31 mmol), 1,10-phenanthroline (110 mg, 0.61 mmol), LiOH·H_2O (250 mg, 6.0 mmol), and 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni reagent I, 1.10 g, 3.3 mmol). The reaction mixture was stirred at 45 °C for 7 h. Brine (25 mL) and CH_2Cl_2 (10 mL) were added and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography (EtOAc/petroleum ether 1/10) to give a mixture (1.07 g) of **3** and **2b** in the molar ratio of 1.0:1.1, as determined by ^{1}H NMR. Compounds **3** and **2b** could not be separated due to the similar chromatographic properties on silica gel. The yield of product **3** was calculated to be 564 mg (48%). R_f 0.52 (EtOAc/petroleum ether 1/3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 9.0 Hz, 1H), 7.71–7.69 (m, 1H), 7.41 (dd, J = 9.0, 2.1 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.65 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H). HMRS (ESI+): *m*/*z* calcd for $C_{13}H_{10}ClF_3NO_4^+$ $[M - i\text{-}C_4H_8 + H]^+$ 336.0245, found 336.0227.[30]

5-Chloro-3-methyl-1*H*-indole-2-carbaldehyde (4). The reduction was conducted by a modified literature procedure for the reduction with $LiAlH_4$.[12]

A solution of the above prepared mixture of **3** and **2b** (1.0:1.1 mol ratio, 269 mg; 0.36 mmol of **3**) in dry THF (5 mL) was cooled to 0 °C, and $LiAlH_4$ (1 M in THF, 0.8 mL, 0.8 mmol) was slowly added. The reaction mixture was stirred for 2 h at room temperature, quenched with 20% aqueous KOH solution (1 mL) and filtered. The filtrate was concentrated *in vacuo*. Activated MnO_2 (313 mg) and CH_2Cl_2 (5 mL) were added to the residue, and the reaction mixture was stirred at room temperature overnight, filtered, and the filtrate was concentrated under reduced pressure. Mass-spectral and NMR analyses of the crude product revealed the presence of compound **4** as the major product, which was not purified.

4: ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.82 (br s, 1H), 7.68 (s, 1H), 7.32–7.34 (m, 2H), 2.62 (s, 3H). HMRS (ESI+): *m*/*z* calcd for $C_{10}H_9ClNO^+$ $[M + H]^+$ 194.0367, found

194.0366.

5-Chloro-1*H*-indole-2-carbaldehyde (6). The reduction was conducted by a modified literature procedure for the reduction with $LiAlH_4$.[12]

A solution of indole **2a** (2.28 g, 10.2 mmol) in dry THF (20 mL) was cooled to 0 °C under argon atmosphere, and a solution of $LiAlH_4$ (1 M in THF, 15.6 mL, 15.6 mmol, 1.5 equiv) was added dropwise. The mixture was allowed to warm to room temperature and the stirring was continued for 2 h, until the reaction was considered complete as determined by TLC analysis. Then, THF (20 mL) and 20% of aqueous KOH (1.5 mL) were added sequentially to the reaction mixture, which was stirred for additional 15 min and filtered. The solid residue was extracted with hot (refluxing) THF (20 mL) and filtered. The combined filtrates were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford crude alcohol **5** (1.67 g), which was used without further purification in the next step as follows. A suspension of crude **5** (1.67 g) and activated MnO_2 (8.70 g, 100 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite, the filtrate was evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1/7) to provide product **6** (1.45 g, 79% over two steps) as a pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 9.09 (br s, 1H), 7.74–7.72 (m, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.8, 1.8 Hz, 1H), 7.23–7.21 (m, 1H). Spectroscopic data were in agreement with the literature report.[31]

5-Chloro-2-(cyclopropylidenemethyl)-1*H*-indole (8). To a stirred solution of 1-(*tert*-butyl)-5-(cyclopropylsulfonyl)-1*H*-tetrazole (**7**, 555 mg, 2.40 mmol) in dry THF (15 mL) was added dropwise, under argon atmosphere, at –78 °C, sodium bis(trimethylsilyl)amide (1 M in THF, 3.40 mL, 3.40 mmol). Within 10 minutes yellow suspension formed. The reaction mixture was stirred at –78 °C for 30 minutes, followed by a dropwise addition of a THF solution (4 mL) of 5-chloro-1*H*-indole-2-carbaldehyde (**6**, 240 mg, 1.35 mmol) *via* syringe. The reaction mixture was stirred at –78 °C for 1 h, quenched with aqueous solution of NH_4Cl (15 mL), allowed to warm to room temperature, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to afford crude product, which was subjected to silica gel column chromatography (EtOAc/petroleum ether 1/20) purification to afford **8** (65 mg, 24%) as a white solid. R_f 0.45 (EtOAc/petroleum ether 1/3). Mp 85–87 °C. IR (ATR): 3465, 2977, 1573, 1455, 1404, 1306 cm^{-1}. ^{1}H NMR (500

MHz, $CDCl_3$): δ 8.43 (br s, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.0 Hz, 1H), 6.82–6.80 (m, 1H), 6.41–6.39 (m, 1H), 1.46–1.42 (m, 2H), 1.35–1.30 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.2, 134.7, 129.9, 125.4, 123.6, 122.3, 119.8, 111.4, 109.9, 101.1, 3.2, 1.5. HMRS (ESI+): m/z calcd for $C_{12}H_{11}ClN^+$ $[M + H]^+$ 204.0575, found 204.0567.

***tert*-Butyl 5-chloro-2-formyl-1*H*-indole-1-carboxylate (10).** To a solution of carbaldehyde **6** (1.80 g, 10.0 mmol) in THF (100 mL) were added di-*tert*-butyl dicarbonate (Boc_2O, 3.19 g, 14.6 mmol), 4-dimethylaminopyridine (DMAP, 160 mg, 1.3 mmol), and Et_3N (1.74 mL, 12.4 mmol). The reaction mixture was stirred at room temperature for 12 h, concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1/10) to give product **10** (2.57 g, 92%) as a pale yellow solid. R_f 0.39 (EtOAc/petroleum ether 1/7). Mp 91–93 °C (MeOH). IR (ATR): 2978, 2924, 1731, 1664, 1526, 1348, 1159, 1134, 1089, 1068 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.42 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.43 (dd, J = 9.0, 2.1 Hz, 1H), 7.35 (s, 1H), 1.71 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.9, 149.4, 138.7, 136.0, 129.4, 128.5, 128.4, 122.4, 117.2, 115.1, 86.1, 28.1. HMRS (ESI+): m/z calcd for $C_9H_7ClNO^+$ $[M – Boc + 2H]^+$ 180.0211, found 180.0208.

Ethyl 2-((4-chloro-2-(2,2,2-trifluoroacetyl)phenyl)amino)-2-oxoacetate (13). To a solution of 1-(2-amino-5-chlorophenyl)-2,2,2-trifluoroethan-1-one (**12**, 250 mg, 1.12 mmol) and pyridine (230 μL, 2.8 mmol) in dry CH_2Cl_2 (4 mL), ethyl 2-chloro-2-oxoacetate (145 μL, 176 mg, 1.29 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C and then for 20 h at room temperature. Then, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with aqueous HCl (1 M, 15 mL), saturated aqueous solution of $NaHCO_3$ (15 mL), brine (15 mL), and the organic layer was dried (Na_2SO_4), and evaporated to dryness to give product **13** (330 mg, 91%) as a yellow solid. Mp 142–143.5 °C. IR (ATR): 3275, 3142, 2997, 1724, 1688, 1574, 1518, 1397, 1307, 1278, 1203, 1144 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.28 (br s, 1H), 8.86 (d, J = 9.1 Hz, 1H), 7.99–7.97 (m, 1H), 7.73 (dd, J = 9.1, 2.3 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.0 (q, J = 35.5 Hz), 159.7, 155.0, 139.6, 137.5, 131.4 (q, J = 4.5 Hz), 129.7, 122.7, 117.4, 116.1 (q, J = 291.0 Hz), 64.1, 14.0. HMRS (ESI+): m/z calcd for $C_{12}H_{10}ClF_3NO_4^+$ $[M + H]^+$ 324.0245, found 324.0247.

Ethyl 5-chloro-3-(trifluoromethyl)-1*H*-indole-2-carboxylate (14). To an ice-cold stirred

suspension of zinc powder (262 mg, 4 mmol) in dimethoxyethane (DME, 5 mL) was slowly added $TiCl_4$ (221 μL, 2 mmol). The resulting black slurry was heated under reflux for 2 hours. A solution of ethyl 2-((4-chloro-2-(2,2,2-trifluoroacetyl)phenyl)amino)-2-oxoacetate (**14**, 323 mg, 1 mmol) in DME (5 mL) was added and the heating was continued for 2 hours. The reaction mixture was allowed to cool to ambient temperature. The inorganic residues were removed by filtration through a short pad of silica and the pad was thoroughly rinsed with EtOAc (5 × 10 mL). The combined filtrates were concentrated to dryness under reduced pressure. From the residue, the product was isolated by extraction into hot (refluxing) toluene (10 mL). The supernatant hot was separated by decantation from the oily residues, and allowed to cool down to room temperature. The precipitate was collected by filtration, washed with cold hexane (3 × 10 mL) and dried to afford **14** (135 mg, 46%) as a white solid. Mp 149–151 °C. IR (ATR): 3296, 3010, 2959, 1686, 1543, 1452, 1386, 1346 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.54 (br s, 1H), 7.95–92 (m, 1H), 7.44–7.36 (m, 2H), 4.51 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.0, 132.7, 128.6, 127.1 (q, J = 3.7 Hz), 126.8, 125.7 (q, J = 1.5 Hz), 123.3 (q, J = 268.2 Hz), 121.2 (q, J = 3.5 Hz), 113.2, 109.4 (q, J = 37.9 Hz), 62.4, 13.9. HMRS (ESI+): m/z calcd for $C_{12}H_{10}ClF_3NO_2^+$ $[M + H]^+$ 292.0347, found 292.0345.

***N*-(4-Chloro-2-(2,2,2-trifluoroacetyl)phenyl)cyclobutanecarboxamide (17).**

To an ice-cold stirred solution of 1-(2-amino-5-chlorophenyl)-2,2,2-trifluoroethan-1-one (**12**, 357 mg, 1.60 mmol), pyridine (139 mg, 142 μL, 1.75 mmol), and CH_2Cl_2 (12 mL) was slowly added cyclobutanecarbonyl chloride (**15c**, 189 mg, 184 μL, 1.60 mmol). After being stirred for 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and the stirring was continued for additional 16 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and was washed with aqueous HCl (1M, 15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1/5) to give the product **17** (401 mg, 82%). R_f 0.36 (EtOAc/petroleum ether 1/3). Mp 82–83 °C. IR (ATR): 3346, 2986, 2947, 2869, 1758, 1707, 1674, 1572, 1506, 1453, 1337 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 10.81 (br s, 1H), 8.89 (d, J = 9.2 Hz, 1H), 7.91–7.89 (m, 1H), 7.65 (dd, J = 9.2, 2.3 Hz, 1H), 3.28 (quint, J = 8.6 Hz, 1H), 2.44–2.28 (m, 4H), 2.11–2.00 (m, 1H), 1.98–1.90 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.3 (q, J = 35.0 Hz), 174.5, 142.3, 137.6, 130.9 (q, J = 4.5 Hz), 127.7, 122.6, 116.3 (q, J = 291.9 Hz), 116.0, 41.6, 25.3, 17.9. HMRS (ESI+): m/z calcd for $C_{13}H_{12}ClF_3NO_2^+$ $[M + H]^+$ 306.0503, found 306.0498.

Attempted synthesis of methyl 5-chloro-3-(trifluoromethyl)-1*H*-indole-2-carboxylate following the patent procedure:[20] A mixture of 1-(2-amino-5-chlorophenyl)-2,2,2-trifluoroethan-1-one (**13**, 1.76 g, 7.8 mmol), methyl 2-bromoacetate (1.43 g, 890 μL, 9.4 mmol), and K_2CO_3 (3.23 g, 23.4 mmol) in dry CH_3CN (7.5 mL) was heated under reflux in argon atmosphere for 17 h. The resulting mixture was filtered and evaporated to yield a crude product which contained methyl 2-amino-5-chlorobenzoate (**19**) and 2,8-dichloro-6,12-bis(trifluoromethyl)-5,6,11,12-tetrahydro-6,12-epoxydibenzo[b,f][1,5]diazocine (**20**) in the 1:1 ratio as determined by ^{1}H NMR. The crude product was subjected to column chromatography (EtOAc/petroleum ether 1/3) to obtain compounds **19** and **20** in pure form.

Methyl 2-amino-5-chlorobenzoate (19). R_f 0.35 (EtOAc/petroleum ether 1/3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 2.5 Hz, 1H), 7.20 (dd, J = 8.8, 2.5 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 5.73 (br s, 2H), 3.87 (s, 3H). Spectroscopic data were consistent with those reported in the literature.[32]

2,8-dichloro-6,12-bis(trifluoromethyl)-5,6,11,12-tetrahydro-6,12-epoxydibenzo[*b,f*][1,5]diazocine (20). R_f 0.48 (EtOAc/petroleum ether 1/3). Mp 219–220 °C. Mp (lit.[21]) 222 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.41 (m, 2H), 7.21 (dd, J = 8.7, 2.3 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.90 (br s, 2H). Spectroscopic data were consistent with those reported in the literature.[21]

***N*-(4-Chloro-2-methylphenyl)cyclobutanecarboxamide (22).** To an ice-cold solution of 4-chloro-2-methylaniline (**21**, 2.124 g, 15.0 mmol) and pyridine (1.51 mL, 18.8 mmol) in dry CH_2Cl_2 (40 mL) was added cyclobutanecarbonyl chloride (**15c**, 1.956 g, 16.5 mmol) dropwise. The reaction mixture was stirred for 1 h at 0 °C and then for 16 h at room temperature. Afterwards, the reaction mixture was washed with aqueous HCl (1M, 30 mL), saturated aqueous solution of $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4), and evaporated to dryness to give pure product **22** (3.15 g, 94%) as a white solid. Mp 151–152 °C. IR (ATR): 3260, 2979, 2943, 2865, 1647, 1521, 1397, 1269, 1191 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 8.5 Hz, 1H), 7.19–7.15 (m, 2H), 6.78 (br s, 1H), 3.19 (quint, J = 8.5 Hz, 1H), 2.43–2.33 (m, 2H), 2.30–2.23 (m, 2H), 2.22 (s, 3H), 2.09–1.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1, 134.3, 130.3, 130.1, 129.7, 126.7, 123.9, 40.7, 25.4, 18.1, 17.5. HMRS (ESI+): m/z calcd for $C_{12}H_{15}ClNO^+$ $[M + H]^+$ 224.0837, found 224.0839.

5-Chloro-2-cyclobutyl-1*H*-indole (23). Following literature procedure.[33] To a solution of *N*-

(4-chloro-2-methylphenyl)cyclobutanecarboxamide (**22**, 3.345 g, 15.0 mmol) in anhydrous THF (200 mL), *n*-butyl lithium (24 mL, 60.0 mmol, 2.5 M in hexanes) was added dropwise at –40 °C. The reaction mixture was stirred for 1 h at –40 °C, 1 h at 0 °C, and then overnight at room temperature. The reaction mixture was quenched by slow addition of water (100 mL) at 0 °C, and the product was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether 1/10) to afford 2-cyclobutyl-5-chloro-1*H*-indole (**23**, 1.370 g, 45%) of as a brown solid. R_f 0.49 (EtOAc/petroleum ether 1/3). Mp 61–62.5 °C. IR (ATR): 3394, 2941, 2862, 1683, 1614, 1574, 1464, 1445, 1313 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (br s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 8.6, 2.0 Hz, 1H), 6.23–6.21 (m, 1H), 3.62 (quint, J = 8.6 Hz, 1H), 2.44–2.37 (m, 1H), 2.28–2.19 (m, 1H), 2.12–2.03 (m, 1H), 1.99–1.92 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.2, 134.2, 129.8, 125.2, 121.2, 119.3, 111.2, 97.9, 33.7, 29.0, 18.7. HMRS (ESI+): *m*/*z* calcd for $C_{12}H_{13}ClN^+$ $[M + H]^+$ 206.0731, found 206.0723.

5-Chloro-2-cyclobutyl-3-(trifluoromethyl)-1*H*-indole (18). A mixture of 5-chloro-2-cyclobutyl-1*H*-indole (**23**) (0.820 g, 4.0 mmol), 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (Togni Reagent II) (1.893 g, 6.0 mmol) and methylene blue (29.3 mg, 0.09 mmol) in dry DMF (40 mL) was purged by argon gas for 15 min. Then, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (1.20 mL, 8.0 mmol) was added and the reaction mixture was irradiated with a bulb (40 W) for 18 h. After irradiation, the reaction mixture was diluted with Et_2O (150 mL), washed with brine (5 × 50 mL) dried (Na_2SO_4), and evaporated to dryness to give an oily residue. Silica gel column chromatography purification (EtOAc/petroleum ether 1/15) afforded pure 5-chloro-2-cyclobutyl-3-(trifluoromethyl)-1*H*-indole (**18**, 0.36 g, 33%) as a brown solid. R_f 0.37 (EtOAc/petroleum ether 1/3). Mp 72–73 °C. IR (ATR): 3465, 2987, 2943, 2867, 1578, 1558, 1449, 1326, 1143 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 7.66–7.64 (m, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.16 (dd, J = 8.6, 2.0 Hz, 1H), 4.03–3.94 (m, 1H), 2.48–2.40 (m, 1H), 2.29–2.09 (m, 3H), 1.97–1.89 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.9 (q, J = 3.6 Hz), 132.4, 127.1, 126.4 (q, J = 1.7 Hz), 124.7 (q, J = 267.0 Hz), 122.8, 118.8 (q, J = 1.3 Hz), 111.8, 101.6 (q, J = 36.1 Hz), 32.2, 28.8, 18.5. HMRS (ESI+): *m*/*z* calcd for $C_{13}H_{12}ClF_3N^+$ $[M + H]^+$ 274.0605, found 274.0606.

Ethyl 5-chloro-2-cyclobutyl-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (24). Following

a modified literature procedure.[25] To a solution of indole **18** (200 mg, 0.72 mmol), Et_3N (1.0 mL, 7.2 mmol), and 4-dimethylaminopyridine (DMAP, 44 mg, 0.36 mmol) in dry DMF (8 mL) was added diethyl pyrocarbonate (584 mg, 3.6 mmol) under argon atmosphere. The reaction mixture was stirred for 1 h at 50 °C, allowed to cool to room temperature, and diluted with a mixture of EtOAc/petroleum ether (1/3, 20 mL). The organic layer was washed with aqueous HCl (1 M, 5 mL), brine (3 × 5 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography (EtOAc/petroleum ether 1/20) to afford ethyl 5-chloro-2-cyclobutyl-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (**24**, 195 mg, 78%) of as a colorless oil. R_f 0.53 (EtOAc/petroleum ether 1/3). IR (ATR): 2985, 2873, 1749, 1582, 1456, 1372, 1300, 1258, 1188, 1152, 1110 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 9.0 Hz, 1H), 7.66–7.64 (m, 1H), 7.26 (dd, J = 9.0, 2.0 Hz, 1H), 4.50 (q, J = 7.1 Hz, 2H), 4.20–4.11 (m, 1H), 2.52–2.44 (m, 2H), 2.38–2.29 (m, 2H), 2.08–1.98 (m, 1H), 1.49 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.8, 147 (q, J = 4.2 Hz), 133.5, 129.3, 126.6, 124.8, 123.9 (q, J = 268.7 Hz), 119.2 (q, J = 2.6 Hz), 115.3, 108.8 (q, J = 36.4 Hz), 64.4, 34.5, 29.5 (q, J = 2.2 Hz), 18.3, 14.1. HMRS (ESI+): m/z calcd for $C_{16}H_{16}ClF_3NO_2^+$ $[M + H]^+$ 346.0816, found 346.0815.

Bromination of compound 24. The reaction was conducted following a modified literature procedure for the bromination.[18] A mixture of ethyl 5-chloro-2-cyclobutyl-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (**24**, 201 mg, 0.58 mmol), *N*-bromosuccinimide (620 mg, 3.48 mmol), 2,2′-azobis(2-methylpropionitrile) (AIBN, 40 mg, 0.24 mmol) in dry CCl_4 (2 mL) was stirred in an Ace pressure tube for 4 h at 90 °C under argon atmosphere. Then, the reaction mixture was allowed to cool to room temperature and diluted with EtOAc (20 mL). The organic layer was washed with water (10 mL), brine (2 × 10 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography (EtOAc/petroleum ether 1/20) to give monobrominated product **25** (47 mg, 19%) of as a pale oil and dibrominated product **26** (199 mg, 68%) of as a colorless viscous oil.

Ethyl 2-(1-bromocyclobutyl)-5-chloro-3-(trifluoromethyl)-1H-indole-1-carboxylate (25). R_f 0.19 (EtOAc/petroleum ether 1/20). ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 9.0 Hz, 1H), 7.72–7.70 (m, 1H), 7.35 (dd, J = 9.0, 2.0 Hz, 1H), 4.56–4.49 (m, 2H), 3.02–2.87 (m, 4H), 2.65–2.54 (m, 1H), 1.89–1.82 (m, 1H), 1.52 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.3, 145.0 (q, J = 3.8 Hz), 133.4, 129.9, 126.4, 125.9, 123.0 (q, J = 267.1 Hz), 119.8 (q, J = 2.2 Hz), 115.6, 108.8 (q, J = 37.2 Hz), 65.0, 54.0, 41.2, 16.2, 14.1. HMRS (ESI+): m/z calcd for $C_{16}H_{14}ClF_3NO_2^+$ $[M – Br]^+$ 344.0660, found 344.0662.

Ethyl 5-chloro-2-(1,2-dibromocyclobutyl)-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (26). R_f 0.23 (EtOAc/petroleum ether 1/20). IR (ATR): 2984, 1756, 1581, 1553, 1451, 1373, 1256 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 9.0 Hz, 1H), 7.79–7.77 (m, 1H), 7.37 (dd, J = 9.0, 2.1 Hz, 1H), 5.07 (t, J = 5.8 Hz, 1H), 4.67–4.51 (m, 2H), 3.61–3.54 (m, 1H), 3.42–3.34 (m, 1H), 3.09–3.03 (m, 1H), 2.22–2.16 (m, 1H), 1.56 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.1, 141.5 (q, J = 4.1 Hz), 132.9, 130.0, 126.7, 125.8 (q, J = 1.6 Hz), 123.2 (q, J = 270.1 Hz), 120.2 (q, J = 3.7 Hz), 116.8, 110.7 (q, J = 37.1 Hz), 64.9, 57.5, 57.1, 39.6 (q, J = 5.6 Hz), 29.2, 14.2. HMRS (ESI+): m/z calcd for $C_{16}H_{13}BrClF_3NO_2^+$ $[M - Br]^+$ 421.9765, found 421.9759.

Ethyl 5-chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (1a)

*Method A (via 5-chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1H-indole (**1**)):*

To a stirred solution of indole **26** (127 mg, 0.25 mmol) in DMF (3.5 mL) was added sodium sulfide nonahydrate ($Na_2S \times 9H_2O$, 271 mg, 1.12 mmol) in small portions at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was poured into ice cold water (10 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and evaporated to dryness to give crude product **1**, which was used in the next step without purification.

1: ^1H NMR (500 MHz, $CDCl_3$): δ 8.29 (br s, 1H), 7.73–7.71 (m, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.20 (dd, J = 8.7, 1.9 Hz, 1H), 6.50 (s, 1H), 2.99–2.96 (m, 2H), 2.67–2.65 (m, 2H). HMRS (ESI+): m/z calcd for $C_{13}H_{10}ClF_3N^+$ $[M + H]^+$ 272.0448, found 272.0442.

5-Chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole (1)

To a solution of crude 5-chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole (**1**) from the above step, Et_3N (253 mg, 348 μL, 2.5 mmol), and 4-dimethylaminopyridine (DMAP, 16 mg, 0.13 mmol) in DMF (1.5 mL) was added diethyl pyrocarbonate (162 mg, 147 μL, 1.0 mmol), and the stirred for 1 h at 50 °C. The reaction mixture was allowed to cool to room temperature, diluted with a mixture of EtOAc/petroleum ether (1/3, 30 mL), and washed with aqueous HCl (1 M, 10 mL), brine (3 × 10 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was subjected to column chromatography purification (EtOAc/petroleum ether 1/20 with 1% Et_3N) to afford 5-chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole (**1a**, 50 mg, 58% yield over two steps) as a white solid.

Method B:

Sodium sulfide nonahydrate ($Na_2S \times 9H_2O$, 270 mg, 1.1 mmol) was added in small portions to a stirred solution of ethyl 5-chloro-2-(1,2-dibromocyclobutyl)-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (**26**, 131 mg, 0.26 mmol) in dry DMF (3.5 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was diluted with Et_2O (15 mL), followed by a slow addition of a ice cold Na_2HPO_4/NaH_2PO_4 buffer solution (0.5 M, pH 7, 10 mL). The biphasic system was vigorously stirred for 10 minutes at 0 °C, the layers were separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). Combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by column chromatography (EtOAc/petroleum ether 1/20 with 1% of Et_3N) to afford ethyl 5-chloro-2-(cyclobut-1-en-1-yl)-3-(trifluoromethyl)-1*H*-indole-1-carboxylate (**1a**, 65 mg, 73%) as a white solid.

R_f 0.46 (EtOAc/petroleum ether 1/20 with 1% of Et_3N). Mp 53–54 °C. IR (ATR): 2984, 2928, 1756, 1603, 1580, 1452, 1372, 1256 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 9.0 Hz, 1H, H7), 7.73–7.70 (m 1H, H4), 7.33 (dd, J = 9.0, 2.0 Hz, 1H, H6), 6.32 (s, 1H, $H2^{cyclobutene}$), 4.51 (q, J = 7.1 Hz, 2H, CH_2), 2.94–2.91 (m, 2H, $H4^{cyclobutene}$), 2.64–2.61 (m, 2H, $H3^{cyclobutene}$), 1.48 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.6 (CO), 138.1 (q, J = 2.2 Hz, $C2^{cyclobutene}$), 136.6 (q, J = 4.0 Hz, C2), 136.2 ($C1^{cyclobutene}$), 133.5 (C7a), 129.8 (C5), 126.3 (q, J = 1.1 Hz, C3a), 125.8 (C6), 123.5 (q, J = 269.2 Hz, CF_3), 119.6 (q, J = 2.5 Hz, C4), 116.5 (C7), 110.3 (q, J = 35.3 Hz, C3), 64.2 (CH_2), 34.0 ($C4^{cyclobutene}$), 28.2 ($C3^{cyclobutene}$), 14.0 (CH_3). ^{19}F NMR ($CDCl_3$, 471 MHz): δ –54.52. HMRS (ESI+): m/z calcd for $C_{16}H_{14}ClF_3NO_2^+$ $[M + H]^+$ 344.0660, found 344.0664.

Associated Content

Supporting Information: The Supporting Information is available free of charge on the ACS Publications website at DOI: ___.

Copies of NMR spectra for new products.

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