JOC The Journal of Organic Chemistry

Article

Palladium-Catalyzed Tandem Carbocyclization and Hetroarylation for the synthesis of 2-(trifluoromethyl)indenylmethyleneindoles

Tao Zhang, Fan Chen, Xiao-Hong Zhang, Peng-Cheng Qian, and Xing-Guo Zhang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02781 • Publication Date (Web): 07 Dec 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

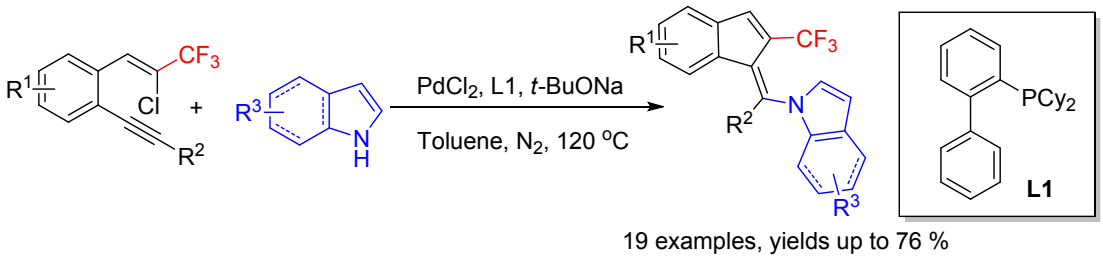
Palladium-Catalyzed Tandem Carbocyclization and Hetroarylation for the synthesis of 2-(trifluoromethyl)indenylmethyleneindoles

Tao Zhang, Fan Chen,* Xiao-Hong Zhang, Peng-Cheng Qian, Xing-Guo Zhang*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, China; Author to whom correspondence should be addressed; E-Mail: fanchen@wzu.edu.cn; zxg@wzu.edu.cn

RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

Abstract



19 examples, yields up to 76 %

A palladium-catalyzed tandem cyclization and cross-coupling reaction of the *ortho*-(2-chlorovinyl)-alkynylbenzenes with indoles/pyrroles is developed. The process proceeds *via* intramolecular carbocyclization and subsequent hetroarylation to afford previously unknown trifluoromethyl-containing indenylmethyleneindoles, which are potentially useful in drug design.

INTRODUCTION

Both the indene [1] and indole [2] are essential and important structural motifs found in natural occurring products, pharmaceutical active compounds and functional materials. For example, sulindac and indriline are clinically used as an efficient non-steroidal

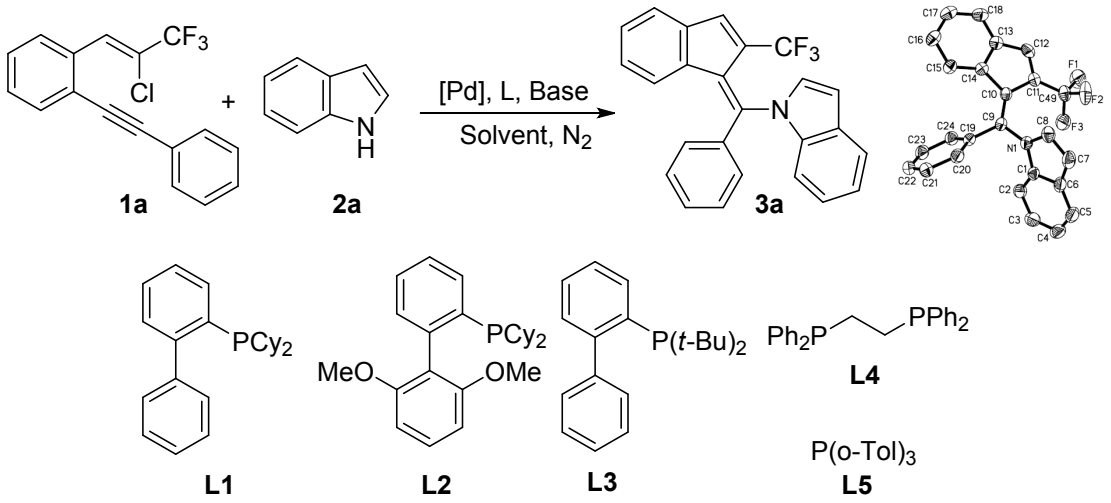
anti-inflammatory drug and an antidepressant agent. [3] The pharmacologically active ergot alkaloids and the antitumor agent ellipticine contain the indole framework. [4] Therefore, the development of novel methods to construct these compounds is important in synthetic organic and pharmaceutical fields. In the past decades, a large number of attractive and valuable procedures have been reported for the synthesis of indene [5] and indole skeletons, [6] including many CF_3-substituted indenes [7] or indoles. [8] However, example for the synthesis of molecules bearing both indene and indole moieties still remains unexplored. These polycyclics are previously unknown and potentially useful in the drug discovery process. As part of our continuing interest in trifluoromethylated molecules, [7b, 9] we wish to develop some simple reactions to construct polycyclic compounds with the introduction of trifluoromethyl group.[10] Herein, we report a palladium-catalyzed cascade carbocyclization and hetroarylation of *ortho*-(2-chlorovinyl)-alkynylbenzenes with indoles or pyrroles, leading to CF_3-containing indenylmethyleneindoles. .

RESULTS AND DISCUSSION

The model reaction of *o*-phenylethynyl-β-chloro-β-trifluoromethylstyrene (**1a**) (Z/E = 97:3) [11] with indole (**2a**) was chosen to screen reaction conditions, and the results were summarized in Table 1. Based on our previous work, [7b] the reaction was firstly conducted in the presence of 10 mol% $Pd(OAc)_2$, 0.2 eq. ligand L1, 2.0 eq. *t*-BuONa in toluene at 120 °C for 24 h. The desired product **3a** was successfully isolated in 67% yield (entry 1), and the structure of product **3a** was confirmed by X-ray crystallography. Encouraged by these results, various Pd catalysts were investigated and $PdCl_2$ was the most effective catalyst, affording the targeted product **3a** in 72% yield (entries 2-5), whereas the reaction did not occur in the absence of the palladium catalyst (entry 6). Subsequently, other phosphorus ligands were tested, but all gave worse results than ligand L1 (entries 7-10). To further enhance the reaction yield, different bases such as K_2CO_3, K_3PO_4, Cs_2CO_3 and Na_2CO_3 were investigated, and *t*-BuONa was proved to be the best base for the tandem reaction (entries 11-14). Other solvents including DMSO, DMF, and CH_3CN were also examined, but all gave

lower yields than toluene (entries 15-17). The elevated temperature did not enhance the yield (entry 18).

Table 1 Optimization of the Reaction Conditions [a]



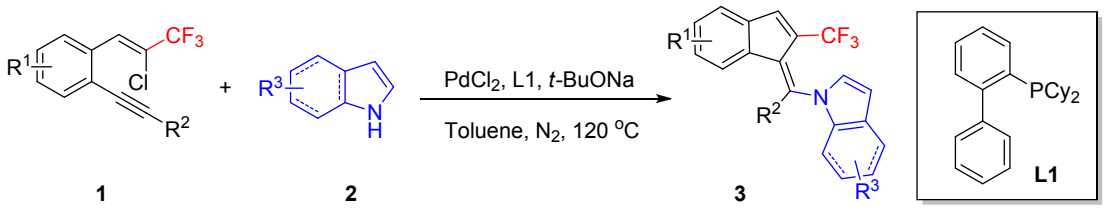
Entry	Catalyst	L	Base	Solvent	Yield[b]
1	$Pd(OAc)_2$	L1	*t*-BuONa	Toluene	67
2	$Pd(PPh_3)_2Cl_2$	L1	*t*-BuONa	Toluene	56
3	$PdCl_2$	L1	*t*-BuONa	Toluene	72
4	$Pd(CH_3CN)_2Cl_2$	L1	*t*-BuONa	Toluene	70
5	$Pd(PPh_3)_4$	L1	*t*-BuONa	Toluene	61
6	-	L1	*t*-BuONa	Toluene	NR
7	$PdCl_2$	L2	*t*-BuONa	Toluene	53
8	$PdCl_2$	L3	*t*-BuONa	Toluene	10
9	$PdCl_2$	L4	*t*-BuONa	Toluene	11
10	$PdCl_2$	L5	*t*-BuONa	Toluene	23
11	$PdCl_2$	L1	K_2CO_3	Toluene	33
12	$PdCl_2$	L1	K_3PO_4	Toluene	48
13	$PdCl_2$	L1	Cs_2CO_3	Toluene	60
14	$PdCl_2$	L1	Na_2CO_3	Toluene	53
15	$PdCl_2$	L1	*t*-BuONa	DMSO	Trace
16	$PdCl_2$	L1	*t*-BuONa	DMF	Trace
17	$PdCl_2$	L1	*t*-BuONa	CH_3CN	45
18	$PdCl_2$	L1	*t*-BuONa	Toluene	58 [b]

[a] Reaction conditions: **1** (0.1 mmol), **2** (1.2 eq), [Pd] (0.1 eq), Ligand (0.2 eq), base (2.0 eq), Solvent (1.0 mL), N_2, 120 °C, 24 h. [b] At 140 °C.

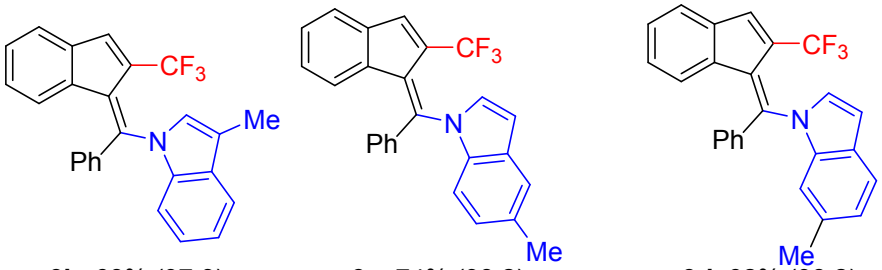
Under the optimal reaction conditions, the substrate scope of various indoles was initially investigated. As shown in Table 2, indoles with both electron-donating and electron-withdrawing substituents underwent the tandem carbocyclization and

hetroarylation smoothly, affording the products **3a-3i** in moderate to good yields. For example, 3, 5, 6 or 7-methyl indoles and 5-methoxyl indole provided 2-(trifluoromethyl)indenylmethyleneindoles **3a-3e** in 58-74% yields with high regioselectivity, while fluoro and chloro substituents **3f-3i** were isolated in 61-76% yields. Subsequently, various alkynes (R^2 moiety) were tested to afford the methyl and methoxyl equivalents **3j** and **3k** in good yields. Notably, aliphatic alkyne also carried out the tandem reaction, giving product **3l** in 36% yield. During the examination of substitution effect on the phenyl group (R^1 moiety), the results showed that the tandem reaction seemed to be insensitive to the electronic effects of R^1 group. Methyl, methoxyl, 1,4-methylenedioxy and fluoro products **3m-3p** were isolated in good yields. And some heterocyclic groups, such as thiophene underwent the reaction smoothly, giving product **3q** in 59% yield. Moreover, the reaction conditions were also applicable to pyrrole, furnished their corresponding 2-(trifluoromethyl)indenylmethylenepyrroles **3r** and **3s** in 65% and 47% yields, respectively.

Table 2. Substrate Scope [a,b]



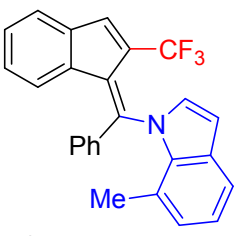
1 2 3



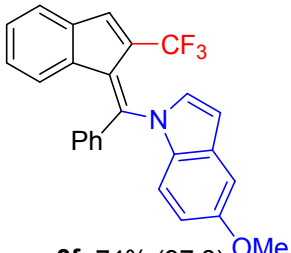
3b, 68% (97:3)

3c, 74% (98:2)

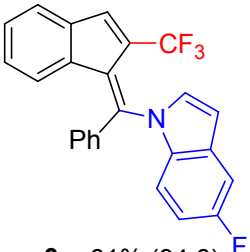
3d, 62% (98:2)



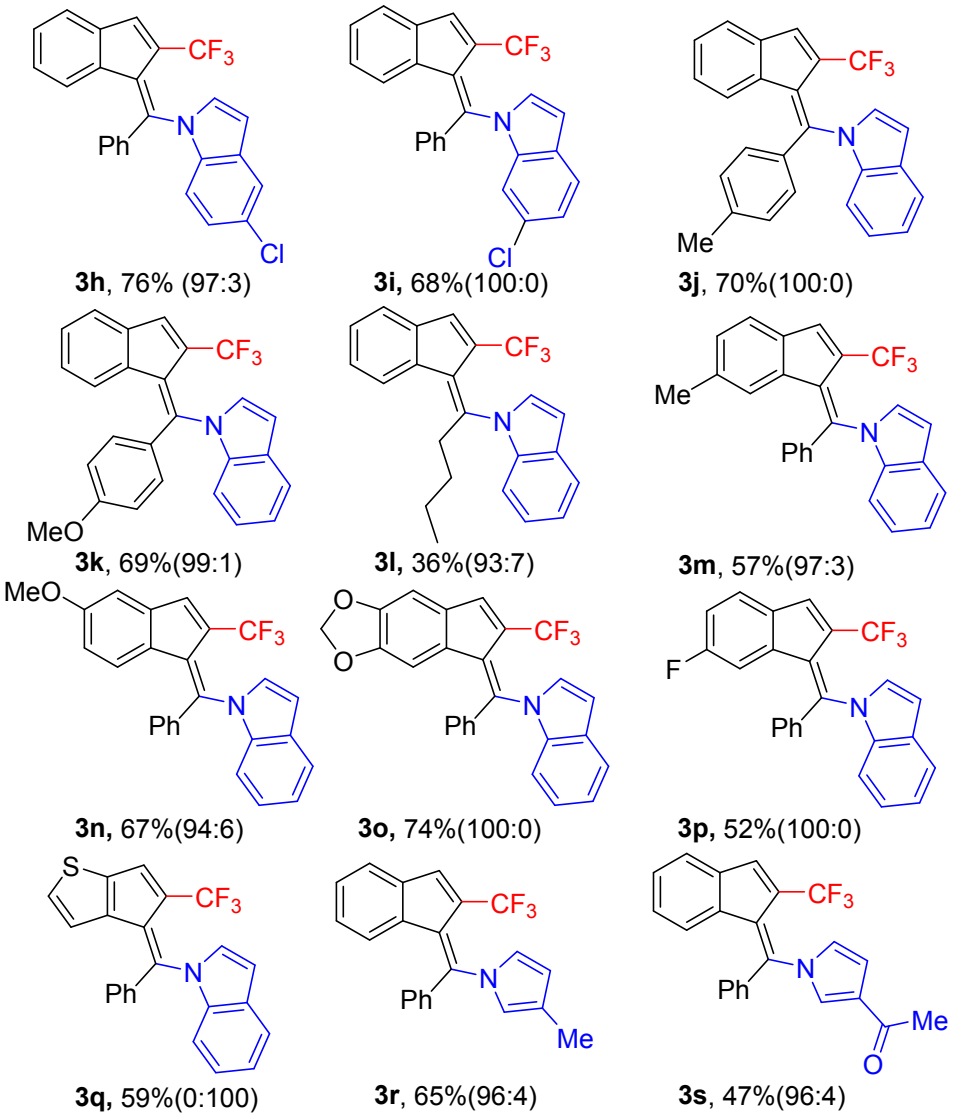
3e, 58% (100:0)



3f, 74% (97:3)



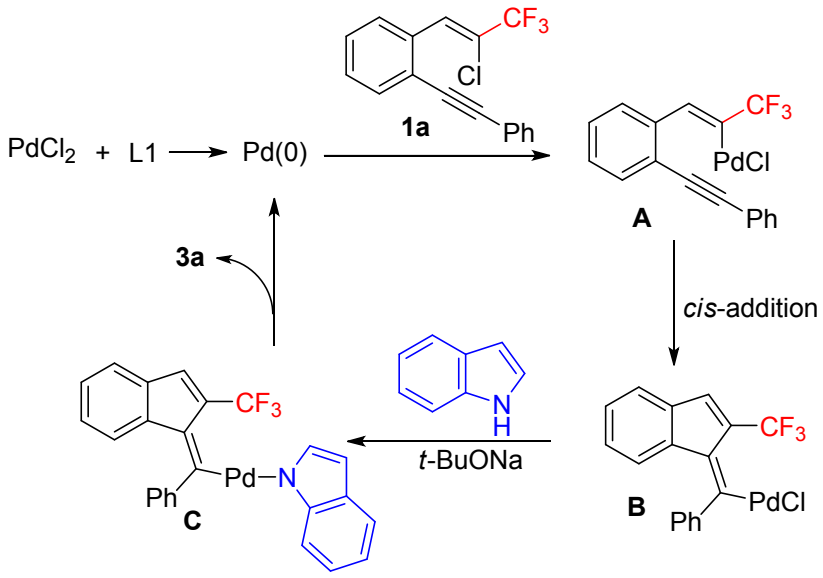
3g, 61% (94:6)



[a] Reaction conditions: **1** (0.1 mmol), **2** (1.2 eq), $PdCl_2$ (0.1 eq), **L1** (0.2 eq), *t*-BuONa (2.0 eq), Toluene (1.0 mL), N_2, 120 °C, 24 h.

[b] The ratio of Z/E isomers is shown in parentheses and was determined by ^{19}F NMR spectroscopy.

On the basis of previous reports,[7b] a possible mechanism for this transformation was proposed in Scheme 1. Firstly, the Pd(0) species is produced *in situ* from the reduction of $PdCl_2$ with phosphorus ligand. Then, oxidative addition of Pd(0) with vinyl chloride **1a** generates Pd(II) intermediate **A**. Intramolecular *cis*-addition of Pd(II) to the carbon-carbon triple bond provides *cis*-isomer of vinylpalladium complex **B**. Subsequently, ligand exchange with indole in the presence of *t*-BuONa gives intermediate **C**. Finally, reductive elimination process delivers the target indenylmethyleneindole **3a**, and regenerates the Pd(0) species.



Scheme 1. Possible Mechanism.

CONCLUSIONS

In conclusion, we have developed a facile method for the synthesis of CF_3-containing indenylmethyleneindoles. A variety of *o*-alkynyl-β-chloro-β-trifluoromethylstyrenes were compatible to the palladium-catalyzed cascade carbocyclization and hetroarylation with various indoles and pyrroles, affording the corresponding indenylmethylene-indoles/pyrroles in moderate to good yields. This simple synthetic protocol provides new route to the trifluoromethylated polycyclic molecules bearing indene and indole moieties, which might be potentially useful in medicine chemistry.

EXPERIMENTAL SECTION

General Information

Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (^{1}H: 500 MHz, ^{13}C{^{1}H}: 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in Hz. ^{19}F NMR spectra were recorded on a 500MHz spectrometer (^{19}F at 470 MHz) and are reported relative to the $CDCl_3$ as the internal standard. High resolution mass spectra were recorded on an

ESI-Q-TOF mass spectrometry. All reactions under N_2 atmosphere were conducted using standard Schlenk techniques. Melting points were measured on X4 melting point apparatus and uncorrected. Column chromatography was performed using EM Silica gel 60 (300-400 mesh).

General Procedure for the Synthesis of 1-bromo-2-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)benzene

Zn (3923.4 mg, 60.0mmol), 2-bromobenzaldehyde (5550.6 mg, 30.0 mmol), CF_3CCl_3 (8432.1 mg, 45.0 mmol) were added to DMF (20 mL) at room temperature for 1 h. After stirring, the mixture was stirring at 50 °C for 24 hours. Then, Zn (1961.7 mg, 30.0 mmol) and acetic anhydride (4.23 mL, 45.0 mmol) were added to the mixture and the reaction was stirring for further 12 h. After the reaction was complete, the reaction mixture was washed with saturated brine twice and extracted with diethyl ether. The organic phase was dried over sodium sulfate and evaporated under vacuum. The resulting oil was purified by column chromatography using petroleum ether /EtOAc = 30:1 as the eluent on silica gel.

General Procedure for the Synthesis of 1-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2-(phenylethynyl)benzene [11]

$Pd(Ph_3P)_2Cl_2$ (0.1 mmol, 70.2 mg), CuI (0.05 mmol, 9.6 mg), 1-bromo-2-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)benzene (5.0 mmol, 1427.4 mg) were added to Et_3N (20 mL) at room temperature. The flask was filled with nitrogen. Ethynylbenzene (10.0 mmol, 1021.3 mg) was added dropwise to the mixture by a syringe. After stirring at room temperature for 10 min, the mixture was stirred at 60 °C overnight. The reaction mixture was washed with saturated brine twice and extracted with diethyl ether. The organic phase was dried over sodium sulfate and evaporated under vacuum. The resulting oil was purified by column chromatography using petroleum ether/EtOAc = 100:1 as the eluent on silica gel.

General Procedure for the Synthesis of 1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole derivatives 3a-3s

To a flame-dried Schlenk tube with a magnetic stirring bar was charged with **1** (0.1 mmol), **2** (0.12 mmol), $PdCl_2$ (1.8 mg, 0.01 mmol), 2-(dicyclohexylphosphino)biphenyl (0.02 mmol, 7.0 mg) and *t*-BuONa (19.2 mg, 0.2 mmol) in toluene (1 mL) under N_2 atmosphere. The reaction mixture was stirred at 120 °C for 24 h. After the reaction was finished, the mixture was washed with ethyl acetate and the combined organic layers were evaporated under vacuum. The residue was purified by flash column chromatography using petroleum ether/EtOAc = 100:1-30:1 to afford the desired products **3a-3s.**

(Z)-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3a**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow solid (27.9 mg, 72% yield, Z/E = 98:2), m.p. 104-106 ^oC; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.65 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.41-7.38 (m, 3H), 7.32-7.30 (m, 2H), 7.16-7.11 (m, 2H), 7.01-7.00 (m, 1H), 6.99-6.96 (m, 1H), 6.94-6.91 (m, 1H)，6.74-6.72 (m, 2H), 6.01 (d, J = 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 143.4, 138.0, 137.2, 136.8, 136.7, 136.5, 132.4, 132.0, 131.3, 130.6, 130.2, 129.3 (q, J_{C-F} = 33.75 Hz), 128.2, 127.8, 127.4, 123.6, 123.3, 123.0 (q, J_{C-F} = 268.75 Hz), 122.7, 121.8, 121.3, 112.7, 106.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ: -53.67 (s, 2.96 F), -57.52 (s, 0.04 F); LRMS (EI, 70 eV) m/z (%): 387 (M^+, 39); HRMS (ESI) Calcd for $C_{25}H_{17}F_3N^+$ ($[M + H]^+$) 388.1308, Found: 388.1306.

(Z)-3-methyl-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3b**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as an orange solid (27.3 mg, 68% yield, Z/E = 97:3), m.p. 121-124 ^oC; ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.62 (d, J = 8.0 Hz, 1H), 7.54-7.51 (m, 2H), 7.47-7.43 (m, 2H), 7.39-7.36 (m, 3H), 7.21-7.17 (m, 2H), 7.02-7.00 (m, 1H), 6.98-6.96 (m, 1H), 6.83 (s, 1H), 6.69 (d, J = 8.5 Hz, 1H), 6.15 (d, J = 8.5 Hz, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 143.7, 137.9, 137.4, 137.1, 136.5, 135.9, 132.4, 131.2, 131.1, 129.3 (q, J_{C-F} = 33.75 Hz), 128.2, 128.0, 127.6, 127.0, 126.1, 123.6, 123.3, 123.1 (q, J_{C-F} = 268.75 Hz), 122.6,

121.5, 119.3, 116.3, 112.8, 9.81; ^{19}F NMR (470 MHz, $CDCl_3$) δ: -53.64 (s, 2.90 F), -57.44 (s, 0.10 F),; LRMS (EI, 70 eV) m/z (%): 401 (M^+, 62); HRMS (ESI) Calcd for $C_{26}H_{19}F_3N^+$ ([M + H]$^+$) 402.1464, Found: 402.1455.

(Z)-5-methyl-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3c**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as an orange oil (29.7 mg, 74% yield, Z/E = 98:2); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.53 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.46-7.43 (m, 4H), 7.38-7.35 (m, 1H), 7.32-7.31 (m, 1H), 7.22-7.19 (m, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 6.99-6.97 (m, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 3.0 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 6.10 (d, *J* = 8.0 Hz, 1H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 143.7, 138.0, 137.2, 136.55, 136.48, 135.0, 132.6, 131.9, 131.3, 130.9, 130.6, 129.3 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.2, 127.7, 127.3, 126.8, 124.8, 123.6, 123.0 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.7, 121.0, 112.5, 106.4, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.67 (s, 2.94 F), −57.46 (s, 0.06 F); LRMS (EI, 70 eV) m/z (%): 401 (M^+, 48); HRMS (ESI) Calcd for $C_{26}H_{19}F_3N^+$ ([M + H]$^+$) 402.1464, Found: 402.1460.

(Z)-6-methyl-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole **(3d)** Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow solid (24.9 mg, 62% yield, Z/E = 98:2), m.p. 118-121 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.56 (s, 1H), 7.55-7.54 (m, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.46-7.44 (m, 3H), 7.38-7.35 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.22-7.19 (m, 1H), 7.00-6.96 (m, 3H), 6.72 (d, *J* = 3.5 Hz, 1H), 6.52 (s, 1H), 6.07 (d, *J* = 3.5 Hz, 1H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 143.7, 138.0, 137.3, 137.1, 136.7, 136.5, 133.1, 132.6, 131.9, 131.2, 130.1, 129.3 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.2, 128.0, 127.8, 127.3, 123.6, 123.5, 123.0 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.7, 120.8, 112.7, 106.5, 21.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.67 (s, 2.96 F), −57.57 (s, 0.04 F); LRMS (EI, 70 eV) m/z (%): 401 (M^+, 94); HRMS (ESI) Calcd for $C_{26}H_{19}F_3N^+$ ([M + H]$^+$) 402.1464, Found: 402.1477.

(Z)-7-methyl-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3e**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow oil (23.3 mg, 58% yield, Z/E =

100:0); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.58 (d, *J* = 8.0 Hz , 1H), 7.56 (s, 1H), 7.52-7.48 (m, 1H), 7.41-7.40 (m, 5H), 7.18-7.15 (m, 1H), 7.13-7.10 (m, 1H), 6.90 (d, *J* = 3.0 Hz, 2H), 6.87-6.84 (m, 1H), 6.77 (d, *J* = 3.0 Hz, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 143.9, 138.8, 138.7, 138.0, 137.5, 136.6, 136.2, 132.7, 131.2, 130.5, 130.3, 129.5, 128.8 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.2, 127.7, 126.4, 123.0 (q, $J_{C\text{-}F}$ = 267.5 Hz), 122.80, 122.77, 121.9, 119.4, 106.3, 19.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.72 (s, 3.00 F); LRMS (EI, 70 eV) m/z (%): 401 (M^+, 26); HRMS (ESI) Calcd for $C_{26}H_{18}F_3NaN^+$ ([M + Na]$^+$) 424.1284, Found: 424.1278.

(Z)-5-methoxy-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3f**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1, v/v) affords the title compound as a red oil (30.9 mg, 74% yield, Z/E = 97:3); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.53-7.50 (m, 2H), 7.45-7.40 (m, 3H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.22-7.19 (m, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 3.5 Hz, 1H), 6.99-6.97 (m, 1H), 6.70 (d, *J* = 3.5 Hz, 1H), 6.65-6.63 (m, 1H), 6.60-6.58 (m, 1H), 6.10 (d, *J* = 7.5 Hz, 1H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 155.5, 143.7, 138.0, 137.2, 136.5, 136.4, 132.6, 132.0, 131.7, 131.4, 131.0, 129.3 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.2, 127.7, 127.2, 126.7, 123.6, 123.0 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.7. 113.6, 112.9, 106.6, 103.2, 55.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ: ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.72 (s, 2.93 F), −57.42 (s, 0.07 F); LRMS (EI, 70 eV) m/z (%): 417 (M^+, 46); HRMS (ESI) Calcd for $C_{26}H_{19}F_3NO^+$ ([M + H]$^+$) 418.1413, Found: 418.1408.

(Z)-5-fluoro-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3g**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 75:1, v/v) affords the title compound as a yellow Solid (24.7 mg, 61% yield, Z/E = 94:6), m.p. 114-117 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.53-7.49 (m, 2H), 7.45 (d, *J* = 7.0 Hz, 2H), 7.41-7.38 (m, 2H), 7.31 (d, *J* = 9.0 Hz, 2H), 7.23-7.20 (m, 1H), 7.08 (s, 1H), 6.99-6.96 (m, 1H), 6.76-6.73 (m, 2H), 6.67-6.64 (m, 1H), 6.01 (d, *J* = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 158.9 (d, $J_{C\text{-}F}$ = 236.25 Hz), 143.1, 138.1, 137.14, 137.12, 136.4, 133.2, 132.3, 132.0, 131.4, 130.8 (d, $J_{C\text{-}F}$ = 10.0 Hz),

129.3 (q, J_{C-F} = 33.75 Hz), 128.3, 127.9, 127.7, 127.6, 123.5, 122.9 (q, J_{C-F} = 268.75 Hz) , 122.8, 113.5 (d, J_{C-F} = 10.0 Hz), 111.6 (d, J_{C-F} = 26.25 Hz), 111.4, 106.5, 106.4 (d, J_{C-F} =26.25 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.86 (s, 2.82 F), −57.64 (s, 0.18 F), −122.12 (s, 0.94 F), −122.94 (s, 0.06 F); LRMS (EI, 70 eV) m/z (%): 405 (M^+, 21); HRMS (ESI) Calcd for $C_{25}H_{16}F_4N^+$ ($[M + H]^+$) 406.1213, Found: 406.1239.

(Z)-5-chloro-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3h**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow solid (32.0 mg, 76% yield, Z/E = 97:3) m.p. 117-119 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.64 (s, 1H), 7.54 (s, 1H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.40-7.36 (m, 2H), 7.31 (d, *J* = 7.0 Hz, 1H), 7.23-7.20 (m, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.99-6.95 (m, 2H), 6.71 (d, *J* = 3.0 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 5.99 (d, *J* = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 142.7, 138.1, 137.4, 136.9, 136.3, 132.3, 131.9, 131.8, 131.5, 131.2, 129.2 (q, J_{C-F} = 33.75 Hz), 128.3, 128.0, 127.8, 127.7, 127.4, 123.6, 123.5, 122.91, 122.88 (q, J_{C-F} = 268.75 Hz), 120.8, 113.6, 106.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.86 (s, 2.92F), −57.64 (s, 0.08F); LRMS (EI, 70 eV) m/z (%): 421 (M^+, 32); HRMS (ESI) Calcd for $C_{25}H_{16}F_3ClN^+$ ($[M + H]^+$) 422.0918, Found: 422.0941.

(Z)-6-chloro-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole **(3i)** Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow solid (28.6 mg, 68% yield, Z/E = 100:0), m.p. 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.59 (d, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.41-7.37 (m, 2H), 7.32-7.31 (m, 1H), 7.24-7.21 (m, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 3.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 2H), 5.99 (d, *J* = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 142.6, 138.2, 137.7, 137.0, 136.8, 136.2, 132.3, 131.7, 131.5, 131.2, 129.23, 129.22 (q, J_{C-F} = 33.75 Hz), 128.6, 128.4, 128.0, 127.8, 123.5, 123.0, 122.9 (q, J_{C-F} = 268.75 Hz), 122.5, 122.1, 112.6, 106.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.85 (s, 3.00 F); LRMS (EI, 70 eV) m/z (%): 421 (M^+, 100); HRMS (ESI) Calcd for $C_{25}H_{16}F_3ClN^+$ ($[M + H]^+$) 422.0918, Found: 422.0931.

(Z)-1-(p-tolyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole **(3j)**

Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as an orange oil (28.1 mg, 70% yield, Z/E = 100:0); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.69 (d, *J* = 7.5 Hz, 1H), 7.54 (s, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.32-7.28 (m, 2H), 7.23-7.16 (m, 4H), 7.06 (d, *J* = 3.5 Hz, 1H), 7.04-7.01 (m, 1H), 6.98-6.95 (m, 1H), 6.78 (d, *J* = 3.5 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 143.7, 142.0, 138.0, 136.8, 136.5, 136.3, 134.4, 132.5, 132.1, 130.7, 130.2, 129.3 (q, $J_{C\text{-}F}$ = 33.75 Hz), 129.0, 127.6, 127.2, 123.5, 123.2, 123.1 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.7, 121.8, 121.2, 112.8, 106.6, 21.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.57 (s, 3.00 F); LRMS (EI, 70 eV) m/z (%): 401 (M^+, 46); HRMS (ESI) Calcd for $C_{26}H_{18}F_3NaN^+$ ([M + Na]$^+$) 424.1284, Found: 424.1276.

(Z)-1-((4-methoxyphenyl)(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-indole (**3k**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 75:1, v/v) affords the title compound as a red oil (28.8 mg, 69% yield, Z/E = 99:1); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.58 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.09-7.04 (m, 2H), 6.96 (d, *J* = 3.5 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.87-6.83 (m, 2H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 162.5, 143.6, 137.9, 136.8, 136.6, 135.8, 134.4, 133.9, 130.8, 130.3, 129.3 (q, $J_{C\text{-}F}$ = 33.75 Hz), 127.5, 127.0, 125.8, 123.3, 123.22, 123.19 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.6, 121.8, 121.2, 113.8, 112.9, 106.6, 55.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.56 (s, 2.98 F), −57.45 (s, 0.02 F); LRMS (EI, 70 eV) m/z (%): 417 (M^+, 100); HRMS (ESI) Calcd for $C_{26}H_{18}F_3NaNO^+$ ([M + Na]$^+$) 440.1233, Found: 440.1233.

(Z)-1-(1-(2-(trifluoromethyl)-1H-inden-1-ylidene)pentyl)-1H-indole (**3l**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow solid (13.2 mg, 36% yield, Z/E = 93:7), m.p. 112-114 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.62 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.24-7.18 (m, 3H), 7.14-7.11 (m, 2H), 7.05-7.02 (m, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.59 (s, 1H), 6.06 (d, *J* = 7.5 Hz, 1H), 3.77-3.72 (m, 2H), 2.17-2.12 (m,

2H), 1.50-1.45(m, 2H), 0.89 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 145.3, 142.8, 141.4, 136.3, 132.4, 131.1 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.8, 128.2, 128.1, 127.4, 127.3, 124.1, 123.7 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.5, 121.7, 121.2, 120.3, 111.4, 103.6, 38.1, 30.7, 22.4, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −56.26 (s, 2.79 F), −63.70 (s, 0.21 F); LRMS (EI, 70 eV) m/z (%): 367 (M^+, 51); HRMS (ESI) Calcd for $C_{23}H_{21}F_3N^+$ ($[M + H]^+$) 368.1621, Found: 368.1612.

(Z)-1-((6-methyl-2-(trifluoromethyl)-1H-inden-1-ylidene)(phenyl)methyl)-1H-indole (**3m**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as an orange oil (22.8 mg, 57% yield, Z/E = 97:3); ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.67 (d, J = 7.5 Hz, 1H), 7.52-7.49 (m, 2H), 7.46-7.42 (m, 2H), 7.35 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 2H), 7.16-7.13 (m, 1H), 7.04-6.99 (m, 3H), 6.77-6.73 (m, 2H), 5.81 (s, 1H), 2.03 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 142.9, 137.9, 137.3, 137.0, 136.8, 136.7, 135.6, 132.4, 131.2, 130.6, 130.2, 128.3, 128.19, 128.16 (q, $J_{C\text{-}F}$ = 33.75 Hz), 127.6, 124.5, 123.2, 123.1 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.4, 121.7, 121.2, 112.8, 106.4, 21.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.73 (s, 2.91 F), −57.59 (s, 0.09 F); LRMS (EI, 70 eV) m/z (%): 401 (M^+, 38); HRMS (ESI) Calcd for $C_{26}H_{19}F_3N^+$ ($[M + H]^+$) 402.1464, Found: 402.1473.

(Z)-1-((5-methoxy-2-(trifluoromethyl)-1H-inden-1-ylidene)(phenyl)methyl)-1H-indole (**3n**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow oil (27.9 mg, 67% yield, Z/E = 94:6); ^1H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.67 (d, J = 7.5 Hz, 1H), 7.49-7.47 (m, 2H), 7.46 (s, 1H), 7.41-7.33 (m, 4H), 7.16-7.13 (m, 1H), 7.03-6.99 (m, 2H), 6.95 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.73 (s, 1H), 6.49 (d, J = 8.5 Hz, 1H), 5.90 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 159.6, 141.7, 139.6, 137.4, 136.8, 136.7, 131.9, 131.0, 130.4, 130.2, 130.0, 129.6 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.2, 127.6, 124.8, 123.2, 122.9 (q, $J_{C\text{-}F}$ = 268.75 Hz), 121.7, 121.2, 114.0, 112.7, 107.8, 106.3, 55.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.86 (s, 2.83 F), −57.80 (s, 0.17 F); LRMS (EI, 70 eV) m/z (%): 417 (M^+, 37); HRMS (ESI) Calcd for $C_{26}H_{19}F_3NO^+$ ($[M + H]^+$) 418.1413, Found: 418.1438.

(Z)-1-(phenyl(6-(trifluoromethyl)-5H-indeno[5,6-d][1,3]dioxol-5-ylidene)methyl)-1H-indole (**3o**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as a yellow solid (31.9 mg, 74% yield, Z/E = 100:0), m.p. 123-125 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.66 (d, *J* = 7.5 Hz, 1H), 7.52-7.49 (m, 1H), 7.44-7.41 (m, 1H), 7.38-7.36 (m, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.17-7.14 (m, 1H), 7.04-7.01 (m, 2H), 6.86 (s, 1H), 6.77-6.75 (m, 2H), 5.86 (s, 1H), 5.83 (s, 1H), 5.45 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 148.2, 147.5, 142.9, 137.2, 136.64, 136.61, 132.8, 132.4, 132.1, 131.3, 131.2, 130.4, 130.2, 128.2, 127.5 (q, $J_{C\text{-}F}$ = 33.75 Hz), 123.3, 122.9 (q, $J_{C\text{-}F}$ = 268.75 Hz), 121.9, 121.4, 112.6, 106.8, 104.7, 102.9, 101.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.33 (s, 3.00 F); LRMS (EI, 70 eV) m/z (%): 431 (M^+, 76); HRMS (ESI) Calcd for $C_{26}H_{17}F_3NO_2^+$ ([M + H]$^+$) 432.1206, Found: 432.1228.

(Z)-1-((6-fluoro-2-(trifluoromethyl)-1H-inden-1-ylidene)(phenyl)methyl)-1H-indole (**3p**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 75:1, v/v) affords the title compound as a yellow solid (21.0 mg, 52% yield, Z/E = 100:0), m.p. 121-123 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.69 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.49 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.41-7.36 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.19-7.16 (m, 1H), 7.04-7.01 (m, 2H), 6.93-6.89 (m, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.74-5.72 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ: 163.2 (d, $J_{C\text{-}F}$ = 243.75 Hz), 144.6, 138.2 (d, $J_{C\text{-}F}$ = 8.75 Hz), 136.9, 136.6, 135.8, 134.1, 132.5, 132.1, 131.8, 131.6, 130.4, 129.2 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.3, 123.6 (d, $J_{C\text{-}F}$ = 8.75 Hz), 123.5, 122.8 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.1, 121.5, 114.6 (d, $J_{C\text{-}F}$ = 23.75 Hz), 112.6, 111.0 (d, $J_{C\text{-}F}$ = 26.25 Hz), 107.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.88 (s, 3.00 F), -113.31 (s, 1.00 F); LRMS (EI, 70 eV) m/z (%): 405 (M^+, 49); HRMS (ESI) Calcd for $C_{25}H_{16}F_4N^+$ ([M + H]$^+$) 406.1213, Found: 406.1234.

(E)-1-(phenyl(5-(trifluoromethyl)-4H-cyclopenta[b]thiophen-4-ylidene)methyl)-1H-indole (**3q**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1, v/v) affords the title compound as a red oil (23.2 mg, 59% yield, Z/E = 0:100); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.66 (d, *J* = 7.5 Hz, 1H), 7.55-7.51 (m,

1H), 7.42-7.38 (m, 5H), 7.17-7.14 (m, 1H), 7.11 (d, 3.5 Hz, 1H), 7.03-7.00 (m, 2H), 6.76-6.74 (m, 2H), 5.65 (d, J = 3.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ: 144.7, 143.0, 138.8, 137.2, 136.4, 132.4, 131.6, 131.1, 130.9, 130.2, 128.7, 128.3, 126.9 (q, $J_{C\text{-}F}$ = 33.75 Hz), 124.7, 123.3, 122.7 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.4, 121.9, 121.3, 112.8, 106.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −52.56 (s, 3.00 F); LRMS (EI, 70 eV) m/z (%): 393 (M^+, 43); HRMS (ESI) Calcd for $C_{23}H_{15}F_3NS^+$ ($[M + H]^+$) 394.0872, Found: 394.0882.

(Z)-3-methyl-1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-pyrrole (**3r**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1, v/v) affords the title compound as an orange oil (22.8 mg, 65% yield, Z/E = 96:4); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.52-7.50 (m, 1H), 7.46 (s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.42-7.39 (m, 2H), 7.36-7.33 (m, 2H), 7.26-7.23 (m, 1H), 7.17-7.14 (m, 1H), 6.60-6.59 (m, 1H), 6.44-6.42 (m, 2H), 6.22 (s, 1H), 2.14 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ: 145.7, 137.9, 137.4, 137.1, 136.0, 132.6, 132.4, 131.2, 129.5 (q, $J_{C\text{-}F}$ = 33.75 Hz), 127.9, 127.5, 127.1, 124.4, 123.5, 123.0 (q, $J_{C\text{-}F}$ = 268.75 Hz), 122.7, 122.5, 121.6, 113.7, 12.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −53.93 (s, 2.89 F), -56.55 (s, 0.11 F); LRMS (EI, 70 eV) m/z (%): 351 (M^+, 68); HRMS (ESI) Calcd for $C_{22}H_{17}F_3N^+$ ($[M + H]^+$) 352.1308, Found: 352.1308.

(Z)-1-(1-(phenyl(2-(trifluoromethyl)-1H-inden-1-ylidene)methyl)-1H-pyrrol-3-yl)ethan-1-one (**3s**) Purification by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1, v/v) affords the title compound as a red solid (17.8 mg, 47% yield, Z/E = 96:4) m.p. 113-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ: 7.54-7.52 (m, 2H), 7.45-7.41 (m, 3H), 7.34-7.32 (m, 3H), 7.28 (d, J = 7.5 Hz, 1H), 7.15-7.12 (m, 1H), 6.81 (s, 1H), 6.70 (s, 1H), 6.23 (d, J = 7.5 Hz, 1H), 2.40 (s, 3H); **$^{13}C\{^{1}H\}$** NMR (125 MHz, $CDCl_3$) δ: 193.5, 143.5, 138.6, 138.3, 136.6, 136.3, 132.0, 131.6, 129.4 (q, $J_{C\text{-}F}$ = 33.75 Hz), 128.5, 128.32, 128.30, 128.25, 125.4, 123.4, 123.1, 122.6 (q, $J_{C\text{-}F}$ = 268.75 Hz), 111.2, 27.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −54.39 (s, 2.88 F), −56.95 (s, 0.12 F); LRMS (EI, 70 eV) m/z (%): 379 (M^+, 47); HRMS (ESI) Calcd for $C_{23}H_{16}F_3NaNO^+$ ($[M + Na]^+$) 402.1076, Found: 402.1098.

SUPPLEMENTARY INFORMATION

Copies of ^{1}H and ^{13}C NMR spectra for products **3a-3s** and X-ray data for compound **3a.** This material is available free of charge *via* the Internet at http://pubs.acs.org.

Supplementary crystallographic data was deposited at the Cambridge Crystallographic Data Centre (CCDC) under the number CCDC-1881771 (**3a**) and can be obtained free of charge from via www.ccdc.cam.ac.uk/data_request.cif.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (No. 21272177), Natural Science Foundation of Zhejiang Province (No. LR15B020002) and Project of Wenzhou Science and Technology Bureau (W20170003) for financial supports.

REFERENCES

(1) (a) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.;, Ohtani, M. Potent Inhibitors of Secretory Phospholipase A2: Synthesis and Inhibitory Activities of Indolizine and Indene Derivatives. *J. Med. Chem.* **1996**, *39,* 3636-3658. (b) Barberá, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. Breaking the Mold of Discotic Liquid Crystals. *Angew. Chem. Int. Ed.* **1998**, *37,* 296-299. (c) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. Comparative QSAR Analysis of Estrogen Receptor Ligands. *Chem. Rev.* **1999**, *99,* 723-744. (d) Yang, J.; Lakshmikantham, M. V.; Cava, M. P. Synthesis and Characterization of 5,10-Bis(2-thienyl)indeno[2,1-*a*]indene Derivatives: The First Examples of Conducting Polymers Containing a Rigid Bis(thienyl)butadiene Core. *J. Org. Chem.* **2000**, *65,* 6739-6742. (e) Alcalde, E.; Mesquida, N.; López-Pórez, S.; Frigola, J.; Merce, R. Indene-Based Scaffolds. 2. An Indole-Indene Switch: Discovery of Novel Indenylsulfonamides as 5-HT_6 Serotonin Receptor Agonists. *J. Med. Chem.* **2009**, *52,* 675-687. (f) Majetich, G.; Shimkus, J. M. The Taiwaniaquinoids: A Review. *J. Nat. Prod.* **2010**, *73,* 284-298. (g) He, Y.-J.; Chen, H.-Y.; Hou, J.-H.; Li,Y.-F. Indene-C_{60} Bisadduct: A New Acceptor for High-Performance Polymer Solar Cells. *J. Am. Chem.*

Soc. **2010**, *132,* 1377-1382. (h) Li, Y.-F. Molecular Design of Photovoltaic Materials for Polymer Solar Cells: Toward Suitable Electronic Energy Levels and Broad Absorption. *Acc. Chem. Res.,* **2012**, *45,* 723-733.

(2) (a) Kawasaki, T.; Higuchi, K. Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. *Nat. Prod. Rep*. **2005**, *22*, 761-793. (b) Borschberg, H-J. New Strategies for the Synthesis of Monoterpene Indole Alkaloids. *Curr. Org. Chem.* **2005**, *9*, 1465-1491. (c) Ogata, M.; Matsumoto, H.; Shimizu, S.; Kida, S.; Shiro, M.; Tawara, K. Synthesis and Antifungal Activity of New 1-Vinylimidazoles. *J. Med. Chem*. **1987**, *30*, 1348-1354. (d) Brustolin, F.; Castelvetro, V.; Ciardelli, F.; Ruggeri, G.; Colligiani, A. Synthesis and Characterization of Different Poly(1-vinylindole)s for Photorefractive Materials. *J. Polym. Sci. Polym. Chem.* **2001**, *39*, 253-262. (e) Inman, M.; Moody, C. J. Indole synthesis-something old, something new. *Chem. Sci.* **2013**, *4,* 29-41; (f) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845-5859.

(3) (a) Maguire, A. R.; Papot, S.; Ford. A.; Touhey, S.; O'Connor, R.; Clynes, M. Enantioselective Synthesis of Sulindac. *Synlett* **2001**, *1,* 41-44. (b) Liedtke, A. J.; Crews, B. C.; Daniel, C. M.; Blobaum, A. L.; Kingsley, P. J.; Ghebreselasie, K.; Marnett L. J. Cyclooxygenase-1-Selective Inhibitors Based on the *(E)*-2′-Desmethyl-sulindac Sulfide Scaffold. *J. Med. Chem.* **2012**, *55,* 2287-2300. (c) Hueber, D.; Teci, M.; Brenner, E.; Matt, D.; Weibel, J.; Pale, P.; Blanca, A. Regioselective Synthesis of Indene from 3-Aryl Propargylic *gem*-Dipivalates Catalyzed by *N*-Heterocyclic Carbene Gold(I) Complexes. *Adv. Synth. Catal.* **2018**, *360,* 2453-2459. (d) Jongcharoenkamol, J.; Chuathong, P.; Amako, Y.; Kono, M.; Poonswat, K.; Ruchirawat, S.; Ploypradith, P. Selective divergent synthesis of indanols, indanones, and indenes via acid-mediated cyclization of *(Z)*- and *(E)*-(2-stilbenyl)methanols and its application for the synthesis of paucifloral F derivatives. *J. Org. Chem.* **2018**, *83*, 13184-13210..

(4) Hegedus, L. S. Transition Metals in the Synthesis and Functionaiization of Indoles. *Angew. Chem. Int. Ed.* **1988**, *27,* 1113-1126.

(5) The selected examples (a) Tran, D. N.; Cramer, N. Enantioselective Rhodium(I)-Catalyzed [3+2] Annulations of Aromatic Ketimines Induced by Directed C-H Activations. *Angew. Chem. Int. Ed.* **2011**, *50,* 11098-11102. (b) Zhou, F.; Han, X.-L.; Lu, X.-Y. Palladium(II)-Catalyzed Synthesis of Functionalized Indenes from *o*-Alkynylbenzylidene Ketones. *J. Org. Chem.* **2011**, *76,* 1491-1494. (c) Kotipalli, T.; Hou, D.-R. Synthesis of Indenes by a $BF_3{\cdot}OEt_2$-Mediated, One-Pot Reaction of Aryl Homopropargyl Alcohols, Aldehydes, and Arenes. *Org. Lett.,* **2018**, *20,* 4787-4790, and references cited therein. (d) Nahide, P. D.; Jiménez-Halla, J. O. C.; Wrobel, K.; Solorio-Alvarado, C. R.; Alvarado, R. O.; Yahuaca-Juárez, B. Gold(I)-catalysed high-yielding synthesis of indenes by direct C_{sp3}–H bond activation. *Org. Biomol. Chem.*, **2018**, *16,* 7330-7335 and references cited therein, (e) Pei, C,; Rong, G.-W.; Yu, Z.-X.; Xu, X.-F. Copper-Catalyzed Intramolecular Annulation of Conjugated Enynones to Substituted 1*H*-Indenes and Mechanistic Studies. *J. Org. Chem.* **2018**, *83*, 13243-13255.

(6) The selected examples (a) Cacchi, S.; Fabrizi, G. Synthesis and Functionalization of Indoles Through Palladium-catalyzed Reactions. *Chem. Rev.* **2005**, *105*, 2873-2920; (b) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875-2911; (c) Joucla, L.; Djakovitch, L. Transition Metal-Catalysed, Direct and Site-Selective N1-, C2- or C3-Arylation of the Indole Nucleus: 20 Years of Improvements. *Adv. Synth. Catal.* **2009**, *351*, 673-714; (d) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644; (e) Shiri, M. Indoles in Multicomponent Processes (MCPs). *Chem. Rev.* **2012**, *112*, 3508-3549; (f) Maki, Y.; Mori, H.; Endo, T. Xanthate-Mediated Controlled Radical Polymerization of *N*-Vinylindole Derivatives. *Macromolecules* **2007**, *40*, 6119-6130. (g) Roche, M.; Frison, G.; Brion, J.-D.; Provot, O.; Hamze, A.; Alami, M. C_{sp2}-N Bond Formation via Ligand-Free Pd-Catalyzed Oxidative Coupling Reaction of *N*-Tosylhydrazones and Indole Derivatives. *J. Org. Chem.* **2013**, *78,* 8485-8495. (h) Zeng, X.; Cheng, G.; Shen, J.; Cui, X. Palladium-Catalyzed Oxidative Cross Coupling of

N-Tosylhydrazones with Indoles: Synthesis of *N*-Vinylindoles. *Org. Lett.*, **2013**, *15,* 3022-3025.

(7) (a) Hwang, J.-H.; Jung, Y.-H.; Hong, Y.-Y.; Jeon, S.-L.; Jeong, I.-H. Synthesis of novel 2-trifluoromethyl-1-methylene-3-phenylindene derivatives via carbocyclization reaction of 2-trifluoromethyl-1,1-diphenyl-1,3-enynes. *J. Fluorine. Chem*. **2011**, *132*, 1227-1231. (b) Wang, W.-Y.; Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. Palladium-Catalyzed Tandem Carbocyclization–Suzuki Coupling Reactions of Trifluoromethyl-Containing Building Blocks Leading to 2-Trifluoromethylindenes. *Synthesis* **2013**, *45*, 118-126. (c) Iakovenko, R. O.; Kazakova, A. N.; Boyarskaya, I. A.; Gurzhiy, V. V.; Avdontceva, M. S.; Panikorovsky, T. L.; Muzalevskiy, V. M.; Nenajdenko, V. G.; Vasilyev, A. V. Superacid-Promoted Synthesis of CF_3-Indenes Using Brominated CF_3-Enones. *Eur. J. Org. Chem*. **2017**, 5632-5643. (d) Tang, H.-J. Zhang, Y.-F.; Jiang, Y.-W. Feng, C. F- Nucleophilic-Addition-Induced [3+2] Annulation: Direct Access to CF_3 Substituted Indenes. *Org. Lett*. **2018**, *20*, 5190-5193.

(8) (a) Ma, C.-H.; Kang, T.-R.; He, L.; Liu, Q.-Z. Highly Enantioselective Michael Addition of Malonates to β-CF_3-β-(3-Indolyl)-nitroalkenes: Construction of Trifluoromethylated All-Carbon Quaternary Stereogenic Centres. *Eur. J. Org. Chem*. **2014**, 3981-3985. (b) Pedroni, J.; Cramer, N. 2 (Trifluoromethyl)indoles via Pd(0)-Catalyzed C(sp^3)-H Functionalization of Trifluoroacetimidoyl Chlorides. *Org. Lett*. **2016**, *18*, 1932-1935. (c) Zhu, Y.-Y.; Dong, Z.-H.; Cheng, X.; Zhong, X.-L.; Liu, X.-L.; Lin L.; Shen, Z.-Q.; Yang, P.-J.; Li, Y.; Wang, H.-L.; Yan, W.-J.; Wang, K.-R.; Wang, R. Asymmetric Synthesis of CF_3- and Indole-Containing Thiochromanes via a Squaramide-Catalyzed Michael-Aldol Reaction. *Org. Lett*. **2016**, *18*, 3546-3549. (d) Han, G.-F.; Wang, Q.; Chen, L.-W.; Liu, Y.-X.; Wang Q.-M. Copper-Catalyzed Trifluoromethylation of Acrylamides Coupled with Indole Dearomatization: Access to Trifluoromethyl-Substituted Spiro[indole-3,3'-pyrrolidine] Derivatives. *Adv. Synth. Catal*. **2016**, *358*, 561-566. (e) Yamamoto, Y.; Ohkubo, E.; Shibuya, M. Synthesis of 3-Aryl-2-(trifluoromethyl)indoles *via* Copper-Catalyzed Hydroarylation and Subsequent Cadogan Cyclization. *Adv. Synth. Catal*. **2017**, *359*, 1747-1751. (f) Ye,

Y.-B.; Cheung, K. P. S. He L.-S.; Tsui, G. C. Synthesis of 2-(Trifluoromethyl)indoles via Domino Trifluoromethylation/Cyclization of 2-Alkynylanilines. *Org*. L*e*tt. **2018**, *20*, 1676-1679. (g) Chaudhary, B.; Diwaker, M.; Sharma, S. Regioselective indole C2-alkylation using β-CF_3-substituted enones under redox neutral Rh(III) catalysis. *Org*. *Chem*. *Front*. **2018**, *5*, 3133-3137.

(9) (a) Wang, W.-Y.; Hu, B.-L.; Deng, C.-L. Zhang, X.-G. One-pot synthesis of 3-trifluoromethylbenzofurans *via* tandem iodocyclization and trifluoromethylation of 2-alkynylanisoles. *Tetrahedron Lett.* **2014**, *55,* 1501-1503. (b) Wang, C.; Chen, L.-H.; Deng, C.-L.; Zhang, X.-G. Synthesis of 3-Trifluoromethylbenzofurans *via* Palladium-Catalyzed Tandem Elimination/Annulation of β-Chloro-β-(trifluoromethyl)styrenes with 2-Halophenols. *Synthesis* **2014**, *46,* 313-319. (c) Yang, Z.-J.; Liu, C.-Z.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. Oxidative tandem nitrosation/cyclization of N-aryl enamines with nitromethane toward 3-(trifluoromethyl)quinoxalines. *Chem. Commun.,* **2014**, *50,* 14554-14557. (d) Yang, Z.-J.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. Iron-Promoted Electrophilic Annulation of Aryl Enynes with Disulfides or Diselenides Leading to Polysubstituted Naphthalenes. *Adv. Synth. Catal.* **2014**, *356,* 1962-1966. (e) Liu, Y.-R.; Tu, H.-Y.; Zhang, X.-G. Silver-Catalyzed Tandem Trifluoromethylation and Cyclization of Aryl Isonitriles with the Langlois Reagent. *Synthesis* **2015**, *47*, 3460-3466. (f) Wei, F.; Shen, X.-Q.; Chu, J.-J.; Hu, B.-L.; Zhang, X.-G. Palladium-catalyzed intramolecular aerobic C-H amination of enamines for the synthesis of 2-trifluoromethylindoles. *Tetrahedron* **2018**, *74,* 720-725.

(10) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320-330. (b) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med*. *Chem*. **2008**, *51*, 4359-4369. (c) O'Hagan, D. Fluorine in health care: Organofluorine containing blockbuster drugs. *J. Fluorine Chem*. **2010**, *131*, 1071-1081. (d) Wang, J.; Sanchez-Rosello, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001-2011). *Chem*. *Rev*. **2014**, *114*, 2432-2506.

(11) These compounds were prepared by the reaction of 2-bromobenzaldehyde with CF_3CCl_3, followed by a Sonogashira reaction with phenylacetylene. The detailed reaction process with the measured spectroscopic data can be seen in our reported ref: Shi, S.; Sun, L-L.; Liao, Z-Y.; Zhang, X-G. Copper-Catalyzed Thiolation Cyclization of 1-Chloro-1,5-enynes with Sodium Hydrosulfide: Synthesis of CF_3-Containing 1*H*-Isothiochromenes. *Synthesis* **2012**, 44, 966-972.