Carbene-Catalyzed Indole 3-Methyl C(sp^3)-H Bond Functionalization

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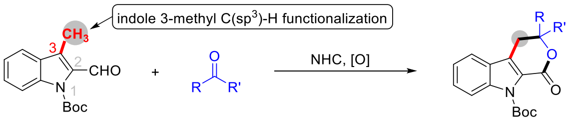
Supporting Information Placeholder

ABSTRACT: Metal-free catalytic functionalization of aromatic sp^2-carbons and benzylic sp^3-carbons remains challenging. Here we report a carbene-catalyzed functionalization of the 3-methyl sp^3-carbon attached to 2-formyl-indoles. The reaction proceeds through an NHC-bound *o*-quinodimethane as the key intermediate generated from 2-formyl-3-methylindoles under oxidative conditions. Reactive ketones are found to be effective substrates to produce substituted hydropyrano[3,4-*b*]indoles in good to excellent yields.



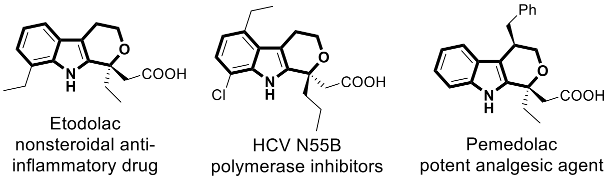
INTRODUCTION

The indole rings are common fragments in natural products, agrichemicals and pharmaceuticals.[1] Among the various indole-containing structures, hydropyrano[3,4-*b*]indole represents an important subtype core scaffold frequently found in bio-active molecules (Scheme 1a).[2] For example, Etodolac and its derivatives have been widely used as anti-inflammatory drugs,[3a] potent analgesic agents,[3b] and polymerase inhibitors.[3c] Analogs and derivatives of hydropyrano[3,4-*b*]indoles also exhibit important bioactive properties and are frequently evaluated for biomedical applications.[3d-f] Thus, synthetic methods that can effectively functionalize the sp^2 aromatic carbons and the sp^3-carbons attached to the indole framework have received considerable attentions. Progress in this area mainly comes from transition-metal catalyzed C-H bond activations.[4] Metal-free catalytic approaches are much less explored.[5]

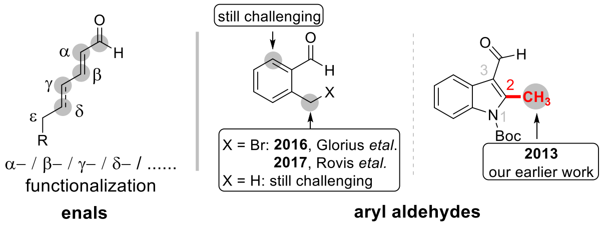
Our laboratories are interested in developing metal-free N-heterocylic carbene (abbreviated as NHC or carbene) organic catalysis for unique activation and reaction modes.[6] To date, it has been established that multiple carbons (e.g. α, β, γ, δ-carbons) of (unsaturated) aldehydes can be efficiently activated via carbene organic catalysis (Scheme 1b).[7] In contrast, functionalization of the sp^2- and sp^3-carbons of aromatic aldehydes remains difficult. We disclosed carbene-catalyzed functionalization of the 2-methyl sp^3 carbon attached to heterocyclic aromatic aldehydes.[8] Glorius and Rovis developed the functionalization of the sp^3 carbon on 2-(bromomethyl)-benzaldehyde through NHC organocatalysis.[9] Here we report a carbene-mediated functionalization of the

Scheme 1. Hydropyrano[3,4-*b*]indoles and NHC-Catalyzed Functionalization of Enals and Aryl Aldehydes.

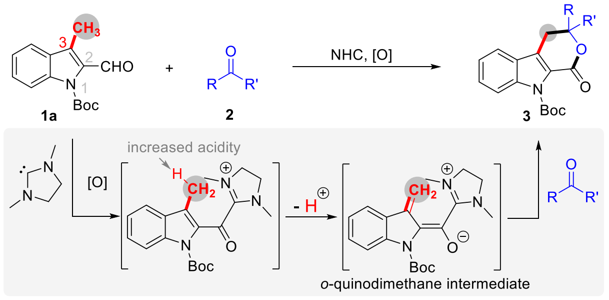
a) Bio-active molecules containing hydropyrano[3,4-*b*]indole:



b) NHC-mediated functionalization of enals and aryl aldehydes:



c) *This work*:

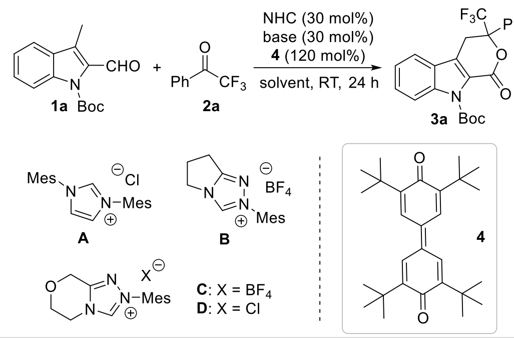


sp^3-carbon of the 3-methyl group on 2-formyl-indoles (Scheme 1c). The reaction goes through a carbene-catalyzed addition of 2-formyl-3-methylindoles to different reactive ketones. An NHC-bound *o*-quinodimethane is formed as the key intermediate. Substituted 3,4-dihydropyrano[3,4-*b*]indoles (indole-derived lactones) are afforded as the products.

RESULTS AND DISCUSSION

We chose the 2,2,2-trifluoroacetophenone **2a** as a model electrophile and tested the model reaction using different NHC catalysts. Imidazolium NHC precursor **A** was not efficient for this transformation (Table 1, entry 1). Triazolium typed NHC precursors could give the product in good isolated yields and NHC precursor **C**[10] bearing a morpholine motif behaved better (entries 2 and 3). Switching the conjugate anion in NHC precursors from BF_4^- to Cl^-, the product yield could be consistently improved (entry 4 *v.s.* entry 3). A variety of organic and inorganic bases could be used in this reaction (entries 5 to 7). THF was found to be the best solvent for this reaction; other organic solvents we tested gave trace amount of the desired product (entries 8 to 10).

Table 1. Optimization of reaction conditions.[a]



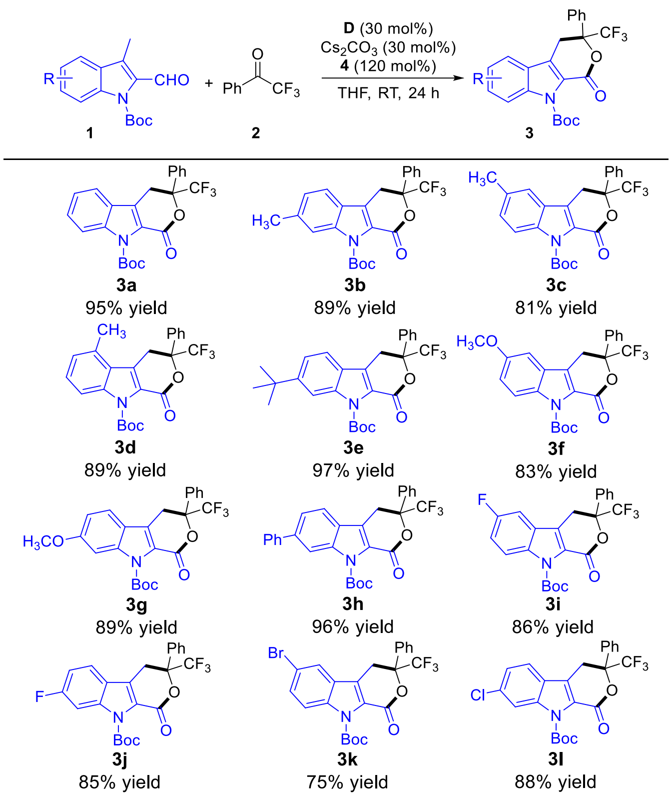
entry	NHC	base	solvent	yield (%)[b]
1	**A**	Cs_2CO_3	THF	<5
2	**B**	Cs_2CO_3	THF	63
3	**C**	Cs_2CO_3	THF	70
4	**D**	Cs_2CO_3	THF	95
5	**D**	K_2CO_3	THF	88
6	**D**	DMAP	THF	82
7	**D**	DBU	THF	76
8	**D**	Cs_2CO_3	CH_2Cl_2	<5
9	**D**	Cs_2CO_3	EtOAc	10
10	**D**	Cs_2CO_3	CH_3CN	<5

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), NHC (0.03 mmol), base (0.03 mmol), **4** (0.12 mmol), solvent (2.0 mL), RT, 24 h. [b] Isolated yield of **3a**.

With an optimized condition on hand, we next examined the substrate scope. Examples of substituted 2-formyl-3-methylindoles **1** were first tested (Table 2). Both electron donating groups (**3b** to **3h**) and electron withdrawing groups (**3i** to **3l**) were well tolerated. All the desired hydropyrano[3,4-*b*]indole products were isolated in good to excellent yields. Attempts were also made to synthesize other 3-substituted indoles, but they were not successfully generated.

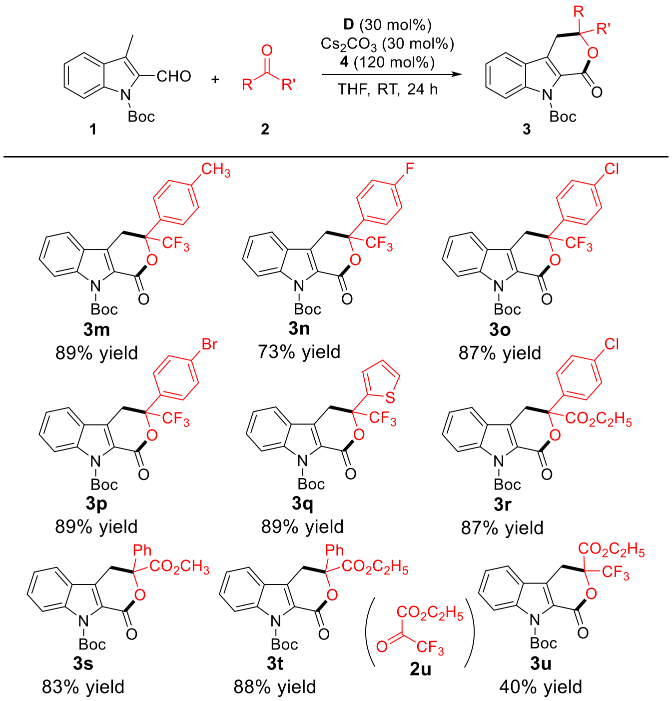
Meanwhile, different activated ketones **2** were also investigated (Table 3). The benzene ring of the 2,2,2-trifluoroacetophenone **2a** could be changed from substituted benzene groups to heterocyclic aromatic groups and the corresponding products were isolated in good yields (**3m** to **3q**). To our delight, α-ketoesters also worked very well in this

Table 2. Examples of 2-formyl-3-methylindoles.[a]



[a] Reaction conditions as stated in Table 1, entry 4. Yields are isolated yields after purification by column chromatography.

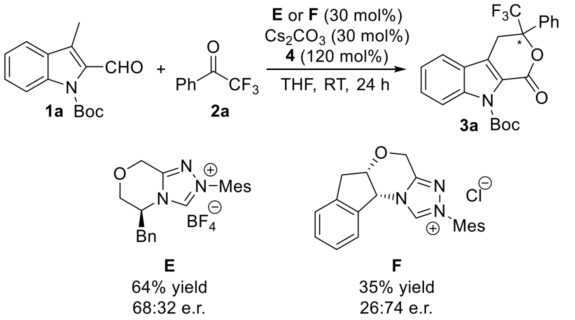
Table 3. Examples of Substituted Ketones.[a]



[a] Reaction conditions as stated in Table 1, entry 4. Yields are isolated yields after purification by column chromatography.

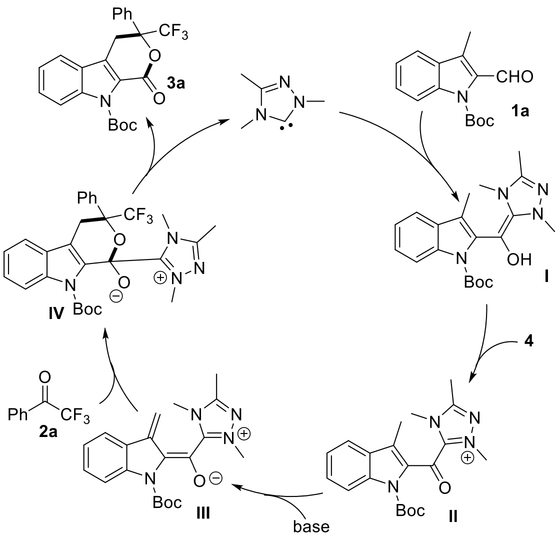
process and 3,4-dihydropyrano[3,4-*b*]indole-3-carboxylate compounds were formed smoothly as the products (**3r** to **3t**). However, the highly activated ketone **2u** bearing both an ester group and a trifluoromethane group on the carbonyl carbon gave the desired product **3u** in poor yield.

Scheme 2. Enantioselective [4+2] Reactions using Chiral NHC Catalysts.



We also examined chiral NHC catalysts for this reaction. Preliminary studies showed that the use of chiral NHC catalysts **E**[11] and **F**[12] could lead to product with low to moderate enantioselectivities (Scheme 2). Additional studies using known chiral NHC catalysts did not lead to acceptable enantioselectivities. It appears either new NHC catalysts or the introduction of a co-catalyst is necessary to achieve good stereo-selectivities for this reaction.

Scheme 3. Proposed Reaction Mechanism.



The plausible catalytic cycle is summarized in Scheme 3. NHC catalyst first attacks the 3-methylindole-2-carboxaldehyde **1a**, and then goes through proton transfer to afford the Breslow intermediate **I**. Breslow intermediate **I** is then oxidated by **4** to form the acyl azolium intermediate **II**, which is easily to be deprotonated to afford the *o*-quinodimethane intermediate **III**. Intermediate **III** could react with trifluoroacetophenone **2a** through either a stepwise Michael reaction / cycloaddition sequence or a concerted [4+2] annulation reaction to give intermediate **IV**, which then regenerates the NHC catalyst and yield the final product **3a**.

In summary, we have developed a carbene-catalyzed functionalization of the 3-methyl sp^3-carbon attached to 2-formyl-indoles. The reaction proceeds through an NHC-bound *o*-quinodimethane as the key intermediate, which is generated from 2-formyl-3-methylindoles under oxidative conditions. 2,2,2-Trifluoroacetophenones and α-ketoesters are found to be effective substrates to produce substituted 3,4-dihydropyrano[3,4-*b*]indole compounds in good to excellent yields. Additional studies on aromatic compound functionalizations and evaluation on the biological activities of the products are in progress.

EXPERIMENTAL SECTION

General Information. Commercially available materials purchased from J&K or Aladdin were used as received. DCM was dried over Pure Solv solvent purification system. THF was distilled over sodium. Ethyl acetate were dried over 4Å molecular sieve prior use. Unless otherwise specified, all reactions were carried out under an atmosphere of nitrogen in 10 mL Schlenk tube. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker (400 MHz) spectrometer and JEOL-ECX-500 (500 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00) or chloroform (δ = 7.26, singlet). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), or m (multiplets). All firstorder splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (101 MHz) spectrometer and JEOL-ECX-500 (126 MHz) spectrometer. The melting points (M.P.) of the title compounds were determined when left untouched on an XT-4-MP apparatus from Beijing Tech. Instrument Co. (Beijing, China). High resolution mass spectral analysis (HRMS) was performed on a quadrupole/electrostatic field orbitrap mass spectrometer. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp or potassium permanganate stain. The aldehyde substrates **1** were synthesized through reported procedures.[13]

General procedure for the catalytic reactions of aldehydes 1 with trifluoromethyl aryl ketones 2. To a dry Schlenk reaction tube equipped with a magnetic stir bar, was added indolealdehyde **1a** (0.12 mmol), triazolium salt **D** (8.4 mg, 0.03 mmol), oxidant **4** (49 mg, 0.12 mmol) and Cs_2CO_3 (10 mg, 0.03 mmol). The schlenk tube was then closed with septum, evacuated and refilled with N_2. Freshly distilled anhydrous THF (2 mL) was added, followed by injection of trifluoromethyl aryl ketone **2a** (0.1 mmol). The mixture was stirred at 25 ℃ for 24 h. After completion of the reaction, monitored by TLC and 1H NMR, solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel with hexane/EtOAc (20:1) as eluent to afford the product **3a**.

General procedure for the enantioselective catalytic reactions of aldehyde 1a with trifluoromethyl aryl ketones 2a. To a dry Schlenk reaction tube equipped with a magnetic stir bar, was added indolealdehyde **1a** (0.12 mmol), chiral pre-NHC **E**(12.6 mg, 0.03 mmol) or chiral pre-NHC **F** (11.0 mg, 0.03 mmol), oxidant **4** (49 mg, 0.12 mmol) and Cs_2CO_3 (10 mg, 0.03 mmol). The schlenk tube was then closed with septum, evacuated and refilled with N_2. Freshly distilled anhydrous THF (2 mL) was added, followed by injection of trifluoromethyl aryl ketone **2a** (0.1 mmol). The mixture was stirred at rt for 24 h. After completion of the reactions, monitored by TLC and ^{1}H NMR, solvent was removed under reduced pressure and the residue was purified via column chromatography on silica gel with hexane/EtOAc (20:1) as eluent to afford the products **3a**.

*tert-butyl-2-formyl-3-methyl-1H-indole-1-carboxylate (**1a**):* White solid; 0.6 g, 22% yield; M.P. 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.1 Hz, 1H), 2.57 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3, 150.0, 136.6, 132.8, 129.4, 128.4, 128.3, 123.4, 121.0, 115.9, 85.1, 28.2, 10.1 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{17}NO_3Na^+$ 282.1100, found 282.1100.

*tert-butyl-2-formyl-3,6-dimethyl-1H-indole-1-carboxylate (**1b**):* White solid; 0.52 g, 19% yield; M.P. 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.99 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 2.55 (s, 3H), 2.51 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.1, 150.0, 139.1, 137.2, 132.5, 128.8, 127.2, 125.1, 120.7, 116.0, 85.0, 28.2, 22.4, 10.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{19}NO_3Na^+$ 296.1257, found 296.1257.

*tert-butyl-2-formyl-3,5-dimethyl-1H-indole-1-carboxylate (**1c**):* White solid; 0.43 g, 16% yield; M.P. 88-89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.37 (s, 1H), 7.27 (dd, *J* = 8.6, 1.4 Hz, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.4, 150.0, 134.9, 133.0, 130.1, 129.5, 128.1, 120.7, 115.6, 84.9, 28.2, 21.3, 10.1 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{19}NO_3Na^+$ 296.1257, found 296.1255.

*tert-butyl-2-formyl-3,4-dimethyl-1H-indole-1-carboxylate (**1d**):* Red solid; 0.54 g, 20% yield; M.P. 89-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.38 - 7.28 (m, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 2.73 (s, 3H), 2.71 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 149.8, 137.3, 134.0, 132.7, 128.9, 128.0, 127.8, 125.4, 113.5, 85.1, 28.1, 20.8, 12.6 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{19}NO_3Na^+$ 296.1257, found 296.1255.

*tert-butyl-6-(tert-butyl)-2-formyl-3-methyl-1H-indole-1-carboxylate (**1e**):* Yellow solid; 0.81 g, 21% yield; M.P. 84-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.19 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.7 Hz, 1H), 2.56 (s, 3H), 1.71 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3, 152.4, 150.2, 136.90, 133.0, 128.5, 127.2, 121.6, 120.5, 112.4, 84.7, 35.5, 31.6, 28.2, 10.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{19}H_{25}NO_3Na^+$ 338.1726, found 338.1722.

*tert-butyl-2-formyl-5-methoxy-3-methyl-1H-indole-1-carboxylate (**1f**):* White solid; 0.51 g, 13% yield; M.P. 117-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.11 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.01 (d, *J* = 2.5 Hz, 1H), 3.88 (s, 3H), 2.54 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4, 156.2, 149.9, 133.4, 131.3, 130.1, 127.9, 118.2, 116.9, 102.0, 85.0, 55.6, 28.2, 10.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{19}NO_4Na^+$ 312.1206, found 312.1203.

*tert-butyl-2-formyl-6-methoxy-3-methyl-1H-indole-1-carboxylate (**1g**):* White solid; 0.45 g, 11% yield; M.P. 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 7.68 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 3.90 (s, 3H), 2.55 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6, 161.0, 150.1, 138.3, 132.2, 129.5, 123.2, 121.8, 113.7, 98.9, 84.9, 55.6, 28.2, 10.3 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{19}NO_4Na^+$ 312.1206, found 312.1200.

*tert-butyl-2-formyl-3-methyl-6-phenyl-1H-indole-1-carboxylate (**1h**):* White solid; 0.45 g, 23% yield; M.P. 144-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.42 (s, 1H), 7.69 (dd, *J* = 15.1, 7.6 Hz, 3H), 7.58 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 2.59 (s, 3H), 1.70 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.3, 150.1, 141.9, 141.3, 137.3, 133.3, 129.0, 128.7, 128.5, 127.6, 127.5, 123.1, 121.4, 114.6, 85.3, 28.3, 10.3 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{21}H_{21}NO_3Na^+$ 358.1413, found 358.1409.

*tert-butyl-5-fluoro-2-formyl-3-methyl-1H-indole-1-carboxylate (**1i**):* White solid; 0.63 g, 16% yield; M.P. 117-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.10 (dd, *J* = 9.2, 4.5 Hz, 1H), 7.39 - 7.12 (m, 2H), 2.51 (s, 3H), 1.69 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2, 160.5, 158.1, 149.7, 133.9, 132.8, 130.3 (d, $J_{C\text{-}F}$ = 9.2 Hz), 127.4 (d, $J_{C\text{-}F}$ = 4.5 Hz), 117.2 (d, $J_{C\text{-}F}$ = 8.7 Hz), 116.6 (d, $J_{C\text{-}F}$ = 25.4 Hz), 106.0 (d, $J_{C\text{-}F}$ = 23.3 Hz), 85.5, 28.2, 10.1 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{16}NO_3FNa^+$ 300.1006, found 300.1004.

*tert-butyl-6-fluoro-2-formyl-3-methyl-1H-indole-1-carboxylate (**1j**):* Red solid; 0.72 g, 18% yield; M.P. 95-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.84 (dd, *J* = 10.5, 2.3 Hz, 1H), 7.58 (dd, *J* = 8.7, 5.5 Hz, 1H), 7.15 - 6.95 (m, 1H), 2.54 (s, 3H), 1.70 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8, 164.5, 162.1, 149.7, 137.0 (d, $J_{C\text{-}F}$ = 13.2 Hz), 133.3 (d, $J_{C\text{-}F}$ = 4.0 Hz), 128.2, 125.7, 122.2 (d, $J_{C\text{-}F}$ = 10.4 Hz), 112.2 (d, $J_{C\text{-}F}$ = 24.9 Hz), 103.1 (d, $J_{C\text{-}F}$ = 28.9 Hz), 85.6, 28.1, 10.18 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{16}NO_3FNa^+$ 300.1006, found 300.1002.

*tert-butyl-5-bromo-2-formyl-3-methyl-1H-indole-1-carboxylate (**1k**):* White solid; 0.48 g, 19% yield; M.P. 125-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.56 (dd, *J* = 9.0, 1.8 Hz, 1H), 2.51 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.36, 150.02, 136.63, 132.89, 129.42, 128.45, 128.35, 123.40, 121.07, 115.95, 85.16, 28.22, 10.14 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{16}NO_3BrNa^+$ 360.0205, found 360.0201.

*tert-butyl-6-chloro-2-formyl-3-methyl-1H-indole-1-carboxylate (**1l**):* White solid; 0.93 g, 16% yield; M.P. 111-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.17 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.53 (s, 3H), 1.70 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0, 149.5, 136.8, 134.4, 133.1, 127.8, 127.8, 124.1, 121.8, 116.2, 85.8, 28.1, 10.0 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{16}NO_3ClNa^+$ 316.0710, found 316.0711.

*tert-butyl-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate (**3a**):* Yellow solid; M.P. 128-129 °C; 41 mg, yield: 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.37 - 7.32 (m, 3H), 7.30 (t, *J* = 7.4 Hz, 1H), 3.88 (d, *J* = 17.3 Hz, 1H), 3.74 (d, *J* = 17.3 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 148.6, 139.9, 133.8, 129.7, 129.4, 128.7, 127.6, 126.6, 125.0, 124.4, 123.8, 122.2, 120.6, 115.3, 84.9, 83.8 (q, *J* = 30.6 Hz), 27.6, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{20}NO_4F_3Na^+$ 454.1236, found 454.1231.

*tert-butyl-7-methyl-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate (**3b**):* Yellow solid; M.P. 177-178 °C; 39 mg, yield: 89%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.60 - 7.54 (m, 2H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.35 - 7.30 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 1H), 3.84 (d, *J* = 17.3 Hz, 1H), 3.72 (d, *J* = 17.3 Hz, 1H), 2.47 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 148.8, 140.4, 133.9, 129.6, 128.7, 127.8, 126.6, 125.5, 124.4, 123.2, 122.8, 122.2, 120.2, 115.3, 84.8, 83.7 (q, *J* = 30.9 Hz), 27.6, 26.2, 22.4 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{22}NO_4F_3Na^+$ 468.1393, found 468.1391.

tert-butyl-6-methyl-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3c)****:* Yellow solid; M.P. 145-146 °C; 36 mg, yield: 81%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.6 Hz, 1H), 7.57 (dd, J = 6.1, 3.1 Hz, 2H), 7.39 (s, 1H), 7.35 - 7.32 (m, 3H), 7.31 (dd, J = 8.7, 1.4 Hz, 1H), 3.85 (d, J = 17.3 Hz, 1H), 3.71 (d, J = 17.2 Hz, 1H), 2.45 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 148.7, 138.2, 133.9, 133.5, 131.1, 129.7, 128.7, 127.4, 126.6, 125.2, 124.4, 123.7, 120.1, 115.0, 84.7, 83.7 (q, J = 30.2 Hz), 27.6, 26.2, 21.3 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{22}NO_4F_3Na^+$ 468.1393, found 468.1395.

tert-butyl-5-methyl-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3d)****:* White solid; M.P. 153-154 °C; 39 mg, yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.5 Hz, 1H), 7.58 (dd, J = 6.5, 2.7 Hz, 2H), 7.38 - 7.30 (m, 4H), 7.03 (d, J = 7.3 Hz, 1H), 4.14 (d, J = 17.4 Hz, 1H), 3.90 (d, J = 17.4 Hz, 1H), 2.71 (s, 3H), 1.57 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 148.7, 140.2, 133.8, 132.7, 129.7, 129.1, 128.8, 127.5, 126.7, 125.0, 124.1, 123.6, 122.2, 112.8, 84.8, 83.5 (q, J = 30.2 Hz), 28.4, 27.6, 20.0 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{22}NO_4F_3Na^+$ 468.1393, found 468.1391.

tert-butyl-7-(tert-butyl)-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3e)****:* White solid; M.P. 116-117 °C; 47 mg, yield: 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.57 (dd, J = 6.0, 3.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.40 (dd, J = 8.5, 1.5 Hz, 1H), 7.37 - 7.30 (m, 3H), 3.86 (d, J = 17.3 Hz, 1H), 3.72 (d, J = 17.3 Hz, 1H), 1.60 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 153.6, 148.7, 140.2, 133.9, 129.5, 128.6, 127.5, 126.5, 124.6, 123.5, 122.7, 122.1, 119.9, 111.7, 84.6, 83.6 (q, J = 61.0, 30.4 Hz), 35.6, 31.4, 27.6, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{27}H_{28}NO_4F_3Na^+$ 510.1862, found 510.1861.

tert-butyl-6-methoxy-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3f)****:* White solid; M.P. 159-160 °C; 38 mg, yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 9.2 Hz, 1H), 7.58 (dd, J = 6.1, 2.7 Hz, 2H), 7.38 - 7.31 (m, 3H), 7.10 (dd, J = 9.2, 2.5 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 3.87 (s, 3H), 3.84 (d, J = 17.3 Hz, 1H), 3.72 (d, J = 17.3 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 154.0, 148.7, 134.8, 133.9, 129.7, 128.7, 127.1, 126.6, 125.6, 124.0, 122.2, 119.4, 116.4, 101.5, 84.8, 83.7 (q, 33.1 Hz), 55.8, 27.6, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{22}NO_5F_3Na^+$ 484.1342, found 484.1349.

tert-butyl-7-methoxy-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3g)****:* Yellow solid; M.P. 177-178 °C; 41 mg, yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.6, 2.8 Hz, 3H), 7.47 (d, J = 8.8 Hz, 1H), 7.35 - 7.31 (m, 3H), 6.93 (dd, J = 8.8, 2.3 Hz, 1H), 3.86 (s, 3H), 3.82 (d, J = 17.3 Hz, 1H), 3.70 (d, J = 17.3 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 154.0, 149.0, 141.7, 134.0, 129.6, 128.7, 128.3, 126.5, 124.4, 122.4, 121.3, 118.7, 114.7, 97.8, 84.8, 83.5 (q, J = 30.4 Hz), 55.8, 27.6, 26.3 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{22}NO_5F_3Na^+$ 484.1342, found 484.1349.

tert-butyl-1-oxo-3,7-diphenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3h)****:* White solid; M.P. 86-87 °C; 48 mg, yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33(s, 1H), 7.65 (dd, J = 16.6, 7.8 Hz, 3H), 7.61 - 7.54 (m, 3H), 7.45 (t, J = 7.5 Hz, 2H), 7.40 - 7.32 (m, 4H), 3.90 (d, J = 17.3 Hz, 1H), 3.77 (d, J = 17.3 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 148.6, 142.9, 140.7, 140.5, 133.8, 129.6, 128.9, 128.7, 127.8, 127.5, 127.4, 126.5, 124.6, 124.0, 123.5, 121.8, 120.7, 113.7, 85.0, 83.8 (q, J = 30.7 Hz), 27.6, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{29}H_{24}NO_4F_3Na^+$ 530.1549, found 530.1551.

tert-butyl-6-fluoro-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3i)****:* Yellow solid; M.P. 161-162 °C; 39 mg, yield: 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 9.2, 4.4 Hz, 1H), 7.57 (s, 2H), 7.38 - 7.33 (m, 3H), 7.28 - 7.23 (m, 1H), 7.21 (dd, J = 9.1, 2.4 Hz, 1H), 3.82 (d, J = 17.3 Hz, 1H), 3.73 (d, J = 17.3 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 158.5, 153.8, 148.4, 136.2, 133.7, 129.8, 128.8, 126.8 (d, J_{C-F} = 4.2 Hz), 126.5, 125.6 (d, J_{C-F} = 9.7 Hz), 125.0, 124.3, 122.1, 117.7 (d, J_{C-F} = 25.6 Hz), 116.8 (d, J_{C-F} = 8.9 Hz), 105.6 (d, J_{C-F} = 24.0 Hz), 85.3, 83.8 (q, J = 30.5 Hz), 27.6, 26.1 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{19}NO_4F_4Na^+$ 472.1142, found 472.1140.

tert-butyl-7-fluoro-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3j)****:* White solid; M.P. 159-160 °C;38 mg, yield: 85%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 10.0, 2.3 Hz, 1H), 7.56 (dd, J = 8.7, 5.3 Hz, 3H), 7.37 - 7.31 (m, 3H), 7.07 (td, J = 8.8, 2.3 Hz, 1H), 3.84 (d, J = 17.3 Hz, 1H), 3.73 (d, J = 17.4 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 162.8, 153.7, 148.4, 140.5 (d, J_{C-F} = 13.3 Hz), 133.7, 129.8, 128.8, 127.5, 126.5, 124.2 (d, J_{C-F} = 34.3 Hz), 121.8 (d, J_{C-F} = 10.5 Hz), 121.4, 113.0 (d, J_{C-F} = 25.2 Hz), 102.6 (d, J_{C-F} = 28.7 Hz), 85.4, 83.7 (q, J = 30.2 Hz), 27.6, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{19}NO_4F_4Na^+$ 472.1142, found 472.1140

tert-butyl-6-bromo-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3k)****:* White solid; M.P. 132-134 °C; 38 mg, yield: 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 6.1, 1H), 7.58 (dd, J = 6.1, 3.1 Hz, 2H), 7.52 - 7.45 (m, 1H), 7.33 (t, 3H), 3.88 (d, J = 17.3 Hz, 1H), 3.75 (d, J = 17.3 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 148.6, 139.9, 133.8, 129.7, 129.4, 128.7, 127.6, 126.6, 125.0, 124.4, 123.8, 122.1, 120.6, 115.4, 85.0, 83.8 (q, J = 30.4 Hz), 27.6, 26.2 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{19}NO_4F_3BrNa^+$ 532.0341, found 532.0340.

tert-butyl-7-chloro-1-oxo-3-phenyl-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3l)****:* White solid; M.P. 158-160 °C; 41 mg, yield: 88%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 1.6 Hz, 1H), 7.58 - 7.54 (m, 2H), 7.53 (d, J = 8.5 Hz, 1H), 7.37 - 7.32 (m, 3H), 7.29 (dd, J = 8.5, 1.7 Hz, 1H), 3.85 (d, J = 17.3 Hz, 1H), 3.74 (d, J = 17.3 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 148.3, 140.1, 135.6, 133.6, 129.8, 128.8, 127.2, 126.5, 124.7, 124.2, 123.5, 122.1, 121.3, 115.6, 85.5, 83.8 (q, J = 30.7 Hz), 27.6, 26.1 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{23}H_{19}NO_4F_3ClNa^+$ 488.0846, found 488.0844.

tert-butyl-1-oxo-3-(p-tolyl)-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3m)****:* White solid; M.P. 158-159 °C;39 mg,yield: 89%; ^{1}HNMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.54-7.40 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 3.85 (d, J = 17.2 Hz, 1H), 3.72 (d, J = 17.2 Hz, 1H), 2.29 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 148.7, 139.8, 139.7, 130.8, 129.4, 129.3, 127.6, 126.4, 125.0, 124.4, 123.8, 122.2, 120.6, 115.4, 84.9, 83.8 (q, J = 30.3 Hz), 27.7, 26.2, 21.1 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{24}H_{22}NO_4F_3Na^+$ 468.1393, found 468.1390.

tert-butyl-3-(4-fluorophenyl)-1-oxo-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate ***(3n)****:* Yellow solid; M.P. 147-149 °C； 33 mg, yield: 73%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 8.7, 5.0 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 8.6 Hz, 2H), 3.84 (d, J = 17.3 Hz, 1H), 3.76

(d, J = 17.3 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.6, 162.1, 153.7, 148.5, 139.8, 129.6 (d, $J_{C\text{-}F}$ = 3.4 Hz), 129.5, 128.5 (d, $J_{C\text{-}F}$ = 8.5 Hz), 127.4, 124.8, 123.8, 123.5, 120.4, 115.9, 115.7, 115.3, 85.0, 83.4 (q, J = 30.9 Hz), 27.6, 26.1 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{23}H_{19}NO_4F_4Na^+$ 472.1142, found 472.1140.

*tert-butyl-3-(4-chlorophenyl)-1-oxo-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate (**3o**):* White solid; M.P. 170-171 °C; 40 mg, yield: 87%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, J = 8.6 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 9.1 Hz, 3H), 7.32 (t, J = 8.5 Hz, 3H), 3.83 (d, J = 17.3 Hz, 1H), 3.75 (d, J = 17.3 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.7, 148.5, 139.9, 136.0, 132.5, 129.6, 129.0, 128.0, 127.3, 124.8, 123.9, 123.5, 121.9, 120.5, 115.4, 85.1, 83.48 (d, J = 31.0 Hz), 27.7, 26.1 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{23}H_{19}NO_4F_3ClNa^+$ 488.0846, found 488.0841.

*tert-butyl-3-(4-bromophenyl)-1-oxo-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate (**3p**):* White solid; M.P. 169-170 °C; 41 mg, yield: 89%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.55-7.39 (m, 5H), 7.32 (t, J = 7.5 Hz, 1H), 3.82 (d, J = 17.3 Hz, 1H), 3.75 (d, J = 17.3 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.6, 148.4, 139.8, 133.0, 131.9, 129.5, 128.2, 127.2, 124.8, 124.2, 123.8, 123.4, 121.5, 120.4, 115.4, 85.1, 83.4 (q, J = 30.7 Hz), 27.6, 26.0 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{23}H_{19}NO_4F_3BrNa^+$ 532.0341, found 532.0348.

*tert-butyl-1-oxo-3-(thiophen-2-yl)-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-9(1H)-carboxylate (**3q**):* White solid; M.P. 149-150 °C; 39 mg, yield: 89%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 5.1 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 6.95 (t, J = 4.3 Hz, 1H), 3.76 (s, 2H), 1.60 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.4, 148.7, 139.9, 137.5, 129.5, 128.0, 127.4, 127.3, 125.0, 123.9, 123.2, 121.6, 120.5, 115.4, 85.1, 82.5 (q, J = 31.9 Hz), 27.8, 27.7 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{21}H_{18}NO_4F_3SNa^+$ 460.0800, found 460.0800.

*9-tert-butyl-3-ethyl-3-(4-chlorophenyl)-1-oxo-3,4-dihydropyrano[3,4-b]indole-3,9(1H)-dicarboxylate (**3r**):* White solid; M.P. 121-122 °C; 41 mg, yield: 87%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.19 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 7.9 Hz, 1H), 7.56-7.50 (m, 1H), 7.42 (d, J = 8.6 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 4.19 (d, J = 17.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.33 (d, J = 17.0 Hz, 1H), 1.67 (s, 9H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.3, 155.4, 148.9, 139.9, 135.8, 135.1, 129.6, 129.4, 129.0, 126.7, 124.9, 123.9, 123.8, 121.0, 115.5, 85.0, 84.6, 62.9, 31.4, 27.8, 14.0 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{25}H_{24}NO_6ClNa^+$ 492.1184, found 492.1189.

*9-tert-butyl-3-methyl-1-oxo-3-phenyl-3,4-dihydropyrano[3,4-b]indole-3,9(1H)-dicarboxylate (**3s**):* White solid; M.P. 158-160 °C; 35 mg, yield: 83%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.49 -7.38 (m, 3H), 7.34 (t, J = 7.5 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.67 (s, 3H), 3.40 (d, J = 15.7 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.2, 155.7, 149.0, 140.1, 137.0, 130.0, 129.3, 129.1, 128.8, 125.2, 125.0, 124.2, 123.7, 121.1, 115.4, 85.2, 84.9, 53.5, 31.5, 27.8 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{24}H_{23}NO_6Na^+$ 444.1417, found 444.1419.

*9-tert-butyl-3-ethyl-1-oxo-3-phenyl-3,4-dihydropyrano[3,4-b]indole-3,9(1H)-dicarboxylate (**3t**):* Yellow solid; M.P. 157-158 °C; 38 mg, yield: 88%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18 (d, J = 8.5 Hz, 1H), 7.79 - 7.73 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.57 - 7.48 (m, 1H), 7.46 -7.41 (m, 2H), 7.41 - 7.36 (m, 1H), 7.34 (t, J = 7.6 Hz, 1H), 4.21 (d, J = 17.1 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.37 (d, J = 17.1 Hz, 1H), 1.67 (s, 9H), 1.12(t, J=7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.6, 155.7, 149.0, 139.9, 137.2, 129.9, 129.3, 129.0, 128.8, 125.2, 125.0, 124.1, 123.7, 121.0, 115.4, 85.1, 84.9, 62.7, 31.4, 27.8, 14.0 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{25}H_{25}NO_6Na^+$ 458.1574, found 458.1579.

*9-tert-butyl-3-ethyl-1-oxo-3-(trifluoromethyl)-3,4-dihydropyrano[3,4-b]indole-3,9(1H)-dicarboxylate (**3u**):* White solid; M.P. 109-110 °C; 17 mg, yield: 40%; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.19 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 11.9, 4.4 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.89 (d, J = 17.1 Hz, 1H), 3.45 (d, J = 17.0 Hz, 1H), 1.66 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 165.2, 152.9, 148.6, 139.9, 129.8, 126.8, 124.5, 124.0, 122.7, 120.9, 115.5, 85.4, 82.8, 82.6, 64.0, 27.7, 25.1, 13.9 ppm. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd. for $C_{20}H_{20}NO_6F_3Na^+$ 450.1134, found 450.1139.

ASSOCIATED CONTENT

Supporting Information

Spectral data for all new compounds and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) (a) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep*. **2000**, *17*, 175. (b) Chen, H.; Bai, J.; Fang, Z.-F.; Yu, S.-S.; Ma, S.-G.; Xu, S.; Li, Y.; Qu, J.; Ren, J.-H.; Li, L.; Si, Y.-K.; Chen, X.-G. *J. Nat. Prod*. **2011**, *74*, 2438. And references cited therein.

(2) (a) Demerson, C. A.; Abraham, N. A.; Schilling, G.; Martel, R. R.; Asciak, C. J. *J. Med. Chem*. **1983**, *26*, 1778. (b) Humber, L. *Med. Res. Rev*. **1987**, *7*, 1. (c) Rabindran, S. K.; He, H.; Singh, M.; Collins, E.; Annable, K. I.; Greeberger, L. M. *Cancer Res*. **1998**, *58*, 5850. (d) Larghi, E. L.; Kaufman, T. S. *Synthesis*, **2006**, 187. (e) LaPorte, M. G.; Draper, T. L.; Miller, L. E.; Blackledge, C. W.; Leister, L. K.; Amparo, E.; Hussey, A. R.; Young, D. C.; Chunduru, S. K.; Benetatos, C. A.; Rhodes, G.; Gopalsamy, A.; Herbertz, T.; Burns, C. J.; Condon, S. M. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 2968.

(3) (a) Demerson, C. A.; Humber, L. G.; Philipp, A. H.; Martel, R. R. *J. Med. Chem*. **1976**, *19*, 391. (b) Katz, A.; Demerson, C. A.; Shaw, C. C.; Asselin, A. A.; Humber, L. G.; Conway, K.; Gavin, G.; Jensen, N. P.; Noureldin, R.; Schmid, J.; Shah, U.; Van Engen, D.; Chau, T.; Weichman, B. *J. Med. Chem*. **1988**, *31*, 1244. (c) Gopalsamy, A.; Lim, K.; Ciszewski, G.; Park, K.; Ellingboe, J. W.;

Bloom, J.; Insaf, S.; Upeslacis, J.; Mansour, T. S.; Krishnamurthy, G.; Damarla, M.; Pyatski, Y.; Ho, D.; Howe, A. Y. M.; Orlowski, M.; Feld, B.; O'Connell, J. *J. Med. Chem*. **2004**, *47*, 6603. (d) Demerson, C. A.; Santroch, G.; Humber, L. G.; Charest, M. P. *J. Med. Chem.* **1975**, *18*, 577. (e) Queiroz, M.-J. R. P.; Calhelha, R. C.; Vale-Silva, L. A.; Pinto, E.; São-Jose, N. M. *Eur. J. Med. Chem*. **2009**, *44*, 1893.

(4) For selected reviews, see: (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res*. **2008**, *41*, 1013. (b) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev*. **2017**, *117*, 9333. And references cited therein.

(5) For recent reviews, see: (a) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev*. **2010**, *39*, 4449. (b) Valla, C. M. R.; Atodireser, I.; Rueping, M. *Chem. Rev*. **2014**, *114*, 2390. (c) Dalpozzo, R. *Chem. Soc. Rev*. **2015**, *44*, 742. (d) Glinsky-Olivier, N.; Guinchard, X. *Synthesis* **2017**, *49*, 2605. (e) Caruana, L.; Fochi, M.; Bernardi, L. *Synlett* **2017**, *28*, 1530. for selected examples, see: (f) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc*. **2011**, *133*, 15212. (g) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed*. **2011**, *50*, 8638. (h) Liu, Y.; Nappi, M.; Escudero-Adan, E. C.; Melchiorre, P. *Org. Lett*. **2012**, *14*, 1310.

(6) For selected reviews on NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606. (b) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev*. **2015**, *115*, 9307. And references cited therein.

(7) For pioneering works on enolate activation in NHC catalysis, see: (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc*. **2004**, *126*, 8126. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc*. **2004**, *126*, 9518. For pioneering works on homoenolate activation in NHC catalysis, see: (c) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed*. **2004**, *43*, 6205. (d) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. For pioneering work on oxidative NHC catalysis of enals, see: (e) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed*. **2010**, *49*, 9266. For pioneering examples on γ- and δ-carbon activation of enals through oxidative NHC catalysis, see: (f) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc*. **2012**, *134*, 8810. (g) Zhu, T.; Mou, C.; Li, B.; Smetankova, M.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc*. **2015**, *137*, 5658.

(8) Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed*. **2013**, *52*, 11134.

(9) (a) Janssen-Muller, D.; Singha, S.; Olychlager, T.; Daniliuc, C. G.; Glorius, F. *Org. Lett*. **2016**, *18*, 4444. (b) Chen, D.-F.; Rovis, T. *Synthesis*, **2017**, *49*, 293.

(10) For pioneering report on NHC catalyst **C** and **D**, see: Chiang, P.-C; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc*. **2009**, *131*, 8714.

(11) For pioneering report on NHC catalyst **E**, see: Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2007**, *129*, 10098.

(12) For pioneering report on NHC catalyst **F**, see: He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc*. **2006**, *128*, 8418.

(13) Tan, W.; Li, X.; Gong, Y.-X.; Ge M.-D.; Shi, F. *Chem. Commun*. **2014**, *50*, 15901.