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二氟卡宾参与下从邻乙烯基苯胺出发构建 3-取代吲哚酮类化合物

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摘要 开发了一种新型的无需过渡金属参与的合成 1-烷基-3-(2-氧代-2-芳基/烷基-乙基)吲哚酮的方法. 这项工作揭示了氧吲哚骨架可以直接由邻乙烯基苯胺和市售的卤代二氟烷基试剂通过 C—N 裂解/新 C—N 键和 C—C 键形成来构建. 该反应具有高效和优异的官能团兼容性, 在药物分子和天然产物的后期修饰中具有巨大潜力.

关键词 卤代二氟试剂; 3-取代吲哚酮; 二氟卡宾

Difluorocarbene-Enabled Synthesis of 3-Substituted-2-oxoindoles from *o*-Vinylanilines

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Abstract A novel transition-metal-free protocol for the synthesis of 1-alkyl-3-(2-oxo-2-aryl/alkyl-ethyl)indolin-2-ones is developed. This work reveals that oxoindole skeletons can be directly constructed from *ortho*-vinylanilines and commercially available halogenated difluoroalkyl reagents via a C—N cleavage/new C—N bonds and C—C bond formation cascade. This reaction portrays high efficiency and excellent functional group compatibility, and has great potential in the late-stage modifications of pharmaceutical molecules and natural products.

Keywords halo difluoro reagent; 3-substituted 2-oxindole; difluorocarbene

1 Introduction

Oxindole motifs obtained from synthetic or natural sources have diverse pharmacological activities, thus make themselves important medicinal chemical scaffolds (Scheme 1, A).[1] They are ubiquitous in mammalian tissues, body fluids, and a range of natural products produced by plants, bacteria and invertebrates. In addition, 3-substituted oxindole derivatives exhibit broad biological activities, such as antitumor,[2] antioxidant,[3] kinase inhibition,[4] *etc*. Due to their diverse pharmacological profiles,[5] industry and academia[6] have shown great interests in developing novel methods for the construction of oxindole derivatives.

However, to the best of our knowledge, efficient synthetic methods for building those frameworks are very rare. In general, there are three approaches[7] to access those target molecules (Scheme 1, B). (1) Starting from biscarbonyl indole compounds, different 3-alkenyl-2-oxindole skeletons were constructed with Wittig reagent. Subsequent hydrogenation and reduction catalyzed by Pd/C afforded the corresponding target products (Strategy 1). (2) The reaction between *α*,*β*-unsaturated amides and cyclopropanal under O_2 atmosphere delivered the target molecules (Strategy 2). (3) The C-3 alkylation of oxindole catalyzed by nickel phosphide nanoalloys using alcohols as alkylating reagents was developed (Strategy 3). It is worth noting that almost all existing methods require the construction of the indole framework first, or transition metal catalysts, which is disadvantageous for the efficiency and

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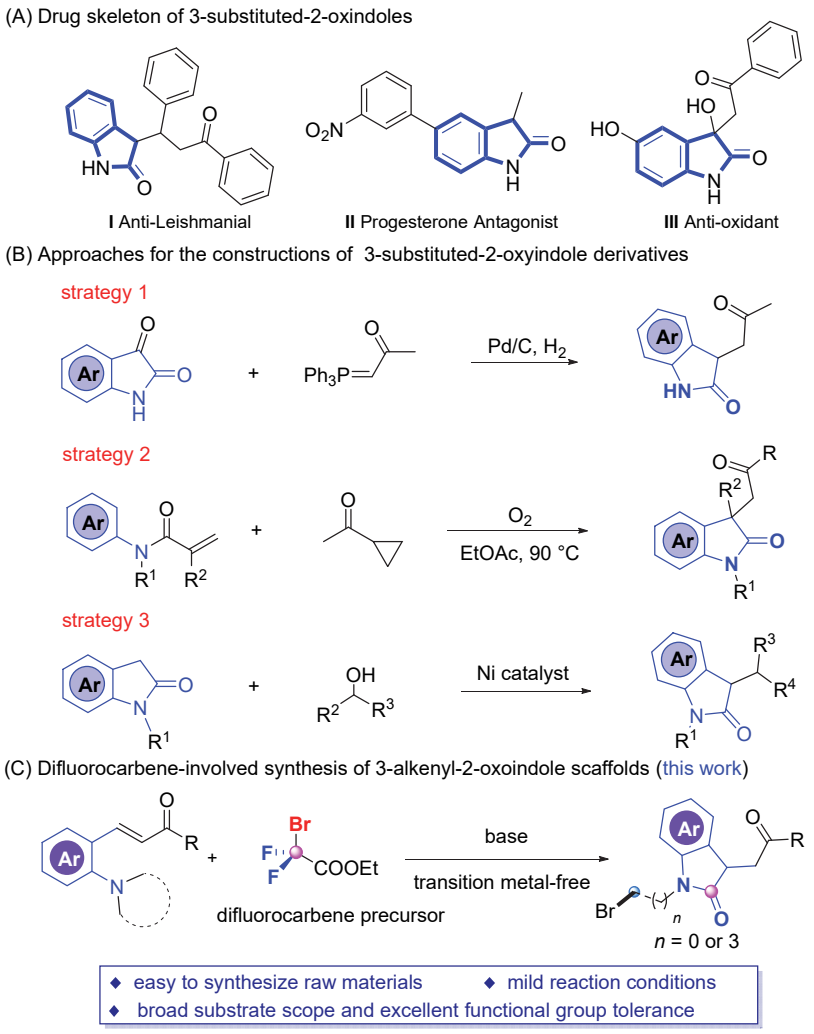
cost. Given the importance of 2-oxoindoles and the lack of efficient synthetic methods, the development of a facile method to construct 3-substituted-2-oxindole derivatives becomes appealing and demanding. Considering the difficulty in accessing the starting materials and the limitations of substrate scopes in the previous strategies, we wondered whether a novel strategy could be developed by using readily accessible starting materials. Retrosynthetic analysis of 3-substituted-2-oxindoles pointed to *o*-alkenyl-anilines and a reagent which could provide both C and O atoms. Based on previous work, we found that halodifluoroalkylative reagents are ideal carbonyl sources.[8] In 2017, Shi *et al*.[9] reported that difluoroalkylative reagents can provide monofluorine-containing C1 sources through a triple cleavage (cleavage of C—Cl, C—F and C—C bonds) to prepare various (*Z*)-fluoroalkenes. We recently also reported the transformations of *in situ* generated difluorocarbene (:CF_2) as a C1 synthon to assemble various valuable nitrogen-containing compounds.[10] In addition, after literature research, we were aware of that the fluorine atom on the indole ring is vulnerable to hydrolysis.[11] Based on the above works, we envisaged that difluorocarbene could be inserted into the target molecule to form a 2-fluoroindole skeleton, which could be then hydrolyzed to form the target molecule.

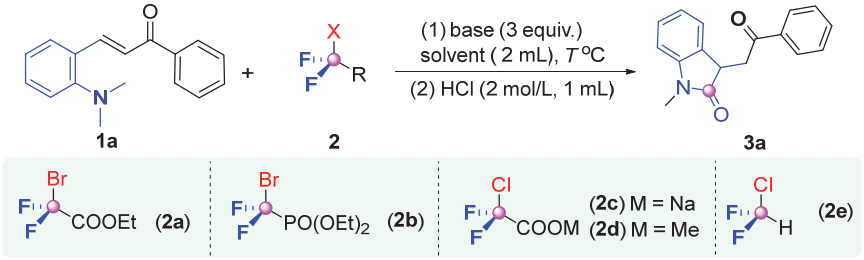
2 Results and discussion

To verify our hypothesis, 3-(2-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one (**1a**) and $BrCF_2COOEt$ (**2a**) were selected as the model substrates using K_2CO_3 as a base. To our delight, the desired indole product **3a** was obtained in 76% isolated yield without any additives in CH_3CN (Table 1, Entry 1). After that, various bases were screened. Comparing with KOH, Na_2CO_3, Na_3PO_4, K_3PO_4, *etc*., K_3PO_4 was the best choice, and the isolated yield could reach 90% (Entry 5). Encouraged by this promising result, we further screened other solvents, such as tetrahydrofuran (THF), dimethyl ether (DME) and toluene (Entries 6～8), and found that CH_3CN was the most efficient one. Difluorinated reagents were subsequently examined and the results revealed that among $BrCF_2COOEt$ (**2a**), $BrCF_2PO(OEt)_2$



Scheme 1 Drug skeleton of 3-substituted-2-oxindoles and synthetic approaches to 3-substituted-2-oxindoles

Table 1 Screening of conditions for the difluorocarbene enabled 3-substituted 2-oxindoles synthesis[a]



Entry	Base	[:CF_2]	Solvent	T/℃	Yield[b]/%
1	K_2CO_3	**2a**	CH_3CN	90	76
2	KOH	**2a**	CH_3CN	90	45
3	Na_2CO_3	**2a**	CH_3CN	90	61
4	Na_3PO_4	**2a**	CH_3CN	90	56
5	K_3PO_4	**2a**	CH_3CN	90	93 (90[c])
6	K_3PO_4	**2a**	THF	90	15
7	K_3PO_4	**2a**	DME	90	Trace
8	K_3PO_4	**2a**	Toluene	90	n.r.
9	K_3PO_4	**2b**	CH_3CN	90	88
10	K_3PO_4	**2c**	CH_3CN	90	66
11	K_3PO_4	**2d**	CH_3CN	90	Trace
12	K_3PO_4	**2e**	CH_3CN	90	49
13	K_3PO_4	**2a**	CH_3CN	80	81
14	K_3PO_4	**2a**	CH_3CN	100	93
15	K_3PO_4	**2a**	CH_3CN	110	88

[a] Reaction condition: **1a** (0.2 mmol), **2** (3 equiv., 0.6 mmol), base (3 equiv.), solvent (2 mL), for 12 h, N_2. [b] NMR yields. [c] Isolated yields. n.r.=no reaction.

(**2b**), $ClCF_2COONa$ (**2c**), $ClCF_2COOMe$ (**2d**) and $ClCF_2H$ (**2e**), **2a** and **2b** were superior (Entries 9～12). Then the temperature was evaluated and 90 ℃ was still the best option. Given the price and availability of raw materials, we finally decided to choose **2a** as the difluorocarbene source.

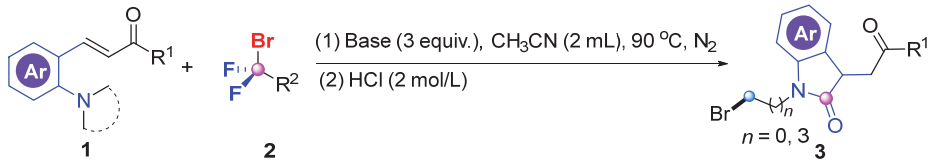
With the optimized conditions in hand, the reaction between difluorocarbene and *o*-vinylaniline was systematically studied (Table 2). First, the scope of *α*,*β*-unsaturated ketone moiety was explored. For aromatics ones, substrates bearing electron-neutral (**1a**, **1b**), electron-deficient (**1c**), as well as electron-rich substituents (**1d**, **1e**) at the *para*-position of the aromatic rings all successfully provided the desired 3-substituted-2-oxoindole products (**3a**～**3e**) efficiently. For electronically neutral bis-methyl (**1f**) and *ortho*-methyl (**1g**) substrates, the corresponding products **3f** and **3g** were obtained in 91% and 80% yields, respectively.

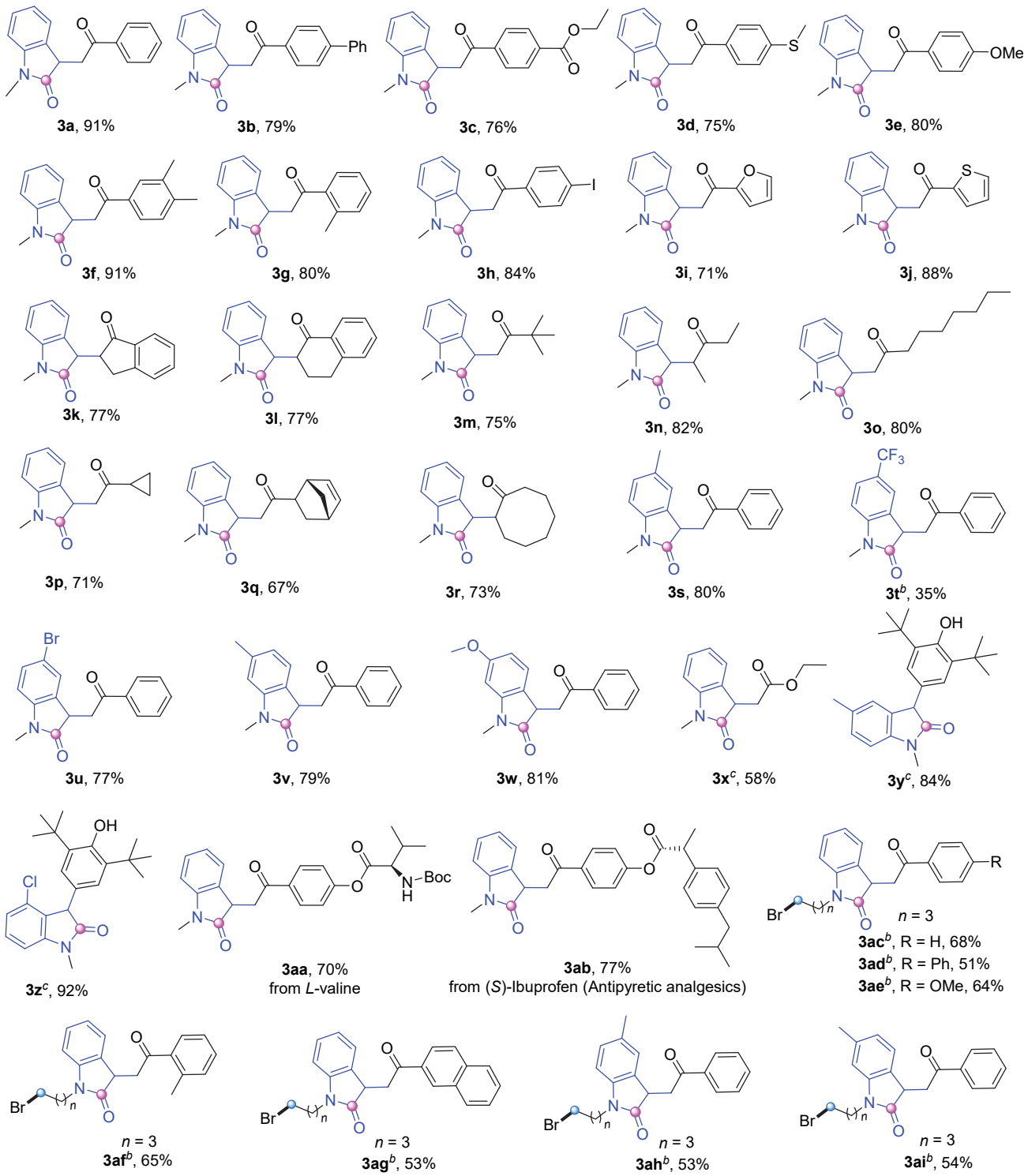
The accommodation of iodine (**1h**) facilitated further transformations. Ketones bearing heteroaromatic furan (**3i**) and thiophene (**3j**) cores were also compatible, so did cyclic aryl ketones (**3k**, **3l**). Notably, this protocol was also applicable to a wide range of aliphatic ketone substrates. The corresponding desired products **3m**～**3r** were delivered smoothly (67%～82% yields), indicating that our reaction was compatible with both aryl and aliphatic *α*,*β*-unsaturated ketones. The scope of anilines was further explored. To our delight, a series of functionalities were compatible under our standard conditions. Alkyl (**1s**, **1v**), trifluoromethyl (**1t**), alkoxy (**1w**) and halogen (**1u**) substituted substrates all converted to the corresponding products (**3s**, **3w**) in moderate to excellent yields. The evaluation on the Michael acceptors indicated that the target 3-substituted-2-oxoindole products were obtained in moderate to excellent yields under marginally reoptimized conditions [Br-$CF_2PO(OEt)_2$ (**2b**), K_2CO_3 in MeCN, 90 ℃ for 12 h under N_2]. First, ethyl acrylate was a suitable substrate and the corresponding product was obtained in moderate yield (**3x**, 58%). Second, other Michael acceptors such as *para*-quinone methides could also be compatible and afforded the desired products in high yields (**3y**～**3z**, 84%～92%). Noteworthily, they are very valuable structural motifs in medicinal chemistry.

The above results clearly demonstrated that our method has a broad substrate scope and wide functional group compatibility, which further prompted our endeavors to apply this strategy to late-stage modifications of bioactive molecules and medicines. Gratifyingly, bioactive molecule *L*-valine was derivatized to the corresponding Michael acceptor and the latter reacted smoothly under the standard conditions (**3aa**). In addition, pharmaceutical compound such as (*S*)-ibuprofen was also compatible, giving the corresponding 3-substituted-2-oxoindole product in moderate yield (**3ab**). The results indicated that our system was capable of discovering more potential biologically active molecules.

The substrates bearing different cyclic tertiary amines were also investigated, which would add more value for further structural modifications (Table 2). The results

Table 2 Scope of the α,β-unsaturated ketone-containing anilines[a]



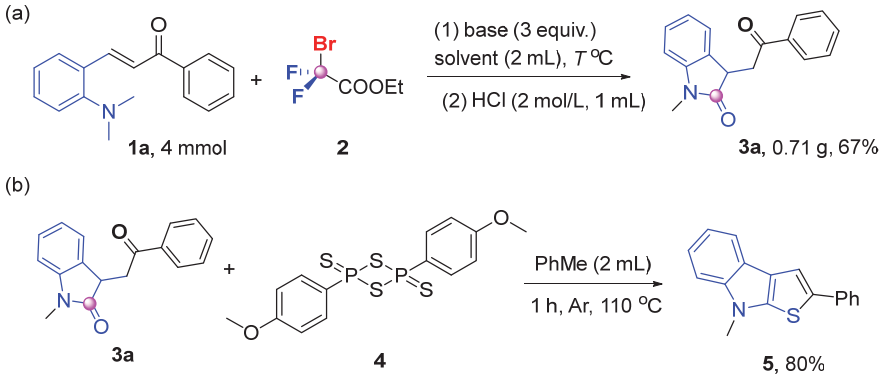


[a] (1) **1** (0.2 mmol), **2a** (3 equiv., 0.6 mmol), K_3PO_4 (3 equiv.), CH_3CN (2 mL) at 90 ℃ for 12 h, N_2; (2) HCl (2 mol/L, 1 mL). [b] 24 h. [c] **1** (0.2 mmol), **2b** (3 equiv., 0.6 mmol), K_2CO_3 (3 equiv.), CH_3CN (2 mL) at 90 ℃ for 12 h, N_2.

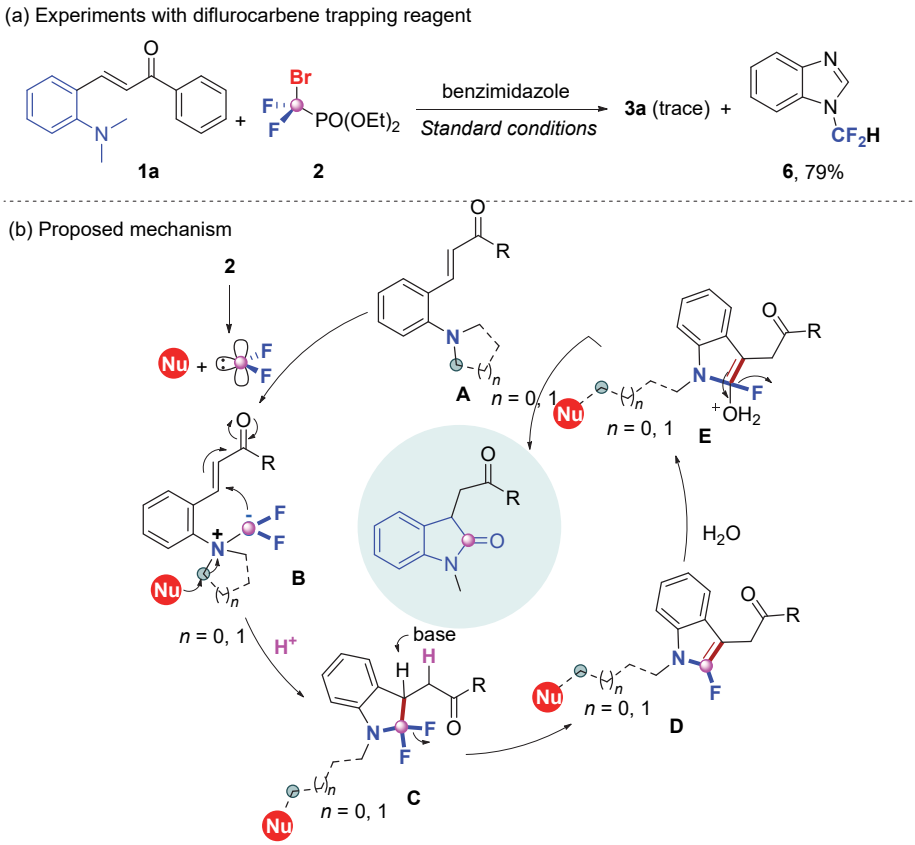
showed that five-membered cyclic tertiary amines were suitable for this transformation, affording the corresponding products **3ac**～**3ai** in moderate yields.

In order to exhibit the synthetic value of our strategy, a gram-scale reaction was performed (Scheme 2, a). When the reaction was scaled up to 4 mmol, the target product **3a** was obtained in good yield with significant loss of efficiency. Further transformation on the target molecule was performed and the product was transformed into 2-substituted thiophene[2,3-*b*]indole **5** with Lawesson's reagent **4** in an excellent 80% yield (Scheme 2, b).

In order to better understand the mechanism of this transformation, control experiment was performed to elucidate the reaction mechanism (Scheme 3, a). When the difluorocarbene trapping agent benzimidazole was added to the reaction system, the trapping product 1-(difluoromethyl)-1*H*-benzimidazole (**6**) was isolated in 79% yield without detection of the target molecule **3a**, indicating the presence of difluorocarbene species. Based on this result and previous reports,[11] a tentative plausible mechanism was proposed (Scheme 3, b). In the presence of base, ethyl bromodifluoroacetate is decomposed into difluorocarbene *in situ*, which is captured by a tertiary amine **A** to generate an intermediate ammonium salt **B**. Bromide ion acts as a nucleophile to attack the *α*-C of ammonium salt **B** to promote C—N bond cleavage. The newly formed difluoro



Scheme 2 Scale-up reaction and synthetic applications



Scheme 3 Control experiment and plausible mechanism

methyl anion further attacks the unsaturated double bond in Michael acceptor to generate the intermediate **C**. The C(sp^3)—F bond adjacent to the N atom is unstable, and it further breaks to deliver the intermediate **D**. It is further hydrolyzed in acidic condition to produce the intermediate **E**, which ultimately forms the final product (in the middle of the cycle).

3 Conclusions

In summary, a facile method for the synthesis of 3-substituted-2-oxindoles from readily available *ortho*-vinylanilines and halogenated difluoroalkylating reagents as difluorocarbene sources was developed. This versatile and highly selective transformation provides a simple but efficient way to construct 3-substituted-2-oxindoles under mild and transition-metal-free conditions. The obtained products can be further transformed to other valuable compounds. This work simplifies the synthesis of 3-substituted oxoindole derivatives and enriches the diversity of those compounds. Further research is currently underway to expand the reaction range and other applications in our laboratory.

4 Experimental section

4.1 General information

Chemicals were purchased from Adamas Reagent, Energy Chemical Company [$BrCF_2COOEt$, $BrCF_2PO(OEt)_2$, $ClCF_2COONa$], Bide Pharmatech Ltd ($TMSCF_2Br$), J&K SCIENTIFIC LTD (ICF_2COOEt) and Shang Fluoro Company ($ClCF_2H$). Unless otherwise stated, all experiments were conducted in a sealed tube under N_2 atmosphere. Reactions were monitored by thin layer chromatography (TLC) or gas chromatography-mass spectrometer (GC-MS) analysis. Flash column chromatography was performed over silica gel (200～300 mesh).

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Avance 500 spectrometer [500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR (CPD), 471 MHz for ^{19}F NMR] at room temperature. Chemical shifts were reported on the scale relative to $CDCl_3$ (δ=7.26 for ^1H NMR, δ=77.00 for ^{13}C NMR) as an internal reference.

4.2 Synthesis of 3-substituted-2-oxoindoles

4.2.1 Synthesis of 3-substituded-2-oxoindoles from chalcones or *p*-quinone methide

In air, chalcones or *p*-quinone methide (0.2 mmol) and K_3PO_4 (3 equiv., 0.6 mmol) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with N_2 (three cycles). $BrCF_2COOEt$ (3 equiv., 0.6 mmol) and CH_3CN (2 mL) were added in turn by syringe under N_2 atmosphere. The resulting reaction mixture was stirred vigorously at 90 ℃ for 12 h. Upon completion of the reaction, 1 mL of 2 mol/L HCl was added, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt, V∶V=20∶1) to give the desired products.

1-Methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**3a**): Eluant: petroleum ether/AcOEt (V∶V=5∶1), yellow solid (48.3 mg, 91%). m.p. 134～135 ℃; ^1H NMR (500 MHz, Chloroform-*d*) δ: 7.97 (dd, J=8.4, 1.3 Hz, 2H), 7.60～7.54 (m, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.28～7.22 (m, 2H), 6.98 (td, J=7.5, 1.0 Hz, 1H), 6.84 (d, J=7.7 Hz, 1H), 4.06 (dd, J=9.3, 3.0 Hz, 1H), 3.82 (dd, J=18.2, 3.1 Hz, 1H), 3.38 (dd, J=18.2, 9.2 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 176.64, 153.23, 142.01, 136.10, 132.01, 129.39, 128.33, 127.26, 125.92, 125.07, 107.74, 51.97, 34.40, 30.28, 26.44, 21.12; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1176, found 266.1178.

3-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-1-methylindolin-2-one (**3b**): Yellow solid, 53.9 mg, 79% yield. m.p. 196～198 ℃; ^1H NMR (500 MHz, Chloroform-*d*) δ: 8.10～8.02 (m, 2H), 7.71～7.67 (m, 2H), 7.65～7.60 (m, 2H), 7.47 (dd, J=8.4, 6.8 Hz, 2H), 7.43～7.38 (m, 1H), 7.32～7.26 (m, 2H), 7.01 (td, J=7.6, 1.0 Hz, 1H), 6.90～6.83 (m, 1H), 4.11 (dd, J=9.3, 3.0 Hz, 1H), 3.87 (dd, J=18.2, 3.1 Hz, 1H), 3.43 (dd, J=18.1, 9.3 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.59, 177.76, 146.14, 144.34, 139.76, 135.10, 129.17, 128.99, 128.77, 128.34, 128.12, 127.34, 127.29, 124.47, 122.55, 108.04, 41.26, 40.13, 26.43; HRMS (ESI-TOF) calcd for $C_{23}H_{20}NO_2$ $[M+H]^+$ 342.1489, found 342.1490.

Ethyl 4-(2-(1-methyl-2-oxoindolin-3-yl)acetyl)benzoate (**3c**): Yellow solid, 51.2 mg, 76% yield. m.p. 141～144 ℃; ^1H NMR (500 MHz, Chloroform-*d*) δ: 8.11 (dd, J=8.6, 1.9 Hz, 2H), 8.01 (dd, J=8.5, 1.8 Hz, 2H), 7.26 (dd, J=22.2, 7.6 Hz, 2H), 6.99 (t, J=7.6 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 4.39 (q, J=7.1 Hz, 2H), 4.05 (d, J=9.1 Hz, 1H), 3.88～3.81 (m, 1H), 3.42 (dd, J=18.4, 9.1 Hz, 1H), 3.26 (s, 3H), 1.40 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.60, 177.50, 165.63, 144.34, 139.39, 134.57, 129.88, 128.87, 128.22, 128.02, 124.34, 122.57, 108.10, 61.51, 41.11, 40.39, 26.43, 14.28; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$ 338.1387, found 338.1388.

1-Methyl-3-(2-(4-(methylthio)phenyl)-2-oxoethyl)indolin-2-one (**3d**): Yellow solid, 6.7 mg, 75% yield. m.p. 153～155 ℃; ^1H NMR (500 MHz, Chloroform-*d*) δ: 7.87 (d, J=8.1 Hz, 2H), 7.29～7.22 (m, 4H), 6.98 (t, J=7.5 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 4.10～4.03 (m, 1H), 3.77 (dd, J=18.1, 3.0 Hz, 1H), 3.33 (dd, J=18.1, 9.2 Hz, 1H), 3.26 (d, J=1.1 Hz, 3H), 2.50 (d, J=1.4 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 195.92, 177.76, 146.46, 144.30, 132.67, 129.17, 128.53, 128.08, 125.02, 124.44, 122.51, 108.01, 41.23, 39.82, 26.41, 14.74; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$ 312.1053, found 312.1055.

3-(2-(4-Methoxyphenyl)-2-oxoethyl)-1-methylindolin-2-one (**3e**): Yellow solid, 47.2 mg, 80% yield. m.p. 88～90 ℃; ^1H NMR (500 MHz, Chloroform-*d*) δ: 7.96～7.91 (m, 2H), 7.27～7.22 (m, 2H), 6.97 (td, J=7.5, 1.0 Hz, 1H), 6.94～6.90 (m, 2H), 6.83 (d, J=7.7 Hz, 1H), 4.05

(dd, J=9.3, 3.0 Hz, 1H), 3.84 (s, 3H), 3.76 (dd, J=18.0, 3.0 Hz, 1H), 3.33 (dd, J=17.9, 9.3 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 195.43, 177.88, 163.75, 144.29, 130.43, 129.52, 129.29, 128.02, 124.46, 122.48, 113.84, 107.97, 55.50, 41.30, 39.69, 26.38; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281, found 296.1283.

3-(2-(3,4-Dimethylphenyl)-2-oxoethyl)-1-methylindolin-2-one (**3f**): Yellow solid, 53.4 mg, 91% yield. m.p. 204～206 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.76 (d, J=2.0 Hz, 1H), 7.70 (dd, J=7.9, 2.0 Hz, 1H), 7.28～7.23 (m, 2H), 7.21 (d, J=7.8 Hz, 1H), 7.01～6.95 (m, 1H), 6.85 (d, J=7.7 Hz, 1H), 4.08 (dd, J=9.4, 2.9 Hz, 1H), 3.80 (dd, J=18.1, 2.9 Hz, 1H), 3.36 (dd, J=18.1, 9.4 Hz, 1H), 3.27 (s, 3H), 2.31 (d, J=4.9 Hz, 6H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.85, 177.90, 144.30, 143.04, 137.05, 134.33, 129.91, 129.30, 128.02, 125.88, 124.51, 122.50, 107.96, 41.26, 40.01, 26.40, 20.05, 19.77; HRMS (ESI-TOF) calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1489, found 294.1491.

1-Methyl-3-(2-oxo-2-(*o*-tolyl)ethyl)indolin-2-one (**3g**): Yellow solid, 44.7 mg, 80% yield. m.p. 126～129 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.65 (dd, J=8.2, 1.5 Hz, 1H), 7.38 (td, J=7.5, 1.4 Hz, 1H), 7.31～7.23 (m, 4H), 7.01 (td, J=7.5, 1.0 Hz, 1H), 6.85 (d, J=7.7 Hz, 1H), 4.09 (dd, J=9.1, 3.4 Hz, 1H), 3.72 (dd, J=18.0, 3.4 Hz, 1H), 3.31 (dd, J=18.0, 9.0 Hz, 1H), 3.25 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 200.79, 177.69, 144.34, 138.40, 137.15, 132.06, 131.67, 129.14, 128.67, 128.11, 125.78, 124.32, 122.53, 108.06, 42.75, 41.48, 26.39, 21.39; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332, found 280.1334.

3-(2-(4-Iodophenyl)-2-oxoethyl)-1-methylindolin-2-one (**3h**): Yellow solid, 65.7 mg, 84% yield. m.p. 180～183 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.84～7.79 (m, 2H), 7.70～7.65 (m, 2H), 7.28 (dt, J=7.8, 1.1 Hz, 1H), 7.22 (dd, J=7.4, 1.3 Hz, 1H), 6.99 (td, J=7.5, 1.0 Hz, 1H), 6.85 (d, J=7.8 Hz, 1H), 4.05 (dd, J=9.1, 3.1 Hz, 1H), 3.77 (dd, J=18.2, 3.1 Hz, 1H), 3.34 (dd, J=18.2, 9.1 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.34, 177.54, 144.32, 138.05, 135.62, 129.50, 128.91, 128.20, 124.35, 122.57, 108.08, 101.52, 41.12, 39.94, 26.43; HRMS (ESI-TOF) calcd for $C_{17}H_{15}INO_2$ $[M+H]^+$ 392.0142, found 392.0144.

3-(2-(Furan-2-yl)-2-oxoethyl)-1-methylindolin-2-one (**3i**): Yellow solid, 36.2 mg, 71% yield. m.p. 137～139 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.58 (d, J=1.6 Hz, 1H), 7.26 (dd, J=17.9, 7.5 Hz, 2H), 7.21 (d, J=3.6 Hz, 1H), 6.99 (td, J=7.6, 0.9 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 6.54 (dd, J=3.6, 1.7 Hz, 1H), 4.04 (dd, J=9.3, 3.4 Hz, 1H), 3.67 (dd, J=18.0, 3.4 Hz, 1H), 3.25 (s, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 186.15, 177.41, 152.28, 146.64, 144.30, 128.81, 128.16, 124.44, 122.53, 117.48, 112.40, 108.03, 40.82, 39.58, 26.41; HRMS (ESI-TOF) calcd for $C_{15}H_{14}NO_3$ $[M+H]^+$ 256.0968, found 256.0969.

1-Methyl-3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one (**3j**): Yellow solid, 47.7 mg, 88% yield. m.p. 147～149 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.06 (dd, J=2.9, 1.2 Hz, 1H), 7.55 (dd, J=5.1, 1.2 Hz, 1H), 7.31 (dd, J=5.1, 2.9 Hz, 1H), 7.28～7.23 (m, 2H), 6.98 (td, J=7.5, 1.0 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 4.03 (dd, J=9.2, 3.1 Hz, 1H), 3.73 (dd, J=18.0, 3.1 Hz, 1H), 3.32～3.27 (m, 1H), 3.25 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 191.27, 177.61, 144.28, 141.57, 132.35, 129.03, 128.13, 126.84, 126.59, 124.47, 122.55, 108.02, 41.12, 41.04, 26.41; HRMS (ESI-TOF) calcd for $C_{15}H_{14}NO_2S$ $[M+H]^+$ 272.0740, found 272.0741.

1-Methyl-3-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)indolin-2-one (**3k**): Yellow solid, 42.7 mg, 77% yield. m.p. 123～126 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.85 (dt, J=7.7, 1.0 Hz, 1H), 7.54 (td, J=7.5, 1.3 Hz, 1H), 7.40～7.37 (m, 1H), 7.29 (dt, J=7.7, 0.9 Hz, 1H), 7.23～7.19 (m, 1H), 6.84～6.79 (m, 3H), 4.33 (d, J=3.3 Hz, 1H), 3.59 (ddd, J=8.2, 5.0, 3.3 Hz, 1H), 3.27 (s, 3H), 3.11 (dd, J=16.9, 8.1 Hz, 1H), 2.23 (dd, J=17.0, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 206.35, 176.79, 153.57, 144.61, 136.67, 135.07, 128.45, 127.61, 126.61, 125.23, 124.43, 123.97, 122.64, 108.03, 47.97, 45.64, 28.00, 26.41; HRMS (ESI-TOF) calcd for $C_{18}H_{16}NO_2$ $[M+H]^+$ 278.1176, found 278.1178.

1-Methyl-3-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-indolin-2-one (**3l**): Yellow solid, 44.8 mg, 77% yield. m.p. 185～187 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.15 (dd, J=7.9, 1.5 Hz, 1H), 7.48 (td, J=7.5, 1.5 Hz, 1H), 7.39～7.32 (m, 1H), 7.26～7.18 (m, 2H), 7.10 (d, J=7.5 Hz, 1H), 6.94 (td, J=7.5, 1.0 Hz, 1H), 6.83 (d, J=7.8 Hz, 1H), 4.57 (d, J=2.7 Hz, 1H), 3.48 (ddd, J=13.8, 4.5, 2.7 Hz, 1H), 3.26 (s, 3H), 3.09 (ddd, J=17.3, 13.1, 4.6 Hz, 1H), 2.83 (ddd, J=16.7, 4.2, 2.6 Hz, 1H), 1.76 (ddq, J=10.5, 4.6, 2.3 Hz, 1H), 1.64 (qd, J=13.2, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 197.66, 177.64, 144.63, 144.22, 133.72, 132.31, 128.85, 128.04, 127.62, 126.78, 126.67, 125.10, 122.57, 108.01, 50.02, 45.84, 29.06, 26.35, 24.59; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1332, found 292.1333.

3-(3,3-Dimethyl-2-oxobutyl)-1-methylindolin-2-one (**3m**): Yellow oil liquid, 36.8 mg, 75% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.26 (tt, J=7.7, 1.1 Hz, 1H), 7.11 (dd, J=7.4, 1.5 Hz, 1H), 6.99 (td, J=7.5, 1.1 Hz, 1H), 6.86～6.79 (m, 1H), 3.91～3.85 (m, 1H), 3.30 (dd, J=18.4, 3.1 Hz, 1H), 3.23 (s, 3H), 2.93 (dd, J=18.4, 9.0 Hz, 1H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 212.92, 177.93, 144.33, 129.20, 128.00, 123.92, 122.44, 108.00, 43.95, 41.04, 38.31, 26.45, 26.34; HRMS (ESI-TOF) calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489, found 246.1489.

1-Methyl-3-(3-oxopentan-2-yl)indolin-2-one (**3n**): Yellow oil liquid, 37.9 mg, 82% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.28 (dt, J=7.8, 1.1 Hz, 1H), 7.20～7.16 (m, 1H), 7.03～6.99 (m, 1H), 6.82 (dd, J=7.9, 1.1 Hz, 1H), 3.94 (d, J=3.2 Hz, 1H), 3.35 (qd, J=7.3, 3.2 Hz, 1H), 3.22 (s, 3H), 2.60 (q, J=7.3 Hz, 2H), 1.30 (d, J=7.2 Hz, 1H), 1.12 (d, J=7.3 Hz, 2H), 1.03 (t, J=7.2 Hz, 1H), 0.93 (d, J=7.3 Hz, 2H); ^{13}C NMR (126 MHz, Chloro-

form-*d*) *δ*: 212.13, 177.08, 144.73, 128.13, 125.42, 123.83, 122.45, 107.97, 47.23, 46.86, 33.65, 26.28, 11.82, 7.97; HRMS (ESI-TOF) calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$ 232.1332, found 232.1335.

1-Methyl-3-(2-oxononyl)indolin-2-one (**3o**): Yellow oil liquid, 46.0 mg, 80% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.29～7.24 (m, 1H), 7.20～7.15 (m, 1H), 7.00 (td, *J*=7.5, 1.0 Hz, 1H), 6.82 (d, *J*=7.7 Hz, 1H), 3.87 (dd, *J*=9.0, 3.4 Hz, 1H), 3.23 (d, *J*=3.4 Hz, 1H), 3.22 (s, 3H), 3.20 (d, *J*=3.4 Hz, 1H), 2.83～2.76 (m, 1H), 2.44 (dtd, *J*=16.7, 9.2, 7.4 Hz, 2H), 1.59 (p, *J*=7.3 Hz, 2H), 1.29～1.23 (m, 8H), 0.87 (t, *J*=6.6 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 208.03, 177.56, 144.27, 129.06, 128.06, 124.14, 122.48, 108.00, 43.52, 42.89, 41.02, 31.64, 29.12, 29.02, 26.34, 23.84, 22.59, 14.05; HRMS (ESI-TOF) calcd for $C_{18}H_{26}NO_2$ $[M+H]^+$ 288.1958, found 288.1959.

3-(2-Cyclopropyl-2-oxoethyl)-1-methylindolin-2-one (**3p**): Yellow oil liquid, 32.5 mg, 71% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.26 (dt, *J*=15.4, 1.1 Hz, 1H), 7.20～7.15 (m, 1H), 7.00 (td, *J*=7.6, 1.0 Hz, 1H), 6.82 (d, *J*=7.6 Hz, 1H), 3.87 (dd, *J*=9.2, 3.2 Hz, 1H), 3.40 (dd, *J*=18.1, 3.3 Hz, 1H), 3.22 (s, 3H), 2.96 (dd, *J*=18.1, 9.1 Hz, 1H), 1.96 (tt, *J*=7.8, 4.5 Hz, 1H), 1.09～1.04 (m, 2H), 0.94～0.88 (m, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 196.16, 177.52, 143.48, 138.04, 135.57, 129.51, 128.96, 128.19, 124.39, 122.49, 108.30, 101.55, 41.11, 39.77, 39.14, 33.15, 29.79, 25.96; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_2$ $[M+H]^+$ 230.1176, found 230.1178.

3-(2-((1*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl)-2-oxoethyl)-1-methylindolin-2-one (**3q**): Yellow solid, 37.7 mg, 67% yield. m.p. 103～105 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.29～7.23 (m, 1H), 7.16～7.08 (m, 1H), 7.03～6.95 (m, 1H), 6.82 (d, *J*=7.7 Hz, 1H), 6.16 (ddd, *J*=25.6, 5.7, 3.1 Hz, 1H), 5.80 (dt, *J*=6.7, 3.4 Hz, 1H), 3.85 (ddd, *J*=14.7, 8.9, 3.3 Hz, 1H), 3.31～3.24 (m, 2H), 3.22 (s, 3H), 3.05 (ddt, *J*=24.7, 8.3, 3.9 Hz, 1H), 2.93～2.88 (m, 1H), 2.88～2.80 (m, 1H), 1.81～1.73 (m, 1H), 1.53～1.42 (m, 2H), 1.32 (t, *J*=6.9 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 207.80, 177.70, 144.32, 138.08, 137.95, 131.27, 131.09, 129.07, 128.03, 128.00, 124.02, 122.37, 108.01, 51.73, 49.98, 46.10, 42.80, 42.70, 41.13, 27.69, 26.34; HRMS (ESI-TOF) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ 282.1489, found 282.1490.

1-Methyl-3-(2-oxocyclooctyl)indolin-2-one (**3r**): Yellow solid, 39.6 mg, 73% yield. m.p. 129～131 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.50～7.45 (m, 1H), 7.30～7.25 (m, 2H), 7.03 (td, *J*=7.6, 1.1 Hz, 1H), 6.82～6.78 (m, 1H), 3.76 (d, *J*=4.9 Hz, 1H), 3.42 (dt, *J*=10.4, 4.7 Hz, 1H), 3.21 (s, 3H), 2.57 (ddd, *J*=14.5, 7.9, 3.3 Hz, 1H), 2.38 (ddd, *J*=14.4, 10.9, 3.4 Hz, 1H), 2.09～2.01 (m, 1H), 1.85～1.75 (m, 3H), 1.65 (s, 1H), 1.52 (ddt, *J*=10.5, 5.8, 3.6 Hz, 3H), 1.36 (ddt, *J*=11.5, 4.9, 2.2 Hz, 1H), 1.18～1.10 (m, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 217.22, 177.04, 144.65, 128.11, 126.97, 125.93, 122.20, 107.96, 50.84, 47.81, 43.70, 30.20, 27.73, 26.24, 25.15, 24.98, 24.26; HRMS (ESI-TOF) calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$ 272.1645, found 272.1646.

1,5-Dimethyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**3s**): Yellow solid, 44.7 mg, 80% yield. m.p. 148～150 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 8.02～7.94 (m, 2H), 7.60～7.54 (m, 1H), 7.46 (t, *J*=7.8 Hz, 2H), 7.06 (d, *J*=5.9 Hz, 2H), 6.74 (d, *J*=8.4 Hz, 1H), 4.05 (dd, *J*=9.4, 2.9 Hz, 1H), 3.82 (dd, *J*=18.3, 2.9 Hz, 1H), 3.38 (dd, *J*=18.3, 9.3 Hz, 1H), 3.24 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 197.08, 177.67, 141.92, 136.39, 133.45, 132.07, 129.20, 128.71, 128.28, 128.17, 125.32, 107.74, 41.20, 40.19, 26.44, 21.09; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332, found 280.1335.

5-Bromo-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**3u**): Yellow solid, 52.8 mg, 77% yield. m.p. 162～164 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.99～7.94 (m, 2H), 7.61～7.56 (m, 1H), 7.47 (t, *J*=7.8 Hz, 2H), 7.42～7.34 (m, 2H), 6.73 (d, *J*=8.2 Hz, 1H), 4.03 (dd, *J*=9.0, 2.9 Hz, 1H), 3.84 (dd, *J*=18.4, 2.9 Hz, 1H), 3.41 (dd, *J*=18.4, 9.0 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 196.59, 177.11, 143.45, 136.09, 133.64, 131.11, 130.94, 128.76, 128.18, 127.62, 115.22, 109.40, 41.15, 39.89, 26.53; HRMS (ESI-TOF) calcd for $C_{17}H_{15}BrNO_2$ $[M+H]^+$ 344.0281, found 344.0283.

1,6-Dimethyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**3v**): Yellow solid, 44.1 mg, 79% yield. m.p. 163～165 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.99～7.93 (m, 2H), 7.60～7.53 (m, 1H), 7.45 (t, *J*=7.8 Hz, 2H), 7.12 (dd, *J*=7.5, 1.1 Hz, 1H), 6.81～6.77 (m, 1H), 6.68 (d, *J*=1.4 Hz, 1H), 4.02 (dd, *J*=9.4, 3.0 Hz, 1H), 3.80 (dd, *J*=18.2, 3.0 Hz, 1H), 3.36 (dd, *J*=18.2, 9.3 Hz, 1H), 3.24 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 197.09, 178.04, 144.39, 138.19, 136.42, 133.42, 128.69, 128.15, 126.15, 124.17, 122.98, 109.02, 41.01, 40.20, 26.37, 21.79; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332, found 280.1334.

6-Methoxy-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (**3w**): Yellow solid, 47.8 mg, 81% yield. m.p. 156～158 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 7.96 (dd, *J*=8.4, 1.3 Hz, 2H), 7.58～7.54 (m, 1H), 7.47～7.43 (m, 2H), 7.14 (dd, *J*=8.2, 1.2 Hz, 1H), 6.47 (dd, *J*=8.2, 2.3 Hz, 1H), 6.43 (d, *J*=2.3 Hz, 1H), 4.00 (ddd, *J*=9.4, 3.0, 1.2 Hz, 1H), 3.82～3.76 (m, 4H), 3.33 (dd, *J*=18.1, 9.4 Hz, 1H), 3.23 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 197.18, 178.37, 160.21, 145.55, 136.43, 133.42, 128.69, 128.14, 125.10, 121.07, 106.13, 96.22, 55.52, 40.72, 40.40, 26.42; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281, found 296.1283.

4-(2-(1-Methyl-2-oxoindolin-3-yl)acetyl)phenyl(*tert*-butoxycarbonyl)-*D*-valinate (**3aa**): Yellow solid, 67.2 mg, 70% yield. m.p. 100～102 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) *δ*: 8.02 (d, *J*=8.3 Hz, 2H), 7.30～7.26 (m, 1H), 7.22 (ddd, *J*=12.5, 8.0, 1.3 Hz, 3H), 6.99 (t, *J*=7.6 Hz, 1H), 6.86 (d, *J*=7.8 Hz, 1H), 5.07 (d, *J*=9.1 Hz, 1H), 4.46 (dd, *J*=9.0, 4.9 Hz, 1H), 4.07 (dd, *J*=9.3, 2.9 Hz, 1H), 3.90～3.72 (m, 1H), 3.38 (ddd, *J*=18.2, 9.2, 1.1 Hz, 1H), 3.27 (d, *J*=1.2 Hz, 3H), 2.32 (dt, *J*=8.8, 4.8 Hz, 1H), 1.46

(s, 9H), 1.09 (d, J=6.7 Hz, 3H), 1.02 (d, J=6.9 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 195.72, 177.62, 155.73, 154.37, 144.30, 134.18, 129.87, 128.98, 128.16, 124.38, 122.58, 121.80, 108.06, 58.84, 41.17, 40.04, 31.23, 28.32, 26.43, 19.15, 17.74; HRMS (ESI- TOF) calcd for $C_{27}H_{33}N_2O_6$ $[M+H]^+$ 481.2333, found 481.2335.

4-(2-(1-Methyl-2-oxoindolin-3-yl)acetyl)phenyl-(2*R*)-2-(4-isobutylphenyl)propanoate (**3ab**): Yellow solid, 72.3 mg, 77% yield. m.p. 182～184 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.97 (d, J=8.7 Hz, 2H), 7.30～7.25 (m, 3H), 7.22 (dd, J=7.5, 1.4 Hz, 1H), 7.15 (d, J=7.9 Hz, 2H), 7.11 (d, J=8.8 Hz, 2H), 6.99 (td, J=7.6, 1.1 Hz, 1H), 6.85 (d, J=7.8 Hz, 1H), 4.06 (dd, J=9.2, 2.9 Hz, 1H), 3.95 (q, J=7.1 Hz, 1H), 3.79 (dd, J=18.2, 3.0 Hz, 1H), 3.36 (dd, J=18.2, 9.2 Hz, 1H), 3.26 (s, 3H), 2.48 (d, J=7.2 Hz, 2H), 1.87 (dt, J=13.6, 6.8 Hz, 1H), 1.61 (d, J=7.2 Hz, 3H), 0.91 (d, J=6.6 Hz, 6H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 195.77, 177.69, 172.65, 154.88, 144.29, 141.05, 136.83, 133.86, 129.71, 129.63, 129.02, 128.14, 127.21, 124.40, 122.59, 121.80, 108.06, 45.32, 45.06, 41.18, 40.01, 30.20, 26.43, 22.41, 18.45; HRMS (ESI-TOF) calcd for $C_{30}H_{32}NO_4$ $[M+H]^+$ 470.2326, found 470.2328.

4.2.2 Synthesis of 3-substituded-2-oxoindoles from α,β-unsaturated esters or acrylonitrile

In air, α,β-unsaturated esters (0.2 mmol) or acrylonitrile and K_2CO_3 (3 equiv., 0.6 mmol) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with N_2 (three cycles). $BrCF_2PO(OEt)_2$ (3 equiv., 0.6 mmol) and CH_3CN (2 mL) were added in turn by syringe under N_2 atmosphere. The resulting reaction mixture was stirred vigorously at 90 ℃ for 12 h. Upon completion of the reaction, 1 mL of 2 mol/L HCl was added, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt, V∶V=20∶1) to give the desired products.

Ethyl 2-(1-methyl-2-oxoindolin-3-yl)acetate (**3x**): Yellow oil liquid, 27.0 mg, 58% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.30～7.24 (m, 2H), 7.03 (t, J=7.8 Hz, 1H), 6.83 (d, J=7.8 Hz, 1H), 4.13 (qd, J=7.1, 5.0 Hz, 2H), 3.78 (dd, J=8.1, 4.4 Hz, 1H), 3.22 (s, 3H), 3.07 (dd, J=16.9, 4.5 Hz, 1H), 2.78 (dd, J=16.9, 8.1 Hz, 1H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 176.76, 171.06, 144.40, 128.31, 128.23, 123.85, 122.50, 108.06, 60.90, 41.88, 35.00, 26.33, 14.11; HRMS (ESI-TOF)$^+$ calcd for $C_{13}H_{16}NO_3$ $[M+H]$ 234.1125, found 234.1126.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,5-dimethylindolin-2-one (**3y**): Yellow solid, 61.4 mg, 84% yield. m.p. 238～240 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.12 (dd, J=8.0, 1.8 Hz, 1H), 7.03 (d, J=19.1 Hz, 3H), 6.79 (d, J=7.9 Hz, 1H), 5.18 (s, 1H), 4.51 (s, 1H), 3.25 (s, 3H), 2.33 (s, 3H), 1.42 (s, 18H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 176.64, 153.23, 142.01, 136.10, 132.01, 129.39, 128.33, 127.26, 125.92, 125.07, 107.74, 51.97, 34.40, 30.28, 26.44, 21.12; HRMS (ESI-TOF) calcd for $C_{24}H_{32}NO_2$ $[M+H]^+$ 366.2428, found 366.2430.

4-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-methylindolin-2-one (**3z**): Yellow solid, 70.9 mg, 92% yield. m.p. 201～203 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.28 (d, J=8.1 Hz, 1H), 7.03 (dd, J=8.3, 0.8 Hz, 1H), 6.95 (s, 2H), 6.79 (dd, J=7.9, 0.7 Hz, 1H), 5.14 (s, 1H), 4.55 (s, 1H), 3.22 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 175.93, 153.23, 146.06, 135.84, 131.61, 129.57, 126.65, 124.83, 124.71, 123.23, 106.42, 51.62, 34.34, 30.27, 26.67; HRMS (ESI-TOF) calcd for $C_{23}H_{29}ClNO_2$ $[M+H]^+$ 386.1881, found 386.1882.

4.2.3 Synthesis of N-tethered long chain aliphatic bromine

In air, cyclic tertiary amines (0.2 mmol) and K_3PO_4 (3 equiv., 0.6 mmol) were added to a Schlenk tube equipped with a stir bar. The vessel was evacuated and filled with N_2 (three cycles). $BrCF_2COOEt$ (3 equiv., 0.6 mmol) and CH_3CN (2 mL) were added in turn by syringe under N_2 atmosphere. The resulting reaction mixture was stirred vigorously at 90 ℃ for 24 h. Upon completion of the reaction, 1 mL of 2 mol/L HCl was added, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt, V∶V=20∶1) to give the desired products.

1-Methyl-3-(2-oxo-2-phenylethyl)-5-(trifluoromethyl)-indolin-2-one (**3t**): Yellow solid, 23.3 mg, 35% yield. m.p. 178～180 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.97 (d, J=7.1 Hz, 2H), 7.59 (q, J=9.1, 8.3 Hz, 2H), 7.52～7.45 (m, 3H), 6.93 (d, J=8.2 Hz, 1H), 4.06 (dd, J=8.6, 2.9 Hz, 1H), 3.89 (dd, J=18.4, 3.0 Hz, 1H), 3.48 (dd, J=18.5, 8.7 Hz, 1H), 3.31 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.49, 177.63, 147.37, 136.05, 133.68, 129.57, 128.78, 128.18, 125.95, 125.91, 124.63, 121.37, 107.72, 41.03, 39.73, 26.63.; ^{19}F NMR (471 MHz, Chloroform-*d*) δ: －61.37; HRMS (ESI-TOF) calcd for $C_{18}H_{15}F_3NO_2$ $[M+H]^+$ 334.1049, found 334.1051.

1-(4-Bromobutyl)-3-(2-oxo-2-phenylethyl)indolin-2-one (**3ac**): Yellow oil liquid, 52.4 mg, 68% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.01～7.93 (m, 2H), 7.62～7.55 (m, 1H), 7.47 (t, J=7.8 Hz, 2H), 7.28 (d, J=7.8 Hz, 1H), 7.25 (d, J=7.6 Hz, 1H), 6.99 (td, J=7.5, 0.9 Hz, 1H), 6.89 (d, J=7.8 Hz, 1H), 4.05 (dd, J=8.9, 3.1 Hz, 1H), 3.87～3.76 (m, 3H), 3.54～3.39 (m, 3H), 2.00～1.89 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.81, 177.71, 143.49, 136.37, 133.46, 129.20, 128.70, 128.15, 128.08, 124.49, 122.44, 108.22, 41.19, 39.94, 39.12, 33.15, 29.80, 25.97; HRMS (ESI-TOF) calcd for $C_{20}H_{21}BrNO_2$ $[M+H]^+$ 386.0750, found 386.0752.

3-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-1-(4-bromobutyl)-indolin-2-one (**3ad**): Yellow solid, 47.0 mg, 51% yield. m.p. 157～159 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.05 (d, J=8.4 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H), 7.64～7.61 (m, 2H), 7.49～7.45 (m, 2H), 7.42～7.38 (m, 1H), 7.28 (td, J=7.6, 1.1 Hz, 2H), 7.00 (td, J=7.6, 1.0 Hz, 1H),

6.90 (d, J=7.6 Hz, 1H), 4.08 (dd, J=8.8, 3.1 Hz, 1H), 3.90～3.80 (m, 3H), 3.53～3.42 (m, 3H), 2.01～1.90 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.41, 177.75, 146.15, 143.50, 139.76, 135.06, 129.23, 128.99, 128.77, 128.34, 128.11, 127.34, 127.29, 124.51, 122.48, 108.25, 41.25, 39.97, 39.14, 33.20, 29.82, 25.99; HRMS (ESI-TOF) calcd for $C_{26}H_{25}BrNO_2$ $[M+H]^+$ 462.1063, found 462.1065.

1-(4-Bromobutyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-indolin-2-one (**3ae**): Yellow oil liquid, 53.1 mg, 64% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.95 (d, J=8.9 Hz, 2H), 7.28～7.24 (m, 2H), 6.98 (td, J=7.6, 1.0 Hz, 1H), 6.95～6.91 (m, 2H), 6.88 (d, J=7.8 Hz, 1H), 4.04 (dd, J=8.9, 3.1 Hz, 1H), 3.86 (s, 3H), 3.82～3.75 (m, 3H), 3.48 (t, J=6.3 Hz, 2H), 3.38 (dd, J=17.9, 8.9 Hz, 1H), 2.00～1.88 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 195.26, 177.89, 163.76, 143.45, 130.45, 129.50, 129.37, 128.01, 124.55, 122.42, 113.84, 108.18, 55.51, 53.43, 41.29, 39.57, 39.10, 33.17, 29.80, 25.97; HRMS (ESI-TOF) calcd for $C_{21}H_{23}BrNO_3$ $[M+H]^+$ 416.0856, found 416.0857.

1-(4-Bromobutyl)-3-(2-oxo-2-(*o*-tolyl)ethyl)indolin-2-one (**3af**): Yellow oil liquid, 51.0 mg, 65% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.66 (dd, J=8.1, 1.4 Hz, 1H), 7.40～7.34 (m, 1H), 7.30～7.23 (m, 4H), 7.01 (t, J=7.7 Hz, 1H), 6.88 (d, J=7.7 Hz, 1H), 4.04 (dd, J=8.6, 3.5 Hz, 1H), 3.83～3.69 (m, 3H), 3.47 (t, J=6.4 Hz, 2H), 3.35 (dd, J=18.0, 8.5 Hz, 1H), 2.49 (s, 3H), 2.01～1.86 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 200.59, 177.70, 143.53, 138.42, 137.09, 132.08, 131.68, 129.20, 128.65, 128.09, 125.78, 124.34, 122.43, 108.27, 42.56, 41.47, 39.09, 33.18, 29.78, 25.96, 21.38; HRMS (ESI-TOF) calcd for $C_{21}H_{23}BrNO_2$ $[M+H]^+$ 400.0907, found 400.0909.

1-(4-Bromobutyl)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-indolin-2-one (**3ag**): Yellow oil liquid, 46.1 mg, 53% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.83 (d, J=8.6 Hz, 2H), 7.61 (d, J=8.6 Hz, 2H), 7.28 (d, J=7.7 Hz, 1H), 7.23 (d, J=7.4 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 6.89 (d, J=7.8 Hz, 1H), 4.02 (dd, J=8.7, 3.2 Hz, 1H), 3.83～3.73 (m, 3H), 3.48 (t, J=6.3 Hz, 2H), 3.39 (dd, J=18.2, 8.6 Hz, 1H), 2.00～1.88 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 195.84, 177.52, 143.49, 135.05, 132.04, 129.65, 128.97, 128.73, 128.19, 124.40, 122.49, 108.29, 41.12, 39.84, 39.14, 33.12, 29.79, 25.96; HRMS (ESI-TOF) calcd for $C_{24}H_{23}BrNO_2$ $[M+H]^+$ 436.0907, found 436.0909.

1-(4-Bromobutyl)-5-methyl-3-(2-oxo-2-phenylethyl)-indolin-2-one (**3ah**): Yellow solid, 42.3 mg, 53% yield. m.p. 94～97 ℃; ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.03～7.91 (m, 2H), 7.61～7.54 (m, 1H), 7.47 (t, J=7.8 Hz, 2H), 7.06 (dd, J=5.9, 2.3 Hz, 2H), 6.78 (d, J=8.3 Hz, 1H), 4.02 (dd, J=8.9, 3.0 Hz, 1H), 3.85～3.76 (m, 3H), 3.52～3.38 (m, 3H), 2.27 (s, 3H), 2.01～1.84 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.90, 177.66, 141.05, 136.37, 133.46, 132.02, 129.28, 128.70, 128.27, 128.18, 125.36, 107.96, 41.20, 40.03, 39.12, 33.22, 29.80, 25.98, 21.06; HRMS (ESI-TOF) calcd for $C_{21}H_{23}BrNO_2$ $[M+H]^+$ 400.0907, found 400.0908.

1-(4-Bromobutyl)-6-methyl-3-(2-oxo-2-phenylethyl)-indolin-2-one (**3ai**): Yellow oil liquid, 43.1 mg, 54% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.99～7.95 (m, 2H), 7.60～7.55 (m, 1H), 7.46 (t, J=7.8 Hz, 2H), 7.12 (dd, J=7.5, 1.1 Hz, 1H), 6.80 (d, J=7.5 Hz, 1H), 6.71 (s, 1H), 4.00 (dd, J=8.9, 3.0 Hz, 1H), 3.86～3.75 (m, 3H), 3.49 (t, J=6.4 Hz, 2H), 3.40 (dd, J=18.2, 8.8 Hz, 1H), 2.37 (s, 3H), 2.00～1.89 (m, 4H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 196.92, 178.05, 143.55, 138.19, 136.41, 133.42, 128.69, 128.15, 126.21, 124.22, 122.93, 109.16, 41.00, 40.05, 39.05, 33.19, 29.81, 26.01, 21.84; HRMS (ESI-TOF) calcd for $C_{21}H_{23}BrNO_2$ $[M+H]^+$ 400.0907, found 400.0907.

4.3 Synthesis of **5**

In air, 3-alkenyl-2-oxoindole (**3a**, 0.2 mmol) and Lawesson's reagent (1 equiv., 0.2 mmol) were added to a Schlenk tube equipped with a stirring bar. The vessel was evacuated and filled with N_2 (three cycles). PhMe (2 mL) was added in turn by syringe under N_2 atmosphere. The resulting reaction mixture was stirred vigorously at 110 ℃ for 1 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate, V∶V=20∶1) to give 8-methyl-2-phenyl-8*H*-thieno[2,3-*b*]indole (**5**). ^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.85 (dt, J=7.8, 1.0 Hz, 1H), 7.70～7.63 (m, 3H), 7.42 (t, J=7.8 Hz, 2H), 7.38～7.32 (m, 2H), 7.27 (dddd, J=15.9, 8.0, 4.5, 1.3 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ: 144.08, 142.02, 135.82, 135.75, 128.99, 126.63, 125.16, 123.56, 122.26, 122.05, 119.59, 119.37, 114.32, 109.16, 32.29; HRMS (ESI-TOF) calcd for $C_{17}H_{14}NS$ $[M+H]^+$ 264.0841, found 264.0843.

Supporting Information The detailed procedure for the synthesis of **3** and **5**, and ^{1}H NMR and ^{13}C NMR spectra of compounds **3** and **5**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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