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Catalyst-Controlled Chemoselective Reaction of 3-Indolylmethanols with Cyclic Enaminones Leading to C2-Functionalized Indoles

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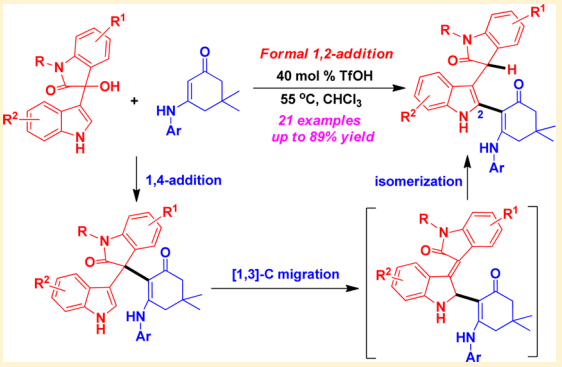
Supporting Information

ABSTRACT: A catalyst-controlled chemoselective formal 1,2-addition of 3-indolylmethanols with cyclic enaminones has been established in the presence of TfOH as a strong acid, which afforded C2-functionalized indole derivatives in generally good yields (up to 89% yield). This reaction not only confronted the great challenge in 1,2-addition of 3-indolylmethanols but also provided a good strategy for C2-functionalization of indole derivatives. The investigation on the reaction mechanism revealed that this formal 1,2-addition included a tandem sequence of 1,4-addition/[1,3]-C migration/isomerization, in which the [1,3]-C migration of the 1,4-addition product was a key step and the acidity of the catalyst played a decisive role in the observed chemoselectivity.



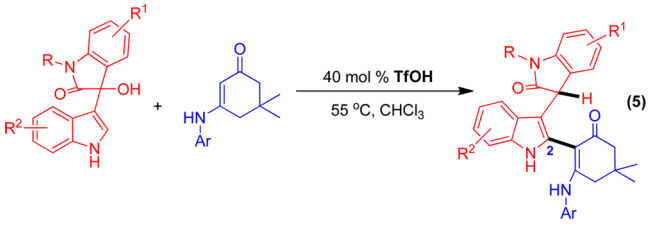
INTRODUCTION

The functionalization of indoles has become one of the most intriguing issues in the community of organic chemistry[1] because the indole scaffold exists in a lot of natural products and man-made compounds with biological significance.[2] Among numerous approaches, the formal substitution of 3-indolylmethanols by nucleophiles has proven to be an efficient method to obtain functionalized indoles, which proceeds via a 1,4-addition to vinyliminium intermediates produced from 3-indolylmethanols in the presence of an acid (Scheme 1).[3,4] As a result, elegant developments have been achieved in the 1,4-additions of 3-indolylmethanols, leading to the production of C3-functionalized indoles (eq 1).[4] *On the contrary, the 1,2-additions of 3-indolylmethanols have rarely been reported because the vinyliminium intermediates have little tendency to perform this unusual transformation (eq 2) despite the fact that this transformation will generate C2-functionalized indoles.*[5] Therefore, the 1,2-additions of 3-indolylmethanols become much more challenging, which require intensive investigation.

On the other hand, due to the importance of cyclic enaminones both in synthetic chemistry as versatile building blocks[6] and in medicinal chemistry as potential drug candidates,[7] the reactions of 3-indolylmethanols with cyclic enaminones have attracted much attention from the organic community for the purpose of synthesizing functionalized indoles bearing a cyclic enaminone motif (Scheme 2).[4l,8] Ji, Wang, and co-workers established an elegant work on iodine-catalyzed formal [3 + 3] cycloadditions of isatin-derived 3-indolylmethanols with cyclic enaminones, leading to the construction of a spirodihydrocarboline framework **1** (eq 3).[8] We also reported a chiral phosphoric acid[9] (CPA)-catalyzed enantioselective 1,4-addition of 3-indolylmethanols with cyclic enaminones to afford enantioselective indole derivatives **2** (eq 4).[4l] Interestingly, although the two reactions employed the same type of reactants, the chemoselectivity of the reactions varied greatly, which indicated that the reaction conditions played a crucial role in the chemoselectivity.

Considering the great challenge in 1,2-addition of 3-indolylmethanols and as a continuation of our interests in 3-indolylmethanol-involved transformations,[4k,l,10] we wondered whether the 1,2-addition of 3-indolylmethanols with cyclic enaminones could take place under other reaction conditions such as stronger acidic catalyst and higher reaction temperature. Fortunately, when we treat the same reaction in the presence of trifluoromethanesulfonic acid (TfOH) at 55 °C, a desired 1,2-addition reaction occurred and thus accomplished the C2-functionalization of 3-indolylmethanols (eq 5). Herein, we report the details on this chemoselective 1,2-addition of 3-indolylmethanols with cyclic enaminones leading to efficient synthesis of C2-functionalized indoles in high yields (up to 89% yield).

This work: 1,2-addition of 3-indolylmethanols with cyclic enaminones



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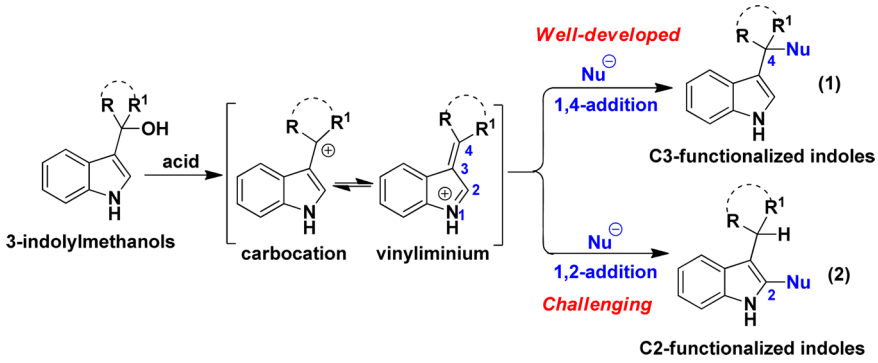
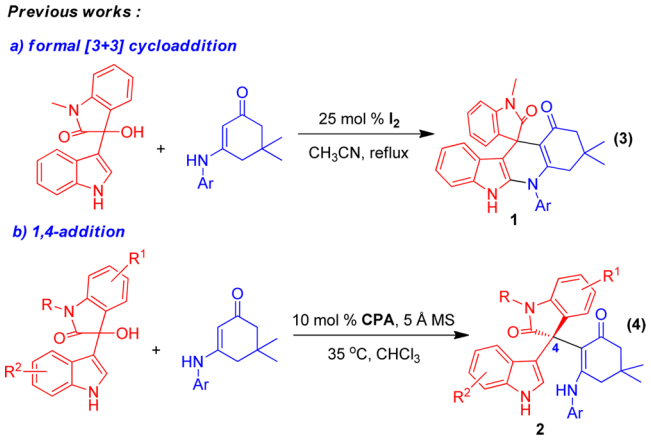
Scheme 1. Profile of 3-Indolylmethanol-Involved Additions



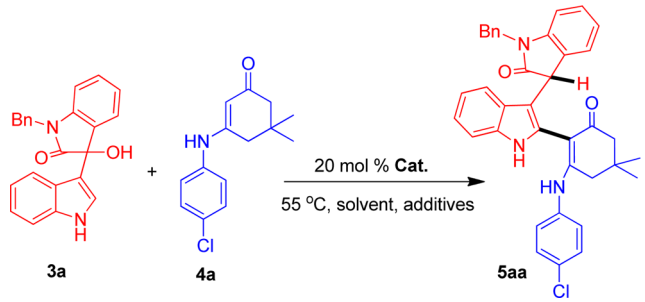
Scheme 2. Previous Works on the Reactions of 3-Indolylmethanols with Cyclic Enaminones



RESULTS AND DISCUSSION

Initially, the reaction of *N*-benzyl isatin-derived 3-indolylmethanol **3a** and dimedone-derived enaminone **2a** at 55 °C in the presence of 20 mol % TfOH was employed to investigate the influence of conditions on the chemoselectivity of the reaction. To our delight, this reaction afforded the desired 1,2-addition product **5aa** as a main product in a good yield of 68% (Table 1, entry 1). Because TfOH belongs to a class of strong acids (p*K*a = −15), we utilized several Brønsted acids with varied acidity to study the effect of the acidity on the reaction (entries 2−4). It was found that the acidity of the catalysts played a crucial role in the desired 1,2-addition reaction since the yields of **5aa** dropped greatly with the decrease of the acidity of the catalysts. In detail, 4-methylbenzenesulfonic acid (TsOH, p*K*a = −2.8) could catalyze the 1,2-addition reaction in a moderate yield of 55% (entry 2), while trifluoroacetic acid (p*K*a = 0.23) just gave the product **5aa** in a poor yield of 32% (entry 3). Not surprising, acetic acid with very weak acidity (p*K*a = 4.75) failed to catalyze the reaction (entry 4). Then, in the presence of TfOH as the most suitable catalyst, a series of representative solvents were evaluated (entries 1 and 5−10), which revealed that no other solvents were better than chloroform in terms of yield (entries 5−10 vs 1). In the course of generating a vinyliminium intermediate, one molecule of water was supposed to be released. Therefore, some additives such as molecular sieves (MS) and anhydrous sulfates as water absorbers were added to the reaction system (entries 11−15). However, MS seemed to be detrimental to the reaction (entries 11−13 vs 1), and anhydrous sulfates

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	solvent	additives	3a:4a	yield (%)[b]
1	TfOH	$CHCl_3$		1:1.5	68
2	TsOH	$CHCl_3$		1:1.5	55
3	CF_3CO_2H	$CHCl_3$		1:1.5	32
4	CH_3CO_2H	$CHCl_3$		1:1.5	trace
5	TfOH	$ClCH_2CH_2Cl$		1:1.5	40
6	TfOH	$Cl_2CHCHCl_2$		1:1.5	55
7	TfOH	toluene		1:1.5	21
8	TfOH	EtOAc		1:1.5	36
9	TfOH	CH_3CN		1:1.5	21
10	TfOH	1,4-dioxane		1:1.5	trace
11	TfOH	$CHCl_3$	3 Å MS	1:1.5	20
12	TfOH	$CHCl_3$	4 Å MS	1:1.5	31
13	TfOH	$CHCl_3$	5 Å MS	1:1.5	20
14	TfOH	$CHCl_3$	$MgSO_4$	1:1.5	59
15	TfOH	$CHCl_3$	Na_2SO_4	1:1.5	63
16	TfOH	$CHCl_3$		1:1	51
17	TfOH	$CHCl_3$		1:3.5	23
18	TfOH	$CHCl_3$		1.5:1	43
19	TfOH	$CHCl_3$		2.5:1	31
20[c]	TfOH	$CHCl_3$		1:1.5	56
21[d]	TfOH	$CHCl_3$		1:1.5	60
22[e]	TfOH	$CHCl_3$		1:1.5	88

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale catalyzed by 20 mol % cat. in solvent (1 mL) at 55 °C for 48 h. [b]Isolated yield. [c]5 mol % TfOH was used. [d]10 mol % TfOH was used. [e]40 mol % TfOH was used.

could not further improve the yield (entries 14−15 vs 1). Hence, in the absence of any additives, the reagent ratio was carefully modulated. Nevertheless, neither varying the stoichiometry of **4a** nor increasing the usage of **3a** could enhance the yield (entries 16−19 vs 1). Finally, the impact of catalyst loading on the reaction was studied (entries 20−22), which disclosed that properly increasing the mole percentage of catalyst could remarkably increase the yield to a high level of 88% (entry 22).

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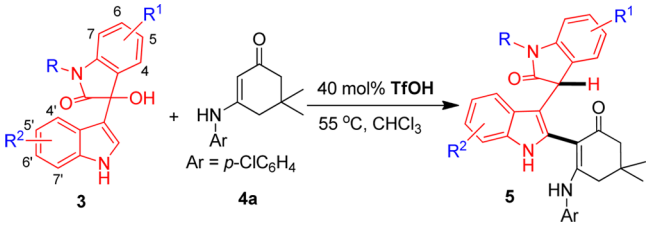
With the optimal conditions known, we then carried out the investigation on the substrate scope of the reaction. As shown in Table 2, a variety of isatin-derived 3-indolylmethanols **3** with

Table 2. Substrate Scope of Isatin-Derived 3-Indolylmethanols 3[a,b]



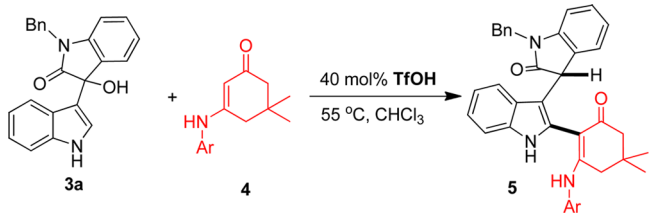
entry	5	R/R^1/R^2 (3)	yield (%)[b]
1	**5aa**	Bn/H/H (**3a**)	88
2	**5ba**	*p*-$CH_3C_6H_4CH_2$/H/H (**3b**)	69
3	**5ca**	*p*-*t*-$BuC_6H_4CH_2$/H/H (**3c**)	66
4	**5da**	*m*-$ClC_6H_4CH_2$/H/H (**3d**)	66
5	**5ea**	CH_3/H/H (**3e**)	44
6	**5fa**	Bn/4-Br/H (**3f**)	52
7	**5ga**	Bn/5-CH_3/H (**3g**)	65
8	**5ha**	Bn/5-Cl/H (**3h**)	75
9	**5ia**	Bn/6-Cl/H (**3i**)	60
10	**5ja**	Bn/7-CH_3/H (**3j**)	59
11	**5ka**	Bn/H/5'-CH_3 (**3k**)	66
12	**5la**	Bn/H/5'-Br (**3l**)	52
13	**5ma**	Bn/H/6'-CH_3 (**3m**)	85
14	**5na**	Bn/H/6'-F (**3n**)	82
15	**5oa**	Bn/H/6'-Cl (**3o**)	87
16	**5pa**	Bn/H/7'-CH_3 (**3p**)	80
17	**5qa**	Bn/H/7'-Br (**3q**)	82

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale catalyzed by 40 mol % TfOH in chloroform (1 mL) at 55 °C for 48 h, and the ratio of **3**:**4a** was 1:1.5. [b]Isolated yield.

different R/R^1/R^2 groups were amenable to the unusual 1,2-addition reaction, affording the desired C2-functionalized products **5** in generally good yields. In detail, both *N*-benzyl groups and *N*-methyl group were applicable to the reaction (entries 1−5) and there was no obvious difference among various *N*-benzyl groups regardless of their electronic nature (entries 2−4). However, the *N*-methyl group exhibited much lower reactivity than *N*-benzyl ones in terms of yield (entry 5 vs 1−4). Besides, a series of *N*-benzyl isatin-derived 3-indolylmethanols bearing either electron-donating or electron-withdrawing R^1 groups at C4−C7 positions of the isatin moiety could smoothly take part in the reaction to generate the anticipated products **5** (entries 6−10). Moreover, the R^2 substituents at different positions of the indole moiety could also be successfully altered, leading to C2-functionalization of 3-indolylmethanols in overall high yields (entries 11−17). It seemed that the electronic nature of the R^2 substituents had little effect on the reaction, because there was no significant difference between electron-donating and electron-withdrawing groups with regard to the yield (entry 13 vs 14−15, entry 16 vs 17). Nevertheless, the position of the substituent seemed to exert some effect on the reactivity, since C5′-substituted substrates gave much lower yields than C6′- and C7′-substituted counterparts (entries 11−12 vs 13−17).

Furthermore, the applicability of this 1,2-addition reaction was examined by several enaminones **4** that were derived from different anilines bearing either electronically poor or rich substituents on the phenyl ring. As shown in Table 3, all the

Table 3. Substrate Scope of Dimedone-Derived Enaminones 2[a]



entry	5	Ar (4)	yield (%)[b]
1	**5aa**	4-ClC_6H_4 (**4a**)	88
2	**5ab**	4-FC_6H_4 (**4b**)	71
3	**5ac**	4-$PhOC_6H_4$ (**4c**)	68
4	**5ad**	4-$EtOC_6H_4$ (**4d**)	72
5	**5ae**	3,4-$(MeO)_2C_6H_3$ (**4e**)	89

[a]Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale catalyzed by 40 mol % TfOH in chloroform (1 mL) at 55 °C for 48 h, and the ratio of **3a**:**4** was 1:1.5. [b]Isolated yield.

tested enaminone substrates successfully took part in the desired reaction in good yields (68%−89%). Among them, disubstituted aniline derived substrate **4e** delivered the highest yield of 89% (entry 5).

The structures of all the products **5** were unambiguously determined by IR, ^{1}H NMR, ^{13}C NMR, and HRMS. Moreover, the structure of compound **5la** was further confirmed by single-crystal X-ray diffraction analysis.[11]

In order to gain some insight into the reaction pathway of this chemoselective 1,2-addition reaction of 3-indolylmethanols, some control experiments were carried out (Scheme 3). In our previous work,[4l] the same reactions of 3-indolylmethanols **3** with cyclic enaminones **4** under the catalysis of 3,3′-(9-anthracenyl)-substituted CPA (9-AnCPA) afforded the 1,4-addition product rather than 1,2-addition product. Therefore, it seemed that the chemoselectivity was controlled by the catalyst. To testify our hypothesis, the same reaction of 3-indolylmethanol **3a** with enaminone **4a** was carried out under the similar conditions in the presence of 10 mol % 9-AnCPA and TfOH, respectively (eqs 6−7). As expected, the 9-AnCPA-catalyzed reaction exclusively generated the corresponding 1,4-addition product **2aa** in 84% yield (eq 6). Instead, TfOH-catalyzed reaction produced the unusual 1,2-addition product **5aa** as a main product in 60% yield along with a tiny little amount of 1,4-addition product **2aa** (22% isolated yield) and the formal [3 + 3] cycloaddition product[8] **1aa** (15% isolated yield) (eq 7). This result indicated that the acidity of the catalysts played a crucial role in the chemoselectivity of the reaction, because the acidity of TfOH is much higher than that of 9-AnCPA. Besides, the 1,4-addition product **2aa** was observed as a minor product in the TfOH-catalyzed reaction (eq 7), which implied that the formation of 1,2-addition product **5** might have

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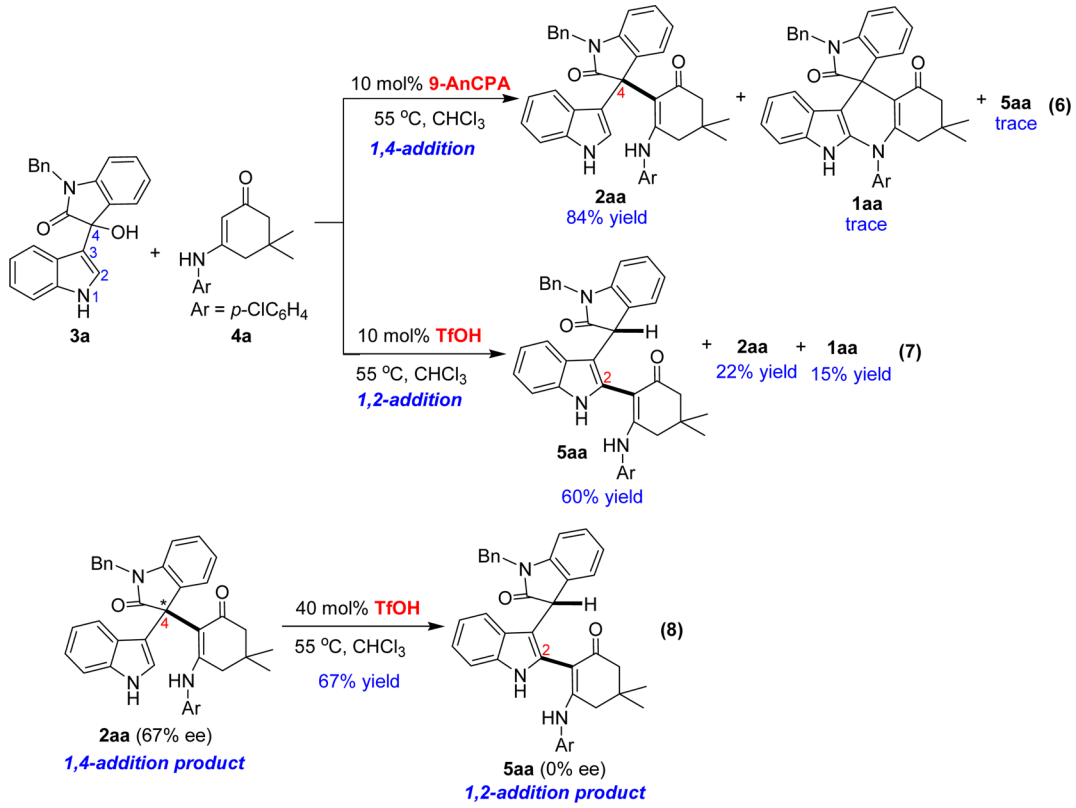
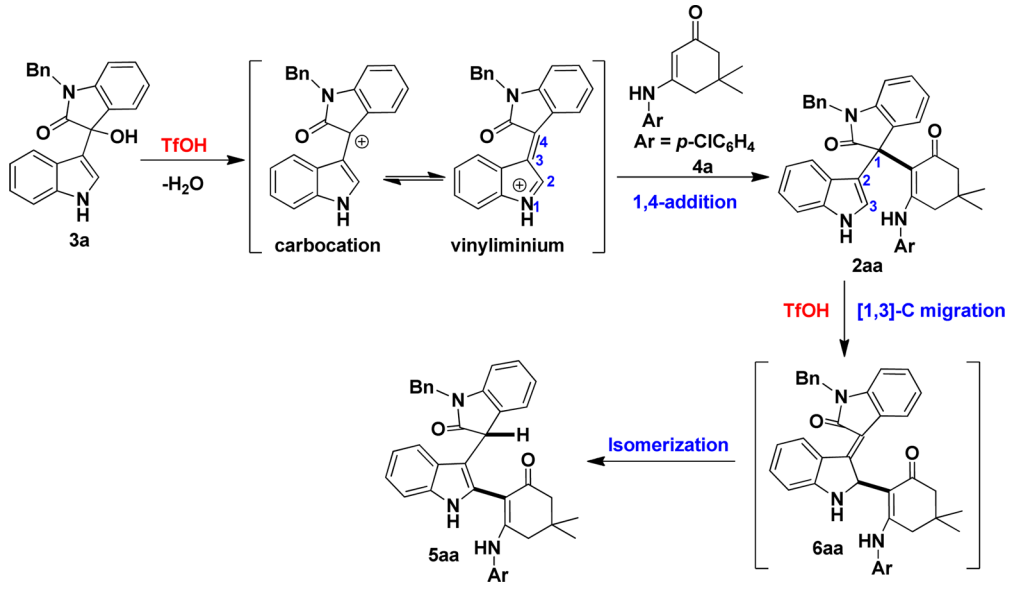
Scheme 3. Control Experiments to Investigate the Reaction Pathway



Scheme 4. Suggested Reaction Pathway



occurred via a rearrangement of 1,4-addition product **2**. For the aim to test this possible reaction pathway, the 1,4-addition product **2aa** was further subjected to the treatment of TfOH under the optimal reaction conditions for 1,2-additions (eq 8). Indeed, this reaction smoothly afforded the desired 1,4-addition product **5aa** in a yield of 67%. This transformation greatly supported our suggestion that the 1,2-addition product **5** was generated via the formation of 1,4-addition product **2**. To examine whether the enantioselectivity could be maintained or not, chiral 1,4-addition product **2aa** with 67% *ee* was employed to the same reaction, which nevertheless generated the 1,2-addition product **5aa** in a racemic form (0% *ee*, eq 8). This outcome implied that a process of racemization occurred during this transformation.

On the basis of the experimental results, we suggested a possible reaction pathway to explain the chemistry of the unusual 1,2-addtions of 3-indolylmethanols (Scheme 4). As exemplified by the formation of 1,2-addtion product **5aa**, under the catalysis of TfOH, 3-indolylmethanol **3a** was easily transformed into a carbocation or vinyliminium intermediate, which initially

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performed a Michael addition with cyclic enaminone **4a** to give the 1,4-addition product **2aa**. Then, this compound further underwent a [1,3] carbon migration in the presence of TfOH as a strong acid to generate a transient intermediate **6aa**, which was quickly isomerized into the final product **5aa**. Therefore, the experimentally observed formal 1,2-addition of 3-indolylmethanols with cyclic enaminones actually included a tandem sequence of 1,4-addition/[1,3]-C migration/isomerization. During this process, the [1,3]-C migration of 1,4-addition product was a key step that led to the formation of the formal 1,2-addition product. Besides, the acidity of the catalyst played a decisive role in the observed chemoselectivity because the [1,3]-C migration could hardly take place in the presence of a weak acid.

CONCLUSIONS

In summary, we have established a catalyst-controlled chemoselective formal 1,2-addition of 3-indolylmethanols with cyclic enaminones in the presence of TfOH as a strong acid, which afforded C2-functionalized indole derivatives in generally good yields (up to 89% yield). The investigation on the reaction mechanism revealed that this formal 1,2-addition included a tandem sequence of 1,4-addition/[1,3]-C migration/isomerization, in which the [1,3]-C migration of the 1,4-addition product was a key step and the acidity of the catalyst played a decisive role in the observed chemoselectivity. This reaction not only confronted the great challenge in 1,2-addition of 3-indolylmethanols but also provided a good strategy for C2-functionalization of indole derivatives. Besides, this approach served as a good example for catalyst-controlled chemoselectivity, which will enrich the research content of chemoselective reactions and 3-indolylmethanol-involved transformations.

EXPERIMENTAL SECTION

General Information. ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS spectra were recorded on an LTQ-Orbitrap mass spectrometer (ionization mode: ESI$^-$). Analytical grade solvents for the column chromatography and commercially available reagents were used as received. Substrates **3** and **4** were synthesized according to the literature methods.[4a,g,12]

General Procedure for the Synthesis of Products 5. Catalyst TfOH (0.04 mmol) was added to the solution of 3-indolylmethanols **3** (0.1 mmol) and cyclic enaminones **4** (0.15 mmol) in chloroform (1 mL). Then, the reaction mixture was stirred at 55 °C for 48 h. After stopping the reaction, the reaction mixture was directly purified through flash column chromatography on silica gel to afford pure products **5**.

*1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5aa**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 88% (51.4 mg); pale yellow solid; m.p.153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.59 (s, 1H), 7.41 (d, J = 6.7 Hz, 2H), 7.38−7.31 (m, 3H), 7.29 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 7.13−7.07 (m, 3H), 6.99−6.92 (m, 2H), 6.90 (t, J = 7.6 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 6.45 (d, J = 7.8 Hz, 1H), 5.17 (d, J = 15.3 Hz, 1H), 4.89 (d, J = 15.3 Hz, 1H), 4.76 (s, 1H), 2.60 (d, J = 16.5 Hz, 1H), 2.45 (d, J = 18.5 Hz, 3H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 177.6, 161.3, 143.0, 137.0, 135.9, 131.4, 130.6, 129.3, 129.2, 128.8, 128.1, 128.0, 127.9, 126.8, 125.8, 125.4, 123.2, 122.0, 119.2, 118.4, 111.3, 109.5, 109.0, 103.5, 50.8, 44.9, 44.4, 41.0, 32.9, 29.1, 27.7; IR (KBr): 3294, 2958, 1704, 1610, 1546, 1492, 1462, 1394, 1274, 1217, 1159, 1091, 1012, 830, 746, 699 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{32}ClN_3O_2 - H)^-$ requires m/z 584.2105, found m/z 584.2109.

*3-(2-(2-((4-Chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)-1-(4-methylbenzyl)indolin-2-one (**5ba**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 69% (41.4 mg); pale yellow solid; mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63(s, 1H), 8.53 (s, 1H), 7.32−7.27 (m, 4H), 7.23−7.18 (m, 2H), 7.16−7.09 (m, 5H), 7.01−6.89 (m, 3H), 6.69 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 7.9 Hz, 1H), 5.11 (d, J = 15.2 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.73 (s, 1H), 2.66−2.52 (m, 1H), 2.50−2.40 (m, 3H), 2.35 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 177.6, 161.2, 143.0, 137.6, 137.1, 137.0, 132.9, 131.5, 129.4, 129.3, 129.2, 128.0, 128.0, 126.9, 125.4, 123.1, 122.1, 119.3, 118.5, 111.2, 109.7, 109.0, 103.4, 50.9, 44.9, 44.1, 41.1, 32.9, 29.1, 27.7, 21.2, 1.1; IR (KBr): 3744, 3281, 2956, 2362, 1705, 1546, 1491, 1462, 1394, 1270, 1163, 1095, 1012, 812, 747, 680 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{38}H_{34}ClN_3O_2 - H)^-$ requires m/z 598.2262, found m/z 598.2273.

*1-(4-(tert-Butyl)benzyl)-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ca**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 66% (42.3 mg); pale yellow solid; mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H) 8.54 (s, 1H), 7.37−7.28 (m, 6H), 7.22 (d, J = 8.2 Hz, 2H), 7.14−7.09 (m, 3H), 7.01−6.92 (m, 3H), 6.67 (s, 1H), 6.43 (d, J = 7.9 Hz, 1H), 5.06 (d, J = 15.2 Hz, 1H), 4.88 (d, J = 15.2 Hz, 1H), 4.72 (s, 1H), 2.60−2.41 (m, 4H), 1.33 (s, 9H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 177.5, 161.1, 150.8, 143.1, 137.1, 137.0, 132.9, 131.4, 130.7, 129.3, 129.2, 128.0, 127.8, 126.8, 125.9, 125.7, 125.4, 123.1, 122.1, 119.3, 118.5, 111.2, 109.7, 109.0, 103.4, 50.9, 44.9, 44.0, 41.1, 34.6, 32.9, 31.4, 29.0, 27.7; IR (KBr): 3744, 3288, 2959, 2362, 1705, 1547, 1492, 1463, 1271, 1162, 1094, 1017, 745, 686 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{41}H_{40}ClN_3O_2 - H)^-$ requires m/z 640.2731, found m/z 640.2726.

*1-(3-Chlorobenzyl)-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5da**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 66% (40.6 mg); pale yellow solid; mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.51 (s, 1H), 7.39 (s, 1H), 7.32−7.27 (m, 5H), 7.23−7.20 (m, 2H), 7.15−7.09 (m, 3H), 7.01−6.94 (m, 2H), 6.88 (d, J = 7.8 Hz, 1H), 6.73 (t, J = 7.4 Hz, 1H), 6.45 (d, J = 7.9 Hz, 1H), 5.10 (d, J = 15.5 Hz, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.75 (s, 1H), 2.62−2.42 (m, 4H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 177.6, 161.3, 142.7, 138.0, 137.0, 134.8, 131.6, 130.8, 130.1, 129.3, 129.1, 128.2, 127.9, 126.9, 126.1, 125.8, 125.6, 123.4, 122.2, 119.5, 118.3, 111.3, 109.5, 108.7, 103.3, 50.8, 44.9, 43.8, 41.0, 32.8, 29.0, 27.8; IR (KBr): 3742, 3279, 2957, 2362, 1705, 1547, 1491, 1464, 1394, 1273, 1092, 1013, 748, 686 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{37}H_{31}Cl_2N_3O_2 - H)^-$ requires m/z 618.1715, found m/z 618.1744.

*3-(2-(2-((4-Chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)-1-methylindolin-2-one (**5ea**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 44% (22.3 mg); pale yellow solid; mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.42 (s, 1H), 7.32−7.28 (m, 3H), 7.23 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.4 Hz, 3H), 7.01−6.95 (m, 3H), 6.77 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 7.9 Hz, 1H), 4.64 (s, 1H), 3.35 (s, 3H), 2.63−2.56 (m, 1H), 2.47−2.39 (m, 3H), 1.16 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 177.4, 161.2, 143.9, 137.0, 131.5, 130.6, 129.3, 129.1, 128.2, 126.7, 125.3, 123.2, 122.1, 119.4, 118.2, 111.2, 109.9, 107.9, 103.4, 50.8, 44.8, 41.0, 32.9, 29.7, 29.2, 27.5, 26.6; IR (KBr): 3559, 3495, 3388, 2928, 2363, 1704, 1614, 1546, 1493, 1395, 1273, 1089, 748, 680 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{31}H_{28}ClN_3O_2 - H)^-$ requires m/z 508.1792, found m/z 508.1809.

*1-Benzyl-4-bromo-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5fa**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 52% (34.4 mg); pale yellow solid; mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67−8.60 (m, 1H), 8.40−8.37 (m, 1H), 7.19−7.17 (m, 2H), 7.16−7.12 (m, 4H), 7.11−7.08 (m, 3H), 7.06−7.03 (m, 2H), 6.95 (t, J = 8.0 Hz, 1H), 6.56−6.53 (m, 1H), 6.51 (d, J = 2.6 Hz, 1H), 6.06 (d, J = 8.6 Hz, 2H), 4.88 (d, J = 16.2 Hz, 1H), 4.74 (d, J = 16.2 Hz, 1H), 2.32−2.19 (m, 4H), 1.67 (s, 1H), 1.19 (s, 3H),

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1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 177.5, 160.6, 145.7, 137.3, 136.5, 136.2, 131.5, 131.3, 129.1, 129.0, 128.5, 127.0, 126.3, 125.8, 123.7, 123.2, 123.1, 120.5, 117.7, 111.9, 109.9, 108.3, 105.1, 55.3, 50.3, 44.2, 41.7, 32.1, 29.2, 27.3, 1.1; IR (KBr): 3743, 3314, 2957, 2362, 1721, 1561, 1455, 1399, 1328, 1275, 1228, 738, 697 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{31}BrClN_3O_2 - H)^-$ requires m/z 662.1210, found m/z 662.1204.

1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)-5-methylindolin-2-one (**5ga**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 65% (38.6 mg); pale yellow solid; mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.53 (s, 1H), 7.40−7.36 (m, 2H), 7.35−7.28 (m, 5H), 7.22 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.02−6.94 (m, 3H), 6.80 (d, J = 7.9 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.45 (d, J = 7.9 Hz, 1H), 5.13 (d, J = 15.3 Hz, 1H), 4.85 (d, J = 15.3 Hz, 1H), 4.71 (s, 1H), 2.63−2.56 (m, 1H), 2.51−2.41 (m, 3H), 2.18 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 177.6, 161.3, 140.6, 137.1, 137.0, 136.0, 132.8, 131.5, 130.6, 129.3, 129.1, 128.8, 128.3, 128.0, 127.8, 126.9, 126.1, 122.1, 119.3, 118.6, 111.2, 109.9, 108.7, 103.4, 50.9, 44.9, 44.4, 41.1, 32.9, 29.1, 27.8, 20.9; IR (KBr): 3743, 3284, 2956, 2362, 1701, 1547, 1494, 1393, 1273, 810, 736, 695 cm^{-1}; ESI FTMS exact mass calcd for $(C_{38}H_{34}ClN_3O_2 - H)^-$ requires m/z 598.2262, found m/z 598.2277.

1-Benzyl-5-chloro-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ha**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 75% (46.5 mg); pale yellow solid; mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.48 (s, 1H), 7.37−7.34 (m, 4H), 7.33−7.32 (m, 1H), 7.31−7.28 (m, 2H), 7.22−7.17 (m, 2H), 7.13−7.09 (m, 3H), 7.01−6.96 (m, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 5.14 (d, J = 15.3 Hz, 1H), 4.83 (d, J = 15.3 Hz, 1H), 4.72 (s, 1H), 2.62−2.55 (m, 1H), 2.48−2.42 (m, 3H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 177.2, 161.4, 141.5, 137.0, 137.0, 135.5, 131.6, 130.8, 129.3, 128.9, 128.8, 128.1, 128.1, 128.0, 126.9, 125.7, 125.7, 122.2, 119.4, 118.3, 111.3, 109.9, 108.9, 103.2, 50.8, 44.9, 44.5, 41.0, 32.9, 28.9, 27.9; IR (KBr): 3732, 3622, 3283, 2956, 2362, 1707, 1547, 1489, 1394, 1272, 813, 738, 673 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{31}Cl_2N_3O_2 - H)^-$ requires m/z 618.1715, found m/z 618.1728.

1-Benzyl-6-chloro-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ia**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 60% (36.8 mg); pale yellow solid; mp 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.32 (s, 1H), 7.37−7.33 (m, 5H), 7.32−7.29 (m, 3H), 7.11 (d, J = 8.5 Hz, 2H), 7.06 (t, J = 7.7 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.93−6.89 (m, 2H), 6.74 (t, J = 7.4 Hz, 1H), 6.43 (d, J = 7.9 Hz, 1H), 5.11 (d, J = 15.3 Hz, 1H), 4.83 (d, J = 15.3 Hz, 1H), 4.67 (s, 1H), 2.63−2.56 (m, 1H), 2.48−2.42 (m, 3H), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 177.6, 161.2, 144.1, 136.9, 135.4, 133.8, 131.6, 129.3, 128.9, 128.1, 127.9, 127.4, 126.8, 126.3, 123.1, 122.3, 119.6, 118.4, 111.3, 109.6, 109.2, 103.2, 50.8, 44.5, 41.0, 32.9, 29.7, 29.0, 27.8; IR (KBr): 3555, 3415, 3236, 2363, 2026, 1617, 1546, 1492, 1398, 622 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{31}Cl_2N_3O_2 - H)^-$ requires m/z 618.1715, found m/z 618.1727.

1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)-7-methylindolin-2-one (**5ja**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 59% (35.5 mg); pale yellow solid; mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.54 (s, 1H), 7.35−7.31 (m, 2H), 7.29−7.26 (m, 3H), 7.25−7.23 (m, 3H), 7.08 (d, J = 8.7 Hz, 2H), 7.04−6.97 (m, 3H), 6.88 (t, J = 7.5 Hz, 1H), 6.79 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 7.9 Hz, 1H), 5.35−5.21 (m, 2H), 4.76 (s, 1H), 2.64−2.54 (m, 1H), 2.48−2.41 (m, 6H), 1.16 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 178.7, 161.3, 141.1, 137.7, 137.1, 137.0, 132.1, 131.4, 130.9, 129.8, 129.2, 128.8, 127.4, 126.8, 126.3, 125.9, 123.5, 123.3, 122.1, 119.6, 119.3, 118.6, 111.3, 109.9, 103.5, 50.9, 45.7, 44.6, 41.1, 32.9, 29.1, 27.7, 19.0; IR (KBr): 3743, 3275, 2957, 2362, 1700, 1547, 1494, 1394, 1273, 1181, 1017, 731 cm^{-1}; ESI FTMS exact mass calcd for $(C_{38}H_{34}ClN_3O_2 - H)^-$ requires m/z 598.2262, found m/z 598.2277.

1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-methyl-1H-indol-3-yl)indolin-2-one (**5ka**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 66% (39.6 mg); pale yellow solid; mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.45 (s, 1H), 7.43 (d, J = 6.7 Hz, 2H), 7.37−7.32 (m, 3H), 7.31 (s, 1H), 7.28 (s, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.14−7.11 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 7.4 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.82−6.78 (m, 1H), 6.25 (s, 1H), 5.26 (d, J = 15.3 Hz, 1H), 4.78 (d, J = 15.3 Hz, 1H), 4.70 (s, 1H), 2.65−2.57 (m, 1H), 2.47−2.40 (m, 3H), 2.08 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 177.7, 161.2, 143.0, 137.1, 136.1, 135.4, 131.4, 130.72 129.3, 129.2, 128.8, 128.5, 128.0, 127.8, 126.8, 125.4, 123.7, 123.2, 118.0, 111.0, 109.2, 108.9, 103.6, 50.8, 44.9, 44.4, 41.0, 32.9, 29.1, 27.7, 21.4, 1.0; IR (KBr): 3556, 3484, 3236, 2956, 2363, 2029, 1704, 1617, 1547, 1491, 1394, 751, 623 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{38}H_{34}ClN_3O_2 - H)^-$ requires m/z 598.2262, found m/z 598.2272.

1-Benzyl-3-(5-bromo-2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5la**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 52% (34.2 mg); pale yellow solid; mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.56 (s, 1H), 7.41−7.36 (m, 4H), 7.32−7.28 (m, 3H), 7.23 (d, J = 7.8 Hz, 1H), 7.14−7.08 (m, 3H), 6.99 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.86−6.75 (m, 2H), 6.57 (s, 1H), 5.21 (d, J = 15.4 Hz, 1H), 4.82 (d, J = 15.4 Hz, 1H), 4.73−4.66 (m, 1H), 2.61−2.41 (m, 4H), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 177.4, 161.7, 142.9, 136.8, 135.7, 131.9, 131.7, 129.3, 129.1, 128.6, 128.4, 127.9, 127.6, 127.0, 125.0, 124.9, 123.3, 120.4, 112.6, 112.6, 109.3, 109.0, 103.0, 50.8, 44.7, 44.5, 41.0, 32.8, 29.7, 29.0, 27.8, 1.0; IR (KBr): 3631, 3269, 2927, 2365, 1704, 1543, 1391, 1274, 1220, 973, 750 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{37}H_{31}BrClN_3O_2 - H)^-$ requires m/z 662.1210, found m/z 662.1203.

1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-6-methyl-1H-indol-3-yl)indolin-2-one (**5ma**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 85% (51.1 mg); pale yellow solid; mp 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.55 (s, 1H), 7.41 (d, J = 6.5 Hz, 2H), 7.37−7.32 (m, 3H), 7.29 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.69 (s, 1H), 6.41 (d, J = 8.1 Hz, 1H), 6.30 (d, J = 8.1 Hz, 1H), 5.15 (d, J = 15.3 Hz, 1H), 4.88 (d, J = 15.3 Hz, 1H), 4.71 (s, 1H), 2.64−2.57 (m, 1H), 2.49−2.41 (m, 3H), 2.07 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 177.6, 161.3, 143.0, 137.6, 137.1, 136.0, 131.6, 131.4, 129.4, 129.3, 128.8, 128.0, 127.8, 126.8, 125.4, 123.1, 120.9, 117.7, 111.2, 109.3, 108.9, 103.8, 50.9, 44.9, 44.3, 41.0, 32.9, 29.7, 29.1, 27.8, 21.5; IR (KBr): 3554, 3480, 3415, 3236, 2957, 2363, 2028, 1705, 1616, 1547, 1389, 1270, 1091, 751, 624 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{38}H_{34}ClN_3O_2 - H)^-$ requires m/z 598.2262, found m/z 598.2265.

1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-6-fluoro-1H-indol-3-yl)indolin-2-one (**5na**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 82% (49.2 mg); pale yellow solid; mp 148−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.63 (s, 1H), 7.39−7.36 (m, 2H), 7.34−7.28 (m, 5H), 7.23 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.11 (d, J = 8.6 Hz, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.60−6.56 (m, 1H), 6.35−6.29 (m, 1H), 6.28−6.21 (m, 1H), 5.14 (d, J = 15.2 Hz, 1H), 4.85 (d, J = 15.2 Hz, 1H), 4.72 (s, 1H), 2.62−2.53 (m, 1H), 2.48−2.42 (m, 3H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 177.6, 161.6, 142.9, 137.0, 135.9, 131.6, 129.3, 129.0, 128.8, 128.2, 128.0, 127.9, 127.0, 125.4, 123.3, 122.2, 118.9, 109.5, 109.1, 103.3, 50.8, 44.8, 44.4, 41.0, 32.8, 29.0, 27.8; IR (KBr): 3555, 3414, 2957, 2363, 1704, 1616, 1549, 1492, 1392, 1273, 1093, 751, 619 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{31}ClFN_3O_2 - H)^-$ requires m/z 602.2011, found m/z 602.2028.

1-Benzyl-3-(6-chloro-2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5oa**). Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 87% (53.8 mg); pale yellow solid; mp 156−

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157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.60 (s, 1H), 7.39−7.36 (m, 2H), 7.34−7.27 (m, 5H), 7.22 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 1.5 Hz, 1H), 6.51−6.46 (m, 1H), 6.27 (d, J = 8.5 Hz, 1H), 5.14 (d, J = 15.3 Hz, 1H), 4.85 (d, J = 15.3 Hz, 1H), 4.70 (s, 1H), 2.60−2.40 (m, 4H), 1.18 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 177.5, 161.9, 142.9, 137.4, 136.9, 135.8, 131.7, 129.3, 129.0, 128.8, 128.2, 128.0, 127.9, 127.7, 127.0, 125.4, 123.4, 119.8, 118.9, 110.9, 109.5, 109.1, 103.2, 50.8, 44.7, 44.4, 41.0, 32.8, 29.7, 29.0, 27.8; IR (KBr): 3653, 3301, 2957, 2362, 1704, 1543, 1462, 1389, 1272, 1014, 806, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{31}Cl_2N_3O_2 - H)^-$ requires m/z 618.1715, found m/z 618.1743.

*1-Benzyl-3-(2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-7-methyl-1H-indol-3-yl)indolin-2-one (**5pa**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 80% (47.8 mg); pale yellow solid; mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.57 (s, 1H), 7.42−7.39 (m, 2H), 7.37−7.29 (m, 5H), 7.22 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 7.3 Hz, 1H), 6.97−6.90 (m, 2H), 6.75 (d, J = 7.1 Hz, 1H), 6.62 (t, J = 7.5 Hz, 1H), 6.31 (d, J = 7.9 Hz, 1H), 5.17 (d, J = 15.3 Hz, 1H), 4.87 (d, J = 15.3 Hz, 1H), 4.73 (s, 1H), 2.67−2.58 (m, 1H), 2.51−2.44 (m, 3H), 2.24 (s, 3H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 177.6, 161.3, 143.0, 137.1, 136.6, 135.9, 131.4, 130.3, 129.3, 129.2, 128.8, 128.0, 127.9, 126.8, 125.4, 123.1, 122.7, 120.6, 119.5, 116.1, 110.2, 108.9, 103.6, 50.9, 45.0, 44.4, 41.1, 33.0, 29.5, 27.5, 16.5, 1.1; IR (KBr): 3741, 3290, 2956, 2362, 1704, 1548, 1492, 1392, 1271, 1172, 1090, 748 cm^{-1}; ESI FTMS exact mass calcd for $(C_{38}H_{34}ClN_3O_2 - H)^-$ requires m/z 598.2262, found m/z 598.2280.

*1-Benzyl-3-(7-bromo-2-(2-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5qa**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 82% (54.2 mg); pale yellow solid; mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.50 (s, 1H), 7.40−7.36 (m, 2H), 7.34−7.29 (m, 5H), 7.22 (d, J = 7.6 Hz, 2H), 7.14−7.10 (m, 3H), 6.98−6.92 (m, 2H), 6.59 (d, J = 7.7 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 5.16 (d, J = 15.3 Hz, 1H), 4.85 (d, J = 15.3 Hz, 1H), 4.71 (s, 1H), 2.66−2.56 (m, 1H), 2.48−2.41 (m, 3H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 177.4, 161.6, 142.9, 136.9, 135.8, 135.7, 131.6, 129.3, 128.8, 128.7, 128.3, 128.0, 128.0, 127.2, 126.9, 125.5, 124.6, 123.3, 120.6, 117.8, 111.2, 109.1, 104.8, 102.7, 50.8, 44.9, 44.4, 41.1, 32.9, 29.2, 27.6; IR (KBr): 3555, 3414, 3235, 2956, 2363, 2028, 1704, 1616, 1491, 1389, 1216, 749, 623 cm^{-1}; ESI FTMS exact mass calcd for $(C_{37}H_{31}BrClN_3O_2 - H)^-$ requires m/z 662.1210, found m/z 662.1214.

*1-Benzyl-3-(2-(2-((4-fluorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ab**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 71% (40.2 mg); pale yellow solid; mp 148−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.53 (s, 1H), 7.42−7.38 (m, 2H), 7.37−7.30 (m, 3H), 7.24−7.18 (m, 2H), 7.16−7.11 (m, 3H), 7.06−7.00 (m, 2H), 6.99−6.90 (m, 3H), 6.68 (t, J = 7.4 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 5.15 (d, J = 15.3 Hz, 1H), 4.88 (d, J = 15.3 Hz, 1H), 4.76 (s, 1H), 2.59−2.50 (m, 1H), 2.46 (s, 2H), 2.44−2.36 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 177.6, 161.8, 143.0, 137.0, 136.0, 134.4, 134.4, 130.9, 129.2, 128.8, 128.0, 128.0, 127.9, 127.8, 127.7, 125.8, 125.4, 123.2, 122.0, 119.3, 118.5, 116.2, 115.9, 111.2, 109.6, 108.9, 102.7, 50.8, 44.9, 44.4, 41.0, 32.7, 29.1, 27.8; IR (KBr): 3742, 3303, 2957, 2362, 1704, 1547, 1510, 1394, 1211, 1016, 745 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{37}H_{32}FN_3O_2 - H)^-$ requires m/z 568.2401, found m/z 568.2411.

*1-Benzyl-3-(2-(4,4-dimethyl-6-oxo-2-((4-phenoxyphenyl)amino)-cyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ac**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 68% (43.8 mg); pale yellow solid; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.51 (s, 1H), 7.43−7.28 (m, 7H), 7.25−7.18 (m, 2H), 7.16−7.10 (m, 4H), 7.06−6.89 (m, 7H), 6.69 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 7.9 Hz, 1H), 5.15 (d, J = 15.3 Hz, 1H), 4.89 (d, J = 15.3 Hz, 1H), 4.78 (s, 1H), 2.64−2.41 (m, 4H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 177.6, 162.0, 156.7, 155.7, 143.0, 137.0, 136.0, 133.3, 131.0, 129.9, 129.2, 128.8, 128.0, 127.8, 127.5, 125.9, 125.4, 123.7, 123.2, 122.0, 119.3, 119.0, 118.5, 111.2, 109.6, 108.9, 102.4, 50.9, 44.9, 44.3, 41.0, 32.7, 29.1, 27.8; IR (KBr): 3740, 3621, 3280, 3057, 2956, 2362, 1705, 1547, 1395, 1240, 746, 694 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{43}H_{37}N_3O_3 - H)^-$ requires m/z 642.2757, found m/z 642.2775.

*1-Benzyl-3-(2-(2-((4-ethoxyphenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ad**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 72% (42.9 mg); pale yellow solid; mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.43 (s, 1H), 7.41 (d, J = 6.5 Hz, 2H), 7.36−7.28 (m, 3H), 7.24−7.18 (m, 2H), 7.13 (d, J = 7.3 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.01−6.89 (m, 3H), 6.86 (d, J = 8.9 Hz, 2H), 6.68 (t, J = 7.4 Hz, 1H), 6.45 (d, J = 7.9 Hz, 1H), 5.14 (d, J = 15.3 Hz, 1H), 4.88 (d, J = 15.3 Hz, 1H), 4.79 (s, 1H), 4.06−3.97 (m, 2H), 2.56−2.35 (m, 4H), 1.42 (t, J = 7.0 Hz, 3H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 177.5, 162.6, 157.5, 143.0, 137.0, 136.0, 130.9, 129.3, 128.8, 128.0, 128.0, 127.8, 127.6, 125.4, 123.1, 121.9, 119.2, 118.4, 114.9, 111.2, 109.4, 108.8, 101.8, 63.7, 50.8, 44.9, 44.3, 40.9, 32.5, 29.0, 27.9, 14.8; IR (KBr): 3732, 3283, 2957, 2362, 1706, 1547, 1512, 1395, 1244, 745, 696 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{39}H_{37}N_3O_3 - H)^-$ requires m/z 594.2757, found m/z 594.2774.

*1-Benzyl-3-(2-(2-((3,4-dimethoxyphenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-indol-3-yl)indolin-2-one (**5ae**).* Flash column chromatography eluent, petroleum ether/ethyl acetate = 2/1; reaction time = 48 h; yield: 89% (54.4 mg); pale yellow solid; mp 148−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.44 (s, 1H), 7.44−7.38 (m, 2H), 7.36−7.29 (m, 3H), 7.23−7.18 (m, 2H), 7.13 (d, J = 7.3 Hz, 1H), 7.00−6.89 (m, 3H), 6.84−6.78 (m, 2H), 6.73−6.65 (m, 2H), 6.46 (d, J = 7.9 Hz, 1H), 5.11 (d, J = 15.3 Hz, 1H), 4.91 (d, J = 15.3 Hz, 1H), 4.78 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 2.63−2.40 (m, 4H), 1.18 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 177.6, 162.4, 149.2, 147.5, 143.0, 137.0, 136.0, 131.3, 129.3, 128.8, 128.0, 127.9, 127.9, 125.5, 123.2, 122.0, 119.2, 118.4, 118.2, 111.2, 111.0, 110.2, 109.5, 108.8, 102.0, 56.0, 56.0, 50.8, 44.9, 44.3, 40.9, 32.6, 29.2, 27.7; IR (KBr): 3743, 3623, 3308, 2957, 2362, 1705, 1547, 1514, 1461, 1398, 1259, 1027, 745 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{39}H_{37}N_3O_4 - H)^-$ requires m/z 610.2706, found m/z 610.2719.

*Compound **1aa**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.44 (d, J = 6.9 Hz, 1H), 7.35 (dd, J = 8.3, 5.3 Hz, 2H), 7.30−7.27 (m, 4H), 7.21 (t, J = 7.8 Hz, 1H), 7.12 (dd, J = 8.5, 2.4 Hz, 1H), 7.06−7.00 (m, 2H), 6.86 (dd, J = 6.4, 2.7 Hz, 2H), 6.75 (t, J = 7.5 Hz, 1H), 6.68−6.61 (m, 2H), 6.23 (d, J = 7.9 Hz, 1H), 5.02 (d, J = 15.7 Hz, 1H), 4.68 (d, J = 15.7 Hz, 1H), 2.46−2.34 (m, 2H), 2.16 (d, J = 17.2 Hz, 1H), 1.94 (d, J = 17.2 Hz, 1H), 1.08 (s, 6H).

*Compound **2aa**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.9 Hz, 1H), 8.33 (s, 1H), 7.36−7.30 (m, 2H), 7.28 (d, J = 7.5 Hz, 3H), 7.24−7.17 (m, 4H), 7.15−7.11 (m, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.97 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 6.02 (d, J = 8.5 Hz, 2H), 4.95 (d, J = 16.1 Hz, 1H), 4.81 (d, J = 16.0 Hz, 1H), 2.39 (d, J = 16.5 Hz, 1H), 2.27 (d, J = 16.6 Hz, 1H), 2.16 (t, J = 17.4 Hz, 2H), 1.19 (s, 3H), 0.98 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

Characterization data (including ^{1}H and ^{13}C NMR spectra) for all products **5**, and crystal data of compound **5la**. 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 interest.

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