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Synthesis of 3-Amino-3-hydroxymethyloxindoles and 3-Hydroxy-3-hydroxymethyloxindoles by $Rh_2(OAc)_4$-Catalyzed Three-Component Reactions of 3-Diazooxindoles with Formaldehyde and Anilines or Water

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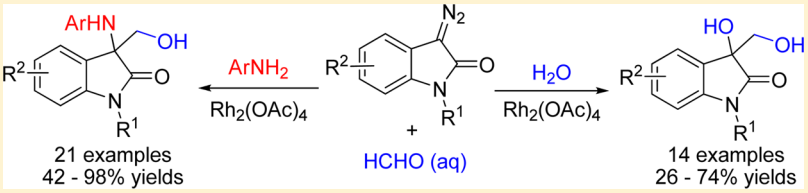
Supporting Information



ABSTRACT: Efficient Rh(II)-catalyzed three-component reactions of 3-diazooxindoles and formaldehyde with either anilines or water were developed to give a series of substituted 3-amino-3-hydroxymethyloxindoles or 3-hydroxy-3-hydroxymethyloxindoles in good to excellent yields. In this atom- and step-economic transformation, $Rh_2(OAc)_4$-catalyzed decomposition of 3-diazooxindoles with anilines or water forms the corresponding active ammonium or oxonium ylides. Electrophilic trapping of the resulting ammonium ylides or oxonium ylides by formaldehyde in the form of formalin efficiently produces the title compounds in one step.

INTRODUCTION

3,3-Disubstituted oxindoles are widely recognized as valuable structural motifs, forming the core structure of a large number of natural products and pharmaceutical agents.[1,2] Among those compounds, 3-amino-3-alkyloxindoles and 3-hydroxy-3-alkyloxindoles are readily derivatized to the central framework of an array of alkaloids that display novel biological activities.[3] For example, AG-041R has been reported as a potent gastrin/CCKB receptor antagonist that exhibits selective binding to CCKB rather than CCKA.[3a,b] Compound **A** has been used as the key precursor leading to unusual marine alkaloid chartelline A.[3c] YK-4-279 can block RNA helicase A binding to EWS-FLI1 and, therefore, shows potent anti-EWS activity.[3d] Convolutamydine A shows a potent activity in the differentiation of HL-60 human promyelocytic leukemia cells (Figure 1).[3e]

Owing to their structural importance in medicinal chemistry, a number of strategies have been developed for the synthesis of 3-amino-3-alkyloxindoles and 3-hydroxy-3-alkyloxindoles. Methods for the synthesis of 3-amino-3-alkyloxindoles include nucleophilic additions to isatin imines,[4a−c] the Ritter reaction,[4d] alkylation of 3-aminooxindoles,[4e] amination of 3-substituted oxindoles,[4f] intramolecular arylation,[4g,h] and [3 + 2] dipolar cycloadditions.[4i] On the other hand, nucleophilic addition to isatins,[5a−e] arylation and allylation of isatins,[5f−k] and direct hydroxylation of 3-alkyl-substituted oxindoles[5l−q] were generally applied for the synthesis of 3-hydroxy-3-alkyloxindole derivatives. Despite these advances, highly efficient synthetic strategies that can conveniently lead to both 3-amino-3-alkyloxindoles and 3-hydroxy-3-alkyloxindoles are still in great demand. Herein, we describe efficient rhodium(II)-catalyzed three-component reactions of 3-diazooxindoles with formaldehyde and anilines or water via aldol-type trapping of either ammonium or oxonium ylides, leading to both 3-amino-3-hydroxymethyloxindoles and 3-hydroxy-3-hydroxymethyloxindoles in an atom- and step-economic fashion (Scheme 1). The 3-hydroxymethyl group existed in these products could be easily functionalized into different types of 3-amino-3-alkyloxindoles or 3-hydroxy-3-alkyloxindoles.

In the past few years, our research group has developed a series of multicomponent reactions (MCRs) via electrophilic trapping of active onium ylides or zwitterionic intermediates that generated from metal carbenes.[6] Among those transformations, aldol-type trapping of ammonium or oxonium ylides with active aromatic ketones or aldehydes has been extensively developed as efficient methods for the synthesis of nitrogen- and/or oxygen-containing molecules,[7,8] such as different types of amino acid derivatives and heterocycles. However, aliphatic aldehydes were seldom applied as the trapping reagents owing to their weak electrophilicity. Very recently, we disclosed that aqueous formaldehyde solution (formalin) could efficiently trap the ammonium ylides generated from aryl diazoacetate derived metal carbenes and anilines to establish three-component transformations.[9] With

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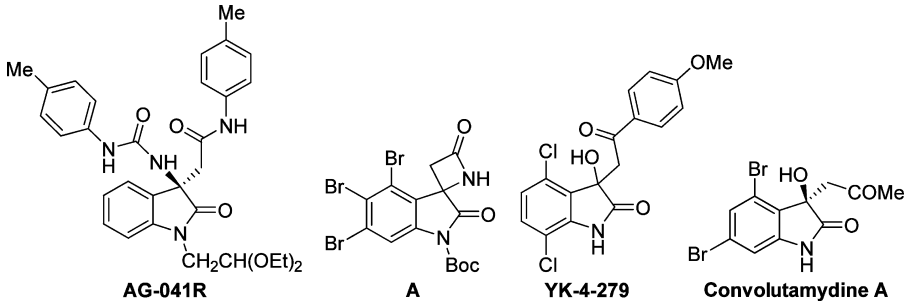
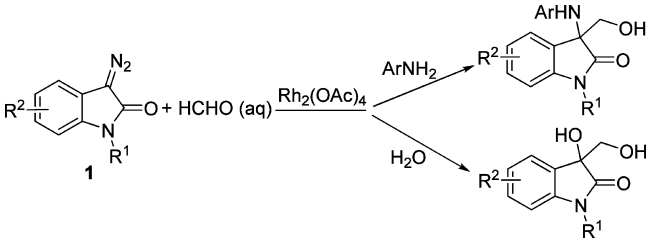


Figure 1. Representative biologically active molecules containing 3-amino-3-alkyloxindole or 3-hydroxy-3-alkyloxindole motifs.

Scheme 1. $Rh_2(OAc)_4$-Catalyzed Three-Component Strategy for the Synthesis of 3-Amino-3-hydroxymethyloxindoles and 3-Hydroxy-3-hydroxymethyloxindoles

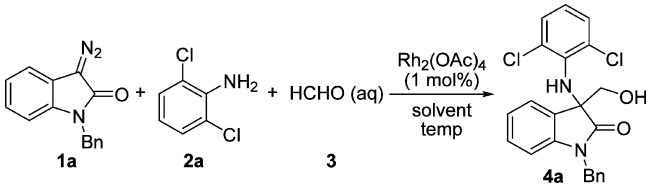


these preliminary results, we envisioned that formalin could be applied as the suitable electrophile to trap active ylide intermediates derived from 3-diazooxindoles for the synthesis of 3,3-disubstituted oxindoles. However, the use of formalin as the trapping reagent may cause an array of undesired side reactions. For example, water and methanol that existed in the solution may act as nucleophiles to react with 3-diazooxindoles to afford O−H insertion products or oxonium ylide trapping products,[10a] and under such reaction conditions, oxidation and polymerization of 3-diazooxindoles are also possible side reactions.[10b,c] On the other hand, 3-diazooxindoles were less reactive diazo sources;[11] as a result, the generated ammonium ylide or oxonium ylide intermediates may undergo rapid N−H or O−H insertions instead of being trapped by formaldehyde to establish three-component transformations.

RESULTS AND DISCUSSION

Our studies commenced with the ammonium ylide trapping process with formalin. *N*-Benzyl-3-diazooxindole **1a** and 2,6-dichloroaniline **2a** were allowed to react with formalin **3** in the presence of rhodium catalyst. Since our initial investigation indicated that the $Rh_2(OAc)_4$-catalyzed decomposition of **1a** was very slow at room temperature, the reaction was allowed to react at 60 °C. Under such reaction conditions, the desired three-component product **4a** was obtained in 70% yield after reacting for 12 h (Table 1, entry 1). The major side products being observed for this reaction included *N*-benzyl isatin produced by oxidation of **1a**, as well as the N−H and O−H insertion products of 3-diazooxindole generated from aniline and water, respectively. Encouraged by this preliminary result, further condition optimizations were conducted. Among different water-miscible solvents being screened, the use of dioxane as the solvent gave relatively poor yield after reacting for 11 h (Table 1, entry 2). When dimethoxyethane (DME) or diethoxyethane was used as the solvent, the desired three-component reaction was completed within 1 h and afforded **4a** in much improved yields (Table 1, entries 3 and 4). On the other hand, solvents immiscible with water, such as CH_2Cl_2 or toluene, were also applied, giving **4a** in slightly reduced yields (Table 1, entries 5 and 6). The best result was obtained when ethyl acetate (EA) was used as the solvent, affording **4a** in 94% yield within 1 h (Table 1, entry 7).

Table 1. Condition Optimization for the Ammonium Ylide Trapping Process[a]



entry	solvent	temp (°C)	*T* (h)	yield (%)[b]
1	THF	60	12	70
2	dioxane	60	11	49
3	DME	60	1	84
4	diethoxyethane	60	1	89
5	CH_2Cl_2	40	1	75
6	toluene	60	1	72
7	EtOAc	60	1	94

[a]Reaction conditions: To a mixture of **2a** (0.10 mmol), **3** (37% aqueous formaldehyde solution, 0.60 mmol), $Rh_2(OAc)_4$ (0.001 mmol), and the corresponding solvent (1 mL) at the given temperature was added **1a** (0.10 mmol) in the corresponding solvent (1 mL) via a syringe pump over 1 h. After completion of the addition, the reaction mixture was stirred for the given time until complete decomposition of diazo compound. [b]Isolated yield of **4a** after column chromatography.

With the optimized reaction conditions in hand, the substrate scope of this Rh(II)-catalyzed ammonium ylide trapping process was investigated. Different protecting groups on the nitrogen atom of 3-diazooxindoles, including benzyl (**1a**), methyl (**1b**), and acetyl (**1c**), proved to be effective in providing the corresponding three-component products in good yields (Table 2, entries 1−3). Different substituents on the aromatic ring of 3-diazooxindoles were also tested, and the corresponding three-component products were generally afforded in good yields regardless of their electronic features (Table 2, entries 4−7, 15, and 21). On the other hand, different substituted anilines were also investigated. With aniline as the substrate, the desired three-component product **4h** was obtained in relatively low yield (Table 2, entry 8). Anilines bearing halogen substituents at the para-position were suitable substrates, giving the corresponding three-component products in high yields (Table 2, entries 9−11). When 4-nitroaniline or 3-nitroaniline were used as the substrates, even higher yields of the desired products were obtained (Table 2, entries 12 and

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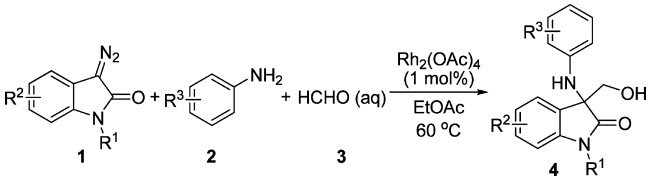
Table 2. Substrate Scope of the Ammonium Ylide Trapping Process[a]



entry	1 (R^1, R^2)	R^3	4	yield (%)[b]
1	**1a** (Bn, H)	2,6-dichloro	**4a**	94
2	**1b** (Me, H)	2,6-dichloro	**4b**	78
3	**1c** (Ac, H)	2,6-dichloro	**4c**	89
4	**1d** (Bn, 5-Me)	2,6-dichloro	**4d**	84
5	**1e** (Bn, 5-Br)	2,6-dichloro	**4e**	89
6	**1f** (Bn, 4-Cl)	2,6-dichloro	**4f**	74
7	**1g** (Bn, 7-Cl)	2,6-dichloro	**4g**	93
8	**1a** (Bn, H)	H	**4h**	42
9	**1a** (Bn, H)	4-Cl	**4i**	89
10	**1a** (Bn, H)	4-Br	**4j**	86
11	**1a** (Bn, H)	4-I	**4k**	88
12	**1a** (Bn, H)	4-NO_2	**4l**	94
13	**1a** (Bn, H)	3-NO_2	**4m**	95
14	**1a** (Bn, H)	2-Cl	**4n**	84
15	**1d** (Bn, 5-Me)	2-Cl	**4o**	73
16	**1a** (Bn, H)	2-I	**4p**	76
17	**1a** (Bn, H)	3-Cl	**4q**	82
18	**1a** (Bn, H)	2,4-dichloro	**4r**	98
19	**1a** (Bn, H)	2,5-dichloro	**4s**	94
20	**1a** (Bn, H)	4-F-2-NO_2	**4t**	64
21	**1d** (Bn, 5-Me)	2,4,6-tribromo	**4u**	84

[a]Reaction conditions: To a mixture of **2** (0.1 mmol), **3** (37% aqueous formaldehyde solution, 0.6 mmol), $Rh_2(OAc)_4$ (0.001 mmol), and EtOAc (1 mL) at 60 °C was added **1** (0.1 mmol) in EtOAc (1 mL) via a syringe pump over 1 h. After the completion of the addition, the reaction mixture was stirred for an additional 1 h. [b]Isolated yield of **4** after column chromatography.

13). These results indicated that electron-deficient anilines favored the desired three-component reactions. This might be explained by the fact that electron-deficient aniline had decreased electron density on the nitrogen atom; therefore, preventing the unwanted formation of a hemiacetal resulted from the addition to formaldehyde. Changing the position of the halogen substituent had little effect on the yields of the desired three-component products (Table 2, entries 14−17). The reaction conditions were also compatible with other disubstituted anilines, which gave the desired three-component products in good yields (Table 2, entries 18−20). 2,4,6-Tribromoaniline was also applicable to this three-component reaction, affording the desired product **4u** in 84% yield (Table 2, entry 21). The structures of the three-component products were further confirmed by the single-crystal X-ray analysis of compound **4a** (Figure 2). It was also worth mentioning that, when other aliphatic aldehydes, such as ethanal, propanal, or butanal, were applied, no desired three-component products were observed. This might be caused by the relatively weak electrophilicities of other aliphatic aldehydes or increased steric hindrance. These results indicated the unique feature of formaldehyde as the suitable trapping agent.

Having successfully established the Rh(II)-catalyzed ammonium ylide trapping process with formalin, we set out to further expand this electrophilic trapping process to oxonium ylides. As

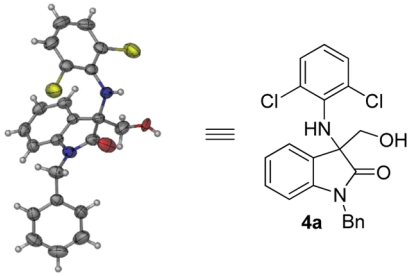


Figure 2. X-ray crystal structure of **4a**.

a 37% aqueous solution of formaldehyde, formalin contains a considerable amount of water, which could be directly used as the precursor to generate the corresponding oxonium ylide, and the reaction between 3-diazooxindoles and formalin could potentially lead to a three-component oxonium ylide trapping transformation. With this hypothesis, *N*-benzyl-3-diazooxindole **1a** and formalin **3** were allowed to react in the presence of $Rh_2(OAc)_4$ in EtOAc at 60 °C, and the desired oxonium ylide trapping product **5a** was obtained in 70% yield along with the formation of *N*-benzyl isatin derived from oxidation of **1a**, *N*-benzyl-3-hydroxyoxindole, and *N*-benzyl-3-methoxyoxindole (O−H insertion products from H_2O and MeOH, respectively) as the major side products (Table 3, entry 1). This is the first time that a three-component reaction based on trapping of oxonium ylides with formaldehyde was realized. With this preliminary result in hand, further condition optimizations were conducted. However, among different solvents being tested, only the use of EtOAc provided the most satisfactory result (Table 3, entries 1−6). Other transition-metal catalysts, including copper(I) and copper(II) salts, iron porphyrin, and palladium(II) complex, were also screened, but no encouraging results were achieved (Table 3, entries 7−13). Therefore, the use of $Rh_2(OAc)_4$ as the catalyst and EtOAc as the solvent was chosen as the conditions for investigating the substrate scope.

Under standard reaction conditions, the substrate scope of this oxonium ylide trapping three-component reaction was tested. *N*-Alkyl or *N*-acetyl substituted 3-diazooxindoles were applicable to the desired three-component reaction, yielding the desired three-component products in moderate to good yields (Table 4, entries 1−3). Substrates bearing ester substituents, such as *N*-methoxycarbonyl, *N*-ethoxycarbonyl, and *N*-Boc substituted 3-diazooxindoles, were also suitable substrates to give the desired three-component products in moderate to good yields (Table 4, entries 4−6). On the other hand, different substituents on the aromatic ring of 3-diazooxindoles were also tested. 5-Methyl substituted 3-diazooxindole gave the desired three-component product in 73% yield (Table 4, entry 7); however, halogen substituents at the 5-position of 3-diazooxindoles caused declined yields, while relatively poor yields were observed when 5-fluoro 3-diazooxindoles were used as the substrates (Table 4, entries 8−11). Substituents on other positions of 3-diazooxindoles were also proved to be suitable for the desired three-component reaction, giving the desired products in moderate to good yields (Table 4, entries 12−14). Similar to the previously developed ammonium ylide trapping process, the use of other aliphatic aldehydes, including ethanal, propanal, and butanal, failed to afford the desired three-component products in this oxonium ylide trapping process.

A plausible reaction pathway for this Rh(II)-catalyzed three-component approach is shown in Scheme 2. $Rh_2(OAc)_4$

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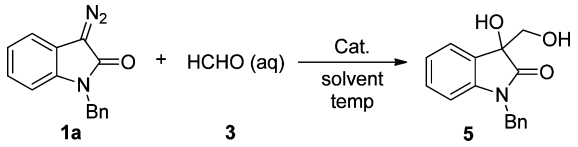
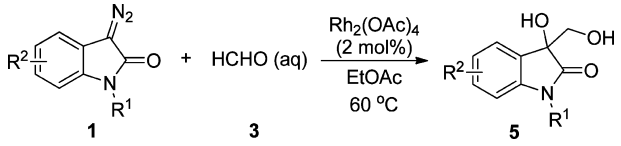
Table 3. Condition Optimization for the Oxonium Ylide Trapping Process[a]



entry	solvent	cat.	temp (°C)	T (h)	yield (%)[b]
1	EtOAc	$Rh_2(OAC)_4$ (2%)	60	1	70
2	THF	$Rh_2(OAC)_4$ (2%)	60	9	47
3	dioxane	$Rh_2(OAC)_4$ (2%)	60	9	22
4	DME	$Rh_2(OAC)_4$ (2%)	60	1	41
5	DCM	$Rh_2(OAC)_4$ (2%)	35	1	45
6	toluene	$Rh_2(OAC)_4$ (2%)	60	1	44
7	EtOAc	CuOTf (10%)	60	12	<5
8	EtOAc	$Cu(OTf)_2$ (10%)	60	12	<5
9	EtOAc	$Cu(OAc)_2·H_2O$ (10%)	60	12	0
10	EtOAc	$CuSO_4$ (50%)	60	30	<5
11	EtOAc	$CuPF_6(MeCN)_4$ (10%)	60	12	14
12	EtOAc	Fe(TPP)Cl (1%)	60	18	<5
13	EtOAc	$(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2$ (2.5%)	60	18	15

[a]Reaction conditions: To a mixture of the catalyst and formalin **3** (1.2 mmol) (37% aqueous formaldehyde solution) in the corresponding solvent (2.0 mL) at 60 °C was added **1a** (0.20 mmol) in the corresponding solvent (2.0 mL) via a syringe pump over 1 h. After the completion of the addition, the reaction mixture was stirred for the given time. [b]Isolated yield of **5a** after column chromatography.

Table 4. Substrate Scope of the Oxonium Ylide Trapping Process[a]



entry	R^1	R^2	5	yield (%)[b]
1	Bn	H (**1a**)	**5a**	70
2	Me	H (**1b**)	**5b**	46
3	Ac	H (**1c**)	**5c**	54
4	CO_2Me	H (**1h**)	**5d**	62
5	CO_2Et	H (**1i**)	**5e**	31
6	Boc	H (**1j**)	**5f**	45
7	Bn	5-Me (**1d**)	**5g**	73
8	Bn	5-Br (**1e**)	**5h**	54
9	Bn	5-F (**1k**)	**5i**	30
10	Me	5-F (**1l**)	**5j**	26
11	Bn	5-Cl (**1m**)	**5k**	55
12	Bn	4-Cl (**1f**)	**5l**	74
13	Bn	6-Cl (**1n**)	**5m**	46
14	Bn	7-Cl (**1g**)	**5n**	73

[a]Reaction conditions: To a mixture of $Rh_2(OAc)_4$ (0.004 mmol) and formalin **3** (1.2 mmol) (37% aqueous formaldehyde solution) in EtOAc (2.0 mL) at 60 °C was added **1** (0.20 mmol) in EtOAc (4.0 mL for 5-substituted 3-diazooxindoles and 2.0 mL for other 3-diazo oxindoles) via a syringe pump over 1 h. After the completion of the addition, the reaction mixture was stirred for an additional 1 h. [b]Isolated yields after column chromatography.

decomposes 3-diazooxindole **1** to form the corresponding rhodium carbene species **I**, which further reacts with aniline or water to give active ammonium ylides or oxonium ylides **IIa**/**IIb**. In the presence of formaldehyde, the active ylide species undergo aldol-type addition to afford the desired three-component products.

To further demonstrate the synthetic potential of this Rh(II)-catalyzed three-component strategy in synthesizing valuable 3,3-disubstituted oxindole derivatives, the three-component product **4t** derived from 3-diazooxindole, 4-fluoro-2-nitroaniline, and formaldehyde was first converted into the corresponding Boc-protected product **6t** in 90% yield. Compound **6t** then underwent Pd/C-catalyzed hydrogenation to afford **7t** (95%), which was further cyclized into novel benzimidazole **8t** (96% yield) (Scheme 3).

CONCLUSION

In conclusion, we have developed an efficient Rh(II)-catalyzed three-component reaction of 3-diazooxindoles with anilines and formalin. This transformation proceeded through an electrophilic trapping of the ammonium ylides generated from 3-diazooxindoles and anilines with formaldehyde. A series of substituted 3-amino-3-hydroxymethyloxindoles were synthesized in high to excellent yields. On the other hand, the reaction between 3-diazooxindoles and formalin in the presence of Rh(II) catalyst also resulted in an efficient oxonium ylide trapping three-component reaction, yielding a series of 3-hydroxy-3-hydroxymethyloxindoles in moderate to good yields. This three-component approach provides an efficient and convenient way for the synthesis of both 3-amino-3-hydroxymethyloxindoles and 3-hydroxy-3-hydroxymethyloxindoles. Exploration of the asymmetric version of the reactions is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Diazo compounds **1a**−**1n** were prepared according to the literature methods.[11b,12] All isolated compounds were characterized on the basis of ^{1}H NMR and ^{13}C NMR spectroscopic data and HRMS (TOF-Q) data. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. All reactions were run in open flasks, and an inert atmosphere was not required. A.R. grade solvents were directly used, and further purification or degas of the solvents was not required.

General Procedure for the Synthesis of 3-Amino-3-hydroxymethyloxindoles. To a mixture of $Rh_2(OAc)_4$ (0.001 mmol), aniline **2** (0.10 mmol), and formalin **3** (37% aqueous solution of

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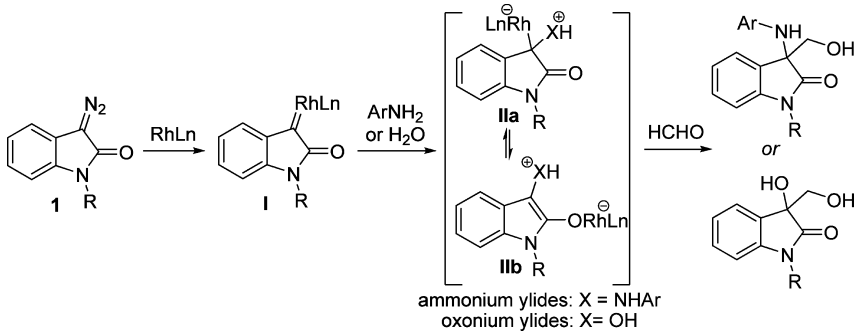
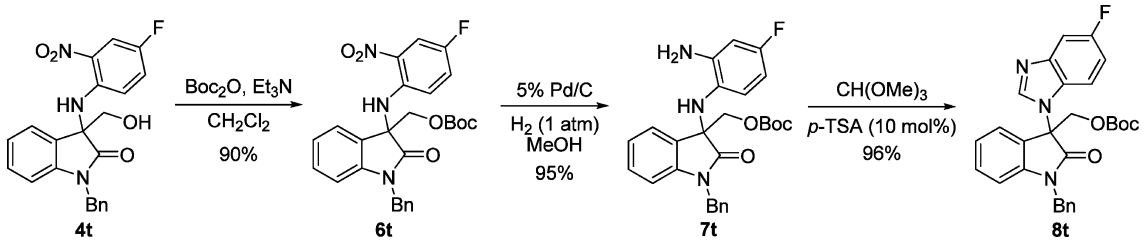
Scheme 2. Proposed Reaction Pathways



Scheme 3. Synthesis of Valuable 3,3-Disubstituted Oxindoles



formaldehyde, 0.60 mmol) in EtOAc (1.0 mL) at 60 °C was added diazo compound **1** (0.1 mmol) in EtOAc (1.0 mL) via a syringe pump for 1 h. After the completion of the addition, the reaction mixture was stirred for an additional 1 h. Solvents were removed under reduced pressure to give crude products, which were purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:10 to 1:1).

*1-Benzyl-3-((2,6-dichlorophenyl)amino)-3-(hydroxymethyl)-indolin-2-one (**4a**).* A white solid (39 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.27 (m, 5H), 7.15 (td, J = 7.8, 1.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.78 (dt, J = 12.4, 4.1 Hz, 3H), 6.69−6.59 (m, 1H), 5.27 (s, 1H), 5.04 (d, J = 15.4 Hz, 1H), 4.82 (d, J = 15.4 Hz, 1H), 3.97 (t, J = 10.9 Hz, 1H), 3.87 (dd, J = 11.3, 3.0 Hz, 1H), 3.15 (dd, J = 10.4, 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 143.0, 140.0, 135.5, 129.7, 129.4, 128.8, 128.1, 127.9, 127.8, 125.8, 124.1, 123.7, 122.3, 109.6, 69.8, 66.5, 44.1. HRMS (ESI) calcd for $C_{22}H_{19}Cl_2N_2O_2$ [M + H]$^+$ = 413.0824, found 413.0838.

*3-((2,6-Dichlorophenyl)amino)-3-(hydroxymethyl)-1-methyl-indolin-2-one (**4b**).* A white solid (26 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 6.5 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.86−6.73 (m, 3H), 6.68 (d, J = 7.3 Hz, 1H), 5.22 (s, 1H), 3.92 (t, J = 10.8 Hz, 1H), 3.83 (dd, J = 11.3, 3.2 Hz, 1H), 3.24 (s, 3H), 3.15 (d, J = 9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 143.8, 140.0, 129.6, 129.5, 128.2, 125.9, 124.1, 123.7, 122.3, 108.6, 69.5, 66.5, 26.3. HRMS (ESI) calcd for $C_{16}H_{14}Cl_2N_2NaO_2$ [M + Na]$^+$ = 359.0330, found 359.0323.

*1-Acetyl-3-((2,6-dichlorophenyl)amino)-3-(hydroxymethyl)-indolin-2-one (**4c**).* A white solid (32 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.81 (t, J = 8.0 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.12 (s, 1H), 3.92 (s, 2H), 2.73 (s, 3H), 2.62 (d, J = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 170.8, 140.3, 139.0, 129.9, 129.7, 128.3, 125.2, 124.9, 124.1, 123.7, 116.9, 69.6, 66.6, 26.7. HRMS (ESI) calcd for $C_{17}H_{16}Cl_2N_2NaO_3$ [M + Na]$^+$ = 389.0436, found 389.0443.

*1-Benzyl-3-((2,6-dichlorophenyl)amino)-3-(hydroxymethyl)-5-methylindolin-2-one (**4d**).* A light yellow solid (36 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.23 (m, 5H), 6.94 (dd, J = 8.0, 0.8 Hz, 1H), 6.77 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 0.6 Hz, 1H), 5.25 (s, 1H), 5.00 (d, J = 15.4 Hz, 1H), 4.80 (d, J = 15.4 Hz, 1H), 3.95 (t, J = 10.7 Hz, 1H), 3.85 (d, J = 10.1 Hz, 1H), 3.19 (d, J = 9.9 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 140.5, 140.0, 135.6, 132.0, 129.7, 129.6, 128.8, 128.1, 127.8, 126.0, 124.9, 123.6, 109.3, 69.8, 66.5, 44.1, 20.9. HRMS (ESI) calcd for $C_{23}H_{20}Cl_2N_2NaO_2$ [M + Na]$^+$ = 449.0800, found 449.0822.

*1-Benzyl-5-bromo-3-((2,6-dichlorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (**4e**).* A light yellow solid (44 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.27 (m, 6H), 7.14 (d, J = 8.0 Hz, 2H), 6.83 (t, J = 8.0 Hz, 1H), 6.78 (d, J = 1.8 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 5.18 (s, 1H), 5.01 (d, J = 15.4 Hz, 1H), 4.79 (d, J = 15.5 Hz, 1H), 3.91 (dd, J = 24.3, 11.0 Hz, 2H), 3.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 142.0, 139.4, 135.0, 132.2, 129.7, 128.90 128.3, 128.0, 127.7, 127.4, 124.2, 115.1, 111.0, 69.4, 66.6, 44.2. HRMS (ESI) calcd for $C_{22}H_{17}BrCl_2N_2NaO_2$ [M + Na]$^+$ = 512.9748, found 512.9773.

*1-Benzyl-4-chloro-3-((2,6-dichlorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (**4f**).* A white solid (33 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 7.13 (t, J = 8.1 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.74 (t, J = 8.0 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 5.50 (s, 1H), 4.99 (d, J = 15.5 Hz, 1H), 4.81 (d, J = 15.5 Hz, 1H), 4.43 (t, J = 11.0 Hz, 1H), 3.98−3.85 (m, 1H), 3.18−2.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 145.0, 140.1, 135.0, 131.5, 130.7, 128.9, 128.3, 128.0, 127.7, 127.2, 124.1, 123.7, 122.5, 108.1, 67.3, 66.7, 44.3. HRMS (ESI) calcd for $C_{22}H_{17}Cl_3N_2NaO_2$ [M + Na]$^+$ = 469.0253, found 469.0248.

*1-Benzyl-7-chloro-3-((2,6-dichlorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (**4g**).* A white solid (42 mg, 93% yield). ^{1}H NMR (400 MHz, CDCl3): δ 7.31 (q, J = 8.1 Hz, 4H), 7.25 (dd, J = 8.4, 5.1 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.77 (dt, J = 15.7, 8.0 Hz, 2H), 6.60 (t, J = 8.0 Hz, 1H), 5.43 (d, J = 15.9 Hz, 1H), 5.36−5.25 (m, 1H), 5.22 (s, 1H), 3.96−3.88 (m, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.10 (d, J = 36.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 139.6, 139.1, 137.2, 132.0, 129.5, 128.6, 128.3, 127.4, 127.2, 123.9, 123.3, 122.7, 115.8, 69.8, 66.0, 45.01. HRMS (ESI) calcd for $C_{22}H_{17}Cl_3N_2NaO_2$ [M + Na]+ = 469.0253, found 469.0276.

*1-Benzyl-3-(hydroxymethyl)-3-(phenylamino)indolin-2-one (**4h**).* A sticky oil (14 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.16 (m, 8H), 7.06 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.8 Hz, 2H), 6.84 (d, J = 7.8 Hz, 1H), 6.70 (t, J = 7.3 Hz, 1H), 6.27 (d, J = 8.0 Hz, 2H), 5.18 (s, 1H), 5.11 (d, J = 15.5 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 3.92 (t, J = 10.9 Hz, 1H), 3.75−3.64 (m, 1H), 3.12 (d, J = 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 145.6, 141.9, 135.3, 129.6, 129.1, 128.8, 127.9, 127.6, 124.0, 123.6, 119.6, 115.5, 110.1, 68.1, 65.0, 44.1. HRMS (ESI) calcd for $C_{22}H_{21}N_2O_2$ [M + H]$^+$ = 345.1603, found 345.1598.

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*1-Benzyl-3-((4-chlorophenyl)amino)-3-(hydroxymethyl)-indolin-2-one (**4i**).* A white solid (32 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J = 8.7, 4.9 Hz, 4H), 7.26−7.22 (m, 1H), 7.22−7.16 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 6.88 (t, J = 6.0 Hz, 2H), 6.84 (d, J = 7.9 Hz, 1H), 6.24−6.12 (m, 2H), 5.24 (s, 1H), 5.09 (d, J = 15.4 Hz, 1H), 4.73 (d, J = 15.4 Hz, 1H), 3.97−3.82 (m, 1H), 3.75−3.66 (m, 1H), 3.46 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 144.2, 141.9, 135.2, 129.8, 129.0, 128.9, 128.0, 127.6, 127.3, 124.4, 124.1, 123.7, 117.0, 110.1, 67.9, 65.2, 44.1. HRMS (ESI) calcd for $C_{22}H_{20}ClN_2O_2$ $[M + H]^+$ = 379.1213 found 379.1216.

*1-Benzyl-3-(hydroxymethyl)-3-((4-bromophenyl)amino)indolin-2-one (**4j**).* A white solid (36 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 6.2 Hz, 4H), 7.18 (d, J = 6.3 Hz, 1H), 7.14 (d, J = 6.0 Hz, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 7.8 Hz, 2H), 6.78 (d, J = 7.7 Hz, 1H), 6.05 (d, J = 7.9 Hz, 2H), 5.18 (s, 1H), 5.02 (d, J = 15.4 Hz, 1H), 4.67 (d, J = 15.4 Hz, 1H), 3.83 (s, 1H), 3.63 (d, J = 11.5 Hz, 1H), 3.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 144.6, 141.8, 135.2, 131.9, 129.8, 128.9, 128.0, 127.6, 127.2, 124.0, 123.7, 117.3, 111.6, 110.2, 67.9, 65.0, 44.1. HRMS (ESI) calcd for $C_{22}H_{19}BrNaN_2O_2$ $[M + Na]^+$ = 445.0528, found 445.0529.

*1-Benzyl-3-(hydroxymethyl)-3-((4-iodophenyl)amino)indolin-2-one (**4k**).* A yellow solid (41 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 7.1 Hz, 4H), 7.17 (dd, J = 10.7, 4.9 Hz, 3H), 7.11 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 5.94 (d, J = 7.6 Hz, 2H), 5.18 (s, 1H), 5.02 (d, J = 15.4 Hz, 1H), 4.68 (d, J = 15.4 Hz, 1H), 3.82 (s, 1H), 3.63 (d, J = 11.5 Hz, 1H), 3.25 (d, J = 43.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 145.3, 141.8, 137.8, 135.2, 129.8, 128.9, 128.1, 127.7, 127.1, 124.0, 123.7, 117.6, 110.2, 81.0, 68.0, 64.9, 44.2. HRMS (ESI) calcd for $C_{22}H_{19}IN_2NaO_2$ $[M + Na]^+$ = 493.0389, found 493.0372.

*1-Benzyl-3-(hydroxymethyl)-3-((4-nitrophenyl)amino)indolin-2-one (**4l**).* A yellow solid (39 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 9.0 Hz, 2H), 7.40−7.28 (m, 6H), 7.26 (s, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.14 (d, J = 9.0 Hz, 2H), 6.03 (s, 1H), 5.11 (d, J = 15.3 Hz, 1H), 4.85 (d, J = 15.3 Hz, 1H), 3.92 (d, J = 11.5 Hz, 1H), 3.78 (d, J = 11.6 Hz, 1H), 3.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 151.1, 141.6, 139.6, 135.1, 130.3, 129.0, 128.9, 127.9, 125.9, 124.0, 123.8, 113.2, 110.5, 67.9, 64.1, 44.4. HRMS (ESI) calcd for $C_{22}H_{19}N_3NaO_4$ $[M + Na]^+$ = 412.1273, found 412.1264.

*1-Benzyl-3-(hydroxymethyl)-3-((3-nitrophenyl)amino)indolin-2-one (**4m**).* A yellow solid (37 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0 Hz, 1H), 7.28−7.13 (m, 8H), 6.98 (dt, J = 16.0, 7.6 Hz, 3H), 6.86 (d, J = 7.8 Hz, 1H), 6.43 (d, J = 8.1 Hz, 1H), 5.64 (s, 1H), 4.96 (d, J = 15.5 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 3.87 (t, J = 10.0 Hz, 1H), 3.69 (d, J = 11.5 Hz, 1H), 3.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 146.5, 141.8, 135.1, 130.2, 129.7, 129.0, 128.1, 127.5, 126.3, 123.9, 120.6, 113.7, 110.5, 108.8, 67.9, 64.7, 44.3. HRMS (ESI) calcd for $C_{22}H_{20}N_3O_4$ $[M + H]^+$ = 390.1454, found 390.1460.

*1-Benzyl-3-((2-chlorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (**4n**).* A light yellow solid (32 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.12 (m, 8H), 6.98 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.55 (dt, J = 23.2, 7.4 Hz, 2H), 5.81 (s, 1H), 5.62 (d, J = 7.9 Hz, 1H), 5.06 (d, J = 15.4 Hz, 1H), 4.72 (d, J = 15.3 Hz, 1H), 3.91 (t, J = 10.8 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H), 3.01 (d, J = 10.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 146.8, 141.7, 135.2, 134.8, 129.8, 129.0, 127.9, 127.5, 123.7, 120.9, 119.3, 115.0, 113.1, 110.3, 68.1, 64.7, 44.2. HRMS (ESI) calcd for $C_{22}H_{19}ClN_2O_2$ $[M + H]^+$ = 379.1213, found 379.1221.

*1-Benzyl-3-((2-chlorophenyl)amino)-3-(hydroxymethyl)-5-methylindolin-2-one (**4o**).* A light yellow solid (36 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 7.24 (dd, J = 8.1, 1.9 Hz, 1H), 7.12 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.66 (td, J = 7.8, 1.5 Hz, 1H), 6.60 (td, J = 7.6, 1.5 Hz, 1H), 5.87 (s, 1H), 5.71 (dd, J = 8.0, 1.4 Hz, 1H), 5.12 (d, J = 15.3 Hz, 1H), 4.78 (d, J = 15.3 Hz, 1H), 3.97 (d, J = 11.5 Hz, 1H), 3.72 (d, J = 11.5 Hz, 1H), 3.05 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 141.8, 139.3, 135.5, 133.5, 130.1, 129.4, 128.9, 127.9, 127.8, 127.5, 127.0, 124.6, 120.8, 119.1, 113.1, 109.9, 68.2, 64.4, 44.2, 21.1. HRMS (ESI) calcd for $C_{23}H_{21}ClN_2NaO_2$ $[M + Na]^+$ = 415.1189, found 415.1181.

*1-Benzyl-3-(hydroxymethyl)-3-((2-iodophenyl)amino)indolin-2-one (**4p**).* A white solid (36 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, J = 7.8, 1.3 Hz, 1H), 7.34−7.27 (m, 7H), 7.07 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.72 (dd, J = 11.3, 4.2 Hz, 1H), 6.45−6.34 (m, 1H), 5.72 (s, 1H), 5.64 (dd, J = 8.1, 1.1 Hz, 1H), 5.13 (d, J = 15.3 Hz, 1H), 4.81 (d, J = 15.3 Hz, 1H), 4.00 (t, J = 11.4 Hz, 1H), 3.72 (dd, J = 11.5, 2.5 Hz, 1H), 2.95 (dd, J = 11.3, 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 145.0, 141.8, 139.4, 135.4, 129.7, 129.1, 128.9, 128.0, 127.8, 126.9, 123.9, 123.7, 120.4, 112.5, 110.1, 87.1, 68.3, 65.0, 44.2. HRMS (ESI) calcd for $C_{22}H_{19}IN_2NaO_2$ $[M + Na]^+$ = 493.0389, found 493.0367.

*1-Benzyl-3-((3-chlorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (**4q**).* A white solid (31 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.11 (m, 8H), 6.99 (t, J = 7.5 Hz, 1H), 6.75 (t, J = 8.2 Hz, 2H), 6.57 (d, J = 7.8 Hz, 1H), 6.21 (s, 1H), 6.01 (d, J = 8.1 Hz, 1H), 5.26 (s, 1H), 5.06 (d, J = 15.5 Hz, 1H), 4.70 (d, J = 15.5 Hz, 1H), 3.86−3.75 (m, 1H), 3.62 (d, J = 11.5 Hz, 1H), 3.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 141.7, 135.4, 129.8, 129.4, 128.9, 128.0, 127.8, 127.5, 127.1, 124.0, 123.7, 119.2, 113.1, 110.1, 68.2, 64.5, 44.2. HRMS (ESI) calcd for $C_{22}H_{19}ClNaN_2O_2$ $[M + Na]^+$ = 401.1033, found 401.1025.

*1-Benzyl-3-((2,4-dichlorophenyl)amino)-3-(hydroxymethyl)-indolin-2-one (**4r**).* A white solid (40 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (dd, J = 17.6, 10.1 Hz, 8H), 6.98 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.51 (d, J = 8.7 Hz, 1H), 5.77 (s, 1H), 5.50 (d, J = 8.7 Hz, 1H), 5.04 (d, J = 15.3 Hz, 1H), 4.70 (d, J = 15.3 Hz, 1H), 3.88 (t, J = 10.6 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H), 3.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 141.7, 140.5, 135.3, 130.0, 129.1, 128.9, 128.2, 127.9, 127.5, 126.7, 124.0, 123.8, 123.3, 121.4, 113.8, 110.2, 68.0, 64.6, 44.3. HRMS (ESI) calcd for $C_{22}H_{18}Cl_2NaN_2O_2$ $[M + Na]^+$ = 435.0643, found 435.0625.

*1-Benzyl-3-((2,5-dichlorophenyl)amino)-3-(hydroxymethyl)-indolin-2-one (**4s**).* A white solid (39 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.14 (m, 7H), 7.07 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.88 (s, 1H), 5.67 (s, 1H), 5.09 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 3.88 (t, J = 9.7 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H), 3.11 (d, J = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 142.6, 141.7, 135.1, 130.2, 130.1, 129.2, 127.9, 127.3, 126.2, 123.9, 123.9, 119.1, 119.0, 112.9, 110.4, 68.2, 64.4, 44.4. HRMS (ESI) calcd for $C_{22}H_{18}Cl_2NaN_2O_2$ $[M + Na]^+$ = 435.0643, found 435.0642.

*1-Benzyl-3-((4-fluoro-2-nitrophenyl)amino)-3-(hydroxymethyl)-indolin-2-one (**4t**).* A yellow solid (26 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.27 (dd, J = 13.3, 6.2 Hz, 6H), 7.19 (d, J = 7.3 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 11.0, 5.3 Hz, 1H), 5.63 (dd, J = 9.1, 3.9 Hz, 1H), 5.09 (d, J = 15.2 Hz, 1H), 4.77 (d, J = 15.2 Hz, 1H), 3.92 (t, J = 10.2 Hz, 1H), 3.76 (d, J = 11.4 Hz, 1H), 2.91 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 153.3 (d, $J_{C\text{-}F}$ = 239.0 Hz), 141.5, 139.9, 135.3, 133.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 130.2, 129.0, 128.3, 128.1, 126.3, 123.9 (d, $J_{C\text{-}F}$ = 7.0 Hz), 123.9, 116.2 (d, $J_{C\text{-}F}$ = 7.1 Hz), 112.7 (d, $J_{C\text{-}F}$ = 26.0 Hz), 110.4, 68.2, 64.6, 44.4. HRMS (ESI) calcd for $C_{22}H_{18}FNaN_3O_4$ $[M + Na]^+$ = 430.1179, found 430.1186.

*1-Benzyl-3-(hydroxymethyl)-5-methyl-3-((2,4,6-tribromophenyl)-amino)oxindole (**4u**).* A light yellow solid (50 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 2H), 7.40−7.35 (m, 2H), 7.29 (dt, J = 14.1, 6.6 Hz, 3H), 6.98 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.34 (s, 1H), 5.27 (s, 1H), 5.00 (d, J = 15.3 Hz, 1H), 4.79 (d, J = 15.3 Hz, 1H), 3.99 (t, J = 10.6 Hz, 1H), 3.80 (d, J = 11.3 Hz, 1H), 3.26 (s, 1H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 141.9, 140.7, 135.4, 134.2, 132.1, 129.9, 128.8, 128.0, 127.9, 125.2, 121.0, 115.8, 109.4, 70.0, 66.4, 44.1, 21.0. HRMS (ESI) calcd for $C_{23}H_{19}Br_3N_2NaO_2$ $[M + Na]^+$ = 614.8894, found 614.8865.

General Procedure for the Synthesis of 3-Hydroxy-3-hydroxymethyloxindoles. To a mixture of $Rh_2(OAc)_4$ (0.004 mmol) and formalin **3** (37% aqueous formaldehyde solution, 1.2 mmol of formaldehyde) in EtOAc (2.0 mL) at 60 °C was added diazo compound **1** (0.20 mmol) in EtOAc (4.0 mL for 5-substituted 3-diazo

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oxindoles and 2.0 mL for other 3-diazo oxindoles) via a syringe pump for 1 h. After the completion of the addition, the reaction mixture was stirred for an additional 1 h. Solvents were removed under reduced pressure to give the crude products, which were purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:10 to 3:1).

*1-Benzyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5a**).* A light yellow solid (38 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 7.2 Hz, 1H), 7.15 (s, 5H), 7.08 (t, J = 8.0 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 4.91 (s, 1H), 4.81 (d, J = 15.8 Hz, 1H), 4.63 (d, J = 15.8 Hz, 1H), 3.79 (s, 2H), 3.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 142.6, 135.2, 129.9, 128.9, 128.3, 127.7, 127.2, 124.6, 123.4, 109.7, 76.2, 66.9, 43.7. HRMS (ESI) calcd for $C_{16}H_{15}NNaO_3$ $[M + Na]^+$ = 292.0950, found 292.0953.

*3-Hydroxy-3-(hydroxymethyl)-1-methylindolin-2-one (**5b**).* A white solid (18 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.23 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.80 (t, J = 9.6 Hz, 1H), 4.01 (s, 1H), 3.76 (q, J = 11.6 Hz, 2H), 3.13 (s, 3H), 2.98 (d, J = 25.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.60, 143.61, 130.2, 127.5, 124.3, 123.4, 108.7, 75.4, 66.9, 26.2. HRMS (ESI) calcd for $C_{10}H_{11}NNaO_3$ $[M + Na]^+$ = 216.0645, found 216.0637.

*1-Acetyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5c**).* A sticky oil (24 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 14.5, 7.6 Hz, 2H), 7.17 (dd, J = 13.2, 5.7 Hz, 1H), 3.75 (q, J = 11.7 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 170.6, 140.1, 130.6, 126.9, 125.8, 123.9, 116.8, 75.7, 67.0, 26.5. HRMS (ESI) calcd for $C_{11}H_{11}NNaO_4$ $[M + Na]^+$ = 244.0586, found 244.0595.

*Methyl 3-Hydroxy-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (**5d**).* A white solid (29 mg, 62% yield). ^{1}H NMR (400 MHz, MeOD): δ 7.90 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 3.97 (s, 3H), 3.89 (d, J = 10.5 Hz, 1H), 3.81 (d, J = 10.5 Hz, 1H). ^{13}C NMR (100 MHz, MeOD): δ 176.6, 151.2, 140.0, 129.5, 129.0, 124.8, 124.0, 114.7, 76.2, 66.0, 52.8. HRMS (ESI) calcd for $C_{11}H_{11}NNaO_5$ $[M + Na]^+$ = 260.0535, found 260.0548.

*Ethyl 3-Hydroxy-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (**5e**).* A white solid (16 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 12.2, 7.6 Hz, 2H), 7.20−7.15 (m, 1H), 4.39 (q, J = 7.0 Hz, 2H), 3.77 (s, 2H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 150.5, 139.4, 130.7, 126.4, 125.4, 124.2, 115.5, 75.2, 67.0, 63.8, 29.7. HRMS (ESI) calcd for $C_{12}H_{13}NNaO_5$ $[M + Na]^+$ = 274.0691, found 274.0691.

*tert-Butyl 3-hydroxy-3-(hydroxymethyl)-2-oxoindoline-1-carboxylate (**5f**).* A white solid (25 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.0 Hz, 1H), 7.42−7.24 (m, 2H), 7.13 (t, J = 7.4 Hz, 1H), 3.75 (s, 2H), 1.58−1.45 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.50, 148.80, 139.64, 130.39, 125.09, 124.28, 115.32, 85.05, 75.33, 66.98, 28.04. HRMS (ESI) calcd for $C_{14}H_{17}NNaO_5$ $[M + Na]^+$ = 302.1004, found 302.1013.

*1-Benzyl-3-hydroxy-3-(hydroxymethyl)-5-methylindolin-2-one (**5g**).* A white solid (41 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.16 (m, 6H), 7.00 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 7.9 Hz, 1H), 4.91 (d, J = 15.7 Hz, 1H), 4.76 (d, J = 15.7 Hz, 1H), 4.48 (s, 1H), 3.88 (q, J = 11.8 Hz, 2H), 3.36 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 140.2, 135.3, 133.1, 130.3, 128.9, 127.8, 127.7, 127.1, 125.2, 109.5, 75.8, 67.0, 43.7, 21.0. HRMS (ESI) calcd for $C_{17}H_{17}NNaO_3$ $[M + Na]^+$ = 306.1111, found 306.1106.

*1-Benzyl-5-bromo-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5h**).* A white solid (38 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.21 (ddd, J = 21.5, 15.1, 7.8 Hz, 6H), 6.49 (d, J = 8.3 Hz, 1H), 4.85 (d, J = 15.8 Hz, 1H), 4.69 (d, J = 15.8 Hz, 1H), 4.42 (s, 1H), 3.81 (s, 2H), 3.22 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 141.6, 134.7, 132.8, 129.9, 129.0, 128.0, 127.9, 127.1, 116.2, 111.2, 75.8, 66.8, 43.9. HRMS (ESI) calcd for $C_{16}H_{14}BrNNaO_3$ $[M + Na]^+$ = 370.0055, found 370.0061.

*1-Benzyl-5-fluoro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5i**).* A white solid (17 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.21 (m, 5H), 7.21−7.15 (m, 1H), 6.90 (t, J = 8.4 Hz, 1H), 6.68−6.55 (m, 1H), 4.92 (d, J = 16.3 Hz, 2H), 4.76 (d, J = 15.8 Hz, 1H), 3.90 (s, 2H), 3.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 159.6 (d, $J_{C\text{-}F}$ = 241.0 Hz), 138.3, 134.77, 129.7 (d, $J_{C\text{-}F}$ = 9.0 Hz), 129.0, 127.9, 127.1, 116.2 (d, $J_{C\text{-}F}$ = 24.0 Hz), 112.8 (d, $J_{C\text{-}F}$ = 25.0 Hz), 110.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 76.2, 66.8, 43.9. HRMS (ESI) calcd for $C_{16}H_{14}FNNaO_3$ $[M + Na]^+$ = 310.0855, found 310.0865.

*5-Fluoro-3-hydroxy-3-(hydroxymethyl)-1-methylindolin-2-one (**5j**).* A white solid (12 mg, 26% yield). ^{1}H NMR (400 MHz, MeOD): δ 7.21 (dd, J = 7.9, 2.6 Hz, 1H), 7.08 (td, J = 9.1, 2.6 Hz, 1H), 6.95 (dd, J = 8.5, 4.1 Hz, 1H), 3.80 (q, J = 10.7 Hz, 2H), 3.17 (s, 3H). ^{13}C NMR (101 MHz, MeOD): δ 179.1, 161.0 (d, $J_{C\text{-}F}$ = 268 Hz), 141.5, 133.2 (d, $J_{C\text{-}F}$ = 8.0 Hz), 116.6 (d, J_{C-F} = 24.0 Hz), 113.3 (d, $J_{C\text{-}F}$ = 25.0 Hz), 110.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 78.0, 66.8, 26.6. HRMS (ESI) calcd for $C_{10}H_{10}FNaNO_3$ $[M + Na]^+$ = 234.0542, found 234.0541.

*1-Benzyl-5-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5k**).* A white solid (33 mg, 55% yield). ^{1}H NMR (400 MHz, MeOD): δ 8.86 (s, 1H), 8.81−8.69 (m, 4H), 8.65 (dd, J = 15.5, 7.8 Hz, 2H), 8.15 (d, J = 8.3 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 6.32−6.19 (m, 5H), 5.31 (s, 2H). ^{13}C NMR (100 MHz, MeOD): δ 179.1, 143.3, 136.8, 133.3, 130.3, 129.8, 129.4, 128.7, 128.3, 125.82, 111.8, 77.9, 66.9, 44.4. HRMS (ESI) calcd for $C_{16}H_{14}ClNNaO_3$ $[M + Na]^+$ = 326.0560, found 326.0548.

*1-Benzyl-4-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5l**).* A white solid (45 mg, 74% yield). ^{1}H NMR (400 MHz, MeOD): δ 8.78 (d, J = 7.2 Hz, 2H), 8.68 (dt, J = 23.3, 6.9 Hz, 3H), 8.59 (t, J = 8.0 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 6.25 (s, 1H), 5.82 (d, J = 10.1 Hz, 1H), 5.41 (d, J = 10.1 Hz, 1H). ^{13}C NMR (100 MHz, MeOD): δ 179.2, 146.9, 136.8, 132.8, 132.0, 129.7, 128.6, 128.2, 127.2, 125.1, 109.3, 79.0, 64.0, 44.5. HRMS (ESI) calcd for $C_{16}H_{14}ClNNaO_3$ $[M + Na]^+$ = 326.0560, found 326.0560.

*1-Benzyl-6-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5m**).* A white solid (28 mg, 46% yield). ^{1}H NMR (400 MHz, MeOD): δ 7.43−7.19 (m, 6H), 7.07 (dd, J = 7.9, 1.2 Hz, 1H), 6.76 (s, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.86 (d, J = 9.4 Hz, 1H), 3.89 (s, 2H). ^{13}C NMR (100 MHz, MeOD): δ 179.5, 146.0, 136.7, 136.2, 130.0, 129.8, 128.7, 128.2, 126.5, 123.8, 111.1, 77.5, 66.8, 44.4. HRMS (ESI) calcd for $C_{16}H_{14}ClNNaO_3$ $[M + Na]^+$ = 326.0560, found 326.0551.

*1-Benzyl-7-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (**5n**).* A white solid (44 mg, 73% yield). ^{1}H NMR (400 MHz, MeOD): δ 7.40 (d, J = 7.3 Hz, 1H), 7.26 (t, J = 6.2 Hz, 4H), 7.21 (dd, J = 8.3, 3.7 Hz, 2H), 7.07 (t, J = 7.7 Hz, 1H), 5.32 (q, J = 16.5 Hz, 2H), 3.91 (q, J = 10.4 Hz, 2H). ^{13}C NMR (100 MHz, MeOD): δ 180.2, 140.7, 138.8, 134.7, 133.0, 129.5, 128.0, 127.3, 125.3, 124.2, 116.6, 77.2, 67.1, 45.8. HRMS (ESI) calcd for $C_{16}H_{14}ClNNaO_3$ $[M + Na]^+$ = 326.0560, found 326.0562.

(1-Benzyl-3-((4-fluoro-2-nitrophenyl)amino)-2-oxoindolin-3-yl)methyl *tert*-Butyl Carbonate (6t). To a solution of alcohol **4t** (83 mg, 0.2 mmol), DMAP (2 mg, 0.02 mmol), and Et_3N (61 mg, 0.60 mmol) in CH_2Cl_2 (15 mL) was added Boc_2O (87 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. After the completion of the reaction, the mixture was diluted with sat. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel (hexanes:EtOAc, 20:1 → 8:1) provided **6t** as a yellow solid (93 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.87 (dd, J = 8.9, 3.0 Hz, 1H), 7.41 (d, J = 7.3 Hz, 2H), 7.38−7.29 (m, 5H), 7.05 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.73−6.62 (m, 1H), 5.73 (dd, J = 9.4, 4.4 Hz, 1H), 5.10 (d, J = 15.3 Hz, 1H), 4.91 (d, J = 15.3 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.33 (d, J = 11.1 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 153.4 (d, J = 239.0 Hz), 152.8, 141.7, 139.3, 135.2, 133.1 (d, J = 8.0 Hz), 130.3, 129.0, 128.2, 128.1, 125.9, 124.6, 124.0 (d, J = 23.0 Hz), 123.6, 116.3 (d, J = 7.1 Hz), 112.6 (d, J = 26.0 Hz), 110.2, 83.4, 69.4, 63.8, 44.6, 27.6; HRMS (ESI) calcd for $C_{27}H_{26}FN_3NaO_6$ $[M + Na]^+$ = 530.1703, found 530.1707.

(3-((2-Amino-4-fluorophenyl)amino)-1-benzyl-2-oxoindolin-3-yl)methyl *tert*-Butyl Carbonate (7t). To a solution of compound **6t** (80 mg, 0.16 mmol) in MeOH (10 mL) was added 5% Pd/C, and the mixture was stirred at room temperature under a hydrogen balloon

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for 4 h. Then the catalyst was filtered off through a Celite bed and washed with MeOH (20 mL). The filtrate was concentrated in vacuo to give crude product, which was purified on silica gel (hexanes:EtOAc, 10:1 → 2:1) to provide **7t** as a white solid (72 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 7.3 Hz, 1H), 7.24−7.19 (m, 3H), 7.17 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.97 (dd, J = 5.3, 3.6 Hz, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.34 (dd, J = 10.1, 2.8 Hz, 1H), 6.25 (dd, J = 8.7, 5.9 Hz, 1H), 6.01 (td, J = 8.5, 2.8 Hz, 1H), 5.02 (d, J = 15.9 Hz, 1H), 4.72 (d, J = 15.8 Hz, 1H), 4.63 (d, J = 10.9 Hz, 1H), 4.31 (d, J = 10.9 Hz, 1H), 4.15 (s, 2H), 3.89 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 160.2 (d, J = 239.0 Hz), 153.1, 143.6 (d, J = 10.8 Hz), 142.8, 134.9, 129.7, 128.7, 127.6, 126.9, 126.9, 126.7, 125.5 (d, J = 9.7 Hz), 125.1, 123.0, 109.7, 104.8 (d, J = 22.0 Hz), 103.3 (d, J = 25.0 Hz), 82.8, 69.4, 66.5, 43.9, 27.7; HRMS (ESI) calcd for $C_{27}H_{28}FN_3NaO_4$ $[M + Na]^+$ = 500.1962, found 500.1938

(1-Benzyl-3-(5-fluoro-1*H*-benzo[*d*]imidazol-1-yl)-2-oxoindolin-3-yl)methyl *tert*-Butyl Carbonate (8t). To a 25 mL round-bottom flask equipped with a magnetic stir bar was added **7t** (72 mg, 0.15 mmol), 10.0 mL of triethyl orthoformate, and *p*-toluenesulfonic acid monohydrate (3 mg, 0.015 mmol), and the resulting solution was stirred for 8 h. The solution was then diluted with ethyl acetate (15 mL) and washed with $NaHCO_3$ (15 mL). The aqueous layer was back-extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown solid (70 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.45 (dt, J = 9.1, 4.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.33 (dt, J = 9.4, 5.0 Hz, 5H), 7.28 (d, J = 7.5 Hz, 1H), 7.06 (dd, J = 17.0, 9.5 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.71 (td, J = 9.1, 2.4 Hz, 1H), 6.45 (dd, J = 9.0, 4.5 Hz, 1H), 5.16 (d, J = 11.8 Hz, 1H), 5.06−4.94 (m, 2H), 4.82 (d, J = 11.8 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 159.4 (d, J = 238.0 Hz), 152.4, 144.8 (d, J = 13.0 Hz), 143.0, 142.5, 134.6, 131.2, 129.0, 128.2, 127.7, 125.8, 124.4, 123.8, 111.9 (d, J = 9.0 Hz), 119.6 (d, J = 26.0 Hz), 110.5, 106.3 (d, J = 24.0 Hz), 83.6, 66.3, 65.5, 44.6, 27.6. HRMS (ESI) calcd for $C_{28}H_{26}FN_3NaO_4$ $[M + Na]^+$ = 510.1805, found 510.1812.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **4a**−**4u**, **5a**−**5n**, **6t**, **7t**, and **8t**; and X-ray crystal data for compound **4a**. 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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