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Synergistic Catalysis-Enabled Reaction of 2-Indolymethanols with Oxonium Ylides: Construction of 3-Indolyl-3-Alkoxy Oxindole Framework

Chun Ma, Jia-Yu Zhou, Yi-Zhu Zhang, Yinchun Jiao, Guang-Jian Mei and Feng Shi*

Abstract: A synergistic catalysis-enabled reaction of 2-indolymethanols with oxonium ylides has been established, which makes use of the three-component reaction of 3-diazooxindoles, alcohols and 2-indolymethanols under the cooperative catalysis of metal complex and Brønsted acid. This reaction has not only provided a new approach for constructing 3-indolyl-3-alkoxy oxindole scaffolds by utilizing the indole C3-electrophilicity, but also realized a nucleophilic addition of metal associated ylide to 2-indolylmethanols for the first time. In addition, this reaction has also established a rarely reported trapping of onium ylides with aryl electrophiles.

Introduction

Indole derivatives represent one of the most important class of heterocyclic compounds, which played important roles in pharmaceuticals, agriculture and material science.[1] Among indole derivatives, 3-indolyl-3-alkoxy oxindole or 3-indolyl-3-hydroxy oxindole constitutes the core structures of many natural products and bioactive synthetic compounds (Figure 1).[2-3] For instance, shewanellines A is an alkaloids from deep-sea bacterium Shewanella piezotolerans with antitumor activity.[2] Compound **I** shows cytotoxic activity to U937 cell line,[3] and compound **II** is a lead compound of antimicrobial agents.[4] In addition, this class of indole derivatives serve as versatile reactants and building blocks in organic synthesis.[5-6] Therefore, the construction of 3-indolyl-3-alkoxy oxindole framework has drawn great attention from the chemistry community.

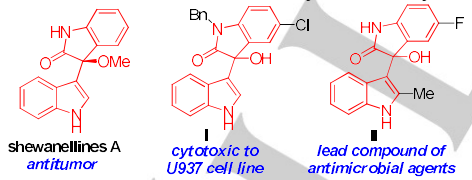

Figure 1. Selected bioactive compounds containing 3-indolyl-3-alkoxy (or hydroxyl) oxindole scaffolds

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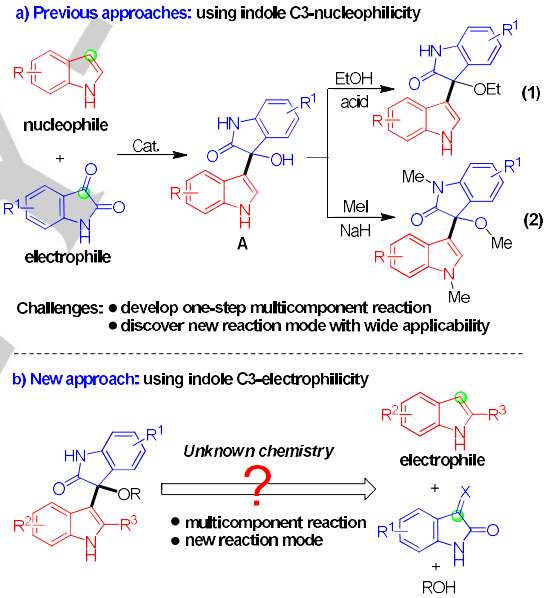
In previous approaches for constructing 3-indolyl-3-alkoxy oxindole scaffolds (Scheme 1a), indoles were used as nucleophiles and isatins were employed as electrophiles, which underwent an aldol reaction to generate 3-indolyl-3-hydroxy oxindoles **A**.[7] Then, under acidic conditions, intermediate products **A** could derive into 3-indolyl-3-ethoxy oxindoles by the reactions with ethanol (eq. 1).[8] Alternatively, under basic conditions, intermediate products **A** could transform into 3-indolyl-3-methoxy oxindoles by methylation (eq. 2).[9]



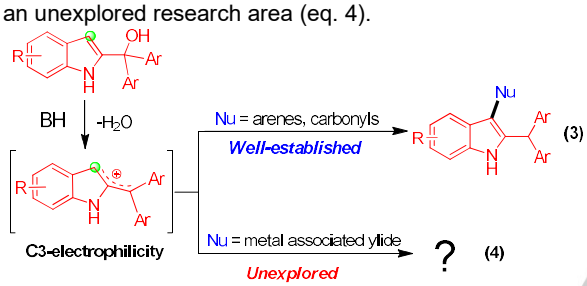
Scheme 1. Approaches for constructing 3-indolyl-3-alkoxy oxindole scaffolds

In spite of the established approaches, the methods for constructing 3-indolyl-3-alkoxy oxindole scaffolds are still very limited. In addition, there are still some challenges in developing new methods for constructing such scaffolds. The first one is to develop one-step multicomponent reaction because a two-step process is needed in previous approaches. The second one is to discover new reaction mode with wide applicability because previous approaches utilized the well-established C3-nucleophilicity of indoles and the substrate scope was not broad. So, it has become an urgent task to develop one-step multicomponent reaction with new reaction mode and wide applicability for the construction of 3-indolyl-3-alkoxy oxindole frameworks, which requires specific design of the reaction.

In order to fulfill this task, we considered whether 3-indolyl-3-alkoxy oxindole frameworks could be constructed by a new approach involving a multicomponent reaction of

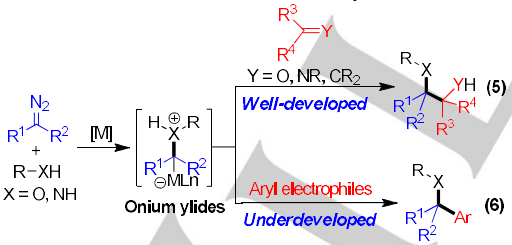
indole derivatives, isatin derivatives and alcohols (Scheme 1b). This approach would utilize the indole C3-electrophilicity, which remains a dark side of indole chemistry[10] and requires to be exploited.

Indolylmethanols have proven to be versatile reactants for constructing indole-related frameworks.[5-6,11-12] Recently, we have discovered that the C3-position of 2-indolylmethanol displays unusual electrophilicity because it can transform into a delocalized cation via dehydration in the presence of a Brønsted acid (BH), which is readily to be attacked by nucleophiles (Nu) at the C3-position (Scheme 2).[13-14] However, the nucleophiles are confined to arenes (such as 2-naphthol and indole)[14] and carbonyls (such as pyrazol-5-one and enolizable anhydride),[13] and the reactions between such nucleophiles and 2-indolylmethanols are well-established (eq. 3).[13-14] In sharp contrast, metal associated ylide has never been employed as nucleophiles to react with 2-indolylmethanols, which remains to be an unexplored research area (eq. 4).



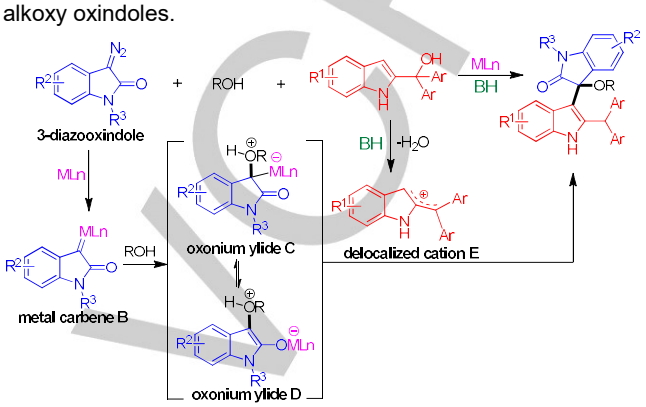
Scheme 2. Profile of 2-indolylmethanol-involved C3-substitutions

Among metal associated ylides, onium ylides bearing both acidic protons and basic carbanions in vicinal proximity, generated in situ from diazocompounds and anilines/alcohols, have recently been recognized as active nucleophiles, which can be trapped by electrophiles (Scheme 3).[15] So, elegant achievements have been obtained in this research field by using aldimines, carbonyls and activated alkenes as electrophiles (eq. 5).[15-16] However, on the contrary, the reactions between onium ylides and aryl electrophiles are still underdeveloped (eq. 6), which remains to be an unknown chemistry.



Scheme 3. Profile of reactions trapping onium ylides

In order to develop new approach for constructing 3-indolyl-3-alkoxy oxindole scaffolds, and to explore the above mentioned unknown chemistry, we designed a synergistic catalysis-enabled reaction of 2-indolylmethanols with oxonium ylides based on the great advantages of cooperative catalysis.[17-18] As illustrated in Scheme 4, the three-component reaction of 3-diazooxindoles, alcohols and 2-indolylmethanols would construct 3-indolyl-3-alkoxy oxindole scaffolds under the synergistic catalysis of metal complex (MLn) and Brønsted acid (BH).[19] In the presence of MLn, 3-diazooxindole would transform into metal carbene species **B**, which would be attacked by alcohol to form active oxonium ylide **C** or **D**. Meanwhile, in the presence of BH, 2-indolylmethanols would transform into delocalized cation **E** via dehydration. Then, the delocalized cation **E** would act as an aryl electrophile to trap the oxonium ylide **C** or **D**, leading to the generation of 3-indolyl-3-alkoxy oxindoles.



Scheme 4. Design of the reaction between 2-indolymethanols and oxonium ylides

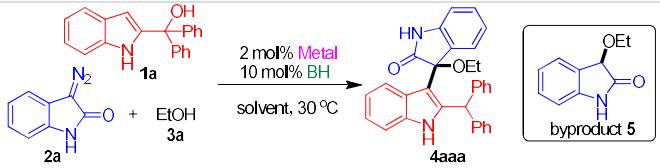
Herein, we report the details of our designed reaction of 2-indolymethanols with oxonium ylides, which was enabled by a synergistic catalysis of metal complex and Brønsted acid. This three-component reaction of 3-diazooxindoles, alcohols and 2-indolymethanols provided an alternative method for constructing 3-indolyl-3-alkoxy oxindole scaffolds.

Results and Discussion

To testify the possibility of our design, the three-component reaction of 2-indolymethanol **1a**, 3-diazooxindole **2a** and ethanol **3a** was employed as a model reaction under the cooperative catalysis of a metal complex and a Brønsted acid in chloroform at 30 °C (Table 1). Initially, in the presence of an iridium complex and racemic binaphthol-derived phosphoric acid (RPA), the desired reaction indeed occurred to afford 3-indolyl-3-alkoxy oxindole **4aaa** albeit with a low yield of 28% (entry 1). Then, a series of metal complexes were screened (see the Supporting Information for details), which found that $Rh_2(OAc)_4$ was the best metal catalyst (entry 2) because it could promote the reaction in the highest yield of 45% (entry 2). Next, different solvents were evaluated (entries 2-7), which revealed chloroform was still the most suitable solvent in terms of the yield (entry 2 vs entries 3-7). Subsequently, several Brønsted acids were screened (entries 8-11), only diphenyl phosphoric acid (entry 8) and trifluoroacetic acid (entry 10) could catalyze the reaction. Among them, diphenyl phosphoric acid could deliver the reaction in the highest yield of 53% (entry 8). Furthermore, slightly modulating the ratio of the reagents led to a higher yield of 58% (entry 12). In order to further improve the yield, other reaction parameters such as additives, reaction temperature, reagents ratio and catalyst loading were carefully modulated, however, no improvement could be obtained (see the Supporting Information for details).

This is because a byproduct **5** was always generated during the condition optimization, which was formed via proton transfer of oxonium ylide **C**. So, the optimal reaction conditions were finally chosen as what entry 12 illustrated.

Table 1. Optimization of reaction conditions[a]

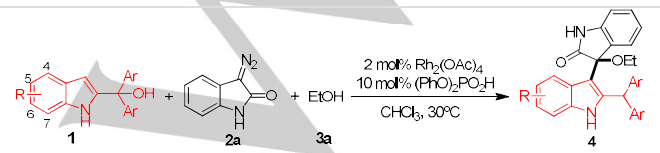


entry	Metal complex	BH	solvent	yield (%)[b]
1	$[Ir(COE)_2Cl]_2$	RPA	$CHCl_3$	28
2	$Rh_2(OAc)_4$	RPA	$CHCl_3$	45
3	$Rh_2(OAc)_4$	RPA	EtOAc	34
4	$Rh_2(OAc)_4$	RPA	CH_3CN	trace
5	$Rh_2(OAc)_4$	RPA	THF	trace
6	$Rh_2(OAc)_4$	RPA	acetone	43
7	$Rh_2(OAc)_4$	RPA	toluene	40
8	$Rh_2(OAc)_4$	$(PhO)_2PO_2H$	$CHCl_3$	53
9	$Rh_2(OAc)_4$	TsOH	$CHCl_3$	trace
10	$Rh_2(OAc)_4$	CF_3COOH	$CHCl_3$	46
11	$Rh_2(OAc)_4$	CF_3SO_3H	$CHCl_3$	trace
12[c]	$Rh_2(OAc)_4$	$(PhO)_2PO_2H$	$CHCl_3$	58

[a] Unless otherwise indicated, the reaction was carried out at the 0.1 mmol scale in a solvent for 12 h, the molar ratio of **1a**:**2a**:**3a** was 1:1.5:8.5. [b] Isolated yield of product **4aaa**. [c]The molar ratio of **1a**:**2a**:**3a** was 1:2:8.5. RPA = racemic binaphthol-derived phosphoric acid.

After establishing the optimal reaction conditions, we carried out the investigation on the substrate scope of the reaction. First, the generality of 2-indolylmethanols **1** was investigated. As shown in Table 2, this three-component reaction was applicable to a wide range of 2-indolylmethanols **1** bearing different R/Ar groups, offering 3-indolyl-3-alkoxy oxindoles **4** in moderate yields. In detail, C4 to C6-substituted 2-indolylmethanols **1b-1g** regardless of their electronic nature could smoothly participate in the reaction (entries 2-7), while the position and the electronic nature of the substituents seemed to have no evident effect on the yield. In addition, several phenyls groups bearing either electron-donating or electron-withdrawing substituents could serve as suitable Ar groups of 2-indolylmethanols **1**, which took part in the three-component reaction with moderate yields (entries 8-10).

Table 2. Substrate scope of 2-indolylmethanols **1**[a]

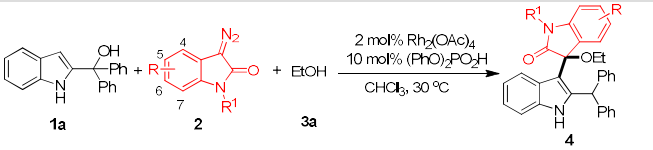


entry	**4**	R/Ar (**1**)	yield (%)[b]
1	**4aaa**	H/Ph (**1a**)	58
2	**4baa**	4-Cl/Ph (**1b**)	47
3	**4caa**	5-Cl/Ph (**1c**)	40
4	**4daa**	5-MeO/Ph (**1d**)	46
5	**4eaa**	6-Cl/Ph (**1e**)	42
6	**4faa**	6-Br/Ph (**1f**)	56
7	**4gaa**	6-MeO/Ph (**1g**)	40
8	**4haa**	H/*p*-MeC_6H_4 (**1h**)	51
9	**4iaa**	H/*p*-$MeOC_6H_4$ (**1i**)	40
10	**4jaa**	6-Cl/*p*-FC_6H_4 (**1j**)	48

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in $CHCl_3$ (2 mL) for 12 h, and the molar ratio of **1**:**2a**:**3a** was 1:2:8.5. [b] Isolated yield.

Next, the substrate scope of 3-diazooxindoles **2** was studied by the reactions with 2-indolylmethanol **1a** and alcohol **2a** (Table 3). Obviously, this reaction was amenable to a wide scope of 3-diazooxindoles **2** bearing various R substituents at different positions of the phenyl ring (entries 1-10), which generated structurally diversified products **4** in moderate to good yields (41% to 78%). Specifically, C5 or C6-substituted 3-diazooxindoles **2b-2h** could be applicable to the reaction (entries 1-7). In addition, disubstituted 3-diazooxindoles **2i-2k** also served as suitable substrates (entries 8-10). Among them, 6-chloro-substituted 3-diazooxindole **2f** delivered the corresponding product **4afa** in the highest yield of 78% (entry 5). Notably, *N*-Boc protected 3-diazooxindole **2l** could be successfully employed to the reaction in a considerable yield of 64% (entry 11), which demonstrated that the N-H group of 3-diazooxindoles **2** was not a necessity for carrying out the desired three-component reaction.

Table 3. Substrate scope of 3-diazooxindoles **2**[a]

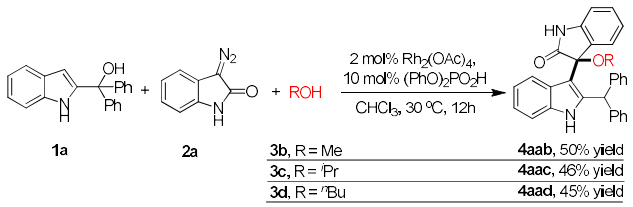


entry	**4**	R/R^1 (**2**)	yield (%)[b]
1	**4aba**	5-F/H (**2b**)	47
2	**4aca**	5-Cl/H (**2c**)	41
3	**4ada**	5-Br/H (**2d**)	64
4	**4aea**	5-NO_2/H (**2e**)	63
5	**4afa**	6-Cl/H (**2f**)	78
6	**4aga**	6-Br/H (**2g**)	52
7	**4aha**	6-Me/H (**2h**)	40
8	**4aia**	4,6-F_2/H (**2i**)	64
9	**4aja**	5,6-F_2/H (**2j**)	48
10	**4aka**	5,7-Me_2/H (**2k**)	60

11	**4ala**	H/Boc (**2l**)	64

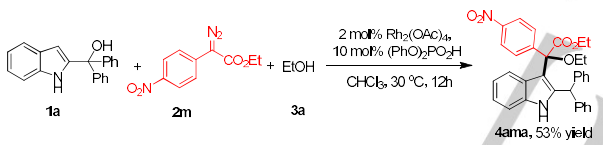
[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in $CHCl_3$ (2 mL) for 12 h, and the molar ratio of **1a**:**2**:**3a** was 1:2:8.5. [b] Isolated yield.

Finally, the applicability of alcohols **3** in the three-component reaction was investigated (Scheme 5). Apart from ethanol **3a**, this reaction could also be applicable to methanol **3b**, isopropanol **3c** and butanol **3d**, which afforded the corresponding products **4** in acceptable yields.



Scheme 5. Applicability of alcohols **3**

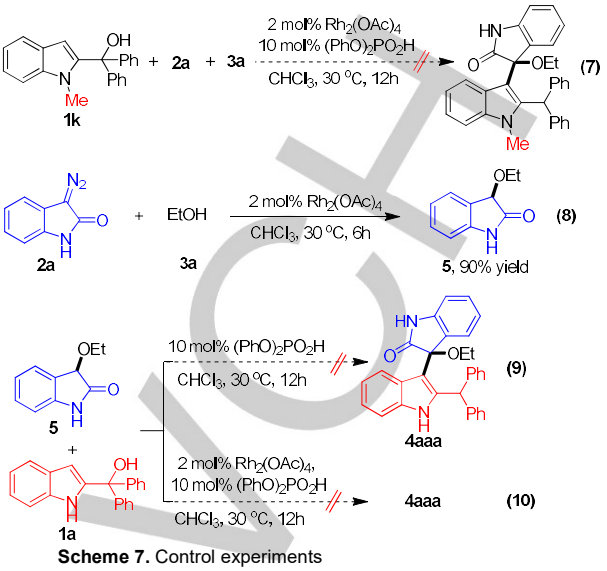
In addition to 3-diazooxindoles **2**, ethyl 4-nitrophenyldiazoacetate **2m** could also be employed as a competent substrate in the three-component reaction under the standard reaction conditions, which offered product **4ama** in a moderate yield of 53% (Scheme 6). This result further enlarged the applicability of the designed three-component reaction.



Scheme 6. Using ethyl 4-nitrophenyldiazoacetate **2m** as a substrate

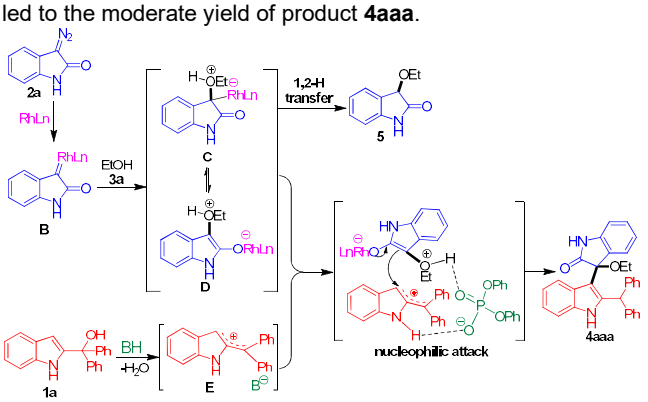
The structures of all products **4** were unambiguously identified by ^1H and ^{13}C NMR, IR and HRMS. Moreover, the structure of product **4aaa** was determined by single crystal X-ray diffraction analysis (see the Supporting Information for details).[20]

In order to gain some insights into the reaction mechanism, we performed some control experiments (Scheme 7). First, *N*-methyl protected 2-indolylmethanol **1k** was utilized as a substrate, which failed to perform the three-component reaction with 3-diazooxindole **2a** and ethanol **3a** (eq. 7). This result indicated that the N-H group of 2-indolylmethanols played an important role in controlling the reactivity of the three-component reaction. Second, we studied the formation of byproduct **5** by reacting 3-diazooxindole **2a** with ethanol **3a** under the catalysis of $Rh_2(OAc)_4$. As expected, this reaction generated byproduct **5** in a high yield (eq. 8), which implied that the formation of byproduct **5** is a competitive side reaction of the designed three-component reaction. At last, byproduct **5** was subject to the reaction with 2-indolylmethanol **1a** either under the mono-catalysis of diphenyl phosphoric acid (eq. 9) or under the cooperative catalysis of $Rh_2(OAc)_4$ and diphenyl phosphoric acid (eq. 10). In both cases, product **4aaa** could not be generated, which indicated that byproduct **5** was not an intermediate product toward the generation of desired products **4**.



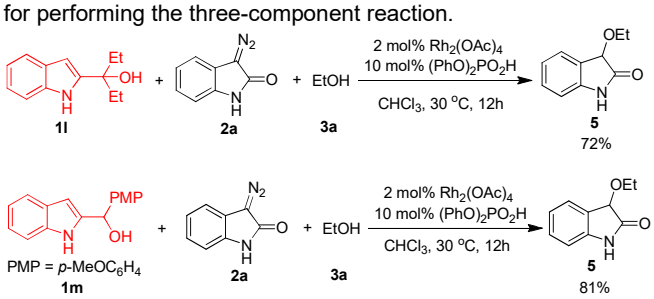
Scheme 7. Control experiments

Based on the control experiments, we suggested a possible reaction pathway (Scheme 8). As exemplified by the formation of product **4aaa**, under the catalysis of RhLn, 3-diazooxindole **2a** transform into a rhodium carbene species **B**, which was attacked by ethanol **3a** to form active oxonium ylides **C** and **D**. The 1,2-hydrogen transfer of oxonium ylide **C** led to the generation of byproduct **5**. At same time, under the catalysis of BH, 2-indolymethanol **1a** transformed into delocalized cation **E** via dehydration. Then, activated by the anion of BH via forming hydrogen-bonding and ion-paring interactions, the oxonium ylide **D** performed a nucleophilic attack to the delocalized cation **E**, thus affording the desired product **4aaa**. In the whole process, the synergistic catalysis of RhLn and BH enabled the proceeding of the designed three-component reaction. Among the reaction process, the nucleophilic attack of intermediate **D** to cation **E** might be the rate-determining step. This is because byproduct **5** could rapidly generated in the reaction system, which means that the formation of oxonium ylide **C** is very quickly. In addition, the formation of delocalized cation **E** from 2-indolymethanol **1a** in the presence of an acid is also very fast, which could be detected by TLC. So, the step of nucleophilic attack of intermediate **D** to cation **E** is relatively slow and difficult, which led to the moderate yield of product **4aaa**.



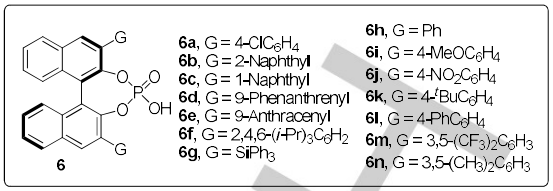
Scheme 8. Suggested reaction pathway

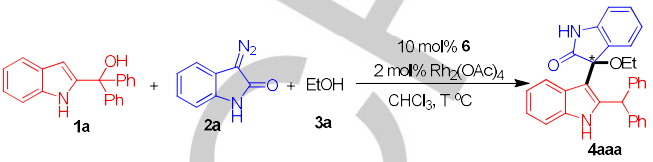
In the three-component reactions, 2-indolylmethanols **1** bearing two phenyl groups are employed as substrates in all cases. This is because the two phenyl group could stabilize the delocalized cation **E**. In order to investigate the possible substrate limitation of the reaction, we utilized 2-indolylmethanols **1l** and **1m** as substrates, which have two alkyl groups or one phenyl group instead of two phenyl groups (Scheme 9). However, the two substrates **1l** and **1m** failed to participate in the reaction, and only byproduct **5** was generated in both cases. This result demonstrated that the two phenyl groups in the structure of 2-indolylmethanols **1** were necessary for performing the three-component reaction.



Scheme 9. Substrate limitation

Finally, we performed a preliminary investigation on the catalytic asymmetric version of this three-component reaction. As shown in Table 4, we initially utilized several representative chiral phosphoric acids (CPAs) **6a-6g** bearing different substituents on the 3,3'-position as chiral Brønsted acids to catalyze the reaction (entries 1-7). It was found that CPAs **6a-6d** could catalyze the reaction to give product **4aaa** albeit with low enantioselectivities (entries 1-4), while CPAs **6e-6g** failed to catalyze the reaction (entries 5-7). Among them, CPA **6a** bearing two *para*-chlorophenyl substituents on the 3,3'-position could promote the reaction to afford product **4aaa** in 15% ee (entry 1). So, we further screened a series of CPAs **6h-6n** bearing different substituted phenyl groups (entries 8-14). However, most of these CPAs failed to catalyze the reaction (entries 8-9, 12, 14). Although CPAs **6j-6k** and **6m** could catalyze the reaction, the enantioselectivities were still in an extremely low level (entry 10-11, 13). Then, in the presence of CPA **6a**, we changed the reaction temperature (entries 15-17). Elevating the reaction temperature from 30 °C to 50 °C led to a sharp decrease of the enantioselectivity (entry 1 vs entry 15). Although lowering the reaction temperature from 30 °C to 0 °C could slightly improve the enantioselectivity, the yield of product **4aaa** was dropped sharply (entry 1 vs entry 16). In addition, when the reaction temperature was lowered to -30 °C, the three-component reaction could hardly occur (entry 17). Thus, it seemed that it is a great challenge to control the enantioselectivity of this three-component reaction.





entry	6	T (°C)	yield (%)[b]	ee (%)[c]
1	**6a**	30	58	15
2	**6b**	30	38	11
3	**6c**	30	16	0
4	**6d**	30	41	12
5	**6e**	30	trace	-
6	**6f**	30	trace	-
7	**6g**	30	trace	-
8	**6h**	30	trace	-
9	**6i**	30	trace	-
10	**6j**	30	52	15
11	**6k**	30	51	8
12	**6l**	30	trace	-
13	**6m**	30	41	12
14	**6n**	30	trace	-
15	**6a**	50	42	0
16	**6a**	0	19	18
17	**6a**	-30	trace	-

Table 4. Preliminary investigation on the catalytic asymmetric version[a]

[a] Unless indicated otherwise, the reaction was carried out at 0.1 mmol scale in $CHCl_3$ (2 mL) for 12 h, and the molar ratio of **1**:**2a**:**3a** was 1:1.2:8.5. [b] Isolated yield. [c] The *ee* value was determined by HPLC.

Conclusions

In summary, we have established a synergistic catalysis-enabled reaction of 2-indolylmethanols with oxonium ylides, which makes use of the three-component reaction of 3-diazooxindoles, alcohols and 2-indolylmethanols under the cooperative catalysis of metal complex and Brønsted acid. This reaction has not only provided a new approach for constructing 3-indolyl-3-alkoxy oxindole scaffolds by utilizing the indole C3-electrophilicity, but also realized a nucleophilic addition of metal associated ylide to 2-indolylmethanols for the first time. In addition, this reaction has also established a rarely reported trapping of onium ylides with aryl electrophiles. This approach will not only advance the chemistry of 2-indolylmethanols and onium ylides, but also provide a good example of synergistic catalysis.

Experimental Section

General information

^{1}H and ^{13}C NMR spectra were measured respectively at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS instrument. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated. The X-ray source used for the single crystal X-ray diffraction analysis of compound **4aaa** was GaKα (λ = 1.34139), and the thermal ellipsoid was drawn at the 30% probability level. Analytical grade solvents for the column chromatography were distilled before use. All starting materials commercially available were used directly.

General procedure for the synthesis of products 4

Under argon atmosphere, $Rh_2(OAc)_4$ (0.002 mmol), diphenyl phosphate (0.01 mmol) and 2-indolylmethanols **1** (0.1 mmol) were added to a dry Schlenk tube. Then, chloroform (1 mL) was added to the reaction mixture, which was stirred at 30 °C for 5 minutes. Subsequently, a solution of the diazo compounds **2** (0.2 mmol) and alcohols **3** (0.85 mmol) in chloroform (1 mL) was slowly added to the reaction mixture, which was further stirred at 30 °C for 12 h. Finally, the reaction mixture was directly purified through preparative thin layer chromatography on silica gel to afford pure products **4**.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4aaa): 58% yield (26.7 mg); white solid; m.p. 184–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.51 (s, 1H), 7.65 (s, 1H), 7.33 (s, 1H), 7.26 – 7.13 (m, 9H), 7.09 – 6.91 (m, 7H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.19 (s, 1H), 3.52 – 3.41 (m, 1H), 3.34 – 3.22 (m, 1H), 1.14 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.6, 142.8, 142.6, 141.2, 137.6, 135.2, 129.8, 129.2, 129.0, 128.5, 128.3, 127.0, 126.6, 126.5, 126.2, 122.9, 121.6, 121.1, 119.9, 110.6, 110.4, 109.5, 82.5, 60.0, 48.4, 15.2; IR (KBr): 2359, 1722, 1470, 1261, 745, 699, 668 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{26}N_2O_2+Na)^+$ requires m/z 481.1892, found m/z 481.1895; The enantiomeric excess: 15%, determined by HPLC (Daicel Chiralpak IA, hexane/ isopropanol = 70/ 30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 4.787 (major), t_R = 8.657 (minor).

3-(2-benzhydryl-4-chloro-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4baa): 47% yield (23.3 mg); white solid; m.p. 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1H NMR (400 MHz, CDCl3) δ 8.17 (s, 1H), 7.57 (s, 1H), 7.32 – 7.26 (m, 2H), 7.26 – 7.20 (m, 3H), 7.19 – 7.14 (m, 3H), 7.07 (d, J = 8.0 Hz, 1H), 7.03 – 6.91 (m, 6H), 6.91 – 6.86 (m, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.37 (s, 1H), 3.47 – 3.39 (m, 1H), 3.31 – 3.23 (m, 1H), 1.08 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.4, 141.1, 140.9, 140.8, 135.2, 132.7, 132.5, 130.5, 130.3, 130.0, 128.8, 128.7, 128.6, 126.6, 126.3, 123.2, 121.9, 120.7, 120.1, 110.8, 110.2, 109.9, 82.3, 60.0, 47.4, 15.2; IR (KBr): 2360, 1722, 1469, 1260, 1232, 765, 751 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}ClN_2O_2+Na)^+$ requires m/z 515.1503, found m/z 515.1501.

3-(2-benzhydryl-5-chloro-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4caa): 40% yield (19.6 mg); light yellow solid; m.p. 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.98 (s, 1H), 7.65 (s, 1H), 7.48 (s, 1H), 7.26 – 7.12 (m, 8H), 7.12 – 7.02 (m, 2H), 7.02 – 6.99 (m, 1H), 6.98 – 6.89 (m, 4H), 6.72 (d, J = 7.7 Hz, 1H), 5.93 (s, 1H), 3.50 – 3.41 (m, 1H), 3.32 – 3.24 (m, 1H), 1.17 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.9, 142.3, 142.1, 141.1, 138.6, 133.4, 130.1, 129.1, 128.9, 128.6, 128.5, 128.3, 126.8, 126.7, 126.1, 125.6, 123.1, 122.0, 121.1, 111.6, 110.5, 109.5, 82.2, 60.1, 48.4, 15.2; IR (KBr): 2359, 1723, 1469, 1261, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}ClN_2O_2+Na)^+$ requires m/z 515.1503, found m/z 515.1505.

3-(2-benzhydryl-5-methoxy-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4daa): 46% yield (22.4 mg); white solid; m.p. 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.29 (s, 1H), 7.54 (s, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.25 – 7.17 (m, 6H), 7.13 (m, 1H), 7.05 – 6.96 (m, 6H), 6.80 (s, 1H), 6.76 – 6.69 (m, 2H), 6.10 (s, 1H), 3.66 (s, 3H), 3.50 – 3.43 (m, 1H), 3.35 – 3.26 (m, 1H), 1.14 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.4, 153.9, 142.8, 142.6, 141.3, 138.4, 130.3, 129.9, 129.2, 128.9, 128.8, 128.5, 128.2, 127.4, 126.6, 126.4, 126.3, 122.9, 111.9, 111.3, 110.3, 109.1, 102.9, 82.4, 59.9, 55.5, 48.5, 15.2; IR (KBr): 2360, 1659, 1401, 1261, 764, 750, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{32}H_{28}N_2O_3+Na)^+$ requires m/z 511.1998, found m/z 511.1997.

3-(2-benzhydryl-6-chloro-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4eaa): 42% yield (20.7 mg); white solid; m.p. 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H), 7.62 (s, 1H), 7.42 – 7.31 (m, 1H), 7.25 – 7.08 (m, 9H), 7.02 – 6.86 (m, 6H), 6.71 (d, J = 7.7 Hz, 1H), 5.99 (s, 1H), 3.50 – 3.39 (m, 1H), 3.31 – 3.19 (m, 1H), 1.15 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.1, 142.4, 142.2, 141.1, 137.9, 135.5, 130.0, 129.1, 128.9, 128.6, 128.4, 127.6, 126.8, 126.6, 126.1, 125.7, 123.0, 122.3, 120.6, 110.6, 110.5, 109.8, 82.2, 60.1, 48.3, 15.2; IR (KBr): 2360, 1722, 1470, 1261, 764, 749, 672 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}ClN_2O_2+Na)^+$ requires m/z 515.1503, found m/z 515.1505.

3-(2-benzhydryl-6-bromo-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4faa): 56% yield (30.2 mg); white solid; m.p. 171–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.26 (s, 1H), 7.63 (s, 1H), 7.40 – 7.27 (m, 2H), 7.24 – 7.14 (m, 8H), 7.08 – 7.03 (m, 1H), 6.99 – 6.91 (m, 5H), 6.72 (d, J = 7.8 Hz, 1H), 6.01 (s, 1H), 3.49 – 3.41 (m, 1H), 3.31 – 3.23 (m, 1H), 1.15 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.2, 142.4, 142.1, 141.1, 137.9, 135.9, 130.0, 129.1, 128.9, 128.6, 128.4, 126.8, 126.6, 126.1, 126.0, 123.2, 123.0, 122.7, 115.3, 113.6, 110.5, 109.8, 82.2, 60.1, 48.3, 15.2; IR (KBr): 2359, 1720, 1469, 1261, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}BrN_2O_2+Na)^+$ requires m/z 559.0997, found m/z 559.1000.

3-(2-benzhydryl-6-methoxy-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4gaa): 40% yield (19.7 mg); white solid; m.p. 99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.90 (s, 1H), 7.49 (s, 1H), 7.31 (s, 1H), 7.24 – 7.15 (m, 8H), 7.02 – 6.93 (m, 5H), 6.70 (d, J = 7.9 Hz, 1H), 6.67 – 6.61 (m, 2H), 5.99 (s, 1H), 3.75 (s, 3H), 3.50 – 3.42 (m, 1H), 3.33 – 3.26 (m, 1H), 1.14 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.1, 156.0, 142.9, 142.6, 141.0, 135.9, 129.8, 129.1, 129.0, 128.9, 128.4, 128.3, 126.6, 126.4, 126.2, 122.9, 122.0, 121.3, 110.2, 109.8, 109.4, 94.1, 82.3, 60.0, 55.5, 48.3, 15.2; IR (KBr): 2359, 1727, 1462, 1261, 764, 750, 668 cm^{-1}; ESI FTMS exact mass calcd for $(C_{32}H_{28}N_2O_3+Na)^+$ requires m/z 511.1998, found m/z 511.2000.

3-(2-(di-p-tolylmethyl)-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4haa): 51% yield (24.9 mg); white solid; m.p. 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60 (d, J = 7.8 Hz, 2H), 7.54 – 7.44 (m, 1H), 7.23 – 7.18 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.08 – 7.02 (m, 3H), 6.99 – 6.92 (m, 4H), 6.89 – 6.81 (m, 4H), 6.67 (d, J = 7.9 Hz, 1H), 5.96 (s, 1H), 3.51 – 3.44 (m, 1H), 3.36 – 3.29 (m, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.8, 140.9, 139.8, 139.6, 136.0, 135.9, 135.0, 129.6, 129.2, 129.1, 129.0, 128.9, 128.8, 126.2, 122.9, 121.5, 119.8, 110.6, 110.0, 109.2, 101.7, 82.2, 59.9, 47.6, 21.1, 21.0, 15.3; IR (KBr): 2359, 1513, 1470, 1275, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_2O_2+Na)^+$ requires m/z 509.2205, found m/z 509.2198.

3-(2-(bis(4-methoxyphenyl)methyl)-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4iaa): 40% yield (20.9 mg); white solid; m.p. 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (s, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 7.25 – 7.18 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.00 – 6.93 (m, 2H), 6.92 – 6.82 (m, 4H), 6.77 (d, J = 8.7 Hz, 2H), 6.73 – 6.64 (m, 3H), 5.90 (s, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.51 – 3.44 (m, 1H), 3.37 – 3.30 (m, 1H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm): 176.6, 158.2, 140.9, 135.0, 130.0, 129.9, 129.6, 129.2, 126.2, 122.9, 121.5, 119.8, 113.7, 113.6, 110.6, 109.9, 109.1, 82.2, 59.9, 55.2, 46.7, 15.3; IR (KBr): 2359, 1520, 1461, 1275, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_2O_4+Na)^+$ requires m/z 541.2104, found m/z 541.2109.

3-(2-(bis(4-fluorophenyl)methyl)-6-chloro-1*H*-indol-3-yl)-3-ethoxyindolin-2-one (4jaa): 48% yield (25.3 mg); white solid; m.p. 100–102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H), 7.57 (s, 1H), 7.29 – 7.25 (m, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.17 – 7.16 (m, 1H), 7.13 (s, 1H), 7.02 – 6.98 (m, 1H), 6.97 – 6.85 (m, 9H), 6.75 (d, J = 7.8 Hz, 1H), 6.14 (s, 1H), 3.47 – 3.38 (m, 1H), 3.30 – 3.22 (m, 1H), 1.11 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.2, 162.9, 160.4, 160.3, 141.0, 138.2, 137.8, 135.5, 130.5 (d, J = 7.8 Hz), 130.3 (d, J = 7.8 Hz), 130.2, 128.5, 127.9, 126.1, 125.4, 123.2, 122.1, 120.8, 115.5 (d, J = 16.1 Hz), 115.3 (d, J = 16.1 Hz), 110.5 (d, J = 29.0 Hz), 110.0, 82.1, 60.1, 46.9, 15.2; IR (KBr): 2359, 1723, 1505, 1276, 764, 751, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{23}ClF_2N_2O_2+Na)^+$ requires m/z 551.1314, found m/z 551.1320.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-5-fluoroindolin-2-one (4aba): 47% yield (22.5 mg); white solid; m.p. 126–127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H), 7.65 (s, 1H), 7.53 – 7.27 (m, 2H), 7.25 – 7.15 (m, 6H), 7.10 – 7.06 (m, 1H), 7.04 (d, J = 7.1 Hz, 2H), 7.01 – 6.93 (m, 3H), 6.92 – 6.87 (m, 1H), 6.86 – 6.81 (m, 1H), 6.67 – 6.59 (m, 1H), 6.22 (s, 1H), 3.52 – 3.44 (m, 1H), 3.35 – 3.27 (m, 1H), 1.16 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.2, 160.5, 142.5 (d, J = 53.0 Hz), 136.7, 135.1, 130.9, 129.01, 129.0, 128.5, 128.4, 126.7, 121.8, 120.7, 120.1, 116.2 (d, J = 23.7 Hz), 113.8 (d, J = 24.4 Hz), 110.8, 108.9, 82.6, 60.1, 48.5, 15.2; IR (KBr): 2360, 1722, 1401, 1276, 764, 750, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}FN_2O_2+Na)^+$ requires m/z 449.1798, found m/z 449.1791.

3-(2-benzhydryl-1*H*-indol-3-yl)-5-chloro-3-ethoxyindolin-2-one (4aca): 41% yield (20.0 mg); white solid; m.p. 128–129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.17 (s, 1H), 7.65 (s, 1H), 7.54 – 7.27 (m, 2H), 7.25 – 7.13 (m, 7H), 7.10 – 7.06 (m, 1H), 7.03 (d, J = 7.1 Hz, 3H), 7.01 – 6.91 (m, 3H), 6.63 (d, J = 8.3 Hz, 1H), 6.20 (s, 1H), 3.51 – 3.43 (m, 1H), 3.35 – 3.27 (m, 1H), 1.17 (t, J = 6.9 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.9, 142.7, 142.1, 139.2, 135.0, 130.9, 129.7, 129.1, 129.0, 128.5, 128.4, 126.7, 126.3, 121.8, 120.7, 120.1, 111.2, 110.8, 108.7, 82.4, 60.2, 48.6, 15.2; IR (KBr): 2360, 1725, 1265, 744, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}ClN_2O_2+Na)^+$ requires m/z 515.1503, found m/z 515.1501.

3-(2-benzhydryl-1*H*-indol-3-yl)-5-bromo-3-ethoxyindolin-2-one (4ada): 64% yield (34.1 mg); white solid; m.p. 188–190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 7.71 (s, 1H), 7.39 (s, 1H), 7.34 – 7.31 (m, 1H), 7.28 – 7.25 (m, 2H), 7.25 – 7.21 (m, 4H), 7.21 – 7.14 (m, 2H), 7.14 – 7.09 (m, 1H), 7.09 – 7.01 (m, 4H), 7.01 – 6.96 (m, 1H), 6.62 (d, J = 8.3 Hz, 1H), 6.25 (s, 1H), 3.53 – 3.44 (m, 1H), 3.37 – 3.27 (m, 1H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.2, 142.7, 142.1, 139.9, 135.0, 132.6, 131.3, 129.2, 129.1, 129.0, 128.6, 128.5, 126.8, 121.8, 120.7, 120.2, 115.8, 111.8, 110.8, 108.7, 82.5, 60.2, 48.6, 15.2; IR (KBr): 2360, 1717, 1457, 1187, 764, 743, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}BrN_2O_2+H)^+$ requires m/z 559.0997, found m/z 559.1005.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-5-nitroindolin-2-one (4aea): 63% yield (31.7 mg); white solid; m.p. 210–211 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H), 8.15 – 8.09 (m, 1H), 8.02 – 7.94 (m, 1H), 7.67 (s, 1H), 7.50 – 7.42 (m, 1H), 7.31 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.18 – 7.13 (m, 3H), 7.13 – 7.08 (m, 1H), 7.07 – 6.97 (m, 3H), 6.97 – 6.86 (m, 2H), 6.76 (d, J = 8.6 Hz, 1H), 6.11 (s, 1H), 3.54 – 3.46 (m, 1H), 3.41 – 3.32 (m, 1H), 1.19 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.9, 146.1, 143.8, 142.3, 141.7, 135.0, 130.4, 128.9, 128.7, 128.6, 127.0, 126.9, 126.5, 122.1, 121.9, 120.5, 111.0, 109.9, 107.6, 81.7, 60.4, 48.7, 29.7, 15.2; IR (KBr): 2359, 1732, 1455, 1275, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}N_3O_4+H)^+$ requires m/z 526.1743, found m/z 526.1741.

3-(2-benzhydryl-1*H*-indol-3-yl)-6-chloro-3-ethoxyindolin-2-one (4afa): 78% yield (38.4 mg); brown solid; m.p. 126–127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 (s, 1H), 7.65 (s, 1H), 7.46 (s, 1H), 7.28 – 7.16 (m, 7H), 7.13 – 7.08 (m, 2H), 7.07 – 6.95 (m, 5H), 6.95 – 6.91 (m, 1H), 6.70 (s, 1H), 6.18 (s, 1H), 3.52 – 3.42 (m, 1H), 3.39 – 3.30 (m, 1H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.1, 142.6, 142.2, 141.9, 135.3, 135.1, 129.1, 129.0, 128.5, 128.4, 127.5, 127.1, 126.9, 126.7, 126.6, 122.9, 121.8, 121.0, 120.1, 110.8, 110.7, 108.9, 81.9, 60.1, 48.5, 15.2; IR (KBr): 2360, 1723, 1400, 1261, 748, 700 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}ClN_2O_2+Na)^+$ requires m/z 515.1503, found m/z 515.1497.

3-(2-benzhydryl-1*H*-indol-3-yl)-6-bromo-3-ethoxyindolin-2-one (4aga): 52% yield (27.8 mg); pink solid; m.p. 134–136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (s, 1H), 7.66 (s, 1H), 7.41 (s, 1H), 7.24 – 7.14 (m, 7H), 7.09 – 7.04 (m, 2H), 7.04 – 7.00 (m, 3H), 6.99 – 6.93 (m, 3H), 6.84 (s, 1H), 6.18 (s, 1H), 3.49 – 3.41 (m, 1H), 3.34 – 3.26 (m, 1H), 1.16 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.5, 142.6, 142.2, 137.5, 135.1, 129.1, 128.9, 128.5, 128.4, 127.9, 127.3, 126.9, 126.7, 126.6, 125.8, 123.3, 121.8, 120.9, 120.1, 113.8, 110.8, 108.8, 82.1, 60.1, 48.6, 15.2; IR (KBr): 2359, 1727, 1401, 1275, 764, 750, 701 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{25}BrN_2O_2+Na)^+$ requires m/z 559.0997, found m/z 559.0999.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-6-methylindolin-2-one (4aha): 40% yield (19.0 mg); white solid; m.p. 108–109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (s, 1H), 7.61 (s, 1H), 7.47 – 7.27 (m, 2H), 7.23 – 7.17 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 7.07 – 7.05 (m, 1H), 7.04 – 6.98 (m, 4H), 6.96 – 6.91 (m, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.54 (s, 1H), 6.18 (s, 1H), 3.48 – 3.39 (m, 1H), 3.34 – 3.22 (m, 1H), 2.33 (s, 3H), 1.13 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.5, 142.9, 142.6, 141.2, 140.1, 135.2, 129.2, 128.9, 128.6, 128.4, 128.2, 126.5, 126.4, 126.0, 125.9, 123.5, 121.6, 119.8, 111.0, 110.6, 109.7, 82.3, 59.9, 48.4, 21.8, 15.2; IR (KBr): 2359, 1722, 1454, 1275, 764, 750, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{32}H_{28}N_2O_2+Na)^+$ requires m/z 495.2049, found m/z 495.2050.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-4,6-difluoroindolin-2-one (4aia): 64% yield (31.6 mg); white solid; m.p. 115–117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.88 (s, 1H), 7.68 (s, 1H), 7.40 (s, 1H), 7.28 – 7.23 (m, 3H), 7.23 – 7.18 (m, 3H), 7.16 – 7.06 (m, 4H), 7.03 – 6.95 (m, 3H), 6.46 – 6.39 (m, 1H), 6.32 (d, J = 7.9 Hz, 1H), 6.20 (s, 1H), 3.48 – 3.35 (m, 2H), 1.16 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.3, 161.3, 158.7, 143.8, 142.5, 142.3, 137.4, 135.1, 129.2, 128.8, 128.6, 128.3, 126.8, 126.6, 121.8, 120.8, 120.1, 110.7, 107.5, 98.3, 95.7 (d, J = 27.3 Hz). 81.6, 60.6, 48.6, 15.1; IR (KBr): 2359, 1732, 1455, 1274, 764, 750, 705 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{24}F_2N_2O_2+Na)^+$ requires m/z 517.1704, found m/z 517.1705.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-5,6-difluoroindolin-2-one (4aja): 48% yield (23.8 mg); white solid; m.p. 207–208 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.69 (s, 1H), 7.41 (s, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.28 – 7.19 (m, 6H), 7.14 – 7.09 (m, 1H), 7.07 (d, J = 7.1 Hz, 2H), 7.04 – 6.95 (m, 3H), 6.94 – 6.86 (m, 1H), 6.57 – 6.48 (m, 1H), 6.23 (s, 1H), 3.52 – 3.44 (m, 1H), 3.39 – 3.29 (m, 1H), 1.20 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.4, 142.3 (d, J = 60.4 Hz), 135.0, 129.1, 129.0, 128.6, 128.5, 128.4, 126.8, 126.7, 126.6, 121.9, 120.5, 120.4, 120.2, 115.4 (d, J = 20.4 Hz), 110.9, 108.6, 100.3 (d, J = 22.5 Hz), 82.2, 60.1, 48.6, 15.2; IR (KBr): 2360, 1728, 1463, 1275, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{31}H_{24}F_2N_2O_2+Na)^+$ requires m/z 517.1704, found m/z 517.1716.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-5,7-dimethylindolin-2-one (4aka): 60% yield (29.2 mg); white solid; m.p. 152–153 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (s, 1H), 7.57 (s, 2H), 7.23 – 7.13 (m, 7H), 7.09 – 7.05 (m, 1H), 7.01 – 6.91 (m, 5H), 6.85 (d, J = 8.8 Hz, 2H), 5.96 (s, 1H), 3.51 – 3.43 (m, 1H), 3.38 – 3.29 (m, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.18 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.4, 142.8, 142.5, 137.3, 135.2, 132.3, 131.6, 129.1, 128.9, 128.5, 128.4, 128.3, 127.3, 126.6, 126.5, 124.1, 121.6, 119.9, 119.0, 110.5, 109.9,

82.9, 59.9, 48.2, 21.0, 16.1, 15.3; IR (KBr): 2360, 1715, 1400, 1275, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_2O_2+Na)^+$ requires m/z 509.2205, found m/z 509.2201.

***tert*-butyl 3-(2-benzhydryl-1*H*-indol-3-yl)-3-ethoxy-2-oxoindoline-1-carboxylate (4ala):** 64% yield (35.8 mg); white solid; m.p. 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.26 – 7.20 (m, 3H), 7.20 – 7.15 (m, 5H), 7.15 – 7.06 (m, 2H), 7.03 – 6.99 (m, 1H), 6.97 – 6.93 (m, 2H), 6.92 – 6.89 (m, 2H), 5.86 (s, 1H), 3.47 – 3.40 (m, 1H), 3.34 – 3.27 (m, 1H), 1.59 (s, 9H), 1.14 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 148.9, 142.5, 142.2, 140.3, 137.5, 135.1, 130.1, 129.1, 128.8, 128.5, 128.3, 127.5, 127.2, 126.7, 126.6, 125.7, 124.7, 121.8, 121.7, 120.1, 115.4, 110.6, 109.7, 84.2, 81.8, 60.2, 48.2, 28.1, 15.2; IR (KBr): 2360, 1728, 1463, 1276, 764, ,751, 669 cm^{-1}; ESI FTMS exact mass calcd for $(C_{36}H_{34}N_2O_4+Na)^+$ requires m/z 581.2417, found m/z 581.2416.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-methoxyindolin-2-one (4aab): 50% yield (22.4 mg); white solid; m.p. 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 (s, 1H), 7.66 (s, 1H), 7.37 (s, 1H), 7.26 – 7.21 (m, 3H), 7.21 – 7.14 (m, 6H), 7.10 – 7.05 (m, 1H), 7.04 – 6.98 (m, 4H), 6.98 – 6.93 (m, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.09 (s, 1H), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.7, 142.7, 142.3, 141.2, 137.5, 135.1, 129.9, 129.1, 128.9, 128.5, 128.4, 127.2, 126.7, 126.6, 126.4, 122.9, 121.7, 121.1, 120.0, 110.7, 110.3, 109.0, 82.7, 52.2, 48.4; IR (KBr): 2359, 1728, 1402, 1275, 764, 749, 704 cm^{-1}; ESI FTMS exact mass calcd for $(C_{30}H_{24}N_2O_2+Na)^+$ requires m/z 467.1736, found m/z 467.1737.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-isopropoxyindolin-2-one (4aac): 46% yield (21.8 mg); white solid; m.p. 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (s, 1H), 7.60 (s, 1H), 7.26 – 7.15 (m, 9H), 7.13 (d, J = 8.1 Hz, 1H), 7.06 – 6.88 (m, 7H), 6.75 (d, J = 7.6 Hz, 1H), 6.20 (s, 1H), 3.57 – 3.49 (m, 1H), 1.27 (d, J = 6.2 Hz, 3H), 0.87 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.9, 143.1, 142.8, 141.0, 135.1, 129.8, 129.7, 129.2, 129.0, 128.5, 128.2, 126.8, 126.6, 126.4, 122.8, 121.5, 119.7, 110.6, 110.2, 82.3, 68.5, 48.5, 24.3, 23.5; IR (KBr): 2360, 1720, 1401, 1192, 743, 699 cm^{-1}; ESI FTMS exact mass calcd for $(C_{32}H_{28}N_2O_2+Na)^+$ requires m/z 495.2049, found m/z 495.2043.

3-(2-benzhydryl-1*H*-indol-3-yl)-3-butoxyindolin-2-one (4aad): 45% yield (21.9 mg); white solid; m.p. 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (s, 1H), 7.64 (s, 1H), 7.26 – 7.18 (m, 8H), 7.17 – 7.12 (m, 2H), 7.11 – 7.03 (m, 3H), 7.03 – 6.97 (m, 3H), 6.95 – 6.88 (m, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.26 (s, 1H), 3.44 – 3.37 (m, 1H), 3.21 – 3.13 (m, 1H), 1.50 – 1.43 (m, 2H), 1.23 – 1.14 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.3, 142.9, 142.8, 141.2, 137.7, 135.2, 129.8, 129.2, 129.0, 128.9, 128.5, 128.2, 126.9, 126.6, 126.4, 126.3, 122.9, 121.5, 120.9, 119.8, 110.6, 110.2, 109.6, 82.4, 64.1, 48.4, 31.9, 19.3, 13.9; IR (KBr): 2360, 1722, 1401, 1275, 764, 750, 699 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_2O_2+Na)^+$ requires m/z 509.2205, found m/z 509.2202.

ethyl 2-(2-benzhydryl-1*H*-indol-3-yl)-2-ethoxy-2-(4-nitrophenyl)acetate (4ama): 53% yield (28.5 mg); yellow solid; m.p. 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 – 7.89 (m, 2H), 7.84 (s, 1H), 7.82 – 7.77 (m, 2H), 7.31 – 7.26 (m, 1H), 7.26 – 7.22 (m, 3H), 7.22 – 7.20 (m, 3H), 7.17 (d, J = 8.2 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.02 – 6.90 (m, 5H), 5.71 (s, 1H), 4.26 – 4.14 (m, 1H), 4.12 – 4.03 (m, 1H), 3.48 – 3.40 (m, 1H), 3.25 – 3.17 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 148.5, 147.2, 142.0, 141.5, 138.9, 135.1, 129.3, 128.8, 128.7, 128.6, 128.5, 127.5, 126.9, 126.8, 122.5, 121.9, 120.7, 120.1, 111.1, 111.0, 83.0, 61.9, 61.1, 48.2, 15.3, 13.7; IR (KBr): 2359, 1728, 1463, 1275, 764, 750 cm^{-1}; ESI FTMS exact mass calcd for $(C_{33}H_{30}N_2O_5+Na)^+$ requires m/z 557.2053, found m/z 557.2056.

ethyl 2-(2-benzhydryl-1*H*-indol-3-yl)-2-ethoxy-2-(4-nitrophenyl)acetate (5): 90% yield (16.1 mg); pink solid; m.p. 180–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.20 – 7.06 (m, 1H), 6.92 (d, J = 7.8 Hz, 1H), 4.98 (s, 1H), 3.91 – 3.80 (m, 1H), 3.79 – 3.65 (m, 1H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.6, 141.5, 129.9, 125.7, 125.5, 122.9, 110.5, 76.3, 64.3, 15.4. ESI FTMS exact mass calcd for $(C_{10}H_{11}NO_2+Na)^+$ requires m/z 200.0687, found m/z 200.0691.

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[20] CCDC-1828670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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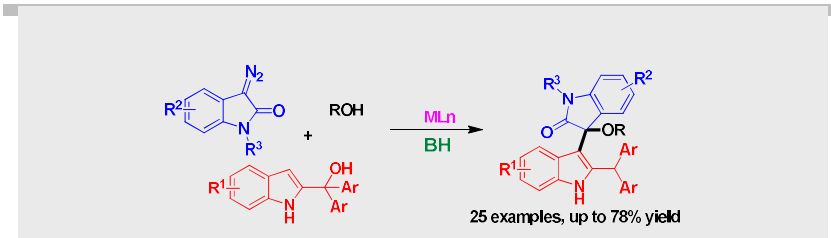

A synergistic catalysis-enabled reaction of 2-indolymethanols with oxonium ylides has been established, which makes use of the three-component reaction of 3-diazooxindoles, alcohols and 2-indolymethanols under the cooperative catalysis of metal complex and Brønsted acid.

*Chun Ma, Jia-Yu Zhou, Yi-Zhu Zhang, Yinchun Jiao, Guang-Jian Mei and Feng Shi**

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Synergistic Catalysis-Enabled Reaction of 2-Indolymethanols with Oxonium Ylides: Construction of 3-Indolyl-3-Alkoxy Oxindole Framework