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## Graphical Abstract

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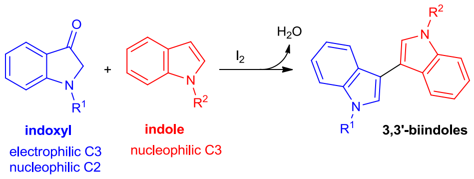

- inexpensive $I_2$ as catalyst
- metal-, peroxide-, acid- and base-free
- 24 examples, up to 98% yield
- gram-scale

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# Indoxyl-Based Umpolung Strategy for the Synthesis of Unsymmetrical 3,3'-Biindoles

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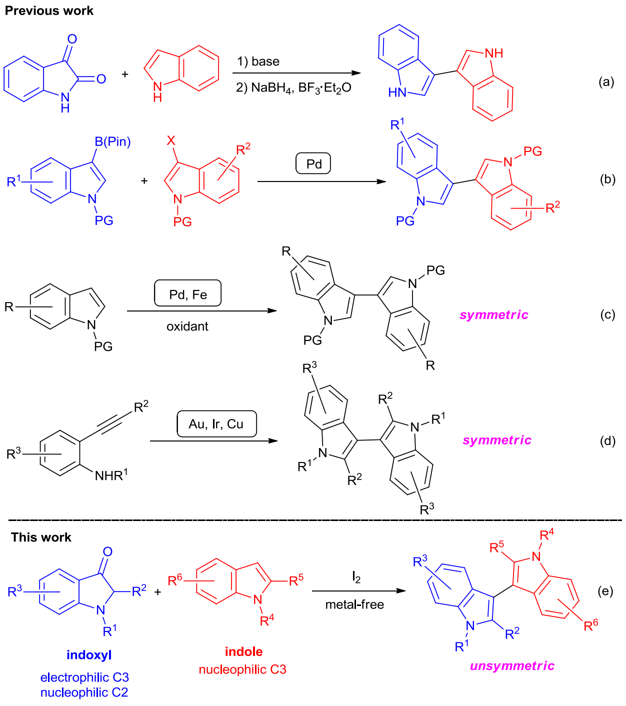
ABSTRACT

3,3'-Bisindoles are known to be important structural motifs found in bioactive natural products, pharmaceuticals, and functional materials. Herein, a novel indoxyl-based approach was established for the synthesis of unsymmetrical 3,3'-biindoles from indoles and indoxyls. This approach generated moderate to excellent yields of the desired products (24 examples, up to 98% yield). The present method features broad substrate scope, operational simplicity, high atom economy, and utilization of non-toxic and inexpensive molecular iodine as catalyst. The applicability of this method has been demonstrated by the facile gram-scale synthesis.

Biindoles are privileged structural moieties in bioactive natural products, pharmaceuticals, and functional materials.[1] They are also important building blocks in the synthesis of heterocycles and molecules with medicinal properties.[2] Thus, considerable efforts have been contributed to the construction and functionalization of biindolyl scaffolds.[3]

Up to now, most of the available protocols focused upon the synthesis of 2,2'- and 2,3'-biindoles,[4,5] but efficient approaches for the generation of 3,3'-biindoles remain limited.[6-11] 3,3'-Biindoles are conventionally prepared through nucleophilic attack of indoles on isatin under basic conditions to give intermediate 3-(3-indoly)-3-hydroxyoxindole; the intermediate is then reduced in the presence of a Lewis acid to generate the desired products in moderate yields (Scheme 1a).[6] Moreover, 3,3'-biindole scaffolds can be synthesized through transition metal-catalyzed cross-coupling reactions, including Pd-catalyzed Suzuki-Miyaura cross-coupling of two appropriate pre-functionalized indoles (Scheme 1b),[7] Pd and Fe catalyzed oxidative homo-dimerization of indoles (Scheme 1c),[8] cyclizative homo-dimerization of 2-alkynylanilines (Scheme 1d),[9] Pd catalyzed reductive coupling of 3-iodoindole,[10] and other cyclization reactions.[11] However, some of these methods suffer from drawbacks, such as requiring harsh conditions and relative inaccessibility of pre-functionalized indoles or specific symmetrical products. Therefore, it is highly desirable to develop straightforward and highly efficient methods for the construction of unsymmetrical 3,3'-biindolyl scaffolds.

The study presents the synthesis of unsymmetrical 3,3'-biindoles through an indoxyl-based umpolung strategy. The underlying principle is shown in Scheme 1e. The C3 of indole is the most nucleophilic site that reacts with various electrophiles. Indoxyls (3-indolinones), which are azaheterocycles, have been less investigated compared with indoles.[12] In contrast to indoles, indoxyls are electrophilic at C3 and nucleophilic at C2. As



**Scheme 1.** The structures of common sphingoid-type bases

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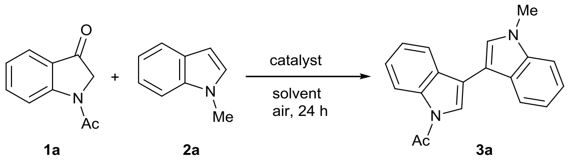
such,the reversed reactivities of indoxyls can be utilized as alternative and distinct strategy to synthesize indole derivatives, which are difficult to prepare using conventional methods. The nucleophilic reactivity of indoxyl at C2 has been demonstrated in many examples.[13] However, the electrophilic reactivity at C3 has only been illustrated in limited cases.[14] As a continuation of our work on indoles,[15] the present study reports an indoxyl-based umpolung strategy, which proceeds *via* unprecedented metal-free iodine-catalyzed nucleophilic attack of indoles on indoxyls. This simple protocol could be an efficient and practical method for the synthesis of various unsymmetrical 3,3’-biindoles.

Readily available *N*-acetyl indoxyl **1a** and *N*-methylindole **2a** were chosen as model substrate and nucleophile, respectively. The initial reaction was carried out without a catalyst in air atmosphere at 120 °C for 24 h (entry 1, Table 1). The desired 3,3’-biindole **3a** was obtained with 38% yield. The structure of **3a** was confirmed by spectroscopy and single-crystal X-ray diffraction analyses.[16] Based on this result, we screened several Lewis acid and Bronsted acid catalysts such as $FeCl_3$, $Ni(OTf)_2$, AgOTf, CuI, acetic acid and trifluoroacetic acid to promote the reaction. However, the reactions failed to complete after 24 h even when 2.0 equivalents of catalysts were used (entries 2-7). To develop an environment-friendly method, we conducted the experiment under metal-free iodine-catalyzed conditions. Fortunately, the yield of **3a** increased to 80% when molecular iodine (2.0 equiv.) was employed (entry 8). Other iodine sources, such as KI, NIS and TBAI also produced 3,3’-biindole **3a** but exhibited lower reactivity than molecular iodine.[17] Hence, we chose molecular iodine as catalyst to optimize the reaction because it is inexpensive, nontoxic, and environmentally benign.[18] Reactions at various temperatures were also investigated.[19] The yield of **3a** slightly increased to 85% when the reaction temperature was decreased to 80 °C (entry 9). Furthermore, the yield of **3a** slightly increased to 87% when the amount of iodine was decreased to 20 mol% (entry 11). Different solvents, including toluene, chlorobenzene, MeCN, 1,2-dichloroethane (DCE), 1,4-dioxane and 1,2-dimethoxyethane (DME) were investigated (entries 13-18). DCE was the optimal choice (entry 16). Besides, we performed this transformation under $N_2$ and $O_2$ atmosphere respectively, and obtained lower yield in $O_2$ (entries 19-20), which indicated that oxygen is not necessary in this process. Finally, the optimal reaction conditions included 20 mol % $I_2$ as the catalyst, DCE as solvent, reaction temperature of 80 °C under air atmosphere.

**Table 1.** Screening of reaction condition[a]

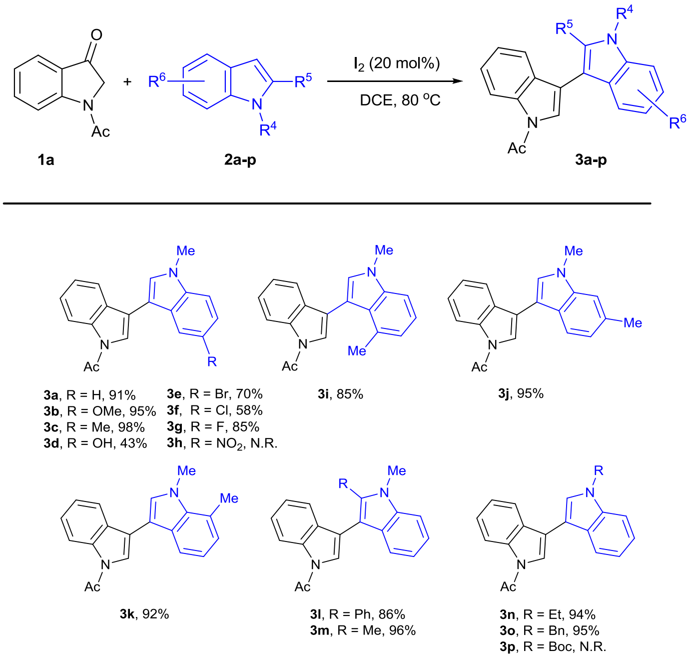


| entry[a] | catalyst (equiv.) | solvent | T (°C) | yield (%)[b] |
|---|---|---|---|---|
| 1 | none | PhMe/PhCl[c] | 120 | 38 |
| 2 | $FeCl_3$ (2.0) | PhMe/PhCl[c] | 120 | 35 |
| 3 | $Ni(OTf)_2$ (2.0) | PhMe/PhCl[c] | 120 | 72 |
| 4 | AgOTf (2.0) | PhMe/PhCl[c] | 120 | 36 |
| 5 | CuI (2.0) | PhMe/PhCl[c] | 120 | 40 |
| 6 | $CH_3CO_2H$ (2.0) | PhMe/PhCl[c] | 120 | 65 |
| 7 | $CF_3CO_2H$ (2.0) | PhMe/PhCl[c] | 120 | 72 |
| 8 | $I_2$ (2.0) | PhMe/PhCl[c] | 120 | 80 |
| 9 | $I_2$ (2.0) | PhMe/PhCl[c] | 80 | 85 |
| 10 | $I_2$ (0.5) | PhMe/PhCl[c] | 80 | 79 |
| 11 | $I_2$ (0.2) | PhMe/PhCl[c] | 80 | 87 |
| 12 | $I_2$ (0.1) | PhMe/PhCl[c] | 80 | 81 |
| 13 | $I_2$ (0.2) | PhMe | 80 | 69 |
| 14 | $I_2$ (0.2) | PhCl | 80 | 56 |
| 15 | $I_2$ (0.2) | MeCN | 80 | 82 |
| 16[d] | $I_2$ (0.2) | DCE | 80 | 91 |
| 17 | $I_2$ (0.2) | 1,4-dioxane | 80 | 65 |
| 18[e] | $I_2$ (0.2) | DME | 80 | 69 |
| 19[f] | $I_2$ (0.2) | DCE | 80 | 84 |
| 20[g] | $I_2$ (0.2) | DCE | 80 | 49 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst, solvent (3 mL), under air for 24 h. [b] Isolated yield. [c] PhMe/PhCl=1:1. [d] DCE=1,2-dichloroethane. [e] DME=1,2-dimethoxyethane. [f] Under $N_2$ atmosphere. [g] Under $O_2$ atmosphere.

The substrate scope of the reaction for the syntheses of various 3,3’-biindoles (Tables 2 and 3) was evaluated under the optimal reaction conditions. Substituted indoles **2a-2p** were combined with Ac-protected indoxyl **1a** under the optimal conditions (Table 2). The results showed that a broad range of substituted indoles reacted smoothly with indoxyl **1a** to generate the desired products in moderate to excellent yields. Indoles containing electron-donating substituents showed improved results than electron-withdrawing substituents in the following transformations (**3b-3c** and **3i-3k** vs. **3e-3h**). For example, 1,5-dimethyl-1*H*-indole **2c** was transformed into **3c** in 98% yield, whereas substrate **2h** with strong electron-withdrawing $NO_2$

**Table 2.** Substrate scope of indoles[a,b]



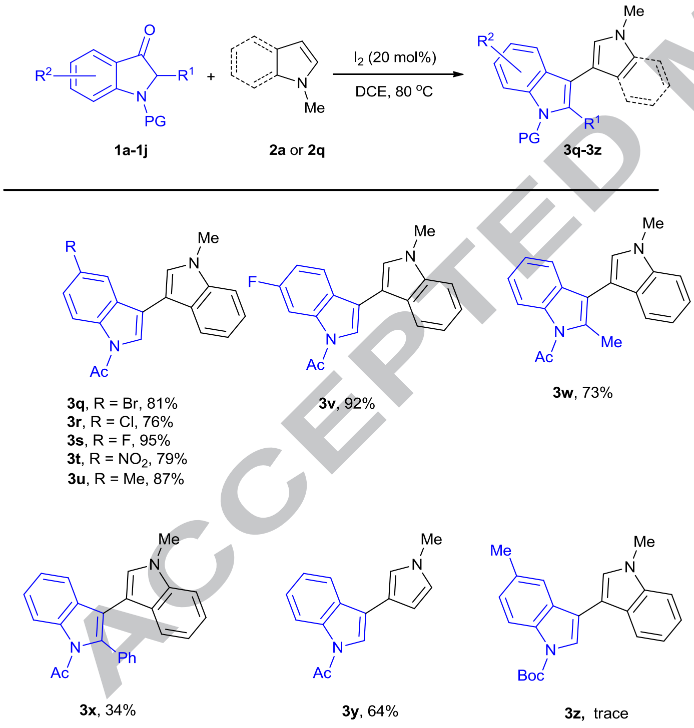
[a] Reaction conditions**: 1a (**0.2 mmol), **2a-2p** (0.4 mmol) and iodine (0.04 mmol, 20 mol%) in DCE (3 mL) at 80 °C for 24 h. [b] Isolated yield.

group at C5-position disfavored the transformation (**3h**). Indole **2d** with free C5-hydroxyl group was also tolerant to iodine-catalyzed transformation, and produced **3d** with 43% yield.

The steric effects of the substituents at C2, C4, C5, C6, and C7 positions of indoles (**3c**, **3i-3m**) were also investigated. The steric hindrance of the substituent on the indole ring did not significantly affect the reaction. The C2 phenyl-substituted indole **2l** produced the desired 3,3’-bisindole **3l** in 86% yield. Furthermore, *N*-ethyl and *N*-benzyl indoles (**2n** and **2o**) tolerated the reaction conditions and generated **3n** and **3o** in high yields. However, **3p** was not observed when the protective group on *N* atom of indole was switched to Boc.

Further exploration of the substrate scope focused on various substituted indoxyls. As shown in Table 3, substrates bearing electron-withdrawing and electron-donating groups, such as 5-F, 5-Cl, 5-Br, 5-$NO_2$, 6-F and 5-Me, on the backbone of indoxyls reacted smoothly with *N*-methylindole **2a** and afforded the corresponding 3,3’-biindoles **3q-3v** in good yields (76-95%). Notably, the substituents ($R^1$=Me and phenyl) on the C2 position of indoxyls were also applicable, and the corresponding products, namely, **3w** and **3x**, were obtained in relatively lower yields because of the steric hindrance effect. *N*-methyl pyrrole **2q** can also be used to obtain 3-(3-pyrrolyl)indole **3y** with 64% yield. Unfortunately, *N*-Boc indole was found to be incompatible with the developed protocol and gave only traces of **3z**.

**Table 3**. Substrate scope of indoxyls[a,b]



**1a-1j** **2a** or **2q** **3q-3z**

**3q**, R = Br, 81%
**3r**, R = Cl, 76%
**3s**, R = F, 95%
**3t**, R = $NO_2$, 79%
**3u**, R = Me, 87%

**3v**, 92%

**3w**, 73%

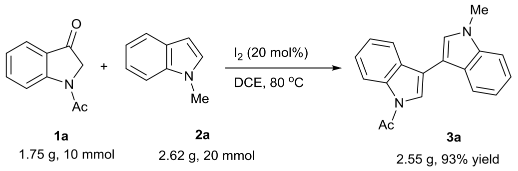
**3x**, 34%

**3y**, 64%

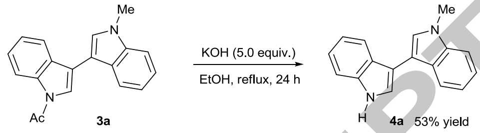
**3z**, trace

[a] Reaction conditions: **1a-1i** (0.2 mmol), **2a** (or **2q**) (0.4 mmol) and iodine (0.04 mmol, 20 mol%) in DCE (3 mL) at 80 °C for 24 h. [b] Isolated yield.

We also explored the synthetic applicability of the proposed method. The scaled-up experiment was performed using **1a** and **2a**. The reaction generated **3a** with minimal loss (93% yield from 10 mmol of **1a**, Scheme 2). The acetylamide could be smoothly cleaved under basic condition. Treatment of 3,3’-biindole **3a** with potassium hydroxide in EtOH under reflux produced **4a** in 53% yield (Scheme 3). Therefore, this simple protocol could be a practical and scalable method for the synthesis of various 3,3’-biindoles.

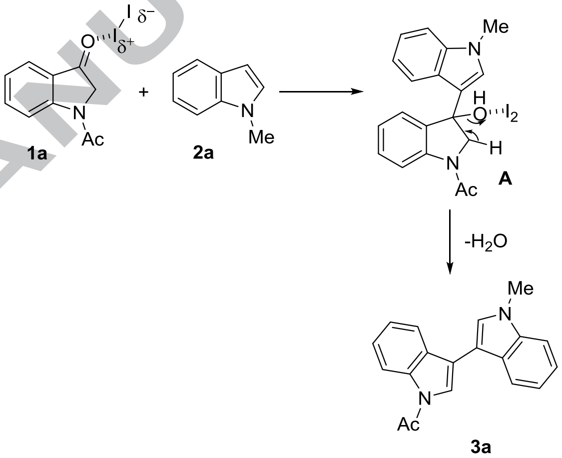


**Scheme 2.** Gram-scale synthesis of 3,3’-biindole **3a**



**Scheme 3.** Deprotection of 3,3’-biindole **3a**

We proposed that the reaction proceeds through the activation of indoxyl with molecular iodine as weak Lewis acid. Nucleophilic attack of indole on indoxyl led to the formation of 3-hydroxy-3,3’-biindole (intermediate **A**). Subsequent dehydration of intermediate A produced the desired 3,3’-biindole **3a** (Scheme 4).



**Scheme 4**. A proposed reaction pathway

In summary, we have developed a novel protocol for the synthesis of unsymmetrical 3,3’-biindoles *via* an indoxyl-based umpolung strategy between indoxyls and indoles. The proposed method features broad substrate scope, operational simplicity, high atom economy, and utilization of non-toxic and inexpensive molecular iodine as catalyst. Further practical application of this methodology is currently underway in our laboratory.

## Acknowledgements

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## Supplementary Material

Supplementary data (typical experimental procedures, physical data of new compounds, copies of $^1H$ and $^{13}C$ NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/xxxxx.

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19. 120 $^{o}$C, 80% yield; 100 $^{o}$C, 84% yield; 80 $^{o}$C, 85% yield; 60 $^{o}$C, 73% yield; rt, 17% yield (48 h).

**Highlights**

- A novel indoxyl-based approach for the synthesis of unsymmetrical 3,3'-biindoles.
- Broad substrate scope, good to excellent yields (24 new compounds, up to 98% yield).
- Mild reaction conditions: metal-free; iodine-catalyzed reactions; operational simplicity