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# Catalytic Asymmetric Four-Component Reaction for the Rapid Construction of 3,3-Disubstituted 3-Indol-3′-yloxindoles

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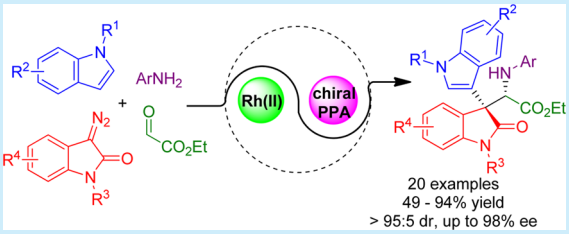
Supporting Information

**ABSTRACT:** A Rh(II)/chiral phosphoric acid cocatalyzed four-component reaction of indoles, 3-diazooxindoles, arylamines, and ethyl glyoxylate is developed, offering an extremely efficient strategy for the construction of 3,3-disubstituted 3-indol-3′-yloxindoles with excellent diastereoselectivities and high to excellent enantioselectivities. This transformation is proposed to proceed through a Mannich-type trapping of the zwitterionic intermediate generated from a metal carbene and an indole with an iminoester derived from an arylamine and a glyoxylate.




3,3-Disubstituted 3-indol-3′-yloxindoles (mixed 3,3′-bisindoles) that contain an all-carbon quaternary stereogenic center at the C3 position of the oxindole rings (Figure 1, **A**) belong to an important class of indole structural motifs, which show significant biological and pharmaceutical activities.[1] Such skeletons also serve as key intermediates for the total synthesis of a number of hexahydropyrroloindoline alkaloids (Figure 1).[2] These characteristics have promoted the development of an array of catalytic asymmetric transformations to access such molecules. Overman developed an elegant Mukaiyama-aldol reaction of 2-siloxyindole with enantioenriched aldehydes and further applied this method to the total synthesis of (+)-gliocladin C.[3] Trost reported an efficient Pd(0)-catalyzed enantioselective hydrocarbonation of allenes with 3-indol-3′-yloxindoles and furnished the synthesis of the pyrrolidinoline core of the gliocladin family.[4] Guo, Peng[5] and the research group of Gong[6] developed organocatalyzed asymmetric α-alkylation of cyclic ketones or aldehydes with 3-hydroxy-3-indol-3′-yloxindoles to afford 3,3-disubstituted oxindoles. On the other hand, by starting from oxindole-derived nitroalkenes[1c] or α,β-unsaturated aldehydes[7] to react with indoles, Arai's and Zhang's research group developed efficient catalytic asymmetric Michael-type reactions, offering alternative ways for the synthesis of enantioenriched mixed 3,3′-bisindoles.

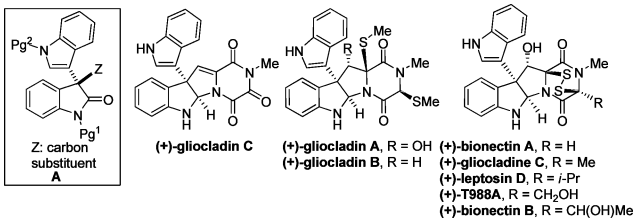



**Figure 1.** Mixed 3,3′-bisindoles as key intermediates for the total synthesis of natural hexahydropyrroloindoline alkaloids.

In recent years, catalytic asymmetric multicomponent reactions (MCRs) have emerged as powerful synthetic tools over traditional methods for their high efficiency and step-economic feature.[8] When disconnecting the mixed 3,3′-bisindole skeleton **A** into three parts: the oxindole ring, the C3-indolyl substituent, and the C3-carbon substitution (Z), catalytic asymmetric MCRs that may efficiently assemble these three parts in one single step, ideally from readily accessible starting materials, into the desired mixed 3,3′-bisindole skeleton with excellent stereoselective controls, would be highly desirable and would offer an ideal platform for diversity-oriented synthesis (DOS) of mixed 3,3′-bisindole derivatives for potential biological evaluations.[9]

Under transition metal catalysis, 3-diazooxindole reacted with indole to provide 3-indol-3′-yloxindole,[10] which has been used as the key precursor for asymmetric synthesis of 3,3-disubstituted mixed 3,3′-bisindoles.[3,4,11] This process is believed to proceed through active zwitterionic intermediate formation followed by rapid proton transfer (Scheme 1, path a). Very recently, Gong's research group has merged this process with a one-pot subsequent Michael addition with nitroalkenes via relay catalysis, thus offering an efficient way for the construction of mixed 3,3′-bisindoles (Scheme 1, path a′).[12] As part of our continuous efforts in exploring catalytic asymmetric MCRs via electrophilic trapping of active zwitterionic intermediates generated from metal carbenes,[13] we envisioned that the use of an *in situ* generated iminoester from an arylamine and a glyoxylate would act as an efficient trapping agent to intercept the zwitterionic intermediate, followed by delayed proton transfer (rather than a stepwise

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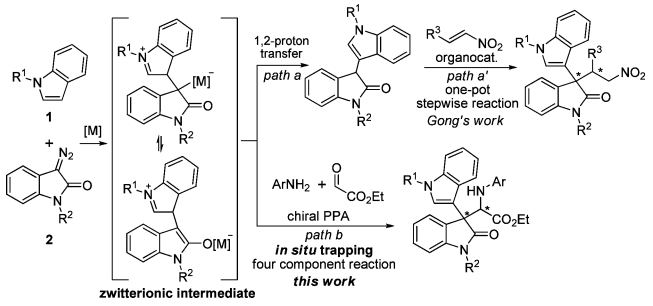
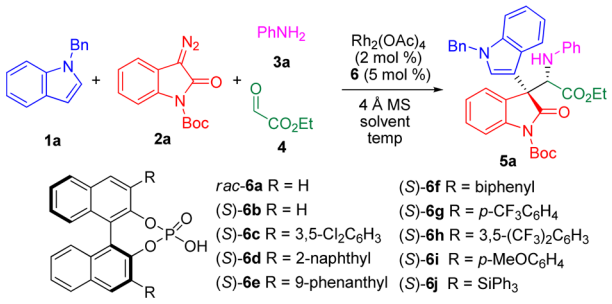
**Scheme 1. Design of MCRs *via* Electrophilic Trapping of the Zwitterionic Intermediate Generated from 3-Diazooxindole and Indole**




C−H functionalization/Mannich reaction pathway), to establish new MCRs (Scheme 1, path b). By introducing chiral phosphoric acids as cocatalysts, the formation of an iminoester can be facilitated and meanwhile efficient stereoselective control could be achieved during the electrophilic trapping process. However, the existence of four components and two catalysts makes the desired transformation relatively complicated, and a series of competitive reactions may occur. For example, the glyoxylate may undergo aldol-type trapping of the zwitterionic intermediate.[14] Yet, arylamine may react with metal carbene to generate ammonium ylide, which could be further trapped by either the glyoxylate[15] or iminoester. Furthermore, an indole may directly react with the glyoxylate[16] or iminoester[17] in the presence of chiral phosphoric acid catalysts. Nonetheless, herein we demonstrate a rhodium(II)/chiral phosphoric acid cocatalyzed four-component reaction of indoles, 3-diazooxindoles, anilines, and ethyl glyoxylate for the rapid construction of mixed 3,3′-bisindoles with high diastereo- and enantioselectivities. Control experiments revealed that this catalytic asymmetric four-component reaction proceeded through electrophilic trapping of active zwitterionic intermediates rather than a stepwise C−H functionalization/Mannich reaction pathway.

Initially, we started our investigation by examining the reaction of *N*-Boc 3-diazooxindole **1a**, *N*-benzyl indole **2a**, aniline **3a**, and ethyl glyoxylate **4** in the presence of both $[Rh_2(OAc)_4]$ (2 mol %) and racemic BINOL-derived phosphoric acid **6a** (5 mol %). To our delight, the desired four-component product **5a** was formed in 43% yield with >95:5 diastereoselectivity (Table 1, entry 1). In contrast, in the absence of **6a**, this four-component reaction became very messy and the formation of **5a** was not observed (Table 1, entry 2), indicating the indispensable role of phosphoric acid (PPA) for this transformation. To improve the reactivity as well as fulfill catalytic asymmetric control, a series of chiral BINOL-derived PPA catalysts were evaluated. Among them, (*S*)-3,3′-bis-(triphenylsilyl)-BINOL phosphoric acid (**6j**) gave the best result, yielding **5a** in 80% yield with >95:5 dr and 86% ee (Table 1, entries 3−11). Different solvents were then screened, and the use of xylene as the solvent gave a further improved result, yielding **5a** in 75% yield with >95:5 dr and 92% ee (Table 1, entries 12−14). Decreasing the reaction temperature to 0 °C caused reduced the yield of **5a** while the stereoselectivity remained almost unaffected (Table 1, entry 15). Increasing the reaction temperature to 40 °C resulted in both reduced yield and enantioselectivity of **5a** (Table 1, entry 16).

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | 6 | solvent | *t*, °C | yield, %[b] | dr[c] | ee, %[d] |
|---|---|---|---|---|---|---|
| 1 | **6a** | toluene | 25 | 43 | >95:5 | – |
| 2 | – | toluene | 25 | <5 | – | – |
| 3 | **6b** | toluene | 25 | 40 | >95:5 | 28 |
| 4 | **6c** | toluene | 25 | 34 | >95:5 | 71 |
| 5 | **6d** | toluene | 25 | 60 | >95:5 | 59 |
| 6 | **6e** | toluene | 25 | 59 | >95:5 | 73 |
| 7 | **6f** | toluene | 25 | 62 | >95:5 | 38 |
| 8 | **6g** | toluene | 25 | 61 | >95:5 | 62 |
| 9 | **6h** | toluene | 25 | 59 | >95:5 | 64 |
| 10 | **6i** | toluene | 25 | 60 | >95:5 | 56 |
| 11 | **6j** | toluene | 25 | 80 | >95:5 | 86 |
| 12 | **6j** | DCE | 25 | 74 | >95:5 | 66 |
| 13 | **6j** | $CH_2Cl_2$ | 25 | 72 | >95:5 | 86 |
| 14 | **6j** | xylene | 25 | 75 | >95:5 | 92 |
| 15 | **6j** | xylene | 0 | 20 | >95:5 | 91 |
| 16 | **6j** | xylene | 40 | 57 | >95:5 | 74 |

[a]Reactions were conducted in 0.10 mmol scale of **3a**. **1a**:**2a**:**3a**:**4** = 1.1:1.0:1.1:1.2. [b]Isolated yield after column chromatography. [c]Determined by $^1$H NMR of crude mixture. [d]Determined by chiral HPLC of major diastereomer.

With the optimized reaction conditions in hand, the substrate scope of this transformation was investigated (Scheme 2). A variety of substituted anilines were first examined. For all substituted anilines being tested, the desired four-component products were obtained in good yields with excellent diastereoselectivities (>95:5 for all cases). While electron-deficient anilines generally provided the products with excellent enantioselectivities (**5b**, **5c**, **5f**, and **5g**), electron-rich ones such as *p*-toluidine gave the desired products with much lower enantioselectivity (**5d**, 49% ee). This poor enantioselectivity might be caused by the relatively higher reactivity of the *in situ* generated iminoester from *p*-toluidine and ethyl glyoxylate. Next, the generality for indoles and 3-diazooxindoles was investigated. For C5-substituted indoles, electron-withdrawing substituents gave higher enantioselectivities than electron-donating ones (**5h** and **5j** vs **5i**). C6- and C7-substituted indoles were also tolerated, yielding **5k** and **5l** in good yields with excellent diastereoselectivities and high enantioselectivities. Substituents on C5, C6, and C7 positions of *N*-Boc 3-diazooxindoles also gave the desired four-component products in good yields with excellent diastereoselectivities and high to excellent enantioselectivities (**5m**−**5p**). Different *N*-substituents on indoles and 3-diazooxindoles were also examined. Replacing the *N*-benzyl substituent of indole to *N*-methyl caused apparently reduced enantioselectivity (**5b** vs **5q**). Yet, *N*-benzyl 3-diazooxindoles gave the desired products with comparably high enantioselectivities (**5r**−**5t**). Finally, the absolute configuration of the four-component product was unambiguously determined as 2*S*,3*S* by X-ray analysis of **5t**.[18]





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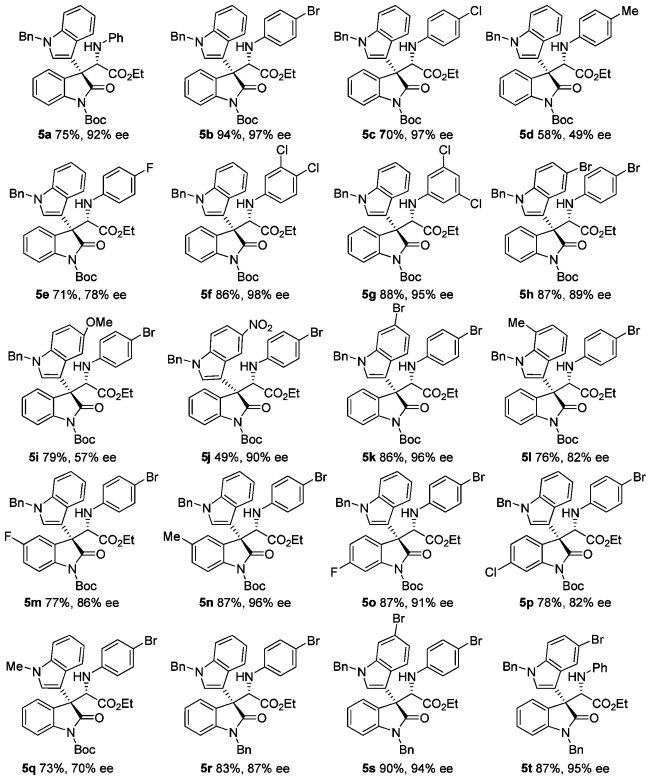
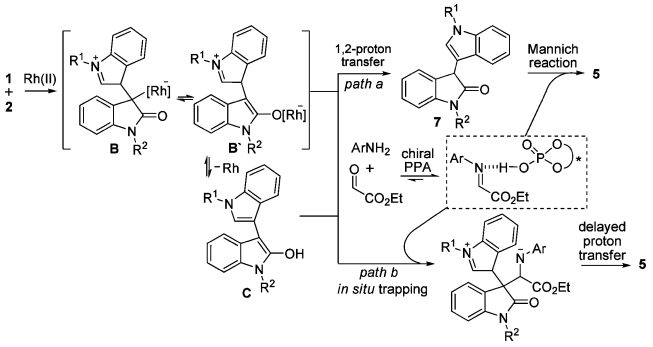
**Scheme 2. Substrate Scope**[a]




[a]dr >95:5 for all cases.

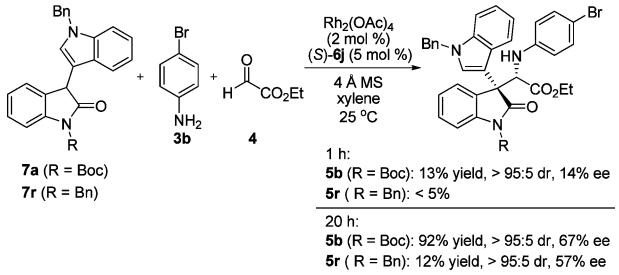
To gain some insight into the pathway of this catalytic asymmetric four-component reaction, several control experiments were conducted. First, in view of the indispensable role of chiral phosphoric acid for this transformation (Table 1, entry 1 vs 2), *p*-bromoaniline **3b** was allowed to react with ethyl glyoxylate **4** either with or without PPA **6j** (5 mol %). As monitored by $^1$H NMR, in the presence of **6j**, **3b** and **4** were fully converted into the iminoester immediately; in contrast, in the absence of **6j**, only a trace amount of the iminoester was observed in 10 min.[19] These results suggest that the chiral PPA catalyst not only provides efficient stereoselective control but also regulates the reaction pathway in the desired four-component manner by efficiently facilitating the formation of the iminoester. With the rapid generation of the iminoester, this four-component reaction undergoes either a stepwise C−H functionalization/Mannich reaction pathway with 3-indol-3′-yloxindoles **7** as the intermediates or an electrophilic trapping of the active zwitterionic intermediates followed by a delayed proton transfer. A control experiment starting from the C−H functionalization product **7a** was conducted with **3b** and **4**. After reaction for 1 h, **5b** was formed in 13% yield with 14% ee (Scheme 4).[20] In contrast, under identical conditions, the four-component reaction between indole **1a**, 3-diazooxindole **2a**, **3b**, and **4** gave **5b** in 94% yield with 97% ee (Scheme 2, **5b**). When starting from *N*-benzyl-substituted 3-indol-3′-yloxindole **7r**, the formation of **5r** was not observed after reacting for 1 h (Scheme 4), while the corresponding four-component transformation gave **5r** in 83% yield with 87% ee (Scheme 2, **5r**). These results clearly indicated that this four-component reaction proceeded through electrophilic trapping of the zwitterionic intermediate (Scheme 3, path b) rather than a stepwise C−H functionalization/Mannich reaction pathway (Scheme 3, path a). The

**Scheme 3. Plausible Reaction Pathways**




stepwise transformation from **7a** could be completed in 20 h, yielding **5b** in 92% yield with 67% ee (Scheme 4). The poor

**Scheme 4. Control Experiments**




enantioselectivity observed for the stepwise transformation further illustrated the advance of the electrophilic trapping pathway for more efficient control of the enantioselectivity, presumably through a metal/chiral PPA cooperatively activating manner.[21] Yet, the possibility of a pathway involving demetalation of zwitterionic intermediate **B′** into enol **C**, which further underwent tautomerization to give **7** or reacted with the PPA-activated iminoester to afford the desired four-component product **5**, could not be excluded at the current stage.

An interaction model was proposed to explain the stereoselective outcome of this four-component reaction (Figure 2).

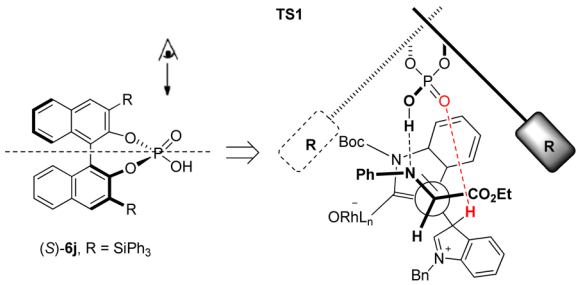



**Figure 2.** Proposed transition state.

Chiral PPA (*S*)-**6j** first facilitates the formation of the iminoester in its energetically favored *E* configuration from aniline and ethyl gloyxylate. The imino group is protonated by PPA while the iminoester maintains its *E* form.[22] The *N*-phenyl group of the iminoester is oriented toward the empty pocket of the PPA catalyst. Meanwhile, weak hydrogen bonding between the Lewis basic phosphoryl oxygen atom and the acidic C−H proton at the C3 position of the indole ring in the zwitterionic intermediate through the sterically favored configuration is





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formed (the *N*-benzyl substituent on the indole ring is away from the ester group of the iminoester; see Figure 2, **TS1**). With subsequent proton transfer through the PPA catalyst, the four-component product is formed with efficient asymmetric control through this dual hydrogen bonding activation mode.

In summary, we have developed an extremely efficient strategy for the construction of 3,3-disubstituted mixed 3,3′-bisindoles by a Rh(II)/chiral phosphoric acid cocatalyzed enantioselective four-component reaction of indoles, 3-diazooxindoles, arylamines, and ethyl glyoxylate. With this method, a series of highly valuable 3-(2-arylamino-)-3-indol-3′-yloxindoles were synthesized in good yields with excellent diastereoselectivities and high to excellent enantioselectivities. This transformation is proposed to proceed through electrophilic trapping of zwitterionic intermediates generated from metal carbenes and indoles with iminoesters derived from arylamines and ethyl glyoxylate. With its high efficiency in accessing complicated chiral products in one step, this transformation may have great potential in the synthesis of related natural products and diversity-oriented synthesis of complicated chiral compounds.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02160.

Experimental procedures and full spectroscopic data for all new compounds (PDF)
Crystallographic data for **5t** (CIF)

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### Notes

The authors declare no competing financial interest.

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(19) The formation of the iminoester was appraently incomplete even after reacting **3b** and **4** for 20 h. For a detailed monitoring of the iminoester formation by $^1$H NMR spectroscopy, see Scheme S1 of theSupporting Information. See also: Xu, X. F.; Zhou, J.; Yang, L. P.; Hu, W. H. *Chem. Commun.* **2008**, 6564.

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