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Research Highlight

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A breakthrough in 2-indolylmethanol-involved organocatalytic asymmetric reactions

Wei Tan, Feng Shi*

School of Chemistry and Materials Science, Jiangsu Normal University, Xuzhou 221116, Jiangsu, China.

***Correspondence to:** Prof. Feng Shi, School of Chemistry and Materials Science, Jiangsu Normal University, Shanghai Road No. 101, Tongshan District, Xuzhou 221116, Jiangsu, China. E-mail: fshi@jsnu.edu.cn

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The organocatalytic asymmetric construction of chiral indole-based scaffolds has become an important research field because the wide distribution of such scaffolds in natural products, pharmaceuticals, chiral organocatalysts, and ligands[1]. Among different approaches, 2-indolylmethanols have been recognized as a class of versatile platform molecules in organocatalytic asymmetric transformations for constructing chiral indole-based scaffolds[1-3]. As summarized in Figure 1A, under the catalysis of chiral Brønsted acid (B*-H)[4-5], 2-indolylmethanols readily undergo dehydration to generate carbocation intermediates **A**-**B** and vinyliminiums **C**, which can be illustrated as delocalized cations **D**. Due to the steric effect of the two R groups (particularly when R is an aryl group), nucleophiles (Nu) more readily attack carbocation **B** than carbocation **A**, thus resulting in the C3-umpolung reactivity of 2-indolylmethanols[1-2]. Namely, the C3-position of the indole ring is changed from nucleophilic to electrophilic. Nevertheless, in some cases, 2-indolylmethanols can also display C3-nucleophilicity to undergo catalytic asymmetric (4 + 3)[6] and (3 + 3)[7] cycloadditions. Based on these unique reactivities, a series of organocatalytic asymmetric C3-substitutions and (3 + n) cycloadditions of 2-indolylmethanols have been achieved in a high regio- and enantioselective manner, leading to the construction of a variety of chiral indole-based scaffolds.

Despite the rapid progress in this research field, there are still some challenges in 2-indolylmethanol-involved organocatalytic asymmetric reactions. As shown in Figure 1B, most of the above-mentioned

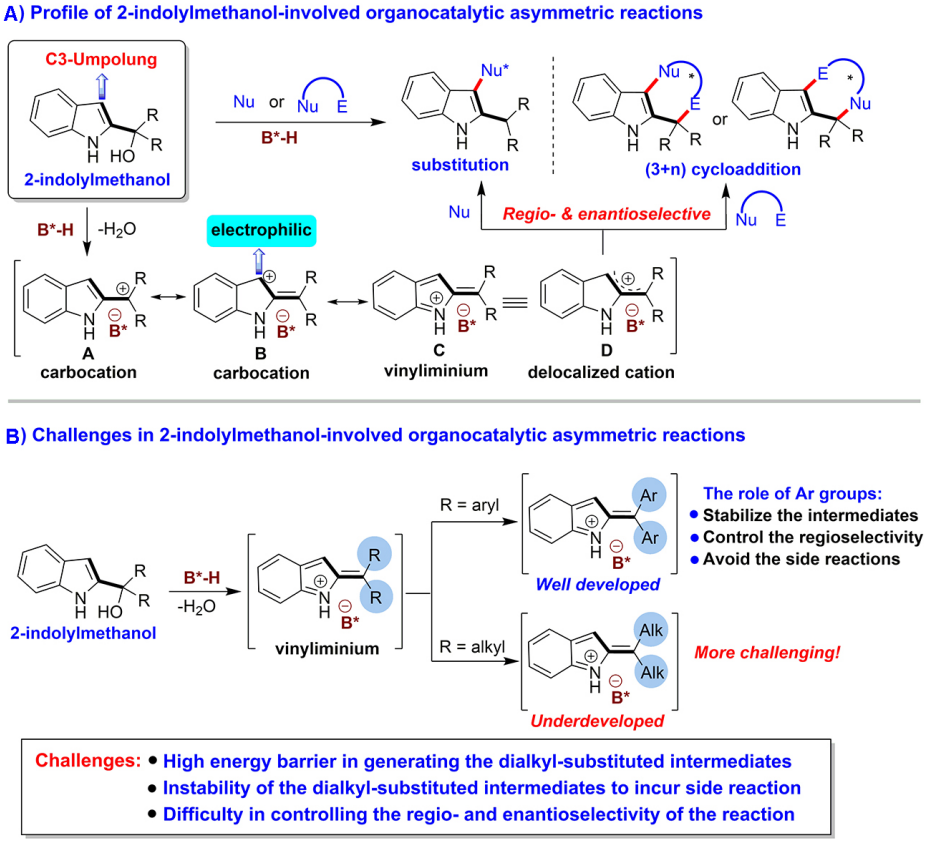

Figure 1. Profile of 2-indolylmethanol-involved organocatalytic asymmetric reactions and the existing challenges.

transformations utilize diaryl-substituted 2-indolylmethanols as reactants. However, in sharp contrast, dialkyl-substituted 2-indolylmethanols have scarcely been utilized as successful reactants in organocatalytic asymmetric reactions. This is because the two aryl groups play important roles in stabilizing the intermediates (vinyliminium and carbocation), controlling the regioselectivity, and avoiding the side reactions. On the contrary, there are great challenges in realizing highly regio- and enantioselective transformations of dialkyl-substituted 2-indolylmethanols, which mainly include: (1) high energy barrier in generating the dialkyl-substituted intermediates; (2) instability of the dialkyl-substituted intermediates to incur side reaction; and (3) difficulty in controlling the regio- and enantioselectivity of the reaction. Therefore, developing innovative strategies to solve these challenges is highly valuable.

To solve these challenging issues, on the basis of their previous studies on silylium-based asymmetric counteranion-directed catalysis (Si-ACDC)[8-9], List and coworkers recently designed an asymmetric (4 + 3) cycloaddition of dialkyl-substituted 2-indolylmethanols **1** with dienolsilane **2a** by using IDPi (imidodiphosphorimidates) as strongly acidic and confined organocatalysts [Figure 2][10]. Specifically, they utilized dialkyl-substituted 2-indolylmethanols **1** as three-atom building blocks to participate in the enantioselective (4 + 3) cycloaddition with dienolsilane **2a** under the catalysis of strongly acidic and confined IDPi **4a** or **4b**. After a subsequent TFA-promoted removal of silyl group, a series of novel bicyclo[3.2.2]cyclohepta[*b*]indoles **3** bearing three stereogenic centers were synthesized in overall excellent yields with high enantioselectivities. In addition, considering the accessibility of these intriguing bicyclo[3.2.2]cyclohepta[*b*]indole frameworks, they performed some useful synthetic transformations of products **3** and accomplished the synthesis of enantioenriched indole derivatives **5-8**.

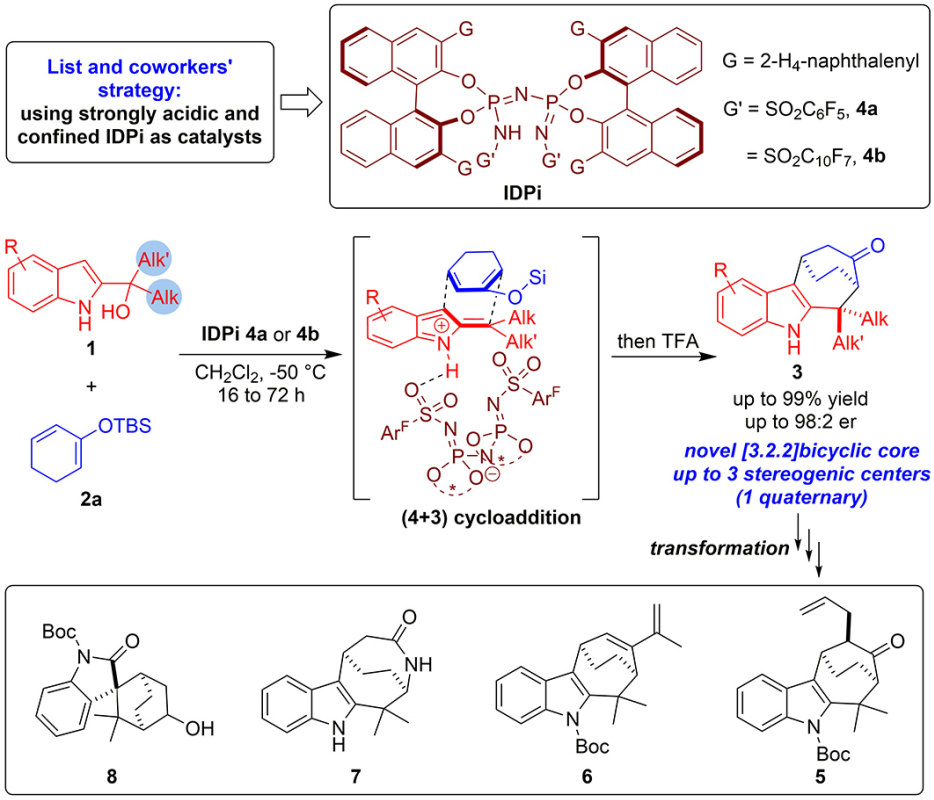

Figure 2. Organocatalytic asymmetric (4 + 3) cycloaddition of dialkyl-substituted 2-indolylmethanols with dienolsilane.

To gain some insights into the reaction mechanism, they performed a series of control experiments and theoretical calculations on this organocatalytic asymmetric (4 + 3) cycloaddition. Based on these investigations, they suggested a possible reaction pathway, which involved an overall concerted yet asynchronous cycloaddition process. As illustrated in Figure 3, initially, strongly acidic and confined IDPi reacted with dienolsilane **2a** via a silyl transfer process to generate the active silylium Lewis acid **I**, which could deliver silyl group to 2-indolylmethanol **1a** and form complex **II** via hydrogen-bonding interaction. Then, complex **II** underwent the C-O bond cleavage to produce intermediate **III** along with the release of TBSOH, which was the rate-limiting step with an energy barrier of 14.0 kcal/mol. Subsequently, intermediate **III** reacted with dienolsilane **2a** to undergo a concerted yet highly asynchronous (4 + 3) cycloaddition, which was the enantio-determining step with an energy barrier of 9.6 kcal/mol. The resulted adduct **IV** underwent a rearomatization process to give intermediate product **3aa'** with the regeneration of IDPi. Finally, the target product **3aa** was obtained by TFA-promoted removal of the silyl group in **3aa'**.

In short, List and coworkers established an organocatalytic asymmetric (4 + 3) cycloaddition of dialkyl-substituted 2-indolylmethanols with dienolsilane by using strongly acidic and confined imidodiphosphorimidates as competent organocatalysts, which afforded novel bicyclo[3.2.2]cyclohepta[*b*]-indoles in overall high yields with excellent enantioselectivities. This approach provides a powerful strategy to overcome the great challenges in realizing highly regio- and enantioselective transformations of dialkyl-substituted 2-indolylmethanols, which is a breakthrough in the field of 2-indolylmethanol-involved organocatalytic asymmetric reactions. This work has made indelible contributions to the chemistry of 2-indolylmethanols and demonstrated the power of asymmetric organocatalysis, which will further promote the development of the related fields.

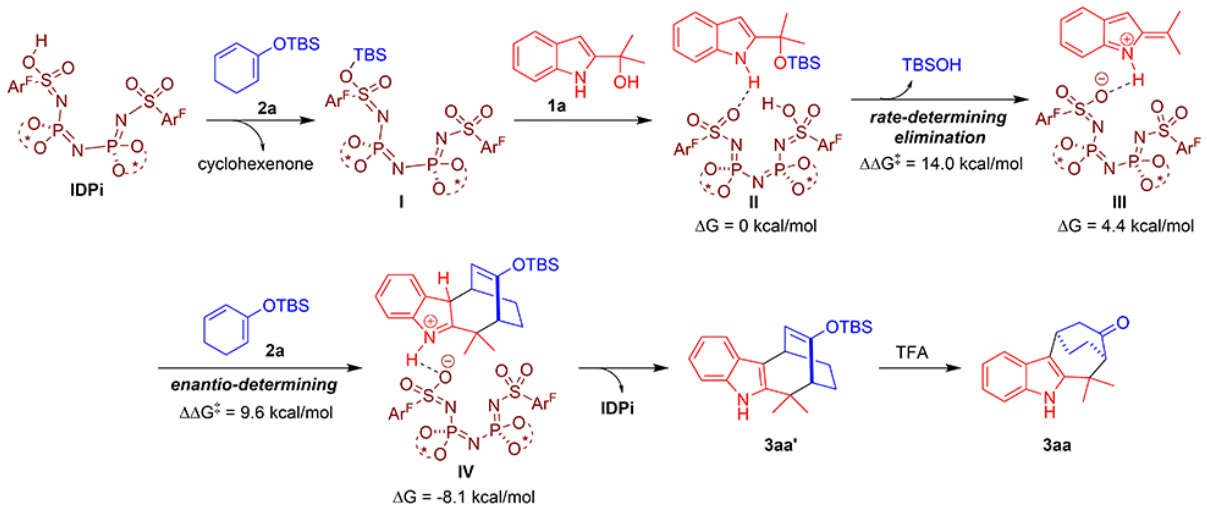

Figure 3. Suggested reaction pathway and activation mode.

DECLARATIONS

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Authors' contributions

Wrote the draft manuscript: Tan W

Revised and rewrote some parts of the manuscript: Shi F

Availability of data and materials

Not applicable.

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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