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Indolylmethanols as Reactants in Catalytic Asymmetric Reactions

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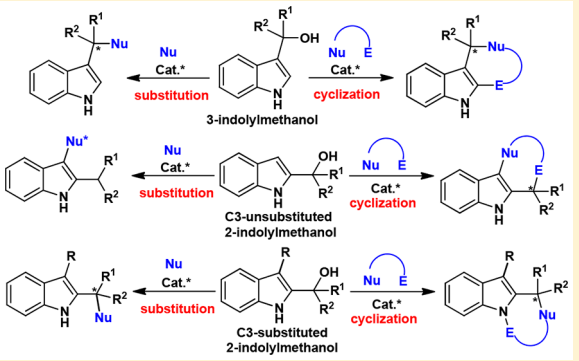
ABSTRACT: Indolylmethanols have emerged as versatile reactants in catalytic asymmetric reactions because of the facile generation of reactive intermediates from these compounds. The most common indolylmethanols are 3-indolylmethanols and 2-indolylmethanols, and the reaction types applicable to these heterocycles mainly include catalytic enantioselective substitutions and cyclizations. Using indolylmethanols as reactants in catalytic asymmetric reactions enables the enantioselective construction of a variety of indole-containing frameworks.



1. INTRODUCTION

As fascinating heterocyclic compounds, indole derivatives have extensive applications in pharmaceuticals, agricultural chemicals, and materials.[1] In addition, enantioenriched indole derivatives compose the core structures of many biologically significant natural products and synthetic compounds (Figure 1). Consequently, the efficient synthesis of structurally diverse

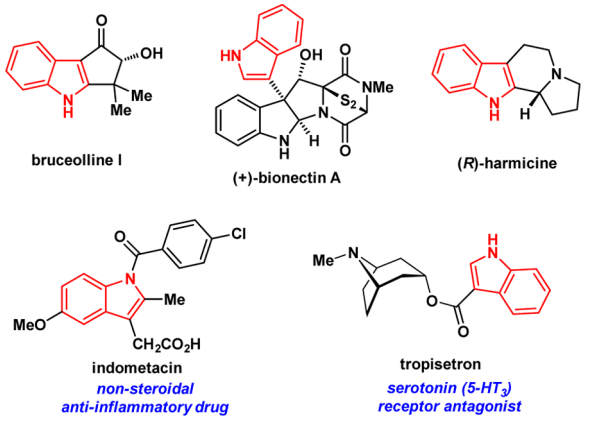
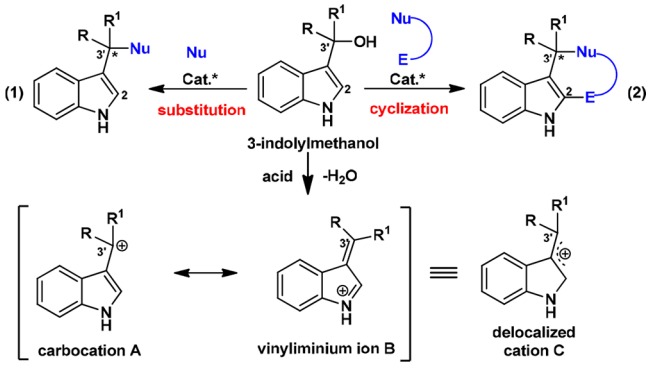


Figure 1. Representative natural alkaloids and biologically important compounds containing indole frameworks.

indole derivatives, especially in an enantioselective manner, has attracted considerable attention from the chemistry community.[2] Moreover, the synthesis of indole derivatives from indole-containing building blocks has proven to be one of the most direct and efficient approaches to these heterocycles.[3] Among indole derivatives, indolylmethanols have emerged as versatile reactants because of their ability to generate reactive intermediates in situ, which greatly contributes to the enantioselective synthesis of indole derivatives.

Generally, the reactive resonance structures of carbocation **A** and vinyliminium ion **B** are generated from 3-indolylmethanols via an acid-catalyzed dehydration pathway (Scheme 1).[3a]

Scheme 1. Profile of Catalytic Asymmetric Reactions of 3-Indolylmethanols



Resonance structures **A** and **B** and their resonance hybrid, delocalized cation **C**, are stabilized by forming ion pairs with counteranions or hydrogen bonds. Therefore, when a chiral catalyst is employed in the formation of the ion pairs or hydrogen bonds, catalytic asymmetric reactions of 3-indolylmethanols can be achieved. The reactive intermediates generated from 3-indolylmethanol can be easily attacked at the C3′ position by different nucleophiles. Therefore, catalytic asymmetric nucleophilic substitutions of 3-indolylmethanols have been well documented (eq 1). Despite the low reactivity of the C-2 position in the indole moiety, 3-indolylmethanol can be used as a 3C synthon. Recently, various catalytic enantioselective [3 + *n*] cyclizations of 3-indolylmethanols for

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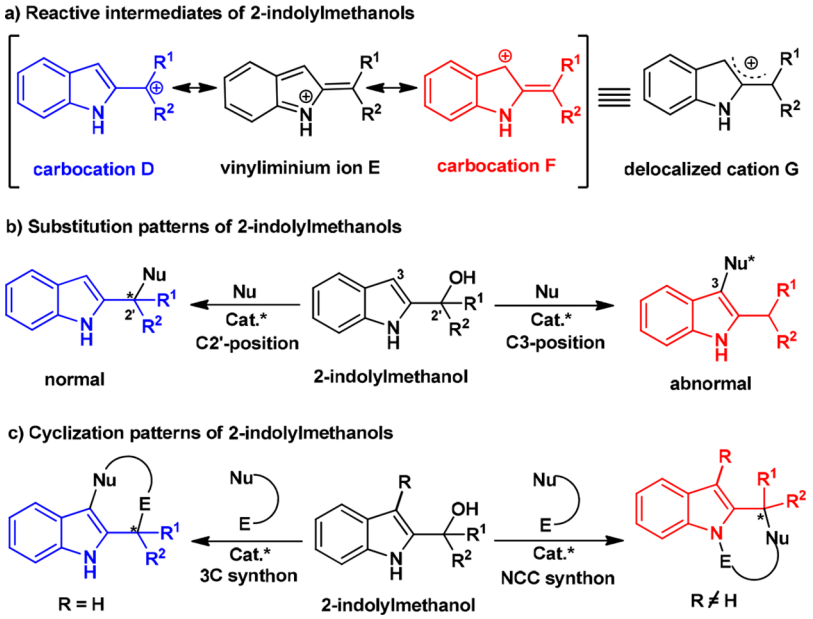
Scheme 2. Profile of 2-Indolylmethanol-Involved Catalytic Asymmetric Reactions



constructing chiral indole-fused cyclic frameworks via stepwise or concerted pathways have been developed (eq 2).

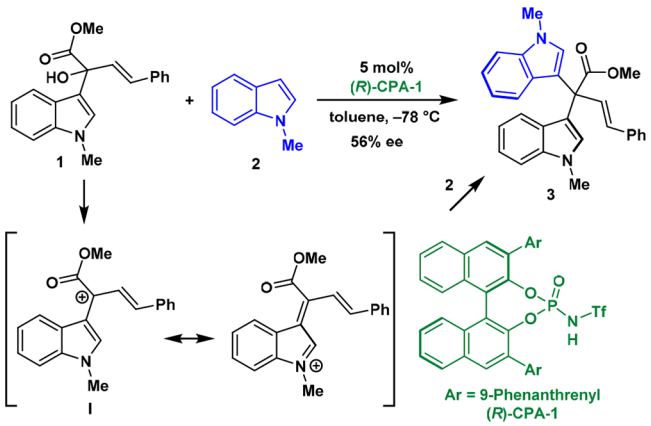
Similarly, 2-indolylmethanols have also been utilized as versatile reactants in the catalytic asymmetric synthesis of indole derivatives. In the presence of a Brønsted acid (B–H), reactive intermediates **D**–**F** were generated from 2-indolylmethanols in situ (Scheme 2a). Compared to 3-indolylmethanols, the intermediates generated from 2-indolylmethanols have more reactive sites. Consequently, more types of catalytic asymmetric reactions are possible when using 2-indolylmethanols. First, there are two reactive carbocations (**D** and **F**) of 2-indolylmethanol. In carbocation **F**, the reactivity of the C3-position of indole motif is switched from nucleophilic to electrophilic, which is a scarcely reported umpolung strategy in indole chemistry.[4] Therefore, two kinds of regioselective asymmetric substitutions of 2-indolylmethanols have been developed (Scheme 2b). In addition, 2-indolylmethanols can act as 3C or NCC (nitrogen–carbon–carbon) building blocks in enantioselective [3 + *n*] cyclizations to construct different types of indole-fused chiral cyclic frameworks (Scheme 2c).

The reactions of indolylmethanols are usually considered atom-economic and environmentally benign because the only byproduct is water. Moreover, because of the multiple reactive sites on indolylmethanols, the products that can be obtained from them have broad structural and functional diversity. In this synopsis, recent advances in the catalytic asymmetric reactions of indolylmethanols are presented. The catalytic asymmetric reactions of protected indolylmethanol derivatives[3a] and tetrahydro-*β*-carboline-derived indolylmethanols[5] are not included.

2. CATALYTIC ASYMMETRIC REACTIONS OF 3-INDOLYLMETHANOLS

2.1. Catalytic Asymmetric Substitutions of 3-Indolylmethanols. Early research on reactions with 3-indolylmethanols can be traced back to a formal [3 + 2] cycloaddition described in 1995.[6] However, it was not until 2008 that Rueping and co-workers reported the first catalytic asymmetric reaction of 3-indolylmethanol (Scheme 3).[7] In the presence of

Scheme 3. Catalytic Asymmetric Substitution of 3-Indolylmethanol 1 with *N*-Methylindole (2)



a chiral phosphoric acid (CPA),[8] 3-indolylmethanol **1** underwent an enantioselective nucleophilic substitution with *N*-methylindole **2** to provide bisindole **3** as an atropisomer. The ion pair of carbocation **I** with **(*R*)-CPA-1** anion was proposed to contribute to controlling the enantioselectivity. Despite the moderate enantioselectivity observed, this reaction not only represents pioneering work in the catalytic asymmetric reaction of 3-indolylmethanols but also provides access to enantioenriched atropisomers.

More recently, this concept of asymmetric counteranion-directed catalysis (ACDC)[9] has been successfully applied to CPA-catalyzed reactions of indolylmethanols. In 2009, the Gong group reported a catalytic asymmetric alkylation reaction of enamides **4** with 3-indolylmethanols **5** (Scheme 4).[10] The chiral ion pair between the phosphate anion and carbocation or vinyliminium ion was proposed to activate enamide **4** via a hydrogen-bonding interaction. Ultimately, *α*-alkylation products **6** were obtained in high yields and with excellent enantioselectivities. Later, the same group successfully completed the enantioselective total synthesis of (+)-folicanthine

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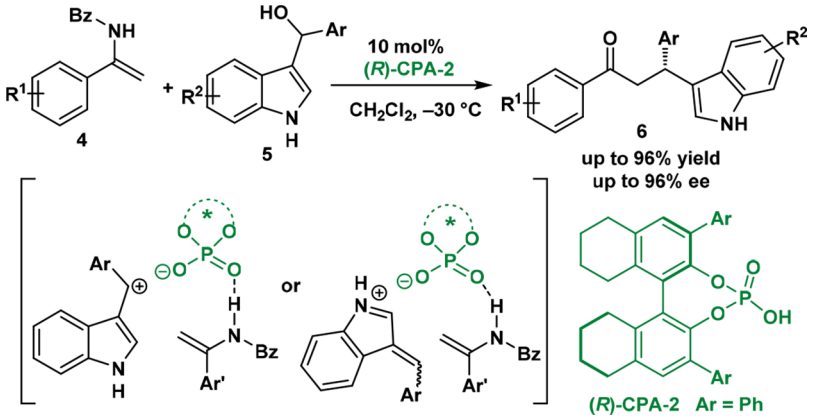
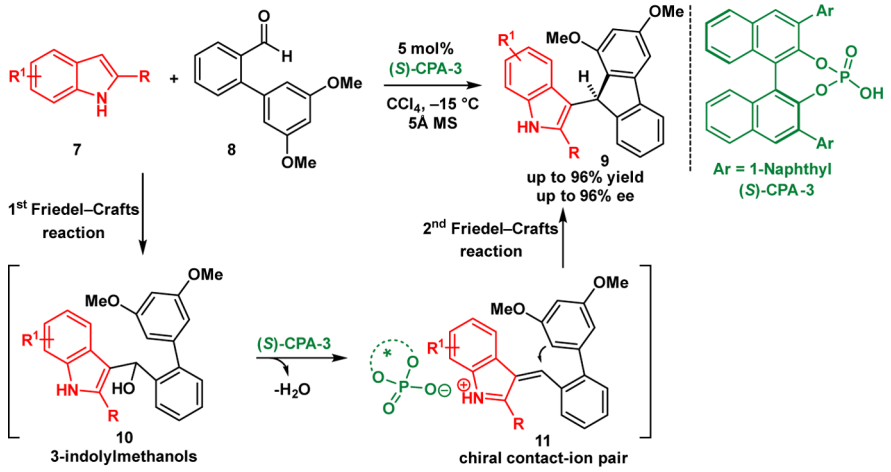
Scheme 4. Catalytic Asymmetric Alkylation Reaction of Enamides with 3-Indolylmethanols



Scheme 5. Catalytic Asymmetric Tandem Double Friedel–Crafts Reaction Involving 3-Indolylmethanols

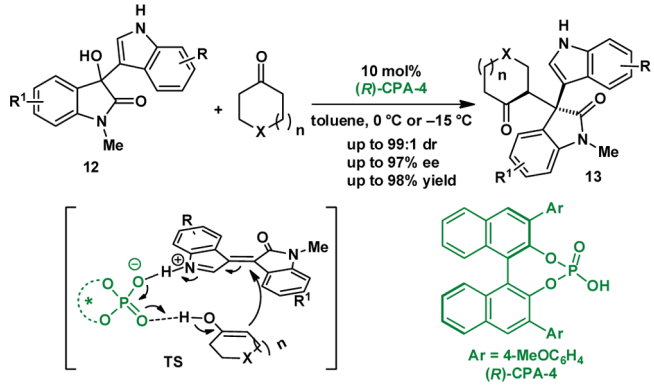


and (+)-gliocladin C using this CPA-catalyzed asymmetric substitution of 3-indolylmethanols.[11]

At nearly the same time, You and co-workers demonstrated a CPA-catalyzed tandem double-Friedel–Crafts reaction (Scheme 5).[12] In the first Friedel–Crafts reaction, 3-indolylmethanols **10** were generated in situ from substrates **7** and **8**. In the second Friedel–Crafts reaction, an intramolecular enantioselective substitution reaction occurred. 3-Indolylmethanols **10** transformed into the corresponding vinyliminium ions **11** via **(*S*)-CPA-3**-catalyzed dehydration. The enantioselectivity of the latter cyclization was controlled by the chiral contact-ion pair of **(*S*)-CPA-3** and the vinyliminium ion. The fluorene derivative products were ultimately obtained with good to excellent enantioselectivities.

The direct α-alkylation of carbonyl compounds is one of the most powerful reactions for constructing carbon–carbon bonds. Therefore, the catalytic asymmetric α-alkylation of carbonyl compounds with 3-indolylmethanols is highly valuable, which has been achieved by Peng, Guo, and co-workers using **(*R*)-CPA-4** as a chiral catalyst (Scheme 6).[13] High yields, excellent diastereoselectivities, and enantioselectivities of products **13** were observed in this catalytic asymmetric α-alkylation of unmodified ketones with 3-indolylmethanols **12**, wherein a dual activation mode was suggested in the transition state. Later, the CPA-catalyzed enantioselective alkylation of acyclic alkyl ketones with 3-indolylmethanols through a decarboxylative process was developed by the Ma group.[14]

Scheme 6. Catalytic Asymmetric α-Alkylation of Unmodified Ketones with 3-Indolylmethanols



Despite the progress on the catalytic asymmetric alkylation of 3-indolylmethanols with carbonyl compounds, there have been only limited examples of CPA-catalyzed asymmetric allylation of 3-indolylmethanols. In 2014, the Shi group reported a catalytic asymmetric substitution of 3-indolylmethanols **13** with *o*-hydroxystyrenes **14**, which afforded formal allylation products **15** in excellent enantio- and (*Z*)-selectivities (up to 97% ee, > 20:1 *Z*/*E*) (Scheme 7, eq 3).[15] It was proposed that **(*R*)-CPA-5** could simultaneously activate the vinyliminium ion intermediate and *o*-hydroxystyrene **14** via hydrogen-bonding interactions. Then, a cascade reaction involving an asymmetric vinylogous

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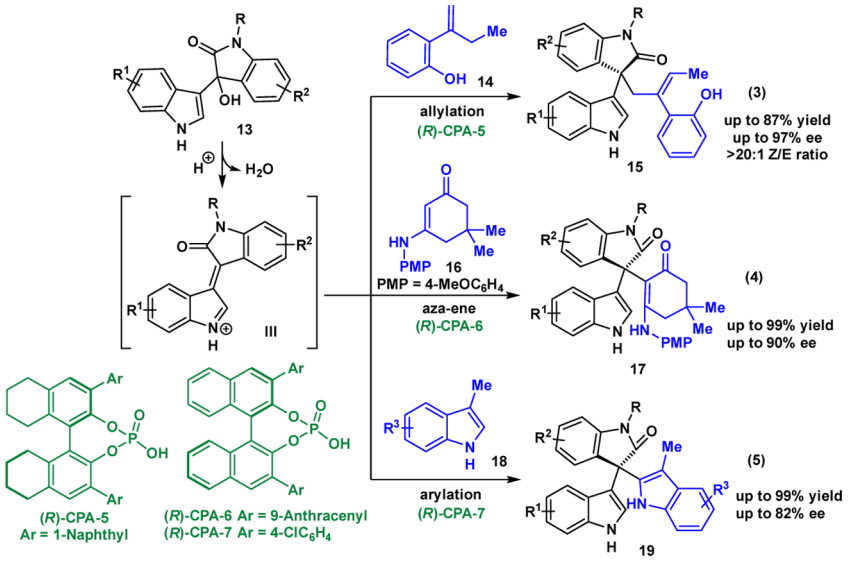
Scheme 7. Catalytic Asymmetric Substitutions of 3-Indolylmethanols with Different Nucleophiles



Michael addition and an allylic hydrogen-elimination occurred smoothly, resulting in the formation of allylation products **15**.

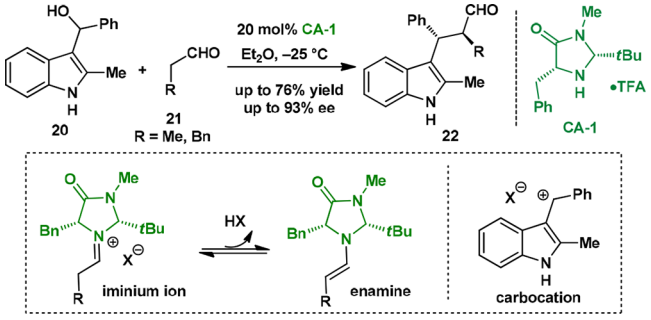
The Shi group has also successfully applied the same activation mode to a catalytic asymmetric aza-ene reaction of 3-indolylmethanols **13** with cyclic enaminones **16** (eq 4). This reaction is especially notable because of the limited number of examples of catalytic enantioselective aza-ene reactions. Using this strategy provided a series of C3-funcionalized chiral indoles **17** in high yields and good enantioselectivities (up to 99% yield, up to 90% ee).[16] This reaction also effected a catalytic asymmetric formal alkenylation of 3-indolylmethanols.

Although the substitution reactions of 3-indolylmethanols have developed rapidly, the catalytic asymmetric arylation of 3-indolylmethanols with aromatic compounds has scarcely been studied. Following the successful synthesis of C6-functionalized indoles via arylation reactions,[17] the Shi group realized the catalytic asymmetric arylation of 3-indolylmethanols.[18] Biologically important chiral 3,3′-bis(indolyl)oxindoles **19** were synthesized in an atom-economic fashion by the enantioselective substitutions of 3-indolylmethanols **13** with 3-methylindoles **18** in the presence of **(*R*)-CPA-7** (eq 5). Later, the same group evaluated the substitutions of 3-indolylmethanols with tryptamines, which led to the generation of structurally complex indole derivatives via a catalytic asymmetric cascade dearomatization process.[19]

In addition to the ACDC strategy, chiral nucleophiles generated in situ from chiral catalysts have also contributed to the enantioselective substitutions of 3-indolylmethanols. Chiral enamines have been widely used in organic chemistry as chiral nucleophiles. In this context, asymmetric enamine catalysis has emerged as an efficient strategy for enantioselective substitutions of 3-indolylmethanols. Generally, chiral amines (CAs) such as MacMillan catalysts,[20] chiral thioureas,[21] and diarylprolinol silyl ethers[22] have proven to be effective catalysts for asymmetric substitutions of 3-indolylmethanols with aldehydes.

A report by the Cozzi group on a catalytic asymmetric alkylation of aldehydes with alcohols showed that in the presence of **CA-1**, the reaction of 3-indolylmethanol **20** with aldehydes **21** proceeded smoothly at room temperature.[23] Indole derivatives **22** were obtained in good yields and high enantioselectivities but low diastereoselectivities (1.5:1−3:1 dr) (Scheme 8). The authors proposed that the free acid (HX)

Scheme 8. Catalytic Asymmetric Substitution of 3-Indolylmethanol with Aldehydes



formed from the equilibrium between the iminium ion and enamine was responsible for the generation of the carbocation. Then, the whole reaction occurred smoothly through an S_N1-type mechanism, which led to the catalytic asymmetric alkylation of the aldehydes. Similarly, in 2013, Wang, Ji and co-workers reported an asymmetric α-alkylation of aldehydes with isatin-derived 3-indolylmethanols in aqueous media in the presence of a MacMillan catalyst.[24]

In the studies of intramolecular imino−ene reactions from the Chen group, substrates **26** were prepared via the enantioselective substitution of 3-indolylmethanols **23** with α,β-unsaturated aldehydes **24** followed by $NaBH_4$ reduction (Scheme 9).[25] The cooperation between chiral catalyst **CA-2** and AcOH furnished nucleophilic chiral enamines from aldehydes **24** and electrophilic carbocations or vinyliminium ions from 3-indolylmethanols **23**, thus facilitating an enantioselective and regioselective α-alkylation of aldehydes **24** with 3-indolylmethanols **23** to generate intermediate products **25**, which were easily reduced to yield stable products **26**. Substrates **26** underwent a subsequent $AlCl_3$-mediated intramolecular imino-ene cyclization to afford cyclopentyl[*b*]-indolines **28** in high yields and excellent enantioselectivities. Moreover, the Xiao and Loh groups found that this Brønsted

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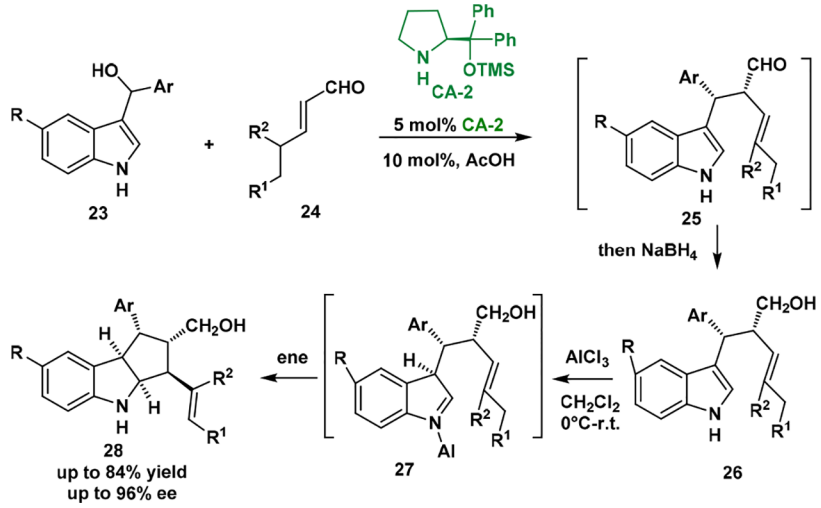
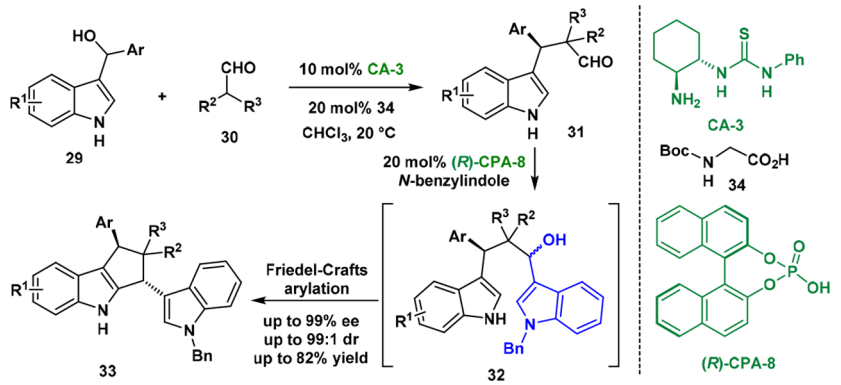
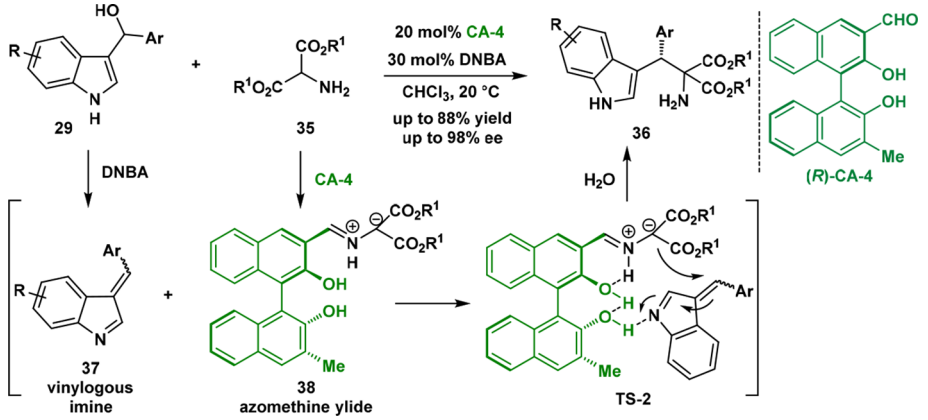
Scheme 9. Catalytic Asymmetric Substitutions of 3-Indolylmethanols with Unsaturated Aldehydes and Subsequent Intramolecular Ene Reactions



Scheme 10. Catalytic Asymmetric Inter- and Intramolecular Substitutions of 3-Indolylmethanols through a One-Pot Method



Scheme 11. Catalytic Asymmetric Substitutions of 3-Indolylmethanols with Amino Esters



acid/CA activation mode could be further extended to Lewis acid/CA and even protic solvent/CA systems.[26]

The Guo group utilized the catalytic asymmetric α-alkylation of aldehydes with 3-indolylmethanols to synthesize enantioenriched cyclopenta[*b*]indoles, which involved the one-pot reaction of 3-indolylmethanols **29** with aldehydes **30** (Scheme 10).[27] The initial step was an enantioselective substitution of 2-indolylmethanols **29** with aldehydes **30** catalyzed by chiral thiourea−primary amine **CA-3** and Brønsted acid **34**. Then, α-alkylation products **31** reacted with *N*-benzylindole through an intermolecular Friedel−Crafts arylation in the presence of (***R***)-**CPA-8**. Interestingly, in situ generated intermediate **32** also possessed a 3-indolylmethanol motif. Subsequently, the intramolecular substitution of 3-indolylmethanol **32** occurred smoothly via a Friedel−Crafts arylation, providing enantioenriched polysubstituted cyclopenta[*b*]indoles **33** in high yields and with excellent diastereoselectivities and enantioselectivities. In later work, the Guo group applied this methodology to the

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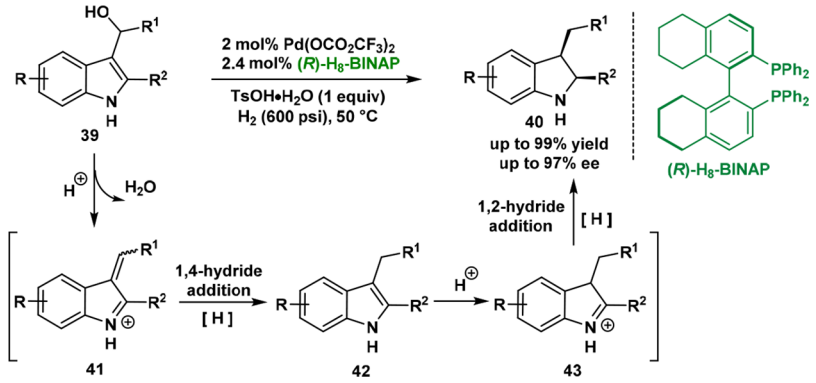
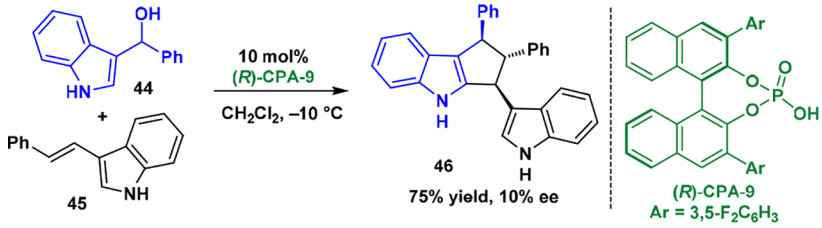
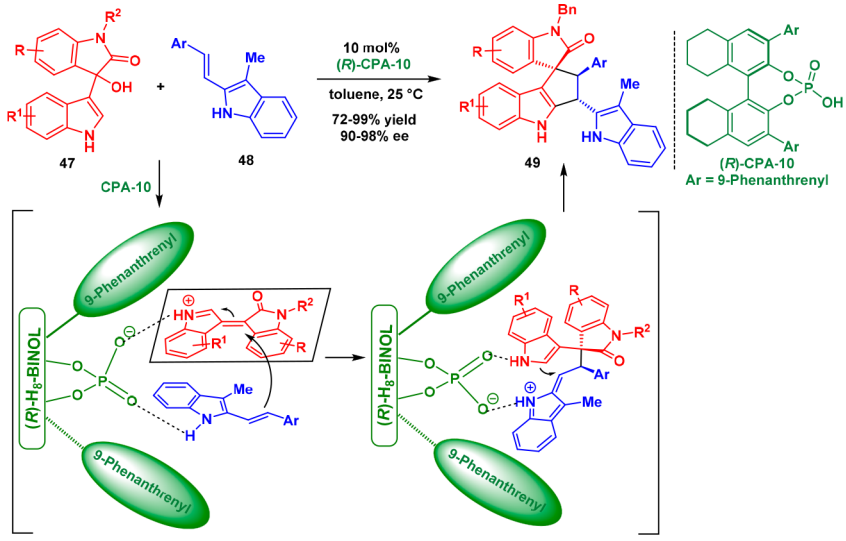
Scheme 12. Catalytic Asymmetric Hydrogenation of 3-Indolylmethanols



Scheme 13. Preliminary Attempt of a Catalytic Asymmetric [3 + 2] Cyclization of 3-Indolylmethanol with 3-Vinylindole



Scheme 14. Catalytic Asymmetric [3 + 2] Cyclization of 3-Indolylmethanols with 3-Methyl-2-vinylindoles



direct asymmetric alkylation reaction of α-amino aldehydes with 3-indolylmethanols.[28]

Despite the well-studied CPA- and CA-catalyzed reactions of 3-indolylmethanols, new chiral organocatalysts are still desired to establish more transformations of 3-indolylmethanols. In 2014, the Guo group found that chiral aldehyde **CA-4** could act as an organocatalyst in the enantioselective substitutions of 3-indolylmethanols **29** with amino esters **35** (Scheme 11).[29] Bearing a chiral BINOL skeleton, chiral aldehyde **CA-4** exhibited excellent chiral induction activity, generating tryptophan derivatives **36** in good yields and with high enantioselectivities. The reactive intermediates, vinylogous imines **37** and azomethine ylides **38**, which were identified by high resolution mass spectrometry, were obtained in situ under the cooperative catalysis of 3,5-dinitrobenzoic acid (DNBA) and **CA-4**. The authors proposed a hydrogen-bonding interaction between reactive intermediates **37** and **38**, which underwent subsequent 1,4-addition and hydrolysis reactions to afford final products **36**.

In addition to commonly used nucleophiles, a hydride can also serve as a nucleophile in catalytic asymmetric substitutions of 3-indolylmethanols. In 2011, Zhou and Jiang reported the catalytic asymmetric hydrogenation of 3-indolylmethanols **39** (Scheme 12).[30] The enantioselective hydrogenation reaction was initiated by a sequence of the 1,4-hydride addition to vinyliminium ion **41** and 1,2-hydride addition to iminium ion **43**. This asymmetric hydrogenation of 3-indolylmethanols **39**, which was catalyzed by a chiral palladium complex with H_8–BINAP, afforded chiral indolines **40** in excellent yields and high enantioselectivities. The authors also found that 3-indolylmethanols could be generated in situ from simple indoles and aldehydes.[31]

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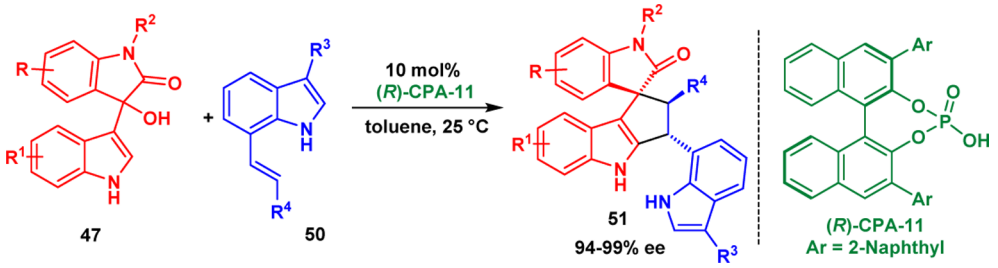
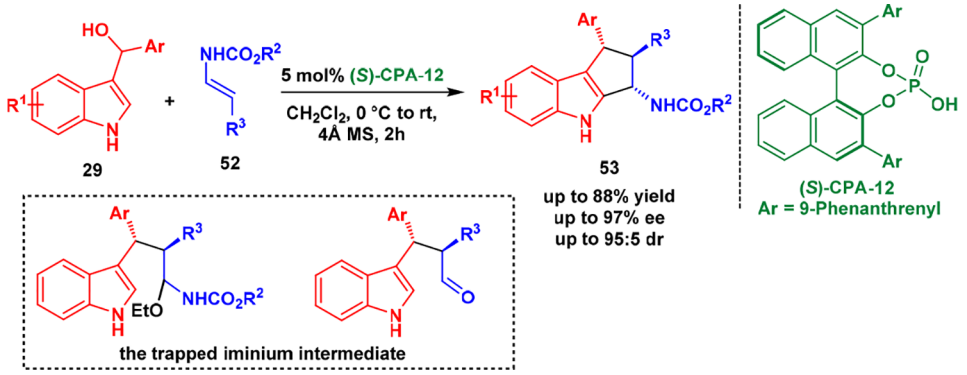
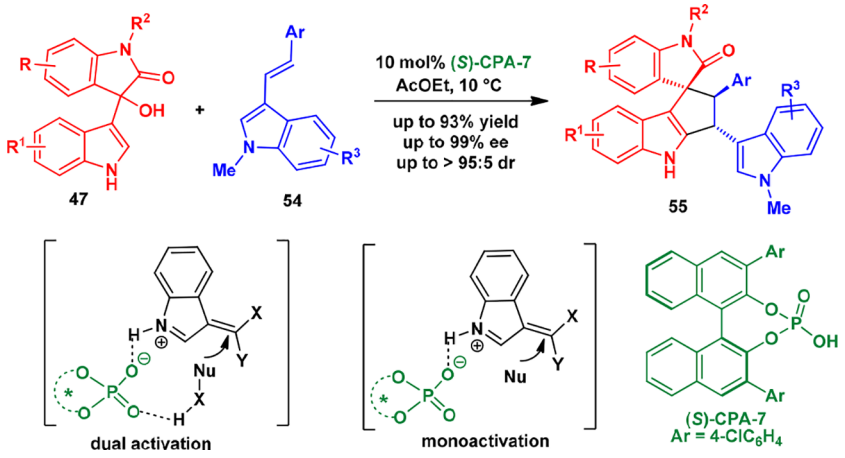
Scheme 15. Catalytic Asymmetric [3 + 2] Cyclization of 3-Indolylmethanols with 7-Vinylindoles



Scheme 16. Catalytic Asymmetric [3 + 2] Cyclization of 3-Indolylmethanols with Enecarbamates



Scheme 17. Catalytic Asymmetric [3 + 2] Cyclization of 3-Indolylmethanols with *N*-Methyl-3-vinylindoles via a Monoactivation Mode



2.2. Catalytic Asymmetric Cyclizations of 3-Indolylmethanols. In comparison with the substantial success achieved in catalytic asymmetric substitutions, enantioselective cyclizations with 3-indolylmethanols have been rarely reported. When 3-indolylmethanols are employed as 3C synthons, the C2-position of the indole moiety exhibits relatively low nucleophilicity. Hence, enantioselective [3 + *n*] cyclizations involving 3-indolylmethanols require specific synthetic design and selection of suitable reaction components. For instance, in the catalytic asymmetric [3 + 2] cyclization of 3-indolylmethanol **44** with 3-vinylindole **45**, the enantioselectivity of product **46** was poor (10% ee; Scheme 13).[32] Conversely, the Shi group showed that the catalytic asymmetric [3 + 2] cyclization of isatin-derived 3-indolylmethanols **47** with 3-methyl-2-vinylindoles **48** yielded spiro-oxindole scaffolds **49** with excellent enantioselectivities of 90%−98% ee. (Scheme 14).[33] The proposed reaction pathway involves an enantioselective vinylogous Michael addition of vinyliminium ion intermediates with 3-methyl-2-vinylindoles, affording a transient intermediate. Then, triggered by the force of restoring the stable indole structure, an intramolecular Friedel−Crafts reaction occurred, producing the final products (**49**). The excellent control of the enantioselectivity was ascribed to the formation of H-bonds and an ion pair between (***R*)-CPA-10** and the substrates.

The catalytic asymmetric [3 + 2] cyclization of 7-vinylindoles **50** with 3-indolylmethanols **47** has been established by the same group (Scheme 15).[34] 2-Vinylindoles and 3-vinylindoles bearing vinyl groups on the more reactive pyrrole ring have been employed as versatile reactants for catalytic asymmetric reactions. By contrast, 7-vinylindoles have scarcely been utilized as reactants in catalytic asymmetric reactions because of the considerable challenges associated with such a transformation. Nevertheless, this approach not only provided spirooxindoles **51** from 3-indolylmehtanols **47** with excellent enantioselectiv-

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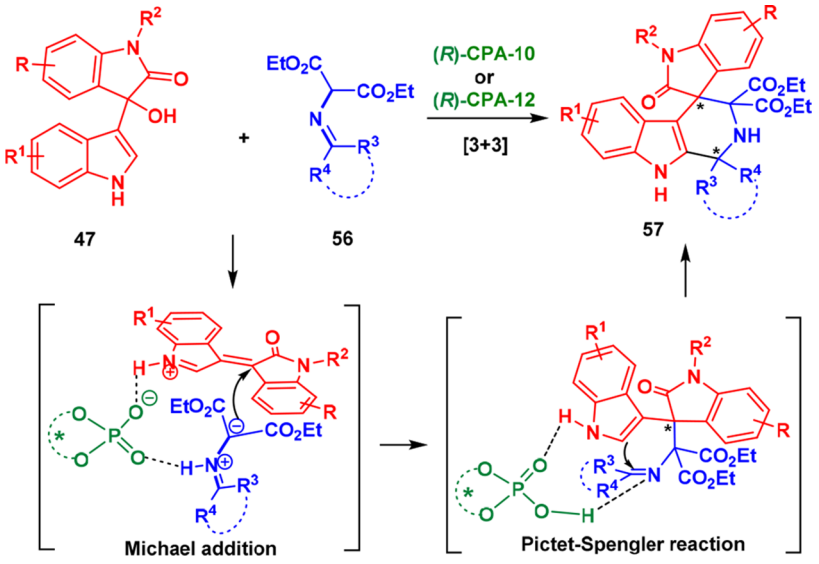
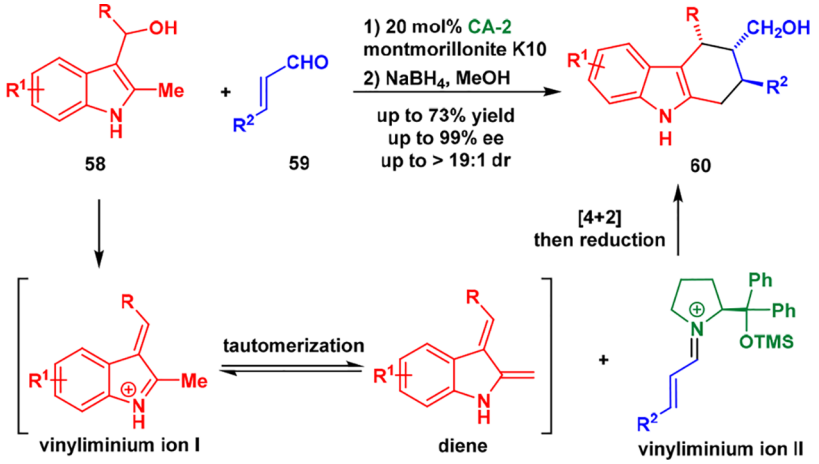
Scheme 18. Catalytic Asymmetric [3 + 3] Cyclization of 3-Indolylmethanols with Azomethine Ylides



Scheme 19. Catalytic Asymmetric [4 + 2] Cyclization of 3-Indolylmethanols with Aldehydes



ities but also augmented the catalytic asymmetric reactions of 7-vinylindoles.

In 2015, the Masson group developed a similar catalytic asymmetric [3 + 2] cyclization of 3-indolylmethanols **29** with enecarbamates **52** (Scheme 16),[35] wherein the proposed stepwise pathway was supported by the trapped iminium intermediate.

In CPA-catalyzed asymmetric reactions of 3-indolylmethanols, the control of the enantioselectivity via the dual activation mode of the catalyst is well established. In other words, CPAs act as a bifunctional catalyst, activating both the vinyliminium ion and nucleophiles simultaneously via hydrogen-bonding and/or ion pair interactions. Monoactivation of vinyliminium ions by CPAs usually resulted in a failed reaction or a reaction with low enantioselectivity. However, the Shi group found that the enantioselective [3 + 2] cyclization of 3-indolylmethanols **47** with *N*-methyl-3-vinylindoles **54** occurred smoothly in the presence of **(*S*)-CPA-7** (Scheme 17).[36] Because of the difficulty in forming a hydrogen bond formation between *N*-methyl-3-vinylindoles **54** and **(*S*)-CPA-7**, a monoactivation mode was proposed to explain the excellent enantioselectivities observed. This approach should serve as a useful strategy for developing CPA-catalyzed asymmetric reactions of 3-indolylmethanols.

In addition to [3 + 2] cyclization, the catalytic asymmetric [3 + 3] cyclization of 3-indolylmethanols has been of substantial interest to organic chemists because of the remarkable ability of this class of reaction to construct indole-fused six-membered rings with optical activity.[37] In 2014, the Shi group established the CPA-catalyzed highly enantioselective [3 + 3] cyclizations of 3-indolylmethanols **47** with azomethine ylides **56** generated in situ from aldehydes or isatins, affording structurally diverse spirooxindoles or bispirooxindoles **57** in high yields and good enantioselectivities (68% to >99% ee) (Scheme 18).[38] The reaction was initiated by an enantioselective intermolecular Michael addition of azomethine ylides **56** to vinyliminium ion generated in situ from 3-indolylmethanols **47**. The sequential intramolecular Pictet−Spengler reaction effected the enantioselective formal 1,3-dipolar [3 + 3] cycloaddition. The hydrogen-bonding interaction between the CPA and two reactants was presumed to play a crucial role in controlling the enantioselectivity.

In the aforementioned catalytic asymmetric cyclizations, the 3-indolylmethanols always acted as 3C synthons. However, when a methyl group is introduced at the C2-position of the indole moiety, 3-indolylmethanols can act as a 4C building block in the cyclization event. In 2012, the Chen group found

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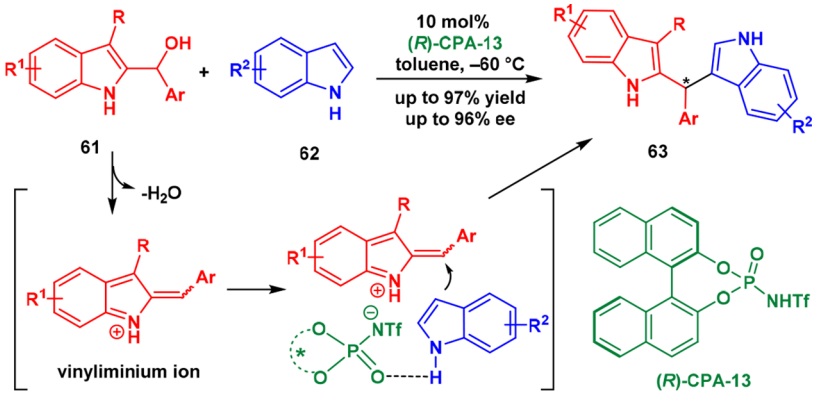
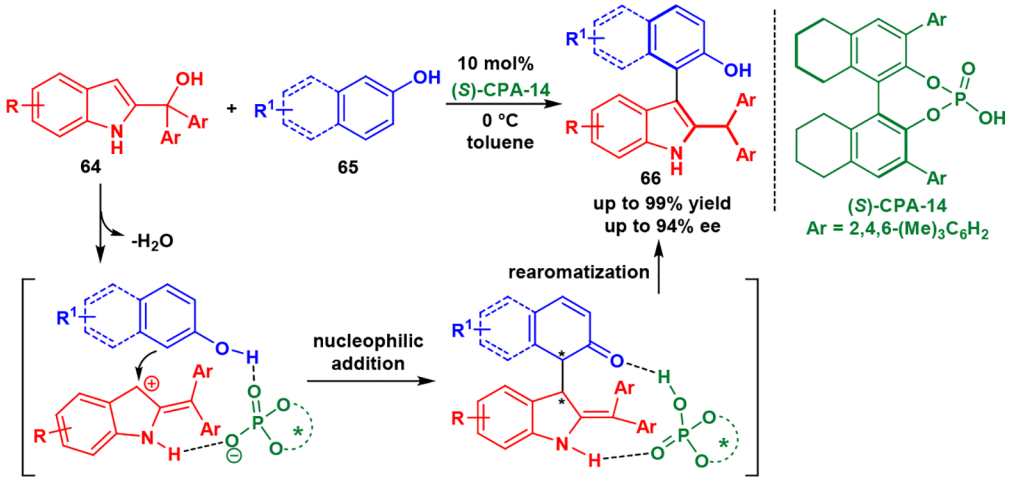
Scheme 20. Catalytic Asymmetric Substitution of 2-Indolylmethanols with Indoles



Scheme 21. Catalytic Asymmetric Substitutions of 2-Indolylmethanols with 2-Naphthols or Phenols to Construct Axially Chiral Indole−Aryl Skeletons



that 2-methyl vinyliminium ions **I** generated from 3-indolylmethanols **58** could tautomerize into dienes, namely, indole-2,3-quinodimethanes (Scheme 19).[39] This class of intermediate could act as a special type of *o*-quinodimethane (*o*-QDM). These dienes reacted with vinyliminium ion **II** generated in situ from catalyst **CA-5** and α,β-unsaturated aldehydes **59**, resulting in an asymmetric [4 + 2] cyclization. After reduction, the final products (**60**) were obtained with excellent enantioselectivities.

3. CATALYTIC ASYMMETRIC REACTIONS OF 2-INDOLYLMETHANOLS

3.1. Catalytic Asymmetric Substitutions of 2-Indolylmethanols. As analogues of 3-indolylmethanols, 2-indolylmethanols show great potential for the synthesis of indole derivatives and have promising applications in the synthesis of natural products.[5a,6,40] However, catalytic asymmetric reactions with 2-indolylmethanols have been scarcely reported.[5b,c,41] The pioneering work was the enantioselective substitution of 2-indolylmethanols with indoles developed by Han and co-workers (Scheme 20).[42] In the presence of (*R*)-**CPA-13**, chiral 2,3′-diindolylarylmethanes **63** were obtained in high yields and with excellent enantioselectivities. Based on a control experiment that showed that *N*-methylindole gave poor enantioselectivity, it was suggested that in addition to the ion pair interaction between the vinyliminium ion and (*R*)-**CPA-13**, the hydrogen-bonding interaction between indoles **62** and (*R*)-**CPA-13** also played a crucial role in chiral induction. Later, enamides and 3-alkylindoles were also employed as nucleophiles to perform catalytic asymmetric substitutions with 2-indolylmethanols via this dual activation mode.[43]

The nucleophilicity of the C3-position of the indole ring is the foundation of transformations involving indoles. The Shi group found that the C3-position of 2-indolylmethanols exhibited unusual electrophilicity, thus affording substitution products with a different type of regioselectivity.[44] Using this strategy, this group designed and constructed a series of axially chiral indole-aryl frameworks, which are a new and privileged class of axially chiral heterobiaryl backbones (Scheme 21).[45] In the presence of (*S*)-**CPA-14**, active carbocations were generated from 2-indolylmethanols **64** bearing two bulky Ar substituents. The sequential enantioselective nucleophilic addition of 2-naphthols or phenols to the carbocations and subsequent rearomatization furnished axially chiral indole-aryl products **66** in high yields and good enantioselectivities. In this process, the axial chirality of this process was entirely controlled by the hydrogen-bonding interaction between (*S*)-**CPA-14** and the two substrates.

Subsequently, the same group took advantage of the C3-electrophilicity of 2-indolylmethanols **64** to perform an asymmetric direct α-arylation of pyrazol-5-ones **67** under the organo-metal cooperative catalysis of CPAs and palladium (Scheme 22).[46] This reaction was initiated by the (*R*)-**CPA-15**-catalyzed dehydration of 2-indolylmethanols **64**, affording

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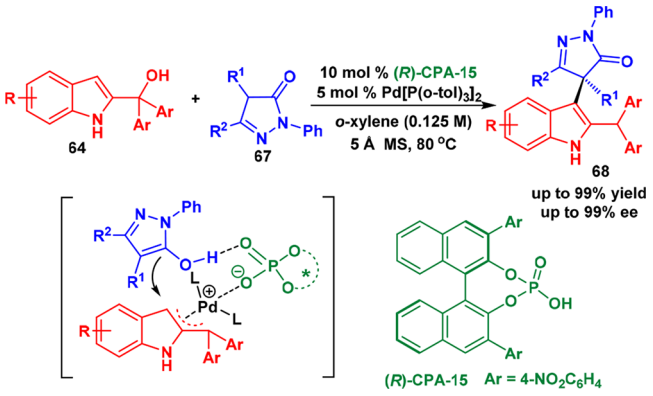
Scheme 22. Catalytic Asymmetric Substitution of 2-Indolylmethanols with Pyrazol-5-ones via Organometal Cooperative Catalysis



delocalized cations that were further stabilized by Pd/ligand. (*R*)-**CPA-15** was suggested to simultaneously activate enolized pyrazol-5-one **67** and the delocalized cation−Pd complex via H-bonding and ion pair interactions. Consequently, α-arylation products **68** were obtained in generally high yields and good enantioselectivities (up to 99% yield, >99% ee). The control experiments showed that both the yield and enantioselectivity of the reaction were decreased in the absence of the Pd complex, which demonstrated the synergistic effect of the dual catalyst system.

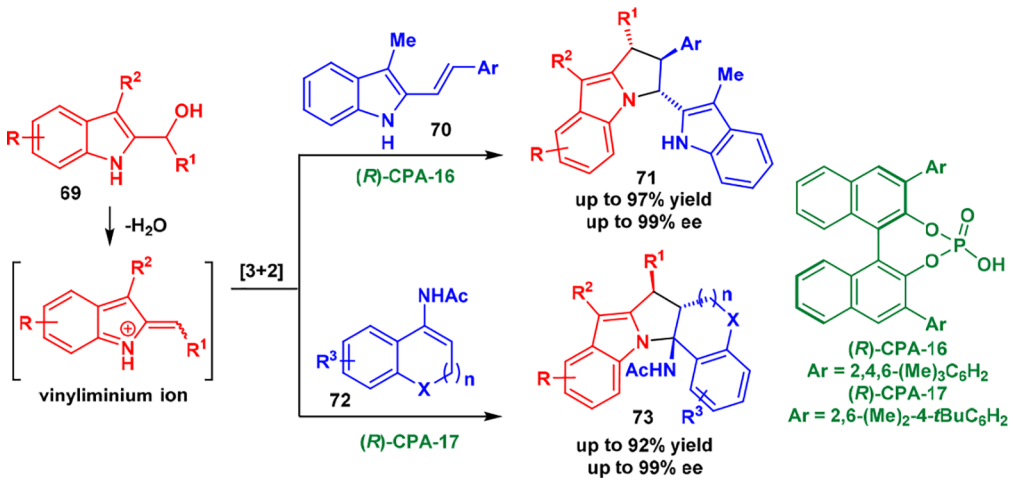
3.2. Catalytic Asymmetric Cyclizations of 2-Indolylmethanols. Because of the multiple reactive sites on 2-indolylmethanols, this class of reactants can act as 3C or NCC building blocks in cyclization reaction. In 2016, the Schneider group utilized C3-substituted 2-indolylmethanols **69** as NCC building blocks in CPA-catalyzed [3 + 2] cyclizations (Scheme 23).[47] In the presence of (*R*)-**CPA-16**, 3-substituted 2-indolylmethanols **69** transformed into reactive vinyliminium ion intermediates via dehydration and then underwent an enantioselective [3 + 2] cyclization[47a] with 3-methyl-2-vinylindoles **70**.[33,48] Enamides **72** are also suitable reaction components in a similar enantioselective [3 + 2] cyclization catalyzed by (*R*)-**CPA-17**.[47b] Using this strategy enabled the synthesis of polycyclic products **71** and **73** in high yields and with good enantioselectivities.

The Shi group also found that C-3-unsubstituted 2-indolylmethanols **64** could be utilized as 3C building blocks in catalytic asymmetric [3 + 2] cycloadditions with 3-vinylindoles **74** (Scheme 24).[49] Based on the observed diastereomers of the products (**75**), a stepwise reaction pathway was proposed. The divergent regioselectivity of this transformation arose from the nucleophilic attack of 3-vinylindoles **74** on the C3-position of the indole ring in the delocalized cation generated in situ from 2-indolylmethanols **64**. The hydrogen-bonding and ion pair interactions between (*S*)-**CPA-18** and the two substrates might play an important role in the observed enantioselectivity. A wide range of cyclopenta[*b*]indole derivatives **75** were efficiently constructed in high yields (up to 99%) and good diastereo- and enantioselectivities (up to >95:5 dr, 96:4 er).

Moreover, the Shi group demonstrated the catalytic asymmetric [3 + 3] cycloadditions of 2-indolylmethanols in the same year.[50] A survey of the literature revealed that racemic [3 + 3] cyclizations of 2-indolylmethanols were sporadically reported[40a,51] and that catalytic asymmetric versions of these reactions had not been reported yet. Using a similar activation mode to the one described above, this group realized a regio-, diastereo-, and enantioselective [3 + 3] cyclization of 2-indolylmethanols **64** with azomethine ylides generated in situ from aldehydes **76** and amino-ester **77**; this reaction delivered products **78** in excellent enantioselectivities (Scheme 25). In the proposed transition state, (*R*)-**CPA-19** activated both the delocalized cation and the azomethine ylide via dual hydrogen-bonding and ion-pair interactions, which contributed to the high enantioselectivity observed.

Recently, the same group also utilized C-3-substituted 2-indolylmethanols **69** as NCC building blocks in catalytic asymmetric [3 + 3] cyclizations with azomethine ylides **56** formed in situ from amino esters and aldehydes or isatins; this reaction furnished tetrahydropyrimido[1,6-*a*]indole frameworks **79** in generally good yields and high stereoselectivities (Scheme 26).[52] The reaction pathway of the [3 + 3] cyclization was suggested to be a cascade process, which included sequential inter- and intramolecular nucleophilic additions. Throughout the whole process, the CPA could activate both the vinyliminium ion intermediate and the azomethine ylides via hydrogen-bonding and ion pair interactions, which increased the reactivity and the enantioselectivity.

Scheme 23. Catalytic Asymmetric [3 + 2] Cyclizations Using C3-Substituted 2-Indolylmethanols as NCC Building Blocks



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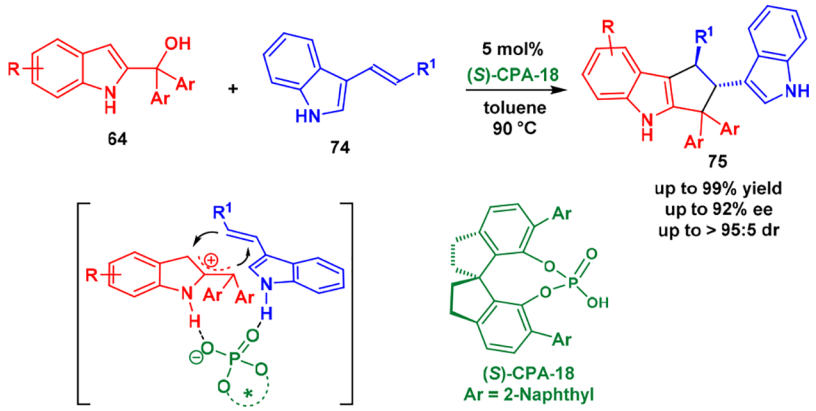
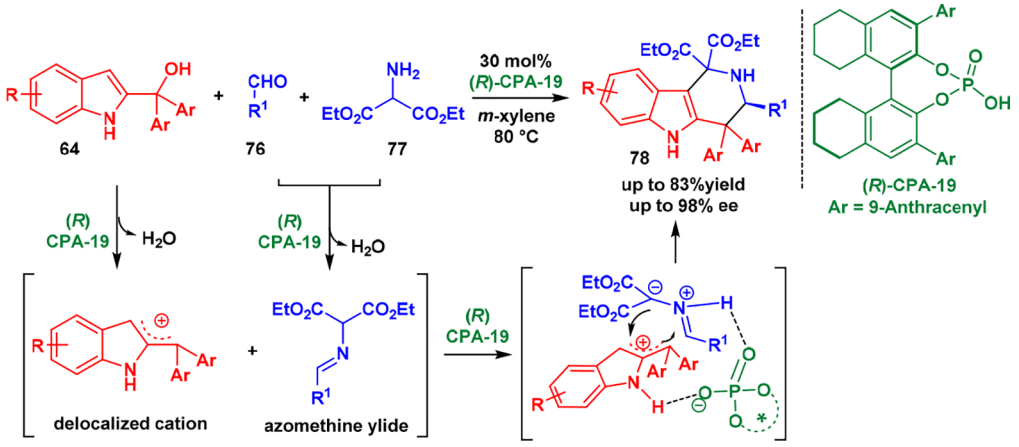
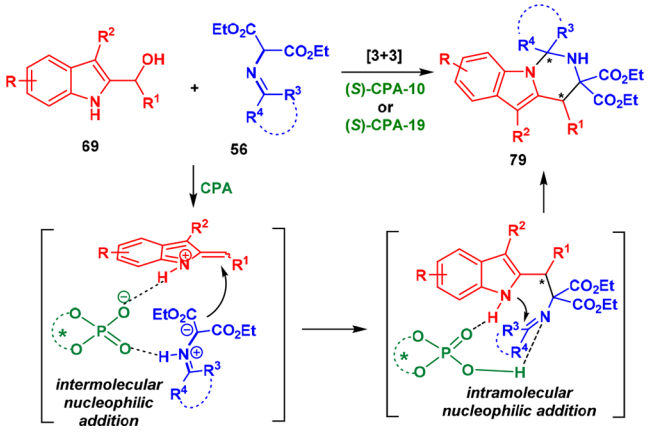
Scheme 24. Catalytic Asymmetric [3 + 2] Cycloaddition Using C-3-Unsubstituted 2-Indolylmethanols as 3C Building Blocks



Scheme 25. Catalytic Asymmetric [3 + 3] Cycloaddition Using C-3-Unsubstituted 2-indolylmethanols as 3C Building Blocks



Scheme 26. Catalytic Asymmetric [3 + 3] Cyclizations Using C-3-Substituted 2-Indolylmethanols as NCC Building Blocks



4. SUMMARY AND OUTLOOK

In summary, indolylmethanols have emerged as versatile reactants in catalytic asymmetric reactions, which have provided useful methods for synthesizing chiral indole derivatives with structural diversity and complexity. In this synopsis, recent advances in this field are outlined. In CPA-catalyzed asymmetric transformations, the chiral induction was accomplished by ion pair or hydrogen-bonding interactions between the catalysts and the substrates. CAs can also act as chiral catalysts in asymmetric reactions involving indolylmethanols, especially enantioselective substitutions, wherein the chiral nucleophiles are generated in situ. Although catalytic asymmetric substitutions of 3-indolylmethanols have been well-developed, catalytic asymmetric cyclizations of 3-indolylmethanols are still not fully investigated. For instance, enantioselective [4 + 3] cyclizations using 3-indolylmethanols as 3C building blocks have not been established. Moreover, compared with 3-indolylmethanols, catalytic asymmetric reactions with 2-indolylmethanols are rather underdeveloped. The unique "umpolung" reactivity of the C3-position in 2-indolylmethanols and the abnormal regioselectivity of reactions with 2-indolylmethanol are expected to open a new avenue for discovering interesting, useful catalytic transformations and realizing important applications. More importantly, to find new catalytic asymmetric transformations and robust strategies for synthesizing enantioenriched indole derivatives, designing and developing new classes of indolylmethanols, such as 4-indolylmethanols and 7-indolylmethanols, with multiple reactive sites to serve as potential reactants for cyclizations is highly desirable.

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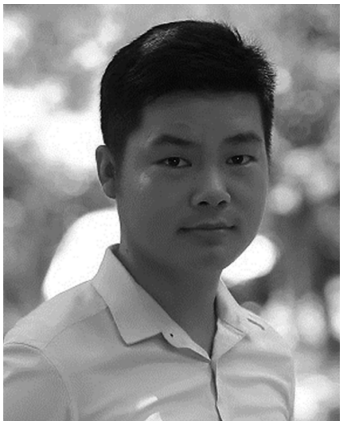
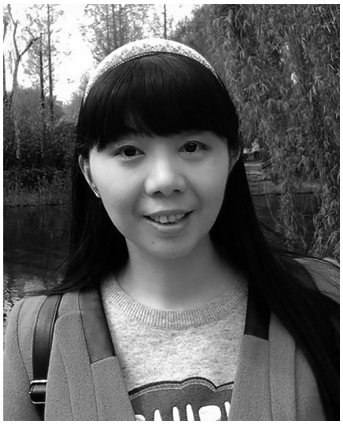
Notes

The authors declare no competing financial interest.

Biographies



Guang-Jian Mei is a researcher in the Shi group at Jiangsu Normal University. His current research interests involve chiral metal-catalyzed asymmetric cycloadditions.



Feng Shi is a Full Professor at Jiangsu Normal University. Her research interests involve catalytic asymmetric reactions for the enantioselective construction of heterocyclic frameworks.

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