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Review

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The recent advances in the contribution of chiral triarylmethanes and tetraarylmethanes with organocatalysts

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Abstract

Chiral triarylmethane skeleton is an important structural unit of many known compounds that are widely applied in organic functional materials and pharmaceuticals. Thus, the efficient construction of this class of compounds has attracted intensive attention from chemists. There are two main difficulties in synthesizing this type of compound: (i) the steric resistance of molecular structures would make it hard to be constructed; (ii) there are three similar aryl groups on the stereocenter, which is difficult to achieve stereo-identification. At present, the most common strategy is to introduce the third aryl group into a diarylmethane framework through the asymmetric Friedel-Crafts reaction or addition reaction of electron-rich arenes, so as to construct chiral triarylmethanes. In this review, we summarized the recent developments in the construction of various chiral triarylmethanes and chiral tetraarylmethanes from easily accessible compounds under organocatalytic conditions. This article describes based on the types of electrophilic reagents, mainly including quinone methides, indole imine methides, and azadienes. At the same time, we also emphasize the mechanism of each representative reaction, which might enlighten the future development of this field.

Keywords: Chiral triarylmethanes, chiral tetraarylmethanes, oraganocatalysts, Friedel-Crafts reaction, conjugate addition, enantioselectivity

INTRODUCTION

Benefiting from the unique structural characteristics, triarylmethanes are widely used in many fields, including pharmaceuticals, functional materials, and organic synthesis[1-4]. In terms of spatial structure, triarylmethane looks like a three-blade propeller. Therefore, the whole triarylmethane molecule is very crowded as there are three bulky aryl groups on the same carbon atom at the same time.

In early studies, the common methods to construct such a challenging molecule were mainly focused on introducing the third aryl group on the methyl position of diaryl methane derivatives through the metal-catalyzed cross-coupling reaction. In 2015, Nambo and Crudden[5] reported a review focused on the synthesis of triarylmethanes using well-defined transition metal catalysts including Pd, Ni, Cu, Rh and Fe. For the above transition metal-catalyzed cross-coupling method, the synthesis of chiral triarylmethanes is purely difficult and relatively less explored, and presynthesized chiral diary methane derivatives are generally used.

Notably, organocatalytic asymmetric synthesis was awarded the 2021 Nobel Prize in Chemistry, which has been demonstrated as one of the most efficient strategies for constructing chiral compounds, benefiting from metal-free, mild condition, excellent stereocontrol, etc. The construction of triarylmethanes and tetraarylmethanes under organocatalytic system has been widely developed in recent years. Among them, the electron-rich aromatic Friedel-Crafts reaction has become an essential tool. In addition to overcoming the potential steric hindrance of molecules, the synthesis of chiral triarylmethanes also requires accurate identification of three similar aryl groups. In other words, the enantioselective transformation can only occur when the three similar aryl groups are clearly divided in a specific chiral environment. Generally, in order to provide the ability to identify similar aryl groups, one of the aryl groups generally undergoes dearomatization to form an active intermediate; after the introduction of the third aryl group, this aryl group is re-formed through aromatization. At present[6], the most widely used intermediates include quinone methides, indole imine methides, azadienes, etc[7-10]. Although Mondal *et al.* had already reviewed the synthesis of diarylmethanes and triarylmethanes in 2017, including scientific reports of chiral triarylmethanes, many excellent works have emerged in recent years, which are worth summarizing again[11]. In this review, we summarize the synthetic methods for chiral triarylmethanes implemented by organocatalysts, and we discuss the mechanism of each reaction in detail, especially the chirality-determining steps. Generally, reactions need a bifunctional organocatalyst that can grab the active intermediate and nucleophilic substrate into its chiral pocket through the hydrogen bonds, and then undergo the enantioselective functionalization to provide the final chiral triarylmethanes [Figure 1]. Meanwhile, we also summarize a small number of reports on the synthesis of chiral tetraarylmethanes *via* a similar reaction manner. The potential applications of some products were also highlighted.

CONSTRUCTION OF CHIRAL TRIARYLMETHANES WITH QUINONE METHIDES

Quinone methides (QMs) are very short-lived, polar and highly reactive synthetic intermediates that easily participate in conjugate additions[12-19]. The common structure of QMs consists of a cyclohexadiene ring and an exocyclic methylene group with a reactive carbonyl group binding either on the *ortho* or *para* position. Therefore, QMs usually have two topological isomers: one is *ortho*-quinone methides (*o*-QMs) and the other is *para*-quinone methides (*p*-QMs)[7]. Over the past few decades, the synthetic potential and properties of *o*- and *p*-QMs have been widely explored because of their potential applications in bioactive compounds and natural product synthesis. For the conjugate additions of QMs, if electron-rich arenes are employed as nucleophiles, it would provide an efficient route for the asymmetric construction of triarylmethanes, as shown in Scheme 1. Generally, the carbonyl group of QMs can form a hydrogen bond with the organocatalysts, which is crucial in obtaining superior enantioselectivity.

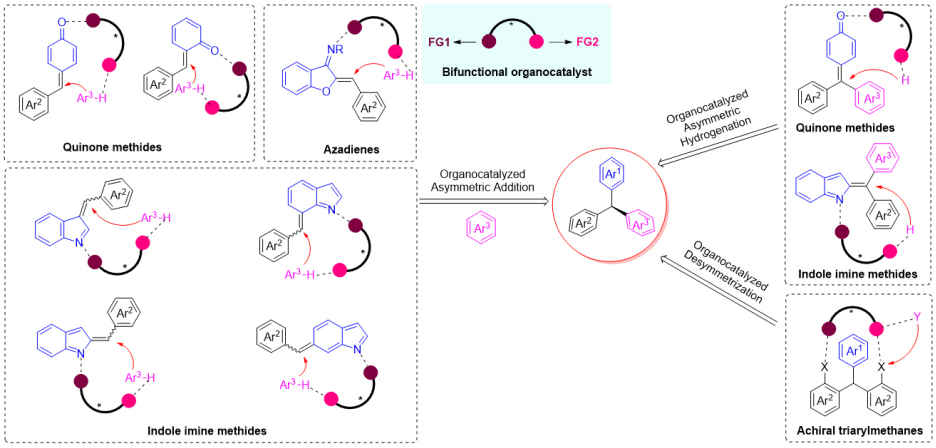
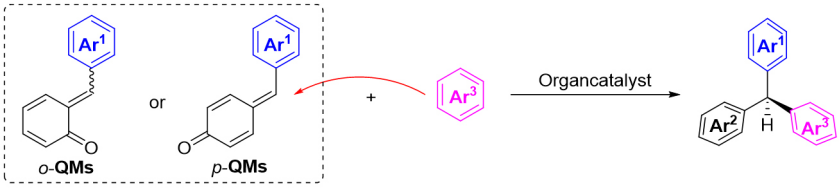


Figure 1. The summary of the synthetic methods for chiral triarylmethanes.

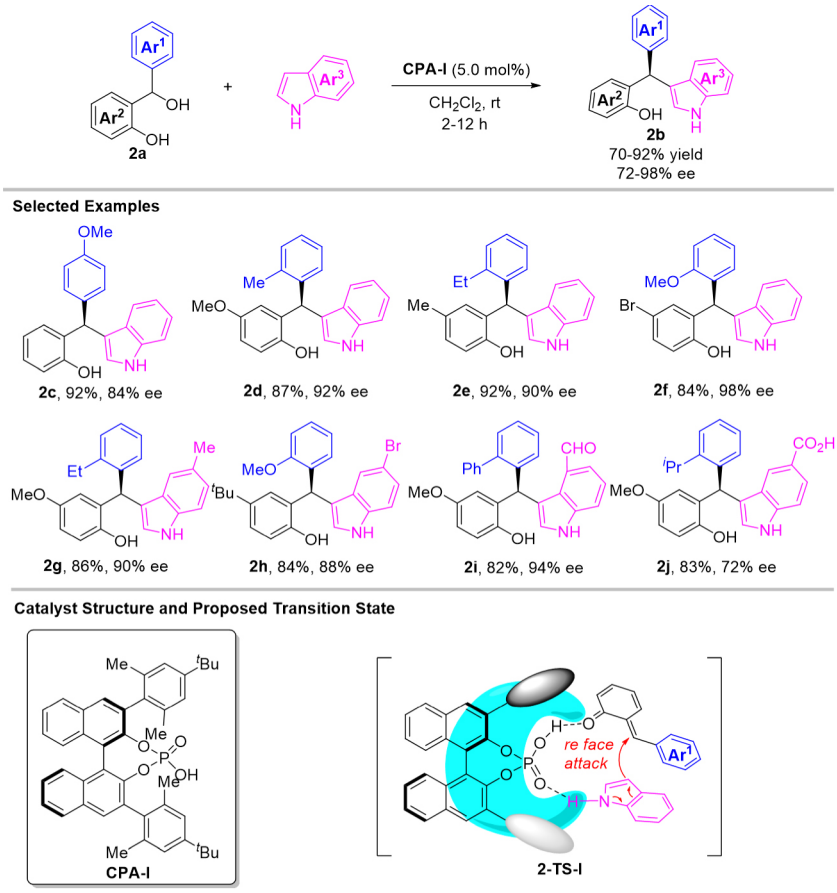


Scheme 1. The construction of chiral triarylmethanes from Quinone methides.

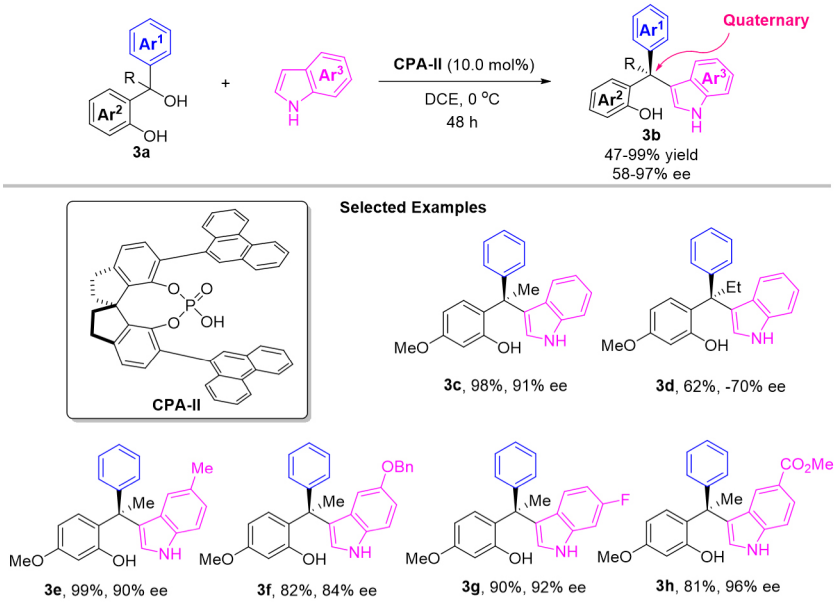
o-QMs. In 2014, Schneider and co-workers[6] disclosed a chiral phosphoric acid (CPA)-catalyzed highly enantioselective 1,4-addition of *in situ* generated *o*-QMs with indoles, providing an efficient protocol for the synthesis of broadly substituted chiral triarylmethanes [Scheme 2]. This process has excellent functional group tolerance. A broad set of heteroaryl-substituted triarylmethanes 2b were obtained in good yields and enantioselectivities, irrespective of the electronic properties of the substituents on the indole ring. In the proposed transition state 2-TS-I, CPA-1 played as a bifunctional catalyst which activated both the *o*-QM and the indole by forming double hydrogen bondings. Then, the indole selectively attacked the *o*-QM from the *re*-face because the opposite face was effectively shielded by the neighboring bulky group. In addition, electron-rich 1-naphthols and 2-naphthols were further successfully extended in this strategy replacing the role of indoles. Very recently, Zhang *et al.* reported enantioselective alkylation of aniline with *in situ* generated *o*-QMs catalyzed by chiral phosphoric acid, which further broadened the methodologies of asymmetric synthesis of triphenylmethanes[20].

To generate acyclic all-carbon quaternary stereocenters, tertiary alcohols **3a** were selected by Sun *et al.* as a suitable electrophile to achieve a stereo-control addition with indoles [Scheme 3][21]. This reaction overcame the unfavorable steric hindrance around reactive centers and the competitive elimination process to provide a range of chiral triarylmethanes 3b with excellent yields and enantioselectivities. The author speculated that the *in situ* generation of *o*-QMs was the key to forming the all-carbon quaternary stereocenter.

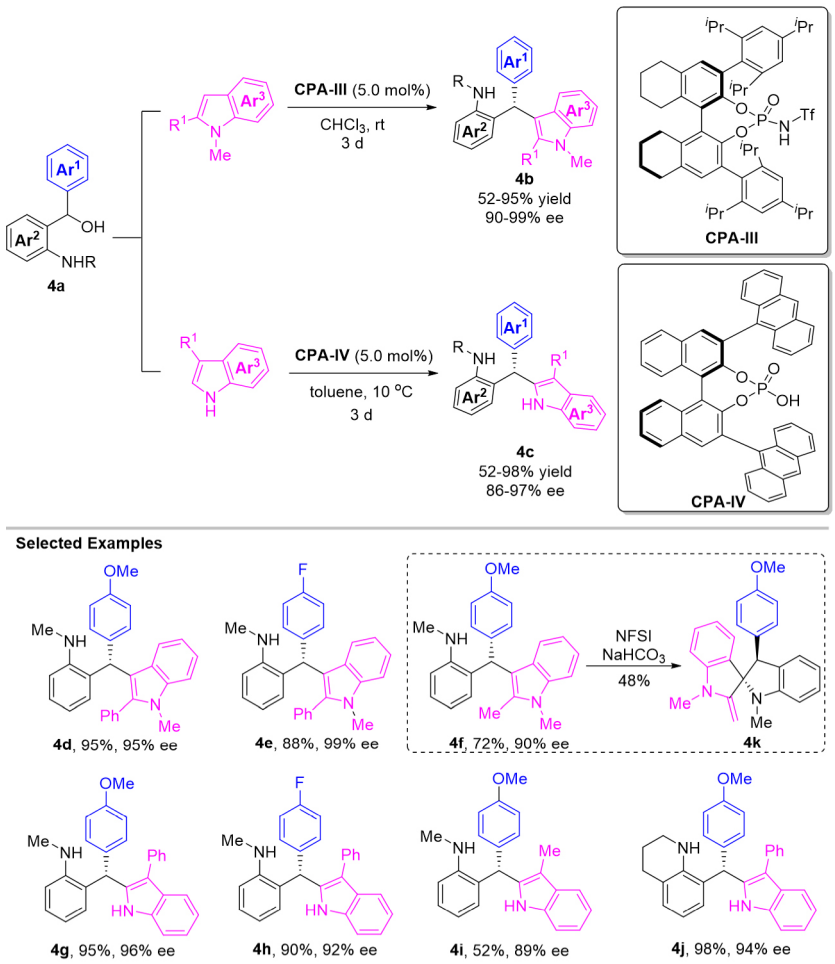
Replacing the oxygen atom of *o*-QMs with nitrogen, another reactive intermediate, namely aza-*ortho*-quinone methide (aza-*o*-QM), can be skillfully obtained. Recently, aza-*o*-QMs have also been widely used in catalytic asymmetric synthesis[22]. In 2015, Liao *et al.* reported a substrate-controlled strategy for the enantioselective synthesis of two types of diarylindolylmethanes 4b-4c [Scheme 4][23]. Firstly, under chiral *N*-triflylphosphoramide CPA-3, *N*-methyl 2-substituted indoles were successfully employed as nucleophiles to



Scheme 2. Asymmetric addition of diaryl methanol 2a and indoles.



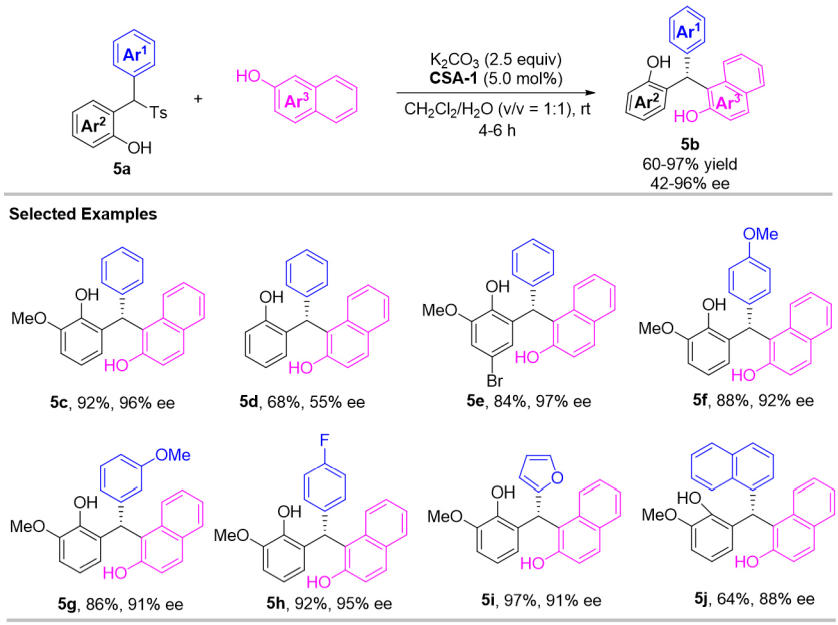
Scheme 3. Asymmetric addition of tertiary alcohols 3a and indoles.



Scheme 4. Asymmetric addition of aza-*o*-QMs with N-methyl 2-substituted indoles and 3-substituted indoles.

achieve the 1,4-conjugate addition of aza-*o*-QM for the enantioselective synthesis of triarylmethanes 4b with indol-3-yl substitutions. Notably, an important enantioenriched spiroindoline 4k could be obtained by a NFSI-mediated cascade process of addition/deprotonation/deprotonation/spirocyclization from the compound 4f[24]. Subsequently, 3-substituted indoles were utilized as nucleophiles in this process to provide a series of chiral triarylmethanes 4c with indol-2-yl substitutions by optimizing the catalyst CPA-4. The author also demonstrated that the steric and electronic nature of the substituents had little influence on the reaction outcome, and all products could be delivered in high yields and good to excellent enantioselectivities.

In 2016, Wang *et al.* developed an efficient enantioselective 1,4-addition of *in situ* generated *o*-QMs with electron-rich 2-naphthols [Scheme 5][25]. Different from Schneider's work, diaryltosylmethane derivatives 5a were chosen as the precursor of *o*-QMs, and cinchonidine-derived squaramide CSA-1 was employed as organocatalyst. As a result, a range of the chiral triarylmethane derivatives 5b were obtained in good to high yields (up to 97% yield) with high enantioselectivities (up to 97% ee) under mild conditions. For mechanism, both the methoxy group and carbonyl group of the *o*-QM fragment were important H-bonding acceptors that can form hydrogen bonds with squaramide part of the catalyst CSA-1 at the same time. The proposed transition state 5-TS-I is the key for the stereo-controlled addition with 1-naphthols.

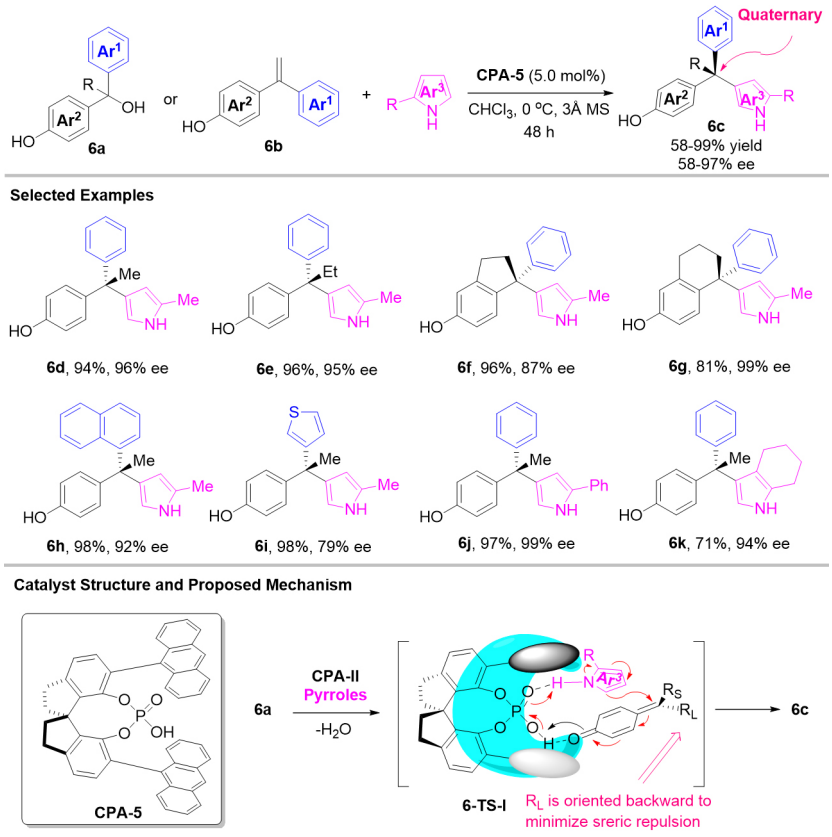


Scheme 5. Quaramide CSA-I catalyzed asymmetric addition of *o*-QMs and 2-naphthols.

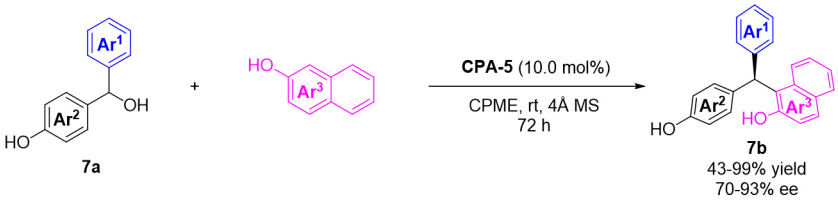
p-QMs. In their continuous work, Sun *et al.* designed and synthesized the tertiary alcohol derivatives 6a, which could act as the precursor of *p*-QMs [Scheme 6][26]. Then, starting from tertiary alcohols 6a, a mild catalytic asymmetric 1,6-conjugate addition was achieved to construct chiral triarylmethanes bearing all-carbon quaternary stereocenters. In this reaction, 2-substituted pyrroles were first utilized as electron-rich arene nucleophiles to give a range of chiral triarylmethanes 6c bearing pyrrol-2-yl groups with excellent efficiency and enantioselectivity. Through the screening of CPAs, indole can be compatible in this process. However, the author only gave one example, and ee value of the final product was 90%. They also confirmed that the 4-vinylphenol derivatives 6b were also competent substrates that could also generate *p*-QMs under the optimized conditions achieving an equally high enantioselective 1,6-addition. For mechanism, CPA-5 activated both pyrroles and *p*-QMs by forming two hydrogen bonds, and the larger δ substituent is oriented towards the back to minimize steric repulsion with the top-front bulky group, which was responsible for the stereo-control.

In their following work, 2-naphthols were also successfully employed in the asymmetric 1,6-addition of *in situ* generated *p*-QMs[27]. And this reaction was also catalyzed by chiral phosphoric acid CPA-5 and delivered a range of useful chiral triarylmethanes 7b containing a tertiary chiral stereocenters with good efficiency and enantioselectivity [Scheme 7].

Indeed, aryl boronic acids can also be used as aryl sources for the organocatalytic addition reaction[28]. Based on this, Huang *et al.* reported a chiral binaphthol (BINOL) catalyzed 1,6-addition of arylboronic acids to the presynthesized *p*-QMs 8a [Scheme 8][29]. The final chiral triarylmethanes 8b could be obtained in 61%-99% yields with excellent enantioselectivities. Mechanistically, the remote stereo-control of this reaction could be realized with the *ortho*-hydroxyl group which is designed on the δ-aryl group. Thus, both *p*-QMs and BINOL-1 can undergo dehydration with aryl boronic acids to form aryl borate intermediate 8-I which transfer into the products *via* an asymmetric intramolecular 1,6-addition. In addition, this designed *ortho*-hydroxyl group could also be utilized as a nucleophilic group in the following oxidation process to provide a spiro compound 8j.

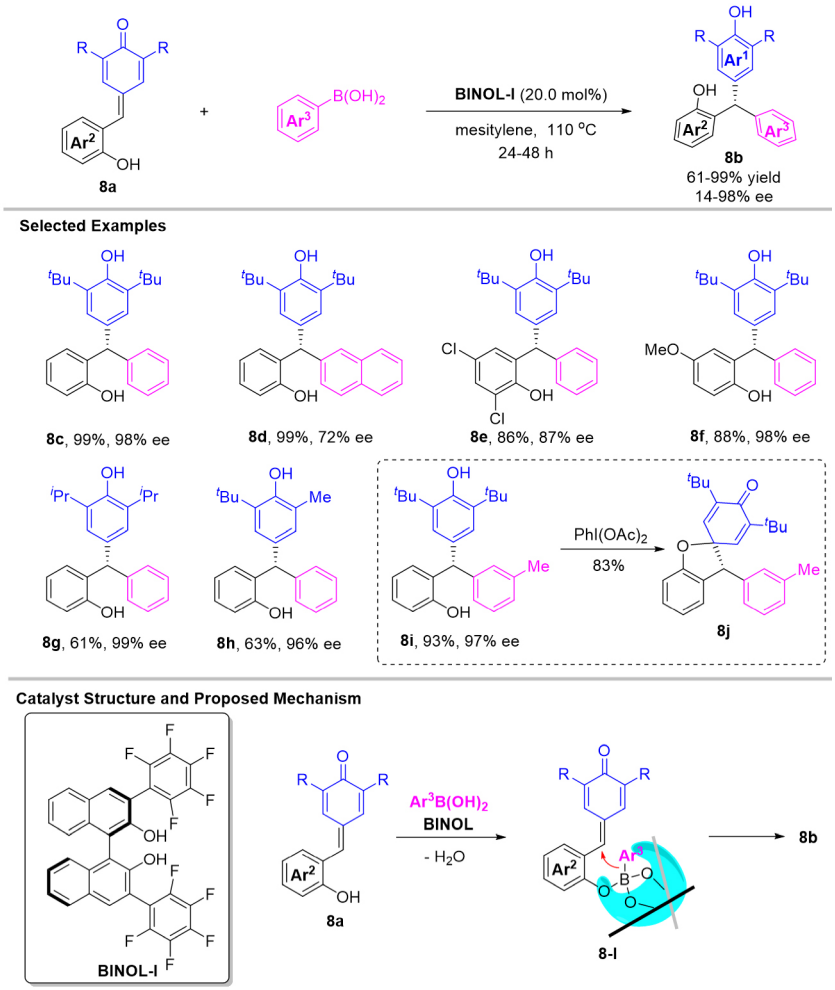


Scheme 6. Asymmetric addition of tertiary alcohols 6a or 4-vinylphenols 6b with 2-substituted pyrroles.



Scheme 7. Asymmetric addition of diary alcohols 7a and 2-naphthols.

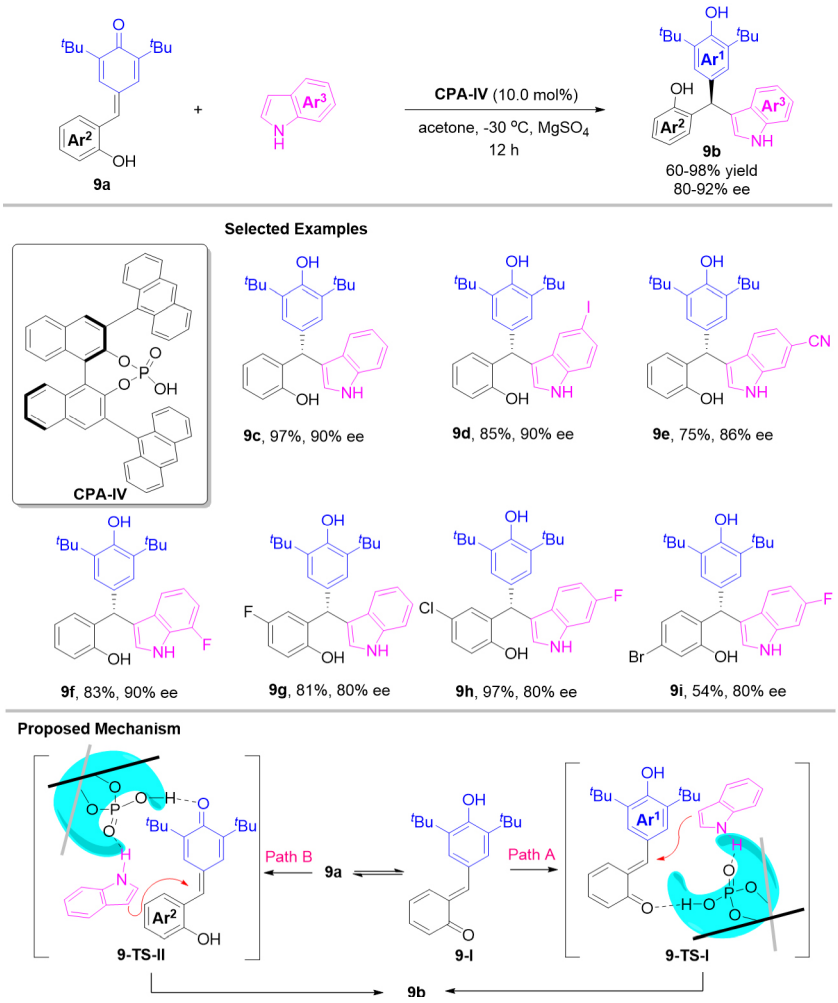
In 2019, Wang *et al.* established a catalytic asymmetric conjugate addition of indoles to presynthesized *p*-QMs 9a in the presence of chiral phosphoric acid CPA-4, which afforded a range of chiral triarylmethanes 9b with indol-3-yl groups in generally high yields (54%-98%) and good enantioselectivities [Scheme 9][30]. After mechanism experiments, a more likely reaction path A was proposed. *p*-QMs 9a was transformed into *o*-QMs 9-I in the presence of CPA-4 first. Then, CPA-4 worked as a bifunctional organocatalyst to activate both *o*-QMs and indoles by forming two hydrogen bonds with the N-H group of indoles and the carbonyl group of *o*-QMs 9-I, thus facilitating an asymmetric 1,4-addition. Another proposed mechanism (path B) of CPA-4 catalyzed direct 1,6-addition is less likely, but it should not be totally excluded. Following the same strategy, Cheng *et al.* achieved a similar enantioselective conjugate addition of 2-naphthols to the presynthesized *p*-QMs 9a providing a series of enantioenriched triarylmethanes with 2-hydroxynaphthalen-1-yl groups[31].



Scheme 8. Chiral binaphthol catalysed 1,6-addition of *p*-QMs and arylboronic acids.

Recently, a direct and enantioselective oxidative cross dehydrogenative coupling of racemic 2,2-diarylacetonitriles 10a with electron-rich arenes has been developed by Wang *et al.*, which provides an efficient way to construct various triarylmethanes 10b bearing all-carbon quaternary stereocenters [Scheme 10][32]. The reaction has shown an excellent functional group tolerance, and exhibits a broad scope with respect to electron-rich arenes including indoles, pyrroles, 1-naphthols and phenols. Most importantly, other valuable chiral triarylmethanes with aldehyde or acylamin substitution, which are otherwise difficult to access, could be synthesized *via* the transformation of the cyano group. For mechanism, preliminary investigations by the author suggested *p*-QMs were firstly *in situ* generated by DDQ-promoted oxidation, and then the final products were given by the following 1,6-addition process, in which *p*-QMs and nucleophiles were stuffed into the unique chiral pocket of CPA-6 *via* hydrogen bonding interactions to ensure the excellent enantioselectivities.

Except for the above addition of *p*-QMs, the asymmetric reduction of *p*-QMs with δ,δ-diaryl substitutions was also an alternative strategy for chiral triarylmethanes synthesis. But the greatest difficulty of this strategy is the stereo-identification of two similar aryl groups on the δ position of *p*-QMs. In 2019, Fan and co-workers reported a Cu-catalyzed asymmetric reduction of the presynthesized *p*-QMs for the synthesis of chiral triarylmethanes[33], they designed an *ortho*-chlorine directing group on one of the two similar aryl

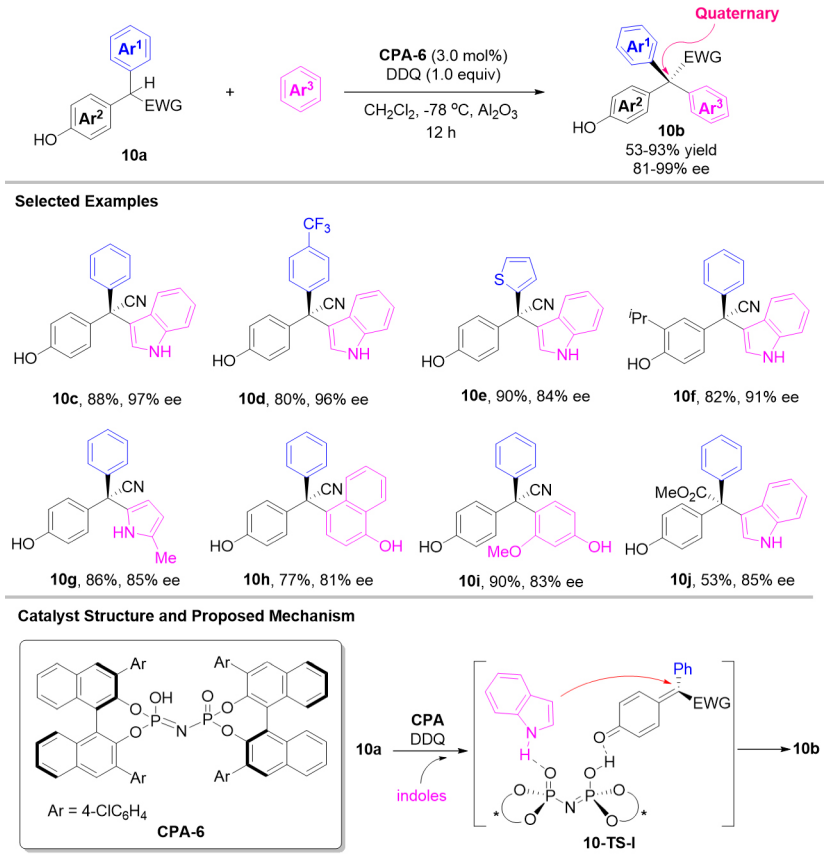


Scheme 9. Asymmetric addition of presynthesized *p*-QMs 9a and indoles.

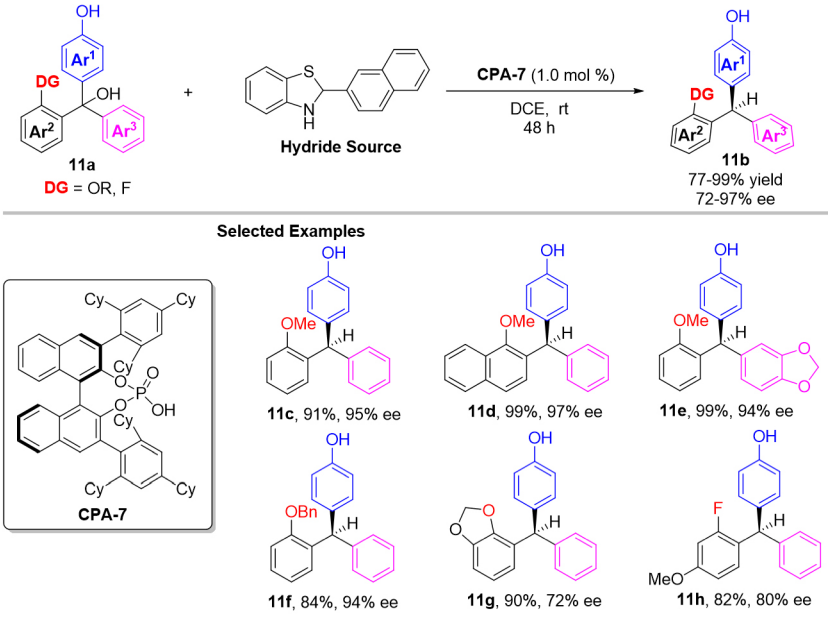
groups. Owing to the crucial Cu-Cl interaction, an excellent asymmetric control has been achieved. More recently, Han *et al.* developed a chiral phosphoric acid CPA-7 catalyzed transfer hydrogenation of *in situ* generated *p*-QMs with benzothiazoline as the hydride source [Scheme 11][34]. A series of racemic triarylmethanols 11a participated in this reduction reaction smoothly, providing the corresponding enantioenriched triarylmethanes 11b in excellent yields and enantioselectivities. Compared with Fan's work[33], this hydrogenation process took place under oraganocatalytic conditions and pre-synthesis of the *p*-QMs bearing bulky groups was unnecessary. Mechanism experiments revealed that the hydrogen bond donating ability of this directing group on the *ortho*-position was crucial for excellent enantiocontrol.

CONSTRUCTION OF CHIRAL TRIARYLMETHANES WITH INDOLE IMINE METHIDES

Similar to QMs, indole imine methides (IIMs) are another important family of active electrophiles facilitated by aromatization to indoles. Typically, IIMs are *in situ* generated by acid- or base-promoted elimination of a leaving group at the benzylic group of the corresponding indolyl compounds[35]. Since the pioneering work of Rueping's group involving the *in situ* generation of the 3-indole imine methides (3-IIM) iminium ion pair[36], IIMs derivatives have become important electrophiles that can undergo nucleophilic attacking to give diverse compounds in synthetic chemistry[37-39]. If electron-rich arenes are selected as nucleophilic reagents, IIMs can undergo Friedel-Crafts type reaction to provide another efficient strategy



Scheme 10. Enantioselective oxidative cross dehydrogenative coupling of 2,2-diarylacetonitriles 10a and electron-rich arenes.



Scheme 11. Asymmetric reduction of *p*-QMs for the synthesis of chiral triarylmethanes.

for synthesizing triarylmethanes containing indolyl groups. It is worth mentioning that the nitrogen atom of

IIMs can form a hydrogen bond with the organocatalysts to promote the stereo-control. So far, only 2-, 3-, 6- and 7-IIMs could be employed for the construction of chiral triarylmethanes 12 [Scheme 12].

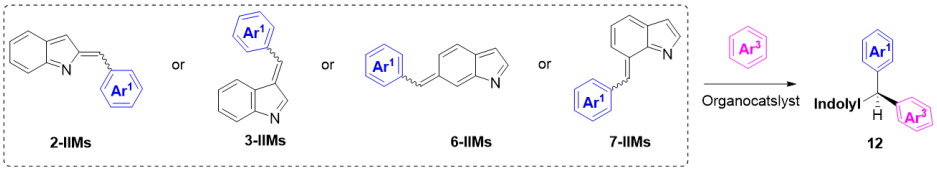
3-IIMs. In 2009, Sun *et al.* developed a CPA-catalyzed tandem double Friedel-Crafts reaction of 2-substituted indoles with 2-formylbiphenyl derivatives 13a, which provides a feasible access to the fluorene derivatives 13b bearing triarylmethane unit with up to 96% ee [Scheme 13][40]. For mechanism, the 2-substituted indoles first reacted with 2-formylbiphenyl derivatives 13a to provide an indol-3-yl methanol intermediate 13-I. Indol-3-yl methanol 13-I were unstable under Brønsted acid condition and would further undergo dehydration to give a counterion 13-II of 3-IIMs with CPA-8. Under the chiral environment of chiral phosphate anion, counterion 13-II underwent the intermolecular and enantioselective Friedel-Crafts reaction to form the final fluorene derivatives 13b.

Later on, Sun *et al.* reported a chiral phosphoric acid catalyzed Friedel-Crafts alkylation of electron-rich arenes with indol-3-yl methanamine 14a for the enantioselective synthesis of chiral triarylmethane 14b [Scheme 14][41]. If *N*-methyl indole was employed as nucleophilic electron-rich arenes, the corresponding products generally have moderate *ee* value. Interestingly, the maximum *ee* value of the product could reach 91% ee when using 1,3,5-trimethoxybenzene as nucleophile despite the unsatisfactory yield. For mechanism, the author observed an interesting feature that this process involves a kinetic resolution of the starting material (3-indolyl)methanamine 14a. In addition, although the author did not mention it, 3-IIM was the most likely key intermediate for this asymmetric Friedel-Crafts reaction.

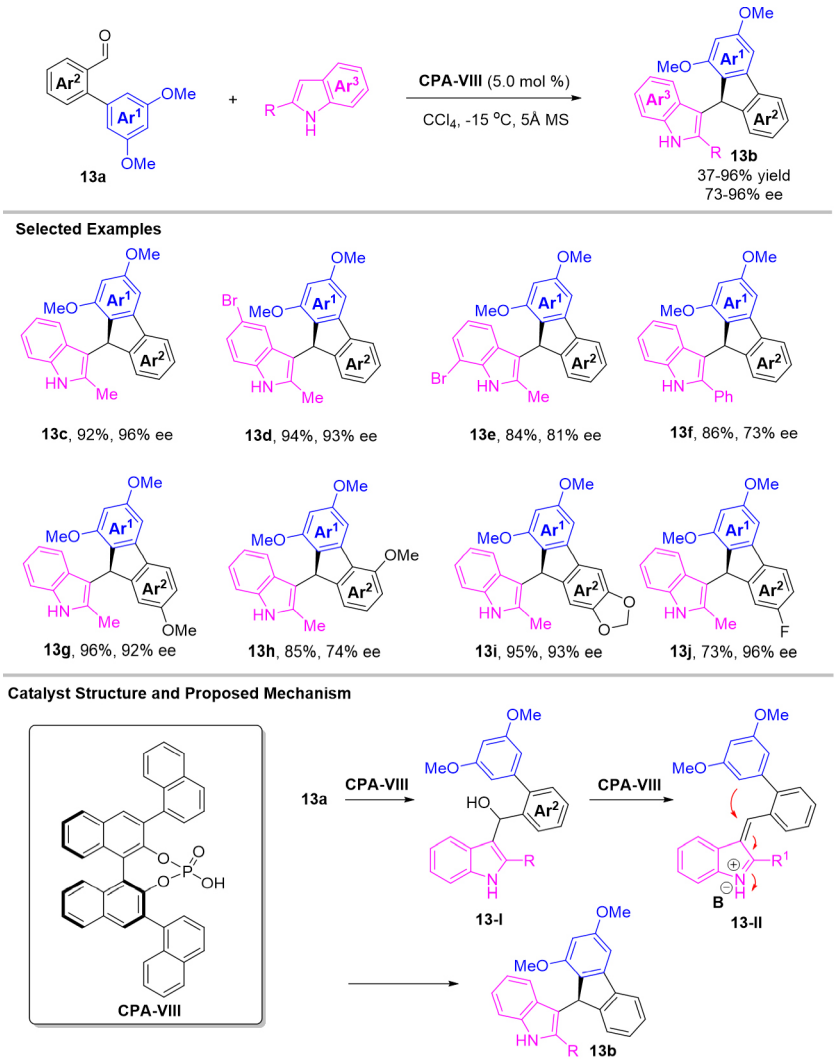
In an attempt to improve the enatioselectivity of the Friedel-Crafts reaction of 3-IIMs, Zhuo *et al.* developed a chiral imidodiphosphoric acid CPA-10 catalyzed highly efficient and enantioselective Friedel-Crafts alkylations of TMS-protected 3-arylindolylmethanol 15a for the construction of chiral triarylmethanes [Scheme 15][42]. Under a low catalyst loading (as low as 1.0 mol%) condition, a range of chiral triarylmethane 15b was provided in high yields (up to 99%) with excellent enantioselectivities (up to 96% ee) unprecedentedly. Remarkably, enantioenriched triarylmethane 15a was first synthesized at that time. For mechanism, a stable 3-IIMs iminium ion pair 15-I derived from TMS-protected 3-arylindolylmethanol 15a in the absence of CPA-10 undergo intramolecular nucleophilic attacking with pyrroles or *N*-methyl indoles to form the final products. Compared with You's work, the enantioselectivity of this work has been greatly improved, which may be related to the unique chiral environment created by imidodiphosphoric acid catalyst CPA-10 derived from two (*R*)-BINOL frameworks with different 3,3′-substituents.

In their following research, Zhuo *et al.* developed a general method for the direct transformation of 3-hydroxy-3-indolyloxindoles 16a into 3,3-diaryloxindoles 16b-16c bearing triarylmethanes motif based on the activating strategy above [Scheme 16][43]. As a result, a range of quaternary carbon centered 3,3-diaryloxindoles 16b and 16c were synthesized in 75%-99% yield and 83%-98% ee with low catalyst loadings (as low as 0.5 mol%). Mechanistically, a similar 3-IIMs iminium ion pair intermediate 16-I generated from 16a and CPAs *via* dehydration was proposed to be the key intermediate for this transformation.

As a further development, Zhang *et al.* utilized 3-vinyl indole 17a as the precursor of 3-IIMs to achieve a Friedel-Crafts reaction with indoles to afford the chiral triarylmethane 17b with all-carbon quaternary stereocenter [Scheme 17][44]. This method was a highly efficient atom-economic process and could provide the chiral triarylmethane 17b in excellent yields with excellent enantioselectivities. For mechanism, the acidic proton of CPA-13 protonated the 3-vinylindole 17a and formed a hydrogen bond with the stable 3-IIMs iminium intermediate 17-I. In addition, the basic P=O group of CPA-13 activated the indoles through the second hydrogen bond. The simultaneous formation of the two hydrogen bonds fixed 3-IIMs and



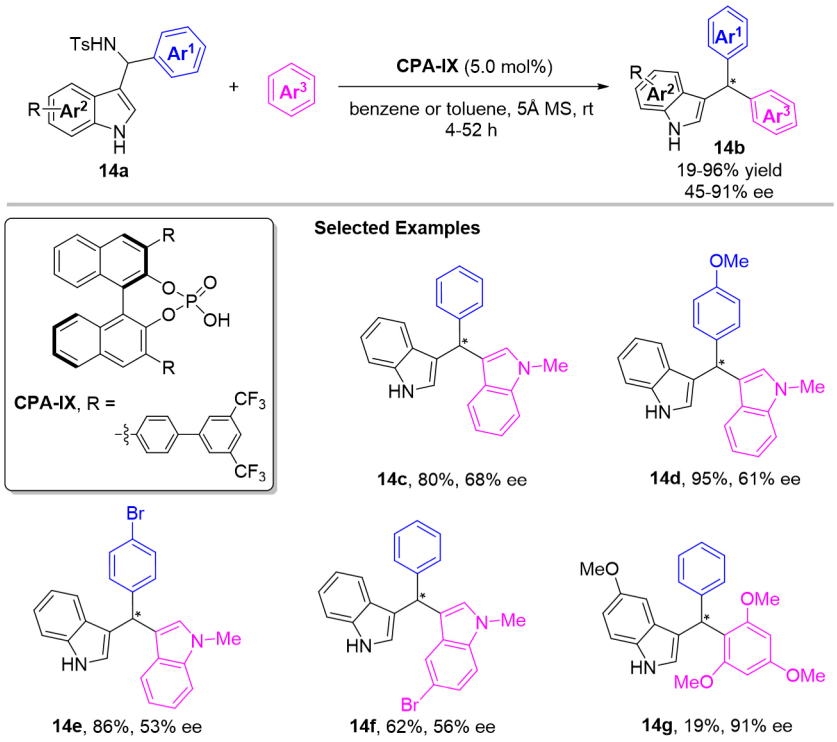
Scheme 12. The construction of triarylmethanes form indole imine methides.



Scheme 13. The tandem double Friedel-Crafts reaction of indoles with 2-formylbiphenyl derivatives.

indoles into a specific chiral pocket of CPA-13, which was the key factor in obtaining good enantioselectivities.

2-IIMs. In 2014, Qi *et al.* was the first to demonstrate the formation of 2-IIMs iminium intermediate from indol-2-yl methanols 18a through the CPA-catalyzed dehydration [Scheme 18][45]. 2-IIMs iminium intermediate 18-I then undergo an asymmetric 1,6-conjugate addition under a chiral environment with indoles to form highly enantioenriched 2,3'-diindolylarylmethane 18b. As a result, a series of

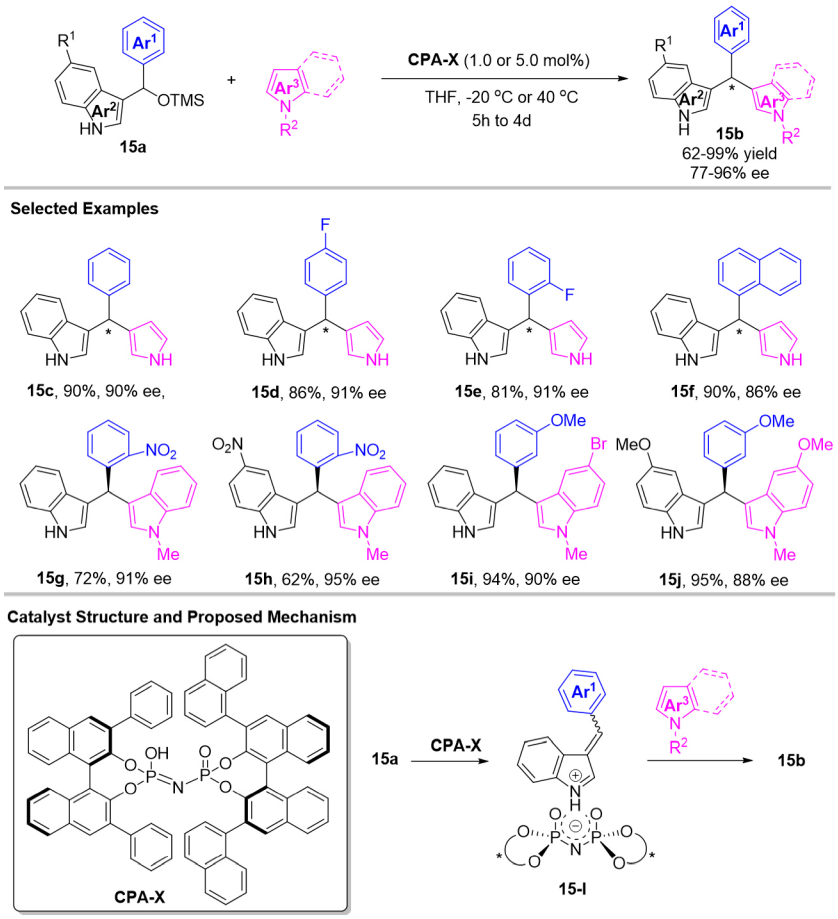


Scheme 14. Asymmetric Friedel-Crafts alkylation of electron-rich arenes with (3-indolyl) methanamines.

2,3'-diindolylarylmethanes 18b have been synthesized in excellent yields (up to 95%) and high enantioselectivity (up to 96% ee). Later, the author determined the absolute configuration of the final products to *R* by using the combination of NMR spectroscopic and circular dichroism techniques[46]. After Han's pioneer work, 2-IIMs have been extensively studied for the synthesis of diverse chiral 2-substituted indole derivatives, of which Shi and Sun have done excellent summaries[47-48].

Converting nucleophiles from common indoles to 3-substituted indoles, Gong *et al.* developed a CPA-catalyzed Friedel-Crafts reaction of indol-2-yl methanol 18a for the asymmetric contribution of triarylmethanes [Scheme 19][49]. This protocol provides an efficient method for constructing biologically important 2,2'-bisindolylarylmethane 19b in high yields with moderate to good enantioselectivities. For mechanism, the author proposed that carbocation intermediate 19-I was initially generated from indol-2-ylmethanol 18a through a Brønsted acid-catalyzed dehydration. CPA-15 could then form an ion pair with the carbocation intermediates 19-I and its basic P=O group activated the 3-substituted indoles by forming a hydrogen bond with the N-H group, thus triggering the nucleophilic attacking in the chiral pocket which controlled the stereoselectivity of this reaction. It is worth mentioning that, in retrospect, carbocation intermediate 19-I was likely to form 2-IIMs iminium intermediate.

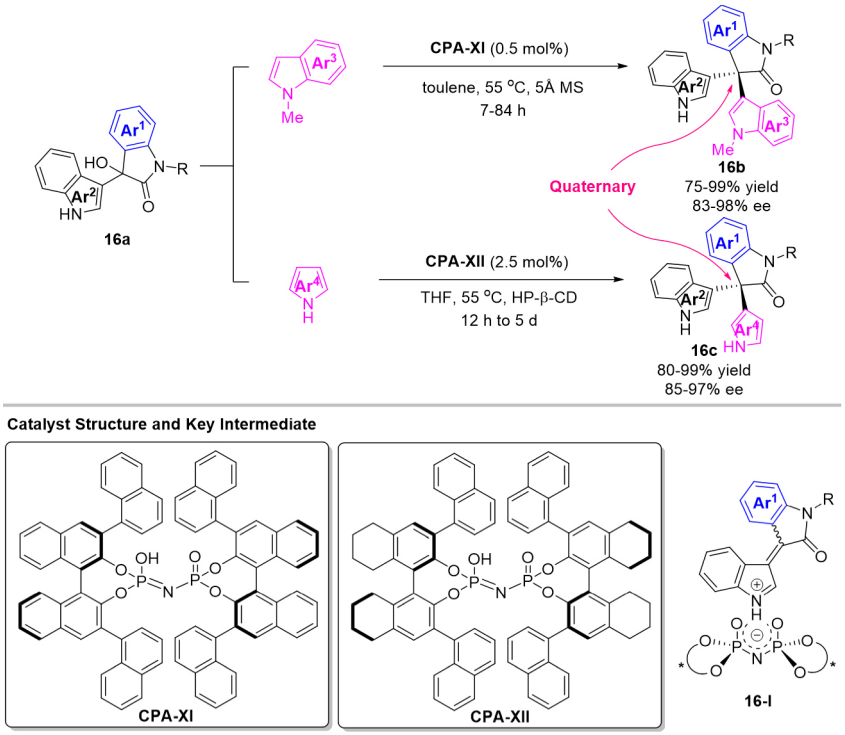
In their subsequent work, Lan *et al.* employed 2-naphthols as nucleophiles in the strategy above, developing a convenient approach to the synthesis of chiral triarylmethanes [Scheme 20][50]. A series of diversified 2-naphthyl based triarylmethane derivatives 20b were obtained in 43%-97% yields and good enantioselectivities (up to 90% ee). For mechanism, 2-IIMs were generated after dehydration in the presence of CPA-16 which then worked as a bifunctional catalyst to form two hydrogen bonds with both the NH group of 2-IIMs and the OH group of 2-naphthols. The following enantioselective nucleophilic attacking of 2-naphthols to 2-IIMs finished the reaction through the proposed transition state 20-TS-I.



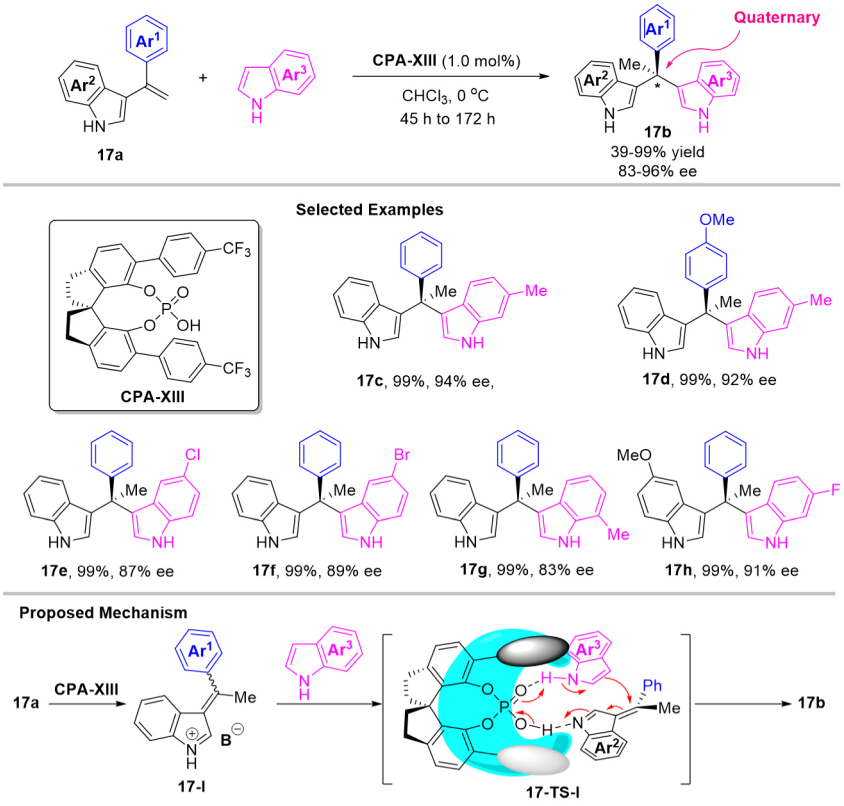
Scheme 15. Enantioselective Friedel-Crafts alkylations of TMS-protected 3-arylindolylmethanol 15a.

Similar to Zhang *et al.*'s work, Han *et al.* utilized 2-vinyl indole derivative 21a as the precursor of 2-IIMs to achieve an enantioselective hydroarylation to give enantioenriched triarylmethanes bearing all-carbon quaternary stereocenter [Scheme 21][44,51]. As a result, a series of 2,3'-bis(indolyl)methanes 21b could be obtained with good functional group tolerance and excellent enantioselectivies. Mechanistically, this reaction begins with the protonation of the electron-rich C=C bond in the substrate by CPA-15 to generate the corresponding indolyl carbocation 21-I, which is indeed stabilized in an IIM form. Due to the different substituents on the methide carbon, this intermediate might be a mixture of *Z*/*E* isomers, which are in equilibrium with each other. The CPA then serves as a bifunctional catalyst to activate both the imine motif of the IIM intermediate and the indole nucleophile through two hydrogen bonds. The hydrogen bond between the catalyst and the imine motif prefers to place the small methyl group toward the chiral pocket (21-TS-II), because the large phenyl group in 21-TS-I experiences increased steric repulsion with the chiral catalyst. In the favored transition state 21-TS-I, the nucleophile is directed to the electrophilic site from the front bottom side by the hydrogen bond with the P=O group to form the final (*R*)-products. In addition, the final 2,3′-BIM product 21b generated in this reaction showed promising anticancer activities through preliminary biological activity tests.

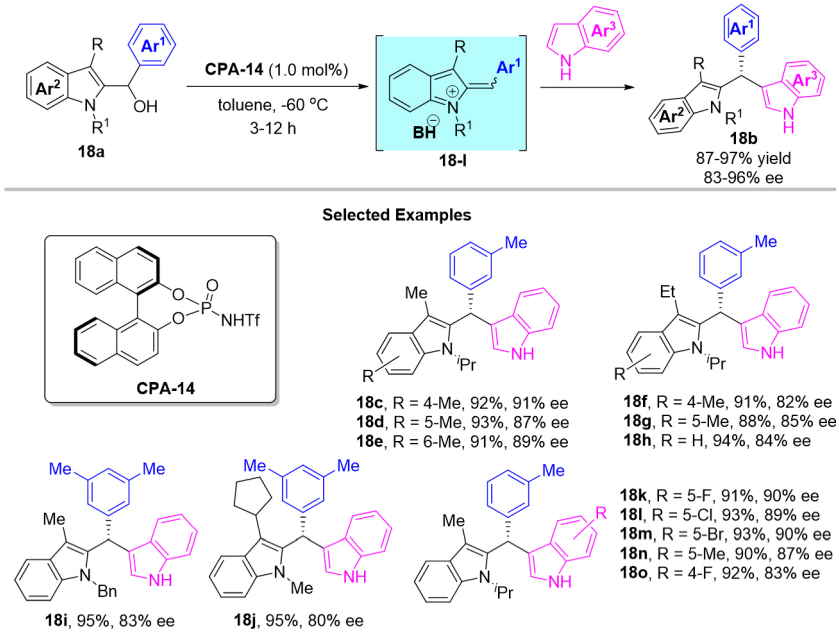
In fact, nucleophiles can occur attacking on both C3 and C3' positions of 2-IIMs to provide the final products 22a and 22b [Scheme 22]. As described above, the nucleophilic attack of electron-rich arenes on C3' position of 2-IIMs provided an efficient strategy for the synthesis of chiral triarylmethanes. As we all



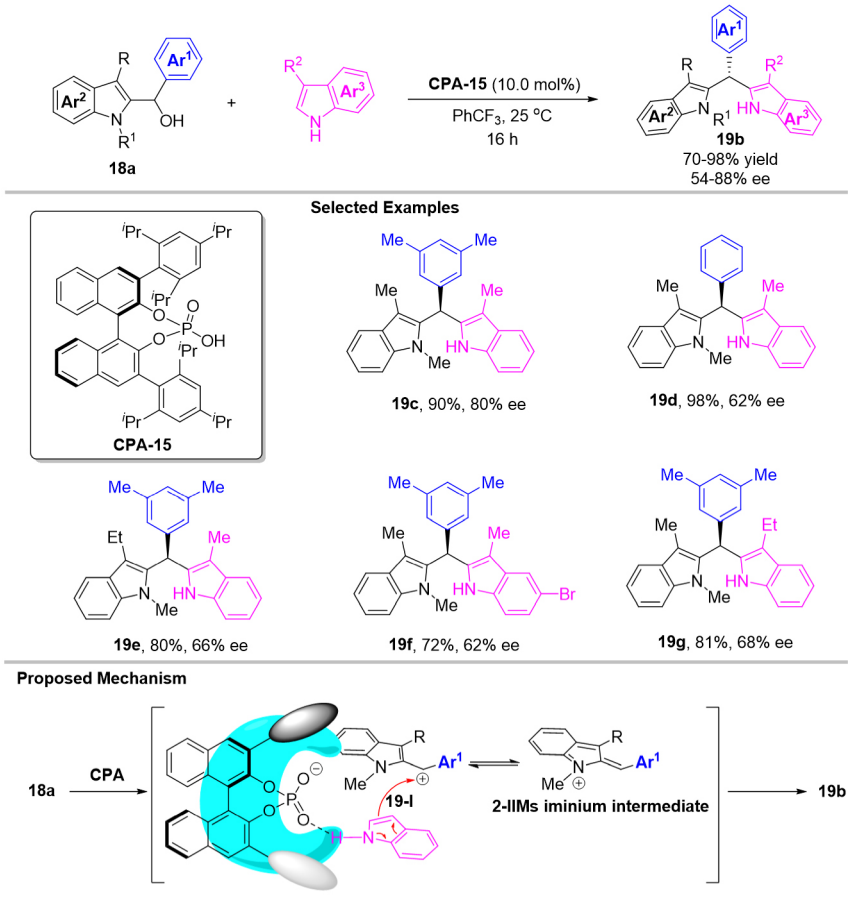
Scheme 16. Enantioselective Friedel-Crafts alkylations of 3-hydroxy-3-indolyloxindole 16a, HP-β-CD = hydroxypropyl-β-cyclodextrin.



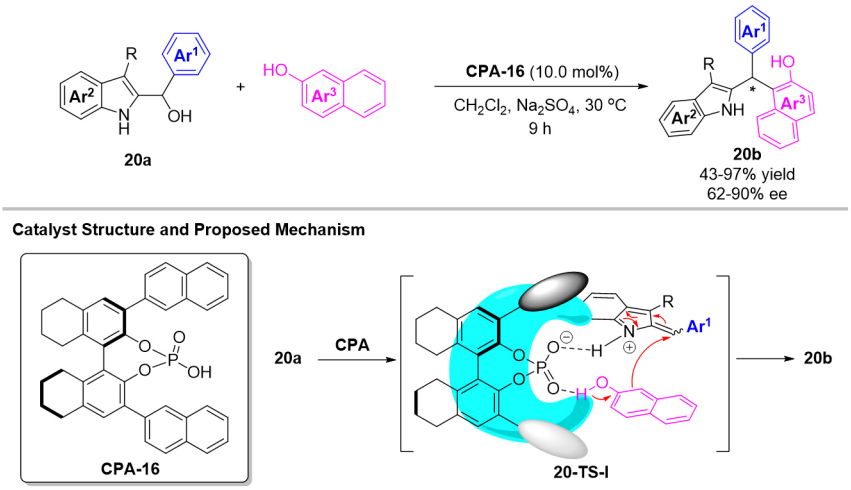
Scheme 17. Enantioselective Friedel-Crafts alkylations of 3-vinylindole 17a.



Scheme 18. Enantioselective Friedel-Crafts alkylations of indol-2-yl methanols 18a.



Scheme 19. Enantioselective Friedel-Crafts alkylations of indol-2-yl methanols 18a and 3-substituted indoles.

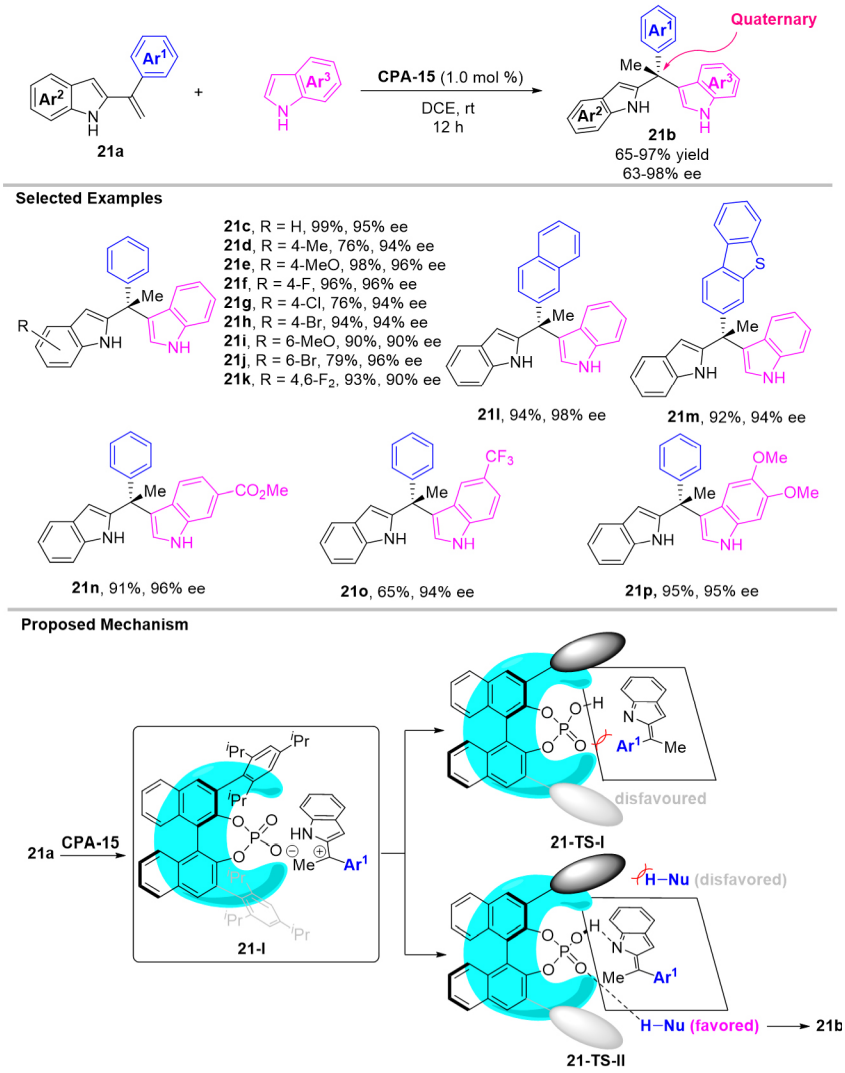


Scheme 20. Enantioselective Friedel-Crafts alkylations of indol-2-yl methanols 20a and 2-naphthols.

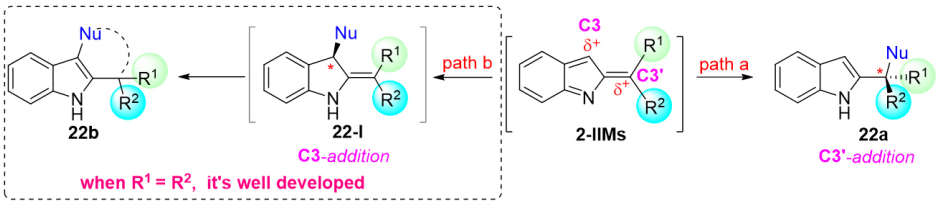
know, to achieve nucleophilic attack on C3 position instead of C3' position, two bulky aryl groups substituted at C3' carbon of 2-IIMs were usually needed to help generate the intermediate 22-I which then undergo further aromatization or cycloisomerization to give final products 22b[52-56]. However, both two bulky aryl groups ($R^1 = R^2$) were almost the same, probably due to synthetic reasons.

Very recently, in order to verify what changes that might cause the differences between the two bulky aryl groups ($R^1 \neq R^2$), Han *et al.* designed and synthesized a 2-indolylmethanol derivative 23a which has two different aryl groups on C3' position [Scheme 23][57]. Interestingly, they confirmed that a similar intermediate 22-I ($R^1 \neq R^2$) could be generated after nucleophilic addition, which further undergoes aromatization involving a central-to-central chirality transfer progress to construct the chiral triarylmethanes. As the scope testing, a broad scope of indol-2-yl methanols 23a can be coupled with various indoles to produce chiral triarylmethane 23b in high yields with up to 96% ee value. The challenge in this work was the stereo identification of two aryl groups (Ar^1 *vs* Ar^3). The author cleverly designed the methoxyl group on one of two aryl groups, and they confirmed that the hydrogen bonding between N-H and methoxyl group was the most important for distinguishing these two similar aryl groups. For the proposed mechanism, 2-indolylmethanol 23a could undergo dehydration to give the ion pair 23-I which could resonate with the CPA-activated indole imine methide 23-II. Although 2-IIM 23-II has not been successfully synthesized, the author believes that such a IIM 23-II might be a *Z* isomer due to the hydrogen bonding interaction between N-H and methoxyl group which is important for enantio-determination. Next, a CPA controlled enatioselective nucleophilic addition on C3 position of 23-II occurred to form chiral enamine specie 23-III. The next olefin isomerization to form final product 23b is thermodynamically driven by rearomatization. While concerted[1,3]-sigmatropic H-migration is forbidden, the author believes that this step can proceed with good enantioselective control by using CPA-16 as the proton shuttle *via* transition state 23-IV.

Fully substituted 2-IIMs (Scheme 22, $R^1 \neq R^2 \neq H$) can also undergo nucleophilic addition with hydrogen anion that provides a potential pathway for chiral triarylmethanes if R^1 and R^2 are both aryl groups. However, the biggest challenge of this approach is how to effectively distinguish the two similar aryl groups. In their previous work, Han *et al.* demonstrated that the methoxy group can be introduced as a directing group to identify these two similar aryls by the hydrogen bond between the methoxy group and the catalyst[34]. Very recently, Yan *et al.* also addressed this challenge by using a robust organocatalytic system

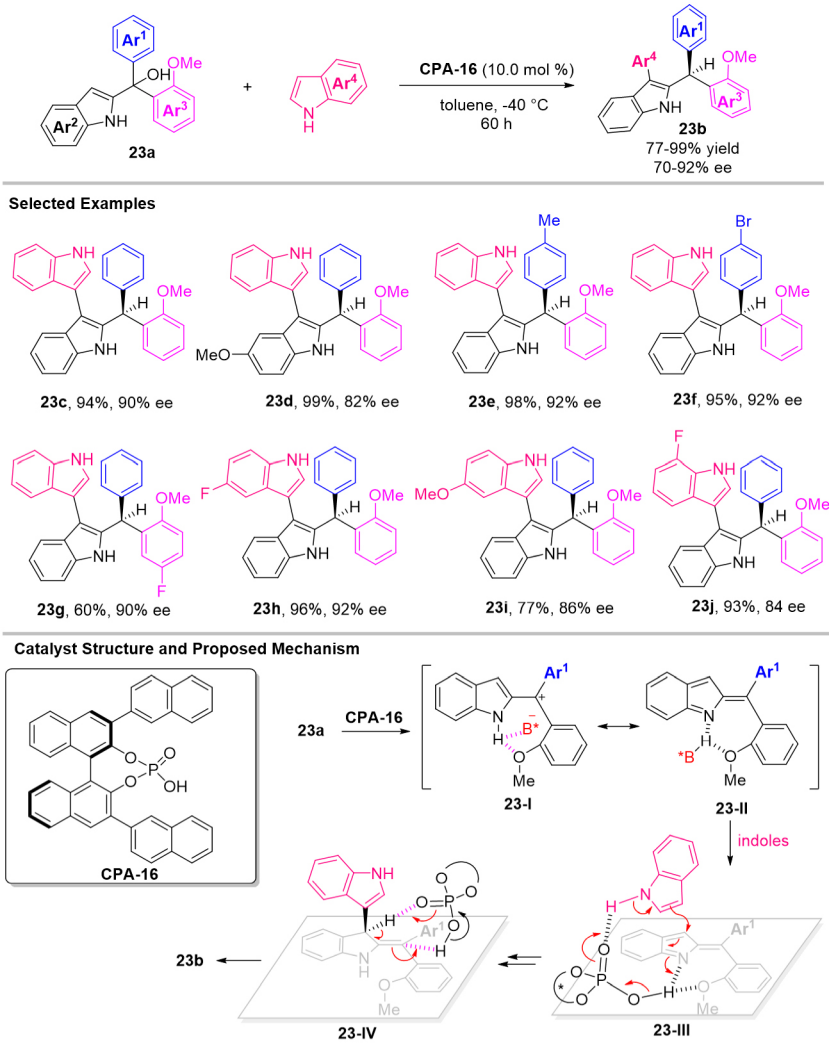


Scheme 21. Enantioselective hydroarylation of 2-vinyl indoles 21a.



Scheme 22. Two nucleophilic attacking ways of 2-IIMs.

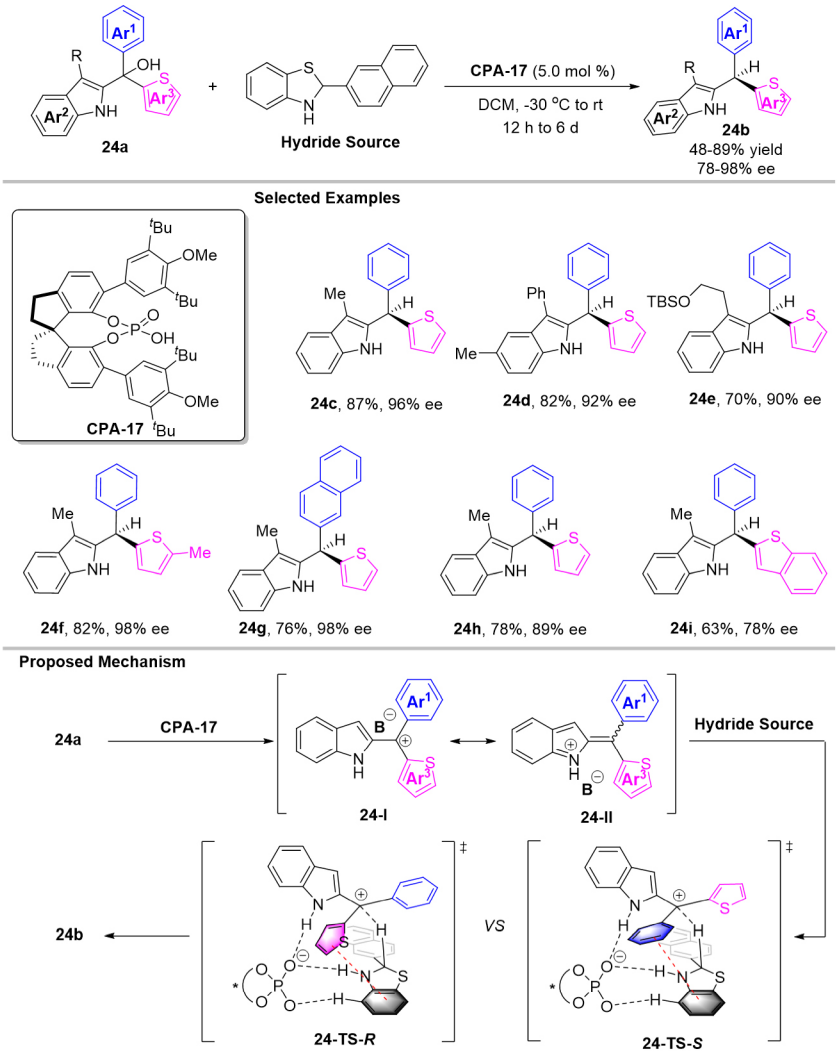
leading to excellent enantioselection between aryl and heteroaryl groups without directing group in which versatile 2-indole imine methide 24-II bearing aryl and heteroaryl groups was employed [Scheme 24][58]. This protocol provided efficient access to a wide range of highly enantioenriched triarylmethane 24b bearing both indolyl and thienyl groups in good yields and excellent enantioselectivities from the corresponding racemic tertiary alcohol 24a. For mechanism, they proposed that an indolyl cation 24-I was first generated by pairing with a phosphate counter anion. This ion pair might be in equilibrium with the



Scheme 23. Catalytic asymmetric allylic substitution/isomerization for chiral triarylmethanes.

activated 2-IIMs 24-II. Subsequently, the hydride source approaches benzylic carbon to furnish the product 24b. Computational studies showed that the key interaction for the discrimination of these two aryl groups is mainly - stacking. Therefore, 24-TS-*R* was the major transition state because the electron-deficient thienyl is in closer contact with the electron-rich benzo ring of benzothiazoline. They also did a biological study that demonstrated the great potential of these triarylmethane 24b for anticancer and antiviral drug development.

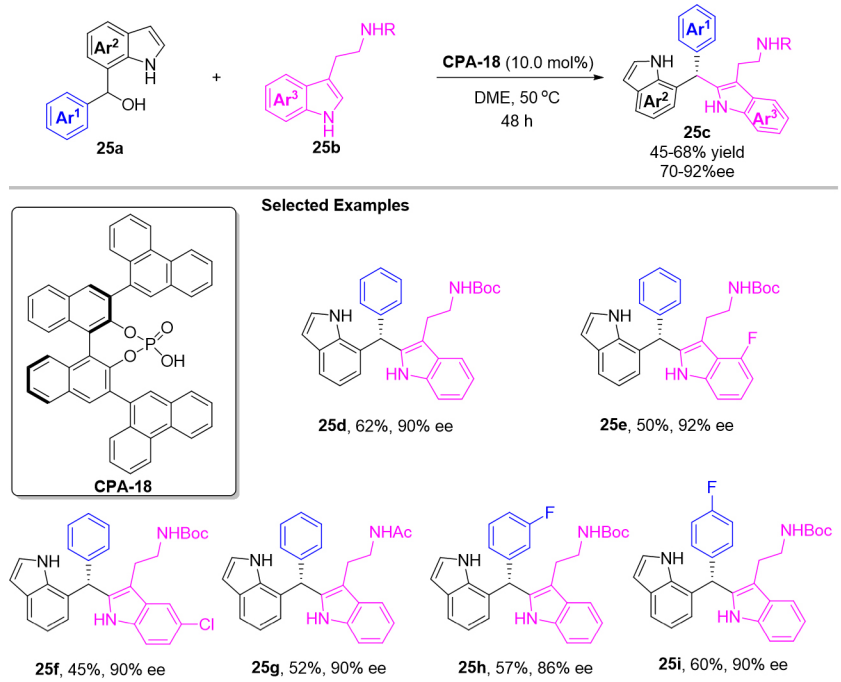
6-IIMs and 7-IIMs. Compared with 3-IIMs and 2-IIMs, there is less research on other IIM derivatives, which may be difficult to synthesize their precursors. So far, only 6-IIMs and 7-IIMs have been successfully applied to contribute to the chiral triarylmethanes by asymmetric Friedel-Crafts reaction. In 2018, Wang *et al.* established the first catalytic asymmetric Friedel-Crafts reaction of indol-7-yl methanol 25a with tryptamine 25b as nucleophiles in the presence of CPA-18, which afforded a series of diverse chiral triarylmethane 25c with 7-indolyl group substitutions in moderate to good yields and generally excellent enantioselectivities [Scheme 25][59]. The mechanism study indicated that there was a kinetic resolution of 7-indolylmethanol 25a during the reaction process.



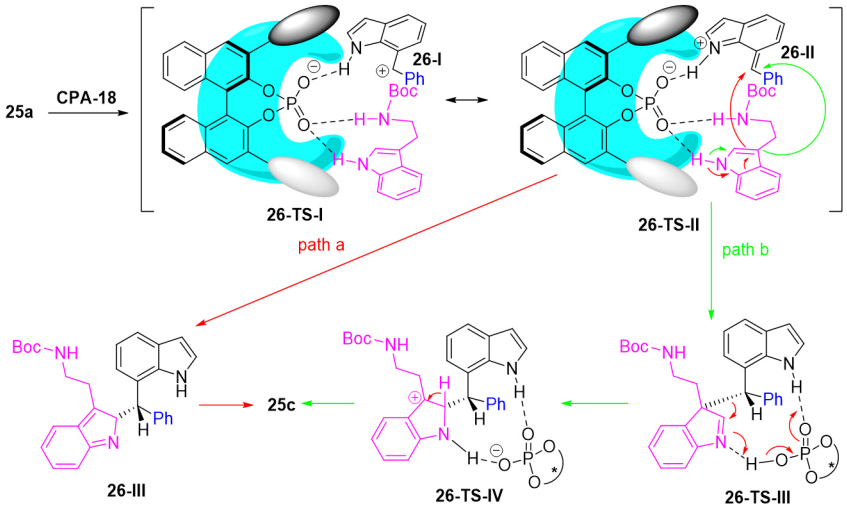
Scheme 24. Asymmetric reduction of tertiary alcohols 24a.

Mechanistically, they proposed two possible reaction pathways for this transformation [Scheme 26]. The active carbocation 26-I, which may exist stably in form 26-II, was first generated from indol-7-yl methanol 25a *via* dehydration under the catalysis of CPA-18. In the transition state, CPA-18 was proposed to activate 7-IIMs and tryptamine 25b simultaneously *via* hydrogen-bonding and ion-pairing interactions. Then, the transient intermediate 26-III was generated *via* nucleophilic trapping by the C2-position of tryptamine 25b. Finally, the corresponding triarylmethane 25c was formed after aromatization. Similar to pathway a, a dearomatized intermediate 26-TS-III was formed through the C3-attacking of tryptamine 25b. Then, intermediate C underwent a migration to generate a transient intermediate 26-TS-IV due to the driving force of rearomatization, which rapidly aromatized into final products.

In the same year, Yue *et al.* employed 7-indolylmethanol 27a as the precursor of 7-IIMs to achieve enantioselective 1,4-arylations providing an efficient approach for the synthesis of diverse hetero-triarylmethanes 27b with indol-3-yl and indol-6-yl substitutions, which provided in high yields and excellent enantioselectivities [Scheme 27][60]. For mechanism, 7-IIMs were proposed to be the possible intermediate for this reaction. With control experiments investigation, they also suggested that a formal S_N1



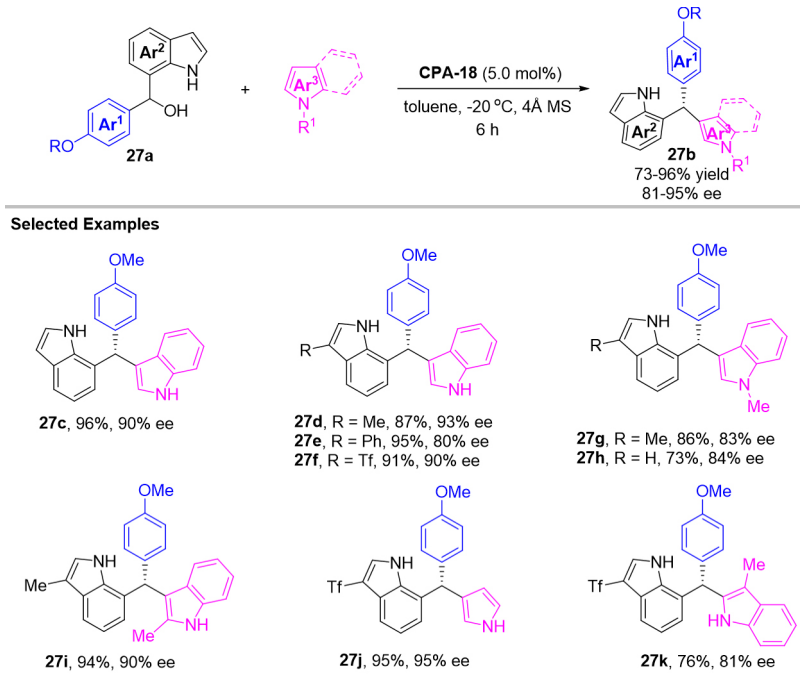
Scheme 25. Asymmetric Friedel-Crafts reaction of indol-7-yl methanol 25a and tryptamine 25b.



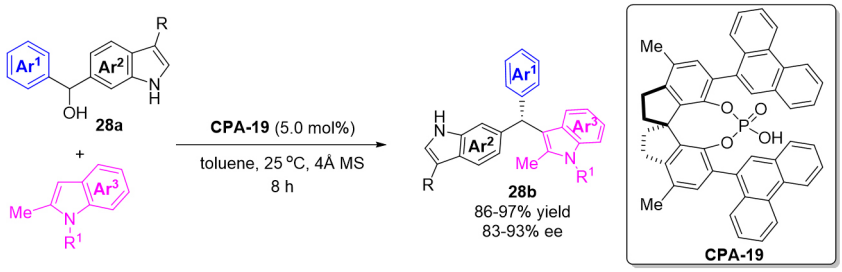
Scheme 26. The proposed mechanism for asymmetric Friedel-Crafts reaction of indol-7-yl methanols 25a.

substitution was compatible with this catalytic system.

In their work, the author further extended the 1,4-addition reaction to the remote 1,8-addition reaction by utilizing the indol-6-yl methanols 28a as the precursor of 6-IIMs [Scheme 28]. As a result, a series of triarylmethanes 28b were provided in excellent yields and enantioselectivities. Mechanistically, the successful formation of 6-IIMs intermediate was suggested to be the key to the process.



Scheme 27. Asymmetric Friedel-Crafts reaction of indol-7-yl methanols 27a and indoles.

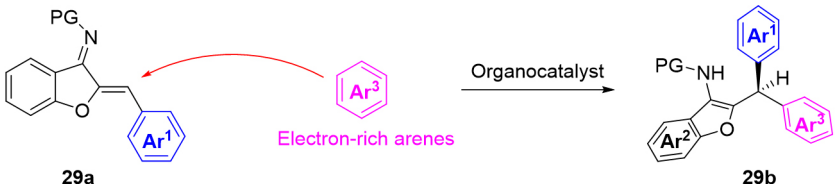


Scheme 28. Asymmetric Friedel-Crafts reaction of indol-6-yl methanols 28a and indoles.

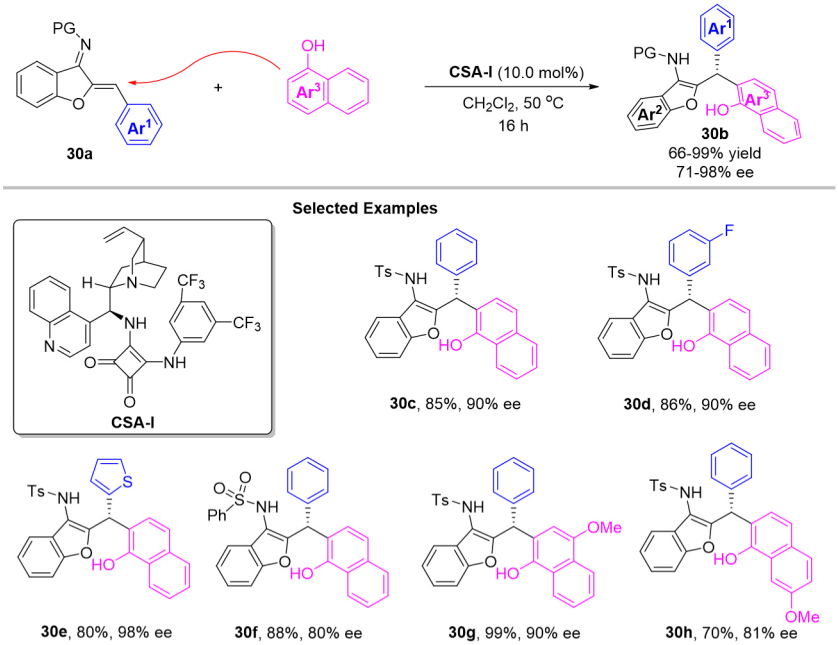
CONSTRUCTION OF CHIRAL TRIARYLMETHANES WITH AZADIENES

Due to the driving force of aromatization, 2,3-dihydrobenzofuran fused azadienes, which can undergo nucleophilic 1,4-addition, have also been regarded as a pivotal class of highly reactive intermediates in organocatalytic asymmetric reactions for the synthesis of functional benzofuran derivatives[61-66]. If electron-rich arenes are selected as nucleophiles, the above 1,4-addition can also construct chiral triarylmethanes with 2-benzofuranyl substitution, which provides another alternative approach to chiral triarylmethanes constructions [Scheme 29].

In 2019, Zhang *et al.* developed an organocatalyst-controlled positionselectivity switchable enantioselective Friedel-Crafts reaction of 1-naphthols for the synthesis of two types of chiral triarylmethanes bearing naphthalen-2-yl groups [Scheme 30][67]. With cinchonidine-derived squaramide CSA-1 as organocatalyst, 1-naphthols underwent *o*-selective Friedel-Crafts alkylation to provide the first type of chiral triarylmethane 30b with 1-hydroxynaphthalen-2-yl group substitution. As a result, a series of azadiene 30a were employed in the Friedel-Crafts reaction to afford the corresponding products 30b in high yields (66%-99%) and enantioselectivities (71%-98%). This approach could tolerate both electron-withdrawing groups (including



Scheme 29. Asymmetric 1,4-addition of azadienes.

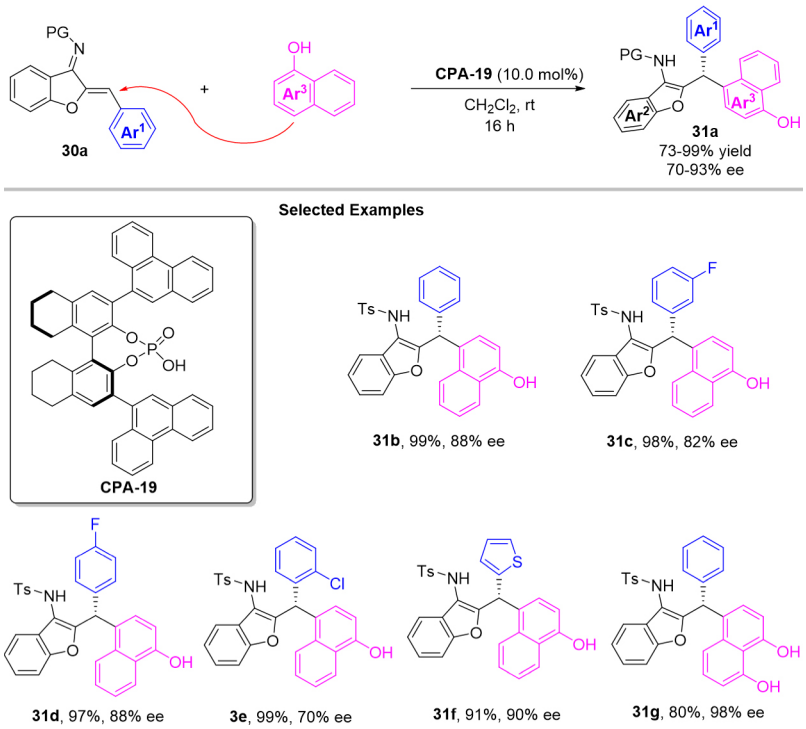


Scheme 30. Asymmetric 1,4-addition of azadienes 30a and 1-naphthols.

F, Cl, Br, *etc.*) and electron-donating groups (including Me, OMe, *etc.*).

Meanwhile, when chiral phosphoric acid CPA-20 was employed instead of squaramide CSA-1 as organocatalyst, a *p*-selective Friedel-Crafts alkylation of 1-naphthols could be achieved for the synthesis of second type chiral triarylmethanes with 1-hydroxynaphthalen-4-yl group substitution [Scheme 31]. The *p*-selective reaction also has good functional group tolerance to form a series of chiral triarylmethanes in 73%-99% yield with 70%-93% ee, which is the same as the *o*-selective Friedel-Crafts alkylation. Most importantly, no isomeric *o*-selective products were formed to a detectable extent under this reaction condition. Although the author did not propose a detailed mechanism, the results of control experiments indicated that the free hydroxyl group of 1-naphthols played a key role in this catalyst-controlled position-selectivity switchable enantioselective Friedel-Crafts alkylation, probably due to the hydrogen bonding formation.

Indoles could also be utilized as electronic-rich arenes in the Michael addition of azadienes for chiral triarylmethanes synthesis which was first revealed by Xie *et al.* With chiral phosphoric acid CPA-15 as organocatalyst, a broad scope of indoles underwent conjugate addition to azadienes preparing a series of structurally important indolyl and benzofuranyl based triarylmethanes 32a in excellent yields and enantioselectivities [Scheme 32][68]. The author proposed a mechanism that chiral phosphoric acid acted as a bifunctional catalyst to active the NH group of the indoles and the imine group of the azadienes by the hydrogen bonding, which facilitates the enantioselective 1,4-conjugate addition of indole to azadiene 30a to



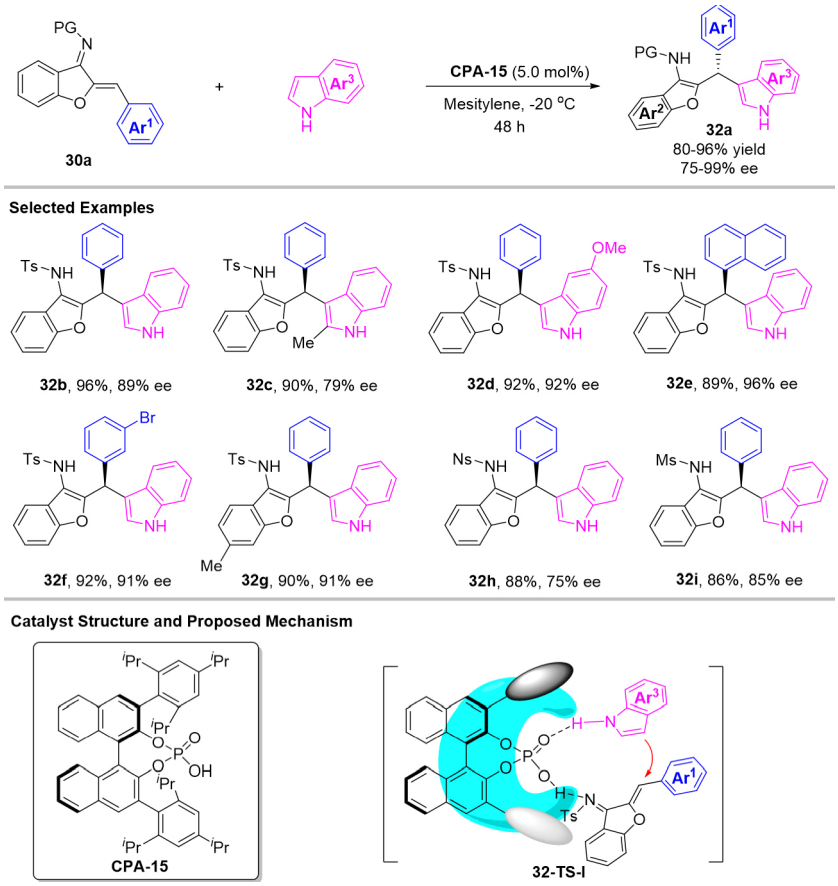
Scheme 31. CPA-catalyzed Asymmetric 1,4-addition of azadienes 30a and 1-naphthols.

give the final products 32a.

Recently, by using chiral phosphoric acid CPA-5 as catalyst, Lu *et al.* also developed an efficient catalytic enantioselective 1,4-addition of azadienes with 3-methyl indoles which provided a promising approach for the enantioselective construction of structurally diverse 2-indolyl triarylmethane derivatives 33b with moderate to good yields (up to 98%) and moderate to excellent enantioselectivities(up to 99% ee) [Scheme 33][69]. In this catalytic system, other electron-rich arenes, such as pyrroles and furans, could also work as nucleophiles to give the chiral triarylmethanes containing 2-pyrrolyl or 2-furanyl groups in good to excellent yields, albeit the enantioselectivities were unsatisfactory. Different from Zhou's work[68], the C2 position of 3-methyl indoles underwent nucleophilic attack to the azadiene 33a, giving a temporary chiral intermediate 33-I induced by CPA, followed by rapid aromatization to form 33b.

In 2020, Wang *et al.* achieved an enantioselective 1,4-conjugate addition of 1-azadienes with 2-naphthols as the nucleophiles for triarylmethanes bearing 2-hydroxynaphthalen-1-yl group synthesis by applying cinchonidine-driven urea catalyst CUC-1 [Scheme 34][70]. This protocol efficiently enabled access to a variety of important benzofuran-containing hetero-triarylmethanes 34a in up to 98% yields and 99% ee. Electron-rich phenol derivatives could also be compatible in this catalytic system, such as the synthesis of product 34g. As shown in Scheme 34, both 2-naphthols and azadienes were activated by CUC-1 *via* hydrogen bonding to finish this reaction through the favored transition state 34-TS-I.

As a continuous work, Xie *et al.* recently developed 1,4-addition of azadienes with pyrazolin-5-ones providing a series of chiral triarylmethanes 35a bearing pyrazole moiety in moderate to excellent yields with excellent enantioselectivities [Scheme 35][71]. In this reaction, cinchonidine-drived squaramide CSA-2 exhibited the optimal catalytic activity, which acted as a bifunctional organocatalyst. In the proposed



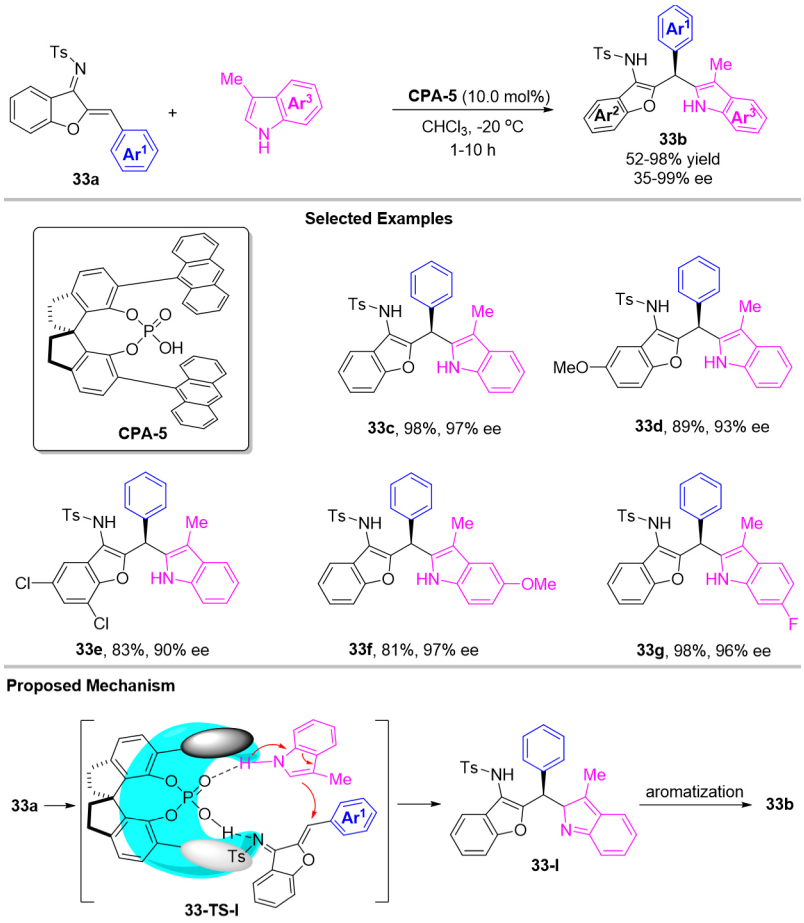
Scheme 32. Asymmetric 1,4-addition of azadienes 30a and indoles.

catalytic model 35-TS-I, the Brønsted base part of squaramide catalyst CSA-2 captured the proton of pyrazol-5-ol intermediate and the Brønsted acid part of squaramide activated the imine group of azadiene *via* hydrogen bonding, then the final products 35a were given by the following enantioselective Michael addition, and base-catalyzed tautomerization.

CONSTRUCTION OF CHIRAL TRIARYLMETHANES *VIA* OTHERS METHODS

The chiral 3,3'-diaryloxindoles with structural characteristics of triarylmethane unit are biologically interesting compounds[72-75]. In 2014, Shirakawa *et al.* reported a phase-transfer-catalyzed S_NAr reaction of 3-aryloxindoles 36a to provide chiral 3,3'-diaryloxindoles by using a chiral bifunctional quaternary phosphonium bromide catalyst [Scheme 36][76]. To improve the enantioselectivity, a series of phase-transfer catalysts PTC-1 to PTC-6 possessing a urea group were designed and applied in the reaction. The urea moiety interacts with the nitroarene through two hydrogen bonds to generate an orderly transition state 36-TS-I that provides the high stereo-control. As the scope testing, all the electron-donating and electron-withdrawing substituents on both the oxindole ring and the 3-aryl group uniformly could be tolerated to furnish the target 3,3'-diaryloxindoles 36b in good to high enantioselectivities.

As an alternative strategy, the desymmetrization of achiral triarylmethanes was also efficient in obtaining the enantioenriched triarylmethanes [Scheme 37], among which Pd-catalyzed desymmetric C-H arylation of achiral triarylmethanes developed by Yu group is the most popular strategy (not shown)[77-79].

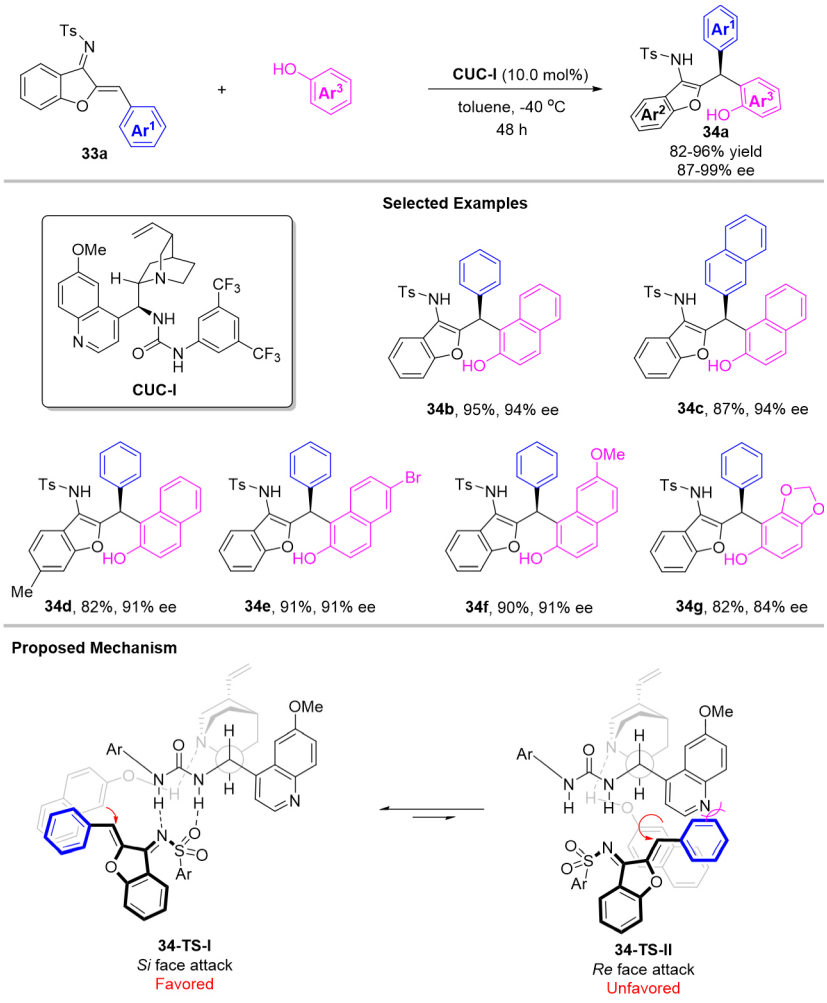


Scheme 33. Asymmetric 1,4-addition of azadienes 33a and 3-methyl indoles.

Until 2017, Lu *et al.* developed an efficient process for chiral triarylmethanes synthesis through a NHC-catalyzed acylative desymmetrization of 2,2'-(phenylmethylene)diphenols 38a [Scheme 38][80]. As a result, a wide range of enantioenriched triarylmethanes 38c was provided in uniformly high yields and excellent enantioselectivities. And the phenol unit of these chiral triarylmethanes could be further derivatized into other functionalized triarylmethanes. It is worth mentioning that when the Ar^1 group was replaced with an alkyl group, such a desymmetrization strategy is still applicable, providing a good strategy for the synthesis of chiral diarylmethanes. For mechanism, 2,2'-(phenylmethylene)diphenol 38a undergoes deprotonation under DIPEA condition to give an ion pair complex 38-I, which undergoes a nucleophilic attack to acyl azolium 38-II, giving an oxyanion tetrahedral intermediate 38-III. The intermediate 38-III was characterized by a strong intramolecular hydrogen bond, and the ester product, which adopts the *Z* conformation. The author pointed out that the *in situ* generated NHC catalyst in this process has no hydrogen bond donors or acceptors that can interact with either the aldehyde or triphenyl moiety. Thus, the potential resistance effect of the NHC catalyst is most likely an important factor in the stereo-determining step.

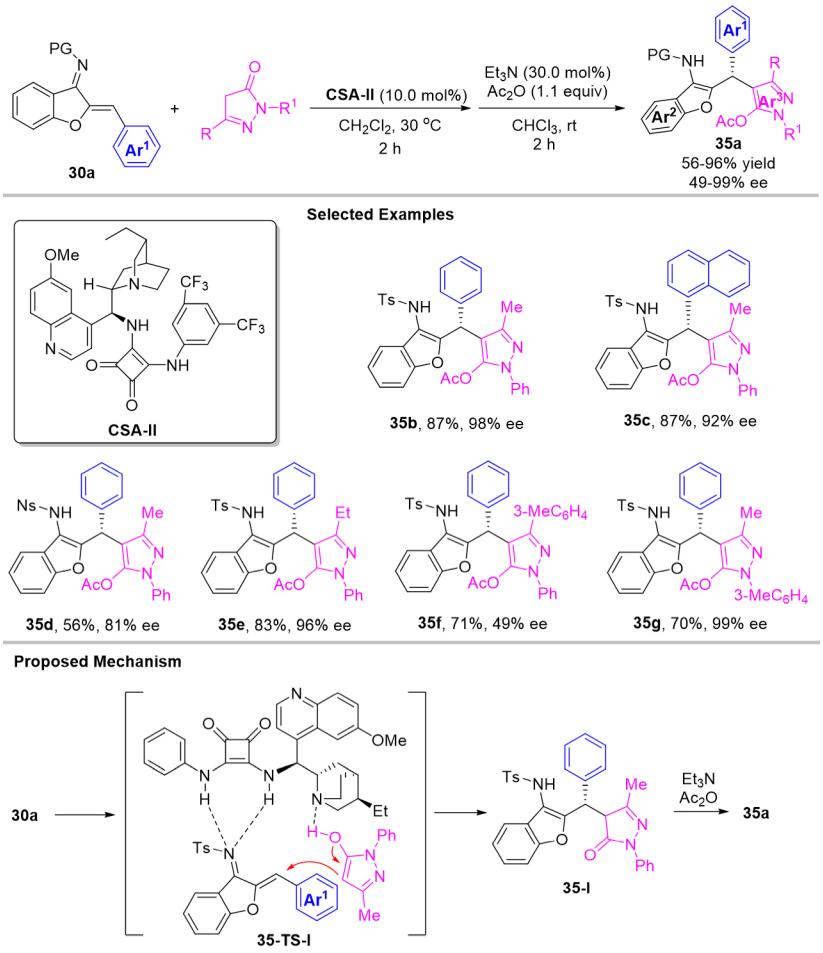
CHIRAL TETRAARYLMETHANES SYNTHESIS

Compared with triarylmethanes, the synthesis of tetraarylmethanes is more challenging, especially in the chiral version, which lies in not only the high barrier in making the extremely congested C-C bond connecting the central carbon and new aryl rings, but also the difficult stereo-identification between the



Scheme 34. Asymmetric 1,4-addition of azadienes 33a and 2-naphthols.

existing similar aryl rings with the new introduced aryl ring. Therefore, there has been a lack of methods to directly construct the chiral tetraarylmethanes with concomitant establishment of the quaternary stereogenic center[81]. Until 2020, Li *et al.* extended the 1,6-addition strategy of *p*-QMs employing pyrroles as nucleophiles for the synthesis of chiral tetraarylmethanes, triarylmethanol 39a were introduced in the catalytic system, in which they skillfully designed two similar aryl groups (Ar^2 and Ar^3) at δ-positions of the *in-situ* generated *p*-QMs and these two similar aryl groups were identified by a "tag group", the identification of these two similar aryl groups could be achieved by the hydrogen bonding interaction between the direction group and the CPA catalyst, thus compensating the shortage of direct construction of chiral tetraarylmethane 39b [Scheme 39][82]. Similarly, the triarylmethanol 39k as precursors of 2-IIMs were also expanded into the asymmetric synthesis of chiral tetraarylmethane 39l bearing indol-2-yl groups. As a result, a series of chiral tetraarylmethanes 39b and 39l were provided in good yields and enantioselectivities. Furthermore, the biological activity experiments indicate that these bright new chiral products are highly promising anticancer agents. For mechanism, the *ortho*-methoxy group considered as directing group was also replaced with *o*-Me, *m*-OMe, *p*-OMe, *o*-CH_2OMe or *o*-Et, resulting in a uniformly dramatic decrease in enantioselectivity, suggesting that this *o*-OMe group mainly functions as a hydrogen-bond donor.

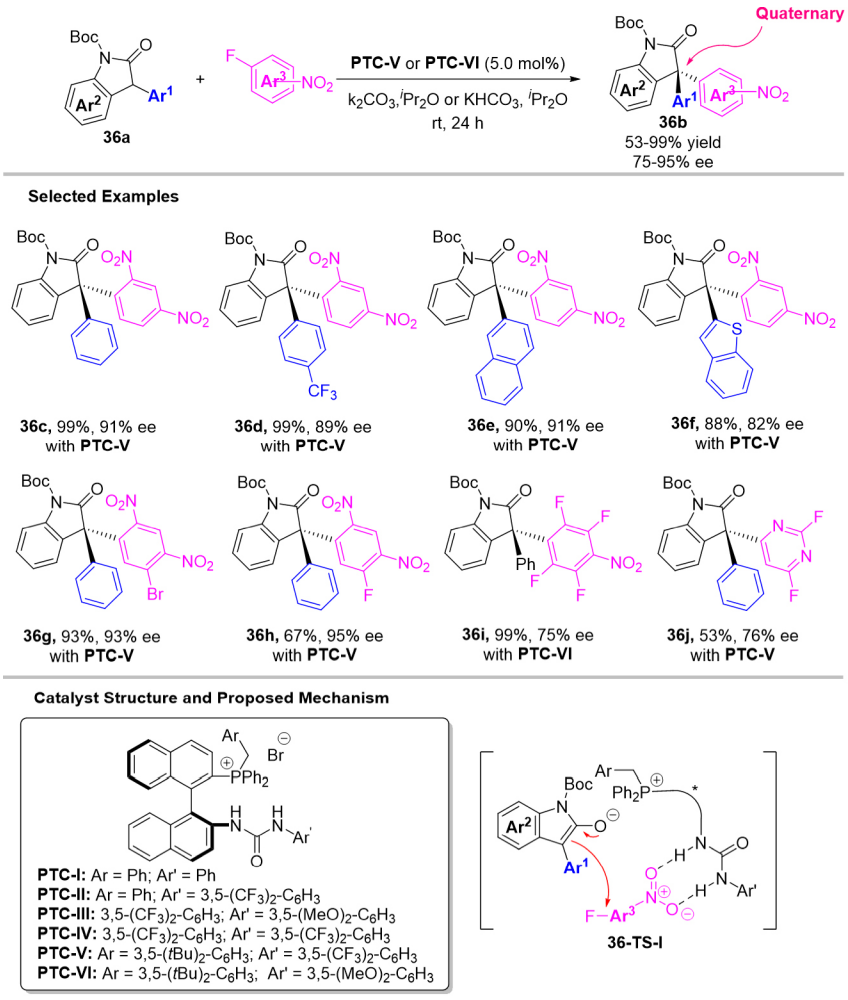


Scheme 35. Asymmetric 1,4-addition of azadienes 30a and pyrazolin-5-ones.

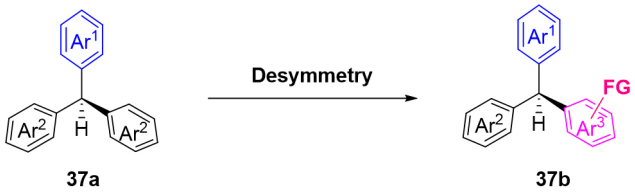
Combined with density functional theory calculations, they give a possible reaction process, as shown in Scheme 40. Firstly, the chiral phosphoric acid CPA-7 forms a hydrogen bond with the substrate 39a to generate the intermediate 39-I which then undergoes dehydration *via* 39-TS-I to afford an identical *p*-QM intermediate 39-II, requiring an activation free energy of 21.2 kcal/mol. Next, the nucleophile 2-methyl pyrrole attacks the *p*-QM intermediate *via* 39-TS-II releasing free energy of 15.8 kcal mol^{-1} to give the intermediate 39-III, which was considered to be the enantio-determining step. The subsequent intermolecular proton shift process *via* 39-TS-III gave the final products.

In their subsequent work, Li *et al.* developed a catalytic asymmetric formal cross dehydrogenative coupling process for the construction of chiral tetraarylmethanes, racemic triarylmethane 41a underwent oxidation to form a *p*-QMs intermediate, then, the asymmetric 1,6-addition of *p*-QMs occurred following the same catalytic process to finish the reaction [Scheme 41][83]. As a result, a series of enantioenriched tetraarylmethanes were prepared in both excellent yield and enantioselectivity. It is worth mentioning that these tetraarylmethane products 41b were verified to have promising antiviral activity.

It was well known that benzylic carbocations bearing an *ortho*- or *para*-hydroxyl group can be stabilized by forming *o*-QMs or *p*-QMs, which has been summarized above. However, those benzylic carbocations with *meta*-hydroxyl group have remained almost unexplored in organic synthesis due to the lacking of resonance

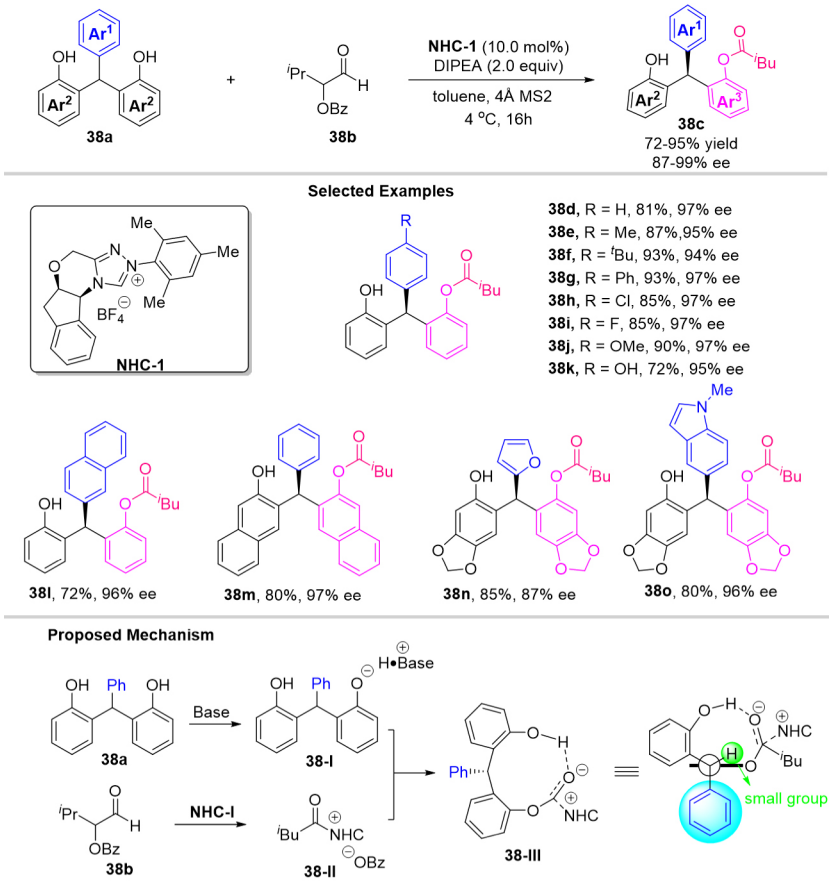


Scheme 36. The phase-transfer-catalyzed SNAr reaction of 3-aryloxindoles 36a.



Scheme 37. The strategy of chiral triarylmethanes forms a desymmetrization of achiral triarylmethanes.

stabilization by a typical quinone methide form. Very recently, Tan *et al.* reported a novel and catalytic enantioselective addition of *meta*-hydroxyl triarylmethanols 42a with indoles via triaryl carbocation intermediates, providing an efficient access to chiral tetraarylmethanes with excellent enantiocontrol [Scheme 42][84]. These chiral tetraarylmethane products 42b also show anticancer activities. For mechanism, the CPA-21 firstly activated the *meta*-hydroxyl triarylmethanols 42a by hydrogen bonding *via* 42-I which finishes the dehydration to give a triarylmethyl cation 42-II bearing a chiral phosphate anion. Notably, the key hydrogen bond between the *meta*-hydroxyl and the catalyst phosphoryl oxygen not only enhances the catalyst acidity to facilitate this step, but also benefits asymmetric nucleophilic attacking by bringing the chiral phosphate motif closer to the reactive center. Then, the indole nucleophile approaches to form the

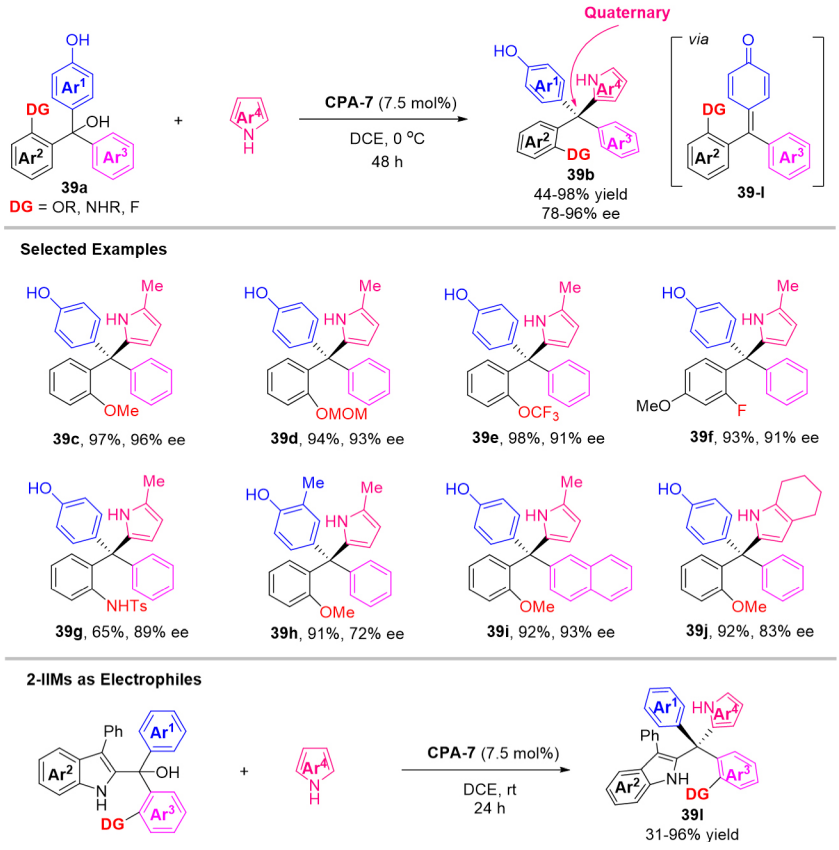


Scheme 38. NHC-catalyzed acylative desymmetrization of 2,2' (phenylmethylene)diphenols 38a.

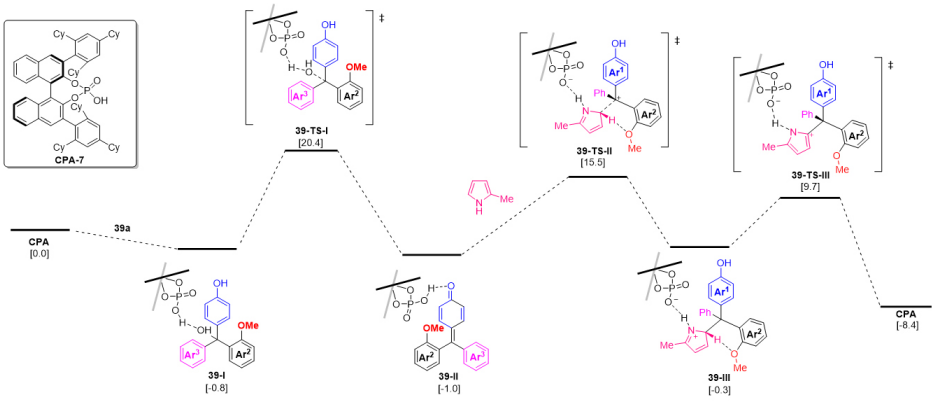
final products *via* the transition state 42-TS-III. The hydrogen-bonding between the phosphate anion and the N–H motif of indole helps organize the key enantiodetermining transition state. Meanwhile, the two similar aryl groups (Ar^2 and Ar^3) were accurately discriminated by the secondary hydrogen bond between the *ortho*-directing group and the indole C(3)-H motif.

CONCLUSION AND OUTLOOK

This review has summarized a series of efficient methods for the synthesis of chiral triarylmethanes and chiral tetraarylmethanes with structural diversity and complexity under organocatalytic conditions. The whole field has only been developed for about 15 years since the pioneer report was published. Therefore, it is still in its infancy. For the development of this field, the following directions can be considered: (a) Although the types of electrophilic reagents have been extensively developed, the types of nucleophiles are still limited in electron-rich arenes, focussing on indoles, pyrroles and naphthols. Therefore, the expansion of electron-rich arenes is worth studying; (b) At present, the synthesis of chiral triarylmethanes mainly relies on the asymmetric Friedel-Crafts reaction and conjugate addition of electron-rich arenes. The development of new construction strategies and new catalytic models is also a hot topic in this field; (c) With more synthetic challenges, chiral tetraarylmethanes have shown great potential in anticancer activities due to their unique chiral spherical structures; however, there are few efficient strategies to achieve their synthesis. Therefore, more research can be focused on the synthesis of chiral tetraarylmethanes; (d) The development of synthetic methods needs to be further expanded to the synthesis of known active molecules and natural products, and the potential realization of chiral triarylmethanes in the field of drug development is also an

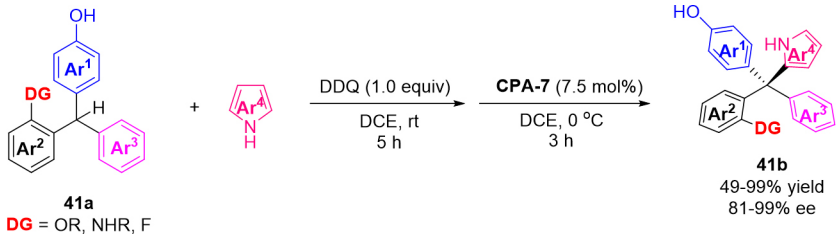


Scheme 39. The 1,6-additoion of *p*-QMs and pyrroles for the synthesis of chiral tetraarylmethanes.

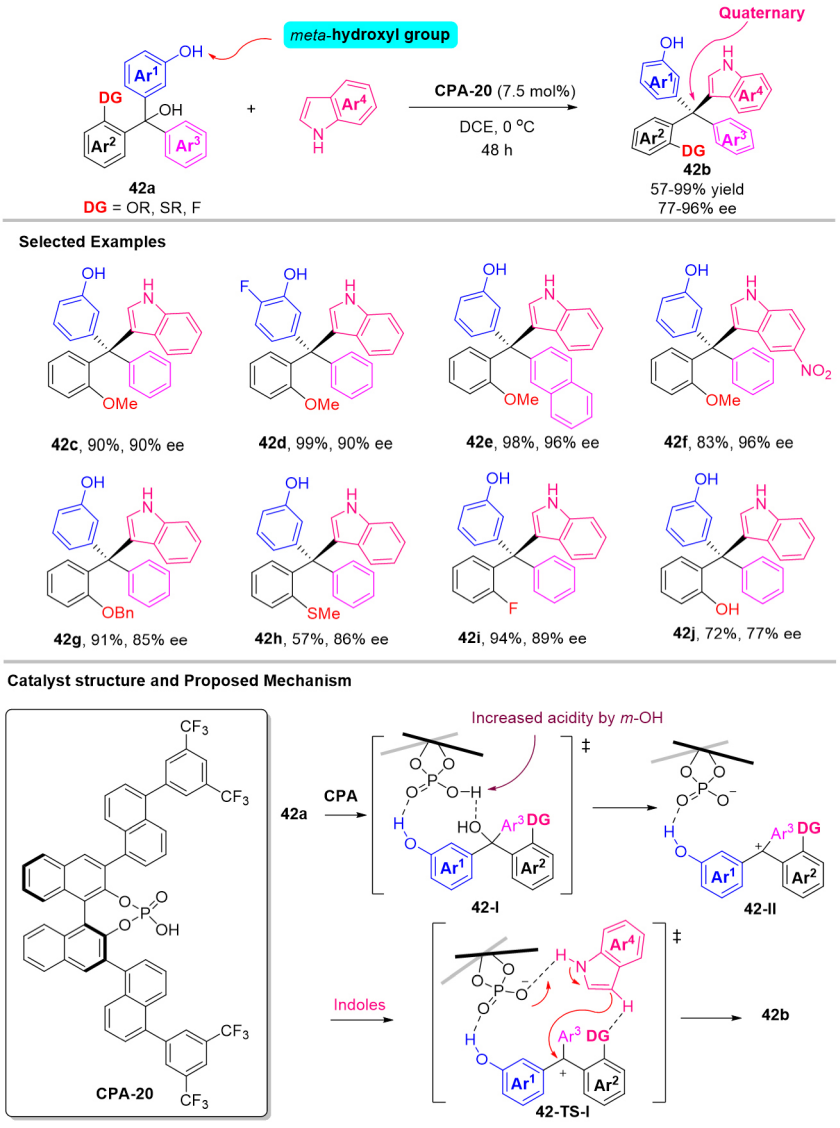


Scheme 40. The proposed mechanism.

encouraging research direction.



Scheme 41. The contribution of chiral tetraarylmethanes through a formal cross dehydrogenative coupling.



Scheme 42. The enantioselective addition of *meta*-hydroxyl triarylmethanols 42a with indoles.

DECLARATIONS

Authors' contributions

Prepared and corrected the manuscript: Han Z, Liu R, Huang H

Availability of data and materials
Not applicable.

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Conflicts of interest
All 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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