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Beyond 1,4-addition of *in-situ* generated (aza-)quinone methides and indole imine methides

Yan-Li Li[a], Zhi-Ming Li[c], Kai-Kai Wang[b,*], Xiao-Long He[c,*]

[a] *Medical College, Xinxiang University, Xinxiang 453000, China*
[b] *School of Pharmacy, Xinxiang University, Xinxiang 453000, China*
[c] *School of Food and Bioengineering, Xihua University, Chengdu 610039, China*

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ABSTRACT

The conjugate addition of *in-situ* generated (aza-)quinone methides (QMs) and indole imine methides (IIMs) emerged as a powerful protocol to access densely functionalized benzenes and indoles. Hydroxybenzyl alcohols, aminobenzhydryl alcohols, and varied indolylmethanols served as most effective precursors for the *in-situ* generation of such reactive species under acid conditions. The relevant propargylic alcohol has proven to be an elegant precursor to generate the propargylic-QMs and -IIMs *via* the acid promoted dehydration process, thus enabling diverse challenging remote activation to proceed conjugate 1,6- and 1,8-additions. Moreover, the heteroarene has proven to be workable to transfer the LUMO of the *p*-QMs and 2-IIMs, thus inducing the remote nucleophilic dearomative additions. The conjugate additions of (aza-)*p*-QMs and varied IIMs has made significant contribution in the field of remote activation chemistry in past decade. This review summarizes the latest advances of the remote conjugate additions of the *in-situ* generated QMs and IIMs.

1. Introduction

The conjugate 1,4-addition of α,β-unsaturated ketones/ketimines is deeed as a powerful approach for the formation of new C–C and C-heteroatom bonds (Scheme 1a) [1–4]. Among them, the (aza-)*ortho*-quinomethides (*o*-QMs), bearing a special α,β-unsaturated ketone/ketimine motif endowed with the dearomatized benzene, served as a highly reactive C4-synthon or Michael-acceptor in a variety of [4 + n] annulations or conjugate 1,4-additions, thus providing a facile pathway to construct structural diversified aromatic backbones (Scheme 1b) [5–9]. Due to the considerable lability but high reactivity, *o*-QMs are often prepared *via* the *in-situ* elimination of a leaving group from the *o*-hydroxybenzyl alcohols and its derivatives under mild acidic or basic conditions [10–15]. Accordingly, the *ortho*-aminobenzhydryl alcohol and its derivatives are utilized as the precursor of aza-*o*-QMs to perform the conjugate 1,4-addition involved reactions for accessing functionalized anilines or aza-cycloadducts [16–23]. Recently, Jiang's and Liu's group independently developed a cascade annulation of *o*–hydroxyl propargylic alcohols initiated by the conjugate 1,6-addition of *in-situ* generation of propargylic *o*-QMs under Brønsted acid catalysis, that expanded the synthetic potential of the *o*-QMs (Scheme 1c) [24,25]. Nevertheless, due to the decrease of reactivity and resulting regioselectivity, the study of the remote activation strategy with *in-situ* generation of *o*-QMs is still in its infancy.

On the other hand, (aza-)*para*-quinomethides (*p*-QMs), which display an exocyclic methylene group and carbonyl/imine residue disposed in a *para*-position, performing as an intrinsic 1,6-Michael acceptor, have been widely applied in the conjugate 1,6-additions with various nucleophiles in recent years (Scheme 2a) [26,27]. Besides the pre-synthesized *p*-QMs [28–30], the 1,6-conjugate addition of *in-situ* generated *p*-QMs has made significant achievements over the past decade. This protocol effectively obviates preparing the unstable *p*-QMs, thus expanding the reaction scope and simplifying operations. Moreover, the electrophilic affinity of the *p*-QMs would be further transmitted to some remote sites via an extended π-system based on the principle of vinylogy, thereby allowing challenging 1,8- and even 1,10-additions (Scheme 2b) [31]. Sun and coworkers have pioneered this concept by introducing an alkynyl group conjugated with the *p*-QMs *via* the elimination of a water from *para*-hydroxybenzyl alcohols under CPA catalysis, providing an efficient approach for the catalytic asymmetric synthesis of tetrasubstituted chiral allenes [32].

* Corresponding authors.
E-mail addresses: wangkaikaii@163.com (K.-K. Wang), xlhe1021@sina.com (X.-L. He).

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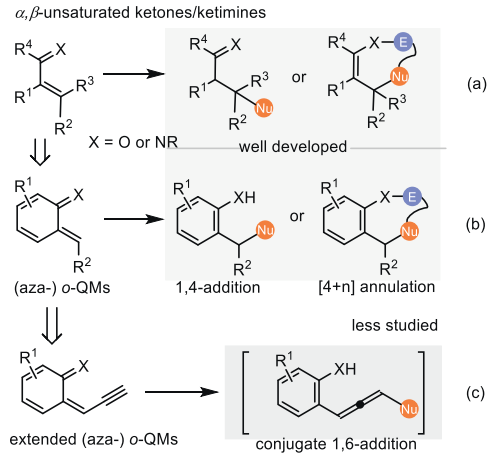
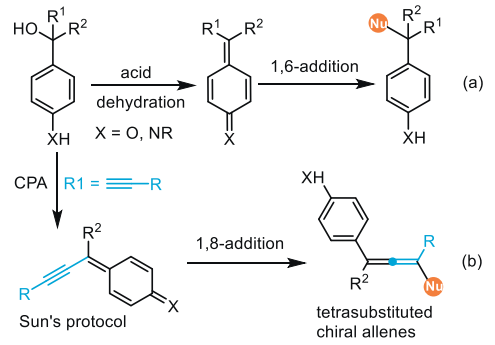
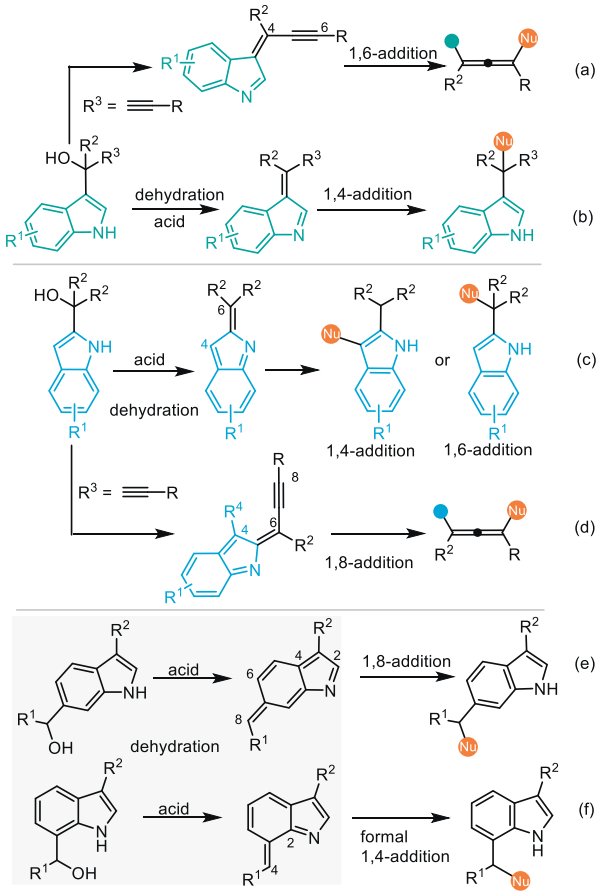


Scheme 1. Overview of the conjugate additions of (aza-)*o*-QMs.



Scheme 2. Conjugate 1,6-/1,8-additions of *in-situ* generated (aza-)*p*-QMs.



Scheme 3. Conjugate 1,4-/1,6-/1,8-additions of *in-situ* generated IIMs.

Indole imine methides (IIMs), which feature an exocyclic methylene group and a conjugated endocyclic imine unit in the indole framework, perform as another highly reactive dearomatized electrophilic species for the straightforward functionalization of indoles. Similar to the QMs, IIMs are always prepared *in-situ* from the corresponding indolylmethanol and its derivatives under acidic or basic conditions *via* the elimination process (Scheme 3). In this context, 3-indolylmethanols and relevant derivatives are recognized as the most common one for the *in-situ* generation of 3-alkylideneindolenines, thus resulting in various conjugate 1,4-additions to afford structural diversified indole derivatives (Scheme 3b) [33–36]. Inspired by the principle of vinylogy and the seminal work of Tan [32], α-indolyl propargylic alcohols was discovered as an ideal precursor of the propargylic 3-IIMs for the conjugate 1,8-additions to access 3-indole containing tetrasubstituted allenes (Scheme 3a). Moreover, 2-indolylmethanols display similar behaviors compared to 3-indolylmethanols under acidic conditions, generating 2-IIMs with multiple electrophilic sites, thus initiating the nucleophilic attack *via* conjugate 1,4-additions or 1,6-additions, as well as 1,8-additions by using corresponding propargylic alcohols (Schemes 3c and d) [37,38]. Intriguingly, 6-indolylmethanols and 7-indolylmethanols were discovered by Antilla as the precursor of 6-IIMs and 7-IIMs respectively under acidic conditions, thus allowing 1,8-additions or formal 1,4-addions with nucleophiles to afford C6- and C7-functionalized indoles (Schemes 3e and f) [39].

Due to the conjugate 1,4-addition of *o*-QMs and 3-IIMs has been extensively studied and well reviewed, we herein focus on summarizing recent progresses of the remote nucleophilic conjugate addition involved reactions rather than 1,4-additions *via* the *in-situ* formation of (aza-)*p*-QMs and IIMs in this review. Therefore, these newly developments of this topic will be discussed systematically and comprehensively in four parts: (1) remote conjugate additions of *in-situ* generated (aza-)*p*-QMs, (2) 1,6-addition reactions of *in-situ* generated 3-IIMs, (3) remote conjugate addition involved reactions of *in-situ* generated 2-IIMs, (4) remote conjugate additions of other type of *in-situ* generated IIMs. Most of the reactions are facilitated by the chiral phosphoric acid (CPA) [40–43], which has wide applications in the catalytic dehydration reactions. All the CPAs involved in this review are listed and numbered as shown in Fig. 1.

2. Remote conjugate additions of *in-situ* generated (aza-)*p*-QMs

2.1. 1,6-Addition reactions of (aza-)p-QMs

Generally, extended π-systems and electron-donation-group would make the transient dearomatized QMs stable but less reactive. Therefore, the pre-synthesized *p*-QMs with steric bulky alkyl group adjacent to carbonyl moiety has been widely explored in various nucleophilic 1,6-additions. However, the additional removal of the useless bulky substituents and pre-synthesizing procedures limit the synthetic diversity of this substrate. Inspired by the *in-situ* generated strategy of *o*-QMs, Sun and co-workers developed a CPA-catalyzed asymmetric 1,6-conjugate addition of the *in-situ* generated *p*-QMs from *p*-hydroxybenzyl alcohols **1** [44]. Pyrrole derivatives **2** with various substituents were well adapt in this reaction, delivering a series of chiral triarylmethanes **3** with a quartenary stereocenter in high yields with good to excellent enantioselectivities. Additionally, the indole was demonstrated to be feasible in this reaction under modified conditions (under the catalysis of **C28**). Moreover, styrenes **4** were workable in this protocol, giving the target products **5** in comparable results. The control experiment with Me-protected alcohol **1a-Me** failed to give

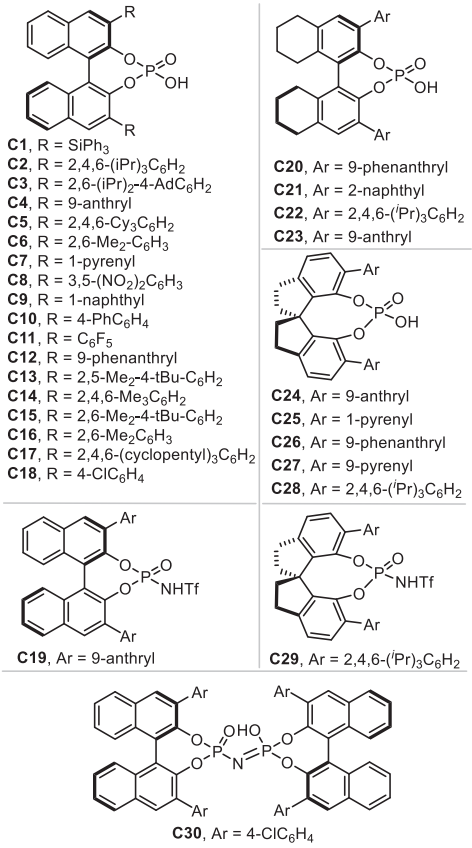
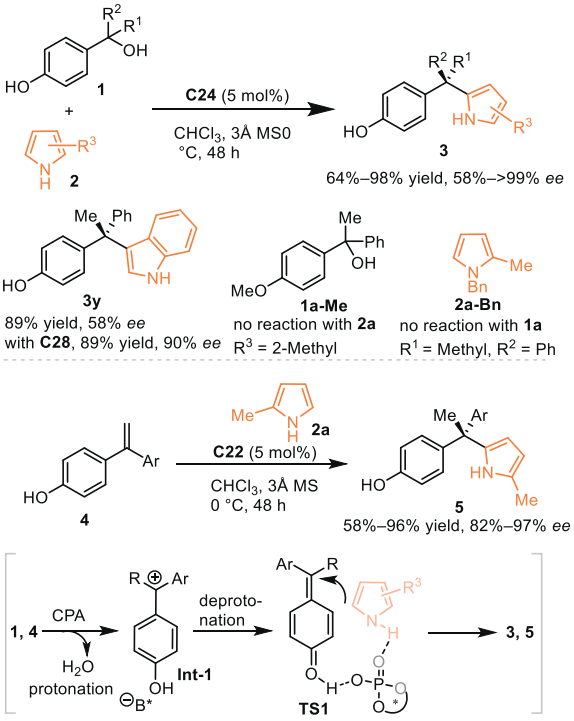


Fig. 1. Chiral phosphoric acids (CPAs) **C1-C30** involved in this review.

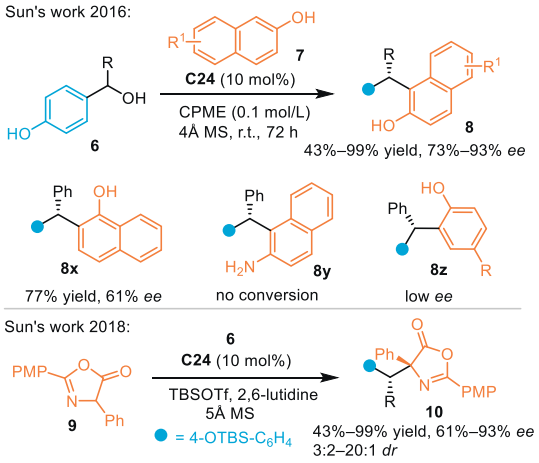
the desired product under identical condition, that implying this reaction probably proceeded *via* the 1,6-conjugate addition to the *in-situ* generated *p*-QMs. The Bn-protected pyrrole **2a-Bn** was invalid in this protocol, indicating the CPA might act as a bifunctional role *via* the simultaneous formation of hydrogen-bond interactions with both two substrates. As depicted in Scheme 4, the smooth protonation of the tertiary alcohol **1** or the styrene **4** resulted in an extrusion of H_2O to give the ion-pair **Int-1**. Then, a deprotonation induced by the phosphate anion gave rise to the reactive *p*-QMs, which incurred the 1,6-conjugate addition to fulfill the process (Scheme 4).

In 2016, Sun's group employed 2-naphthols **7** as nucleophiles in the reaction with *p*-hydroxybenzyl alcohols **6** under the catalysis of **C24**. A series of triarylmethanes **8** were obtained in moderate to excellent yields and enatioselectivities [45]. Besides, 1-naphthol was compatible in this reaction, delivering the target product **8x** in high yield with lower enantioinduction. However, the 2-aminonaphthanene and phenol demonstrated to be inert in this reaction (**8y** and **8z**). In 2018, Sun's group discovered that azlactones **9** were compatible in the reaction with *p*-hydroxybenzyl alcohols **6** under the catalysis of **C24** *via* the conjugate 1,6-addition route [46]. A collection of chiral β,β-diaryl-α-amino acid derivatives **10** were obtained in moderate to high yields with good enantioselectivities and diastereoselectivities (Scheme 5).

In addition to hydroxybenzyl alcohols, the styrene **11** endowed with an *ortho*- or *para*-phenol group serves as an alternative precursor for the *in-situ* generation of QMs *via* the protonation process under Brønsted acid conditions. The protonation of olefin gives rise to a carbocation species **Int-2**, then phosphate anion approaches the phenol group to generate the QMs, thereby inducing the nucleophilic addition reactions. In 2014, Sun and co-workers developed a convergent asymmetric transfer hydrogenation of the



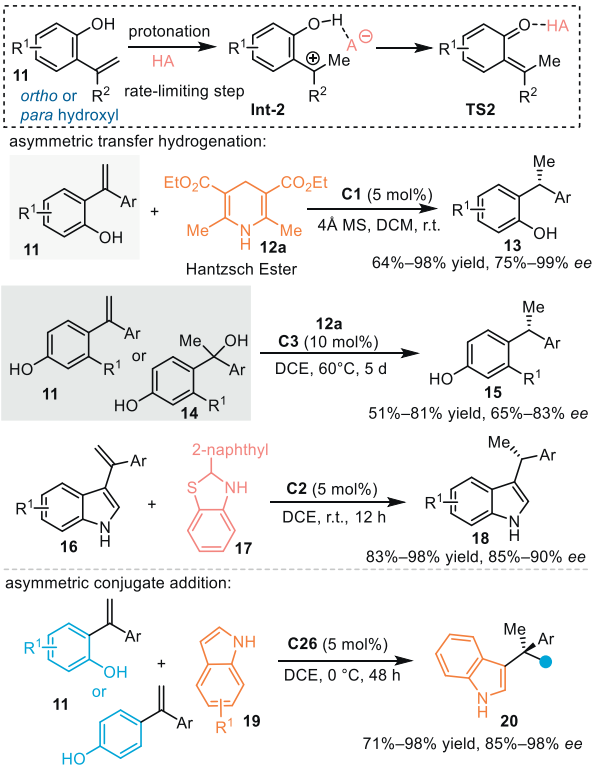
Scheme 4. Asymmetric 1,6-additions of *in-situ* generated *p*-QMs with pyrroles.



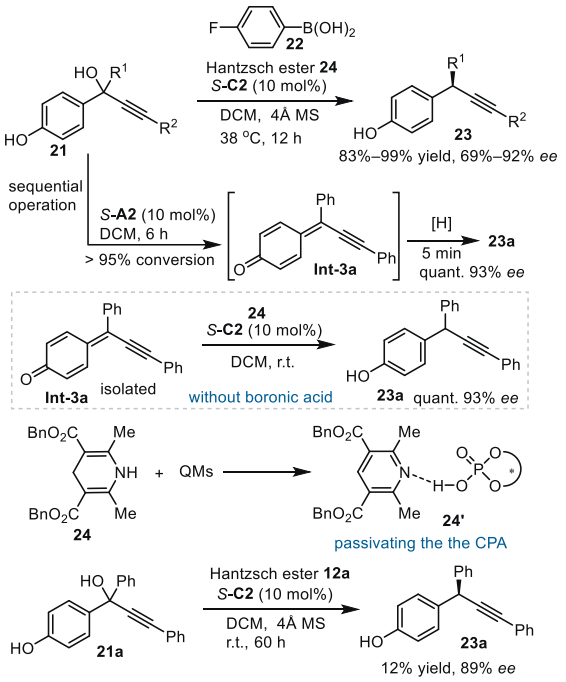
Scheme 5. Asymmetric 1,6-additions of *in-situ* generated *p*-QMs with pyrroles and azlactones.

styrenes with Hantzsch ester in the presence of **C1** [47]. A series of styrenes **11**, including the *ortho*-/*para*–hydroxyl-substituted styrenes and indole-substituted 1,1-diarylethylenes **16**, were well tolerant in the reaction with Hantzsch ester **12a** for the construction of various chiral diarylethanes **13/15/18**, which have wide applications in medicinal chemistry and agricultural domain. Furthermore, indoles **19** were smoothly applied in the nucleophilic conjugate addition with *para*-/*ortho*–hydroxyl styrenes **11** to synthesize chiral triarylethanes **20** under modified conditions. It was noteworthy that the electron-donating-group on one of the two aryls of the styrene was necessary for the efficient protonation of the vinyl group (benifit for the stabilization of the carbocation), that would enhance the reactivity and accelerate the reaction rate. Furthermore, the synthetic utility of the product was verified by a variety of derivatizations with phenol hydroxyl group (Scheme 6).

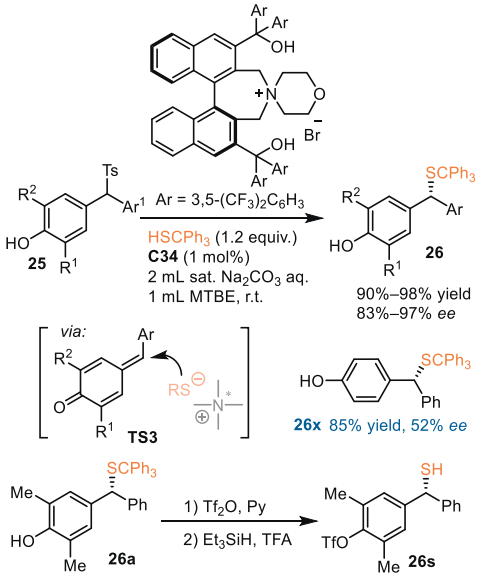
In 2017, Sun and co-workers discovered that alkynyl group affixed *p*-hydroxybenzyl alcohols **21** were applicable in the asym-



Scheme 6. Asymmetric transfer hydrogenation and conjugate nucleophilic addition of hydroxyl styrenes.



Scheme 7. The acid additive effect in the CPA-catalyzed transfer hydrogenation of the Hantzsch ester.

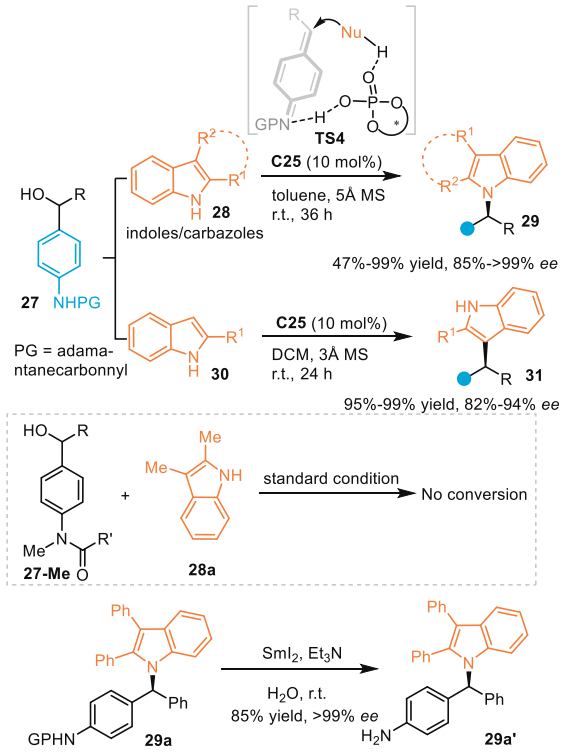


Scheme 8. PTC-catalyzed 1,6-conjugate addition of *in-situ* generated *p*-QMs with tritylthiol.

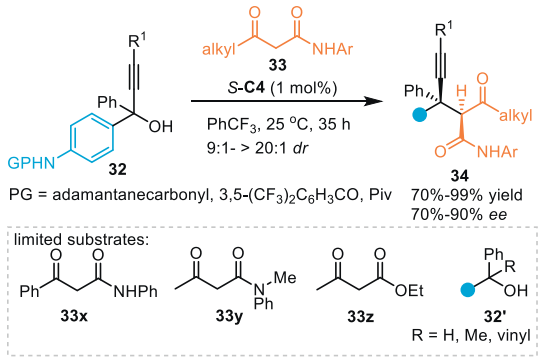
metric transfer hydrogenation with Hantzsch ester under CPA catalysis [48]. Mechanistically, the *in-situ* generated *p*-QMs **Int-3** was attacked by the hydride generated from the Hantzsch ester **24** *via* the conjugate 1,6-addition, affording a series of chiral diarylmethyl alkynes **23** in excellent yields with high enantioselectivities. Notably, this work expounded how an additive was involved in the improvement of the reaction outcome. Due to the simutaneous formation of pyridine by-product **24′** during the reaction process, whose basicity might passivate the activity of CPA, the reaction of **21a** suspended in only 12% conversion, although with high enantiocontrol (89% *ee*). Thus, the addition of additional acid additive aims to neutralize the basicity of pyridine by-product becomes a key to promote the coversion of the reaction. Importantly, the acidity of the additive should be just enough to quench the pyridine by-product but without promoting the 1,6-addition in a nonselective pathway. After extensive investigations, the arylboronic acid **22** was found to be optimal to balance the conversion and enantio–control. Notably, the control experiment of presynthesized *p*-QMs **Int-3a** with Hantzsch ester **24** under the catalysis of *S*-**C2** in the absence of the additive gave the desired product **23a** in high yield with excellent enantionselecivity. Furthermore, the sequential addition of Hantzsch ester after the completion of dehydration step with the aid of *S*-**C2** in the absence of boronic acid also smoothly delivered the desired product with satisfactory result. Such results indicated the pyridine by-product just retarded the first dehydration step but without passivating the second asymmetric nucleophilic addition process. Eventually, they conducted this protocol through the sequential procedures without requirement of the boronic acid, and the products were obtained in equally results (Scheme 7).

In 2018, Li and co-workers employed 4-hydroxybenzyl *p*-tolyl sulfones **25** as the precursor for the *in-situ* generation of *p*-QMs under basic conditions [49]. As a result, the phase transfer catalyst **C34** was applicable for the asymmetric transformation of this substrate with tritylthiols, delivering a collection of α-substituted benzyl thioethers **26** in generally excellent yields and enantioselectivities. Unfortunately, **25x** without substituents on the phenyl motif leaded the product **26x** with inferior enantioselectivity probably due to relatively small steric effect. Notably, the trityl group could be smoothly removed in the presence of the trifluoroacetic acid (TFA) and triethylsilane (Et_3SiH) without enantioselectivity erosion (Scheme 8).

Aza-*p*-QMs exhibit similar characteristics in respect to the nucleophilicity of the *p*-QMs. Accordingly, the *N*-protected amino benzhydryl alcohols are used as the precursor of the aza-*p*-QMs *via* the dehydration process under acid conditions. In 2017, the Sun's group disclosed an asymmetric *N*-alkylation of C2-C3 dis-



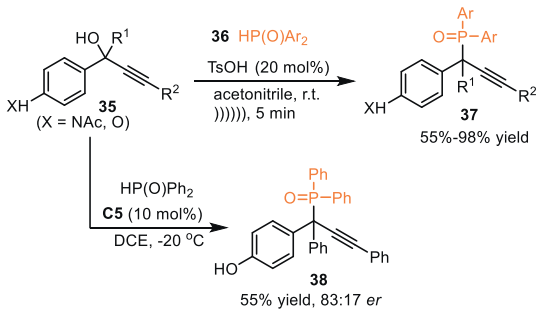
Scheme 9. Asymmetric *N*-alkylation of indoles or carbazoles *via* 1,6-conjugate addition of *in-situ* generated aza-*p*-QMs.



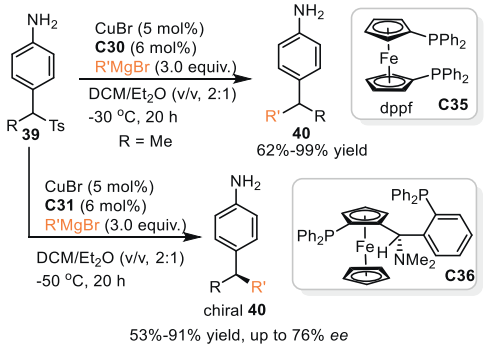
Scheme 10. Asymmetric 1,6-additions of *N*-aryl-3-oxobutanamides with aza-*p*-QMs.

ubstituted indoles or carbazoles **28** with *N*-protected amino benzhydryl alcohols **27** under CPA catalysis [50]. The aza-*p*-QMs were generated *in-situ* and attacked by indoles or carbazoles through the aza-1,6-conjugate addition, giving *N*-alkylation products **29** in high yields with excellent enantiomeric excess. Meanwhile, C2-substituted indoles **30** were also employed in this protocol to undergo the C3-selective nucleophilic 1,6-additions for achieving chiral triarylmethanes **31** in satisfactory results. As expected, the *N*-methylated substrate **27-Me** was not capable to proceed this process. The amide group could be smoothly transformed to amines *via* simple procedures (Scheme 9).

In 2020, Li and co-workers utilized propargylic alcohols **32** in the reaction with *N*-aryl-3-oxobutanamides **33** in the presence of *S*-**C4**, an unexpected 1,6-addition occurred exclusively without the generation of 1,8-adducts [51]. A series of diarylmethyl alkynes **34** containing vicinal quaternary and tertiary carbon stereocenters in high yields with good diastereo-/enantioselectivities. However, the *N*-protected amino benzhydryl alcohols and other ketones **33x**-**33z** failed to participate in this protocol (Scheme 10).



Scheme 11. Brønsted acid-catalyzed 1,6-hydrophosphination of the *in-situ* generated (aza-)*p*-QMs.

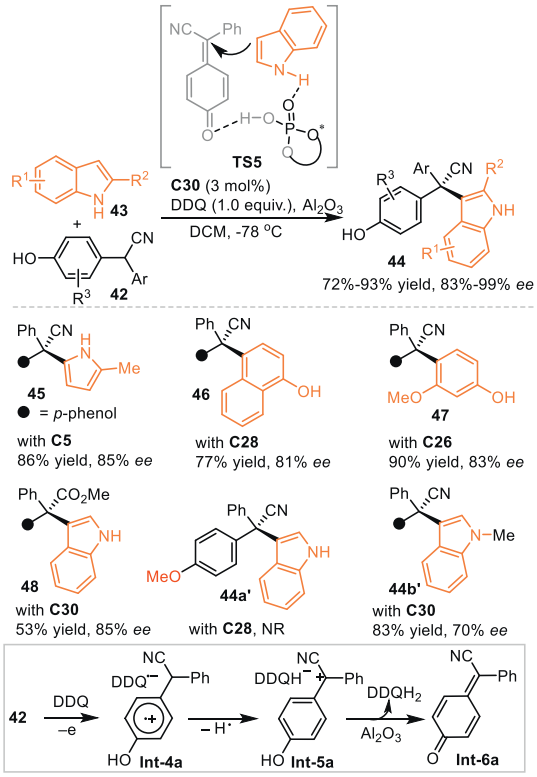


Scheme 12. The conjugate 1,6-addition of Grignard reagents to *in-situ* generated aza-*p*-QMs.

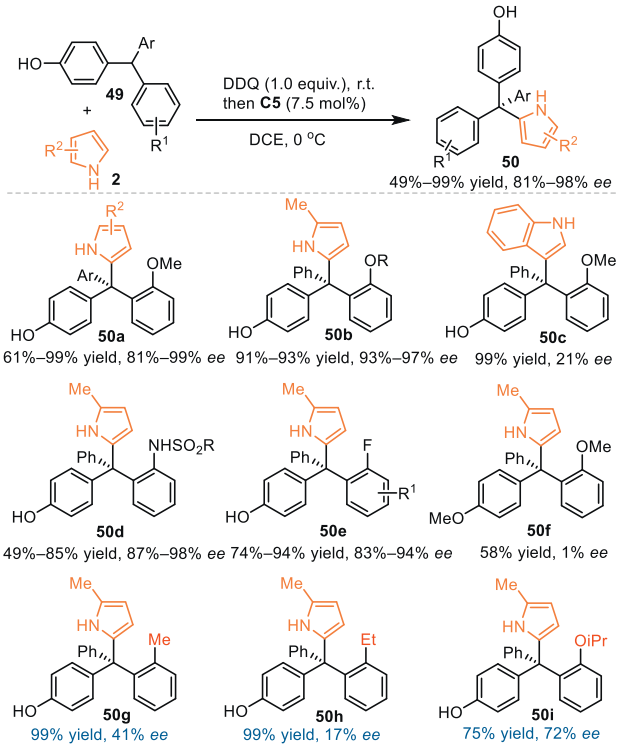
In 2021, Jiang and co-workers employed diphenylphosphine oxides **36** to react with propargylic tertiary alcohols **35** under Brønsted acid catalysis with the aid of ultrasonic irradiation [52]. A site-selective 1,6-hydrophosphination of *in-situ* generated aza-*p*-QMs was realized, giving diarylmethyl phosphorus oxides **37** bearing phosphorus-substituted quaternary carbon centers in high yields within about 5 min. Moreover, the chiral CPA was utilized in this reaction for the construction of chiral diarylmethyl phosphorus oxides. However, the product **38** was obatained with just 66% *ee* after extensive explorations (Scheme 11).

In 2022, Harutyunyanv and co-workers developed the first example of metal-catalyzed 1,6-addition of *in-situ* generated aza-*p*-QMs from 4-amino *p*-tolyl sulfones **39** with Grignard reagents [53]. In the presence of CuBr/dppf, this reaction smoothly delivered a wide variety of 4–*sec*-(alkyl) aniline derivatives **40** in good to excellent yields. Moreoer, the enantioselective version of this protocol proceeded smoothly by using chiral ferrocenyl diphosphine ligand Taniaphos **C36** in the presence of CuBr, giving the chiral aniline derivatives in high yields with moderate to good enantioselectivities (Scheme 12).

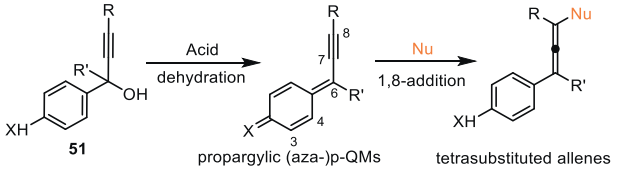
In addition to the acid-promoted dehydration of relevant alcohols or styrenes to access the *p*-QMs, Liu and coworkers discovered that the oxidization of 2-aryl substituted 4-(hydroxyphenyl)acetonitrile **42** was another pathway for accessing the *p*-QMs [54]. With the one-pot treatment of DDQ and chiral phosphoric acid **C28** in DCM in the presence of Al_2O_3 at −78 °C, the *in-situ* generated *p*-QMs was trapped by indoles **43** to afford the triarylmethanes **44** bearing all-carbon quaternary stereocenters in high yields with excellent enantioselectivities (Scheme 13). Besides indoles, other aromatic nucleophiles such as 1-naphthol, phenol and 2-methyl pyrrole demonstrated to be competent in this protocol. Moreover, 2-aryl substituted 4-(hydroxyphenyl)acetate was feasible to produce the *p*-QMs, thus allowig the asymmetric conjugate 1,6-additon in comparable result (product **48**). It was noteworthy that *O*-Me protected diaryl ace-



Scheme 13. Asymmetric 1,6-addition of the *in-situ* generated *p*-QMs from diarylacetonitrile by DDQ oxidation.



Scheme 14. Asymmetric 1,6-addition of the *in-situ* generated *p*-QMs from triarylmethanes by DDQ oxidation.



Scheme 15. The generation of propargylic *p*-QMs for the conjugate 1,8-addition.

tonitrile failed to give the desired product **44a′** under the identical condition, the *N*-Me protected indole gave the desired product **44b′** with much lower enantioselectivity compared with NH-free ones. Such results indicated the hydrogen-bonding interaction betrween the CPA and two reaction partners was a key to the enantioinduction (**TS5**).

In 2021, Sun and coworkers expanded this oxidization strategy by using triarylmethanes for the *in-situ* generation of *p*-QMs in the presence of DDQ [55]. With the aid of **C5**, the pyrrole **2** approached the *in-situ* generated *p*-QMs in an enantioselective pathway, hence producing the valuable chiral tetraarylmethanes **50** in good yields with high enantioselectivities. It was noteworthy that the overloading of DDQ (1.5 equiv.) was detrimental to the enantiocontrol, that preventing the two-step protocol merging into one-pot operation. The methylated substrate smoothly delivered the desired product **50f** without enantiocontrol due to the reactive intermediate was oxonium cation rather than *p*-QMs, that implying the execellent enantiocontrol might be ascribed to the hydrogen-bonding interaction bewttwen the chiral acid and the *p*-QMs. Moreover, control experiments verified the *ortho*-alkoxy group was indispensable (product **50g-i**) for the enantiocontrol *via* its capability to form the hydrogen-bond rather than its steric hindrance (Scheme 14).

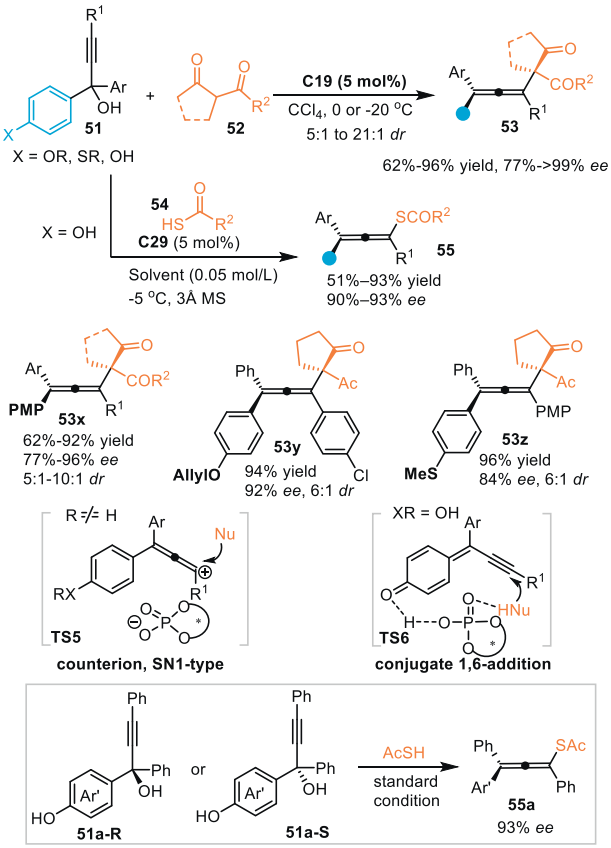
2.2. 1,8-Addition involved reactions of in-situ generated (aza-)p-QMs

2.2.1. Mono-step 1,8-addition to access tetrasubstituted allenes

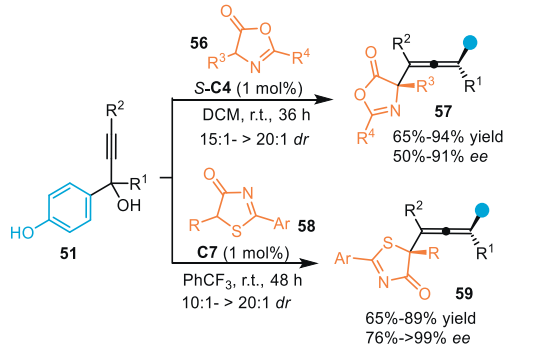
Based on the principle of vinylogy, the inserted vinyl or alkynyl in the cojugated π-system is deemed as an efficient and staightforward avenue to achieve remote activation [56–58]. In this context, the propargylic alcohols **51** affixed with the *para*-phenol/aniline emerged as the protocol for the generation of propargylic (aza-)*p*-QMs, that might result in the conjugate 1,8-addition to access the multi-substituted allenes or structural diversified cycles (Scheme 15).

In 2017, the Sun's group reported the first example of 1,8-addition with alcohols **51** under Brønsted acid conditions, providing an efficient and unified method for the synthesis of tetrasubstituted allenes [32]. Under the catalysis of **C17**, the extended *p*-QMs was generated *in-situ*, thus attacked by 1,3-diketones **52** or thioacids **54** exclusively at ζ-position and giving tetrasubstituted chial allenes **53** in high yields with satisfactory stereoselectivities. It was noteworthy that alcohols without free hydroxyl (usually electron-rich substituent such as OMe, OAllyl and SMe for stabilization of the generated cations) on the *para*-site also smoothly delivered the chiral allenes **53y-53z** in good yields with high diastereo-/enantioselectivities. In fact, this one would be protonated to form a cation species with a chial counter anion in the presence of CPA (**TS5**), thus resulting in an enantioselective S_N1-type subsitution. Moreover, the enantiopure (+)–**51a** and (-)–**51a** were both subjected to this protocol and giving the chiral allene **55a** with identical enantiomeric excess, indicating the enantiocontrol was just determined by the addition step (Scheme 16).

In 2018, Li and co-workers employed the propargylic alcohols **51** to proceed the conjugate 1,8-addition with thiazolones **56** and azlactones **58** with the aid of CPA [59]. On one hand, the thiazolone **56** with broad scope of substituents could be well-tolerated under the optimized conditions, smoothly producing the tetrasubstituted alkenes **57** bearing a quaternary stereocenter in high yields with remarkable diastereo- and enantioselectivities. On the other hand, the azlactone **58**, which have similar structure and nucle-



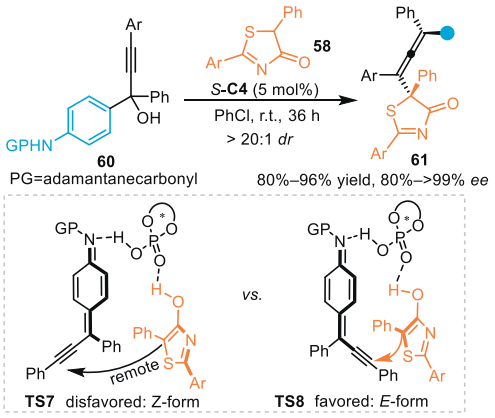
Scheme 16. Asymmetric conjugate 1,8-addition of *in-situ* generated propargylic *p*-QMs to access the chiral tetra-substituted allenes.



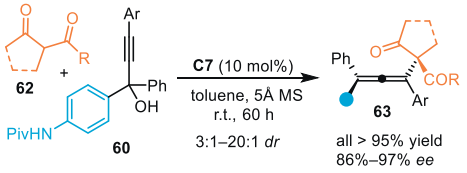
Scheme 17. Asymmetric conjugate 1,8-addition of *in-situ* generated propargylic *p*-QMs with thiazolones and azlactones.

ophilicity compared with the thiazolone, was also workable in this protocol and afforded the tetrasubstituted chiral allenes **59** in good results under slightly modified conditions (Scheme 17).

In 2019, the Li's group extended this alkynylogous 1,8-addition to the aza-*p*-QMs [60]. By employing the aniline-incorporated propargylic tertiary alcohols **60**, the aza-*p*-QMs was generated *in-situ* to react with thiazolones **58** under the CPA catalysis, delivering the chiral allenes **61** endowed with vicinal sulfur-containing quaternary stereocenters in excellent yields and stereoselectivities. In the control experiment of propargylic tertiary alcohols with the aid of CPA, the ESI-MS analysis undoubtly showed the molecular weight of aza-*p*-QMs, which indicated this reaction indeed proceeded *via* the conjugate 1,8-addition of *in-situ* generated aza-*p*-QMs. Notably, they also proposed a bifunnctional activation transition state for this reaction, in which the planar aza-*p*-QM intermediate was formed in an "*E*" form to react with the nucleophiles



Scheme 18. Asymmetric 1,8-addition of *in-situ* generated propargylic aza-*p*-QMs with thiazolones.



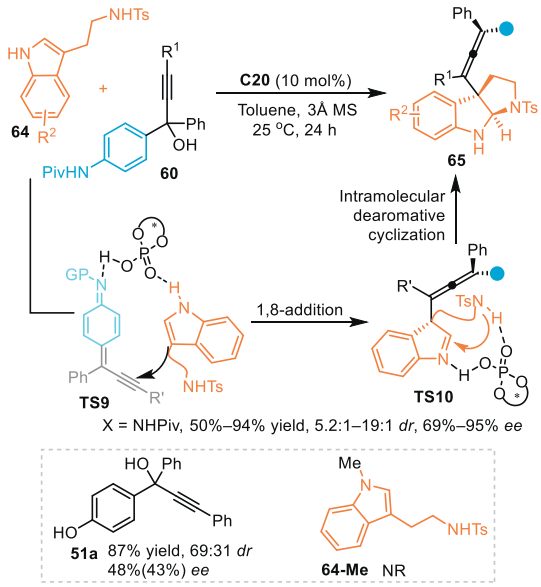
Scheme 19. Asymmetric 1,8-addition of *in-situ* generated propargylic aza-*p*-QMs with ketoesters.

in a closer route assisted by the H-bonding interaction compared with the "*Z*" form (Scheme 18, **TS7** *vs.* **TS8**) [61].

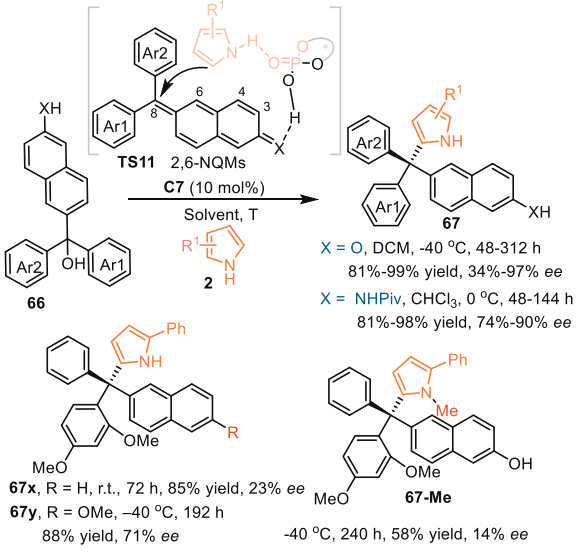
Almost simutaneously, Sun's group disclosed an asymmetric 1,8-addition of the aza-*p*-QMs with ketoesters **62** [61]. Under the catalysis of **C7**, propargylic alcohols **60** was dehydrated to form the aza-*p*-QMs, which was trapped by the nucleophile **62** to form 1,8-adducts in high yields with generally excellent diastereo- and enantioselectivities (Scheme 19).

In 2022, Shi's group described an asymmetric cascade 1,8-addition/dearomative cyclization process of propargylic alcohols **60** with tryptamines with the aid of **C20** [62]. The *in-situ* generated reactive aza-*p*-QMs was smoothly attacked by tryptamines **64** to form the allene intermediate with a dearomative indole imine motif, thus inducing the intramolecular Mannich-type cyclization process to form tetrasubstituted allenes **65** with vicinal contiguous carbon stereocenters with good to excellent stereoselectivities. Additionally, the *p*-hydroxylphenyl propargylic alcohol **51a** was also engaged in this reaction to give the desired product in high yield albeit with moderate stereocontrol. However, the *N*-Me protected tryptamine **64-Me** failed to participate in this reaction, which implied this reaction might proceed *via* a bifunctional activation mode through the interaction between the catalyst and the both two substrates (Scheme 20).

The 2-naphthol exhibited lower aromaticity but higher nucleophilicity compared with the simple phenol. Therefore, the 2-naphthol derived 6-(hydroxydiarylmethyl)naphthalen-2-ols **66O** might be served as a valid precursor for the generation of the 2,6-naphthoquinone methides (**2,6-NQMs**), thus allowing the remote 1,8-addition with nucleophiles. In 2023, Li and co-workers pioneered this strategy by utilizing 6-(hydroxydiarylmethyl)naphthalen-2-ols **66** in the reaction with pyrroles **2** under the catalysis of **C7**, affording a series of tetraarylmethanes **67** in high to excellent yields with high enantioselectivities [63]. Meanwhile, the 6-(hydroxydiphenylmethyl)naphthalen-2-amines 66 N, which served as the precursor of the aza-2,6-NQMs, were well compatible in this reaction, giving the desired products in good results. Notably, the reactivity of the tertiary alcohol dramatically decreased when the naphthol was replaced by the



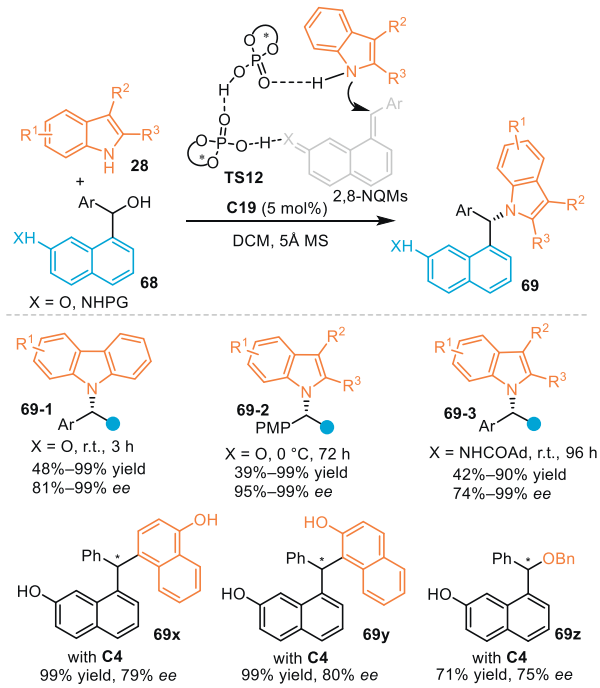
Scheme 20. Asymmetric tandem 1,8-addition and cyclization of *in-situ* generated propargylic aza-*p*-QMs with tryptamines.



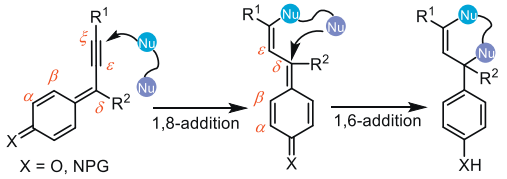
Scheme 21. CPA-catalyzed 1,8-addition of the *in-situ* generated 2,6-NQMs with pyrroles.

naphthalene group **66x** (no reaction under standard condition and inferior enantioinduction at room temprature). Moreover, the *O*-Me protected alcohol **66y** or the *N*-Me protected pyrrol resulted in lower enantioselectivity under the identical conditions. Such results indicated this reaction proceeded via the CPA's dual activation mode (**TS11**). Besides, the *ortho*-heterosubstituent (OMe, F) on one of the aryls was essential for the reactivity and enantio–control, because it not only stabilize the carbocation intermediate but also played as the hydrogen-acceptor for the pyrrole motif in the transition state (Scheme 21).

Almost simultaneously, Sun and co-workers discovered that 8-hydroxyarylmethyl adorned naphthols and corresponding napthylamines **68** performed as the precursor for the generation of (aza-)2,8-naphthoquinone methides **(2,8-NQMs)** in the presence of chiral phosphoric acid *via* the elimination process, thus inducing a formal asymmetric aza-1,6-addition with indoles or carbazoles **28** at benzylic position to access a variety of remotely functionalized chiral naphthols and napthylamines **69** with excellent enantioselectivities [64]. Besides, other nucleophilies such as α-naphthol, β-naphthol and benzylic alcohols were well compatible in this protocol under slightly modified conditions **(69x**, **69y** and **69z)**. Furthermore, the two phosphoric acids binded-transition states **TS12** were proposed based on the DFT calculations, that explained the excellent remote enantioselecvity and the observed nonlinear results between the product *ee* and catalyst *ee* (Scheme 22).



Scheme 22. CPA-catalyzed 1,6-addition of the *in-situ* generated 2,8-NQMs with pyrroles.

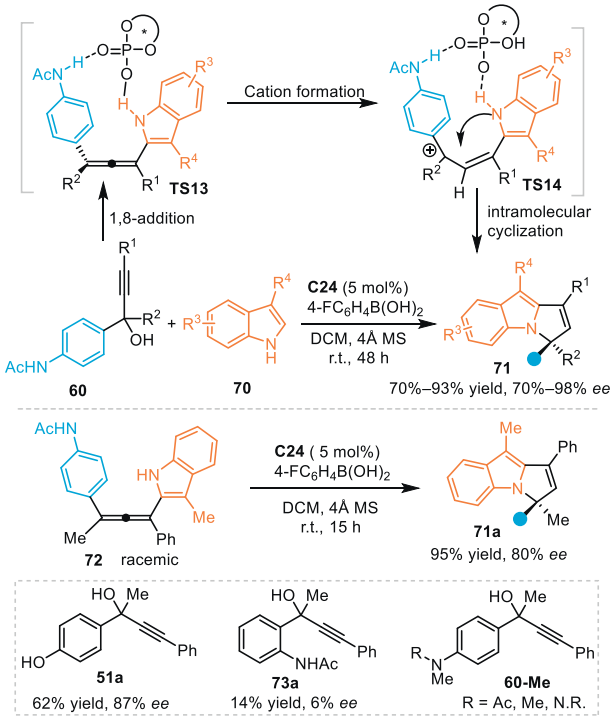


Scheme 23. Conjugate 1,8-addition initiate cyclizations of the *in-situ* generated propargylic (aza-)*p*-QMs.

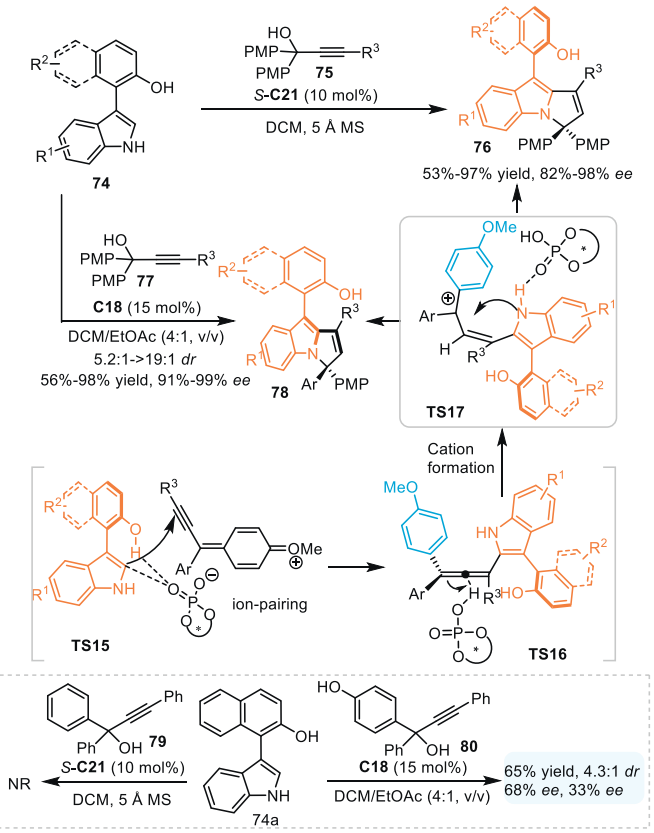
2.2.2. Tandem 1,8-addition/annulation to access structurally complex cyclic skeletons

Progargylic (aza-)*p*-QMs play as a reactive electron-deficient $\alpha,\beta,\gamma,\delta,\varepsilon,\zeta$-conjugated π-system, featuring multiple reactive electrophilic sites, thus leading rich synthetic versatility for this intermediate. Besides terminal ζ-position, the δ-position is another latent reactive electrophilic site in this reactive species. Therefore, the progargylic (aza-)*p*-QMs would serve as a biselectrophilic 3C synthon to proceed cascade [3 + n] annulations with dinucleophiles for the construction of polycyclic structures (Scheme 23).

In 2020, Li and co-workers realized the first example of asymmetric [3 + 2] cycloaddition of the *in-situ* generated progargylic aza-*p*-QMs with 3-substituted 1*H*-indoles **70** under CPA catalysis [65]. Catalyst **C22** promoted the dehydration of propargylic alcohols **60** and delivered extended aza-*p*-QMs, thus inducing the 1,8-addition to afford chiral allene intermediate (**TS13**). Subsequently, a hydrogen-bonding assisted protonation occurred to form the benzylic cation (**TS14**), which initiated the intramolecular cyclization process to give the chiral pyrrolo[1,2-*a*]indole skeleton **71**. Notably, the pre-synthesized racemic allene **72** was successfully engaged



Scheme 24. CPA-catalyzed [3 + 2] cycloaddition of the *in-situ* generated propargylic aza-*p*-QMs with indoles.



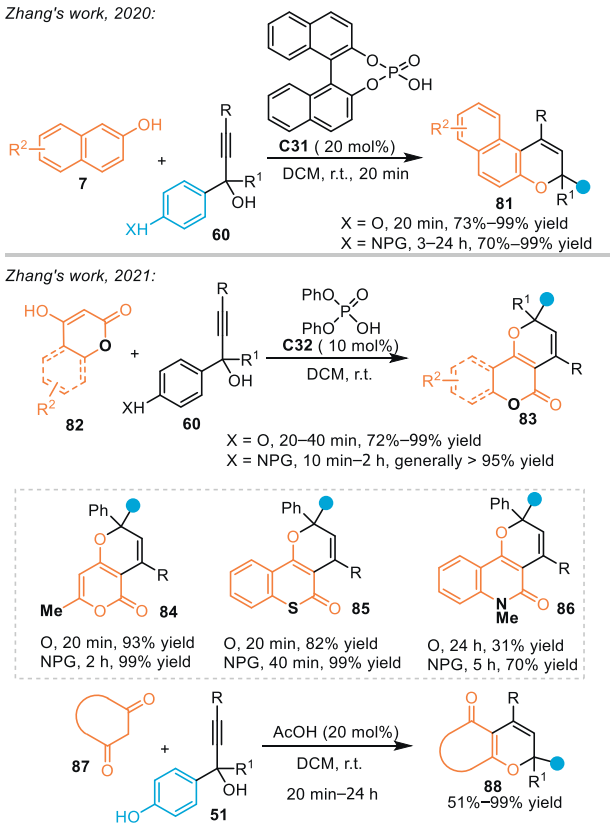
Scheme 25. CPA-catalyzed [3 + 2] cycloaddition of the *in-situ* generated propargylic aza-*p*-QMs with 3-arylindoles.

under the established conditions, giving the desired product **71a** in a comparable result. This result validated this reaction indeed proceeded *via* a cascade 1,8-addition/intramolecular cyclization process. Additionally, propargylic alcohol **51a** with a *p*–hydroxy phenyl substituent was feasible for this conversion to give a corresponding product in good result. However, the propargylic alcohol **73a** with the acetamido group at the *ortho*-position delivered the product in inferior conversion without enantioselectivity. The propargylic alcohols **60-Me** without an *NH*-free group were inactive in this protocol (Scheme 24). Almost simultaneously, Zhang and co-workers disclosed the racemic version of this reaction under the catalysis of camphorsulfonic acid [66].

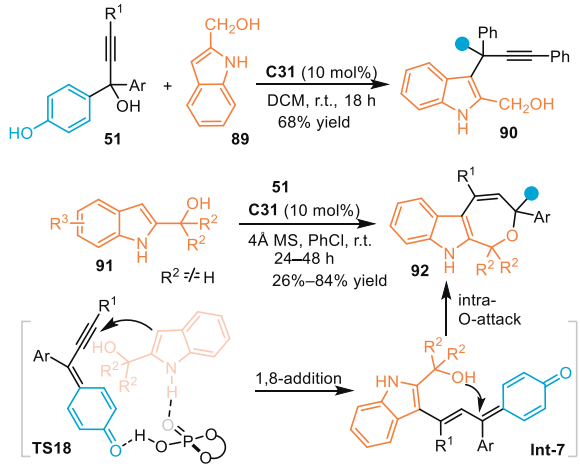
In 2023, Shi and coworkers extended this protocol by using the pro-axialchiral 3-arylindoles **74** in the reaction with propargylic alcohols **75**/**77** for the synthesis of axially chiral 3-arylindoles **76** including the ones **78** containing the chiral pyrrolo[1,2-*a*]indole motif with a central chiral center with excellent diastereo- and enantioselectivities [67]. Notably, the propargylic alcohol **79** without OMe group on the phenyl ring failed to participate in this reaction, implying this reaction proceeded *via* the formation of *p*-QMs other than the generation of the carbocation intermediate. Furthermore, the *p*-OMe substituted phenyl group of the propargylic alcohol was superior to the *p*-OH substituted one **80** with respect to the enantiocontrol, indicating the formation of *p*-QM cation species (**TS15**), which would form an ion-pairing interaction with the chiral phosphoric acid anion, was essential for the enantioinduction (Scheme 25).

The phenol and its derivatives, particularly the naphthol and the 4-hydroxycoumarin, demonstrated to be a versatile dinucleophilic 3C synthon for cascade [3 + n] annulations to access oxa-heterocycles [68–70]. As a result, Zhang and co-workers employed 2-naphthols **7** in the reaction with *in-situ* generated propargylic *p*-QMs for [3 + 3] annulations under the catalysis of **C31** in 2020 [71]. An array of functionalized naphthopyrans **81** were synthesized in execellent yields within 20 min. Meanwhile, *p*-aminophenyl propargylic alcohols were also tolerable in this reaction to afford corresponding adducts in good results within prolonged reaction time. In 2021, this group extended this strategy by using 4-hydroxycoumarins **82** or 1,3-dicarbonyl compounds **87** under the catalysis of **C32** [72]. On one hand, an array of 4-hydroxycoumarins **82** and its analogs, such as 4-hydroxythiocoumarin and 4-hydroxyquinolinone, were applicable in the reaction with *in-situ* generated (aza-)*p*-QMs, affording pyranocoumarins **83** in relatively low to high yields. On the other hand, cyclic 1,3-diketones **87** were also well tolerated in this reaction to afford various pyran products **88** in generally high yields (Scheme 26). Moreover, these valuable coumarin-containing heterocycles indeed exhibited significant α-glucosidase inhibitory activity in their initial bioactivity explorations.

2-Indolylmethanols were deemed as a kind of intrigued substance because of the changeable electron affinity at C3 position. The Shi's group has made significant achievements with this property to access structural diversified indole-based skeletons [37]. In principle, this substrate could be served as a dinucleophilic 4C synthon in respect to the nucleophilicity of C3 position and the hydroxyl group to undergo [4 + n] cycloadditions. Therefore, Zhang and co-workers employed the *in-situ* generated propargylic *p*-QMs to react with 2-indolylmethanols **91** for the [4 + 3] annulation in the presence of **C31** [73]. Interestingly, the 2-indolylmethanol **89** without a steric bulky group at benzylic site exclusively gave the 1,6-adduct **90** toward C3 position of the indolylmethanol. Probably, due to the small steric hindrance that would accommodate the formation of a triarylmethane unit. In contrast, 2-indolylmethanols **91** with steric diaryl groups at the benzylic site impelled the reaction proceeding *via* the 1,8-addition mediated [3 + 4] annulation process. A series of valuable polysubstituted indole-fused oxepines **92** were facilely obtained in high yields *via* this protocol (Scheme 27).



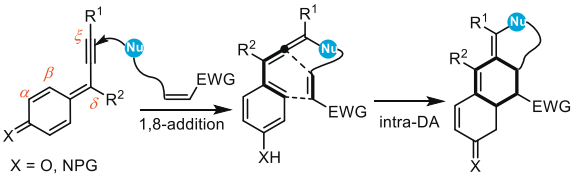
Scheme 26. Cascade [3 + 3] cycloaddition of the *in-situ* generated propargylic aza-*p*-QMs with phenols.



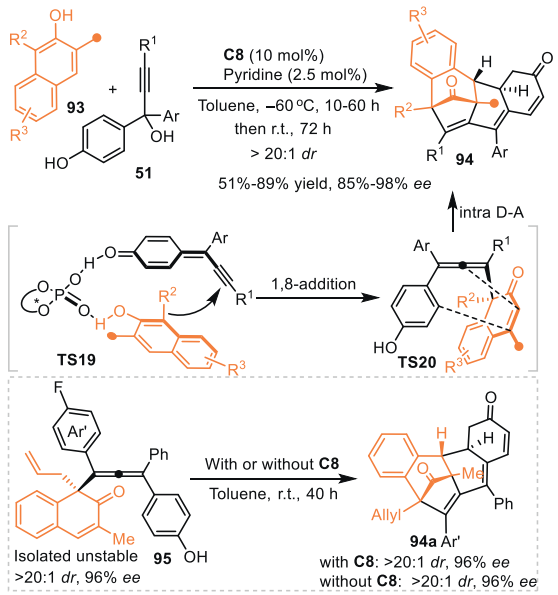
Scheme 27. Cascade [3 + 4] cycloaddition of the *in-situ* generated propargylic *p*-QMs with 2-indolylmethanols.

In view of the 4-hydroxystyrene motif in the allene species generated from the 1,8-addition of the progargylic (aza-)*p*-QMs, which would be served as an electron-rich diene for the Diels-Alder reaction with appropriate dienophiles to access ring-fused skeletons (Scheme 28).

Based on this consideration, Wang and co-workers employed propargylic alcohols **51** to react with 1,3-disubstituted 2-naphthols **93** [74], whose nucleophilicity has been confirmed in various catalytic dearomative reactions along with the generation of an unsaturated ketone fragment [75]. As expected, an asymmetric conjugate 1,8-addition mediated intramolecular Diels-Alder reaction occurred in the presence of **C8**, giving a variety of structurally com-



Scheme 28. The resulting-formed 4-hydroxystyrene motif inducing intramolecular Diels-Alder reaction.



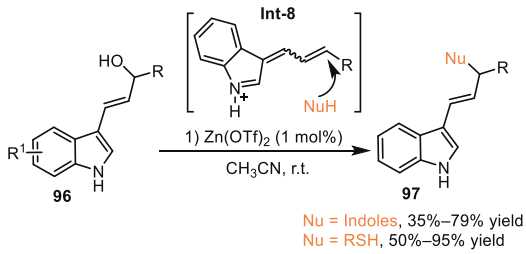
Scheme 29. Cascade 1,8-addition and intramolecular Diels–Alder reaction of the *in-situ* generated propargylic *p*-QMs with naphthols.

plex polycyclic skeletons **94** in good to excellent yields with remarkable stereoselectivities. Notably, the isolated allene intermediate **95** was determined in high enantioselectivity, which could smoothly deliver the Diels-Alder product **94a** in the absence of the chiral acid with comparable *ee* value. This result undoubtly expounded the stereocontrol of this cascade multiple dearomative process was determined by the first 1,8-addition process, the stereo-carbon center and axial chirality would induce an enantioselective Diels-Alder reaction. This protocol represented an elegant asymmetric approach *via* multiple dearomatization processes in two different aromatic molecules under mild conditions. That confirmed this strategy was an efficient route to obtain structurally complex polycyclic systems (Scheme 29).

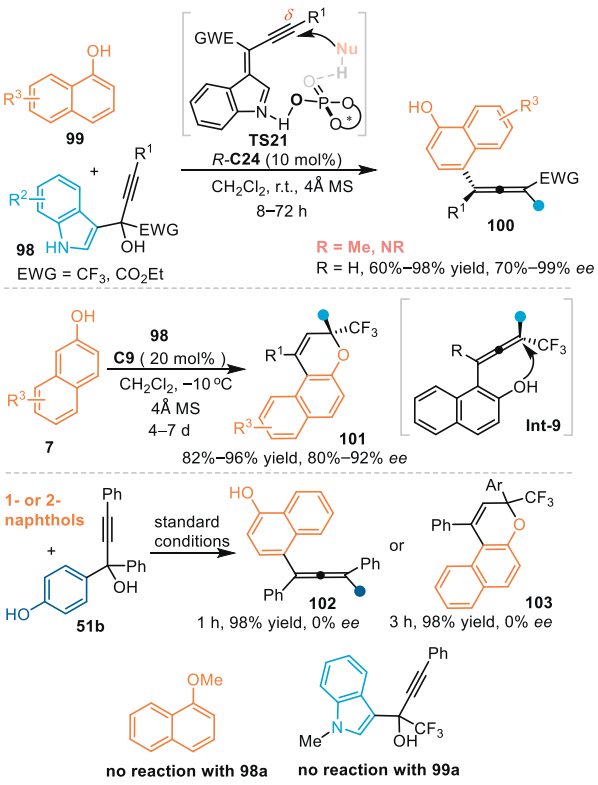
3. 1,6-Addition reactions of *in-situ* generated 3-IIMs

3-Indole imine methides (3-IIMs) emerged as energetic intermediates for the functionalization of indoles through the formal 1,4-addition process [33–36]. The 3-indolylmethanol and its derivatives were deemed as effective precursors to form 3-IIMs under acid or basic conditions *via* an elimination process. In 2017, Bernardi and co-workers extended this protocol to conjugate 1,6-addition by using indole-based allylic alcohol 96 *via* the generation of vinylogous indole imine methides Int-8 under Lewis acid catalysis, that extended the synthetic potential of the 3-IIMs (Scheme 30) [76].

In 2020, Lu's group employed α-indolyl-α-trifluoromethyl propargylic alcohols **98** as the precursor of propargylic-IIMs under acid conditions [77]. Under the catalysis of *R*-**C24**, the alkynylogous 3-IIMs was generated (**TS21**), which was attacked by 1-naphthols **99** in a stereoselective manner at δ-position, thus producing tetra-



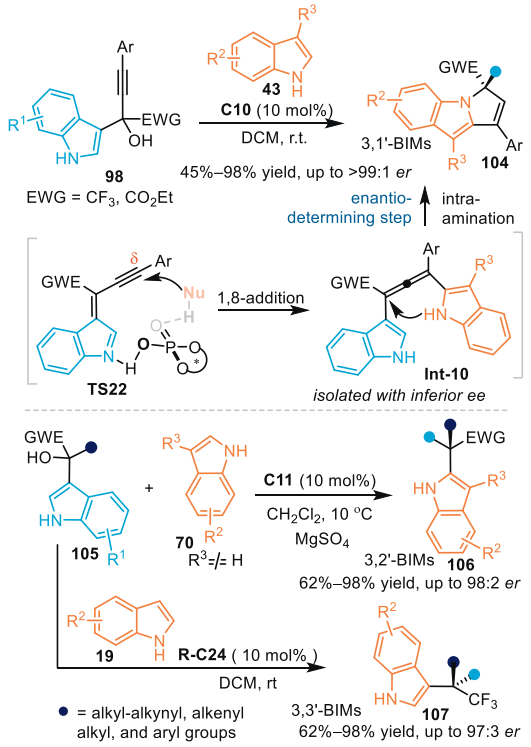
Scheme 30. The conjugate 1,6-addition of *in-situ* generated vinyl 3-IIMs.



Scheme 31. The conjugate 1,6-addition and the following cyclization of the *in-situ* generated 3-IIMs with naphthols.

substituted chiral allenes **100** with wide substrate scope in high yields and enantioselectivities. However, 2-naphthols **7** failed to give the tetrasubstituted allene [78] under the identical condition, but producing the valuable chiral naphthopyran **101** by a subsequent *O*-nucleophilic cyclization process of the allene species **Int-9** in good results under modified conditions. It was noteworthy that *p*-hydroxybenzyl derived propargylic alcohols **51b** smoothly delivered the chiral allene **102** or naphthopyran **103** with naphthols *via* the *in-situ* formation of propargylic *p*-QMs under standard conditions, albeit without enantio–control. The OMe-protected naphthol or *N*-Me-protected propargylic alcohols failed to participate in this reaction, which indicated this reaction probably proceeded in a dual-activation mode (Scheme 31).

In 2022, the Lu's group employed 3-indolyl propargylic alcohols for the convergent synthesis of chiral 3,n'-bis(indolyl)methanes (3,n'-BIMs) under CPA catalysis [79]. When propargylic alcohols **98** bearing phenylethynyl group were used in the reaction with 3-substituted indoles **43** in the presence of **C10**, a conjugate 1,6-addition initiated cyclization occurred smoothly to afford the chiral cyclic 3,1′-BIMs **104** featuring quaternary stereogenic centers in moderate to excellent yields with generally remarkable enantiomeric excesses. Notably, the allene intermediate **Int-10** was



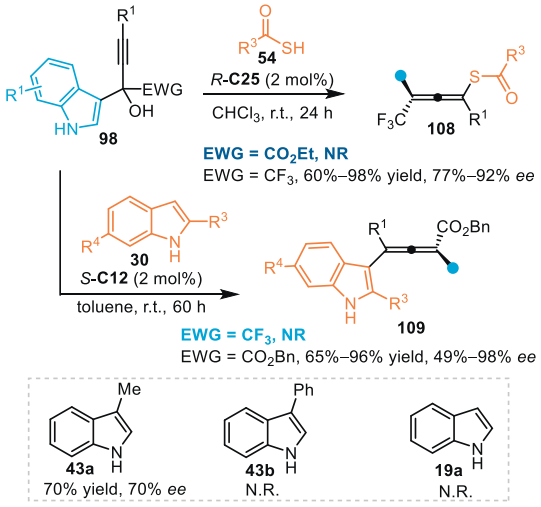
Scheme 32. The convergent asymmetric synthesis of the 3,n'-BIMs *via* the conjugate additions of the *in-situ* generated 3-IIMs.

observed and isolated with inferior enantioselectivity, that indicated this reaction probably proceeded *via* a cascade 1,6-addition and intramolecular hydroamination process. Moreover, the excellent enantio–control for this reaction was determined by the intramolecular cyclization step *via* a dynamic kinetic resolution process. Interestingly, other type of 3-indolyl propargylic alcohols **105** with different substituent, such as the alkyl-alkynyl, alkenyl, alkyl, and aryl groups, performed an asymmetric 1,4-type addition under modified conditions. A wide range of 3,3′-BIMs **107** and 3,2′-BIMs **106** were obtained in good results by using relevant indoles **19** and 3-substituted indoles **70**, respectively (Scheme 32). Furthermore, these obtained products exhibited promising antibacterial activity.

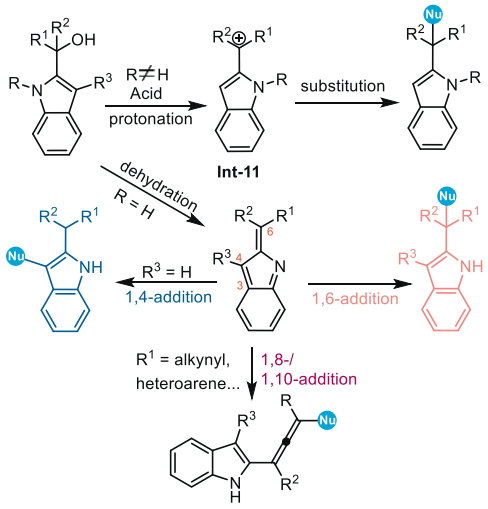
In 2021, Li and co-workers adopted thiolacetic acids **54** as nucleophiles to perform the asymmetric 1,6-addition with α-indolyl-α-trifluoromethyl propargylic alcohols **98** under CPA catalysis [80]. A wide range of axially chiral sulfur-containing tetrasubstituted allenes **108** were obtained in high yields and enantioselectivities. However, α-(3-indolyl)propargylic alcohol with α-ester group was not tolerable in this protocol. Subsequently, this group discovered that 2-substituted indoles **30** were feasible in this conjugate 1,6-addition under modified conditions, furnishing the tetrasubstituted chiral allenes **109** in generally high yields with moderate to excellent enantioselectivities [81]. Besides, 3-Me-indole **43a** was compatible in this reaction, giving the desired product in 70% yield with 70% *ee*. However, 3-Me-indole **43b** and indole **19a** failed to participate in this protocol (Scheme 33).

4. Remote conjugate addition involved reactions of *in-situ* generated 2-IIMs

Pioneered by the work of Martin [82] and Han [83,84], 2-indolylmethanols emerged as another powerful reactants to achieve structurally diversified indole derivatives *via* the acid-promoted dehydration nucleophilic functionalizations [37,38]. Mechanistically, *N*-protected 2-indolylmethanols, the hydroxyl



Scheme 33. The asymmetric 1,6-addition of the *in-situ* generated propargylic 3-IIMs with thioacetic acids and indoles.

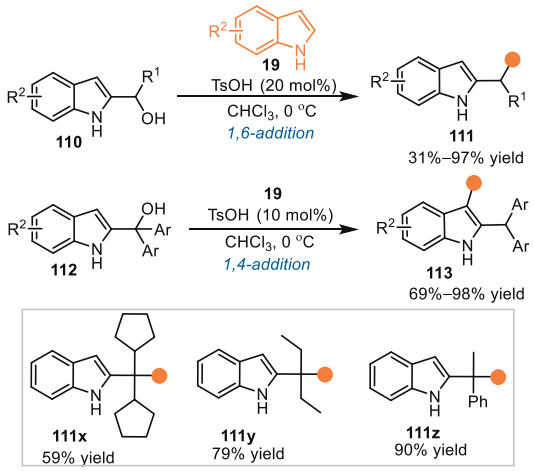


Scheme 34. The conjugate addition of *in-situ* generated 2-IIMs from 2-indolylmethanols.

group is readily protonated to give benzylic carbocation intermediate **Int-11**, thus allowing formal nucleophilic substitutions rather than nucleophilic conjugate additions. In contrast, the NH-free 2-indolylmethanols prefer to give the 2-indole imine methides (2-IIMs) *via* the dehydration process under acid conditions, that enabling nucleophilic conjugate additions at benzylic position (formal 1,6-addition). It is noteworthy that an umpolung reaction would be induced at C3 position (formal 1,4-addition) of the 2-IIMs, that provides a novel approach for the nucleophilic functionalization of indoles. In this context, the Shi's group has made significant developments, achieving a variety of umpolung C3-functionalizations and that initiating cascade cyclizations under Brønsted acid conditions [85–89]. For the theme of this review, we will discuss the transformations at the benzylic site *via* the conjugate 1,6-addition and that initiated cascade cyclizations. Intriguingly, the extended 2-IIMs with the alkynyl-group and even the hetero-arene would result in challenging 1,8- and 1,10-additions (Scheme 34).

4.1. Mono-step 1,6-/1,8-/1,10-addition of the 2-IIMs

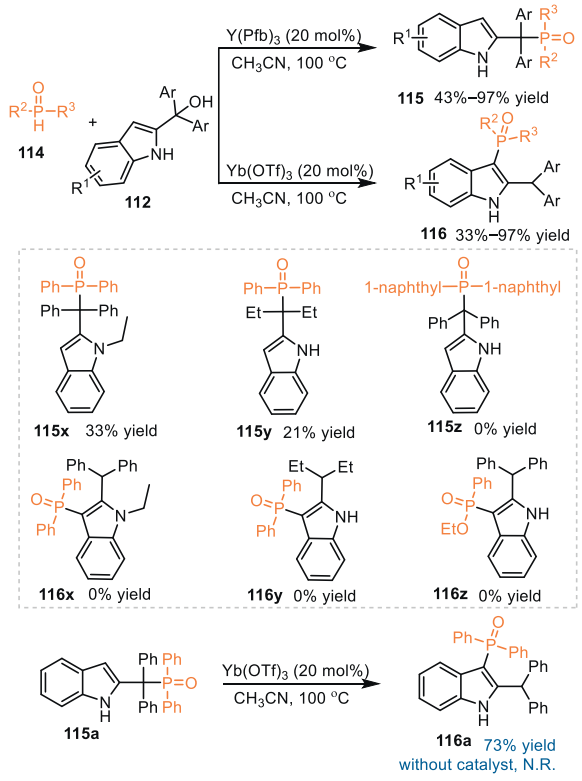
Generally, C3-unsubstituted 2-indolylmethanols would be transformed to 2-IIMs with two electrophilic sites under acidic conditions, including C3 and benzylic sites. Therefore, it is a challenging task to achieve an elegant regioselective nucleophilic addition with this type of 2-indolylmethanols. In 2017, Shi and co-workers discovered a substrate-controlled regioselective nucleophilic arylations of 2-indolylmethanols **110/112** with indoles **19** under acidic conditions [90]. The 2-indolylmethanol **110** bearing a phenyl group proceeded the 1,6-addition at benzylic position with indoles **19** in the presence of catalytic amount of TsOH, a series of bis(indolyl)methane **111** were produced in moderate to excellent yields. Interestingly, the 2-indolylmethanol **112** containing two aryls at the benzylic site, thus increasing the steric repulsion and compelling the nucleophilic addition at the C3-position. A wide range of 3,3′-bisindole derivatives **113** were smoothly obtained in high yields *via* this pathway. However, the tertiary alcohol also reacted with indoles at benzylic site to give **111x-111z** in good yields, implying the existence of the two aryl groups was essential for the umpolung pathway (Scheme 35).



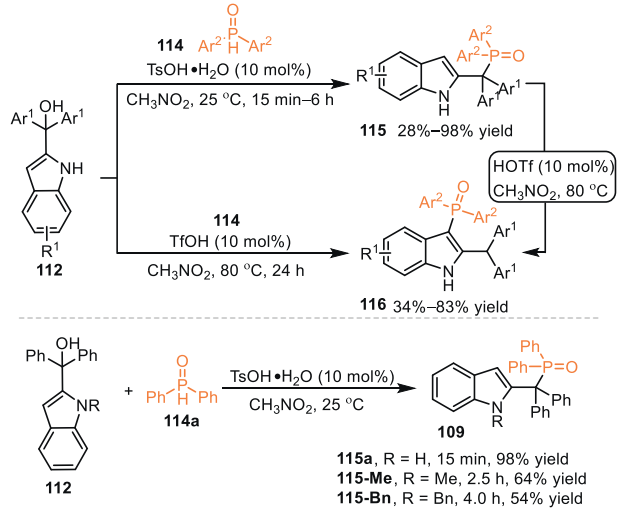
Scheme 35. Substrate-controlled regioselective arylations of 2-indolylmethanols.

The diphenylphosphine oxide performs as an effective nucleophilic phosphorylation reagent for the synthesis of phosphine reagents. As a result, the utilization of diphenylphosphine oxides in the reaction with 2-indolylmethanols under acid catalysis might result in the formation of structural diversified indole-based phosphines. In 2018, Wang and co-workers discovered a switchable conversion of 2-indolylmethanols **112** with diphenylphosphine oxides **114** by the utilization of different Lewis acids [91]. Under the catalysis of $Y(Pfb)_3$, the benzylic phosphorylated products **115** were produced in moderate to excellent yields. In contrast, the $Yb(OTf)_3$, which features stronger acidity, promoted C3-functionalized products **116** *via* the 1,4-addition pathway, giving a plenty of valuable triphenyl phosphine oxides in moderate to high yields. The control experiment of **115a** with the treatment of $Yb(OTf)_3$ under 100 °C smoothly gave rise to the C3-functionalized products **116a**, that indicated the C3-phosphorylated product was a thermodynamic product and the benzylic product probably was an intermediate during the formation of the C3-phosphorylation process. Meanwhile, the treatment of **115a** at 100 °C in the absence of $Yb(OTf)_3$ delivered no desired product, indicating this rearrangement was not a thermal stimulation process (Scheme 36).

Almost simultaneously, Chen and co-workers discovered a Brønsted acid promoted regio-divergent phosphorylation of the 2-indolylmethanol **112** with diarylphosphine oxides **114** [92]. With the aid of TsOH, the benzylic phosphorylated product **115** was produced in good yields within 15 min to 6 h at ambient temperature. When the reaction was subjected to stronger acid TfOH at higher temperature, the C3-phosphorylation occurred to give indole-based



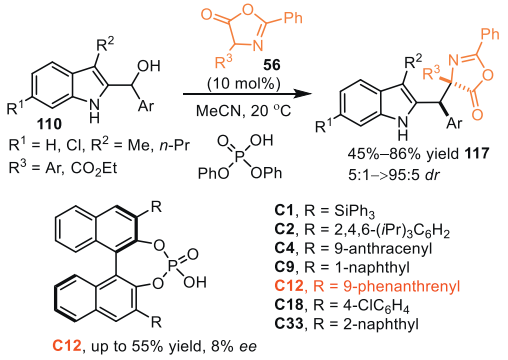
Scheme 36. Lewis acid-controlled regioselective phosphorylation of 2-indolylmethanols.



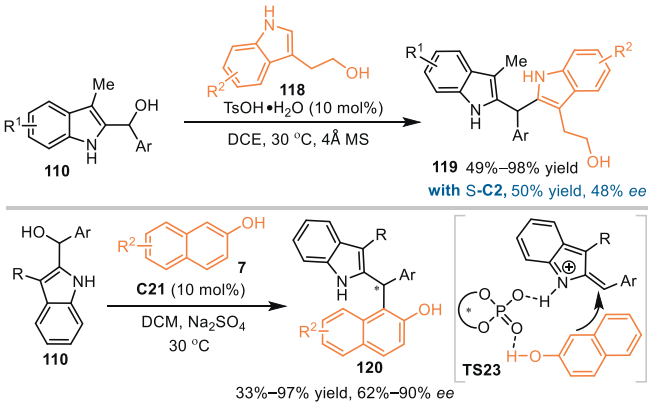
Scheme 37. Brønsted acid-catalyzed regiodivergent phosphorylation of 2-indolylmethanols.

triarylphosphine oxides **116** in moderate to good yields. Consistent with Wang's findings, the control experiment in Chen's work also indicated the C3-phosphorylated product was dominantly derived from the benzylic-functionalized *via* a [1,3]-P migration process under a slightly harsh condition. Notably, the *N*-alkylated alcohol has lower reactivity in the reaction with the diphenylphosphine oxide, giving the benzylic phosphorylated products **115-Me/115-Bn** in moderate yields after prolonged reaction time (Scheme 37).

The 2-indolylmethanol was substituted at C3-position was a direct route to exclude C3-functionalization, thus allowing the 1,6-addition and its successive *N*-cascade process. In 2017, Shi and co-workers utilized azlactones **56** as nucleophiles to react with the



Scheme 38. Brønsted acid-catalyzed benzylic functionalization of 2-indolylmethanols with azlactones.

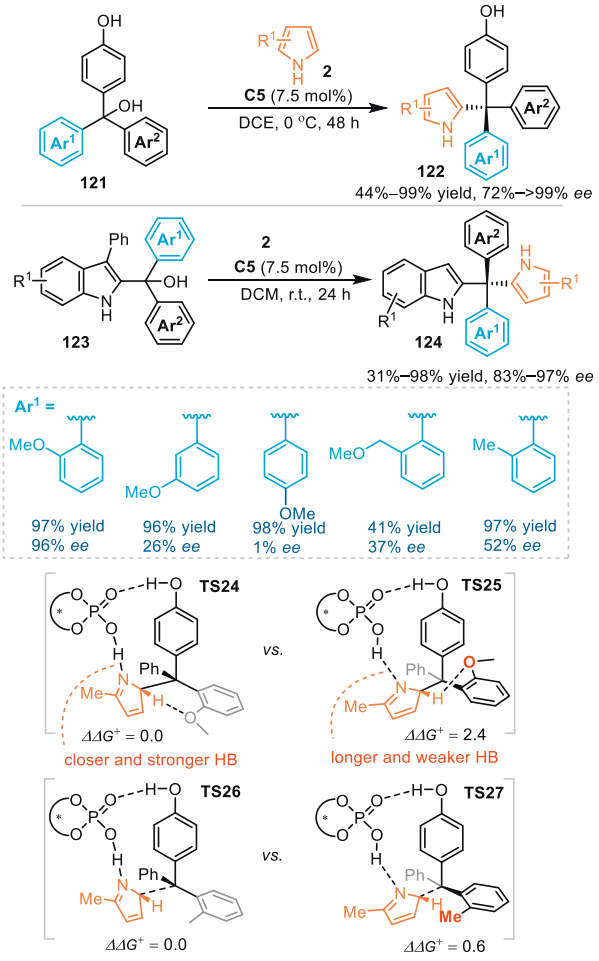


Scheme 39. The CPA-catalyzed asymmetric benzylic arylations of 2-indolylmethanols.

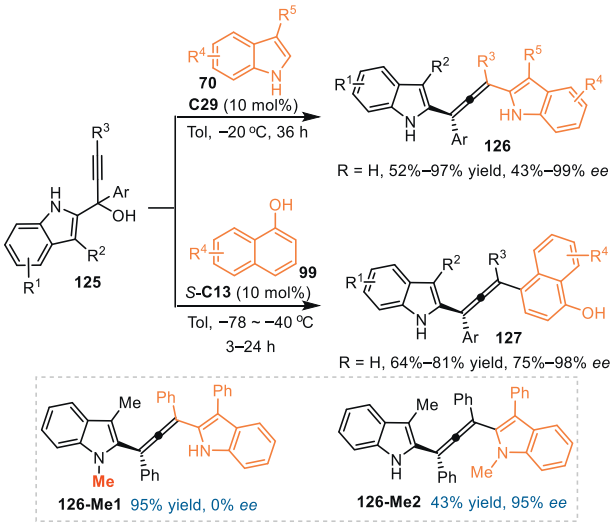
in-situ generated C3-blocked 2-IIMs [93]. The acid-promoted dehydration of 2-indolylmethanols **110** gave rise to the formation of 2-IIMs, which was trapped by the azlactones to exclusively give the 1,6-adducts **117** in good yields and diastereoselectivities. Moreover, a series of CPA were explored in this protocol to fulfill its enantioselective pattern, though no positive results was observed (Scheme 38).

In 2020, the Shi's group developed a benzylic-functionalization of 2-indolylmethanols **110** with tryptophols **118** under the catalysis of TsOH, the 2,2′-bisindolylmethane framework **119** was observed in generally high yields [94]. Furthermore, after an extensive investigation of the CPAs and other parameters, such as solvents, molecular sieves and temperatures, this reaction was realized in up to 50% yield with 48% *ee*. Subsequently, the Shi's group developed a CPA-catalyzed asymmetric benzylic substitution of the 2-indolylmetanol **110** with 2-naphthols **7**. The acid-promoted dehydration delivered the 2-IIMs, thus inducing the following enantioselective nucleophilic attack with the dual aid of the **C21**. A collection of chiral triarylmethane derivatives **120** were produced in moderate to high yields with promising enantioselectivities (Scheme 39).

The conjugate 1,6-addition of indolylmethanols and hydroxybenzyl alcohols with nucleophiles emerged as an efficient approach for the synthesis of various multi-aryl substituted methanes. Especially, that might provide a facile approach to access desirable tetra-arylmethane derivatives, which belong to a class of spherical molecule and is of great significance in drug discovery and functional materials [95–97]. Nevertheless, the enantioselective synthesis of tetra-aryl substituted methanes still remains elusive due to the overwhelming steric repulsion and enantiodifferentiation encountered during the stereo-center formation stage. In 2020, Sun



Scheme 40. Asymmetric synthesis of chiral tetra-arylmethanes with *in-situ* generated *p*-QMs and 2-IIMs.

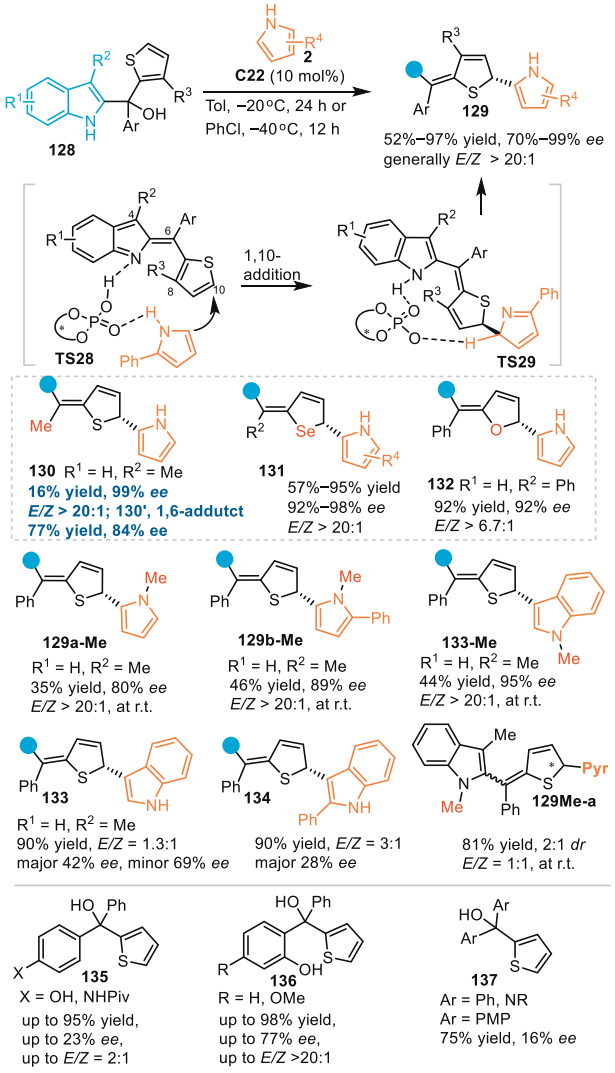


Scheme 41. Asymmetric 1,8-addition of *in-situ* generated propargylic 2-IIMs with indoles and 1-naphthols.

and co-workers developed a stereoconvergent synthesis of pyrrole-based tetra-aryl methane derivatives **122** by the conjugate addition of pyrroles **2** to the *in-situ* generated *p*-QMs or 2-IIMs under the CPA catalysis [98]. Interestingly, the *ortho*-alkoxyl group substituted-aryl contained alcohols delivered generally excellent stereocontrol in the conjugate addition. However, the *ortho*-alkyl or *meta*-/*para*-OMe substituted ones resulted in inferior results. Based on the proposed transition states **TS24** and **TS25**, the *o*-OMe or other heteroatom groups would form a stable hydrogen bond with the pyrrole motif. However, for the minor **TS25**, the methoxy group was impelled to orientate towards the cyclohexyl groups of the catalyst, leading to a longer and weaker hydrogen bond between the catalyst and the pyrrole nitrogen. Therefore, the energy of **TS25** was higher than the **TS24** (2.4 kcal/mol), that enforced the addition step *via* the **TS24** in an excellent enantiosetive mode. However, the *ortho*-methyl substituted one has no hydrogen bond interaction with the pyrrole motif (**TS26** and **TS27**), thus made the methyl group rotates away from the cyclohexyl substituents to lower the energy. As a result, the energy of the **TS27** is only 0.6 kcal/mol higher than the **TS26**, leading to a low differentiation and low enantioselectivity. With this strategy, *p*-hydroxybenzyl alcohols **121** and 2-indolymethanols **123** were well tolerated to provide two libraries of structurally distinct chiral tetra-aryl substituted methanes in remarkable yields with high enantioselectivities (Scheme 40).

Based on the vinylogy principle, the propargylic 2-IIMs would transmit the electrophilic site to some remote site, thus achieving 1,8- and even 1,10-addition. In 2020, Sun and co-workers developed a CPA-promoted asymmetric 1,8-addition of propargylic 2-indolylmethanols **125** with 3-substituted indoles **70**, providing a number of multi-functionalized tetrasubstituted allenes **126** in excellent yields with high enantioselectivities [99]. Besides indoles, 1-naphthols **99** were well compatible in this protocol. Notably, the *N*-Me protected **125a-Me** smoothly gave the desired product **126-Me1** but without enantiocontrol. The *N*-Me protected 3-phenyl indole was well tolerant in this protocol to give the product **126-Me2** in good result. Such results implied the hydrogen-bonding interaction between the 2-IIMs and the catalyst was crucial for the excellent stereoinduction (Scheme 41).

Besides the alkynyl group, the heteroaryl also played as an excellent π-system for the transfer of the HOMO or LUMO effect, thus affording remote functionalizations on the heteroarene [100–103]. In 2021, Sun and co-workers employed the benzylic thiophene contained 2-indolyl methanol **128** in the reaction with pyrroles **2** under the catalysis of **C22** [104]. Under the catalysis of the **C22**, 2-indolylmethanols **128** were dehydrated to form 2-IIMs with a conjugated thiophene motif, thus lowering the LUMO of the thiophene and inducing an asymmetric nucleophilic dearomative 1,10-addition with pyrroles **2** by the CPA's dual activation. A series of densely functionalized dearomatized thiophenes **129** were obtained in excellent yields with high enantioselectivities and *E*/*Z* selectivities. Notably, the methyl-substituted alcohol gave the 1,6-adduct triarylethane **130′** as a major product in 77% yield with 84% *ee*, that was ascribed to the lower steric hindrance at the benzylic position. As a result, the 1,10-adduct **130** was obtained in 16% yield with excellent enantioselectivity and *E*/*Z* selectivity. Additionally, the furan and selenophene were successfully compatible in the extended 2-IIMs, giving the dearomatized products **131** and **132** in comparable results. On the other hand, *N*-methyl protected indole and pyrroles were workable in this protocol, offering the desired products **(129a-Me**, **129b-Me** and **133-Me)** in moderate yields with excellent enantioselectivities and *E*/*Z* selectivities. However, the NH-free indoles produced the desired products **133** with inferior stereoselectivity albeit in high yield. The *N*-methyl indole-based alcohol delivered the product **129Me-a** with a rotation-hindered axis, thus resulting an additional challenge for the stereocontrol in a single process. Besides, the QM-conjugated thiophenes, including the *p*-QMs, aza-*p*-QMs, and *o*-QMs conjugated ones **(135–137)**, smoothly proceeded the additions but with inferior enantioselectivities and *E*/*Z*-control (Scheme 42).

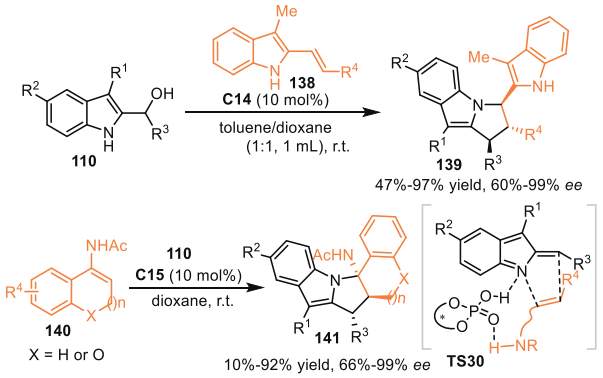


Scheme 42. Asymmetric dearomatization of thiophenes by 1,10- addition of *in-situ* generated indole imine methides.

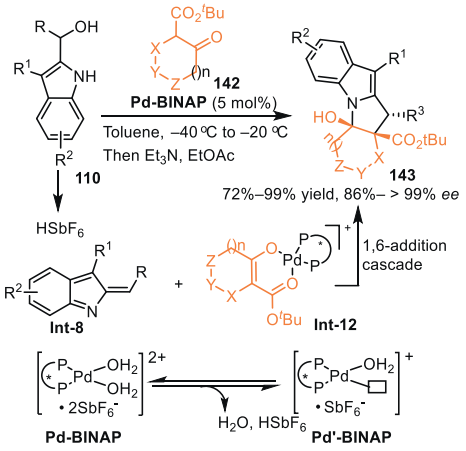
4.2. Cascade 1,6-addition and cyclization of the 2-IIMs

Alternatively, C3-substituted indolylmethanols would perfom as C,N-dipolar surrogates in the presence of Brønsted acid, thus initiating the cascade [3 + n] annulations with nucleophiles to afford indole-based heterocycles. In 2016, Schneider and co-workers developed a CPA-catalyzed asymmetric [3 + 2] cycloaddition of the indolylmethanol **110** with 2-vinylindoles **138** [105]. The *in-situ* generated 3-substituted 2-IIMs and 2-vinylindoles were then binded by the double hydrogen bonding of the CPA to forge ensusing enantioselective [3 + 2] cycloaddition. A wide range of pyrrolo[1,2-*a*]indoles **139** with three continuous stereogenic centers were produced as a single diastereoisomer in excellent yields and enantioselectivities. Subsequently, this group adopted cyclic enamides **140** as the nucleophilic 2C synthon in the reaction with 2-indolylmethanols to perform [3 + 2] cycloaddition in the presence of **C15**, generating the indolo[1,2-*a*]indoles **141** in good results (Scheme 43) [106].

In 2020, Schneider and co-workers developed an enantioselective [3 + 2] cycloaddition of the 2-indolylmethanol **110** with *β*-keto esters **142** by employing chiral Pd-aqua complex in a cooperative catalysis [107]. The Pd-aqua complex performed as a Brønsted acid/base system by the equilibrium between Pd-catalyst



Scheme 43. CPA-catalyzed asymmetric [3 + 2] cycloaddition of the 2-indolylmethanols.

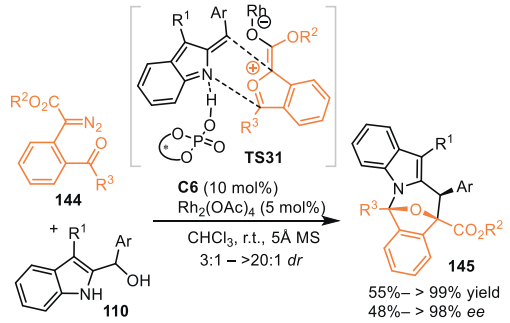


Scheme 44. Palladium-catalyzed asymmetric [3 + 2] cycloaddition of 2-indolylmethanols with *β*-keto esters.

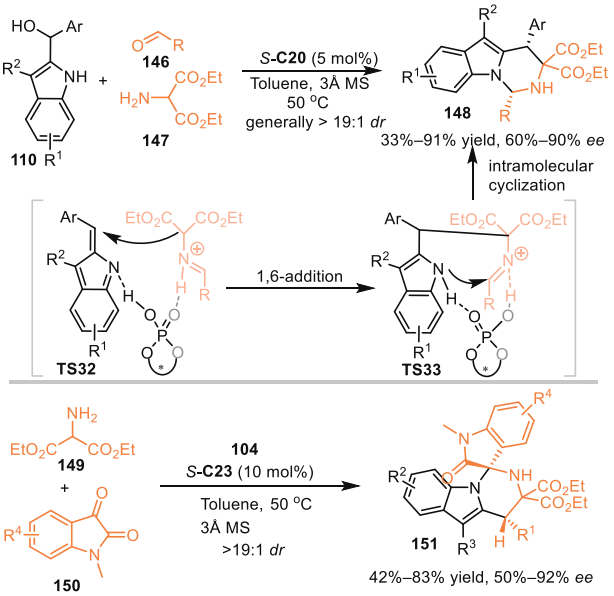
A and Pd−OH-complex B. The Brønsted basic complex B deprotonated the keto-ester to form the chiral Pd-enolate **Int-12**, and the concomitantly released $HSbF_6$ facilitated dehydration to form the 2-IIMs, thus inducing the enantioselective cascade conjugate 1,6-addition and *N*-cyclization to provide enantio–enriched pyrrolo[1,2-*a*]indoles **143** in excellent yields and stereoselectivities (Scheme 44).

Carbonyl ylides, which were *in-situ* generated by the insertion of the metal-carbene into carbonyl group, performed as highly reactive 1,3-dipolar surrogates to undergo various cycloaddition including the enantioselective conversions [108,109]. In 2021, Schneider's group extended the 2-IIMs to perform [3 + 3] cycloadditions with transient carbonyl ylides enabled by the cooperative catalysis of $Rh_2(OAc)_4$ and chiral phosphoric acid **C6** [110]. The Rh-enabled the formation of Rh-carbene intermediate, that was trapped by the carbonyl group to form the reactive carbonyl ylide (**TS31**). Subsequently, the *in-situ* generated hydrogen-bonded 2-IIMs by the CPA was involved in the reaction with the above-resulted carbonyl ylide species *via* a cascade [3 + 3] cycloannulation process in an enantioselective pathway (**TS31**), delivering oxa-bridged azepino[1,2-*a*]indoles **145** in excellent yields with moderate to high diastereo- and enantioselectivities (Scheme 45).

Azomethine ylides served as versatile 1,3-dipolars in a variety of [3 + n] cycloadditions to prepare densely functionalized heterocycles [111–113]. In 2017, Shi's group employed this reactive species to react with the *in-situ* generated 3-substituted 2-IIMs to fulfill a 1,6-addition induced cascade [3 + 3] cycloaddition [114]. Under the catalysis of *S*-**C20**, the azomethine ylide was formed *via* the condensation of benzaldehydes **146** and amino-esters **147**, then



Scheme 45. Asymmetric [3 + 3] cycloaddition of the 2-indolylmethanol with carbonyl ylides.



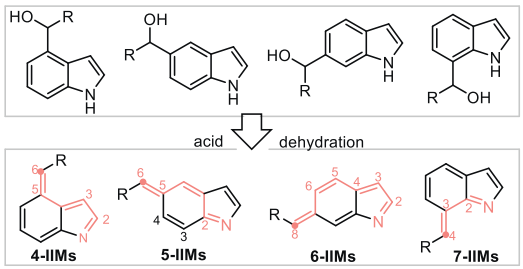
Scheme 46. Asymmetric [3 + 3] cycloaddition of the 2-indolylmethanol with azomethine ylides.

resulted in the cascade 1,6-addition to the *in-situ* generated 2-IIMs and intramolecular cyclization with the aid of double hydrogen bonding interactions of the CPA. As a result, a collection of tetrahydropyrimido[1,6-*a*]indole skeletons **148** were obtained in moderate to good yields, as well as the stereoselectivities. Besides, the isatin-derived azomethine was demonstrated to be workable in this protocol, giving the spirooxindoles **151** in considerable yields with moderate to good enantioselectivities and excellent diastereoselectivities (Scheme 46) [115].

5. Remote conjugate addition involved reactions of other *in-situ* generated IIMs

Theoretically, besides 2-/3-indolylmethanols, other type of indolylmethanols with methylol group at C4, C5, C6, or C7 position would result in corresponding 4-, 5-, 6-, 7-IIMs *via* the acid-promoted dehydration process, thus allowing corresponding remote activation for the convergent synthesis of functionalized indole-backbones (Scheme 47).

In 2018, Antilla and co-workers pioneered an elegant remote addition with 6- and 7-indolylmethanols **157/152** under the catalysis of CPA [39]. On one hand, the 7-indolylmethanol **152** was dehydrated smoothly to give 7-IIMs, that was smoothly attacked by indoles **30** or pyrroles **2** *via* the formal 1,4-addition with the aid of hydrogen bonding interaction of the CPA. Interestingly, *N*-Me protected indolylmethanol worked well in the reaction with the NH-



Scheme 47. The generation of abnormal 4-/5-/6-/7-IIMs from corresponding indolylmethanols.

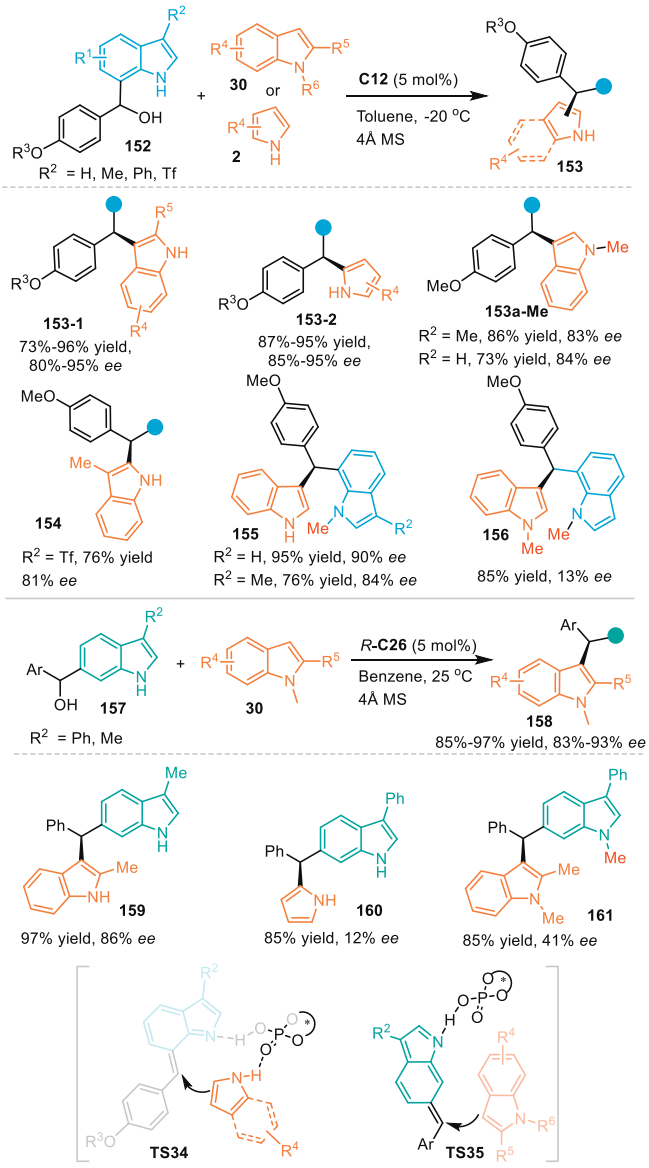
free indole, delivering the chiral triarylmethanes **155** in good yields with high enantioselectivities. However, the *N*-Me protected indole gave the product **156** with 13% *ee* in the reaction with the *N*-Me protected indolylmethanol. These results implied that a formal SN1 substitution was compatible in this catalytic system. On the other hand, they also explored the reactivity of 6-indolylmethanols **157** under the catalysis of CPA. Mechanistically, the acid-promoted dehydration of the 6-indolylmethanol gave rise to the 6-IIMs, that induced the conjugate 1,8-addition with indoles to afford the desired triarylmethanes **158** in excellent outcomes. Notably, the *N*-Me protected indolylmethanol failed to give the product **161** with good enantiocontrol, that implied the formation of 6-IIMs was crucial for the stereoinduction. This protocol provides a convergent pathway for the functionalization of the indole (Scheme 48).

In 2020, Li and co-workers extended the conjugate 1,8-addition of the *in-situ* generated 6-IIMs with heteroatom nucleophiles [116]. By employing 6-indolylmethanols **157** as the precursor of 6-IIMs in the presence of *R*-**C28**, benzotriazoles **162** were successfully trapped to perform the asymmetric conjugate 1,8-addition, delivering the N2-selective alkylation products **163** in good yields and enantioselectivities. Additionally, sulfur nucleophiles **54** including thioacetic and thiobenzoic acids were applicable in this protocol under the slightly modified condition, giving the desired product **164** in satisfactory results. Control experiments with the *N*-Me protected indolylmethanol exhibited dramatically decreased reactivity and enantioselectivity under the standard conditions, that implied this reaction proceeded *via* the generation of the 6-IIMs and the enantio–control relied on the double activation of CPA (Scheme 49).

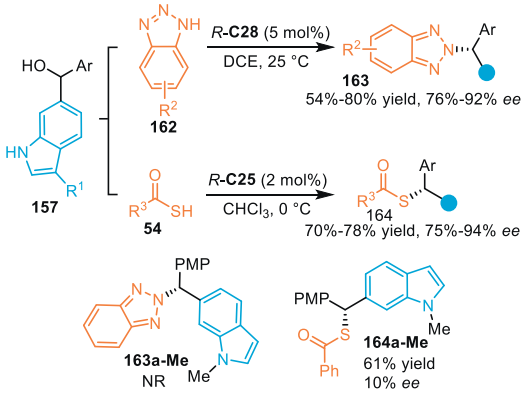
Based on the vinylogy principle, propargylic 6-IIMs was practicable in the conjugate 1,10-addition for the construction of indole-based tetrasubstituted allenes. In 2022, the Li's group employed the propargylic 6-indolylmethanols **165** as the precursor of the extended 6-IIMs under the catalysis of CPA, which was subjected to the nucleophilic thiazolones **58** *via* the desired 1,10-addition process [117]. A wide variety of chiral tetrasubstituted allenes **166** bearing a quaternary stereocenter were obtained in moderate to good yields with high enantioselectivities and diastereselectivities. Subsequently, they discovered that indoles **30** were also feasible in this protocol under CPA catalysis, giving the desired products **167** in high yields and enantioselectivities (Scheme 50) [118].

In 2022, Li and co-workers extended this 1,8-addition of *in-situ* generated 6-IIMs in the reaction with the isoxazol-5(4*H*)-ones **170** under the catalysis of **C24** [119]. A *N*-selective stereoselective 1,8-addition was achieved, giving the target chiral indoles **171** in good yields with moderate to excellent *ee* values. Moreover, the *N*-Me protected indolylmethanol delivered the product without enantioselectivity, indicating the formation of the 6-IIMs was pivotal for the remote enantiocontrol (Scheme 51).

Generally, 7-indolylmethanols performed as the precursor of 7-IIMs *via* an elimination of a water under acid conditions, which played as a Michael acceptor to afford formal 1,4-additions [120].

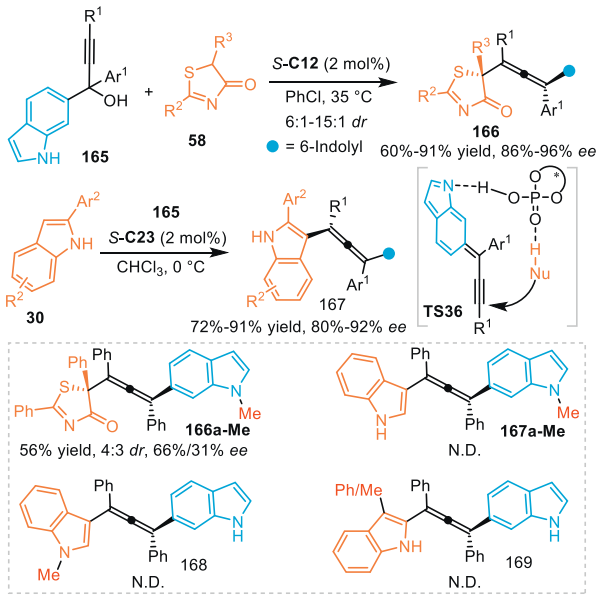


Scheme 48. Asymmetric 1,4- and 1,8-addition of the *in-situ* generated 7-/6-IIMs.

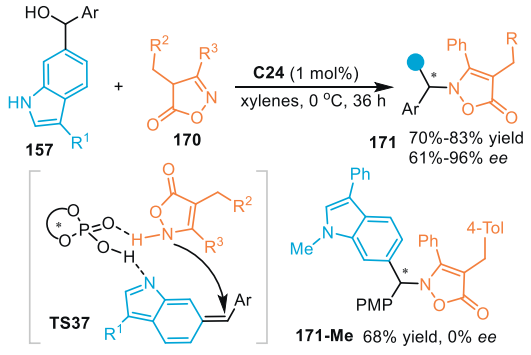


Scheme 49. Asymmetric aza- and thio-1,8-addition of the 6-indolylmethanol.

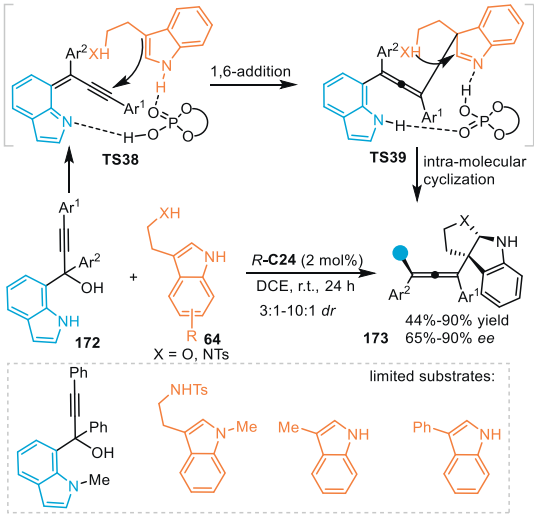
Herein, propargylic 7-indolylmethanols would act as the precursor of extended 7-IIMs to undergo the 1,6-addition for the synthesis of indole-based chiral allenes. In 2023, Li and coworkers realized this protocol by using α-(7-indolyl) propargylic alcohols **172** in the reaction with tryptamines **64** under the catalysis of *R*-**C24** [121]. The reaction was initiated by the remote 1,6-attack of the indole to the



Scheme 50. Asymmetric 1,10-addition of the *in-situ* generated propargylic 6-IIMs.



Scheme 51. Asymmetric 1,8-addition of the *in-situ* generated propargylic 6-IIMs with isoxazol-5(4*H*)-ones.



Scheme 52. Asymmetric tandem 1,6-addition and cyclization of *in-situ* generated propargylic 7-IIMs with tryptamines.

in-situ generated propargylic 7-IIMs **(TS38)** to generate the chiral allene species **(TS39)** with a dearomatized indole motif, that triggered an intramolecular cyclization to afford the enantio–enriched tetra-substituted allenes **173** in good yields with high enantio– and diastereoselectivities (Scheme 52).

6. Summary and outlook

QMs and IIMs have proven to be as a very highly reactive and versatile species to perform nucleophilic conjugate additions, including 1,4-/1,6-/1,8-/1,10-additions, providing a convenient pathway to afford structural diversfied and valuable arene-contained structures, that really enrich the remote activation approach. The acid-promoted dehydration of hydroxybenzyl alcohols, aminobenzhydryl alcohols, and varied indolylmethanols emerged as an efficient protocol for the *in-situ* generation of such reactive intermediates. As a result, CPAs are demonstrated to be the most powerful tool for the *in-situ* generation of the QMs and IIMs, thus enabling the asymmetric conjugate additions to access structural diversified enantio–enriched structures. Intriguingly, the introduction of the alkynyl group on the abovementioned alcohols provides a facile and universal approach to access extended propargylic-QMs and -IIMs, thus allowing remote regioselective nucleophilic additions and the resulted cyclizations for the construction of structural complicated molecules. Besides, the heteroarene is likely to extend the electrophilicity of the QMs or IIMs on the heteroarene, thus inducing a remote dearomative nucleophilic additions. Despite such significant achievements connected with the remote activation have been made by the *in-situ* generated QMs and IIMs, there exist some apparent research gap in this field. For instance, the allylic QMs and IIMs, which feature rich synthetic potential to achieve remote conjugate addition or cycloaddition, are rarely expolred. Moreover, besides the well explored *in-situ* generated 2-/3-/6-/7-IIMs, the conjugate addition of 4- and 5-IIMs are still elusive, which is an important precursor to access C4 and C5 functionalized indoles. Therefore, sustained efforts shoud be paid in this field to excavate the potential of such important species.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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